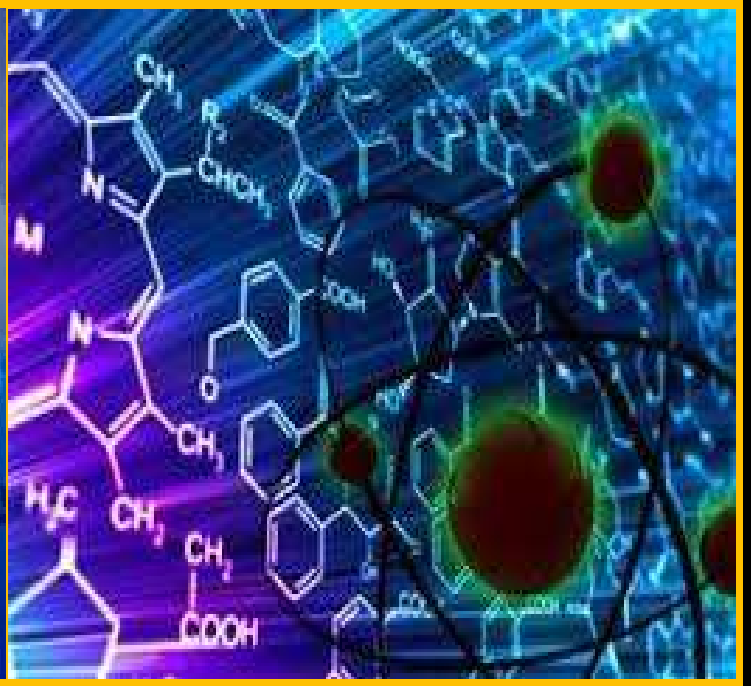
MSCCH-606

M. Sc. IV Semester

ORGANIC SYNTHESIS



SCHOOL OF SCIENCES
DEPARTMENT OF CHEMISTRY
UTTARAKHAND OPEN UNIVERSITY

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UNIT-1 ORGANOMETALLIC REAGENTS

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1.8 Other elements; B and Si compounds.
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1.1 OBJECTIVES

After studying this module, you shall be able to:

- Know about the principles of Organic reagents.
- Know about the preparations of Organic reagents.
- Know about the properties of Organic reagents.
- Know about the synthesis of different Organic reagents.
- Learn about metallocenes and their basic structure

1.2 INTRODUCTION

Compounds with a metal-carbon link are referred to as organometallic compounds. Metals and carbon have very different electronegativities, making them very polar in nature. Although many substances considered to be organometallic in nature do not have a metal carbon link, this classification is not entirely clear. There is no metal-carbon link in the Wilkinson catalyst ($RhCl_2(PPh_3)_2$), a prominent organometallic catalyst for hydrogenation reactions. As a result, the above definition of organometallic compounds may be modified to include compounds that have metal- electronegative atom linkages.

Organometallic compounds are substances that have direct, more or less polar connections between carbon atoms and metal atoms. Although most of its uses have just recently been found, organometallic chemistry has expanded significantly since Zeise created the first organometallic chemical, $K[PtCl_3(CH_2 =CH_2)$, in 1827. Some of the important factors in the rapid development of organometallic Chemistry are the selectivity of organometallic complexes in organic synthesis (discovered with Grignard reagents at the end of the 19th century), 2,3, and the intriguing function that metals play in biological systems (e.g. enzymes, hemoglobin, etc.).

One of the most interesting properties of organometallic compounds is their ability to control as homogeneous catalysts in reactions when all of the reactants are concentrated in a single phase, often a liquid. Different actions of transition metal complexes in the catalytic process include bringing the substrates together, activating the substrates by coordinating to the metal, and reducing the activation energy of the interaction between the substrates. Because the

reactants interact with the metallic complex, using a homogeneous catalyst in a process typically opens up a new channel. These interactions allow for the rapid completion of thermodynamically favorable processes that take a long time to reach equilibrium. As a result, homogenous catalysts can be used to synthesis substances that are difficult to acquire using standard techniques.

1.3 PROPERTIES OF ORGANOMETALLIC COMPOUNDS

Organic reagents having following characteristic properties.

- They have relatively low melting points.
- They are insoluble in water.
- They are soluble in ether.
- They are highly reactive. That is why they are kept in organic solvents.
- In organometallic compounds, carbon has an electronegativity of 2.5 while most metals have electronegativities less than 2.0.
- The majority of organometallic compounds, especially those containing aromatic or ring-structured hydrocarbon groups, are solid.
- The metal-carbon atom link is usually covalent in character.
- These compounds, especially those produced by highly electropositive metals, have the ability to reduce.
- Highly electropositive metals, such as sodium or lithium, are highly volatile and can spontaneously fire.
- In many cases, organometallic compounds have been shown to be harmful to people.

1.4 CLASSIFICATION OF ORGANOMETALLIC COMPOUNDS

Organic reagents can be classified in to following classes-

a) Main group organometallic compounds

b) Transition metal organometallic compounds

c) Lanthanide and actinide organometallic compounds

(a) Main Group Organometallic Compounds:

These organometallic compounds have s or p – block elements (metals) in them. The most common example of a main group organometallic compound is Grignard reagent –RMgX. Cacodyl oxide $[(CH_3)_2As]_2O$ was the first main group organometallic compound which was isolated by Louis Claude Cadet de Gassicourt in 1760. Other examples include organoborane, $AlEt_3$, etc

(b)Transition Metal Organometallic Compounds:

In these organometallic compounds d-block metals are present. Following are the main examples of transition metal organometallic compounds –

- **Gillmann's Reagent –** R_2CuLi
- **Collmann's Reagent –** $[Fe(CO)_4]^{2-}$
- **Wilkinson's Catalyst -** $[Rh(PPh_3)_3Cl]$
- **Palladium Catalyst –** $Pd(PPh_3)_4$ for coupling reaction is also an example of a transition metal organometallic compound.
- **Vaska's Complex –** $[Ir(PPh_3)(CO)Cl]$

(Image will be added soon)

(c) Lanthanide and Actinide Organometallic Compounds:

In these organometallic compounds f-block metal/s are present. Following are the main examples of lanthanide and actinide metal organometallic compounds-

- Uranocene

- Cyclopentadienides ($C_5H_5^-$) Compound

1.5 APPLICATIONS OF ORGANOMETALLIC COMPOUNDS

Organometallic compounds are very useful in various fields. A few of them are listed below –

1. Organometallic compounds are used as reagents.
2. Wilkinson's catalyst is used in the hydrogenation of alkenes.
3. Ziegler – Natta catalyst [$(C_2H_5)_3AlTiCl_4$] is used for the polymerization of alkenes.
4. Organoarsenic compounds are used for the treatment of syphilis.
5. Palladium catalysts are used in coupling reactions.
6. The Grignard reagent is used in the synthesis of many compounds such as secondary alcohols, aldehydes, etc.
7. Organometallic compounds have a wide range of industrial applications. Such an organolithium is highly basic and so useful in many polymerization reactions stoichiometrically.
8. Cp_2TiCl_2 (Cp is cyclopentadienyl anion) organometallic compound is used as a drug.
9. Cis-Platin is used as an anticancer drug.
10. Organometallic compounds are used as additives such as TEL (Tetraethyl lead) is used as an anti-knocking agent in fuels.

1.6 GROUP I AND II METAL ORGANIC COMPOUNDS Li, Hg AND Zn COMPOUNDS

1.6.1 Organo Magnesium Halides or Grignard reagents:

Organometallic compounds known as Grignard reagents are very helpful in the study of organic chemistry. They possess potent nucleophilic properties and the capacity to create fresh carbon-carbon bonds. As a result, they exhibit traits that organolithium reagents also exhibit, and the two reagents are seen as being similar.

What are Grignard Reagents?

Organomagnesium compounds, such as Grignard reagents, have the chemical formula R-Mg-X, where R denotes an alkyl or aryl group and X denotes a halogen.

A Grignard reagent or Grignard compound is a chemical compound with the generic formula R−Mg−X, where X is a halogen and R is an organic group, normally an alkyl or aryl. Two typical examples are methylmagnesium chloride $Cl{-}Mg{-}CH_3$ and phenylmagnesium bromide $(C_6H_5){-}Mg{-}Br$. They are a subclass of the organomagnesium compounds. Grignard compounds are popular reagents in organic synthesis for creating new carbon-carbon bonds. For example, when reacted with another halogenated compound R'−X' in the presence of a suitable catalyst, they typically yield R−R' and the magnesium halide MgXX' as a byproduct; and the latter is insoluble in the solvents normally used. In this aspect, they are similar to Organolithium reagents.

Pure Grignard reagents are extremely reactive solids. They are normally handled as solutions in solvents such as diethyl ether or tetrahydrofuran; which are relatively stable as long as water is excluded. In such a medium, a Grignard reagent is invariably present as a complex with the magnesium atom connected to the two ether oxygens by coordination bonds.

1.6.1.1 Preparation of Grignard Reagents:

The carbon atom of organic halide which is directly attached to the halogen is, of course, electrophilic. This electrophilic reactivity can be switched to nucleophilic reactivity by conversion to an organomagnesium halide, i.e., a Grignard reagent.

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

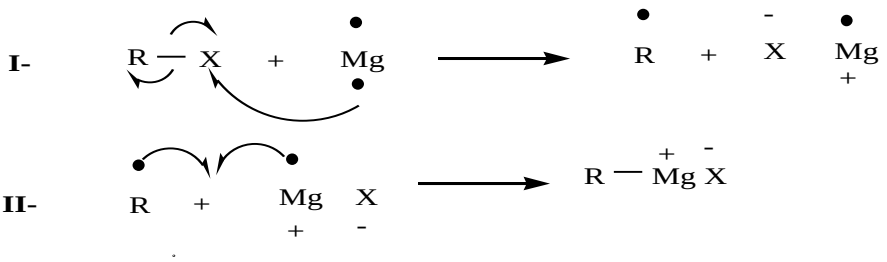
For example, where R is CH_3 and X is Cl then-

$$CH_3Cl + Mg \xrightarrow{\text{Ether}} CH_3MgCl$$

The carbon-magnesium bond in a Grignard reagent is polar and covalent with carbon being the negative end of the dipole. Thus the nucleophilicity of carbon in a Grignard reagent. Note also that the magnesium-halogen bond is largely ionic, as shown in the structure above.

Mechanism:

The mechanism of formation of a Grignard reagent is shown below. It involves radical intermediates. There is one major difference that should be noted. Grignard formation does not involve a radical chain mechanism. It is a non-chain radical reaction.

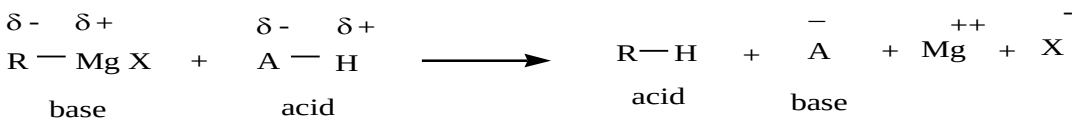


The first step is rate-determining and involves the transfer of one electron from Mg (which has two electrons in its valence shell) to the carbon-halogen bond. This forms Mg^{+1}, which is a radical. This then couples with the alkyl radical formed.

1.6.1.2 Chemical reactions of Grignard Reagent:

1. Reactions with Compounds containing acidic hydrogen:

Grignard reagents react with compound having acidic hydrogen to form hydrocarbon. The reaction is an example of acid base reaction because in this reaction it behaves as a base.



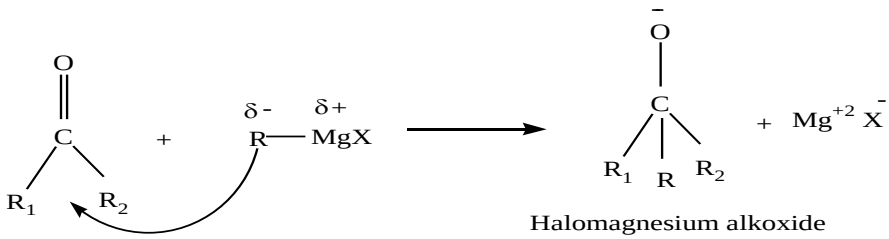
Where A-H = HOH, C_6H_5OH, ROH, RSH, C_6H_5SH, RCOOH, $RCONH_2$, NH_3, RNH_2, R_2NH, HX, H_2SO_4, H_3PO_4 etc.

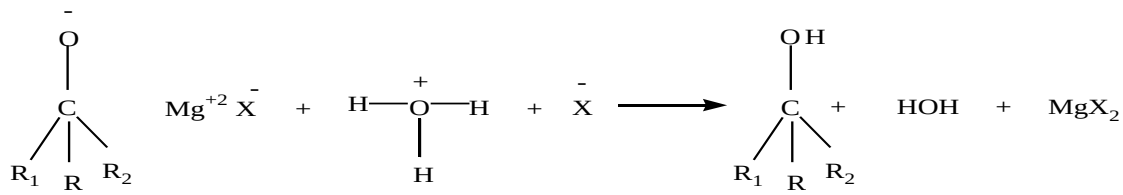
2. Nucleophilic addition reactions:

(i) Addition with aldehyde and ketones:

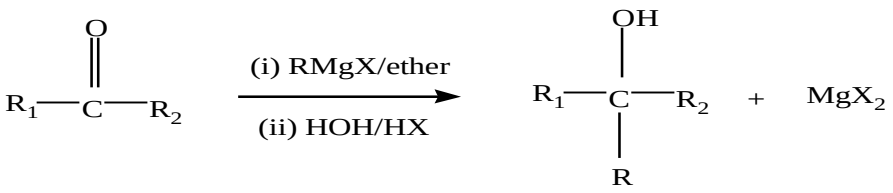
Addition of a Grignard reagent to a carbonyl compound is a versatile reaction that leads to the formation of a new bond. The reaction can produce compounds with a variety of structures because both the structure of the carbonyl compound and the structure of the Grignard reagent can be varied.

Grignard reagents react with carbonyk compound (aldehyde and ketones) in the following way:

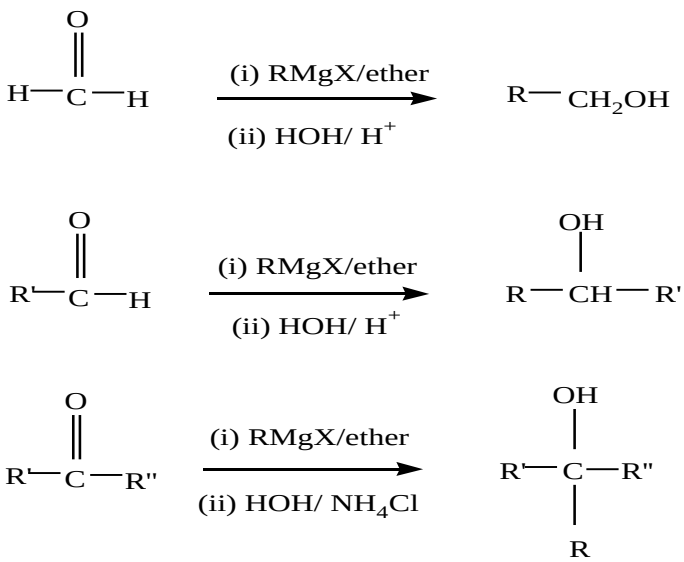




The overall reaction is:

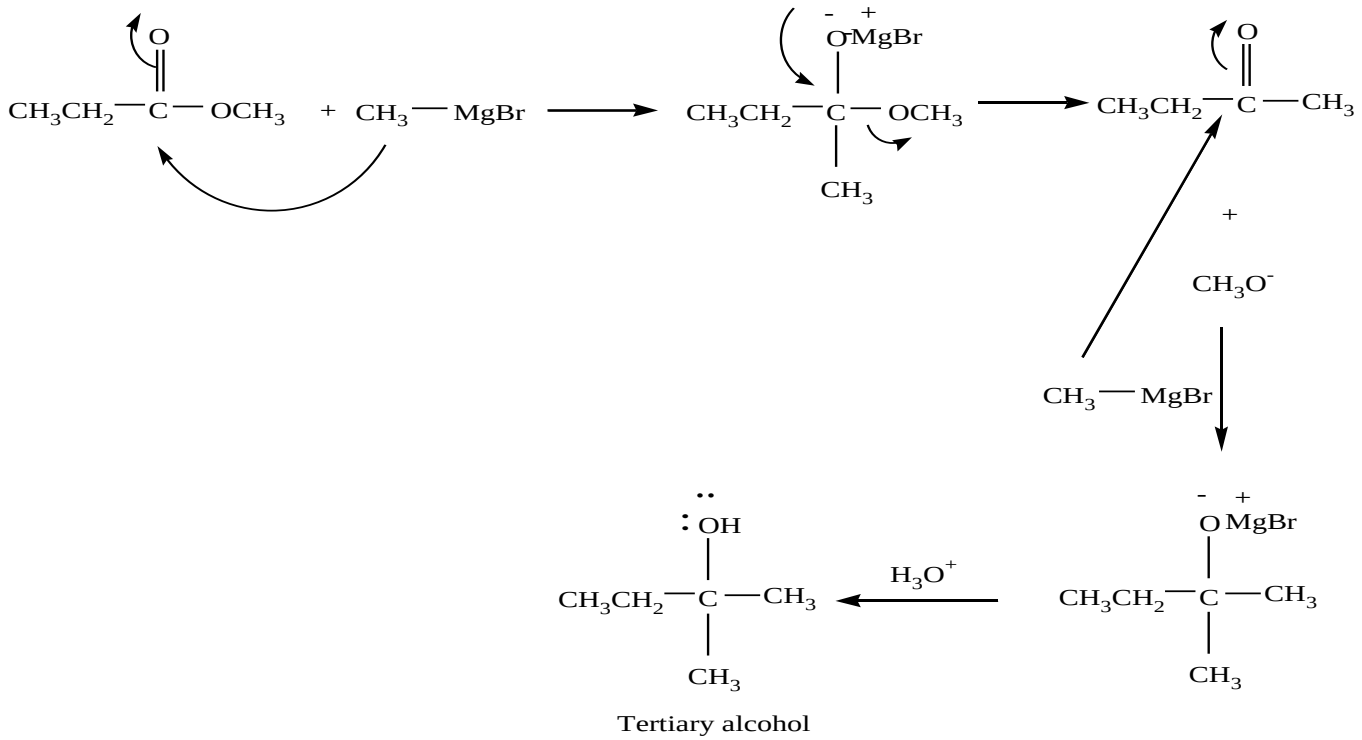


Some other examples of Grignard reagents with carbonyl compounds.



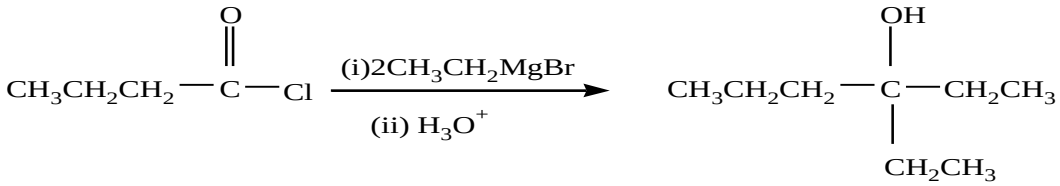
(ii) Reaction with esters:

When an ester reacts with a Grignard reagent, the first reaction is a *nucleophilic acyl substitution reaction* because an ester, unlike an aldehyde or a ketone, has a group that can be replaced by the Grignard reagent. The product of the reaction is a ketone. The reaction does not stop at the ketone stage, however, because ketones are more reactive than esters toward nucleophilic attack. Reaction of the ketone with a second molecule of the Grignard reagent forms a tertiary alcohol. Because the tertiary alcohol is formed as a result of two successive reactions with a Grignard reagent, the alcohol has two identical groups bonded to the tertiary carbon.



(iii) Reaction with Acid Chlorides

Tertiary alcohols are also formed from the reaction of two equivalents of a Grignard reagent with an acyl halide.

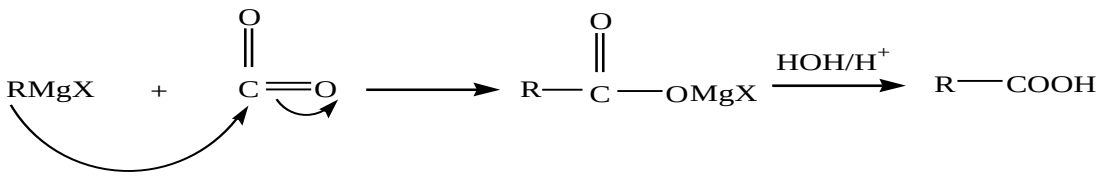


butyryl chloride

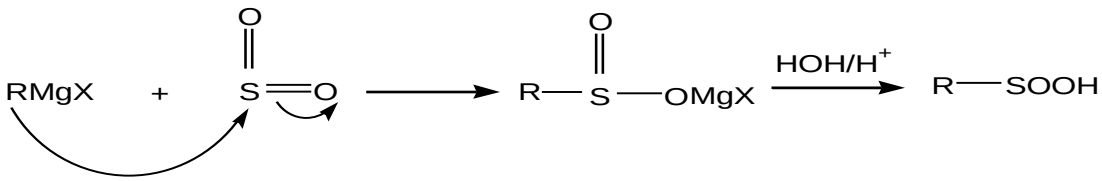
3-methyl-3-hexanol

(iv) Addition reaction with CO_2, SO_2 and CS_2:

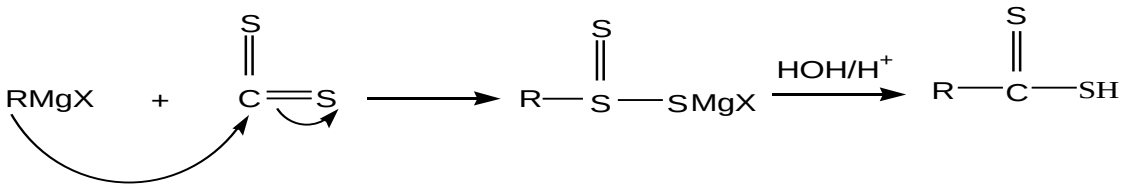
(a) Addition with CO_2: Carboxylic acids are formed as a result of addition of Grignard reagent to CO2.



(b) Addition with SO_2: Grignard reagents react with sulphur dioxide to give addition product which on acid hydrolysis gives alkanesulphonic acid.



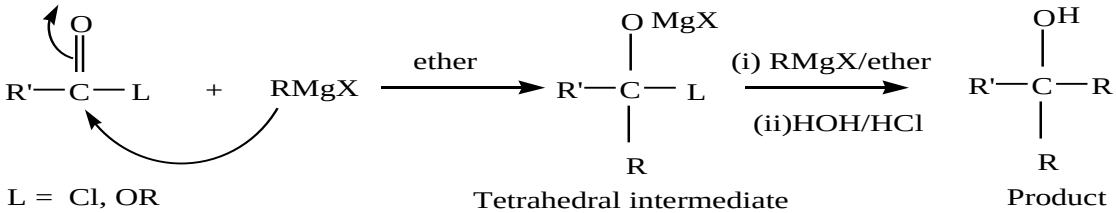
(c) Addition with CS_2: Grignard reagents react with carbon disulphide to give addition product which on acid hydrolysis gives thionic acid.



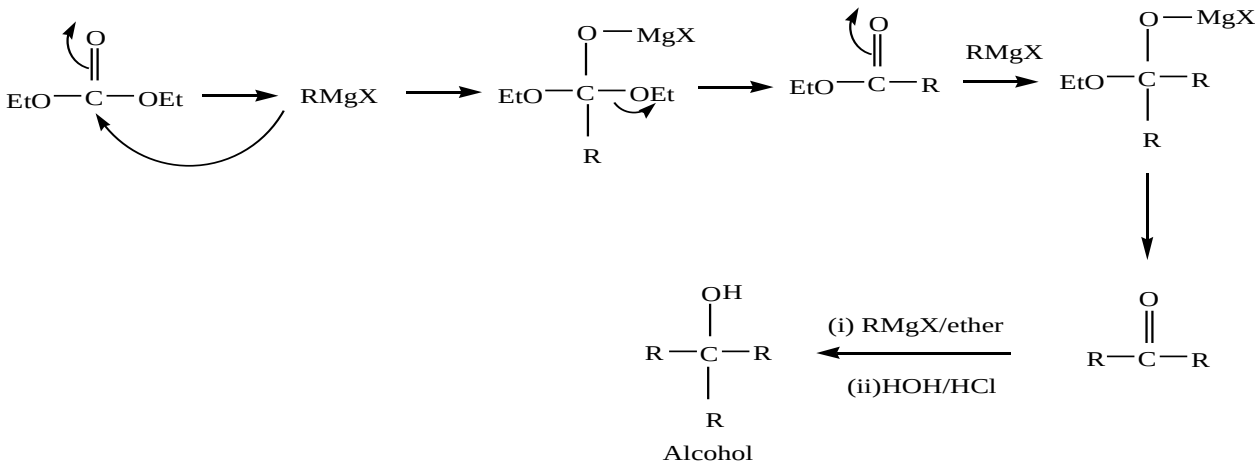
3. Nucleophilic substitution reaction at SP^2 hybrid carbons:

(i) Reaction with acid chlorides, esters, Amides and Lactones:

Acid chloride, esters and lactones react with two equivalents of Grignard reagents to give alcohols, the first equivalent leads to an aldehyde and ketone which react with second equivalent of the reagent in the given reaction.



(ii) Reaction with carbonate: Carbonates react with Grignard reagents to give esters if one equivalent is used, ketones if two equivalents are used, or tertiary alcohols if excess of Grignard reagents is added.



1.6.2 Organolithium Reagents:

In organometallic chemistry, organolithium reagents are chemical compounds that contain carbon–lithium (C–Li) bonds. These reagents are important in organic synthesis, and are frequently used to transfer the organic group or the lithium atom to the substrates in synthetic steps, through nucleophilic addition or simple deprotonation. Due to the large difference in electronegativity between the carbon atom and the lithium atom, the C−Li bond is highly ionic.

1.6.2.1 Preparation of Organolethium compound:

1. Metals with Organic Halides:

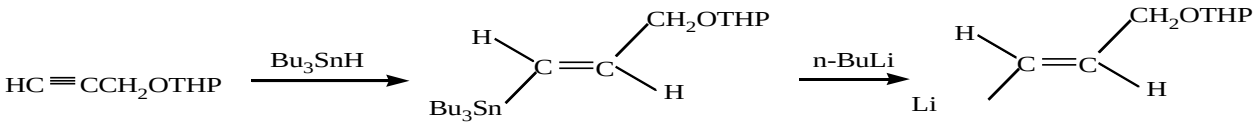
The reaction of a metal with an organic halide is a convenient method for preparation of organometallic compounds of reasonably active metals such as lithium, magnesium, and zinc. Ethers, particularly diethyl ether and oxacyclopentane (tetrahydrofuran), provide inert, slightly polar media in which organometallic compounds usually are soluble.

$$CH_3Br + 2Li \xrightarrow{(CH_3CH_2)_2O} CH_3Li + LiBr$$

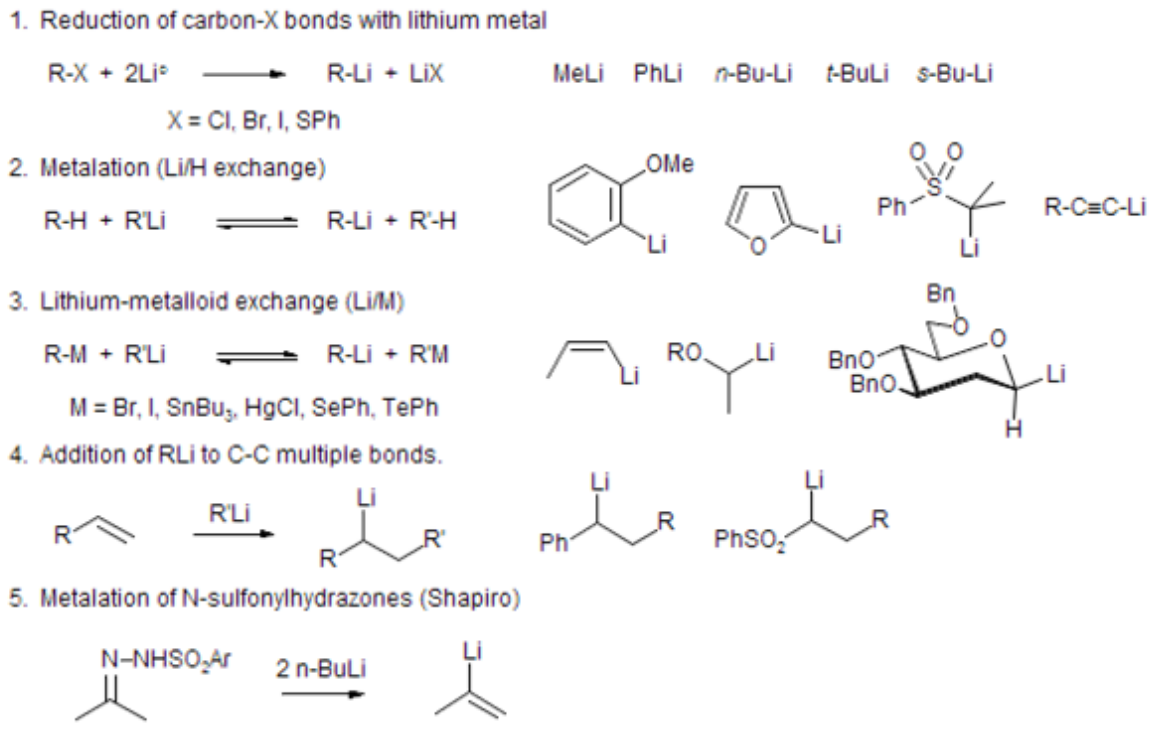
The reactivity order of the halides is I>Br>Cl≫F. whereas magnesium and lithium react well with chlorides, bromides, and iodides, zinc is satisfactory only with bromides and iodides. Mercury only reacts when amalgamated with sodium. Sodium and potassium present special problems because of the high reactivity of alkylsodium and alkylpotassium compounds toward ether and organic halides. Alkane solvents usually are necessary.

2. Preparation by Metal-Metal Exchange:

A other useful method of preparing organolithium reagents involves metal-metal exchange or transmetallation. The reaction between two organometallic compounds proceeds in the direction of placing the more electropositive metal at the more acidic carbon position. Exchanges between organotin reagents and alkyllithium reagents are particularly significant from a synthetic point of view. Terminal alkenyllithium compounds can be made from vinylstannanes, which are available by addition of stannanes to terminal alkynes.

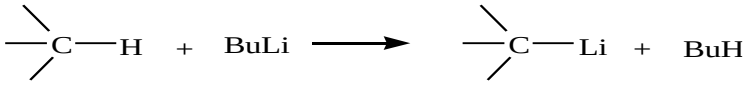


Some common preparation of organo lithium reagents:



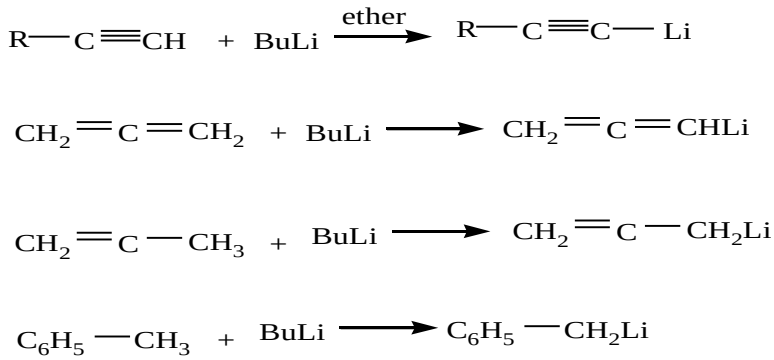
1.6.2.2 Chemical Properties of Organolithium reagents:

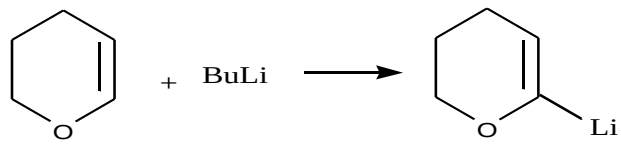
1. Deprotonation: Butyllithium will deprotonate protons that are more acidic than those of butane.

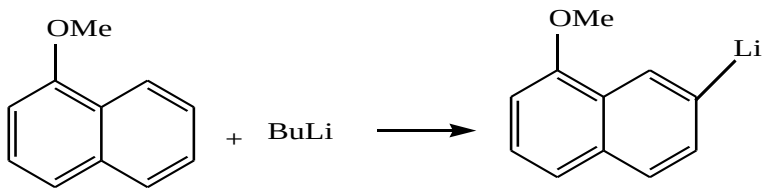


Addition of tertiary amines especially TMEDA accelerates this reaction. The reaction is also known as metalation or lithiation. This reaction is an important means of preparing a variety of organolithium compounds.

Organolithium compounds by deprotonation reaction are given in the following reactions.

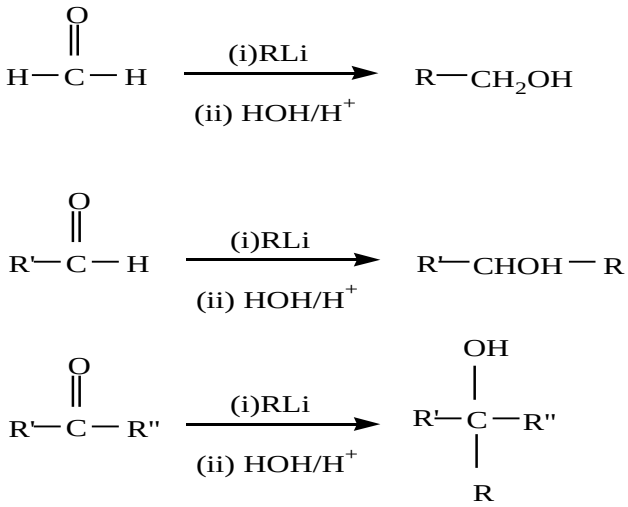






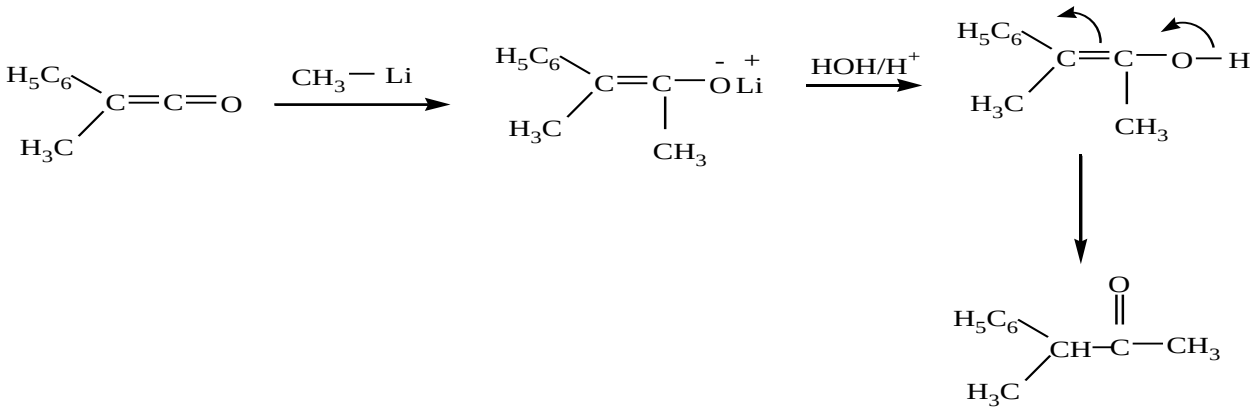
2. Nucleophilic additions:

(i) Aldehydes and ketones: Carbonyl compounds react with alkyllithium to form lithium alkoxide which on hydrolysis give hydroxyl compounds.

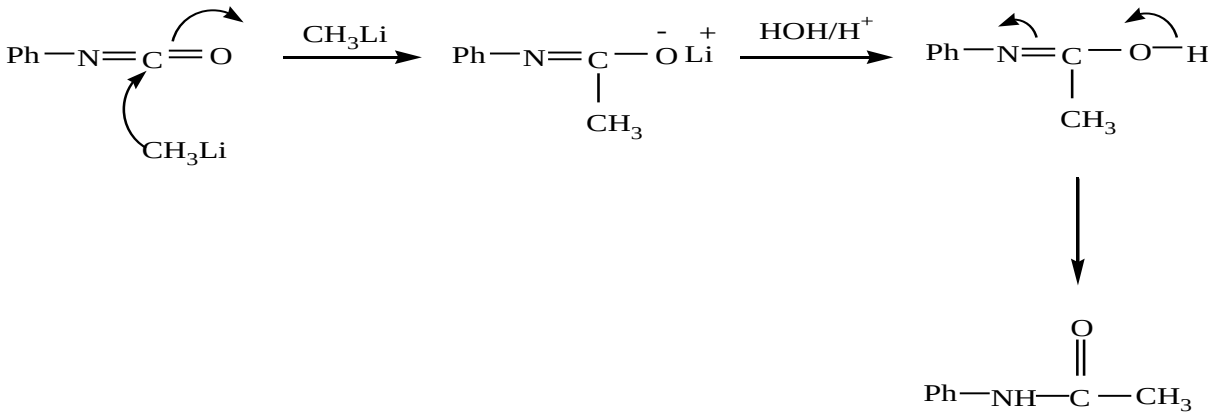


(ii) Addition with ketones and Isocyanate:

Organolitium added to ketones to give ketones. Nucleophilic attack occurs at the carbonyl group to produce an enolate which, on hydrolysis, gives ketones.

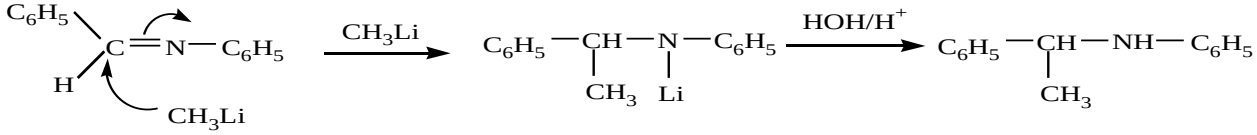


Isocyanates undergo the completely analogous reaction in which the intermediate break down to an amide.

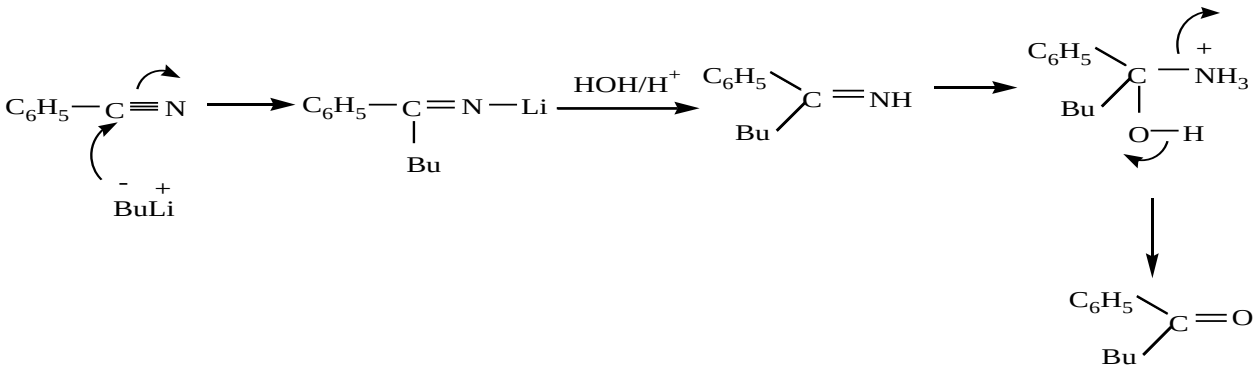


(iii) Addition reactions with Imines, Nitriles and isonitriles:

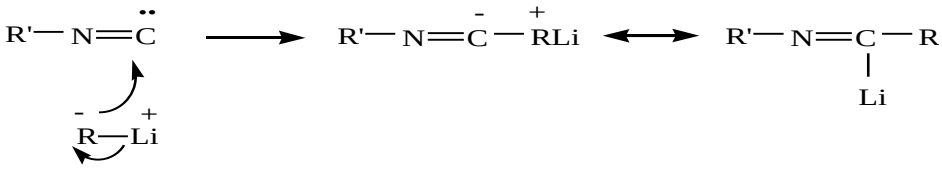
Imines: Organilithium react with imines to form amines after hydrolysis



Nitriles: Nitriles react with organolithium by nucleophilic addition reaction. The intermediate imines are hydrolysed to the corresponding ketones.

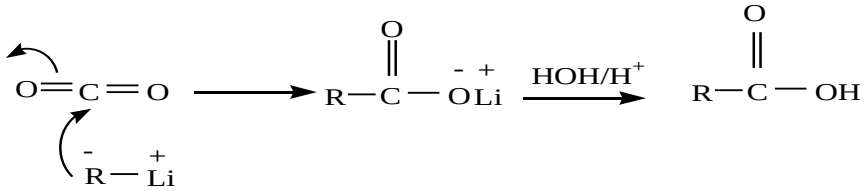


Isonitriles: Isonitriles undergo nucleophilic addition reaction with organometallic reagents to give lithioimines.

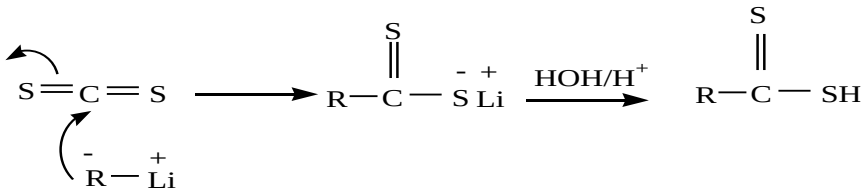


(vi) Addition reaction with CO_2 and CS_2:

(i) CO_2: Organolithium reactants add to carbon dioxide to give carboxylic acid on hydrolysis.



(ii) CS_2: Organolithium reagents react with carbon disulphide to give addition product which on acid hydrolysis, yield thioacids.



1.6.3 Organo Mercury compounds:

Organomercury chemistry refers to the study of organometallic compounds that contain mercury. Typically the Hg–C bond is stable toward air and moisture but sensitive to light. Important organomercury compounds are the methylmercury(II) cation, CH_3Hg^+; ethylmercury(II) cation, $C_2H_5Hg^+$; dimethylmercury, $(CH_3)_2Hg$, diethylmercury and merbromin ("Mercurochrome"). Thiomersal is used as a preservative for vaccines and intravenous drugs.

The toxicity of organomercury compounds presents both dangers and benefits. Dimethylmercury in particular is notoriously toxic, but found use as an antifungal agent and insecticide. Merbromin and phenylmercuric borate are used as topical antiseptics, while nitromersol is used as a preservative for vaccines and antitoxins.

1.6.3.1 Preparation Organo Mercury compounds:

(i) From alkyl halides: Simple alkyl iodides react readily with mercury under the influence of light to give alkyl mercury iodides.

$$RI + Hg \xrightarrow{h\nu} RHgI$$

(ii) From organomagnesium and organolithium compounds: Organolithium and organomagnesium compounds react with mercuric halides to give mercuric halides or dialkyl mercury.

$$HgX_2 + RLi \longrightarrow RHgX + LiX$$

$$RHgX + RLi \longrightarrow R_2Hg \quad LiX$$

$$HgX_2 + RMgX \longrightarrow RHgX + MgX_2$$

$$RHgX + RMgX \longrightarrow R_2Hg + MgX_2$$

(iii) From trialkylboranes and trialkenylboranes: Trialkylboranes react with mercuric salt to give organomercuric acetate.

$$R{-}CH{=}CH_2 \xrightarrow{BH_3/THF} (R{-}CH_2{-}CH_2)_3 \equiv R_3B$$

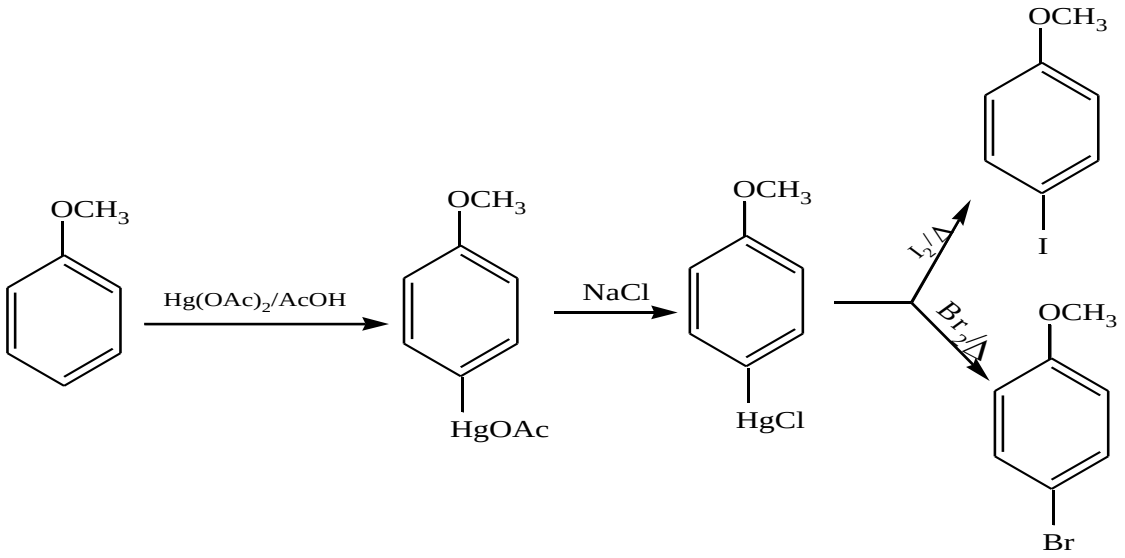
$$R_3B + 3Ag(OAC)_3 \longrightarrow 3RHgOAC$$

(iv) From aromatic carboxylic acid: Carboxilic acids react with HgX2 to give mercuric carboxylates. This on photodecarboxylation gives diaryl mercury.

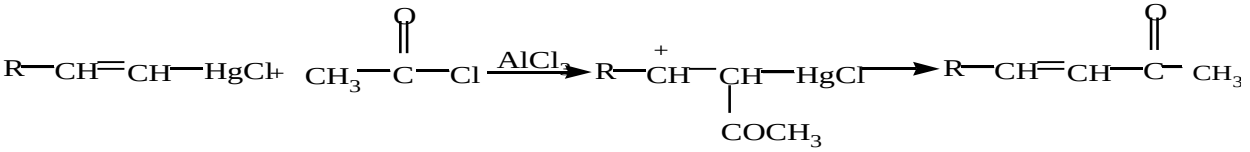
$$ArCOOH \xrightarrow{HgX_2} (ArCOO)2Hg \xrightarrow{h\nu} Ar-Hg-Ar + 2CO_2$$

1.6.3.2 Chemical reactions of Organo Mercury compounds:

(i) Electrophilic substitution reaction (Replacement of mercury by electrophiles): Aromatic compounds undergo mercuration reaction with mercuric acetate in the presence of suitable acid. The aryl mercuric salt produced can be used for the synthesis of aryl halides.



Organomercury does not react with ketones or aldehydes but Lewis acids cause reaction with acyl chloride. An Alkenyl mercury compound gives carbonyl compounds with acylchlorides.



1.6.4 Organozinc Reagents:

Organozinc reagents are one of the most important of organometallic compounds. The first instance of an organozinc compound goes back to 1849 when Edward Frankland discovered that heating a mixture of zinc and ethyl iodide gives highly pyroporric diethyl zinc. Organozinc compounds in general are sensitive to oxidation; dissolve in a wide variety of solvents whereas

protic solvents cause decomposition. Organozinc compounds also exhibit the Schlenck equilibrium like Grignard reagents (Scheme 1).

$$R_2Zn + ZnX_2 \rightleftharpoons 2RZnX$$

In terms of reactivity, organozinc compounds are less reactive than Grignard reagents. This can be explained on the basis of relative position of Mg and Zn in the periodic table. Since zinc is more electropositive than Mg thus the Zn-C bonds have a higher degree of covalency compared to the Mg-C bond. In a typical case, the electrons forming the C-Zn bond reside in two *sp* hybridized molecular orbitals resulting in linear geometry about thezinc centre.

Organozinc compounds contain carbon bonded to zinc. These compounds are less reactive than other equivalent organometallic reagents, such as organolithium reagents and Grignard reagents.

1.6.4.1 Preparation:

1. Reaction between zinc and alkyl halides:

The most important fundamental methods for preparing Organozinc compounds are the reaction between zinc and alkyl halides and the reaction between zinc halide and an organolithium compound or organomagnesium compound.

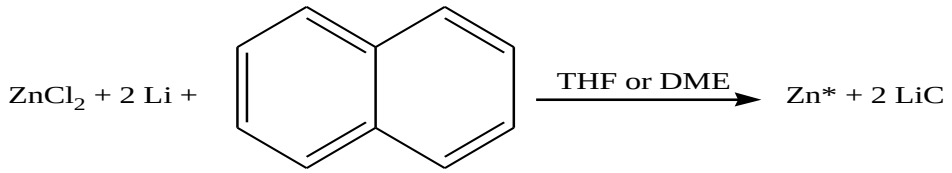
$$2RX + 2\,Zn \longrightarrow 2RZnX \rightleftharpoons R_2Zn + ZnX_2$$

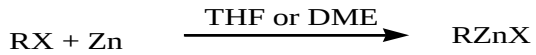
$$R{-}Li + ZnX_2 \longrightarrow RZnX + LiX \xrightarrow{R{-}Li} R_2Zn + LiX$$

$$RMgX + ZnX_2 \longrightarrow R{-}Zn{-}X + MgX_2 \xrightarrow{RMgX} R_2Zn + MgX_2$$

2. Preparation of organozinc halide using highly reactive zinc:

The zinc prepared by the reduction of ZnCl 2 with alkali metals such as Li, Na or K using electron carriers like naphthalene shows higher reactivity than the commercial zinc powder and reacts with unreactive alkyl as well as aryl bromides in less polar solvents like THF to give corresponding organozinc bromides in excellent yield.





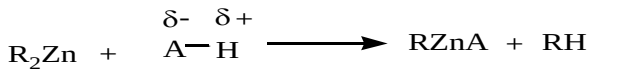
Zn* = highly reactive zinc

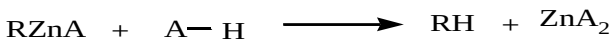
RX = 1°, 2° or 3° alkyl bromides, simple or functionalized aryl bromides and iodides

1.6.4.2 Chemical reaction of Organozinc compounds:

(1) Protonation or Reaction with compounds containing acidic hydrogen:

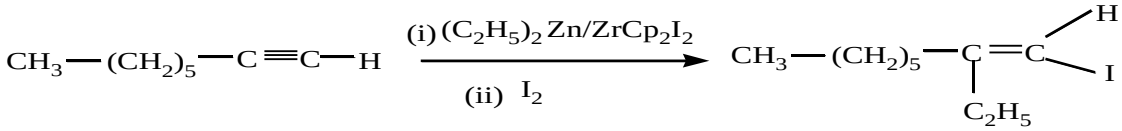
Dialkyl zinc compounds react with compounds having acidic hydrogen to form hydrocarbon. This reaction is example of acid base reaction and dialkylzinc behave as a base.

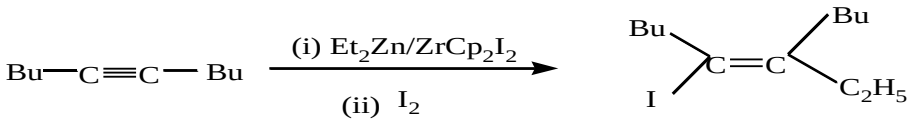




(2) Reaction with carbon-carbon multiple bonds:

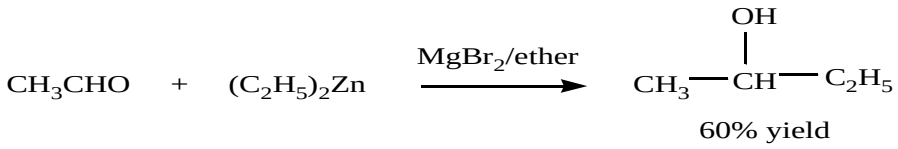
In general simple organozinc compounds are uncreative towards alkenes and non-terminal alkynes. Exceptions are allylic zinc derivatives which can add to carbon-carbon double and triple bonds. The addition is assisted by conjugation and by suitable placed electron donating groups. The addition reaction is carried out in the presence of THF/CuCN, LiCl.



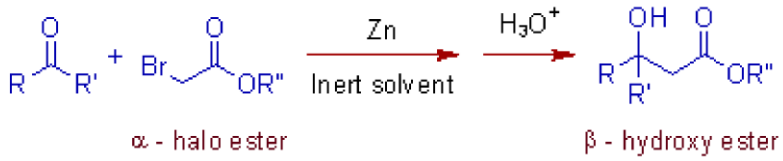


(3) Addition of carbonyl compounds:

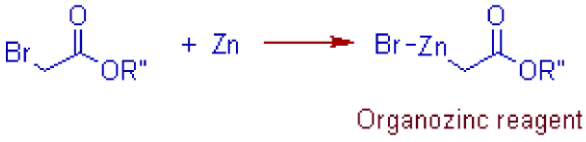
Dialkyl zinc reagents react with carbonyl compounds. Reactivity of lower dialkylzinc is more that of the higher dialkylzinc reagents. Acetaldehyde reacts with diethylzinc in few hours. The reaction with higher homologues require several days. Allylic zinc compounds are more reactivethan simple dialkylzinc reagents. Addition reaction of dialkylzinc compounds are promoted by Lewis acid metal halides.

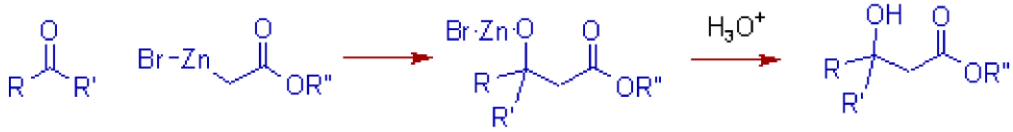


(4) Reformatsky Reaction: The **Reformatsky reaction** involves the treatment of a α-halo ester with zinc metal and subsequent reaction with aldehyde/ ketone to get β- hydroxy ester.

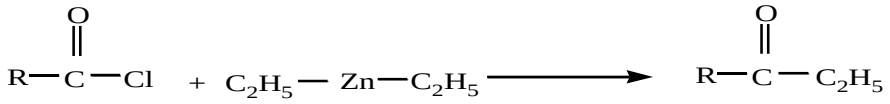


Mechanism:





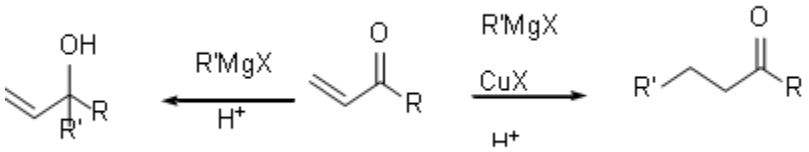
(5) Reaction with acid chloride: Organozinc compound react readily with acid chlorides to form ketone.



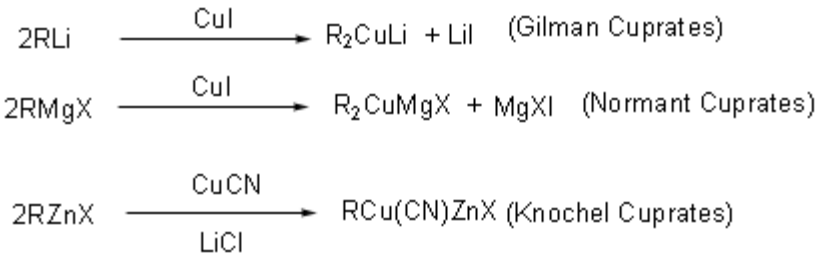
1.7 TRANSITION METALS, Pd, Ni, Fe, Ti, Cu, Rh AND Cr COMPOUNDS

1.7.1 ORGANOCOPPER REAGENTS:

The pioneering work from the Gilman group in 1936 marked the beginning of the era of organocopper reagents, describing the preparation of mono-organocopper reagents and their considerable synthetic potential in organic chemistry. The use of copper salts as catalysts in organometallic reactions has then been become popular. The observation that catalytic amounts of copper halides favored 1,4-addition over the usually observed 1,2- addition in the reaction between Grignard reagents and α,β-unsaturated ketones was of crucial importance for the further development of organocopper reagents as synthetic tools in organic chemistry.



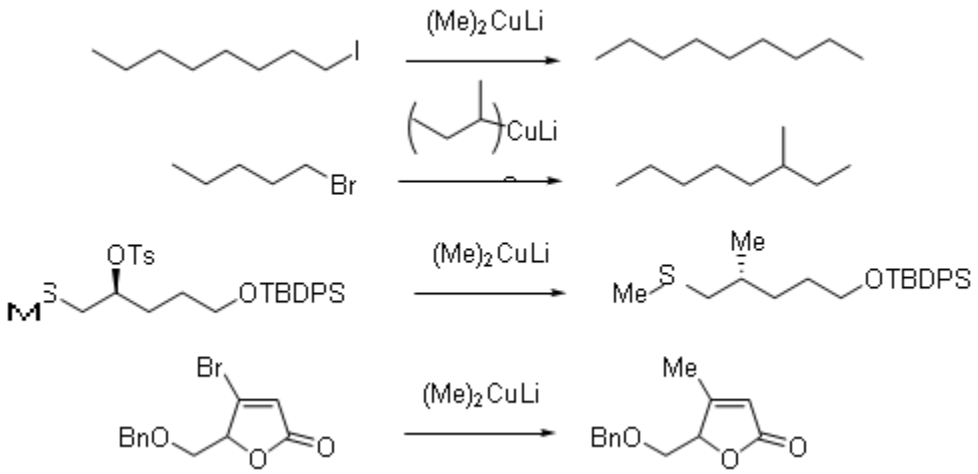
Organocopper reagents can be prepared by transmetallating the Grignard or organolithium reagent.



1.7.1.2 Chemical Reactions of Organocupper reagents:

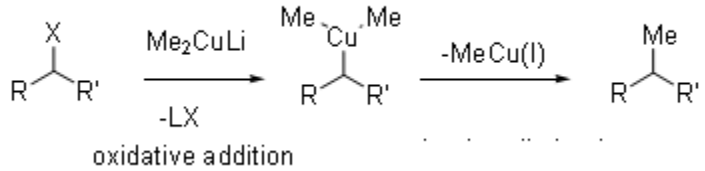
(1) Reactions with Alkyl or Aryl or vinyl Halides and Tosylates

Alkyl, aryl or vinyl halides and tosylates react with organocuprates to give cross-coupled products. The method affords an effective route for the synthesis of hydrocarbon from two different alkyl, aryl or vinyl halides.



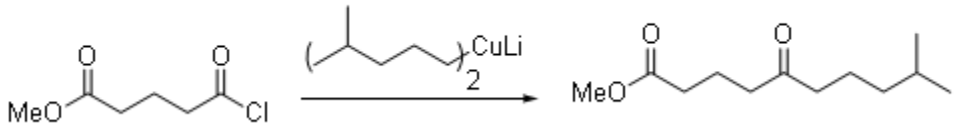
Mechanism:

The reaction takes place via oxidative addition followed by reductive elimination (Scheme 4).



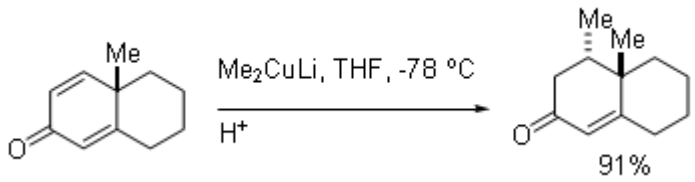
(2) Reactions with Acid Chlorides:

Acid chlorides react with organocopper reagents to give ketones (Scheme 5).



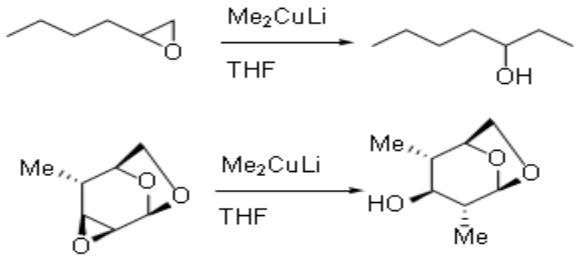
(3) Conjugate Addition

Organocopper reagents undergo 1,4-addition to α,β,γ-unsaturated carbonyl compounds. The reaction can be stereoselective. For example, the less substituted double bond undergoes reaction from the less hindered side to give stereoselective product.



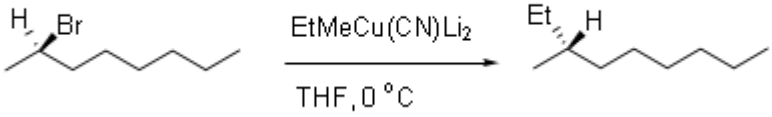
(4) Reactions with Epoxides:

Epoxide reacts with organocopper reagents at the least substituted carbon atom to provide the corresponding alcohol.



Higher Order Cuprates

The reaction of organolithium reagent with cuprous cyanide yields higher order cuprate (Scheme 10). Higher order cuprate is more reactive compared to Gilman reagent towards alkyl halides. For example, (*S*)-2-bromooctane reacts with EtMeCu(CN)Li at 0°C to give (*R*)-3-methylnonane in 72% yield (Scheme 11).



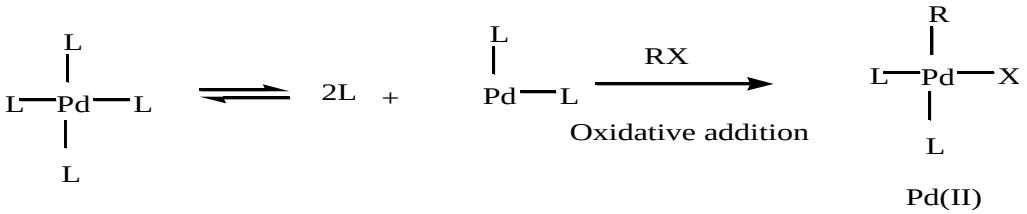
1.7.2 Organo Palladium compounds:

Organopalladium intermediates are very important in synthetic organic chemistry. Usually, organic reactions involving palladium do not involving palladium do not involve the preparation of stochiometric organopalladium reagents. Rather, Organopalladium species are generated in situ during the course of the reaction. In the most useful processes only acatalytic amount of palladium is used. The overall reaction mechanisms typically involve several steps in which Organopalladium species are formed, react with other reagents, give product, and are reagenerated in a catalytically active form.

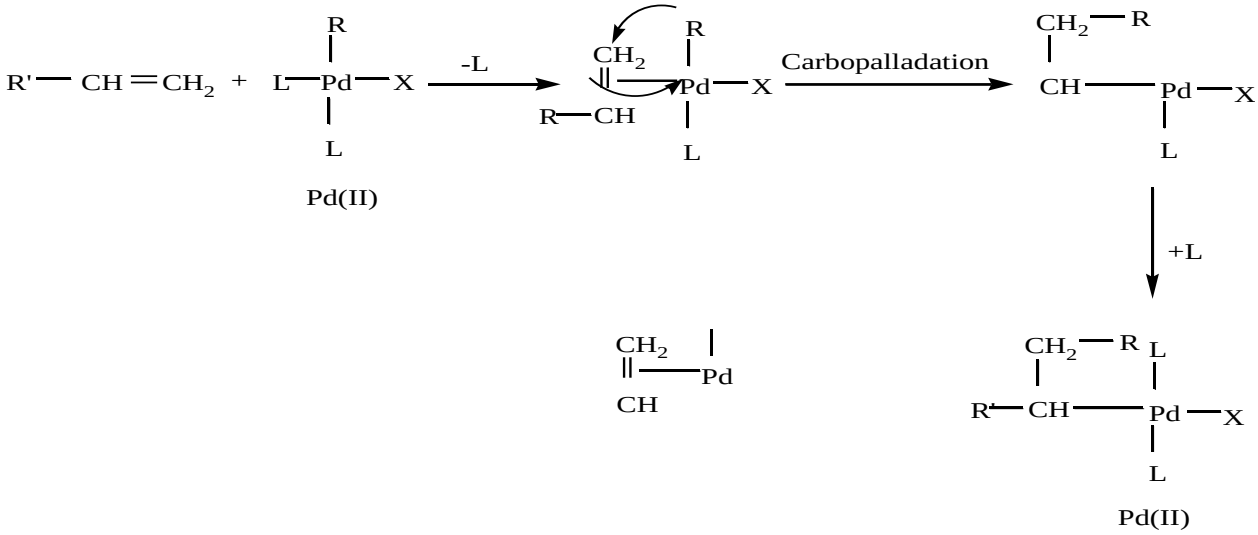
Let us review the basic chemistry of Palladium. Palladium chemistry id dominated by two oxidation states, the zero and +2. The most common complex of Pd(O) tetrakis(triphenylphosphine) palladium $(PPH_3)_4Pd$.

1.7.2.1 Reaction given by Pd(O) complexes:

(1) Oxidative addition with halides and triflates: Electron rich palladium (O) complexes undergoes oxidative addition reaction with substrates having very good nucleophilic group as leaving group. This reaction takes place as follows.

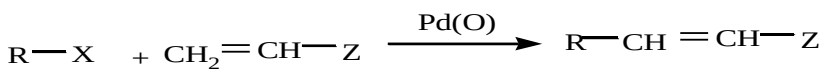


(2) Oxidative addition followed by carbopalladation: The σ alkyl-metal bond in oxidative addition product is very reactive especially towards carbon-carbon π bond. Thus alkene coordinates with the complex to form π complex. Π complex then undergoes migratory inversion reaction. This process involves migration of one of the ligands from the metal to the other ligand and inserction of one of the ligands into the metal-ligand bond.



(3) The Heck Reaction:

Another important type of reactivity of palladium, namely oxidative addition to Pd(0), is the foundation for several methods of forming carbon-carbon bonds. Aryl and alkenyl halides react with alkenes in the presence of catalytic amounts of palladium to give net substitution of the halide by the alkenyl group. The reaction, known as the Heck reaction, is quite general and has been observed for simple alkenes, aryl-substituted alkenes, and substituted alkenes such as acrylate esters, vinyl ethers, and N –vinylamides.



R=alkenyl,aryl

X = halide, sulfonate

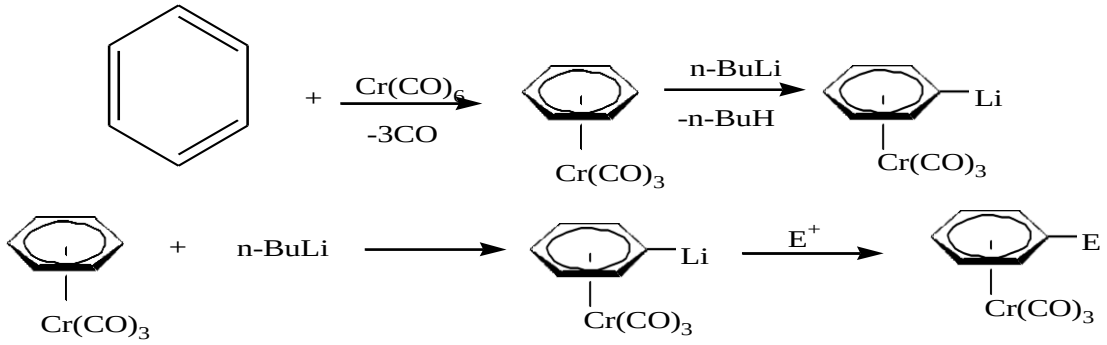
1.7.3 Organochomium compounds:

Organochromium based methods have been studied for a wide range of important organic transformations. This section covers the more significant methodological developments.

1.7.3.1 Reactions of Chromium-Arene Complex

(1) Nucleophilic Substitution:

Benzene and its derivatives react with chromium hexacarbonyl to give arylchromiumtricarbonyl complexes. In the complex, chromium resides in a position perpendicular to the plane of the ring, and the aryl ring is activated towards nucleophilic attack by metal complexes. For example, arylchromiumtricarbonyl complexes can be used for the synthesis of alkyl substituted products by treatment with organolithium reagents, followed by treatment with electrophiles.



Ring Lithiation

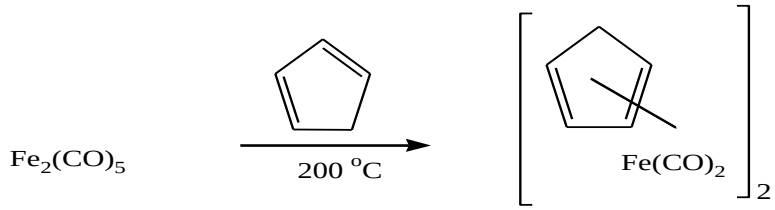
The ring deprotonation of arylchromiumtricarbonyl complex occurs to allow the regioselective preparation of a variety of alkylated complexes under mild conditions. Highly enantioselective deprotonation of prochiral substrates is possible in the presence of chiral bases.

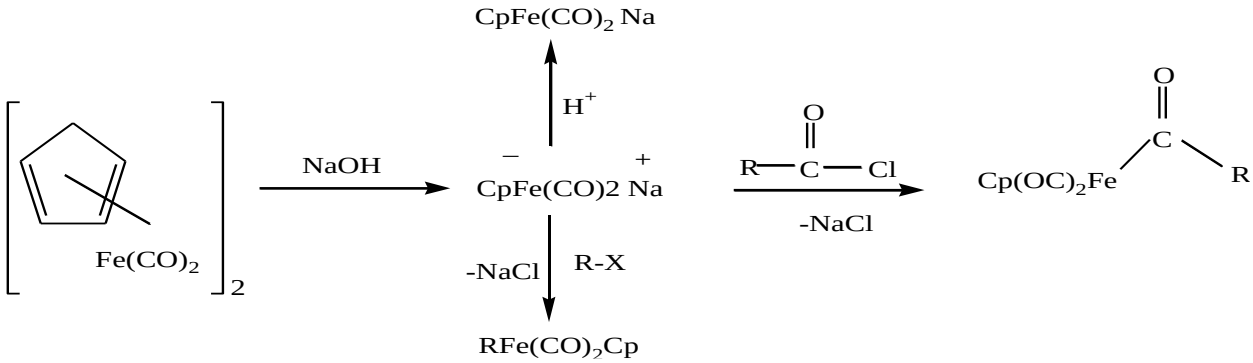
1.7.4 Organoiron Compounds:

A number of organoiron compounds have been developed. The Fe-C bond can be commonly cleaved by treatment with water, acid, alcohol or alkyl halide. Two most important organoiron reagents that are commonly used are cyclopentadienylirondicarbonyl ($CpFe(CO)_2$ and sodium tetracarbonyl ferrate ($Na_2Fe(CO)_2$.

1.7.4.1 Cyclopentadienylironcarbonyl

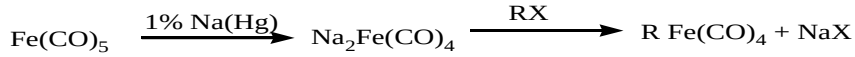
Reaction of $Fe(CO)_4$ with cyclopentadiene gives the dimeric irondicarbonyl complex that can be converted into the anionic $CpFe(CO)_2M$ complex in the presence of base. The latter can be reacted with an array of acid chlorides, alkyl halides and acids to give the corresponding organoiron derivatives.

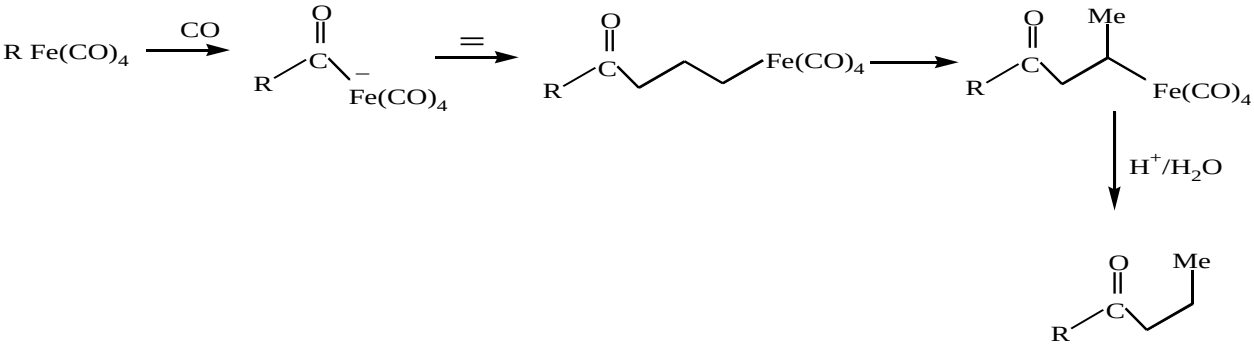




1.7.4.2 Sodium Tetracarbonyl Ferrate:

It is known as Colloman reagent and can be prepared by the reduction of iron pentacarbonyl. Using this reagent the synthesis of ketones, aldehydes, carboxylic acids, amides and esters can be accomplished.





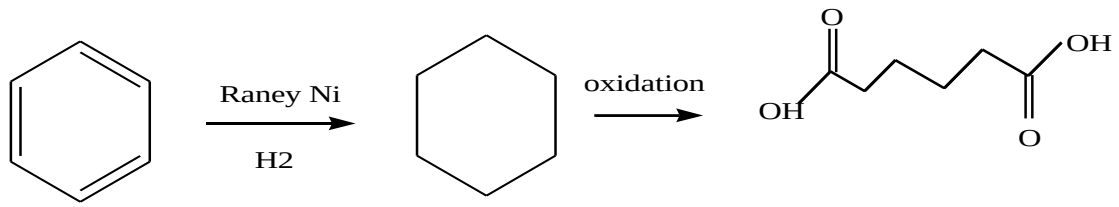
1.7.5 Organonickel Compounds:

Similar to organopalladium compounds, organonickel compounds are generated *in situ* for organic synthesis. Indeed the use of organonickel complexes for the construction of carbon-

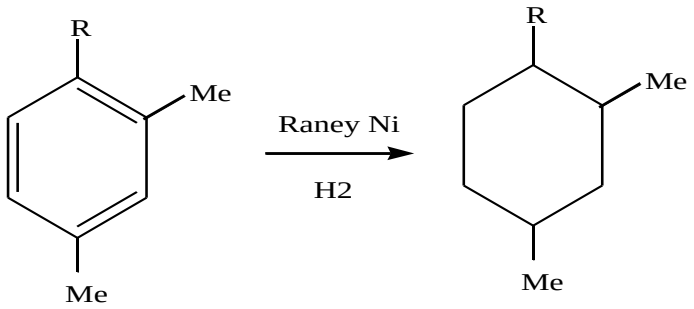
carbon bonds is synthetically older than the analogues organopalladium chemistry. Some of the important processes are here covered.

1.7.5.1 Hydrogenation:

Raney nickel is one of the common catalysts used for the saturation of aromatic compounds. A practical example of the use of Raney nickel in industry is shown in Scheme 1, where benzene is reduced to cyclohexane. Similarly, naphthalene and anthracene are reduced to give *trans*-decalin and perhydroanthracene.



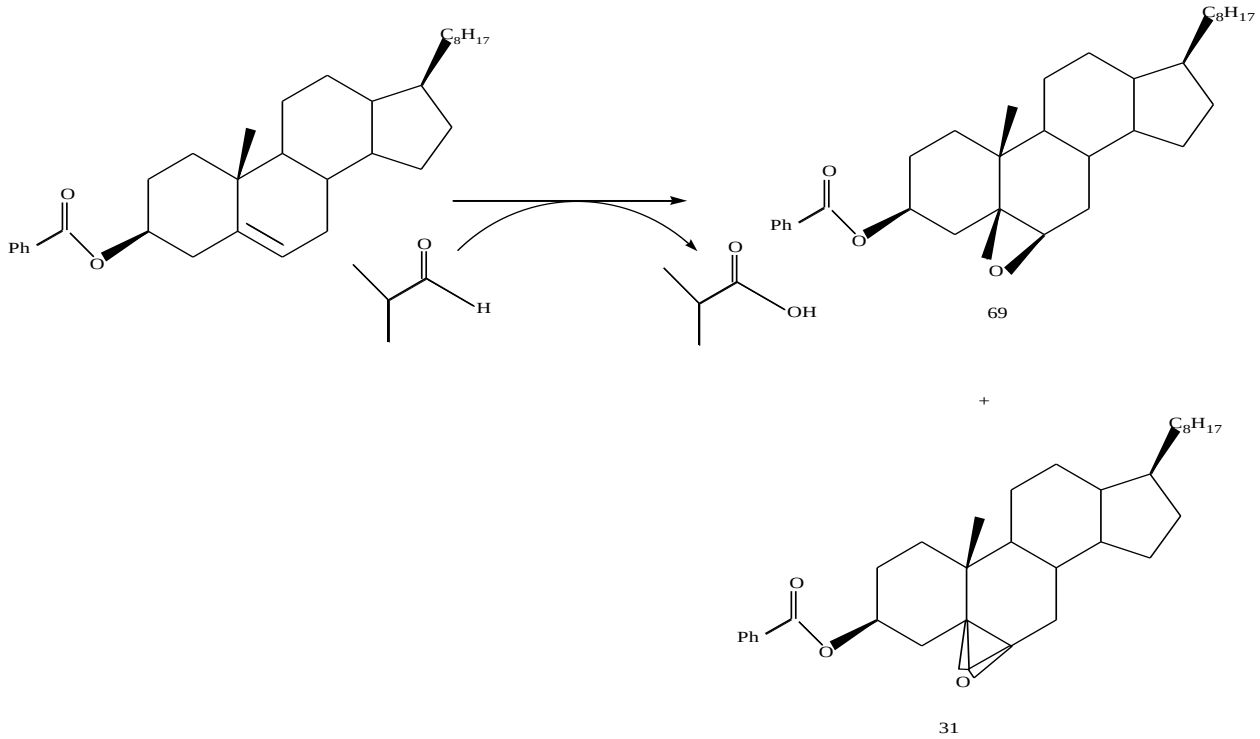
Under these conditions, substituted benzenes such as benzoic acids, phenols and anilines more easily undergo hydrogenation to give substituted cyclohexanes.



R = CO_2, NH_2, OH

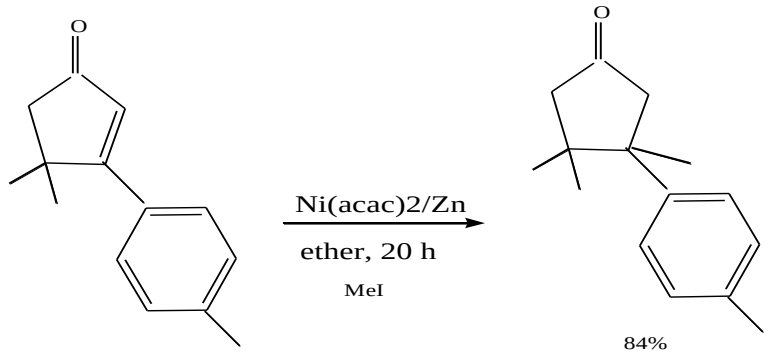
1.7.5.2 Epoxidation:

The aerobic epoxidation of functinalized alkenes can be accomplished using nickel(II) complex in the presence of aliphatic aldehydes as co-reductant. For an example, nickel(II)-1,3-diketonato complex catalyzes the epoxidation of cholesterol derivative to give a mixture of and epoxides in quantitative yield in the presence of 2-butanal under molecular oxygen.



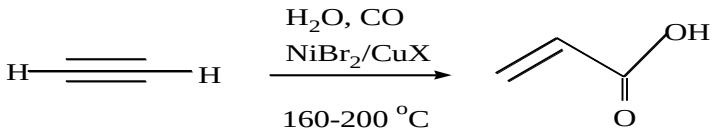
1.7.5.3 Carbon-Carbon Bond Formation

Carbon-carbon bond formation is heart of organic synthesis. Ni(0) generated *in situ* from Ni(acac)2/Zn catalyzes the conjugate addition of alkyl aryl iodides to give α,β -conjugated carbonyl compounds under sonication. An interesting example is the methylation shown in Scheme 5, which fails to take place under other conditions.



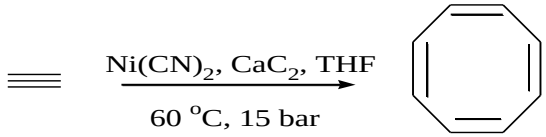
1.7.5.4 Carbonylation:

Nickel-complexes catalyze the addition of carbon monoxide to alkynes. The industrial production of acrylic acid at one time consisted of combining acetylene, carbon monoxide and water at 40-55 atm and 160-200 °C with NiBr2 and a copper halide.



1.7.5.5 Alkene/Alkyne Oligomerization Reactions:

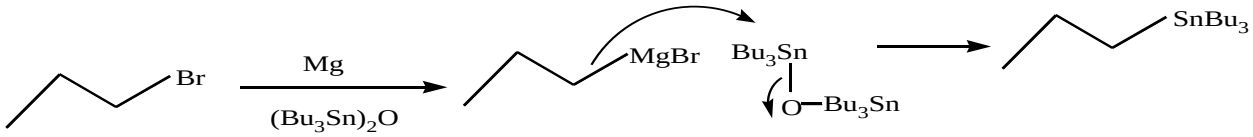
Nickel catalysts have been extensively studied for the polymerization and dimerization of alkynes and alkenes. One practical implementation of alkyne oligomerization is the Reppe synthesis for example in the synthesis of cyclooctatetraene.

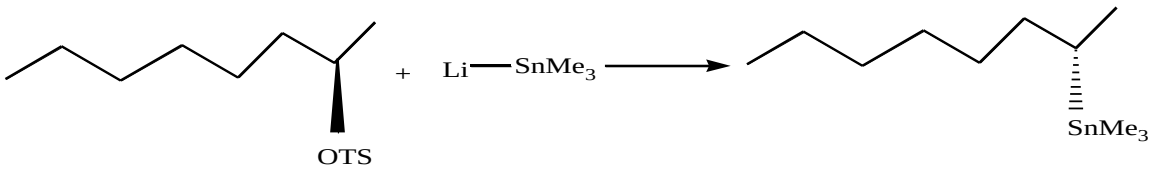


90 %

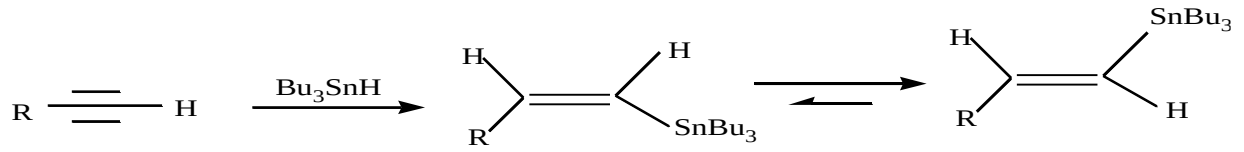
1.7.6 Organotin Compounds:

The preparation of organotin compounds is similar to that of organosilicones. Alkyl tributyltin can be prepared from alkyl Grignard reagent and bis(tributyltin) oxide. Alternatively, the polarity can be reversed and stannyl lithium can add to organic electrophiles. The first reaction is SN_2 at tin and the second reaction is SN_2 at carbon.

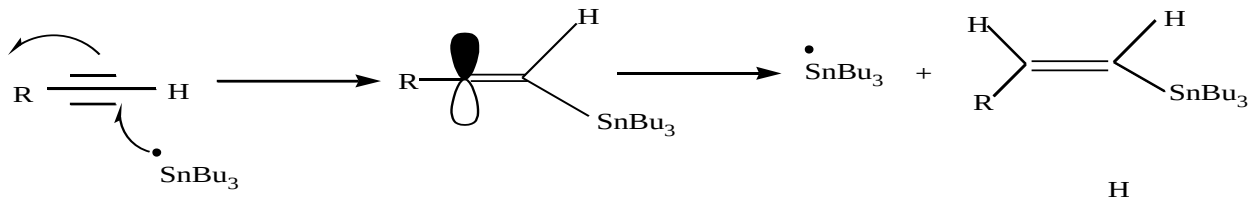




The hydrostannylation of an alkyne with tin hydride can be radical-initiated to afford kinetically controlled vinyl stannane with Z-geometry. However, if there is an excess of tin hydride or sufficient radicals are present, isomerization can lead to the more stable E-isomer.



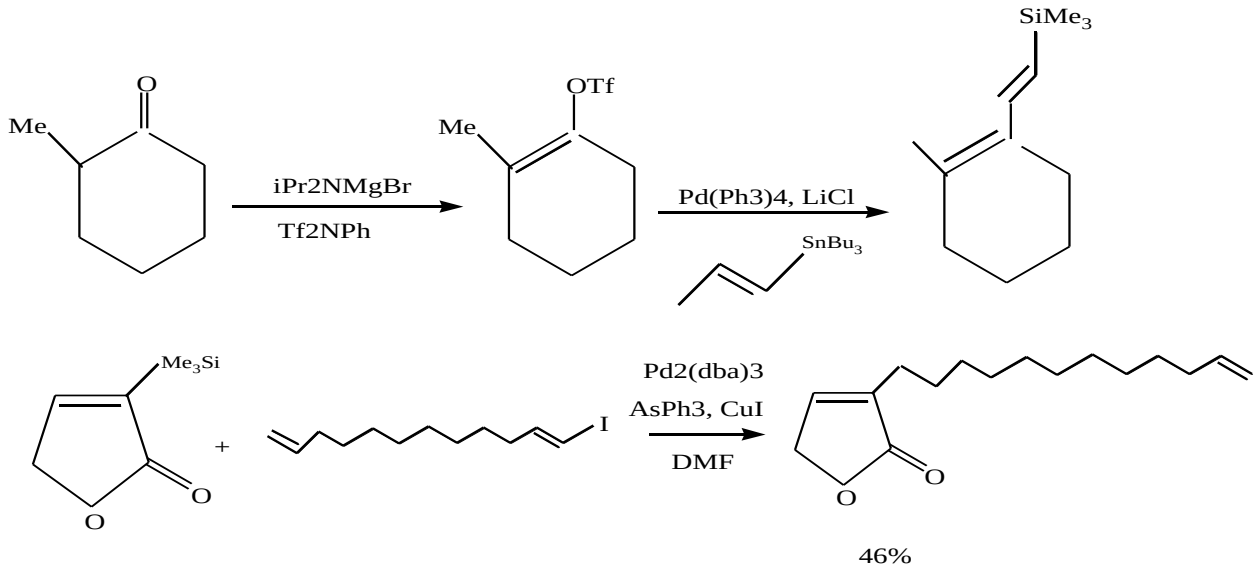
Mechanism:



In this section we will some important organostannane mediated organic transformations.

