Organic Chemistry

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Enolate Anions

Chapter 18
Enolate Anions

Enolate anions are nucleophiles and participate in $S_N2$ reactions.

\[
\begin{align*}
\text{R} & \quad + \quad \text{RCH}_2\text{-Br} \quad \xrightarrow{S_N2} \quad \text{CH}_2\text{R} + \text{Br}^- \\
\end{align*}
\]

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Enolate Anions

- and function as nucleophiles in carbonyl addition reactions

An enolate anion + A ketone → A tetrahedral carbonyl addition intermediate

The special value of these two reactions is that each results in formation of a new C-C bond
The Aldol Reaction

The most important reaction of enolate anions is nucleophilic addition to the carbonyl group of another molecule of the same or different compound.

Although these reactions may be catalyzed by either acid or base, base catalysis is more common.
The Aldol Reaction

The product of an aldol reaction is

- a β-hydroxyaldehyde

\[
\begin{align*}
\text{CH}_3\text{-C-H} & \quad + \quad \text{CH}_2\text{-C-H} & \quad \xrightarrow{\text{NaOH}} \quad \text{CH}_3\text{-CH-CH}_2\text{-C-H} \\
\text{Ethanal} & \quad \text{(Acetaldehyde)} & \quad \text{Ethanal} & \quad \text{(Acetaldehyde)} & \quad \text{3-Hydroxybutanal} \\
& & & & \text{(a β-hydroxyaldehyde)}
\end{align*}
\]
The Aldol Reaction

• or a \( \beta \)-hydroxyketone

\[
\text{Propanone (Acetone)} + \text{Propanone (Acetone)} \rightleftharpoons \text{4-Hydroxy-4-methyl-2-pentanone (a \( \beta \)-hydroxyketone)}
\]
The mechanism of a base-catalyzed aldol reaction can be divided into three steps:

**Step 1:** formation of a resonance-stabilized enolate anion

\[
\text{HO}^- + \text{H-CH}_2\text{-C-H} \rightleftharpoons \text{HO-H} + \left[ \begin{array}{c} \text{CH}_2\text{-C-H} \\ \text{Enolate anion} \end{array} \right]
\]
The Aldol Reaction: base

Step 2: addition of the enolate anion to the carbonyl group of another carbonyl-containing molecule to form a TCAI

\[
\text{CH}_3\text{-C-H} + \text{CH}_2\text{-C-H} \rightarrow \text{CH}_3\text{-C-CH-CH}_2\text{-C-H} \quad \text{A tetrahedal carbonyl addition intermediate}
\]
Step 3: reaction of the TCAI with a proton donor to give the aldol product

\[
\begin{align*}
\text{CH}_3\text{-CH-CH}_2\text{-C-H} + \text{H-OH} & \rightleftharpoons \text{CH}_3\text{-CH-CH}_2\text{-C-H} + \text{OH}^- \\
\end{align*}
\]
The key step in an acid-catalyzed aldol reaction is attack of the enol of one molecule on the protonated carbonyl group of another. Proton transfer completes the reaction.

\[
\text{CH}_3\text{-C-H} + \text{CH}_2=\text{C-H} \rightarrow \text{CH}_3\text{-CH-CH}_2\text{-C-H} + \text{H-A}
\]
Aldol products are very easily dehydrated

- the major product is an $\alpha,\beta$-unsaturated aldehyde or ketone

\[ \text{OH} \quad \text{O} \quad \text{warm in either} \quad \text{acid or base} \quad \text{CH}_3\text{CHCH}_2\text{CH} \rightarrow \text{CH}_3\text{CH}=\text{CHCH} + \text{H}_2\text{O} \]

- aldol reactions are reversible and, especially for ketones, there is often little aldol present at equilibrium. $K_{eq}$ for dehydration is generally large and, if reaction conditions bring about dehydration, good yields of product can be obtained
In base-catalyzed dehydration, an α-hydrogen is removed to form a new enolate anion, which then expels hydroxide ion.

