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|---|---|
| Name of Unit | Reactions of Synthetic Importance |
| Subject /Course Name | Pharmaceutical Organic Chemistry-III |
| Subject/Course ID | BP401T |
| Class: B.Pharm. Semester | 4th |
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## Learning Outcome of Module 5

| LO | Learning Outcome | Course Outcome Code |
|---|---|---|
| LO1. | To gain knowledge about Synthesis of Some Important Organic Compounds. | BP401.5 |
| LO2. | To understand about Metal Hydride Reduction. | BP401.5 |
| LO3. | To gain knowledge about reactions of Synthetic Importance. | BP401.5 |
| LO4. | To get the knowledge about Some Natural Products. | BP401.5 |
| LO5. | To get the knowledge about Applications of some Organic Compounds. | BP401.3 |

## Content Table

| Topic |
|---|
| • Introduction of Metal Hydride Reduction.<br>• $LiAlH_4$ and $NaBH_4$<br>• Clemmensen Reduction<br>• Birch Reduction<br>• Wolff-Kishner Reduction<br>• Oppenauer-Oxidation<br>• Dakin Reduction<br>• Beckmann Rearrangement<br>• Schmidt Rearrangement<br>• Claisen-Schmidt Condensation |

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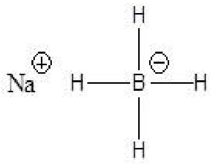
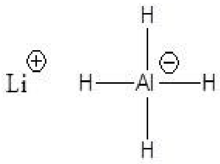
## Metal Hydride Reduction Reaction ($NaBH_4$ and $LiAlH_4$)

The most common sources of the hydride Nucleophile are **Lithium Aluminum Hydride ($LiAlH_4$)** and **Sodium Borohydride ($NaBH_4$).**

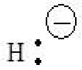
**Lithium Aluminum Hydride ($LiAlH_4$): -** The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because Aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making **$LiAlH_4$ a stronger reducing agent.**



Sodium borohydride

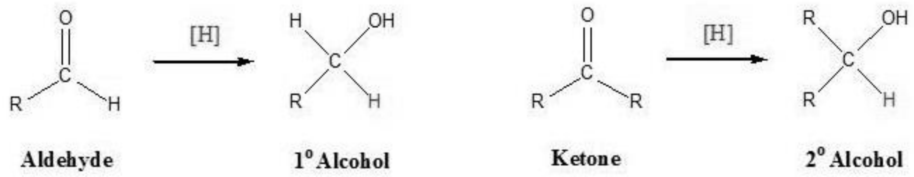


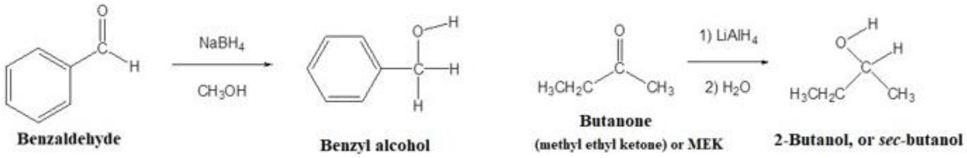
Lithium Aluminum Hydride



Hydride Nucleophile

Addition of a hydride anion ($H:^-$) to an **aldehyde** or **ketone** gives an **alkoxide anion**, which on protonation yields the corresponding alcohol. **Aldehydes produce $1^0$-alcohols and ketones produce $2^0$-alcohols.**





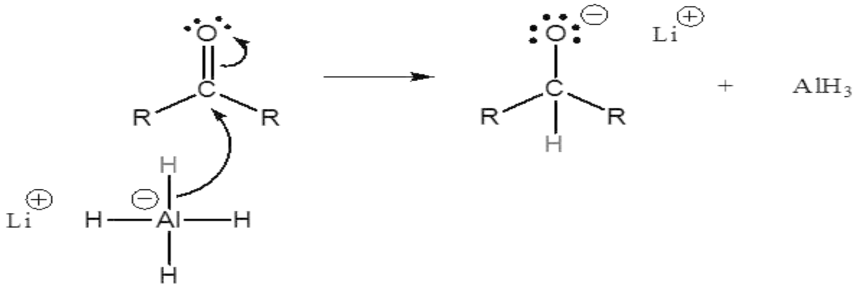
It reacts violently with water by producing hydrogen gas. Hence it should not be exposed to moisture and the reactions are performed in inert and dry atmosphere. The reaction must be carried out in anhydrous non protic solvents like diethyl ether, THF etc. It is highly soluble in diethyl ether.

$$LiAlH_4 + 4H_2O \rightarrow Li\,OH + Al\,(OH)_3 + 4H_2$$

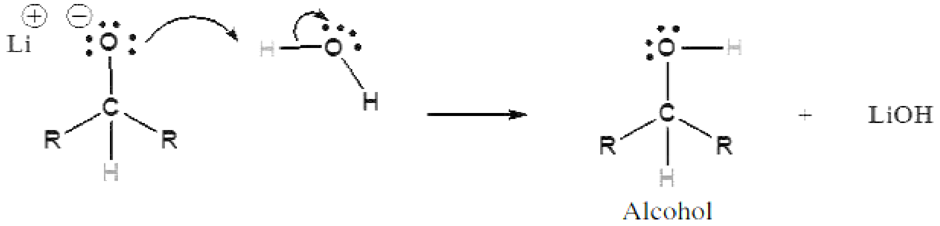
***$LiAlH_4$ is prepared by the reaction of lithium hydride (Li H) with aluminum chloride ($AlCl_3$). Sodium borohydride is prepared by the reaction of sodium hydride (Na H) with trimethyl borate, $B(OMe)_3$.***

