Lecture 18 Agenda...
Malonic Ester Synthesis (22.7)
Acetoacetic Ester Synthesis (22.7)
Aldol Reaction (23.1, 23.3-23.6)
Claisen Condensation (23.7-23.9)

Suggested Ch 22 Problems:
22.9 – 22.16, 22.25 – 22.30, 22.37, 22.45(a,c,f), 22.47

Suggested Ch 23 Problems:
23.1 – 23.15, 23.27 – 23.40, 23.47, 23.57, 23.58, 23.61, 23.62, 23.63

Exam 3:
Tuesday, July 1
Covers Lectures 15 to 21!
The haloform reaction involves the transformation of a methyl ketone to a carboxylic acid. An enolate is the first intermediate formed. Note: need to transform the CH$_3$ group into CX$_3$, a better leaving group.

\[
\text{A methyl ketone} \quad \xrightarrow{X_2, \text{NaOH}} \quad \text{Enolate intermediate} \quad \xrightarrow{\cdot \cdot \cdot} \quad \text{Carboxylic acid} + \text{CX}_3
\]

where $X = \text{Cl, Br, I}$

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Malonic ester synthesis yields a carboxylic acid product. The steps of this reaction include:
1. Enolate formation of the malonic ester
2. $\alpha$-Alkylation of the enolate with an alkyl halide
3. Hydrolysis of esters
4. Decarboxylation (elimination of $\text{CO}_2$)

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{CH}_2(\text{CO}_2\text{Et})_2 \xrightarrow{1. \text{Na}^+ \text{-OEt}} \xrightarrow{2. \text{H}_3\text{O}^+, \text{heat}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COH}
\]

Note the lengthening of the carbon chain!
Acetoacetic ester synthesis is very similar to the malonic ester synthesis. The product of this reaction is a ketone.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{Br} & + \text{EtOC}\text{CH}_2\text{CCH}_3 \\
& \xrightarrow{1. \text{Na}^+ - \text{OEt}} \xrightarrow{2. \text{H}_3\text{O}^+, \text{heat}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CCH}_3 \\
& \text{2-Pentanone}
\end{align*}
\]
The aldol reaction yields a product that contains a carbonyl (either ketone or aldehyde) and an alcohol functionality; thus the name aldol. You can start with aldehydes or ketones; note that you need two equivalents of the aldehyde or ketone.

**Aldehydes**

Phenylacetaldehyde (10%)

(90%)

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Below is an example of a mixed aldol reaction. “Mixed” means that two different aldehydes (or ketones) are used.

Here, only one product is seen. Why not a mixture?
Aldol products (β-hydroxycarbonyls) can undergo dehydration to yield α,β-unsaturated carbonyl products, either under acidic or basic conditions.

A β-hydroxy ketone or aldehyde  

A conjugated enone
The Claisen condensation reaction involves using esters to make β-keto esters.

\[
\begin{array}{c}
\text{H}_3\text{C} & \text{C} & \text{OEt} \\
\text{H}_3\text{C} & \text{C} & \text{OEt}
\end{array}
\xrightarrow{1. \text{Na}^+ - \text{OEt, ethanol}}
\begin{array}{c}
\text{H}_3\text{C} & \text{C} & \text{C} & \text{C} & \text{OEt} \\
\text{H}_3\text{C} & \text{C} & \text{H} & \text{H} & \text{H}
\end{array}
\xrightarrow{2. \text{H}_3\text{O}^+}
\begin{array}{c}
\text{H}_3\text{C} & \text{C} & \text{C} & \text{OEt} \\
\text{CH}_3\text{CH}_2\text{OH}
\end{array}
\]

2 Ethyl acetate

Ethyl acetoacetate, a β-keto ester (75%)
Below is an example of a mixed Claisen condensation reaction, using two different esters as starting materials.

\[
\text{Ethyl benzoate (acceptor)} \quad + \quad \text{Ethyl acetate (donor)} \quad \rightarrow \quad \frac{1. \text{NaH, THF}}{} \quad \frac{2. \text{H}_3\text{O}^+}{\text{Ethyl benzoylacetate}} \quad + \quad \text{EtOH}
\]

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Below is an example of an intramolecular Claisen condensation reaction (a.k.a. Dieckmann cyclization).

\[
\begin{array}{c}
\text{Diethyl hexanedioate} \\
\text{(a 1,6-diester)}
\end{array}
\quad \begin{array}{c}
\xrightarrow{1. \text{Na}^+ - \text{OEt, ethanol}} \\
\xrightarrow{2. \text{H}_3\text{O}^+}
\end{array}
\quad \begin{array}{c}
\text{Ethyl 2-oxocyclopentanecarboxylate} \\
\text{(82\%)}
\end{array}
\]

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