

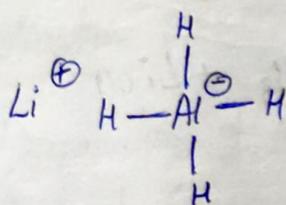
Unit-5

Reactions of Synthetic Importance

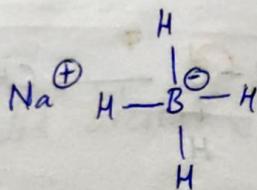
1) Metal Hydride Reduction (NaBH_4 & LiAlH_4):

→ Aldehydes and ketones are converted to primary and secondary alcohols by metallic hydrides such as lithium aluminum hydride (LiAlH_4) and sodium borohydride (NaBH_4). Such a reaction is called metal hydride reduction reaction.

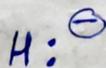
→ The hydride ion (H^-) acts as a nucleophile in this case. By hydride transfer, these metallic hydrides are also used to reduce acid halides, carboxylic acids, esters, amides and other compounds.



Lithium Aluminium Hydride



Sodium Borohydride

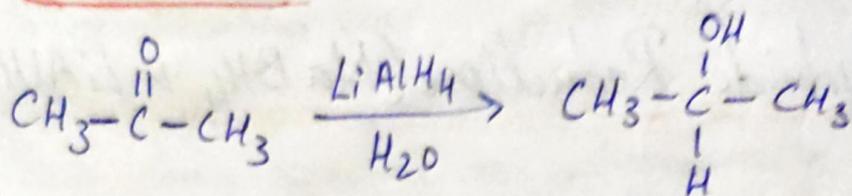


Hydride nucleophile.

Note: H_2O is taken with LiAlH_4
 CH_3OH is taken with NaBH_4

Reactions :

1) With ketone

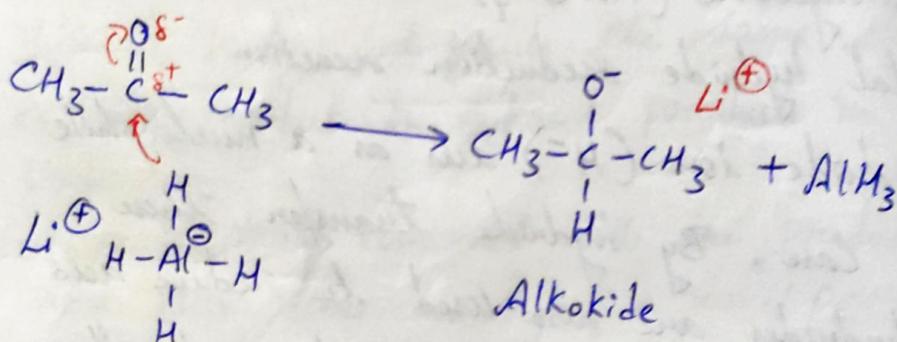


Propanone

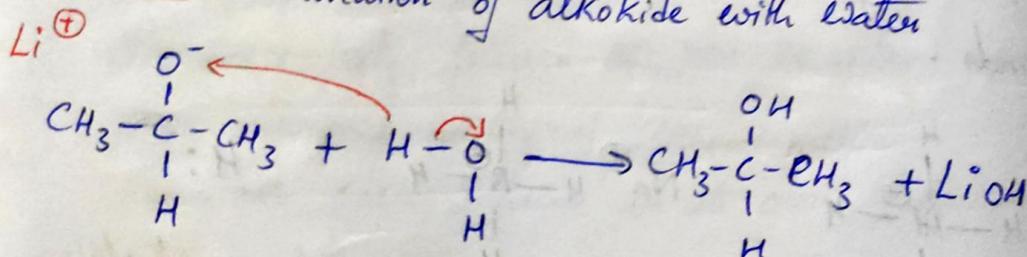
Propanol

Mechanism :

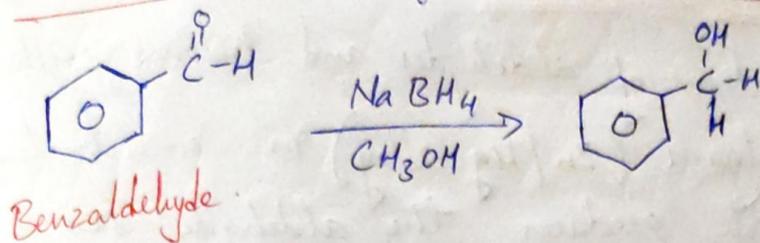
Step 1 : Nucleophilic attack by hydride ion



Step 2 : Protonation of alkoxide with water

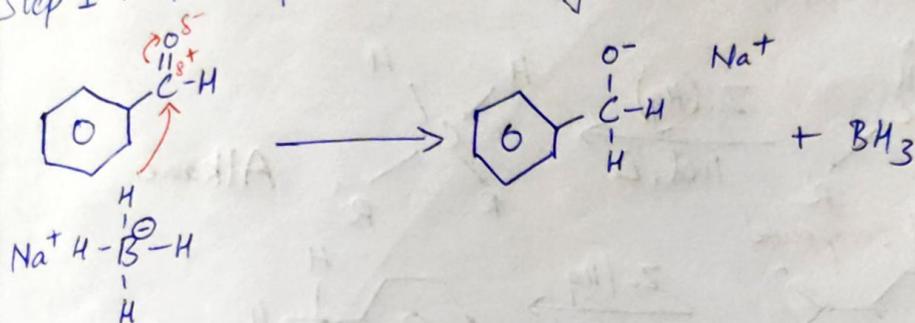


2) Reduction of Aldehyde by NaBH₄ :

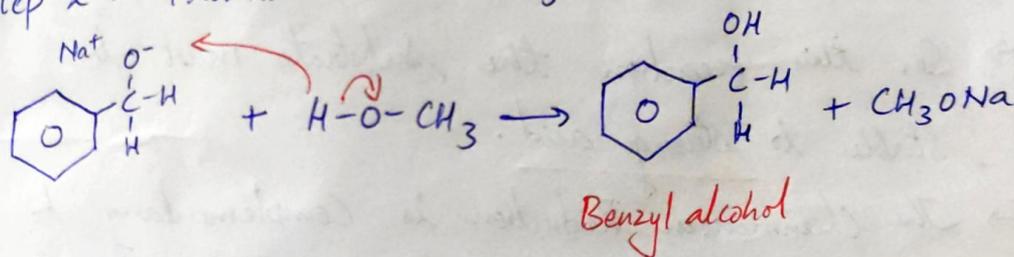


Mechanism :

