Chapter 22
The Chemistry of Enolate Ions, Enols, and $\alpha,\beta$- Unsaturated Carbonyl Compounds

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Chapter 22 Overview

• 22.1 Acidity of Carbonyl Compounds
• 22.2 Enolization of Carbonyl Compounds
• 22.3 $\alpha$-Halogenation of Carbonyl Compounds
• 22.4 Aldol Addition and Aldol Condensation
• 22.5 Condensation Reactions Involving Ester Enolate Ions
• 22.6 Biosynthesis of Fatty Acids
• 22.7 Alkylation of Ester Enolates
• 22.8 Conjugate-Addition Reactions
• 22.9 Reduction of $\alpha,\beta$-Unsaturated Carbonyl Compounds
• 22.10 Reactions of $\alpha,\beta$-Unsaturated Carbonyl Compounds with Organometallic Reagents
• 22.11 Organic Synthesis with Conjugate-Addition Reactions
Enolates and Enols

- The $\alpha$-H of carbonyl compounds are relatively acidic
- The $\alpha$-C of enolates and enols can serve as a nucleophile

22.1 Acidity of Carbonyl Compounds
Formation of Enolate Anions

• The $\alpha$-H of aldehydes, ketones, esters, and even nitriles can be deprotonated

\[ \text{B}^- + \text{H}_2\text{C} = \text{C} - \text{Ph} \rightleftharpoons [\text{H}_2\text{C} = \text{C} - \text{Ph}]^- + \text{B}^- \]

\[ \text{B}^- + \text{H}_2\text{C} = \text{C} - \text{OC}_2\text{H}_5 \rightleftharpoons [\text{H}_2\text{C} = \text{C} - \text{OC}_2\text{H}_5]^- + \text{B}^- \]

22.1 Acidity of Carbonyl Compounds
Formation of Enolate Anions

• An ester $\alpha$-H is about $10^7$ times less acidic than aldehydes and ketones ($pK_a \approx 25$)

\[
\begin{align*}
\text{[resonance structure]} & \quad \text{repulsion between negative charges} \\
\text{this resonance structure is relatively unimportant}
\end{align*}
\]

• The $N$-$H$ of primary and secondary amides is more acidic than the $\alpha$-H

\[
\begin{align*}
B^- + \text{C}$\text{--N}$H_2 & \quad pK_a = 15-17 \\
\text{resonance structure} & \quad \text{resonance structure}
\end{align*}
\]

22.1 Acidity of Carbonyl Compounds
• The $\alpha$-C and carbonyl oxygen bear a significant amount of electron density

22.1 Acidity of Carbonyl Compounds
22.1 Acidity of Carbonyl Compounds
Reactions of Enolate Ions

\[
\text{D}_2\text{O/dioxane} \quad \text{(C}_2\text{H}_5)_3\text{N}^- \quad \text{(a base)} \quad \text{heat, 48 h}
\]

Further reactions

22.1 Acidity of Carbonyl Compounds
Reactions of Enolate Ions

22.1 Acidity of Carbonyl Compounds
22.2 Enolization of Carbonyl Compounds
**Enols**

- Some **enols** are more stable than their corresponding carbonyl compounds.

\[ \text{enol} \rightleftharpoons \text{carbonyl} \]

\[ K_{eq} \approx 10^{14} \]

**2,4-pentanedione**

(a β-dicarbonyl compound)

enol form

92% in hexane solution

22.2 Enolization of Carbonyl Compounds
Enols

- Conversion of a carbonyl compound into its enol is called **enolization**
- The process is facilitated by acid or base
- Base-catalyzed enolization:

\[
\begin{align*}
\text{aldehyde or ketone} & \quad \leftrightarrow \quad \text{enol} \\
\text{enolate ion} & \quad \text{(conjugate base of both the carbonyl compound and the enol)}
\end{align*}
\]

22.2 Enolization of Carbonyl Compounds
Enols

• Acid-catalyzed enolization:

\[
\begin{align*}
\text{aldehyde or ketone} & \quad \leftrightarrow \\
(\text{conjugate acid of both the carbonyl compound and the enol}) & \quad \leftrightarrow \\
\text{enol}
\end{align*}
\]
Enols

