



UNIT-V

REACTIONS OF SYNTHETIC IMPORTANCE

Metal hydride reduction (NaBH_4 and LiAlH_4), Clemmensen reduction, Birch reduction, Wolff Kishner reduction.

Oppenauer-oxidation and Dakin reaction.

Beckmanns rearrangement and Schmidt rearrangement.

Claisen-Schmidt condensation

Reduction

Reduction is the loss of oxygen atom from a molecule or the gaining of one or more electrons. A **reduction reaction** is seen from the point of view of the molecule being **reduced**, as when one molecule gets **reduced** another gets oxidised. The full **reaction** is known as a **Redox reaction**.

Reduction of aldehydes and ketones.

The most common sources of the hydride nucleophile are lithium aluminium hydride (LiAlH_4) and sodium borohydride (NaBH_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.



LiAlH₄ can reduce aldehydes to primary alcohols, ketones to secondary alcohols, carboxylic acids and esters to primary alcohols, amides and nitriles to amines, epoxides to alcohols and lactones to diols.

The two factors combined to make **LiAlH₄** a **stronger** reducing agent **than NaBH₄**. This general reduction in the strength of the bond to the hydrogen may also help to increase the reactivity of **LiAlH₄** when it is compared with LiBH₄.

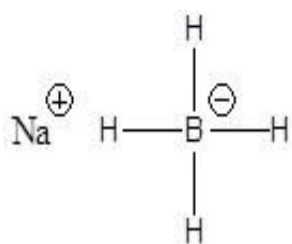
NaBH₄ is preferred for aldehydes and ketones because it does not react with water, the way **LiAlH₄** does and can be **used** as an aqueous solution, whereas the **LiAlH₄** must be delivered in an anhydrous solution of diethyl-ether, Et₂O, and then neutralized by water and acid to isolate the product.

The reaction mechanism for **metal hydride reduction** is based on **nucleophilic addition of hydride** to the carbonyl carbon. In some cases, the alkali **metal** cation, especially Li⁺, activates the carbonyl group by coordinating to the carbonyl oxygen, thereby enhancing the electrophilicity of the carbonyl.

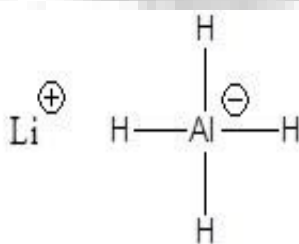
Metal Hydride Reduction Reaction (NaBH₄ and LiAlH₄)

The most common sources of the hydride Nucleophile are **lithium aluminum hydride (LiAlH₄)** and **sodium borohydride (NaBH₄)**.

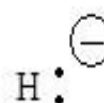
Example



Sodium Borohydride



Lithium Aluminum Hydride

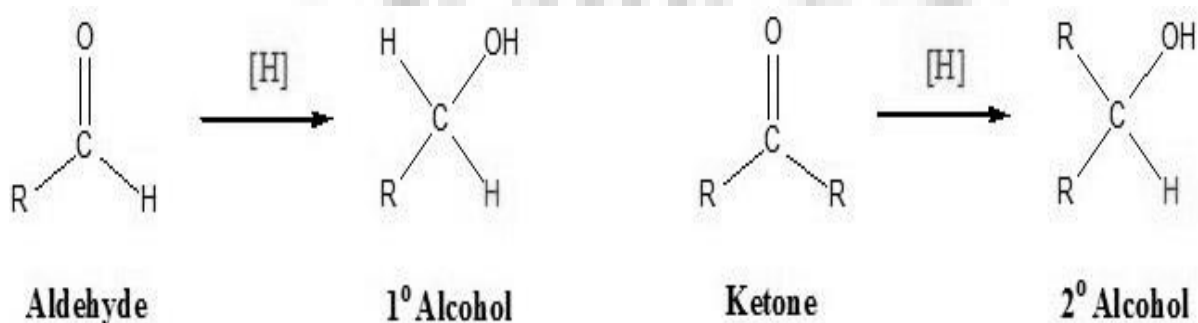


Hydride Nucleophile

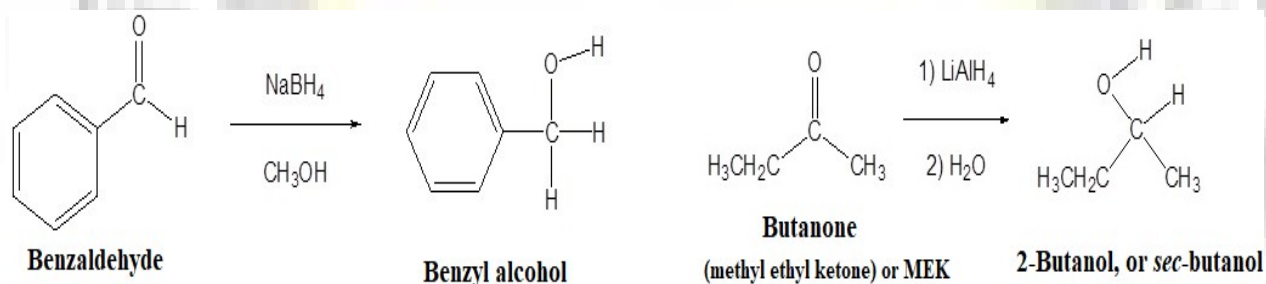
Addition of a hydride anion (H^-) to an **aldehyde** or **ketone** gives an **alkoxide anion**, which on protonation yields the corresponding alcohol.

Aldehydes produce 1^o-alcohols and ketones produce 2^o-alcohols.

Reaction of aldehyde and ketone



Example of aldehyde and ketone

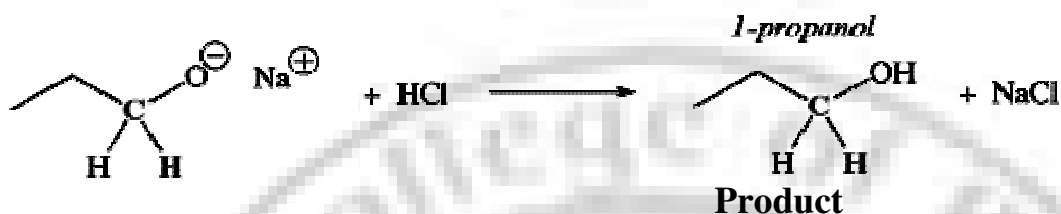
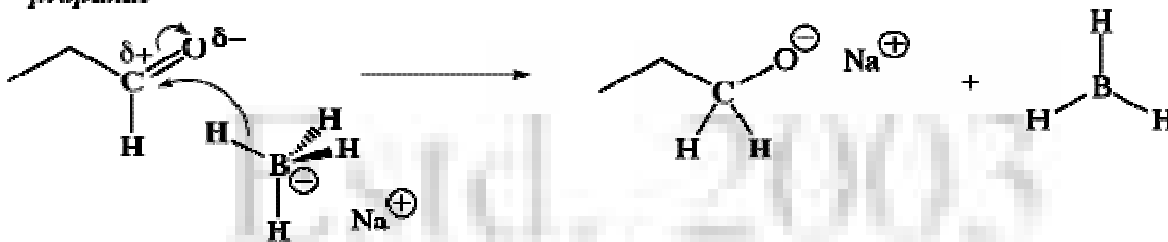


