TOPIC 6: ALDOL REACTIONS AND THE SYNTHESIS AND REACTIONS OF β-DICARBONYL COMPOUNDS (Chapters 17 and 19)

OBJECTIVES

1. Provide a rationale for the acidity of α-hydrogens

2. Illustrate the behavior of enols and enolates as nucleophiles in reactions with a variety of electrophiles

3. Develop strategies for the formation of complex molecules from simple starting materials by making carbon-carbon bonds

4. Describe the reactions of ester enolates (nucleophiles) with esters (electrophiles) to give β-keto esters via Claisen and crossed Claisen condensations.

5. Describe the synthesis of ketones using the above products.

6. Describe the reactions of other active methylene compounds and the synthesis of acid derivatives.

7. Describe the preparation and alkylation of enamines.

8. Use this knowledge to predict the products of reactions of this type and to be able to synthesize compounds using these procedures.
REVIEW OF THE ELECTROPHILICITY OF CARBONYLS

Aldehydes and ketones undergo addition-elimination pathways

\[ \text{Nucleophile: H-Nu} \]

Acid Derivatives undergo substitution via addition-elimination pathways

PREVIEW OF ENOLATE CHEMISTRY

Hydrogens \( \alpha \)- to a carbonyl are acidic

Enolates are nucleophilic
Enolates react with….

**Alkyl halides**

\[
\text{R--Br} \quad \xrightarrow{\text{enolate}} \quad \text{R--OR}
\]

**Aldehydes and ketones**

\[
\text{C}--\text{O} \quad \xrightarrow{\text{enolate}} \quad \text{C}--\text{O}^-
\]

**Esters**

\[
\text{C}--\text{O}--\text{R} \quad \xrightarrow{\text{enolate}} \quad \text{C}--\text{O}^--\text{R}
\]

---

**THE ACIDITY OF THE α-HYDROGENS OF CARBONYL COMPOUNDS:**

**ENOLATE ANIONS**

Protons \(\alpha\)-to Carbonyl Groups are More Acidic Than Other Protons on Carbon

\[
\begin{array}{ccc}
\text{Proton} & \text{pK}_a & \text{Proton} \\
\text{C}--\text{H} & 19.2 & \text{H}_2\text{C}--\text{CH}_3 & 50 \\
\text{C}--\text{O} & 9.0 & \text{H}_2\text{C}--\text{CH}_2 & 44 \\
\end{array}
\]

Note: Protons attached to the carbonyl carbon of aldehydes are not particularly acidic, the conjugate base is not resonance stabilized.
KETO AND ENOL TAUTOMERS

Base Catalyzed Tautomerization

Keto and enol forms are in equilibrium
Rapidly interconverting are called tautomers

Acid Catalyzed Tautomerization

The keto form is usually more stable
Equilibrium Constants for Tautomerization

\[ \begin{align*}
\text{H}_2\text{O} & \quad K = 3 \times 10^{-7} \\
\text{H} & \quad K = 6 \times 10^{-9} \\
\text{H} & \quad K = 1 \times 10^{-2} \\
\text{H} & \quad K > 10^{+13}
\end{align*} \]
REATIONS VIA ENOLS AND ENOLATE ANIONS

Preview: Both Enols and enolates are nucleophilic

\[
\begin{array}{c}
\text{ENOL} \quad \text{ENOLATE} \\
\text{E}^+ \quad \text{E}^+ \quad \text{E}^+ \\
\end{array}
\]

compare to:

\[
\begin{array}{c}
R_\text{CH} \quad CR_2=CR_2 \\
\end{array}
\]

Diethylpropion is a stimulant, is marketed as Tenuate™ for appetite suppression. Propose a synthesis of diethylpropion from benzene and any other starting materials.
α-Halogenation of Aldehydes and Ketones

Under Acidic conditions
Enolizable protons are subject to substitution with bromine upon treatment with Br₂.

Mechanistic Rationale: The nucleophilic enol undergoes reaction with bromine

Under basic conditions:
All of the enolizable protons are substituted with bromine and the resulting trihalomethyl group itself is cleaved.

