Lecture 22

The Aldol Condensation

an Aldol!
A Quick Review from Tuesday
Lithium diisopropylamide (LDA)

- Enolates generated from esters and LDA can be alkylated.

$$\text{CH}_3\text{CH}_2\text{CHCOCH}_3 \xrightarrow{\text{CH}_3\text{CH}_2\text{I}} \text{CH}_3\text{CH}_2\text{CHCOCH}_3$$

(92%)
Two moles of ethyl acetate condense to give ethyl 3-oxobutanoate or ... ethyl acetoacetate aka acetoacetic ester
A versatile synthesis of $\beta$-ketoesters and \textit{symmetrically} substituted acetones

$$A\text{CH}_2\text{C--OCH}_2\text{CH}_3 \rightarrow A\text{CH}_2\text{C--CH--C--OCH}_2\text{CH}_3$$

Heat, $\text{H}_3\text{O}^+$

$$A\text{CH}_2\text{C--CH}_2 \leftarrow A\text{CH}_2\text{C--CH}_2 + \text{CO}_2 + \text{HOCH}_2\text{CH}_3$$

Acetone
Alkylation of Acetoacetic Ester gives *unsymmetrically* substituted acetone.
Ketone Synthesis

Let’s work another example together
Malonic Ester Synthesis

CH₃CH₂OCOCOCH₂CH₃

CH₃(CH₂)₈CH₂CH₃

1. NaOH, H₂O
2. H⁺
3. heat, -CO₂O

CH₃(CH₂)₈CH₂CH₂CHCOH

Versatile Synthesis of Carboxylic acids
Apply Malonic Ester Synthesis

Write the structure of the malonic ester derivative which would yield this acid and the conditions required to run the reaction.
The Aldol Condensation

- The product of an aldol condensation is a β-hydroxyaldehyde...nucleophilic acyl substitution is not possible here....why??

an Aldol!

\{Aldehyde / Alcohol\}
Loss of water!

- Aldol products are easily dehydrated so the major product is an \( \alpha,\beta \)-unsaturated aldehyde or ketone.
The reaction actually proceeds via the resonance stabilized enolate anion and unlike the E2, it proceeds in a stepwise fashion!

“E₂ like” Elimination
A Note about Aldol Reactions

Aldol reactions are reversible and, particularly for ketones, there is often little aldol present at equilibrium. $K_{eq}$ for dehydration is generally large and, if reaction conditions bring about dehydration, good yields of product can be obtained.

It takes special efforts to isolate an Aldol...the product is generally the $\alpha,\beta$-unsaturated aldehyde or ketone.
What are the starting materials that lead to these products via the Aldol condensation?
Crossed Aldol Reactions

- In a “crossed aldol” reaction, one kind of molecule provides the enolate anion and another kind provides the carbonyl group.

In most cases, this makes a big fat mess!!
The Crossed Aldol Reaction
Crossed Aldol Reactions

Crossed aldol reactions only work if:
- one of the reactants has no $\alpha$-hydrogen and, therefore, cannot form an enolate anion and
- the other reactant has a very reactive carbonyl group, namely an aldehyde

Look…no $\alpha$-hydrogens…. so no enolate anions!!

Formaldehyde
Benzaldehyde
Furfural
2,2-Dimethylpropanal
Let’s discuss a plan for actually running a crossed aldol reaction

Does the addition sequence matter??

What goes into the pot first, second and third?
The Signature Page

Claisen Condensation: $\beta$-ketoesters
Dieckmann: Cyclic $\beta$-ketoesters
Acetoacetic ester synthesis: decorated acetones
Malonic ester synthesis: decorated acetic acids
Aldol: $\alpha, \beta$-unsaturated aldehydes and ketones
Grignard Reaction: Alcohols..., etc.
Wittig:
From what??
Aldol reactions of ketones

- the equilibrium constant for aldol addition reactions of ketones is usually unfavorable but can be driven by dehydration

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

\[
\text{CH}_3\text{CCH}_2\text{CCH}_3 + \text{OH}^- \rightarrow \text{CH}_3\text{C} = \text{C}\text{CCH}_3
\]
Aldol Reactions

- Intramolecular aldol reactions (when the enolate anion and the carbonyl acceptor are in the same molecule) are most successful for formation of five- and six-membered rings.
Intramolecular Aldol Condensation

- Ketones give very good yields of aldol condensation products when the reaction is intramolecular and driven by dehydration.

