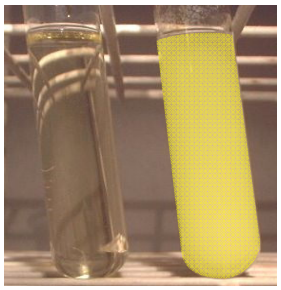
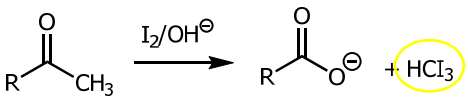
Topic 6: Reactions at the α-carbon and β-carbon of Carbonyl Compounds (Chapters 18 & 19)



Qualitative Iodoform Test
for methyl ketones



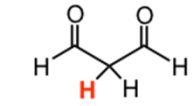
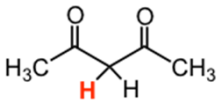
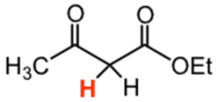
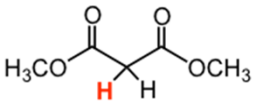
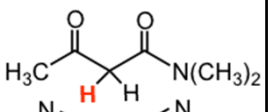
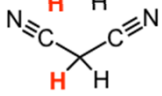
1

In this chapter :

1. Reactions that derive from the weak acidity of hydrogen atoms on carbon atoms adjacent to a carbonyl group. These hydrogen atoms are call the **α hydrogens**, and the carbon to which they are attached is called the **α carbon**
2. The processes by which enols and enolates can be formed
3. The concept of kinetic and thermodynamic deprotonations to generate different enolates from the same starting material
4. Alkylations, acylations, and other electrophile additions to enols and enolates
5. A special version of the same chemistry using the nitrogen analog of an enol—that is, an **enamine**

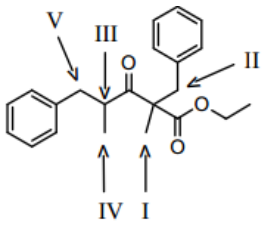
2

α-Acidity

	pK_a			pK_a	
$HCH_2-C(=O)-H$	17	weaker than H-OH	stronger than H-OH	5	
$HCH_2-C(=O)-CH_3$	19			9	
$HCH_2-C(=O)-OEt$	24			11	
$HCH_2-C\equiv N$	24			13	
$CH_3-C(=O)-NH_2$	18		*except*	18	
$HCH_2-C(=O)-NR_2$	25			11	

3

Which is the most acidic hydrogen in the compound shown?



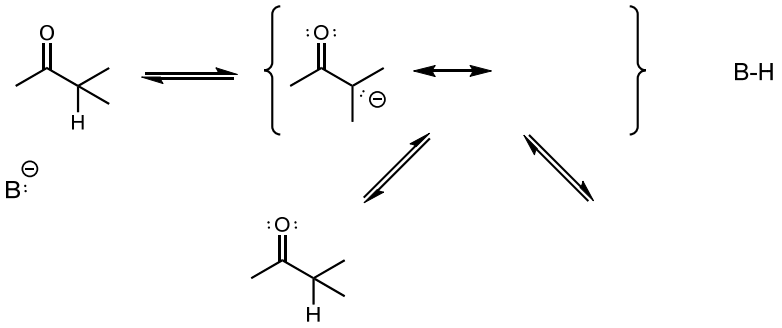
?

a) I
b) II
c) III
d) IV
e) V

4

Keto–Enol Tautomerization

- **Base Catalyzed Tautomerization**



- Keto and enol forms are in equilibrium. The interconversion process is called tautomerization or enolization

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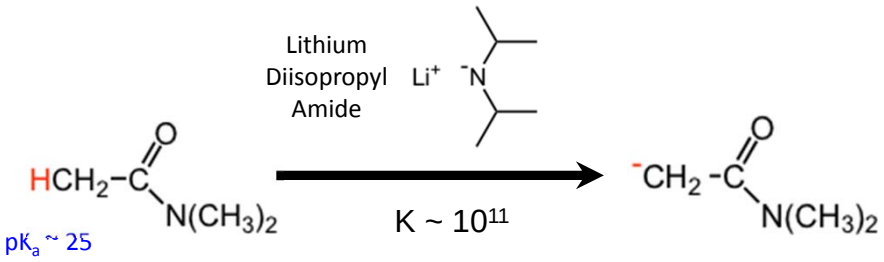
LDA: Hindered Strong Base (pKa = 36)



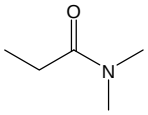
complete formation
even of amide enolate

not just a little at equilibrium
(slow attack on C=O, none on enolate)

6

- Which base should be used to quantitatively convert this N,N-dimethyl amide in its enolate ion?

?



1) $LiOCCH_3$ (with O)

2) $LiOCH_2CH_3$

3) $LiN[CH(CH_3)_2]_2$

4) LiOH

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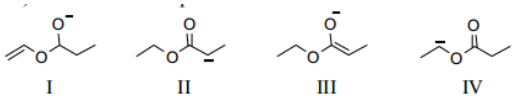
In Class Practice: Which structure represents an ester enolate?

?



I II III IV

a) I
b) II
c) III
d) IV
e) Two of these choices.

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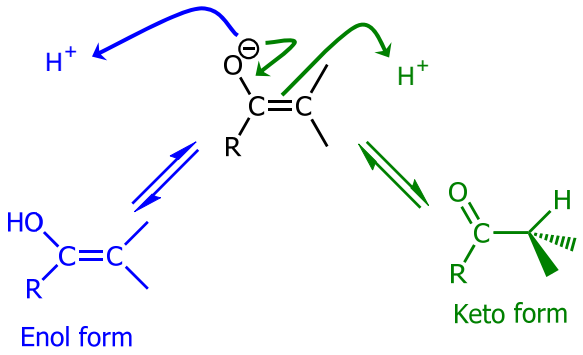
Keto–Enol Tautomerization

Interconvertible keto and enol forms are called t**automers**, and their interconversion is called **tautomerization**



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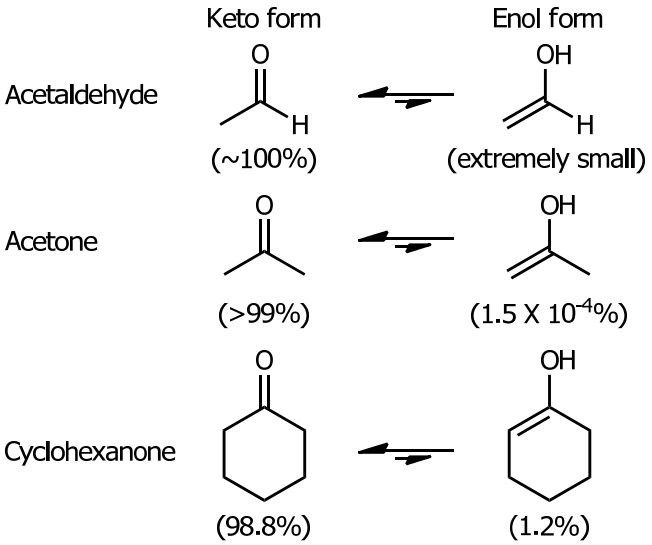
Keto-Enol Equilibrium



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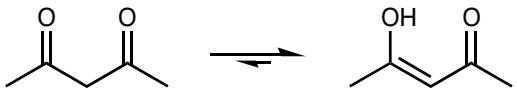
Keto-Enol Equilibrium



Pentane-2,4-dione (24%) ⇌ Enol form (76%)

Why is the Enol form the major form in this case?

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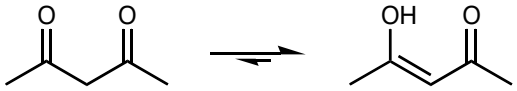
Keto-Enol Equilibrium



Pentane-2,4-dione (24%) ⇌ Enol form (76%)

Why is the Enol form the major form in this case?

1. Resonance stabilization
2. Hydrogen bonding

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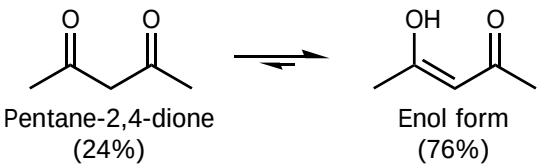
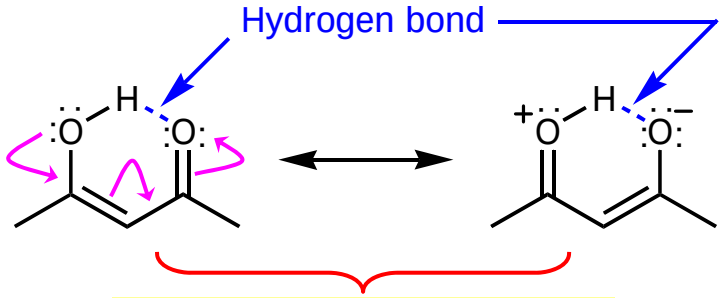
Keto-Enol Equilibrium



Pentane-2,4-dione (24%) ⇌ Enol form (76%)

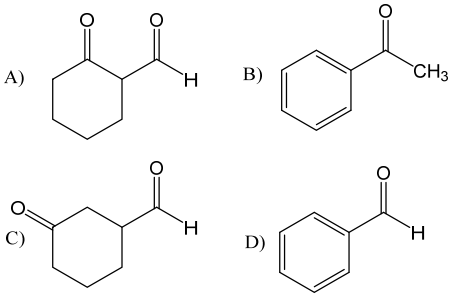


Resonance stabilization of the enol form

13

Which compound forms the greatest equilibrium concentration of the enol tautomer?

?



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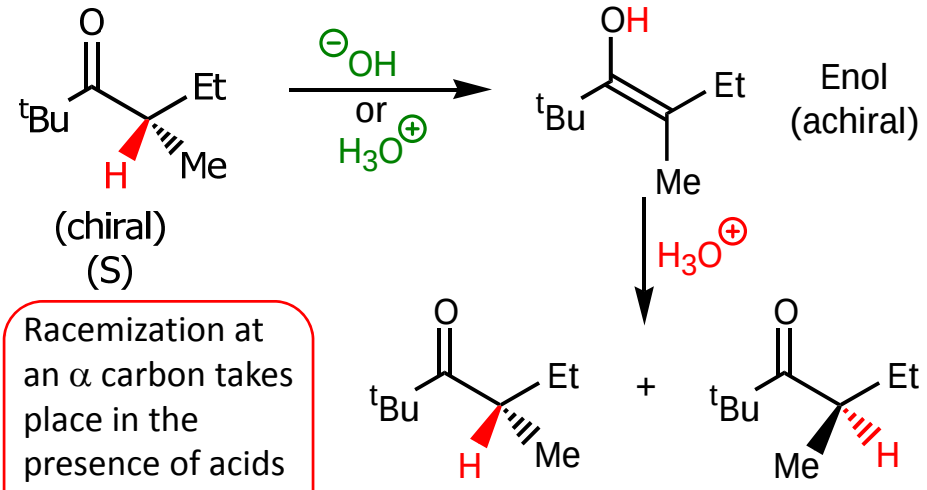
Reactions via Enols & Enolates



Racemization at an α carbon takes place in the presence of acids or bases

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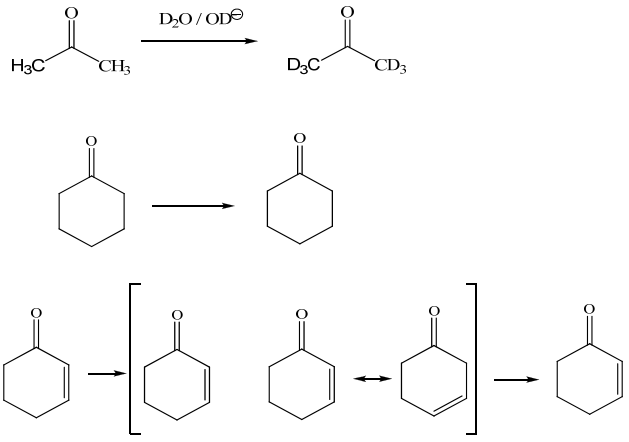
Reactions via Enols & Enolates: Deuterium Exchange



