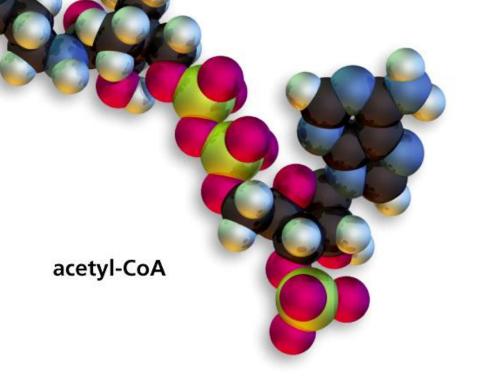


4th Edition
Paula Yurkanis Bruice

Chapter 19

Carbonyl Compounds III

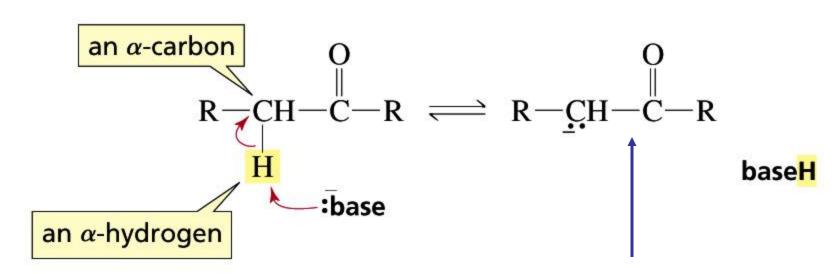
Reactions at the α -Carbon



Disampaikan oleh: Dr. Sri Handayani 2013

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The α -Hydrogen Is Acidic



the anion is stabilized by resonance

A carbon acid is a compound with a relatively acidic hydrogen bonded to an *sp*³-hybridized carbon

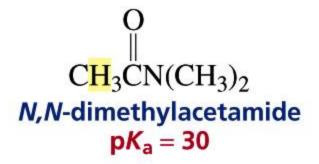
TABLE 19.1 The pK_a Values of Some Carbon Acids pK_a pK_a N≡CCHC≡N 11.8 30 CH₂CN(CH₃)₂ CH₃CCHCOCH₂CH₃ 10.7 CH2COCH2CH3 25 H O O || || -CCHCCH3 25 $CH_2C \equiv N$ 9.4 H CH₃CCHCCH₃ 20 CH2CCH3 8.9 ÇH₂CH 17 CH₃CCHCH 5.9 CH₃CHNO₂ 8.6 O2NCHNO2 3.6

Esters Are Less Acidic Than Aldehydes and Ketones

The electrons are not as readily delocalized

In these compounds, the electrons left behind from deprotonation can be delocalized onto a more electronegative atom

 $CH_3CH_2NO_2$ nitroethane $pK_a = 8.6$ $CH_3CH_2C \equiv N$ propanenitrile $pK_a = 26$



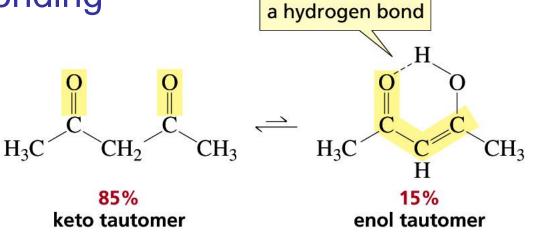
The acidity of the α -hydrogens is attributed to charge stabilization by resonance