Reaction Mechanism

NaBH_4 Reduction: (for aldehyde)

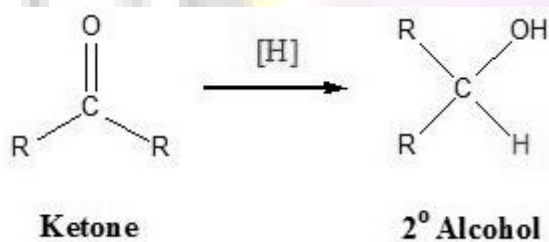
Example: mechanism of Reaction between propanal and NaBH_4

propanal



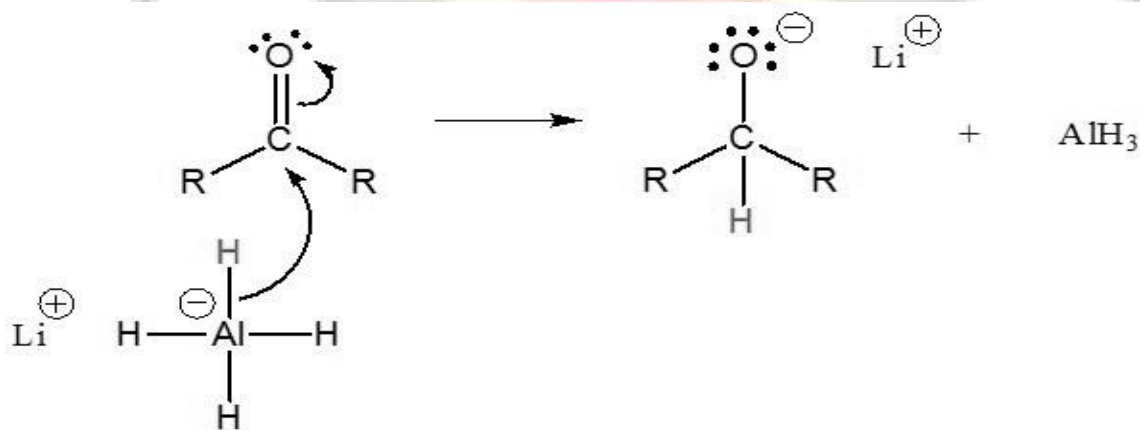
LiAlH₄ Reduction (for ketone)

Mechanism can be easily explained by simple reaction :



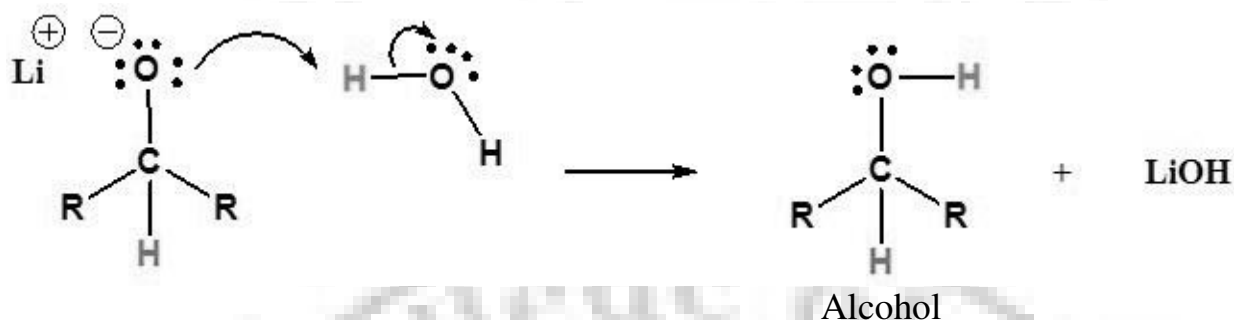
It includes two steps

Step 1: Nucleophilic attack by the hydride anion



Alkoxide

Step 2: The alkoxide is protonated



Protonated alkoxide give alcohol

Birch Reduction

The reduction of aromatic substrates with alkali metals, alcohol in liquid ammonia is known as "Birchreduction".

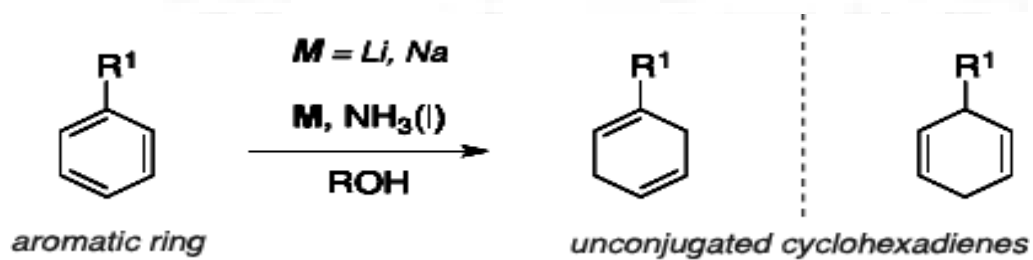
The Birch reduction is an organic reaction where aromatic rings undergo a **1,4-reduction** to provide unconjugated **cyclohexadienes**.

The reduction is conducted by **sodium** or **lithium** metal in **liquid ammonia** and in the presence of an **alcohol**.