- α-H exchange and racemization also occur under acidic conditions

\[
\begin{align*}
\text{Enolization of Carbonyl Compounds}
\end{align*}
\]
Acid-Catalyzed $\alpha$-Halogenation

$p$-bromoacetophenone $\rightarrow$ 1-(4-bromophenyl)-2-bromoethanone (69–72% yield)

• Enols are the reactive intermediates

22.3 $\alpha$-Halogenation of Carbonyl Compounds
Acid-Catalyzed $\alpha$-Haloegenation

$$\text{rate} = k[\text{ketone}][\text{H}_3\text{O}^+]$$

- In acid, only a single haloegenation occurs

22.3 $\alpha$-Haloegenation of Carbonyl Compounds
Halogenation of Aldehydes and Ketones

- In base, all α-H’s are substituted by halogens

\[
3\text{NaOH} + (\text{CH}_3)_2\text{C} = \text{C} - \text{CH}_3 + 3\text{Br}_2 \xrightarrow{\text{NaOH, 0 °C, H}_2\text{O/dioxane}} (\text{CH}_3)_3\text{C} = \text{CBr}_3 + 3\text{Na}^+\text{Br}^- + 3\text{H}_2\text{O}
\]

- Haloform reaction: When acetaldehyde or a methyl ketone are used, a carboxylic acid and haloform (HCX$_3$) are produced

\[
(\text{CH}_3)_3\text{C} = \text{C} - \text{CBr}_3 \xrightarrow{\text{OH}} (\text{CH}_3)_3\text{C} = \text{C} - \text{OH} + \text{HBr}_3
\]

(71–74% yield)
The Haloform Reaction

\[\text{R-CH}_2\text{CO} + \text{OH}^- \rightarrow \text{R-CH}_2\text{CH}_2\text{CO}^{-} + \text{H}_2\text{O}\]

\[\text{R-CH}_2\text{CO}^{-} + \text{Br}_2 \rightarrow \text{R-CH}_2\text{CHBr}_2 + \text{Br}^-\]

22.3 \(\alpha\)-Halogenation of Carbonyl Compounds
The Haloform Reaction

\[
\text{R—C—CHBr}_2 \xrightarrow{\text{Br}_2/\text{OH}^-} \text{R—C—CB}_3 + \text{Br}^- + \text{H}_2\text{O}
\]

22.3 \(\alpha\)-Halogenation of Carbonyl Compounds
α-Bromination of Carboxylic Acids

- This is the Hell-Volhard-Zelinsky (or HVZ) reaction

\[
\text{hexanoic acid} \quad \xrightarrow{\text{P or PBr}_3} \quad \text{2-bromohexanoic acid (83–89% yield)}
\]

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} + \text{Br}_2 \xrightarrow{\text{P or PBr}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCO}_2\text{H} + \text{HBr}
\]
α-Bromination of Carboxylic Acids

\[
3 \text{CH} - \text{C} - \text{OH} + \text{PBr}_3 \rightarrow 3 \text{CH} - \text{C} - \text{Br} + \text{P(OH)}_3
\]

(carboxylic acid with α-hydrogens) an acid bromide

\[
\text{CH} - \text{C} - \text{Br} \quad \overset{\text{Br}_2}{\text{CH}} - \text{C} - \text{Br} + \text{HBr}
\]

(acid bromide) enol form (α-bromo acid bromide)

22.3 α-Halogenation of Carbonyl Compounds
α-Bromination of Carboxylic Acids

- When a small amount of PBr₃ catalyst is used:

\[
\begin{align*}
\text{CH₃C} = \text{O} + \text{C} = \text{C} \text{Br} \quad \rightarrow \quad \text{CH₃C} = \text{C} \text{Br} + \frac{1}{2}\text{CH₃C} = \text{O} \\
\end{align*}
\]

