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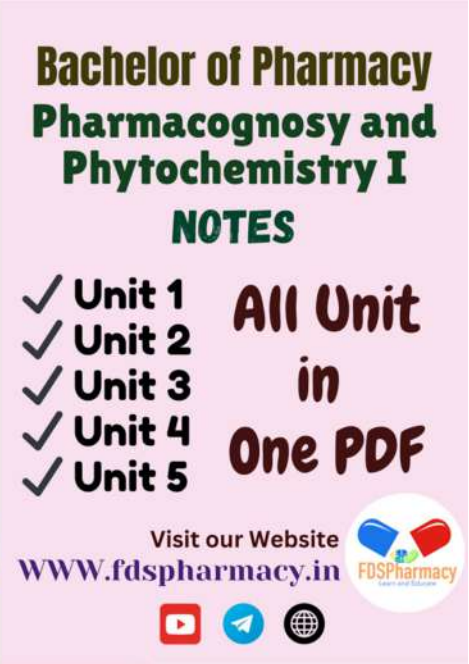

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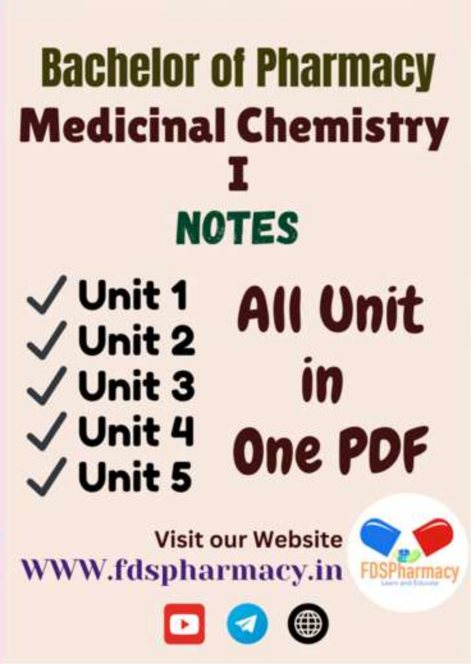

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PHARMACEUTICAL ORGANIC CHEMISTRY – III

UNIT 5

TOPIC :

- **Reactions of synthetic importance**

  Metal hydride reduction (NaBH4 and LiAlH4), Clemmensen reduction, Birch reduction, Wolff Kishner reduction.

  Oppenauer-oxidation and Dakin reaction.

  Beckmanns rearrangement and Schmidt rearrangement.

  Claisen-Schmidt condensation

Reactions of Synthetic Importance

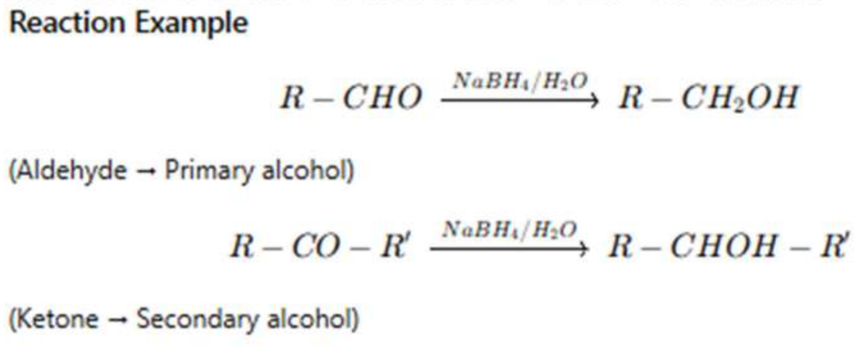
- In organic and medicinal chemistry, certain reactions are called synthetically important reactions because they are widely applied in the preparation of complex organic molecules, drug intermediates, and heterocycles.
- These reactions allow functional group transformations, oxidation-reduction, rearrangements, and condensation essential for pharmaceutical synthesis.

Metal Hydride Reduction

- Metal hydride reduction refers to the use of metal hydride reagents like:
  - Sodium borohydride ($NaBH_4$)
  - Lithium aluminium hydride ($LiAlH_4$)
- These reagents act as sources of hydride ions (H^-).
- Mainly used to reduce carbonyl compounds (aldehydes, ketones, esters, carboxylic acids, amides) into corresponding alcohols.