**Reaction Mechanism for $LiAlH_4$ Reduction:**

***Step 1*: Nucleophilic attack by the hydride anion.**

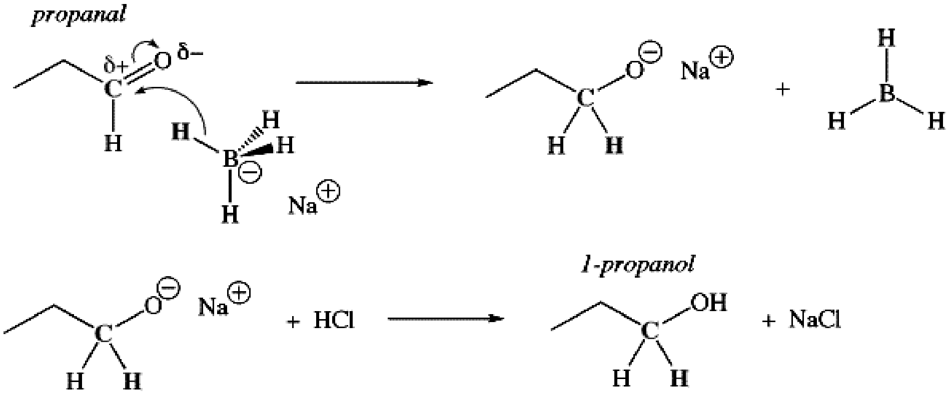


***Step 2:* The alkoxide is protonated.**



**$NaBH_4$ Reduction: -**

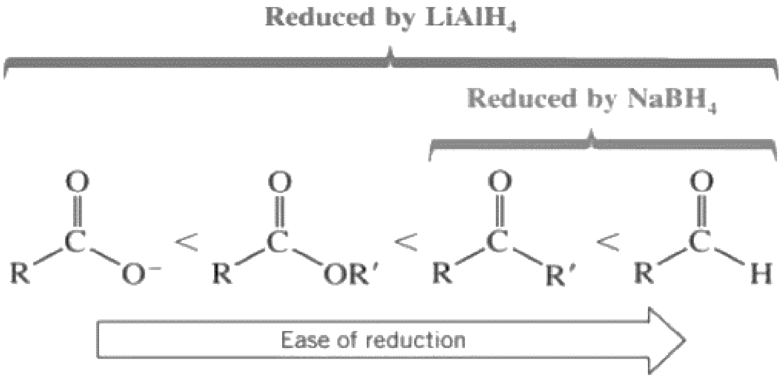
**Reaction Mechanism:-**



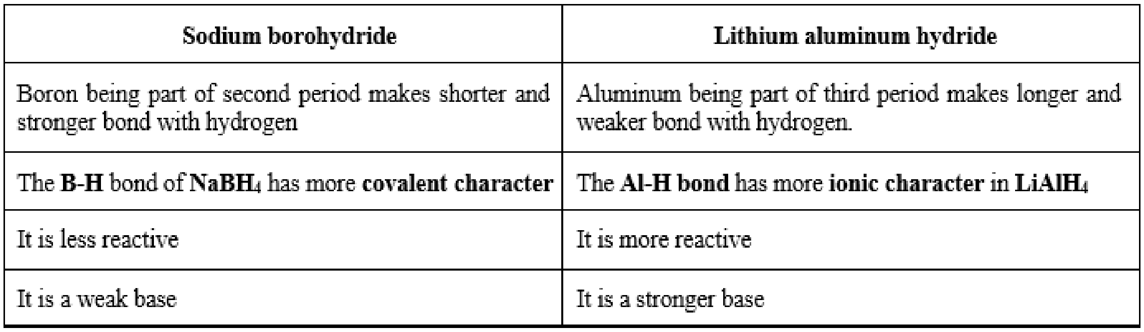
**Why does $LiAlH_4$ reduce esters, amides, or carboxylic acids, while $NaBH_4$ cannot reduce them?**

- Carboxylic acids and esters are much less reactive to reduction than are ketones and aldehydes and sodium- borohydride, **$NaBH_4$** (aq) is too weak a reducing agent for them.

- **$NaBH_4$** is preferred for aldehydes and ketones because it does not react violently with $H_2O$, the way $LiAlH_4$ does and can be used as an aqueous solution, whereas the **$LiAlH_4$** must be delivered in an anhydrous solution of **diethyl-ether**, **$Et_2O$**, and then neutralized by water and acid to isolate the product/s. But, ultimately, **$LiAlH_4$** can be used for all of these reactions.



## Difference Between $LiAlH_4$ and $NaBH_4$



| Sodium borohydride | Lithium aluminum hydride |
|---|---|
| Boron being part of second period makes shorter and stronger bond with hydrogen | Aluminum being part of third period makes longer and weaker bond with hydrogen. |
| The **B-H** bond of **$NaBH_4$** has more **covalent character** | The **Al-H bond** has more **ionic character** in **$LiAlH_4$** |
| It is less reactive | It is more reactive |
| It is a weak base | It is a stronger base |

**Clemmensen Reduction:** *-Clemmensen reduction* is a chemical reaction described as ***a reduction of ketones (or aldehydes) to alkanes using zinc amalgam and hydrochloric acid.*** Clemmensen reduction is an organic reduction reaction shown by both aldehydes and ketones, But Carboxylic acid (-COOH) group can't be reduced by this method (but the -COOH group can be reduced by treating it with soda lime [**NaOH+ CaO**] and then heating).

