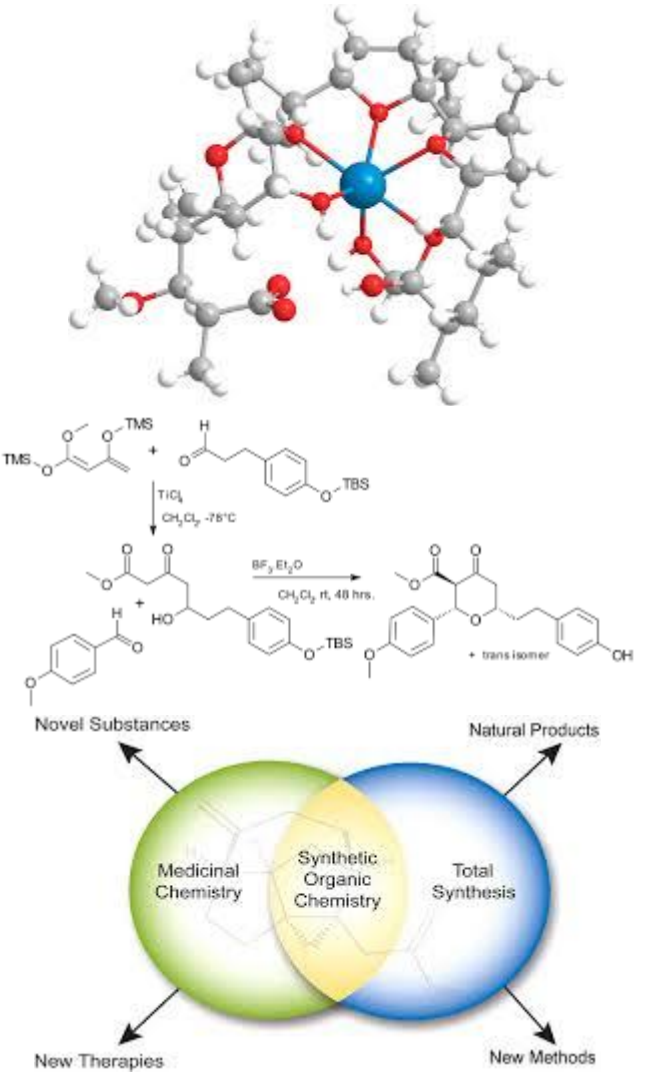
MScCH-07

Vardhman Mahaveer Open University, Kota



Synthetic Organic Chemistry

MScCH-07

Vardhman Mahaveer Open University, Kota

Synthetic Organic Chemistry

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Editing and Course Writing

Editor

Prof. P.S. Verma (Retd.)
Department of Chemistry
University of Raj, Jaipur

Dr. Sushil Kumar Sharma
Assistant Professor, Department of Pure and Applied Chemistry

University of Kota, Kota

Writers:

Dr. Shobhana Sharma 1,2,3,6
Assistant Professor,
Department of Chemistry
S.S.Jain Subodh
P.G.College,Jaipur

Dr.Sushil Kr. Sharma 4 ,8,11,14,
Assistant Professor,
Department of Pure and
Applied Chemistry
University of Kota, Kota

Mr. Ankit Sharma 5.7,12
Assistant Professor,
Department of Pure and
Applied Chemistry
University of Kota, Kota

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Department of Chemistry
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University,
Udaipur

Dr. Neetu Kumari 19,20
Assistant Professor,
Department of Chemistry
Mohan lal Sukhadia University,
Udaipur

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Preface

The present book entitled "Synthetic Organic Chemistry" has been designed so as to cover the unit-wise syllabus of MScCH-07 course for M.Sc. Chemistry (Final) students of Vardhman Mahaveer Open University, Kota. The basic principles and theory have been explained in simple, concise and lucid manner. Adequate examples, diagrammes , photographs and self-learning exercises have also been included to enable the students to grasp the subject easily. The unit writers have consulted various standard books and internet as their reference on the subject and they are thankful to the authors of these reference books.

Unit - 1

Organometallic Reagents-I

Structure of unit:

1.0 Principle of organolithium compounds
1.1 Preparations of organolithium compounds
- 1.1.1 Oxidative- Addition reaction
- 1.1.2 Metal-metal exchange (Transmetallation)
- 1.1.3 Carbanion-halide exchange
- 1.1.4 Metal hydrogen exchange reactions (Metallation)
- 1.1.5 Metal hydride addition to alkenes
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- 1.1.7 By reduction of sulphides

1.2 Properties of organolithium compounds
- 1.2.1 Addition reaction with aldehydes and ketones
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- 1.2.3 Addition reaction with immines, nitriles and isonitriles
- 1.2.4 Addition with CO_2 and CS_2
- 1.2.5 Nucleophilic substitution reactions at sp^2 hybrid carbon
- 1.2.6 Nucleophilic substitution reactions at saturated atoms

1.3 Applications of organolithium compounds
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- 1.5.1 Oxidative- addition reaction
- 1.5.2 Carbanion-halide exchange
- 1.5.3 By vinyl halide
- 1.5.3 Metallation
- 1.5.4 By alkynes

1.6 Properties of organomagnesium halides
- 1.6.1 Reaction with compounds having acidic hydrogens
- 1.6.2 Addition with aldehydes and ketones

1.0 Principle of organolithium compounds

Organolithium compounds are often schematically depicted as monomeric species with one lithium atom and a carbanionic group [MeLi or nBuLi] . But actually the structure of these compounds are much more complicated e.g- n-alkyl lithium are found to be hexameric in solvent.The simplest Li-R bond represents lithium atom as electron deficient and explains its tendency for polymerization like other electron deficient molecules.

Infrared studies show that the strong tendency of methyl lithium to associate which persists in vapour phase also. Raman bands in diethyl ether solutions of methyl lithium indicates cluster mode of tetrameric units.

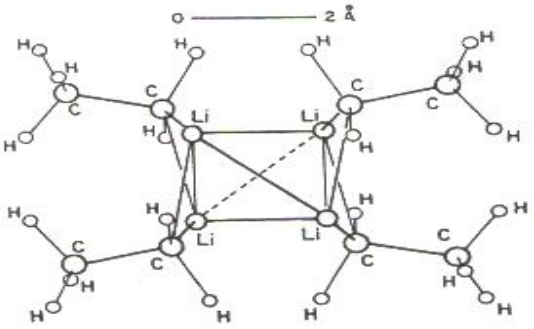


Fig.1 Structure of $(LiC_2H_5)_4$ with tetrahedral geometry

NMR studies also indicate that methyl lithium retains the tetrameric solid state structure in solution. The structures of $(Li\text{-}R)_4$ units i.e tetrameric depicted by X-

ray techniques . These comprises of four lithium atoms at the corners of a tetrahedron and the alkyl groups are located at each face of the tetrahedron.

1.1 Preparations of organolithium compounds

The following methods can be adopted to prepare various organolithium compounds:

1.1.1 Oxidative- Addition reaction

It is an important method for the preparation of simplest organolithium reagents. The most important alkyl lithium reagent is butyl lithium. This method involves the oxidation of a metal M by the addition of a group R-X.

1.1.2 $R\text{-}X + 2Li \xrightarrow[-20\ ^{\circ}C]{Et_2O} R\text{-}Li + LiX$ Metal-metal exchange
(Transmetallation)

This route depends on the difference in the free energies of the formation of the two species Li-R and Mg-R_2.

$$2Li + Mg\text{-}R_2 \longrightarrow 2Li\text{-}R + Mg$$

1.1.3 Carbanion-halide exchange

This reaction involve the interchange of the carbanion (alkyl/ aryl) and halide groups present on two different metals.

$$MX_n + M'R_m \longrightarrow MX_{n-a}R_a + MR_{m-a}X_a$$

(X = halogen, R = alkyl / aryl , M' = Li)

$$Li\text{-}R + Mg\text{-}X_2 \xrightarrow{ether} Mg(R)X + LiX$$

1.1.4 Metal hydrogen exchange reactions (Metallation)

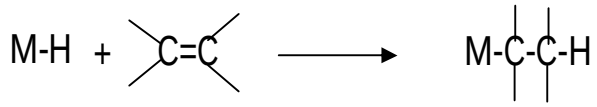
Due to strong polarisation ($M^{\delta+}$- $C^{\delta-}$) of the alkali metal carbon bond, the carbon atom bound to an alkali metal should be a strong base which is capable of abstracting protons from more acidic hydrocarbons.

$$MR' + RH \longrightarrow MR + R'H$$
(R = alkyl / aryl , M = Li)

$$LiC_2H_5 + Ph_3CH \longrightarrow LiCPh_3 + C_2H_6$$

1.1.5 Metal hydride addition to alkenes

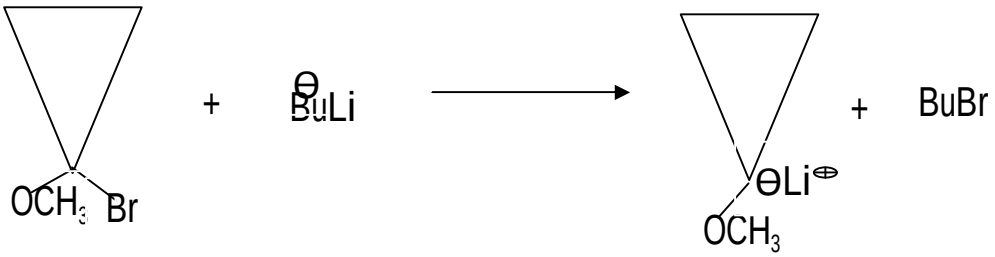
This route involves insertion of an alkene in a metal hydrogen bond which lead the formation of metal –carbon bond.



$$LiAlH_4 + 4CH_2{=}CH_2 \xrightarrow[100^\circ C]{\text{Pressure}} Li[Al(CH_2CH_3)_4$$

1.1.6 Halogen –metal exchange or inversion or Lithiation

The halogen metal exchange is useful for converting aryl and alkenyl halides to the corresponding lithium compounds by the use of of butyl lithium.Driving force of this reaction is the greater stability of sp^2 carbanion than the sp^3 carbanion.

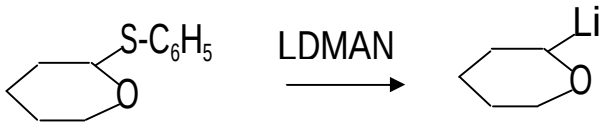


More stable carbanion due to OCH_3

1.1.7 By reduction of sulphides

Alkyllithium can be prepared by the reduction of sulphides. This method is generally useful for the preparation of α- lithioether and silanes.

For this reaction LDMAN (Dilithium dimethyl aminonaphthalene) is used as a reducing agent



1.2 Properties of organolithium compounds

Organolithium compounds possess ionic structure Li^+R^- due to small size of Li cation it possess greater polarizing power and provide special properties to its compounds.Organolithium derivatives are appreciably covalent and soluble in hydrocarbon or non polar solvents.

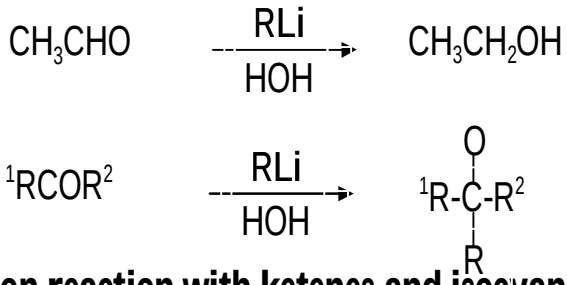
Organolithium derivatives are extremely reactive (super Grignard reagent). Organolithium compounds are oxygen and moisture sensitive and show Lewis acidic character.

Butyllithium deprotonate protons which are more acidic than butane. (Lithiation). Position of lithiation is determined by the relative acidity of the available hydrogen and directing effect of substitutent groups.

Benzyl and allylic hydrogens are relatively more reactive towards lithiation due to resonance stabilization of resulting anion. Organolithium compounds exhibit nucleophilic addition and substitution reactions which are as follows:

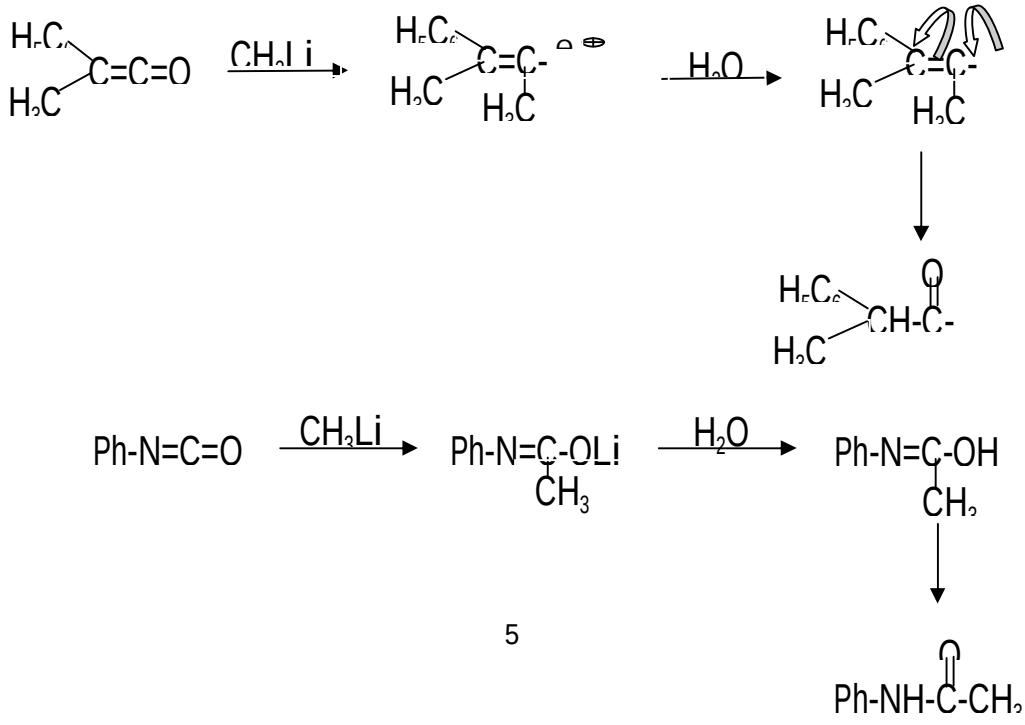
1.2.1 Addition reaction with aldehydes and ketones

Carbonyl compounds react with alkyl lithium to form lithium alkoxides which on hydrolysis give hydroxyl compounds.



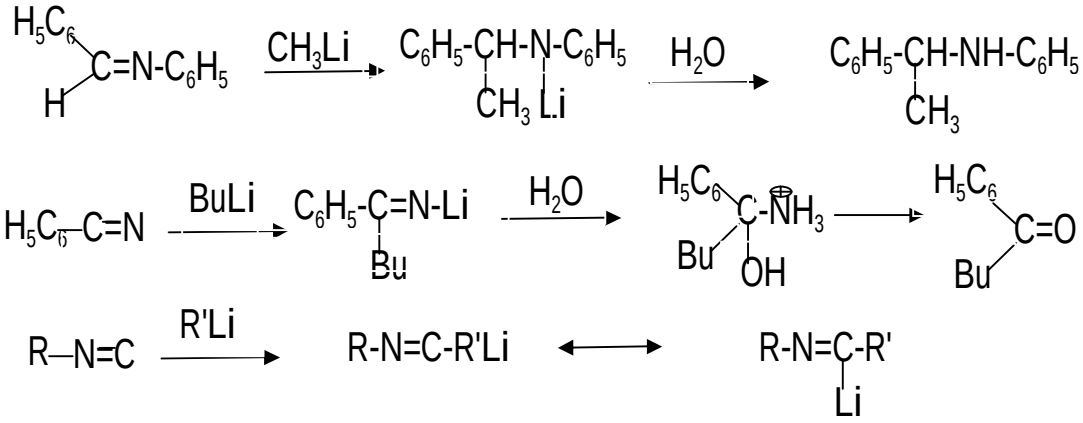
1.2.2 Addition reaction with ketenes and isocyanates

Organolithium adds to carbonyl group of ketene to produce an enolate which on hydrolysis gives ketones and isocyanates give secondary amides.



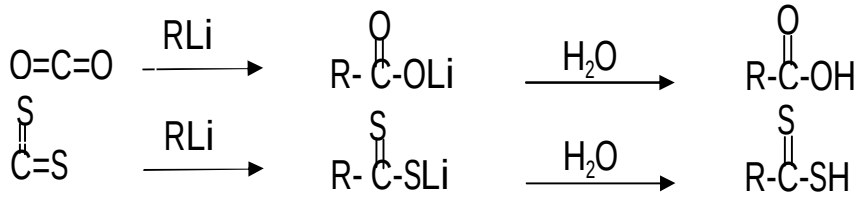
1.2.3 Addition reaction with imines, nitriles and isonitriles

Organolithium compounds react with imines, nitrile and isonitriles to synthesize amines, ketones and lithioimines.



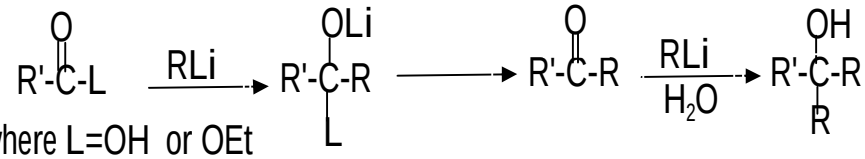
1.2.3 Addition with CO_2 and CS_2

Organolithium compounds adds with carbon dioxide and carbon disulphide to synthesize carboxylic acid and thioacids respectively.



1.2.5 Nucleophilic substitution reactions at sp^2 hybrid carbon

Organolithium compounds react with carboxylic acids and carbonates to give ketones and tertiary alcohol respectively.



where L=OH or OEt

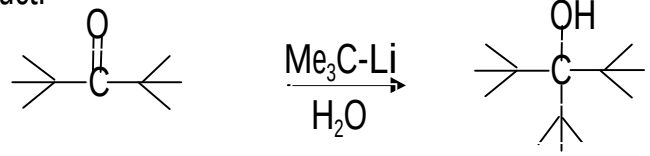
1.2.6 Nucleophilic substitution reactions at saturated atoms

Organolithium compounds give nucleophilic substitution reactions with those compounds which have nucleophilic groups as leaving groups i.e X, Ts, OR, N_3 etc.

1.3 Applications of organolithium compounds

Organolithium compounds are the most versatile reagents in all fields of chemistry . Thus some of the important applications of these compounds are as follows:

1. Organolithium compounds are highly reactive nucleophiles and strong bases due to the presence of strongly polarized Li-C bond.
2. Organolithium compounds are used in simple deprotonation, anionic polymerization and in asymmetric synthesis.
3. Organolithium compounds has advantage over Grignard reagent as Grignard reagent fail to react with highly hindered carbonyl compound but organolithium compounds react with such compound to give normal product.



Tritertiary butyl carbinol.

4. Organolithium compounds can bring selective monometallation adjacent to an electronegative group.
5. Organolithium compounds can be used as powerful metallating agents.

1.4 Principle of organomagnesium halides

Organomagnesium halides i.e Grignard reagents MgRX are generally tetrahedral but penta-coordinated trigonal bipyramidal species are also found.

A higher coordination number six for magnesium has been found in the complex $[Mg_2Cl_3Et)(THF)_3]_2$ and this complex can be obtained by crystallizing MgClEt from THF.

Grignard reagents are associated with halogen bridges. Diorganomagnesium compounds are similar to Grignard reagents in forming monomeric structures having tetrahedral environment around magnesium. Dialkylmagnesium compounds are associated with symmetrical bridging of alkyl groups to afford linear polymeric molecules. Lower alkyls of magnesium like bis (neopentyl) magnesium shows linear monomeric structure in the gas phase.

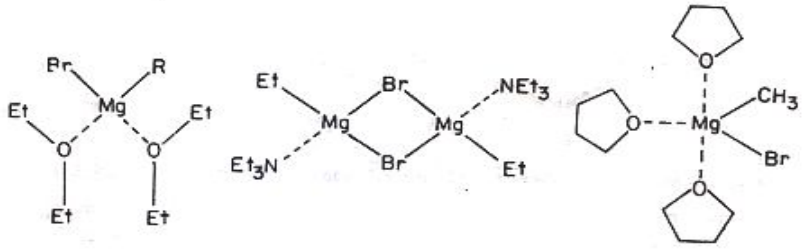


Fig.2 Structure of (a) $Mg(Br)R(Et_2O)_2$, (b) $[Mg(Br)Et(NEt_3)]_2$ and (c)$MgBr(Me)(THF)_3$

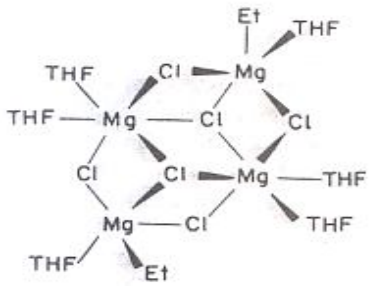


Fig.3 Structure of $[Mg_2Cl_3(Et)(THF)_3]_2$ with five coordinated magnesium

1.5 Preparations of organomagnesium halides

Organomagnesium halides can be prepared by the following methods:

1.5.1 Oxidative- addition reaction

Grignard reagents are usually prepared by the action of organic halides and magnesium turnings in an ether solvent. This is the well known example of two electron oxidative- addition reaction.

$$R\text{-}X + Mg \xrightarrow{\text{ether}} RMgX$$

1.5.2 Carbanion-halide exchange

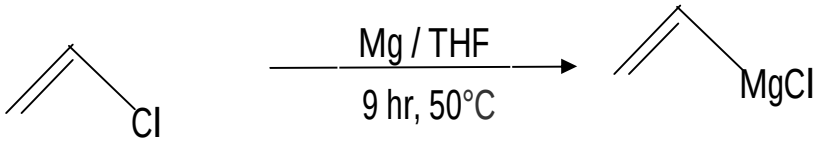
This reaction may be a route for potential value for grignard reagents which are difficult to be prepared by direct reaction.

$$Li\text{-}R + Mg\text{-}X_2 \xrightarrow{\text{ether}} Mg(R)X + LiX$$

(X = halogen, R = alkyl / aryl)

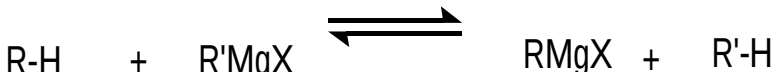
1.53 By vinyl halide

Alkyl halide readily react with diethyl ether but vinyl halide do not react with diethyl ether , so this reaction require longer time ,high temperature and require THF solvent.



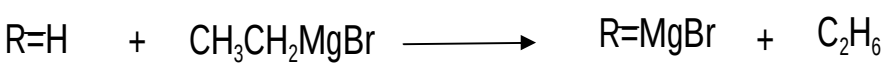
1.5.4 Metallation

Grignard reagent can be frequently prepared by this method. But this method is only suitable when atom attached to magnesium in the compound is more electronegative than the other one.



1.5.5 By alkynes

Alkynyl Grignard are normally prepared by this method.



1.6 Properties of organomagnesium halides

Organomagnesium halides were discovered by the French chemist Victor Grignard thus these compounds are named as Grignard reagents.

Organomagnesium halides are appreciably covalent and moderately reactive due to greater polarity of Mg-C bond.

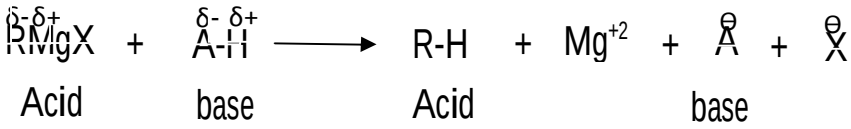
Organomagnesium halides are used in various organic and organometallic transformations.

The equilibrium of dialkylmagnesium and magnesium dihalides is an important factor which governs the reactivity of Grignard reagent.

Organomagnesium halides mainly exhibit nucleophilic addition and substitution reactions . Also show reactions with hydrocarbons having acidic hydrogens.

1.6.1 Reaction with compounds having acidic hydrogens

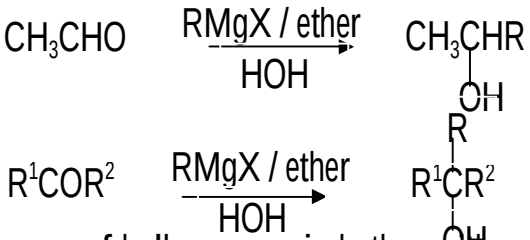
Grignard reagents react with compounds having acidic hydrogens to form hydrocarbon.



where A-H is H_2O, C_6H_5OH, ROH, RSH, RCOOH, HX etc.

1.6.2 Addition with aldehydes and ketones

Grignard reagent react with carbonyl compounds as shown below:

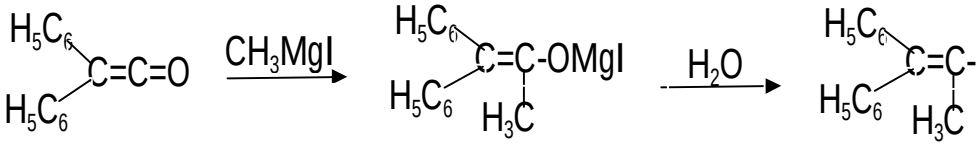


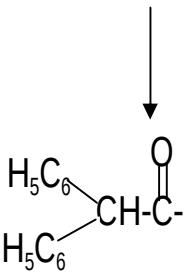
Due to the presence of bulky groups in both or either of the reactants in Grignard reagent the extent of addition is reduced or the reaction not take place or some abnormal product is formed.

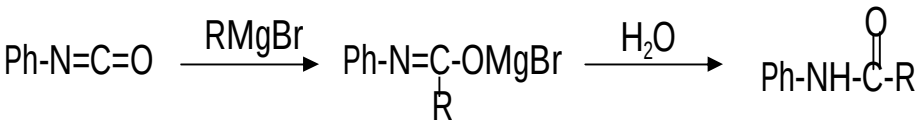
If Grignard reagent has β-hydrogen atom, then in some hindred ketone also show reduction of carbonyl group , may be due to β-hydrogen transfer by the formation of six membered transition state.

1.6.3 Addition reaction with ketenes and isocyanates

Grignard reagents attack at the carbonyl group of ketene to produce enolate and on hydrolysis give ketones. It react with isocyanate to synthesize secondary amines.

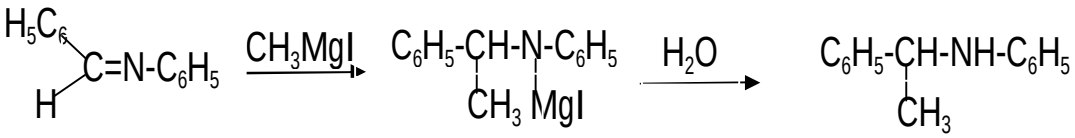


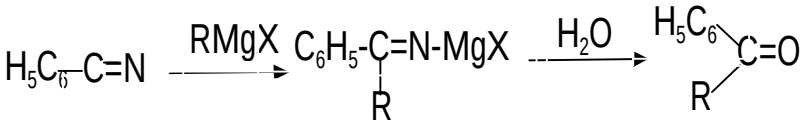




1.6.4 Addition reaction with imines and nitriles

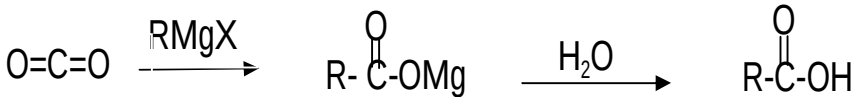
Grignard reagents react with imines and nitriles to form amines and ketones respectively. Its better if imine not contain any α-hydrogen as it give major side reaction (deprotonation).

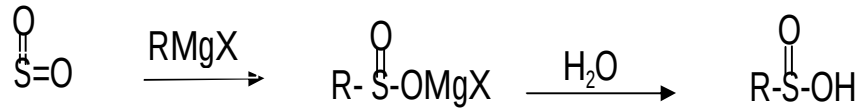


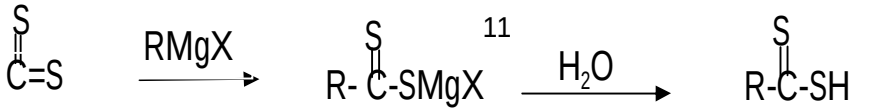


1.6.5 Addition with CO_2 ,SO_2 and CS_2

Grignard reagents react with CO_2, SO_2 and CS_2 to synthesize carboxylic acid, alkane sulphinic acid and thionic acid.

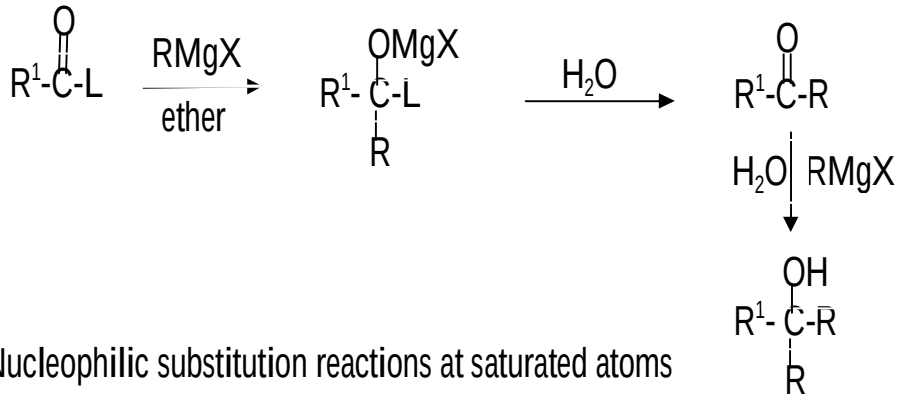






1.6.6 Nucleophilic substitution reactions at sp^2 hybrid carbon

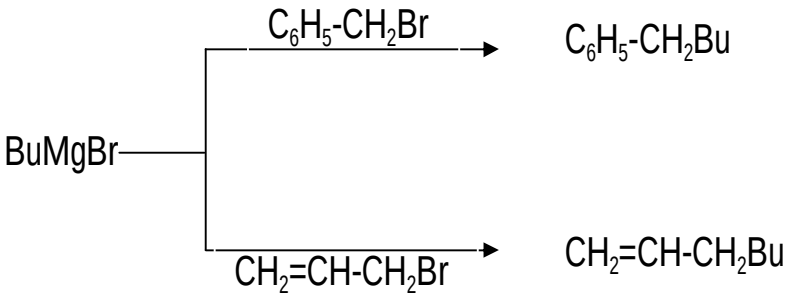
Grignard reagents react with acid chlorides, esters and lactones to give alcohols whereas Carbonates react with Grignard reagents to give esters.



2 Nucleophilic substitution reactions at saturated atoms

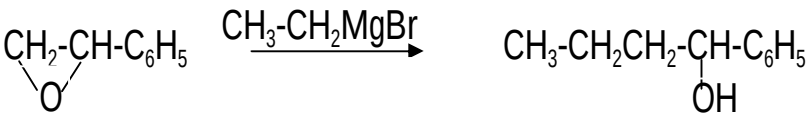
Grignard reagents react with those compounds having nucleophiiic groups as leaving group to give nucleophilic substitution reaction.

i. Organic halides



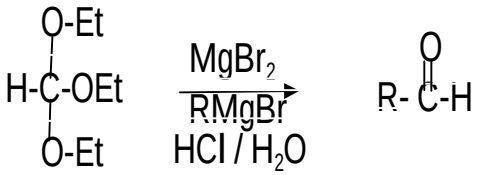
ii. Oxiranes

Epoxides react with Grignard reagents to give alcohol.



iii. Ortho esters and acetals

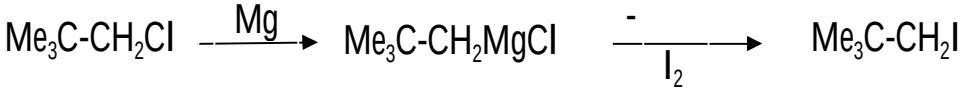
Ortho esters react with Grignard reagents in the presence of $MgBr_2$ as Lewis acid catalyst.



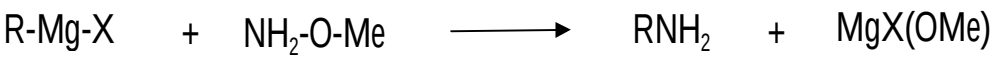
2.5 Applications of organomagnesium halides

Organomagnesium halides possess a variety of important applications some of which are as follows:

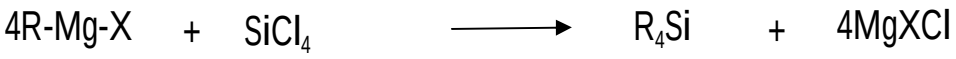
1. Grignard reagent is one of the most versatile reagents in organic and organometallic synthesis.
2. The application of Grignard reagent in the synthesis of transition metal alkyl which do not undergo facile decomposition by β- hydrogen elimination pathways.
3. Grignard reagent formed from neopentyl chloride and react with iodine to give neopentyl iodide in good yield.



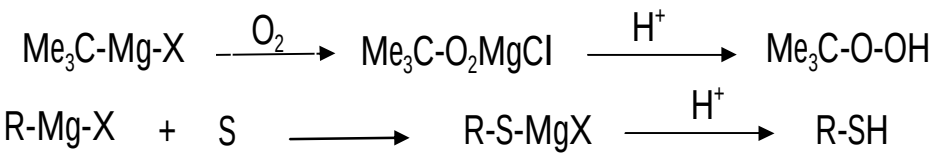
4. Grignard reagent provides a useful method for the preparation of t-alkyl amines like $Me_3C\text{-}NH_2$, as such amines are not obtained from SN2 reaction between t-alkyl halides and ammonia.



5. Grignard reagent plays a important role in the isolation of intermediate silanes.



6. Grignard reagent can be used to attached various other elements to carbon.e.g-hydroperoxides, thiols etc



1.8 Summary

- Organolithium compounds have a tendency of polymerization like other electron deficient molecules, so they show association e.g- $(Li\text{-}R)_4$.
- Organolithium compounds can be prepared by oxidative addition method, transmetallation, carbanion-halide exchange method, metallation, inversion or metal-hydride addition to alkenes.
- For the preparation of α-lithioether and silanes reduction of sulphides method by using LDMAN as a reducing agent can be adopted.
- Organolithium compounds are appreciably ionic in nature and are extremely reactive. These compounds are moisture sensitive and possess Lewis acid character.
- Organolithium compounds exhibit nucleophilic addition reactions and substitution reactions.
- Organolithium compounds react with carbonyl compounds to prepare hydroxyl compounds.
- Organolithium compounds react with immines, nitrile and isonitriles to synthesize amines, ketones and lithioimines.
- Organolithium compounds adds with carbon dioxide and carbon disulphide to synthesize carboxylic acid and thioacids respectively.
- Organolithium compounds gives nucleophilic substitution reactions with carboxylic acids and carbonates to synthesize ketones and tertiary alcohols respectively.
- Organolithium compounds are highly reactive nucleophiles and bases so they are used in deprotonation and bring selective monometallation.
- Organomagnesium halides are generally tetrahedral in nature with monomeric units but trigonal bipyramidal species are also found.
- Organomagnesium halides can be prepared by oxidative- addition method, carbanion-halide exchange, by vinyl halide, by metallation and by alkynes.

- Alkyl halide readily react with diethyl ether but vinyl halide do not react with diethyl ether , so reaction required more duration ,high temperature and THF solvent.
- Organomagnesium halides are covalent and moderately reactive due to which it is used in various organic and organometallic transformations.
- Grignard reagents react with active hydrogen containing compounds to synthesize alkanes.
- Grignard reagent react with ketenes and isocyanate to synthesized ketones and secondary amides.
- Grignard reagents react with imines and nitriles to form amines and ketones respectively.
- Grignard reagents react with CO_2, SO_2 and CS_2 to synthesize carboxylic acid, alkane sulphinic acid and thionic acid.
- Due to the presence of bulky groups in both or either of the reactants in Grignard reagent the extent of addition is reduced or the reaction not take place or some abnormal product is formed.
- Grignard reagent give nucleophilic substitution reactions as epoxides react with Grignard reagents to give alcohol.
- Ortho esters react Grignard reagents in the presence of $MgBr_2$ as Lewis acid catalyst to prepare aldehydes.
- Grignard reagent is used in asymmetric , stereospecific synthesis and in the synthesis of transition metal alkyl.
- Grignard reagent formed from neopentyl chloride and react with iodine to give neopentyl iodide in good yield.
- Grignard reagent used in the preparation of t-alkyl amines which are not obtained by SN2 reactions.
- Grignard reagent used in the isolation of intermediate silanes and also used to attached other elements to carbon like thiols.

1.9 Review Questions

1. Discuss the structure of organolithium compounds.

2. Why organolithium compounds show polymerization?
3. What are the various methods employed for the preparation of organolithium compounds?
4. Why organolithium compounds possess an advantage over Grignard reagent?
5. Explain various nucleophilic addition reactions given by organolithium compounds.
6. What are the various applications of organolithium compounds?
7. Explain deprotonation nature of butyl lithium.
8. Explain nucleophilic substitution reactions at sp^2 hybrid carbon and saturated atoms with organolithium compounds.
9. Discuss the nature of bonding and structure of organomagnesium halides.
10. Why Grignard reagents react with active hydrogen containing compounds?
11. Explain various nucleophilic addition reactions given by organomagnesium halides.
12. Discuss various preparative methods of Grignard reagents.
13. What are the various applications of organomagnesium halides?
14. Explain the effect of steric hinderance on Grignard addition.
15. Discuss nucleophilic substitution reactions at sp^2 hybrid carbon and saturated atoms with organomagnesium halides.
16. Why organolithium compounds are called super Grignard reagents?
17. Why vinyl halides not react in ether to prepare Grignard reagent and what special conditions it required?

1.10 References and Suggested Readings

- Organometallic Chemistry: A Unified Approach ,R .C. Mehrotra and A. Singh, New Age International Publisher, 2000 (Second Edition).
- Principles of Organic Synthesis, R. Norman and J.M.Coxon, Blackie Academic and Professional , 1993 (Third Edition).

- Synthesis of Organometallic compounds: A Practical Guide, S. Komiya, Wiley-Blackwell,1997.
- The Organometallic Chemistry of the Transition metals, R.H. Crabtree, Wiley and Sons, 1992 (Second Edition).

Unit-2

Organometallic Reagents-II

Structure of unit:

2.0 Principle of organocopper compounds

2.1 Preparations of organcopper compounds

- 2.1.1 From lithium compounds
- 2.1.2 From alkenyl compounds
- 2.1.3 From Alkynes

2.2 Properties of organocopper compounds

- 2.2.1 Nucleophilic substitution of halides (Corey-House synthesis)
- 2.2.2 Nucleophilic substitution on sp2 hybridized carbon
- 2.2.3 Alkylation of epoxides
- 2.2.4 Ketones from acid chlorides
- 2.2.5 Conjugated addition reactions

2.3 Applications of organocopper compounds

2.4 Principle of organozinc compounds

2.5 Preparations of organozinc compounds

- 2.5.1 From alkyl halides
- 2.5.2From trialkyl borane
- 2.5.3 Metal-metal exchange reaction (Transmetallation)

2.6 Properties of organozinc compounds

- 2.6.1 Protonation
- 2.6.2 Reaction with carbon-carbon multiple bonds
- 2.6.3 Addition with carbonyl compounds
- 2.6.4 Reformatsky reaction
- 2.6.5 Reaction with acid chlorides

2.0 Principle of organocopper compounds

The most popular synthetic reagent is lithium dialkyl cuprate, R_2CuLi. Lithium dialkyl cuprate was first synthesized by Henry Gilman, so it is often called Gilman reagent. In solution this lithium dialkyl cuprate exist as a dimer $[(CH_3)_2CuLi]_2$. The compound is often represented as four methyl groups attached to a tetrahedral cluster of Li and Cu atoms.

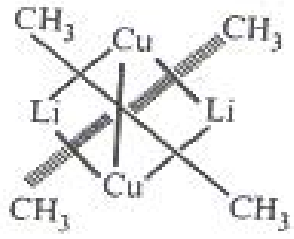


Fig.1: Tetrahedral cluster of lithium and copper atoms

In the presence of lithium iodide, this lithium dialkyl cuprate appears to be a monomer having composition $(CH_3)_2CuLi$.

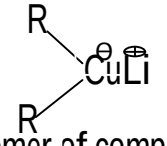


Fig.2: Monomer of composition $[(CH_3)_2CuLi]$

2.1 Preparations of organocopper compounds

Two types of copper (I) in synthesis are of value in synthesis : organocopper compound and lithium dialkyl cuprate, R_2CuLi where R is alkyl group (either primary, secondary or tertiary), alkenyl or aryl group.

2.1.1 From lithium compounds

These compounds can be prepared from lithium compounds and copper (I) iodide with an aprotic solvent ether in inert atmosphere.

$$R\text{-}Li + CuI \longrightarrow [R\text{-}Cu] + LiI$$

$$2R\text{-}Li + CuI \longrightarrow R_2\text{-}CuLi + LiI$$

$$3R\text{-}Li + CuI \longrightarrow R_3\text{-}CuLi + LiI$$

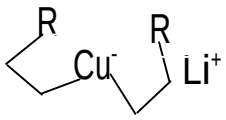
$$2LiCH_3 + CuI_2 \longrightarrow Li[Cu(CH_3)_2] + LiI$$

$Li[Cu(CH_3)_2]$ is the first example of copper catalysts and this reagent prepared from methyl lithium and cuprous iodide.

2.1.2 From alkenyl compounds

Alkenyl compounds are of two types which can be prepared from alkynes. Acetylene reacts with an organocopper compound or an organocuprate with complete syn stereoselectivity.

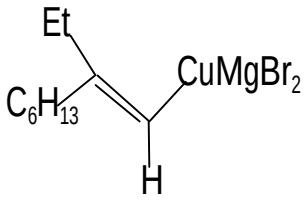
$$2CH{\equiv}CH + R_2CuLi \longrightarrow$$



2.1.3 From Alkynes

Alkynes of the type $RCH_2C{\equiv}CH$ react with the complex of RCu and $MgBr_2$ (not with R_2CuLi) with both regioselectivity (the copper atom becoming attached to the less substituted carbon atom) and syn stereoselectivity .

$$C_6H_{13}\text{-}C{\equiv}CH \xrightarrow{EtCuMgBr_2}$$



2.2 Properties of organocopper compounds

Organo copper compounds are very reactive towards oxygen and water forming copper(I) oxide which is thermally unstable. Cuprate salts are insoluble in non polar solvents.

The chemical reactivity exhibited by cuprate reagents is due to its powerful nucleophilicity towards carbon and its preferability for reaction at halide or alkene site rather than the carbonyl group .

Lithium dialkyl cuprate under goes a large number of synthetically useful transformations which can be divided into two groups of reaction – substitution and 1,4 addition reactions.

2.2.1 Nucleophilic substitution of halides (Corey-House synthesis)

This method provides the coupling of the alkyl groups of the two alkyl halides to synthesize alkane . For this coupling we have to transform one alkyl halide into dialkyl lithium cuprate.

The R of R_2CuLi may be primary, secondary or tertiary alkyl groups .It may be vinyl , allyl, phenyl and benzyl groups. The R' of R'-X may be methylhalide, primary halide, secondary alkyl halide, cycloalkyl halide, vinyl halide, allyl halide ,aryl halide etc.

$$R\text{-}X + 2Li \xrightarrow{\text{ether}} R\text{-}Li + LiX$$

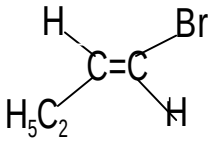
$$2R\text{-}Li + CuI \longrightarrow R_2CuLi + LiI$$

$$R_2CuLi + R'\text{-}X \longrightarrow R\text{-}R' + R\text{-}Cu + LiX$$

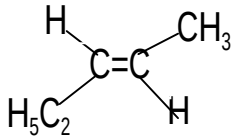
In the presence of dialkyl lithiumcuprate halides not show elimination reaction as R_2CuLi is a weak base.

2.2.2 Nucleophilic substitution on sp^2 hybridized carbon

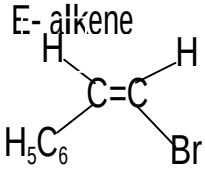
Nucleophilic substitution of a vinyl halide is not possible with organolithium and magnesium reagents but it is readily achieved by cuprates. This substitution is difficult to achieve by other nucleophile. It occur with complete rentented product.



Me_2-CuLi



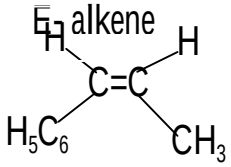
E- alkene



Z- isomer

Me_2-CuLi

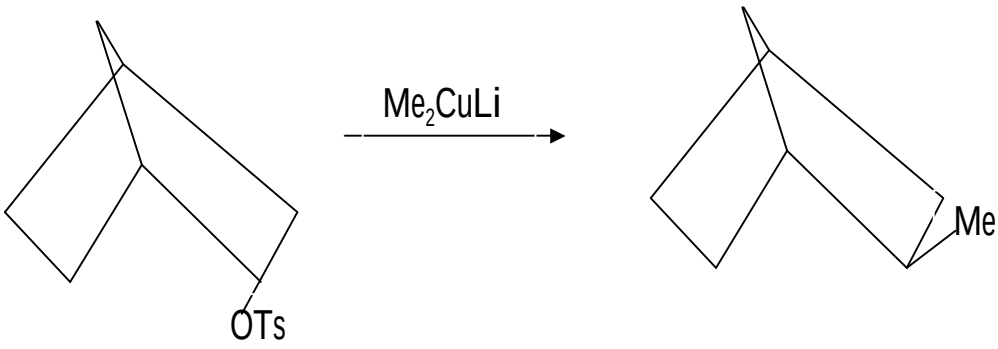
E- alkene



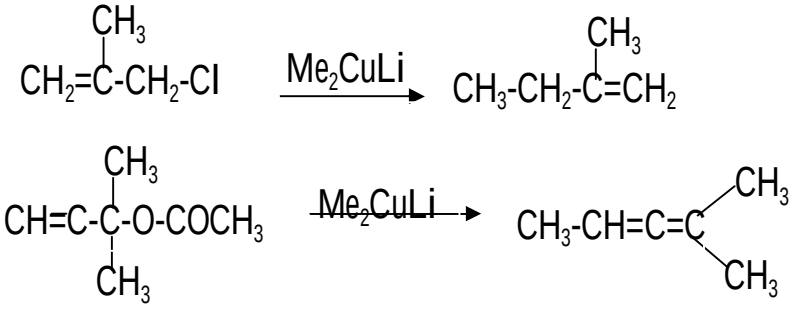
Z-

2.2.2 **Nucleophilic displacement of other leaving groups**

Dialkyl lithium cuprate displace tosyl group from the organic moity with inversion of configuration as reaction occurs by SN2 mechanism.

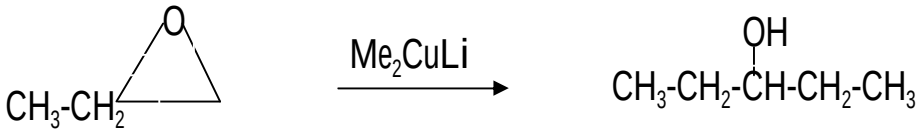


Allyl halides and allyl acetates give this reaction by allylic rearrangement where as propargyl acetates are converted into allenes in the presence of dialkyl lithiumcuprate.



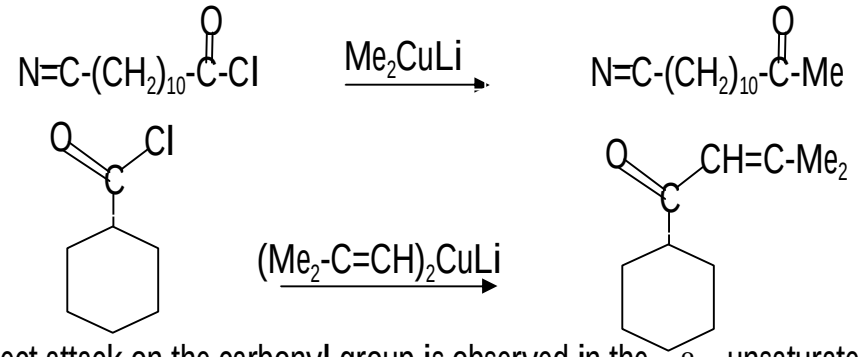
2.2.3 Alkylation of epoxides

During alkylation of epoxides the methyl group is introduced at the less hindered carbon of the epoxide.



2.2.4 **Ketones from acid chlorides**

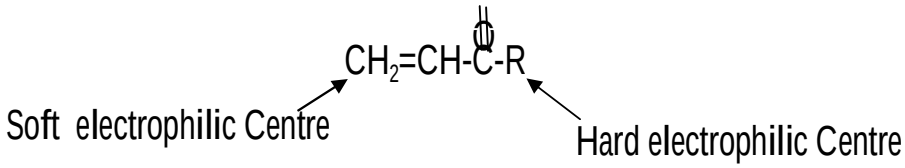
The cuprate reagents can act as an alternative to alkylcadmium reagents in generating ketones from acid chlorides.



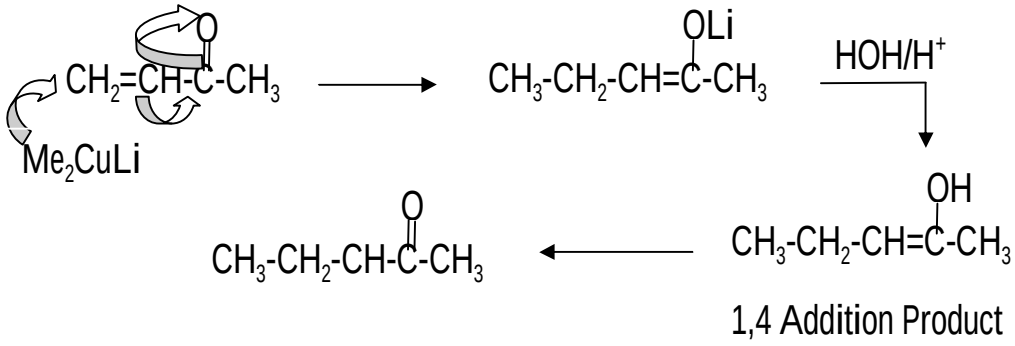
Direct attack on the carbonyl group is observed in the α,β – unsaturated acid chlorides .

2.2.5 **Conjugated addition reactions**

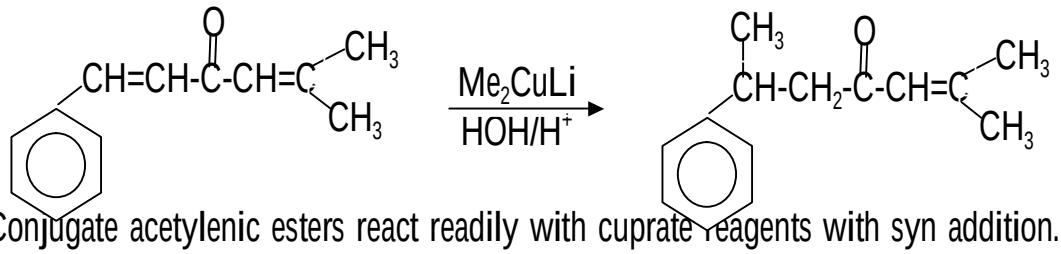
Dialkyl lithium cuprate react with α,β – unsaturated carbonyl compounds by conjugate addition as α,β – unsaturated carbonyl compounds possess two types of functional groups , a hard electrophilic centre at the carbonyl carbon and a soft electrophilic centre at the β-carbon.



Organocopper reagents are soft nucleophiles, thus these reagents give 1,4 addition reaction which is known as Michael addition reaction. This reaction is 1,4 addition reaction but the product is 1,2 addition product on carbon –carbon double bond.



In case when carbonyl group is conjugated with two carbon-carbon double bonds then conjugated addition takes place on the less substituted conjugated carbon.



Conjugate acetylenic esters react readily with cuprate reagents with syn addition. Mixed type of cuprates can be used instead of simple dialkyl lithium cuprate. Mixed cuprates can be prepared from 2;1 ratio of an alkyl lithium and CuCN.

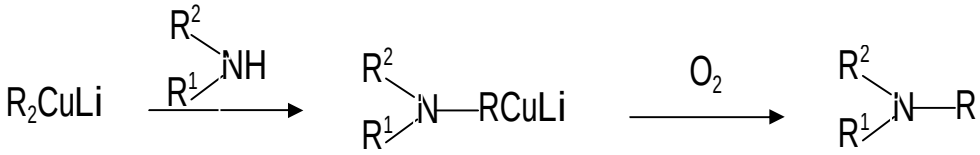
$$2RLi + CuCN \longrightarrow R_2Cu(CN)Li_2$$

Mixed cuprates are more stable than dialkyl lithium cuprate and possess same reactivity.

2.3 Applications of organocopper compounds

Organocopper compounds used frequently in organic chemistry as alkylating agents due to more functional group tolerance.

1. Copper hydrides are used as mild reducing agents and thus play a important role in organic synthesis.
2. Alkylation of amines by using the Gilman reagent is an efficient synthetic method for the alkylation of amines. This method is based on the oxidative coupling of lithium alkyl copper amide which is synthesized during the reaction between dialkyl lithium cuprate and primary or secondary amides.



This method is proved to be effective for the oxidative coupling of amines and alkyl ,including tertiary butyl and aryl halides.

3. Cuprates are used for the nucleophilic substitution of a vinyl halide which is not possible with organolithium and organomagnesium reagents. Nucleophilic substitution take place on sp^2 carbon which is very difficult with other nucleophile. In this nucleophilic substitution

reactions d^{10} cuprates gives addition with halides to produce a planar copper (III) d^8 intermediate.

4. Organocopper reagents are soft nucleophiles and give 1,4 addition reaction which is known as Michael addition reaction.
5. Organocopper compounds can undergo a large number of synthetically useful organic transformations.

2.4 Principle of organozinc compounds

Edward Frankland synthesized the first organozinc compound, diethyl zinc $Zn(C_2H_5)_2$. Alkyls of zinc appears to monomeric, volatile and covalent. Shapes of the alkyl of zinc can be easily explained on the basis of VSEPR theory. In sp hybridization of the metal atom the two bond pairs are as far as possible. [Fig. 3(a)]

Zinc dialkyls , ZnR_2 can form various types of adducts. ZnR_2L having coordination number three possess planar geometry where L is monodentate Lewis base. ZnR_2L_2 and ZnR_2L' [fig. 3 (b),(c)] having coordination number four and acquire tetrahedral geometry where L' = chelating diether or amines.

Heteroleptic derivatives like ZnXR (X = halogen, OR, SR, NR_2, PR_2) adopt dimeric structures. Derivatives like $(ZnRX)_2$[fig. 3 (d)] and $(ZnRX)_4$ [fig. 3 (e)] possess cubane type tetramers. Evidences indicates simple , unassociated structure with linear C-Zn-C skeletons.

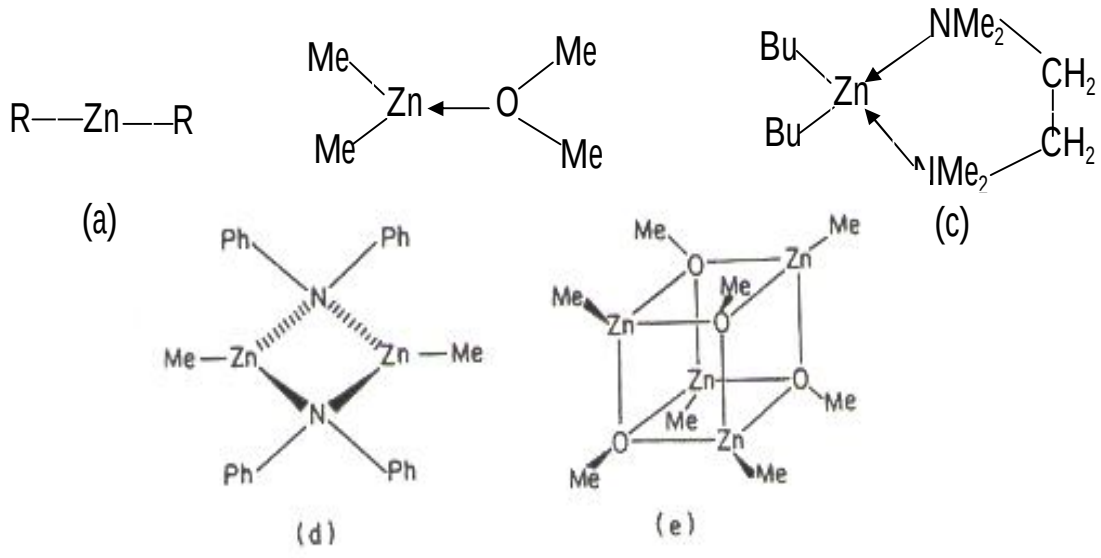
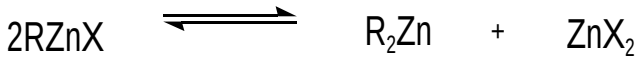


Fig 3. Some representative structures of organozinc compounds

Diarylzinc compound and higher dialkyl zinc are of same structures. Dialkylzinc compound form complexes with electron donars. Ether, amines and sulphides form weak complexes and difunctional donars form stable crystalline complexes. The existence of a Schlenk type equilibrium in solution of alkylzinc halides is well established.



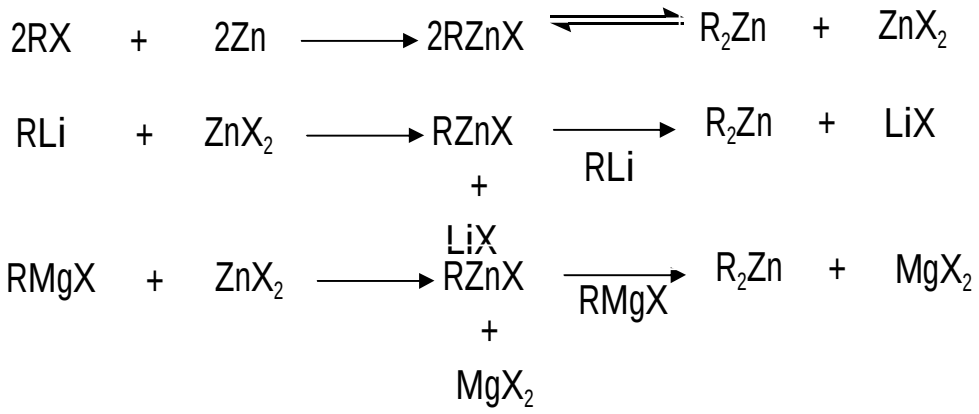
$$2RZnX \rightleftharpoons R_2Zn + ZnX_2$$

2.5 Preparations of organozinc compounds

The following methods can be employed to prepare organozinc compounds:

2.5.1 From alkyl halides

Organozinc compounds can be prepared by the reaction between zinc and alkyl halides as a result zinc halide is formed which further reacts with an organolithium or organomagnesium compounds. Instead of organolithium or organomagnesium compounds organoaluminium and organoboron compounds can also be used.



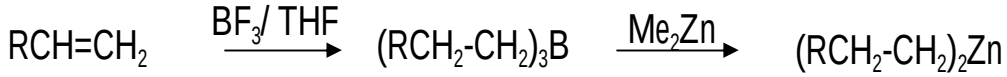
$$2RX + 2Zn \longrightarrow 2RZnX \rightleftharpoons R_2Zn + ZnX_2$$

$$RLi + ZnX_2 \longrightarrow RZnX + LiX \xrightarrow{RLi} R_2Zn + LiX$$

$$RMgX + ZnX_2 \longrightarrow RZnX + MgX_2 \xrightarrow{RMgX} R_2Zn + MgX_2$$

2.5.2 From trialkyl boranes

Organozinc compounds can be prepared from trialkyl boranes by exchange with dimethyl zinc.



$$RCH{=}CH_2 \xrightarrow{BF_3/\ THF} (RCH_2\text{-}CH_2)_3B \xrightarrow{Me_2Zn} (RCH_2\text{-}CH_2)_2Zn$$

2.5.3 Metal-metal exchange reaction (Transmetallation)

For the preparation of organozinc compounds this method can be used as the Hg-C bonds are exceptionally weak. Thus HgR_2 derivatives are used in this reaction.

$$2Zn + HgR_2 \longrightarrow ZnR_2 + Hg(Zn)$$

2.6 Properties of organozinc compounds

The lower dialkyl zinc compounds are volatile , non polar liquids. Diarylzinc compounds and higher dialkyl zinc compounds are usually low melting solids with similar structure.

2.6.1 Protonation

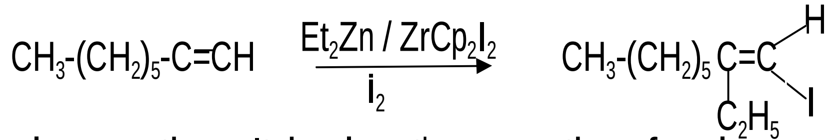
Dialkyl zinc compounds react with acidic hydrogen containing compounds to form hydrocarbon. In this reaction dialkyl zinc compounds behaves as base so this is a acid-base reaction. The protonation of dialkyl and alkyl zinc reagents take place in two stages.

$$R_2Zn + A\text{-}H \longrightarrow RZnA + RH$$

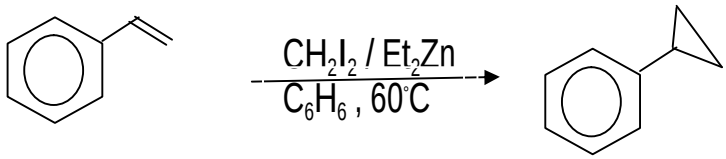
$$RZnA + A\text{-}H \longrightarrow RH + ZnA_2$$

2.6.2 Reaction with carbon-carbon multiple bonds

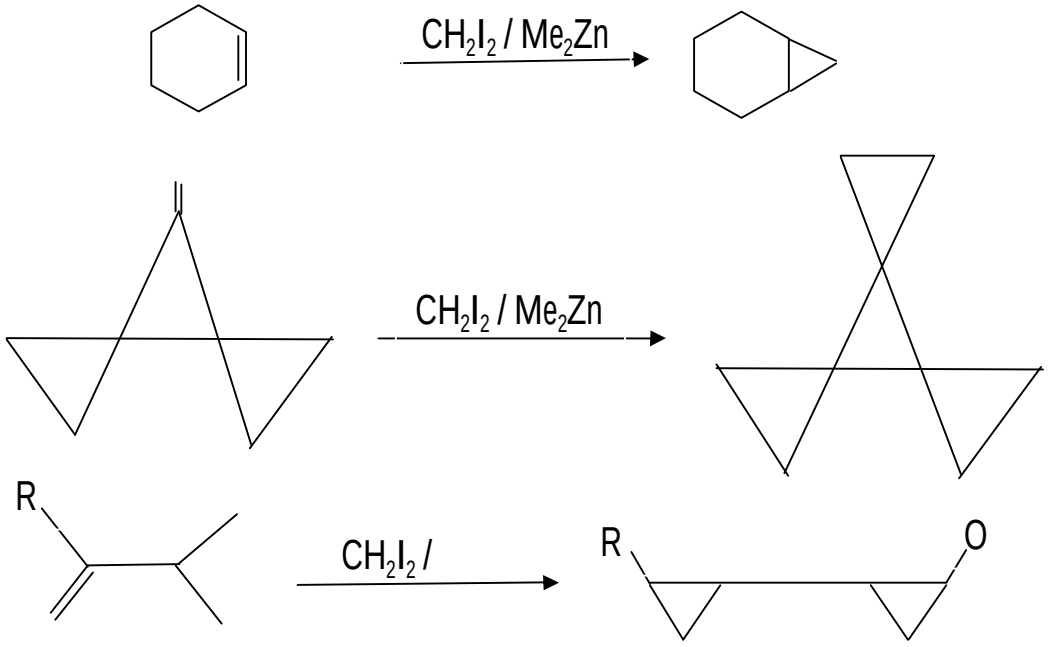
Organozinc compounds are unreactive towards alkenes and non terminal alkynes but allylic zinc derivatives are exceptional which can add carbon-carbon double and triple bond. Conjugation and electron donating groups assist addition reaction. If such assistance is available addition is preferred to metallation of terminal alkynes. Least reactive alkynes also give syn addition in the presence of catalyst $ZrCp_2I_2$.



Cyclopropanation : It involves the preparation of cyclopropane by organozinc carbenoids. Generally iodomethyl zinc derivatives are used as cyclopropanation reagent and these derivatives can be easily generated by diethyl zinc by Furukawa method.

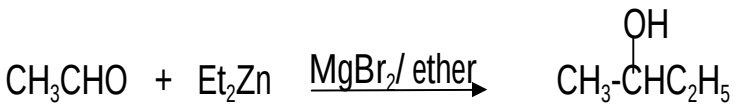


Simmons Smith reaction: Cyclopropanation of alkenes by iodomethyl zinc iodide (Simmon-Smith reagent) is known as Simmons Smith reaction. Electron rich alkenes facilitating such type of reaction. The combination of CH_3CHI_2 or Ph-CHI_2 with Me_2Zn or Et_2Zn also provide active cyclopropanating reagents.

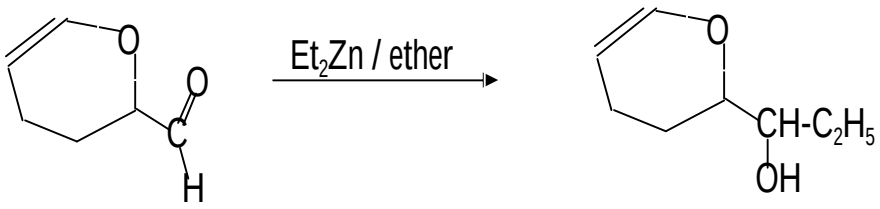


2.6.3 Addition of carbonyl compounds

Lower dialkyl zinc is more reactive than the higher dialkyl zinc reagents but allylic zinc compounds are more reactive than simple dialkyl zinc reagents.

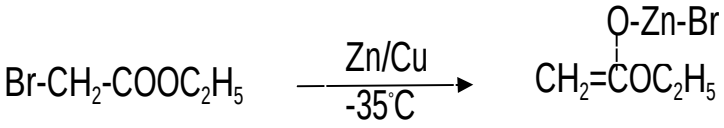


Presence of heteroatom at α-position to the carbonyl group accelerates the addition reaction and reactive titanium catalysts [$TiCl_4$, $Ti(OiPr)_4$] increases reactivity of higher dialkylzinc reagents.

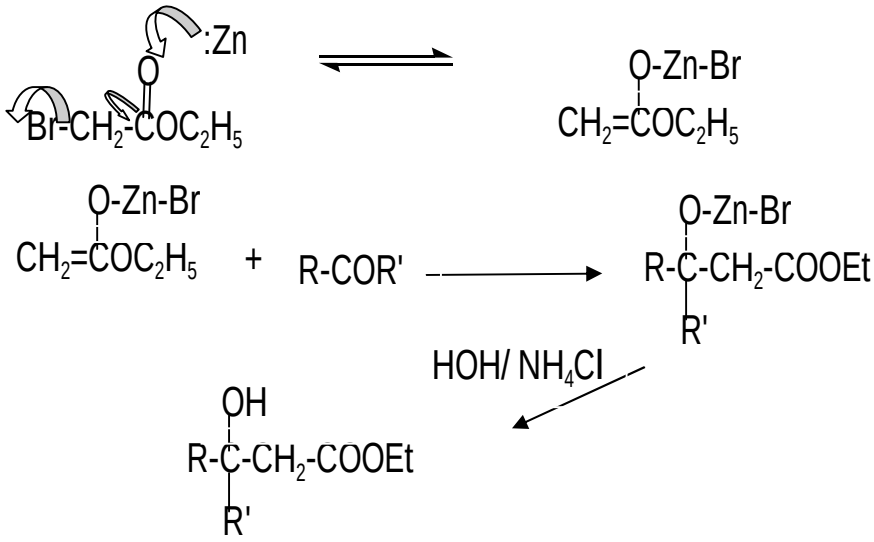


2.6.4 Reformatsky reaction

This reaction involves interaction of an α-haloester , zinc and an aldehyde or ketone to synthesize β-hydroxy ester. In this reaction firstly zinc enolate (halogen zinc intermediate) is formed and then this intermediate show addition reaction with carbonyl compound or Grignard reagent.

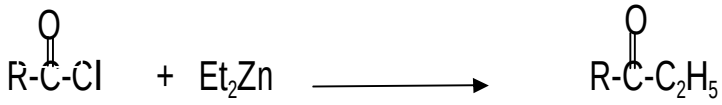


Organocopper reagents are soft nucleophiles, thus these reagents give 1,4 addition reaction which is known as Michael addition reaction.



2.6.5 Reaction with acid chlorides

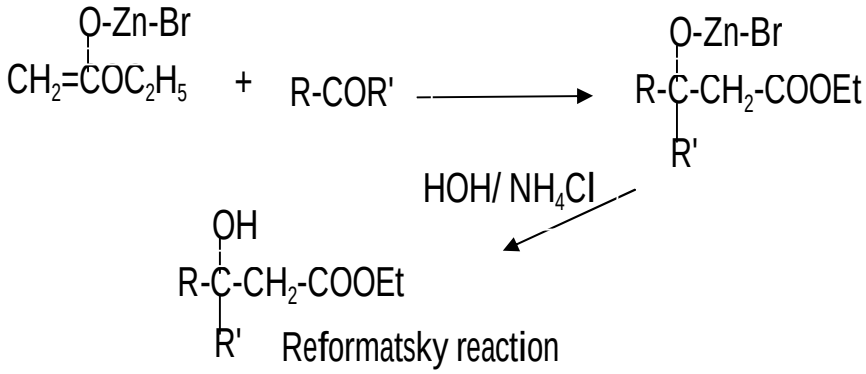
Organozinc compounds react readily with acid chlorides to synthesize ketones but these compounds not show any reaction with esters, amides and many other groups.



2.6 Applications of organozinc compounds

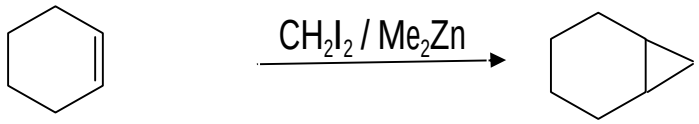
1. Zinc alkyl were the first organometallic compound used as an intermediate in organic synthesis.
2. Organozinc compounds also useful in important synthetic reaction like Reformatsky reaction , Simmans-Smith synthesis of cyclopropanes and applicability of allylzinc bromide in organic synthesis.

a.



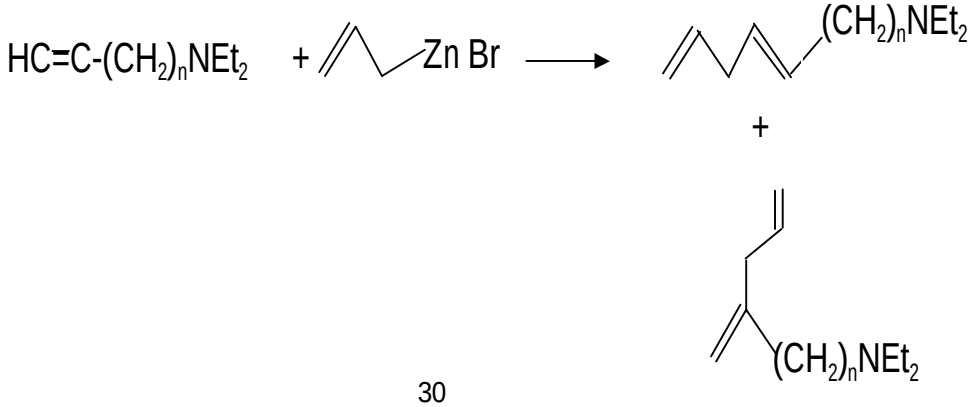
Reformatsky reaction

b.

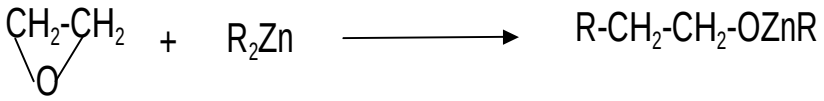


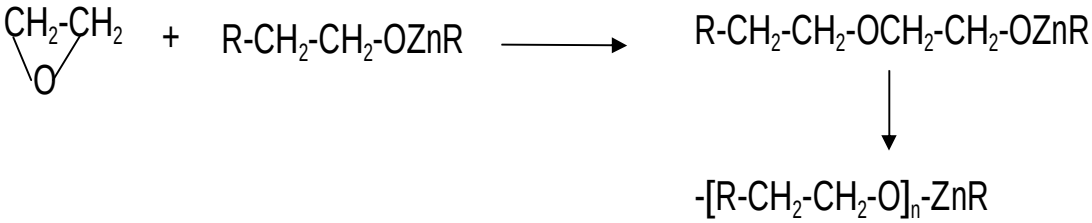
Simmans-Smith synthesis

3. Reactions of alkyl zinc bromide with carbon-carbon and carbon-nitrogen multiple bonds provide useful route for some alkenic compounds.



4. Organozinc compounds used as a component of Zeiglar Natta catalyst and initiate the polymerization of a variety of vinyl monomers. e.g –it is used in polymerization of oxirane.





Polymerization of dialkyl zinc is catalysed by water or alcohol . polymers obtained in the presence of dialkyl zinc is stereoregular.

2.8 Summary

- Lithium dialkyl cuprate is called Gilman reagent. In solution it exists as dimer but in the presence of LiI it appears monomer.
- Organocopper compounds can be prepared from lithium compound , alkenyl compound and from alkynes.
- Cuprate reagents are powerful nucleophiles and thus used in large number of synthetically useful transformations.
- In Corey-House synthesis coupling of alkyl groups of the two alkyl halides to synthesize alkanes.
- Organocopper compounds exhibit nucleophilic substitution and addition reaction.
- Organocopper reagents are soft nucleophiles, thus these reagents give 1,4 addition reaction which is known as Michael addition reaction.
- Mixed cuprates are more stable than dialkyl lithium cuprate and possess same reactivity.

- Gilman reagent is used in alkylation of amines which is based on the oxidation coupling of dialkyl lithium cuprate and primary or secondary amides.
- E. Frankland synthesize the first organozinc compound i.e diethyl zinc.
- Zinc dialkyls form various types of adducts with variable coordination numbers and geometry. Like ZnR_2L, ZnR_2L_2 and ZnR_2L',
- Dialkyl zinc compound form complexes with electron donar ligands.
- Heteroleptic derivatives like ZnXR (X = halogen, OR, SR, NR_2, PR_2) adopt dimeric structures but derivatives like $(ZnRX)_2$ and $(ZnRX)_4$ possess cubane type tetramers.
- Organozinc compounds can be prepared from alkyl halides, trialkyl boranes and transmetallation.
- Organozinc compounds can be prepared from trialkyl boranes by exchange with dimethyl zinc.
- For the preparation of organozinc compounds transmetallation method involves the use of HgR_2 derivatives , as the Hg-C bonds are exceptionally weak.
- Dialkyl zinc compounds react with acidic hydrogen containing compounds to form hydrocarbon. In this reaction dialkyl zinc compounds behaves as base so this is a acid-base reaction.
- Least reactive alkynes give syn addition with dialkyl zinc compounds in the presence of catalyst $ZrCp_2I_2$.
- Cyclopropanation involves the preparation of cyclopropane by organozinc carbenoids. Iodomethyl zinc derivatives are used as cyclopropanation reagent which can be easily generated by diethyl zinc in Furukawa method.
- Cyclopropanation of alkenes by iodomethyl zinc iodide (Simmon-Smith reagent) is known as Simmons Smith reaction. Electron rich alkenes increases the rate of such type of reaction.
- Reformtsky reaction involves interaction of an α-haloester , zinc and an aldehyde or ketone to synthesize β-hydroxy ester.

- Organozinc compounds react readily with acid chlorides to synthesize ketones but these compounds not show any reaction with esters, amides and many other groups.
- Organozinc compounds also useful in synthetic important reaction like Reformatsky reaction, Simmans-Smith synthesis of cyclopropanes and applicability of allylzinc bromide in organic synthesis.
- Organozinc compounds used as a component of Zeiglar Natta catalyst and initiate the polymerization of a variety of vinyl monomers. Like polymerization of oxirane.
- Reactions of alkyl zinc bromide with carbon-carbon and carbon-nitrogen multiple bonds provide useful route for some alkenic compounds.

2.9 Review Questions

1 What is Gilman reagent ?

2 Write short note on-

i. Correy House Synthesis
ii. Reformatsky reaction
iii. Simman Smith reaction

3 Why organocopper reagents exhibit 1,4 addition reaction?

4 How can we prepare organocopper compounds?

5 Why cuprates undergo nucleophilic substitution with vinyl halides but organolithium and magnesium reagents were not able to do so?

6 Discuss various Nucleophilic substitution reactions exhibited by dialkyl lithium cuprates.

7 Explain conjugation addition reaction given by dialkyl lithium cuprates.

8 Give some important uses of organocopper reagents.

9 Discuss the structures of various adducts and heteroleptic complexes of zinc dialkyls.

10 How can we achieve organozinc compounds from-

i. Trialkyl boranes
ii. Alkyl halides
iii. Mercury derivatives

11 Write short note on-
   a. Cyclopropanation
   b. Deprotonation by dialkyl zinc compounds

12 Explain important uses of organo zinc compounds with suitable examples.

13 Discuss the various addition reactions given by dialkylzinc compounds.

2.10 References and Suggested Readings

- The Chemistry of Organocopper Compounds: Part-2, Z.Rappoport and I. Marek, Wiley,2009.
- Organometallic Chemistry: A Unified Approach ,R .C. Mehrotra and A. Singh, New Age International Publisher, 2000 (Second Edition).
- Principles of Organic Synthesis, R. Norman and J.M.Coxon, Blackie Academic and Professional , 1993 (Third Edition).
- Synthesis of Organometallic compounds: A Practical Guide, S. Komiya, Wiley-Blackwell,1997.
- The Organometallic Chemistry of the Transition metals, R.H. Crabtree, Wiley and Sons, 1992 (Second Edition).

Unit-3

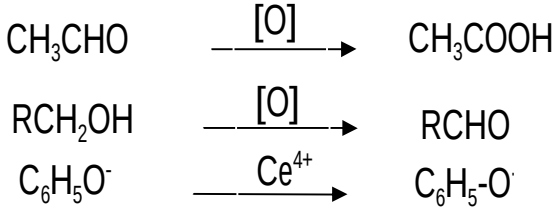
Oxidation

Structure of unit:

3.0 Introduction

Oxidation of organic compound can be defined as addition of oxygen , removal of hydrogen or removal of electrons from that compound.

e.g-



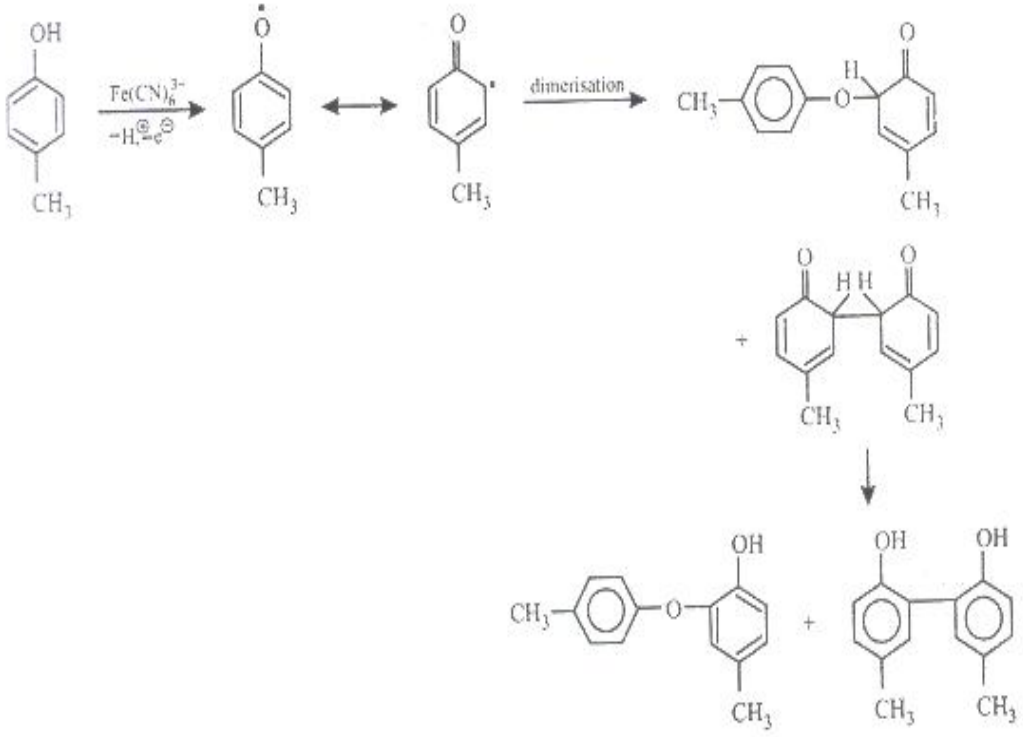
Oxidation and reduction processes are complementary in any system. Thus, if one specie of the system is oxidized, another is reduced.

3.1Different oxidative processes

Oxidation can be carried out from any one of the following ways:

3.1.1 Direct electron transfer

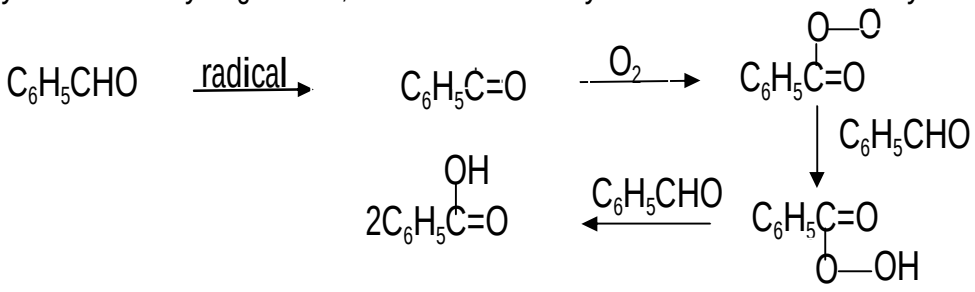
Removal of an electron from the organic moity lead oxidation . e.g- oxidation of phenols by ferricyanide.



For such type of oxidation there is a requirement of an oxidizing agent which is capable of an electron reduction and organic compound which gives relatively stable radical on oxidation.

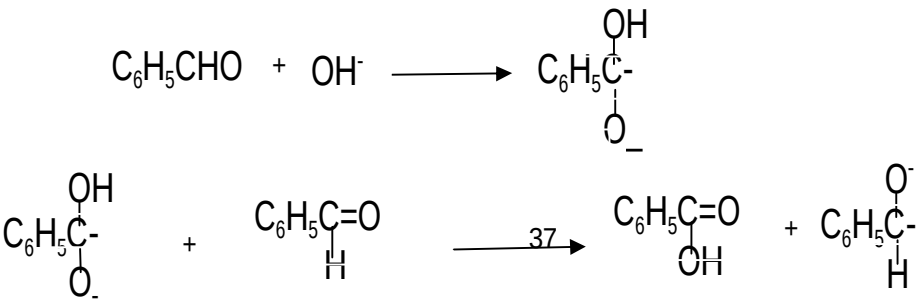
3.1.2 Hydrogen atom transfer

By removal of a hydrogen atom,as in the radical catalysed auto-oxidation of aldehydes.



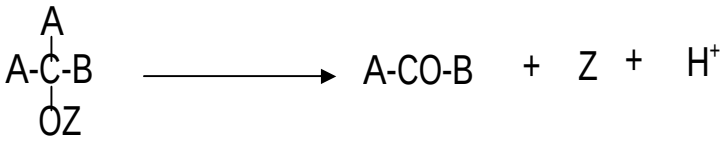
3.1.3 Hydride transfer

Removal of hydride ion lead oxidation process ,as in the cannizaro reaction.



3.1.4 Formation of ester intermediates

A number of oxidations involve the formation of an ester intermediate and then cleavage of this intermediate.

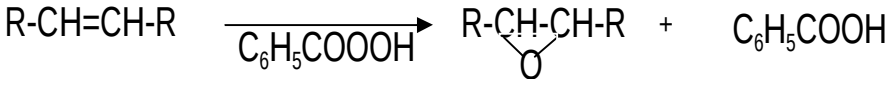


Where A and B are alkyl or aryl groups and Z is usually CrO_3H or MnO_3.

e.g- Oxidation of glycols by lead tetra acetate

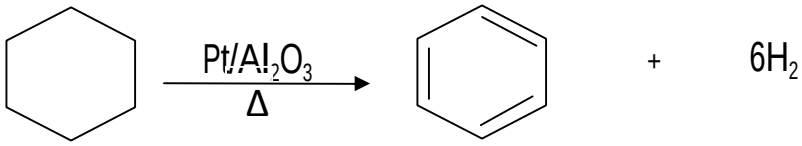
3.1.5 Insertion of oxygen

Insertion of oxygen as in epoxidation of an alkene by a per acid .



3.1.6 By catalytic dehydrogenation

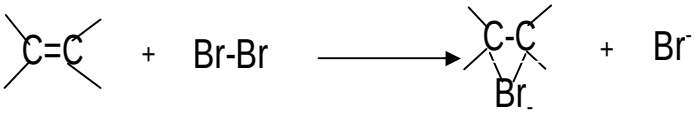
Catalytic dehydrogenation occurs in palladium catalysed conversion of cyclohexane into benzene.



3.1.7 Displacement mechanisms

In these reactions, the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent.

e.g- Addition of bromine to an alkene



3.1.8 Addition elimination mechanisms

In the reaction between α,β-unsaturated ketones and alkaline peroxide, the oxidizing agent adds to the substrate and part of it is lost. e.g-Oxidation of ketones with SeO_2.

3.2 Oxidation of alkenes

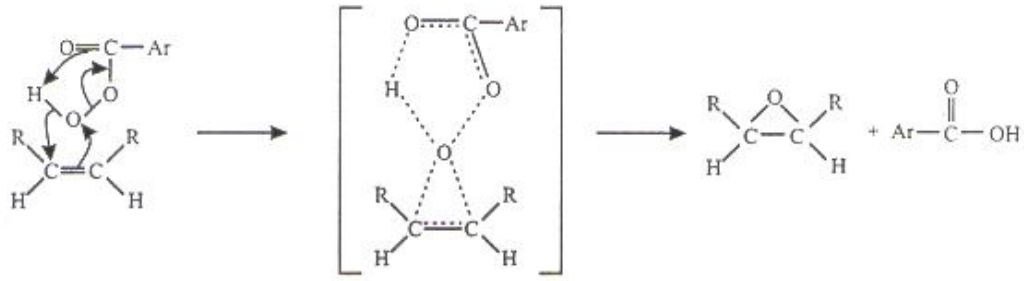
3.2.1 Epoxidation

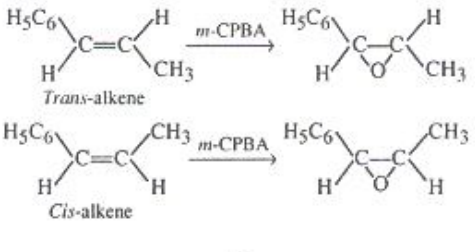
Olefinic double bonds react with per acids to give epoxides. Useful reagent in epoxidation is (m- CPBA) metachloroperbenzoic acid. It is an electrophilic reagent and reacts well with nucleophilic alkenes.

Thus , electron releasing groups in alkene and electron attracting groups in per acid facilitates the reaction.

This reaction is stereospecific (syn addition to double bond) and proceeds in a concerted manner. More substituted alkenes react faster than the less substituted ones if one equivalent of oxidant is used it is possible to oxidize more substituted alkenes in the presence of less substituted one.

In cyclic alkenes the reagent approaches from the less hindered side of the double bond. α,β-unsaturated acids and esters, required stronger reagent at elevated temperature for successful oxidation because conjugation reduces the rate of epoxidation.





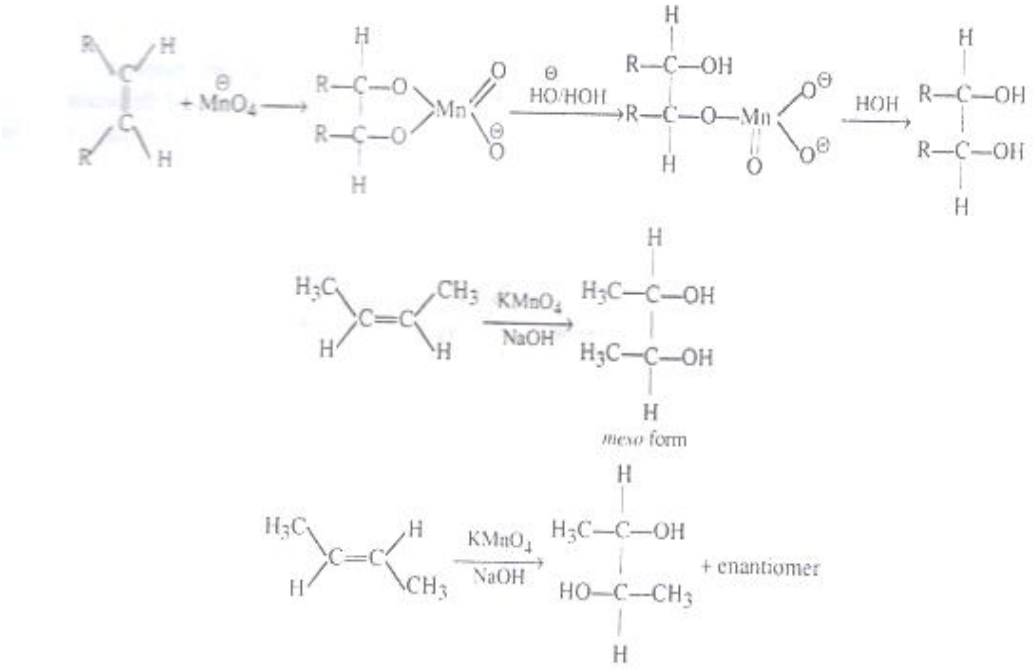
Epoxidation of allylic alcohol can be done by Sharpless method,which is used for converting allyl alcohols to chiral epoxy alcohols with very high enantioselectivity.

3.5.2 Perhydroxylation

Generally different reagents like potassium permanganate, osmium tetraoxide and iodine are used for perhydroxylation of carbon–carbon double bond in organic synthesis.

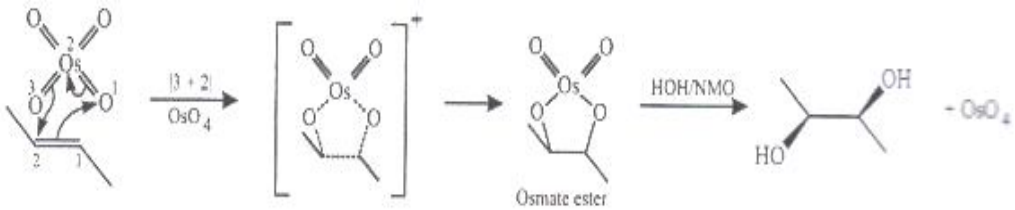
a. Potassium permanganate

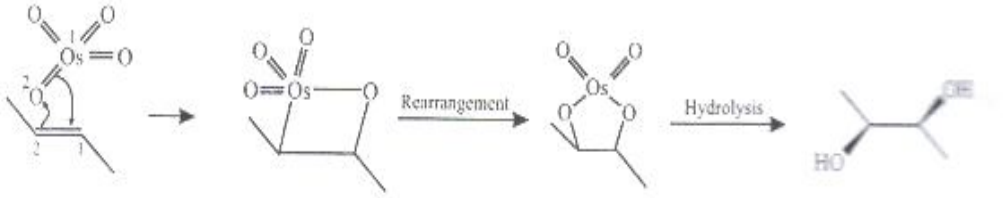
Oxidation with $KMnO_4$ in alkaline solution is used for cis hydroxylation of alkenes. This reaction is stereospecific reaction, Cis -2-butene on hydroxylation gives meso form and trans-2-butene gives racemic mixture.



b. Osmium tetraoxide butene on hydroxylation gives meso form and trans-2-butene.

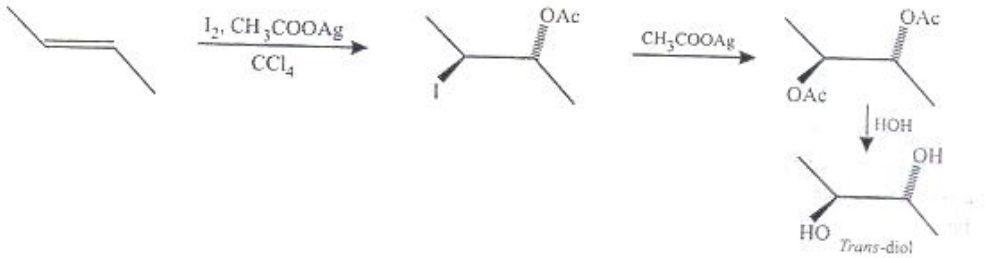
The addition of an alkene to OsO_4, causes rapid precipitate of cyclic osmate ester, which further hydrolysed with aqueous sodium sulphite to give a cis vic diol in the presence of pyridine.

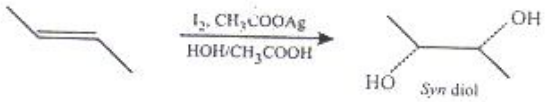




3.2.3 Oxidation with iodine and silver carbonate

Under anhydrous conditions Prevost reagent (a solution of iodine in CCl_4 with an equivalent of silver acetate or benzoate) directly yields the diacetyl derivatives of the trans-glycol.





3.2.4 Wacker process

By wacker's process oxidation of alkenes to form ketones can be achieved by reaction of Pd (II) salts and oxygen in the presence of $CuCl_2$ in aqueous medium. Terminal alkenes are almost five times more reactive than 1,2 disubstituted alkenes.

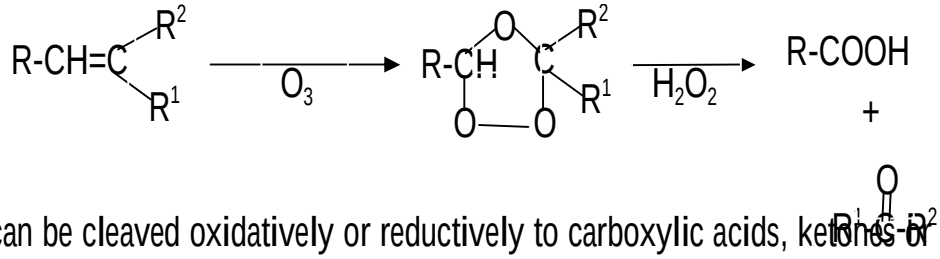
$$CH_3\text{-}CH_2\text{-}CH{=}CH_2 \xrightarrow[CuCl_2 / O_2]{PdCl_2/H_2O} CH_3\text{-}CH_2\text{-}CO\text{-}CH_3$$

3.2.5 Oxidative cleavage of carbon-carbon double bonds

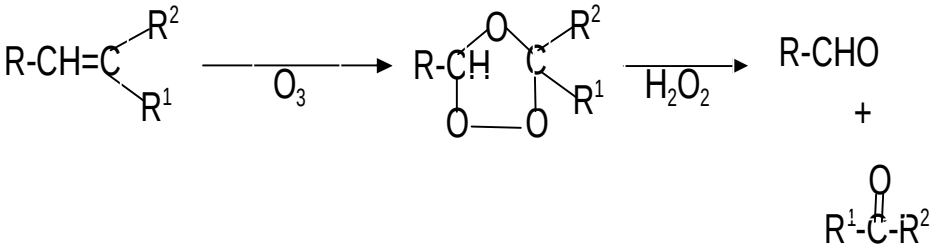
Oxidative cleavage reactions are those which lead to cleavage of C-C bond (single or multiple) and the introduction of new bonds between carbon and electronegative element.

I. Oxidative cleavage of alkenes by ozone

Ozone is an electrophilic reagent and react faster with electron rich alkenes. It is very convenient method for oxidative cleavage of carbon –carbon double bonds . In ozonolysis reaction of an alkene with ozone followed by splitting of the resulting ozononide.



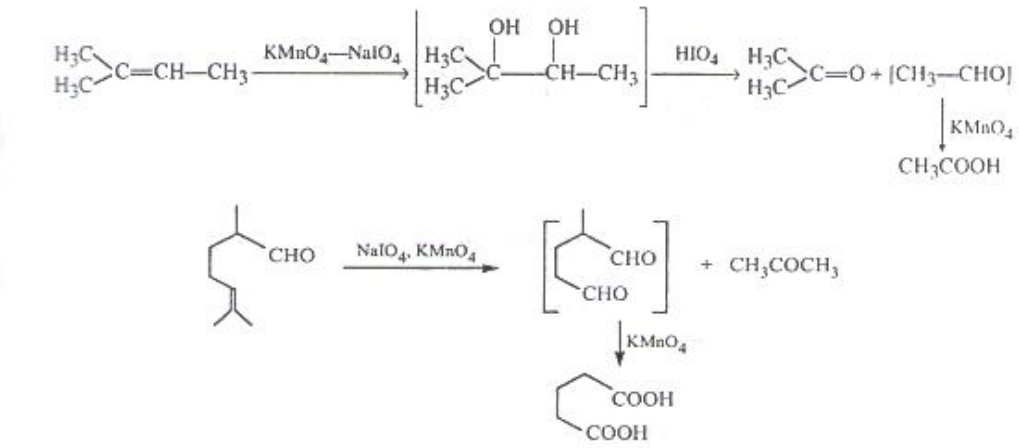
Ozonides can be cleaved oxidatively or reductively to carboxylic acids, ketones or aldehydes.



Mechanism of the reaction : Ozone is 1,3- dipolar species and reaction is an example of 1,3- dipolar cycloaddition reaction. This reaction lead the formation of primary ozonide which gives reverse [1,3] cycloaddition.

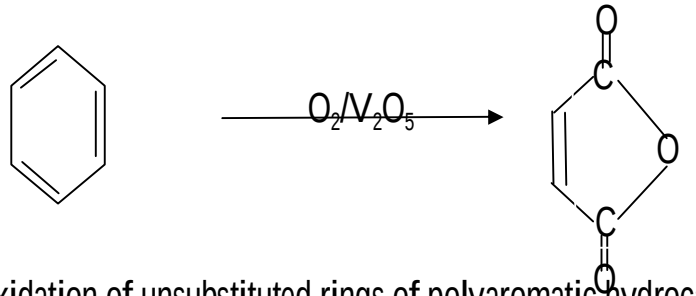
II. Oxidative cleavage of alkenes by Lemiex reagents

One of the most important limitation of ozone, is the unpleasant nature of ozone and it is not selective for tertiary C-H group. Thus, ozone is displaced by the Lemieux reagents (dilute aqueous solution of $NaIO_4$ with a catalytic quantity of potassium permanganate and of osmium tetroxide respectively). In this case, alkene first oxidized to the cis diol and then cleaved by periodate to give aldehyde or ketone.

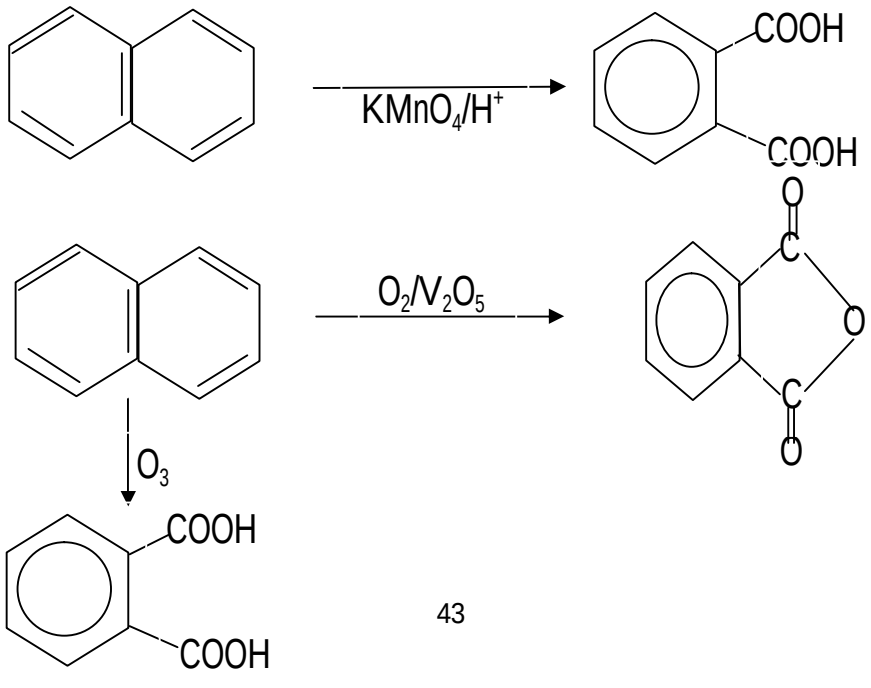


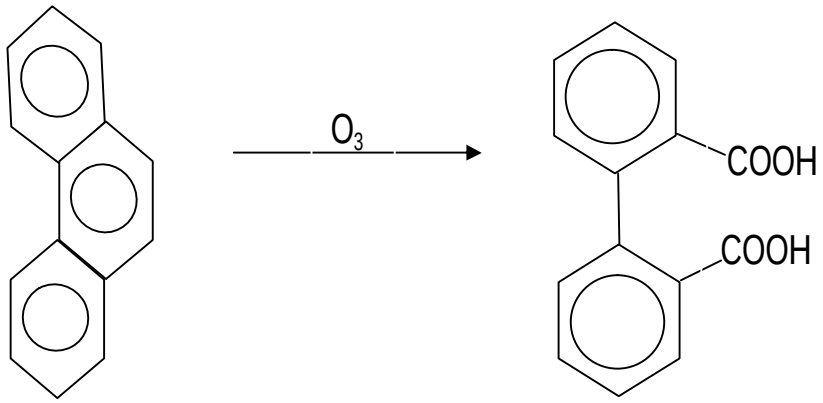
3.3 Oxidation of aromatic rings

Benzene is a very stable compound and usually not affected by most of the oxidizing agents . Benzene undergo aerial oxidation in the presence of V_2O_5.

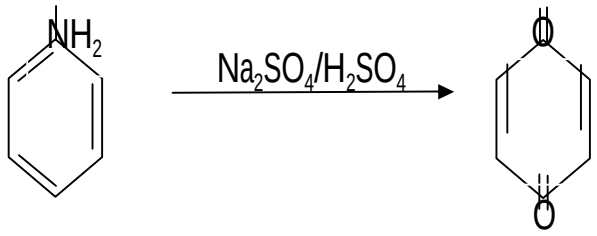


The oxidation of unsubstituted rings of polyaromatic hydrocarbons results in the loss of the stabilization energy requires vigourous conditions.





Phenols on oxidation give quinine and then convert into 1,4 quinoone . If 4-position is blocked then give 1,2-quinone. The best reagent for this transformation is Fremy's salt. On oxidation of aniline it gives p-benzoquinone in 60% yield.

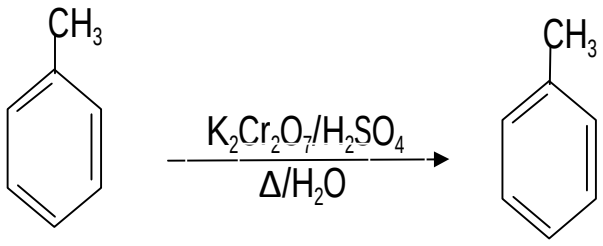


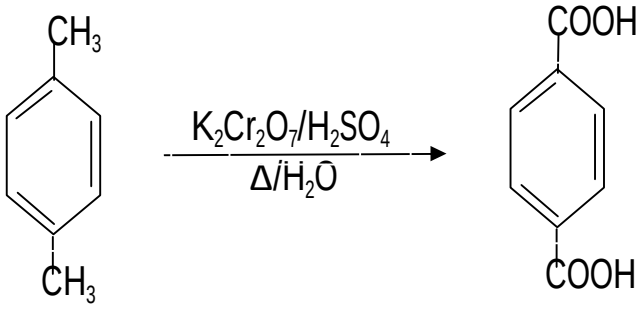
3.4 Oxidation of activated saturated C-H groups

Those saturated C-H groups which are adjacent to a carbon-carbon multiple bonds or carbon heteroatom multiple bonds are the examples of activated C-H groups . e.g- allylic system , benzylic system and $-CH_2-CO$ systems.

3.4.1 Oxidation of benzylic system

Alkyl group present on benzene ring is oxidized to corresponding carboxylic acid. Although , benzene is an exceptionally stable compound and not affected by most of the oxidizing agents.



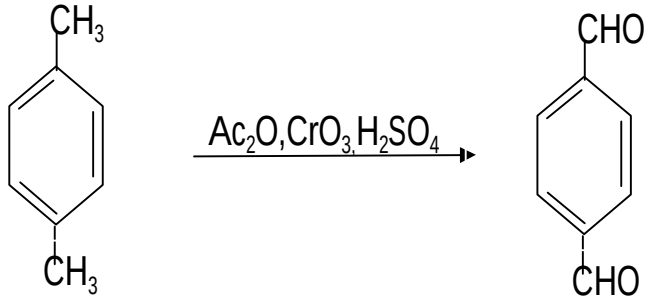


It is used for the preparation of benzene carboxylic acids and for the determination of the orientation of the unknown polyalkyl benzene. If side chain is longer than methyl , initial attack take place at benzylic carbon atom.

Etard reaction

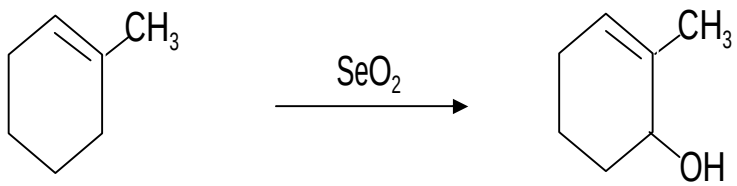
The conversion of a methyl group attached to benzene ring into formyl group by oxidation with chromium (VI) oxide in acetic anhydride in the presence of strong acid or with a solution of chromyl chloride in CCl_4 or CS_2.

$Ac_2O/CrO_3/H_2SO_4$ lead the formation of diacetate which protect aldehydic group for further oxidation.

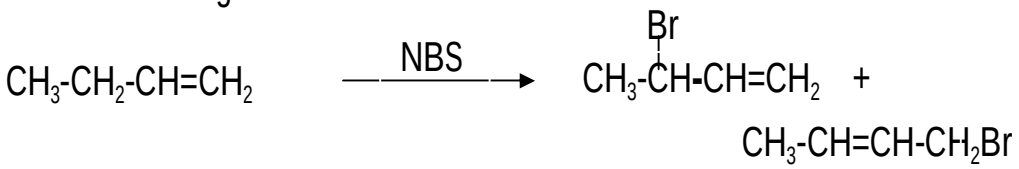


3.3.1 Oxidation of allylic positions

Selenium dioxide is used as a reagent for the oxidation of alkenes into allylic alcohol. For reaction in ethanol the order of reactivity of allylic groups is CH_2 > CH_3 > CH .



N-Bromosuccinimide is another reagent that is effective at oxidizing allylic positions. NBS works in a non polar solvent such as CCl_4 and with a small amount of radical initiator e.g- AIBN.

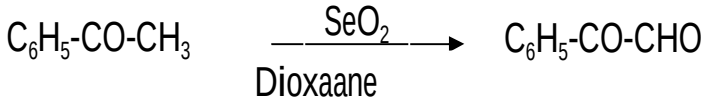


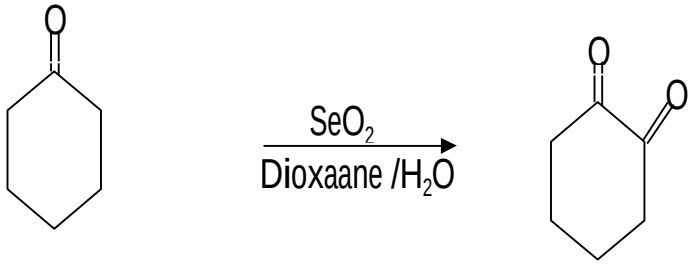
Allylic methylene group can be oxidized into CO group by the use of PCC (pyridinium chloro chromate) under nitrogen atmosphere. $Hg(OAc)_2$ and $Pb(OAc)_4$ can also be used for the oxidation at allylic positions.

3.3.2 Oxidation of $-CH_2-CO-$ system

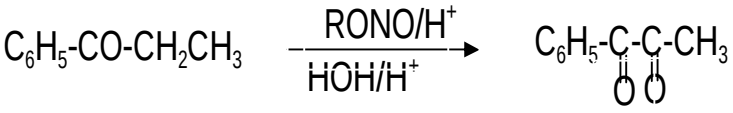
Activated C-H group adjacent to carbonyl group can be oxidized by three reagents

1. Aldehyde and ketones with a methyl or methylene group α-to the carbonyl group are oxidized to the 1,2-dicarbonyl compounds by the use of SeO_2.





2. The methlene group is activated by the carbonyl group towards reaction with organic nitrites in the presence of acid or base. The nitroso compound tautomerises to the oxime which on hydrolysis gives α-dicarbonyl compound.

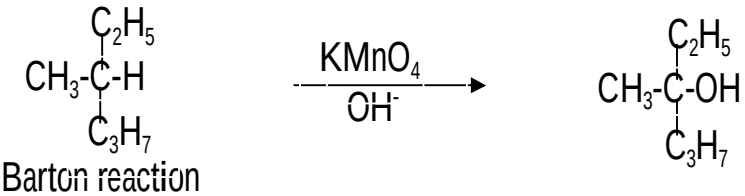


3. Hydroxy group can be introduced adjacent to CO group in ketones, esters and lactones on oxidation with N-sulphonyloxaziridine. In this reaction compounds having $-CH_2CO$ is first deprotonated with strong base ,KHMDS and then the enolate is treated with the reagent.

3.5 Oxidation of unactivated saturated C-H groups

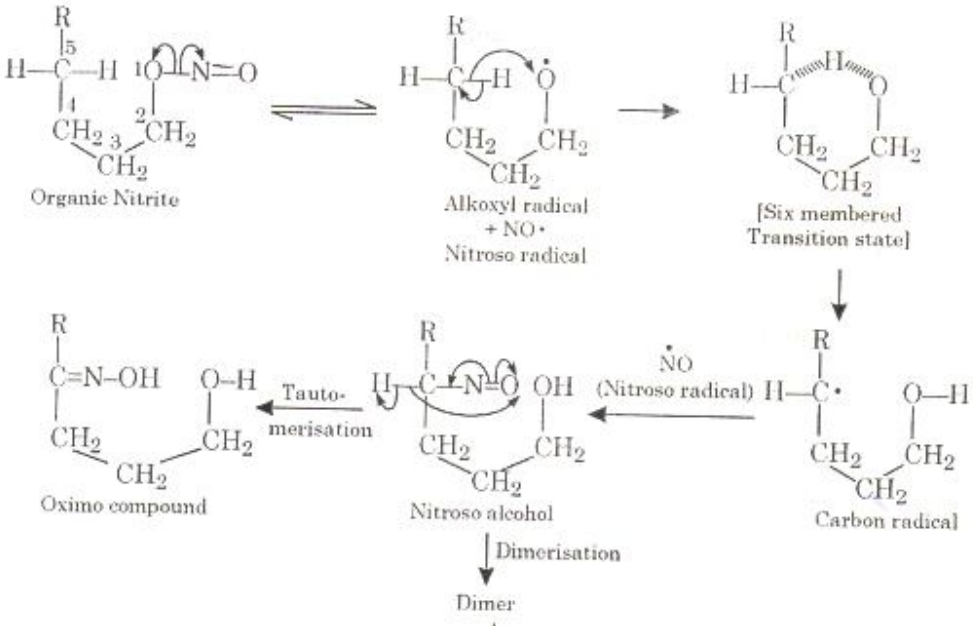
Oxidation of unactivated C-H group can be performed by the following methods:

1. The alkaline permangnate
   The oxidation of tertiary C-H to C-OH group can be achieved directly with alkaline permangnate.