1. Sodium Borohydride ($NaBH_4$)

- Mild and selective reducing agent.
- Stable in alcohol and water.
- **Reduces selectively:**
  - Aldehydes → Primary alcohols
  - Ketones → Secondary alcohols
- Does not reduce esters, carboxylic acids, or amides.



Reaction Example

$$R-CHO \xrightarrow{NaBH_4/H_2O} R-CH_2OH$$

(Aldehyde → Primary alcohol)

$$R-CO-R' \xrightarrow{NaBH_4/H_2O} R-CHOH-R'$$

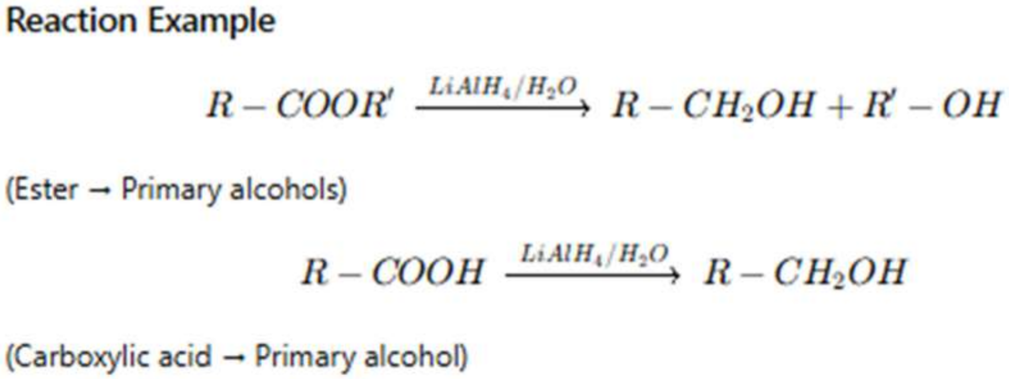
(Ketone → Secondary alcohol)

Mechanism

1. **Step I: Nucleophilic attack**
    - Hydride ion (H^-) from $NaBH_4$ attacks the electrophilic carbon of the carbonyl group → forms an alkoxide ion.
2. **Step II: Protonation**
    - Alkoxide ion is protonated by water/alcohol → alcohol is formed.

2. Lithium Aluminium Hydride ($LiAlH_4$)

- Very strong and reactive reducing agent.
- Reacts violently with water → reactions carried out in dry ether, then hydrolyzed.
- **Reduces:**
    - Aldehydes → Primary alcohols
    - Ketones → Secondary alcohols
    - Esters → Primary alcohols
    - Carboxylic acids → Primary alcohols
    - Amides → Amines
    - Nitriles → Amines



Reaction Example

$$R - COOR' \xrightarrow{LiAlH_4/H_2O} R - CH_2OH + R' - OH$$

(Ester → Primary alcohols)

$$R - COOH \xrightarrow{LiAlH_4/H_2O} R - CH_2OH$$

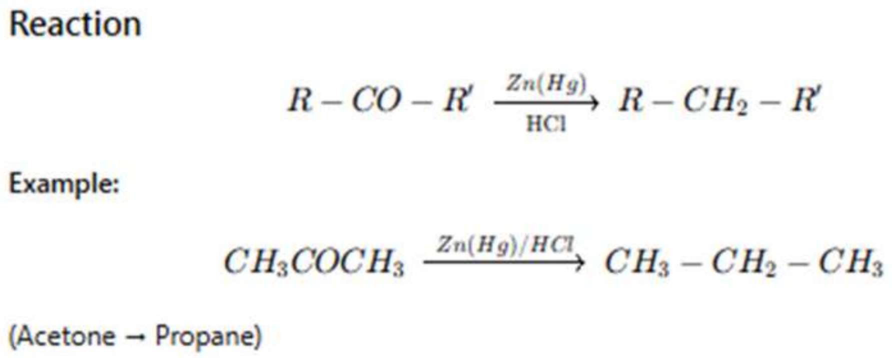
(Carboxylic acid → Primary alcohol)

Mechanism

1. **Step I: Nucleophilic attack**
    - Hydride ion (H^-) from $LiAlH_4$ attacks carbonyl carbon → alkoxide ion formed.
2. **Step II: Protonation**
    - Alkoxide ion protonated by water during work-up → alcohol/amine obtained.