resonance contributors for the 2,4-pentanedione anion

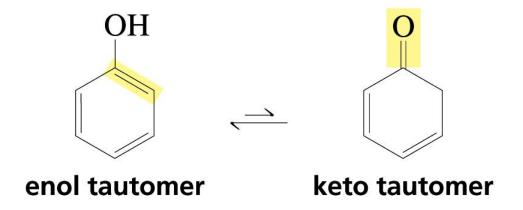
Keto-Enol Tautomerism

The enol tautomer can be stabilized by intramolecular

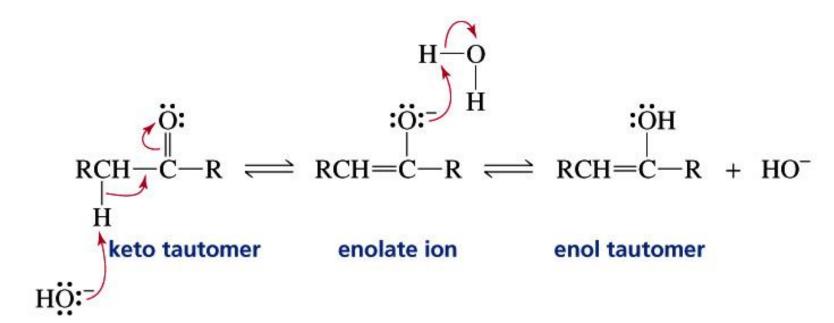
hydrogen bonding



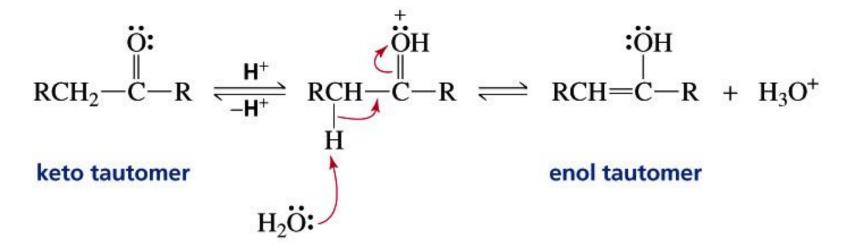
In phenol, the enol tautomer is aromatic



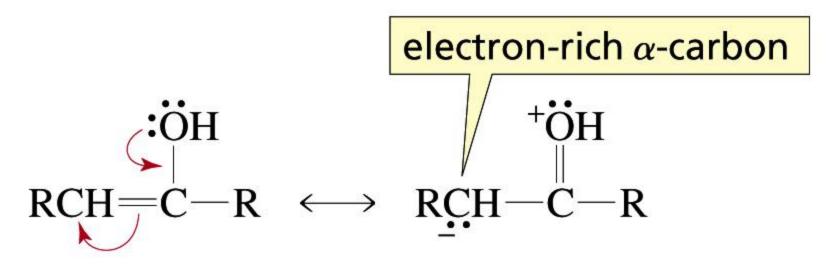
base-catalyzed keto-enol interconversion



acid-catalyzed keto-enol interconversion



An Enol Is a Better Nucleophile Than an Alkene



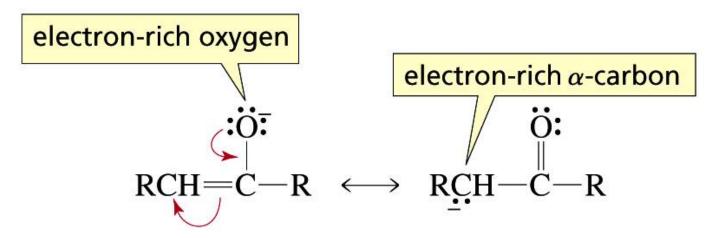
resonance contributors for an enol

Carbonyl compounds that form enol undergo substitution reactions at the α -carbon: an α -substitution reaction

An Acid-Catalyzed α-Substitution Reaction

A Base-Catalyzed α-Substitution Reaction

An Enolate Is an Ambident Nucleophile



resonance contributors for an enolate ion

Reaction at the C or O site depends on the electrophile and on the reaction condition

Protonation occurs preferentially on the O site

Otherwise, the C site is likely the nucleophile

Acid-Catalyzed Halogenation

$$CH_{3} - C \longrightarrow H^{+} \longrightarrow CH_{2} - C \longrightarrow H^{+} \longrightarrow CH_{2} - C \longrightarrow H^{+} \longrightarrow H^{+}$$

Under acidic conditions, one α -hydrogen is substituted for a bromine

Base-Promoted Halogenation

$$\begin{array}{c} RCH-C-R \longrightarrow RCH-C-R \longrightarrow RCH-C-R \longrightarrow RCH-C-R \xrightarrow{\text{repeat first}} \begin{array}{c} Br & O \\ \downarrow & \downarrow \\ H & Br \end{array}$$

