Wolff-Kischner Reduction ⇒
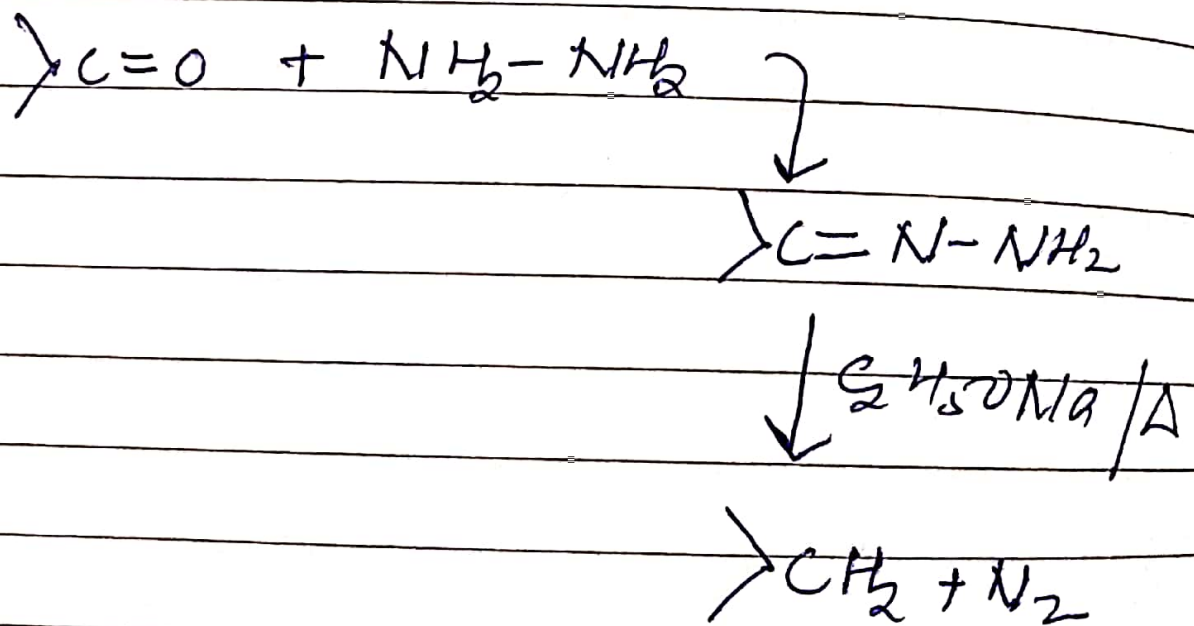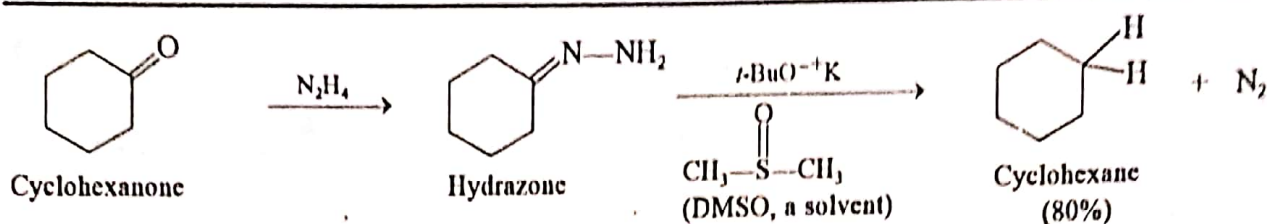
The reduction of Hydrazones, Semicarbazones or azines of aldehydes and ketones in alkaline medium (C_2H_5ONa or NaOH) at high temp. to give hydrocarbons and Nitrogen is known as wolff-Kishner reduction.

$$>C=O + NH_2-NH_2$$

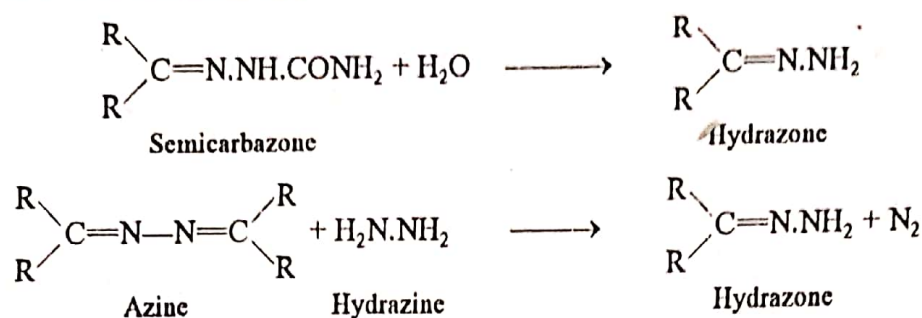$$>C=N-NH_2$$

$$\downarrow C_2H_5ONa/\Delta$$

$$>CH_2 + N_2$$

- by using this reduction, Ketone and aldehyde can be reduced conveniently to hydrocarbons by this method.