Clemmensen Reduction

- Clemmensen reduction is an organic redox reaction in which carbonyl compounds (aldehydes & ketones) are reduced to hydrocarbons.
- Discovered by Erik Christian Clemmensen.
- Very useful in removing =O group from carbonyl compounds.



Reaction

$$R - CO - R' \xrightarrow[\text{HCl}]{Zn(Hg)} R - CH_2 - R'$$

Example:

$$CH_3COCH_3 \xrightarrow{Zn(Hg)/HCl} CH_3 - CH_2 - CH_3$$

(Acetone → Propane)

Reagents

- **Zinc a**
- **Conce**

Mechanism (Simplified)

- Occurs under acidic conditions.
- Exact mechanism is complex but involves:
    1. Adsorption of carbonyl compound onto Zn surface.
    2. Electron transfer from Zn → reduction of carbonyl group.
    3. Protonation by HCl → removal of oxygen as water.
    4. Final product: hydrocarbon.

Applications in Organic & Medicinal Chemistry

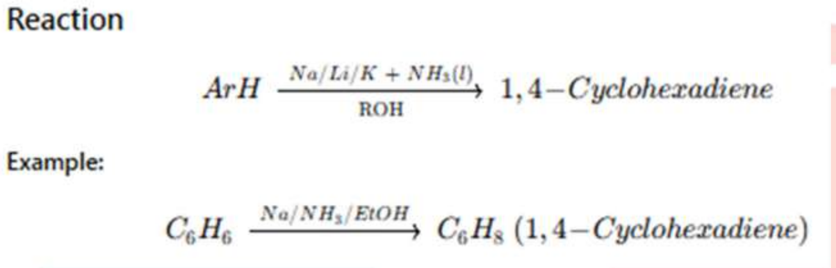
1. Converts aldehydes & ketones → alkanes.
2. Widely used in drug & steroid synthesis.
3. Important in industrial organic chemistry to simplify carbon skeletons.
4. Complements Wolff–Kishner reduction (which works in basic medium).

Limitations

- Reaction requires strongly acidic medium → not suitable for compounds unstable in acid.
- Does not work well with compounds containing acid-sensitive groups (like –OH, $-NH_2$, –COOH, etc.).
- Wolff–Kishner is preferred if substrate is acid-sensitive.

Birch Reduction

- Birch Reduction is an organic redox reaction used to partially reduce aromatic rings to 1,4-cyclohexadienes.
- Discovered by Arthur Birch in 1944.
- Involves alkali metals (Na, Li, or K) in liquid ammonia with an alcohol (ethanol, tert-butanol) as proton source.



Reaction

$$ArH \xrightarrow[\text{ROH}]{Na/Li/K + NH_3(l)} 1,4-Cyclohexadiene$$

Example:

$$C_6H_6 \xrightarrow{Na/NH_3/EtOH} C_6H_8\ (1,4-Cyclohexadiene)$$

Mechanism (Stepwise)

1. Electron transfer: An electron from alkali metal reduces the aromatic ring → radical anion.
2. Protonation: Proton source (alcohol) donates H^+ to the anion.
3. Second electron transfer: Another electron reduces the intermediate → carbanion.
4. Final protonation: Carbanion picks up H^+ → forms non-conjugated diene (1,4-cyclohexadiene).