Step 1 : Nucleophilic attack by H⁻ ion



Step 2 : Protonation with CH₃OH

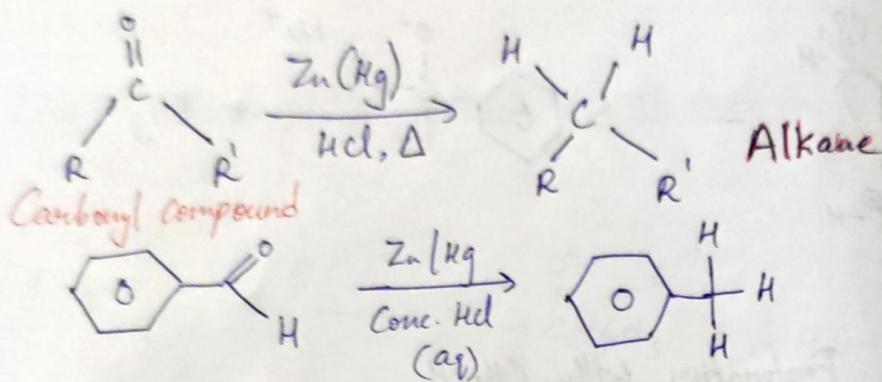


Applications :

- 1) Preparation of unsaturated alcohol from unsaturated Carbonyl compounds.
- 2) Reduction of ester to alcohol
- 3) Reduction of Carboxylic acid to alcohol
- 4) Reduction of acid halide to alcohol.

Clemmensen Reduction :-

→ The reaction of aldehydes and ketones with Zinc amalgam (Zn/Hg alloy) in concentrated HCl, which reduces the aldehyde or ketone to a hydrocarbon, is called Clemmensen reduction.



→ In this reaction the substrate must be stable to strong acid.

→ The Clemmensen Reduction is complementary to the Wolff-Kishner Reduction, which is run under strongly basic conditions.

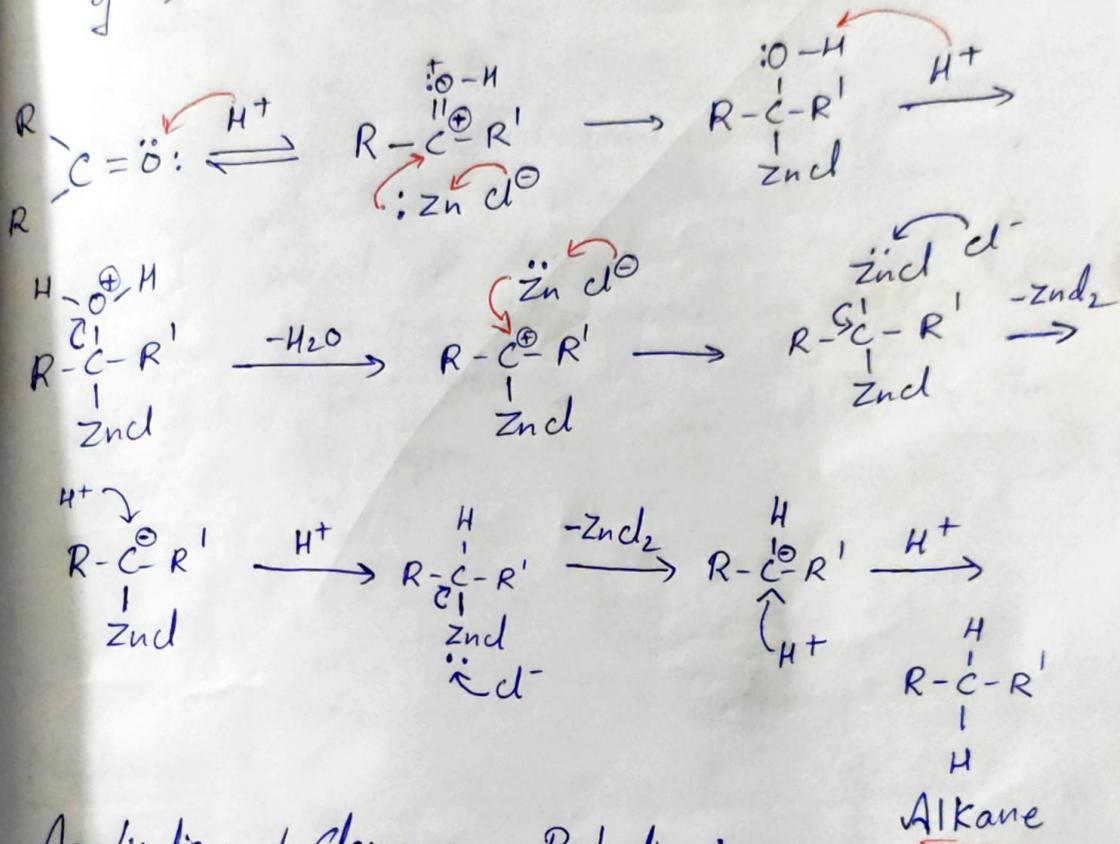
Mechanism :

→ The reduction takes place at the surface of the Zinc catalyst.

→ In this reaction, alcohols are not postulated as intermediates, because substitution of the corresponding alcohols to these same reaction

Conditions does not lead to alkanes.

→ (The following) It employs the intermediacy of zinc carbenoids to rationalize the mechanism of the Clemmensen Reduction.



Applications of Clemmensen Reduction:

- 1) Alkane from alkanyl chloride (halide) can be prepared from any organic compound which can be transformed into alkanyl halide.
- 2) The reaction is widely used to convert the carbonyl group into a methyl group.
- 3) Preparation of polycyclic aromatics and aromatics containing unbranched side hydrocarbon chain.
- 4) The reaction helps to reduce the aliphatic and

and mixed aliphatic - aromatic carbonyl compounds

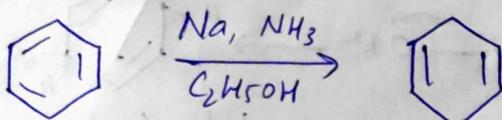
5. The Clemmensen reduction is most widely used to transform acyl benzene to alkyl benzene.

Birch Reduction :-

→ Reduction of Arenes (Aromatic rings) in liquid NH_3 and Alkali metals ($\text{Na}, \text{K}, \text{Li}$) and alcohol to cyclohexadienes.