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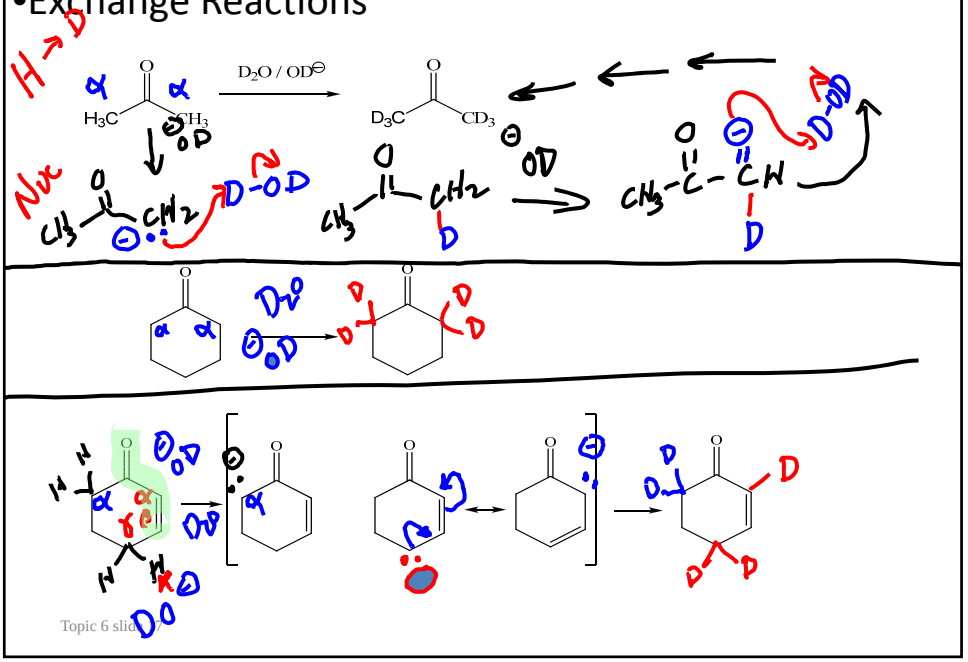
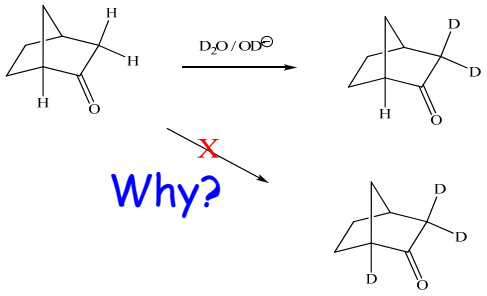
•Exchange Reactions



Reactions via Enols & Enolates: Deuterium Exchange



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In Class Practice: When the (S)-2,2,4-trimethylhexan-3-one is dissolved into in THF-water solvent mixture in presence of 5% HCl or 5% NaOH, racemization is observed.
Explain why.

?

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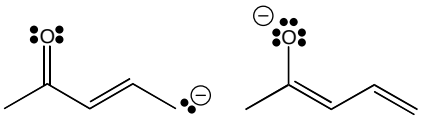
In Class Practice: What is the relationship between the following two structures?

?



A. tautomers
B. constitutional isomers, but not tautomers
C. resonance structures
D. stereoisomers

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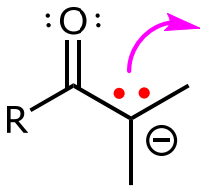
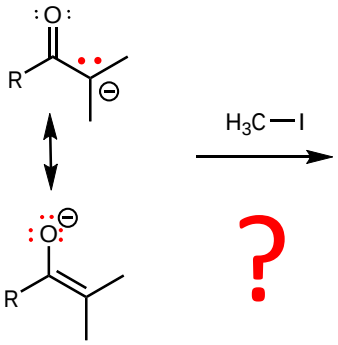
Nucleophilic α-Carbon





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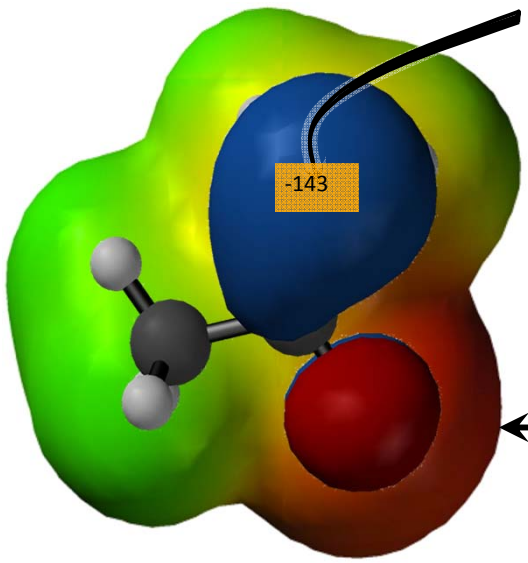

π attack

HOMO favors C

σ attack

Electrostatic Potential

favors O

McBride, Chem 125

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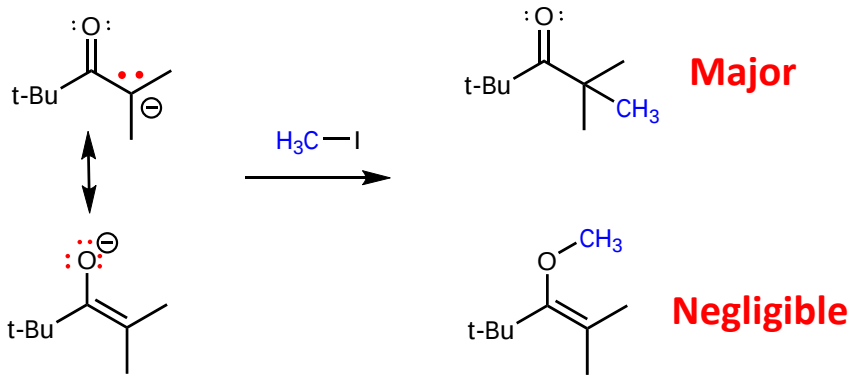
Nucleophilic α-Carbon

- SN_2 reaction of enolate on methyl iodide



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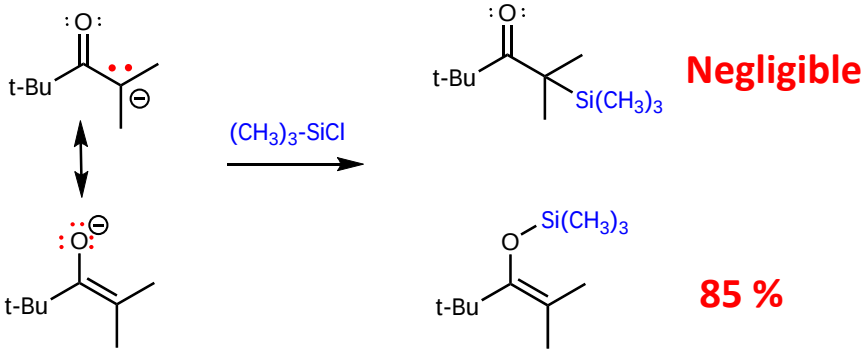
"Trapping" of the Enolic Form

- Hindered Electrophiles



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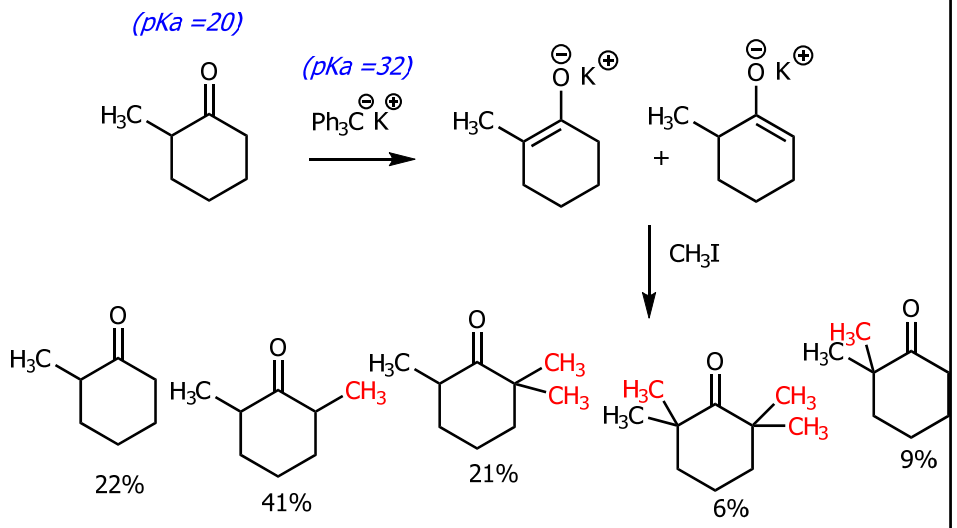
α-Alkylation of Ketones and Aldehydes



House and Kramar, JOC, 38, 3368 (1963) Org. Syn. Coll vol 76, p. 239, 1999

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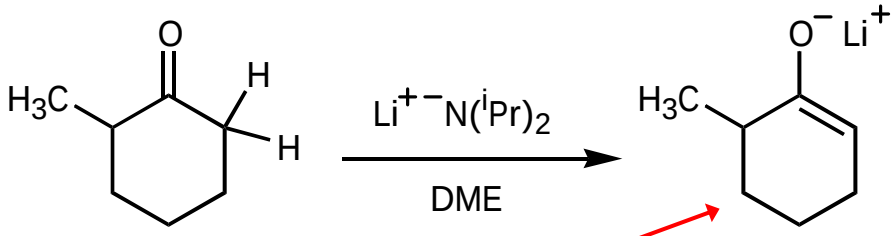
Regioselective Formation of Enolates
Kinetically Favored Enolate



This enolate is formed faster because the hindered strong base removes the less hindered proton faster.

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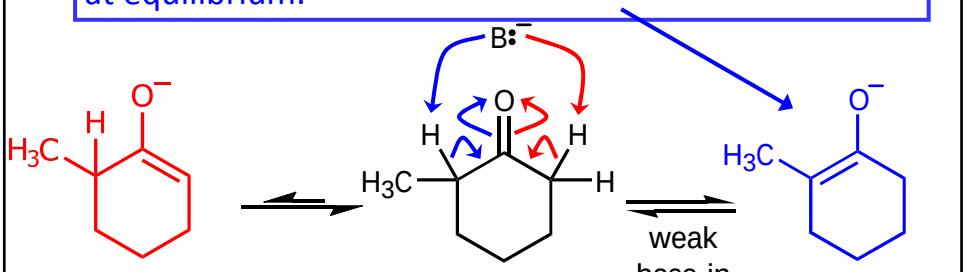
Regioselective Formation of Enolates
Thermodynamically Favored Enolate

This enolate is more stable because the double bond is more highly substituted. It is the predominant enolate at equilibrium.



Kinetic (less stable) enolate

2-Methylcyclo-hexanone

Thermodynamic (more stable) enolate

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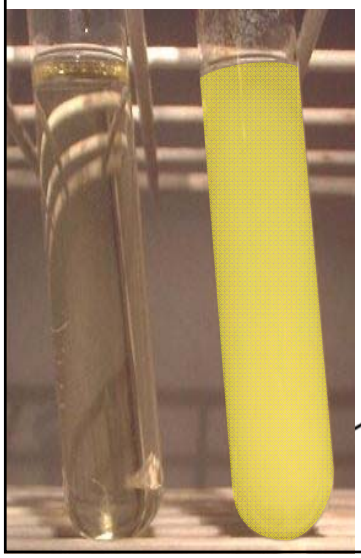
α-Halogenation
Ketones / Aldehydes

Diiodomethyl



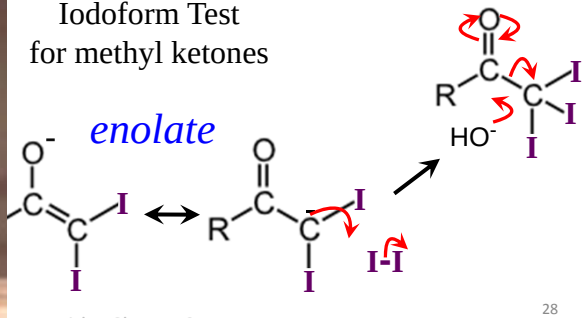
Iodoform is a bright yellow solid

pK_a ~14

$R\text{-}COO^- + HCI_3$

$R\text{-}COOH + {}^-CI_3$

Thus the Iodoform Test for methyl ketones



McBride, Chem 125

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In Class Practice: Which compound will not react in the iodoform test to produce a yellow precipitate?

a) $CH_3CCH_2CH_2CH_3$ (O)

b) $CH_3CH_2CCH_2CH_3$ (O)

c) $CH_3CH_2CH_2CH_2CCH_3$ (O)

d) CH_3CCH_2OH (O)

?

