

Organic Chemistry II / CHEM 252

Chapter 19 – Synthesis and Reactions of β -Dicarbonyl Compounds

Bela Torok

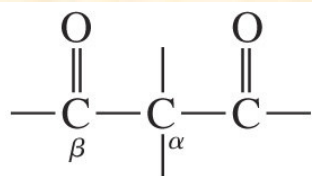
Department of Chemistry

University of Massachusetts Boston

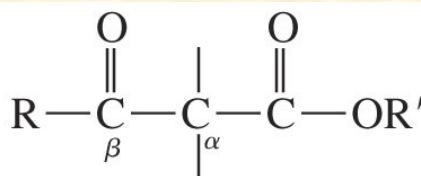
Boston, MA

Introduction

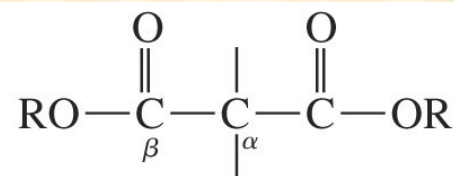
β -Dicarbonyl compounds have two carbonyl groups separated by a carbon



The β -dicarbonyl system

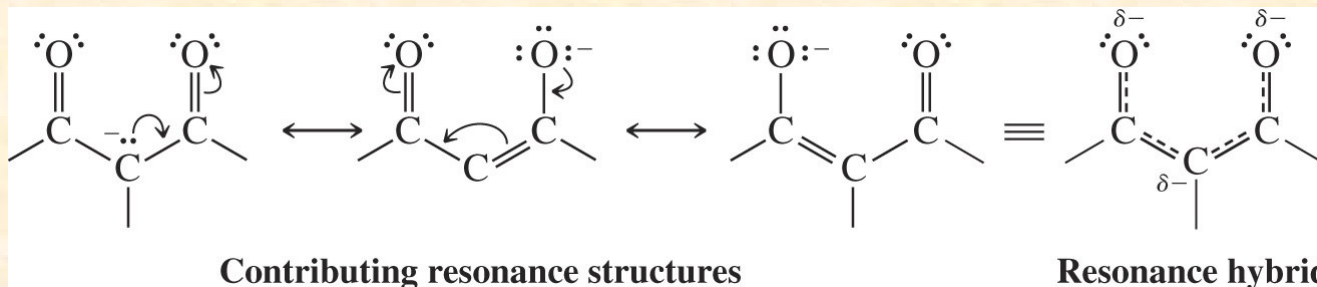
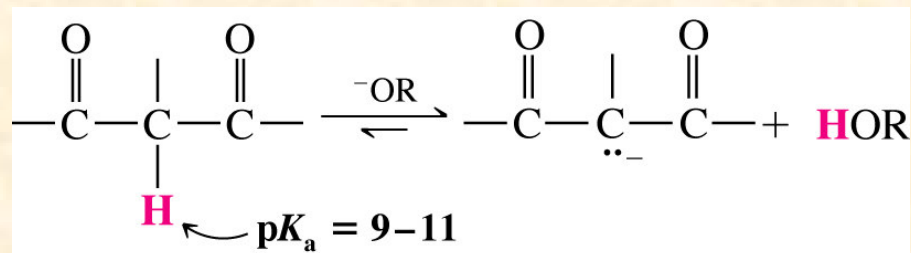


A β -keto ester (Section 19.2)



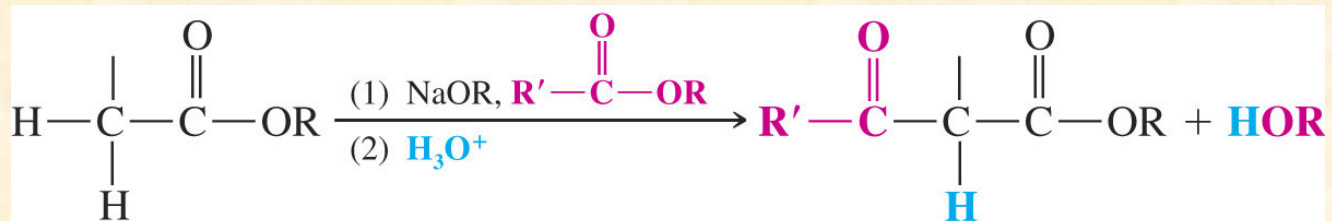
A malonic ester (Section 19.4)

- Protons on the α -carbon of β -dicarbonyl compounds are acidic ($\text{p}K_a = 9-10$)
 - The acidity can be explained by resonance stabilization of the corresponding enolate by two carbonyl groups

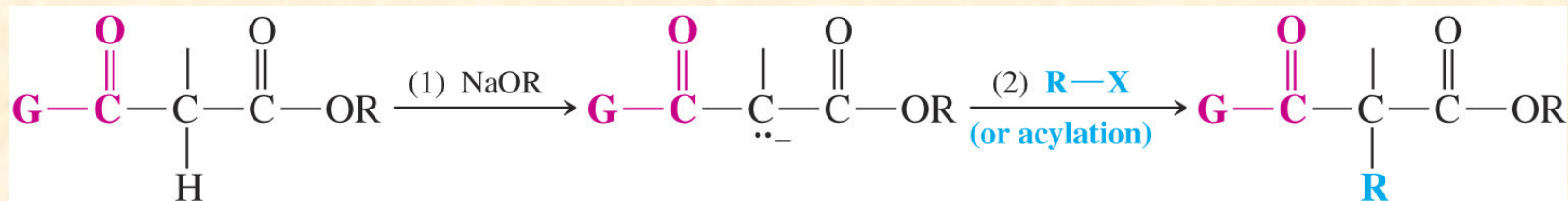


Synthesis

Claisen condensation



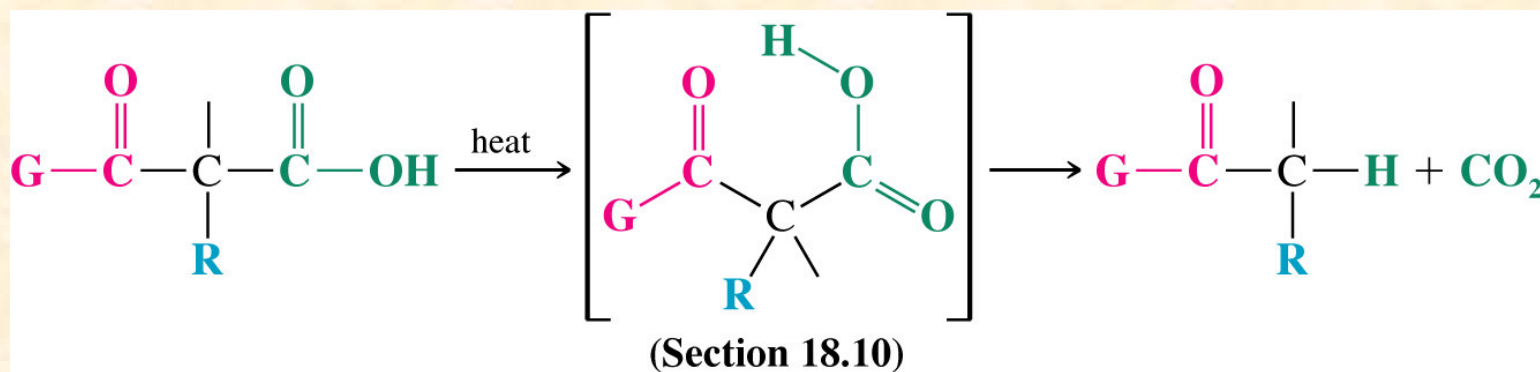
- The acetoacetic ester and malonic acid syntheses use β -dicarbonyl compounds for carbon-carbon bond forming reactions



Acetoacetic ester synthesis, $\text{G} = \text{CH}_3$

Malonic ester synthesis, $\text{G} = \text{RO}$

- The acetoacetic ester and malonic ester syntheses usually conclude with decarboxylation of a β -keto acid

