Chapter 19
More Chemistry of Enolate Anions
Condensation Reactions (Aldol Reactions) and Conjugate Additions

Carbonyl Condensation Reactions

The Aldol Reaction
• In the aldol reaction, two molecules of an aldehyde or ketone react with each other in the presence of a base to form a \( \beta \)-hydroxy carbonyl compound.

\[
\text{Aldol reaction product} \quad \text{Aldol addition product}
\]

The Claisen Condensation
• In the Claisen condensation, two molecules of an ester react with each other in the presence of a base to form \( \beta \)-Keto ester.

\[
\text{Claisen condensation product}
\]

The Claisen Condensation: Synthesis of \( \beta \)-Keto Esters
• Ethyl acetate undergoes a Claisen condensation when treated with sodium ethoxide. The product is commonly called an acetoacetic ester, whose chemistry we studied in previous chapter (18).

\[
\text{Ethyl acetate} \quad \text{Ethyl acetoacetate}
\]

• Ethyl pentanoate undergoes an analogous reaction to form 3-oxo-2-propylheptanoate.

The Claisen Condensation - Mechanism
• Please note that the overall reaction involves loss of an \( \alpha \) hydrogen from one ester and loss of ethoxide from another.

\[
\text{Claisen condensation mechanism}
\]

• The mechanism is very straightforward and follow the general process of nucleophilic addition-elimination at an ester carbonyl.

\[
\text{Claisen condensation mechanism steps}
\]
The alkoxide base must have the same alkyl group as the alkoxyl group of the ester. If a different alkoxide is used, some transesterification products will be formed.

Esters with only one $\alpha$-hydrogen do not undergo Claisen condensation. A second hydrogen on the $\alpha$-carbon is necessary so that it can be deprotonated in Step 3. This deprotonation and formation of the resonance-stabilized $\beta$-keto ester ion drives the reaction to completion.

The Dieckmann condensation is an intramolecular Claisen condensation. Only 5- and 6-membered rings can be prepared this way.

Crossed Claisen Condensations

Crossed Claisen condensations between two esters can lead to one major product when one of the esters has no $\alpha$-hydrogen. Detailed mechanism for this Claisen condensation is given on page 874 (Solved problem 19.1).
Esters with one \( \alpha \) hydrogen can, however, react in Claisen condensations if they are deprotonated with a strong base and acylated with an acyl chloride to give \( \beta \)-keto ester.

\[
\text{CH}_3\text{C}(-\text{OC}_2\text{H}_5)\text{CH}_2\text{C}(-\text{OC}_2\text{H}_5)\text{CH}_3 + \text{H}_2\text{C}(-\text{OC}_2\text{H}_5)\text{CH}_3 \rightarrow \text{CH}_3\text{C}(-\text{OC}_2\text{H}_5)\text{CH}_2\text{C}(-\text{OC}_2\text{H}_5)\text{CH}_3 + \text{H}_2\text{C}(-\text{OC}_2\text{H}_5)\text{CH}_3
\]

Acylation of Other Carbanions

- Ketone enolates formed with strong bases can also be acylated to form \( \beta \)-dicarbonyl compounds.
- Addition of strong base to 2-pentanone results in formation of the kinetic enolate (Why?) which can be acylated with an ester.

Carbonyl Condensation Reactions - The Aldol Reaction

- In the aldol reaction, two molecules of an aldehyde or ketone react with each other in the presence of a base to form a \( \beta \)-hydroxy carbonyl compound.

Aldol additions represent an important class of carbon-carbon bond-forming reaction.

\[
\text{2H} + 10\% \text{NaOH} \rightarrow \text{\textit{2-hydroxybutanal} (90\%)
}\]

Because the product contains both an aldehyde and an alcohol functional group, reaction of this type is known as aldol addition.

*OH is the base typically used in an aldol reaction. Although with *OH only a small amount of enolate is formed, this is appropriate because the starting aldehyde is needed to react with the enolate in the second step of the reaction.

The Aldol Reaction

The mechanism of the aldol reaction occurs in three steps.
Dehydration of the aldol addition product: Conversion of the β-hydroxy carbonyl adduct to a conjugated α,β-unsaturated carbonyl system

- Under the basic reaction conditions, the initial aldol product is often not isolated. Instead, it loses the elements of H₂O from the α and β carbons to form an α,β-unsaturated carbonyl compound.
- Regular alcohols dehydrate only in the presence of acid, not base, because hydroxide is a poor leaving group. However, when the hydroxy group is β to a carbonyl, loss of H and OH from the α and β carbons forms a conjugated double bond, and the stability of the conjugated system makes up for having such a poor leaving group.
- The dehydration (elimination of water molecule) equilibrium is essentially irreversible.

Aldol reaction of the propanal as the starting material:
- The two molecules of the aldehyde that participate in the aldol reaction react in opposite ways.
- One molecule of propanal becomes an electrophile— an electron-deficient carboxylate.
- One molecule of propanal serves as the nucleophile because its carbonyl carbon is electron deficient.