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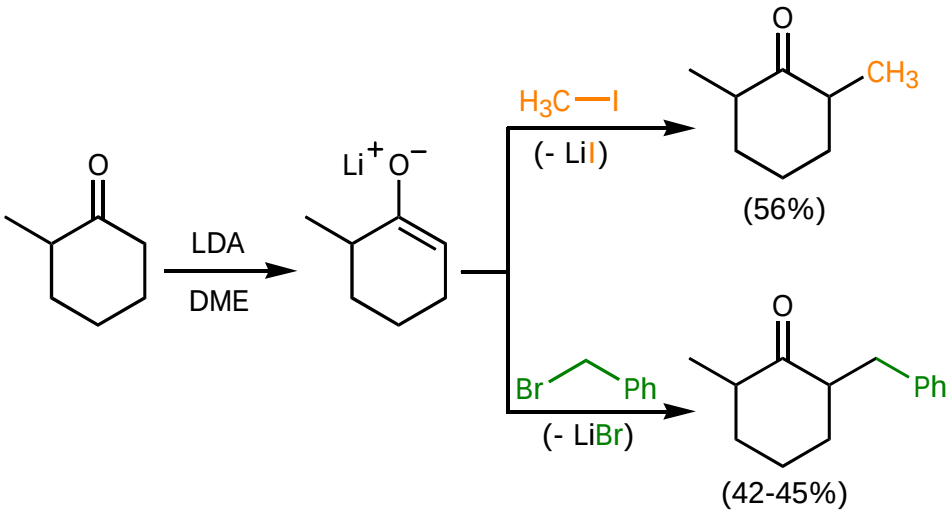
α-Alkylation of Ketones and Aldehydes via Lithium Enolates



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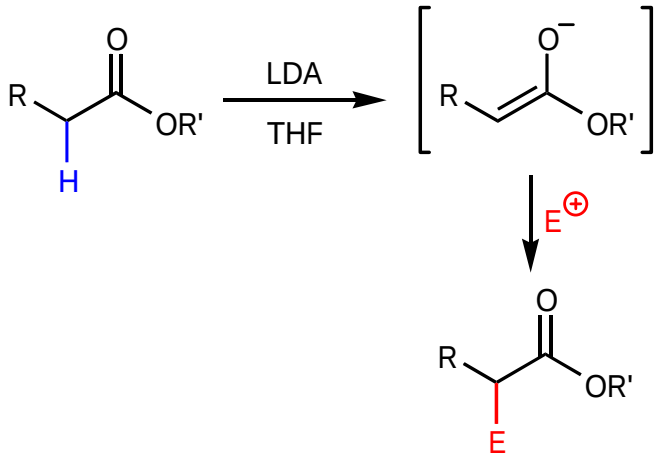
α-Alkylation of Esters

- Analogous to Ketones and aldehydes



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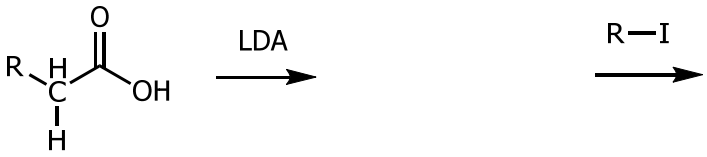
α-Alkylation of Carboxylic Acids



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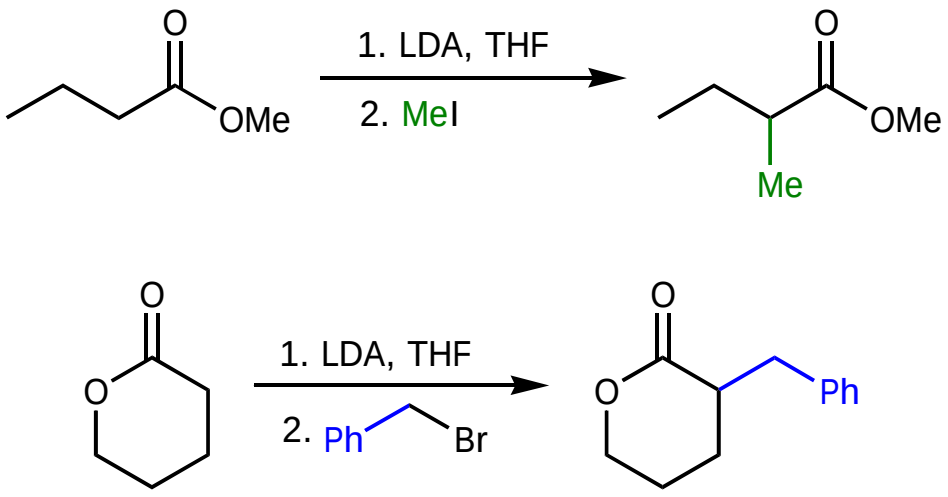
Examples



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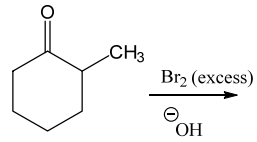
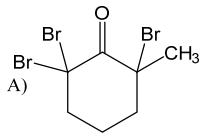
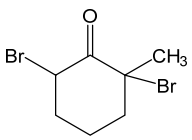
In class Practice: what is the product of this reaction?

?



A)


C)


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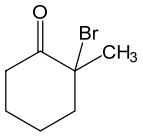
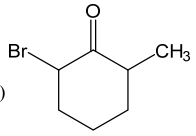


D)


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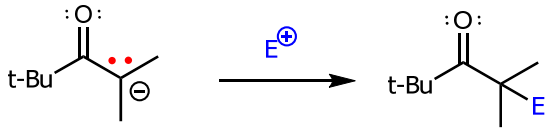
Electrophilic addition to Enols and Enolates



1. Aldol reaction and condensation (Enolates and Aldehydes & ketones)
2. Lithium Enolates (Alkylation and Michael 1,4 additions)
3. β-dicarbonyl compounds (Claisen and Dieckman condensations)
4. Acetoacetic ester synthesis (Alkylation, hydrolysis and decarboxylation)
5. Malonic ester synthesis

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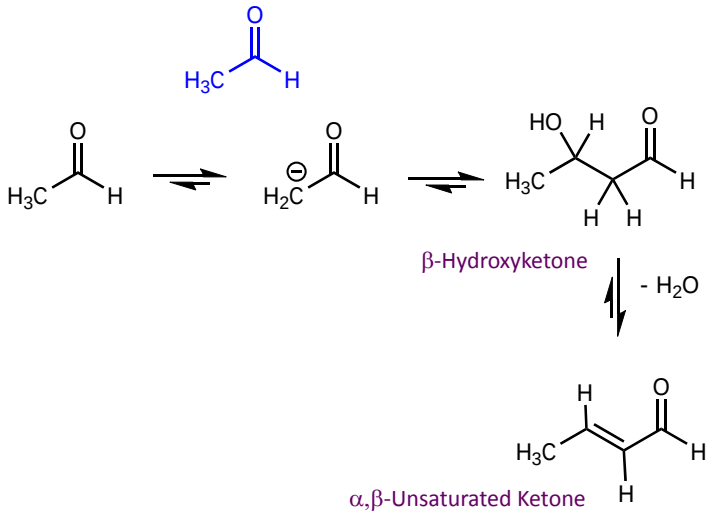
Aldol Condensation

- The aldol reaction: The reaction of an aldehyde with an aldehyde enolate



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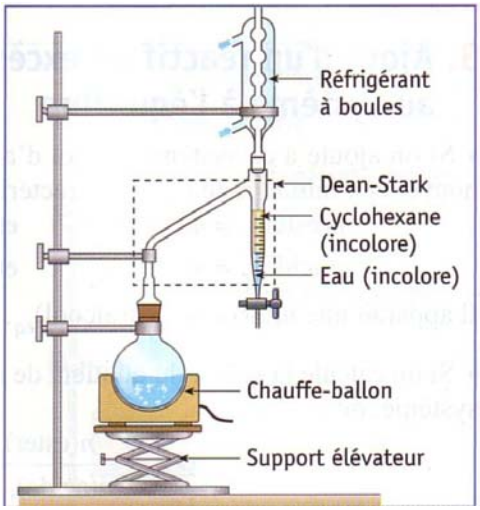
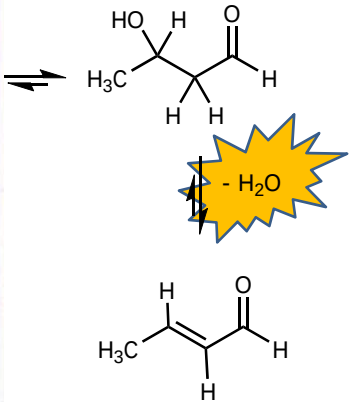
Aldol Condensation

- The aldol reaction: The reaction of an aldehyde with an aldehyde enolate





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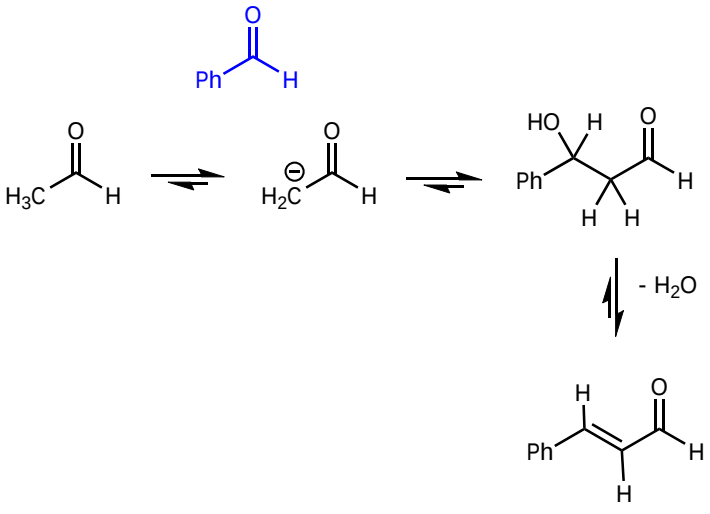
Crossed Aldol Condensation

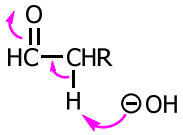
- The aldol reaction: The reaction of an aldehyde with an aldehyde enolate

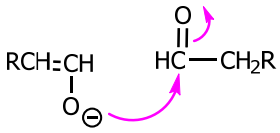


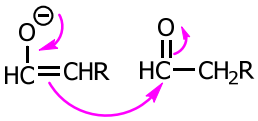
38

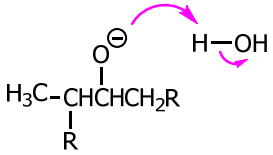
In Class practice: What is not a step in the mechanism of the aldol reaction?

?

a) 

c) 

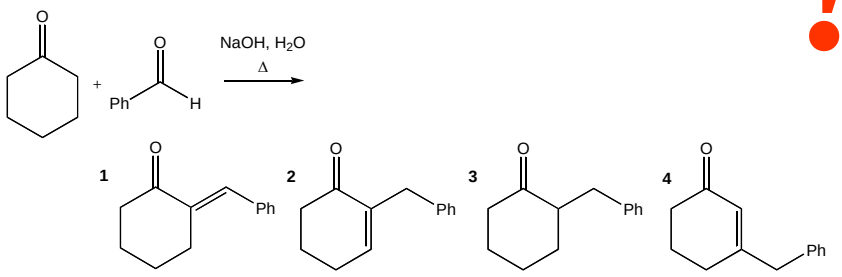
b) 

d) 

39

In Class Practice: What is the major organic product obtained from the following reaction?

?



A. 1

B. 2

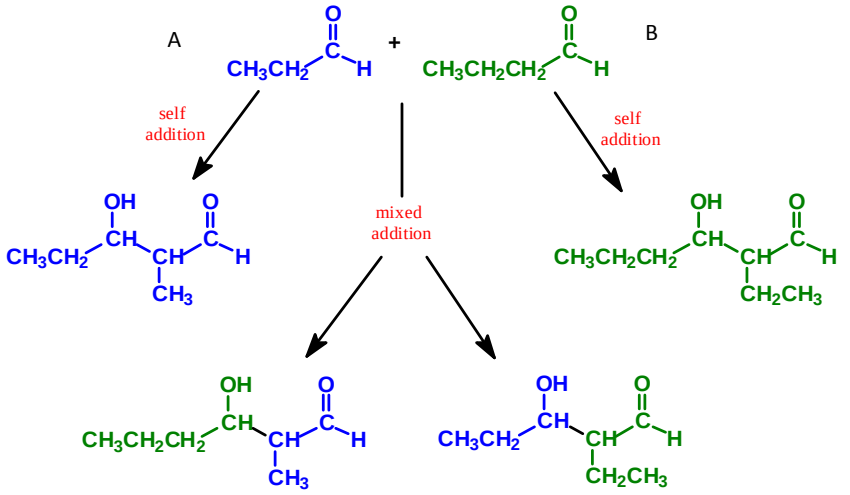
C. 3

D. 4

40

Limitations of the Aldol Addition

- Mixed aldol additions where both carbonyl compounds have α-hydrogens give mixtures of products.