An enolate anion

An α,β-unsaturated aldehyde
The Aldol Reaction: $-\text{H}_2\text{O}$

In acid, proton transfer to $-\text{OH}$ and loss of $\text{H}_2\text{O}$ gives the protonated form of the final product.
In a crossed aldol reaction, one kind of molecule provides the enolate anion and another kind provides the carbonyl group.

\[
\text{CH}_3\text{CCH}_3 + \text{HCH} \xrightleftharpoons{\text{NaOH}} \text{CH}_3\text{CCH}_2\text{CH}_2\text{OH}
\]

4-Hydroxy-2-butanone
Crossed aldol reactions are most successful if:

- one of the reactants has no $\alpha$-hydrogen and, therefore, cannot form an enolate anion and
- the other reactant has a more reactive carbonyl group, namely an aldehyde

Formaldehyde

Benzaldehyde

Furfural

2,2-Dimethylpropanal
Aldol Reactions

Intramolecular aldol reactions (when the enolate anion and the carbonyl acceptor are in the same molecule) are most successful for formation of five- and six-membered rings.

2,7-Octanedione
Aldol Reactions

The α-hydrogens of nitroalkanes are removed by strong bases such as KOH and NaOH.

\[
\text{Nitromethane} \quad \text{pK}_a \ 10.2 \\
\text{(stronger acid)}
\]

\[
\text{Water} \quad \text{pK}_a \ 15.7 \\
\text{(weaker acid)}
\]

Resonance stabilized anion
Reduction of a nitro group gives a 1° amine.

\[
\text{Ox} + \text{CH}_3\text{NO}_2 \xrightarrow{\text{NaOH}} \quad \text{(aldol)}
\]

1-(Nitromethyl)-cyclohexanol

\[
\text{H}_2, \text{Ni} \quad \rightarrow
\]

1-(Aminomethyl)-cyclohexanol
Directed Aldol Reactions

- Kinetic vs thermodynamic control
  - when alkali metal hydroxides or alkoxides are used as bases, the position of equilibrium for formation of enolate anions favors reactants

\[
\begin{align*}
\text{CH}_3\text{CCH}_3 + \text{NaOH} &\quad \xleftrightarrow{\text{Keq} = 5 \times 10^{-5}} \quad \text{CH}_2=\text{CCH}_3 + \text{H}_2\text{O} \\
pK_a \ 20 &\quad \text{(weaker base)} &\quad pK_a \ 15.7 &\quad \text{(stronger acid)}
\end{align*}
\]

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Directed Aldol Reactions

- With stronger bases, however, the formation of enolate anion can be driven to the right.
- One of the most widely used bases for this purpose is lithium diisopropylamide, LDA:

\[(\text{CH}_3)_2\text{CH}^-\text{N}^\text{-Li}^+\]

Lithium diisopropylamide
(LDA)

- LDA is a very strong base but, because of crowding around nitrogen, is a poor nucleophile.
 Directed Aldol Reactions

LDA is prepared by treatment of diisopropylamine with butyllithium

\[
\begin{align*}
[(\text{CH}_3)_2\text{CH}]_2\text{NH} + \text{CH}_3(\text{CH}_2)_3\text{Li} & \quad \xrightarrow{K_{eq} = 10^{10}} \\
\text{Diisopropylamine} & \quad \text{Butyllithium} \\
pK_a 40 & \quad \text{(stronger base)} \\
(\text{stronger acid}) & \\
\end{align*}
\]

\[
[(\text{CH}_3)_2\text{CH}]_2\text{N}^-\text{Li}^+ + \text{CH}_3(\text{CH}_2)_2\text{CH}_3 \\
\text{Lithium diisopropylamide (LDA)} & \quad \text{Butane} \\
pK_a 50 & \quad \text{(weaker base)} \\
(\text{weaker acid}) & 
\]
Directed Aldol Reactions

With 1 mol of LDA, an aldehyde, ketone, or ester can be converted completely to its enolate anion.

\[ \text{O} \quad \text{CH}_3\text{CCH}_3 \quad + \quad [(\text{CH}_3)_2\text{CH}]_2\text{N}^- \quad \text{Li}^+ \quad + \quad \text{Keq} = 10^{20} \]

\[ \text{pK}_a \quad 20 \quad \text{(stronger acid)} \quad \text{LDA} \quad \text{(stronger base)} \]

\[ \text{O}^- \quad \text{Li}^+ \]

\[ \text{CH}_2=\text{CCH}_3 \quad + \quad [(\text{CH}_3)_2\text{CH}]_2\text{NH} \quad \text{pK}_a \quad 40 \quad \text{(weaker base)} \quad \text{(weaker acid)} \]
For a ketone with two different sets of $\alpha$-hydrogens, is formation of the enolate anion regioselective?