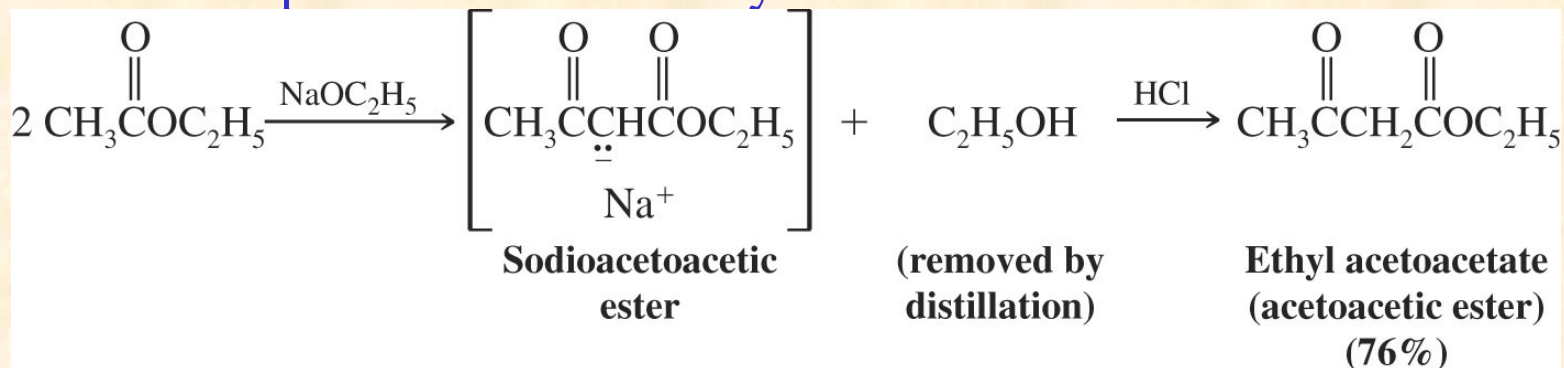


Synthesis

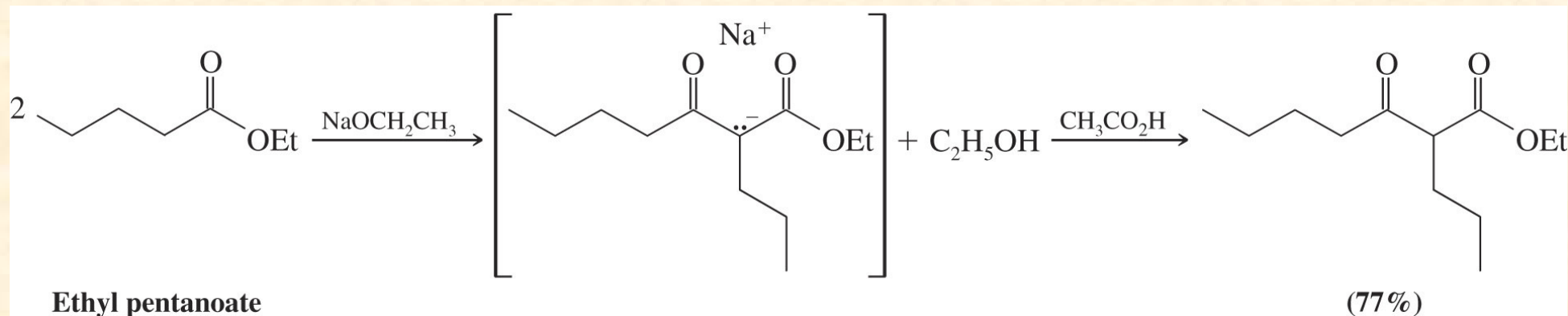
- The Claisen Condensation: Synthesis of β -Keto Esters

- Ethyl acetate undergoes a Claisen condensation when treated with sodium ethoxide

– The product is commonly called an acetoacetic ester

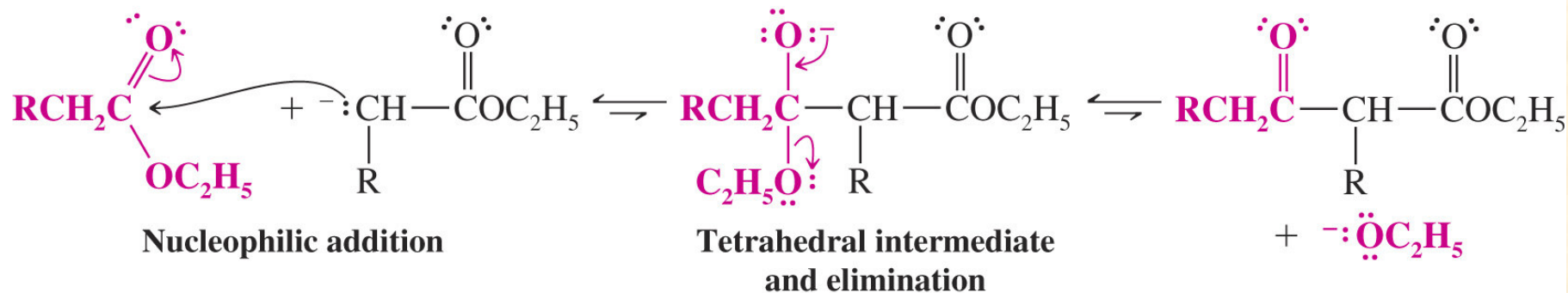


- Ethyl pentanoate undergoes an analogous reaction

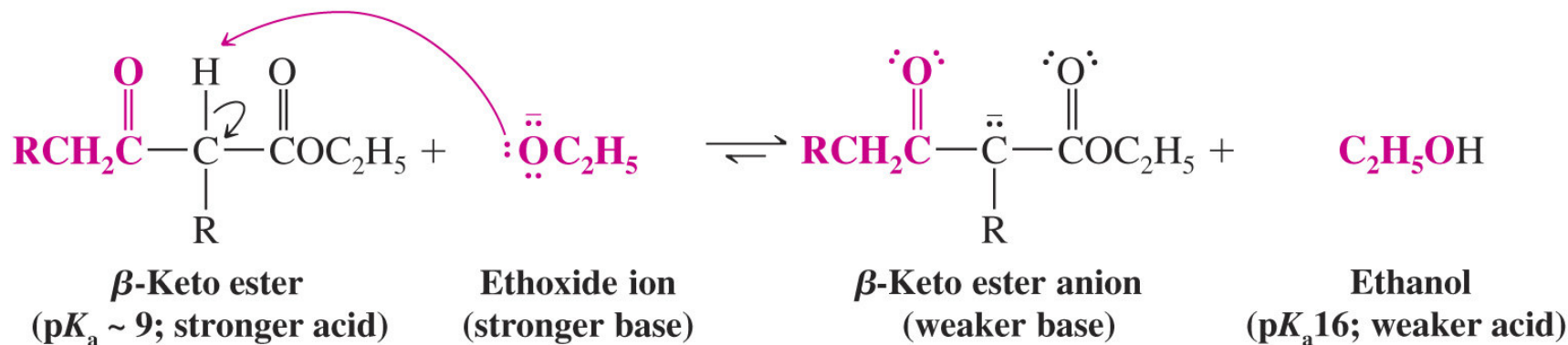


Synthesis

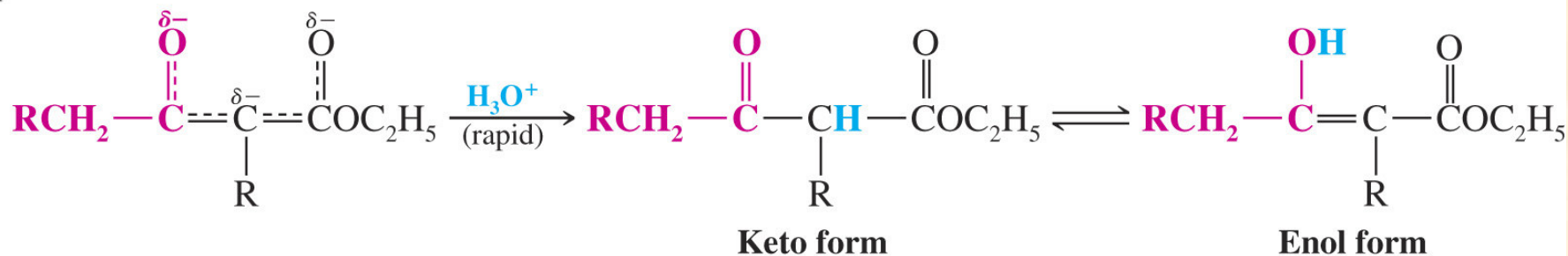
Step 2



Step 3



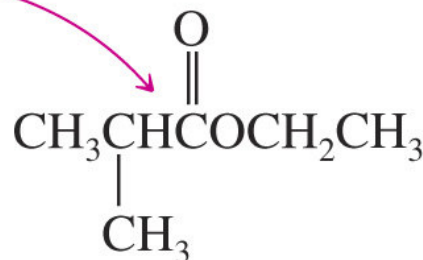
Step 4



Synthesis

- The alkoxide base must have the same alkyl group as the alkoxy group of the ester
 - The use of a different alkoxide would result in formation of some transesterification products
- Esters with only one α hydrogen do not undergo Claisen condensation
 - A second hydrogen on the α carbon is necessary so that it can be deprotonated in Step 3
 - This deprotonation drives the reaction to completion

Only one α hydrogen

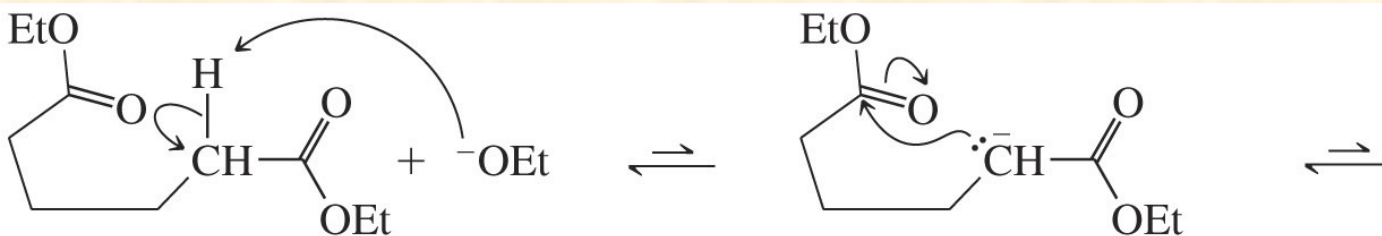


Ethyl 2-methylpropanoate

This ester does not undergo a Claisen condensation.