→ [Solution of alkali metals in liquid NH_3 gives electride salt]

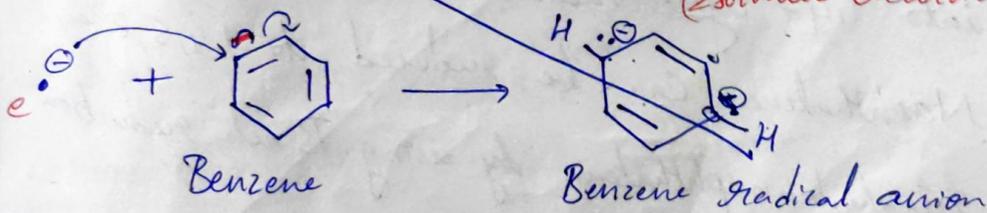
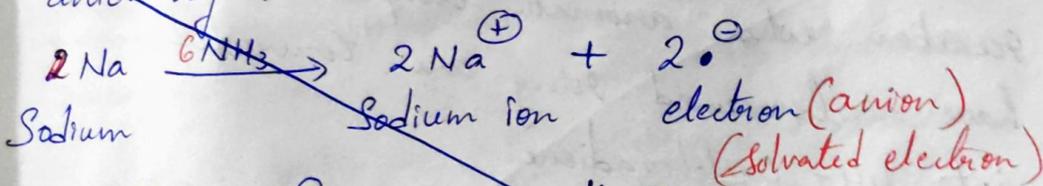
→ Birch reduction of benzene takes place through a single electron transfer from sodium metal to the benzene ring to form a radical anion. The anion is protonated by alcohol. This process is repeated twice until two hydrogen atoms are added to the ring.



1,4-cyclohexadiene

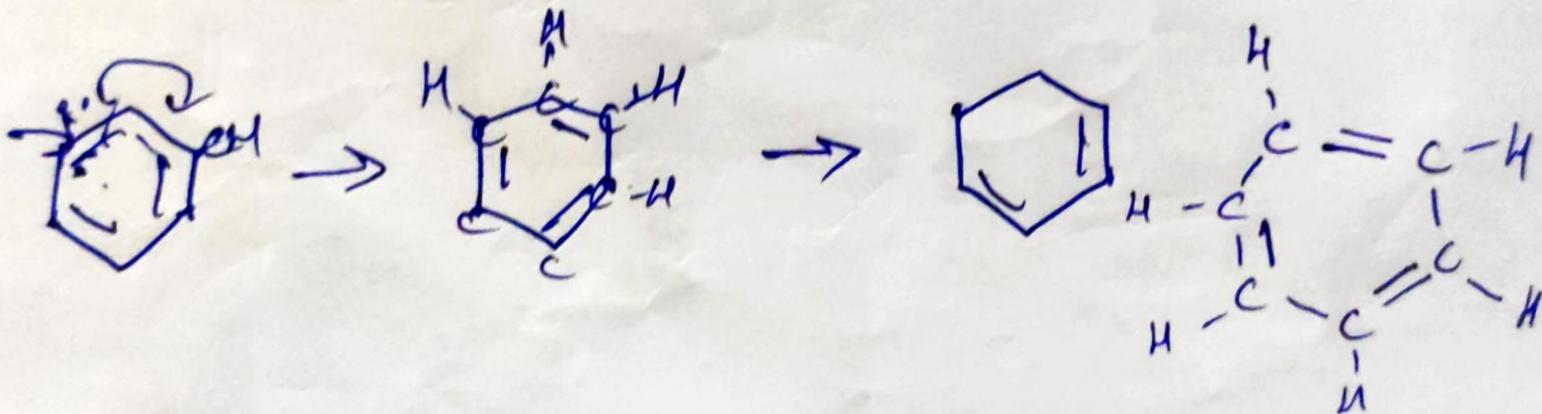
Mechanism :

Step-1: Reduction of benzene to benzene radical anion by sodium



Applications:

- 1) Birch reduction is an organic chemical reaction where aromatic compounds which have a benzenoid ring are converted into 1,4-cyclohexadiene.
- 2) Naphthalene can be reduced to 1,4,5,8-tetrahydronaphthalene by using Birch reduction.



Wolff-Kishner Reduction :

→ The Wolff-Kishner reduction is a chemical reaction used to convert carbonyl compounds such as ketones and aldehydes into their corresponding hydrocarbons.

→ This reaction is a useful tool in organic chemistry for deoxygenating compounds.

→ The key reagent in this reduction reaction is hydrazine (N_2H_4) and the reaction is carried out in the presence of a strong base like potassium hydroxide (KOH) or sodium hydroxide (NaOH).

→ The mechanism of Wolff-Kishner reduction involves several steps :

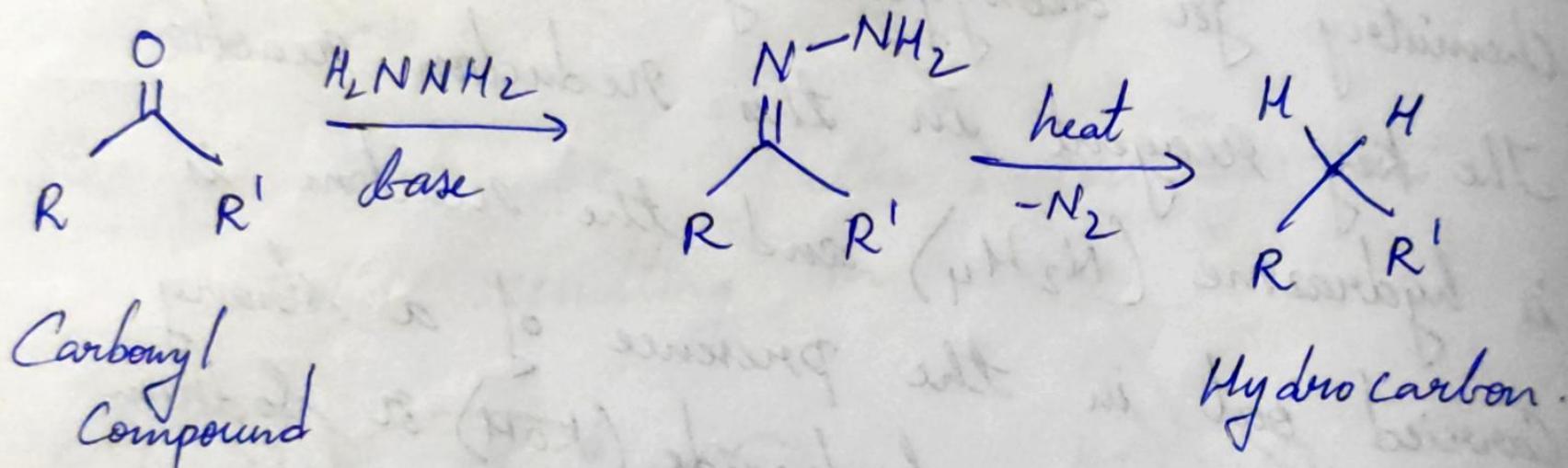
1) Formation of the Hydrazone : The carbonyl compound (ketone/aldehyde) reacts with hydrazine to form a hydrazone intermediate. This reaction is typically catalyzed by a base.

2) Formation of Alkane : In the next step, the hydrazone is converted into the corresponding alkane.

