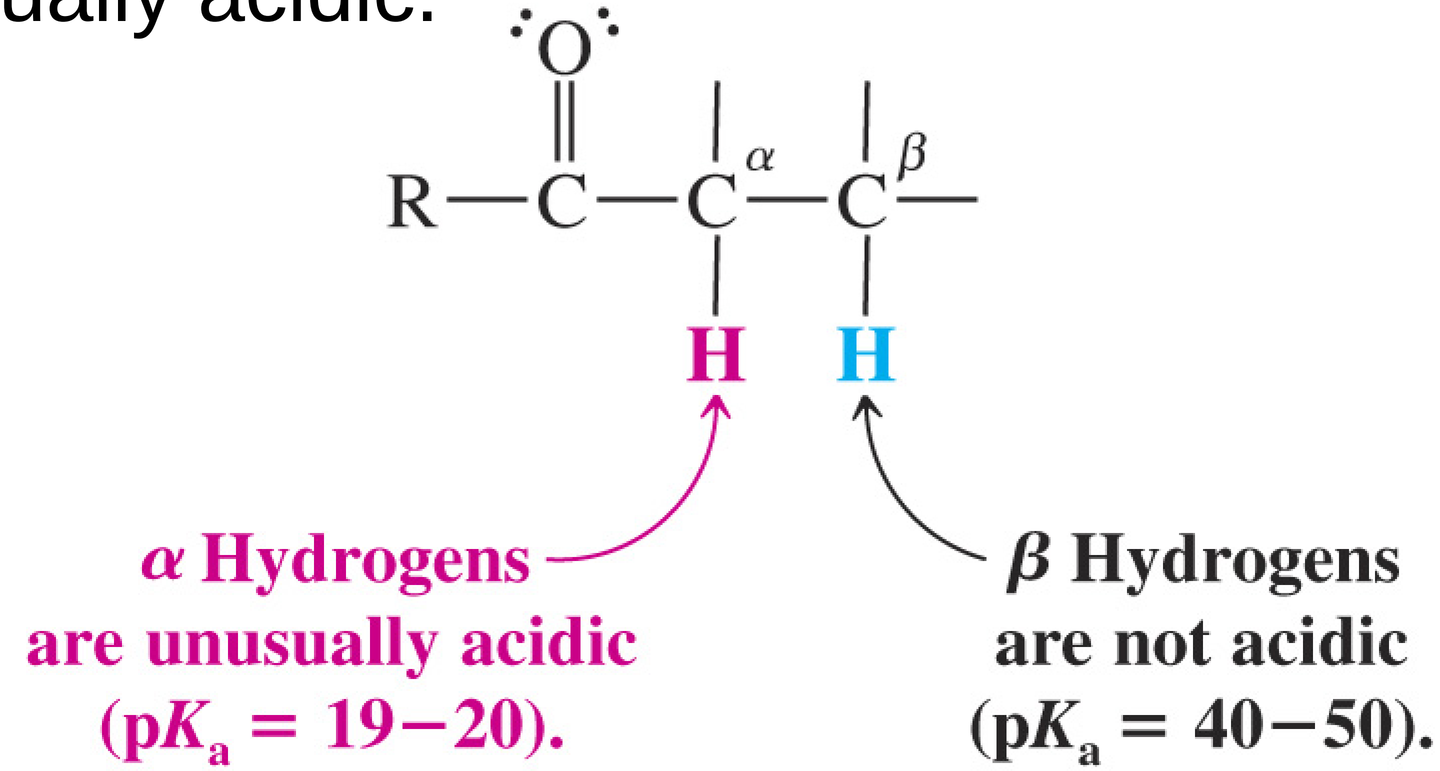
CHAPTER 17

Enolates and Carbanions: Building Blocks for Organic Synthesis

The Acidity of the α Hydrogens of Carbonyl Compounds

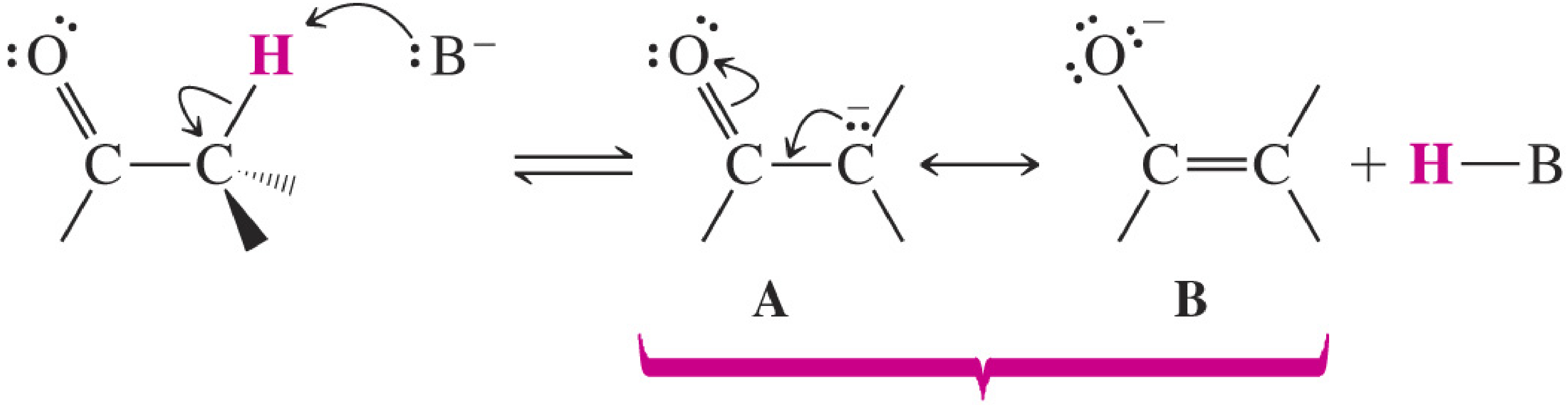
- Hydrogens on carbons α to carbonyls are unusually acidic.



α Hydrogens are unusually acidic ($pK_a = 19–20$).

β Hydrogens are not acidic ($pK_a = 40–50$).

Why α hydrogen is acidic

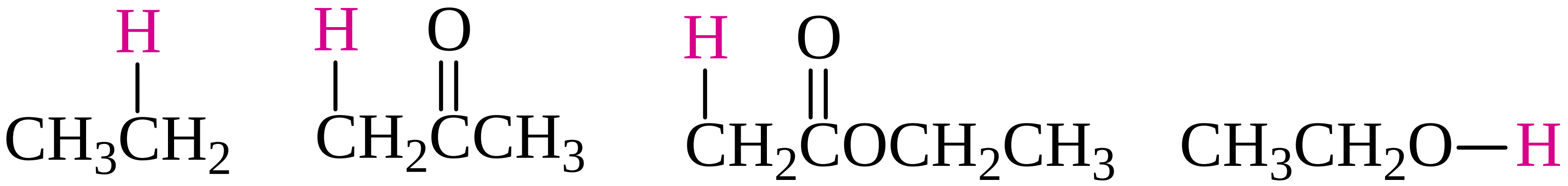


Resonance-stabilized anion **(enolate ion)**

Extremely strong bases are needed to form the enolate ion. Such as :

$NaNH_2$	**NaH**	**$CH_3CH_2CH_2CH_2Li$**	**$[(CH_3)_2CH]_2NLi$**
sodamide	**Sodium hydride**	**Butyllithium**	**Lithium diisopropylamide (LDA)**

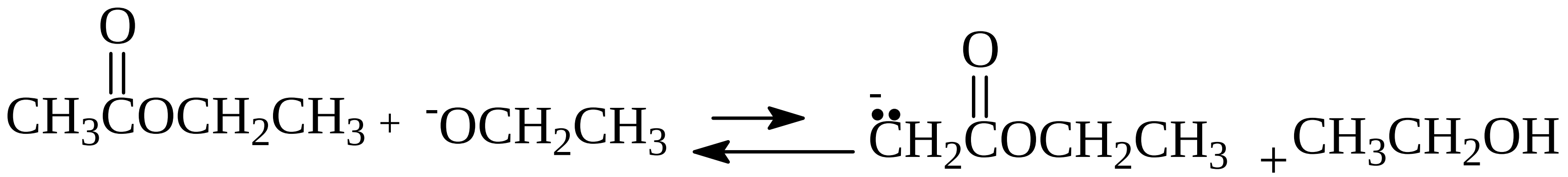
A hydrogen alpha to a single carbonyl is less acidic than a hydroxyl hydrogen



$CH_3CH_2\text{–}H$ $\quad$ $H\text{–}CH_2C(=O)CH_3$ $\quad$ $H\text{–}CH_2C(=O)OCH_2CH_3$ $\quad$ $CH_3CH_2O\text{—}H$

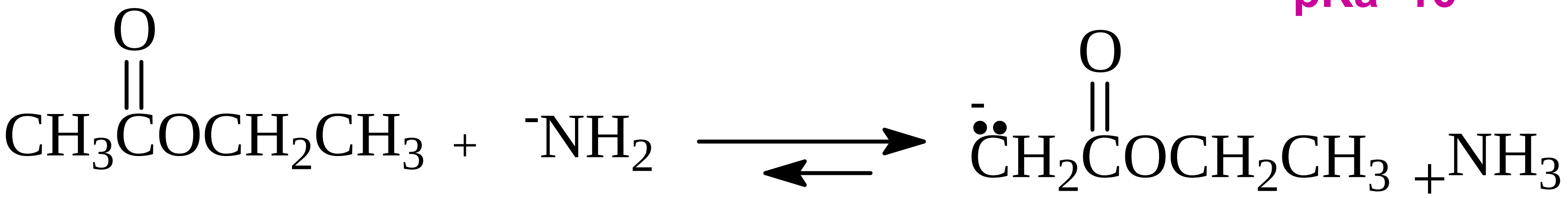
pKa 50 20 25 16

Thus, alkoxide ion is not a good base to form the enolate ion from acetone or ethyl acetate.



$$CH_3C(=O)OCH_2CH_3 + {}^-OCH_2CH_3 \rightleftharpoons {}^-\!:CH_2C(=O)OCH_2CH_3 + CH_3CH_2OH$$

pKa=16

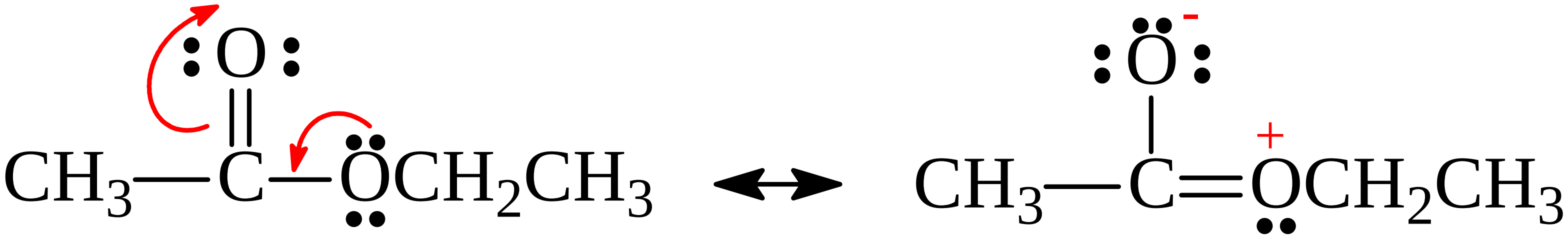


$$CH_3C(=O)OCH_2CH_3 + {}^-NH_2 \rightleftharpoons {}^-\!:CH_2C(=O)OCH_2CH_3 + NH_3$$

favored

pKa=35

The α hydrogen of an ester is less acidic than that of a ketone

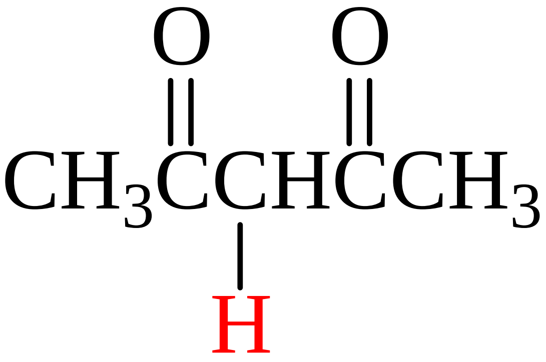


Ethyl acetate

Major contributor

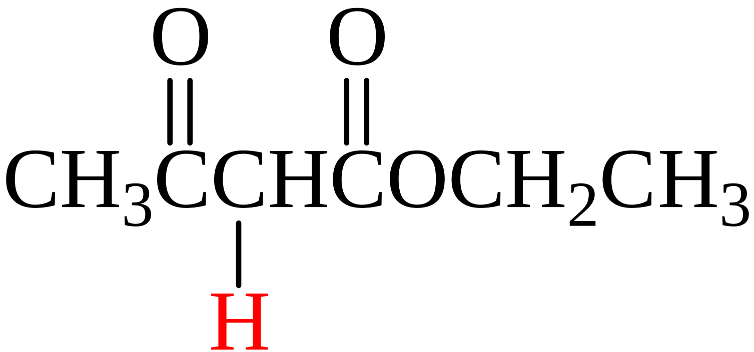
The ester carbonyl is less able to delocalize the negative charge of the enolate because the carbonyl oxygen already carries a partial negative charge.

Protons on the α-carbon of β-dicarbonyl compounds are acidic (pK_a = 9-13)



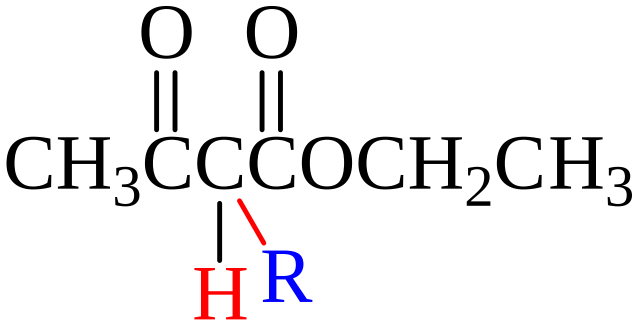
$CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{H}{|}}{C}H\overset{\overset{O}{\|}}{C}CH_3$

acetylacetone
pKa=9



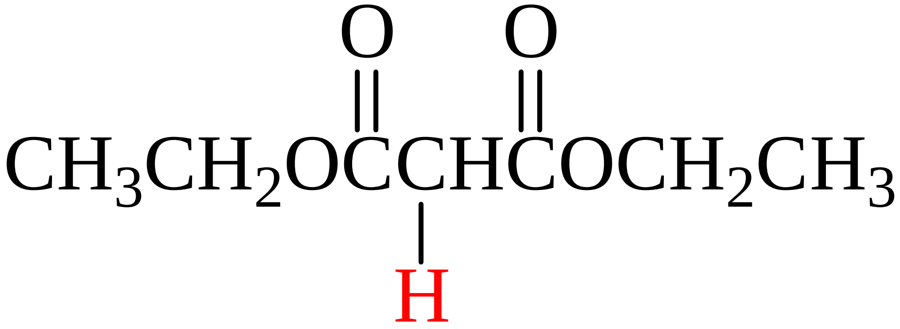
$CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{H}{|}}{C}H\overset{\overset{O}{\|}}{C}OCH_2CH_3$

Ethyl acetoacetae
pKa=11



$CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{H\ \ R}{|\ \ \backslash}}{C}\overset{\overset{O}{\|}}{C}OCH_2CH_3$

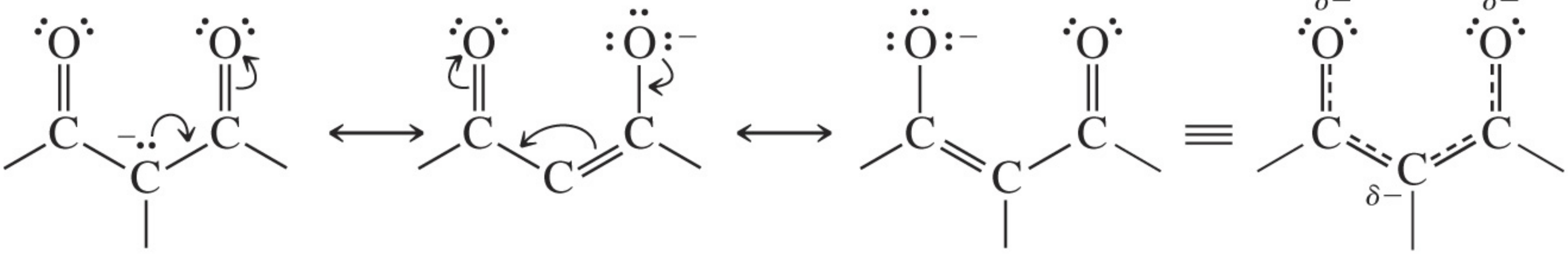
Acetoacetic ester
pKa=13



$CH_3CH_2O\overset{\overset{O}{\|}}{C}\underset{\underset{H}{|}}{C}H\overset{\overset{O}{\|}}{C}OCH_2CH_3$

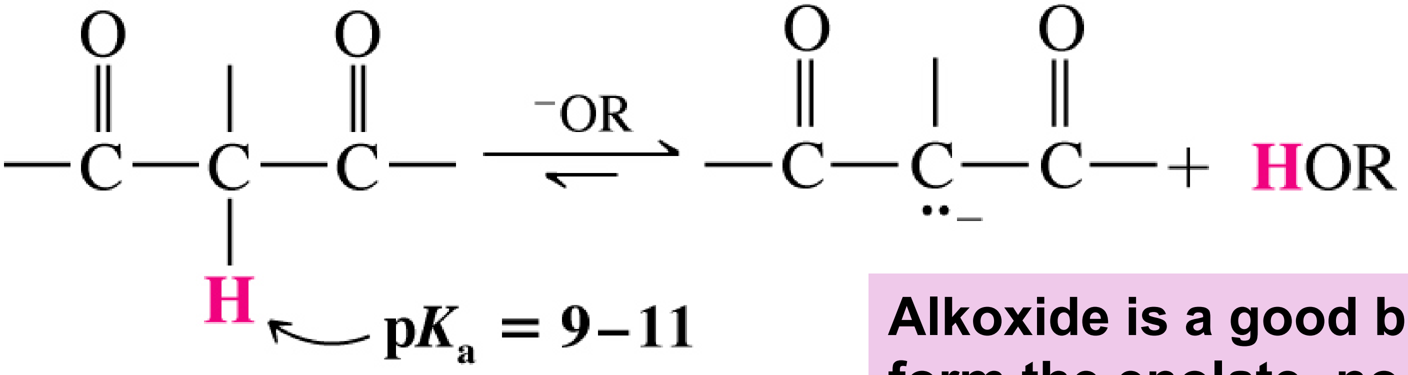
diethyl malonate
pKa=13

The acidity can be explained by resonance stabilization of the corresponding enolate by two carbonyl groups



Contributing resonance structures

Resonance hybrid



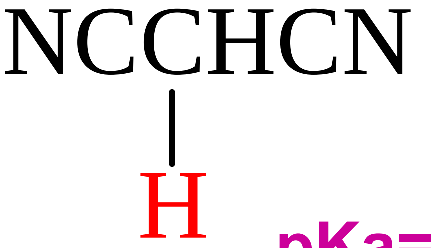
pKa=16

Alkoxide is a good base to form the enolate- no need for a stronger base.

Nitro and cyanide groups enhance the acidity of α hydrogen

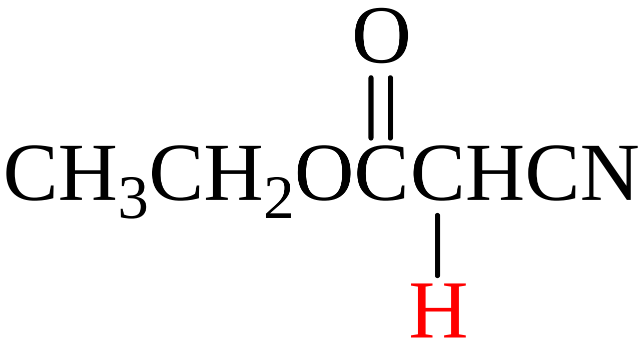
$\underset{\underset{H}{|}}{C}H_2NO_2$

pKa=9



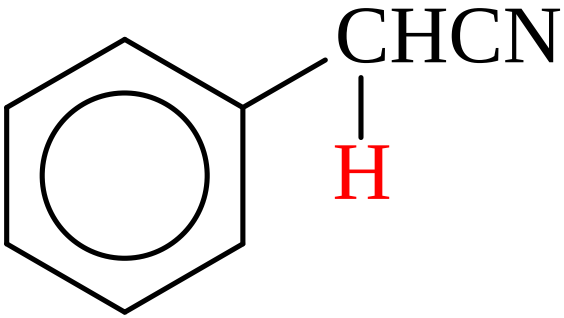
$NC\underset{\underset{H}{|}}{C}HCN$

pKa= 13



$CH_3CH_2O\overset{\overset{O}{\|}}{C}\underset{\underset{H}{|}}{C}HCN$

pKa=13



Alkylation of Malonic Ester

General: Synthesis of Substituted Acetic Acids

$$CH_2(CO_2C_2H_5)_2 \xrightarrow[2)\ RX]{1)\ Na^{+-}OC_2H_5} RCH(CO_2C_2H_5)_2 \xrightarrow[\substack{\text{heat} \\ {}^{-}CO_2}]{H^+,\ H_2O} RCH_2CO_2H$$

Diethyl malonate

(malonic ester)

α substituted acid

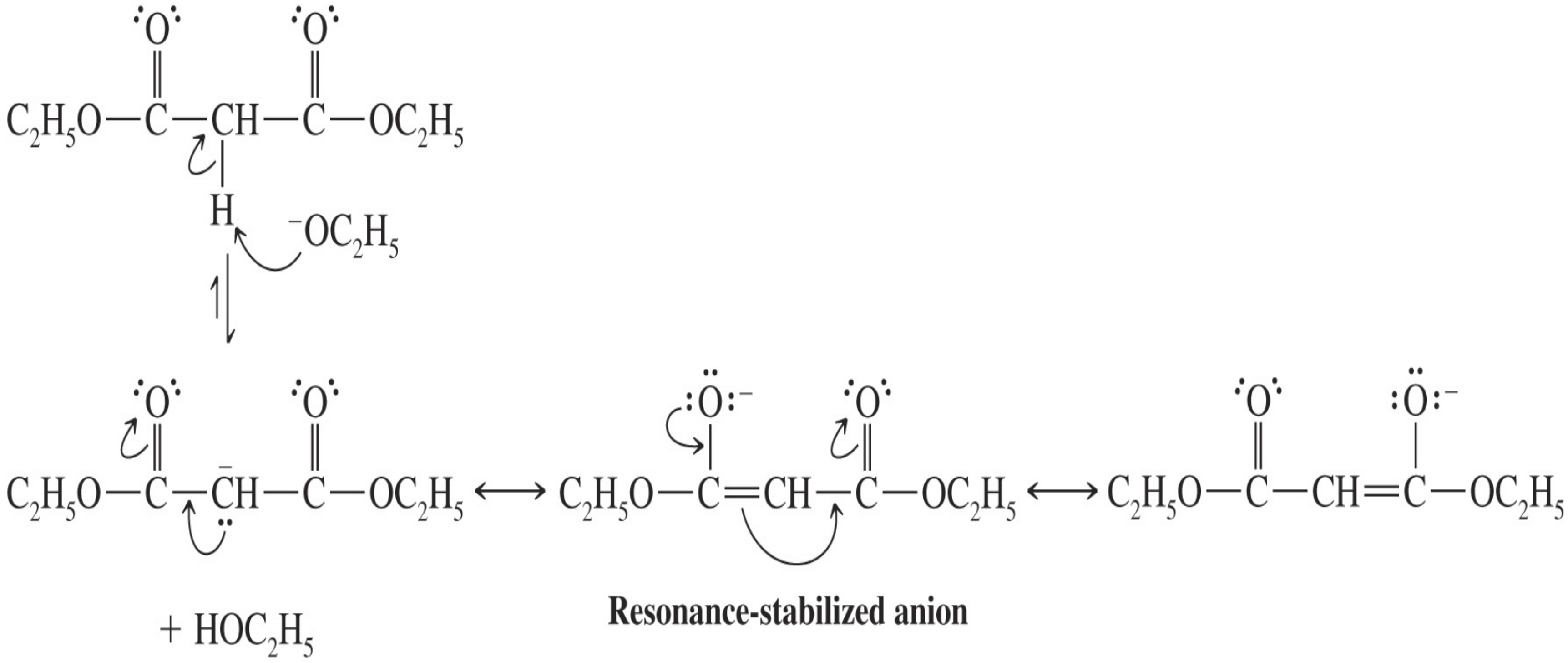
Example

$$CH_2(CO_2C_2H_5)_2 \xrightarrow[2)\ CH_3CH_2Br]{1)\ Na^{+-}OC_2H_5} CH_3CH_2CH(CO_2C_2H_5)_2 \xrightarrow[\substack{\text{heat} \\ {}^{-}CO_2}]{H^+,\ H_2O}$$

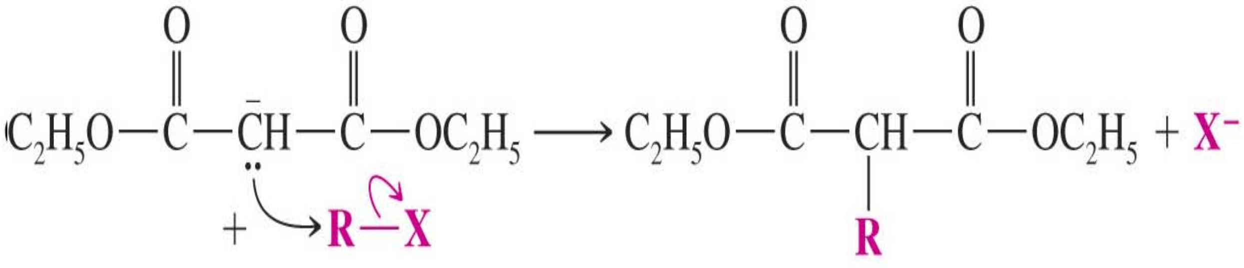
From RX → $CH_3CH_2CH_2CO_2H$

Mechanism

- Step1: formation of the enolate



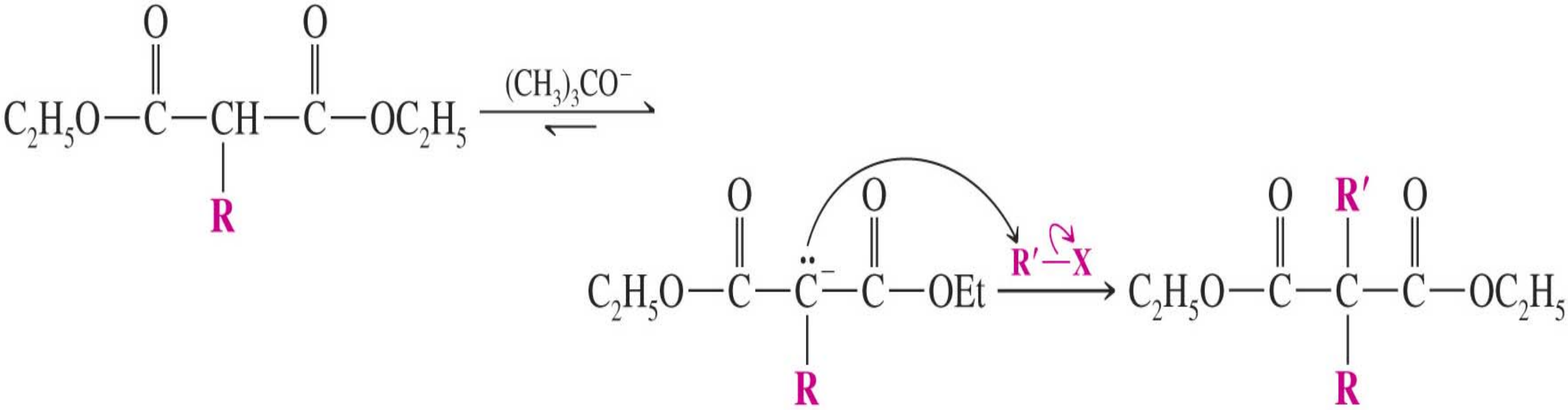
Step 2 This enolate anion can be alkylated in an S_N2 reaction,



$$C_2H_5O-\overset{\overset{O}{\|}}{C}-\overset{-}{\underset{\cdot\cdot}{C}}H-\overset{\overset{O}{\|}}{C}-OC_2H_5 + R-X \longrightarrow C_2H_5O-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{C}H-\overset{\overset{O}{\|}}{C}-OC_2H_5 + X^-$$