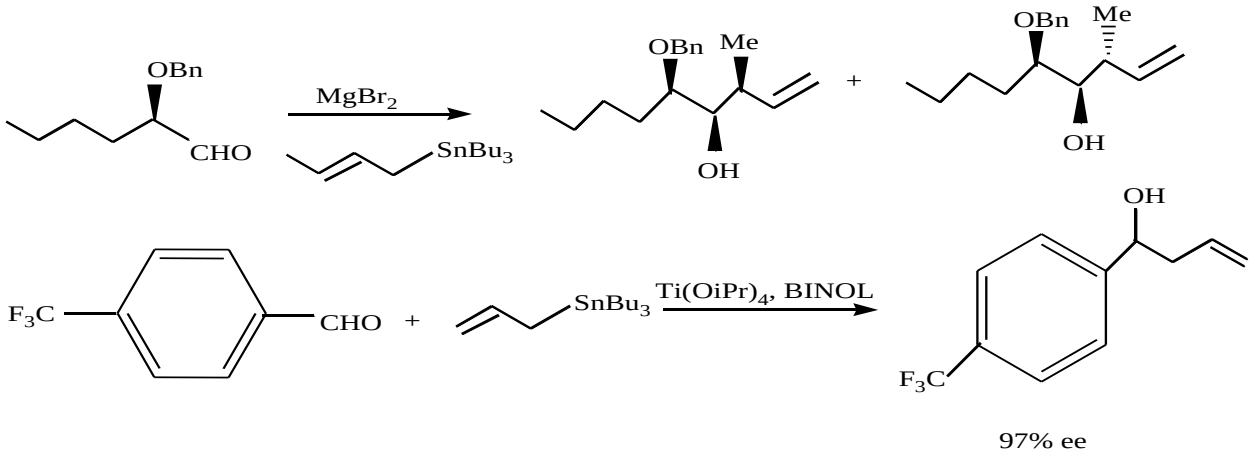
1.7.6.1 *Reactions of Vinyl Stannanes (Stille Coupling):*

Vinyl stannanes react with vinyl halides or triflates in the presence of palladium catalyst to give dienes (Scheme 3). The reaction is compatible with a variety of functional groups and is run under relatively neutral conditions. Both inter- and intramolecular reactions have been explored and widely applied in the synthesis of complex molecules.



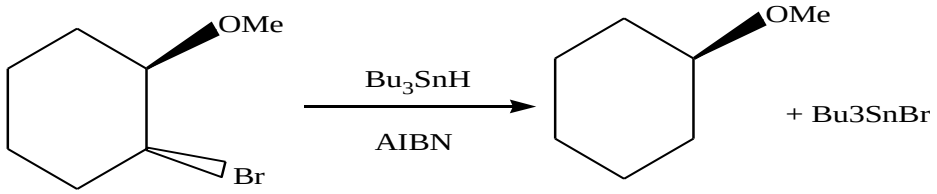
1.7.6.2 ***Reactions of Allyl Stannanes:***

Allyl stannanes are important reagents in organic synthesis because they can be obtained with control over the double bond geometry and don't affect the presence of other functional groups. Asymmetric allyllation of aldehydes with ally stannanes has also been extensively explored with excellent stereocontrol in the presence of Lewis acids.



1.7.6.3 *Reactions of Tributyltinhydride:*

Tributyltinhydride (Bu4SnH) is a useful reagent for the removal of halogen (I and Br) from alkyl halide by H (Scheme 5). The reaction is performed in the presence of light or radical initiator AIBN. The mechanism involves formation of an alkyl radical by abstraction of the halogen by Bu3Sn·. This alkyl radical abstracts H· form Bu3SnH.



1.7.7 Organorhodium Compounds:

Organorhodium compounds are used as soluble catalysts for effecting many useful organic transformations. This section covers some of the important processes.

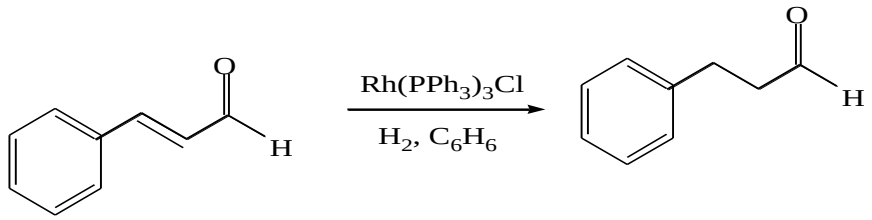
1.7.7.1 Reactions of Alkenes:

The addition of hydrogen to alkenes using transition metal catalysis occupies an important position in organic synthesis. Homogeneous hydrogenation processes offer distinct advantage over their heterogeneous counterparts, for example, superior chemo-, regio- and stereoselectivity.

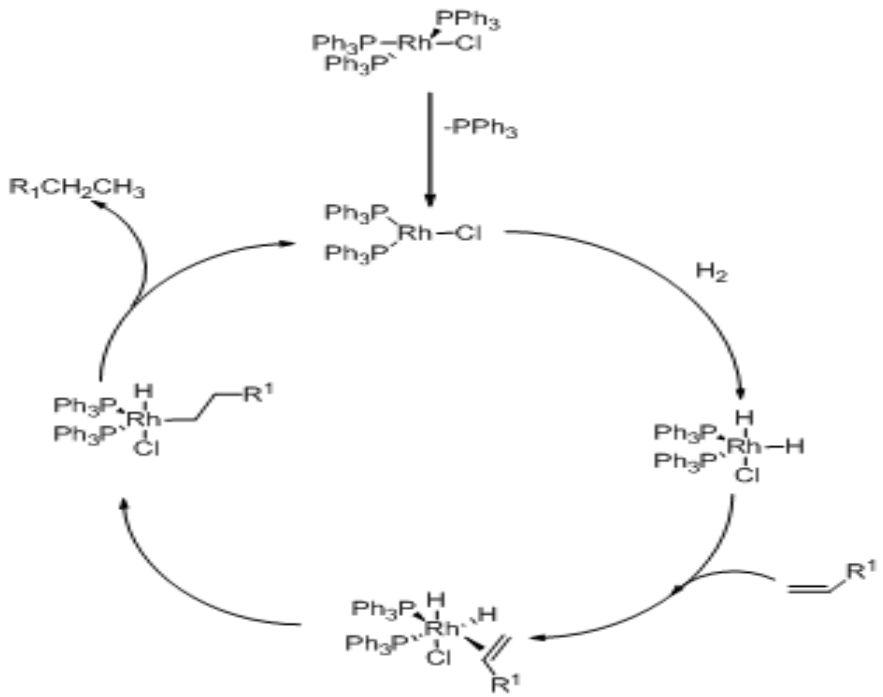
One of the most versatile metal catalysts for double bond saturation in the homogeneous phase is Wilkinson's catalyst, $[RhCl(PPh_3)_3]$. It is prepared by the reaction of $RhCl_3$ with excess of PPh_3 in boiling EtOH.

$$RhCl_3\ 3H_2O + PPh_3 \xrightarrow[\text{Boiling}]{\text{EtOH}} (PPh_3)_3RhCl$$

Wilkinson's catalyst and its modified forms have been extensively used for the hydrogenation of alkenes (Scheme 2). Functional groups like oxo, cyano, nitro, choro and azo are compatible under ordinary temperature and pressure. If the functional groups are properly situated chelate on the active Rh and can thus direct hydrogenations providing high degree of selectivity.



Mechanism:



The coordination complex is a square planar 16 electron complex whose stability is due to filled bonding molecular orbitals (Scheme 3). The complex loses a PPh_3 to form a14 electron complex which coordinates with alkene and then undergoes oxidative addition with hydrogen. This is followed by transfer of hydrogen to carbon from Rh to form alkyl Rh intermediate. Then, second

hydrogen migrates to carbon leading to reductive elimination of saturated product. In this step, rhodium is electrophilic and hydride transfer is nucleophilic. In some cases, however, an alternative reaction pathway seems to have been operating. This pathway first involves the addition of hydrogen to rhodium prior to the complexation of alkene. The evidence for this path comes from the fact that addition of hydrogen to the $[RhCl(PPh_3)_2(\eta\text{-}C_2H_4)]$ is not feasible.

1.7.7.2 Hydrosilylation

Hyrosilylation of alkenes is not only of industrial importance, but also one of the most practical means that afford functionalized organosilicon compounds of synthetic applications. The rhodium(I)-catalyzed hydrosilylation of alkenes with anti-Markovnikov selectivity provides an effective route for the synthesis of 1- silylalkanes. The adducts can be subjected to an efficient oxidative cleavage of the silicon-carbon bond transforming into 1-alkanols.

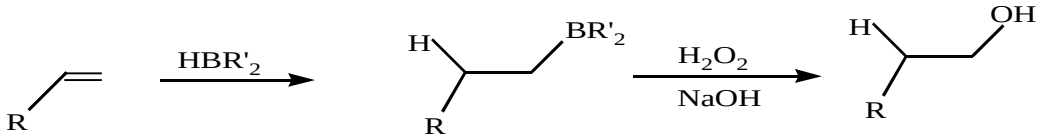
1.8 OTHER ELEMENTS; B AND Si COMPOUNDS

1.8.1 Organoboranes:

Borane (BH_3) exists as the gaseous diborane (B_2H_6). It is commercially available in the form of complexes generally with THF, Et_2O and Me_2S. It can also be prepared from the reaction of $NaBH_4$ with BF_3. Organoboranes can be prepared rapidly by the addition reaction of borane to alkenes and alkynes.

1.8.1.2 Hydroboration of Alkenes:

Boranes react with alkenes to form alkylboranes that could be oxidized in the presence of alkaline hydrogen peroxide to give alcohols. The result is a *cis*, anti- Markownikoff addition of water. The C-B bond is converted into a C-OH with retention of stereochemistry.

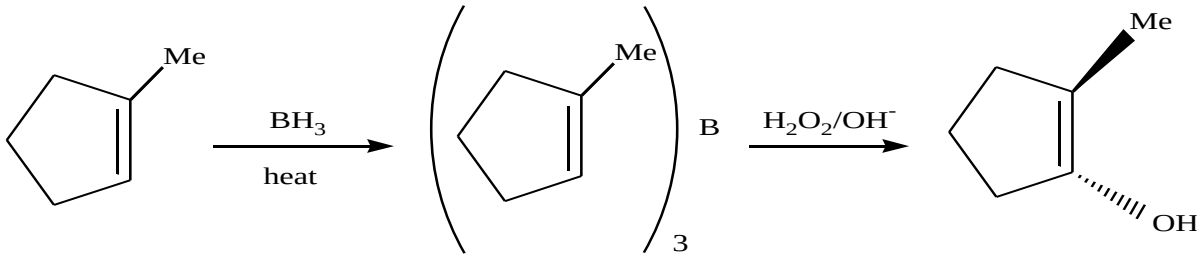


$HBR'_2 = BH_3, B_2H_6$ or other borane derivatives.

1.8.1.3. Reactions of Alkylboranes

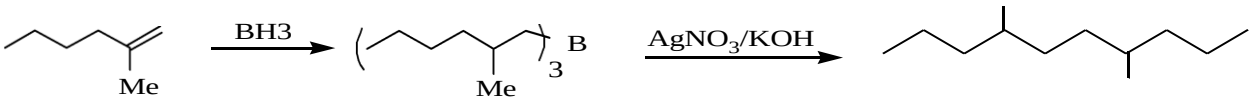
(1) Synthesis of Alcohols

The transformation of alkenes to alcohols proceeds with complete retention of configuration at the boron-bearing carbon.



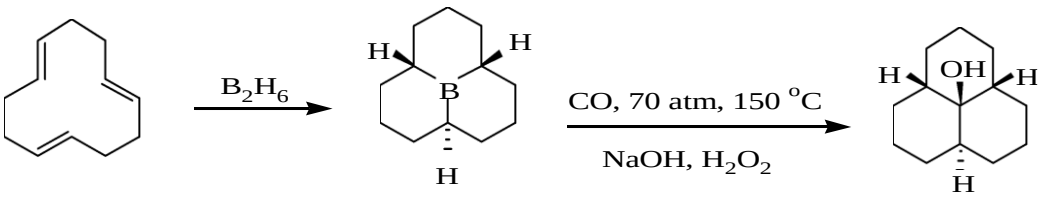
(2) Coupling:

Alkylboranes on treatment with basic silver nitrate lead to coupling of the alkyl groups. The reaction probably proceeds via an alkyl silver intermediate and affords a useful tool for the carbon-carbon bond formation.



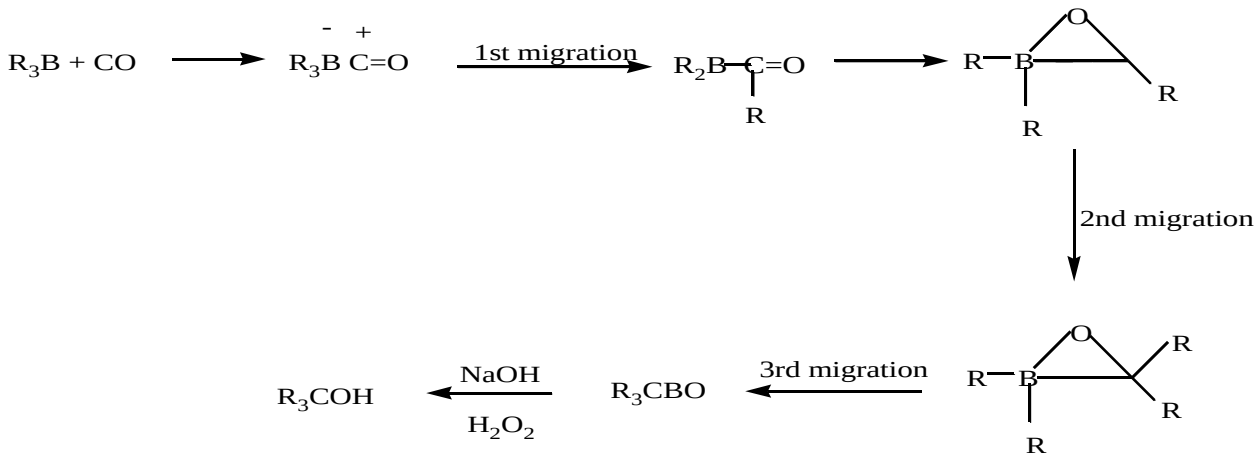
(3) Carbonylation: Formation of Alcohols, Aldehydes and Ketones

Alkylboranes can be transformed into alcohols, aldehydes and ketones on reaction with CO followed by oxidation. These reactions require high pressure and high temperature. For example, 1,5,9-cyclododecatriene proceeds reaction with B_2H_6 to give tricyclic borane that could be converted into tricylic alcohol by carbonylation and oxidation.



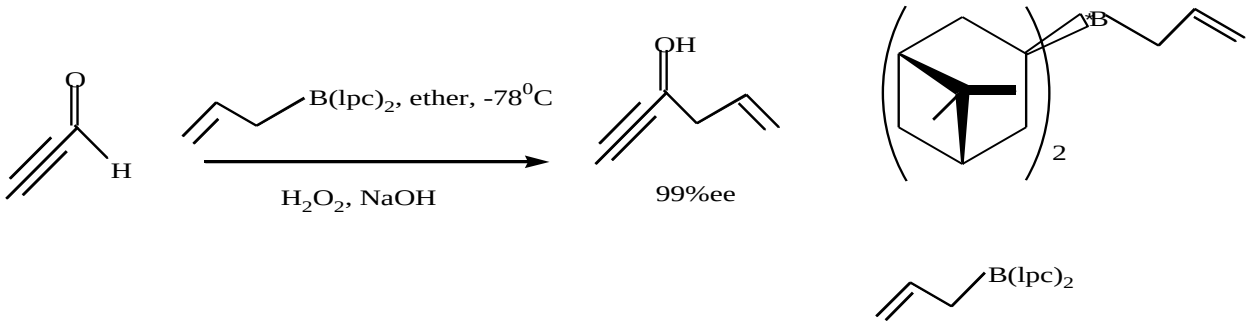
Mechanism

The reaction involves an intramolecular migration of alkyl groups from boron to the carbon atom of CO.



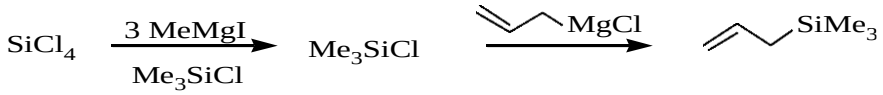
1.8.1.4. Addition of Allylboranes to Carbonyl Compounds:

Carbonyl compounds react with allylboranes to give the corresponding alcohols. For an example, propiolaldehyde could be transformed into hex-5-ene-1-yn-3-ol *via* 1,2-addition with (-)-B-allyl(diisopinocampheyl)borane followed by oxidation



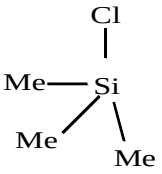
1.8.2 Organosilicon Compounds:

Organosilicon compounds can be prepared from metallic silicon and silicon halides. For examples, chlorotrimethylsilane is prepared by the reaction of methylmagnesium iodide with silicon chloride. Likewise, allylic silanes are prepared from chlorotrialkylsilanes and allylmagnesium halide. The reactions involve nucleophilic displacement of halogen from silicon halides by organomagnesium halide.

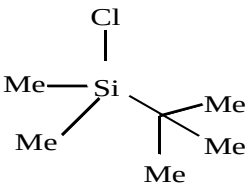


1.8.2.1. Formation of Silyl Ethers

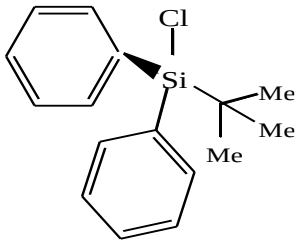
Alcohols react with chlorotrialkysilanes in the presence of amines to give silyl ethers which are useful having a number of applications. The silyl ethers can be easily removed by nuelophilic displacement with fluoride or oxygen nucleophiles and the rate of the removal depends mostly on the steric bulk for the silyl group. Some of the silicon based protecting groups follow:



TMSCl

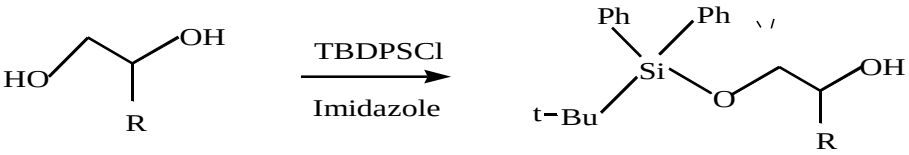


TBDMSCl



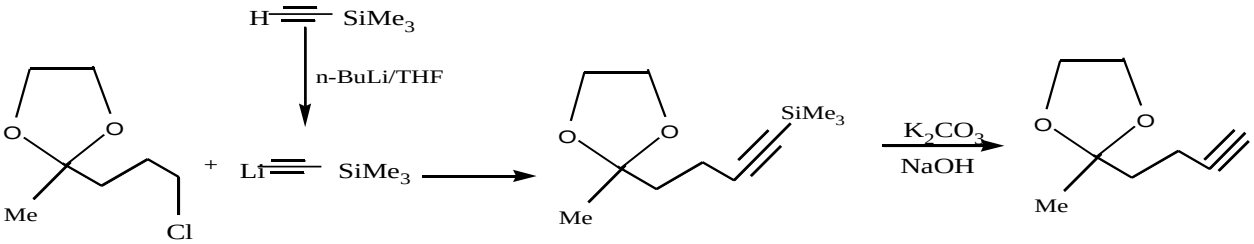
TBDPSCl

A protecting group is useful only if it can be introduced and removed easily without affecting the rest of the molecule and survives during the reaction. For an example, the extreme bulkiness of the TBDPS group makes it useful for the selective protection of unhindered primary alcohol in the presence of secondary alcohols. In addition, it has excellent stability but can still be easily removed with fluoride.



1.8.2.2. Formation of Alkynyl Silane

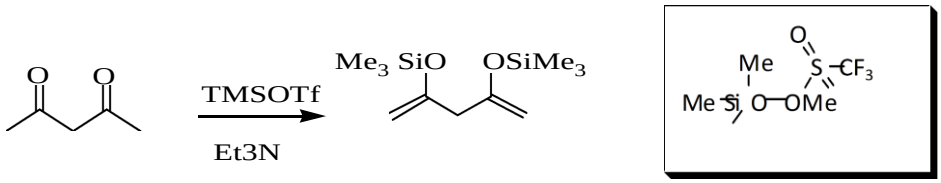
In some circumstances terminal alkynes having an acidic proton lead to unwanted side-reactions. To circumvent this problem, $SiMe_3$ is used for the protection of the terminus of alkyne during the reaction, which can be easily removed with fluoride or K_2CO_3 in MeOH.



1.8.2.3. Formation of Silyl Enol Ethers

Trialkylchlorosilane can trap the enolate ion, formed by the base treatment of ketones, to give silyl enol ethers that are useful intermediates for a variety of reactions. For examples, the silyl enol ether formed from aldehydes and ketone can proceed aldol condensation. The advantage of using pre-formed enolate reagent is that the coupling takes place on the desired site of an unsymmetrical ketone. This is known as directed aldol condensation.

Alternatively, silyl enol ether can also be prepared from ketones using TMSOTf, which acts as a Lewis acid.



1.9 METALLOCENES

The metallocenes term is related to bis(cyclopentadiene) metal complexes (‘sandwich’), but wide usage is now accepted to include cyclopentadienyl complexes (‘half sandwich’) Figure 1 and multicyclopentadienyl complexes (‘multidecker sandwich’) as well as complexes with additional substitution at the metal centre. The metallo- prefix can’t be used when one considers the development of complexes involving non-metallic elements such as boron, silicon or arsenic. In fact, metallocene-like complexes are now known for many elements in the periodic table.

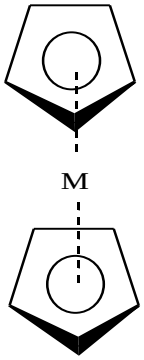


Figure 1: Metallocene structure

1.9.1 The Cyclopentadiene Ligand:

Cyclopentadienyl moiety acts as an important “spectator” ligand and possesses ubiquitous inorganometallic chemistry. It remains inert to most nucleophiles and electrophiles

and solely engages in stabilizing organometallic complexes.

The cyclopentadienyl ligands are used in formation of wide array of organometallic compounds. These compounds exhibit different formulations that begin with the so- called "piano stool" CpMLn (n = 2, 3 or 4) type and most commonly observed "metallocene" Cp^2M type and other is "bent metallocene" Cp^2MXn (n = 1,2 or 3) type. In the "piano stool" CpMLn structure, the cyclopentadienyl (Cp) ligand is regarded as the "seat" of the piano stool while the remaining L ligands are referred to as the "legs" of the piano stool. Though the cyclopentadienyl ligand often binds to metal in a η5 (pentahapto) fashion, e. g. as in ferrocene, the other form of binding to metal at lower hapticities, like that of the η3 (trihapto) binding e.g., as in $(\eta5-Cp)(\eta^3-Cp)W(CO)_2$ and that of the η1 (monohapto) binding e.g., as in $(\eta5-Cp)(\eta1-Cp)Fe(CO)_2$, are also seen on certain rare occasions. The binding modes of the cyclopentadienyl ligand in metal complexes can be ascertained to a certain degree by ^1H NMR in the diamagnetic metal complexes, in which the Cp−protons appear as a singlet between 5.5−3.5 ppm while the β and γ hydrogens come at 7−5 ppm.

1.9.2 The interaction of cyclopentadiene with metal:

We can understand the interaction of cyclopentadiene and metal through molecular orbital diagram. The frontier molecular orbital of the cyclopentadienyl ligand contains 5 orbitals ($\Psi_1-\Psi_5$) residing in three energy levels (Figure 2). 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.

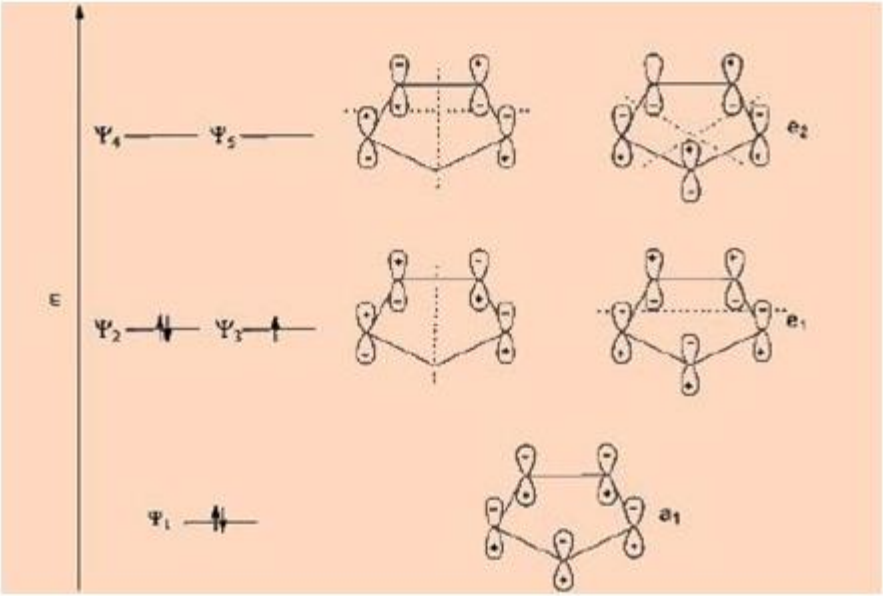


Figure 2. Molecular orbital diagram of cyclopentadienyl ligand

The above frontier molecular orbital diagram becomes more captivating on moving over to the metallocenes that contain two such cyclopentadienyl ligands. Specially, in the Cp_2M system, (*e.g.*, 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 3).

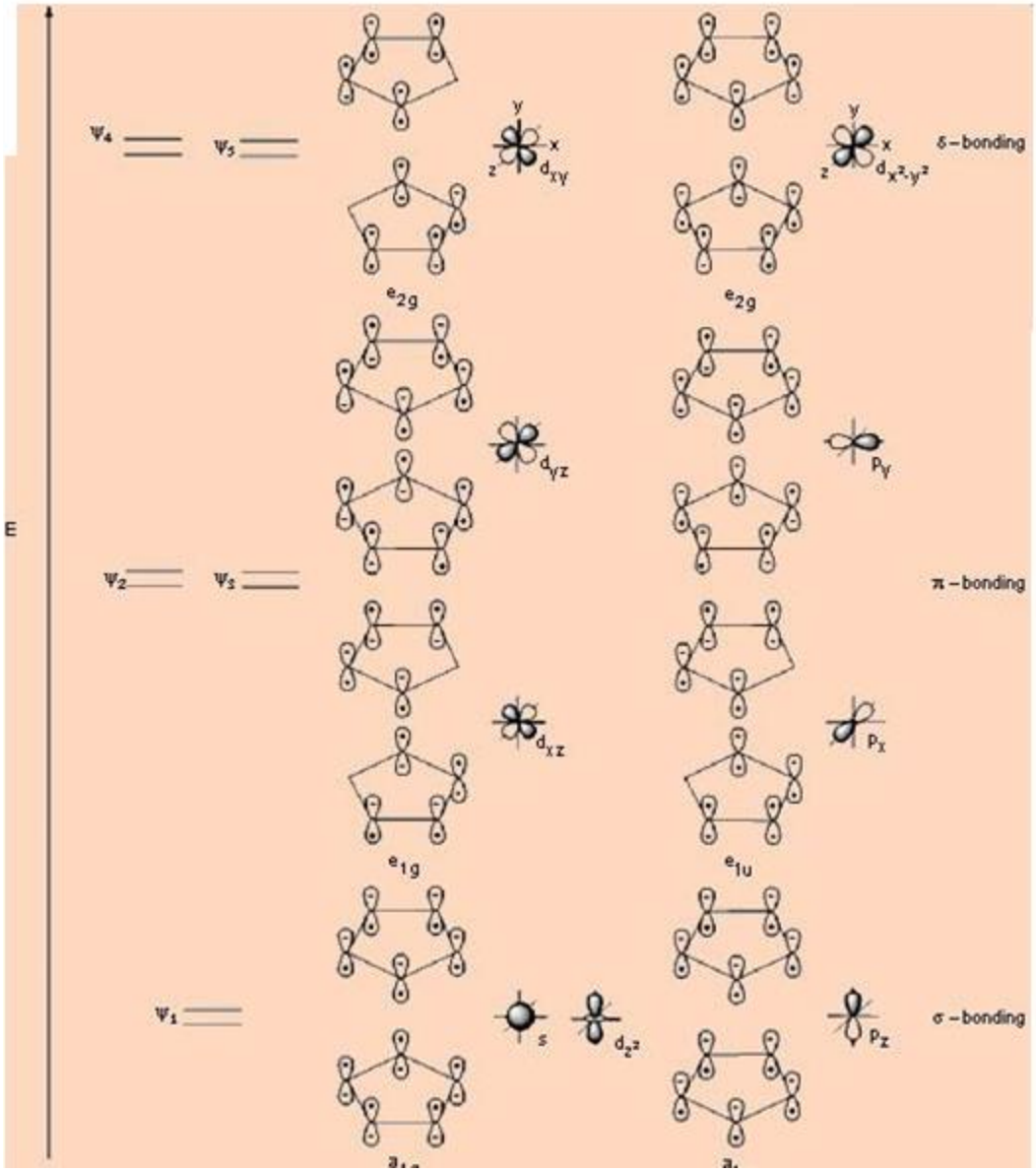


Figure 3. Metal−cyclopentadienyl bonding interactions.

1.9.3 Bent metallocenes:

Bent metallocenes are Cp2MXn type complexes formed of group 4 and the heavier elements of groups 5−7. In these complexes the frontier doubly degenerate e_{2g} orbitals of Cp_2M fragment interacts with the filled lone pair orbitals of the ligand (Figure 4).

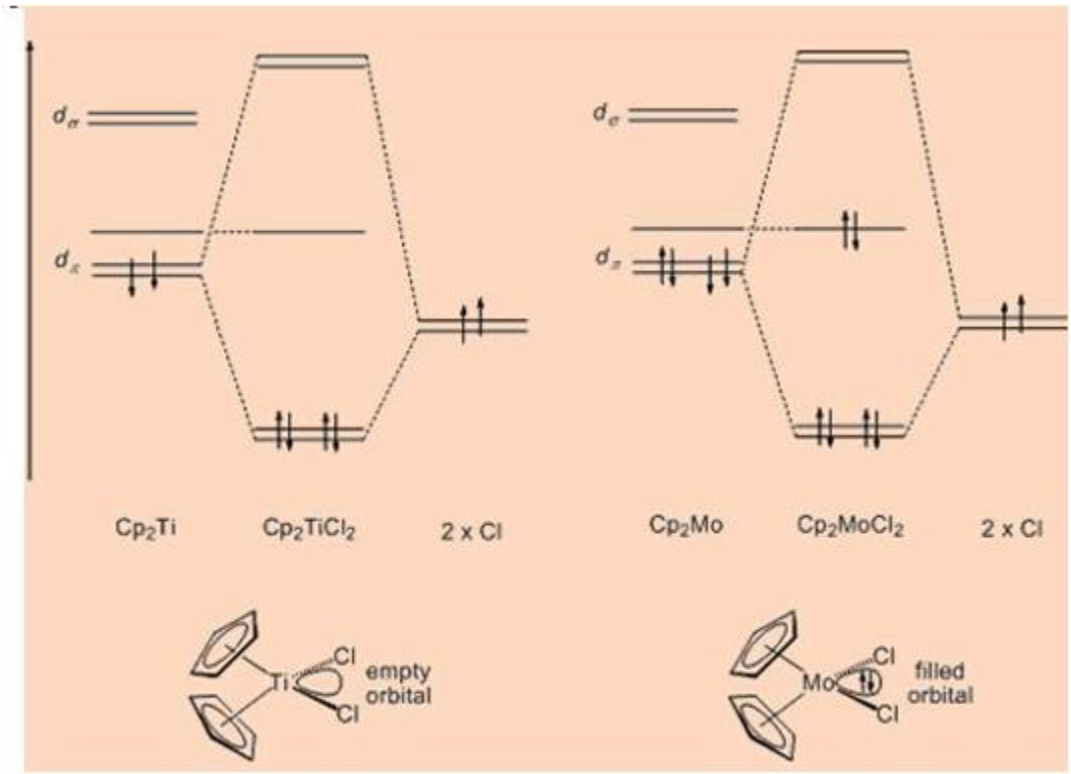


Figure 4: Bent Metallocenes.

1.9.4 Synthetic Procedures of Metallocenes:

The metathesis reaction is widely used in the synthesis of metallocenes. The alkali metal cyclopentadienides, magnesium dicyclopentadienides and thallium cyclopentadienides are important in synthetic sources of Cp' ligands. This and other generally applicable methods, as well as specific reactions (used for particular complexes) are classified below with key examples, and synthetic procedures for particular complexes.

1. *Reaction using Cyclopentadienes*:

1. $2E + 2Cp'H \longrightarrow 2ECp' + H_2$ $\quad E + 2Cp'H \longrightarrow ECp'_2 + H_2$ (1^{-1})
2. $ER + Cp'H \longrightarrow ECp' + RH$ (1-2)
3. $EH + Cp'H \longrightarrow ECp' + H_2$ (1-3)
4. $ENH_2 + Cp'H \longrightarrow ECp' + NH_3$ (1-4)

According to Eq. (1-1), Cyclopentadiene carries a relatively acidic proton and reacts smoothly with a number of the more reactive main group elements such as sodium and magnesium and certain metallocenes can be prepared by co-condensation of thecyclopentadiene with the element. Eq.(1-2) has been extrapolated to other Cp' derivatives and applies to other organometallic reagents such as $MgMe_2$ and Al_2Me_6. The metallocene compound of Sodium or potassium metal can be obtained from reaction of the element hydride with cyclopentadiene Eq. (1-3), or reaction of the element amide with the cyclopentadiene in liquid ammonia Eq. (1-4). A similar amide displacement reaction is used for calcocene and barocene derivatives.

2. Salt Metathesis Reactions:

$$nMCp' + EXn \longrightarrow Cp'nE + nMX \ (M = Li, Na) \quad (1\text{-}5)$$

or

$$n/_2MgCp'_2 + EXn \longrightarrow Cp'nE + n/2MgXm$$

Salt metathesis reaction is the most generally applied procedure for the preparation of metallocenes involving the elements of groups 2, 13, 14 and 15, is the appropriate stoichiometric combination of an element halide (X) or polyhalide with an alkali metal cyclopentadienide salt (usually lithium or sodium) or a magnesium dicyclopentadienide salt. Complexes of aluminum and gallium involving the element in less familiar low oxidation states are obtained from metastable halides ‘AlCl’ and ‘GaCl’, which are formed *in situ*.

3. Disproportionation, Comproportionation and Decomposition:

$$2Cp'EX \longrightarrow Cp'_2E + EX_2 \quad \text{and} \quad 2Cp'EX \longrightarrow Cp'_2E + EX_2 \quad (1\text{-}6)$$

This method is useful for the synthesis of magnesocene and its methylated derivatives by thermal decomposition of Cp'MgBr. The comproportionation reaction used to obtain substituted derivatives of half sandwich complexes for magnesium, germanium and tin. Reductive elimination of Cp ligands from Cp_3In and of phenyl groups from Cp_2PbPh_2 is also thermally induced.

4. Halide Ion Abstraction:

$$Cp'nEX + A \longrightarrow [Cp'nE][AX] \quad (1\text{-}7)$$

The procedure used for the formation of half sandwich complexes (n = 1) of boron, germanium and tin and the sandwich complexes (n = 2) of arsenic, antimony and bismuth.

5. Substitution onto the Cp Ligand Frame:

$$ECpn + AR^{\cdot\cdot\bullet} \longrightarrow CpRECpn.1 + AH \quad \text{or} \quad ECpn + nAR^{\cdot\cdot\bullet} \longrightarrow ECpRn.1 + nAH \quad (1\text{-}8)$$

Thallium and tin metallocenes have a relatively high stability, which allows for modification of the Cp ligand with retention of the complex. The procedure useful for the preparation of a particularly extensive series of stannocenes, including Cp' ligands bearing silyl, stannyl, phosphine or phosphenium moieties, and is responsible for the formation of the novel $Cp^{tricyanovinyl}$ Tl.

$$Cp'nEX_2 + M^{\cdot\cdot\bullet} \longrightarrow Cp'nE + MX_2 \quad (1\text{-}9)$$

Reductive dehalogenation can be used for silicon, germanium and tin in Cp^*2EX_2 and for aluminum in $[Cp^*AlCl_2]_2$ and for Cp_3In and Cp_2PbPh_2 can be thermally promoted.

7. Addition of Cp Anions:

$$Cp'E + [Cation][Cp']^{\cdot\cdot\bullet} \longrightarrow [Cation][Cp'2E] \quad (1\text{-}10)$$

Anionic multicyclopentadienyl complexes can be achieved by the addition of cyclopentadienide anions onto lithium, sodium, cesium, thallium and tin. This is achieved by reaction of the neutral metallocene with sources of nucleophilic cyclopentadienide in salts with complex cations such as tetraphenylphosphonium and trisdimethylaminosulfonium.

1.9.5 Structural type of metallocenes:

The structure of main group metallocene chemistry are varied with the position of the element with respect to the Cp' ligand, the number of Cp' ligands associated with a element center and their relative orientation, the involvement of auxiliary ligands (other than Cp' derivatives) with the element, and the association of the complexes into dimers, oligomers or polymers. The general cyclic fluxionality of the Cp' ligand implies that all five of the carbon atoms in the Cp' frame are involved in the Cp'–element π-interaction and systems exhibiting low hapticity. The non-equivalent element–carbon distances obtained from X-ray crystallographic data often illustrate a closer interaction to some framework carbon atoms than others. This can be defined by the similarity or difference between the $Cp'_{centroid}$–E distance and the Cp'_{plane}–E distance.

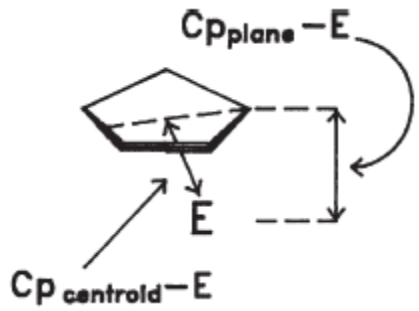


Figure 5: $Cp'_{centroid}$–E distance and the Cp'_{plane}–E distance

Sandwich Complexes:

As shown by the term, sandwich compounds represent the prototypical metallocenes and they involve two Cp' ligands, one on either side of the element. There are many examples of sandwich complexes with the two ligand planes parallel figure 6 (usually staggered D_{5d} and eclipsed D_{5h} conformations). Also examples of sandwich complexes with the two ligand planes nonparallel figure 7 (often referred to as 'bent' sandwich structure) complexes.

Figure 6: staggered D_{5d} and eclipsed D_{5h} conformations

Figure 7: Bent 'sandwich' structure

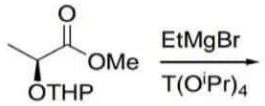
1.10 SUMMARY

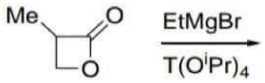
- Discussion about general introduction of Organometallic compounds.
- Discussion about classification of Organometallic compounds.
- Discussion about various organic reagents with their preparation, properties and its applications.
- An extensive series of main group metallocene complexes have now been identified and comprehensively examined.
- Most elements of groups 1, 2, 13, 14 and 15 engage Cp' ligands in a π-interaction.
- A wide structural diversity observed in metallocenes by a relatively weaker Cp'–E bond.
- Flexible Cp'–E interaction and the ability of Cp' to behave as a leaving group, allowing for an extensive substitution chemistry.
- Further diversification involving isolobal analogs of Cp' has already begun and represents the future of main group metallocene chemistry.

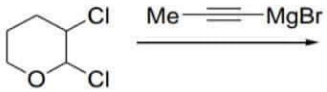
1.11 TERMINAL QUESTIONS

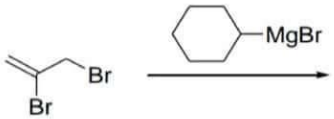
(A)

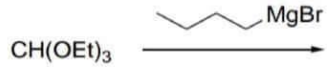
1. Provide major products for the following reactions

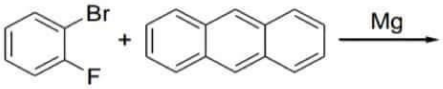
1. 

2. 

3. 

4. 

5. 

6. 

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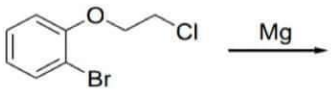
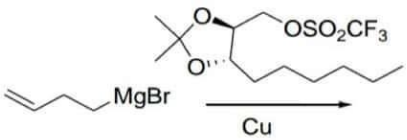
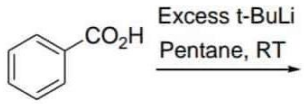
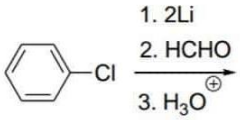
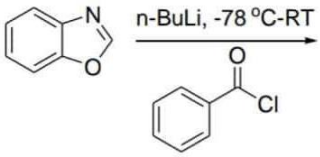
8. 

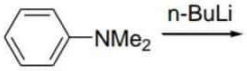
9. 

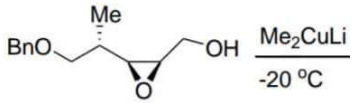
2. Complete the following Reactions.

1. 

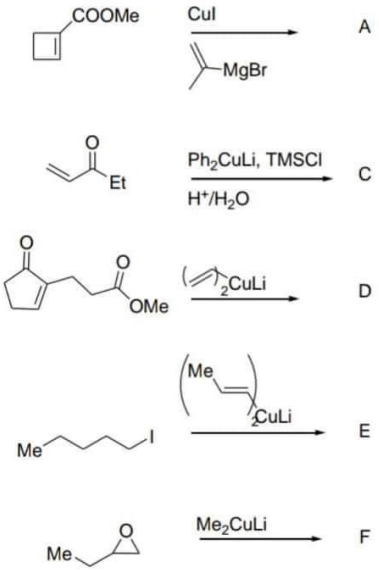
2. 

3. 

4. 

5. 

3. Predict the products of the following reactions



(B) Objective type questions:

1. Alkyl halides can be converted into Grignard reagents by _____
   a) Boiling them with Mg ribbon in alcoholic solution
   b) Warming them with magnesium powder in dry ether
   c) Refluxing them with $MgCl_2$ solution
   d) Warming them with $Mgcl_2$

Answer: B

2. Which is not present in Grignard reagent?
   a) Methyl group
   b) Magnesium
   c) Halogen
   d) −COOH group

Answer: B

3. Which of the following compounds does not give a tertiary alcohol upon reaction with methylmagnesium bromide?
   a) 3-methylpentanal
   b) Ethyl benzoate
   c) 4,4-dimethylcyclohexanone
   d) 4-heptanone

Answer: D

4. Which of the following compounds would not give tert-butyl alcohol when treated with excess methylmagnesium bromide?
   a) acetyl chloride
   b) acetaldehyde
   c) methyl acetate
   d) acetic anhydride

Answer: B

Answer: 1 (B), 2 (B), 3 (D), 4 (B)

1.12 REFERENCES

1. *NPTEL – Chemistry – Reagents and Organic reactions. Joint initiative of IITs and IISc – Funded by MHRD.*
2. *Organic Synthesis by Jagdamba Singh and LDS Yadav, Vol. 2.* Pragati Prakashan Meerut.
3. *Organic Chemistry- IV (Advanced Organic Synthesis, supramolecular chemistry and carbocyclic rings)by e PG Pathshala.*
4. *Advanced Organic Chemistry part B: Reactions and synthesis Francis A. Carey and Richard J. Sundberg, Fifth Edition.*

UNIT-2 OXIDATION

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2.4.10 Oxidation by Ceric ammonium nitrate (CAN) $NH_4[Ce(NO_3)_6]$

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2.5.2 Oxidation by Ceric ammonium nitrate (CAN) $NH_4[Ce(NO_3)_6]$

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2.1 OBJECTIVES

After reading this unit students will be able -

- For organic synthesis student know, how to plane oxidation reaction for different functional group
- Different function group introduce by oxidation reaction.
- Oxidative cleavage of C-C bond

2.2 INTRODUCTION

A reaction in which transfer of electron happened called oxidation reduction reaction or redox reaction. Oxidation and reduction is complementary in which one species is oxidized and another is reduced. This reaction is very important for biological system because it produce energy.

The release of energy during cellular respiration is cellular oxidation of glucose

$$\text{Glucose + Oxygen} \longrightarrow \text{Carbon dioxide + water + energy}$$

The species that loses electron is oxidized and the compound gains electron is reduced. *LEO the lion says GER; Lose of electron is oxidation and Gain of electron is reduction. Mainly in inorganic chemistry one specie. In organic chemistry the term "Oxidation " means addition of oxidation to substrate e.g. oxidation of aldehyde to carboxylic acid

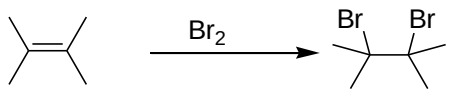
$$RCHO \xrightarrow{O} RCOOH$$

OR

Removal of hydroden content e.g. oxidation of alcohol to aldehyde.

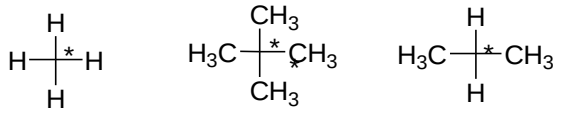
$$RCH_2OH \xrightarrow{[O]} RCHO$$

Increase of electronegative content e.g. oxidation of alkene to dibromo alkene.



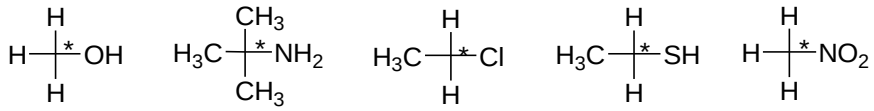
Whether the organic reaction is oxidation or reduction in a given reaction can be known by the oxidation levels of the carbon atom of the functional group. The carbon of functional group is classified into the following five oxidation levels.

Level Zero :- When the carbon is bonded to only hydrogen or carbon or both hydrogen and carbon by single bond only then in this case oxidation level is zero.



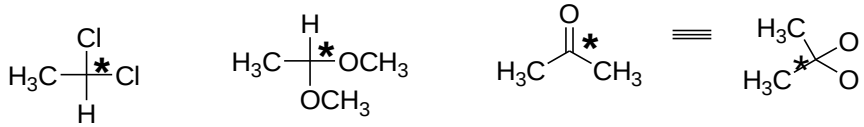
*Carbon is Zero level

Level 1 :- In this category the saturate carbon is bonded with one electronegative carbon and alkene carbon comes in this group. Example Alcohol, thiol, amine,halides, nitro alkane etc.



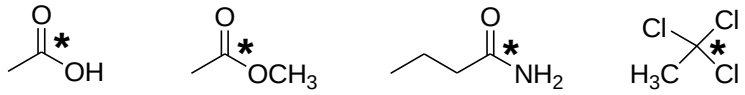
*Carbon is first level

Level 2:- In this category the saturate carbon is bonded with two electronegative atoms and double bondedelectronegative atom(C=O) consider to two electronegative atoms bonded to carbon.



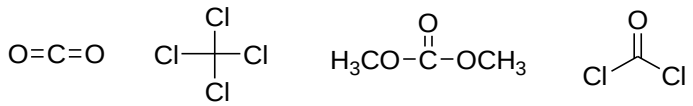
*Carbon is second level

Level 3:-In this level the carbon is bonded to three electronegative atoms or groups, or double bonded hetro atom and one electronegative atom or groups.



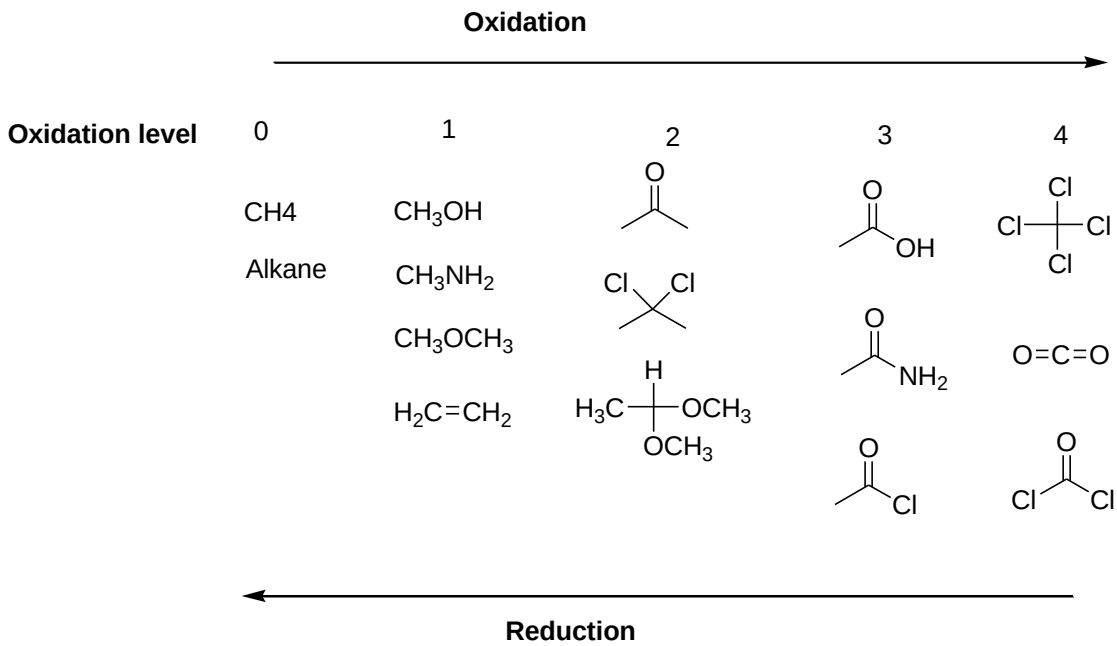
*Carbon is third level.

Level 4:-In this level the carbon is bonded with four electronegative atom or groups, or two hetro atoms and one double bond with hetro atom, or two double bonded hetro atoms.



Notice If the of C-H bond decrease or C-N,C-O or C-X bond has increases the compound has been oxidized and if the no of C-H bond increases or C-N,C-O or C-X bond has decrease the compound has been reduced.

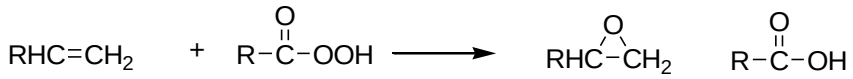
Oxidation state of carbon atom equals the no of its C-N,C-O or C-X bonds



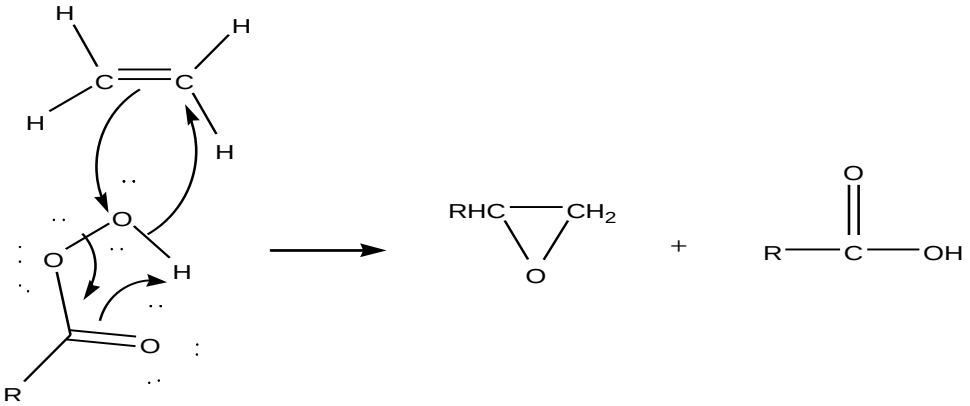
2.3 OXIDATION OF ALKENE

2.3.1 OXIDATION OF ALKENE BY PEROXYACIDS:

Peroxyacids have weak an O-O single bond which transfers oxygen.

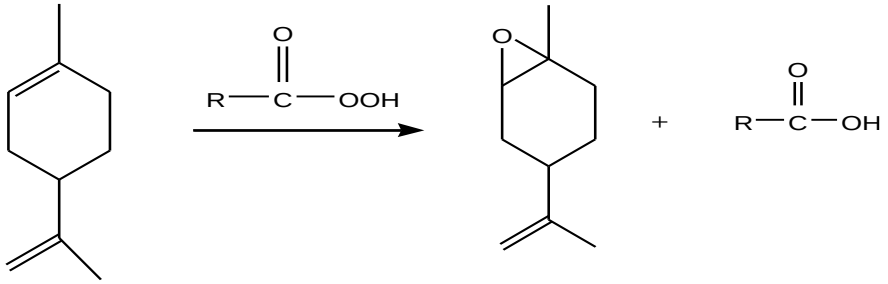


The oxygen atom of the OH group of the peroxyacid accepts a pair of e from the π bond of the alkene, causing the weak O-O single bond to break and oxygen transfer to alkene, form epoxide and carboxylic acid removed. This epoxidation of alkene is a concerted reaction.



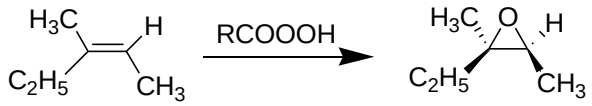
Oxygen of peroxyacid act as $E^{\ominus}$ and alkene act as Nu^{-} so increasing the electron density of the double bond of the alkene increase the rate of epoxidation.

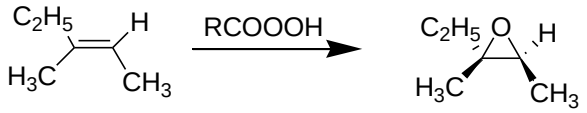
Therefore if a alkene is treated with limited amount of peroxyacid than only highly substituted double bond will be oxidized in the presence of less substituted alkene.



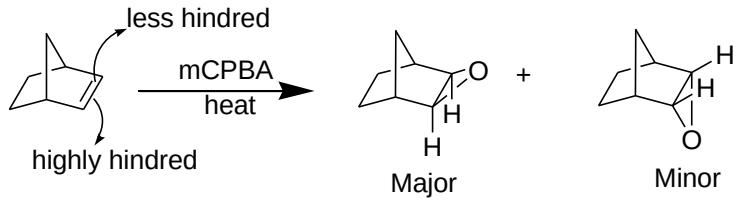
Some of the points related to this reaction are given below

- Syn addition to double bond.
- It is stereospecific reaction; Means reactant has the cis configuration the epoxide will also has cis configuration similarly vice versa. Example are below

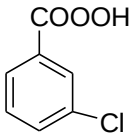




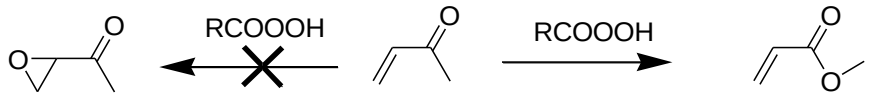
- In case of cyclic alkenes, the reagent approaches from the less hindered side of the double bond



mCPBA = m-chloro perbenzoic acid



- Stronge CF_3CO_3H reagent is used when the electron withdrawing group attach to alkene.
- Exception when electron withdrawing group attach to alkene is aldehyde or ketone than the epoxidation is best performed by the action of nucleophile reagent such as H_2O_2 or t-Butyl hydroperoxide (TBHP). Because in presence of peroxide reagent gives Baeyer Villeger oxidation (insertion of oxygen to aldehyde and ketones gives carboxylic acid and ester respectively).

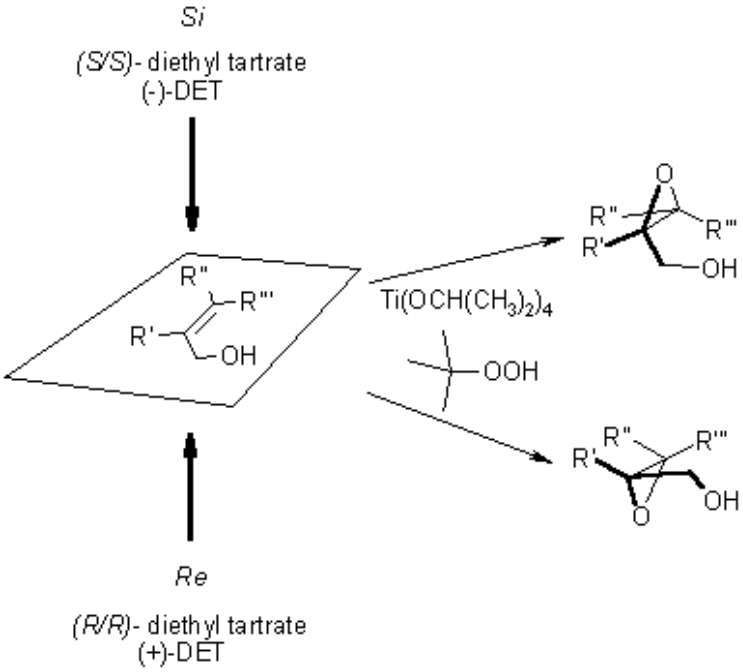


2.3.2 OXIDATION OF ALKENE BY PEROXYACIDS IN PRESENCE OF CATALYST:

- Oxidation of alkene with t-butyl hydroperoxide in the presence of $VO(acac)_2$ (vanadyl acetylacetone) or $MoO_2(acac)_2$(Molybdenum acetylacetone) catalysts provides another excellent method for preparation of epoxide.
- For allylic alcohol $VO(acac)_2$/t-buOOH is good reagent while for isolated alkene $MoO_2(acac)_2$/t buOOH is good reagent.

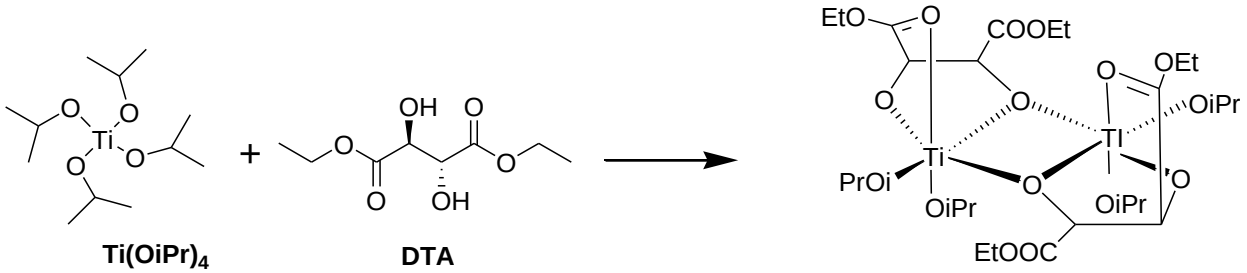
2.3.2.1 SHARPLESS ASYMMETRIC EPOXIDATION:

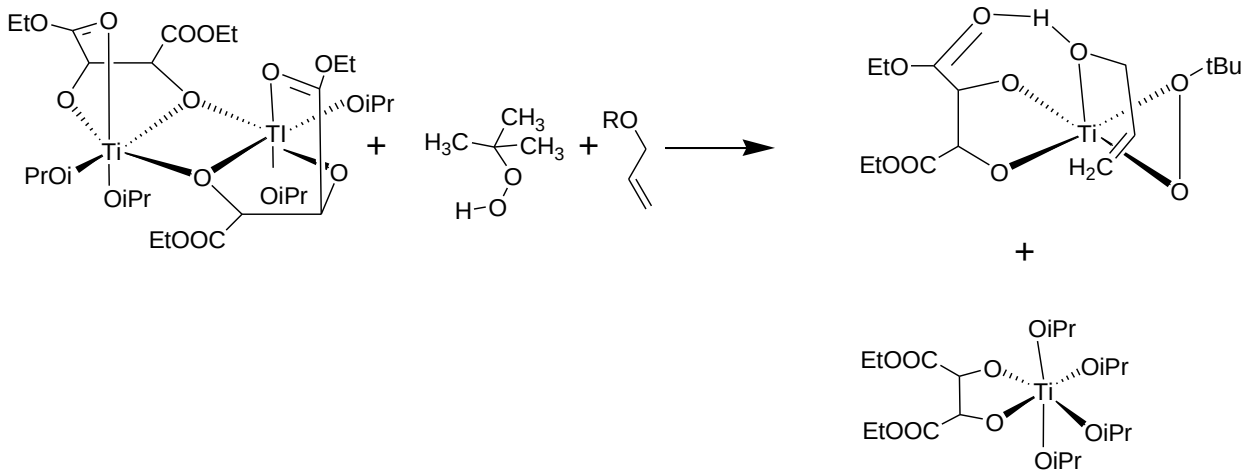
The sharpless asymmetric oxidation is a method for converting prochiral allylic alcohol into c enantioselective epoxy alcohols.



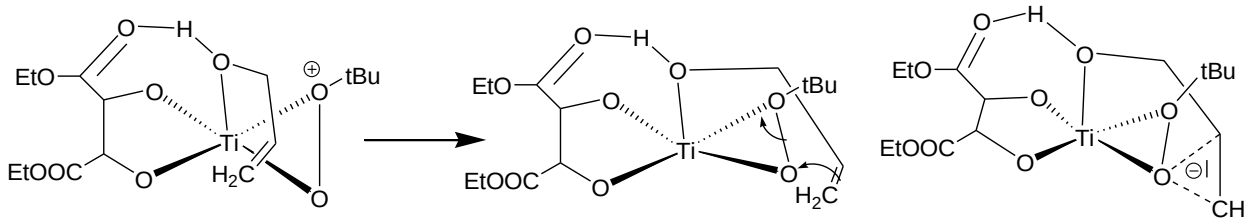
TBHP, Titanium (IV) tetraisopropoxide in conjugated with chiral ligand diethyl tatrate(DET)

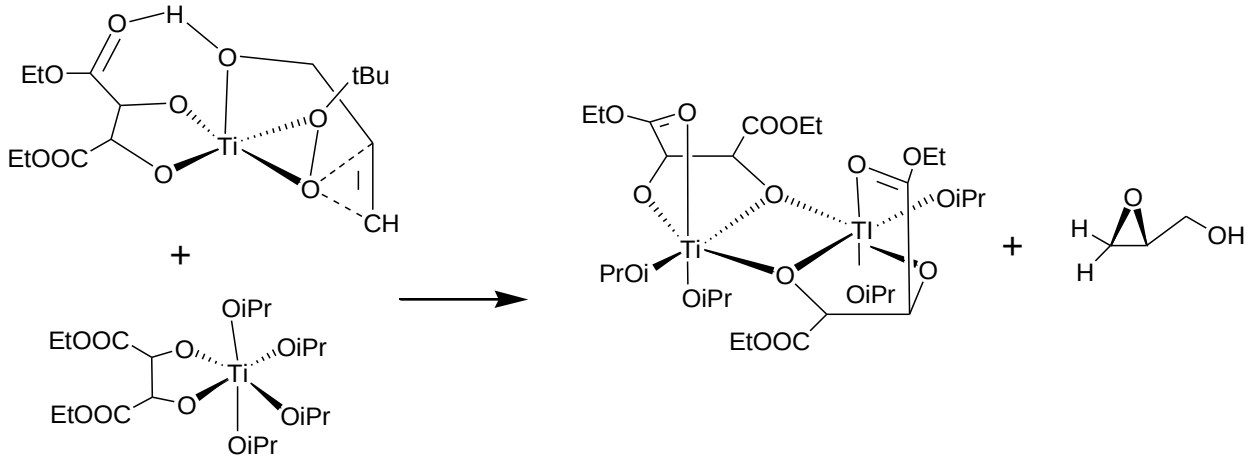
Mechanism of Sharpless oxidation





Transition state



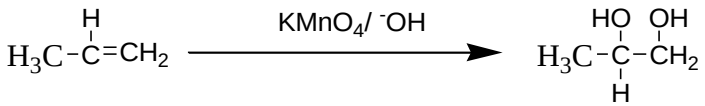


2.3.3 HYDROXYLATION OF ALKENE:

There are the different reagents for hydroxylation process of alkene such as Potassium permaganate, osmium tetraoxide, iodine/silver salt etc. Oxidation of alkene by using these reagents is given below.

2.3.3.1 Potassium permanganate ($KMnO_4$) Baeyer test:

Reaction of alkene with potassium permaganate is used to prepare cis diol (cis diol is also called a glycol). The OH groups are on adjacent carbon so 1-2 diol also known as vicinal diols or vicinal glycol.

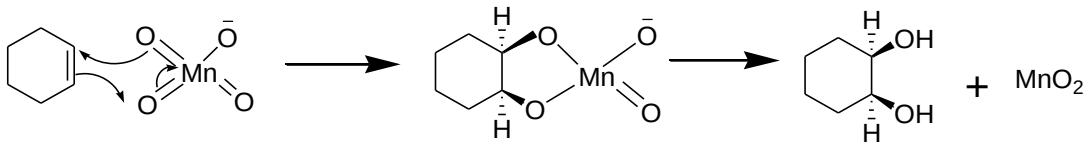


The solution of potassium permaganate must be basic and oxidation must be carried out at room temperature or blow. If the solution is heated or acidic condition than the diol will further oxidized by oxidative cleavage into ketones and carboxylic acid or carbon dioxide (see the section **2.3.4.1**.)

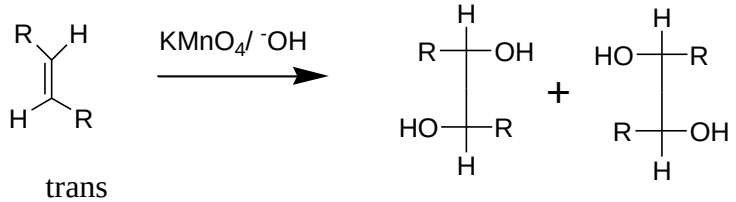
Best result we get if reaction occurs in aquous condition but yield is very poor because the substrate is insoluble in aqueous solution. To improve the yield the reaction must occure in phase transfer catalyst such as quatanary ammonium halide or crown ether.

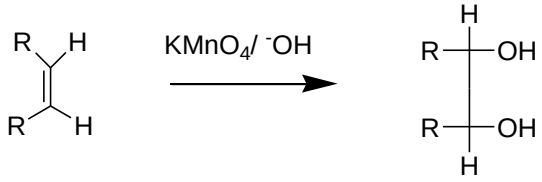
$KMnO_4$ form a cyclic intermediate when they react with an alkene because Magnese is in a highly positive oxidation state +7 and therefore attract electron. Formation of the cyclic intermediate is a syn addition because both oxygen are delivered to the same side of double bond.

Stereochemistry:



It is a stereospecific reaction means cis alkene gives meso form whether trans alkene gives dl(mixture).

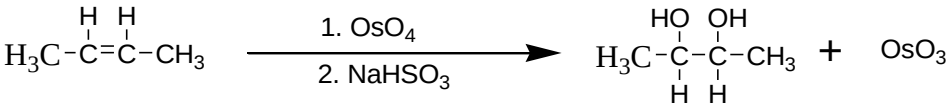




CAR	**C**is substrate by **A**nti addition gives **R**acemic mixture.
TAM	**T**ran substrate by **A**nti addition gives **M**eso product.
CSM	**C**is substrate by **S**yn addition gives **M**eso product.
TSR	**T**ran substrate by **S**yn addition gives **R**acemic mixture.

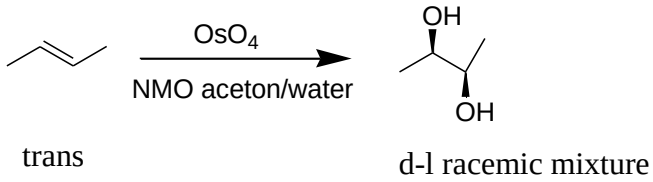
2.3.3.2 Osmium tetroxide (OsO_4):

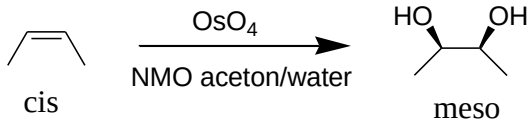
The addition of an alkene to OsO_4 in ether causes rapid precipitate of cyclic intermediate osmate ester. This intermediate is then hydrolysed by sodium bisulfate.



- Less reactive osmate ester has tendency to undergo less side reaction, high yield of the diol are obtained when OsO_4 is used.
- However OsO_4 is expensive and toxic
- **B**ut to minimize the cost of reaction new technique have develop in which OsO_4 act as a catalyst.
- This catalyst used catalytic amount of OsO_4 together with an equivalent of N-methyl morpholine N-oxide(NMO),and known as Upjohn dihydroxylation.

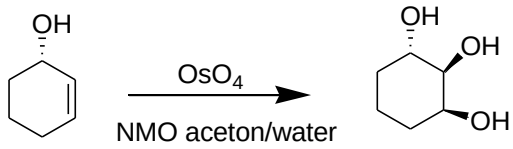
- N-methyl morpholine N-oxide(NMO) in the reaction reoxidize the osmium (VI) to osmium (VIII)
- Stereochemistry of Upjohn reagent is same as $KMnO_4$



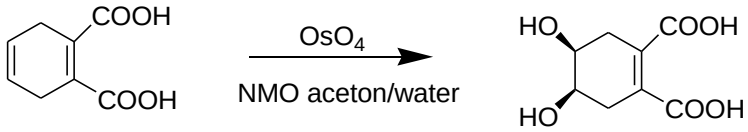


- **Oxidation of allylic alcohol or allylic ether:-**

OsO_4 is highly stereoselective giving preferentially the isomer in which the original OH or alkoxy group is anti to newly introduced hydroxyl groups.



- OsO_4 is electophile so the presence so electron withdrawing groups to the alkene double bond retards the hydroxylation. Thus if more than one double bond are present hydroxylation occurs at the most electron rich double bond.

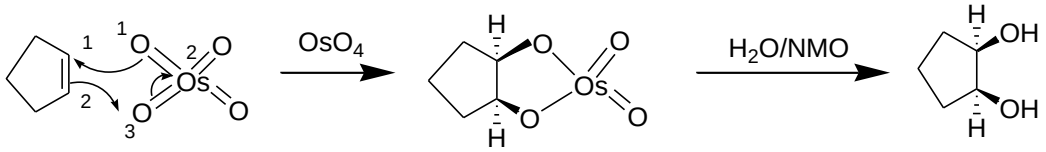


Mechanism:-

OsO_4 form a cyclic intermediate when they react with an alkene because osmium is in a highly positive oxidation state +8 and therefore attract electron. Formation of the cyclic intermediate is a syn addition because both oxygen are delivered to the same side of double bond then this intermediate is hydrolysed by sodium bisulfate or Upjohn reagent.

Formation of cyclic osmate ester can be possible via two ways.

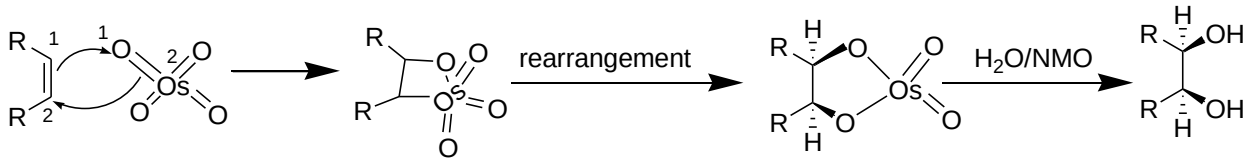
I [3+2] cycloaddition



[3+2 cyclo addition]

II [2+2] cyclo addition

[2+2] cyclo addition gives osmaoxetane which on rearrangement produce osmate, which on hydrolysis form 1-2 diol.

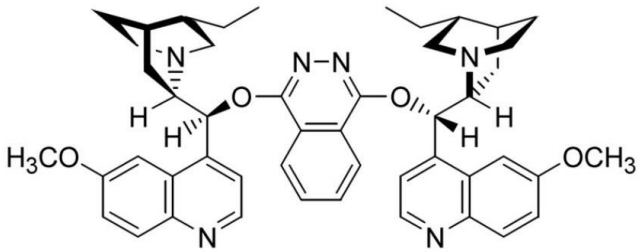


[2+2 cyclo addition] Osmaoxetane osmate

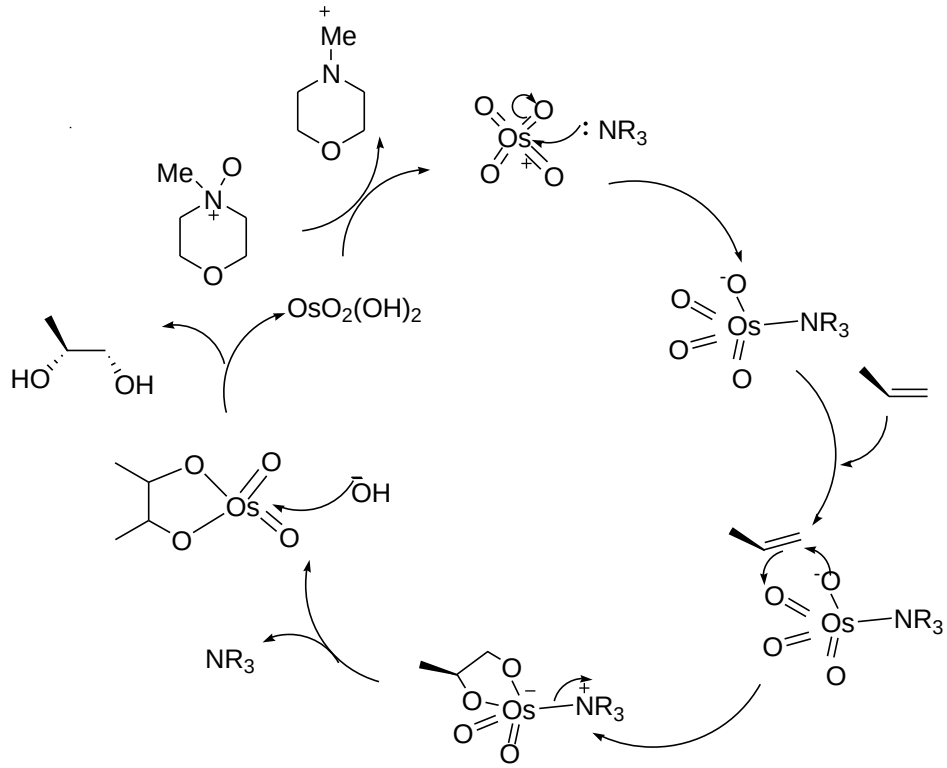
2.3.3.3 SHARPLESS ASYMMETRIC DIHYDROXYLATION

Dihydroxylation of trans alkene forms d-l enantiomers. Selectively formation of one enantiomer is known as sharpless asymmetric dihydroxylation.

$(DHQ)_2$PHAL 1,4-bis (9-O-**dih**ydro**q**uinidine)**ph**th**al**izine ligand coordinate to the OsO_4 and form asymmetric complex.



Mechanism:-

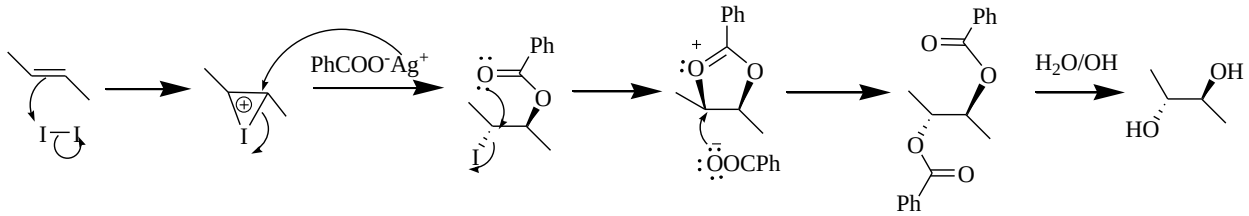


NR_3 = $(DHQ)_2$ PHAL

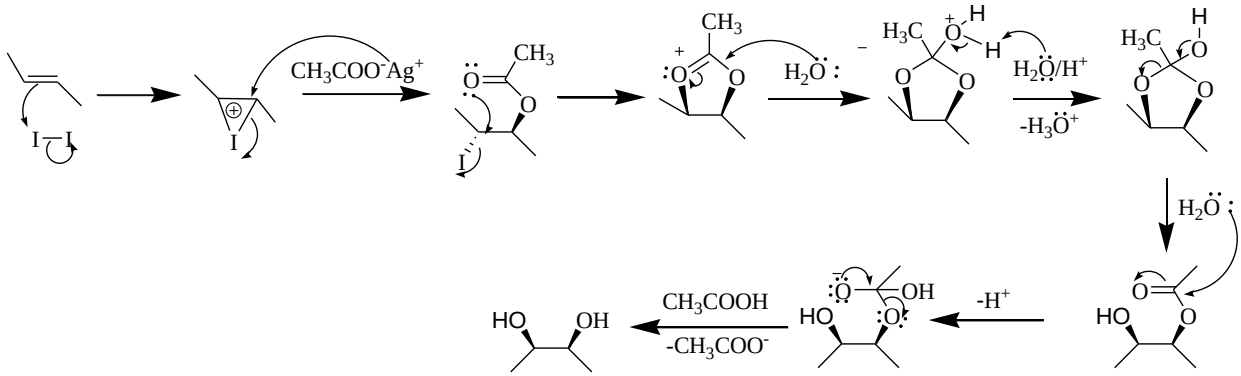
2.3.2.4 OXIDATION WITH SILVER SALT AND I_2

There is two conditions from which diol is formed viz. Prevost reaction and Woodward reaction.Oxidation of alkene by using both these reagents can be defined as.

Prevost reaction:- Reaction of PhCOOAg/ I_2 in anhydrous condition (solvent CCl_4) gives the anti substituted dibenzoate product, which on hydrolysis to yield trans diols.

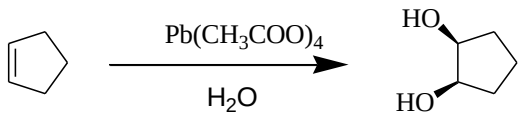


Woodward reaction:-



2.3.2.4 OXIDATION BY LEAD TETRA ACETATE $Pb(CH_3COO)_4$:

It also show syn addition but is less selective than Woodward dihydroxylation.



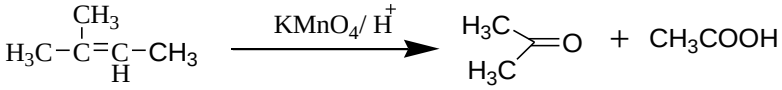
2.3.4 OXIDATIVE CLEAVAGE OF ALKENE:

The oxidation reaction cuts the molecule in two pieces, it is called oxidative cleavage.

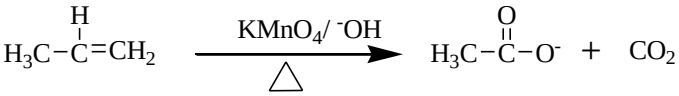
2.3.4.1 OXIDATIVE CLEAVAGE BY $KMnO_4$:

We saw in section 2.3.3.1 $KMnO_4$ oxidised alkene to diol by abasic solution at room temperature or below. However if the basic reaction is heated or if the $KMnO_4$ is acidic, the reaction is not stop at diol. Instead the alkene will be cleavage and reaction product will be ketone,carboxlic acid carbondioxide etc depand upon reactant and reaction condition. If reaction conditionis acidic carboxlic acid is formed and in basic condition carboxilate ion form. Terminal alkene forms CO_2 as a product.

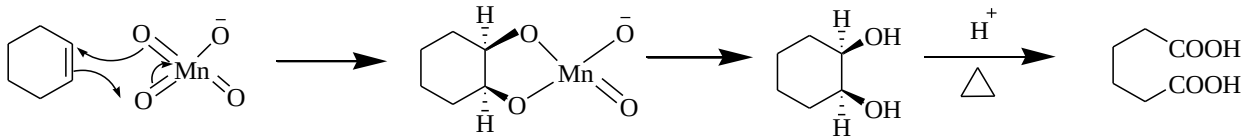
In acidic condition



In basic condition



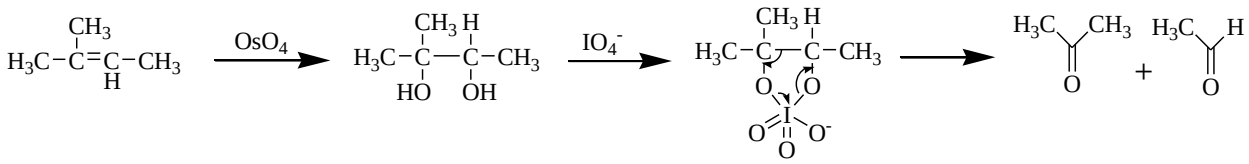
Mechanism:



2.3.4 .2 OXIDATIVE CLEAVAGE BY LEMIEUX-JOHNSON REAGENT ($NaIO_4$/ OsO_4):

This reagent consist dil aqueous solution of $NaIO_4$ with a catalytic amount of OsO_4. Alkene oxidized to 1-2 diol($KMnO_4$, OsO_4, Prevost reaction) and that 1-2 diol can be futher oxidized to aldehyde and ketones by periodic acid(HIO_4).

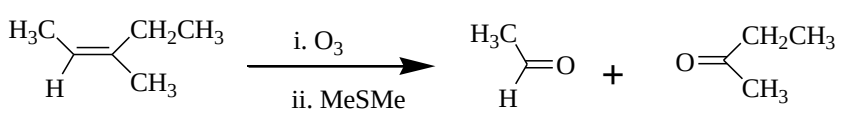
Dihydroxy alkane react with $NaIO_4$and formed cyclic intermediate. The reaction take place because I is in +7 oxidation state act as nucleophile so readily accept electrons from dihydroxy alkane and formed cyclic intermediate,and this intermediate break down from the bond between the two carbon bonded OH group. If the carbon bonded to an OH group is also bonded to two alkyl group , the product will be ketone, If is bonded to an alkyl and a hydrogen atom or two hydrogen atom the product will be a aldehyde.



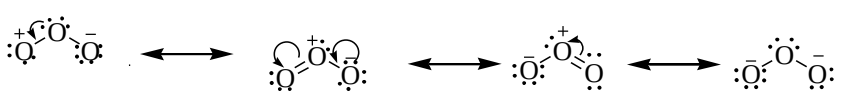
Osmium tetraoxide act as catalyst because it is reoxidized by $NaIO_4$.

2.3.4.3 OZONOLYSIS OF ALKENE:

In Lemieux and Johnsion reagent alkene is first converted into syn diol than $NaIO_4$ break the C-C bond and formed keton, aldehyde, carboxylic acid or CO_2.But we can directly convert alkene to keton, aldehyde, carboxylic acid or CO_2 by ozonolysis.

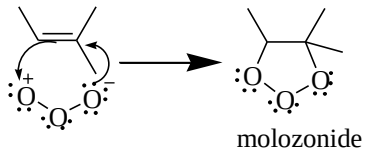


O_3 structure can be represented by the following resonating structure



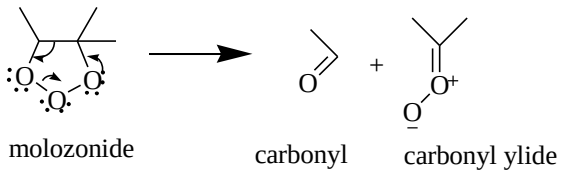
Resonance contributors of ozone

Step I:- In the first step ozone react with alkene by 1,3-dipolar cycloaddition reaction. It is concerted reaction.

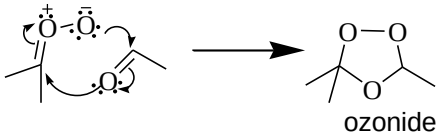


The product of ozone addition to an alkene is an unstable molozonide.

Step II:- The molozonide decomposed by retro 1,3-dipolar cycloaddition reaction. Forms a carbonyl compound and a carbonyl ylide.

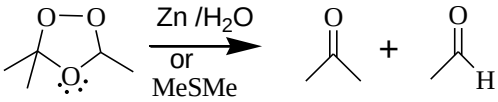


Step III:- A carbonyl compound and a carbonyl ylide react with each other to formed more stable ozonide.

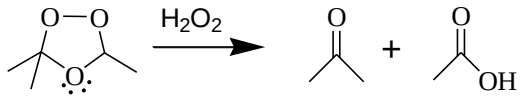


Ozonide are explosive, they are seldom isolated . The ozonide is easily cleaved.

Reductive condition:- If it cleaved in the presence of reducing agent as Zn or di methyl sulphide or phosphite the product will be ketones and aldehyde. The reducing agent prevents the oxidation of aldehyde.

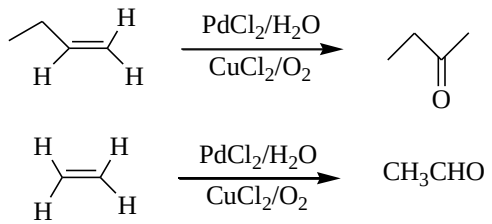


Oxidativetive condition:- If it cleaved in the presence oxidising agent as H_2O_2 the product will be ketone and carboxylic acid. Aldehyde formed by cleavage of ozonide will futher oxidized by H_2O_2 to carboxylic acid.



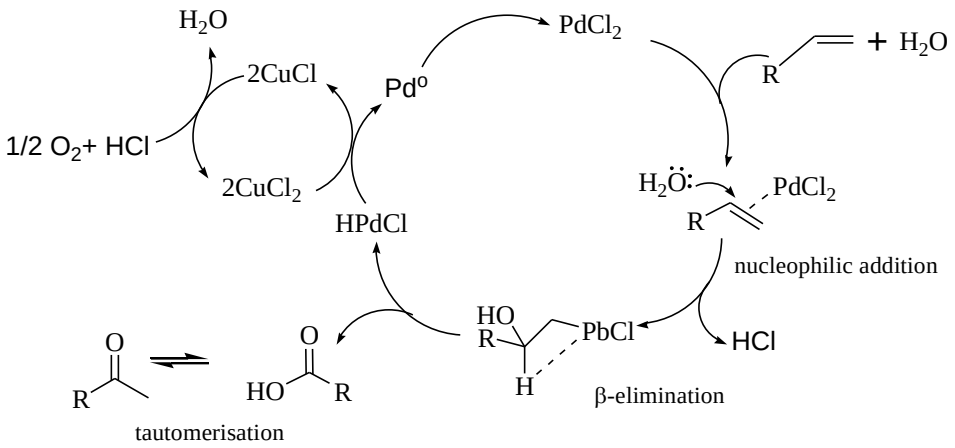
2.3.5 OXIDATION OF ALKENE INTO ALDEHYDE AND KETONES:

Wacker process:- The oxidation of alkene to form ketones can be achieved by reaction with Pd(II) salt and oxygen in the presence of $CuCl_2$ in aquous medium known as Waker process.



