

# Unit-5

## Pharmaceutical Organic Chemistry-III

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### **B.Pharma 4<sup>st</sup> Sem Notes**

#### **UNIT-V**

##### **Reactions of synthetic importance**

- Metal hydride reduction ( $\text{NaBH}_4$  and  $\text{LiAlH}_4$ ), Clemmensen reduction, Birch reduction, Wolff Kishner reduction.
- Oppenauer-oxidation and Dakin reaction.
- Beckmanns rearrangement and Schmidt rearrangement.
- Claisen-Schmidt condensation

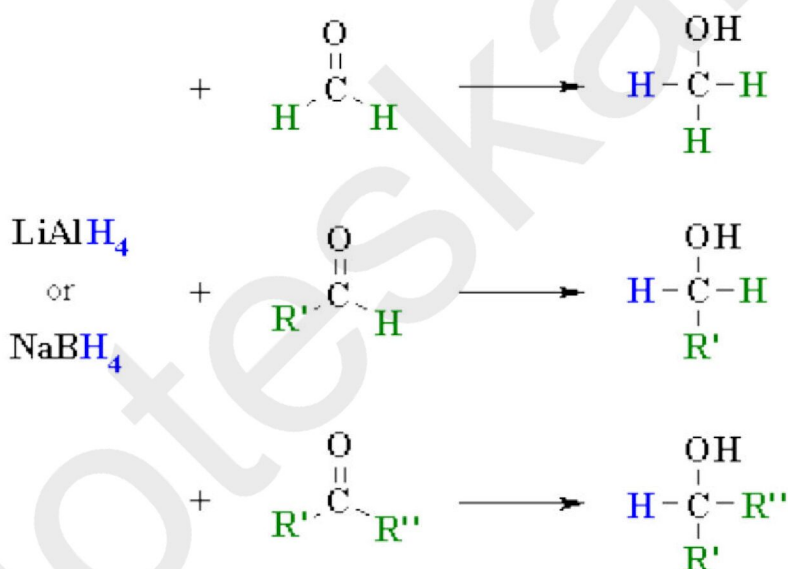
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## Reactions of synthetic importance:

### Metal hydride reduction ( $\text{NaBH}_4$ and $\text{LiAlH}_4$ ):

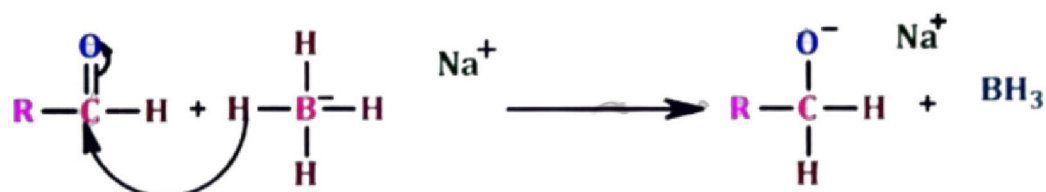
- Reduction of various carbonyl compounds is done by using reagents that transfer a hydride from boron or aluminium.
- The most common sources of the hydride nucleophile are lithium aluminium hydride and sodium borohydride.
- The hydride anion is not present during this reaction rather these reagents serve as a source of hydride due to the presence of a polar metal hydrogen bond. Because aluminium is less electronegative than boron the Al-H bond in  $\text{LiAlH}_4$  is more polar, thereby making  $\text{LiAlH}_4$  a stronger reducing agent.