Applications in Organic & Medicinal Chemistry

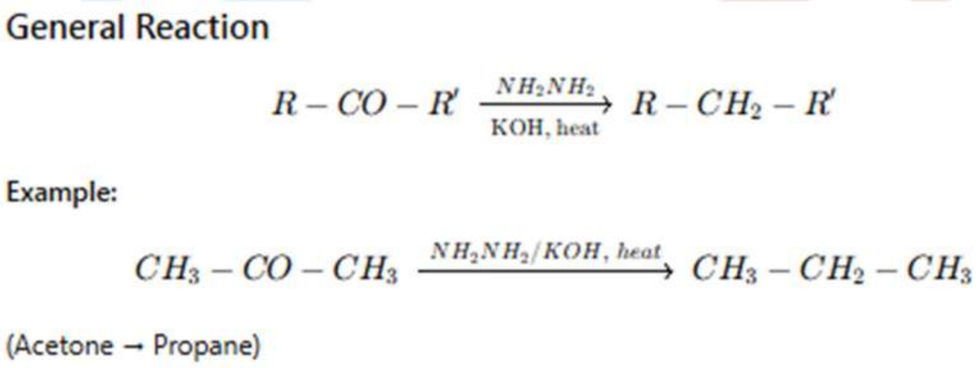
1. Partial reduction of aromatic rings in synthesis of pharmaceuticals and natural products.
2. Preparation of intermediates for steroids, alkaloids, and antibiotics.
3. Useful in structure modification of aromatic drugs (reduces aromaticity without total saturation).
4. Helps in producing cyclohexadiene building blocks for drug synthesis.

Limitations

- Reaction requires anhydrous liquid ammonia (hazardous to handle).
- Not suitable for highly sensitive functional groups.
- Does not reduce double bonds in alkenes (selective for aromatic systems).

Wolff–Kishner Reduction

- The Wolff–Kishner reduction is an important organic reaction where aldehydes and ketones are reduced to hydrocarbons (–CH_2–).
- Discovered by Ludwig Wolff (1912) and later modified by Nikolai Kishner.
- Works under strongly basic conditions (unlike Clemmensen reduction which uses acidic medium).



General Reaction

$$R-CO-R' \xrightarrow[\text{KOH, heat}]{NH_2NH_2} R-CH_2-R'$$

Example:

$$CH_3-CO-CH_3 \xrightarrow{NH_2NH_2/KOH,\ heat} CH_3-CH_2-CH_3$$

(Acetone → Propane)

Reagents

- Hydrazine (NH_2–NH_2)
- Strong base (KOH or NaOH)
- High temperature (180–200 °C)
- Solvent: high boiling (ethylene glycol, diethylene glycol).

Mechanism

1. **Formation of Hydrazone**

$$R-CO-R' + NH_2NH_2 \rightarrow R-C=NNH_2$$

(Carbonyl compound + hydrazine → hydrazone)

2. Base-catalyzed deprotonation of hydrazone.
3. Nitrogen gas (N_2) is eliminated → leaving behind a carbanion.
4. Protonation of carbanion → final hydrocarbon.

Applications in Organic & Medicinal Chemistry

1. Conversion of carbonyl compounds into alkanes in drug synthesis.
2. Useful in steroid & alkaloid modifications.
3. Produces intermediates for antibiotics, vitamins, and anticancer agents.
4. Alternative to Clemmensen reduction when substrate is unstable in acid.

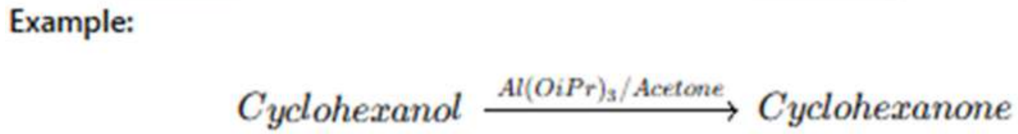
Limitations

- Requires high temperature (not suitable for heat-sensitive molecules).
- Not effective for molecules containing base-sensitive groups.
- Reaction is slow compared to other reduction methods.

Oppenauer Oxidation

- Oppenauer Oxidation is an oxidation reaction in organic chemistry where secondary alcohols are oxidized to ketones using a hydride transfer mechanism.
- Discovered by Rupert Viktor Oppenauer.
- It is the reverse of Meerwein–Ponndorf–Verley (MPV) reduction.