Under basic conditions, all the α -hydrogens are substituted for bromines

Conversion of a Methyl Ketone to a Carboxylic Acid

the haloform reaction

$$\begin{array}{c} : \ddot{O} \\ R-C-CH_3 \xrightarrow{\text{excess}} \\ \downarrow \\ \text{excess} \end{array} \xrightarrow{\text{R}-C-CI_3} \Longleftrightarrow \begin{array}{c} : \ddot{O} : \ddot{O} \\ R-C-CI_3 : \ddot{O} : \ddot{O} \\ R-C-OH + CI_3 : \ddot{O} : \ddot{O} \\ OH : \ddot{O} : \ddot{O} : \ddot{O} : \ddot{O} \\ R-C-O^- + CHI_3 : \ddot{O} : \ddot{O}$$

Halogenation of the α-Carbon of Carboxylic Acids

mechanism for the Hell-Volhard-Zelinski reaction

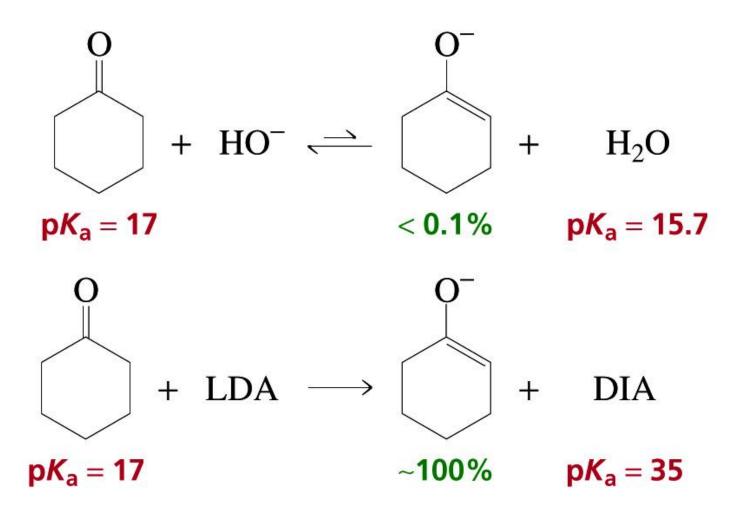
When the α -carbon is halogenated, it becomes electrophilic

An E2 elimination will occur if a bulky base is used

$$\frac{\mathsf{Br}}{\mathsf{tert}\text{-}\mathsf{BuO}^{-}} + \mathsf{Br}^{-}$$

$$\frac{\mathsf{an} \ \alpha,\beta\text{-}\mathsf{unsaturated}}{\mathsf{carbonyl} \ \mathsf{compound}}$$

Using LDA to Form an Enolate



Alkylation of the α-Carbon of Carbonyl Compounds

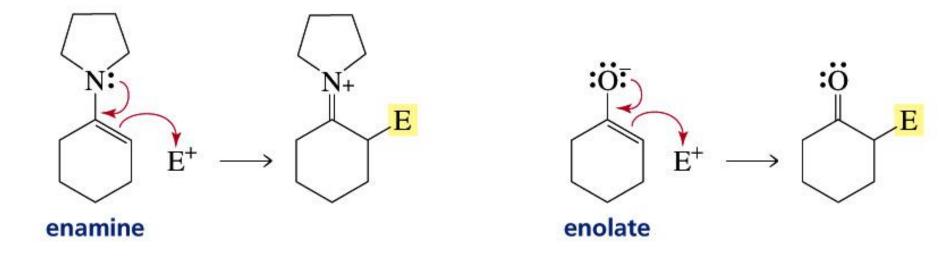
Two different products can be formed if the ketone is not symmetrical

2-methylcyclohexanone
$$\begin{array}{c} CH_3 \\ \downarrow CH_3 \\ \downarrow CH_3 I \\ \downarrow CH_3 I \\ \downarrow CH_3 I \\ \downarrow CH_3 I \\ \downarrow CH_3 \\ \downarrow C$$

The less substituted α -carbon can be alkylated if ...