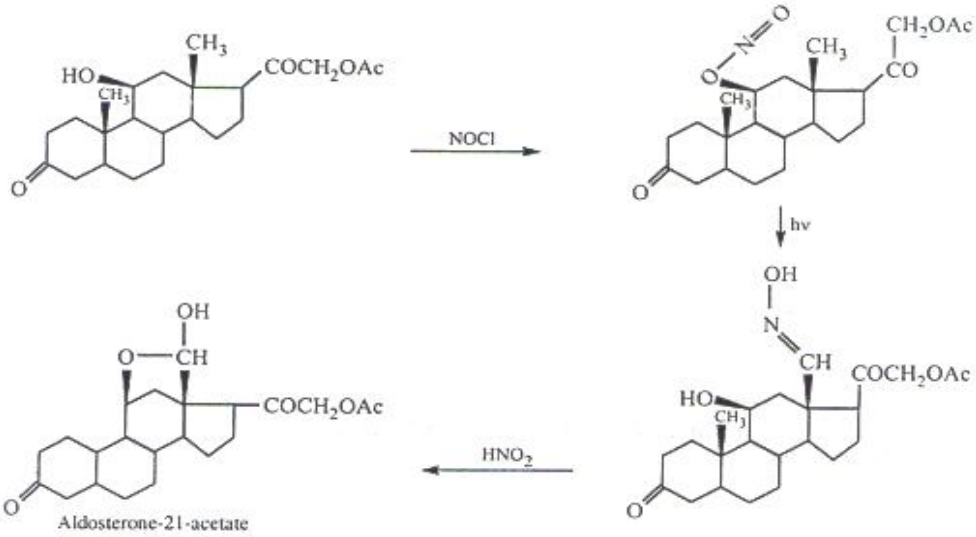


2. Barton reaction

Photolytic conversion of organic nitrites having hydrogen on δ-carbon into nitroso alcohols is known as Barton reaction. When a compound consists of the C-O-NO group and a C-H bond is brought into close proximity (generally 1,5-position), the alkoxyl radicals are formed by photolysis of nitrites, in the solution phase , which have suffficient energy to bring about selective intramolecular abstraction of hydrogen atom and produce a carbon radical.

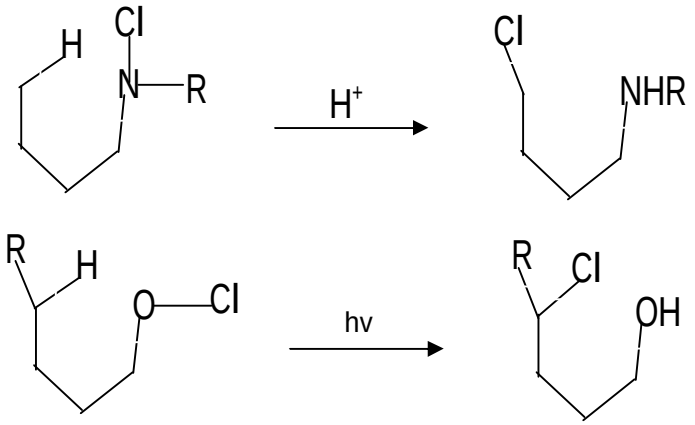


Importance : This method can be used in the synthesis of aldosterone 21-acetate from corticosterone acetate.



3. The Hofmann-Loeffler –Freytag reaction

This reaction is given by N-haloamines having hydrogen on δ carbon . The reaction is affected by warming a solution of the halogenated amine in strong acid or by irradiation of acid solution with UV light. The product of the reaction is the δ-halogenated amine and thus oxidation take place at unactivated δ-carbon having hydrogen.



3.6 Summary

- Addition of oxygen , removal of hydrogen or removal of electrons from the compound is known as oxidation.
- Oxidation is the converse reaction of reduction.
- Oxidation is normally lead by the removal of an electron, hydrogen atom, removal of hydride ion , insertion of oxygen ,catalytic dehydrogenation.
- Oxidation of alkene can be done by epoxidation, perhydroxylation and also by using Prevost reagent.
- In case of perhydroxylation potassium permanganate and osmium tetroxide is used.
- Oxidative cleavage of alkene can be done by ozone and Lemieux reagent.
- Benzene is very stable compound and usually not affected by common oxidizing agents, due to this reason , benzene is used as a solvent in most of the organic reactions.

- Aromatic rings of phenols are susceptible to oxidation by one electron oxidants for the removal of a hydrogen atom gives a delocalized aryloxy radical.
- Phenols oxidized into quinine in the presence of Fremy's salt and than further oxidized into 1,4 quinone or 1,2 quinone (if 4-position is blocked).
- In case of oxidation of aniline, amino group is oxidized into nitro group.
- Activated saturated C-H groups are those groups which are adjacent to a carbon-carbon multiple bonds or carbon –heteroatom multiple bonds.
- Benzylic systems can be oxidized into its corresponding carboxylic acid.
- Benzylic systems can be oxidized in the presence of SeO_2, Ce^{+2} into its corresponding aldehyde and ketones .
- In the presence of SeO_2 activated C-H groups at allylic positions can be oxidized into allylic alcohol.
- With the help of SeO_2 and alkyl nitrite active methylene group oxidized into 1,2 dicarbonyl compound.
- N-sulphonyloxaziridine can oxidized active methylene group into α-hydroxy carbonyl compound.
- Oxidation of unactivated C-H group can be performed by the alkaline permanganate , Barton reaction and Hofman-Loeffler-Freytag reaction.

3.7 Review Questions

1 What is oxidation?

2 How it is different from reduction?

3 What is the driving force for allylic oxidation? Discuss the role of SeO_2 for such oxidation.

4 Give the use of m-CPBA in oxidation .

5 Describe the varous methods of oxidation.

6 Write short note on-

a. Epoxidation

b. Perhydroxylation

c. Lemieux reagent

7 Discuss Wacker process.

8 What do you understand by the term oxidative cleavage of carbon-carbon double bond?

9 Why benzene is used as a solvent in various organic reactions?

10 Write a short note on oxidation of phenol .

11 What is activated saturated C-H group?

12 Why t-butyl benzene is resistant to oxidation?

13 What is Etard reaction ?Which reagent is used in this reaction and why?

14 Which reagents are used to oxidized activated C-H group adjacent to carbonyl group?

15 Write short note on-

a. SeO_2

b. Alkyl nitrite

c. N-sulphonyloxazeridine

16 Discuss the oxidation of unactivated C-H group.

17 Write short note on-

a. Barton reaction

b. Hofmann-Loeffler-Freytag reaction

18 What is Prevost reagent?

19 How can we lead the conversion of a methyl group attached to benzene ring into formyl group?

20 What are the different ways to oxidized the activated saturated C-H group?Explain by giving suitable examples.

21 Discuss oxidation of aromatic rings.

3.8 Suggested Readings and References

- Organic Chemistry ,R. T.Morrison, R. N. Boyd and S. K. Bhattacharjee, Pearson, 2011 (Seventh Edition)
- Advanced Organic Chemistry: Reactions Mechanisms and Structure, J. March, Wiley,2003,(Fourth Edition).
- Organic Mechanisms- Reaction, Stereochemistry and Synthesis ,R. Brückner, Springer, 2002 (First Edition).
- Advance Organic Chemistry: Reaction mechanism, R.Bruckner, Academic Press , 2001 .

Unit - 4

Oxidation of – OH group

Structure of Unit:

4.0 Objective

At the end of the unit learner will be able to learn how to hydroxy group oxidised into aldehyde, ketone and carboxylic acid in the presence of various reagents.

4.1 Introduction

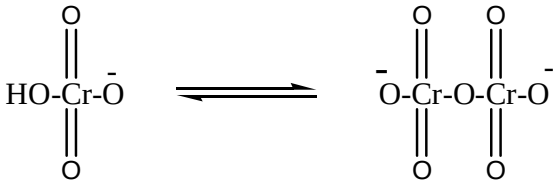
Oxidation of –OH group is the most useful and widespread area of oxidation, as it encompasses the alcohol ⟶ aldehyde/ketone ⟶ carboxylic acid sequence that is used so often in organic synthesis.

Oxidation of alcohols yields a carbonyl compounds. Whether the carbonyl compounds is an aldehyde, ketone or a carboxylic acid depends on the oxidizing agent.

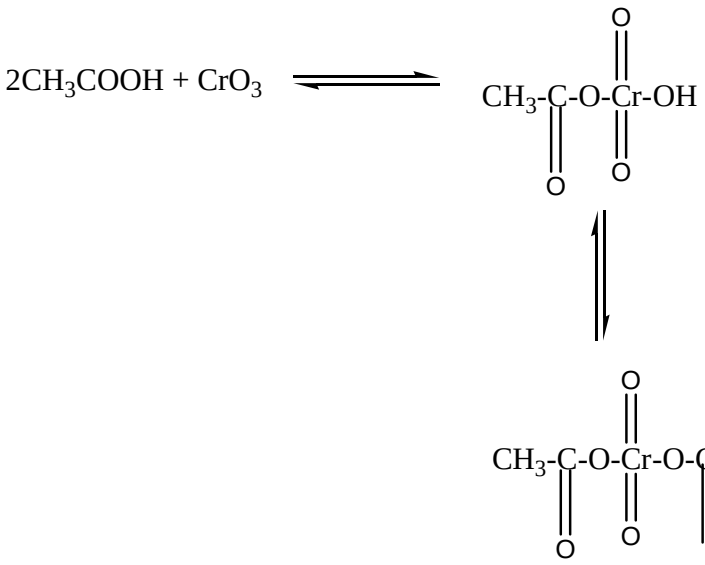
4.2 Oxidation of alcohol by transition metal oxidants

The most widely employed transition metal oxidants for alcohols are based on Cr(VI). The specific reagents are generally prepared from chromic trioxide, CrO_3, or a dichromate salt, $Cr_2O_7^{2-}$. The form of Cr(VI) in aqueous solution depends upon concentration and pH; the pK1 and pK2 of H_2CrO_4 are 0.74 and 6.49, respectively.

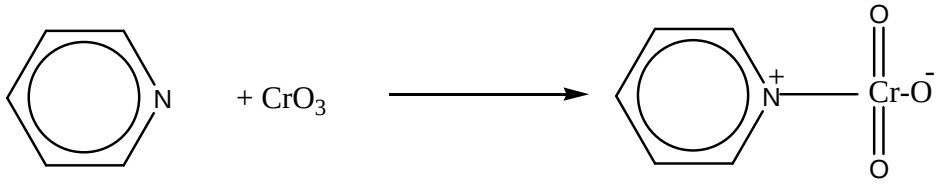
In dilute solution, the monomeric acid chromate ion $HCrO^{3-}$ is the main species present; as concentration increases, the dichromate ion dominates.



In acetic acid, Cr(VI) is present as mixed anhydrides of acetic acid and chromic acid.

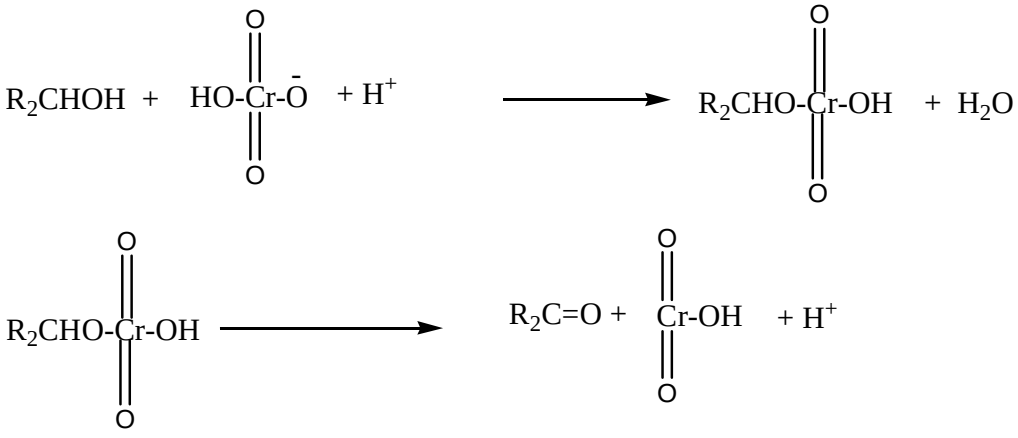


In pyridine, an adduct involving Cr–N bonding is formed.



The oxidation state of Cr in each of these species is (VI) and they are all powerful oxidants. The precise reactivity depends on the solvent and the chromium ligands, so substantial selectivity can be achieved by the choice of the particular reagent and conditions.

The general mechanism of alcohol oxidation involves coordination of the alcohol at chromium and a rate-determining deprotonation.



An important piece of evidence for this mechanism is the fact that a primary isotope effect is observed when the α-hydrogen is replaced by deuterium. The Cr(IV) that is produced in the initial step is not stable and is capable of a further oxidation. It is believed that Cr(IV) is reduced to Cr(II), which is then oxidized by Cr(VI) generating Cr(V). This mechanism accounts for the overall stoichiometry of the reaction.

$$R_2CHOH + Cr(VI) \longrightarrow R_2C{=}O + Cr(IV) + 2H^+$$

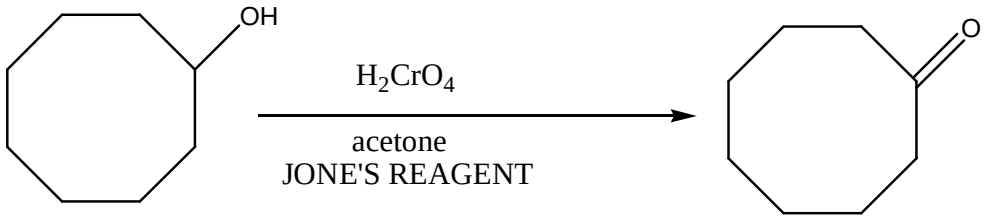
$$R_2CHOH + Cr(IV) \longrightarrow R_2C{=}O + Cr(II) + 2H^+$$

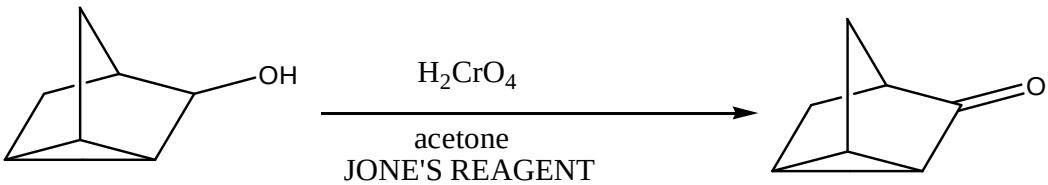
$$Cr(II) + Cr(VI) \longrightarrow Cr(III) + Cr(V)$$

$$R_2CHOH + Cr(V) \longrightarrow R_2C{=}O + Cr(III) + 2H^+$$

$$R_2CHOH + Cr(VI) \longrightarrow R_2C{=}O + Cr(III) + 6H^+$$

For secondary alcohols, oxidation can be done by addition of an **acidic aqueous solution containing chromic acid** (**known as *Jones' reagent***) to an acetone solution of the alcohol. Oxidation normally occurs rapidly, and over oxidation is minimal. In acetone solution, the reduced chromium salts precipitate and the reaction solution can be decanted.

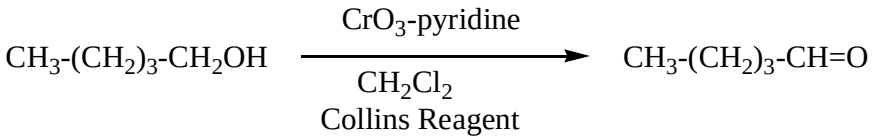


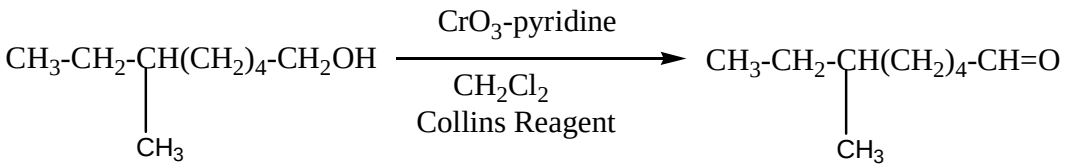


The chromium trioxide-pyridine complex **(Collins reagent)** is useful in situations when other functional groups might be susceptible to oxidation or the molecule is sensitive to acid. A procedure for utilizing the CrO_3-pyridine complex, which was developed by **Collins,** has been widely adopted. The CrO_3-pyridine complex is

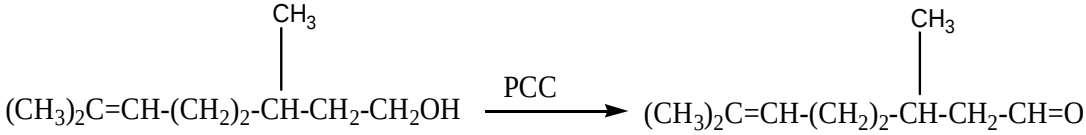
isolated and dissolved in dichloromethane. With an excess of the reagent, oxidation of simple alcohols is complete in a few minutes, giving the aldehyde or ketone in good yield. A procedure that avoids isolation of the complex can further simplify the experimental operations.

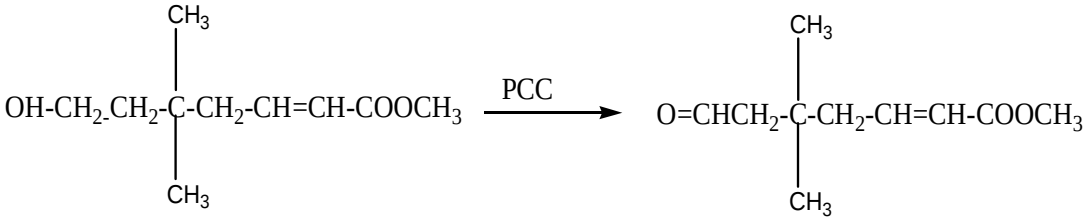
Chromium trioxide is added to pyridine in dichloromethane. Subsequent addition of the alcohol to this solution results in oxidation in high yield



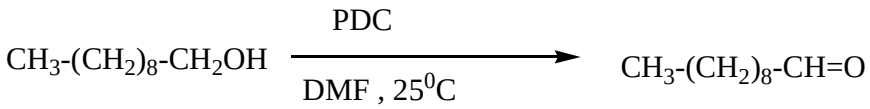


Another very useful Cr (VI) reagent is pyridinium chlorochromate (PCC), which is prepared by dissolving CrO_3 in hydrochloric acid and adding pyridine to obtain a solid reagent having the composition $CrO_3ClpyrH$. This reagent can be used in amounts close to the stoichiometric ratio.





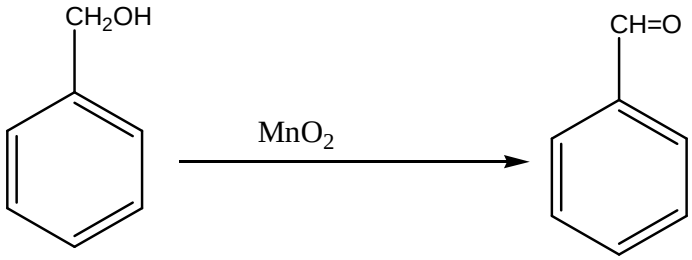
Reaction of pyridine with CrO_3 in a small amount of water gives pyridinium dichromate (PDC), which is also a useful oxidant.As a solution in DMF or a suspension in dichloromethane, this reagent oxidizes secondary alcohols to ketones. Allylic primary alcohols give the corresponding aldehydes. Depending upon the conditions, saturated primary alcohols give either an aldehyde or the corresponding carboxylic acid.

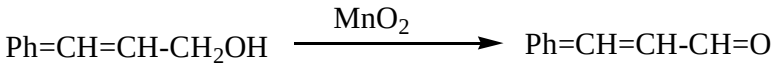


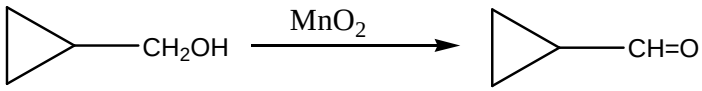
Although Cr (VI) oxidants are very versatile and efficient, they have one drawback, which becomes especially serious in larger-scale work: the toxicity and environmental hazards associated with chromium compounds. The reagents are used in stoichiometric or excess amount and the Cr (III) by-products must be disposed of safely.

Potassium permanganate, $KMnO_4$, is another powerful transition metal oxidant, but it has found relatively little application in the oxidation of alcohols to ketones and aldehydes. The reagent is less selective than Cr (VI), and over oxidation is a problem.

On the other hand, manganese (IV) dioxide is quite useful. This reagent, which is selective for allylic and benzylic alcohols, is prepared by reaction of $Mn(II)SO_4$ with $KMnO_4$ and sodium hydroxide. The precise reactivity of MnO_2 depends on its mode of preparation and the extent of drying.

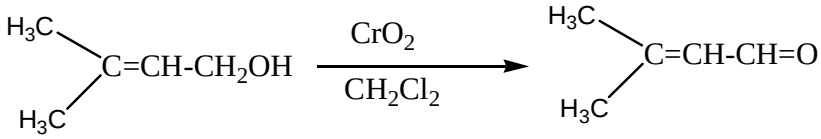




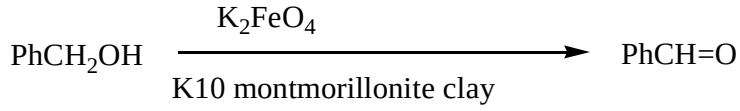


Another recently developed oxidant is CrO_2, a solid known as Magtrieve™ that is prepared commercially (for other purposes), which oxidizes allylic and benzylic alcohols in good yield. It is also reactive toward saturated alcohols. Because the solid remains ferromagnetic, it can be recovered by use of a magnet and can be

reactivated by exposure to air at high temperature, making it environmentally benign.

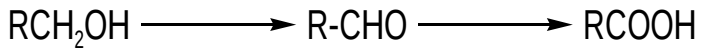


Another possible alternative oxidant that has recently been investigated is an Fe (VI) species, potassium ferrate, K_2FeO_4, supported on montmorillonite clay. This reagent gives clean, high-yielding oxidation of benzylic and allylic alcohols, but saturated alcohols are less reactive.



4.3 Oxidation of primary alcohols

Primary alcohols may be oxidised either to an aldehyde or to a carboxylic acids.

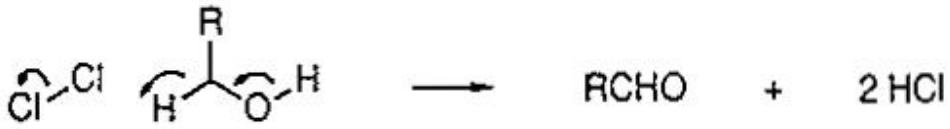


4.3.1 Oxidation of primary alcohols to aldehydes

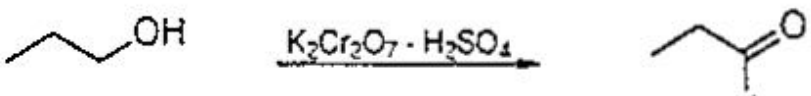
Primary alcohols can be oxidised to aldehydes by the folowing methods:

(a) By Chlorine:

Chlorine oxidizes by the acceptance of hydride ion from the alcohol.

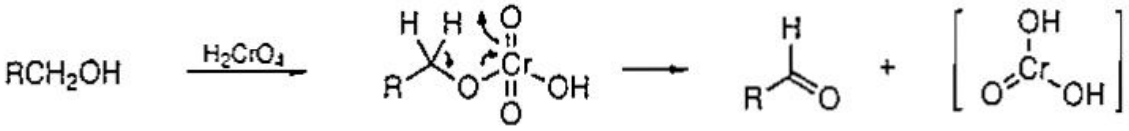


(b) By Chromium (VI)



oxide:

Reaction occurs through a cyclic transition state (chromate ester)



(c) By Catalytic dehydrogenation:

Dehydrogenation over copper or copper chromite occurs at about 300°C.

$$RCH_2OH \xrightarrow{Cu/300^oC} RCHO+H_2$$

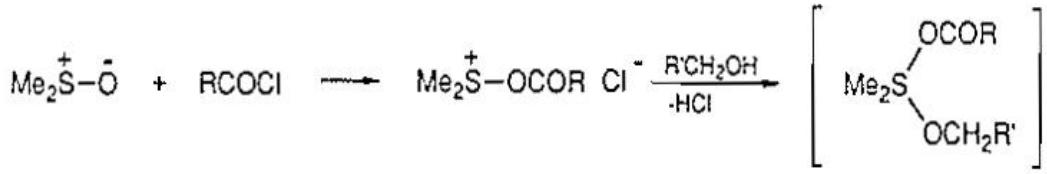
Industrially, silver is employed as the catalyst for the production of formaldehyde and acetaldehyde.

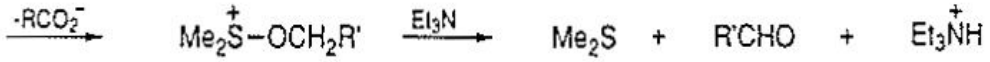
$$CH_3OH \xrightarrow{Ag} HCHO+H_2$$

(d) By Dimethyl sulfoxide (DMSO):

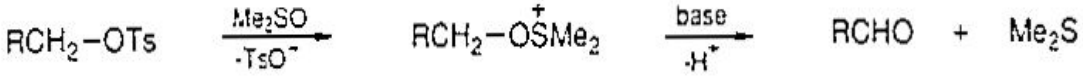
There are two methods of using dimethyl sulfoxide.

First method: In this method the dimethyl sulfoxide is treated with an electrophile to form a species which is activated towards addition of the alcohol to the sulfur atom and which also possesses a good leaving group.



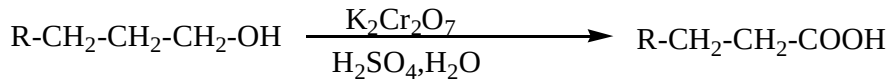


Second method (Kornblum's method): In this method, the tosylate is treated with dimethyl sulfoxide in the presence of sodium hydrogen carbonate for a few minutes at 150°C.



4.3.2 Oxidation of primary alcohols to carboxylic acids

By the reagents such as chromic (VI) acid,nitric acid and potassium permanganate primary alcohols can be oxidised directly to carboxylic acids.

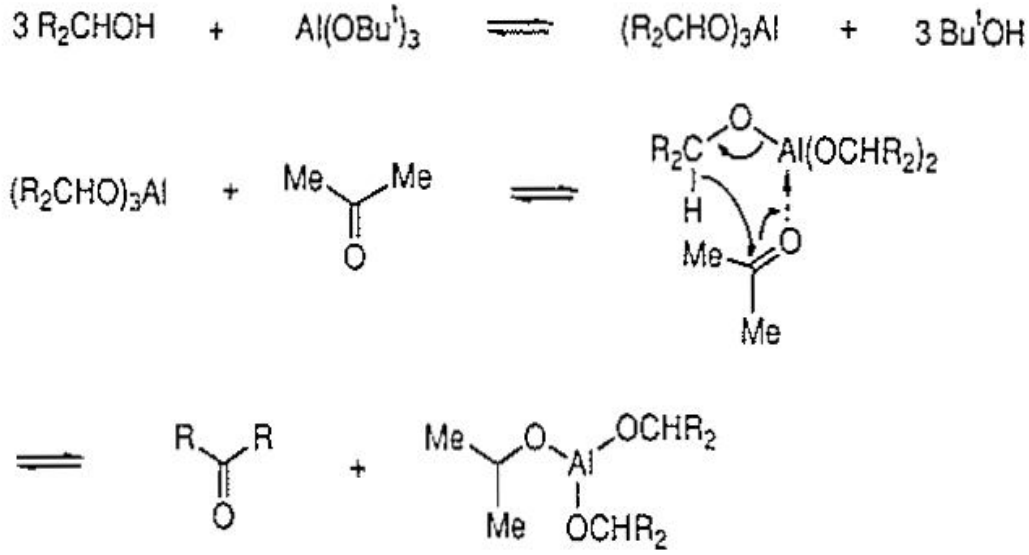


4.4 Oxidation of secondary alcohols

Three methods are widely used for the oxidation of secondary alcohols.

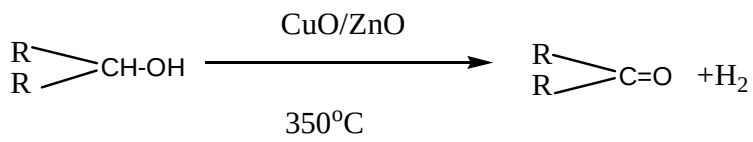
(i) Oppenauer method:

By heating in the presence of aluminium t-butoxide, secondary alcohol converted in to ketone which is equilibrated with the secondary alcohol.By using excess amount of added ketone (usually acetone) the equilibrium is forced to the right side.



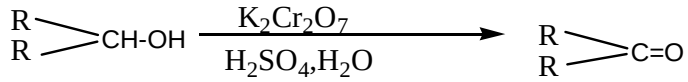
(ii) Catalytic hydrogenation:

Like primary alcohols, secondary alcohols are dehydrogenated when passed over certain heated catalysts.



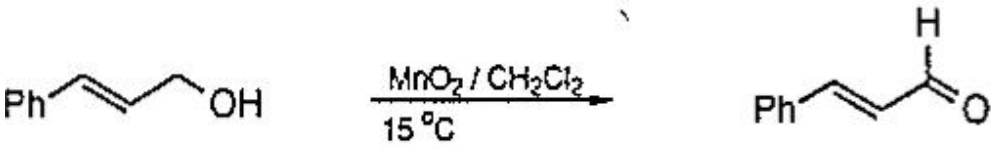
(iii) Oxidation by chromic acid:

Secondary alcohol oxidised in the presence of chromic acid in to ketone.

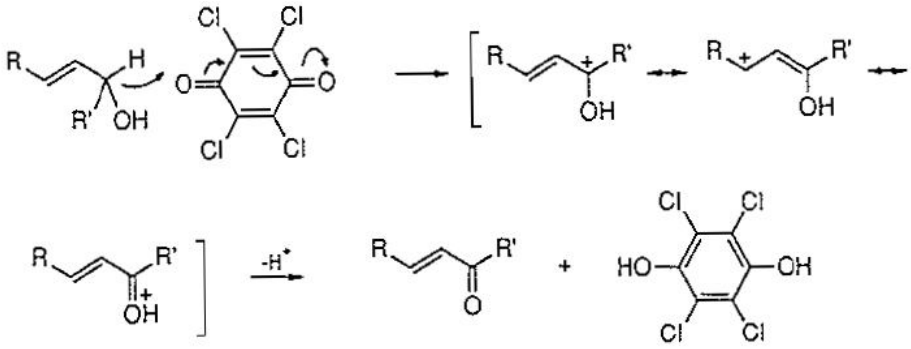


4.5 Oxidation of allylic alcohols

Allylic alcohols are oxidised to α,β unsaturated carbonyl compounds on the surface of manganese dioxide suspended in an inert solvent such as dichlromethane.

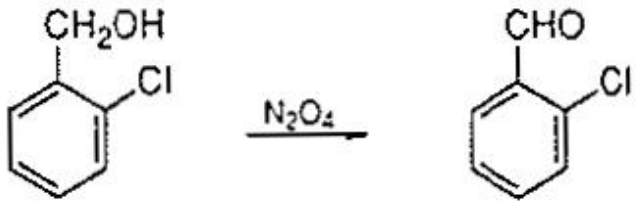


Several high potential quinines for example, chloranil are capable of oxidizing allylic, benzylic and propargylic alcohols.The reaction occurs through the relatively stable carbocation formed by the loss of hydride ion.

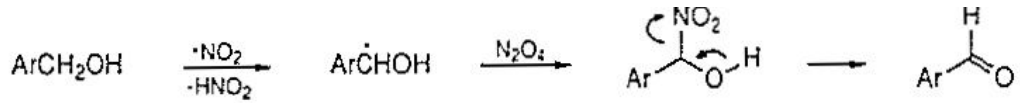


4.6 Oxidation of benzylic alcohols

Primary and secondary benzyl alcohols oxidised by the dinitrogen tetraoxide in the presence of chloroform at 0°C.

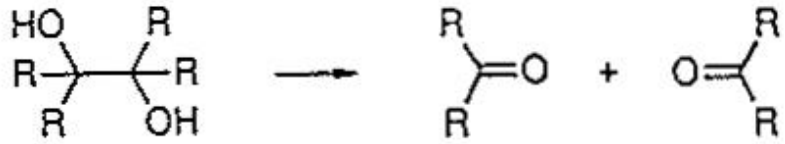


Reaction occurs through (the radical) nitrogen dioxide with the formation and decomposition of a hydroxynitro compounds.



4.7 Oxidation of 1,2-diols

1, 2-Diols are cleaved by lead tetra-acetate, phenyliodoso acetate and periodic acid or sodium metaperiodate.

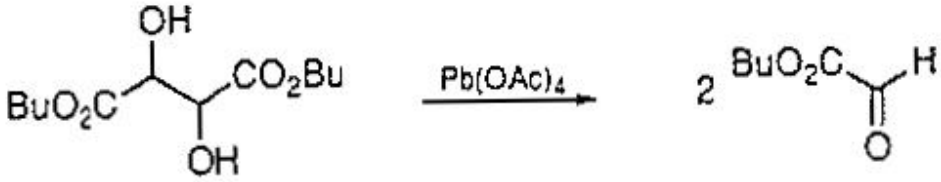


The first two reagents are used in an organic medium, commonly glacial acetic acid, whereas periodate is used in aqueous solution.

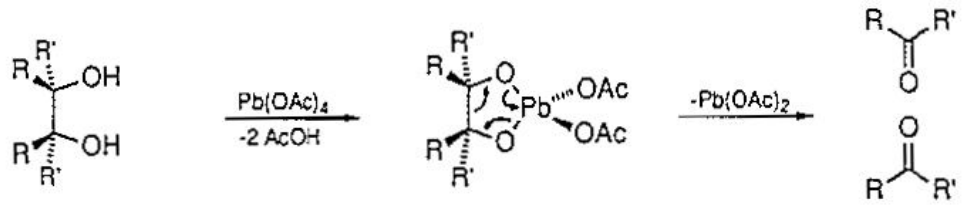
4.7.1 Oxidation of 1,2-diol by Lead tetra-acetate

1,2 –Diols are cleaved under mild conditions with lead tetra-acetate to give aldehyde and/or ketone which depends upon the structure of the 1,2-diols.For example

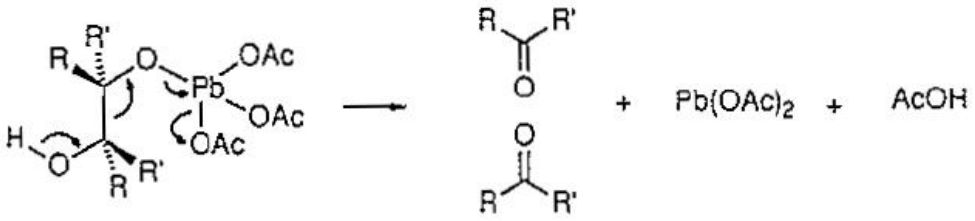
Dibutyl tartrate and lead tetra-acetate give butyl glyoxylate in good yields.



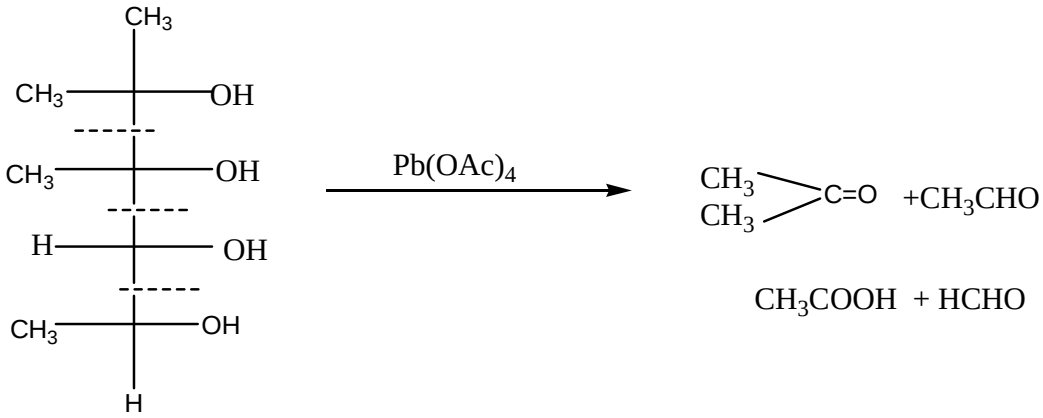
Oxidation normally occurs by two electron oxidation Pb (IV) to Pb (II) within a cyclic intermediate. Since, cyclic intermediates is formed rapidly with *cis*-diols, therefore *cis*-diols are oxidised faster than the *trans*-diols. Reaction takes place as follows:



In the case of *trans*-diols reaction probably takes place as follows:

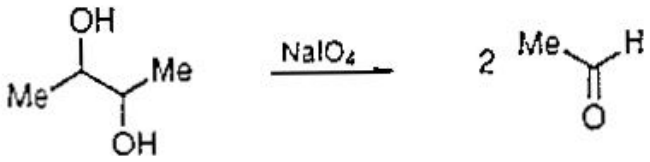


When compound has more than one diol group, the terminal carbons convert into carbonyl groups and middle carbons oxidised into carboxylic groups.



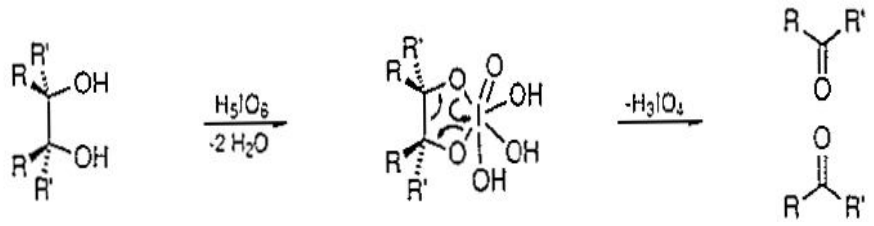
4.7.2 Oxidation of 1,2-diol by Periodate

2,3-butane diol and sodium periodate give acetaldehyde.



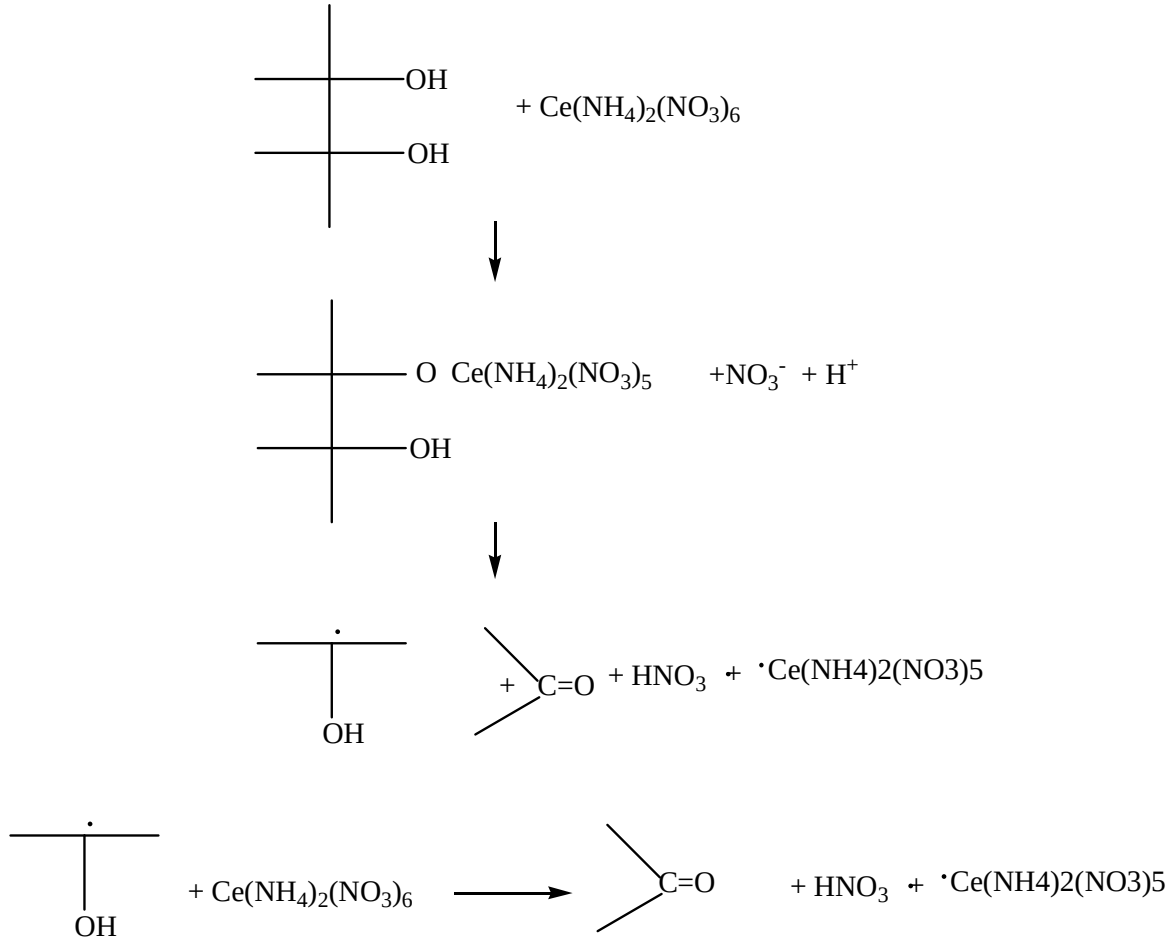
This is also two-electron oxidation I (VII) to I (V) within a cyclic intermediate, so that *cis*-diols are oxidised faster than *trans*-diols, e.g.cis-cyclohexane-1,2-diol reacts 25 times faster than its trans isomer.

Reaction takes place as follows:



4.7.3 Oxidation of 1,2-diol by Ceric Ammonium Nitrate (CAN)

Ceric ammonium nitrate can also used for the oxidative cleave of an 1, 2-diols,in this oxidation two successive one electron transfer involved.



4.8 Summery

- Oxidation of primary alcohols and secondary alcohols gives aldehyde and ketones respectively in the presence of various reagents.
- 1, 2-diols are cleaved by lead tetra-acetate, periodate and ceric ammonium nitrate in to carbonyl groups and carboxylic acids.

4.9 Review Question

1 Describe the oxidation of alcohol by sulfur dioxide.

2 Give the oxidation reaction of primary alcohol which will be done by various reagents.

3 Explain the oxidation of benzylic alcohol.

4 Explain the oxidation of allylic alcohol.

5 Write short notes on:

(a) Oppenauer Oxidation

(b) Oxidation of secondary alcohol

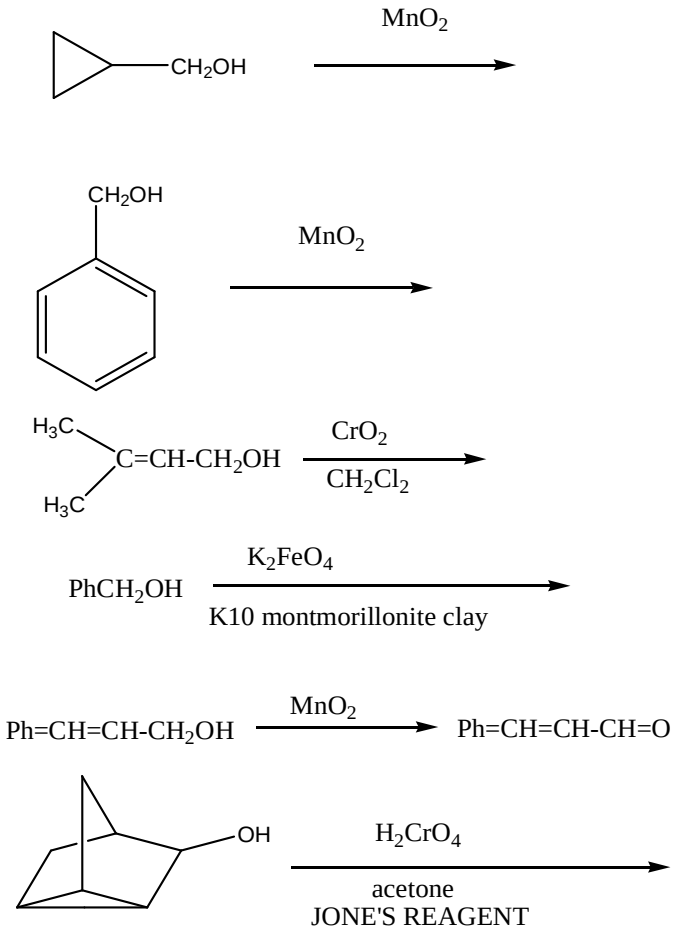
6 How to 1,2-diols cleaved in the presence of following reagents: Explain

(a) Ceric ammonium nitrate

(b) Periodic acid

(c)Lead tetra acetate

7 Complete the following reactions:



4.10 Reference and Suggested reading

- Advanced Organic Chemistry Part-B, F. A. Carey and R. J. Sundberg, 5th Ed. Springer.
- Organic Chemistry, J. Clayden, N. Greeves, S. Warren, Oxford University, Second Edition.
- Advanced Organic Chemistry, J. March, 6th Ed.
- Principles of organic synthesis, Norman and Coxon , Blackie Academic &Professional
- Reaction Mechanism in Organic Chemistry, S.M.Mukherji , S.P.Singh ,Macmillan

- Reaction Mechanism in Organic Chemistry, P.S.Kalsi , New Age International Publishers

Unit - 5

Oxidation of Carbonyl And Carboxylic Groups

Structure of Unit :

5.0 Objective

this topic mainly deals with the oxidation of the carbonyl compounds and carboxylic acids,during oxidation the oxidation number changes with the change in the functional group in the compound .the oxidation involves the removal of hydrogen addition of oxygen or the change in the functionasl group in the molecule the mechanism may take place the ionic or free radical path . sometime itt has been observed that reaction conditions and the choice of the solvent also have an impact on the nature of the final product.

5.1 Introduction

In organic chemistry the oxidation is defined either loss of electron (s) or increase in the oxidation number but in actual practice following two difficulties arise which appear to challenge the above definition of the oxidation.

(1) Most of the organic reaction not involves a direct transfer of electron(s).

(2) The oxidation number concept of oxidation appears easy to apply but in most of the cases some apparent absurdities are noticed due to the fraction values of oxidation number. However the above difficulty has been removed by assigning different oxidation state to the different carbon atoms but it requires a lot of arbitrary assumption and very little is gained by this procedure.

Organic chemists, however, have set up a series of functional group qualitatively in the order of increasing oxidation state and have diffused oxidation as the process of conversion of a functional group in a molecule from one category to higher one. This is shown below.

group	Approximate oxidation number
R-H	-4
$-\overset{|}{C}=\overset{|}{C}-$, ROH, RCl, RNH_2 etc	-2
$-C\equiv C-$, $R-\overset{O}{\overset{\|\|}{C}}-R$, $-\overset{Cl}{\overset{\|}{C}}-Cl$, $-\overset{Cl}{\overset{\|}{C}}-\overset{Cl}{\overset{\|}{C}}-$, $-\overset{OH}{\overset{\|}{C}}-\overset{OH}{\overset{\|}{C}}-$, *etc*	0
R-CO-OH, $R-CO-NH_2$, $-\overset{Cl}{\overset{Cl}{\overset{\|}{\overset{\|}{C}}}}-Cl$ etc	+2
CO_2, CCl_4	+4

Most oxidation reactions in organic chemistry a gain of oxygen and / or a loss of hydrogen (Lavosier definition)

We know that, there is no oxidation without a concurrent reduction but we classify oxidation as the process in which the given organic compound is oxidised.It should be noted oxidation has nothing to do with mechanism. This is because the mechanisms are too diverse. More over the mechanism

of an oxidation reaction can vary greatly with oxidizing agent employed for the oxidation. However following are main mechanistic categories.

(a) Direct electron transfer

(b) Hydride transfer

(c) hydrogen atom transfer

(d) Formation of ester intermediate

(e) displacements

(f) Addition elimination

5.2 Oxidation of carbonyl compounds

Carbonyl compounds include aldehydes and ketones. Aldehydes are easy to oxidised. Even air can oxidise an aldehyde into corresponding peroxides and carboxylic acids. The reagent used for this purpose is hydrogen peroxide, paracids, chromic acid, permagnate and silver oxide.

Mild oxidising agent oxidise aldehydes into carboxylic acids. They do not work on ketones. Following are the mild oxidizing for aldehydes.

(a) Fehling's solution and Benedict's solution

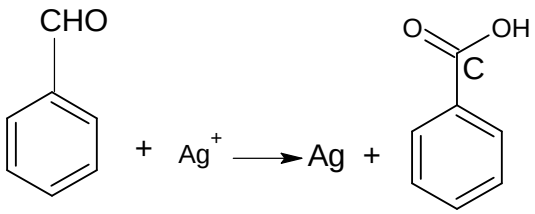
$$CH_3 - CHO + Cu^{2+} \rightarrow CH_3COOH + Cu^{1+}\underset{\text{Red ppt}}{(Cu_2O)}$$

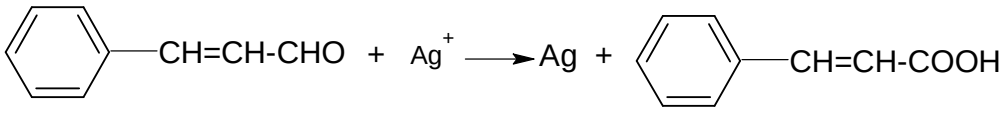
$$CH_3 - CH = CH - CHO \xrightarrow[solution]{Fehling} CH_3 - CH = CH - COOH$$

Reacting species in Fehling's solution and Benedict's solution is Cu^{+2}. These two reagent oxidise only aliphatic aldehydes and have no effect on carbon-carbon multiple bond and other functional group present in aldehyde for example

Tollen's reagent:

Tollen's reagent is an ammonical solution $AgNO_3$. The reacting species present in this reagent Ag^{1+} and it oxidises aliphatic and aromatic aldehydes into corresponding carboxylic acids without affecting the carbon-carbon multiple bond.For example





$$CH_3-CH_2-CH=CH-CHO+Ag^+ \rightarrow Ag+CH_3-CH_2-CH=CH-COOH$$

The Ag in its reduced form gets deposited on the inner wall's of the test tube. As a silver mirror mirror and this is generally taken as a qualitative test for aldehydes.

5.2.1 Oxidations of aldehydes by strong oxidising agents

Aldehydes oxidise into corresponding carboxylic acids by strong oxidising agents.

$$CH_3CHO \xrightarrow[Conc.HNO_3]{MnO_4^-/H^+ \quad Cr_2O_7^{2-}/H^+\Delta} CH_3COOH$$

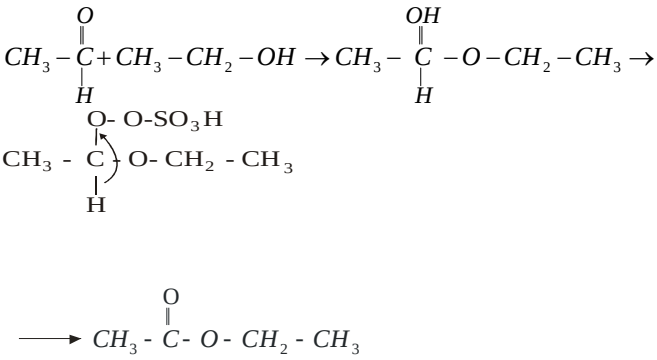
Hydrogen peroxides and its derivatives

The machanism for oxidation of aldehydes to carboxylic acids with hydrogenperoxide or its derivatives involves the formation of peroxide.

$$CH_3\overset{O}{\overset{\|}{C}}-H+CH_3-CH_2-O-O-H \rightarrow CH_3-\overset{OH}{\underset{H}{\overset{|}{\underset{|}{C}}}}-O-O-CH_2-CH_3 \rightarrow CH_3\overset{O}{\overset{\|}{C}}-OH$$

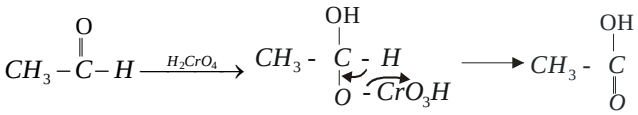
Aldehydes also get oxidised by Caro's acid [H_2SO_5]. while carring out this reaction in alcoholic medium, the oxidation final product is an ester in place of an acid. In this first step an hemiacetal is formed which ultimately is converted finally to corresponding acid.

This is shown below.



Chromic acid

The machanism of oxidation of an aldehyde into corresponding acid takes following route.

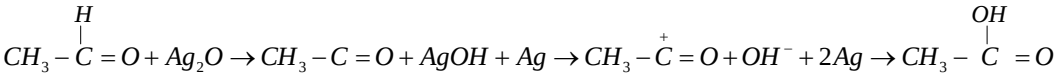


Potassium permangnate ($KMnO_4$)

Aliphatic and aromatic aldehydes undergo oxidation by $KMnO_4$ in acidic, neutral an alkaline medium. In acidic and neutral medium it is similar to that with cromic acid but in alkaline medium the oxidation occurs through free radical machanism.

Silver Oxide

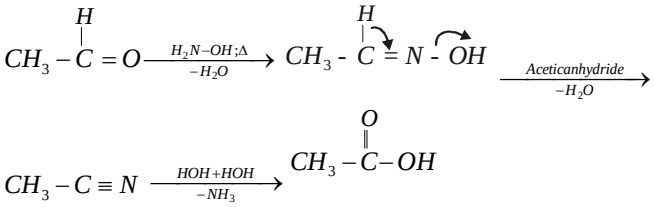
Aldehydes undergo oxidation with silver oxide in aqeous medium also in organic solvent. Silver oxide for this purpose is prepared by reaction of $AgNO_3$ and KOH in site. It is believed that the reaction proceeds through free radical machanism ie,



5.2.2 Intermolecular Oxidation of aldehyde

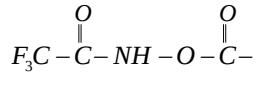
In this process their occurs a transfer of electron pair from one part of the molecule to another part.

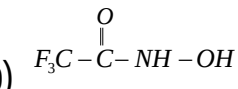
In this process the aldehyde first converted to an Oxime by the reaction of hydroxylamine. This oxime is treated with acetic anhydride. The anhydride causes the dehydration of oxime by an internal oxidation reduction process to produce a nitrile. The nitrile is hydrolysed than to produce the final product acid. This is shown below



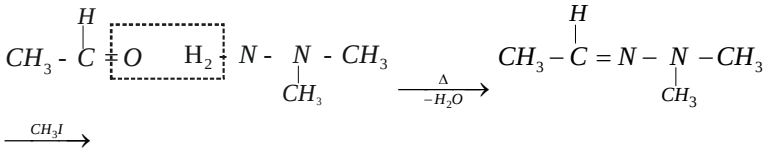
It is evident that in oxime the carbon atom is oxidised whereas nitrogen atom is reduced during dehydration.

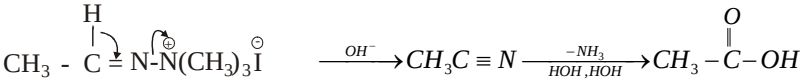
There is another way to convert the aldehyde into nitrite. This is done by treating the aldehyde by one of another following reagent.

(a)  ; O,N-bis (trifluoroacetyl hydroxylamine)

(b)  Trifluorohydroxamic acid.

The reaction is carried out in benzene in the presence of pyridine. The above mentioned reagents are prepared by the reaction of hydroxylamine, hydroxylamide, hydrochloride with trifluoroaceticanhydride. Some times the aldehydes are converted to corresponding hydrogens by reaction with hydrazine or dimethyhydrazine. When these are treated with CH_3I and then with base, undergo internal redox reaction to produce nitrile. These nitrile upon hydrolysis produces finally acid. This is shown below.

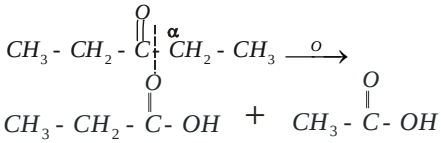




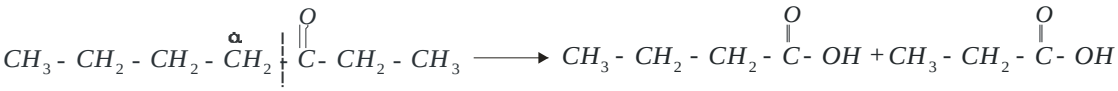
5.3 Oxidations of Ketones

Ketones are resistance towards oxidation by mild oxidising agents, they undergo oxidation only by strong oxidising agents and that too under drastic conditions.

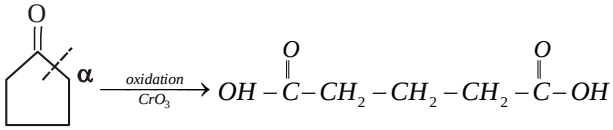
In this case symmetrical ketone the C-C bond between carbonyl carbon and alpha carbon carbon atom takes place during oxidation and both these carbon atoms is oxidised to carboxylic group. Thus we get two molecules of carboxylic acids by one molecule of ketone. This is shown below.

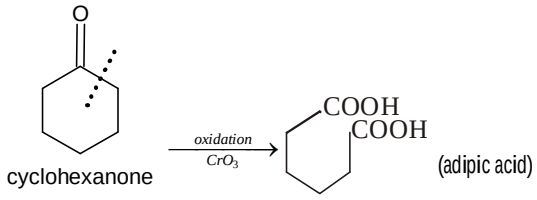


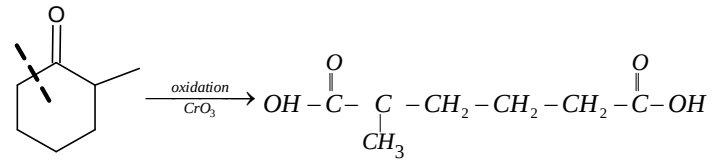
In case of unsymmetical ketones also the breaking of the bond takes place between carbonyl carbon atom and alpha carbon atom belongs to the alkyl group which has larger number of carbon atom. This is also called as Popoff's rule ie,



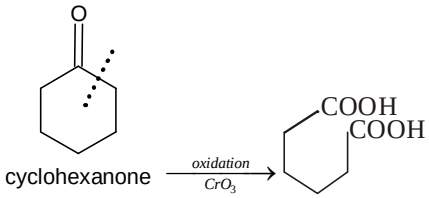
In case of cyclic ketones the product of their oxidation is a dibasic acid when strong oxidising agents are used Viz-

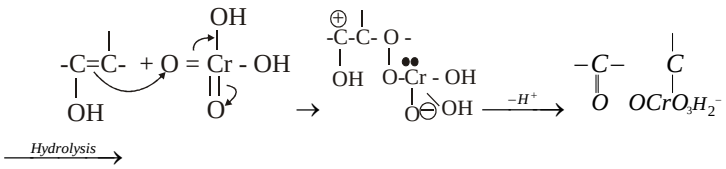


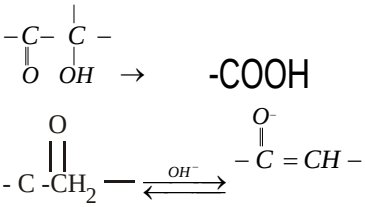


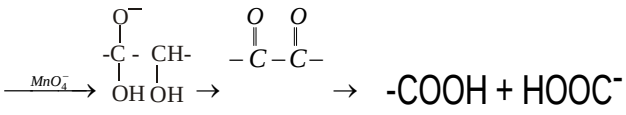


The product of oxidation of cyclohexanone is adipic acid and it is an industrial process as adipic acid is used in the preparation of many useful polymers. Oxidising agents used for the purpose are cromic acid or alkaline potassium permangnate. In acidic medium the carboxylic acid is produced through enol formation whereas in alkaline solution the pathway is through enolate anion. These are shown below.









5.4 Some specific oxidation of carbonyl compounds

Following are some specify oxidation reaction shown by some carbonyl compounds having specify structures

(a) Haloform reaction: This reaction is shown by methyl ketones and also by all those compound which can be easily oxidised to given methyl ketones. The reaction is

$$CH_3-\overset{O}{\overset{\|}{C}}-H \xrightarrow[H_3O^+]{I_2/NaOH} HCOOH + CHI_3$$

$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[H_3O^+]{I_2/NaOH} CH_3-\overset{O}{\overset{\|}{C}}-CH_3 + CHI_3$$

The above charactristic reaction of methyl ketone is used as their qualitative test. Methyl ketone are oxidised by chlorine, Bromine or Iodine in alkaline solution to produced acids and corresponding haloform. The process is abase catalysed halogenation followed by elimination by conjugate base of the haloform. By this process various useful acid (aliphatic and aromatic) can be prepared.

The halogen atom are electron withdrawing species and so the hydrogen situated at -carbon atom of the carbonyl group becomes more acidic in the firstly formed α -Haloketone as shown below.

$$\left[\bar{C}H_2-\overset{O}{\overset{\|}{C}}-CH_3 \leftrightarrow CH_2=\overset{O^-}{\overset{|}{C}}-CH_3\right] \equiv \left[CH_3-CO-CH_3\right]^-$$

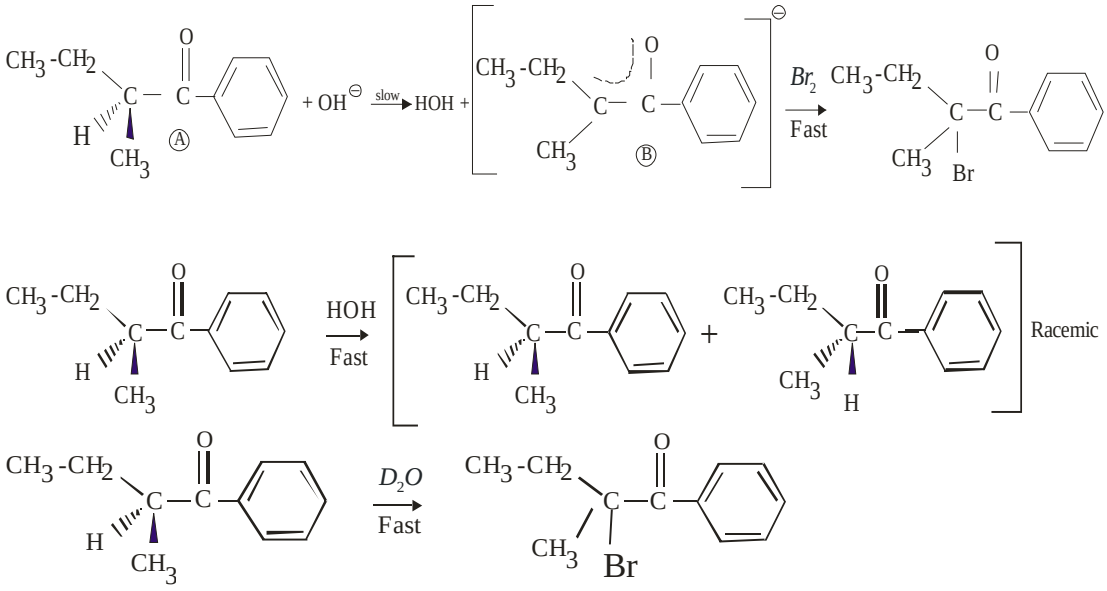
$$\left[CH_3-CO-CH_3\right]^- + Br_2 \xrightarrow{Fast} CH_3-CO-CH_2Br + Br^-$$

The firstly formed α -haloketone undergoes further halogenation ie,

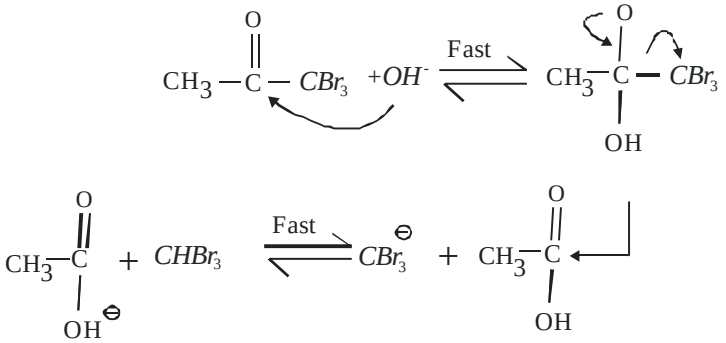
$$CH_3-CO-CH_2-Br \xrightleftharpoons{OH^-} CH_3-CO-\bar{C}HBr \xrightarrow[OH^-]{Br_2} CH_3-CO-CHBr_2 \xrightarrow[OH^-]{Br_2} CH_3-CO-CBr_3$$

In the above process the carbanion is formed as an intermediate. The evidance for the formation carbanion is obtained by the base catalysed recemisation of D-phenyl-sec-butyl ketone (a).

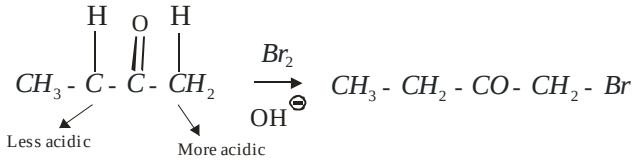
In this compound the base OH^- abstracts a proton and produces carbanion and because the carbanion is flat and the reaction is reversible, the proton may get attached from either side there by resulting in the formation of a recemic mixture. Moreover the rate constant for recemisation and bromination are found to be identical. This rate is also found to be equal to rate of destruction, thus all these experminetal finding support the formation of a planar enolate ion (B) in the rate determining step.



The carbonyl carbon atom of the trihaloketone formed in this reaction is highly positive because of the coupled inductive effect of three halogen atoms and thus it is attacked by the base with a cleavage of carbon-carbon bond. This is shown below.



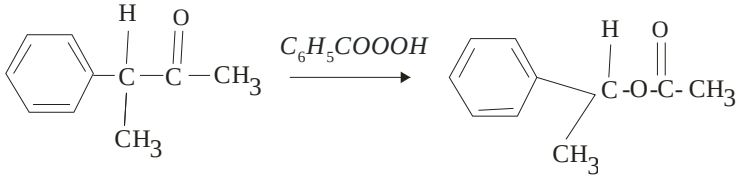
Because alkyl groups are electron, repelling in nature, the -alkyl substituents are accepted to retard the base catalysed halogination of ketones. It is because of this reason, the haloginations of unsymmetrical ketones takes place on that carbon atom which contain lesser number of alkyl groups Viz-



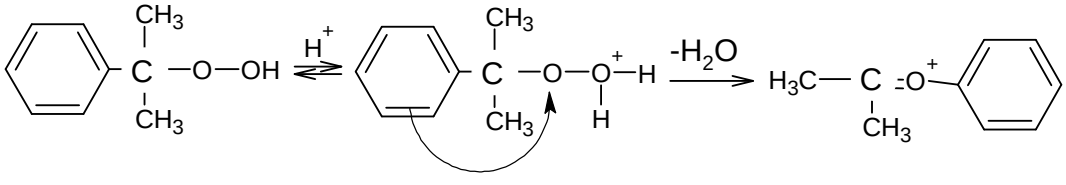
In case of unsymmetrical ketones the group which a better electron donor is the migrating group.Consequently the following sequence is followed.

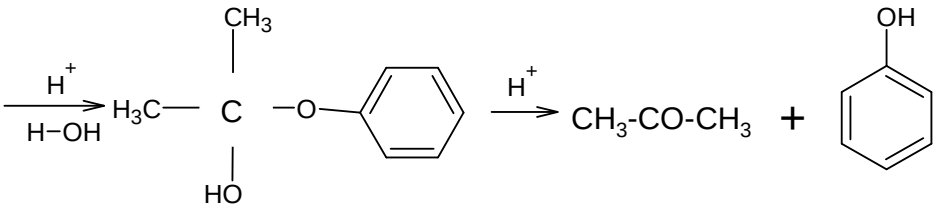
$$(CH_3)_3C- > (CH_3)_2CH- > CH_3-CH_2- > CH_3-$$

If one of the group is aromatic than this migrates in preference to primary alkyl group if the migrating group is chiral in nature its configuration is retained and thus this proves that the reaction is intramolecular in nature ie,

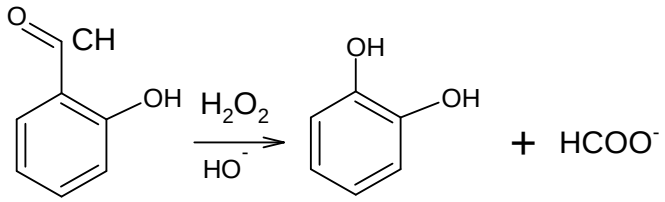


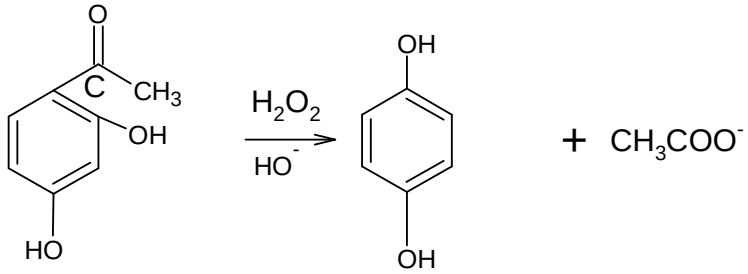
Cumene is easily prepared by propevalkylation of benzene of Friedel crafts reaction. This is readily converted to cumene hydroperoxide and this undergos an acid catalysed rearrangement and an hemiacetal is produced which is hydrolysed at pH<7. This is shown below.

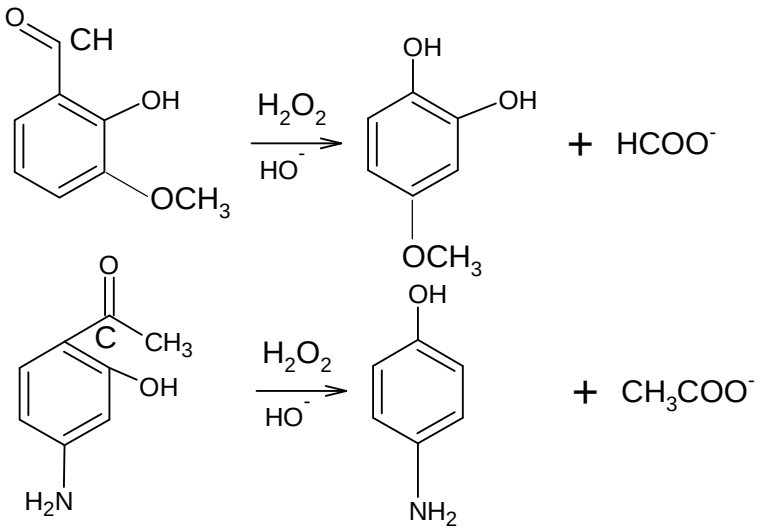




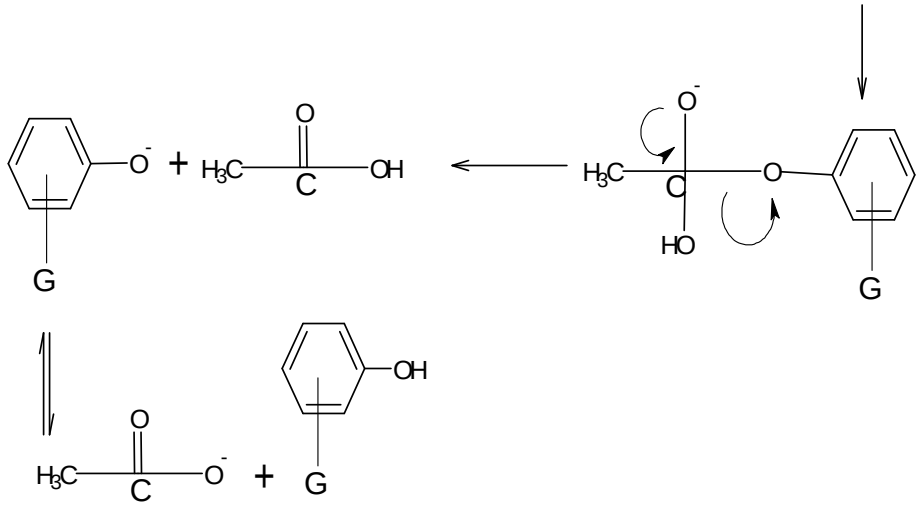
Aromatic aldehydes and ketones when treated with alkaline H_2O_2 are converted to phenol. The essential conditions for the reaction is that there should be an -OH or -NH_2 group on the aromatic ring relative to carbonyl group Viz-





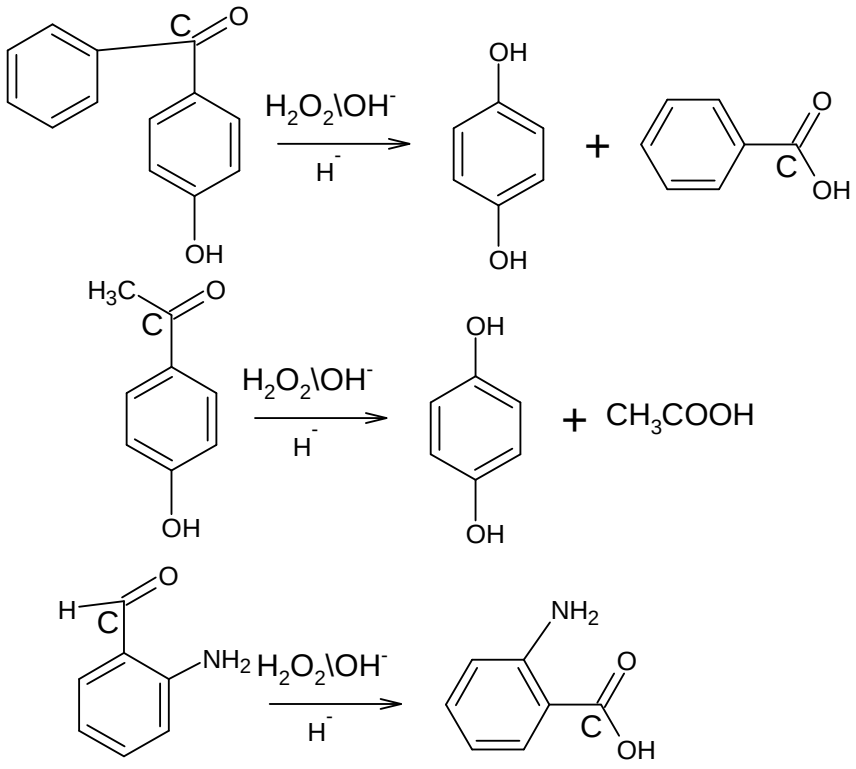


The carbonyl compound undergoes nucleophilic addition with hydro peroxide ion, thus a tetrahedral intermediate (A) is produced. This intermediate undergoes 1,2-shift to give an ester(B). Which upon further hydrolysis finally gives phenol? The mechanistic path of this reaction is depicted below.



The possible isolation of the ester intermediate (B) is a strong evidance in favour of the above machanism.

It has been observed that presence of electron donating substituents is an essential condition for the migration of aromatic ring. In case of benzaldehyde derivatives it is the hydride migration which is favoured over the phenyl migration whereas in case of mixed ketones if is the aromatic ring which migrate. This is shown below.



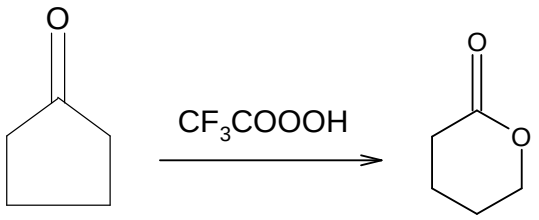
5.5 Baeyer-Villiger reaction

Both aldehyde and ketones undergo oxidation when treated with peracids. The reactions is called Baeyer-Villiger reaction.

$$CH_3-\overset{O}{\overset{\|}{C}}-H \xrightarrow{CF_3COOOH} CH_3-\overset{O}{\overset{\|}{C}}-OH$$

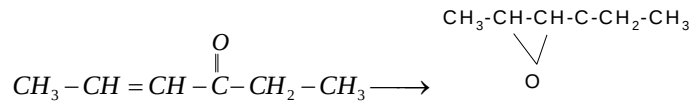
$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{CF_3COOOH} CH_3-\overset{O}{\overset{\|}{C}}-OCH_3$$

Cyclic ketones are converted to lactonse with ring expansion



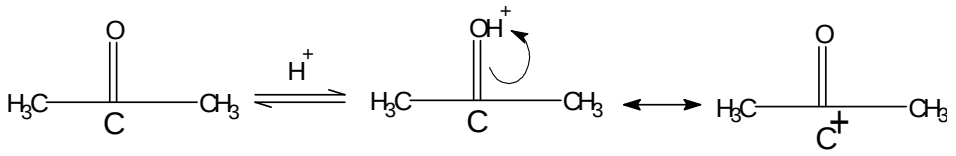
The overall reaction insertion of oxygen atom between the carbonyl group adjacent carbon in ketone. Inert solvents are used for the reaction. The choice of the solvent depends upon the solubility of reactants. Usually chloroform, glycol, acetic acid etc are used as solvents. The paraads acetic acid per monosulphuric acid, m-bromobenzoic per acid, Magnesium-peroxyphthalate etc.

The reaction is of less important for aldehyde because the product is carbxylic acid which can be obtained from other reaction also. However for ketone it is especially useful for ketone because it converts them into carboxylic esters. Moreover ketones are resistant to most of the oxidising agent for less reactive ketones. the oxidising agent used is CF_3COOH. Some times oxidising agents likeH_2O_2 - BF_3 - $(C_2H_5)_2O$ and caro's acid ($K_2S_2O_8$-H_2O_2) have also been used. Hydrogen peroxideis weakly alkaline medium has also been found useful. The only limitation associated with the reaction is that if C-C double bond is present in the ketone it undergoes epoxidation and This ethers get oxidised to sulphoxides or sulphones Viz-

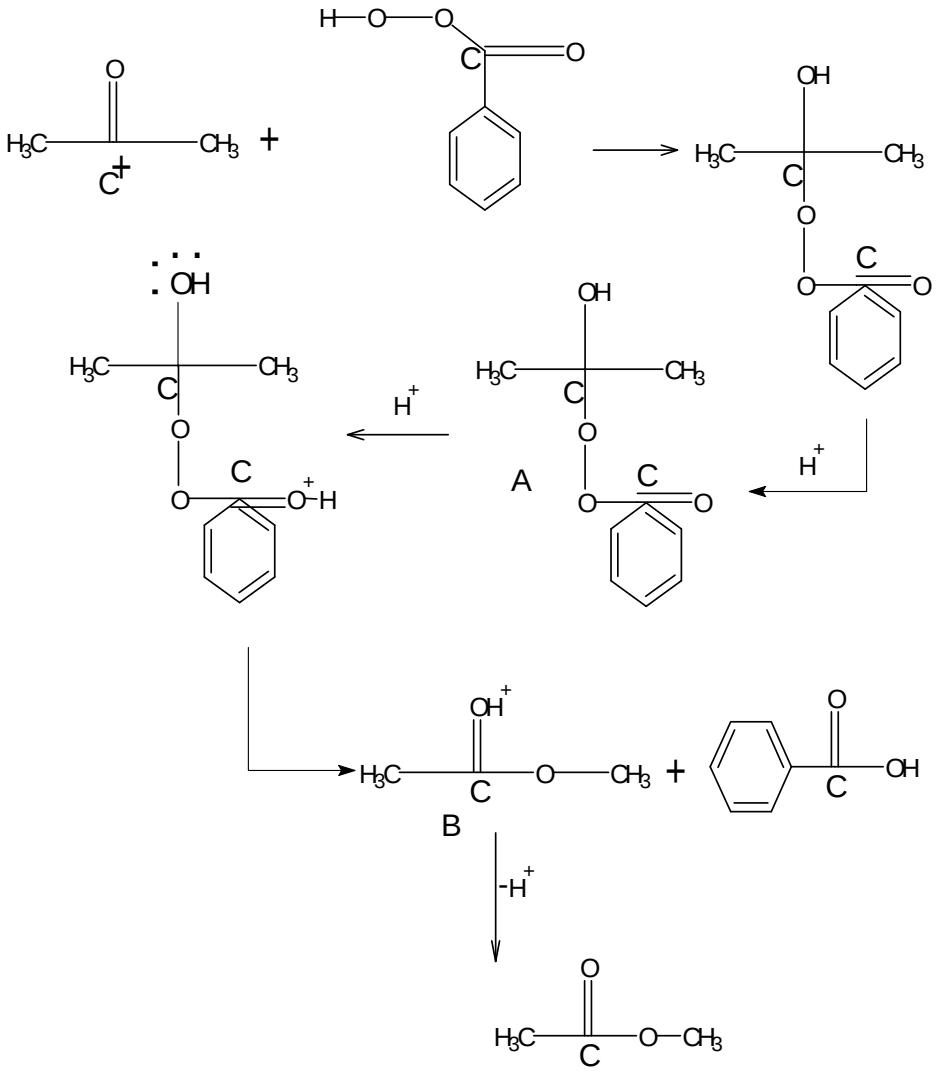


The accepted machnism of the reaction is as follows

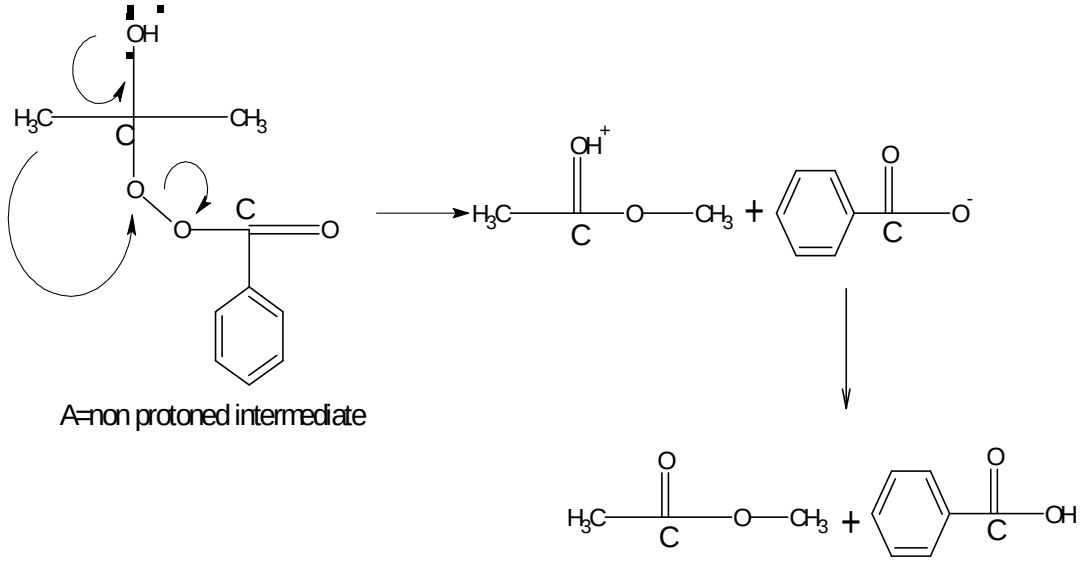
First of all the ketone is protonated. This protoned ketone attacked by paraacid (Nucleophilic) to give an intermediate peroxide (A). This peroxide than losses carbocylate anion migration of a group from carbon to electron deficient oxygen to give the potonated ester. Which finally losses a proton to produce the ester. Viz-



Now

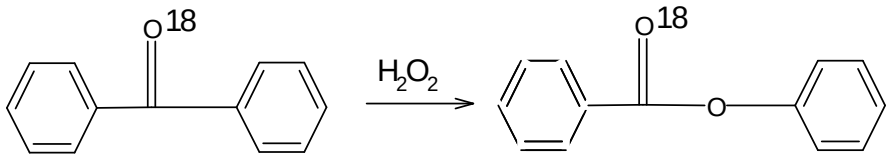


In the above machanism it is evident the rearrangement occurs on potonated intermediate. However the absence of an acid the rearrangement occurs through non protonated intermediate. This is shown below



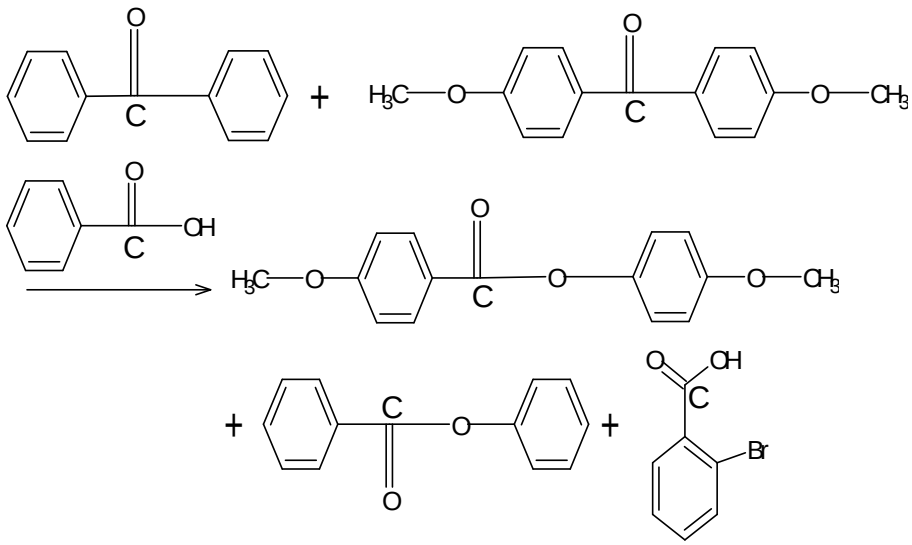
A=non protoned intermediate

When benzophenone labelled with O^{18} is subjected to Baeyer-Villiger reaction, phenylbenzoate is obtained in which O^{18} is retained in the carboxylic group ie,

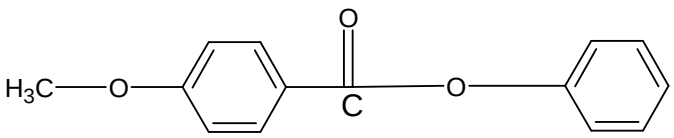


The above result shows that the rearrangement takes place by the formation of unprotonated intermediate (A). This is sometimes called as oviege intermediate.

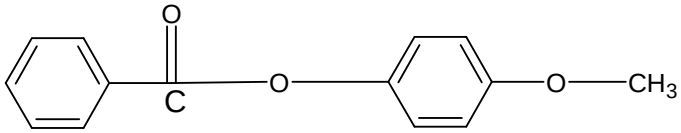
The rearrangement is a concerted reaction and this can be confirmed by the following experiments.



If the rearrangement were intermolecular the expected products would have been



And

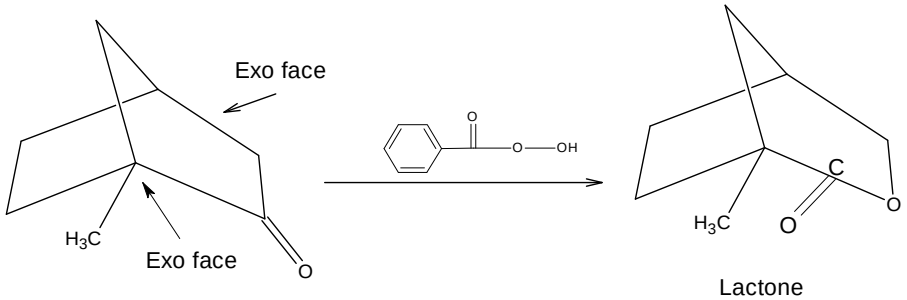


In unsymmetrical ketones the group which migrates is one which is more electron releasing. Thus the migration follows the order tertiary > secondary > primary > CH_3 in case of alkyl groups. The migration is facilitate by the presence of electron releasing groups on aryl group. Thus the order is p-anisyl > p-tolyl >phenyl >p-chlorophenyl >p-nitorphenyl etc in case of aromatic groups. However in case of aryl alkyl ketones it is the aryl group which migrates (tertiary butyl group is an exception).

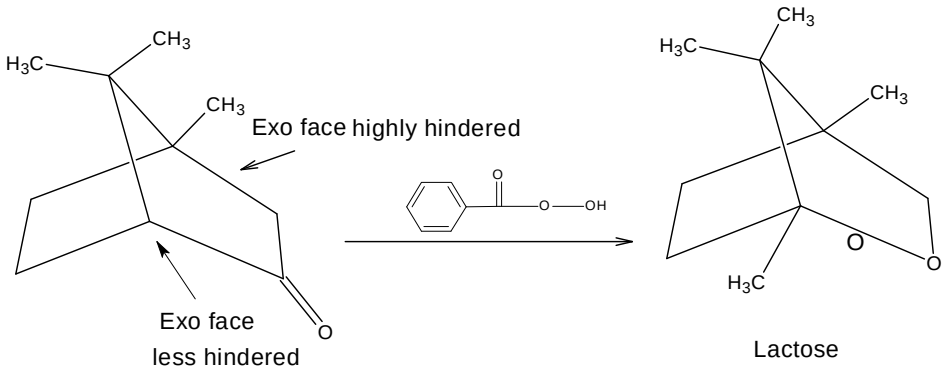
This shows that Baeyer's Villiger reaction is highly regioselective in case of unsymmetrical ketones.

The above discussed migratory aptitude of various groups iin this reaction can be related to their ability to sustain a positive charge in the transition state which, in turn indicates the movement of some bridged non classical species in the migrating step. This also provides evidence in support of concerted mechanism of the reaction.

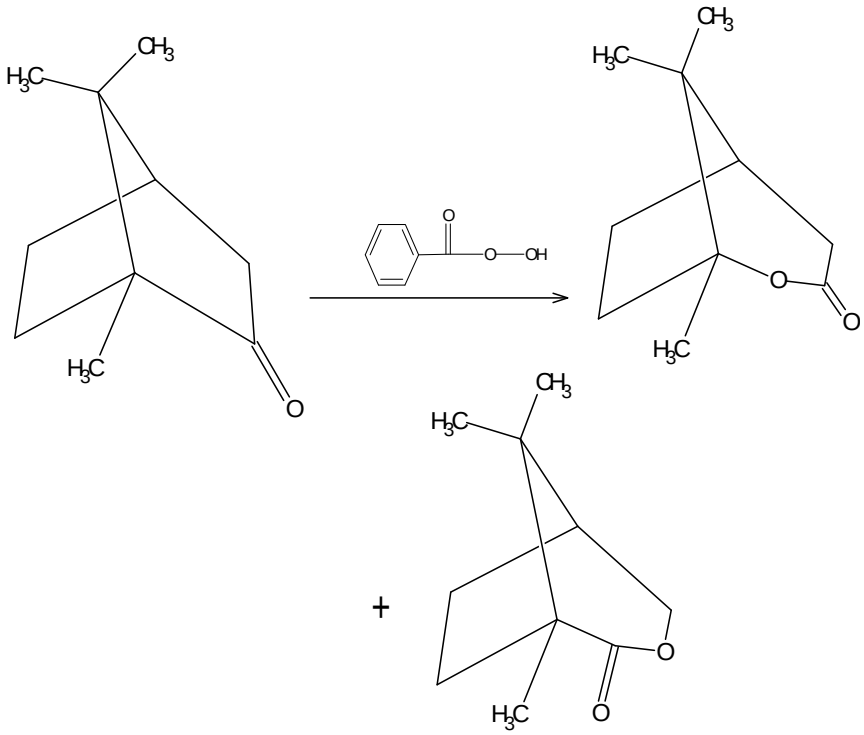
Migration tendency of the groups is also affected by steric and structural hinderances. Thus if a ketone having a bicycle [2,2,1] heptanone skeleton is taken the oxidation takes place from the exoface due to structural hinderance.



On the other hand if epicamphor is taken the oxidation takes place on the ends side because the exo side is highly sterically hindered.

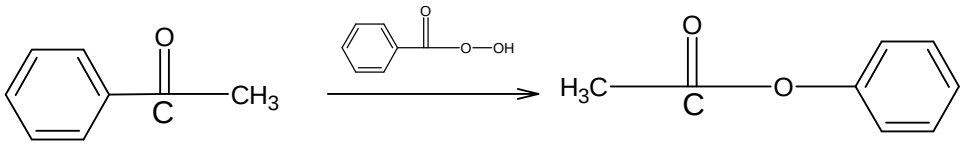


However camphor on oxidation gives a mixture of lactones thereby undergoing oxidations both at exo and endo faces Viz-

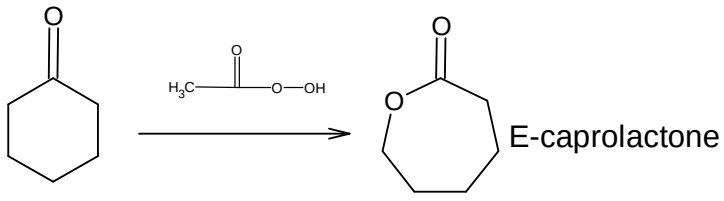


Following are some more examples of Baeyer Villiger reactions.

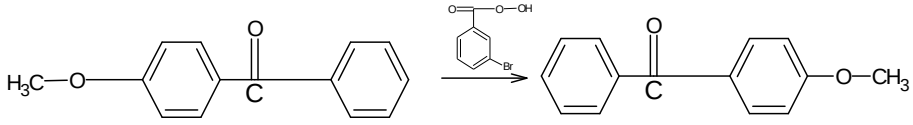
(i)



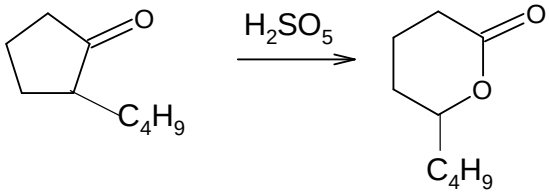
(ii)



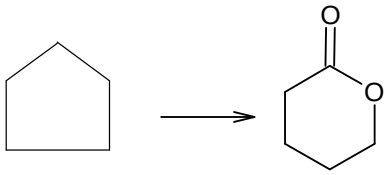
(iii)



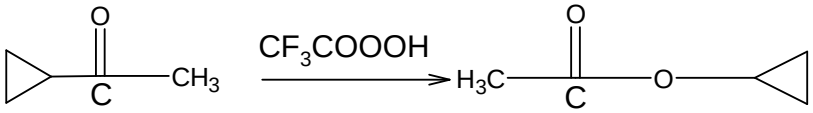
(iv)



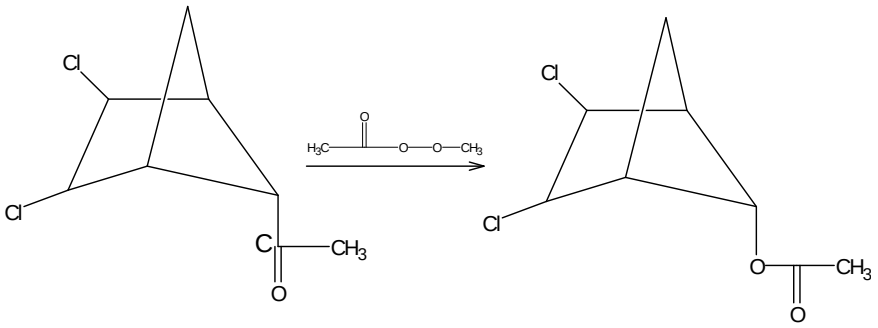
(v)



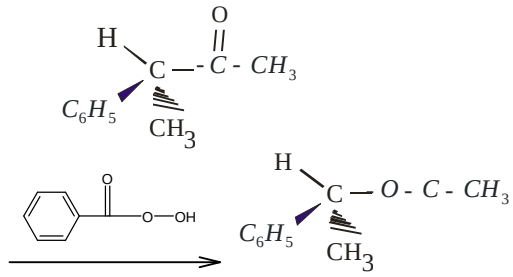
(vi)



(vii)



In Baeyer Villiger reaction when optically active ketones are taken in which the chiral carbon atom is bonded to carbonyl group, it is fournd that the configuration of chiral carbon is retained in the product Viz-

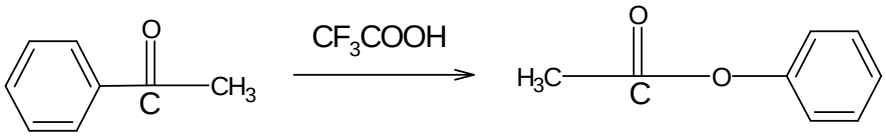


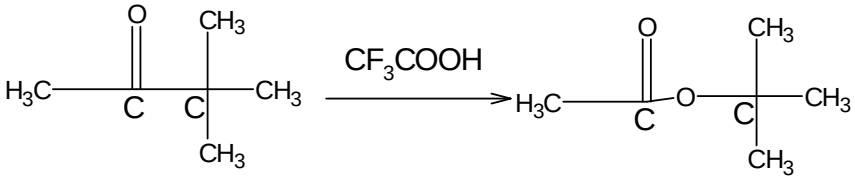
Thus it is evident that the chiral centre migrates to oxygen with its electron but without inversion. Isotopic study also shows that migration is involved in rate determining step.

5.5.1 Application of Baeyer-Villiger reaction

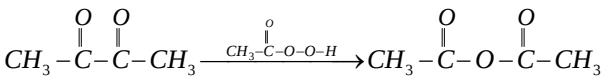
Baeyer Villiger reaction has following synthetic applications.

(1) Those esters which are difficults to prepared can be synthesized by this reaction.

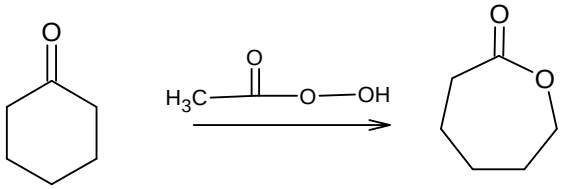


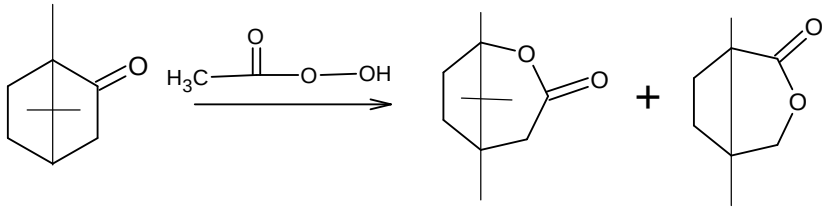


(2) Anhydrides can be prepared by taking 1,2-diketones.



(3) Lactones can be prepared by using cyclic ketones

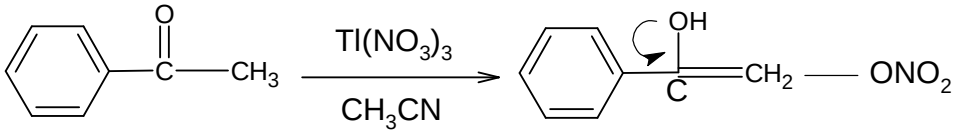




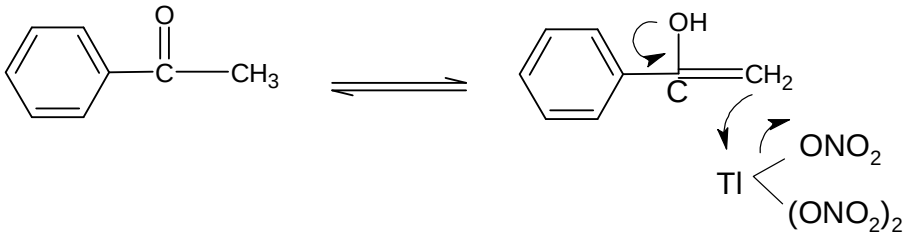
(4) The reaction is useful to elucidate the structure of substrate.

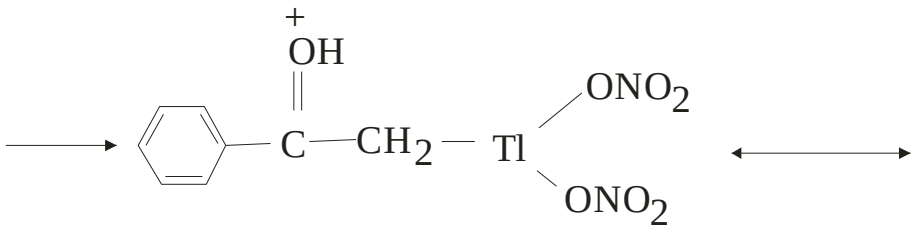
Oxidation of ketones by Thalium Nitrate

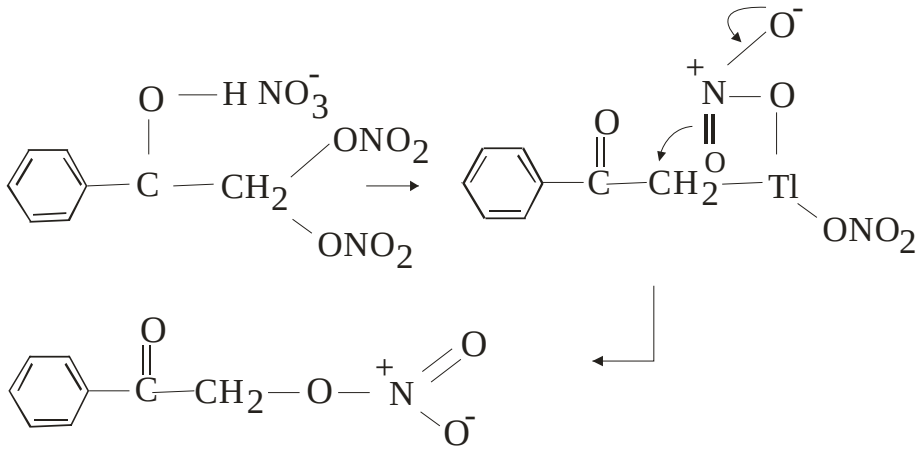
When aliphatic and aromatic methyl ketones are treated with Thallium nitrate in CH_3CN, d-nitrato-ketones are obtained.



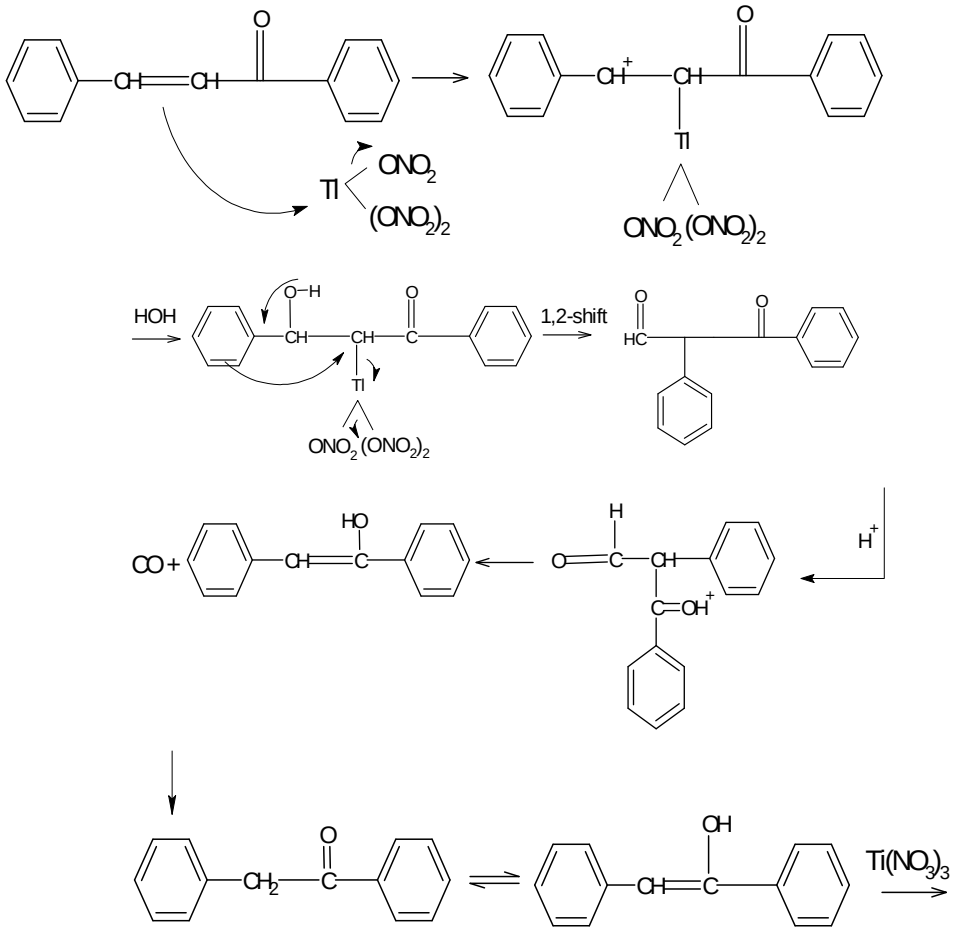
The reaction proceeds as follows

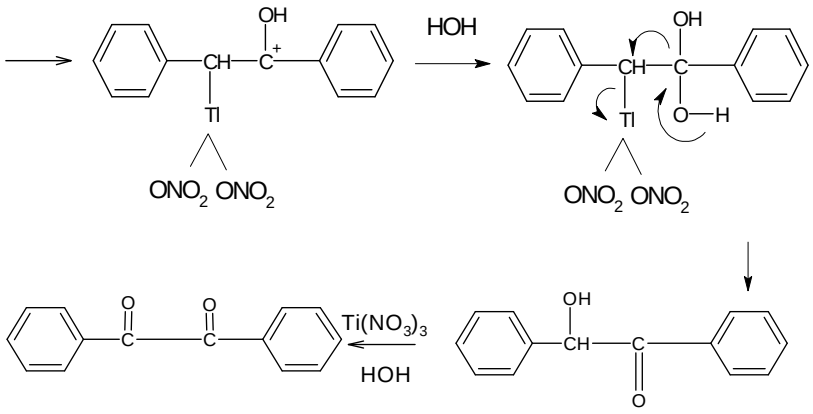






α,β un saturated ketones upon oxidation give 1,2-diketones.





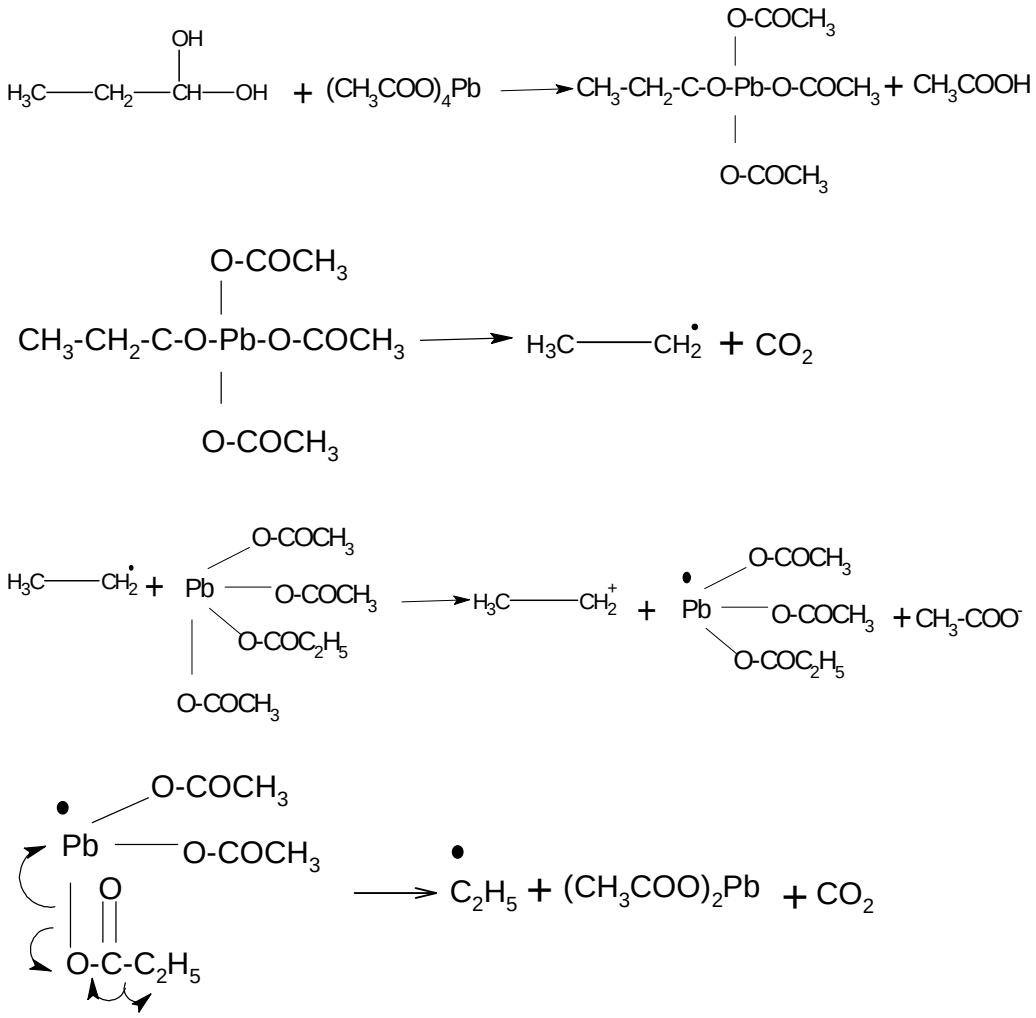
5.6 Oxidation of caboxylic acids

In carboxylic acid the oxidation state of carbon is three and carbon can have a maximum oxidation state of four thus it is evident that if a carboxylic acid in a chemical reaction, produces CO_2 it should be regarded as its oxidation.

Now in general chemistry we know that formation of CO_2 from -COOH is called as decarbxylation, it is for this reason all the oxidation reactions of carbxylic acid are termed as oxidative decarboxylation.

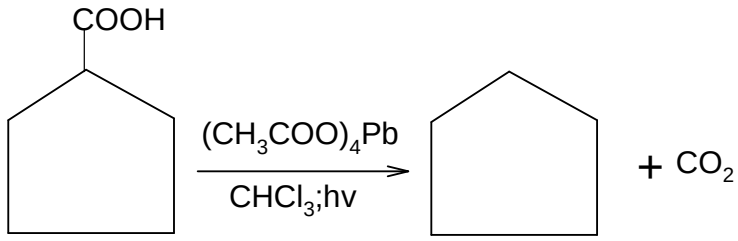
Generally the reagent used for oxidation is lead tetraacetate. The reactions takes up free radical mechanistic path and the products depend upon products may be an alkane, alkene, ester or sometimes an halide also. Sometimes Cu(II) salts are also used . The function of these salt is to oxidise the free radical intermediate into a carbocation.

The reaction is shown below.

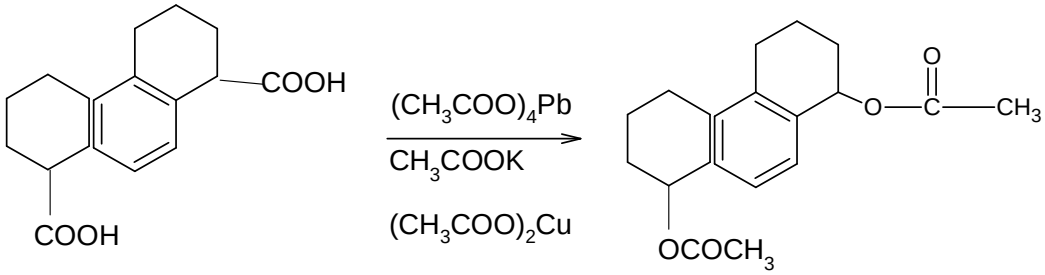


Free Radicals are formed they abstract H from the solvent molecular and give alkane R-H on the otherhand if carbocations are formed they eliminate a proton ie, H^+ from carbon atom to give alkene. The alkene reacts with acetic acid to give esters. Sometime the dimerisation of free radicals R produces R-R. In case when free radicals produced are primary and for secondary, Cu^{2+} ions used in the system oxidise them into alkenes. No such effect of Cu^{2+} ions is seen in case when tertiary free radicals are formed.