General Reaction


Example:

$$Cyclohexanol \xrightarrow{Al(OiPr)_3/Acetone} Cyclohexanone$$

Reagents

- Aluminium isopropoxide [$Al(OiPr)_3$] (Lewis acid catalyst).
- A non-enolizable ketone (commonly acetone or benzophenone) acts as a hydride acceptor.
- Solvent: Often benzene or toluene (non-polar).

Mechanism

1. **Coordination**: Alcohol reacts with $Al(OiPr)_3$ forming an alkoxide complex.
2. **Hydride transfer**: Hydrogen from the α-carbon of the alcohol is transferred to the ketone (hydride acceptor).
3. **Product release**: Alcohol is oxidized to ketone, while the acceptor ketone is reduced to a secondary alcohol.

Applications in Organic & Medicinal Chemistry

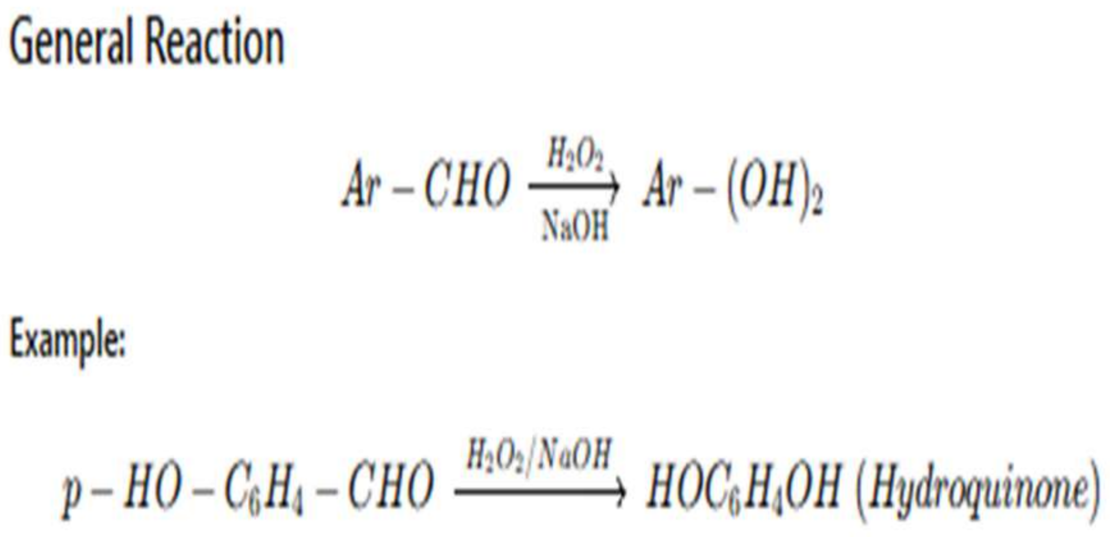
1. Oxidation of steroids and terpenes in drug synthesis.
2. Useful for the structural modification of hormones (e.g., progesterone, testosterone).
3. Applied in synthesis of intermediates for antibiotics and anticancer agents.

Limitations

- Only useful for secondary alcohols.
- Requires a suitable ketone acceptor.
- Not effective for acid- or base-sensitive substrates.

Dakin Reaction

- The Dakin reaction is an oxidation reaction where an aryl aldehyde or aryl ketone (with –OH group in ortho or para position) is oxidized by hydrogen peroxide in alkaline medium.
- Named after Henry Drysdale Dakin.
- Produces hydroquinones (di-hydroxybenzenes) or aminophenols depending on the substrate.



General Reaction

$$Ar-CHO \xrightarrow[NaOH]{H_2O_2} Ar-(OH)_2$$

Example:

$$p-HO-C_6H_4-CHO \xrightarrow{H_2O_2/NaOH} HOC_6H_4OH\ (Hydroquinone)$$

Reagents

- **Hydrogen peroxide (H_2O_2)** – oxidizing agent.
- **Strong base (NaOH or KOH)** – alkaline medium.

Mechanism

1. Nucleophilic attack: Hydroperoxide anion ($–OOH^-$) attacks carbonyl carbon of aldehyde/ketone.
2. Rearrangement: Migration of aryl group → peroxy intermediate.
3. Cleavage: Intermediate decomposes to form phenol derivative.