The answer depends on experimental conditions

- when a slight excess of LDA, a ketone is converted to its lithium enolate anion, which consists almost entirely of the less substituted enolate anion
- this reaction is said to be under kinetic control
Kinetic Control

- with slight excess of LDA

2-Methyl-cyclohexanone + slight excess LDA → 0°C →

99% 1% + (i-pr)₂NH

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For a reaction under kinetic control, the composition of the product mixture is determined by the relative rates of formation of each product.

For formation of lithium enolates, kinetic control refers to the rates of removal of alternative $\alpha$-hydrogens.
In a reaction under thermodynamic control:

- reaction conditions permit equilibration of alternative products, under which conditions
- the composition of the product mixture is determined by their relative stabilities
Thermodynamic Control

- with the ketone in slight excess, the lithium enolate is richer in the more substituted (the more stable) enolate anion

\[
\begin{align*}
\text{2-Methyl-cyclohexanone} & \quad + \quad \text{LDA} & \quad \text{0}\degree\text{C} & \quad \text{O}^\text{-} \text{Li}^+ \\
10\% & \quad + \quad 90\% & \quad + \quad (\text{i-pr})_2\text{NH}
\end{align*}
\]
Consider the crossed aldol reaction between phenylacetaldehyde and acetone.

\[
\begin{align*}
\text{Phenylacetaldehyde} & : \quad \text{C}_6\text{H}_5\text{CH}_2\text{CH} \quad + \quad \text{CH}_3\text{CCH}_3 \\
\text{Acetone} & : \quad \text{C}_6\text{H}_5\text{CH}_2\text{CHCH}_2\text{CCH}_3
\end{align*}
\]

Each reactant has \(\alpha\)-hydrogens and a mixture of four aldol products is possible.

4-Hydroxy-5-phenyl-2-pentanone
Directed Aldol Reactions

The desired reaction can be carried out by preforming the lithium enolate anion of acetone and treating it with benzaldehyde.

\[
\text{CH}_3\text{CCH}_3 \xrightarrow{\text{LDA, -78}\degree\text{C}} \text{O}^{-} \text{Li}^{+} \xrightarrow{} \text{CH}_2=\text{CCH}_3
\]

A lithium enolate

1. C\text{6H}_5\text{CH}_2\text{CH}
2. H\text{2O} \rightarrow \text{C}_6\text{H}_5\text{CH}_2\text{CHCH}_2\text{CCH}_3

18-30
Esters also form enolate anions which participate in nucleophilic acyl substitution.

\[
2 \text{CH}_3\text{COEt} \rightarrow \underset{\text{1. EtO}^- \text{Na}^+}{\text{CH}_3\text{CCH}_2\text{COEt}} + \text{EtOH}
\]

Ethyl ethanoate (Ethyl acetate) + Ethyl 3-oxobutanoate (Ethyl acetoacetate)

As illustrated by the above example, the product of a Claisen condensation is a \(\beta\)-ketoester.
Claisen Condensation

Claisen condensation of ethyl propanoate gives the following $\beta$-ketoester.

$$\text{Ethyl propanoate} + \text{Ethyl propanoate} \xrightarrow{1. \text{EtO}^- \text{Na}^+} \text{EtOH}$$

1. Reaction with base to form the salt.
2. Hydrolysis with water and HCl to yield the product.

Product: Ethyl 2-methyl-3-oxopentanoate.
Claisen Condensation

Step 1: formation of an enolate anion

\[ \text{C}_2\text{H}_5\text{O}^- + \text{H-CH}_2\text{-COEt} \rightleftharpoons \text{EtO}^-\text{H} + \text{CH}_2\text{-COEt} \]

- \( pK_a = 22 \) (weaker base) (weaker acid)
- \( pK_a = 15.9 \) (stronger acid) (stronger base)