In warker oxidation terminal alkene converted into methy ketone. But the oxidation of ethylene formed aldehyde.

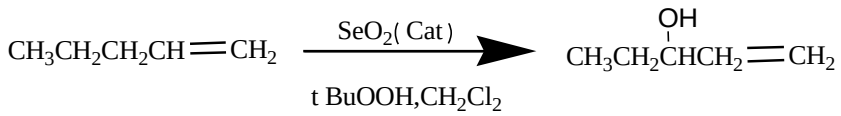
Mechanism:-



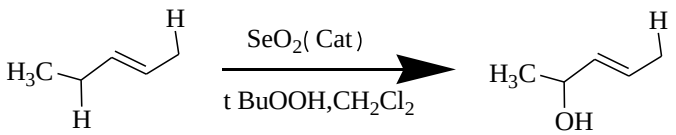
2.3.6 OXIDATION AT ALLYLIC POSITION:

2.3.6.1Allylic Oxidation by Selenium dioxide, SeO_2

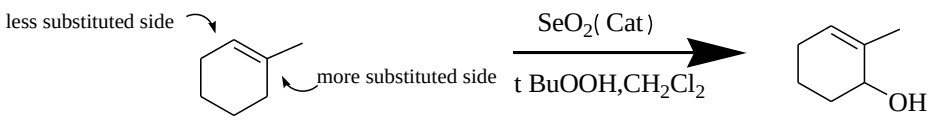
Selenium dioxide transforms alkenes into allylic alcohol in one step.



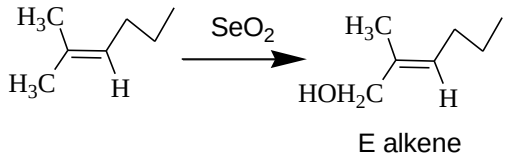
- t-butyl perhydroxide used to reoxidised spent catalyst to SeO_2.
- Reactivity order of allylic position is $2^0 > 3^0 > 1^0$



- In unsymmetrical alkene, it oxidized more substituted side of double bond, because catalyst acts as enophile (lover of ene).

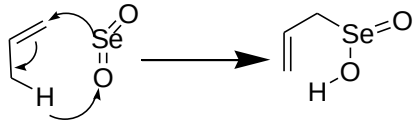


- If 1-1 dimethyl alkene is oxidized by SeO_2 E allylic alchole is formed by selectively attack of E methyl group because of concerted [2-3] sigmatropic rearrangement.

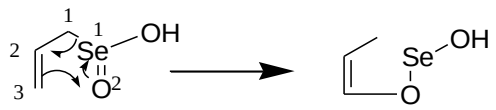


Mechanism:- The reaction proceeds following way

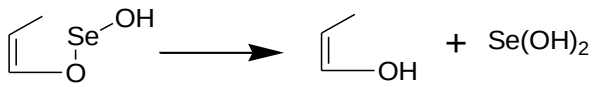
Step I:- Selenium dioxide react with alkene via ene reaction (Ene reaction involves the reaction of an alkene (called ene)having an allylic hydrogen with a compound multiple bond double.)



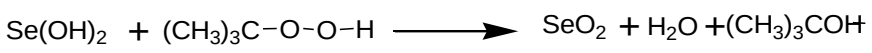
Step II:- Allylic seleninic acid undergo 2-3 sigmatropic reaction



Step III:- On hydrolysis gives allylic alcohol.

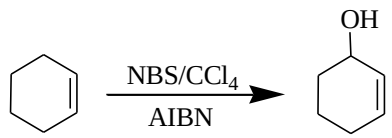


Step VI:- Catalyst reoxidised by t-butyl perhydroxide.

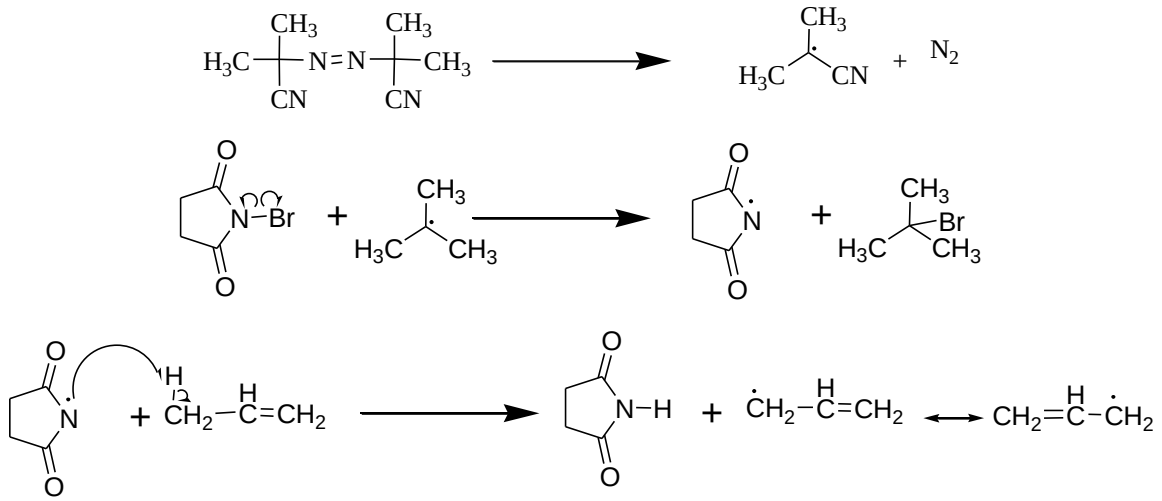


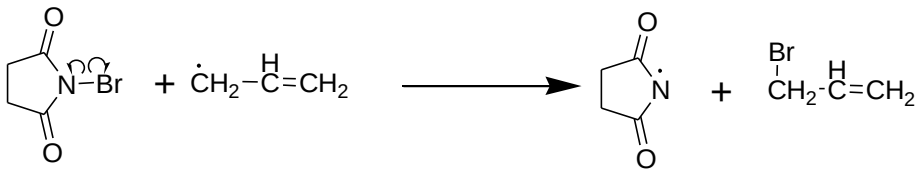
2.3.6.2 Allylic Oxidation By N-Bromo succinamide [NBS]:

It is also a effective regent for allylic position. NBS transform alkenes into allylic bromide.

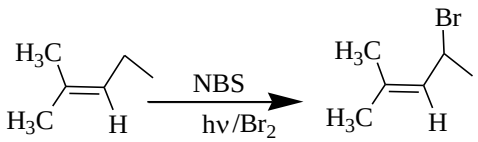


- The reaction takes place by radical mechanism.NBS best work in a non polar solvent such as carbon tetra chloride with small radical inititor sach as **a**zobis **i**so**b**utyl**n**itrile AIBN, hν etc.



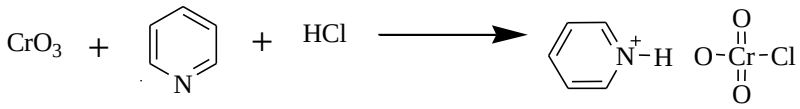


- Stability of radical is $3^0>2^0>1^0$ so it prefer CH> CH_2> CH_3 position for allylic bromination.

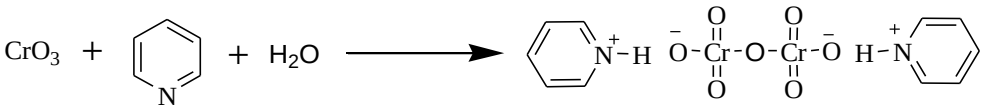


2.3.6.3 OXIDATION BY PYRIDINIUM CHLORO CHROMATE OR PYRIDIUM DICHROMATE:

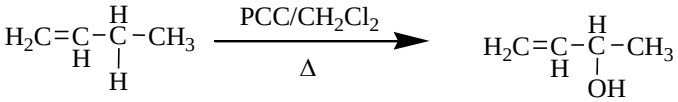
PCC is obtained by the adding pyridine to a solution of chromium oxide in hydrochloric acid.



Pyridinium dichromate is obtained by adding of pyridine to a solution of chromium trioxide in water.

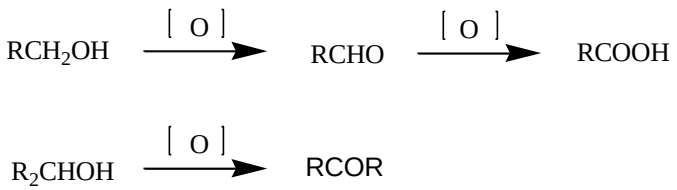


By this reagent allylic position is oxidized into carbonyl group. It is a milder version of chromic acid that why it oxidized primary alcohol into aldehyde sees section.



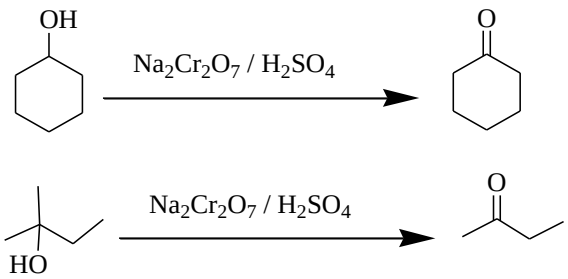
2.4 OXIDATION OF ALCOHOL

Oxidation of alcohol gives different product aldehyde, ketone, carboxylic acid depends upon the alcohol and oxidizing agent.



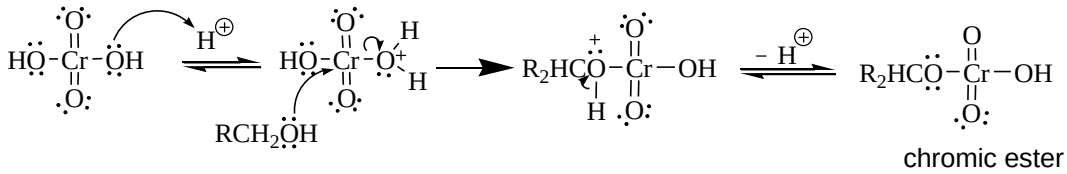
2.4.1 Oxidation by stronge oxidizing agent chromic acid:

Stronge oxidizing agent chromic acid, 1^0 alcohol oxidized to carboxylic acid and 2^0 alcohol oxidized to ketone. Chromic acid is formed when chromium trioxide or sodium dichromate desolved in concentrated sulfuric acid.

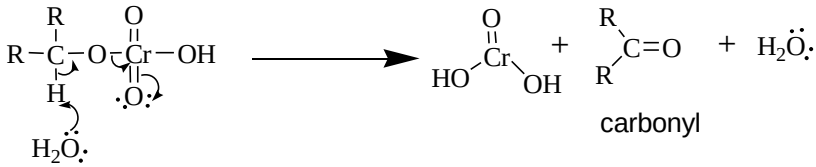


Mechanism:

Chromic acid oxidized alcohol by first forming a chromic ester.



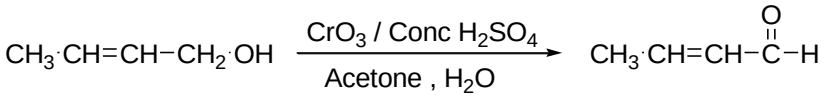
Chromic ester undergo E2 elimination gives carbonyl compound.



Note:- That the oxidation of either primary alcohol or secondary alcohol involves removal of a hydrogen from the carbon which the hydroxyl is attached. But in tertiary alcohol the carbon bearing the hydroxyl does not have hydrogen to remove so tertiary alcohol not oxidized by this reagent.

2.4.2 Oxidation by Jones reagent:

Chromic trioxide dissolves in concentrated H_2SO_4 and diluted by acetone and water known as jones reagent.It relatively mild oxidizing agent. It is useful for oxidation of alcohols which contain double bond or triple bond or allylic or benzylic C-H bonds and other acidic sensitive groups. The reaction is carried out at 0-20^{0}C.

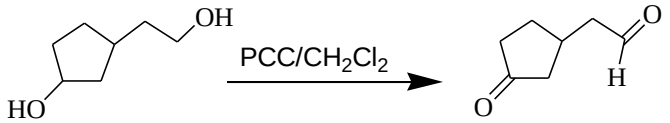


The main task of oxidizing agent to stop oxidizing reaction of 1^0 alcohol at aldehyde and oxidizing agent should be chemoselective.

For this task many oxidizing agent are used such as dimethyl sulfoxide /oxalyl chloride/triethylamine (swern oxidation), pyrdinium chloro chromate (PCC), pyridinium chloro dichromate(PDC), dess martin reagent, N oxo ammonium salt (TEMPO), Manganese dioxide, Fetizon oxidation, ceric ammonium nitrate(CAN).

2.4.3 Oxidation by Pyridinium chloro chromate (PCC) or pyridinium dichromate (PDC):

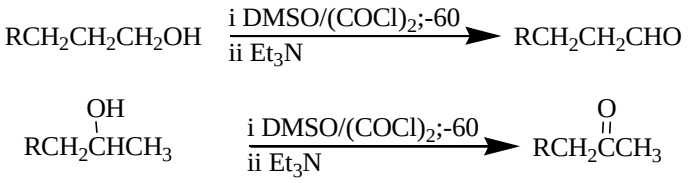
These are mild oxidizing reagent, used in oxidation of alcohol to aldehyde. The reaction is carried out in anhydrous solvent such as CH_2Cl_2.



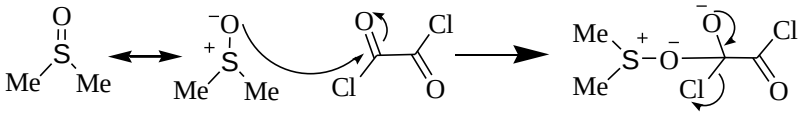
- It is chemoselective to alcohol in presence of double bonds.

2.4.4 Swern Oxidation:

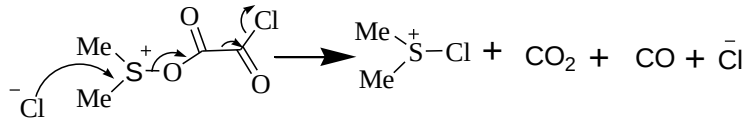
The oxidation of primary or secondary alcohol by dimethyl sulfoxide(DMSO), oxalyl chloride ($COCl_2$) and trimethyl amine form aldehydes or ketones respectively.



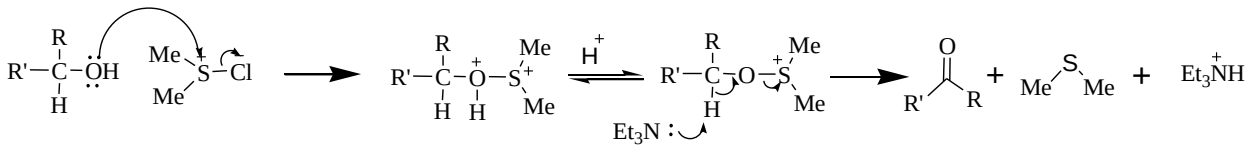
Mechanism:- Firstly oxalyl chloride react with dimethyl sulfoxide gives dimethyl sulfonium ion.



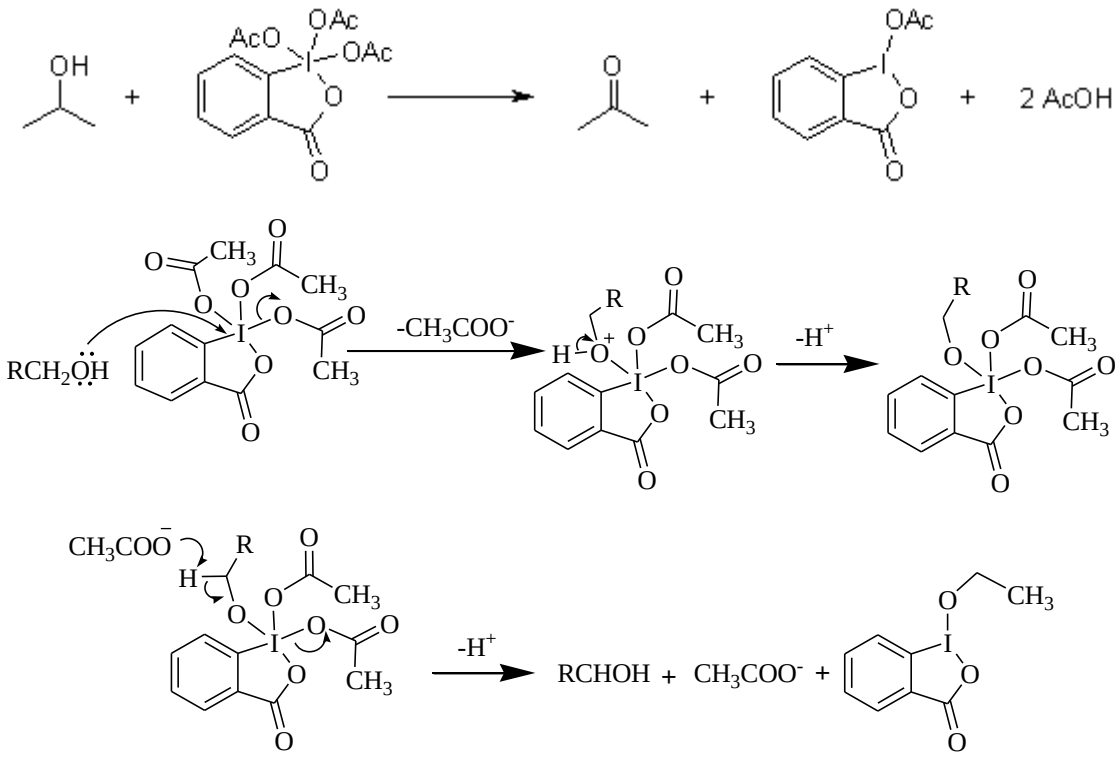
Dimethyl chlorosulfonium ion reacts with alcohol.



Like chromic acid oxidation the swern oxidation uses an E2 reaction to form the aldehde or ketone.



2.4.5 Oxidation by Dess Martin Reagent (Periodinane):

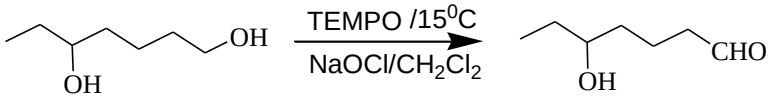


The reagent used to oxidation of primary and secondary alcohol to aldehyde and ketone respectively.

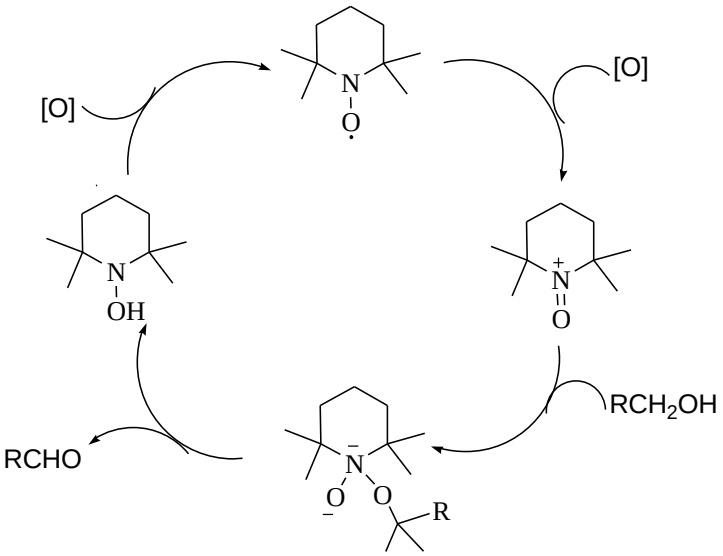
It has several advantage then chromic acid and DMSO based oxidant such as room temperature, neutral solvent. This reagent is inert for other oxidisable group present in the substrate. Benzylic and allylic alcohols react faster than saturate alcohols.

2.4.6 Oxidation by Tetra Methyl Piperidine Nitroxide (TEMPO):

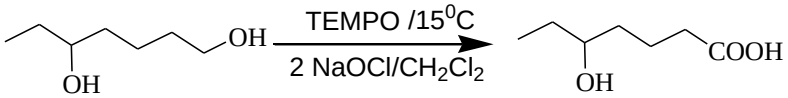
It is radical 1-Piperidinyloxy, 2,2,6,6-tetramethyl-(TEMPO). TEMPO is employed in organic reaction as a catalyst for the oxidation of primary alcohols to aldehydes.



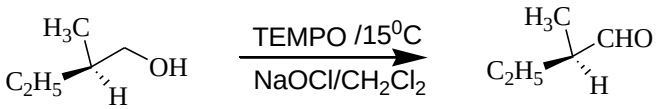
The actual oxidant is the N-oxoammonium salt. In a catalytic cycle with sodium hypochlorite generates the N-oxoammonium salt from TEMPO.



- If 2 equivalent sodium hypochlorite have taken the aldehyde further oxidized to carboxylic acid.

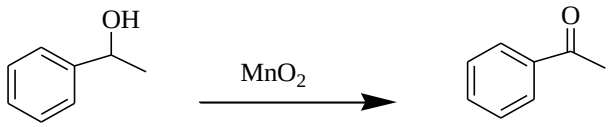


- The stereochemistry of chiral center does not change.

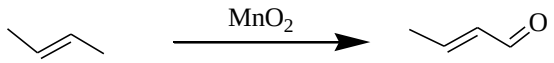


2.4.7 Oxidation by Manganese Dioxide (MnO_2):

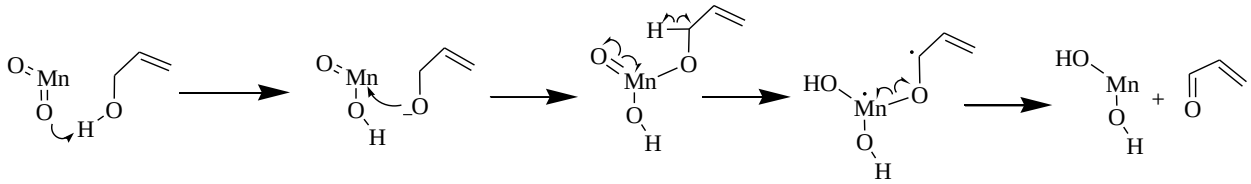
It is hetrogenous catalyst, specially oxidized benzylic and allylic alcohol to aldehyde or ketone under mild condition.



The configuration of the double bond is conserved in the reaction.

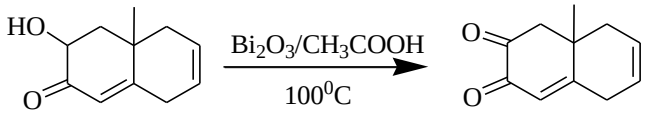


Mechanism:



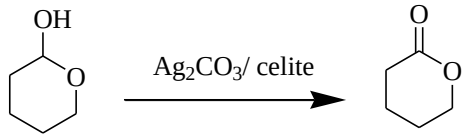
2.4.8 Oxidation by Bismuth Oxide (Bi_2O_3):

It is used for the oxidation of α hydroxyl ketones (acyloins) to diketones. α hydroxyl ketones is warm with bismuth oxide in acetic acid solvent gives diketone.



2.4.9 Oxidation by Silver Carbonate (Fetizone Oxidation):

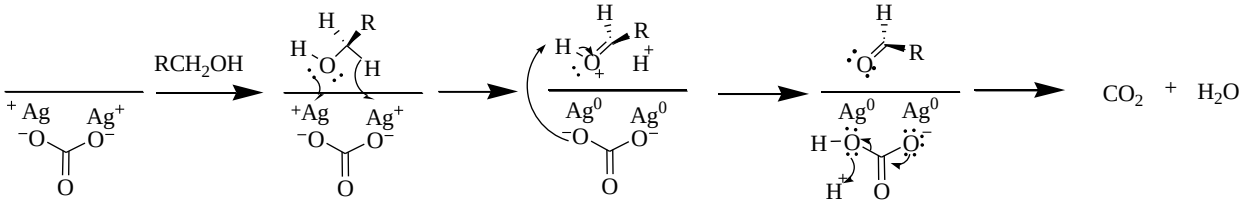
In fetizon oxidation, primary and secondary alcohol to aldehyde and ketone respectively in the presence of reagent silver carbonate adsorbed onto the surface of celite. It is a mild reagent, suitable for both acid and base sensitive compounds. Its great reactivity with lactols makes the Fétizon oxidation a useful method to obtain lactones from a diol.



It is single e oxidation of the both the alcoholic oxygen and the α- hydrogen to the alcohol by two Ag (I) with in celite.

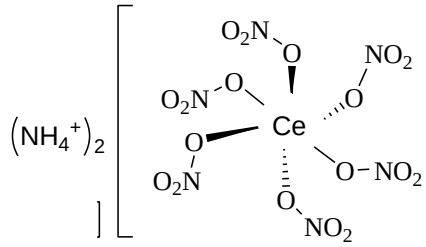
A proposed mechanism for the oxidation of an alcohol by Fétizon's reagent involves two silver I ions accept single- single electron from the alcoholic oxygen and the hydrogen alpha to

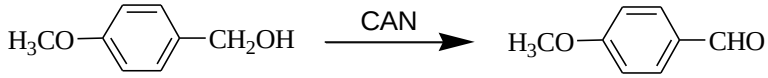
the alcohol and two atoms of silver(I) within the celite surface. The carbonate ion then proceeds to deprotonate the resulting carbonyl generating bicarbonate which is further protonated by the additionally generated hydrogen cation to cause elimination of water and generation of carbon dioxide.[4]



2.4.10 Oxidation by Ceric ammonium nitrate (CAN) $NH_4[Ce(NO_3)_6]$:

This reagent gives poor yield for ketone from secondary alcohol but good yield for the selective oxidation of primary alcohol to aldehyde.





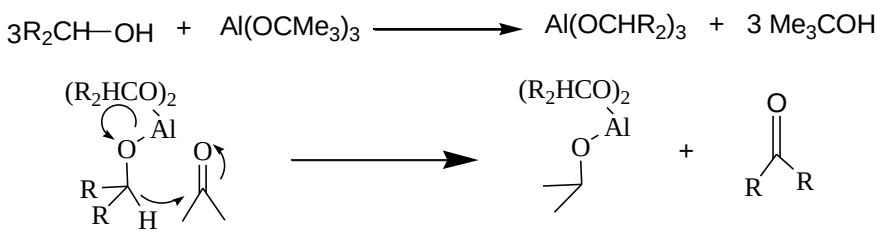
2.4.11 Oppenaur Oxidation ($Al(OtBu)_3$/acetone):

This reaction involves selectively conversion of secondary alcohols to ketones. The alcohol is oxidized with aluminium t-butoxide in excess of acetone to ketone.

$$R_2CHOH + (CH_3)_2CO \xrightarrow{Al(OCMe_3)_3} R_2CO + (CH_3)_2CHOH$$

It does not oxidize other sensitive functional groups such as amines and sulfides. Though primary alcohols can be oxidized under Oppenauer conditions, primary alcohols are seldom oxidized by this method due to the competing aldol condensation of aldehyde products. The Oppenauer oxidation is still used for the oxidation of acid labile substrates.

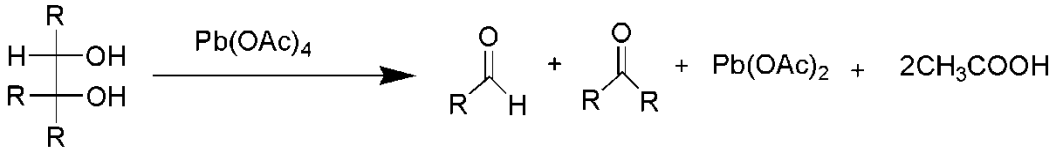
MECHANISM



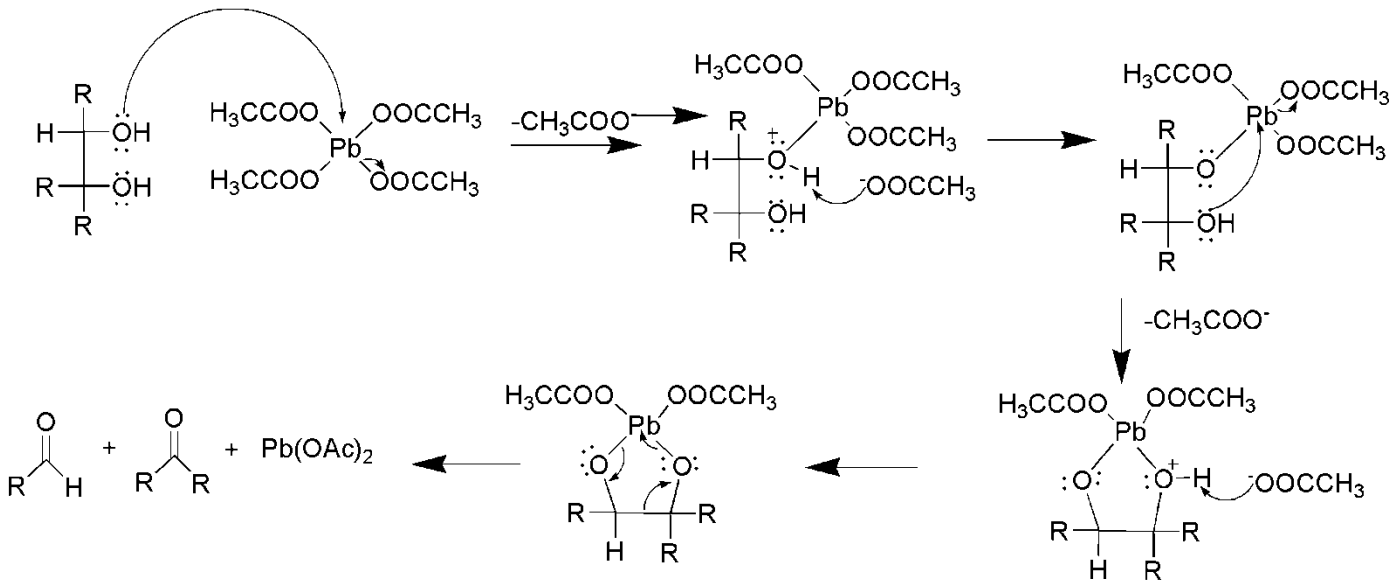
2.5 OXIDATION OF 1-2 DIOLS

There are different reagent such as Dess Martin periodinane, periodic acid,Lead tetra acetate, ceric ammonium nitrate which can be used for the oxidation of 1-2 diols , these reagents as well as oxidation process by them can be defined as:

2.5.1 Oxidation by Lead tetra acetate:- LTA at room temperature oxidized vicinal diol with cleavage of bond to yield aldehydes, ketones or both depending upon the structure of glycols.

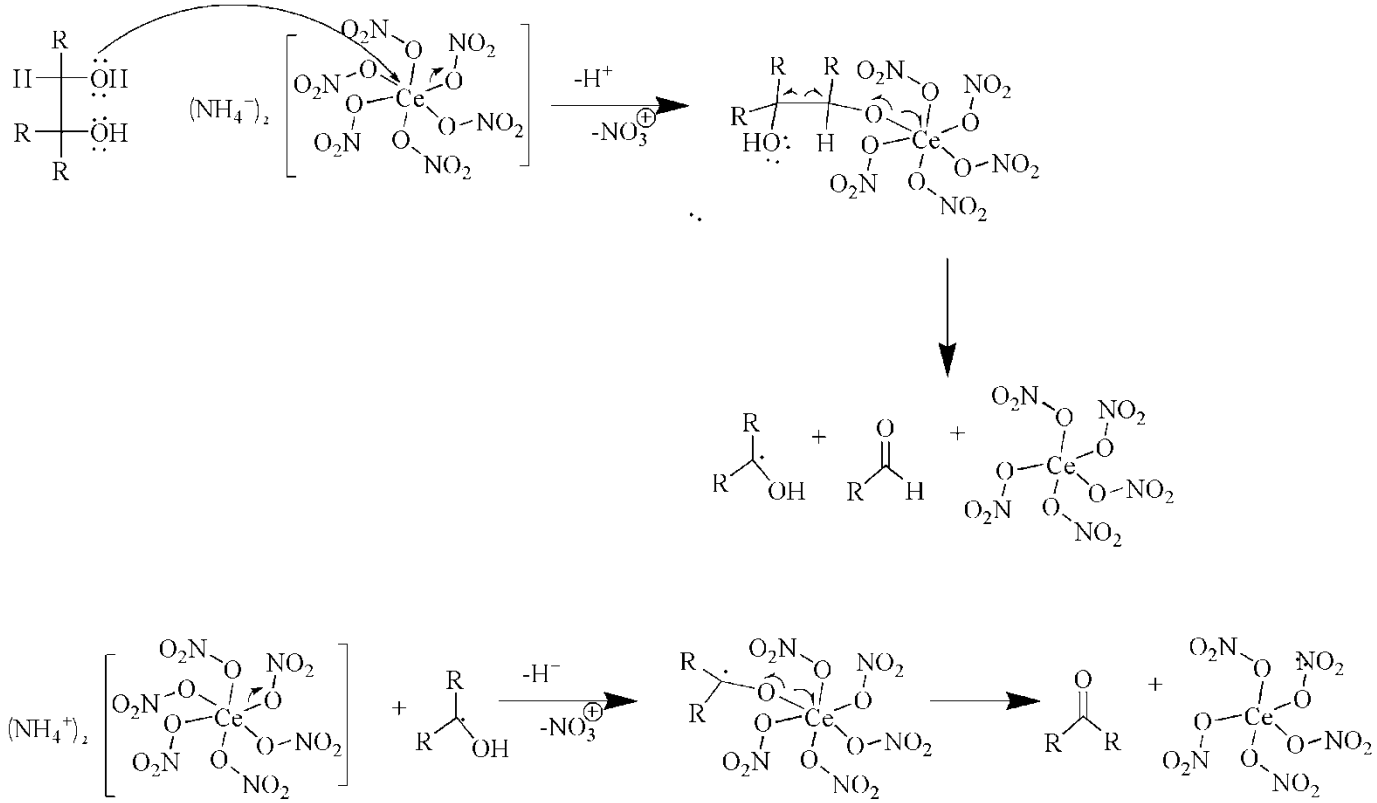


Mechanism:-

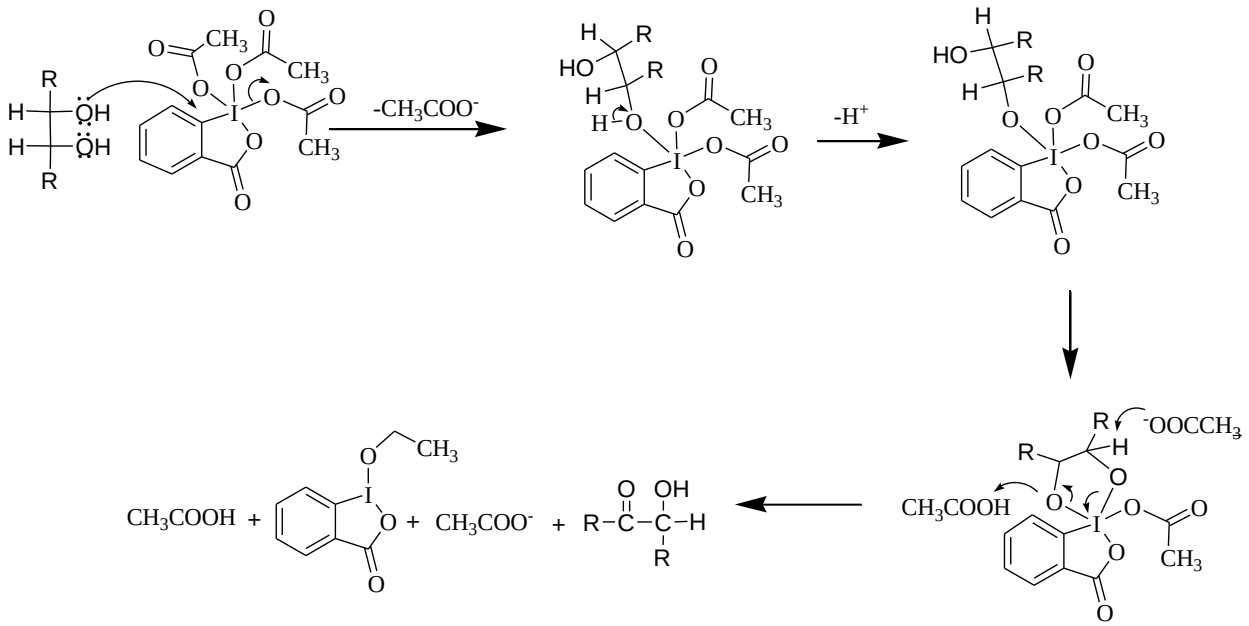


2.5.2 Oxidation by Ceric ammonium nitrate (CAN) $NH_4[Ce(NO_3)_6]$:

It is also show oxidative cleavage of vicinal diol to aldehyde and ketones depend upon the structure of diol.It is two successive one electron transfer.



2.5.3Oxidation by Dess Martin Reagent (Periodinane):



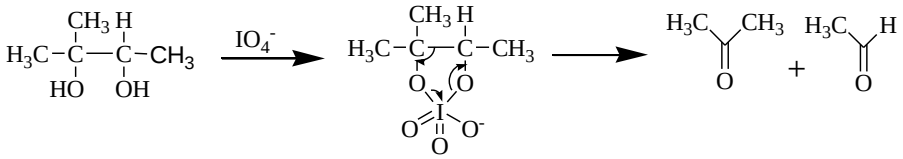
The reagent also used to oxidation of vicinal diol to α hydroxyl carbonyl.

This reagent is inert for other oxidisable group present in the substrate.

Chemoselectivity to furan ring, sulphide, vinyl ether, secondary amides.

2.5.4 Oxidation by Sodium Periodate ($NaIO_4$):

Dihydroxy alkane react Sodium periodate and gives ketone or aldehyde. See section **2.3.4 .2**



2.6 OXIDATION OF ALDEHYDE AND KETONE:

Aldehydes are easily oxidized to carboxylic acid. There are many reagents such as $KMnO_4$, chromic acid, sodium dichromate etc. Some more we have discuss in alcohol oxidation selection.

2.6.1 Oxidation by Tollen Reagent:

A dilute solution of silver nitrate in aqueous ammonia is known as tollen's reagent.It oxidized –CHO and α-hydroxyl ketone. So this reagent used to distinguish between aldehyde and ketone.It does not oxidized ketone.

Silver nitrate in alkali solution gives silver oxide.

$$2\ AgNO_3 + 2\ NaOH \longrightarrow Ag_2O + 2\ NaNO_3 + H_2O$$

Silver oxide in ammonical solution form diamminesilver(I) complex .

$$Ag_2O + 4\ NH_3 + 2\ NaNO_3 + H_2O \longrightarrow 2\ [Ag(NH_3)_2]NO_3 + 2\ NaOH$$

Diamminesilver(I) complex oxidised aldehyde to carboxylic acid and complex reduced to silver which stick on test tube and make mirror.

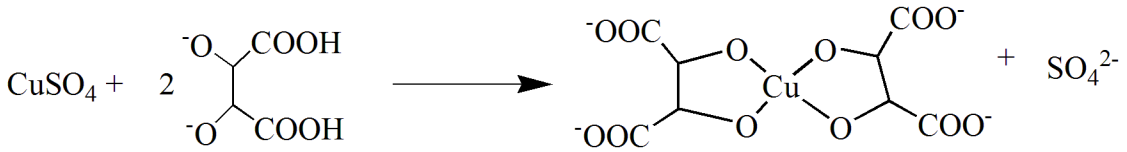
$$2\ [Ag(NH_3)_2]^{+} + RCHO + H_2O \longrightarrow 2\ Ag + 4\ NH_3 + RCOOH + 2\ H^{+}$$

2.6.2 Oxidation by Fehling Reagent:

Like tollen's reagent it oxidized only aldehyde and α-hydroxyl ketone.It does not oxidized ketone. It Fehling's solution is prepared by combining two separate solutions, known as Fehling's A and Fehling's B. Fehling's A is aqueous solution of copper(II) sulfate, which is deep blue. Fehling's B is a colorless solution of aqueous potassium sodium tartrate (also known as Rochelle salt) made in sodium hydroxide. The copper(II) complex in Fehling's solution is an oxidizing agent and the active reagent in the test.

When mixing equal volumes of solution A and B, formed the bis(tartrate) complex of Cu^{2+}.

This complex oxidised aldehyde to carboxylic acid and complex reduced to Cu^{+}(red).



Structure of the main complex in Fehling's solution.

$$RCHO + 2\ Cu(C_4H_4O_6)_2^{2-} + 5\ OH^{-} \longrightarrow RCOO^{-} + Cu_2O + 4\ C_4H_4O_6^{2-} + 3\ H_2O$$

2.6.3 Oxidation by Benedict's reagent:

Benedict's solution is a chemical reagent and complex mixture of sodium carbonate, sodium citrate and copper(II) sulfate pentahydrate. It is often used in place of Fehling's solution to detect the presence of reducing sugars. Benedict's test detects the presence of aldehydes, alpha-hydroxy-ketones, and hemiacetals. Generally, it is used to test for the presence of monosaccharides and reducing disaccharide sugars in food.

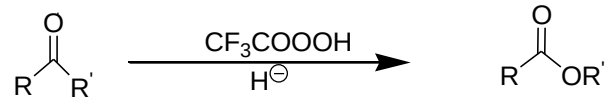
$CuSO_4.5H_2O + Na_2CO_3 + Na_3C_6H_5O_7 \longrightarrow$ Benedict 's Reagent

$Cu^{+2} + RCHO \longrightarrow RCOOH + Cu_2O$

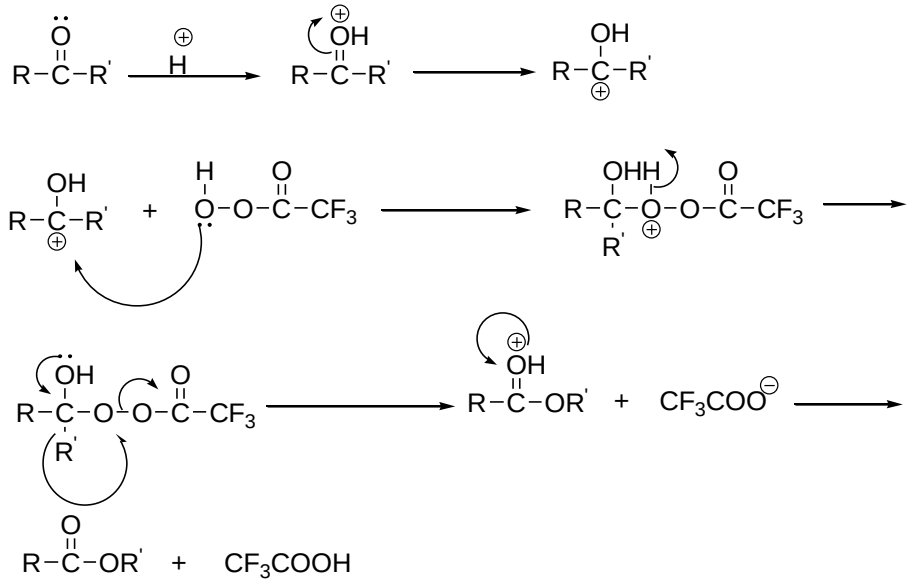
Copper II ion (blue color solution) change into copper I(cuprous oxide Cu_2O red precipitate) after reaction.

2.6.4 Baeyer Villiger Oxidation Reaction:

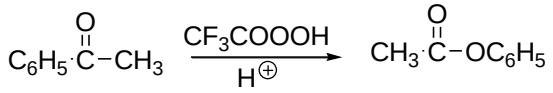
Conversion of ketones into esters on treating with peracids like trifluoro per acetic acid , per acetic acid , mono per sulphuric acid m-CPBA (meta chloro per benzoic acid) etc in the presence of acid catalyst is known as Baeyer Villiger oxidation reaction . Out of various per acids the trifluoro per acetic acid is is the most reactive due to good leaving nature of the trifluoro acetate ion.



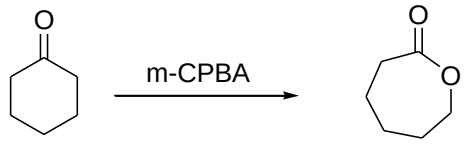
Mechanism -

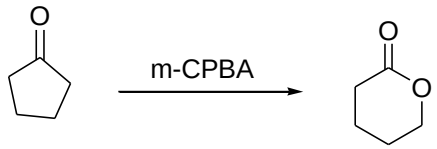


In the case of unsymmetrical ketone migrating aptitude of the group having the following order H> tertiary alkyl> secondary alkyl, aryl, benzyl>primry alkyl> methyl



Cyclic ketones undergo ring expansion with the peracids.

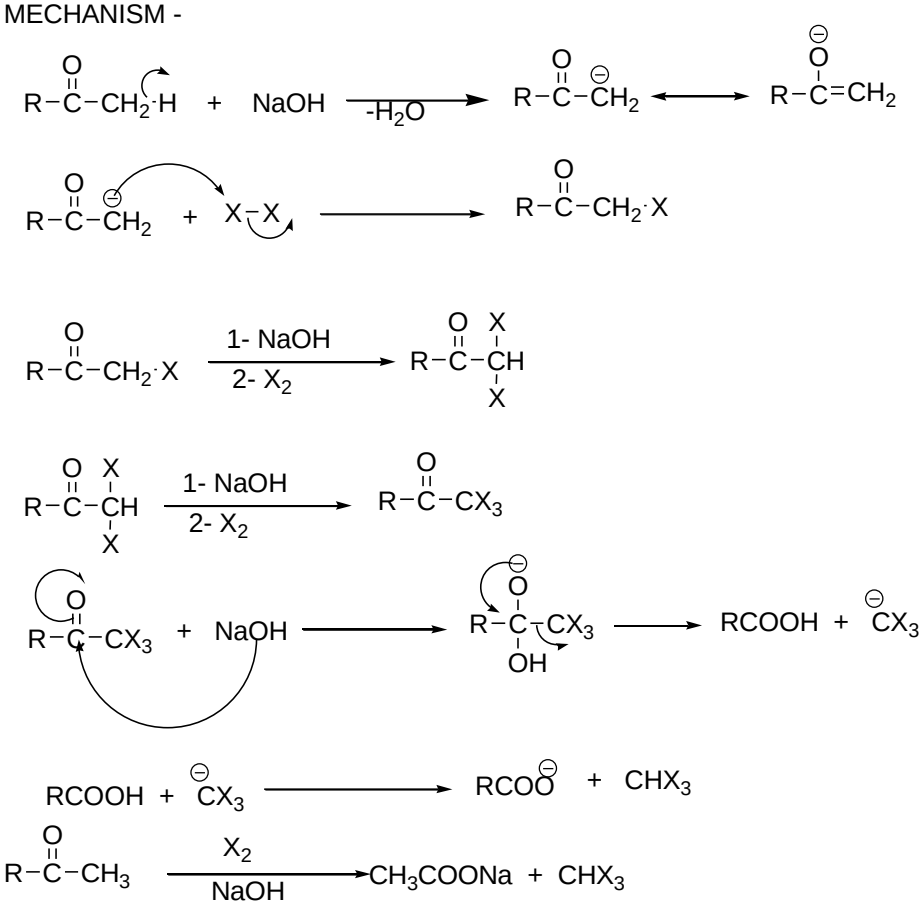




2.6.5 Haloform Reaction:

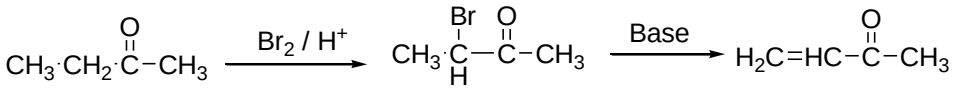
Formation of haloform (CHF_3) with the sodium or potassium salt of carboxylic acid on treating the α-methyl carbonyl compound with halogen (X_2) in the presence of NaOH or KOH is known as haloform reaction

MECHANISM -

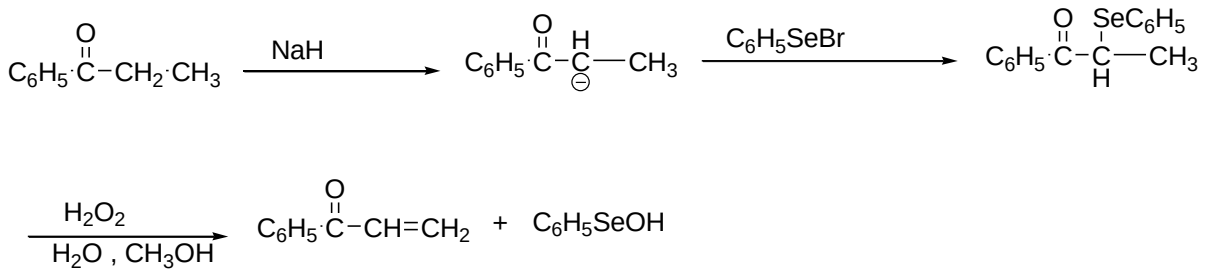


2.6.6 Oxidation of Ketone to α,β Unsaturated Ketone:

When the carbonyl compounds containing atleast one hydrogen at α as well as β position react with the halogens and base then there occur the formation of the α,β unsaturated ketones



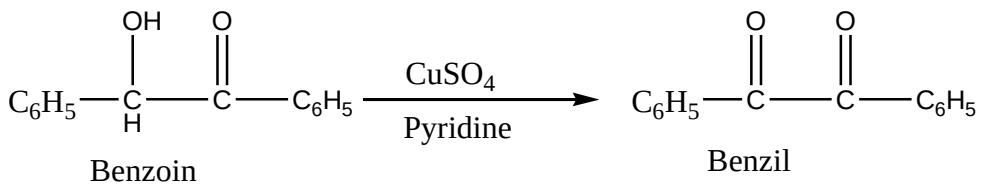
This method is not considered as the effective method to prepare the α,β unsaturated ketone due to poor yield of product obtained during this reation .In order to obtain the α,β unsaturated carbonyl compound with good yield at first enolate derivative of carbonyl compound obtained by the reaction of carbony compound with NaH is treated with phenyl selenyl chloride to generate the α-phenylseleno carbonyl compound .This α-phenylseleno carbonyl compound .This α-phenylseleno carbonyl compound on oxidation reaction with H_2O_2 give corresponding selenoxide which undergo syn β-elimination to give α,β-unsaturated ketone in high yield .



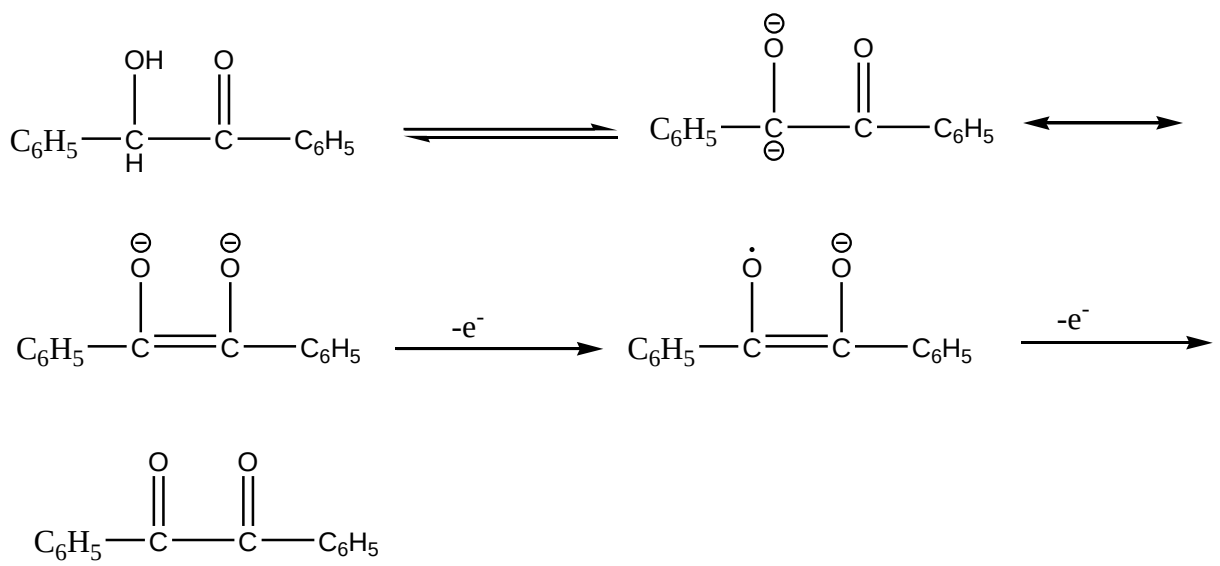
2.6.7 Oxidation of α-Ketols:

Ketones containing hydroxyl group at α-position with respect to ketonic group are called as α-ketols which can be oxidized into the α-diketones by using single electron oxidant in the basic medium.

Benzoin an α-ketol is oxidized into benzil (α-diketone) by using $CuSO_4$ in pyridine at 95^0C with 90% yield.



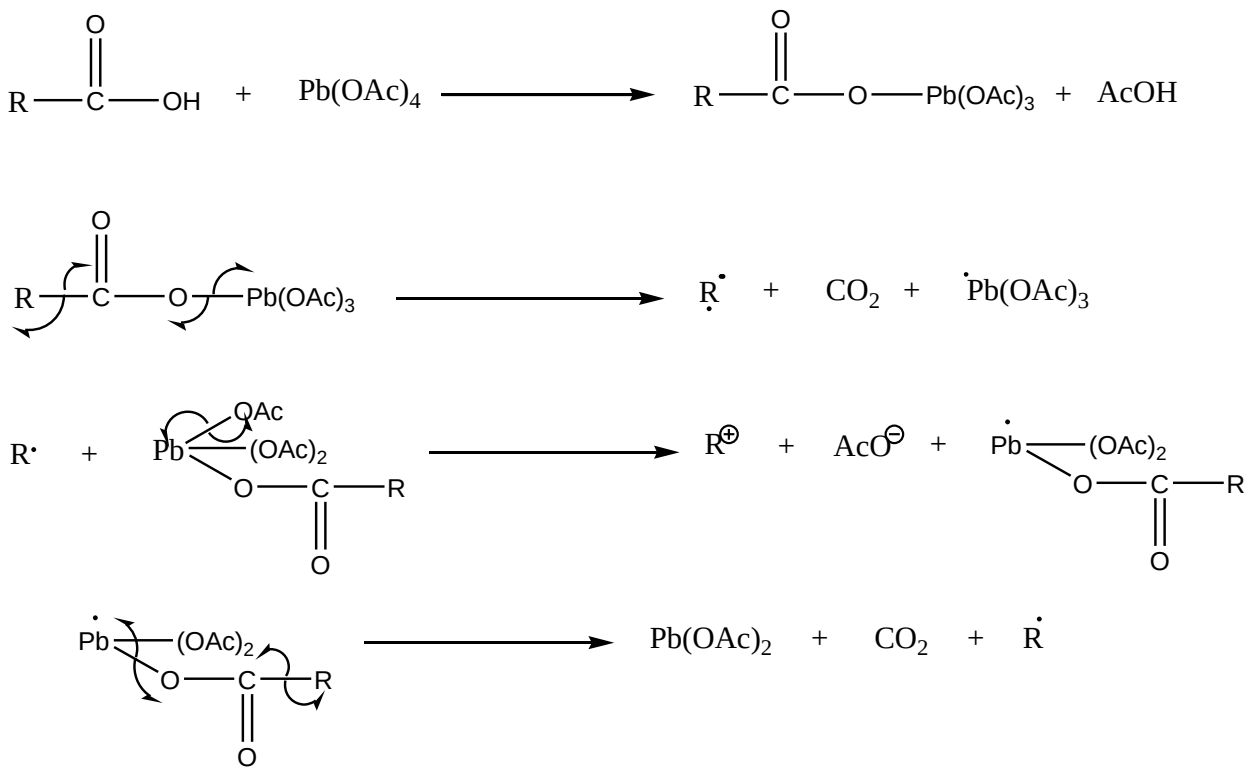
MECHANISM



2.7 OXIDATION OF CARBOXYLIC ACIDS (DECARBOXYLATION PROCESS)

Maximum oxidation level of carbon is CO_2 (level 4) and carbon atom of carboxylic acid belongs to the lower level (level 3) with respect to the oxidation level of carbon in CO_2 .Thus the carboxylic acid on oxidation will generate CO_2 .This process is known as oxidative decarboxylation process .

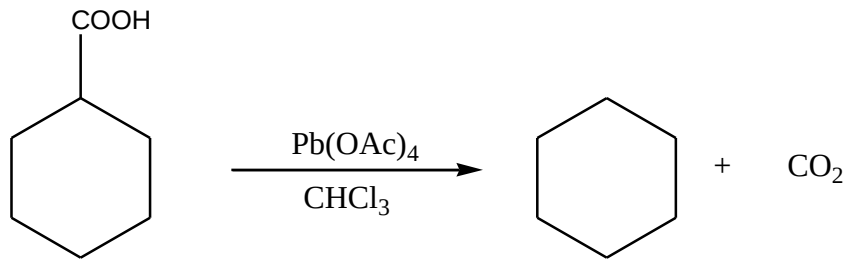
Oxidative decarboxylation process of carboxylic acid is done by using lead tetraacetate and as a result of this process alkane, alkene or esters can be obtained with CO_2 gas .General representation for the oxidative decarboxylation process through the combination of ionic and radical mechanism can be given as

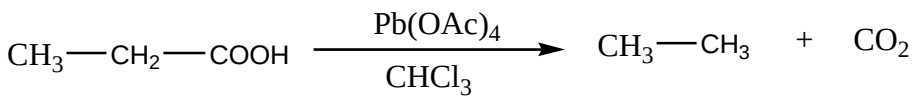


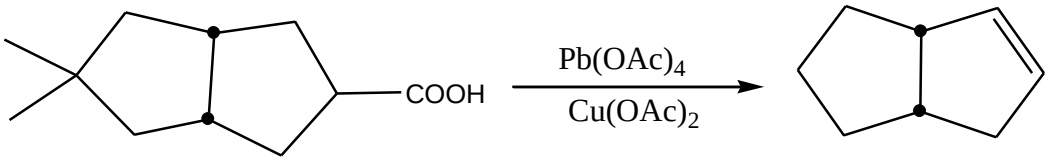
Now the free radical or carbocation obtained from the above reaction can generate alkane, alkene or esters. When free radical obtained from above reaction will abstract the hydrogen from the solvent then alkane will be obtained. If β position will lose H^+ ion in carbocation then alkene will be formed .R^+ react with the acetic acid formed in the primary stage

to give the ester .Presence of Cu(II) salts like $Cu(OAc)_2$ increases the yield of product during this type of reaction .

Examples



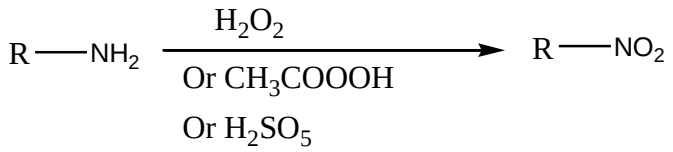




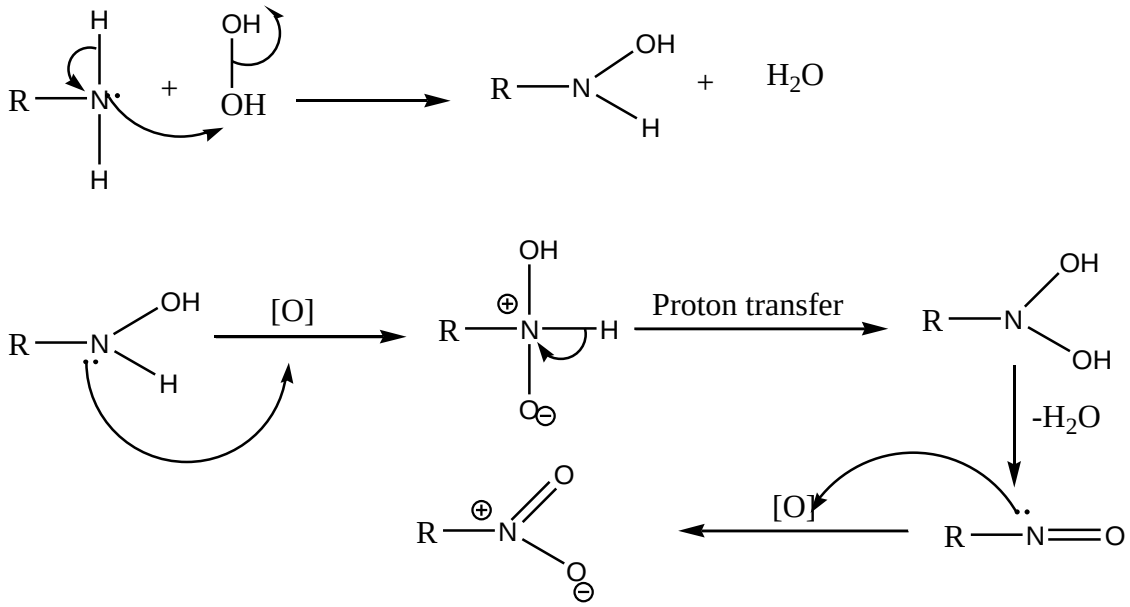
2.8 OXIDATION OF AMINES

Primary,secondary and tertiary amine undergo oxidation in the different fashion with the different oxidizing agents like H_2O_2, peracids, caro's acid (H_2SO_5), $KMnO_4/H^+$,dry ozone etc .Oxidation pattern of primary, secondary and tertiary amine with the different oxidizing agent can begiven as .

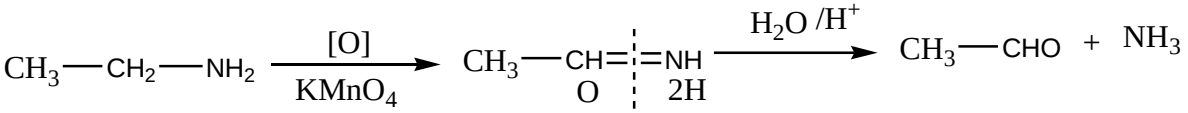
Primary amine on oxidation with peracids like CH_3COOOH, H_2O_2, H_2SO_5 give initially N-alkyl hydroxyl amine which on further oxidation gives nitroso alkane and finally nitro alkane.



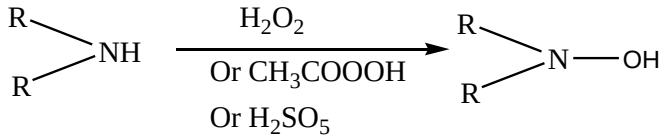
MECHANISM-



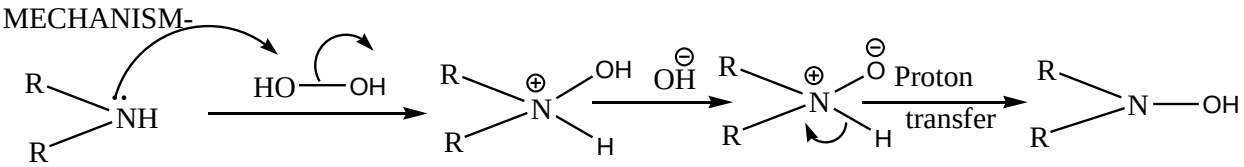
Primary amine on oxidation reaction with the $KMnO_4/H^+$ give initially imine which on reaction with H_2O/H^+ give aldehyde.



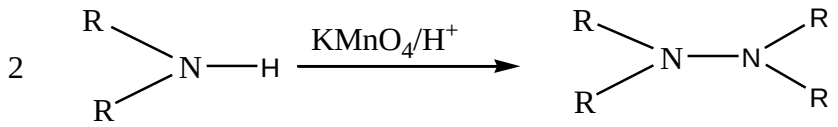
As like to primary amine, secondary amine on oxidation with peracids like CH_3COOOH, H_2O_2, H_2SO_5 give N,N-dialkyl hydroxyl amine .



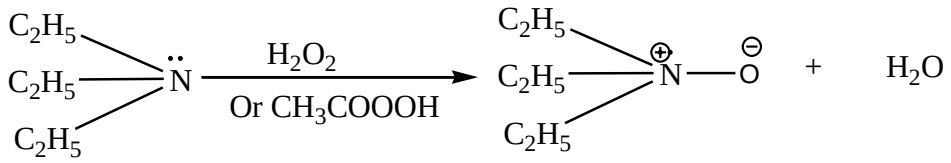
MECHANISM-



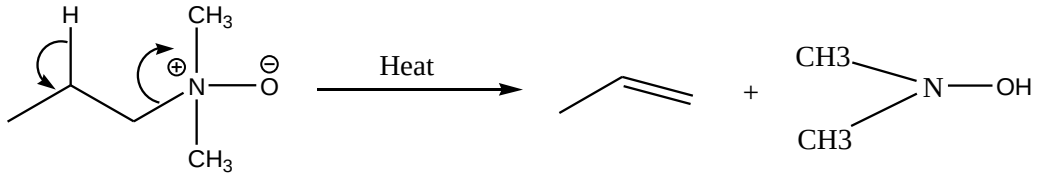
Secondary amine on reaction with $KMnO_4/H^+$ gives the N, N,N',N'tetra alkyl hydrazine .



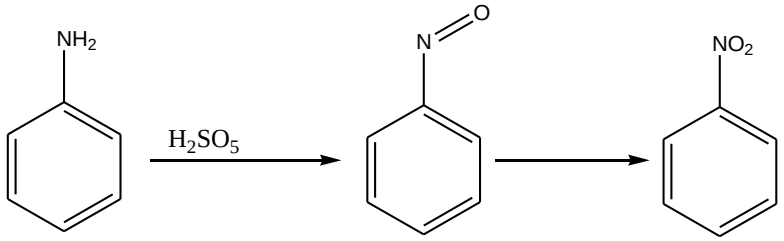
Unlike to primary and secondary amine, tertiary amine on reaction with the peracids or H_2O_2 gives the tertiary amine N-oxide.



If the tertiary amine N-oxide containing β-hydrogen then on heating there occur the β-elimination reaction to give the alkene. This type of β-elimination in tertiary amine N-oxide is called as **Cope elimination reaction.**



Aromatic amine like aniline give initially nitroso arene then finally nitro arene on reaction with the oxidizing agent like H_2O_2 , H_2SO_5 , RCOOOH .

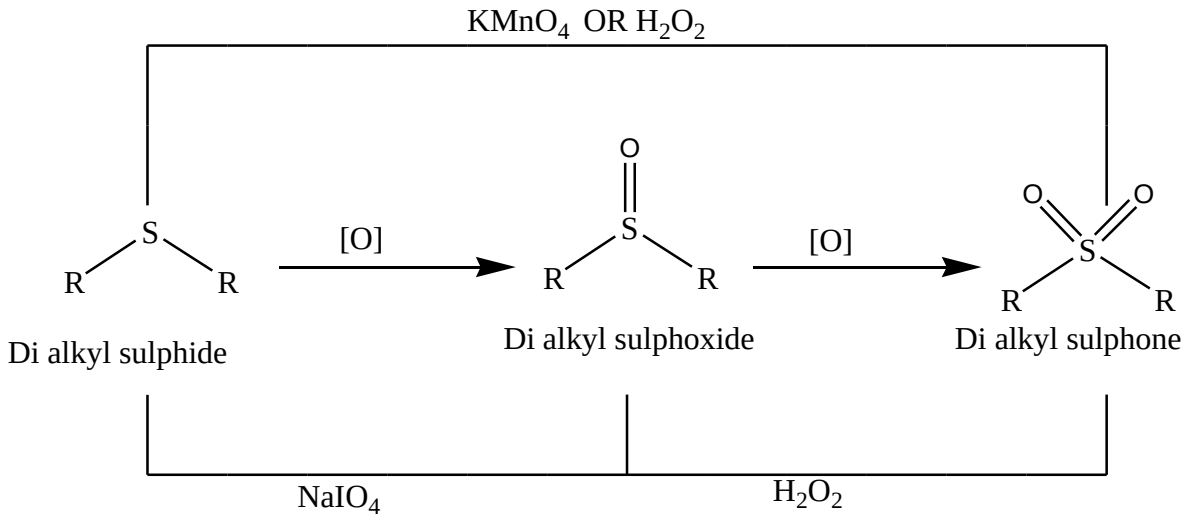


These reducing agent can reduce the $–NH_2$ group as well as ring due to electron donating ability of $-NH_2$ group toward the ring, but if the electron withdrawing group like $–NO_2$ group being attached to the ring then electron donating nature of $–NH_2$ group is counter balanced by the electron withdrawing group due to which under such condition possibility of the oxidation in the ring is quenched.

2.9 OXIDATION OF SULPHIDES

Dialkyl sulphides are the sulphar derivatives of the ether so dialkyl sulphides can also be called as thio ether .Dialkyl sulphides on partial oxidation with the sodium periodate ($NaIO_4$)

gives the dialkyl sulphoxide which on further reaction with the oxidizing agent H_2O_2 gives dialkyl sulphone .The dialkyl sulphone can also be obtained as an oxidation product of dialkyl sulphide by using the H_2O_2 or $KMnO_4$ as an oxidizing agent .Complete representation of the oxidation process by sulphides can be given as -



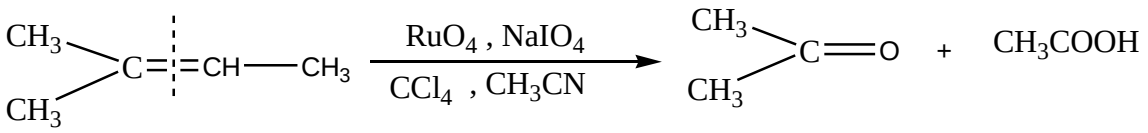
2.10 OXIDATION REACTION OF HYDRAZINE

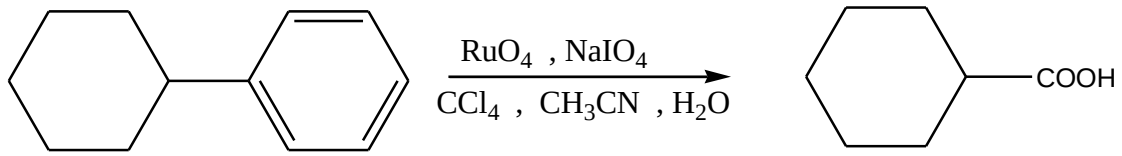
When the hydrazine reacts with the H_2O_2 then there occurs the formation of N_2 with H_2O. During this process oxidation state of each nitrogen is changed from (-2) to zero, on this way this reaction is called as oxidation reaction of N_2H_4.

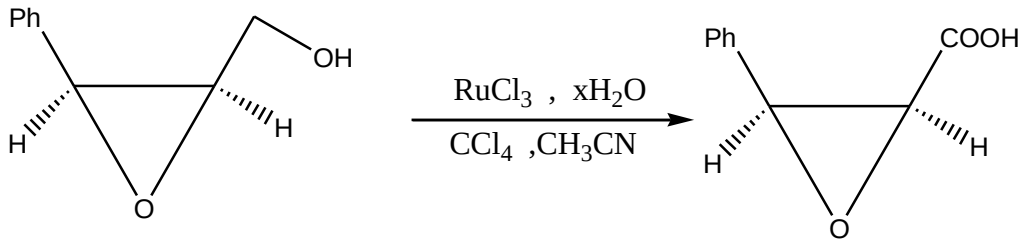
$$N_2H_4 + 2H_2O_2 \longrightarrow N_2 + 4H_2O$$

2.11 RUTHENIUM TETROXIDE (RuO_4)

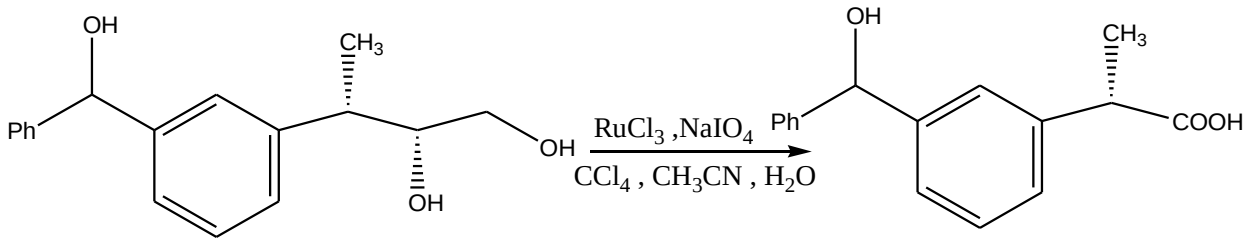
RuO_4 is a yellow coloured volatile ,highly reactive ,toxic nature of inorganic solid .It is used as an oxidizing agent in the various form like RuO_4 , $RuCl_3.x\ H_2O$, $RuO_2.x\ H_2O$, RuO_2 +NaOCl , $RuCl_3.3\ H_2O$+$NaIO_4$. It is a strong oxidizing agent that can oxidise any hydrocarbon (like olefins, benzene etc), alcohol into carboxylic acids or ketones and can cleave c= c bond. Some of the reaction which involve the RuO_4 as an oxidizing agent can be represented as –



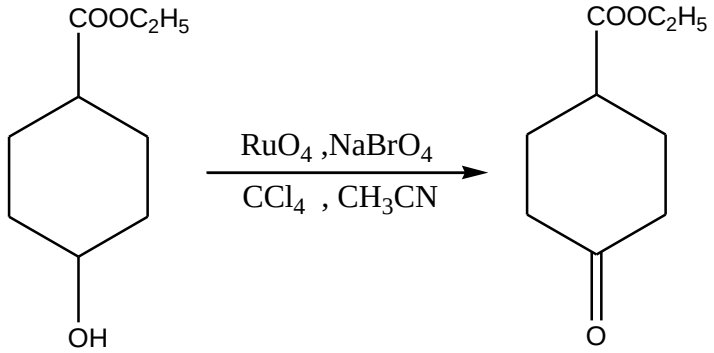




It can also cause the oxidation of vicinal diol into the carboxylic acids.



During some oxidation reactions it is also used as a co-oxidising agent . eg-During the oxidation of cyclic alcohol RuO_4 is used as a co-oxidant with sodium bromate .



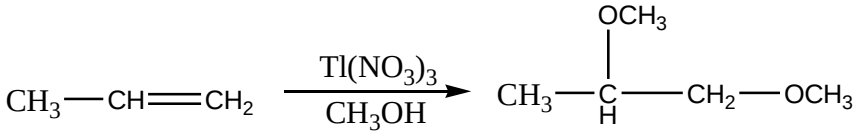
Due to expensive, reactive, less stable and poisonous nature it is generated in situ by the reaction of $RuCl_3$ and $NaIO_4$ in aquous medium.

$$8RuCl_3(aq) + 5NaIO_4(aq) + 12H_2O(l) \longrightarrow 8RuO_4(s) + 5NaI(aq) + 24HCl$$

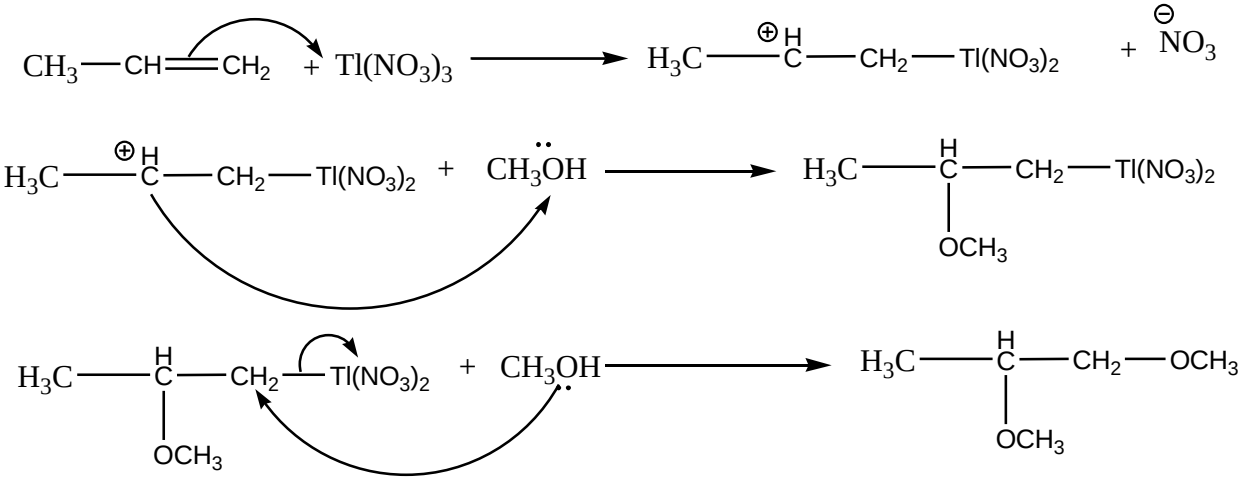
It is not used as a good oxidizing agent during the oxidation reaction of the substrate having different functionality because it can cause the unwanted side reaction due to its highly reactive nature.

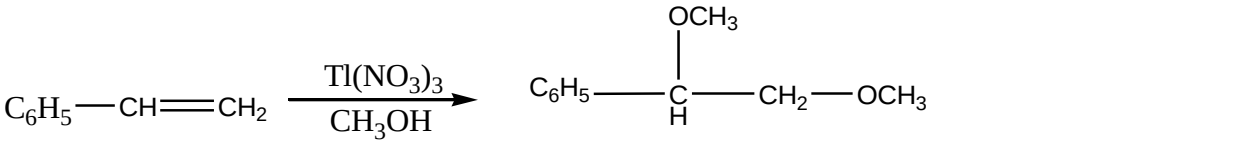
2.12 THALLIUM NITRATE, $Tl(NO_3)_3$

Thallium nitrate is also called as thallic nitrate which having the chemical formula $Tl(NO_3)_3$. It is a colourless toxic nature of solid behaves as an oxidizing agent for the carbon-carbon multiple bonded species like alkene and alkyne. The effectiveness of this reagent in oxidation is due to the high reduction potential and weakness of the C-M bond. When it react with the alkene in methanol solution then there occur the formation of 1,2 glycol dimethyl ether .

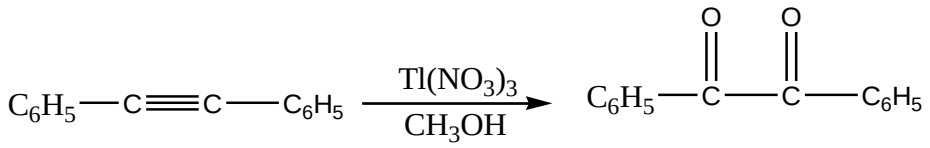


MECHANISM-



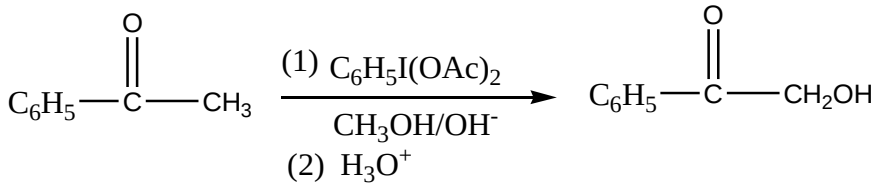


Thallium nitrate on reaction with alkyne in methanol solution gives the benzile in high yield.

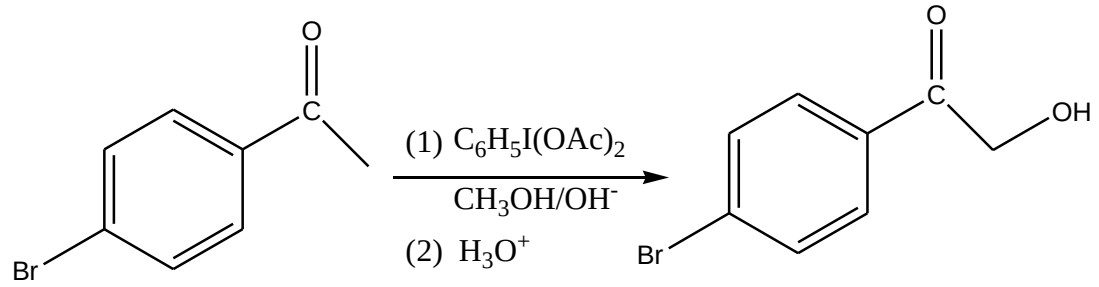


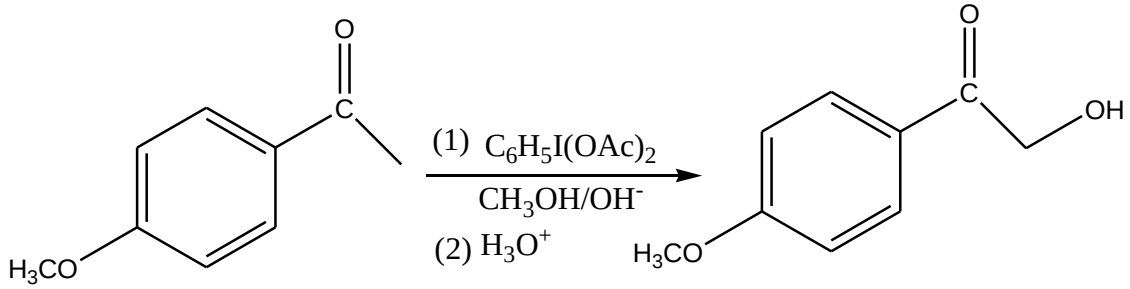
2.13 IDOBENZENE DIACETATE $C_6H_5I\ (OAc)_2$

Idobenzene diacetate is also known as phenyl idosodiacetate. It is a specific oxidizing agent specially used to convert the α-hydrogen containing ketone into α-hydroxy ketone which is also known as acyloin in good yield.

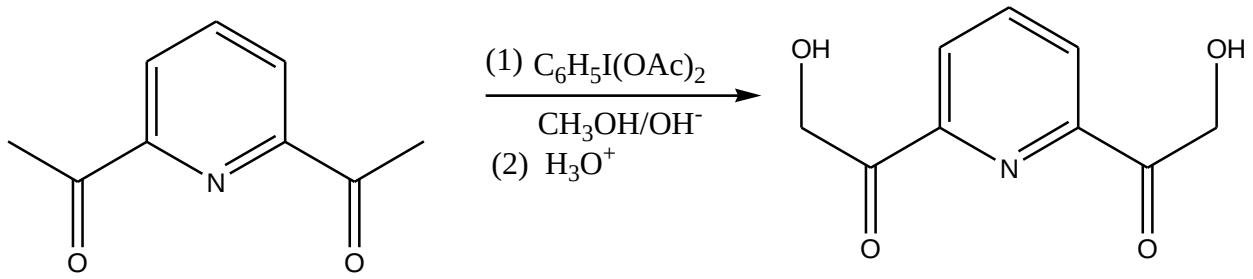


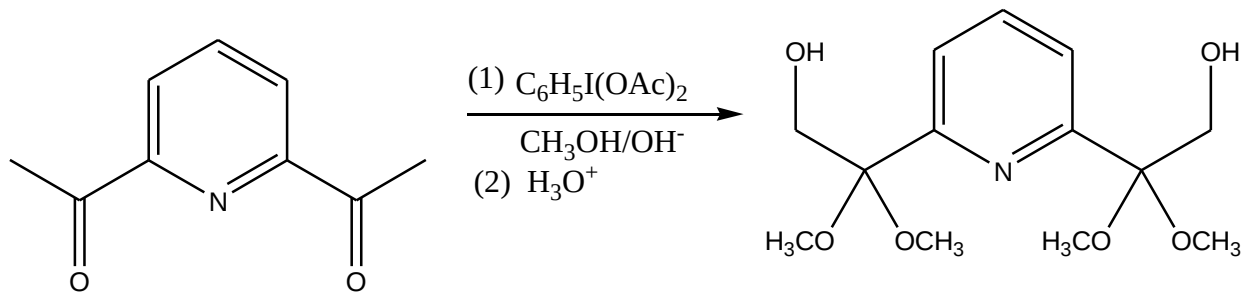
Its functioning is meant only for ketonic group as it is selective for the enolate ion .Some other examples related to this reagent can be given as –



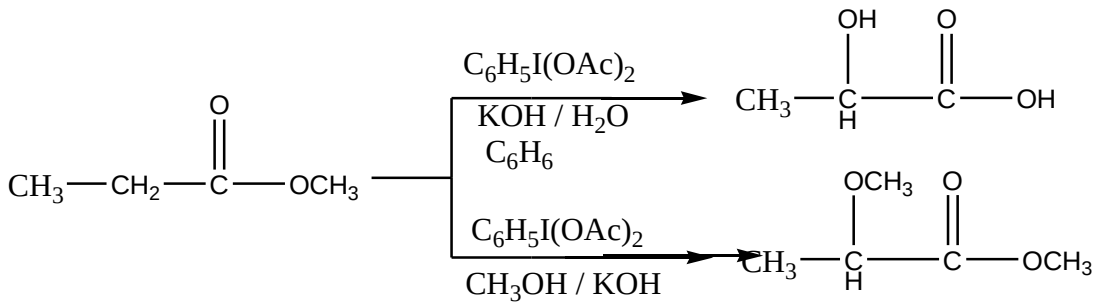


If these oxidation reactions are carried out in the alkaline medium followed by acidification then acyloins are obtained but if acidification step is avoided then dimethyl ketal of acyloins are obtained.





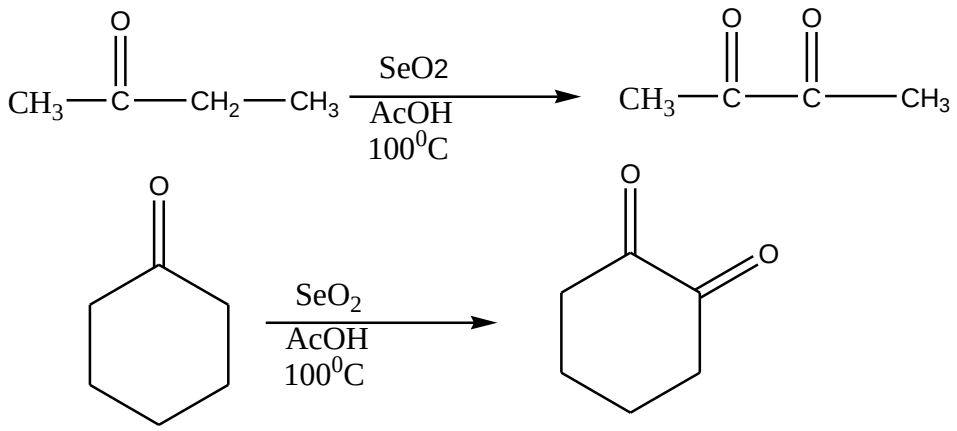
When the idobenzene diacetate is used as an oxidizing agent for esters then there occur the role of solvent to generate a particular product .This is observed from the following examples.