4. Final product: Hydroquinone (benzene-1,4-diol) or catechol (benzene-1,2-diol).

Applications in Organic & Medicinal Chemistry

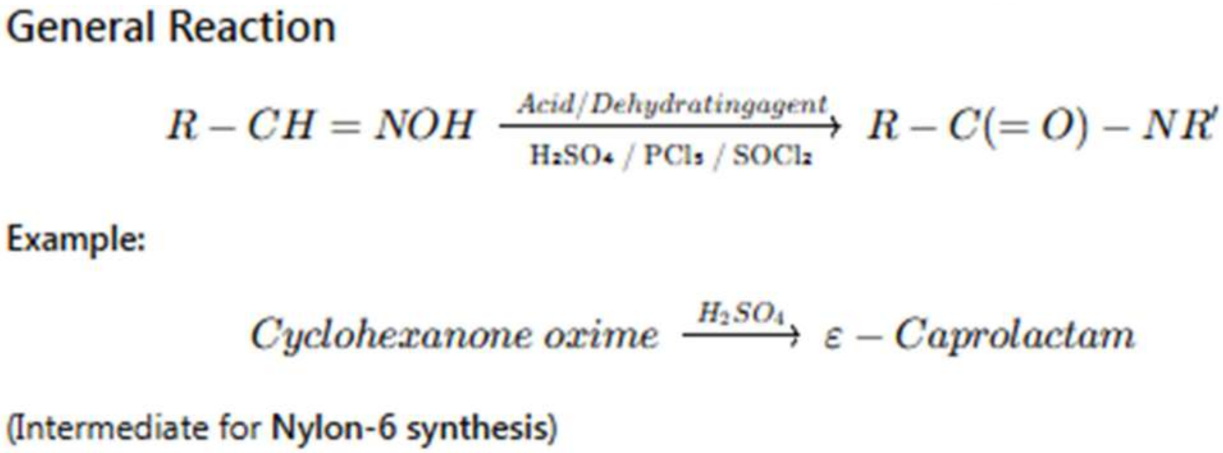
1. Synthesis of hydroquinones – useful in antioxidants & photographic developers.
2. Preparation of aminophenols (important intermediates in drug synthesis like paracetamol).
3. Used in industrial synthesis of dyes, polymers, and agrochemicals.
4. Important in drug discovery for modifying aromatic aldehydes/ketones.

Limitations

- Only works with aryl aldehydes & aryl ketones (not aliphatic).
- Requires alkaline hydrogen peroxide (unstable & hazardous to handle).
- Sensitive to substituents on aromatic ring.

Beckmann Rearrangement

- The Beckmann Rearrangement is an acid-catalyzed rearrangement of oximes to form amides or lactams.
- Discovered by Ernst Otto Beckmann in 1886.
- Very important in pharmaceutical and polymer synthesis.



General Reaction

$$R - CH = NOH \xrightarrow[H_2SO_4\ /\ PCl_5\ /\ SOCl_2]{Acid/Dehydratingagent} R - C(=O) - NR'$$

Example:

$$Cyclohexanone\ oxime \xrightarrow{H_2SO_4} \varepsilon - Caprolactam$$

(Intermediate for **Nylon-6 synthesis**)

Reagents

- Strong acids: H_2SO_4, HCl, PCl_5, $SOCl_2$, $POCl_3$.
- Lewis acids: $ZnCl_2$, $AlCl_3$.

Mechanism

1. **Protonation** of oxime (–OH group activated by acid).
2. **Migration**: One substituent (anti to –OH) migrates from carbon to nitrogen.
3. **Rearrangement**: Nitrogen-carbon bond forms, and leaving group departs.
4. **Amide/lactam formation**: Hydrolysis of intermediate produces final product.