Mechanistic Rationale:
1. The nucleophilic enolate undergoes reaction with bromine

All enolizable H’s substituted with Br
Chemical Tests for Functional Groups

Methyl ketones give positive iodoform test

\[
\begin{align*}
\text{Cl}_2 & \rightarrow \text{HCCl}_3 \quad \text{- chloroform} \\
\text{Br}_2 & \rightarrow \text{HCBr}_3 \quad \text{- bromoform} \\
\text{I}_2 & \rightarrow \text{HCl}_3 \quad \text{- iodoform, pale yellow solid} \\
& \quad \text{good test for presence of a methyl ketone}
\end{align*}
\]
α-Halo Carboxylic Acids

*Hell-Volhard-Zelinski reaction*

1. P, Br₂
2. H₂O

Reactions of α-halo acids

1. NaOH
2. H₃O⁺

NH₃

KCN

Racemization of Aldehydes and Ketones

*Experimental Observation:* Compounds with a stereogenic center bearing a hydrogen atom adjacent to a carbonyl group undergo rapid racemization in mildly acidic or basic conditions.

![Image of racemization reaction](image-url)
Mechanistic Rationale:

Ibuprofen • Ibuprofen marketed as racemate
• Only the $S$ isomer is active
• Body converts $R$ to $S$ by inversion of stereogenic center adjacent to carbonyl

H/D Exchange Reactions
Experimental Observation: Treatment of ketones with NaOD/D$_2$O results in replacement of $\alpha$-hydrogen atoms with deuterium.
via allylic anion

NaOD
D₂O

H-D exchange

NaOD
D₂O

H-D exchange
THE ALDOL REACTION: ADDITION OF ENOLATES TO ALDEHYDES & KETONES – SYNTHESIS OF 3-HYDROXY CARBONYL COMPOUNDS AND α,β-UNSATURATED CARBONYL COMPOUNDS

The Aldol Reaction: The Reaction of an Aldehyde with an Aldehyde Enolate

\[
\begin{align*}
\text{CH}_3\text{C} &= \text{H} \quad \text{H}_3\text{C} \quad \text{H} \\
\text{NaOH, H}_2\text{O} \quad 5 \degree \text{C} \\
\end{align*}
\]
Aldol Condensation

Heating causes dehydration to form α,β-unsaturated aldehyde

**Mechanism:**

\[ \text{H}_3\text{C} = \text{O} \xrightarrow{\Delta} \text{H}_3\text{C} - \text{C} = \text{O} \]  

\[ \text{H}_3\text{C} - \text{OH} \]

*e.g.*

\[ \text{Ph} = \text{C} \xrightarrow{\Delta} \text{Ph} - \text{C} = \text{O} \]  

\[ \text{Ph} - \text{OH} \]

**Recognizing Products and Starting Materials of Aldol Reactions**

Aldol condensations give α,β-unsaturated carbonyl compounds
Crossed-Aldol (or “Mixed Aldol”) Reactions

Problem: Propose starting materials to prepare 2-methyl-2-pentenal by an aldol reaction

Mixed aldols between two aldehydes with enolizable protons can give four different products
Crossed aldol condensations are only useful when one of the components is non-enolizable and a good electrophile (e.g., an aldehyde)

\[ 
\text{H} - \text{O} 
\quad \text{H} - \text{O} 
\quad \text{H} - \text{C} - \text{H} 
\quad \text{H} - \text{C} - \text{H} 
\quad \text{H} - \text{C} - \text{H} 
\quad \text{H} - \text{C} - \text{H} 
\]

Examples of Aldol Reactions with Ketones

Remember: Avoid proposing crossed-aldol reactions if both components are enolizable
**Problem [Solomons 17.31b]** - How would you achieve the following transformation?

![Chemical Structure](image1.png)

Aldol Reactions are also Catalyzed by Acid....

**Problem**: Write the mechanistic steps of the following reaction (show curved arrows and intermediates)

![Mechanistic Steps](image2.png)

**Notes**: D.M. Collard, 2009
... and Reversible

The aldol reaction is reversible. The reverse reaction proceeds through exactly the same intermediates as the forward reaction.

