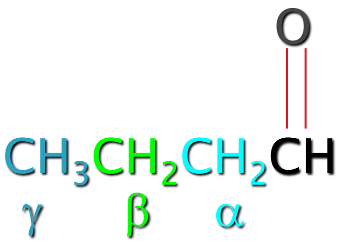
Enolates and Carbanion

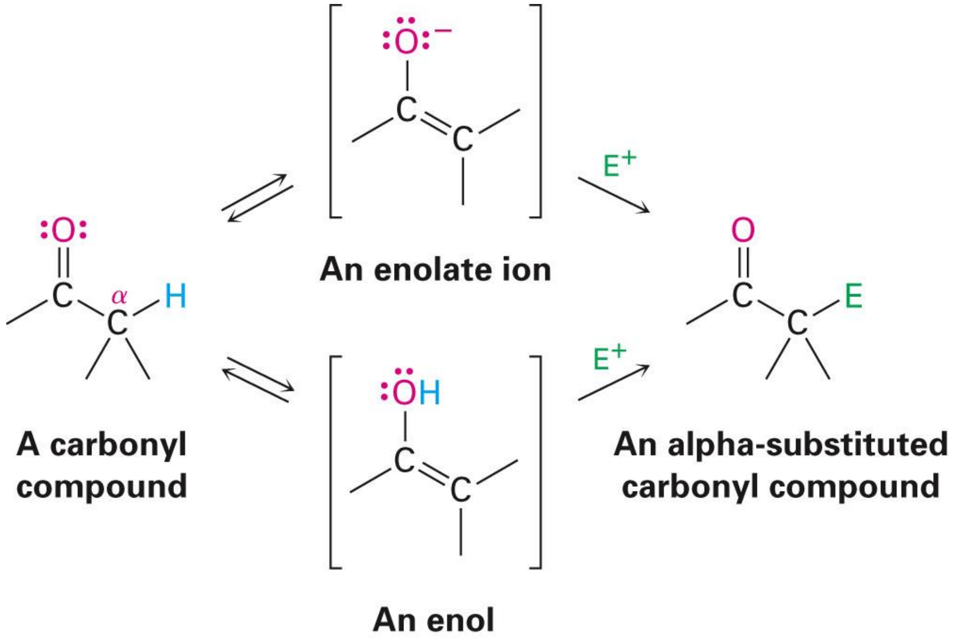
Terminology



$$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H$$

- The reference atom is the carbonyl carbon.
- Other carbons are designated α, β, γ, etc. on the basis of their position with respect to the carbonyl carbon.
- Hydrogens take the same Greek letter as the carbon to which they are attached.

α–Substitution and Carbonyl Condensation Reactions

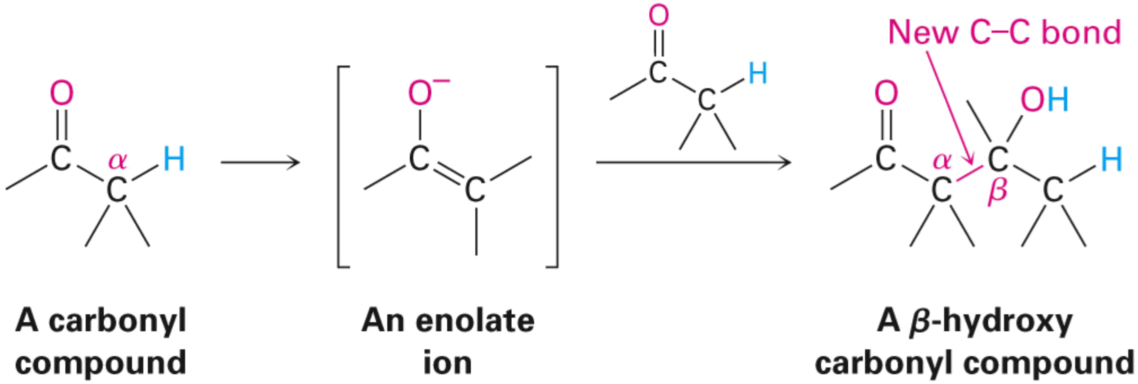


A carbonyl compound

An enolate ion

An enol

An alpha-substituted carbonyl compound



A carbonyl compound

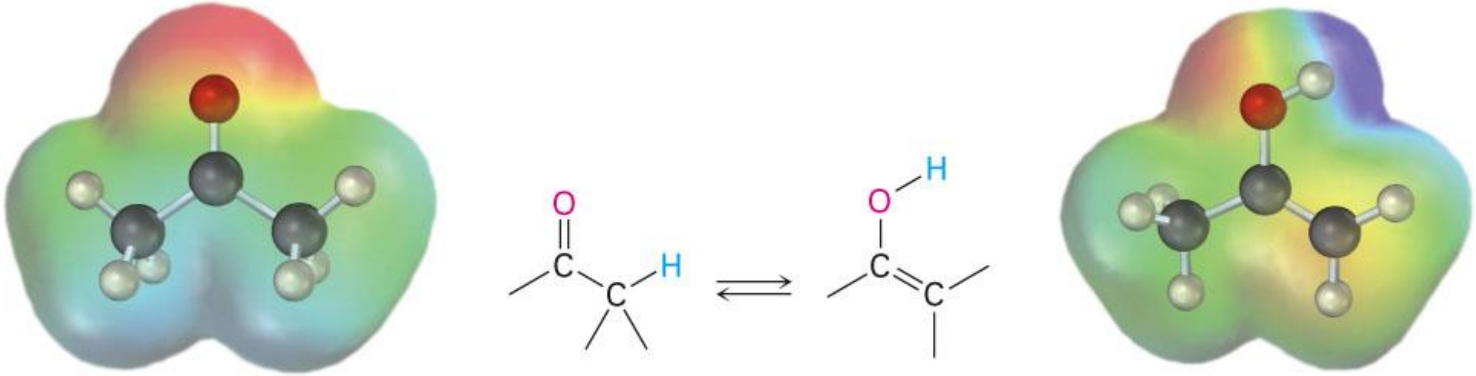
An enolate ion

A β-hydroxy carbonyl compound

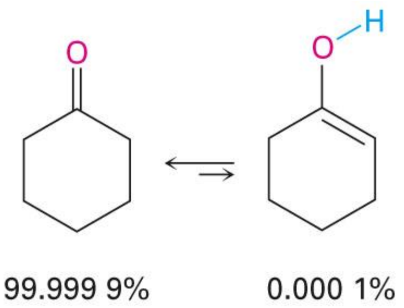
Keto–Enol Tautomerism

Carbonyl compounds with α–hydrogens rapidly equilibrate with corresponding **enol** (*ene* + alcohol)

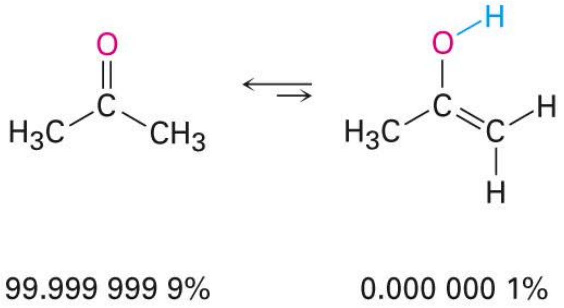
- Interconversion known as *keto–enol* tautomerism
  - Greek *tauto*, meaning “the same,” and *meros*, meaning “part”
- Individual isomers called **tautomers**



Keto tautomer **Enol tautomer**



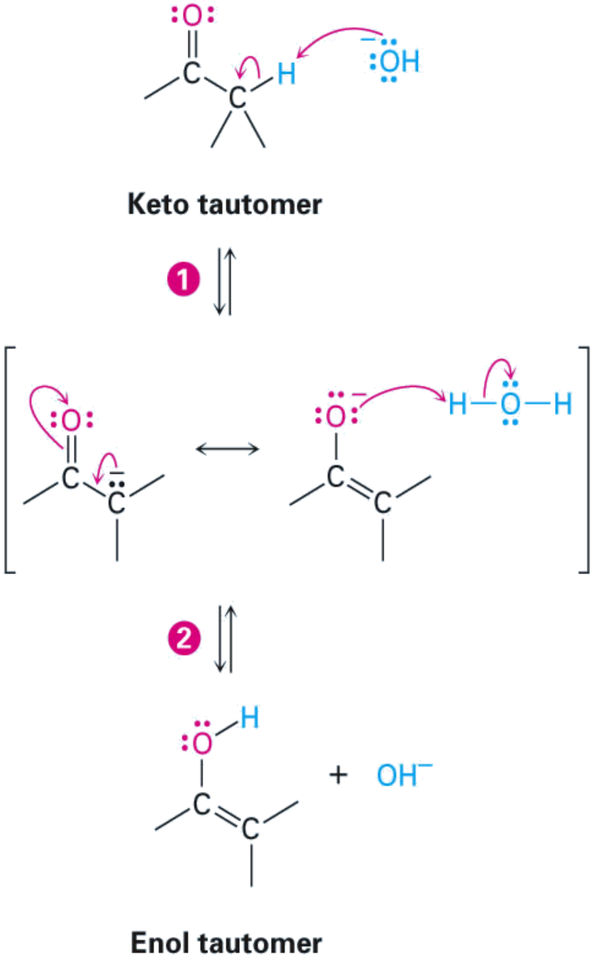
Cyclohexanone



Acetone

Mechanism of base-catalyzed enol formation

- The intermediate enolate ion, a resonance hybrid of two forms, can be protonated either on carbon to generate the starting keto tautomer or on oxygen to give an enol tautomer

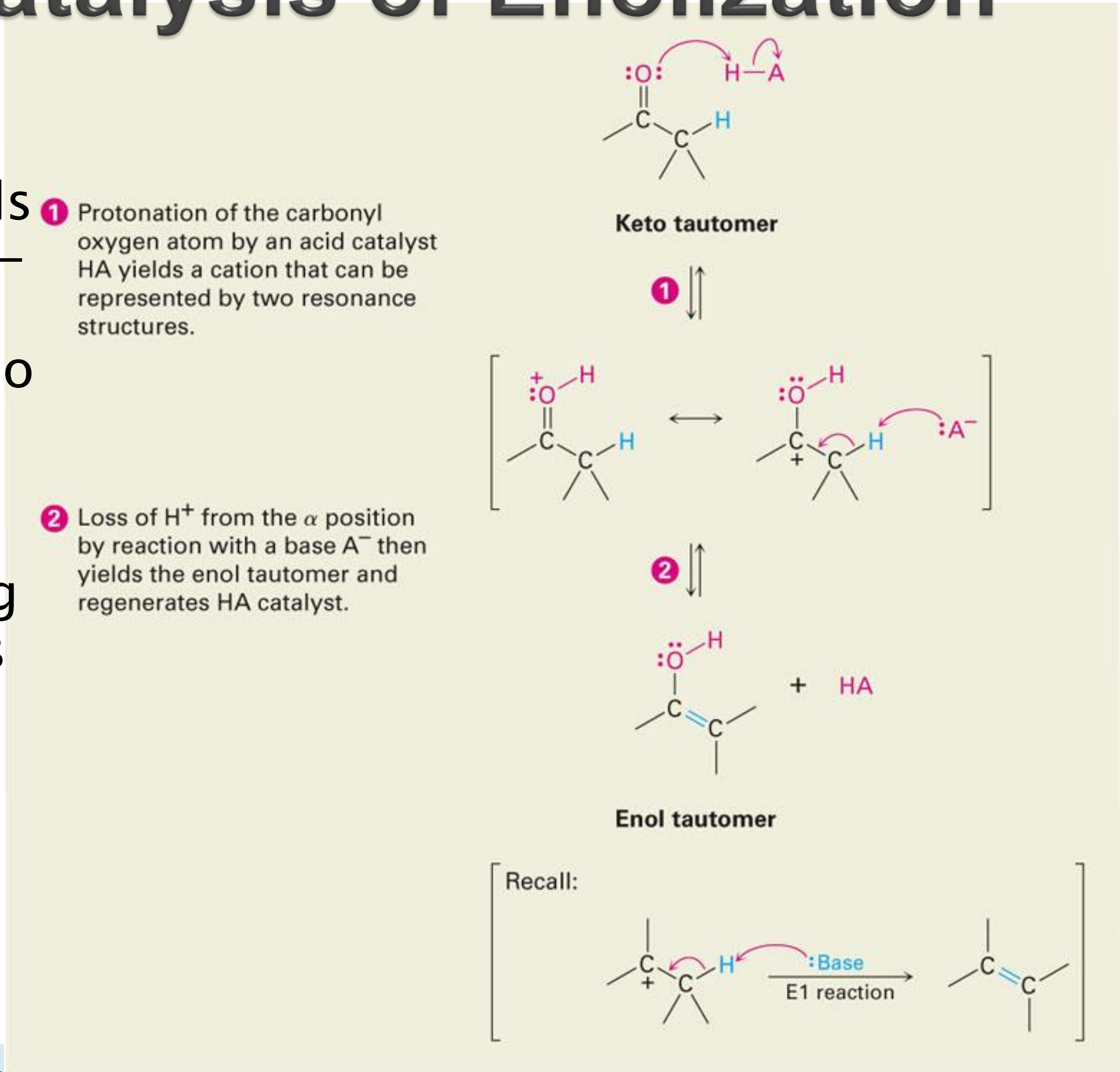


❶ Base removes an acidic hydrogen from the α position of the carbonyl compound, yielding an enolate anion that has two resonance structures.

❷ Protonation of the enolate anion on the oxygen atom yields an enol and regenerates the base catalyst.

Acid Catalysis of Enolization

- Brønsted acids catalyze keto-enol tautomerization by protonating the carbonyl and activating the α protons

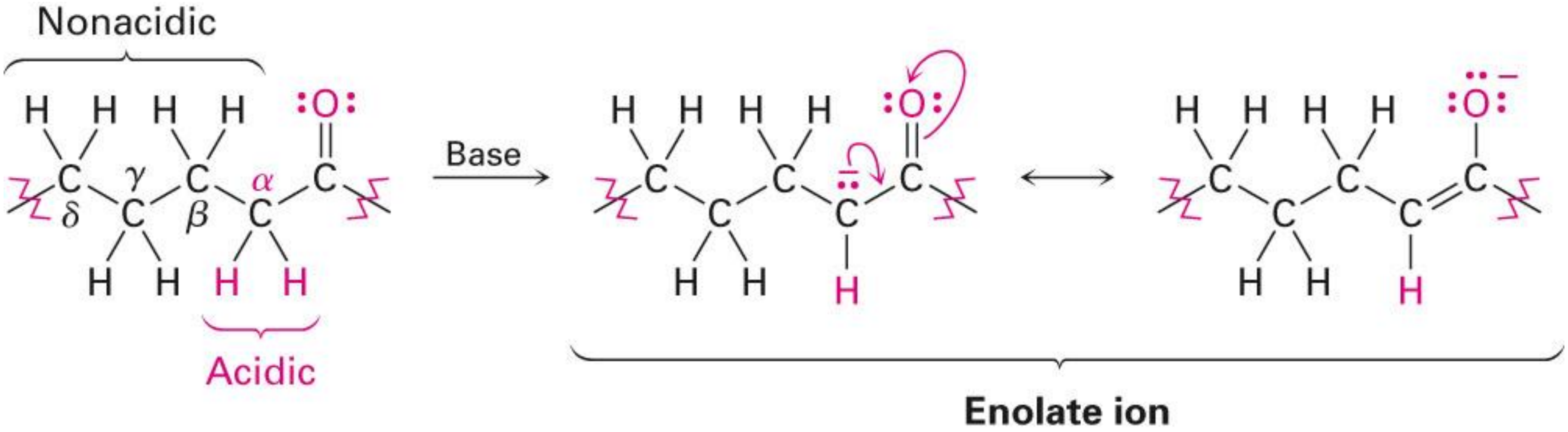


① Protonation of the carbonyl oxygen atom by an acid catalyst HA yields a cation that can be represented by two resonance structures.

② Loss of H^+ from the α position by reaction with a base A^- then yields the enol tautomer and regenerates HA catalyst.

Only α–hydrogens are acidic

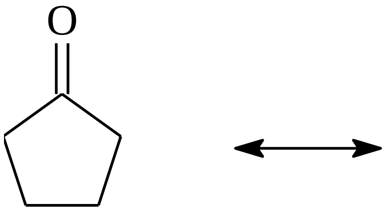
- α–Hydrogens are acidic because the enolate ion that results from deprotonation is resonance stabilized with the electronegative oxygen of the carbonyl
- β–, γ–, δ–Hydrogens (and so on) are not acidic because the ion that results from deprotonation is not resonance stabilized



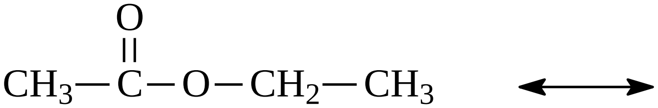
Learning Check:

- Name the following and draw structures for their enol tautomers :

A.

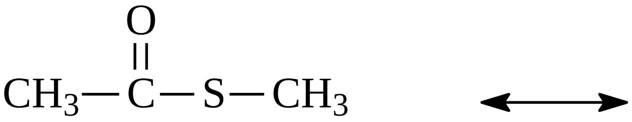


B.



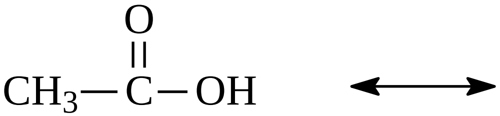
$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-O-CH_2-CH_3 \longleftrightarrow$

C.



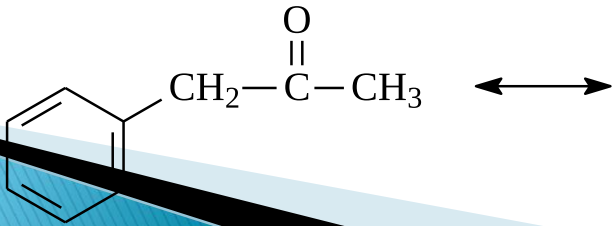
$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-S-CH_3 \longleftrightarrow$

D.



$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-OH \longleftrightarrow$

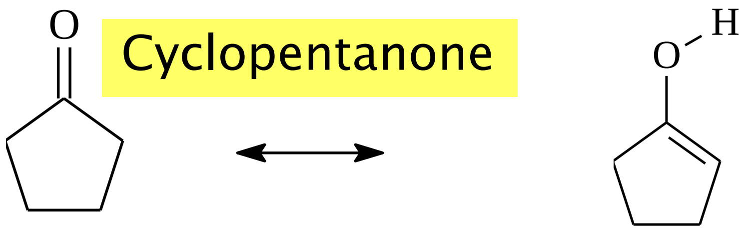
E.



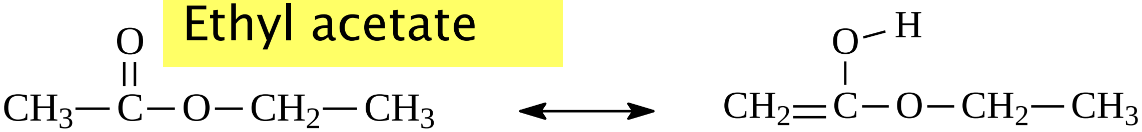
Solution:

- Name the following and draw structures for their enol tautomers :

A. Cyclopentanone

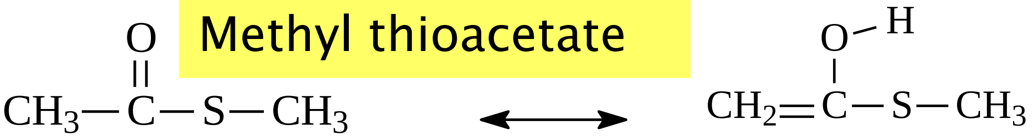


B. Ethyl acetate



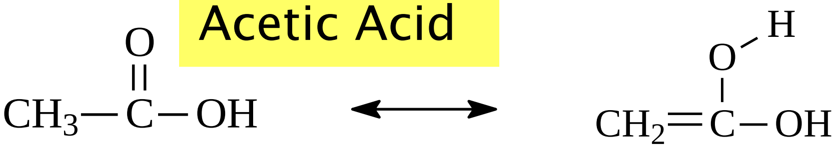
$$CH_3-\overset{\overset{O}{\|}}{C}-O-CH_2-CH_3 \longleftrightarrow CH_2=\overset{\overset{O-H}{|}}{C}-O-CH_2-CH_3$$

C. Methyl thioacetate



$$CH_3-\overset{\overset{O}{\|}}{C}-S-CH_3 \longleftrightarrow CH_2=\overset{\overset{O-H}{|}}{C}-S-CH_3$$

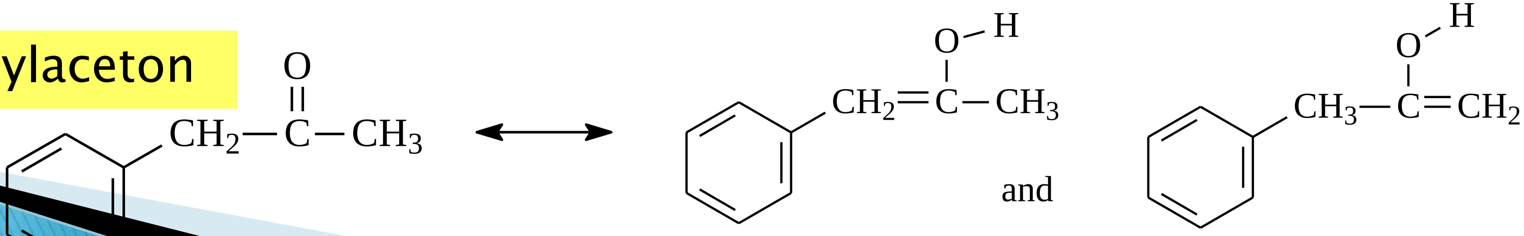
D. Acetic Acid



$$CH_3-\overset{\overset{O}{\|}}{C}-OH \longleftrightarrow CH_2=\overset{\overset{O-H}{|}}{C}-OH$$

Phenylacetone

E.

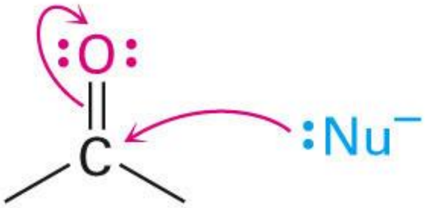


and

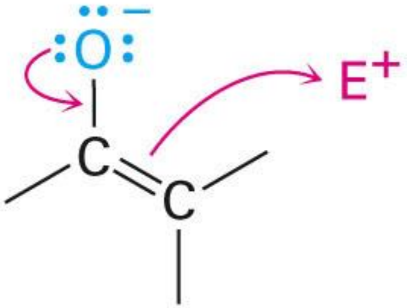
(major form: more resonance)

Condensation Reactions

- Carbonyl compounds are *both* the electrophile and nucleophile in carbonyl condensation reactions



Electrophilic carbonyl group reacts with nucleophiles.

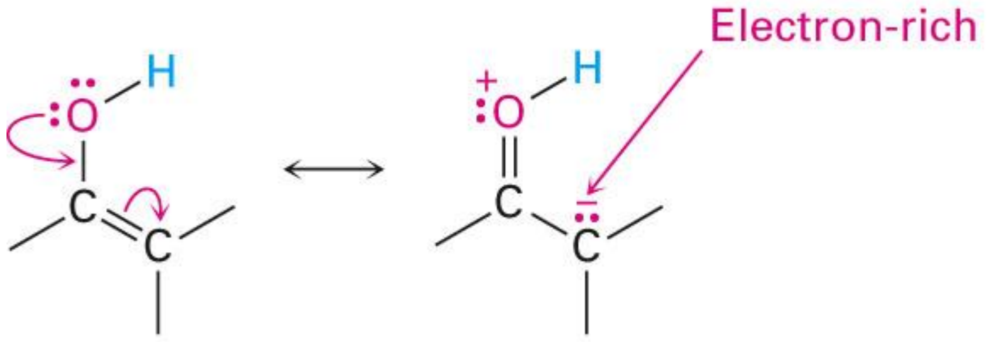


Nucleophilic enolate ion reacts with electrophiles.

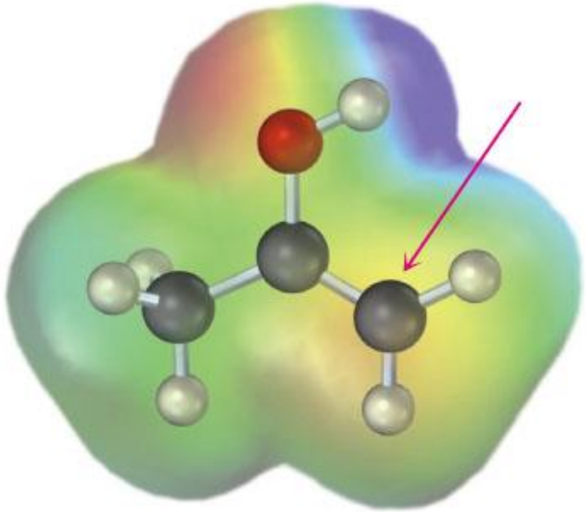
Reactivity of Enols: α–Substitution Reactions

Enols are nucleophiles that react with electrophiles

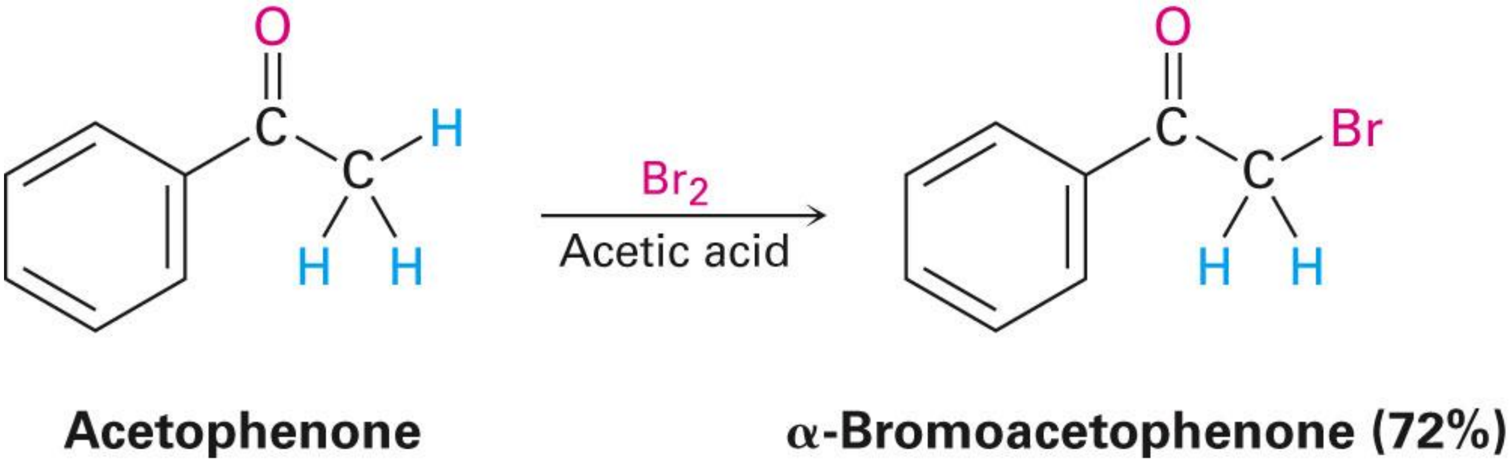
- There is a substantial build-up of electron density on the α carbon of the enol



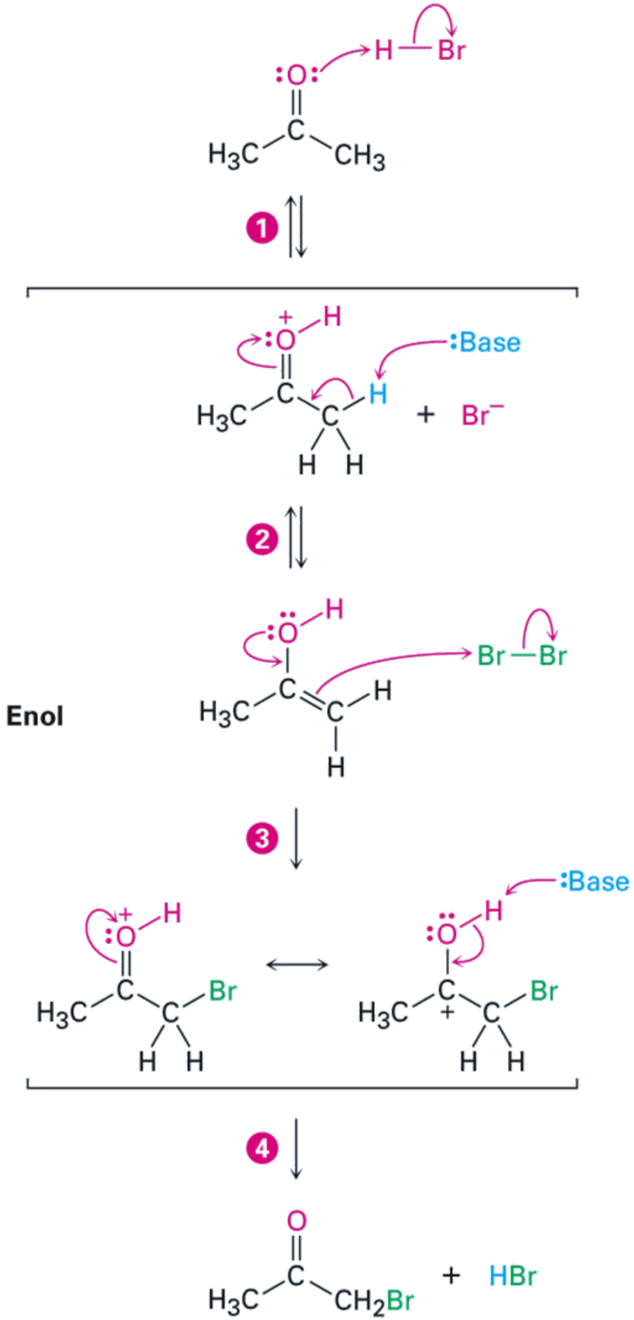
Enol tautomer



- Common α–substitution reaction in the laboratory is halogenation of aldehydes and ketones at their α positions by reaction with Cl_2, Br_2, or I_2 in acidic solution



Mechanism of acid-catalyzed bromination of acetone



① The carbonyl oxygen atom is protonated by acid catalyst.

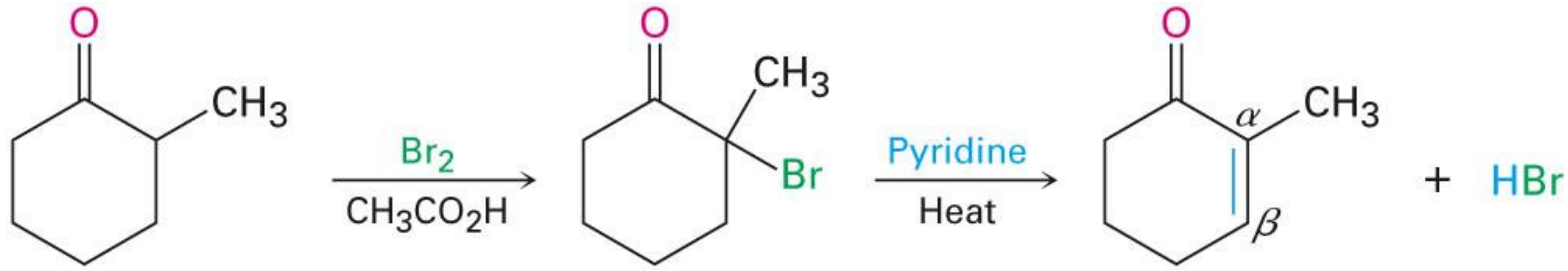
② Loss of an acidic proton from the alpha carbon takes place in the normal way to yield an enol intermediate.

③ An electron pair from the enol attacks bromine, giving an intermediate cation that is stabilized by resonance between two forms.

④ Loss of the –OH proton then gives the alpha-halogenated product and generates more acid catalyst.

α–Bromoketones are dehydrobrominated by base to yield α,β–unsaturated ketones

- E2 reaction mechanism
- 2-Methylcyclohexanone gives 2-methylcyclohex-2-enone on heating in pyridine



2-Methylcyclohexanone **2-Bromo-2-methylcyclohexanone** **2-Methylcyclohex-2-enone (63%)**

Alpha Bromination of Carboxylic Acids

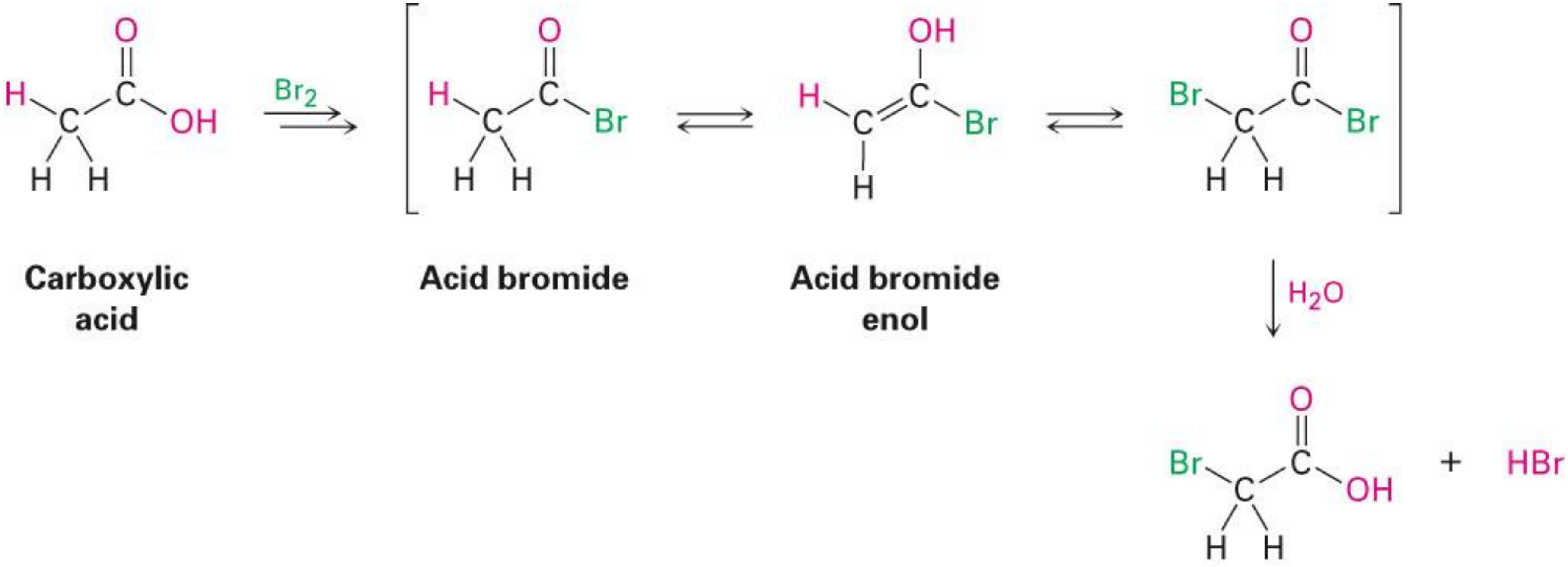
Carboxylic acids can be α brominated by a mixture of Br_2 and PBr_3 in the Hell–Volhard–Zelinskii (HVZ) reaction

$$CH_3CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow[2.\ H_2O]{1.\ Br_2,\ PBr_3} CH_3CH_2CH_2CH_2CH_2\underset{Br}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}OH$$

Heptanoic acid

2-Bromoheptanoic acid (90%)

- Mechanism involves α substitution of an *acid bromide enol*



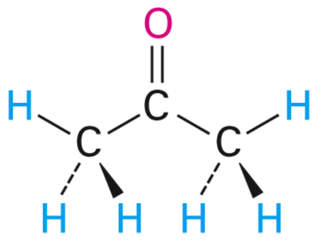
Carboxylic acid

Acid bromide

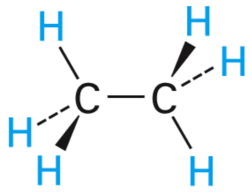
Acid bromide enol

Acidity of α Hydrogen Atoms: Enolate Ion Formation

Presence of neighboring carbonyl group increases the acidity of the ketone over the alkane by a factor of 10^{40}



Acetone
(pK_a = 19.3)

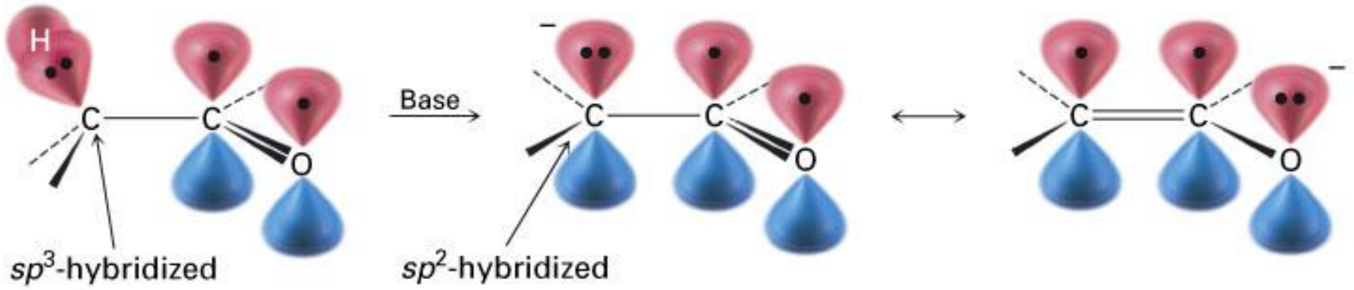


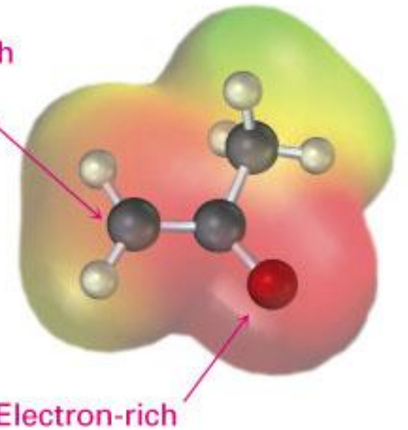
Ethane
(p$K_a \approx 60$)

Proton abstraction from carbonyl occurs when the α C–H bond is oriented parallel to the *p* orbitals of the carbonyl group

A carbon of the enolate ion has a *p* orbital that overlaps neighboring *p* orbitals of the carbonyl group

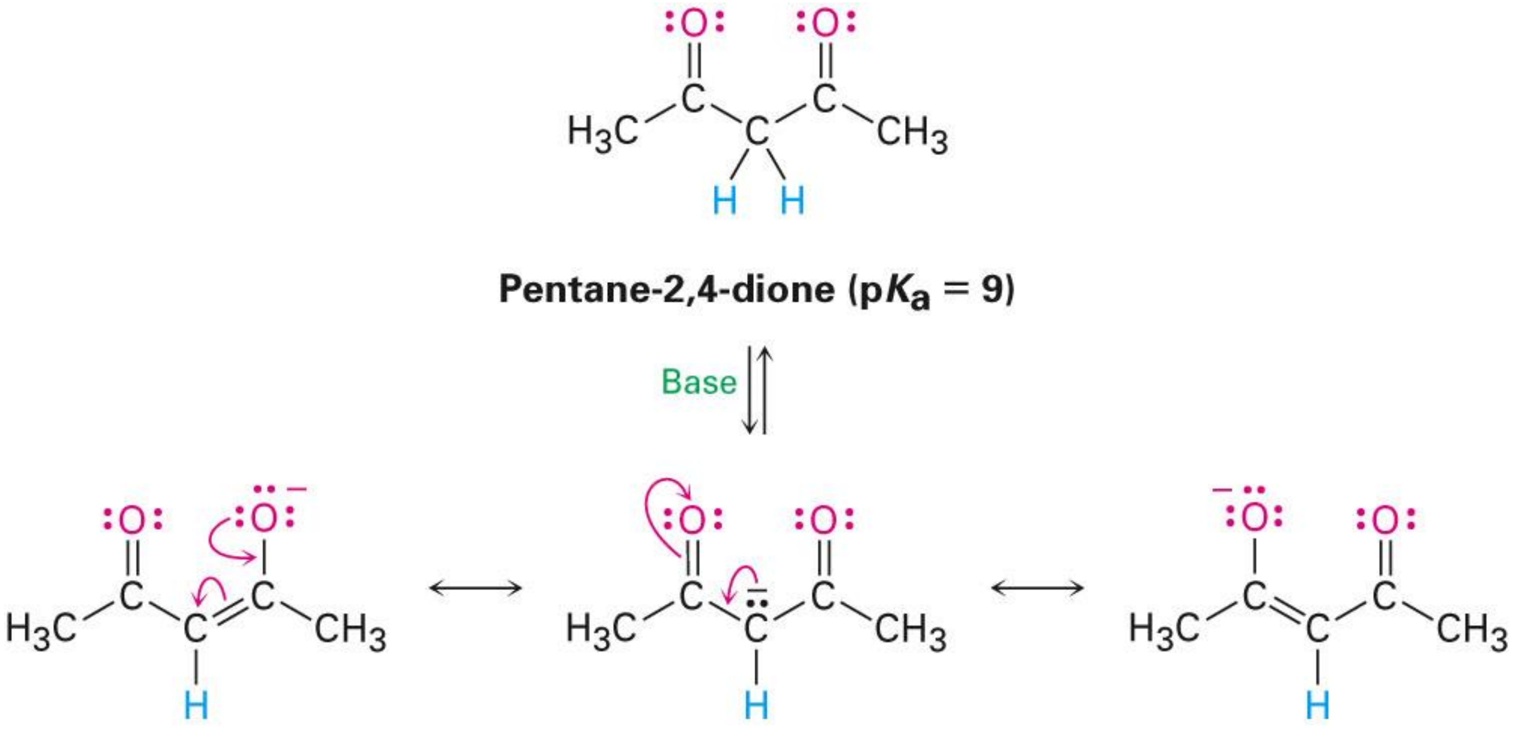
Negative charge shared with oxygen atom by resonance