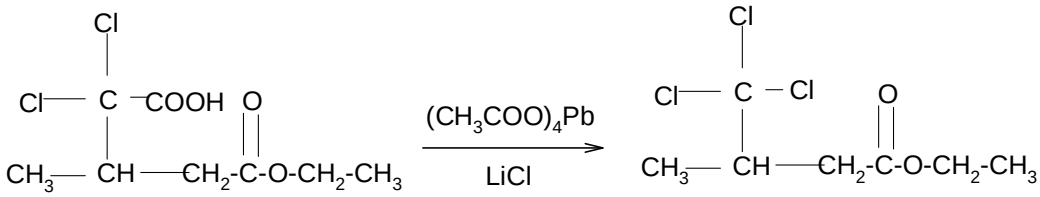
Alkanes are produced in good yield by photo chemical decomposition of carboxylic acids in chloroform.



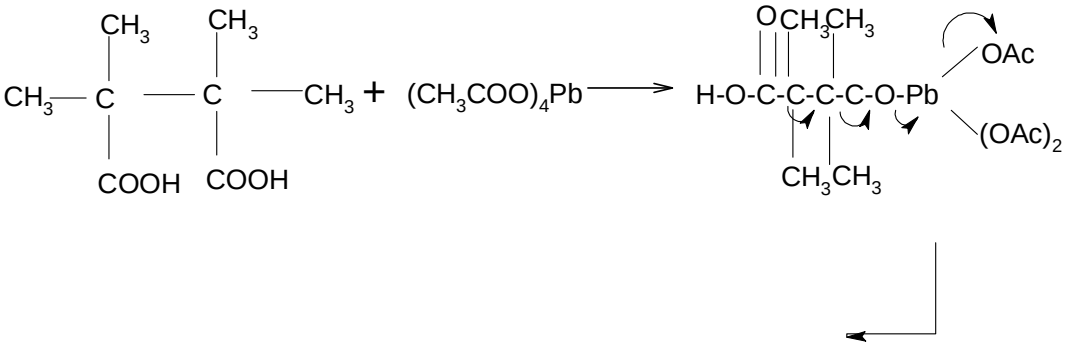
If potassium acetate is taken the ratio of alkene; ester is found to increase eg.

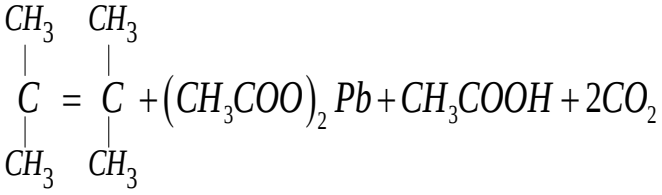


If LiCl is used the product is a halide .

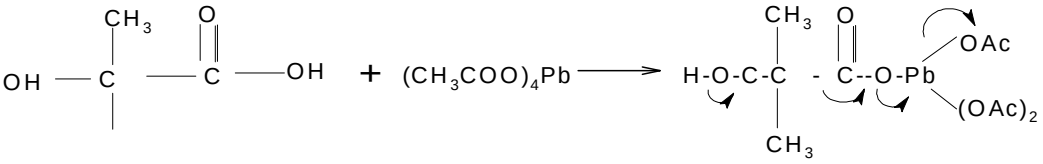


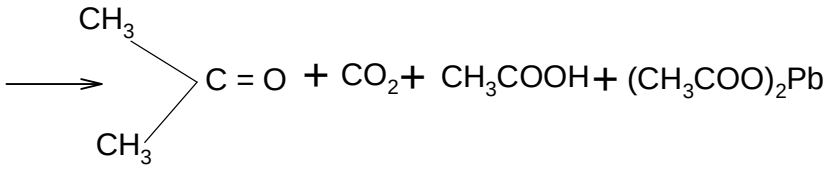
Compounds having carboxylic groups on adjacent carbon atom ie 1, 2-dicarbxylic acids undergo bidecarbocylation to produce alkene when treated with lead tetraacetate Viz-





In case of α- hydroxyl carboxylic acids, their oxidative decarboxylation produces ketones.





5.7 Summary

- During oxidation process there is a change in the oxidation number of the carbon atom bearing the functional group this achieved by a change in functional group.
- the oxidizes product of carbonyl compound are carboxylic acids which finds applications in various field

- the acids further can be converted into various derivative and so I opens a way to synthesize a galaxy of compounds
- oxidation of carboxylic acids mainly produces hydrocarbon the formation of these hydrocarbons opens a way to obtain new compounds
- If the process of oxidation is industrial interest than reaction conditions cost and availability of oxidizing agent affect the cost and purity of product.

5.8 Review Questions

1. What happens when following acids react with CF_3COOOH
   (A) Propanoic acid
   (B) Phenyl acetic acid
   (C) benzoic acid.
   (D) Cyclopentanone.
2. Discuss the mechanism of Baeyer Villiger Reaction.
3. Discuss the mechanism of oxidative decarboxylation with reference various carboxylic acids.
4. Explain the term selectivity and reactivity of an oxidizing agent with example.

5.9 Reference Books

- Advance dorganic Chemistry ,Jery March,4th edition,johnwiley and sons.
- Organic synthesi ,jagdamba singh,Dr. L.D.S Yadav,Pragati Prakashan
- Organic Chmistry ,I.L Finar Volume II,ELBS
- Organic reaction mechanism ,P.S.kalsi, New Age Publication.
- Reaction rearrangement and reagent ,s.N.sanyal,Bharti Bhavan Publication.

Unit-6

Reduction

Structure of unit:

6.1 Introduction

The removal of oxygen or the addition of hydrogen or the addition of electrons to an organic substrate is called reduction.

6.2 Different reductive processs

Reductive processes fall into three categories:

1. The removal of oxygen
2. The addition of hydrogen – This processs further subdivided into two types:
   a. Hydrogenation – Addition of hydrogen to an unsaturated system.

b. Hydrogenolysis- Addition of hydrogen with concomitant bond rapture.

$C_6H_5\text{-}CH_2\text{-}O\text{-}CH_2\text{-}R + H_2 \xrightarrow{\text{catalyst}} C_6H_5\text{-}CH_3 + R\text{-}CH_2\text{-}OH$

c. The gain of electrons

6.3 Reduction of alkenes

Following methods are used for the reduction of alkenes.

6.3.1 Catalytic hydrogenation –

It involves stirring of substrate with a catalyst in a suitable solvent in an atmosphere of hydrogen. Catalytic hydrogenation can be classified into two categories

a. Heterogeneous hydrogenation - Numerous heterogeneous catalysts have been used for catalytic hydrogenation. It involves transition metal catalysts absorbed on a solid support. The reduction take place at the surface of the catalyst which adsorbs both hydrogen and organic compound and facilitates their contact.

   Elevated temperature and pressure invariably increase the rate of hydrogenation.

   The addition of hydrogen is syn. Thus reaction is stereospecific.

b. Homogeneous hydrogenation – Wilkinson's catalyst ($[Ph3\ P]_3RhCl$) is a most useful homogeneous catalyst of alkenes.

6.3.2 Reduction with diimide

Diimide is an unstable compound and it is prepared in situ by the following processes:

1.Oxidation of hydrazine

$NH_2\text{-}NH_2 \xrightarrow{H_2O_2/Cu} NH{=}NH$

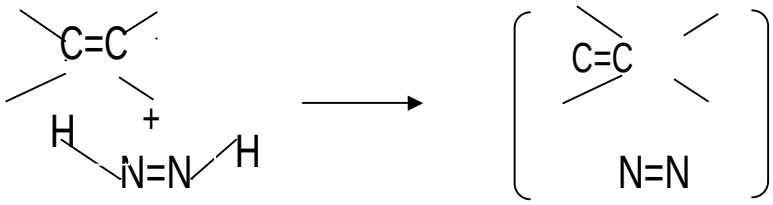
1. By thermal decomposition of p-toluenesulphonylhydrazine

$CH_3\text{-}C_6H_5\text{-}SO_2NH\text{-}NH_2 \xrightarrow{\Delta} CH_3\text{-}C_6H_5\text{-}SO_2H + NH{=}NH$

2. By thermal decomposition of azo dicarboxylic acid

$HOOC\text{-}N{=}N\text{-}COOH \xrightarrow{\Delta} NH{=}NH + 2CO_2$

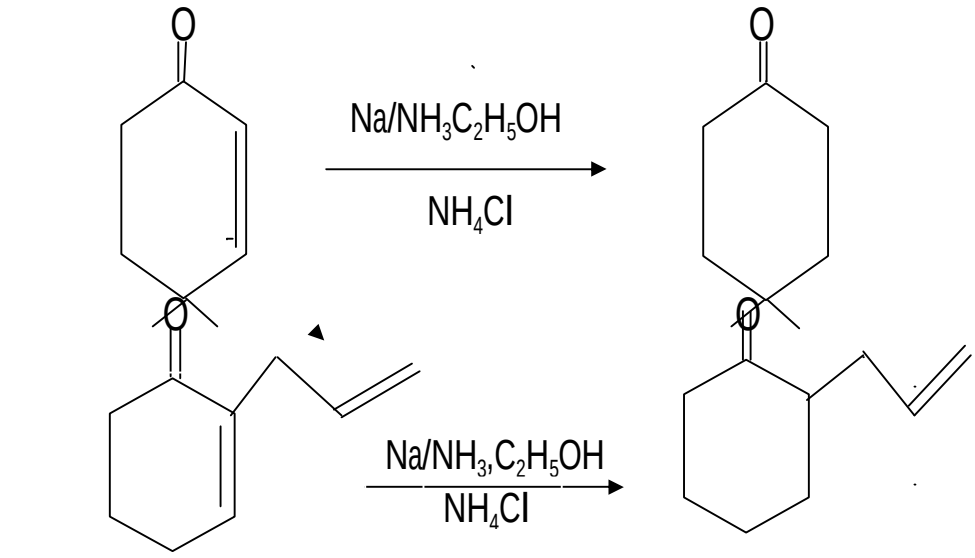
Diimide is a highly selective reagent for the reduction of carbon –carbon double bond.

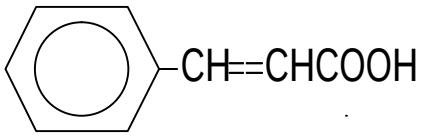


6.3.3 Reduction with alkali metal in liquid ammonia

Alkenes that are substituted with an electron-withdrawing group on olefinic carbon can be reduced with lithium , sodium or potassium in liquid ammonia at low temperature. The reduction is carried out in the presence of proton donor,i.e., ethyl alcohol

$$CH_3\text{-}CH{=}CH\text{-}CO\text{-}CH_3 \xrightarrow[NH_4Cl]{Na/NH_3,C_2H_5OH} CH_3\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}CH_3$$



O_2N-  Azo dicarboxylic acid

$\xrightarrow{\Delta}$

6.4 Reduction with alkynes

Following methods are used for the reduction of alkynes:

6.4.1 Catalytic hydrogenation

When alkynes undergo catalytic hydrogenation, the first addition of hydrogen yields an alkene and a second addition of hydrogen gives an alkane

The catalyst may be homogeneous or heterogeneous.

$$R\text{-}C{\equiv}C\text{-}R \xrightarrow[\text{catalyst}]{H_2} R\text{-}CH{=}CH\text{-}R \xrightarrow[\text{catalyst}]{H_2} R\text{-}CH_2\text{-}CH_2\text{-}R$$

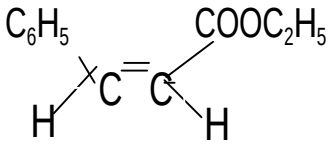
Hydrogenation of an alkyne may be stopped at alkene stage which is known as partial reduction of alkynes. Partial reduction of alkynes can be done by heterogeneous hydrogenation with Lindlar's catalyst [Pd poisoned with Pb^{+2} and an amine (quinoline or pyridine)].

Lindlar's catalyst convert non terminal alkenes into cis –alkenes and give stereoselective reaction.

6.4.2 Reduction with borane or hydroboration of alkynes

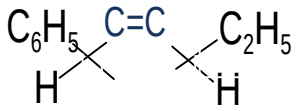
A sterically hindered dialkyl borane reacts with alkyne to give vinyl borane. The reaction is stereoselective and followed syn addition. The vinyl derivative on protonolysis give cis alkenes. Protonolysis carried out in the presence of boiling acetic acid and inert towards NO_2, COOR and halo groups.

$$C_6H_5\text{-}C{\equiv}C\text{-}COO\text{-}C_2H_5 \xrightarrow[\text{Sia2BH/THF}]{\text{Acetic acid/ }\Delta}$$



Diisobutyl aluminium hydride (DIBAL) can also used to reduced alkynes into cis alkenes.which is inert for most of the functional groups except alkynes, -COOR and –CN.

$$C_6H_5\text{-}C{\equiv}C\text{--}C_2H_5 \xrightarrow[\text{DIBAL}]{\text{N}}$$



Reduction with alkali metals in liquid ammonia

Reaction of a non terminal alkynes with a solution of an alkali metal in liquid ammonia gives a trans-alkene. Reduction of alkynes with sodium in liquid ammonia is complementary to catalytic hydrogenation.

Mechanism : reduction proceeds via addition of an electron to the alkyne to form a radical anion which adopts trans geometry. The radical anion is strong base which readily removes a proton from ammonia to give vinylic radical . The vinylic radical picks up another electron to give the vinyl anion. Thus protonation of this anion loads to the observed trans-alkene.

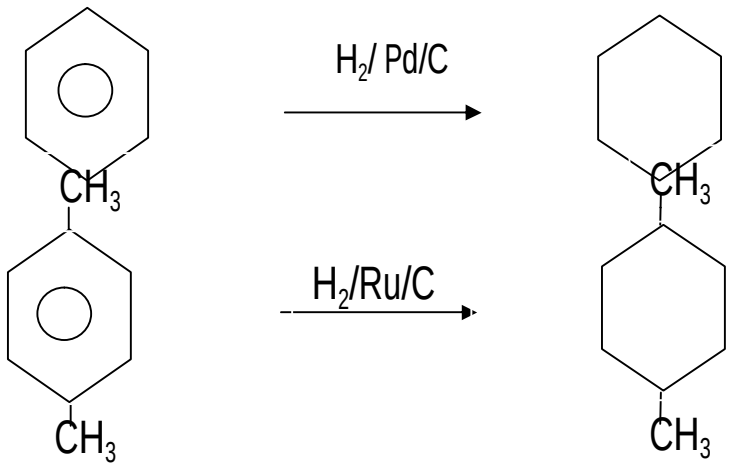
6.5 Reduction of aromatic rings

Following methods are used for the rduction of aromatic rings:

6.5.1 Catalytic hydrogenation

Reduction of aromatic rings by catalytic hydrogenation is more difficult than that of most functional groups because aromatic stabilization energy is lost in the process. The conditions vary according to the amount of resonance energy which is lost during the course of reduction. e.g – naphthalene is reduced to tetralin more readily than benzene which is reduced to cyclohexane because resonance energy for per benzene ring of naphthalene is 29 kcal/ mole whereas for benzene is 36 kcal / mole

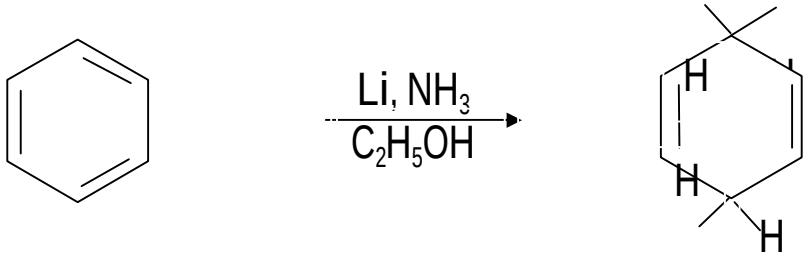
The catalyst used for this purpose are platinum , rhodium and ruthenium.



Aromatic rings do not give partial reduction in the presence of heterogeneous catalyst.

6.5.2 Reduction by electron transfer reagents

The Birch reduction is useful to accomplish the partial reduction oef aromatic rings. Electrons are the reducing agent which come from the alkali metals in liquid ammonia. When aromatic rings are reduced by Li in liquid ammonia in the presence of alcohol 1,4 addition of hydrogen takes place and non conjugated cyclohexadienes are produced.



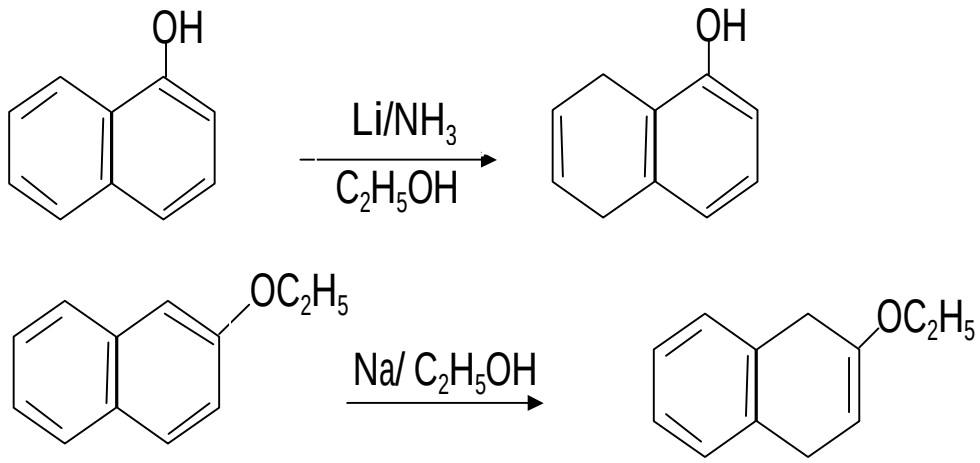
Mechanism of reduction: it involves sequential addition of an electron followed by protonation of the radical anion species so formed

In case of substituted aromatic compounds the electron donating groups decreases the rate of the Birch reduction and the presence of electron donating groups promote ortho , meta reduction as these groups stabilize electron density at ortho, meta positions.

If electron withdrawing groups are substituted on aromatic compounds increases the rate of the Birch reduction and the presence of electron withdrawing groups promote ipso, para reduction as these groups stabilize electron density at ipso, para positions.

Variety of products can be obtained with naphthalene. Nature of products depends on the nature of proton donar and reaction conditions.

The reduction of 1-naphthol can be done by lithium in ammonia containing ethanol and reduced in the unsubstituted ring whereas 2-etoxynaphthol is reduced in the substituted ring.



6.6 Summary

- An increase in hydrogen content or a decrease in oxygen content of an organic compound is known as reduction.
- Three different reductive processes are addition of hydrogen, removal of oxygen and gain of electrons.
- Reduction of alkene can be done by catalytic hydrogenation, reduction with diimide and reduction with alkali metal in liquid ammonia.
- Catalytic hydrogenation may be homogeneous or heterogeneous.
- Reduction of alkynes can be done by catalytic hydrogenation, reduction with borane and reduction with alkali metal in liquid ammonia.
- Reduction of aromatic rings can be done by catalytic hydrogenation and reduction by electron transfer reagents.

6.7 Review Questions

1 Define reduction ?

2 What are the three pathways for reduction?

3 Write short note on the following.

1. Catalytic hydrogenation

2. Reduction with diimide
3. Reduction of alkene with alkali metal in liquid ammonia
4. Reduction of alkene

4 What is catalytic hydrogenation and how many types it is divided?

5 Discuss hydroboration of alkynes.

6 Explain the role of catalytic hydrogenation in reduction of alkene, alkynes and aromatic rings.

7 Why reduction of aromatic rings by catalytic hydrogenation is more difficult than that of other functional groups?

8 What is Birch reduction. Discuss the effect of the presence of electron donating and electron withdrawing groups on the rate of Birch reduction.

9 Why electron donating groups promote ortho, meta reduction?

10 Write short note on-

1. Reduction of alkyne
2. Reduction of aromatic rings

6.8 References and Suggested readings

- Organic Chemistry , J.G.Smith, Tata Mc-Graw Hill, 2008
- Organic Chemistry, R.T.Morrison, R.N.Boyd and S.K. Bhattacharjee, Pearson , 2011 (Seventh edition)
- Organic Synthesis , J. Singh and L.D.S. Yadav, Pragati Prakashan, 2006.
- Organic Reactions and their mechanisms , P.S.Kalsi, New Age International Publication, 2008 (Second edition)

Unit-7

Reduction of Carbonyl and Carboxylic Group

Structure of Unit:

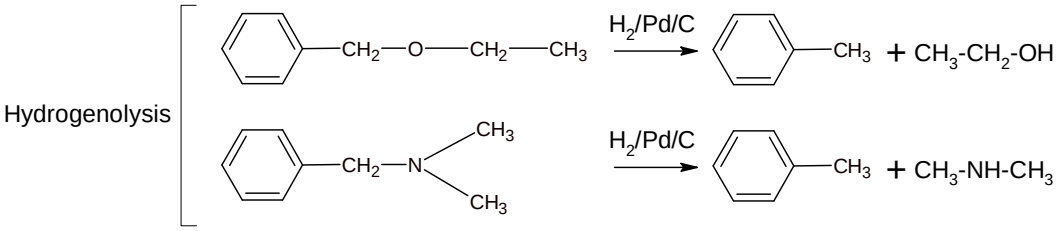
7.0 Objective

Reduction is a process of electronation of compound in a broder sence in general chemistry, while dealing with the organic compounds the reduction results in achange in the functional group of the compound to be reduced. this results in the synthesis of various organic compounds having different functionalities in the present unit the reduction of carbonyl compounds ,acids and their derivatives have been discussed nature of the reagents presence of other active groups and reaction conditions are the main points of concern.

7.1 Introduction

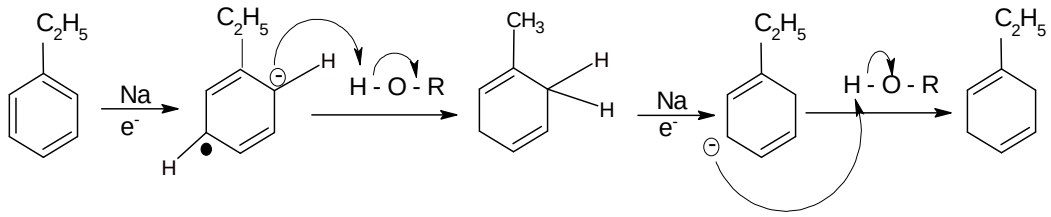
In organic chemistry reductions is defined as a process in which an increase in the hydrogen content or a decrease in the oxygen content occurs in an organic compound. It is for the reason the reduction is sometime called as hydrogenation and hydrogenolysis. All reduction processes involves three phenomenon, removal of oxygen, addition of hydrogen and the gain of electrons. Hydrogenation means the addition of hydrogen to an unsaturated system whereas hydrogenolysis means the addition of hydrogen with concomitant sulphur Viz:

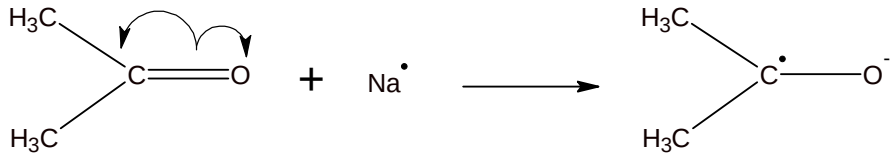
$$R-CH=CH_2+H_2 \xrightarrow{Catalysis} R-CH_2-CH_3;\ \text{hydrogenation}$$

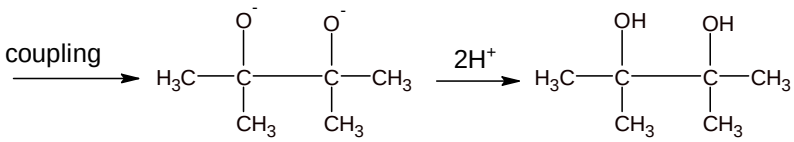


There are three mechanical routes for reduction. These are

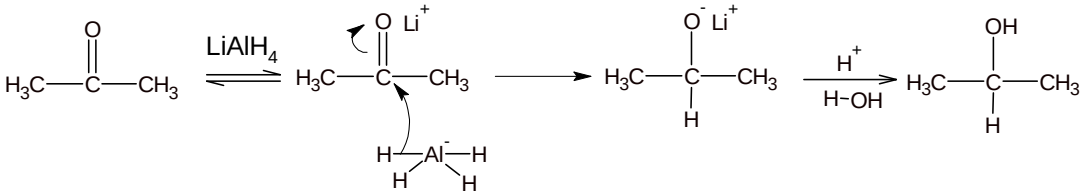
(A) Addition of electrons, followed either by update of H^+ or followed coupling Viz



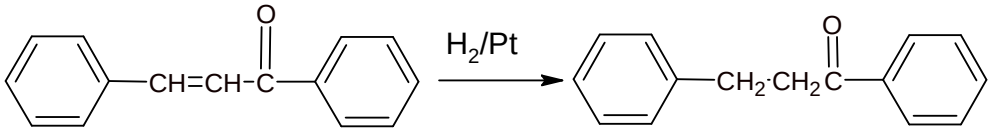




(B) There is and H^- transfer. This hydride ion comes from complex metal hydrides of Boron and Aluminium or from alkoxide of aluminium ie-

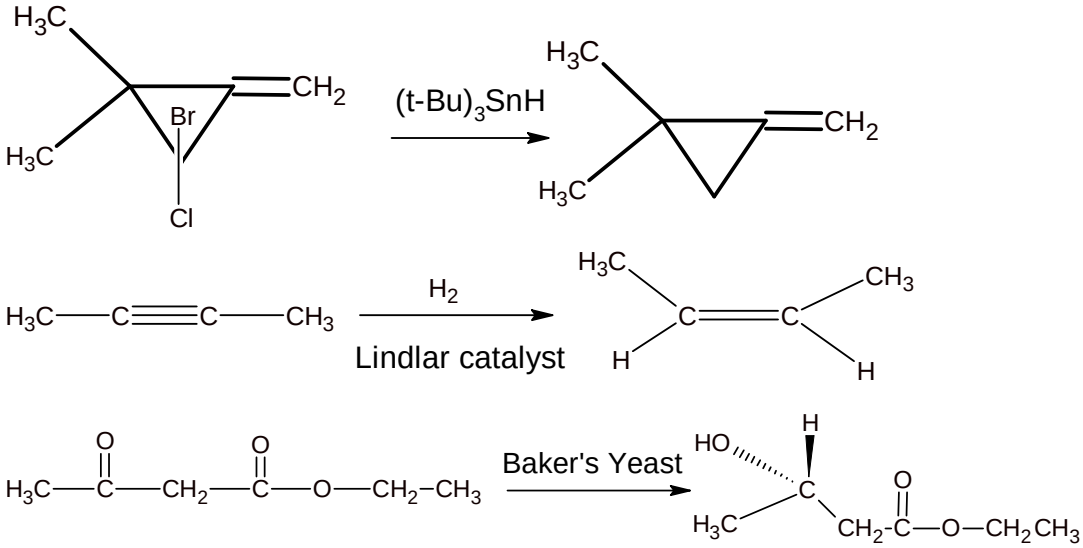


(C) This rotate involves the addition of molecular hydrogen in the presence of some catalyst such as palladium, Adams catalyst or raney nickel etc. for example



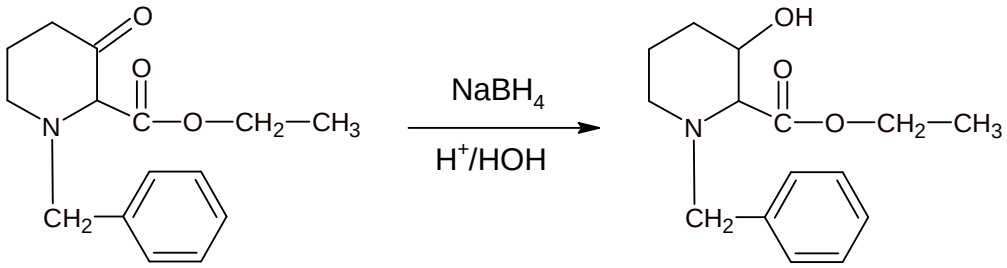
$$CH_3 - CH_2 - CH = CH - CH_3 \xrightarrow{H_2/Ni;\Delta} CH_3 - CH_2 - CH_2 - CH_2 - CH_3$$

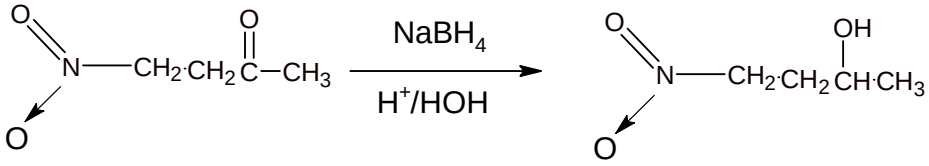
It is to be noted that each method of reduction has its own advantages. Complete reduction of an unsaturated compound can be done without any difficulty, however in selective reduction which involves a reduction of a particular group in the presence of other reducible group is of great importance Here the selectivity and stereochemistry of the product is the main points of concern. For example



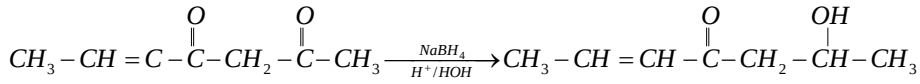
7.2 Reduction of Aldehydes and Ketones

Aldehydes on reduction give primary alcohols whereas ketones produce secondary alcohols. The reagents used for this purpose are lithium aluminium hydride or sodium borohydride. Although lithium aluminium hydride is a versatile and stron reducing agent and can reduce a wide range of organic functional groups like –COOH,_COOR,-$CONH_2$, epoxides etc but he main difficulty associated with the use of this reagent is that it catches fire when comes in contact with water or alcohol. On the other hand sodium borohydride is more specifically used for the reduction of aldehydes and ketones. It has a selective reducing effect in the sense that it reduces carbonyl group with affecting the C=C, C≡C, C≡N, ester, -N=N- and –NO_2 group present in the substrate molecule Viz.

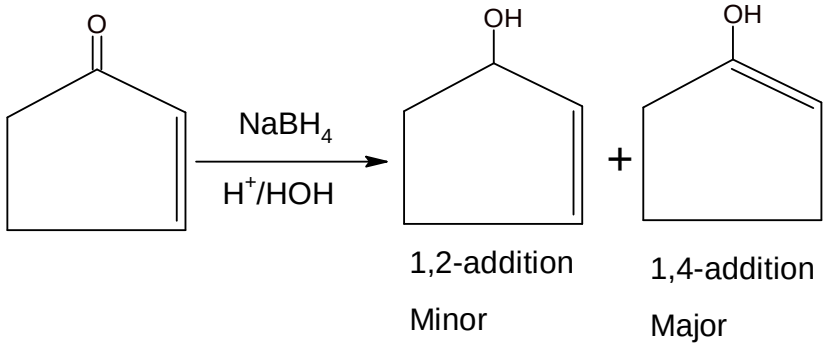




The selective reductive action of $NaBH_4$ is also observed when the compound to be reduced, contains carbonyl groups in different situations. For instance if a compound, containing carbonyl groups in conjugated and non conjugated position, is reduced with sodium borohydride, the non conjugated carbonyl group is reduced selectively. For example

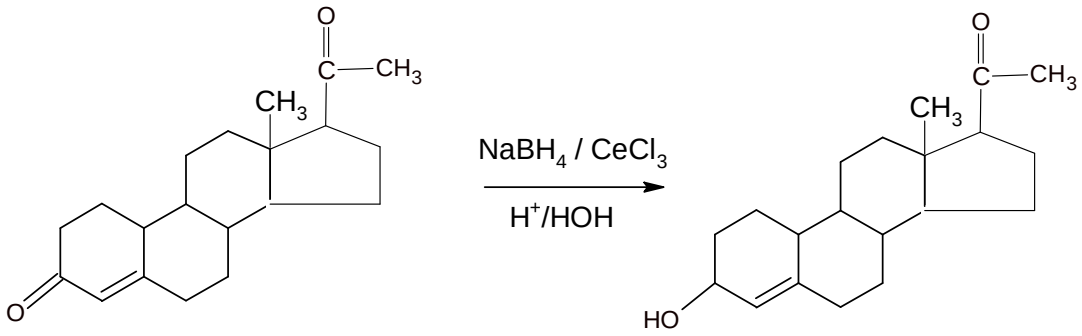


If the compound to be reduced is an $\alpha,\beta-$ unsaturated before it can give 1,2 as well as 1,4-addition product when treated with sodium borohydride.

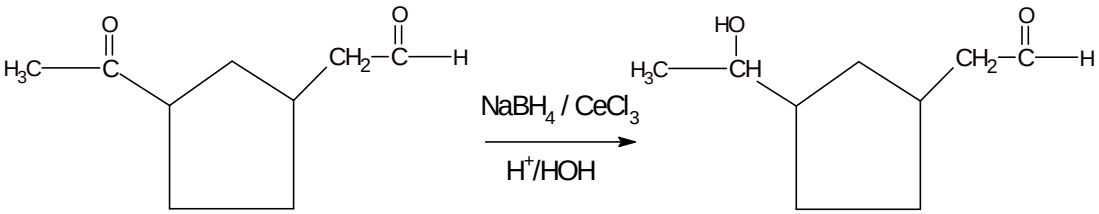


The above reaction,if carried out in the presence of traces of $CeCl_3$ gives 1,2-addition product only.

The use of $CeCl_3$ alongwith $NaBH_4$ makes thelater more selective reducing agent to reduce ketones in the presence of aldehyde. Thus a less reactive carbonyl group is selectively reduced. Viz-

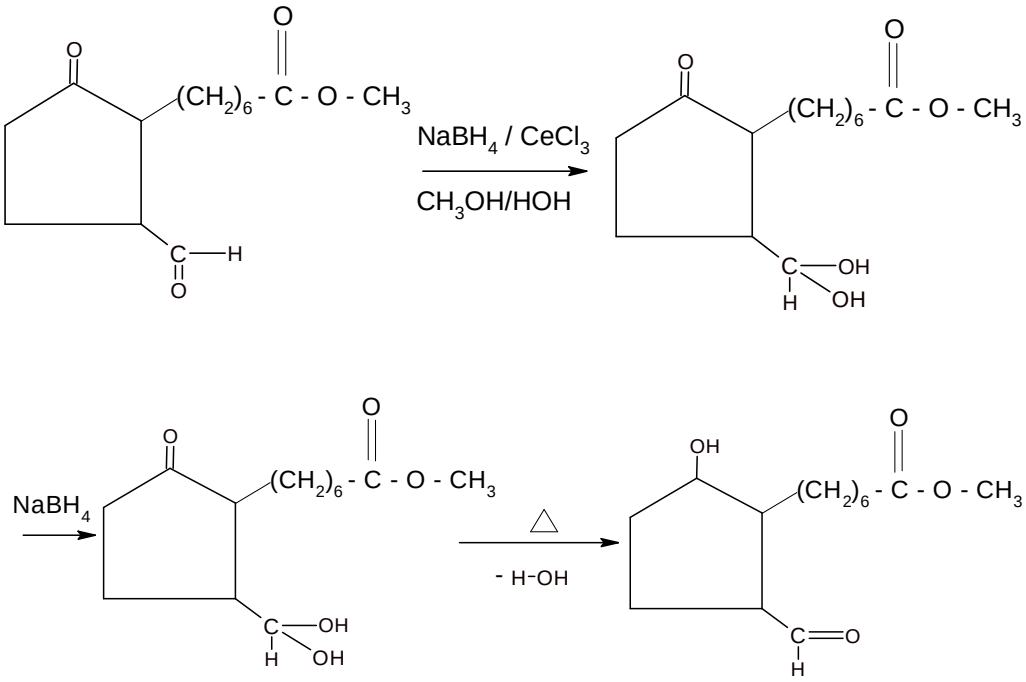


(α,β unsaturated ketonic group is reduced in the presence of saturated ketonic group)



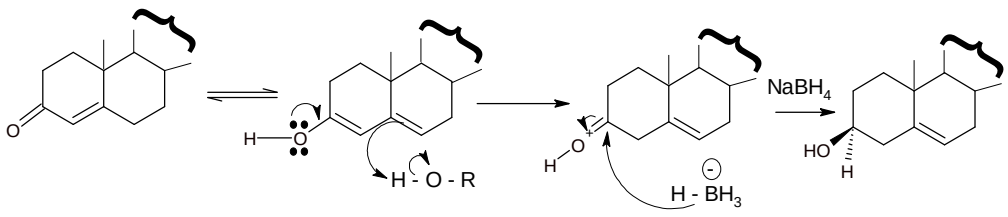
(Ketonic group is reduced in the presence of aldehyde group)

It is believed that when the substrate contains aldehyde and ketonic group the aldehyde group, being more reactive is protected through hydrate formation which inturn is stabilized through the process of complexation with Ce^{3+} ion and is then regenerated finally when the product is isolated.

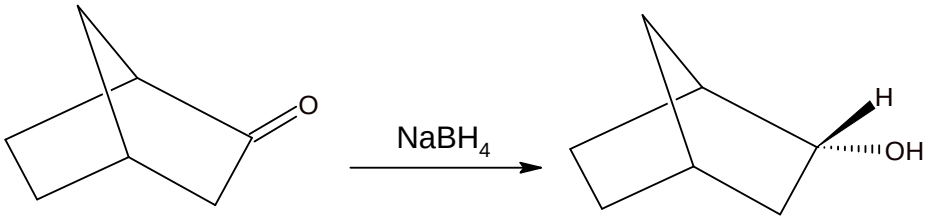


Although sodium borohydride is a less powerful reducing agent than lithium aluminium hydride but it has an advantage that unlike $LiAlH_4$ it can be used in protic solvents like HOH, CH_3OH etc. Indead in protic solvents its level of reduction becomes more high than by $LiAlH_4$ or $NaBH_4$ in aprotic solvents.

$NaBH_4$ reduces cholest -4-ene-3-one to cholesterol in protic solvents. In this reaction the reagent approaches the substrate from less hindered side to give a more stable alcohol.

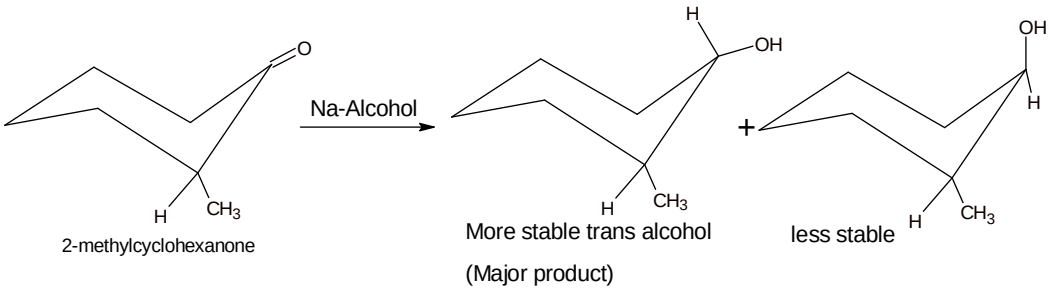


$NaBH_4$ gives when allowed to react with acyclic and cyclic ketones, the reduction product is a more thermodynamically stable alcohol provided the steric factor should not dominant against the approach of BH_4^- to the carbonyl group. If the steric factors dominate then a less stable alcohol is formed. For example norbornanone is reduced to a less stable alcohol because the BH_4^- attacks from less hundred exo side.



7.2.1 Reduction of carbonyl compounds with Na & C_2H_5OH

When cyclic ketones are reduced with sodium alcohol reduction method. The formation of that alcohol takes place which is thermodynamically more stable.For example when 2-methylcyclohexanone is reduced with sodium and alcohol the more stable trans alcohol is produced in 99% yield.

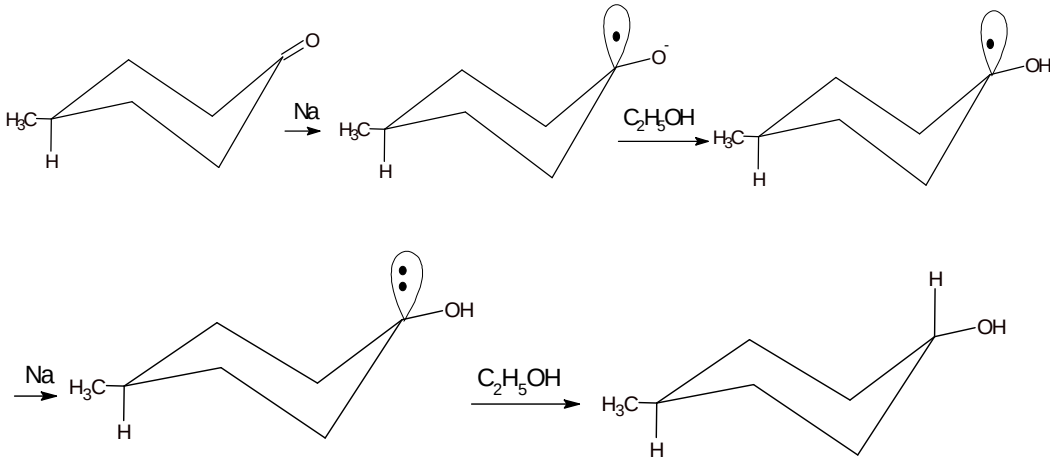


It is to be noted that the percentage of trans alcohols becomes 82% with $LiAlH_4$, 69% with $NaBH_4$ and 7-35% when reduction is carried out with hydrogen and catalyst.

To explain the formation of the above alcohol two mechanisms have been proposed .According to one view firstly a tetrahedral dianion is formed which adopt more stable configuration with equatorial oxygen is formed. This equatorial oxygen upon protonation produces more stable alcohol.

According to another view, the reaction proceeds by donation of one electron from Na to carbonyl group followed by a protonation on oxygen.

This produces a free radical intermediate which adopt a stable configuration with –OH group on equatorial side as shown below.



7.2.2 Reduction of carbonyl compounds with lithium aluminium hydride

Lithium aluminium hydride $LiAlH_4$ is prepared by the reaction of LiH with $AlCl_3$.

$$4LiH + AlCl_3 \xrightarrow{C_2H_5-O-C_2H_5} LiAlH_4 + 3LiCl.$$

Lithium aluminium hydride is a more powerful reducing agent than $NaBH_4$. It reacts with water and other compounds which contain active hydrogen ie,

$$LiAlH_4 + 4HOH \rightarrow LiOH + Al(OH)_3 + 4H_2$$

$$LiAlH_4 + 4C_2H_5OH \rightarrow LiOH + Al(OC_2H_5)_3 + 4H_2$$

$$LiAlH_4 + 4CH_3COOH \rightarrow LiOH + Al(OCOCH_3)_3 + 4H_2$$

$$LiAlH_4 + 4(CH_3)_2NH \rightarrow LiN(CH_3)_2 + Al\left[N(CH_3)_2\right]_3 + 4H_2$$

Because of its high sensitivity with water, it should be used under anhydrous condition and in a non-hydroxylic solvents. The solvents used are ethers and tetrahydrofurane (THF). It is a less selective reducing agent than $NaBH_4$.

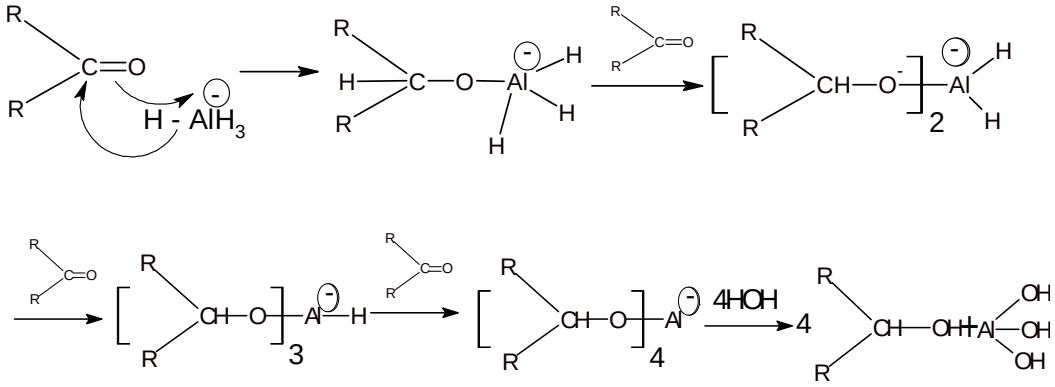
In the reduction of aldehydes and ketones by Lithium aluminium hydride the following steps are involved >

a) There is a H^- ion transfer from the nucleophile AlH_4^- to the carbon atom of the carbonyl group to produce alkoxytrihydroaluminate ion.

b) The above intermediate reacts with the second molecule of carbonyl compound to produce a dialkoxydihydroaluminate ion.

c) The above ion adds to third molecule of carbonyl compound to produce trialkoxyhydroaluminate ion.

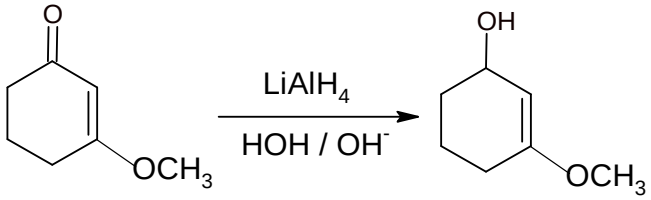
d) This step involve the involvement of foruth molecule of carbonyl compound to produce tetraalkoxyaluminate which now reacts with water or with 10% solution of NaOH or NH_4Cl to produce four molecules of the product alcohol. Schematically it is shown below.



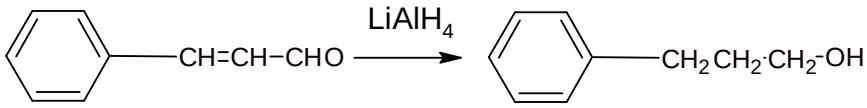
The above four step occur with a decreasing velocity order which makes it possible to carryout following reductions.

$$CH_3-(CH_2)_5-CHO \xrightarrow[HOH/OH^-]{LiAlH_4} CH_3(CH_2)_5-CH_2OH$$

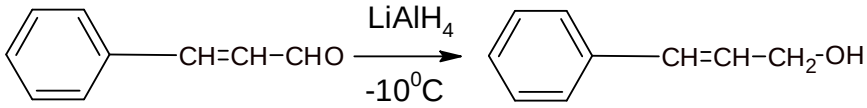
$$CH_3-CH=CH-\overset{\overset{O}{\|}}{C}-CH_3 \xrightarrow[HOH/OH^-]{LiAlH_4} CH_3-CH=CH-\overset{\overset{OH}{|}}{C}H-CH_3$$



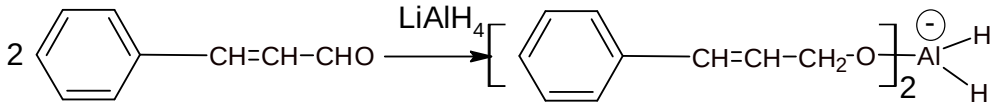
$LiAlH_4$ has no effect on carbon-carbon multiple bond but if the substrate is a $\beta-$ aryl or $\alpha,\beta-$ unsaturated compound then double bond is also get reduced.

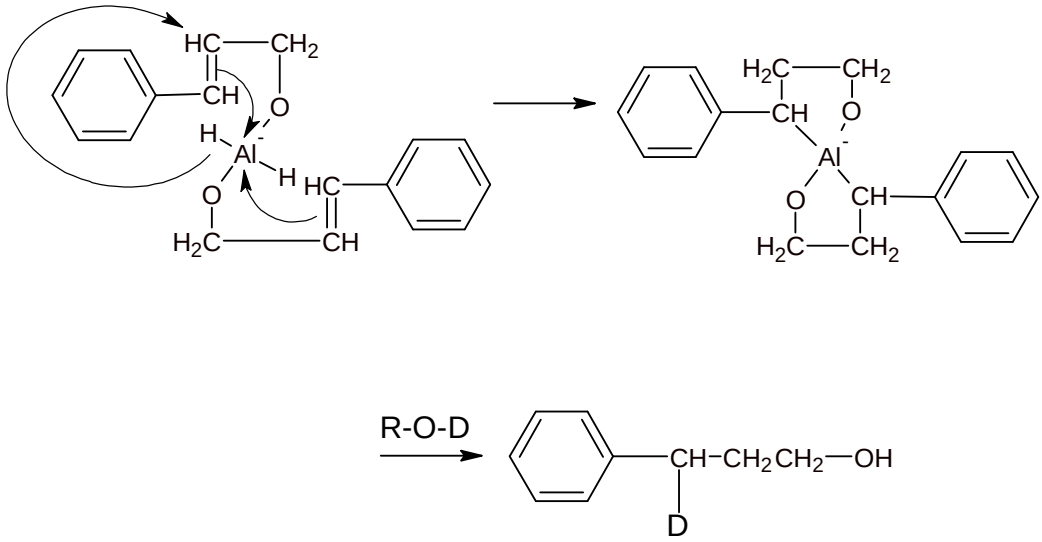


The reason for above is quite logical. It is known that a carbon-carbon multiple bond being electron rich and offers electrophillic attack whereas hydrideion is a nucleophile so it is repelled and fails to attack. However the presence of electron withdrawing aromatic ring on on side and that of a carbonyl group on other side os the carbon-carbon double bond makes it less electron rich and thus affords the attack of hydride ion on it and get reduced. Under such situation, a selective reduction can be carried out by carrying out the reaction at low temperature Viz-



In the reduction of aldehyde with $LiAlH_4$, firstly an allyl alcohol is formed. The reduction of the double bond occurs through the formation of cyclic organolithium compound which than reacts with allyl alcohol to produce the final product.Viz- Of the two hydrogen atoms needed for the reduction of double bond one hydrogen comes from the reagent and the other comes from the alcohol ie,

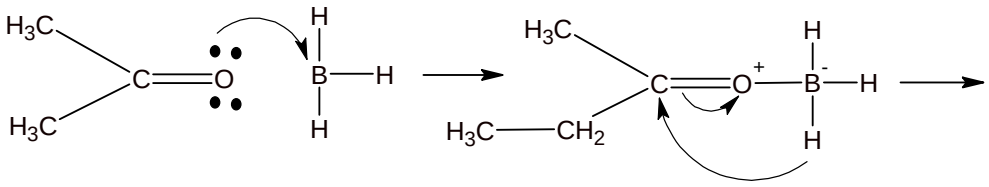


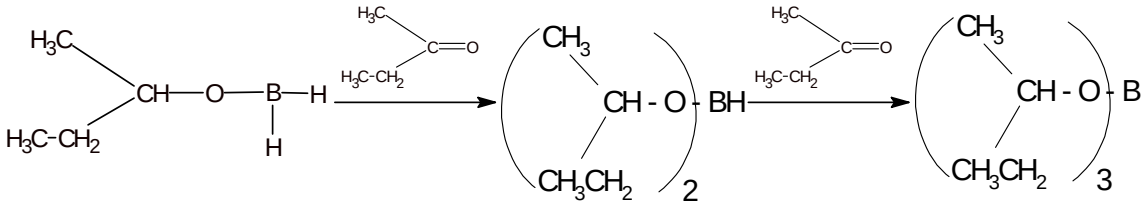


7.2.3 Reduction of carbonyl compounds by Boranes and alkylboranes

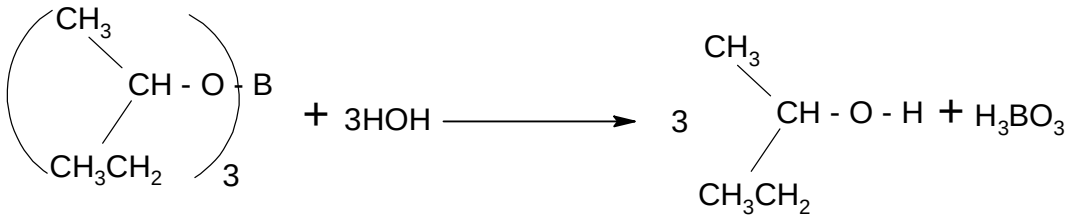
Borane, BH_3 is a strong reducing agent as it can reduce aldehydes and ketones at room temperature. Reduction followed by hydrolysis produces corresponding alcohols.

There is a remarkable difference in the reducing action of borane and that of $NaBH_4$ and $LiAlH_4$. The reason for this difference is that in case of $NaBH_4$ and $LiAlH_4$ the initial attacking reagent is nucleophile and it attacks through hydride ion (H^-) transfer to the electron deficient carbon atom but on the other hand BH_3 is a lewis acid (Boron with incomplete octet) and so attacks on the substrate at electron rich centre. Thus reduction of aldehydes and ketones by boranes occurs by the addition of BH_3 at carbonyl oxygen followed by the transfer of H^- from boron to carbon as shown below.

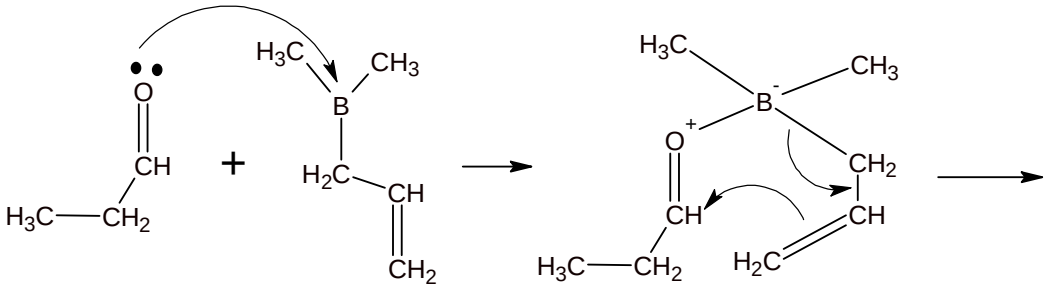


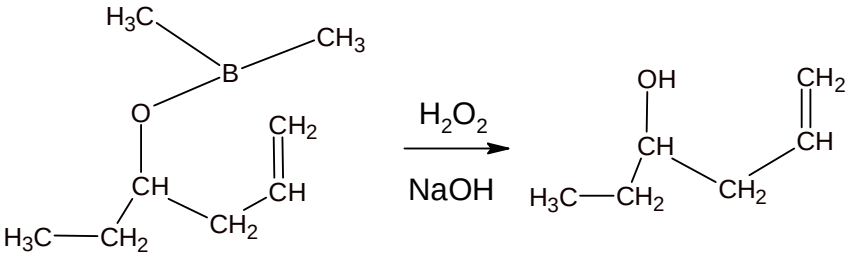


The trialkoxyborane so formed is then subjected to hydrolysis to give corresponding hydroxyl compound



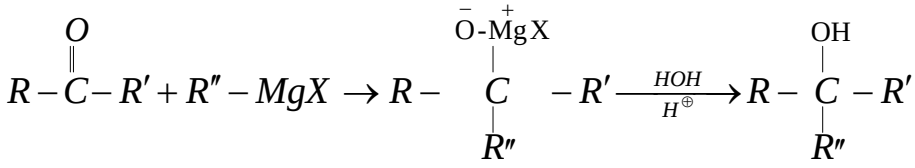
Reduction of aldehydes and ketones with allyl boranes takes place in a different way. The first step involves the coordinatation of electron deficient boron with carbonyl oxygen atom. This coordination brings about two effects. Firstly the carbonyl carbon becomes more electrophilic and secondly the allylic carbon-carbon bond becomes weaker which helps in its easy migration. The coordinated intermediate now gives [3,3] sigmatropic rearrangement. This results in a six membered transition state in which transfer of boron from carbon to oxygen takes place with the simultaneous formation of carbon-carbon bond. This is shown below.



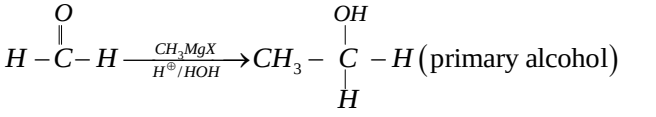


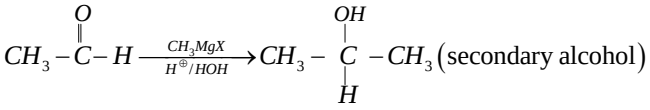
7.2.4 Reduction of aldehydes and ketones by Grignard's reagent followed by hydrolysis

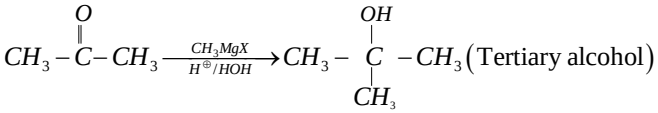
Following reaction shows the reduction of a carbonyl compound by Grignard's reagent



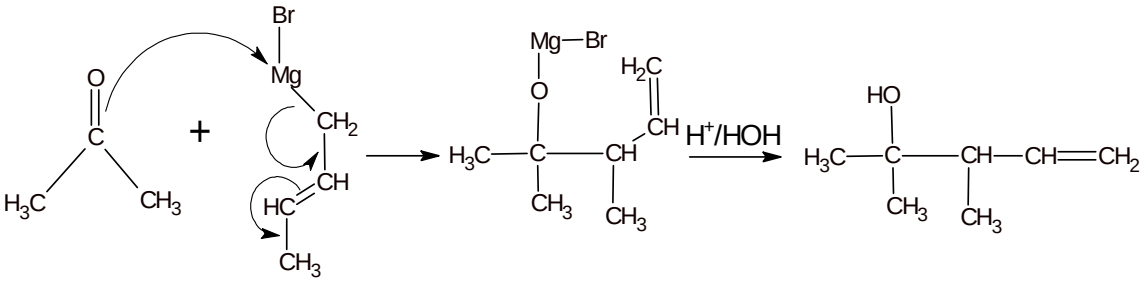
Thus





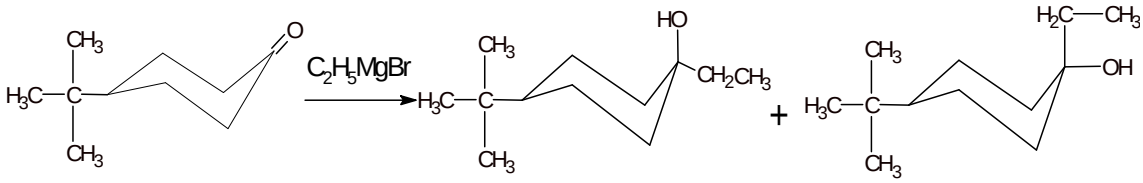


When the reduction of carbonyl compounds is carriedout with an allylic Grignard's reagent, there occurs an allylic shift through a six membered transition state as shown below.



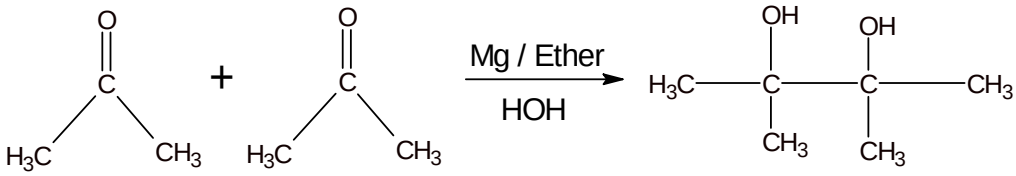
It is to be noted that reaction of a Grignard's reagent with a carbonyl group can create a stereocentre. If the carbonyl compound possess an adjacent stereocentre, one of the possible two diastereoisomers predominates. This occurs according to well known Cram's rule.

If the ketone is unhindered, as is the case with unhindered cyclohexanone, the Grignard's reagent prefers to attack from equatorial side to give an axial alcohol as the major product.



7.3 Reduction of ketones by Mg

Ketones are reduced by Mg-Ether. The product is an diol which is obtained after hydrolysis of the precursor.

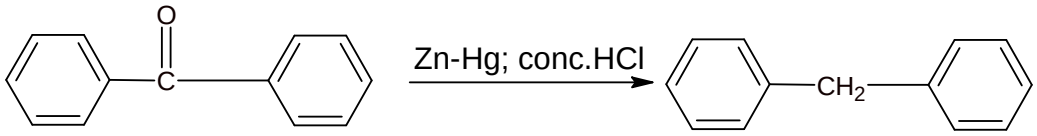


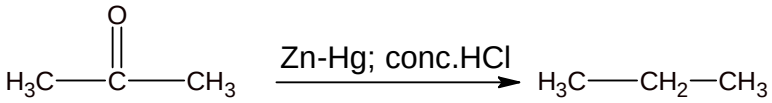
7.3.1 Reductive Deoxygenation of aldehydes and ketones

Reductive deoxygenation of aldehyde and ketones involves the removal of carbonyl group and its conversion to $>CH_2$ group in organic molecules. Several reagents are available for the complete reduction of $>C=O$ group to $>CH_2$ group. The choice of the reagent depends upon the sensitivity of the aldehyde and ketone to be reduced. Following methods are available.

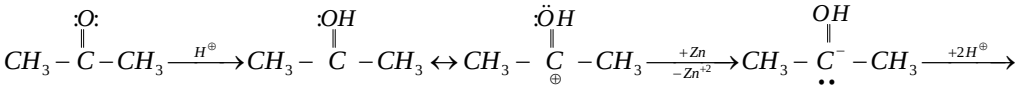
7.4 Clemmensen method

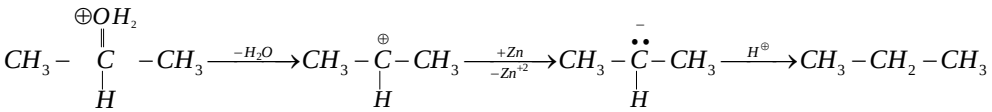
In clemmensen reduction the carbonyl group of aldehydes and ketones is reduced to methylene group ($\diagup\!\!\diagdown CH_2$) with amalgamated zinc and conc. Hydrochloric acid.





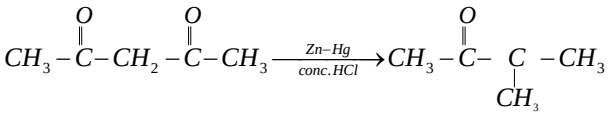
The carbonyl compound to be reduced is refluxed with amalgamated zinc and and excess of conc.hydrochloric acid. Ketones are reduced more easily than aldehydes. This reduction, however fails with acid-sensitive aldehydes and ketones and also for those carbonyl compound which have high molecular weights. If there is an unsaturation at $\alpha,\beta-$ position, both the olefinic system and carbonyl group is reduced. The reduction is specific if aldehydes and ketones contains other functional group and reducible groups. clemmensen reduction is specially useful for those ketones which contain phenolic or carboxylic group because these groups remains unaffected Various mechanism have been proposed. The most accepted mechanism is due to Nakabayaski who suggested that under acidic conditions of the reaction the carbonyl group of te substrate is protonated and then the electrons are transferred to it by metal. Viz-



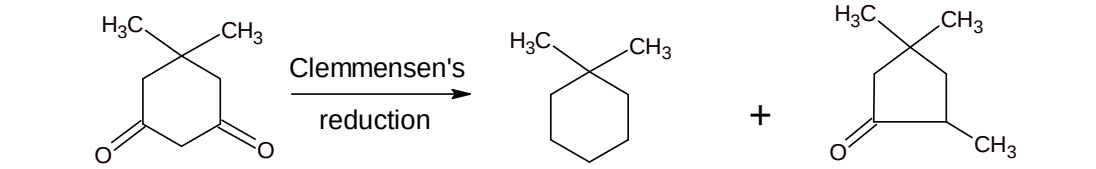


Certain types of carbonyl compounds do not produce normal products. For example α-hydroxy ketones give either ketones through hydrogenolysis because of the cleavage of carbon-heteroatom bond by catalystic

hydrogenation whereas 1,3 diketone (β-ketones) gives monoketones with rearrangement. Viz-

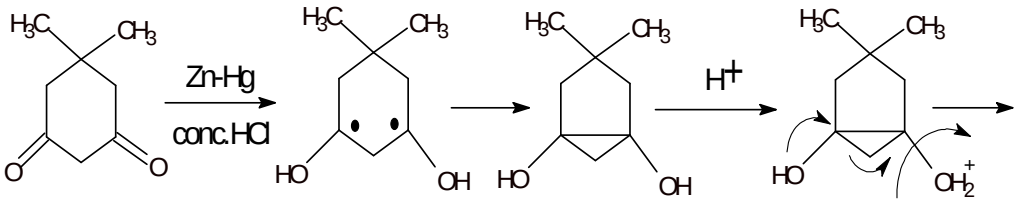


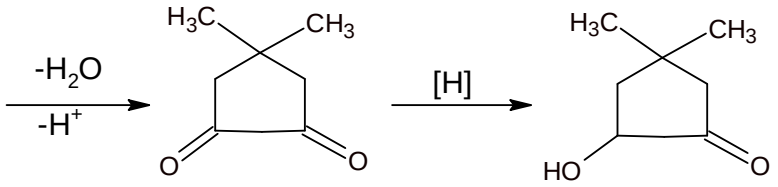
Some cyclic 1,3-diketones give a fully reduced product when subjected to clemmensen reduction. A monoketone with ring contraction is also produced. For example



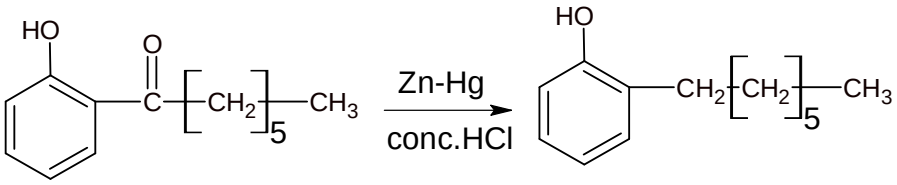
5,5-dimethylcyclohexane-1,3-dione 1,1-dimethylcyclohexane 2,4,4-trimethylcyclopentanone

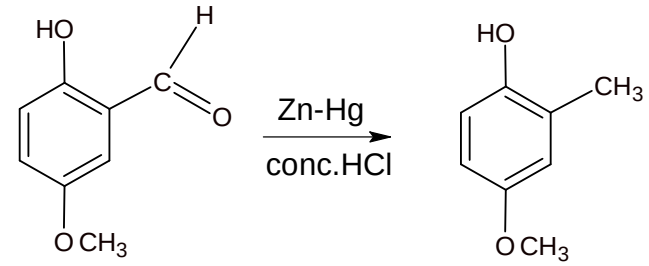
It is assumed that the monoketone is produced through a diradical with subsequent intermolecular carbon-carbon bond formation and pinacal type rearrangements.

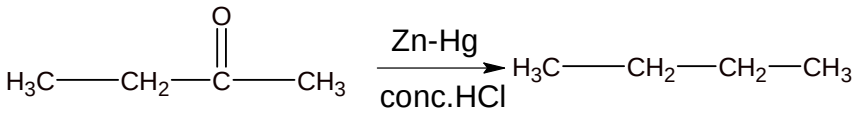




Other examples of Clemmensen's reduction are



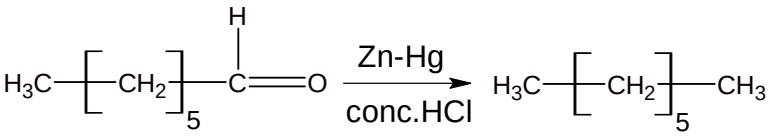


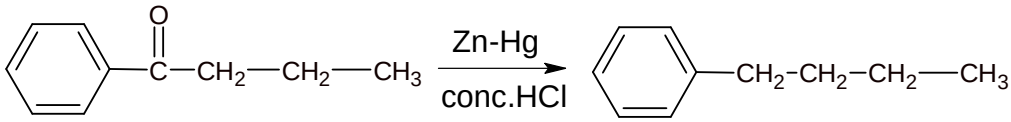


7.4.1 Applications of Clemmensen's reduction

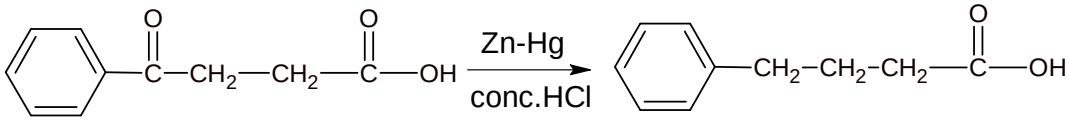
Clemmensen's reduction has following synthetic applications

(i) Aliphatic and mixed aliphatic aromatic carbonyl compounds can be reduced. Viz-

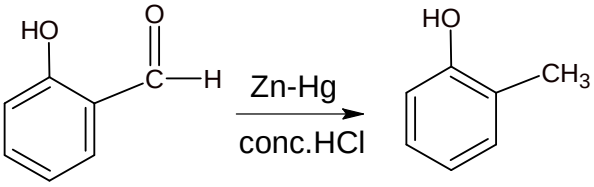




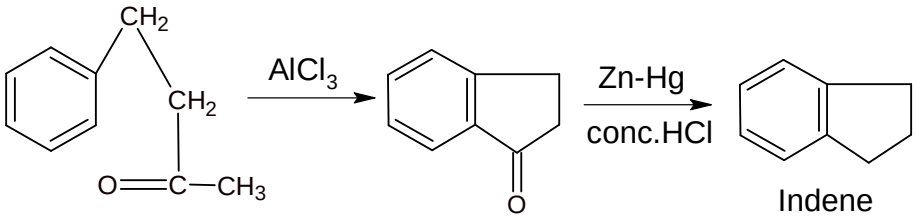
(ii) keto acids can be reduced.



(iii) Phenolic carbonyl compounds can be reduced

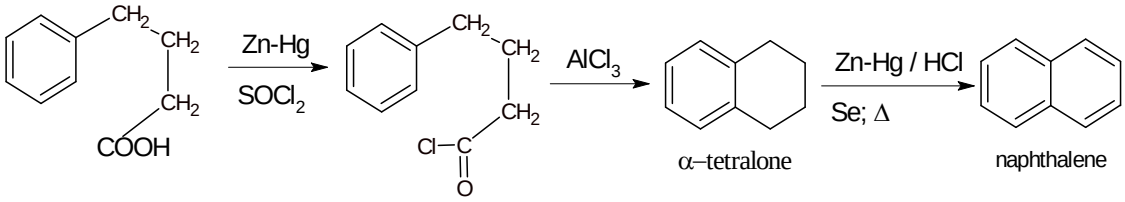


(iv) Cyclic ketones can be reduced



Indene

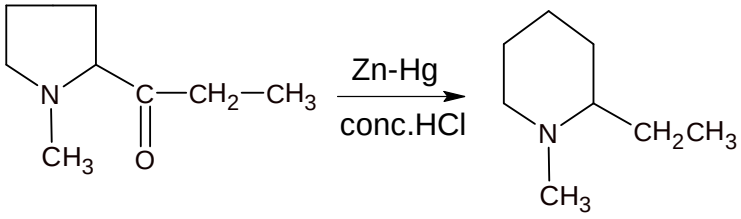
(v) Nephthanlene can be synthesized

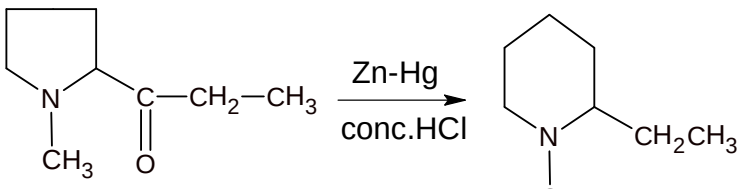


α–tetralone

naphthalene

(vi) Reduction with ring expansion can be affected

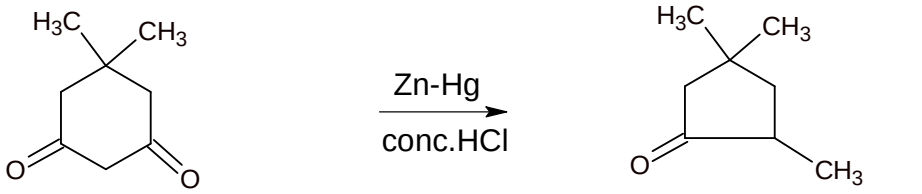




1-Methyl-2-propionyl pyrrolidine

2-ethyl-1-methylpiperidine

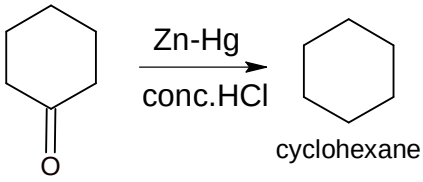
(vii) Reduction with ring contraction may be affected



5,5-dimethylcyclohexane-1,3-dione

2,4,4-trimethylcyclopentanone

(viii) Cycloparaffins can be synthesized



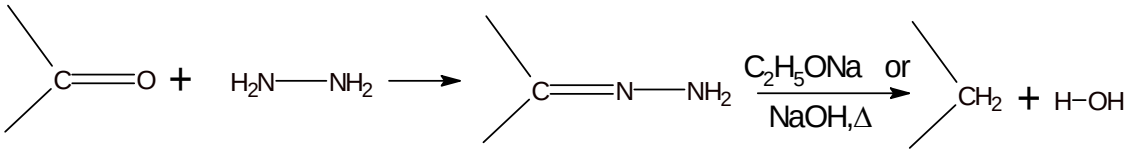
cyclohexanone

cyclohexane

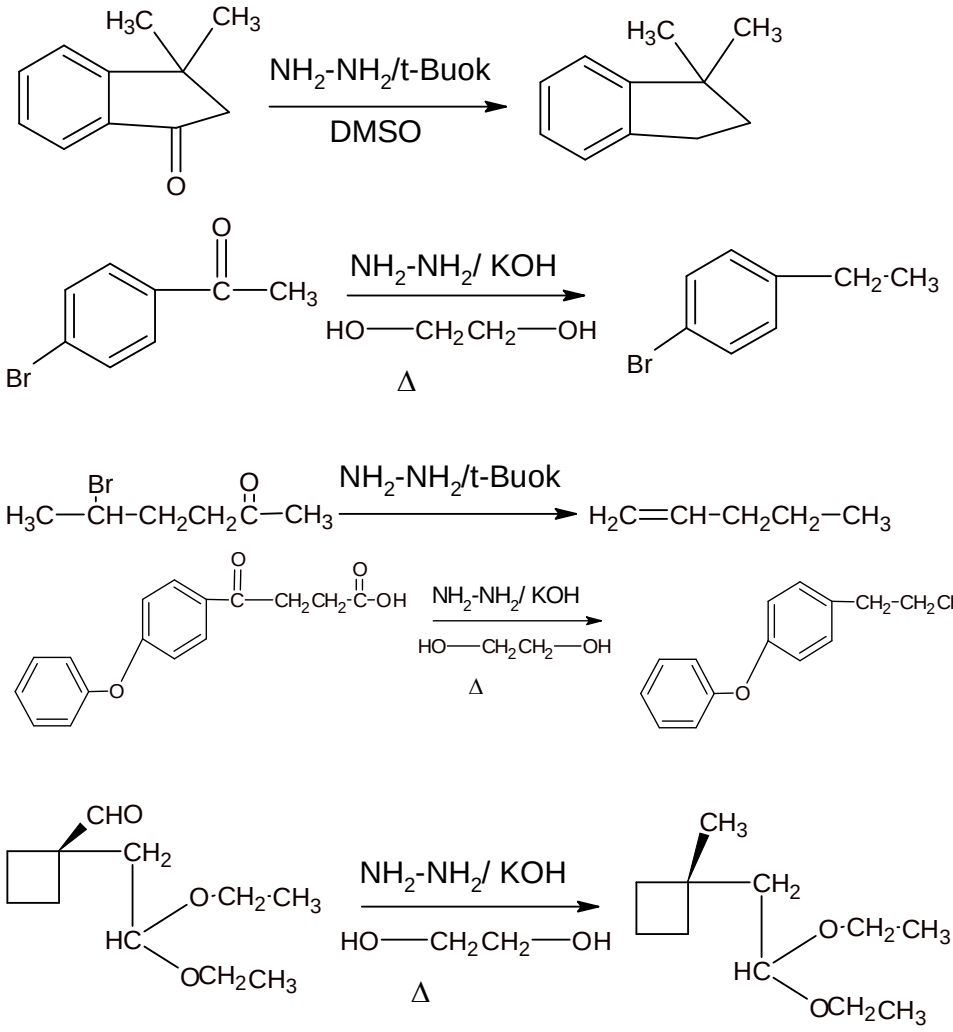
7.5 Wolff-Kishner reduction

Reduction of $>C=O$ group of aldehydes and ketones into $>CH_2$ group by heating their hydrazones, semicarbazones and azines in the presence of strong base like C_2H_5ONa or NaOH is called as wolf-kishner reduction. The solvent used in the reaction is diethylene glycol. The water formed in the reaction causes a lowering in the boiling point of the mixture consequently the reaction can go to completion by distilling out the water formed.

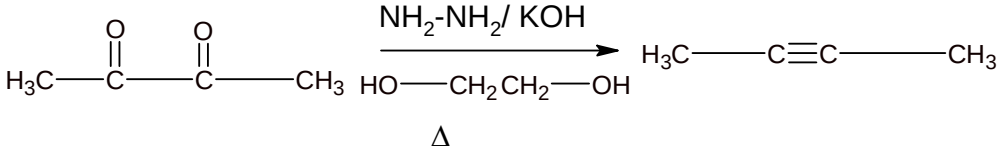
Wolf-kishner reaction takes place in strongly basic conditions and so it can be used for those aldehydes and ketones which are sensitive towards for acids. On the other hand it is unsuitable for those carbonyl compounds which are sensitive towards alkalies. The reaction can be represented as



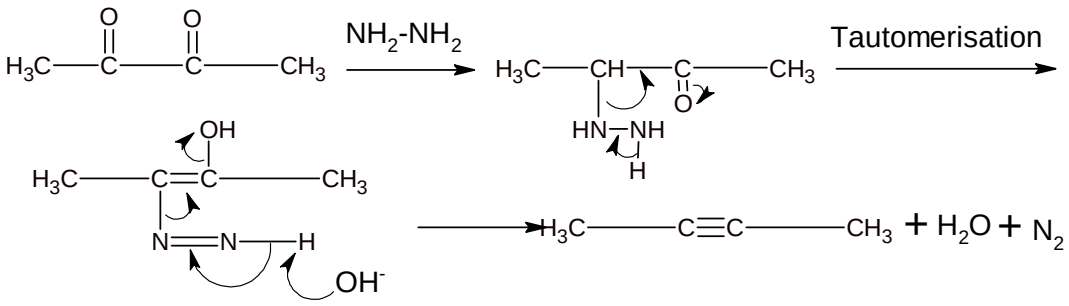
The reduced product is obtained in excellent yield if potassium t-butoxide is used in D.M.S.O. carbonyl compounds containing base sensitive halo group tosyl groups etc are not found suitable for Wolff-kishner reduction.



In case of α diketones the reduced product is alkynes

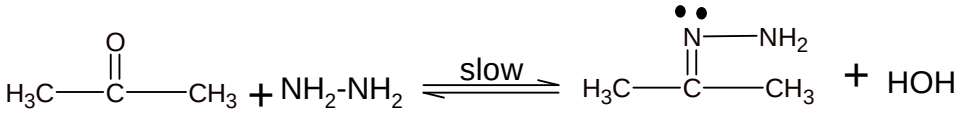


It is believed that reaction takes place as follows



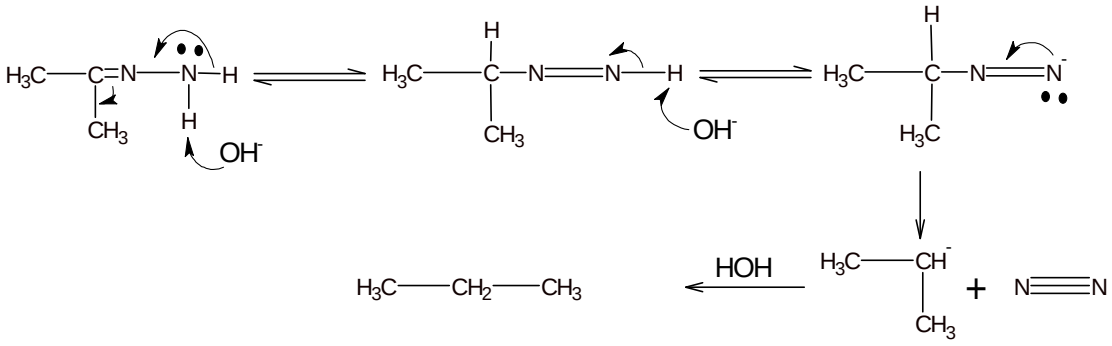
The mechanism of Wolff Kishner reduction takes the following route.

Step I : In this step the hydrazine reacts with the carbonyl compound to produce corresponding hydrazone.

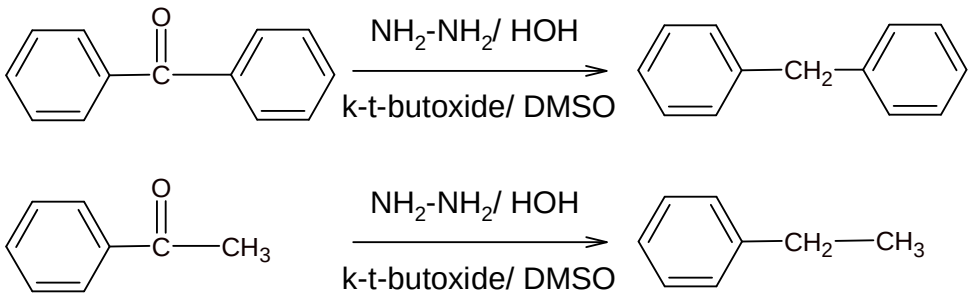


The hydrazone formed is isolated in the free state by removing the water

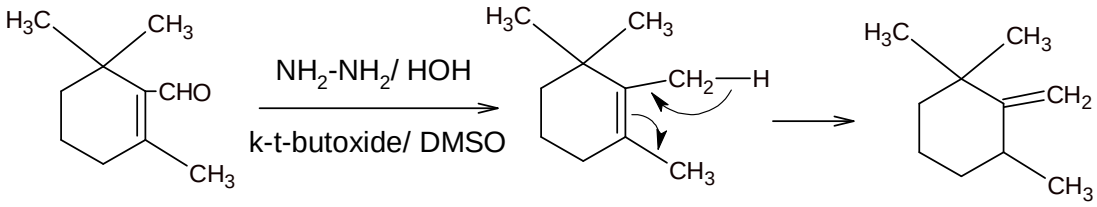
Step II : This step involves tautomerisation of hydrazone and elimination of nitrogen in presence of a strong base. Viz-



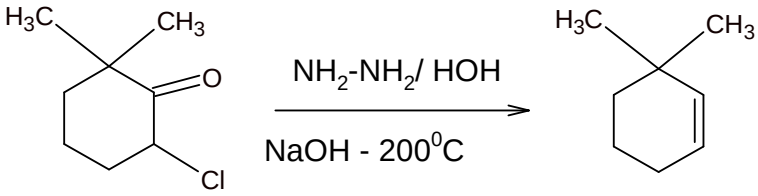
Wolff Kishner reduction occurs of very elevated temperature but can be carried out at comparatively low temp. by heating a mixture containing hydrazine hydrate, carbonyl compound and KOH in ethylene glycol. Even potassium –t-butoxide is used in DMSO. This modification has been made by Huang-Minlon. Viz-



If we take conjugated or unsaturated carbonyl compound, a shift in the position of double bond is observed ie,



If a carbonyl compound have a good leaving group at α position, elimination also occurs simultaneously



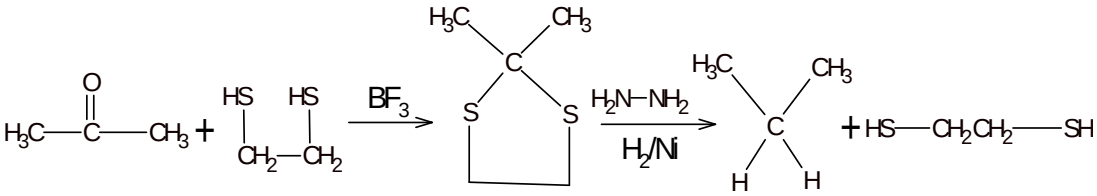
Clemmensen's and Wolf Kishner reduction cannot be used for those carbonyl compounds which are sensitive to both acids and alkalies. In such cases the reduction of $>C=O$ group to $>CH_2$ group is done by Mozingo-method. Which runs as follows

$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[H_2/Ni]{HS-CH_2-CH_2-SH;C_2H_5-O-C_2H_5;BF_3} CH_3-CH_2-CH_3$$

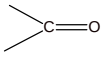
Or

$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[NH_2-NH_2;\Delta]{HS-CH_2-CH_2-SH;C_2H_5-O-C_2H_5;BF_3} CH_3-CH_2-CH_3$$

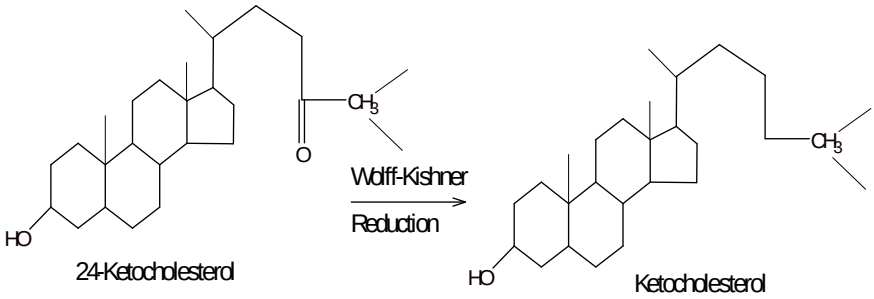
The reactions occurs as follows



7.5.1 Applications of Wolff-Kishner reduction

Wolff – Kishner reduction which mainly converts a  group to  group has following synthetic application.

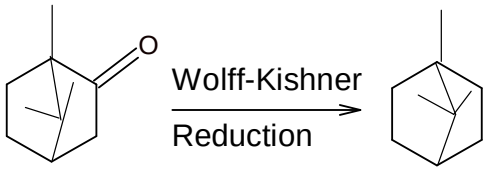
(i) It can be employed for the reduction of high molecular but carbonyl compounds



24-Ketocholesterol

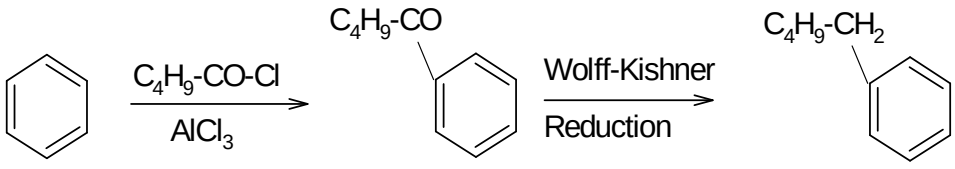
Ketocholesterol

(ii) It can be used to reduce camphor to comphane

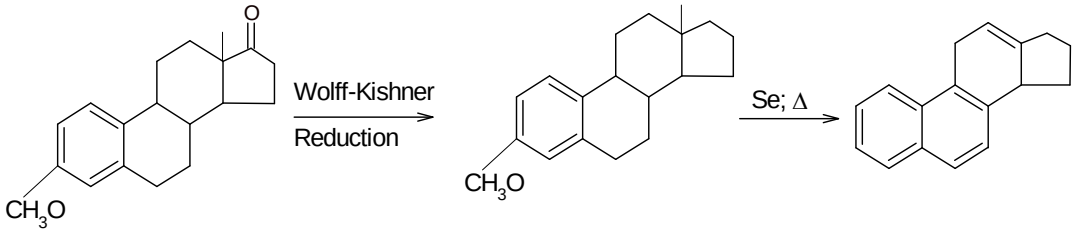


Camphore

(iii) Long alkyl straight chains can be introduced in benzene ring with the help of Wolff kishner reaction coupled with Freidal Crafts acylation as shown below



(iv) It can be used in the determination of structure of oestrone by the following sequence.



7.6 Meerwain-ponndorf- verley reduction

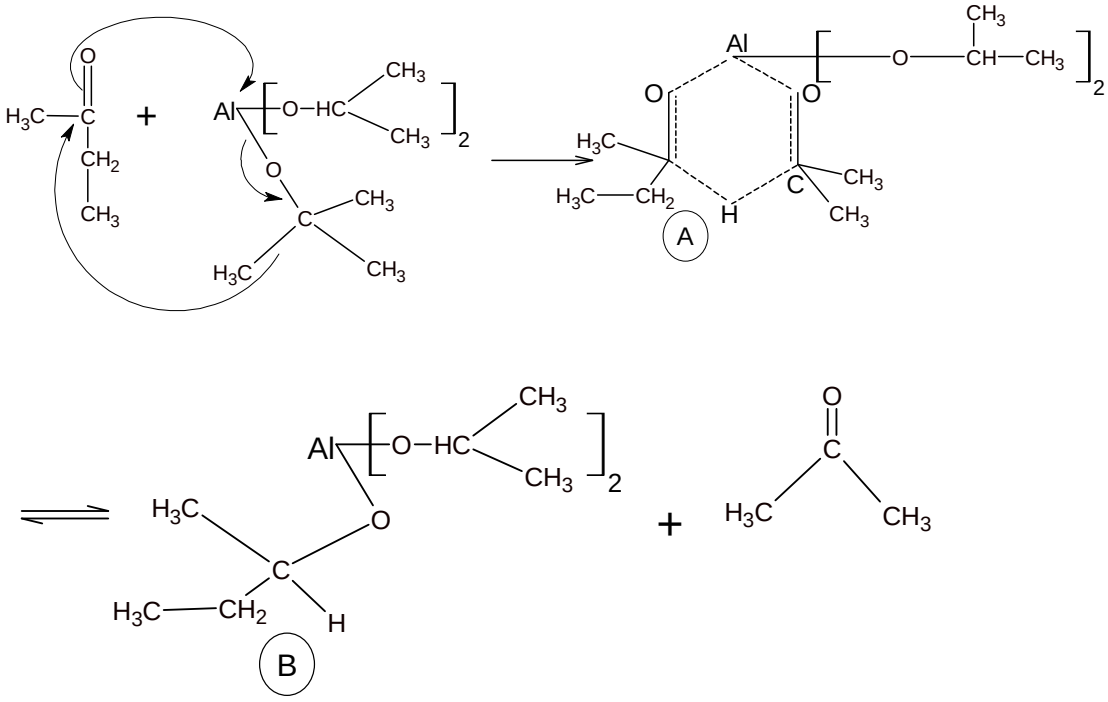
In this reaction of reduction of aldehydes and ketones the carbonyl compound is treated with aluminium isopropoxide in excess of isopropyl alcohol. The product are corresponding alcohols.

$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-CH_3+CH_3-\overset{OH}{\overset{|}{C}}H-CH_3 \xrightarrow{Al(i-tropoxide)} CH_3-\overset{OH}{\overset{|}{C}}H-CH_2-CH_3+CH_3-CO-CH_3$$

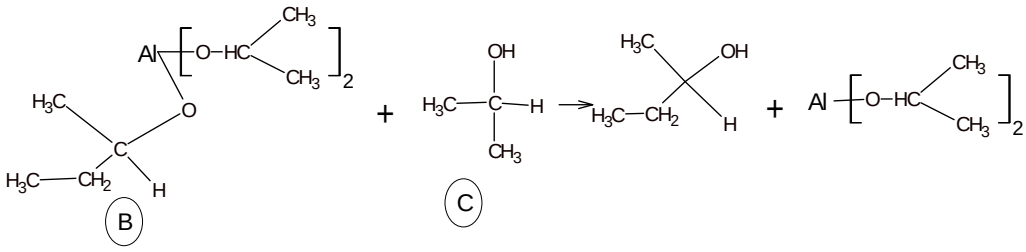
The reaction is reversible and can be shifted in forward direction by removing the acetone formed through distillation. The reaction is rapid, with high yield of product and has no side reactions. The reaction is specific for carbonyl group reduction because other reducible groups, if present in the substrate, remain unaffected. Even one carbonyl group out of the two present in the substrate can be protected through acetal formation. The reaction is not shown by β-diketones, β-ketoesters etc.

Mechanism

The accepted mechanism suggest that firstly a cyclic transition state (A) of formed in which there occurs a migration of H^- from α-C-H bond of the alkoxide takes place to the carbonyl carbon to produce a mixed alkoxide (B). Now the excess of isopropyl alcohol undergoes exchange with the mixed alkoxide (B) to liberate the reduced product (C) which is an alcohol. The whole sequence is shown below.



Now,



The hydride ion (H^-) transfer has been proved analytically by using deuterium which is a strong evidence in the favour of the formation of a cyclic transition state. As a modification of the reaction various metal alkoxides have been used but aluminium isopropoxide has been found to be the best reagent.

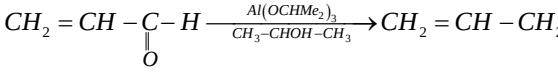
Actually aluminium alkoxides are much less polar than other alkali-metal alkoxide and contains a considerable covalent character. This hinders its dissociation to produce free alkoxide ion which otherwise will polymerise the carbonyl compound used in the reaction. This also reduces the possibility of side reactions to occur. Lastly the removal of acetone by distillation shifts

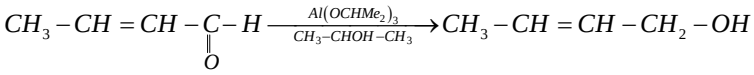
the equilibrium to forward direction and thus the reaction goes to competition without any complication.

7.6.1 Applications

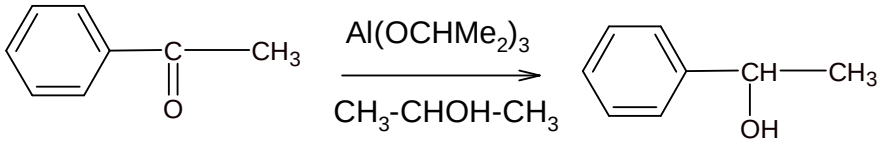
Meerwein-Ponndorf-verley reaction has numerous synthetic applications. Some of them are listed below.

(i) α,β unsaturated aldehydes can be reduced to corresponding α,β unsaturated alcohols

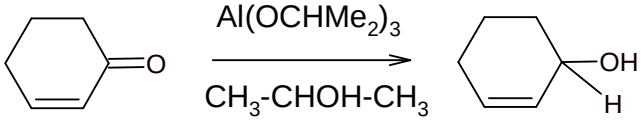




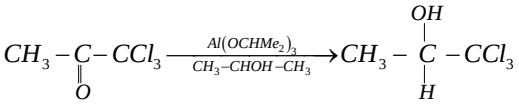
(ii) Aromatic ketones can easily be reduced to corresponding alcohols



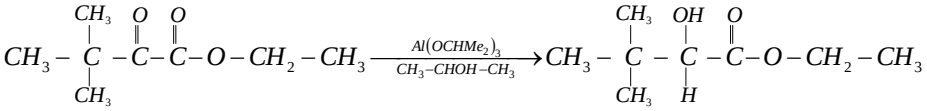
(iii) Alicyclic ketones can also be reduced



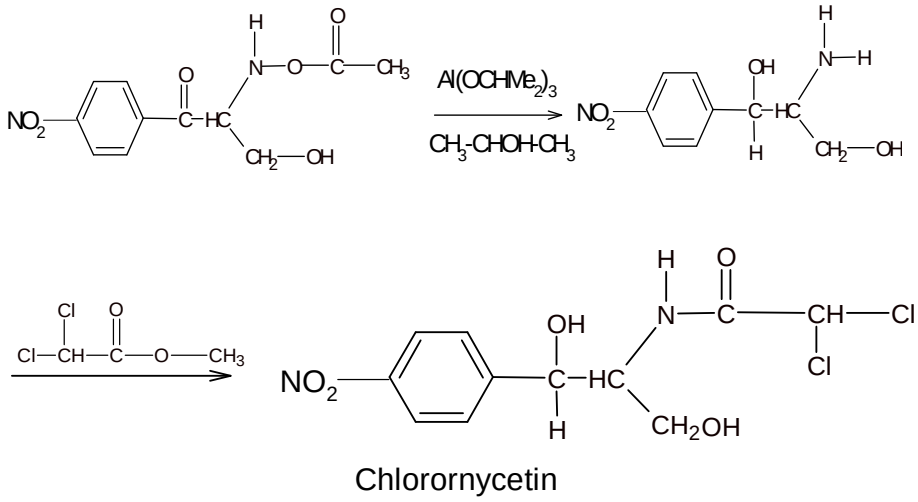
(iv) α - halogenated ketones can be reduced



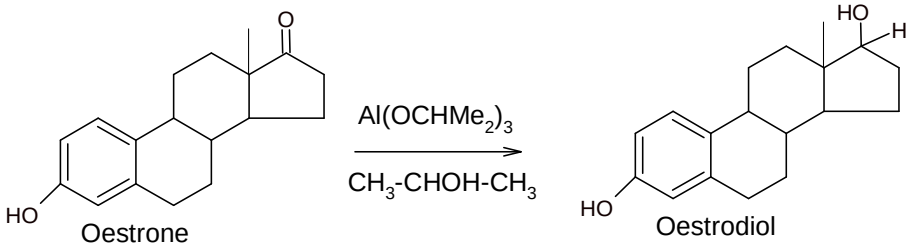
(v) Ketoesters can be reduced



(vi) compounds like chloromycatin can be synthesized



(vii) Oestradiol can be synthesized



7.7 Reduction of carboxylic acids and their Derivatives

Reductions of carboxylic acids and their derivatives have been systemtically described below

7.7.1 Reduction of carboxylic acids

Reduction of carboxylic acids can be carried out with the help of following reagents.

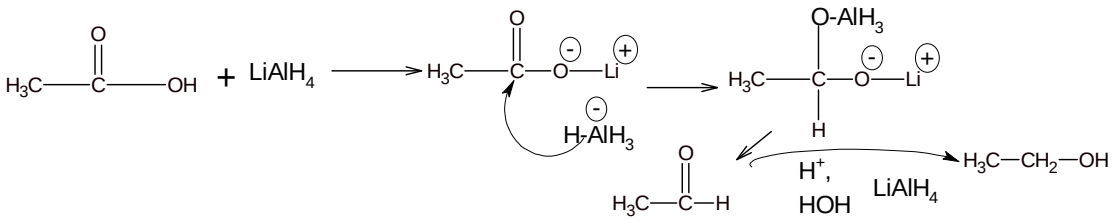
Lithium aluminium hydride

$LiAlH_4$ reduces carboxylic acids to corresponding primary alcohol. Viz-

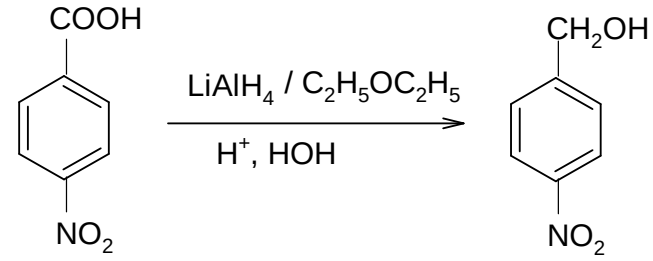
$$CH_3-(CH_2)_4-COOH \xrightarrow[H^{\oplus}/HOH]{LiAlH_4} CH_3-(CH_2)_4-CH_2-OH$$

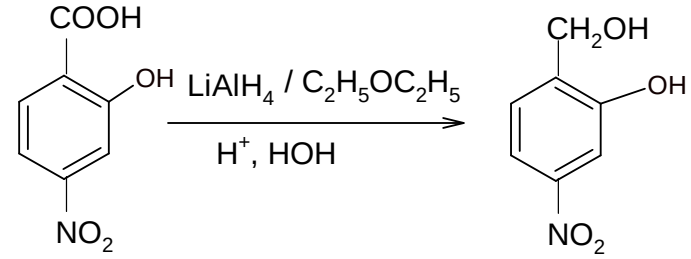
$$HOOC-(CH_2)_4-COOH \xrightarrow[H^{\oplus}/HOH]{LiAlH_4} HO-CH_2-(CH_2)_4-CH_2-OH$$

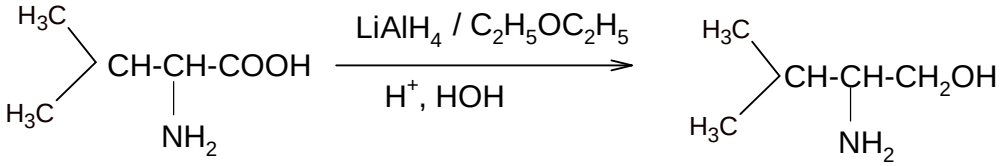
During reductions the acid is firstly reduced to aldehydes which then finally produces corresponding alcohol. Viz-



Being least reactive, acids are more difficult to be reduced than their derivatives. Thus vigorous condition to be reduced than their derivatives. Thus vigorous conditions are needed. Moreover because $LiAlH_4$ is not a selective reducing agnets, it reduces other reducible group like carbonyl ester, amide, cyanide etc if present in the acid eg:



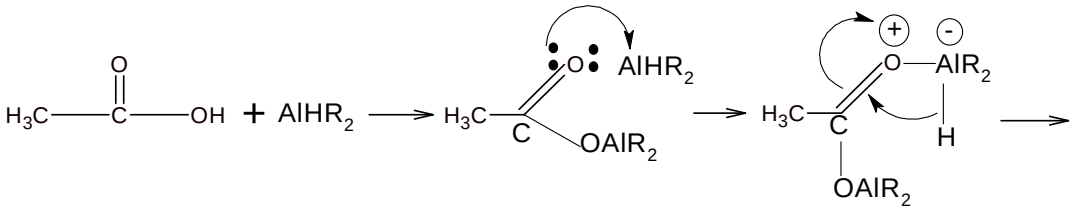


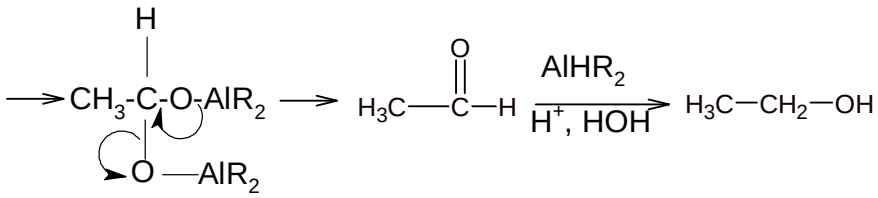


a. Alanes : Alanes is a group of reducing agents of which $(CH_3)_2AlH$ and disobutyl aluminium hydride (DIBAL-H) are most commonly used.

$$CH_3-(CH_2)_4-CH_2-COOH \xrightarrow[Benzene,25^0C]{DIBAL-H} CH_3-(CH_2)_4-CH_2-CH_2OH$$

In these reactions the acids show maximum reactivity for reduction. The mechanism follows following route.



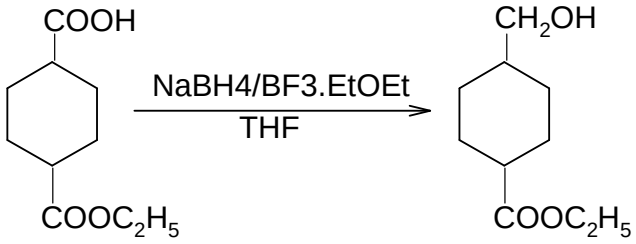


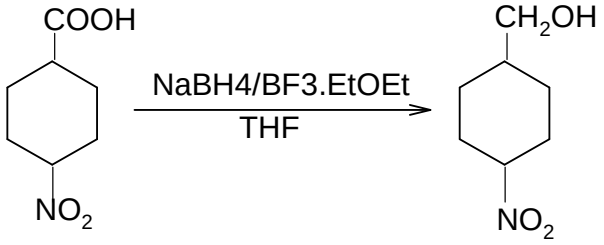
(i) Diborane

Diborane is found to be a useful reducing agent for acids and reduces them to primary alcohols. Contrarory to $LiAlH_4$ it reacts fastely with acids. Viz-

$$CH_3-\overset{O}{\overset{\|}{C}}-O-\underset{\underset{COOC_2H_5}{|}}{\overset{\overset{CH_3}{|}}{\underset{|}{C}}}-CH_2-COOH \xrightarrow[THF]{BH_3} CH_3-\overset{O}{\overset{\|}{C}}-O-\underset{\underset{COOC_2H_5}{|}}{\overset{\overset{CH_3}{|}}{\underset{|}{C}}}-CH_2-CH_2-OH$$

It is to be noted $NaBH_4$ doesn't reduce free carboxylic group but borane converts acid to alcohols at room temperature. For example



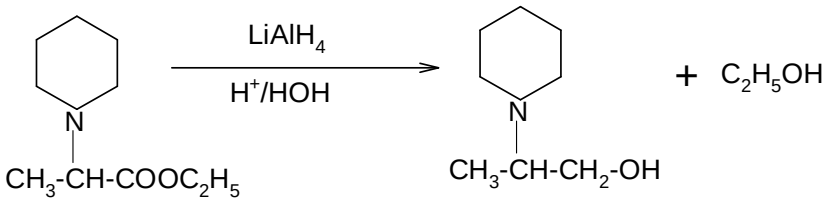


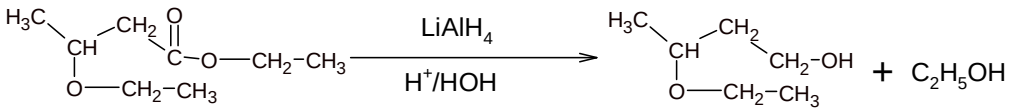
7.7.2 Reduction of esters

The common reducing agents used for the reduction of esters are $LiAlH_4$, diisobutyl aluminium hydride and lithium borohydride.

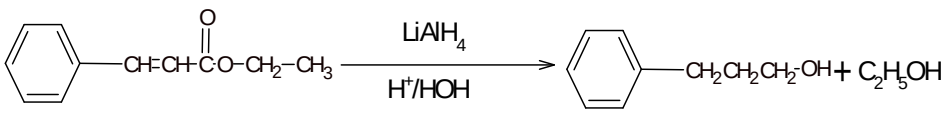
Lithium aluminium hydride

$LiAlH_4$ reduces esters to corresponding alcohols.



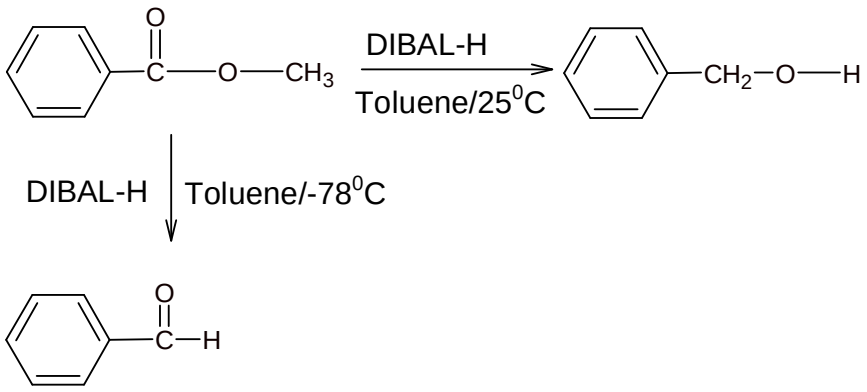


In case of α,β - unsaturated ester the double bond is also reduced.

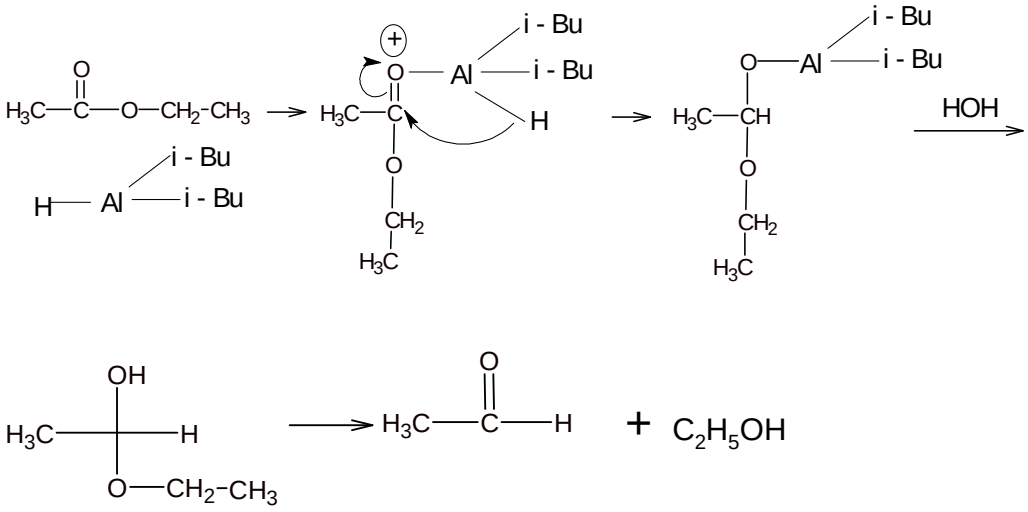


$$CH_3-CH=CH-COOC_2H_5 \xrightarrow[H^+/HOH]{LiAlH_4} CH_3-CH_2-CH_2-CH_2OH + C_2H_5OH$$

DIBAL-H reduces esters to alcohol at ordinary temperature but at low temperature esters and lactones are easily reduced to aldehydes.



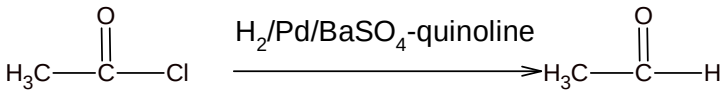
The mechanism has following route.



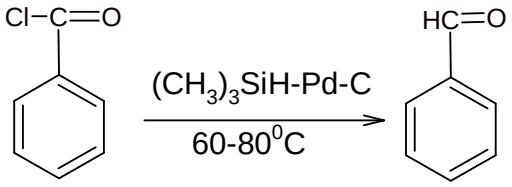
7.7.3 Reduction of acid chlorides

Acid chlorides can easily be reduced. The product is either aldehyde or a alcohol. This depends upon the nature of reducing agent used.

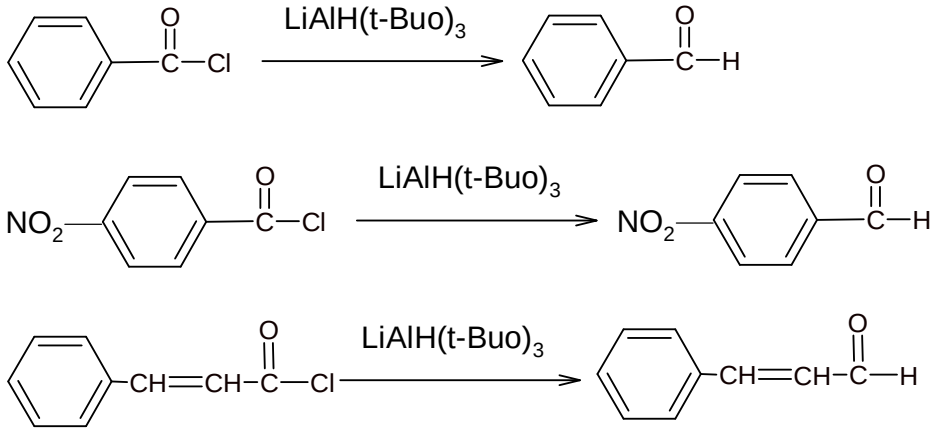
In Rosenmund reaction acid chlorides are catalytically hydrogenated in the presence of a catalytic poison.



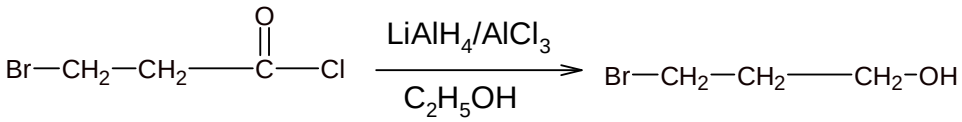
Sometimes in this reaction trimethylsilane is also used in presence of palladium on charcoal.