→ This step is accomplished by heating the reaction mixture.

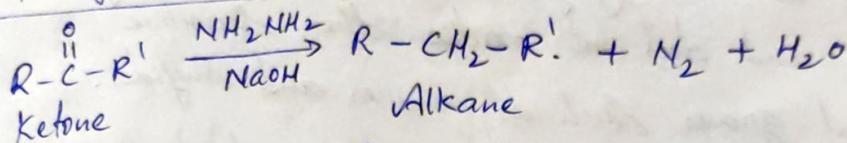
→ The hydrazone undergoes a complex rearrangement, resulting in the expulsion of nitrogen gas (N_2) and the formation of the desired hydrocarbon.

→ This reaction can be used for compounds which can withstand to strong base and high temperature conditions used in the reaction.



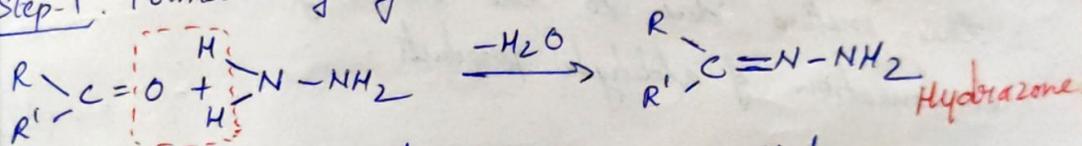
Applications:

- 1) Reducing aliphatic Carbonyl Compounds
- 2) Reducing cyclic ketones
- 3) Reducing α, β -unsaturated ketone
- 4) Reducing high molecular weight carbonyl compounds
- 5) Organic Synthesis of multiwalled carbon nanotube.
- 6) Synthesis of functionalized imidazole substrate.

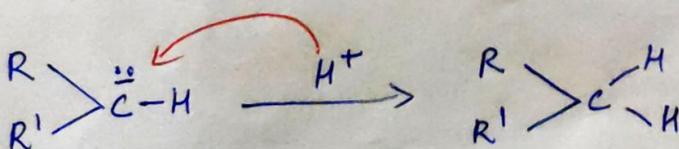
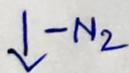
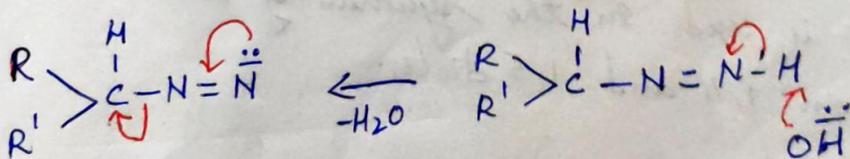
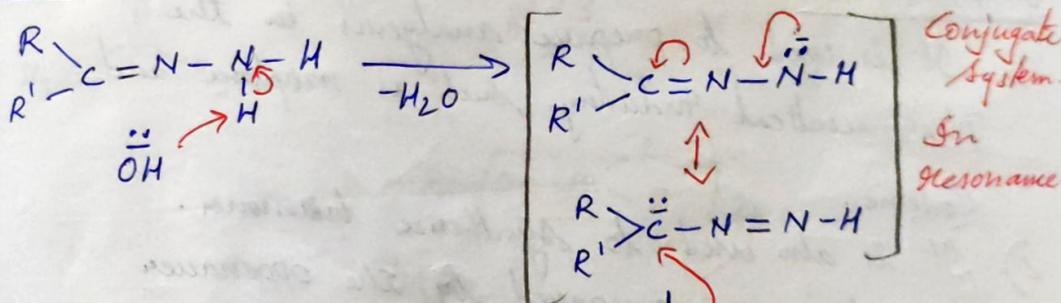


Mechanism: In 2 steps

Step-1: Formation of Hydrazone.



Step-2: Attack of Hydroxy (OH) ion on Hydrazone



Alkane.

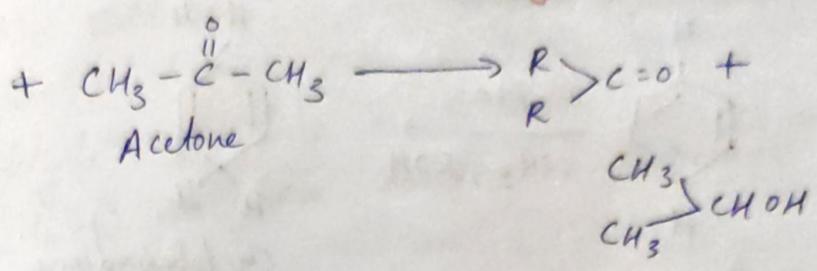
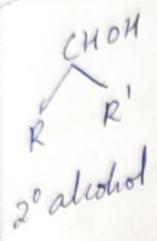
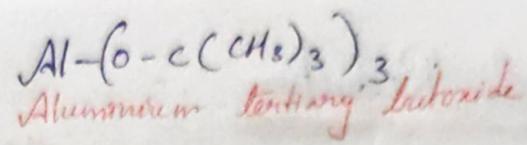
Oppenauer Oxidation :

- Oppenauer oxidation is a gentle method for selectively oxidizing secondary alcohols to ketones. The alcohol is oxidized with aluminium ^{tertiary butoxide} isopropoxide in excess acetone. This shifts the equilibrium towards the product side.
- The oxidation is highly selective for secondary alcohols and does not oxidize other sensitive functional groups such as amines and sulfides.
- Primary alcohols are seldom (rarely) oxidized by this method due to the competing aldol condensation of aldehyde products.

Applications :

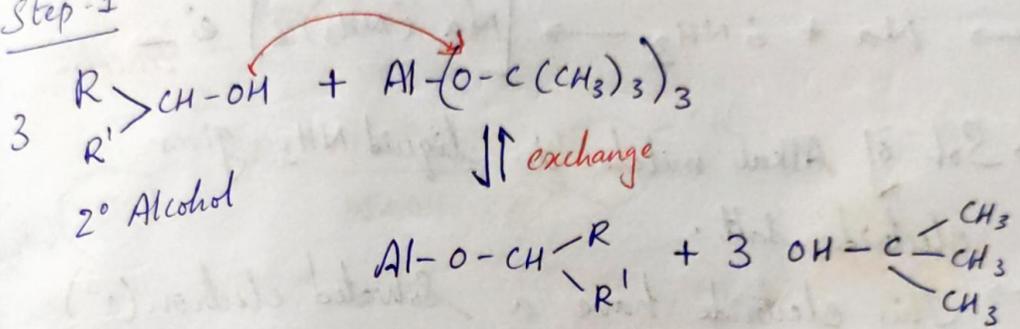
- 1) It is used to prepare analgesics in the pharmaceutical industry such as morphine and codeine.
- 2) It is also used to synthesize hormones. Progesterone is prepared by the Oppenauer oxidation of pregnenolone.
- 3) It is used in the synthesis of lactones from 1,4 and 1,5 diols.

