Chapter 17
Aldehydes and Ketones II
Aldol Reactions

Hydrogen on a carbons α to a carbonyl is unusually acidic
- The resulting anion is stabilized by resonance to the carbonyl

\[
pK_a \text{ of } \alpha\text{-H} \approx 20
\]

Enolate Anions

Protonation of an enolate
1. The enolate anion is stable in the absence of acids
2. In protic solvents or other sources of protons, the enolate may be reprotonated at the carbon or the oxygen
- The resultant enol and keto forms of the carbonyl are formed reversibly and are interconvertible

Keto and Enol Tautomers
Enol-keto tautomers are constitutional isomers that are easily interconverted by a trace of acid or base
- Most aldehydes and ketones exist primarily in the keto form because of the greater strength of the carbon-oxygen double bond

\[
\text{Acetaldehyde} \\
\text{Acetone} \\
\text{Cyclohexanone}
\]

β-Dicarbonyl compounds exist primarily as enols
- The enol is more stable because:
  - a conjugated π system
  - additional resonance involving the lone pair on oxygen
  - hydrogen bonding

Reactions via Enols and Enolate Anions
Racemization
- Optically active aldehydes or ketones with a chiral center at the α - carbon racemize in the presence of catalytic acid or base
- The intermediate enol or enolate has no stereocenter at the α position

\[
\text{R} - (\alpha) \\
(\alpha\text{-}) = \text{racemic}
\]

enol is achiral
Mechanisms for racemization

Acid catalyzed

Base catalyzed

Acid-catalyzed halogenation proceeds via the enol

Step 1

Step 2

C=C of enol is electron rich because of resonance with the oxygen

Step 3

Haloformation Reaction

Reaction of methyl ketones with X₂ in the presence of base results in multiple halogenation at the methyl carbon

Each step is faster than the previous one, because enolate is made more stable by X

Haloformation Reaction - continued

The reaction of a methyl ketone with X₂ in aqueous hydroxide continues to yield a carboxylate anion and a haloform (CX₃H)

- The trihalomethylanion is a relatively good leaving group

Iodoform test = water insoluble yellow solid

One of oldest organic reactions, 1822

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 β-hydroxy carbonyl compound.

Product is an aldehyde alcohol (hence ald-ol)

New C-C bond formed
Mechanism of the Aldol Reaction

1. Formation of enolate anion

2. Nucleophilic addition of enolate to carbonyl group of a second molecule of the aldehyde

3. Protonation completes the nucleophilic addition

Aldol Reaction with Propanal

One molecule forms the enolate = nucleophile
Second aldehyde molecule undergoes nucleophilic addition

Dehydration of the Aldol Product

- If the aldol reaction mixture is heated, dehydration to an α,β-unsaturated carbonyl compound takes place
  - Dehydration is favorable because the product is stabilized by conjugation of the alkene with the carbonyl group
  - α-H is acidic

- Under many conditions, the aldol product cannot be isolated because it rapidly dehydrates to the α,β-unsaturated compound

Dehydration of initial aldol may shift equilibrium

- If the double bond will also be conjugated with an aromatic ring, the initial aldol cannot be isolated
  - Loss of water is the reason the aldol reaction is classified as, and often called, a condensation reaction

Some conditions regarding the Aldol Reaction

- A reversible equilibrium
- OH is the base typically used in an aldol reaction.
- Aldol reactions can be carried out with either aldehydes or ketones.
- With aldehydes, the equilibrium favors products
- With ketones the equilibrium favors the starting materials. (there are ways of driving the equilibrium to the right.)

Synthetic Applications of Aldol Reaction

Converts two small molecules into a larger one with a new carbon-carbon bond
Using the Aldol Reaction in Synthesis

• Work backwards in the retrosynthetic direction.

1. Locate a carbonyl group, with either a,β-unsaturation or a β-hydroxy group
2. Break the molecule between the α and β carbons

How would you make this compound, via an aldol reaction?

Using the Aldol Reaction in Synthesis

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Acid-Catalyzed Aldol Condensation

This reaction proceeds to the dehydration product

2 H₂C=CH₂ → 2 H₂C=CH-CH=CH₂ + H₂O

Enol form of ketone attacks protonated C=O of another molecule

Dehydration is rapid in acid

Crossed Aldol Reactions

• Crossed aldol reactions involve two different aldehydes
• Of little use when they lead to a mixture of products

Useful Crossed Aldol Reactions

• Practical if one of the reaction partners has no α hydrogens
• The carbonyl with no α hydrogens is put in basic solution, and the carbonyl with one or two α hydrogens is added slowly
• Dehydration usually occurs immediately, especially if an extended conjugated system results

Crossed aldol reactions: Claisen-Schmidt Reaction

• Crossed-aldehyde reactions in which one partner is a ketone are called Claisen-Schmidt reactions
• The product of ketone self-condensation is not obtained because the equilibrium is not favorable
Mechanism of Claisen-Schmidt Reaction

\[ \text{HO}_2^+ + \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{HO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \]

Condensation with Nitroalkanes

The \( \alpha \) hydrogens of nitroalkanes are acidic (\( pK_a = 10 \)) because the resulting anion is resonance stabilized.

\[ \text{RC} = \text{NO}_2 + \text{H}_2\text{O} \rightarrow \text{RC} = \text{O} + \text{H}_2\text{NO}_2^- \]

- Nitroalkane anions can undergo aldol-like condensation with aldehydes and ketones.
- The nitro group can be easily reduced to an amine.