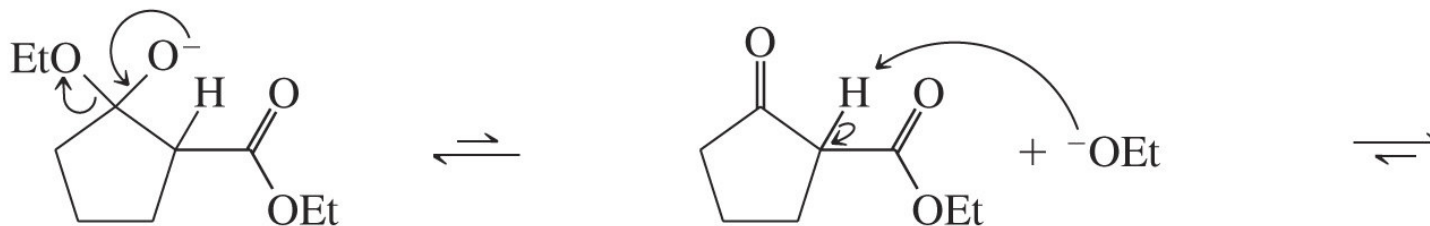
Synthesis

- The Dieckmann condensation is an intramolecular Claisen condensation
 - Only 5- and 6-membered rings may be prepared in this way



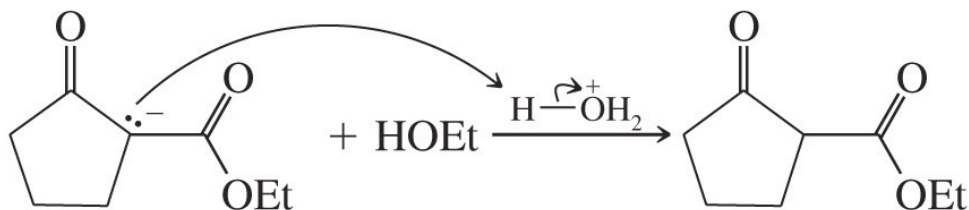
Ethoxide anion removes an α hydrogen.

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.

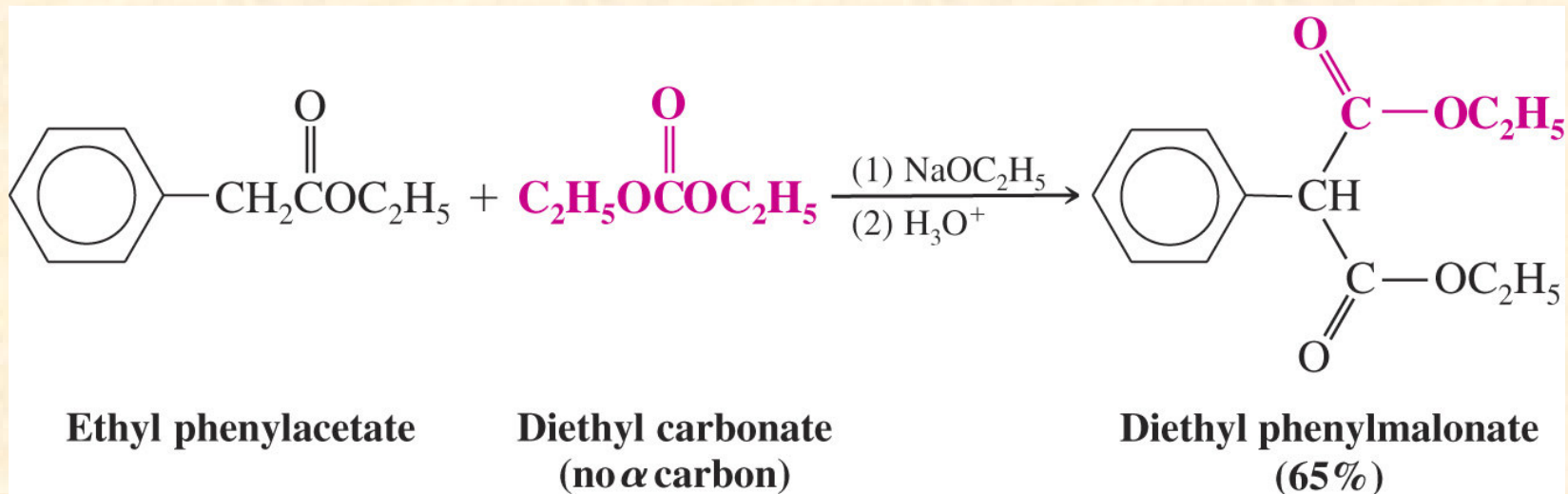
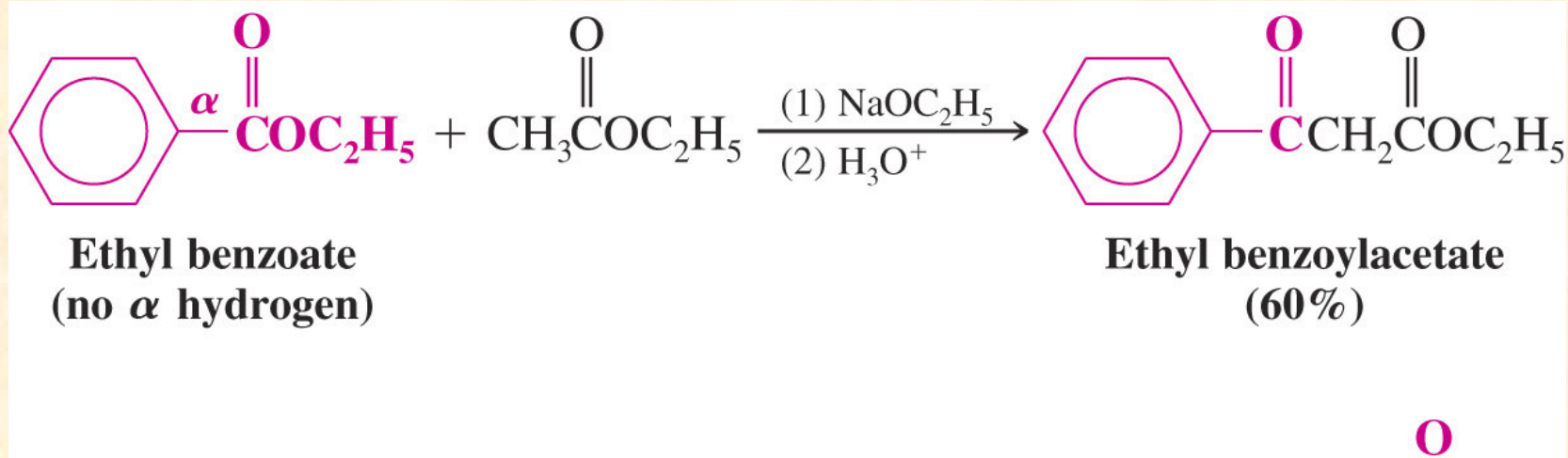


Addition of aqueous acid rapidly protonates the anion, giving the final product.

