Chapter 19
Synthesis and Reactions of \( \beta \)-Dicarbonyl Compounds: More Chemistry of Enolate Anions
Introduction

β-Dicarbonyl compounds have two carbonyl groups separated by a carbon.

The β-dicarbonyl system  
A β-keto ester (Section 19.2)  
A malonic ester (Section 19.4)

Protons on the α-carbon of β-dicarbonyl compounds are acidic ($pK_a = 9-10$)

The acidity can be explained by resonance stabilization of the corresponding enolate by two carbonyl groups.

Contributing resonance structures  
Resonance hybrid
\( \Rightarrow \beta \text{-Dicarbonyl compounds can be synthesized by the Claisen condensation} \)

![](image)

\( \Rightarrow \text{The acetoacetic ester and malonic acid syntheses use } \beta \text{-dicarbonyl compounds for carbon-carbon bond forming reactions} \)

![](image)

Acetoacetic ester synthesis, \( G = \text{CH}_3 \)

Malonic ester synthesis, \( G = \text{RO} \)

\( \Rightarrow \text{The acetoacetic ester and malonic ester syntheses usually conclude with decarboxylation of a } \beta \text{-keto acid} \)

![](image)

(Section 18.10)
The Claisen Condensation: Synthesis of $\beta$-Keto Esters

$\Rightarrow$ Ethyl acetate undergoes a Claisen condensation when treated with sodium ethoxide

$\Rightarrow$ Ethyl pentanoate undergoes an analogous reaction
The overall reaction involves loss of an α hydrogen from one ester and loss of ethoxide from another.

\[
\text{R} \text{CH}_2\text{C} \text{OC}_2\text{H}_5 + \text{H} \xrightarrow{\text{(2) H}_3\text{O}^+} \text{R} \text{CH}_2\text{C} \text{CHCOC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OH}
\]

(R may also be H)

A β-keto ester

The mechanism is an example of the general process of nucleophilic addition-elimination at an ester carbonyl.

**Step 1**

\[
\alpha \text{RCH} \equiv \text{COC}_2\text{H}_5 + \cdot \text{OC}_2\text{H}_5 \leftrightarrow \text{RCH} \equiv \text{COC}_2\text{H}_5 \leftrightarrow \text{RCH} \equiv \text{COC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OH}
\]
Step 2

\[
\begin{align*}
\text{Nucleophilic addition} & \quad \text{Tetrahedral intermediate and elimination} \\
\text{RCH}_2\text{C} & \quad \text{RCH}_2\text{C} \\
\text{OC}_2\text{H}_5 & \quad \text{OC}_2\text{H}_5
\end{align*}
\]

Step 3

\[
\begin{align*}
\beta\text{-Keto ester} & \quad \text{Ethoxide ion} \\
(pK_a \approx 9; \text{stronger acid}) & \quad (\text{stronger base}) \\
\text{RCH}_2\text{C} & \quad \text{RCH}_2\text{C} \\
\text{C}_2\text{H}_5\text{O}^- & \quad \text{C}_2\text{H}_5\text{O}^- \\
\text{R} & \quad \text{R} \\
\text{C}_2\text{H}_5 & \quad \text{C}_2\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{\beta-Keto ester anion} & \quad \text{Ethanol} \\
(\text{weaker base}) & \quad (pK_a 16; \text{weaker acid}) \\
\text{RCH}_2\text{C} & \quad \text{C}_2\text{H}_5\text{OH}
\end{align*}
\]

Step 4

\[
\begin{align*}
\text{Keto form} & \quad \text{Enol form} \\
\text{RCH}_2\text{C} & \quad \text{RCH}_2\text{C} \\
\text{C}_2\text{H}_5 & \quad \text{C}_2\text{H}_5
\end{align*}
\]

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The alkoxide base must have the same alkyl group as the alkoxy group of the ester

- The use of a different alkoxide would result in formation of some transesterification products

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 drives the reaction to completion

Only one $\alpha$ hydrogen

This ester does not undergo a Claisen condensation.

Ethyl 2-methylpropanoate
The Dieckmann condensation is an intramolecular Claisen condensation

Only 5- and 6-membered rings may be prepared in this way.