- When one full equivalent of PBr₃ is used:

\[
\begin{align*}
\text{CH₃CH₂C} = \text{O} \quad \text{P (1 equiv.):} \quad \text{Br₂} \quad \text{Br} \quad \text{Br₂} \quad \text{Br} \\
\rightarrow \quad \text{CH₃CHC} = \text{Br} \quad \text{(CH₃)₂COH} \quad \text{(CH₃)₂N} \quad \text{Ph} \quad \text{Br}^{-} \\
\rightarrow \quad \text{CH₃CHC} = \text{O(CH₃)₃} + \text{(CH₃)₂NH} \text{Br}^{-} \\
\end{align*}
\]

22.3 α-Halogenation of Carbonyl Compounds
Reactions of $\alpha$-Halo Carbonyl Compounds

- Most $\alpha$-halo carbonyl compounds are highly reactive in $S_N2$ reactions

\[ (\text{CH}_3)_2\text{S}:\text{Br} \rightarrow \text{CH}_2\text{C} = \text{Ph} \quad \xrightarrow{25^\circ \text{C}, 30 \text{ min}} \quad \text{H}_3\text{C} = \text{S} \text{CH}_2\text{C} = \text{Ph} :\text{Br}^- \quad (85\% \text{ yield}) \]

$\text{N} = \text{C}^- + \text{Cl} = \text{CH}_2\text{CO}_2^- \quad \xrightarrow{\text{H}_3\text{O}^+} \quad \text{N} = \text{C} = \text{CH}_2\text{CO}_2\text{H} + \text{Cl}^-$

- Chloroacetate anion
- Cyanoacetate acid

(77–80% yield)

\[ \text{Cl} = \text{CH}_2\text{C} = \text{CH}_3 + \text{KI} \quad \xrightarrow{\text{acetone}} \quad \text{I} = \text{CH}_2\text{C} = \text{CH}_3 + \text{KCl} \quad \text{relative rate: 35,000} \]

\[ \text{Cl} = \text{CH}_2\text{CH}_2\text{CH}_3 + \text{KI} \quad \xrightarrow{\text{acetone}} \quad \text{I} = \text{CH}_2\text{CH}_2\text{CH}_3 + \text{KCl} \quad 1 \]

22.3 $\alpha$-Halogenation of Carbonyl Compounds
Reactions of $\alpha$-Halo Carbonyl Compounds

- $S_N1$ reactions generally do not occur
Base-Catalyzed Aldol Reactions

- The term **aldol** is also used generically for β-hydroxyaldehydes
- **Aldol reaction**: A reaction of two aldehyde molecules to form a β-hydroxyaldehyde
The aldol addition is *reversible* and more favorable for aldehydes than ketones.
The Aldol Condensation

- With higher base concentration and/or higher temperatures the aldol product can *dehydrate*

\[
2 \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}==\text{O} \xrightleftharpoons{1 \text{ M NaOH} 80^\circ\text{C}} \text{CH}_3\text{CH}_2\text{CH}==\text{CHCH}==\text{O} \xrightarrow{} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}==\text{CCH}==\text{O} + \text{H}_2\text{O}
\]

- Aldol addition product
- 2-ethyl-3-hydroxyhexanal (the aldol addition product)
- 2-ethyl-2-hexenal (86% yield)
- Aldol condensation reaction
- Carbanion intermediate
- \(\alpha,\beta\)-unsaturated carbonyl compound
Acid-Catalyzed Aldol Condensation

- With acid, aldol \textit{condensation products} are formed; addition products cannot be isolated.

\[2 \text{CH}_3\text{C} \equiv \text{CH} \rightarrow \text{CH}_3\text{C} \equiv \text{CH} + \text{H}_2\text{O}\]  

\text{acetone}  

\[\text{mesityl oxide} \quad (79\% \text{ yield})\]
Acid-Catalyzed Aldol Condensation

A second molecule of the protonated ketone

The carbonyl carbon accepts π electrons from the enol

An α-hydroxy carbocation (a protonated ketone; Sec. 19.6)