Mech -

Cyclohexanone N_2H_4 Hydrazone $t\text{-BuO}^{-+}K$ CH_3-S-CH_3 (DMSO, a solvent)   Cyclohexane (80%) $+ N_2$

It is to be noted that during the reduction of semicarbazones or azines the derivatives are first converted to hydrazones, e.g.,

$$\underset{R'}{\overset{R}{>}}C=N.NH.CONH_2 + H_2O \longrightarrow \underset{R'}{\overset{R}{>}}C=N.NH_2$$

Semicarbazone   Hydrazone

$$\underset{R'}{\overset{R}{>}}C=N-N=C\underset{R}{\overset{R}{<}} + H_2N.NH_2 \longrightarrow \underset{R'}{\overset{R}{>}}C=N.NH_2 + N_2$$

Azine   Hydrazine   Hydrazone

Mechanism

The mechanism of the Wolff-Kishner reduction follows a sequence of logical steps. The formation of the hydrazone proceeds by the same mechanism as the formation of an imine. The reduction step, with elimination of nitrogen, occurs in a strongly basic solution. The mechanism involves proton removal from nitrogen, with reprotonation on carbon. Another deprotonation sets up the intermediate for loss of nitrogen to form a carbanion. This carbanion is quickly reprotonated to give the product.
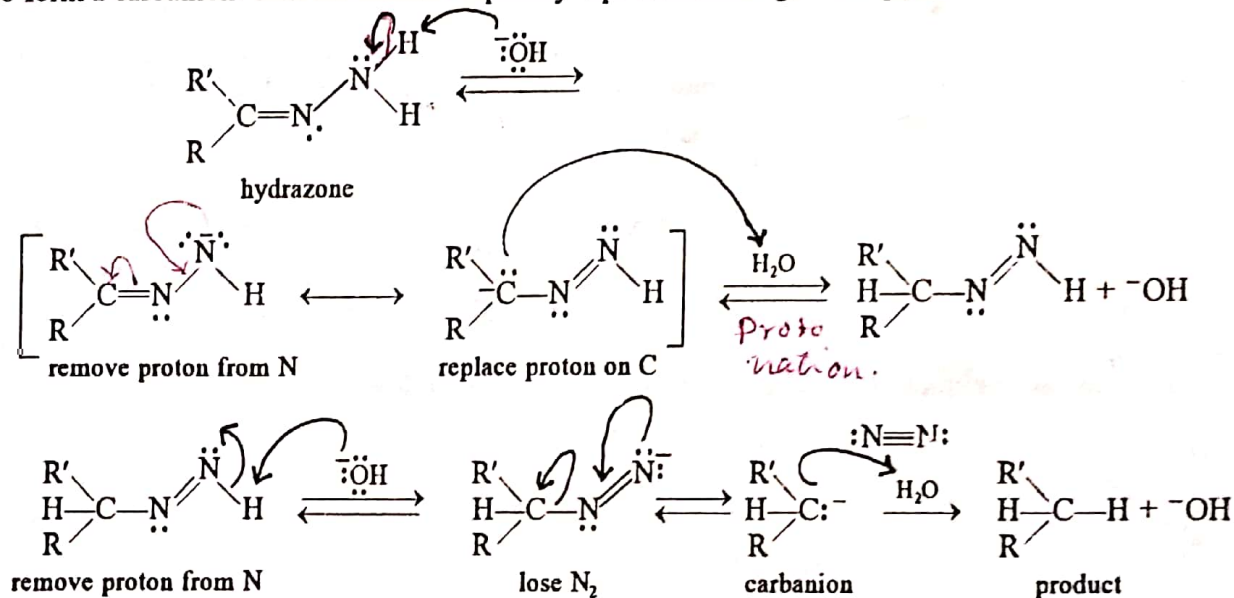

The method is specific for the reduction of carbonyl groups only, for other functional groups in the substrate remain unaffected. The method is, however, not suitable for α, β-unsaturated ketones.

Applications

Wolff-Kishner reduction is used mainly for the reduction of carbonyl group ($>C=O$) to methylene ($>CH_2$) during the synthesis of many natural products. This method unlike Clemmensen reduction is applicable for the reduction of high molecular weight and acid-sensitive compounds.

(a) *Reduction of camphor to camphane :*

| Camphor | | | Camphane |

$$\text{Camphor} \xrightarrow{H_2N.NH_2} \xrightarrow{C_2H_5ONa} \text{Camphane}$$
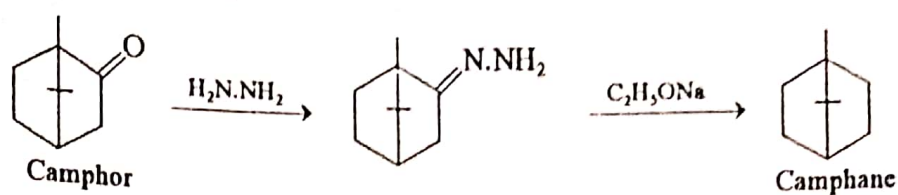
(b) *Elucidating the structure of oestrone :* When oestrone methyl ether is subjected to Wolff-Kishner reduction followed by selenium dehydrogenation, it yields a compound, 7-methoxy-1, 2-cyclopentenophenanthrene, of known structure.
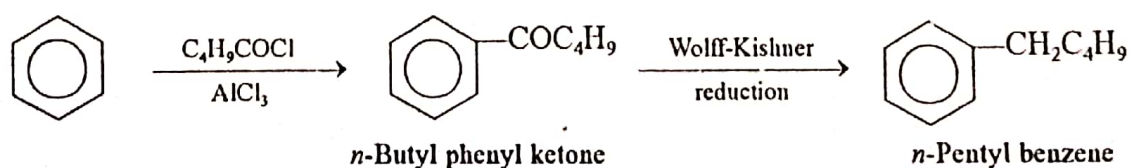