Synthesis

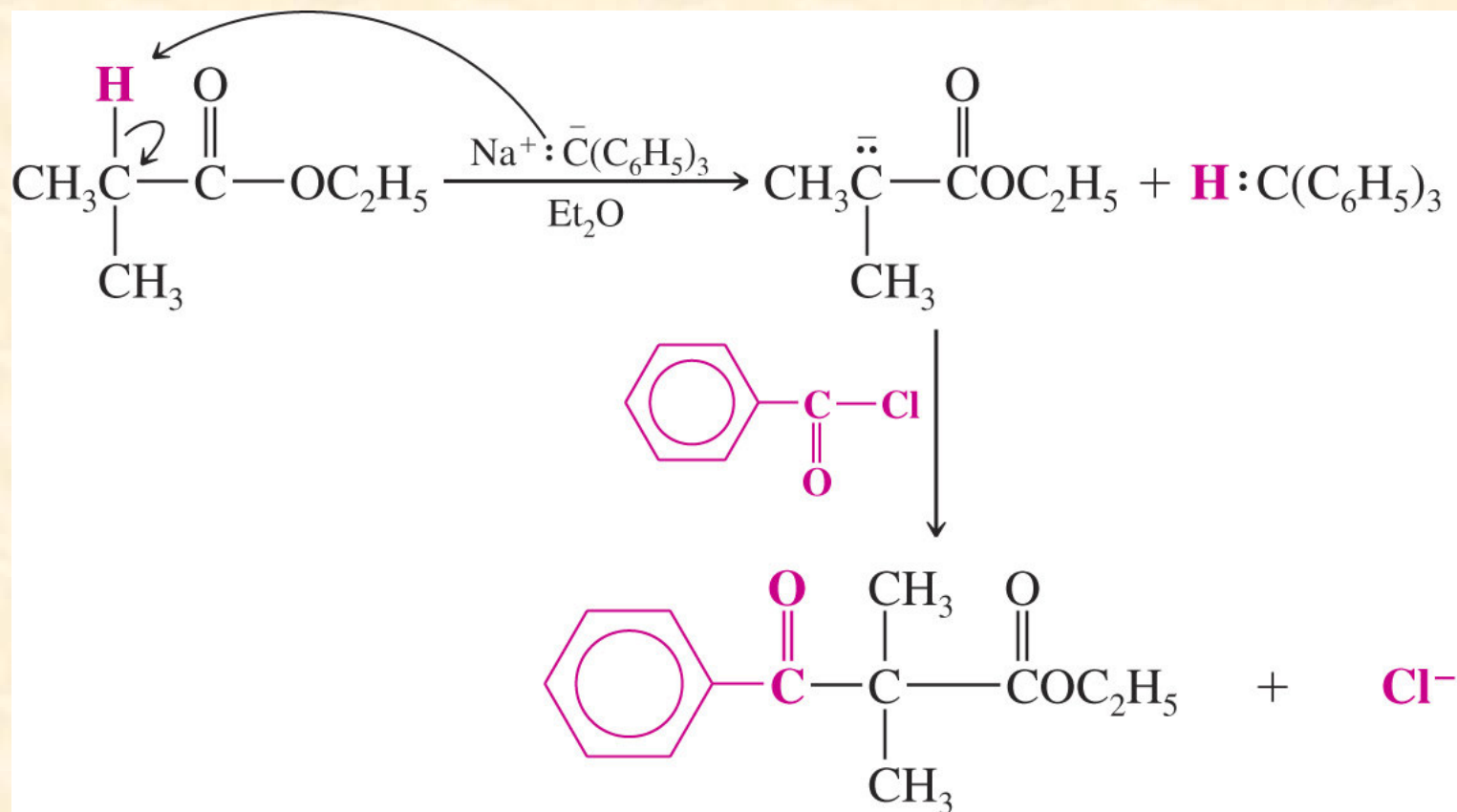
– Crossed Claisen Condensations

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



Synthesis

- Esters with one α hydrogen can react in Claisen condensations if they are deprotonated with a strong base and acylated with an acyl chloride