A C–H bond flanked by two carbonyl groups is even more acidic

- Enolate ion is stabilized by delocalization of negative charge over both carbonyl groups
- Pentane-2,4-dione has three resonance forms



Acidity of α Hydrogen Atoms: Enolate Ion Formation

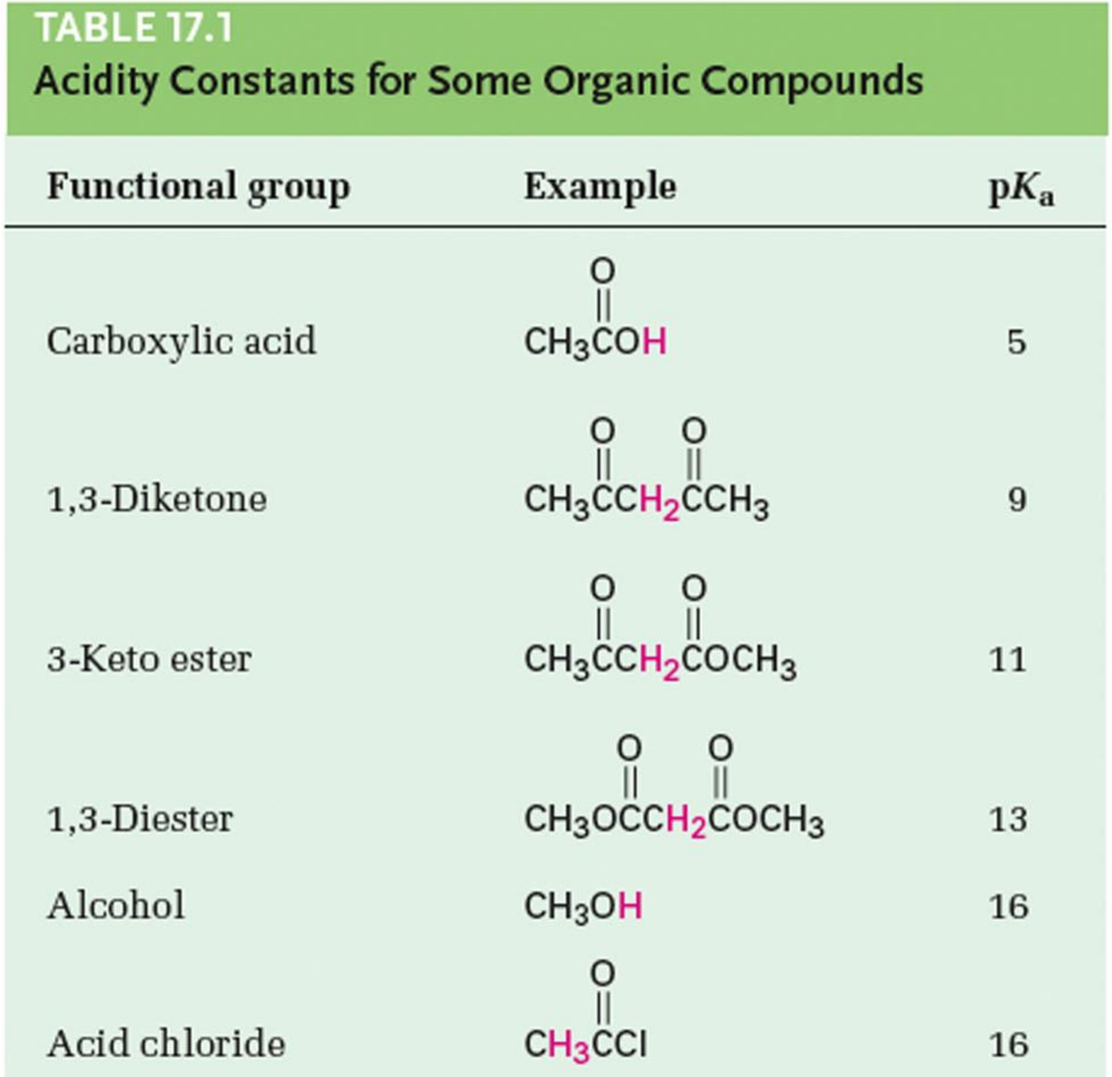


TABLE 17.1

Acidity Constants for Some Organic Compounds

Functional group	Example	pK_a
Carboxylic acid	$CH_3\overset{O}{\overset{\|}{C}}OH$	5
1,3-Diketone	$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$	9
3-Keto ester	$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_3$	11
1,3-Diester	$CH_3O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_3$	13
Alcohol	CH_3OH	16
Acid chloride	$CH_3\overset{O}{\overset{\|}{C}}Cl$	16

Acidity of α Hydrogen Atoms: Enolate Ion Formation

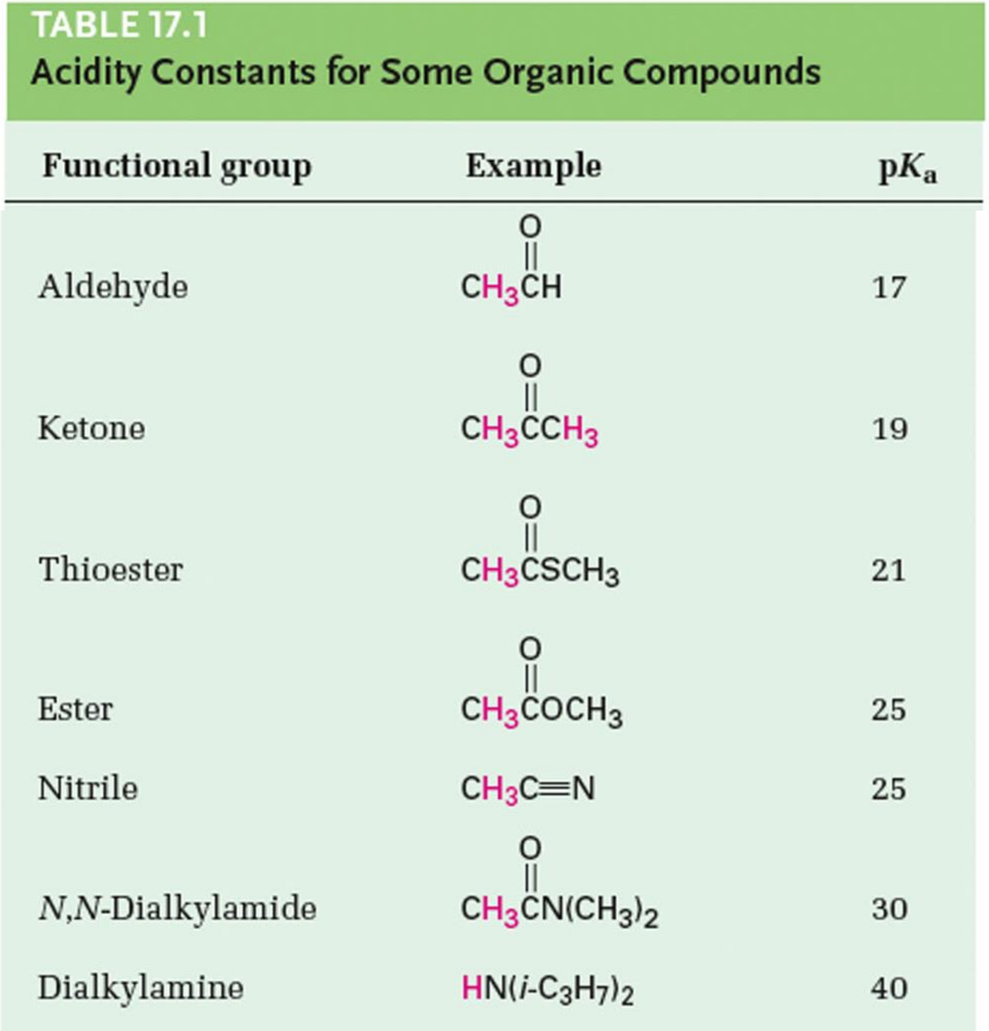


TABLE 17.1

Acidity Constants for Some Organic Compounds

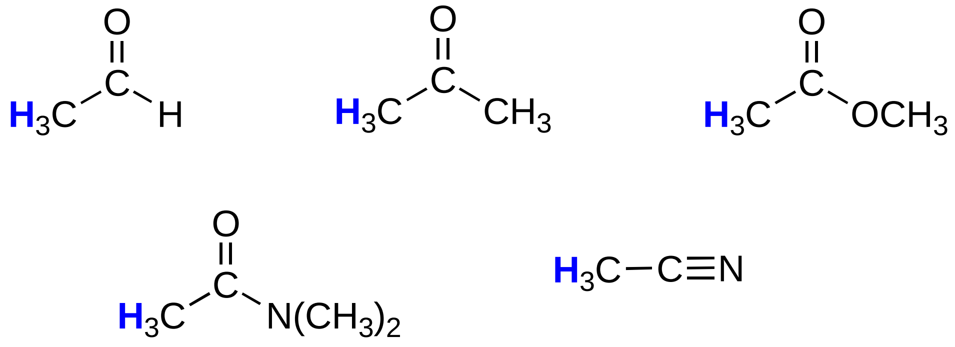
Functional group	Example	pK_a
Aldehyde	$CH_3\overset{O}{\overset{\|}{C}}H$	17
Ketone	$CH_3\overset{O}{\overset{\|}{C}}CH_3$	19
Thioester	$CH_3\overset{O}{\overset{\|}{C}}SCH_3$	21
Ester	$CH_3\overset{O}{\overset{\|}{C}}OCH_3$	25
Nitrile	$CH_3C{\equiv}N$	25
N,N-Dialkylamide	$CH_3\overset{O}{\overset{\|}{C}}N(CH_3)_2$	30
Dialkylamine	$HN(i\text{-}C_3H_7)_2$	40

Acidity of α Hydrogens and Their pK_a's

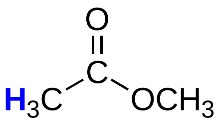
The α-protons of esters are less acidic that ketones and aldehydes.

Typical pK_a's of carbonyl compounds (α-protons):

aldehydes	17
ketones	19
esters	24
amides	30
nitriles	25

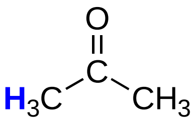


Acidity of 1,3-dicarbonyl compounds



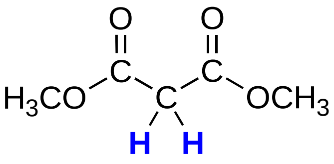
ester

pK_a= 24



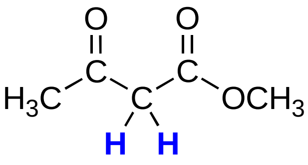
ketone

pK_a= 19



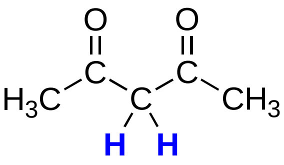
1,3-diester

pK_a= 13



1,3-keto ester

pK_a= 11

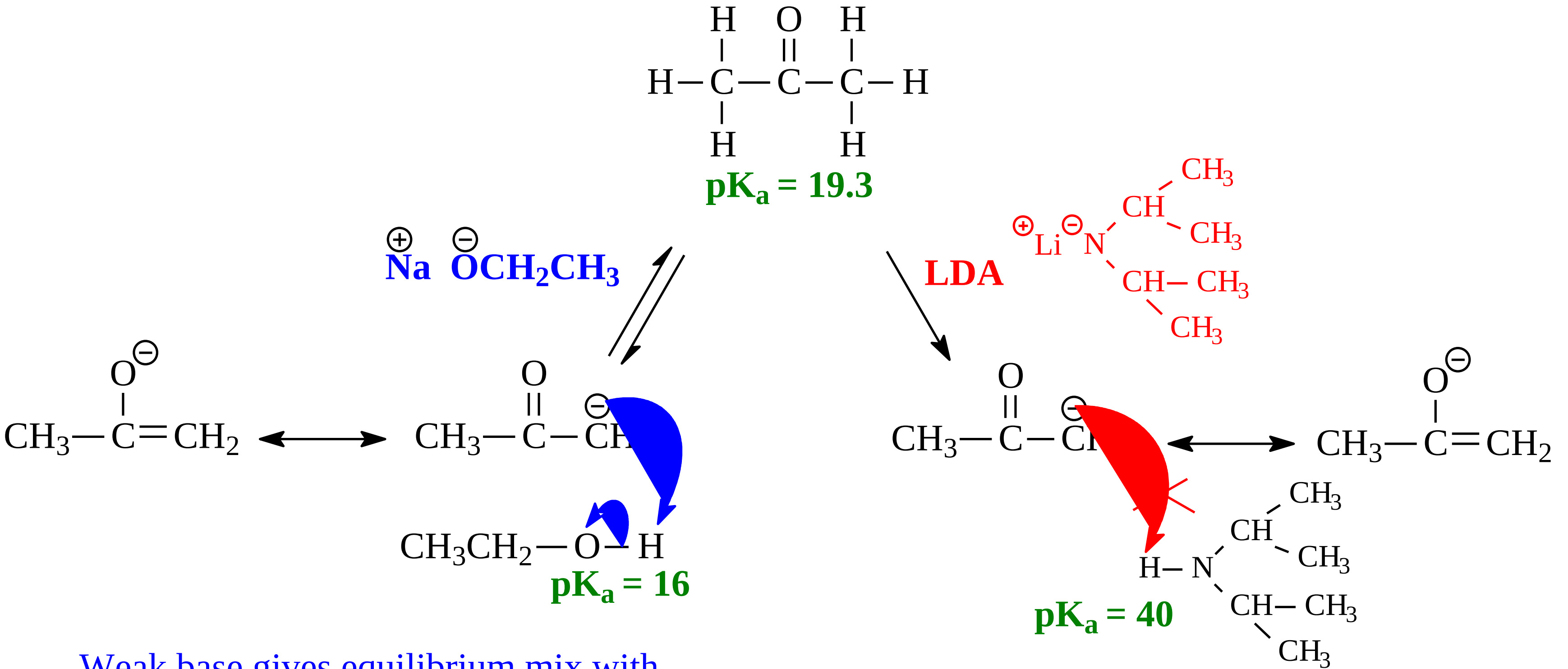


1,3-diketone

pK_a= 9

Reagents for Enolate Formation

- Ketones are weaker acids than the OH of alcohols so a more powerful base than an alkoxide is needed to form the enolate



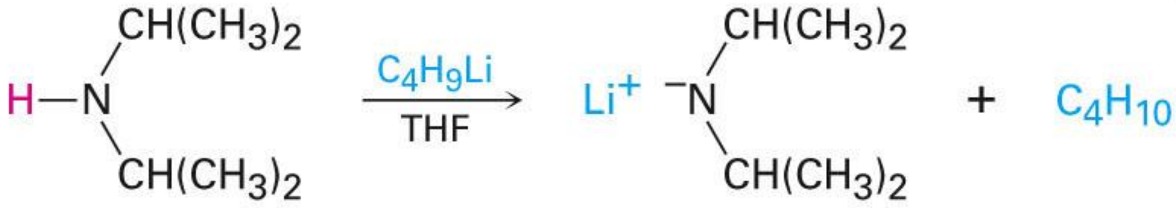
Weak base gives equilibrium mix with only about 0.1% enolization

Strong base gives 100% (complete) enolization

Sodium hydride (NaH) or Lithium diisopropylamide [LiN(*i*–$C_3H_7)_2$] are strong enough to form the enolate

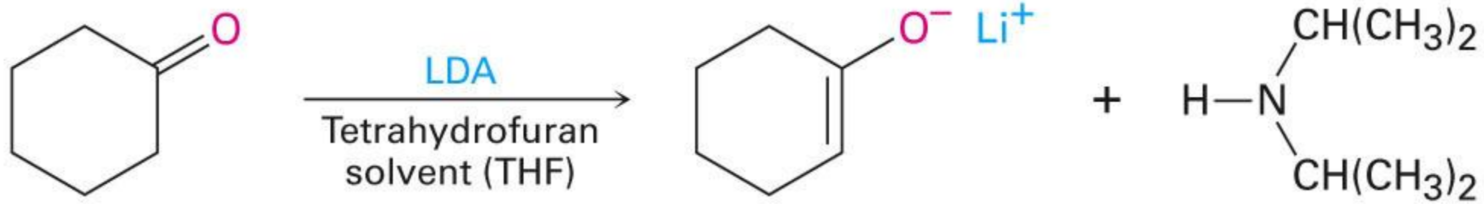
Lithium Diisopropylamide (LDA)

- LDA is from butyllithium (BuLi) & diisopropylamine (pK_a ≈ 40)
- Soluble in organic solvents and effective at low temperature with many compounds
- Not nucleophilic



Diisopropylamine

Lithium diisopropylamide (LDA)



Cyclohexanone

Cyclohexanone enolate ion

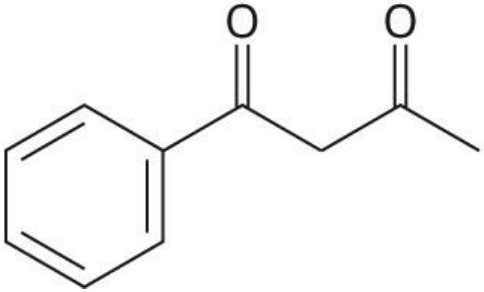
Diisopropylamine

Worked Example

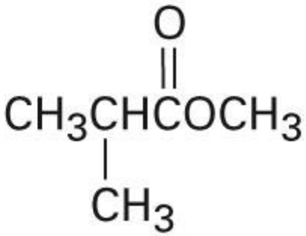
Identifying Acidic Hydrogens in a Compound

Identify the most acidic hydrogens in each of the following compounds, and rank the compounds in order of increasing acidity:

(a)

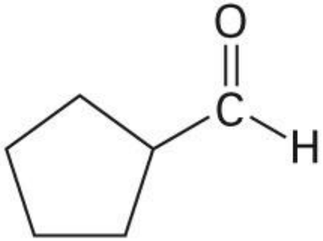


(b)



$CH_3\underset{CH_3}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}OCH_3$

(c)



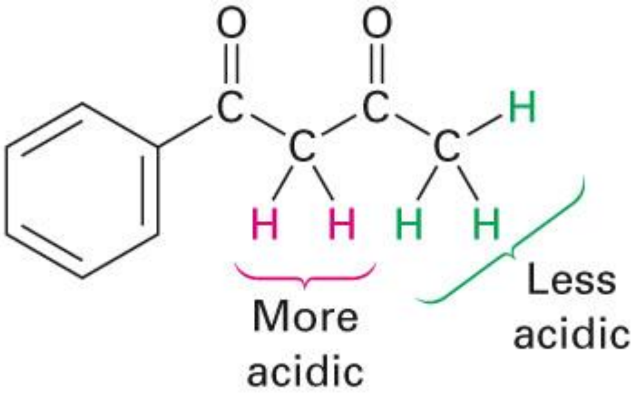
Worked Example

Identifying Acidic Hydrogens in a Compound

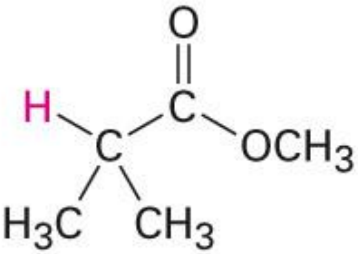
Solution

- The acidity order is (a) > (c) > (b). Acidic hydrogens are shown in red:

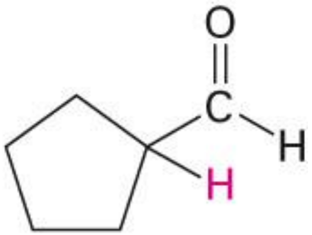
(a)



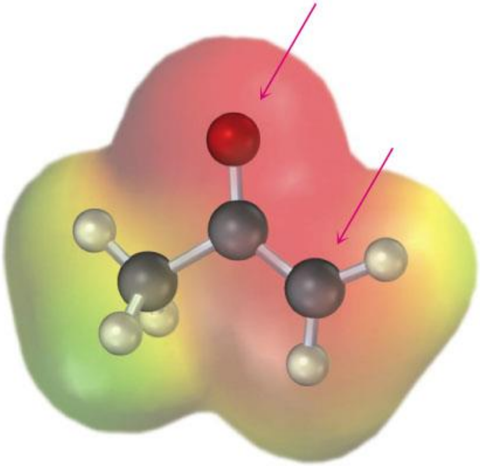
(b)

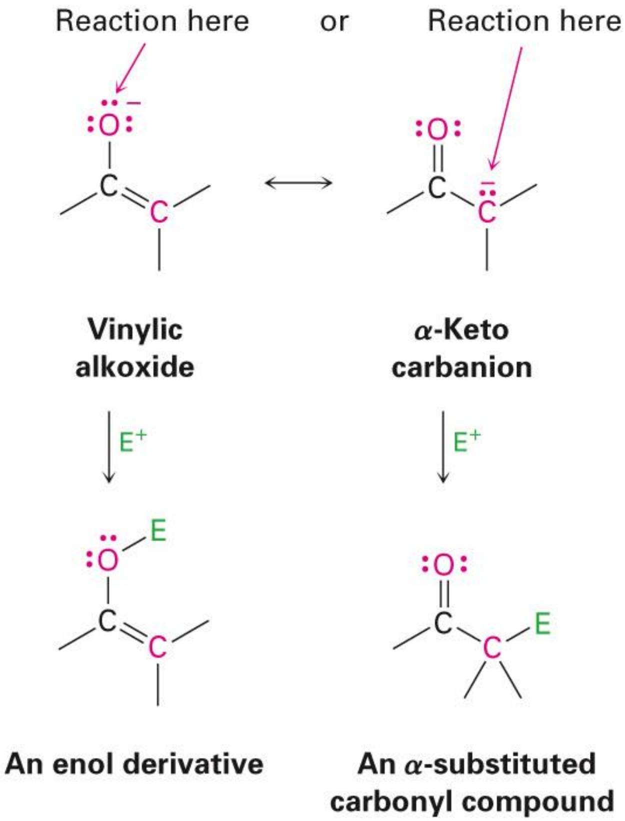


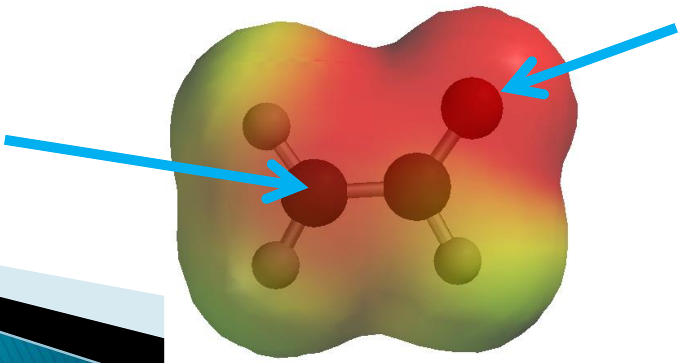
(c)



Alkylation of Enolate Ions





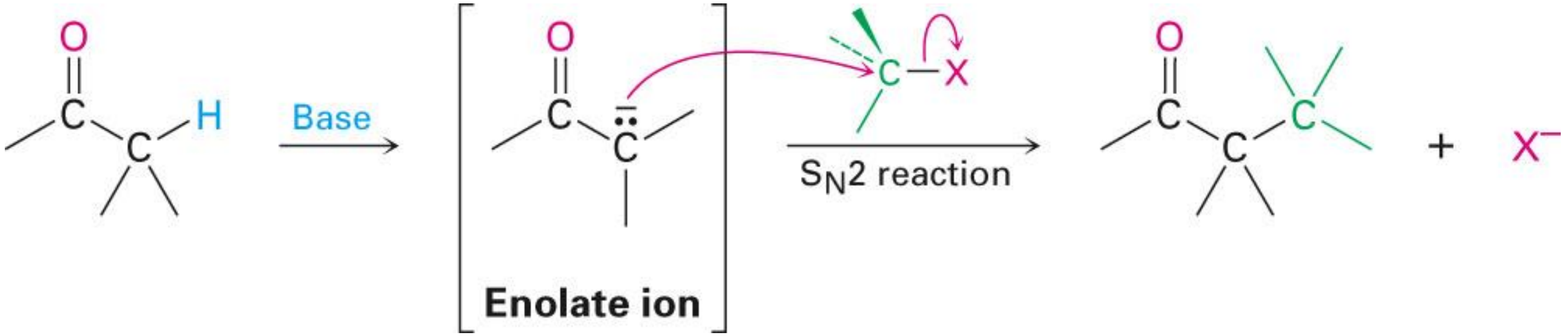


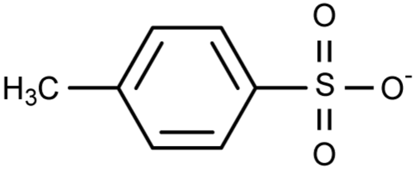
oxygen

Reactive carbon

Enolate ions undergo *alkylation* by treatment with an alkyl halide or tosylate

- Nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction
- Leaving group displaced by backside attack
- Alkyl group R should be **primary or methyl** and preferably allylic or benzylic
- Secondary alkyl halides react poorly and tertiary are unreactive due to competing E2 reaction



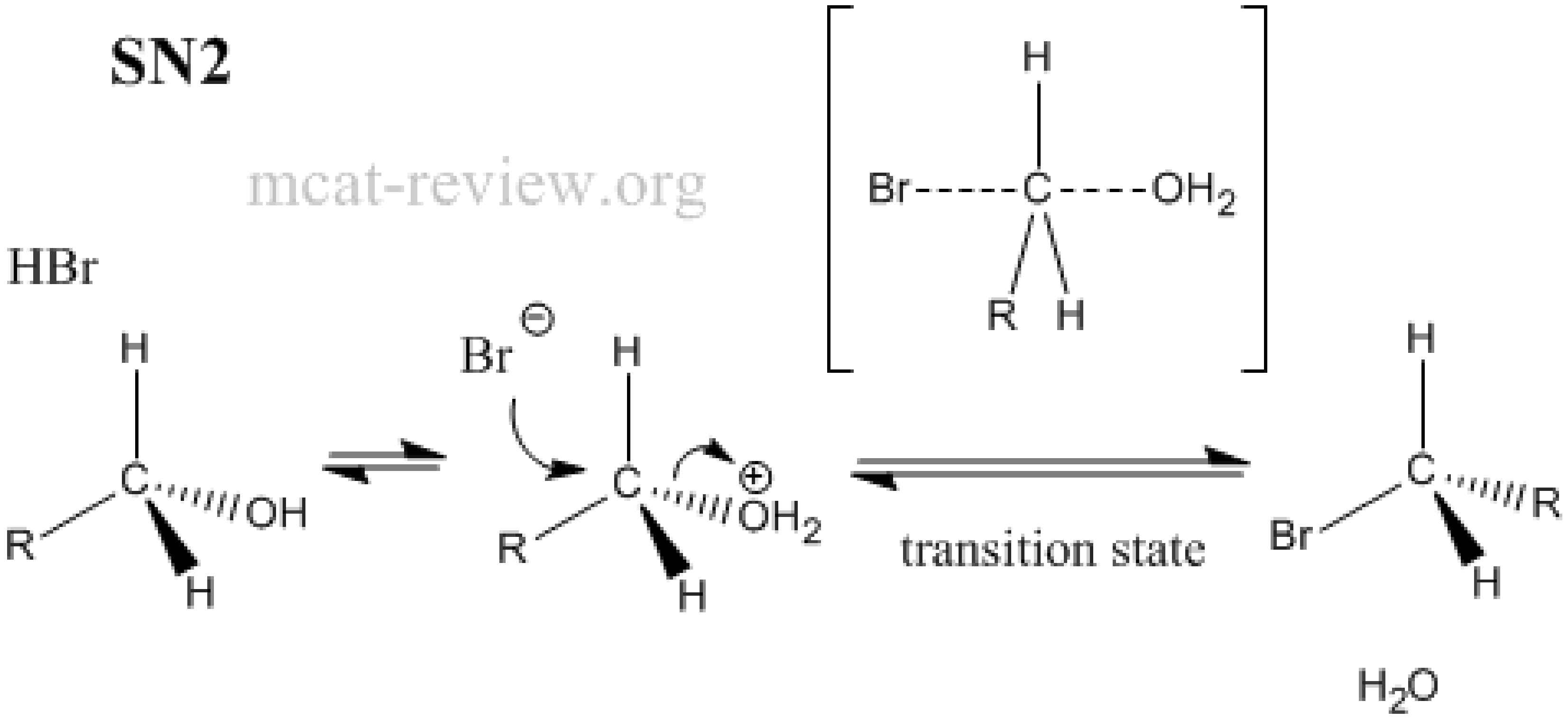


Ts

$R-X$

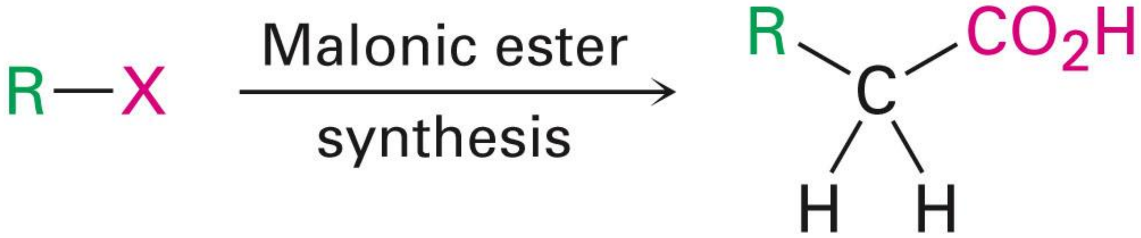
–X: Tosylate > –I > –Br > –Cl

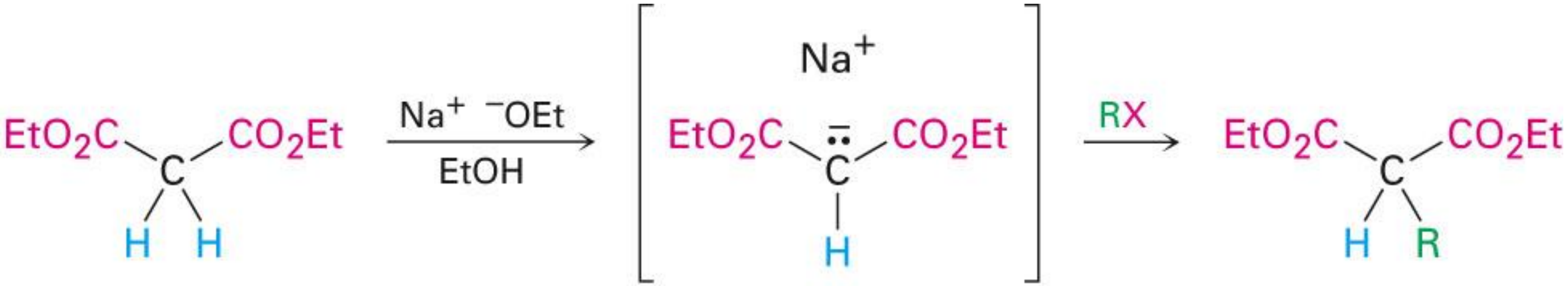
R–: Allylic ≈ Benzylic > H_3C– > RCH_2–


SN2
mcat-review.org
HBr
H
C
R
OH
H
Br⊖
H
C
R
⊕
OH₂
H
H
Br
C
OH₂
R
H
transition state
H
Br
C
R
H
H₂O

The Malonic Ester Synthesis

- Preparation of carboxylic acids from alkyl halides while lengthening the carbon chain by two atoms
- Easily converted to enolate ion by sodium ethoxide in ethanol.





Diethyl propanedioate (malonic ester)

Sodio malonic ester

An alkylated malonic ester

Formation of Enolate and Alkylation

- Malonic ester (diethyl propanedioate) is easily converted into its enolate ion by reaction with sodium ethoxide in ethanol

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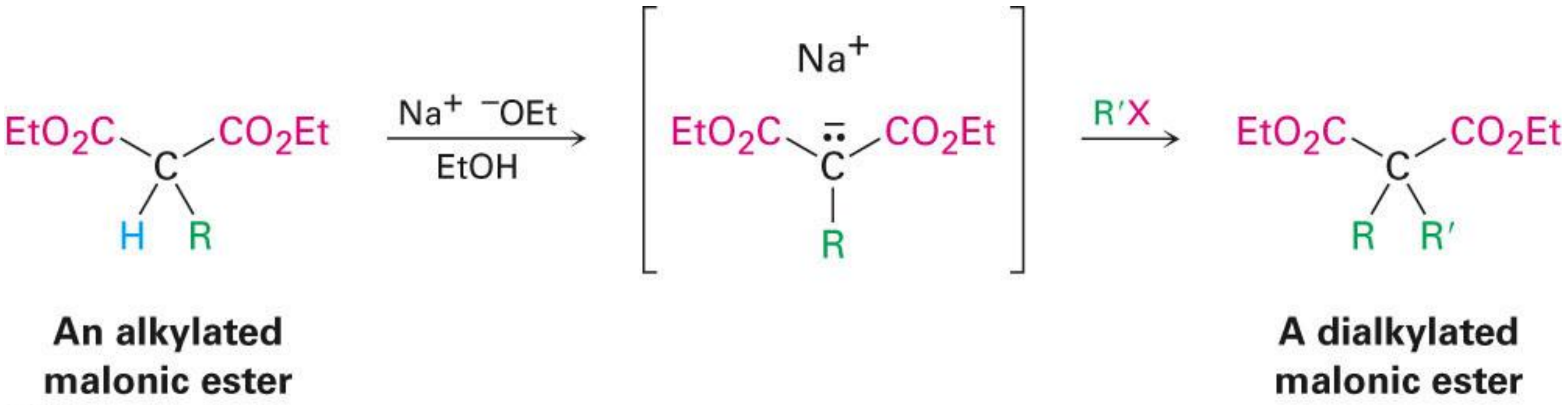
- The enolate is a good nucleophile that reacts rapidly with an alkyl halide to give an α-substituted malonic ester

Dialkylation

- The product has an **acidic α–hydrogen**, allowing the alkylation process to be repeated



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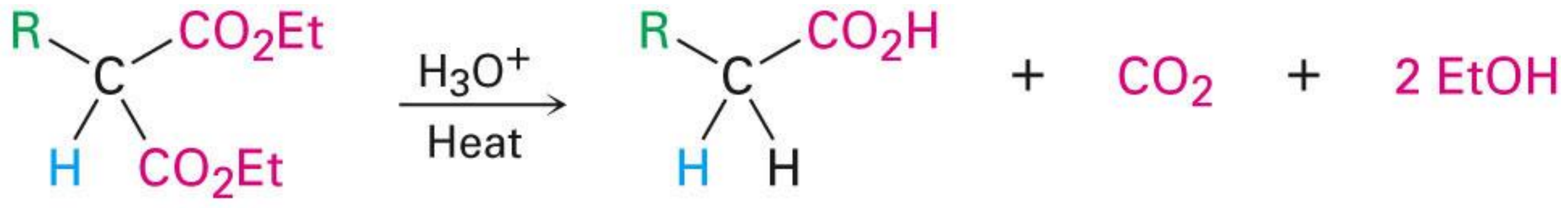
Hydrolysis and Decarboxylation

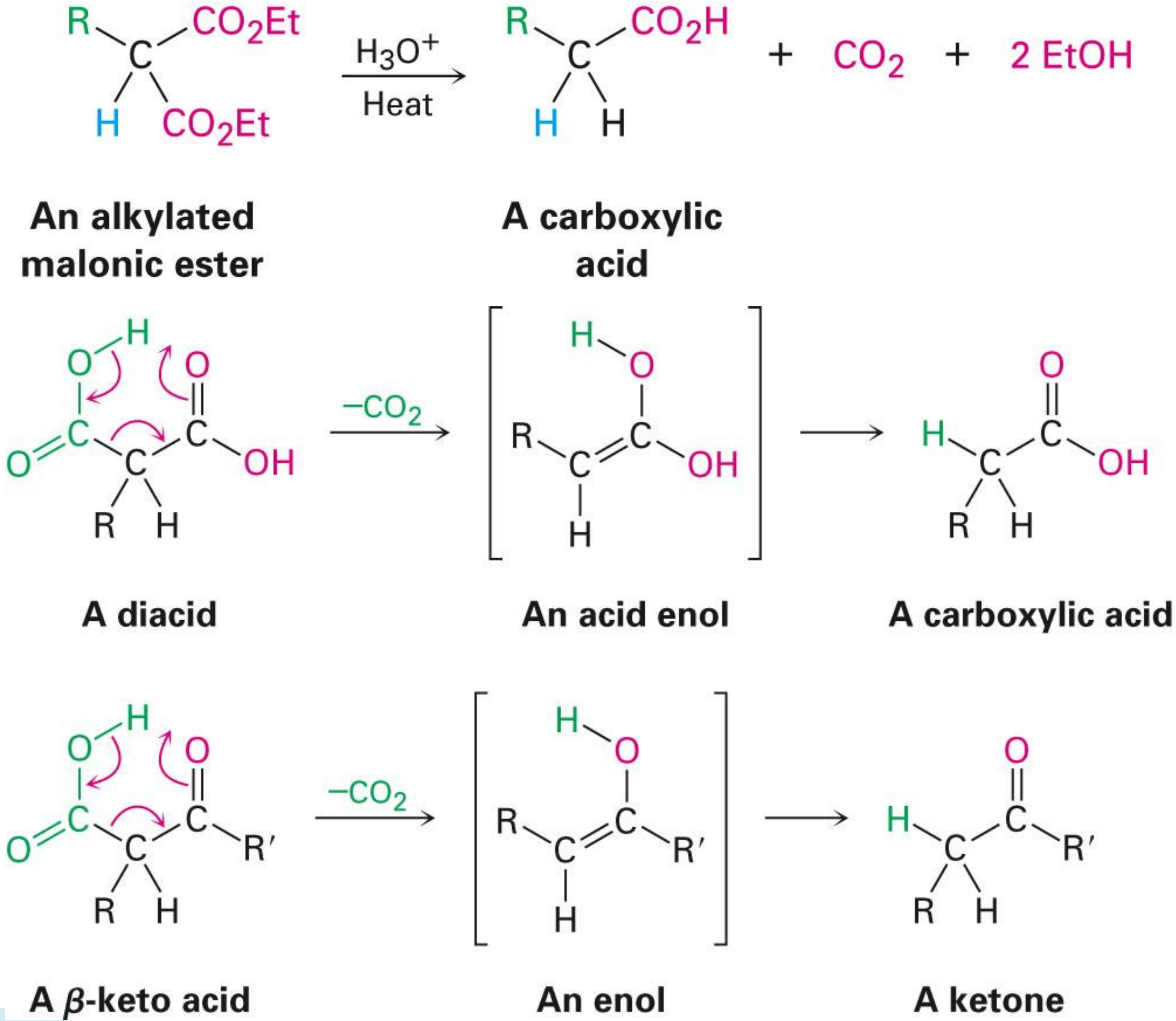
- The malonic ester derivative hydrolyzes in acid and loses CO_2 (“decarboxylation”) to yield a substituted monoacid