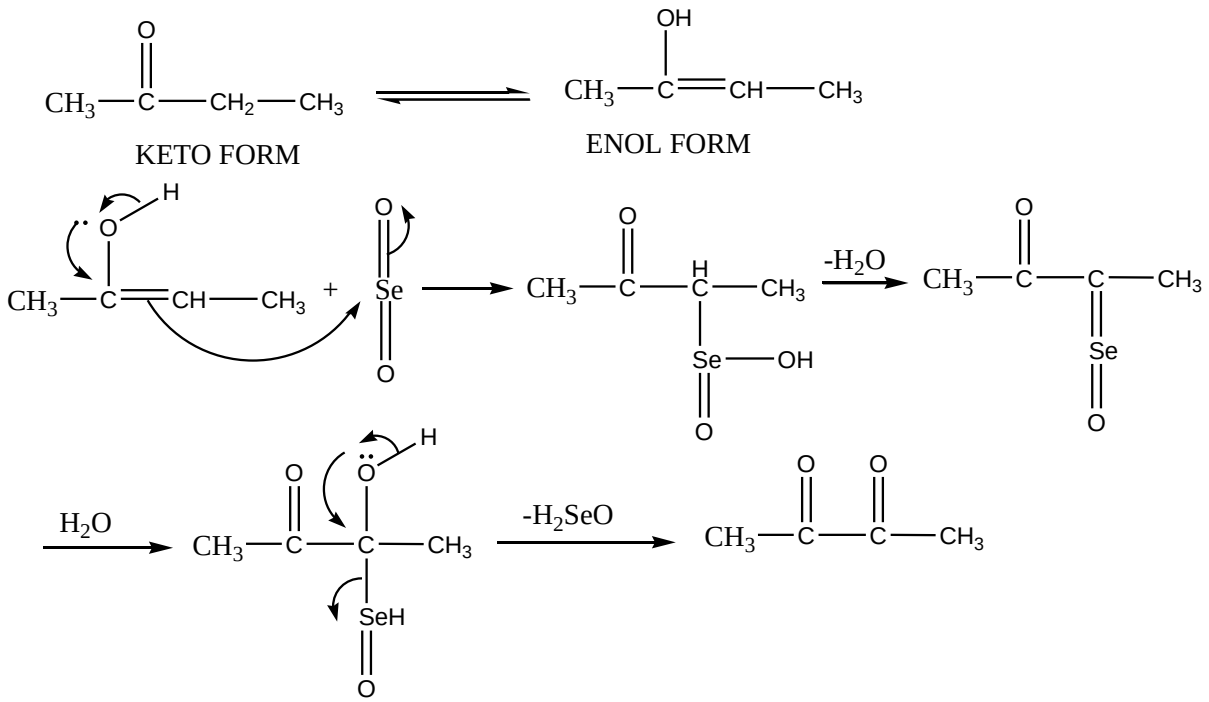
But bulkiness of the substrate decreases the yield of the product.

2.14 SELENIUM DIOXIDE (SeO_2)

When the carbonyl compound like aldehyde or ketone containing active methylene group (-CH_2-group) or active methyl group (-CH_3 group) react with the SeO_2 then there occur the formation of α-dicarbonyl compounds.



Mechanism: Mechanism of this oxidation reaction involve the electrophilic attack of the SeO_2 on the enol form of aldehyde or ketone .This followed by hydrolytic elimination of the selenium.



The yield of product being high if the carbonyl compound containing only one type of active methyl or methylene group adjacent to the carbonyl group.

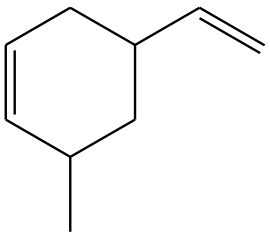
3.16 BOOKS SUGGESTED

1. *Advanced Organic Chemistry, Reaction and Synthesis, Francis A.Carey and Richard J.Sundberg.*
2. *Modern Methods of Organic Synthesis, William Carruthers and Iain Coldham.*
3. *Organic Synthesis, Jagdamba Singh, L.D.S.Yadav.*
4. *Organic Synthesis, the Disconnection Approach, Stuart Warren.*
5. *Organic Reaction and Their Mechanism, P.S.Kalsi.*
6. *Principles of Organic Synthesis, R.O.C.Norman and J.M.Coxon.*
7. *Advanced Organic Chemistry, Reaction Mechanism and Structure, Jerry March, John Wiley.*

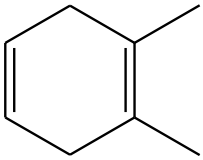
2.16 TERMINAL QUESTIONS

Question 1- Give the name of mono epoxidation product obtained by the reaction of peracids with the following compounds.

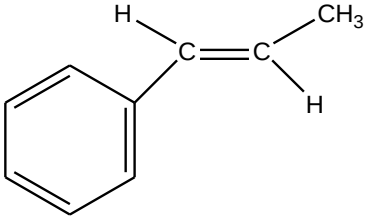
(a)



(b)



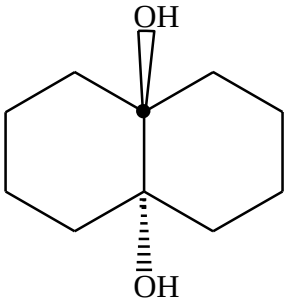
(c)



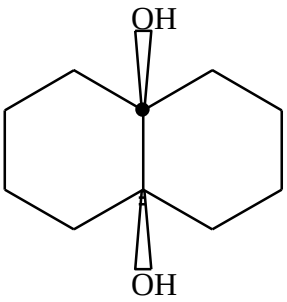
Question 2- Explain why trifluoroacetic acid is used as an effective reagent in place of peracetic acid during the epoxidation of alkenes?

Question 3- Which of the following diols will undergo faster reaction with lead tetraacetate .

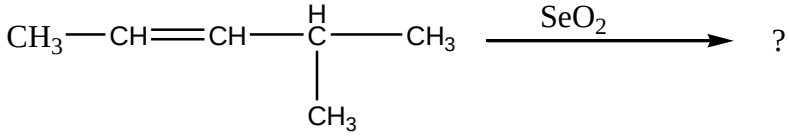
(a)

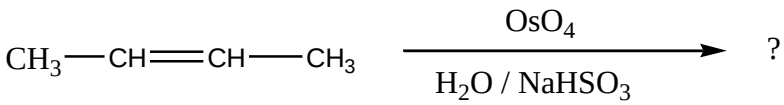


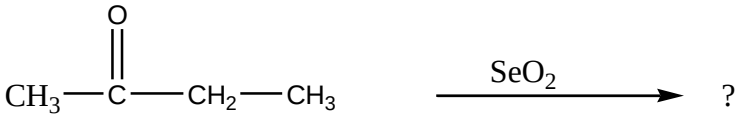
(b)

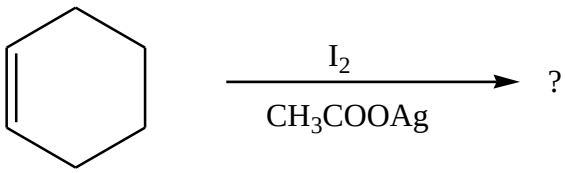


Question 4- Which product will be formed during the following oxidation reactions?

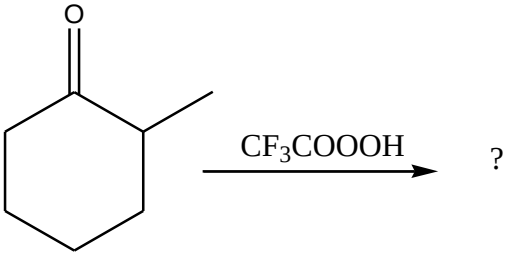
(a) 

(b) 

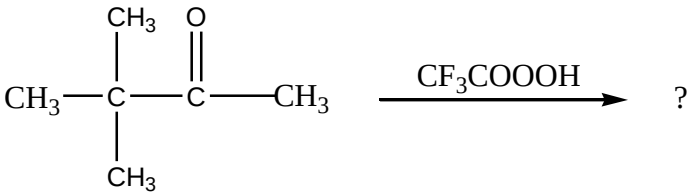
(c) 

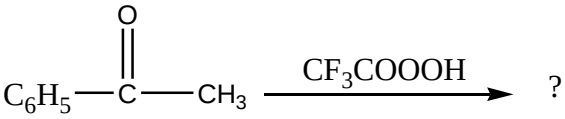
(d) 

Question 5- What oxidation product is obtained by the Baeyer Villiger oxidation reaction of 2-Methyl cyclohexanone. Give the mechanism.



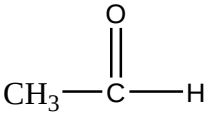
Question 6- Predict the product obtained from the following oxidation reactions?

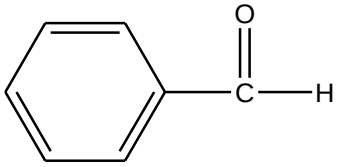
(a) 

(b) 

Question 7- What is the difference in the stereochemistry of product during the Prevost and Woodward oxidation reaction?

Question 8- How you can differentiate the following carbonyl compounds by using Tollens reagent (mild oxidizing agent).

(a) 

(b) 

UNIT-3 –REDUCTION

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3.0 OBJECTIVES

Purpose of reduction is to convert the higher functional groups into lower functional groups by using appropriate reagent .We should be careful about the following during the reduction reaction –

1. Yield of product should be high during the course of reaction.
2. If compound containing more then one functional groups then to reduce a particular functional group selectivity condition should be considerable.
3. If green path of reduction would be possible then it should be preferentially follow.
4.

3.1 INTRODUCTION

There are three different way to define the reduction process in chemical science which can be given as-

(a) Removal of oxygen.

(b) Addition of hydrogen.

(c) Decrease in the +ve oxidation state or increase in the –ve oxidation state of the element present in the species.

Reduction of the various organic compounds by using the different reducing agents with some specificity as well as selectivity can be given as.

3.2 REDUCTION OF ALKENES

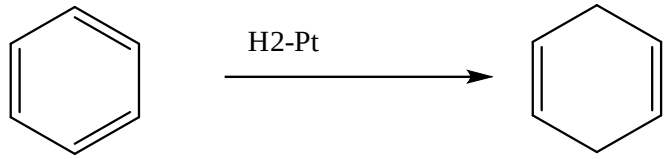
Reduction of alkene can be divided into the following three different categories-

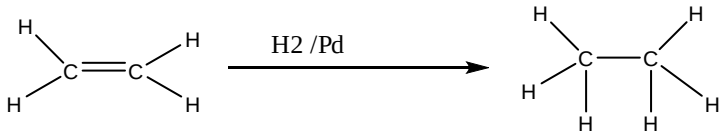
3.2.1 Catalytic hydrogenation:

This is the most widely used method for the reduction of alkene. The catalytic hydrogenation is divided into following two different categories –

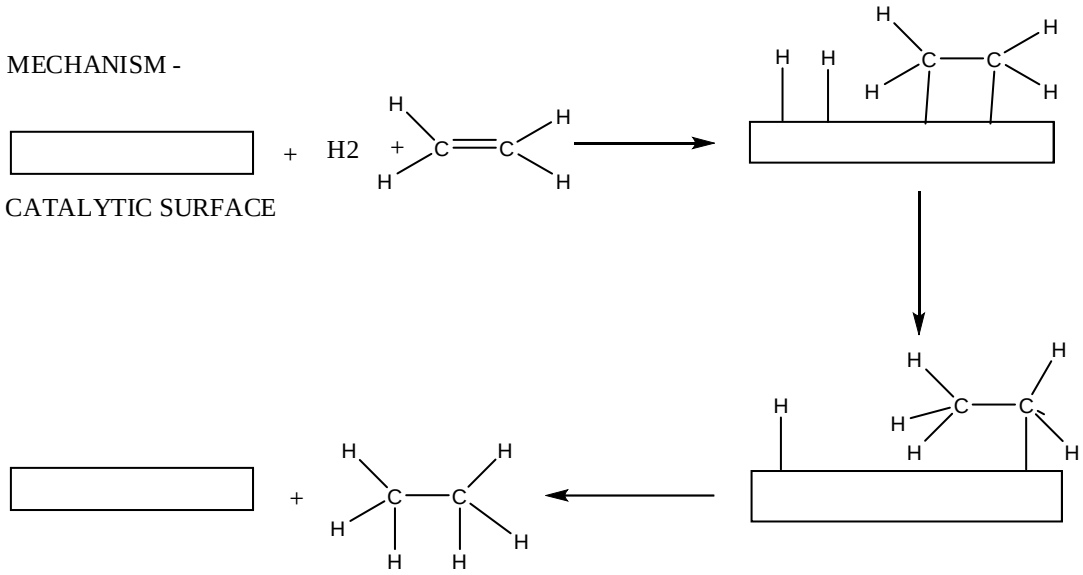
(a)Heterogeneous hydrogenation : In this type of hydrogenation process the gaseous hydrogen and alkene are initially adsorbed at the surface of metal catalyst like Pt,Ni,Pd,Rh,Ruetc over the solid support (carbon or Al_2O_3) then after that they comes in the contact for the reaction to give the reduction product .

General representation for the heterogeneous hydrogenation process of alkene with its mechanism can be given as.





MECHANISM -

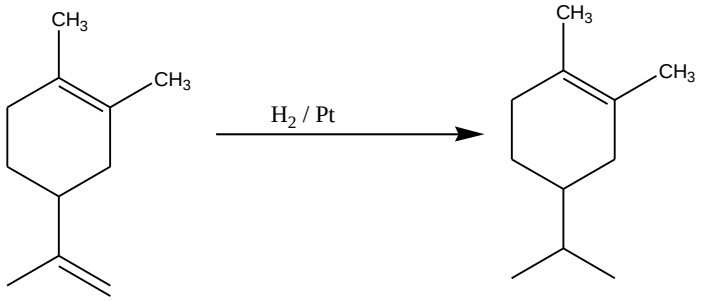


During this hydrogenation process addition of hydrogen is syn due to which this reaction may be called as stereospecific reaction .Stereospecificity during this reaction can be given as

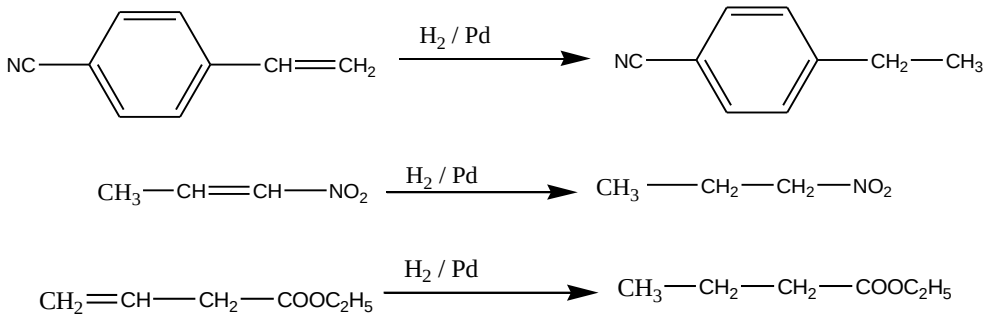
CIS ALKENE $\xrightarrow[\text{1atm}]{\text{H2 /Pd}}$ MESO COMPOUND

TRANS ALKENE $\xrightarrow[\text{1atm}]{\text{H2 /Pd}}$ RACEMIC MIXTURE

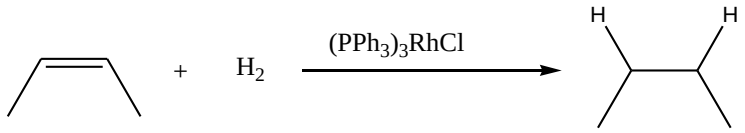
If the compound containing more than one double bonds then hydrogenation occur selectivily at the less substituted double bond.



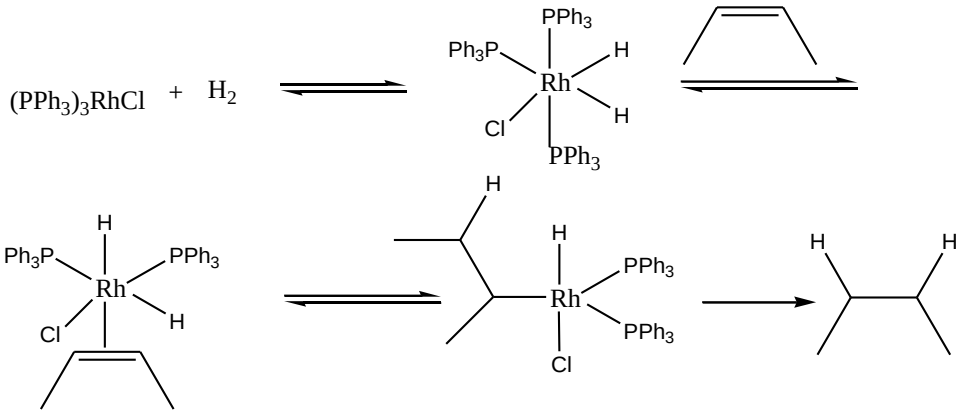
Heterogeneous hydrogenation can cause the selective reduction of carbon –carbon double bond in the presence of some other functionalities except in the presence of -C≡C-,-COX, aromatic –NO_2 group . H_2/Pd behaves as like to one of the best selective reducing agent.



(b) Homogeneous hydrogenation: Wilkinson' s catalyst PPh_3RhCl is used as a good catalyst for the homogeneous hydrogenation process of alkene .General representation for the homogeneous hydrogenation by using Wilkinson's catalyst can be given as.



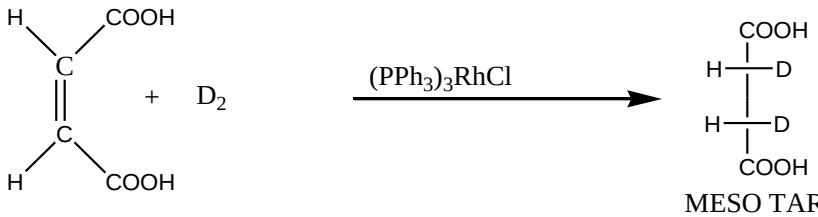
MECHANISM -



During the hydrogenation of alkene by using Wilkinson catalyst both the hydrogens are added in the syn fashion i.e. there will occur the following stereo changes during this reaction-

CIS ALKENE ⟶ MESO COMPOUND

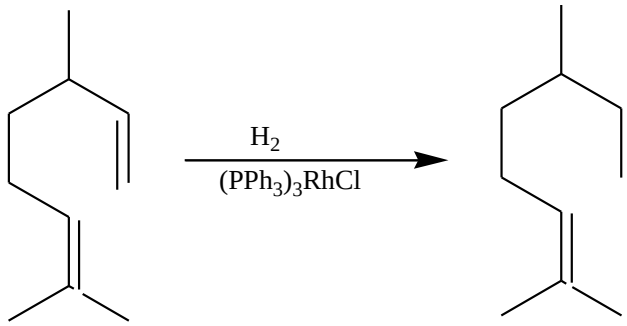
TRANS ALKENE ⟶ RACEMIC MIXTURE



CIS ALKENE

MESO TARTARIC ACID

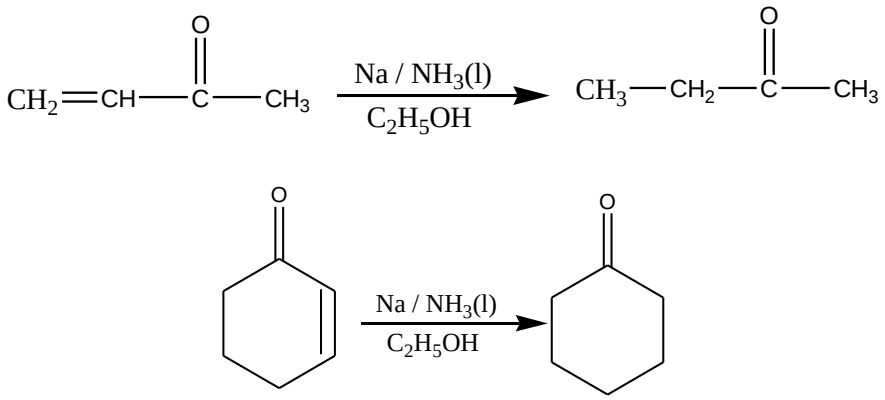
This catalyst is mainly used for the hydrogenation of non conjugatedalkene.If the compound containing more than one differently substituted double bonds then Wilkinsoncatalyst will preferentially reduce the less substituted double bond.



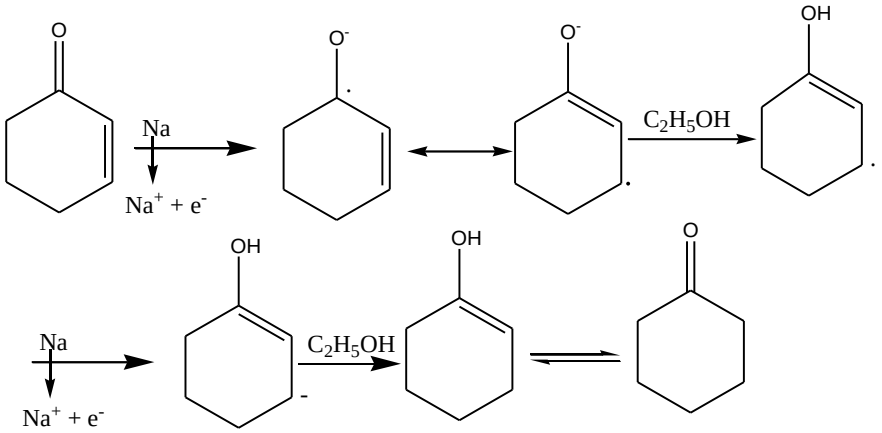
During the reduction of alkene by using Wilkinson catalyst functional groups like nitro,cyano, halo and azo are not affected .

3.2.2 -Reduction by IA metal in liquid NH_3:

That alkene which containing electron withdrawing substituents directly attached to the double bonded carbon can be reduced by Li, Na, K in liquid ammonia at the low temperature condition in the presence of proton doner species like CH_3OH, C_2H_5OH etc.

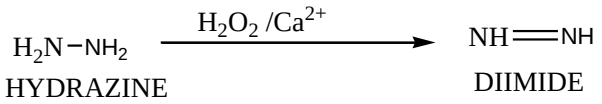


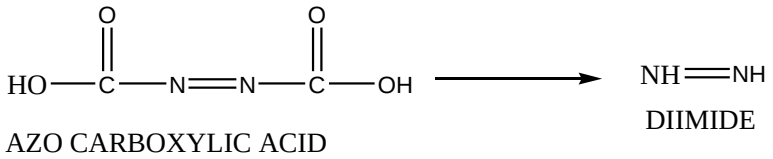
Mechanism: Radical anion mechanism for this type of reduction reaction can be represented as-



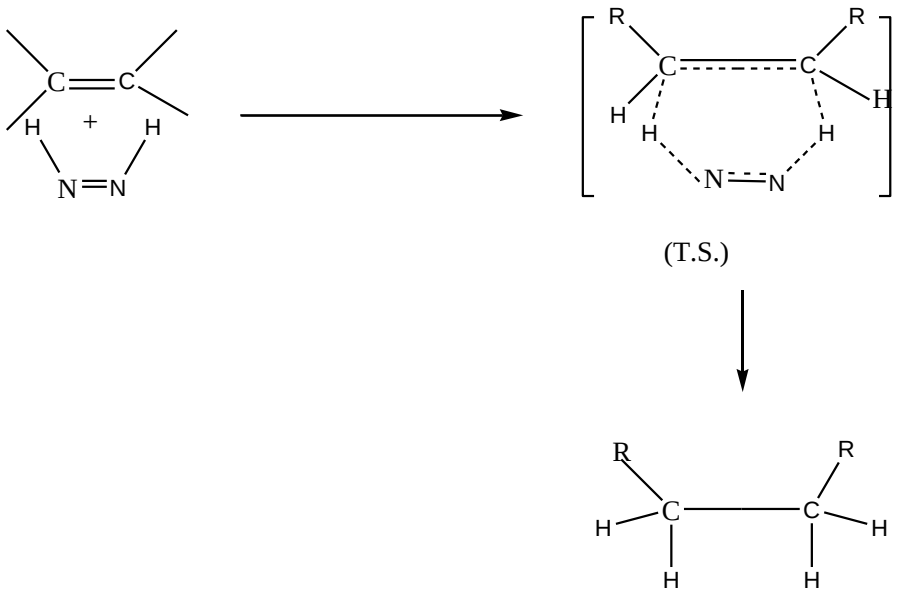
3.2.3 Reduction by diimide:

Diimide as a reducing agent for alkene exhibit best stereospecific nature because it give the 100% syn addition with alkene through the 6 membered T.S. but this reagent being unstable in nature due to which in situ formation of the diimide is done from the following reagents

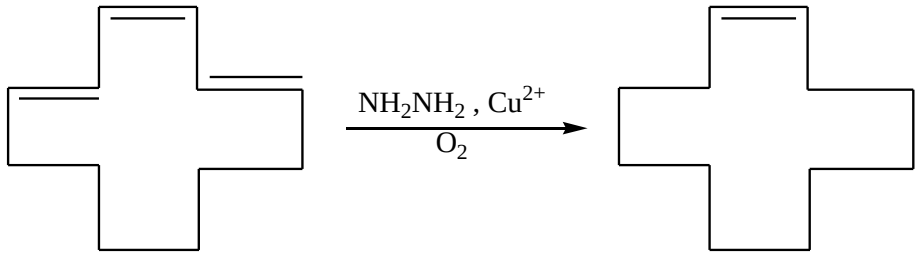


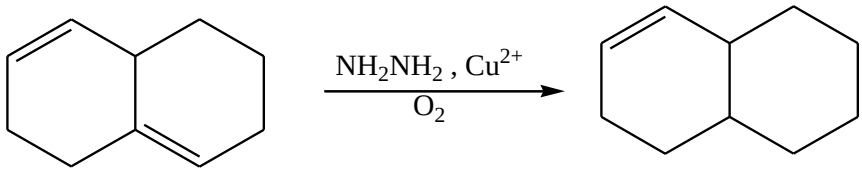


Mechanism: General mechanism for the reduction of alkene by using diimide as a reducing agent can be given as-



Diimide cause the selective reduction of strained double bond in compare to less strained double bond .In polyene terminal double bonds are selectivily reduced by diimide.



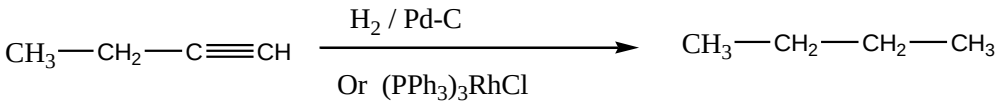


3.3 REDUCTION OF ALKYNE

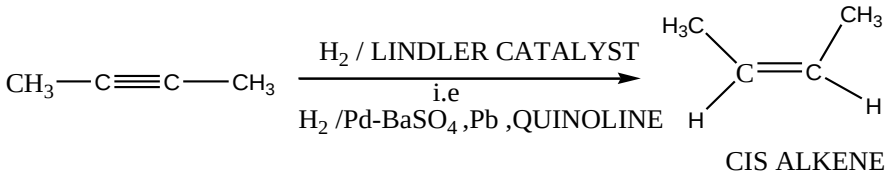
Reduction of alkyne is divided into following three different categories.

3.3.1 Catalytic hydrogenation:

When the alkynes undergo hydrogenation in the presence of heterogeneous metal catalyst like Ni,Pt,Pd, or homogeneous catalyst (Wilkinson catalyst) then they are reduced into alkane . This type of reduction reaction is called as complete hydrogenation reaction of alkyne .



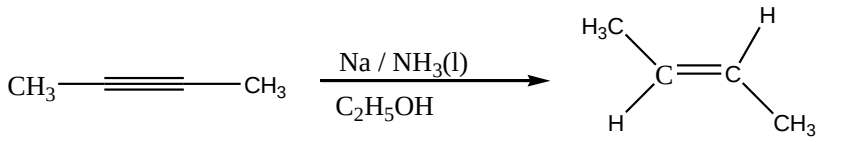
But if hydrogenation reaction occur in the presence of Lindlercatalyst (Pd/$BaSO_4$, Pb , Quinoline or Pyridine)then alkyne are reduced into cis alkene (stereoselective reaction). This type of reduction reaction of alkyne is called as partial reduction reaction.



Nickel boride (Ni_2B) / H_2 can also be used as an alternative reagent to obtain the cis alkene from alkyne.

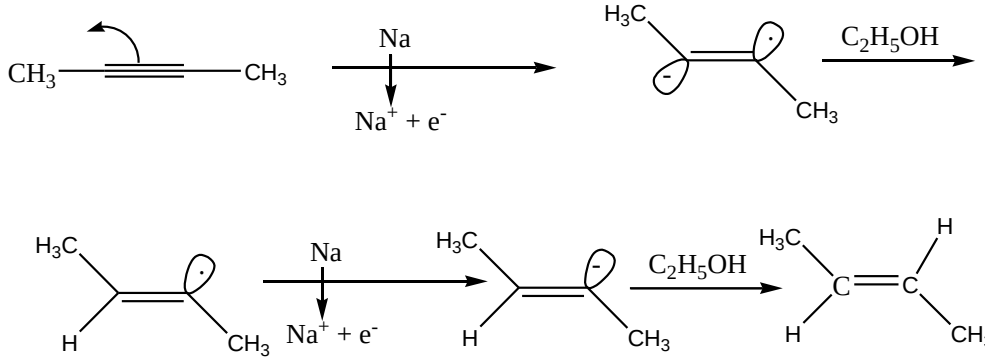
3.3.2 Reduction by IA metal in liquid NH_3:

When alkynes are treated with alkali metals like Na, Li in liquid NH_3, in the presence of proton doner species like CH_3OH, C_2H_5OH or t-butanol then stereoselectivily alkynes are reduced into Tran's alkene as a partial reduction product.



ALKYNE TRANS ALKENE

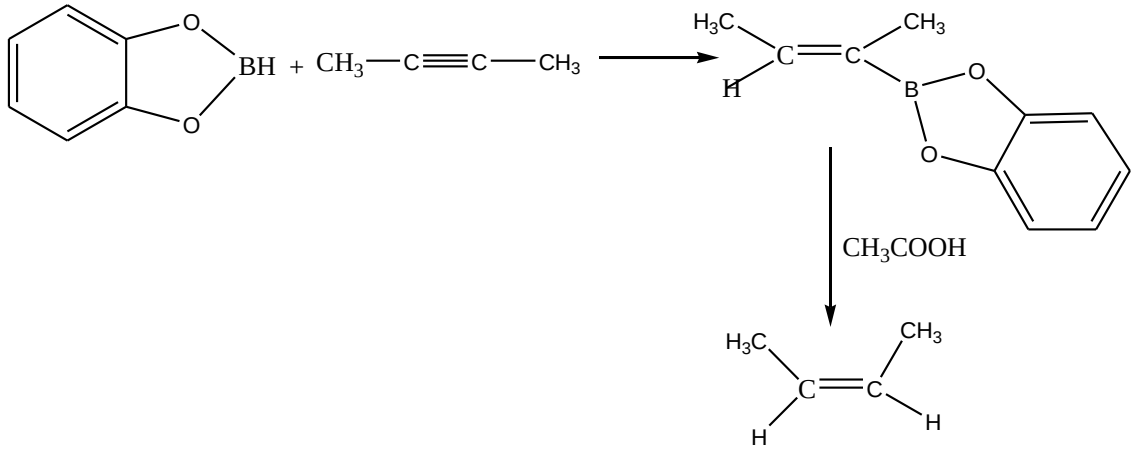
MECHANISM -



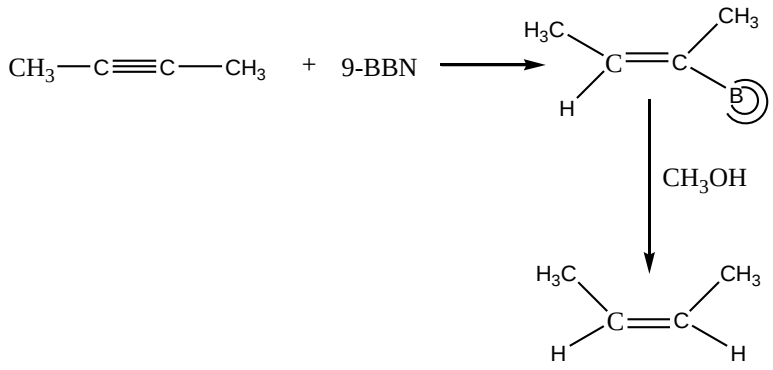
TRANS ALKENE

3.3.3 Reduction by hydroboration process:

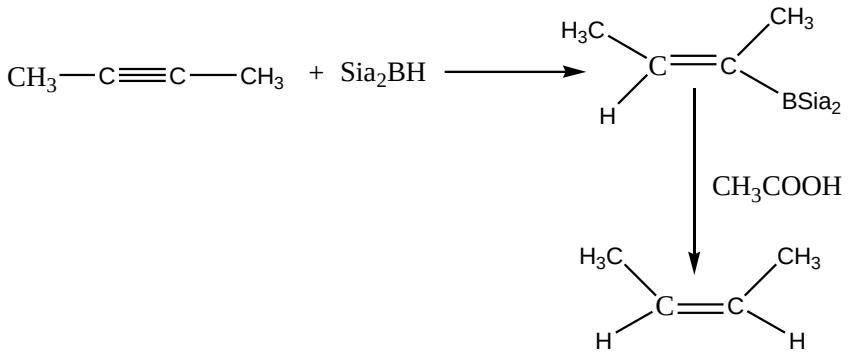
When alkynes are treated with borane (BH_3) then there occur the formations of polymeric product due to which disubstitutedborane is used for hydroboration of alkynes. Protonation of the adduct with acetic acid gives the reducyion product alkene (stereoselectivilycis alkene).



9-BBN{ 9-borobicyclo(3,3,1)nonane } can also be used as a disubstitutedborane during the hydroboration of alkyne , which on protonolysis with methanol give the reduction product cisalkene orZ-alkene.



Disiamylborane (Sia_2BH) can also be used to prepare the cis alkene from alkyne.

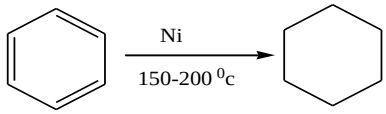


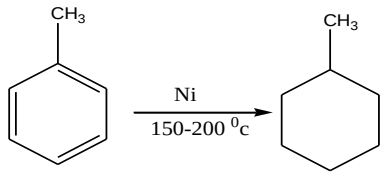
3.4 REDUCTION OF AROMATIC HYDROCARBON

Reduction of aromatic hydrocarbon is divided into following three different categories–

3.4.1 Complete reduction:

When the aromatic hydrocarbon undergo catalytic hydrogenation process in the presence of metal catalyst like Ni , Pt , Pd , Rh , Ruetc then they are converted into alicyclic compound . In this process all the double bonds present in the aromatic compound are hydrogenated.

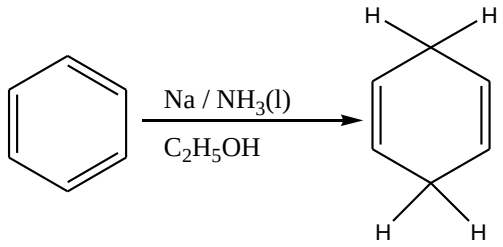




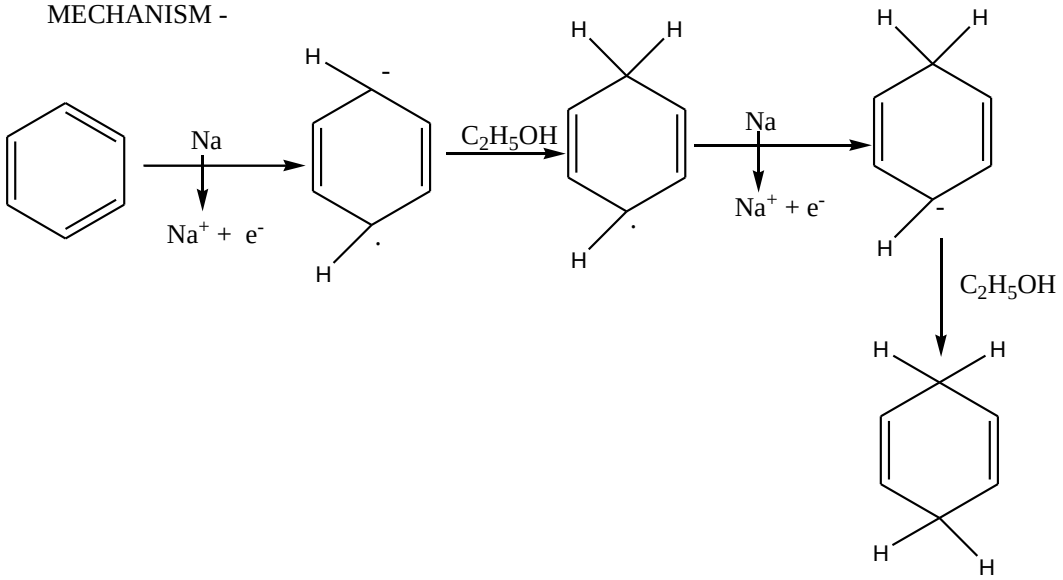
Catalytic hydrogenation of the aromatic compound being too much difficult in compare to the hydrogenation of alkene. This is due to very high resonance associated with the aromatic compounds.Thus high temperature and pressure condition will be required for catalytic hydrogenation of the aromatic compounds.

3.4.2 Partial reducion (birch reduction):

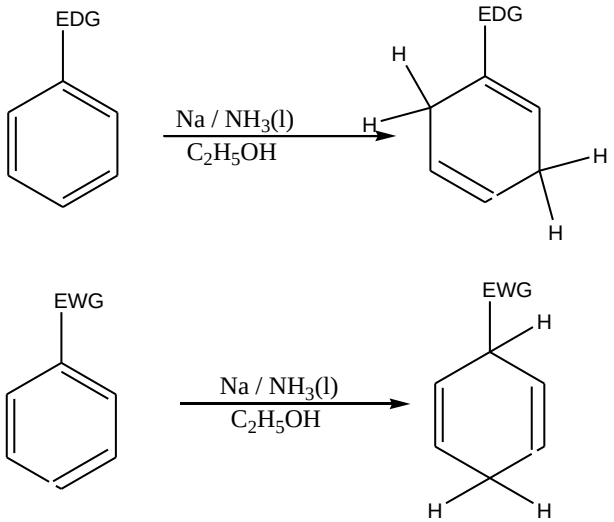
Birch reduction is used for the partial reduction of aromatic hydrocarbons .This involve the reaction of aromatic hydrocarbon with alkali metal like Li, Na in liquid ammonia. In this reaction proton donar species like methanol, ethanol is also involved. As a result of this reaction there occur the formation of non conjugatedcyclohexadiene by the 1,4 addition of hydrogen atoms .



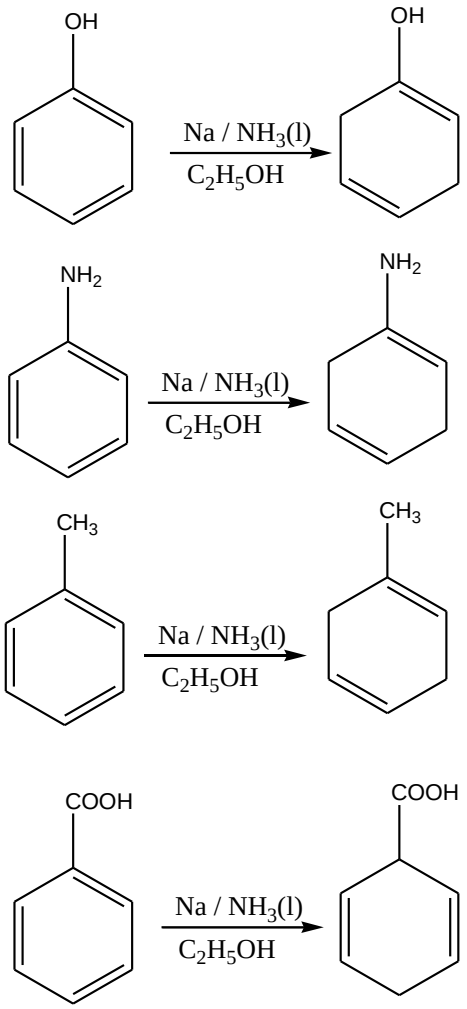
MECHANISM -



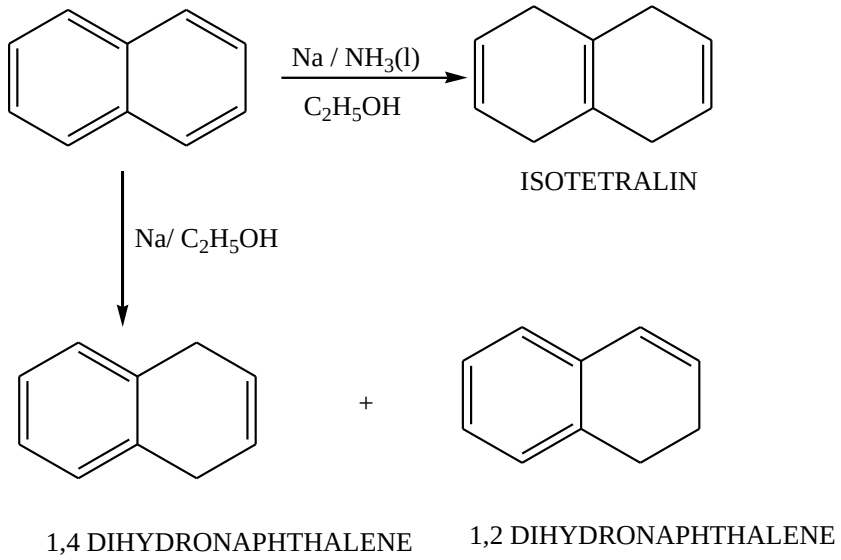
When the aromatic ring containing the electron donating substituents or electron withdrawing substituent then mode of Birch reduction can be representation as-



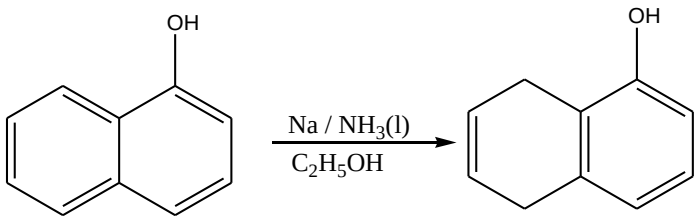
Some other examples of Birch reduction can be representation as-



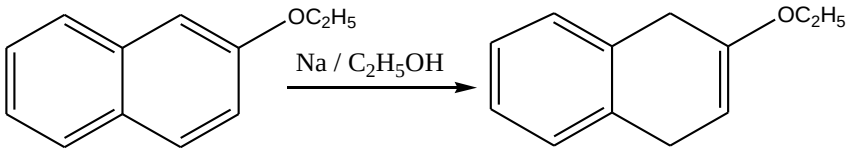
Naphthalene gives different partial reduction product with the different reagents:



1-Naphthol gives the Birch reduction in benzene ring because other ring containing the electron donating substituents (-OH)

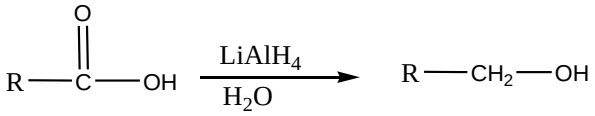


While 2-ethoxy naphthalene gives the reaction unlike to 1-naphthol.

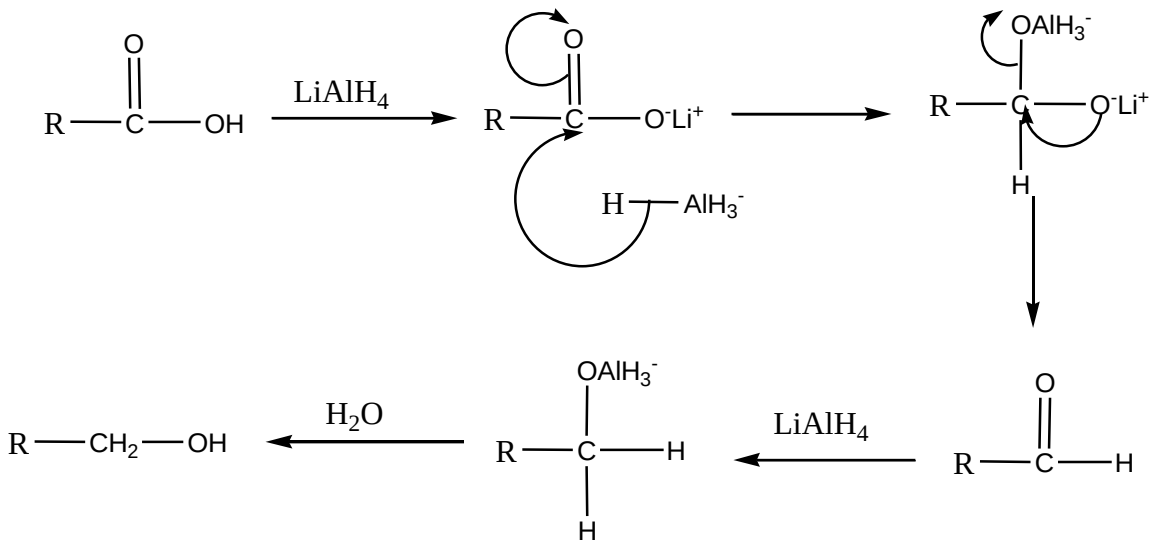


3.5 REDUCTION OF CARBOXYLIC ACIDS

Carboxylic acids are reduced into the primary alcohols by using lithium aluminium hydride (LiAlH4), alanes and boranes.



MECHANISM: Mechanism during the reduction by lithium aluminium hydride involve the hydride transfer process that can be represented as.



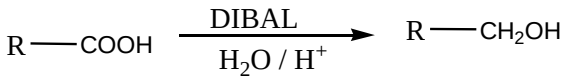
Carboxylic acid is least reactive among the carboxylic acid derivatives as like to the reactivity of acid derivatives toward the nucleophilic addition reaction.

RCOOH < RCOOR < RCOOCOR < RCOX

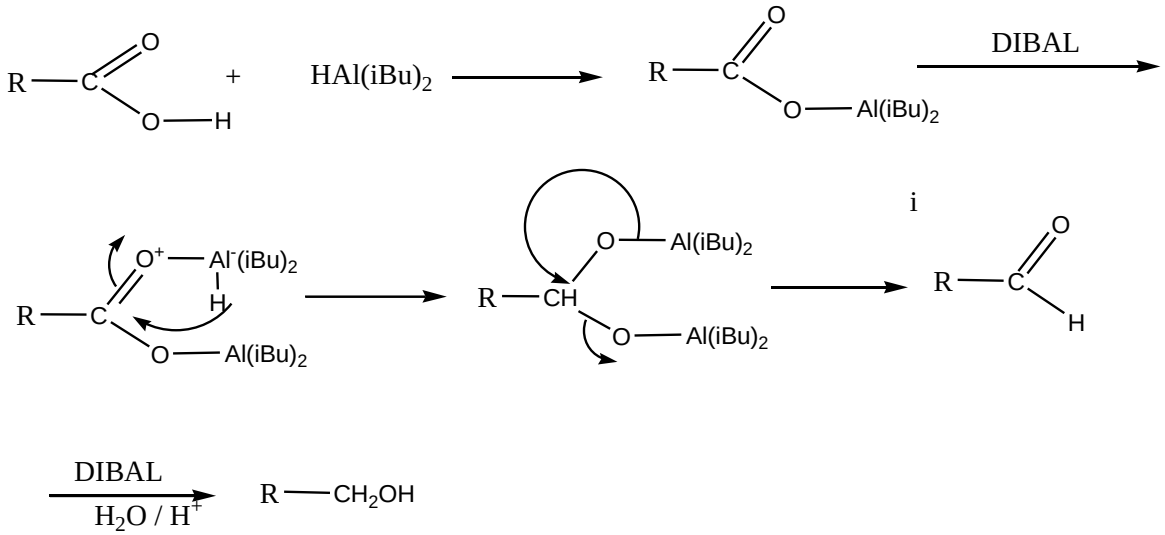
Thus the carboxylic acid will be reduced under the vigorous conditions. $LiAlH_4$ behaves as a powerful reducing agent due to which it will exhibit very low selectivity .With the decrease in the no of hydrogen at the aluminium atom reactivity is decreases and selectivity is increases .Alanes like diisobutylaluminium hydride (DIBAL) can also >reduce the carboxylic acid into primary alcohol but the reactivity order of various carboxylic acid derivatives during the reduction by DIBAL being exactly opposite.

RCOOH > RCOOR > RCOOCOR > RCOX

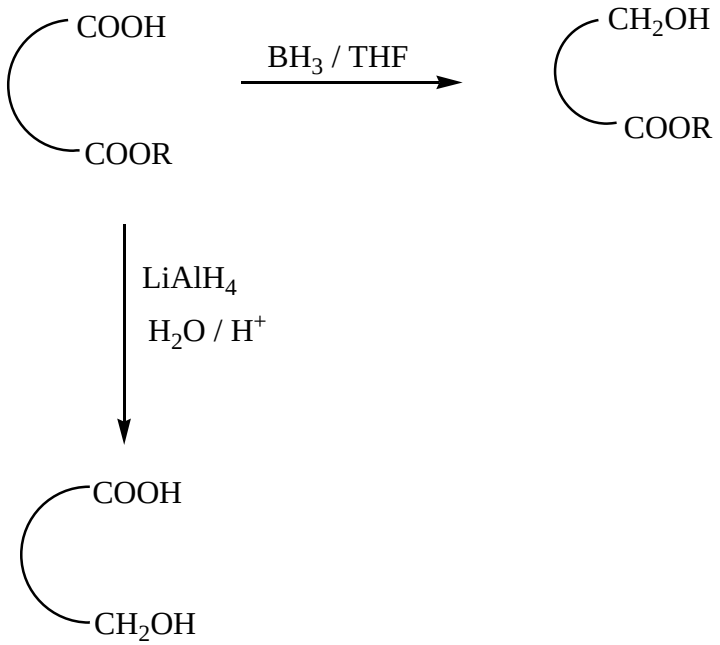
Mechanism: Mechanism for the reduction of carboxylic acids by using DIBAL can be given as-



MECHAMISM -



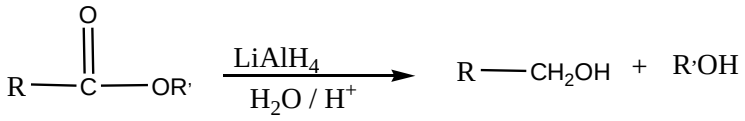
Diborane can also reduce the carboxylic acids into primary alcohol but it exhibit selectivity to reduce the carboxylic acids in the presence of esters.



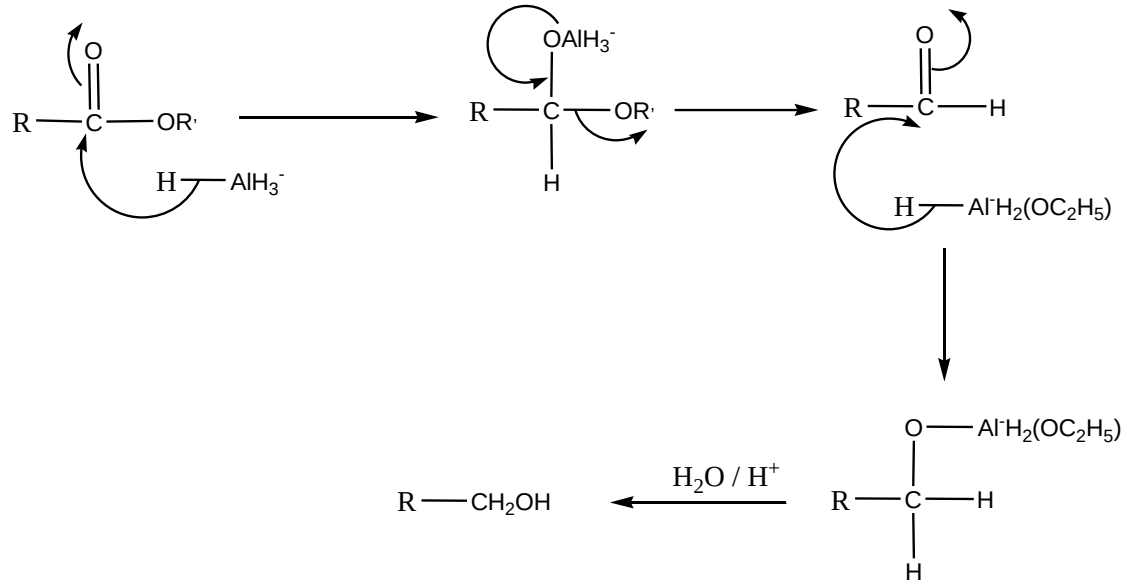
$NaBH_4$ itselfcan not reduce the carboxylic acids but combination of $NaBH_4$and BF_3 is identical with diborane to reduce the carboxylic acids.

3.6 REDUCTION OF ESTER

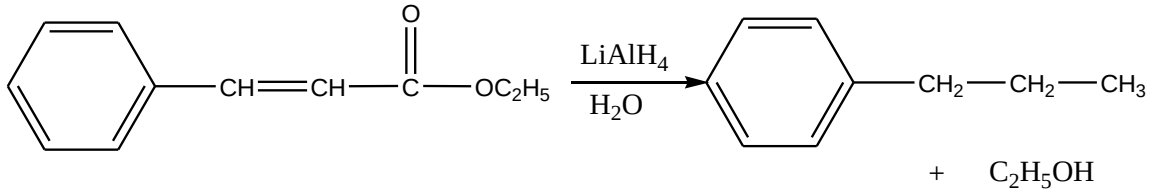
Esters are reduced into primary alcohol by using lithium aluminium hydride ($LiAlH_4$) reducing agent.

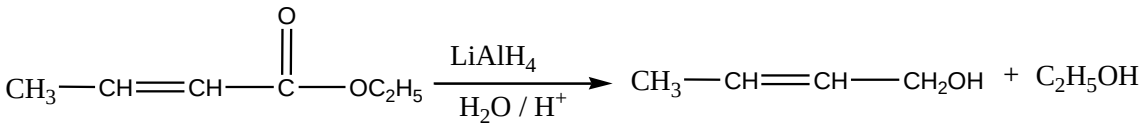


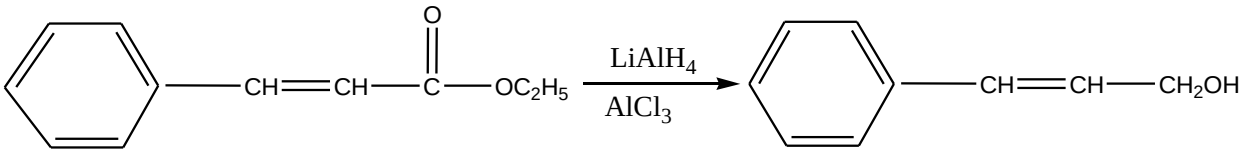
MECHANISM -



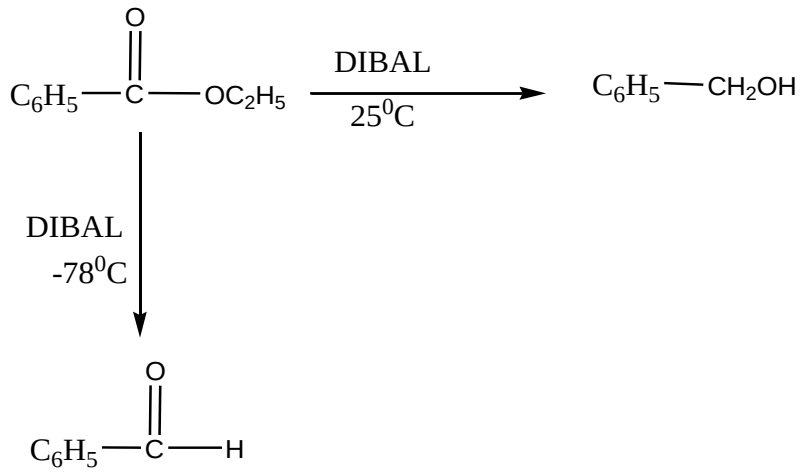
Reduction of ester by using aluminium hydride ($LiAlH_4$) does not exhibit selective nature because $LiAlH_4$ is a powerful reducing agent that can also reduce other functionality like cyano, carbonyl, acid halide, nitro etc. Some selectivity during the reduction of esters by using $LiAlH_4$ can be given as-



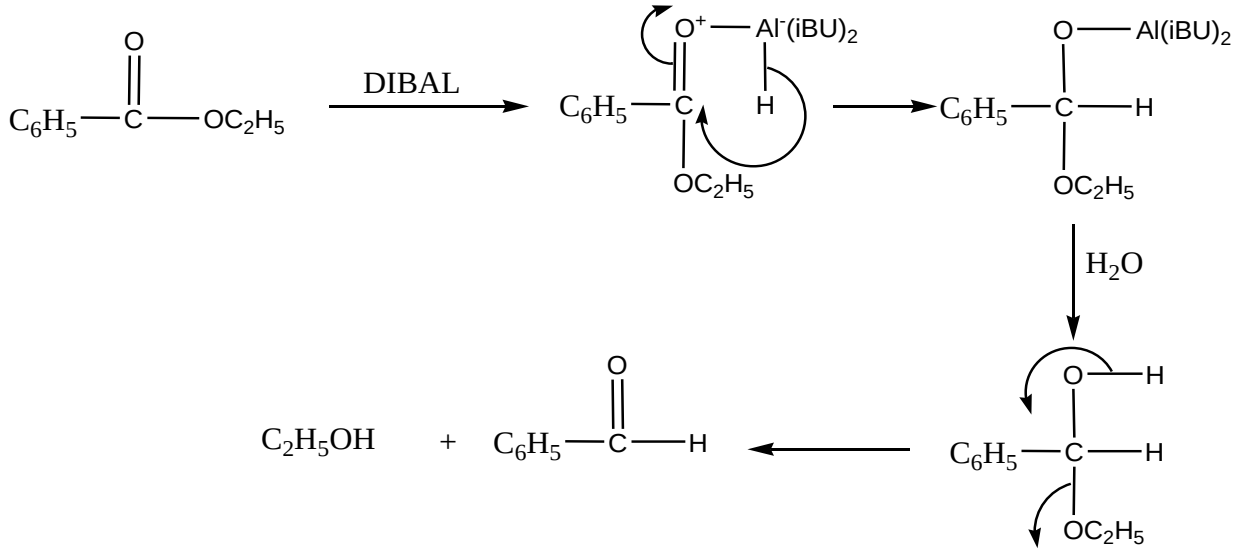




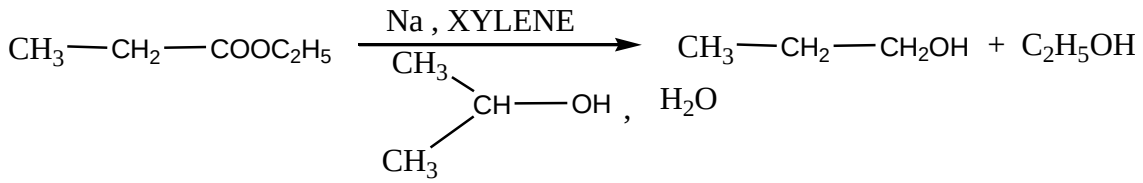
DIBAL can also reduce the ester into primary alcohol as well as aldehyde at the different temperature condition



MECHANISM -



Combination of Na with alcohol can also reduce the esters into primary alcohol this type of reduction called as.Bauveault-Blancereaction .Bauveault-Blance method can reduce the ester into alcohol but yield of product being very low because there can occur the Claisen condensation product formation as a side reaction. The yield in this reaction can be improved by using inert solvent like toluene or xylene.

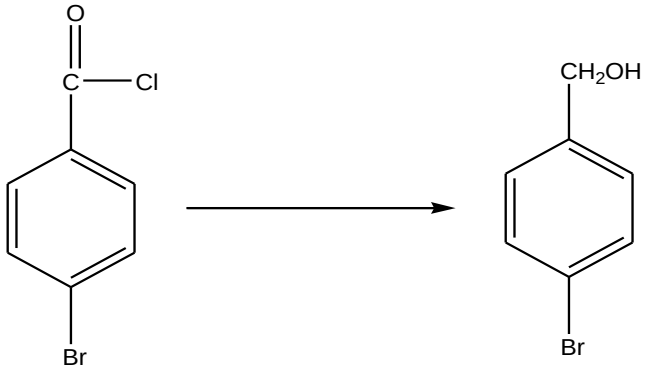


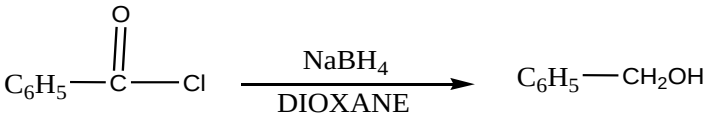
3.7 REDUCTION OF ACID CHLORIDE

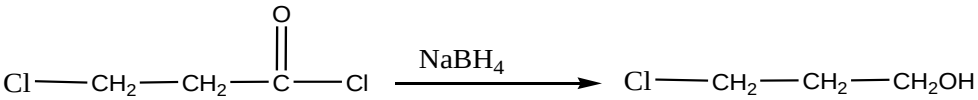
Two types of reagents can cause the reduction of acid chlorides which are given below.

3.7.1 Reduction by strong reducing agents:

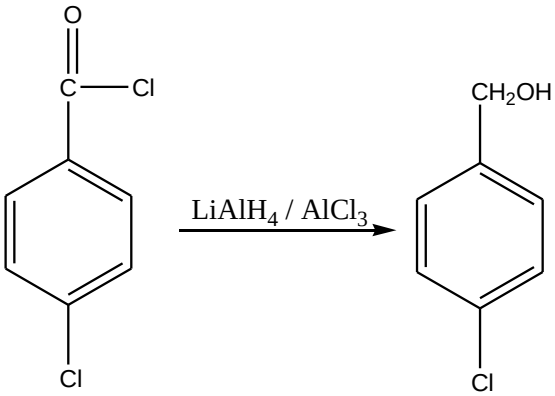
Reducing agent like $LiAlH_4$, NaBH4, alanes and sodium trimethoxy boron hydride cause the reduction of acid chlorides into primary alcohol. $NaBH_4$ and alane can be suitable to cause the reduction of halogenated acid chlorides.







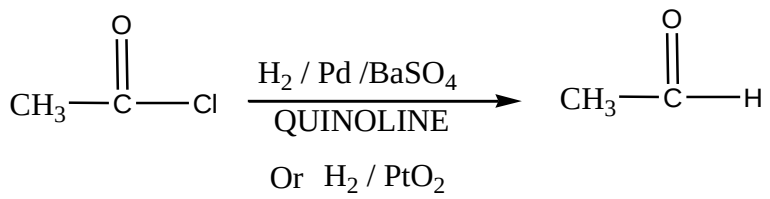
$LiAlH_4$ in combination with $AlCl_3$ can also be applicable to cause the reduction of halogenated acid chlorides.



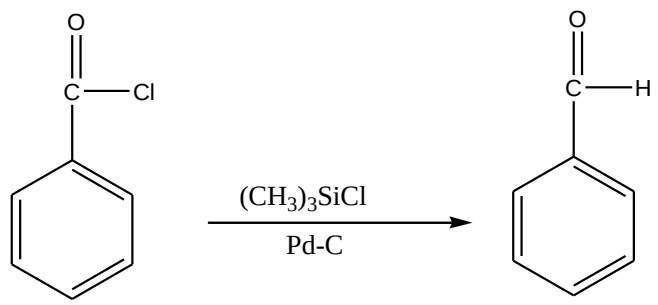
Combination of $NaBH_4$ with Al_2O_3 can also reduce the acid chloride into primary alcohol with good yield.

3.7.3 Reduction by mild reducing agent:

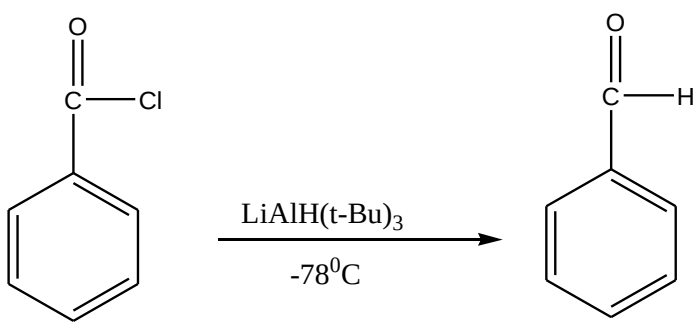
Catalytic hydrogenation of the acid chloride in the presence of $Pd/BaSO_4$ and quinoline cause the reduction of acid halide into aldehyde. This reaction is called as Rosenmund reduction reaction.



Trimethylsilane $(CH_3)_3SiCl$ in the presence of Pd-C can also reduce the acid halide into aldehyde.

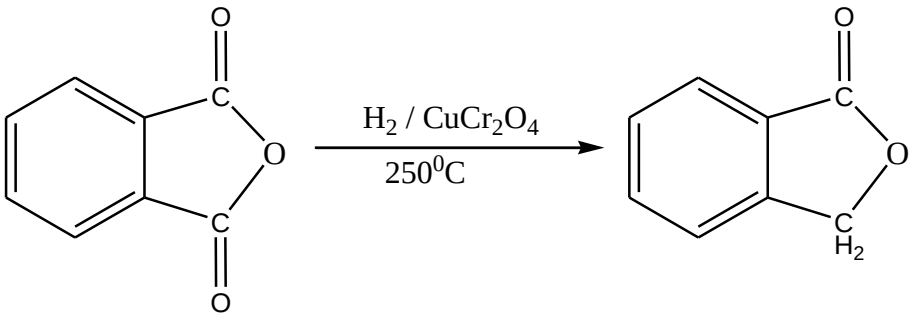


Alkoxy derivatives of metal hydrides like lithium tri t-butoxyaluminium hydride LiAlH $(t\text{-}Bu)_3$ can also cause the reduction of acid chloride into aldehyde without affecting the other functionalities like nitro , cyano , halo ,as well as unsaturation .

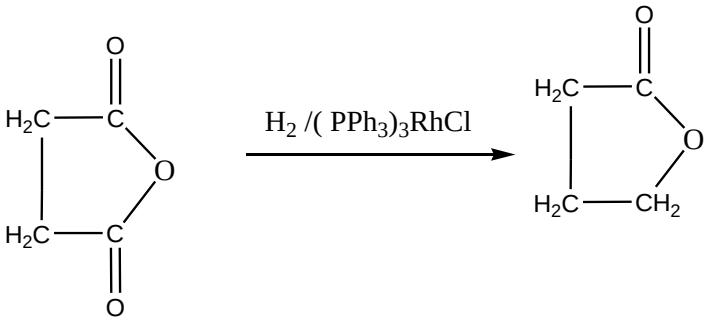


3.8 REDUCTION OF ANHYDRIDES

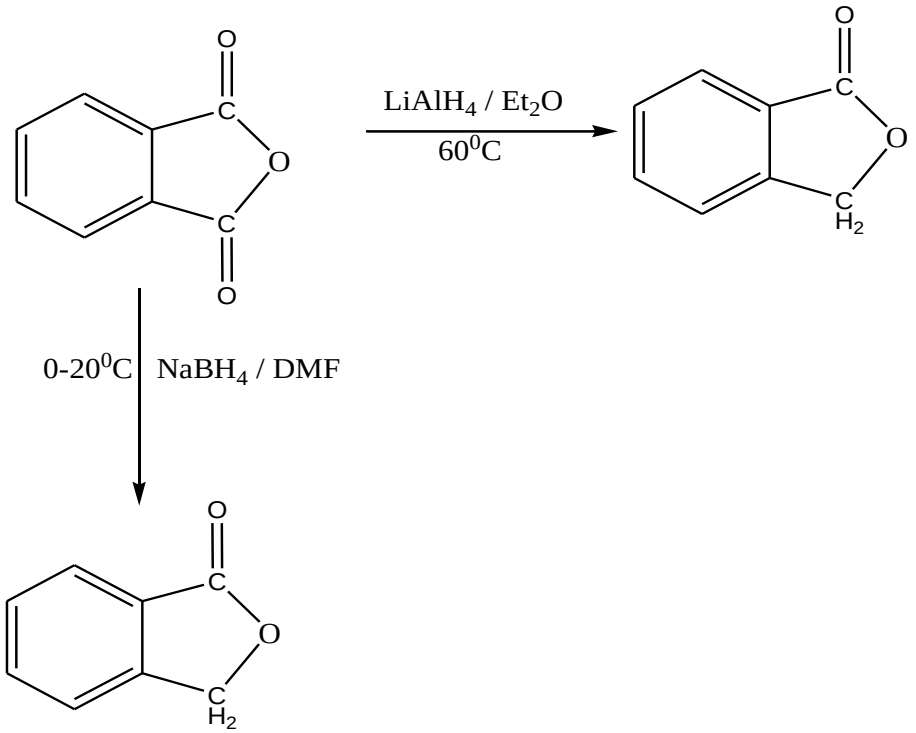
Cyclic anhydride can be reduced into lactones or diols depending on the selection of reducing agents. Hydrogenation of cyclic anhydride in the presence of copper chromite at 250 ^{0}C gives lactone with high yield.



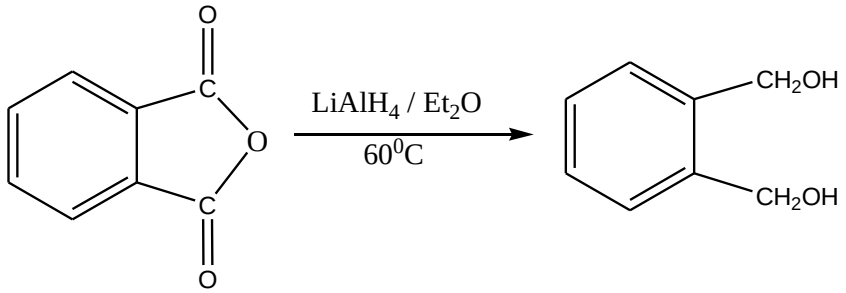
Anhydride can also be reduced into lactone by hydrogenation in the presence of Wilkinson catalyst.



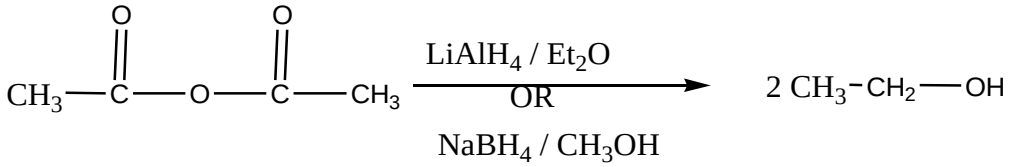
Under low temperature condition $LiAlH_4$ aswell as $NaBH_4$ can also reduce the anhydrides into lactone with good yield.



But if the cyclic anhydride are reduced in the presence of reducing agents like $LiAlH_4$, $NaAlH_2$ $(O\text{-}CH_2CH_2\text{-}OCH_3)_2$ then diol formation occur.

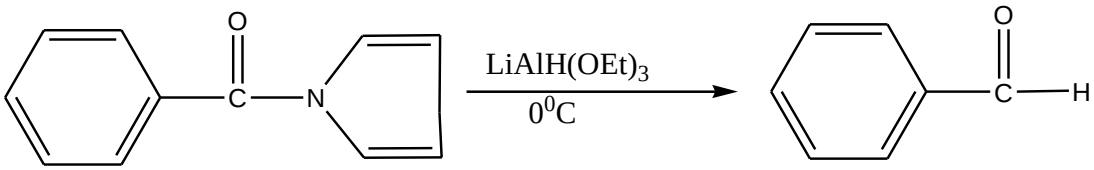


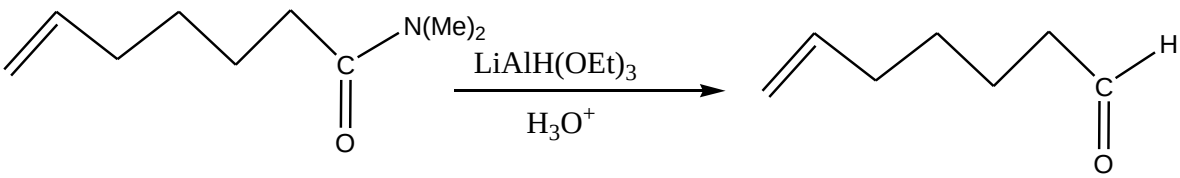
Anhydrides of monocarboxylic acids are reduced into alcohol by using $LiAlH_4$, $NaAlH_2$ $(O\text{-}CH_2CH_2\text{-}OCH_3)$ or $NaBH_4$.

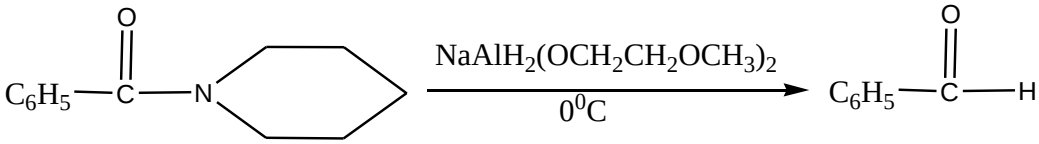


3.9 REDUCTION OF AMIDES

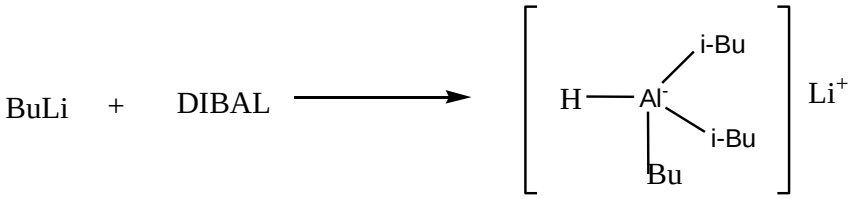
Amides on reduction can give the aldehyde, alcohol, or amines depending on the nature of amide , reducing agent , or reaction conditions. 3^0 amides on reaction with reducing agents like lithium aluminium hydride and sodium bis-(2-methoxy ethoxy) aluminium hydride gives aldehyde while primary and secondary amides can not be reduced into aldehyde.





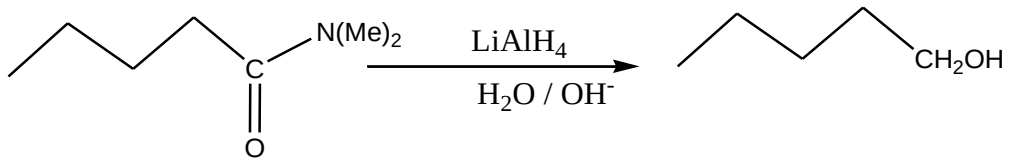


Low temperature condition favours to these reactions. Combination of butyl lithium and DIBAL i.e. ATE complex gives the best reduction of amides into aldehyde.

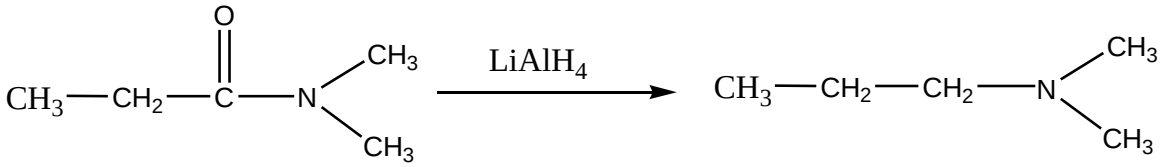


ATE COMPLEX

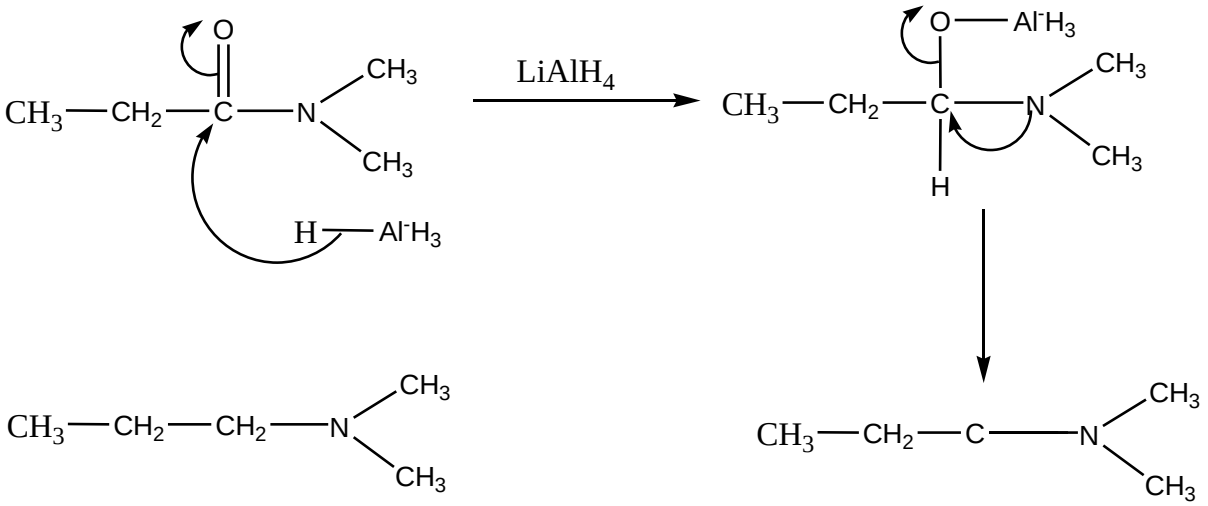
When tertiary amide is treated with $LiAlH_4$ then they are converted into primary alcohol.



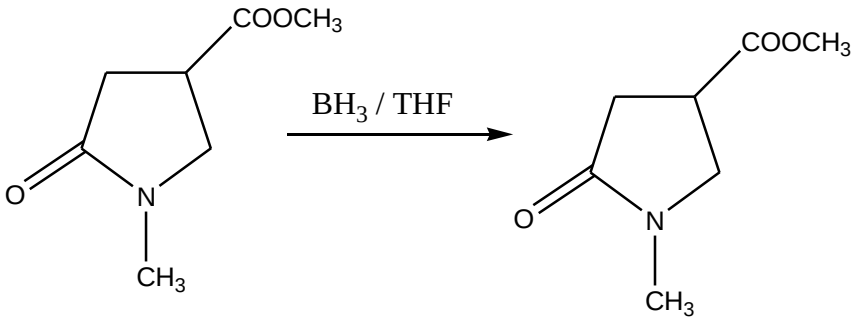
Lithium aluminiumhydride reduces the amides into corresponding amines

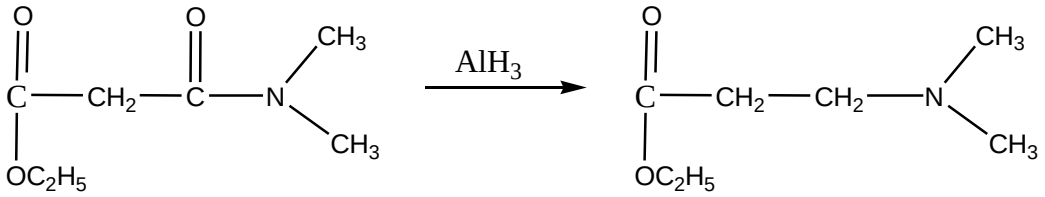


MECHANISM -

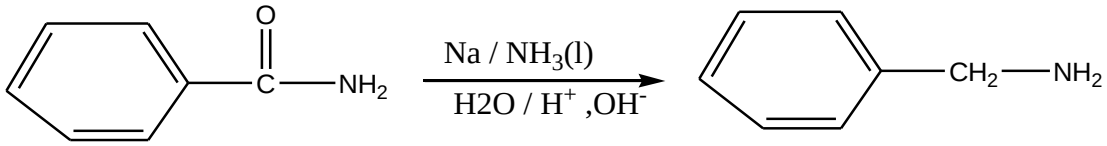


Alane (AlH_3) as well as BH_3/THF can also reduce the amides into corresponding amines without affecting ester functionality.





Sodium in liquid ammonia is also used for the reduction of amides into the corresponding amines.



3.10 REDUCTION OF CARBONYL COMPOUNDS

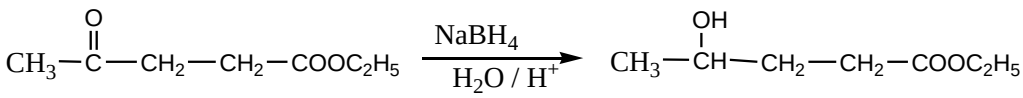
Carbonyl compounds on reduction reaction with various types of reducing agents can generate the alcohol, alkane, alkene, vicinal diol. Formation of this entire reduction product by using different reducing agents can be given as-

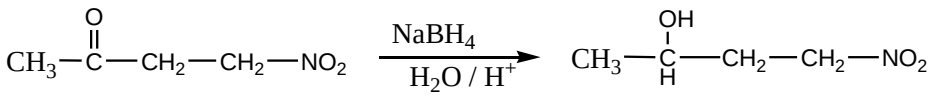
3.10.1 REDUCTION BY HYDRIDE TRANSFER REAGENTS:

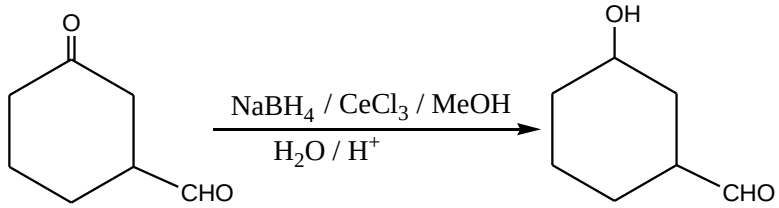
When the aldehyde and ketones are treated with the hydride transfer reagents like $LiAlH_4$ and $NaBH_4$ then they are reduced into primary alcohol and secondary alcohol respectively. $LiAlH_4$ is a powerful reducing agent that can also cause the reduction of other functionalities like esters, carboxylic acids, amides, nitriles etc due to which it can not exhibit the selectivity during the reduction reactions. $NaBH_4$ is a poor reducing agent that can notaffect the other

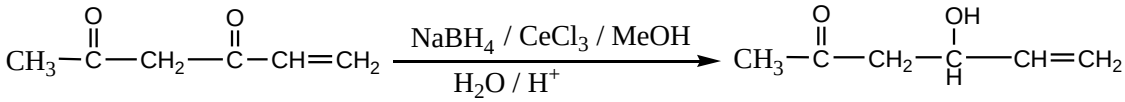
functionalities like C=C, C≡C, ester, nitrile and nitro group. Thus it can be used as the selective reducing agent for the carbonyl compounds.

NaBH

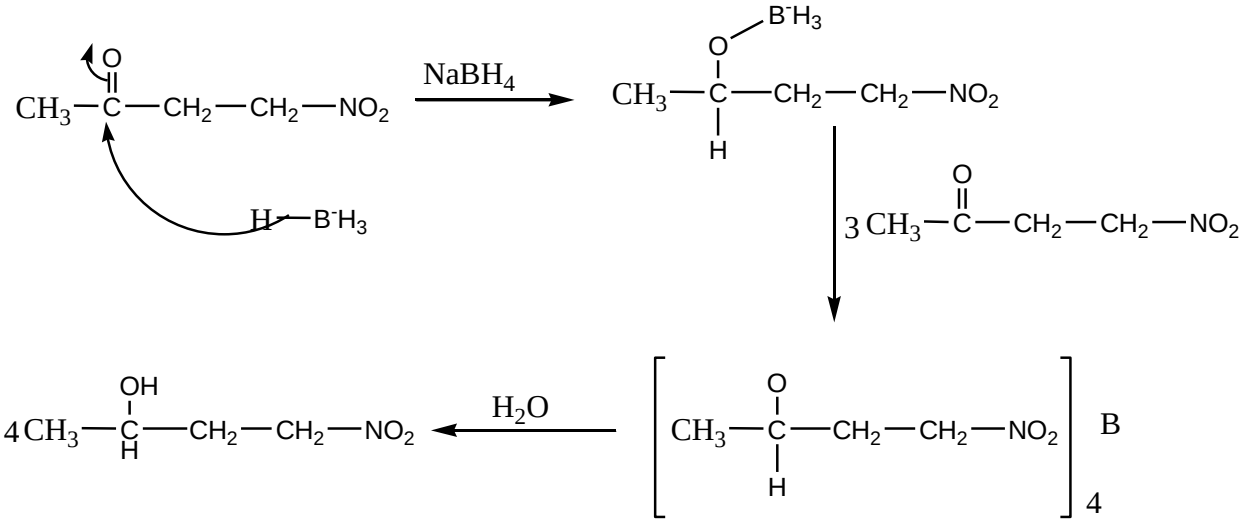




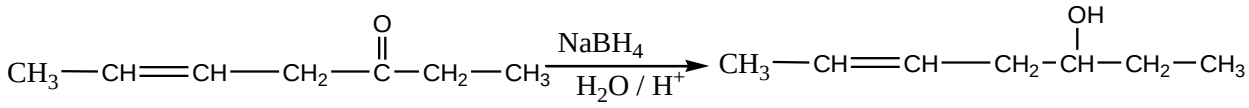




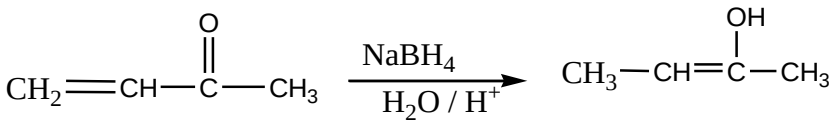
MECHANISM -

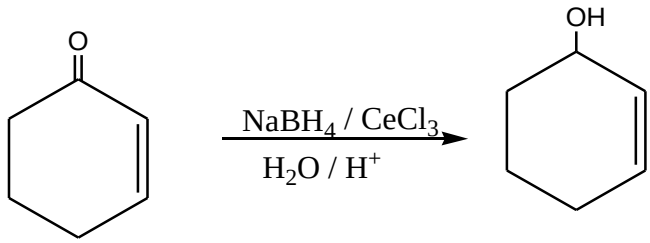


If the compound containing conjugated as well as non conjugated carbonyl group then $NaBH_4$ cause the reduction of non conjugated carbonyl group selectivily.