Enolate ion **Monoalkylmalonic ester**

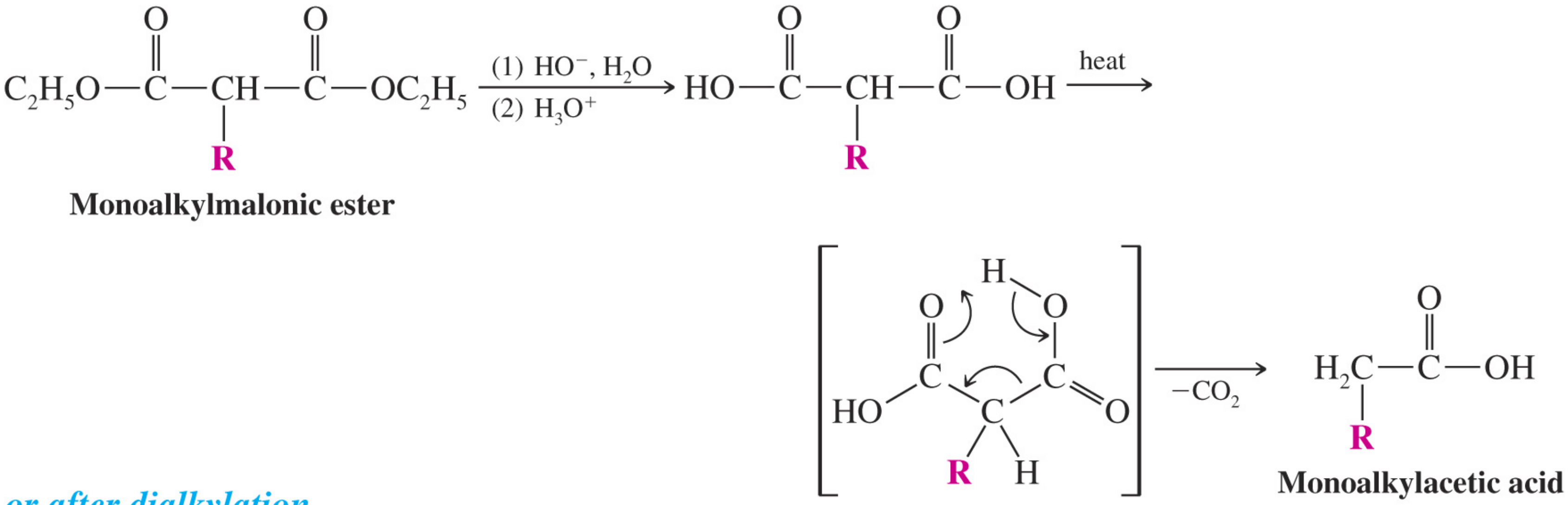
and the product can be alkylated again if our synthesis requires it:



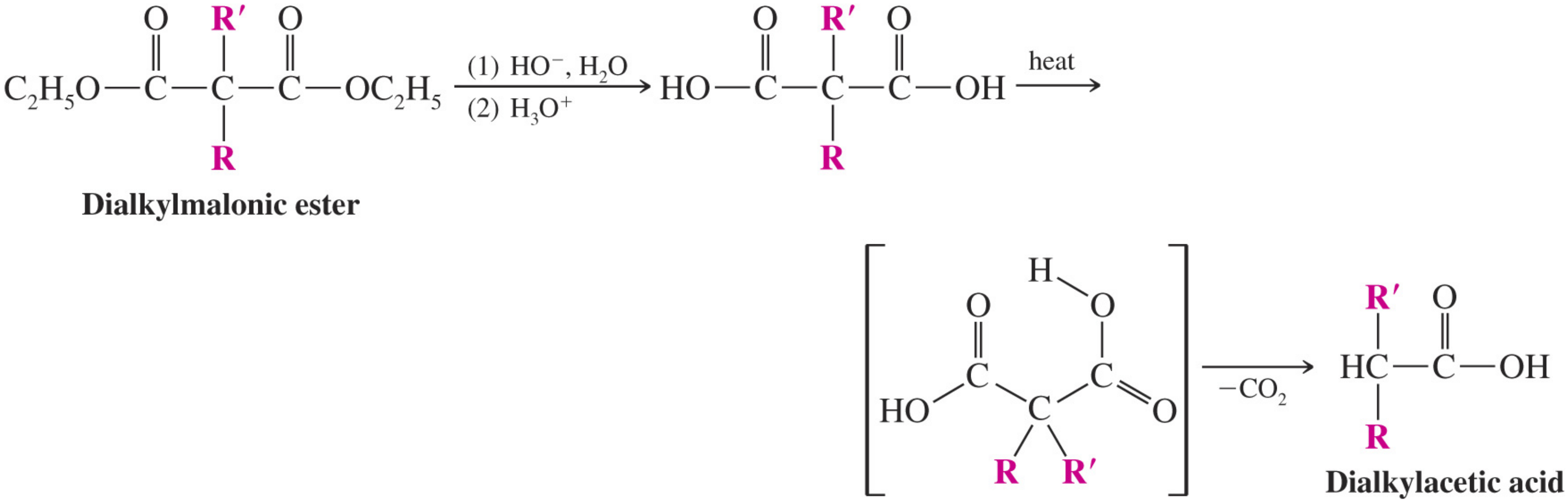
$$C_2H_5O-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{C}H-\overset{\overset{O}{\|}}{C}-OC_2H_5 \underset{}{\overset{(CH_3)_3CO^-}{\rightleftharpoons}} C_2H_5O-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\cdot\cdot}{C}}{}^{-}-\overset{\overset{O}{\|}}{C}-OEt \xrightarrow{R'-X} C_2H_5O-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\overset{R'}{|}}{C}}-\overset{\overset{O}{\|}}{C}-OC_2H_5$$

Dialkylmalonic ester

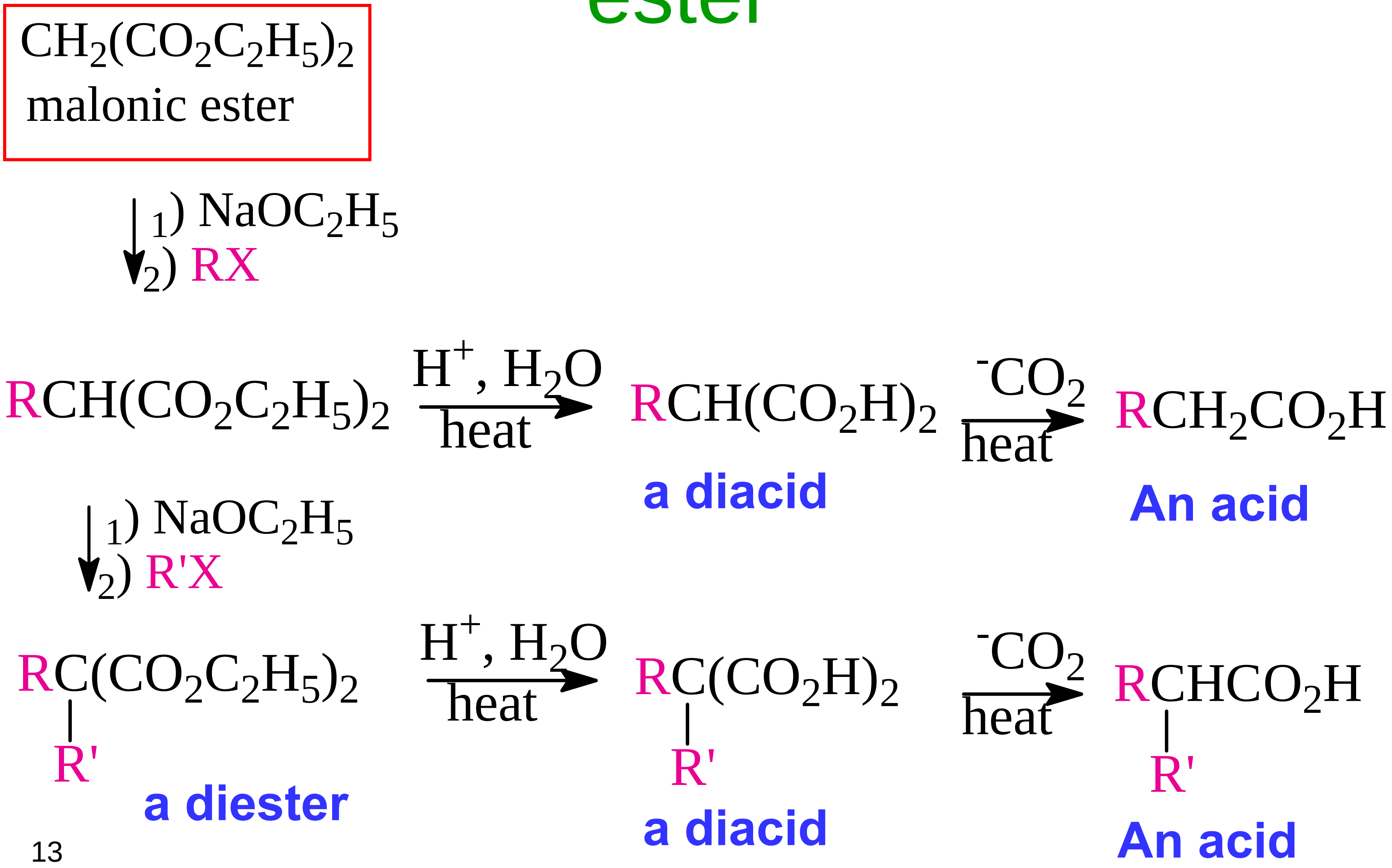
- Step 3: Hydrolysis and Decarboxylation



or after dialkylation,



Summary of alkylation of malonic ester



$\mathrm{CH_2(CO_2C_2H_5)_2}$

malonic ester

$\downarrow$ 1) $\mathrm{NaOC_2H_5}$ 2) RX

$$\mathrm{RCH(CO_2C_2H_5)_2 \xrightarrow[heat]{H^+,\ H_2O} RCH(CO_2H)_2 \xrightarrow[heat]{{}^-CO_2} RCH_2CO_2H}$$

a diacid

An acid

$\downarrow$ 1) $\mathrm{NaOC_2H_5}$ 2) R'X

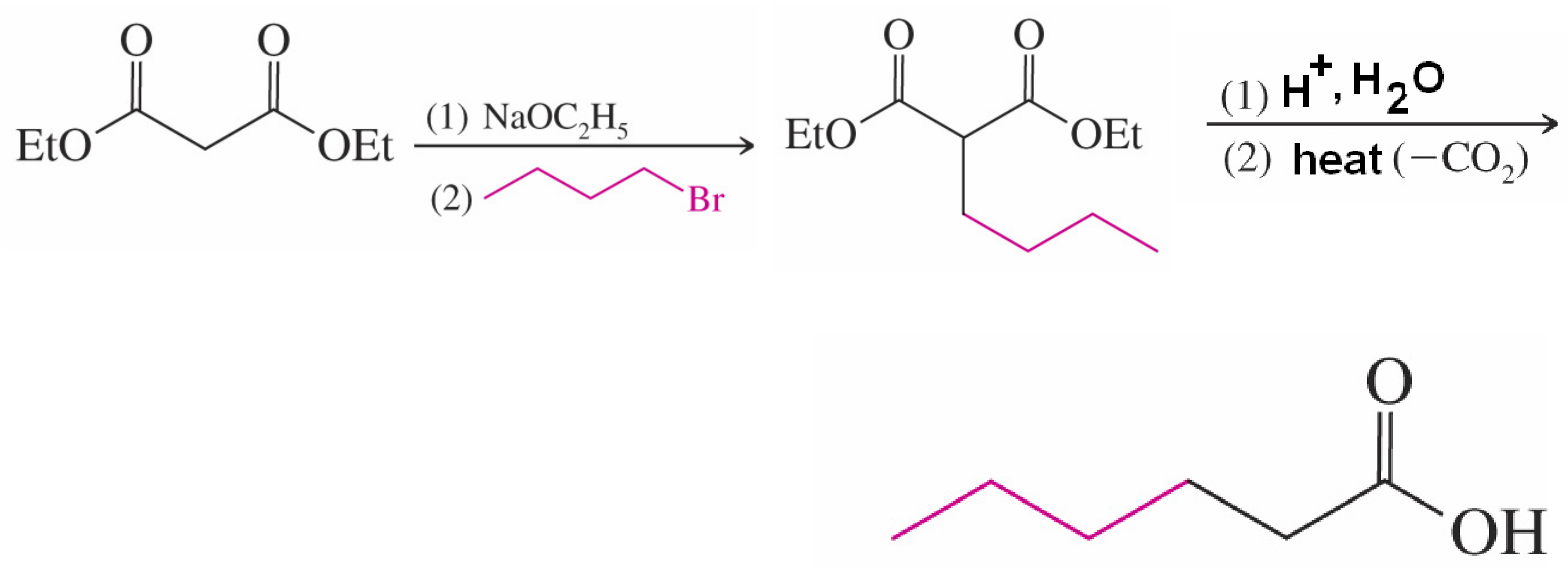
$$\mathrm{R\underset{\underset{R'}{|}}{C}(CO_2C_2H_5)_2 \xrightarrow[heat]{H^+,\ H_2O} R\underset{\underset{R'}{|}}{C}(CO_2H)_2 \xrightarrow[heat]{{}^-CO_2} R\underset{\underset{R'}{|}}{CH}CO_2H}$$

a diester

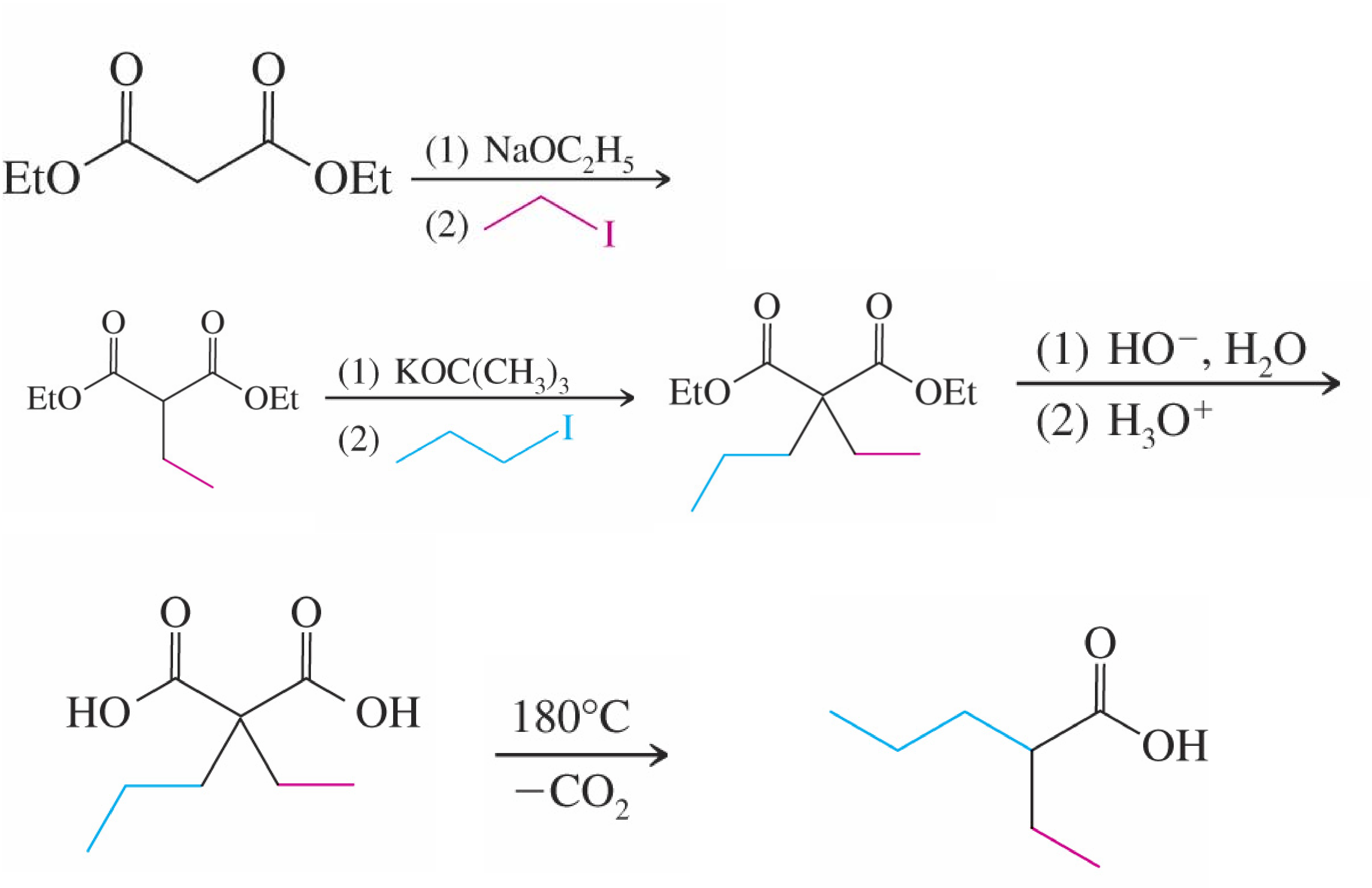
a diacid

An acid

Examples

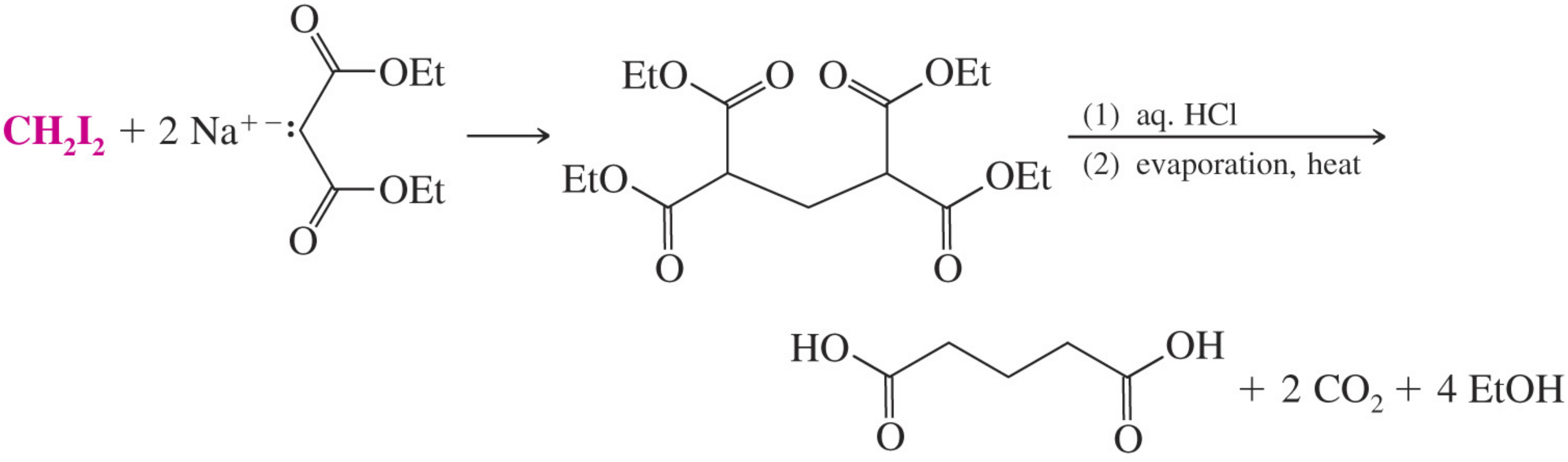


Hexanoic acid (75%)



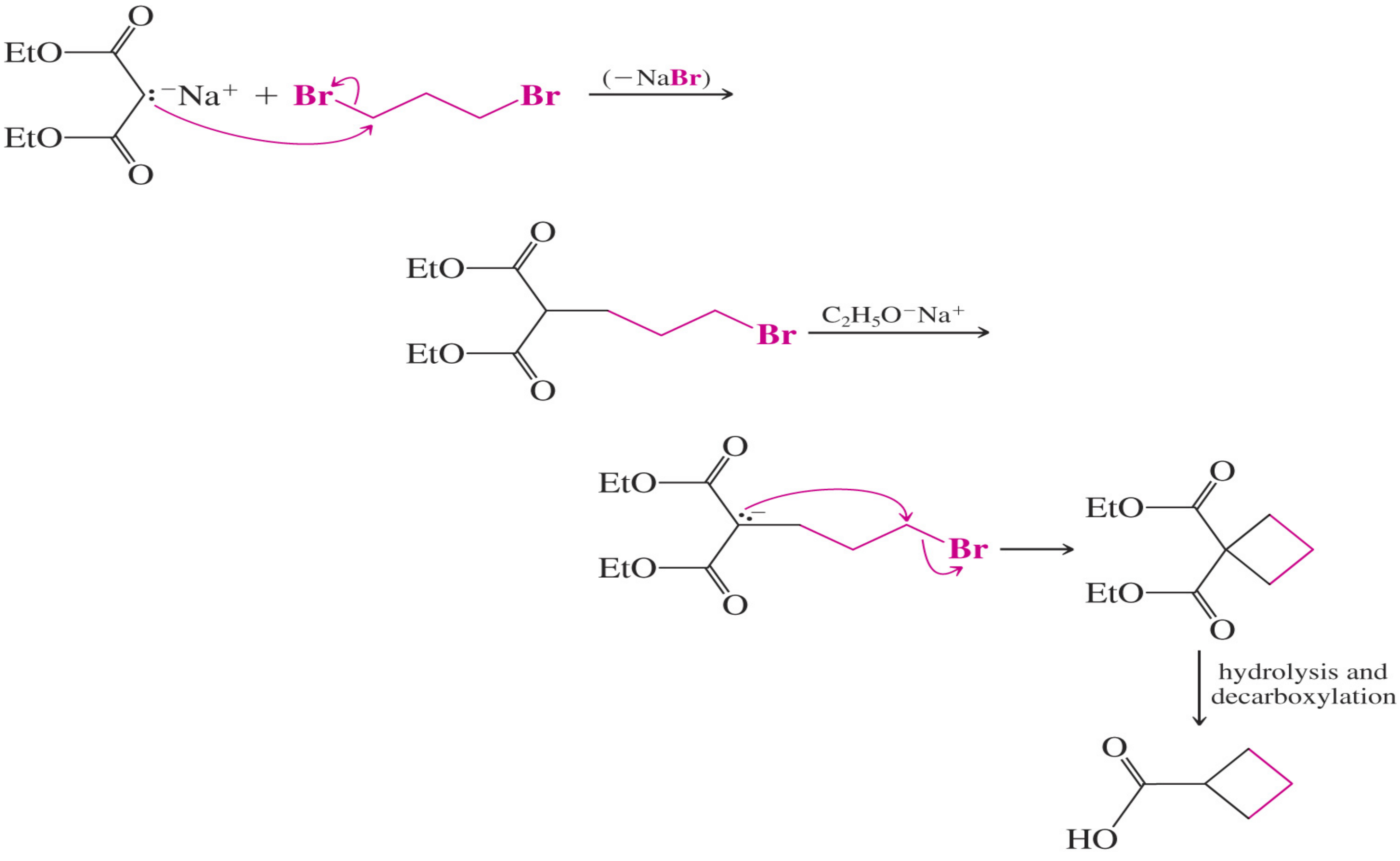
2-Ethylpentanoic acid

- By using two molar equivalents of malonate anion and a dihalide, the dicarboxylic acid is obtained



Glutaric acid
(80% from tetraester)

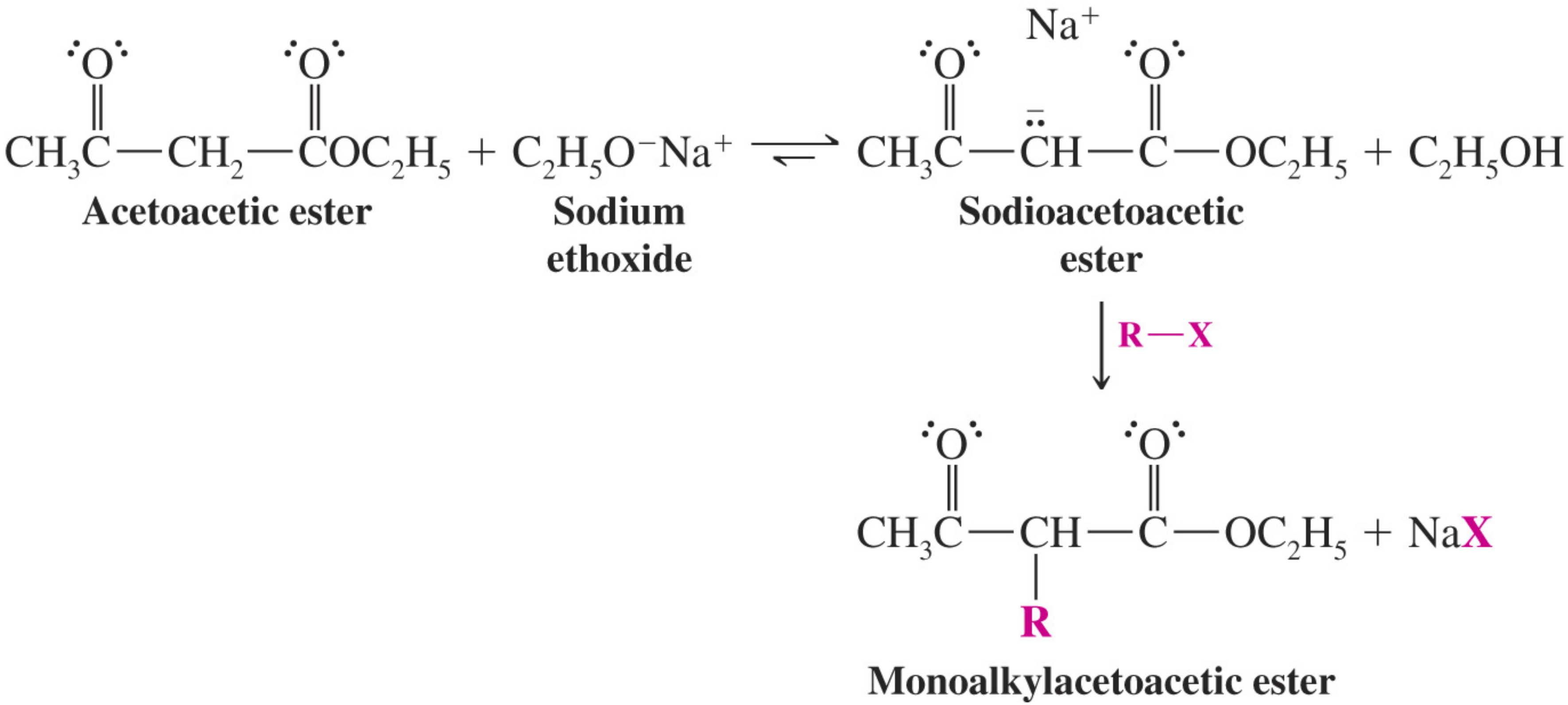
- C2 through C5 terminal dihalides can react to form rings by dialkylation of one molar equivalent of malonate



Cyclobutanecarboxylic acid

Alkylation of Acetoacetic ester

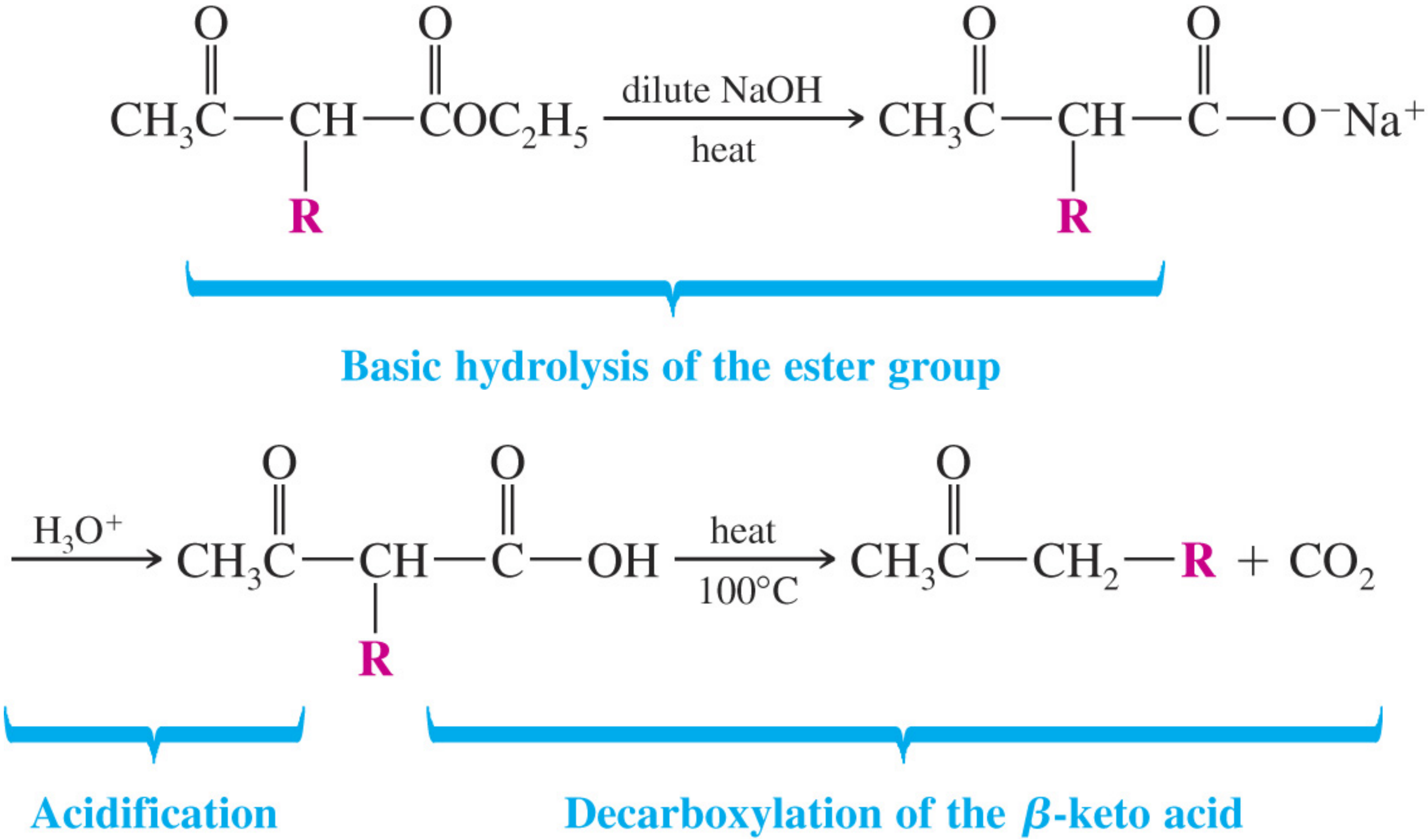
- Synthesis of Methyl Ketones



$$CH_3\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5O^-Na^+ \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}-\overset{Na^+}{\ddot{C}H}-\overset{O}{\overset{\|}{C}}-OC_2H_5 + C_2H_5OH$$

$$\xrightarrow{R-X} CH_3\overset{O}{\overset{\|}{C}}-\underset{R}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-OC_2H_5 + NaX$$