Oestrone methyl ether

$$\xrightarrow[\text{reduction}]{\text{Wolff-Kishner}}$$

$$\xrightarrow{Se, \Delta}$$

7-Methoxy-1 : 2-cyclopentan-phenanthrene
(I)
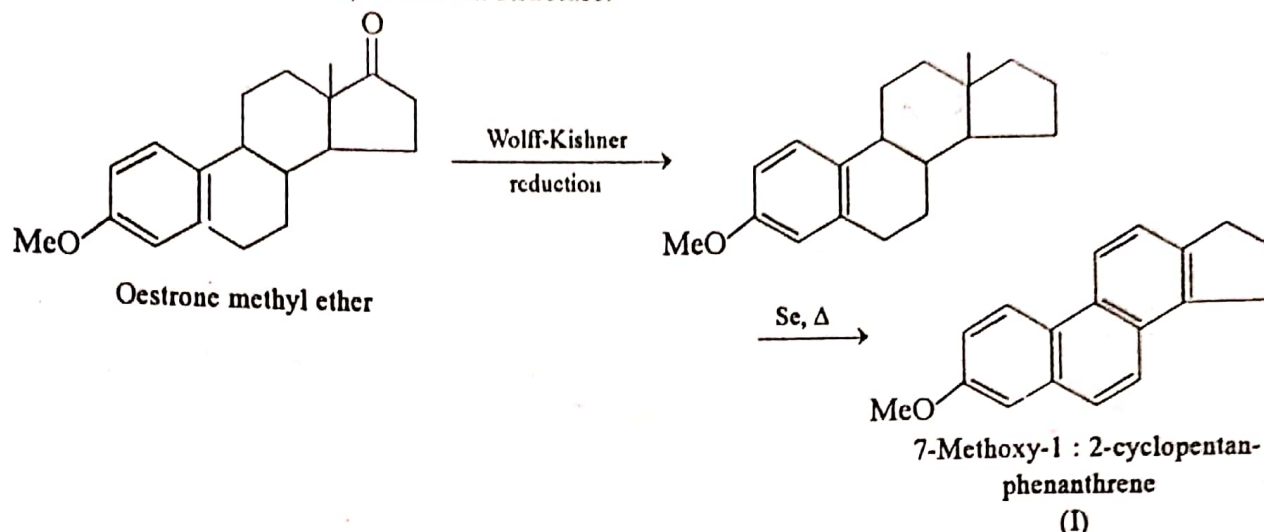
The known structure of degarded product, I clearly reveals the carbon skeleton of oestrone. Further, it also ascertains the position of the phenolic group in oestrone.

(c) *Reduction of high molecular weight compounds :* This reaction has been successfully used for the reduction of high molecular weight compounds such as cholesterol.
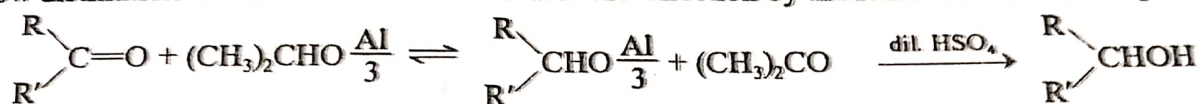

$$\xrightarrow[\text{reduction}]{\text{Wolff-Kishner}}$$

24-Ketocholesterol

Cholesterol
(I)
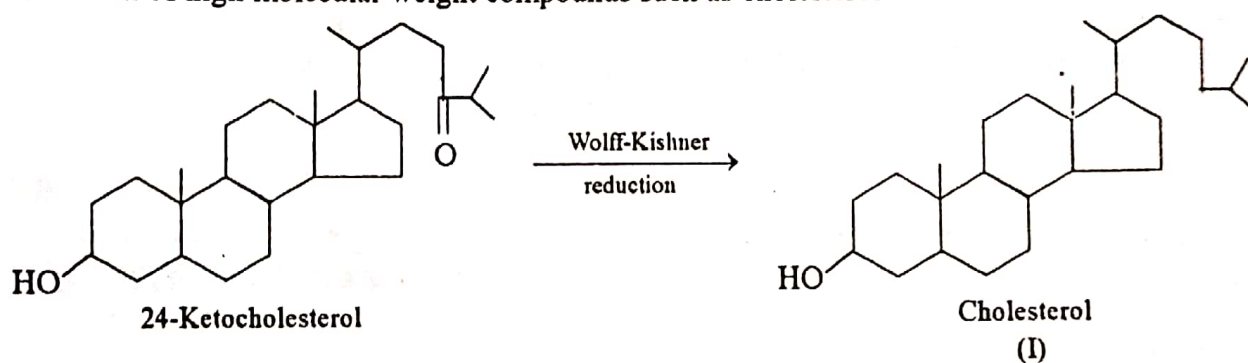
(d) *Introduction of long straight-chain alkyl groups in aromatic rings :* By using Friedel-Crafts alkylation, it is not possible to introduce a straight chain alkyl group longer than ethyl group into an aromatic ring because of rearrangement of the alkyl group. However, this has been achieved by acylation followed by reduction.
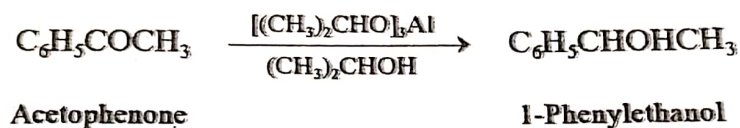

