Chapter 19: Carbonyl Compounds III

Learning Objectives:

1. Write the mechanism for keto-enol tautomerization and explain the consequence of such tautomerization in the optical chiral of compound.
2. Remember the approximate pKa value for the α-hydrogen of a carbonyl group.
3. Provide appropriate bases for the formation of enolate and use such enolate for halogenation and alkylation.
4. Be able to write the general electron-pushing (arrow-pushing) mechanisms of Aldol reaction, Michael reaction, Claisen condensation, and Dieckmann condensation.
5. Be able to write the general electron-pushing (arrow-pushing) mechanisms for decarboxylation of 3-oxocarboxylic acids.
6. Be able to employ the above-mentioned reaction for the formation of new carbon-carbon bond.

Sections:

19.1 Acidity of α-hydrogens*
19.2 Keto-Enol Tautomerism*
19.3 How Enols and Enolate Ions React*
19.4 Halogenation of the α-Carbon of Aldehydes and Ketones*
19.5 Halogenation of the α-Carbon of Carboxylic Acids: The Hell-Volhard-Zelinski (HVZ) Reaction
19.6 α-Halogenated Carbonyl Compounds in Synthesis*
19.7 Using LDA to form an Enolate*
19.8 Alkylation of the α-Carbon of Carbonyl Compounds*
19.9 Alkylation and Acylation of the α-Carbon via an Enamine Intermediate
19.10 Alkylation of the β-Carbon: the Michael Reaction*
19.11 The Aldol Reaction*
19.12 Dehydration of Aldol Addition Products: Formation of α,β-Unsaturated Aldehydes and Ketones*
19.13 The Mixed Aldol Reaction
19.14 The Claisen Condensation*
19.15 The Mixed Claisen Condensation
19.16 Intramolecular Condensation and Addition Reactions*
19.17 Decarboxylation of 3-Oxocarboxylic Acids*
19.18 The Malonic Ester Synthesis: Synthesis of Carboxylic Acids
19.19 The Acetoacetic Ester Synthesis: Synthesis of Methyl Ketones
19.20 Designing a Synthesis VI: Making New Carbon-Carbon Bonds
19.21 Reactions at the α-carbon in Biological Systems#

* Sections that will be focused
# Sections that will be skipped

Recommended additional problems

19.44 – 19.52, 19.54 – 19.64, 19.66 – 19.80
Class Note

19.1 Acidity of $\alpha$-hydrogens

A. pKa of $\alpha$-hydrogen of carbonyl derivatives

\[ R'\alpha\text{NHR} \quad R'\alpha\text{OR} \quad R'\alpha\text{R} \quad R'\alpha\text{H} \]

\[ R'\alpha\text{OR} \quad R'\alpha\text{R} \quad R'\alpha\text{H} \]

B. Resonance effect
19.2 Keto-Enol Tautomerism

\[ \begin{align*}
\text{R'} & \text{C} = \text{O} \quad \text{R} \\
\text{H} & \\
\text{R} & \rightarrow \quad \text{R'} \quad \text{C} = \text{O} \\
\text{R} & \\
\end{align*} \]

A. Mechanism in acidic condition

B. Mechanism in basic condition
19.3 How Enols and Enolate Ions React

A. Analysis of enols and enolates
19.4 Halogenation of the α-Carbon of Aldehydes and Ketones

A. Acid-catalyzed halogenation

\[
\text{RCOCH}_3 + \text{X}_2 (\text{Cl}_2, \text{Br}_2, \text{I}_2) + \text{H}_3\text{O}^+ \rightarrow \text{RCOCH}_2\text{X}
\]
B. Base-promoted halogenation

\[
\begin{align*}
\text{O} & \quad \text{CH}_2 \quad R \\
\text{H} & \quad \text{O} & \quad \text{X}_2 \quad (\text{excess}) & \quad \text{HO}^{-} \\
\end{align*}
\]

C. Haloform reaction

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 \\
\text{H} & \quad \text{O} & \quad \text{X}_2 \quad (\text{Cl}_2, \text{Br}_2, \text{I}_2) & \quad (\text{excess}) & \quad \text{HO}^{-} \\
\end{align*}
\]
19.5 Halogenation of the $\alpha$-Carbon of Carboxylic Acids: The Hell-Volhard-Zelinski (HVZ) Reaction

$$\text{R-COOH} \xrightarrow{1) \text{PBr}_3, \text{Br}_2, 2) \text{H}_2\text{O}} \text{R-COBr}$$
19.6  \( \alpha \)-Halogenated Carbonyl Compounds in Synthesis