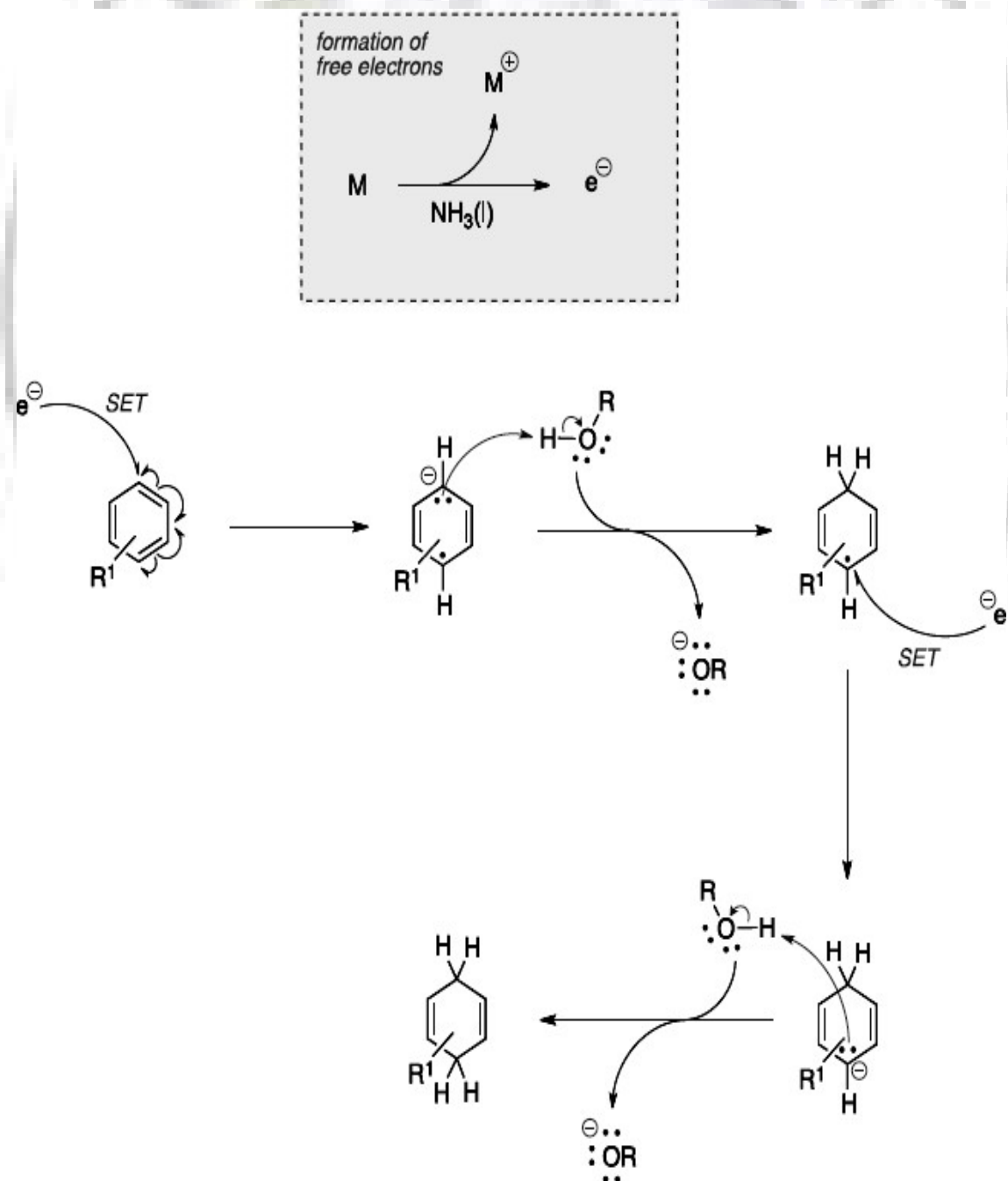
The mechanism begins with a **Single Electron Transfer (SET)** from the metal to the aromatic ring, forming a radical anion.

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 by-product.

REACTION



MECHANISM OF REACTION



Clemmensen Reduction Reaction

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 **-CH₂-** 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.)

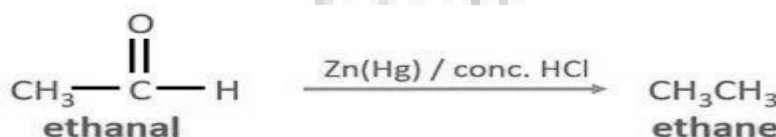
REACTION



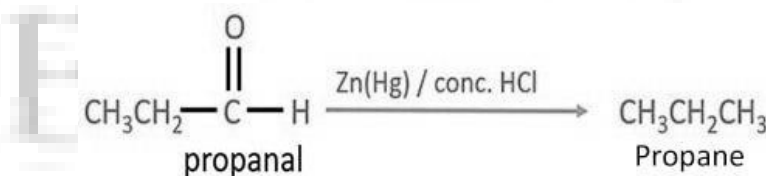
EXAMPLE

1. Ethanal is reduced to ethane by Clemmensen reduction.

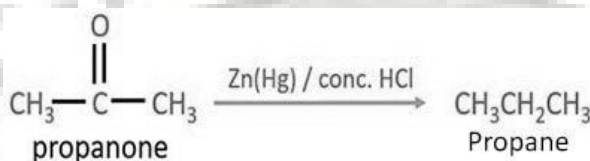
Zinc amalgam and **concentrated HCl** is used as the Clemmensen reducing reagent.



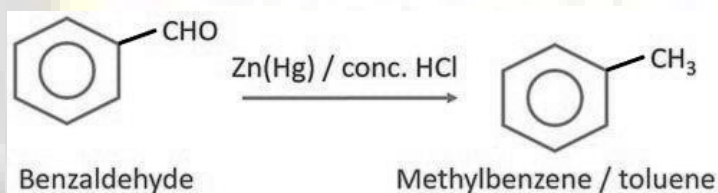
2. Propanal and **Zn(Hg)/conc. HCl**, propane is given as the product.



3. Propanone gives propane as the product with **Zn(Hg)/conc. HCl**.

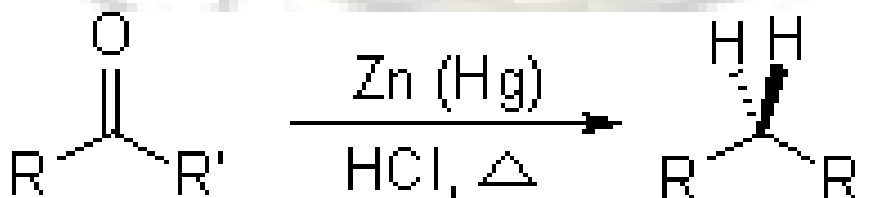


4. **Benzaldehyde** gives **Methylbenzene** (toluene) when reacted with **Zn(Hg) / concentrated HCl**.