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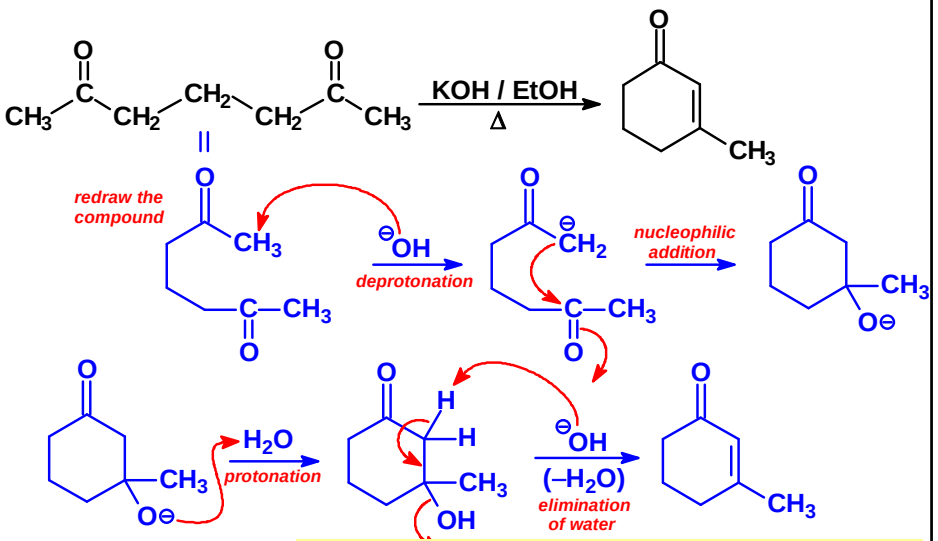
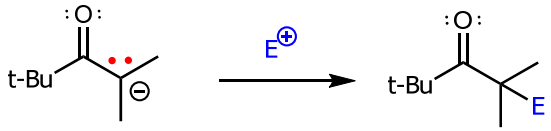
Intramolecular (Internal) Aldol Condensation



A poor LG, but …extended conjugation product is formed

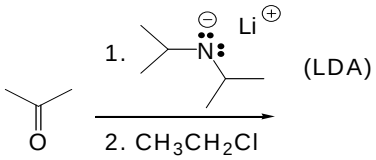
Electrophilic addition to Enols and Enolates

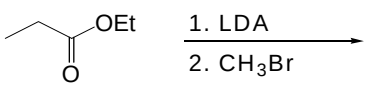


1. Aldol reaction and condensation (Enolates and Aldehydes & ketones)
2. Lithium Enolates (Alkylation and Michael 1,4 additions)
3. β-dicarbonyl compounds (Claisen and Dieckman condensations)
4. Acetoacetic ester synthesis (Alkylation, hydrolysis and decarboxylation)
5. Malonic ester synthesis

43

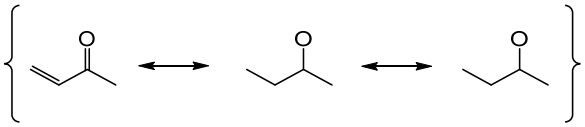
Direct Alkylation of Ketones & Esters



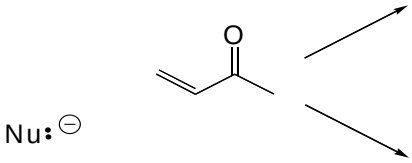


44

What about Alkylation of α,β-Unsaturated Ketones?

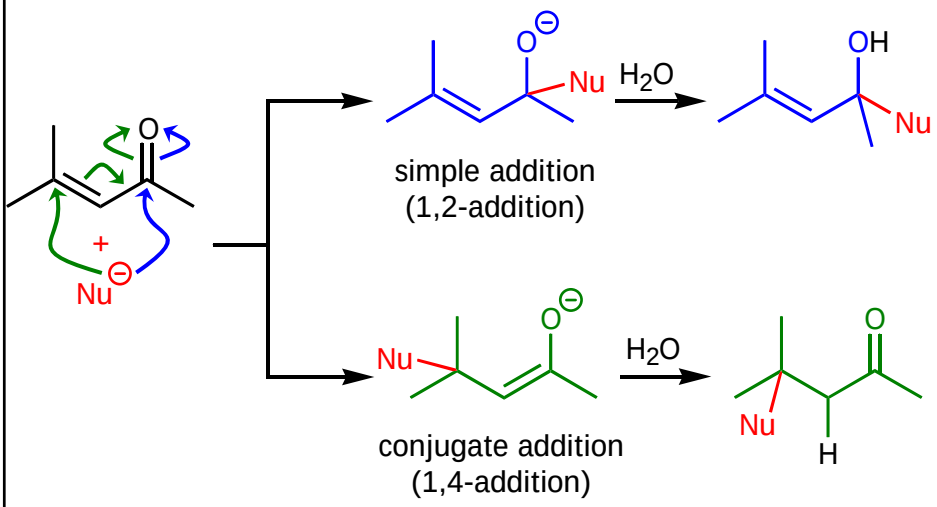


- As a result, there is competition:



45

Additions to α,β-Unsaturated Aldehydes and Ketones



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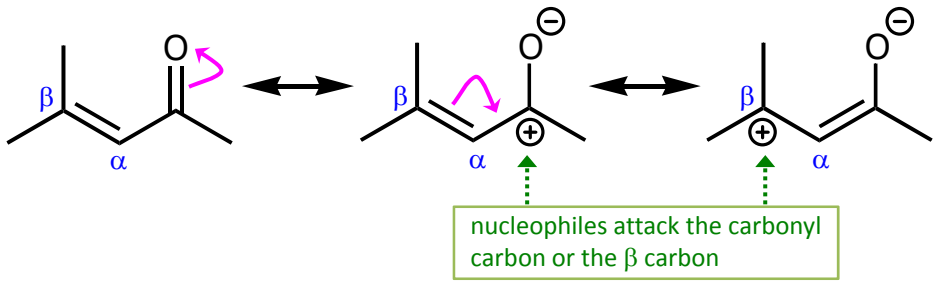
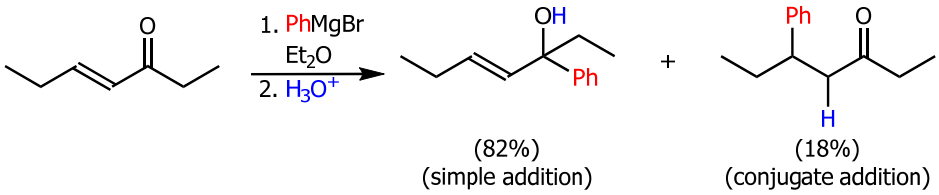
α-Position Vs. β-Position





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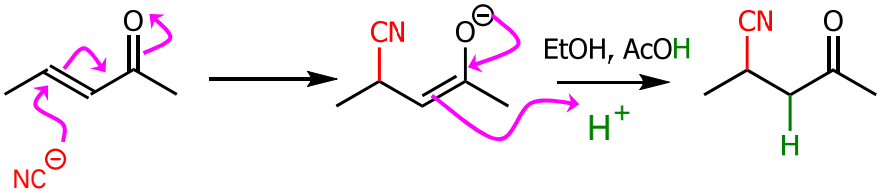
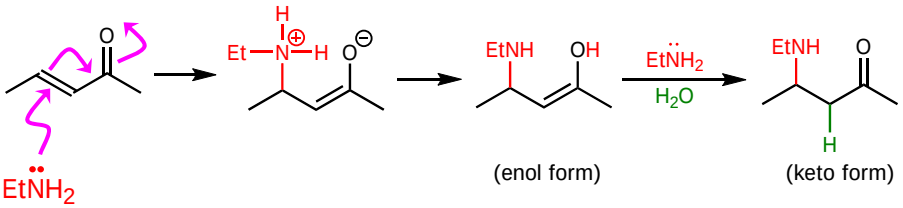
Conjugate Additions: Michael Additions

- Addition of HCN



- Addition of amines



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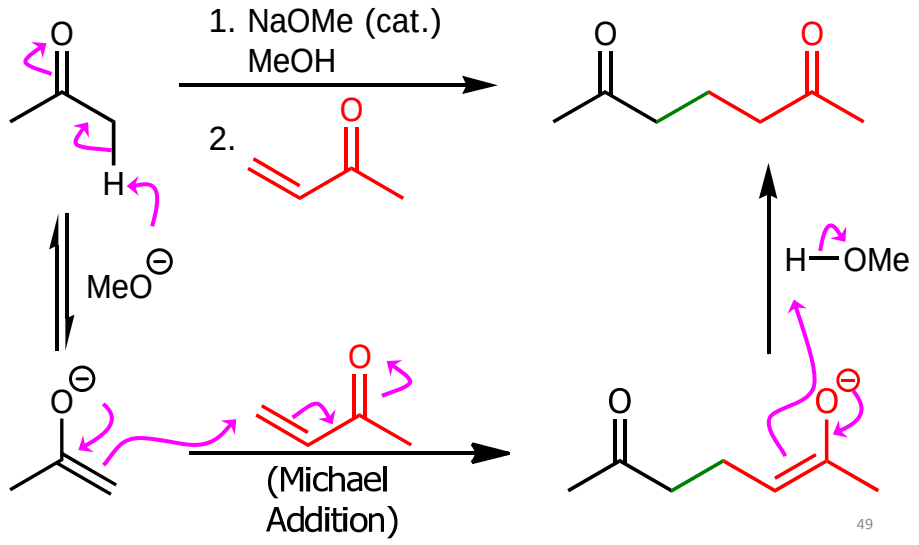
Conjugate Additions of Enolates: Michael Additions



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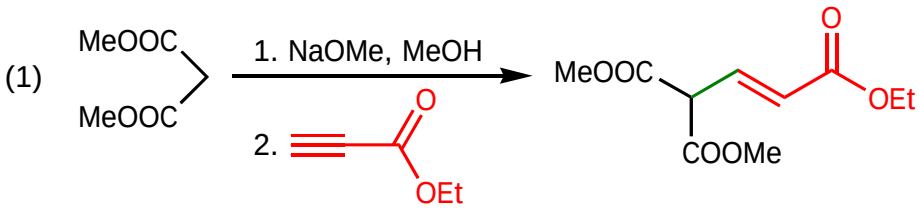
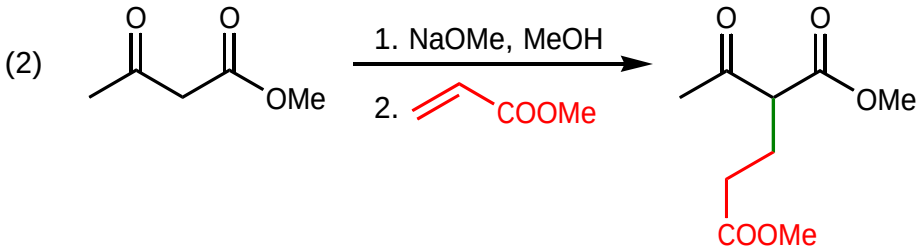
Michael Additions: Examples





50

1,2- Vs. 1,4- Addition

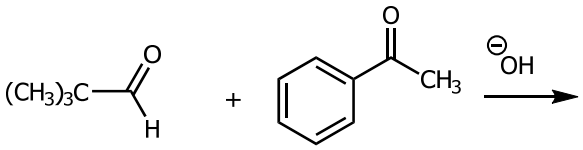
Nucleophile ($Nu:^{\ominus}$)

- RMgBr
- RLi

- $^{\ominus}:CN$
- $R\ddot{N}H_2$
- R_2CuLi
- enolate anions

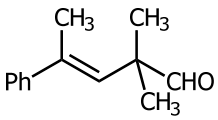
51

In class practice: what would e the major organic product of this base-catalyzed reaction?