- Hydrolysis of the ester and heating of the resultant β-ketoacid causes decarboxylation
  - – The product is a substituted acetone derivative



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}-\underset{\underset{R}{|}}{CH}-\overset{O}{\overset{\|}{C}}OC_2H_5} \xrightarrow[\text{heat}]{\text{dilute NaOH}} \mathrm{CH_3\overset{O}{\overset{\|}{C}}-\underset{\underset{R}{|}}{CH}-\overset{O}{\overset{\|}{C}}-O^-Na^+}$$

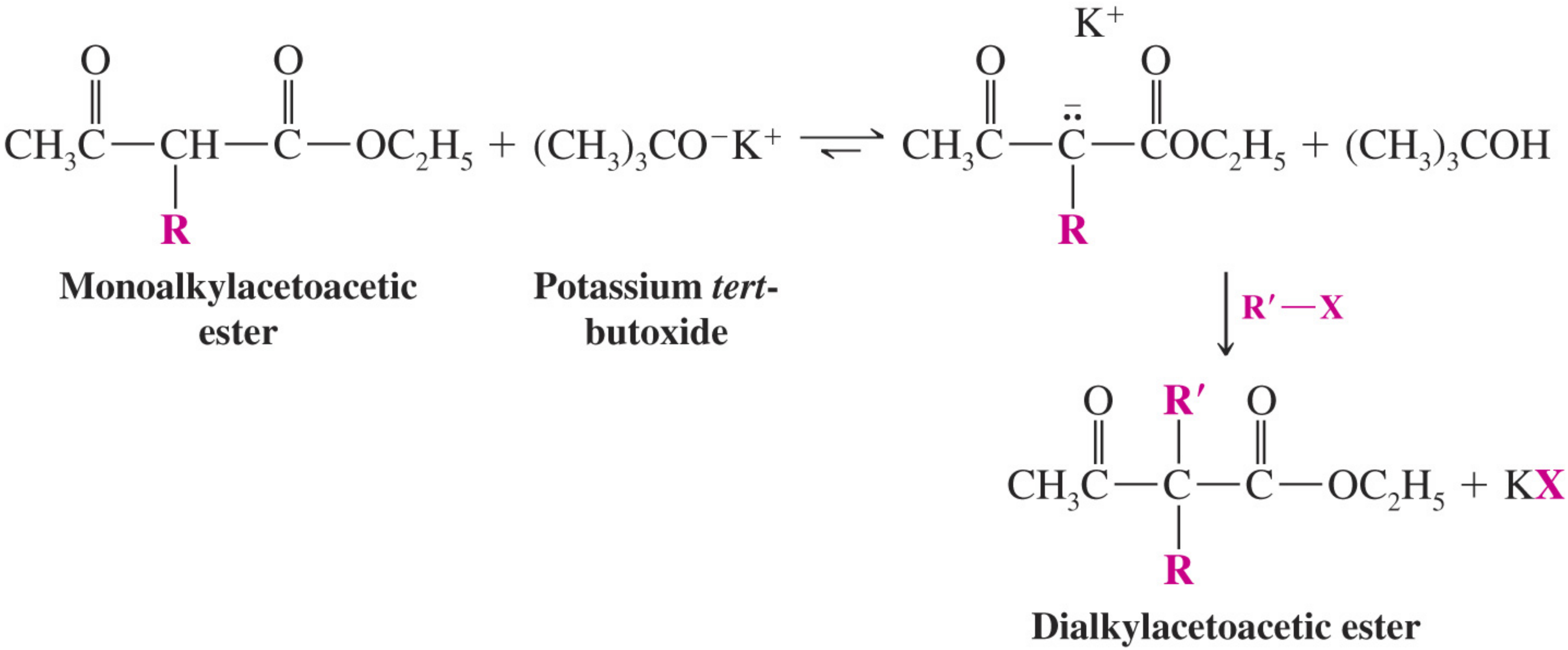
Basic hydrolysis of the ester group

$$\xrightarrow{\mathrm{H_3O^+}} \mathrm{CH_3\overset{O}{\overset{\|}{C}}-\underset{\underset{R}{|}}{CH}-\overset{O}{\overset{\|}{C}}-OH} \xrightarrow[100^\circ\mathrm{C}]{\text{heat}} \mathrm{CH_3\overset{O}{\overset{\|}{C}}-CH_2-R + CO_2}$$

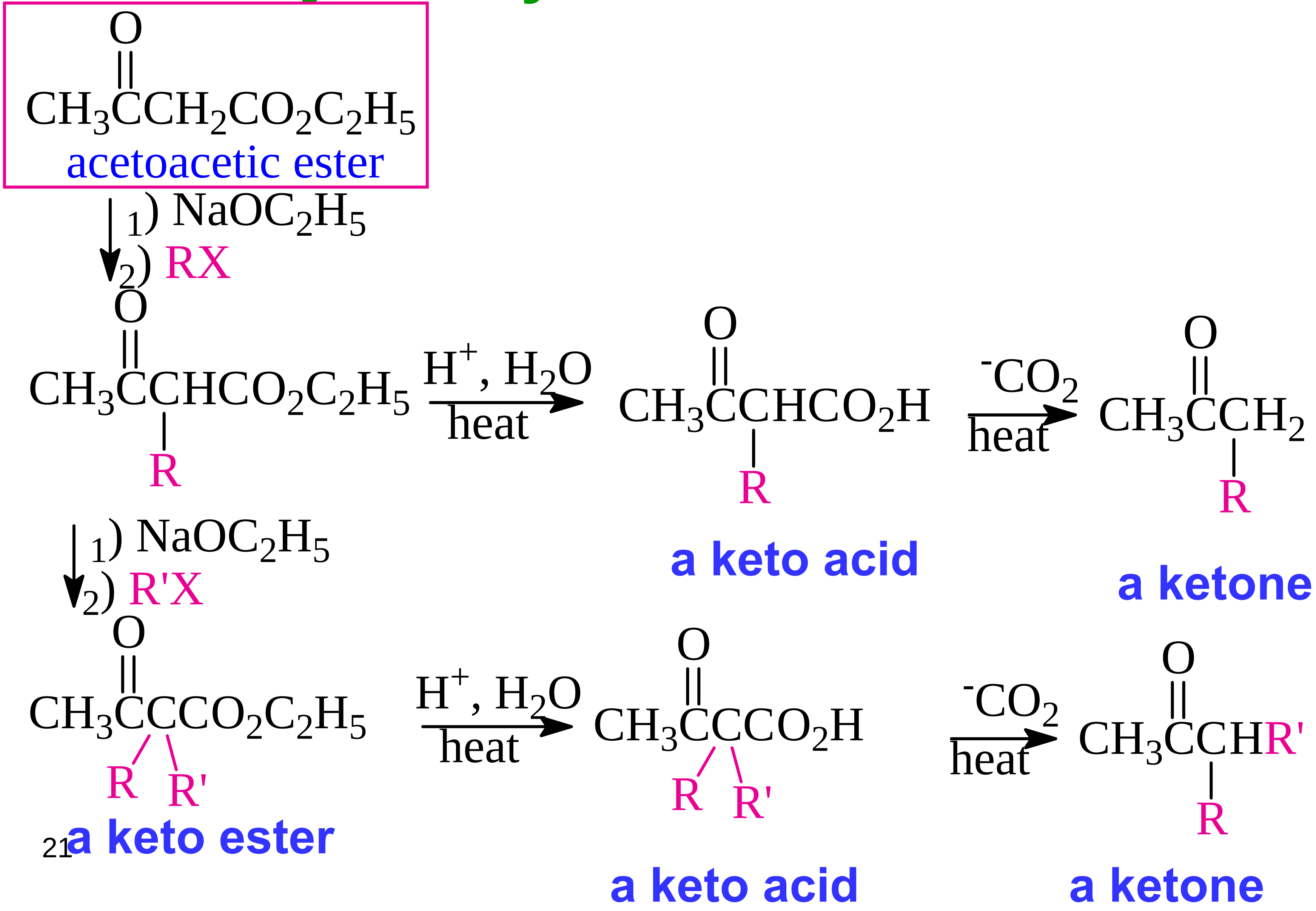
Acidification

Decarboxylation of the *β*-keto acid

- A second alkylation can be performed



Summary of alkylation of acetoacetic ester



$CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2C_2H_5$

acetoacetic ester

$\xrightarrow[\text{2) RX}]{\text{1) NaOC}_2\text{H}_5}$

$CH_3\overset{O}{\overset{\|}{C}}\underset{R}{\underset{|}{C}}HCO_2C_2H_5 \xrightarrow[\text{heat}]{H^+,\ H_2O} CH_3\overset{O}{\overset{\|}{C}}\underset{R}{\underset{|}{C}}HCO_2H \xrightarrow[\text{heat}]{^-CO_2} CH_3\overset{O}{\overset{\|}{C}}\underset{R}{\underset{|}{C}}H_2$

a keto acid

a ketone

$\xrightarrow[\text{2) R'X}]{\text{1) NaOC}_2\text{H}_5}$

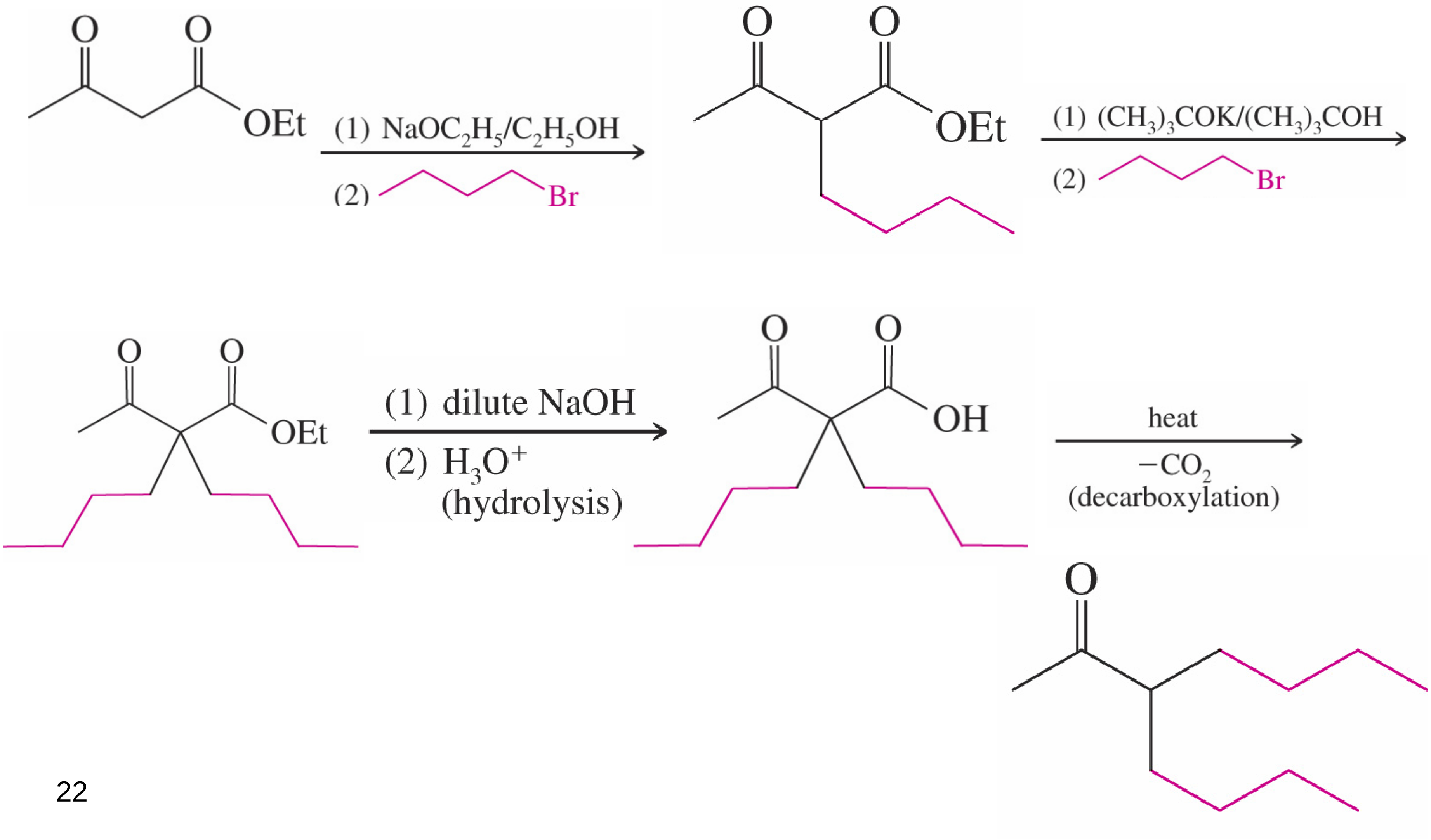
$CH_3\overset{O}{\overset{\|}{C}}\underset{R\ \ R'}{C}CO_2C_2H_5 \xrightarrow[\text{heat}]{H^+,\ H_2O} CH_3\overset{O}{\overset{\|}{C}}\underset{R\ \ R'}{C}CO_2H \xrightarrow[\text{heat}]{^-CO_2} CH_3\overset{O}{\overset{\|}{C}}\underset{R}{\underset{|}{C}}HR'$

a keto ester

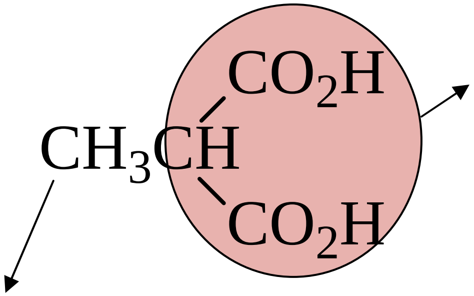
a keto acid

a ketone

example


O
O
OEt
(1) $NaOC_2H_5/C_2H_5OH$
(2) Br
O
O
OEt
(1) $(CH_3)_3COK/(CH_3)_3COH$
(2) Br
O
O
OEt
(1) dilute NaOH
(2) H_3O^+
(hydrolysis)
O
O
OH
heat
$-CO_2$
(decarboxylation)
O

Syntheses Using Alkylation Reactions

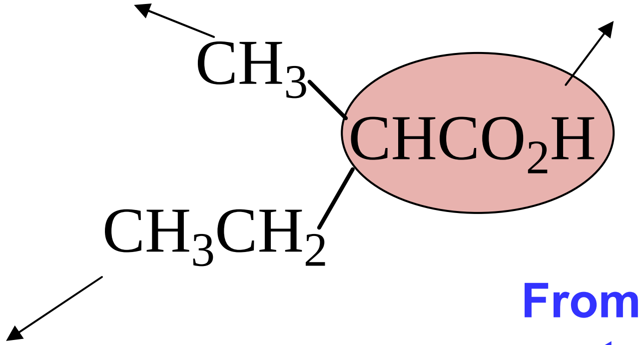


From malonic ester

From CH$_3$X

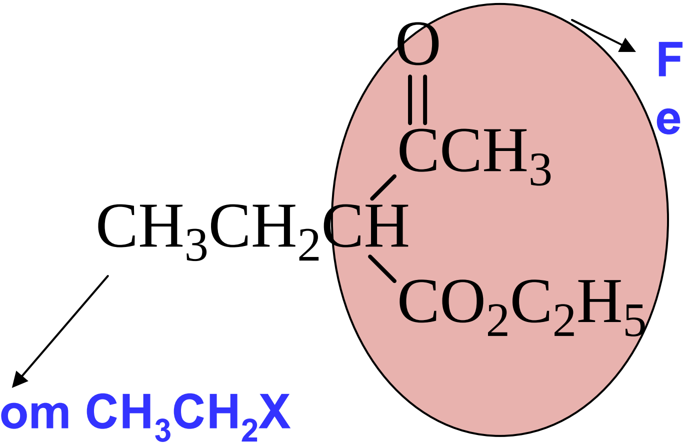
From CH$_3$X

From malonic ester

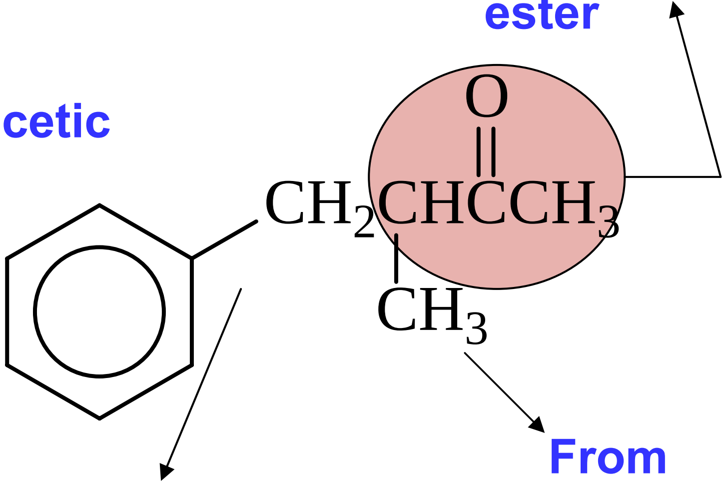


From CH$_3$CH$_2$X

From acetoacetic ester



From acetoacetic ester

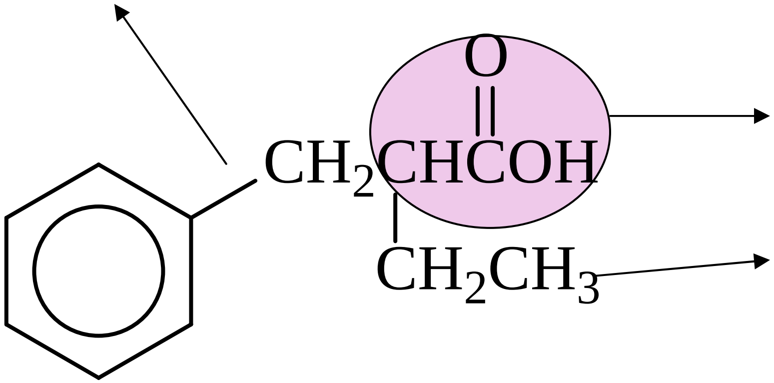


From CH$_3$CH$_2$X

From C$_6$H$_5$CH$_2$X

From CH3X

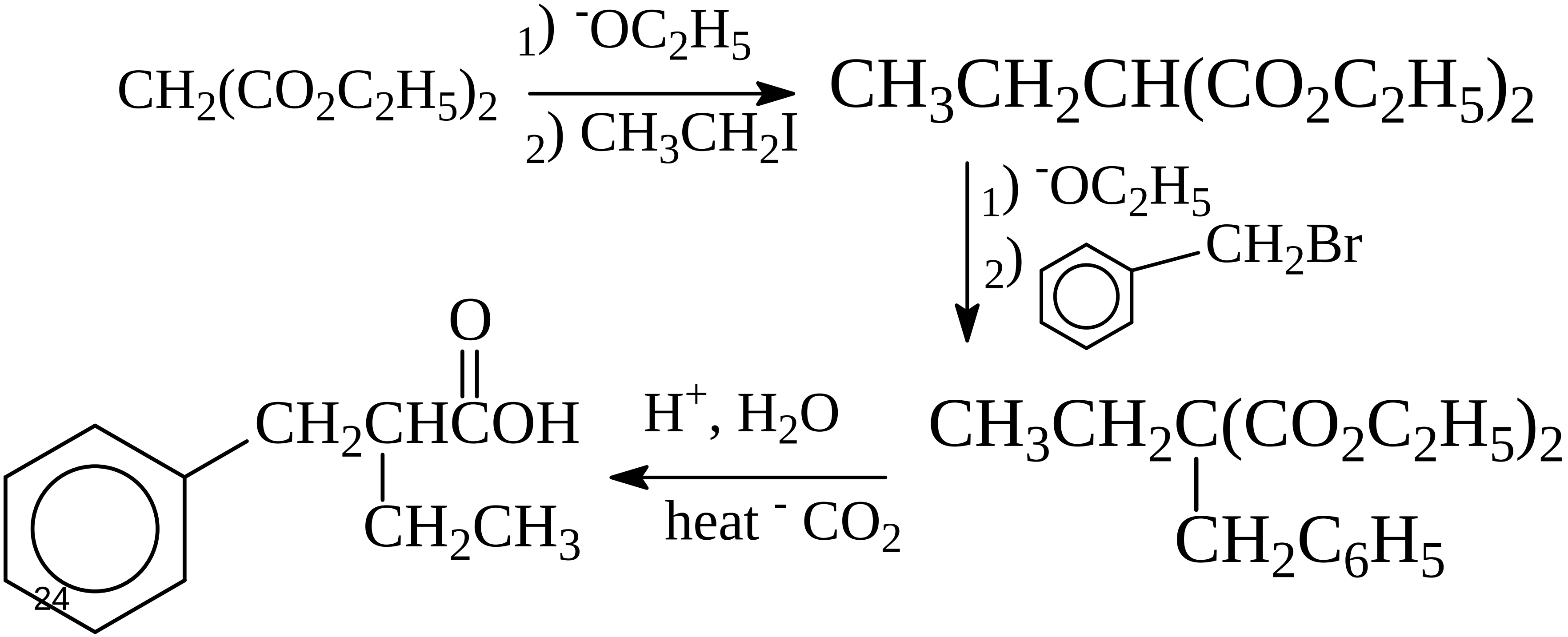
Example



From $C_6H_5CH_2X$

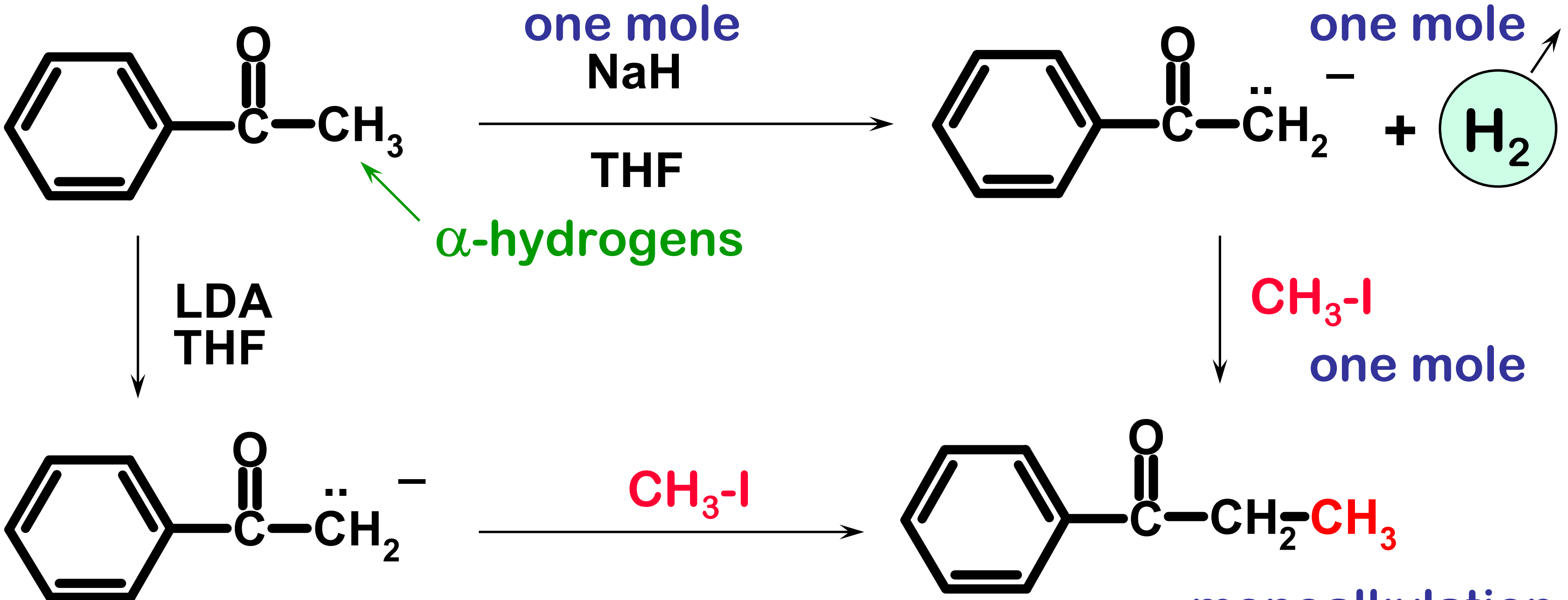
From diethyl malonate

From CH_3CH_2X



Alkylation of a Ketone

NON-CATALYTIC BASES REACT ONCE



one mole

NaH

THF

one mole

H_2

α-hydrogens

LDA

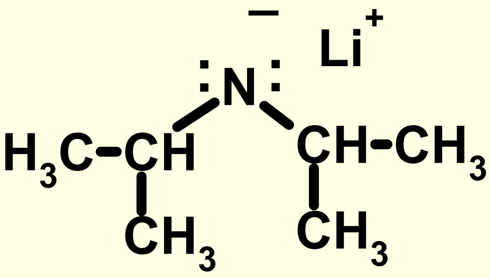
THF

CH_3-I

one mole

CH_3-I

monoalkylation



Sodium Hydride

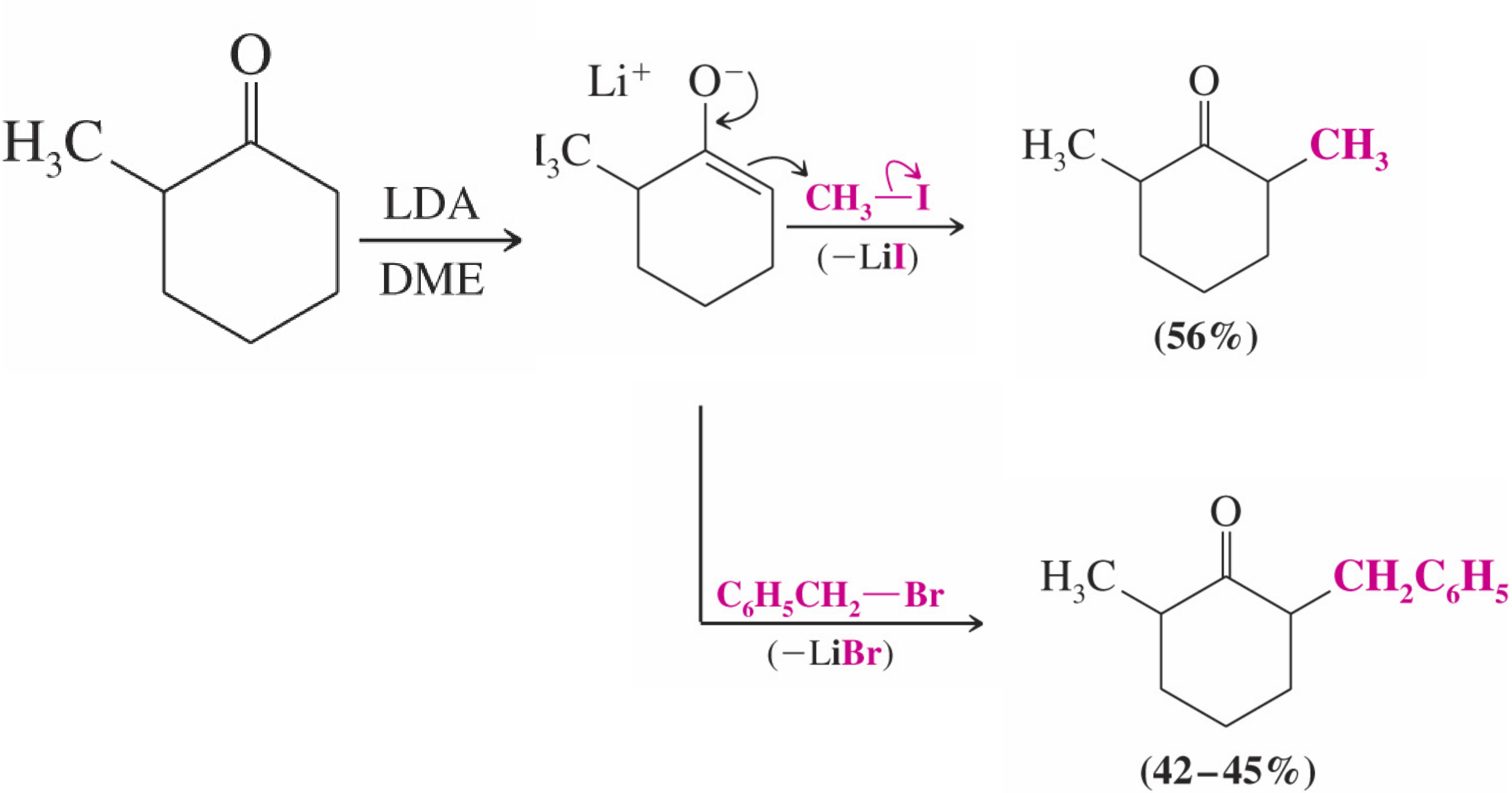
NaH

“LDA”