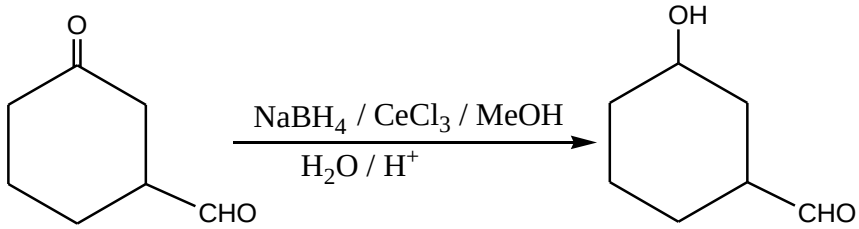


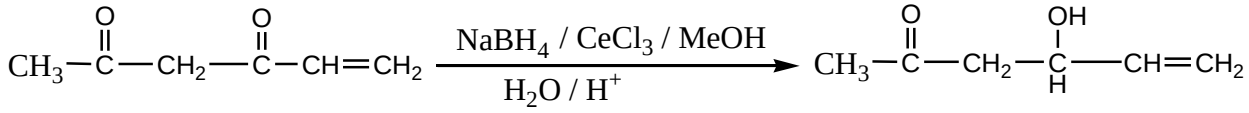
α,β –unsaturated carbonyl compound give the 1,4 addition product on reduction reaction with the $NaBH_4$ but reduction reaction of α,β –unsaturated carbonyl compound with $NaBH_4$ in the presence of $CeCl_3$ gives 1,2 addition product .



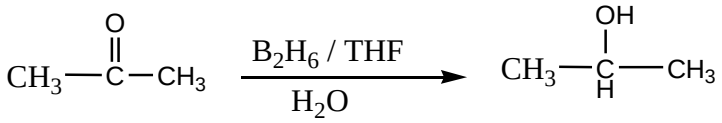


Presence of $CeCl_3$ with $NaBH_4$ can also reduce the ketone selectivily in the presence of aldehyde. In other word less reactive nature of carbonyl group undergo reduction preferentially.

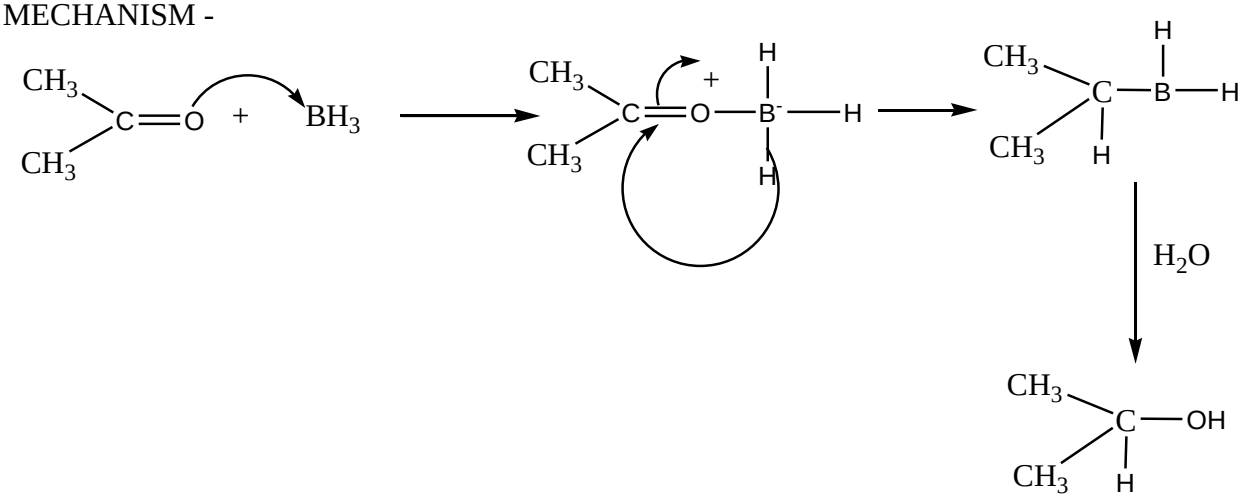




Carbonyl compounds can also be reduced into alcohol by the boranes.



MECHANISM -



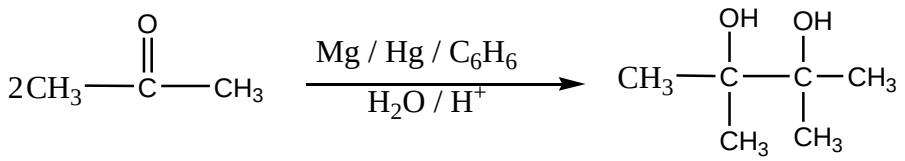
3.10.2 Enzymatic reduction:

Backer's yeast reduce the ketonic group situated at the β position with respect to the ester functional group ,into alcohol selectivily .

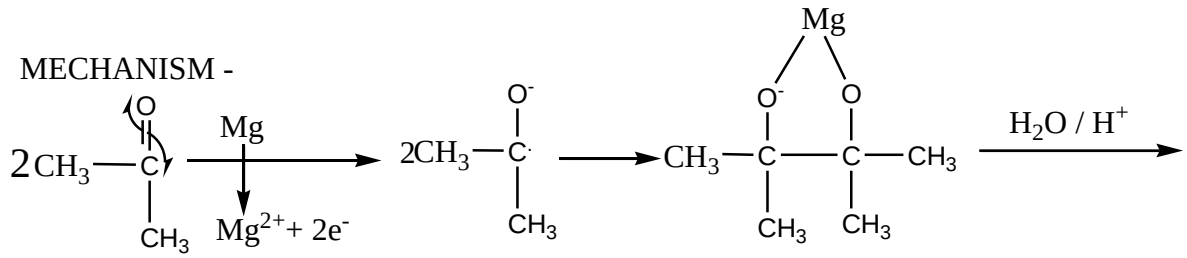
EAA

3.10.3 Reduction into vicinal diol and alkene:

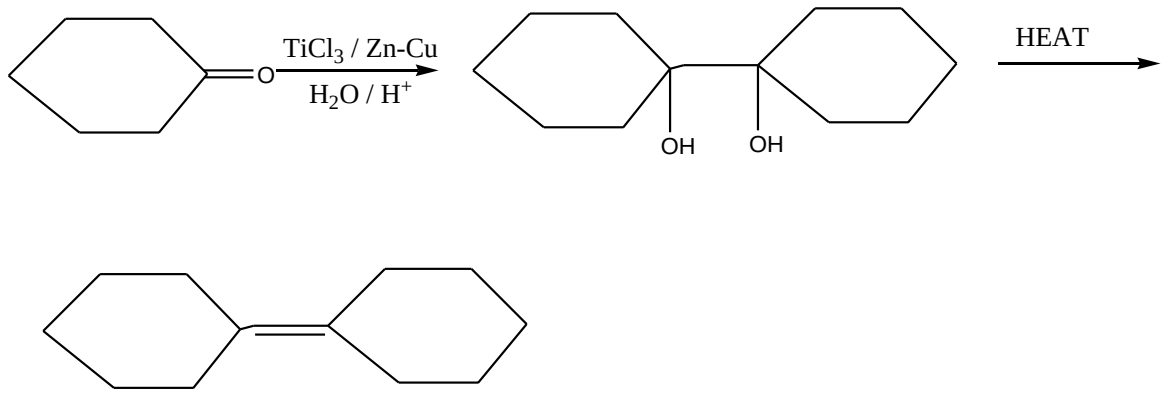
When ketones are treated with the Mg/Hg or Al/Hg in the presence of aprotic solvent then there occur the formation of a product which on acidification gives vicinal diol (pinacol).



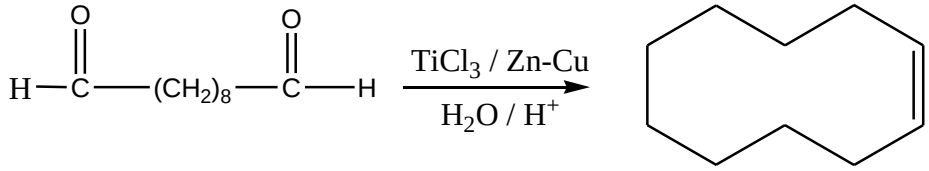
MECHANISM -



The titanium metal obtained from $TiCl_3$ can further react with pinacol to give alkene . This type of conversion is called as McMurryreaction.



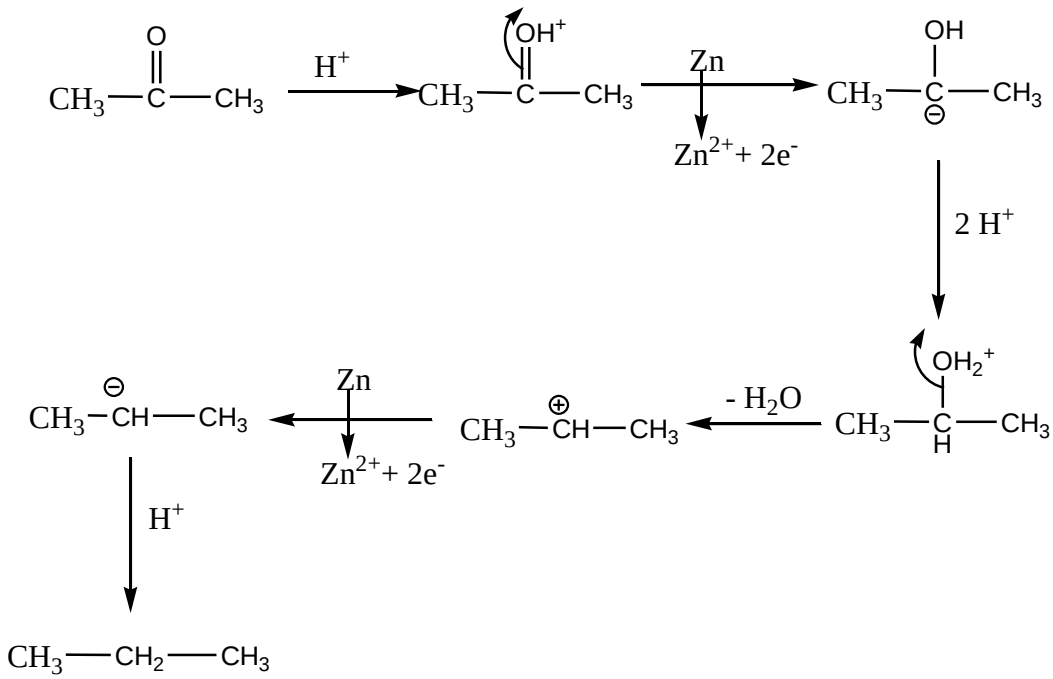
This reaction can also occur in the dialdehyde of the long hydrocarbon chain by the intramolecularfashion.



3.10.4 Clemenson reduction reaction:

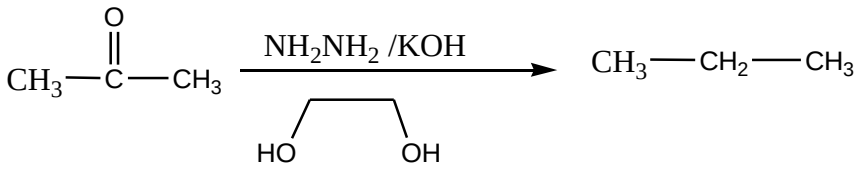
When the carbonyl compounds react with the Zn-Hg and concentrated HCl then carbonyl group is converted into methylene group. This type of the reduction reaction of carbonyl compounds is called as Clemenson reduction reaction.

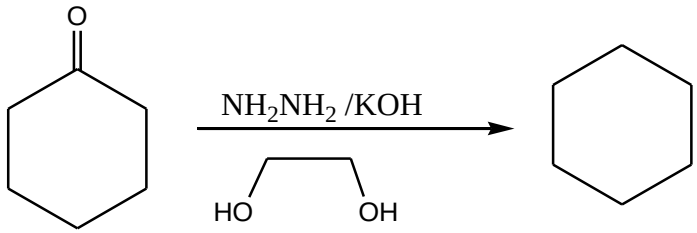
MECHANISM -



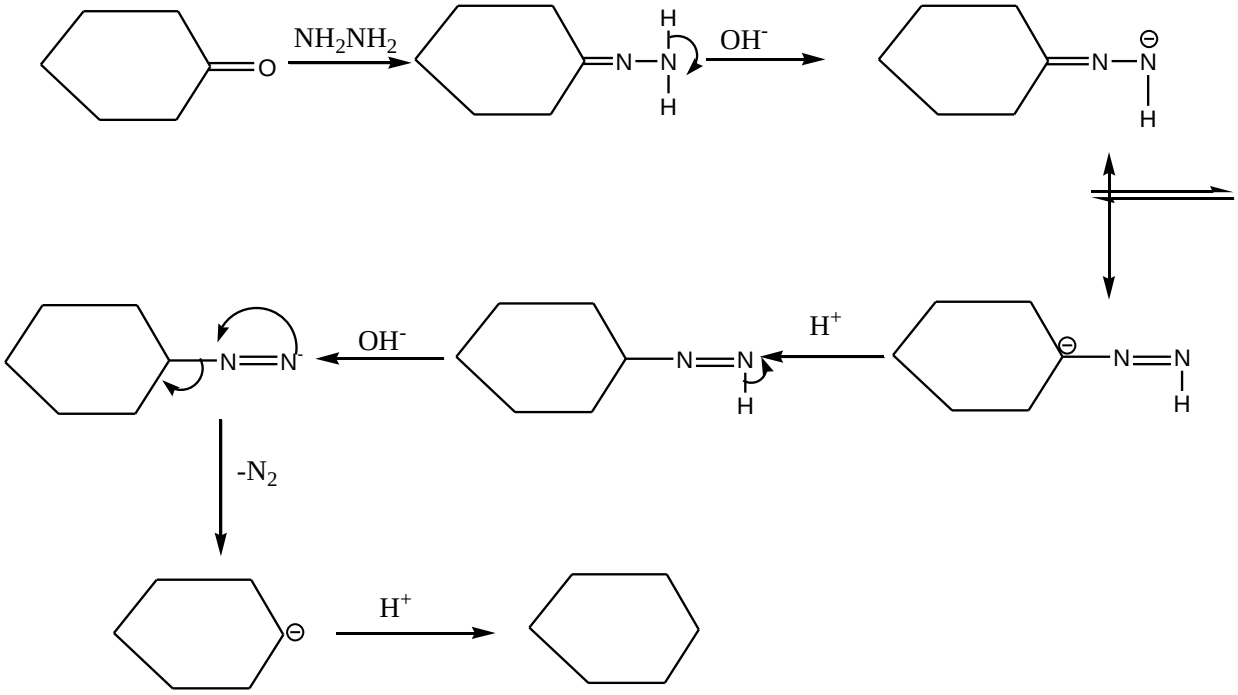
3.10.5 Wolf kishner reduction reaction:

When the carbonyl compound reacts with the hydrazine and potassium hydroxide or sodium hydroxide in the ethylene glycol solvent then carbonyl group is converted into the methylene group. This type of reduction reaction is called as Wolf Kishner reduction reaction.

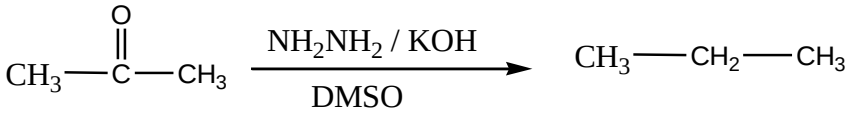




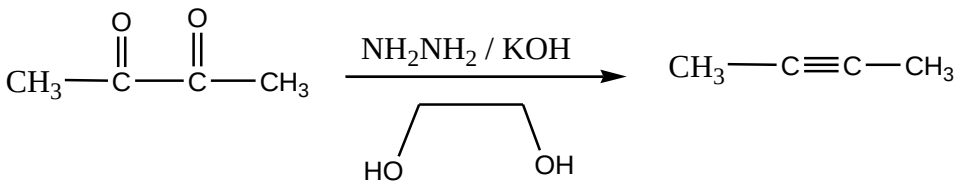
MECHANISM -



Use of the potassium t-butoxide in DMSO solvent with hydrazine gives better result in this reaction.



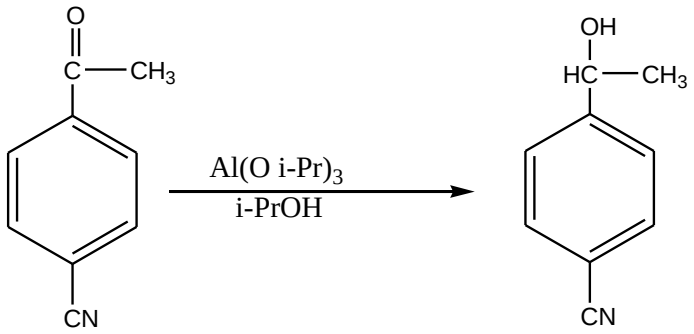
α –diketone gives alkyne under this reaction condition.

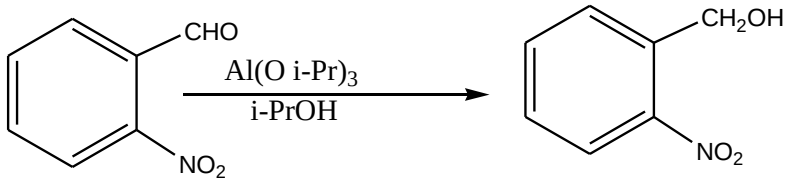


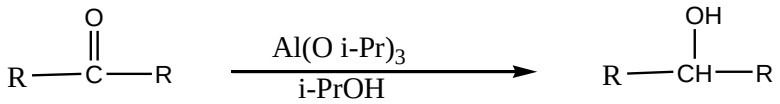
3.10.6 Meerwein-ponndorf-vereley reduction:

When carbonyl compounds like aldehyde or ketone react with the aluminiumisopropoxide and isopropyl alcohol then the carbonyl compounds are reduced into corresponding alcohol through the 6 membered transition state (T.S). This type of reduction reaction is called as MPV reduction reaction.

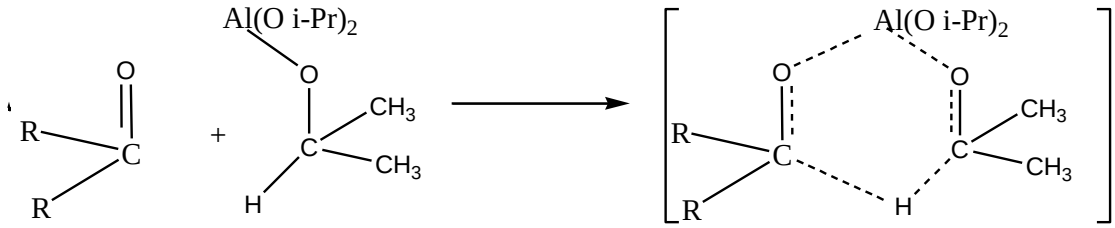
This reduction reaction is highly specific for aldehydes and ketones, other functionalities like C=C, C≡C, NO_2, COOH, COOR, $CONH_2$ etc remain unaffected under this reaction condition.


O
C
CH3
CN
Al(O i-Pr)3
i-PrOH
OH
HC
CH3
CN

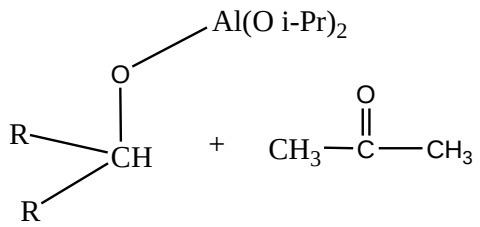

CHO
NO2
Al(O i-Pr)3
i-PrOH
CH2OH
NO2


O
R
C
R
Al(O i-Pr)3
i-PrOH
OH
R
CH
R

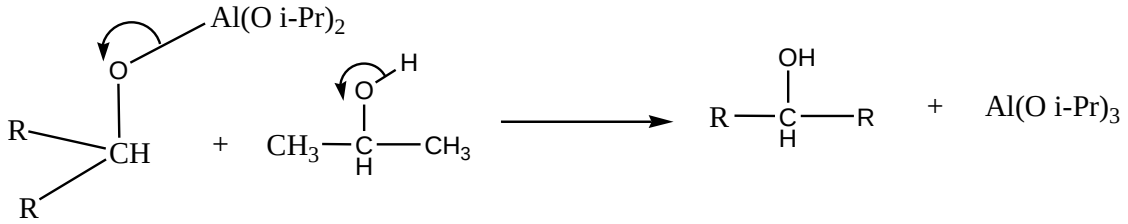
MECHANISM - STEP I -



6 MEMBERED T.S



STEP II -

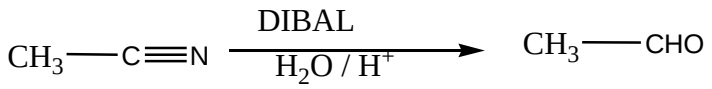


3.11 REDUCTION OF NITRILES

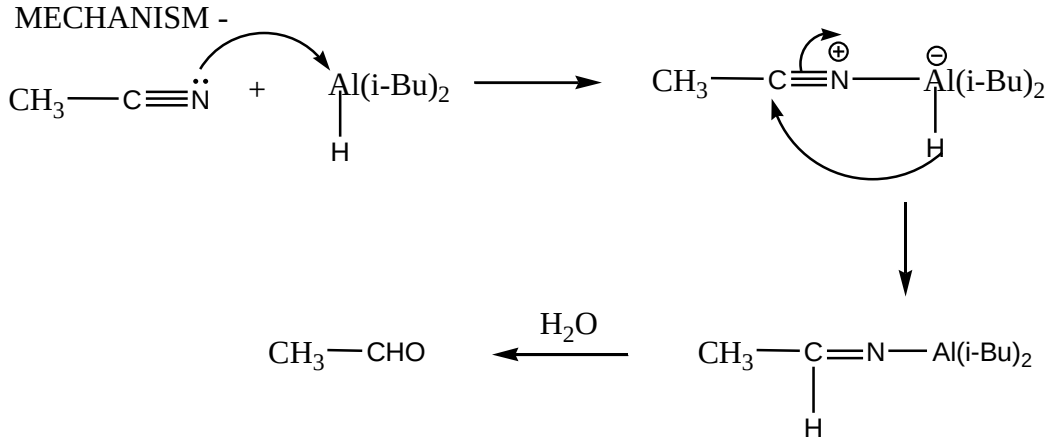
Nitriles on reduction reaction gives two type of the reduction product aldehyde and amines according to the nature of reducing agent used for the reaction.

3.11.1 - REDUCTION TO ALDEHYDES:

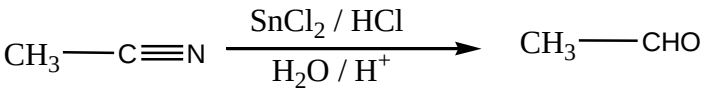
When the nitriles react with the hydride reducing agent like DIBAL, sodium tri ethoxyaluminium hydride NaAlH $(OC_2H_5)_3$, lithium tri ethoxyaluminium hydride $LiAlH(OC_2H_5)_3$ then they are converted into aldimine which on hydrolysis gives aldehyde .



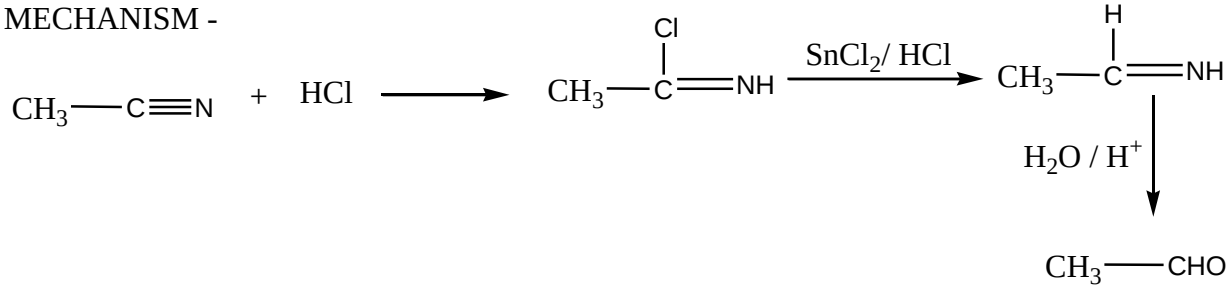
MECHANISM -



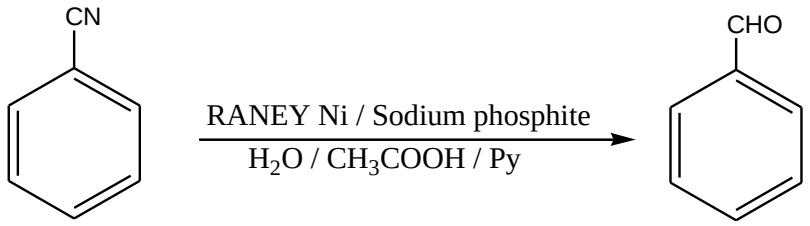
Nitriles can also be reduced into the aldehyde by the Stephen aldehyde synthesis. In this reaction nitriles are treated with $SnCl_2$ and HClby which aldimines are obtained which on hydrolysis gives the aldehyde.



MECHANISM -

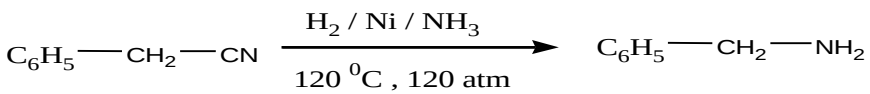


During the reduction by Stephen reaction other functional groups like carbonyl, NO_2, COOH, COOR, $CONH_2$ etc. remain unaffected. At the same time aromatic aldehyde are prepared by the reduction of aromatic nitriles by using Raney nickel and sodium phosphite in water/CH_3COOH and pyridine.

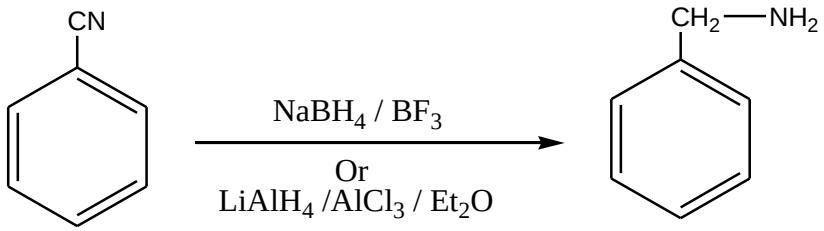


3.11.2 Reduction to amines:

When the nitriles are treated with the powerful reducing agent then they are reduced into amines. Powerful reducing like H_2/Ni, H_2/Rh/Al_2O_3 in the presence of ammonia can be used for this purpose .



$NaBH_4/BF_3$ or $LiAlH_4/AlCl_3/Et_2O$ can be used for the reduction of aromatic nitriles into amines .

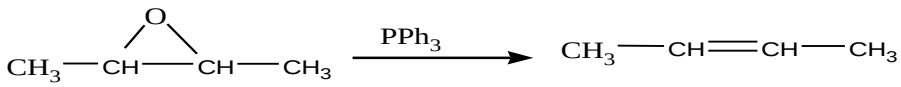


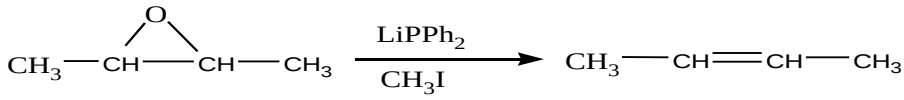
3.12 REDUCTION OF EPOXIDES

Epoxides are reduced into alcohol or alkene according to the nature of reducing agent.

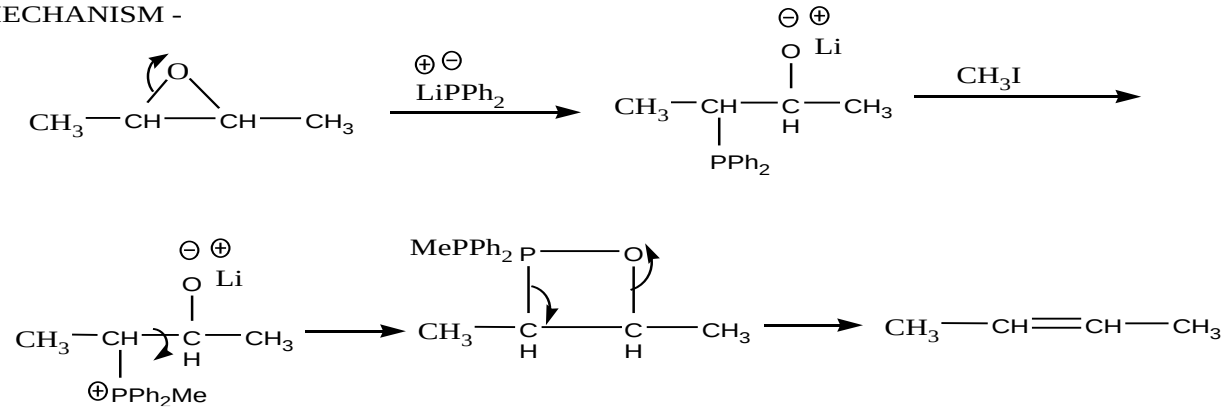
3.12.1 Reduction of epoxide into alkene:

Epoxides are reduced into alkene by using the phosphorous ligands like PPh_3, $LiPPh_2$ because phosphorous ligands having strong nucleophilic nature for this reaction.





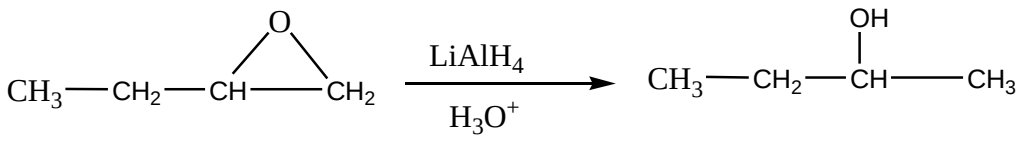
MECHANISM -



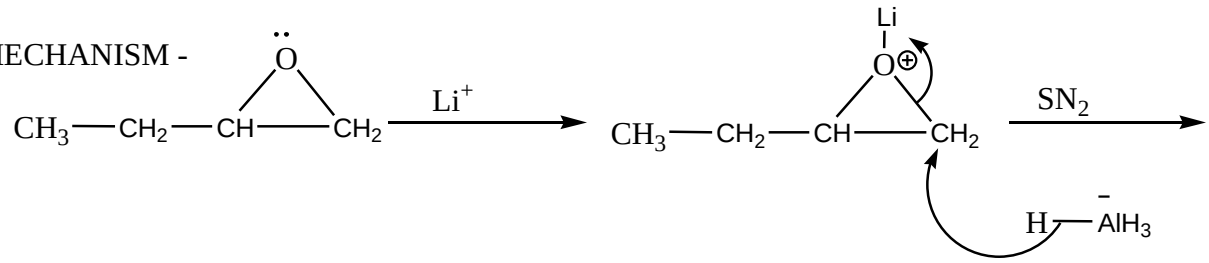
During this reduction reaction following stereo changes are observed –

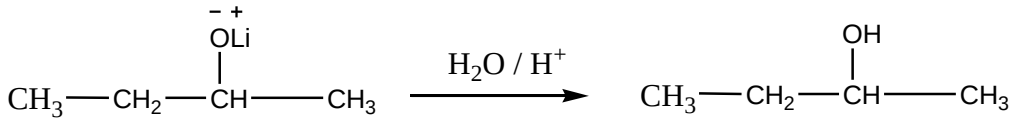
3.12.2 Reduction of epoxides into alcohol:

When the epoxide reacts with the lithium aluminium hydride $LiAlH_4$ then they are reduced into the alcohol.

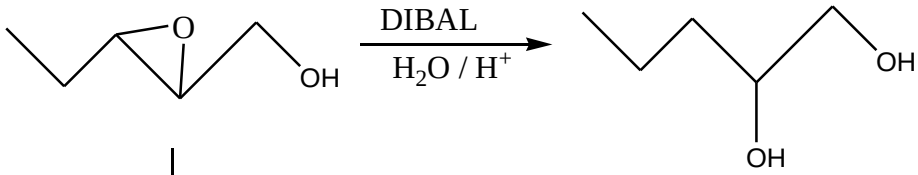


MECHANISM -



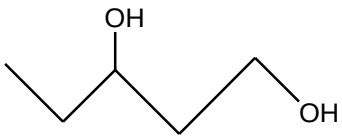


Epoxi alcohol obtained after the epoxidation of allylic alcohol can give 1,2diol or 1,3 diol depending on the nature of reducing agent.



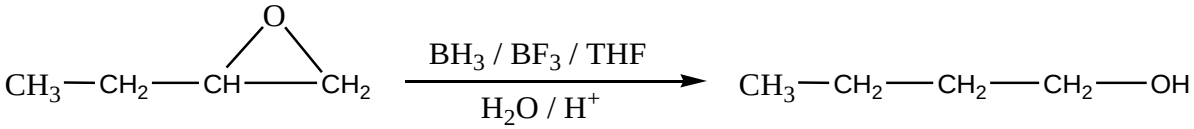
1,2 DIOL

Sodium bis-(2-methoxy ethoxy) aluminium hydride



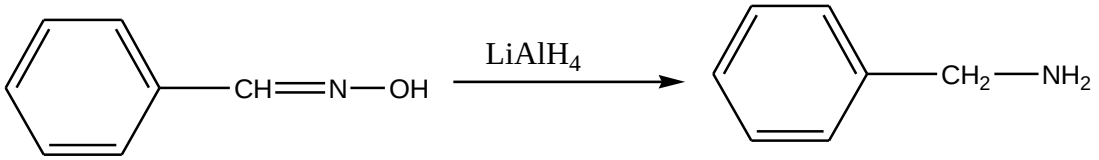
1,3 DIOL

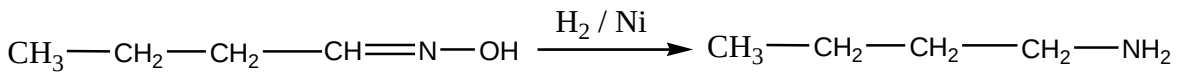
Unlike to $LiAlH_4$ the electrophilic nature of hydride like borane ,alane in the presence of BF_3 cause the ring opening from the more substituted side to give the less substituted alcohol

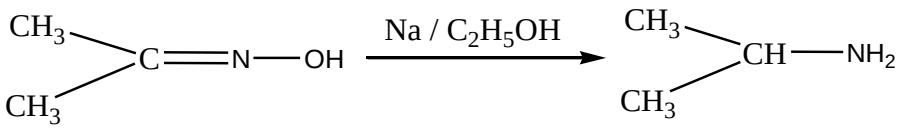


3.13 REDUCTION OF OXIMES

Oximes obtained from the reaction of aldehyde or ketones with the hydroxyl amine are reduced into the primary amine by using the reducing agent like lithium aluminiumhydride, Raney nickel /H_2 or Na /C_2H_5OH.





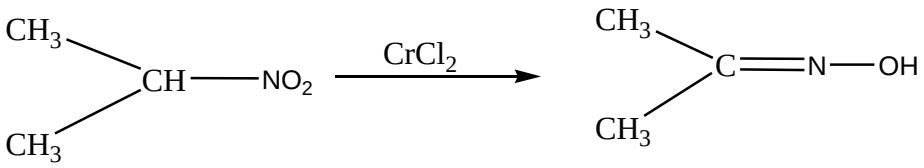


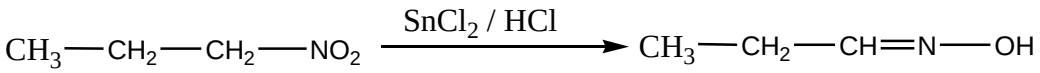
3.14 REDUCTION OF NITRO COMPOUNDS

Both the nitro alkane and nitro arene gives the different types of reduction product on reduction reaction in the different medium which can be given as-

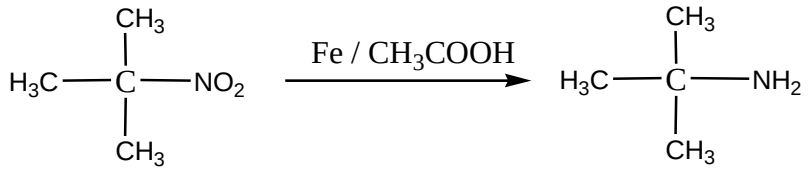
3.14.1 Reduction of nitro alkane:

Aliphatic nitro compound in which nitro group being attached to the primary or secondary carbon atom are reduced into aldoxime and ketoxime respectively by using $CrCl_2$, $SnCl_2$ /HCl

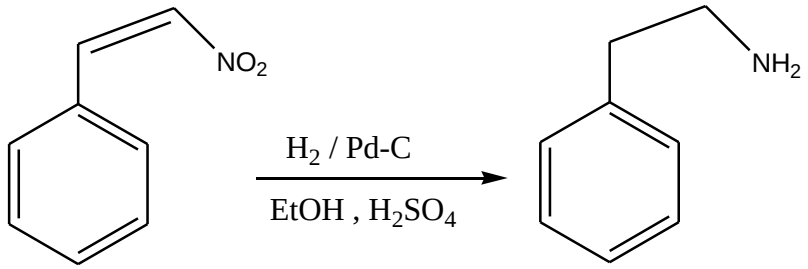




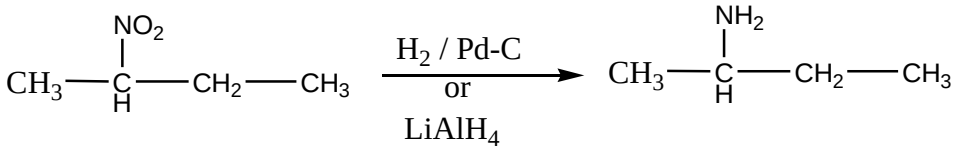
Nitro compound in which nitro group being attached to tertiary carbon are reduced into amines by using Fe / CH_3COOH or Al-Hg.

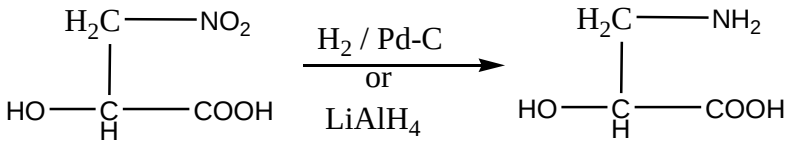


When the α, β-unsaturated nitro compounds are treated with H_2 in the presence of Pd-C, C_2H_5OH ,H_2SO_4 then nitro group is reduced into amino group with the α,β hydrogenation.

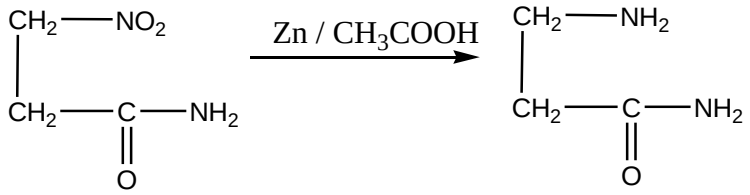


H_2 / Pd-C or $LiAlH_4$ reduce the nitro group into amino group .





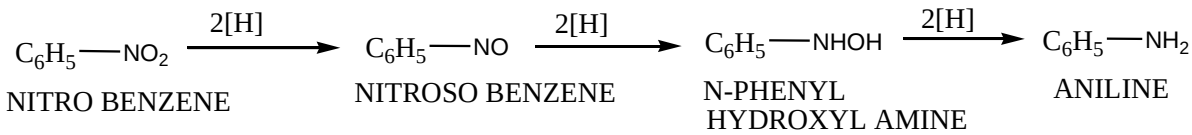
Zn / CH_3COOH cause the selective reduction of nitro group in the presence of amide functionality.



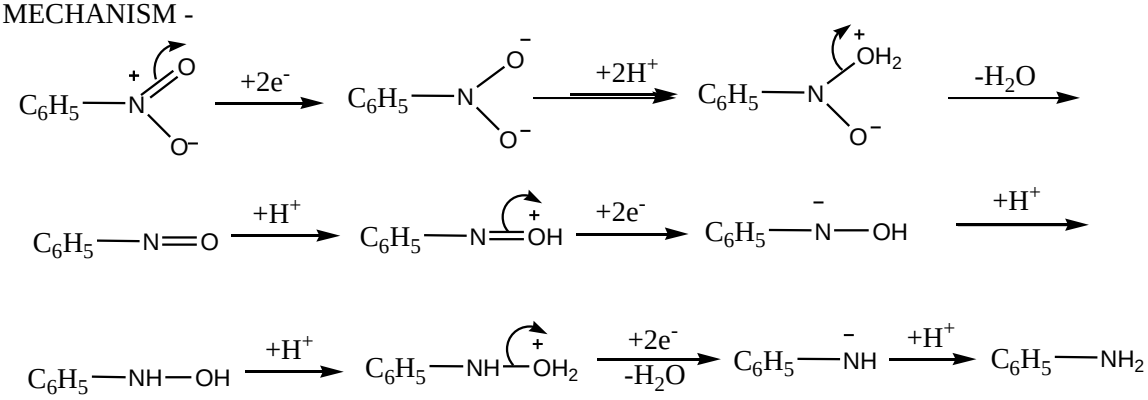
3.14.2 Reduction of nitro arene:

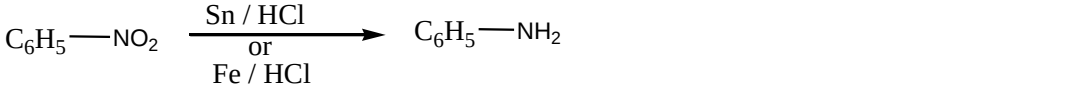
Nitro arene gives the variety of reduction product with the different reducing agents. General Rute for the reduction of nitro arene with the different reduction products can be represented as-

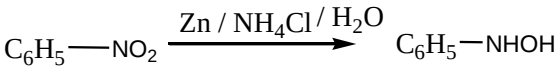
H_2O



MECHANISM -







Nature of the reduction product depends on the nature of reducing agent as well as PH during the reaction condition

Reduction in acidic medium:

$$C_6H_5-NO_2 \xrightarrow[\text{or}]{\text{Sn / HCl}} C_6H_5-NH_2$$
Fe / HCl

Reduction in neutral medium:

$$C_6H_5-NO_2 \xrightarrow{\text{Fe / STEAM}} C_6H_5-NHOH$$

$$C_6H_5-NO_2 \xrightarrow{\text{Zn / NH}_4\text{Cl / H}_2\text{O}} C_6H_5-NHOH$$

Reduction in basic medium:

$$C_6H_5-NO_2 \xrightarrow[\text{or}]{\text{CH}_3\text{ONa / CH}_3\text{OH}} C_6H_5-\overset{\overset{O}{\uparrow}}{N}=N-C_6H_5$$
GLUCOSE / NaOH

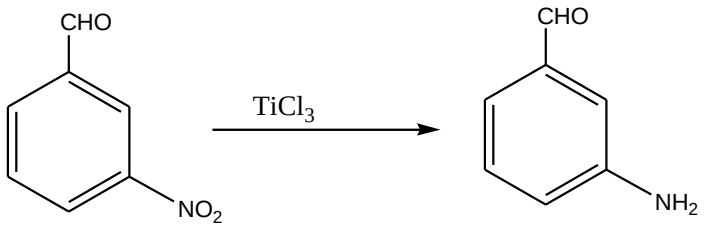
AZOXY BENZENE

$$C_6H_5-NO_2 \xrightarrow{\text{Zn DUST / NaOH}} C_6H_5-NH-NH-C_6H_5$$
HYDRAZOBENZENE

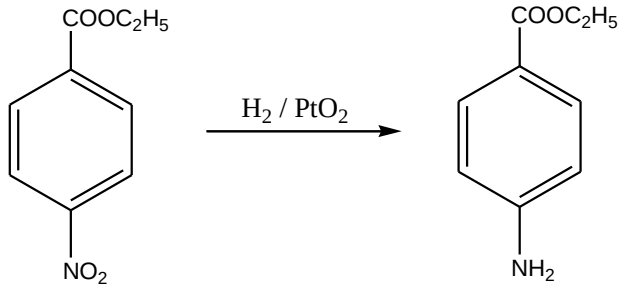
$$C_6H_5-NO_2 \xrightarrow{\text{LiAlH}_4} C_6H_5-N=N-C_6H_5$$
AZO BENZENE

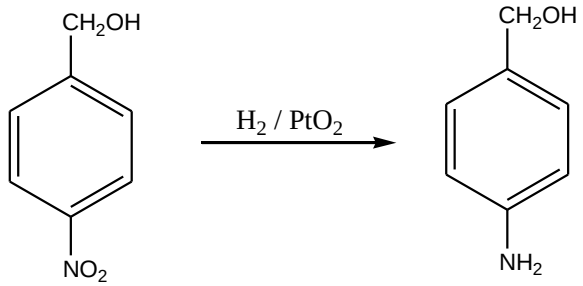
Some selective reducing agent which can reduce the nitro group in the presence of other functionalities are given below-

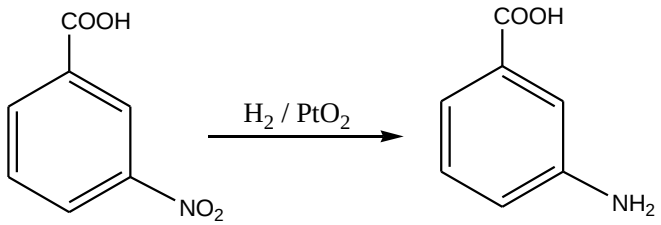
(a) $SnCl_2$ / HCl or $TiCl_3$ cause the selective reduction of nitro group in the presence of aldehydicgroup.



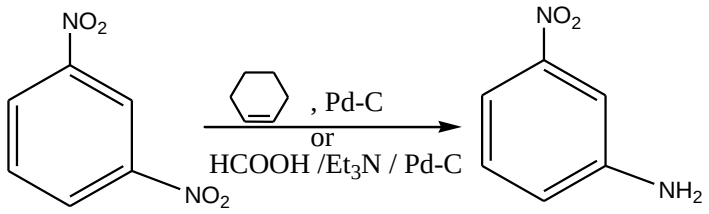
(b) Hydrogenations in the presence of metel or metel oxide cause the selective reduction of nitro group in the presence of ester, carboxylic, or hydroxyl group.



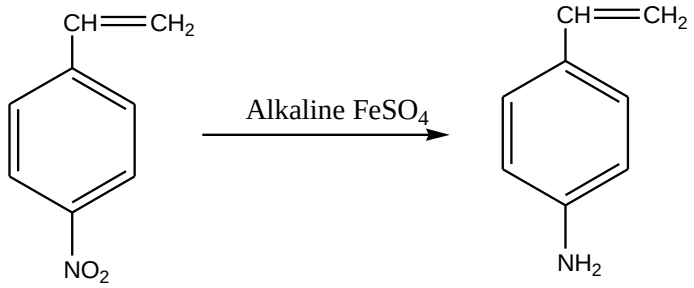




(c) If the dinitroarenes are reduced by using tri ethyl ammonium formate or cyclohexene / Pd-C then there occur the selective reduction of one of the nitro group while other remain as such .

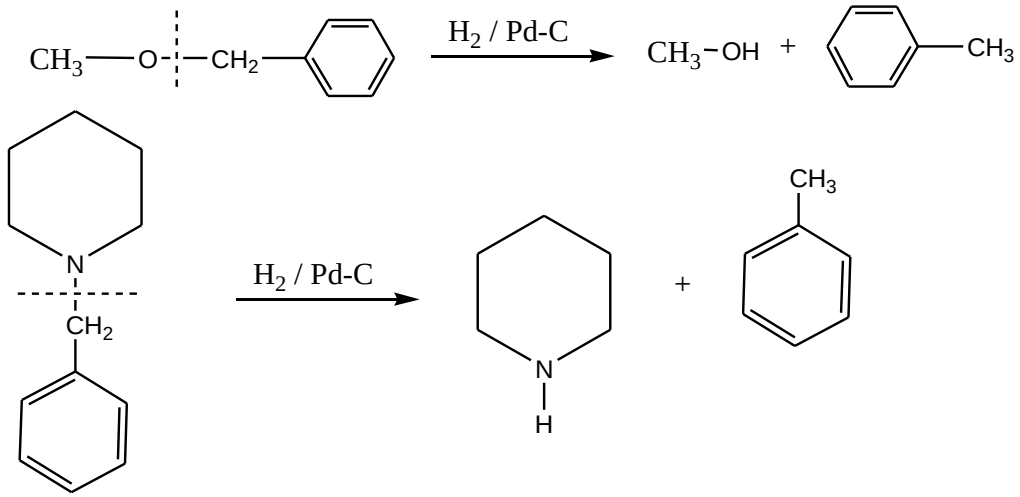


(d) Alkaline $FeSO_4$ cause the reduction of nitro group in the presence of vinylicgroup.



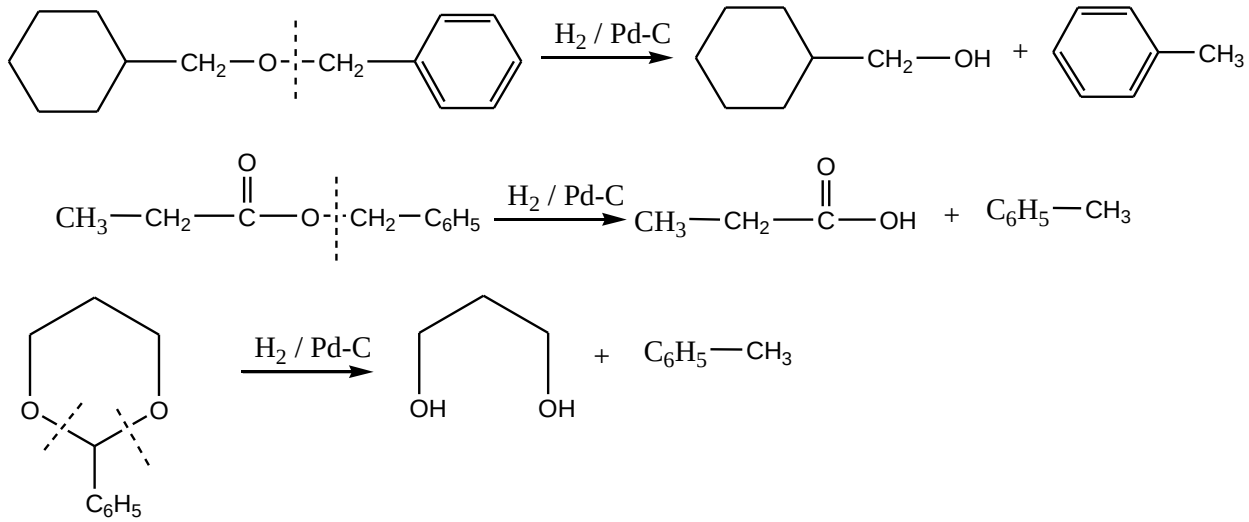
3.15 HYDROGENOLYSIS

Cleavage of the bond between carbon and an electronegative atom like O, N, X with the addition of hydrogen in the presence of metal catalyst is called as hydrogenolysis or reductive cleavage.



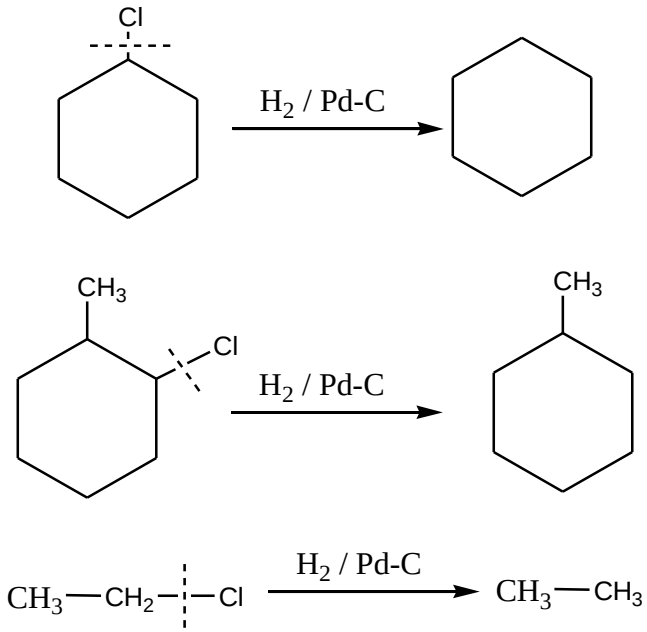
3.15.1 HYDROGENOLYSIS OF ETHER, ESTERS AND CARBAMATES:

When the ether, esters, orcarbamate containing oxygen atom directly attached to the benzylic substituent react with the H_2 in the presence of Pd /C then there occur the hydrogenolysis to give the carboxylic acids and alcohols.



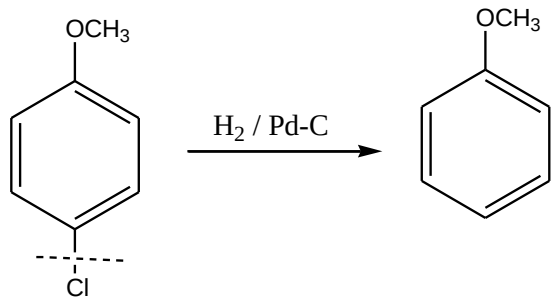
3.15.2 - Hydrogenolysis of halo compound:

When the halo compounds react with H_2 in the presence of Pd /C then there occurs the reductive cleavage of C-X bond which is known as hydrogenolysis of halo compounds.

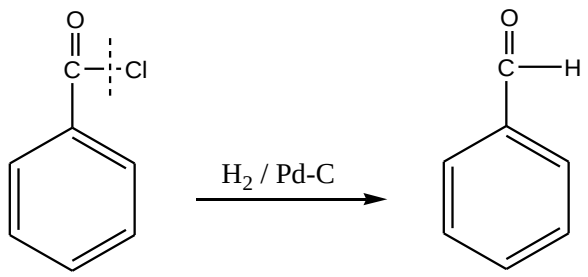


Order of C-X bond breaking in this reaction having the following order –

C-I > C-Br > C-Cl > C-F

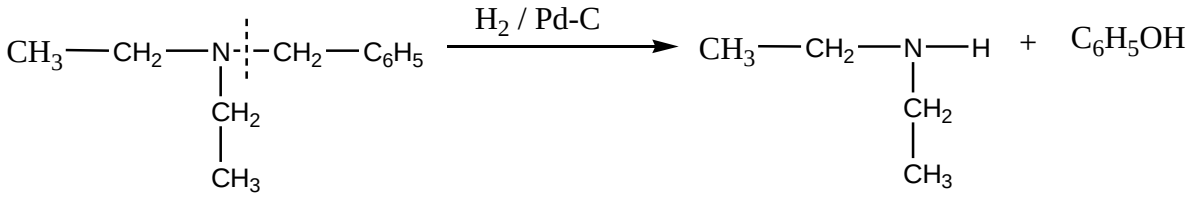


Hydrogenolysis of the acid chloride gives the aldehyde. This reaction is called as Rosenmund reduction reaction.



3.15.3 Hydrogenolysis of amines:

When the amines containing the benzylic substituent directly attached to the N atom react with H_2 in the presence of Pd /C then there occurs the formation of new amine by reductive cleavage. This type of reductive cleavage of C-N bond with the addition of H_2 in the presence of Pd /C hydrogenolysis of amines.



3.18TERMINAL QUESTIONS

Q 1. Define the reactivity order of carboxylic acid and its derivatives toward the reduction reactions?

Q 2. Which reducing agent causes the selective reduction of alkynes into cis and Trans alkenes .Define these reactions with their mechanism?

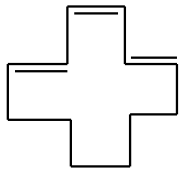
Q 3. Which of the reducing agents can be used for selective reduction of nitro group in the presence of other functional groups like ester, carboxylic and hydroxyl groups ?

Q 4. Why $NaBH_4$ behave as a better reducing agent in compare to the $LiAlH_4$ during the reduction of carbonyl compounds?

Q 5. Define the mechanism for the reduction of carbonyl compounds by using metal hydride reducing agents?

Q 6. Complete the following reduction reaction –

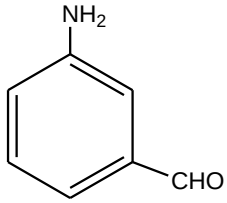
(a)



$\xrightarrow[O_2]{NH_2NH_2\ ,\ Cu^{2+},}$?

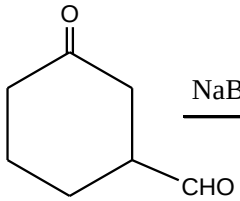
(b) $CH_3-C\equiv C-CH_3 \xrightarrow{H_2\ /\ Ni_2B}$?

(c)



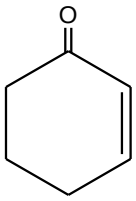
$\xrightarrow[C_2H_5OH]{Na\ /\ NH_3(l)}$?

(d)



$\xrightarrow{NaBH_4\ /\ CeCl_3\ /\ CH_3OH}$?

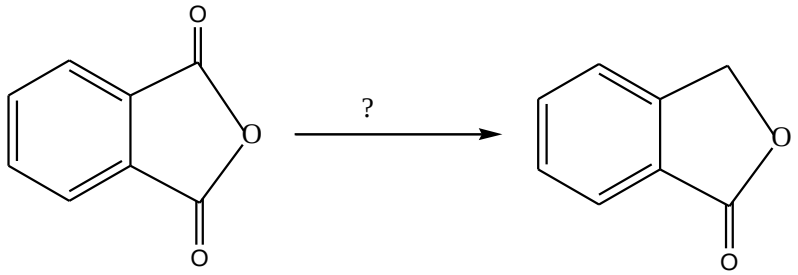
(e)



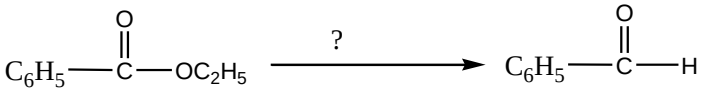
$\xrightarrow[H_2O\ /\ H^+]{NaBH_4\ /\ CeCl_3}$?

Q 7. Which reducing agents can be used during the following reduction reactions?

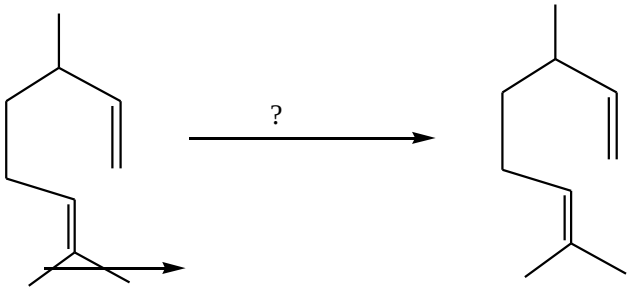
(a)



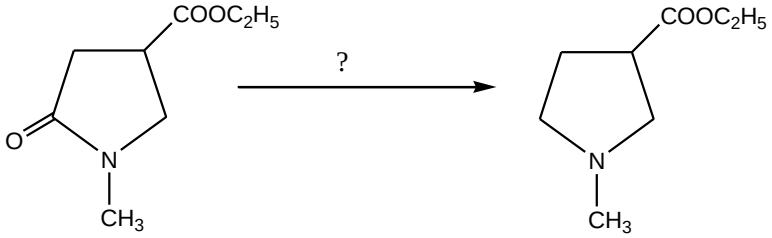
(b)



(c)



(d)



3.17 BOOKS SUGGESTED

1. *Advanced Organic Chemistry, Reaction and Synthesis, Francis A.Carey and Richard J.Sundberg.*
2. *Modern Methods of Organic Synthesis, William Carruthers and Iain Coldham.*
3. *Organic Synthesis, Jagdamba Singh, L.D.S.Yadav.*
4. *Organic Synthesis, the Disconnection Approach, Stuart Warren.*
5. *Organic Reaction and Their Mechanism, P.S.Kalsi.*
6. *Principles of Organic Synthesis, R.O.C.Norman and J.M.Coxon.*
7. *Advanced Organic Chemistry, Reaction Mechanism and Structure, Jerry March, John Wiley.*

UNIT- 4 DISCONNECTION APPROACH

CONTENTS

4.1. Objectives

4.2. Introduction

4.3. Order of event in organic synthesis and its importance

4.4. Functional group interconversion (FGI)

4.5. One group C-X disconnections

4.6. Two group C-X disconnections

4.7. C-C disconnections

4.8. Disconnection of α-β unsaturated carbonyls

4.9. Umpolung (reversal of polarity)

4.10. Cyclization reaction and disconnection approach

4.11. Summary

4.12 Terminal Questions

4.1 OBJECTIVES

After going through this unit student will be able to:

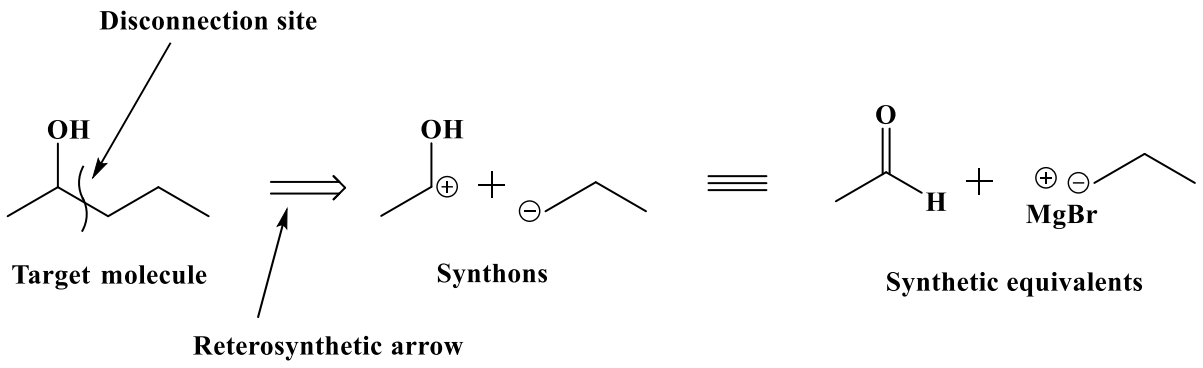
- Various terms used in disconnection approach
- Know the importance of order of events in disconnection approach of an organic molecule
- Differentiate between different types of disconnection approach and possible steps involved.
- Carry on the step of FGI and their requirement
- Understand the concept of umpolung
- Carry out the disconnection of cyclic molecules

4.2 INTRODUCTION

Retrosynthesis: Retrosynthesis (*Retro* reverse, *synthesis* preparation) is an approach in organic synthesis where reverse of forward direction reaction is carried (i.e., formation of reactants from product). Retrosynthesis is considered to be an imaginary process (breaking of bond) where the target molecule is change to the possible starting material by some set of rules known as **disconnection approach** and **functional Group Interconversion (FGI)**.

The simple theme of this approach is to find out simple molecule which could be employed for generation of any target (desired) molecule. For this purpose, some specific chemically established reaction and procedures are required to be followed with use of some well-known chemicals/reagents. If fragments/chemicals which doesn't exist, is difficult to find or is expensive then they can be carried for the process of FGI. Retrosynthesis do also have benefit of establishing alternate route for synthesis of any target molecule, thus can be helpful in generating benefits especially in pharma sector.

Retrosynthesis and disconnection approach involves various terms and species, which should be known well to a reader so as to apply the approach in right manner to get the molecule of interest.



Scheme 1: A typical retrosynthetic reaction with all involved terms

Target molecule: The molecule which undergoes retrosynthesis to give.

Disconnection site: The position of bond which undergo disconnection shown by wiggly line (/)

Retrosynthetic arrow: This demonstrates the process of conversion of target molecule to synthons.

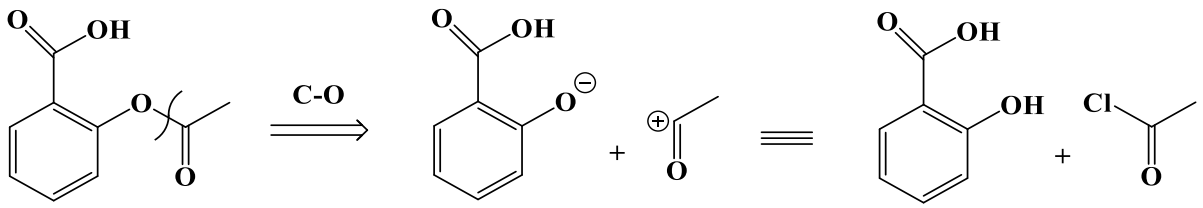
Synthons: Charged species which are formed during the process of disconnection approach, on disconnection less electronegative species get positive charge while negative charge is on more electronegative counterpart.

Synthetic equivalent: The molecule which are formed from synthons after satisfying synthons with opposite charges.

4.3. ORDER OF EVENT IN ORGANIC SYNTHESIS AND ITS IMPORTANCE

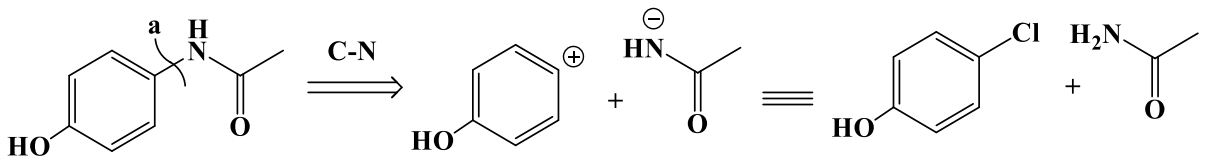
For any reaction in organic chemistry the sequence/order of the reaction have prime importance, so is true for the disconnection approach also. Specific steps or rules can be followed to get a reliable disconnections and desired synthetic equivalents (reagents for forward reaction).

For heteroatom containing molecule it is important to ***disconnect the bond next to heteroatom***, this can be understood by taking an example of retrosynthesis of Aspirin molecule (Scheme 2).

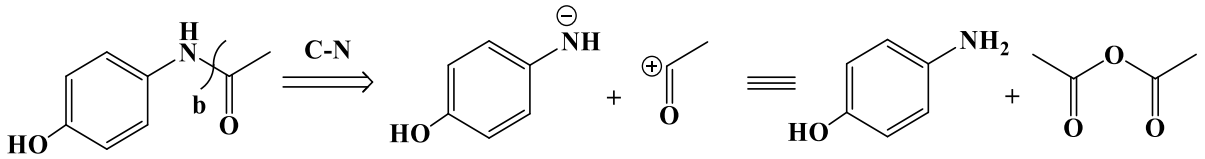


Scheme 2: Retrosynthetic approach of Aspirin

Disconnection is carried next to heteroatom oxygen which synthons and further gives reliable synthetic equivalents, these two reagents in forward reaction can leads towards a reliable organic reaction known as *esterification*.However, one thing should be noted and strictly followed that if heteroatom is connected to cyclic species (aryl or non-aryl) and an alkyl species, in that case bond disconnection between heteroatom and aryl group should not be preferred, as disconnection between aryl group and heteroatom may not generate reliable synthetic equivalents (Scheme 3a and 3b).



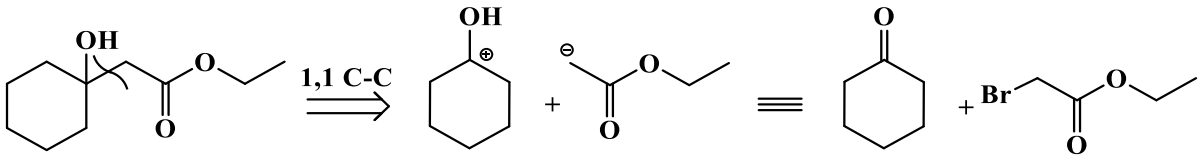
Scheme 3a: Retrosynthetic approach of Paracetamol (non-reliable synthetic equivalents)



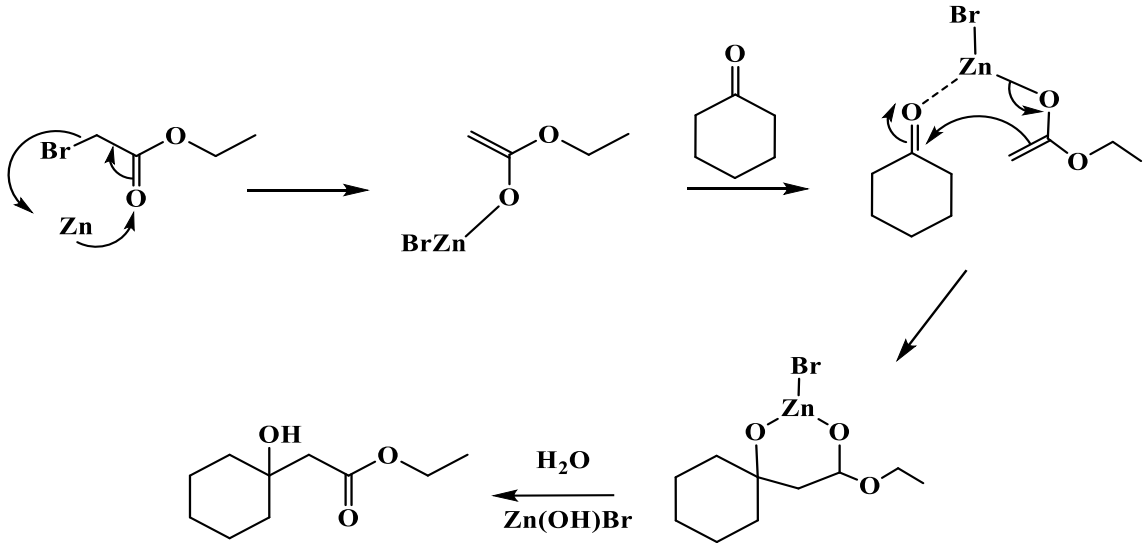
Scheme 3b: Retrosynthetic approach of Paracetamol (reliable synthetic equivalents)

Scheme 3a is considered as non-reliable as on disconnection next to the ring produces such synthetic equivalents which are not found suitable to undergo synthetic reaction to produce the target molecule i.e., paracetamol, which is an established reaction with the two synthetic equivalents obtained via scheme 3b.

Disconnection leading to known and easily available molecules can be considered better. In other words, it can be said that the disconnection must leads to reliable reaction scheme (scheme 4a).

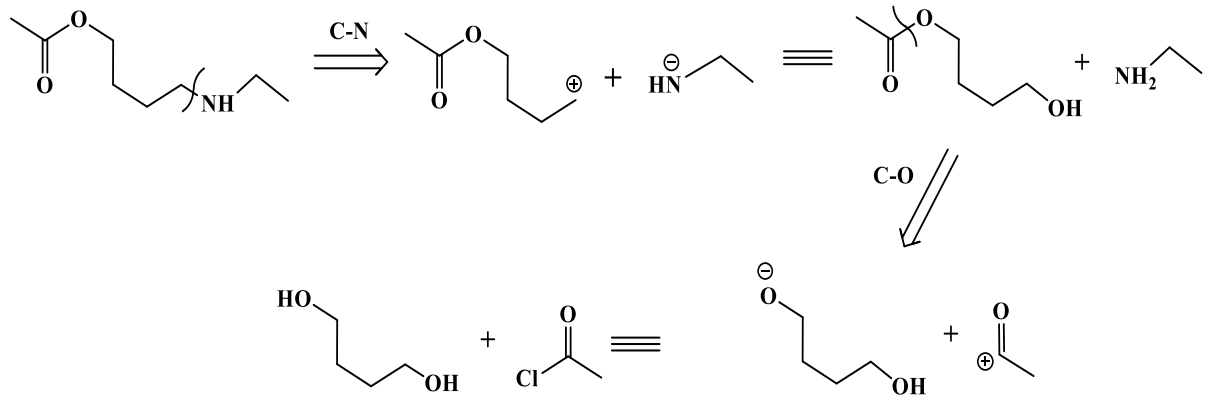


Scheme 4a: Retrosynthesis of Reformatsky reaction Product



Scheme 4b: Mechanism of Reformatsky reaction from the synthetic equivalent obtained by retrosynthesis in scheme 4a

Molecules often contains more than one function groups (heteroatoms) which can cause condition of **Chemoselective reactions** which should be avoided, which an be done by ***disconnecting more reactive group (heteroatom) in preference***. This is because in the synthetic route the synthetic equivalent disconnected first is reacted at the last and vice-versa.



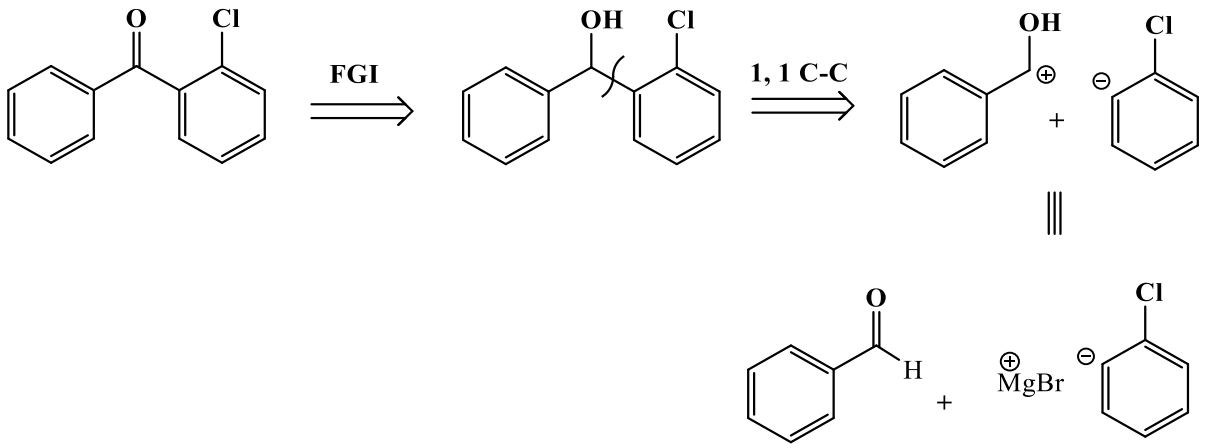
Scheme 5. Retrosynthetic route to avoid chemoselectivity in 4-(ethylamino) butyl acetate (impurity present in paracetamol)

Here in the above scheme as amide linkage is disconnected first and then the ester linkage subsequently according to previous guidelines, so in the synthetic route oxygen (-OH) will react first and then nitrogen (-NH_2).

4.4 FUNCTIONAL GROUP INTERCONVERSION (FGI)

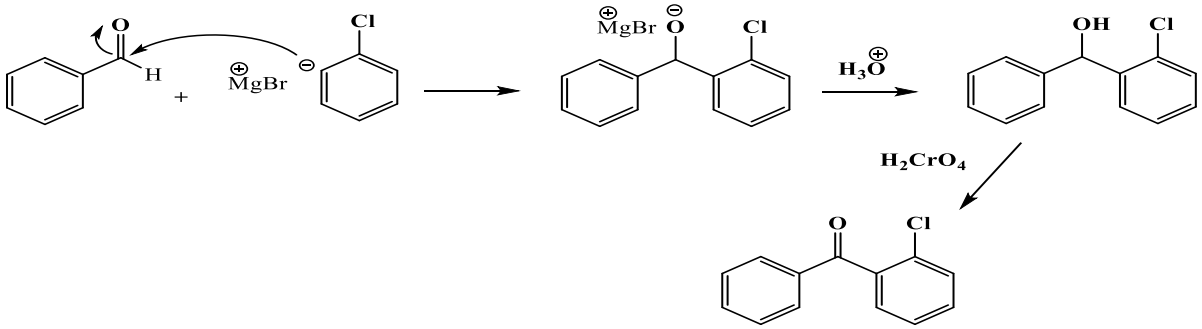
FGI is a specific process involved in organic reaction mechanism, where one functional group is converted to another (vice-versa) via few specific ways like oxidation, reduction, etc. These reactions are established mechanism or process which brought about the desired mechanism. These FGI's are many a time required for carrying a reaction in forward direction. Here in disconnection approach FGI (a) helps in bringing the desired disconnection to a complex molecule which would not be possible with the earlier functional group, (b) to decrease the chances of such possible reactions which are not desired (multiple reactions).

In FGI of any molecule, one of the factors should be always kept in mind that what ever functional group is converted to another desired functional group, during the forward direction reaction the previous functional group should be achieved again.



Scheme 6: Retrosynthetic approach of Chlorphedianol, involving FGI of ketone to alcohol

In the scheme 6 above, during the retrosynthetic approach of Chlorphedianol, ketone is converted to alcohol for making the chance of disconnection of the molecule as in case of carbonyls 1, 2 C-C disconnection is preferred (discuss later) which is not possible in the example above, while if ketone is converted to alcohol, it can undergo 1,1 C-C disconnection which is preferred in alcohol containing molecule.

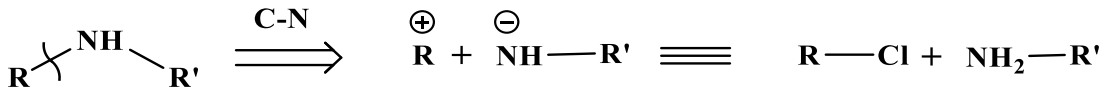


Scheme 7: Synthetic approach of Chlorphedianol, involving conversion of alcohol back to ketone

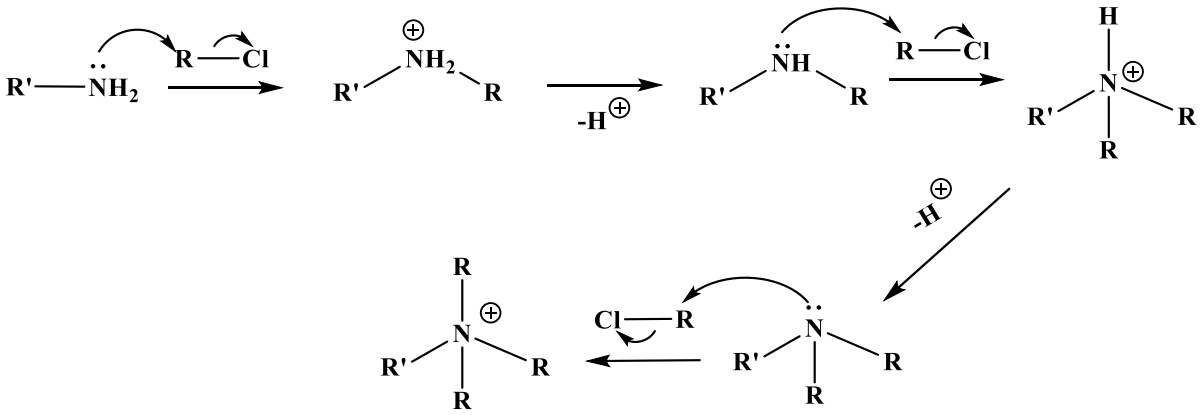
Scheme 7 shows the conversion of alcohol function group back to ketone (formation of target molecule) thus suggesting that the function group which was present before FGI should be prepared during synthesis process.(More example of FGI wherever applicable will be discussed in coming sections.)

FGI of Amines: Disconnection of amine and its retrosynthesis is a normal process, where a target molecule can be easily converted to possible synthetic equivalents. However many a

time the forward direction synthesis doesn't leads to the desired target molecule due to the fact that it leads to multiple time reaction of amine owing to the strong basic character of theirs.



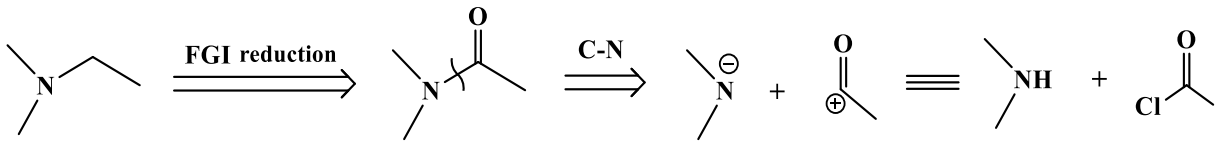
Scheme 8a. Retrosynthesis of an amine molecule



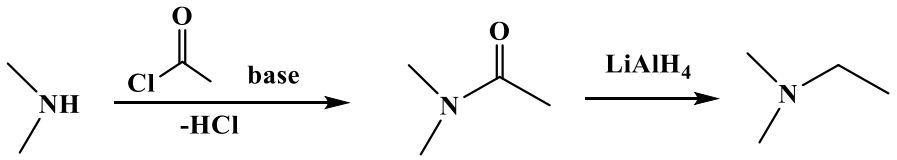
Scheme 8b. Reaction showing non desired multiple step reaction occurring in certain amines

So, by looking the above possibility it is important to convert amine to specific other functional group by the process called FGI. FGI of amine can be done into two specific function groups namely amides (-$CONH_2$) and imine (-C=N-), let us look for disconnection of amine followed by these FGI's.

Amine to amide:



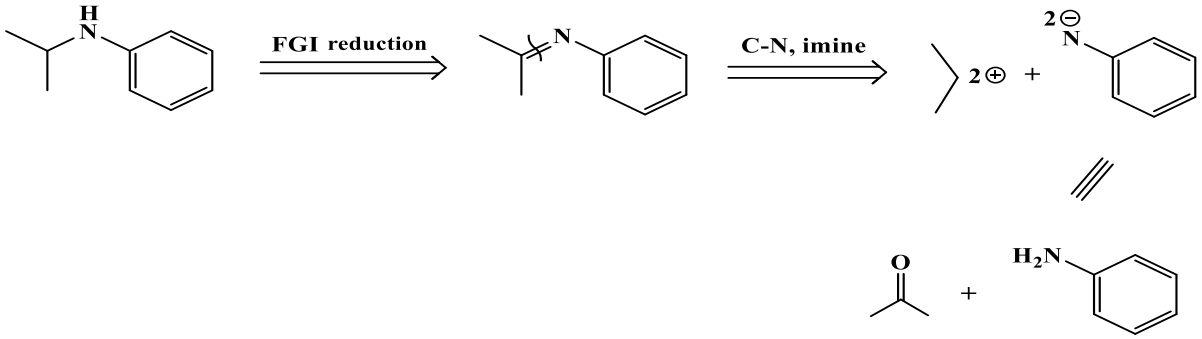
Scheme 9a. Disconnection approach involving FGI of a simple amine to amide



Scheme 9b. Synthesis of target molecule involving reduction of amide

Here in scheme 9a, 3º amine is first converted to amide and further disconnected to 2º amine for restricting the condition of multiple reactions in forward direction. Here one thing is to mandatorily remember that along with the term FGI, the process should be written which is being employed for converting the functional group back to previous one (in synthesis process), here in this case as it is written "FGI reduction" that means that FGI of amine is done to amide while in forward direction for conversion of amide to amine is a reduction process.

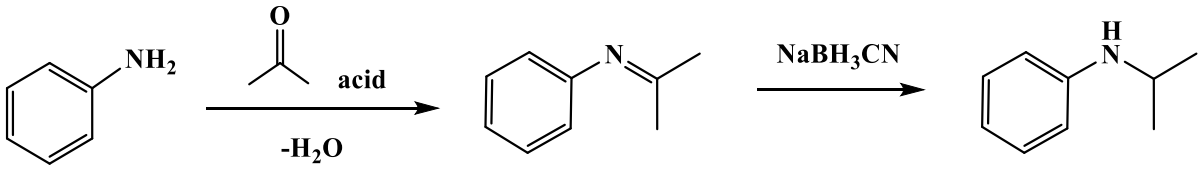
Amine to imine: Another possible way of stopping multiple reaction chances of amine is to convert them to corresponding imines (-C=N-) species.



Scheme 10a. Disconnection approach involving FGI of a simple amine to imine

In the scheme 10a above, amine is first converted to imine functional group, one thing is to be remembered here is that if carbon next to nitrogen (C-N between which bond is to be disconnected) is if that carbon is 2º it can be converted to amide and/or amine both, while if the carbon is 3º it only can be converted to imine (as example above).

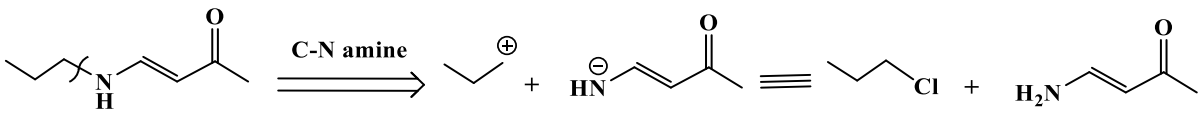
During synthesis step the synthetic reagents are reacted to each other in presence of acidic catalyst to generate imine which further can be reduced with suitable reducing agent to amine (target molecule).



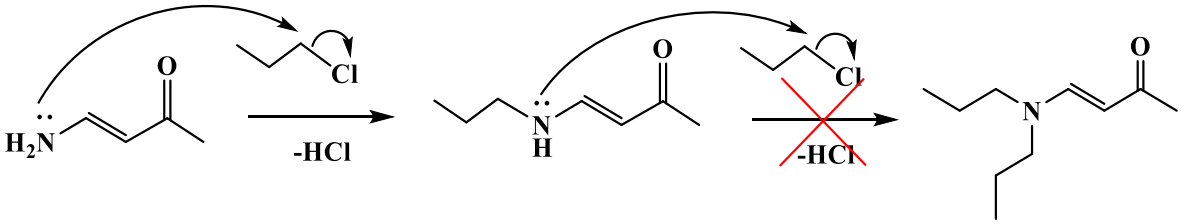
Scheme 10b. Synthesis of target molecule involving reduction of imine

In the reaction scheme 10b above, the synthetic approach is shown where the synthetic equivalents are first reacted to form imine which further is reduced to desired compound.

However, an exception from the above rule is observed, if nitrogen in an amine is attached to bulky species or electron withdrawing species (EDG) the need of FGI is restricted (Scheme 11a and 11b).