- Ethoxide anion removes an α hydrogen.
- The enolate anion attacks the carbonyl group at the other end of the chain.
- An ethoxide anion is expelled.
- The ethoxide anion removes the acidic hydrogen located between two carbonyl groups. This favorable equilibrium drives the reaction.
- Addition of aqueous acid rapidly protonates the anion, giving the final product.
• Crossed Claisen Condensations

Crossed Claisen condensations can lead to one major product when one of the two esters has no α hydrogen.

\[
\text{Ethyl benzoate (no \( \alpha \) hydrogen)} + \text{CH}_3\text{COC}_2\text{H}_5 \xrightarrow{(1) \text{NaOCC}_2\text{H}_5} \xrightarrow{(2) \text{H}_2\text{O}^+} \text{Ethyl benzoylacetate (60\%)}
\]

\[
\text{Ethyl phenylacetate (no \( \alpha \) carbon)} + \text{C}_2\text{H}_5\text{OCOC}_2\text{H}_5 \xrightarrow{(1) \text{NaOCC}_2\text{H}_5} \xrightarrow{(2) \text{H}_2\text{O}^+} \text{Diethyl phenylmalonate (65\%)}
\]
Esters with one $\alpha$ hydrogen can react in Claisen condensations if they are deprotonated with a strong base and acylated with an acyl chloride.

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{CH}_3\text{C} & \quad \text{C} \quad \text{OC}_2\text{H}_5 \\
\text{CH}_3 & \\
\text{Na}^+ : \text{C}(\text{C}_6\text{H}_5)_3 & \quad \text{Et}_2\text{O} \\
\text{CH}_3\text{C} & \quad \text{C} \quad \text{CO}_2\text{H}_5 + \text{H} : \text{C}(\text{C}_6\text{H}_5)_3 \\
\text{CH}_3 & \\
\text{C} & \quad \text{Cl} \\
\text{O} & \\
\text{CH}_3\text{C} & \quad \text{C} \quad \text{CO}_2\text{H}_5 + \text{Cl}^- \\
\text{CH}_3 & \\
\text{C} & \quad \text{Cl} \\
\text{O} & \\
\text{CH}_3\text{C} & \quad \text{C} \quad \text{CO}_2\text{H}_5 & + \text{Cl}^- \\
\text{CH}_3 & \\
\text{C} & \quad \text{Cl} \\
\text{O} & \\
\text{CH}_3\text{C} & \quad \text{C} \quad \text{CO}_2\text{H}_5 & + \text{Cl}^-
\end{align*}
\]

Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate
• **Acylation of Other Carbanions**
  
  → Ketone enolates formed with strong bases can also be acylated to form β-dicarbonyl compounds
  
  → Addition of strong base to 2-pentanone results in formation of the kinetic enolate which can be acylated with an ester

\[
\begin{align*}
\text{CH}_3\text{C(CH}_2\text{)}_2\text{CH}_3 & \xrightarrow{\text{NaNH}_2, \text{Et}_2\text{O}} \text{Na}^+ \xrightarrow{\text{CH}_2\text{C(CH}_2\text{)}_2\text{CH}_3} \text{CH}_3\text{(CH}_2\text{)}_2\text{C} & \xrightarrow{\text{O}} \text{OC}_2\text{H}_5 \\
2\text{-Pentanone} & & 4,6\text{-Nonanedione (76%)}
\end{align*}
\]
The Acetoacetic Ester Synthesis: Synthesis of Methyl Ketones (Substituted Acetones)

- **Alkylation**

  - Alkylation of the enolate derived from acetoacetic ester is called the acetoacetic ester synthesis.
  - This is an $S_{N}2$ reaction with the ethyl acetoacetate enolate acting as the nucleophile.