Lithium Diisopropyl Amide

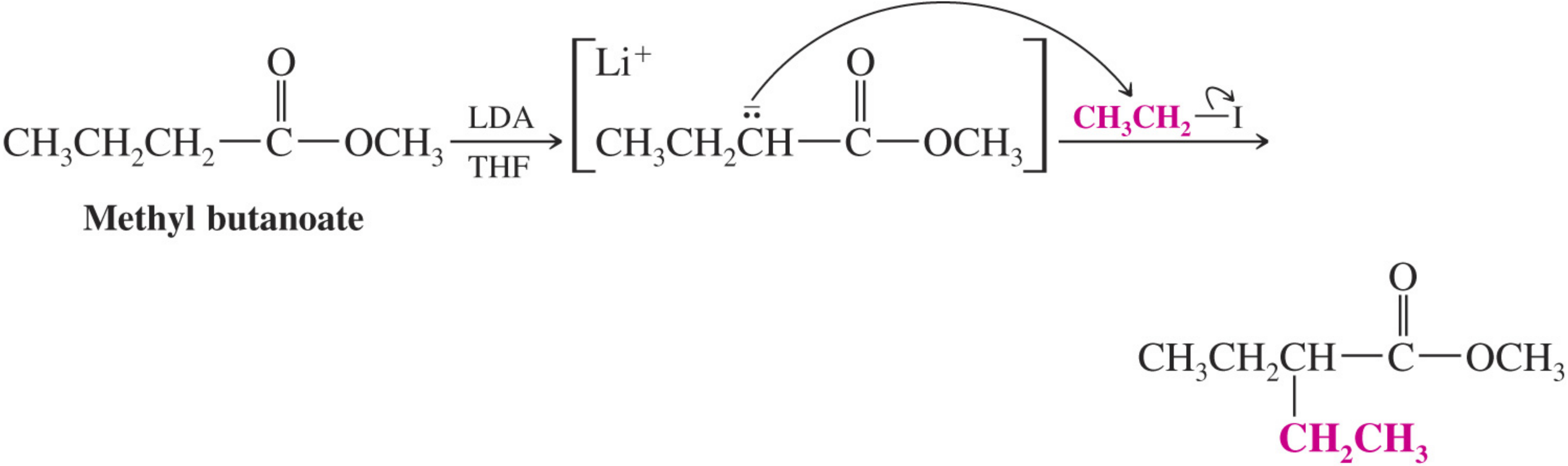
a strong base

EXAMPLE



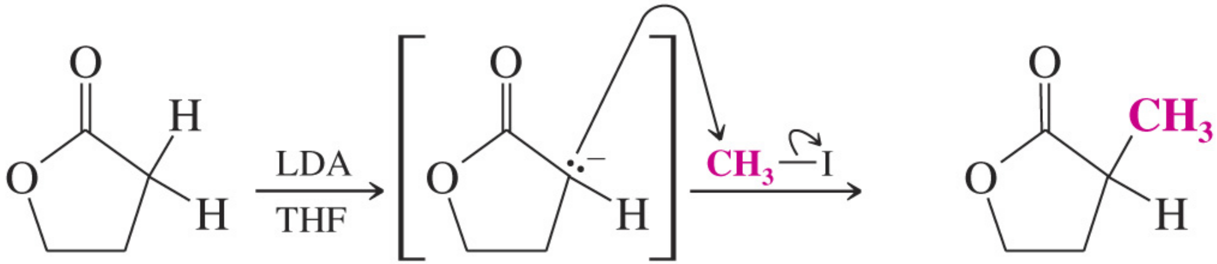
O
H3C
LDA
DME
Li+ O−
H3C
CH3—I
(−LiI)
O
H3C
CH3
(56%)
C6H5CH2—Br
(−LiBr)
O
H3C
CH2C6H5
(42–45%)

Alkylation of esters



Methyl butanoate

Methyl 2-ethylbutanoate
(96%)

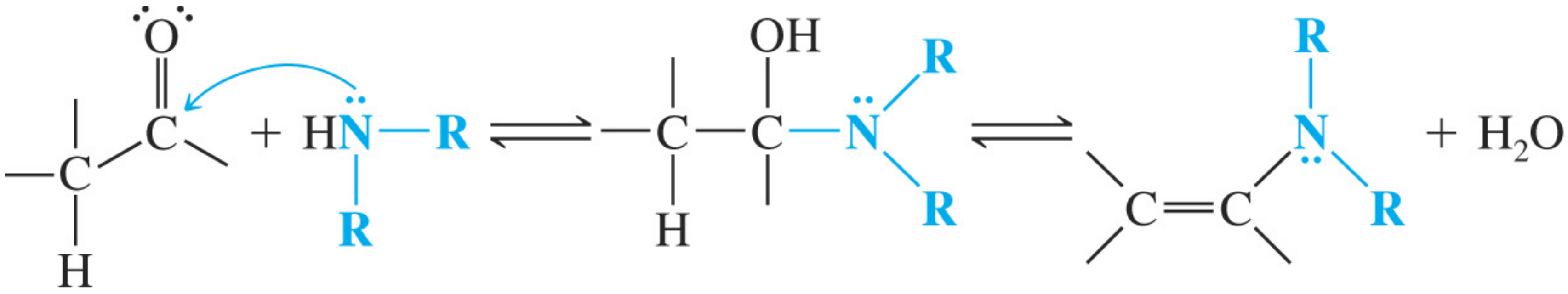


Butyrolactone

2-Methylbutyrolactone
(88%)

Alkylation and Acylation of Enamines

- Aldehydes and ketones react with secondary amines to form enamines.

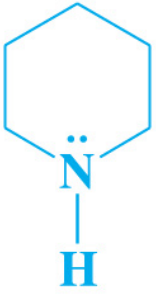


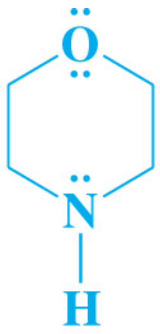
Aldehyde or ketone

2° Amine

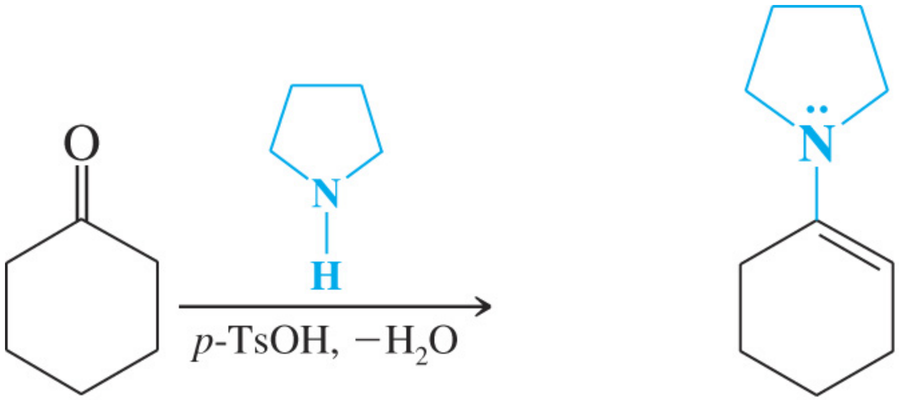
Enamine


Pyrrolidine

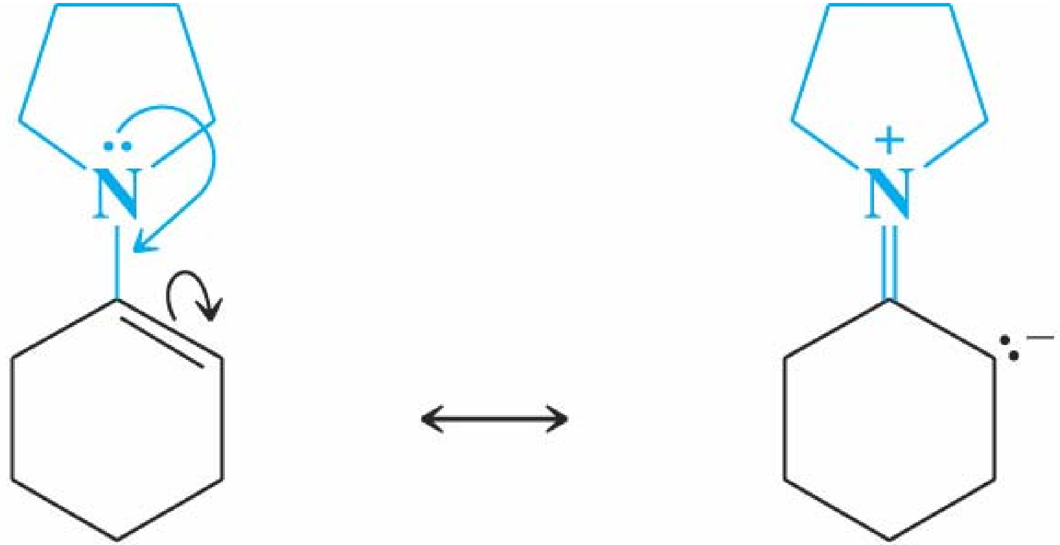

Piperidine


Morpholine

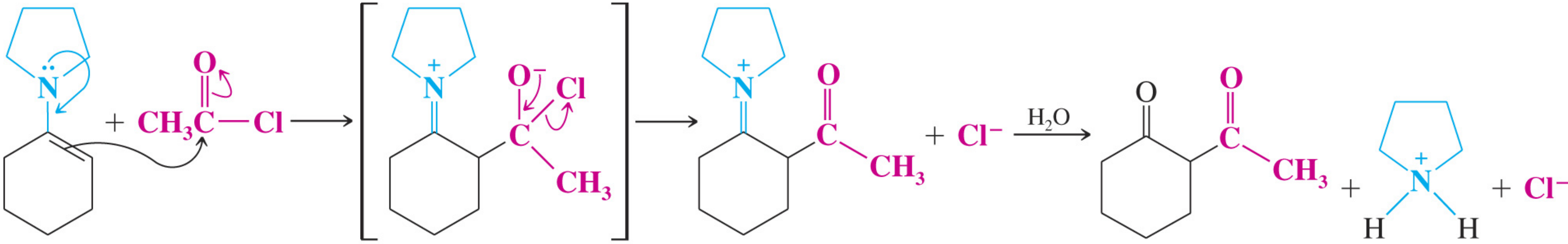
Enamines have a nucleophilic carbon and are the equivalent of ketone and aldehyde enolates



***N*-(1-Cyclohexenyl)pyrrolidine**
(an enamine)

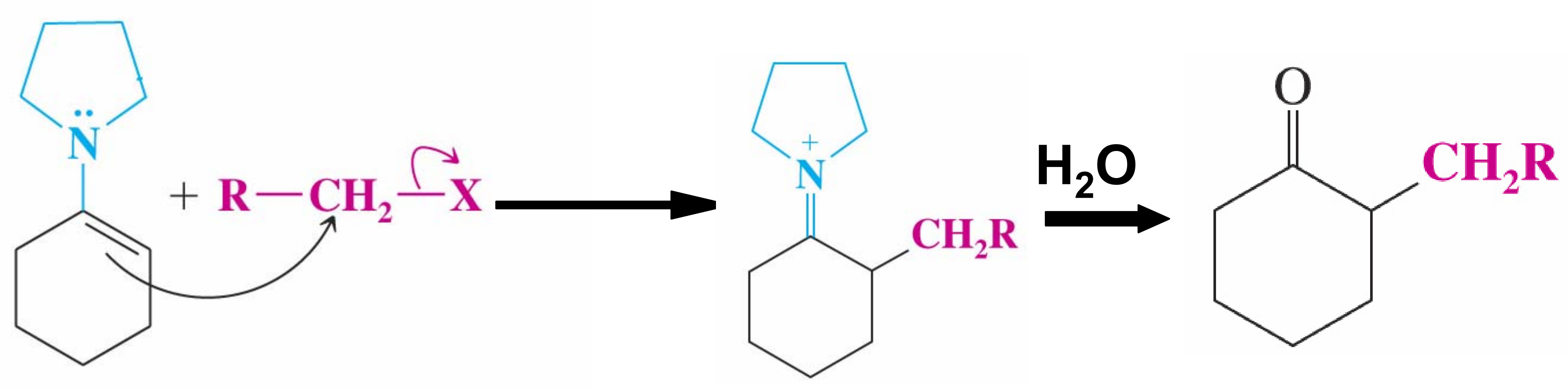


C-Acylation leads to β-diketones



Iminium salt

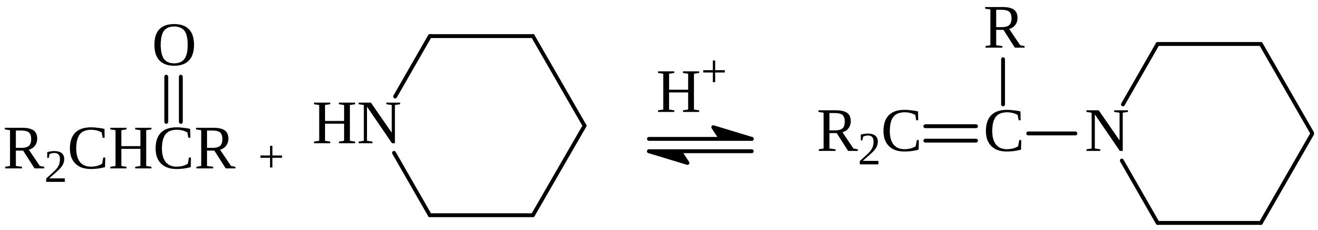
2-Acetylcyclohexanone
(a *β*-diketone)



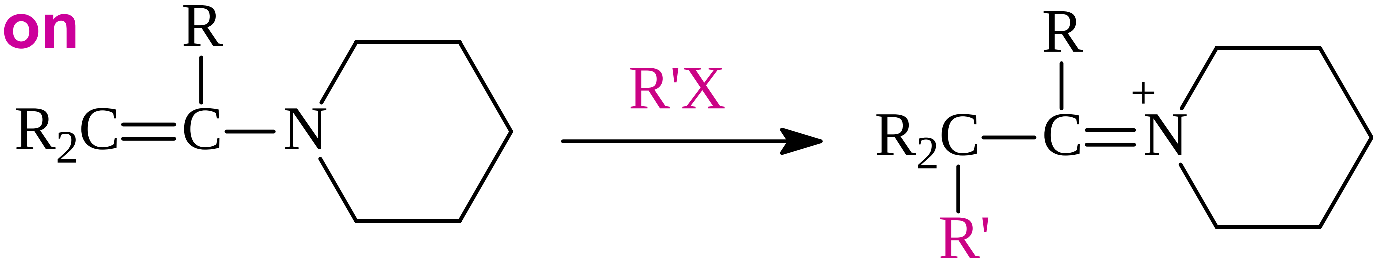
R = CH_2=CH— or C_6H_5—

Enamine alkylation steps

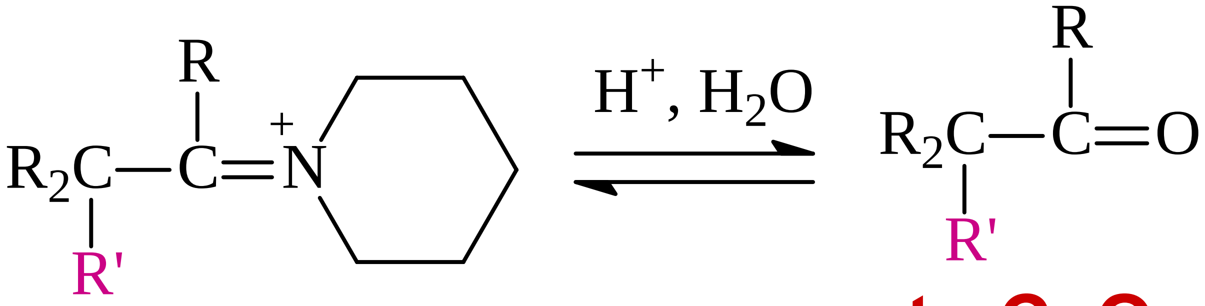
1) Enamine formation



2) Substitution

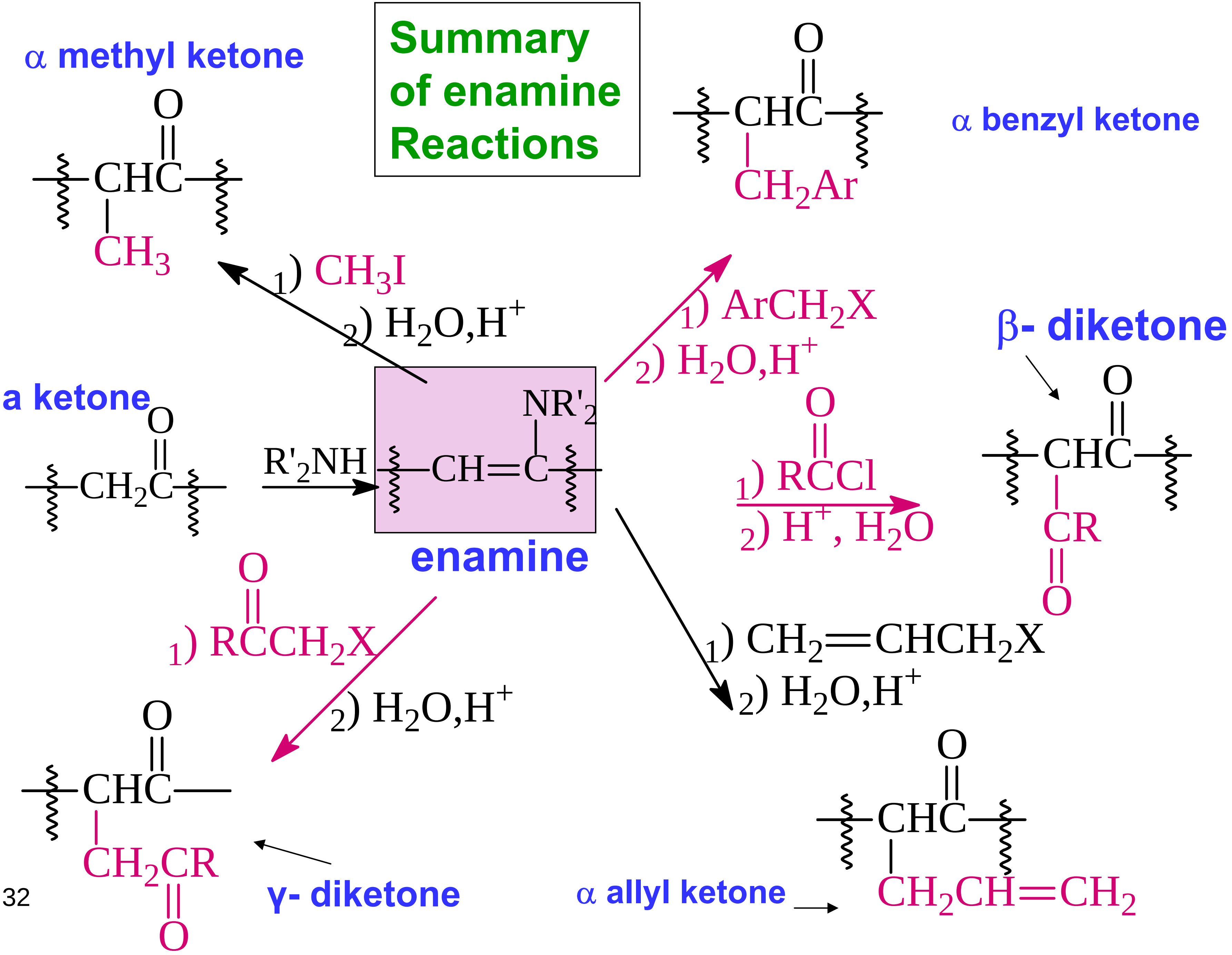


3) Hydrolysis



α to C=O

Summary of enamine Reactions



a ketone

R'_2NH

enamine

α methyl ketone

1) CH_3I
2) H_2O, H^+

α benzyl ketone

1) $ArCH_2X$
2) H_2O, H^+

β- diketone

1) $RCCl$ (with $=O$)
2) H^+, H_2O

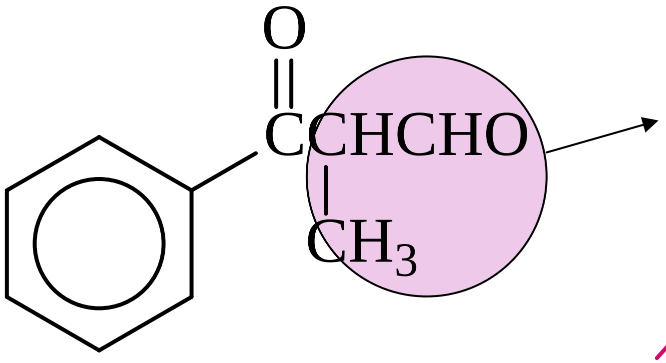
α allyl ketone

1) $CH_2{=}CHCH_2X$
2) H_2O, H^+

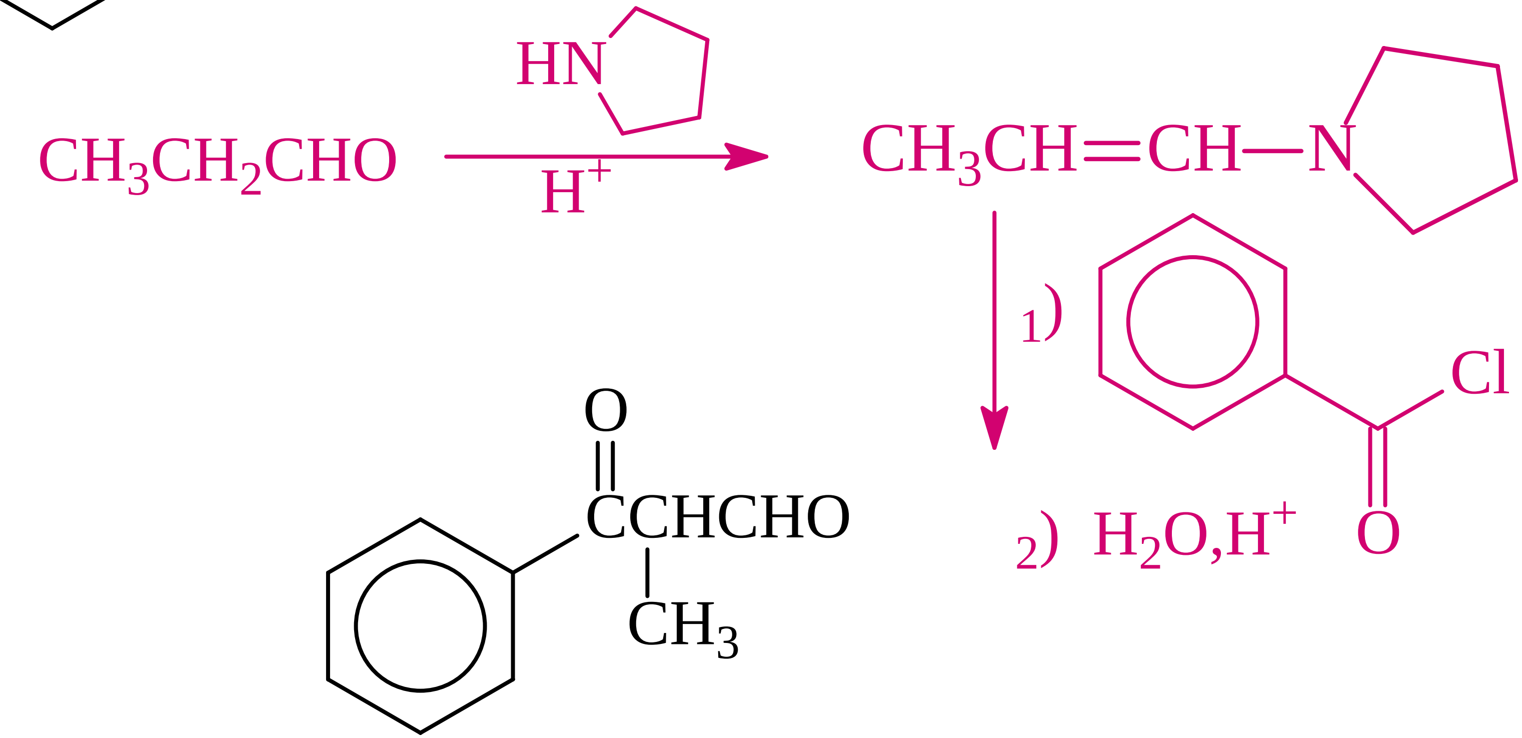
γ- diketone

1) $RCCH_2X$ (with $=O$)
2) H_2O, H^+

How would you synthesis the following compound

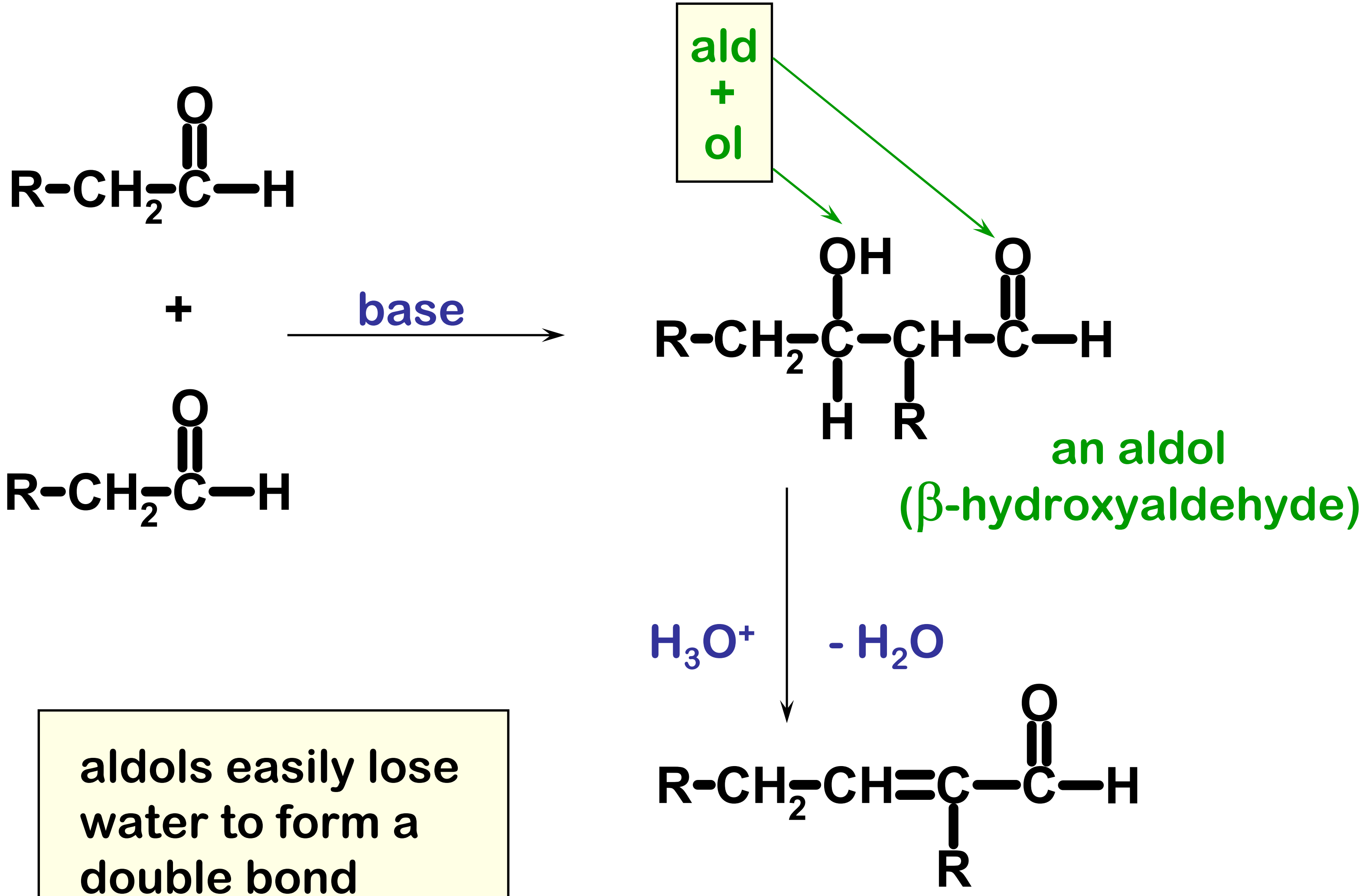


From propanal



ALDOL CONDENSATION

The Aldol Condensation



$$R{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}H \;+\; R{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}H \xrightarrow{\text{base}} R{-}CH_2{-}\underset{H}{\overset{OH}{C}}{-}\underset{R}{CH}{-}\overset{O}{\overset{\|}{C}}{-}H$$

$$\xrightarrow[-\,H_2O]{H_3O^+} R{-}CH_2{-}CH{=}\underset{R}{C}{-}\overset{O}{\overset{\|}{C}}{-}H$$

ald
+
ol

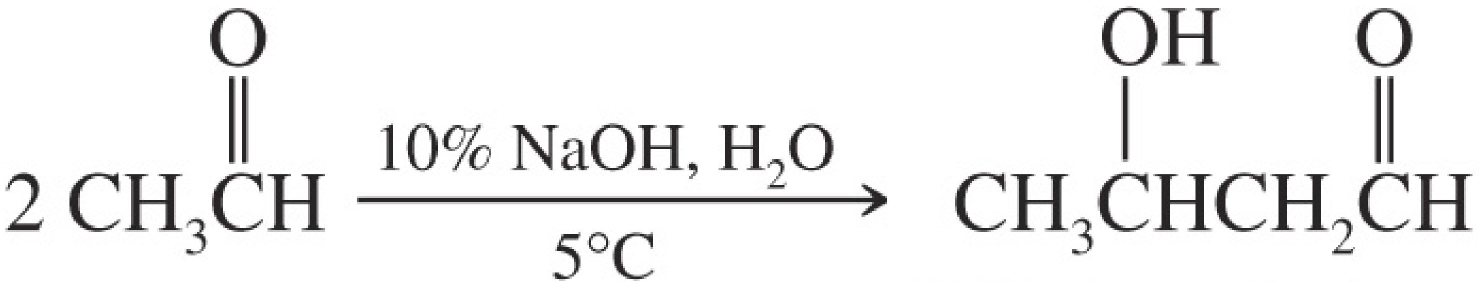
an aldol
(β-hydroxyaldehyde)