?

a)



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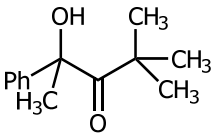

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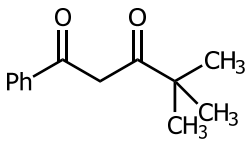

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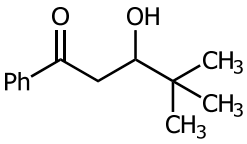

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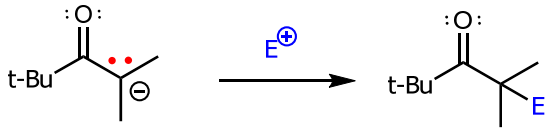
Electrophilic addition to Enols and Enolates



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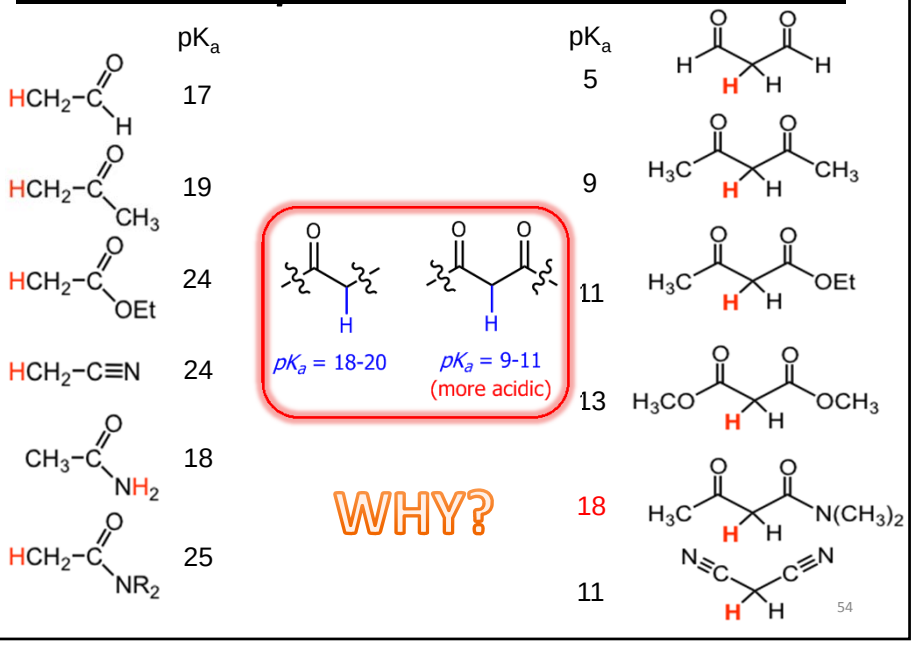
5. Malonic ester synthesis

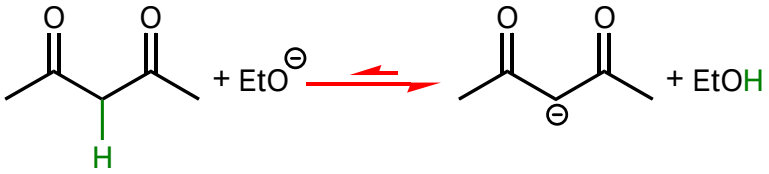
53

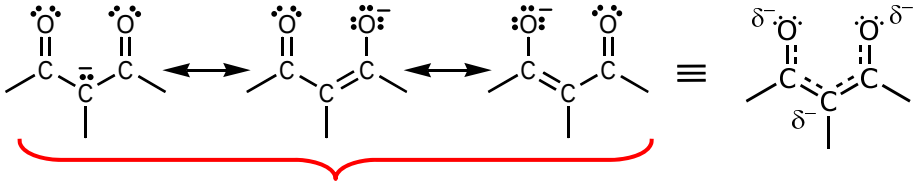
Enolates of β-Dicarbonyl Compounds



54

Enolates of β-Dicarbonyl Compounds



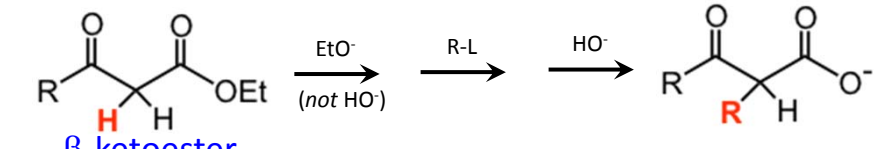


Contributing resonance structures

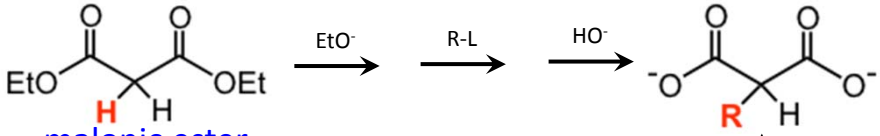
Resonance hybrid

55

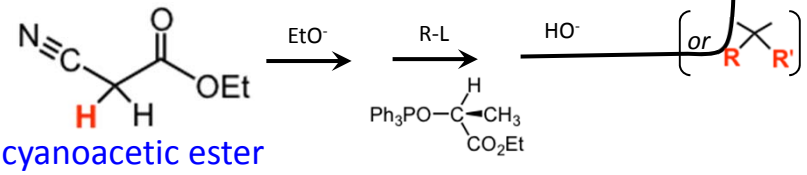
α-Alkylation of β-Dicarbonyls



β-ketoester



malonic ester



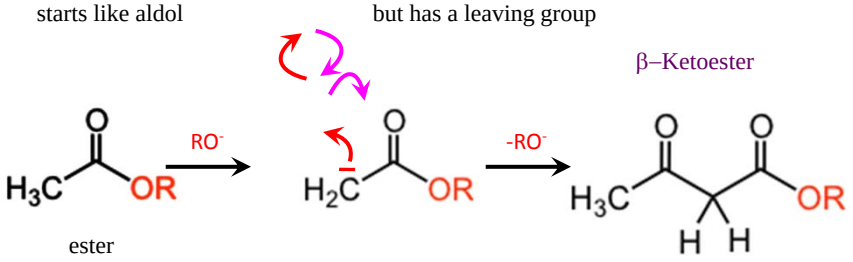
cyanoacetic ester

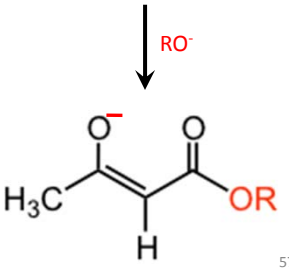
56

Claisen Condensation

starts like aldol

but has a leaving group





Driving force is the formation of a stable β-keto-enolate, which is protonated to the final product. No reaction if only one alpha hydrogen is present

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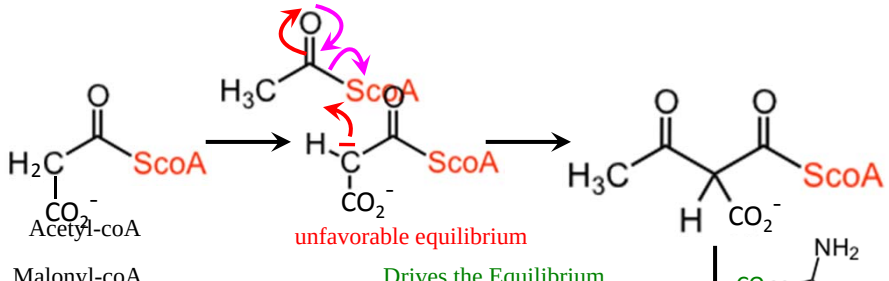
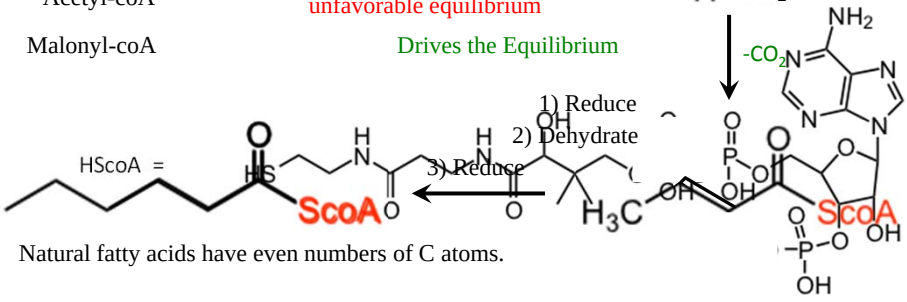
Nature's Claisen Condensation





Natural fatty acids have even numbers of C atoms.

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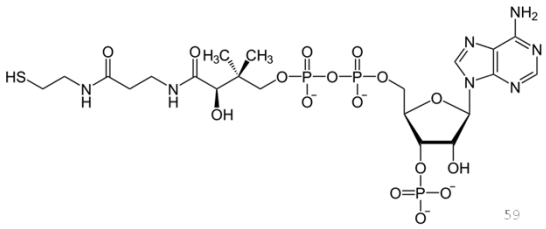
McBride, Chem 125

Nature's Claisen Condensations

- Formation of new C-C bond in both fatty acid and polyketide biosynthesis
- Two classes:
  - Decarboxylating Claisen
  - Non-decarboxylating Claisen
- Coenzyme A (CoASH or HSCoA)
  - Nobel Prize 1953 awarded to Fritz Lipmann
- It form acetyl thioesters (acetyl-CoA) to act as an acyl group carrier



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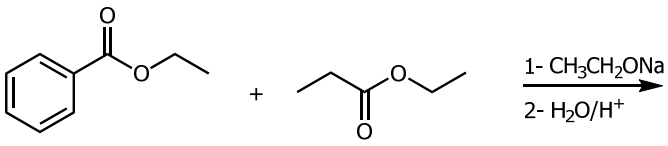
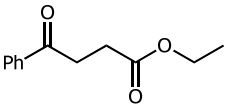
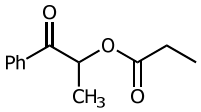
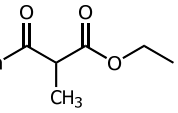
In class practice: What would be the major product of this reaction sequence?

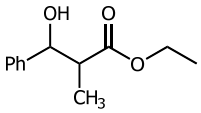


?

a) 

c) 

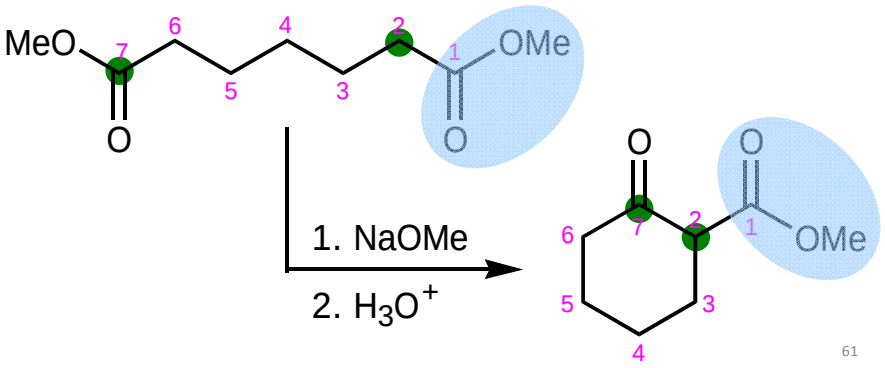
b) 

d) 

60

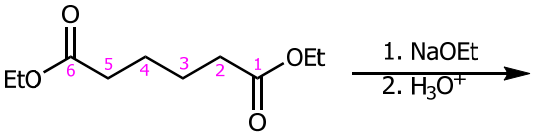
Intramolecular (Internal) Claisen Condensation

- **Dieckmann condensation**
  - Synthesis of 5 and 6-membered rings



61

In Class Practice: what is the product of the aldol condensation for the diethyladipate.

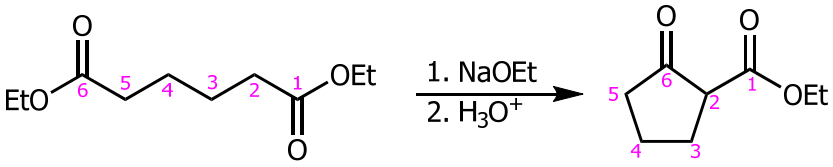


?

62

In Class Practice: what is the product of the aldol condensation for the diethyl-adipate.

?



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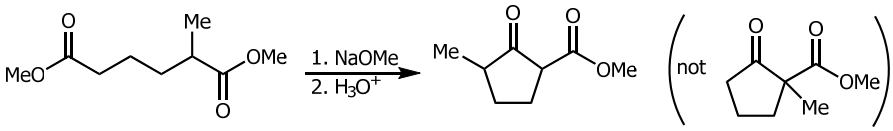
In Class Practice: Explain the regiochemistry of the reaction.
Hint: write the mechanism.

?