A. Analysis of \( \alpha \)-halogenated carbonyl Compounds

B. Examples
19.7 Using LDA to form an Enolate

\[
\text{\begin{tikzpicture}
  \node (n1) at (0,0) {\text{N}};
  \node (n2) at (-1,1) {\text{H}};
  \node (n3) at (1,1) {\text{H}};
  \node (n4) at (-0.5,0) {\text{H}};
  \node (n5) at (0.5,0) {\text{H}};
  \node (n6) at (0,-1) {\text{H}};
  \node (n7) at (0,-1.5) {\text{H}};
  \node (n8) at (0,1.5) {\text{H}};

draw (n1) -- (n2) -- (n3) -- (n4) -- (n5) -- (n6) -- (n7) -- (n8);
\end{tikzpicture}}
\]

lithium diisopropylamide (LDA)

19.8 Alkylation of the $\alpha$-Carbon of Carbonyl Compounds

A. Analysis of the reaction
B. Examples

(i)

\[
\begin{array}{c}
\text{OCH}_3 \\
\end{array}
\]

1) LDA, THF
2) CH\textsubscript{3}I

(ii)

\[
\begin{array}{c}
\text{CN} \\
\end{array}
\]

1) LDA, THF
2) CH\textsubscript{3}CH\textsubscript{2}I
C. Potential problem in alkylation of the α-carbon of carbonyl compounds

\[
\text{O} \quad \begin{array}{c}
\text{CH}_3
\end{array}
\xrightarrow{1) \text{ LDA, THF} \atop 2) \text{ CH}_3}\]


Alkylation and Acylation of the $\alpha$-Carbon via an Enamine Intermediate

A. Examples
19.10 Alkylation of the β-Carbon: the Michael Reaction

A. Michael reaction

\[
\begin{align*}
\text{H}_3\text{C} & : \text{CHCH}_3 + \text{CH}_2=\text{CCH}_3 & \text{CH}_3\text{O}^- \\
\end{align*}
\]
B. Examples

(i)  
\[
\text{OCH}_3 + \text{H}_3\text{COOCH}_3 \xrightarrow{\text{base (?)}}
\]

(ii)  
\[
\text{CH}_2=\text{CHCOCH}_2\text{CH}_3 + \text{H}_3\text{COCN} \xrightarrow{\text{base (?)}}
\]
C. Stork enamine reaction

\[
\text{pyrrolidine} + \text{ethyl vinyl ketone} \rightarrow \text{HCl, H}_2\text{O}
\]
19.11 The Aldol Reaction

A. Mechanism
19.12 Dehydration of Aldol Addition Products: Formation of $\alpha,\beta$-Unsaturated Aldehydes and Ketones

A. Aldol condensation

B. Examples

(i) $\text{MeOH} + \text{MeO}^- \rightarrow \text{MeO}^- \text{MeOH}$

(ii) $\text{EtOH} \rightarrow \text{EtO}^- \text{Na}^+$
19.13 The Mixed Aldol Reaction

A. Potential problem in aldol reaction

(i)

(ii)
B. Solution

(i)

\[
\text{HOH} + \text{MeOH} \rightarrow \text{MeO}^- \text{Na}^+ \rightarrow \text{MeOH}
\]
19.14 The Claisen Condensation and 19.15 The Mixed Claisen Condensation

\[
\begin{align*}
R &\quad \text{base} \quad \rightarrow \\
\text{OR} &\quad \text{OR'} \quad + \\
\text{OR} &
\end{align*}
\]

A. Mechanism
B. Examples

(i) \[
\begin{array}{c}
\text{base (?)} \\
\text{OCH}_2\text{CH}_3
\end{array}
\]

(ii) \[
\begin{array}{c}
\text{base (?)} \\
\text{OCH}_3 + \text{OCH}_2\text{CH}_3
\end{array}
\]
A. Intramolecular Claisen reaction (Dieckmann condensation)

(i) $\text{H}_3\text{CO} \xrightarrow{\text{MeO}^- \text{Na}^+} \text{MeOH} \xrightarrow{\text{MeO}^- \text{Na}^+} \text{OCH}_3$ 

(ii) $\text{H}_3\text{CH}_2\text{CO} \xrightarrow{\text{EtO}^- \text{Na}^+} \text{EtOH} \xrightarrow{\text{EtO}^- \text{Na}^+} \text{OCH}_2\text{CH}_3$
B. Intramolecular aldol reaction

(i)

(ii)
(iii) Robinson annulation

(iv) Robinson annulation
Decarboxylation of 3-Oxocarboxylic Acids

A. Easier in acidic condition: mechanism

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

B. Examples of compounds containing 3-oxocarboxylic acid

\[
\begin{align*}
\text{HO} & \quad \text{R} \\
\text{R} & \quad \text{OH}
\end{align*}
\]
A. Examples:
19.20 Designing a Synthesis VI: Making New Carbon-Carbon Bonds

synthesis of

from

\[
\text{CO}_2\text{H}
\]

\[
\text{H}_3\text{CO} \quad \text{O}
\]

\[
\text{O} \quad \text{OCH}_3
\]