Resonance-stabilized enolate anion
Claisen Condensation

Step 2: attack of the enolate anion on a carbonyl carbon to give a TCAI

\[
\begin{align*}
\text{CH}_3\text{-COEt} & \quad + \quad \text{CH}_2\text{-COEt} \\
& \quad \xrightarrow{\text{O}^-} \\
& \quad \xrightarrow{\text{O}^-} \\
& \quad \xrightarrow{\text{O}^-} \\
& \quad \xrightarrow{\text{O}^-} \\
\end{align*}
\]

A tetrahedral carbonyl addition intermediate

\[
\begin{align*}
\text{CH}_3\text{-C-CH}_2\text{-COEt} \\
\text{OEt} \\
\end{align*}
\]
Claisen Condensation

Step 3: collapse of the TCAI to form a $\beta$-ketoester and an alkoxide ion

$$\text{CH}_3\text{-C-CH}_2\text{-COEt} \rightleftharpoons \text{CH}_3\text{-C-CH}_2\text{-COEt} + \text{EtO}^-$$
Step 4: formation of the enolate anion of the \( \beta \)-ketoester, which drives the Claisen condensation to the right.

\[
\text{CH}_3\text{-CH-COEt} + \text{EtO}^- \rightarrow \text{CH}_3\text{-CH-COEt} + \text{EtOH}
\]

\( pK_a \) 10.7 (stronger base) vs. 15.9 (weaker base).
Dieckman Condensation

An intramolecular Claisen condensation

\[
\text{EtOCCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COEt} \underset{1. \text{Et O}^- \text{ Na}^+}{\xrightarrow{\text{2. H}_2\text{O, HCl}}} \text{COEt} + \text{EtOH}
\]

Diethyl hexanedioate (Diethyl adipate)

Ethyl 2-oxocyclopentanecarboxylate
Crossed Claisen Condensations

- Crossed Claisen condensations between two different esters, each with $\alpha$-hydrogens, give mixtures of products and are not synthetically useful.

- Crossed Claisen condensations are possible, however, if there is an appreciable difference in reactivity between the two esters, for example, when one of the esters has no $\alpha$-hydrogens.
The following esters have no $\alpha$-hydrogens:

- **Diethyl ethanedioate** (Diethyl oxalate)
  \[ \text{Et O-C-OEt} \]

- **Diethyl carbonate**
  \[ \text{Et O-COEt} \]

- **Ethyl formate**
  \[ \text{HCOEt} \]

- **Ethyl benzoate**
  \[ \text{Et-COEt} \]
The ester with no $\alpha$-hydrogens is generally used in excess.

\[
\text{PhCOCH}_3 + \text{CH}_3\text{CH}_2\text{COCH}_3 \xrightarrow{1. \text{CH}_3\text{O}^- \text{Na}^+} \xrightarrow{2. \text{H}_2\text{O}, \text{HCl}} \text{PhCCHCOCH}_3
\]

Methyl benzoate + Methyl propanoate → Methyl 2-methyl-3-oxo-3-phenylpropanoate
Saponification of a β-ketoester followed by acidification with HCl gives a β-ketoacid.

Heating the β-ketoacid leads to decarboxylation.

\[
\text{CH}_3\text{CH}_2\text{C(CH}_3\text{)COEt} \xrightarrow{3. \text{NaOH, } H_2O} \text{CH}_3\text{CH}_2\text{C(CH}_3\text{)COH} \xrightarrow{4. \text{H}_2O, \text{HCl}} \xrightarrow{5. \text{heat}} \text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_3 + \text{CO}_2
\]
Claisen Condensation

The result of Claisen condensation, saponification, acidification, and decarboxylation is a ketone

\[ \text{R-CH}_2\text{-C}=\text{O} + \text{CH}_2\text{-C-OR'} \rightarrow \text{R-CH}_2\text{-C}=\text{O} + 2\text{HOR'} + \text{CO}_2 \]

from the ester furnishing the carbonyl group

from the ester furnishing the enolate anion

several steps
Carbonyl condensations are among the most widely used reactions in the biological world for formation of new carbon-carbon bonds in such biomolecules as

- fatty acids
- cholesterol, bile acids, and steroid hormones
- terpenes

One source of carbon atoms for the synthesis of these biomolecules is acetyl coenzyme A (acetyl-CoA)
Claisen condensation of acetyl-CoA is catalyzed by the enzyme thiolase.