α,β-unsaturated aldehyde

aldols easily lose water to form a double bond

The Aldol Reaction: The Addition of Enolate Anions to Aldehydes and Ketones

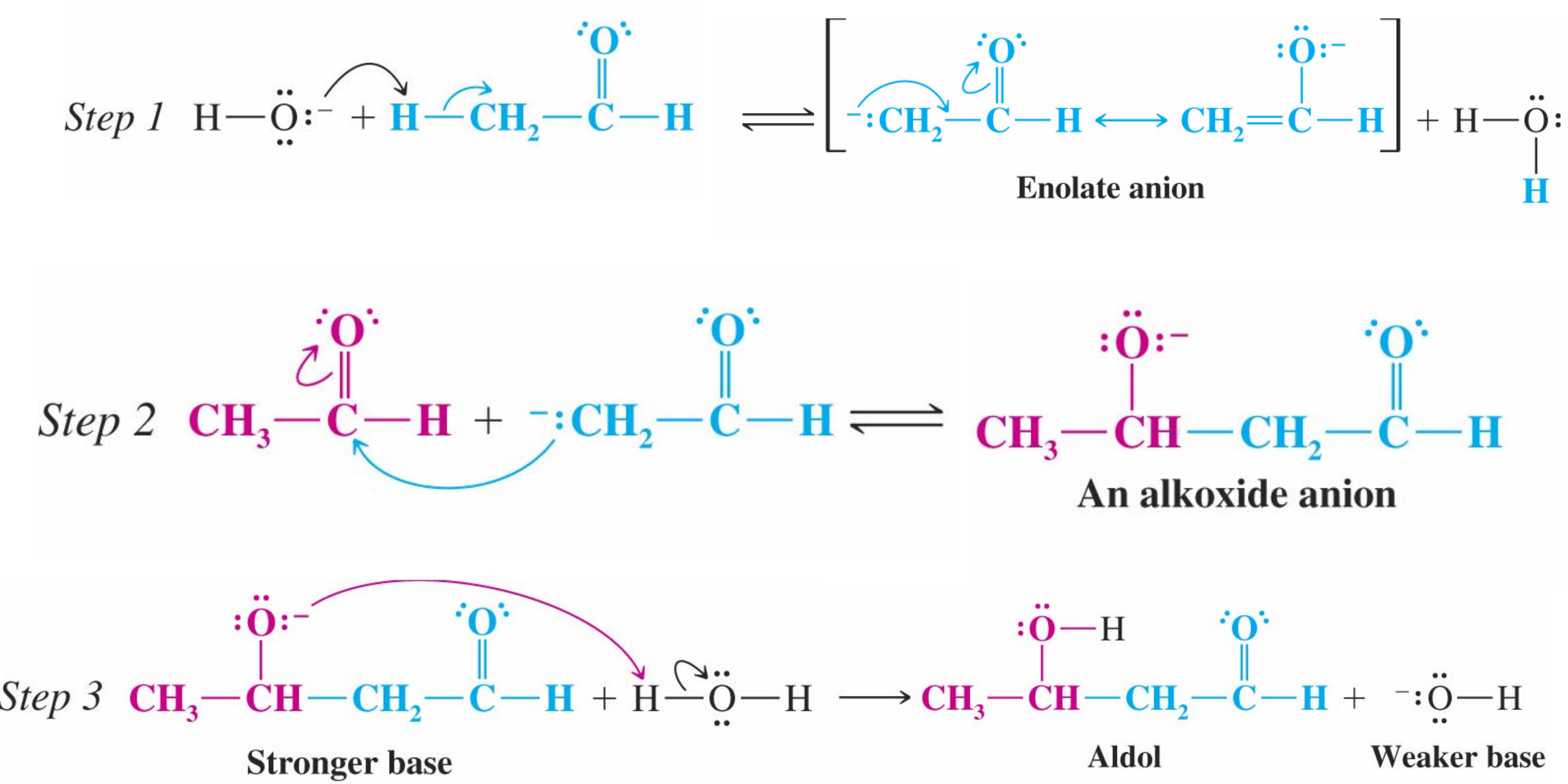
- Acetaldehyde dimerizes in the presence of dilute sodium hydroxide at room temperature



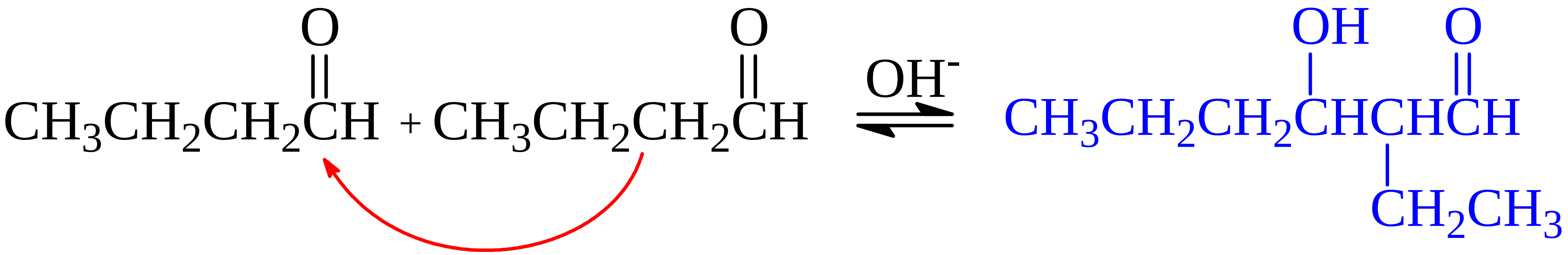
$$2\,\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H} \xrightarrow[5^\circ\mathrm{C}]{10\%\ \mathrm{NaOH,\ H_2O}} \mathrm{CH_3}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}\mathrm{HCH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H}$$

3-Hydroxybutanal
(“aldol”)
(50%)

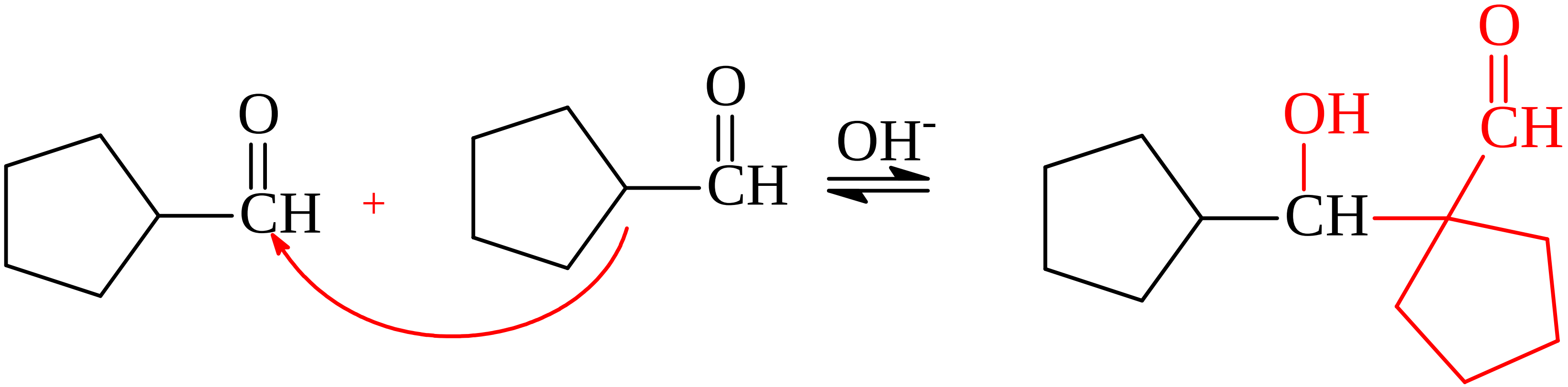
Mechanism


Step 1
Enolate anion
Step 2
An alkoxide anion
Step 3
Stronger base
Aldol
Weaker base

Examples

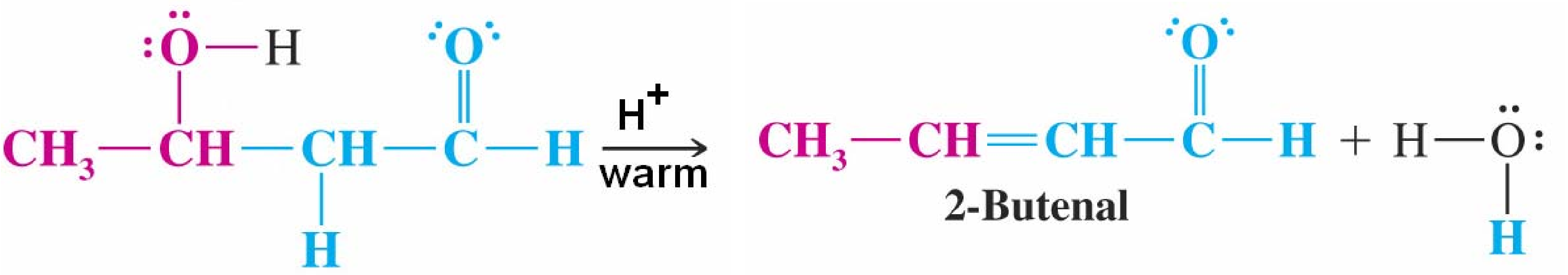


$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H + CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H \xrightleftharpoons{OH^-} CH_3CH_2CH_2\overset{OH}{\overset{|}{C}}H\underset{CH_2CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}H$$



Dehydration of the Aldol Product

- The aldol product easily undergo dehydration to an α,β-unsaturated aldehyde
- Dehydration is favorable because the product is stabilized by conjugation of the alkene with the carbonyl group

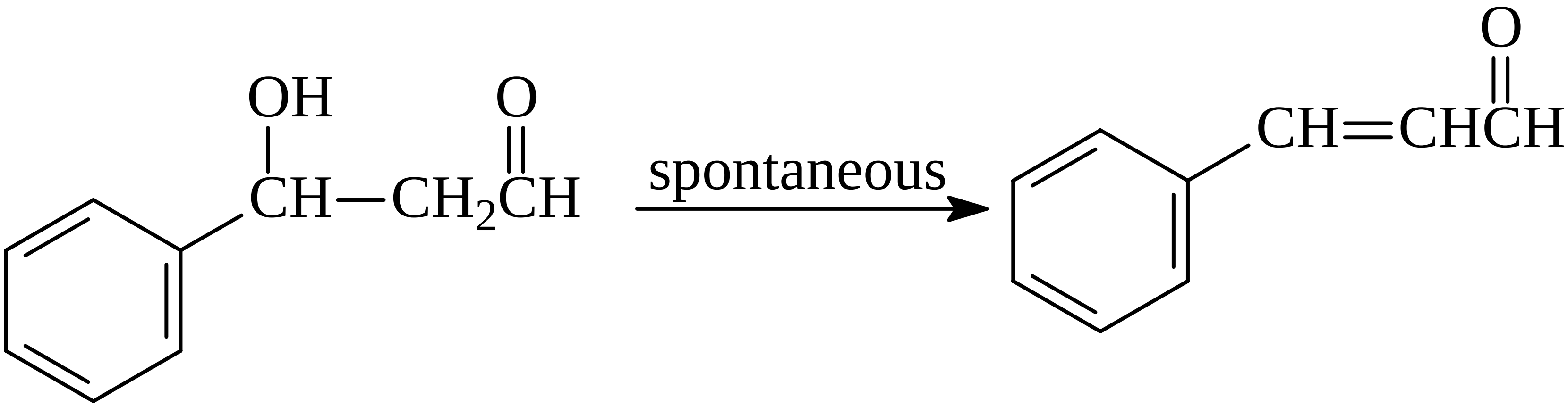


$$CH_3-\underset{}{\overset{:\ddot{O}-H}{\overset{|}{CH}}}-\underset{\underset{H}{|}}{CH}-\overset{\overset{\ddot{O}}{\|}}{C}-H \xrightarrow[\text{warm}]{H^+} CH_3-CH=CH-\overset{\overset{\ddot{O}}{\|}}{C}-H + H-\underset{\underset{H}{|}}{\ddot{O}}:$$

2-Butenal

β-hydroxy aldehyde

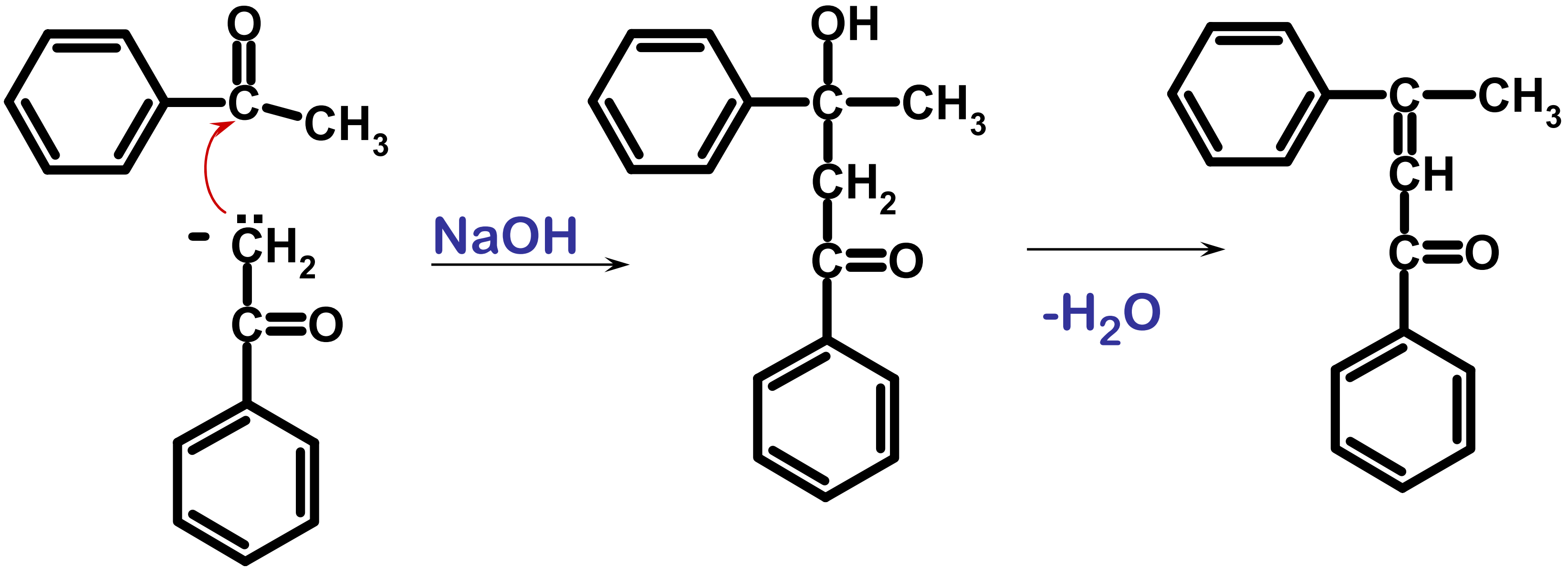
Dehydration is Spontaneous if the double bond is in conjugation with aromatic ring



3-hydroxy-3-phenylpropanal

3-phenylprpenal

Ketones Also Give Aldol Condensations

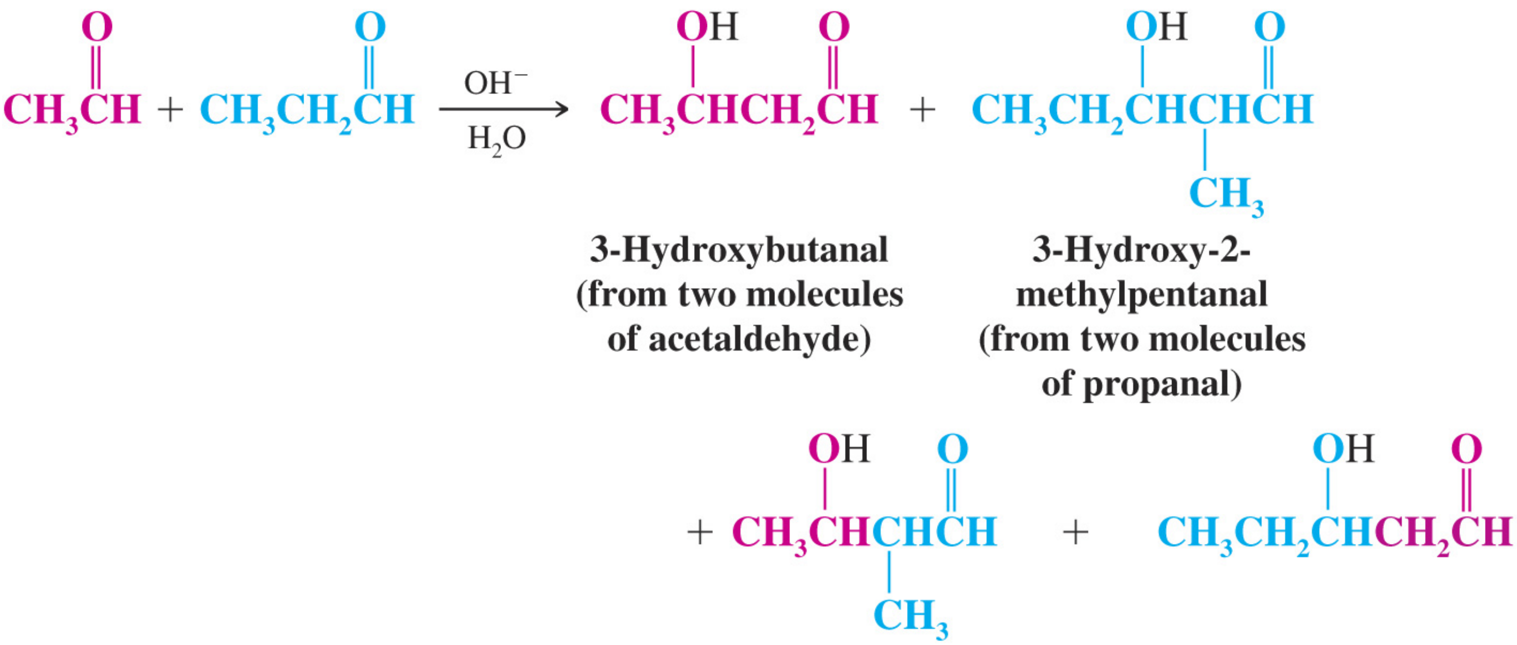


“aldol”

“CROSSED” ALDOL CONDENSATIONS

• Crossed Aldol Reactions

- Crossed aldol reactions (aldol reactions involving two different aldehydes) are of little use when they lead to a mixture of products



$$CH_3\overset{O}{\overset{\|}{C}}H + CH_3CH_2\overset{O}{\overset{\|}{C}}H \xrightarrow[H_2O]{OH^-} CH_3\overset{OH}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}H + CH_3CH_2\overset{OH}{\overset{|}{C}}H\underset{CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}H$$

3-Hydroxybutanal
(from two molecules
of acetaldehyde)

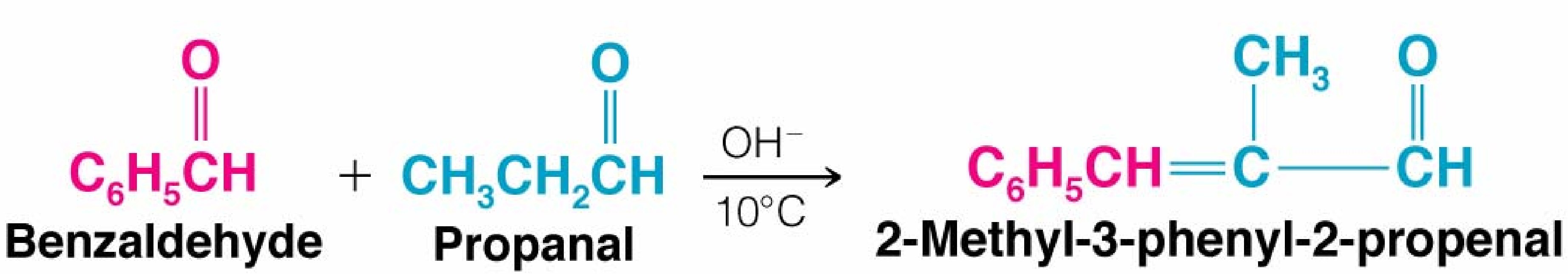
3-Hydroxy-2-
methylpentanal
(from two molecules
of propanal)

$$+ CH_3\overset{OH}{\overset{|}{C}}H\underset{CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}H + CH_3CH_2\overset{OH}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}H$$

3-Hydroxy-2-methylbutanal 3-Hydroxypentanal
(from one molecule of acetaldehyde and one molecule of propanal)

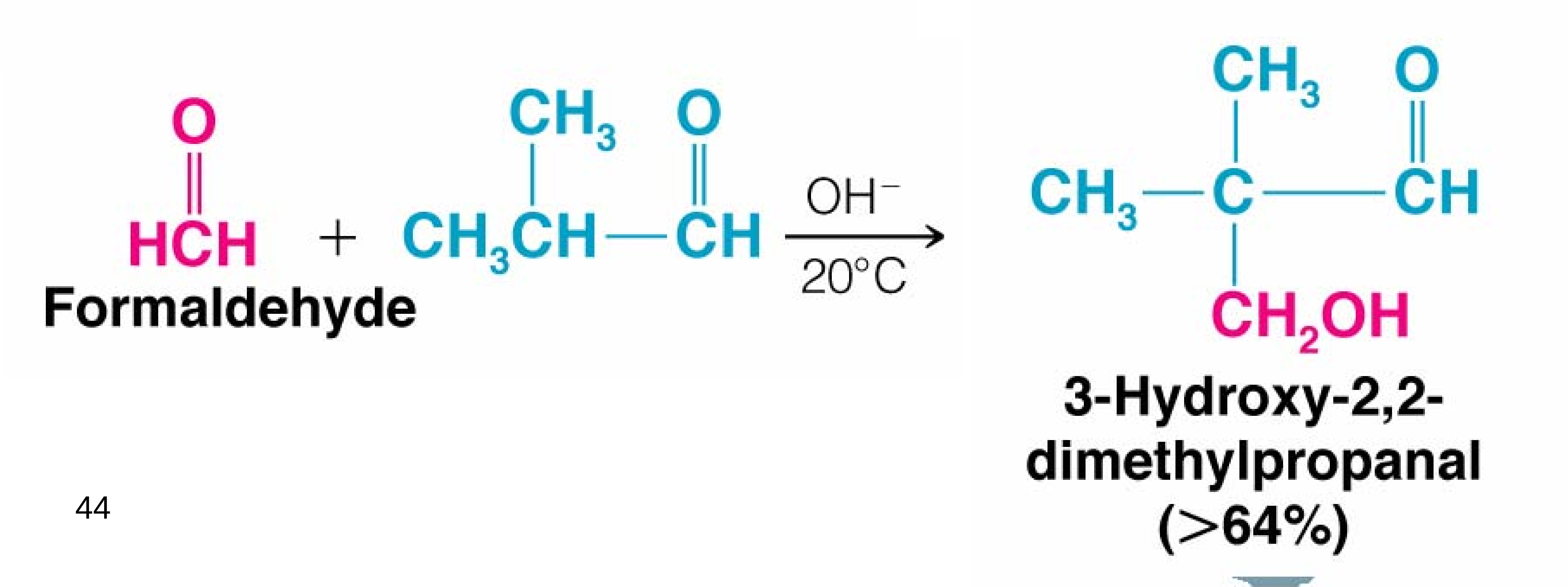
Practical Crossed Aldol Reactions

- Crossed aldol reactions give one predictable product when one of the reaction partners has no α hydrogens



$$C_6H_5CHO + CH_3CH_2CHO \xrightarrow[10^\circ C]{OH^-} C_6H_5CH{=}C(CH_3)CHO$$

Benzaldehyde Propanal 2-Methyl-3-phenyl-2-propenal

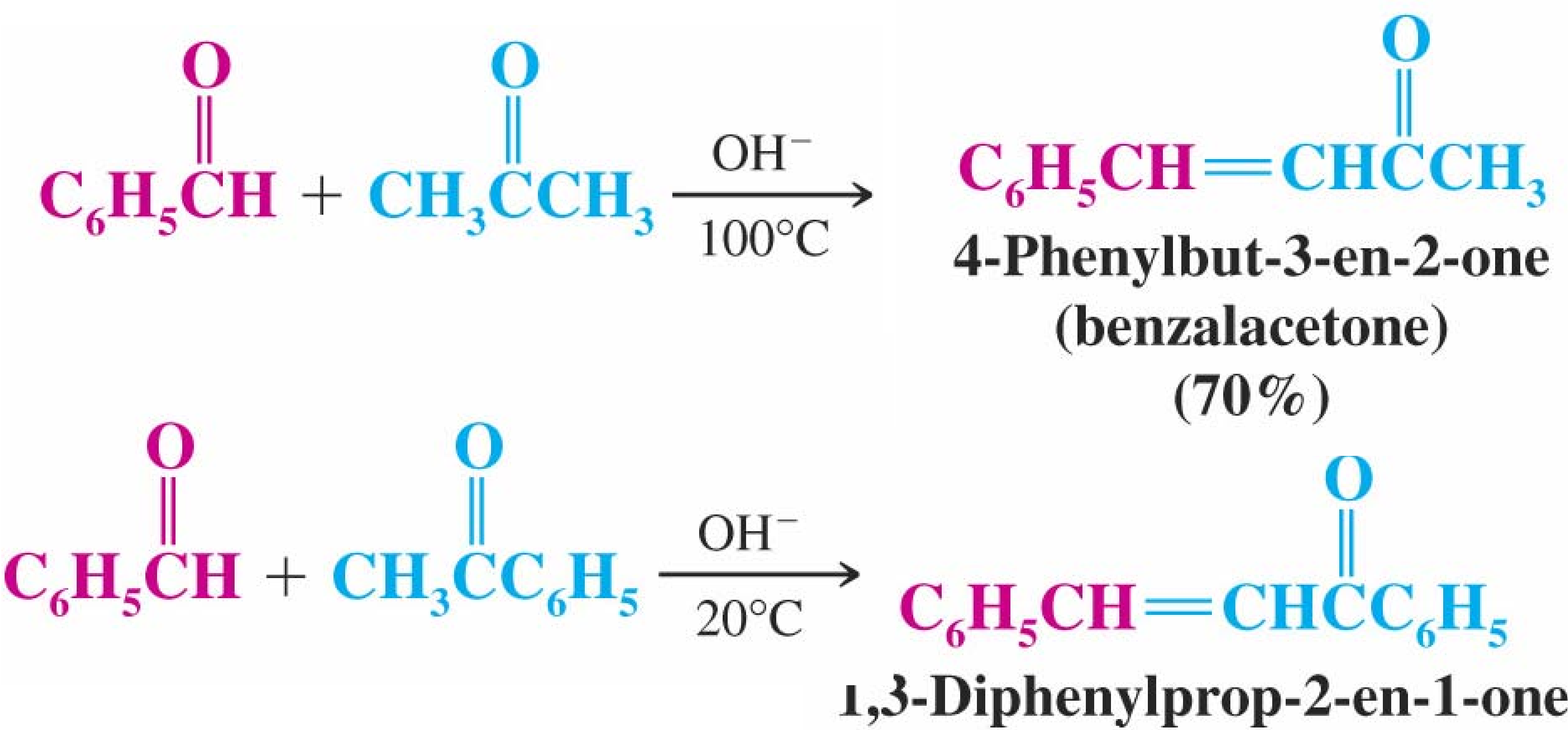


$$HCHO + CH_3CH(CH_3)CHO \xrightarrow[20^\circ C]{OH^-} CH_3C(CH_3)(CH_2OH)CHO$$

Formaldehyde

3-Hydroxy-2,2-dimethylpropanal (>64%)

Crossed-aldol reactions in which one partner is a ketone



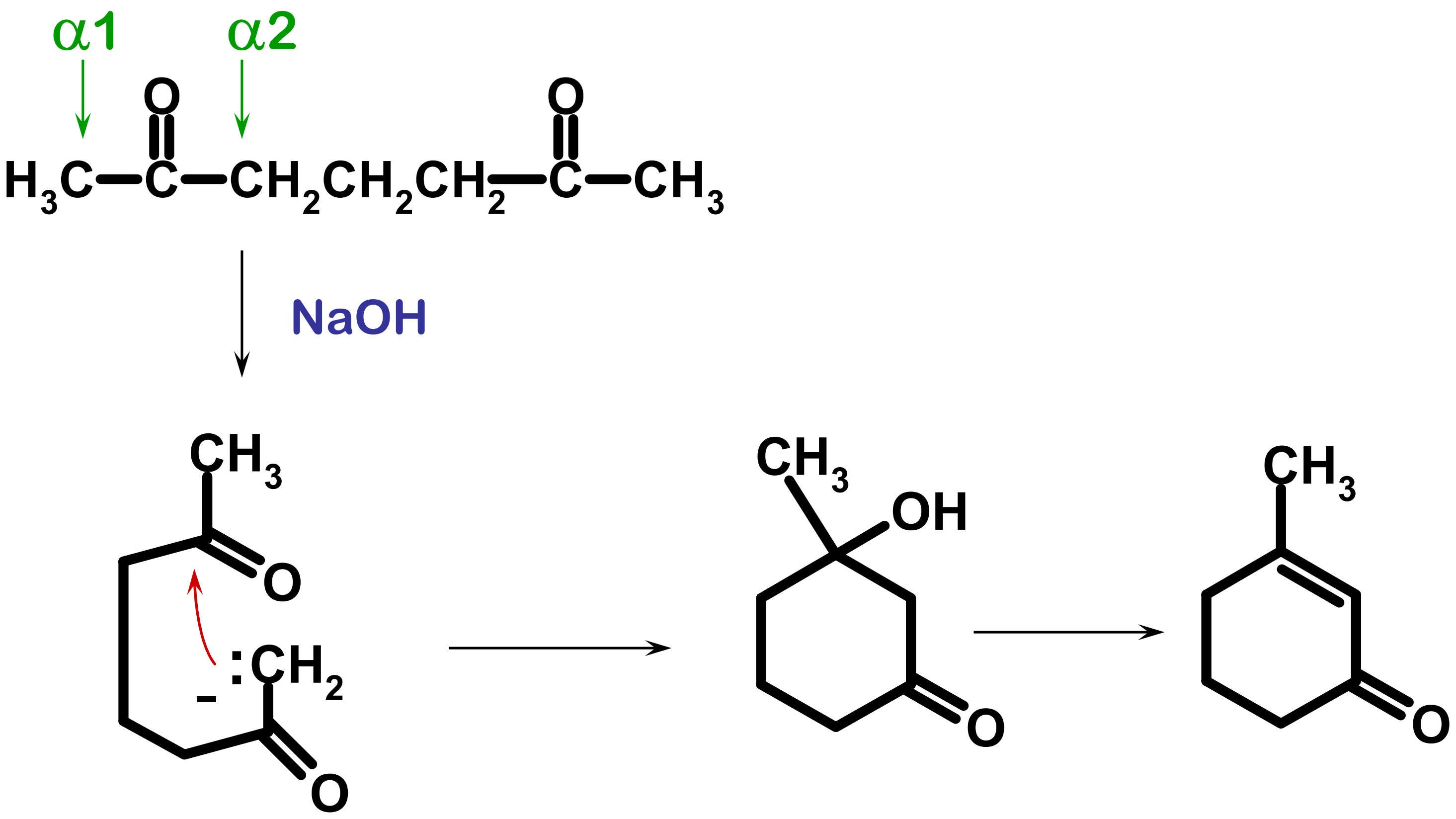
$$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}H + CH_3\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[100^\circ C]{OH^-} C_6H_5CH{=}CH\overset{O}{\overset{\|}{C}}CH_3}$$

4-Phenylbut-3-en-2-one
(benzalacetone)
(70%)

$$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}H + CH_3\overset{O}{\overset{\|}{C}}C_6H_5 \xrightarrow[20^\circ C]{OH^-} C_6H_5CH{=}CH\overset{O}{\overset{\|}{C}}C_6H_5}$$

1,3-Diphenylprop-2-en-1-one

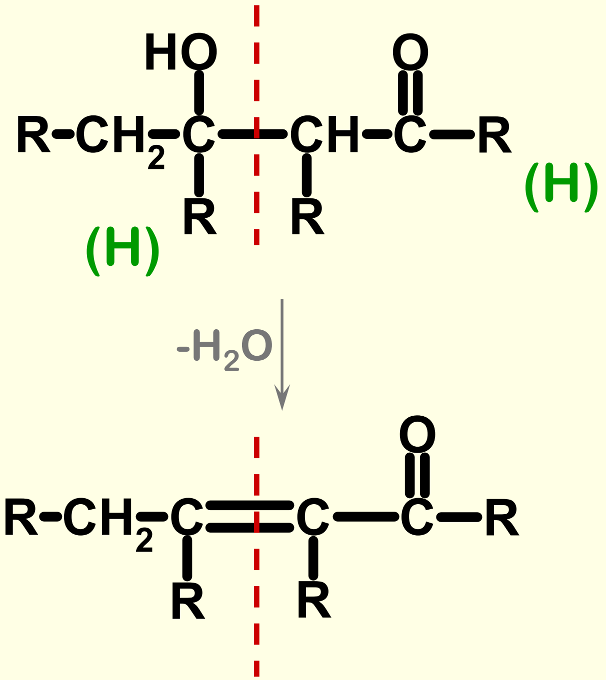
Formation of Rings



$H_3C-\overset{\overset{\large O}{\|}}{C}-CH_2CH_2CH_2-\overset{\overset{\large O}{\|}}{C}-CH_3$

Why don't α2 hydrogens react ?