Applications in Organic & Medicinal Chemistry

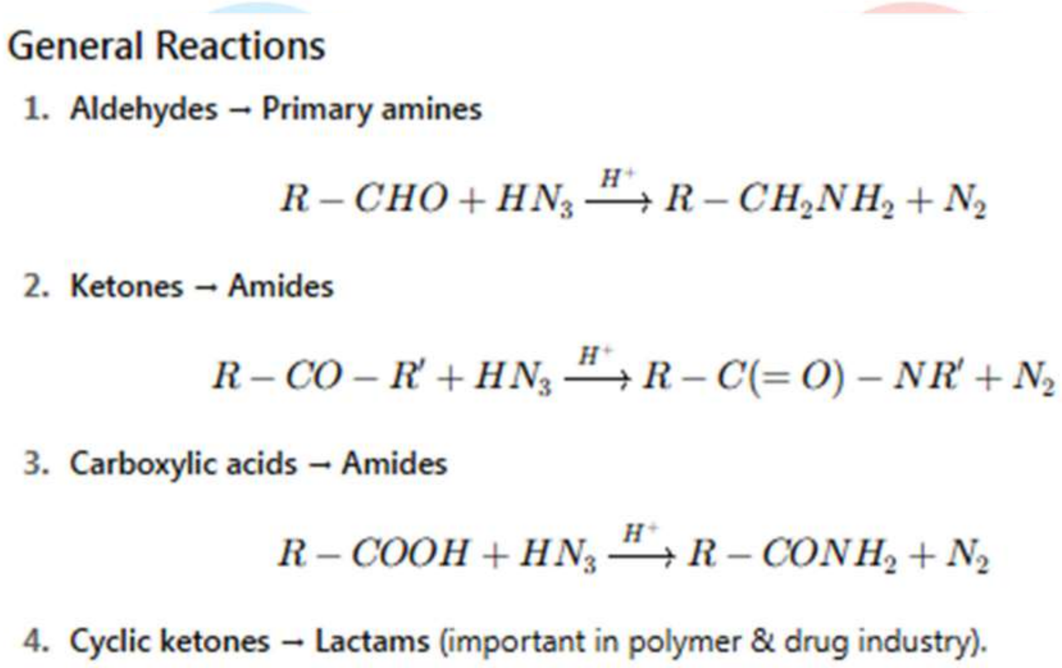
1. Nylon-6 synthesis via cyclohexanone oxime → ε-caprolactam.
2. Preparation of lactam intermediates used in antibiotics (penicillins, cephalosporins).
3. Conversion of ketones → amides in drug intermediates.
4. Used in fine chemical industry for heterocyclic compound synthesis.

Limitations

- Requires strong acids or dehydrating agents.
- Sensitive functional groups may not survive acidic conditions.
- Not suitable for all oximes (depends on stability).

Schmidt Rearrangement

- ➢ The Schmidt rearrangement is an acid-catalyzed reaction of carbonyl compounds (aldehydes, ketones, carboxylic acids, or their derivatives) with hydrazoic acid (HN_3) to form amines, amides, or lactams.
- ➢ Discovered by Karl Friedrich Schmidt in 1924.
- ➢ It involves rearrangement with nitrogen gas (N_2) elimination.



General Reactions

1. Aldehydes → Primary amines

$$R - CHO + HN_3 \xrightarrow{H^+} R - CH_2NH_2 + N_2$$

2. Ketones → Amides

$$R - CO - R' + HN_3 \xrightarrow{H^+} R - C(=O) - NR' + N_2$$

3. Carboxylic acids → Amides

$$R - COOH + HN_3 \xrightarrow{H^+} R - CONH_2 + N_2$$

4. Cyclic ketones → Lactams (important in polymer & drug industry).

Reagents

- Hydrazoic acid (HN_3)
- Strong acids: H_2SO_4, HCl, H_3PO_4

Mechanism (Simplified)

1. **Protonation** of carbonyl oxygen (activation).
2. **Nucleophilic attack** of HN_3 on carbonyl carbon.
3. **Rearrangement**: Migration of an alkyl group from carbon to nitrogen with loss of N_2.
4. **Product formation**: Amide, amine, or lactam depending on substrate.