![Chemical Reaction Diagram]

- $\text{Acetoacetic ester} + \text{Sodium ethoxide} \rightarrow \text{Sodioacetoacetic ester} + \text{Ethanol}$
- $\text{Sodioacetoacetic ester} + \text{R-X} \rightarrow \text{Monoalkylacetoacetic ester} + \text{NaX}$
A second alkylation can be performed

A stronger base such as potassium tert-butoxide must be used to deprotonate the monoalkyl ester.

\[
\text{Monoalkylacetoacetic ester} \quad \leftrightarrow \quad \text{Potassium tert-butoxide} \quad \rightarrow \quad \text{Dialkylacetoacetic ester}
\]
Hydrolysis of the ester and heating of the resultant \( \beta \)-ketoacid causes decarboxylation

The product is a substituted acetone derivative

Basic hydrolysis of the ester group

Acidification

Decarboxylation of the \( \beta \)-keto acid
Example:

\[ \text{Ethyl butylacetoacetate (69–72%)} \]

\[ \text{Ethyl dibutylacetoacetate (77%)} \]

\[ \text{3-Butyl-2-heptanone} \]
Ethylacetoacetate serves as a *synthetic equivalent* of the acetone enolate

It is possible to use acetone enolate directly, but this would require a much stronger base and special reaction conditions.

\[
\begin{align*}
\text{Ethyl acetoacetate anion} & \quad \text{is the synthetic equivalent of} \quad \text{Acetone enolate} \\
H_3C\text{--C}--\text{CH}--\text{C}--\text{OC}_2\text{H}_5 & \quad \text{H}_3C\text{--C}--\text{CH}_2
\end{align*}
\]

If \( \alpha \)-halo esters are used to alkylate the enolate, \( \gamma \)-keto acids are obtained.

\[
\begin{align*}
\text{CH}_3\text{C}--\text{CH}_2--\text{C}--\text{OC}_2\text{H}_5 & \xrightarrow{\text{C}_2\text{H}_3\text{ONa}} \text{CH}_3\text{C}--\text{CH}--\text{C}--\text{OC}_2\text{H}_5 \\
\text{CH}_3\text{C}--\text{CH}--\text{C}--\text{OC}_2\text{H}_5 & \xrightarrow{\text{dilute NaOH}} \text{CH}_3\text{C}--\text{CH}--\text{C}--\text{OH} \\
\text{CH}_3\text{C}--\text{CH}_2--\text{CH}_2--\text{CH}_2--\text{CH}_2--\text{CH}_2--\text{CH}_2 & \xrightarrow{\text{heat}} \text{CH}_3\text{C}--\text{CH}--\text{C}--\text{OH}
\end{align*}
\]

4-Oxopentanoic acid
**Acylation**

Acetoacetic ester anion can also be acylated with acyl halides or anhydrides.

The reaction is carried out in aprotic solvents such as DMF or DMSO because these will not destroy the acylating reagents.
Acetoacetic Ester Dianion: Alkylation at the Terminal Carbon

Treating acetoacetic ester with two equivalents of a very strong base produces the dianion.

\[ \text{CH}_3\text{CCH}_2\text{COC}_2\text{H}_5 + 2\text{K}^+ + 2\text{NH}_3 \rightarrow \text{[Dianion]} + 2\text{K}^+ \]

The terminal carbanion is more nucleophilic and more basic because it is stabilized by only one carbonyl group.

Alkylation of the dianion occurs first at the terminal carbon.

The terminal carbanion is more nucleophilic and more basic because it is stabilized by only one carbonyl group.
The Malonic Ester Synthesis: Synthesis of Substituted Acetic Acids

- Alkylation of diethylmalonate, hydrolysis of the diester to the β-dicarboxylic acid, and decarboxylation can be used to synthesize mono- and disubstituted acetic acids

  - The mechanism is analogous to that for the acetoacetic ester synthesis

- In step 1 the stabilized anion is formed

\[
\begin{align*}
C_2H_5O-\overset{\cdot}{C}-\overset{\cdot}{C}-\overset{\cdot}{CH}_2-\overset{\cdot}{C}-\overset{\cdot}{OC}_2H_5 & \\
\text{Diethyl malonate} & \\
(\text{a } \beta\text{-dicarboxylic acid ester})
\end{align*}
\]
In step 2 the anion is mono- or dialkylated using $S_N^2$ reactions

Step 2  This enolate anion can be alkylated in an $S_N^2$ reaction,

\[
\begin{align*}
\text{Enolate ion} & \quad + \quad \text{R} \quad \text{X} \\
\text{Monoalkylmalonic ester} & \quad \rightarrow \quad \text{C}_2\text{H}_5\text{O} - \text{C} - \text{CH} - \text{C} - \text{OC}_2\text{H}_5 + \text{X}^{-}
\end{align*}
\]

and the product can be alkylated again if our synthesis requires it:

\[
\begin{align*}
\text{Dialkylmalonic ester}
\end{align*}
\]
In step 3 the mono- or dialkylated product is hydrolyzed and decarboxylated.