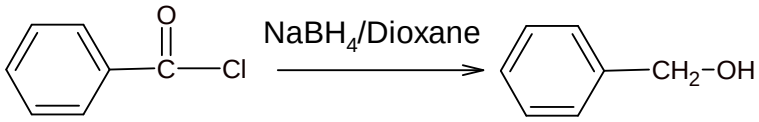


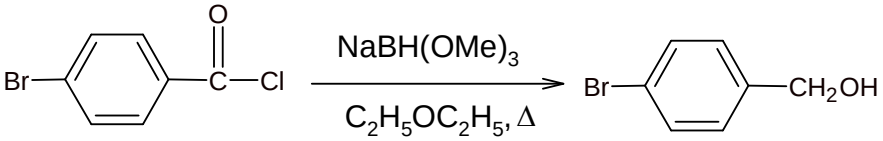
Metal hydrides can also be used for the reduction of acid chlorides. Lithium tri-t-butoxy aluminium hydride is generally used. It is somewhat less reactive because of its bulkiness. Because of its low reactivity it doesn't reduce the aldehyde further to alcohol and also carbon-carbon double bond is not affected.

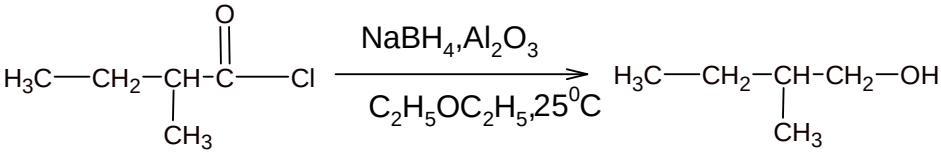


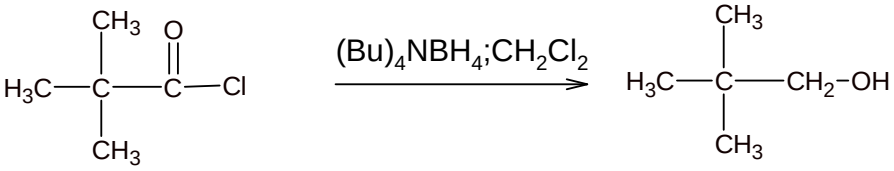
Complete reduction of acid chlorides into primary alcohols is not synthetically important because alcohols can be obtained by usual reduction of other class of organic compounds. This can be done as follows





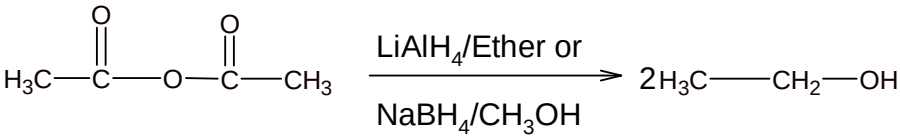




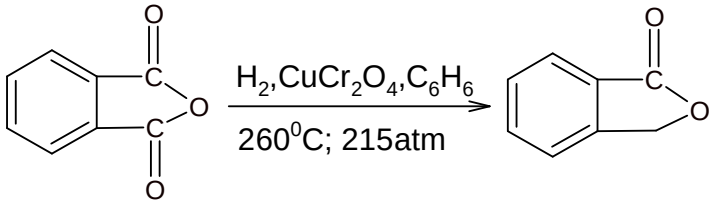


7.7.4 Reduction of Acid anhydrides

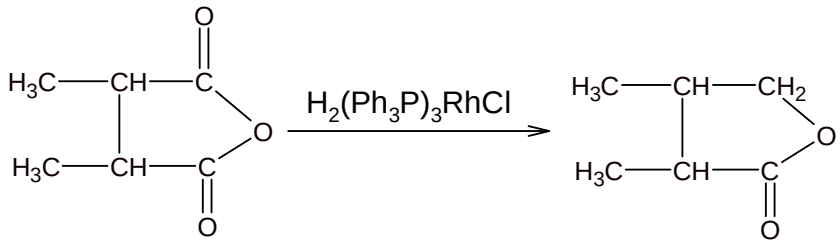
Reduction of anhydrides of monocarboxylic acids can be carried out by complex hydrides. Viz-



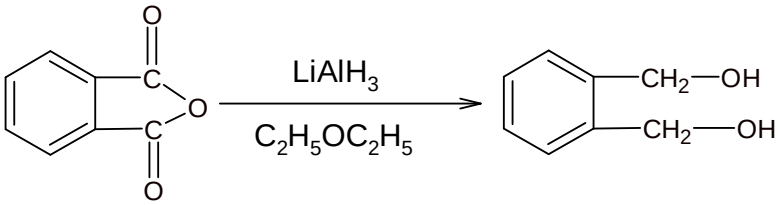
Complex metal hydrides also reduce cyclic anhydrides to lactones. For example hydrogenation of phthalic anhydride by copper chromic produces lactones in 80% yield.

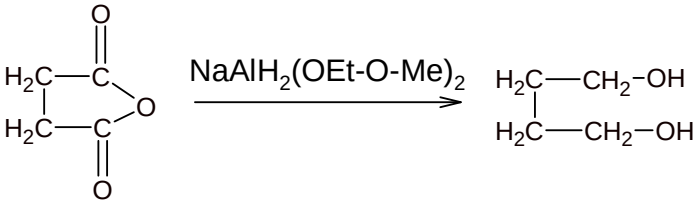


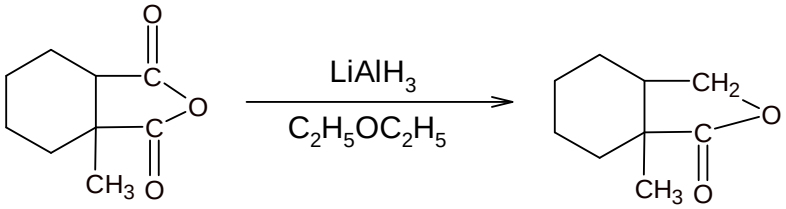
Wilikinson catalyst can also be used for the reduction of anhydrides.

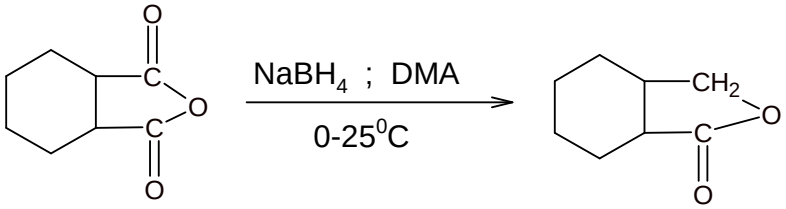


Similarly other metal complex hydrides may also be used.

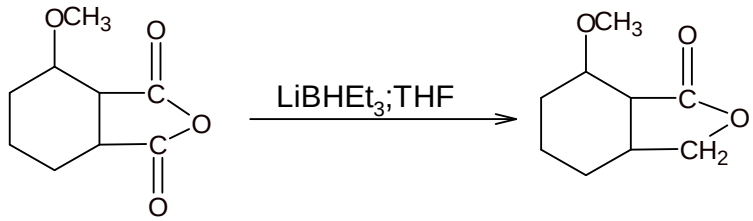


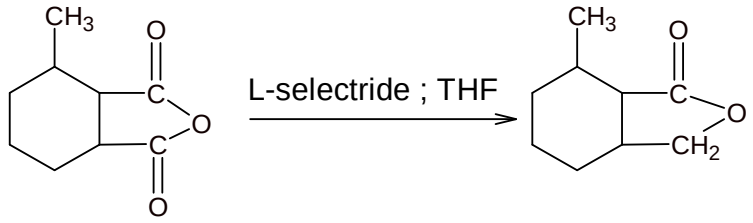


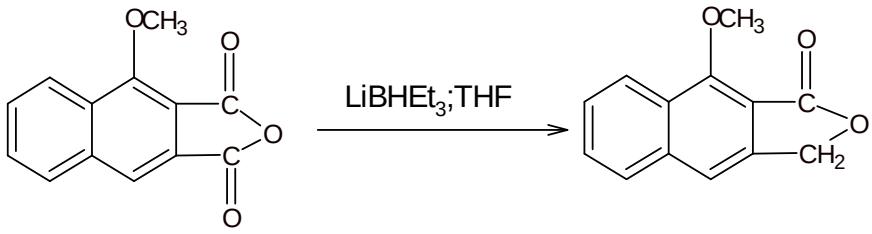




Lactones can also be obtained from anhydrides by following reagents also



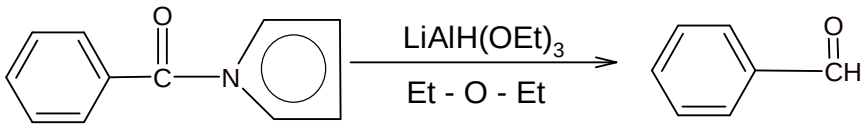


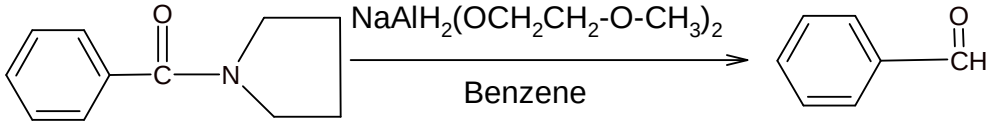


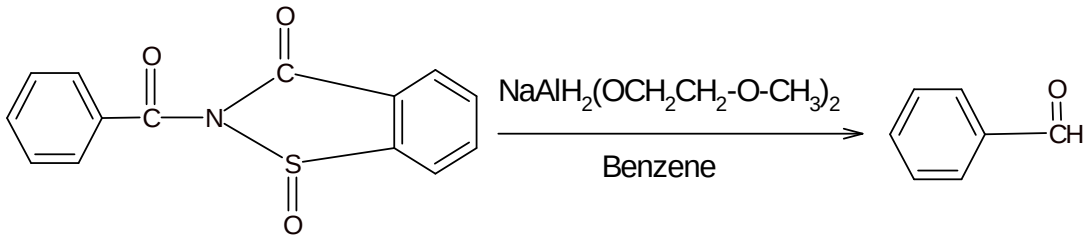
7.7.5 Reduction of Amides

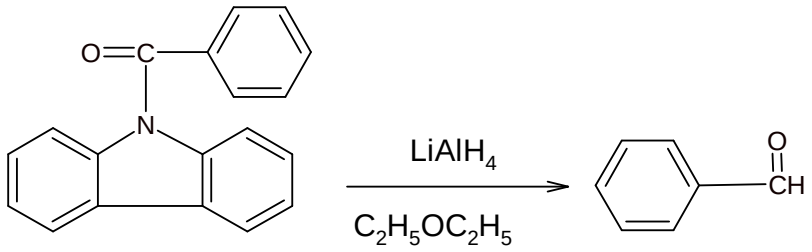
Amides on reduction give aldehydes, alcohols or amines. The nature of the reduction product depends upon (a) structure of amide (b) reducing agent & (c) reaction conditions.

Tertiary amides when treated with $LiAlH_4$, Lithium triethoxy hydride etc give aldehydes. Primary and secondary donot give this reaction.

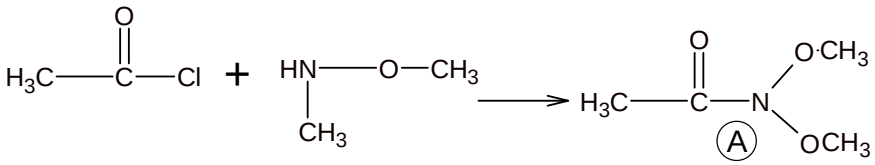




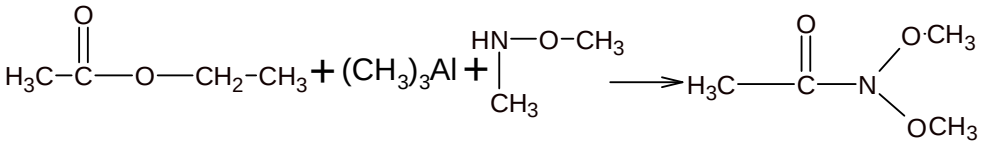




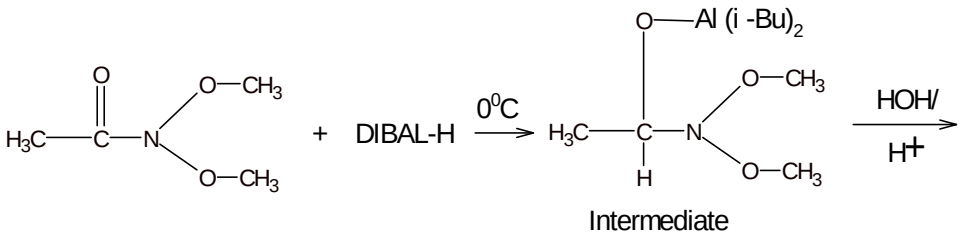
One better way of reduction of amides involves the formation of Weinreb amide (A). This can be prepared by the reaction of acid chloride with either methoxy methyl amine or with ester with $(CH_3)_3Al$ and methoxy methylamine.

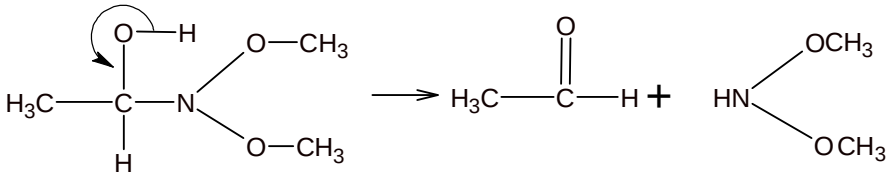


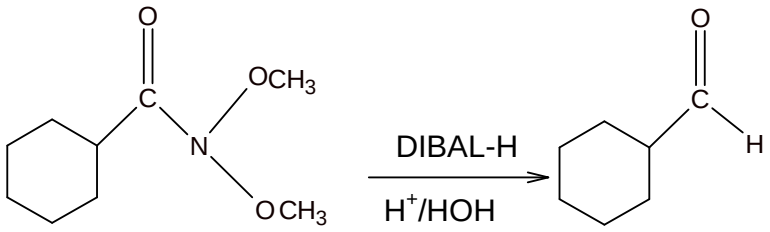
Or

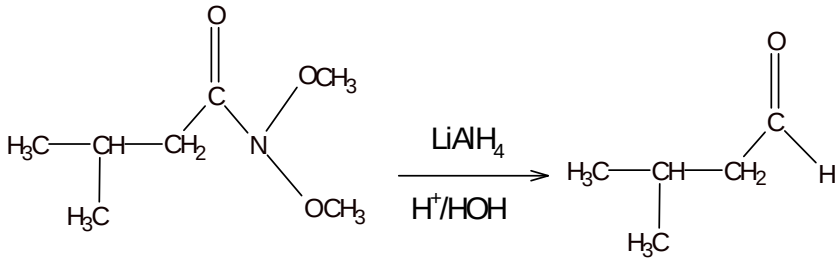


This amide than reacts with either with $LiAlH_4$ or DIBAL-H to form stable chelated intermediates which upon subsequent hydrolysis produce corresponding aldehydes. This is shown below.

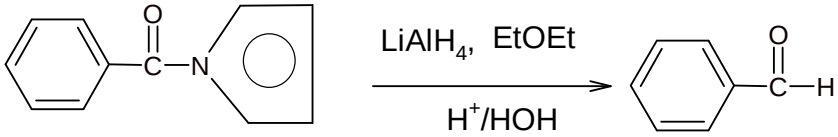




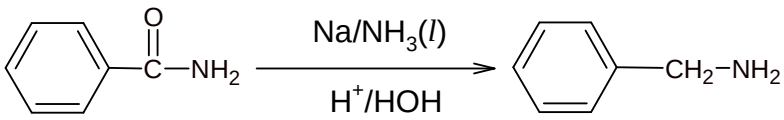




Tertiary amides can also be reduced to alcohols as follows



Sodium and Sodium amalgam may also be used for the reduction of amide into amine.



7.8 Summary

A large number of reducing agents are available to carry out the reduction of various compounds coming in the territory of carbonyl compounds acids and their derivatives,the selectivity and reactivity of the reducing agents changes the nature of the product and thus a product of desired structure can be obtained, these products in turn cn be used eiher as a starting material or precursors of various complex molecules of synthetic importance.

7.9 Review questions

1 Give the mechanism of reduction by lithium aluminium hydride with carbonyl compounds.

2 Give the stereo chemical attack of the hydride ion during the reduction of rhe carbonyl compounds

3. Discuss the order of reduction of various derivatives of carboxylic acids.

4 Discuss the role of ALANES in the reduction of organic compounds.

7.10 Reference Books

- Advance dorganic Chemistry ,Jery March,4th edition,johnwiley and sons.
- Organic synthesi ,jagdamba singh,Dr. L.D.S Yadav,Pragati Prakashan
- Organic Chmistry ,I.L Finar Volume II,ELBS
- Organic reaction mechanism ,P.S.kalsi, New Age Publication.

- Reaction rearrangement and reagent ,s.N.sanyal,Bharti Bhavan Publication.

Unit - 8

Reduction of Nitrogen containing group

Structure of Unit:

8.0 Objective

At the end of the unit learner will be able to learn how to nitrile , nitro ,nitroso, axo and oxime compounds reduced into aldehyde, amines, hydrazo compounds , azoxy compounds in the presence of various reagents.

8.1 Introduction

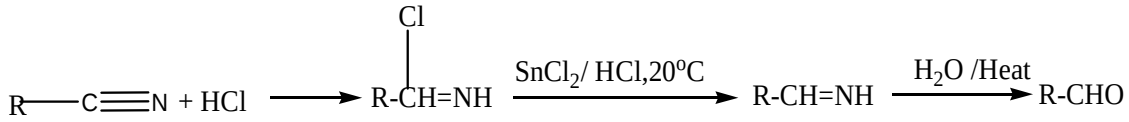
In inorganic chemistry, the term **reduction** indicates a process in which a substrate absorbs electrons. Of course, the same is true in organic chemistry as well.
There are the following reducing reagents in organic chemistry:

- electron donors (metals, which dissolve in suitable solvents in the presence or absence of a proton donor)
- elemental hydrogen (in catalytic hydrogenations or hydrogenolyses)
- H-atom transfer reagents [Bu_3SnH, $(Me_3Si)_3SiH$ and reagents that transfer nucleophilic hydrogen.

8.2 Reduction of nitrile group

(1) Stephen Reduction:

When nitrile reacts with anhydrous stannous chloride and gaseous hydrogen chloride in the presence of diethyl ether then nitrile reduced to aldehyde.



There are two principal methods for the reduction of nitriles to aldehydes. In one of these, known as the Stephen reduction, the nitrile is treated with HCl to form an iminium salt.
Iminium salt is reduced with anhydrous $SnCl_2$ to RCH=NH, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed to the aldehyde. The Stephen reduction is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons. It is also possible to prepare in a different way, by treating ArCONHPh with PCl_5, which can then be converted to the aldehyde. This is known as the Sonn–Mu¨ller method. Aqueous formic acid in the presence of PtO_2, followed by treatment with aqueous acid, converts aryl nitriles to aryl aldehydes.
The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 equivalent of hydrogen and hydrolysis, in situ, of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with $LiAlH_4$, $LiAlH(OEt)_3$, $LiAlH(NR_2)_3$, and DIBALH. The metal hydride method is useful for aliphatic and aromatic nitriles.
(2)

$$RCN + LiAlH_4 \longrightarrow RCH_2NH_2$$

Nitriles can be reduced to primary amines with many reducing agents, including $LiAlH_4$, and $H_3B.SMe_2$. The reagent $NaBH_4$ does not generally reduce nitriles except in alcoholic solvents with a catlayst, such as $CoCl_2$, $NiCl_2$, or Raney nickel. A mixture of $NaBH_4/NiCl_2$ in acetic anhydride reduces the nitrile to the amine, which is trapped as the acetamide. Lithium dimethylamino- borohydride ($LiBH_3NMe_2$) reduces aryl nitriles to the corresponding benzylamines.

The reduction of nitriles is of wide scope and has been applied to many nitriles. When catalytic hydrogenation is used, secondary amines, $(RCH_2)_2NH$, are often side products. These can be avoided by adding a compound, such as acetic anhydride, which removes the primary amine as soon as it is formed, or by the use of excess ammonia to drive the equilibria backward. Sponge nickel or nickel on silica gel have been used for the catalytic hydrogenation of aryl nitriles to amines.

Attempts to stop with the addition with only 1 equivalent of hydrogen, have failed that is, to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed .

N-Alkylnitrilium ions are reduced to secondary amines by $NaBH_4$.

$$RCN \xrightarrow{R'_3O + BF_4^-} R\text{-}CN\text{-}R' \xrightarrow[\text{diglyme}]{NaBH_4} R\text{-}CH_2\text{-}NH\text{-}R'$$

Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts , this is a method for the conversion of nitriles to secondary amines.

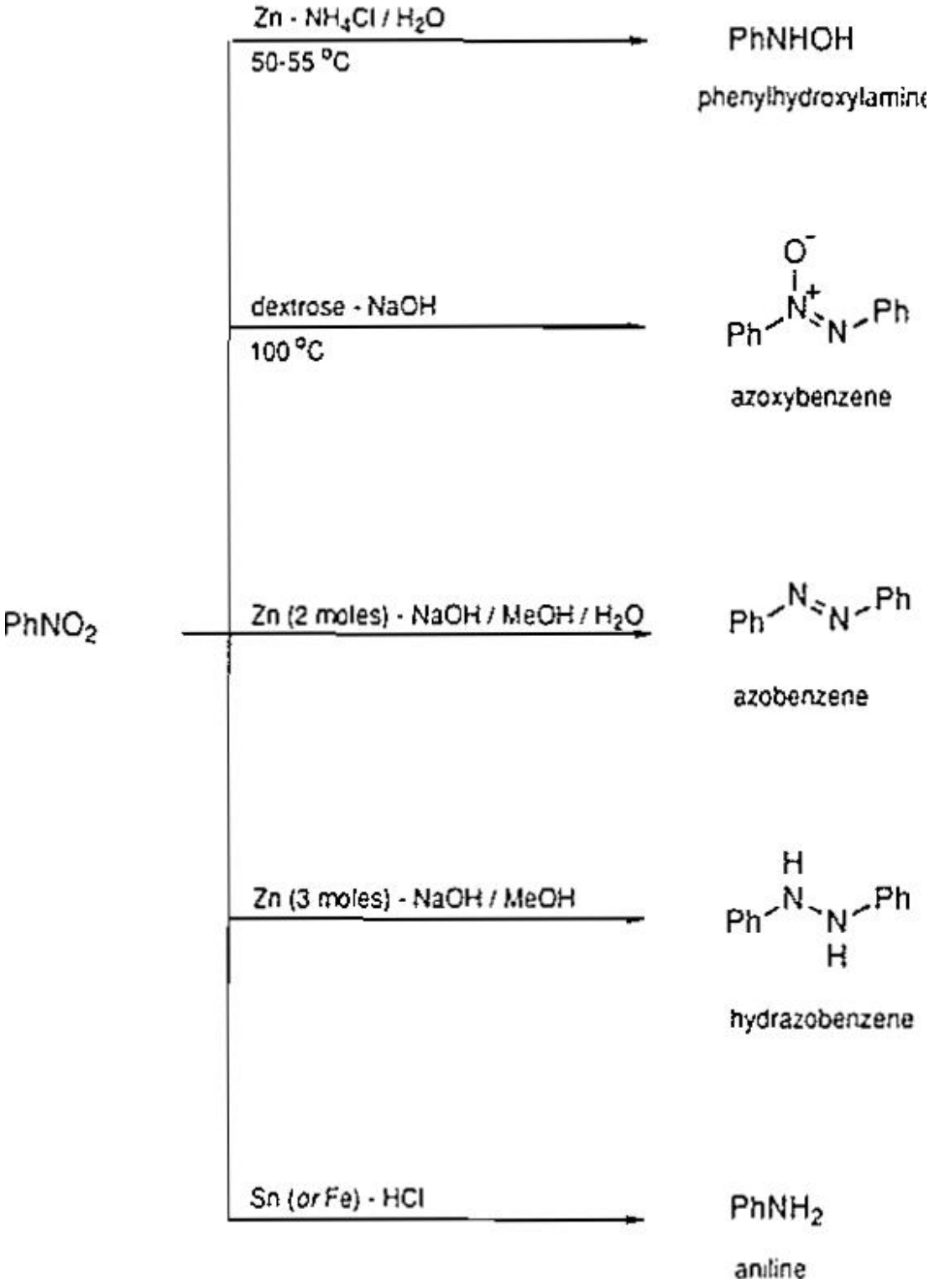
8.3 Reduction of nitro group

The reduction of aliphatic nitro compounds is of little importance because the amino group is easily introduced in a number of other ways.

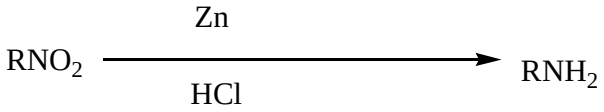
The reduction of aromatic nitro compounds is much more important because the nitro group can be introduced into a wide variety of aromatic systems by nitration whereas the amino group can only be introduced directly into those aromatic compounds which are strongly activated to nucleophiles.

Several types of reduction products are obtainable from the nitrobenzene in the different medium.

-In neutral solution buffered with ammonium chloride, phenylhydroxylamine is the main product.


Zn - NH4Cl / H2O
50-55 °C
PhNHOH
phenylhydroxylamine
dextrose - NaOH
100 °C
azoxybenzene
PhNO2
Zn (2 moles) - NaOH / MeOH / H2O
azobenzene
Zn (3 moles) - NaOH / MeOH
hydrazobenzene
Sn (or Fe) - HCl
PhNH2
aniline

8.3.1 Reduction of nitro compounds to amines



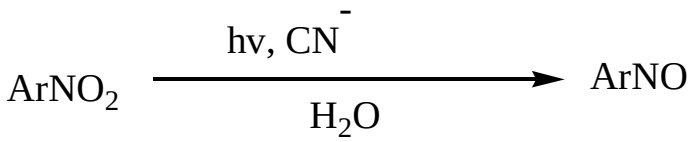
Both aliphatic and aromatic nitro compounds can be reduced to amines, although the reaction has been applied much more often to aromatic nitro compounds.

Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn, or Fe and acid, and catalytic hydrogenation.

Indium metal in aqueous ethanol with ammonium chloride or with water in aq. THF also reduces aromatic nitro compounds to the corresponding aniline derivative.

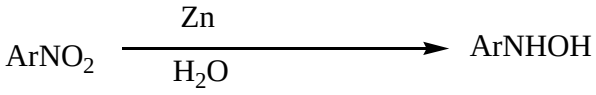
Indium metal in methanol, with acetic anhydride and acetic acid, converts aromatic nitro compounds to the acetanilide.

8.3.2 Reduction of nitro compounds to nitroso compounds



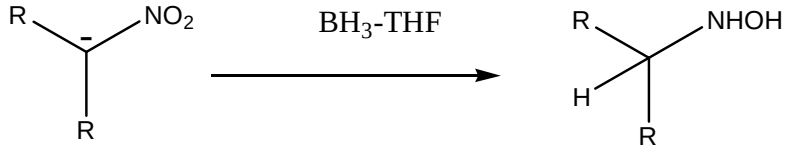
Certain aromatic nitroso compounds (Ar-NO) can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 M aq. KCN with uv light. The reaction has also been performed electrochemically. When nitro compounds are treated with most reducing agents, nitroso compounds are either not formed or react further under the reaction conditions and cannot be isolated.

8.3.3 Reduction of nitro compounds to hydroxylamines

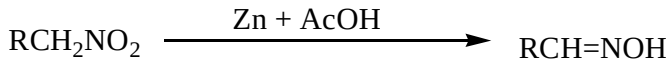


When aromatic nitro compounds are reduced with zinc and water under neutral conditions, hydroxylamines are formed. Among other reagents used for this purpose have been SmI_2, N_2H_4-Rh-C, and $NaBH_4$-Se

Borane in HF reduces aliphatic nitro compounds to hydroxylamines.



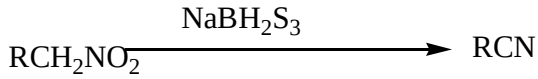
8.3.4 Reduction of aliphatic nitro compounds to oximes or nitriles



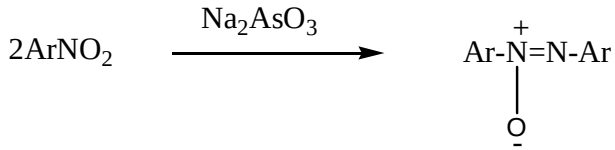
Nitro compounds that contain an α hydrogen can be reduced to oximes with zinc dust in

acetic acid or with other reagents, among them Co-Cu(II) salt in alkanediamines,CS_2-NEt3, $CrCl_2$, and (for a-nitro sulfones) $NaNO_2$.

Primary aliphatic nitro compounds can be reduced to aliphatic nitriles with sodium dihydro (trithio)borate.



8.3.5 Reduction of nitro compounds to azoxy compounds



Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, NaTeH,lead, $NaBH_4$–PhTeTePh,and glucose. The most probable mechanism with most reagents is that one molecule of nitro compound is reduced to a nitroso compound and another to a

hydroxylamine and these combine . The combination step is rapid compared to the reduction process.

8.3.6 Reduction of nitro compounds to azo compounds

$$2ArNO_2 \xrightarrow{LiAlH_4} Ar\text{-}N{=}N\text{-}Ar$$

Nitro compounds can be reduced to azo compounds with various reducing agents, of which $LiAlH_4$ and zinc and alkali are the most common. A combination of triethyl ammonium formate and lead in methanol is also effective. With many of these reagents, slight differences in conditions can lead either to the azo or azoxy compound.

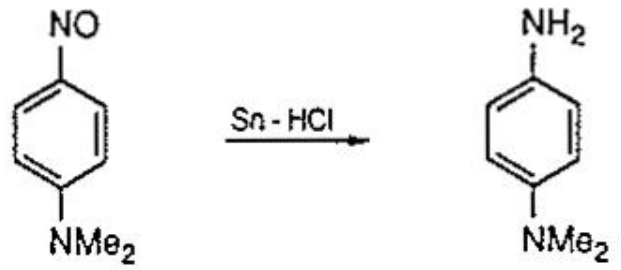
8.3.7 Reduction of nitro compounds to hydrazo compounds

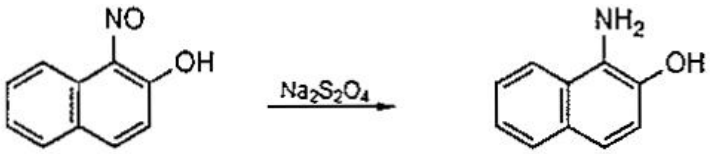
$$2ArNO_2 \xrightarrow{Zn + NaOH} Ar\text{-}NH\text{-}NH\text{-}Ar$$

Nitro compounds can be further reduced to hydrazo compounds with zinc and sodium hydroxide, with hydrazine hydrate and Raney nickel, or with $LiAlH_4$ mixed with a metal chloride such as $TiCl_4$ or VCl_3. The reduction has also been accomplished electrochemically.

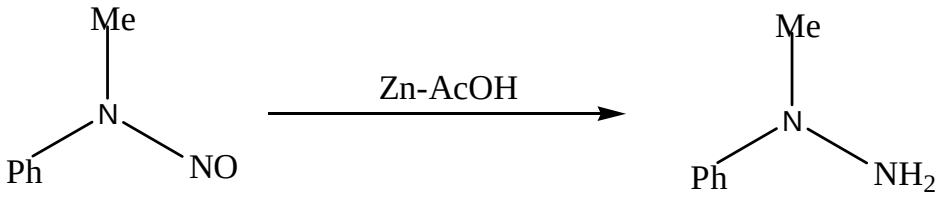
8.4 Reduction of nitroso group

(i) C-nitroso groups are readily reduced to the corresponding amines by electron transfer reagents.e.g.

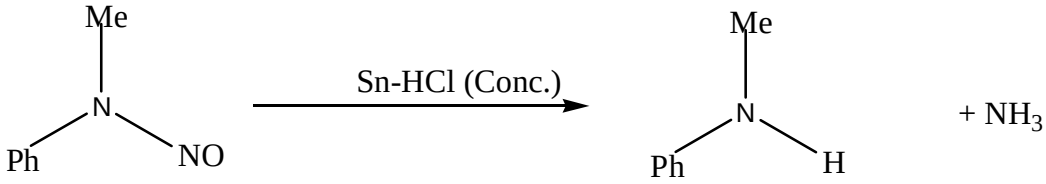




(ii) N-nitroso compounds are reduced by mild electron –transfer reagents to substituted hydrazines.e.g.

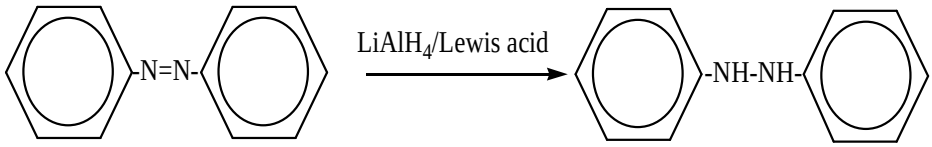


Stronger reducing agents rupture the N-N bond, e.g



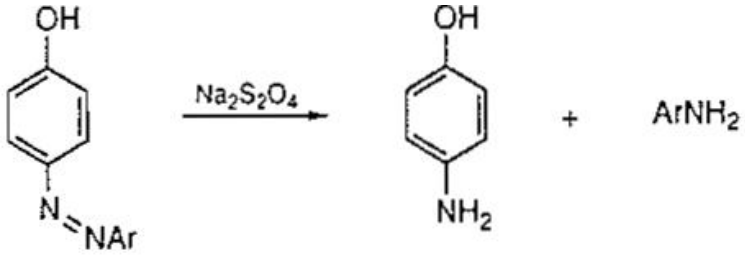
8.5 Reduction of azo group

Azo compounds are reduced to hydrazo-compounds by lithium aluminium hydride in the presence of a Lewis acid



Azobenzene Hydrazobenzene

In the presence of sodium dithionite azo compounds reduced in to the amines.

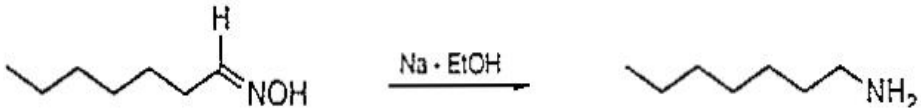


8.6 Reduction of oxime group

Oximes give primary amines on reduction by various reagents.

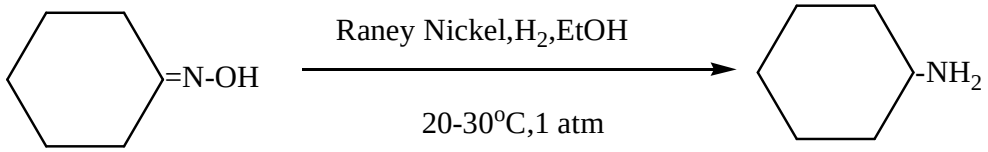
(a) Reduction of oxime by sodium in ethanol:

In the presence of sodium in ethanol oxime gives primary amine

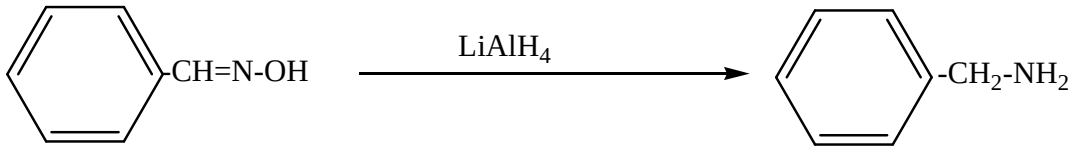


(b) Reduction of oxime by catalytic method:

In the presence of raney nickel, 20-30°C temp. and 1 atm pressure oxime gives primary amine.



(c) Reduction by Lithium aluminum hydride: $LiAlH_4$ reduced oxime in to primary amine.



8.7 Summery

- Nitriles can be reduced to primary amines with many reducing agents, including $LiAlH_4$, and $H_3B.SMe_2$.
- In the presence of of gaseous hydrogen chloride and stannous chloride nitriles reduce to aldehyde. **(Stephen Reduction)**
- When aromatic nitro compounds are reduced with zinc and water under neutral conditions, hydroxylamines are formed
- In the presence of Zn and HCl nitro compounds are reduce to amines.
- In the presence of uv light and KCN nitro compounds are reduce to nitroso compounds.
- Nitro compounds that contain an α hydrogen can be reduced to oximes with zinc dust in acetic acid
- Azoxy compounds can be obtained from nitro compounds with certain reducing agents, like sodium arsenite, sodium ethoxide etc.
- Nitro compounds can be reduced to azo compounds with various reducing agents, such as $LiAlH_4$ and zinc and alkali.
- Nitro compounds can be reduced to hydrazo compounds with zinc and sodium hydroxide.
- Azo compounds are reduced to hydrazo-compounds by lithium aluminium hydride in the presence of a Lewis acid
- In the presence of sodium dithionite azo compounds reduced in to the amines.
- In the presence of sodium in ethanol oxime gives primary amine.
- In the presence of raney nickel, 20-30^{0}C temp. and 1 atm pressure oxime gives primary amine.

- $LiAlH_4$ reduced oxime in to primary amine.

8.8 Review Question

1 Give the various products which are obtained from the reduction of nitro compounds in the different media.

2 Explain Stephen reduction of nitrile compounds.

3 Give the chemical reaction of reduction of oxime to amines.

4 Give the chemical reaction of reduction of azo compounds.

5 Give the chemical reaction of reduction of nitro compounds to nitroso compounds.

6 Give the chemical reaction of reduction of nitroso compounds.

7 Give the chemical reaction of reduction of nitro compounds to hydroxylamines.

8 Give the chemical reaction of reduction of nitro compounds to azoxy compounds.

9 Give the chemical reaction of reduction of nitro compounds to hydrazo compounds.

10 Give the chemical reaction of reduction of nitro compounds to azo compounds.

11 Complete the following reactions:

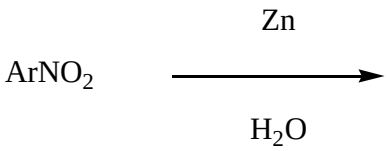
(i)

$$RNO_2 \xrightarrow[HCl]{Zn}$$

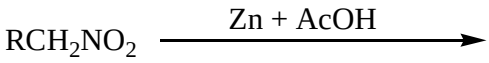
(ii)

$$ArNO_2 \xrightarrow[H_2O]{hv,\ CN^-}$$

(iii)



(iv)



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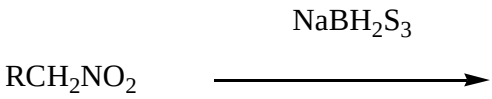
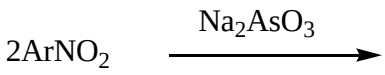


(vi)



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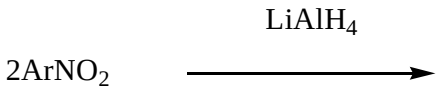

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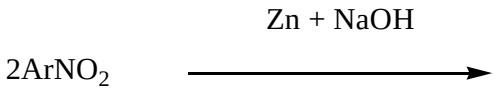

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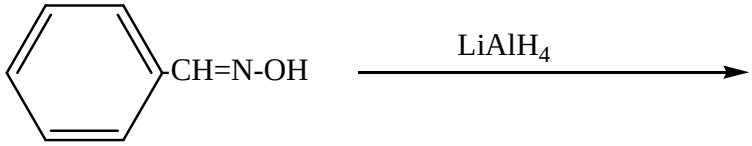

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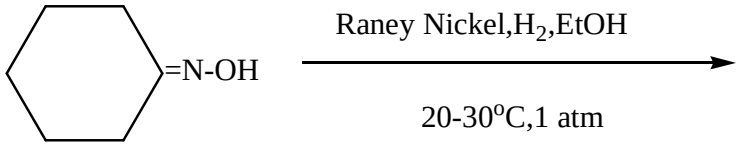

8.9 Reference and Suggested reading

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- Organic Chemistry, J. Clayden, N. Greeves, S. Warren, Oxford University, Second Edition.
- Advanced Organic Chemistry, J. March, 6th Ed.
- Principles of organic synthesis, Norman and Coxon , Blackie Academic &Professional
- Reaction Mechanism in Organic Chemistry, S.M.Mukherji , S.P.Singh ,Macmillan
- Reaction Mechanism in Organic Chemistry, P.S.Kalsi , New Age International Publishers

Unit - 9

Metallocene : Introduction, Synthesis and Chemical reactions of Ferrocene.

Structure of unit

9.0 Objective

Metallocene compounds are organometallic compounds, in which covalent metal-carbon bond present. The first metallocene, Ferrocene is importance in to chemistry of metal sandwich compounds.

9.1 Organometallic compound

An organometallic compound is defined as in which carbon of organic group is directly attached with metal. Organometallic chemistry combines aspects of inorganic chemistry and organic chemistry.

9.2 Metallocene

Metallocene is an organometallic compound with the formula $(C_5H_5)_2M$, (Here M=Fe, Cr, Co, Ni and V). It is the prototypical metallocene, in which a metal atom is found between two parallel cyclopentadienyl anion rings i.e. metal ligand bond between a metal and the π orbital of two cyclopentadienyl anion rings (Cp, which $C_5H_5^-$). The oxidation state of metal is (II) in metallocene.

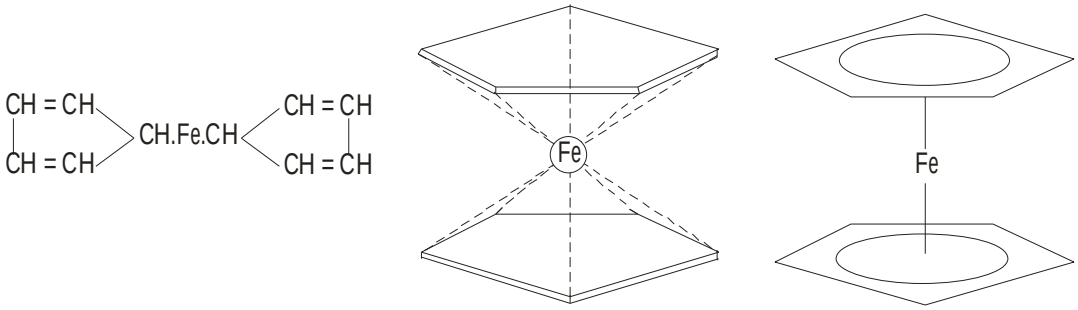
Metallocene are "Sandwich" compounds in which the metal atom (Fe, Cr, Co, Ni nad V) has been described as the meat between two flat organic molecules ($C_5H_5^-$) which are the slices of the bread.

9.3 Ferrocene

Ferrocene $[(C_5H_5)_2Fe$, Bis (η5-cyclopentadienyl) iron (II)] was the first π-cyclopentadienyl metallocene compound. It was discovered by peter L. Pauson and Tom Kealy in 1951. The sandwich structure of ferrocene was first predicted by infrared and nuclear magnetic resonance spectroscopies and later confirmed by X-ray crystallography. Pauson etal. treated cyclopentadienyl magnesium bromide with ferric chloride to form Bis(cyclopentadienyl) iron.

$$2C_5H_5MgBr \xrightarrow{FeCl_3} (C_5H_5)_2Fe$$

This Fe(II) complex was named ferrocene by Woodward et.al. to indicate its aromatic properties.

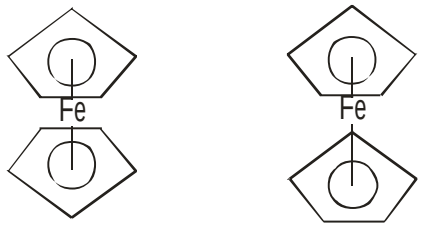


(I) (II) (III)

Originally, structure (I) was assigned to ferrocene, but the high stability of the molecule showed that this was unlikely. Ferrocene has a zero dipole moment, and the molecule is therefore symmetrical. The infra-red spectrum showed that all the C-H bonds are equivalent, and so, on this evidence, structure (II) was proposed and

has been confirmed by X-ray analysis, i.e. that the two five membered rings lie in parallel planes with the iron atom placed symmetrically between the two. In ferrrocene entire ring is bonded uniformly to the metal (Fe) atom, there by giving a delocalized covalent bond between the metal atom and the cyclopentadienyl ring as a whole. Therefore ferrocene, is represented by (III). Iron atom is equidistant (3.4 A^o apart) from the two rings and from all the atoms of carbon.

If has been observed by X-ray diffraction that in gas phase the structure of ferrocene is eclipsed while at low temperature ferrocene is staggered in the solid phase.



Staggered (D_5d) Eclipsed (D_5h)

9.3.1 Synthesis of ferrocene :

Ferrocene are usually prepared by following methods.

(i) when anhydrous ferrous chloride react with cyclopentadiene in the presence of a base like diethylamine to form ferrocene. Here diethylamine act as solvent as well as halogen accepter.

$$2C_5H_6 + FeCl_2 + 2(C_2H_5)_2NH \rightarrow (C_5H_5)_2Fe$$

(ii) The Reaction between ferrous chloride ($FeCl_2$) with sodium cyclopentadienide in THF to form ferrocene.

$$2C_5H_5Na + FeCl_2 \xrightarrow{THF} (C_5H_5)_2Fe + 2NaCl$$

(iii) Reaction of ferrous chloride ($FeCl_2$) with megnocene to form ferrocene.

$$FeCl_2 + (C_5H_5)_2Mn \rightarrow (C_5H_5)_2Fe + Mncl_2$$

(iv) Ferrocene is prepared by the reaction of finely divided iron (Fe) with cyclopentadiene,

$$2C_5H_6 + Fe \xrightarrow[\Delta]{350^oC} (C_5H_5)_2Fe + H_2$$

(v) Ferrocene is prepared from the reaction of cyclopentadiene with potassium hydroxide in 1, 2 dimethoxy ethane (DME) to produce the cyclopentadienyl anion. This is then react with ferrous chloride telrahydrate in DMSO to obtain ferrocene.

$$2C_5H_6 + 2KOH \rightarrow 2C_5H_5K \xrightarrow[FeCl_2.4H_2O]{DMSO} (C_5H_5)_2\,Fe$$

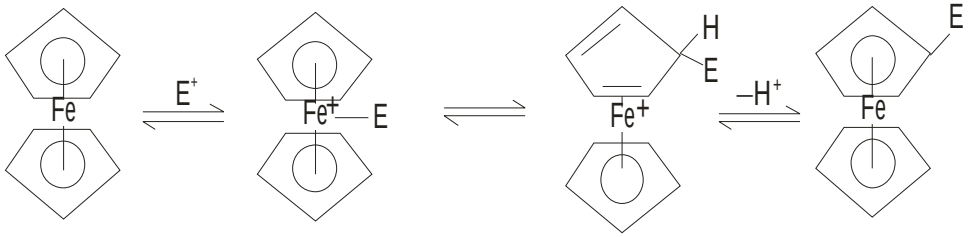
9.3.2. Physical Properties

Ferrocene an orange yellow crystalline solid. It is soluble in organic solvent, such as benzene, but insoluble in water. Ferrocene is an air-stable that readily sublimes, especially upon heating in a vaccum. The melting point of ferroccen is 173^{0}C.

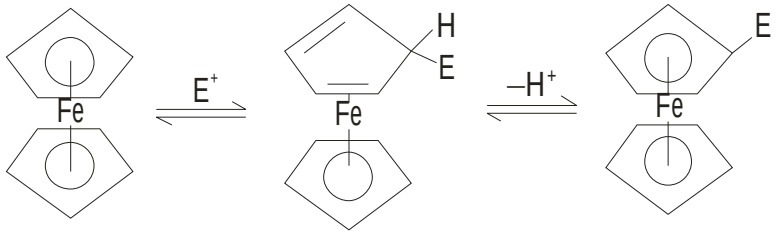
9.3.3 Chemical Reactions of Ferrocene

Ferrocene rections are aromatic. Ferrocene, having six π electorns delocalised over five atoms, is much more prove to electrophilic substitution than benzene. Two main routes have been proposed for the electrophilic substitution of ferrocene.

(a) The electrophile interacts with the central atom, before being transferred to the aromatic ring with subsequent deprotonation.



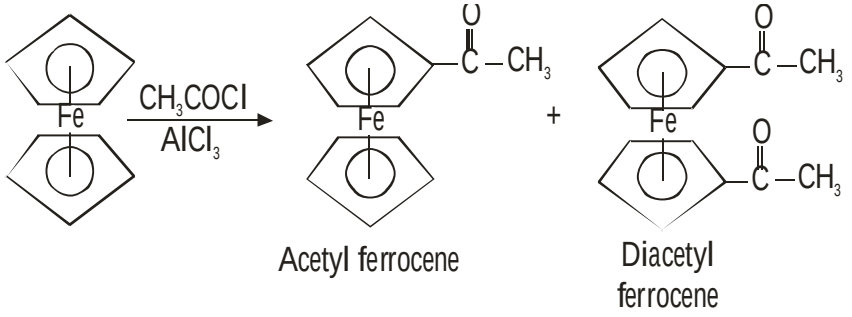
(b) In the second electrophile attack takes place directly at the exo face of the ring, with no direct metal participation.



Following numerious reactions that have been studied :-

(i) Fridal Craft Reaction :

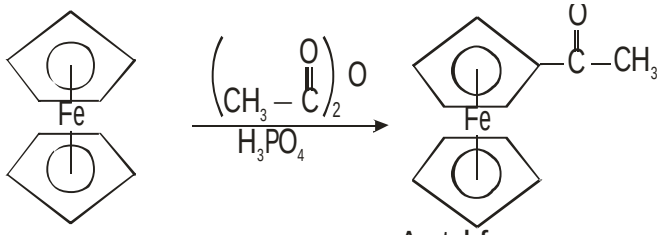
Ferrocene readily undergo acylation in presence of lewis acid as below :



Acetyl ferrocene

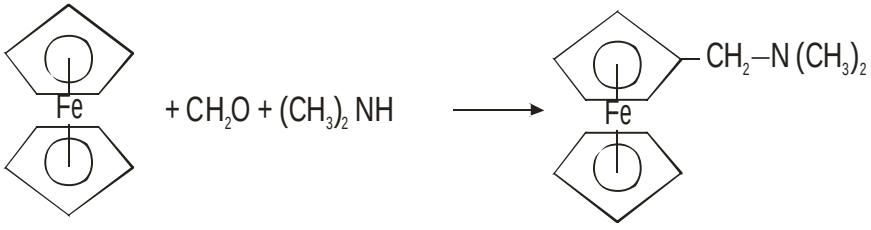
Diacetyl ferrocene

But if reaction of ferrocene carried out with acetic anhydride in presence of H_3PO_4 than only mono acetyl product formed.

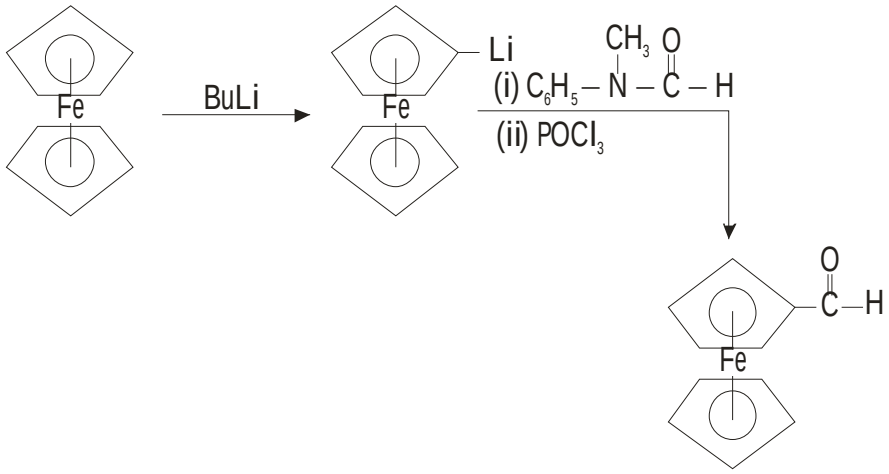


Acetyl ferrocene

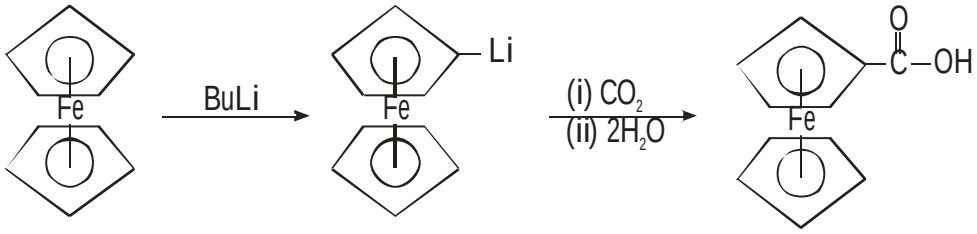
(ii) Mannich Reaction



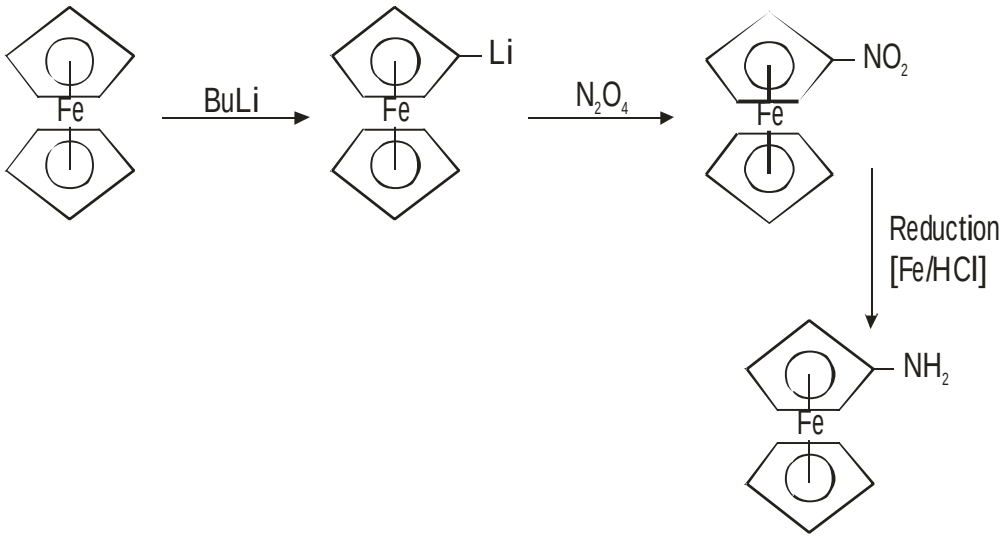
(iii) Vilsmeir Reaction :



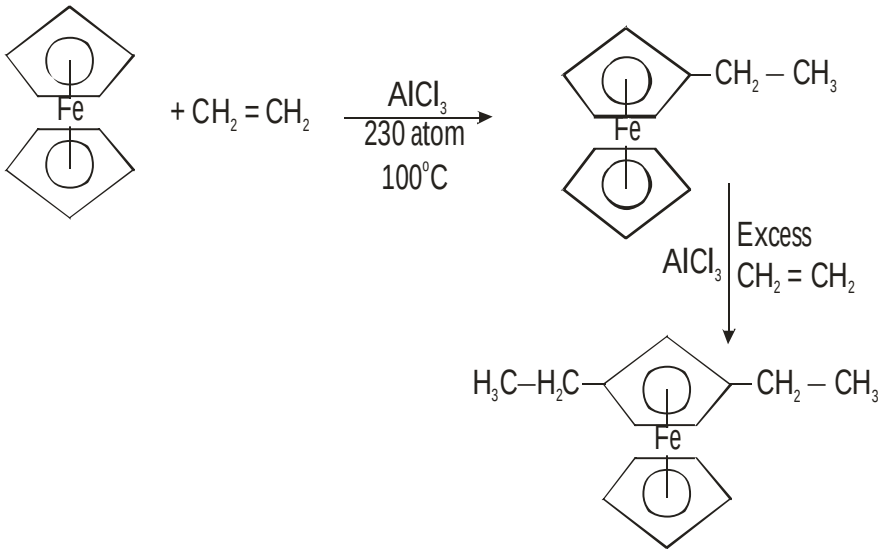
(iv) Carboxylation Reaction :



(v) Nitration :



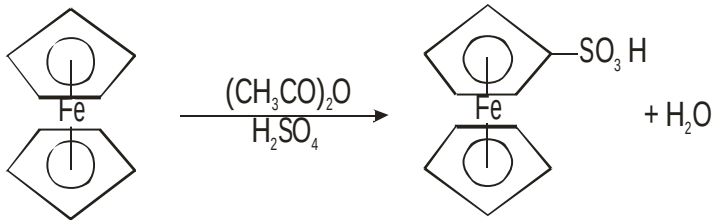
(vi) Alkylation :



Due to presence of alkyl group, electron density increase on the $C_5H_5^-$ ring, hence in the presence of excess of ligand, the distrubiton of alkyl group also occur in the same ring.

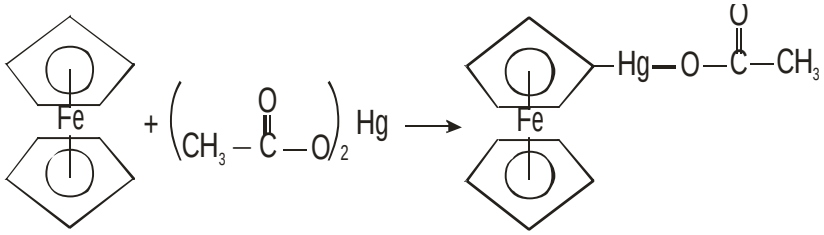
(vii) Sulphonation :

It gets sulphonated by conc. H_2SO_4 in acetic anhydride.

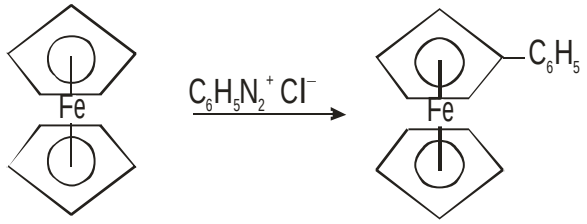


(viii) Mercuration :

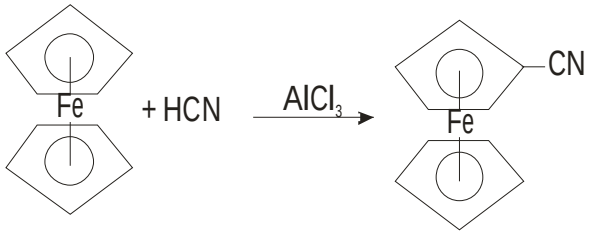
The mercuration of ferrocene with mercury acetate at room temperature.



(ix) Reaction of ferrocene with B.D.C.



(x) Reaction of ferrocene with HCN in presence of lewis acid ($AlCl_3$).



Oxidation Reaction of ferrocene :

Ferrocene gets oxidized by HNO_3 to form blue ferrocinium ion, which may be isolated in the form of solid salts.

$$(C_5H_5)_2Fe \xrightarrow{HNO_3} (C_5H_5)_2Fe^+$$

9.3.4 Cyclopentadienyl (Cp) –metal interaction

The frontier molecular orbital of the cyclopentadienyl ligand contains five orbitals (Ψ_1–Ψ_5) residing in three energy levels (Figure 1). The lowest energy orbital Ψ_1 does not contain any node and is represented by an a_1 state, followed by a doubly degenerate e_1 states that comprise of the Ψ_2 and Ψ_3 orbitals, which precede another doubly degenerate e_2 states consisting of Ψ_4 and Ψ_5 orbitals.

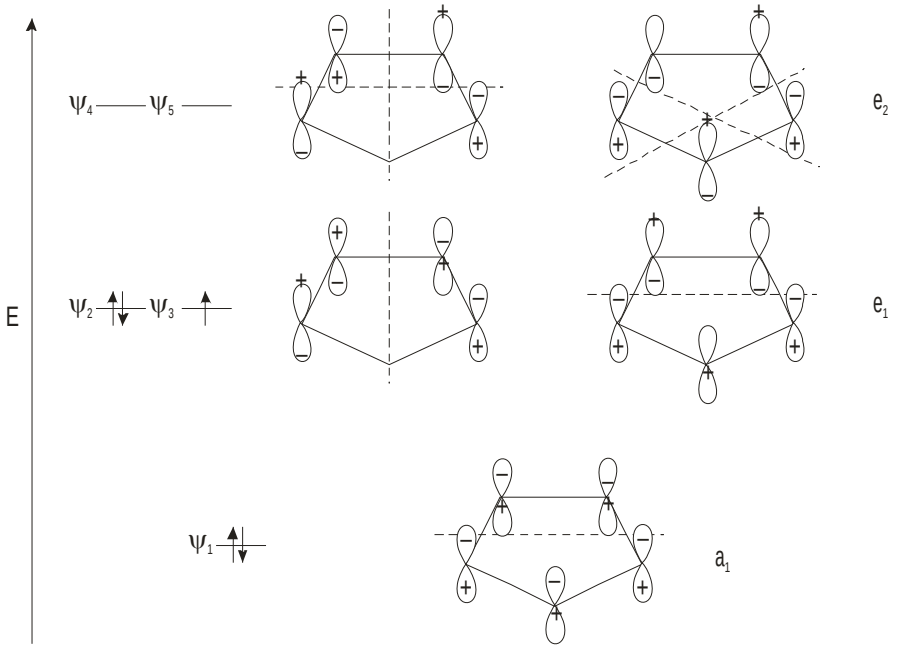
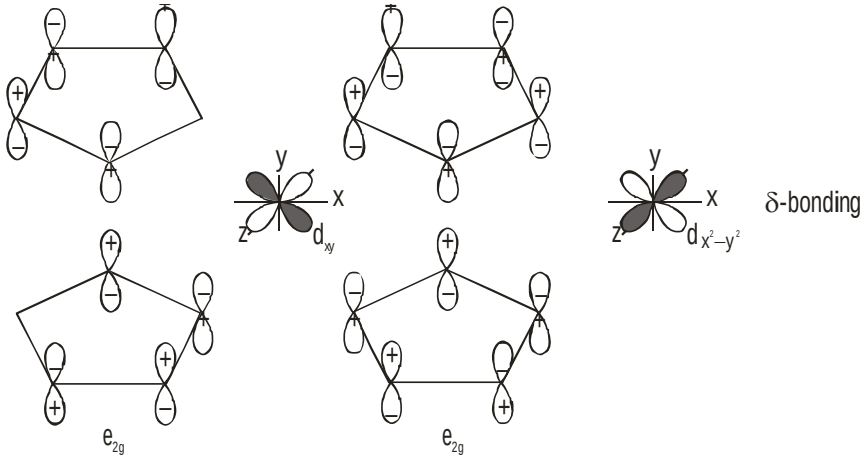


Figure 1. Molecular orbital diagram of cyclopentadienyl ligand.

The above frontier molecular orbital diagram becomes more intriguing on moving over to the metallocenes that contain two such cyclopentadienyl ligands. Specifically, in the $(Cp)_2M$ system, (Ferrocene) each of these above five molecular orbital of the two cyclopentadienyl ligands combines to give ten ligand molecular orbitals in three energy levels (Figure 2).



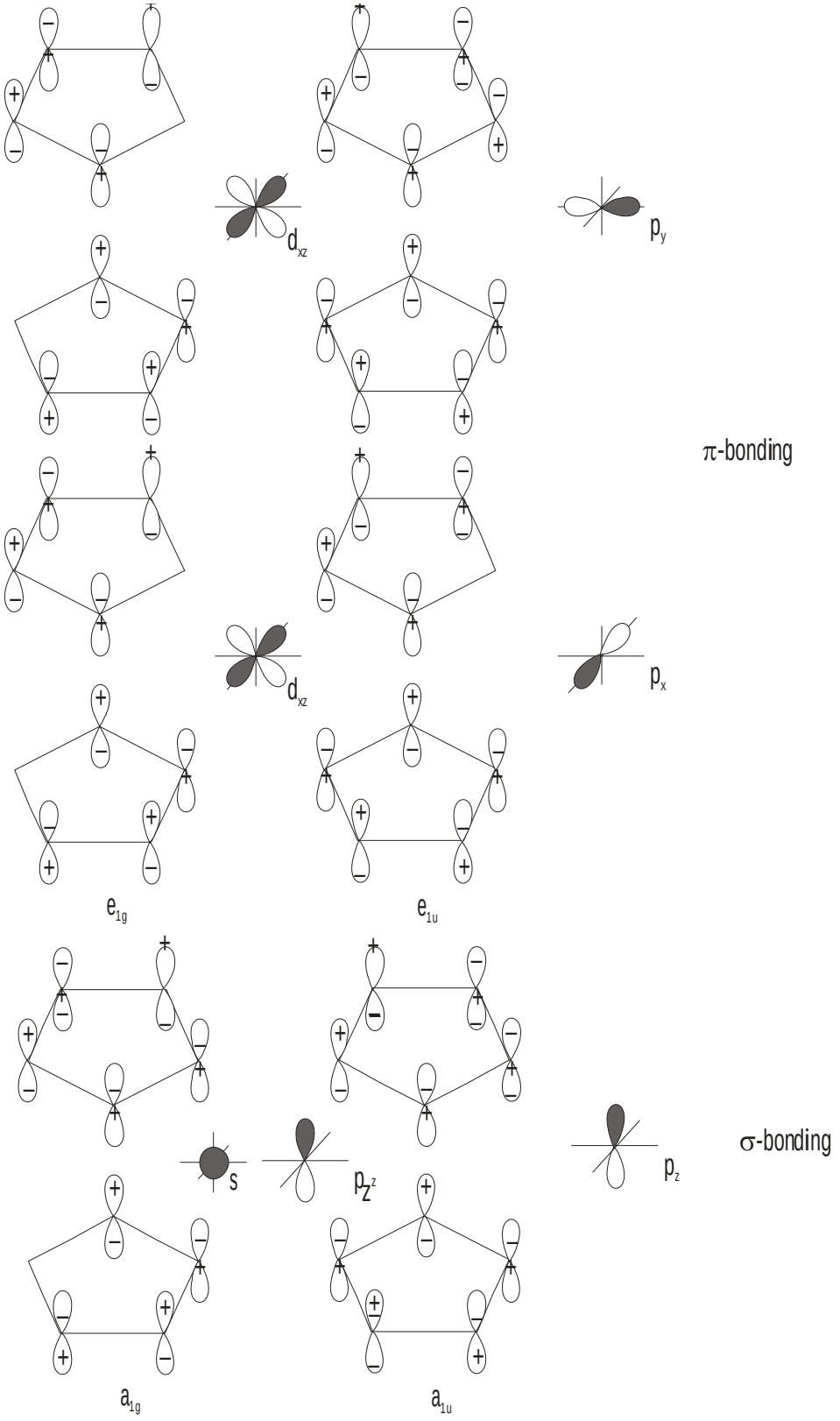


Figure 2. Metal–cyclopentadienyl bonding interactions

9.3.5 Molecular Orbital Diagram of Ferrocene

Ferrocene can be considered as consisting of an Fe^{2+} ion (six d-electrons) bonded to two cyclopentadienyl anions (six π-electrons each), and thus it can be seen that ferrocene follows the 18-electron rule, all valence electrons are located in bonding or non-bonding orbitals. The anti-bonding orbitals are left unpopulated, and hence the compound is stable.

A more informative picture of the bonding within ferrocene is provided by a molecular orbital diagram (Figure- 3), which shows the molecular orbitals, which result form the interactions of the ligand and metal orbitals. Symmetry considerations, the relative energies, and overlap integrals of the ligand π-orbitals and the 3d, 4s and 4p orbitals of the central iron can be used to predict which molecular orbitals will be formed.

The lowest energy orbitals are ligand-based (a_{1g}, a_{2u}), as the metal orbitals with appropriate symmetry requirements ($3dz^2$/4s, and $4p_z$ respectively) are so much higher in energy. The e_{2g} orbitals remain essentially metal based $\left(d_{x^2-y^2}, d_{xy}\right)$, as their δ-overlap with the ligand e_{2g} orbitals is poor. The stability of the ferrocene molecule is largely due to the overlap of the ligand e_{1g} orbitals with the d_{xz} and d_{yz} orbitals of the iron atom, which results in the formation of two strong π-bonds.

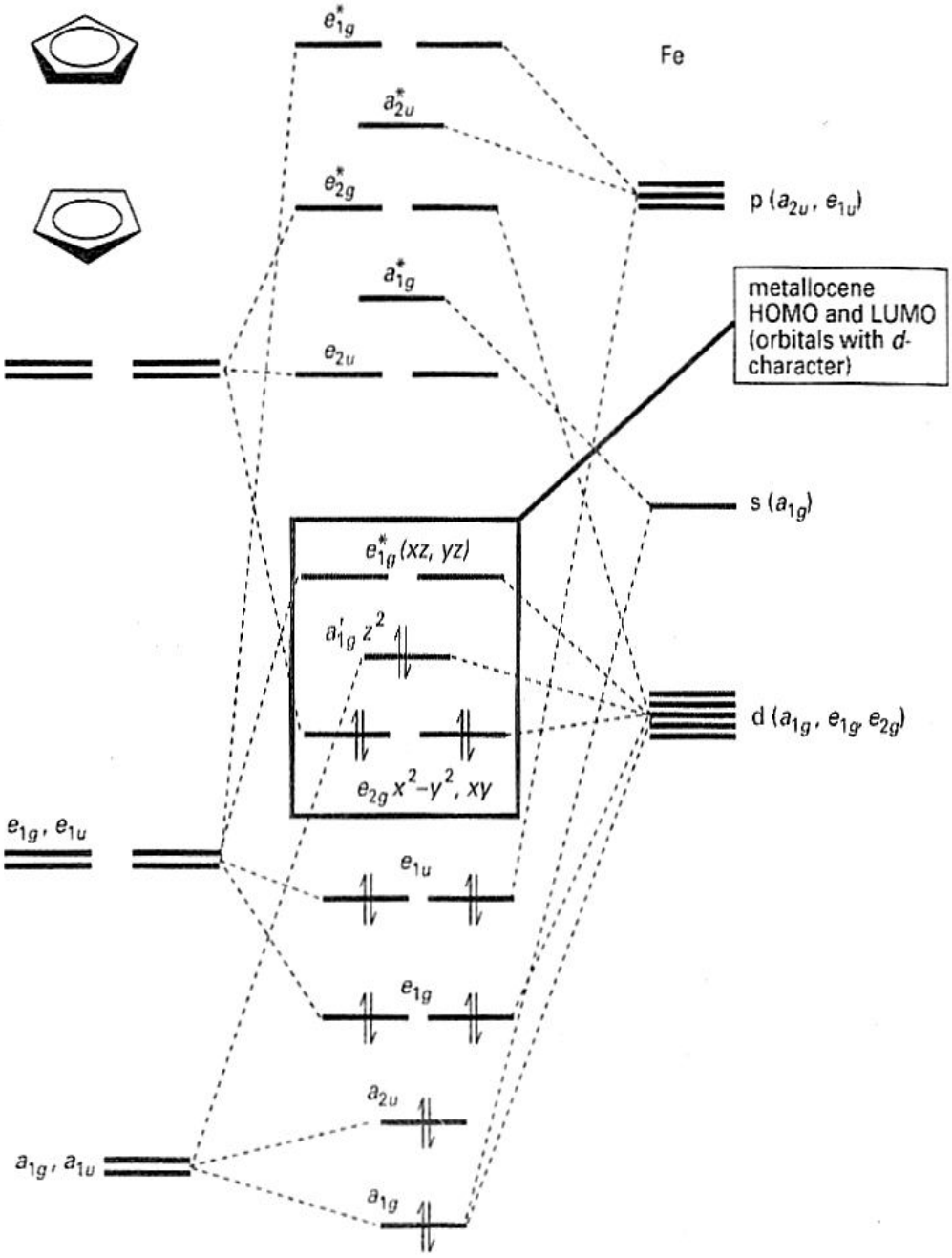


Figure-3: Ferrocene molecular orbital diagram

The frontier orbitals of ferrocene are the weakly bonding e_{2g}, the non-bonding a_{1g}, and the weakly antibonding, unoccupied e_{1g} level. Given that these orbitals are similar in energy, it can be seen that deviations from the 18-electron rule are possible. Depending on the method employed in calculating the relative energies of the frontier orbitals, the HOMO of ferrocene can be considered as being the a_{1g}

($3d_z^2$), or the degenerate e_{2g} $\left(d_{x^2-y^2}, d_{xy}\right)$ pair. This becomes important when considering the electronic structures of ferrocene derivatives, along with their spectroscopic and electrochemical properties. The LUMO of ferrocene is derived from an out of phase π-interaction between the d_{xz}/d_{yz} iron orbitals, and the C_p e_{1g} orbitals.

9.4 Summary

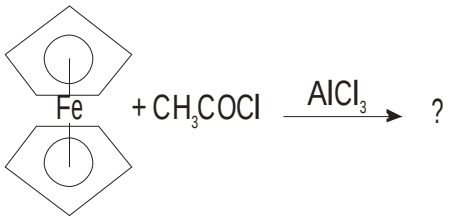
- Ferrocene was the first metallocene compound.
- Metallocene are sandwich compounds.
- The oxidation of metal is II in metallocene.
- A metallocene is compound with general formula $(C_5H_5)_2M$.
- Ferrocene is orange compound which is air-stable, insoluble in water
- The two cyclpentadienyl rings of ferrocene may be arranged in eclipsed (D_5h) or staggered (D_5d) conformation.

9.5 Review Questions

1 How will synthesize ferrocene, give any two method.

2 Complete the following reactions.

(i)



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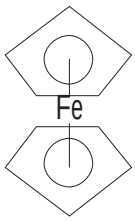


$+ CH_3 - Li \longrightarrow ?$

(iii) $2C_5H_6 + FeCl_2 + 2 (C_2H_5)_2 NH \rightarrow ?$

3 Explain the electronic structure of ferrocene.

4 Explain two mechanic steps of Electrophilic substitution reaction of ferrocene.

9.6 Reference and suggested readings

- Inorganic-chemistry, J.E. Huheey, E.A. Keiter, R.L. Keiter and O.K. Medhi, Pearson-2006 (Fourth Edition)
- Organic reaction and their mechanism – P.S. kalsi, Newage International publishers, 2000 (Second Edition)
- Organic-chemistry – I.L. finar – Pearson – 2010 (Tenth Edition)
- Inorganic chemistry : Principles of structure and reactivity, J.E. Huhey, E.A. Keiter, R.L. keiter-1993.
- Advanced Inorganic chemistry – cotton and Wilkinson (V^{th} Edition)

Unit - 10

Nonbenzenoid Aromatic Compounds: - General consideration, Monocyclic aromatic anions, Synthesis and reactions of Tropone and Tropolone

Structure of Unit

10.0 Objective

In this unit we explain the aromaticity of benzenoid and non-benzenoid compounds; how aromatic compounds differ in behaviour from aliphatic compounds. Tropone and tropolone are aromatic compounds, which are derivatives of cycloheptatriene.

10.1 General consideration:

Organic compound classified into two classes: aliphatic compounds and aromatic compounds.

Aliphatic compounds are open chain structure and those cyclic compounds that resemble open chain compounds.

In addition to the aliphatic compounds, there was a large number of compounds which were obtained from natural sources and have a pleasant smell, such type of compounds were classified as aromatic (Greek; aroma-fragrant smell)

Aromatic compounds were related to benzene and compounds that resemble benzene in chemical behaviour, but their properties are totally different form those of the acylic compounds.

The aromatic hydrocarbon, benzene was first isolated by Michael Faraday (1825) oil condensed in cylinders of compressed illuminating gas. Hoffmann isolated benzene by coal-tar in 1845.

Augus kekule (1858), was proposed the benzene structure, in which carbon atom join to one another to from hexagonal cyclic structure. In kekule structure the double bonds in benzene were in rapid state of oscillation. All the carbon-carbon bond in benzene structure are of equal length (1.39 A^0) and C-H Bond length (1.10 A^0).

The molecular orbital structure in benzene each carbon atom have sp^2 hybridized, each carbon atom form sigma bond with two carbon atoms and one hydrogen atom. The six remaining electrons are in unhybridized p-orbitals each of which overlaps with two neighbour C-atom to form π-bond.

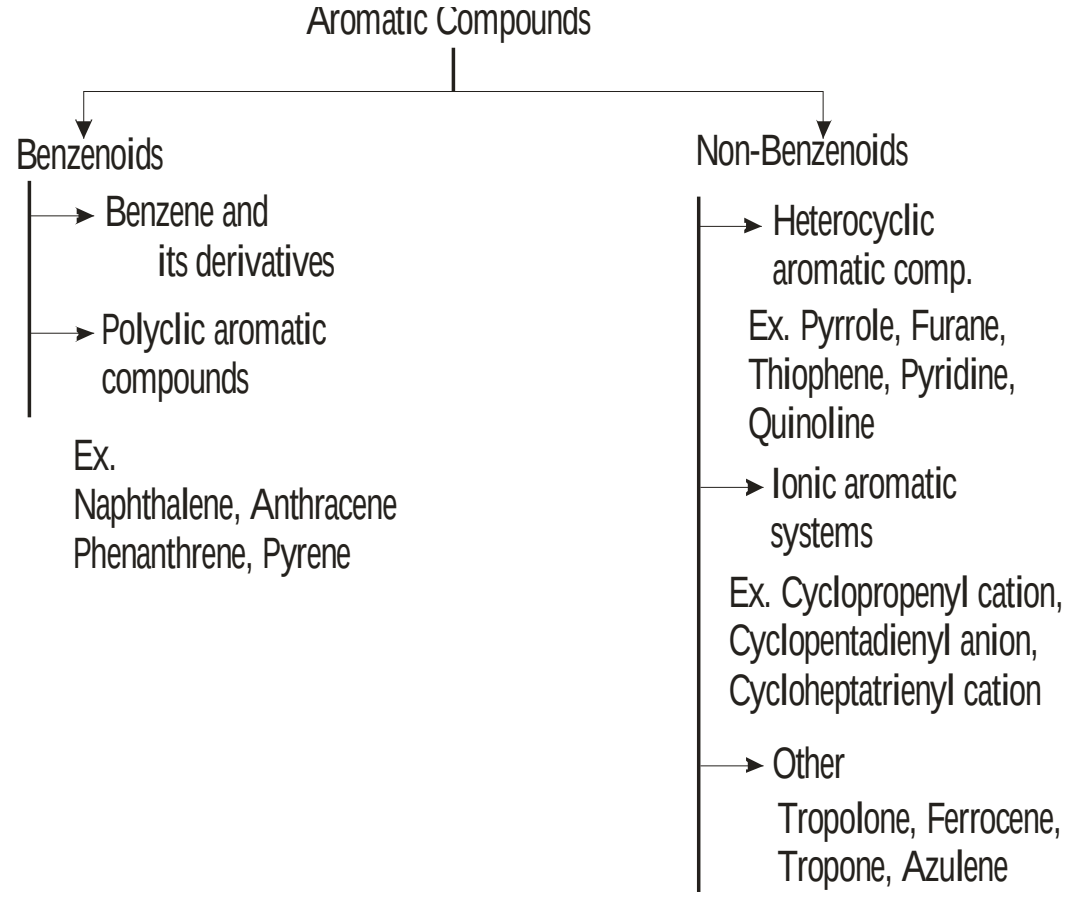
10.2 Aromatic Compounds

Those compounds which resemble benzene are aromatic which differ from unsaturated aliphatic compounds. The aromatic compounds are characterized by a special stability and that they undergo electrophilic substitution reaction more easily than addition reactions.

An aromatic a compounds must have a molecule that contains cycic structure having conjugated π-bonds. For a cyclic systems to be aromatic, it will contain (4n + 2) π electrons. Where n is integer, Thus, to be aromatic, a molecule must have 2(n=0), 6(n=1), 10(n=2), 14(n=3) π electrons. This requirement, known as Huckel (4n +2) rule, based on Quantum mechanics.

In this description of aromaticity, no mention is made of the number of carbon atom in the ring. So planarity as well as (4n+2) π e^- are necessary condition for aromaticity.

Now aromatic compound can be classified in following manner



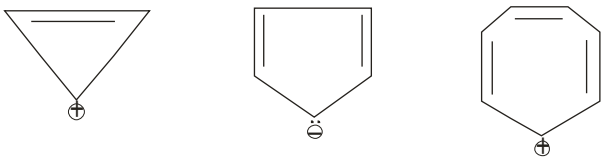
Conjugated cyclic planer monocyclic and polycyclic system which contain (4n+2) π e^- molecules and benzenoid compounds, are known as benzenoid aromatic compounds

Ex. Benzene, Phenol, Aniline, Halo benzene, Toluene, Benzoic Acid, di or tri substituted monocyclic benzene derivatives and polycyclic aromatic compounds like-Naphthalene, Anthracene etc.

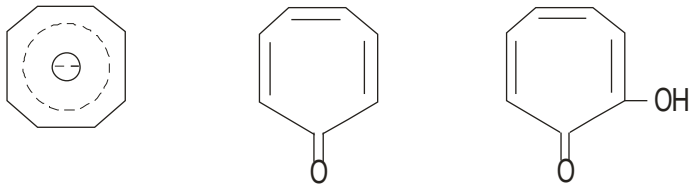
10.3 Non-benzenoid aromatic compounds:

Conjugated cyclic systems either monocyclic and poly cyclic system which have (4n+2) π electrons having no-benzene rings are known as non-benzenoid aromatic compounds.

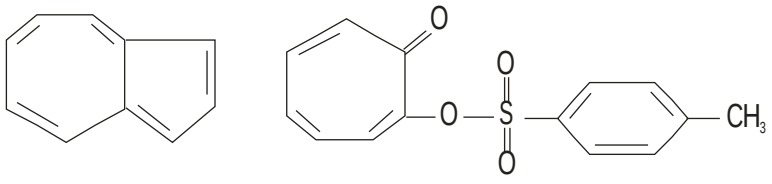
Ex. Cyclo propenyl cation (1), Cyclopentadienyl anion (2), Cycloheptadienyl anion (3), Cyclooctatetraene dianion (4), Tropone (5), Tropolone (6), Azulenes (7), Tropolone tosylate (8), Dibenzo suberenone (9), Heterocyclic compounds like Pyrrole (10), Furane (11), Thiophene(12), Pyridire (13), and Ferrocene (14) are non benzenoid aromatic compounds.



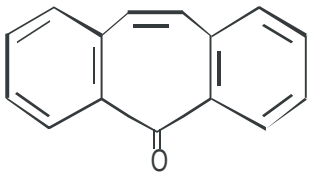
(1) (2) (3)



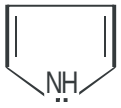
(4) (5) (6)



(7) (8)



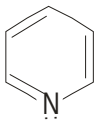
(9)



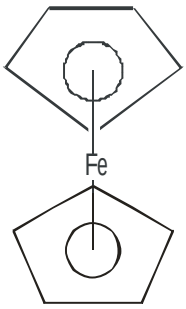
(10)

(11)

(12)



(13)



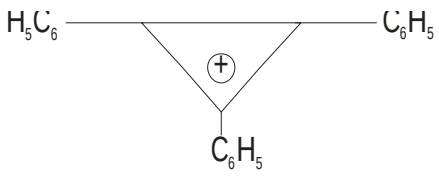
(14)

10.4 Monocyclic aromatic ion:

There are a number a monocyclic species that bear either a positive or a negative charge and show aromatic characters i.e. follow. Huckel (4n+2) π rule are known as monocyclic aromatic ion.

(i) Cyclopropenyl cation:

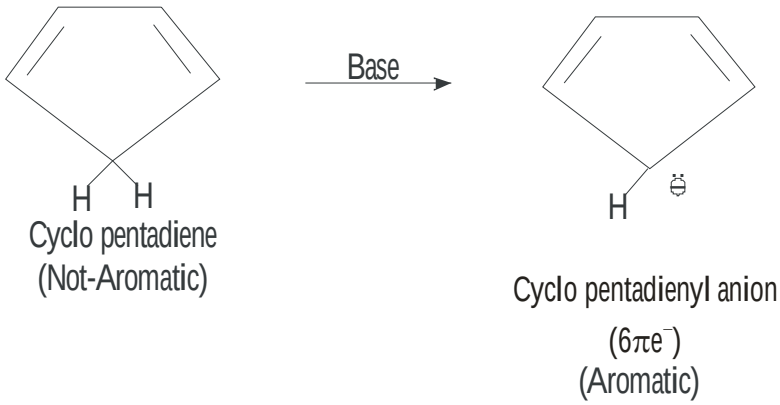
The three membered ring with a double bond and a positive charge on the third C-atom. π e^- are delocalized in ring of cyclopropenyl. The cyclo propenylsalt such as triphenyl cyclopropenium cation (15) are stable and show aromaticity because delocalized 2 π e^- are present.

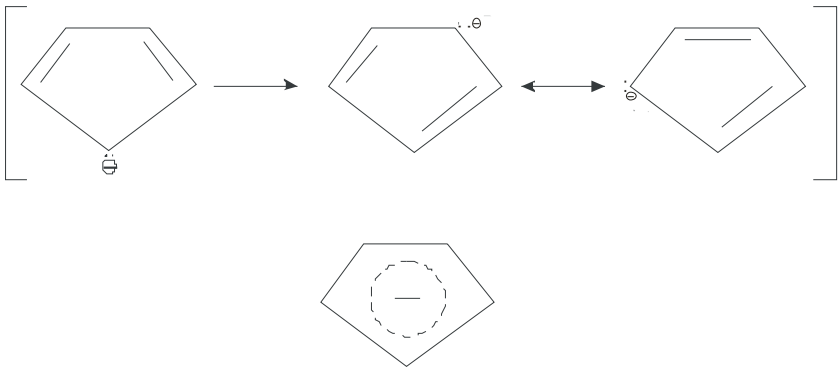


(15)

(ii) Cyclopentadienyl anion:

Cyclopentadiene is not aromatic, but nature is acidic. So it reacts with base to form anion. Which is stable and contain $6\pi e^-$ i.e. it obey the Huckel [(4n+2) π] rule.



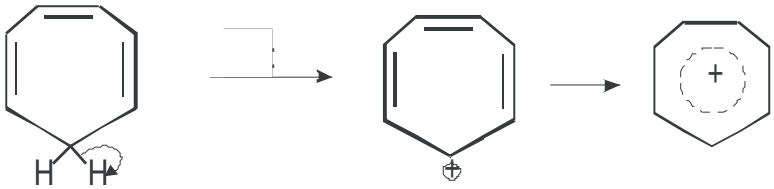


Pyrrole (10), Furane (11) and thiophene (12) are heterocyclic compounds are similar to cyclo pentadienyl anion.

(iii) Cycloheptatrienyl cation

Cyclo heptatriene contain 6π electrons, but 6π electrons can not be delocalized due to the presence of sp^3 hybridized $-CH_2-$ group. The C in $-CH_2$ -group does not have an available p-orbital.

When cyclo heptatriene (16) is loss the hydride ion to from cycloheptatrienyl cation (3) or tropylium cation. In tropylium cation $6\pi e^-$ delocalized over seven carbon atom and according to Huckel rule it aromatic compound.



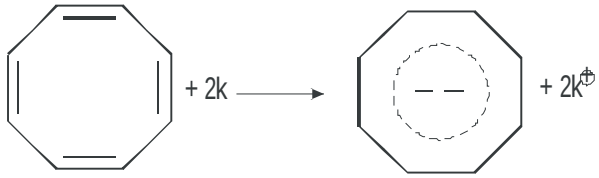
(16)
(Not fully conjugated)

(3)
(Fully Conjugated - $6\pi e^-$)

Tropone (5) and derivatire tropone i.e. Tropolone (6) is another example of seven membered 6π electrons system.

(iv) Cyclo octatetraenyl dianion (18) are prepared as potalssium salts.

Dianion of cyclo-octatetraene (17) is planar and is an aromatic because it contain 10π conjugated electron.



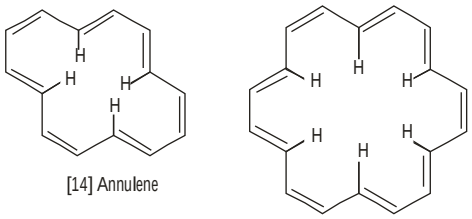
(17)
($8\pi e^-$ - Antiaromatic)

(18)
($10\pi e^-$ - Aromatic)

Annulenes.

Annulenes are monocyclic polyenes. The formula of annulenes are C_nH_n. $(n \geq 10)$. The aromatic character investigated by NMR spectroscopy. The annulenes prepared have n = 12, 14, 16, 18, 20, 24 and 30. Out of these only [14], [18], [30] annulenes are aromatic because they follow Huckel rule. Where as the rest are antiaromatic molecules.

Ex.

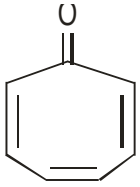


[14] Annulene

[18] Annulene

10.5 Introduction of tropone

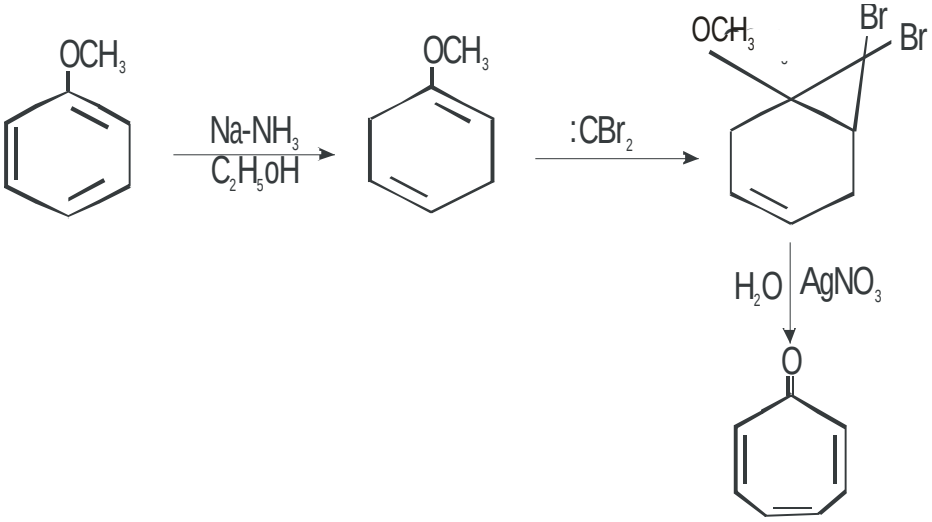
Tropone (cyclohepta 2, 4, 6 triene-1-one) is a non benzenoid aromatic compound with three conjugated double bond and a ketone group. Tropone is derivative of cycloheptatriene.



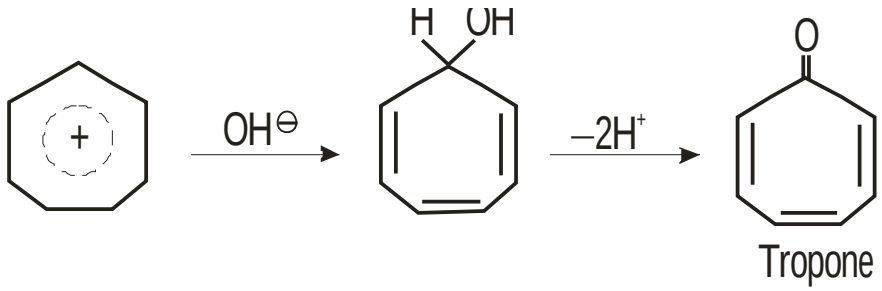
[Tropone - C_7H_6O]

10.5.1Synthesis of tropone:-

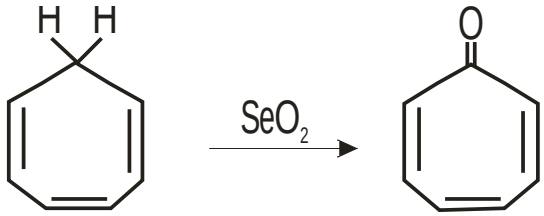
(i) Tropone prepared by anisole by the birch reduction.



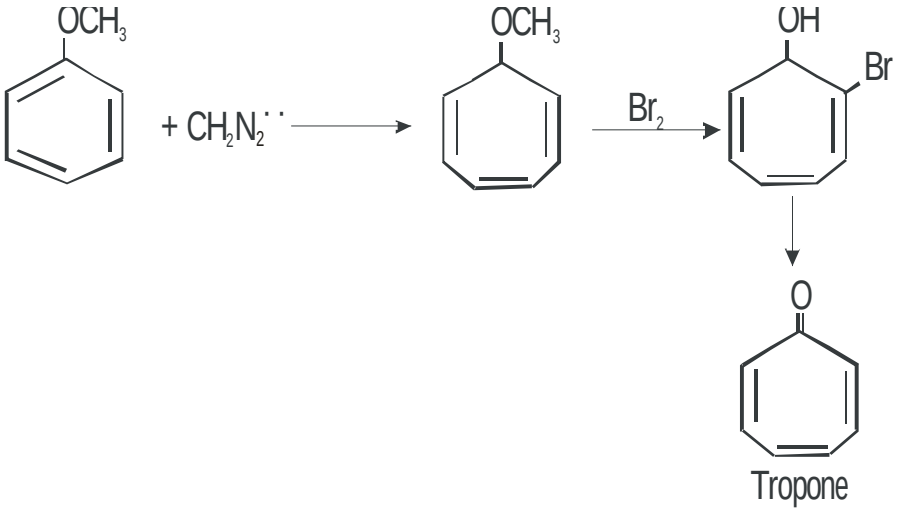
(ii) Tropylium ion reacts with base NaOH to form tropone.



(iii) Oxidation of cycloheptatriene by selenium oxide (SeO_2) to form tropone.



(iv) An anisole when irradiated with light in presence of diazomethane undergo ring expansion to form cycloheptatriene derivatives, which on oxidation with bromine give tropone hydrobromide



10.5.2 Properties of tropone:

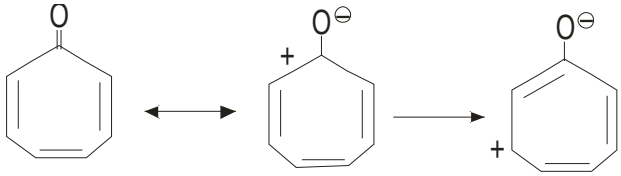
(i) The dipole moment of tropone is 4.3 D.

(ii) Tropone is acidic.

(iii) It gives addition reaction with chlorine and bromine.

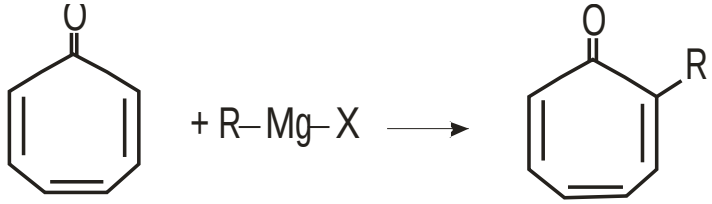
(iv) It decolorizes aqueous potassium permanganate solution.

(v) Tropone is more stable than anticipated because two e^- of C=0 keep away from the ring and are located near the electronegative oxygen. Thus the dipolar structures which provide an aromatic tropylium system provide a better picture of tropone. Such dipolar structure also explain the lack of ketonic properties in tropone.

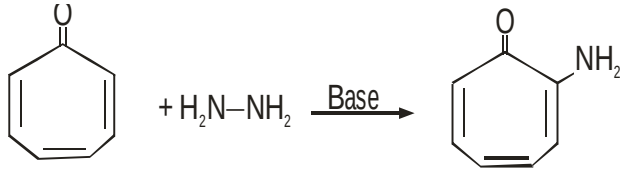


10.5.3 Reactions of tropone:

(i) Reaction of tropone with Grignard reagent or lithium reagent.



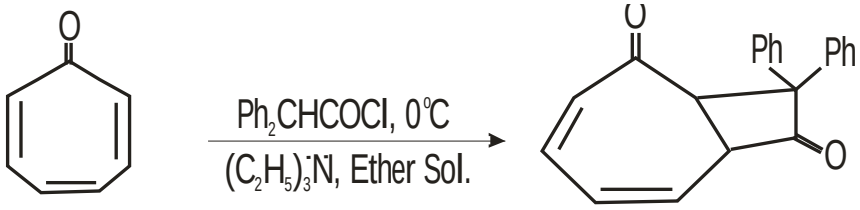
(ii) Reaction of tropone with hydrazine to form 2-amino tropone.



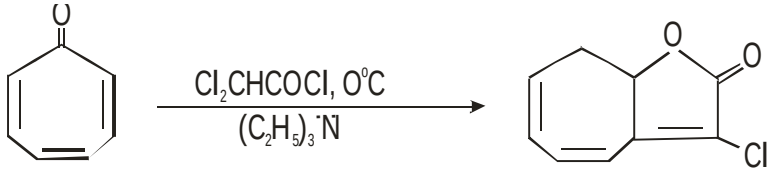
(iii) Cyclo addition reaction of tropone.

There are certain reactions in which tropone take part as an 8π component.

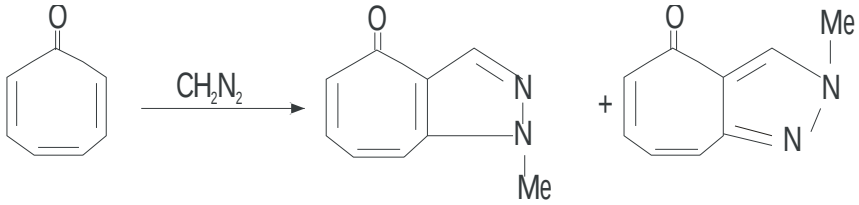
(a)



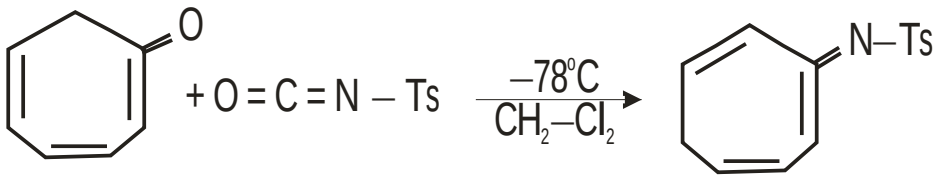
(b)



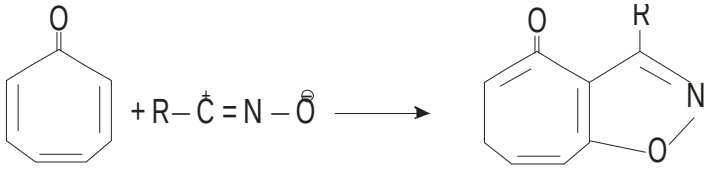
(c) Tropone reacts with diazomethane.



(d) Tropone reacts with isocyanate to form imino derivatives after evolution of CO_2.

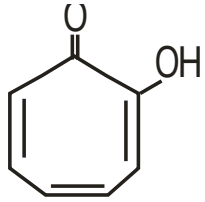


(e) Tropone reacts with cyanate to give adduct product.



10.6 Introduction of tropolone

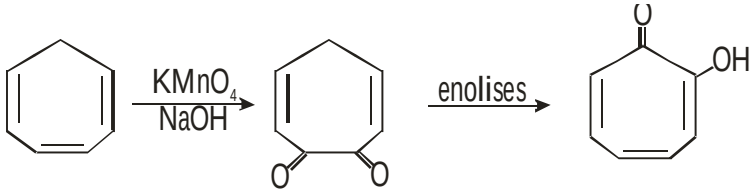
Tropolone or 2-hydroxy tropone is also derivative of cycloheptatriene. Tropolone is also a non-benzenoid aromatic compound.



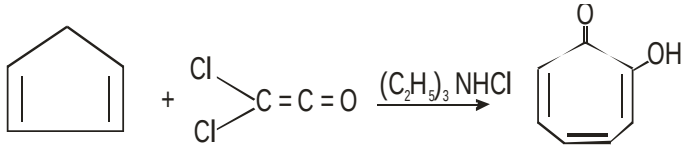
[Tropone, 2-hydroxy, 2, 4, 6 cyclo hepta trienon – $C_7H_6O_2$]

10.6 .1 Synthesis of tropolone

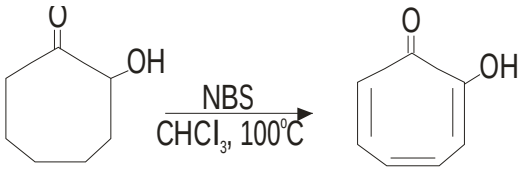
(i) From cycloheptatriene



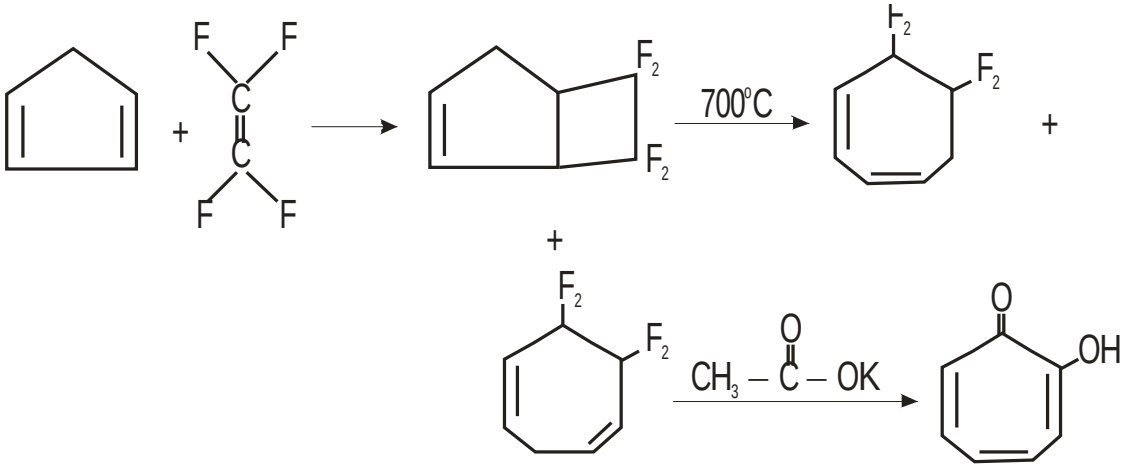
(ii) From reaction between cyclopentadiene and dichloro ketone.



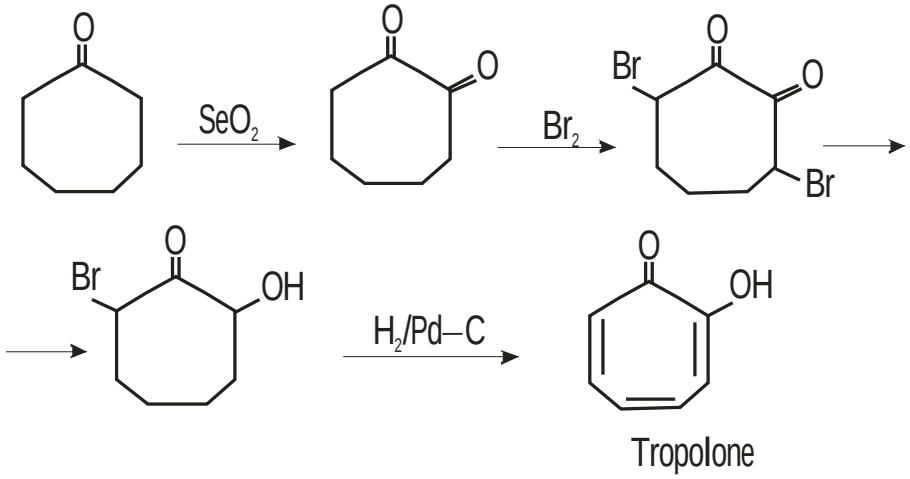
(iii) From 1, 2 cyclo heptaenedione



(iv) From cyclopentadiene:



(v) From cycloheptanone :



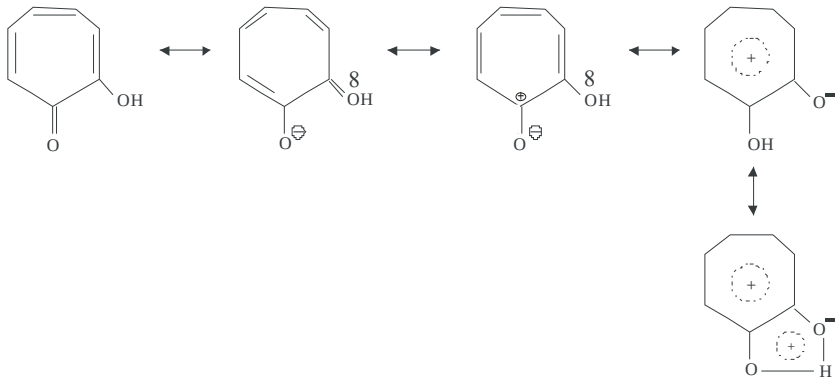
Tropolone

10.6.2 Properties of tropolone:

(i) It has dipole moment 3.17 D.

(ii) Resonance energy 29 K.Cal/mole

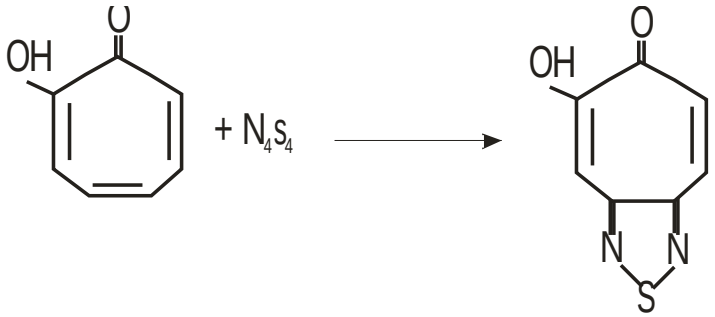
(iii) Tropolone is more acidic than phenol due to resonance stabilized structure; which is shown as following.



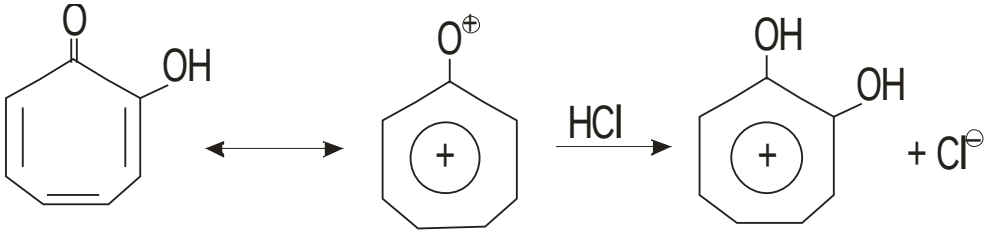
(iv) It soluble in water.

10.6.3 Reaction of tropolone :

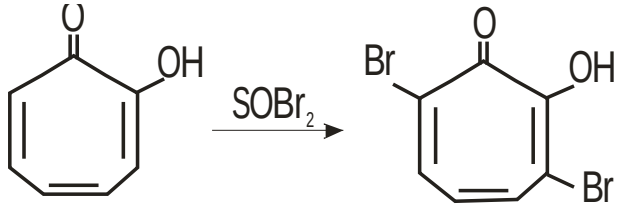
(i) Reaction with N_4S_4 (Tetra sulphure-tetra nitride)



(ii) Reaction with HCl



(iii) Reaction of tropolone with thionyl bromide



3,7 dibromo tropolone

10.7 Summary

- Aromatic compound follow Huckel rule.
- Electrophilic substitutions reactions are characteristic of benzenoid and non-benzenoid aromatic compounds.
- Tropone and tropolone are derivatives of cycloheptatriene.
- Tropone and tropolone is non-benzenoid-aromatic compound, contain delocalized $6\pi e^-$.

10.8 Review questions:

1. Explain Huckel rule with suitable example.
2. Define Benzenoid and Non-benzenoid compounds.
3. What is monocyclic aromatic compound?
4. Give any two preparation method of tropone and tropolne.
5. Define anti aromaticity and apply Huckel rule to it.
6. What are aromatic and anti-aromatic compound.
7. Which of the following ring compounds obey Huckel rule :

$C_{10}H_{10}$, $C_{12}H_{12}$, $C_{12}H_{12}^{2-}$, $C_{12}H_{12}^{2+}$, $C_{20}H_{20}^{-}$, $C_{20}H_{20}^{2+}$

10.9 Reference and suggested readings:

- Organic chemistry R.T. Morrison and R.N. Boyd – (Sixth Edition)
- Advanced-organic chemistry – Jerry – March (Fourth Edition)

- Organic reactions and their mechanism – P.S. kalsi (Second Edition)
- Advanced organic chemistry part-B – F.A. Carrey and R.J. Sundberg.
- Organic chemistry-vod.2, I.L. finar.

Unit – 11

Polycyclic Aromatic Compounds General consideration, synthesis and reactions of phenanthrene

Structure of unit :

11.0 Objective

Naphthalene, anthracene, phenanthrene, fluorine and pyrene etc. are polycyclic aromatic hydrocarbons, which occur in coal-tar. The properties of the polycyclic hydrocarbons relative to benzene. It is important to recognize that we neither expect nor find that all the carbon-carbon bonds in polycyclic hydrocarbons are correspond to benzene bonds.

11.1 General consideration

The chemistry of the compounds of carbon is organic chemistry and compound is organic compound. Organic compound contained the element carbon. Many compounds of carbon are still most conveniently isolated from plant and animal sources, most them are synthesized. There are two large reservoirs of organic

material from which simple organic compounds are obtained like coal and petroleum. These simple compounds are used as building blocks from which larger and more complicated compound can be made. Carbon atoms can form chains thousands of atoms long, or rings of all size. The arrangement of atoms in even relatively small molecules can be very complicated organic chemistry is a field of immerse importance to technology organic chemistry is fundamental to biology and medicine.

The organic compounds known prior to Wohler's synthesis of urea were either derived from fats or natural sources.The term aliphatic is now for compound that has an open chain structure. There were a large number of compounds which were obtained from natural sources and have pleasant odour. Such type of compounds classified as aromatic. It ultimately turned out that aromatic compounds had properties distinct from aliphatic and that benzene was the parent compounds of this class. So the cyclic compound with benzene like properties is known as aromatic compound. Aromatic hydrocarbons are compounds of carbon and hydrogen. Aromatic compounds are monocyclic as well as poly cyclic.

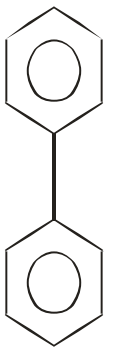
Polycyclic aromatic compounds having two or more benzene rings. Polycyclic aromatic compound can be classified in two groups.

(A) Isolated system

(B) Condensed system

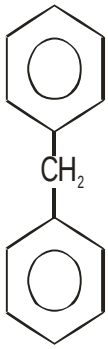
(A) Isolated system:

In this system benzene ring exist as separate isolated units, i.e. one benzene ring is attached to a carbon of another ring, which may be attached to a third or two benzene rings may be linked through a carbon chain.

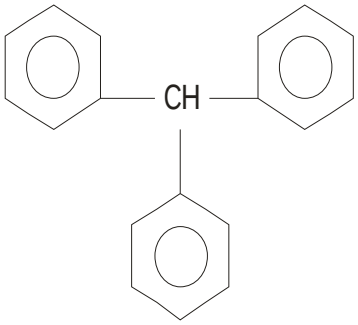


Biphenyl

Terphenyl



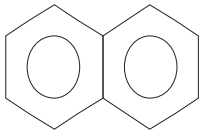
Biphenyl methane



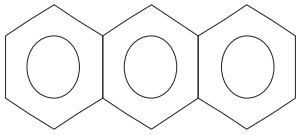
Triphenylmethane

(B) Condensed system:

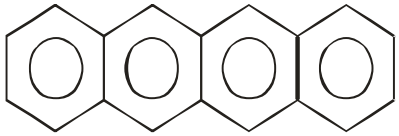
Those polycyclic aromatic compounds, in which two or more benzene rings are fused together so that two carbon atoms are common to adjacent rings, are known as condensed polycyclic aromatic compounds.