An alkylated malonic ester

A carboxylic acid

Alkylated of dialkylated malonic ester undergoes hydrolysis to yield the diacid followed by *decarboxylation* (loss of CO_2) to yield the monoacid



An alkylated malonic ester

A carboxylic acid

A diacid

An acid enol

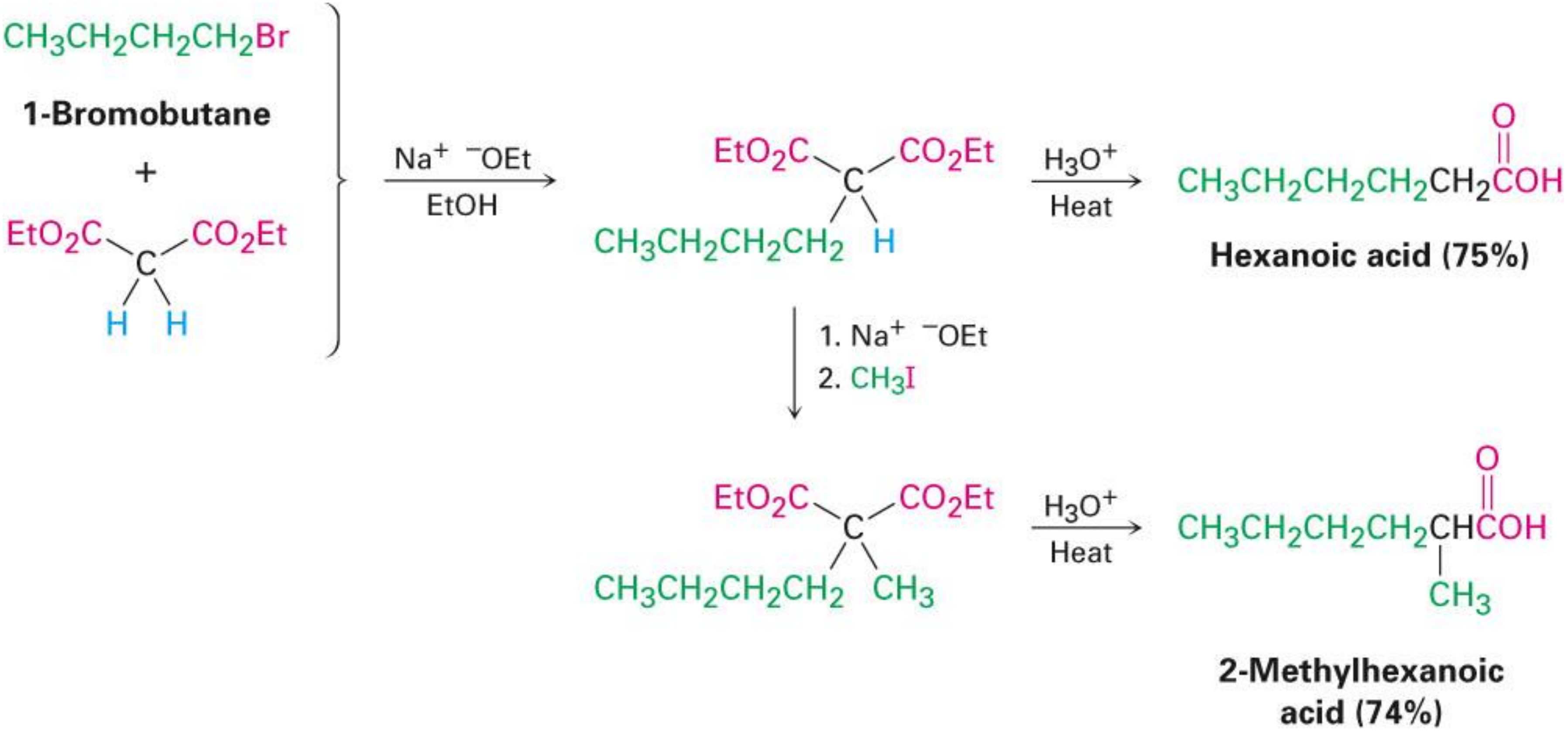
A carboxylic acid

A *β*-keto acid

An enol

A ketone

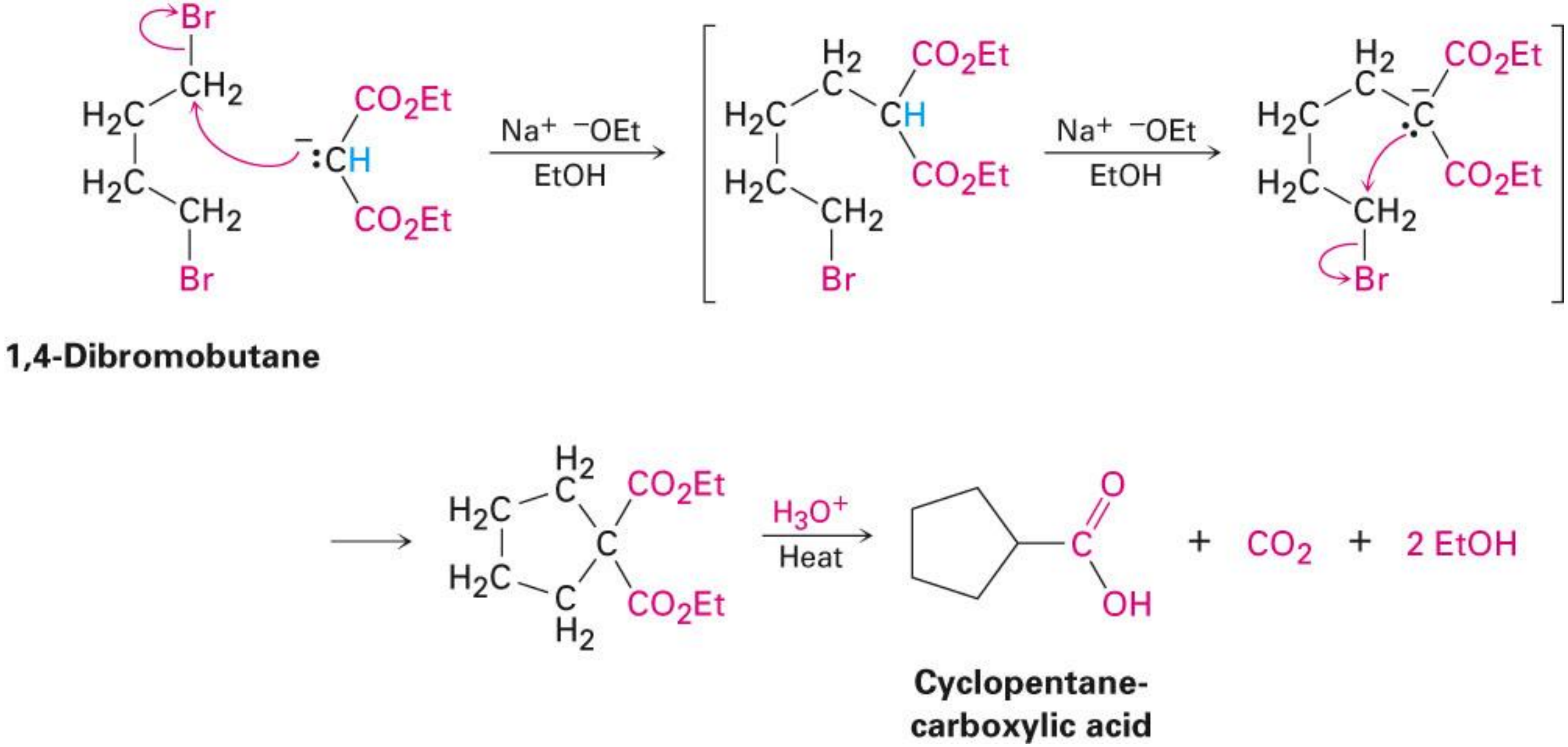
Overall result of malonic ester synthesis is the conversion of an alkyl halide into a carboxylic acid while lengthening the carbon chain by two carbons



Intramolecular alkylation

Malonic ester synthesis can be used to prepare *cyclo*alkane-carboxylic acids via intramolecular alkylation

- Three-, four-, five-, and six-membered rings can all be prepared in this way

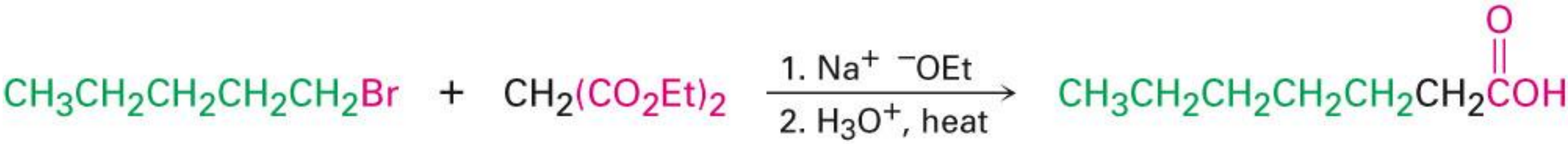


Worked Example

Using the Malonic Ester Synthesis to Prepare a Carboxylic Acid

How would you prepare heptanoic acid using a malonic ester synthesis?

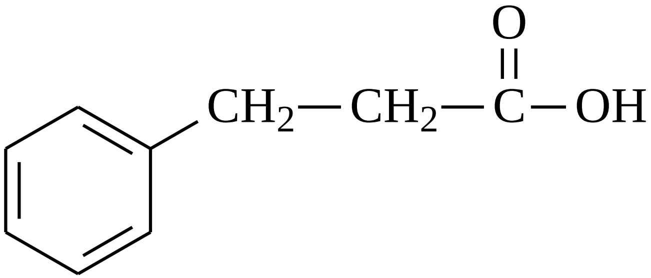
Solution



$$CH_3CH_2CH_2CH_2CH_2Br + CH_2(CO_2Et)_2 \xrightarrow[\text{2. } H_3O^+\text{, heat}]{\text{1. } Na^+ \ {}^-OEt} CH_3CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$$

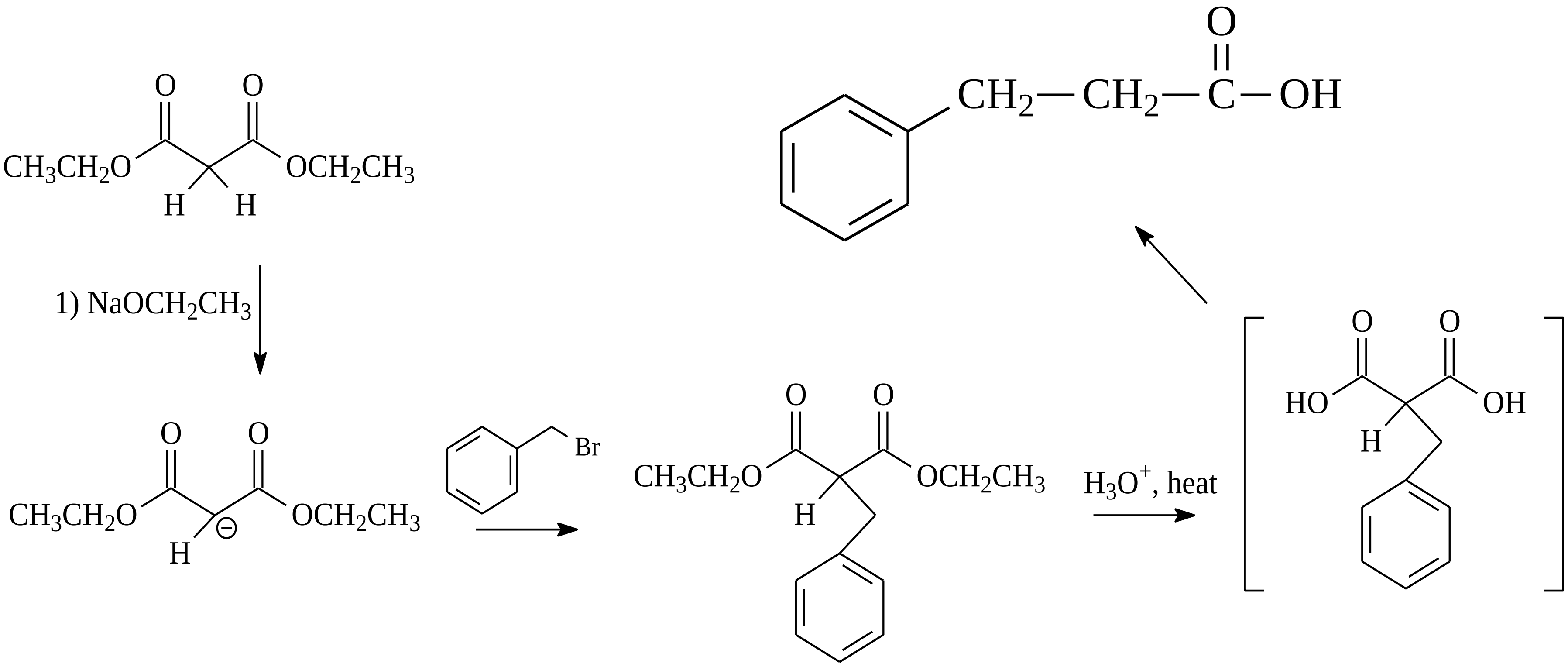
Learning Check:

Use a malonic ester synthesis to prepare the following:



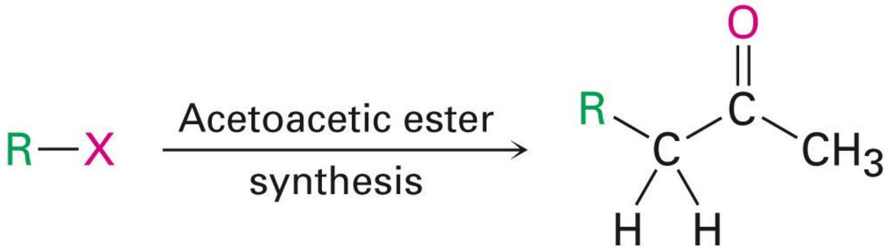
Solution:

Use a malonic ester synthesis to prepare the following:

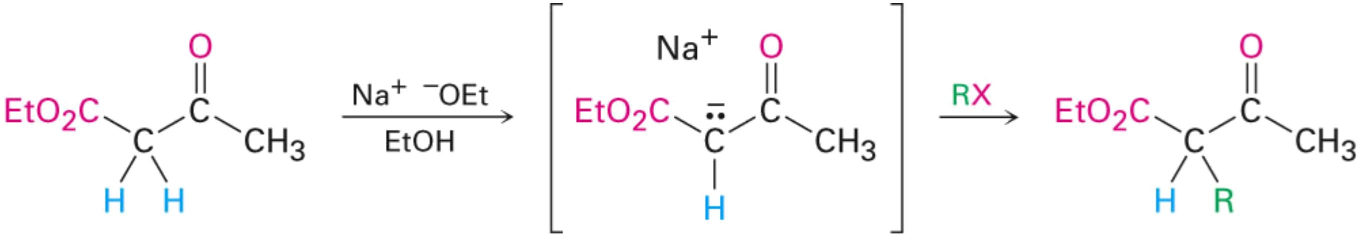


The Acetoacetic Ester Synthesis

- The *acetoacetic ester synthesis* converts an alkyl halide into a **methyl ketone** having three more carbons. Ketone product formed in three-step sequence:



1. Enolate formation

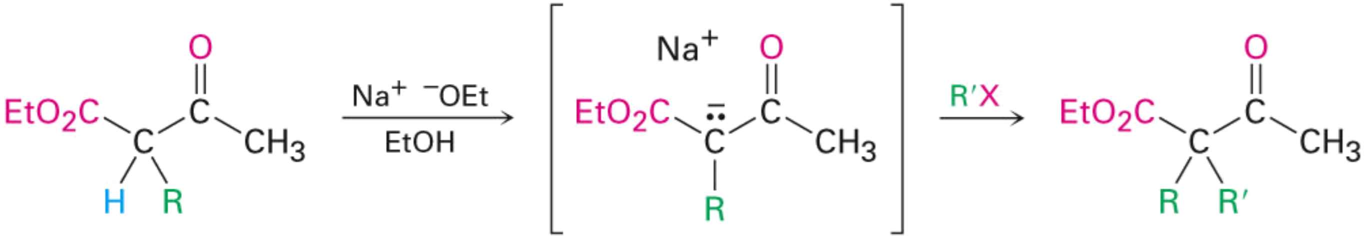


Ethyl acetoacetate (acetoacetic ester)

Sodio acetoacetic ester

A monoalkylated acetoacetic ester

2. Alkylation

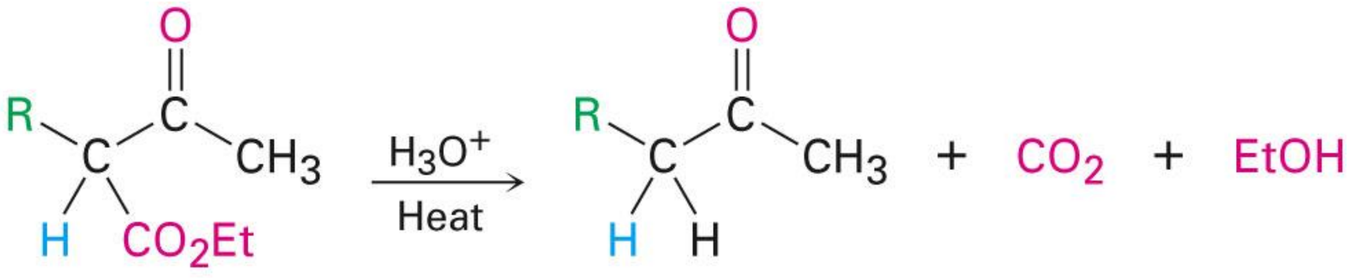


A monoalkylated acetoacetic ester

A dialkylated acetoacetic ester

- Alkylated or dialkylated acetoacetic ester is hydrolyzed in aqueous acid to a β–keto acid
- β–Keto acid undergoes *decarboxylation* to yield ketone product

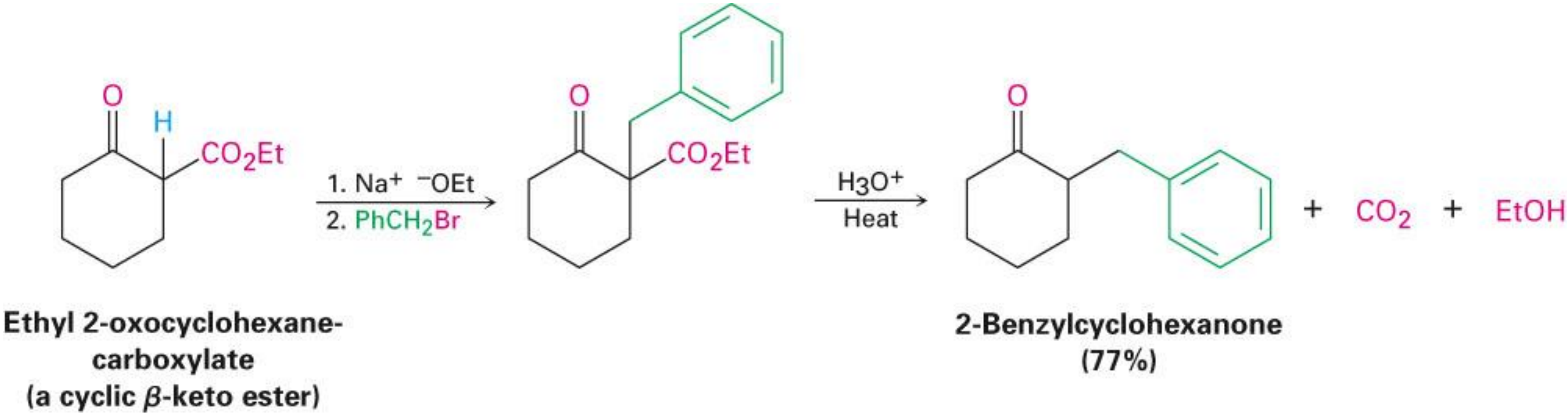
3. Hydrolysis/decarboxylation



An alkylated acetoacetic ester

A methyl ketone

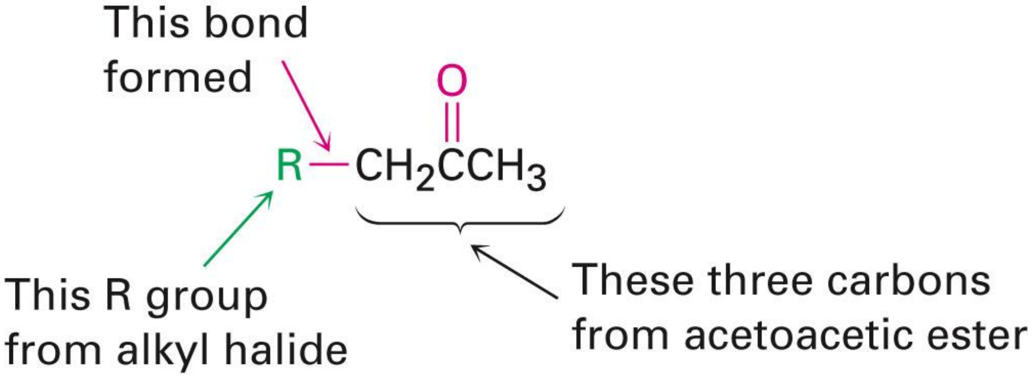
- *Cyclic β*–**keto esters** such as ethyl 2-oxocyclohexanecarboxylate can be alkylated and decarboxylated to give 2-substituted cyclohexanones



Worked Example

Using the Acetoacetic Ester Synthesis to Prepare a Ketone

How would you prepare pentan-2-one by an acetoacetic ester synthesis?



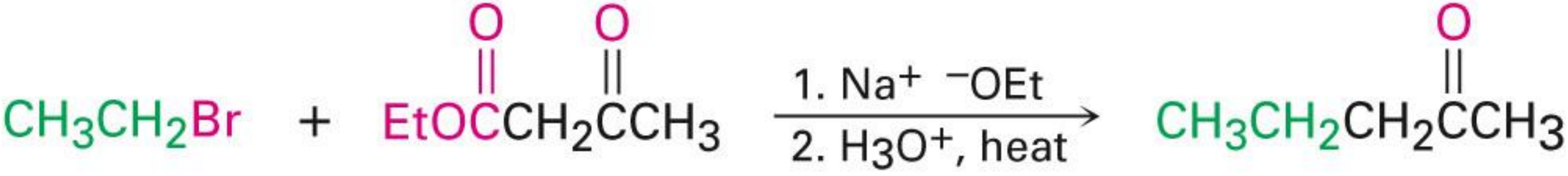
$$R-\underbrace{CH_2\overset{O}{\overset{\|}{C}}CH_3}$$

This bond formed

This R group from alkyl halide

These three carbons from acetoacetic ester

Solution

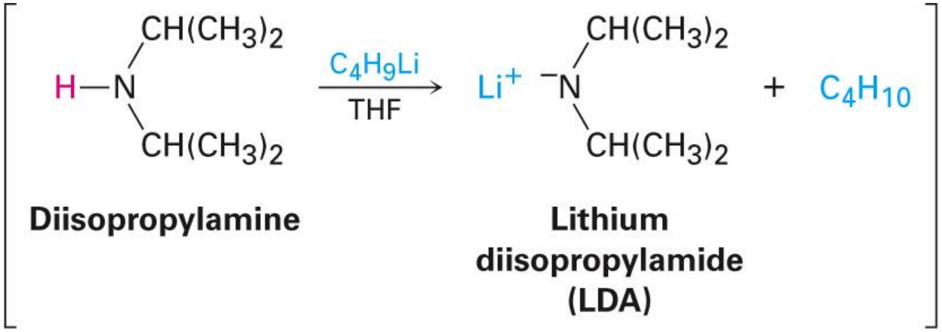


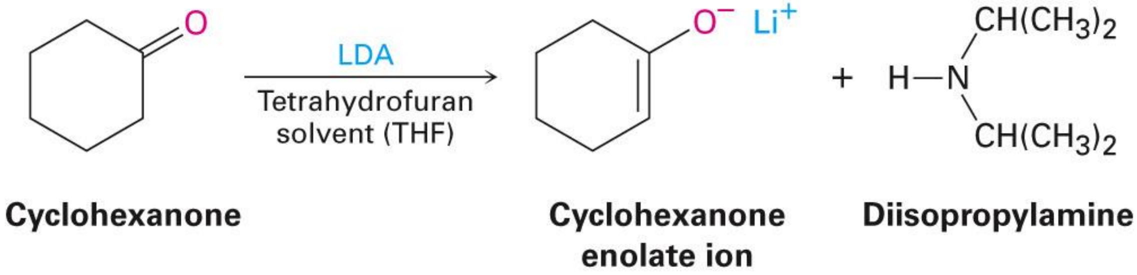
$$CH_3CH_2Br + EtO\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[2.\ H_3O^+,\ heat]{1.\ Na^+\ {}^-OEt} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$$

Pentan-2-one

Strong base required for enolate formation

- If $NaOCH_2CH_3$ is used the extent of enolate formation is only about 0.1%
- If sodium hydride, **NaH**, or lithium diisopropylamide (**LDA**), [$LiN(i\text{–}C_3H_7)_2$], is used the carbonyl is completely converted to its enolate conjugate base
  - LDA is prepared by reaction of butyllithium with diisopropylamine

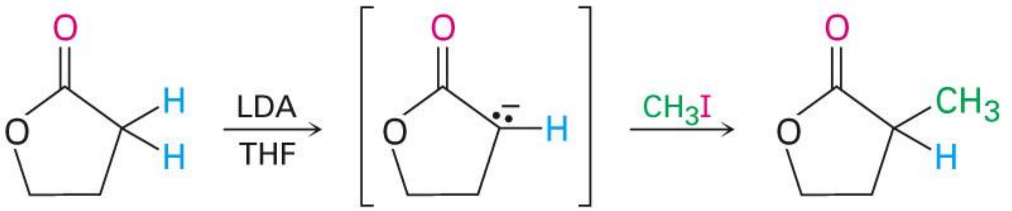




Direct Alkylation of Ketones, Esters, and Nitriles

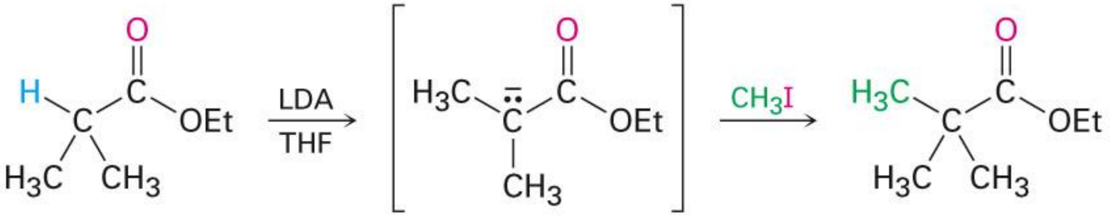
- A strong, sterically hindered base such as LDA converts a ketone, ester, or nitrile to its enolate ion
  - Use of a sterically hindered base avoids nucleophilic addition
  - A nonprotic solvent such as THF is required
- Aldehydes rarely give high yields of alkylation products because their enolate ions undergo carbonyl condensation reactions

Lactone



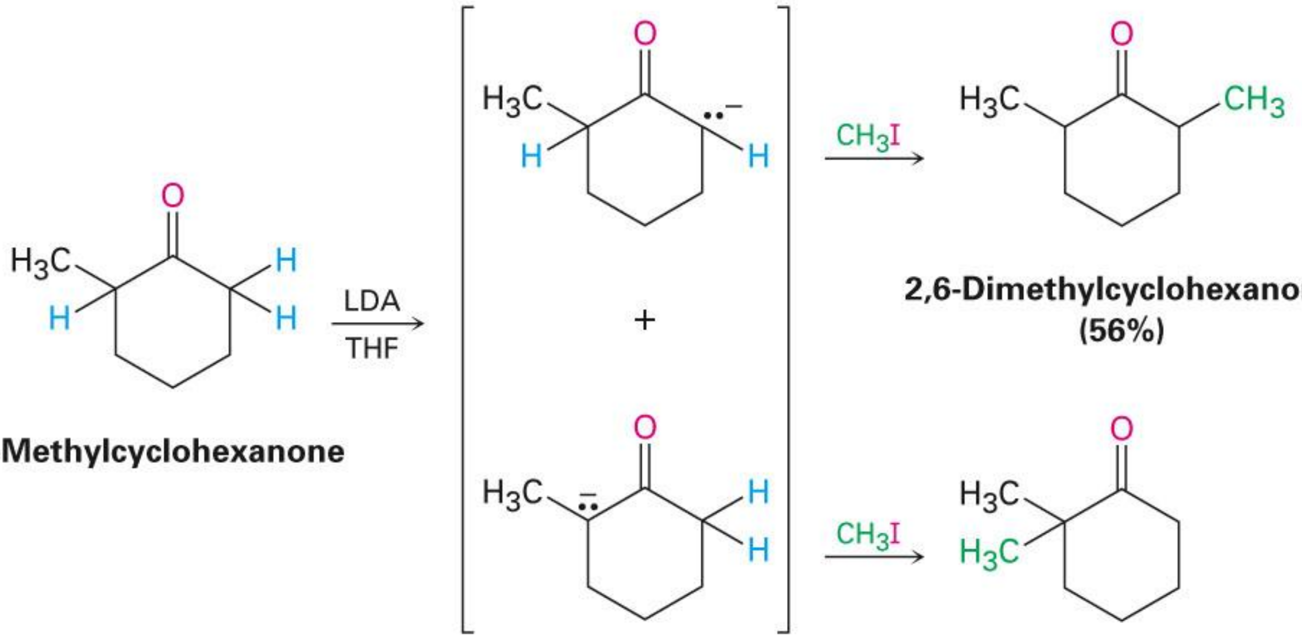
Butyrolactone **2-Methylbutyrolactone (88%)**

Ester



Ethyl 2-methylpropanoate **Ethyl 2,2-dimethylpropanoate (87%)**

Ketone

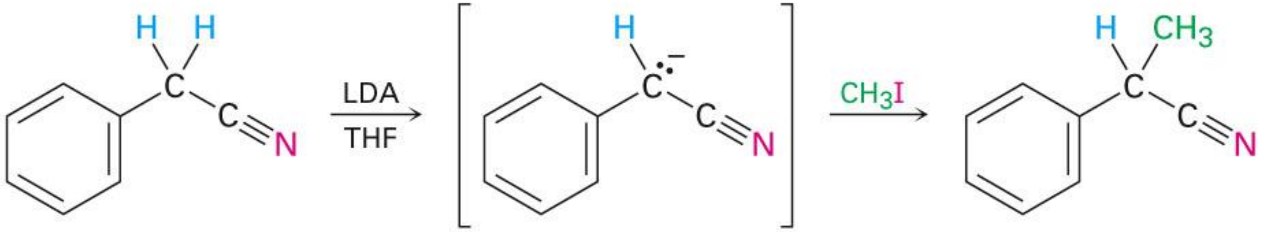


2-Methylcyclohexanone

2,6-Dimethylcyclohexanone (56%)

2,2-Dimethylcyclohexanone (6%)

Nitrile



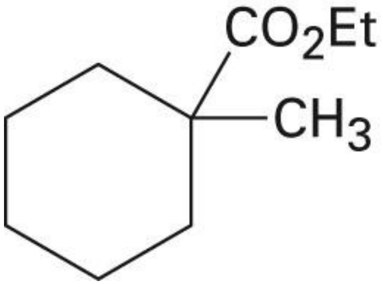
Phenylacetonitrile

2-Phenylpropanenitrile (71%)

Worked Example

Using an Alkylation Reaction to Prepare a Substituted Ester

How might you use an alkylation reaction to prepare ethyl 1-methylcyclohexanecarboxylate?

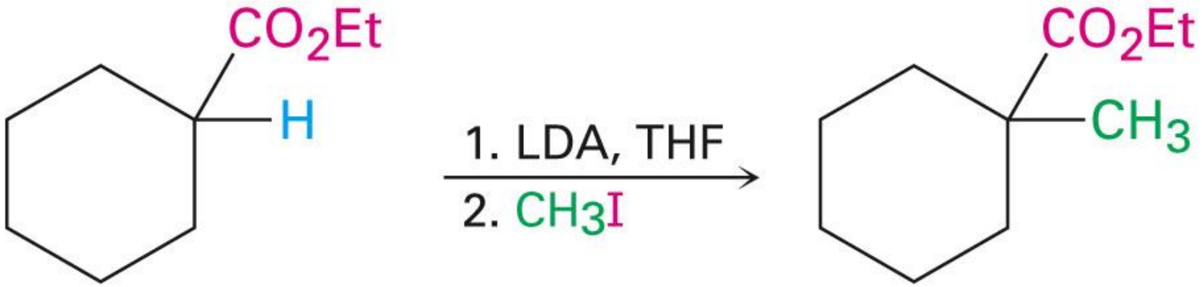


Ethyl 1-methylcyclohexanecarboxylate

Worked Example

Using an Alkylation Reaction to Prepare a Substituted Ester

Solution

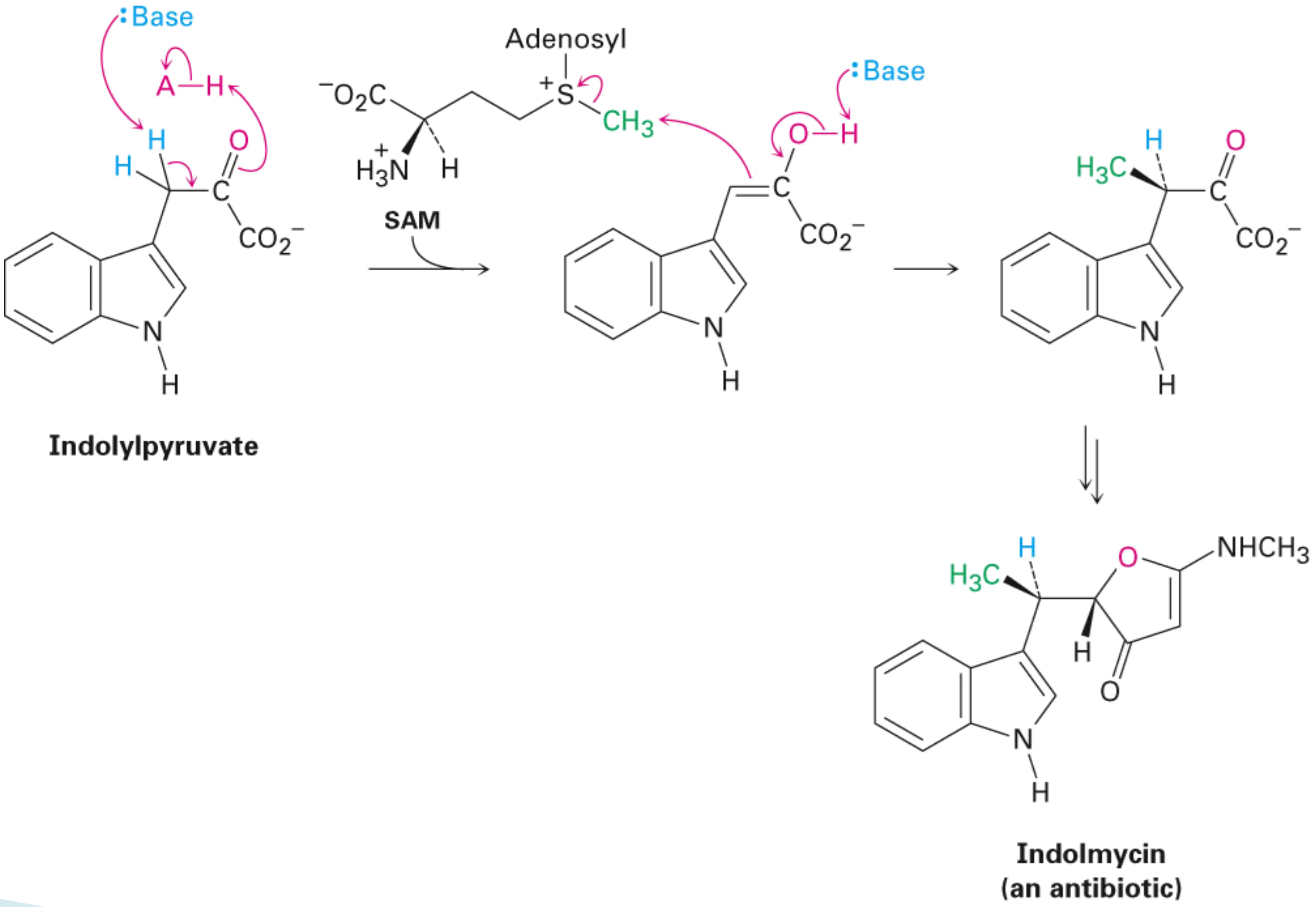


Ethyl cyclohexanecarboxylate

Ethyl 1-methylcyclohexanecarboxylate

Biological Alkylations

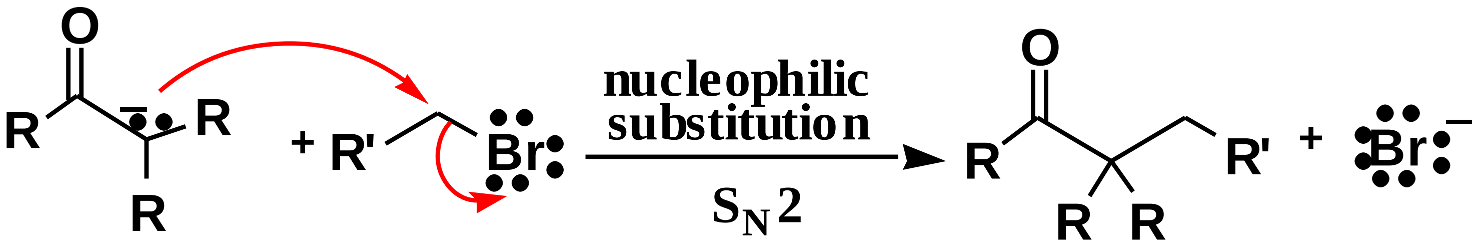
- Alkylations are not common in biological systems
- α–Methylation occurs in the biosynthesis of the antibiotic indolmycin from indolylpyruvate



Enolate Anions

- Enolate anions are nucleophiles in S_N2 reactions and carbonyl addition reactions,

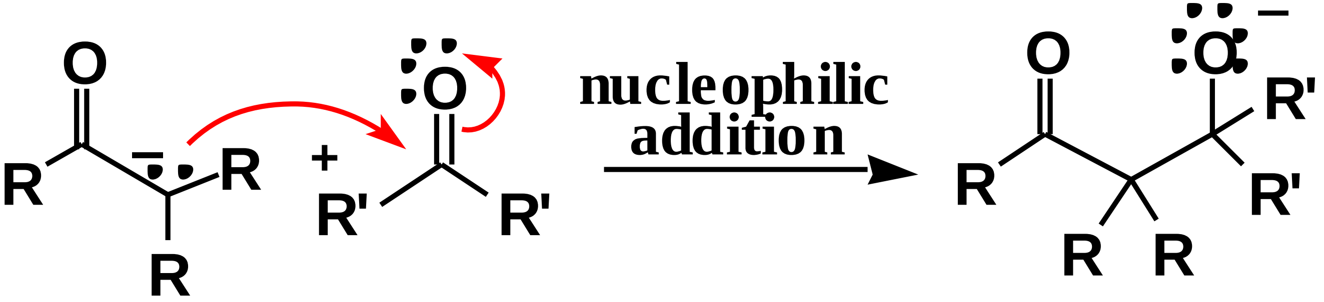
S_N2



An enolate anion

A 1° haloalkane or sulfonate

Carbonyl addition



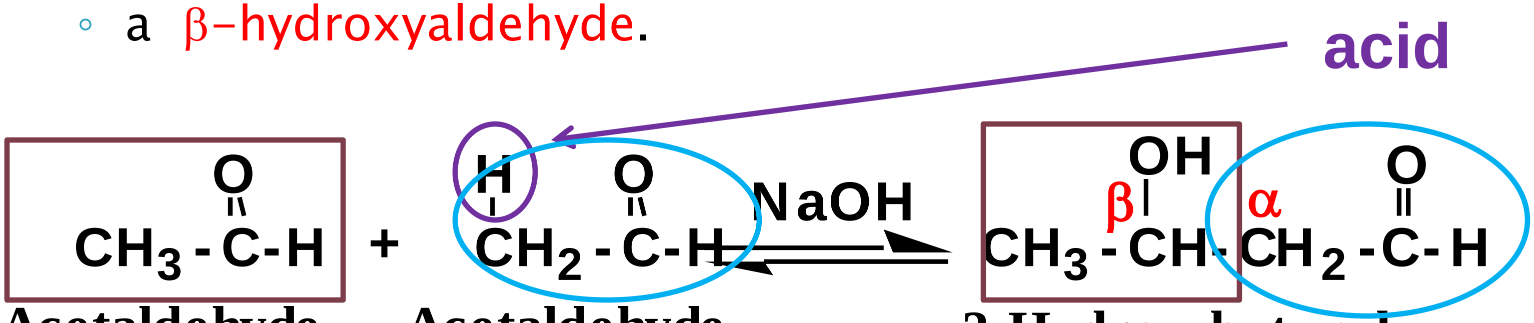
An enolate anion

A ketone

A tetrahedral carbonyl addition intermediate

The Aldol Reaction

- The product of an aldol reaction is:
  - a β−hydroxyaldehyde.