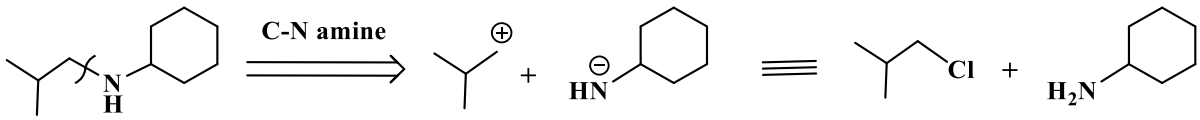


Scheme 11a: Disconnection of amine consisting of EWG generating no need of FGI

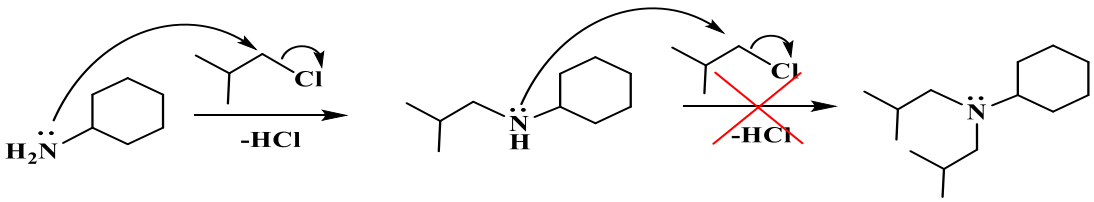


Scheme 11b: Synthesis of amine consisting of EWG, further restricting the multiple reactions

Scheme 11a represents the simple disconnection of EWG containing amine; in this case there is no need of FGI as during the process of synthesis the lone pair of electrons would be attracted towards EWG which will further restrict the chances of multiple reactions (scheme 11b). Similarly, presence of a bulky group can also be considered in same way which can restrict the entry of incoming group near the lone pair of electrons and hence no multiple reaction (scheme 12a and 12b.



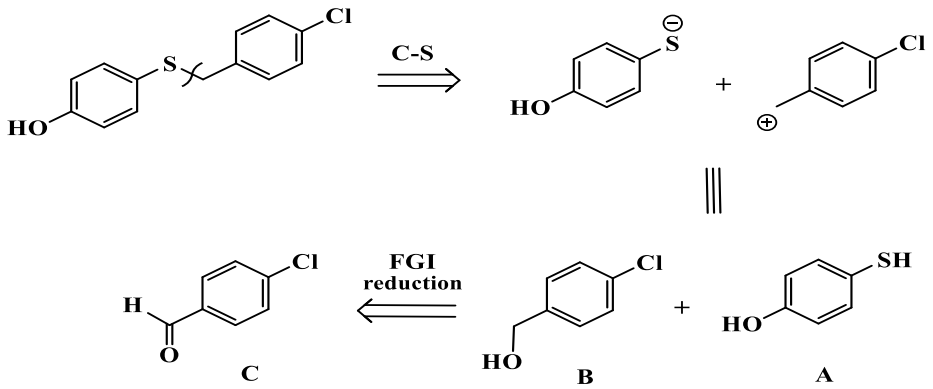
Scheme 12a: Disconnection of amine consisting of bulky groups generating no need of FGI



Scheme 11b: Synthesis of amine consisting of bulky groups, further restricting the multiple reactions

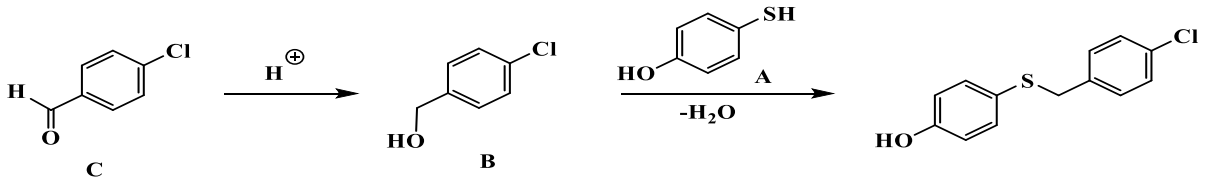
4.5 ONE GROUP C-X DISCONNECTIONS

This disconnection type includes the presence of one carbon (C)-heteroatom (X) bond which is to be disconnected; the bond between the C-X is disconnected where X could be electronegative species such as oxygen, nitrogen, sulphur etc. However, all the guidelines should be followed to get the appropriate disconnection and synthetic equivalents. These disconnections are easy few of the example earlier discuss are having same concept, few more examples are shared below.



Scheme 12a.Disconnection approach involving C-S disconnection and further FGI giving molecules A, B and C

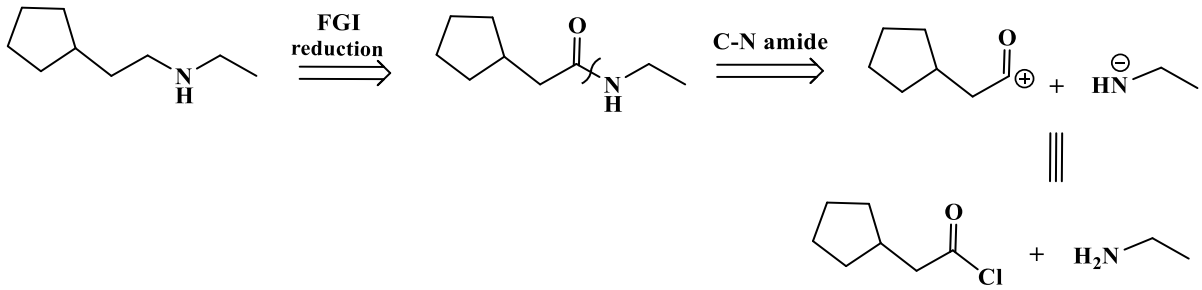
Above scheme reveals the disconnection of C-S bond followed with all the guidelines, C-S bond between allyl carbon and sulphur is disconnected in priority not on the side of ring. While FGI of primary alcohol to aldehyde is carried as another guideline.



Scheme 12b. Synthetic reaction for target molecule from C, B and A molecules

In synthesis during the step aldehydic group is reduced to alcohol in step 1, while in second step molecule A having -SH and -OH functionality is reacted to molecule B. Sulphur

being more reactive as compare to oxygen carries on the desired reaction to give the target molecule.

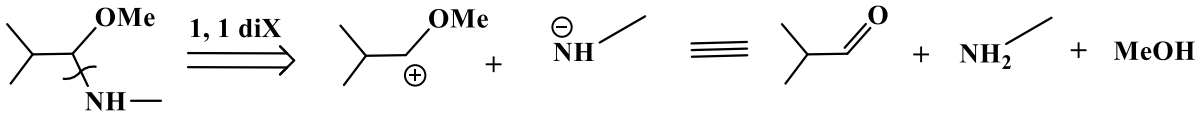


Scheme 13a. Disconnection approach involving C-N disconnection and further FGI giving molecules A, B and C

4.6 TWO GROUP C-X DISCONNECTIONS

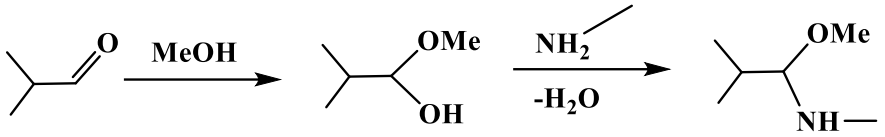
Two group carbon-heteroatom (C-X) disconnections is another way to disconnect the organic molecule present with two heteroatomsplace at specific position to each other (may be on same carbon or two different). Two group disconnection is considered to be better as compared to one group disconnection due to the fact that one group assist the disconnection of another. The basic guidelines of disconnection are followed in this type of disconnection also. These two group C-X disconnection could be of following type:

1, 1 C-X disconnection: In this two group C-X disconnection both the heteroatom are present on the same carbon and one heteroatom assist the disconnection of other.



Scheme 14a: Example showing 1,1 C-X disconnection

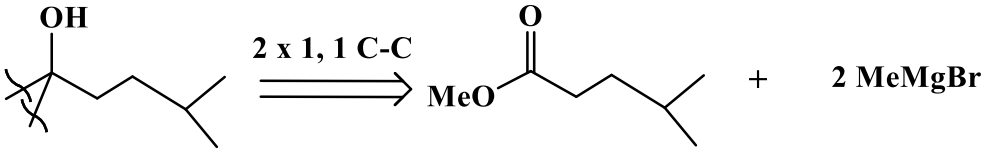
In step 1above (scheme 14) nitrogen (amine) being more reactive is disconnected and prioritize over oxygen (OMe). Over the retrosynthetic arrow the term mentioned designate the relation between the two functional groups. In step 2 the synthon is converted to respective synthetic equivalents by satisfying the charges with suitable counterparts.



Scheme 14b: Synthetic route for synthesis of target molecule

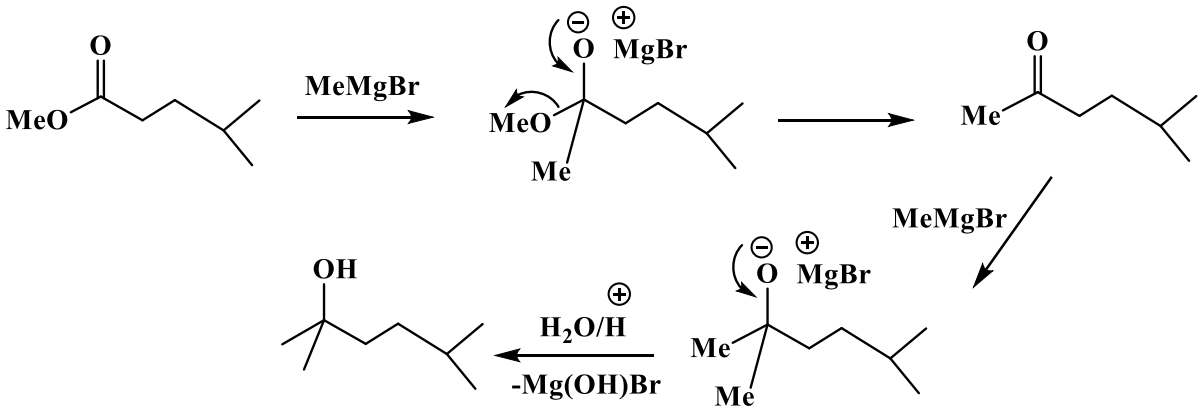
The cationic synthon is converted to aldehyde by removing -Me (methyl) species which leaves a -ve charge over oxygen, and further methyl is added with -OH to give neutral molecule which could be used in synthetic process (Scheme 14b).

1,1 C-X double disconnection: Two identical groups attached to a 3º alcohol have tendency to undergo double disconnection. As discussed earlier, alcohol generally undergo 1,1 C-C disconnection, so this disconnection can be carried twice to generate two Grignard reagents along with ester molecule (Scheme 15a).



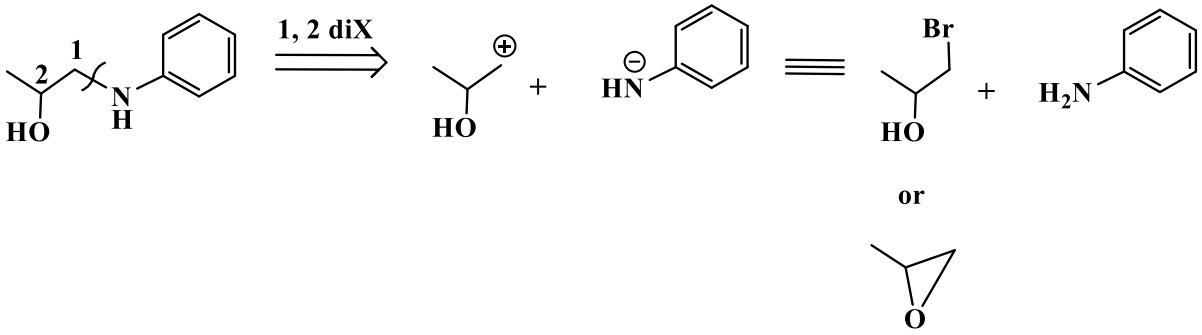
Scheme 15a: Disconnection approach resulting to double disconnection in case of tertiary alcohols

This ester and one mole equivalent of Grignard reagent react to produce ketonic molecule which further is reacted with another mole of Grignard reagent to generate the target molecule (Scheme 15b).



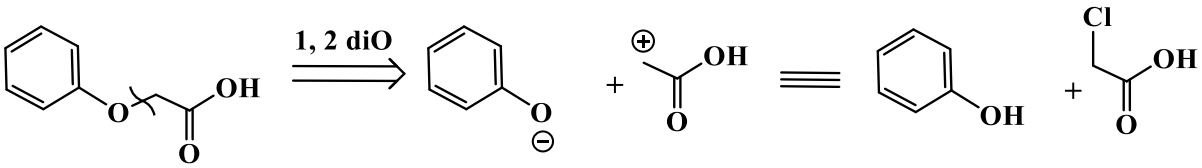
Scheme 15b: Synthetic route for synthesis of 3º alcohol

1, 2 C-X disconnection: In this specific C-X disconnection the two heteroatoms are in 1, 2 relations to each other, i.e., the two heteroatoms will be present at two adjacent carbons. In the example below two hetero atoms are attached to two adjacent carbon (designated as 1 and 2) to establish 1, 2 relations.



Scheme 16a. Retrosynthetic route showing 1, 2 C-X disconnection

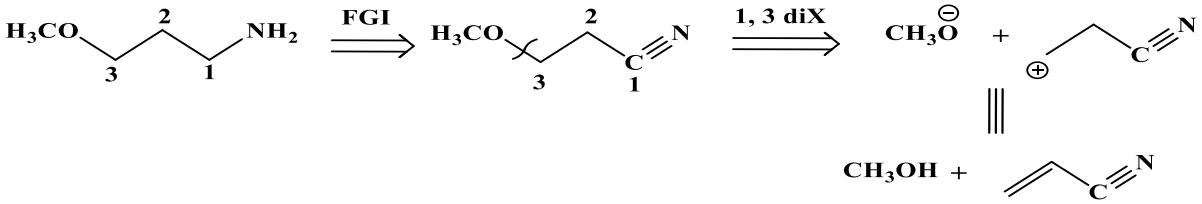
In the example above (scheme 15a) two synthetic equivalents are shown any one of them can be taken, reader should keep in mind that more reactive synthetic equivalent could be better for forward reaction. Above epoxide due to its higher reactivity can be considered as better reagent. The two synthetic equivalents generated here are called as ***umpolung reagents***, (which will be discussed in coming sections).



Scheme 16b. Example of retrosynthetic route involving 1, 2 C-X disconnection

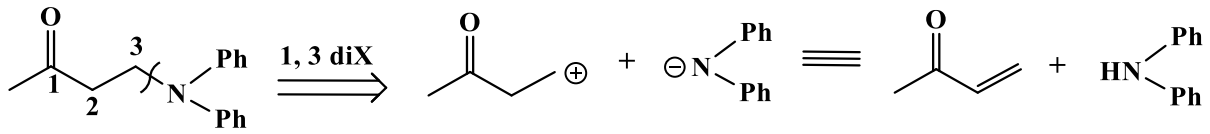
In above scheme again umpolung reagent (α-halo carbonyl) is obtained after carrying 1, 2 diO.

1, 3 C-X disconnection: These C-X disconnection approaches have two heteroatoms in 1 and 3 relation to one another.



Scheme 17a. Example showing 1, 3 C-X disconnections

In the example above nitrogen and oxygen are in 1, 3 relations to each other, however amine's FGI is done (to nitrile, however amide can also be used) as per rule to restrict multiple reaction chances. Further C-O bond disconnection take place where 1, 3 diX designate the relation between both heteroatom and tells two heteroatoms (O and N) of different kind are present.

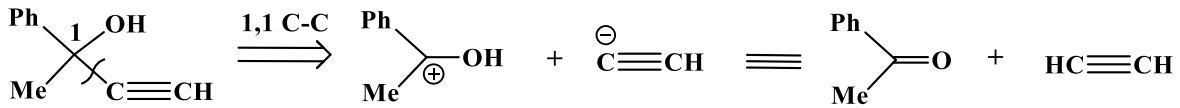


Scheme 17b. Example showing 1, 3 C-X disconnections

In the disconnection above 1, 3 diX occurs to generate +ve synthon, which can be further converted to α-β unsaturated ketone. Here α-β unsaturated ketone is obtained by removal of H^+ from α position of ketone (as discussed earlier retrosynthesis is a mental process to get the right synthetic equivalent).

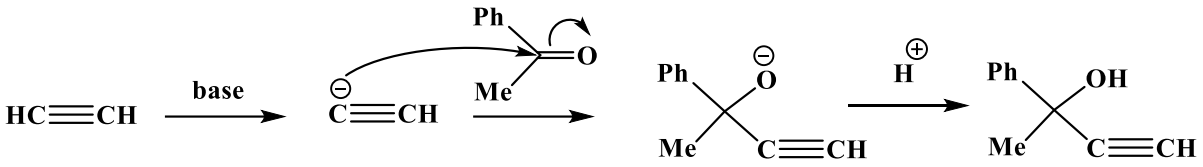
4.7 C-C DISCONNECTIONS

This type of disconnection involves the disconnection between two carbon atoms rather than C-X atom. Likewise, C-X bond disconnection, C-C disconnection is of following type.



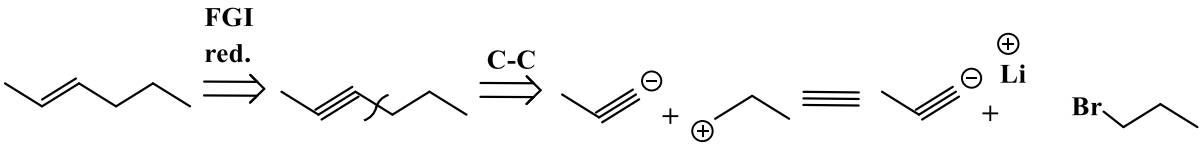
Scheme 18a. C-C disconnection involving alkyne as a functional group

1, 1 C-C disconnection: Here in the scheme above alkyne and OH are present on the same carbon showing 1, 1 relation between the two species here, OH will facilitate the C-C bond disconnection between C-1 and alkyne as OH gives ***1, 1 disconnection***. While C-1 will be +ve synthon and alkyne will get -ve charge on its carbon. Scheme below show the synthetic step for the target molecule



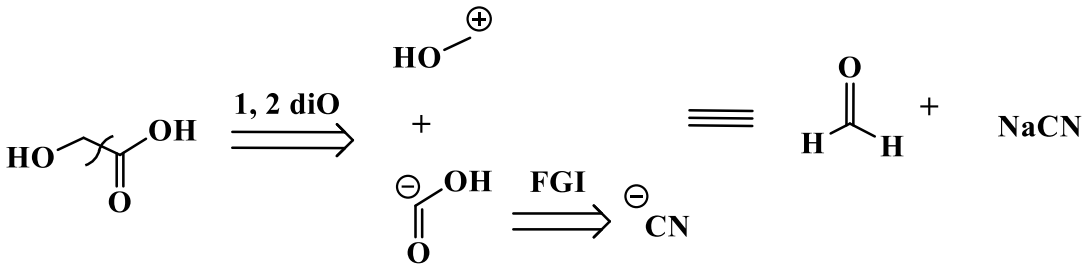
Scheme 18b. C-C disconnection involving alkyne as a functional group

Alkene containing species can also undergo C-C disconnection but prior to that FGI of alkene to alkyne is done so that more reactive species can be generated.



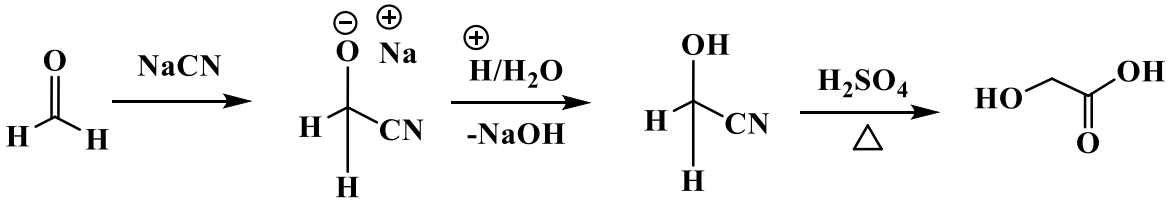
Scheme 19. C-C disconnection involving alkyne as a functional group

1, 2 C-C disconnection: In this specific disconnection, species (functional groups) are present at two adjacent carbons and bond between them is disconnected. This disconnection produces umpolung species.



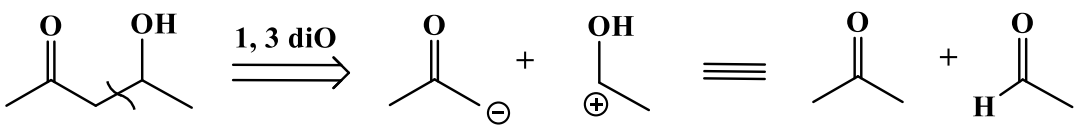
Scheme 20a. Example showing 1, 2 C-C disconnection, -CN acting as umpolung species

In the retrosynthetic approach above (scheme 19a) 2-hydroxy ethanoic acid is disconnected to give alcoholic and carboxylicsynthons, where carbonyl carbon is having -ve charge which is not significant thus is converted to -CN

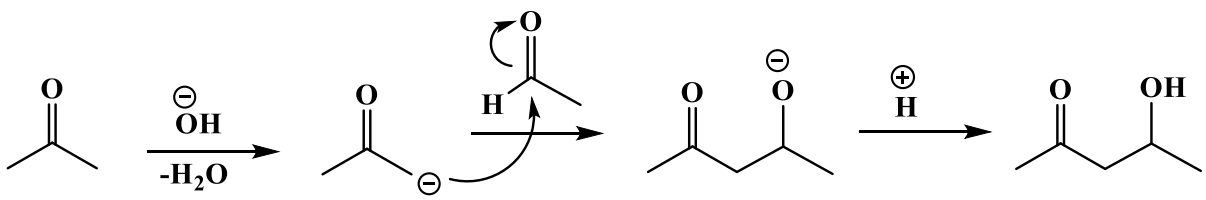


Scheme 20b. Synthetic approach using -CN (an umpolung species)

1, 3 C-C disconnection: Scheme 16b is retro aldol reaction which is an example of 1, 3 C-X disconnection. In the disconnection two function groups are present i.e., carbonyl and alcohol which gives 1, 2 and 1, 1 C-C disconnection respectively thus resulting in 1, 3 diO disconnection (two oxygenated functional groups at 1, 3 relation). After disconnection a ketone and an aldehyde is generated as synthetic equivalents, which can act as reagent for aldol reaction.

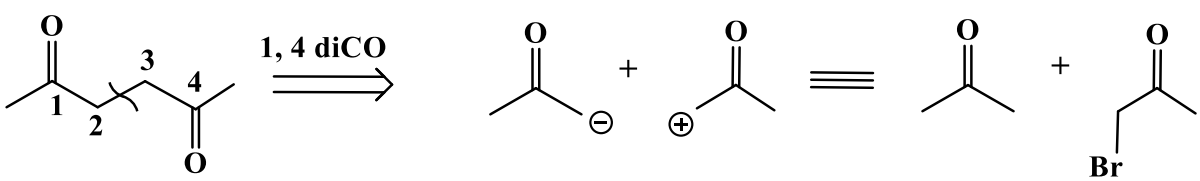


Scheme 21a. Example showing 1, 3 C-X disconnections (retro aldol reaction)



Scheme 21b. Aldol reaction involving reagents formed in retro aldol process.

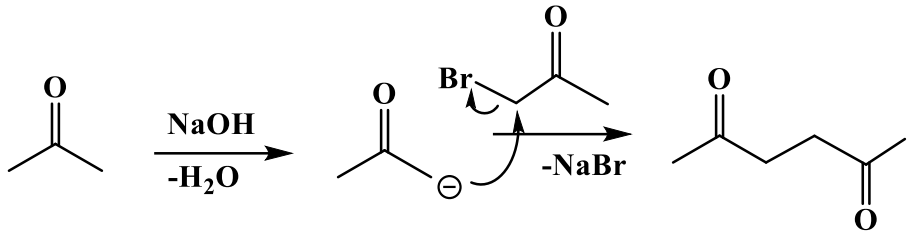
1, 4 C-C disconnection: Likewise, 1, 2 C-C disconnection this disconnection also generates umpolung species, here two functional groups are arranged in 1, 4 relations to one another.



Scheme 22a. Example showing 1, 4 C-C disconnection, generating α-halo ketone as umpolung reagent

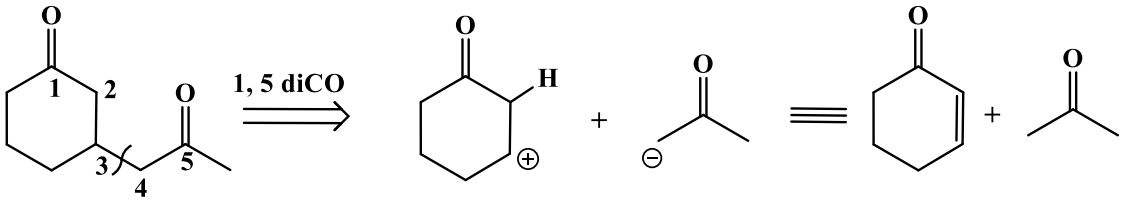
In the retrosynthetic approach above, functional groups having 1, 4 relations are carbonyl in nature, they undergo 1, 2 C-C disconnection individually thus bond between 2nd and 3rd carbon is

disconnected to give you two synthon species, in which the -ve synthon is a regular species while the +ve synthon is umpolung species leading to umpolung reagent.



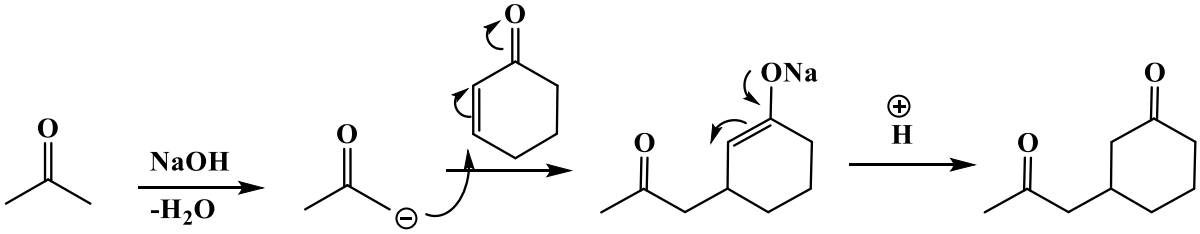
Scheme 22b. Synthetic approach for synthetic equivalents obtained from 1, 4 C-C disconnection

1, 5 C-C disconnection: In this specific disconnection 1, 5 relations is present in between two functional groups. In the scheme below two carbonyls are present which individually undergo 1, 2 disconnections but due to the relation 1, 5 C-C is written over the arrow.



Scheme 23a. Example showing 1, 4 C-C disconnection, generating α-halo ketone as umpolung reagent

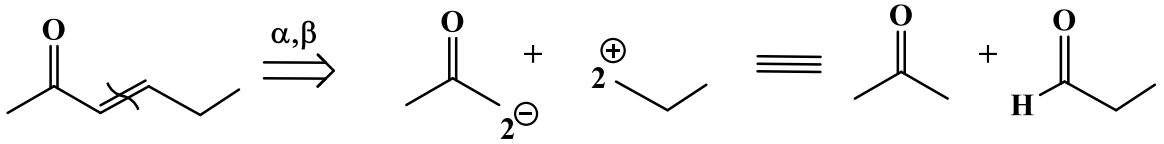
In the disconnection above after getting +ve synthon it is converted to enone by removal of H^+ from alpha position of carbonyl. Enonecan be considered as better reagent in the forward direction reaction shown in the reaction below, which is an example of Michael addition.



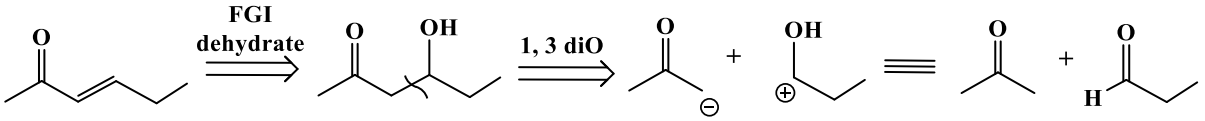
Scheme 23b. Michael addition reaction formation of 1, 5 di functionalized compound.

4.8 DISCONNECTION OF α-β UNSATURATED CARBONYLS

Molecules having α-β unsaturated carbonyls can be very easily disconnected to corresponding reagents. α-β unsaturated carbonyls involve two steps, FGI followed by 1, 3 diOdisconnection shown below with example of Aldol condensation.

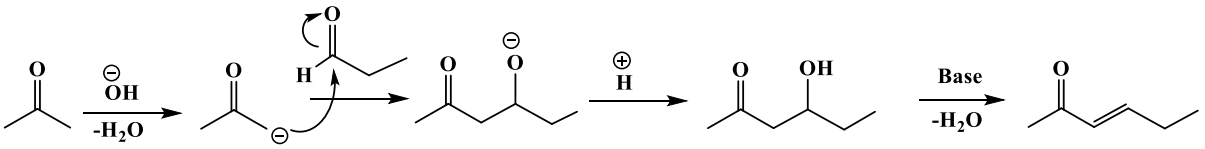


Scheme 24a. Example showing disconnection of α-β unsaturated carbonyls



Scheme 24b. Example showing steps involved in disconnection of α-β unsaturated carbonyls

The reaction scheme below shows the synthetic approach for aldol condensation starting from carbonyl molecules



Scheme 24b. Synthesis of α-β unsaturated carbonyls

4.9 UMPOLUNG (REVERSAL OF POLARITY)

Umpolung term is one of the important componentsin disconnection approach which literally means the polarity inversion or reversal of polarity. In this case the reversal in the polarity (+ve and -ve carbon) is observed where an electrophilic carbon (+ve synthon) is converted to nucleophilic carbon (-ve synthon) while a nucleophilic carbon is converted to an electrophilic carbon. The concept of umpolung is encountered in the molecule having 1, 2difunctionalized, 1, 4difunctionalized, 1, 6difunctionalized etc. structure. For these we already had seen some examples scheme 16b, 20a, 22a etc.

It is to be notice that in any molecule the acceptor synthons always occupy the odd numbers; while the donor synthon gets the even number, in a natural synthon this property is very well establish which get disturb in case of umpolung species. Below are shown some examples of natural synthons and umpolung synthons, which further can be converted to natural reagent and umpolung reagents.

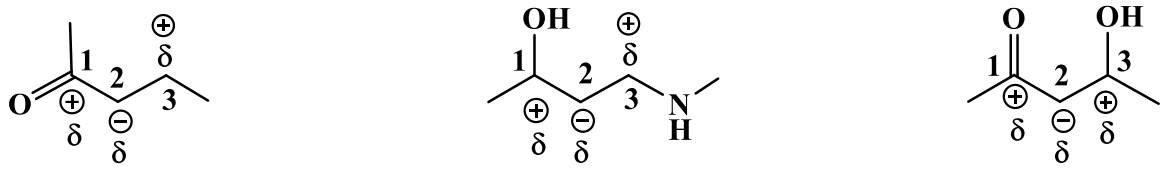
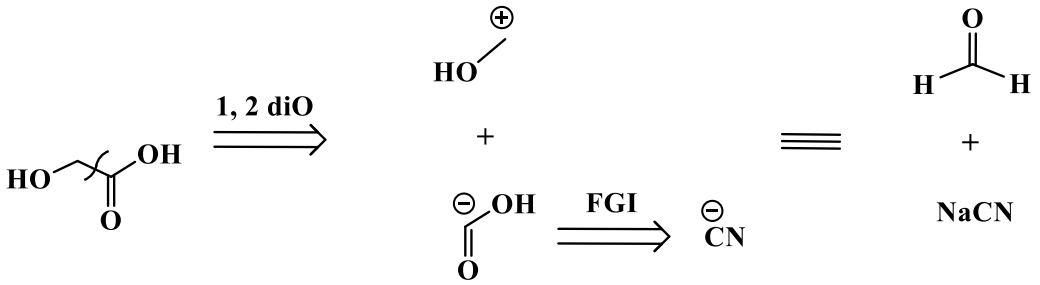


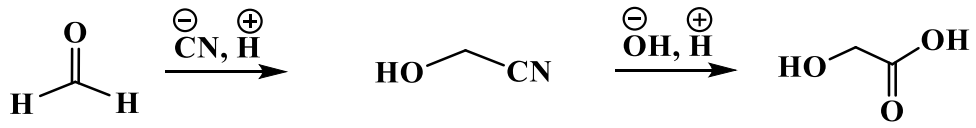
Figure 1. Molecule which can leads to natural synthons the number shows the relation between different carbons, starting from a functional group, partial charges show the related charge when disconnect would be carried on.

Figure 2. Molecule which can leads to umpolung synthons the number shows the relation between different carbons, starting from a functional group, partial charges show the related charge when disconnect would be carried on.

Umpolung in 1, 2 difunctionalized compounds: Already discussed in 1, 2 difunctionalized compound the relation between the functional groups will be 1, 2 to each other, when disconnected (scheme 25a) one umpolung species will be generated in this case -ve charge on carboxylic acid functional group leads to umpolung synthon (as carbonyl carbon should have a +ve charge), so for stability and sake of possible reaction in forward direction umpolung species has been converted to nitrile (-CN), so here nitrile acts as umpolung reagent.

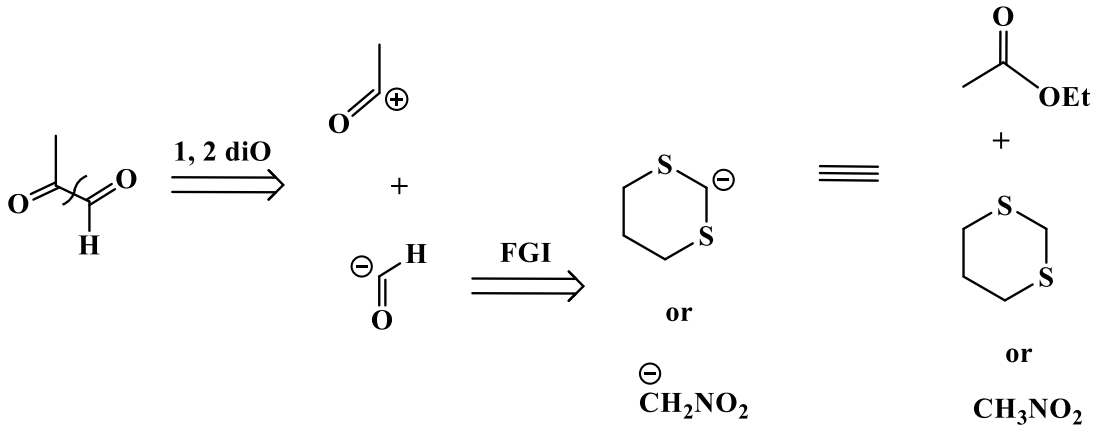


Scheme 25a. Example showing generation of umpolung species, where nitrile acts as umpolung reagent in forward direction reaction.

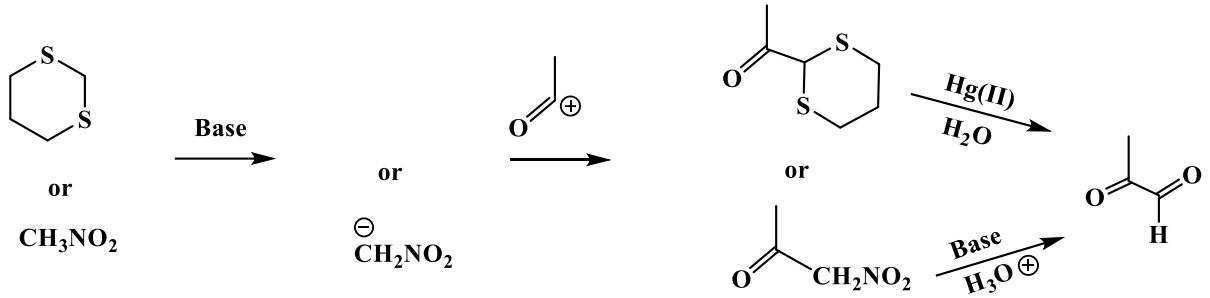


Scheme 25b. synthetic approach showing conversion of umpolung species back to target molecule

In the scheme below, 1, 2 difunctionalized molecule is again disconnected into two synthons, both the carbonyl species can generate a natural and an umpolung reagent. Scheme below shows the generation of dithietane or nitro compound as umpolung reagent from carbonyl molecule.

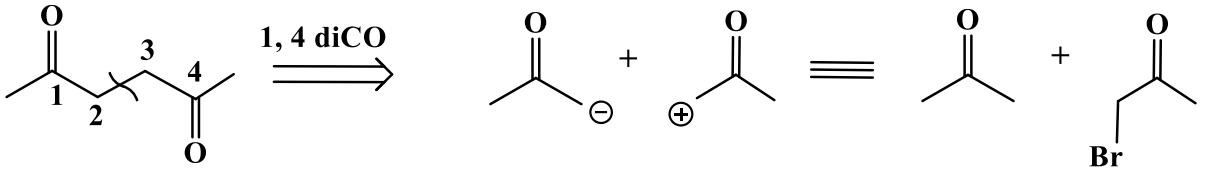


Scheme 26a. Example showing generation of umpolung species, where dithietane or nitro species acts as umpolung reagent in forward direction reaction.

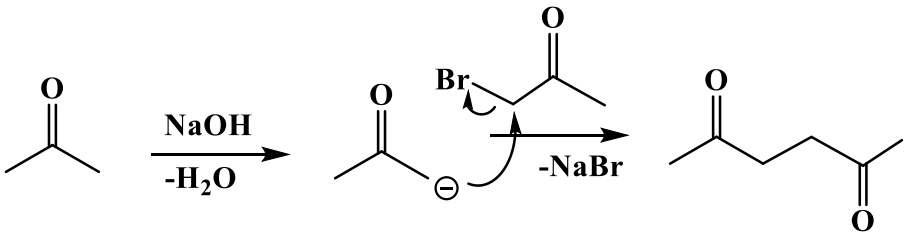


Scheme 26b. synthetic approach showing conversion of umpolung species back to target molecule

Umpolung in 1, 4 difunctionalized compounds: Here in the the relation between the functional groups is 1, 4 to each other, when disconnected one umpolung species will be generated. In the scheme 27a carbonyls generally undergoes 1, 2 C-C disconnection due to which two synthons will be obtained one of them will be umpolung synthon which further can be converted to umpolung regent i.e., α-halo ketone.

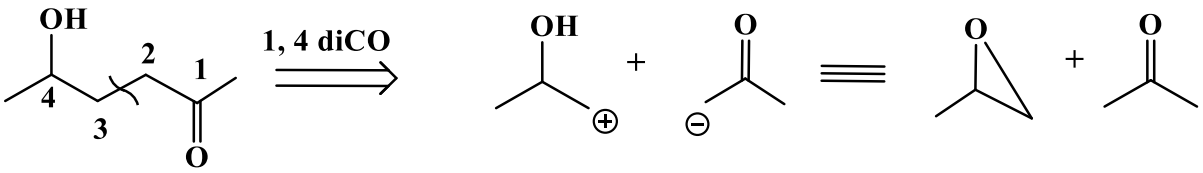


Scheme 27a. Example showing 1, 4 C-C disconnection, generating α-halo ketone as umpolung reagent



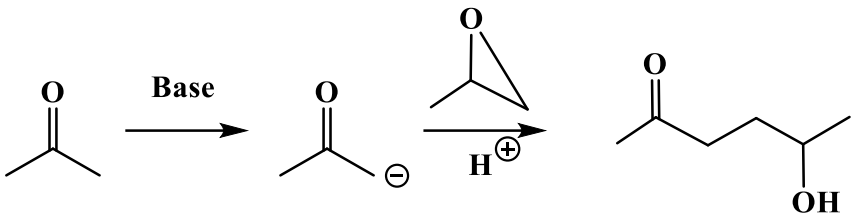
Scheme 27b. Synthetic approach for synthetic equivalents (including α-halo ketone as umpolung reagent) obtained from 1, 4 C-C disconnection

Epoxide can also act as umpolung reagent, in case of 1, 4 difunctionalized compound (scheme 28a) after disconnection if a +ve charge is generated at α position of -OH containing carbon in that case the species can be change to epoxide.



Scheme 28a. Example showing 1, 4 C-C disconnection, generating epoxide as umpolung reagent

The natural and umpolung reagent generated above are allowed to react in presence of some required chemicals to generate the desired targeted molecule.



Scheme 28b. Synthetic approach for synthetic equivalents (including epoxide as umpolung reagent) obtained from 1, 4 C-C disconnection

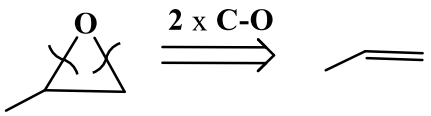
4.10 CYCLIZATION REACTION AND DISCONNECTION APPROACH

Disconnection approach can also be studied for cyclic molecules containing heteroatoms in them. Three, four, five and six member molecules can very easily undergo retrosynthesis, to generate reagents which again can be used to regenerate the cyclic structure along with some required chemical species.

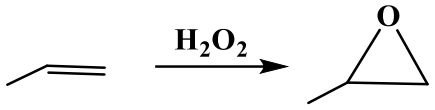
Threemembered heterocyclic saturated molecules: Generally, Oxirane, Aziridine and Thiirane are studied under this class which have following structure.

Figure 3: Three Membered heterocyclic saturated molecules

These molecules are easy to disconnect via single disconnection or double disconnection method.

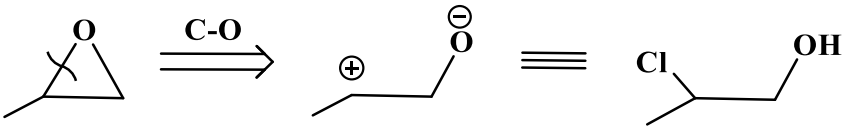


Scheme 29a: retrosynthesis of epoxide

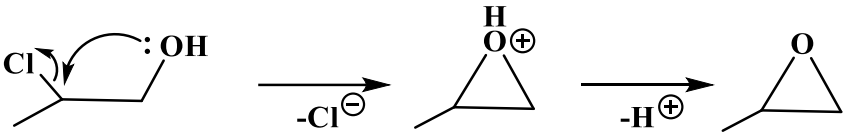


Scheme 29b: Synthesis of an epoxide from alkene

Same molecule can undergo single C-X disconnection to produce desired synthetic molecule

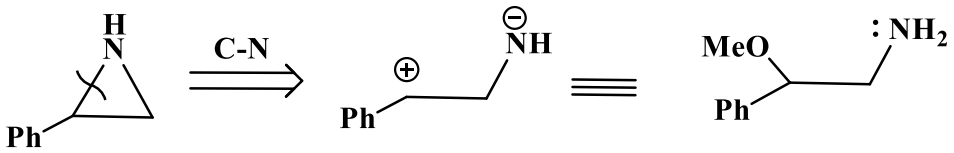


Scheme 29c: Retrosynthesis of epoxide

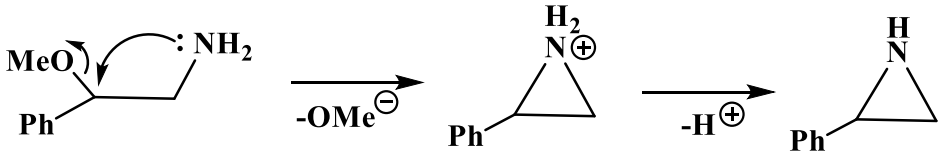


Scheme 29d: Synthesis of an epoxide

Likewise, oxirane aziridine can also under go disconnection to produce the synthetic equivalents.



Scheme 30a: Disconnection approach for nitrogen containing 3 membered saturated ring

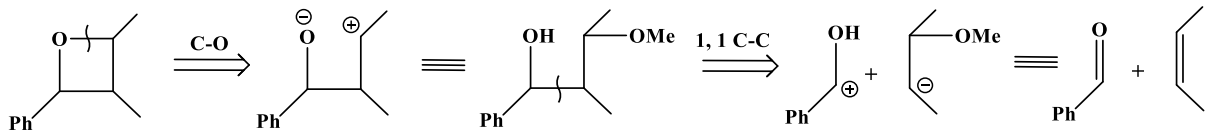


Scheme 29d: Synthesis of an aziridine

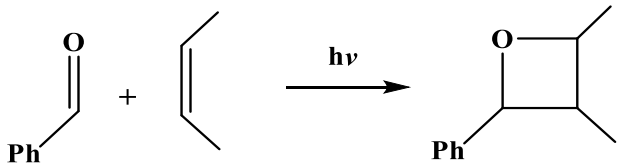
Four membered heterocyclic saturated molecules: Below is the example of heterocyclics having 4 members.

Figure 4: Four membered heterocyclic saturated molecules

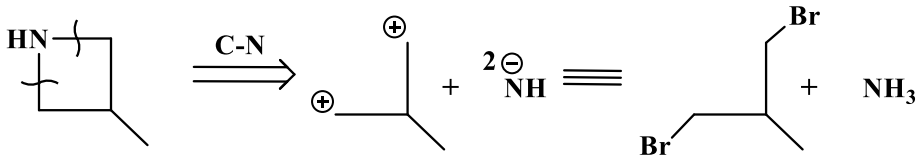
Likewise, three membered species these are also susceptible to undergo disconnection to generate synthetic equivalents. In the example below oxetane is disconnected twice to generate synthetic equivalents which could be the starting material for well known photochemical reaction known as Paterno Buchi reaction.



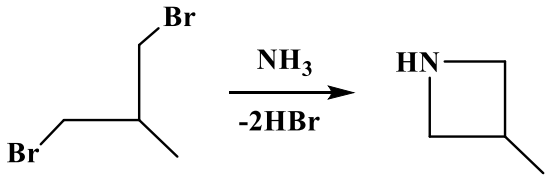
Scheme 31a: Disconnection approach for oxetane



Scheme 31b: Paterno Buchi reaction

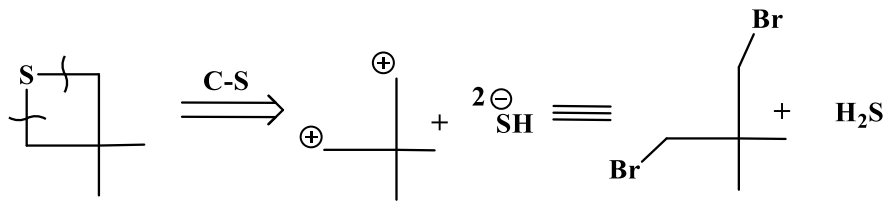


Scheme 32a: Disconnection approach for azetidine

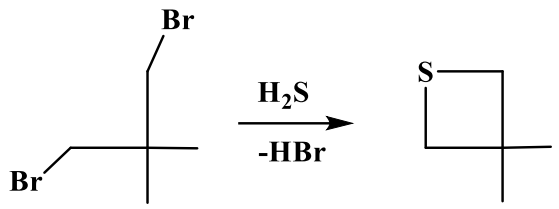


Scheme 32b: Synthesis of azetidine

Similarly, thietane also can be disconnected to corresponding synthetic equivalents; double disconnection can be carried on if the structure is symmetrical.

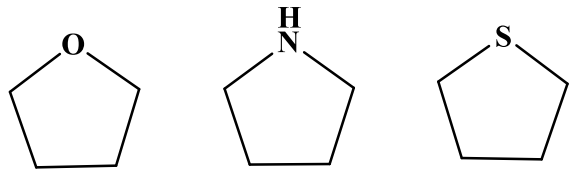


Scheme 33a: Disconnection approach for thietane



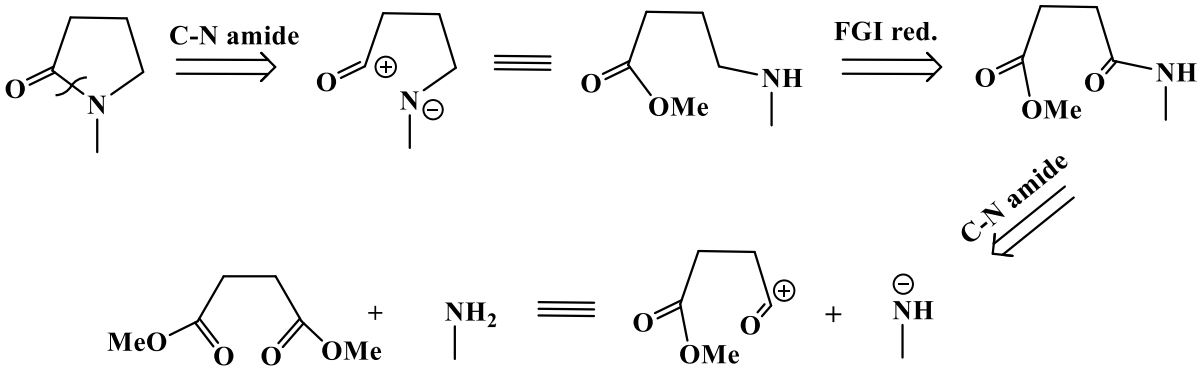
Scheme 33b: Synthesis of a thietane

Five membered heterocyclic saturated/unsaturated molecules: Five membered rings are considered to be stable due to their low degree of angle strain. These molecules can also undergo disconnection via following simple disconnection guidelines discussed in the chapter.

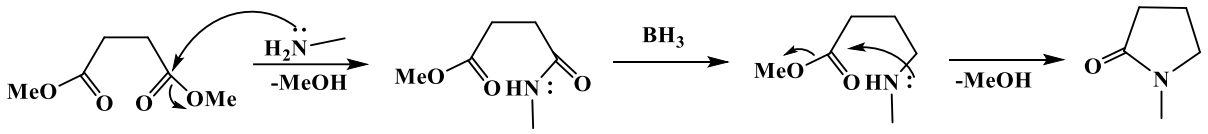


tetrahydrofuran pyrrolidine tetrahydrothiophene

Figure 4: Five membered heterocyclic saturated molecules

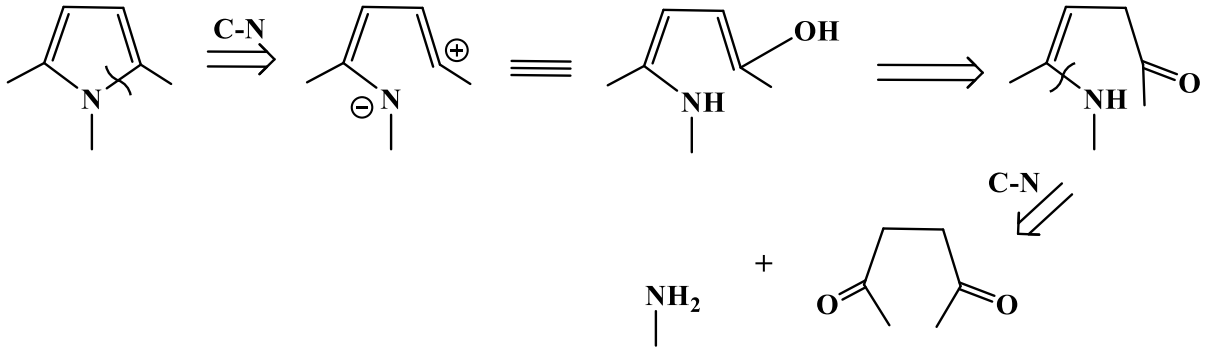


Scheme 34a. Retrosynthesis of nitrogen containing five membered rings

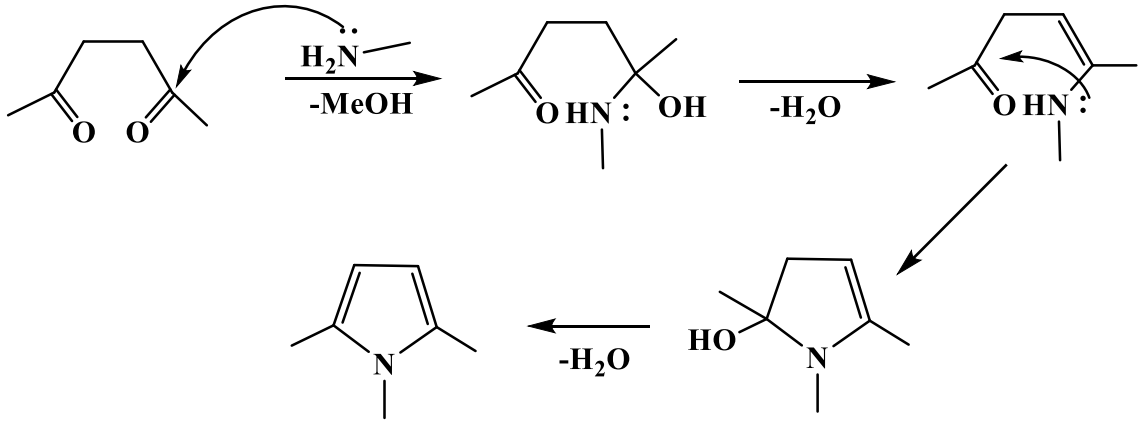


Scheme 34b. Synthesis of nitrogen containing five membered rings

In a similar way unsaturated 5 membered heterocyclic molecules can also be disconnected to corresponding synthetic equivalents

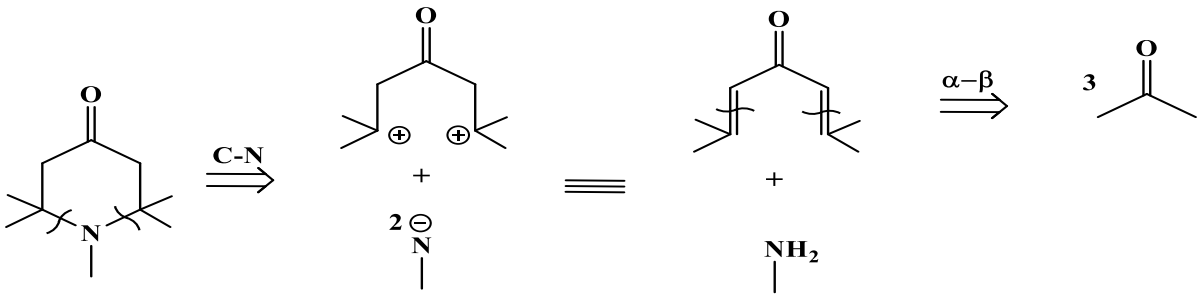


Scheme 35a. Retrosynthetic approach for pyrrole

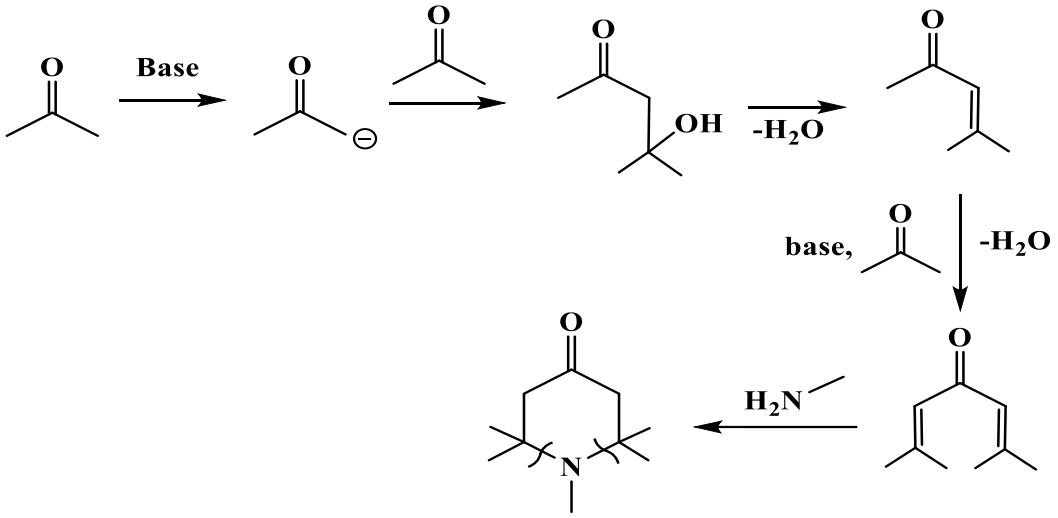


Scheme 35b. Synthetic approach for pyrrole

Six membered heterocyclic saturated/unsaturated molecules: Likewise, 5 membered heterocyclics, six membered heterocyclic rings can be disconnected easily.

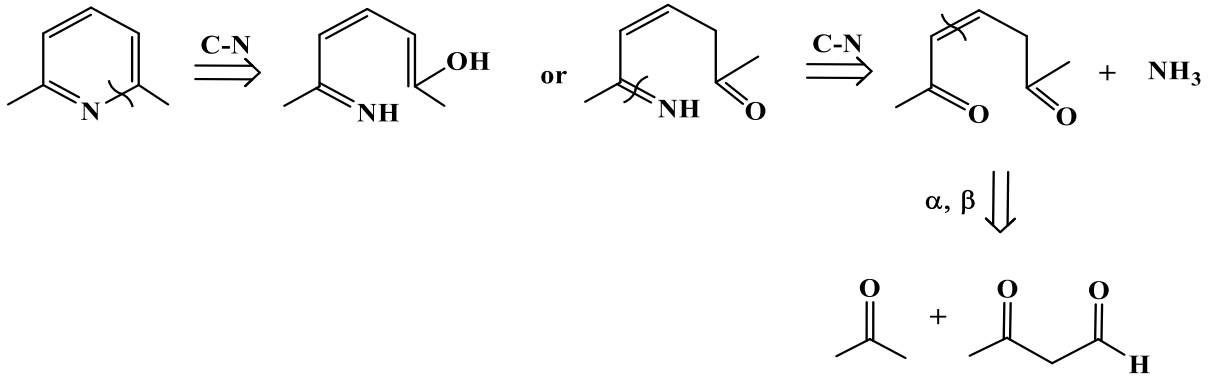


Scheme 36a. Retrosynthetic approach for six membered heterocyclic molecules

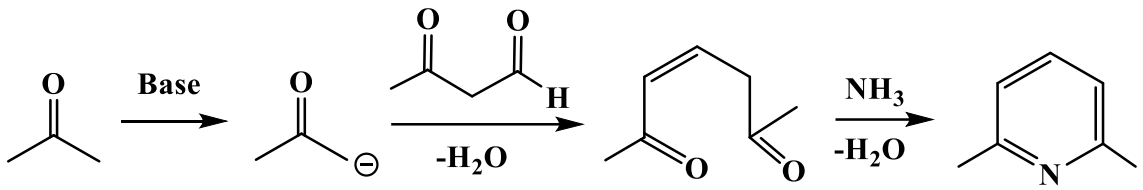


Scheme 36b. Synthetic approach for six membered heterocyclic molecules

Pyridine a six membered heterocyclic compound can be disconnected according to the step mention below.



Scheme 37a. Retrosynthetic approach for pyridine



Scheme 37b. Synthetic approach for pyridine

4.11 SUMMARY

Any organic molecule can undergo the process of disconnection approach following some set of rules.

- Retrosynthesis is an imaginary process to get some possible simple molecules, which can act as reagent in forward direction to give the target molecule.
- Synthons are generated on disconnection which when satisfied with opposite charge species give synthetic equivalents.
- FGI is a specific process in the course of disconnection approach where one function group is converted to another in order to get the desire disconnection and required synthetic equivalents
- C-X and C-C disconnection are easily available in many of the organic molecules.
- Umpolung species are generated when an electrophilic carbon (+ve synthon) is converted to nucleophilic carbon (-ve synthon) while a nucleophilic carbon is converted to an electrophilic carbon.

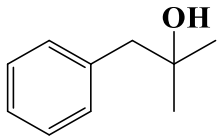
4.12 TERMINAL QUESTIONS

1. Explain the following terms with suitable examples.

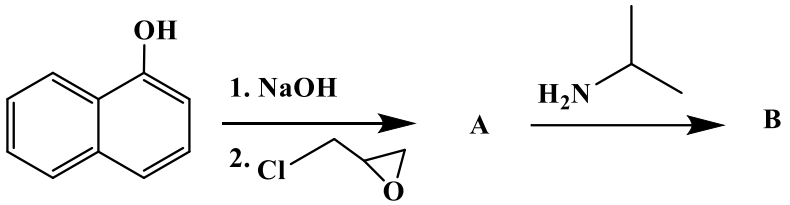
   a. Synthons b. Synthetic equivalent c. Retrosynthesis d. FGI

2. What is FGI? Why there is need of FGI in case of few amines?
3. What is the importance of order of event in the retrosynthesis?
4. What is an Umpolung? Explain with example

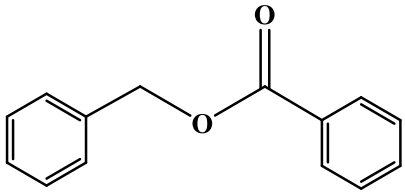
5. What is chemoselectivity? Explain its importance in disconnection approach.
6. Explain the approach towards disconnection? With suitable example explain the 1,2-disconnection (C-X) and 1,3-disconnection (C-X).
7. Show the Disconnection approach for the following molecules, represent synthons and respective synthetic equivalents and forward direction reaction.

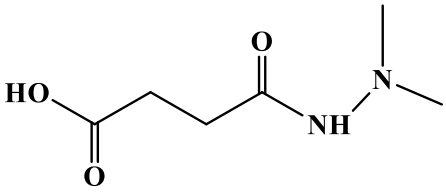


8. What will be A and B in the reaction below?

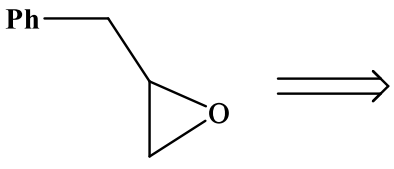


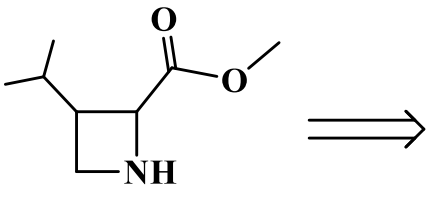
9. Show the Disconnection approach for the following molecules; represent synthons and respective synthetic equivalents and forward direction reaction.

a. 

b. 

10. Show the disconnection approach for the following

a. 

b. 

(B). Multiple choice questions (MCQS):

1. _____ are fragments of molecules with an associated polarity (+ve or -ve) which stand for the reagents we are going to use in the forward synthesis.

   (a) Synthons

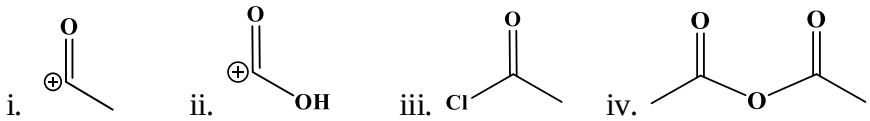
   (b) Synthetic equivalents

   (c) Chemical reagents

   (d) Products

Ans. (a)

2. Which of the following is/are synthons?



   (a) Both i and ii

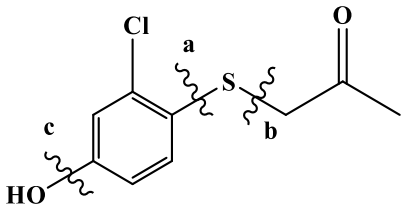
   (b) Both iii and iv

   (c) All i, ii, iii and iv

   (d) None of above

Ans. (a)

3. The preferred site of disconnection for following molecule will be?



   (a) b

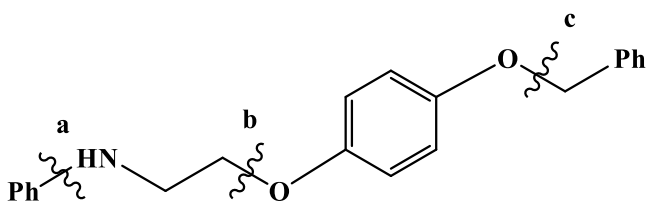
(b) a

(c) c

(d) Any one of above

Ans. (a)

4. Best position for disconnection is?



(a) a

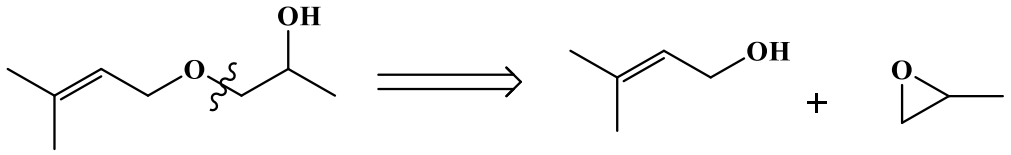
(b) b

(c) c

(d) All of above

Ans. (b)

5. Following reaction is an example of?



(a) 1,2-disconnection (C-O)

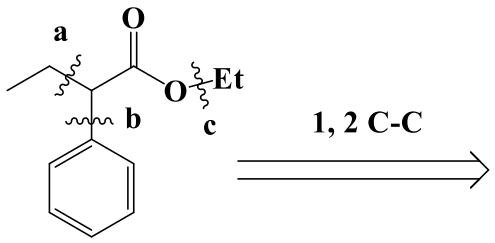
(b) 1,3- disconnection (C-O)

(c) 1,2-disconnection (C-C)

(d) 1,3-disconnection (C-C)

Ans. (a)

6. The preferred disconnection will be?



(a) a

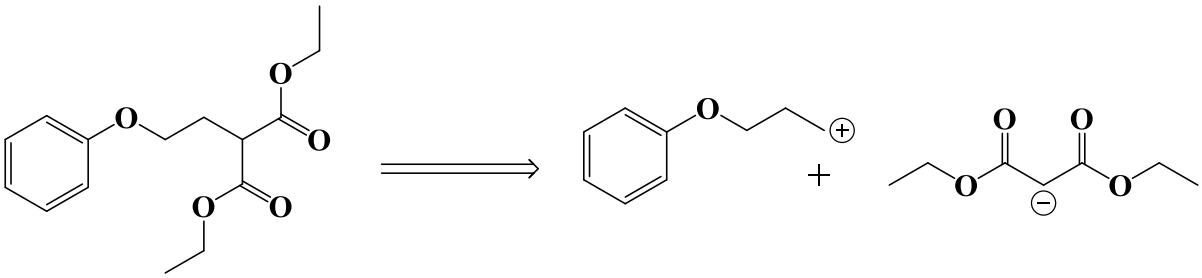
(b) b

(c) c

(d) None of these

Ans. (a)

7. Following is an example of?



(a) 1,1 C-C disconnection

(b) 1,2 C-C disconnection

(c) 1,1 C-X disconnection

(d) 1,2 C-X disconnection

Ans. (b)

8. Following is an example of?

(a) Two group C-C disconnection (1,3 difunctionalized)

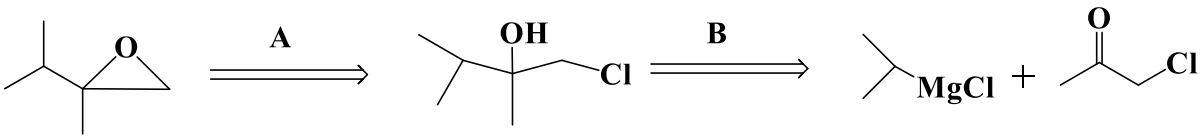
(b) Two group C-X disconnection (1,3 difunctionalized)

(c) Tzwo group C-C disconnection (1,5 difunctionalized)

(d) Two group C-X disconnection (1,5 difunctionalized)

Ans. (a)

9. What will be the step A and B in following disconnection route?



(a) A= C-O dis B= 1, 2 C-C dis

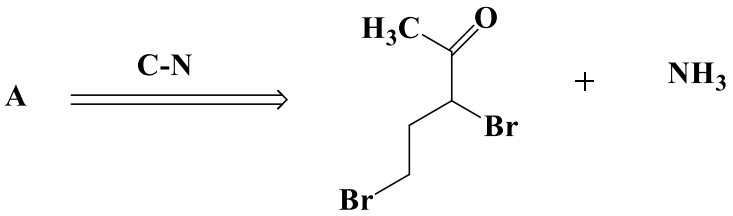
(b) A= C-O dis B= 1, 1 C-C dis

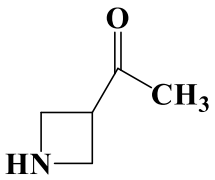
(c) A= C-O dis B= 1, 1 C-O dis

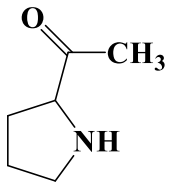
(d) A= C-O dis B= 1, 2 C-O dis

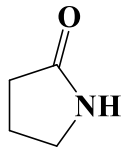
Ans. (b)

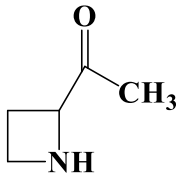
10. What is A in the following disconnection reaction?



(a) 

(b) 

(c) 

(d) 

Ans. (d)

UNIT 5- PROTECTING GROUP

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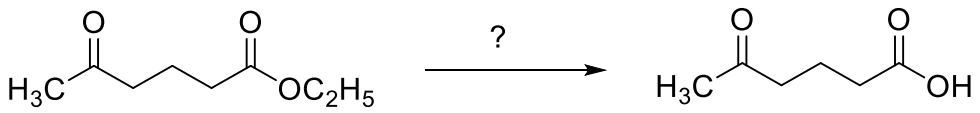
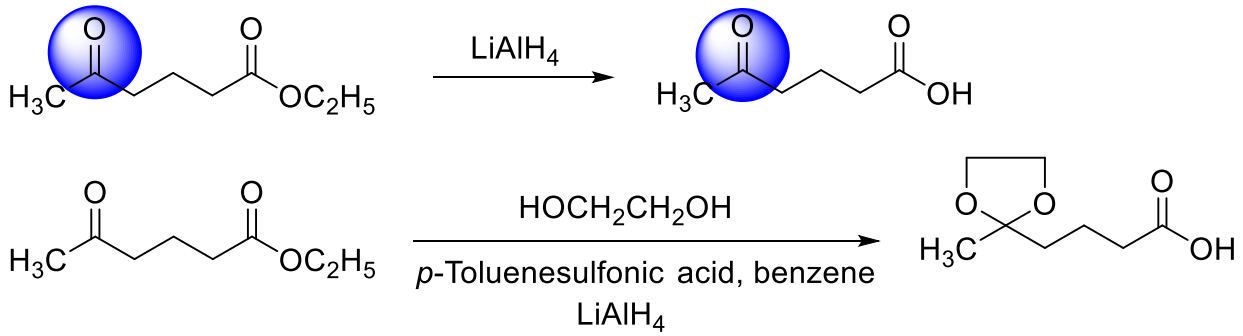
5.1 INTRODUCTION

If more than one functional group (of the same type) is present in a molecule, subtle differences in the reactivity, for instance, caused by steric effects can help to achieve the selective protection of just one functional group while another functional group remains unprotected. The protective group is temporarily attached to decrease the reactivity so that the protected functional group does not react under synthetic experimental conditions to which the molecule is subjected in one or more subsequent steps. The concept of protection-deprotection can be better understood taking the conversion of a ketoester into a desired alcohol as exemplified below.



In general, the desired alcohol from ketoestercould be simply prepared by employing lithium aluminium hydride ($LiAlH_4$)as a reducing agent. However, it should be noted that the keto group present in ester is also reactive towards$LiAlH_4$under identical reaction condition. Consequently, the end product will be totally different as $LiAlH_4$will also reduce the undesired keto group. We can avoid this problem by changing the keto group to a different functional group (protecting group)prior to reaction with $LiAlH_4$. Conceptually, this is like being able to put a cover (as shown below) over the ketone while we perform the metal hydride reduction. Now, the desired conversion can be achieved without affecting other keto function. This is termed as protection of functional group. Finally, the protecting group can be removed by using an appropriate reagent (deprotecting reagent), and this phenomenonis termed as deprotection of functional group.



It is important to note that the nature of the protective group must be chosen carefully to ensure adequate stability throughout all the intermediary synthesis steps. Moreover, the conditions for the protection and deprotection steps and the nature of the protective group itself must not interfere with other functional groups present in the molecule.

Aside from those, not only the selectivity is important, but the yields for the protection and deprotection steps must also be high to avoid making the reaction sequence inefficient. Consequently, in recent years,chemists prefer to design synthesis schemesin such a way that employ steps conducted under more selective reaction conditions, engineered to affect and convert only the desired functional group. As such, harsher and less selective conditions, requiring protection step for differentiation can be avoided.

Another tactic is to employ such reaction conditions, which allowa functional group ‘to protects itself’ temporarily, for example an anion under basic conditions or a cation under acidic conditions. These minimalist yet effective approaches can be abridged in the statements that, "the best protective group is no protective group", and "the best protective group is the one that isn't required". The demands of designing eco-friendly or green synthesis pathways or simply more efficient synthesis pathways with fewer steps and higher overall yieldshave inspired chemists to produce a variety of natural compounds or other synthetic targets that do not relay on protection-deprotection chemistry at all. However, much efforts are still needed in this direction while protection-deprotection chemistry of functional groups firmly holds its ground (and will continue to be) in typical organic synthesis.

In nutshell, a protecting group should fulfill the following conditions, in general, to call it an ideal protecting group-

(a) It should be readily and selectively introduced to the desired functional group, in a poly-functional molecule. Meanwhile, the introduction of protecting group should not be accompanied with the generation of new stereogenic centre.

(b) Its characterization should be easy.

(c) It should be stable or resistant to the reagents employed in subsequent reaction steps in which the group being masked (protected) is desired to remain deactivated (protected).

(d) It should be capable of being selectively removed under mild conditions when its protection is no longer required or simply it should be compatible with the work-up conditions.

The protection-deprotection chemistry of some important functional groups is discussed below.

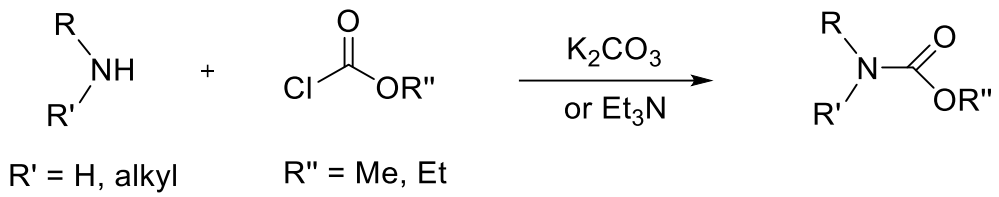
5.2. PROTECTION OF AMINES

Amines, both primary and secondary, play a key role in multistep organic synthesis. However, amine functions are susceptible to undergo reactions when come in contact with certain reagents, for instance, an oxidizing agent, an organometallic reagent, and Grignard reagent. Besides, owing to the presence of lone pair ofelectrons, an amine group can be protonated or may react with electrophiles, posturing difficulties associated with its purification or in terms of reactivity. Consequently, an amine function is appropriately protected in a multistep synthetic campaign, and removed with ease when required. Indeed, the phenomenon of protection-deprotection of amino groups, for instance, amino acids is quite prevalent in peptide synthesis. A variety of protective groups has been developed for amines as discussed below.

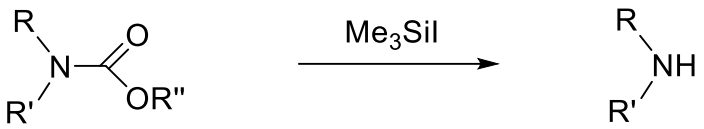
5.2.1 Carbamates:

Carbamates or urethanes (>NCOOR) are mostly prepared by treatment of an amine (primary or secondary) with an alkyl chloroformate. In this way, carbamates serve as protecting groups for amino acids to reduce racemization in peptide synthesis. In general, carbamates are stable towards aqueous bases or oxidizing agents. The simple alkyl carbamates can be cleaved or deprotected using iodotrimethyl silane.

Protection reaction

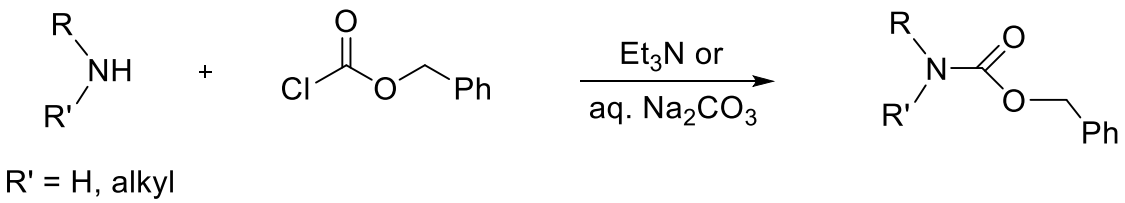


Deprotection reaction

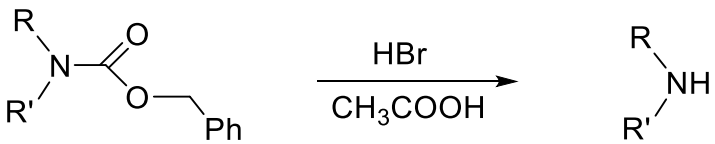


Among protecting groups of utmost importance (forming carbamates), benzyloxy carbonyl (CBZ) and tertiarybutoxy carbonyl (BOC) functional groups are frequently used as N-protecting groups in organic synthesis. A CBZ group is derived from the reaction of benzyloxycarbonyl chloride with an amine, and can be deprotected by making the use of different reagents or conditions, for example, (i) acidic hydrolysis with HBr, (ii) hydrogenation with Pd/C, H_2, and (iii) dissolving metal reduction with Li in liq. NH_3.

Protection reaction

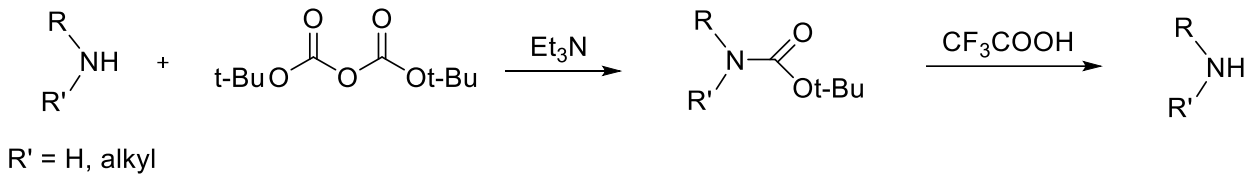


Deprotection reaction

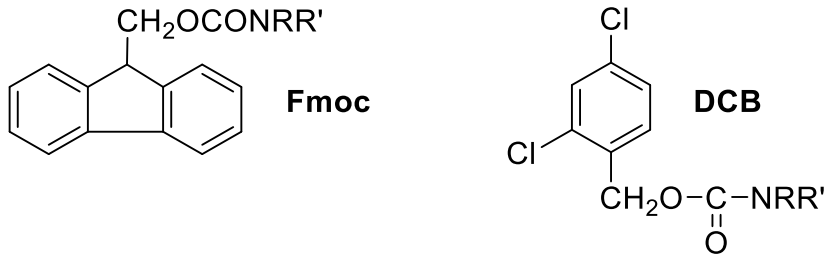


BOC anhydride ($(BOC)_2O$) serves as a potential source for the introduction of BOC group, which easily cleaves by neat trifluoroacetic acid (TFA) in dichloromethane solution. Nevertheless, $AlCl_3$ has proved most effective deprotecting agent for N-BOC group, especially, in the presence of other protecting groups, a phenomenon of 'selective cleaving'.

Protection-deprotection reactions



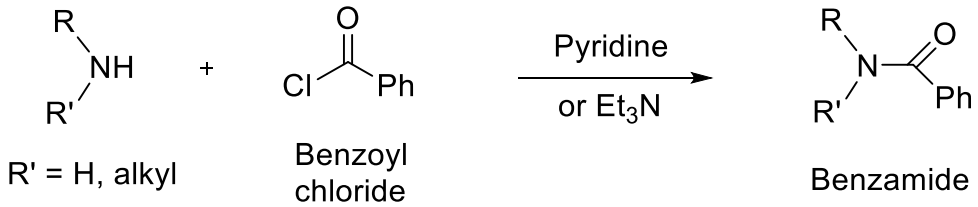
Aside from those of methyl, t-butyl and benzyl carbamates, 9-fluorenylmethyl carbamate (Fmoc) and 2,4-dichlorobenzyl (DCB) carbamates can also be used for protection of amines. The representative chemical structures of these carbamates are appended below.



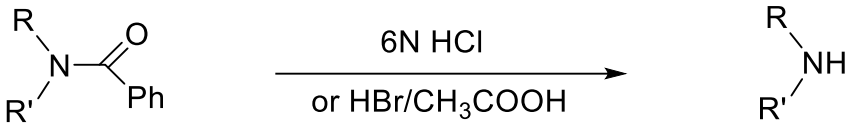
5.2.2 Amides

A relatively low nucleophilic character of amides make them ideal candidate to be used as protecting groups for amines. Amides are simply generated by acylation of primary and secondary amines with well-known acylating agents such as acid chloride or acid anhydride. They are usually cleaved by treatment with strong acids or bases at relatively high temperature. Formamide, acetamide, haloacetamides, acetoacetamide, and benzamide constitute some familiar examples of amides. A protection-deprotection reaction of latter is shown below as a representative case.

Protection reaction

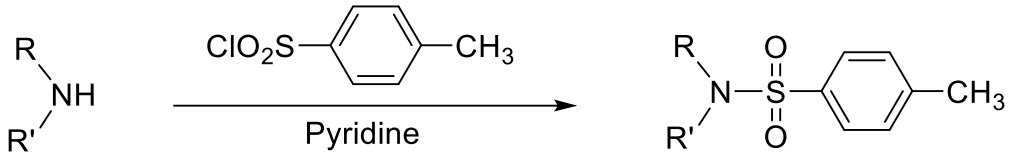


Deprotection reaction

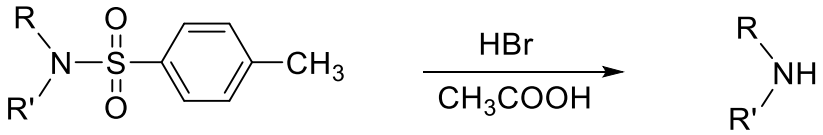


It would be worthwhile to mention here that in analogy to amides, sulphonamides such as benzene sulphonamide, p-toluene sulphonamide, and trifluoromethyl sulphonamide can serve as special types of amine-protecting groups. Sulphonamides are prepared by reacting amines with suitable sulphonyl chloride under basic conditions. Deprotection is done by hydrolysis with strong acids. A general protection-deprotection reaction of amine, utilizing *p*-toluene sulfonyl choloride (*p*-TsCl) as a protecting agent is appended below.

Protection reaction



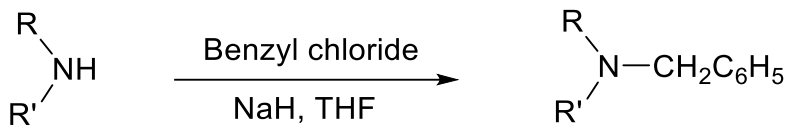
Deprotection reaction



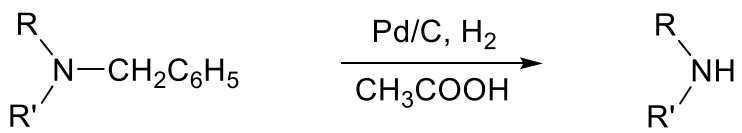
5.2.3 N-Benzyl amine derivatives

The preparation of N-Benzyl derivative is fruitful when primary and secondary amines are susceptible to attack by metal hydride or an organometallic reagent. Specifically, depending upon the experimental conditions, primary amines can generate both mono- and dibenzylated products. The amines can be regenerated back by reaction with Pd catalysts in the presence of an acid and H_2. It is important to note that N-Benzylamines are quite stable towards a variety of Lewis acids.

Protection reaction



Deprotection reaction

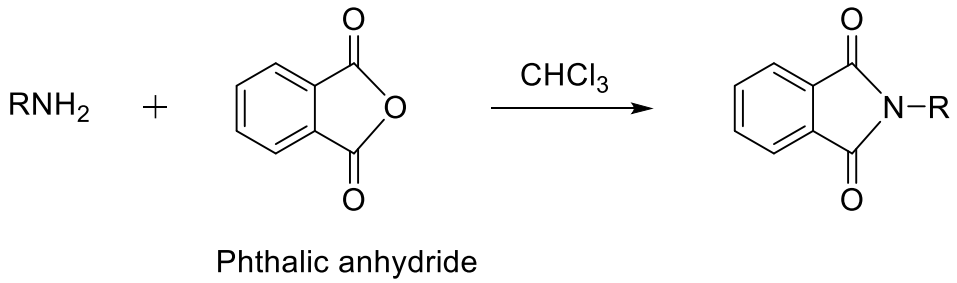


5.2.4 Cyclic imides

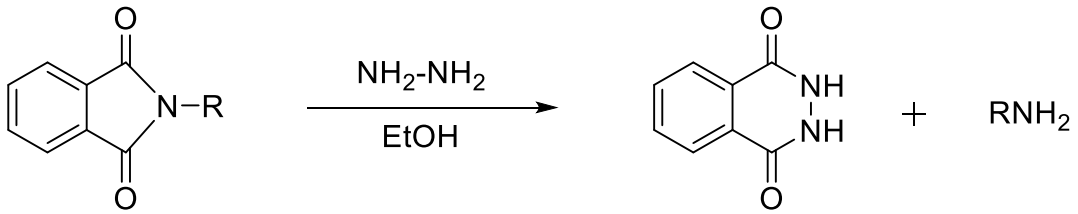
In contrast to acyclic imides, primary amines may also be converted into cyclic imides by reaction with phthalic anhydride. The deprotection reaction is mostly performed in the presence of strong base such as hydrazine. Interestingly, in last few years, a variety of chemical sensing probes for hydrazine have been developed, which chiefly relay on protection-deprotection mechanism of cyclic imide as shown below.

Besides aforesaid-discussed mechanisms, amines can also be protected by converting them into N-alkyl imine, enamine, and N-nitrosoamine derivatives, which are relatively less important and thus not discussed here.

Protection reaction



Deprotection reaction



5.3 PROTECTION OF ALCOHOLS

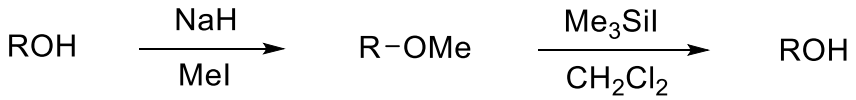
Ethers and acetals constitute the most important protecting groups for isolated hydroxyl functions including 1,2 and 1,3-diols. Notably, nearly all ethers exhibit excellent stability towards basic reaction conditions, and thus can tolerate a variety of metal hydrides ($LiAlH_4$, $NaBH_4$), organometallic reagents (RLi), oxidizing agents (MnO_2, pyridinium chlorochromate; PCC), Grignard reagents, and also some strong bases such as lithium diisopropyl amide (LDA). Further, nearly all ethers and acetals can be cleaved under acidic hydrolysis. A variety of different protecting groups for alcohols is detailed below together with generalized protection-deprotection reactions.

