Alicyclic Compounds

Aldol Condensation

Introduction:

- Aldol condensation is an important carbon–carbon bond-forming reaction in organic chemistry.
- It occurs between two molecules of aldehydes or ketones having at least one α-hydrogen atom in the presence of a base or acid.
- The reaction involves enolate ion formation, nucleophilic addition to a carbonyl compound, followed by dehydration to form an α,β-unsaturated carbonyl compound.

Example:

- Acetaldehyde (CH_3CHO) undergoes aldol condensation under basic conditions:

$$2\ CH_3CHO \rightarrow CH_3CH(OH)CH_2CHO \rightarrow CH_3CH{=}CHCHO + H_2O$$

Mechanism (Base-Catalyzed):

Step 1: Enolate Ion Formation

- The base (commonly OH^-) abstracts an α-hydrogen from the aldehyde/ketone, generating an enolate ion.

$$CH_3CHO + OH^- \rightarrow CH_2^-CHO + H_2O$$

Step 2: Nucleophilic Attack

- The enolate ion attacks the carbonyl carbon of another aldehyde molecule (electrophile), forming a β-hydroxy aldehyde (aldol).

$$CH_2^-CHO + CH_3CHO \rightarrow CH_3CH(OH)CH_2CHO$$

Step 3: Dehydration (Condensation Step)

- Under heating, the β-hydroxy compound undergoes elimination of water to form an α,β-unsaturated carbonyl compound.

$$CH_3CH(OH)CH_2CHO \rightarrow CH_3CH{=}CHCHO + H_2O$$

Applications:

- Widely used in the synthesis of α,β-unsaturated carbonyl compounds, which are versatile intermediates.
- Key step in the synthesis of natural products, steroids, and pharmaceuticals.
- Used in polymer and fragrance industries.

Claisen Condensation

Introduction:

- The Claisen condensation is a base-catalyzed reaction between two esters or one ester and a ketone containing α-hydrogen atoms, leading to the formation of a β-keto ester or β-diketone.

- This reaction is similar in mechanism to aldol condensation, but involves esters instead of aldehydes/ketones.

Example:

- Two molecules of ethyl acetate react to form ethyl acetoacetate:

$$2\ CH_3COOEt \rightarrow CH_3COCH_2COOEt + EtOH$$

Mechanism:

Step 1: Enolate Formation

➢ The base (usually ethoxide ion) removes the α-hydrogen from the ester to form an enolate ion.

$$CH_3COOEt + EtO^- \rightarrow CH_2^-COOEt + EtOH$$

Step 2: Nucleophilic Acyl Substitution

➢ The enolate attacks the carbonyl carbon of another ester molecule, forming a tetrahedral intermediate.

$$CH_2^-COOEt + CH_3COOEt \rightarrow CH_3C(O^-)CH_2COOEt$$

Step 3: Elimination

➢ The tetrahedral intermediate collapses, eliminating an ethoxide ion (EtO^-), forming the β-keto ester.

$$CH_3C(O^-)CH_2COOEt + EtOH \rightarrow CH_3COCH_2COOEt$$

Step 4: Acid Workup

➢ Acidification neutralizes the alkoxide and completes the reaction.

Applications:

- Used in the synthesis of β-keto esters, which are important intermediates in pharmaceuticals and agrochemicals.
- Useful in the synthesis of heterocycles, diketones, and for acetoacetic ester synthesis.
- Precursor to carboxylic acids upon hydrolysis and decarboxylation.

Cannizzaro Reaction

Introduction:

- The Cannizzaro reaction is a redox reaction where non-enolizable aldehydes (i.e., aldehydes lacking α-hydrogen atoms) undergo disproportionation in the presence of a strong base.
- One molecule of aldehyde is reduced to an alcohol, and another is oxidized to a carboxylic acid salt.

Example:

- **Formaldehyde reacts in concentrated NaOH:**

$$2\ HCHO + NaOH \rightarrow HCOONa + CH_3OH$$

Mechanism:

Step 1: Nucleophilic Attack

- Hydroxide ion attacks the carbonyl carbon of the aldehyde to form a tetrahedral intermediate.

$$HCHO + OH^- \rightarrow HOCH_2O^-$$

Step 2: Hydride Transfer (Redox Step)

- A hydride ion is transferred from the intermediate to another molecule of aldehyde.

$$HOCH_2O^- + HCHO \rightarrow HCOO^- + CH_3OH$$

Step 3: Protonation

- The alkoxide ion formed from the reduction step is protonated by water or solvent to give the alcohol.

$$CH_3O^- + H_2O \rightarrow CH_3OH + OH^-$$

Step 4: Ionization

- The oxidized product (formic acid) ionizes under basic conditions to form the carboxylate salt.

$$HCOOH + OH^- \rightarrow HCOO^- + H_2O$$

Applications:

- Used to prepare alcohols and carboxylic acids from non-enolizable aldehydes.
- Useful in synthesis where selective redox control is required.
- Basis for the crossed Cannizzaro reaction with two different aldehydes.