22.4 Aldol Addition and Aldol Condensation
Special Types of Aldol Reactions

- **Claisen-Schmidt condensation**: An example of a *crossed aldol reaction*

  \[
  \text{PhCH} = \text{O} + \text{H}_3\text{C} - \text{C} - \text{CH}_3 \xrightarrow{\text{aqueous NaOH}} \text{PhC} = \text{C} - \text{CH}_3 + \text{H}_2\text{O}
  \]

  benzalacetone (4-phenyl-3-buten-2-one) (65–78% yield)

- **Intramolecular aldol condensations**

  \[
  \text{CH}_2\text{CH}_2\text{CCH}_3 \xrightarrow{\text{H}_3\text{C} - \text{SO}_3\text{H}} \text{CH}_2\text{CH}_2\text{CH} = \text{CHC} = \text{O} + \text{H}_2\text{O}
  \]

22.4 Aldol Addition and Aldol Condensation
Synthesis with the Aldol Condensation

• Recognizing the aldol disconnection is synthetically useful
Some Common Organic Group Abbreviations

<table>
<thead>
<tr>
<th>Group</th>
<th>Structure</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>( \text{H}_2\text{C}— )</td>
<td>Me</td>
</tr>
<tr>
<td>ethyl</td>
<td>( \text{CH}_3\text{CH}_2— )</td>
<td>Et</td>
</tr>
<tr>
<td>propyl</td>
<td>( \text{CH}_3\text{CH}_2\text{CH}_2— )</td>
<td>Pr</td>
</tr>
<tr>
<td>isopropyl</td>
<td>( (\text{CH}_3)_2\text{CH}— )</td>
<td>i-Pr</td>
</tr>
<tr>
<td>butyl</td>
<td>( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2— )</td>
<td>Bu</td>
</tr>
<tr>
<td>isobutyl</td>
<td>( (\text{CH}_3)_2\text{CHCH}_2— )</td>
<td>i-Bu</td>
</tr>
<tr>
<td>tert-butyl</td>
<td>( (\text{CH}_3)_3\text{C}— )</td>
<td>t-Bu</td>
</tr>
<tr>
<td>acetyl</td>
<td>[ \text{H}_3\text{C}—\text{C}— ]</td>
<td>Ac</td>
</tr>
<tr>
<td>acetate (or acetoxy)</td>
<td>[ \text{H}_3\text{C}—\text{C}—\text{O—} ]</td>
<td>AcO</td>
</tr>
</tbody>
</table>

22.5 Condensation Reactions Involving Ester Enolate Ions
Claisen Condensation

• A condensation reaction involving esters

\[
2 \text{H}_3\text{C} = \text{C} - \text{OEt} \xrightarrow{\text{NaOEt (1 equiv.) EtOH}} \xrightarrow{\text{H}_3\text{O}^+} \text{H}_3\text{C} = \text{C} - \text{CH}_2 - \text{C} = \text{OEt} + \text{EtOH}
\]

ethyl acetate

• The product is a \( \beta \)-keto ester

\[
\begin{align*}
\text{H}_3\text{C} & = \text{C} - \text{CH}_2 - \text{C} = \text{OEt} \\
\beta & \rightarrow \alpha
\end{align*}
\]

22.5 Condensation Reactions Involving Ester Enolate Ions
Claisen Condensation

\[ \text{EtO}^- + \text{H}_2\text{C} = \text{C} = \text{OEt} \quad (\text{pK}_a \approx 25) \]

\[ \xrightarrow{\text{enolate ion}} \text{H}_2\text{C} = \text{C} = \text{OEt} + \text{EtOH} \]

\[ \text{H}_3\text{C} = \text{C} = \text{OEt} + \text{H}_2\text{C} = \text{C} = \text{OEt} \]

\[ \xrightarrow{\text{tetrahedral addition intermediate}} \text{H}_3\text{C} = \text{C} = \text{CH}_2 = \text{C} = \text{OEt} \]

\[ \xrightarrow{\text{EtO}^-} \text{H}_3\text{C} = \text{C} = \text{CH}_2 = \text{C} = \text{OEt} + \text{EtOH} \]