\[
\begin{align*}
\text{C}_2\text{H}_5\text{O} & \xrightarrow{(1) \text{HO}^-, \text{H}_2\text{O}} \text{HO} & \xrightarrow{(2) \text{H}_3\text{O}^+} \text{H}_2\text{C} & \xrightarrow{-\text{CO}_2} \text{R} \\
\text{CH} & \xrightarrow{\text{CH}} \text{C} & \xrightarrow{\text{OH}} \text{C} & \xrightarrow{\text{C}} \text{O} & \xrightarrow{\text{H}} \text{R} \\
\text{OC}_2\text{H}_5 & \xrightarrow{\text{R}} \text{R} \\
\text{Monoalkylmalonic ester} & \text{Monoalkylacetic acid}
\end{align*}
\]

or after dialkylation,

\[
\begin{align*}
\text{C}_2\text{H}_5\text{O} & \xrightarrow{(1) \text{HO}^-, \text{H}_2\text{O}} \text{HO} & \xrightarrow{(2) \text{H}_3\text{O}^+} \text{HC} & \xrightarrow{-\text{CO}_2} \text{R'} \text{R} \\
\text{CH} & \xrightarrow{\text{CH}} \text{C} & \xrightarrow{\text{OH}} \text{C} & \xrightarrow{\text{C}} \text{O} & \xrightarrow{\text{R'}} \text{R} \\
\text{OC}_2\text{H}_5 & \xrightarrow{\text{R'}} \text{R'} \\
\text{Dialkylmalonic ester} & \text{Dialkylacetic acid}
\end{align*}
\]
Diethylmalonate anion is the synthetic equivalent of acetic acid dianion

\[
\begin{align*}
\text{Diethylmalonate anion} & \\
\text{Diethyl malonate anion} & \\
\end{align*}
\]
Examples

A Malonic Ester Synthesis of Hexanoic Acid

\[
\text{EtO} \quad \text{O} \quad \text{Et} \quad \xrightarrow{(1) \text{NaOC}_2\text{H}_5} \quad \text{EtO} \quad \text{O} \quad \text{Et} \quad \xrightarrow{(2) \text{Br}} \quad \text{EtO} \quad \text{O} \quad \text{Et} \quad \xrightarrow{(1) 50\% \text{KOH}, \text{reflux}} \quad \text{EtO} \quad \text{O} \quad \text{Et} \quad \xrightarrow{(2) \text{dilute } \text{H}_2\text{SO}_4, \text{reflux}} \quad \text{CO}_2
\]

Diethyl butylmalonate

(80–90%)

\[
\text{Hexanoic acid (75%)}
\]

A Malonic Ester Synthesis of 2-Ethylpentanoic Acid

\[
\text{EtO} \quad \text{O} \quad \text{Et} \quad \xrightarrow{(1) \text{NaOC}_2\text{H}_5} \quad \text{EtO} \quad \text{O} \quad \text{Et} \quad \xrightarrow{(2) \text{I}}
\]

\[
\text{EtO} \quad \text{O} \quad \text{Et} \quad \xrightarrow{(1) \text{KOC(CH}_3)_3} \quad \text{EtO} \quad \text{O} \quad \text{Et} \quad \xrightarrow{(2) \text{I}}
\]

Diethyl ethylmalonate

Diethyl ethylpropylmalonate

\[
\text{HO} \quad \text{O} \quad \text{O} \quad \text{OH} \quad \xrightarrow{180^\circ \text{C}} \quad \text{HO} \quad \text{O} \quad \text{O} \quad \xrightarrow{-\text{CO}_2} \quad \text{HO} \quad \text{O} \quad \text{O} \quad \text{O} \quad \xrightarrow{-\text{CO}_2} \quad \text{CH}_3 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OH}
\]

Ethylpropylmalonic acid

2-Ethylpentanoic acid
By using two molar equivalents of malonate anion and a dihalide, the dicarboxylic acid is obtained.
C2 through C5 terminal dihalides can react to form rings by dialkylation of one molar equivalent of malonate.
Reactions of Other Active Hydrogen Compounds

Compounds in which the hydrogen atoms of a methylene (-CH₂-) group are made acidic by two attached electron-withdrawing groups are called *active hydrogen compounds* or *active methylene compounds*.