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

- When a ketone has two different $\alpha$-hydrogens, is formation of the enolate anion regio-selective?

- The answer depends on experimental conditions
Kinetic Control
- with slight excess of LDA

2-Methylcyclohexanone + LDA → 0°C

99% 1%

slight excess

"fastest" but least stable

Chemistry 328N
Thermodynamic Control

- With slight excess of ketone

\[
\text{slight excess} \quad \text{+ LDA} \quad 0^\circ C \quad \rightarrow \quad \text{slow but most stable}
\]

\[
\text{O}^- \text{Li}^+ \quad 10\% \quad \text{O}^- \text{Li}^+ \quad 90\% \quad \text{+(i-pr}_2\text{)NH}
\]
Kinetic Control

- When a reaction is under kinetic control, the composition of the product mixture is determined by the relative rates of formation of each product

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Thermodynamic Control

- When a reaction is under thermodynamic control, the composition of the product mixture is determined by the relative stabilities of each product
Which position is “thermodynamic”?? Why??
Michael Reaction

- Michael reaction: conjugate addition of an enolate anion to an \( \alpha, \beta \)-unsaturated carbonyl compound!

- Following are two examples:
  - in the first, the nucleophile is the anion of malonic ester
  - in the second, it is the enolate anion of acetoacetic ester

- An excellent route to 1,5-dicarbonyl compounds

Arthur Michael
Michael Reaction

Diethyl propanedioate (Diethyl malonate) + 3-Buten-2-one (Methyl vinyl ketone) →

\[
\begin{align*}
\text{EtOC} & \quad \text{EtOC} \\
\text{CH}_2 & \quad \text{O} \\
\text{EtOC} & \quad \text{EtOC} \\
\text{CO} & \quad \text{CO} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2 = \text{CHCCH}_3 \\
\text{EtOC} & \quad \text{EtOC} \\
\text{CH} & \quad \text{EtOC} \\
\text{CH}_2 & \quad \text{CH}_2 \text{CH}_2 \text{CCH}_3 \\
\end{align*}
\]

EtOH

EtO⁻ Na⁺
Michael Reaction

Ethyl 3-oxobutanoate (Ethyl acetoacetate) + 2-Cyclohexenone \[ \xrightarrow{\text{EtO}^- \text{Na}^+ \text{EtOH}} \]

\[ \text{O} \quad \text{O} \quad \text{EtOC} \quad \text{O} \quad \text{EtOC} \]

\[ \text{CH}_3 \text{C} \quad \text{CH}_2 \quad \text{O} \]

\[ \text{CH}_3 \text{C} \quad \text{CH} \quad \text{EtOC} \quad \text{CO} \]

\[ \text{CH}_3 \text{C} \quad \text{O} \quad \text{EtOC} \quad \text{O} \quad \text{EtOC} \quad \text{O} \]
Retro-synthesis of 2,6-Heptadione

Always gives a 1,5-dicarbonyl product
The Michael reaction is a useful method for forming carbon-carbon bonds...1,5 dicarbonyls.
Michael Addition

- It is also useful in that the product of the reaction can undergo an intramolecular aldol condensation to form a six-membered ring. One such application is called the Robinson annulation.

- This reaction enabled the first synthesis of steroids.
The Robinson Annelation: 1. Michael addition

\[ \text{KOH, methanol} \]

\[ \begin{align*}
\text{CH}_3 & \quad \text{CH}_2\text{CH}_2\text{CCH}_3 \\
\text{O} & \quad \text{O}
\end{align*} \]
Robinson annelation: 2. aldol condensation

\[ \text{NaOH, heat} \]

not isolated; dehydrates under reaction conditions
Robinson annelation: 3. elimination

\[
\begin{align*}
\text{NaOH} & \quad \text{heat} \\
\text{CH}_3 & \\
\text{CH}_2\text{CH}_2\text{CCH}_3 & \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]

Robert Robinson
Nobel 1947