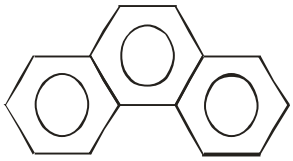
Naphthalene



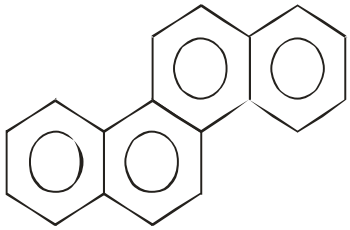
Anthracene



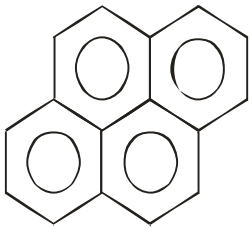
Naphthacene



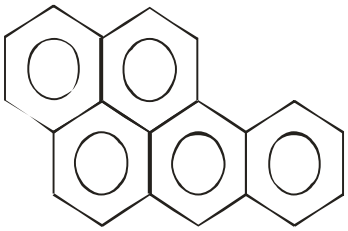
Phenanthrene



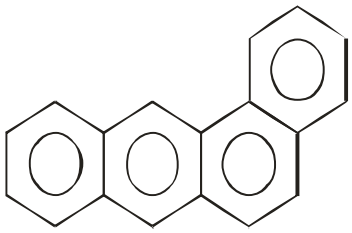
Chrysene



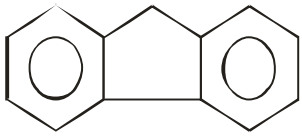
Pyrene



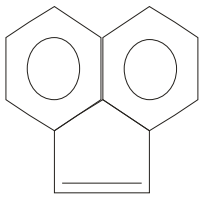
Benzo[a]pyrene



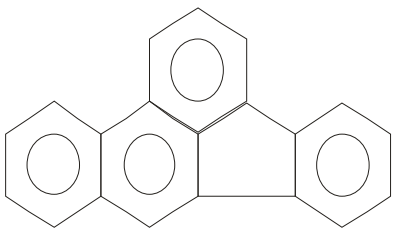
Benz (a) anthracene



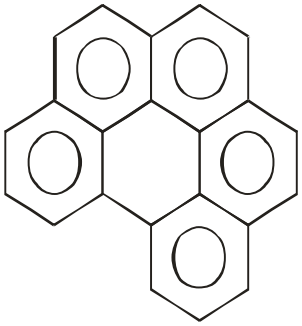
Fluorene



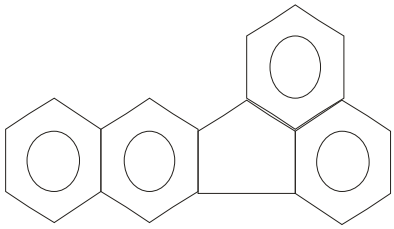
Acenaphthylene



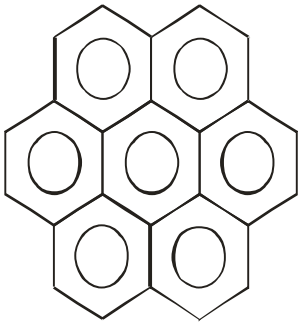
Benz(e)acephenanthylene



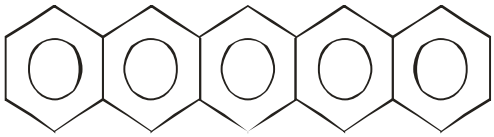
Benzo perylene



Benzo [k] fluoranthene



Coronene

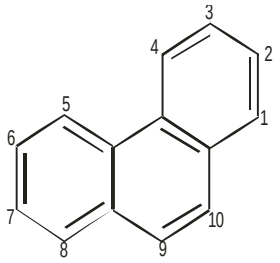


Pentacene

Polycyclic aromatic compounds are a large group of organic compound in which two or more condensed aromatic rings. Polycyclic aromatic compounds are highly lipophilic. Polycyclic aromatic compounds can undergo photo decomposition is ultraviolet light from solar radiation.

11.2 Phenanthrene ($C_{14}H_{10}$)

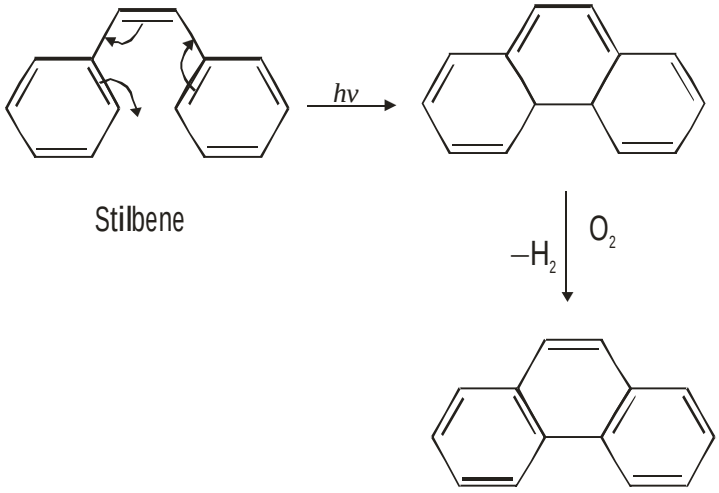
Phenanthrene is polycyclic aromatic compounds which are condensed three benzene rings. Phenanthrene is isomeric with anthracene. It occurs in the anthracene oil fraction of coal tar. Phenanthrene is separated from anthracene by solvent naphtha.



phenanthrene

11.2.1 Synthesis of phenanthrene :

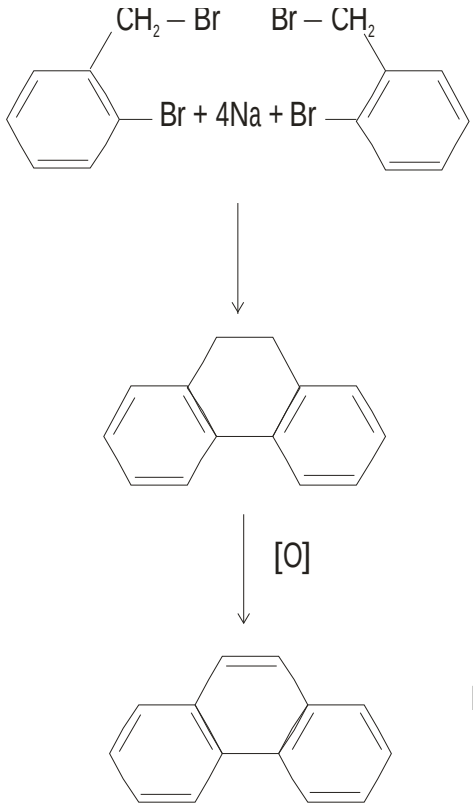
(i) From stilbene:



Stilbene can be converted into phenanthrene in the presence of an oxidizing agent. The reaction is photo chemically allowed conrotatory conversion of 1, 3, 5 hexatriene to a cyclohexadiene followed by removal of two hydrogen atoms.

(ii) Fittig reaction:

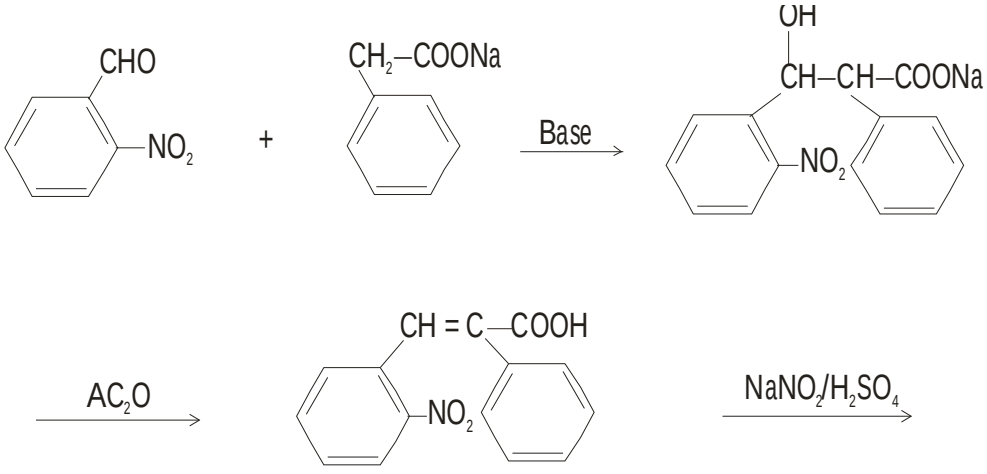
O-Bromobenzyl bromide reacts with sodium to form phenanthrene.

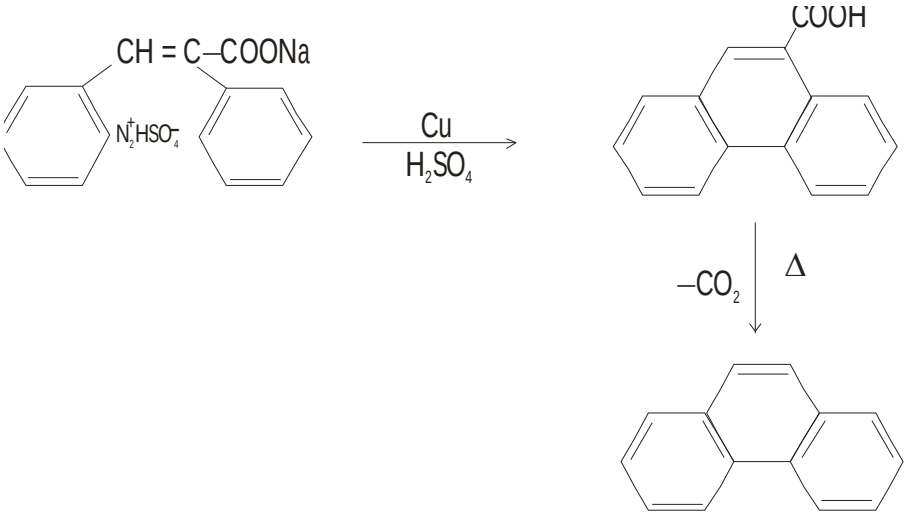


Phenanthrene

(iii) Pschorr synthesis:

Phenanthrene may be prepared with o-nitrobenzaldehyde and sodium β-phenyl acetate.

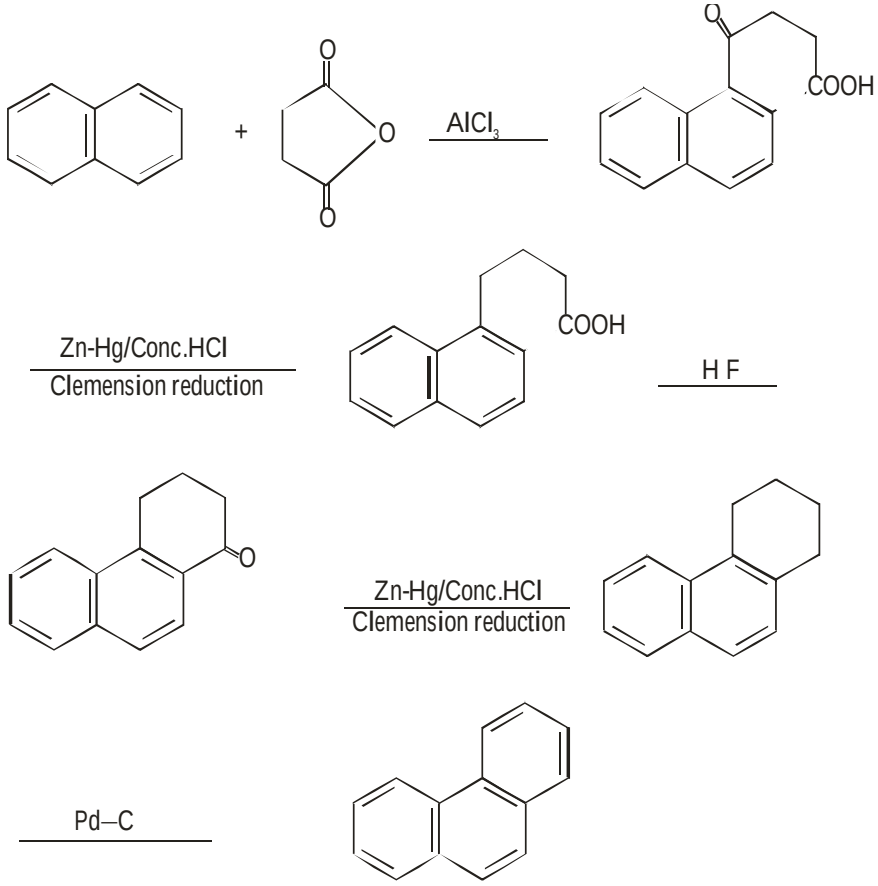




Phenanthrene

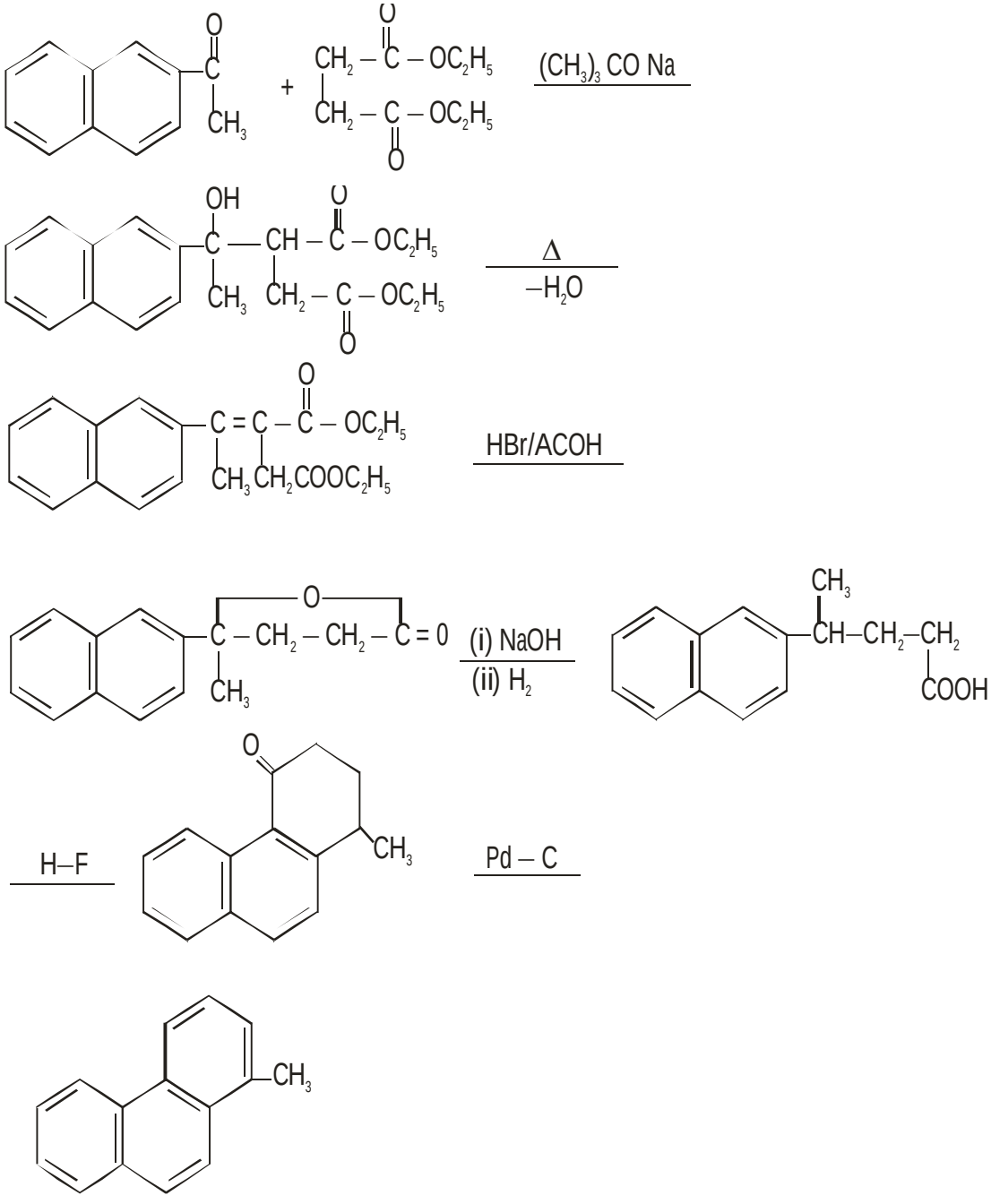
(iv) Haworth synthesis:

Naphthalene reacts with succinic anhydride in the presence of $AlCl_3$.



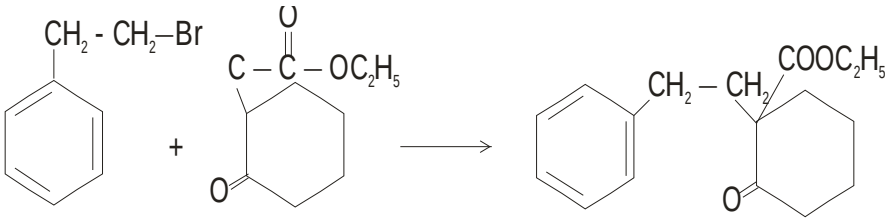
(v) Stobbe condensation:

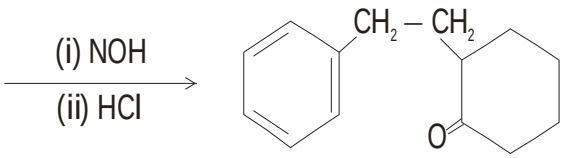
By this method phenanthrene derivatives has been prepared.

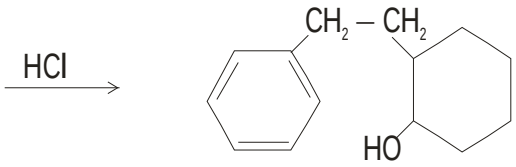


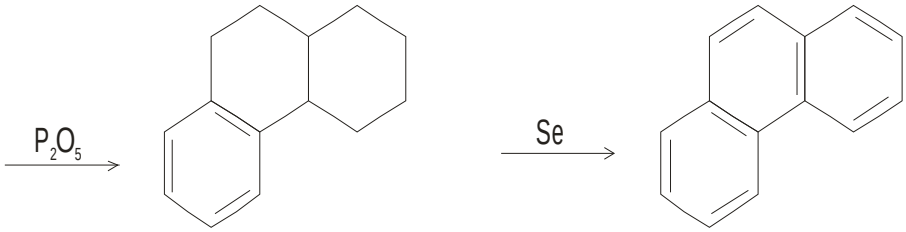
(vi) Bardhan sengupta synthesis:

In this synthesis 2-phenyl ethyl bromide and ethyl cyclohexane-2-carboxylate reacts in following manner.



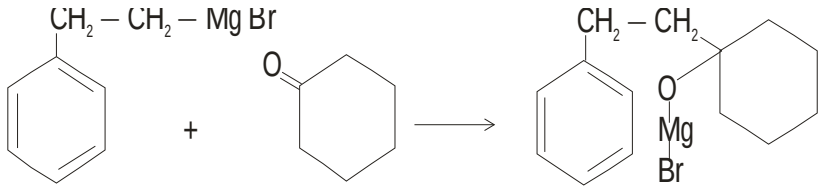


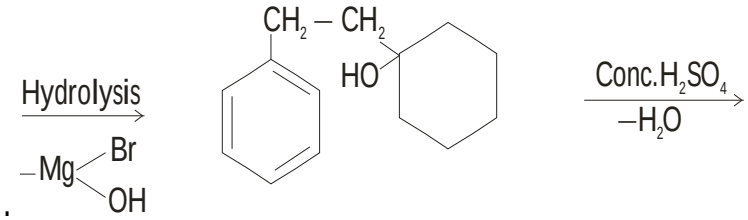




Phenanthrene

(vii) Bogert cook synthesis:





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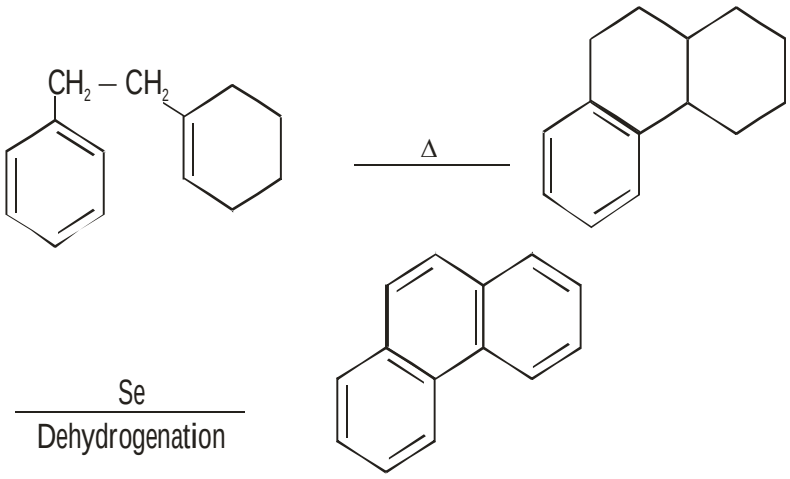
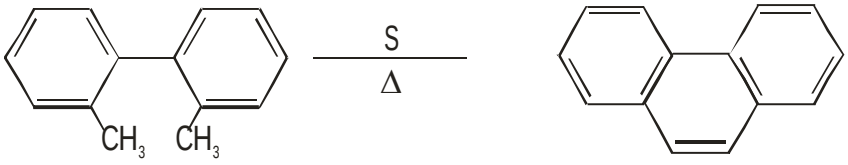


Phenanthrene

(viii) From 2, 2'-dimethyl biphenyl :

Phenanthrene are formed when 2, 2' dimethyl biphenyl passed through a red hot tube in presence of sulphure.



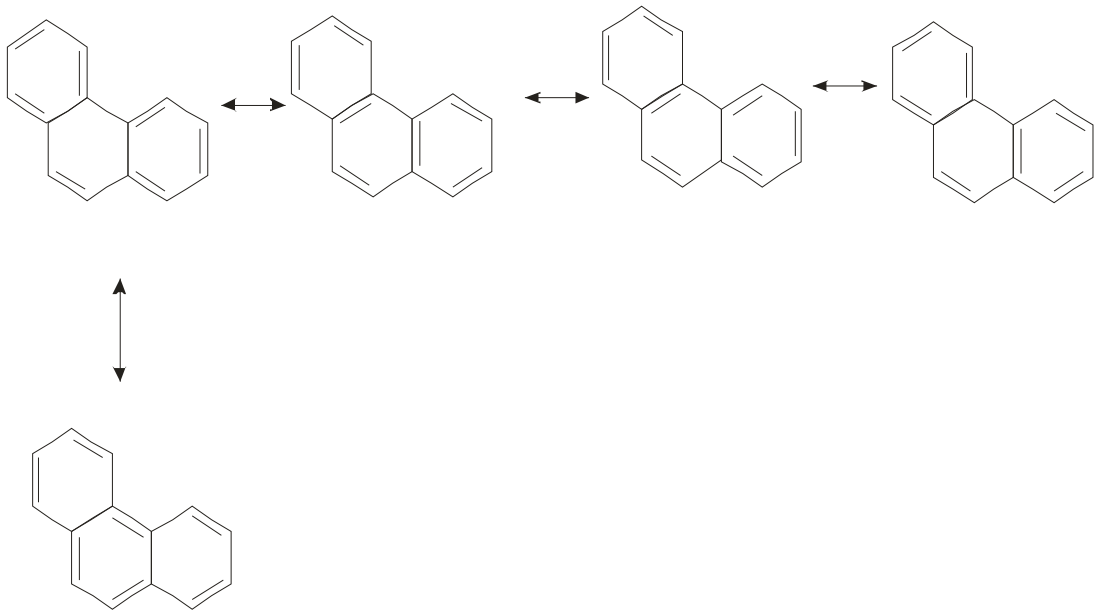
Phenanthrene

11.2.2 Properties of phenanthrene:

The melting point of phenanthrene is 372 K. Phenanthrene shows a blue fluorescence in benzene. The infrared absorption region of phenanthrene shows two bands at 1500 cm^{-1} and 1600 cm^{-1}. Phenanthrene shows a band at 840 cm^{-1}, which is due to two adjacent hydrogen atoms.

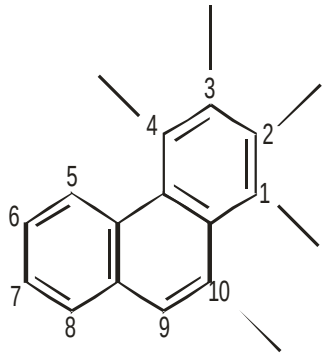
Ultra violet and visible absorption spectra of phenanthrene show three absorption bands (λ_{max}) at 252 nm, 293 nm and 330nm.

11.2.3 Resonance structures of phenanthrene:



11.2.4 Reactions of phenanthrene:

The reactions of the higher hydrocarbons with electrophilic reagents are more complex than of naphthalene. For example, phenanthrene can be nitrated and sulfonated, and the products are mixtures of 1-, 2-, 3-, 4-, and 9-substituted phenanthrenes:

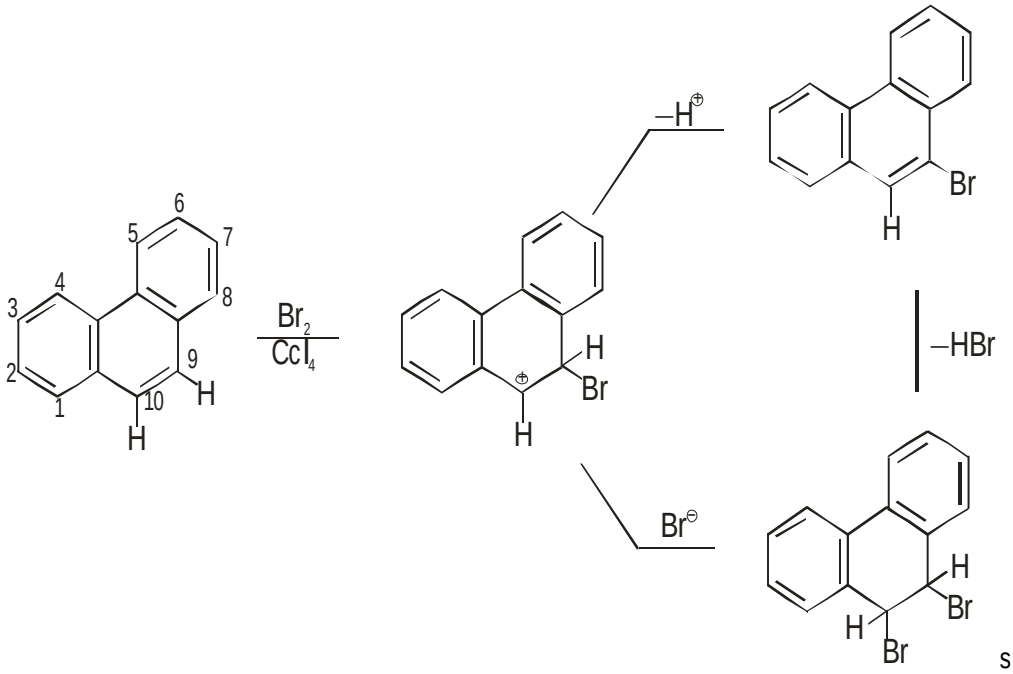


Positions of subsitution of phenanthrene

However, the 9, 10 bond in phenanthrene is quite reactive; in fact it is almost as reactive as an alkene double bond. Phenanthrene gives following reactions.

(i) Bromination

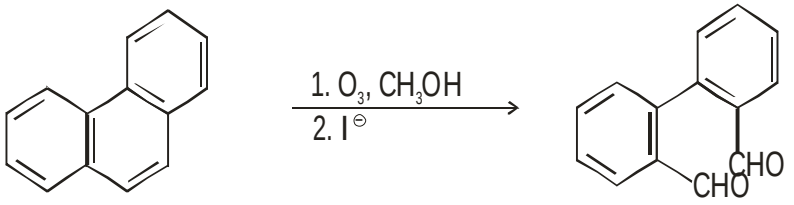
Phenanthrene reacts with bromine in carbon tetrachloride to form 9-bromophenanthrene.



s

(ii) Ozonolysis:

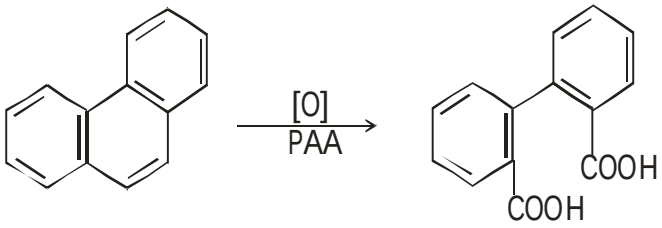
The double bond character of the 9, 10 bond in phenanthrene is particularly evident in ozonization. This bond is attacked preferentially, which leads to the formation of a dialdehyde when the ozonide is reduced with iodide ion.



2,2'-biphenyldicarbaldehyde

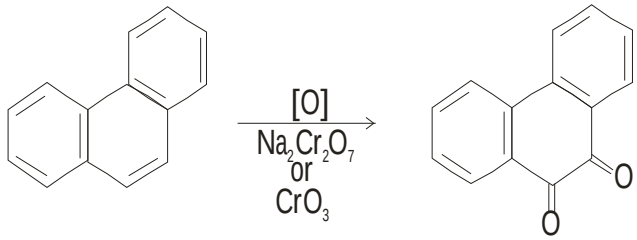
(iii) Oxidation:

(a) Phenanthrene undergoes oxidation with peracetic acid to gives diphenic acid.



9, 10 dicarboxylic phenanthrene.

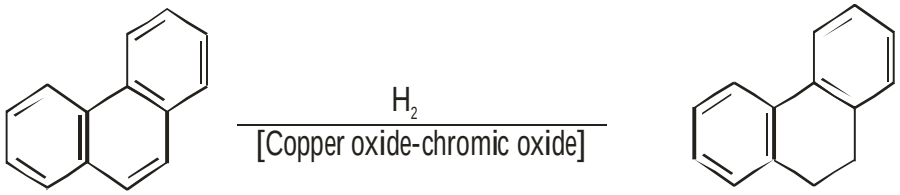
(b) Phenanthrene oxidized with sodium dichromate or chromium trioxide in glacial acetic acid to form phenanthraquinone.



Phenanthraquinone

(vi) Reduction:

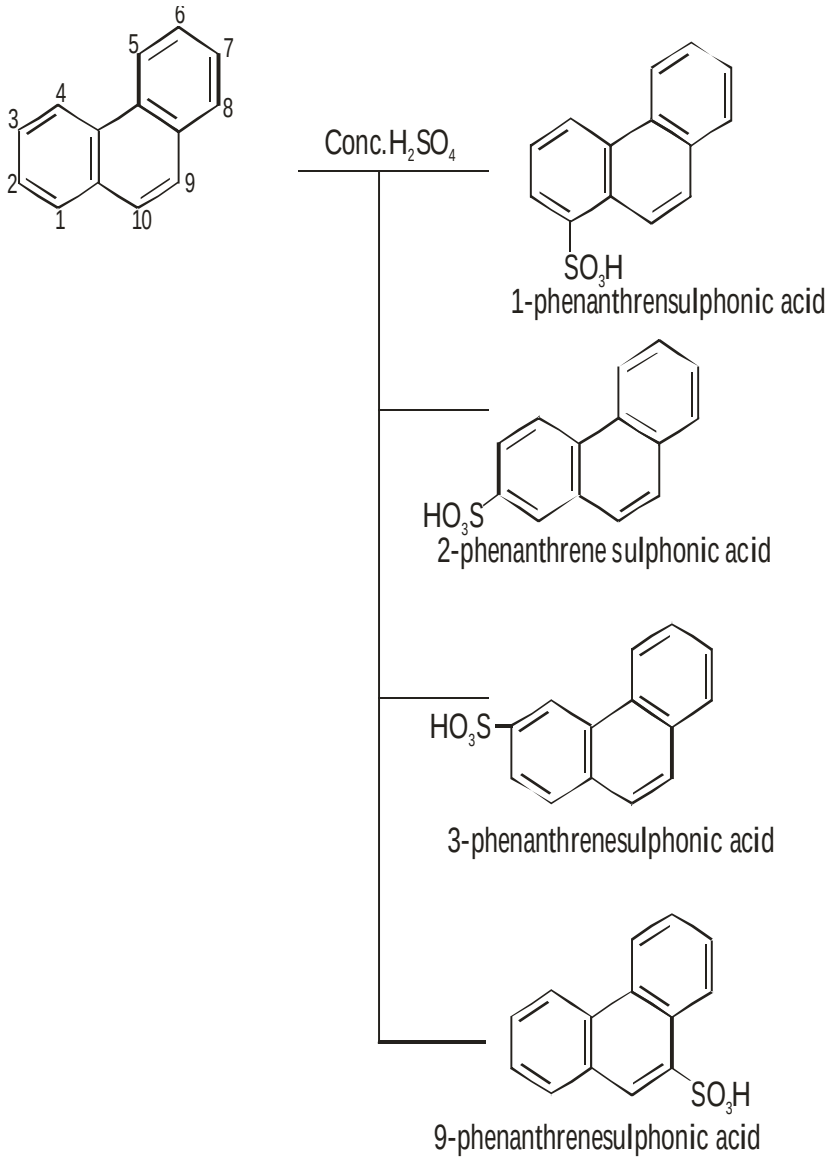
Phenanthrene is readily catalytically reduced to 9, 10 dihydrophenanthrene.



9, 10 dihydro phenanthrene

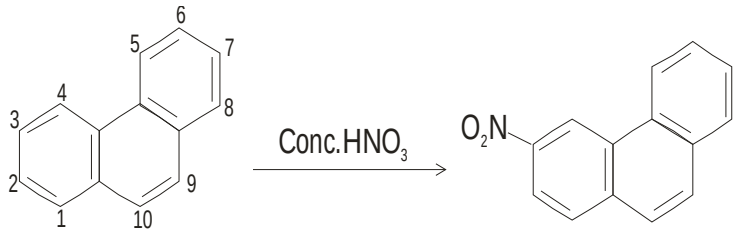
(v) Sulphonation:

Sulphonation of phenanthrene gives a mixture of 1, 2, 3 and 9 phenanthrene sulphonic acids.



(vi) Nitration:

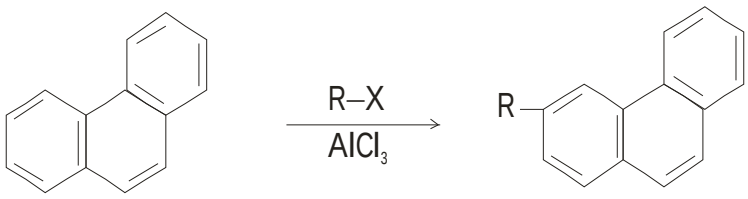
Phenanthrene nitrated with nitric acid to give 3-nitro phenanthrene.



3-Nitrophenanthrene

(vii) Fridal craft reaction:

Phenanthrene reacts with alkyl halide in presence of $AlCl_3$ to form 3-alkyl phenanthrene.



11.3 Summary

Polycyclic aromatic hydrocarbons are a group of organic contaminants that form from the incomplete combustion of coal and gasoline. Polycyclic aromatic hydro carbons are an environmental concern because they are toxic to aquatic life.

11.4 Review questions

1. Convert the following :
   - (i) Phenanthrene $\rightarrow$ Phenanthrene-9-carboxylic acid
   - (ii) Phenanthrene $\rightarrow$ 9-Bromo phenanthrene
   - (iii) Phenanthrene $\rightarrow$ Phenanthraquinone
2. Draw the resonating structure of phenanthrene.
3. How you synthesis phenanthrene, from naphthalene and butyric acid.
4. Define polycyclic aromatic hydrocarbon and draw the structure of following compounds.
   - (a) Naphthacene
   - (b) Fluorene
   - (c) Acenaphthylene
   - (d) Pyrene

5. Give the two preparations methods of phenanthrene.

11.5 Reference and suggested readings :

- Organic chemistry volume-1, I.L. finar
- Organic chemistry volume-2, I.L. finar
- Organic chemistry – R.T. Morrison and R.N. Boyd
- Advance organic chemistry – Jerry march.

Unit -12

Disconnection Approach

Structure of Unit:

An introduction to synthons and synthetic equivalents, Disconnection approach, functional group inters- conversions.

12.0 Objective

organic synthesis takes the central part in sense .various compounds organic as well as inorganic , synthesis by respective chemist have deep impact in the improvements in the quality of human life it will be not wrong to say that no part

of human life can be thought of without organic molecules pharmaceuticals polymers pesticides detergents disinfectants etc are the main classes of the useful compounds the objective of this unit is to synthesise a given compound in such a way that its starting material should be easily available and cost effective . it is establish process that when we plan to synthesis a target molecule a synthetic route is designed for getting it in utmost purity through a convenient procedure in the disconnection approach (also known as retro synthesis) the adopted practise is to evoke various routes for a given target molecule here the initial point is target molecule and the final one is the starting substrate out of various routes one is selected which has logical chemical ground and gives highest yield of the target molecule

12.1 Introduction

In organic chemistry, the compounds which are prepared play important part in various field of life. Polymers, pesticides, Pharmaceuticals, disinfectants, are some example of such compounds. Nature is a very rich source of complex organic molecules which have a wide range of applications and are not inexhaustible thus there appears a strong need to synthesize the compounds for the welfare of humanity.

When a synthesis is planned for a molecule , the problems regarding starting material, determination of structure, isolation of intermediates are of prime importance the essential requirements for a synthesis as that I

(1) It should be started with a swipe and available reagent.
(2) It should involve a easier method.
(3) The desired products should be produced in the minimum period of time.

Prof. R.B. woodward suggested the Art of organic synthesis in which he suggested a logical way in which included the breaking of bonds and remove of various functional groups in the compound to be prepared and to reach the starting material. He was awarded Noble Prize in 1965 for his wonderful contribution. Actually this was reverse of a chemical reaction.

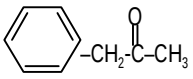
While synthesising a compound we design a route to get the final molecule in is pure form this route involves a chain of steps which converts the commercially available starting molecule into the product in actual practice this route is finalised

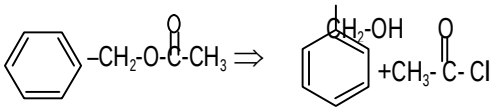
form various route after comparing its merits on the basis of the points such as complexity, intermediates, purity energy barriers, kinetic aspects etc.

12.2 Disconnection Approach

Disconnection approach is a process which involves, breaking of the final product into the starting material by breaking the bonds (disconnection) or by functional group inters conversion. Thus we start up with the product and go backwards towards starting material. In other words it is a reverse break down of the main synthesis or synthesis backwards. Symbolically

$$C \Rightarrow A+B$$

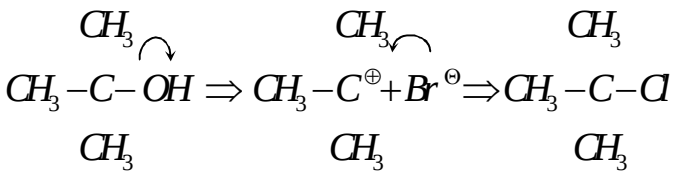
For example let us support let us suppose the molecule to be prepared is  (Benzyethanoate) It is evident hat the above compound, which is an ester, may be prepared in usual way by the chemical reaction (esterificaion) between the benzene alcohol and ethanoyl chloride (in acetyl chloride) Now in the language of retro synthetic way this can be shown as below

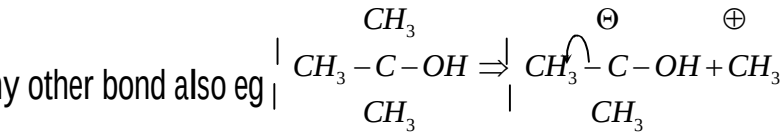


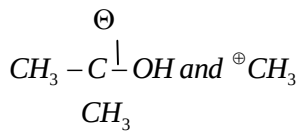
Let us finally take an example in which we synthesis an alcohol from corresponding hands by alkaline hydrolysis ie

$$CH_3-\underset{CH_3}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}-Br \rightarrow CH_3+\underset{CH_3}{\overset{CH_3}{\overset{|}{\underset{|}{C^{\oplus}}}}}+OH^{\ominus} \rightarrow CH_3-\underset{CH_3}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}-OH$$

Now in order to understand the disconnection approach we write the mechanism of the reverse process in the formation of alkyl halide from alcohol ie



The above is the disconnection approach of the synthesis we could have broken any other bond also eg 

But this approach is not satisfactory than the previous one because the intermediates  are highly unlikely and thus the first path is to be preferred because it has a reasonable mechanism also.

In disconnection approach once the target is selected the reaction is developed for the total synthesis. The most critical task is carried out by taking the following points into consideration.

1. Structure of the target.
2. Fundamental knowledge of reactor.
3. Stereo chemical, bounding and reactioly aspects Ace these above factors are then utilised to disconnect various bonds presets in the target.

The total roadmap of synthetic intermediates that insults called retro synthesis.

It is to be noted that the disconnection of certain bonds in the retro synthetic drectian which makes the path simple are called as strategic bonds.

The synthetic route for a retro cyclic synthesis includes some basic and commonly used terms. These are briefly described below.

12.2.1 Disconnection

It is a analytical process or operation which involves breaking of bonds and converting a molecule into a starting material in other words it is reverse of a chemical reaction. The symbol used for this is $\Rightarrow$ and a d curved live (S or nu) put on the bond to be broken.

12.2.2 Reagent

It is a chemical compound which undergoes a chemical reaction to produce either an intermediate or the final molecule.

12.2.3 Target Molcule

It is the chemical compound whose synthesis has been planned by retro cyclic synthesis. The symbol TM is used for it.

12.2.3 Synthons

It is a part or fragment, which generally is an ion, which is produced during disconnection. It may or may not have an involvement is process but indicates about a reageut whither may be of significant use for the synthesis.

12.2.4 Synthetic equivalent

It is an alternate reagent which is used in place of a synthon because of its unusual instability.

12.2.5Transformation

The following transformations get their usual places in retro cyclic synthesis.

(a)Disconnective transformalians

(i) Single fuctional group transformation.

(ii) Multiply fuctional group transformation.

(b) Non-disconnective transformalians

(i) Fuctional group interconversion – This in indicated by writing it over the symbol $\Rightarrow$

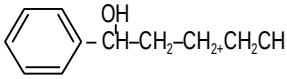
(ii) Fuctional group addition (FGA)

(iii) Fuctional group removal (FGR)

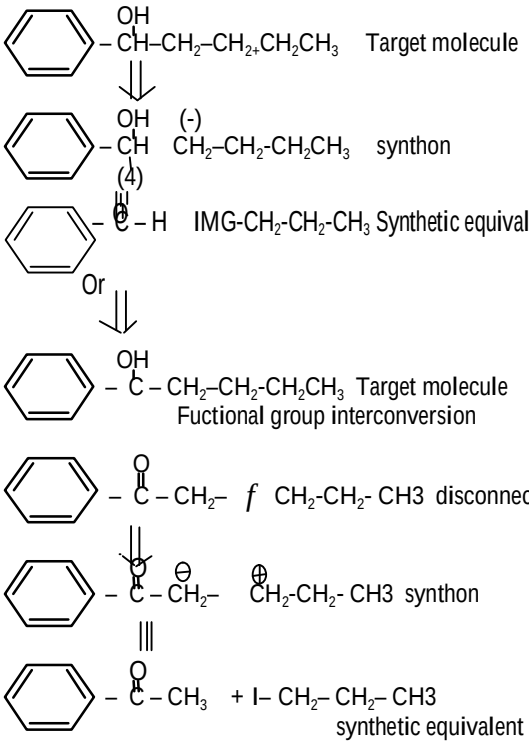
These are also written over the symbol $\Rightarrow$ by putting proper (+ or -) sign before them.

Thus the whole disconnection approach may be represented as

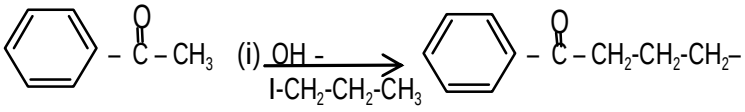
Target molecule $\Rightarrow$ intermediate (a) $\Rightarrow$ Intermediate (b) $\Rightarrow$ Intermediate (c) $\Rightarrow$ Starting material.

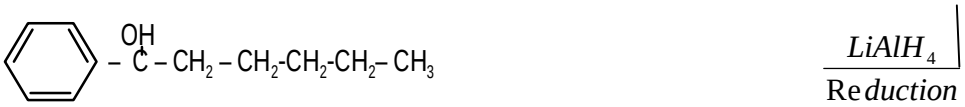
Let us understand it by taking the example of synthesis of 

this can be planned in the following ways.



Synthesis

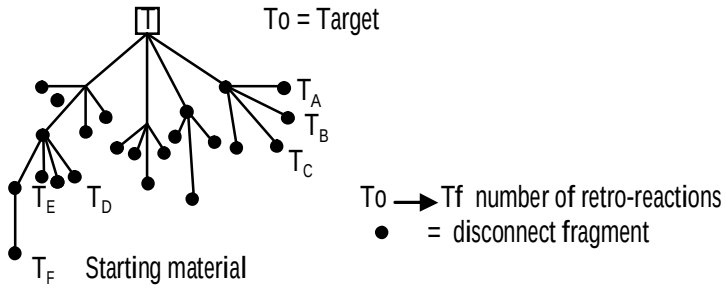




Target – molecule

The process of simplifying the structure V/a disconnection results in the formalian of various fragments which serve as key. Intermediates. These intermediates allow us to connect the starting material to the target molecule in a logical manner. Thus a synthetic tree is constituted following is a synthetic tree for the retro synthesis of a target molecule To which is disconnected to a set of structures which can be

connected is a swingle step leading to the target the subtree shown in the following diagrams show further disconnections. Thus we can have several starting materials which can be used to obtained the target molecule.



(A SYNTHETIC TREE)

Let us now consider the retro synthesis of the compound .

In the above route each succeeding structure has been simplified. Various bonds are disconnected and various functional groups have been transformed till we get the fural simple starting material. Thus we see that the term disconnection means "Mentally breaking bond is such a way so as to get successive simple precursor molecules. But the breaking of these bonds should be done in such a ways so that they can be reformed by simple do usual chemical reactions.

In the above synthesis of target molecule (A) disconnection of bond h gives (B) and its conversion and L- chlorobetone (C) Now a fuctional group transformed is needed to convert (D) into (E) disconnection of bonds R., I land m can also be considered. If the disconnection R is carried out it being be simple and produces (G) and 2- bromobutave which are the real fragmants detailed from disconnection. Consideration of bonds in (G) suggest at least two connections if we disconnect the bond we get (H) whereas disconnection of bond C produces two identical components ie 4- bromoproparol (I) and organocprate derived forms 3- bromocyclopentene (J) Now a fuctional group transformation of (K) Produces the known starting material ie 4- bromobuton -1- oe. After viewing the above retro synthesis the following conclusion may be drawn.

1. There is a correlation between a retrosynthesis tree and refrosynthetic analysis in the sewae that there are several choice corresponding to various brauches of the tree.
2. For a complete synthesis, reageut for each fuctional group transformation and for form swing carbon – carbon bondwing must be provided.
3. The retro synthetic analysis provide only key transformation and not every step.
4. The Structure of target molecule obtained by certain disconnection may result in a different set of strategic bonds so the process should be tried continuously tell a recognizable startwing material is obtained.

12.3 Discorrection of a complex target

In the situation when a complex target molecule is to be synthesised by disconnection approach, the synthetic reconnection this can be illustrated by taking the example of the synthesis of (-) triptolide molecule (A) Its retrosynthesis is shown below. It involves four key steps.

Retrosynthesis of (-) triptolide

(1) The first key step is the construction of triepoxide from benzene precursor.

(2) The record one is the formation of lactone from – COO2H5 subsituted cyclohexanone.

(3) The their step is the formation of a tricyclic ring system by asymmetrical radical cyclisation of (D)

i. The fourth key step is the construction of (D) from 2-isophyephenol (C) by using a chiral alcohol.

Thus we see that the above disconnection approach represents a peculiar one using key chemical transformation viz. Radical cyclization . It is also clear that other disconnection are also possible and they lead to a different synthetic tree.

12.4 Synthons and synthetic equivalents

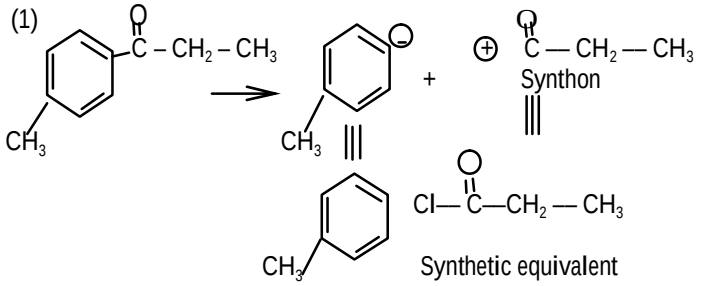
As we have been in our introduction oart the terms sythons and synthetic equivalents are commonly used in retrocyclic synthesis.

A Synthon is either a cation, anion or radical or sometimes a reagent. It is a component which is produced during some step of discormection. It is important to note that this may or may not have an involvement in the synthesis but helps in evaluating a reagent which will be in the retro synthesis of the given target molecule.

In light of the fact that synthons are unstable we use some alternate reagents in place of them to carry out the fuction, of equivalent. At the end of retro synthesis the synthons are replaced by their corresponding synthetic equivalents.

This can be best understood by the following examples.

(1)



(2) $CH_3 - \underset{|}{\overset{OH}{C}}H - CH_2 - CH_3 \Rightarrow CH_3 - \underset{|}{\overset{OH}{C}}H^{\oplus} + {}^{\oplus}CH_2 - CH_2 - CH_3$

Synthons

$CH_3 - \overset{O}{\overset{\|}{C}} - H + Br\,mg - CH_2 - CH_2 - CH_3$

Syntheto equivalent

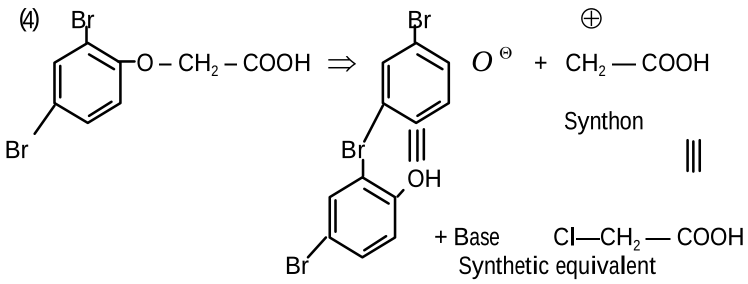
(3) $CH_3 - \underset{|}{\overset{OH}{C}}H - CH_2 - CH_3 \Rightarrow CH_3 - \underset{|}{\overset{OH}{C}}H - CH_2 + CH_2 - CH_3$

Synthons

$CH_3 - \underset{|}{\overset{OH}{C}}H - CH_3 + Br - CH_2 - CH_3$

Syntheto equivalent

(4)



In the following table some commonly used synthetic equivalents and their corresponding synthons are given

Synthon	*Synthetic equvalent*
$\overset{\oplus}{CH_3}$	CH_3Br, CH_3I etc
$\overset{\oplus}{CH_3CH_2}$	CH_3-CH_2Cl, CH_3-CH_2-Br, CH_3-CH_2-I
$C_2H_5-\underset{OH}{C}-\overset{\oplus}{CH_2}$	$C_2H_5-CH-CH_2$ with O bridging CH and CH_2 (epoxide)
$CH_3-CH_2-\underset{OH}{C}-CH_2-CH_3$	$CH_3-CH_2-\underset{O}{C}-CH_2-CH_3$
$CH_3-\overset{O}{\overset{\Vert}{C}}-CH_2-\overset{\oplus}{CH_2}$	$CH_3-\overset{O}{\overset{\Vert}{C}}-CH=CH_2$
$\overset{\ominus}{CH_3}$	CH_3MgBr, CH_3li $licu(ICH_3)_2$
$\overset{\ominus}{C_2H_5}$	C_2H_5MgBr, CH_3li $licu(ICH_5)_2$
$CH_3-\overset{O}{\overset{\Vert}{C}}-\overset{\ominus}{CH_2}$	$CH_3-\overset{O}{\overset{\Vert}{C}}-CH_3$, $CH_3-\overset{O}{\overset{\Vert}{C}}-CH_2-\overset{O}{\overset{\Vert}{C}}-O-CH_2-CH_3$
$CH_3O-\overset{O}{\overset{\Vert}{C}}-\overset{\ominus}{CH_2}$	$CH_3O-\overset{O}{\overset{\Vert}{C}}-CH_3$, $CH_3-O-\overset{O}{\overset{\Vert}{C}}-CH_2-\overset{O}{\overset{\Vert}{C}}-CH_3$
$\times^{\ominus}$	$Na\times$ $\times = cl$ Br or I
$\times^{\oplus}$	$HO\times$ $\times = cl$ Br I
$CN^{\ominus}$	KCN $AgCN$
$NH_2^{\ominus}$	$NaNH_2$
$NO_3^{\ominus}$	$NaNO_3$, KNO_3
$NO_2^{\ominus}$	$NaNO_2$, KNO_2
$\oplus$	$N_2^{\oplus}$

12.5 Fuctional Group Interconversions

Fuctional group interconversion is a very common term used in disconnection approach approach or retrosynthesis. It is abbreviated is FGI and may be defined as.

It is a process which involves the conversion of one fuctional group into the other by usual chemical reaction during a retrosynthesis.

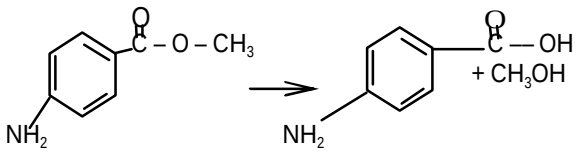
Fuctional group interconversion is carried out through the process of addition, substation, elimination, oxidation or reduction.

It is to be noted that in retro synthesis if the target molecule contains more than one fuctional group, Care should be taken for the relative positions of these groups before planning a systematic route for the underlying synthesis.

A molecule has two pattern of polarity the first one is termed as a consonant pattern and this arised due to the appearance of alternate positive and negative charges due to the presence of atoms of different electro negativities for example - - ----

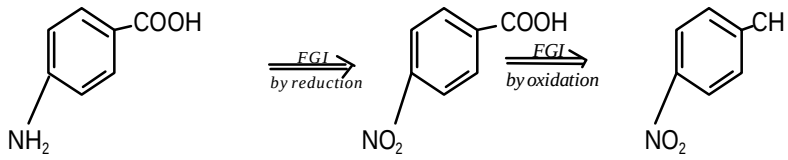
Target molecule having this type of polarity can easily be synthesised by retro synthesis. Another pattern is dissonant pattern in whieto the individual polarities are non- super imposable following examples will make the concept of functional group inter conversion clear.

Example (1) Let us consider the following

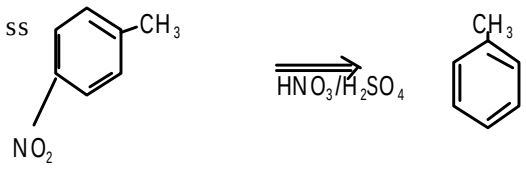


Now the disconnection of ether –COOH or – NH_2 d group from benzene swing is desired, we do not have reverse process of these so the strategy is to operate fuctional group interconversion of these groups into the groups which can easily be disconnected. Now in basic chemistry we know that – NH_2 group is obtained by

the reduction of – NO_2 group and –COOH group can be obtained on benzene ring by the oxidation of –CH_3 group. Thus we plan as follows.



Now to disconnect – NO_2 is easy as follow toluene can easily be nitrated and is available easily also



Example 2

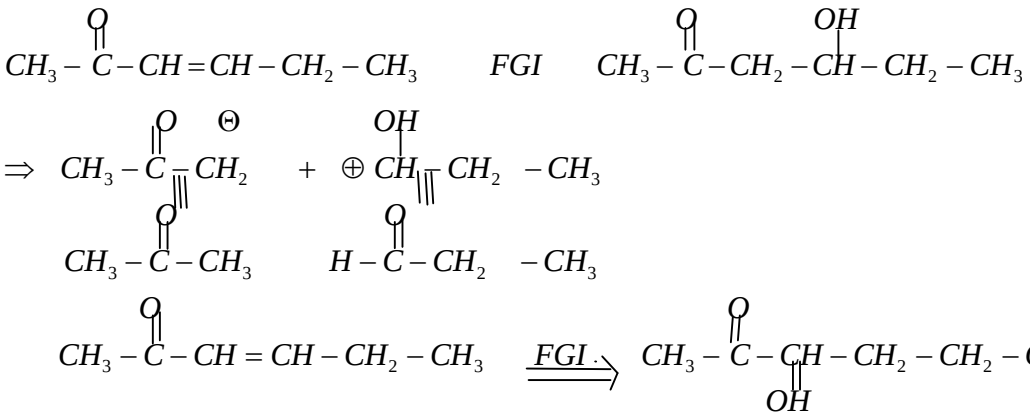
In this let us synthesise a target molecule which contains a double bond and a carbonyl group (>C=O) viz =

||

$$CH_3 - \overset{O}{\overset{\|}{C}} - CH = CH - CH_2 - CH_3$$

Now it is known that dehydration of an alcohol by an acid produces an alkeve so firstly we take up FGI to an alcohol. This has two routes one of consonant and other of dissonant type.

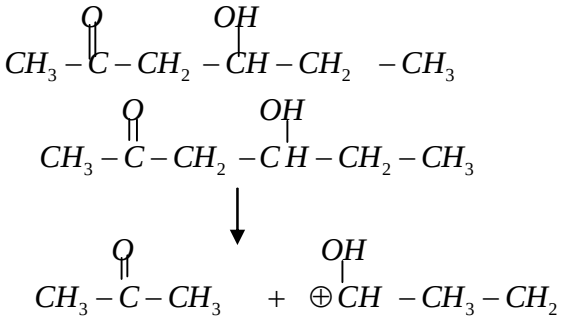
These are show below



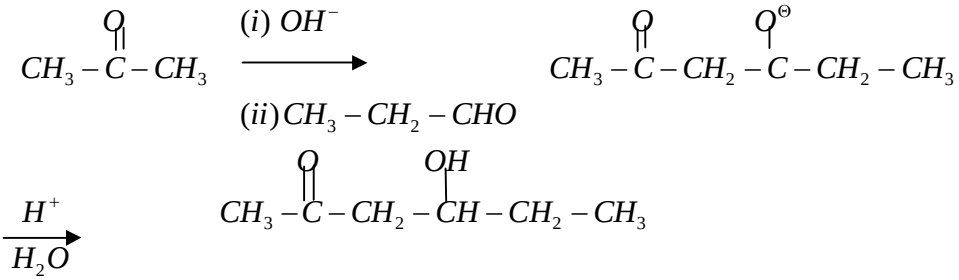
Example 3

Let us consider retrosynthesis of the compound

The route is



Overall Systhesis will be



Following is the sequence which shows some usual fuctional group interconversion

Oxidant	Re*duction*
$-CH_3 \rightarrow -CHO$	$-NO \rightarrow NH_2$
$-NO \rightarrow -NO_2$	$-CH_2OH \rightarrow -CH_3$
$-NH_2 \rightarrow -NO_2$	$-CHO \rightarrow -CH_2cl$
$-CHO \rightarrow -COOH$	$-COOH \rightarrow -CH_2OH$
$-CH_2OH \rightarrow COOH$	$-CHO \rightarrow -CH_3$
$R-CH-OH \rightarrow R-C=O$	$-CX_3 \rightarrow CH_3$
$-CH_3 \rightarrow COOH$	$-CHO \rightarrow CH_2OH$

$-COOH \rightarrow COCl$

$-NH_2 \rightarrow H$

$-C(=O)-Cl \rightarrow -COOH$

$-C(=O)-NH_2 \rightarrow -C\equiv N$

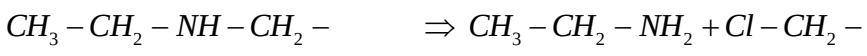
$-COOH \rightarrow CONH_2$

$-C\equiv N \rightarrow COOH$

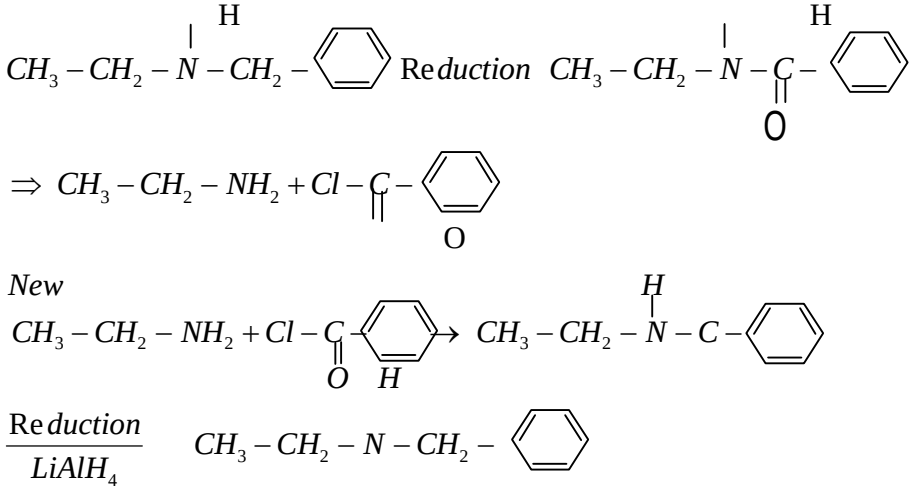
Miscellenious

In some situation the problem of chemo selectivity appear is where the group to be disconnected is more reactive than the starting material (reactant). In such cases the

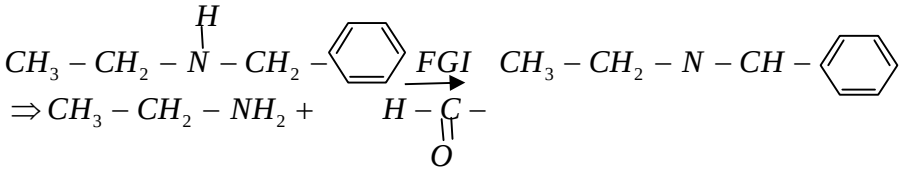

disconnection is affected by a less reactive group through fuction group interconversion. This will be clear from the following example.



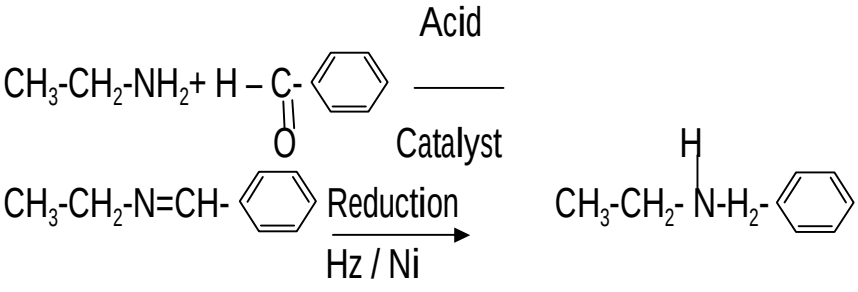
Here we see that the target molecule is more reactive and there is a possibility of poly alkylation. This is solved through FGI by converting the arvives into a less reactive amsde and now the reduction of amide to anmive is feasible. This is shown below



There is a another way also. We convert the anime into imino which in turn can be converted into a amine and carbonyl compound eg.



Thus we have



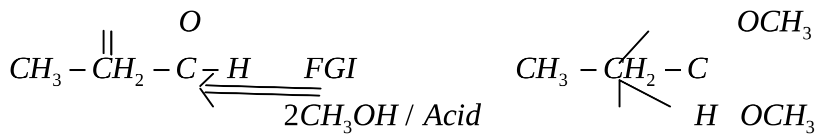
Based upon the oxidation state the following types of fuctional group Interconversions have been categorised.

(A) The first category includes alcohols and all those compounds which are the derivatives of these alcohols, ie ethers triols, amines disulphides the –OH group is replaced by a better leaving group and then the other nucleophile is introduced

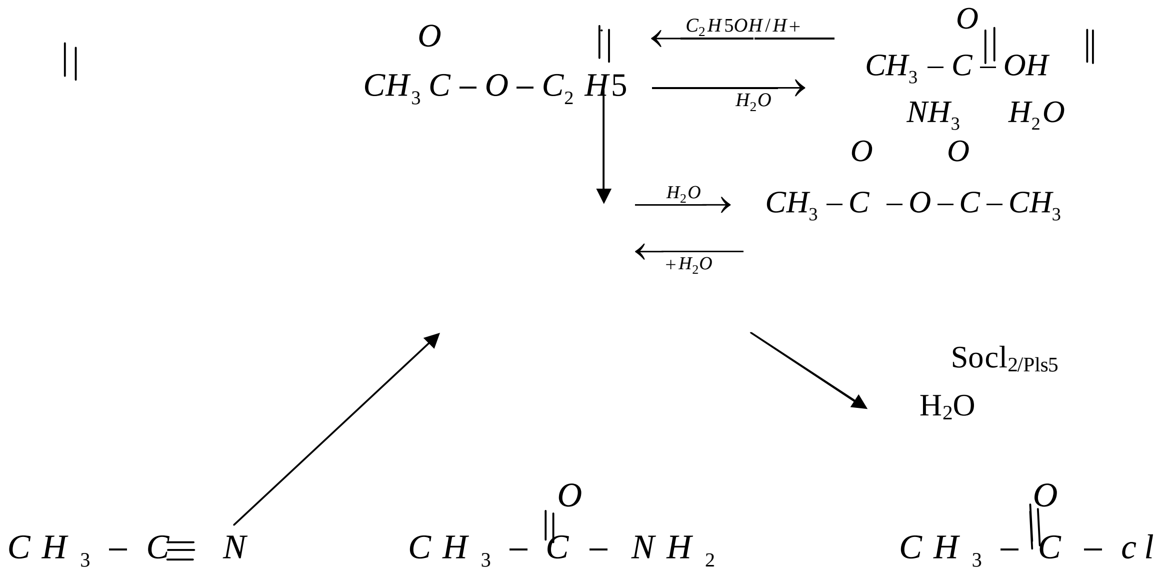
$$CH_3-CH_2-OH \longrightarrow \underset{Z}{CH_3-CH_2} \quad \frac{\overset{\Theta}{Nu}\ SN^2}{-Z} \quad CH_3-CH_2-Nu$$

Z = better leaving group

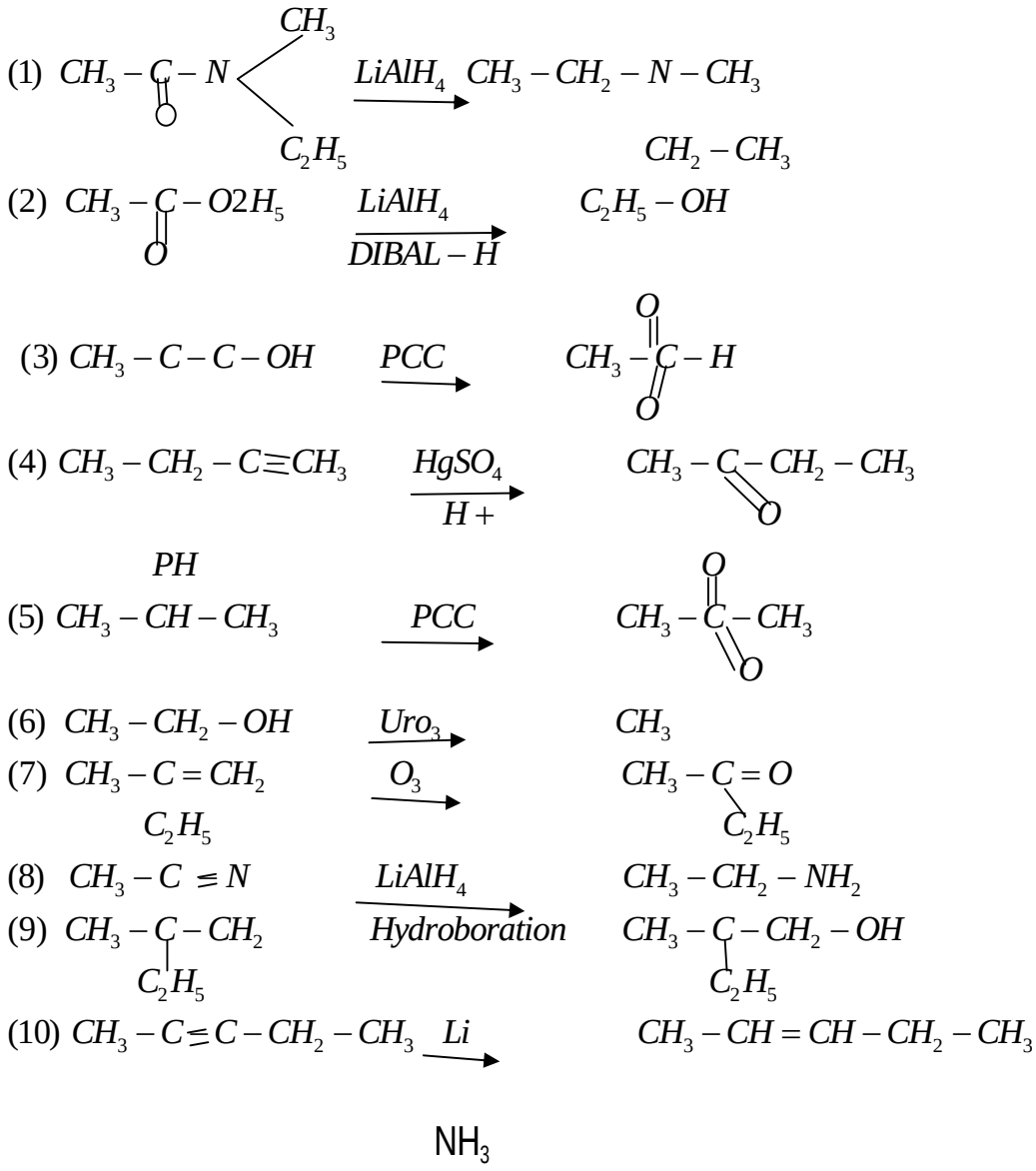
The second category includes aldehydes, ketones and their derivatives like Hydrozone, oximes. Here FGI is carried out by usual addition pr dehydration process.



a. In third category includes carboxylic acids and their derivatives such as ester, amide, chloride and anhydride. The FGI is carried out as show below.



Following are some common reagent used for various interconversions of fuctional groups.



12.6 General guide line for choosing disconnection

The overall goal of disconnection approach is to get back to staring materials that are available with chemical suppliers and also to do this in an maximum possible efficient way. The most important point in a retro synthetic analysis is to spot the stage where the disconnection has to be made the following are guide lines which will helpful in disconnection approach

GUIDELINE 1

Disconnection must correspond to the reverse of real and workable reactions

In disconnection approach we must have a real reaction for the re-establish ment of the disconnected bond during the actual forward synthesis of the target molecule for example in case when oxygen atom is to be disconnected the ease of the formation of ethers is considered. so we choose not to disconnect on the aromatic side of the atom because it is known that there is no real nucleophile attack of an alcohol on a deactivated aromatic ring

GIDELINE II

This guide line is useful for the retro synthesis of esters, amides, ethers amines etc because these compounds can be usually be prepared by substitution reactions

The guide line is if the target molecule has two parts connected by a hetero atom it is advised o disconnect next to the hetero atom. This guide line has been found very useful in the retro synthetic analysis of cat been ethyl esters which is a precursor to a drug used for lowering blood lipid level, because it is an amine and hence a according to the above guideline we disconnect next to the nitrogen atom.

GUIDELINE III

this guide line is related to problem of chemoselectiviy some time it so happens that in a chemical reaction one functional group in a molecule reacts leaving other functional groups which are also potentially reactive such a reaction is said to display chemo selectivity and is called as a chemo selective reaction, the guide line about this problem lies in the consideration of alternate disconnection and to select route or routes which will avoid chemoselectivity.this done by disconnecting first that group which is more reactive. This guide line is usedfd in the synthesis of a potential anti – obesity drug ICI--D7114 which contains an amine and two ether groups and requires several disconnections to take it back to the available starting material.

12.7 Importance of the order of events in organic synthesis

In retro synthesis the question of the order in which reactions should be carried out during the synthesis is a very important task in selecting the order of events or reactions we can laid down some general guidelines which are described below

GUIDELINE I

according to this guide line it is advised to disconnect all groups in turn and see whether the reverse reactions would give right orientations .this is used in the synthesis of ketones here the correct order is the alkylation followed by acylation but not the reverse

GUIDELINE II

this guide line refers to the choice for the disconnecti8on .if there is a choice that group should be disconnected first which is most electron withdrawing because of its deactivating character it will be evidently difficult to introduce any other substituent in its presence. Appropriate reagents needs concern in this reference.

GUIDELIE III

This guide line is related to functional group interconversion in case if FGI is needed during a synthesis it may change the directive influence of the group. in order to avoid it other substituent may be added either before or after the FGI,for example

o,p-directing methyl group→COOH m-directing.

o,p directing Methyl group→CCl_3/CF_3 m – directing

Meta directing NO_2→NH_2 o,p directing

GUIDELINEIV

If a nucleophile is to be substituted on a diazonium salt obtained from an amine these groups are substituted at the amine stage because amino group is strongly orhto and para directing

GUIDELINE V

If two o/p directing groups are to be introduced meta to each other than a dummy amino group is introduced and is than removed by diazotization and reduction

12.8 Summary

- An analytical organic chemist always fights the challenges to prepare the desired organic compound
- The compound has various functional groups which decide their use in a particular field

- Insertion of functional groups is of prime challenge for an organic chemist
- Insertion of a particular group is not a free process
- the process of synthesis is under the constrain of certain regulations which put a limitation on the synthesis of a organic molecule by a specific path
- If the compound to be synthesised has a large scale use the problems associated with pollution and eco environment is also becomes an additional challenge in the way of the synthesis
- Green chemical synthesis usually adopted by the chemist does not solve teh problem on complete basis.
- The above challenges force the synthetic organic chemist to search alternative synthetic route to be developed for the production of the given molecule for this purpose various plausible routes are thought of.
- It is the job of chemist to pick up that path which is (a) most efficient (b) kinetically fast(thermodynamically possible and (d) cost effective
- In the present unit the above problems have been amicably solved with the help of disconnection approach.
- The approach has been discussed from the ground level.
- It involves disconnection of the target molecule at various sites in different ways
- The use of synthones and / or synthetic equivalents has been elaborated so that it may become an easy task for the beginners
- Various reagents have been discussed which are used for disconnecting the functional variability of the target molecule
- Reagent used for the insertion of the various group have been also been given proper considerations
- Intermediates which occur during the course of synthesis have been discussed on the basis their stabilities.
- functional group interconversion which is the most important domain has been given especial priority

12.9 Review Question

1. What is Retrosynthetic analysis?
2. Define FGA and FGI
3. explain Synthons and Synthetic Euivalent?
4. Suggest the routes of disconnection of the following compounds
5. Discuss the importance of the order of events in organic synthetic .support your answere with suitable example

12.10 Refrence Book

- The disconnection Approach,S.C Ameta ,Sadguru publication
- Designing Organic Synthesis , Stuart warren, Wiley india private Limited.
- Organic synthesis, Jagdambha Singh, Paragti Prakashan.

Unit - 13

Disconnections of C-X Group

Structure of unit:

13.0 Objective

Chemistry is above all a creative science. A limited amount of dyes and drugs can be isolated from plants or animals. Therefore we need a plan by which these compound could be synthesized. The aim of this unit is to show how this planning is done : to help learn the disconnection or synthon approach to organic synthesis.

This approach is analytical : we start with the molecule we want to make (the target molecule) and break it down by a series of dissconections in to possible starting materials.

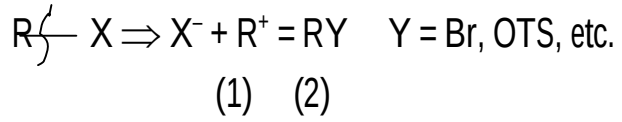
13.1 Introduction

Many organic compounds have molecular skeletons containing heteroatoms i.e. atom other than carbon. In this chapter we will deal with few general points in relation to carbon-heteroatom bond formation.

13.2 One-group C–X Disconnections

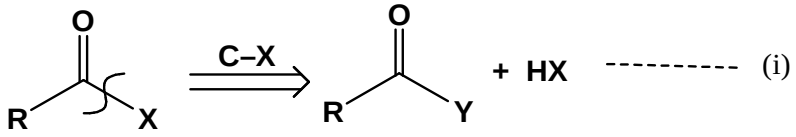
In ethers, amides and sulphides, the position of disconnection can be decided easily. We disconnect a bond joining carbon to the heteroatom (X). First we have recognized a single functional group and then disconnect corresponded to a well known reliable reaction to make that functional group. This approach is known as one group disconnection. The label 'C–X' or 'C–N' etc. can be used.

The corresponding reactions are generally ionic and involve nucleophilic heteroatoms as in amines, alcohols or thiols. Therefore, the disconnection will give a cationic carbon synthon (1). The Reagent for (1) will usually have a good leaving group attached to R (2) or we can say, the reaction is a substitution of some kind and the reagents will be alkyl halides, acid chlorides etc. and best reagents are those which undergo substitution readily.



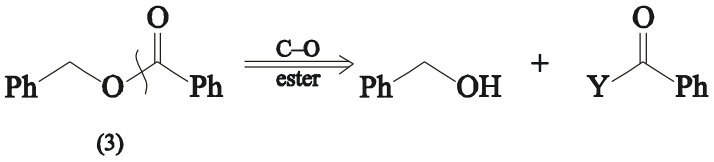
13.2.1 Carbonyl Derivatives (RCOX)

Acid derivatives can be disconnect easily, as we almost always choose the bond between the carbonyl group and the heteroatom for our first disconnection (i)



The ester (3), which is used both as an insect repellent and as a solvent in perfumery can be disconnected as follows.

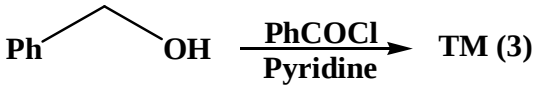
Retrosynthetic analysis of TM (3)



(3)

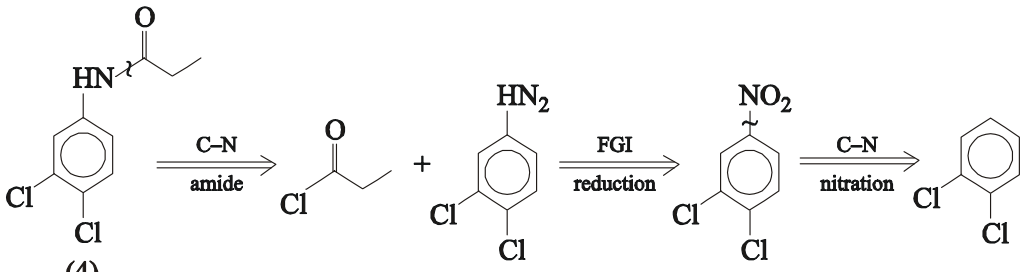
The synthesis can be carried out in a number of ways using acid chloride, acid anhydride etc. Perhaps the acid chloride route (Y = Cl) is the easiest, with pyridine as catalyst and solvent.

Synthesis



The weed Killer Propanil (4) used in rice field is an amide. Its retrosynthestic analysis and synthesis are as follows :

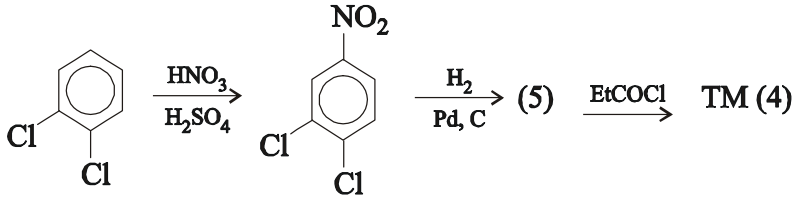
Retrosynthetic analysis of TM (4)



(4) (5)

The orientation for nitration is correct; steric hindrance will prevent formation of much 1,2,3-trisubstituted compound.

Synthesis



13.2.2 Compounds containing –OH (alcohol) or –X (halide) group

Disconnection of C–X in aliphatic compound (RX) gives a nucleophile (HX) and an electrophillic carbon species usually represented by an alkyl halide, tosylate (OTs), mesylate (OMs). All of these compounds can be made from alcohols and as

we know that alcohols can be made by C–C bond formation, so we can treat the alcohol as the central functional group (Table 1).

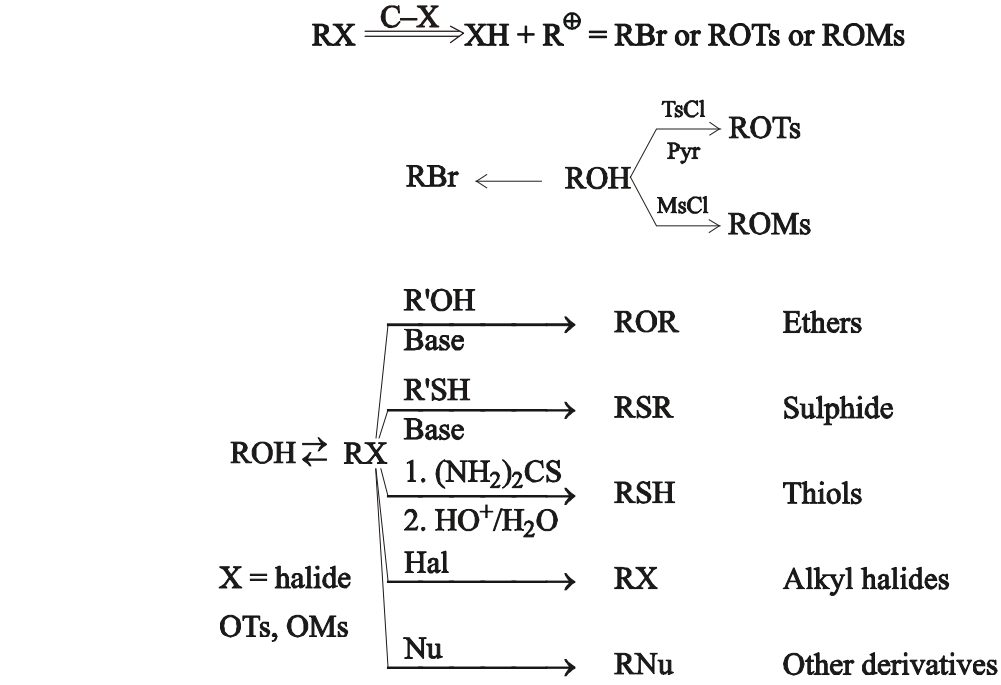


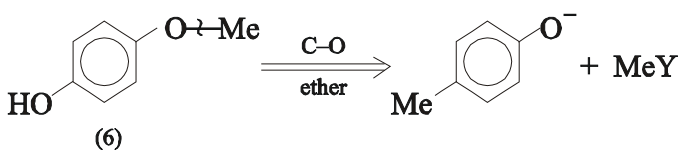
Table 1 : Aliphatic compounds derived from alcohols

When the organic compounds (TM) containing these functional groups are planned to be synthesized, these group are first converted into C–OH or C–X by FGI and then disconnected.

13.2.3 Compounds containing –OR (Ether) or –SR (Sulphide) group

These compounds have two choice where C–X disconnection can be made (Heteroatom is bivalent). One has to choose the reactive side for disconnection.

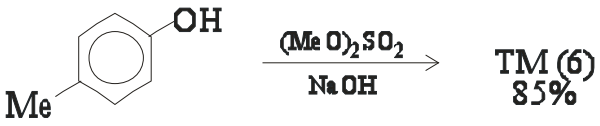
Retrosynthetic analysis of TM (6)



(6)

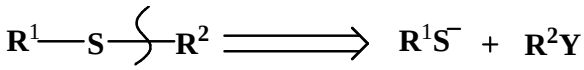
Dimethyl sulphate is used for methylation of phenols in alkaline solution where the phenol is ionised. Since the mechanism is S_N2, the more powerfully nucleophilic anion is an advantage.

Synthesis



In this example oxygen atom has a reactive side (Me, by SN^2) and an unreactive (Ar) side so disconnection is easy.

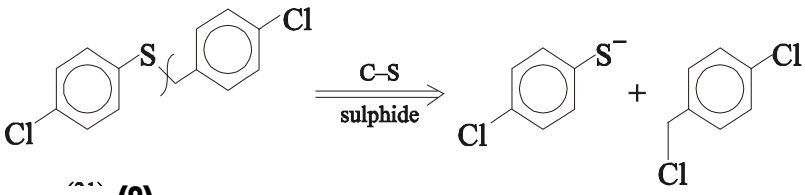
The same strategy can be apply to sulphide (R^1SR^2) synthesis. The reaction is even easier by S_N2 as thiols ionise at a lower pKa than alcohols, the anion (7) is softer than RO^- and thus it is more nucleophilic towards sp^3 carbon.



(7)

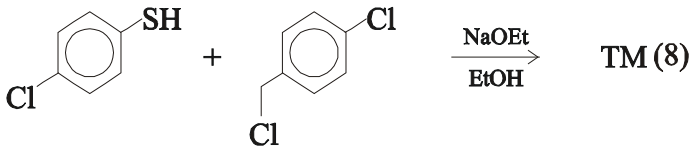
The acaricide is used to kill mites and ticks. Chlorbenside (8) is disconnected on the alkyl rather than the aryl side.

Retrosynthetic analysis of TM (8)



(8)

Synthesis



13.3 Two group C–X disconnections

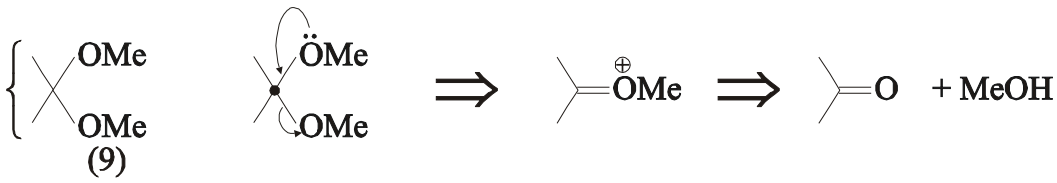
The disconnections which we have used so far have been 'One group' disconnections, that is we have recognised a single functional group and the disconnection corresponded to a reliable reaction to make that functional group. An important extension of this method is to use one functional group to help disconnect another elsewhere in the molecule.

The compounds which shows two group C-X disconnection have two heteroatoms, which are directly linked to carbon. These two heteroatom may be bonded to single carbon atom or bonded to different carbon atoms in a molecule. Disconnection of such type of compounds can be explained as :

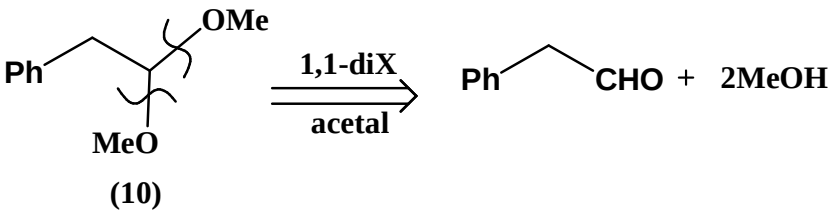
(i) Disconnection of 1,1-difunctionalized compounds
(ii) Disconnection of 1,2-difunctionalized compounds
(iii) Disconnection of 1,3-difunctionalized compounds
(iv) Disconnection of 1,4-difunctionalized compounds
(v) Disconnection of 1,5 and 1,6-difunctionalized compounds

13.3.1 Disconnection of 1,1-difunctionalized compounds

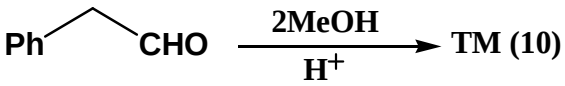
Examples are acetals (9) or ketals where two heteroatom are attached to same carbon. In these compounds we can use one oxygen atom to help disconnect the other. Both C–O bonds therefore should be disconnected and we can label the operation as '1,1-dix to show it.



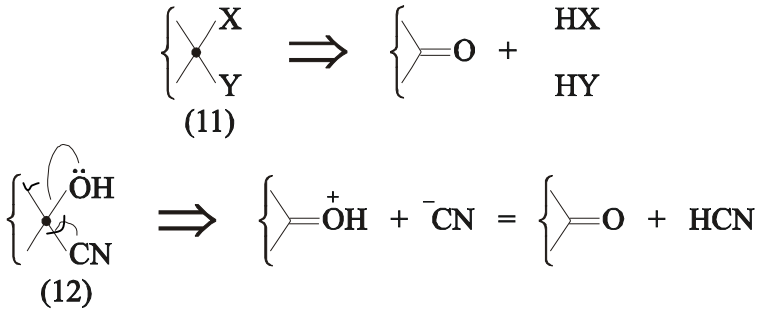
Retrosynthetic analysis of TM (10)



Synthesis

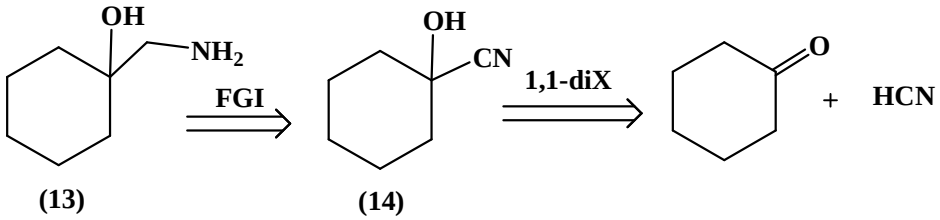


Acetals are examples of a general type of molecule (11) in which two heteroatoms are both joined to the same carbon atom. This carbon atom (• in 11) is then at the oxidation level of a carbonyl group, and the molecule is made from a carbonyl compound and two nucleophiles.

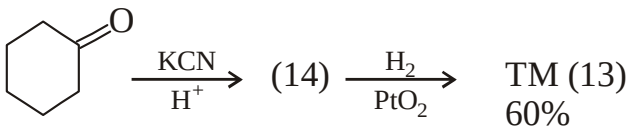


When one of the heteroatoms is present as an OH group then only one nucleophile is involved. The molecules such as cyanohydrins (12) are easily made from carbonyl compounds and HCN. Hence hydroxyl amine (13) can be made by reduction of (14) and hence from cyclohexanone.

Retrosynthetic Analysis of TM (13)

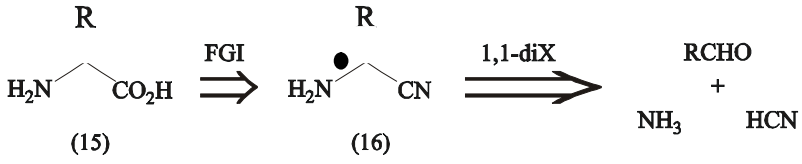


Synthesis

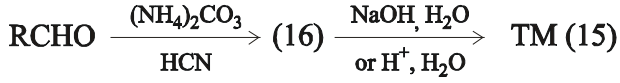


If both oxygen atoms have been replaced by other groups, 1,1-disconnections may be more difficult to spot. The synthesis of α-amino acids (15) can be consider as follows. With cyanide as one 'heteroatom' and nitrogen as the other, disconnection gives an aldehyde, ammonia, and cyanide. The synthesis is known as the Strecker synthesis. The amino cyanide (16) is made in one step from the aldehyde and hydrolysed by acid or base.

Retrosynthetic analysis of TM (15)



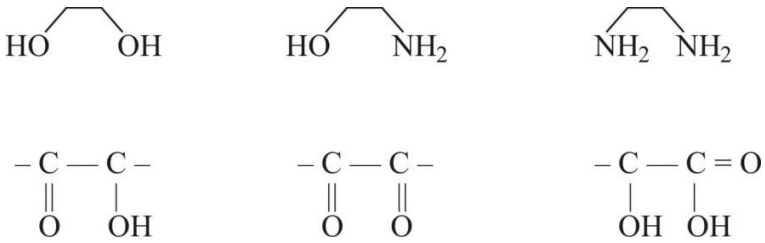
Synthesis



13.3.2 Disconnection of 1,2-difunctionalized Compounds

1,2-Difunctionalized compounds are those in which two heteroatoms are on adjacent carbon atoms. Here unlike 1,1-difunctional compounds, only one C–X bond is disconnected.

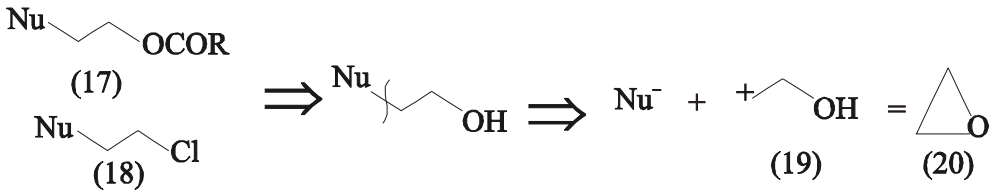
Examples:



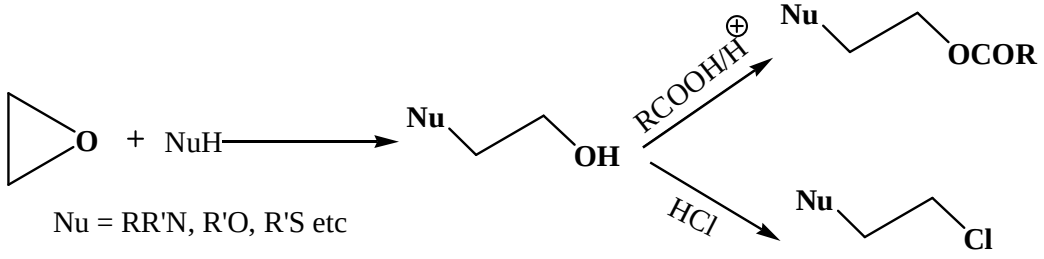
Alcohols

If compounds containing heteroatom on adjacent carbon atoms, e.g. (17) & (18), they can be considered as derivative of alcohols. Disconnection gives the synthon (19) and reagent for this is the epoxide (20).

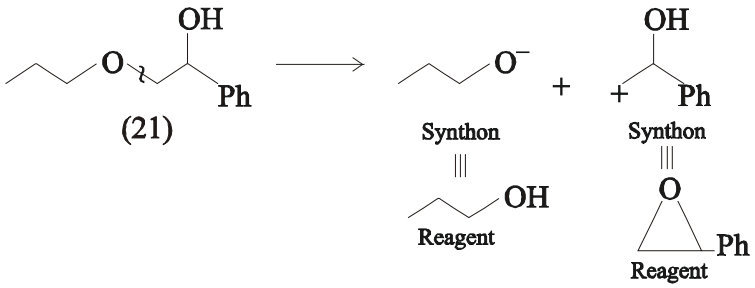
Retrosynthetic analysis of TM (17)



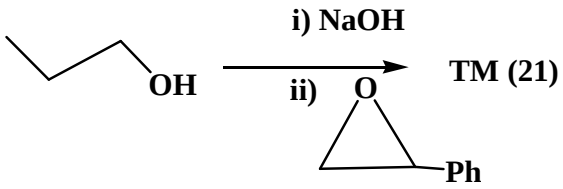
Synthesis



Retrosynthetic analysis of TM (21)

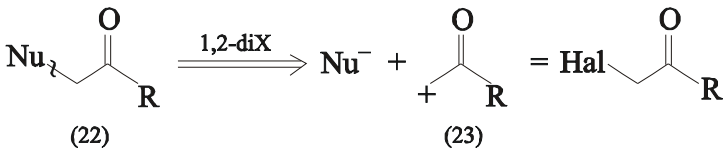


Synthesis



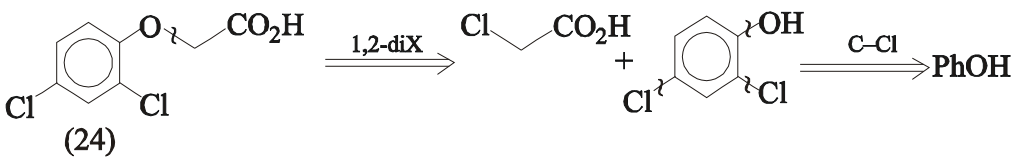
Carbonyl compounds

At a higher oxidation level (22), the electrophilic synthon would be the α-carbonyl cation (23), a very unstable species. α-Halo carbonyl compounds are the best reagents for this synthon, which can be easily made and readily attacked by nucleophiles.

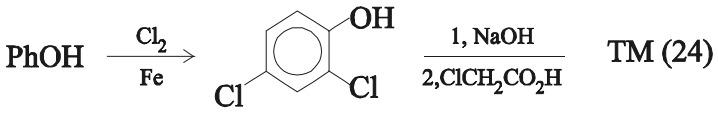


The herbicide '2,4-D' (24), has following disconnection by this approach.

Retrosynthetic analysis of TM (24)

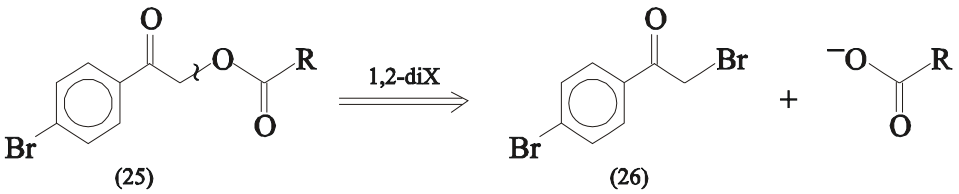


Synthesis



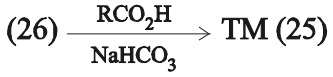
These α-halo carbonyl compounds are reactive enough to consider an alternative disconnection of certain esters (25).

Retrosynthetic Analysis of TM (25)



This reaction is simple to carry out and is a way of making crystalline derivatives of liquid carboxylic acids for purification, identification and protection.

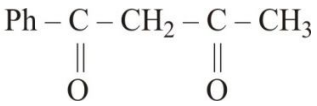
Synthesis



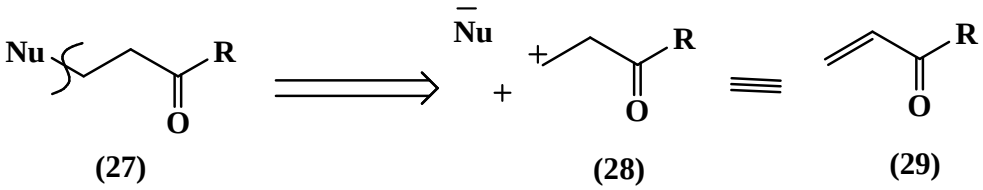
13.3.3 Disconnection of 1,3-difunctionalised compounds

1,3-Difunctionalised compounds are those in which two heteroatom are on the two carbons at 1,3-position.

Examples



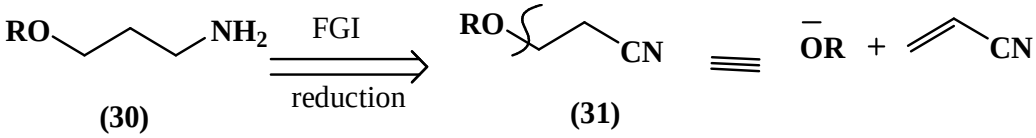
If a carbonyl group or a group at the oxidation level of carbonyl group or acid is present then C–Nu bond will be disconnected and resulted unsaturated compounds (29) are the reagents for the synthon. This is the Michael reaction, effective to all carbonyl compounds, cyanides nitro compounds etc.



(27) (28) (29)

Amines like (30) can be synthesize by the reduction of the cyanides (31). (31) can made by Michael reaction. RO^- is required for this reaction.

Retrosynthetic analysis of TM (30)

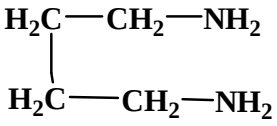


(30) (31)

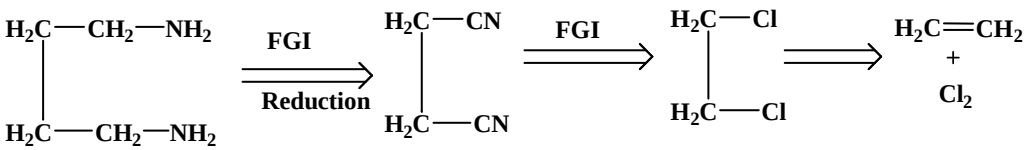
If 1,3-diX compound are not at the carbonyl oxidation level then we must first alter the oxidation level by FGI. If the TM does not have oxygen substituent, then it must be produced by the substitution.

13.3.4 Disconnection of 1,4-difunctionalized compounds

1,4-Difunctionalized compounds are those in which two function groups are on the two carbons at 1,4-position like :

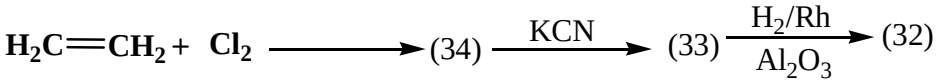


Retrosynthetic analysis of TM (32)



(32) (33) (34)

Synthesis



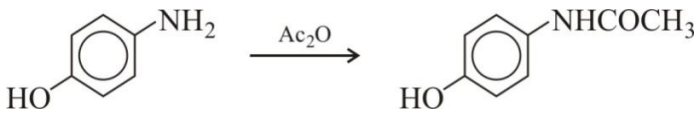
13.3.5 Disconnection of 1,5 and 1,6-difunctionalized compounds

These compounds can be synthesized by same strategy which have been discussed above. These are long chain compounds so besides C-X disconnection, C-C disconnections is also possible. Finally it may be concluded that difunctionalized compound may be disconnection through C-X disconnection and preferred disconnection can be decided accordingly.

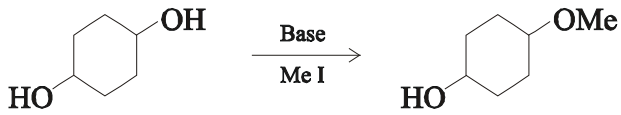
13.4 Chemoselectivity

When a molecule contains two reactive group and if we want to react one of them but not the other, then the question of chemoselectivity arises. In other words we can say that chemoselectivity is the preference reaction of a reagent with one of two or more different functional groups. Following consideration can be undertaken under this reading.

1. Reaction of one of two different functional groups on the basis of relative reactivity; e.g.,



2. Reaction of one of two identical functional groups, e.g.,



3. Reaction of a group once when it may react again, e.g. thiol synthesis.

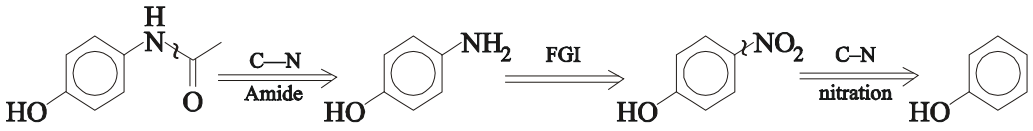
In this chapter we will deal above all three cases, there are some helpful general principles.

Guideline 1

If there are two functional groups of unequal reactivity in a molecule, the more reactive can always be made to react alone.

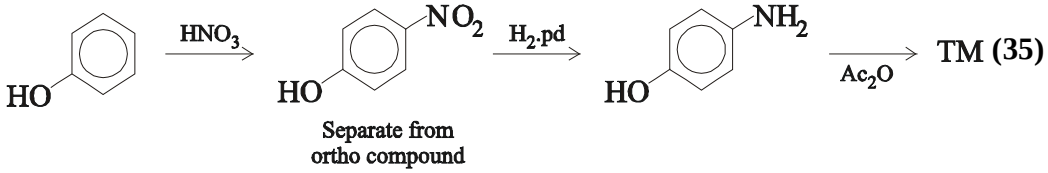
For example Paracetamol (35), which is used as analgesic is a simple amide and should be available by acetylation of *p*-aminophenol. If we keep the phenol unionised then NH_2 will be more reactive then OH (NH_3 is more nucleophilic than water, but less so than HO^-).

Retrosynthetic analysis of TM (35)



(35)

Synthesis

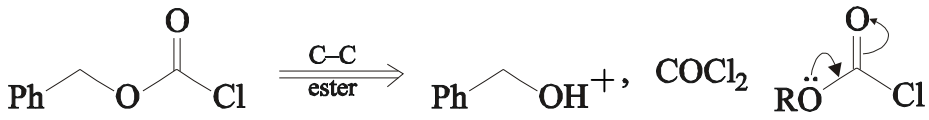


Guideline 2

If one functional group can react twice, the starting material and first product will compete for the reagent. The reaction will be successful only, if the first product is less reactive than the starting material.

Acid chloride (36) is used to protect amino groups in peptide synthesis. Disconnection of its ester bond gives simple starting materials, but the synthesis will require $COCl_2$ (phosgene) to react once only with $PhCH_2OH$. This succeeds since the half ester (36) is less reactive than the double acid chloride $COCl_2$, because of conjugation (37).

Retrosynthetic Analysis of TM (36)



(36) **(37)**

Synthesis

$$PhCH_2OH \xrightarrow{COCl_2} TM \quad (36)$$

Guideline 3

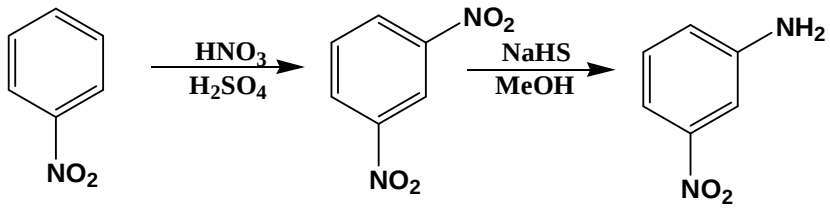
Use of Protecting groups for those cases which are unfavourable from guideline 1 and 2.

If we want to react the less reactive of two different functional groups or if the product of a reaction with one functional group is as reactive or more reactive than the starting material, then we should block the unwanted reaction with a protecting group.

Guideline 4

One of two identical functional groups may react if product is less reactive than the starting material.

For example partial reduction of m-dinitrobenzene is shown below. Reduction involves acceptance of electrons from the reducing agent. The product has only one electron-withdrawing nitro group and so is reduced more slowly than the starting material. The best reducing agent is sodium hydrogen sulphide for this purpose.

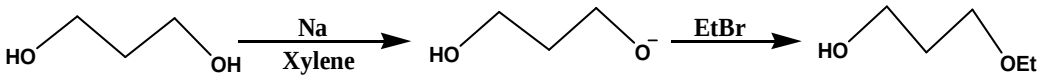


(38)

Guideline 5

One of two identical functional groups may react with one equivalent of reagent using the statistical effect:

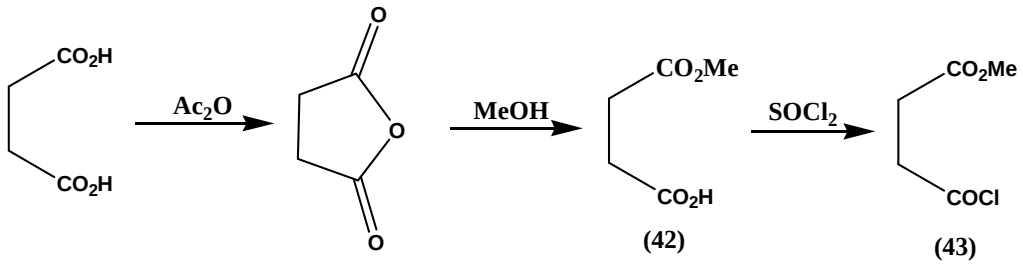
This is an unreliable method, but if successful it avoids protecting groups or roundabout strategy. The diol (39) can be monoalkylated in reasonable yield by using one equivalent of sodium in xylene to generate mostly the monoanion (40). By adding the alkyl halide it gives good yield of hydroxy ether (41)



(39) (40) (41)

Guideline 6

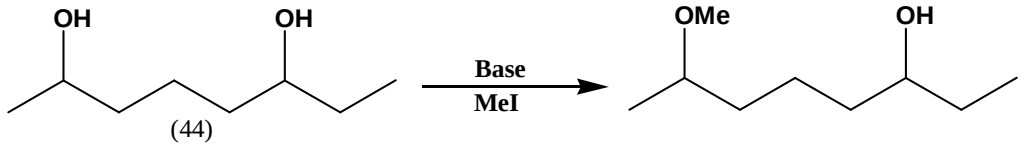
If two identical functional groups are present the more reliable method is to use a derivative which can react once only. When the anhydride has combined once with a nucleophile (e.g. to give 42) the product is no longer reactive. Further reactions can maintain the distinction (e.g. to give the half ester, half acid chloride, 43).



(42) (43)

Guideline 7

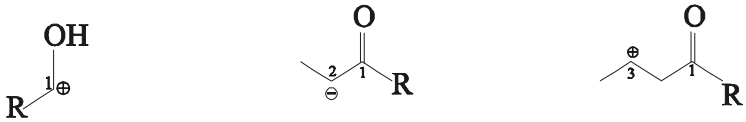
If two groups are nearly same but not quite identical as in (44), we should avoid attemepts to make only one of them react.



(44)

13.5 Reversal of polarity (Umpolung)

The inversion of polarity at the functionalized carbon atom is known as reversal of polarity. During the reversal of polarity an electrophilic carbon convert into a nucleophilic one and a nucleophilic convert into an electrophilic one. See the following synthons which we have used in two-group C–C disconnections.

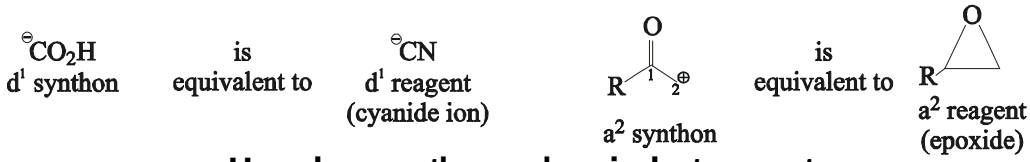


a^1 (equivalent to aldehyde or Ketone)

d^2 (equivalent to enolate of ester or ketone)

a^3 (equivalent to α,β-unsaturated carbonyl compounds)

Here we can see that acceptor synthon have odd numbers; the donar synthon has an even number, donar and acceptor properties alternate along the chain as we move away from a carbonyl group. This (natural reactivity) of carbonyl compounds explains that it is easy to discuss ways of making 1,3 and 1,5-difunctionalized compounds because they are arise from $a^1 + d^2$ and from $a^3 + d^2$. Reagents corresponding to synthons like d^1 or a^2 are rarer, and therefore compounds with 1,2– or 1,4–related functional groups require special consideration retrosynthetically. Here we are given one example of each of the (unnatural) synthon with a^2 and d^1 reactivity. Such synthon are given the Germen name umpolung meaning 'inverse polarity', because their natural reactivity is reversed. Umpolung reagents are the key to the synthesis of 1,2 and 1,4 difunctionalized compounds.