\[
\text{CH}_3\text{CSCoA (Acetyl-CoA)} + \text{CH}_3\text{CSCoA (Acetyl-CoA)} \xrightarrow{\text{thiolase}} \text{CH}_3\text{CCH}_2\text{CSCoA (Acetoacetyl-CoA)} + \text{CoASH (Coenzyme A)}
\]
This is followed by an aldol reaction with a second molecule of acetyl-CoA.

\[
\text{Acetyl-CoA} + \text{Acetyl-CoA} \xrightarrow{\text{enzyme}} \text{Acetoacetyl-CoA} + \text{(S)-3-Hydroxy-3-methylglutaryl-CoA}
\]
Enzyme-catalyzed reduction of the thioester group gives a 1° alcohol.

\[
\begin{align*}
\text{(S)-3-Hydroxy-3-methylglutaryl-CoA} & \quad \text{enzyme} \quad \text{(R)-Mevalonate} \\
\end{align*}
\]
Phosphorylation by ATP followed by $\beta$-elimination gives isopentenyl pyrophosphate.
Isopentenyl pyrophosphate has the carbon skeleton of isoprene and is a key intermediate in the synthesis of these classes of biomolecules:

\[
\text{CH}_3 \quad \text{CH}_2 = \text{CCH}_2 \text{CH}_2 \text{OP}_2 \text{O}_6^{3-}
\]

Isopentenyl pyrophosphate

- terpenes
- cholesterol
- steroid hormones
- bile acids
Enamines

Enamines are formed by the reaction of a 2° amine with the carbonyl group of an aldehyde or ketone (Section 15.10A).

The 2° amines most commonly used to prepare enamines are pyrroolidine and morpholine.

\[
\begin{align*}
\text{Pyrroolidine} & \quad \text{Morpholine} \\
\end{align*}
\]
Enamines

The value of enamines is that the β-carbon is nucleophilic and resembles enols and enolate anions in its reactions.

An enamine as a resonance hybrid of two contributing structures.

The β-carbon of an enamine is nucleophilic.
Enamines - Alkylation

Enamines undergo $S_N^2$ reactions with methyl and $1^\circ$ alkyl halides, $\alpha$-haloketones, and $\alpha$-haloesters.

Step 1: the enamine is treated with one equivalent of an alkylating agent to give an iminium halide.

Step 2: hydrolysis of the iminium halide gives an alkylated aldehyde or ketone.
Enamines - Alkylation

The morpholine enamine of cyclohexanone

Allyl bromide

An iminium bromide

18-52
Enamines - Alkylation

\[
\text{Morpholinium chloride} + 2\text{-Allylcyclohexanone} \rightarrow \text{HCl/H}_2\text{O} \rightarrow \text{Enamine}
\]
Enamines - Acylation

- Enamines undergo acylation when treated with acid chlorides and acid anhydrides.
- The reaction is an example of nucleophilic acyl substitution.
The pyrrolidine enamine of cyclohexanone + Acetyl chloride → An iminium chloride → 2-Acetyl cyclohexanone

HCl/H₂O
Acetoacetic ester (AAE) and other β-ketoesters are versatile starting materials for the formation of new carbon-carbon bonds because

- the α-hydrogens between the two carbonyls (pK$_a$ 10-11) can be removed by alkoxide bases to form an enolate anion and
- the resulting enolate anion is a nucleophile and undergoes S$_N$2 reactions with methyl and 1° alkyl halides, α-haloketones, and α-haloesters
18 Acetoacetic Ester Synth.

\[
\text{Ethyl acetoacetate} \quad \text{Sodium ethoxide} \\
\begin{align*}
pK_a &= 10.7 \\ 
&\text{(stronger base)}
\end{align*}
\]

\[
\text{Sodium salt of ethyl acetoacetate} \quad \text{Ethanol} \\
\begin{align*}
pK_a &= 15.9 \\ 
&\text{(weaker base)}
\end{align*}
\]
The acetoacetic ester (AAE) synthesis is useful for the preparation of mono- and disubstituted acetones of the following types:

- A monosubstituted acetone:
  \[
  \text{CH}_3\text{CCH}_2\text{R} \quad \text{R} \quad \text{A monosubstituted acetone}
  \]

- A disubstituted acetone:
  \[
  \text{CH}_3\text{CCHR} \quad \text{R'} \quad \text{A disubstituted acetone}
  \]

Ethyl acetoacetate (Acetoacetic ester)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CH}_3\text{CCH}_2\text{COEt} 
\end{align*}
\]
Consider the AAE synthesis of this target molecule, which is a monosubstituted acetone.