### Mechanism of ( $\text{NaBH}_4$ and $\text{LiAlH}_4$ ):

#### $\text{NaBH}_4$ :

1. Nucleophilic attack by hydride:

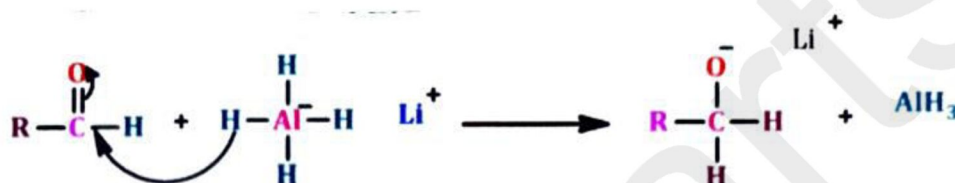


2. Protonation of Alkoxide ion:

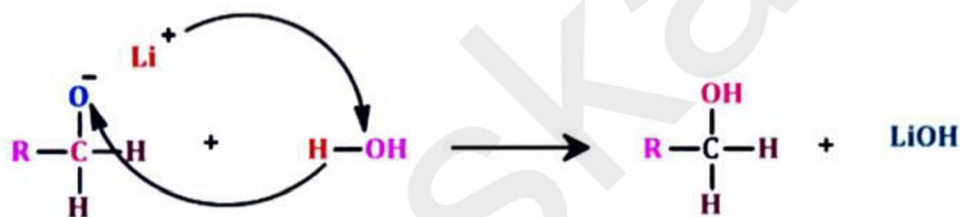


## LiAlH<sub>4</sub>:

1. Nucleophilic attack by hydride:



2. Protonation of Alkoxide ion:



## Application:

- Aldehydes are converted into primary alcohol (Alcohol Preparation).
- Ketones are converted into secondary alcohol (Alcohol Preparation)

## Clemmensen reduction:

- The conversion of a carbonyl group to a methylene group is done by Clemmensen reduction.
- It consists of heating the aldehyde or ketone with zinc amalgam and aq HCl.
- The Clemmensen reduction is named after a Danish chemist, Erik Christian Clemmensen.
- The reaction is highly specific for aldehydes and ketones and can be carried out with many other functional groups present.

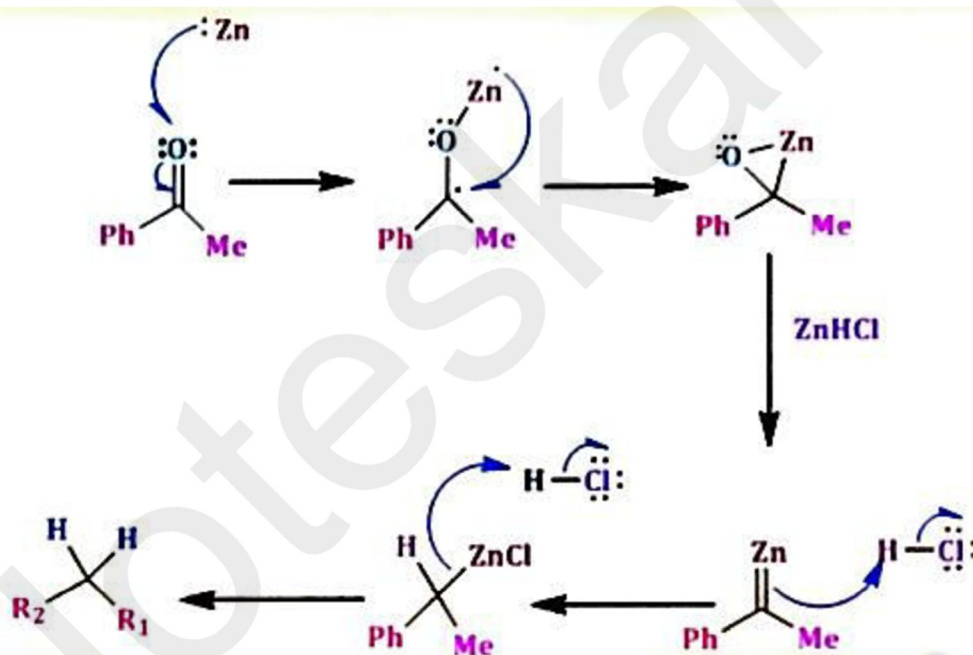
## General Reaction:



R1 = Alkyl, Aryl

R2 = H Alkyl, Aryl

### Mechanism:



### Birch Reduction:

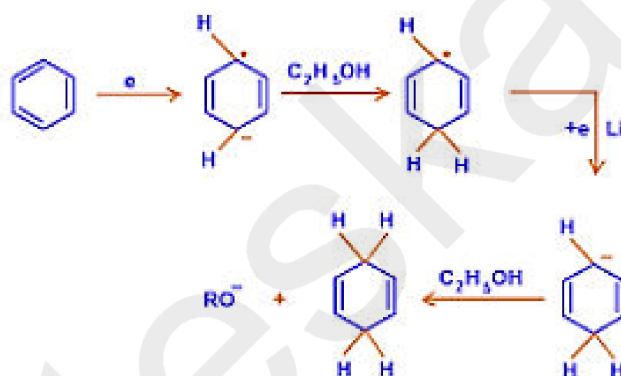
- The Birch reduction is an organic chemical reaction where aromatic compounds which have a benzenoid ring are converted into 1,4-cyclohexadiene which have two hydrogen atoms attached at opposite ends of the molecule.
- It is a very useful reaction in synthetic organic chemistry. The Birch reduction can be classified as an organic redox reaction. Here, an organic reduction of aromatic rings in liquid ammonia with sodium, lithium or

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potassium and alcohol occurs. An example of a Birch reduction reaction is the reduction of naphthalene.

### Mechanism of Birch Reduction:

- The solvated electrons (the free electrons in the solution of sodium in liquid ammonia which are responsible for the intense blue colour) add to the aromatic ring, giving a radical anion.
- This radical anion is supplied with a proton by the alcohol.
- The alcohol also supplies another proton to the penultimate carbanion. Now, with the alcohol present, the products – cyclohexadiene and an alkoxide ion are formed.
- The Birch reduction mechanism is illustrated below.



- Thus, the required 1,4 cyclohexadiene where two hydrogen atoms are attached on opposite ends of the molecule is formed.
- Alternative organic solvents such as tetrahydrofuran can be employed instead of ammonia since liquid ammonia must be condensed into a flask and left to evaporate overnight post the completion of the reaction.

### Wolff Kishner reduction:

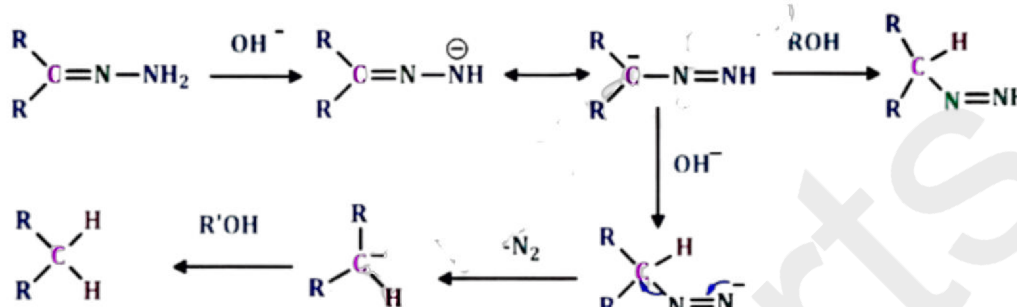
- Wolff-Kishner reduction is a most common reduction used to convert carbonyl groups into methylene groups.
- This reduction is generally used for removing a carbonyl group after it has served its synthetic purpose. It involves reduction of the hydrazones of the aldehydes and ketones in alkaline medium at high temperature to give hydrocarbons.



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### Mechanism:

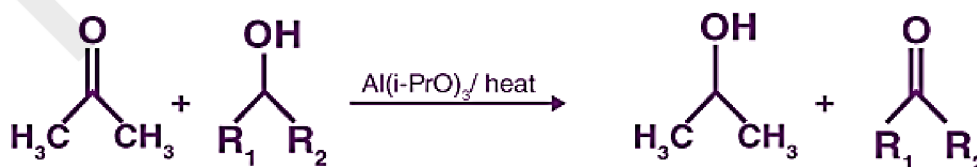
- The classical Wolff-Kishner decomposition of the hydrazones of aldehydes and ketones in alkaline medium at high temperature to give hydrocarbons involves anion followed by isomerization to an azo compound and loss of nitrogen as showed below.