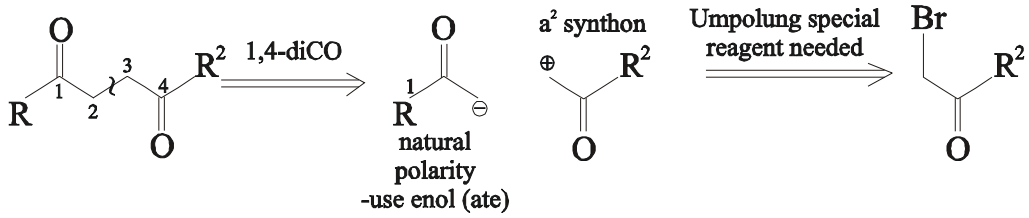


Umpolung synthon and equivalent reagents

Some examples of umpolung reagent are as:

13.5.1 α-halo ketones and esters as umpolung reagent

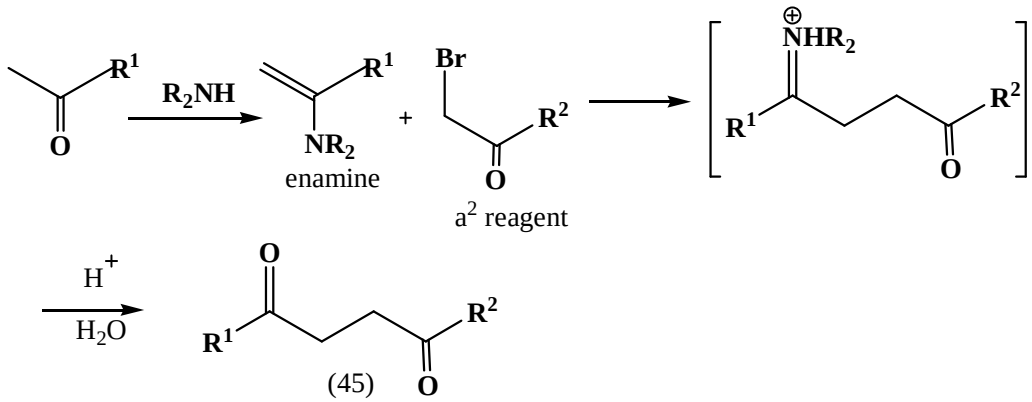
Retrosynthetic analysis of TM (45)



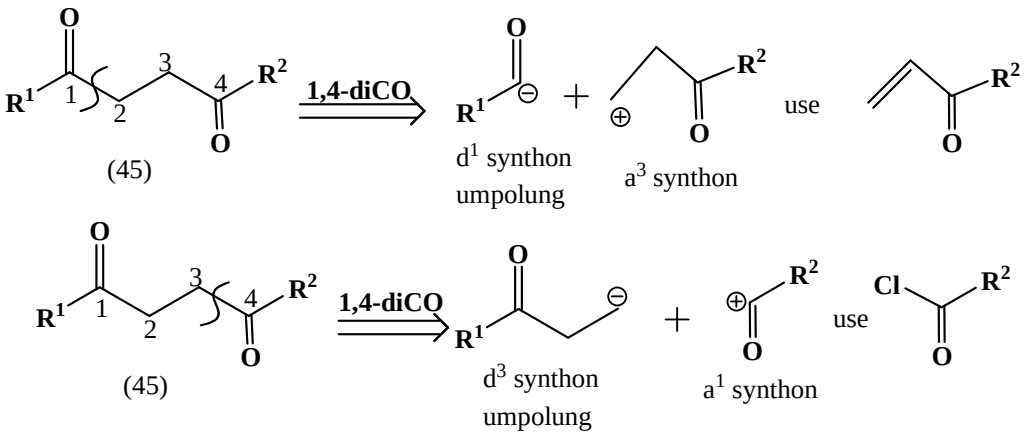
(45)

Here we can use an enolate for one reagent but for the other we have to use umpolung. It is not a very difficult kind of umpolung as an α-bromo carbonyl compounds will do the job nicely, if we select our enolate equivalent carefully.

Synthesis



If we attempt to disconnection of one of the other bonds, two possibilities are available because two fragments are different. We can use either a $d^1 + a^3$ or an $a^1 + d^3$ strategy. In each case we have one natural synthon and one with umpolung (shown below):

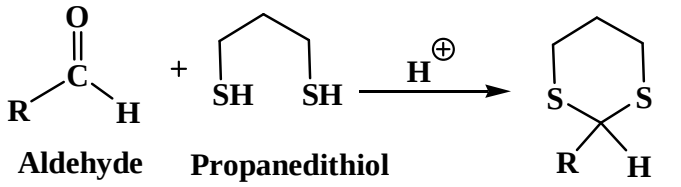


13.5.2 1,3-Dithianes as umpolung reagent

Acid catalysed reaction of an aldehyde or a ketone with 1,3-propanedithiol under dehydrating conditions gives a 1,3-dithiacylohexane (1,3- dithiane). The hydroben atoms on the carbon atom between two sulphur atoms are relatively acidic. Hence reaction with a strong base such as butyllithium results in the formation of the corresponding anion. The anion will react with a variety of electrophiles including epoxides, carbonyl compounds and primary and secondary halides. Now, the dithioacetal function may be hydrolysed in good yield by mercuric salts to give the corresponding carbonyl compound. In the process the electrophilic carbonyl compound has become a nucleophile, i.e., it has undergone reverse polarisation by

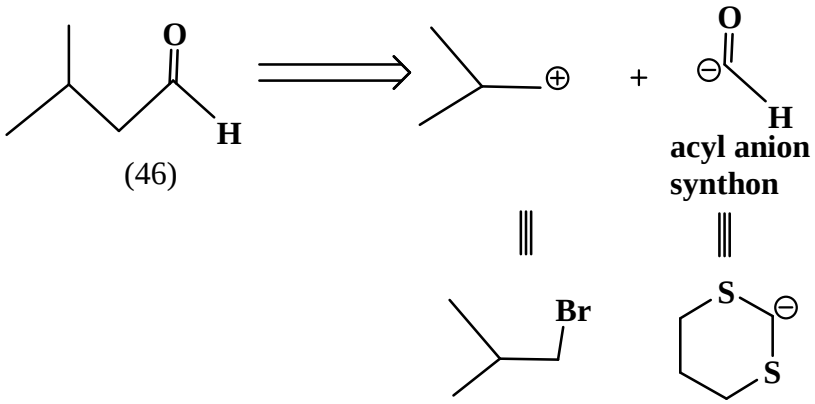
the formation of the dithioacetal. The 1,3-dithiane is known as an acyl anion equivalent.

Preparation of 1,3-dithiane



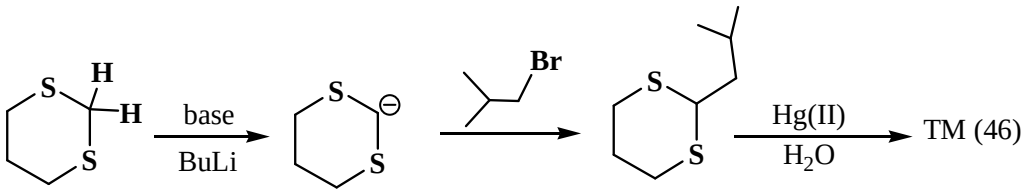
Aldehyde **Propanedithiol** **1,3-Dithiane**

Retrosynthetic analysis of TM (46)



dithiane anion

Synthesis

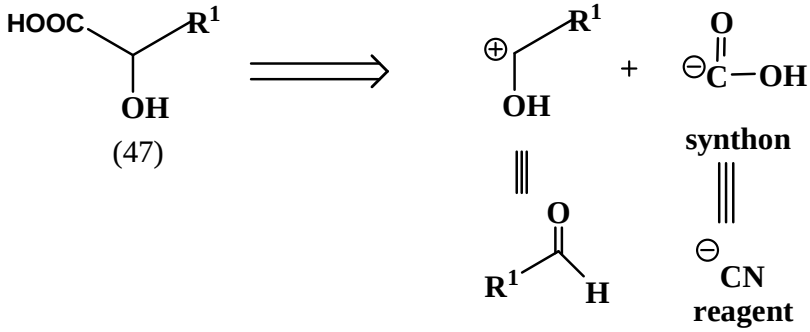


13.5.3 Cyanide as an umpolung reagent

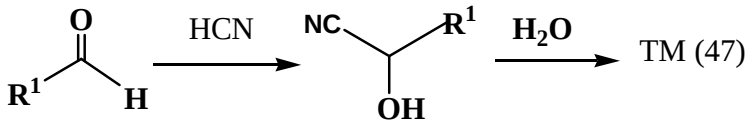
The cyanide ion can act as the synthetic equivalent of the synthon $^{-}$COOH in which the negative charge is located on the carbonyl carbon. Hydrogen cyanide adds to aldehydes and ketones to give adducts as cyanohydrins. The cyanide function may

be further modified, e.g., hydrolysis of cyanohydrin gives 2-hydroxycarboxylic acid. For example:

Retrosynthetic analysis of TM (47)



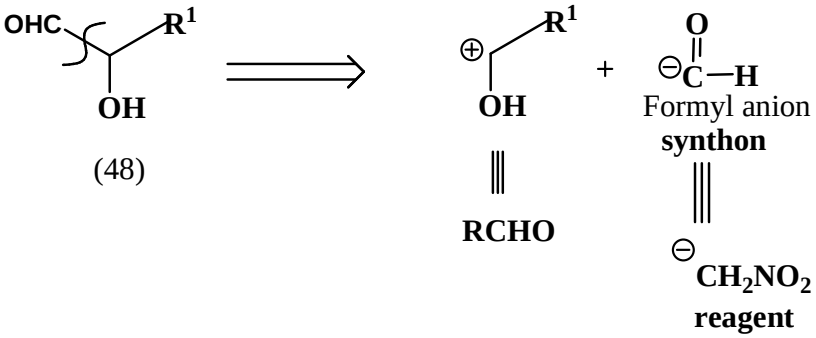
Synthesis



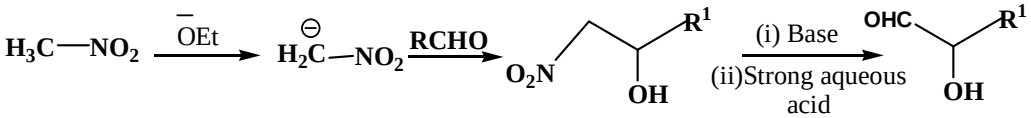
13.5.4 Nitro compounds as umpolung reagents

Deprotonation at the position adjacent to a nitro group may be achieved with a number of bases. The resultant anion is nucleophilic and will undergo typical nucleophilic reactions, e.g., addition to an aldehyde, (Henry reaction). Hydrolysis of nitro group gives an aldehyde.

Retrosynthetic analysis of TM(48)



Synthesis

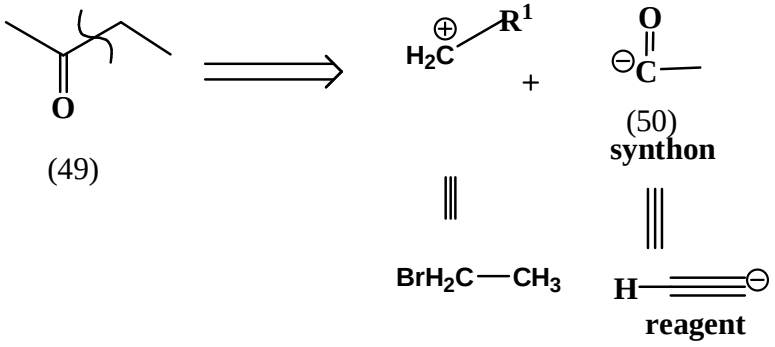


(48)

13.5.5 Alkynes as umpolung reagents

Alkyne forms anion on deprotonation with a strong base. This anion reacts with a range of nucleophiles. Subsequent hydrolysis of the triple bond gives a ketone. This is a further example of an acyl anion equivalent since the acetylene anion (51) is equivalent to the synthon (50).

Retrosynthetic analysis of TM(49)

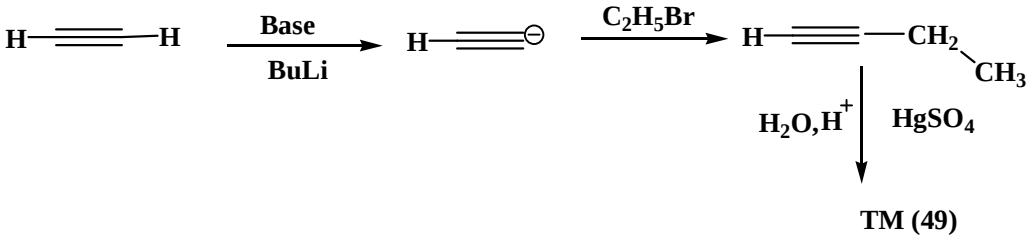


(49)

(50)
synthon

(51)

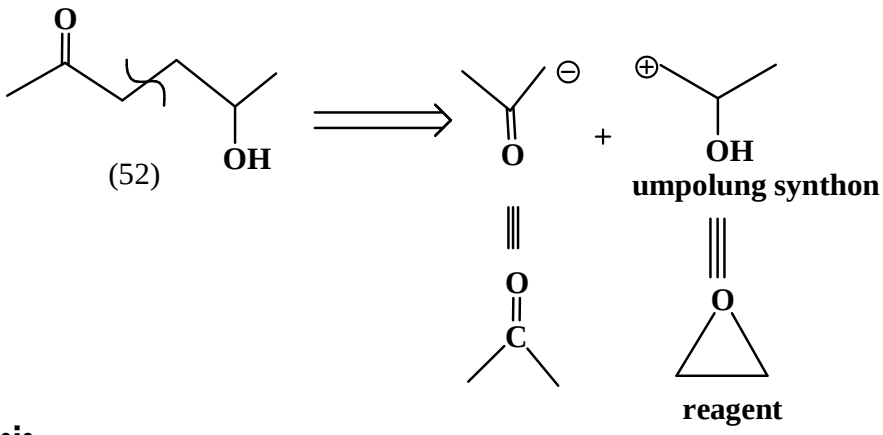
Synthesis



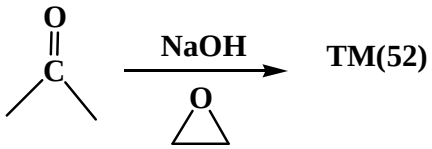
TM (49)

13.5.6 Epoxides as umpolung reagents

Retrosynthetic analysis of TM(52)



Synthesis

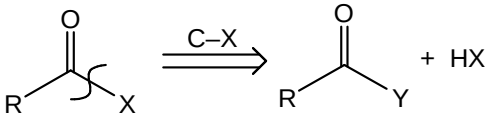


13.6 Summary

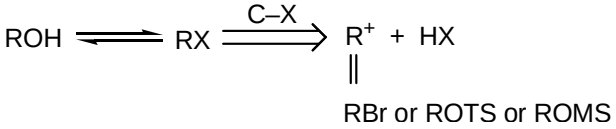
One-Group C–X disconnections

First we have recognized a single functional group and then disconnect corresponded to a well known reliable reaction to make that functional group. Disconnect a bond joining carbon to the heteroatom (X). This approach is known as one group disconnection. The label 'C–X' or 'C–N' etc. can be used.

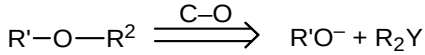
(i) Carbonyl derivatives

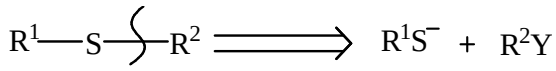


(ii) Alcohol/Halide



(iii) Ether/sulphide

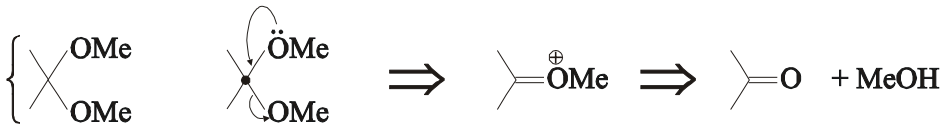


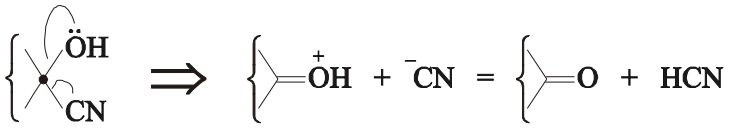


Two Group C–X Disconnections

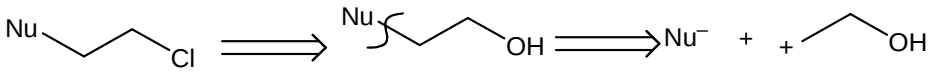
The compounds which shows two group C-X disconnection have two heteroatoms, which are directly linked to carbon. These two heteroatom may be bonded to single carbon atom or bonded to different carbon atoms in a molecule. It can be classified as follows:

(i) Disconnection of 1,1-difunctionalized compounds

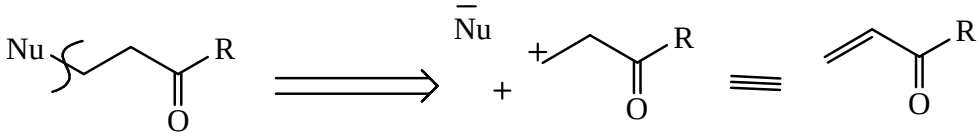




(ii) Disconnection of 1,2-difunctionalized Compounds



(iii) Disconnection of 1,3-difunctionalized compounds



Chemoselectivity

Chemoselectivity is the preference reaction of a reagent with one of two or more different functional groups.

Reversal of Polarity (Umpolung)

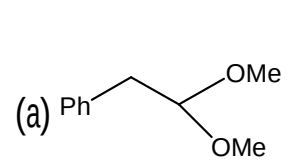
The inversion of polarity at the functionalized carbon atom is known as reversal of polarity. During the reversal of polarity an electrophilic carbon convert into a nucleophilic one and a nucleophilic convert into an electrophilic one.

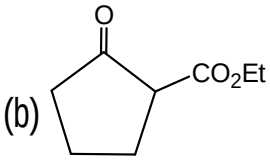
13.7 Review questions

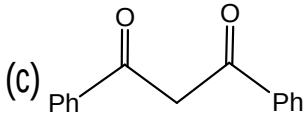
1 Explain one-group C-X disconnection with suitable examples.

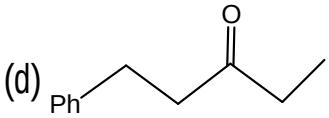
2 Explain two group C-X disconnection with suitable examples.

3 Outline retrosynthetic analysis and designed synthesis of the following target molecules:







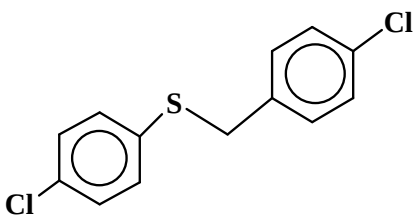


4 What is chemoselectivity ? Explain with suitable example.

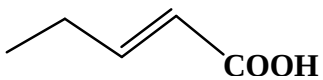
5 What is umpolung? Give any two organic synthesis using umpolung reagents.

6 Outline a suitable retrosynthetic analysis and the corresponding synthesis for the following compounds:

(a)



(b)



13.8 Reference and Suggested Readings

- Organic Synthesis,The Disconnection Approach, S. Warren (Wiley).
- Organic Chemistry , J. Clayden, N. Greeves, S. Warren (Oxford Press).
- Organic Synthesis through Disconnection Approach, P.S. Kalsi, MEDTEC
- Guide book to Organic Synthesis, R.K. Mackie and D. M. Smith, ELBS.
- Organic Synthesis, Jagdamba Singh and L.D.S. Yadav, Pragati Prakashan.

Unit - 14

Protecting Groups I

Structure of Unit:

14.0 Objective

This unit aims to set out the principal features of the use of protective groups in synthetic sequences. When the synthetic target is a relatively complex molecule, a sequence of such reactions that would lead to the desired product must be devised. At the present time, syntheses requiring 15-20 steps are common, and many that are even longer have been developed. In the planning and execution of such multistep syntheses, an important consideration is the compatibility of the functional groups that are already present in the molecule with the reaction conditions required for subsequent steps. It is frequently necessary to modify a functional group in order to prevent interference with some reaction in the synthetic sequence. One way to do this is by use of a protective group.

14.1 Introduction

The group modifying the functional group is known as the protecting group.

Specification for an ideal protecting group:

(i) The group should be introduced under mild conditions

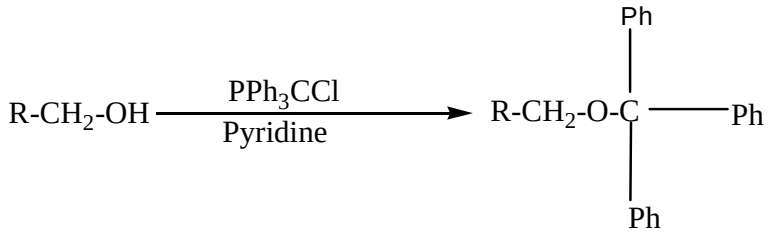
(ii) The group should be removed under mild conditions

(iii) The group must be stable under the reaction conditions necessary to carry out transformations at other centers in the compound.

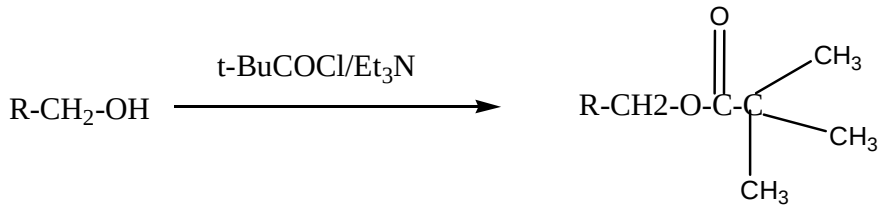
14.2 Protection of alcohols

14.2.1 Principles of protection of alcohol

The lone pairs of electrons on the hydroxyl oxygen of alcohols impart nucleophilicity to them. Therefore, alcohols react rapidly with oxidising agents to give carbonyl compounds and with other electrophiles, ***viz.,*** alkyl halides and acyl halides they give ethers and esters, respectively. Consequently, when electrophilic reagents are to be used in a synthetic step and reactions at selected hydroxyl sites are to be avoided, the nucleophilic behaviour of alcohols must be deactivated. This can be done in two ways: (i) By putting a bulky protecting group on the hydroxyl oxygen which can sterically prevent it from competing effectively for electrophiles, for example:



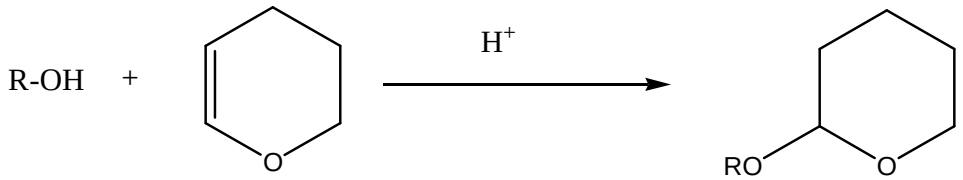
(ii) By delocalizing the lone pairs of electrons by conjugation with, a carbonyl π system. For example:



14.2.1 Protecting groups for alcohols

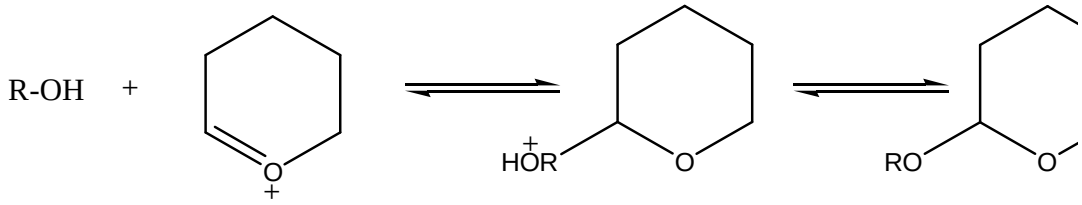
A common requirement in synthesis is that a hydroxyl group be masked as a derivative lacking an active hydrogen. An example of this requirement is in reactions involving Grignard or other organometallic reagents. The acidic hydrogen of a hydroxyl group will destroy one equivalent of a strongly basic

organometallic reagent and possibly adversely affect the reaction in other ways. Converrsion to alkyl or silylethers is the most common means of protecting hydroxyl groups. The choice of the most appropriate ether group is largely dictated by the conditions that can be tolerated in subsequent removal of the protecting group. An important method that is applicable when mildly acidic hydrolysis is an appropriate method for deprotection is to form a tetrahydropyranyl ether (THP group).

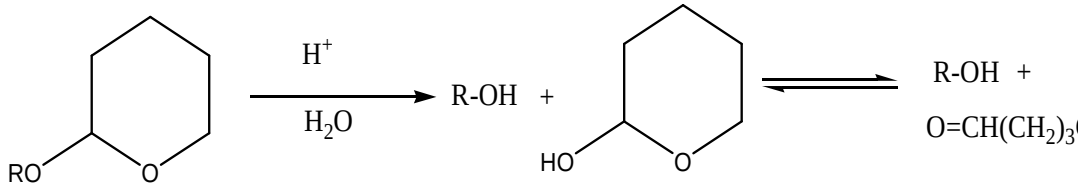


This protective group is introduced by an acid- catalyzed addition of the alcohol to the vinyl ether moiety in dihydropyran. *p*-toluenesulfonic acid or its pyridinium salt is recommended as a catalyst, although other catalysts are advantageous in special cases. The THP group can be removed by dilute aqueous acid. The chemistry involved in both the introduction and deprotection stages is the reversible acid-catalyzed formation and hydrolysis of an acetal.

introduction:



removal:



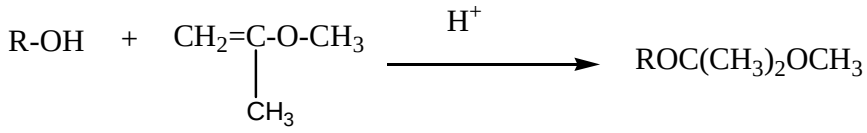
Advantage of THP group:

The THP group, like other acetals and ketals, is inert to nucleophilic reagents and is unchanged under the conditions of hydride reduction, organometallic reactions, or base-catalyzed reactions in aqueous solution. It also protects the hydroxyl group

against oxidation under most conditions.

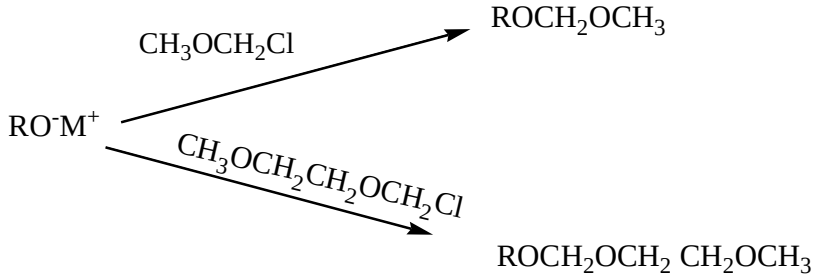
Disadvantage of THP group:

A disadvantage of the THP group is the fact that a chiral center is produced at C-2 of the tetrahydropyran ring. This presents no difficulties if the alcohol is chiral, the reaction may give a mixture of diastereomeric ethers, which can complicate purification and characterization. One way of avoiding this problem is to use methy 2-propenyl ether in place of dihydropyran. No new chiral center is introduced, and this acetal offers those required for THP ethers.

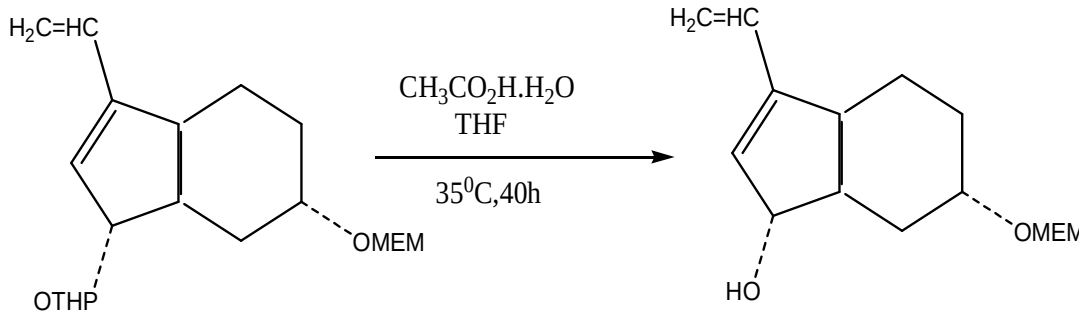


Ethyl vinyl ether is also useful for hydroxyl group protection. The resulting derivative (1-ethoxyethyl ether) is abbreviated as the EE group. As with the THP group, the EE group contains a chiral center.

The methoxymethyl (MOM) and β-methoxyethoxymethyl(MEM) group are used to protect alcohols and phenols as formaldehyde acetals. The group are normally introduced by reaction of an alkali metal salt of the alcohol with methoxy-methy chloride or β-methoxyethoxymethyl chloride.



An attractive feature of the MEM group is the ease with which it can be remover under no aqueous condition. Lewis acids such as zinc bromide, titanium tetra-chloride, dimethylboron bromide ,or trimethylsilyl inodide permit its removal. The MEM group is cleaved in preference to the MOM or THP groups under these condition. Conversely, the MEM group is more stable to acidic aqueous hydrolysis than the THP group. These relative reactivity relationships allow the THP and MEM groups to be used in a complementary fashion when two hydroxyl groups must be deprotected at different points in a synthetic sequence.



The methylthiomethy (MTM) group is a related alcohol-protecting group. There are several methods for introducing the MTM group. Alkylation of an alcoholate by methylthimoethyl choride is efficient if catalyzed by iodide ion. Alcohols are also converted to MTM ethers by reaction with dimethyl sulfoxide in the presence of acetic acid and acetic anhydride or with benzoyl peroxide and dimethyl sulfide. The letter two methods involve the generation of the methyl-thiomethylium ion by ionization of an acyloxysulfonium ion.

$$RO^{-}M^{+} + CH_3SCH_2Cl \xrightarrow{I^-} ROCH_2SCH_3$$

$$ROH + CH_3SOCH_3 \xrightarrow[(CH_3CO)_2O]{CH_3COOH} ROCH_2SCH_3$$

$$ROH + (CH_3)_2S + (PhCO_2)_2 \longrightarrow ROCH_2SCH_3$$

The MTM group is selectively removed under nonacidic conditions in aqueous solutions containing Ag^+ or Hg^{2+} salts. The THP and MOM groups are stable under these conditions. The MTM group can also be removed by reaction with methyl iodide, followed by hydrolysis of the resulting sulfonium salt in moist acetone.

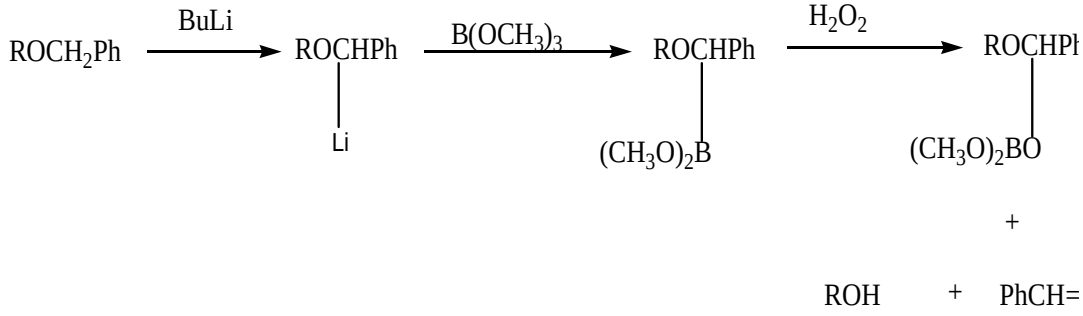
The simple alkyl groups are generally not very useful for protection of alcohols as ethers. Although they can be introduced readily by alkylation, subsequent cleavage requires strongly electrophilic reagents such as boron tribromide. The t-butyl group is an exception and has found some use as a protecting group. Because of the stability of the t-butyl cation, t-butyl ethers can be cleaved under moderately acidic conditions. Trifluoroacetic acid in an inert solvent is frequently used. t-Butyl ethers can also be cleaved by acetic anhydride- $FeCl_3$ in ether. The t-butyl group is normally introduced by reaction of the alcohol with isobutylene in the presence of an acid catalyst. Acidic ion exchange resins effective catalysts.

$$ROH + CH_2=C(CH_3)_2 \xrightarrow{H^+} ROC(CH_3)_3$$

The triphenylmethyl (trityl,Tr) group is removed under even milder conditions than the t-butyl group and is an important hydroxyl group, expecially in carbohydrate chemistry. This group is introduced by reaction of the alcohol with triphenylmethyl chloride by an S_N1 mechanism. Hot aqueous acetic acid suffices to remove the trityl group. The ease of removal can be increased by addition of electron-releasing substituents. The *p*-methoxy derivatives are used in this way. Because of their steric bulk, triarylmethyl groups can usually be introduced only at primary hydroxyl groups.

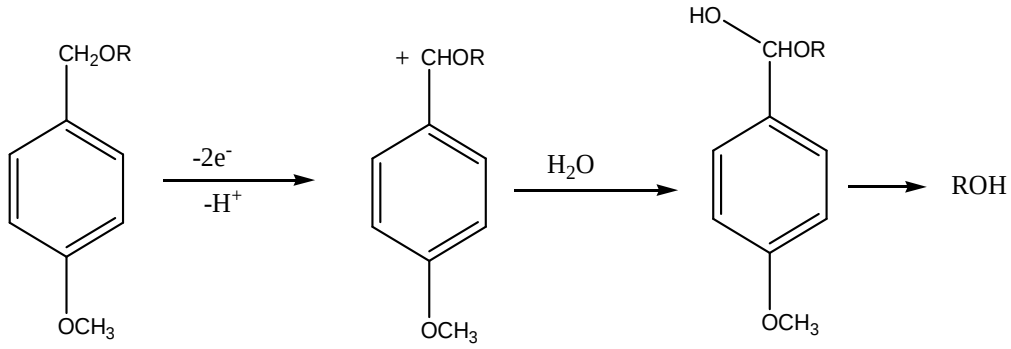
The Benzyl group can serve as an alcohol protecting group when acidic condition for ether cleavage cannot be tolerated. The benzyl C-O bond is cleaved by catalytic hydrogenolysis or with sodium in liquid ammonia. Benzyl ether can also be cleaved with the use of formic acid, cyclohexene, or cyclohexadience as hydrogen source in transfer hydrogenolysis catalyzed by platinum or palladium.

Several nonreductive methods for cleavage of benzyl group have also been developed. Treatment with s-butyllithium followed by reaction with trimethyl borate and then hydrogen peroxide liberates the alcohol. The lithiated ether forms an alkyl boronate, which is oxidized.



Lewis acids such as $FeCl_3$ and $SnCL_4$ also cleave benzyl ether.

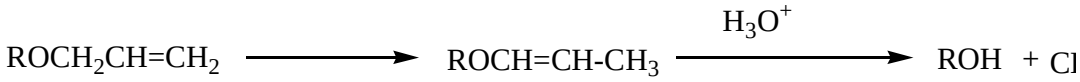
Benzyl group having 4-methoxy or 3, 5-dimethoxy substituent can be removed oxidatively by dichlorodicyanoquinone. These reactions presumably proceed through a benzyl cation and the methoxy substituent is necessary to facilitate the oxidation.



These reaction conditions do not affect most of the other common hydroxyl-protecting group, and the the methoxybenzyl group are therefore useful in synthetic sequence that require selective deprotection of different hydroxyl group.

Benzyl groups are usually introduced by the Williamson reaction. They can also be introduced under nonbasic conditions if necessary. Benzyl ethers are converted to trichloroacetimidates by reaction with tricloroacetonitrile. These then react with an alcohol to transfer the benzyl group.

Allyl ethers can be cleaved by conversion to propenyl ethers, followed by acidic hydrolysis of the resulting enol ether.



The isomerization of an allyl ether to a propenyl ether can be achieved either by treatment with potassium t-butoxide in dimethyl sulfoxide or by Wilkinson's catalyst, tris(triphenylphosphine) chlororhodium.

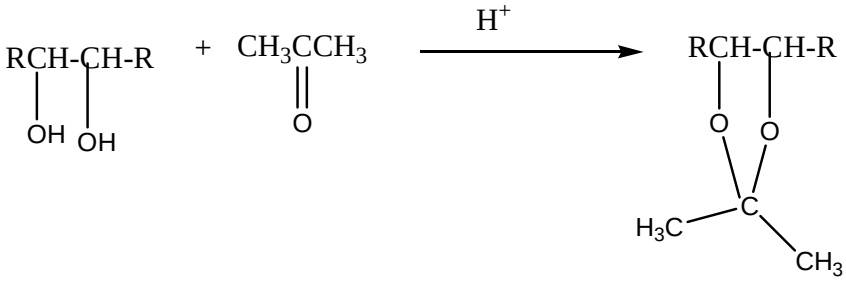
Silyl ethers play a very important role as hydroxyl-protecting groups. Alcohols can be easily converted to trimethylsilyl (TMS) ethers by reaction with trimethylsilyl chloride in the presence of an amine or by heating with hexamethyldisilazane.

t-Butyldimethylsilyl (TBDMS) ethers are also very useful. The increased steric bulk of the TBDMS group improves the stability of the group toward such reactions as hydride reduction and Cr (VI) oxidation. The TBDMS group is normally introduced by the reaction of the alcohol with t-butyldimethylsilyl

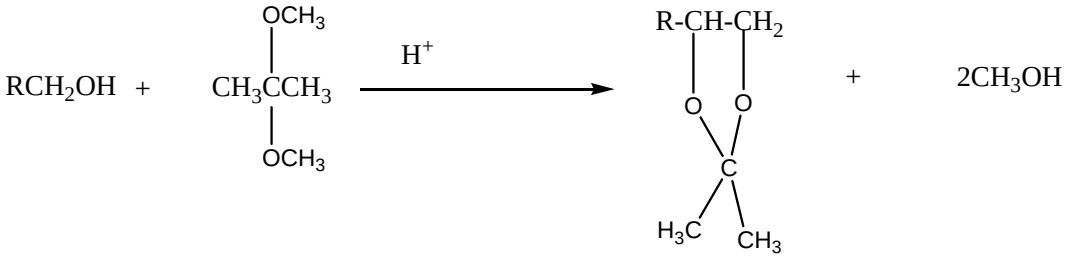
chloride with the use of imidazole as a catalyst. Cleavage of the TBDMS group is slow under hydrolytic conditions, but fluoride ion (from anhydrous tetra-n-butylammonium fluoride), aqueous hydrogen fluoride, or boron trifluoride can be used for its removal. Other highly substituted silyl groups, such as dimethyl (1, 2, 2-trimethylpropyl) silyl and tris (isopropyl) silyl, are even more sterically hindered than the TBDMS group and can be used when added stability is required.

14.2.2 Protecting groups for 1,2-and 1,3-diols

Diols represent a special case in terms of applicable protecting groups. 1,2-Diols and 1,3-diols easily form cyclic acetals with aldehydes and ketones, unless cyclization is precluded by molecular geometry. The isopropylidene derivatives (acetonides) formed by reaction with acetone are a common example.



The isopropylidene group can also be introduced by acid-catalyzed exchange with 2,2-dimethoxypropane.



This ketal protective group is resistant to basic and nucleophilic reagents but is readily removed by aqueous acid. Formaldehyde, acetaldehyde, and benzaldehyde are also used as the carbonyl component in the formation of cyclic acetals. They function in the same manner as acetone. A disadvantage in the

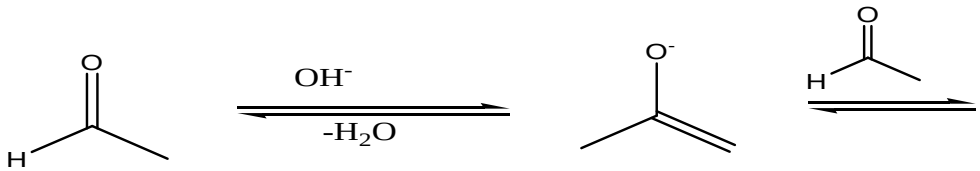
case of acetaldehyde and benzaldehyde is the possibility of forming a mixture of diastereomers, because of the new chiral center at the acetal carbon.

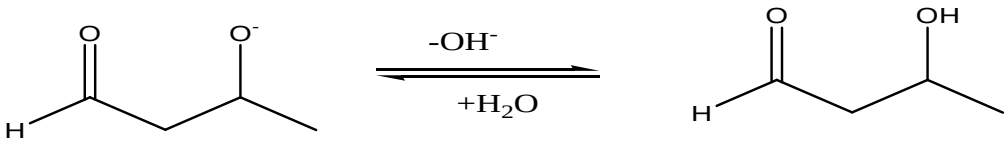
14.3 Proctection of carbonyl group

14.3.1 Principles of protection of carbonyl compounds

The ability of the carbonyl group to act both as an electrophile and as a nucleophile makes it very important in the formation of carbon-carbon bonds.These aspects of carbonyl reactivity is explained by the aldol reaction brought about by either basic or acidic catalysis as follows:

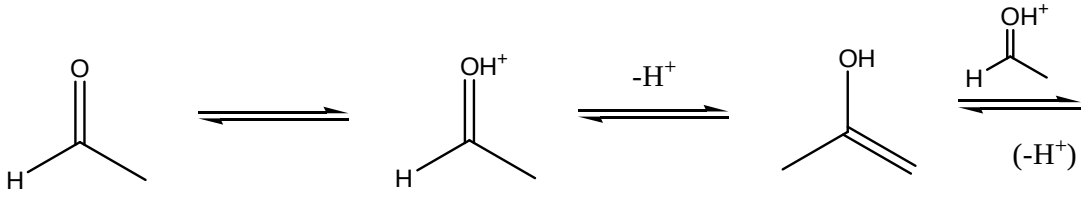
Base catalysed aldol condensation:

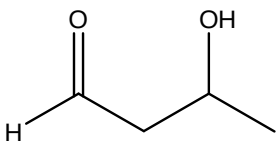




(aldol)

Acid catalysed aldol condensation:





(aldol)

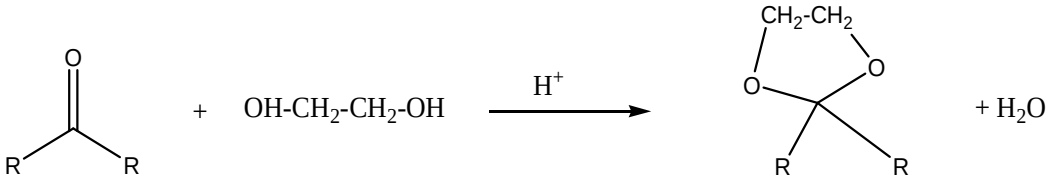
Since the aldol reaction proceeds readily in the prescence of catalytic quantities of acids or base,its occurrence as a competing side reaction is difficult to avod.Thus

protection of carbonyl group is an important requirement for successful organic synthesis.

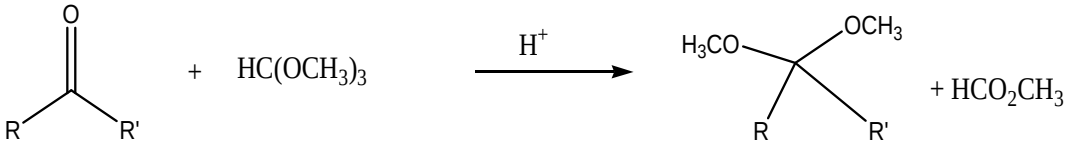
14.3.2 Acetals and ketals as proctecting groups for carbonyl compounds

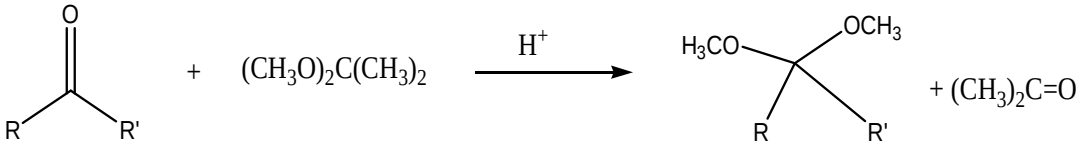
Conversion to acetals of ketals is a very general method for proctecting aldehydes and ketones against addition by nucleophiles or reduction.

Etylene glycol,which gives a cyclic dioxolane derivative is the most frequently employed reagent for this purpose.The dioxolane derivative is usually prepared by heating the carbonyl compound with ethylene glycol in the presence of an acid catalyst, with provision for azeotropic removal of water.

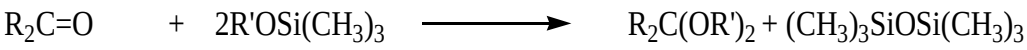


Dimethyl or diethyl acetals and ketals can be conveniently prepared by acid-catalyzed exchange with a ketal such as 2,2-dimethoxypropane or an orthoester.





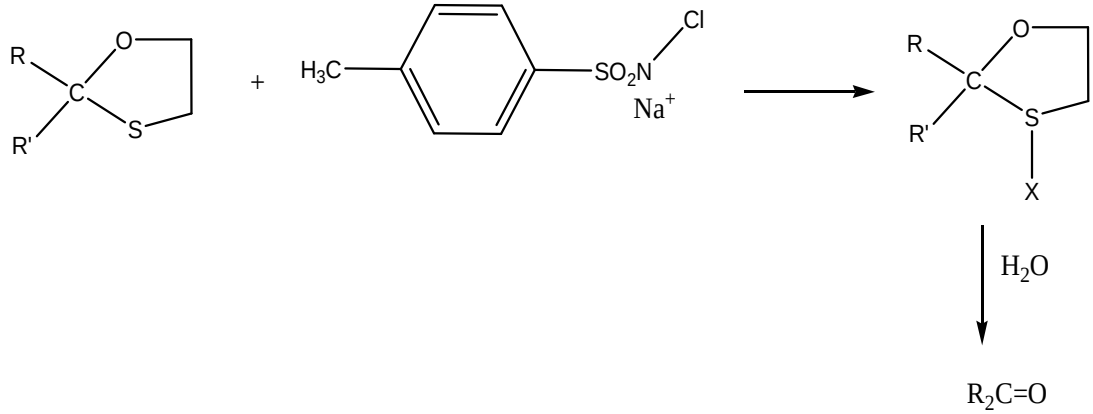
Acetals and ketals can be prepared under very mild conditions by reactions of the carbonyl compound with an alkoxytrimethylsilane, by the use of trimethylsilyl trifluoromethylsulfonate as the catalyst.



The carbonyl group can be deprotected by acid-catalyzed hydrolysis by the general mechanism for acetal hydrolysis

14.3.3 1,3-oxathiolane derivative as proctecting groups for carbonyl compounds

Another type of carbonyl protecting group is the 1,3-oxathiolane derivative, which can be prepared by reaction with mercaptoethanol in the presence of BF_3, or by heaing with an acid catalyst with azeotropic removal of water, The 1,3-oxathiolanes are useful when nonacidic conditions are required for deprotection. The 1,3-oxathiolane group can be removed by treatment with Raney nickel in alcohol, even under slightly alkaline conditions. Deoprotection can also be accomplished by treating with a mild halogenating agent, such as chloramines-T. This reagent oxidizes the sulfur in the 1,3-oxathiolane group, yielding a chlorosulfonium salt and activating the ring to hydrolytic cleavage.



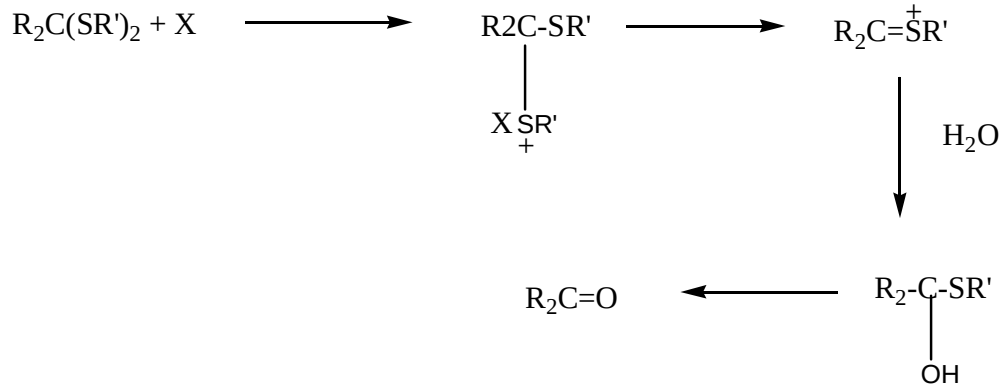
14.3.4 Cyclic dithiolanes and dithianes as proctecting groups for carbonyl compounds

Dithioketals, especially the cyclic dithiolanes and dithianes, are also useful carbonyl-protecting group. These can be formed the corresponding dithiols by Lewrs acid catalyzed reaction. The catalysts that are used include BF_3, $Mg(O_3SCF_3)_2$ and $Zn(O_3SCF_3)_2$.S-Trimethylsilyl ethers of thiols and dithiols also react with ketones to form dithioketals.

$$R_2C{=}O + 2R'SSi(CH_3)_3 \longrightarrow R_2C(SR')_2 + (CH_3)_3SiOSi(CH_3)_3$$

The regeneration of carbonyl compounds from dithioacetals nad dithio ketals is done best with reagents that activate the sulfur as a leaving group and facilitate

hydrolysis. Among the reagents which have been found effective are nitrous acid ($X=NO^+$), t-butyl hypochlorite ($X = Cl^+$), and cupric salts ($X = Cu^{2+}$).



14.4 Summery

- The group modifying the functional group is known as the protecting group.
- Trialkyl ethers used as protecting group for alcohols.
- Acetals and ketals used as protecting group for alcohols.
- Ethers and esters are also used as protecting group for alcohols.
- 1, 2 Diols can be protected as cyclic acetals and ketals.
- Carbonyl group can be protected as acetals and ketals.

14.5 Review Question

1 What is a protecting group? What are its salient features?

2 Describe the use of acetals and ketals as protecting groups for carbonyl compounds.

3 Describe the use of trialkyl ethers as protecting groups for alcohol

14.6 Reference and Suggested readings

- Organic Chemistry , J. Clayden, N. Greeves, S. Warren (Oxford Press).
- Organic Synthesis through Disconnection Approach, P.S. Kalsi, MEDTEC
- Guide book to Organic Synthesis, R.K. Mackie and D. M. Smith, ELBS.
- Organic Synthesis, Jagdamba Singh and L.D.S. Yadav, Pragati Prakashan.

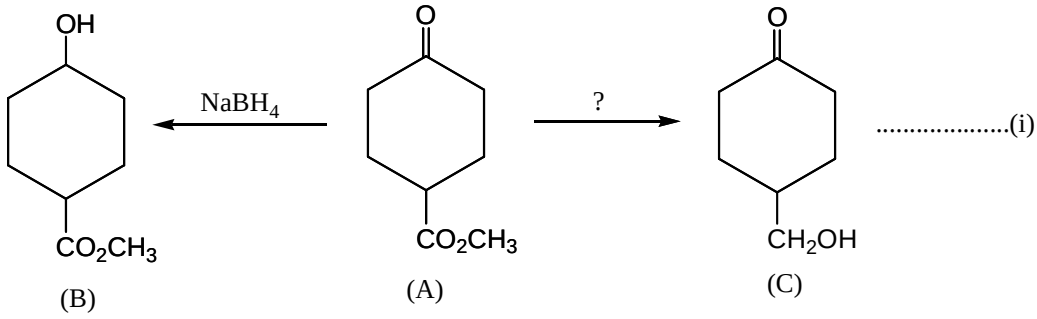
Unit - 15
Protecting Group II

Structure of Unit

15.0 Objective

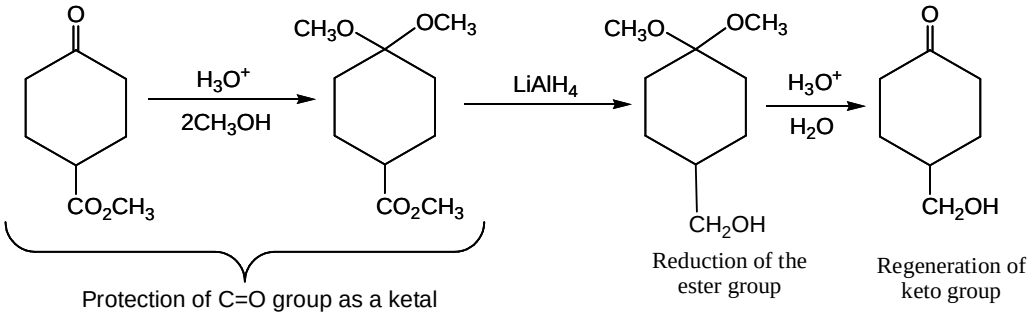
As we know that the desired reaction is accompanied by reaction at other parts of the molecule, especially when more than one functional group is present. Let us take one example (i) to illustrate the purpose and practice of protecting group in organic synthesis: Here it is easy to make alcohol (B) from keto ester by reducing the more reactive carbonyl group, But the reduction of an ester in presence of a

ketone is difficult as there is no reduction reaction that leads directly to the desired ketoalcohol (C). The only common reagent is $LiAlH_4$, which will reduce ester, but it will also reduce to ketone.



(B) (A) (C)

So for this purpose first we have to protect keto group, then we will use $LiAlH_4$, which will reduce only ester group. At the end of the reaction sequence the keto group can be easily regenerated.



The aim of this unit is to learn, how the amine and carboxylic groups can be protected? So that reaction occur only at desirable site.

15.1 Introduction

In the synthesis process, it is frequently necessary to carry out a transformation at one centre while another reactive site remains unchanged. Two principal techniques are used to achieve this purpose. One to which reference has been made in most, if not all, of the remaining chapters, involves the careful choice of a selective reagent and/or of reaction conditions. The other, involves the temporary modification of the site at which reaction is undesirable in such a manner that it remains intact during reaction at the other site and at the end of the reaction sequence to original group can be easily regenerated. The group modifying the

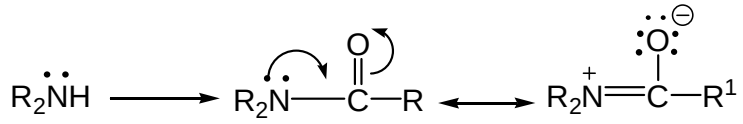
functional group is known as the protective group. For an ideal protective group, the following specification we can make:

(i) The group should be introduced under mild conditions.
(ii) The group should be stable under the reaction conditions necessary to carry out transformations at other centres in the compound.
(iii) The group should be removed under mild conditions.

15.2 Principle of Protection of Amino Group (RNH_2, RNHR', RNR'R")

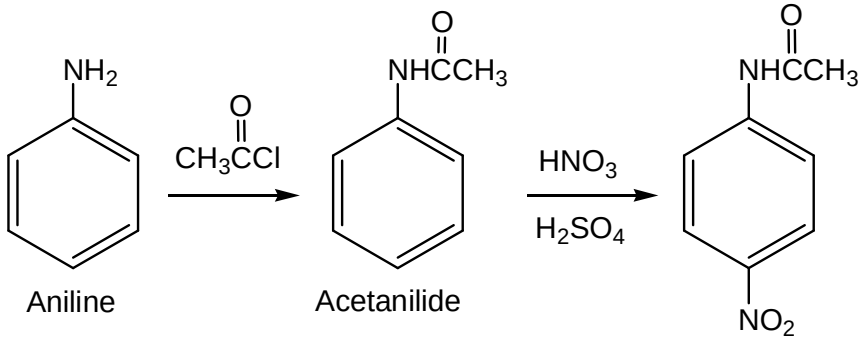
As a reactive lone pair is present on nitrogen which allows the protonation of $-NH_2$ group as well as the reactions with other electrophiles. Hence it can be protected by those reagents, which make lone pair of NH_2 group less reactive. There are several reagents or groups which can be employed for the protection of amino group. Amine groups are protected as amide, carbamate, t-butoxycarbonyl derivative (BOC) and benzyloxycarbonyl group etc.

15.2.1 As amides:



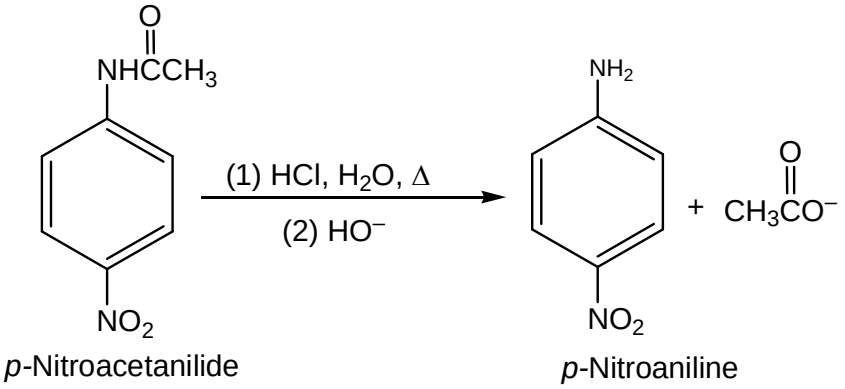
Amine Protected amine (as amide)

Here electron pair is made much less reactive by converting the amine to an amide. Electron pair of nitrogen in the amide is delocalized by resonance on to the oxygen of the carbonyl group and is thus not as available to react as either a base or a nucleophile. The acetyl group is subsequently removed by acid hydrolysis. However, vigorous conditions are needed to hydrolyze it to regenerate the unprotected amine. In scheme-**1** amine group is protected as amide and removal of acetyl group is shown in Scheme-**2**.



(Amides as protecting groups for amines)

Scheme-1

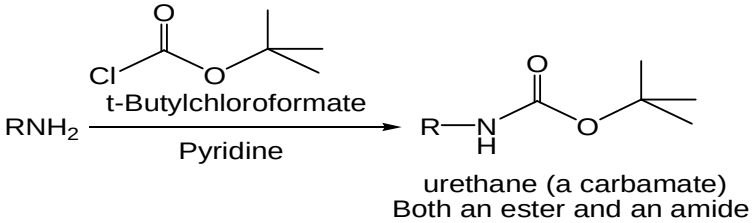


(Deprotection : Regeneration of Amino group)

Scheme-2

15.2.2 As carbamates:

Reaction of a primary amine with t-butyl chloroformate in the presence of a weak base (pyridine) forms a urethane which is known as carbamate (Scheme-3).

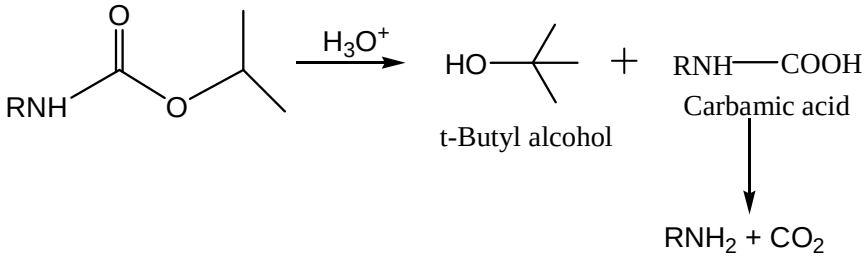


(Carbamate as protecting group for amines)

Scheme-3

The urethane functional group behaves as an ester on one side and as a carboxylic acid amide on the other side.

Regeneration of amino group from the carbamates (scheme-4) are done by hydrolysis which resemble to the hydrolysis of a t-butyl ester, treatment with mild aqueous acid results in the formation of t-butyl alcohol and a nitrogen substituted carboxylic acid, a carbamic acid that undergoes rapid decarboxylation to liberate the amine.

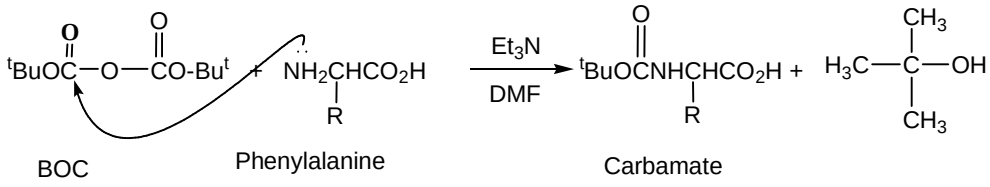


(Deprotection : Regeneration of Amino group)

Scheme-4

15.2.3 As *t*-Butoxycarbonyl derivatives (BOC)

Amino group of amino acid is often protected by t-butoxycarbonyl group (BOC group). The BOC group can be attached by reaction of di-t-butyldicarbonate with amino acid shown in scheme-5.

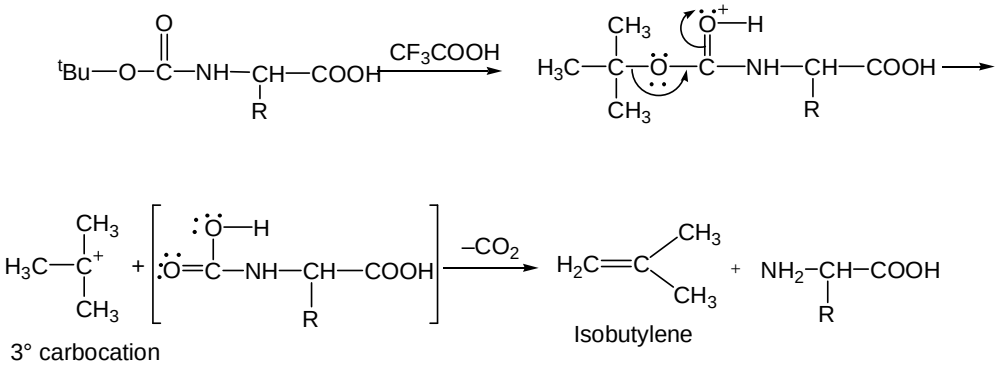


(Di-t-Butyl dicarbonate)

(t-Butoxycarbonyl derivatives as protecting group for amine)

Scheme-5

This protecting group is easily removed on treatment with trifluoroacetic acid (Scheme 6).

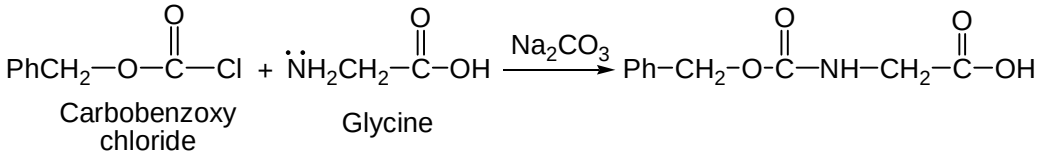


(Deprotection : Regeneration of Amino group)

Scheme-6

15.2.4 As benzyloxycarbonyl group (CBZ group / or benzyl carbamate)

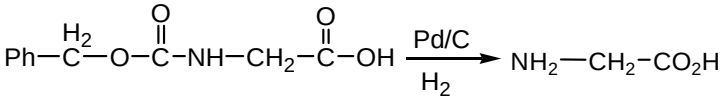
In the case of BOC derivatives, we were using an acid anhydride derivative. Here we use an acyl chloride derivative, carbobenzoxy chloride for protection of amine (Scheme 7). Benzyl carbamate widely used in peptide synthesis since 1932.



(Benzyloxycarboxyl group as protective group for amine)

Scheme-7

This group can be deprotected by the reaction with hydrogen in the presence of a catalyst. (Scheme 8).

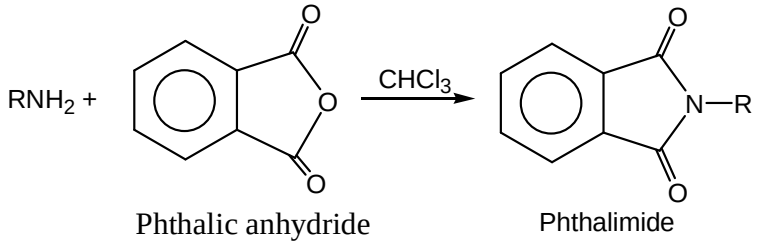


(Deprotection : Regeneration of Amino group)

Scheme-8

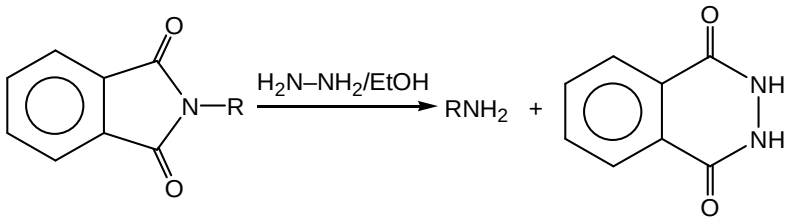
(v) As Cyclic imides (for primary amines)

Primary amines can be protected as cyclic imides; which can be made by reaction of primary amine with phthalic anhydride (Scheme-9).



(Phthalimide as protecting group for primary amine)

Scheme-9



(Deprotection : Regeneration of Amino group)

Scheme-10

15.3 Principle of protection of carboxylic acids:

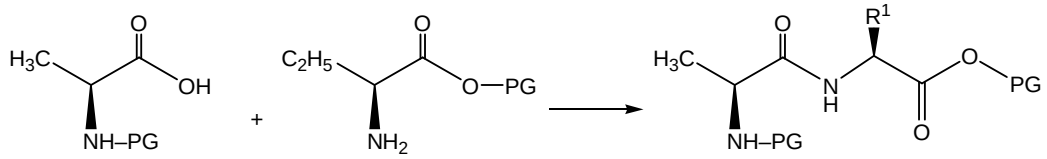
Removal of proton from carboxylic acids represents a threat to potentially valuable organometallic reagents, resulting in an alkane and metal carboxylate.

$$R–COOH + R'–M \longrightarrow RCOOM + R'H$$

(M = Li, MgBr etc.)

If organometallic reagent is readily available and the so-formed carboxylate leads to no undesirable secondary reactions, then use of reagent can be done. But neither of these requirements applies and there is need of suitable carboxyl protecting groups. Further it also necessary that there should be protection against enolisation or attack by nucleophiles. There are few protecting group which have all these properties. Esters and amides removes the problem of carboxyl proton and the latter provide good protection against many nucleophiles.

For e.g. during the condensation of two amino acids with the aid of coupling agent to form a new peptide bond, carboxyl protection is required, otherwise there will be self condensation. For this purpose we need one amino acid which requires a free carboxyl group and a protected amino group and other amino acid should have protected carboxyl group and a free amino group (Scheme-11).



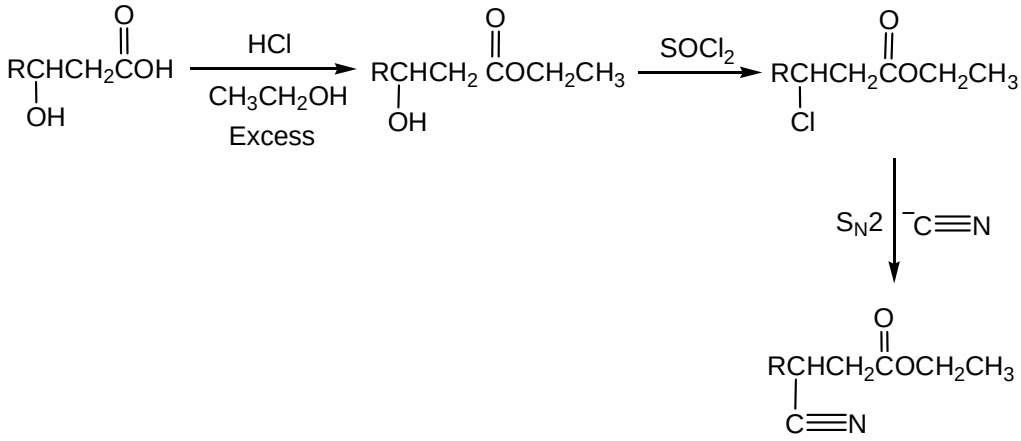
PG = Protecting group

Scheme-11

The carboxylic acids are protected as esters. Methyl or ethyl esters are frequently used. It can also be protected as silyl esters. However, in the case of methyl or ethylesters the strongly acidic or basic conditions are required for the removal, which may be disadvantageous. In such circumstances, t-butyl esters (which can be removed by mild acid treatment), benzyl esters (which can be debenzylated by hydrogenolysis) can be used. Both benzyl and t-butyl esters are widely used in peptide synthesis. The exact choice of protecting group depends on the need to deprotect the carboxyl terminus.

15.3.1 As methyl or ethyl esters

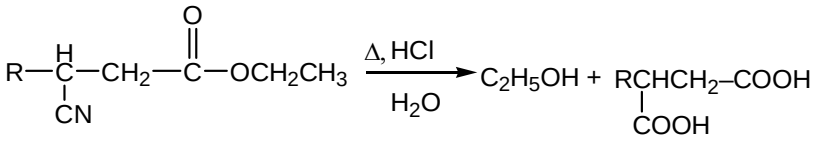
The ester can be made via the ethyl alcohol in presence of HCl or by Fischer esterification. The ester group can be converted back into carboxylic acid under strong acidic and basic conditions.



(Ethyl esters as protecting group for carboxylic acid)

Scheme-12

In this scheme-12 the OH group of the carboxylic acid group is protected as ethyl ester before the reactions are carried out at β-carbon. Regeneration of carboxylic group is done in strong acidic condition as shown in (Scheme-13).

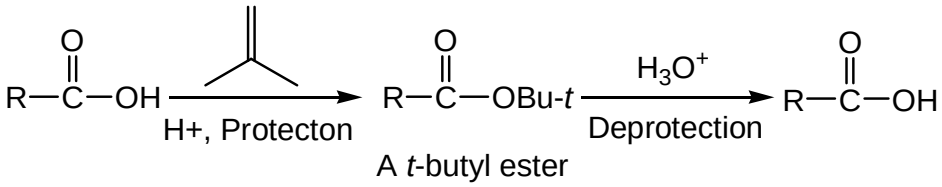


(Deprotection : Regeneration of carboxylic group)

Scheme-13

15.3.2 As *t*-Butyl Esters

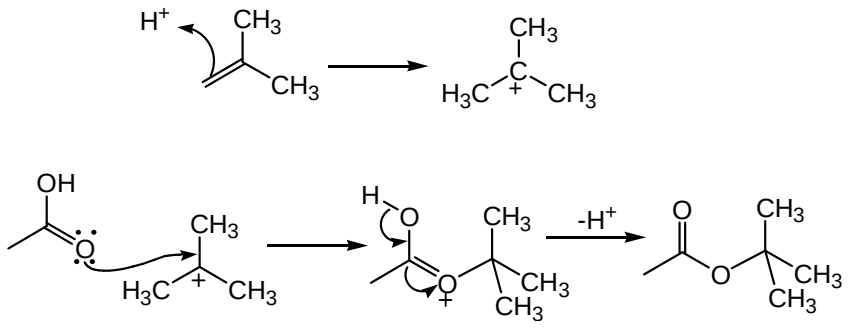
The –OH group of the carboxylic acid can be protected as t-butyl ester. A tertiary butyl ester is prepared by reaction of carboxylic acid with isobutylene under acid catalysis, it can be removed under mild acid treatment. In the Scheme-14, the –OH group of the carboxylic acid is protected as t-butyl ester.



(t-Butyl ester as protecting group for carboxylic acid)

Scheme-14

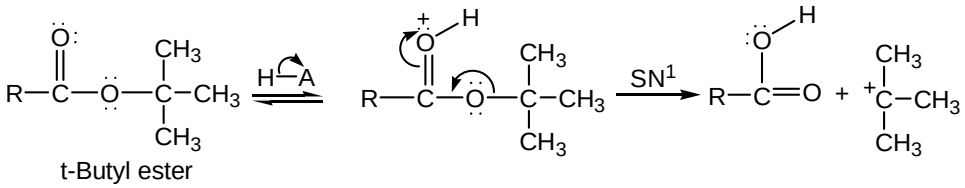
The mechanism of the formation of a *t*-butyl ester is in Scheme-15, the *t*-cation formed by the alkene is trapped by the carboxylic acid.



Scheme-15

Cleavage of t-butyl ester

It can be deprotected by reaction with dilute acid (under milder conditions). It follows an SN^1 mechanism (scheme-16)



(Deprotection : Regeneration of carboxylic group)

Scheme-16

15.3.3 As Silyl esters

Silyl esters are stable to nonaqueous reaction conditions. It can be prepared by reaction of carboxylic acid with trimethyl silyl chloride (Scheme-17). A trimethylsilyl ester can be cleaved by refluxing in alcohol (Scheme 18). More substituted silyl esters are cleaved by mildly acidic or basis hydrolysis.

$$RCOOH + Me_3SiCl \xrightarrow[CH_2Cl_2]{\text{Pyridine}} RCOOSiMe_3$$

(Silyl ester as protecting group for carboxylic acid)

Scheme-17

$$RCOOSiMe_3 \xrightarrow{\text{EtOH or HOH}} RCOOH$$

(Deprotection : Regeneration of carboxylic group)

Scheme-18

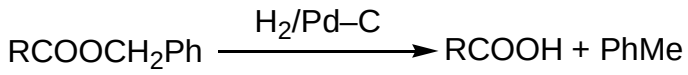
15.3.4 As benzyl esters

It can be synthesized by benzyl alcohol and debenzylated by hydrogenolysis. (Scheme 19 & 20).

$$RCOOH + PhCH_2OH \xrightarrow[Et_2O]{\text{DCC/DMAP}} RCOOCH_2Ph$$

(Benzyl ester as protecting group for carboxylic acid)

Scheme-19



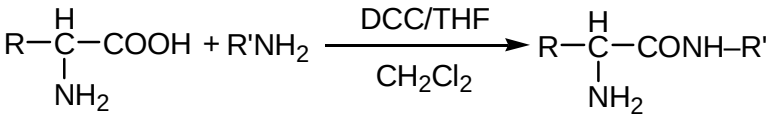
(Deprotection : Regeneration of carboxylic group)

Scheme-20

15.3.5 As Amides and Hydrazides

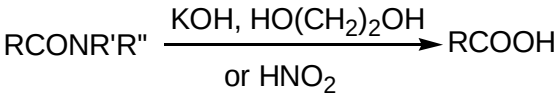
To a limited extent carboxyl group have been protected as amides and hydrazides. Both are stable under mild alkaline hydrolysis that cleaves esters. Esters are stable in acidic conditions, effective in cleaving amides and oxidizing agents that have been used to cleave hydrazides.

As amides: It have been prepared by reaction of acid with an amine (Scheme 21).



(Amides as protecting group for carboxylic acid)

Scheme-21

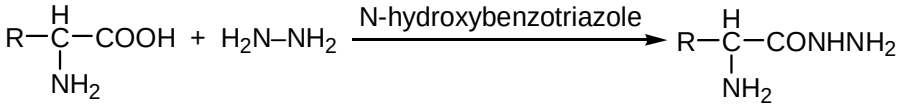


(Deprotection : Regeneration of carboxylic group)

Scheme-22

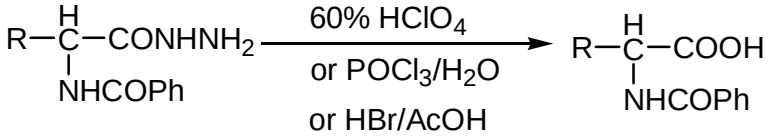
As Hydrazides

It have been prepared by reaction of acid with hydrazine.



(Hydrazides as protecting group of carboxylic acid)

Scheme-23



(Deprotection : Regeneration of carboxylic group)

Scheme-24

15.4 Summary

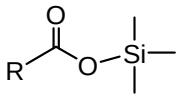
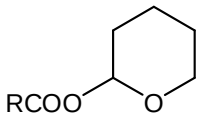
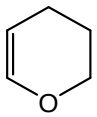
Definition of Protecting Group

Protection of a functional group is an operation, in which a temporary modification of the site at which reaction is undesirable, is done in such a way so that it remain intact and unreactive during the reaction at the other site in the same molecule. At the end of sequence, the original group can be regenerated again easily. The group modifying the functional group is known as protecting group.

Table 1 : Protecting group for Amine (RNH_2)

Protecting group [[PG]	To add	To remove	PG resists	PG reacts with
Amides				
$RNHCOR^1$	R^1COCl	HO^-/ H_2O H^+ / H_2O	Electrophilies	
Urethane $RNHCOOR'$	Chloroformates	R' = CH_2Ph	Electrophiles	Base,nucleophiles
	$R'OCOCl$ $R' = C(CH_3)_3$	H_2, Cat. or HBr		
Phthalimides	Phthalic anhydride	NH_2NH_2/ EtOH		

Table 2 : Protecting group for Carboxylic acid (RCOOH)

Protecting group [[PG]	To add	To remove	PG resists	PG reacts with
Ester				
RCO_2Me	CH_2N_2			
RCO_2Et	$EtOH/H^+$	HO^-/H_2O		
RCO_2CH_2Ph	$PhCH_2OH/H^+$	H_2, Cat, or HBr		
$RCO_2Bu\text{-}t$	H^+, t-BuOH	H^+		
$RCO_2CH_2CCl_3$	Cl_3CCH_2OH	Zn, MeOH		
	Me_3SiCl/Pyr CH_2Cl_2	$Bu_4N^+ F^-$, DMF		
	 TsOH, CH_2Cl_2	ACOH, $THF\text{-}H_2O$		
Anion				
RCO_2^-	Base	Acid	Nucleophiles	Electrophiles

15.5 Review Question

1 What is protecting group? What are its salient features?

2 Discuss the principle of protection of amines.

3 Explain the importance of protecting groups in organic synthesis. Discuss the important methods employed for protection and deprotection of carboxyl group

4 Illustrate the use of the following as protecting group in organic synthesis.

(a) BOC group (b) CBZ group

5 Using a suitable protecting group, how would you carry out the following reactions?

(a) $H_2N–CH_2–CH_2–CHOH \xrightarrow[\text{Pyridine}]{CH_3COCl} H_2NCH_2CH_2–CH_2–OCOCH_3$

(b) $H_2N–CH_2–CH_2CHO \xrightarrow{KMnO_4} H_2N–CH_2–CH_2–COOH$

15.6 Reference and Suggested Readings

- Organic Synthesis,The Disconnection Approach, S. Warren (Wiley).
- Organic Synthesis through Disconnection Approach, P.S. Kalsi, MEDTEC
- Guide book to Organic Synthesis, R.K. Mackie and D. M. Smith, ELBS.
- Organic Synthesis, Jagdamba Singh and L.D.S. Yadav, Pragati Prakashan.

Unit-16

One Group C - C Disconnection Alcohols and Carbonyl Compounds

Structure of the Unit:

16.0 Ojective

the present unit describes the detailed study of one group c-c disconnection in light of retro synthesis of various organic molecules viz alcohols and carbonyl compounds the disconnection approach covers the mechanistic routes logically selected (on analytically basis) for the synthesis of compounds which can be derived from alcohols aldihyde and ketones the main objecive is to convert the product the target molecule into the stationary materials by the disconnecting various groups present in the target molecule. This of great help in finding out a suitable starting material which is easily available.

16.1 Introduction

The main aim of disconnection approach is to work out an analytical approach for designing a synthesis. The essential requirement of this approach is knowledge of some most basic organic reaction and their mechanisms.

When we aim to design an organic synthesis the compound to be synthesized is called a target molecule (TM). We start with target molecule and work backwards. This involves DISCONNECTIONS for one or more functional groups and thus it appears to be imaginary process which is reverse of real chemical reactions. Here we break a bond in the target molecule to obtain the structure of a new compound form which the target molecule can be made.

16.1 Some Basic Terms

Befor we start the discussion the knowledge of following basic terms is important. These are described below.

16.1.2 Disconnection

It is an analytical operation in which we break a bond and convert a molecule into a possible starting material is reverse of a chemical reaction. For this symbol⇒ and a curved line f is used.

16.1.3 Fgi (Functional Group Interconversion)

This is the process which involves writing one functional group for the another to make the disconnection feasible for this FGI is return over the symbol ⇒.

16.1.4 Reagent

Reagent is the compound which reacts to give either an intermediate or target molecule itself.

16.1.5 Synthetic Equivalent

It is a reagent which acts for the function of a synthon(because it cannot be used due to its instability).

16.1.6 Synthon

The term synthon is used for a fragment, generally an ion, produced by a disconnection.

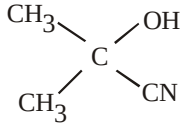
16.1.7 Target Molecule

It is the molecule for which the synthesis is planed. It is usually return as TM or by a number return with in [].

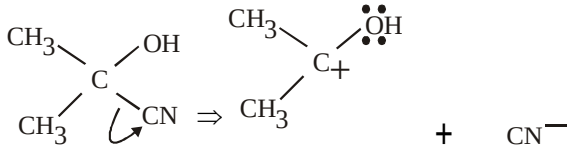
16.2.0 One Group Dissconections

16.2.1 Disconnections of Alcohol

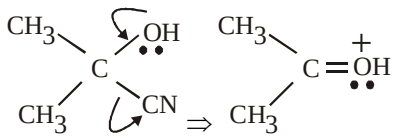
To understand the disconnections of the alcohols let us think of a possible mechanism for the synthesis of the following alcohol. Which actually is are target molecule.



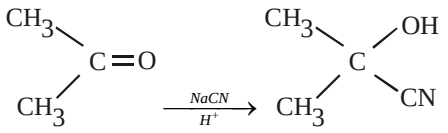
Now let us take the following path



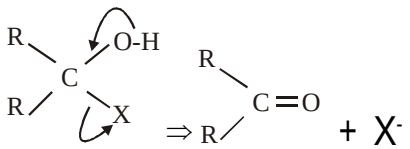
Now by the deatachment of CN^-, the cation so formed is stablised by the lone pair of electrons on oxygen atom on the OH group i.e,



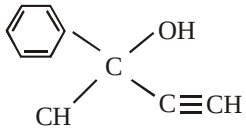
Thus the real reaction shall be the reverse of the above disconnection as shown below.



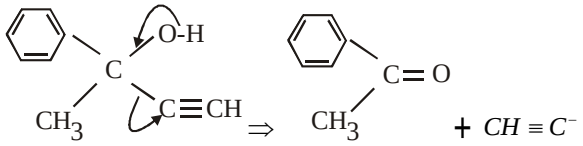
Thus it can be seen all simple alcohols can be disconnected in this way. Actually we simply choose the most stable anion of the subsituents and then disconnect it to a carbonyl compound i.e.,



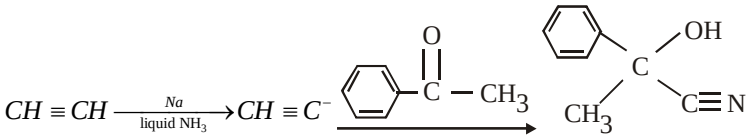
Now let us consider a disconnection for the synthesis of the following target molecule



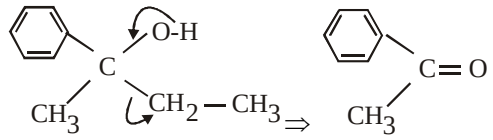
Here we see that the anion is most stable so we can have



So the real reaction comes out to be as follows

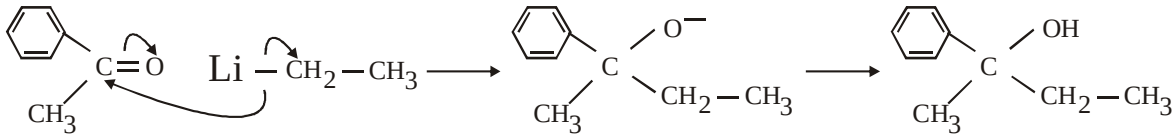


In the case if the subsituent gives a stable anion then we use the synthetic equivalent of the anion which is either a Grignard reagent R - Mg - Br or alkyl lithium.Here the ethyl group i.e. “Et” is refered as a SYNTHON having Et Mg Br is synthetic equivalent.Thus can have



$C_2H_5^- = C_2H_5MgBr$ or C_2H_5Li

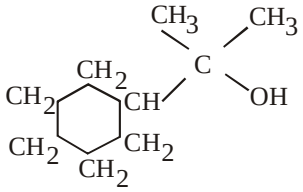
Now we draw the real reaction which is actually a reversal of the above disconnection. This can be written by taking C_2H_5Li

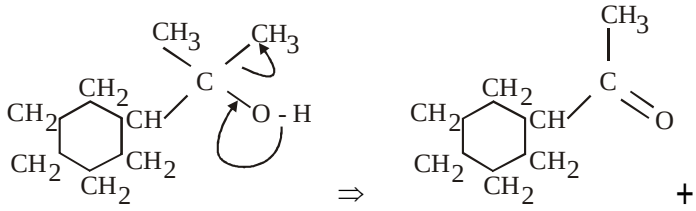


It is evident above synthesis that the unit alkyl- Lithium acts as the synthon $CH_3 - CH_2^-$.

In this because carbon - lithium bond is broken and the electron of the bond go with the carbon atom ethyl moeity.

Further let us consider the disconnection following target molecule.

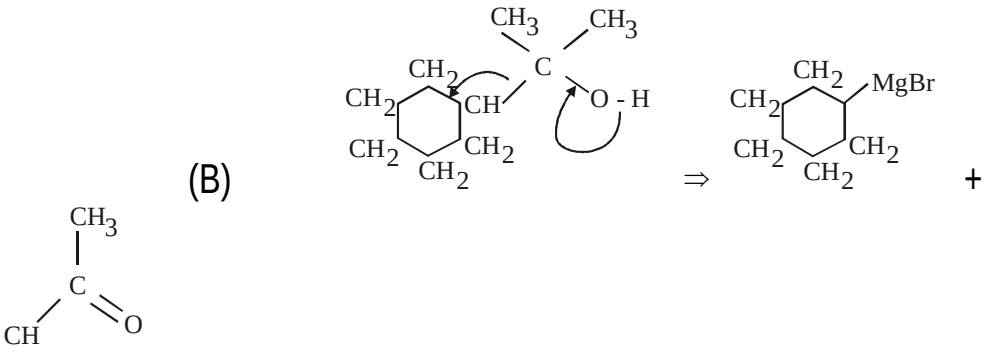




(A)

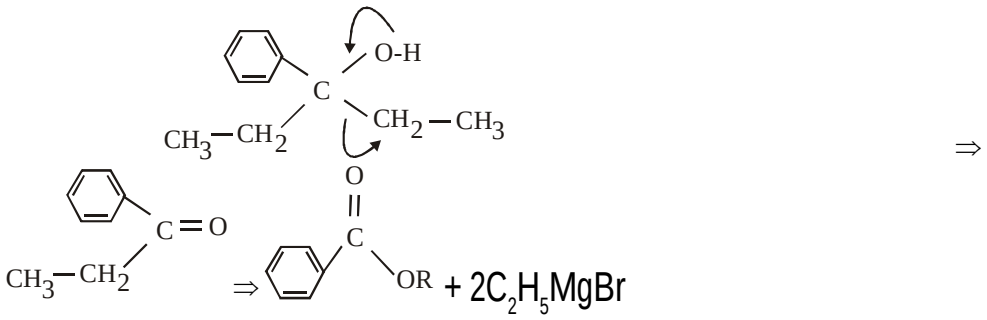
CH_3MgI

and

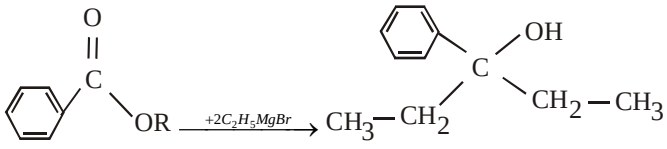


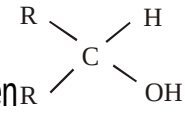
Although both the above two processes have logical mechanism but the path (B) is preferred because of its simple nature. Path (A) reduces one carbon atom and leaves a new target which is difficult to be made. In path (B) the molecule is fragmented into two equal parts namely acetone and cyclohexyl bromide. This indicates that for a good disconnection we should have a logical mechanism and greatest simplification.

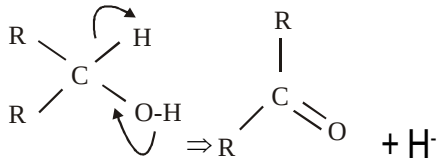
Secondly we can remove both the groups in a simple disoconnection to get ester



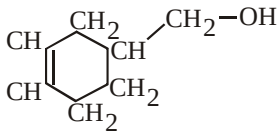
So the overall reaction becomes



If one the group attached to carbon containing -OH group is hydrogen  ie the

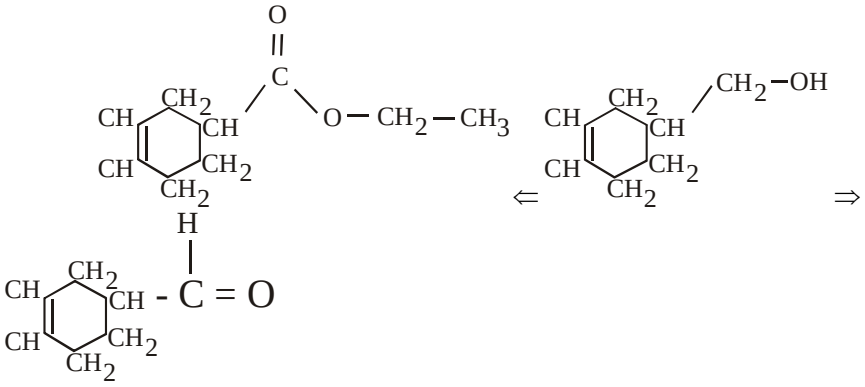
following disconnection may be used 

Now the synthesis is H^- and its synthesis equivalents must be a hydride donor like sodium borohydride $NaBH_4$ or Lithium aluminium hydride $LiAlH_4$.

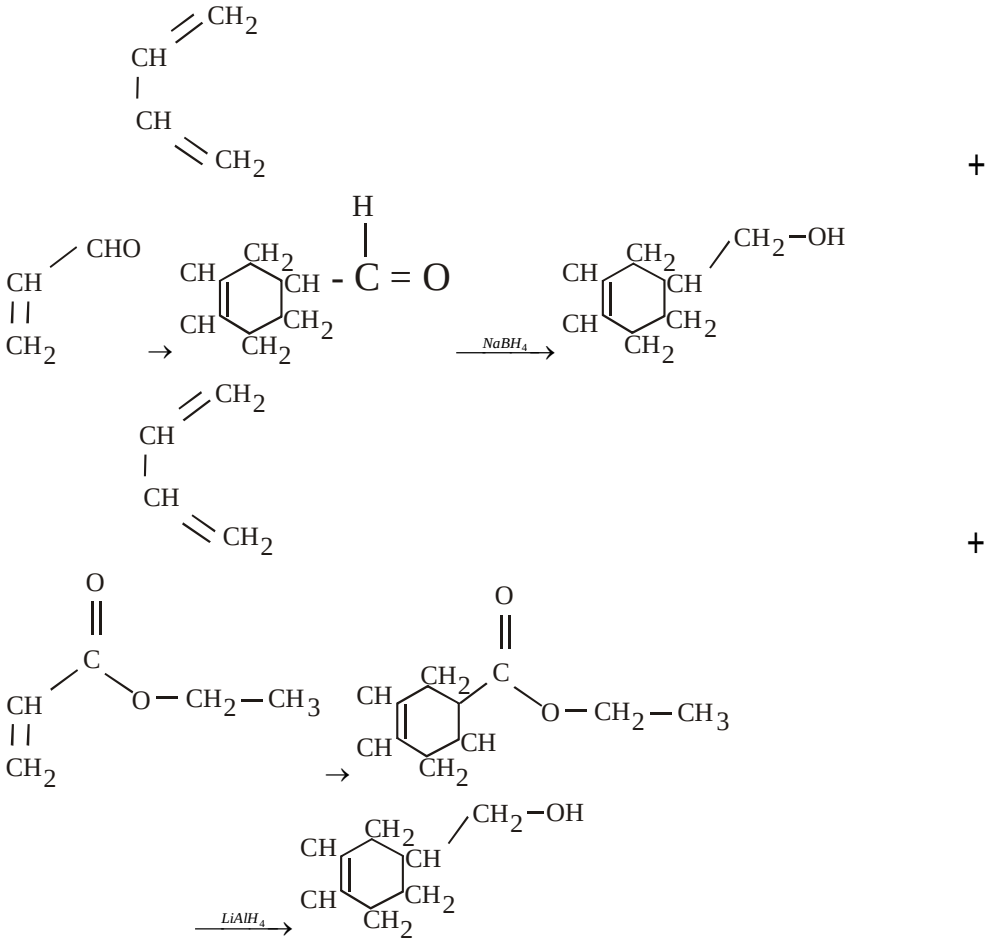
Now let us take the example of preparing . 

This can be planned in the following way. First we remove either one or both the hydrogen atoms from the target molecule

i.e



The above starting material can be obtained by usual Diels-Alder reaction as follows



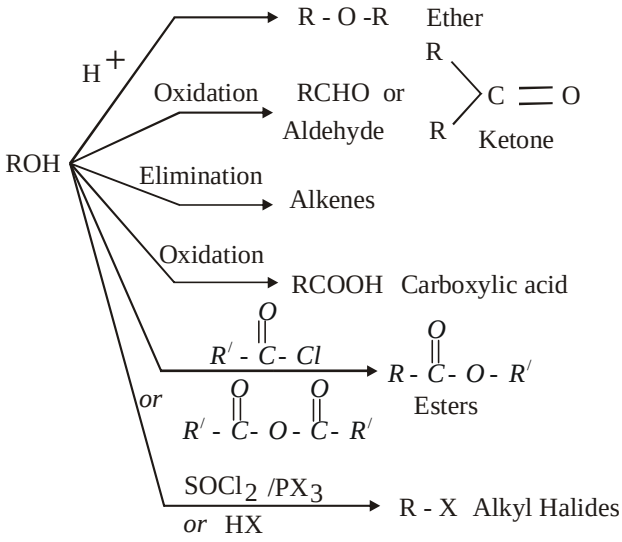
Here it is important to note that $NaBH_4$ reduces aldehydes and ketones but not the esters whereas $LiAlH_4$ reduces all carbonyl compounds (including esters) but none of them reduce an isolated double bond..

16.3 Compounds Derived From Alcohols

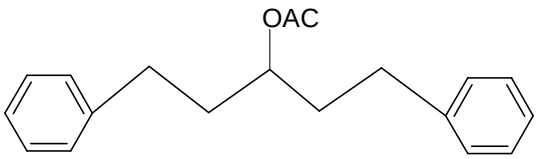
It is clear from the previous discussion that the processes involving H^- can be simply viewed as redox reactions in which the carbon skeleton of the molecule (Starting material) does not undergo a change. These are the not considered as disconnection but are simply functional group interconversions (FGI).

Alcohols are regarded as very versatile compounds in organic synthesis because they can be further connected to various other organic compounds containing other functional groups.

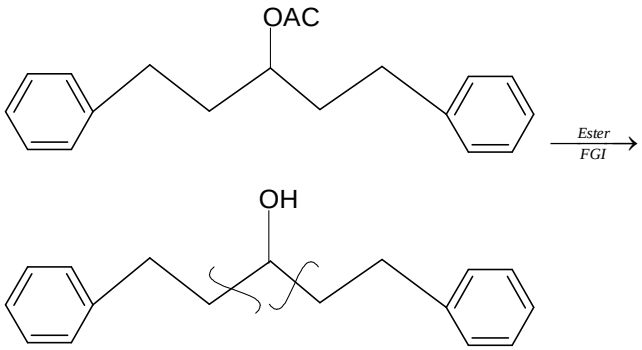
In the following discussion we take up various other molecules which can be prepared from alcohols by functional group Interconversion.

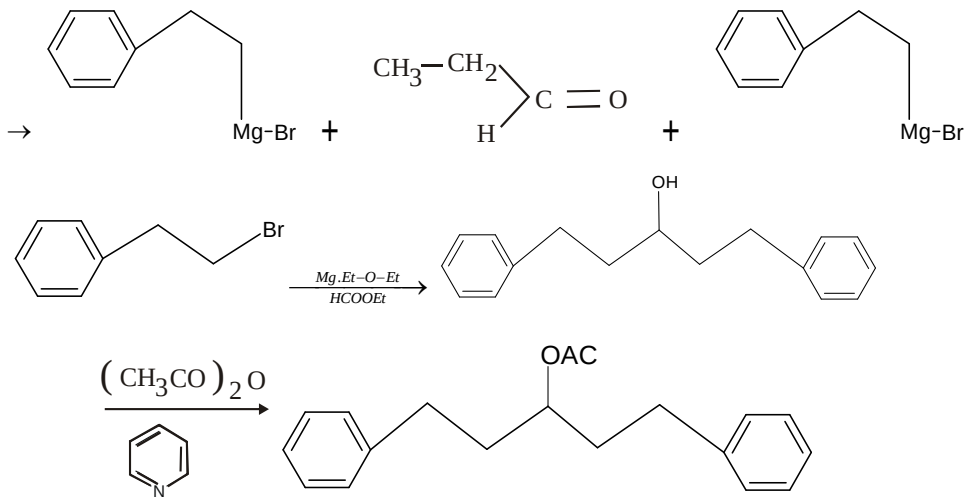


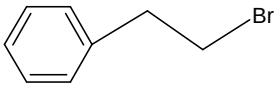
These interconversion can be best carried out by first going to alcohol and then disconnecting it. following examples shall make it clear suppose we want to prepare

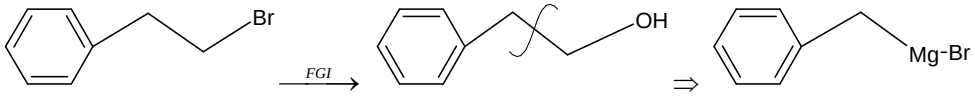


We can proceed as shown below

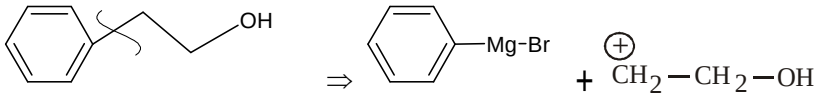




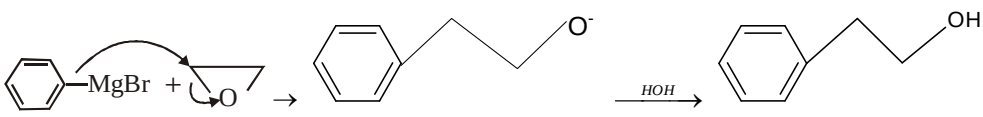
Now the synthesis of  can be done



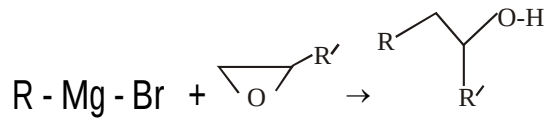
+ HCHO

But the above process results in a poor yield because the Grignard reagent produces free radicals which undergo polymerisation. Thus it can be achieved in the following way 

Here the reagent for the synthon $\overset{\oplus}{C}H_2-CH_2-OH$ can be an epoxide. Thus the overall reaction becomes

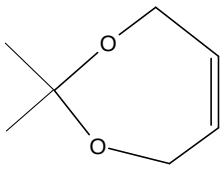


This process is also applicable when the epoxide is even monosubsituted eg.



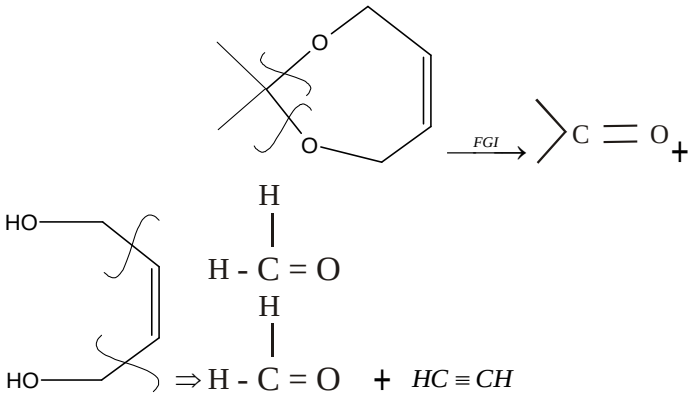
But in case, the number of subsituents in epoxide are more, the results are not encouraging.

16.4 Problem # 1

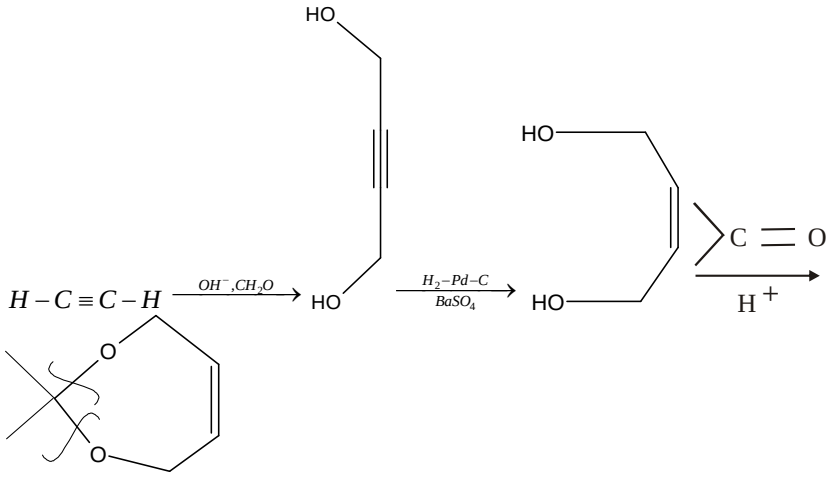
Let us consider the synthesis of 

This molecule is used as an intermediate in the synthesis of the compound maytansine (used as an antitumour drug)

This can be planned in the following way. The functional group in the above molecule is an acetal which is obtained when an alcohol combines with a carbonyl compound now a diol has a cis double bond so we can proceed as follows

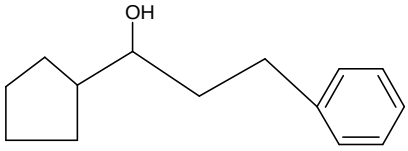


Now the overall synthesis of the compound may be carried out by the following path.

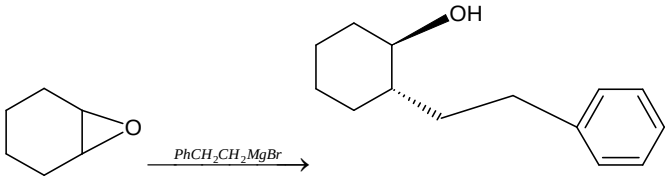


16.4.1 Problem # 2:

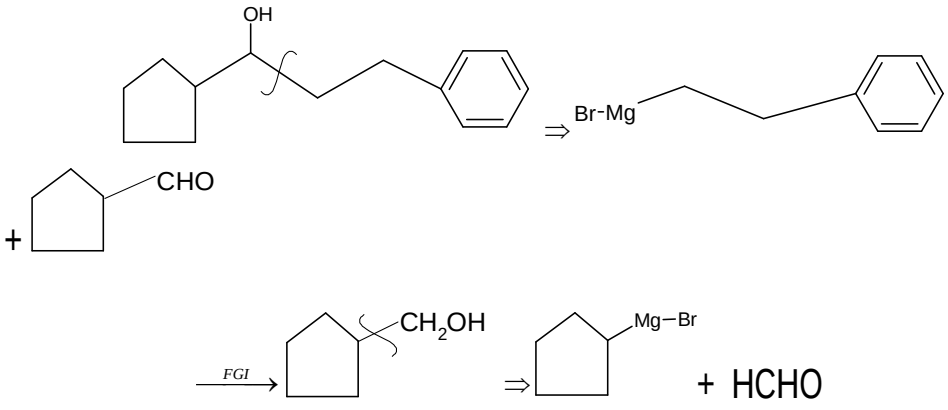
Let us consider the synthesis of the compound

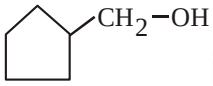


To understand it let us see the following reaction.

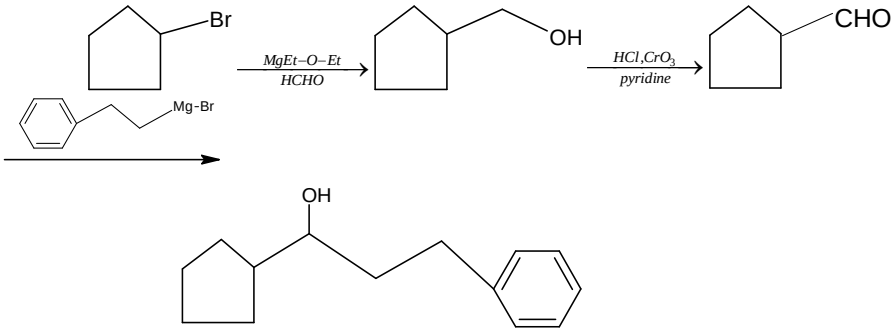


In the above reaction the product was thought to be doubtfull. This was solved by disconnection as follows

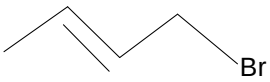


Here the one carbon disconnection 

in is safe because the Grignard reagent is from a normal alkyl halide and so will not undergo polymerisation. Thus the overall synthesis can be visualised as

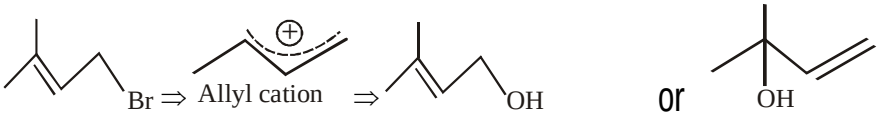


16.4.2 Problem #3:

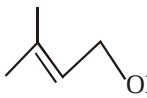
Let us discuss the synthesis of 

The above allyl bromide is an important intermediate of terpenes and also in the preparation of some commonly used flavouring and perfumery compounds.

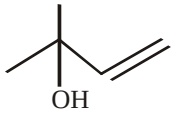
If we see the following path it is evident that an allylic alcohol may be a precursor i.e.,



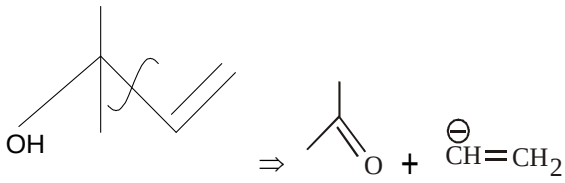
Both the above alcohols will give the desired allyl bromide (Target molecule) on treatment with HBr because the allyl cation will react preferentially with Br^- at less subsituted carbon atom to yield product which contains more subsituted double bond.

Now although the precursor alcohol 

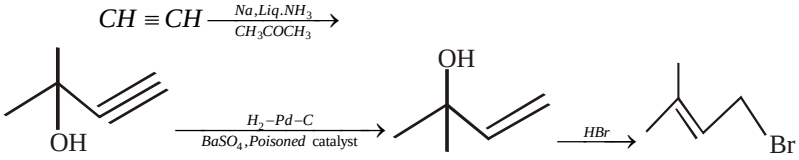
can be obtained by the reaction

of a vinyl Griganrd reagent and formaldehyde but the alcohol  can easily be obtained by the use of an acetylide ion $\overset{\ominus}{C}H{=}CH_2$ as a reagent for the synthon.

i.e.,

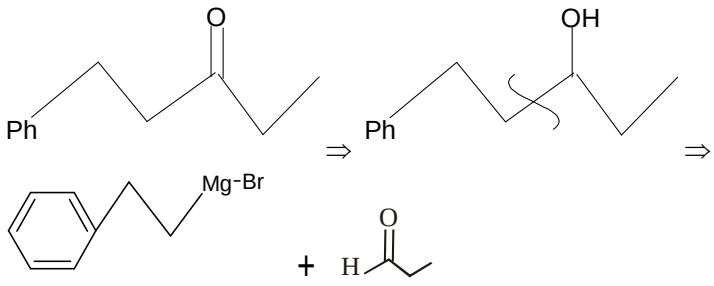


Thus the overall synthesis of the desired target molecule can be written as follows



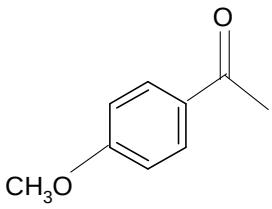
16.5 Disconnection of Simple Ketone

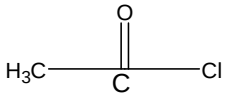
In this section we discuss the synthesis of ketones by disconnection approach.To understand let us see the synthesis of a simple ketone

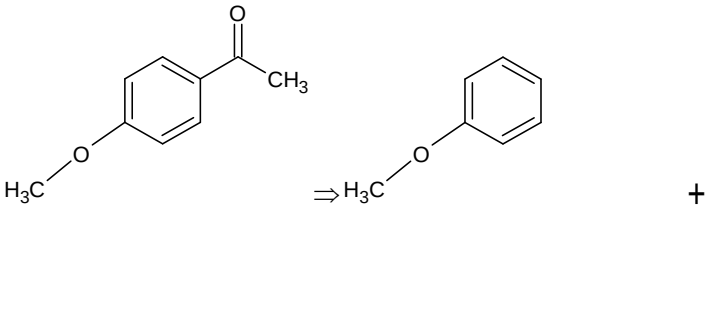


16.5.1 Disconnections of Aryl Ketones

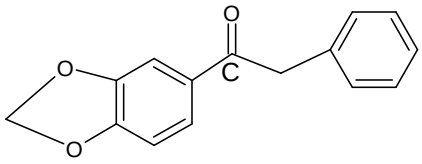
In this the major part involves the disconnection of the bond joining an aromatic ring to an aliphatic side chain. This is discussed below.

Suppose we want to synthesis the compound 

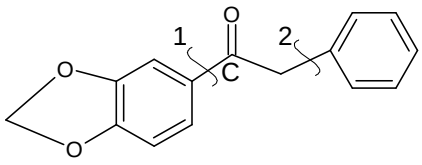
The above compound can be easily be synthesised by well known Fredel-Crafts reaction using  and $AlCl_3$ and a properly subsituted benzene ring namely anisole in this case ie,



Thus at first it appears that one can disconnect any bond next to the benzene ring using the above paths but it is not always possible. For example suppose we want to make the following compound



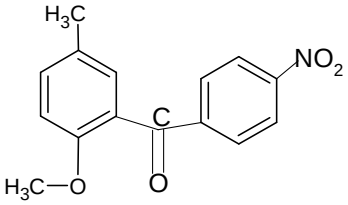
For this two possible disconnections can be operated. These are shown below by 1 and 2.



Thus the disconnection 1 can be safely used.

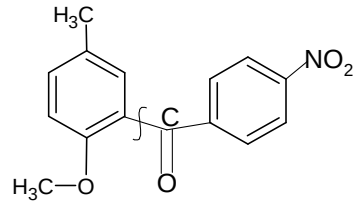
Sometime it so happens that it is the quality of mechanism which decides the selection of a particular disconnection out of various possible disconnections. This is illustrated below.

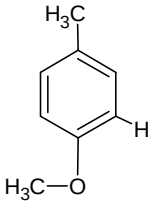
Suppose it is desired to synthesis the following compound.



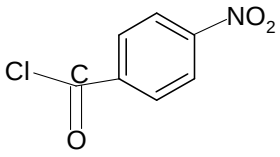
It is evident that there are two possible disconnections for it. These are

(I)



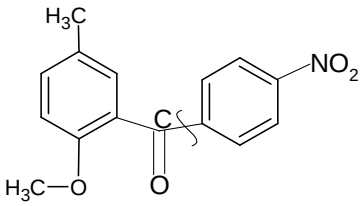


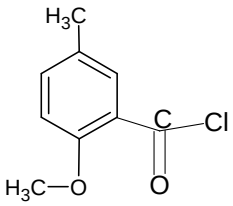
+



and the

(II)





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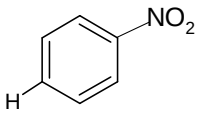
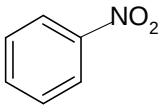
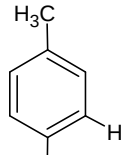
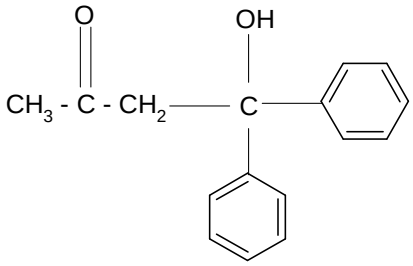


It is evident from the products of (II) that  is one of the fragments and the -NO_2 is highly deactivating and meta directing and so will not undergo Friedel - Craft reaction. On the contrarory in (I) disconnection one of the fragment

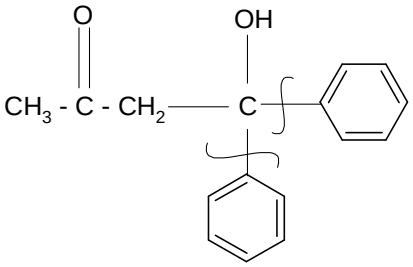


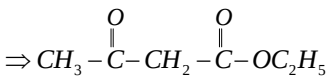
is  and this contains -OCH_3 group as one of the subsituents on benzene ring.This is highly activating and is ortho-directing than -CH_3 group.

