18.9
The Aldol Condensation
A basic solution contains comparable amounts of the aldehyde and its enolate.

Aldehydes undergo nucleophilic addition.

Enolate ions are nucleophiles.

What about nucleophilic addition of enolate to aldehyde?

\[ \text{RCH}_2\text{CH} + \text{HO}^- \leftrightarrow \text{RCHCH} + \text{HOH} \]

\[ pK_a = 16-20 \quad \text{pK}_a = 16 \]

Some thoughts...
Aldol Addition

The product is called an "aldol" because it is both an aldehyde and an alcohol.
Aldol Addition of Acetaldehyde

\[
\begin{align*}
2\text{CH}_3\text{CH} & \xrightarrow{\text{NaOH, } \text{H}_2\text{O}} \\
\text{CH}_3\text{CH} - \text{CH}_2\text{CH} & \quad \text{(50%)}
\end{align*}
\]

Acetaldol

5°C
**Aldol Addition of Butanal**

\[
2\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH} \\
\text{KOH, H}_2\text{O} \rightarrow 6^\circ\text{C} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH} \quad \text{CHCH} \\
\quad \text{OH} \quad \text{CH}_2\text{CH}_3 \\
\text{(75%)}
\]
**Aldol Condensation**

$$2R\text{CH}_2\text{CH} \xrightarrow{\text{NaOH}} R\text{CH}_2\text{CH} \text{CHCH} \text{CH}$$
Aldol Condensation

\[
\text{2RCH}_2\text{CH} \xrightarrow{\text{NaOH}} \text{RCH}_2\text{CHCHCHCH}_2\text{CH} \quad \text{OH} \quad \text{R}
\]
Aldol Condensation

\[
2RCH_2CH \xrightarrow{NaOH} RCH_2CHCHCHCHOH \xrightarrow{heat} RCH_2CH\equivCCH
\]
Aldol Condensation

$$2\text{RCH}_2\text{CH} \xrightarrow{\text{NaOH}} \text{RCH}_2\text{CH}-\text{CHCH}$$

Heat

$$\xrightarrow{\text{heat}} \text{RCH}_2\text{CH}==\text{CCH}$$
Aldol Condensation of Butanal

\[
\text{NaOH, H}_2\text{O} \quad \text{80-100°C}
\]
Aldol Condensation of Butanal

\[ \text{NaOH, H}_2\text{O} \quad 80-100^\circ\text{C} \]

\[ 2\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH} \]

\[ \xrightarrow{\text{NaOH, H}_2\text{O} \quad 80-100^\circ\text{C}} \]

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH} = \text{CCH} \]

\[ \text{CH}_2\text{CH}_3 \]

\( (86\%) \)
Dehydration of Aldol Addition Product

Dehydration of β-hydroxy aldehyde can be catalyzed by either acids or bases.
Dehydration of Aldol Addition Product

in base, the enolate is formed
Dehydration of Aldol Addition Product

The enolate loses hydroxide to form the α,β-unsaturated aldehyde.
Aldol reactions of ketones

The equilibrium constant for aldol addition reactions of ketones is usually unfavorable.

\[2\text{CH}_3\text{CCH}_3 \rightleftharpoons \text{CH}_3\text{CCH}_2\text{CCH}_3 + \text{CH}_3\]

The equilibrium constant for aldol addition reactions of ketones is usually unfavorable.
Intramolecular Aldol Condensation

\[
\text{Na}_2\text{CO}_3, \text{H}_2\text{O} \xrightarrow{\text{heat}} \text{(96%)}
\]

via:

\[
\text{OH}
\]
Intramolecular Aldol Condensation

even ketones give good yields of aldol condensation products when the reaction is intramolecular

\[ \text{Na}_2\text{CO}_3, \text{H}_2\text{O} \text{ heat} \]

(96%)
18.10
Mixed Aldol Condensations
What is the product?

There are 4 possibilities because the reaction mixture contains the two aldehydes plus the enolate of each aldehyde.

$$\text{CH}_3\text{CH} + \text{CH}_3\text{CH}_2\text{CH} \rightarrow \text{NaOH}$$
What is the product?

O
CH₃CH + CH₃CH₂CH

O
:CH₂CH

CH₃CH

O
O

CH₃CH

O
OH

CH₃CH ─ CH₂CH
What is the product?
What is the product?

\[
\begin{align*}
\text{CH}_3\text{CH} & + \text{CH}_3\text{CH}_2\text{CH} \\
\text{CH}_3\text{CHCH} & \rightarrow \text{CH}_3\text{CHCHCHCH}
\end{align*}
\]
What is the product?
In order to effectively carry out a mixed aldol condensation:

need to minimize reaction possibilities
usually by choosing one component that cannot form an enolate
Formaldehyde cannot form an enolate. Formaldehyde is extremely reactive toward nucleophilic addition.
Formaldehyde

\[ \text{HCHO} + (\text{CH}_3)_2\text{CHCH}_2\text{CH} \xrightarrow{\text{K}_2\text{CO}_3} \text{water-ether} \rightarrow (\text{CH}_3)_2\text{CHCH}_2\text{CHCHCHCHCH} \]

(52%)
Aromatic Aldehydes

aromatic aldehydes cannot form an enolate
Aromatic Aldehydes

\[
\text{CH}_3\text{O} - \text{C} = \text{CH} - \text{CH} = \text{CH} - \text{CCH}_3 + \text{CH}_3\text{CCH}_3 \rightarrow \text{CH}_3\text{O} - \text{C}=\text{C} = \text{CCH}_3 \text{CCH}_3 + \text{H}_2\text{O}
\]

[NaOH, H\text{\textsubscript{2}}O] 30°C

(83%)