Chapter 21: Ester Enolates

21.1: Ester α Hydrogens and Their pKₐ’s. The α-protons of esters are less acidic than ketones and aldehydes.

Typical pKₐ’s of carbonyl compounds (α-protons):
- Aldehydes: 17
- Ketones: 19
- Esters: 24
- Amides: 30
- Nitriles: 25

Acidity of 1,3-dicarbonyl compounds
- Ester (pKₐ = 24)
- Ketone (pKₐ = 19)
- 1,3-diketone (pKₐ = 13)
- 1,3-keto ester (pKₐ = 11)

21.2: The Claisen Condensation Reaction. Base-promoted condensation of two esters to give a β-keto-ester product

Mechanism (Fig. 21.1, page 884-5) is a nucleophilic acyl substitution of an ester by an ester enolate and is related to the mechanism of the aldol condensation.
21.3: Intramolecular Claisen Condensation: The Dieckmann Cyclization. Dieckmann Cyclization works best with 1,6-diester, to give a 5-membered cyclic β-keto ester product, and 1,7-diester to give 6-membered cyclic β-keto ester product.

Mechanism: same as the Claisen Condensation

21.4: Mixed Claisen Condensations. Similar restrictions as the mixed aldol condensation.

Four possible products

Esters with no α-protons can only act as the electrophile

Discrete (in situ) generation of an ester enolate with LDA
21.5: Acylation of Ketones with Esters. An alternative to the Claisen condensations and Dieckmann cyclization.

Equivalent to a mixed Claisen condensation

Equivalent to a Dieckmann cyclization

21.6: Ketone Synthesis via β-Keto Esters. The β-keto ester products of a Claisen condensation or Dieckmann cyclization can be hydrolyzed to the β-keto acid and decarboxylated to the ketone.
21.7: Acetoacetic Ester Synthesis. The anion of ethyl acetoacetate can be alkylated using an alkyl halide ($S_N 2$). The product, a $\beta$-keto ester, is then hydrolyzed to the $\beta$-keto acid and decarboxylated to the ketone.

![Diagram of acetoacetic ester synthesis](image)

An acetoacetic ester can undergo one or two alkylations to give an $\alpha$-substituted or $\alpha$-disubstituted acetoacetic ester.

The enolates of acetoacetic esters are synthetic equivalents to ketone enolates.

$\beta$-Keto esters other than ethyl acetoacetate may be used. The products of a Claisen condensation or Dieckmann cyclization are acetoacetic esters ($\beta$-keto esters).

![Diagram of $\beta$-keto ester synthesis](image)
21.8: The Malonic Acid Synthesis.

overall reaction

\[
\text{CO}_2\text{Et} + \text{EtO}^+ \text{Na}^+ \xrightarrow{\text{HCl}, \cdot} \text{EtO}_2\text{C CO}_2\text{Et} \xrightarrow{\text{HCl}, \cdot} \text{HO}_2\text{C CO}_2\text{H} \xrightarrow{\text{HCl}, \cdot} \text{RH}_2\text{C-CH}_2\text{-CO}_2\text{H}
\]

carboxylic acid

- diethyl malonate
- alkyl halide
- ethyl

\[
\text{CO}_2\text{Et} + \text{RH}_2\text{C-X} \xrightarrow{\text{EtO}^+ \text{Na}^+ \cdot \text{EtOH}} \text{HO}_2\text{C CO}_2\text{Et} + \text{EtO}_2\text{C CO}_2\text{Et} \xrightarrow{\text{HCl}, \cdot} \text{HO}_2\text{C CO}_2\text{H} \xrightarrow{\text{HCl}, \cdot} \text{Rh}_2\text{C-CH}_2\text{-CO}_2\text{H}
\]

carboxylic acid

Acid Synthesis.

\[
\text{HO}_2\text{C CO}_2\text{Et} \xrightarrow{\text{HCl}, \cdot} \text{HO}_2\text{C CO}_2\text{Et} \xrightarrow{\text{HCl}, \cdot} \text{HO}_2\text{C CO}_2\text{H}
\]

carboxylic acid

- acetoacetic ester
- pK_a = 19
- acetoacetic ester
- pK_a = 11
- ethyl acetate
- pK_a = 25
- diethyl malonate
- pK_a = 13
Summary:
*Malonic ester synthesis:* equivalent to the alkylation of a carboxylic (acetic) acid enolate

*Acetoacetic ester synthesis:* equivalent to the alkylation of an ketone (acetone) enolate

21.9: Michael Addition of Stablized Anions. Enolates of malonic and acetoacetic esters undergo Michael (1,4-) addition to $\alpha,\beta$-unsaturated ketones.

This Michael addition product can be decarboxylated

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Ester enolates can be generated with LDA in THF rapidly and quantitatively. The resulting enolates can undergo carbonyl addition reactions with other esters, aldehydes, ketones or alkylation reactions with alkyl halides or tosylates.