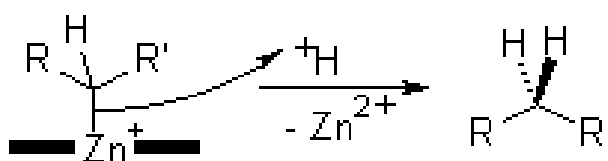
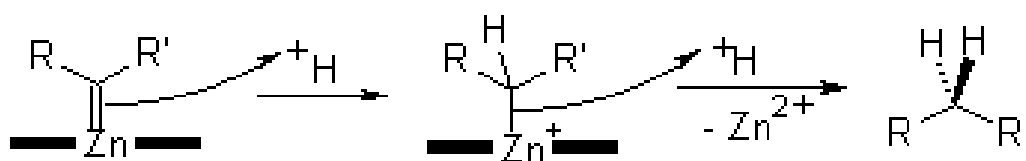
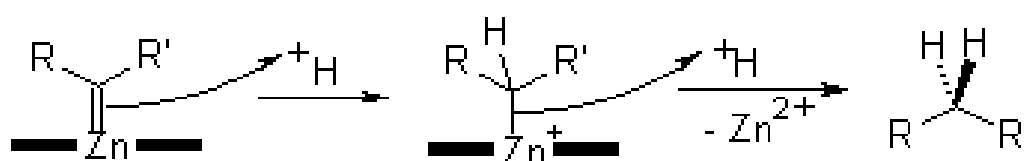
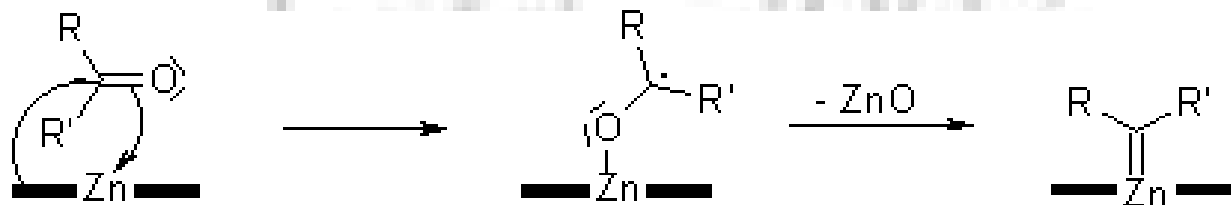


Reaction Mechanism

Reaction



Mechanism

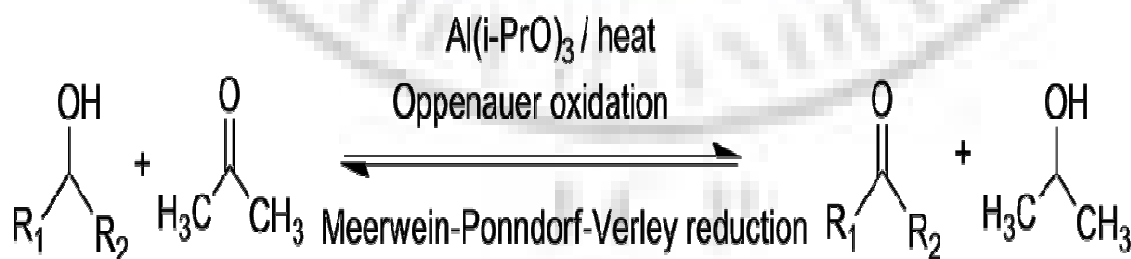


Oppenauer Oxidation Reaction

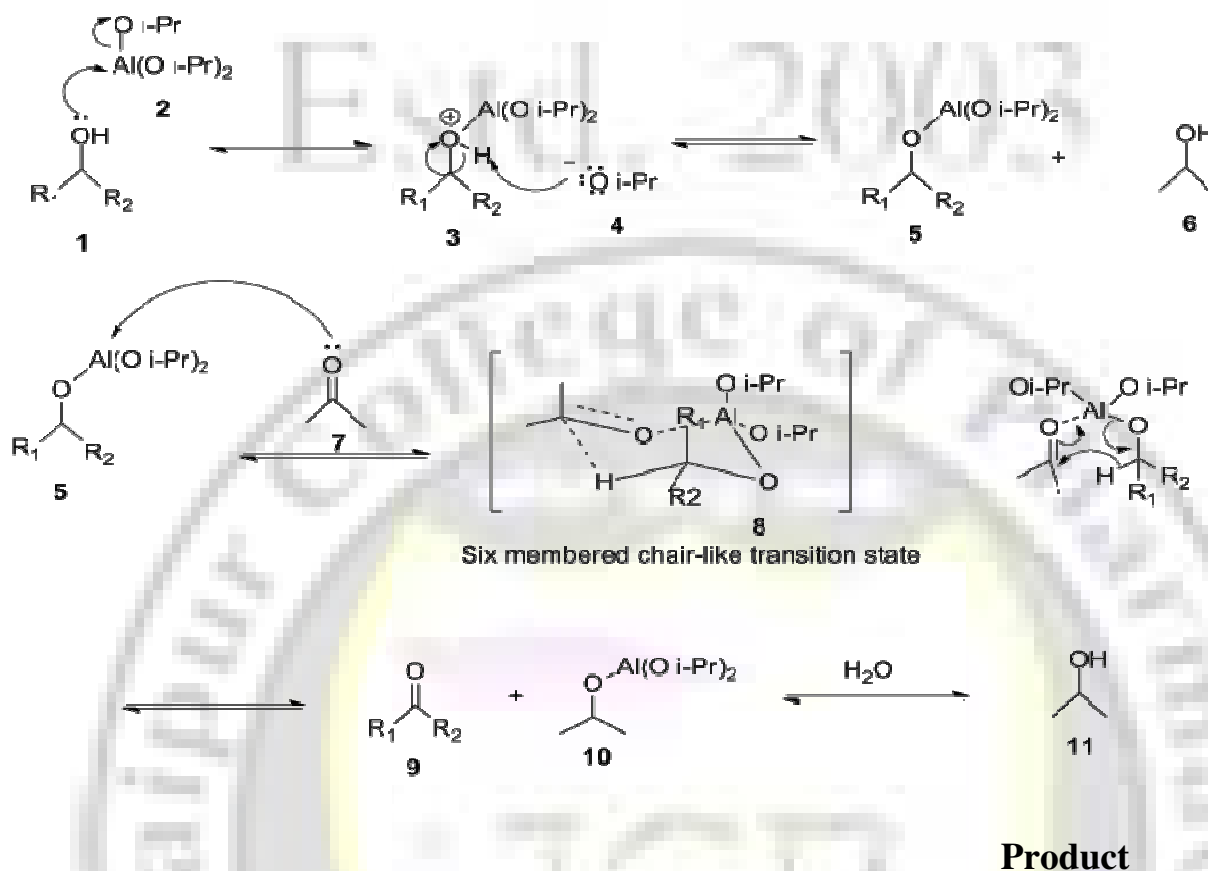
The Oppenauer oxidation is an organic reaction used to convert a **primary or secondary alcohol** to a **ketone** using another excess ketone reagent (such as acetone) and an **aluminium isopropoxide** catalyst.