Reaction:



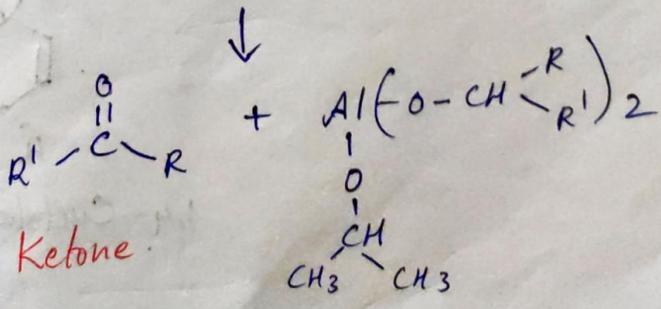
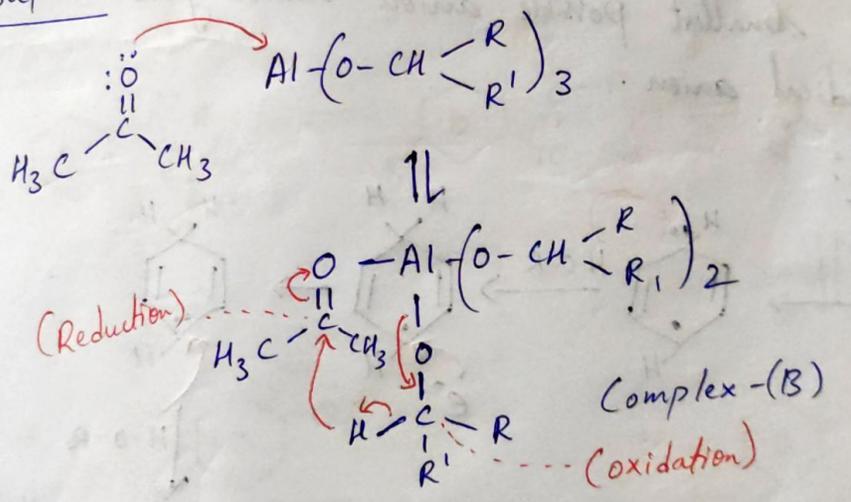
Mechanism:

Step-1:

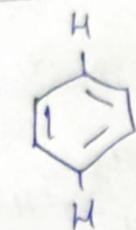


Complex - (A)

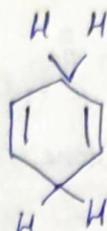
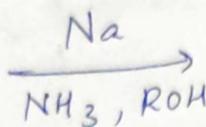
Step-2:



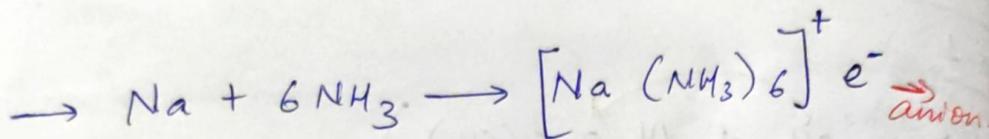
Bioch Reduction :-



Arenes



cyclohexadiene

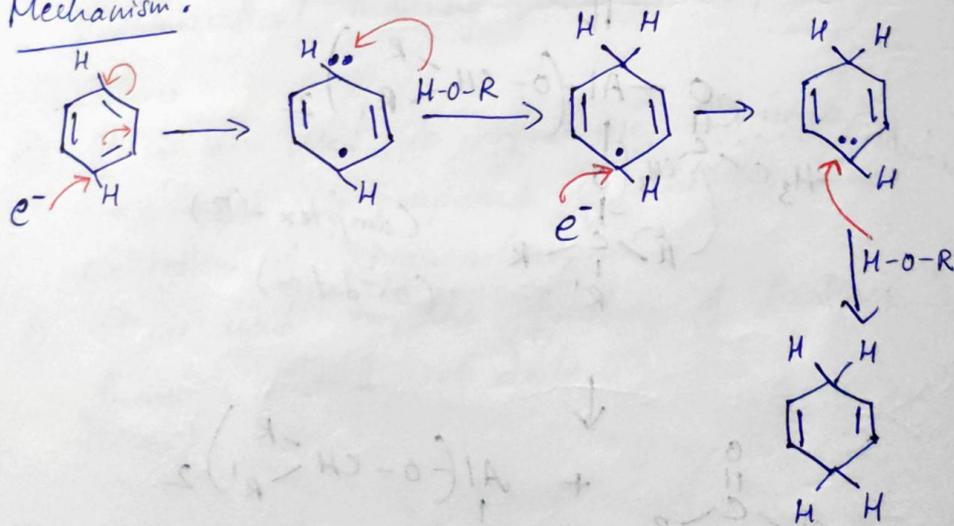


→ Sol. of Alkali metals in liquid NH_3 gives electride salt.

→ This electride have a solvated electron (e^-)

→ This solvated e^- is a free e^- in solution and a smallest possible anion which gives a radical anion.

Mechanism:

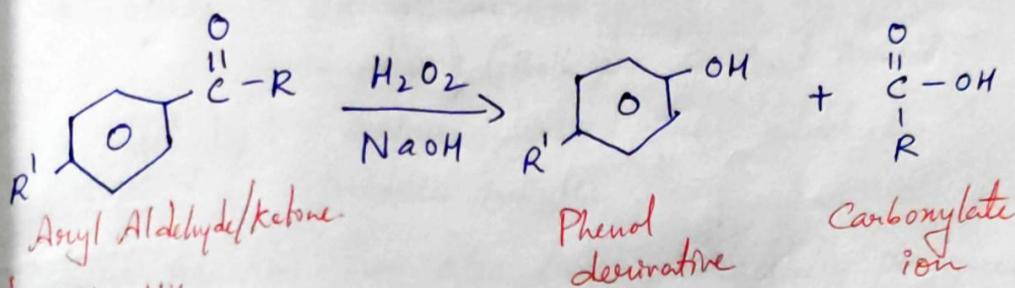


1,4-Cyclohexadiene

Dakin Reaction :

The Dakin oxidation is an organic redox reaction in which an ortho or para hydroxylated phenyl aldehyde or ketone reacts with hydrogen peroxide (H_2O_2) in base to form a phenol and a carboxylate.