$$\begin{array}{c} \text{CH}_{3} \\ \text{CH}_{4} \\ \text{CH}_{5} \\$$

Enamine Reacts with Electrophiles



$$\begin{array}{c}
O \\
H^{+} \\
H
\end{array}$$

$$\begin{array}{c}
O \\
CH_{3} \\
H^{2}O
\end{array}$$

$$\begin{array}{c}
CH_{3} \\
H^{2}O
\end{array}$$

$$\begin{array}{c}
CH_{3} \\
H^{+} \\
H
\end{array}$$

$$\begin{array}{c}
H^{+} \\
H
\end{array}$$

The alkylation step is an S_N 2 reaction

Direct alkylation of a carbonyl compound yields several products

In contrast, alkylation of an aldehyde or a ketone using an enamine intermediate yields the monoalkylated product

Aldehydes and ketones can be acylated via an enamine intermediate

The Michael Addition

$$\begin{array}{c} \text{CH}_3\text{CH} = \text{CHCNH}_2 \\ \text{an } \alpha, \beta\text{-unsaturated} \\ \text{amide} \end{array} + \begin{array}{c} \text{CH}_3\text{CH}_2\text{CCH}_2\text{COCH}_3 \\ \text{a } \beta\text{-keto ester} \end{array} \xrightarrow{\text{CH}_3\text{O}^-} \\ \text{CH}_3\text{CH}_2\text{CH} = \text{CHCOCH}_3 \\ \text{an } \alpha, \beta\text{-unsaturated} \\ \text{ester} \end{array} + \begin{array}{c} \text{O} \\ \text{CH}_3\text{CCH}_2\text{C} = \text{N} \\ \text{a } \beta\text{-keto nitrile} \end{array} \xrightarrow{\text{CH}_3\text{O}^-} \begin{array}{c} \text{CH}_3\text{O}^- \\ \text{CH}_3\text{CH}_2\text{CHCH}_2\text{COCH}_3 \\ \text{CH}_3\text{CH}_2\text{CHCH}_2\text{COCH}_3 \end{array} \xrightarrow{\text{CH}_3\text{CHC}} \\ \text{CH}_3\text{CHC} = \text{CH}_3\text{CHC}_2\text{C} = \text{N} \\ \text{CH}_3\text{CHC} = \text{CH}_3\text{CHC}_2\text{C} = \text{N} \\ \text{CH}_3\text{CHC} = \text{CH}_3\text{CHC}_2\text{C} = \text{N} \end{array}$$

Mechanism of the Michael Reaction

The Stork Enamine Reaction

Enamines are used in place of enolates in Michael reactions

aldol additions

OHO
$$\begin{array}{c}
OHO^{-}\\
CH_{3}CH_{2}CH
\end{array}$$

$$\begin{array}{c}
CH_{3}CH_{2}CH
\end{array}$$

$$\begin{array}{c}
CH_{3}CH_{2}CH
\end{array}$$

$$\begin{array}{c}
CH_{3}CH_{2}CH
\end{array}$$

$$\begin{array}{c}
CH_{3}CH
\end{array}$$

$$\begin{array}{c}
OHO^{-}\\
CH_{3}
\end{array}$$

$$\begin{array}{c}
OHO^{-}\\
CH_{3}C
\end{array}$$

$$\begin{array}{c}
CH_{3}C$$

$$CH_{3}C$$

$$CH_{$$

One molecule of a carbonyl compound acts as a nucleophile and the other carbonyl compound acts as an electrophile