Here, **C=O** group of aldehydes and ketones is reduced to **$-CH_2-$** by Clemmensen reduction. Zinc amalgam and concentrated hydrochloric acid (**Zn (Hg)**/conc. **HCl** ) is used as the reagent for Clemmensen reduction. (Note By: alkenes and alkynes don't react with clemmensen reagent).

$$-\overset{\overset{\displaystyle O}{\|}}{C}- \xrightarrow{\text{Clemmensen Reduction}} -CH_2-$$

**Some examples of Clemmensen Reduction:**

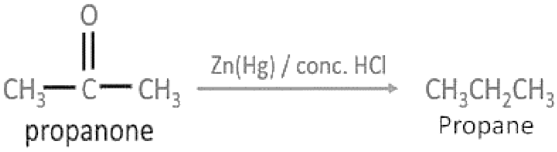
**1.Clemmensen reduction of ethanal:** Ethanal is an aldehyde. Ethanal is reduced to ethane by Clemmensen reduction. **Zinc amalgam** and **concentrated HCl** is used as the Clemmensen reducing reagent. Ethane is an alkanecompound.

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-H \xrightarrow{Zn(Hg)\ /\ \text{conc. HCl}} CH_3CH_3$$

**2. Clemmensen Reduction of Propanal:** When Propanal and **Zn (Hg)/conc. HCl** react, propane is given as the product. **Propane** also an alkane.

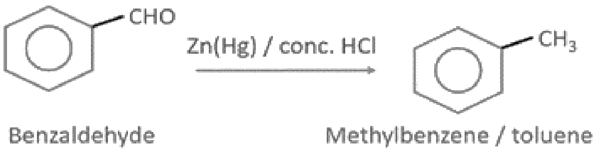
$$CH_3CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-H \xrightarrow{Zn(Hg)\ /\ \text{conc. HCl}} CH_3CH_2CH_3$$

**3.Clemmensen reduction of propanone:** Propanone gives propane as the product with **Zn (Hg)/conc. HCl**. **Propane** is an **alkane** compound.



$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 \xrightarrow{Zn(Hg)\ /\ \text{conc. HCl}} CH_3CH_2CH_3$$

**4. Benzaldehyde and Clemmensen reduction:** **Methylbenzene** (toluene) is given when **benzaldehyde** is reacted with **Zn (Hg)** / concentrated **HCl**.

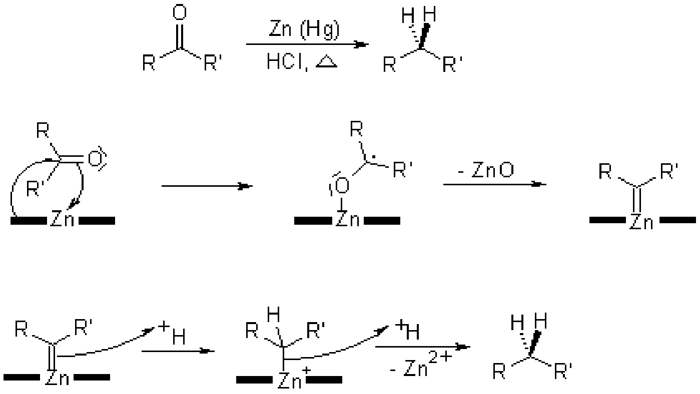


**Preparation of Zinc Amalgam: -**An ***AMALGAM*** is an alloy of **mercury** with another metal, which may be a liquid, a soft paste or a solid, depending upon the proportion of mercury. These alloys are formed through metallic bonding, with the electrostatic attractive force of the conduction electrons working to bind all the positively charged metal ions together into a crystal lattice structure. Almost all metals can form amalgams with mercury, the notable exceptions being **iron, platinum, tungsten, and tantalum**.

***Silver-mercury amalgams*** are important in dentistry, and **gold- mercury amalgam** is used in the extraction of gold from ore.

$$Zn + HgCl_2 \xrightarrow{HCl} ZnCl_2 + Hg$$
$$Zn + Hg \longrightarrow Zn(Hg)$$

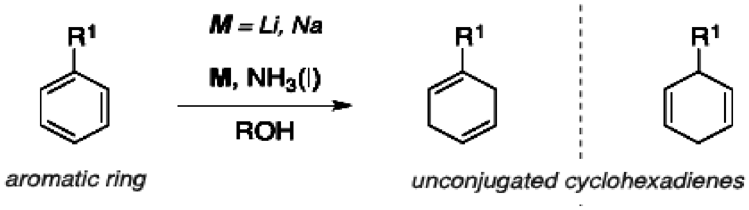
**Reaction Mechanism: -**

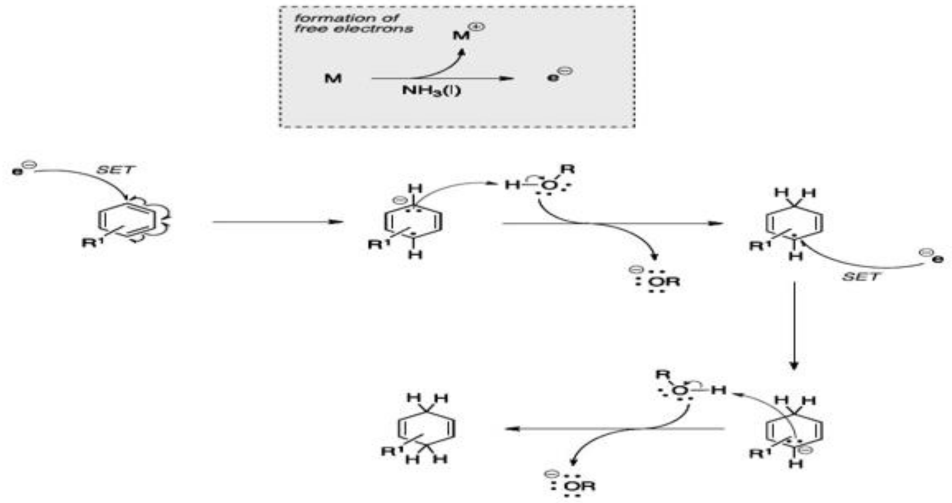


**Birch Reduction: -**The **reduction of aromatic substrates** with **alkali metals, alcohol in liquid ammonia** is known as **"Birch reduction".** This reaction is named after a **Australian chemist** ***Sir Arthur John Birch***. The Birch reduction is an organic reaction where aromatic rings undergo a 1**,4-reduction** to provide **unconjugated.**

**Cyclohexadienes:** -The reduction is conducted by sodium or lithium metal in liquid ammonia and in the presence of an alcohol. The mechanism begins with a Single Electron Transfer (SET) from the metal to the aromatic ring, forming a radical anion.