$$\xrightarrow[AlCl_3]{C_4H_9COCl} \qquad -COC_4H_9 \xrightarrow[\text{reduction}]{\text{Wolff-Kishner}} \qquad -CH_2C_4H_9$$

n-Butyl phenyl ketone

n-Pentyl benzene

Meerwein-Ponndorf-Verley Reduction

Introduction

In this method the compounds having carbonyl group, such as aldehydes and ketones, get reduced to corresponding alcohols. It is brought about by heating the carbonyl compound with aluminium isopropoxide, $[(CH_3)_2CHO]_3Al$ or $[(CH_3)_2CHO.Al/3]$ in isopropanol. $(CH_3)_2CHOH$, solution. During the reaction the isopropoxide is oxidised to acetone, which is continuously removed from the reaction mixture by slow distillation. The reaction shifts in the forward direction by the removal of acetone by distillation.

$$\begin{array}{c} R \\ \diagdown \\ C{=}O \\ \diagup \\ R' \end{array} + (CH_3)_2CHO\,\dfrac{Al}{3} \rightleftharpoons \begin{array}{c} R \\ \diagdown \\ CHO\,\dfrac{Al}{3} \\ \diagup \\ R' \end{array} + (CH_3)_2CO \xrightarrow{\ \text{dil. HSO}_4\ } \begin{array}{c} R \\ \diagdown \\ CHOH \\ \diagup \\ R' \end{array}$$

For example, acetophenone gets reduced to 1-phenylethanol and benzophenone into benzhydrol.

$$C_6H_5COCH_3 \xrightarrow[(CH_3)_2CHOH]{[(CH_3)_2CHO]_3Al} C_6H_5CHOHCH_3$$

$$\text{Acetophenone} \qquad\qquad\qquad\qquad \text{1-Phenylethanol}$$

$$C_6H_5COCH_3 \longrightarrow C_6H_5CHOHC_6H_5$$

Benzophenone   Benzhydrol

The reaction occurs under mild conditions. It is rapid and the yield is high because side reactions are negligible. The reaction has been specific for carbonyl group and other reducible groups such as olefinic bond, NO_2 etc. present in the substrate are not affected. If a compound is having two carbonyl groups, one may be protected by acetal formation and the other is then reduced by this reaction. Ketones having high enol content, e.g., β-diketones, β-ketoesters do not undergo this reaction.

The reaction is reversible. The reverse reaction is called **Oppenauer oxidation** which is used for the oxidation of alcohols using aluminium t-butoxide as catalyst in the presence of excess acetone.

Meerwein, Ponndorf and Verley published almost simultaneously but independently this reaction which therefore bears their names. However, it is to be pointed out that Meerwein and Verley employed aluminium ethoxide in their reduction whereas Ponndorf employed aluminium benzyloxide. Important advantages of this method are the use of mild conditions, high yields (60-90%) and the lack of reactivity with unsaturated systems. However, aluminium isopropoxide is preferred because it carries out the reaction rapidly with very few side reactions and gives higher yields as compared with other alkoxides. Furthermore, irrespective of the alkoxide used, this reaction is preferably carried out in isopropyl alcohol because the acetone formed can be removed from the reaction mixture by slow distillation.