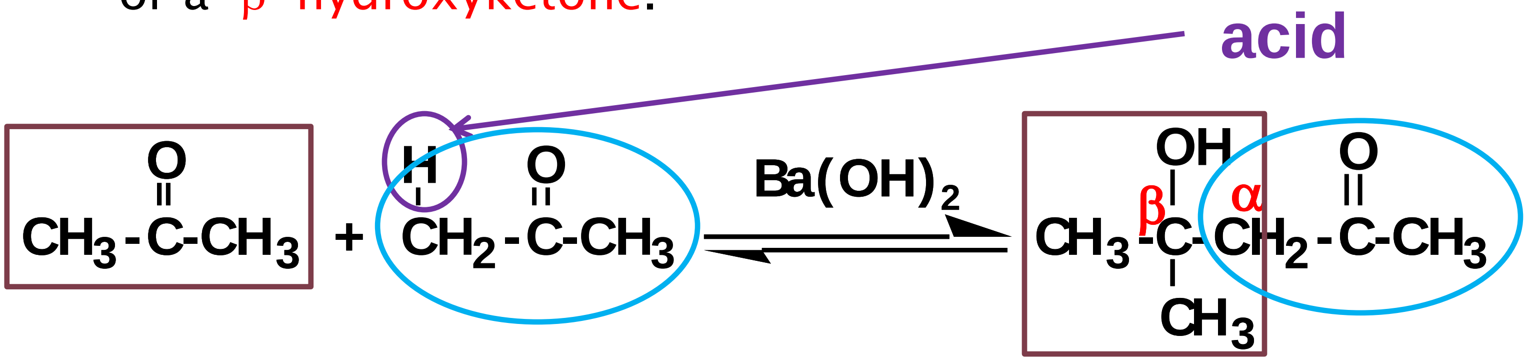


$$CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}H + \overset{H}{C}H_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}H \xrightleftharpoons{NaOH} CH_3\text{-}\overset{\overset{OH}{|}}{C}H\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}H$$

Acetaldehyde Acetaldehyde

3-Hydroxybutanal
(a β-hydroxyaldehyde;
racemic)

  - or a β−hydroxyketone.



$$CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3 + \overset{H}{C}H_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3 \xrightleftharpoons{Ba(OH)_2} CH_3\text{-}\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3$$

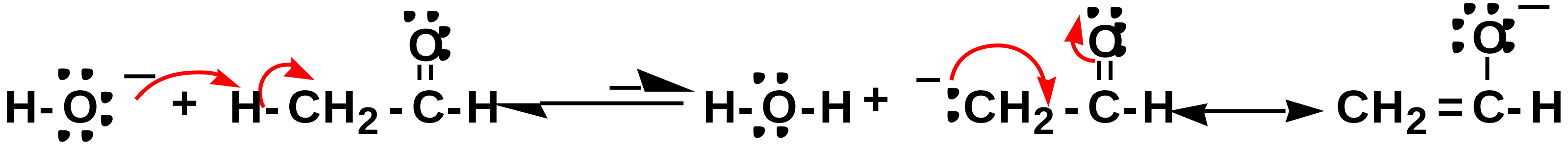
Acetone Acetone

4-Hydroxy-4-methyl-2-pentanone
(a β-hydroxyketone)

Mechanism: the Aldol Reaction, Base

- Base-catalyzed aldol reaction (good nucleophile)

Step 1: Formation of a resonance-stabilized enolate anion.



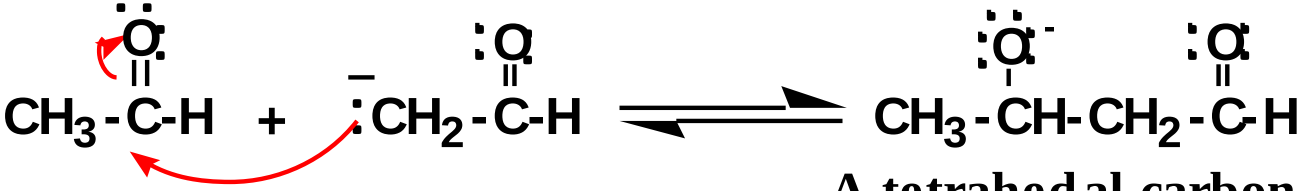
$$H\text{-}\ddot{O}^- + H\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}H \rightleftharpoons H\text{-}\ddot{O}\text{-}H + {}^-\!:CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}H \longleftrightarrow CH_2{=}\overset{O^-}{\overset{|}{C}}\text{-}H$$

pK_a 20 (weaker acid)

pK_a 15.7 (stronger acid)

An enolate anion

Step 2: Carbonyl addition gives a TCAI.



$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + {}^-\!:CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}H \rightleftharpoons CH_3\text{-}\overset{O^-}{\overset{|}{C}}H\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}H$$

A tetrahedal carbonyl addition intermediate

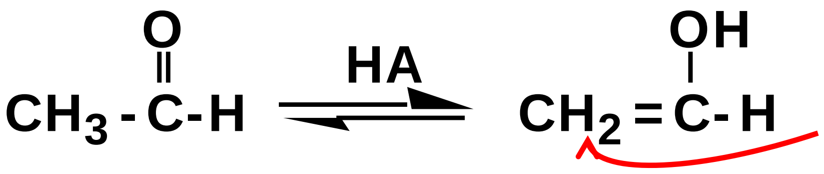
Step 3: Proton transfer to O⁻ completes the aldol reaction.

Mechanism: the Aldol Reaction: Acid catalysis

- Before showing the mechanism think about what is needed.
  - On one molecule the beta carbon must have nucleophilic capabilities to supply an electron pair.
  - On the second molecule the carbonyl group must function as an electrophile.
  - One or the other molecules must be sufficiently reactive.

Mechanism: the Aldol Reaction: Acid catalysis

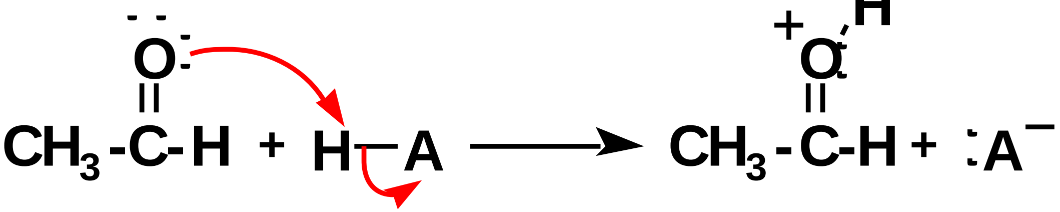
- Acid-catalyzed aldol reaction (good electrophile)
  - Step 1: Acid-catalyzed equilibration of keto and enol forms.



$CH_3-\overset{O}{\overset{\|}{C}}-H \rightleftharpoons CH_2=\overset{OH}{\overset{|}{C}}-H$

Nucleophilic carbon

  - Step 2: Proton transfer from HA to the carbonyl group of a second molecule of aldehyde or ketone.

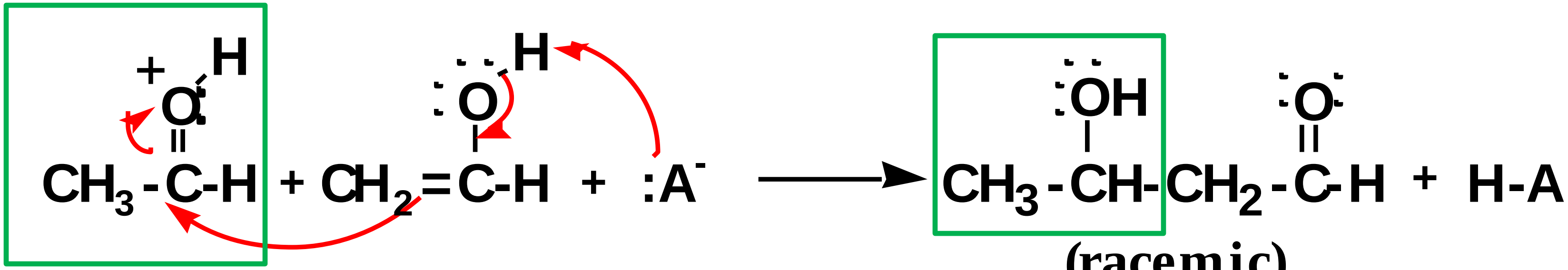


$CH_3-\overset{O}{\overset{\|}{C}}-H + H-A \longrightarrow CH_3-\overset{^{+}O-H}{\overset{\|}{C}}-H + :A^-$

Reactive carbonyl

Mechanism: the Aldol Reaction: Acid catalysis

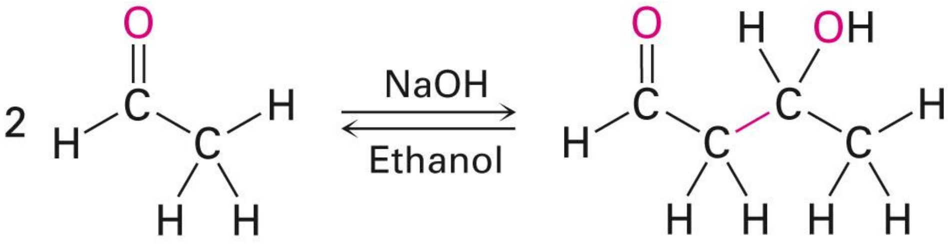
- Step 3: Attack of the enol of one molecule on the protonated carbonyl group of the other molecule.
- Step 4: Proton transfer to A⁻ completes the reaction.



$$CH_3-\overset{\overset{+}{O}H}{\overset{\|}{C}}-H + CH_2=\overset{OH}{\overset{|}{C}}-H + :A^- \longrightarrow CH_3-\overset{OH}{\overset{|}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-H + H-A$$

(racemic)

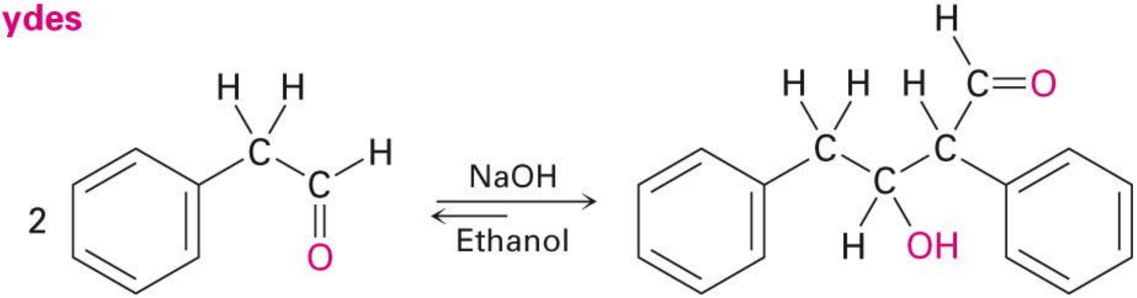
Carbonyl Condensations: The Aldol Reaction



Acetaldehyde

3-Hydroxybutanal (aldol)

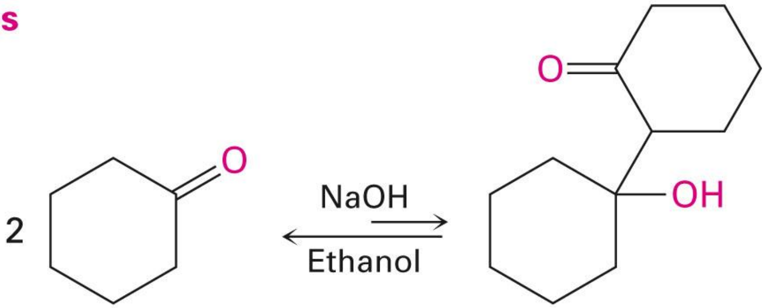
Aldehydes



Phenylacetaldehyde (10%)

(90%)

Ketones



Cyclohexanone (78%)

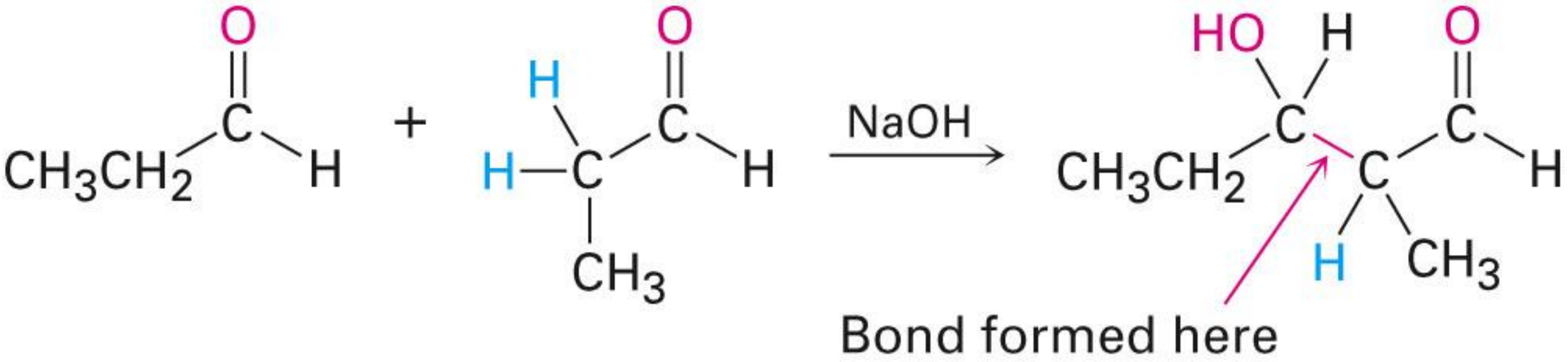
(22%)

Worked Example

Predicting the Product of an Aldol Reaction

What is the structure of the aldol product from propanal?

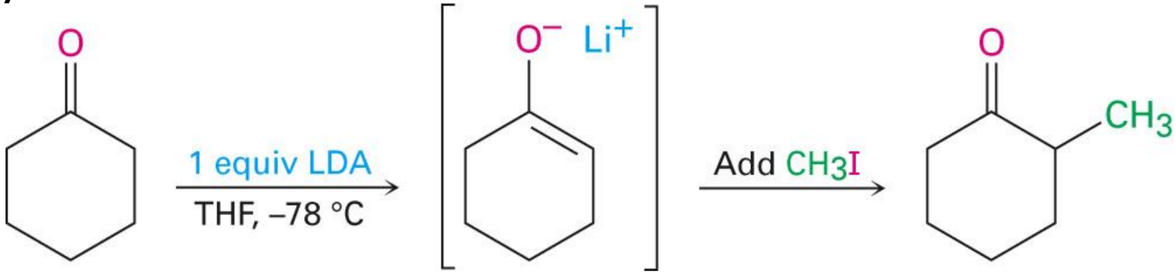
Solution

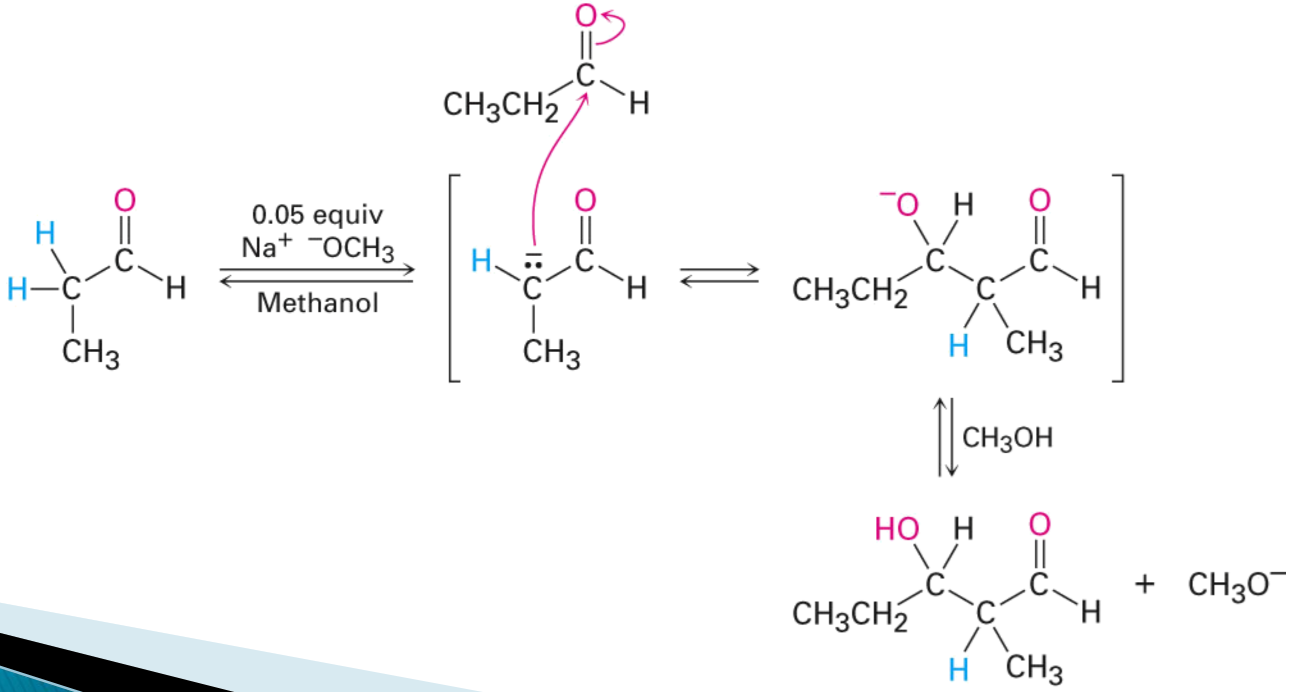


Carbonyl Condensations versus α–Substitutions

Carbonyl condensation reactions and α substitutions take place *under basic conditions* and involve enolate-ion intermediates

- Alpha-substitution reactions require a full equivalent of **strong base**
- Carbonyl condensation reactions require only a *catalytic* amount of a relatively **weak base**

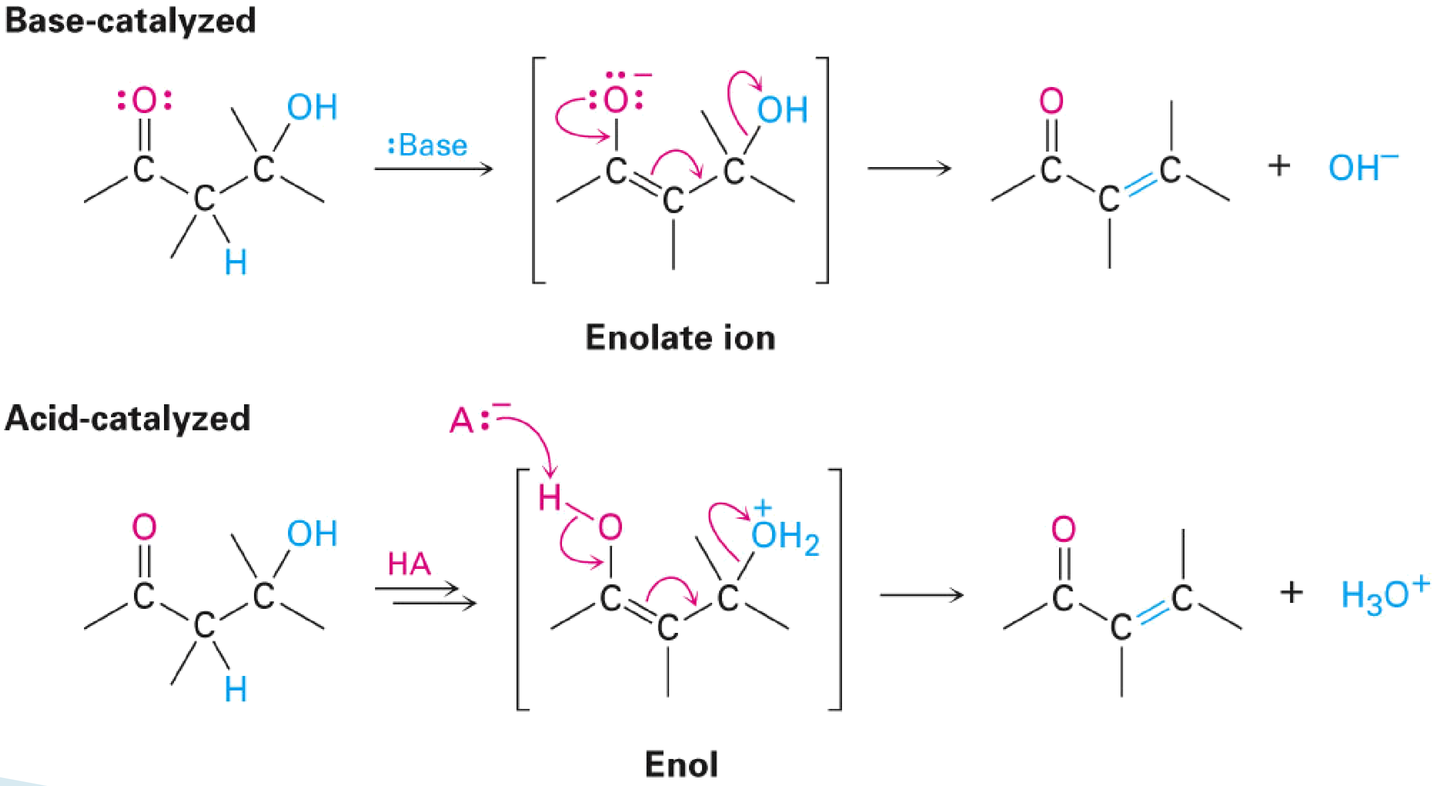




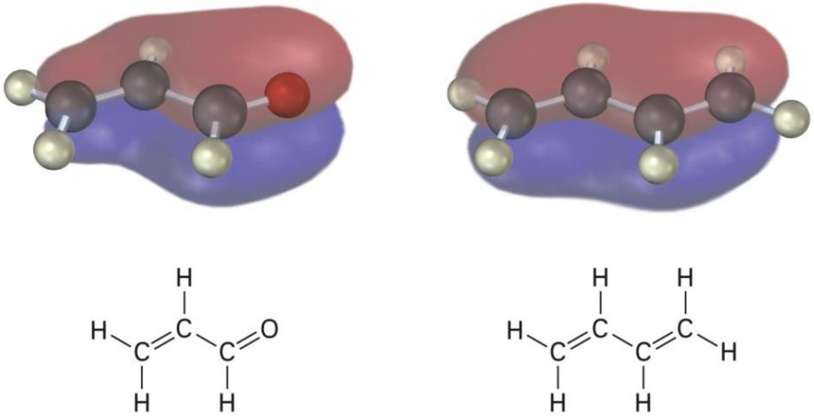
Dehydration of Aldol Products

β–Hydroxy aldehydes or ketones formed in aldol reactions can be easily dehydrated to yield *α,β*–unsaturated products, or *conjugated enones*

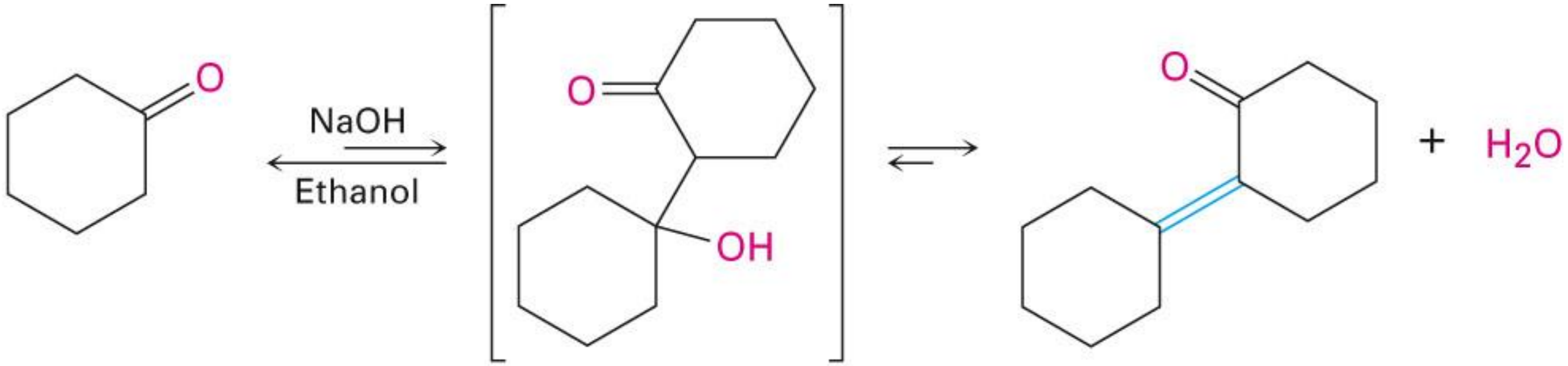
- Aldol reactions were named *condensation* reactions due to the loss of water



- Conjugated enones are more stable than nonconjugated enones
  - The π bonding molecular orbitals of a conjugated enone like propenal are spread over the entire π system,similar to the π bonding molecular orbitals of a conjugated diene



Propenal **Buta-1,3-diene**

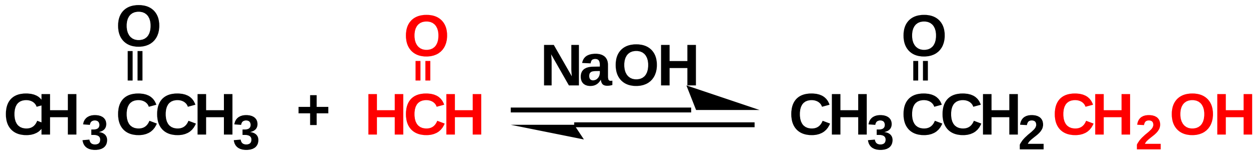


Cyclohexanone

Cyclohexylidenecyclohexanone
(92%)

Crossed Aldol Reactions

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



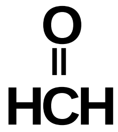
$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_3 + H\overset{O}{\overset{\|}{C}}H \xrightleftharpoons{NaOH} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2OH}$$

4-Hydroxy-2-butanone

acid

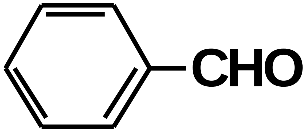
Non-acidic, no alpha hydrogens

- Crossed aldol reactions are most successful if
  - one of the reactants has no α–hydrogen and, therefore, cannot form an enolate anion,

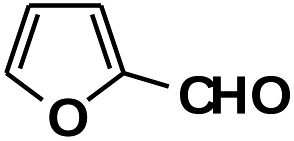


$\mathrm{H}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{H}$

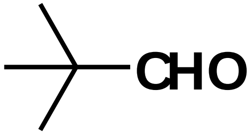
Formaldehyde



Benzaldehyde



Furfural

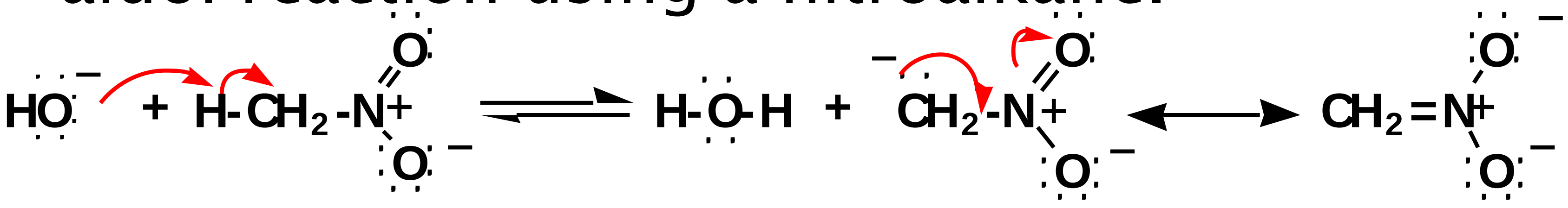


2,2-Dimethylpropanal

  - One reactant has a more acidic hydrogen than the other (next slide)
  - One reactant is an aldehyde which has a more reactive carbonyl group.

Crossed Aldol Reactions, Nitro activation

- Nitro groups can be introduced by way of an aldol reaction using a nitroalkane.

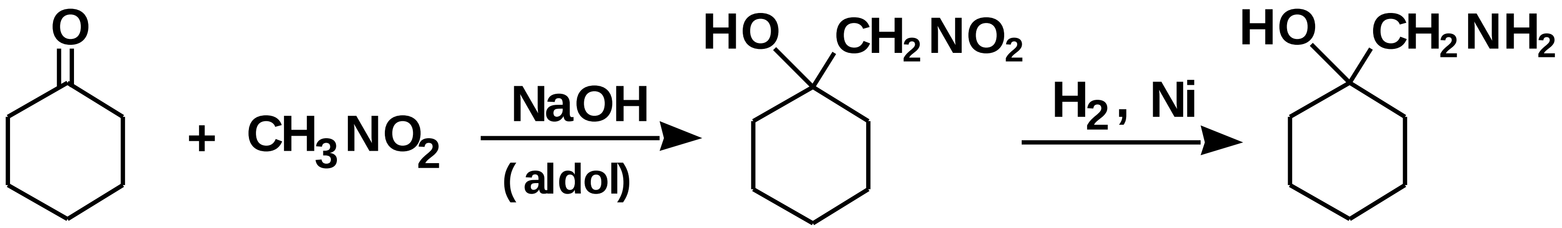


Nitromethane
pK_a 10.2
(stronger acid)

Water
pK_a 15.7
(weaker acid)

Resonance-stabilized anion

  - Nitro groups can be reduced to 1° amines.



Cyclohex-anone

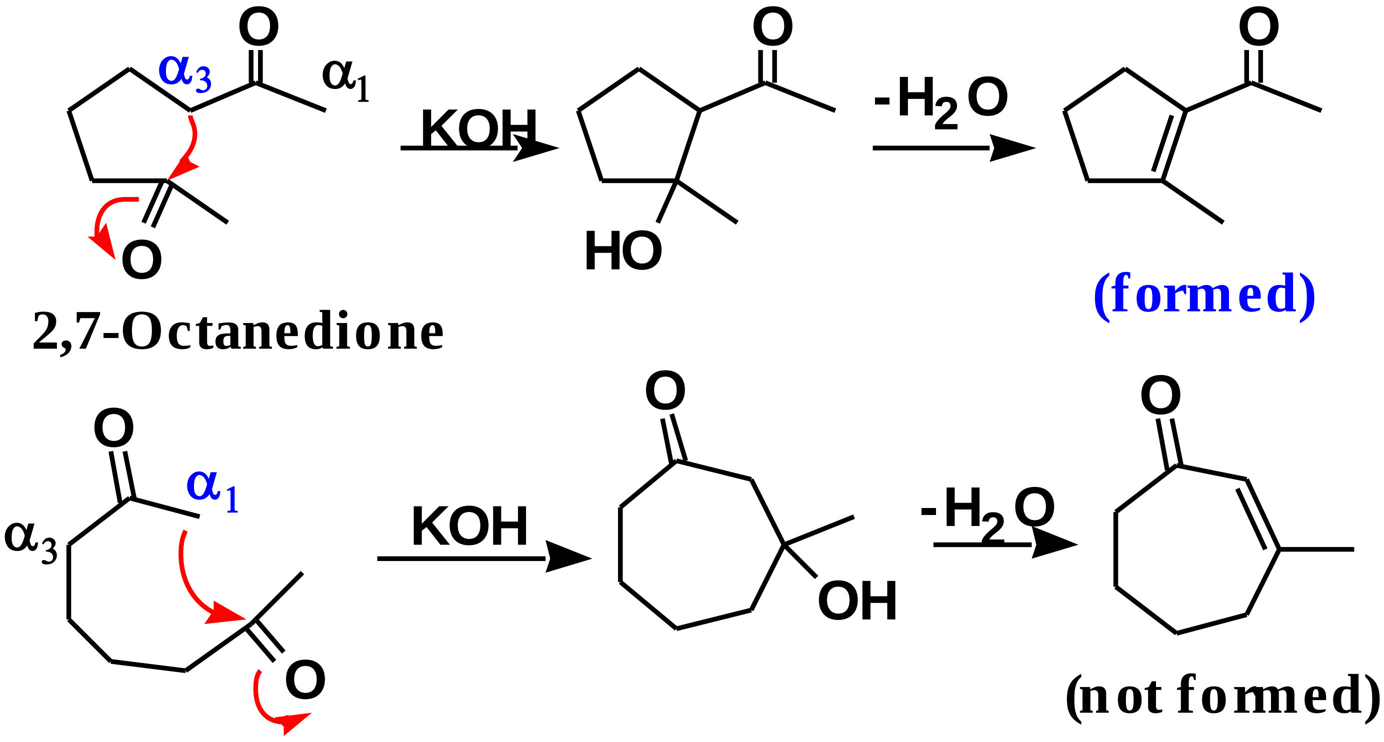
Nitro-methane

1-(Nitromethyl)-cyclohexanol

1-(Aminomethyl)-cyclohexanol

Intramolecular Aldol Reactions

- Intramolecular aldol reactions are most successful for formation of <u>five- and six-membered rings</u>.
- Consider 2,7-octadione, which has two α-carbons.



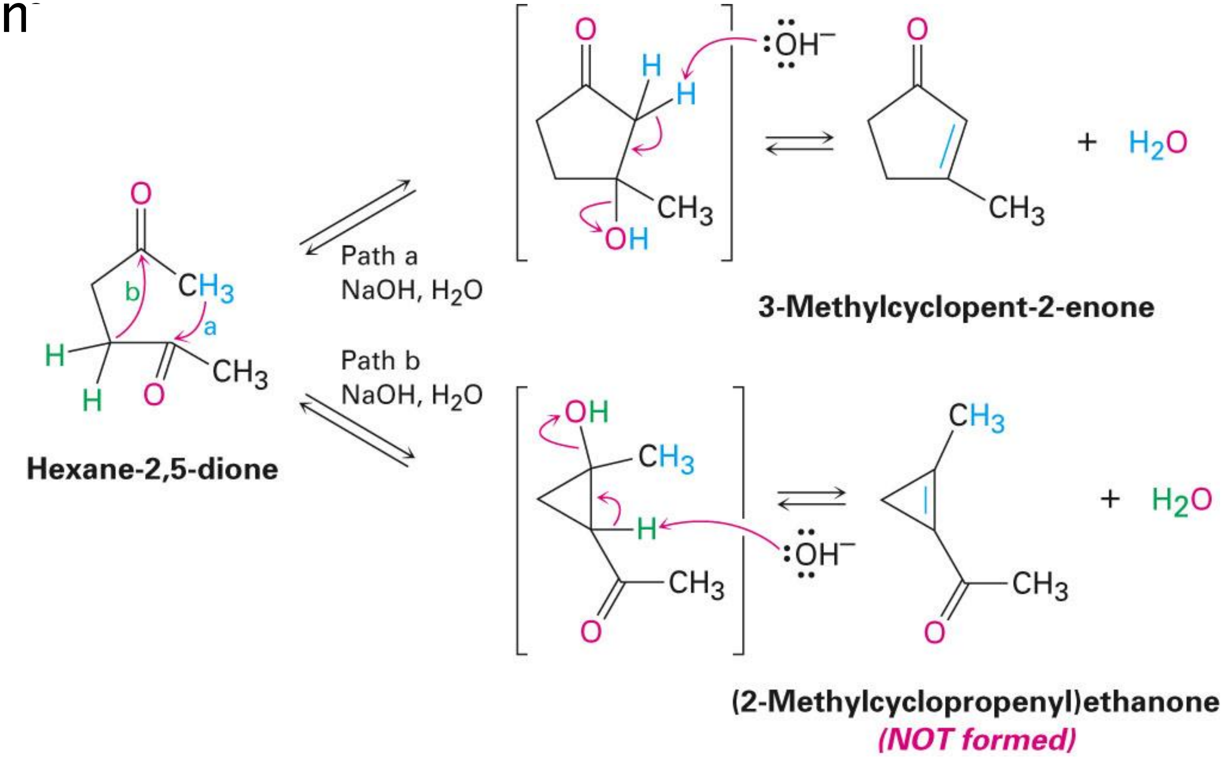
2,7-Octanedione

(formed)

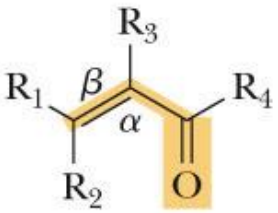
(not formed)

Intramolecular aldol reactions may lead to product mixtures

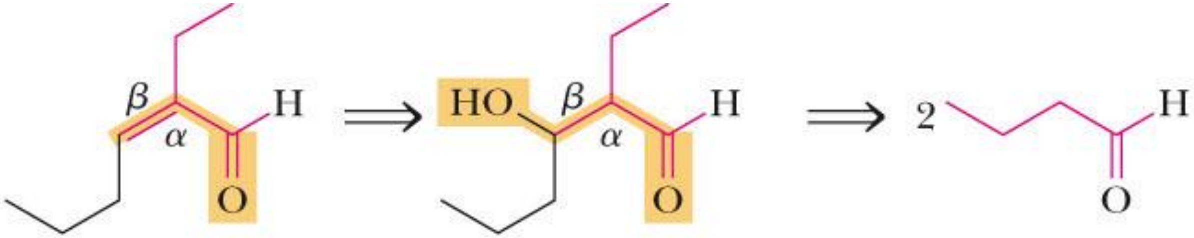
- Most thermodynamically stable product formed selectively
  - All reaction steps are reversible
  - Most thermodynamically stable product predominates at equilibrium



Synthesis: Retrosyntheic Analysis



α, β-Unsaturated carbonyl
R_1–R_4 = alkyl group,
aryl group, H atom



target
product

(racemic)

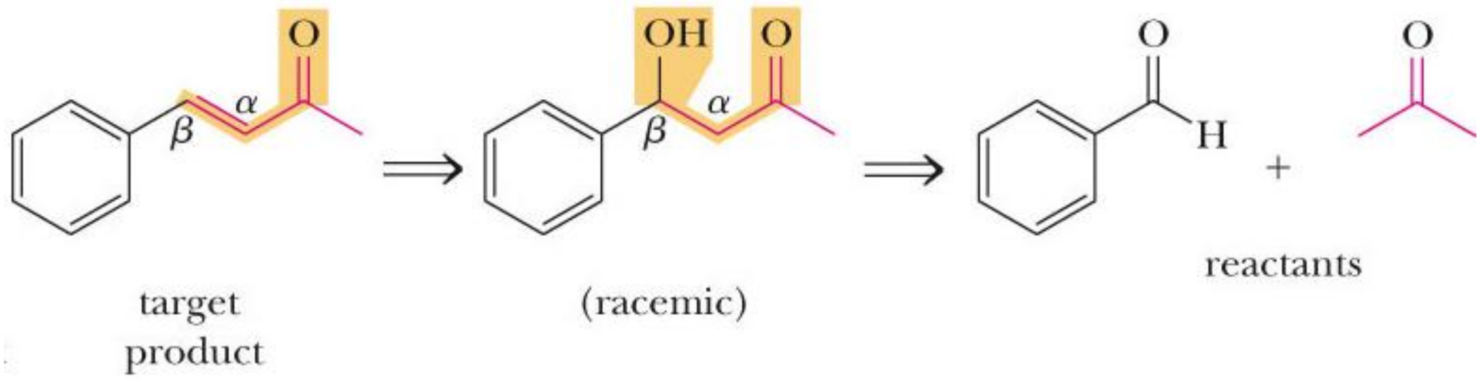
reactants

Recognition pattern

Analysis

Synthesis: Retrosyntheic Analysis

Example



Mixed
aldol

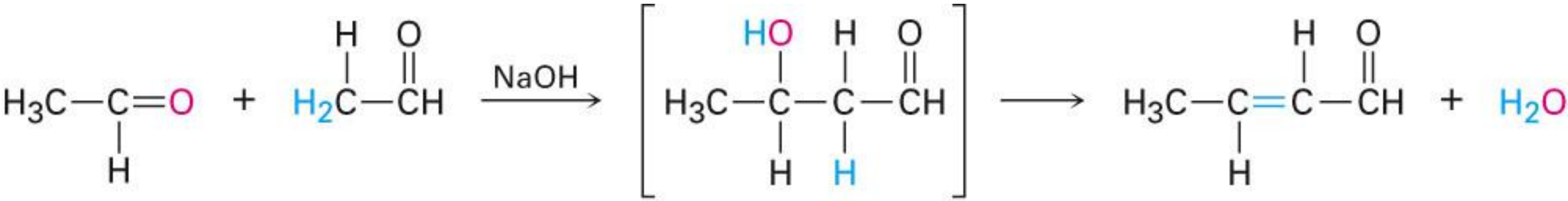
Benzaldehyde
No alpha
hydrogens

Worked Example

Predicting the Product of an Aldol Reaction

What is the structure of the enone obtained from aldol condensation of acetaldehyde?