Crossed Aldol Condensation

Introduction:

- Crossed aldol condensation (also known as mixed aldol condensation) involves the aldol reaction between two different aldehydes or ketones.
- While the regular aldol condensation occurs between identical carbonyl compounds, crossed aldol reactions are more selective and synthetically useful if:
  - Only one reactant has α-hydrogen(s).
  - Or one carbonyl is much more reactive (e.g., formaldehyde).
  - Or a specific enolate is generated beforehand (e.g., using LDA).

Example:

- Reaction between benzaldehyde (no α-H) and acetaldehyde (has α-H):

$$CH_3CHO + C_6H_5CHO \rightarrow C_6H_5CH{=}CHCHO + H_2O$$

- This forms cinnamaldehyde, an α,β-unsaturated aldehyde.

Mechanism (Base-Catalyzed):

Step 1: Enolate Formation

- The base (e.g., OH^- or alkoxide) abstracts an α-hydrogen from acetaldehyde, forming an enolate.

$$CH_3CHO + OH^- \rightarrow CH_2^-CHO + H_2O$$

Step 2: Nucleophilic Addition to Second Carbonyl

- The enolate attacks benzaldehyde (which lacks α-H), forming a β-hydroxy aldehyde.

$$CH_2^-CHO + C_6H_5CHO \rightarrow C_6H_5CH(OH)CH_2CHO$$

Step 3: Dehydration

- The β-hydroxy aldehyde undergoes elimination of water to yield the α,β-unsaturated aldehyde.

$$C_6H_5CH(OH)CH_2CHO \rightarrow C_6H_5CH=CHCHO + H_2O$$

Applications:

- Used in the synthesis of natural products, fragrances, flavoring agents (e.g., cinnamaldehyde).
- Important in targeted carbon-carbon bond formation in organic synthesis.
- Especially useful when one reactant lacks α-hydrogen, reducing side products.

Crossed Cannizzaro Reaction

Introduction:

- The crossed Cannizzaro reaction involves the reaction of two different aldehydes, at least one of which must lack α-hydrogens (i.e., non-enolizable).
- This reaction allows selective oxidation of one aldehyde to a carboxylic acid salt, and reduction of the other to an alcohol.
- It's done in the presence of a strong base (usually NaOH or KOH).
- This reaction is useful when one aldehyde (e.g., formaldehyde) is more reactive and is preferentially oxidized or reduced.

Example:

- Reaction between formaldehyde (HCHO) and benzaldehyde (C_6H_5CHO) in NaOH:

$$HCHO + C_6H_5CHO + NaOH \rightarrow HCOONa + C_6H_5CH_2OH$$

- Here, formaldehyde is oxidized to sodium formate, and benzaldehyde is reduced to benzyl alcohol.

Mechanism:

Step 1: Nucleophilic Addition

- Hydroxide ion attacks the carbonyl carbon of formaldehyde (more electrophilic), forming an alkoxide.

$$HCHO + OH^- \rightarrow HOCH_2O^-$$

Step 2: Hydride Transfer

- The hydride from this alkoxide is transferred to benzaldehyde, reducing it.

$$HOCH_2O^- + C_6H_5CHO \rightarrow HCOO^- + C_6H_5CH_2O^-$$

Step 3: Protonation

- The alkoxide is protonated to give benzyl alcohol.

$$C_6H_5CH_2O^- + H_2O \rightarrow C_6H_5CH_2OH + OH^-$$

Step 4: Salt Formation

- The oxidized formaldehyde (formic acid) forms formate salt in the basic medium.

$$HCOOH + OH^- \rightarrow HCOO^- + H_2O$$

Applications:

- Selective reduction and oxidation in one-pot synthesis.
- Synthesis of alcohols and carboxylic acids from mixtures of aldehydes.
- Industrial preparation of benzyl alcohol, aromatic acids, or formate salts.

Benzoin Condensation

Introduction:

- Benzoin condensation is a reaction between aromatic aldehydes (especially benzaldehyde) in the presence of a nucleophilic catalyst such as cyanide ion (CN^-) or thiazolium salts (used in biological systems).
- It forms benzoin, an α-hydroxy ketone.
- The reaction is not a true aldol condensation, because the aldehyde lacks α-H, and it proceeds via umpolung (polarity inversion) of the carbonyl compound through nucleophilic catalysis.

Example:

$$2\ C_6H_5CHO\ (\text{benzaldehyde}) \rightarrow C_6H_5CH(OH)COC_6H_5\ (\text{benzoin})$$

Mechanism (Using CN^- as Catalyst):

Step 1: Nucleophilic Attack

- CN^- attacks the carbonyl carbon of benzaldehyde, forming a cyanohydrin intermediate.

$$C_6H_5CHO + CN^- \rightarrow C_6H_5CH(CN)O^-$$

Step 2: Resonance and Umpolung

- The intermediate rearranges; the α-carbon now acts as a nucleophile.

$$C_6H_5CH(CN)O^- \leftrightarrow [C_6H_5C^-(CN)OH] \rightarrow \text{nucleophilic α-carbon}$$

Step 3: Nucleophilic Attack on Second Aldehyde

- The carbanion attacks a second benzaldehyde molecule.

$$C_6H_5C^-(CN)OH + C_6H_5CHO \rightarrow C_6H_5CH(OH)CH(CN)C_6H_5$$

Step 4: Elimination of CN^-

- CN^- is eliminated from the intermediate, regenerating the catalyst and forming **benzoin**.

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