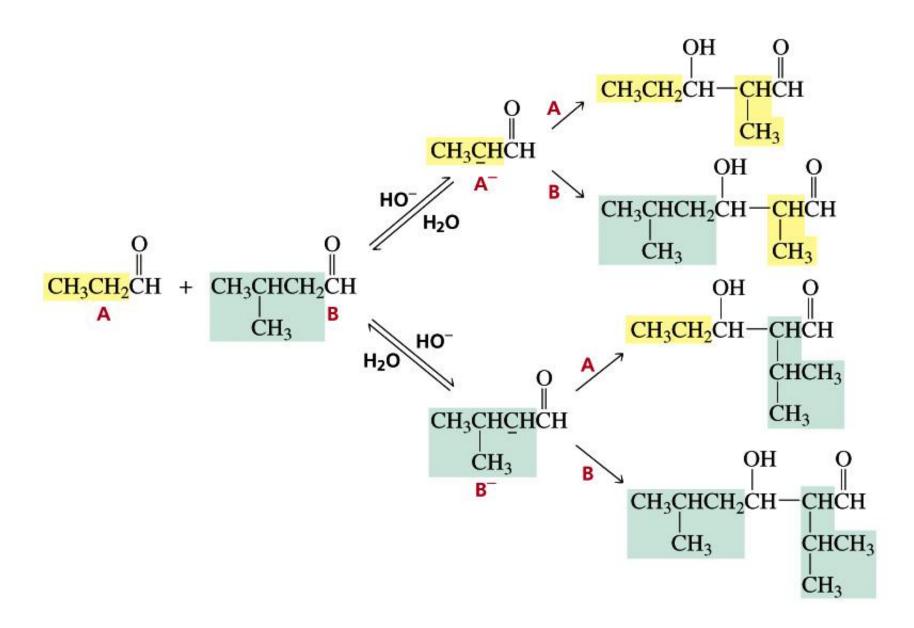
mechanism for the aldol addition

CH₃CH₂CH
$$\stackrel{\bullet}{\longleftarrow}$$
 CH₃CH₂CH $\stackrel{\bullet}{\longleftarrow}$ CH₃CH₂CH $\stackrel{\bullet}{\longrightarrow}$ CH₃CH $\stackrel{\bullet$

Ketones are less susceptible than aldehydes to attack by nucleophiles

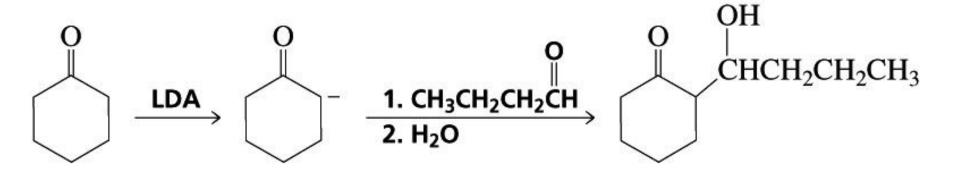
An aldol addition product loses water to form an aldol condensation product

The Mixed Aldol Addition



One product will be formed if one of the carbonyl compounds does not have any α -hydrogen

Primarily one product can be formed by using LDA to deprotonate one of the carbonyl compounds



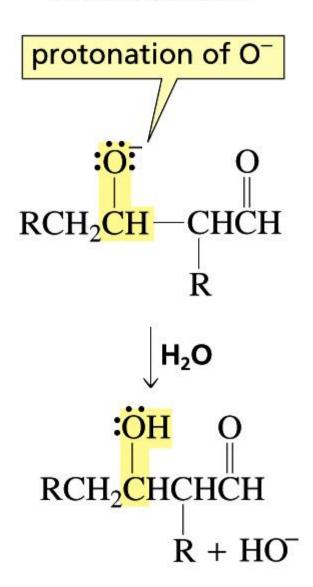
Condensation of Two Ester Molecules

mechanism for the Claisen condensation

Claisen condensation

formation of a π bond by expulsion of RO $^-$

aldol addition



The reaction can be driven to completion by removal of a proton from the β -keto ester

The Claisen condensation requires an ester with two α -hydrogens and an equivalent amount of base

The Mixed Claisen Condensation

$$CH_{3}CH_{2}COCH_{2}CH_{3} + \underbrace{COCH_{2}CH_{3}}_{\textbf{excess}} + \underbrace{COCH_{2}CH_{3}}_{\textbf{excess}} + \underbrace{COCH_{2}CH_{3}}_{\textbf{ch}_{2}CH_{2}OT} + \underbrace{COCH_{2}CH_{3}}_{\textbf{ch}_{2}CH_{2}OH}$$

$$O$$
+ CH_3C
- O
- O
- O
- CCH_3
- O
- O
- CCH_3
- O

Because of the difference in the acidities of the α -hydrogens in the two carbonyl compounds, primarily one product is obtained