The Aldol Reaction

Acid-catalyzed aldol condensation—mechanism

Please note that reaction starts with the protonation of the oxygen from the carbonyl group.

Acid also protonates hydroxyl group in the intermediary adduct changing as a result a poor leaving group into a good one.

Carbonyl Condensation Reactions: The Aldol Reaction

- Recall that the characteristic reaction of aldehydes and ketones, which we studied in Chapter 16, is a nucleophilic addition.
- An aldol reaction is a nucleophilic addition in which an enolate is the nucleophile.

- Aldol reaction of the propanal as the starting material:
  - The two molecules of the aldehyde that participate in the aldol reaction react in opposite ways.
  - One molecule of propanal becomes an electrophile— an electron-deficient carboxylate.
  - One molecule of propanal serves as the nucleophile because its carbonyl carbon is electron deficient.

Please note that in aldol reactions the α carbon of one carbonyl component becomes bonded to the carbonyl carbon of the other component.
Synthetic Applications
- The aldol reaction links two smaller molecules and creates a new carbon-carbon bond.
- The aldol adducts are useful for further synthetic transformations.

Crossed Aldol Condensation
- A aldol reaction which starts with two different carbonyl compounds (aldehydes) is called Cross Aldol.
- It can lead to a mixture of four products.

Crossed Aldol Condensation with weak bases (NaOH)
- To avoid self-condensation:
  1. One carbonyl reactant without \( \alpha \)-hydrogen (e.g., benzaldehyde) used.
  2. The other carbonyl reagent is added slowly to a solution of the first reactant and the base. Under such conditions the concentration of the reactant with an \( \alpha \)-hydrogen is always low.

Crossed Aldol Condensation with strong bases (LDA)
- Lithium Enolates and Directed Aldol Reactions
  - Reactions of lithium enolates obtained from a ketone as one component and an aldehyde or ketone as the other are called Directed Aldol Reactions.
  - So, the crossed aldol reactions proceed effectively when a ketone is first deprotonated with a strong base such as LDA and the aldehyde is added slowly to the enolate.
The regioselectivity of the cross-aldol reactions with unsymmetrical ketones

An unsymmetrical ketone can be selectively deprotonated with LDA in aprotic solvent (THF) to form the kinetic enolate and this will react with an aldehyde to give primarily one product.

Please note that the proton has been removed from the less substituted α-carbon.

Using weaker base (NaOH) under protic conditions would produce mixture of two products via both kinetic and thermodynamic enolates.

Cyclization via Aldol Reactions: Intramolecular Condensation

- Aldol reactions with dicarbonyl compounds can be used to make five- and six-membered rings.
- The enolate formed from one carbonyl group is the nucleophile, and the carbonyl carbon of the other is the electrophile.

In the following example we can generate three different enolates. However it is enolates from ketone side of the molecule that adds to aldehyde:

Recall that aldehyde are more reactive that ketones towards nucleophilic additions. Consider also possible ring sizes.

Michael Additions: Additions to α,β-Unsaturated Aldehydes and Ketones

- A Michael addition involves conjugate addition of the nucleophile or an anion derived from an active hydrogen compound (e.g., an enolate) to an α,β-ununsaturated carbonyl compound.
- α,β-Unsaturated aldehydes and ketones can react by simple (1,2) or conjugate (1,4) addition.

- Both the carbonyl carbon and the β carbon are electrophilic and can react with nucleophiles.

Michael Additions: The conjugate addition of nucleophiles

Most nucleophiles will add to β carbon of the α,β-ununsaturated carbonyl system.
Michael Additions: The conjugate addition of nucleophiles

Amines add to $\beta$ carbon of the $\alpha,\beta$-unsaturated carbonyl system in high yield.

Conjugate Michael Additions

Addition of an enolates (C-nucleophiles) to an $\alpha,\beta$-unsaturated carbonyl compound usually occurs by conjugate addition.

This reaction is called a Michael addition and its pathway involves three steps:

1. A base removes an $\alpha$ proton to form an enolate from the Michael acceptor.
2. The enolate adds to the $\beta$ carbon of the $\alpha,\beta$-unsaturated carbonyl compound, forming a new $\sigma$ bond between them. As this bond is formed, the enolate leaves the $\alpha$ proton to form a new $\pi$ bond.
3. Protonation of the resulting enolate leads to the final Michael addition product.

Carbonyl Condensation Reactions: The Robinson Annulation

- The Robinson annulation is a ring-forming reaction that combines a Michael reaction with an intramolecular aldol reaction.
- The starting materials for a Robinson annulation are an $\alpha,\beta$-unsaturated carbonyl compound and an enolate.
- In overall, the Robinson annulation forms a six-membered ring and three new C—C bonds—two $\sigma$ bonds and one $\pi$ bond.
- It is frequently used to build one ring into another.

The Mannich Reaction

Compounds which can form enols react with imines or iminium ions derived from formaldehyde.

Primary or secondary amines can be used to form the corresponding formaldehyde imines or iminium ions.