Solution



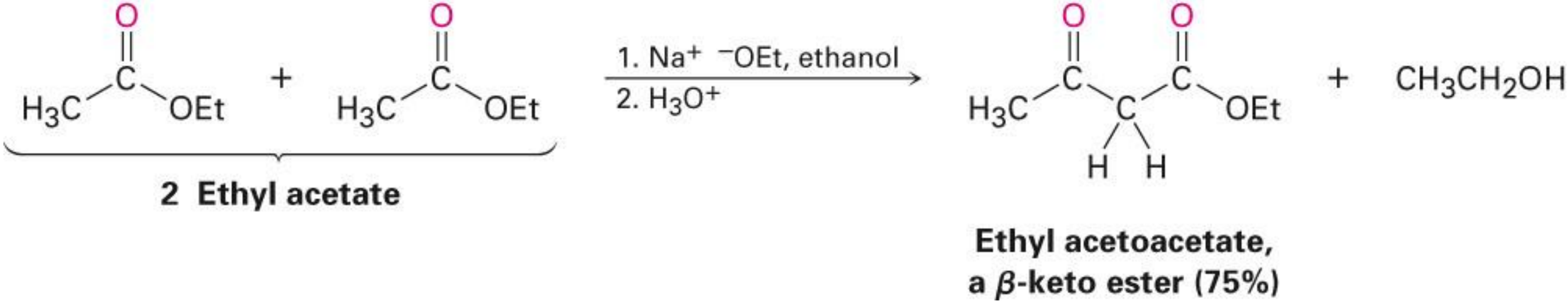
$$H_3C-\underset{H}{C}=O + H_2\overset{H}{C}-\overset{O}{\overset{\|}{C}}H \xrightarrow{NaOH} \left[H_3C-\underset{H}{\overset{HO}{C}}-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}H\right] \longrightarrow H_3C-\underset{H}{C}=\overset{H}{C}-\overset{O}{\overset{\|}{C}}H + H_2O$$

But-2-enal

The Claisen Condensation Reaction, Ester Substitution

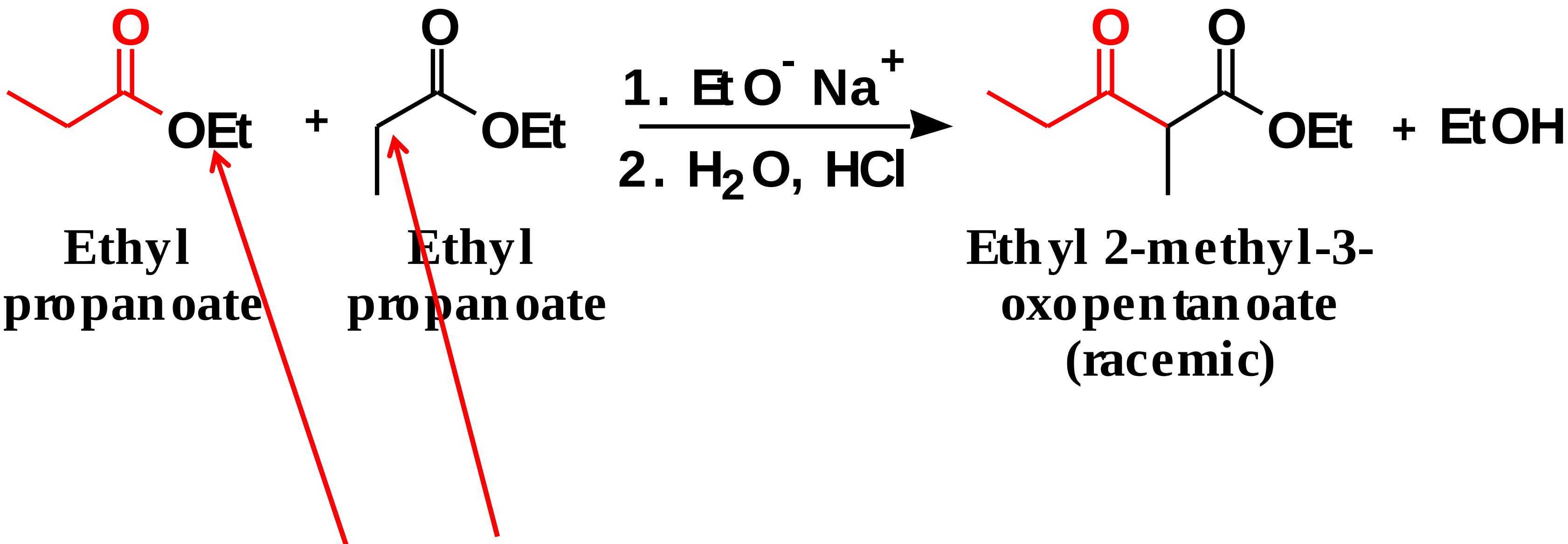
Reversible condensation reaction between two esters is called the **Claisen condensation reaction**

- Esters have weakly acidic α hydrogens
- When an ester with an α hydrogen is treated with 1 equivalent of a base a β–keto ester is formed



Ethyl acetoacetate, a β-keto ester (75%)

- Claisen condensation of ethyl propanoate

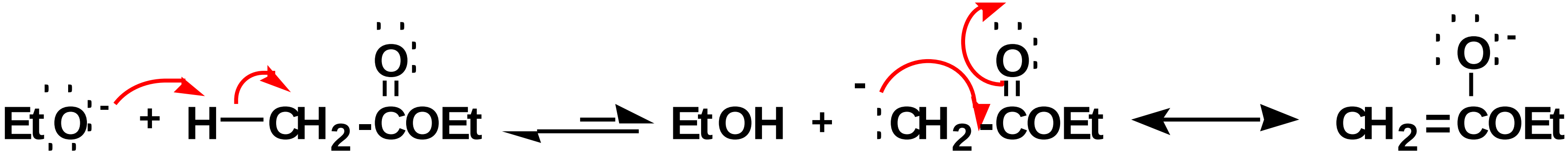


Ethyl propanoate + Ethyl propanoate → Ethyl 2-methyl-3-oxopentanoate (racemic)

Here the enolate part of one ester molecule has replaced the alkoxy group of the other ester molecule.

Mechanism: Claisen Condensation

Step 1: Formation of an enolate anion.



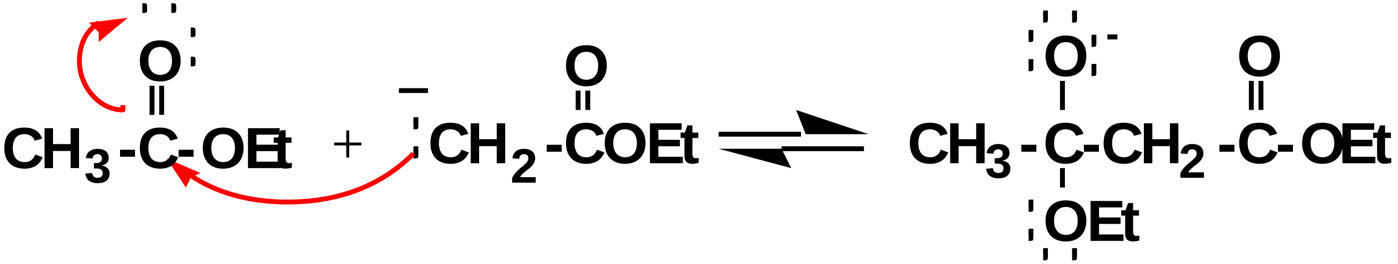
$$EtO^- + H-CH_2-\overset{O}{\overset{\|}{C}}OEt \rightleftharpoons EtOH + {}^-CH_2-\overset{O}{\overset{\|}{C}}OEt \longleftrightarrow CH_2=\overset{O^-}{\overset{|}{C}}OEt$$

pK_a = 22 (weaker acid)

pK_a 15.9 (stronger acid)

Resonance-stabilized enolate anion

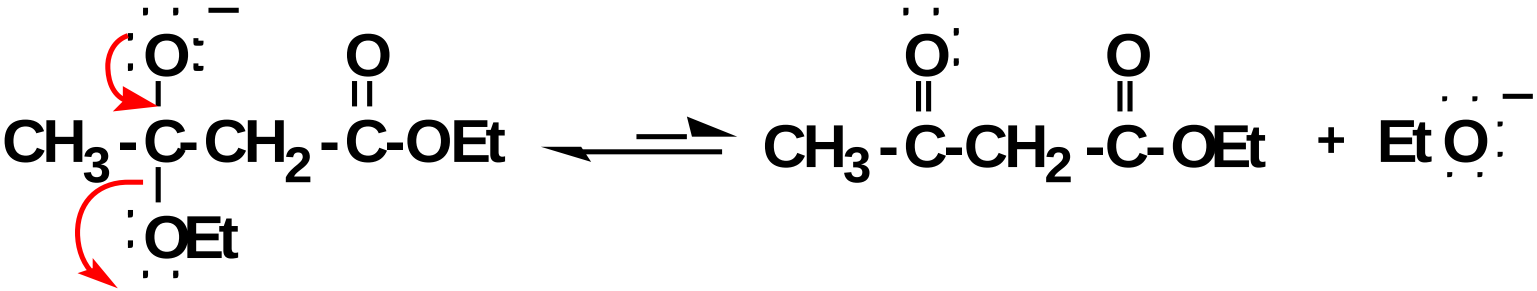
Step 2: Attack of the enolate anion on a carbonyl carbon gives a TCAI.



$$CH_3-\overset{O}{\overset{\|}{C}}-OEt + {}^-CH_2-\overset{O}{\overset{\|}{C}}OEt \rightleftharpoons CH_3-\underset{OEt}{\overset{O^-}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OEt$$

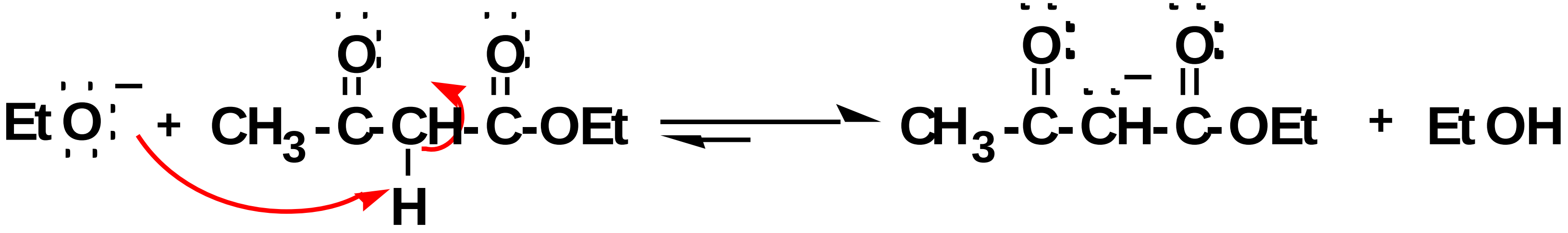
A tetrahedral carbonyl addition intermediate

Step 3: Collapse of the TCAI gives a β-ketoester and an alkoxide ion.



$$CH_3-C(O^-)(OEt)-CH_2-C(=O)-OEt \rightleftharpoons CH_3-C(=O)-CH_2-C(=O)-OEt + EtO^-$$

Step 4: An acid-base reaction drives the reaction to completion. This consumption of base must be anticipated.



$$EtO^- + CH_3-C(=O)-CH_2-C(=O)-OEt \rightleftharpoons CH_3-C(=O)-CH^--C(=O)-OEt + EtOH$$

pK_a 10.7
(stronger acid)

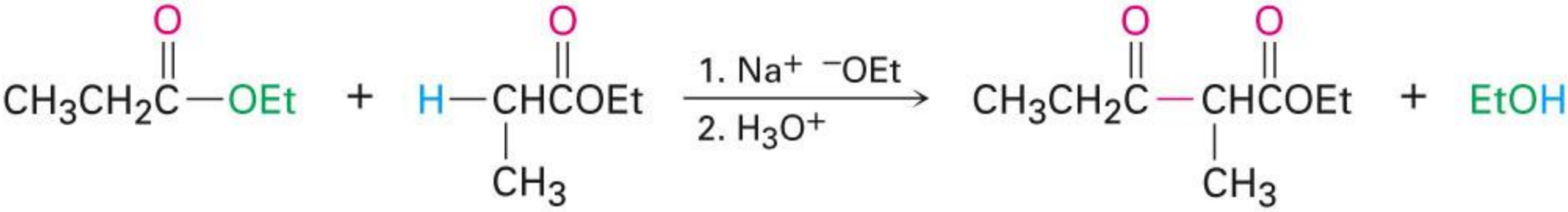
pK_a 15.9
(weaker acid)

Worked Example

Predicting the Product of a Claisen Condensation Reaction

What product would you obtain from Claisen condensation of ethyl propanoate?

Solution



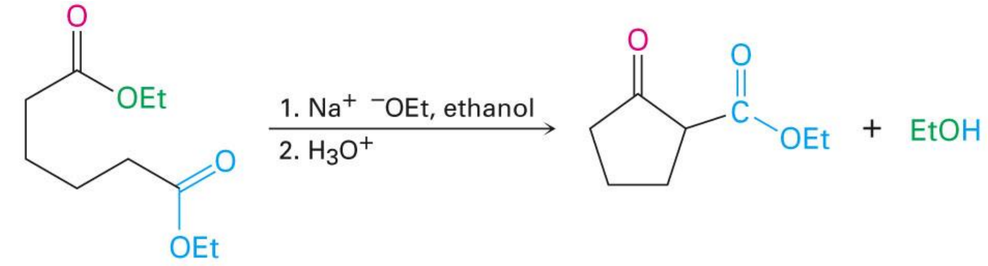
$$\mathrm{CH_3CH_2\overset{O}{\overset{\|}{C}}{-}OEt} + \mathrm{H{-}\underset{CH_3}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}OEt} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{Na^+\ {}^-OEt}} \mathrm{CH_3CH_2\overset{O}{\overset{\|}{C}}{-}\underset{CH_3}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}OEt} + \mathrm{EtOH}$$

2 Ethyl propanoate **Ethyl 2-methyl-3-oxopentanoate**

Intramolecular Claisen Condensations

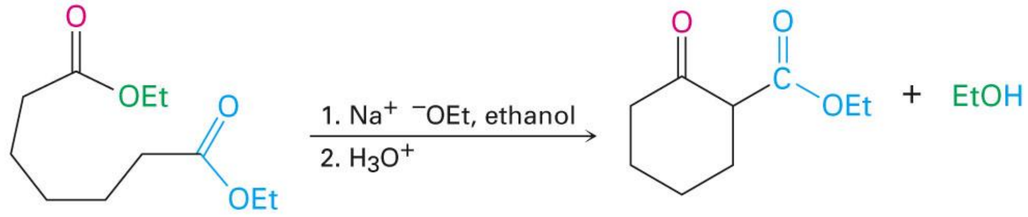
Intramolecular Claisen condensations are called *Dieckmann cyclizations*

- Reaction works best for 1,6 and 1,7 diesters
  - 1,6 Diester gives a five–membered cyclic β–keto ester
  - 1,7 Diester gives a six–membered cyclic β–keto ester



Diethyl hexanedioate (a 1,6-diester)

Ethyl 2-oxocyclopentanecarboxylate (82%)

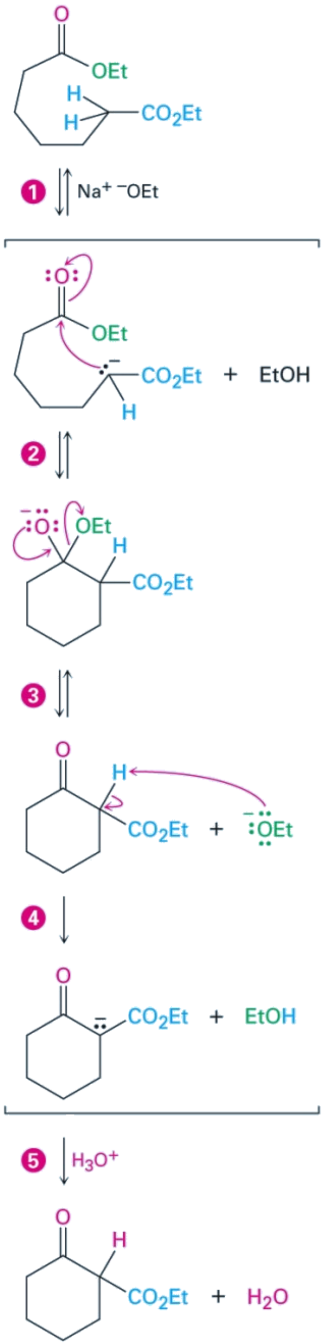


Diethyl heptanedioate (a 1,7-diester)

Ethyl 2-oxocyclohexanecarboxylate

Mechanism of Dieckmann cyclization

- Same as Claisen reaction mechanism



① Base abstracts an acidic α proton from the carbon atom next to one of the ester groups, yielding an enolate ion.

② Intramolecular nucleophilic addition of the ester enolate ion to the carbonyl group of the second ester group at the other end of the chain then gives a cyclic tetrahedral intermediate.

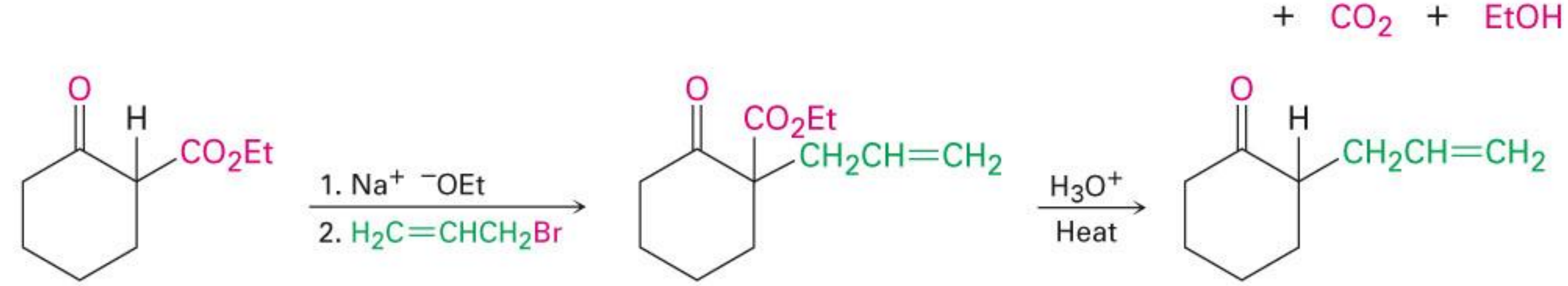
③ Loss of alkoxide ion from the tetrahedral intermediate forms a cyclic β-keto ester.

④ Deprotonation of the acidic β-keto ester gives an enolate ion . . .

⑤ . . . which is protonated by addition of aqueous acid at the end of the reaction to generate the neutral β-keto ester product.

The cyclic β–keto ester produced in an intramolecular Claisen cyclization can be further alkylated and decarboxylated

- 2–substituted cyclohexanones and cyclopentanones are prepared by the following sequence:
  1. Intramolecular Claisen cyclization
  2. β–Keto ester alkylation
  3. Decarboxylation



Ethyl 2-oxocyclohexanecarboxylate

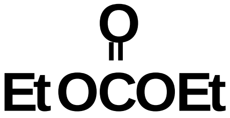
2-Allylcyclohexanone (83%)

Crossed Claisen Condensations

- Crossed Claisen condensations between two different esters, each with α–hydrogens, give mixtures of products and are usually *not useful*.
- But if one ester has no α–hydrogens crossed Claisen is useful.

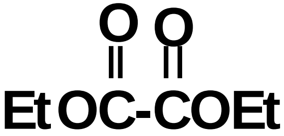
$H\overset{\overset{O}{\|}}{C}OEt$

Ethyl formate



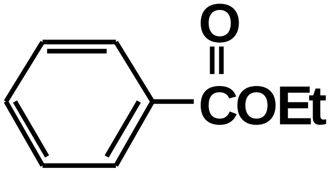
$EtO\overset{\overset{O}{\|}}{C}OEt$

Diethyl carbonate



$EtO\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}OEt$

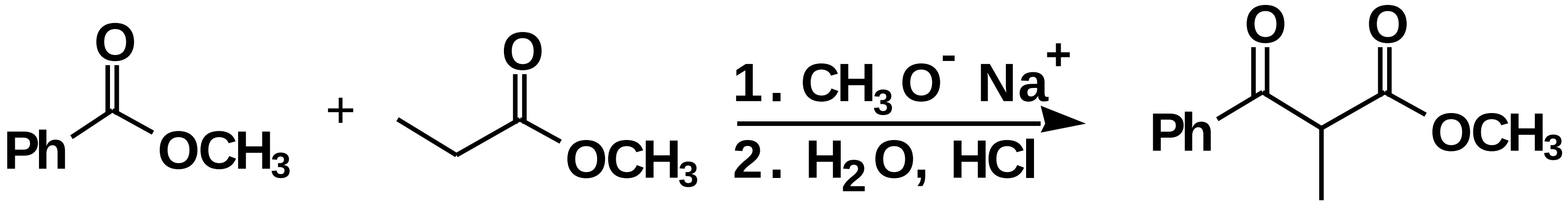
Diethyl ethanedioate (Diethyl oxalate)



Ethyl benzoate

No α-hydrogens

- The ester with no α-hydrogens is generally used in excess.



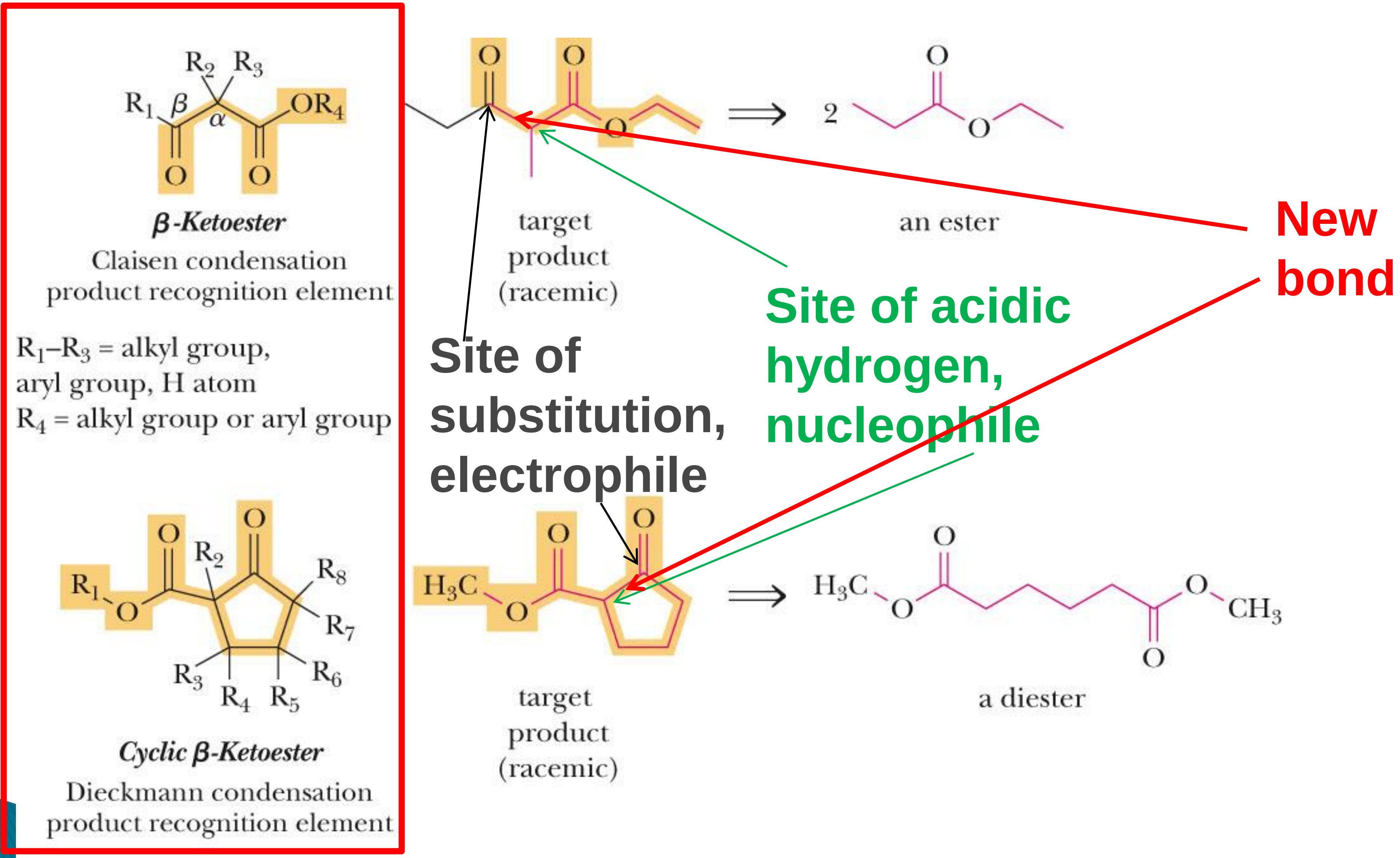
Methyl benzoate

Methyl propanoate

Methyl 2-methyl-3-oxo-3-phenylpropanoate (racemic)

Used in excess

Synthesis: Retrosynthetic Analysis



***β*-Ketoester**

Claisen condensation product recognition element

R$_1$–R$_3$ = alkyl group, aryl group, H atom

R$_4$ = alkyl group or aryl group

target product (racemic)

an ester

Site of substitution, electrophile

Site of acidic hydrogen, nucleophile

New bond

Cyclic β-Ketoester

Dieckmann condensation product recognition element

target product (racemic)

a diester

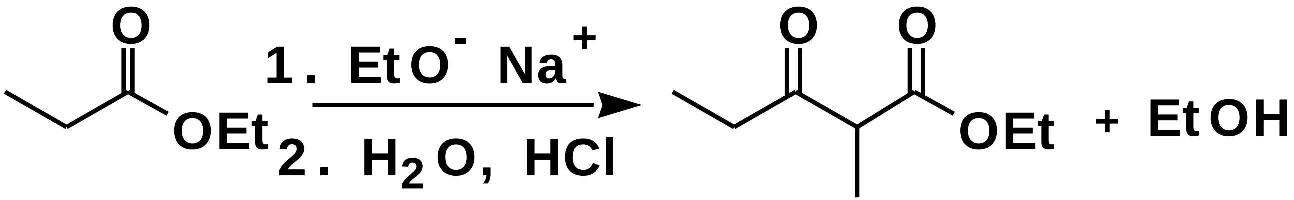
R$_1$ = alkyl group or aryl group

R$_2$–R$_8$ = alkyl group, aryl group, H atom

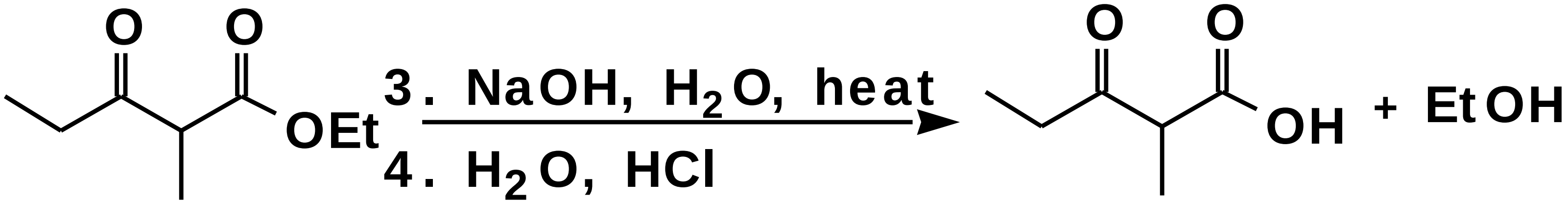
Synthesis: Claisen Condensation

- Claisen condensations are a route to ketones via decarboxylation

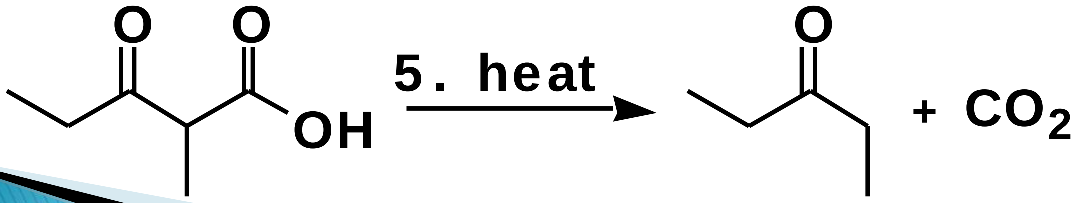
Reactions 1 & 2: Claisen condensation followed by acidification.



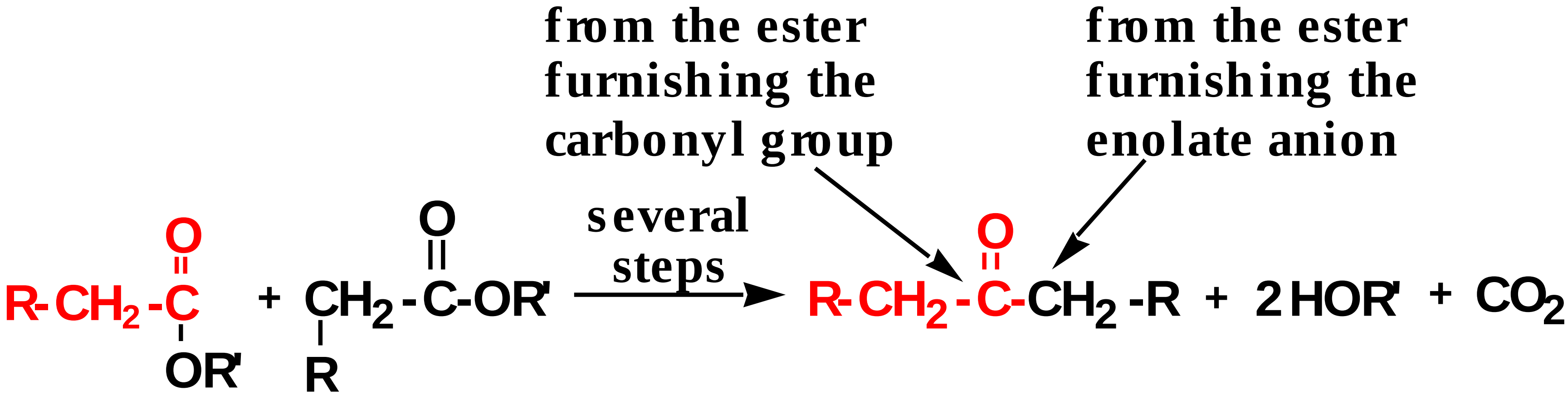
Reactions 3 & 4: Saponification and acidification



Reaction 5: Thermal decarboxylation.



The result of Claisen condensation, saponification, acidification, and decarboxylation is a ketone.



from the ester furnishing the carbonyl group

from the ester furnishing the enolate anion

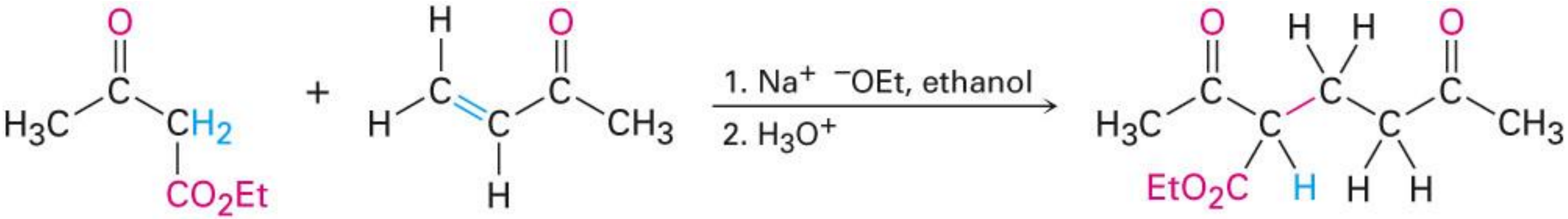
$$R\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{\underset{\underset{OR'}{|}}{C}} + \underset{\underset{R}{|}}{CH_2}\text{-}\overset{\overset{O}{\|}}{C}\text{-}OR' \xrightarrow{\text{several steps}} R\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}R + 2\,HOR' + CO_2$$

Note that in this Claisen (not crossed) the ketone is symmetric. **Crossed Claisen can yield non symmetric ketones.**

Conjugate Carbonyl Additions: The Michael Reaction

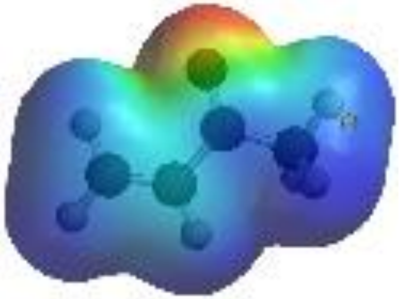
The conjugate addition of a nucleophilic enolate ion to an α,β–unsaturated carbonyl compound is known as the **Michael reaction**

- Best reactions are derived from addition of a β–keto ester or other 1,3–dicarbonyl compound to an unhindered α,β–unsaturated ketone
- Ethyl acetoacetate reacts with but-3-en-2-one in the presence of sodium ethoxide to yield the Michael addition product



Ethyl acetoacetate

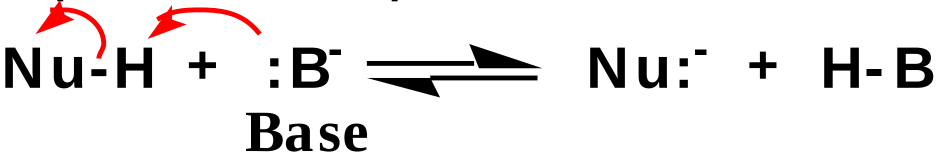
But-3-en-2-one



Mechanism: Michael Reaction

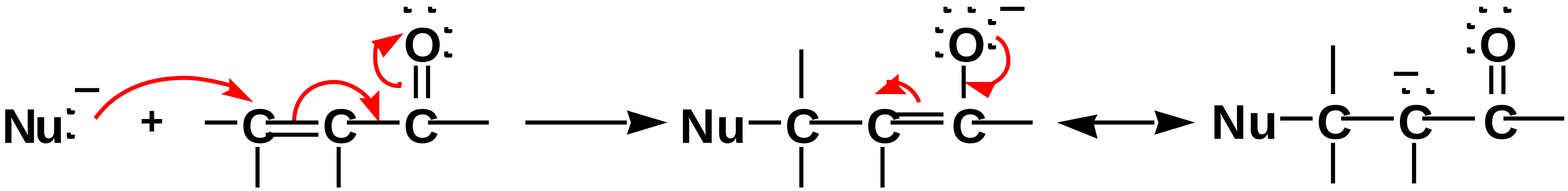
- Mechanism

1: Set up of nucleophile; Proton transfer to the base.



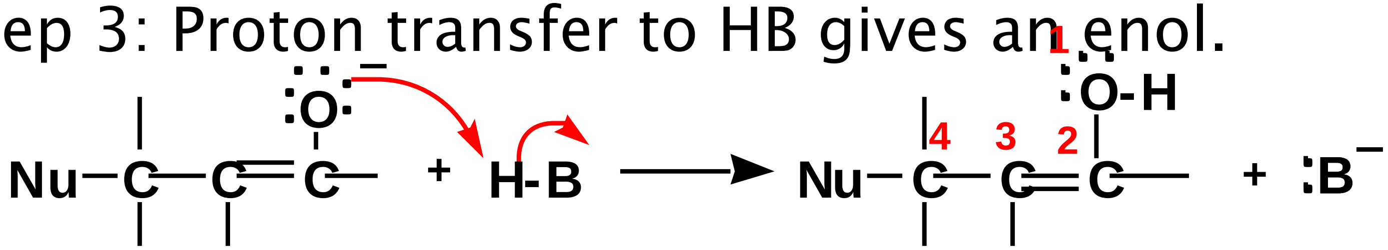
$$\mathrm{Nu{-}H} + :\mathrm{B}^- \rightleftharpoons \mathrm{Nu}:^- + \mathrm{H{-}B}$$

2: Addition of Nu:⁻ to the β carbon of the α,β–unsaturated carbonyl compound.



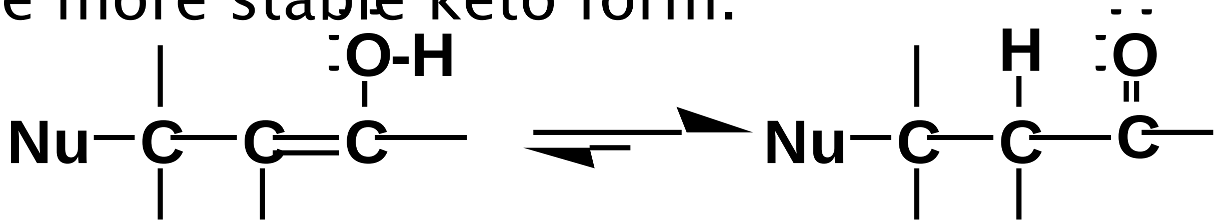
Resonance-stabilized enolate anion

Step 3: Proton transfer to HB gives an enol.



An enol
(a product of 1,4-addition)

Step 4: Tautomerism of the less stable enol form to the more stable keto form.



Less stable enol form **More stable keto form**

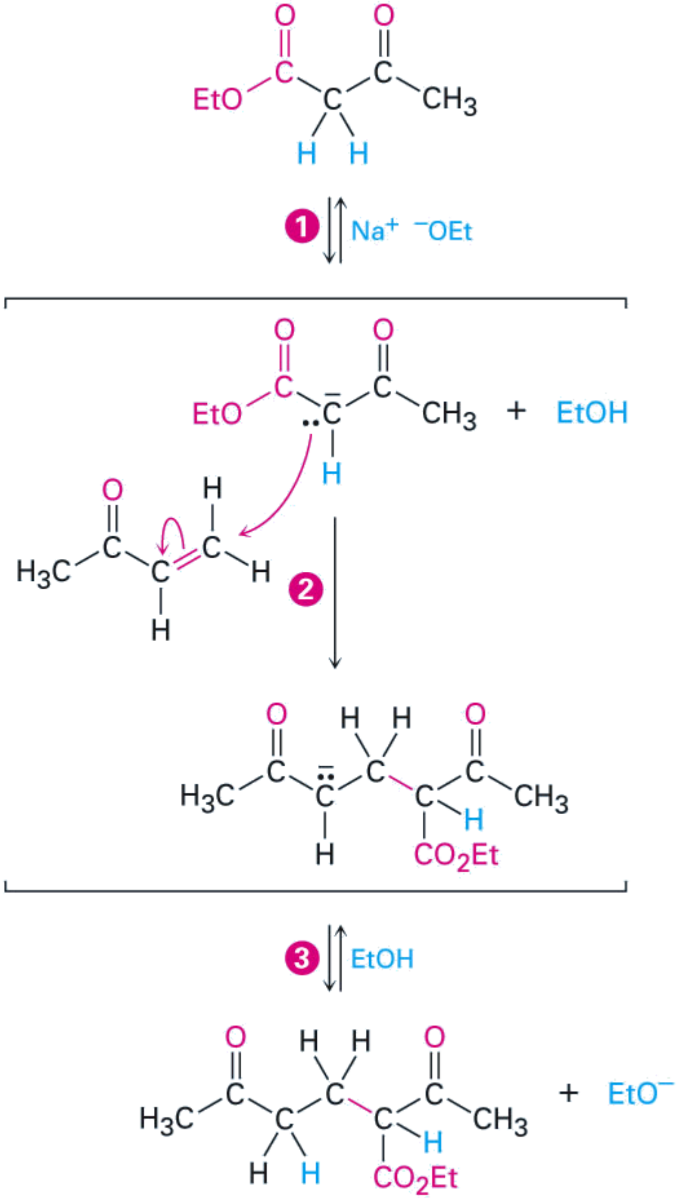
Mechanism of the Michael reaction

- The nucleophile – a Michael donor – is an enolate
- The electrophile – a Michael acceptor – is an α,β–unsaturated carbonyl

① The base catalyst removes an acidic alpha proton from the starting *β*-keto ester to generate a stabilized enolate ion nucleophile.