22.5 Condensation Reactions Involving Ester Enolate Ions
Claisen Condensation

• The reaction is driven to completion by applying Le Châtelier’s principle

• *One full equivalent* of the alkoxide is required

\[
\text{H}_3\text{C} \text{CH}_2 \text{C} \text{OEt} + \text{Na}^+ \text{EtO}^- \quad \rightleftharpoons \quad \text{H}_3\text{C} \text{CH} \text{C} \text{OEt} + \text{EtOH}
\]

\[
pK_a = 10.7 \quad \text{and} \quad pK_a = 15-16
\]

• At least one α-H is required for success

\[
2 \text{(CH}_3)_2\text{CH} \text{C} \text{OEt} \quad \rightleftharpoons \quad \text{(CH}_3)_2\text{CH} \text{C} \text{CO}_2\text{Et}
\]

(no product observed)

22.5 Condensation Reactions Involving Ester Enolate Ions
Dieckmann Condensation

• An *intramolecular* Claisen condensation

![Chemical Reaction Diagram]

**Diethyl Adipate**

NaOEt (1 equiv.)

toluene (solvent)

ethyl 2-oxocyclopentane-carboxylate
(74–81% yield)

22.5 Condensation Reactions Involving Ester Enolate Ions
Crossed Claisen Condensation

• A Claisen condensation of two different esters
• If both have $\alpha$-H’s then a mixture of four compounds results

$$\text{H}_3\text{C}—\text{CO}_2\text{Et} + \text{C}_2\text{H}_5—\text{CO}_2\text{Et} \xrightarrow{\text{NaOEt}} \xrightarrow{\text{H}_3\text{O}^+} \text{H}_3\text{C}—\text{C—CH}_2—\text{C—OEt} + \text{CH}_3\text{CH}_2—\text{C—CH}_2—\text{C—OEt} + \text{H}_3\text{C}—\text{CH—C—OEt} + \text{CH}_3\text{CH}_2—\text{C—CH—C—OEt}$$
Crossed Claisen Condensation

- The reaction can be useful if one ester is especially reactive or has no $\alpha$-H’s

\[ \text{diethyl succinate} + \text{ethyl formate} \xrightarrow{\text{Na (1 equiv.), EtOH (trace), toluene (solvent)}} \xrightarrow{\text{H}_3\text{O}^+} \text{diethyl formylsuccinate} \]

\[ (60\text{–}70\% \text{ yield}) \]

\[ \text{PhCH}_2\text{C}==\text{OEt} + \text{EtO}==\text{C}==\text{OEt} \xrightarrow{\text{heat, NaOEt (1 equiv.)}} \xrightarrow{\text{H}_2\text{O}^+} \text{PhCH}==\text{C}==\text{OEt} + \text{EtOH} \]

\[ \text{diethyl phenylmalonate} \]

\[ (86\% \text{ yield}) \]
Synthesis with the Claisen Condensation

22.5 Condensation Reactions Involving Ester Enolate Ions
Synthesis with the Claisen Condensation

22.5 Condensation Reactions Involving Ester Enolate Ions
Biosynthesis of Fatty Acids

• The starting material, **acetyl-coenzyme A**, is a thiol ester of acetic acid
Biosynthesis of Fatty Acids

- The acetyl-CoA is converted into malonyl-CoA
Biosynthesis of Fatty Acids

\[ \text{H}_3\text{C} - \text{C} - \text{CH}_2 - \text{C} - \text{SR} \xrightarrow{\text{reduction}} \text{H}_3\text{C} - \text{CH}_2 - \text{C} - \text{SR} \xrightarrow{\text{dehydration}} \text{H}_3\text{C} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{SR} \]

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{C} - \text{SR} + \text{O} - \text{C} - \text{CH}_2 - \text{C} - \text{SR} \xrightarrow{\text{H}_3\text{O}^+} \text{CH}_3\text{CH}_2\text{CH}_2\text{C} - \text{CH}_2 - \text{C} - \text{SR} + \text{R} - \text{SH} + \text{CO}_2 \]