A variety of electron-withdrawing groups can produce enhanced α hydrogen acidity.

\[ Z—\text{CH}_2—Z' \]

Active hydrogen compound

(Z and Z' are electron-withdrawing groups.)
Example: Deprotonation of ethyl cyanoacetate forms a resonance-stabilized anion, which can then undergo alkylation.
Direct Alkylation of Esters and Nitriles

A strong and bulky base such as lithium diisopropyl amide (LDA) must be used to directly alkylate esters and nitriles.

- A strong base rapidly converts all of the ester or nitrile molecules into enolates so that they will not undergo Claisen condensation.
- A bulky base will not react as a nucleophile at the ester carbonyl or nitrile carbon.

\[
\begin{align*}
\text{C}_4\text{H}_9\cdot\text{Li}^+ & \quad \xrightarrow{\text{THF}} \quad \text{Li}^+ \\
\text{DN} & \quad \xrightarrow{\text{THF}} \quad \text{Li}^+ \\
\text{Butyllithium} & \quad \text{Diisopropylamine} & \quad \text{Lithium diisopropylamide} & \quad \text{Butane} \\
pK_a = 38 & \quad \text{[LDA or (i-C}_3\text{H}_7)_2\text{NLi]} & \quad pK_a = 50
\end{align*}
\]
Methyl butanoate

\[ \text{LDA}_{\text{THF}} \xrightarrow{\text{Li}^+} \text{CH}_3\text{CH}_2\text{CH} - C - \text{OCH}_3 \xrightarrow{\text{CH}_3\text{CH}_2} \]

Methyl 2-ethylbutanoate

(96%)

Butyrolactone

\[ \text{LDA}_{\text{THF}} \xrightarrow{} \text{CH}_3\text{H} \xrightarrow{\text{CH}_3} \]

2-Methylbutyrolactone

(88%)
Alkylation of 1,3-Dithianes

- Protons on the carbon between the sulfur atoms of a 1,3-dithiane are acidic
  - Strong bases convert the dithiane to its anion

\[
\text{SCH}_2\text{CH}_2\text{S} + \text{C}_4\text{H}_9\text{Li} \rightarrow \text{SCH}_2\text{CH}_2\text{S}^- + \text{C}_4\text{H}_{10}^+
\]

1,3-Dithiane
\[\text{p}K_a = 32\]

Dithianes are 6-membered ring thioacetals
- These can be prepared from an aldehyde and the 1,3-dithiol

\[
\text{RCH} + \text{HSCH}_2\text{CH}_2\text{CH}_2\text{SH} \rightarrow \text{RCH} + \text{H}_2\text{O} + \text{H}_3\text{O}^+ + \text{SCH}_2\text{CH}_2\text{S}
\]

A 1,3-dithiane
A dithioacetal anion is the synthetic equivalent of an aldehyde carbonyl anion

\[ \text{Thioacetal} \rightarrow \text{Ketone} \]

An aldehyde can be converted to a ketone by preparing the thioacetal from the aldehyde, alkylating the corresponding 1,3-dithiane anion, and hydrolyzing the thioacetal.

The reversal of the polarity of the carbonyl carbon in this series of reactions is called *umpolung*

An aldehyde carbonyl carbon normally has a $\delta^+$ charge and is electrophilic.