Mechnism

This reaction involves a cyclic state (I) in which there occurs the migration of the hydride ion from the α-CH bond of the alkoxide to the carbonyl carbon of the ketone to form the mixed alkoxide (II). In this reaction excess of isopropyl alcohol is used so that it is exchanged with the mixed alkoxide (II) to liberate the desired alcohol (III).
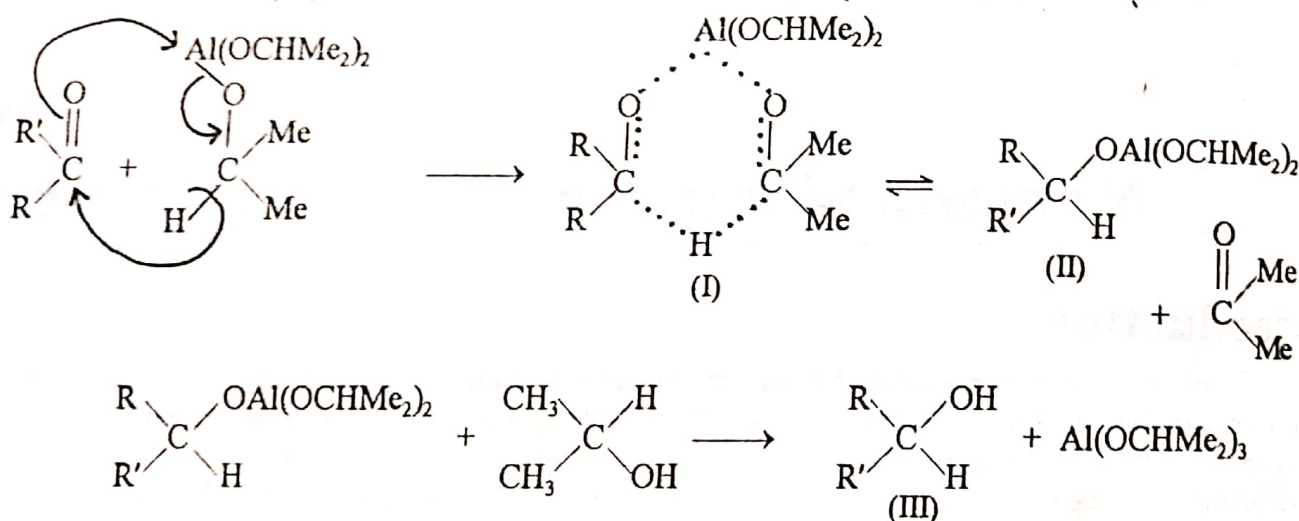
That a hydride ion gets transferred from aluminium isopropoxide to the ketone has been proved by the fact that if $Al(ODCMe_2)_3$ is used the ketone is reduced to alcohol, R_2CDOH which has deuterium. This reveals that the reaction is proceeding *via* a cyclic transition state as shown above.
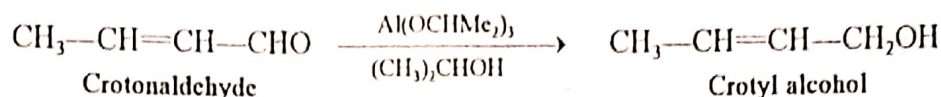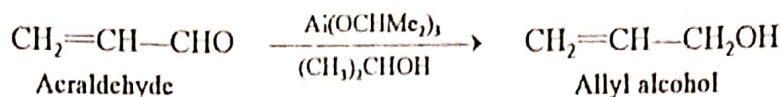
Specificity of aluminium isopropoxide : A number of metal alkoxides are used but aluminium isoproxide is the best reagent.

Aluminium alkoxides are much less polar than alkali metal alkoxides because aluminium-oxygen bond is nearly covalent in nature. Hence this undergoes very little dissociation to yield alkoxide ions which generally bring about some polymerization of the carbonyl compounds, specially the sensitive aldehydes. Thus, the side reactions are negligible. Its boiling point is 140-150°C (12 mm). This makes acetone to be distilled over so as to shift the equilibrium in the forwards direction.
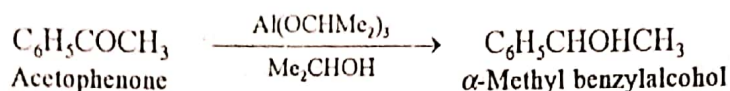
Applications

This method of reduction is specific for carbonyl group and therefore it can be used for reducing aldehydes and ketones containing some other reducible group, such as, a double bond, a nitro or an ester group, which are not reduced under these conditions.
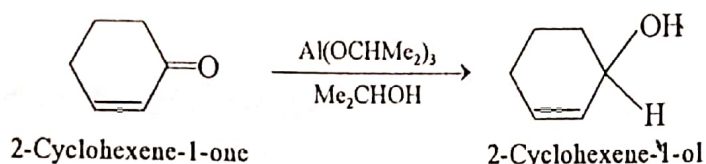
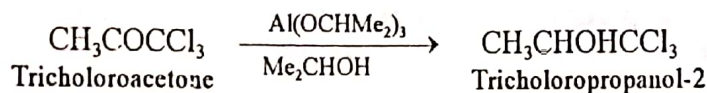1. The reaction has been employed to *reduce α, β-unsaturated aldehydes to α, β-unsaturated alcohols.*

$$CH_2{=}CH{-}CHO \xrightarrow[\text{(CH}_3)_2CHOH]{\text{Al(OCHMe}_2)_3} CH_2{=}CH{-}CH_2OH$$

Acraldehyde → Allyl alcohol

$$CH_3{-}CH{=}CH{-}CHO \xrightarrow[\text{(CH}_3)_2CHOH]{\text{Al(OCHMe}_2)_3} CH_3{-}CH{=}CH{-}CH_2OH$$

Crotonaldehyde → Crotyl alcohol

2. *Reduction of aromatic ketones, e.g.,*

$$C_6H_5COCH_3 \xrightarrow[\text{Me}_2CHOH]{\text{Al(OCHMe}_2)_3} C_6H_5CHOHCH_3$$

Acetophenone → α-Methyl benzylalcohol

3. *Reduction of alicyclic ketones, e.g.,*

2-Cyclohexene-1-one → 2-Cyclohexene-1-ol

4. *Reduction of α-halogenated ketones, e.g.,*

$$CH_3COCCl_3 \xrightarrow[\text{Me}_2CHOH]{\text{Al(OCHMe}_2)_3} CH_3CHOHCCl_3$$

Tricholoroacetone → Tricholoropropanol-2

5. *Reduction of keto esters, e.g.,*

$$Me_3C.CO.COOC_2H_5 \xrightarrow[\text{Me}_2CHOH]{\text{Al(OCHMe}_2)_3} Me_3C.CH(OH).COOC_2H_5$$