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{C} - \text{CH}_2 - \text{C} - \text{SR} \xrightarrow{\text{three reactions like Eq. 22.63b}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C} - \text{C} - \text{SR} \]
Malonic Ester Synthesis

$$\text{EtO}^2- + \text{EtO} \to \text{CH}_2 \to \text{C} \to \text{C} \to \text{OEt} \quad \leftrightarrow \quad \text{EtO}^2- + \text{EtO} \to \text{CH} \to \text{C} \to \text{C} \to \text{OEt}$$

diethyl malonate
$$pK_a = 12.9$$

$$\text{CH}_2\text{CH}_3 \quad \text{Na}^+ \to \text{CH(CO}_2\text{Et})_2 + \text{CH}_3\text{CH} \to \text{Br}$$

$$(83\% \text{ yield})$$

$$\text{CH}_2\text{CH}_3 \quad \text{CH}_3\text{CHCH(CO}_2\text{Et})_2 + \text{Na}^+ \text{ Br}^-$$

ester saponification
(Sec. 21.7A)

protonation
(decarboxylation
(Sec. 20.11))

heat

$$\text{CH}_2\text{CH}_3 \quad \text{CH}_3\text{CHCH(CO}_2\text{H})_2$$

a “substituted acetic acid”

22.7 Alkylation of Ester Enolates
Malonic Ester Synthesis

• Recognizing how a target carboxylic acid can be prepared by the malonic ester synthesis is synthetically useful

![Chemical Structure](image)

22.7 Alkylation of Ester Enolates
Direct Alkylation of Enolate Ions

\[
\begin{align*}
B^- + H_3C&-C-OR &\rightarrow & H_2&-C-OR \\
& &\rightarrow & + B-H \\
& &\rightarrow & CH_3CH_2CH_2&-C-OR + I^-
\end{align*}
\]

- Highly branched nitrogen bases are commonly used

22.7 Alkylation of Ester Enolates
Direct Alkylation of Enolate Ions

\[
\begin{align*}
\text{ethyl 2-methylpropanoate} & \\ 
H_3C-\text{C}-\text{C}-\text{C}-\text{OEt} & \xrightarrow{-78^\circ \text{C} \text{ LCHA} \text{ THF} \text{ < 15 min}} H_3C-\text{C}-\text{C}-\text{C}-\text{OEt}^{+} + \text{H}_2\text{C-}-\text{I} \text{ DMSO} \\
& \xrightarrow{\text{a quaternary } \alpha\text{-carbon}} \text{ethyl 2,2-dimethylpropanoate} \text{ (ethyl pivalate)} \text{ (87% yield)}
\end{align*}
\]

\[
\begin{align*}
\text{N-H} & + \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2-\text{Li} \xrightarrow{-78^\circ \text{C} \text{ THF}} \text{N}^{+} - \text{Li}^{+} + \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3
\end{align*}
\]
Acetoacetic Ester Synthesis

\[ \text{EtO}^- + \text{H}_3\text{C} - \text{C} - \text{CH}_2 - \text{C} - \text{OEt} \rightarrow \text{EtO}^- + \text{H}_3\text{C} - \text{C} - \text{CH} - \text{C} - \text{OEt} \]

*ethyl acetoacetate*

\[ pK_a = 10.7 \]

*ethanol*

\[ pK_a = 16 \]

\[ \text{H}_3\text{C} - \text{C} - \text{CH} - \text{C} - \text{OEt} + \text{CH}_2\text{CH}_2\text{H}_2\text{CH}_3 \rightarrow \text{H}_3\text{C} - \text{C} - \text{CH} - \text{C} - \text{OEt} + \text{Na}^+ + \text{Br}^- \]

*1-bromobutane*

*ethyl 2-acetyhexanoate*  
*(70% yield)*

22.7 Alkylation of Ester Enolates
Acetoacetic Ester Synthesis

22.7 Alkylation of Ester Enolates
Acetoacetic Ester Synthesis

• Recognizing how a target ketone can be prepared by the acetoacetic ester synthesis is synthetically useful

22.7 Alkylation of Ester Enolates
Conjugate Addition

- A unique reactivity is observed for alkenes that are conjugated with carbonyls (C=C–C=O).
- These conjugated compounds are generally called $\alpha,\beta$-unsaturated carbonyl compounds.