The anion then picks up a proton from the alcohol which results in a neutral radical intermediate. Another SET, and abstraction of a proton from the alcohol results in the final cyclohexadiene product and two equivalents of metal alkoxide salt as a by-product.

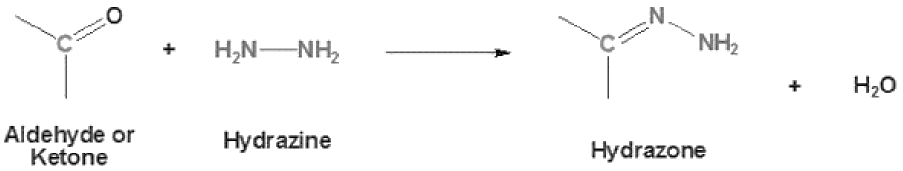




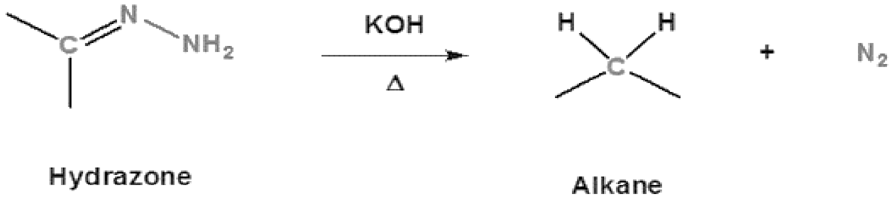
## Wolff Kishner Reduction Reaction: -

**The reduction of aldehydes and ketones to alkanes**. Condensation of the carbonyl compound with hydrazine forms the hydrazone, and treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, to yield the corresponding alkane.

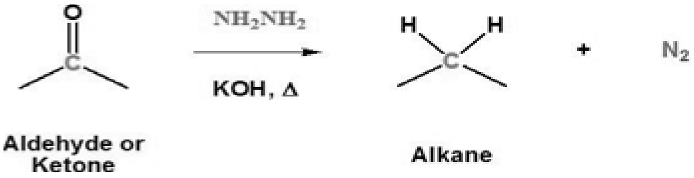
### Reaction of Aldehydes or Ketones with Hydrazine Produces a Hydrazone.

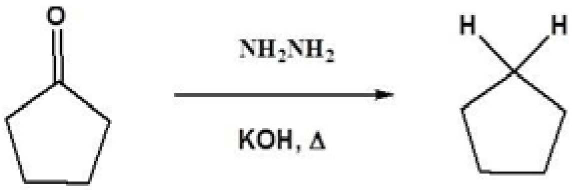


### Reaction with a Base and Heat Converts a Hydrazone to an Alkane



**Examples**:

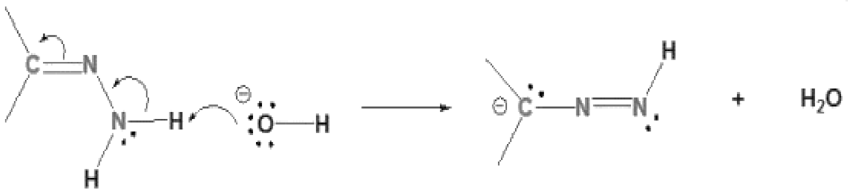




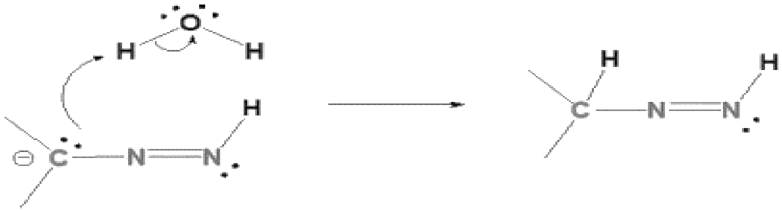
The Wolff-Kishner reduction is used to convert **ketones** to **methylene** groups, and **aldehydes** to **methyl** groups. It cannot be used to reduce the carbonyl groups of **amides** and **esters**.

**Mechanism of the Wolff-Kishner Reduction: -**

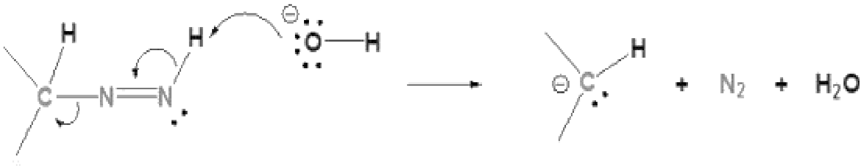
### Step 1: Deprotonation of Nitrogen



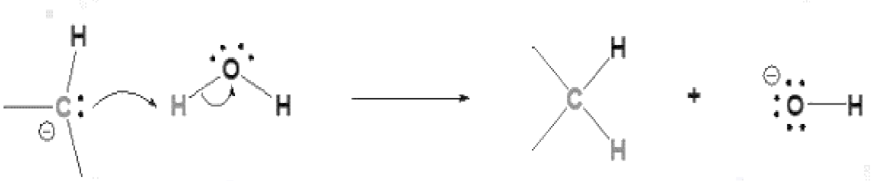
### Step 2: Protonation of the Carbon



### Step 3: Deprotonation of Nitrogen



### Step 4: Protonation of Carbon



Alkane

**Difference Between Clemmensen Reduction and Wolff-Kishner Reduction:**

1. The key difference between Clemmensen and Wolff Kishner reduction is that the Clemmensen reduction involves the conversion of ketone or aldehydes into alkanes whereas the Wolff Kishner

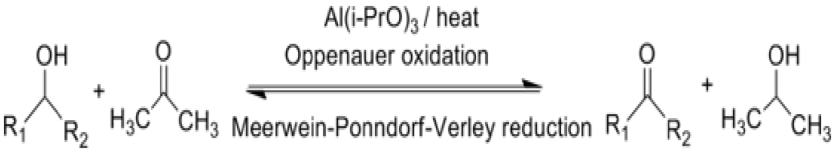
reduction involves the conversion of carbonyl groups into methylene groups.