5.3.1 Ethers as protecting groups for alcohols:

5.3.2 Alkyl ethers

Methyl ethers represent simple yet effective protecting groups for alcohols, and can be readily prepared with CH_3I. However, they are quite difficult to cleave except for phenols. Me_3SiI and BBr_3 are some prominent reagents used in dichloromethane (CH_2Cl_2) solution for the deprotection of methyl ethers.

Protection-deprotection reactions



In case of sugars, the use of silver oxide (Ag_2O) is preferred with methyl iodide as methylating agent, in particular, for secondary hydroxyl groups. Unlike methyl ethers, t-butyl ethers are easily cleaved by dil. acids yet are stable to a variety of bases, oxidizing agents, reducing agents, and organometallic reagents. Consequently, their use as protecting group is preferred over methyl ethers.

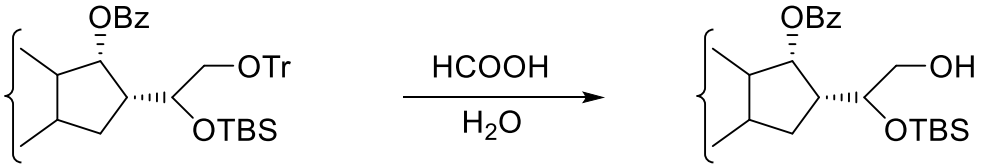
5.3.3Trityl ethers:

Trityl (Tr) or triphenylmethyl ethers are known to selectively protect primary alcohols, and thus were used frequently in past. Trityl ethers can be conveniently prepared by reacting

primary alcohols with triphenylmethyl chloride in pyridine or triethylamine with catalytic amount of DMAP. Trityl ethers exhibit remarkable stability toward bases; however, they can be readily cleaved by hydrogenolysis (Pd, H_2) or by reaction with acids such as formic acid, acetic acid, TFA, and methanesulfonic acid (CH_3SO_3H).

Interestingly, trityl ethers show a remarkable selectivity not only for the protection of primary alcohols but also in the deprotection reaction where other acid labile groups such as benzoyl, triethylsilyl, and *t*-butyldimethyl silyl (TBS) are present. A highly selective deprotection reaction utilizing trityl ethers in conjunction withother acid labile groups is illustrated below.

Deprotection reaction



5.3.4 Benzylic ethers:

Benzyl ethers ($RO-CH_2Ph$) exhibit an excellent stability under a variety of reaction conditions (acidic or basic) and/or reagents (oxidizing or reducing) except *n*-butyl lithium. Specifically, *n*-butyl lithium can abstract a benzylic hydrogen in the presence of hexamethylphosphoramide (HMPA) or tetramethyl ethylenediamine (TMEDA). Benzyl ethers may be cleaved using Pd/C, H_2 or Raney-Nikel (catalytic hydrogenolysis), producing original alcohol under relatively mild conditions. In contrast to benzyl ethers, however, the benzyloxy methyl ethers ($RO-CH_2-O-CH_2Ph$) can be readily cleaved.

5.3.5 Silyl ethers

Silyl ethers represent a class of silicon-containing protecting groups for alcohols, which can be introduced as well as cleaved easily under relatively milder conditions. Owing to the wide availability of silylating agents, their chemoselectivity toward alcohols, and appreciable stability of silyl ethers to a variety of oxidizing and reducing agents, organometallic reagents, acids and

bases, silyl ethers have become the first choice of interest in recent years for tailor-made protection of alcohols. Interestingly, both chemoselectivity of silylating agents and stability of silyl ethers are directly determined by steric factors. In general, both of these properties increase with increasing the bulkiness of the groups attached to silicon atom. The preparation of silyl ethers involves the reaction of an alcohol with an appropriate silylating agent in the presence of a suitable base. The most commonly used bases for the preparation of silyl ethers constitute trialkyl amine(s), imidazole, DBU, and DMAP. However, a hindered hydroxyl group requires relatively more strong bases such as sodium hydride and alkyl lithium prior to silylation. The cleavage of silyl ethers is mostly performed in the presence of fluoride salts, in particular, tetrabutylammonium fluoride (TBAF). This is because of strong affinity of silicon towards fluoride (bond dissociation energy, Kcal/mol; Si-F = 143, Si-O = 111), forcing an O-Si bond to be cleaved readily. Besides TBAF, the deprotection of silyl ethers is done with aqueous acids.

Trimethylsilyl (TMS) ethersrepresent the most basic members of silyl ethers, which can be easily introduced by employing trimethylsilyl chloride as a silylating agent. Interestingly, TMS-ethers can be cleaved within few seconds by making the use of TBAF-THF system at 0°C. Potassium carbonate and citric acid in methanol are some other potential bases being used in the deprotection of TMS-ethers.

Unfortunately, TMS-ethers are not very stable and susceptible to solvolysis in protic media (acids or bases). This issue may be circumvented by employing relatively bulky silylating agents such as *t*-butyldimethyl silyl chloride (*t*-$BuMe_2SiCl$; TBSCl) or *t*-butyldimethyl silyl trifluoromethane sulfonate (*t*-$BuMe_2SiOTf$). The later can be easily prepared by reaction of former with triflic acid. The as-obtained TBS ethers exhibit greater stability to hydrolysis (~ 10^4-fold), however, could still be cleaved by a variety of fluoride salts. In this regime, it should be noted that the silylation of primary alcohols with TBSCl occurs at relatively faster rate than those of secondary and tertiary alcohols. This makes TBSCl a prime choice of silylating agent to protect primary –OH group in glycosides. As such, the ideal condition to protect primary hydroxyl group in the presence of secondary hydroxyl group is the use of TBSCl and trimethylamine with a catalytic amount of DMAP. However, to protect hindered alcohols (secondary and tertiary), one might use the combination of*t*-$BuMe_2SiOTf$ and 2,6-lutidine as a

silylating agent and base, respectively, as shown above. Needless to say that owing to the versatility of TBS group, it is most widely used in protection-deprotection chemistry of alcohols.

Aside from that use of TBSCl, triisopropyl silyl chloride (TIPS-Cl), thexyldimethyl silyl chloride (TDS-Cl) and *t*-butyldiphenyl silyl chloride (BPS-Cl) are some well-known silylating agents to introduce bulky protecting groups.

It would be worthwhile to mention here that TIPS-Cl can selectively protect a primary –OH group even if a secondary –OH group is present. While employing TIPS-Cl, in general, one should use a mild base such as imidazole and catalytic amount of DMAP. Specifically, a TIPS group can tolerate a wide variety of acids, bases, and strong nucleophiles. Nevertheless, a BPS group is even more stable towards acidic hydrolysis than those of TBS and TIPS groups, and can be used to protect both primary and secondary alcohols using BPS-Cl. The generalized protection-deprotection reactions with above-mentioned bulky silyl reagents/silyl ethers are sketched below.

5.4 ESTERS AS PROTECTING GROUPS FOR ALCOHOLS

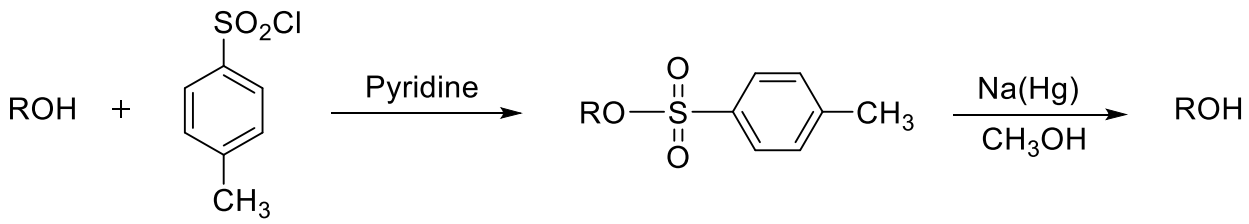
The protection of alcohols as esters can be carried out using a variety of acylating agents such as acetyl chloride, acetic anhydride, trichloroacetyl chloride, benzyl chloride or anhydride, and pivaloyl chloride. However, the use of esters as protecting group for alcohols is usually limited as they are prone to hydrolysis, reduction, and acyl substitution reactions. In general, the selective acylation is chiefly determined by steric factors while their cleavage or deprotection is usually performed under basic conditions. A flow chart describing the protection-deprotection reactions of alchols utilizing esters is depicted below.

It is important to note that the pivalate chloride (*t*-BuCOCl) serves as an excellent and handy protecting agent, offering a convenient method for the selective acylation of primary alcohols, especially, in the presence of a secondary hydroxyl group. Due to the presence of bulky *t*-butyl group, a pivalate ester exhibits good resistance towards nucleophilic attack as well as hydrolysis. The cleavage of a pivalate ester is usually done either with an aqueous solution of metal hydride or tetrabutylammonium hydroxide (TBAOH). In general, the relative reactivities of alcohols toward acylation reaction follows the order as primary alcohol >> secondary alcohol

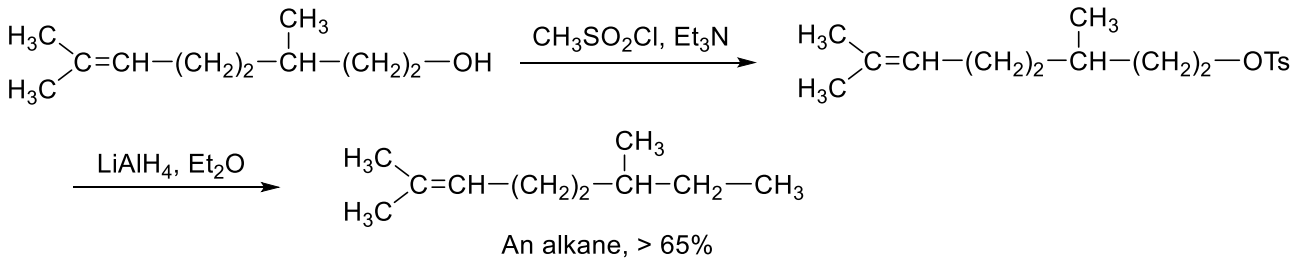
> tertiary alcohol. On the other hand, $RCOOCH_3$> RCOOPh > RCOO-*t*-Bu serves as a general order of relative reactivities of different esters for nucleophilic reagents and/or hydrolysis.

In contrast to carboxylic acid esters, *p*-toluene sulfonate esters (TsOR) are preferably used in carbohydrates and nucleic acid chemistry,in which a regioselective protection of hydroxyl function is desired. Whereas TsCl acts as a protecting agent, Na-Hg in methanol is frequently used for the selective deprotection of tosyl group. However, more greener protocols, for instance, photochemical cleavage can also be carried out for the same.

Protection-deprotection reactions



It should be noted that the reductive cleavage of primary tosylates with reducing agents such as metal hydrides offers a useful method for the synthesis of alkanes *via* cleavage of C-O bond as shown below.



Nevertheless, a hydride may cleave an O-S bond in case of secondary tosylates, which are relatively more hindered. In analogy to esters, carbonates such as alkylmethyl carbonate ($ROCOOCH_3$) and alkyl *p*-nitrophenyl carbonate ($ROCOOC_6H_4NO_2$) can also be used as protecting groups for alcohols. Generally, carbonates are prepared by reacting alcohols with chloroformate while cleaved by basic hydrolysis, similar to those of esters. However, they are seldom used for alcohol protection, and consequently, are worth not to discuss here.

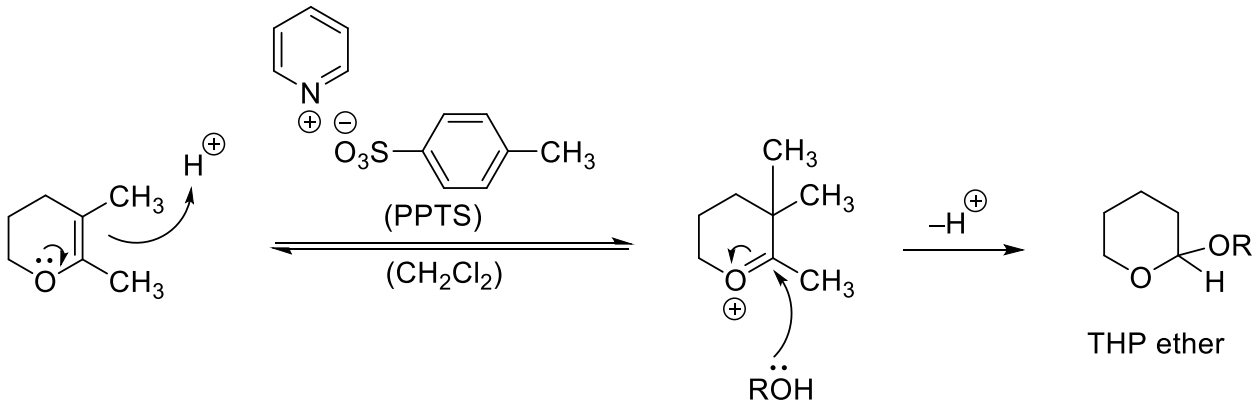
5.5 ACETALS AS PROTECTING GROUPS FOR ALCOHOLS

Acetals represent a class of widely used protecting groups for carbonyl function as will be discussed in the later section. However, they can also be used for the protection of alcohols. Tetrahydropyranyl (THP), methoxymethyl (MOM), 2-methyoxyethoxymethyl (MEM), and methoxyisopropyl (MIP) ethers are some well-known examples of protecting acetals for –OH groups as discussed below appropriately. Typically, an acetal protecting group can be cleaved using aqueous acids.

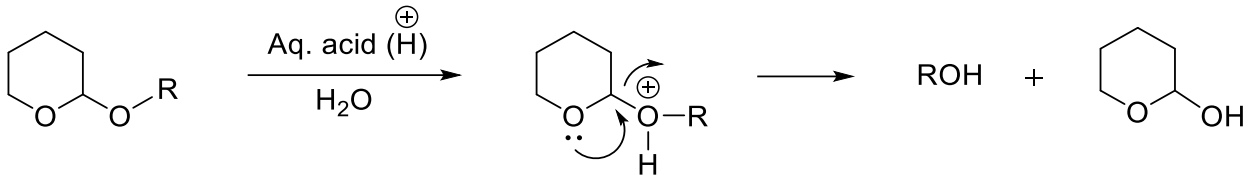
5.5.1 Tetrahydropyranyl (THP) ether

THP and its derivatives are prepared by reaction of dihydropyran, enol ether, with an alcohol in the presence of an acid catalyst. BF_3•Et_2O, phosphorous oxychloride ($POCl_3$), and *p*-toluenesulfonic acid (*p*-TSA) are most commonly used as acid catalysts for this purpose. However, pyridinium *p*-toluenesulfonate (PPTS) is the catalyst of choice for tetrahydropyranylation of relatively sensitive alcohols such as allylic alcohol. The chemistry involved in the protection-deprotection reactions with THP ethers is outlined below.

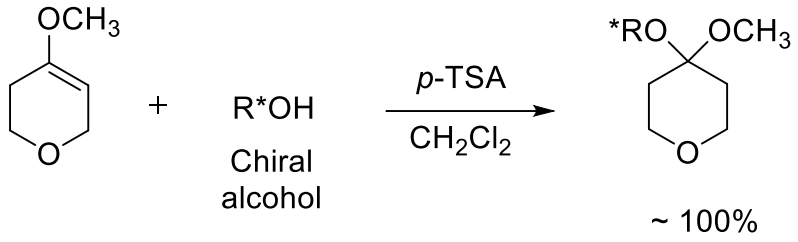
Protection reaction



Deprotection reaction



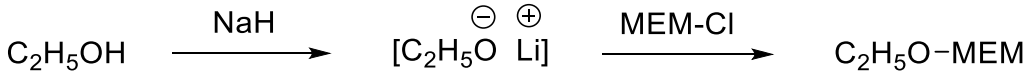
It is important to note that a THP group exhibits an excellent inertness towards metal hydrides and nucleophilic reagents. However, the protection of chiral alcohols with THP produces a mixture of diastereoisomers. This problem can be circumvented by using 5,6-dihydro-4-methoxy-2H-pyran as examplified below.



5.5.2. 2-methyoxyethoxymethyl (MEM) ether:

MEM ethers are yet another acetals being used in the protection of alcohols. An attractive feature of MEM ethers is that they can be used for the protection of not only primary, secondary and tertiary alcohols but also for tertiary allylic alcohols. Generally, the MEM ethers are prepared by reaction of an alkali metal salt of the alcohol with MEM-chloride ($CH_3OCH_2CH_2OCH_2Cl$). The cleavage of MEM ethers is usually carried out using anhydrous zinc bromide in dichloromethane. Nevertheless, PPTS is used as a deprotecting agent in case of allylic alcohols, Similar to that of THP, MEM ethers exhibit reasonable stability toward many oxidizing agents, strong bases and organometallic reagents. However, they are relatively more stable to acidic hydrolysis than THP. This relative reactivity of THP and MEM is of particular interest, and can be used as a complementary method in the protection of two –OH groups at different points sequentially.

Protection reaction



Deprotection reaction

$$C_2H_5O-CH_2OCH_2CH_2OCH_3 \xrightarrow{ZnBr_2} C_2H_5OH$$

5.5.3 Methoxymethyl (MOM) ether:

In analogy to MEM, MOM ethers are also introduced by reacting alkali metal salt of alcohols with methoxymethyl chloride ($ClCH_2OCH_3$). Dilute acids or PPTS in tertiary butanol can cleave the MOM ethers, regenerating the alcohol substrate.

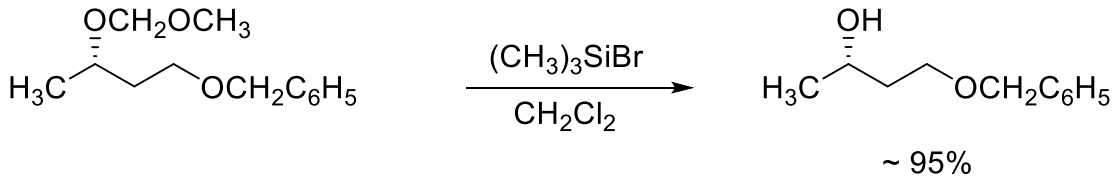
Protection reaction

$$C_6H_5OH \xrightarrow{NaH} [C_6H_5\overset{\ominus}{O}\ \overset{\oplus}{Li}] \xrightarrow{ClCH_2OCH_3} C_6H_5O-CH_2OCH_3$$

Deprotection reaction

$$C_6H_5O-CH_2OCH_3 \xrightarrow[t\text{-BuOH}]{PPTS} C_6H_5OH$$

On a separate note, trimethylsilyl bromide ($(CH_3)_3SiBr$; TMS-Br) serves as a mild and highly selective reagent to deprotect MOM ethers in the presence of a variety of functional groups such as alkyl or benzyl ethers, esters, and many more. However, trityl ethers and other acetals can also be cleaved by TMS-Br.



5.6 PROTECTION OF CARBONYL COMPOUNDS

It is well-known that a carbonyl group can act both as a nucleophile and an electrophile. This can be understood taking into account of an Aldol reaction, which can proceed at faster rate

in the presence of both acid and base catalysts. Consequently, in order to avoid the occurrence of Aldol reaction as a competing side reaction, the protection of carbonyl group becomes very important, especially, in typical multi-steps organic synthesis.

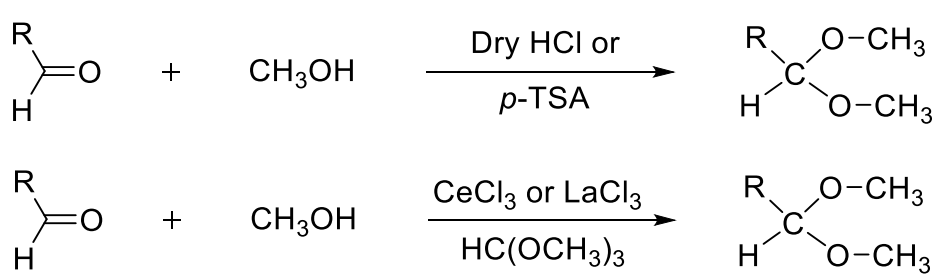
Acyclic and cyclic acetals (*O*,*O*-acetals) are well-established useful groups in the protection-deprotection chemistry of aldehydes and ketones. An acetal protecting group may be introduced by reaction of carbonyl compound with an alcohol, orthoester, and a diol. An acid, preferably, a Lewis acid usually catalyzes this reaction. Both acyclic and cyclic acetals are stable to a variety of nucleophiles, organometallic reagents, strong aqueous bases, hydride reduction, and toward oxidizing agents, especially, under non-acidic conditions. Further, they can be cleaved by acidic hydrolysis, which serves as the most accepted method being used for the deprotection of acetals. Irrespective of the steric effect, the general order of carbonyl group reactivity follows the order-

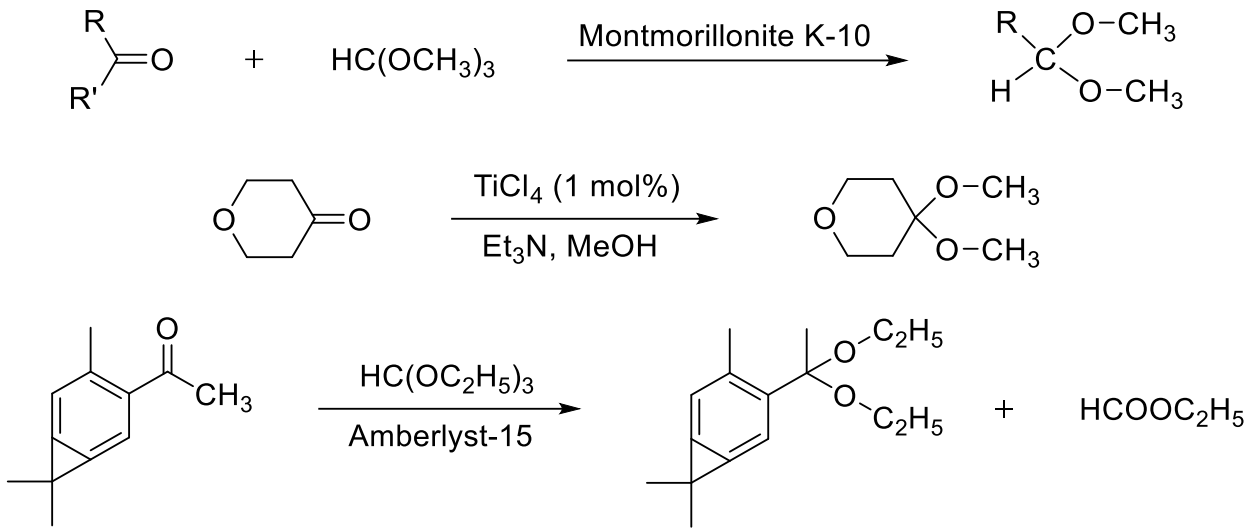
Aldehydes >>> (aliphatic > aromatic) >> acyclic ketones > cyclic ketones (cyclohexanone > cyclopentanone) >α,β-unsaturated ketones > aromatic ketones. Consequently, it is possible to selectively protect a more reactive carbonyl group even in the presence of less reactive carbonyl group. However, the relative rate of acidic hydrolysis in deprotection of acetals is determined by taking into account of inductive effect, steric effect, and stereo-electronic effect.

5.6.1 Acyclic acetals:

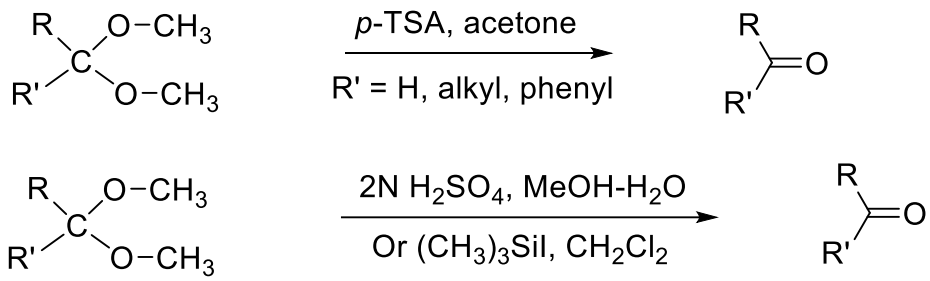
Acyclic acetals such as dimethyl acetals are chiefly used for the protection of aldehydes, which can be simply prepared by warming the aldehyde substrate either in neat MeOH or with trialkyl orthoformate ($CH(OCH_3)_3$) in the presence of acid catalysts. Some generalized protection and deprotection reactions of carbonyl functional groups, utilizing dimethyl acetals are given below.

Protection reactions

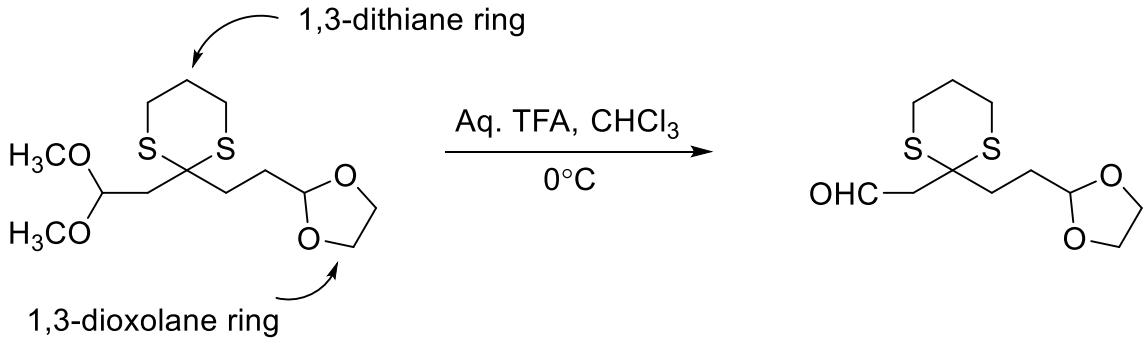




Deprotection reactions

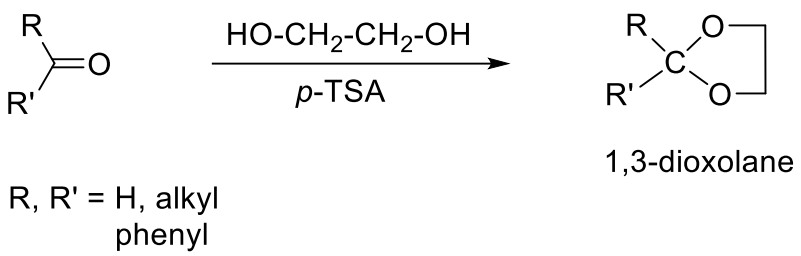


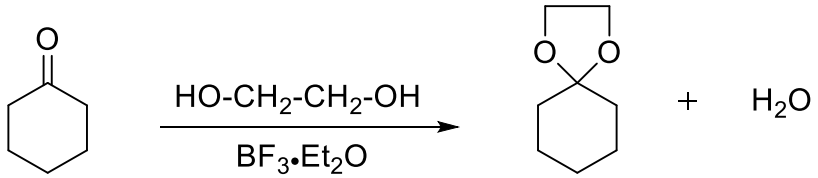
It is important to note that acetalization with trialkyl orthoformate is always accompanied with the concomitant formation of alkyl formate. Furthermore, an aqueous solution of TFA can be used to selectively cleave a dimethyl acetal even in the presence of cyclic (dithio)acetals i.e. both 1,3-dithiane and 1,3-dioxolane (will be discussed later) as shown below.



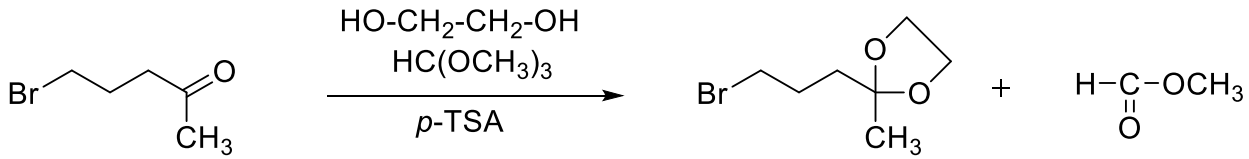
5.6.2 Cyclic acetals

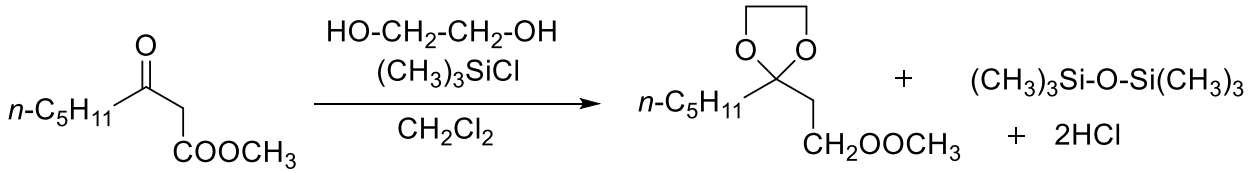
In contrast to acyclic acetals, cyclic acetals are more stable, and can be purified chromatograhically over acidic silica gel. Consequently, they are frequently used in carbonyl group protection. Cyclic acetals can be prepared by acid-catalyzed reaction of carbonyl compounds with diols, for instance, 1,2-ethanediol. Amberlyst-15, BF_3•Et_2O, and *p*-TSA are some popular catalysts used in acetalization. However, for acid-sensitive carbonyl compounds, adipic and oxalic acids are used for protection reactions.





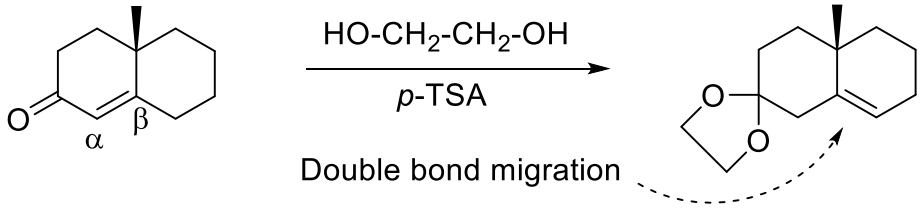
The water formed in the reaction is usually removed by azeotroic distillation. The use of orthoformate esters and trimethylsilyl chloride are known as other standard methods for the removal of water in acetalization reactions. In the former case, water is removed through the generation of an alkyl formate (also see acyclic acetals) while hexamethyldisiloxane (HMDS) is produced with trimethylsilyl chloride.

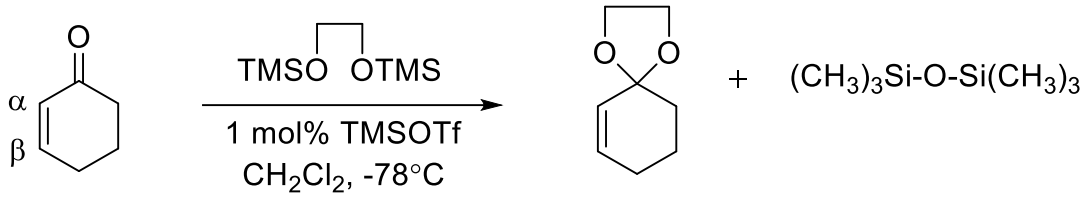




The formation of HMDS instead of water forces the reaction to completion due to its excellent stability. HMDS may also be generated from a silylated diol, namely, 1,2-bis[(trimethylsilyl)oxy] ethane (TMSO-$(CH_2)_2$-OTMS). Interestingly, the use of this silylated diol (instead of 1,2-ethane diol) with catalytic amount of trimeththylsilyl trifluorosulfonate (TMSOTf) provides manyadvantages in the protection chemistry as detailed below.

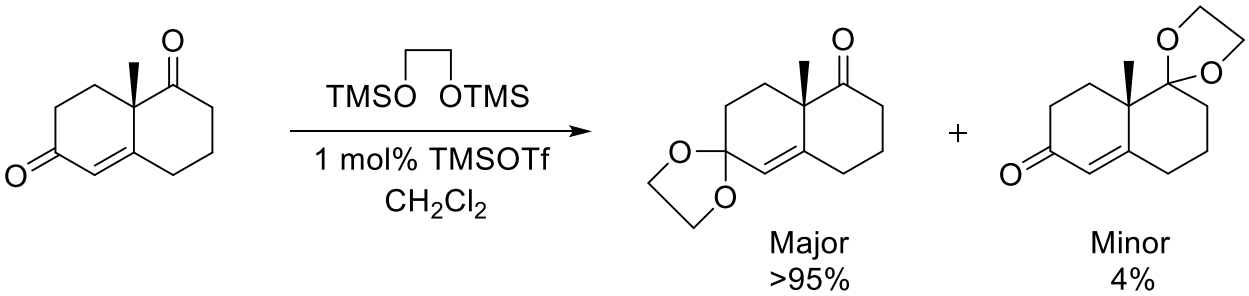
(i) It prevents a double bond migration (unlike 1,2-ethane diol) in the acetalization of α,β-unsaturated ketones.



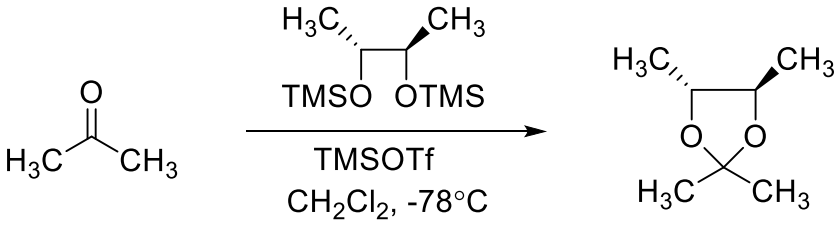


No migration of double bond

(ii) It offers chemoselective acetalization of a conjugated keto group.



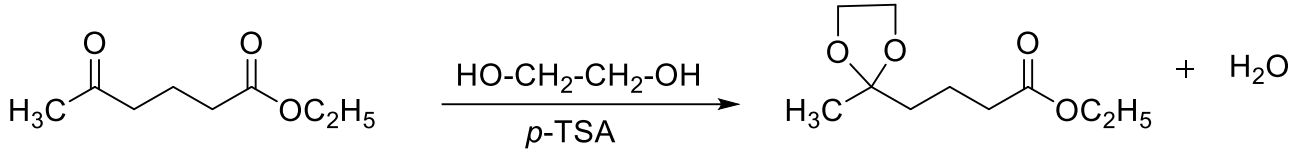
(iii)Chiral cyclic acetals may also be prepared using modified silylated diol.



The as-obtained rigid 1,3-dioxolanes may be used as electrophilic reactant as well as chiral auxiliaries (temporary) for the synthesis of enantiomerically pure compound.

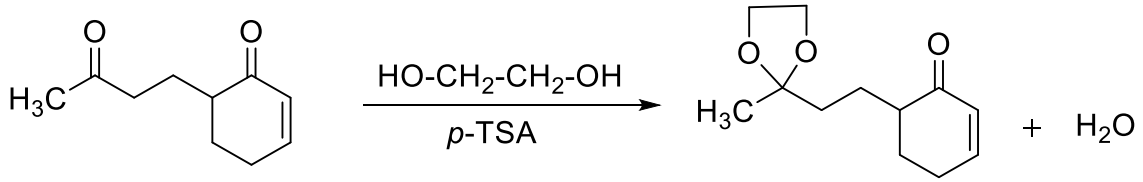
Chemoselectivity vs. acetalization of carbonyl compounds: points to remember

1. Steric and/or electronic effect may influence the chemoselectivity of *O*,*O*-acetal formation in the compounds with two carbonyl groups.

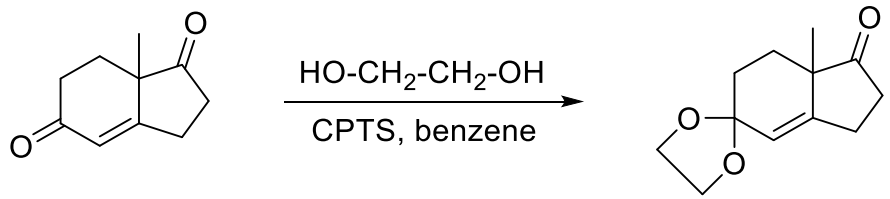


2. In general, a sterically less hindered carbonyl group undergoes acetalization in preference to more hindered carbonyl group.

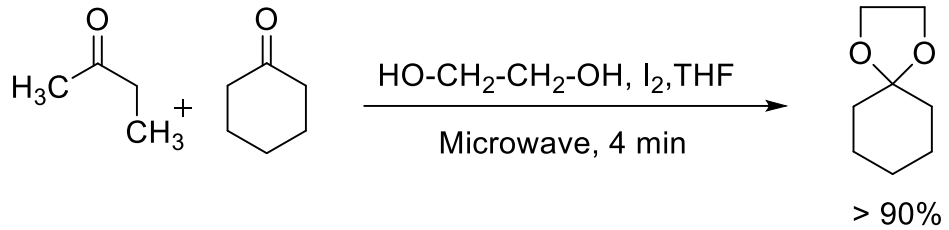
3. An increase in the electron density at carbonyl group decreases its reactivity towards 1,3-dioxolane formation as in the case of enones.



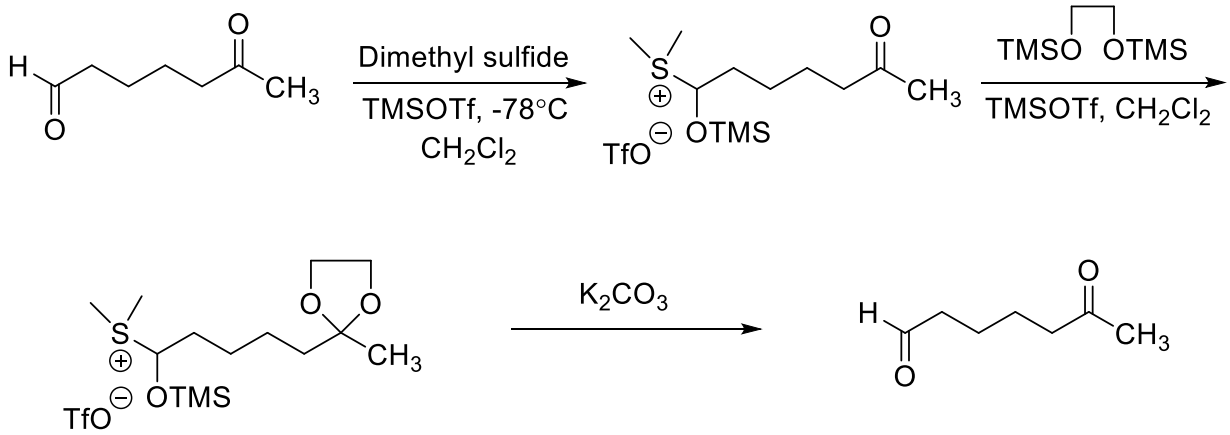
4. The use of some special reagents, catalysts or reaction conditions may direct chemoselective acetalization of carbonyl compounds as demonstrated above with a silylated diol and TMSOTf catalyst. 2,4,6-collodinium *p*-toluene sulfonate (CPTS) is another catalyst which exhibits chemoselectivity in the formation of 1,3-dioxolane in α,β-unsaturated ketone.



Another interesting example of reaction conditions-triggered chemoselectivity is shown below.

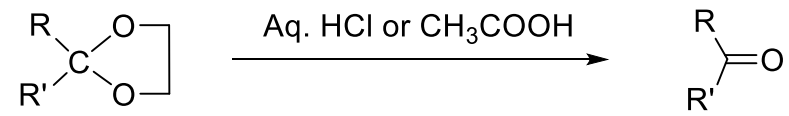


5. If both aldehyde and keto groups are present, selective acetalization takes place at more reactive aldehyde group. Nevertheless, the selective acetalization of a keto group (in the presence of an –CHO group) can also be performed under specialized experimental conditions as given below.

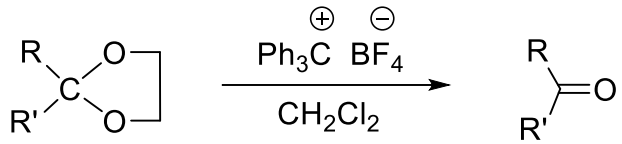


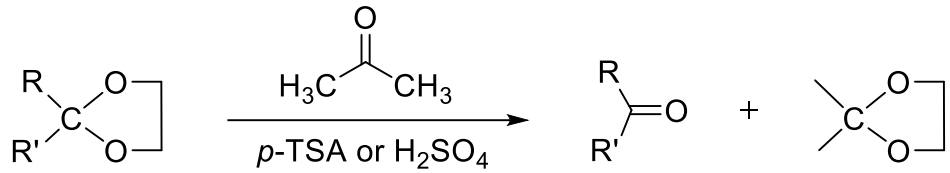
On a final note, 1,3-dioxolanes or O,O-acetals can be cleaved by acidic hydrolysis with ease, similar to those of acyclic acetals. In addition, an oxidative cleavage or acid-triggered exchange dioxolanation can also lead to an effective deprotection.

Deprotection reactions



R' = H, alkyl, phenyl

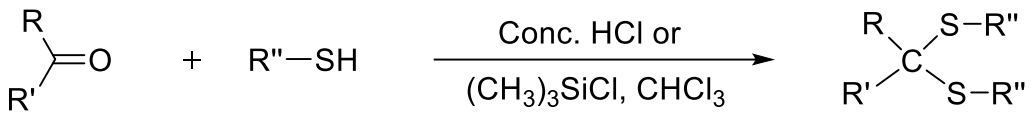




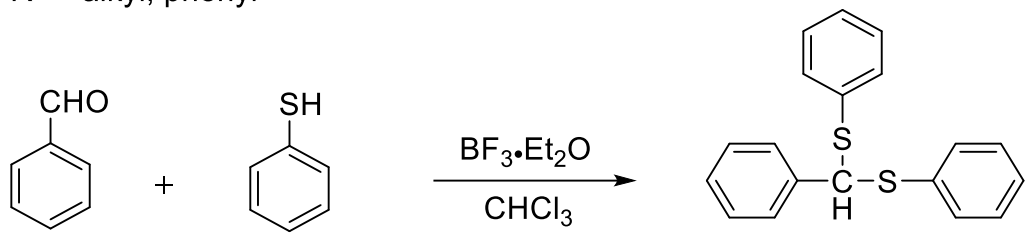
5.6.3 Thioacetals:

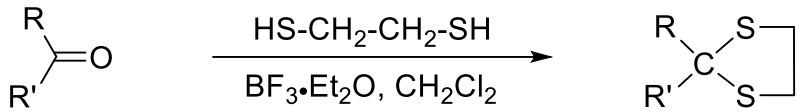
The sulfur analogues of acetals are known as thioacetals, which are introduced by reaction of a carbonyl compound with thiol or dithiol in the presence of acid catalysts (BF_3•Et_2O or *p*-TSA). However, unlike acetals, thioacetals are sufficiently stable to acidic hydrolysis, and thus deprotection of thioacetals is usually done with environmentally questionable Hg (II) salts. Because of this, the frequent use of thioacetals is discouraged in the protection-deprotection chemistry. Despite this, it should be noted that the use of thioacetals as protecting groups offer some inherent advantages over acetals. For instance, due to their reasonable stability toward hydrolysis, water formed in the reaction does not affect thioacetals. Furthermore, a double bond migration in the thioacetalization of enones does not occur. Given below are some examples of protection-deprotection reactions of thioacetals including hemithioacetals.

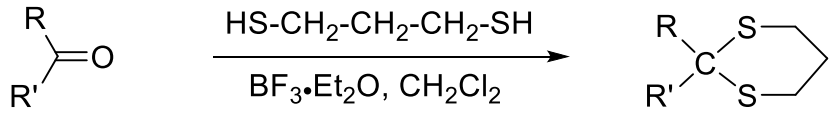
Protection reactions

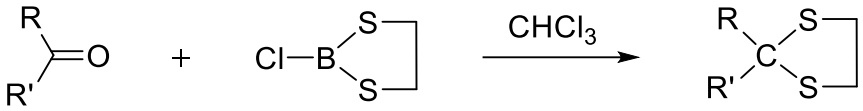


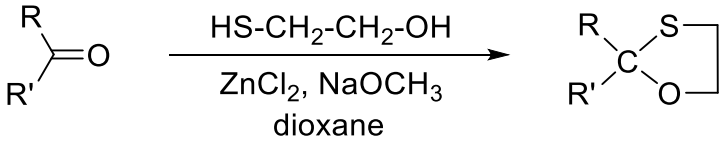
R, R' = H, alkyl, aryl, cycloalkyl
R" = alkyl, phenyl





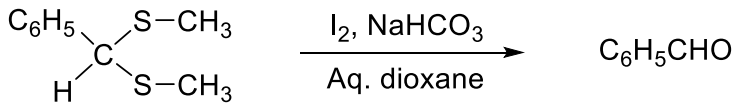


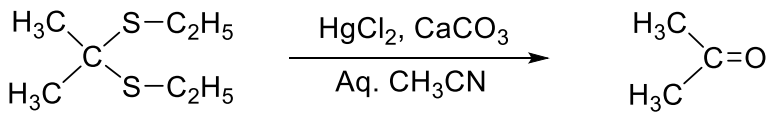


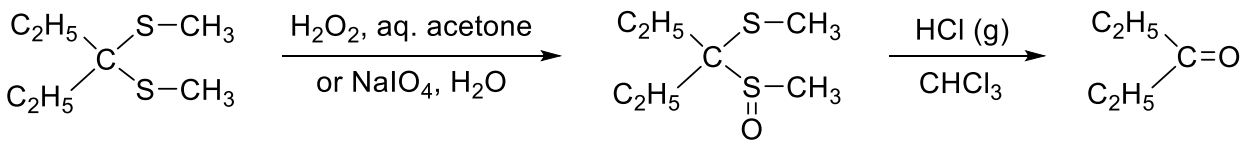


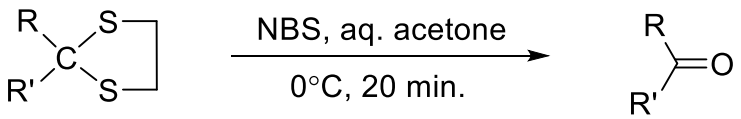
R, R' = H, aryl, cycloalkyl

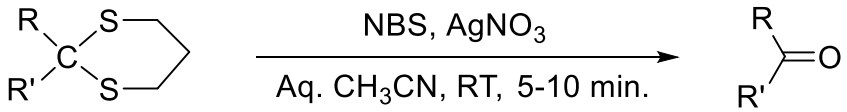
Deprotection reactions

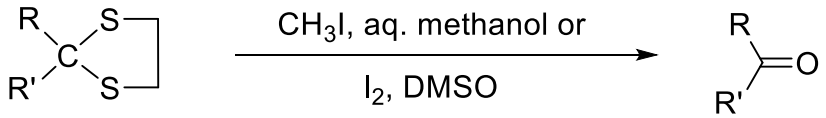


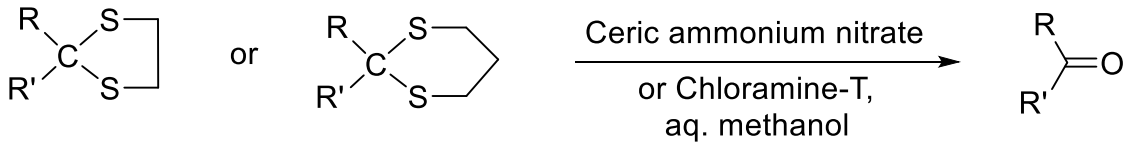


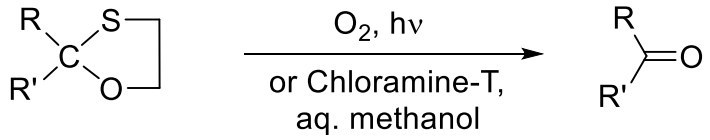












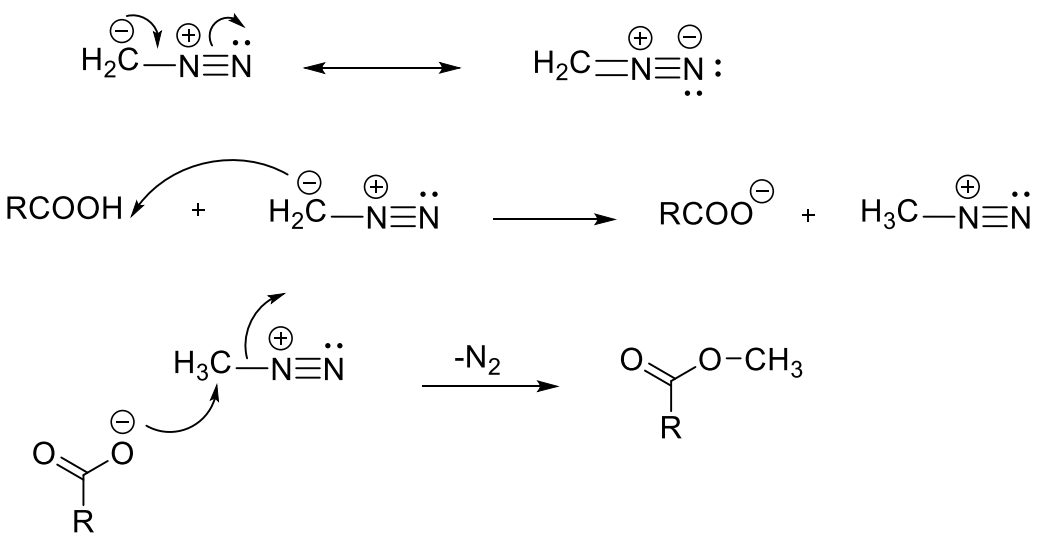
R, R' = aryl, cycloalkyl

5.7 PROTECTION OF CARBOXYLIC ACIDS

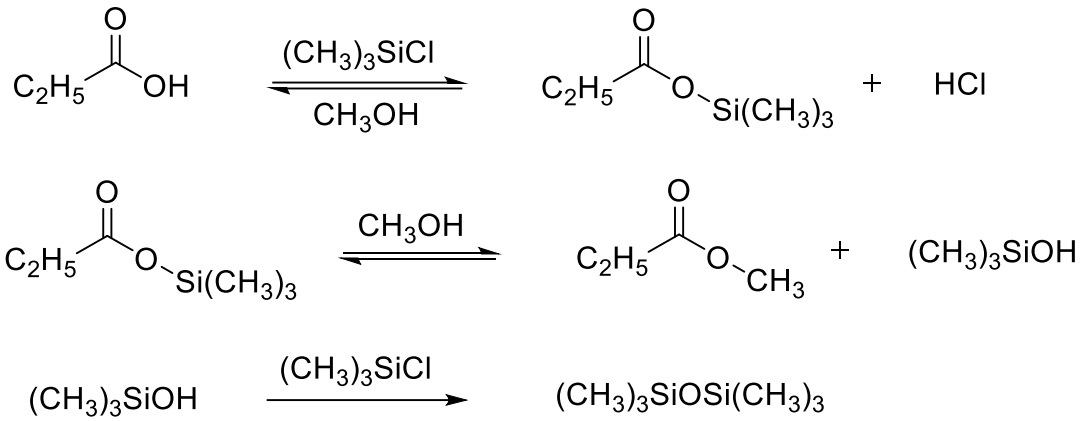
In order to avoid the reaction of acidic hydrogen (COOH) with bases, organometallic reagents and nucleophiles or to prevent the nucleophilic addition reactions at carbonyl carbon, the protection of carboxylic group is required. The frequently used protecting groups for carboxylic acids are esters. A wide variety of esters are readily available, offering moderate to robust protection of acid group as per requirements. Different classes of these esters as protecting groups for carboxylic acid are appropriately discussed below.

5.7.1 Alkyl esters:

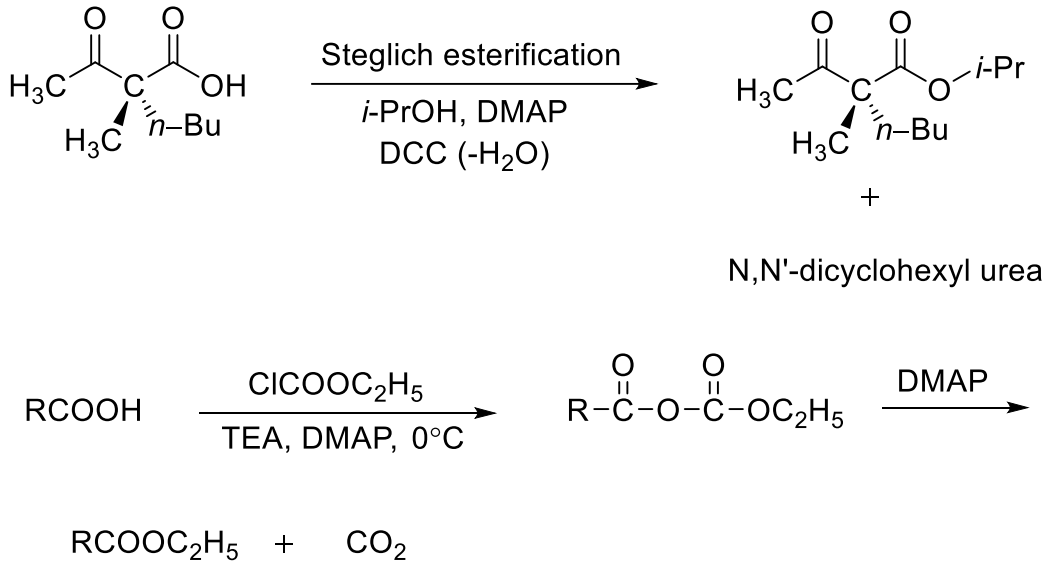
The traditional methods for the preparation of simple alkyl esters include (i) the reaction of carboxylic acids with excess of alcohols in the presence of strong acid catalyst (ii) the reaction of acid halides with alcohols catalyzed by bases (pyridine, TEA or TEA-DMAP) and (iii) the reaction of alkali metal carboxylate with primary halides (S_N2 reaction). Apart from these classical methods, alkyl esters may also be prepared by using special reagents, catalysts, and/or reaction conditions. For instance, the use of diazomethane (CH_2N_2) offers a convenient method for small-scale preparation of methyl esters. In this context, it would be worthwhile to mention here that diazomethane is considered as a potential explosive and toxic material. Consequently, its handling demandsgreat care and attention.The working action of diazomethane toward carboxylic acids is schematized below.



Given harmful properties of diazomethane as well as its limited use, methyl derivatives of carboxylic acid can be alternatively prepared with ease by treatment of a carboxylic acid with trimethylsilyl chloride in methanol.

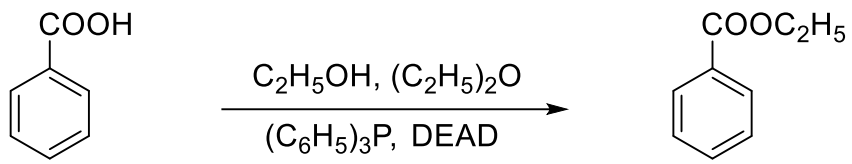


Steglich esterification (DCC + DMAP) provides a mild protocol to prepare corresponding esters in good yields. The method is applicable to primary, secondary and tertiary alcohols. In line with Steglich esterification, the use of alkyl chloroformates with catalytic amount of DMAP also offers a mild esterification method.



Simple alkyl esters may also be prepared under Mitsunobu conditions i.e. the reaction of carboxylix acid with alcohols in the presence of triphenyl phosphine and diethyl azodicarboxylate (DEAD).

$$RCOOH \xrightarrow[(C_6H_5)_3P,\ DEAD]{R'OH,\ (C_2H_5)_2O} RCOOR'$$



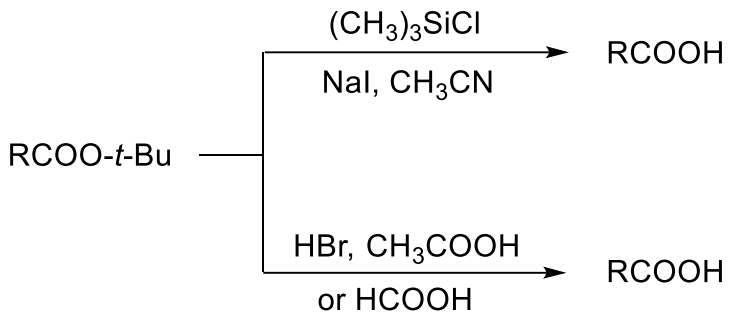
Unlike simple alkyl esters, the bulky group in *t*-butyl esters offers an excellent shielding of the carbonyl carbon, making it less susceptible to attack by nucleophiles. As a result, these esters are considered as special protecting groups for carboxylic acids. The economic method for the preparation of *t*-butyl esters involves the reaction of a carboxylic acid with 2-methyl propene in the presence of an acid catalyst. Alternatively, the reaction of acid chloride with lithium tertiarybutoxide also furnishes *t*-butyl esters. In line with this, Steglich esterification also provides a good handle for the preparation of *t*-butyl esters. The rapid cleavage of *t*-butyl group to corresponding acid occurs with TFA, formic acid, acidic HBr, and *p*-TSA. It is important to note that all these acids also work well in the deprotection of simple alkyl esters.

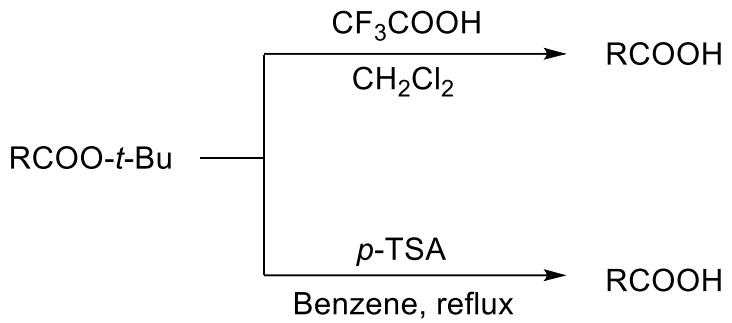
$$RCOOH + H_2C{=}C(CH_3)_2 \xrightarrow[(C_2H_5)_2O,\ RT]{Conc.\ H_2SO_4} RCOOC(CH_3)_3$$

$$RCOCl \xrightarrow{LiO\text{-}t\text{-}Bu} RCOO\text{-}t\text{-}Bu$$

$$RCOOH + t\text{-}BuOH \xrightarrow[(C_2H_5)_2O]{DCC,\ DMAP} RCOO\text{-}t\text{-}Bu$$

Deprotection reactions





5.7.2 Silyl esters:

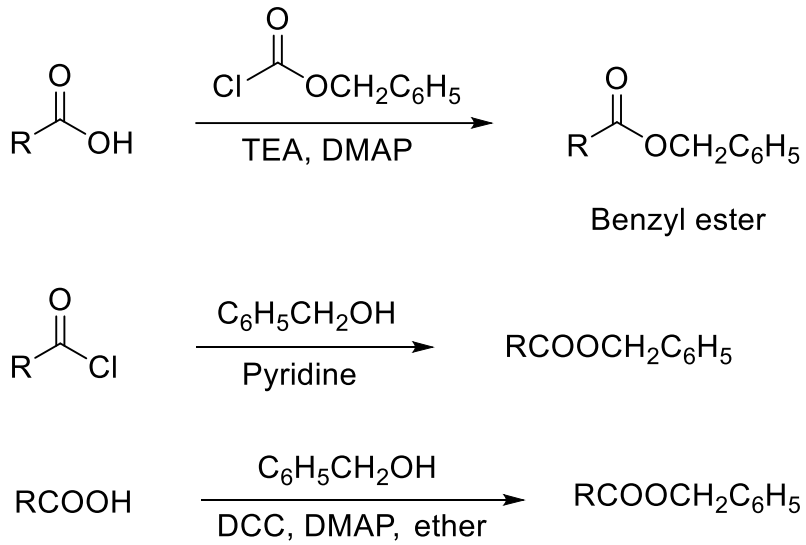
Owing to their rapid introduction as well as removal, the use of silicon-containing protecting groups is highly popular in protection-deprotection chemistry. In the previous section of –OH group protection, we have seen that a wide range of silyl ethers can be conveniently prepared to solve the purpose. In case of –COOH function, silyl esters, for instance, TIPS esters are used to protect the carbonyl group from nucleophilic attack by organolithium and Grignard reagents. TIPS esters can be prepared by reaction of acids with TIPS chloride in the presence of mild base, and can be deprotected by acid hydrolysis.

5.7.3 Benzyl esters:

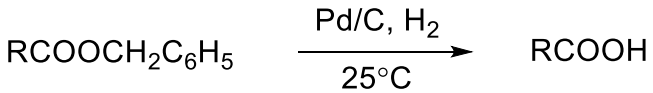
Owing to their easy cleavage (hydrogenolysis), benzyl esters are frequently used for the protection of carboxylic acid functions. Benzyl esters can be simply prepared by reaction of carboxylic acid with benzyl chloroformate under basic conditions together with a catalytic

amount of DMAP. Alternatively, the reaction of an acid chloride with benzyl alcohol in pyridine furnishes benzyl ester in good yield.

Protection reactions



Deprotection reaction



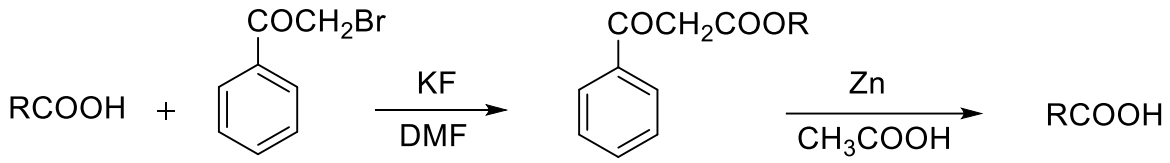
5.8 Others:

Aside from those of above-mentioned esters, occasionally, some other classes of esters may also be used to protect carboxylic acids. The representative protection-deprotection reactions of few of them are given below.

Protection-deprotection reactions

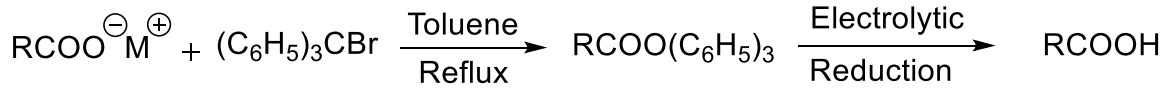
THP ester

THF ester



R = Alkyl, aryl

Phenacyl ester

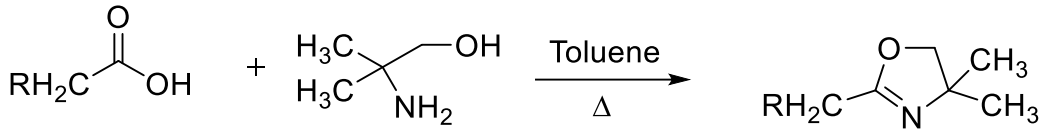


M⊕ = Na⊕, k⊕, Ag⊕

Trityl ester

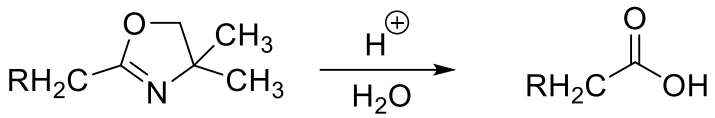
Though esters serve as most prominent protecting groups for carboxylic acids, however, amides, hydrazides and 1,3-oxazolines may also be employed to protect the carboxylic acids. Among them, the latter is especially notable as both hydroxyl and carbonyl functions of a carboxylic acid can be protected using 1,3-oxazolines against metal hydrides (except alkyl lithium) and Grignard reagents. 1,3-oxazolines can be prepared by heating a mixture of desired carboxylic acid with 2-amino-2-methylpropanol in toluene, and can be cleaved by acidic hydrolysisas shown below.

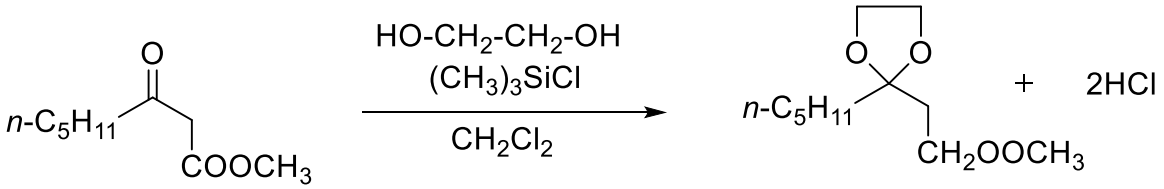
Protection reaction



1,3-oxazoline

Deprotection reaction





+

$(CH_3)_3Si\text{-}O\text{-}Si(CH_3)_3$

5.9 TERMINAL QUESTIONS

1. Discuss the mechanism of protection and deprotection of alcohols as trimethyl ethers.
2. What is the principle of protection of amino groups? Explain the use of 9-fluorenyl methyl carbonyl group for protecting amino group

UNIT: 6 RING SYNTHESES

CONTENTS

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6.3 Conformations of saturated heterocycles

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- 6.4.2 Synthesis of four membered heterocycles
- 6.4.3 Synthesis of five membered heterocycles
- 6.4.4 Synthesis of six membered heterocycles

6.5 Aromatic heterocycles in organic synthesis

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- 6.5.2 Synthesis of alkene and cycloalkenes
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- 6.5.4 Synthesis of aromatic hydrocarbon
- 6.5.4 Synthesis of carboxylic acids
- 6.5.5 Synthesis of carbonyl compounds
- 6.5.6 Synthesis of carboxylic acids and its derivatives
- 6.5.7 Synthesis of nitriles

6.6 Serminal questions

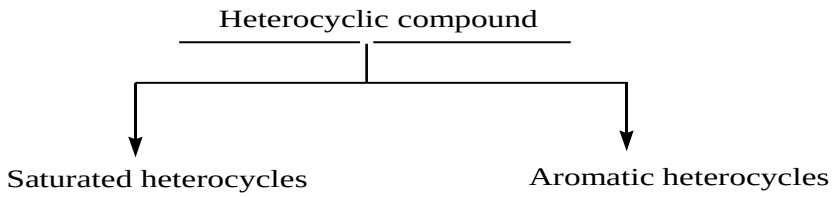
6.7 Suggested books

6.1 OBJECTIVES

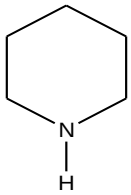
Ring synthesis includes formation of the rings (saturated heterocycles as well as aromatic heterocycles) of the various membered as well as their stability. The ring synthesis also includes thermodynamic, kinetic favoured condition for the synthesis of various membered rings as well as their conformational stability. The ring synthesis also gives the idea about the synthesis of various organic species like alkane, cycloalkane, alkene, cycloalkane, aldehyde and ketone, carboxylic acids as well as nitriles with the help of aromatic heterocycles.

6.2 INTRODUCTION

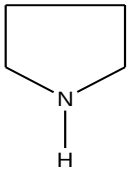
Heterocyclic compounds are those cyclic compounds which containing atleast one heteroatom i.e. lone pair containing atom (Nitrogen,Oxygen,Sulpher,Phosphorusetc atoms)as the member of the ring . Heterocyclic compounds are divided into following two different categories



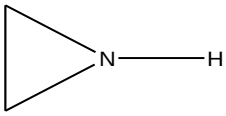
Saturated heterocycles: These are the cyclic compounds having non aromatization with atleast one heteroatom like N , O , S , P etc as the member of the ring.



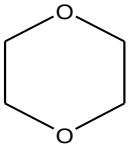
PIPERIDINE



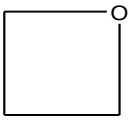
TETRA HYDRO PYRROL



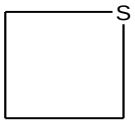
AZIRANE



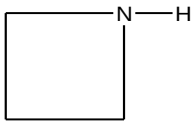
DIOXANE



OXITANE

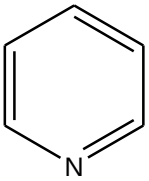


THIETANE

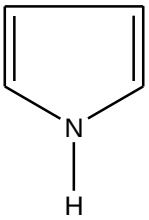


AZETIDINE

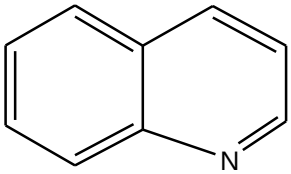
Aromatic heyerocycles: These are the heterocyclic compounds of the aromatic nature with the heteroatom like N , S , O , P etc . All these heterocycles follow the Huckel's rules of aromaticitycompletely.



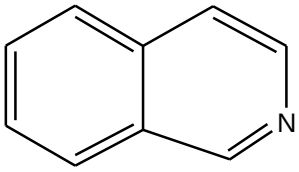
PYRIDINE



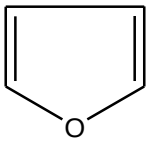
PYRROLE



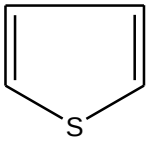
QUINOLINE



ISO QUINOLINE



FURAN



THIOPHENE

Saturated heterocycles are formed by the intramolecular mode of large numbers of intermolecular reactions. During the synthesis of different membered saturatedheterocyclesthermodynamic and kinetic condition should be considered.

Those ring synthesis which require low free energy of activation are said to be kinetically favoured while on the other hand those ring synthesis which involve the stablishment of

equilibrium condition between reactant and product with more negative free energy change are said to be thermodynamically favoured

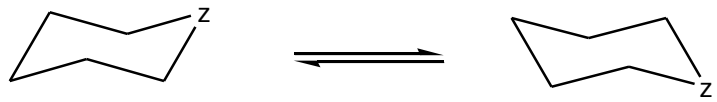
During the synthesis of various membered ring kinetic and thermodynamic favoured condition can be given according to the following table

RING SIZE	KINETIC FACTOR	THERMODYNAMIC FACTOR
3 Membered	Strongly favoured	Not favoured
4 Membered	Not favoured	Not favoured
5 Membered	Normally favoured	Normally favoured
6Membered	Weakly favoured	Strongly favoured

On the other side some organic compounds can also prepared by using the aromatic heterocycles as the precursor .formation of the various type of organic compounds like alkane , cycloalkane , alkene , benzenoid compounds , aldehyde , ketones, carboxylic acids as well as some other organic compounds are used as the alternate metods for these compounds .

6.3 CONFORMATION OF SATURATED HETEROCYCLES

Six membered cyclic compounds like cyclohexane exist in the chair , boat , twisted boat conformation but if one of the carbon atom of cyclohexane is replaced by the heteroatom like oxygen , nitrogen , sulphar , phosphorus etc then the six membered heterocycles which are formed exist mainlyin the chair conformation . Boat conformer is less preferred due to its more energetic nature.

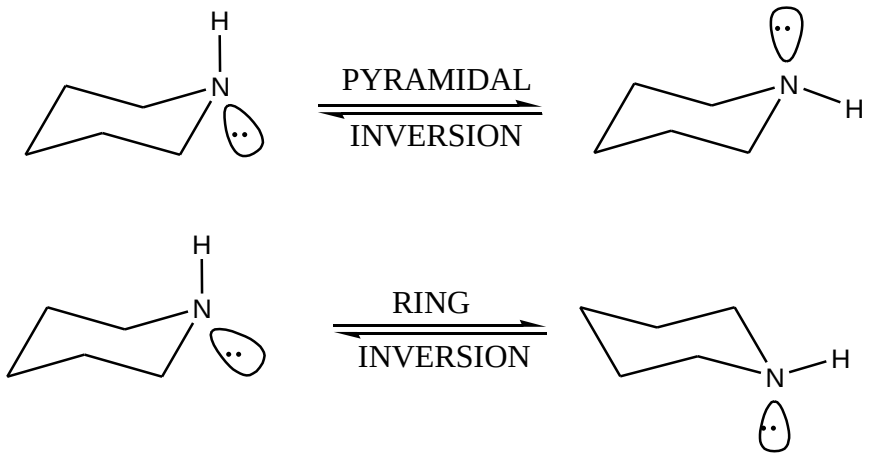


RING INVERSION IN THE SIX MEMBERED HETEROCYCLE

WHERE - Z = O ,S , NH

The conformational energy barrier for the ring inversion in the various six membered heterocycles being closer to that in cyclohexane.

Pyramidal Inversion: Six membered heterocycles unlike to the cyclohexane exhibit the pyramidal inversion with the ring inversion. Molecules like piperidine or other six membered heterocycles exhibit both pyramidal inversion (tetrahedral inversion) as well as ring inversion side by side. Both this type of inversion can not be separated from each other Pyramidal inversion (tetrahedral inversion) and ring inversion in piperidine can be represented as –



N-H group having the preferential tendency to be located in equatorial position. The energy difference between N-H axial and N-H equatorial is about 1.68KJ/mole.

During the pyramidal inversion there occurs change in configuration while during the ring inversion there occurs change in the conformation.

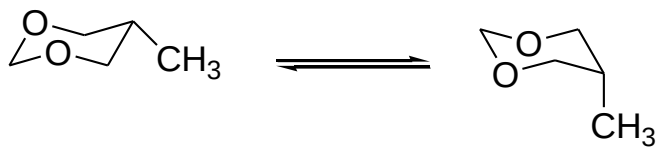
1,3syn axial intraction in the case of six membered heterocycles is increased due to shorter bond distance than in cyclohexane that can affect the stability of substituted six membered heterocycles with respect to cyclohexane.

13 SYN AXIAL INTRACTION

LESS STABLE MORE STABLE

In the case of saturated heterocycles with any one bulky substituent if the heteroatom like N , O , S with one or two lone pair of electron being situated at 3rd position with respect to the bulky substituent then non bonding 1,3 syn axial intraction between the bulky substituent and axial lone pair present at 3rd position being weak in compare to 1,3 syn axial intraction in mono substituted cyclohexane chair conformer due to less bulky nature of lone pair with respect to H .

In the case of 5-Methyl 1,3dioxane following two conformers are possible

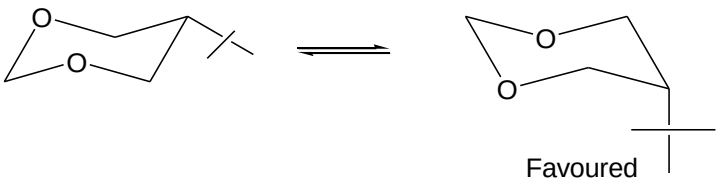


[X] [Y]

Methyl group at equitorial position

Methyl group at axial position (Favoured)

Conformer Y is favoured due to weak nature of 1,3 syn axial intraction of methyl group with lone pair of electron in compare to the 1,3 syn axial intraction between the methyl group and axial H atom present at 3rd position in axial methyl cyclohexane .



In the 1,3dioxanechair conformer bulky substituent like t-butyl group , isopropyl group occupies axial position at 5th position due to same reason i.e. due to weaker 1,3 syn axial intraction . Some time in the saturated heterocycles if hydroxyl group (OH gr) or amino group (NH_2 gr) being present at 3rd position with respect to ring hetero atom (N or O) then intramolecular H-bonding can also be responsible for conformational preference .

6.4 SYNTHESIS OF SATURATED HETEROCYCLES:

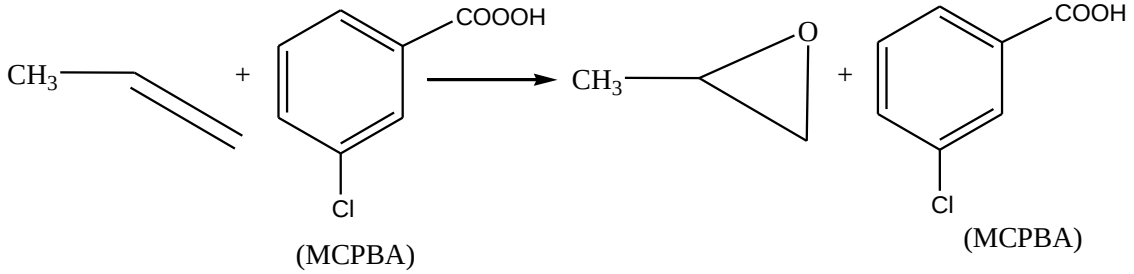
6.4.1 Synthesis of three membered heterocycles:

Three membered ring syntheses is kinetically favoured and thermodynamically not favoured. Some of the three membered ring syntheses with their retrosynthetic analysis can be given as-

Example 1-Epoxides are the three membered heterocycles with oxygen hetero atom. They are formed by the reaction of alkene with peracids like meta chloroperbenzoic acid (MCPBA). The retrosynthetic analysis as well as synthesis of epoxides can be represented as –

RETROSYNTHETIC ANALYSIS :

SYNTHESIS :

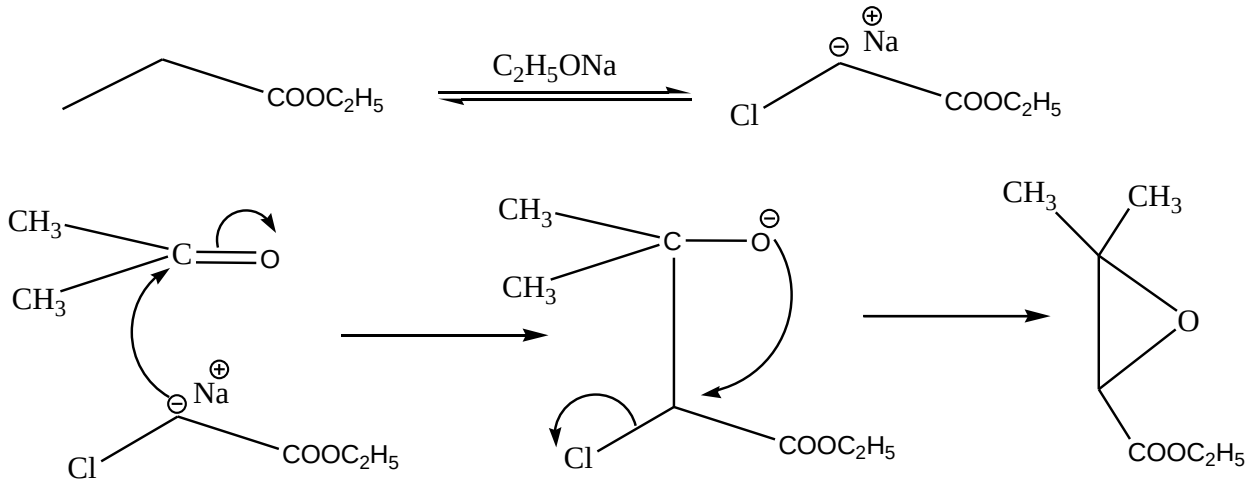


Example 2: Epoxy esters are the three membered heterocycles with oxygen hetero atom. They are formed by the Darzen reaction in which α-halo ester react with carbonyl compound in the presence of sodium ethoxide. Retrosynthetic analysis as well as synthesis of this three memberheterocycle can be represented as-

RETROSYNTHETIC ANALYSIS :

This indicate the carbine as an intermediate but in actualpractice carbine is not formed as an intermediate, this is observed from the following synthesis-

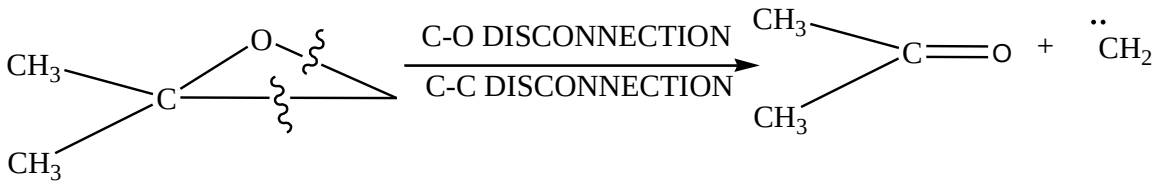
SYNTHESIS :



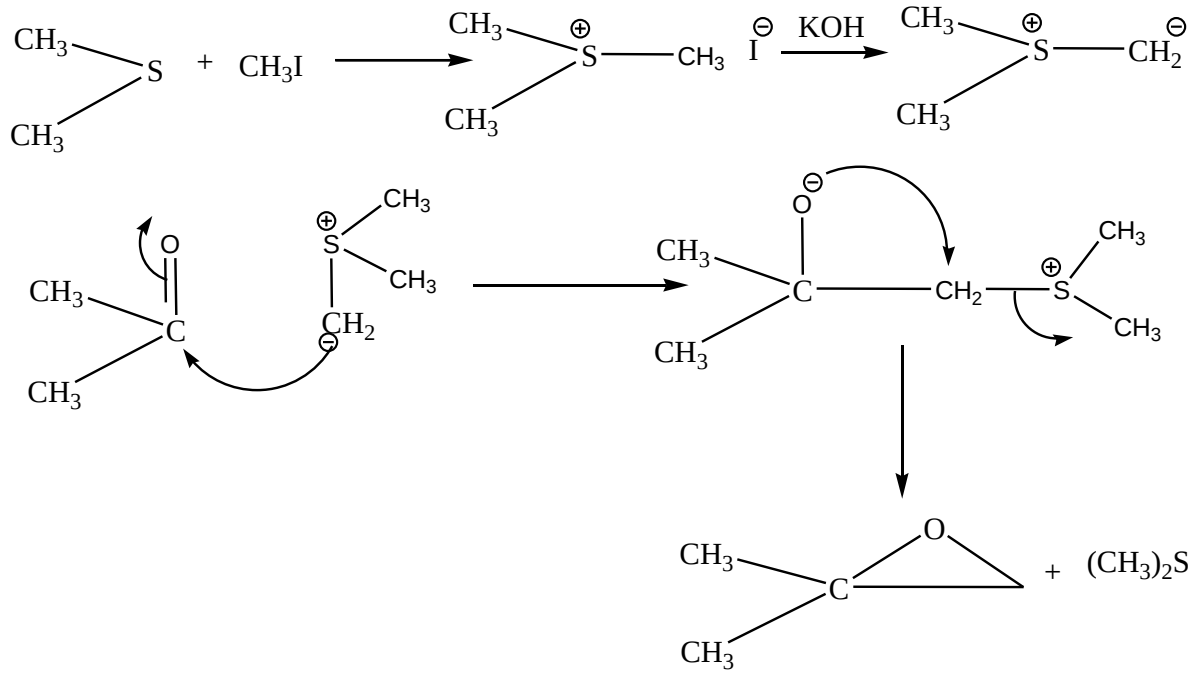
Example 3: Epoxide three membered heterocycle is also formed by the reaction of carbonyl compound with the sulphurylide

Retrosynthetic analysis indicate the carbine as an intermediate but actually carbine is not formed as an intermediate that can be observed from the following synthesis.