The reaction is the opposite of Meerwein–Ponndorf–Verley reduction.

Reaction



Reaction Mechanism:



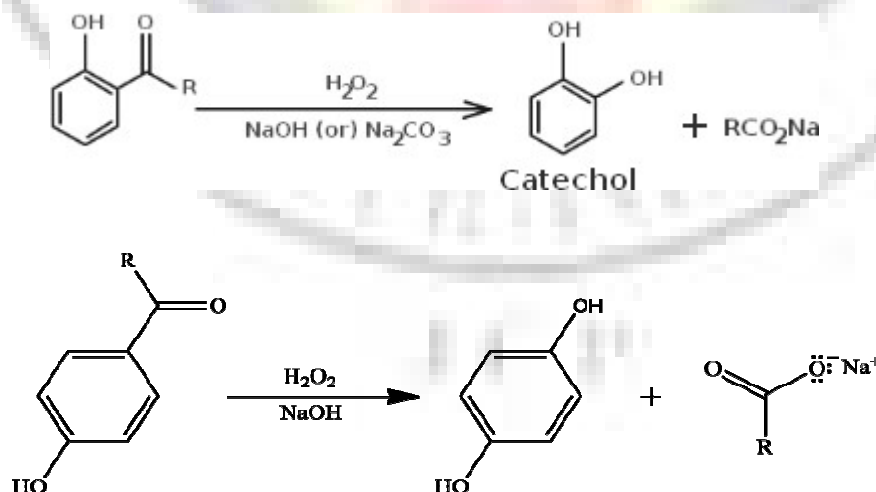
- ✓ Oppenauer oxidation is used to prepare analgesics in the pharmaceutical industry such as morphine and codeine. For instance, codeinone is prepared by the Oppenauer oxidation of codeine
- ✓ The Oppenauer oxidation is also used to synthesize hormones. Progesterone is prepared by the Oppenauer oxidation of pregnenolone
- ✓ A slight variation of the Oppenauer oxidation is also used to synthesize steroid derivatives. For example, an efficient catalytic version of the Oppenauer oxidation which employs a ruthenium catalyst has been developed for the oxidation of 5-unsaturated 3 β -hydroxy steroids to the corresponding 4-en-3-one derivative.
- ✓ The Oppenauer oxidation is also used in the synthesis of lactones from 1,4 and 1,5 diols

Dakin Reaction

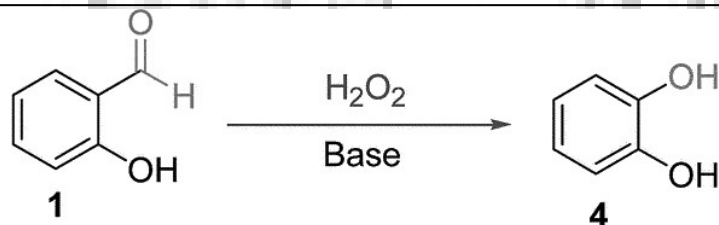
Dakin Reaction is the replacement of the **aldehyde group** of **ortho and parahydroxy** and **orthoamino- benzaldehyde** (or **ketone**) by a **hydroxyl group** on reaction with **alkaline hydrogenperoxide**.

Dakin oxidation is most commonly used to synthesize benzenediols and alkoxyphenols. Catechol for example, is synthesized from *o*-hydroxy and *o*-alkoxy phenyl aldehydes and ketones, and is used as the starting material for synthesis of several compounds, including the catecholamines, catecholamine derivatives, and 4-*tert*-butylcatechol, a common antioxidant and polymerization inhibitor. Other synthetically useful products of the Dakin oxidation include guaiacol, a precursor of several flavorants; hydroquinone, a common photograph-developing agent; and 2-*tert*-butyl-4-hydroxyanisole and 3-*tert*-butyl-4-hydroxyanisole, two antioxidants commonly used to preserve packaged food. In addition, the Dakin oxidation is useful in the synthesis of indolequinones, naturally occurring compounds that exhibit high anti-biotic, anti-fungal, and anti-tumor activities.

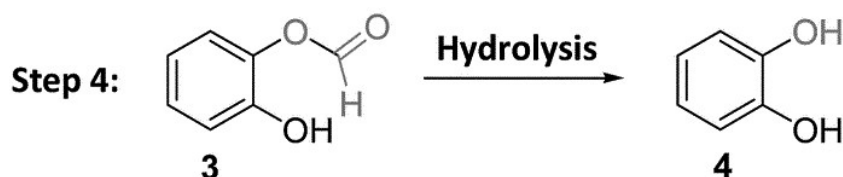
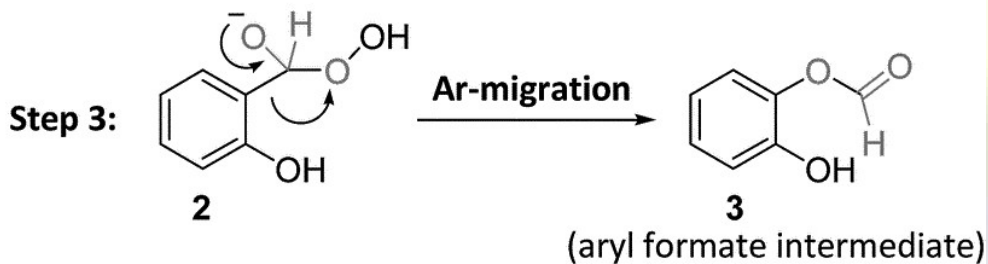
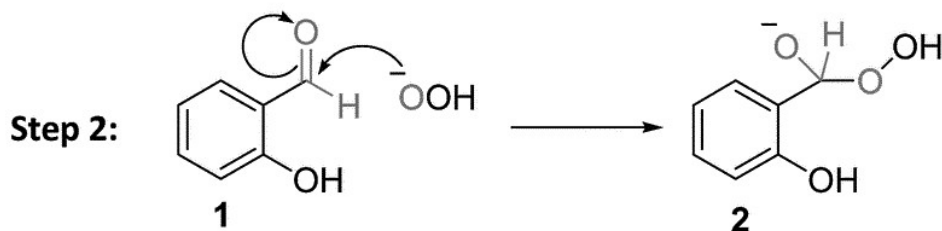
Reaction



Mechanism



Mechanism:



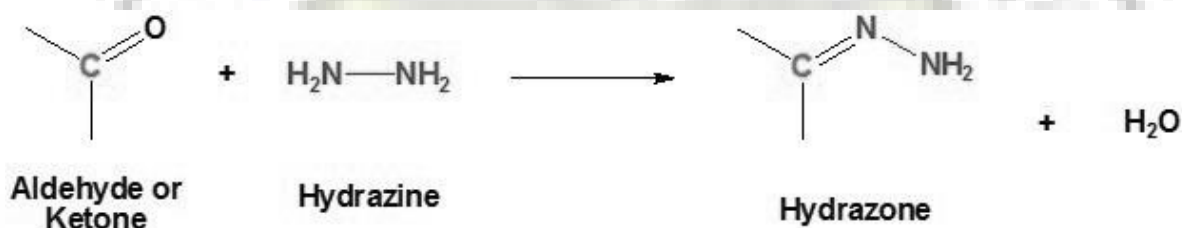
It can be easily explained by this reaction

Wolff Kishner Reduction

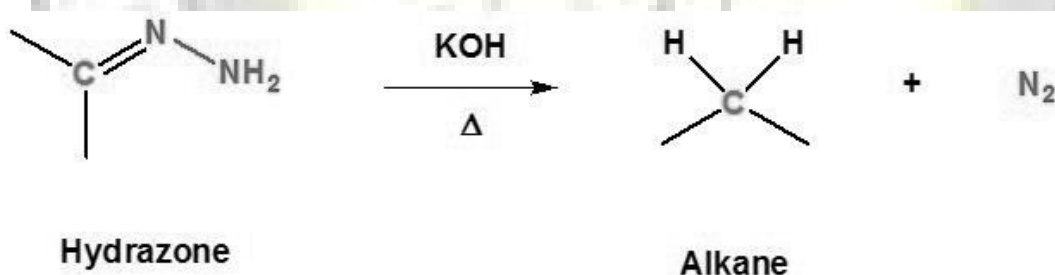
The **reduction** of **aldehydes** and **ketones** to **alkanes**. Condensation of the **carbonyl compound** with **hydrazine** forms the **hydrazone**, and treatment with base induces the reduction of the carbon coupled with oxidation of the **hydrazine** to **gaseous nitrogen**, to yield the corresponding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

Reaction of Aldehydes or Ketones with Hydrazine Produces a Hydrazone.

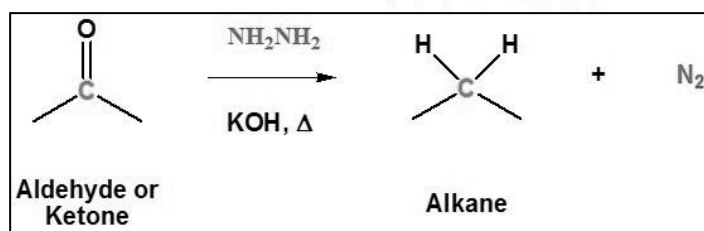
Reaction



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



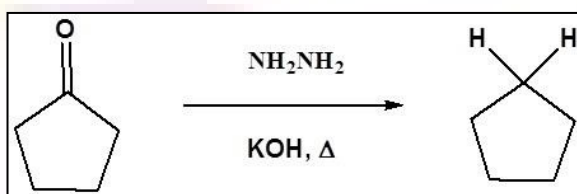
Both Reactions Together Produces the Wolff-Kishner Reduction product



The Wolff-Kisher 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**.

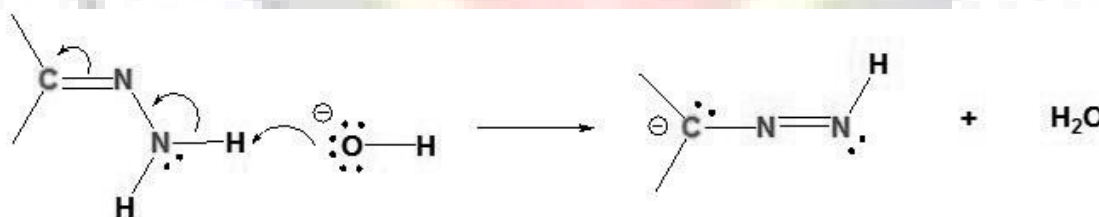
Wolff-Kishner vs. Clemmensen Reductions

- ✓ 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..
- ✓ Wolff-Kishner reduction is also for aldehyde/ ketones in presence of hydrazine (N_2H_4), KOH, H_2O and $180^\circ C$ temperature to form alkane.