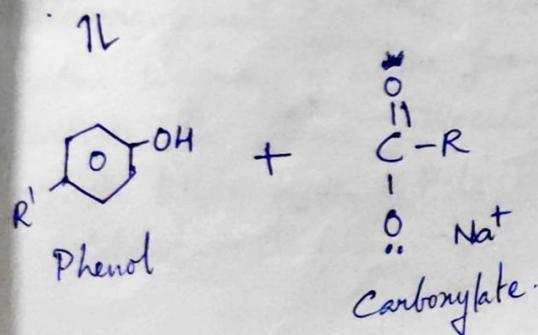
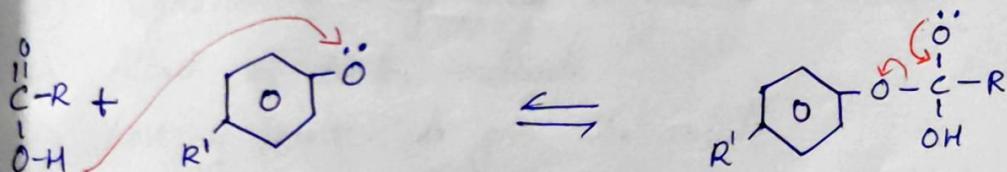
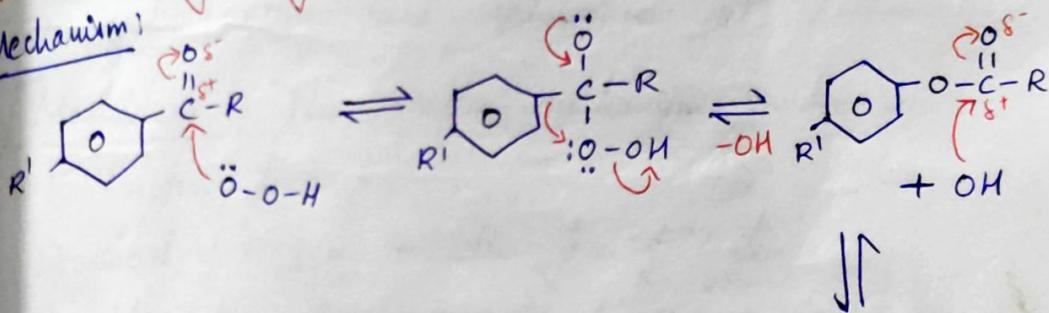
Overall the carbonyl group is oxidised, whereas the H_2O_2 is reduced.



$R' = OH \text{ or } NH_2$

$R = H \text{ or alkyl or aryl}$

Mechanism:



Applications:

- 1) Dakin oxidation is useful in the synthesis of indolequinones; naturally occurring compounds \Rightarrow that exhibit high anti-biotic, anti-fungal and anti-tumor activities.
- 2) Catechol is synthesized by Dakin reaction.

Beckmanns Rearrangement :

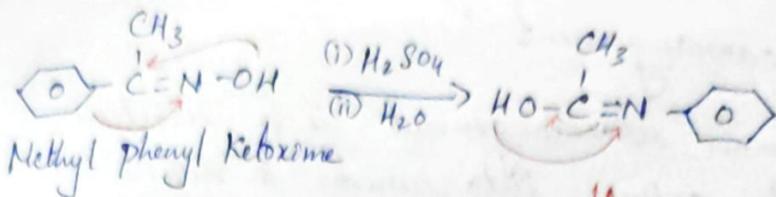
- The Beckmann rearrangement is a reaction that converts oximes into amides & nitriles.
- The reaction works by inserting the nitrogen atom from the $C=N$ bond into the carbon chain forming a $C-N$ bond.
- The reaction can produce either amides or nitriles depending on the starting materials.
- Ketones :- Oximes derived from ketones produce amides (Both are structural isomers).
 - Aldehydes :- Oximes derived from aldehydes produce nitriles.
- The reaction has also been successfully performed on haloimines and nitrones.
- cyclic oximes and haloimines yield lactams.

[Mechanism : The reaction mechanism involves :

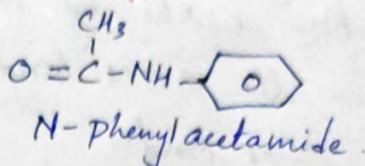
- 1) Proton transfer
- 2) Loss of oxygen in the form of water
- 3) Migration of alkyl group to give a carbocation.
- 4) Attack by water molecule.
- 5) Loss of proton to give the amide.

[Rearrangement reactions involve the migration of an atom & group of atoms from one site to another within the same molecule].

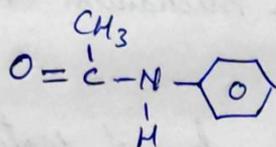
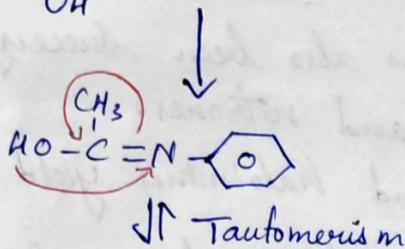
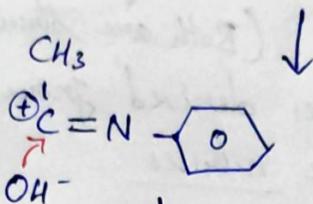
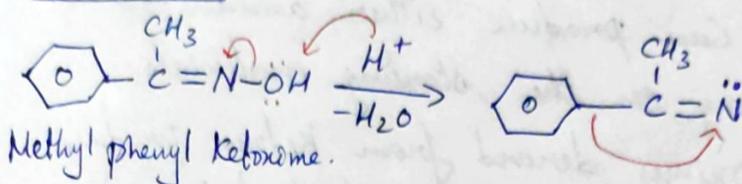
- In BR - H_2SO_4 & PCl_5 in water are used as catalyst.



⇌ Tautomerism



Mechanism :



N-phenyl acetamide

[Tautomerism is a phenomenon where a single chemical compound exists in two or more interconvertible structures. The structures differ in the relative position of hydrogen atom.]

[Oxime is hydroxyl group bonded to nitrogen atom of imine]

Applications:

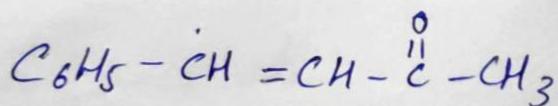
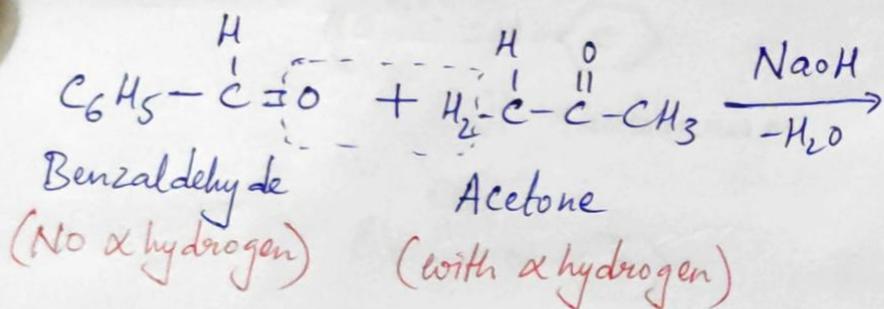
- 1) Caprolactam can be produced by Beckmann rearrangement reaction of cyclohexanone and oxime. Caprolactam is used as raw material in the production of Nylon-6.
- 2) It is used in industries for the synthesis of paracetamol. This is achieved by conversion of a ketone to a ketoxime with the help of hydroxylamine.
- 3) It is used in the synthesis of various steroids and drugs.