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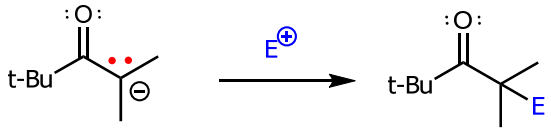
Electrophilic addition to Enols and Enolates



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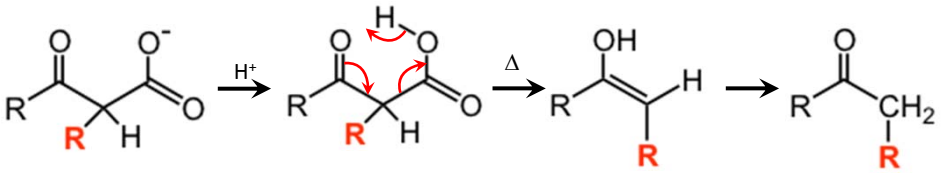
5. Malonic ester synthesis

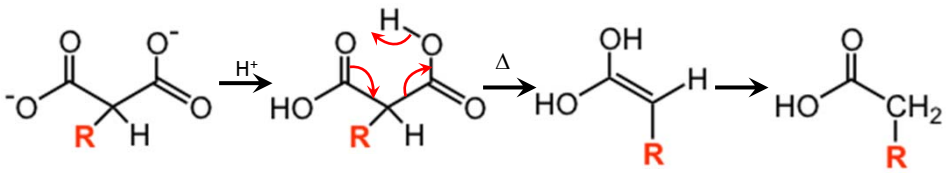
65

α-Alkylation and Decarboxylation Sequence

"Acetoacetic Ester Synthesis" of Methyl Ketone

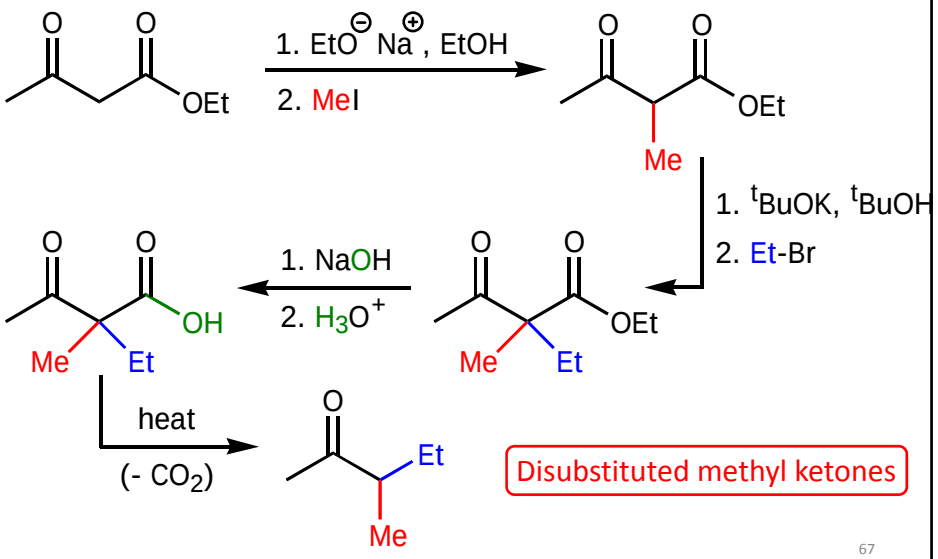


"Malonic Ester Synthesis" of Acids



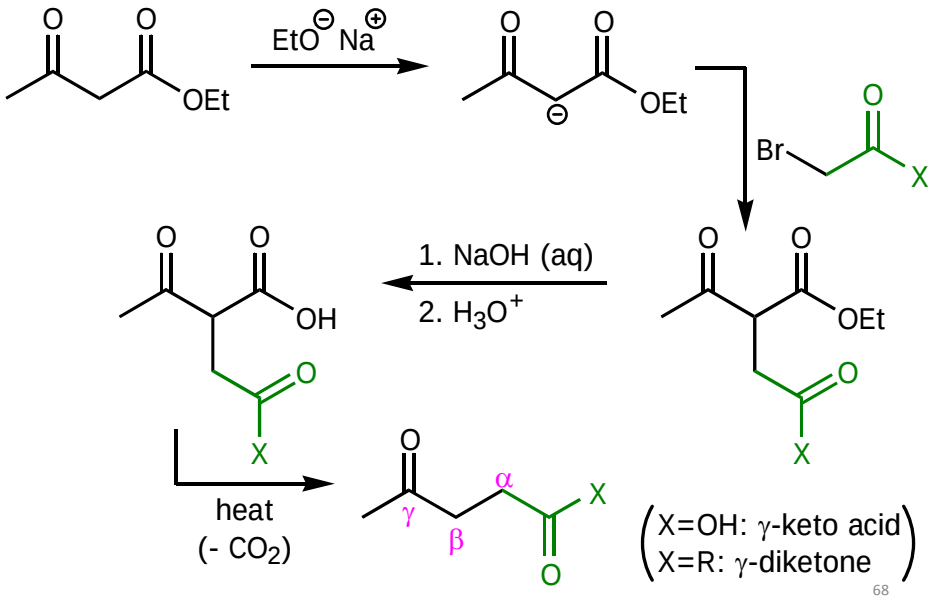
66

α-Alkylation of β-Ketoesters



67

α-Alkylation of β-Ketoesters



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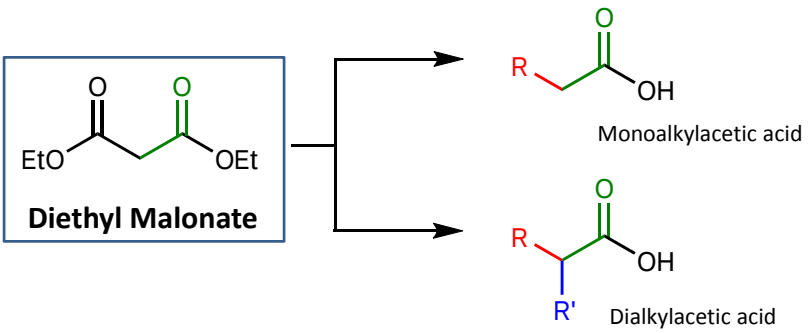
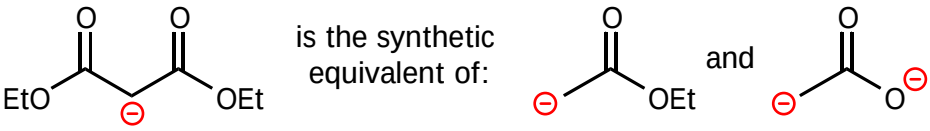
The Malonic Ester Synthesis: Synthesis of Substituted Acetic Acids





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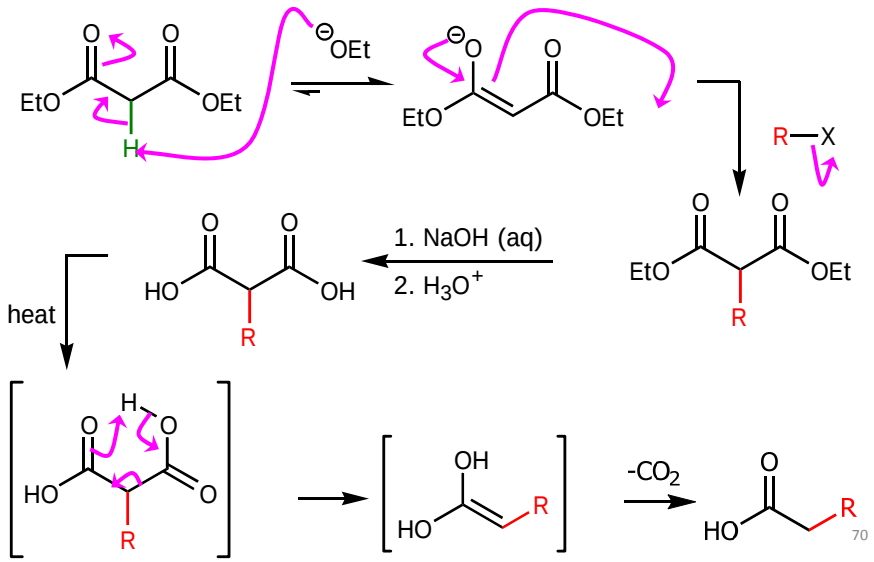
The Malonic Ester Synthesis: Monoalkylacetic acid



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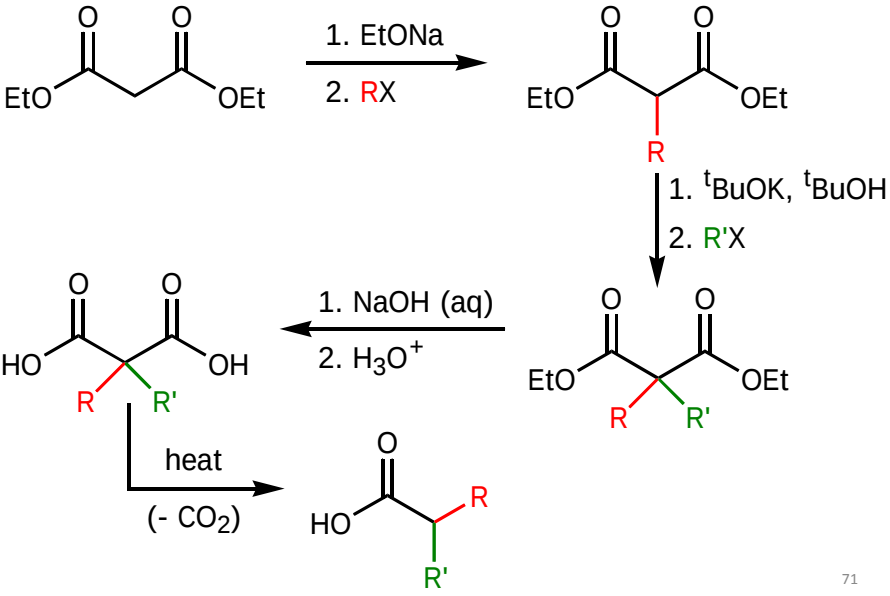
The Malonic Ester Synthesis: Dialkylacetic acid



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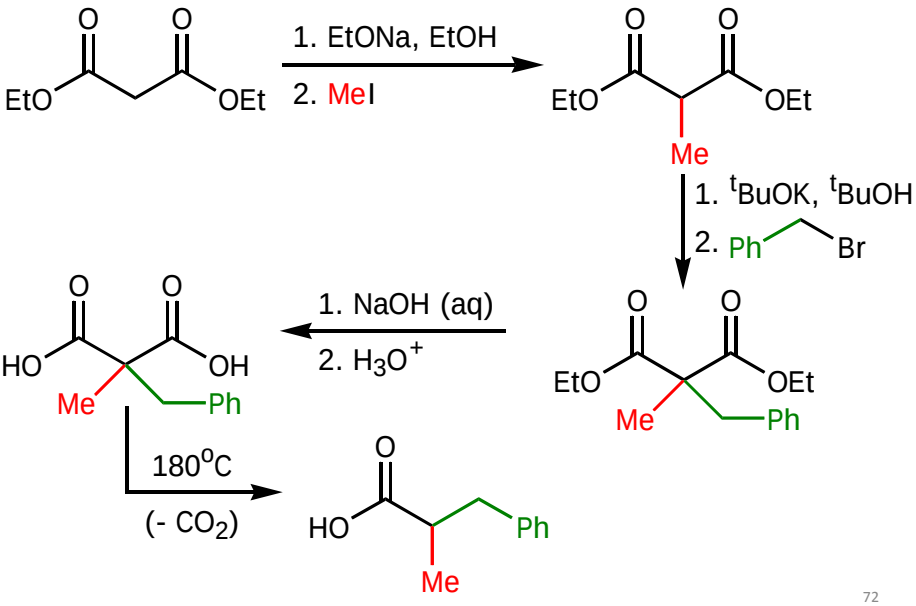
Example



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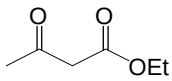
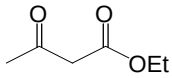
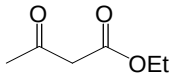
In Class Practice:



1. NaOEt, CH_3I
2. H_2O. NaOH
3. H_3O^+, heat



1. NaOEt, CH_3I
2. NaOEt, CH_3CH_2Br
3. H_2O. NaOH
4. H_3O^+, heat



1. NaOEt
   $BrCH_2CO_2Et$
2. H_2O. NaOH
3. H_3O^+, heat

?

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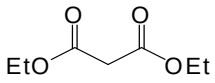
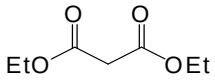
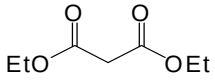
In Class Practice:



1. NaOEt, CH_3I
2. H_2O, NaOH
3. H_3O^+, heat



1. 2NaOEt
   $Br(CH_2)_3Br$
2. H_2O, NaOH
3. H_3O^+, heat



1. NaOEt
   $BrCH_2COPh$
2. H_2O, NaOH
3. H_3O^+, heat

?

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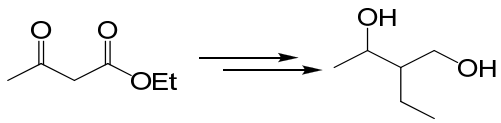
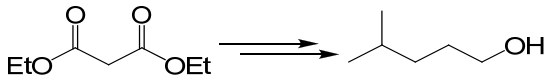
In Class Practice: [Solomons 19.26e,27] - How would you achieve the following transformations?



?