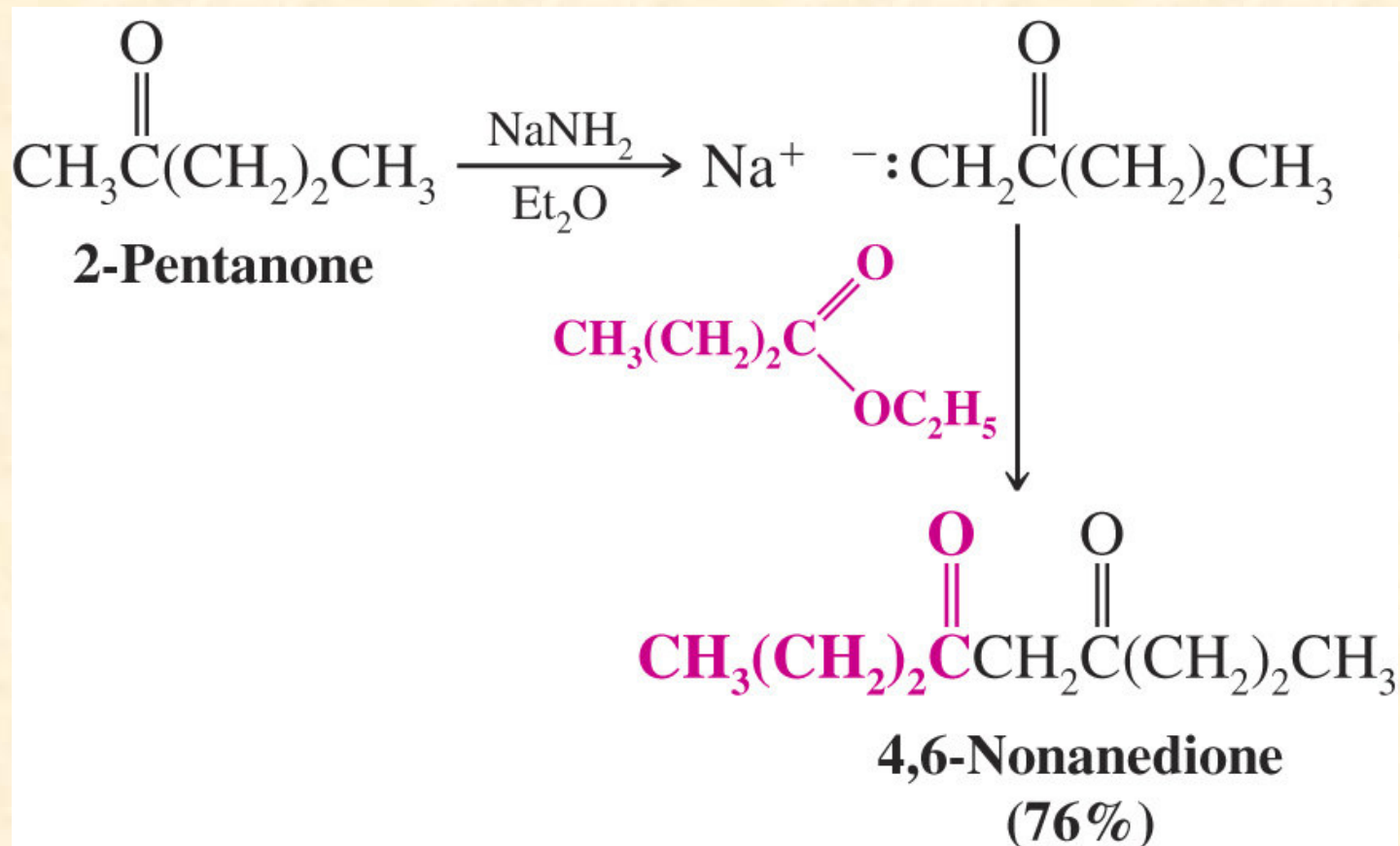


Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate

Synthesis

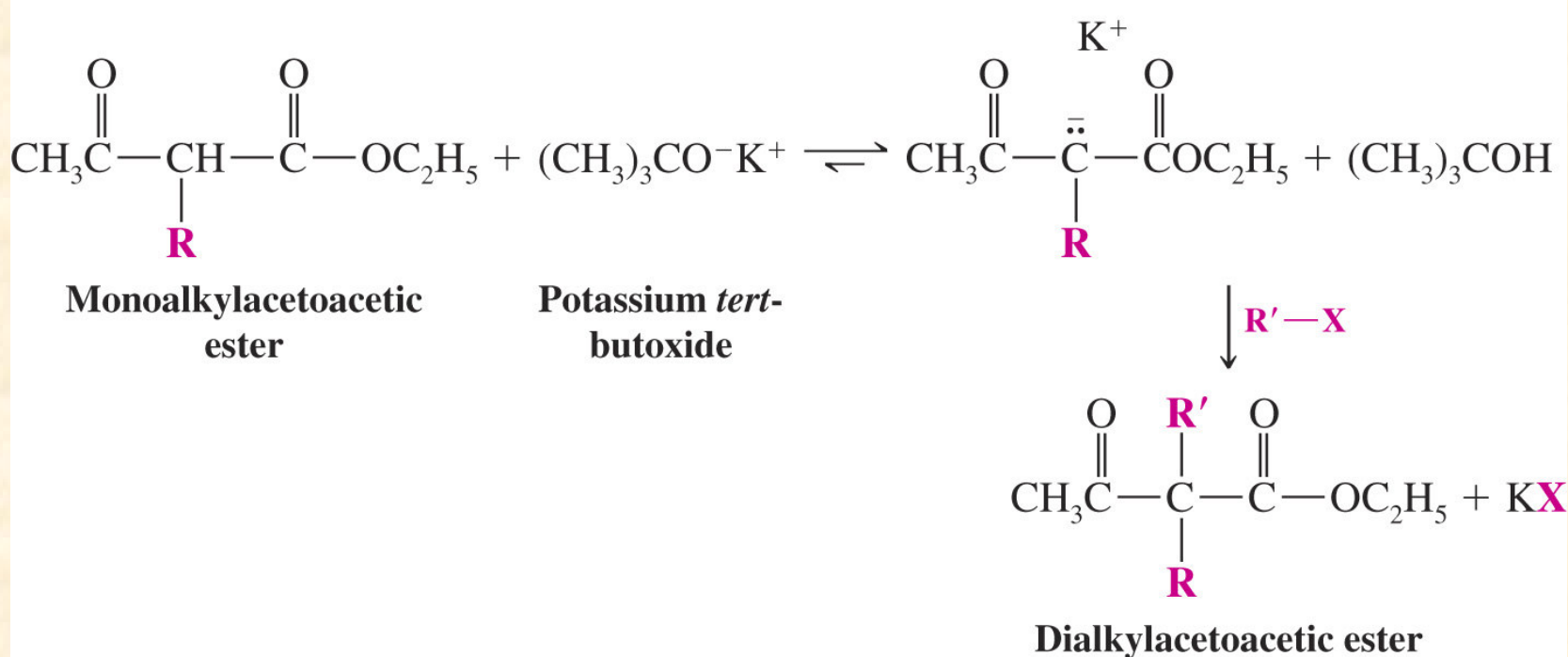
– Acylation of Other Carbanions

- Ketone enolates formed with strong bases can also be acylated to form β -dicarbonyl compounds
- Addition of strong base to 2-pentanone results in formation of the kinetic enolate which can be acylated with an ester



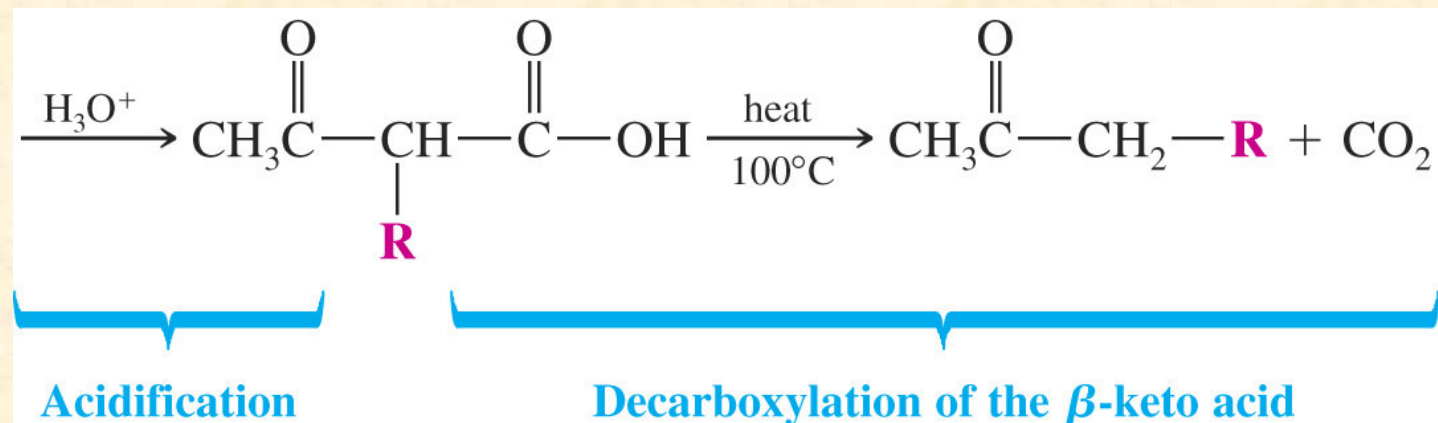
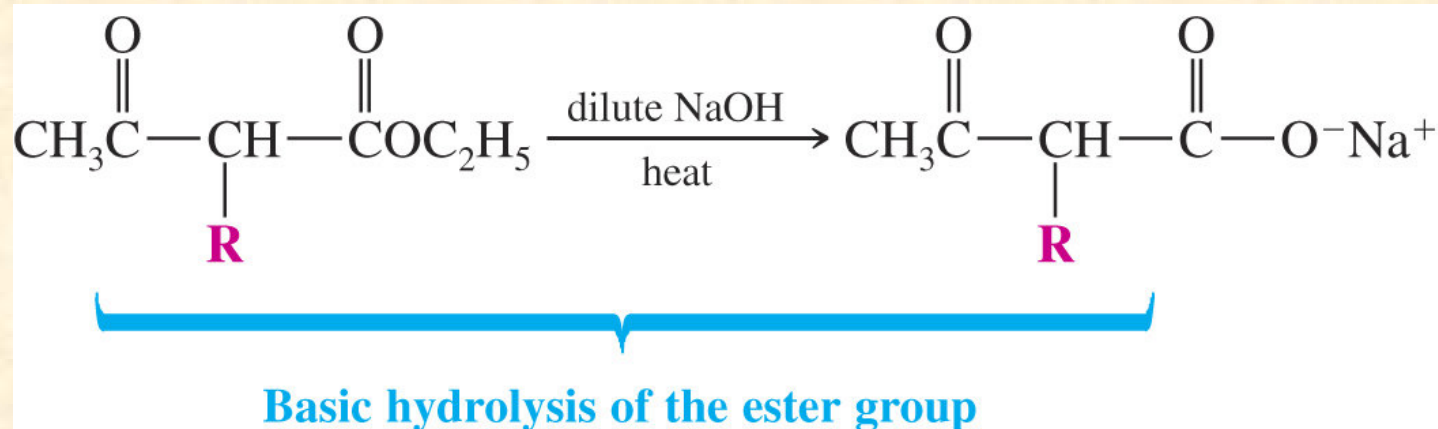
Reactions

- A second alkylation can be performed
 - A stronger base such as potassium *tert*-butoxide must be used to deprotonate the monoalkyl ester



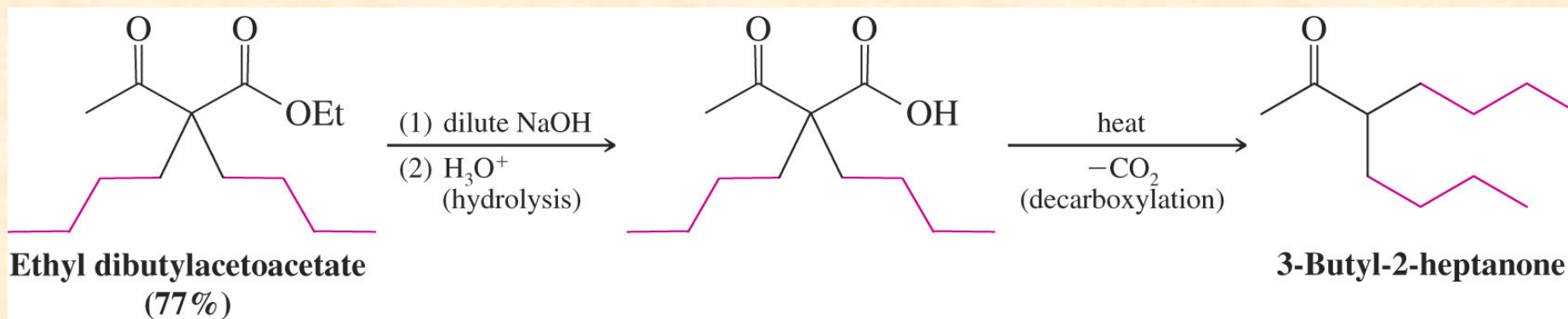
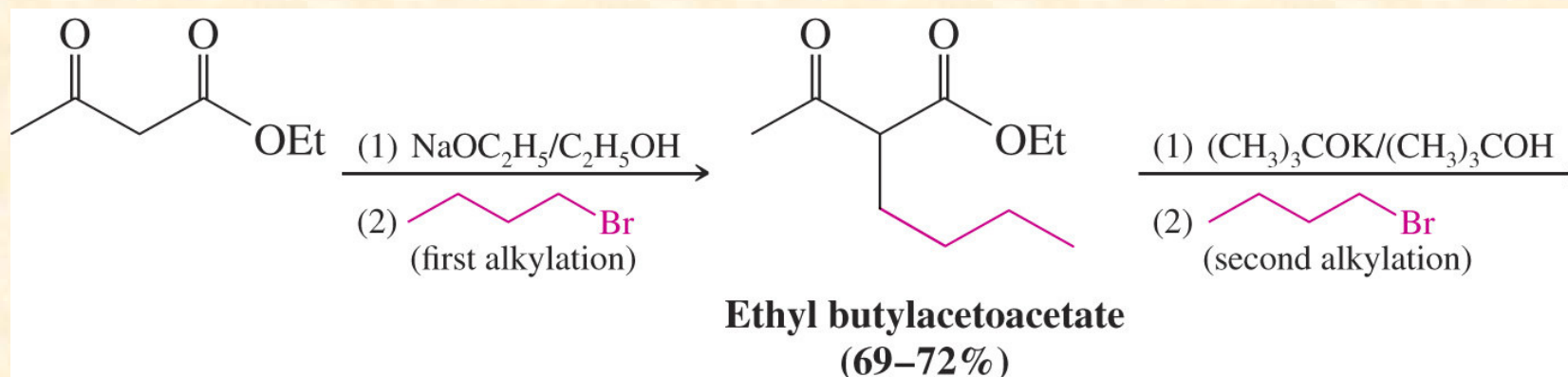
Reactions