In dithioacetal alkylation, the equivalent of the aldehyde carbon is nucleophilic.

\[ \text{Aldehyde} \quad \overset{\delta^+}{\text{C}} \quad \overset{\delta^-}{\text{O}} \]

\[ \text{Aldehyde} \quad \overset{\delta^+}{\text{C}} \quad \overset{\delta^-}{\text{O}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]

\[ \overset{\text{Umpolung}}{\text{Aldehyde}} \]
Michael Additions

- A Michael addition involves conjugate addition of the anion derived from an active hydrogen compound (e.g., an enolate) to an \( \alpha,\beta \)-unsaturated carbonyl compound (see next slide)
- Michael additions take place with a wide variety of \( \alpha,\beta \)-unsaturated compounds
Overall Reaction:

\[
\text{CH}_3\text{O} + \text{CH}_3\text{C}==\text{CHCOC}_2\text{H}_5 + \text{CH}_2\text{COC}_2\text{H}_5 \xrightleftharpoons{\text{C}_2\text{H}_5\text{OH}}^{\text{C}_2\text{H}_3\text{O}^-\text{Na}^+} \xrightarrow{25^\circ\text{C}} \text{CH}_3\text{C}==\text{CH}_{2}\text{COC}_2\text{H}_5 + \text{CH(CO}_2\text{C}_2\text{H}_5)_2
\]

(70%)

Mechanism:

\textit{Step 1}

\[
\text{C}_2\text{H}_3\text{O}^- + \text{H} + \text{CHCOC}_2\text{H}_5 \xrightarrow{\text{C}_2\text{H}_5\text{OH}} \xrightarrow{\text{C}_2\text{H}_3\text{OH} + \text{CHCOC}_2\text{H}_5}\]

An alkoxide anion removes a proton to form the anion of the active methylene compound.
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**Step 2**

Conjugate addition of the anion to the $\alpha,\beta$-unsaturated ester leads to a new enolate anion.

**Step 3**

The enolate anion is protonated by an acid during the workup of the reaction.
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.

\[
\text{CH}_3\text{C-CH}_3 + \text{H-C-H} + (\text{C}_2\text{H}_5)_2\text{NH} \xrightarrow{\text{HCl}} \text{CH}_3\text{C-CH}_2\text{CH}_2\text{N}((\text{C}_2\text{H}_5)_2 + \text{H}_2\text{O}}
\]

A Mannich base

**Step 1**

\[\text{R}_2\text{NH} + \text{C-O} \xrightarrow{\text{H}} \text{R}_2\text{N-OH} \xrightarrow{\text{HA}} \text{R}_2\text{N}=\text{CH}_2\]

Reaction of the secondary amine with the aldehyde forms a hemiaminal.

The hemiaminal loses a molecule of water to form an iminium cation.

**Step 2**

\[\text{CH}_3\text{C-CH}_3 \xrightarrow{\text{HA}} \text{CH}_3\text{C-CH}_2\xrightarrow{+} \text{CH}_3\text{C-CH}_2\text{CH}_2\text{NR}_2 + \text{HA}\]

The enol form of the active hydrogen compound reacts with the iminium cation to form a β-aminocarbonyl compound (a Mannich base).
Synthesis of Enamines: Stork Enamine Reactions

- Aldehydes and ketones react with secondary amines to form enamines (see Section 16.8C)

  - Cyclic amines are often used
  - The reaction is catalyzed by acid
  - Removal of water drives enamine formation to completion

![Chemical Reaction Diagram]
Enamines have a nucleophilic carbon and are the equivalent of ketone and aldehyde enolates.

The nitrogen of enamines is also nucleophilic.
Enamines can be acylated, alkylated, and used in Michael reactions.

- The iminium intermediate is hydrolyzed when water is added.

C-Acylation leads to β-diketones

- N-acylated products can be formed, but they are unstable and act as acylating agents themselves.
Alkylation of enamines can lead to some $N$-alkylation

The $N$-alkylated product can often be converted to the $C$-alkylated product by heating.
**Barbiturates**

- Reaction of diethyl malonate with urea in the presence of sodium ethoxide produces barbituric acid:

\[
\text{CH}_2\text{COC}_2\text{H}_5 + \text{NH}_2\text{C} = \text{O} \xrightarrow{\text{C}_6\text{H}_5\text{O}^-\text{Na}^+} \text{C}_2\text{H}_5\text{C} = \text{O} \]

- Barbiturates are substituted derivatives of barbituric acid.

  - Barbiturates are used in medicine as soporifics (sleep inducers).

- Examples of barbiturates:
  - Veronal (5,5-diethylbarbituric acid)
  - Seconal [5-allyl-5-(1-methylbutyl) barbituric acid]
  - Phenobarbital (5-ethyl-5-phenylbarbituric acid)