② The nucleophile adds to the *α,β*-unsaturated ketone electrophile in a Michael reaction to generate a new enolate as product.

③ The enolate product abstracts an acidic proton, either from solvent or from starting keto ester, to yield the final addition product.



Michael reaction occurs with a variety of α,β–unsaturated carbonyl compounds

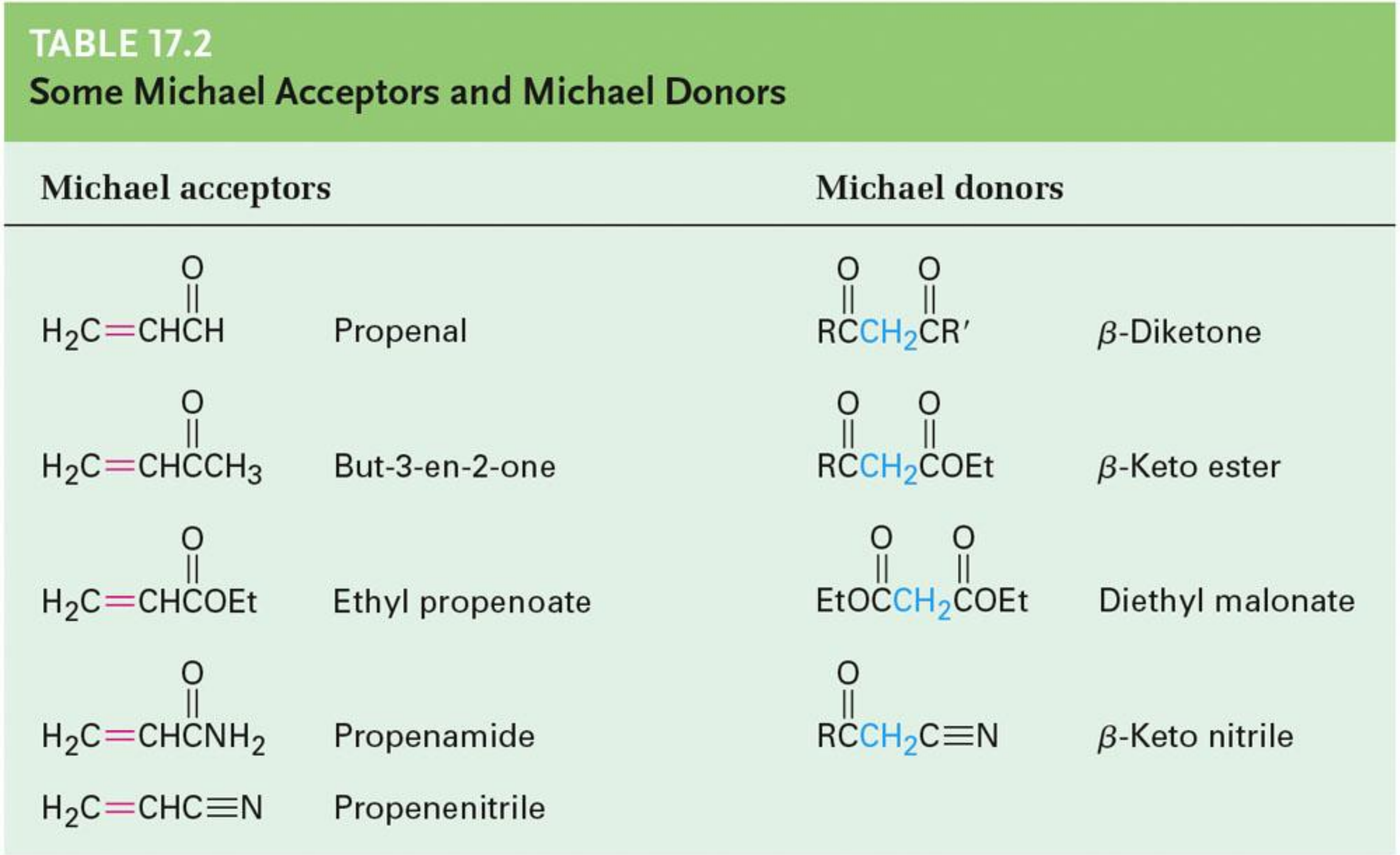


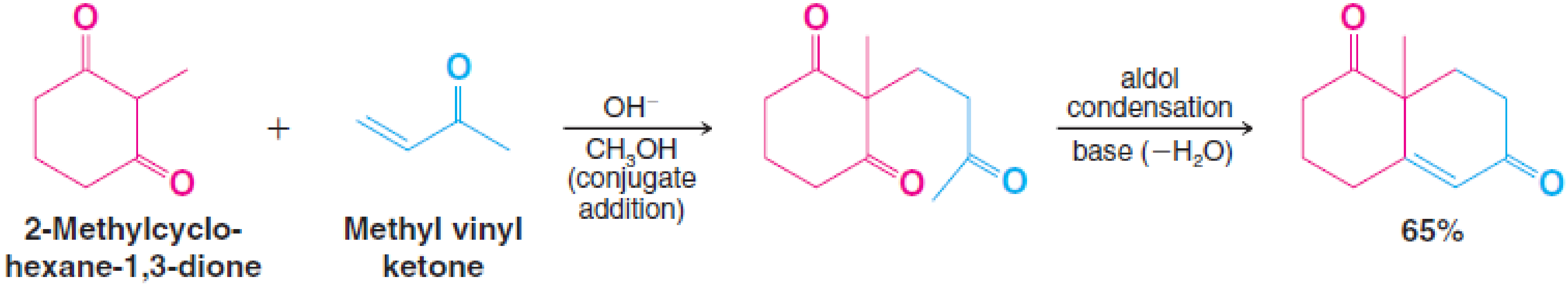
TABLE 17.2

Some Michael Acceptors and Michael Donors

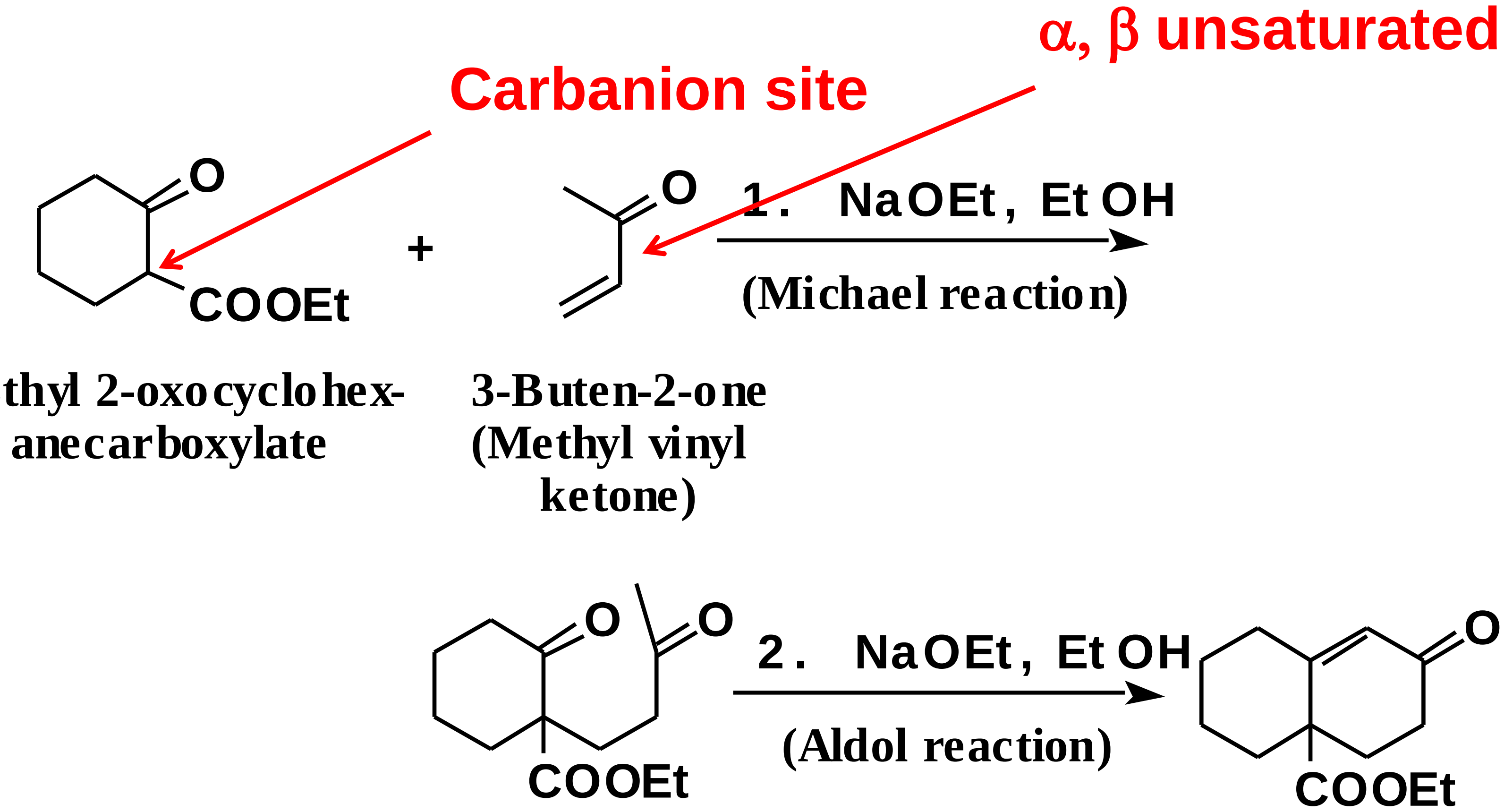
Michael acceptors		Michael donors	
$\mathrm{H_2C{=}CH\overset{\overset{O}{\Vert}}{C}H}$	Propenal	$\mathrm{R\overset{\overset{O}{\Vert}}{C}CH_2\overset{\overset{O}{\Vert}}{C}R'}$	β-Diketone
$\mathrm{H_2C{=}CH\overset{\overset{O}{\Vert}}{C}CH_3}$	But-3-en-2-one	$\mathrm{R\overset{\overset{O}{\Vert}}{C}CH_2\overset{\overset{O}{\Vert}}{C}OEt}$	β-Keto ester
$\mathrm{H_2C{=}CH\overset{\overset{O}{\Vert}}{C}OEt}$	Ethyl propenoate	$\mathrm{EtO\overset{\overset{O}{\Vert}}{C}CH_2\overset{\overset{O}{\Vert}}{C}OEt}$	Diethyl malonate
$\mathrm{H_2C{=}CH\overset{\overset{O}{\Vert}}{C}NH_2}$	Propenamide	$\mathrm{R\overset{\overset{O}{\Vert}}{C}CH_2C{\equiv}N}$	β-Keto nitrile
$\mathrm{H_2C{=}CHC{\equiv}N}$	Propenenitrile		

The Robinson Annulation

A Michael addition followed by a simple aldol condensation may be used to build one ring onto another. This procedure is known as the *Robinson annulation (ring-forming) reaction*



Micheal–Aldol Combination



Ethyl 2-oxocyclohexanecarboxylate

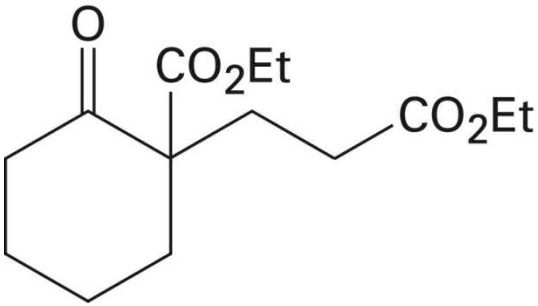
3-Buten-2-one (Methyl vinyl ketone)

Dieckman

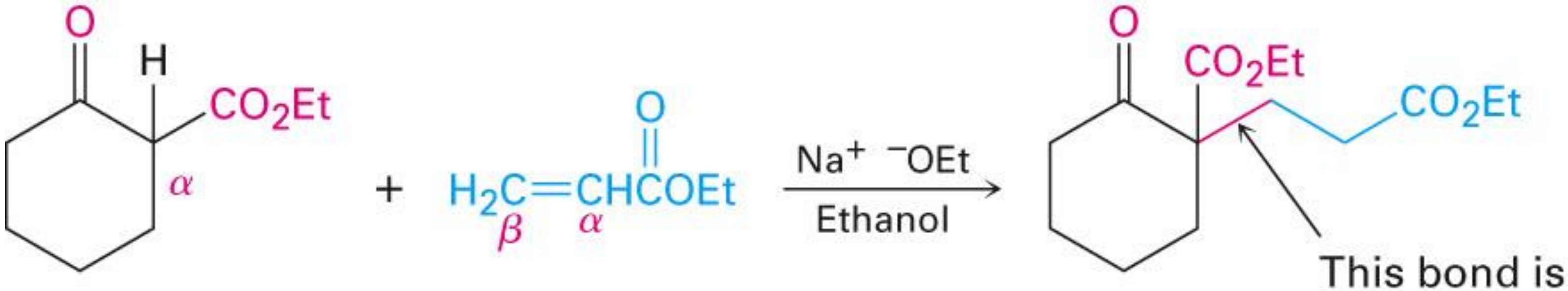
Worked Example

Using the Michael Reaction

How might you obtain the following compound using a Michael reaction?



Solution

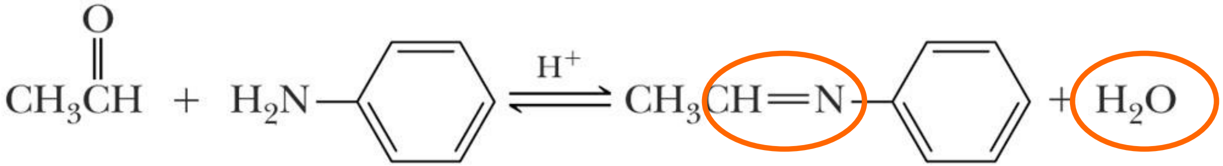


This bond is formed in the Michael reaction.

Enamines (and imines, Schiff bases)

Recall primary amines react with carbonyl compounds to give Schiff bases (imines), RN=CR$_2$.

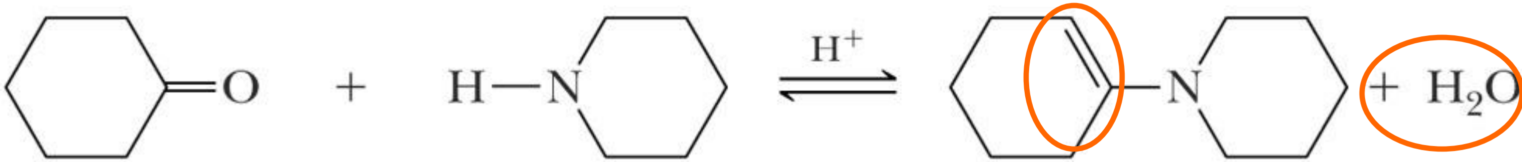
Primary amine



Acetaldehyde Aniline An imine (a Schiff base)

But secondary amines react to give enamines

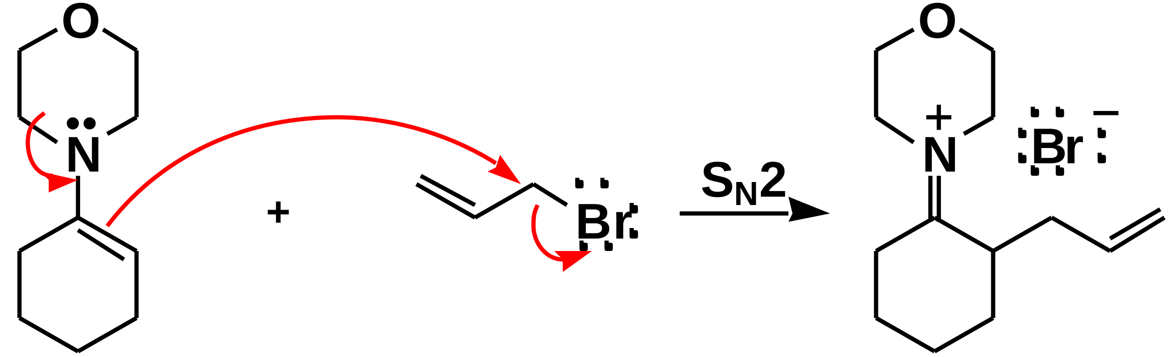
Secondary Amine



Cyclohexanone Piperidine (a secondary amine) An enamine

Enamines – Alkylation at α position.

- The value of enamines is that the β–carbon is nucleophilic.
  - Enamines undergo S_N2 reactions with methyl and 1° haloalkanes, α–haloketones, and α–haloesters.
  - Treatment of the enamine with one equivalent of an alkylating agent gives an iminium halide.

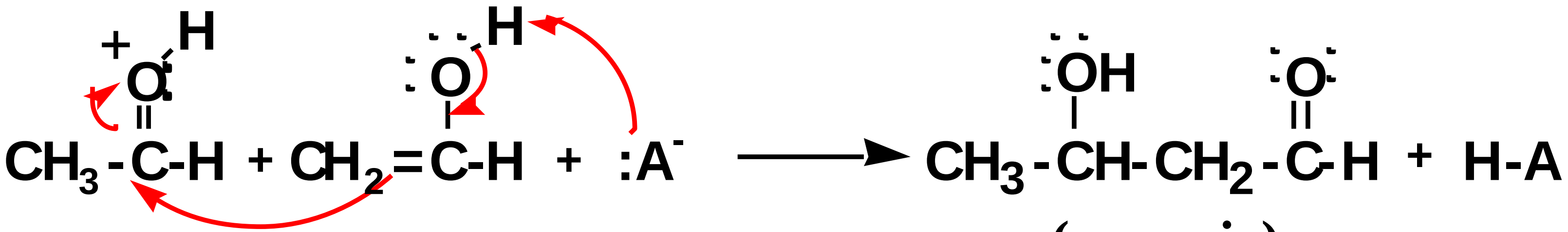


The morpholine enamine of cyclohexanone

3-Bromopropene (Allyl bromide)

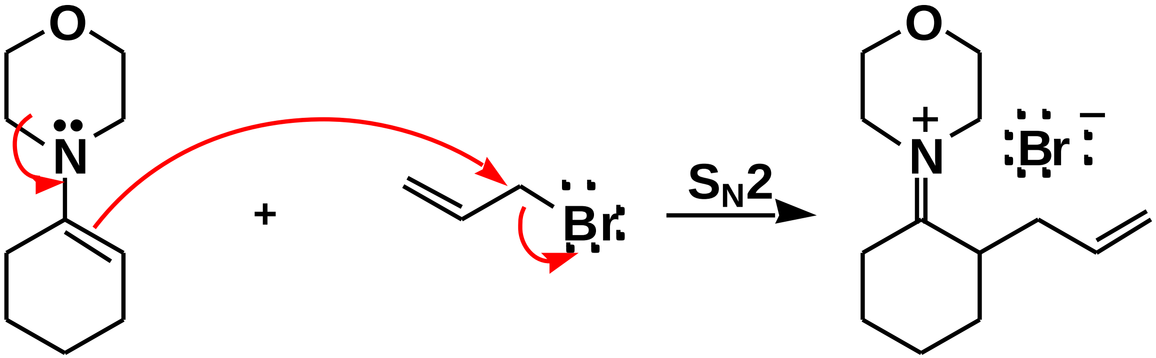
An iminium bromide (racemic)

Compare mechanisms of acid catalyzed aldol and enamine



$$CH_3\text{-}\overset{\overset{+}{O}H}{\overset{\|}{C}}\text{-}H + CH_2{=}\overset{OH}{\overset{|}{C}}\text{-}H + :A^- \longrightarrow CH_3\text{-}\overset{OH}{\overset{|}{C}H}\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + H\text{-}A$$

(racemic)

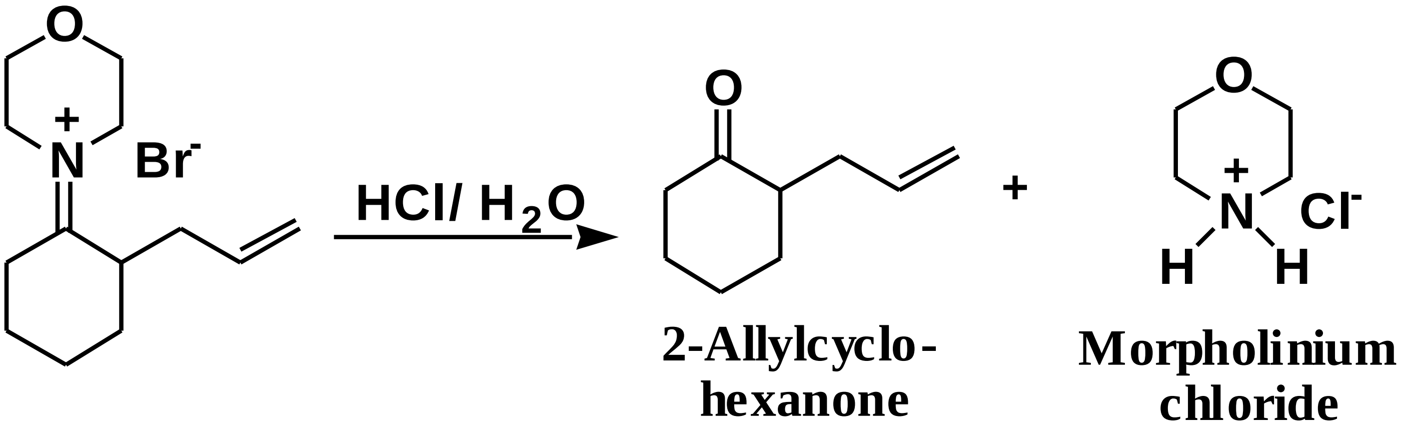


The morpholine enamine of cyclohexanone

3-Bromopropene (Allyl bromide)

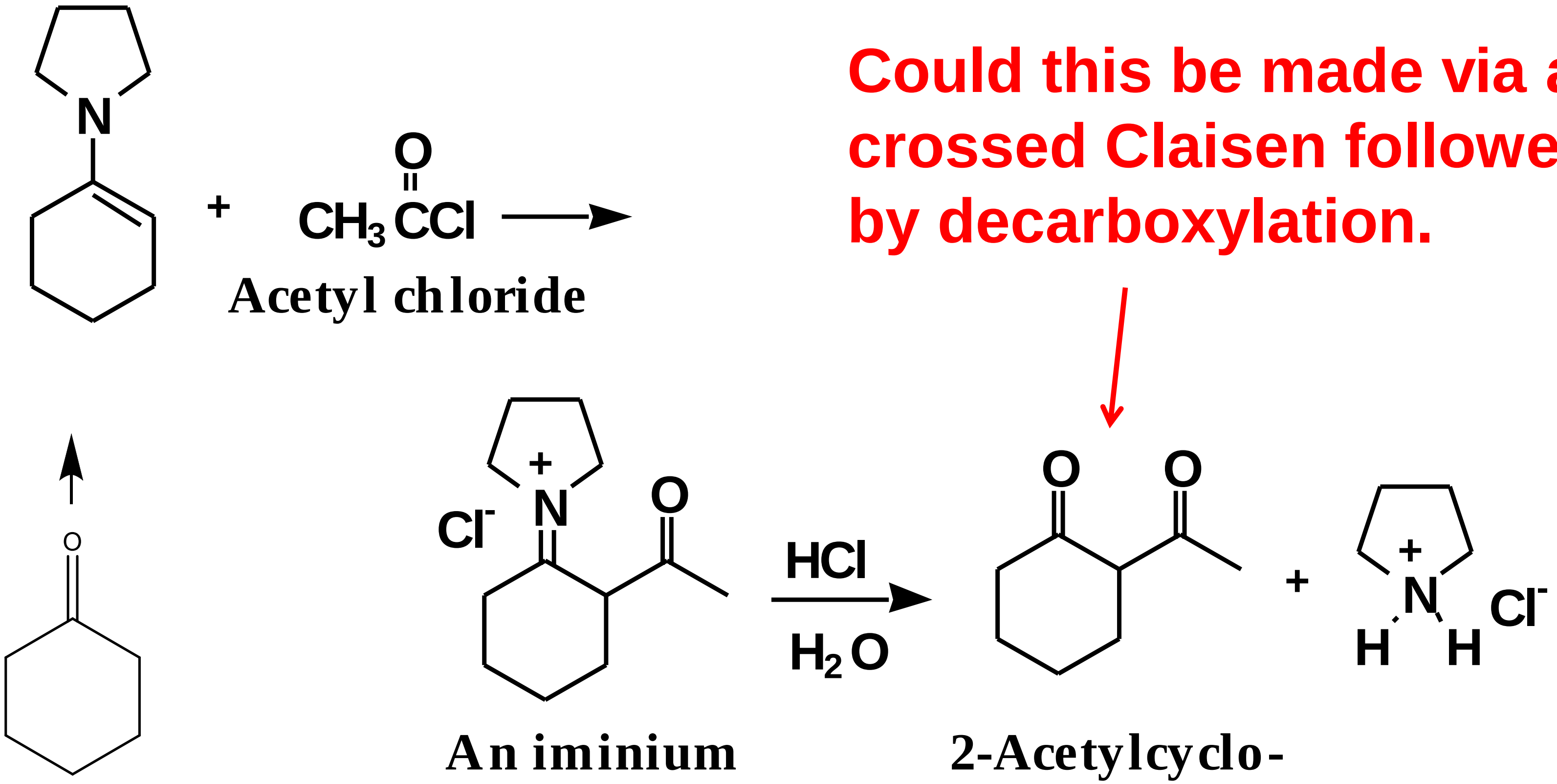
An iminium bromide (racemic)

- Hydrolysis of the iminium halide gives an alkylated aldehyde or ketone.



Overall process is to render the alpha carbonss of ketone nucleophilic enough so that substitution reactions can occur.

- Enamines undergo acylation when treated with acid chlorides and acid anhydrides.



Acetyl chloride

Could this be made via a crossed Claisen followed by decarboxylation.

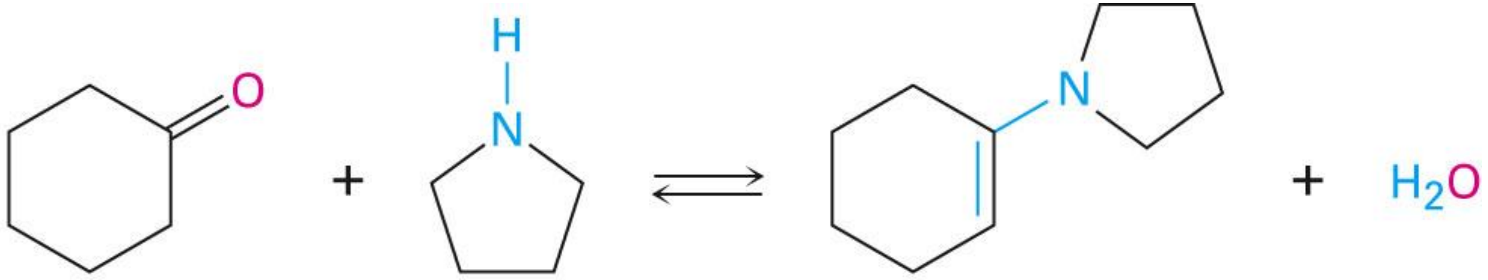
An iminium chloride (racemic)

2-Acetylcyclohexanone (racemic)

Carbonyl Condensations with Enamines: The Stork Reaction

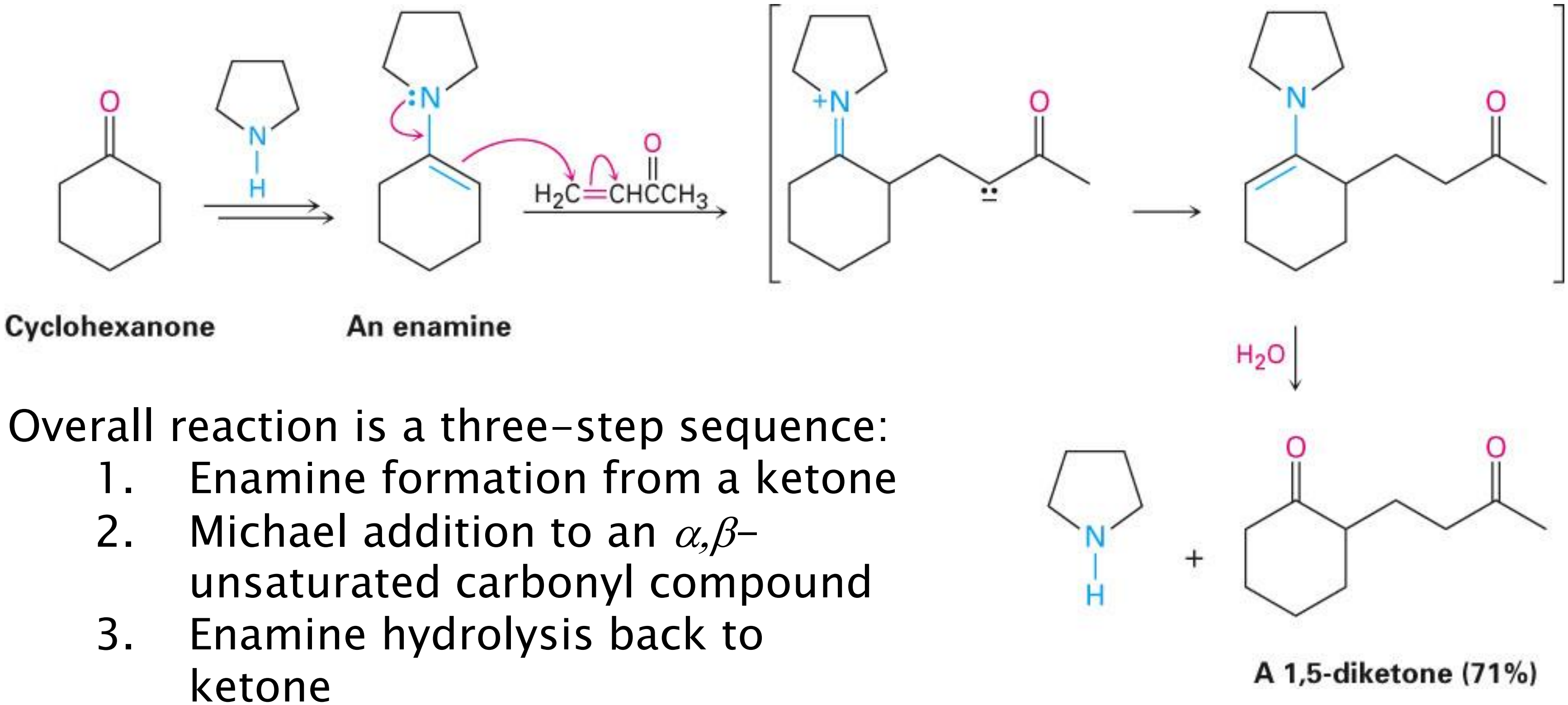
Enamine nucleophiles add to *α,β*–unsaturated acceptors in Michael–like reactions

- Reactions are particularly important in biological chemistry
- Enamines are prepared by reaction between a ketone and a secondary amine



Cyclohexanone **Pyrrolidine** **1-Pyrrolidino-cyclohexene (87%)**

The net effect of the Stork reaction is a Michael addition of a ketone to an α,β–unsaturated carbonyl compound



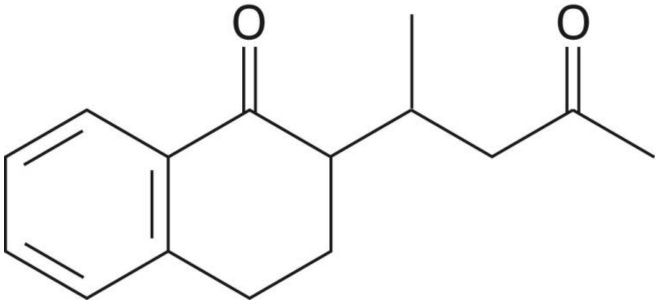
Overall reaction is a three-step sequence:

1. Enamine formation from a ketone
2. Michael addition to an α,β–unsaturated carbonyl compound
3. Enamine hydrolysis back to ketone

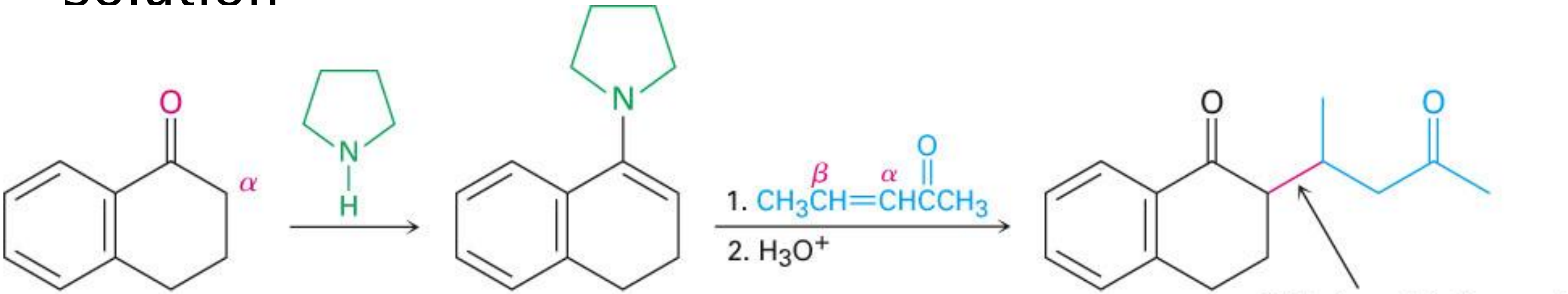
Worked Example

Using the Stork Enamine Reaction

How might you use an enamine reaction to prepare the following compound?



Solution



This bond is formed in the Michael reaction.

Biological Carbonyl Condensation Reactions

Biological Aldol Reactions

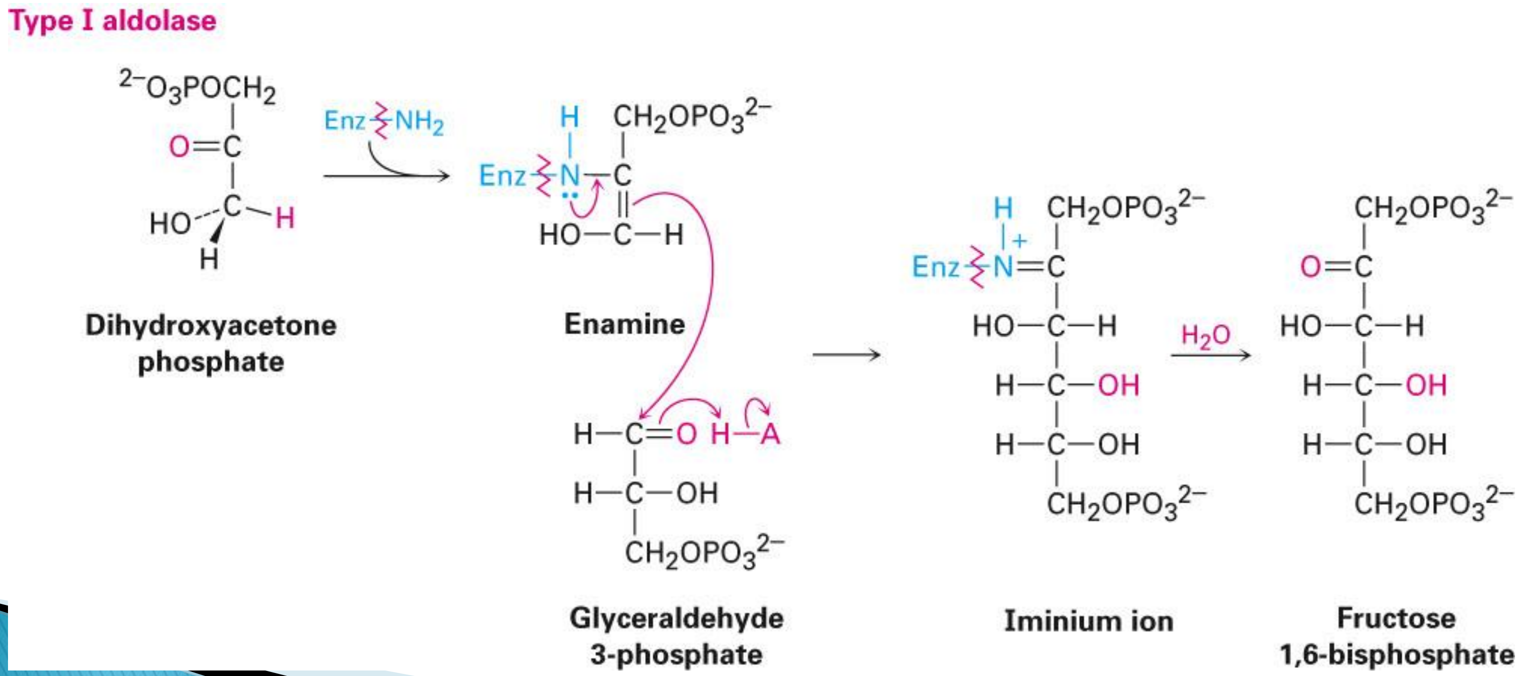
Aldol reactions are particularly important in carbohydrate metabolism

- Enzymes called *aldolases* catalyze addition of a ketone enolate ion to an aldehyde
  - Type I aldolases occur primarily in animals and higher plants
    - Operate through an enolate ion
  - Type II aldolases occur primarily in fungi and bacteria

Biological Carbonyl Condensation Reactions

Mechanism of Type I aldolase in glucose biosynthesis

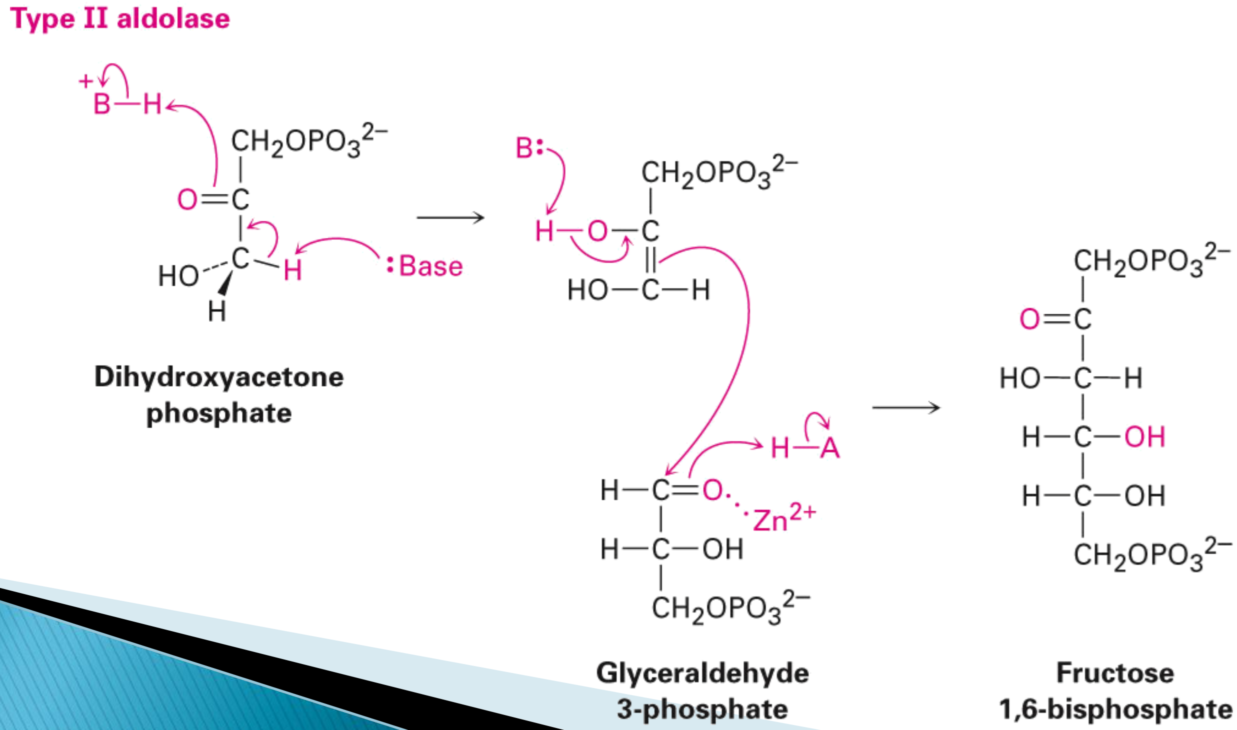
- Dihydroxyacetone phosphate is first converted into an enamine by reaction with the $-NH_2$ group on a lysine amino acid in the enzyme
- Enamine adds to glyceraldehyde 3-phosphate
- Resultant iminium ion is hydrolyzed