Syntheses Pattern



β-hydroxy to C=O

3-hydroxyaldehyde or

3-hydroxyketone

ALDOL

α,β-unsaturated C=O

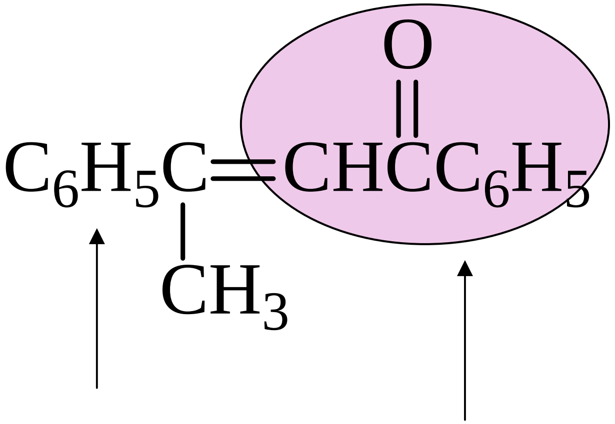
2-propen-1-al or

2-propen-1-one

ALDOL

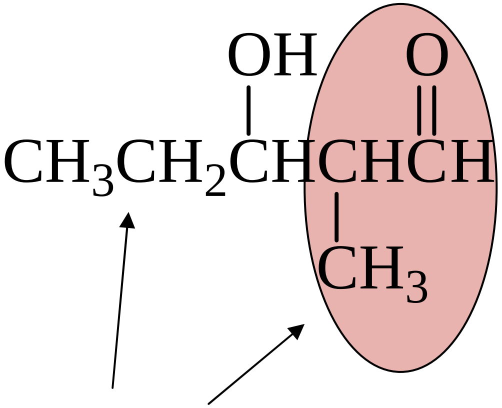
(with loss of H_2O)

Syntheses Using Aldol Condensation



$C_6H_5\underset{\underset{CH_3}{|}}{C}=CH\overset{\overset{O}{\|}}{C}C_6H_5$

From acetophenone

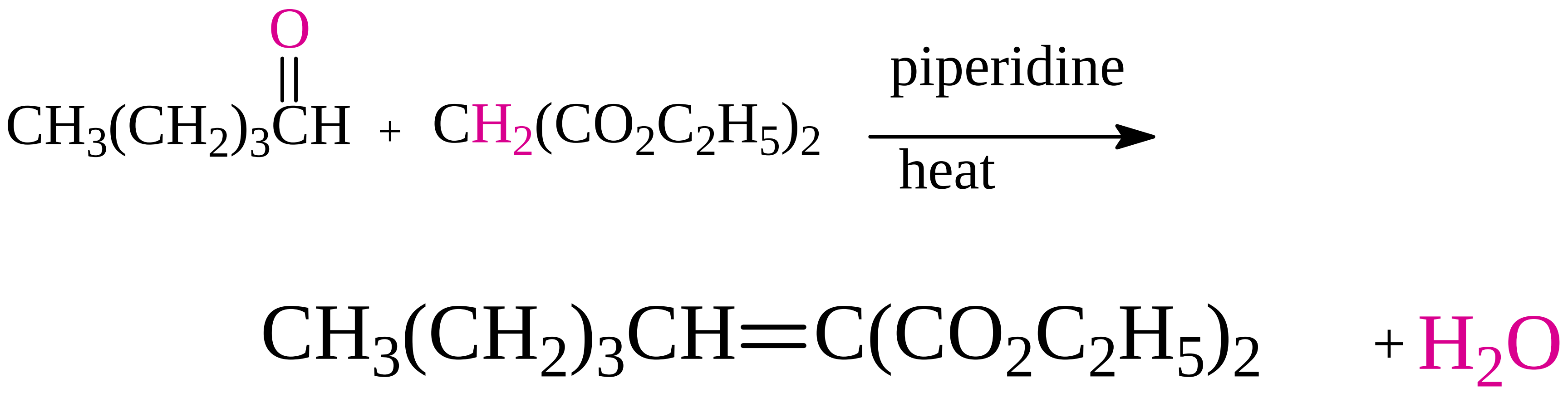


$CH_3CH_2\overset{\overset{OH}{|}}{C}H\underset{\underset{CH_3}{|}}{C}H\overset{\overset{O}{\|}}{C}H$

From prpanal

Knoevenagel Condensation

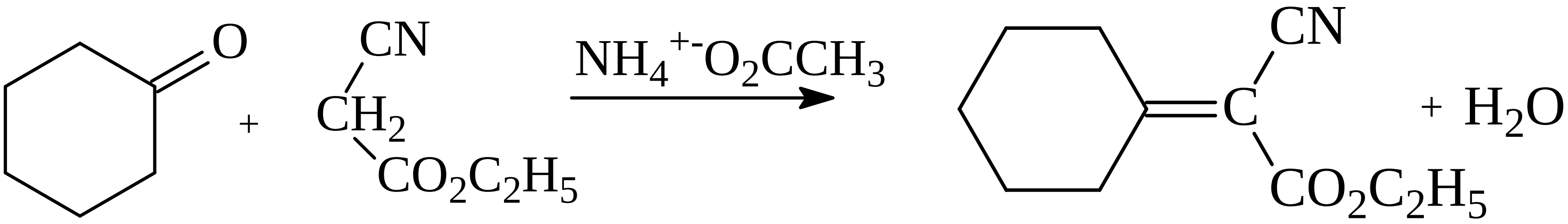
- Reaction of an aldehyde or a ketone with a compound hat has a hydrogen α to two activating groups (C=O or CN). Amine is a catalyst.

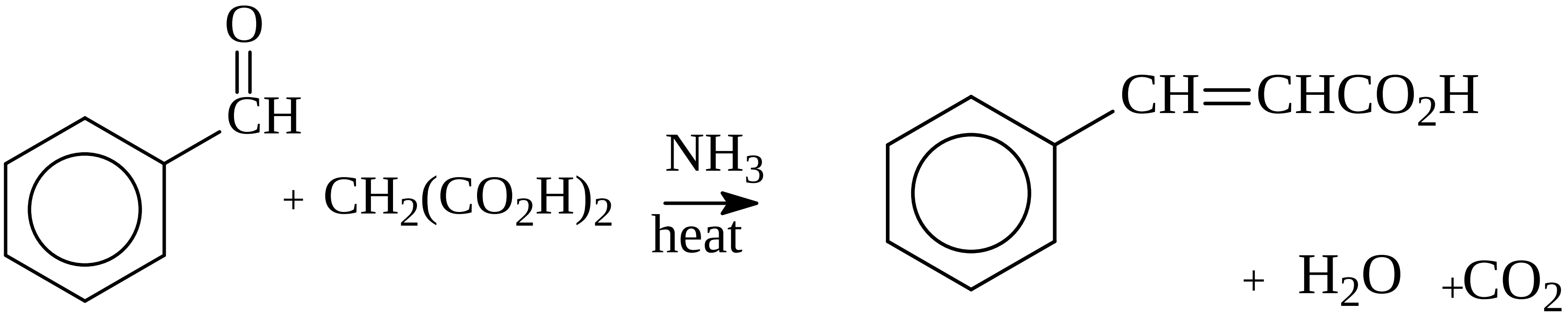


$$CH_3(CH_2)_3\overset{\overset{O}{\|}}{C}H + CH_2(CO_2C_2H_5)_2 \xrightarrow[\text{heat}]{\text{piperidine}}$$

$$CH_3(CH_2)_3CH{=}C(CO_2C_2H_5)_2 + H_2O$$

More examples

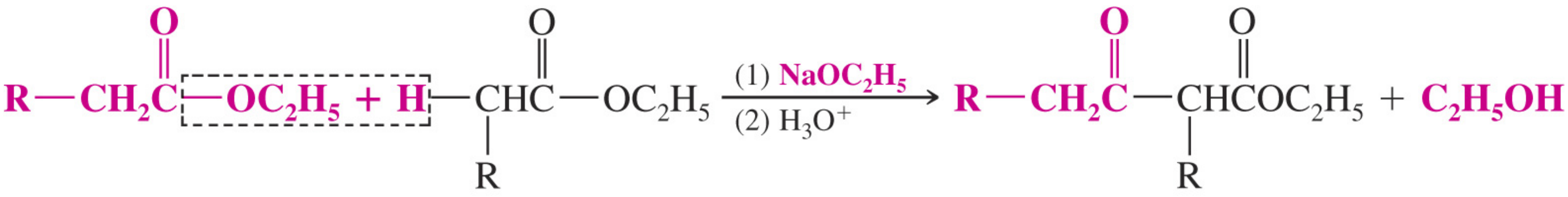




CLAISEN CONDENSATIONS

The Claisen Ester Condensation

General:



$$R{-}CH_2\overset{\overset{O}{\|}}{C}\boxed{{-}OC_2H_5 + H}{-}\underset{\underset{R}{|}}{CH}\overset{\overset{O}{\|}}{C}{-}OC_2H_5 \xrightarrow[(2)\ H_3O^+]{(1)\ NaOC_2H_5} R{-}CH_2\overset{\overset{O}{\|}}{C}{-}\underset{\underset{R}{|}}{CH}\overset{\overset{O}{\|}}{C}OC_2H_5 + C_2H_5OH$$

(R may also be H)

A β-keto ester

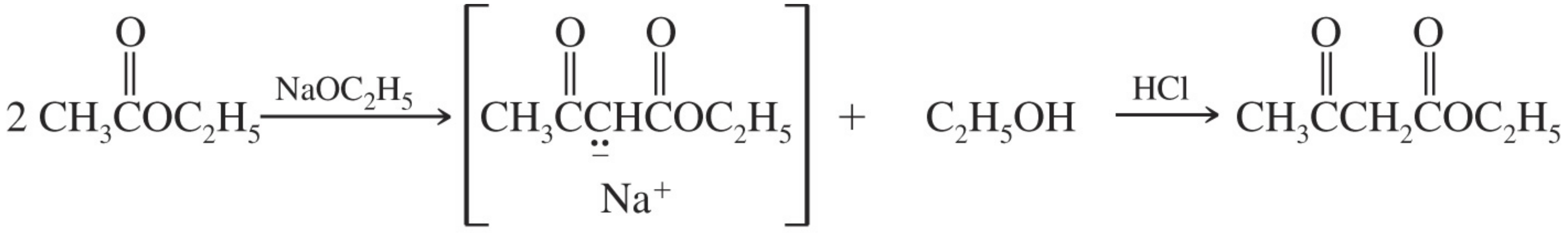
The overall reaction involves loss of an a hydrogen from one ester and loss of ethoxide from another

Notice that
the base, the solvent and the leaving group

$CH_3CH_2O^- Na^+$, CH_3CH_2OH, $CH_3CH_2O^-$

all match (this is required in most cases).

The Claisen Condensation: Synthesis of β-Keto Esters

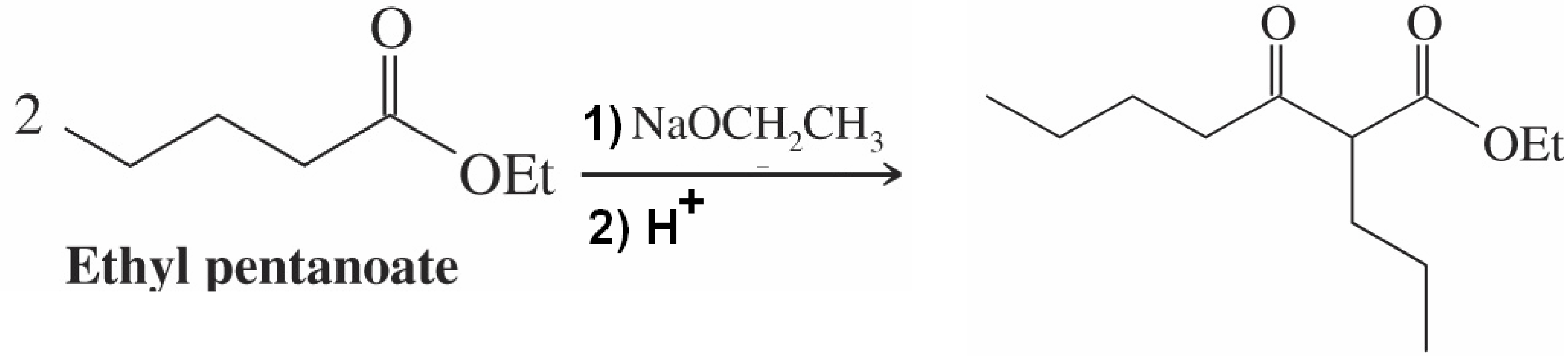


$$2\ \mathrm{CH_3\overset{\overset{O}{\|}}{C}OC_2H_5} \xrightarrow{\mathrm{NaOC_2H_5}} \left[\begin{array}{c}\mathrm{CH_3\overset{\overset{O}{\|}}{C}\underset{\overset{\cdot\cdot}{-}}{C}H\overset{\overset{O}{\|}}{C}OC_2H_5}\\ \mathrm{Na^+}\end{array}\right] + \mathrm{C_2H_5OH} \xrightarrow{\mathrm{HCl}} \mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OC_2H_5}$$

Sodioacetoacetic ester

(removed by distillation)

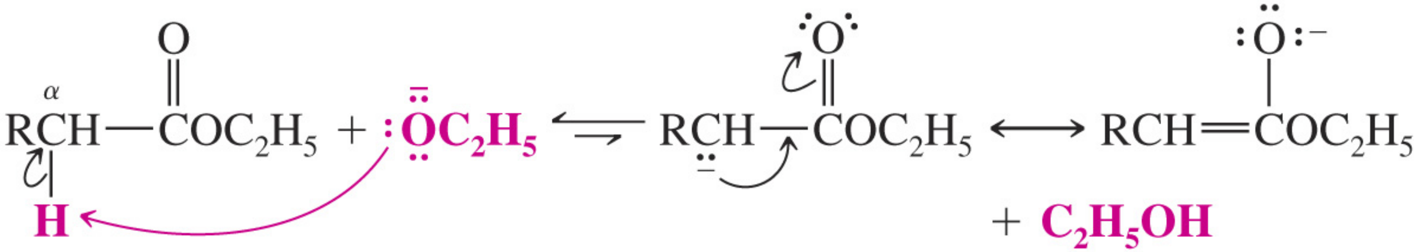
Ethyl acetoacetate (acetoacetic ester) (76%)



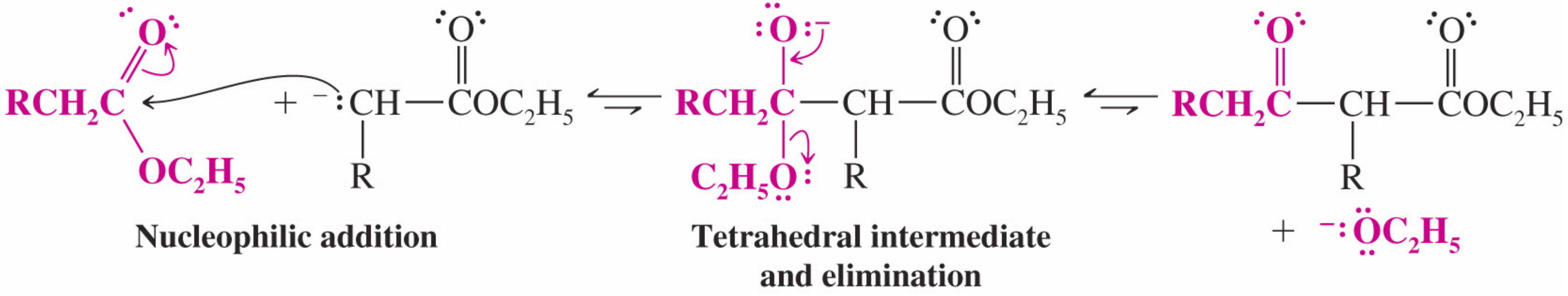
Ethyl pentanoate

Mechanism of Claisen Condensation

Step 1



Step 2



Step 3

$$RCH_2\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\overset{H}{|}}{C}}-\overset{\overset{O}{\|}}{C}OC_2H_5 + {:}\ddot{\underset{..}{O}}C_2H_5 \rightleftharpoons RCH_2\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{..}{\bar{C}}}-\overset{\overset{O}{\|}}{C}OC_2H_5 + C_2H_5OH$$

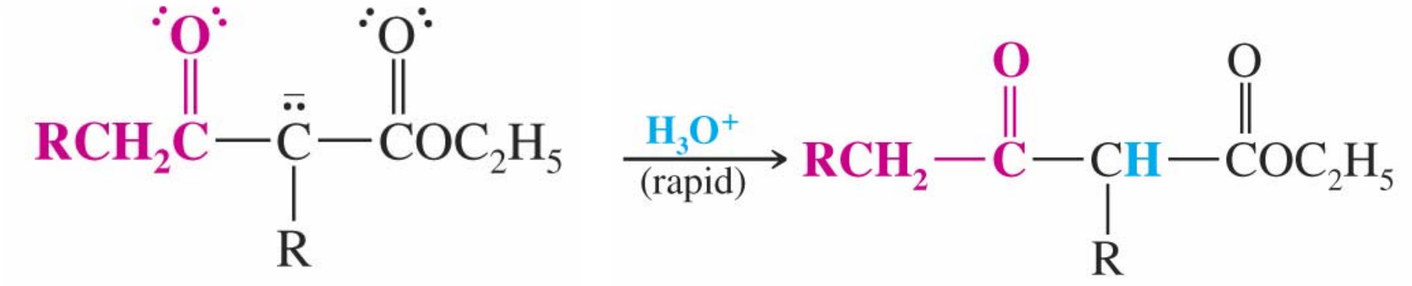
β-Keto ester
(pK_a ~ 9; stronger acid)

Ethoxide ion
(stronger base)

β-Keto ester anion
(weaker base)

Ethanol
(pK_a16; weaker acid)

Step 4

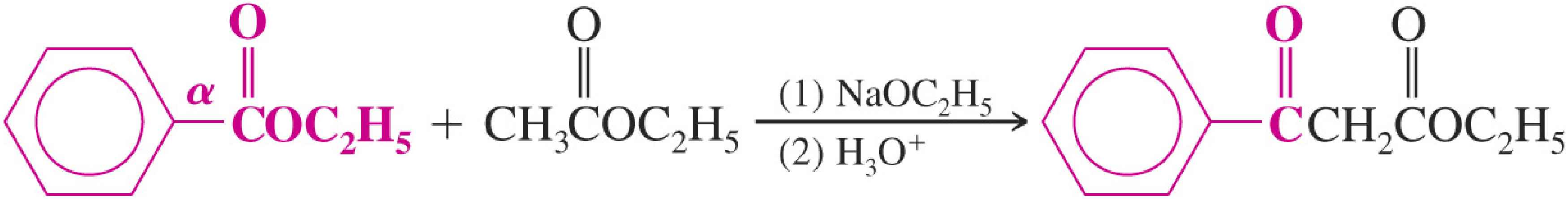


$$RCH_2\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{..}{\bar{C}}}-\overset{\overset{O}{\|}}{C}OC_2H_5 \xrightarrow[\text{(rapid)}]{H_3O^+} RCH_2-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{C}H-\overset{\overset{O}{\|}}{C}OC_2H_5$$

β-Keto ester

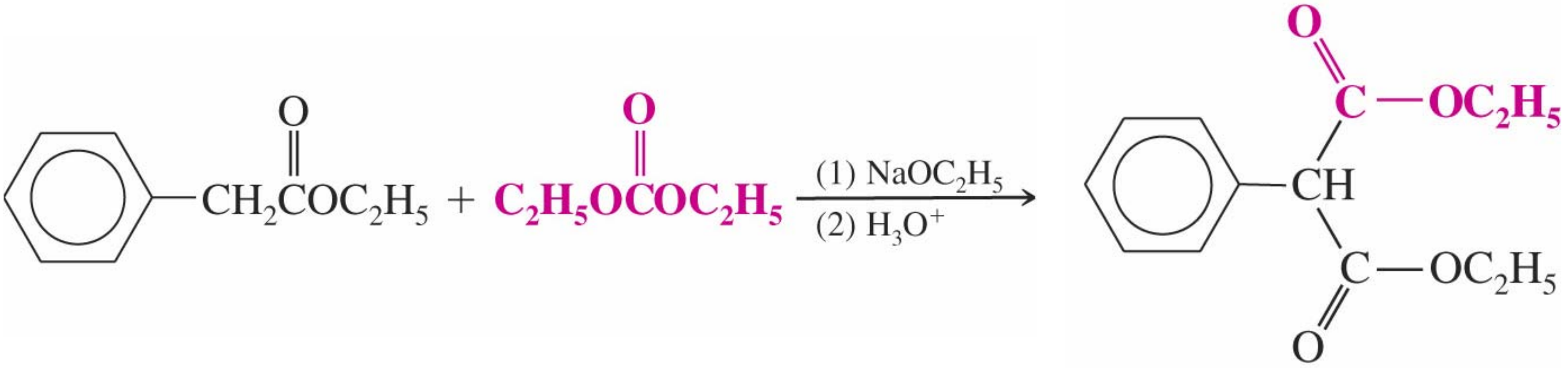
Crossed Claisen Condensations

- Crossed Claisen condensations can lead to one major product when one of the two esters has no α hydrogen

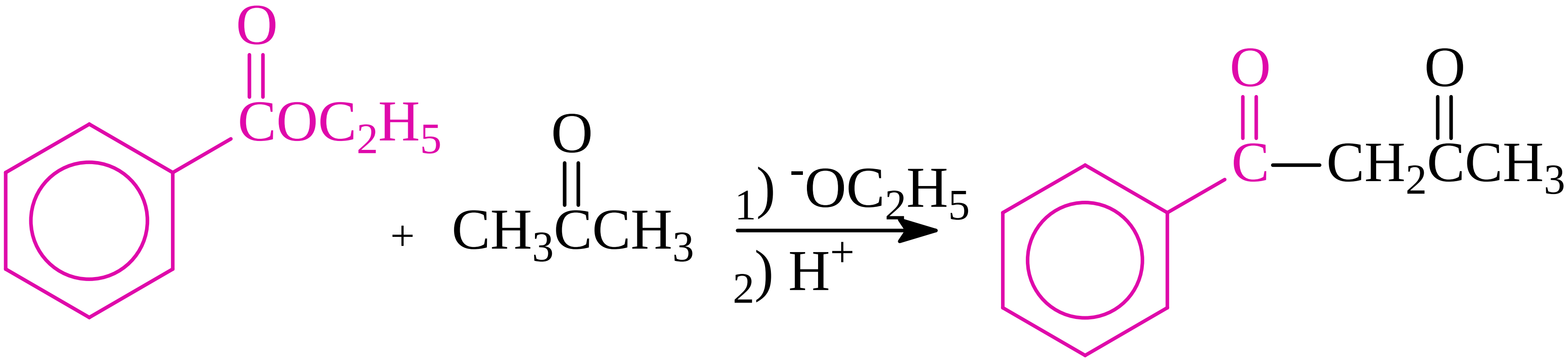


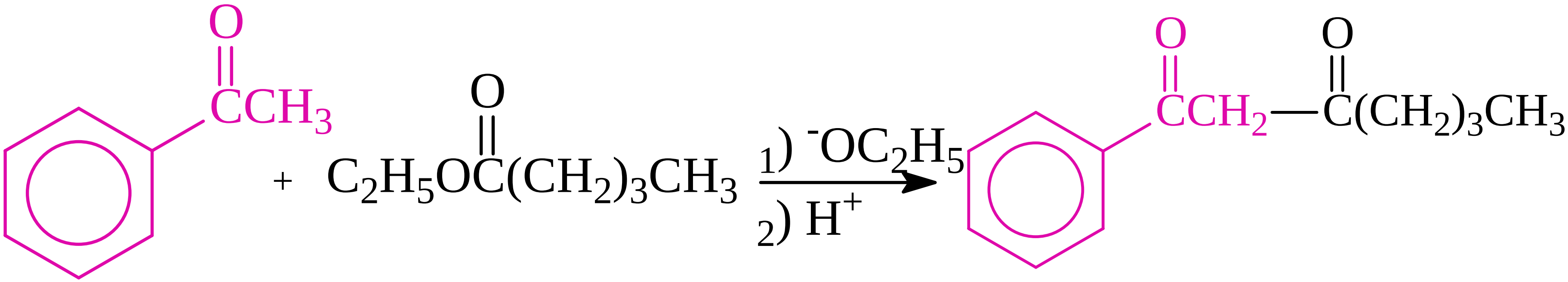
Ethyl benzoate
(no α hydrogen)

Ethyl benzoylacetate
(60%)



Crossed Claisen Condensation Between Ketones and Esters

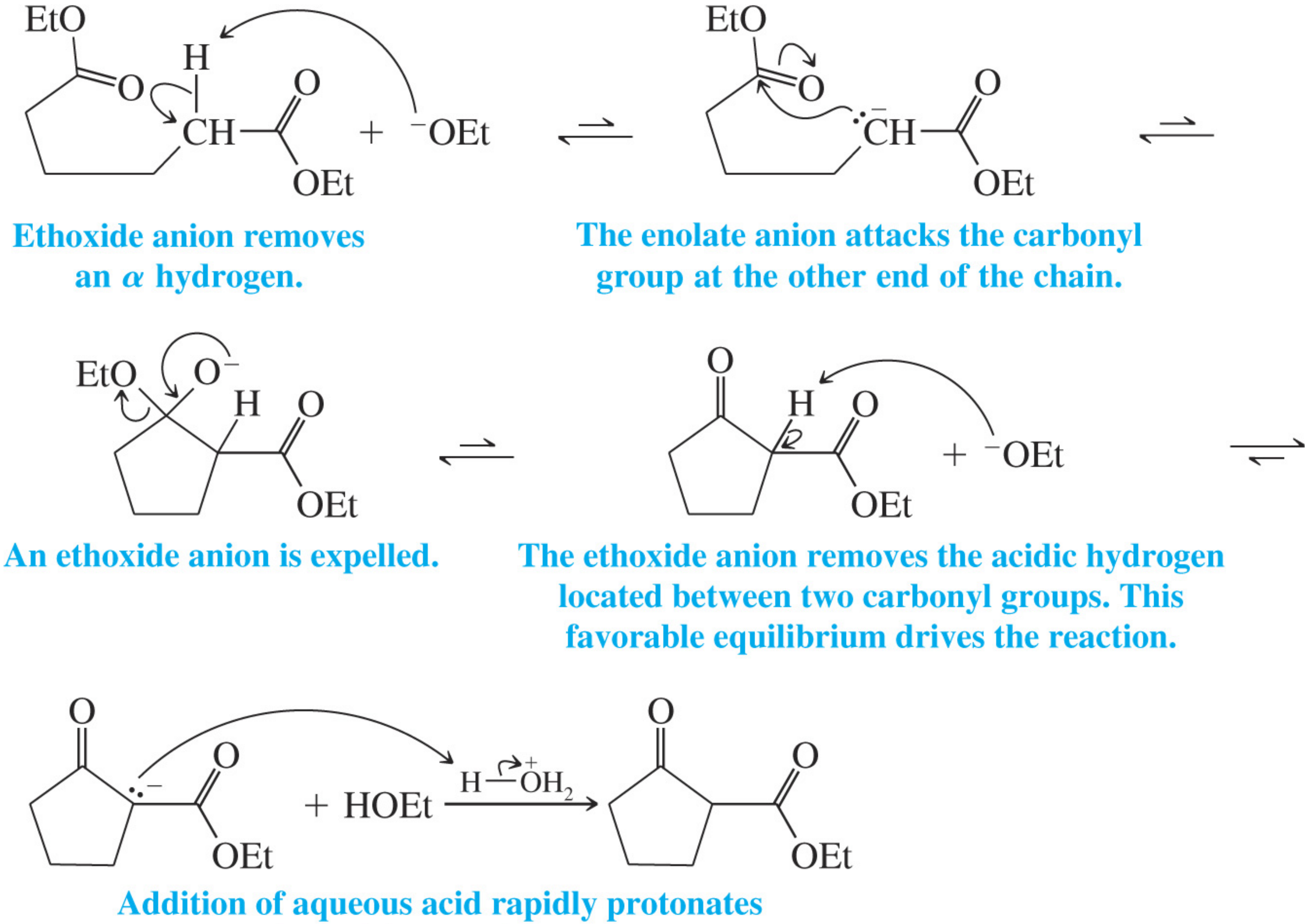




β-diketone

Dieckmann Condensation

A CYCLIC CLAISEN CONDENSATION



Ethoxide anion removes an α hydrogen.