**Problem:** Write the mechanistic steps of the following reaction (show curved arrows and intermediates).

![Mechanistic steps of the reaction](image1)

**Problem:** Pulegone, which has a pleasant peppermint-camphor smell, is isolated from the oil of pennyroyal (pennyroyal tea is commonly used as an herbal remedy; pulegone is extremely toxic). Treatment of pulegone with steam yields 3-methylcyclohexanone. Propose a pathway for this reaction. What is the byproduct of this reaction.
Cyclizations via Aldol Condensations

\[
\text{NaOH, H}_2\text{O} \xrightarrow{\Delta} \text{not} \]

\[
\text{CH}_3\text{OO} + \text{CH}_3\text{OO} \quad \text{major product}
\]
Problem [Solomons 17.33] – Identify the structures of compounds A-C.

1. NaNH₂
2. acetone
3. NH₃Cl, H₂O

HC≡CH → A (C₅H₈O) → B (C₅H₁₀O₂) → C (C₁₂H₁₄O₂)

Problems 17.31, 33, 35
ALKYLATION OF ALDEHYDES AND KETONES

Problem:
With OH\(^-\) or EtO\(^-\), enolates are generated in equilibrium. They are not isolated, but react \textit{in situ} with a second molecule of carbonyl compound (aldehyde or ketone) in an aldol reaction.

\[ \text{CH}_3\text{CH}_3\text{O} \rightleftharpoons \text{CH}_3\text{CH}_2\text{O} + \text{Na}^+ + \text{OH}^- \quad \text{pK}_a = 20 \]
\[ K_{eq} = 10^{-4} \]
\[ \text{CH}_3\text{CH}_2\text{O} \rightleftharpoons \text{CH}_3\text{CH}_2\text{O} + \text{Na}^+ + \text{H}_2\text{O} \quad \text{pK}_a = 16 \]

\[ \text{R} \]
\[ \text{NaOEt} \]
\[ \rightarrow \]
\[ \text{R} \]

Solutions:
1. Use a much stronger base – lithium diisopropylamide (LDA)

\[ \text{CH}_3\text{CH}_3\text{O} \]
\[ \text{1. LDA} \]
\[ \text{2. R\textendash}\text{Br} \]
\[ \rightarrow \]
\[ \text{CH}_3\text{CH}_2\text{O} \text{R} \]

2. Convert ketone to enamine, alkylate and hydrolyze

\[ \text{CH}_3\text{CH}_3\text{O} \]
\[ \text{2° amine} \]
\[ \text{enamine} \]
\[ \text{1. R\textendash}\text{Br} \]
\[ \text{2. H}_2\text{O} \]
\[ \rightarrow \]
\[ \text{CH}_3\text{CH}_2\text{O} \text{R} \]
Lithium Enolates
Use of a stronger base (e.g., lithium diisopropylamide, LDA) allows for generation of the lithium enolate, and then, in a separate step, the addition of an electrophile.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{Li}^+ & \quad \text{N}^+ \\
pK_a = 20 & \quad \text{CH}_3 \quad \text{CH}_2 \\
\end{align*}
\]

K\text{eq} = 10^{16}

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{Li}^+ & \quad \text{N}^+ \\
pK_a = 38 & \quad \text{CH}_3 \quad \text{CH}_2 \\
\end{align*}
\]

Lithium Enolates in Alkylation Reactions

1. LDA in THF, -78 °C
2. R-Br (1° R)
3. H\text{H}_2\text{O}^\oplus

The Effect of Temperature on the Alkylation of Lithium Enolates: Kinetic and Thermodynamic Products
The regiochemistry of lithiation is controlled by temperature.

Major Product via:

1. LDA -78 °C
2. R--Br

kinetic product

1. LDA room temp
2. R--Br

thermodynamic product
Lithium Enolates in Directed Crossed-aldol Reactions

1. LDA in THF, -78 °C
2. 
3. H₃O⁺

not:

Synthesis of Enamines
Recall that aldehydes and ketones react with primary amines to form imines. Analogous reactions with secondary amines form enamines.