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



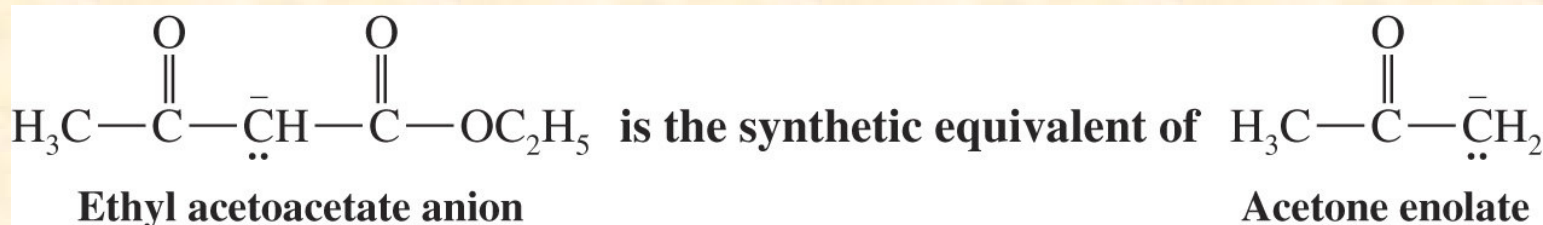
Reactions

- Example:

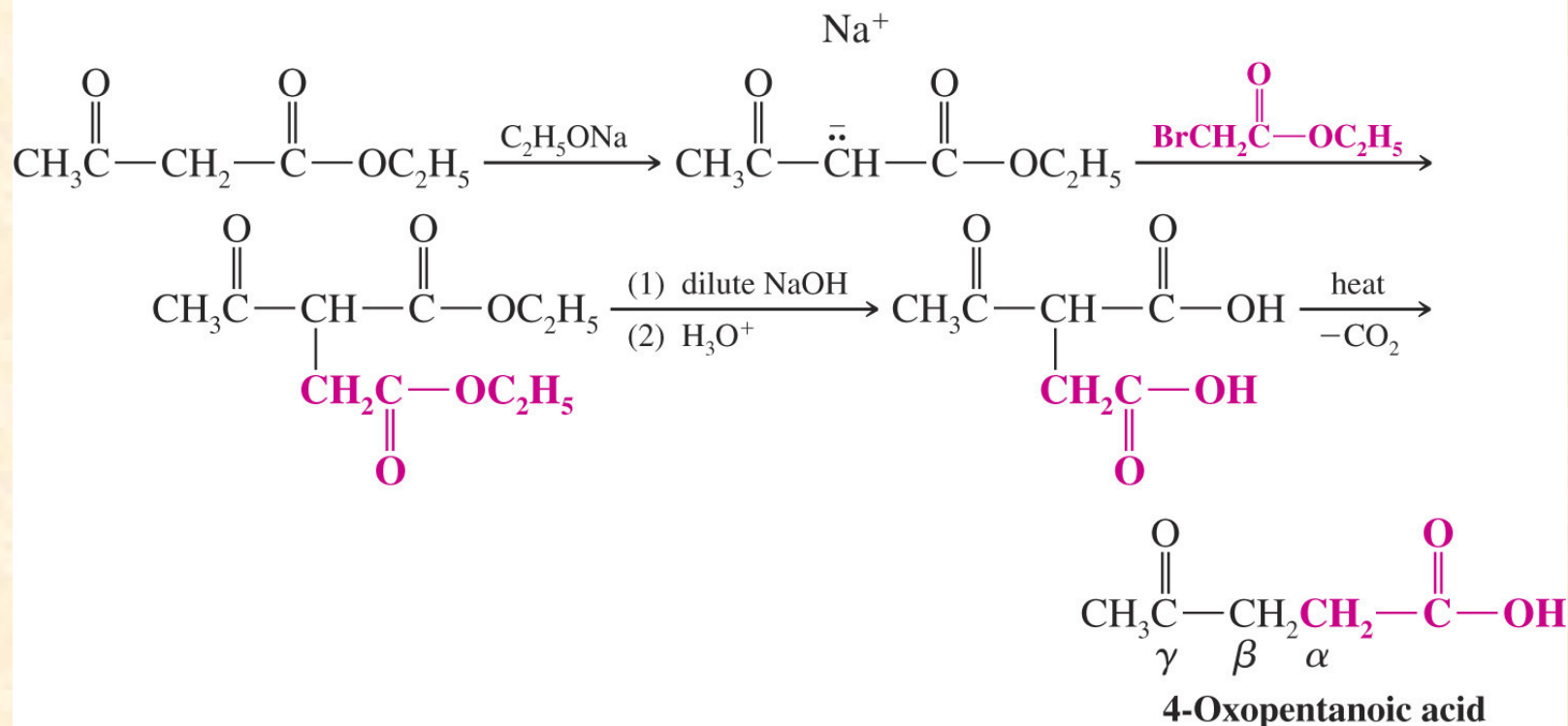


Reactions

- Ethylacetoacetate serves as a *synthetic equivalent* of the acetone enolate
 - It is possible to use acetone enolate directly, but this would require a much stronger base and special reaction conditions



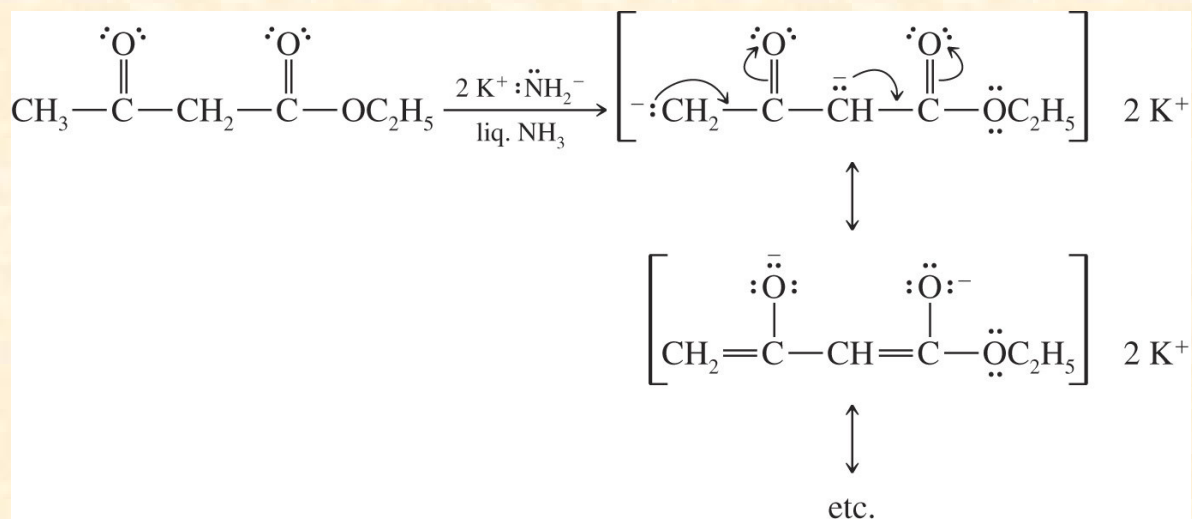
- If α -halo esters are used to alkylate the enolate, γ -keto acids are obtained