Claisen - Schmidt Condensation :-

- It is the reaction between an aldehyde or ketone having an α -hydrogen with an aromatic carbonyl compound lacking an α -hydrogen.
- It can be considered as a specific variation of the aldol condensation. (Crossed Aldol Condensation)

[Aldol Condensation : is an organic reaction that creates carbon-carbon bonds. It is an addition rxn between two aldehydes or two ketones or an aldehyde and a ketone. The rxn produces a β -hydroxy aldehyde or β -hydroxy ketone].

→ NaOH is used as catalyst.

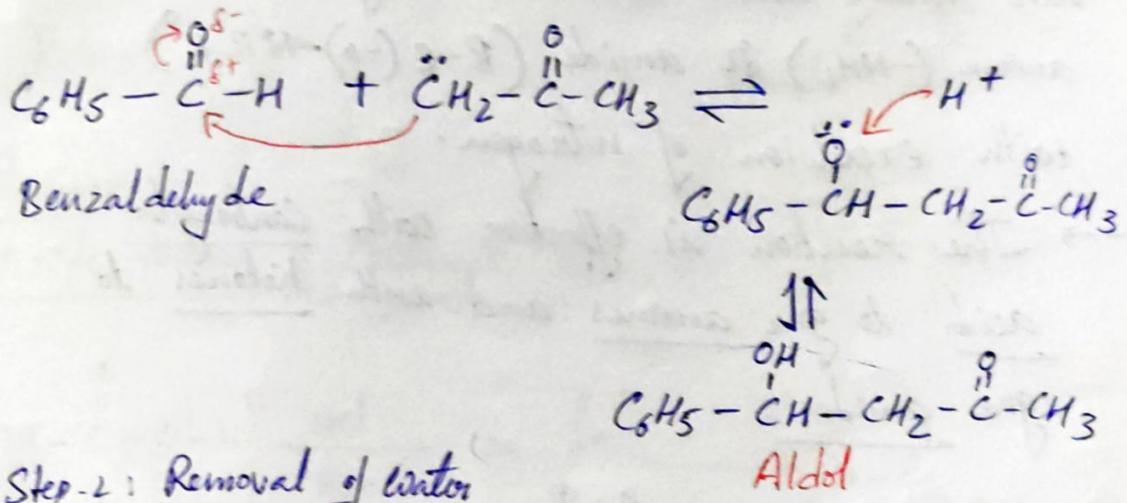
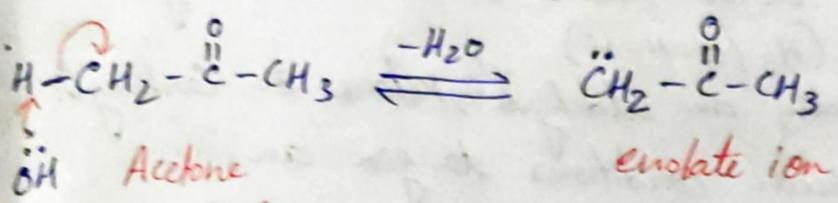


Benzalacetone

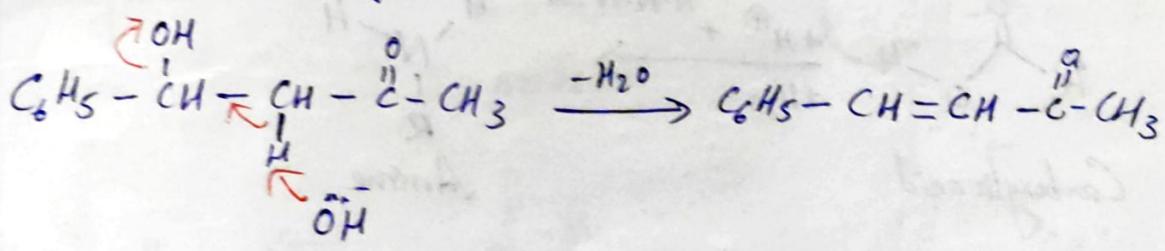
4-Phenyl - 3 butene - 2-one.

Mechanism: It occurs in 2 steps

- ① Formation of Aldol
- ② Removal of H₂O (Dehydration) elimination rxn.



③ Step-2: Removal of water



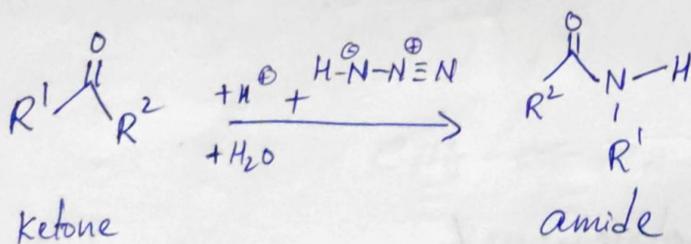
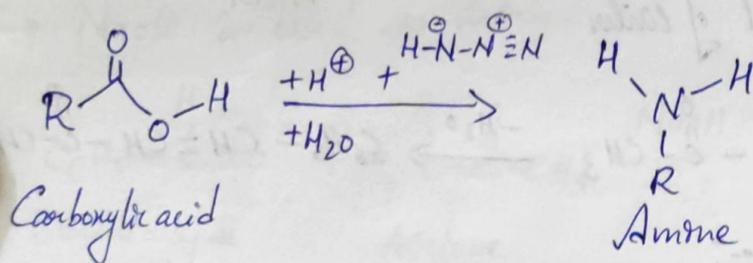
Applications:

- 1) Synthesis of cyclic compounds
- 2) Synthesis of ethyl benzoyl acetate.