1° amines

2° amines
Examples of Enamines Reacting as Nucleophiles

1. \( \text{CH}_3\text{COCl} \)  
   2. \( \text{H}_3\text{O}^+ \)

1. \( \text{PhCH}_2\text{Cl} \)  
   2. \( \text{H}_3\text{O}^+ \)

\( \text{CN} \)

\( \text{CN} \)

\( \alpha,\beta\)-UNSATURATED CARBONYL COMPOUNDS

Synthesis of \( \alpha,\beta\)-unsaturated Carbonyl Compounds

*Aldol reactions (see above)*

\( \alpha\)-Selenation

1. LDA in THF, -78 °C  
2. PhSeCl  
3. \( \text{H}_2\text{O}_2 \)

\( \text{Ph} \)
Selective Reduction of $\alpha,\beta$-Unsaturated Carbonyl Compounds

$\text{H}_3\text{C} - \text{C} = \text{O}$

- $\text{H}_2$ (high pressure) \text{Ni}
- $\text{H}_2$ (2-3 atm) \text{Pd}
- LiAlH$_4$

Electron Distribution in $\alpha,\beta$-unsaturated Ketones

In the absence of the electron-withdrawing C=O, akenes are weakly \textit{nucleophilic}. 
Nucleophilic Additions to $\alpha,\beta$-unsaturated Ketones

$\text{Nu: } \ominus$

Nucleophile
(Nu: $\ominus$)

$\text{RMgBr}$
$\text{RLi}$

$\ominus:\text{CN}$
$\text{RNH}_2$
$\text{R}_2\text{CuLi}$
enolate anions

Use of Nucleophilicity of Enolates and Electrophilicity of Enones in the Design of Syntheses.

$\begin{align*}
\text{Ko} & \quad \Rightarrow \quad \text{O} \\
\text{R} & \quad \Rightarrow \quad \text{O} \\
\text{R} & \quad \Rightarrow \quad \text{R}\text{Br} \\
\text{R} & \quad \Rightarrow \quad \text{R}\text{M}
\end{align*}$
**β-DICARBONYL COMPOUNDS:**

**INTRODUCTION**

\[
\begin{align*}
\beta\text{-dicarbonyl} & \quad \beta\text{-keto ester} \quad \beta\text{-diketone} \quad \beta\text{-diester} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{B}^+ \\
pK_a \approx 10 & \quad \text{enolate} \\
\text{enolate} + \text{B}^- & \quad \text{enolate} + \text{B}^- \\
\end{align*}
\]

**Question:** Why is the β-dicarbonyl system more acidic than an alcohol \((pK_a \approx 18)\)?

**Answer:** The anion is stabilized by resonance

\[
\begin{align*}
\text{enolate} \quad \text{enolate} \quad \text{enolate} \\
\end{align*}
\]

Consequently, there is a lot of enol in equilibrium

\[
\begin{align*}
\text{enol} \\
\end{align*}
\]
SYNTHESIS OF 1,3-DICARBONYL COMPOUNDS: THE CLAISEN CONDENSATION

Overall Reaction: The Reaction of Ester Enolates with Esters

Mechanism

First step
– formation of enolate

Question: How much enolate forms? What are the pKₐ values?
Second step
- attack of enolate (nucleophile) on the carbonyl carbon (electrophile) of another molecule of ester

\[ \text{H} \quad \text{O} \quad \text{Et} \]
\[ \text{R} \quad \text{H} \quad \text{O} \quad \text{Et} \]
\[ \text{R} \quad \text{O} \quad \text{Et} \]

*Question:* Is this reaction favorable?

---

Third step
- deprotonation of β-dicarbonyl compound (product) to form enolate

\[ \text{R} \quad \text{O} \quad \text{Et} \]
\[ \text{R} \quad \text{H} \quad \text{O} \quad \text{Et} \]
\[ ^{\ominus} \text{Et} \]

*Question:* Is this reaction favorable? What are the $pK_a$ values?
Fourth step
- protonation of enolate to form the $\beta$-dicarbonyl product by addition of acid

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

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

Question: Is this reaction favorable? What are the $pK_a$ values?
So, why does the reaction fail when the ester has two substituents on the α carbon?

\[ 2 \text{H}_2\text{C} = \text{O} + \text{R}_2\text{CO} \text{OEt} \xrightarrow{\text{1. NaOEt, EtOH}} \text{R}_2\text{CO} \text{EtO}_2 \xrightarrow{\text{2. H}_3\text{O}^+} \text{No Reaction} \]

---

Cyclizations via Claisen Condensation

\[ \text{EtO} \text{OEt} \xrightarrow{\text{1. NaOEt, EtOH}} \text{OEt} \xrightarrow{\text{2. H}_3\text{O}^+} \text{not} \]