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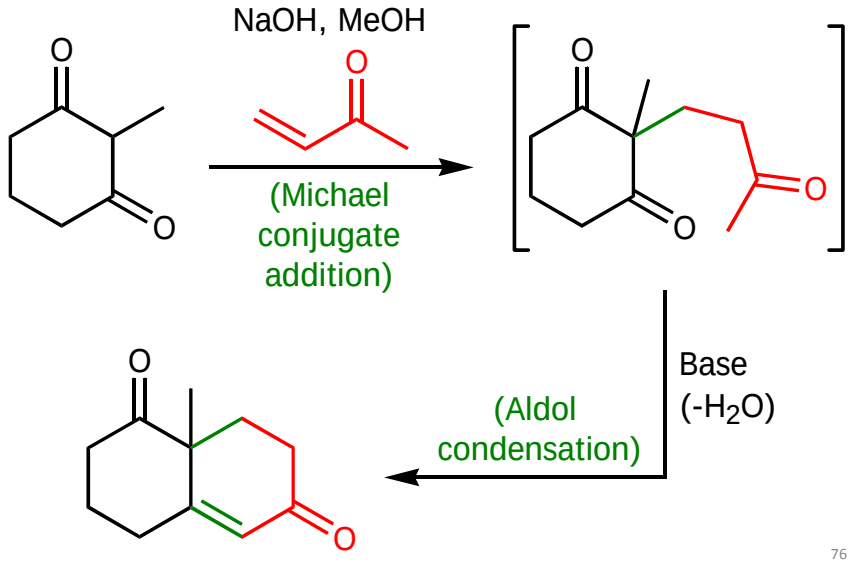
Robinson Annulation



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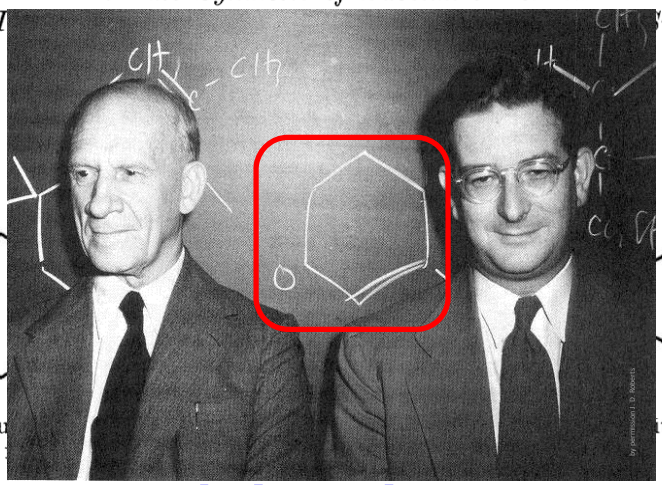
Robinson Annulation - 1935

(*e.g.* J&F Sec 19.11)

307. *Experiments on the Synthesis of Substances related to the Sterols. Part II* ... *Substituted*



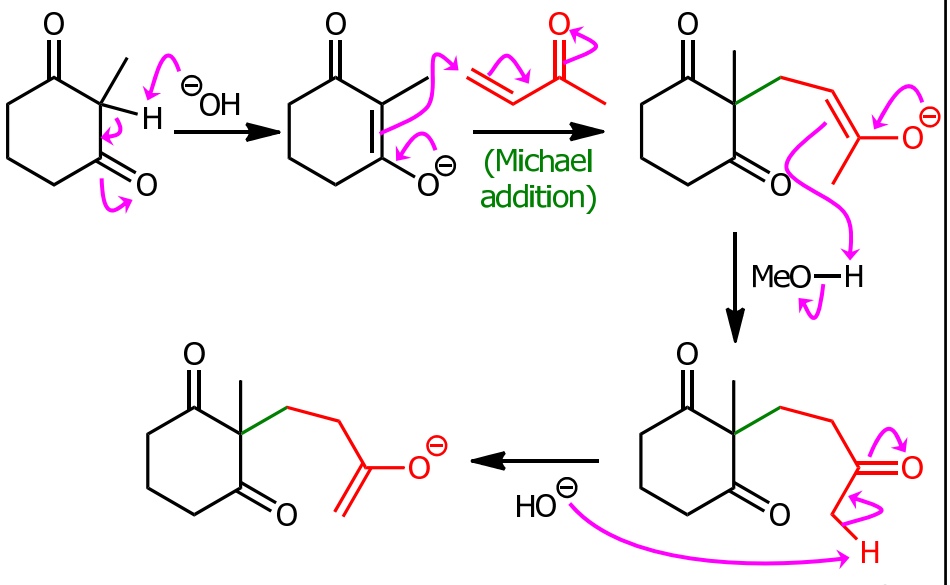
present commu... ...itherto been realised in the ...

Robert Robinson R. B. Woodward

Methyl Vinyl Ketone

Mc Bride, Chem 125

Mechanism



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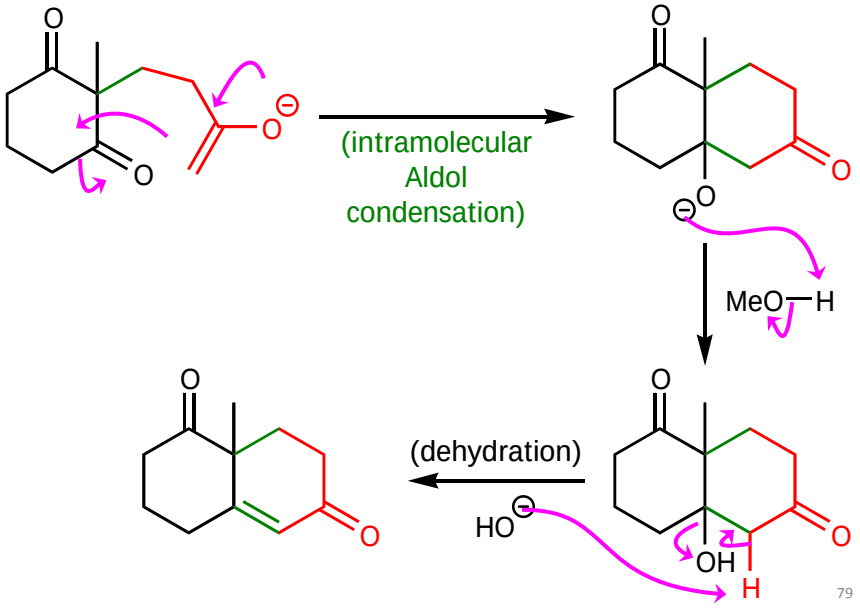
Intramolecular Robinson Annulation



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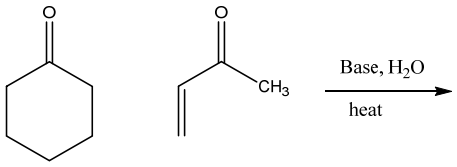
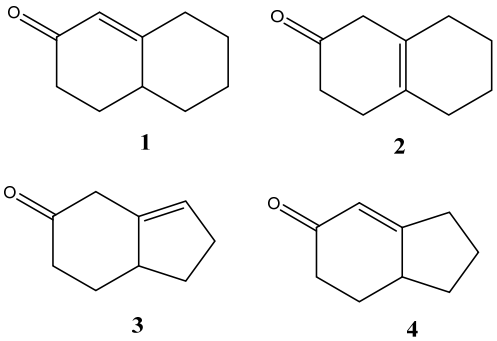


?

(A) 1
(B) 2
(C) 3
(D) 4



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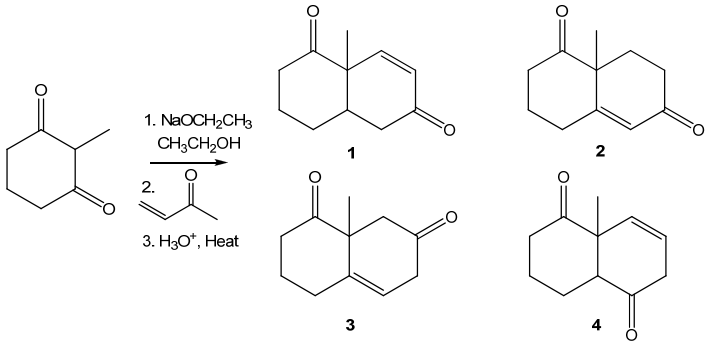
In Class Practice: What is the major organic product obtained from the following reaction?

?



(A) 1
(B) 2
(C) 3
(D) 4

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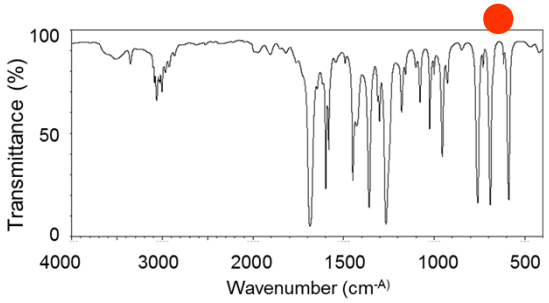
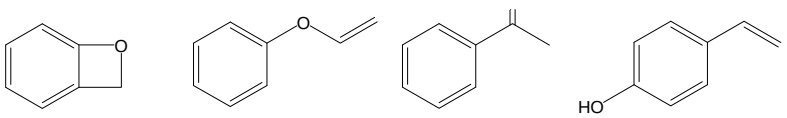
In Class Practice: Which of the following structures is consistent with the data provided?

?

Strong Signal 1700 cm^{-1}

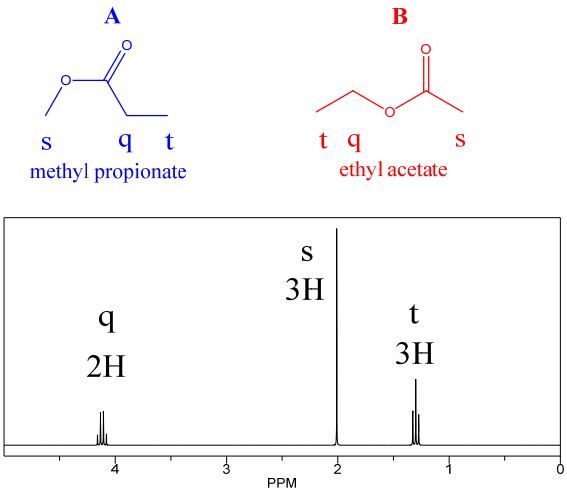
C_8H_8O





A B C D

Which structure corresponds to the proton NMR below?



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Summary of Important Reactions

1. Claisen Condensations
2. Crossed Claisen Condensations
3. Aldol Reaction
4. Directed Aldol Reaction via Lithium Enolates
5. Conjugate Addition
6. Mannich Reaction

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END OF LECTURE

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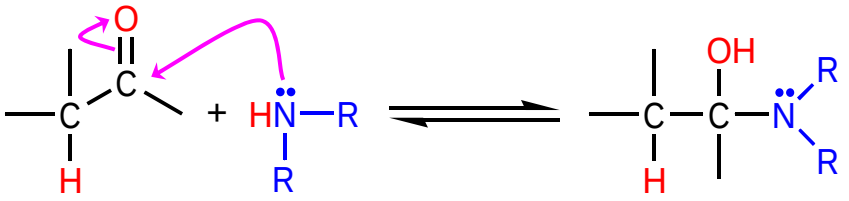
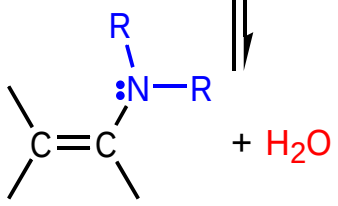
Stork Enamine Reactions: Synthesis of Enamines



Aldehyde or ketone

2^{o} Amine



Enamine

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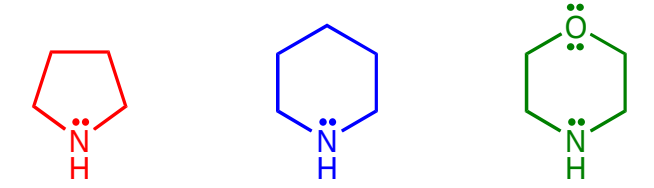
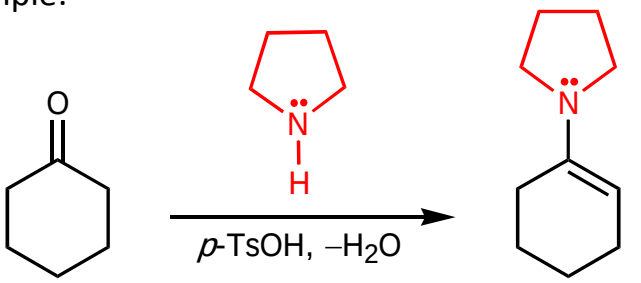
Stork Enamine Reactions:

- Secondary amines are most commonly used.