2.Clemmensen reduction is done under **acidic conditions** whereas the Wolff-Kishner reaction is done under **basic condition.**

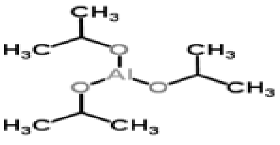
3.Clemmensen reduction is done for aldehyde or ketones **in presence of Zn-Hg (Zinc amalgam)/Conc. HCl** to form alkane. This reaction occurs on the zinc metal surface. Whereas Wolff-Kishner reduction is also for aldehyde/ ketones **in presence of hydrazine ($N_2H_4$) KOH, $H_2O$ and 180 °C temperature** to form methylene groups.

## Oppenauer Oxidation Reaction

The **Oppenauer oxidation** is an organic reaction used to **convert a primary or secondary alcohol** to a **ketone** using another excess ketone reagent (such as acetone) and an **Aluminum Tri Isopropoxide** catalyst. Oppenauer oxidation, named after ***Sir Rupert Viktor Oppenauer***.

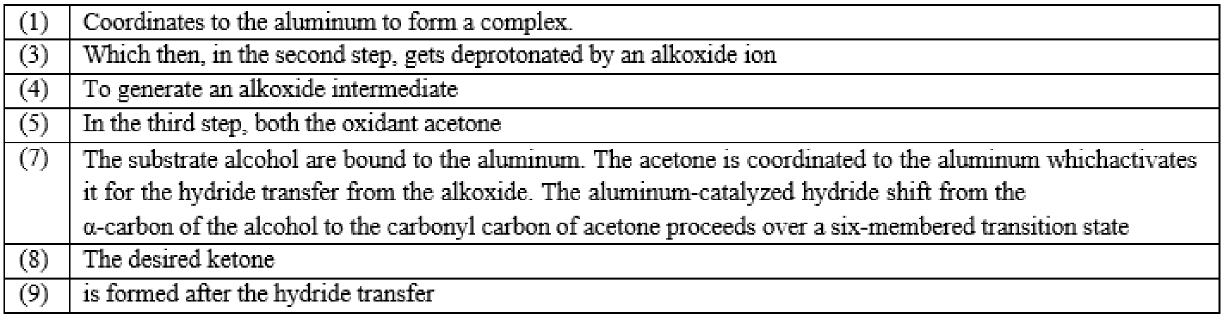


## Reaction Mechanism:

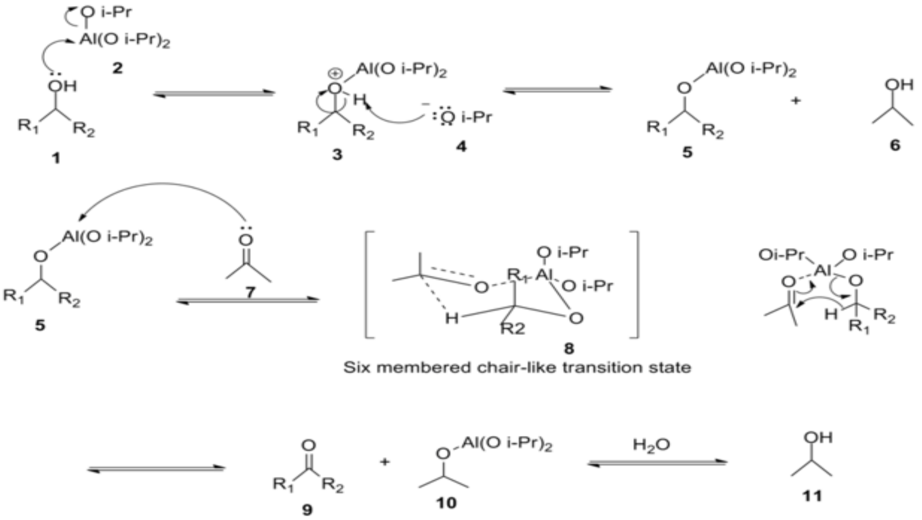


*Aluminum Iso Prop oxide*

## The following Steps involved in this Mechanism.



| | |
|---|---|
| (1) | Coordinates to the aluminum to form a complex. |
| (3) | Which then, in the second step, gets deprotonated by an alkoxide ion |
| (4) | To generate an alkoxide intermediate |
| (5) | In the third step, both the oxidant acetone |
| (7) | The substrate alcohol are bound to the aluminum. The acetone is coordinated to the aluminum whichactivates it for the hydride transfer from the alkoxide. The aluminum-catalyzed hydride shift from the α-carbon of the alcohol to the carbonyl carbon of acetone proceeds over a six-membered transition state |
| (8) | The desired ketone |
| (9) | is formed after the hydride transfer |



## Applications of Oppenauer Reaction: -

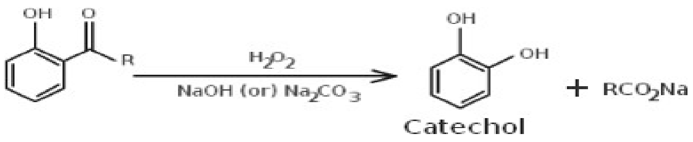
1.Oppenauer oxidation is used to prepare analgesics in the **pharmaceutical industry such as morphine and codeine**. For instance, codeinone is prepared by the Oppenauer oxidation of codeine.