---

Notes: D.M. Collard, 2009
Crossed Claisen and other Condensations

Remember the rule for crossed aldol condensation reactions (i.e., one component cannot form an enolate)

![Chemical structures and reaction equations]

**Problem** – How would you achieve the following transformations?

1. \(\text{Ph} -\text{CO} -\text{OEt} \rightarrow \text{Ph} -\text{CO} -\text{EtO}\)

2. \(\text{CH}_3\text{CH}_2\text{CO} -\text{OEt} \rightarrow \text{CH}_3\text{CH}_2\text{CO} -\text{EtO}\)
THE ACETOACETIC ESTER SYNTHESIS:  
SYNTHESIS OF METHYL KETONES

Overall reaction

Reminder: Simple esters cannot be alkyalted in this fashion
Pathway

**Deprotonation: Enolate formation**

\[
\begin{align*}
\text{OEt} & \quad \text{O} & \quad \text{OEt} \\
\text{OEt} & \quad \text{H} & \quad \text{NaOEt}
\end{align*}
\]

\[
\text{NaOEt} \quad \xrightarrow{} \quad \text{OEt}^{-} \quad \text{OEt} + \text{EtOH}
\]

**Alkylation**

\[
\begin{align*}
\text{R} & \quad \xrightarrow{\text{RX}} & \quad \text{OEt}
\end{align*}
\]

**Saponification**

\[
\begin{align*}
\text{OEt} & \quad \text{O} & \quad \text{OH} \\
\text{OEt} & \quad \text{R} & \quad \text{NaOH} \\
\text{OEt} & \quad \text{R} & \quad \text{H}_3\text{O}^+ \\
\text{OEt} & \quad \text{R} & \quad \text{R}-\text{COOH}
\end{align*}
\]

**Decarboxylation of β-Keto Carboxylic Acids**

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{R} \\
\text{O} & \quad \text{R} & \quad \text{heat to 100-150 °C} \\
\text{O} & \quad \text{R} & \quad \text{R}-\text{CO}_2\text{H}
\end{align*}
\]
Examples

1. NaOEt, CH$_3$I
2. NaOEt, CH$_3$CH$_2$Br
3. H$_2$O, NaOH
4. H$_3$O$^+$, heat

1. NaOEt, BrCH$_2$CO$_2$Et
2. H$_2$O, NaOH
3. H$_3$O$^+$, heat

Synthetic Design

\[
\text{H} \quad \text{C}=\text{O} \quad \text{Cyclic Structure}
\]
THE MALONIC ESTER SYNTHESIS:  
SYNTHESIS OF SUBSTITUTED ACETIC ACIDS  

Prob: 19.27  

Overall reaction

1. NaOEt, EtOH  
2. R-X  
3. H₂O  

R=CH₃, 1° (2°)  

EtO COOEt  
EtO COOEt  
EtO COOEt  
EtO COOEt  

1. NaOH, H₂O  
2. H₂O⁺, heat  

R COOH
**Mechanism**

*Deprotonation: Enolate formation*

\[
\text{EtO} \quad \text{O} \quad \text{EtOEt} \quad \xrightarrow{\text{NaOEt}} \quad \text{EtO} \quad \text{O} \quad \text{EtO} \quad \text{OEt} + \text{EtOH}
\]

*Alkylation*

\[
\text{EtO} \quad \text{O} \quad \text{EtOEt} \quad \xrightarrow{\text{R-X}} \quad \text{EtO} \quad \text{O} \quad \text{EtO} \quad \text{Et}
\]

*Ester hydrolysis (see 18.7B) and decarboxylation (see 18.10)*

\[
\text{EtO} \quad \text{O} \quad \text{EtOEt} \quad \xrightarrow{\text{H}_2\text{O}, \text{NaOH}} \quad \text{HO} \text{C} \quad \text{R} \quad \text{H} \quad \xrightarrow{\text{H}_3\text{O}^+, \text{heat}} \quad \text{HO} \text{C} \quad \text{R} \quad \text{H}
\]