Biological Carbonyl Condensation Reactions

Mechanism of Type II aldolase in glucose biosynthesis

- Aldol reaction occurs directly
- Ketone carbonyl group of glyceraldehyde 3-phosphate complexed to a Zn^{2+} ion to make it a better acceptor

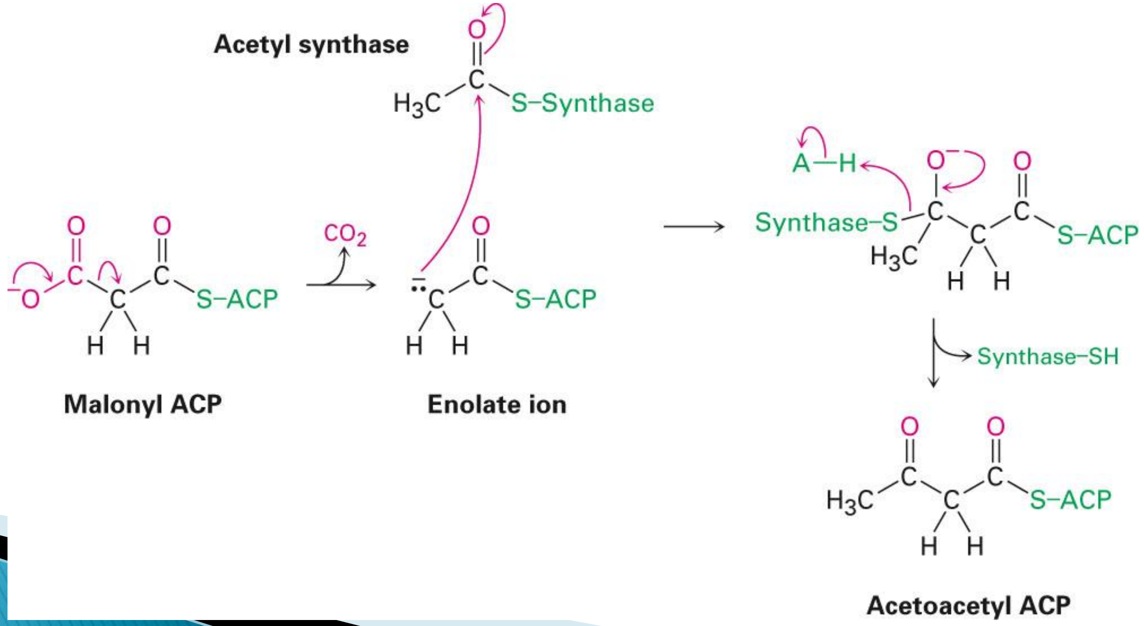


Biological Carbonyl Condensation Reactions

Biological Claisen Condensations

Claisen condensations occur in a large number of biological pathways

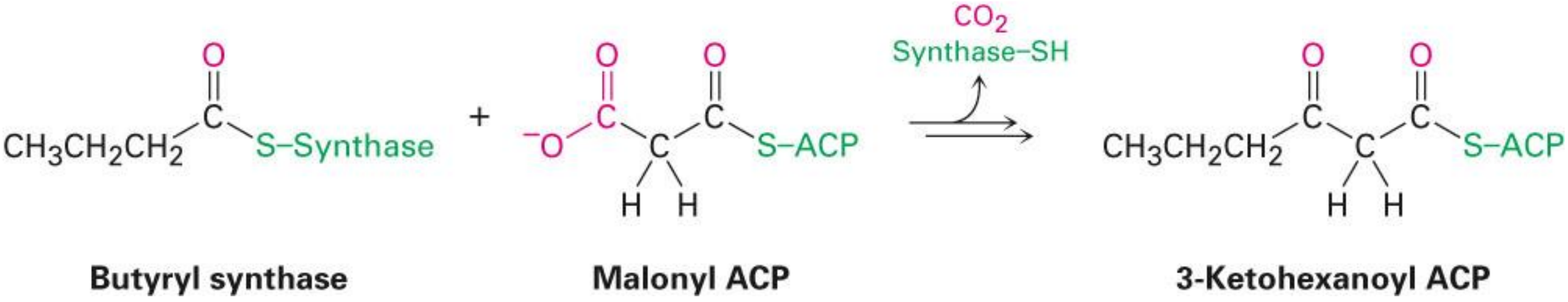
- In fatty acid biosynthesis an enolate ion generated by decarboxylation of malonyl ACP adds to the carbonyl group of another acyl group bonded through a thioester linkage to a synthase enzyme
- The tetrahedral intermediate expels the synthase, giving acetoacetyl ACP



Biological Carbonyl Condensation Reactions

Mixed Claisen condensations occur frequently in living organisms

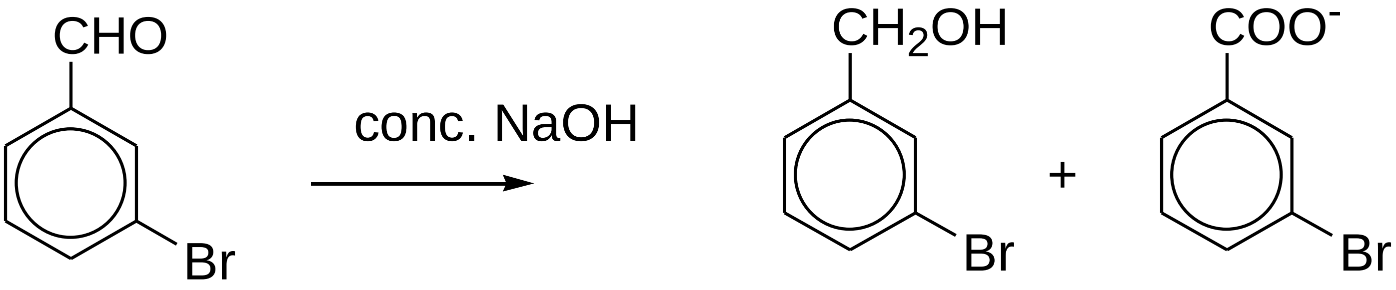
- Butyryl synthase, in the fatty-acid biosynthesis pathway, reacts with malonyl ACP in a mixed Claisen condensation to give 3-ketohexanoyl ACP



Cannizzaro reaction

(self oxidation/reduction)

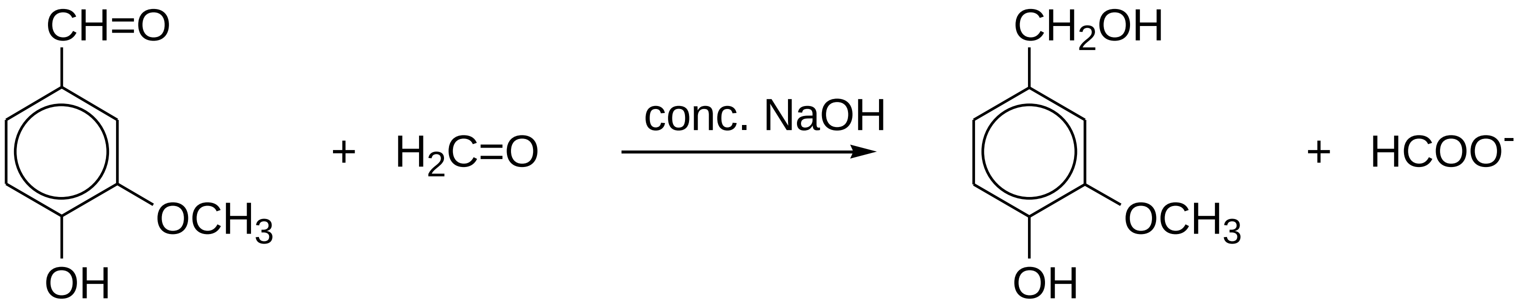
a reaction of **aldehydes without α-hydrogens**



$$H_2C{=}O \xrightarrow{\text{conc. NaOH}} CH_3OH + HCOO^-$$

Formaldehyde is the most easily oxidized aldehyde. When mixed with another aldehyde that doesn’t have any alpha-hydrogens and conc. NaOH, all of the formaldehyde is oxidized and all of the other aldehyde is reduced.

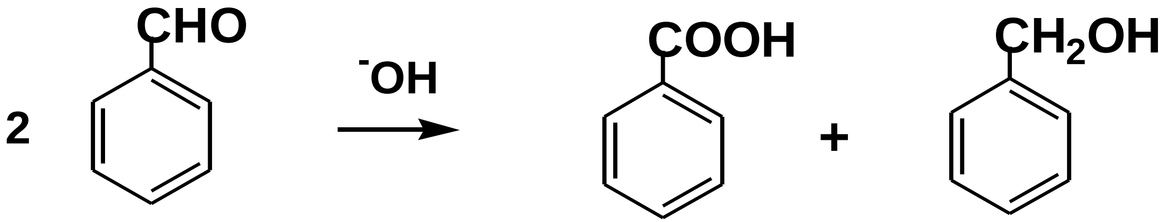
Crossed Cannizzaro:



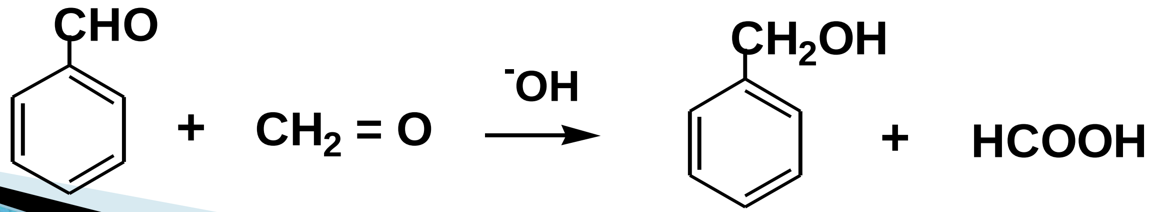
vanillin

The Cannizzaro and Crossed Cannizzaro Reactions:

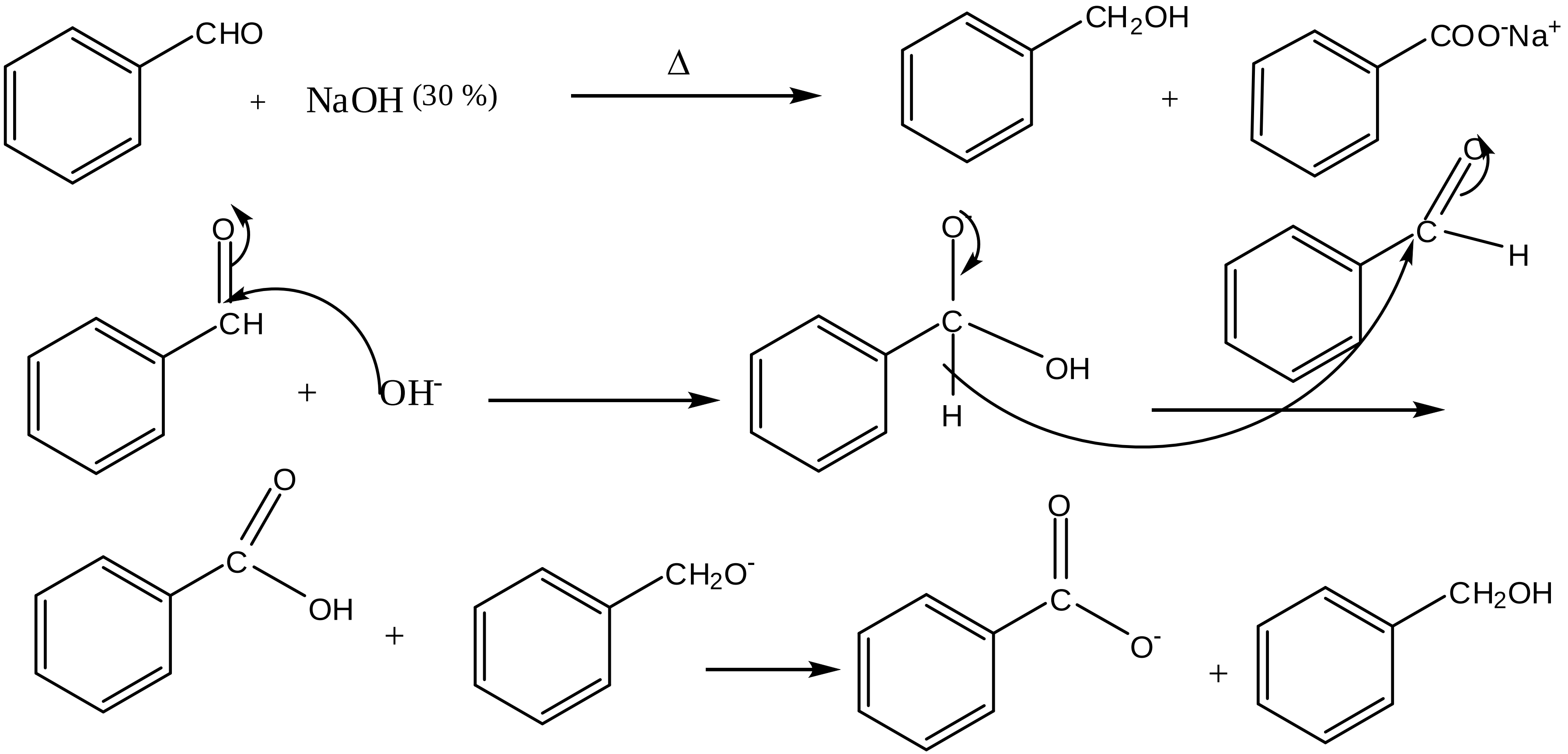
- The result is an oxidation-reduction reaction (a disproportionation) giving a carboxylic acid and an alcohol.



- In the crossed Cannizzaro, different aldehydes are used but still neither has α-hydrogens and hydroxide ion attacks the more reactive carbonyl.



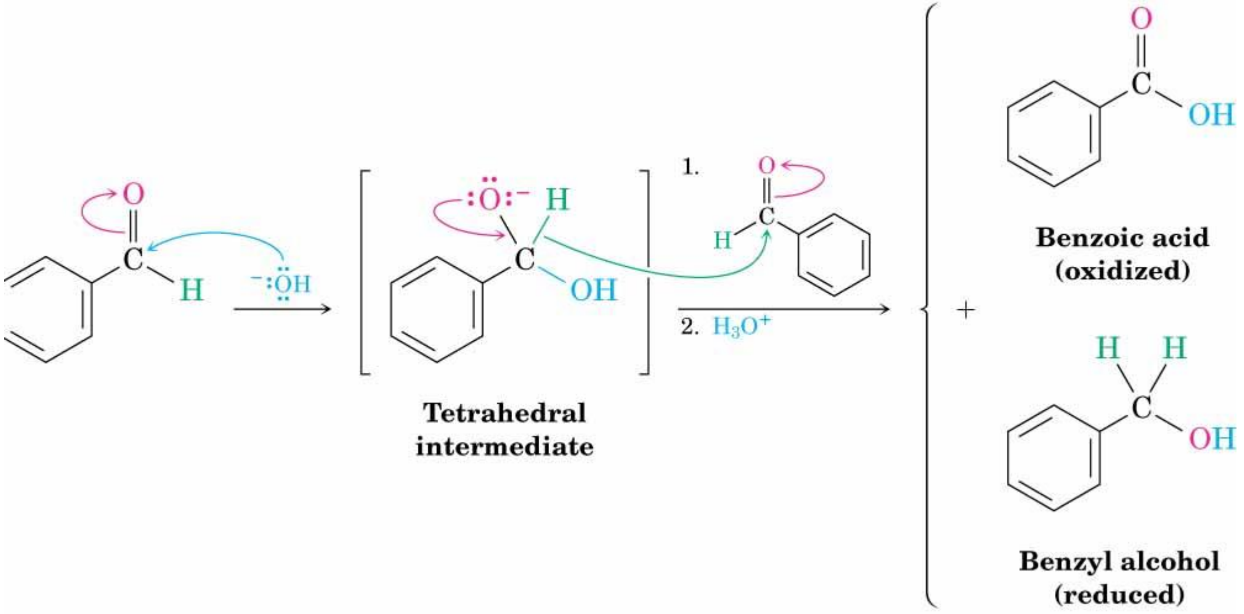
mechanism



more stable anion

The Cannizzaro Reaction: Biological Reductions

- The adduct of an aldehyde and OH⁻ can transfer hydride ion to another aldehyde C=O resulting in a simultaneous oxidation and reduction (*disproportionation)*



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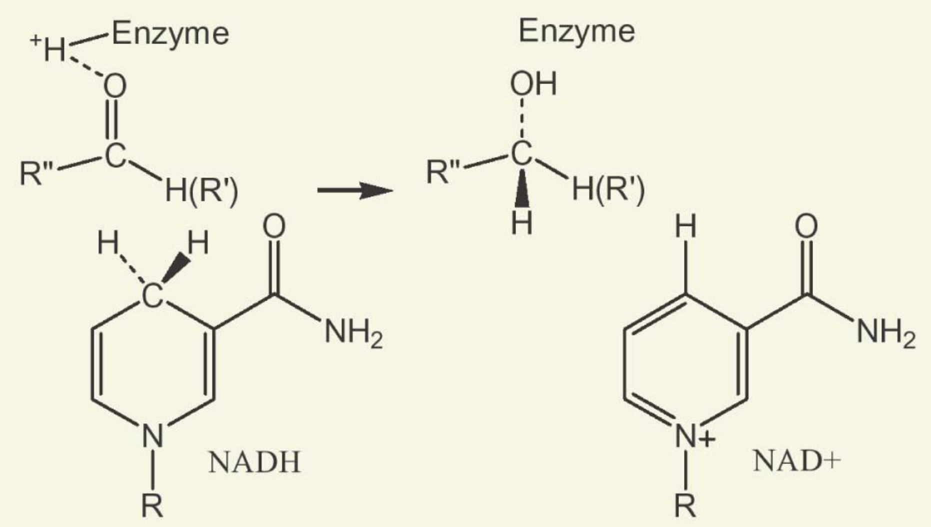
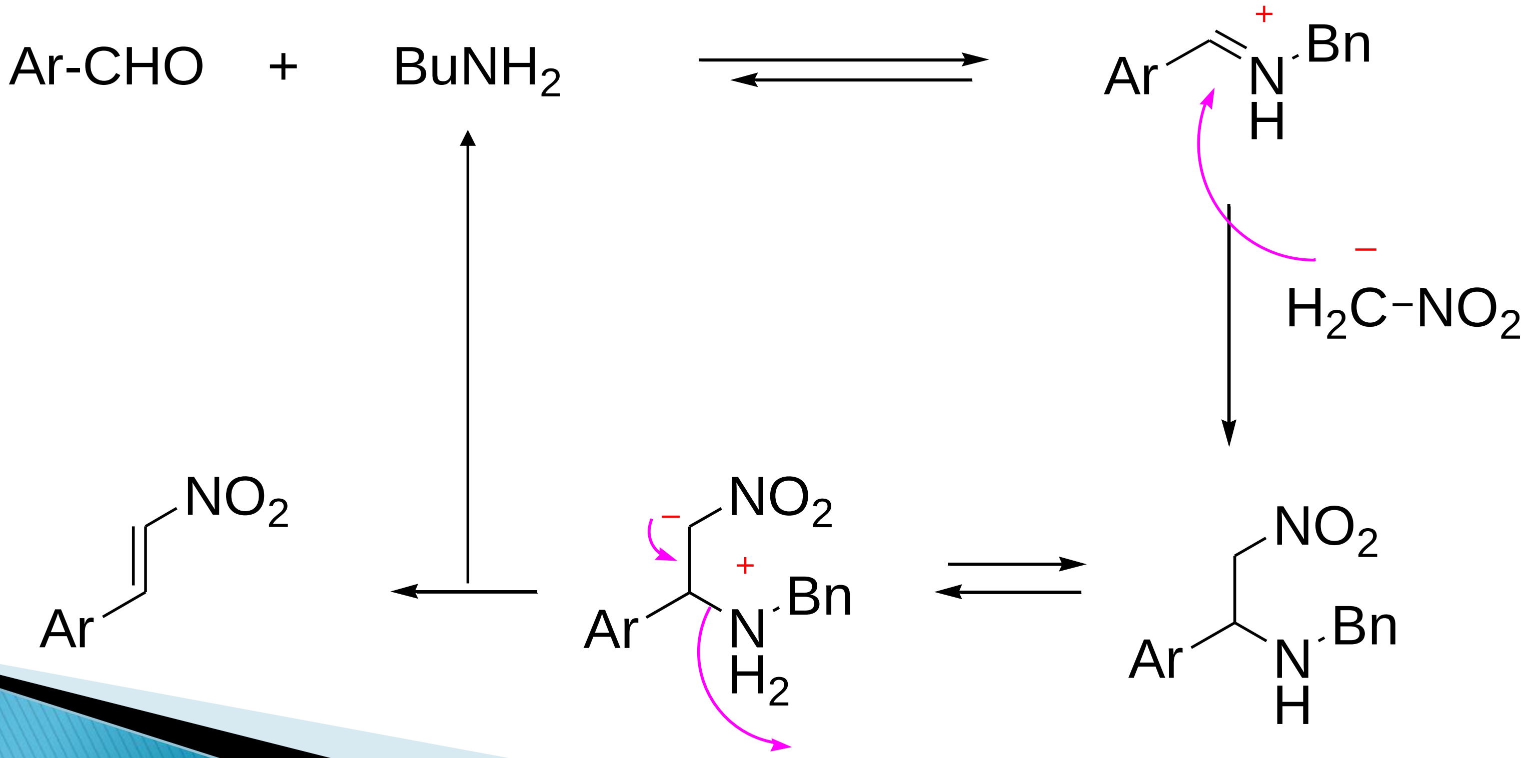
The Biological Analogue of the Canizzaro Reaction

- Enzymes catalyze the reduction of aldehydes and ketones using NADH as the source of the equivalent of H^-
- The transfer resembles that in the Cannizzaro reaction but the carbonyl of the acceptor is polarized by an acid from the enzyme, lowering the barrier

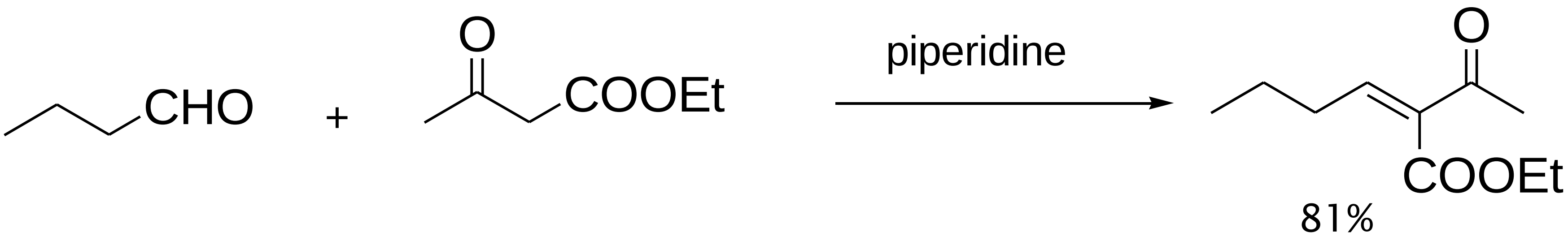


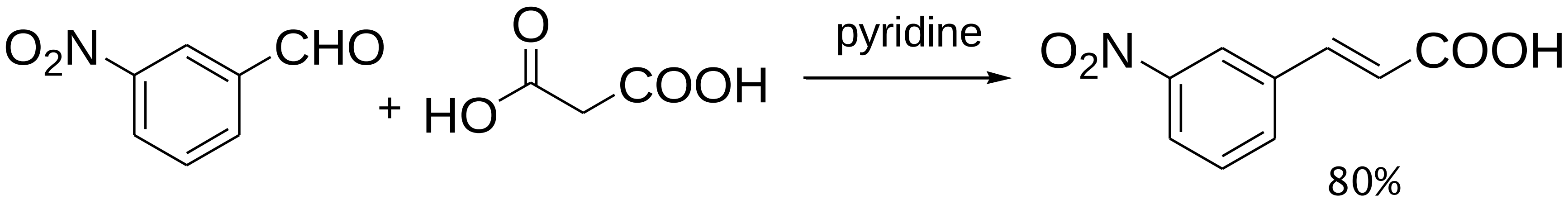
Enzymes are chiral and the reactions are stereospecific. The stereochemistry depends on the particular enzyme involved.

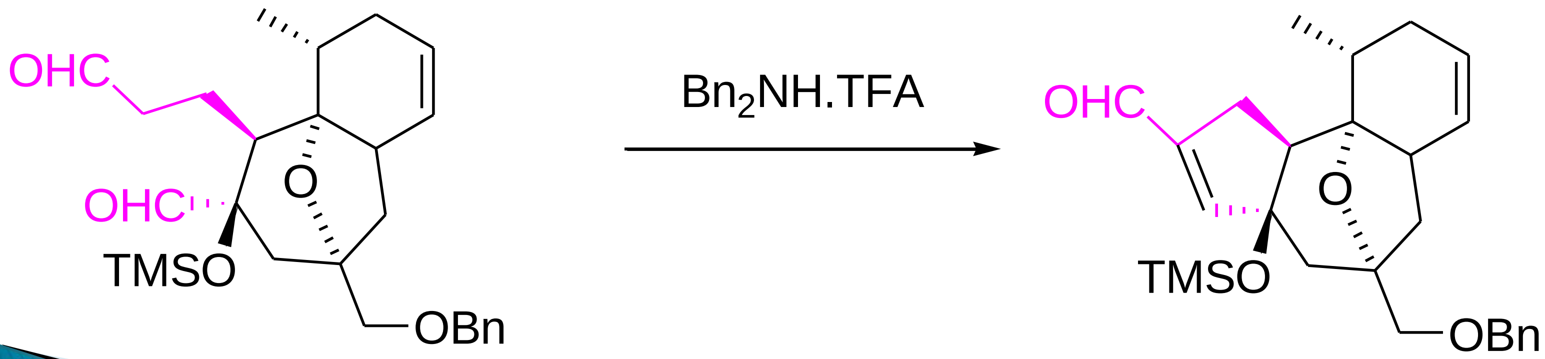
Knoevenagel reaction



Knoevenagel reaction

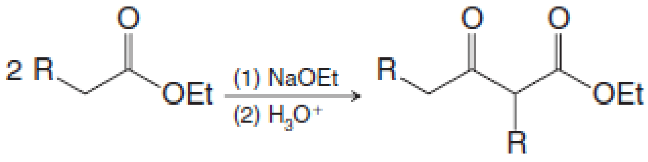




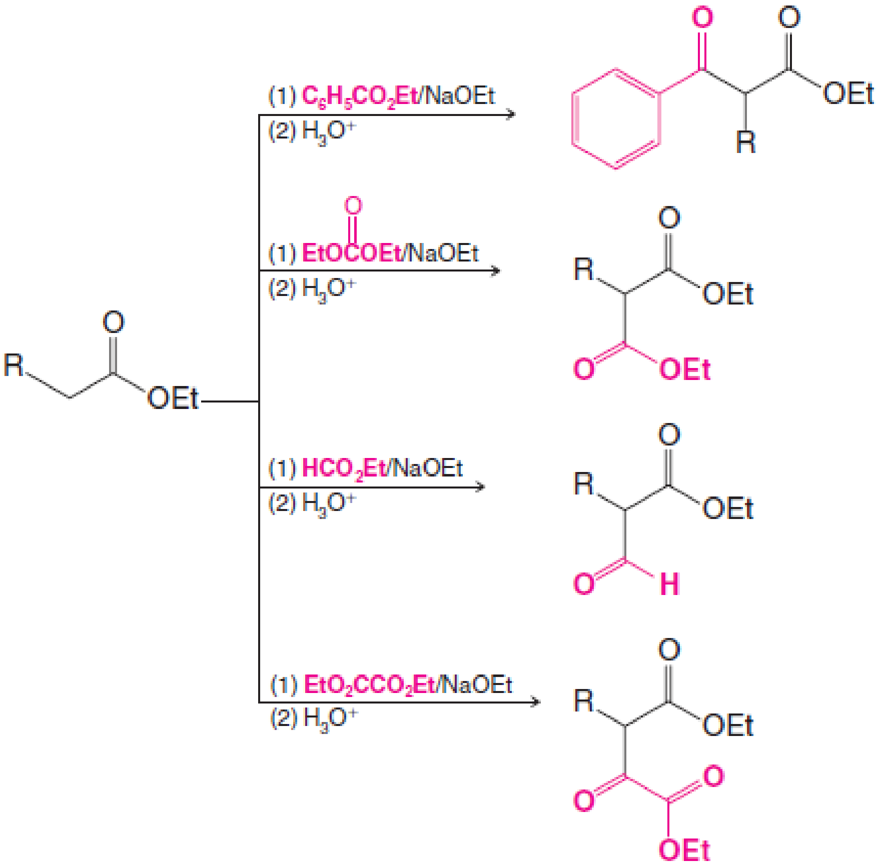


Summary

1. Claisen Condensation (Section 19.2):

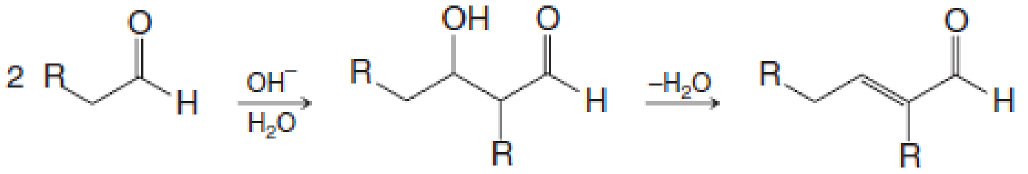


2. Crossed Claisen Condensation (Section 19.2B):

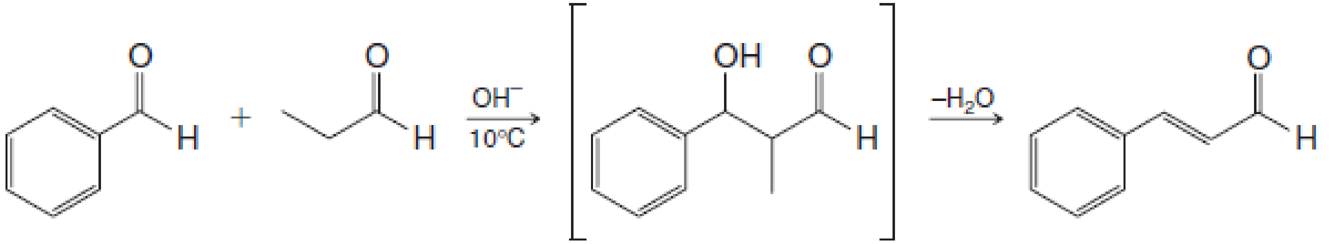


3. Aldol Reaction (Section 19.4)

General Reaction

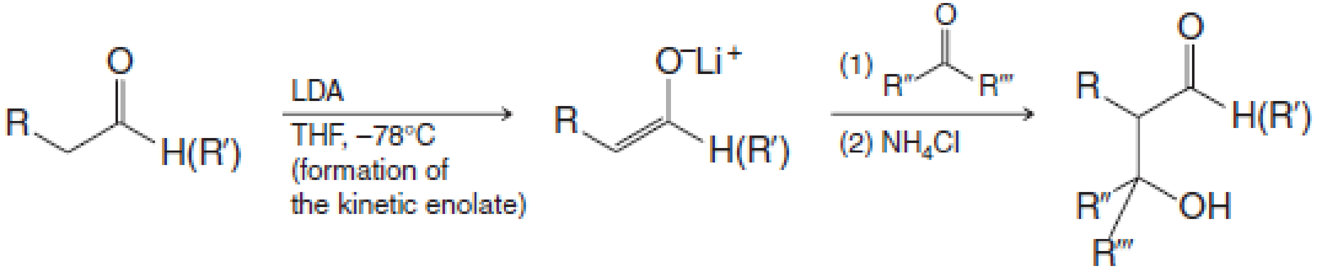


Specific Example

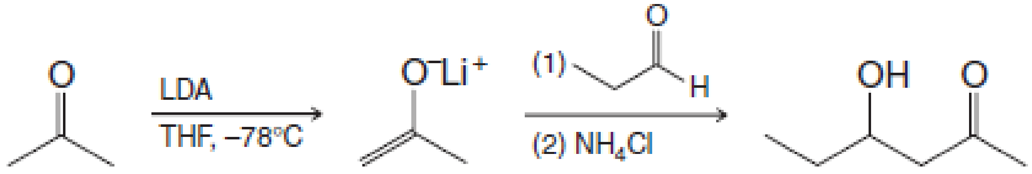


4. Directed Aldol Reactions via Lithium Enolates (Section 19.5B)

General Reaction

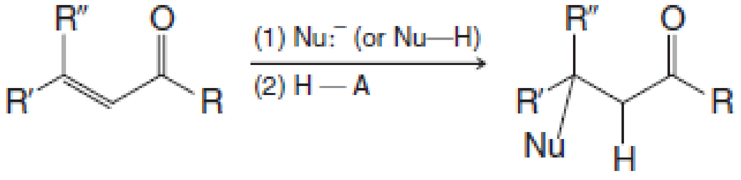


Specific Example



5. Conjugate Addition (Section 19.7)

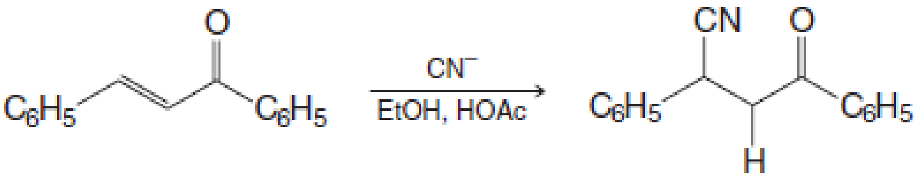
General Example



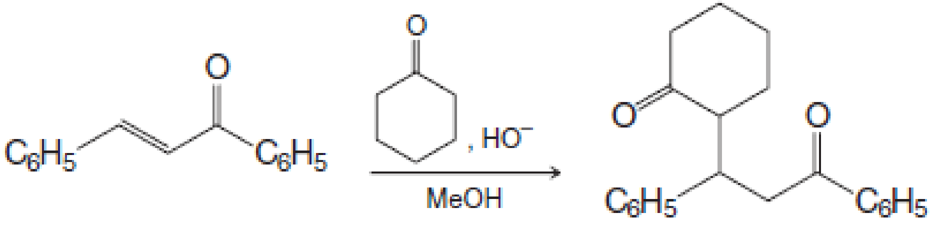
Nu:⁻ = CN⁻; an enolate (Michael addition); R‴MgBr

Nu—H = 1° or 2° amines; an enamine

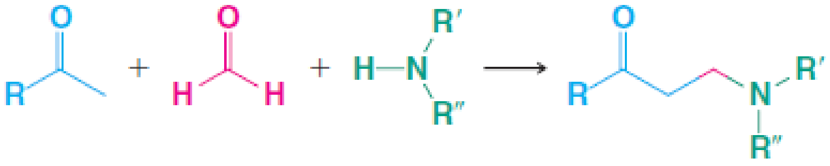
Specific Example



Specific Example (Michael Addition)



6. Mannich Reaction (Section 19.8):

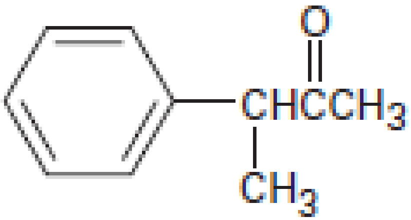


Exercise

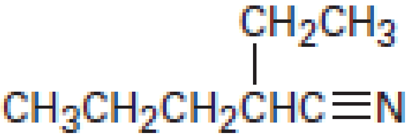
Problem 22.16

Show how you might prepare the following compounds using an alkylation reaction as the key step:

(a)

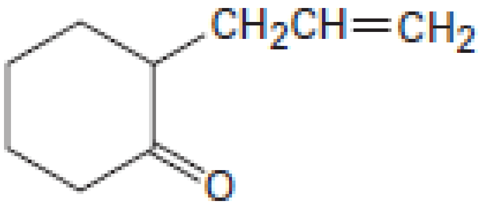


(b)

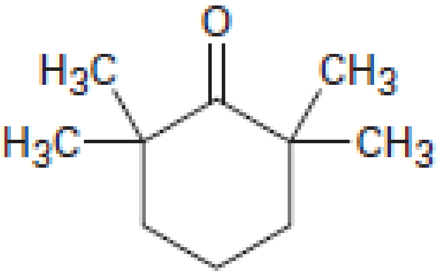


$CH_3CH_2CH_2\overset{CH_2CH_3}{\overset{|}{C}}HC{\equiv}N$

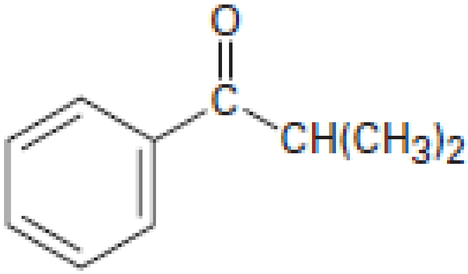
(c)



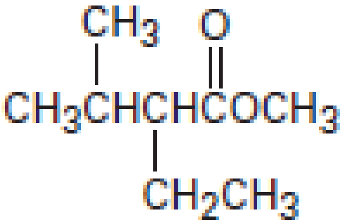
(d)



(e)



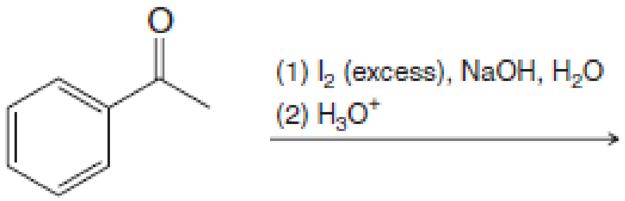
(f)



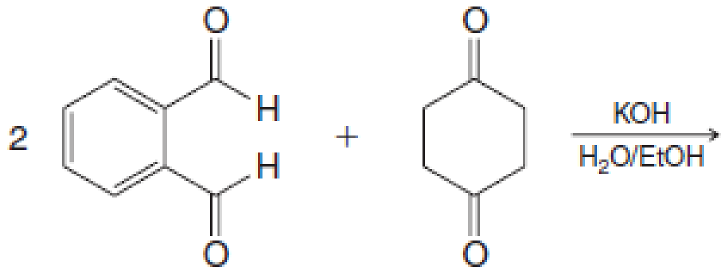
$CH_3\overset{CH_3}{\overset{|}{C}}H\underset{\underset{CH_2CH_3}{|}}{C}H\overset{O}{\overset{\|}{C}}OCH_3$

1. Predict the products from the following reactions.

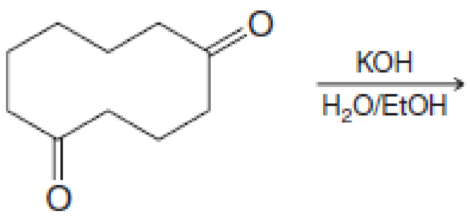
(a)



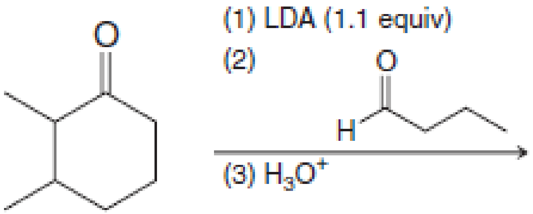
(b)



(c)

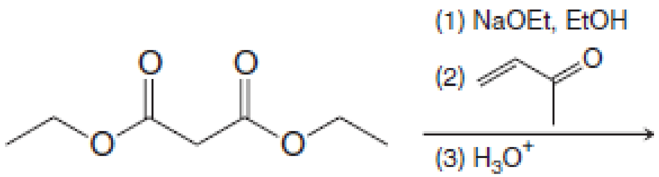


(d)