Ethyl trimethylpyruvate → Ethyl trimethyllactate
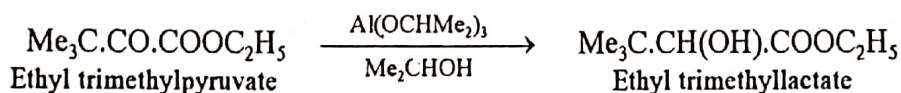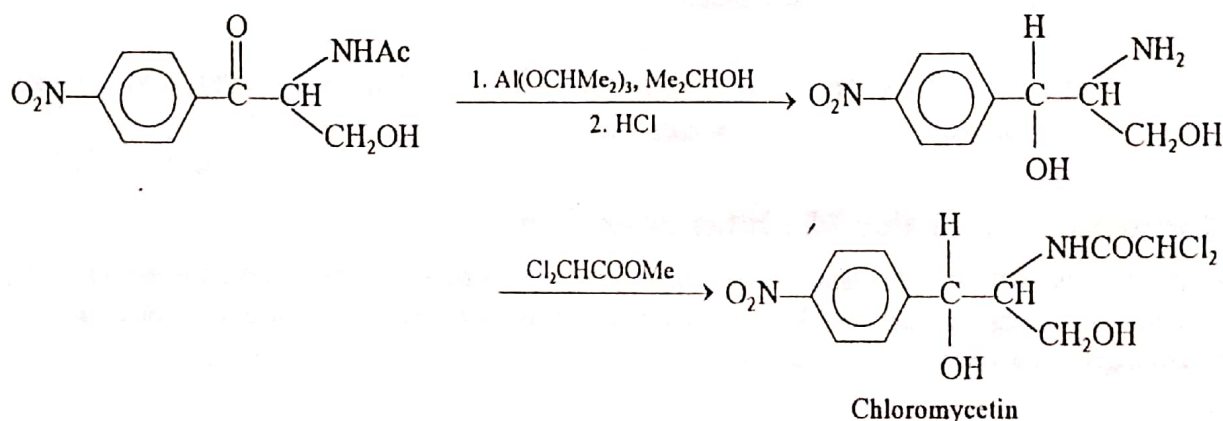
6. As this reduction requires mild conditions, it is accepted widely as a synthetic procedure. However, it is used in the synthesis of chloromycetin and oestradiol.

✓ **(a) Synthesis of chloromycetin is as follows :**
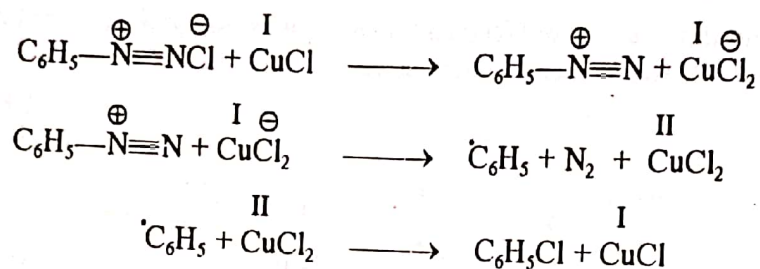

Chloromycetin

Indtroduction

The usual practice to prepare alkyl halides is to react the alcohols with PCl_3, $SOCl_2$ or conc. HCl/$ZnCl_2$. However, this method is not used for preparing aryl halides from phenols. The reason is that direct halogenation of aromatic compounds yields a mixture of isomers from which it is difficult to separate the desired isomer.