- The severity of the reaction condition can be brought down to room temperature if a strong base is used in a highly polar medium.

### Oppenauer Oxidation:

- Oppenauer Oxidation is the process of conversion of secondary alcohols to ketones by selective oxidation.
- This reaction is named after Rupert Viktor Oppenauer. Oxidation reaction takes place in the presence of  $[Al(i-PrO)_3]$  in excess of acetone.
- It is an aluminium alkoxide catalysed oxidation of a secondary alcohol to the corresponding ketone.
- This is the reverse of the Meerwein Ponndorf Verley reduction. It is a very good method to oxidise allylic alcohols to  $\alpha, \beta$ -unsaturated ketones.

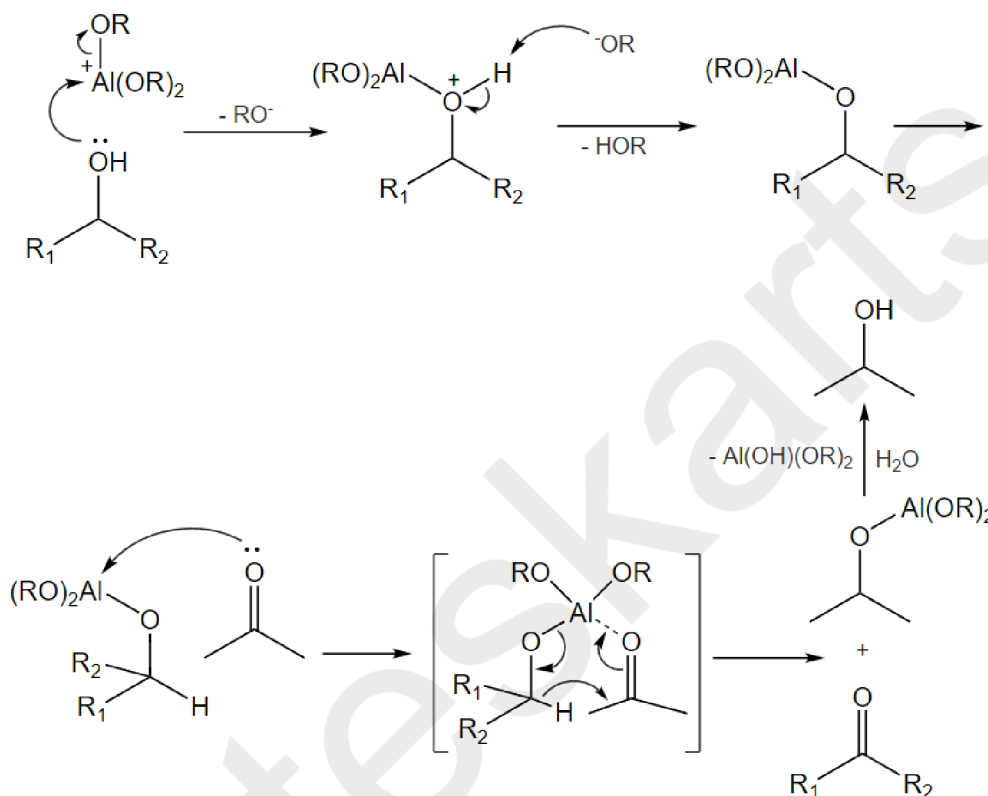


### Oppenauer Oxidation Mechanism:

- In the first step, alcohol coordinates with aluminium isopropoxide to form a complex

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2. This complex reacts with a ketone to form a six-membered transition complex
3. The alpha-carbon of the alcohol is converted to the carbonyl carbon from the aluminium-catalysed hydride shift.
4. The acetone proceeds over a six-membered transition state.
5. The desired ketone is formed after the hydride transfer



### Beckmann Rearrangement:

- The Beckmann Rearrangement is a reaction of the oximes that can bring about either nitriles or amides, contingent upon the beginning material.
- These Oximes that are obtained from the ketones develop into amides; oximes got from the aldehydes shape into nitriles.
- The Beckmann Rearrangement process is a natural reaction that is useful in changing an oxime to that of an amide under some acidic conditions.
- The reaction eventually starts with the process of protonation of the alcohol group gathering shaping a preferred leaving group.
- The R group transition to that of the leaving species then moves to the nitrogen, bringing about a carbocation and the arrival of a water particle.
- The water atom attacks the carbocation, and after the process of deprotonation and tautomerization, the amide is obtained.