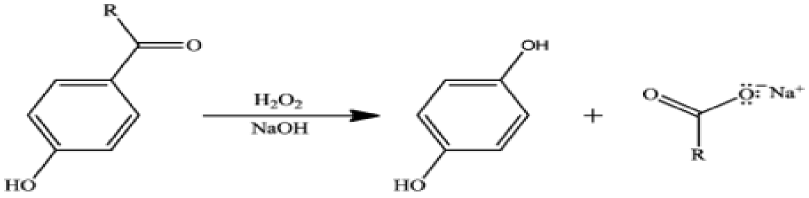
2. The Oppenauer oxidation is also used to **synthesize hormones**. **Progesterone** is prepared by the Oppenauer **oxidation of pregnenolone**.

3. The Oppenauer oxidation is also used in the **synthesis of lactones from 1,4 and 1,5 diols.**

## Dakin Reaction: -

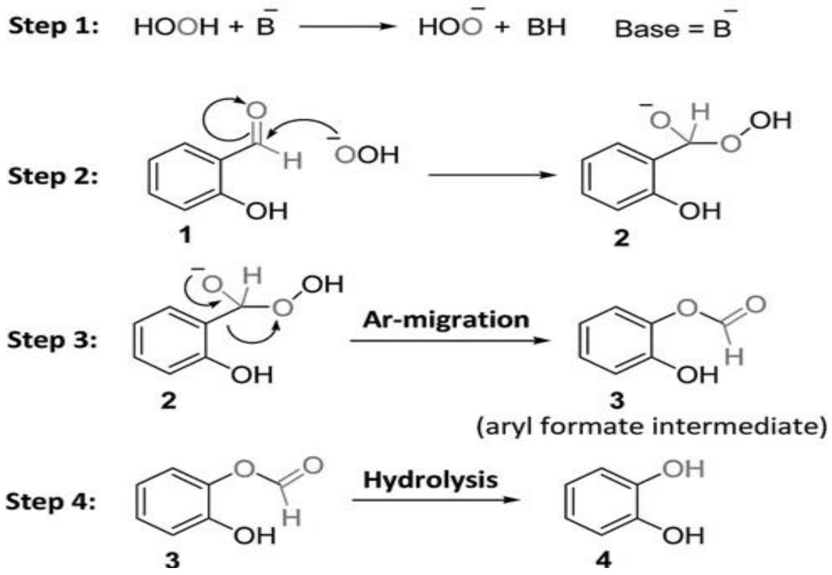
Dakin Reaction is the ***replacement of the aldehyde group of ortho and para hydroxy and ortho amino-benzaldehyde (or ketone)*** *by* ***a hydroxyl group*** *on reaction with* ***alkaline hydrogen peroxide***.





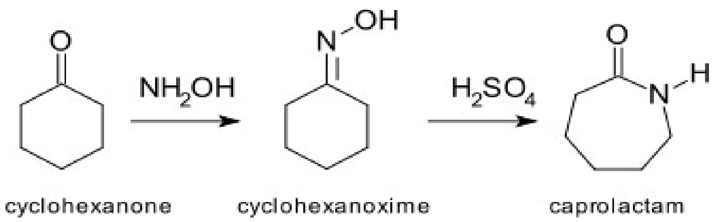
### Mechanism: - The following steps involved in this mechanism.

Reaction starts with nucleophilic addition of hydroperoxide anion to the carbonyl carbon and forms a tetrahedral intermediate. Intermediate then breaks down to cause 1,2 aryl Migration, Hydroxide elimination and formation of phenyl ester which is then hydrolyzed to form product.

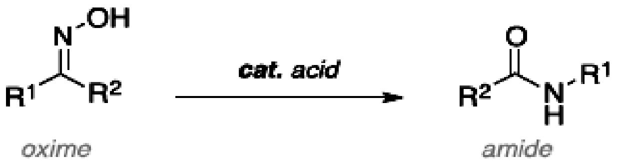


### Beckmann Rearrangement Reaction: -

**The Beckmann rearrangement** is an organic reaction used to convert **an oxime** to an **amide** under **acidic conditions.**

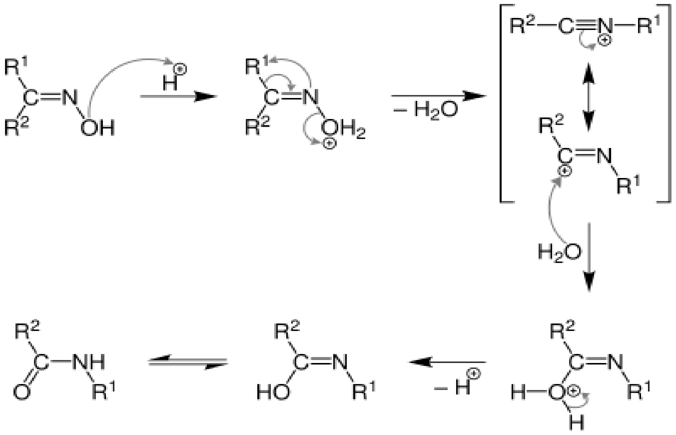


### Reaction Mechanism:



The most common reaction mechanism of the Beckmann rearrangement consists generally of **an**

**alkyl migration anti-periplanar to the expulsion of a leaving group to form a nitrilium ion**. This is followed by solvolysis to an imine and then tautomerization to the amide:

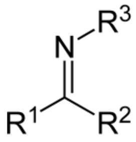


## Applications of Beckmann Rearrangement: -

1.An industrial synthesis of paracetamol developed by Hoechst- Celanese involves the conversion of a methyl ketone to an acetanilide via a Beckmann rearrangement.