Some it is necessary to consider the control factor for the systamatic ongoing of the synthesis under investigation. For example while synthesising the compound

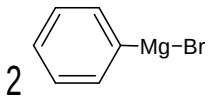


The following disconnection is obvious

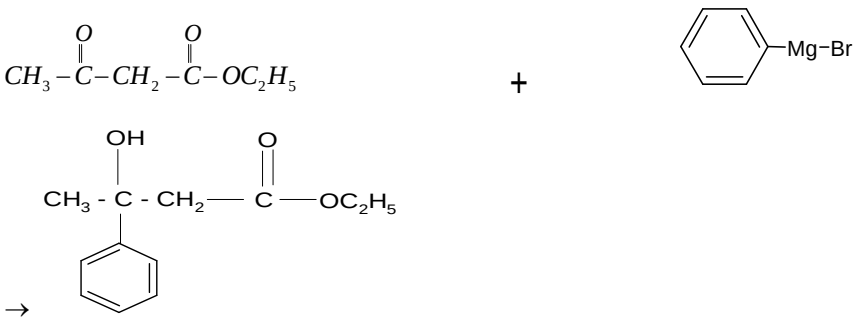




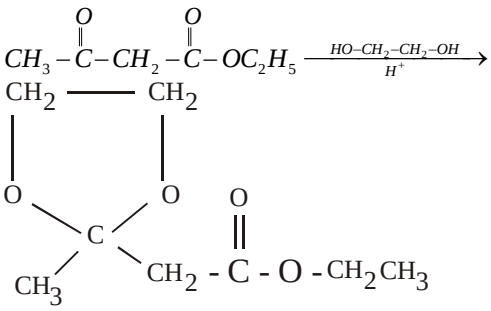
+

2 

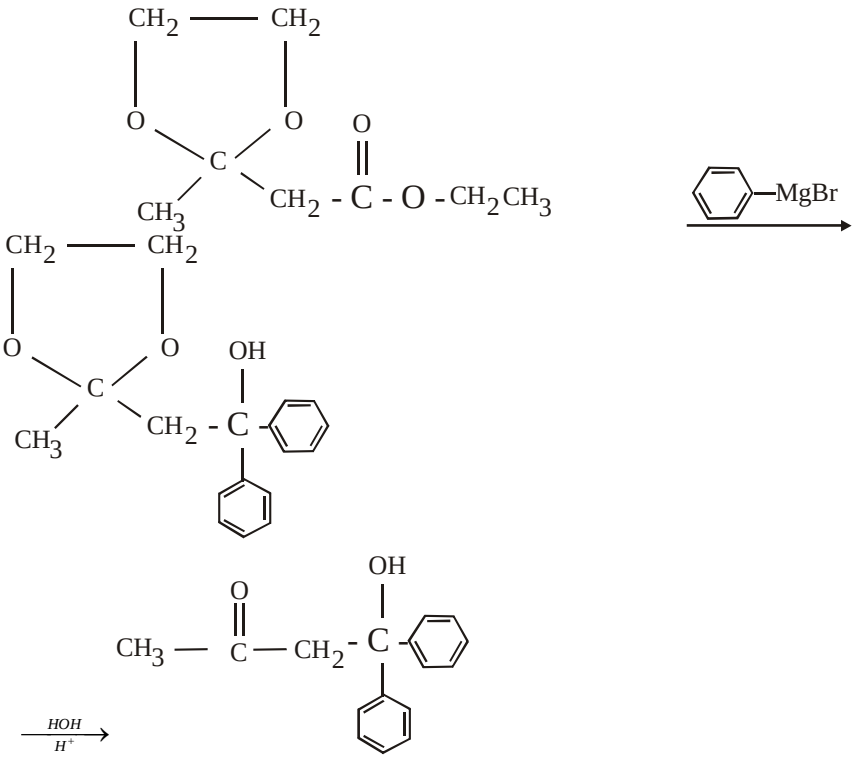
But a complication occurs because the Grignards reagent so formed attacks the ketone to give some undesirable product as shown below



So in order to stop the formation of the above undesirable product the ketone is protected by a reversible functional group interconversion (FGI). One common way to do this is to convert the above ketone into a cycle ketal as depicted below:



The complete sythesis of the target molecule can now be written as shown below

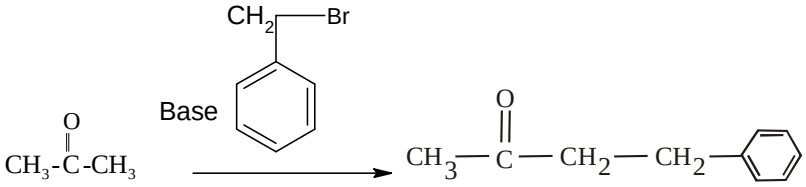


It is to be noted that a group can be used as a protecting group if it satisfies following conditions.

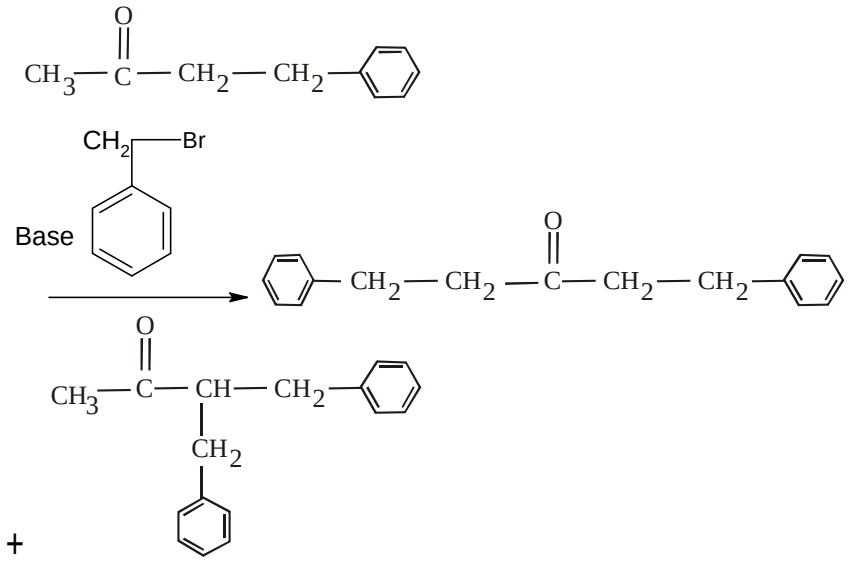
(a) It can easily be added and removed.

(b) It should not react with the reagent added during process.

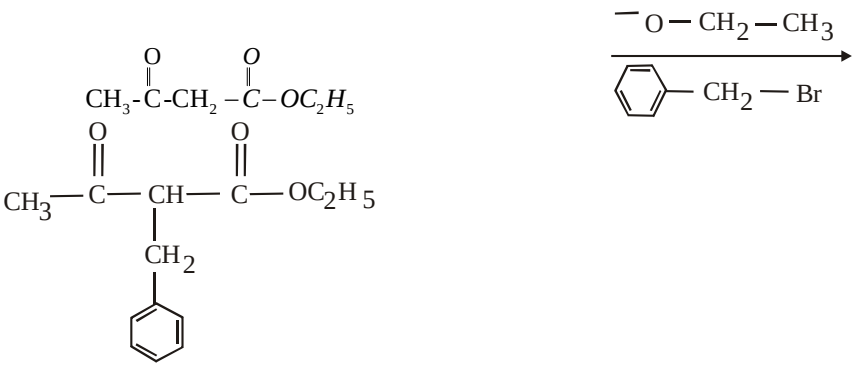
Sometimes it is better to activate some part of the molecule rather than to protect some other part. To understand it let us consider the following sequence of a chemical process



Here the product undergoes enolisation thus resulting in its poor yield.Now as the product here is as active as the starting material the reaction does not stop and proceeds further ie,

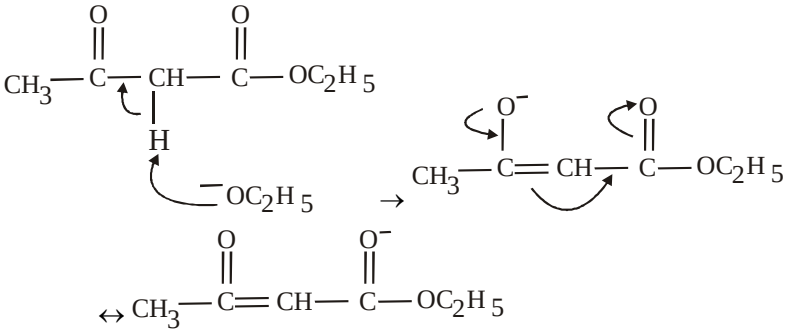


Here we cannot protect carbonyl group without stopping in reaction so it is shall be appropriate to activate one position by introducing $-\overset{O}{\overset{\|}{C}}-O-CH_2-CH_3$ and using this ester. This is synthetic equivalent of $CH_3-\overset{O}{\overset{\|}{C}}-CH_3$ ie,

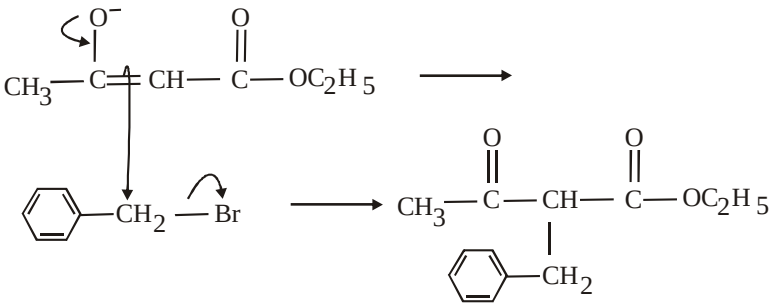


The mechanism of the above reaction can be shown as below

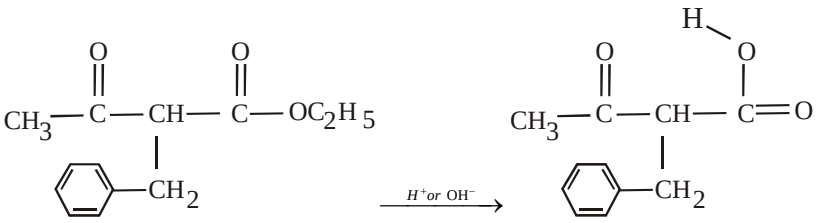
(i)

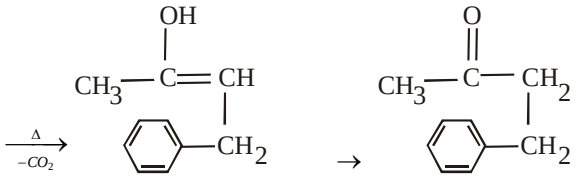


(ii)

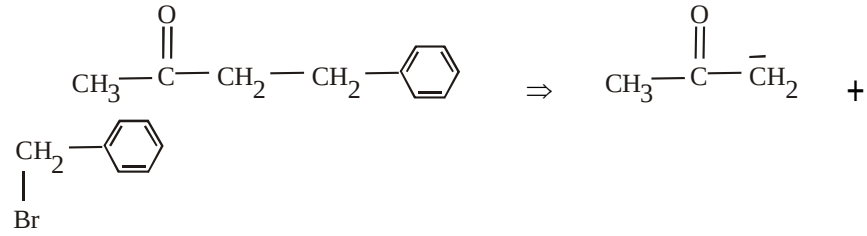


Now the activity group -$COOC_2H_5$ and this is done by hydrolysis followed by decarboxylation. This is shown below

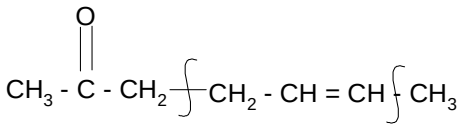




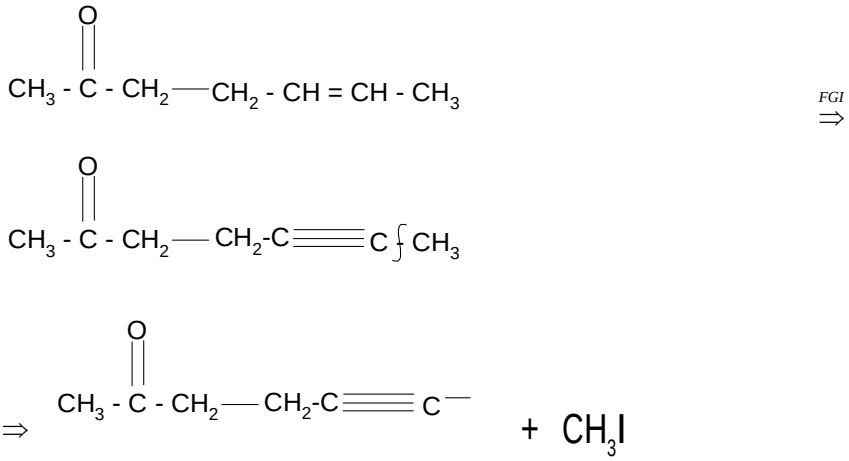
Thus following is the general synthesis for the ketones and the disconnection is

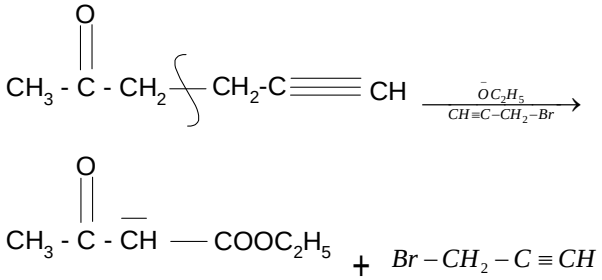


Sometimes a different situation arises. Here we need to use both protection and activation. To illustrate this let us consider the synthesis of the following molecule.

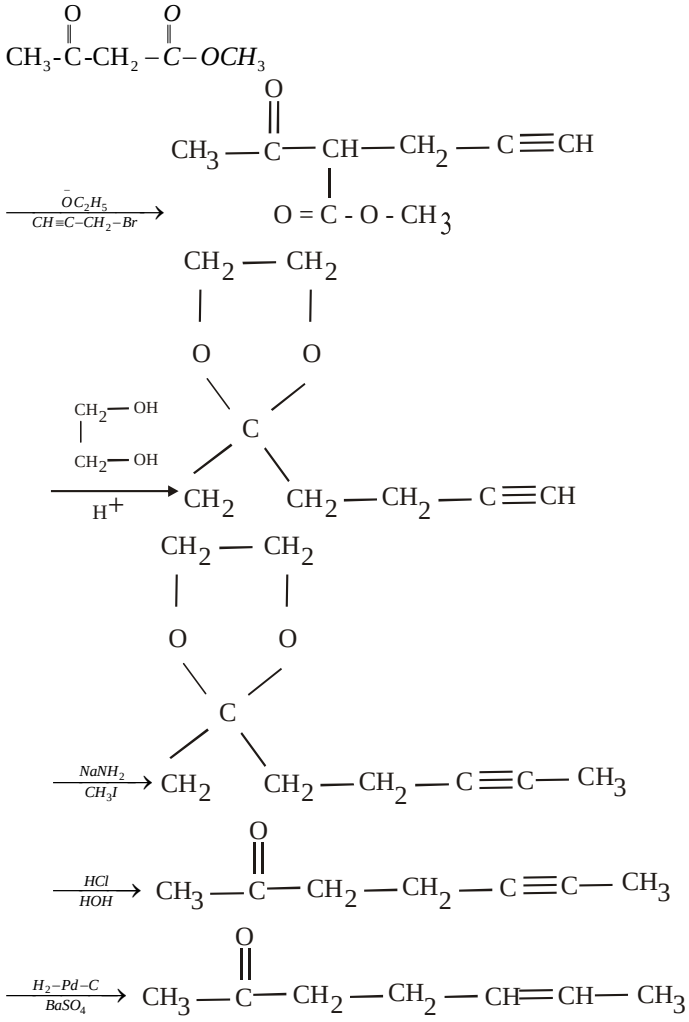


It is evident that the cis olefin can be obtained from acetylene and then acetylide ion can be used as shown below





The Br atom attached to system is called as propargyl bromide and is reactive and readily available. Thus only thing we need is to protect the ketone before making acetylene anion. It appears that protection and decarboxylation can be carried out in a single step. Thus the whole synthesis can be depicted by following sequence.



16.6 Summary

- Alcohols and carbonyl compounds are important organic compounds which find extensive uses in various field of chemistry.
- Various complex organic molecules of industrial and pharmaceutical interest involve the use of alcohols and carbonyl compounds as the substrate in their synthesis.
- The synthons or synthetic equivalent used in the retrosynthesis are selected on the basis of functional groups present in the target molecule
- various functional group intercnversion (FGI) should have the logical mecghanism
- the reaction conditions (mild or drastic) have their specific influences on the thermodynamics and kinetics of the reverse synthesis of the reverse synthesis under examinations.

16.7 Review questions

1 what do you understand by the one group C-C disconnection.

2 Mention the conditions in which a grgnard reagent can be used as a synthetic equivalent.

3 discuss the use of the following in the retro sy6nthesis of Alcohol

(a) Lithium aluminium hydride (b) sodium boro hydride.

4 How an ester group can be interchanged in retro synthesis write in detail.

16.8 Refrence Book

- The disconnection Approach,S.C Ameta ,Sadguru publication
- Designing Organic Synthesis , Stuart warren, Wiley india private Limited.
- Organic synthesis, Jagdambha Singh, Paragti Prakashan.

Unit -17

Two Group C-C Disconnections

Structure of the unit

17.0 Objective

Chemist always try to synthesise organic compounds in organic chemistry laboratory in the world. The disconnection approach is a way to help how he can

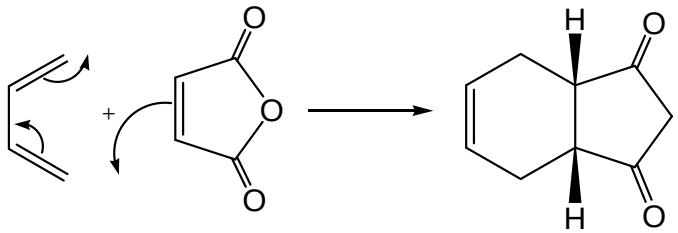
design his own syntheses rather than those derived by others. This approach is analytical : we start with the molecule we want to make (the target molecule) and break it down by a series of dissconections in to possible starting materials. This chapter will help to learn the method for synthesis of C-C bond, which are found in organic molecules.

17.1 Introduction

In one group C-X and two group C-X disconnection we disconnect the bond between the carbon and heteroatom. Now we are discussing C-C disconnections. These are more challenging because organic molecules contain C-C bonds and we should learn which to disconnect. In one way they are easier than C-X disconnections. Reagents are available for both electrophile (e.g. RBr) and nucelophile (e.g. RMgBr) carbon while heteroatoms are almost always added as nucleophiles.

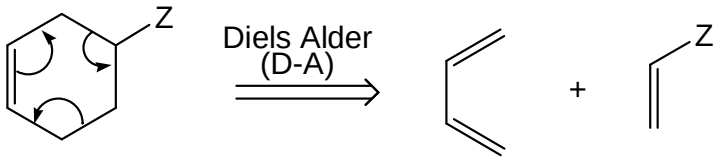
17.2 Diels-Alder reaction

Diels Alder reaction is one of the most important reaction in synthesis because it makes two C-C bonds in one step. It is regio and stereoselective reaction. It belongs to pericyclic reactions. It is a cycloaddition reaction between a conjugated diene (1) and a conjugated alkene (2) (dienophile), forming a six membered ring (Cyclohexene).



(1) **(2)** **(3)**

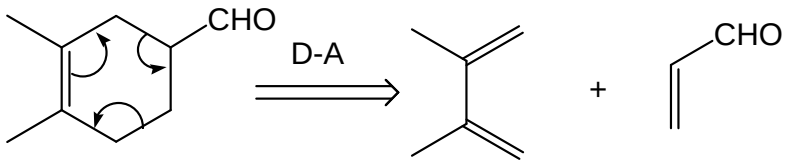
The corresponding disconnection is often best found by drawing the reverse reaction mechanism. Most reactive dienophiles (2) have the alkene double bond conjugated to some electron with drawing group (Z). If we want to make a cyclohexene (4) with at least one electron withdrawing group (Z) on the far side of the ring, draw three arrows round the ring in either direction, starting from the double bond.



(4)

TM (5) can be easily made by Diels Alder reaction. There is no need of special solvents or conditions as ionic intermediate are not formed. TM (5) can be made by simple mixing of two component with heating.

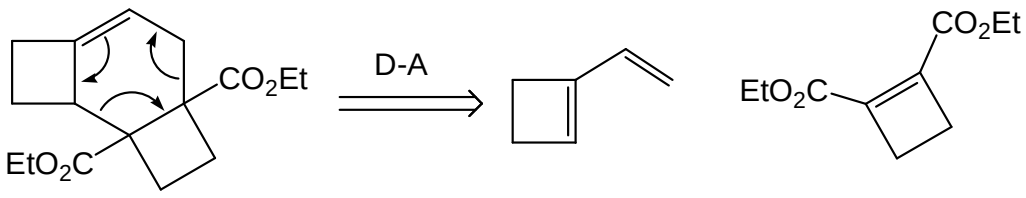
Retrosynthetic analysis of TM (5)



(5)

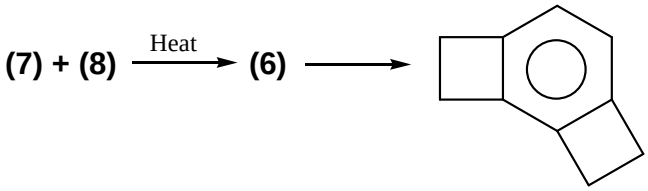
This is a two-group disconnection because it can be carried out only when both features -cyclohexene and electron withdrawing group-are present and the relationship between them recognized. No matter how complicated the target molecule may be, e.g. (**6**), if it contains a cyclohexene and an electron withdrawing group in the right relationship, a Diels-Alder disconnection is worth trying.

Retrosynthetic analysis of TM (6)



(6) **(7)** **(8)**

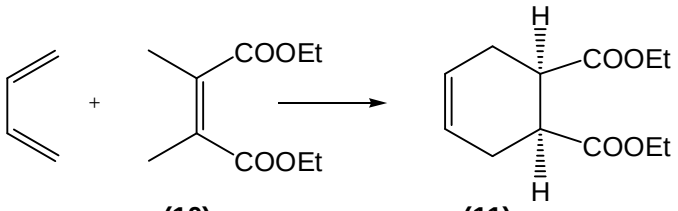
Synthesis



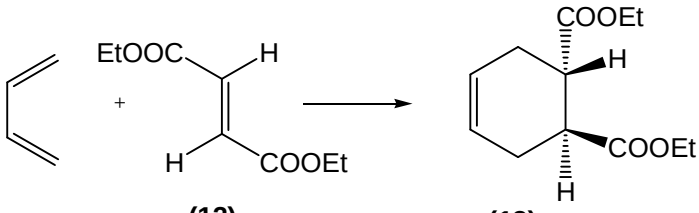
(9)

17.2.1 Stereochemistry of the Diels-Alder reaction

The Diels-Alder reaction is highly stereospecific and stereoselective in predictable fashion within each diene or dienophilic component, substituents will retain the stereochemical relationship to one another in the product that they had in the reactants. As an example, diethyl maleate, in which the carbethoxy groups are *cis*, reacts with butadiene to give diethyl-*cis*-tetra-hydrophthalate, whereas fumarate esters (*trans* – carboxyl groups) give trans products. The stereochemical control here is absolute; i.e. it is not a matter of starting with the *cis* and getting a mixture in which the *cis* predominates. It is, in fact, not possible to detect the other isomer by techniques that would pick up one part in a million if it were there. This is the best evidence that bonding occurs at both ends of the alkene at the same time, i.e., that the reaction is concerted.

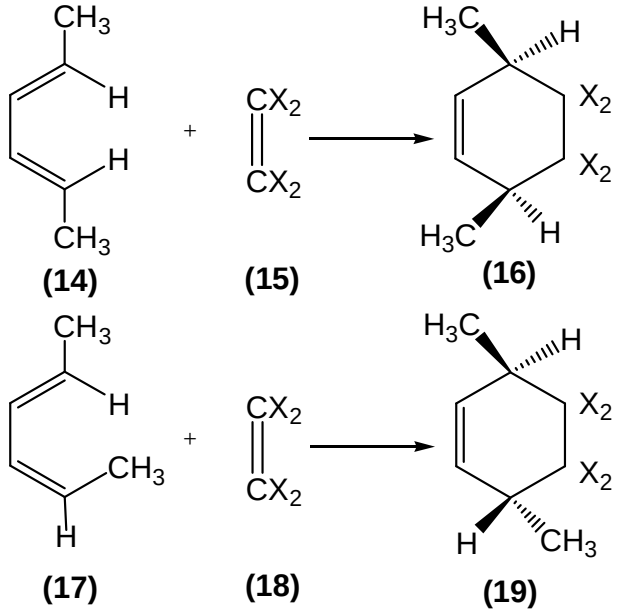


(10) **(11)**



(12) **(13)**

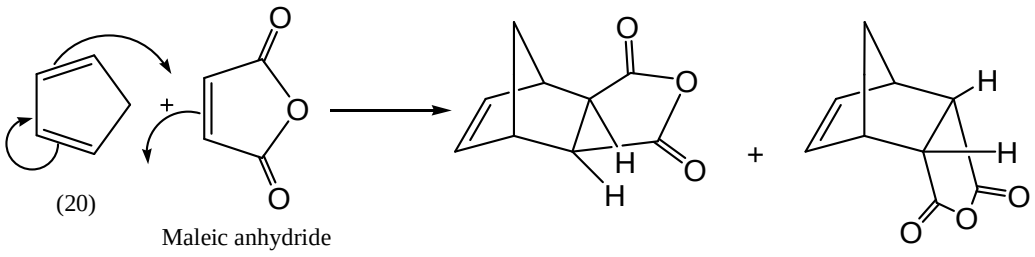
The product stereochemistry is just as precisely controlled by the geometry of the diene. Groups 1,4 on the outside of the cisoid diene (trans, trans-1,4-substituents) end up *cis* to one another on one side of the cyclohexene ring; groups on the inside (*cis, cis*-1,4-substituents) end up *cis* to one another on the opposite side of the ring.



There is one more stereochemical aspect of the Diels Alder reaction which is endoselectivity.

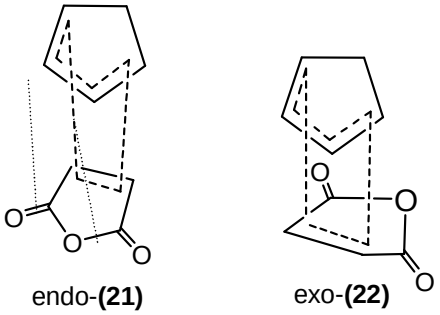
17.2.2 Endo-selectivity of Diels-Alder reaction

A study of a large number of such reactions has led to a generalization that has become known as Alder's rule of endo addition. This rule can be illustrated most easily by considering the reaction of cyclopentadiene (20) with maleic anhydride, here is the possibility of two products exo and endo. The endo form is favoured as it is, the kinetic product, though the exo is usually more stable.



exo-product endo-product

The role of the electron-withdrawing group Z in the dienophile is to attract the diene through space in the endo transition state (**21**). This is a secondary orbital interaction which does not lead to bonding but which does help to hold the transition state together.

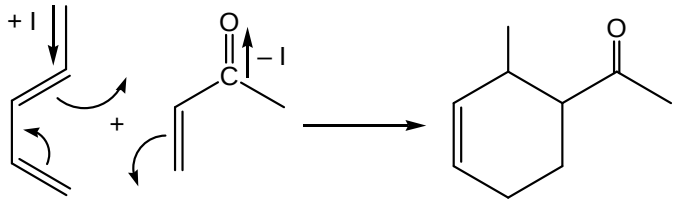


endo-**(21)** exo-**(22)**

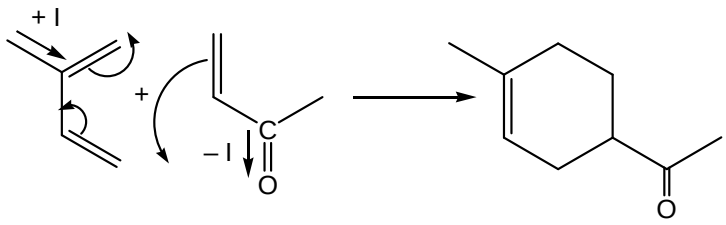
-------interaction leading to bonding
.....secondary orbital interactions

17.2.3 Regioselectivity of Diels-Alder reaction

The Diels-Alder reaction is one of the best known regioselective reaction. The reaction is ortho-para directing, i.e. 1-substituted butadiene gives orthoproduct (1,2-relationship) while 2-substituted butadiene gives para (1,4-relationship) isomer. This can be explained on the basis of inductive effect.



1,2-isomer **(23)**



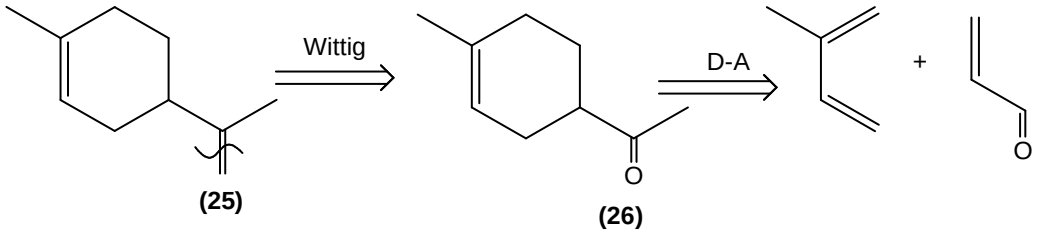
1,4-isomer **(24)**

Thus we can say that it gives a particular isomer of the product instead of a mixture of isomers due to the regio and stereoselective as well as stereospecific nature of the reaction.

17.2.4 FGI on Diels-Alder Products:

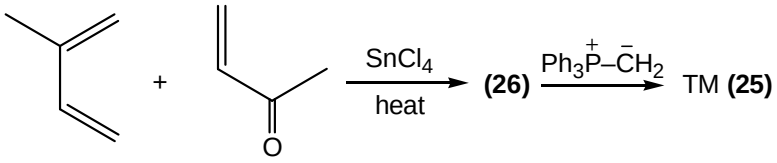
The Diels-Alder is such a powerful reaction that it is good tactics to take advantage of it wherever possible. Here we choose witting step for disconnection of (**25**) as it revealed a para Diels Alder product

Retrosynthetic anslysis of TM (25)



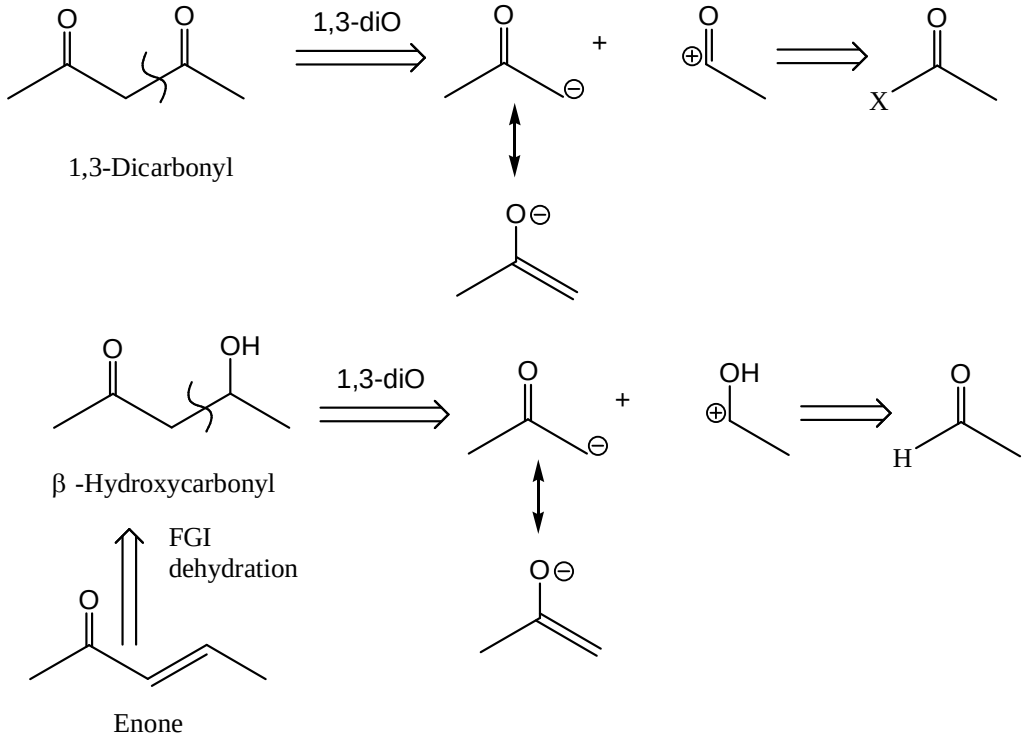
(25) **(26)**

Synthesis



17.3 1,3-Difunctionalised compounds

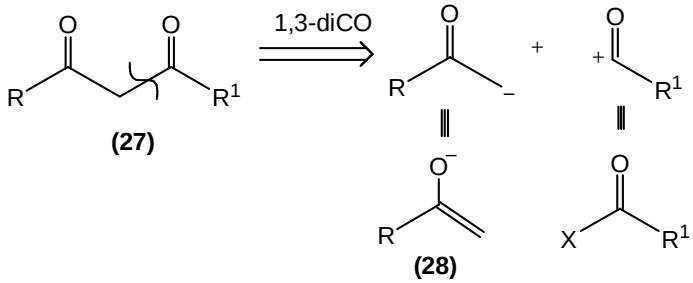
As we know that 1,3-difunctionalized compound can be disconnected easily as they give synthons with their natural polarity. Those compounds in which two functional groups have 1,3-relationship are known as 1,3-difunctionalised compounds. Direct disconnection of this group is possible at two oxidation levels i.e. 1,3-dicarbonyl and β-hydroxy carbonyl. Enones are coming since they are usually made by dehyration of β-hydroxy carbonyl.



17.3.1 1,3-Dicarbonyl compounds:

These are very useful synthetic compounds having with variety of applications. The disconnection of 1,3-dicarbonyl compound gives acyl cation and an anion, which can be enolized as shown below:

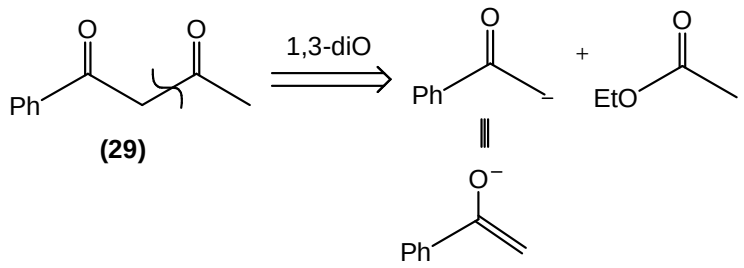
Retrosynthetic analysis of TM (27)



Here in disconnection of TM (27) means that we need a reaction which is the acylation of an enolate anion (28). It is possible with esters (X = OR) or acid chlorides (X = Cl).

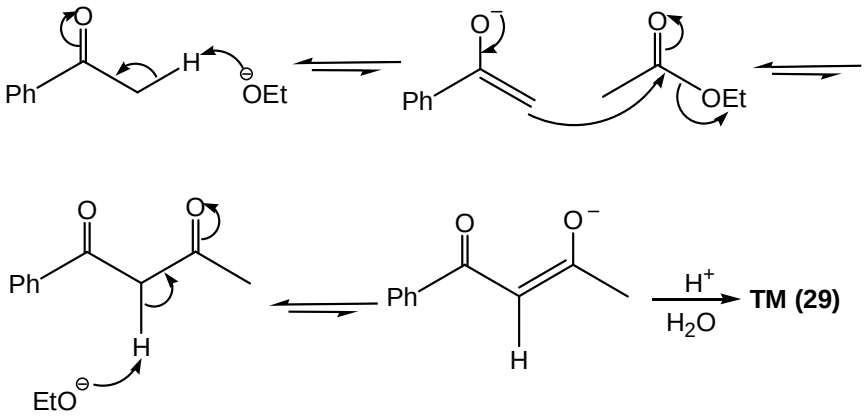
The perfumery compound (29) can be disconnected as follows:

Retrosynthetic analysis of TM (29)



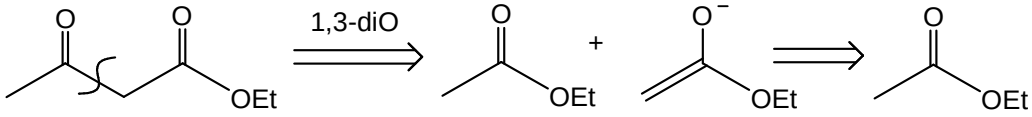
(29)

Synthesis



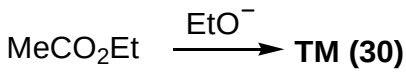
This synthesis was carried out by Claisen and the reaction is known as the Claisen condensation. If we take two molecule of the same ester as the starting materials, the synthesis is known as the Claisen ester condensation, simply involves treating ethyl acetate with base.

Retrosynthetic analysis of TM (30)



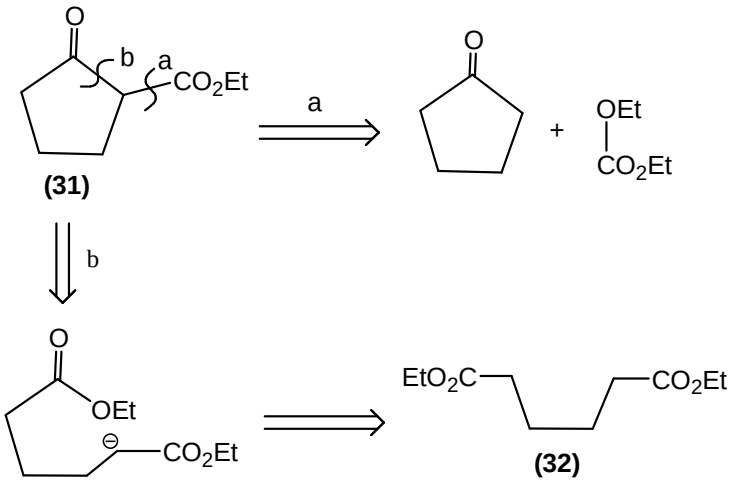
(30)

Synthesis



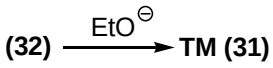
An important keto ester is TM (31), it can be disconnected in two ways as shown below. Path (a) removes only one carbon atom, hence bad strategy but the path (b) gives readily available and symmetrical diester (32).

Retrosynthetic analysis of TM (31)



Reaction in path b is intramolecular and hence fast.

Synthesis

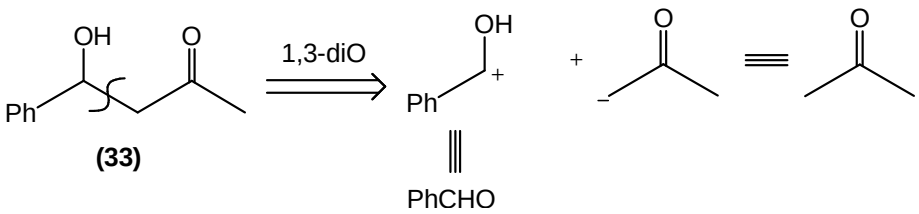


17.3.2 β-Hydroxy carbonyl compounds:

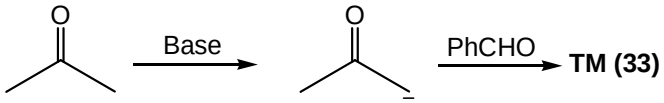
β-Hydroxy compounds can be disconnected by the same strategy as in 1,3-dicarbonyl compounds, but at a lower oxidation level. The ester is being replaced by an aldehyde or ketone. Compound will have only one disconnection, cleavage of the bond next to –OH bond.

The disconnection gives two synthons namely acyl anion and α-hydroxy carbonium ion. The carbonyl compounds are the synthetic equivalents for both the synthons. Out of two, one carbonyl compounds should have α-H atom.

Retrosynthetic analysis of TM (33)



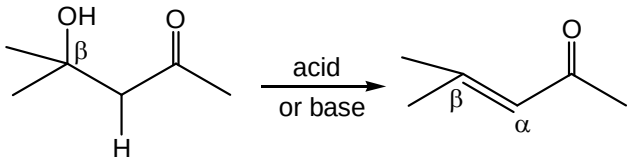
Synthesis



Firstly a base is used which generates enolate ion. Now this carbanion attacks on carbonyl group of other molecule and nucleophilic addition reaction take place, leading to the formation of TM (33).

17.4 α,β-Unsaturated carbonyl compounds

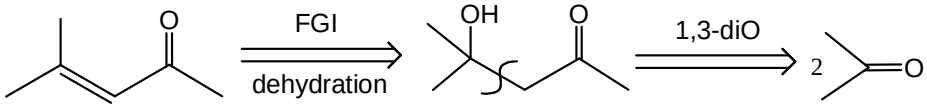
β-Hydroxy carbonyl compounds can be dehydrated easily because the proton to be removed (H in 34) is enolic and the product (35) is conjugated.



(34) **(35)**

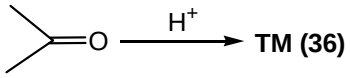
The analysis of enone or α,β--unsaturated carbonyl compound should be an FGI followed by a 1,3-diO disconnection. Dehydration often occur during condensation, hence intermediate need not be isolated. For example TM (36) can be achieve in good yield by acid catalysis.

Retrosynthetic analysis of (36)

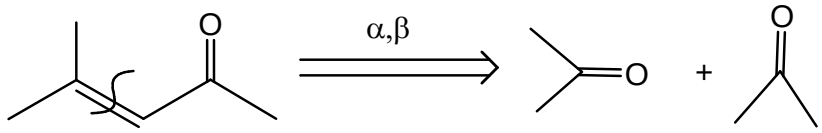


(36) (37)

Synthesis

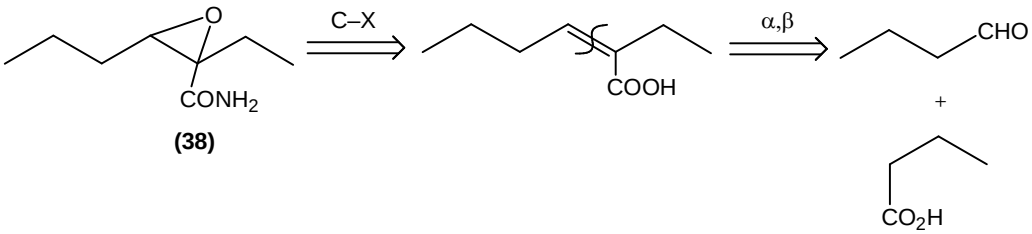


Therefore the shorthand disconnection of the enone will be:



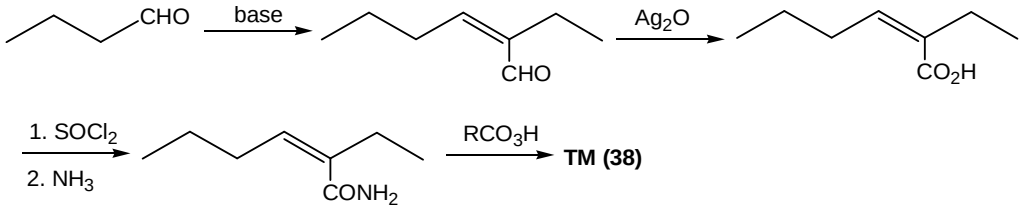
The synthesis of the minor tranquilliser oxanamide (38) is good example where we can see how C-X disconnections and FGI can be added to this general plan. This molecule has amide and epoxide FGs.

Retrosynthetic analysis of (38)



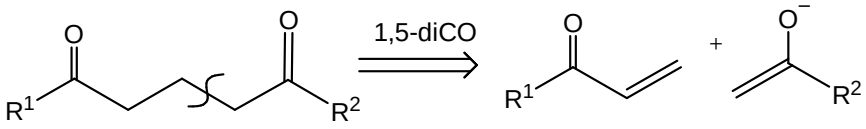
(38)

Synthesis



17.5 1,5-Difunctionalised Compounds

1,5-Dicarbonyl compounds are the best example of this category in which two functional group acquiring 1,5-relationship.

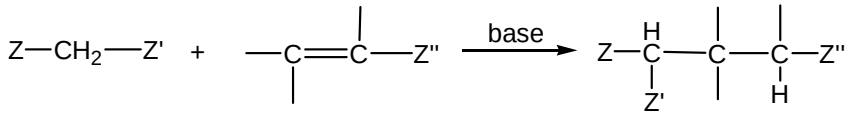


1,5-dicarbonyl compounds can be disconnected at either α,β-bond in a reverse Michael reaction. Therefore first we will discuss Michael reaction.

17.6 Michael Addition

Compounds containing electron withdrawing groups (Z = electron withdrawing group) add, in the presence of bases, to olefines of the form C=C-Z, this is called the Michael reaction and involves conjugate addition.

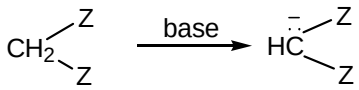
Z = CHO, COR, COOR, $CONH_2$, CN, NO_2, SOR, SO_2R etc.



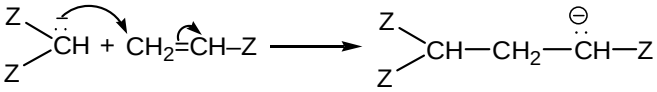
This reaction has been carried out with malonates, cyanoacetates, acetoacetates other β-ketoesters and compounds of the form ZCH_3, ZCH_2R, $ZCHR_2$ and ZCHRZ' including carboxylic esters, ketones, aldehydes, nitrites, nitro compound and sulfones. These reagents do not add to ordinary double bonds. 1,2 addition (to the C=O or C=N group) often competes and sometimes predominates. In particular α,β-unsaturated aldehydes seldom give 1,4 addition. The Michael reaction has traditionally been performed in protic solvents with catalytic amounts of base.

Mechanism

Step-1 Formation of Carbanion

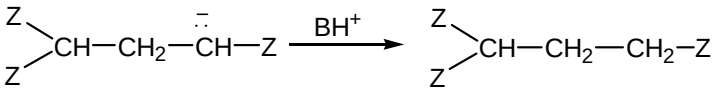


Step II Nucleophilic addition to double bond



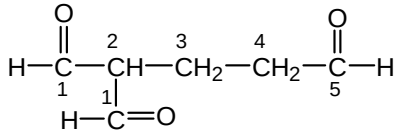
Here, negative charge is present on the intermediate is stabilized by group Z.

Step III Electrophilic addition



1,2-addition product

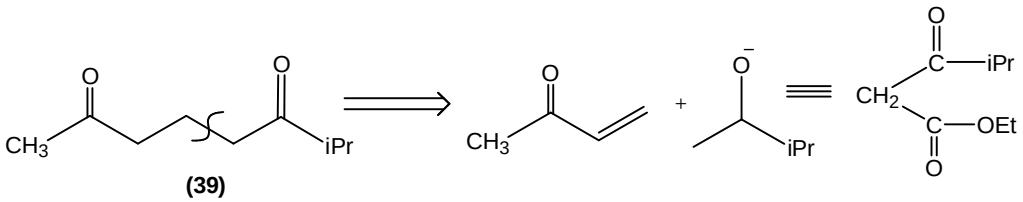
Interesting thing is this that in the product two Z group are having 1,5-relationship e.g. if Z = -CHO then it will be



1,5-dicarbonyl compound

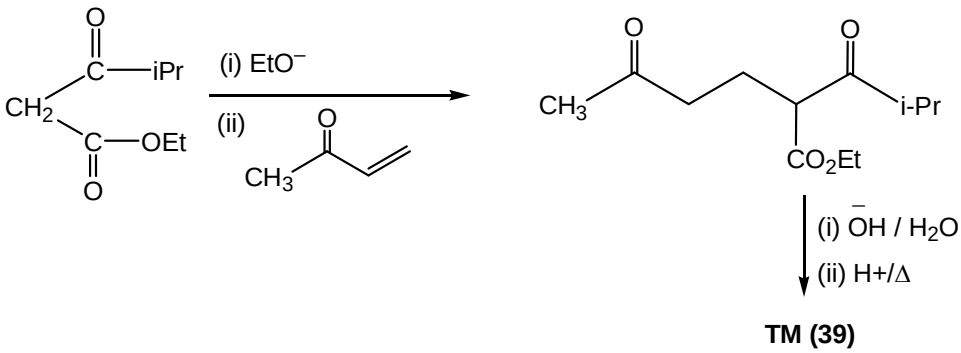
Therefore, 1,5-difunctionalized compounds can be disconnected in such a way that they give those synthetic equivalents, which can undergo Michael addition reaction. Michael reaction which is a reversible reaction, also known as conjugate addition. A C-C bond is formed in Michael reaction, so it has greater synthetic value as alicyclic and polynuclear aromatic compounds can be readily synthesized by this. Some examples are given below, which show the synthetic utility of Michael addition reaction.

Retrosynthetic Analysis of TM (39)



(39)

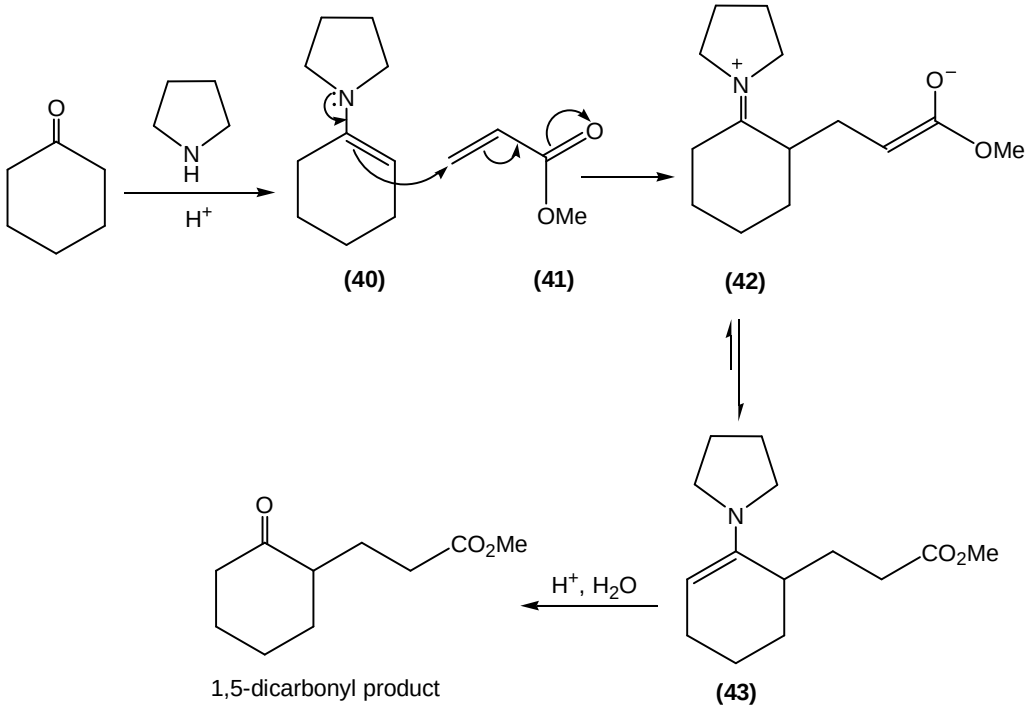
Synthesis



TM (39)

17.6.1 Activation by enamine formation:

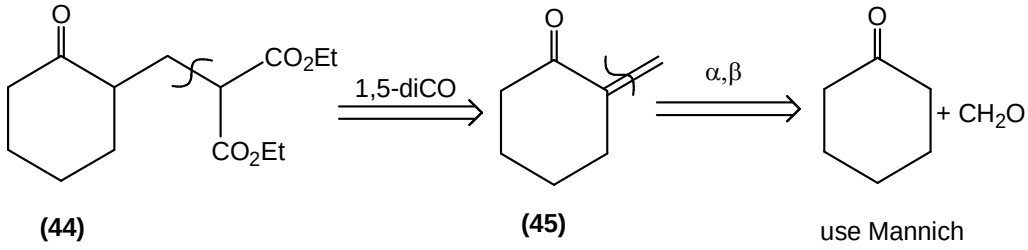
Enamines (40) are used as specific enol derivatives. They are equally useful in Michael reactions. Enamines adds cleanly to acrylic ester (41) in Michael fashion and the first formed product (42) is in equilibrium with (43). Hydrolysis of (43) in aqueous and release the 1,5-dicarbonyl product.



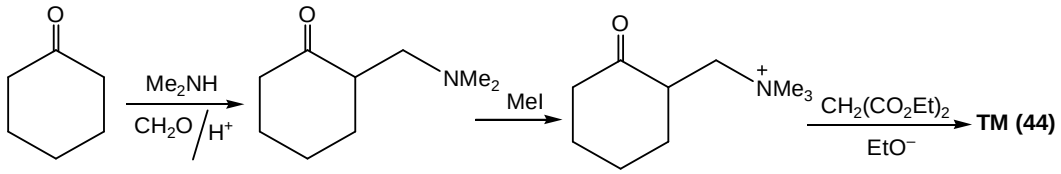
17.6.2 Michael acceptors by the Mannich Reaction:

Vinyl ketones are very relative and undergo dimerization by Diels-Alder reaction rather than a Michael addition so if one want to synthesize Michael addition product then α,β-unsaturated ketones should be generated in situ via Mannich base as follows:

Retrosynthetic analysis of TM (44)



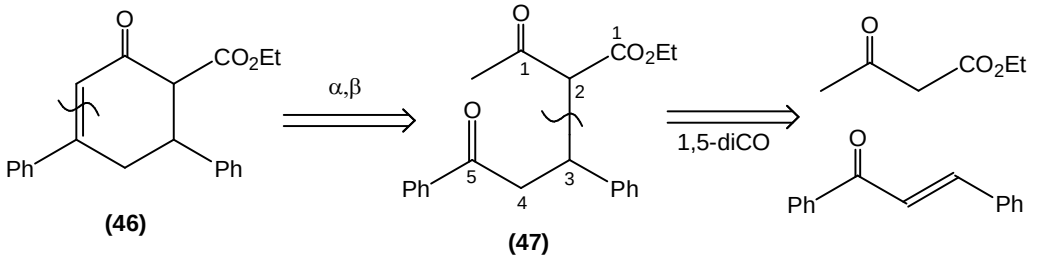
Synthesis



17.7 Robinson Annelation

Robinson Annelation is a combination of Michael addition and intramolecular aldol condensation. At first glance we think a Diels-Alder disconnection for (46) as it is a cyclohexene with carbonyl groups, but it is wrong. Disconnection of α,β-double bond, however reveals a simple 1,5-dicarbonyl disconnection (47).

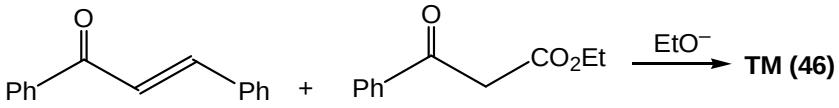
Retrosynthetic analysis of TM (46)



(46) **(47)**

The cyclisation of (47) to (46), often goes spontaneously in second step of the synthesis. The whole process of addition and cyclisation, being a ring formation or annelation, is known as the Robinson annelation (Fig-1).

Synthesis



The Robinson annelation has found extensive use in the synthesis of polycyclic ring synthesis including steroids and other natural products containing six membered rings.

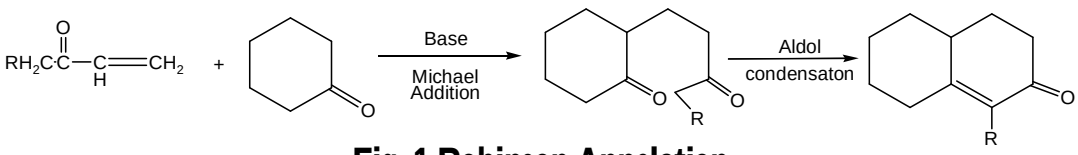
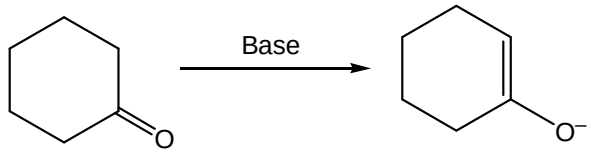


Fig. 1 Robinson Annelation

Mechanism of the reaction:

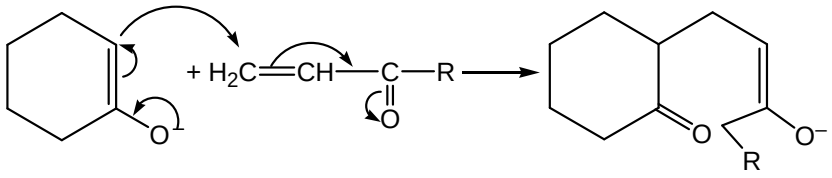
First stage of Robinson annelation is **Michael addition** that form 1,5-diketone it include three steps:

Step I: Formation of enolate

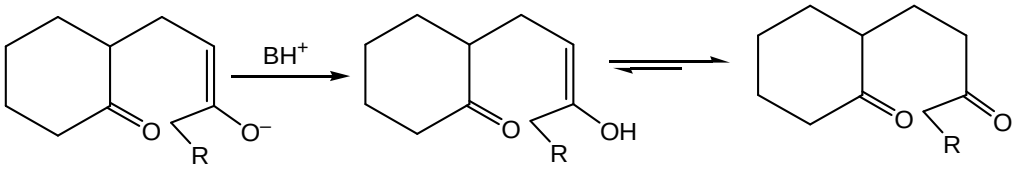


enolate

Step II: Nucleophilic addition to double bond

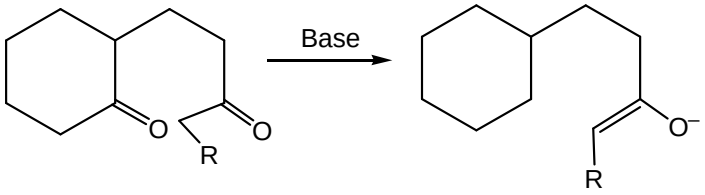


Step III: Addition of electrophile



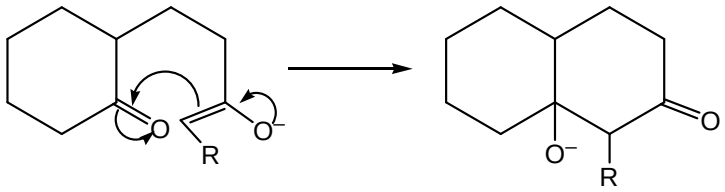
The second stage is intramolecular **Aldol addition** which includes IV and V steps.

Step IV: Formation of enolate



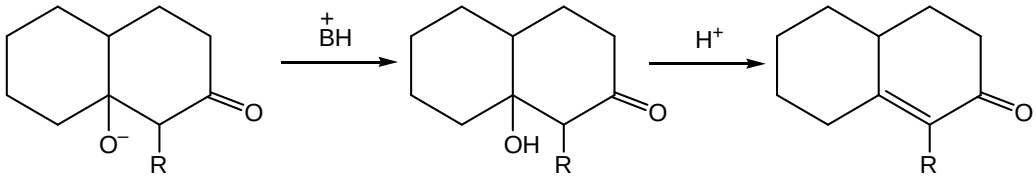
Enolate

Step V: Nucleophilic addition to carbonyl group



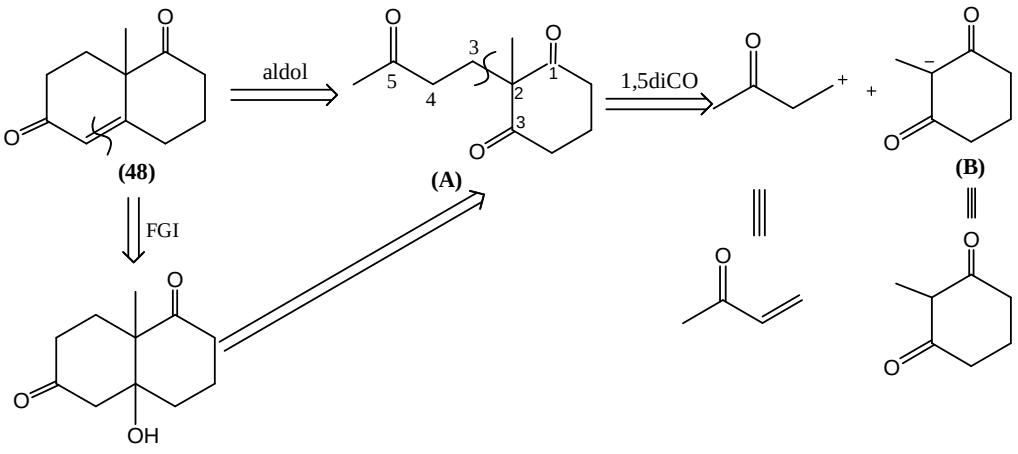
The third stage is heating which dehydrate the alcohol. It includes step VI.

Step VI: Addition of electrophile followed by dehydration



There are two possibilities for dehydration as –C-OH bond is having β-hydrogen atoms on both the sides. But this reaction shows regioselectivity i.e. dehydration occurs only by the elimination of β-H-atom from that side which produces a conjugated double bond. In other way we can say that the driving force of dehydration is the formation of a conjugated system.

Retrosynthetic analysis of TM (48)

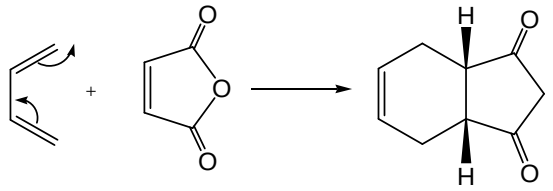


Here we can see that cyclohexenone is synthesized by Robinson annelation reaction and may not be added to an old ring.

17.8 Summary

Diels-Alder reaction

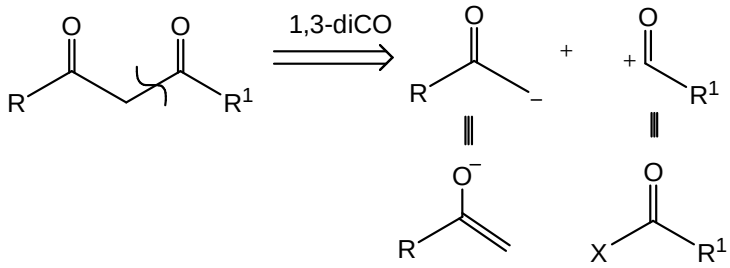
Diels Alder reaction is one of the most important reaction in synthesis because it makes two C-C bonds in one step. It is regio and stereoselective reaction. It is a cycloaddition reaction between a conjugated diene (1) and a conjugated alkene (2) (dienophile), forming a six membered ring.



(1) (2) (3)

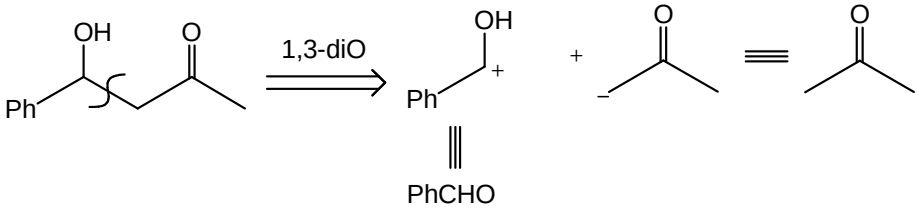
1,3-Dicarbonyl compounds:

The disconnection of 1,3-dicarbonyl compound gives acyl cation and an anion, which can be enolized as shown below:



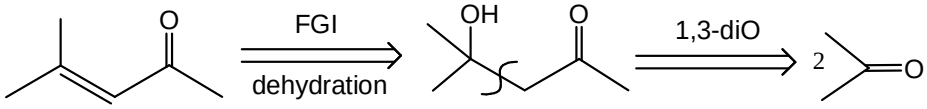
β-Hydroxy carbonyl compounds:

The disconnection gives two synthons namely acyl anion and α-hydroxy carbonium ion.



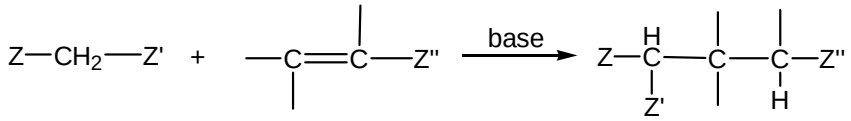
α,β-Unsaturated carbonyl compounds:

The analysis of enone or α,β-unsaturated carbonyl compound should be an FGI followed by a 1,3-diO disconnection.



Michael Addition

Compounds containing electron withdrawing groups (Z = electron withdrawing group) add, in the presence of bases, to olefines of the form C=C-Z. This is called the Michael reaction.

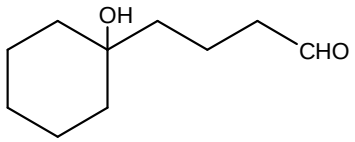


Robinson Annelation

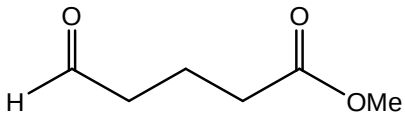
Robinson Annelation is a combination of Michael addition and intramolecular aldol condensation.

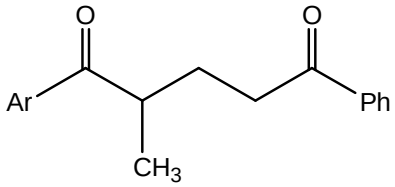
17.9 Review Questions

1 Provide a retrosynthesis and synthesis of the following molecule:

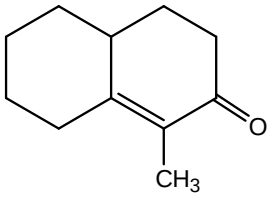


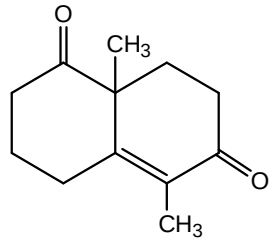
2 Comment on the best disconnection for the compound (i) and (ii).

(i) 

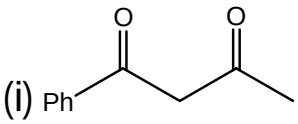
(ii) 

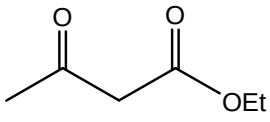
3 Show how you can use Robinson annelation to synthesize the ketones (i) and (ii).

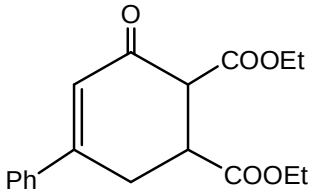
(i) 

(ii) 

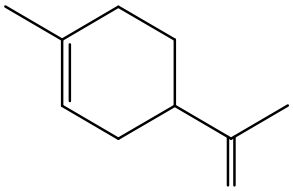
4 Using disconnection approach, design a convenient synthesis for each of the following compounds:

(i) 

(ii) 

(iii) 

5 Discuss two group C-C disconnection with reference to Diels-Alder reaction. Outline the retrosynthetic analysis and the designed synthesis of the following compound :



17.10 Reference and suggested readings

- Organic synthesis –The Disconnection Approach, S. Warren (Wiley).
- Organic chemistry – J. Clayden, N. Greeves, S. Warren (Oxford Press).
- Organic Synthesis through Disconnection Approach, P.S. Kalsi, MEDTEC.
- Guide book to organic synthesis, R.K. Mackie and D. M. Smith, ELBS.
- Organic Synthesis, Jagdamba Singh and L.D.S. Yadav, Pragati Prakashan.

Unit-18

Ring Synthesis

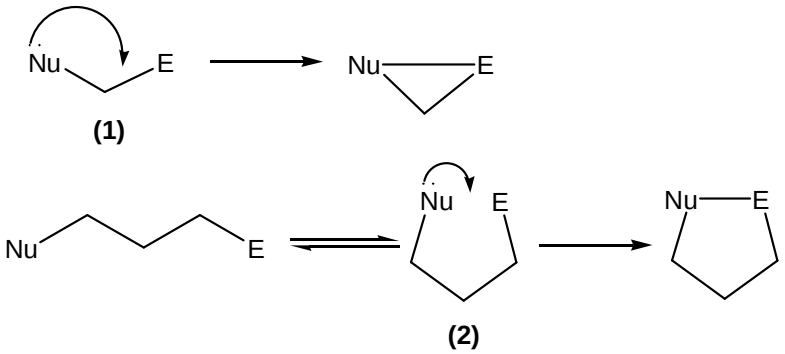
Structure of the unit

18.0 Objective

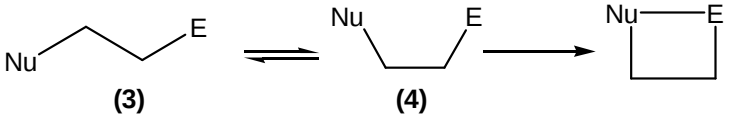
Many interesting targets are cyclic compounds and rings hence ring forming reactions have great significance in retrosynthetic analysis. From retrosynthetic point of view one looks for the same polarities and functional group features as in acyclic systems. Some rings are formed more easily than others. Ring of three five and six members are routinely formed, whereas rings of four or more than six members are formed with difficulty. Here in this unit we will learn retrosynthetic analysis of three to six membered rings and aromatic heterocycles.

18.1 Introduction

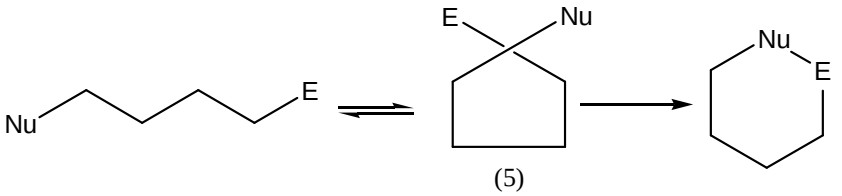
Intramolecular reactions are favoured over intermolecular reactions why it is? Here in this chapter we will deal with the reasons why ring formation by cyclisation is favourable. Usually intramolecular reactions are favoured kinetically over intermolecular reactions for reasons of entropy because two reactive sites are part of the same molecule and there is no need for a bimolecular collision. This factor is greatest in three-membered ring formation. Where two ends of the reagent (1) are close, and for five membered ring formation, where natural thermal motion of (2) brings the reactive site close to each other.



Four-membered ring formation is uniquely slow : the chain can adopt the following conformation (3) & (4) but reactive groups are far apart in both the conformation.



Six membered ring formation is kinetically reasonable: the problem here, as for larger rings, is that rotation brings the reactive sites too close (5) and a folding of the chain is needed before bonding can occur.



(5)

However formation of six membered ring is uniquely favoured thermodynamically in its chair conformation (6) with all groups staggered, especially if large substituents can become equatorial.

(6)

Six and five membered rings are stable, but three and four membered rings are strained with angles of 60° and 90° respectively instead of the usual 109° for sp^3 or 120° for sp^2 atoms.

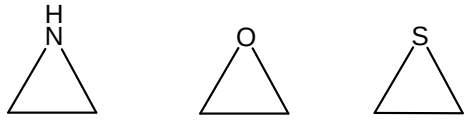
Ring size	Kinetic factors	Thermodynamic factors
3	√√√	x
4	x	x
5	√√	√
6	√	√√
7	√	√

Table: 1-Factors affecting ring formation

If we take both factors into account, we can conclude that five, six and seven membered rings are easy to make, three membered rings are easy to make but often beak down again under the condition of their formation, whereas four membered rings are uniquely difficult to make and often need special methods.

18.2 Saturated heterocycles:

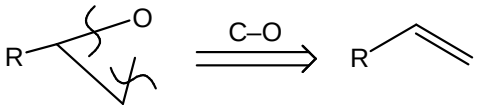
18.2.1 Synthesis of three membered ring:



Aziridine Oxirane Thiirane

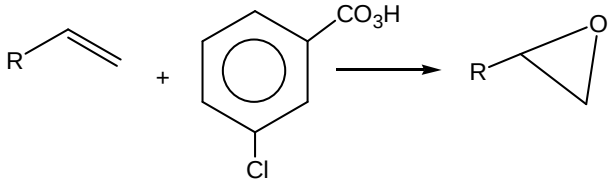
Epoxides or oxiranes are usually made from alkene, both C-O bonds beings disconnected at once. The reagent is a peracid RCO_3H often MCPBA. It is an insertion reaction in which two bonds form in a single step.

Retrosynthetic analysis of TM (7)



(7)

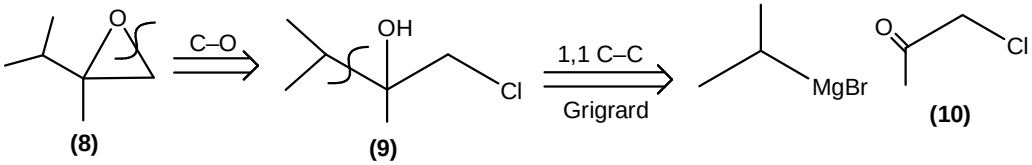
Synthesis



(MCPBA)

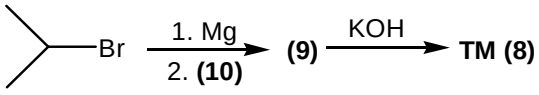
Disconnection of only one C-O bond in epoxide (8), suggests chloroalcohol (9) as an intermediate, and then by C-C disconnection to give an α-chloro ketone (10) as good starting material.

Retrosynthetic analysis of TM (8)



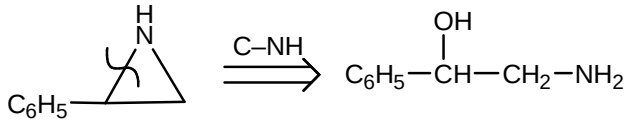
(8) **(9)** **(10)**

Synthesis



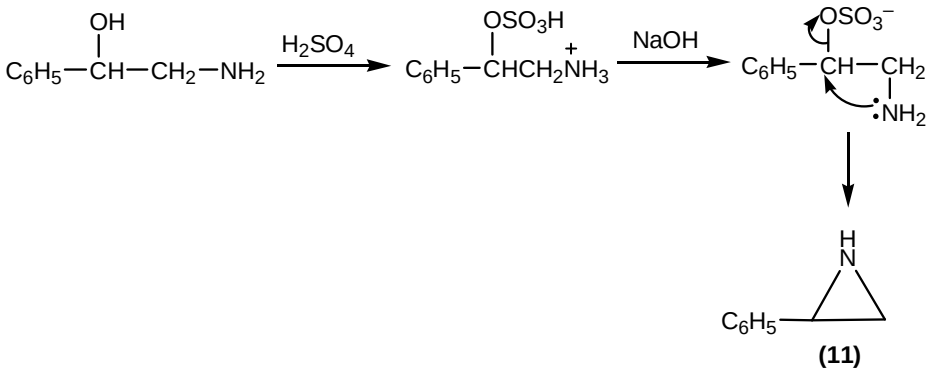
Aziridine (11) and thiiranes (12) can be prepared by cyclization reaction similar to that involved in epoxide formation.

Retrosynthetic analysis of TM (11)



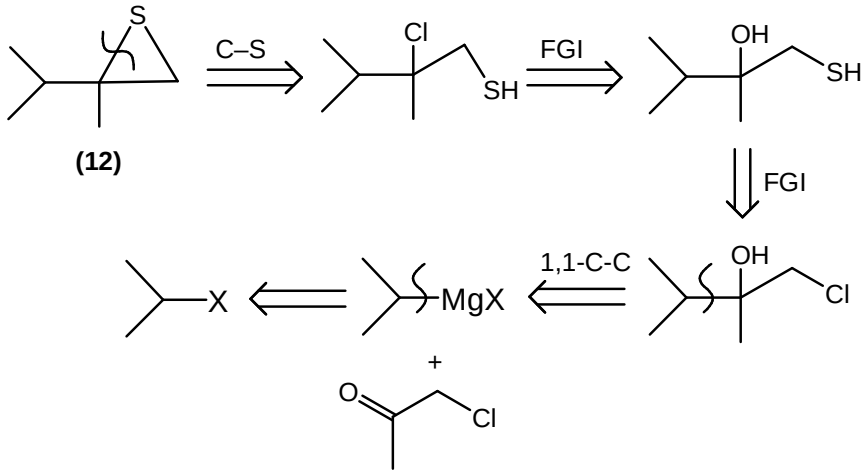
(11)

Synthesis



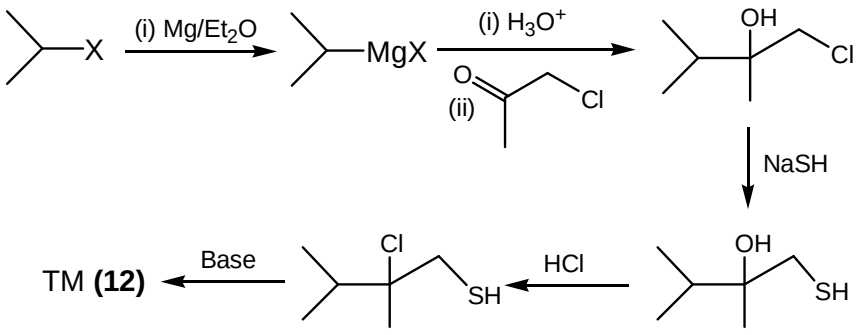
(11)

Retrosynthetic analysis of TM (12)



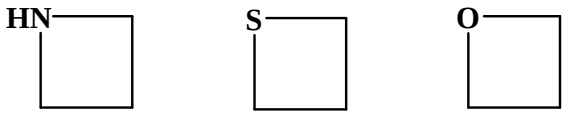
(12)

Synthesis



18.2.2 Synthesis of four membered ring

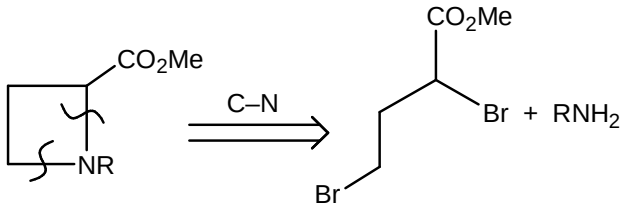
Four membered heterocyclic compounds



Azetanes Thietane Oxetanes

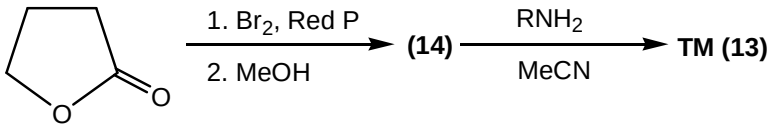
Like four membered carbocyclic rings, four membered heterocycles are also rarer and uniquely difficult to make. The normal cyclization approach often gives poor results but sometimes successful. Straight forward C-N disconnection of amine (13) suggests 1,3-dibromide (14) as a starting material.

Retrosynthetic analysis of TM (13)



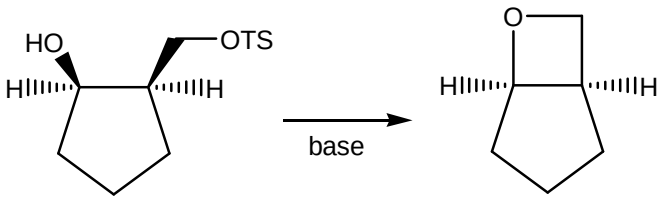
(13) **(14)**

Synthesis:



(15)

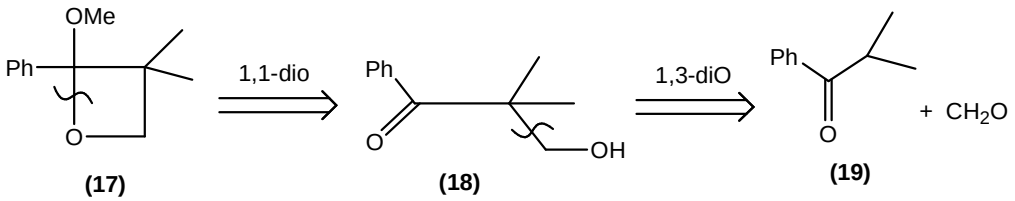
Four membered cyclic ethers can also be made by cyclisation in very favourable cases. For example *cis* (16) cyclizes in presence of base.



(16)

Similar C-O disconnection on cyclic ether (17) takes us back to a β-hydroxyketone (18) and finally to ketone (19).

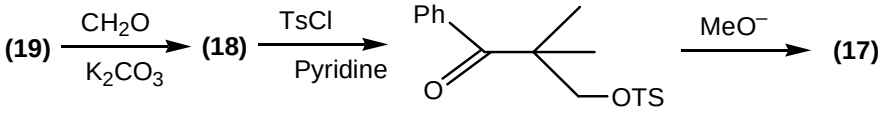
Retrosynthetic analysis of TM (17)



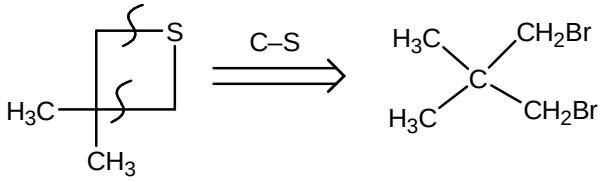
(17) **(18)** **(19)**

We need to make conditions for cyclisation as favourable as possible so the- OH group in (18) is converted into a good leaving group and MeOH is added as the more reactive MeO^-.

Synthesis

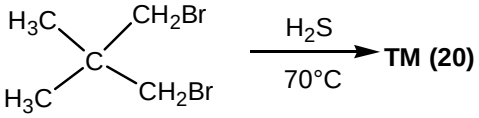


Retrosynthetic analysis of TM (20)



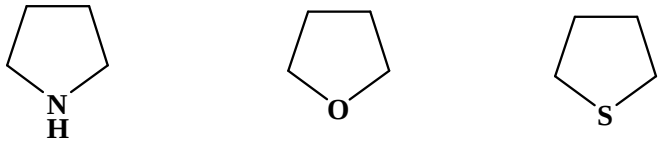
(20)

Synthesis



18.2.3 Synthesis of five membered ring

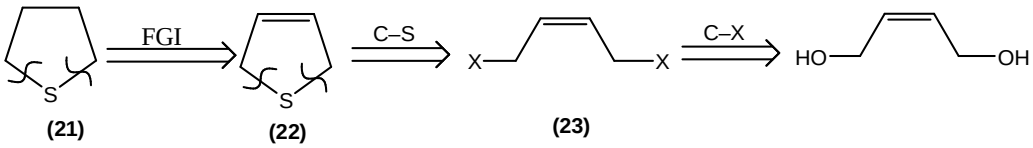
Five membered heterocyclic compounds are



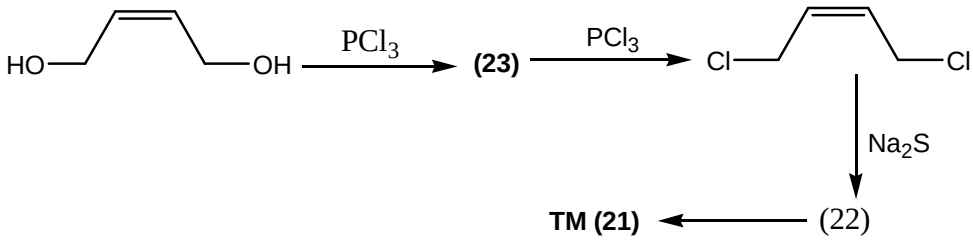
Tetrahydro pyrrole Tetrahydro furan Tetrahydro thiophene

Cyclization reactions are one of the best method for synthesis of five membered rings. The disconnection of both C-X bonds is strategic bond disconnection. In these disconnection, disconnect both C-X bonds and identify the electrophilic carbon fragment needed to add to the nucleophilic heteroatom.

Retrosynthetic analysis of TM (21)

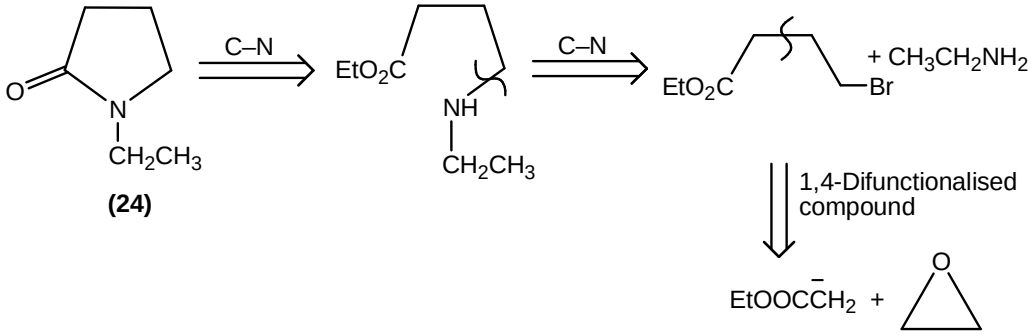


Synthesis



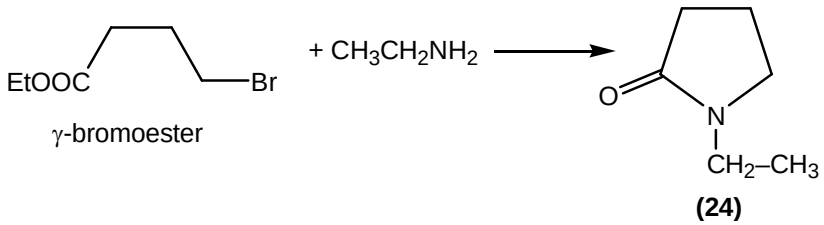
Lactam (24) can be derived from acid derivatives and the synthesis involves a nitrogen nucleophile and a carbon electrophile.

Retrosynthetic analysis of (24)

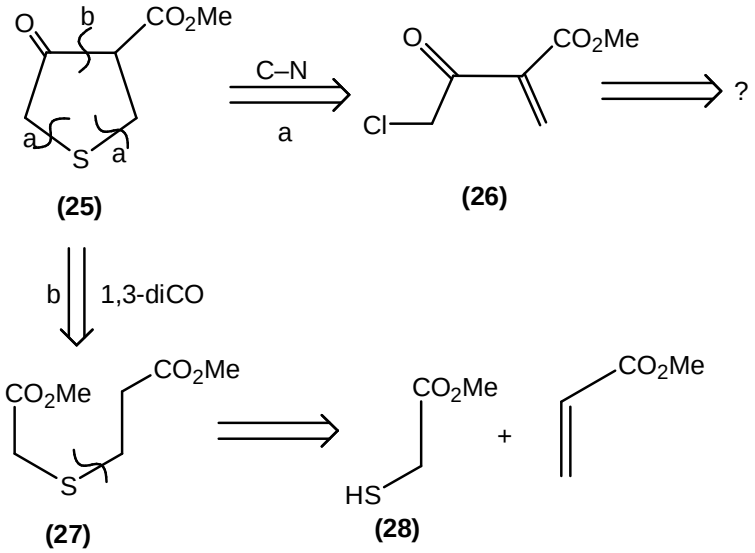


Reaction of ethylamine with ϒ-bromoester affords the lactam (24).

Synthesis:

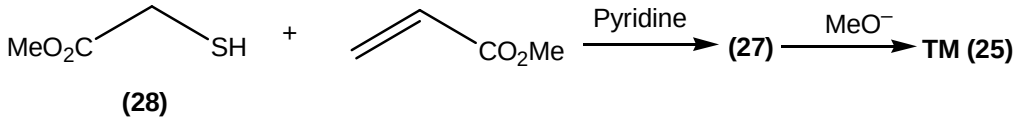


Retrosynthetic analysis of TM (25)

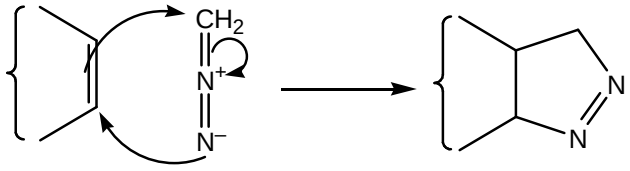


In this example the obvious C-X disconnections of (25) by path-a give a difficult starting material (26), whereas 1,3-dicarbonyl disconnection first to give (27) allows more helpful C-S disconnections.

Synthesis:



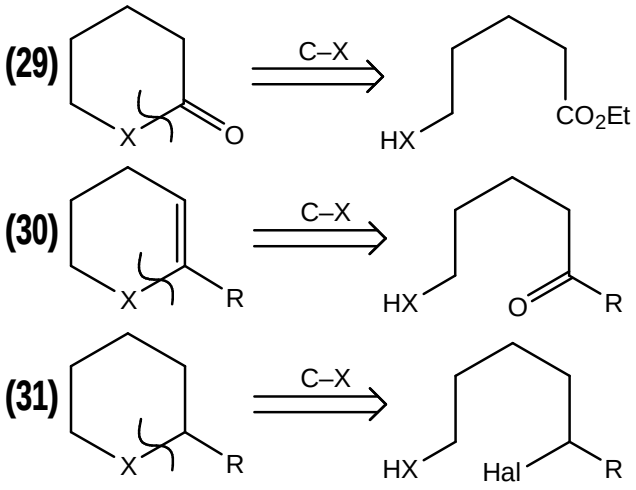
Another helpful special method is 1,3-dipolar cycloaddition for the synthesis of five membered ring. It is just like Diels-Alder reaction where diene has been replaced by the 1,3-dipole, which has four electron.



1,3-dipole

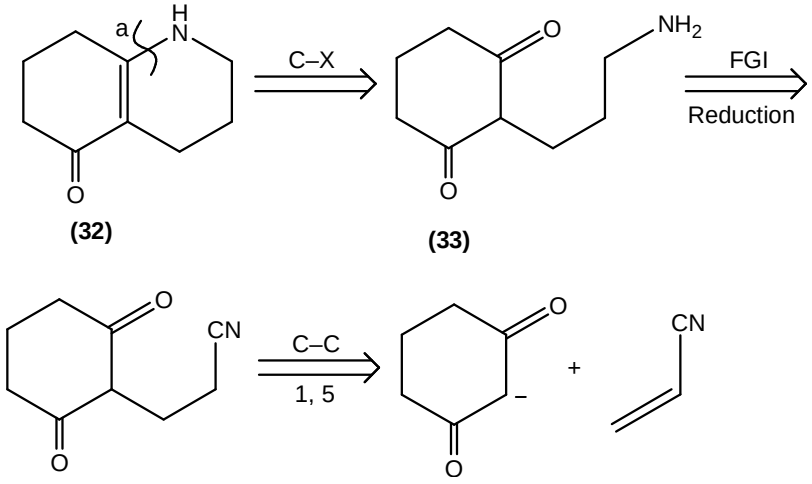
18.2.4 Synthesis of six membered ring

Formation of six membered ring is favoured by both (thermodynamic and kinetic) factors. Therefore cyclization reaction can be employed for the synthesis of it. When the heteroatom is joined to carbon atoms at different oxidation levels. e.g. (29), (30) or (31) the best order of event is usually to disconnect (29) first and (31) last.



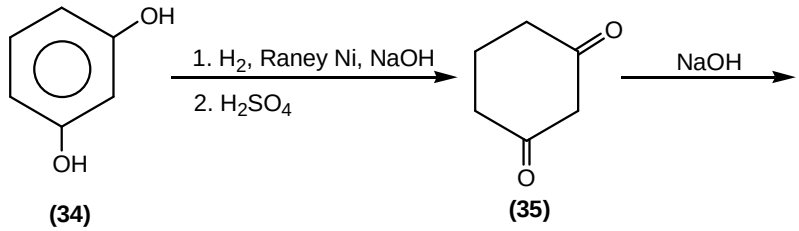
Consider the example (32) and follow this order of events, disconnection (a) on (32) should come first.

Retrosynthetic analysis of TM (32)

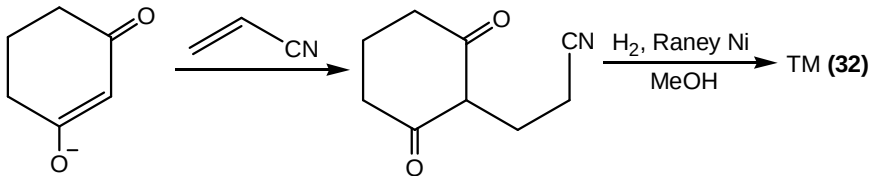


The compound (35) can be made by the reduction of resorcinol (34) and the same catalyst (Raney Ni) promotes reduction of the cyanide in the presence of the carbonyl groups. Cyclization of (33) is spontaneous.

Synthesis

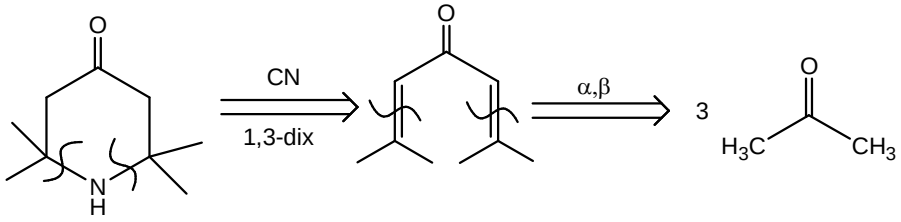


(34) **(35)**



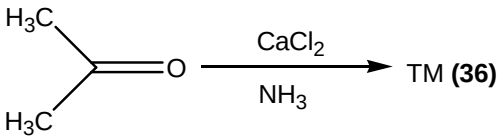
4-Piperidones (36) can be disconnected at C-N by the strategy used for other symmetrical ketones.

Retrosynthetic analysis of TM (36)

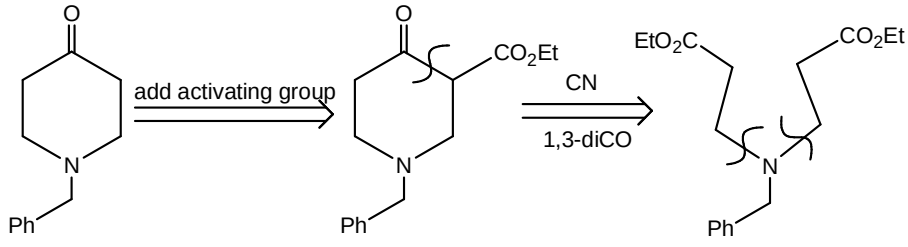


(36)

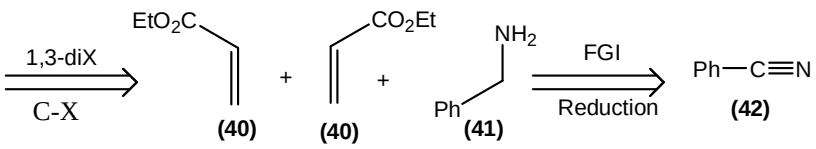
Synthesis



Retrosynthetic analysis of TM (37)

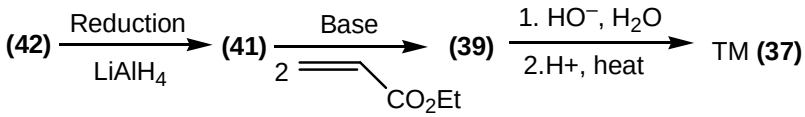


(37) **(38)** **(39)**



(40) **(40)** **(41)** **(42)**

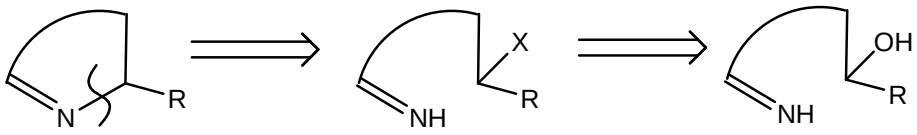
Synthesis



18.3 Aromatic heterocycles

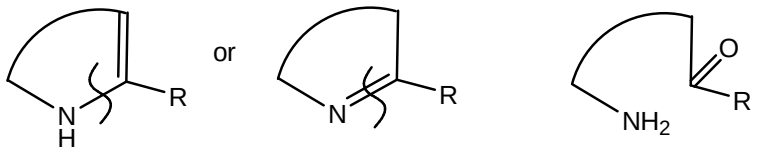
We use same disconnections as we use for saturated heterocycles. Due to the thermodynamic stability of the aromatic rings it is easier task. Again the first important thing is to recognize the oxidation levels of carbon atoms bonded to the heteroatom. As we know how to disconnect at three oxidation levels (43), (44) and (45) (using nitrogen as an example). Like this compound (46), (47) and (48) of the aromatic series, all have carbon atoms (.) at the oxidation level of a carboxylic acid.

Alcohol

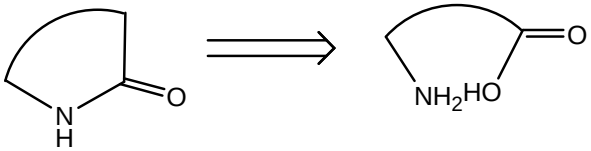


(43)

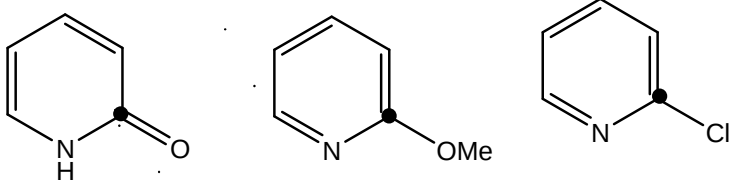
Aldehyde and Ketone



(44)



(45)



(46) **(47)** **(48)**

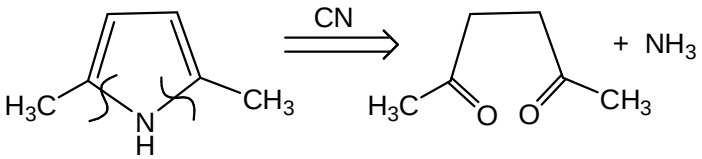
It is impossible to discuss all the aromatic heterocycles. Hence here we will discuss only few important heterocycles.

18.3.1 Synthesis of five membered aromatic heterocycles

Furan, Pyrrole and Thiophene

Simplest disconnection of furan or pyrrole (49) is the removal of the heteroatom leaving a 1,4 dicarbonyl compound.

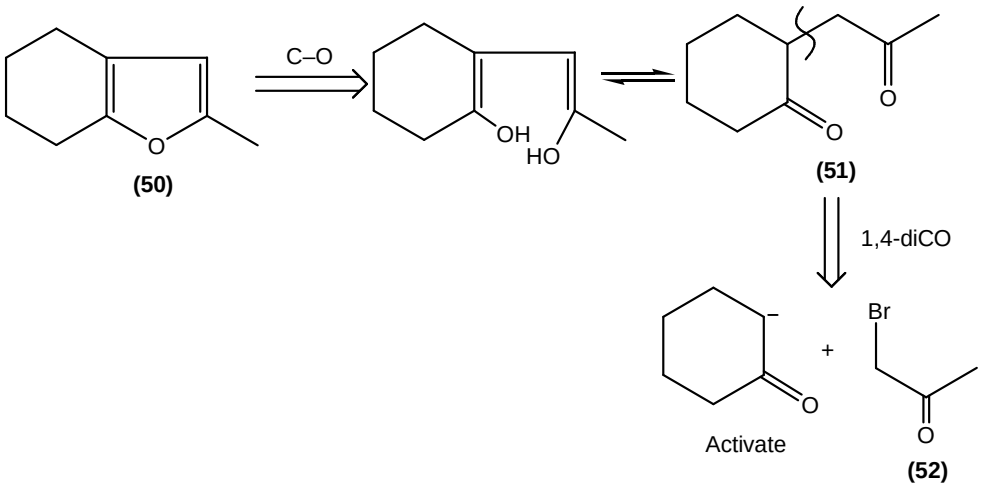
Retrosynthetic analysis of TM (49)



(49)

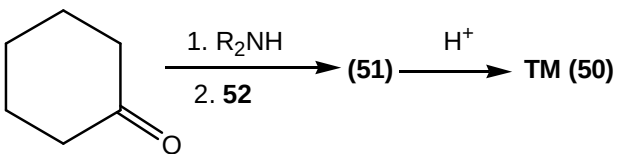
Bicyclic furan (50) comes from diketones and the ring chain disconnection give simple starting materials. The enamine method of control gives good results. Cyclisation to furan occurs readily in acid.

Retrosynthesis analysis of TM (50)

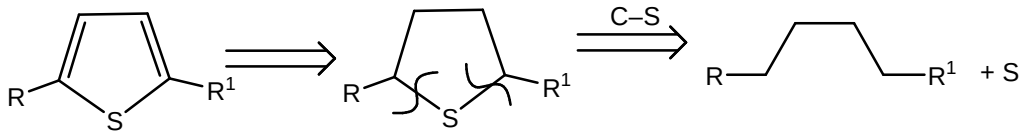


(50) **(51)** **(52)**

Synthesis



Retrosynthetic analysis of TM (52)

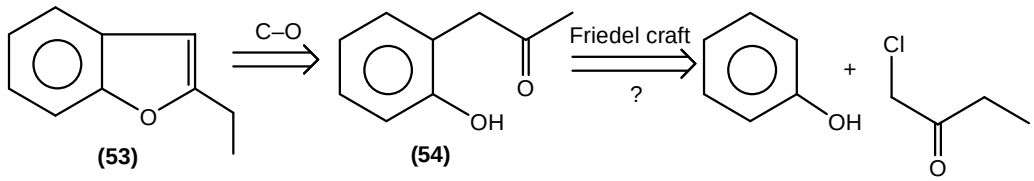


(52)

Benzofurans and Indoles

The benzo derivatives benzofuran and indole cannot be analysed in quite such a simple fashion as the parent molecules. Disconnection of the benzofuran (53) gives a phenolic ketone (54). Further Friedel crafts disconnection is unpromising as the carbonyl group in (54) is in a most unhelpful position. It is one atom further away from the ring so we can use FGA.

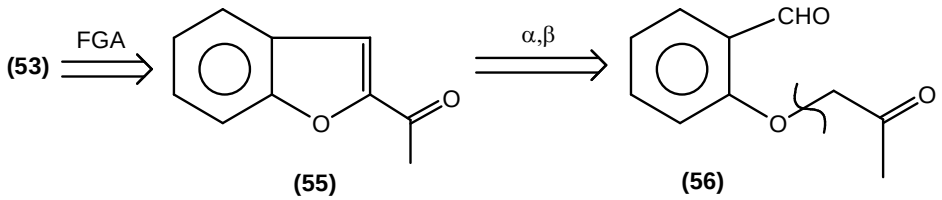
Retrosynthetic analysis 1 for TM (53)



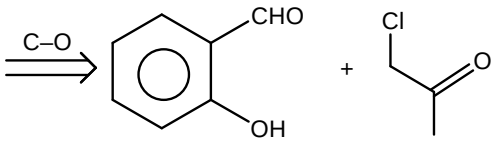
(53) **(54)**

If we add a carbonyl group to (53) we get enone (55), with a helpful α,β-disconnection to (56) and then salicylaldehyde (57) and chloroacetone as starting materials.

Retrosynthetic analysis 2 for TM (53)

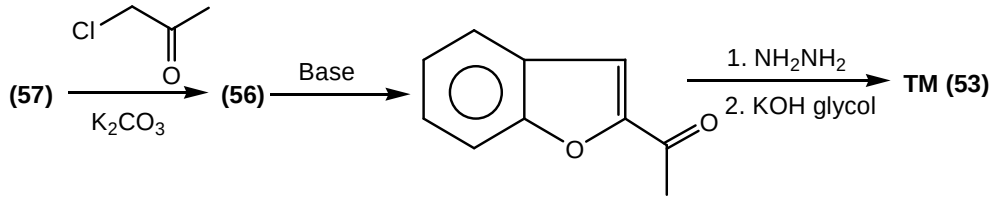


(55) **(56)**



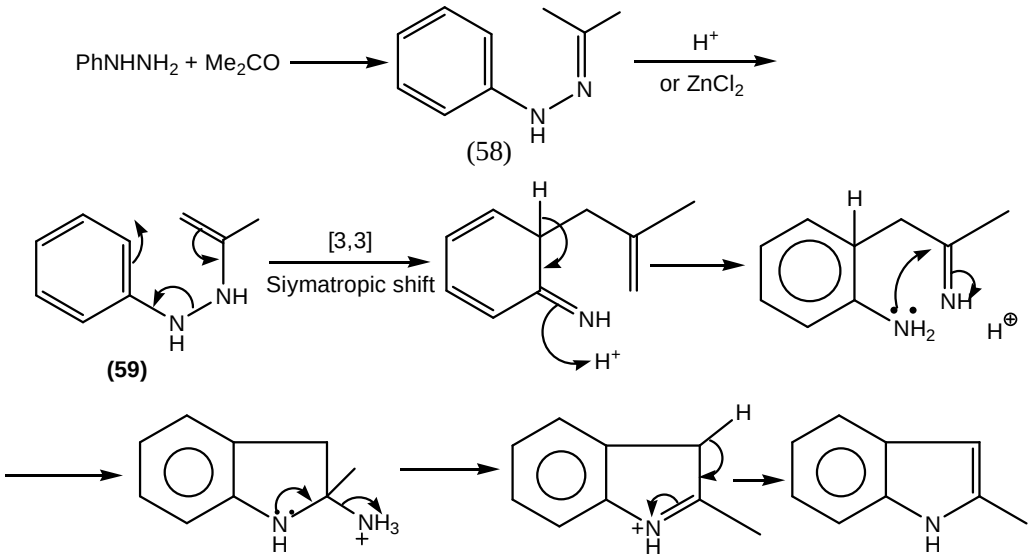
(57)

Synthesis:



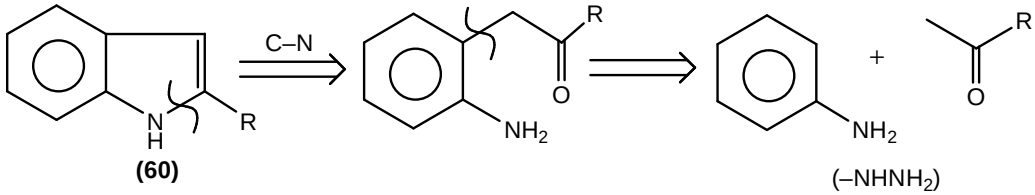
Indoles can be synthesized by Fischer Indole synthesis. The phenylhydrazone (58) of a ketone is treated with acid (or lewis acid –$ZnCl_2$), which gives (59). Tautomerization of (59) is followed via [3,3]sigmatropic rearrangement.

Fischer Indole synthesis



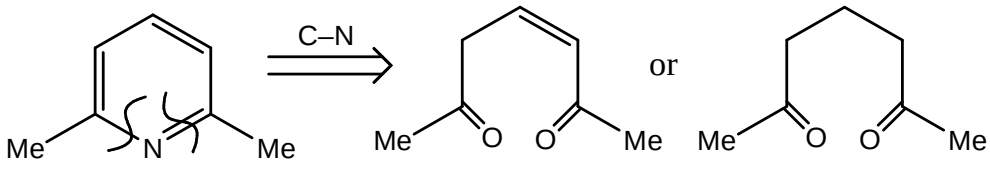
According to this synthesis the obvious disconnection for indoles will be as follows:

Retrosynthetic analysis of TM (60)



18.3.2 Synthesis of six membered aromatic heterocycles

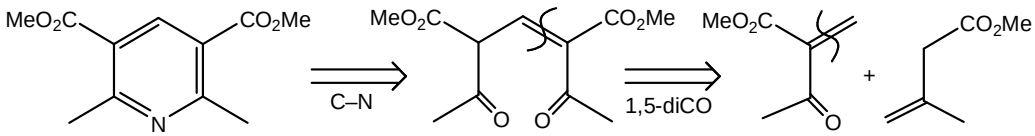
Pyridines: It can be synthesized by usual C-N disconnection, which gives 1,5-dicarbonyls (62). It is often easier to leave out the remaining double bond (63) as dihydropyridines are easily oxidized to pyridines.



(61) (62) (63)

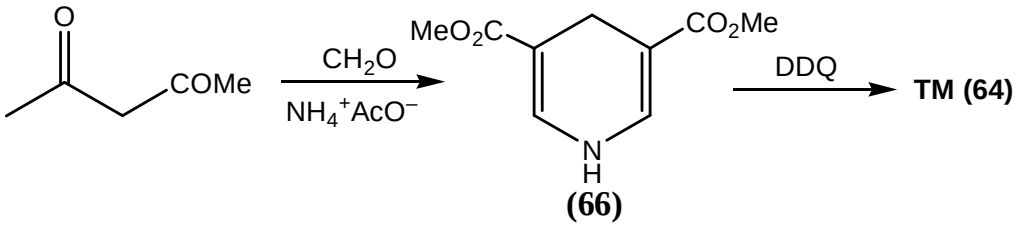
Pyridine diester (64) can be disconnected in 1,5-dicarbonyl (65). Further 1,5-disconnected of symmetrical (65) eventually reveals two acetoacetones and formaldehyde as starting materials.

Retrosynthetic analysis of TM (64)



(64) **(65)**

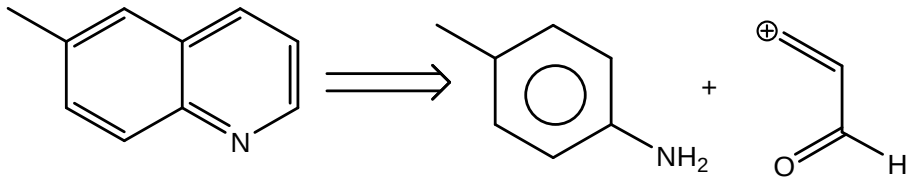
The synthesis is easier than expected as heating together a mixture of acetoacetate ester, formaldehyde and ammonium acetate gives dihydropyridine (66). Oxidation with a quinone such as DDQ gives the pyridine.



(66)

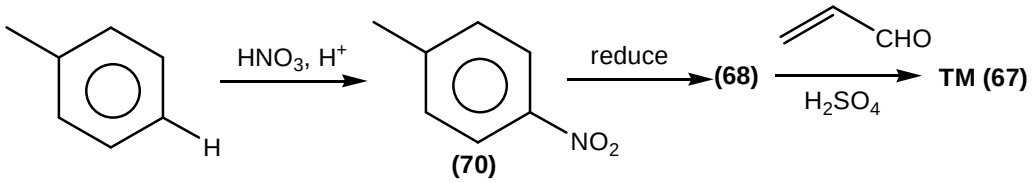
Quinolines

Quinoline might be disconnected to give an amine and a synthon (69).



(67) **(68)** **(69)**

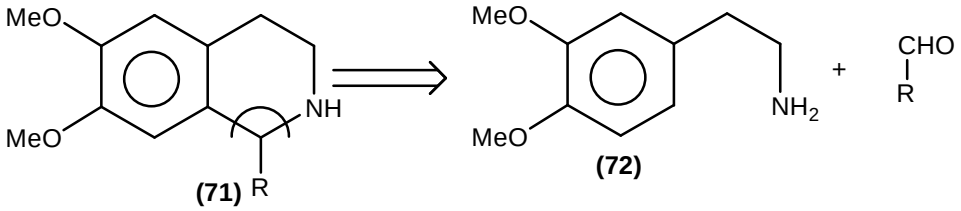
We can use acrolein CH_2=CH.CHO for synthon (69) and oxidize. This is the basis of the Skraup synthesis.



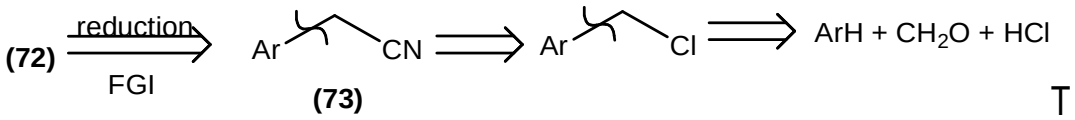
Isoquinolines

An obvious disconnection on isoquinoline (71) removes one carbon atom from the ring at the aldehyde oxidation level.