**Examples**

1. NaOEt, CH₃I
2. H₂O, NaOH
3. H₃O⁺, heat

1. NaOEt
   
   BrCH₂COPh

2. H₂O, NaOH
3. H₃O⁺, heat

1. 2NaOEt
   
   Br(CH₂)₂Br

2. H₂O, NaOH
3. H₃O⁺, heat
What is the major organic product of the following sequence of reactions?

1. NaOEt, EtOH
2. PhCH₂Br
3. NaOH, H₂O
4. H₃O⁺, heat
5. LiAlH₄
6. H₂O

Synthetic Design Using Malonate Ester Synthesis
Problem [Solomons 19.26e,27] - How would you achieve the following transformations?

\[
\text{OEt} \quad \xrightarrow{} \quad \text{OH}
\]

\[
\text{OEt} \quad \xrightarrow{} \quad \text{OH}
\]
Problems 19.36

\[
\text{EtO} \quad \text{O} \\
\text{O} \quad \text{Et} \\
\text{O} + \text{H}_2\text{N} \quad \text{O} \\
\text{H}_2\text{N} \quad \text{NaOEt} \\
\text{NH} \quad \text{NH} \\
\text{O} \quad \text{O} \\
\text{barbituric acid} (pK_a \approx 4)
\]

\[
\text{EtO} \quad \text{O} \\
\text{O} \quad \text{Et} \\
\text{O} + \text{H}_2\text{N} \quad \text{O} \\
\text{H}_2\text{N} \quad \text{NaOEt} \\
\text{NH} \quad \text{NH} \\
\text{O} \quad \text{O} \\
\text{phenobarbital - a highly addictive sleep inducer and tranquilizer}
\]

S:19.12
Prob: 19.27

How would you synthesize this malonic ester? (see prob. 19.24)
OTHER C-C BOND FORMING REACTIONS

Michael addition

Conjugate addition of a stabilized enolate to an \( \alpha,\beta \)-unsaturated carbonyl compound

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\quad & \quad \text{EtONa} \\
\end{align*}
\]

Robinson annulation

Michael addition and subsequent aldol cyclization

\[
\begin{align*}
\text{NaOH, H}_2\text{O} & \\
\text{Michael} & \quad \text{Aldol} \\
\end{align*}
\]
The Knoevenagel Condensation

Aldol condensation of a stabilized enolate

\[
\begin{align*}
\text{1. base} & \quad \text{[} & \quad \text{2.} & \quad \text{H}_2\text{O} \\
\text{2.} & \quad \text{[} & \quad & \text{[} \\
\end{align*}
\]

\text{e.g.,}

\[
\begin{align*}
\text{phenol} & \quad \text{NaOH} \\
\end{align*}
\]

OTHER COMPOUNDS WITH ACIDIC HYDROGEN ATOMS ON CARBON

Esters, nitriles and nitroalkanes can also be deprotonated with a strong base (LDA)...

\[
\begin{align*}
\text{CH}_3\text{C}^-\text{CH}_3 & \quad \rightarrow \quad \{ \text{CH}_2\text{C}^-\text{CH}_3 \} \\
\text{CH}_3\text{C}^-\text{N} & \quad \rightarrow \quad \{ \text{CH}_2\text{C}^-\text{N} \} \\
\text{CH}_3\text{N}^- & \quad \rightarrow \quad \{ \text{CH}_2\text{N}^- \} \\
\end{align*}
\]

…and the conjugate bases react as nucleophiles with alkyl halides (alkylation via S_2), carboxyls (addition, or addition-elimination, e.g., aldol reaction), and esters (addition-elimination, e.g., Claisen condensation).
Compounds with two electron withdrawing groups attached to the same carbon are deprotonated with weaker bases (NaOEt, NaOH).

![Chemical structures](attachment:image.png)

cyanoacetaldehyde  cyanoacetone  ethyl cyanoacetate  malonitrile

![Chemical structures](attachment:image.png)

phenylacetone  benzylcyanide

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**Direct Alkylation of Esters, Nitriles, Nitroalkanes**

![Chemical structures](attachment:image.png)

1. LDA
2. PhCH₂Br

![Chemical structures](attachment:image.png)

1. NaOEt
2. CH₃Br

![Chemical structures](attachment:image.png)

1. LDA
2. PhCH₂CH₂Br
**Methadone**, a synthetic opioid, is used to treat addiction to heroin. Methadone occupies the opioid receptor in the brain hereby blocking the binding of other drugs from attaching to the receptor.