- Example:



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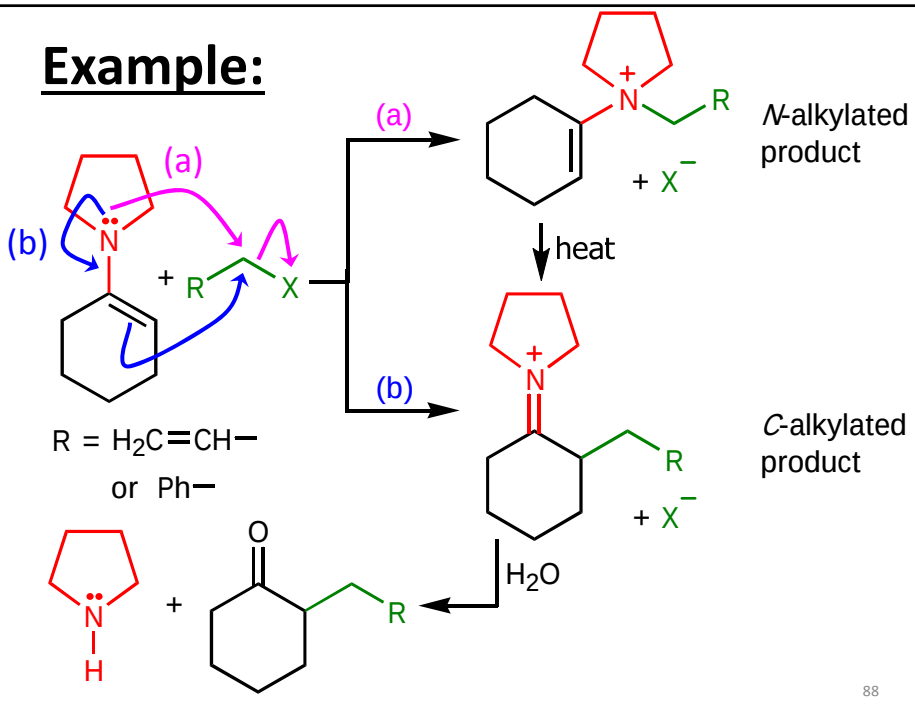
Example:



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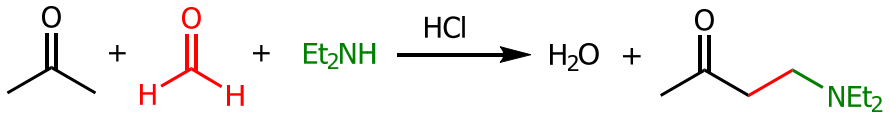
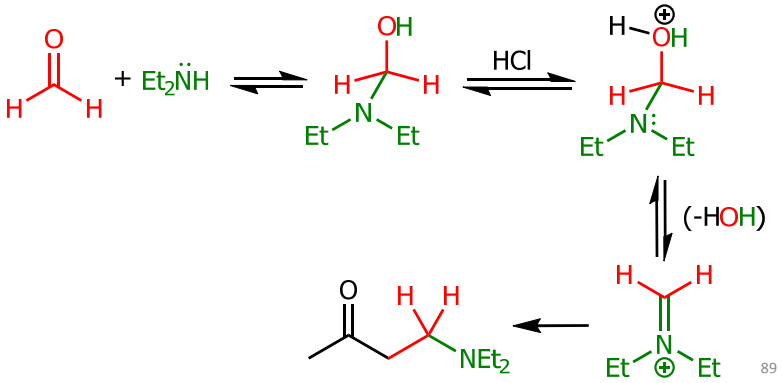
The Mannich Reaction



- Mechanism



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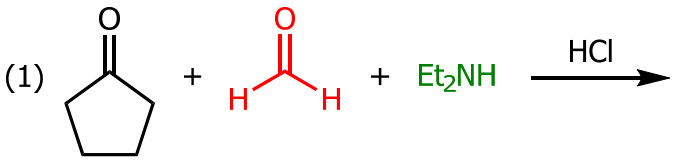
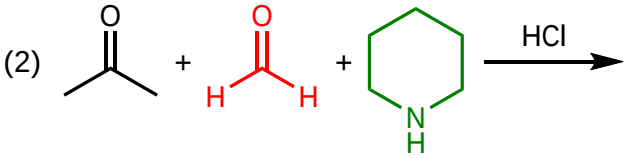
In Class Practice: Write the product from the reactions below.

?





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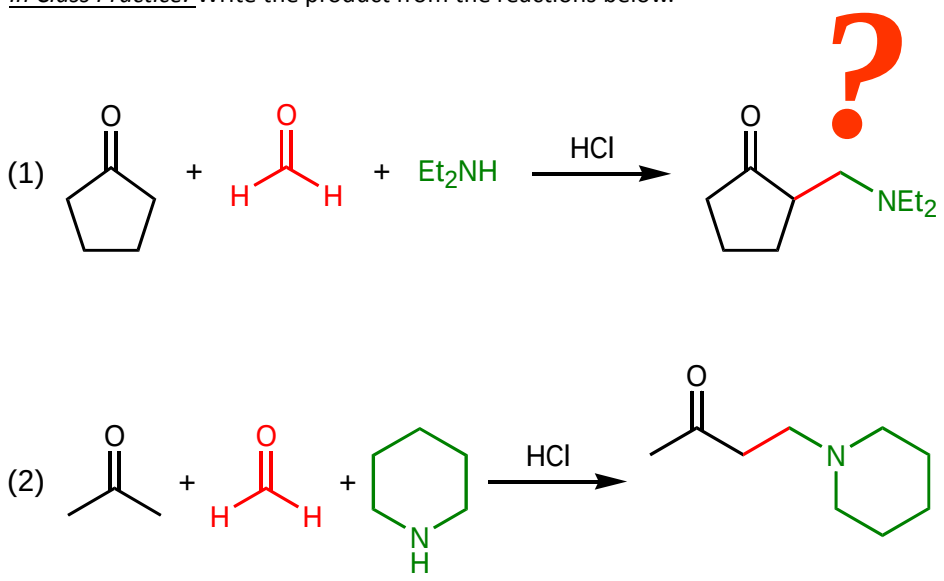
In Class Practice: Write the product from the reactions below.



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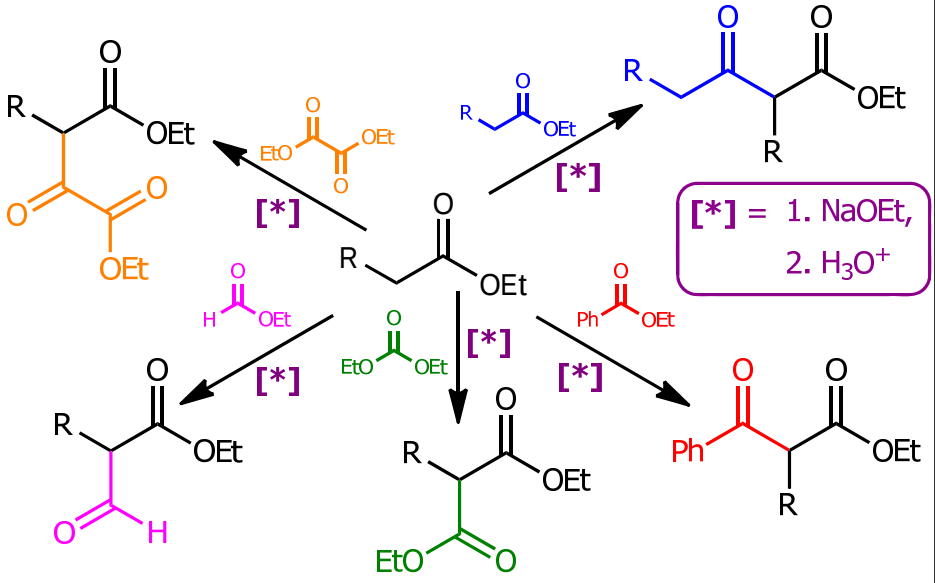
Claisen Condensations



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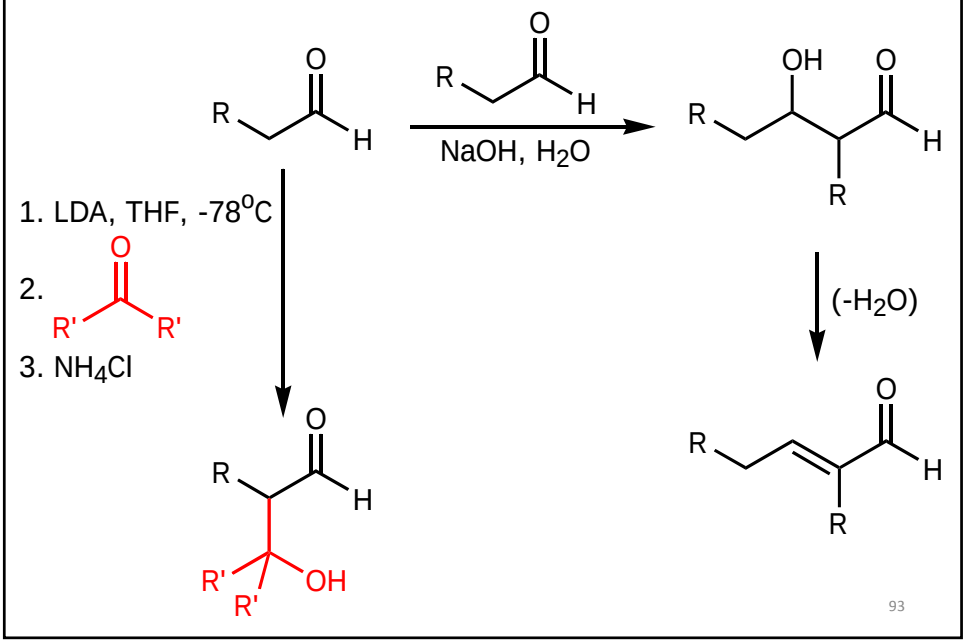
Aldol Condensations



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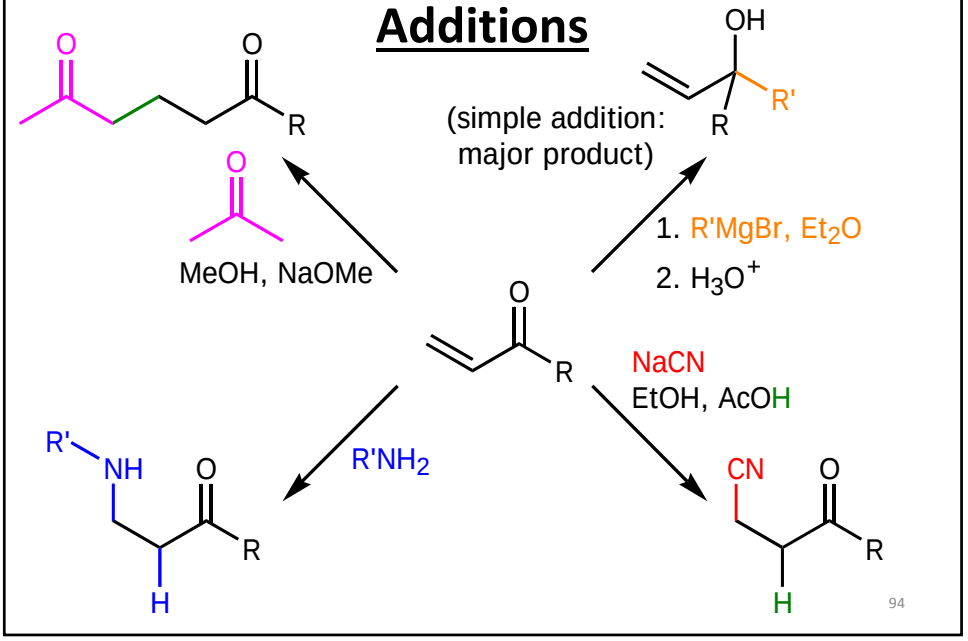
Simple & Conjugate (Michael) Additions



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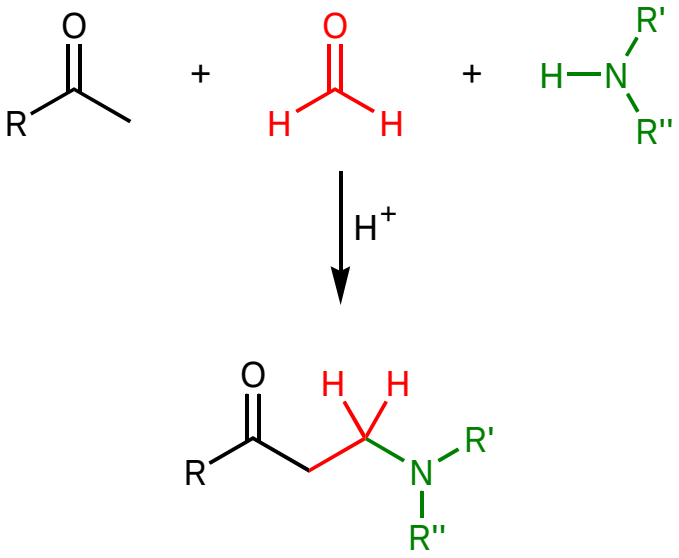
Mannich Reaction



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