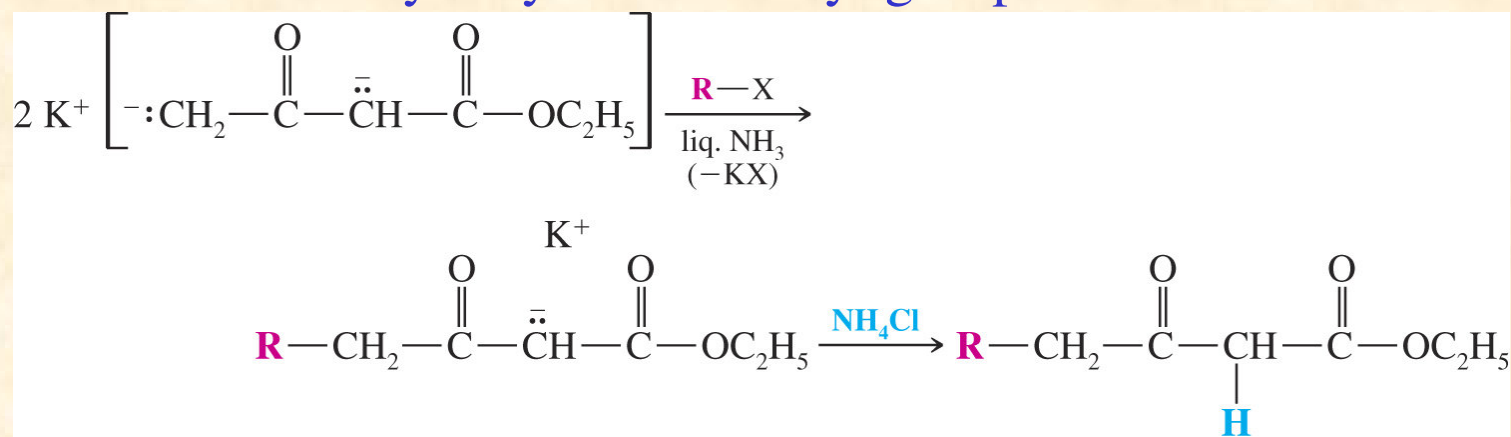
Reactions

– Acetoacetic Ester Dianion: Alkylation at the Terminal Carbon

- Treatment with two eq. of a very strong base produces the dianion



- Alkylation of the dianion occurs first at the terminal carbon
 - The terminal carbanion is more nucleophilic and more basic because it is stabilized by only one carbonyl group

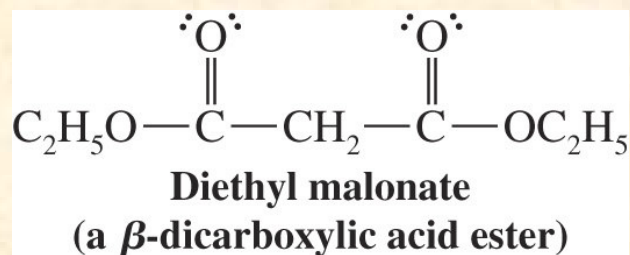


Reactions

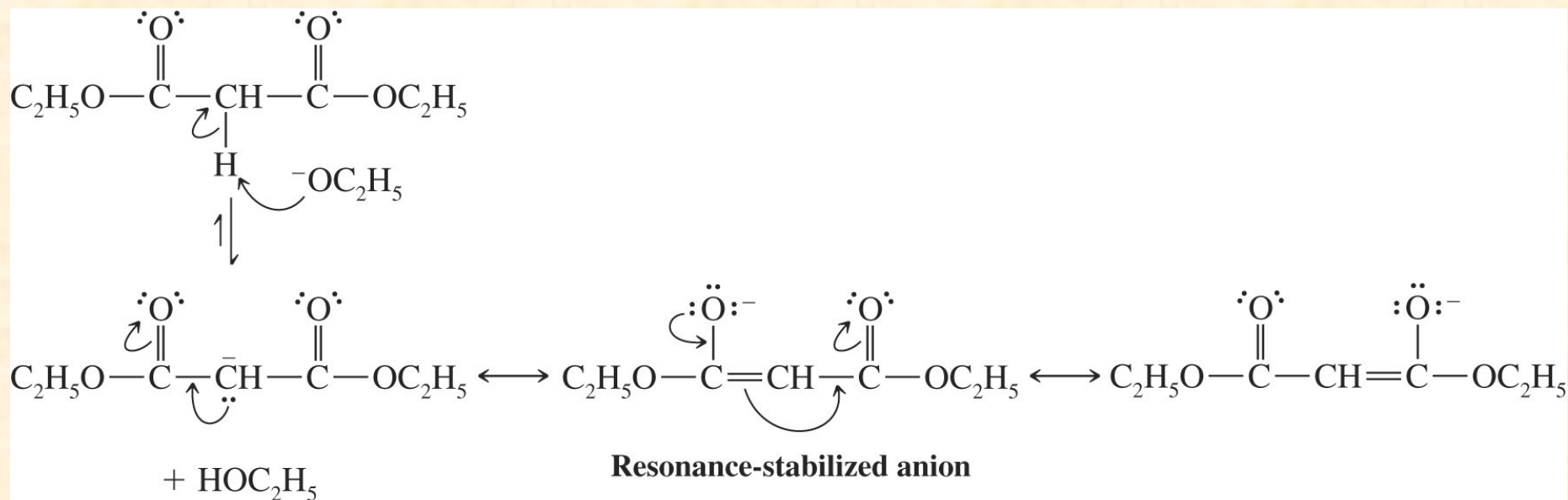
The Malonic Ester Synthesis: Synthesis of Substituted Acetic Acids

- Alkylation of diethylmalonate, hydrolysis of the diester to the β -dicarboxylic acid, and decarboxylation can be used to synthesize mono- and disubstituted acetic acids

– The mechanism is analogous to that for the acetoacetic ester synthesis



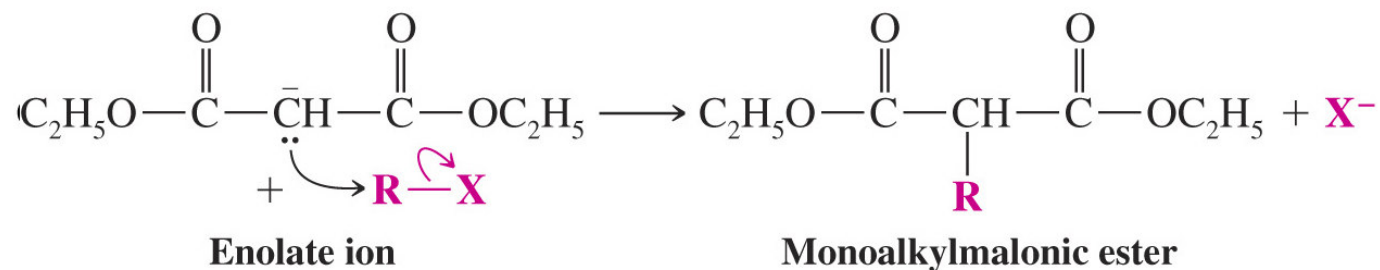
- In step 1 the stabilized anion is formed