\[
\text{Ph} = \text{CH} = \text{CH} = \text{C} = \text{Ph} + \text{HCN} \xrightarrow{\text{35 °C}, \text{EtOH}} \text{Ph} = \text{CH} = \text{CH} = \text{C} = \text{Ph} + \text{CN} (93\% \text{ yield})
\]

\[
\text{CH}_3\text{CH} = \text{CH}_2 + \text{HCN} \xrightarrow{\text{EtOH}} \text{no reaction}
\]
Conjugate Addition

\[
\begin{align*}
\text{Ph} & \text{CH} = \text{CH} \text{CN} \\
\text{Ph} & \text{CH} \text{CN} \\
\text{Ph} & \text{CH} \text{CN} \\
\text{Ph} & \text{CH} \text{CN} \\
\text{Ph} & \text{CH} \text{CN} \\
\text{Ph} & \text{CH} \text{CN} \\
\text{Ph} & \text{CH} \text{CN} \\
\text{Ph} & \text{CH} \text{CN} \\
\text{Ph} & \text{CH} \text{CN} \\
\end{align*}
\]

enolate ion

observed product

enol form of product

22.8 Conjugate-Addition Reactions
Conjugate Addition

• With $\alpha,\beta$-unsaturated esters:

\[
\begin{align*}
(CH_3)_2CH\text{--SH} + H_2C\text{==CH}--CO_2Me & \xrightarrow{\text{NaOMe, MeOH}} (CH_3)_2CH\text{--S}--CH_2--CH_2--CO_2Me \\
2\text{-propanethiol} & \quad \text{methyl acrylate} & \quad \text{methyl 3-(isopropylthio)propanoate} \\
& & \quad \text{(97\% yield)}
\end{align*}
\]

• With $\alpha,\beta$-unsaturated ketones:

\[
\begin{align*}
\text{H}_3\text{C}--\text{C}\text{==CH}--\text{Ph} + \text{HN:} & \xrightarrow{\text{MeOH}} \text{H}_3\text{C}--\text{C}--\text{CH}_2--\text{CH}--\text{Ph} \\
& \quad \text{(85\% yield)}
\end{align*}
\]

• With $\alpha,\beta$-unsaturated nitriles:

\[
\begin{align*}
\text{CH}_3\text{SH} + H_2C\text{==CH}--\text{CN} & \xrightarrow{\text{NaOMe, MeOH}} \text{CH}_3\text{S}--\text{CH}_2--\text{CH}_2--\text{CN} \\
\text{methanethiol} & \quad \text{acrylonitrile} & \quad \text{3-(methylthio)propanenitrile} \\
& & \quad \text{(91\% yield)}
\end{align*}
\]

22.8 Conjugate-Addition Reactions
Conjugate Addition vs Carbonyl-Group Addition

- For *ketones and aldehydes*, relatively weak bases that give *reversible* carbonyl-addition tend to give conjugate addition
Conjugate Addition vs Carbonyl-Group Addition

- For esters conjugate addition *competes* with nucleophilic acyl substitution
Conjugate Addition of Enolate Ions

![Chemical Reaction]

- Common for enolate ions derived from malonic ester derivatives and \( \beta \)-keto esters
- Conjugate additions to \( \alpha,\beta \)-unsaturated carbonyl compounds are called **Michael additions**
The Robinson Annulation

- A synthetically useful variant that utilizes a Michael addition followed by an aldol condensation

\[ \text{KOH} \quad \text{MeOH} \]

\[ \text{Michael addition} \]

\[ \text{benzene} \]

\[ \text{aldol condensation} \]

\[ \text{(63–65\% yield)} \]
Reduction of $\alpha,\beta$-Unsaturated Carbonyls

- Carbonyl reduction is not only faster, but is also irreversible (i.e., kinetically controlled)

\[
\text{KOH} \xrightarrow{\text{LiAlH}} \text{RCH} = \text{CH} - \text{C} - \text{R} + \text{H}_3\text{O}^+ \rightarrow \text{RCH} = \text{CH} - \text{C} - \text{R} + \text{H}_2\text{O}
\]
Reduction of $\alpha,\beta$-Unsaturated Carbonyls