mechanism for the Dieckmann condensation

Intramolecular Aldol Additions

The Robinson Annulation

$$CH_2 = CHCCH_3 + O \longrightarrow HO^-$$
a Michael reaction
$$CH_3$$

$$-H_2O \longrightarrow A$$

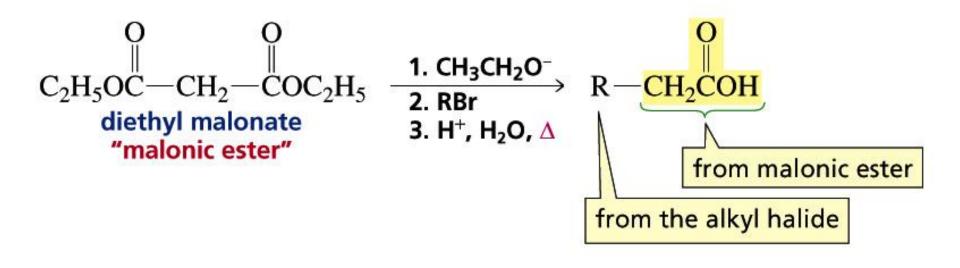
$$-H_2O \longrightarrow A$$

Decarboxylation of 3-Oxocarboxylic Acids

removing CO₂ from an α -carbon

Acid catalyzes the intramolecular transfer of the proton

A malonic ester synthesis forms a carboxylic acid with two more carbon atoms than the alkyl halide



$$C_2H_5OC-CH_2-COC_2H_5 \xrightarrow{\text{CH}_3\text{CH}_2\text{O}^-} C_2H_5OC-\ddot{C}H-COC_2H_5 \xrightarrow{\text{R}^-\text{Br}} C_2H_5OC-CH-COC_2H_5 + Br^-$$

an α-substituted malonic ester

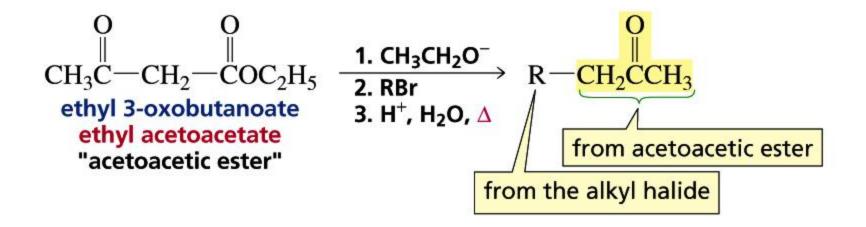
$$H^+$$
, H_2O \triangle

$$R-CH_2-COH + CO_2 \stackrel{\triangle}{\longleftarrow} HOC-CH-COH + 2 CH_3CH_2OH$$

an a-substituted malonic acid

Preparation of Carboxylic Acids with Two Substituents Bonded to the α-Carbon

Synthesis of Methyl Ketone by Acetoacetic Ester Synthesis



Designing a Synthesis to Make New Carbon–Carbon Bonds

$$\begin{array}{c|c} CH_3 & O \\ CH_3 & CH_$$

Preparation of the Ester

A Biological Aldol Condensation

$$O = C$$

$$CH(CH_2)_2CH_2CH_2 \stackrel{\dagger}{NH_3} \stackrel{\dagger}{N}CH_2CH_2(CH_2)_2CH$$

$$NH$$

$$O = C$$

$$CH(CH_2)_2CH_2CH$$

$$O = C$$

$$CH(CH_2)_2CH$$

$$O = C$$

$$O = C$$

$$O = C$$

$$CH(CH_2)_2CH$$

$$O = C$$

$$O$$

A Biological Claisen Condensation

$$CH_{3}CH_{2}CH_{2}C-SR + {}^{O}O-C-CH_{2}C-SR \xrightarrow{\text{condensation}} CH_{3}CH_{2}CH_{2}C-CH_{2}C-CH_{2}C-SR \xrightarrow{\text{condensation}} CH_{3}CH_{2}CH_{2}CH_{2}C-CH_{2}C-SR \xrightarrow{\text{CH}_{3}CH_{2}CH_{2}CH_{2}CH_{2}C-SR}$$