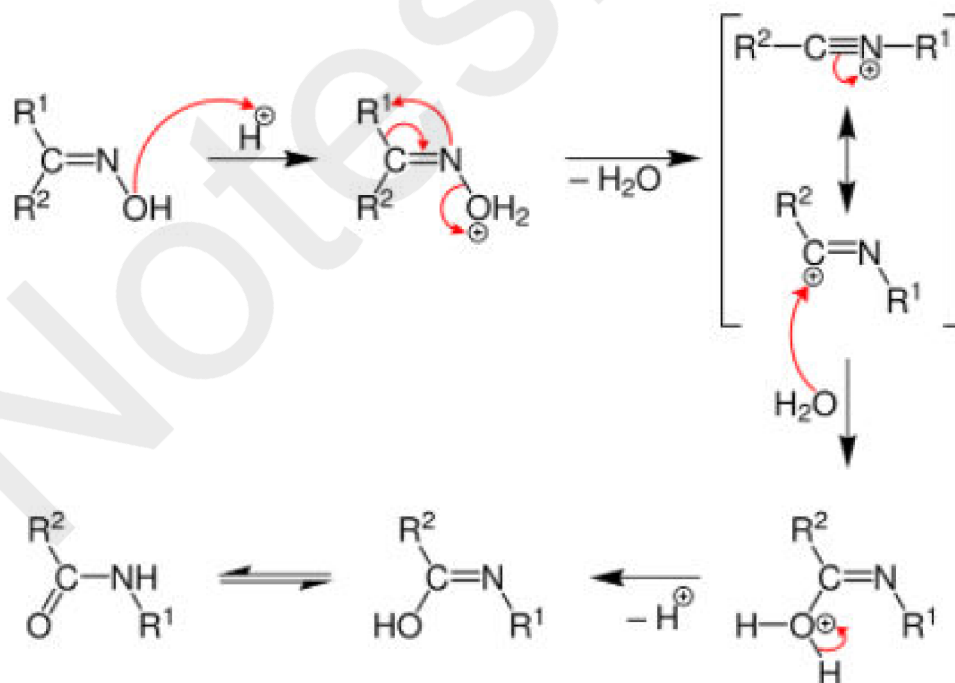
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- In simple, Beckmann Rearrangement is a reaction where oxime is changed over to an amide.
- The oxime is processed by treating an aldehyde or a ketone with hydroxylamine. This Beckmann Rearrangement reaction, is named after Ernst Otto Beckmann, a German scientist.

### Machanism:

The process of Beckmann Rearrangement is as shown below-

1. The oxime is shaped when cyclohexanone responds with the hydroxylamine.
2. The Protonation of hydroxyl of oxime happens after the change of the alkyl substituent "trans" to the nitrogen
3. At the same time, the N-O bond is severed with the expulsion of water.
4. Later, tautomerisation process happens which protonates the molecule of nitrogen and then prompts the production of amine.





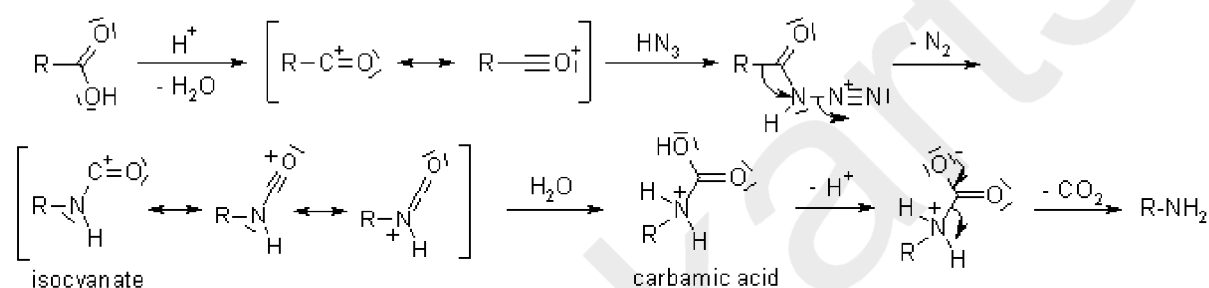
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### Schmidt rearrangement:

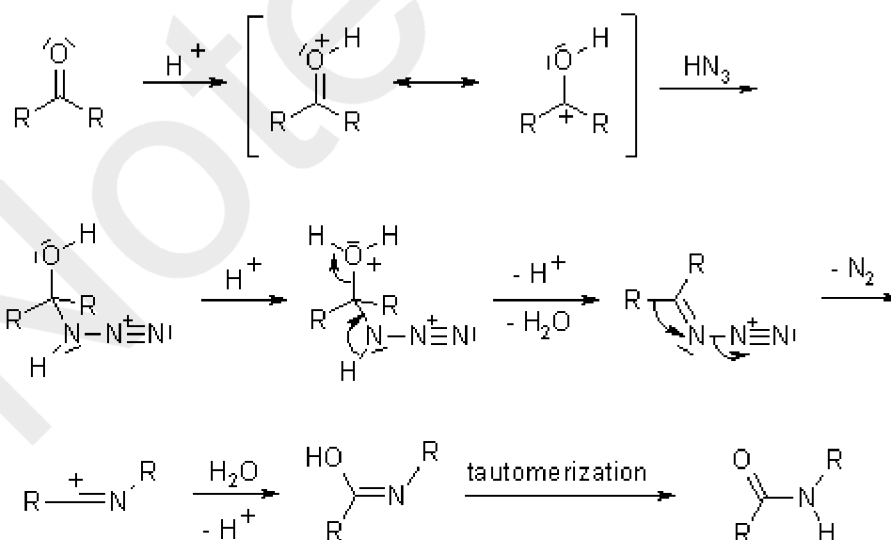
- Schmidt Reaction refers to an organic chemical reaction wherein azides are reacted with the carbonyl group of a compound to give rise to amines or amides.
- This reaction was first reported by Karl Friedrich Schmidt in 1924.

### Mechanism of the Schmidt Reaction

- Reaction of carboxylic acids gives acyl azides, which rearrange to isocyanates, and these may be hydrolyzed to carbamic acid or solvolysed to carbamates. Decarboxylation leads to amines.

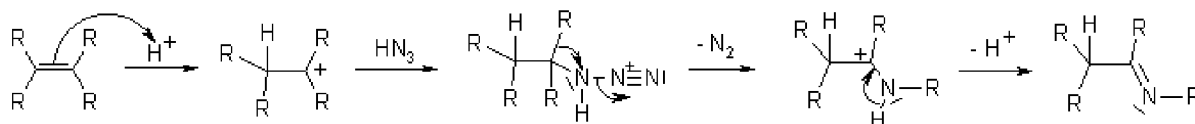


- The reaction with a ketone gives an azido hydrin intermediate, which rearranges to form an amide:



- Alkenes are able to undergo addition of HN<sub>3</sub> as with any HX reagent, and the resulting alkyl azide can rearrange to form an imine:

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- Tertiary alcohols give substitution by azide via a carbenium ion, and the resulting alkyl azide can rearrange to form an imine.

### Claisen-Schmidt condensation:

- A reaction of the vesatile enolate ion. 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.



- When an enolate forms from an aldehyde, the enolate will normally react with unreacted aldehyde to undergo the "aldol addition" or "aldol condensation" reaction.
- Since ketones are less reactive toward nucleophilic addition, the enolate formed from a ketone can be used to react with an aldehyde, a modification called the Claisen-Schmidt reaction.
- In cases where the product formed still has a reactive alpha hydrogen and a hydroxide adjacent to an aromatic ring, the reaction will quickly undergo dehydration leading to the condensation product.