CH_2

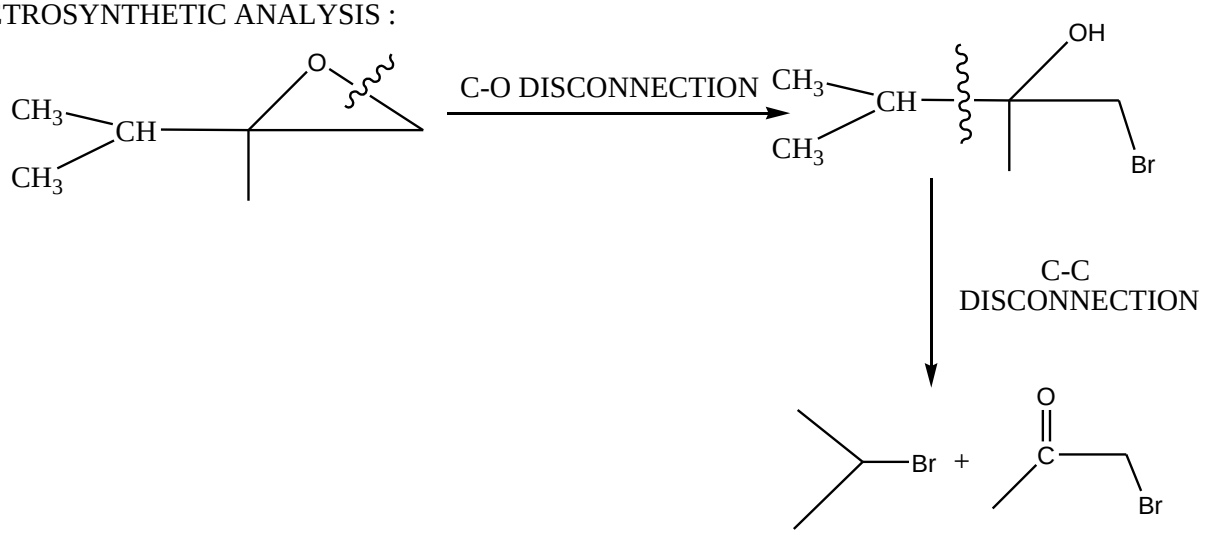


SYNTHESIS :

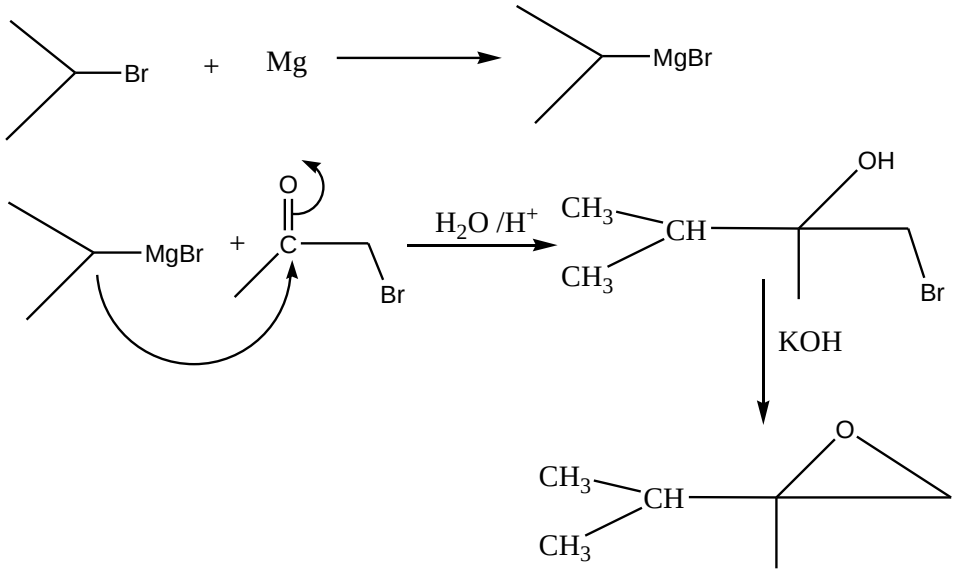


Example 4-Three membered heterocyclewith oxygen atom i.e. epoxides can be formed by the reaction of α-halo carbonyl compounds with alkyl halides. Retrosynthetic analysis as well as synthesis of this three membered heterocycle can be represented as-

RETROSYNTHETIC ANALYSIS :

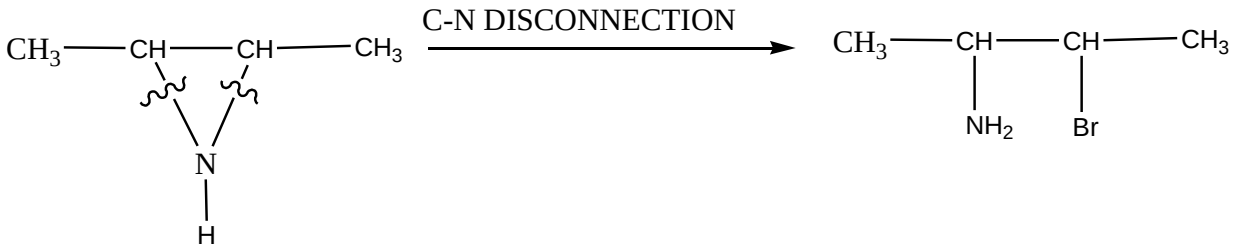


SYNTHESIS :

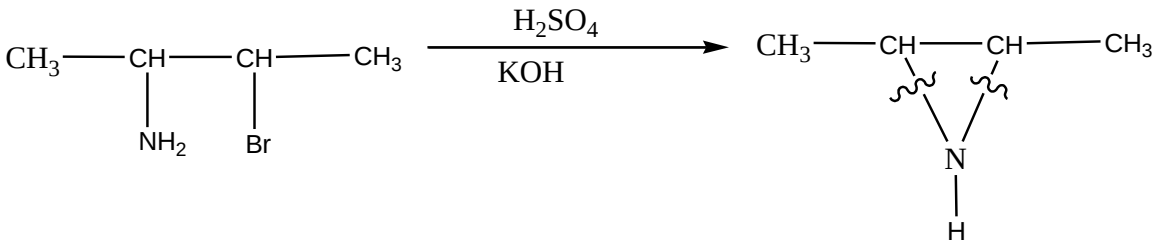


Example 5-Three membered heterocycle with nitrogen hetero atom is prepared from the α-halo amines for which retrosynthetic analysis as well as synthesis can be represented as:

RETROSYNTHETIC ANALYSIS :



SYNTHESIS :



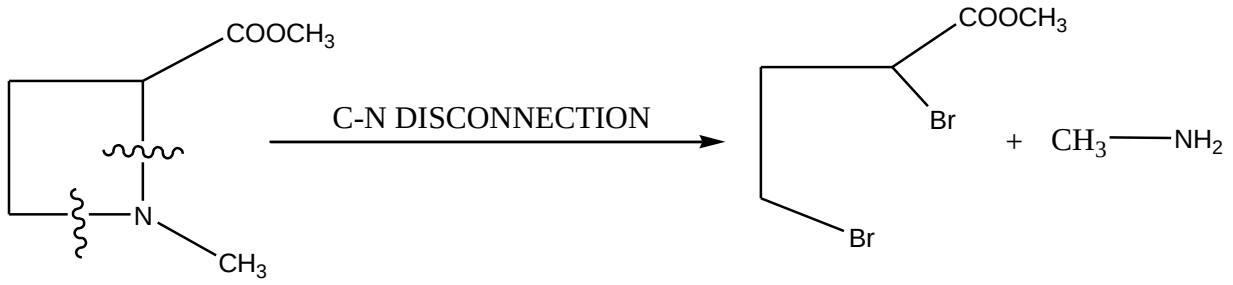
6.4.2 Synthesis of four membered saturated heterocycles:

Four membered ring syntheses is difficult due to kinetic as well as thermodynamic unfavourable nature of the four membered ring synthesis but under some specific condition four membered heterocycles can be synthesized with poor yield.

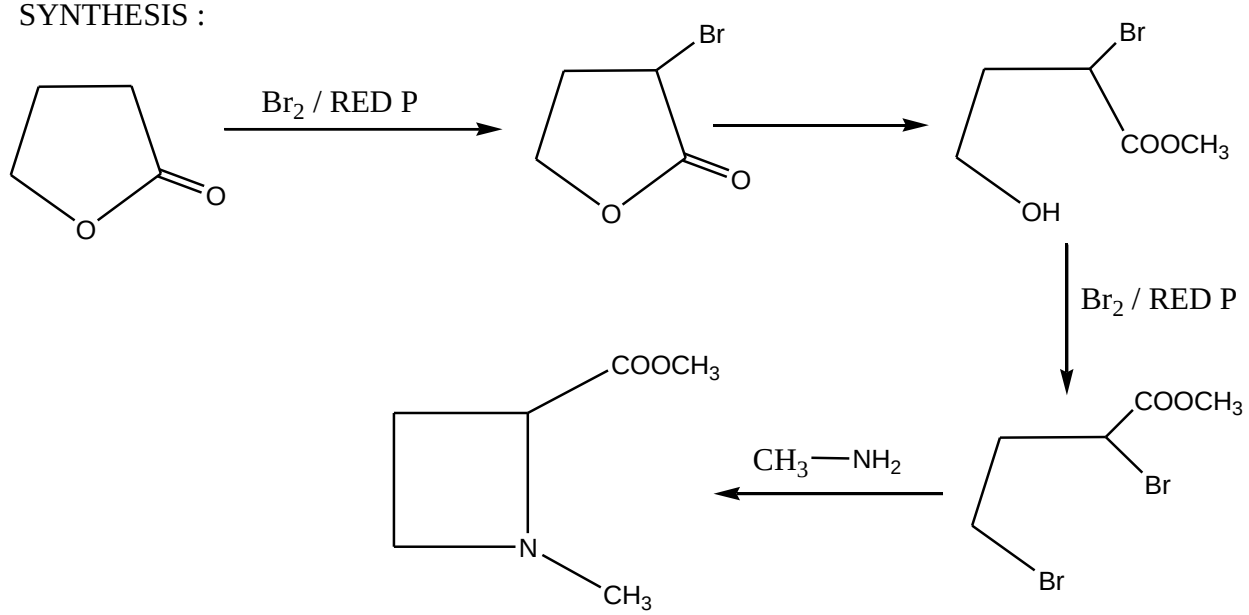
Some examples of four membered ring syntheses with their retrosynthetic analysis can be given as-

EXAMPLE 1-1,3dihalo compounds on reaction with anine give four membered rings with nitrogen hetero atom. Retrosynthetic analysis as well as synthesis to prepare thus heterocycle can be given as-

RETROSYNTHETIC ANALYSIS :

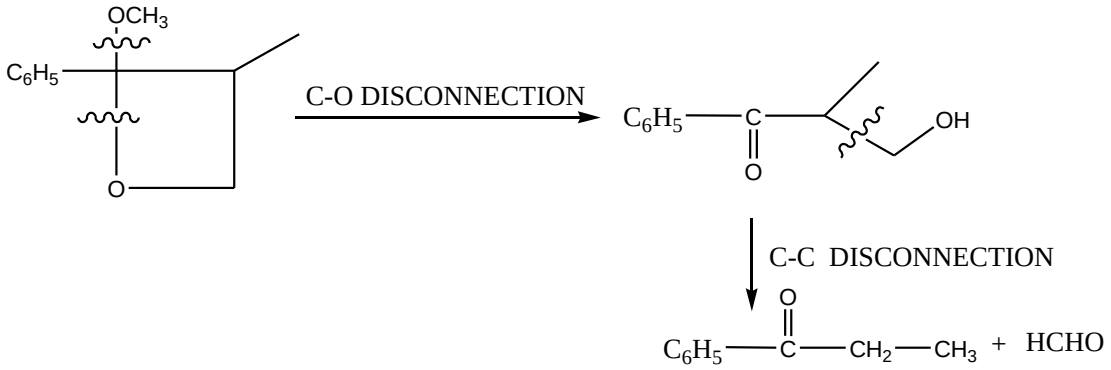


SYNTHESIS :

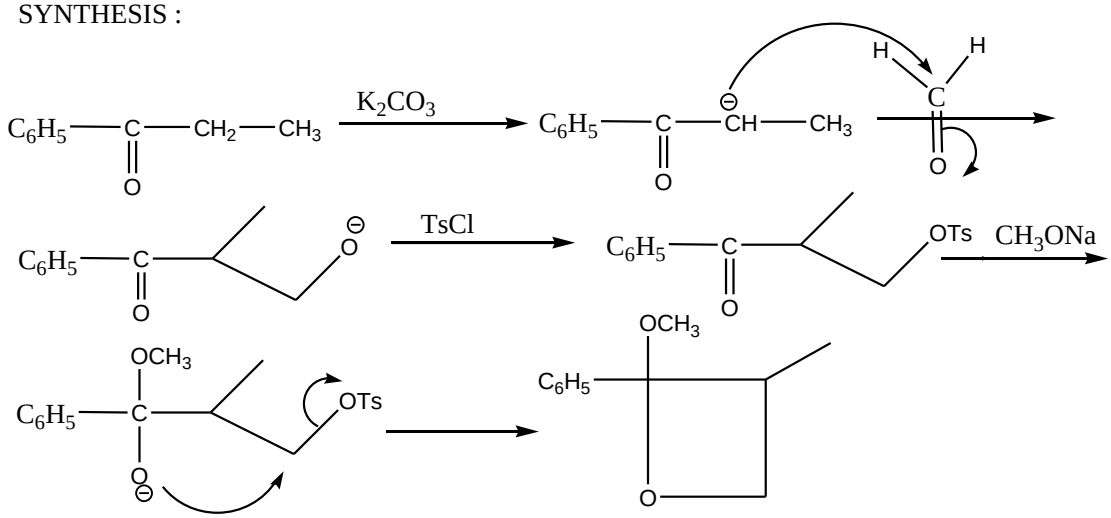


EXAMPLE 2- Four membered cyclic ether can be prepared by the reaction of α-hydrogen containing ketone with HCHO in the presence of base .For this process retrosynthetic analysis as well as synthesis can be represented as-

RETROSYNTHETIC ANALYSIS :



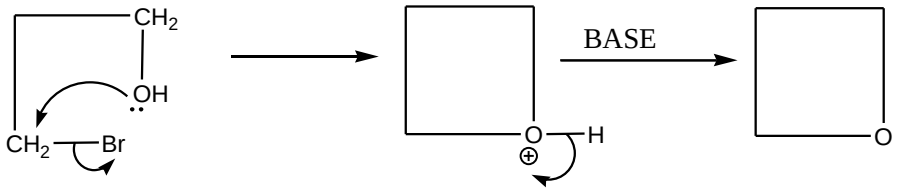
SYNTHESIS :



EXAMPLE 3- Four membered saturated heterocycle with oxygen hetero atom is prepared by the intramolecular reaction of halo hydrine for which retrosynthetic analysis and synthesis can be represented as-

RETROSYNTHETIC ANALYSIS :

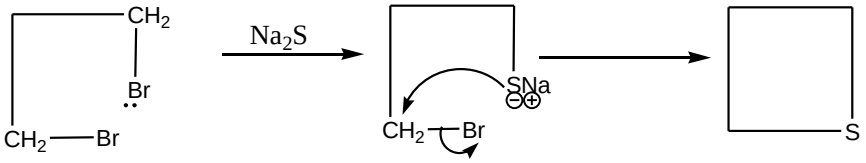
SYNTHESIS :



EXAMPLE 4- Four membered saturated heterocycle with sulphur hetero atom is prepared by the reaction of 1, 3 dihalideswithsodiumsulphide for which retrosynthetic analysis and synthesis can be represented as-

RETROSYNTHETIC ANALYSIS :

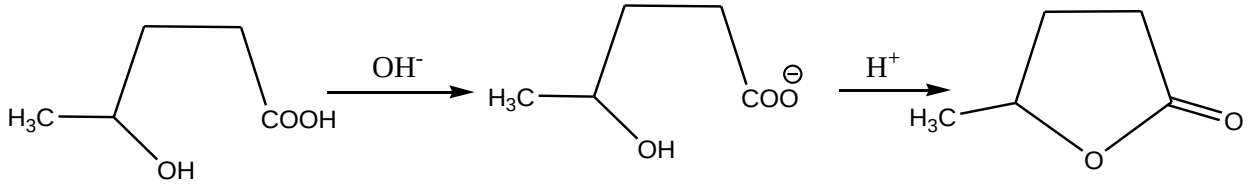
SYNTHESIS :



6.4.3 Synthesis of five membered saturated heterocycles:

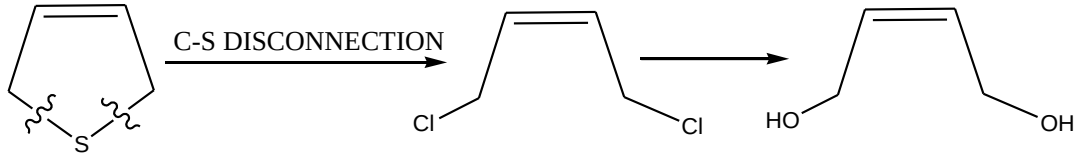
Five membered heterocycles are prepaired easily because synthesis of five membered ring are favoured kinetically as well as thermodynamically over the open chain structure .Some of the examples for the synthesis as well as retrosynthetic analysis of the five membered heterocycles can be five frepresented as –

EXAMPLE 1: γ-hydroxy acid being unstable but its anion being stable which on neutralization gives the γ-lactone, a five membered heterocycle.

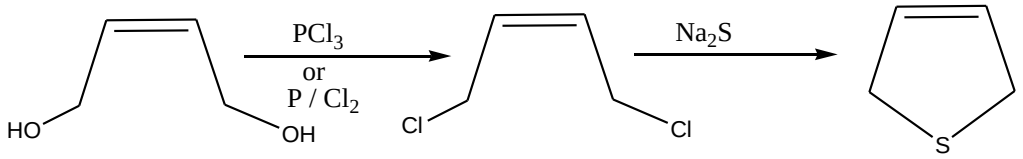


EXAMPLE 2-Cyclic sulphide can be obtained as a five membered heterocycle by treating the nucleophilic nature of the sulphur compound with the electrophilic nature of the carbon species. Retrosynthetic analysis as well as synthesis of this hetrocycle can be represented as-

RETROSYNTHETIC ANALYSIS :

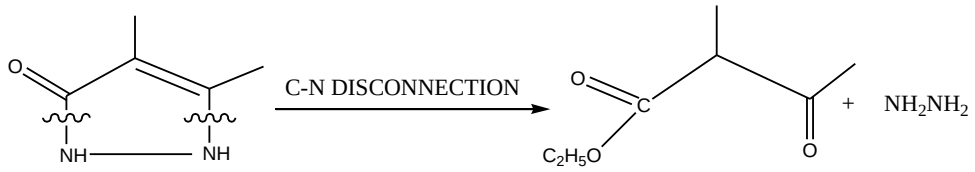


SYNTHESIS :

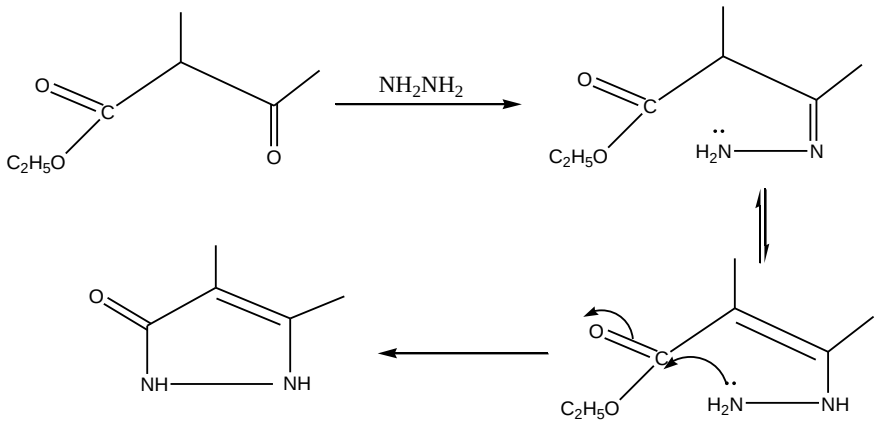


EXAMPLE 3- Two heteroatom containing five membered heterocyclic compounds can be obtained by treating the keto ester with the reagent like hydrazine. Retrosynthetic analysis as well as synthesis of this heterocycle can be represented as.

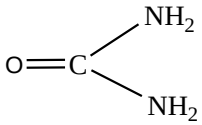
RETROSYNTHETIC ANALYSIS :



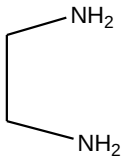
SYNTHESIS :



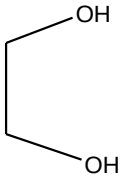
Some other two heteroatom containing reagents which can also be used in this type reaction are given below.



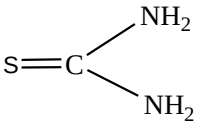
UREA



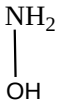
ETHYLENE DIAMINE



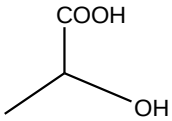
ETHYLENE GLYCOL



THIO UREA



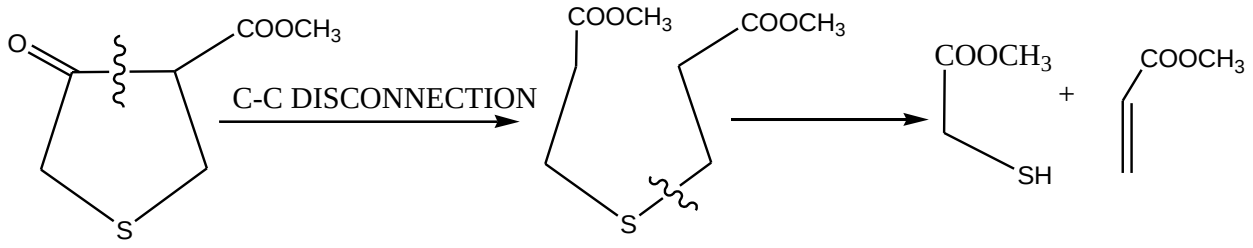
HYDROXYL AMINE



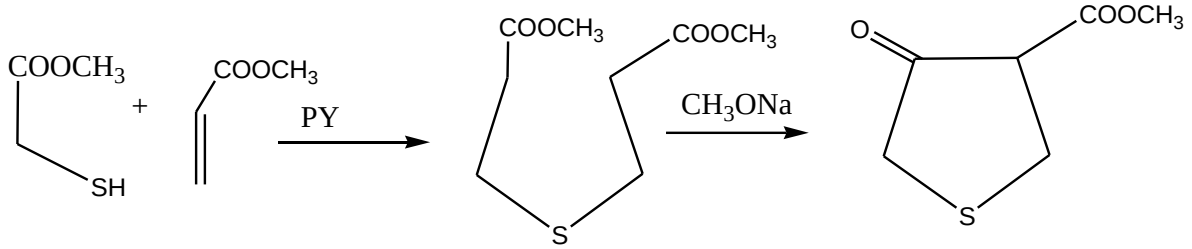
LACTIC ACID

In some cases c-c disconnection being preferred over the c-z (z =heteroatom) disconnection that can be observed through the following example.

RETROSYNTHETIC ANALYSIS :

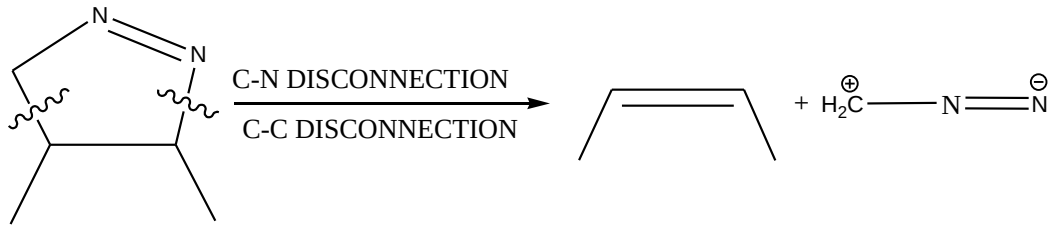


SYNTHESIS :

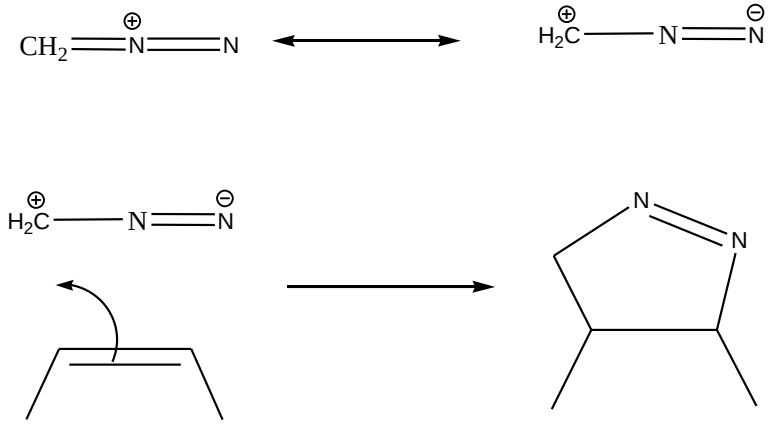


EXAMPLE 4: Five membered heterocycle can be prepared by the 1,3-dipolar cycloaddition reaction for which retrosynthetic analysis as well as synthesis can be represented as.

RETROSYNTHETIC ANALYSIS :



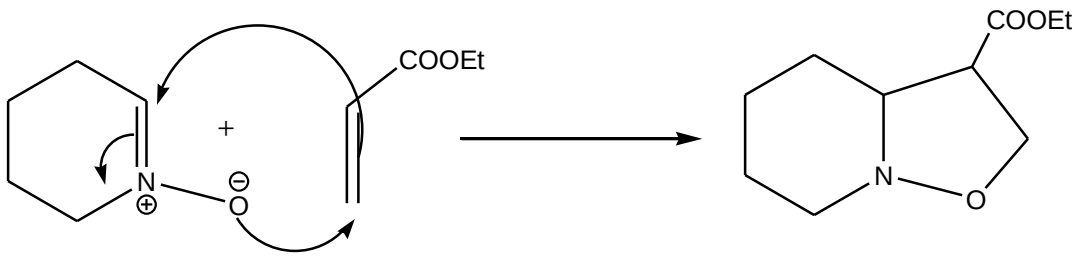
SYNTHESIS :



Other example of the 1,3 dipolar addition to prepare five membered heterocycle can be given as –

RETROSYNTHETIC ANALYSIS :

SYNTHESIS :

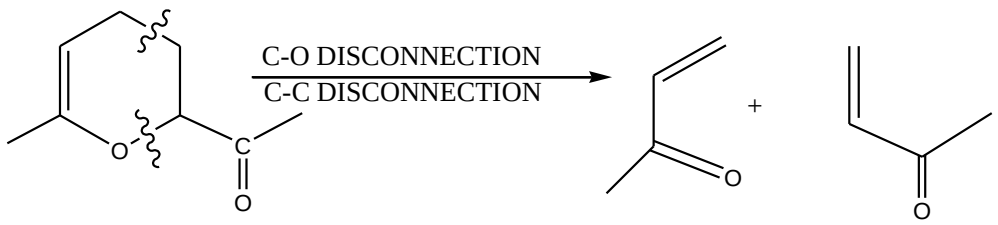


6.4.4 Synthesis of six membered saturated hetreocycles:

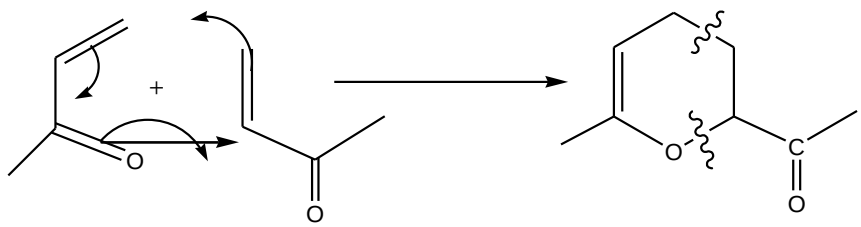
As like to the five membered heterocycle synthesis ,the six membered heterocycle synthesis can be easily possible due to kinetic as well as thermodynamically favoured nature for six membered ring synthesis .some of the six membered ring synthesis with their retrosynthetic analysis can be given as .

EXAMPLE 1- Diel's-Alder reaction –When vinyl ketone undergo dimerization reaction by [4+2]cycloaddition reaction then there ccur the formation of oxygen containing six membered heterocycle for which retrosynthetic analysis as well as synthesis can be given as-

RETROSYNTHETIC ANALYSIS :

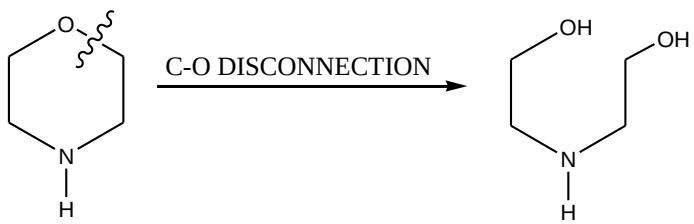


SYNTHESIS :

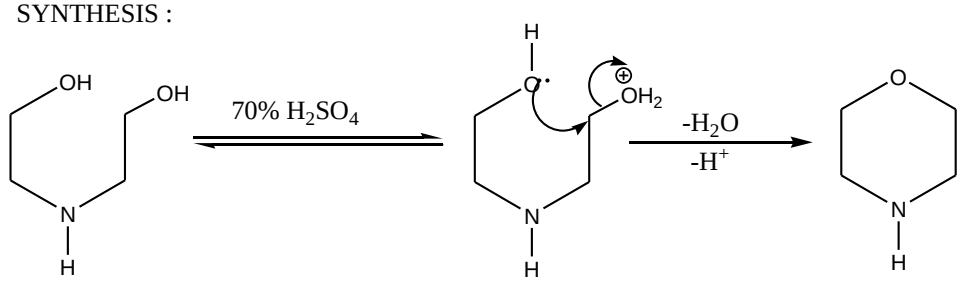


EXAMPLE 2: Diethanolamine give morpholine a six membered heterocycle on treating with 70% H_2SO_4 for this retrosynthetic analysis as well as synthesis can be given as-

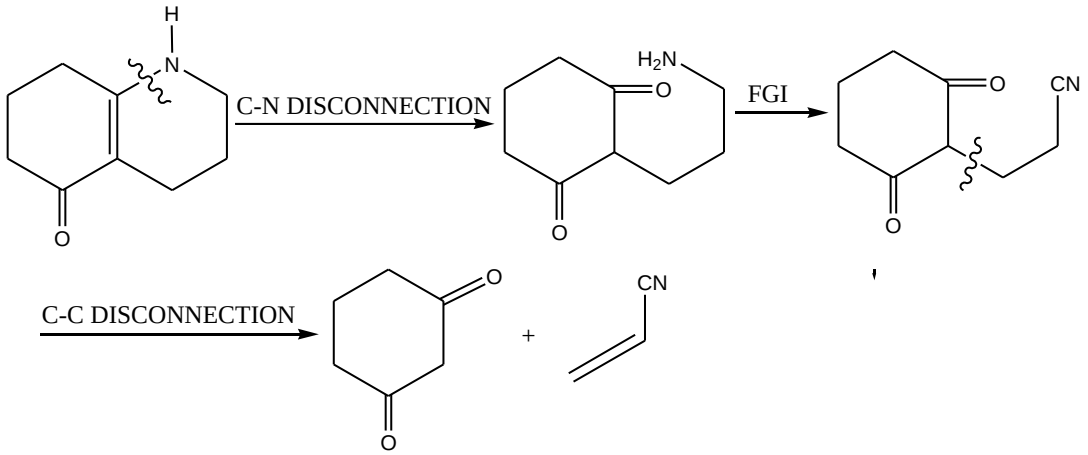
RETROSYNTHETIC ANALYSIS :



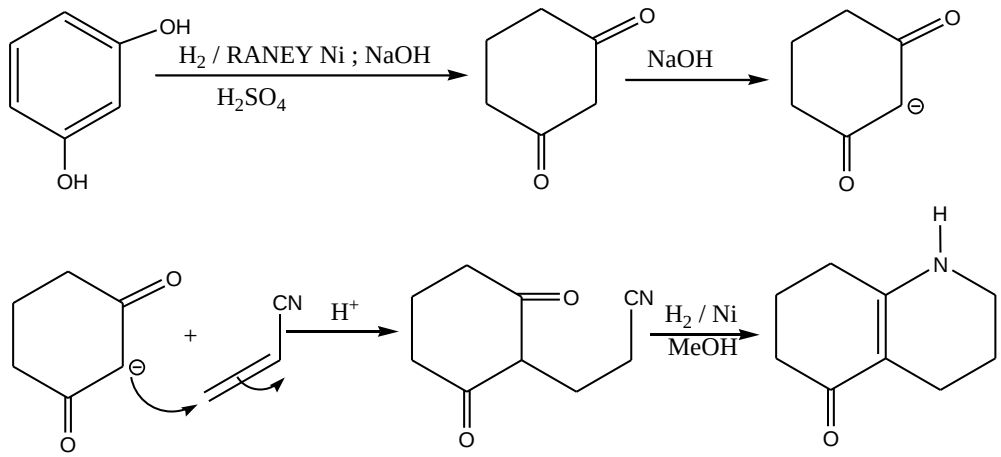
SYNTHESIS :



EXAMPLE 3: Synthesis as well as retrosynthetic analysis of nitrogen containing six membered heterocycle can be represented as-

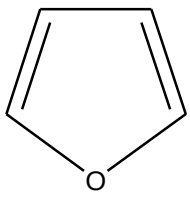


SYNTHESIS :

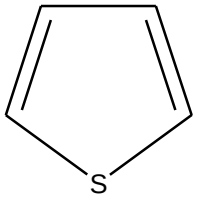


6.5 AROMATIC HETEROCYCLE IN ORGANIC SYNTHESIS:

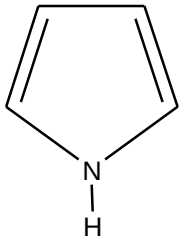
All those heterocyclic compounds which having the aromatic character i.e. which can follow the Huckel's rule of aromaticity are known as aromatic heterocycles .They exhibit highly stable nature due to the high resonance energy associated with these compounds .



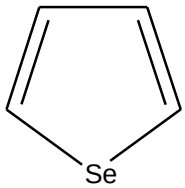
FURAN



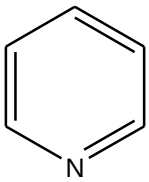
THIOPHENE



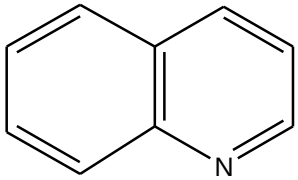
PYRROLE



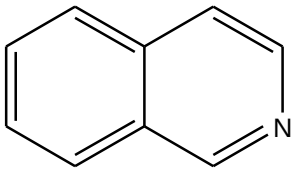
SELENOPHENE



PYRIDINE



QUINOLINE

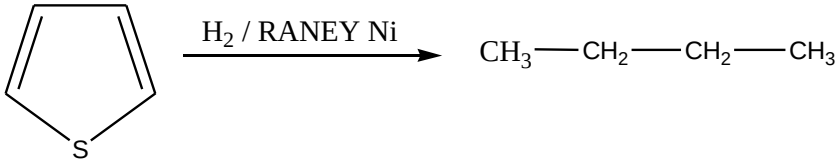


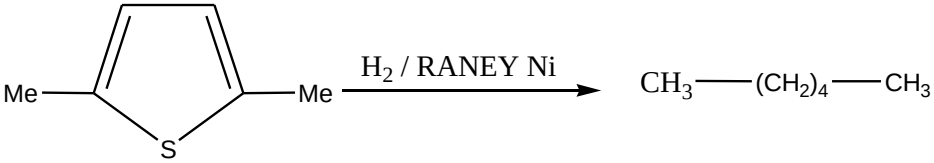
ISOQUINOLINE

Aromatic heterocyclic compounds are used as the source of some non aromatic compounds like alkane, alkene, cycloalkane, aldehydes, ketones, carboxylic acids, amono acids as well as some non heterocyclic aromatic compounds. Synthesis of various compounds by using aromatic heterocyclic compounds can be given as.

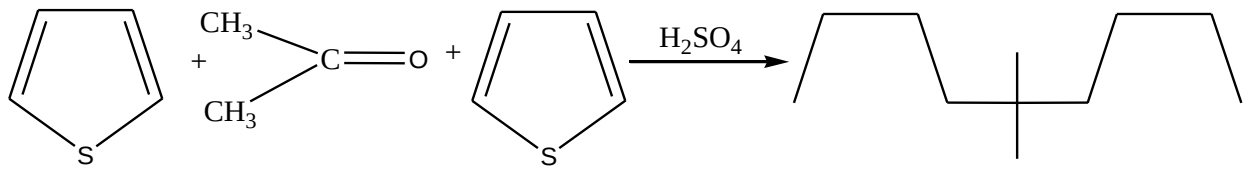
6.5.1 Synthesis of alkane and cycloalkane:

Thiophene and differently substituted thiophene on reductive desulphurization give rise to the various alkanes.

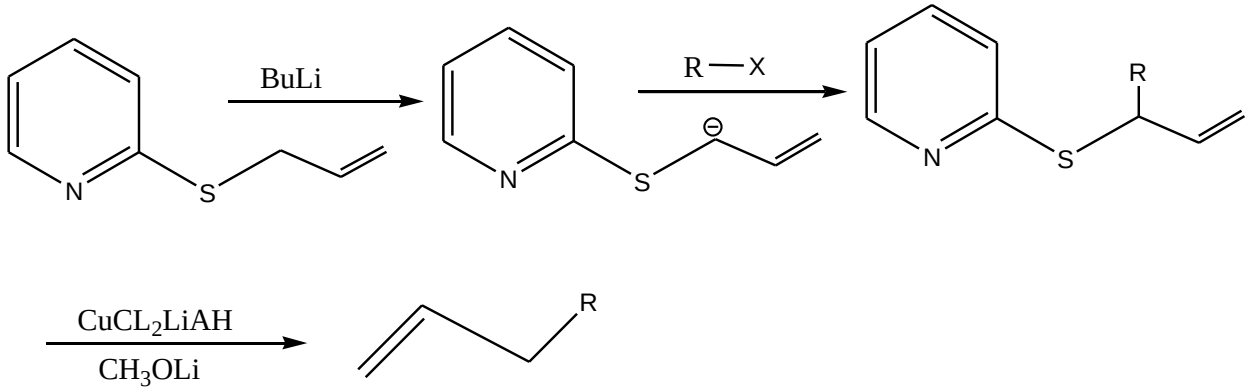




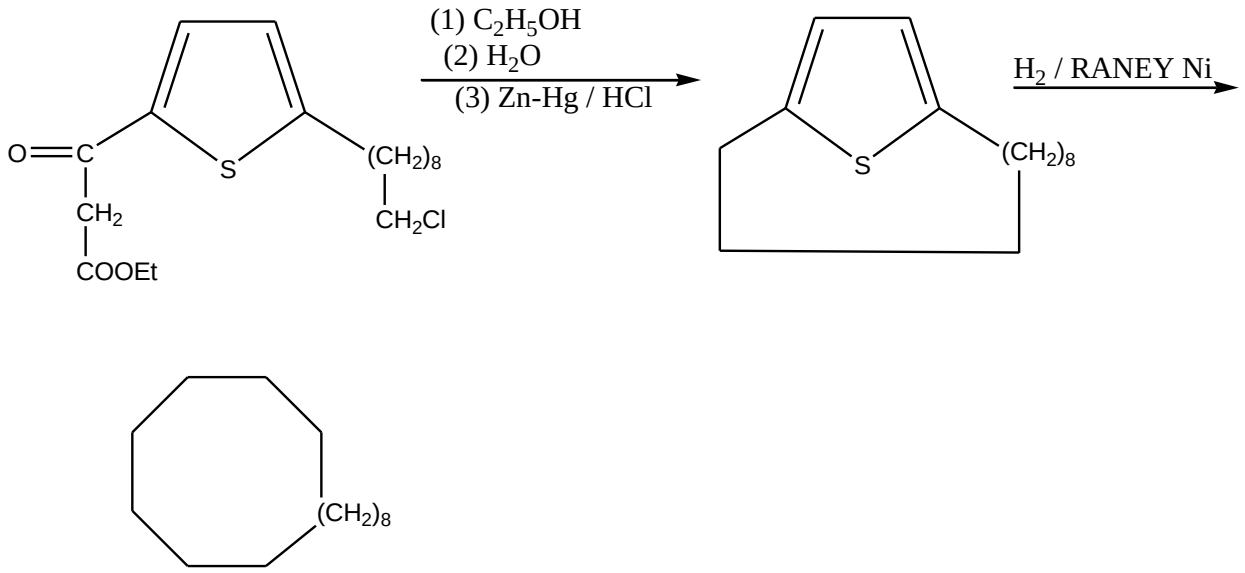
Thiophene on condensation with carbonyl compounds in the presence of H_2SO_4 gives the extended chain hydrocarbons.



2-(alkyl thio) pyridine on reaction with the strong base like butyl lithium gives the carbanion which on reaction with alkyl halide and $CuCl_2LiAH$ gives hydrocarbon.

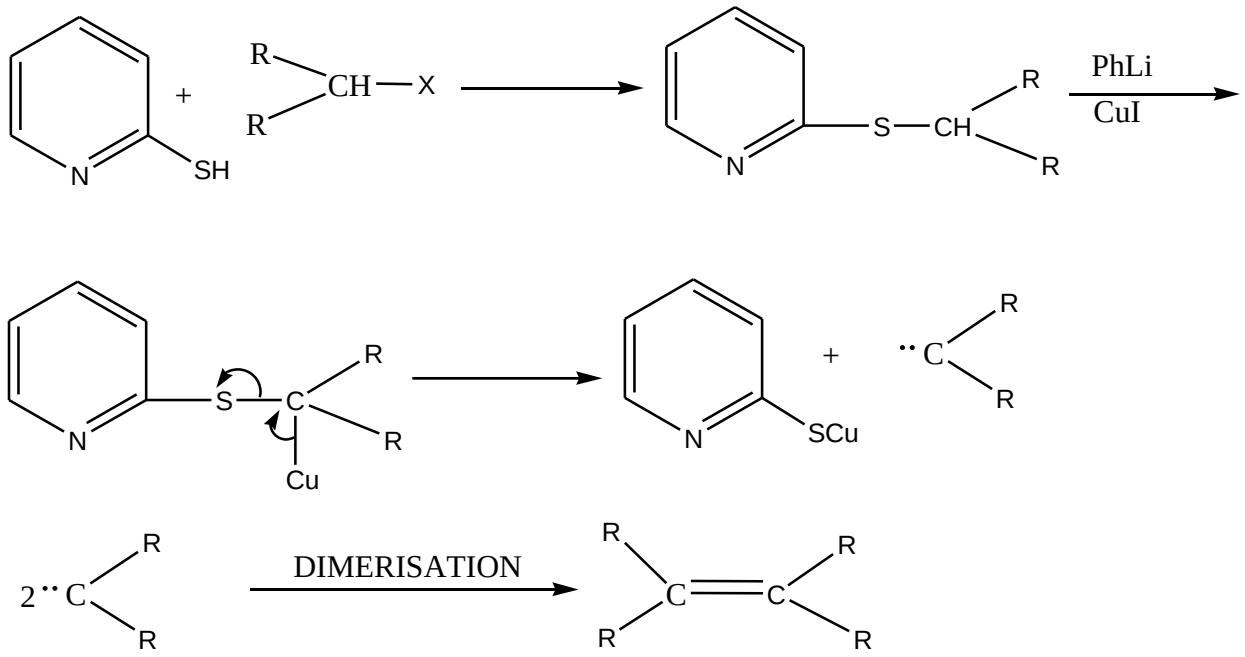


Intramolecular alkylation in active hydrogen containing substituted thiophene followed bydesulphurisation gives the cycloalkane in good yield.

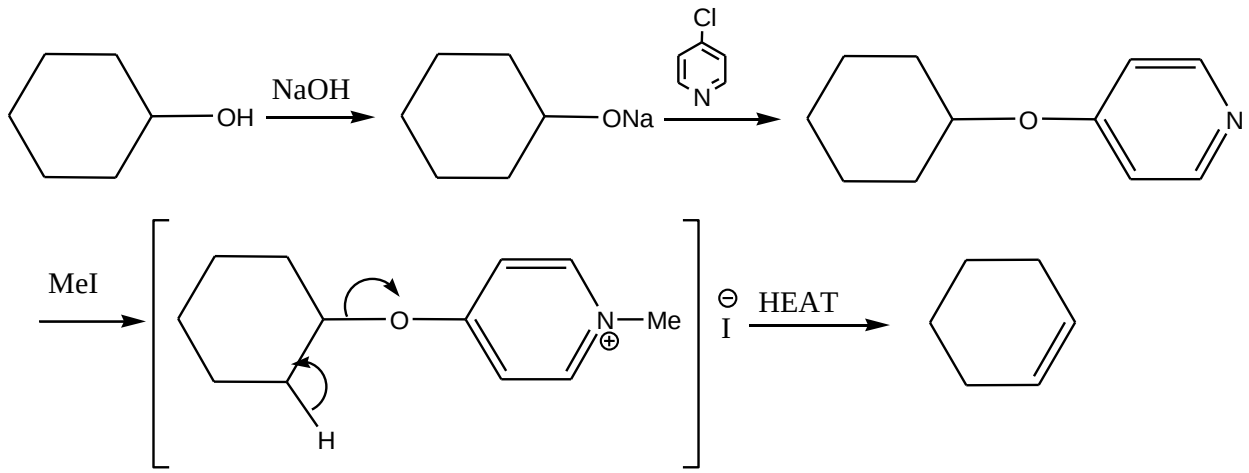


6.5.2 Synthesis of alkene and cycloalkene: By using the aromatic heterocycles as the precursor variety of substituted alkenes as well as cycloalkenes can be synthesized. Synthesis of some alkenes as well as cycloalkane by using aromatic heterocycles can be represented as.

(1) 2-mercapto pyridine can generate the alkene by using the following reaction sequence.

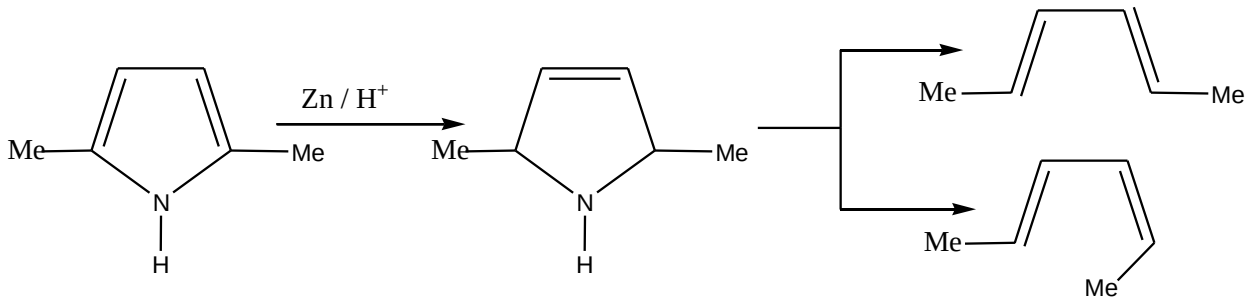


(2) When the six membered aromatic heterocycle like pyridine or substituted pyridine is treated with the alkoxide derivatives of alcohol then there occur the formation of ether which can give the alkene on treating with methyl iodide and heating.

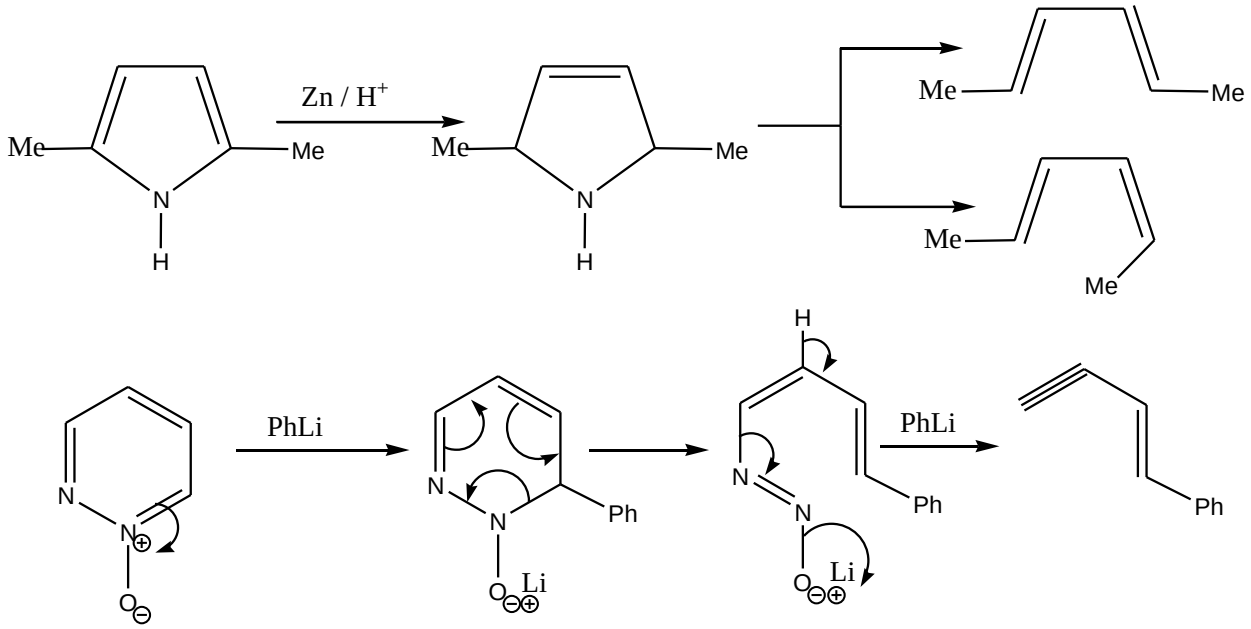


Cycloalkanol gives the good yield in this reaction

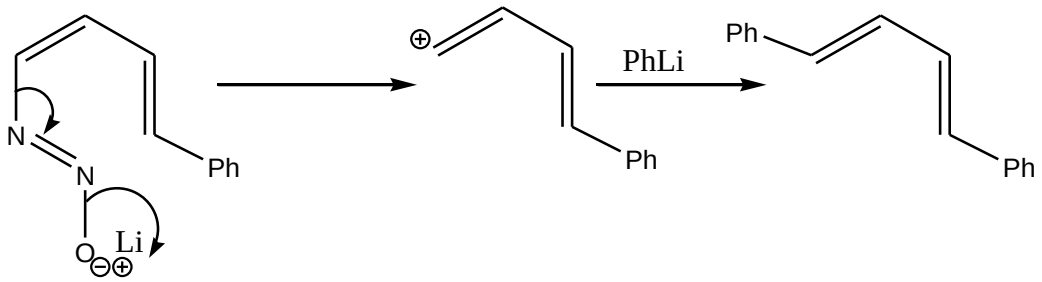
(3) 3-pyrroline obtained from the partial reduction of 2,5dialkylpyrrole on reaction with the nitro hydroxyl amine gives the diene.



(4) When the pyridazine N-oxides are treated with the phenyl lithium then there occur the formations of alkenyne that can be represented as.

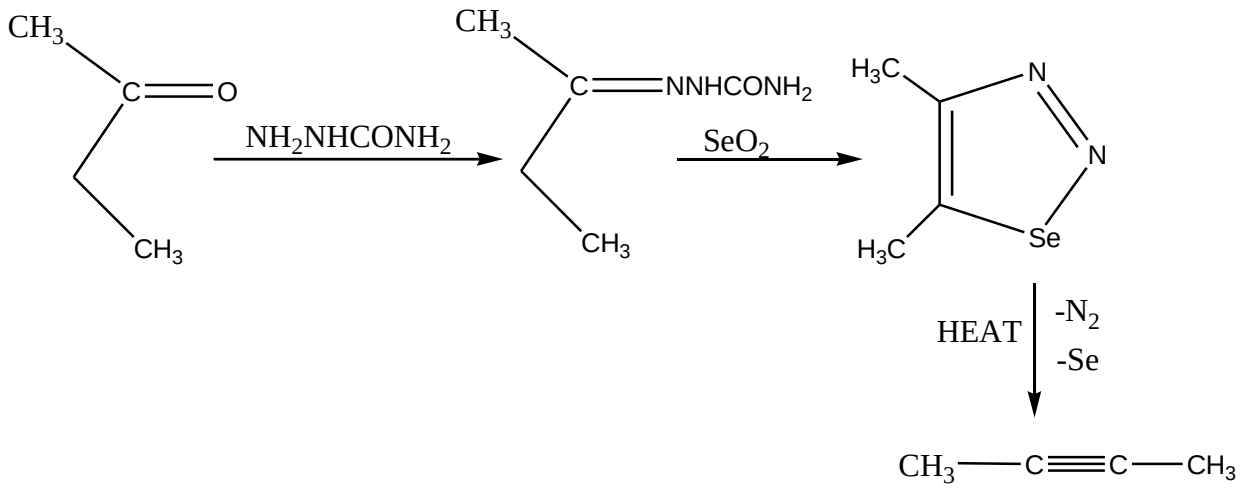


Some timeformation vinyl cation can also be possible which can generate the conjugated diene.

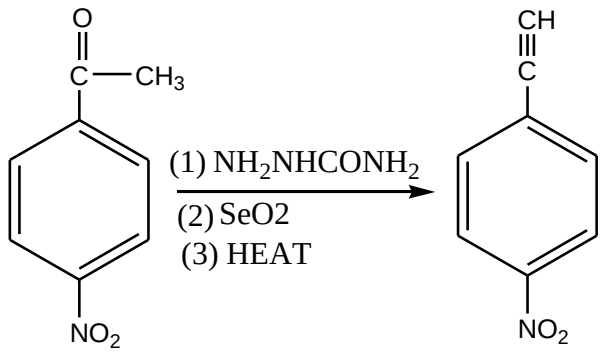


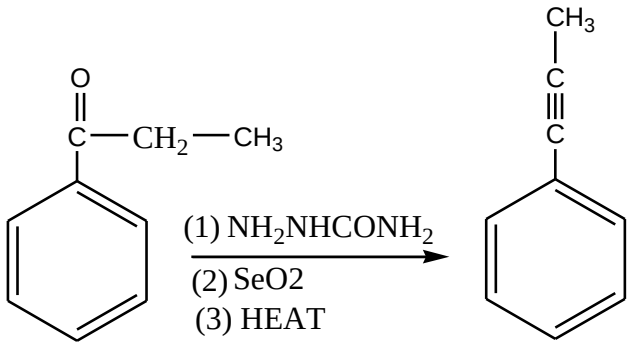
6.5.3 Synthesis of alkynes:

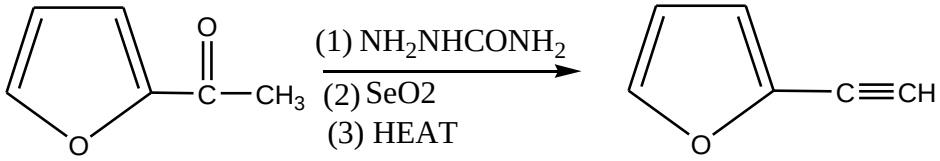
When the selenadizoleheterocycle obtained from the reaction of carbonyl compounds with semicarbazide and SeO_2 undergo heating then alkyne formation can occur.

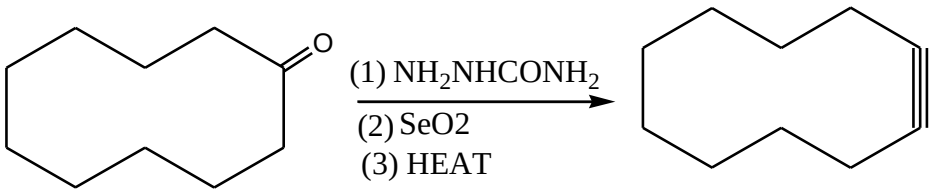


Some other examples to generate the alkynes from selenadizoleheterocycle can be given as-





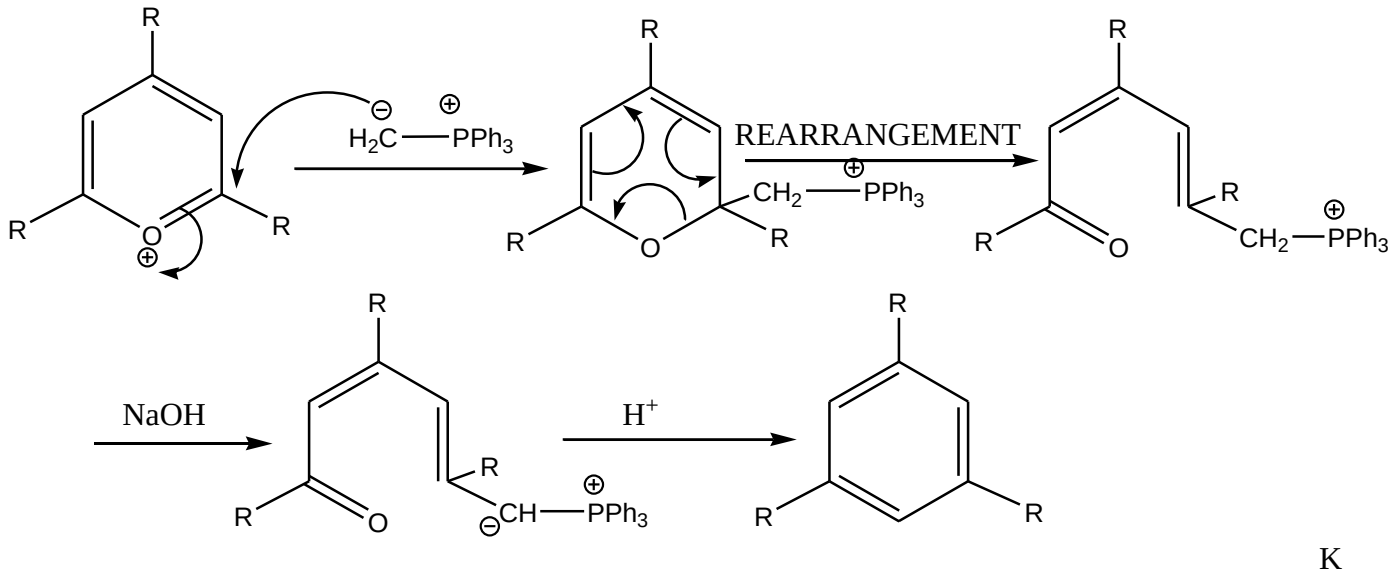




6.5.4 Synthesis of aromatic hydrocarbon:

Large number of the benzenoid compounds can be synthesized by treating the different type of the carbon nucleophile with the pyrilium salt by the successive ring opening and closer processes.

EXAMPLE I:



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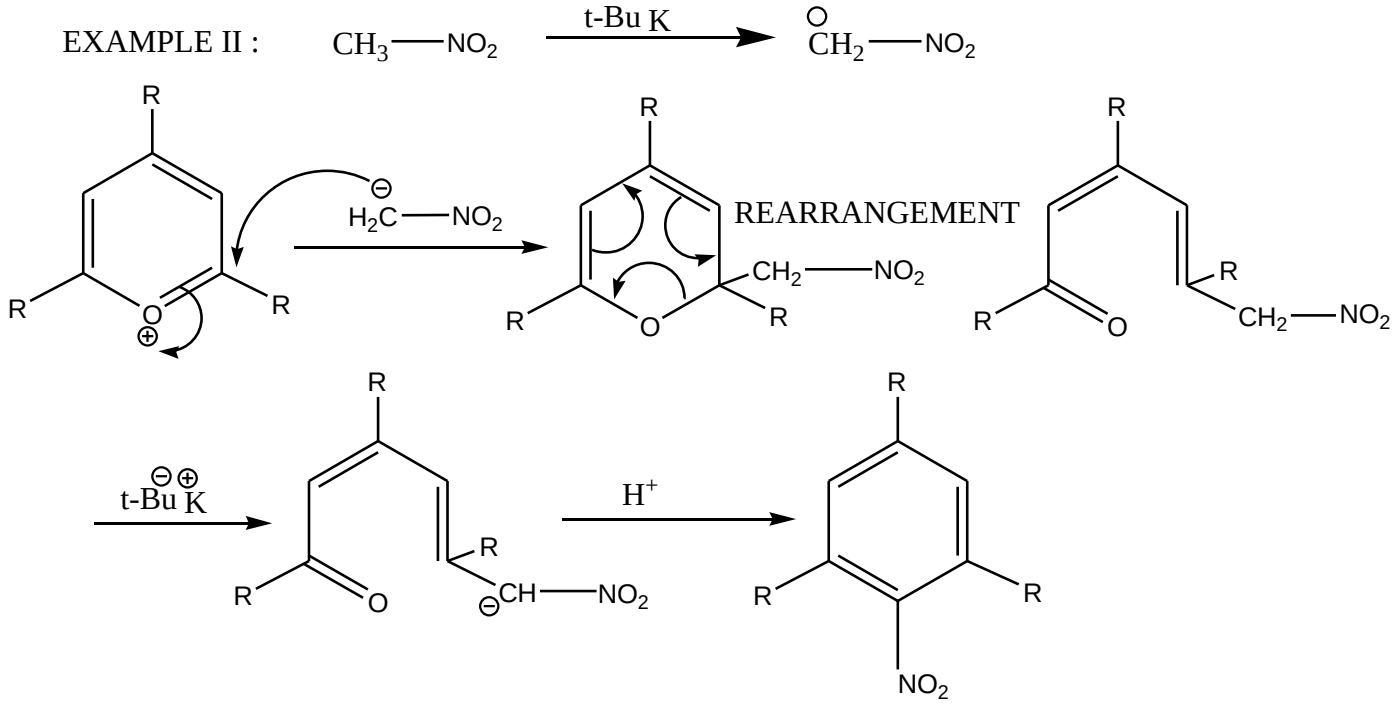
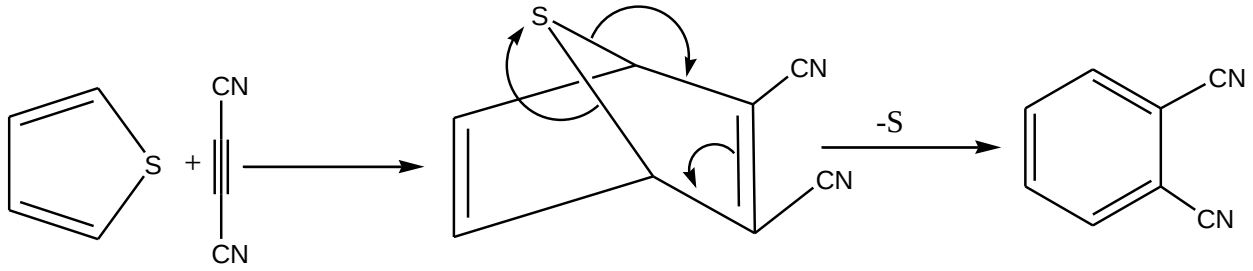
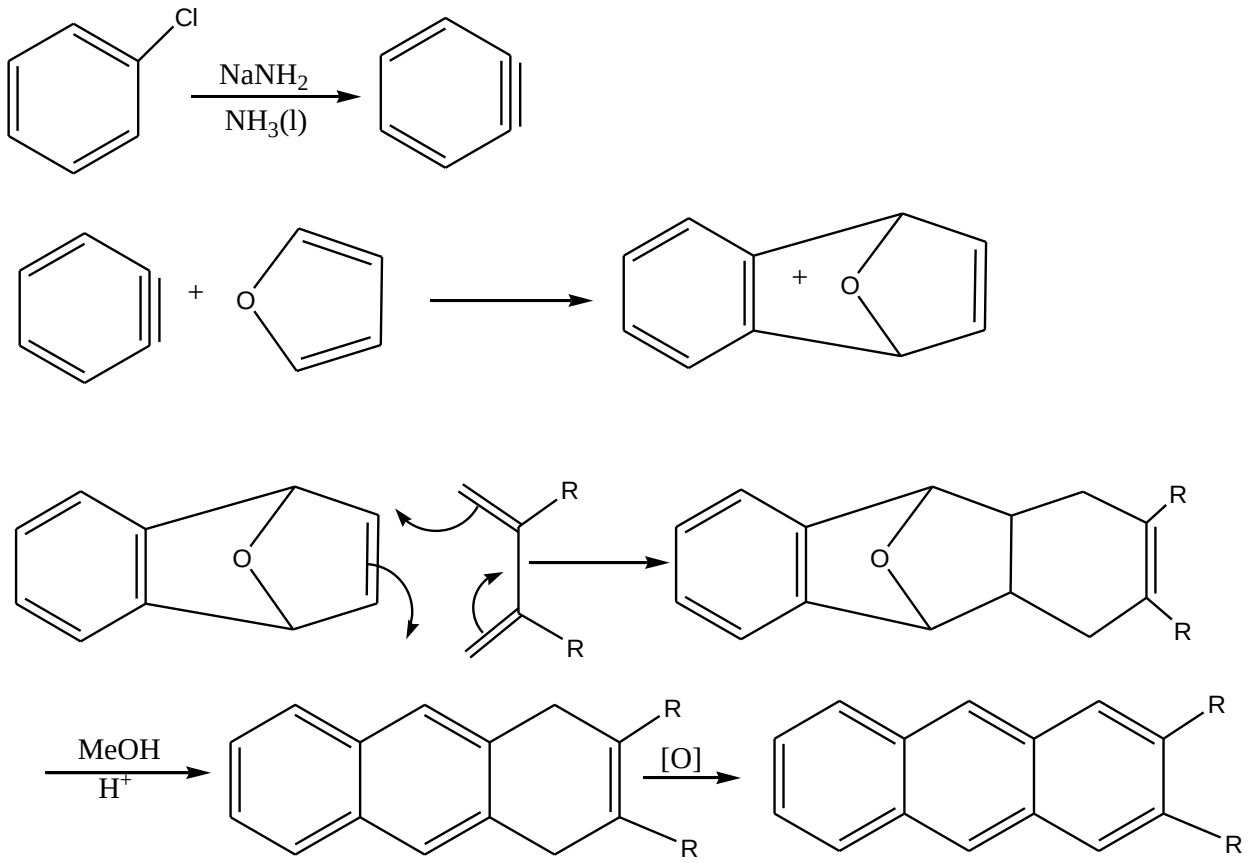
EXAMPLE II :



Thiophene an aromatic heterocycle gives the [4+2] cycloaddition with the substituted alkyne to give the benzenoid compounds.



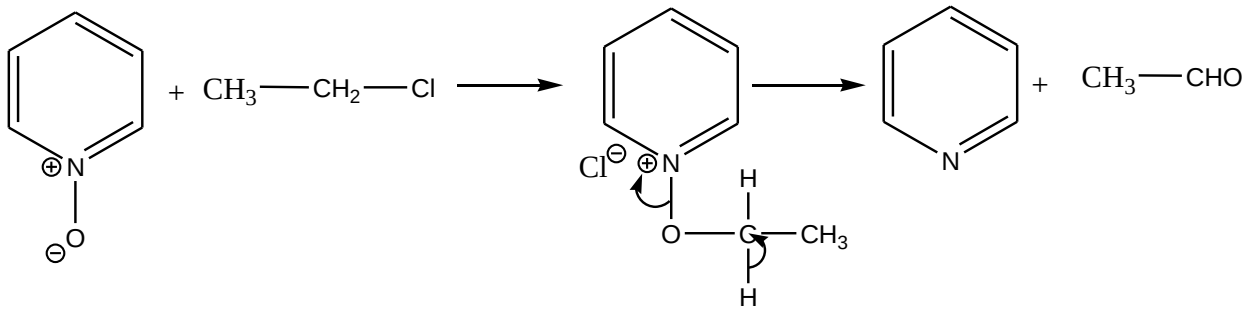
Anthracene or its derivatives can be prepaired from furan by [4+2] cycloaddition reaction



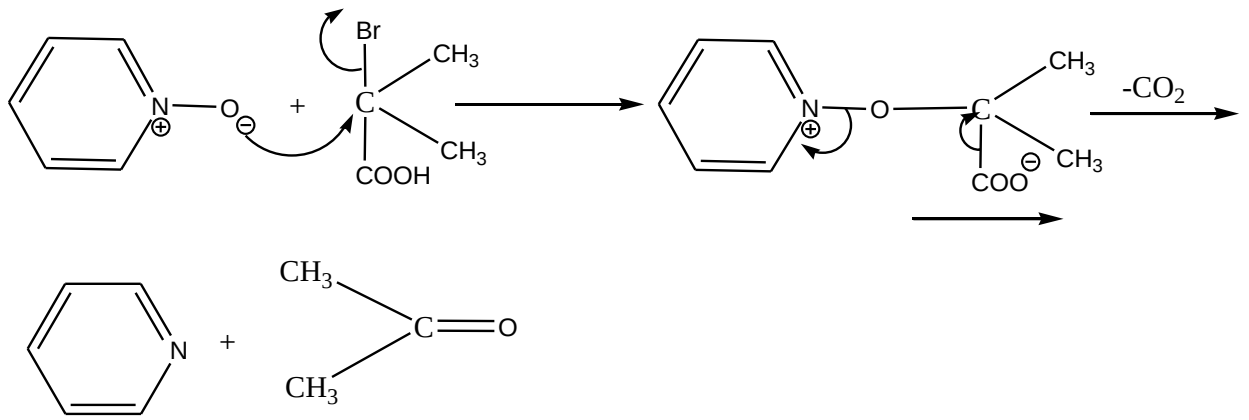
6.5.5 Synthesis of carbonyl compounds:

By using the aromatic heterocycles various type of the carbonyl compounds i.e. aldehyde and ketones can be synthesized, some of them can be represented as-

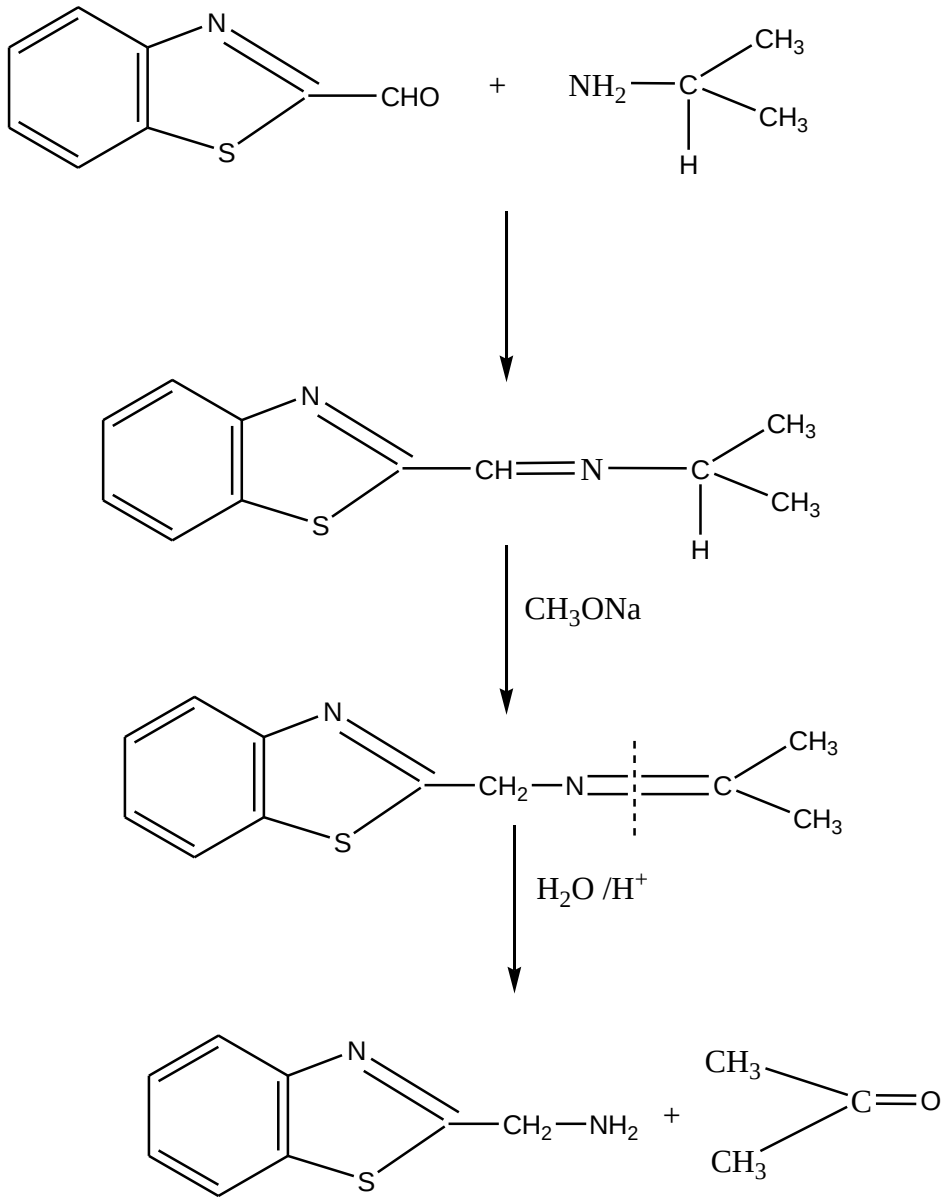
(1)Alkyl halide containing CH_2X, CHX type of the skeleton can generate the aldehyde or ketone on treating with pyridine or pyridine N-oxide.



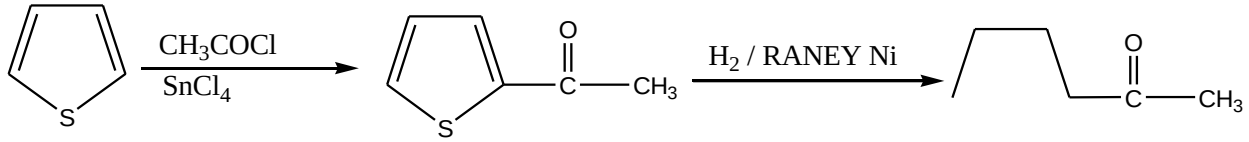
(2) Halo acid containing halogen at α position can also generate the carbonyl compound on reacting with the pyridine N-oxide.



(3) When the primary amine react with the aromatic heterocycles like benzothiazole then there occur the formation of an imine which on hydrolysis gives the carbonyl compounds.

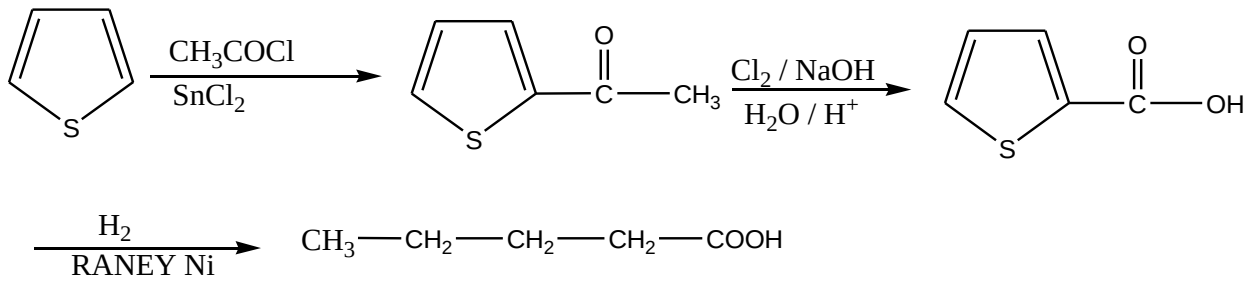


(4) Acylation product of thiophene on reductive desulphurization gives the ketones.

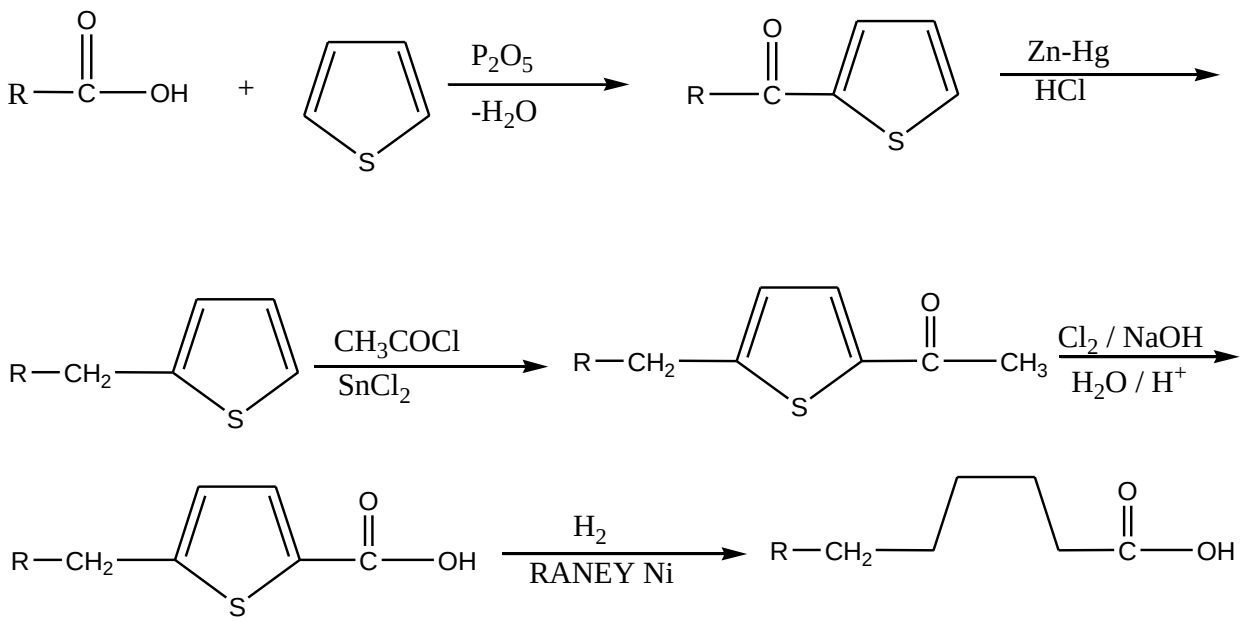


6.5.6 Synthesis of carboxylic acids and its derivatives: With the help of aromatic heterocycles we can generate the large no of carboxylic acids. Some of the methods to generate the carboxylic acids by using aromatic heterocycles can be given as-

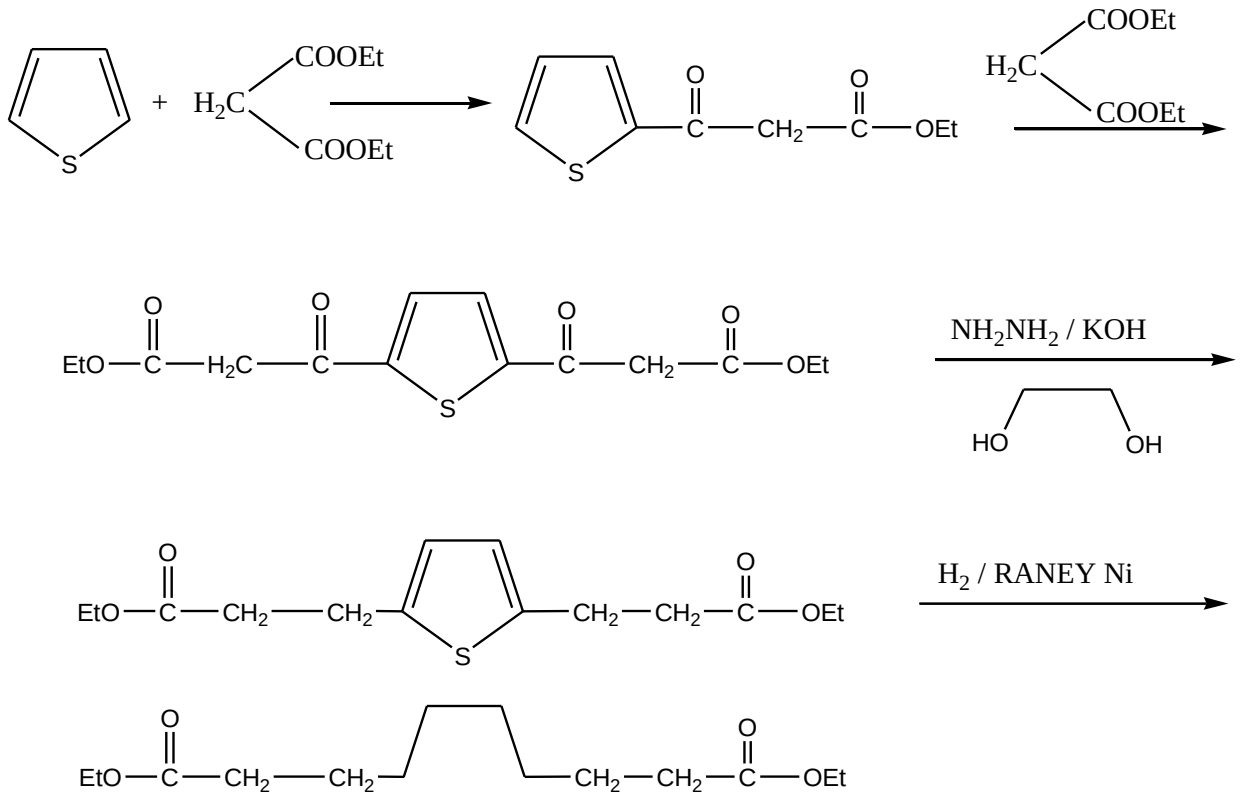
(1)When thiophene undergoes Friedel-Craft acylation and Haloform reaction then there occurs the formation of thiophene 2-carboxylic acid which on desulphurization gives carboxylic acids.



If we have to construct the long hydrocarbon chain containing carboxylic acids by using the thiophene as an aromatic heterocycle then following reaction sequence can be applied.

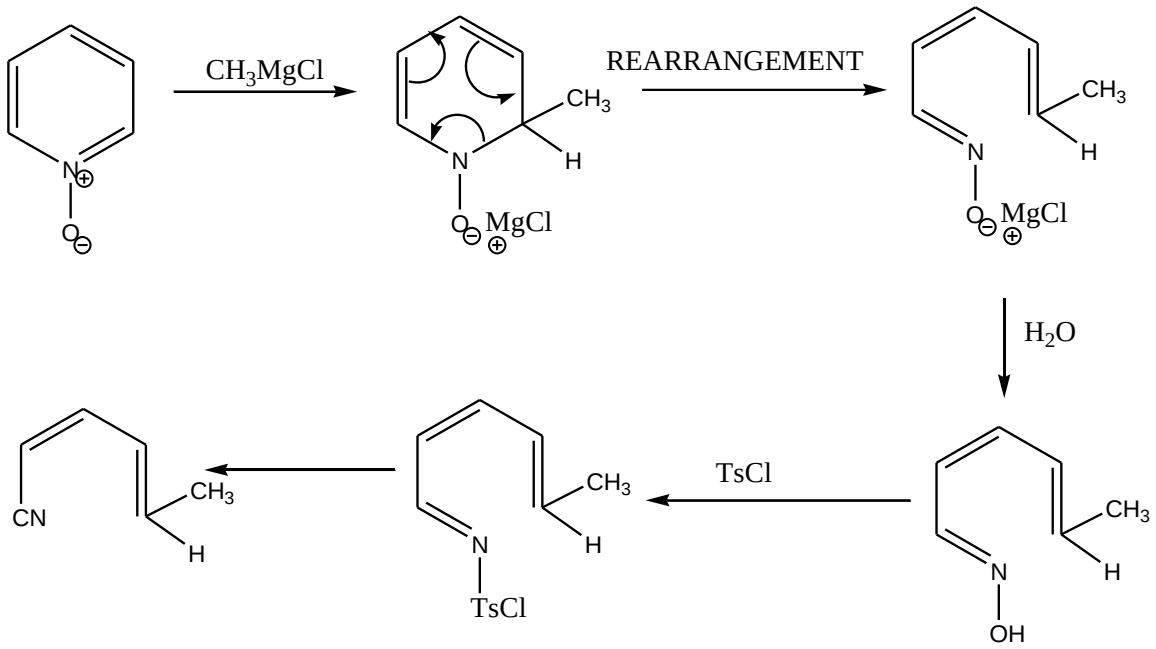


(2) When diesters are treated with the aromatic heterocycle like thiophene then formation of higher esters can occur that can be represented as –



6.5.7 Synthesis of nitriles:

Unsaturated nitriles can be prepaired by treating the pyridine N-oxide with Grignard reagent that can be represented as



6.6 TERMINAL QUESTIONS

Question 1- Explain why synthesis of 3 membered rings is kinetically favoured but thermodynamically not favoured?

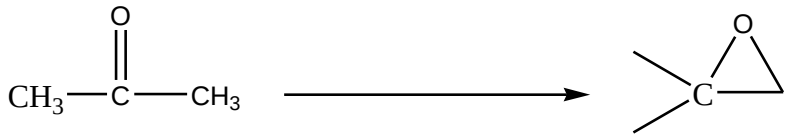
Question 2- Explain why synthesis of 4 membered rings is not favoured by both thermodynamic factor as well as kinetic factor?

Question 3- How the carboxylic acids can be synthesized by using thiophene?

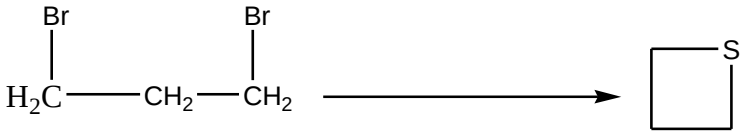
Question 4- Define the pyramidal inversion and ring inversion in piperidine?

Question 5- How will you done the following conversions

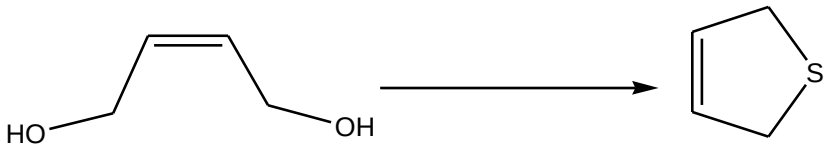
(a)



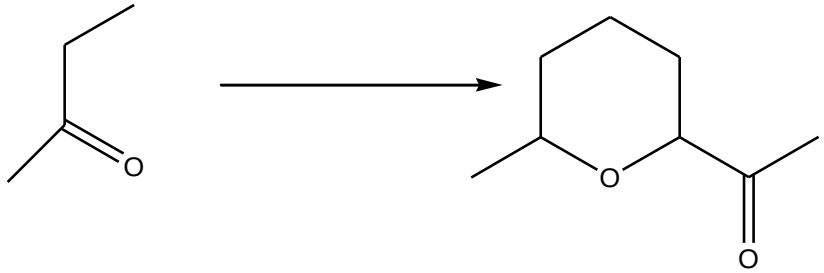
(b)



(c)



(d)



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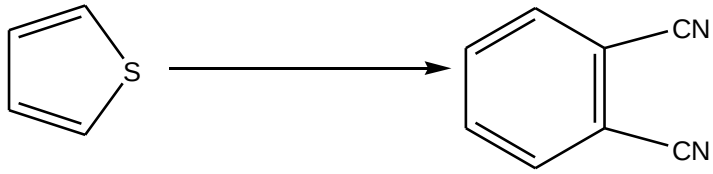
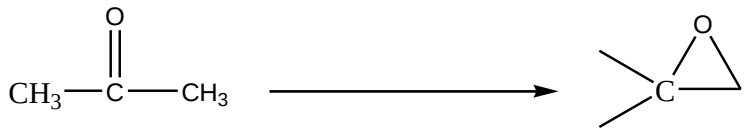


(a)



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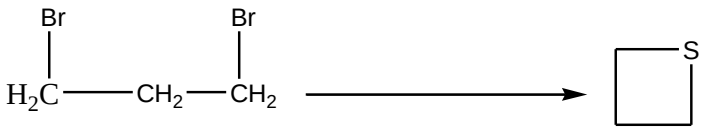

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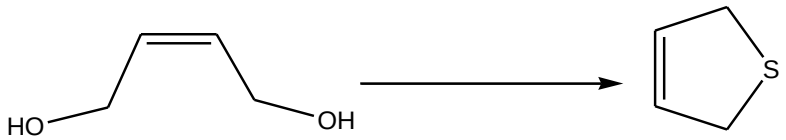

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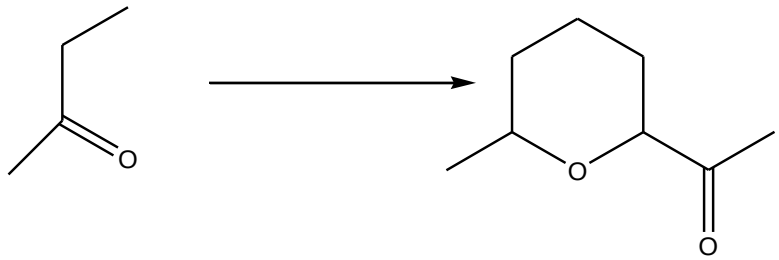

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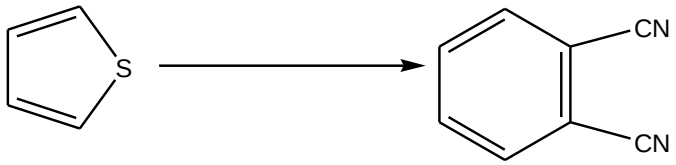

6.7 BOOKS SUGGESTED

1. Advanced Organic Chemistry, Reaction and Synthesis, Francis A.Carey and Richard J.Sundberg.
2. Modern Methods of Organic Synthesis, William Carruthers and Iain Coldham.
3. Organic Synthesis, Jagdamba Singh, L.D.S.Yadav.
4. Organic Synthesis, the Disconnection Approach, Stuart Warren.
5. Organic Reaction and Their Mechanism, P.S.Kalsi.
6. Principles of Organic Synthesis, R.O.C.Norman and J.M.Coxon.
7. Advanced Organic Chemistry, Reaction Mechanism and Structure, Jerry March, John Wiley.
8. Heterocyclic Compounds, Jain, Soni, Sahay and Pimplapuri.