Sandmeyer reaction is considered to be the convenient method for introducing a halogen substituent at the desired position of an aromatic ring. In this method, the first step involves the conversion of an aromatic primary amine into an aryl diazonium salt by treating with nitrous acid in the presence of mineral acids (usually HCl or H_2SO_4) at low temperature ($0 - 5°C$). The second step involves the decomposition of diazonium salt by heating with cuprous chloride or bromide in the presence of an excess amount of corresponding halogen acid to yield aryl chloride or bromide. Thus, the overall reaction involves the replacement of the amino group of the aromatic amine by halogens.
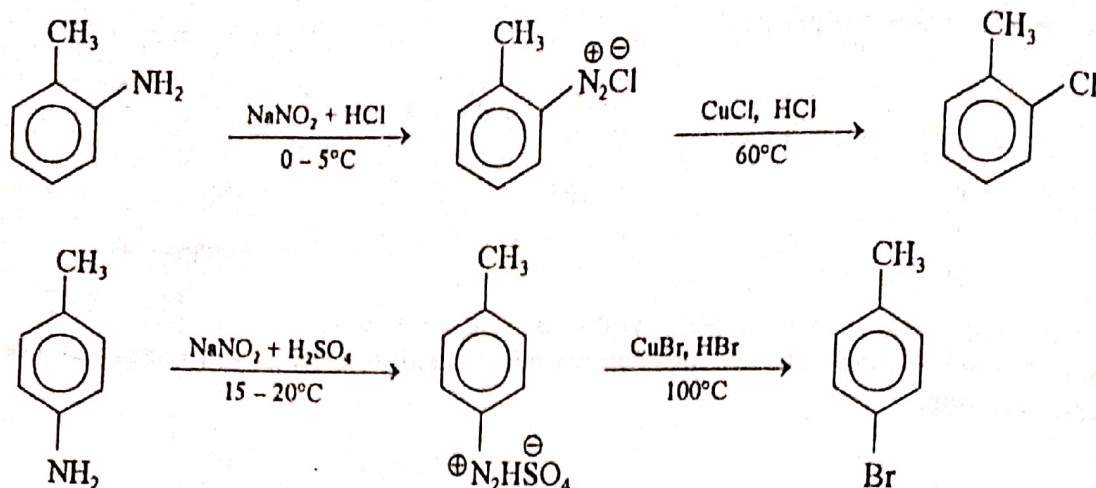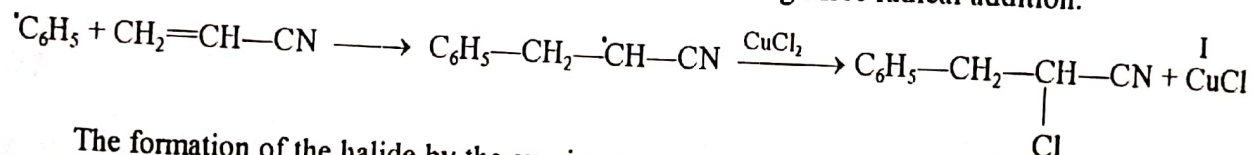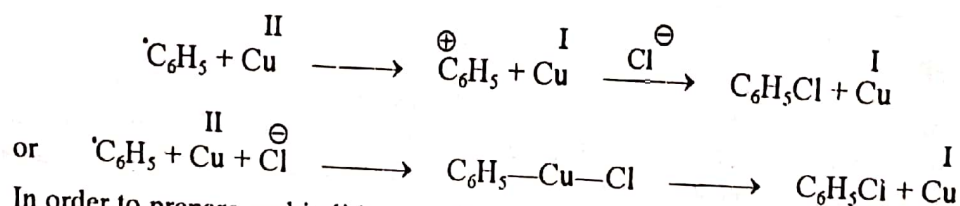
Mechanism

The cuprous copper is having the ability to reduce diazonium ion to aryl radical by oxidation-reduction involving one-electron transfer. First of all copper acts as reducing agent, then as oxidising agent.

$$C_6H_5\overset{\oplus}{-}N\equiv N\overset{\ominus}{Cl} + \overset{I}{Cu}Cl \longrightarrow C_6H_5\overset{\oplus}{-}N\equiv N + \overset{I}{Cu}Cl_2^{\ominus}$$

$$C_6H_5\overset{\oplus}{-}N\equiv N + \overset{I}{Cu}Cl_2^{\ominus} \longrightarrow \dot{C_6H_5} + N_2 + \overset{II}{Cu}Cl_2$$

$$\dot{C_6H_5} + \overset{II}{Cu}Cl_2 \longrightarrow C_6H_5Cl + \overset{I}{Cu}Cl$$

The evidence for the formation of aryl radical comes from the decomposition of benzene diazonium chloride when 2-chloro-3-phenylpropionitrile is obtained through free radical addition.
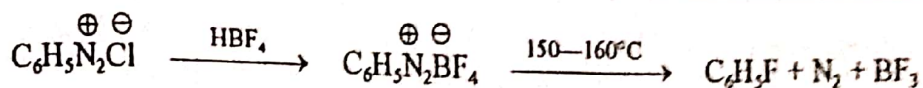
$$\dot{C_6H_5} + CH_2=CH-CN \longrightarrow C_6H_5-CH_2-\dot{C}H-CN \xrightarrow{CuCl_2} C_6H_5-CH_2-\underset{\underset{Cl}{|}}{C}H-CN + \overset{I}{Cu}Cl$$

The formation of the halide by the cupric copper may also involve a carbocation intermediate or an organo-copper compound.

$$\dot{C_6H_5} + \overset{II}{Cu} \longrightarrow \overset{\oplus}{C_6H_5} + \overset{I}{Cu} \xrightarrow{Cl^{\ominus}} C_6H_5Cl + \overset{I}{Cu}$$

$$\text{or} \quad \dot{C_6H_5} + \overset{II}{Cu} + \overset{\ominus}{Cl} \longrightarrow C_6H_5-Cu-Cl \longrightarrow C_6H_5Cl + \overset{I}{Cu}$$

In order to prepare aryl iodide, aryl diazonium salt is reacted with potassium iodide solution. For this reaction, cuprous catalyst is not required because iodide ion is itself able to decompose the diazonium salt. However, in this case the oxidation-reduction may be involved
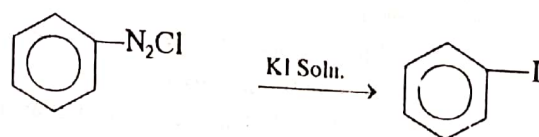
It is possible to prepare aryl fluoride by treating the diazonium salt with fluoboric acid or fluoborate when sparingly soluble diazonium fluoborate separates which is washed and dried. The dried salt on heating decomposes to yield aryl fluoride.

$$C_6H_5\overset{\oplus}{N_2}\overset{\ominus}{Cl} \xrightarrow{HBF_4} C_6H_5\overset{\oplus}{N_2}\overset{\ominus}{BF_4} \xrightarrow{150-160°C} C_6H_5F + N_2 + BF_3$$

This reaction is known as Schiemann reaction.