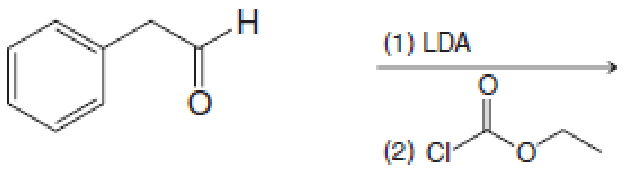


2. Predict the products of the following reactions.

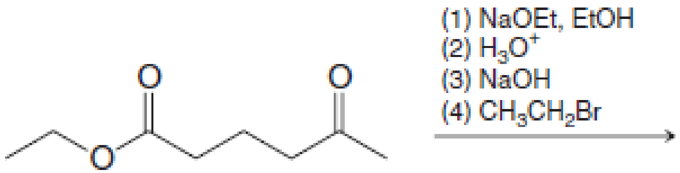
(a)



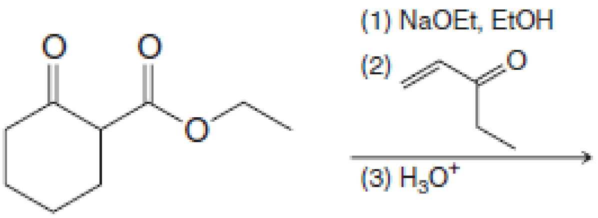
(b)



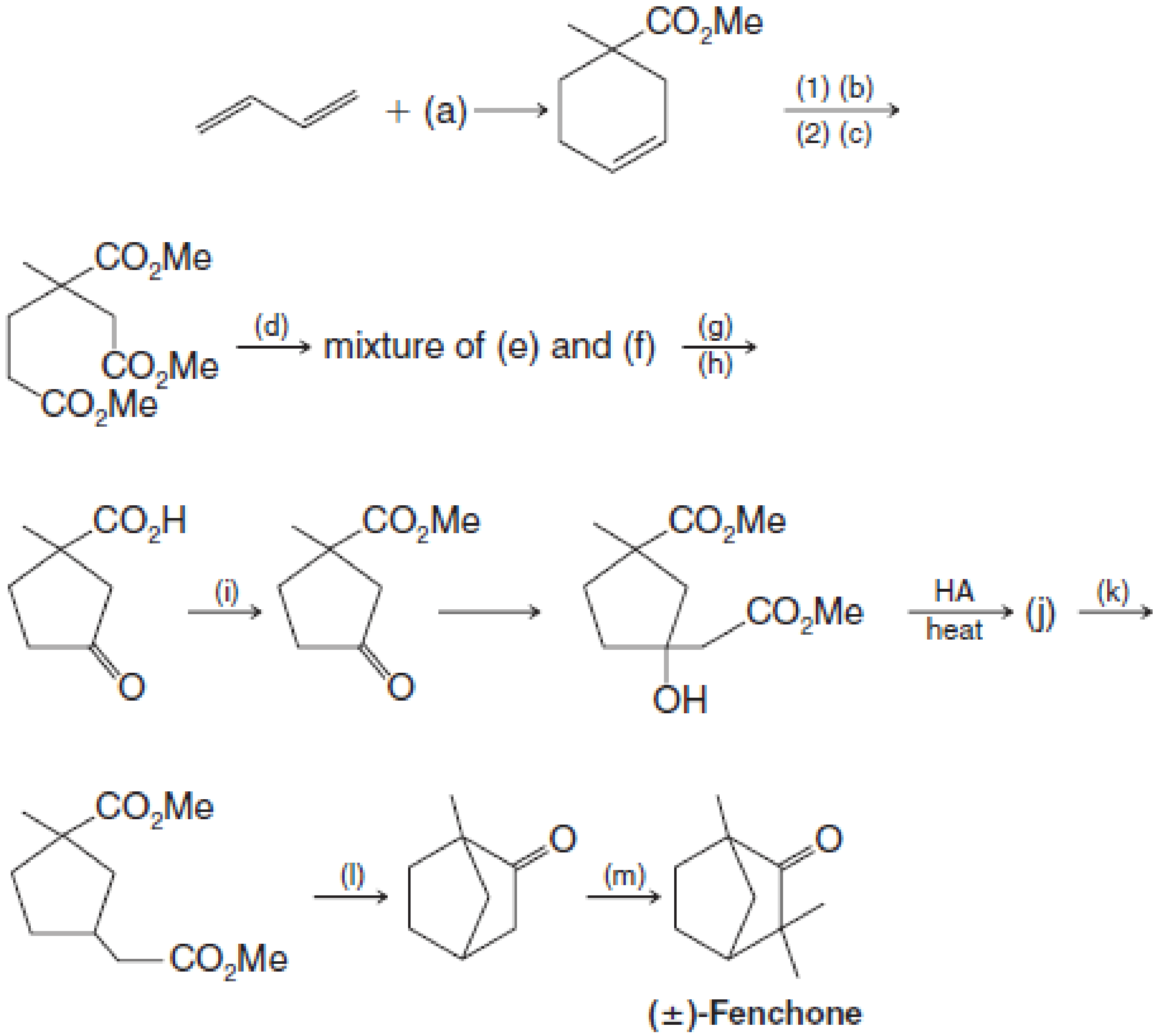
(c)



(d)

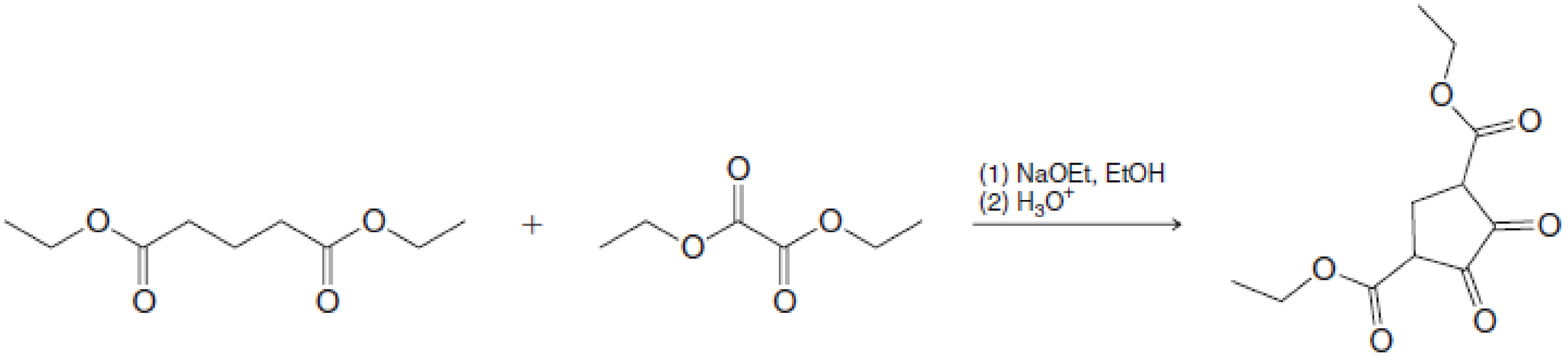


3. (+)–Fenchone is a terpenoid that can be isolated from fennel oil. (+)–Fenchone has been synthesized through the following route. Supply the missing intermediates and reagents.

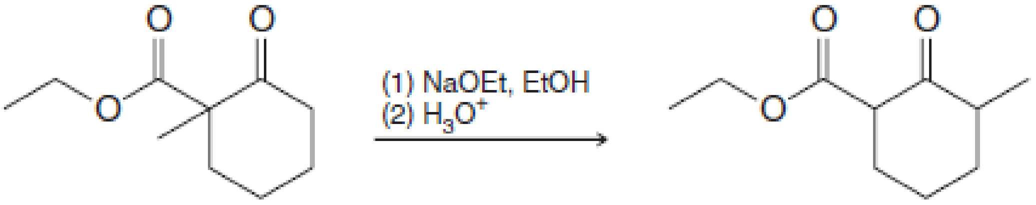


4. Provide a mechanism for each of the following reactions

(a)

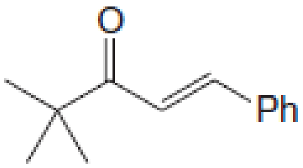


(b)

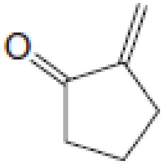


5. What starting materials are needed to synthesize each of the following compounds using an aldol reaction?

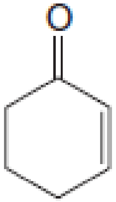
(a)



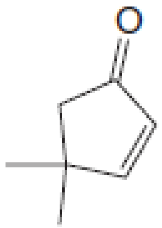
(b)



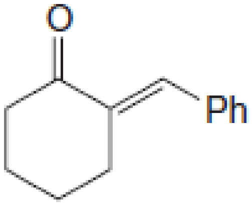
(c)



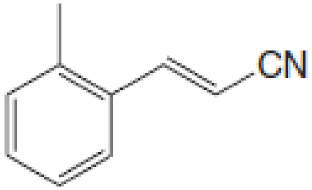
(d)



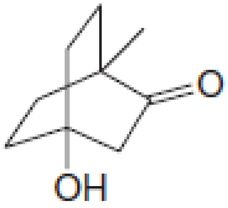
(e)



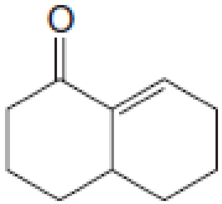
(f)



(g)



(h)



Quiz 19.01

The acidity order (strongest to weakest) of the indicated H in the compounds below is:

CH_3CH_2OH — I

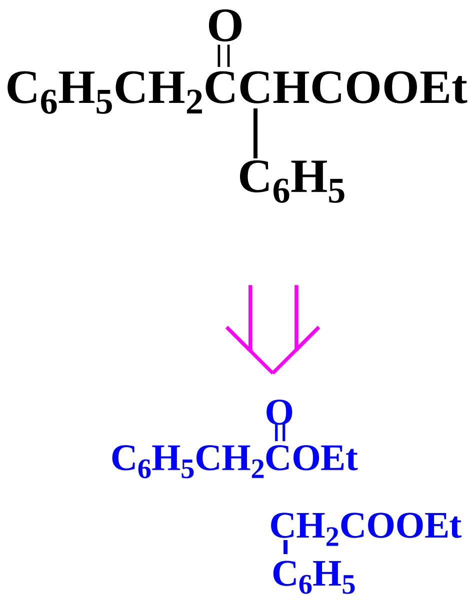
$EtOOCCH_2COOEt$ — II

CH_3COOEt — III

II > I > III

Quiz 19.02

Indicate the ethyl esters needed for forming each of theseβ-keto ester by Claisen condensation.

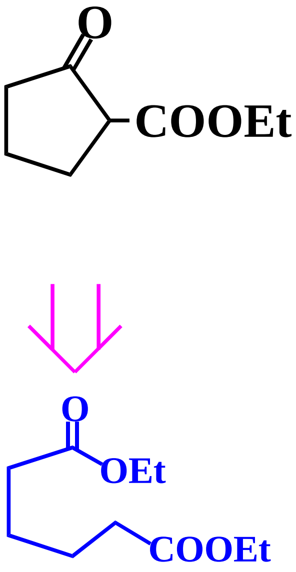


$C_6H_5CH_2\overset{O}{\overset{\|}{C}}\underset{C_6H_5}{CH}COOEt$

$C_6H_5CH_2\overset{O}{\overset{\|}{C}}OEt$

$\underset{C_6H_5}{CH_2}COOEt$

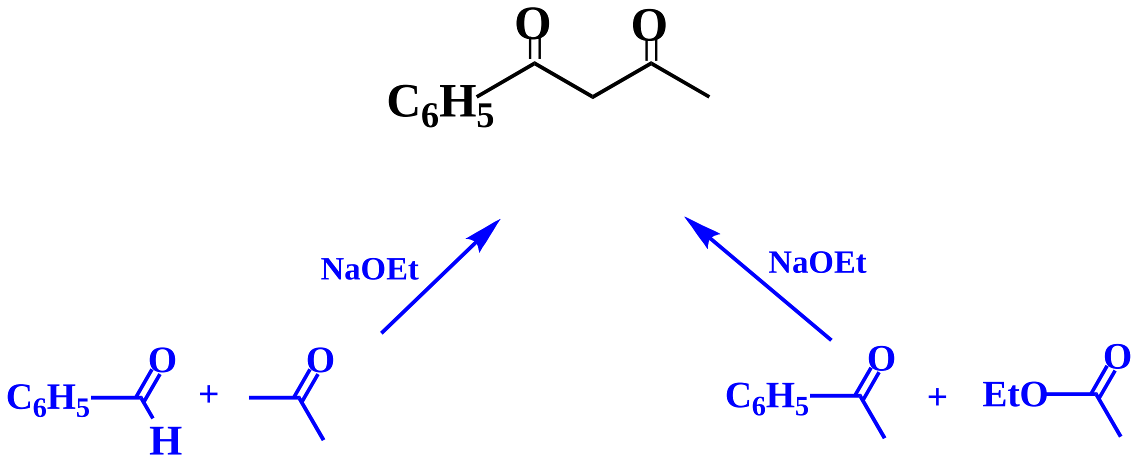
Ethyl phenylacetate



Diethyl adipate

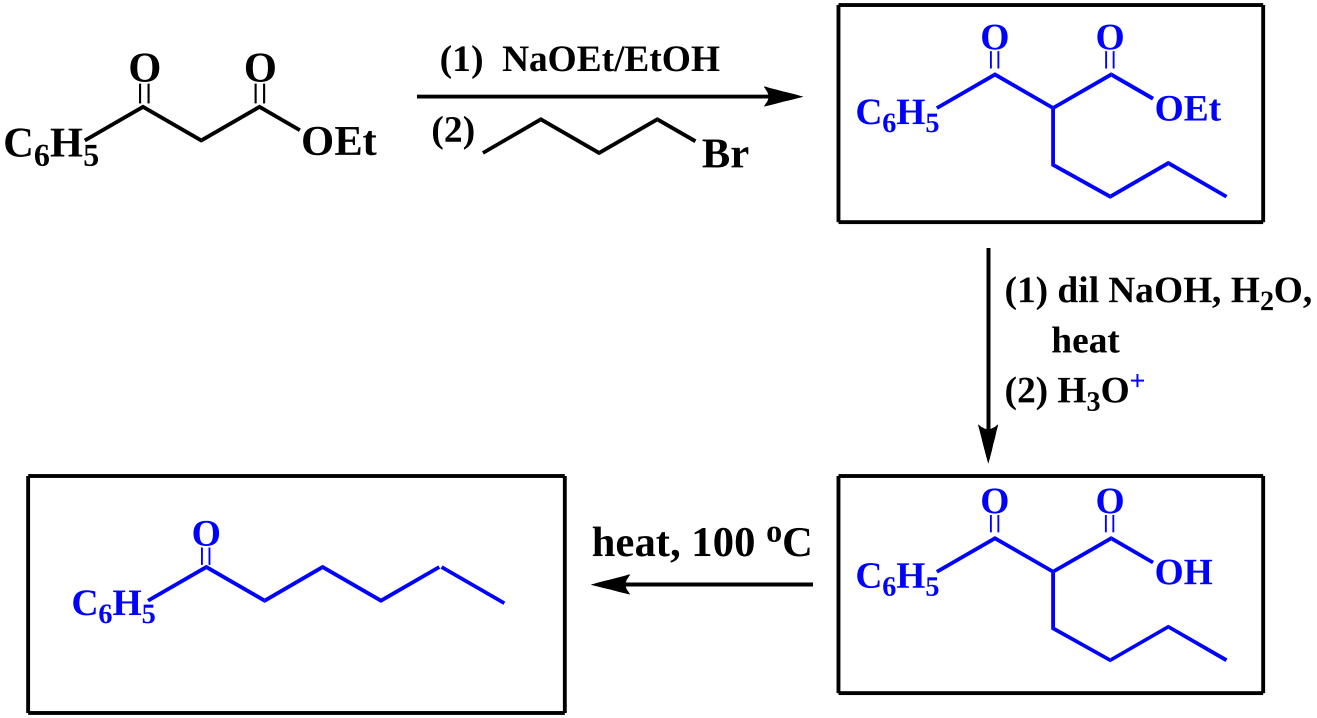
Quiz 19.03

Draw the structures of the starting materials for two ways to prepare this diketone by crossed-Claisen reactions



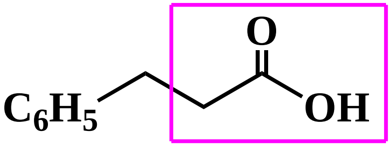
Quiz 19.04

Provide the missing structures in the scheme below.

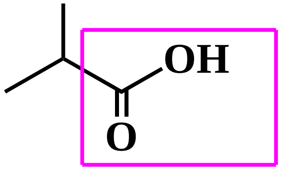


Quiz 19.05

Indicate the alkyl halides needed to prepare the following carboxylic acids by the malonic acid synthesis.



3-Phenylpropanoic acid



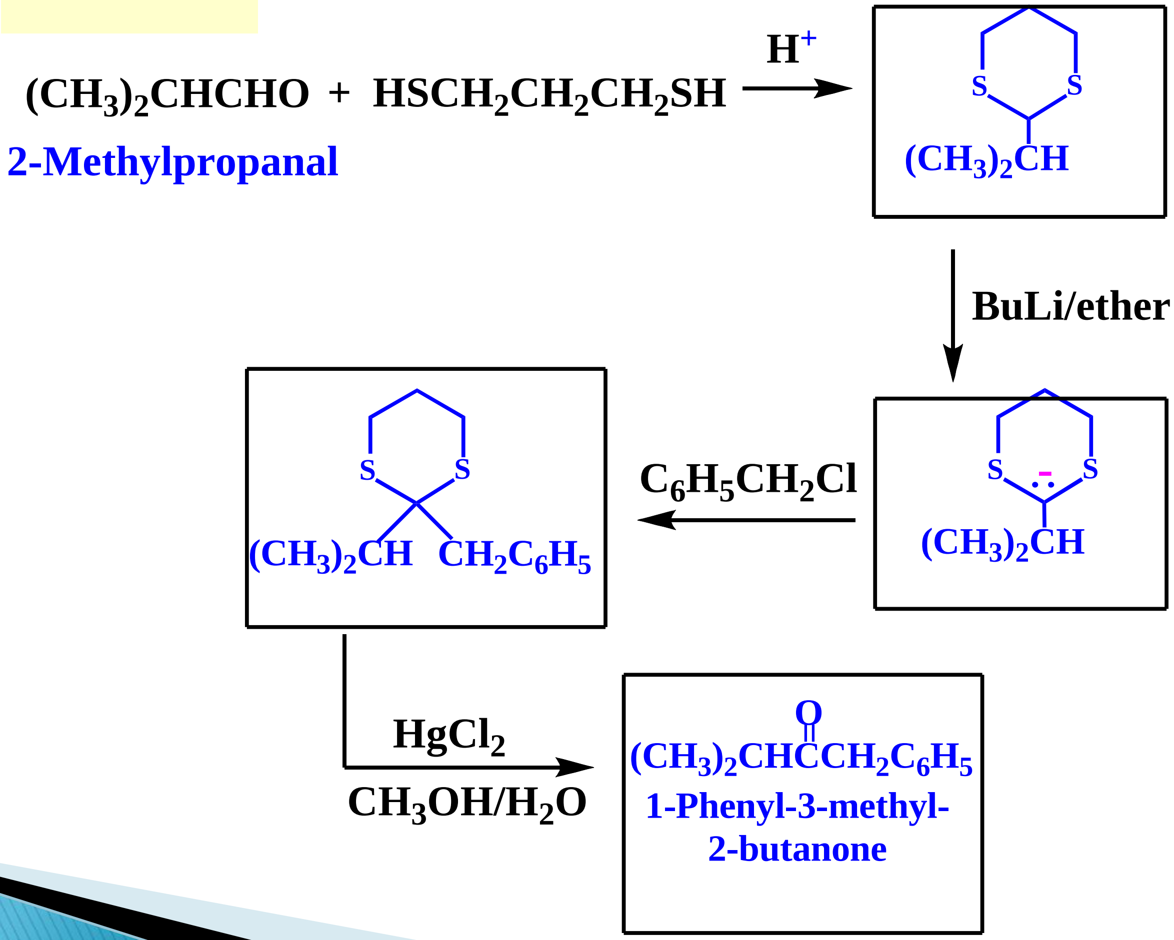
2-Methylpropanoic acid
(Isobutyric acid)

$C_6H_5CH_2Cl$

CH_3I and CH_3I in
a two-stage
synthesis

Quiz 19.06

Provide the missing structures in the following Corey-Seebach synthesis.



$(CH_3)_2CHCHO + HSCH_2CH_2CH_2SH \xrightarrow{H^+}$

2-Methylpropanal

BuLi/ether

$C_6H_5CH_2Cl$

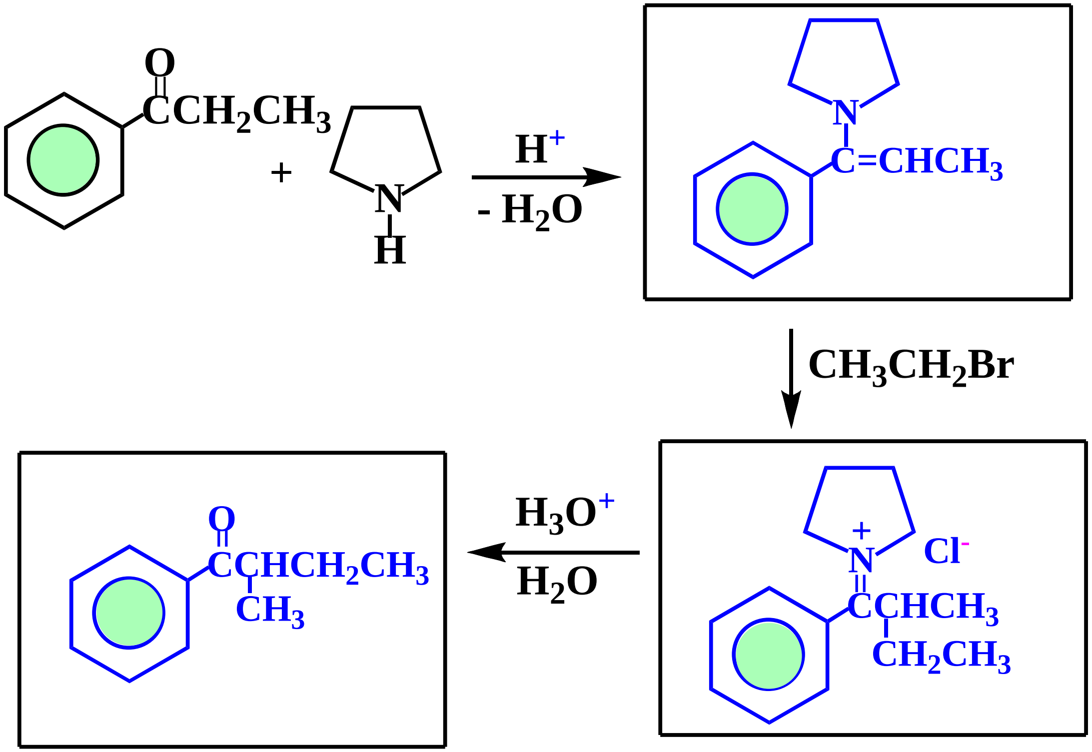
$\xrightarrow[CH_3OH/H_2O]{HgCl_2}$

$(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH_2C_6H_5$

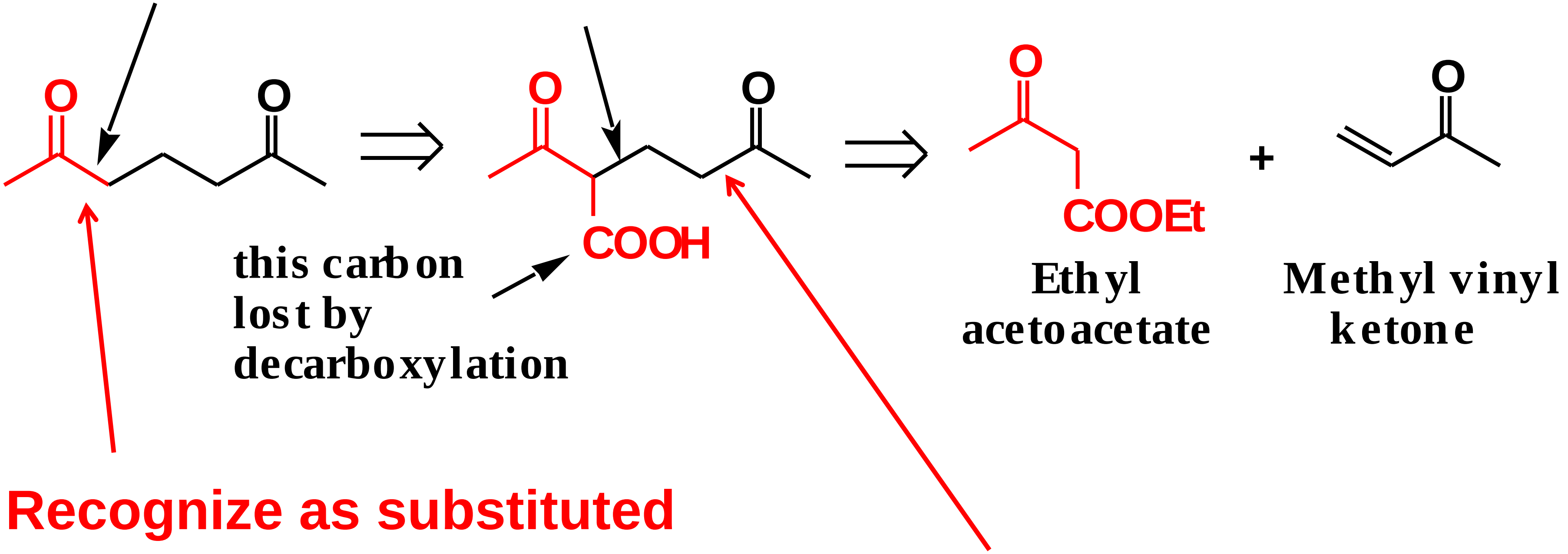
1-Phenyl-3-methyl-2-butanone

Quiz 19.07

Provide the missing structures in the sequence below.



Retrosynthesis of 2,6-Heptadione



these three carbons from acetoacetic ester

this bond formed in a Michael reaction

this carbon lost by decarboxylation

Ethyl acetoacetate

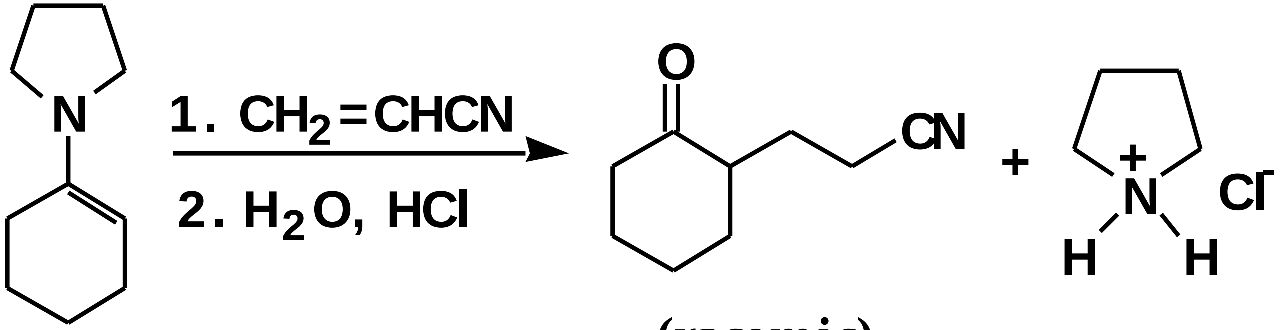
Methyl vinyl ketone

Recognize as substituted acetone, aae synthesis

Recognize as Nucleophile – C – C – CO Michael

Michael Reactions

- Enamines also participate in Michael reactions.

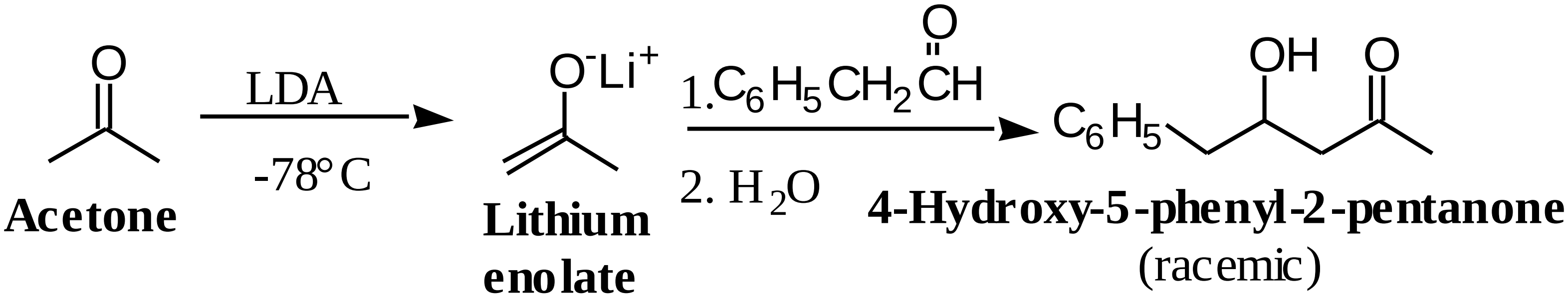


(racemic)

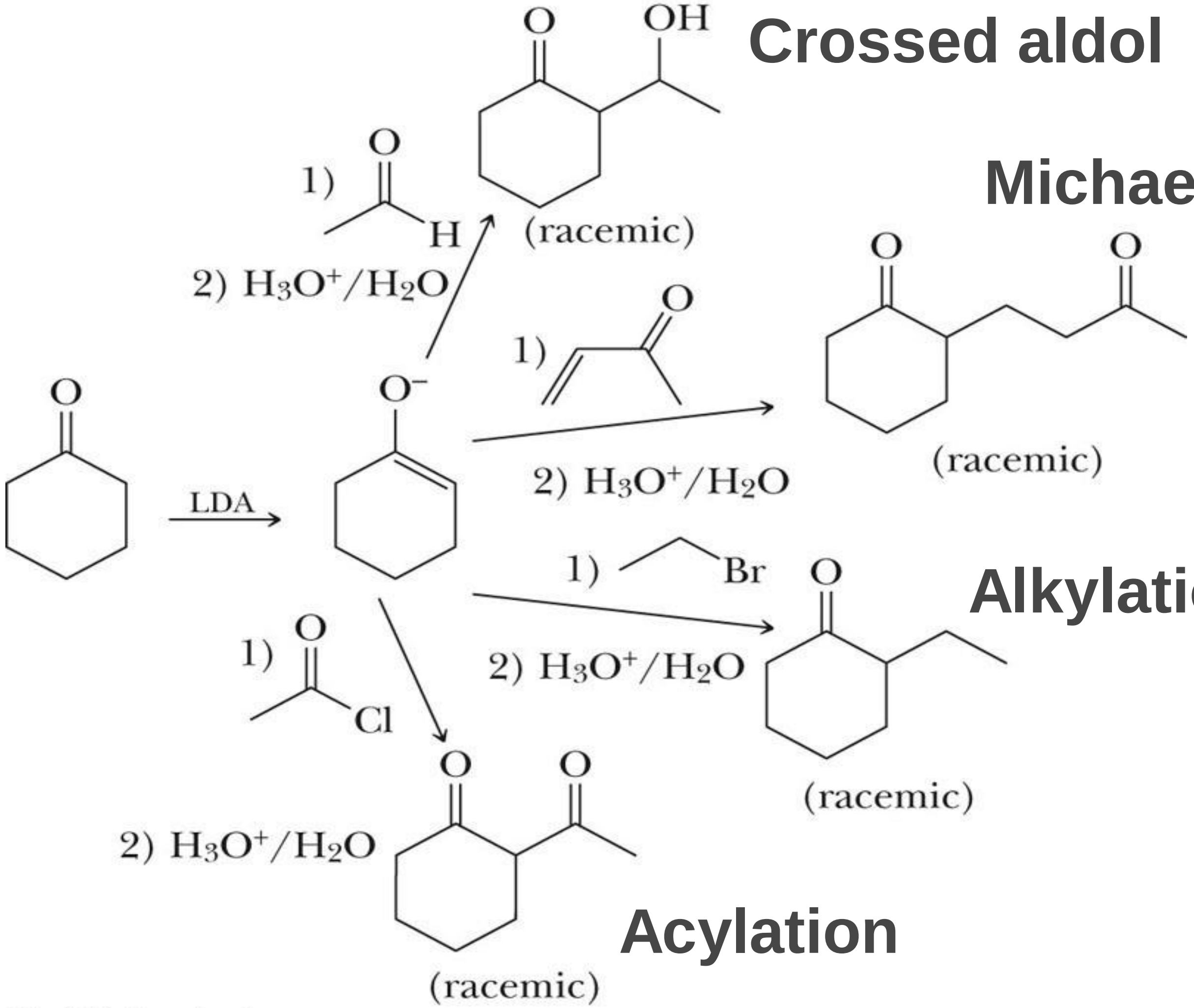
Pyrrolidine enamine of cyclohexanone

Crossed Enolate Reactions using LDA

- The crossed aldol reaction between acetone and an aldehyde can be carried out successfully by adding acetone to one equivalent of LDA to completely preform its enolate anion, which is then treated with the aldehyde.



Examples using LDA



Crossed aldol

Michael

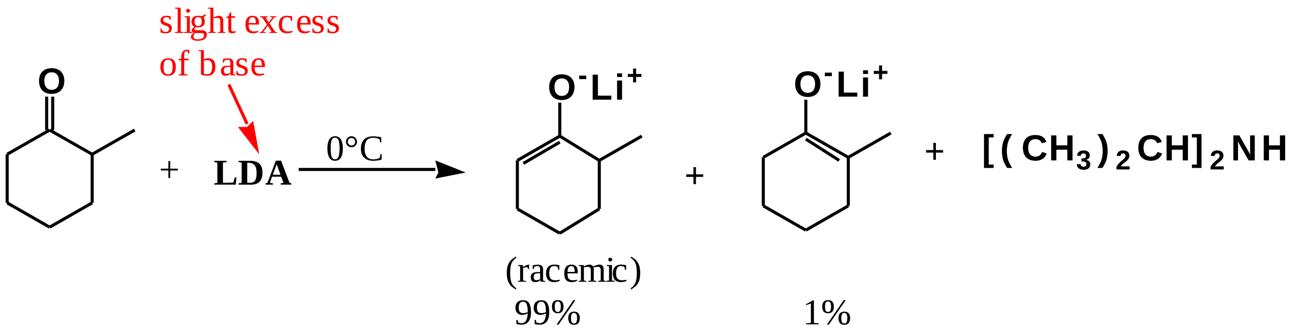
Alkylation

Acylation

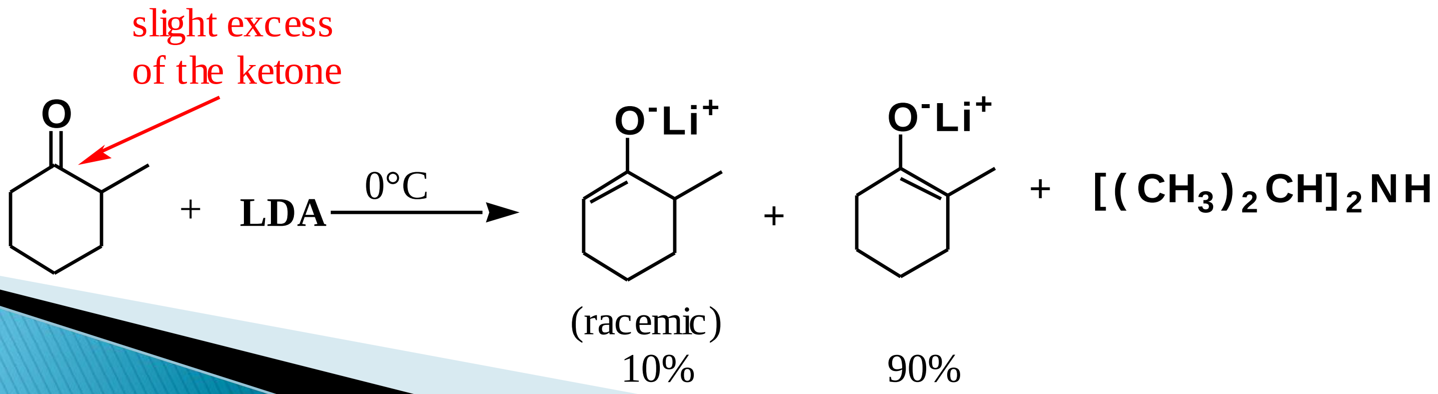
© Brooks/Cole, Cengage Learning

Crossed Enolate Reactions using LDA

- When 2-methylcyclohexanone is treated with a slight excess of LDA, the enolate is almost entirely the less substituted enolate anion.

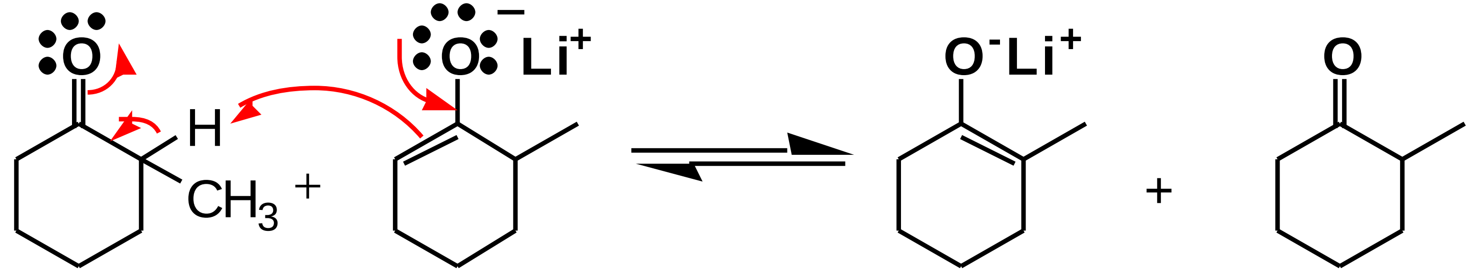

slight excess of base

- When 2-methylcyclohexanone is treated with LDA where the ketone is in slight excess, the product is richer in the more substituted enolate.


slight excess of the ketone

Crossed Enolate Reactions using LDA

- Equilibrium among enolate anions is established when the ketone is in slight excess, a condition under which it is possible for proton-transfer reactions to occur between an enolate and an α-hydrogen of an unreacted ketone. Thus, equilibrium is established between alternative enolate anions.



(racemic)

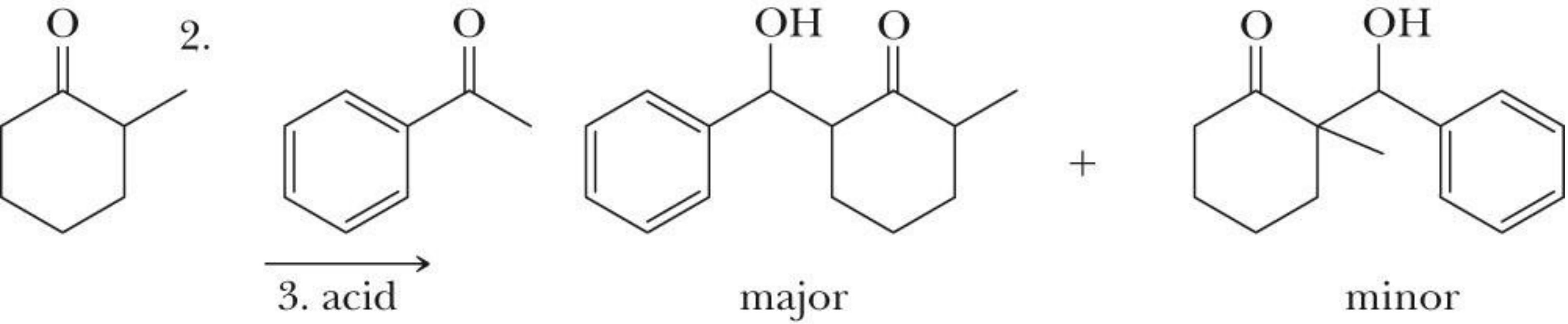
Less stable enolate anion (racemic)

More stable enolate anion

(racemic)

Example

1. 1.01 mol LDA, kinetic control



1. 0.99 mol LDA, thermodynamic control