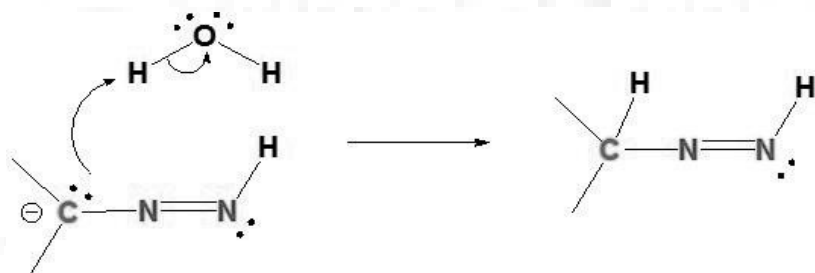


Mechanism of the Wolff-Kishner Reduction

Step 1: Deprotonation of Nitrogen



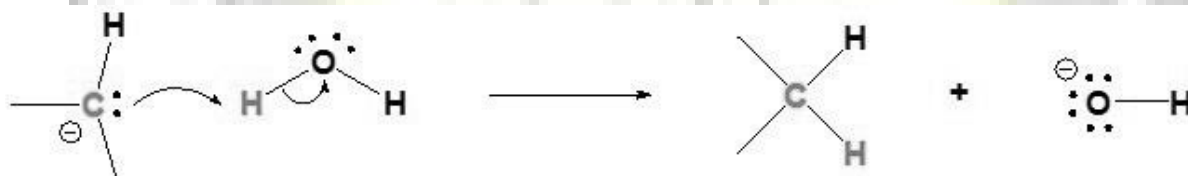
Step 2: Protonation of the Carbon



Step 3: Deprotonation of Nitrogen



Step 4: Protonation of Carbon

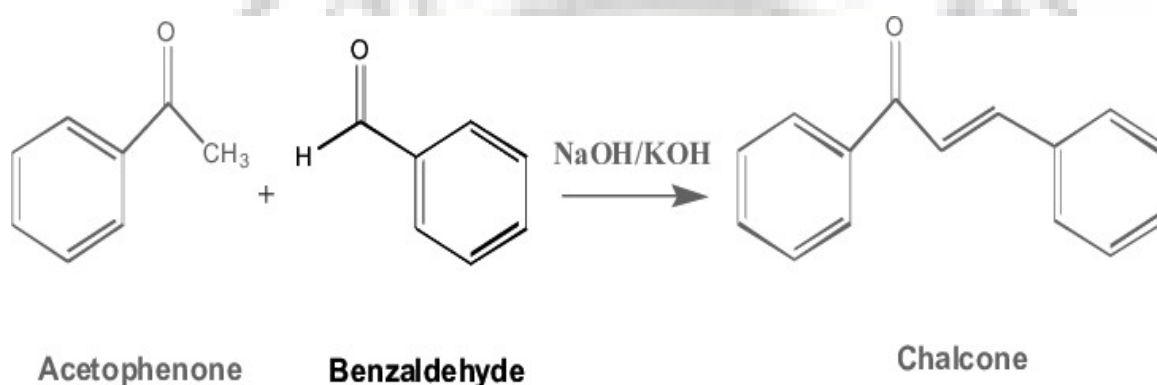


Alkanes

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.

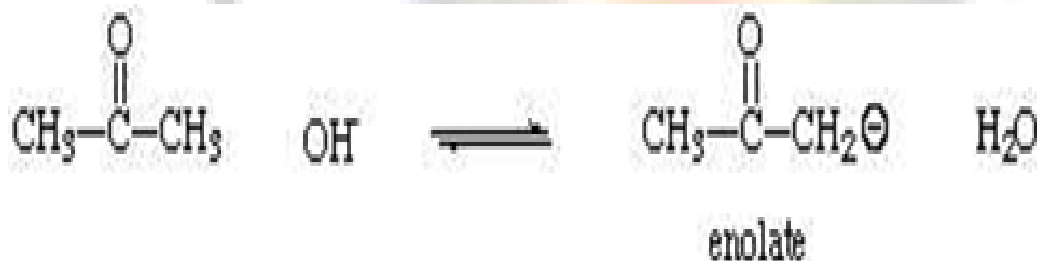
In cases where the product formed still has reactive alpha hydrogen and a hydroxide adjacent to an aromatic ring, the reaction will quickly undergo dehydration leading to the condensation product.



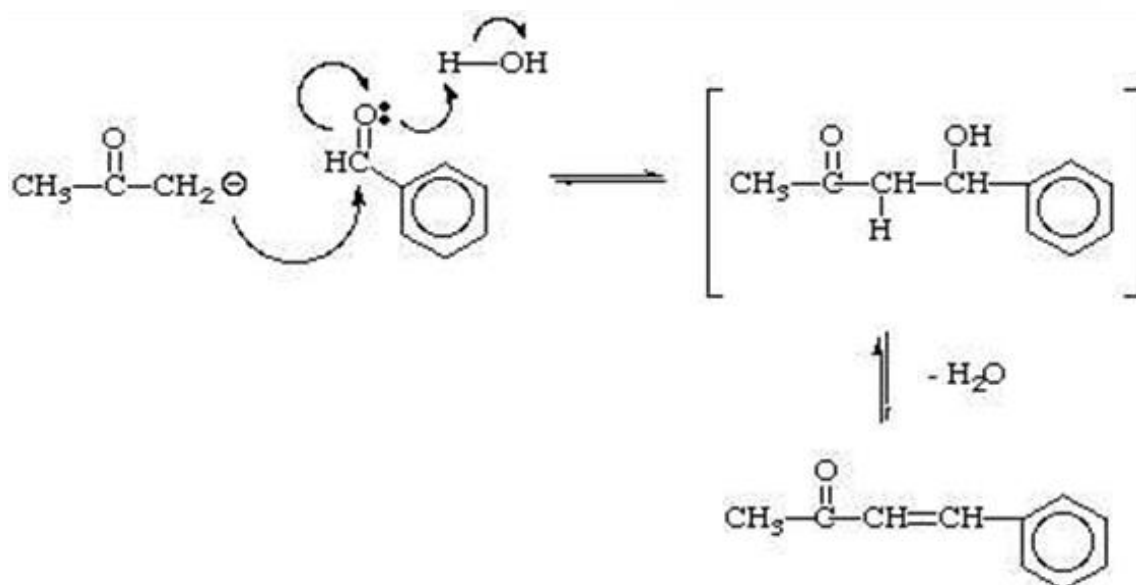
Claisen-Schmidt condensation reaction

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.



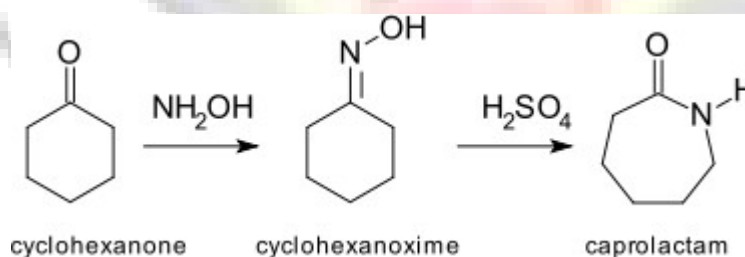
Mechanism involved in reaction



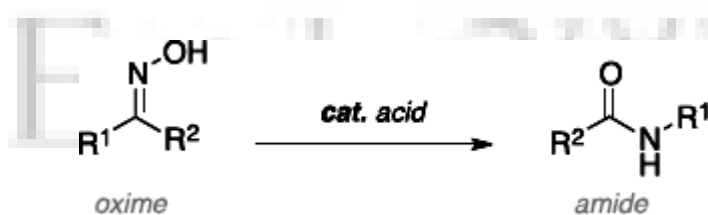
Beckmann Rearrangement Reaction

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

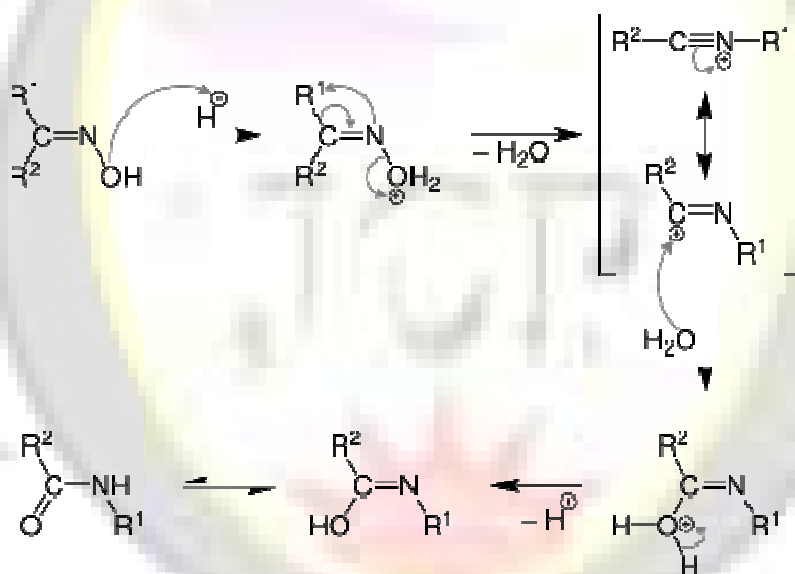
Reaction



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 imidate and then tautomerization to the amide:



- An industrial synthesis of paracetamol developed by Hoechst–Celanese involves the conversion of a methyl ketone to an acetanilide via a Beckmann rearrangement.
- The Beckmann rearrangement is also used in the synthesis of DHEA, benazepril, ceforanide, elanzepine, 17-azaprogesterone, elantrine, prazepine, enprazepine, and etazepine.

Schmidt Rearrangement

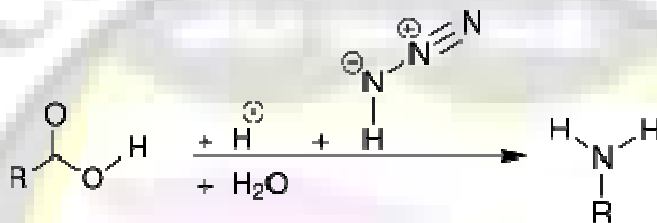
The Schmidt reaction is an organic reaction in which an **azide** reacts with a **carbonyl group** to give an **amine** or **amide**, with expulsion of nitrogen.

It is named after *Sir Karl Friedrich Schmidt*.

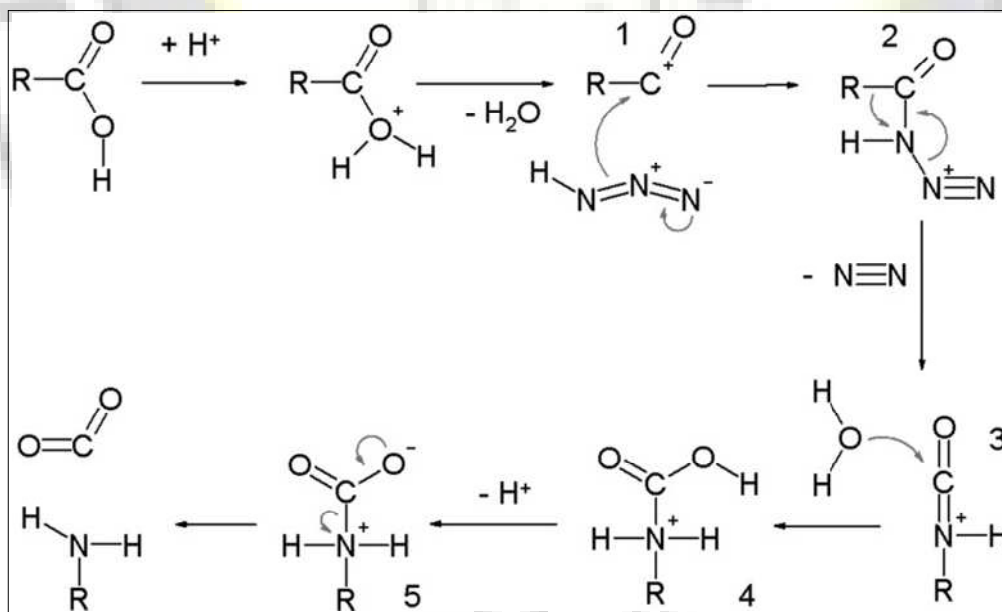
Examples

The reaction is with carboxylic acids to give amines

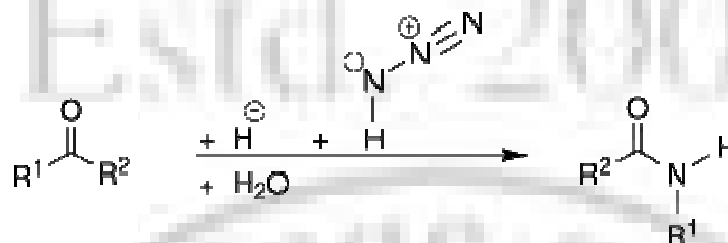
Reaction



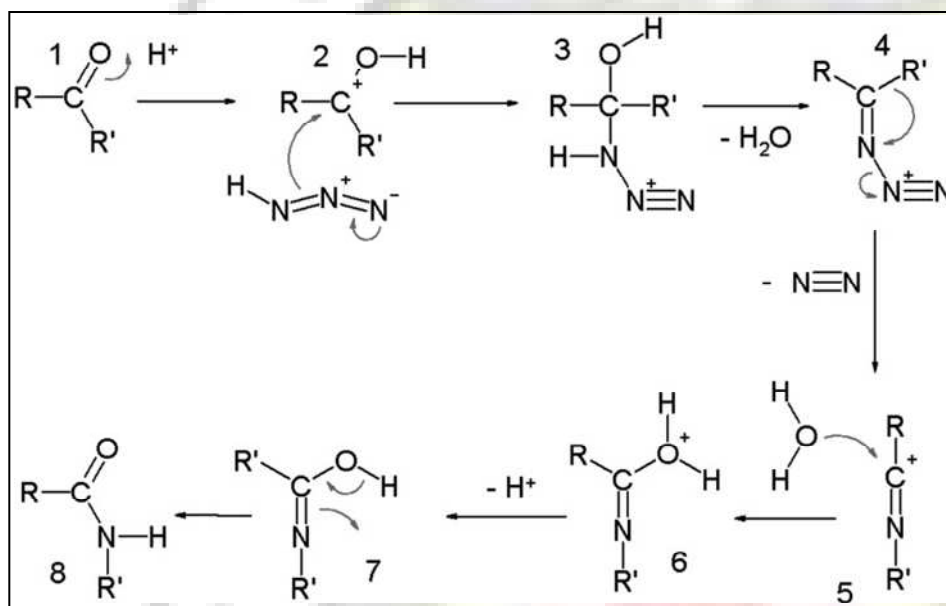
Reaction Mechanism



Reaction with ketones to give amides



Reaction Mechanism



- The scope of this reaction has been extended to reactions of carbonyls with alkyl azides R-N_3
- These are annulation reactions and have some utility in the synthesis of natural products; such as lactams and alkaloids.