2. The Beckmann rearrangement is also used in the synthesis of DHEA, benazepril, ceforanide, elanzepine, 17- aza progesterone, elantrine, prazepine, enprazepine, and etazepine.

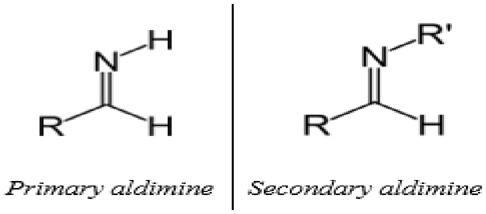
**Imine** An **imine** is a functional group or chemical compound containing a **carbon–nitrogen double bond**.



**Imine**

A **primary imine** in which C is attached to both a hydrocarbyl and a H is called a **primary aldimine**.

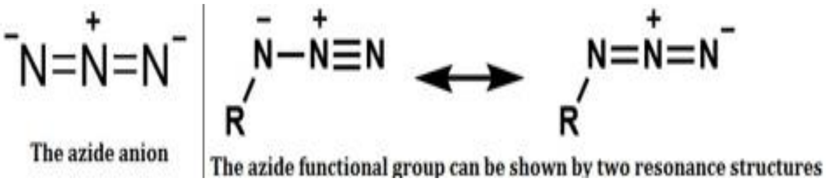
A **secondary imine** with such groups is called a **secondary aldimine**.



## Azide: -

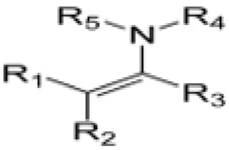
Azide is the anion with the formula **$N^{3-}$**. It is the conjugate base of hydrazoic acid **($HN_3$)**. **$N^{3-}$** is a linear anion.

The dominant application of azides is as a propellant in air bags.



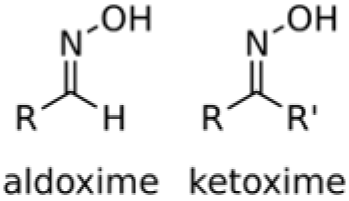
## Enamine: -

An **ENAMINE** is an unsaturated compound derived by the condensation of an aldehyde or ketone with asecondary amine.



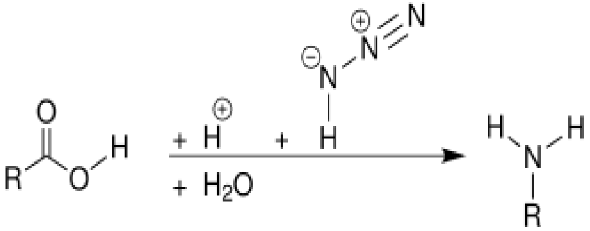
## Oxime: -

An oxime is a chemical compound belonging to the imines, with the general formula RR'C=NOH, where R is anorganic side-chain and R' may be hydrogen, forming an aldoxime, or another organic group, forming a ketoxime.



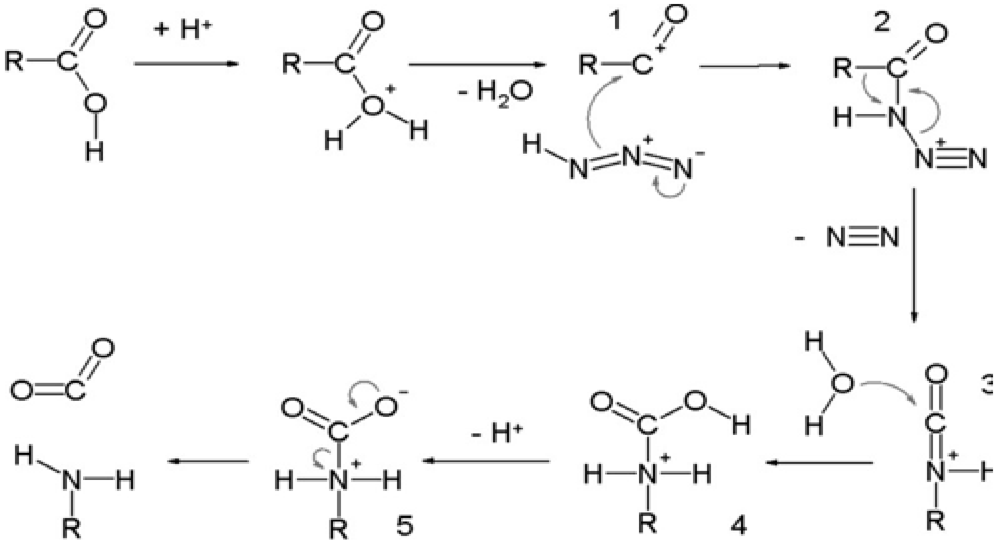
## Schmidt Rearrangement: -

The Schmidt reaction is an organic reaction in which an azide reacts with a carbonyl group to give an amine or amide, with expulsion of nitrogen. It is named after Sir Karl Friedrich Schmidt.