Crossed Aldol Reactions more broadly

Whenever one carbonyl component has especially acidic \( \alpha \) hydrogens.

Mechanism of Crossed Aldol Reactions

With the highly acidic hydrogens of the \( \beta \)-dicarbonyl compounds, the initial \( \beta \)-hydroxy compound loses water to form the conjugated product.

Candidates for Crossed Aldol Reactions

\( \beta \)-Dicarbonyl compounds are sometimes called active methylene compounds because they are more reactive towards base than other carbonyl compounds.

1,3-Dinitriles and \( \alpha \)-cyano carbonyl compounds are also active methylene compounds.

Cyclization via Aldol Condensations

- Intramolecular reaction of dicarbonyl compounds proceeds to form five- and six-membered rings preferentially.
- In the following reaction the aldehyde carbonyl carbon is attacked preferentially because an aldehyde is less sterically hindered and more electrophilic than a ketone.
Reaction of hexan-2,5-dione

In the presence of a very strong base such as lithium diisopropylamide (LDA), stable enolates can be formed.

Weak bases (OH⁻) produce only low concentrations of enolates.

Lithium Enolates

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- Weak bases (OH⁻) produce only low concentrations of enolates.

Unsymmetrical ketones can form two different enolates.

The thermodynamic enolate is the most stable enolate i.e. the one with the more highly substituted double bond.

A weak base favors the thermodynamic enolate because an equilibrium between the enolates is established.

Selective crossed aldol reactions can be run as a 2-step process:
1. Ketone is first deprotonated with a strong base such as LDA.
2. Aldehyde is added slowly to the enolate.

Lithium Enolates in Directed Aldol Reactions

Selective crossed aldol reactions can be run as a 2-step process:
1. Ketone is first deprotonated with a strong base such as LDA.
2. Aldehyde is added slowly to the enolate.

An unsymmetrical ketone can be selectively deprotonated with LDA to form the kinetic enolate and this will react with an aldehyde to give primarily one product.
Enolates can also be alkylated with primary alkyl halides via an $S_{N}2$ reaction.

Unsymmetrical ketones can be alkylated at the least substituted position if LDA is used to form the kinetic enolate.

Lithium enolate can be selenated with benzeneselenyl bromide.

The $\alpha$-selenyl ketone is converted to the $\alpha,\beta$-unsaturated carbonyl compound by reaction with hydrogen peroxide.

Spontaneous elimination of the selenoxide produces the unsaturated carbonyl.

Stronger nucleophiles such as Grignard reagents favor 1,2 addition.

Weaker nucleophiles such as cyanide or amines favor 1,4 addition.

$\alpha,\beta$-Unsaturated aldehydes and ketones can react by simple (1,2) or conjugate (1,4) addition.

Both the carbonyl carbon and the $\beta$ carbon are electrophilic and can react with nucleophiles.
Conjugate Addition of Organocopper Reagents

- Organocopper reagents add almost exclusively in a conjugate manner to α,β-unsaturated aldehydes and ketones.

Michael Additions

- Addition of an enolate to an α,β-unsaturated carbonyl compound usually occurs by conjugate addition.
- This reaction is called a Michael addition.

Robinson annulation

Procedure to build a new six-membered ring on an existing ring:
1. A Michael addition
2. An aldol condensation to close the ring.

The Robinson Annulation

- The starting materials for a Robinson annulation are an α,β-unsaturated carbonyl compound that must also have an α-hydrogens and an enolate.
- The Robinson annulation begins with an enolate executing a Michael addition to the α,β-unsaturated carbonyl compound.
In part two of the mechanism, an intramolecular aldol reaction is followed by dehydration to form a six-membered ring. 

To visualize the product of Robinson annulation:
1. Align the α carbon of the carbonyl compound that becomes the enolate next to the β carbon of the α,β-unsaturated carbonyl compound.
2. Join the appropriate carbons together as shown.
3. The double bond ends up replacing the C=O of the starting ketone.

How would you make this compound by a Robinson Annulation?
1. Identify 2-cyclohexenone ring and redraw in the standard position

2. Use retrosynthesis principles to cleave the two new bonds of the ring, generating the needed components