![Chemistry Diagram](image)

**TOPIC 5 REVIEW**

**Enolate Anions**
Protons α- to carbonyl groups are more acidic than other protons on carbon; enolates are nucleophilic

![Chemistry Diagram](image)

Enolates are nucleophilic

![Chemistry Diagram](image)
The aldol reaction: The reaction of an aldehyde with an aldehyde enolate

Crossed aldol condensations are only useful when one of the components is non-enolizable and a good electrophile (e.g., an aldehyde).

e.g.,
Lithium enolates are useful in directed crossed-aldol reactions and in alkylation reactions

Additions to $\alpha,\beta$-unsaturated ketones

Michael addition and subsequent aldol cyclization (Robinson annulation)
The β-dicarbonyl system more acidic than an alcohol ($pK_a \approx 18$). The anion is stabilized by resonance

The Claisen condensation: the synthesis of β-keto esters

Crossed Claisen and other Condensations
Remember the rule for crossed aldol condensation reactions (i.e., one component cannot form an enolate)
The Acetoacetic Ester Synthesis: Synthesis of Methyl Ketones

1. NaOEt, EtOH
2. R-X
3. H₂O

R=CH₃, 1°

1. NaOH
2. H₂O⁺
heat

The Malonic Ester Synthesis: Synthesis of Substituted Acetic Acids

1. NaOEt, EtOH
2. R-X
3. H₂O

R=CH₃, 1°

Synthesis Of Enamines

Stork Enamine Reactions
Reaction of ketones and aldehydes with secondary amines form enamines

2° amine

enamine
PROBLEM SOLVING AND SYNTHETIC STRATEGIES

Problem - Propose a synthetic pathway to achieve the following transformation.

Problem [Solomons 19.39] - How could you prepare Darvon, a powerful analgesic, from ethyl phenyl ketone?

February 20, 2009
FDA Panel Recommends Darvon Be Removed From Market

An FDA panel, citing safety risks, voted Jan. 30 to remove a pair of painkillers from pharmacy shelves. The panel of outside experts voted to end sales of Darvon because of concerns that their safety risks outweigh their benefits.

Darvon (propoxyphene) is an opioid painkiller used for mild to moderate pain. Like all opioids, it carries a high potential for addiction and abuse and are not safe when combined with alcohol.
Problem [Solomons 19.38] - Fenchone is a terpenoid isolated from fennel oil. Provide the structure of intermediates and reagents (a)-(n) in the following scheme (cont. next slide).

\[
\text{CO}_2\text{CH}_3 + (a) \xrightarrow{\Delta} \text{CO}_2\text{CH}_3 \quad \text{b) CO}_2\text{CH}_3 \quad \text{c) mixture of a and f) }
\]

1. (g) CO_2H
2. (h) (i) (j)

\[
\text{CO}_2\text{CH}_3 \quad \text{CO}_2\text{H} \quad \text{CO}_2\text{CH}_3 \quad \text{CO}_2\text{CH}_3 \quad \text{CO}_2\text{CH}_3
\]

\[
\text{CO}_2\text{CH}_3 \quad \text{H}_3\text{O}^+ \quad (k) \quad (l)
\]

(m) \quad \text{C}) \quad (n) \quad (\text{m}) \quad (\text{n})
Problem [Solomons 17.32] – Describe the key mechanistic steps in the following reaction (i.e., write a mechanism).

\[ \text{Ph-} + \overset{\text{NaOH}}{\text{Ph}} \rightarrow \text{Ph} \]

Problems 19.30, 31, 50
TOPIC 6 (CHAPTER 17,19) ON EXAM 5

Types of Questions
- Predict the products obtained from given starting materials
- Rationalize the outcome of a reaction (i.e., propose a mechanism, draw key intermediates)
- Develop multistep synthetic strategies.
  
  Do the problems in the book; they are great examples of the types of problems on the exam!

Preparing for Exam 5
- Get up-to-date NOW!
- Work as many problems as possible. Do the problems first, then consult the solutions manual.
- Work in groups, discuss chemistry, teach and test each other.
- Do the “Learning Group Problem” at the end of the chapter.