Schmidt Rearrangement Reaction:

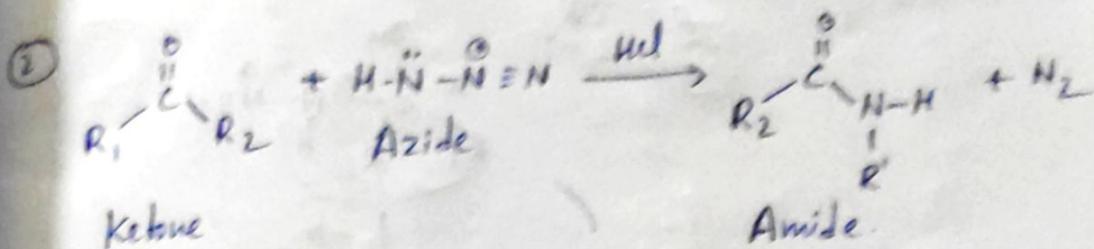
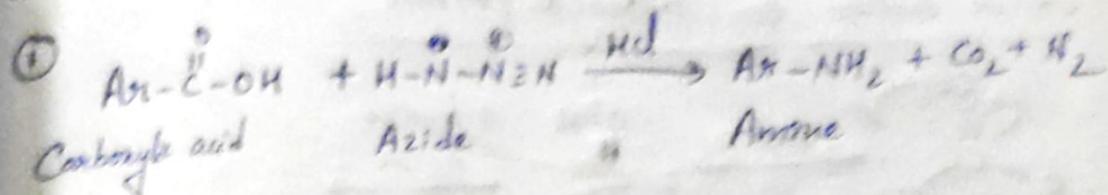
The Schmidt reaction is an organic reaction in which an azide reacts with a Carbonyl ($N_3 / N=N=N$) derivative, usually an aldehyde, ketone or Carboxylic acid under acidic conditions to give an amine ($-NH_2$) or amide ($R-C(=O)-NR'R''$) with expulsion of nitrogen.

→ The reaction is effective with Carboxylic acids to give amines and with Ketones to give amides.



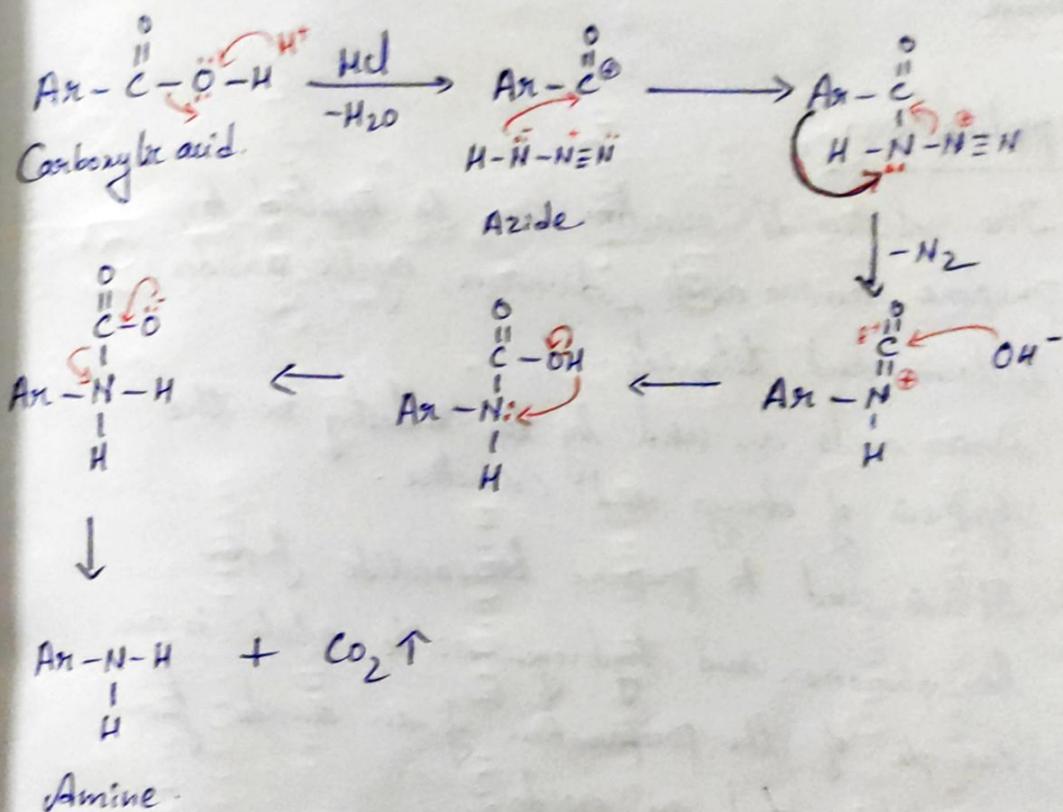
Hydrazoic acid / Hydrogen azide / Azonide: (HN_3)
 $H-N=N\equiv N$

Reaction:

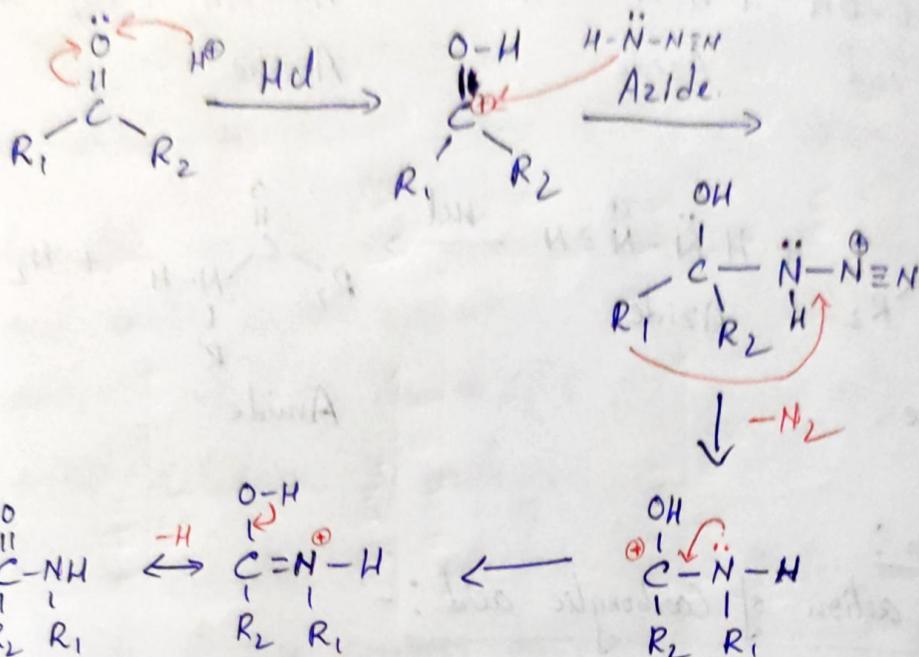


Mechanism:

Azide action of Carboxylic acid. :-



Azide action on Aldehyde / Ketone :-



Amide

Applications

1) The Schmidt reaction can be applied to prepare amino acids, diamines, cyclic amides, lactams and tetraazole.

Amino acids are used by the industry in the synthesis of drugs and cosmetics.

2) It is used to prepare benzanilide from benzophenone and hydrogen azide, which is an example of the preparation of an amide from a ketone and an azide.