These three carbons are from ethyl acetoacetate.

The -R group of a monosubstituted acetone.

5-Hexen-2-one
Alkylation of the enolate anion of AAE with allyl bromide forms the new carbon-carbon bond.

\[
\text{CH}_3\text{C-CH-COEt} + \text{CH}_2=\text{CHCH}_2\text{Br} \xrightarrow{\text{S}_{\text{N}2}} \text{CH}_3\text{C-CH-COEt} + \text{Na}^+\text{Br}^-
\]
Saponification, acidification, and decarboxylation gives the target molecule

\[
\text{CH}_3\text{C-CH-COEt} \quad \xrightarrow{3. \text{NaOH, H}_2\text{O}} \quad \text{CH}_3\text{C-CH-COEt}
\]

\[
\text{CH}_2\text{CH=CH}_2
\]

\[
\xrightarrow{4. \text{HCl, H}_2\text{O}} \quad \text{CH}_3\text{C-CH-COEt} \quad + \quad \text{CO}_2
\]

\[
\text{CH}_2\text{CH=CH}_2
\]
To prepare a disubstituted acetone, treat the monoalkylated AAE with a second mol of base.

\[
\begin{align*}
\text{CH}_3\text{C}-\text{CH}-\text{COEt} + \text{EtO}^- \text{Na}^+ & \rightarrow \\
\text{CH}_2\text{CH=CH}_2 + \text{Na}^+ \\
\text{CH}_3\text{C}-\text{C}-\text{COEt} + \text{EtOH} & \rightarrow \\
\text{CH}_2\text{CH=CH}_2
\end{align*}
\]
Then, a 2nd alkylation, saponification, acidification, and decarboxylation:

1. $\text{Na}^+ \quad \text{O} \quad \text{O}$
   $\text{CH}_3\text{C}-\text{C}-\text{COEt}$
   $\text{CH}_2\text{CH=CH}_2$

2. $2^\prime \cdot \text{CH}_3\text{I}$

3. $\text{NaOH, H}_2\text{O}$

4. $\text{HCl, H}_2\text{O}$

5. $\text{heat}$

$\text{O} \quad \text{CH}_3\text{O}$
$\text{CH}_3\text{C}-\text{C}-\text{COH}$
$\text{CH}_2\text{CH=CH}_2$

$\text{O} \quad \text{CH}_3$
$\text{CH}_3\text{C}-\text{CH}$
$\text{CH}_2\text{CH=CH}_2$

$+ \text{CO}_2$

18-63
The strategy of a malonic ester (ME) synthesis is identical to that of an acetoacetic ester synthesis, except that the starting material is a β-diester rather than a β-ketoester.

Diethyl malonate
(Malonic ester)

A monosubstituted acetic acid

A disubstituted acetic acid
Malonic Ester Synthesis

Consider the synthesis of this target molecule:

These two carbons are from diethyl malonate.

- malonic ester is first converted to its enolate anion by an alkali metal alkoxide.
18 Malonic Ester Synthesis

\[
\text{EtOC-CH-COEt (Stronger acid) } + \text{EtO}^- \text{Na}^+ \text{ (Stronger base) } \rightarrow \text{EtOC-CH-COEt (Weaker base) } + \text{EtOH (Weaker acid)}
\]

\[
\text{Diethyl malonate } \quad \text{Sodium ethoxide }
\]

\[
pK_a \text{ diethyl malonate } = 13.3 \quad \text{pK}_a \text{ Ethanol } = 15.9
\]
Alkylation of this enolate anion with benzyl chloride forms the new carbon-carbon bond.

\[
\begin{align*}
\text{EtOC-CH-COEt} & \quad \text{C}_6\text{H}_5\text{CH}_2\text{Br} \\
\text{S}_{\text{N}2} & \\
\text{EtOC-CH-COEt} & \quad \text{Na}^+\text{Br}^- \\
\end{align*}
\]
Malonic Ester Synthesis