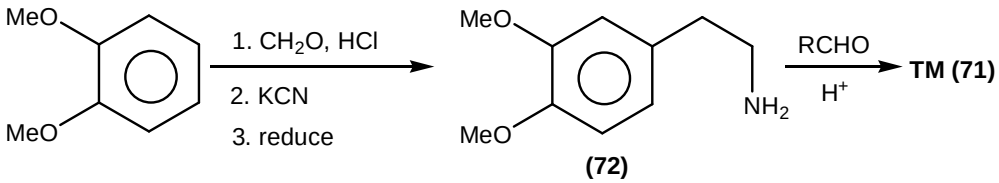
Retrosynthetic analysis of TM (71)



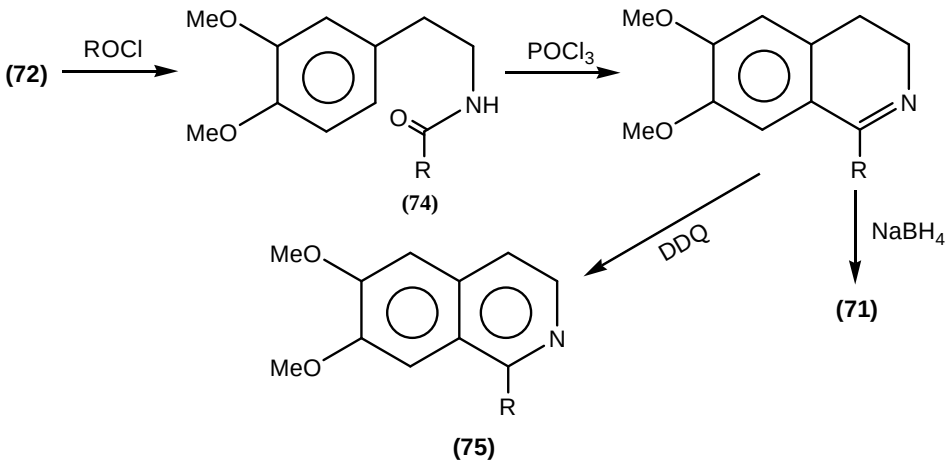
The reaction is an internal Mannich reaction and occurs under mild conditions. The amine (72) is made viz cyanide (73).



The first step is chloromethylation at the most reactive position (less hindered). Cyanide displacement and reduction give (72) which cyclises with the aldehyde to give (71) in acid solution.



An alternative method is to make amide (74) from (72) and to cyclise it with $POCl_3$. The product can be reduced to (71) or oxidized to the isoquinoline (75).



18.4 Aromatic heterocycles in organic synthesis

Nonheterocyclic materials can be obtained by heterocyclic compounds. Heterocyclic compounds have considerable functionality appropriate carbon skeleton and needed driving forces to achieve a chemical transformation and wait for the command to perform. Thus heterocyclic can be used as a precursor or reagent for obtaining functionalized organic compounds and structures of diverse architecture.

18.4.1 General consideration concerning synthetically useful heterocyclic compounds

The chemical behavior of heterocyclic compounds is governed by the same factors which govern the chemical behavior of other compounds and they respond alike to electronic and solvent effects as well as to orbital and strain theories.

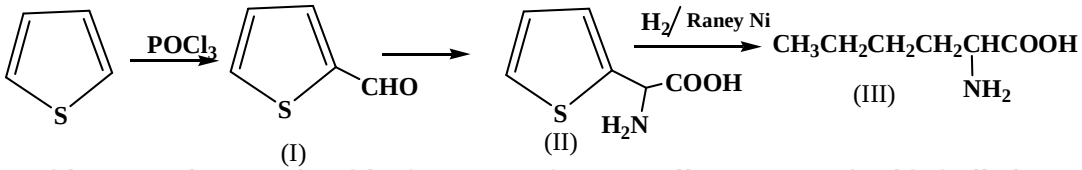
Properties of heterocycles that cause them to be synthetically useful are illustrate here:

(i) Destruction of aromaticity
(ii) Drive towards aromaticity
(iii) Release of ring strain
(iv)Temporary formation of heterocyclic intermediate

These are the four process by which heterocyclic compounds shows their synthetic powers.

(i) Destruction of aromaticity

It can be explained by taking the example of thiophene which serves as a versatile precursor to a variety of amino acids by allowing ready functionalisation to the α-formyl derivative (I), which may be converted to the thiophene amino acid (II) by strecker synthesis which on reductive cleavage gives α-amino hexanoic acid (III)



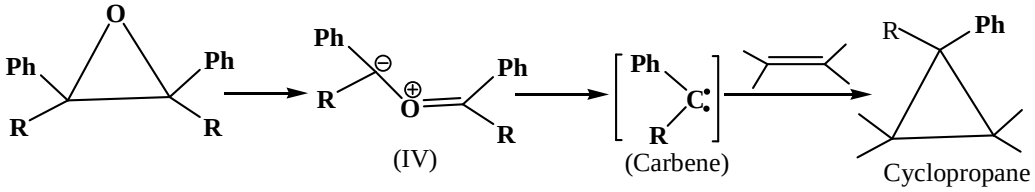
In this example we take thiophene as a heterocyclic compound with built in or latent functionality as well as the appropriate carbon skeleton ready to spring into action upon destruction of its aromaticity.

(ii) Drive towards aromaticity

Many transformation can be accomplish by gaining aromaticity in heterocycles, it can be used as the driving force for the forward reaction. The stereospecific reduction of pyruvate salts to chiral α-hydroxy acids by diphosphopyridine nucleotide (DNP) is a typical example of this type.

(iii) Release of ring strain

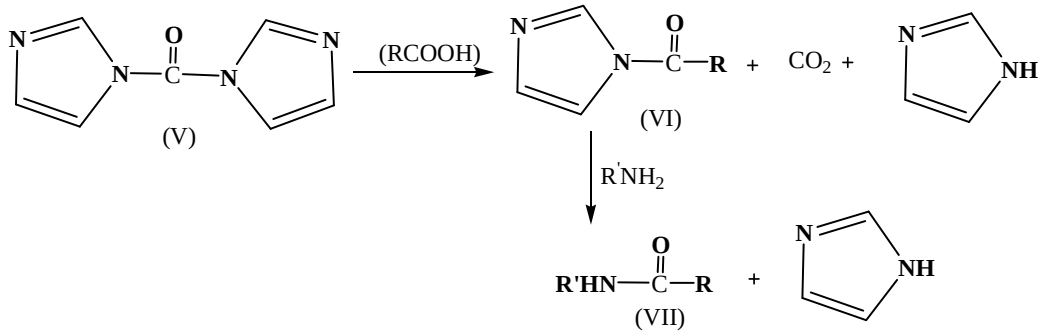
As we know generally small rings (3 or 4 memebered) have ring strain, this property can be used for the formation of various intermediates by ring opening in order to relieve orbital distortions. For e.g. irradiation of oxiranes in the presence of olefins produces the oxonium ylide (IV), which fragments to the carbene and it is trapped by olefins to give cyclopropanes.



(iv) Temporary formation of a heterocyclic intermediate

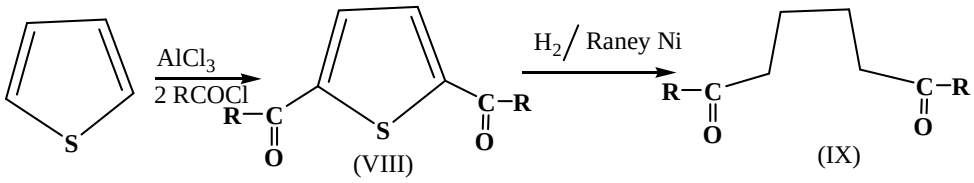
If a heterocycle is employed merely to alter the reactivity of a molecule, i.e. to make it more prone to reaction usually under mild conditions, it is undoubtedly chosen because of its unique properties. An excellent example is use of imidazoles

as reagent in organic synthesis. Diimidazole carbonyl(V) leads the formation of reactive intermediate (VI) under mild condition which allows conversion of the carboxylic acids to amides (VII)



18.4.2 Modification and elaboration of synthetically useful heterocycles

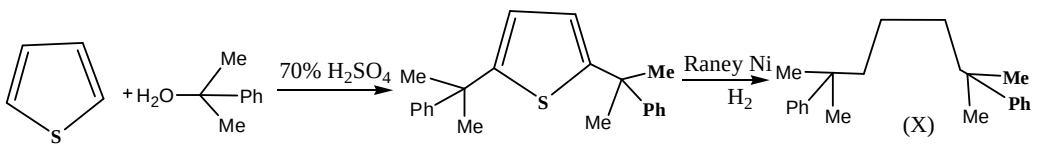
If a heterocyclic system possess one or more of the characteristic as describe above, then modification or elaboration of the molecule to allow for versatility in synthesis. By introduction of a variety of functional groups or carbon skeleton, the heterocyclic indeed serves as a precursor or vehicle for useful chemical transformations. For e.g. Thiophene molecule which can easily cleave in to hydrocarbon can also be easily elaborated. Diacyl derivative of thiophene (VIII) can be made by Friedel Craft acylation of thiophene, which is the precursor of 1,6-diketones (IX).



18.4.3 Use of Aromatic heterocycles in organic synthesis

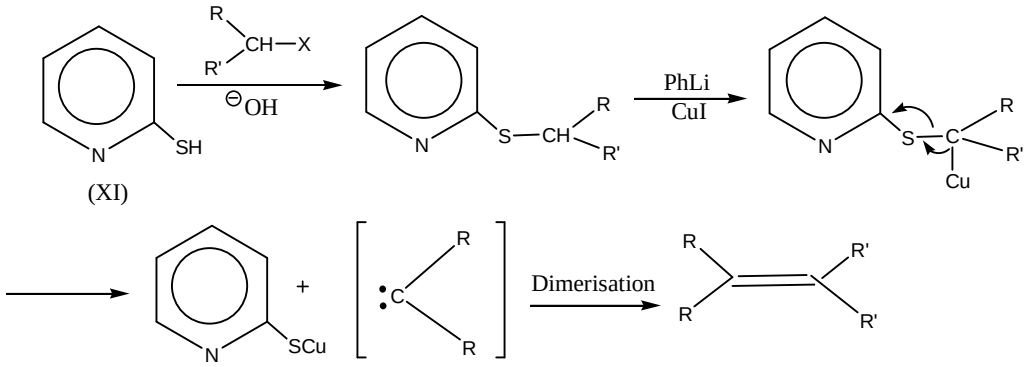
(i) Synthesis of alkanes and cycloalkanes

For e.g. condensation of dimethylphenyl carbinol with thiophene in 70% sulphuric acid gave the dialkylated branched alkane (X) on reaction with Raney Ni.



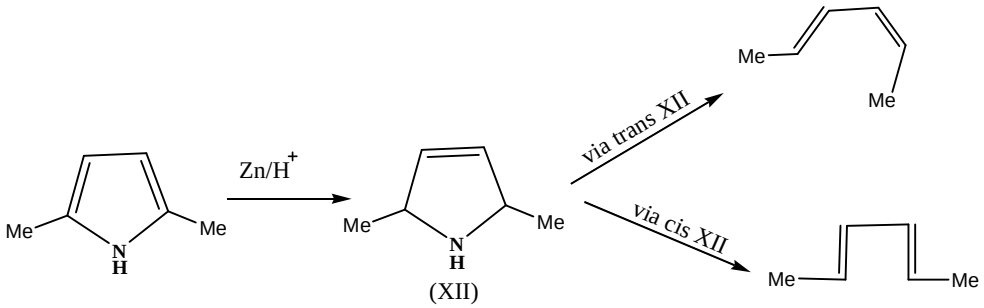
(ii) Synthesis of alkenes and cycloalkenes

By starting with 2-mercaptopyridine (XI) we can synthesize alkene as follows:



(iii) Synthesis of dienes, ene-ynes, acetylene and cycloalkynes

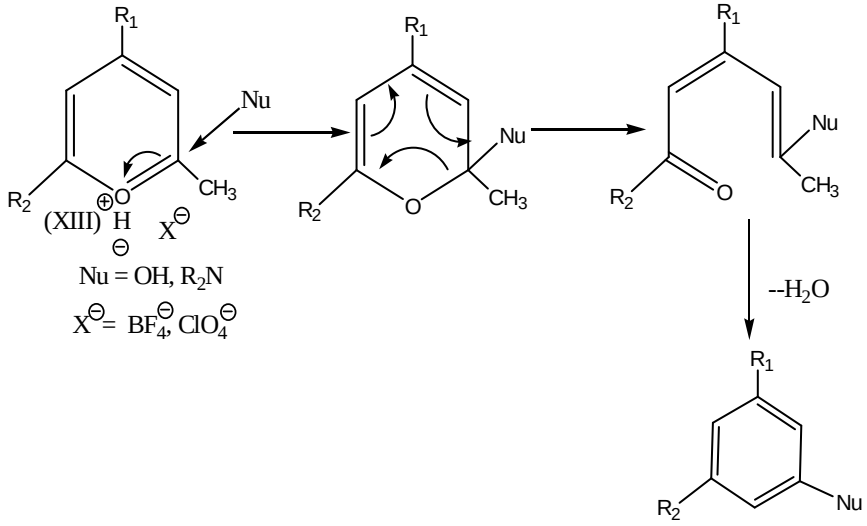
One of the example is reaction of 3-Pyrrolines (XII) with nitrohydroxylamine which gives dienes as shown below.



After reduction of 2,5-dimethylpyrrole, the resulting mixture (cis:trans; 1:3.5) was separated by fractional crystallization of the p-toluenesulphonamide.

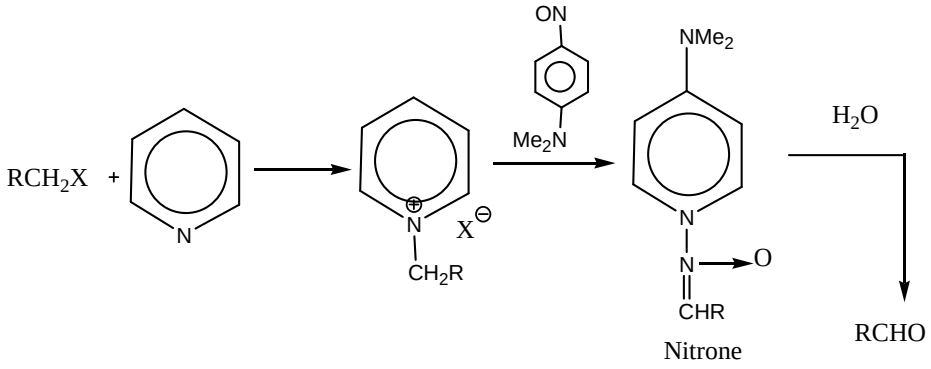
(iv) Synthesis of aromatic compounds

A number of benzenoid nuclei may be contructed from a heterocyclic precursor that undergoes either a rearrangement or an extrusion process. For e.g. the substituted pyrilium salts (XIII) can used as the precursor of polysubstituted aromatic molecules by a successive ring opening –ring closure process. If carbanion are used as nucleophiles, aromatic nitro compounds, esters, ketones, nitriles and hydrocarbons are formed.



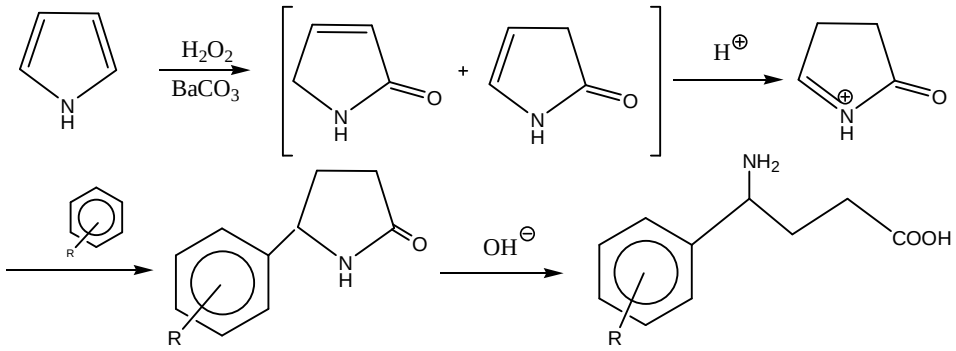
(v) Synthesis of carbonyl compounds (aldehyde and ketone)

Carbonyl compounds may also be produced by heterocyclic compounds. For e.g alkyl halide containing the CH_2X group are directly converted in to aldehydes via pyridinium salt and the nitrone.



(vi) Synthesis of Carboxylic acid and derivatives

Utilizing the same approach that led to carbonyl compounds, thiophene may also be manipulated to produce carboxylic acid. One another example is synthesis of ϒ-amino –ϒ-butyric acids by the use of pyrrole as shown below:



(R= *o*-OH, *p*-Me_2N

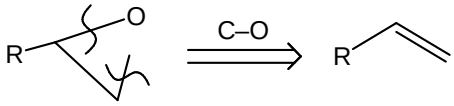
18.5 Summary

Usually intramolecular reactions are favoured kinetically over intermolecular reactions for reasons of entropy because two reactive sites are part of the same molecule and there is no need for a bimolecular collision.

Saturated heterocycles

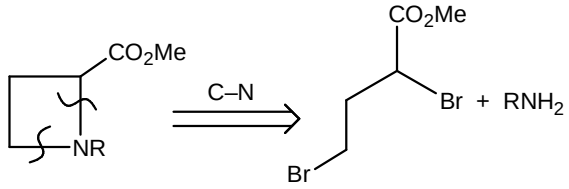
Synthesis of three membered ring

Epoxides or oxiranes are usually made from alkene both C-O bonds beings disconnected at once.



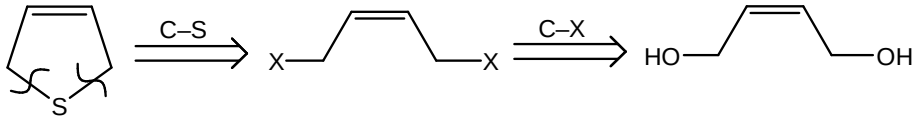
Synthesis of four membered ring

Four membered heterocycles are rarer and are uniquely difficult to make. The normal cyclization approach often gives poor results but sometimes successful.



Synthesis of five membered ring

Cyclization reactions are one of the best method for synthesis of five membered rings. The disconnection of both C-X bonds is strategic bond disconnection.



Synthesis of six membered ring

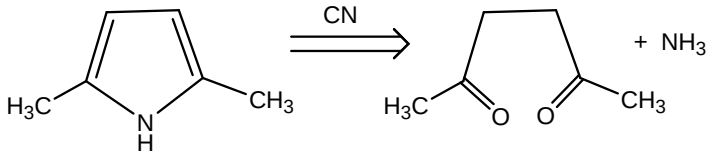
Formation of six membered ring is favoured by both (thermodynamic and kinetic) factors. Therefore cyclization reaction can be employed for the synthesis of it.

Aromatic heterocycles

The first important thing is to recognize the oxidation levels of carbon atoms bonded to the heteroatom.

Synthesis of five membered aromatic heterocycles

Simplest disconnection of furan or pyrrole is the removal of the heteroatom leaving a 1,4 dicarbonyl compound.

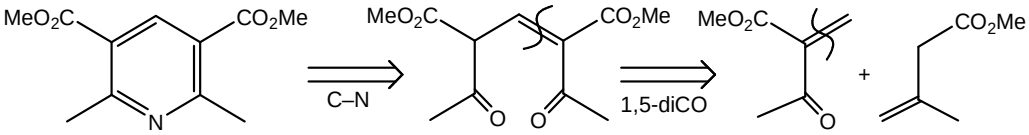


Indoles

Indoles can be synthesized by Fischer Indole synthesis. The phenylhydrazone of a ketone is treated with acid (or lewis acid –$ZnCl_2$), which gives indoles. Reaction proceed via [3,3] sigmatropic rearrangement pathway.

Synthesis of six membered aromatic heterocycles

Pyridines: It can be synthesized by usual C-N disconnection, which gives 1,5-dicarbonyls.



Quinolines: Quinoline should disconnected to give an amine and a synthon.

Aromatic heterocycles in organic synthesis

The heterocyclic can be used as a precursor or reagent for obtaining functionalized organic compounds and structures of diverse architecture**.**

General consideration concerning synthetically useful heterocyclic compounds

Properties of heterocycles that cause them to be synthetically useful are:

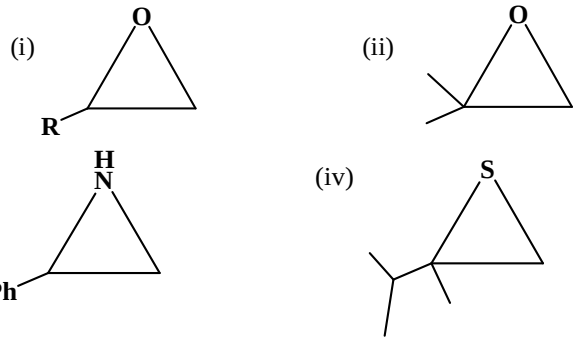
(i) Destruction of aromaticity
(ii) Drive towards aromaticity
(iii) Release of ring strain
(iv) Temporary formation of heterocyclic intermediate

These are the four process by which heterocyclic compounds shows their synthetic powers.

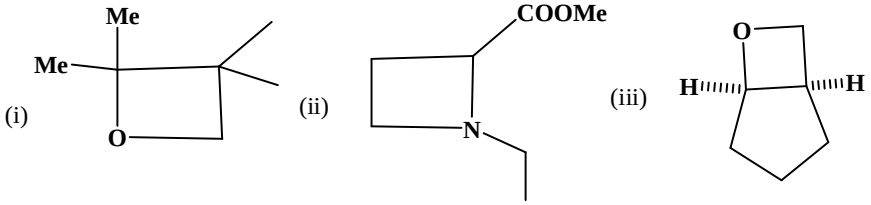
18.6 Review Questions

1 Explain why intramolecular reactions are favoured over intermolecular reactions by taking example of the formation of various sizes of rings.

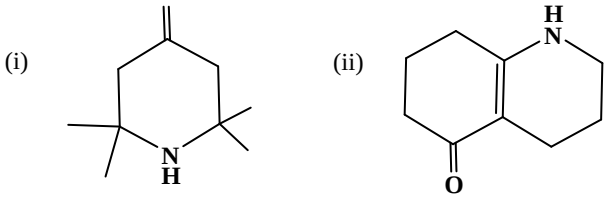
2 Discuss the synthesis of the following compounds and outline the corresponding retrosynthetic analysis in each case:



3 Outline the retrosynthetic analysis and the corresponding synthesis of the following target molecules:



4 Using disconnect approach, suggest the synthesis for each of following molecule:



5 Give a brief note on synthesis of aromatic heterocycles.

18.7 Reference and Suggested Readings

- Organic Synthesis, The Disconnection Approach, S. Warren (Wiley).
- Organic Synthesis through Disconnection Approach, P.S. Kalsi, MEDTEC.
- Organic Synthesis, Jagdamba Singh and L.D.S. Yadav, Pragati Prakashan.

Unit - 19

Synthesis of Some Complex Molecules I

Structure of the Unit

19.0 Objective

At one time, the total synthesis of a compound represents the ultimate proof of its structure. But Now a days Nuclear Magnetic Resonance Spectroscopy and X – Ray Crystallography can supply proof of structure. Nevertheless the synthesis of naturally occurring compounds remains a vigorously pursued field, for two reasons. First is that these material can be obtained only in small quantity from natural sources or with such difficulty that synthesis can provide cheaper and sufficient amount. Besides this the total synthesis will usually give precursors of the natural compound from which related structures can be synthesized and this also will be of value in the pharmaceutical field. Second is natural product

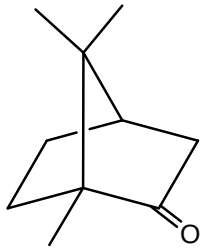
synthesis is a most fruitful source of new synthetic methods : a particular step in the sequence may lead to the development of a new and general method for its successful completion.

19.1 Introduction

The following syntheses have been selected on the basis that each product is of biological importance. The present unit deals with the synthesis of Camphor, Longifoline and Cortisone. First we will discuss the retrosynthetic plans. Retrosynthetic analysis shows the issues that can arise in planning a synthesis.

19.2 Camphor :

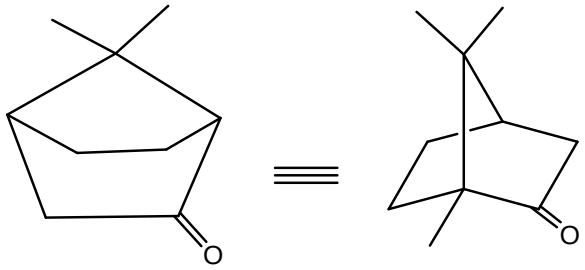
Camphor is a waxy flammable white or transparent solid with a strong aromatic odour. It is a terperoid with the chemical formula $C_{10}H_{16}O$. It is found in the wood of the *Camphor Laurel*, and also of the Kapur tree. A major source of Camphor in Asia is *Camphor basil*.



Camphor (I)

Camphor has two dissimilar chiral centres but only one pair of enantiomers is known, i.e. only one diasteromer exists. This is due to the fact that only the *cis* form is possible : *trans* fusion of the gem – dimethylmethylene bridge to the cyclohexane ring is immpossible.

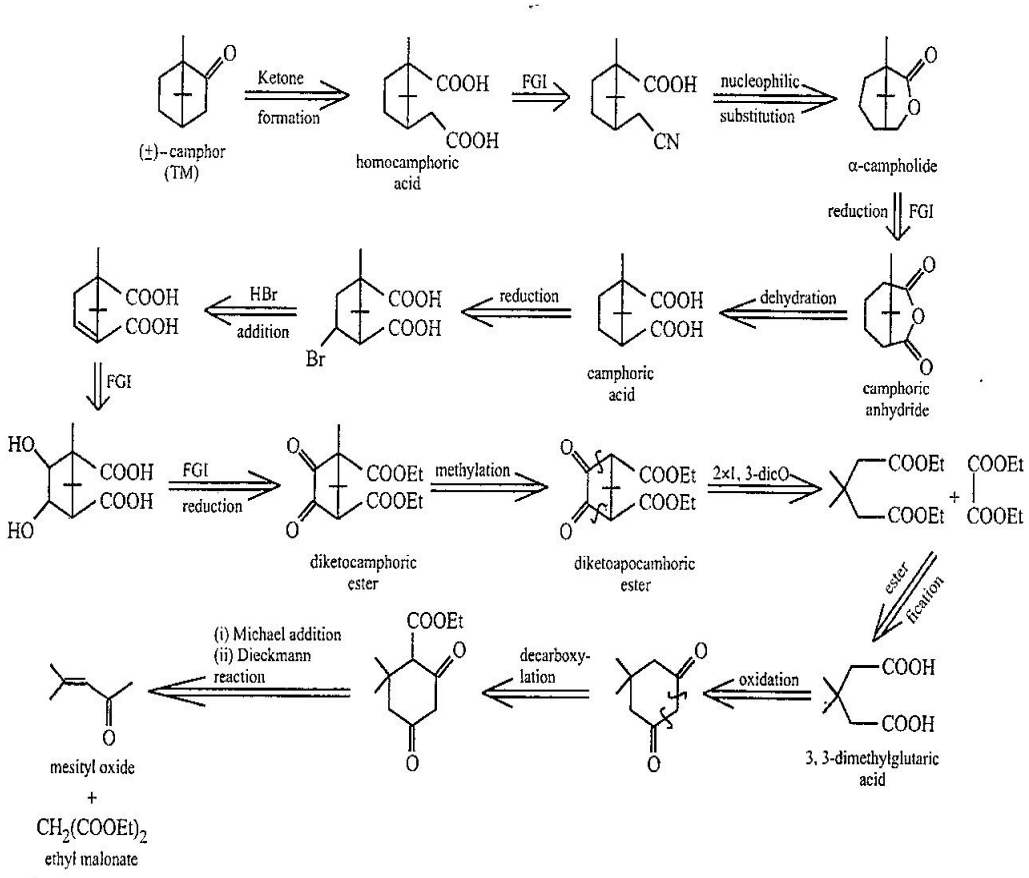
So only the enantiomers of the *cis* isomer are known. Camphor and its derivatives exist in the boat conformation. As the gem dimethylmethylene bridge must be *cis*, the cyclohexane ring must have the boat form (II). This can be represented as (I).



(II) **(I)**

19.2.1 Retrosynthetic analysis of Camphor

It is shown as follows :-

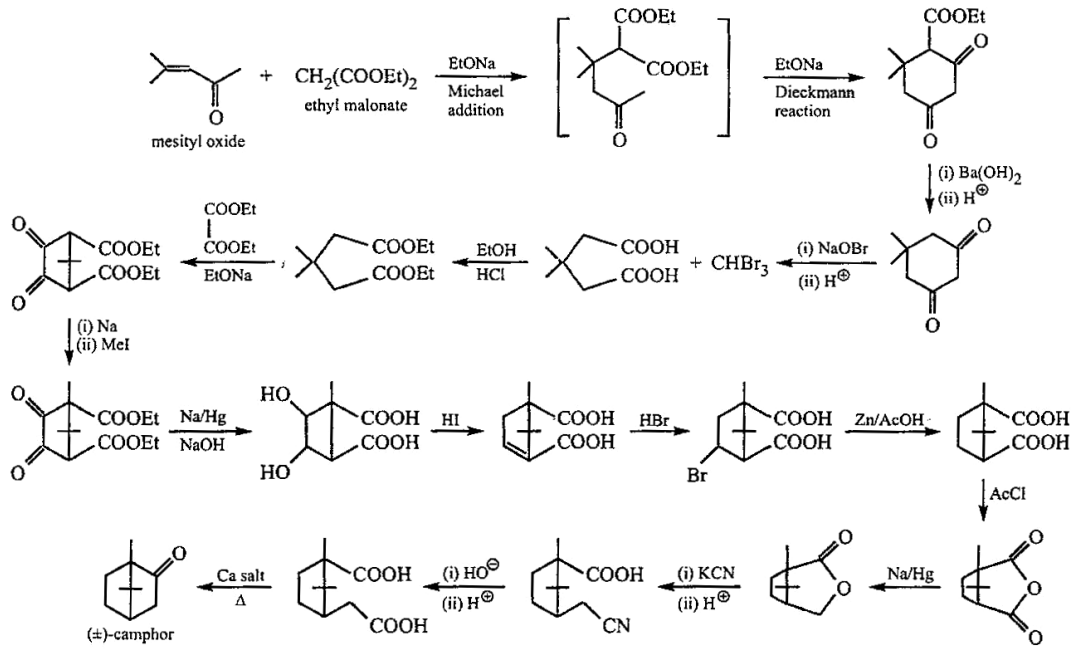


Scheme 1 : Retrosynthetic analysis of Camphor

By this we get mesityl oxide and ethyl malonate as starting material.

19.2.2 Synthesis

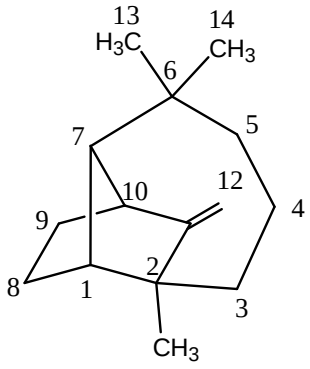
Above mentioned retrosynthetic analysis shows that the total synthesis can be start from mesityl oxide and ethyl malonate. Its total synthesis is shown as follows :



Scheme 2 : Synthesis of Camphor

19.3 Longifolene

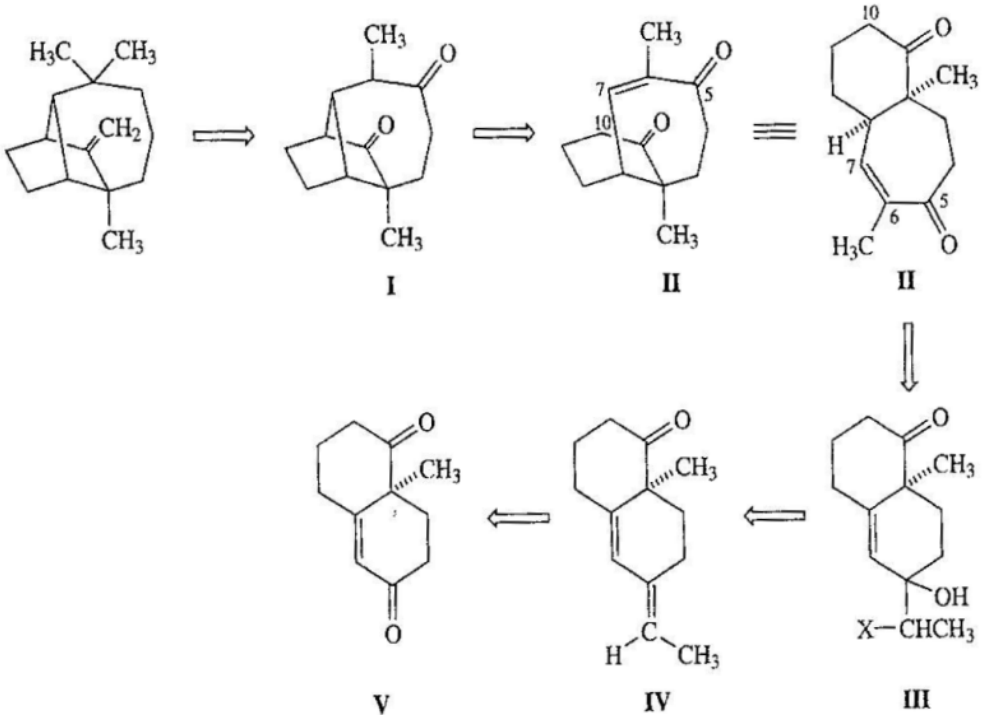
Longifolene is a tricyclic terpene. It is a typical terpene in terms of the structural complexity. There are 4 stereogenic centers is longifolene, but they are not independent of one another because the geometry of ring system requires that they have a specific relative relationship.



Longifolene

First successful synthesis of Longifolene was given by E. J. Corey and Co-workers in 1964.

19.3.1 Retrosynthetic analysis



Scheme 3 : Retrosynthetic analysis of Longifolene

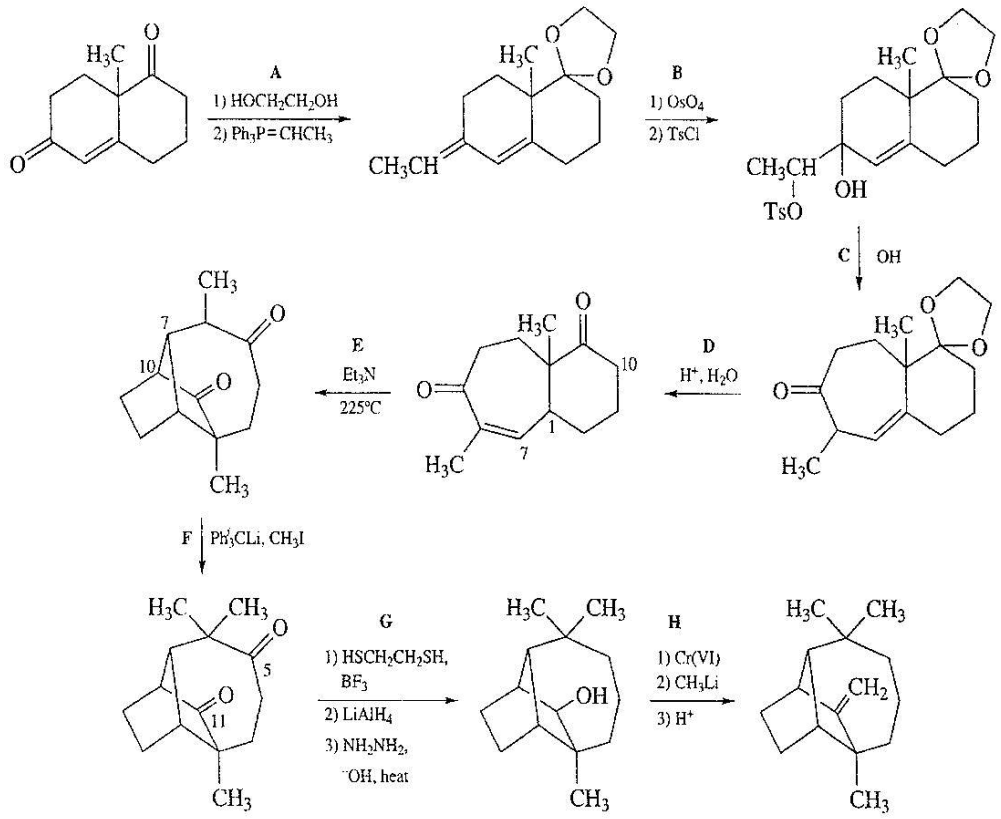
A key disconnection is made for transformation from I ⇨ II, which simplifies the tricyclic structure to a bicyclic one. The 6/7 fused enone (II) is the most significant disconnetion intermediate. The enolate generated by deprotonation at C_{10} in (II) would undergo an intramolecular Michael addition on C_7.

Retrosynthetic step II ⇨ III is attractive as it suggest a decalin derivative (Key intermediate). The synthesis from III to II, which involves the transformation of hydroxyl to carboxyl group with migration and ring expansion corresponds to pinacol–pinacolone rearrangement if X group in (III) is a good leaving group.

The other transformation in retrosynthetic analysis III ⇨ IV ⇨ V are straight forward in concept and lead to identification of (V) as a potential starting material.

19.3.2 Synthesis :

The synthesis corresponding to above retrosynthetic analysis was carried out as shown in scheme **4**. It was given by E. J. Corey and R.B. Mitra and P.A. Vatakencherry



Scheme 4 : **Longifolene Synthesis: E. J. Corey and R.B. Mitra and P.A. Vatakencherry**

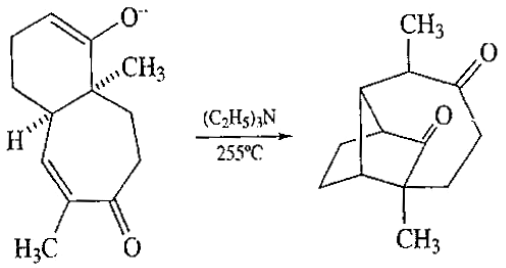
Step A It involves the protection of carbonyl group by ethylene glycol & then reduction of enone with $Ph_3P=CHCH_3$ by witting reaction

Step B It involves oxidation with OsO_4 and leads to formation of cis diol which reacts with TsCl in presence of Pyridine and selectively tosylated at the secondary hydroxyl group.

Step C It is the pinacol rearrangement. Base promotes the skeletal rearrangement.

Step D Stereochemistry of ring junction established in this step when double bond is moved into conjugation.

Step E Intramolecular Michael addition takes place. It is accomplished by using triethylamine using high temperature conditions.



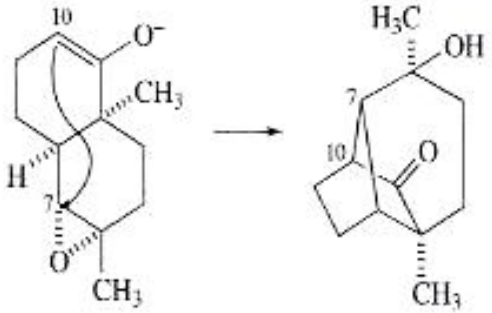
Step F Reaction with Ph_3CLi and CH_3I.

Step G Selective protection of the less hindered C-5 carbonyl was done using a thioketal. The C-11 carbonyl was then reduced to give the alcohol and finally C-5 was reduced to a methylene group under Wolff kishner conditions.

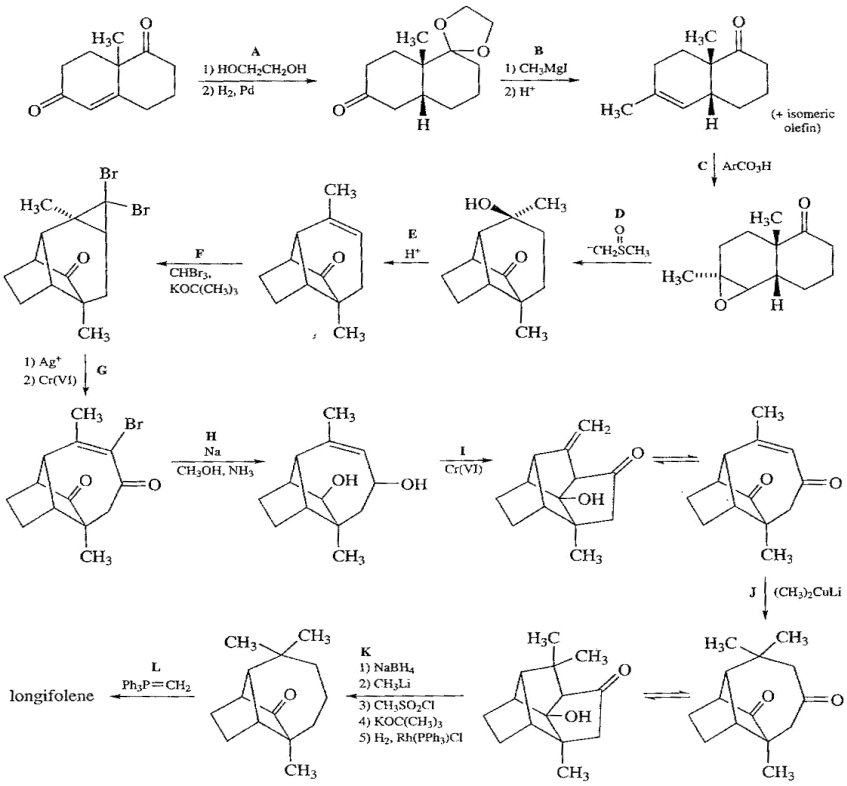
Step H The hydroxyl group at C-11 provides the reactive center necessary to introduce the C-15 methylene group in this step.

Another synthesis of Longifolene which was proposed by J. E. McMurry and S. J. Isser is also discussed here:

The key bond closure in Scheme 5 is somewhat similar to that used in Scheme 4, but is performed on a bicyclo [4.4.0] decane ring system. The ring juncture must be *cis* to permit the intramolecular epoxide ring opening. In step A the required cis ring fusion is established during the catalytic hydrogenation.

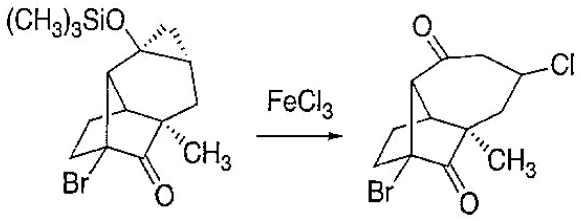


The cyclization is followed by a sequence of steps F – H, which effect a ring expansion via a carbene addition and cyclopropyl halide solvolysis. The products of steps I and J are interesting in that the tricyclic structures are largely converted to tetracyclic derivatives by intramolecular aldol reactions. The extraneous bond is broken in step K. First, a diol is formed by $NaBH_4$ reduction. Now this is converted to a monomesylates. The resulting β - hydroxy mesylate is capable of a concerted fragmentation, which occurs on treatment with potassium t- butoxide.

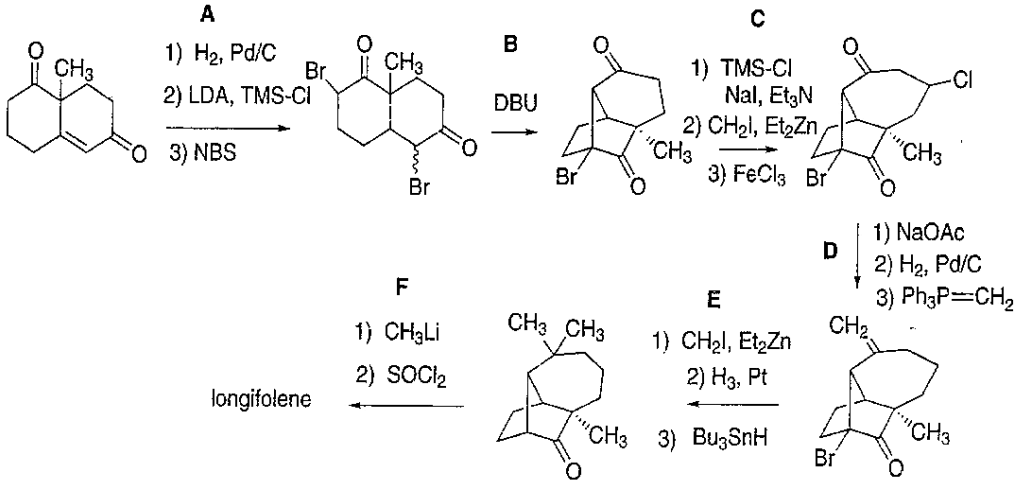


Scheme 5: Longifolene Synthesis: J. E. Mc Murry and S. J. Isser

One another method for synthesis of Longifolene was proposed by S. Karimi and P. Tavares in which It was synthesized from (+) Wieland-Miescher ketone by a series of reactions that feature an intramolecular enolate alkylation and ring expansion, as shown in Scheme **6.** In the first step the starting material was converted in to a dibromo ketone via the bis-silyl enol ether. Then this intermediate underwent an intramolecular enolate alkylation to form the C(7) – C(10) bond. Further the ring expansion was done by conversion of the ketone to a silyl enol ether, cyclopropanation and treatment of the siloxycyclopropane with $FeCl_3$.



Final methyl group was introduced in the final stages by Simmons-Smith cyclopropanation and reductive opening of the cyclopropane ring.

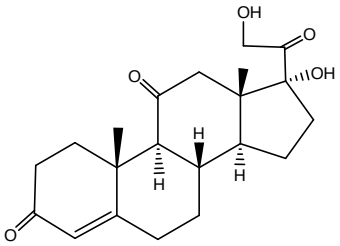


Scheme 6: Longifolene Synthesis: S. Karimi and P. Tavares

19.4 Cortisone

Cortisone (17–hydroxy–11-dehydrocorticosterone) is a 21- carbon steroid hormone. It is one of the main hormones released by the adrenal gland in response to stress. They elevate blood pressure and prepare the body for a fight or flight response. A corticosone injection can also be used to give short term pain relief

and reduce the swelling from inflammation of a joint tendon. It has been used for the treatment is rheumatoid arthritis and rheumatic fever.

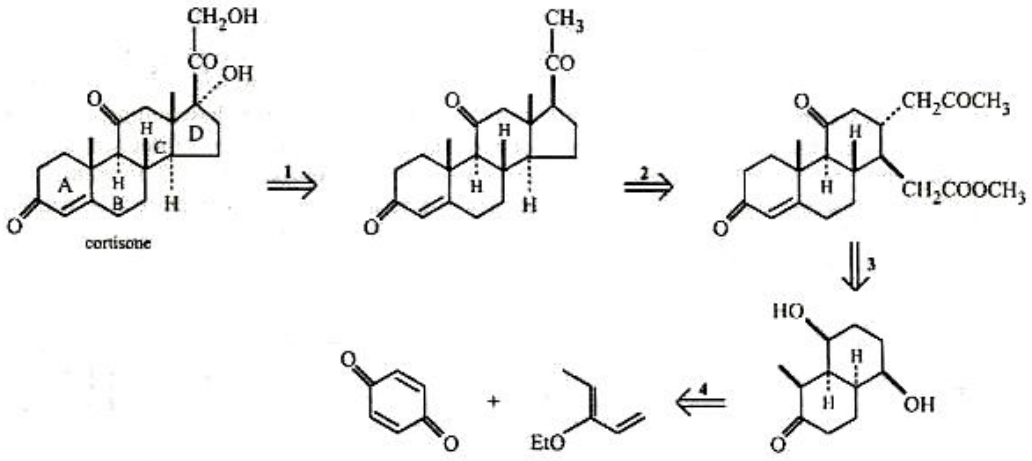


Cortisone

The total synthesis of cortisone was reported by Woodward *et al* in 1951. Further the total synthesis of cortisone reported by Sarett *et al.* in 1952 is noteworthy due to the very high degree of stereospecificity in each step as well as very high yield as compared to that obtained by the synthesis which was reported by Woodward *et al*.

19.4.1 Retrosynthetic analysis

Retrosynthetic analysis leading to the key intermediates used in the synthesis by Sarett *et al* is shown in scheme **7**.



Scheme 7: Retrosynthetic analysis of Cortisone

Remarks :-

1. First disconnection corresponds to the decision that the $COCH_3$ group at C-17 can be converted into the $COCH_2OH$ group and the α-OH group at this position.
2. The Second disconnection is based on the formation of ring D which can be made by intramolecular Claisen condensation.
3. The Third disconnection is corresponding to the formation of the ring **A** by Michael condensation using methyl vinyl ketone followed by cyclization (Robinson annelation)
4. The Fourth disconnection gives the starting material which are p-benzoquinone and 3–ethoxy–1,3–pentadiene. Desired *cis* fused rings B and C can be construct by Diels Alder reaction between p – benzoquinone and 3-ethoxy-1,3–pentadiene.

19.4.2 Synthesis

Remarks:

Step A - Diels Alder reaction.

Step B - Selective catalytic hydrogenation (Ni).

Step C - Reduction with $LiAlH_4$ formed the diol.

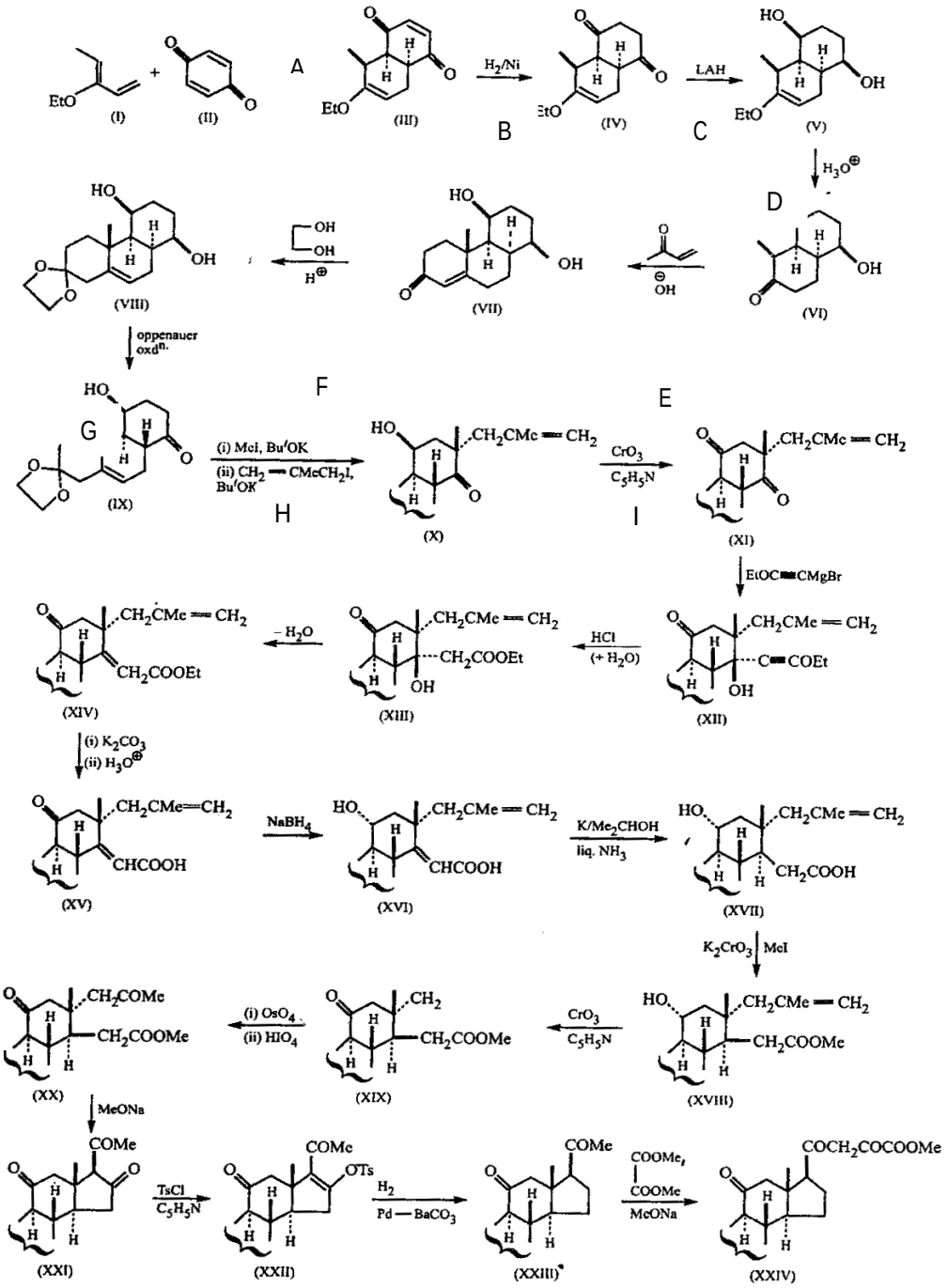
Step D - When V is treated with acid it hydrolysed to VI.

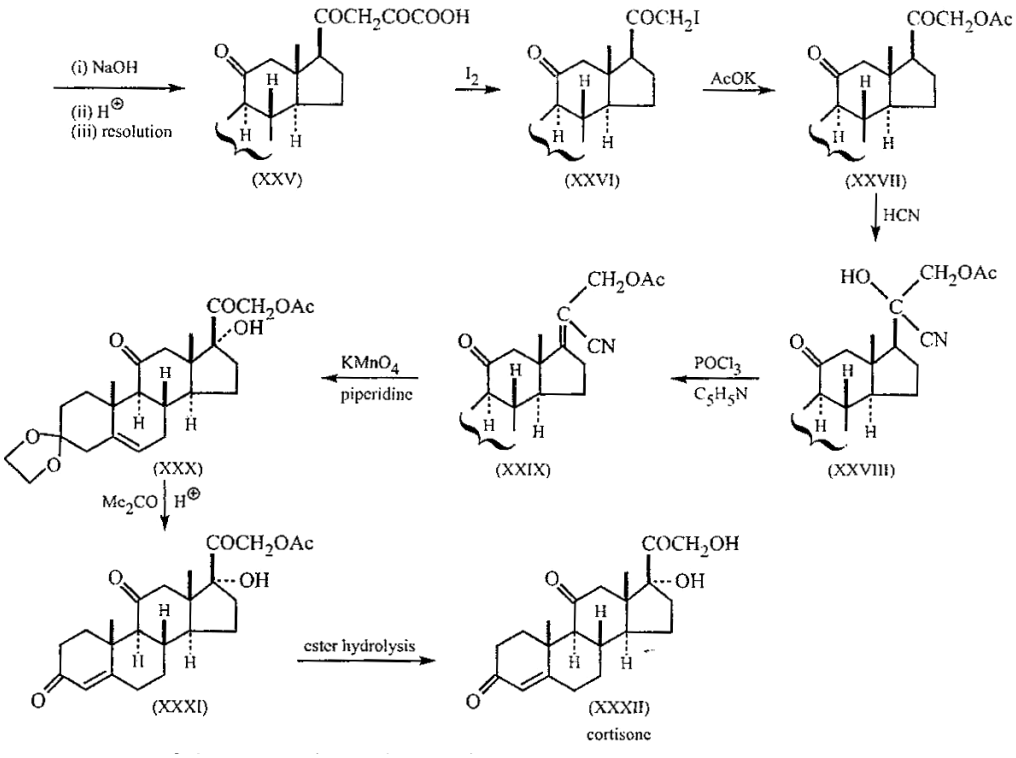
Step E - Michael condensation – VI reacts with methyl vinyl ketone in the presence of alkali (Triton B) underwent Michael addition at the less hindered side followed by cyclisation to give the tricyclic ketone (VII) with a β- methyl group.

Step F - Protection of the oxo group: VII was protected by the reaction with ethylene glycol.

Step G - Oppenauer oxidation –Which selectively oxidize at the less hindered hydroxyl group to IX. IX is formed with inversion to give the more stable *trans* fused rings. Conversion of IX into cortisone acetate (XXXI) are shown is the scheme 7.

Step H - The required configuration of (X) is obtained in which a larger methallyl group in trans to the meta (11-) OH thereby reducing 1, 3 – interactions the hydroxyl group has the β-axial configuration.





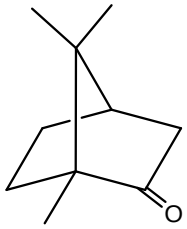
Scheme 8- Synthesis of Cortisone

Ring extension of (VI) to (VII) is an example of the Robinson annelation. To avoid elimination of the 11β-hydroxyl group in step (XIII) to (XIV), (X) was oxidised to give (XI). Hydration of (XII) to (XIII) was carried out under mild conditions to avoid removal of the protecting group (3-position). Sodium borohydride reduction of (XV) gave (XVI) with an 11α(equatorial)-hydroxyl group, and the next step reduced the α, β– double bond (XVI) (XVII). It might also be noted that the α configuration at position 11 produces the correct configuration β at C-14; the β-configuration would have produced the 14α - configuration. Resolution of XXIV was carried out with strychnine after converting it into the corresponding carboxylic acid. The (+) – isomer was used in the next step ((XXIII) in the (±) form.

19.5 Summary

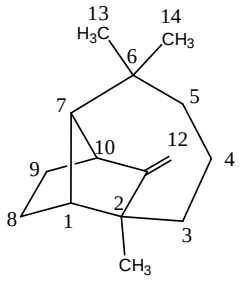
Camphor

Camphor has two dissimilar chiral centres but only one pair of enantiomers is known i.e. only one diasteromer exists. This is due to the fact that only the cis form is possible: *trans* fusion of the gem – dimethyl methylene bridge to the cyclohexane ring is immpossible.



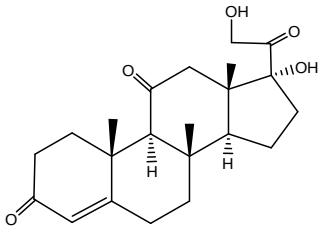
Longifolene

Longifolene is a tricyclic terpene. It is a typical terpene in terms of the structural complexity. There are 4 stereogenic centers is Longifolene, but they are not independent of one another because the geometry of ring system requires that they have a specific relative relationship.



Cortisone

Cortisone (17–hydroxy–11-dehydrocorticosterone) is a 21- carbon steroid hormone. The total synthesis of cortisone was reported by Woodward *et al* in 1951. Further the total synthesis of cortisone reported by Sarett et al. in 1952 is noteworthy due to the very high degree of stereospecificity in each step as well as very high yield as compared to that obtained by the synthesis which was reported by Woodward *et al*.



19.6 Review Questions

1 Outline the retrosynthetic analysis of Camphor and its total synthesis starting from mesityl oxide.

2 Explain why camphor have only one pair of enantiomer yet it has two dissimilar chiral centers.

3 Explain why camphor have boat conformation?

4 Outline the retrosynthetic analysis of Longifolene and corresponding synthesis.

5 Outline the retrosynthetic analysis and synthesis of Cortisone.

19.7 Reference & Suggested readings

- Advanced Organic Chemistry Part-B, F. A. Carey and R. J. Sundberg, 5th Ed. Springer.
- Principles of Organic Synthesis, R.O.C. Norman and J. M. Coxon, CRC Press.
- Organic Synthesis through Disconnection Approach, P.S. Kalsi, MEDTEC.
- Organic Synthesis, Jagdamba Singh and L.D.S. Yadav, Pragati Prakashan.

Unit - 20

Synthesis of Some Complex Molecules II

Structure of the Unit

20.0 Objective

As we have discussed in previous unit that at one time, the total synthesis of a compound represents an ultimate proof for structure determination. Synthesis of Natural products are also demandable as these constituents are found in very little amount in nature, and they have importance in pharmaceutical field.

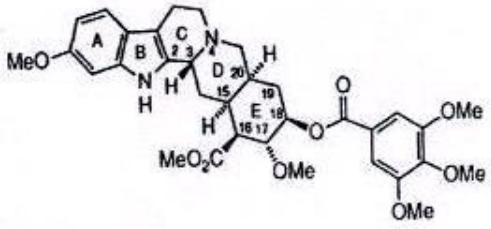
20.1 Introduction

In this chapter we will discuss the synthesis of some complex molecule like : Reserpine, Vitamin D and Juvabione. First we will discuss the retrosynthetic plans, crucial bond forming steps and use of protecting groups. Whenever needs, the means of stereochemical control will also be discussed. Retrosynthetic analysis

shows the issues that can arise in planning a synthesis and also provide examples of solution that have been developed during the successful synthesis.

20.2 Reserpine:

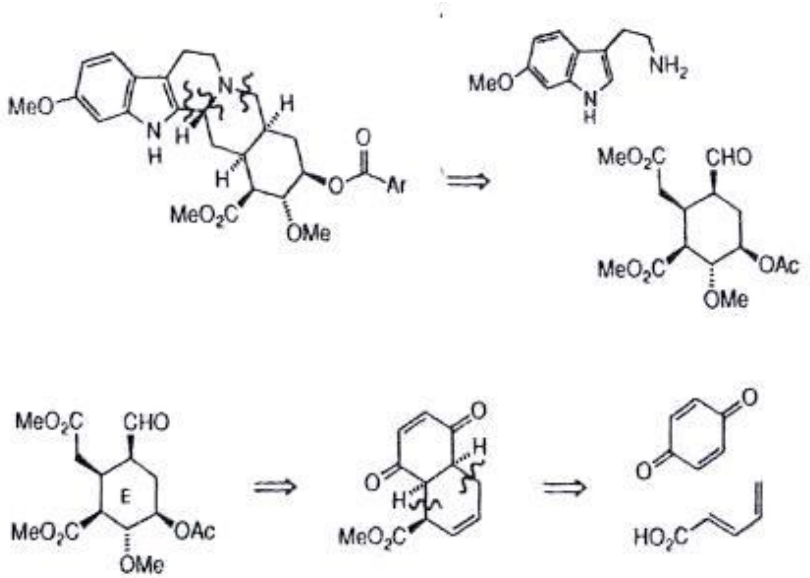
Reserpine is found with other alkaloids in the roots of the plants genus *Rauwolfia*. It is a tranquillizing drug and used for the treatment of some mental disorders and also for the reduction of hypertension. Its total synthesis was given by R.B. Woodward *et al*.



Reserpine

20.2.1 Retrosynthetic Analysis

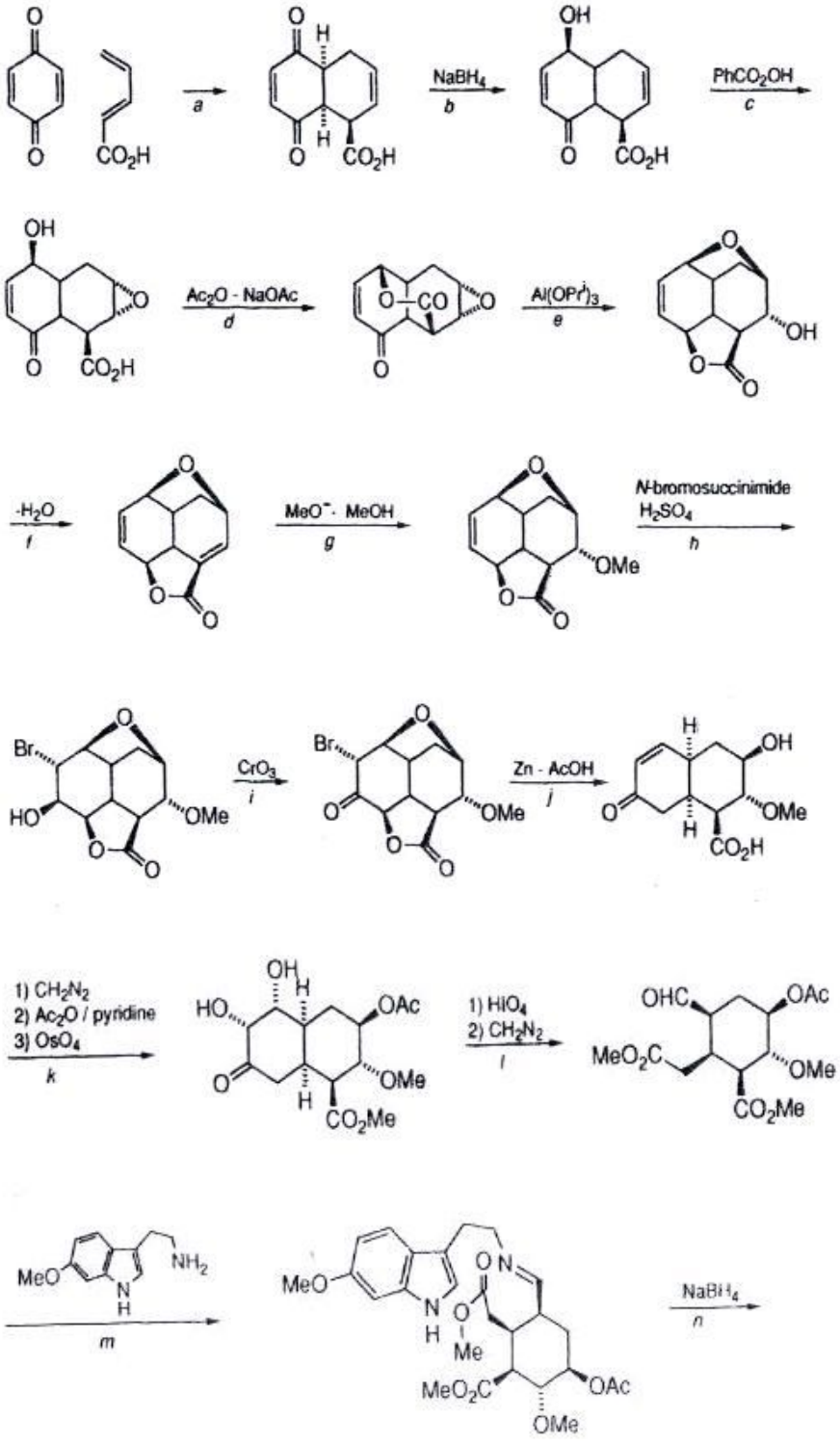
The strategy was based on building five contiguous stereocentres into a decalin derivative which could be opened to a monocyclic compound that would form ring E. It is shown in the following retrosynthetic analysis:

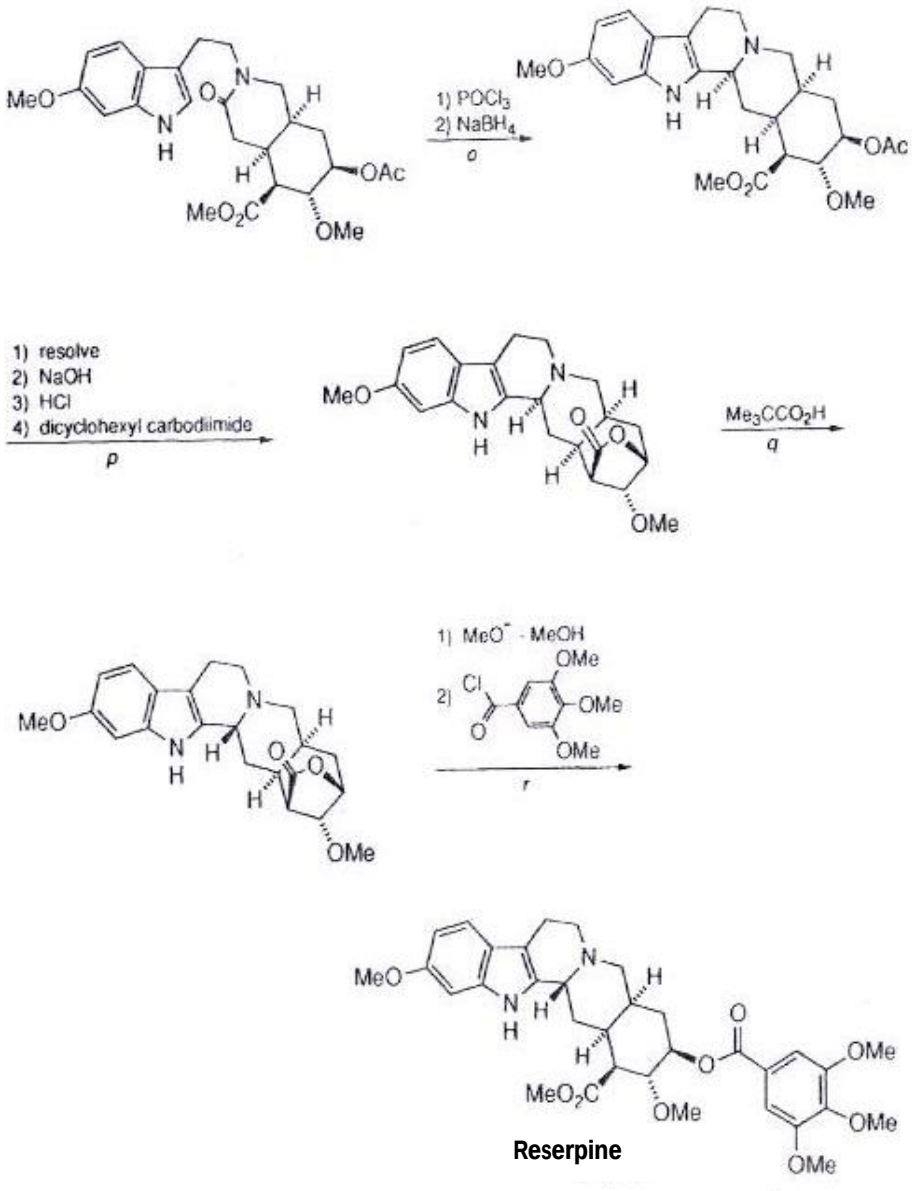


Scheme 1 : Retrosynthetic analysis of Reserpine

20.2.2 Synthesis

The synthesis is as follows :

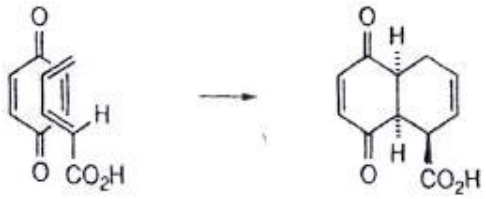




Scheme 2 : Synthesis of Reserpine

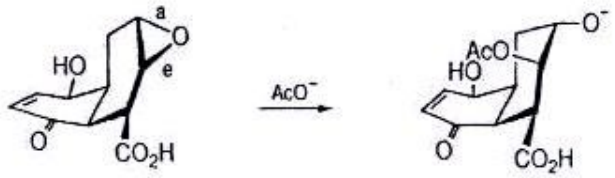
Remarks on synthesis steps:

Step - a Diels Alder reaction: The stereochemical principles governing this reaction lead to the ring junction having *cis* stereochemistry. This step fixes the stereochemistry at C_{15}, C_{16} and C_{20} of reserpine.



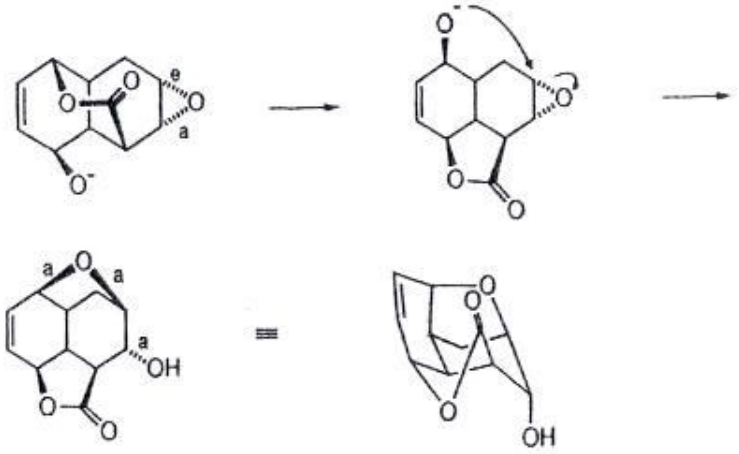
Step - b Sodium borohydride reduces the less hindered one of the two carbonyl groups. The nucleophile can attacks from the less hindered α side.

Step - c Reaction with peroxyacid : peroxyacid reacts more rapidly with the isolated double bond than with the carbonyl conjugated double bond. Attack from the less hindered -α- side.



Step - d Formation of lactone by dehydration takes place. This reaction has the effect of changing the conformation of the system. The epoxide becomes axial at C_{17} and equatorial at C_{18}.

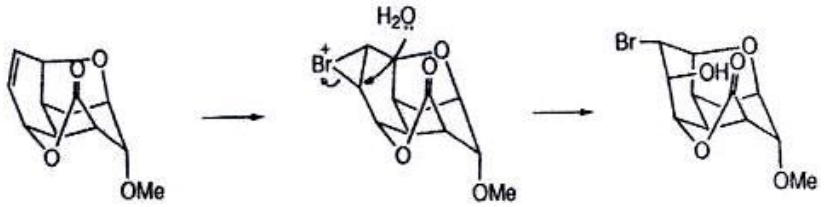
Step - e Meerwein Pondorf Verley Reduction : Conversion of keto group in to hydroxyl group takes place. The resulting nucleophilic oxygen displaces on the carbonyl of the six membered lactone ring giving a five membered lactone, and the hydroxyl group so released brings about opening of the epoxide ring.



Step – f Dehydration : It involves elimination of the axial hydroxyl group and leads to the formation of an α, β- unsaturated carboxyl derivatives readily.

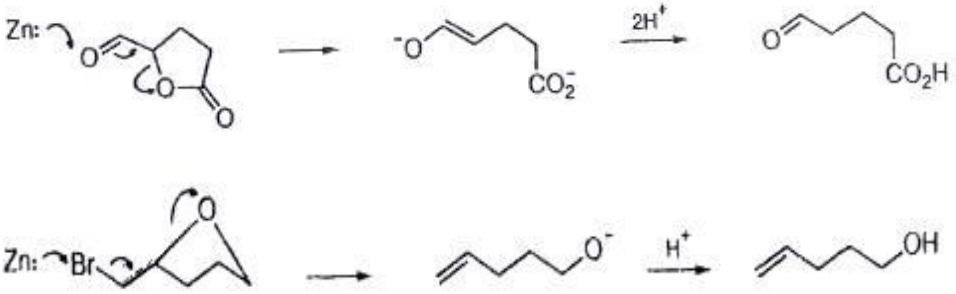
Step – g Attack of the nucleophiles at activated C=C bond. Methoxide ion approaches from the less hindered α– side so that resulting – OCH_3 substituent is in the axial position at C_{17}. Now Ring E has the correct stereochemistry.

Step – h Reaction with N–Bromosuccinimide :- N–Bromosuccinimide is used as an ionic brominating agent and leads to the formation of diaxial bromo-alcohol by following mechanism:

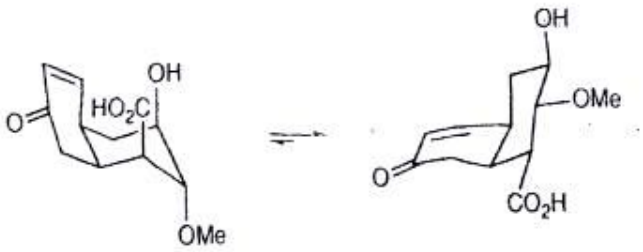


Step – i Mild oxidation of the secondary alcohol.

Step – j Reaction with zinc is acetic acid which brings about the reductive opening of the both the lactone and the strained ether.



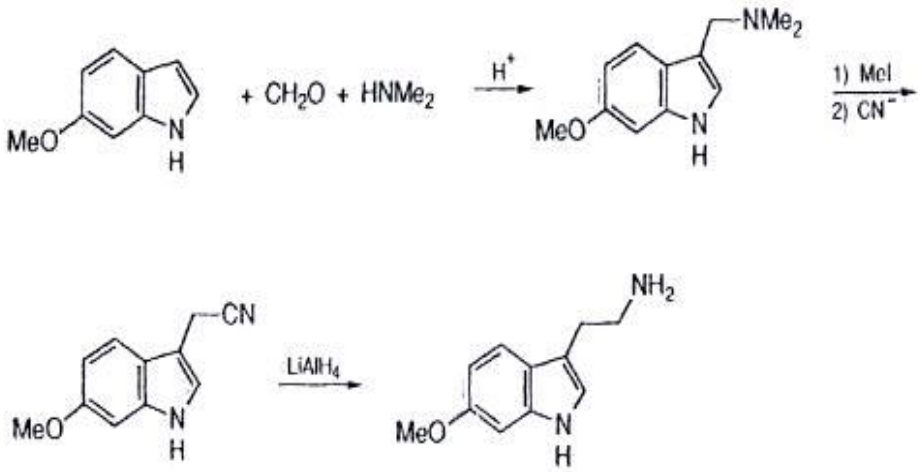
All the substituents in ring E are now able to adopt equatorial conformations:



Step – k Now esterification of carboxyl group is done by diazomethane. Alcoholic group is acetylated and the 1, 2 – diol is formed with Osmium tetroxide.

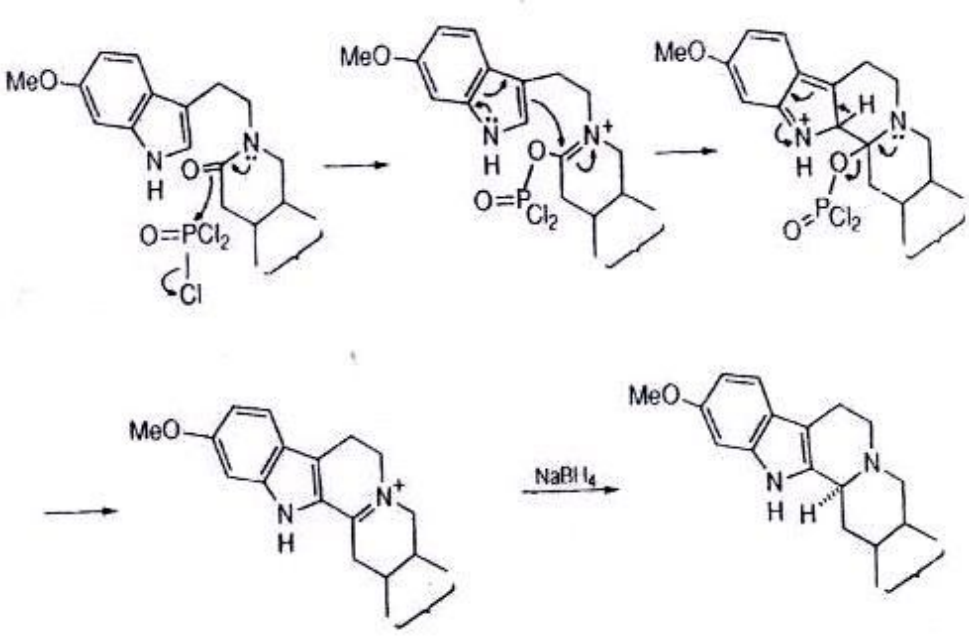
Step – l Treatment with periodate which cleaves ring D and one carbon atom is lost as formic acid. Further the new carboxyl is then esterified by diazomethane.

Step – m 6 – Methoxytryptamine can be prepared as follows :-

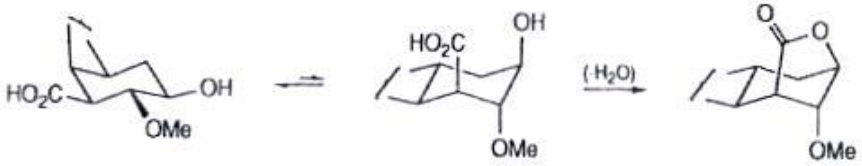


Step –n Reduction of imine gives and an amine and the resulting nucelophilic nitrogen displaces intramolecularly on the ester to close ring D.

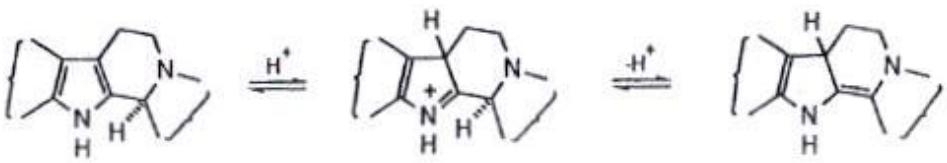
Step – o Reaction with $POCl_3$ brings ring closure as in the Bischler Napieralski synthesis of isoquinolines, gives an immonium salt which is then reduced with $NaBH_4$.

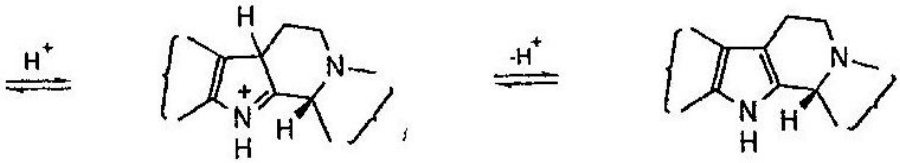


Step – p Treatment with base followed by acid removes acetyl group (C_{18}) and hydrolyzes hte methyl ester (C_{16}). Then free OH and C=O group joined to give a lactone, using dicyclohexyl carbodiimide.



Step – q The Preceding step leads to the less stable molecule than the stereoisomer obtained by altering the configuration of the hydrogen at C_3*. Equilibration of the two isomers therefore yields almost entirely the product with the stereochemistry required for reserpine at this centre.The equilibrating agent is trimethylacetic acid because of its suitable boiling point and the fact that it is too weak a nucleophile to open the lactone ring. Interconversion presumably occurs through protonation (activated by pyrrole nitrogen) and deprotonation.





Step – r Reaction with Methanol: Methanol opens the lactone ring and the molecule then reverts to the more stable conformation in which the three substitutents on ring E are equatorial. At last the aroyl residue is introduced at C_{18} with 3, 4, 5 trimethoxy benzoyl chloride.

20.3 Vitamin D (Antirachitic factor)

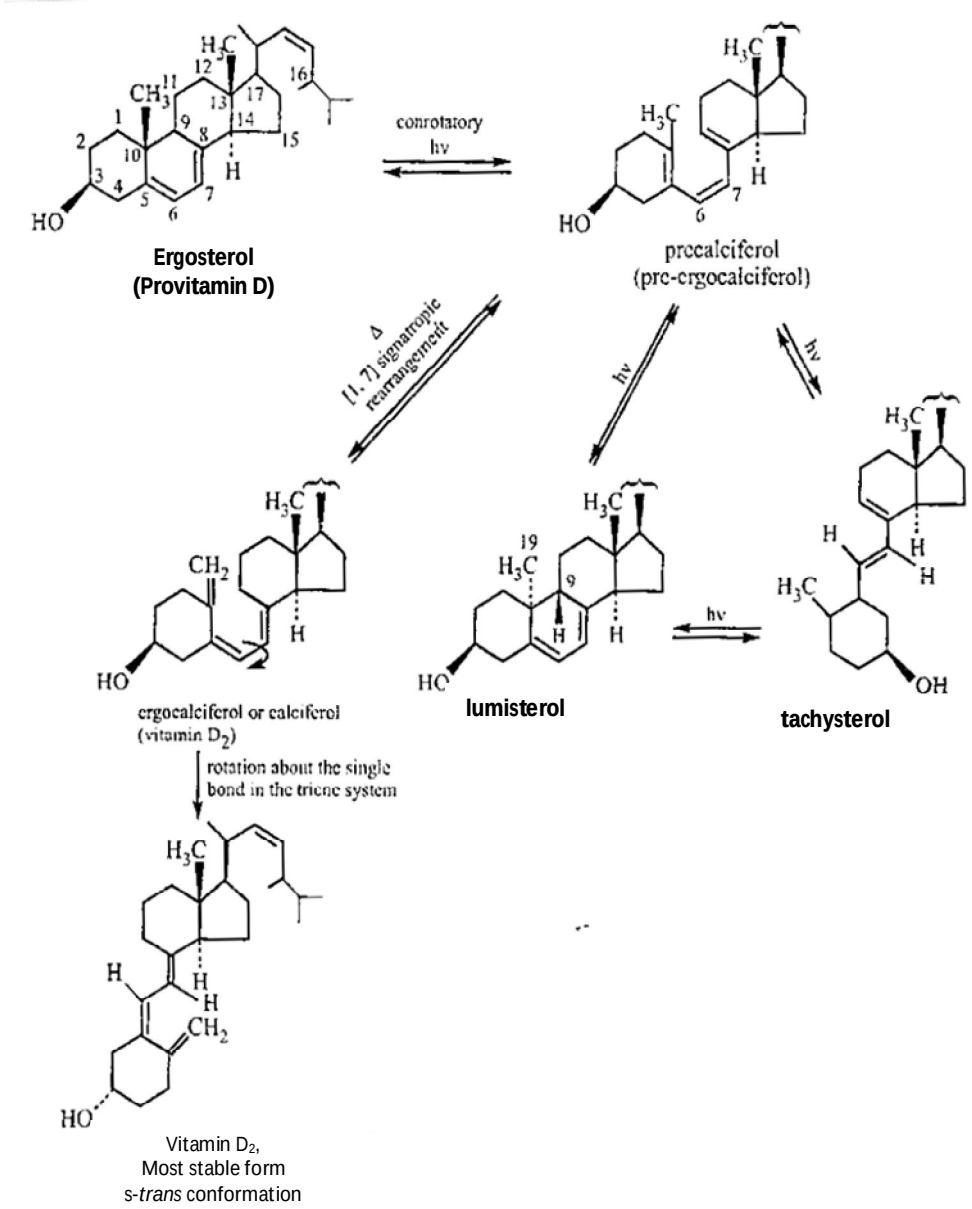
The demonstration, in 1919 that sunlight helped cure rickets a childhood disease characterized by poor bone growth began a search for a chemical explanation. Subsequent investigation showed that Vit D were involved and eventually it became known that one of several D vitamin, called Vitamin D_3 is the curative factor.

Vitamin D's function being the control of calcium and phosphorus metabolism. Mc Collum and his associates, named the antirachitic substance present in cod liver oil vitamin D. Lately it was recognized that certain food contain compounds that can be transformed into Vitamin D by irradiation. There compounds are known as provitamins found in both plant and animals. All these compounds are steroids and have a diene system in the ring B. They donot show vitamin D activity until this ring is opened.

Ergosterol is the most widely investigated provitamin D. It undergoes a photochemical ring opening to give a compound called precalciferol. All the provitamins for vitamin D have the same structure except for variations in the side chain at C-17 of the steroid ring. When ring B (Scheme-3) opens by conrotatory manner then ergosterol transforms to precalciferol. In the next step of the reaction transformation of precalciferol into strongly antirachitic vitamin D_2 – Calciferol occurs, the stereochemical relationship between the methyl group at C-10 and the hydrogen atom at C-9 is particularly important.

The conrotatory ring opening of the cyclohexadine ring (ring B) of ergosterol gives precalciferol in which the methyl group on C-10 points towards C-9 of the steriod

system and the central double bond 6,7 is cis. Scheme-**3**, which is showing the changes in ergosterol by irradaition with UV light (~ 280 nm) is given below.

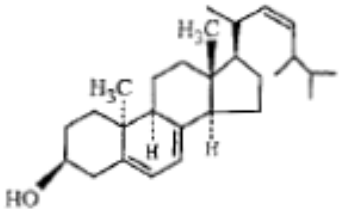


Scheme-3 : Changes in ergosterol by irradaition with UV light (~ 280 nm)

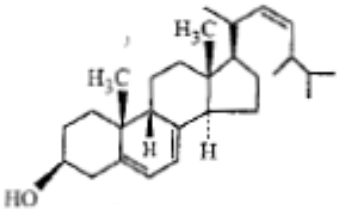
On irradiated, isomerisation of precalciferol about the 6, 7 double bond (to *trans*) takes place to give tachysterol. When this is further irradiated, ring closure occurs to give luminsterol in which the methyl group at C-10 and the hydrogen atom at C-

9 are still trans, but now the methyl group at C-10 are in the α- configuration and the hydrogen at C-9 in the β- configuration.

The most important reaction of precalciferol, from biological point of view, is its transformation into calciferol (vitamin D_2) on heating via a [1,7] sigmatropic rearrangement. Further heating of precalciferol as well as calciferol results in the formation of a mixture of pyrocalciferol and isopyrocalciferol.



Pyrocalciferol

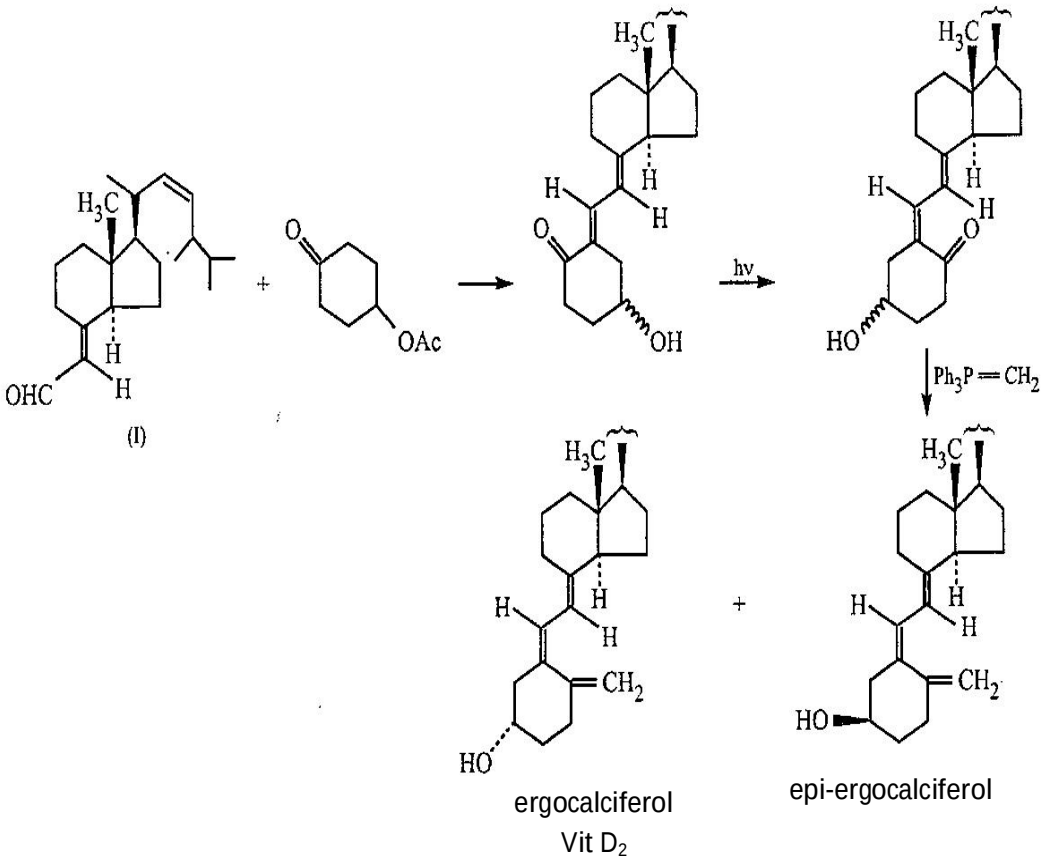


Isopyrocalciferol

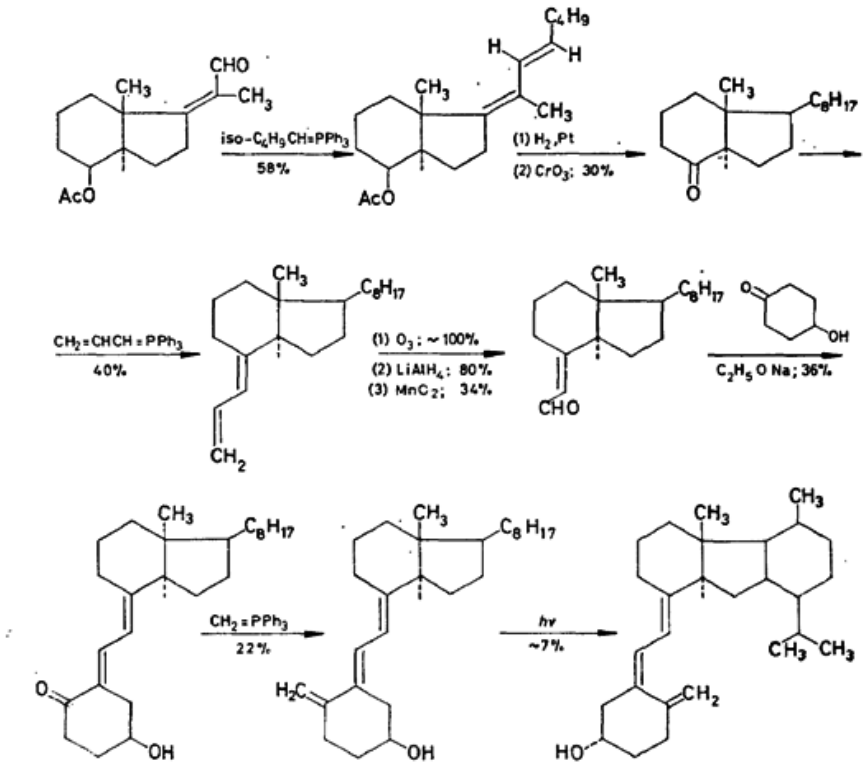
D_1 is simply an equimolar mixture of vitamin D_2 (calciferol) and lumisterol. However, vitamin D_1 was originally named as calciferol by the Medical Research Council (1931), but the Council retained the original name calciferol for vitamin D_2. Name ergocalciferol for vitamin D_2 was proposed by the Chemical Society (1951).

20.3.1 Synthesis

Partial synthesis of ergocalciferol (vitamin D_2) from the aldehyde (I) was given by Lythgoe *et al*. (1958) which as follows (Scheme-4):



Scheme – 4 : Vitamin D Synthesis: Lythgoe *et al.*

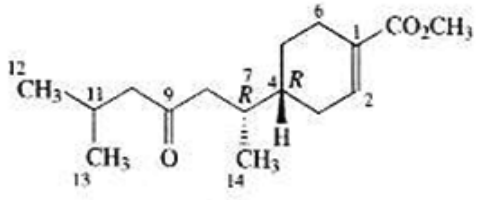


Scheme 5 : Vitamin D Synthesis: Inhoffen

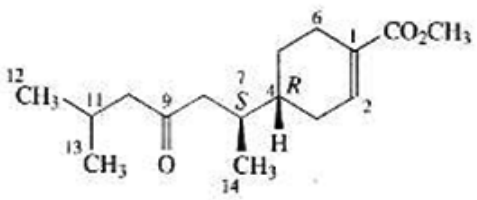
Several other vitamins of this group are also known, viz., D_3, D_4, D_5, D_6, and D_7.

20.4 Juvabione

Juvabione is a terpene derived keto ester that has been isolated from various plant sources. There are two stereoisomers both of which occur naturally with R configuration at C-4 of the cyclohexene ring. These are referred to as erythro and threo juvabione. Juvabione exhibits "juvenile hormone" activity in insects; that is, it can modify the process of metamorphosis.



threo-juvabione

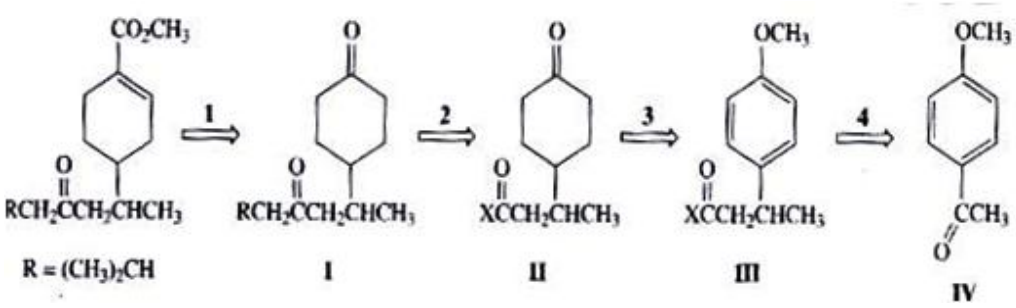


erythro-juvabione

20.4.1 Retrosynthetic analysis

In its retrosynthetic analysis two factors draw special attention to the bond between C-4 and C-7. Stereochemistry of the molecule is established by this bond. The C-4 and C-7 carbon are both chiral and their relative configuration determines which diasteromeric structures will be obtained. In the controlled synthesis it is necessary to establish the desired stereochemistry at C-4 and C-7. The C(4) –C(7) bond also connects the side chain to the cyclohexene ring. As we know a cyclohexane derivative would make a logical candidate for one key intermediate the C(4) – C(7) bond is a potential bond disconnection.

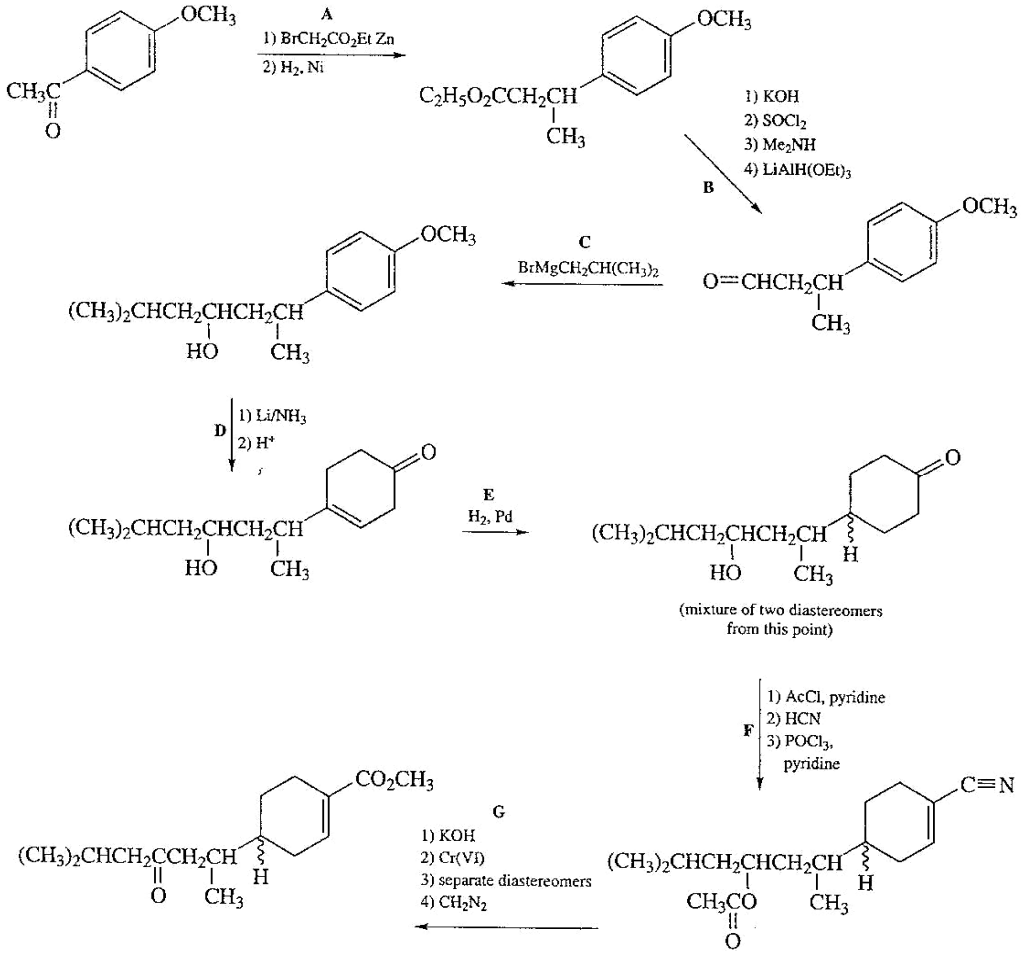
Other bonds which merit attention are those connecting C-7 through C-11. These could be formed by one of the many methods for synthesis of ketoens. The only other point of functionality is the conjugated unsaturated ester. This functionality is remote from the stereochemical centres and the ketone functionality, and in most of the reported syntheses, it does not play a key role. Some of the existing syntheses use similar types of starting materials. Those in Schemes 7 and 8 lead back to a para – substituted aromtic ether. The syntheses in Scheme **10** begin with an accessible terpene intermediate.



Scheme 6: Retrosynthetic Analysis of Juvabione with Disconnection to p- Methoxyacetophenone

A retrosynthetic analysis in Scheme 6 leading to the key intermediates used by the syntheses in Schemes 6 and 7. Here the first disconnection is that of the ester functionality. Hence it can be concluded that the ester group can be added late in the synthesis. Disconnection 2 represents the C(9)-C(10) bond as one that can be readily formed by addition of some nucleophilic group corresponding to C(10)-C(13) to the carbonyl center at C-9. The third retrosynthetic analysis recognizes that the cyclohexanone ring might be obtained by a Birch reduction of an appropriately substituted aromatic ether. The methoxy substituent would provide

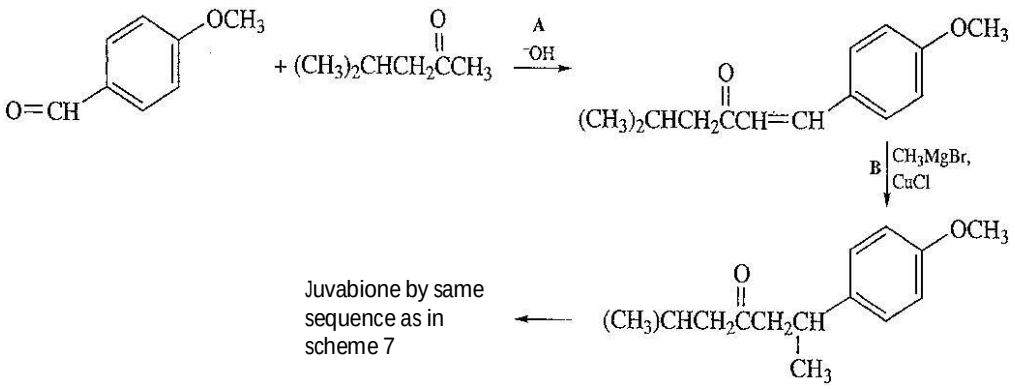
for correct placement of the cyclic carbonyl group. The last disconnection shows a simple starting material, 4- methoxyacetophenone.



Scheme 7: Juvabione Synthesis: K. Mori and M. Matsui

20.4.2 Synthesis

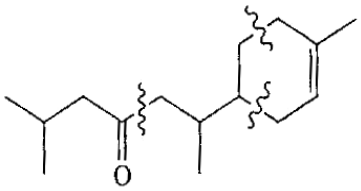
Scheme 7 shows the synthesis corresponding to this pattern. It relies on well-known reaction types. The C(4)-C(7) bond is made by a Reformatsky reaction, and this is followed by benzylic hydrogenolysis. Step **B** and **C** introduce the C-(10)-C(13) isobutyl group. The C(9)-C(10) bond connection is done by a Grignard addition reaction in step **C**. In this synthesis, the relative configuration at and C-4 and C-7 is established in step E by the hydrogenation. In principle, this reaction could be diastereoselective if the adjacent stereocenter at C-7 strongly influenced the direction of addition of hydrogen. In practice, a mixture of isomers was obtained and the reduction is not very selective. Steps **F** and **G** introduce the C-1 ester group.



Scheme 8: Juvabione Synthesis: K.S. Ayar and G.S.K Rao

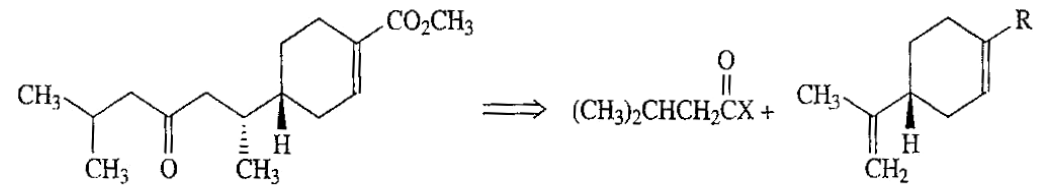
Scheme **8** represents the synthesis by using an aromatic starting material and follows a retrosynthetic plan corresponding to that in Scheme 6. This synthesis is somewhat more convergent in that the entire side chain, except for C-14, is introduced as a single unit. The C-14 methyl is introduced in step B by a copper – catalyzed conjugate addition.

Scheme **9** shows a retrosynthetic outline for the syntheses in Schemes 10 and 11. The common feature of these syntheses is the use of terpene – derived starting materials. Juvabione has the terpenoid structure hence such a starting material is suggested. Juvabione can be divided into "isoprene units". Furthermore, the terpenoid precursors can establish the configuration at C-4.



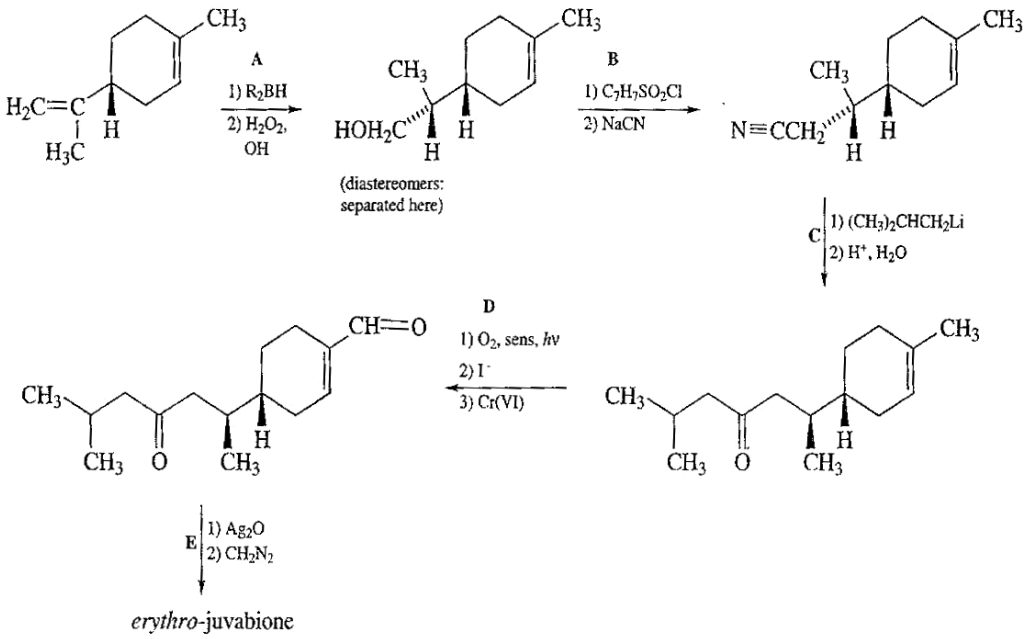
Isoprene Units in Juvabione

The synthesis shown in Scheme 10 used limonene as the starting material (R = CH_3 in Scheme 9) while Scheme 11 uses the corresponding aldehyde (R= -CH=O) (perillaldehyde).



Limonene (R = CH_3) [3]

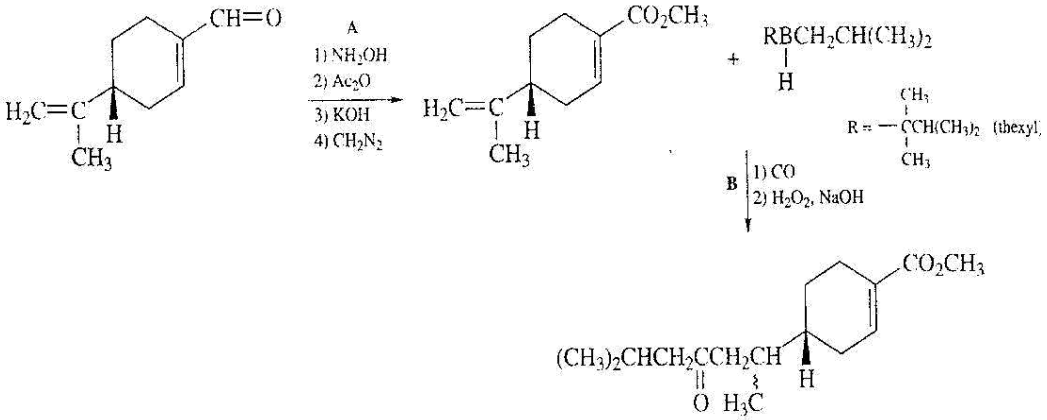
Scheme 9: Retrosynthetic Analysis of Juvabione with disconnection to the terpene Limonene



Scheme 10: Juvabione Synthesis : B.A. Pawson, H. C. Cheung, S. Gurbaxani and G. Saucy.

The use of these starting materials focuses attention on the means of attaching the C-9-C-13 side chain. Furthermore, enantioselectivity controlled by the chiral center at C-4 of the starting material might be feasible. Synthesis in Scheme 10 represents that the C-4-C-7 stereochemistry is established in the hydroboration which is the first step of synthesis. Unfortunately, this reaction shows only very modest stereo-slectivity, and a 3:2 mixture of diastereomers was obtained and separated. The subsequent steps do not affect these chiral centers. The synthesis in Scheme 10 uses a three- step sequence to oxidize the C-15 methyl group at step D. The first reaction is oxidation by singlet oxygen to give a mixture of hydroperoxides, with oxygen bound mainly at C-2. The mixture is reduced to the corresponding alcohols, which are then oxidized to the acid via an aldehyde intermediate.

A very short synthesis is shown in Scheme 11. In this synthesis, the side chain is added in one step by a borane carbonylation reaction. The first four steps are used to transform the aldehyde group in the starting material to a methyl ester. The stereochemistry at C-7 is established in step B in the hydroboration, where the C (7)-H bond is formed. A 1 : 1 mixture of diastereomers was formed, indicating that the configuration at C- 4 did not influence the direction of approach of the borane reagent.



Scheme 11: Juvabione Synthesis : E. Negishi, M. Sabanski, J. J. Katz and H. C. Brown

20.5 Summary

Reserpine

Reserpine is a tranquillizing drug and used for the treatment of some mental disorders and also for the reduction of hypertension. Its total synthesis was given by R.B. Woodward *et al*. The strategy was based on building five contiguous stereocentres into a decalin derivative which could be opened to a monocyclic compound that would form ring E.

Vitamin D

Ergosterol is the most widely investigated provitamin D. It undergoes a photochemical ring opening to give a compound called precalciferol. All the provitamins for vitamin D have the same structure except for variations in the side chain at C-17 of the steroid ring.

Partial synthesis of ergocalciferol (vitamin D_2) from the aldehyde was given by Lythgoe et al (1958).

Juvabione

Juvabione has the terpenoid structure. There are two stereoisomers both of which occur naturally with R configuration at C-4 of the cyclohexene ring. These are referred to as erythro and threo juvabioine.

In its retrosynthetic analysis the bond between C-4 and C-7 has special attention, as stereochemistry of the molecule is established by this bond. The C-4 and C-7 carbon are both chiral and their relation configuration determines which diasteromeric structures will be obtained. Other bonds which merit attention are those connecting C-7 through C-11.

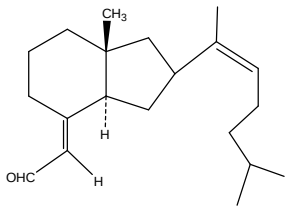
20.6 Review Questions

1 Discuss an enantioselective synthesis of Juvabione.

2 Outline a total synthesis of Reserpine.

3 Discuss the series of changes that occur when ergosterol is irradiated with UV light. What happens when and precalciferol is heated?

4 An aldehyde is given below, how will you synthesize Vitamin D_2 by it?



5 Indicate the isoprene units in Juvabione and Outline a synthesis of Juvabione starting from limonene.

20.7 Reference and Suggested Readings

- Advanced Organic Chemistry Part-B, F. A. Carey and R. J. Sundberg, 5th Ed. Springer.
- Principles of Organic Synthesis, R.O.C. Norman and J. M. Coxon, CRC Press.
- Organic Synthesis through Disconnection Approach, P.S. Kalsi, MEDTEC.
- ssOrganic Synthesis, Jagdamba Singh and L.D.S. Yadav, Pragati