Gattermann modification : According to Gattermann, copper powder or copper bronze in place of cuprous chloride acts similarly to yeld the aryl halides. This may take place because of the formation of cuprous copper on the surface of the copper metal.

Applications and extension

Sandmeyer reaction which is used for the preparation of arylhalides from diazonium salt is more useful than direct halogenation for several reasons.

(i) Direct halogenation of aromatic compounds yields a mixture of isomers so that the yield of the desired isomer becomes low and difficult to separate. On the other hand, the diazonium salts yield only one halogen derivative because the halogen enters at the position which is previously occupied by the diazonium group.

(ii) Aryl iodides and fluorides are seldom prepared by direct halogenetion but they can be prepared by Sandmeyer reaction and Schiemann reaction respectively.

(iii) In some cases direct helogenation at a particular position is not possible because of electronic factors but this becomes possible through Sandmeyer reaction, e.g.,
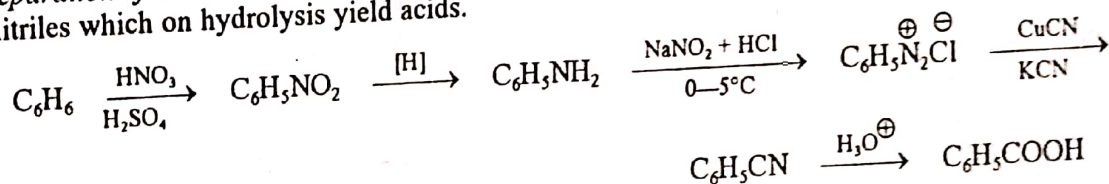
(a) *Preparation of m-dichlorobenzene :* It can be done as follows :
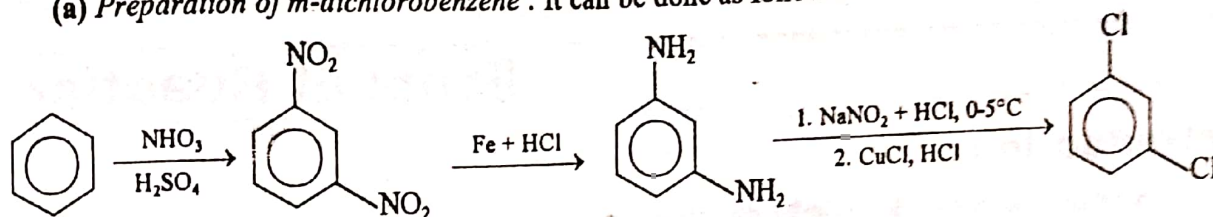
(b) *Preparation of 2-chloronaphthalene :* It may be done as follows :

β-Naphthol

β-Naphthylamine   2-Chloronaphthalene
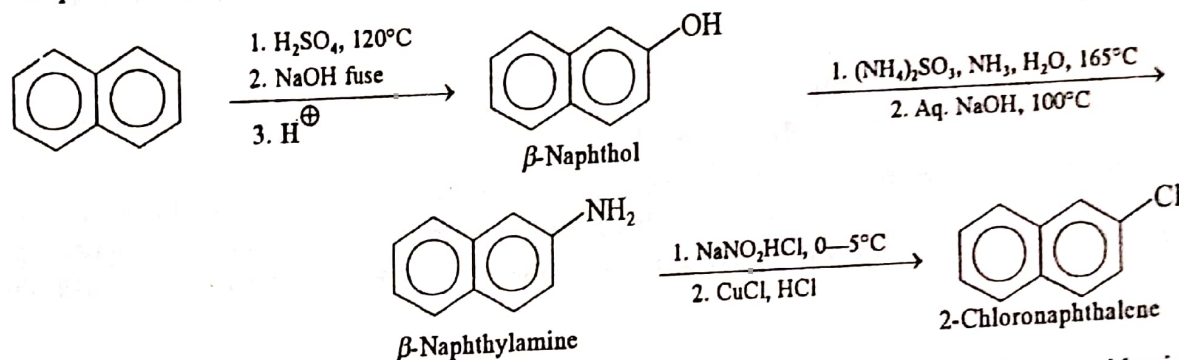
(c) *Preparation of acids :* Diazonium salts when treated with cuprous cyanide and potassium cyanide give nitriles which on hydrolysis yield acids.

$$C_6H_6 \xrightarrow[H_2SO_4]{HNO_3} C_6H_5NO_2 \xrightarrow{[H]} C_6H_5NH_2 \xrightarrow[0-5°C]{NaNO_2 + HCl} C_6H_5\overset{\oplus}{N_2}\overset{\ominus}{Cl} \xrightarrow[KCN]{CuCN}$$

$$C_6H_5CN \xrightarrow{H_3O^{\oplus}} C_6H_5COOH$$

(d) *Removal of amino group from aromatic rings :* Amino groups of aromatic amines on conversion to the corresponding diazonium salt and treatment with hypophosphorus acid are removed from the aromatic rings. The reaction has been successfully used for preparing compounds which cannot be