The enolate anion attacks the carbonyl group at the other end of the chain.

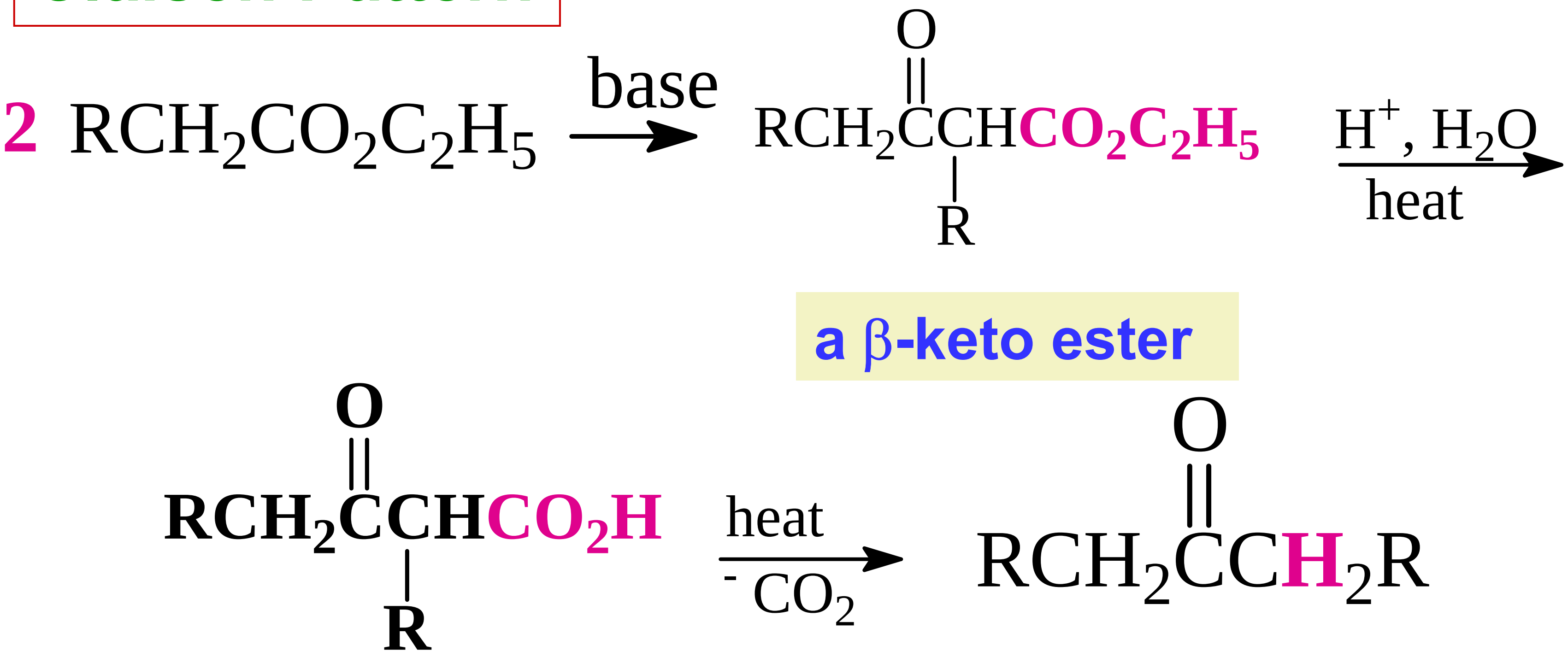
An ethoxide anion is expelled.

The ethoxide anion removes the acidic hydrogen located between two carbonyl groups. This favorable equilibrium drives the reaction.

Addition of aqueous acid rapidly protonates the anion, giving the final product.

Syntheses Using Ester Condensation

Claisen Pattern



$$2\ \mathrm{RCH_2CO_2C_2H_5} \xrightarrow{\text{base}} \mathrm{RCH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\underset{\mathrm{R}}{\mathrm{CH}}\mathrm{CO_2C_2H_5} \xrightarrow[\text{heat}]{\mathrm{H^+,\ H_2O}}$$

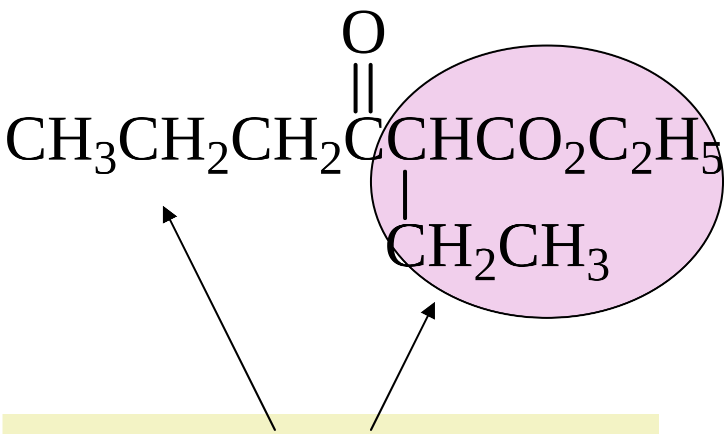
a β-keto ester

$$\mathrm{RCH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\underset{\mathrm{R}}{\mathrm{CH}}\mathrm{CO_2H} \xrightarrow[-\ \mathrm{CO_2}]{\text{heat}} \mathrm{RCH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH_2R}$$

a β-keto acid

a Ketone

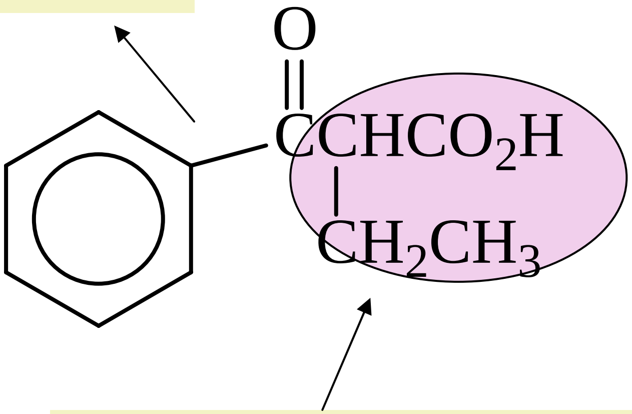
Syntheses problems



$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}\underset{\underset{CH_2CH_3}{|}}{CH}CO_2C_2H_5$

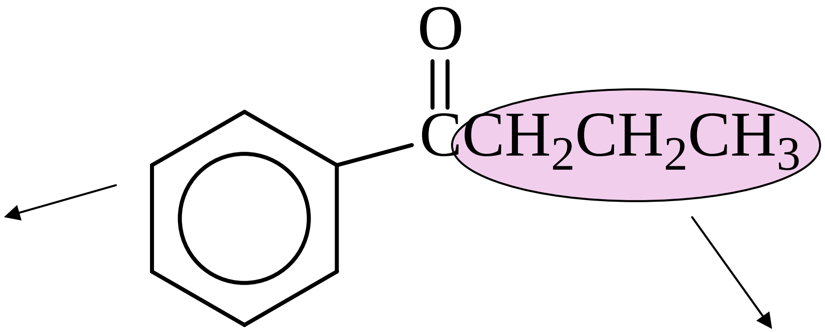
From ethyl butanoate

From ethyl benzoate



$C_6H_5\overset{\overset{O}{\|}}{C}\underset{\underset{CH_2CH_3}{|}}{CH}CO_2H$

From ethyl butanoate

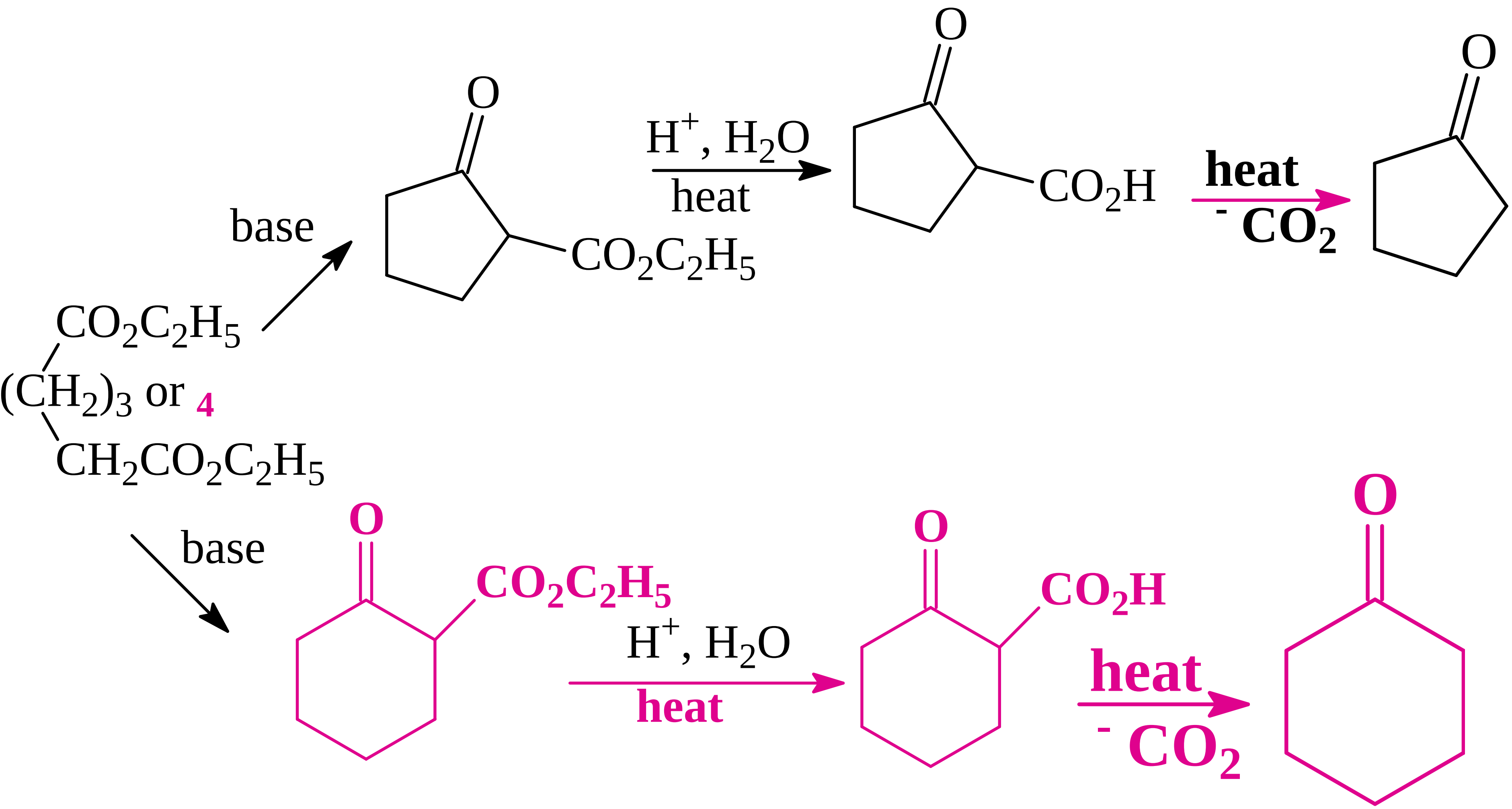


$C_6H_5\overset{\overset{O}{\|}}{C}CH_2CH_2CH_3$

From ethyl benzoate

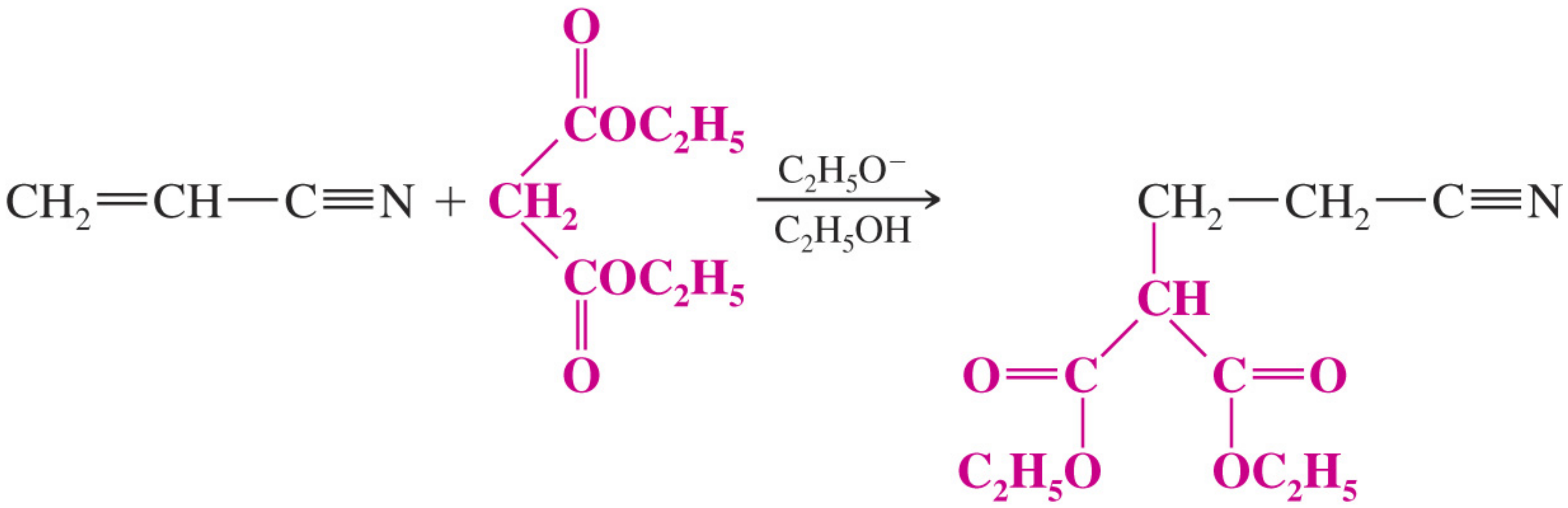
From ethyl butanoate

Dieckmann Condensation Pattern

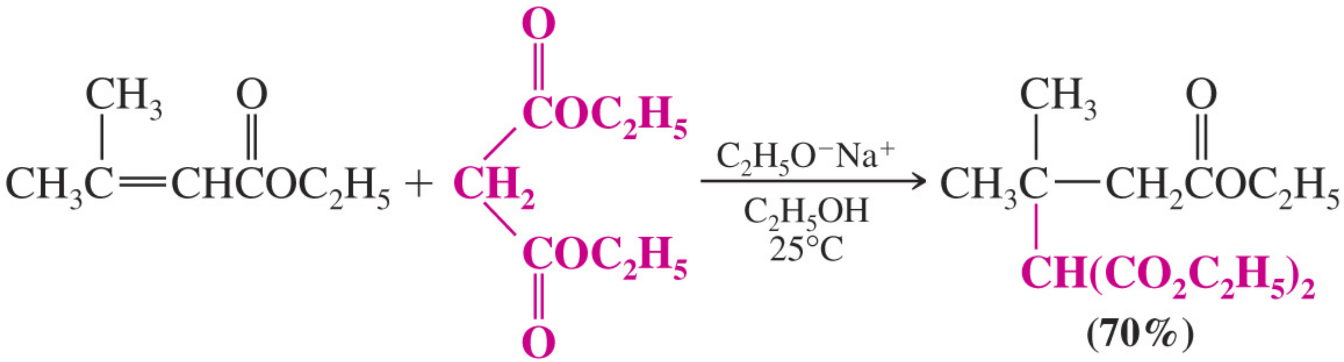


Michael Additions

- A Michael addition involves conjugate addition of the anion derived from an active hydrogen compound (*e.g*., an enolate) to an α,β-unsaturated carbonyl compound



Overall Reaction:

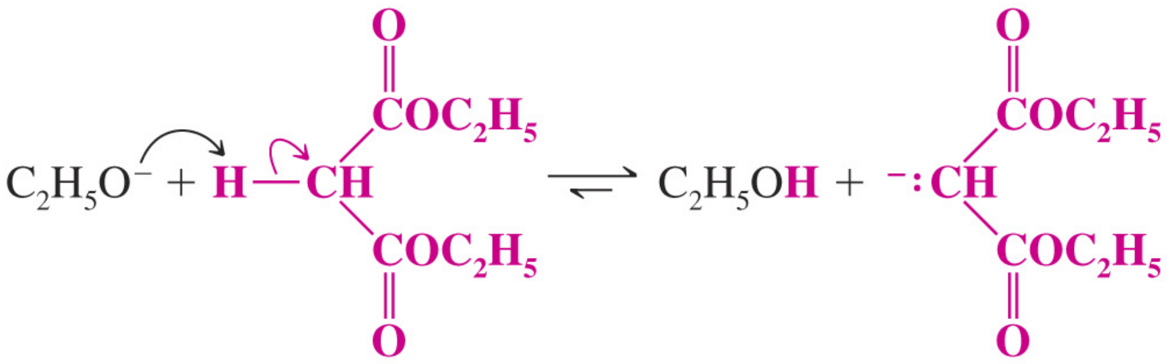


$$\mathrm{CH_3C(CH_3){=}CHCOC_2H_5(=O) + CH_2(COC_2H_5(=O))_2 \xrightarrow[\substack{C_2H_5OH\\25^\circ C}]{C_2H_5O^-Na^+} CH_3C(CH_3)(CH(CO_2C_2H_5)_2){-}CH_2COC_2H_5(=O)}$$

(70%)

Mechanism:

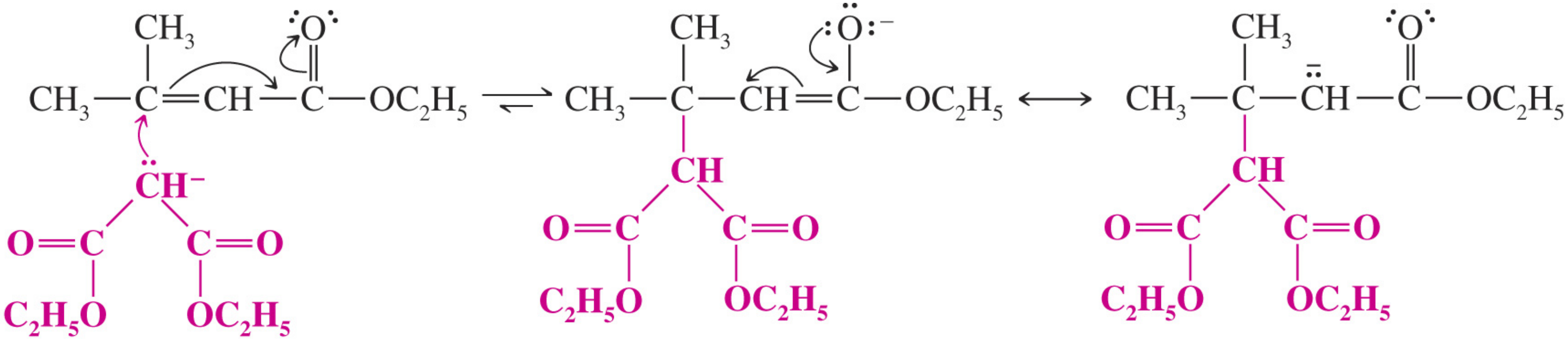
Step 1



$$\mathrm{C_2H_5O^- + H{-}CH(COC_2H_5(=O))_2 \rightleftharpoons C_2H_5OH + {}^-{:}CH(COC_2H_5(=O))_2}$$

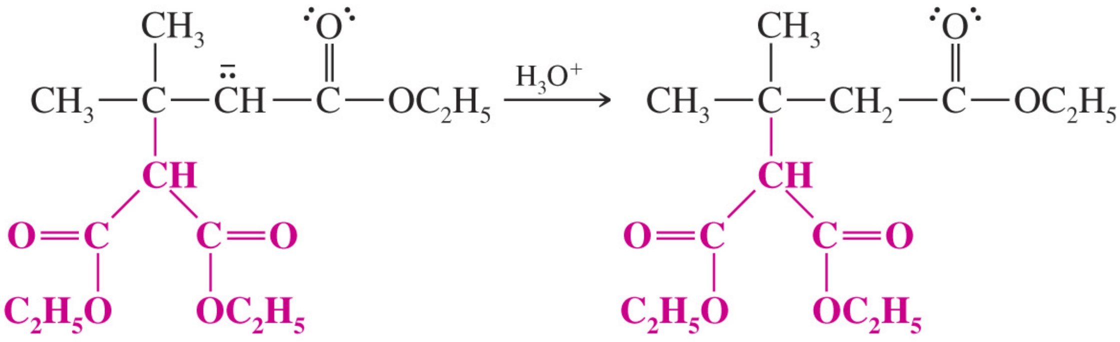
An alkoxide anion removes a proton to form the anion of the active methylene compound.

Step 2



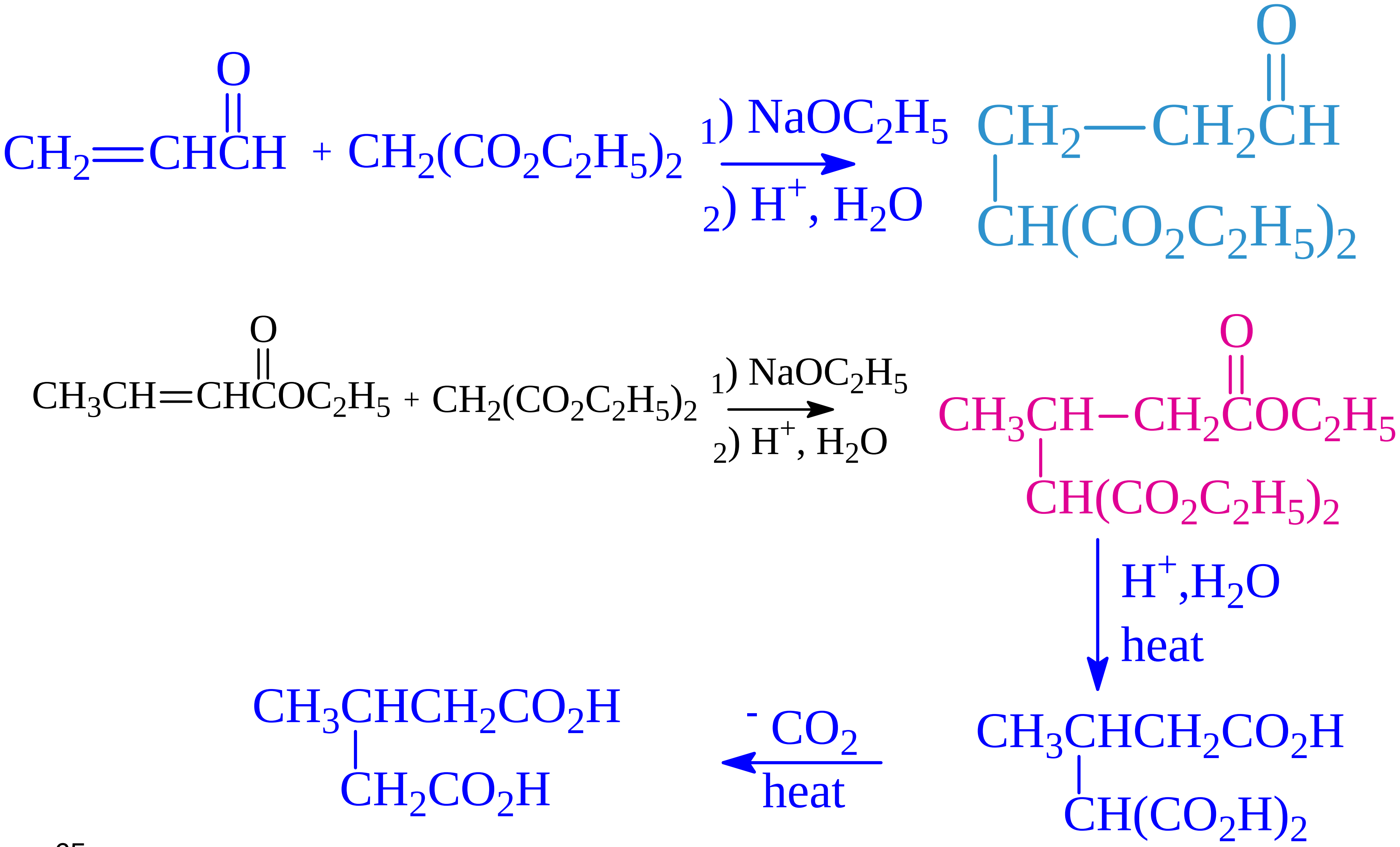
Conjugate addition of the anion to the α,β-unsaturated ester leads to a new enolate anion.

Step 3



The enolate anion is protonated by an acid during the workup of the reaction.