Saponification of the diester followed by acidification and thermal decarboxylation gives the target molecule:

\[
\text{EtOC-CH-COEt} \xrightarrow{3. \text{NaOH, H}_2\text{O}} \text{CH}_2\text{C}_6\text{H}_5
\]

\[
\text{HOC-CH-COEt} \xrightarrow{4. \text{HCl, H}_2\text{O}} \text{CH}_2\text{C}_6\text{H}_5
\]

\[
\text{HOC-CH-COEt} \xrightarrow{5. \text{heat}} \text{HOC-CH}_2\text{COEt} + \text{CO}_2
\]

\[
\text{HOC-CH-COEt} \xrightarrow{5. \text{heat}} \text{HOC-CH}_2\text{COEt} + \text{CO}_2
\]
Michael Reaction

- **Michael reaction**: the nucleophilic addition of an enolate anion to an $\alpha,\beta$-unsaturated carbonyl compound

- Following are two examples
  - in the first, the nucleophile is the enolate anion of malonic ester
  - in the second, it is the enolate anion of acetoacetic ester
Michael Reaction

Diethyl propanedioate (Diethyl malonate) + 3-Buten-2-one (Methyl vinyl ketone) → EtO⁻ Na⁺ in EtOH
Michael Reaction

Ethyl 3-oxobutanoate (Ethyl acetoacetate) + 2-Cyclohexenone →

Ethyl 3-oxohexanoate
Michael Reaction

We can write the following 4 step mechanism for a Michael reaction:

Step 1: proton transfer to the base to form the nucleophile, $\text{Nu}^-$

$$\text{Nu-H} \quad + \quad \cdot \text{B}^- \quad \leftrightarrow \quad \text{Nu}^- \quad + \quad \text{H-B}$$
Michael Reaction

Step 2: addition of $\text{Nu}\cdot$ to the $\beta$ carbon of the $\alpha, \beta$-unsaturated carbonyl compound

Resonance-stabilized enolate anion
Michael Reaction

Step 3: proton transfer to HB to form an enol

An enol
(a product of 1,4-addition)

Step 4: tautomerism of the less stable enol to the more stable keto form gives the observed product
Retro of 2,6-Heptadione

from acetoacetic ester

Lost by decarboxylation

formed in a Michael reaction

\[
\begin{align*}
\text{CH}_3\text{CCH}_2\text{CH}_2\text{CH}_2\text{CCH}_3 & \rightarrow \text{CH}_3\text{CCH}\text{CH}_2\text{CH}_2\text{CCH}_3 \\
& \rightarrow \text{CH}_3\text{CCH}_2 + \text{CH}_2=\text{CHCCH}_3
\end{align*}
\]

Ethyl acetoacetate
Methyl vinyl ketone

18-75
Enamines also participate in Michael reactions.

\[
\text{Pyrrolidine enamine of cyclohexanone} + \text{Acrylonitrile} \rightarrow \text{Product}
\]

\[
\begin{align*}
\text{Pyrrolidine enamine of cyclohexanone} & \quad + \quad \text{Acrylonitrile} \\
& \quad \rightarrow \\
& \quad \text{Product}
\end{align*}
\]
Robinson Annulation

A combination of aldol, Michael, and dehydration reactions

18-77
Gilman Reagents

Gilman reagents undergo conjugate addition to α, β-unsaturated aldehydes and ketones, in a reaction closely related to the Michael reaction.

\[
\begin{align*}
&3\text{-Methyl-2-cyclohexenone} \\
&\xrightarrow{1. \ (\text{CH}_3)_2\text{CuLi, ether, -78°C}} \\
&\xrightarrow{2. \ H_2O, HCl} \\
&3,3\text{-Dimethyl-cyclohexanone}
\end{align*}
\]
Gilman Reagents

- Gilman reagents are unique among organometallic compounds in that they give almost exclusively 1,4-addition.
- Other organometallic compounds, including Grignard reagents, add to the carbonyl carbon by 1,2-addition.
- The mechanism of conjugate addition of Gilman reagents is not fully understood.
Enolate Anions

End Chapter 18