- The C=C of $\alpha,\beta$-unsaturated carbonyls can be selectively reduced by catalytic hydrogenation.

\[
\text{Ph–CH=CH–C–Ph} + \text{H}_2 \xrightarrow{\text{Pt; 3 atm EtOAc}} \text{Ph–CH}_2\text{CH}_2–C–\text{Ph}
\]

1,3-diphenyl-2-propen-1-one

1,3-diphenyl-1-propanone (81–95% yield)
Addition of Organolithium Reagents

- Addition of R-Li results in carbonyl addition

\[
\begin{align*}
\text{H}_3\text{C} & \text{C} & \text{H} & \text{C} & \text{O} & \text{C} & \text{H}_3 + \text{PhLi} \rightarrow \text{H}_3\text{C} & \text{C} & \text{H} & \text{C} & \text{O} & \text{C} & \text{H}_3 + \text{H}_2\text{O} \\
\text{H}_3\text{C} & \text{C} & \text{H} & \text{C} & \text{O} & \text{C} & \text{H}_3 & \text{Ph} & \text{H}_3\text{C} & \text{C} & \text{H} & \text{C} & \text{O} & \text{C} & \text{H}_3 & \text{Ph} \\
\text{4-methyl-3-penten-2-one} & \text{(mesityl oxide)} & \text{4-methyl-2-phenyl-3-penten-2-ol} & \text{(67% yield)}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{C} & \text{C} & \text{C} & \text{O} & \text{C} & \text{H}_3 + 2\text{Bu-Li} \rightarrow \text{H}_2\text{C} & \text{C} & \text{C} & \text{O} & \text{C} & \text{H}_3 + \text{H}_2\text{O}^+ \\
\text{CH}_3 & \text{C} & \text{H}_3 & \text{Bu} & \text{C} & \text{Bu} & \text{C} & \text{Bu} & \text{C} & \text{Bu} \\
\text{methyl} & \text{2-methylpropenoate} & \text{3-butyl-2-methyl-1-hepten-3-ol} & \text{(89% yield)}
\end{align*}
\]

22.10 Reactions of \(\alpha,\beta\)- Unsaturated Carbonyl Compounds with Organometallics
Addition of Lithium Dialkylcuprate Reagents

• Addition of $R_2CuLi$ results in conjugate addition

\[ \text{2-cyclohexenone} \xrightarrow{\text{(CH}_3\text{)}_2\text{Cu}^- \text{ Li}^+ \text{ ether, } -78 \degree \text{C}} \text{H}_2\text{O} \rightarrow \text{3-methylcyclohexanone} \]

(97% yield)

\[ \text{Et}_2\text{C} \equiv \text{CH} \cdots \text{CH} \equiv \text{O} \xrightarrow{\text{(CH}_3\text{)}_2\text{CuLi} \text{ ether, } -50 \degree \text{C}} \text{H}_3\text{O}^+ \rightarrow \text{Et}_2\text{C} \cdots \text{CH}_2 \cdots \text{CH} \equiv \text{O} + \text{Et}_2\text{C} \cdots \text{CH} \cdots \text{CH} \cdots \text{CH}_3 \]

(95% of product) (5% of product)

70% total yield

22.10 Reactions of $\alpha,\beta$-Unsaturated Carbonyl Compounds with Organometallics
Addition of Lithium Dialkylcuprate Reagents

- The addition of the nucleophilic reagent results in the formation of an enolate ion.
Conjugate Addition in Organic Synthesis

- Consider any group at the $\beta$-position of a carbonyl (or nitrile) as a nucleophile in a conjugate addition reaction.

$$R\text{CH}_2\text{CHO} \rightleftharpoons \text{“R}, \text{H}^+ + \text{H}_2\text{C}==\text{CHCO}$$
Summary of C-C Bond Forming Reactions

1. Aldol addition and condensation
2. Claisen and Dieckmann condensations
3. Malonic ester synthesis
4. Alkylation of ester enolates
5. Acetoacetic ester synthesis
6. Conjugate addition of cyanide ions and enolate ions
7. Conjugate addition of $R_2CuLi$