Applications in Organic & Medicinal Chemistry

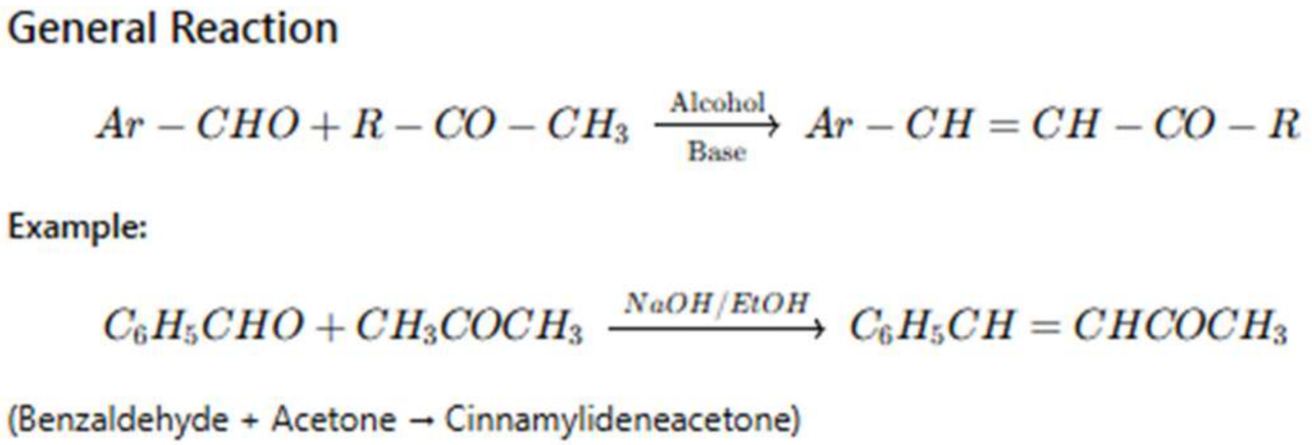
1. Synthesis of lactams (e.g., ε-caprolactam → Nylon-6 production).
2. Preparation of amines and amides from aldehydes, ketones, acids.
3. Used in drug intermediates for antibiotics, alkaloids, and steroids.
4. Valuable for ring expansion reactions in medicinal chemistry.

Limitations

- Uses hydrazoic acid (HN_3) which is highly toxic and explosive.
- Requires strong acidic conditions.
- Side reactions may occur with sensitive functional groups.

Claisen–Schmidt Condensation

- The Claisen–Schmidt condensation is a type of aldol condensation between an aromatic aldehyde and an aliphatic or aromatic ketone in the presence of a base (NaOH, KOH, $Ba(OH)_2$, etc.).
- Discovered by Rainer Ludwig Claisen and later extended by J. G. Schmidt.
- Produces α,β-unsaturated ketones, which are important intermediates in drug synthesis.



General Reaction

$$Ar - CHO + R - CO - CH_3 \xrightarrow[\text{Base}]{\text{Alcohol}} Ar - CH = CH - CO - R$$

Example:

$$C_6H_5CHO + CH_3COCH_3 \xrightarrow{NaOH/EtOH} C_6H_5CH = CHCOCH_3$$

(Benzaldehyde + Acetone → Cinnamylideneacetone)

Reagents

- **Base**: NaOH, KOH, $Ba(OH)_2$.
- **Solvent**: Alcohol (ethanol, methanol).

Mechanism (Stepwise)

1. **Enolate formation**:
    - Base abstracts α-hydrogen from ketone → enolate ion.
2. **Nucleophilic attack**:
    - Enolate ion attacks the carbonyl carbon of aldehyde → β-hydroxy ketone.
3. **Dehydration**:
    - Loss of water under base/heat → α,β-unsaturated ketone (enone).

Applications in Organic & Medicinal Chemistry

1. Synthesis of chalcones (intermediates for flavonoids, anticancer, antimalarial drugs).
2. Useful in steroid chemistry.
3. Applied in perfume, dye, and agrochemical industries.
4. Important in organic synthesis of α,β-unsaturated ketones used as building blocks.

Limitations

- Side reactions (self-condensation of ketones).
- Not suitable for ketones/aldehydes with strong electron-withdrawing substituents.
- Requires controlled conditions to avoid polymerization.