Examples



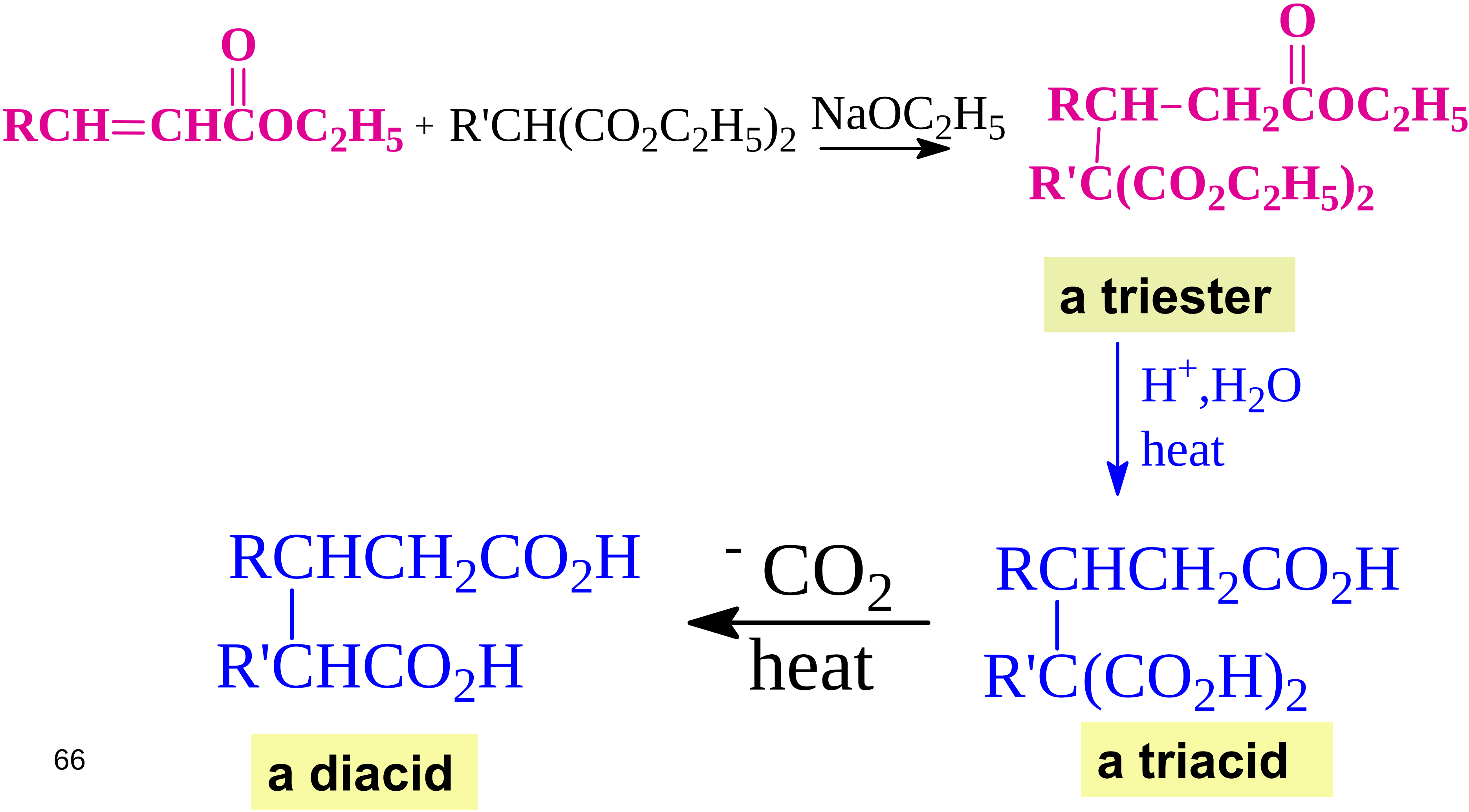
$$CH_2{=}CH\overset{O}{\overset{\|}{C}}H + CH_2(CO_2C_2H_5)_2 \xrightarrow[2)\ H^+,\ H_2O]{1)\ NaOC_2H_5} \begin{array}{l} CH_2{-}CH_2\overset{O}{\overset{\|}{C}}H \\ | \\ CH(CO_2C_2H_5)_2 \end{array}$$

$$CH_3CH{=}CH\overset{O}{\overset{\|}{C}}OC_2H_5 + CH_2(CO_2C_2H_5)_2 \xrightarrow[2)\ H^+,\ H_2O]{1)\ NaOC_2H_5} \begin{array}{l} CH_3CH{-}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 \\ \quad | \\ \quad CH(CO_2C_2H_5)_2 \end{array}$$

$$\downarrow H^+, H_2O,\ heat$$

$$\begin{array}{l} CH_3CHCH_2CO_2H \\ \quad\ \ | \\ \quad\ \ CH_2CO_2H \end{array} \xleftarrow[heat]{-\ CO_2} \begin{array}{l} CH_3CHCH_2CO_2H \\ \quad\ \ | \\ \quad\ \ CH(CO_2H)_2 \end{array}$$

Michael addition products of malonic ester and α,β,-unsaturated ester



$$RCH{=}CH\overset{\overset{O}{\|}}{C}OC_2H_5 + R'CH(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} \underset{R'C(CO_2C_2H_5)_2}{\underset{|}{RCH}}-CH_2\overset{\overset{O}{\|}}{C}OC_2H_5$$

a triester

$$\xrightarrow{H^+, H_2O \text{ heat}} \underset{R'C(CO_2H)_2}{\underset{|}{RCH}}CH_2CO_2H$$

a triacid

$$\underset{R'CHCO_2H}{\underset{|}{RCH}}CH_2CO_2H \xleftarrow[\text{heat}]{-CO_2}$$

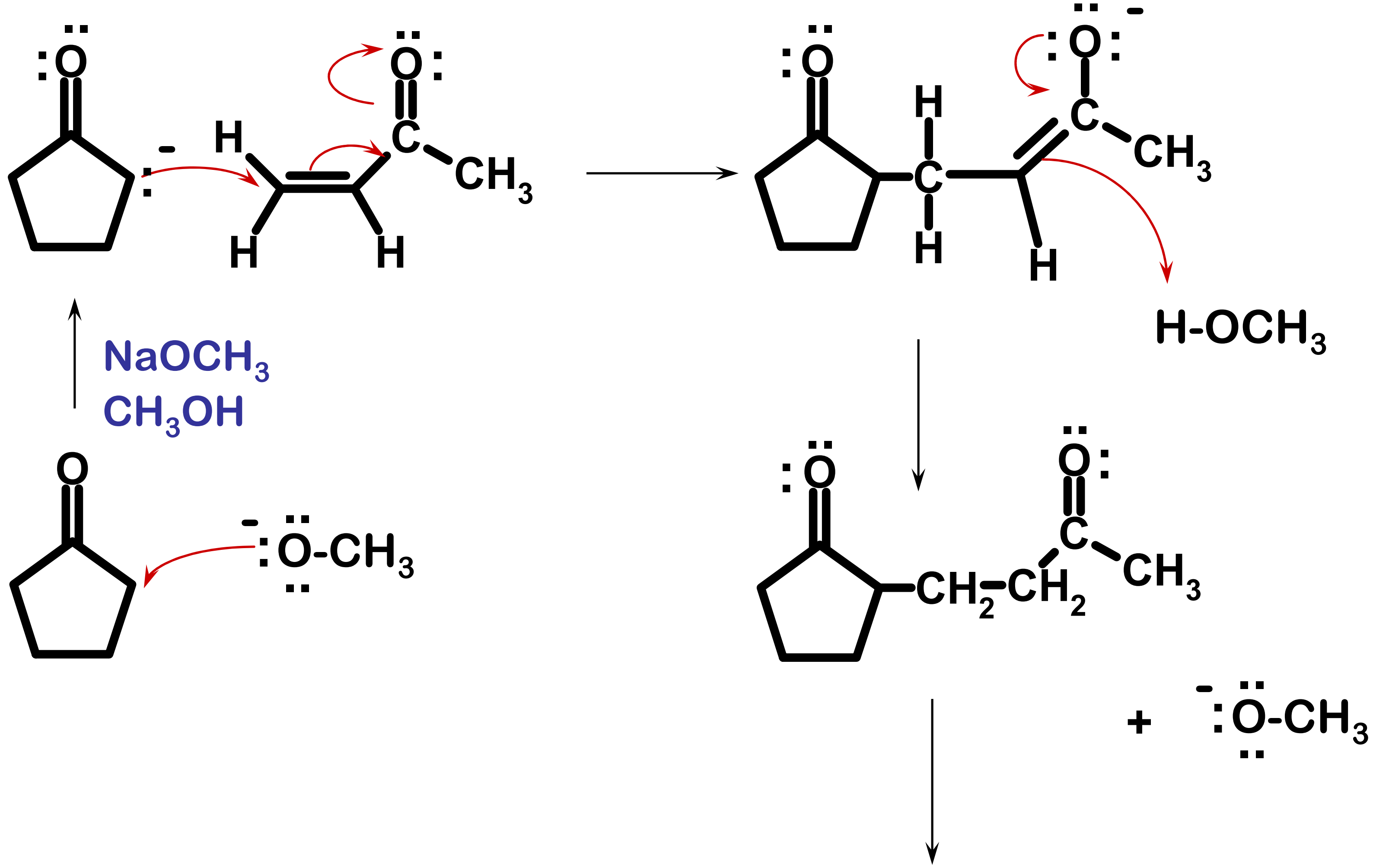
a diacid

ROBINSON ANNULATION

FORMING RINGS BY COMBINING CONJUGATE ADDITION WITH AN ALDOL CONDENSATION

METHYL VINYL KETONE (MVK)

Michael Addition of Cyclopentanone to MVK



enolate
weak base

MVK
methyl vinyl ketone

$NaOCH_3$
CH_3OH

H-OCH_3

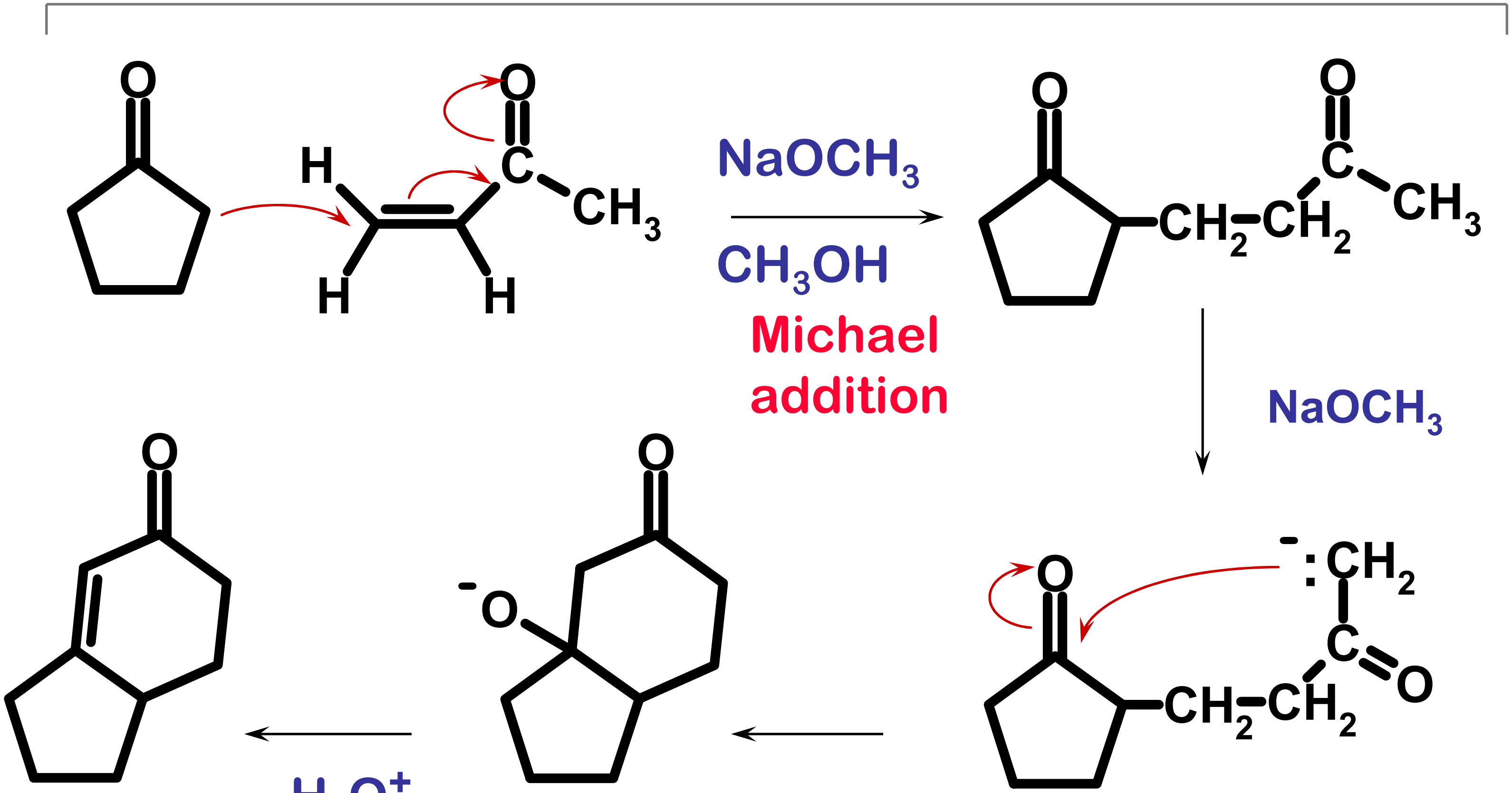
$^-:\ddot{O}-CH_3$

can continue

ROBINSON ANNULATION

USES MVK TO BUILD A RING

FROM PREVIOUS SLIDE



$NaOCH_3$

CH_3OH

Michael addition

$NaOCH_3$

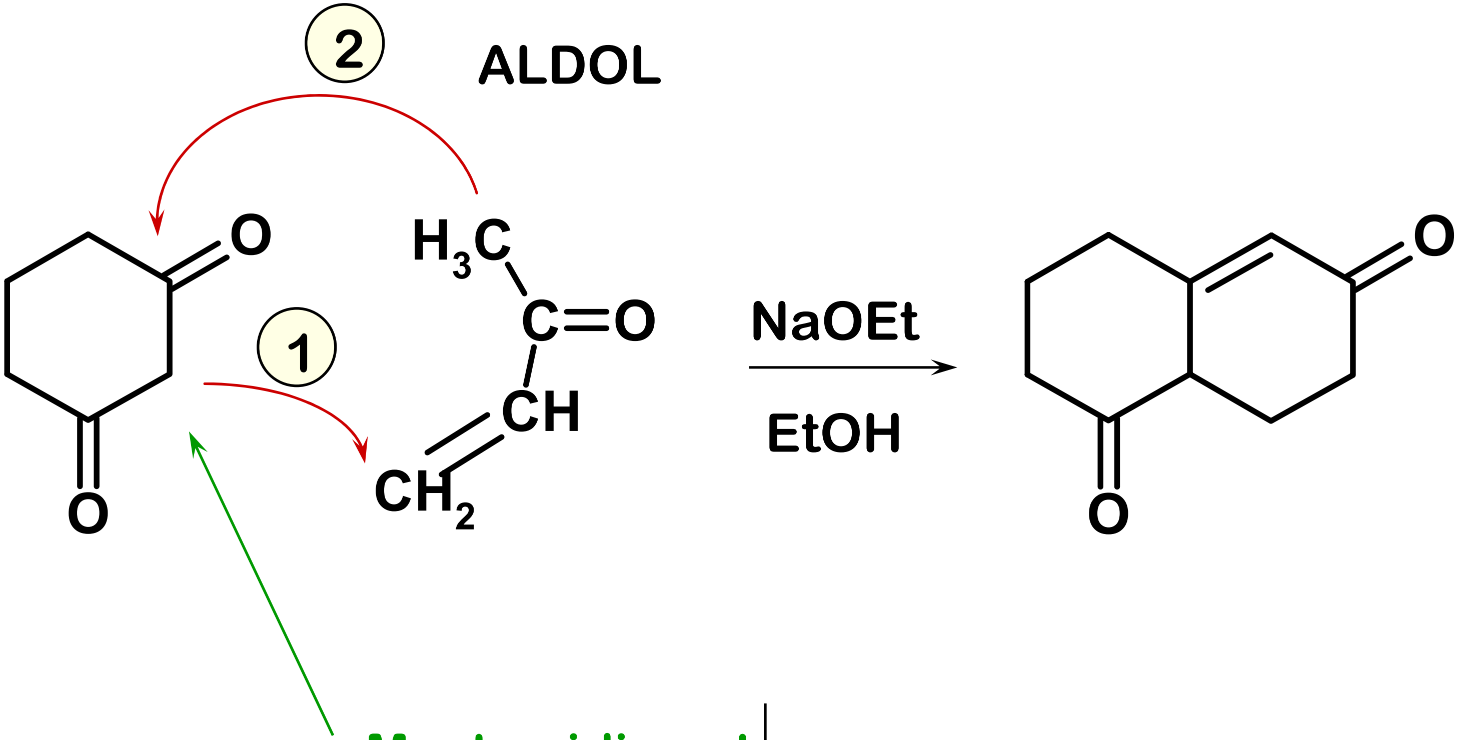
Annelation (ring formation)

H_3O^+ (workup)

internal aldol condensation

ANOTHER EXAMPLE

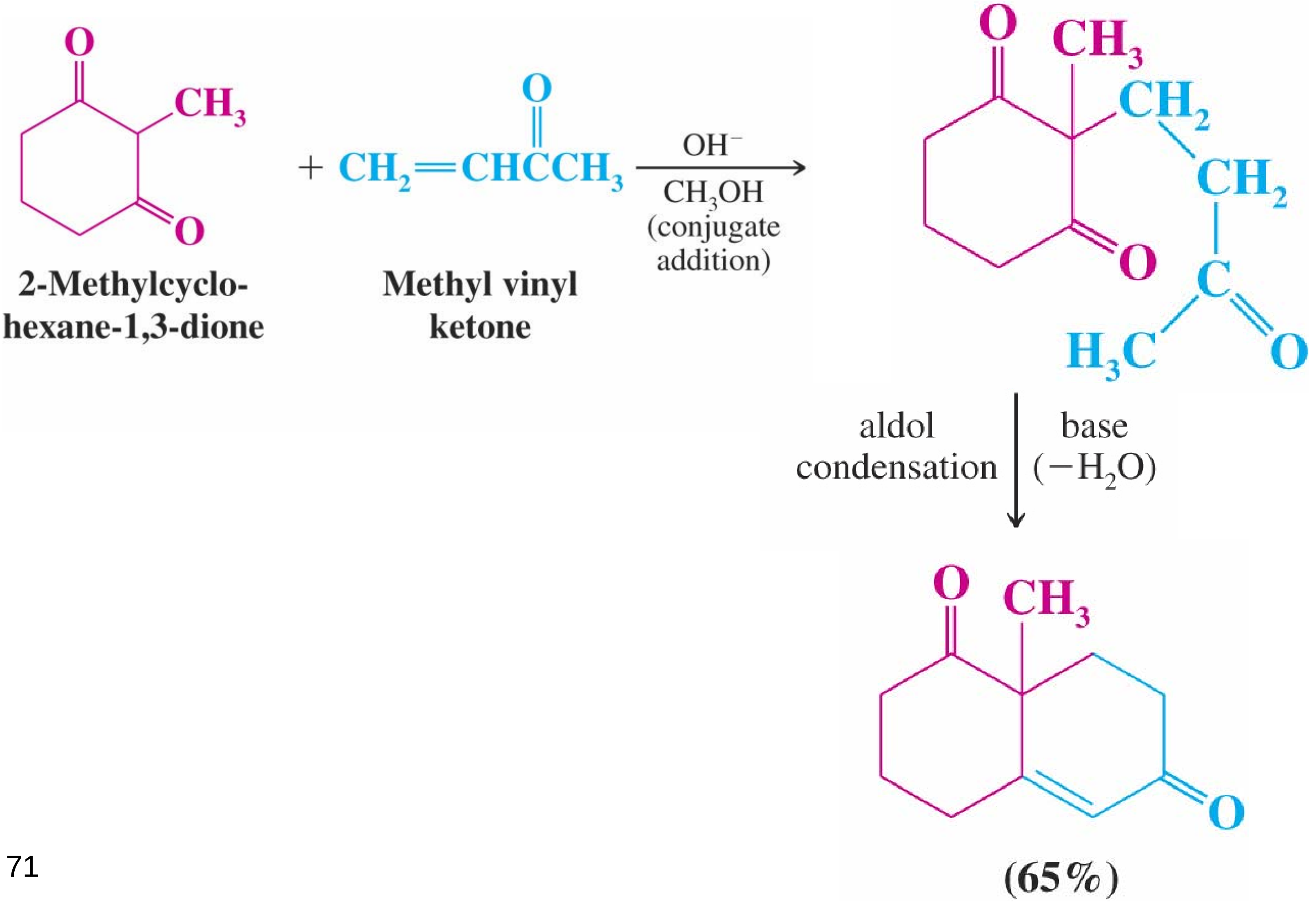
MICHAEL ADDITION + ALDOL CONDENSATION



Most acidic set of hydrogens reacts first.

MICHAEL

Another Example of Robinson Annulation



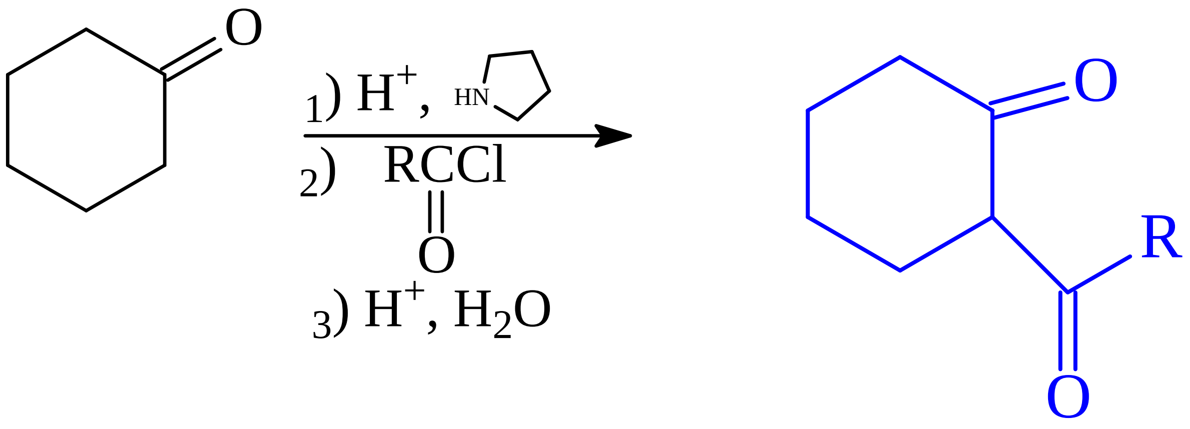
2-Methylcyclohexane-1,3-dione

Methyl vinyl ketone

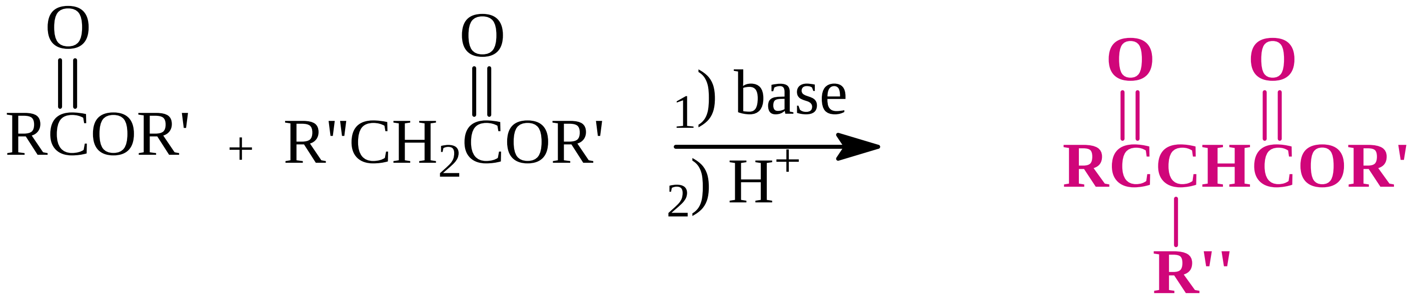
Summary of Synthesis of Dicarbonyl Compouds

1. 1,3- dicarbonyl compounds (β)

a. From enamine + acid chloride



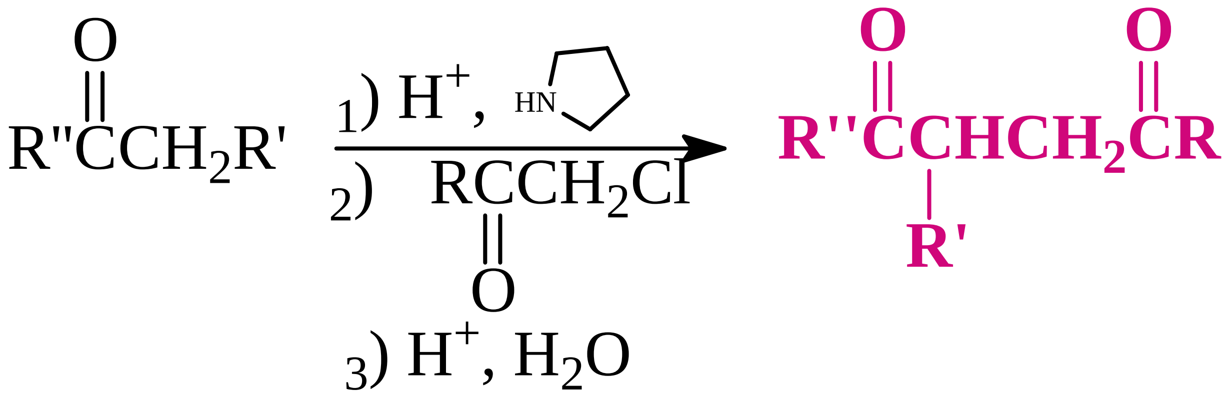
b. From Claisen Condensation.



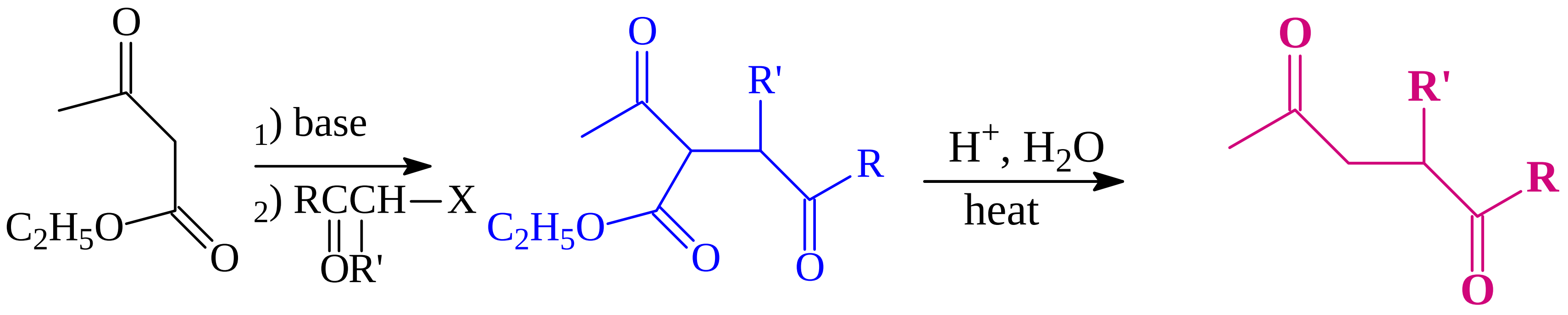
$$R\overset{O}{\overset{\|}{C}}OR' + R''CH_2\overset{O}{\overset{\|}{C}}OR' \xrightarrow[2)\ H^+]{1)\ \text{base}} R\overset{O}{\overset{\|}{C}}\underset{R''}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}OR'$$

2. 1,4- Dicarbonyl compounds.

a. From enamine + α-haloketone

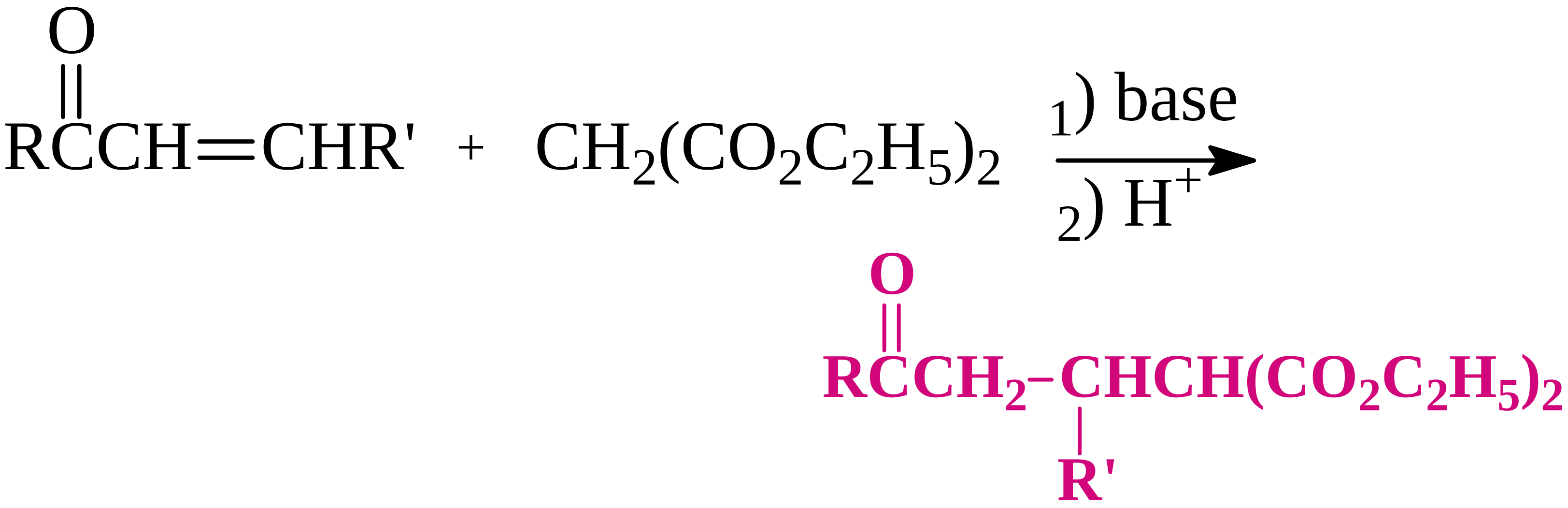


b. From acetoacetic ester + α-haloketone



3. 1,5-Dicarbonyl compounds

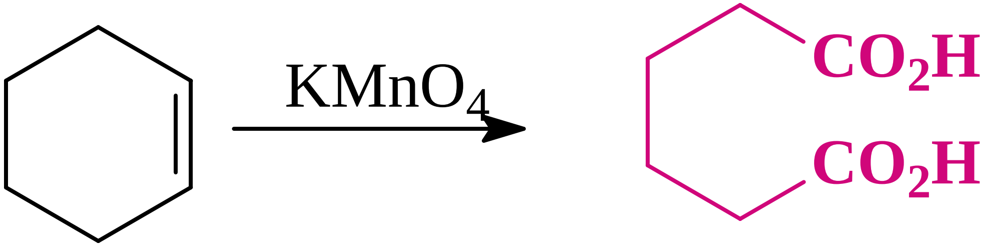
from Michael Addition



$$\mathrm{R\overset{O}{\overset{\|}{C}}CH{=}CHR'} + \mathrm{CH_2(CO_2C_2H_5)_2} \xrightarrow[2)\ \mathrm{H^+}]{1)\ \mathrm{base}} \mathrm{R\overset{O}{\overset{\|}{C}}CH_2{-}\underset{R'}{\underset{|}{C}}HCH(CO_2C_2H_5)_2}$$

4. 1,6-Dicarbonyl componds

By Oxidation of cycolhexene



$$\text{cyclohexene} \xrightarrow{\mathrm{KMnO_4}}$$