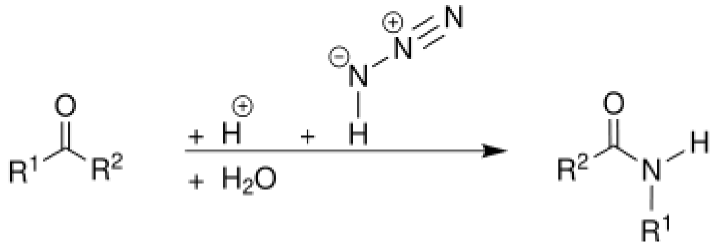


**Mechanism: -**

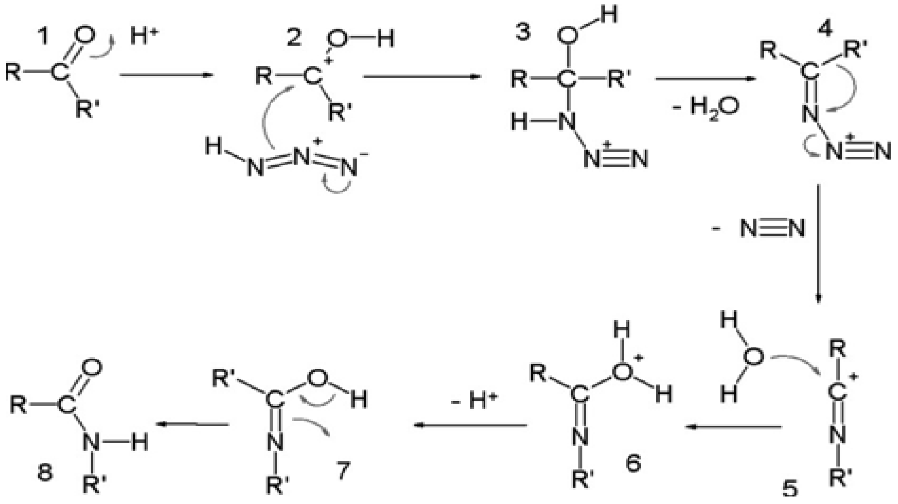
**1.With Carboxylic acid to give Primary Amine**.



## 2. With Ketone to give Amides.



**Mechanism:**



**Applications of Schmidt Reaction: -**

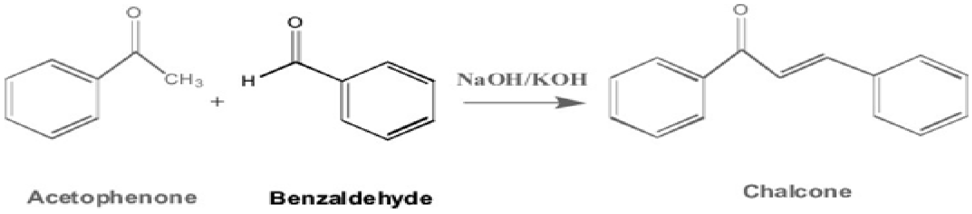
1. The scope of this reaction has been extended to reactions of carbonyls with alkyl azides R-$N_3$.

2. These are annulation reactions and have some utility in the synthesis of natural products such as lactams and alkaloids

## Claisen–Schmidt Condensation Reaction: -

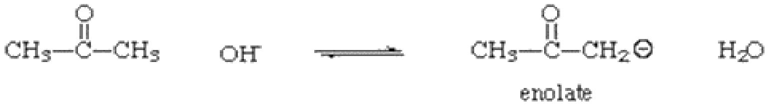
The reaction between an aldehyde or ketone having an alpha-hydrogen with an aromatic carbonyl compound lacking an alpha hydrogen is called the Claisen–Schmidt Condensation.

In cases where the product formed still has reactive alpha hydrogen and a hydroxide adjacent to an aromatic ring, the reaction will quickly undergo dehydration leading to the condensation product.



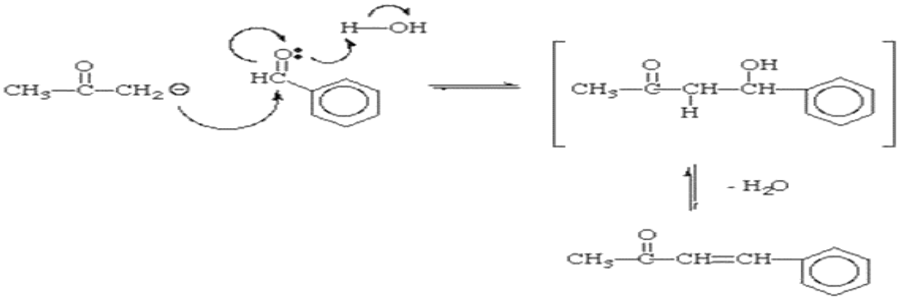
## Mechanism: -

**Step 1: Enolate ions** are formed when molecules with hydrogens alpha to a carbonyl group are treated with a base like sodium hydroxide. For example, acetone reacts with base to give an enolate.



$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \quad OH^- \rightleftharpoons \underset{\text{enolate}}{CH_3-\overset{O}{\overset{\|}{C}}-CH_2^{\ominus}} \quad H_2O$$

**Step 2:** Carbanion attack at carbonyl carbon of an aldehyde to form addition product and hydrolyzed and get a final product chalcone.



## Questions carrying (2 marks)

1. In $LiAlH_4$ and $NaBH_4$ which one more reactive than hydride donar?

2. How will you prepare amines from amides?

3. What is the Clemmensen reduction reaction?

4. Which reduction is useful to convert carbonyl groups into methylene groups.

5. What is Schmidt Reaction?

6. Write Dakin Reaction.

## Questions carrying (5 marks)

1. Give the mechanism involved in Claisen- Schmidt Condensation.

2. Write a note on Dakin Reaction.

3. Explain Clemmensen reduction.

4. write down mechanism involved in Birch Reduction.

5. Write a note on method which is useful for oxidizing secondary alcohol into ketones.

## Questions carrying (10 marks)

1. Explain metal hydride reduction with its mechanism.

2. Write a detailed note on –

a) Clemmensen reduction

b) Birch reduction

3. Explain the mechanism of following reaction-

a) Wolff-Kishner reduction

b) Schmidt reaction

4. What is Claisen-Schmidt Condensation. Give its mechanism and importance.

5 Explain

a) Dakin reaction

b) Beckmann rearrangement