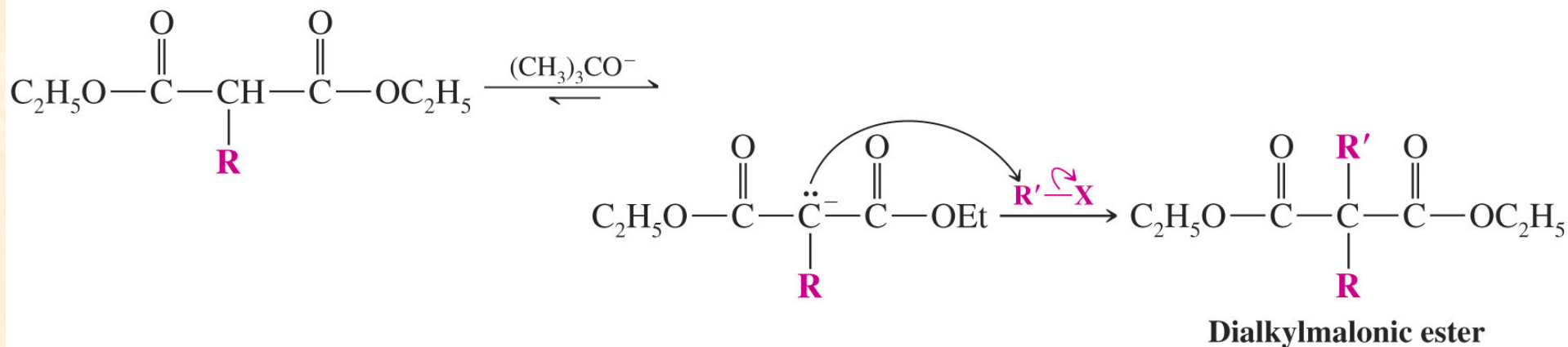
Reactions

- In step 2 the anion is mono- or dialkylated using S_N2 reactions

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

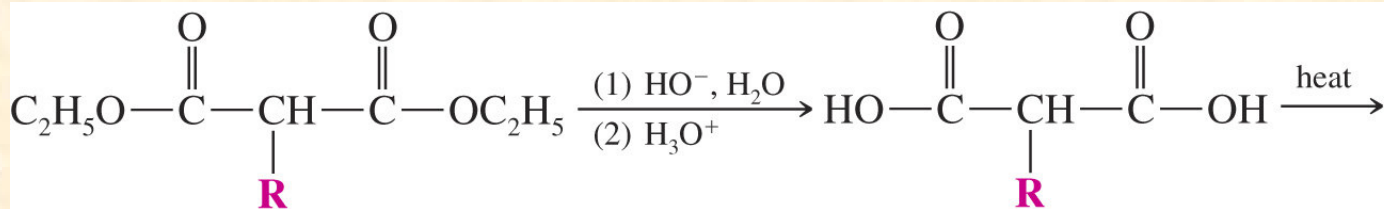


and the product can be alkylated again if our synthesis requires it:

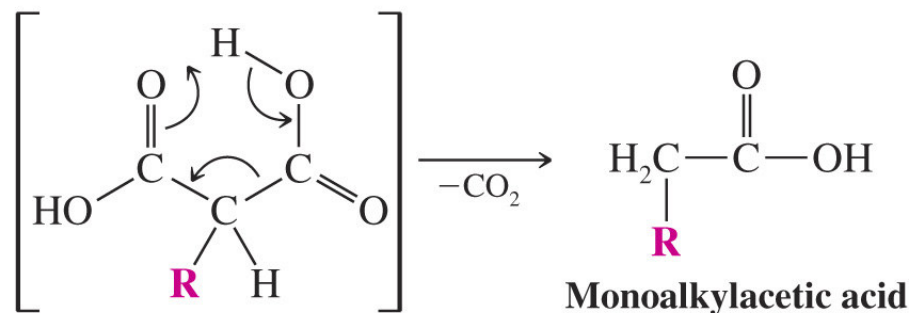


Reactions

- In step 3 the product is hydrolyzed and decarboxylated

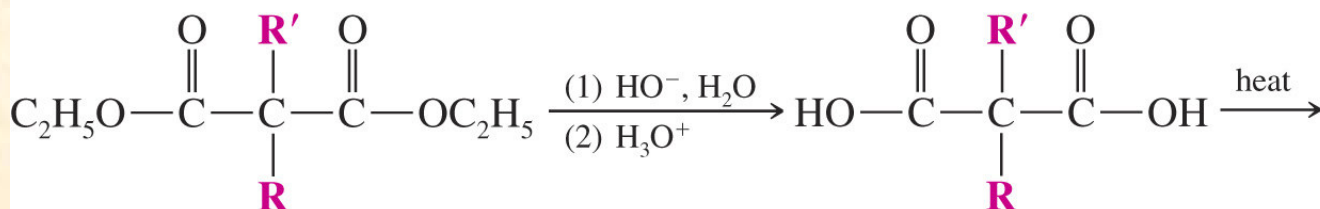


Monoalkylmalonic ester

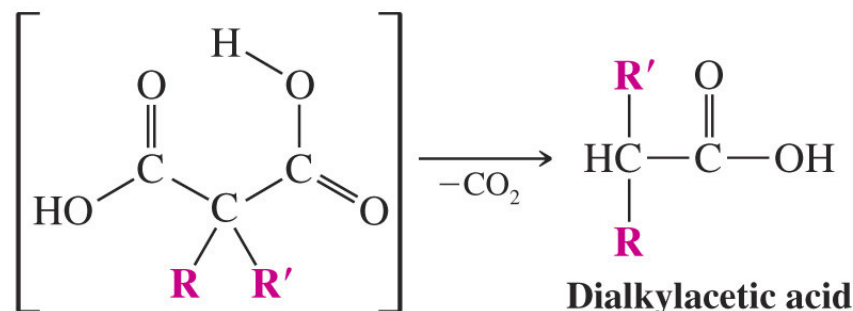


Monoalkylacetic acid

or after dialkylation,



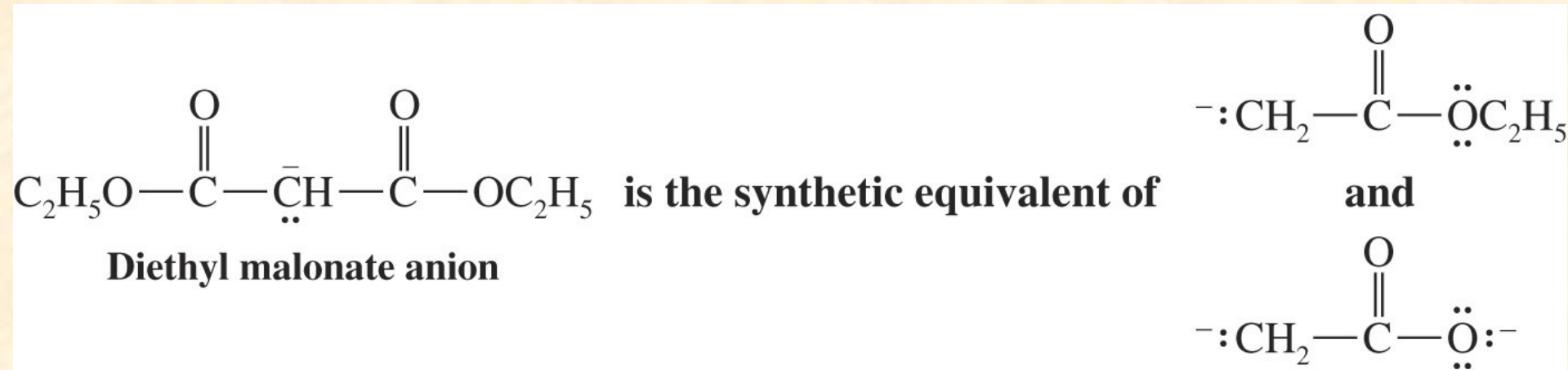
Dialkylmalonic ester



Dialkylacetic acid

Reactions

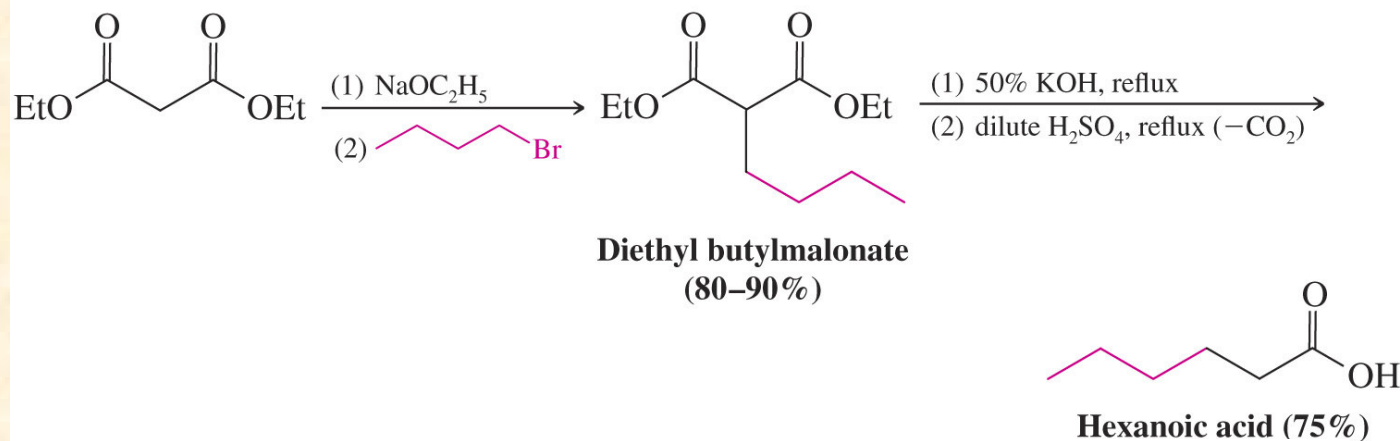
- Diethylmalonate anion is the synthetic equivalent of acetic acid dianion



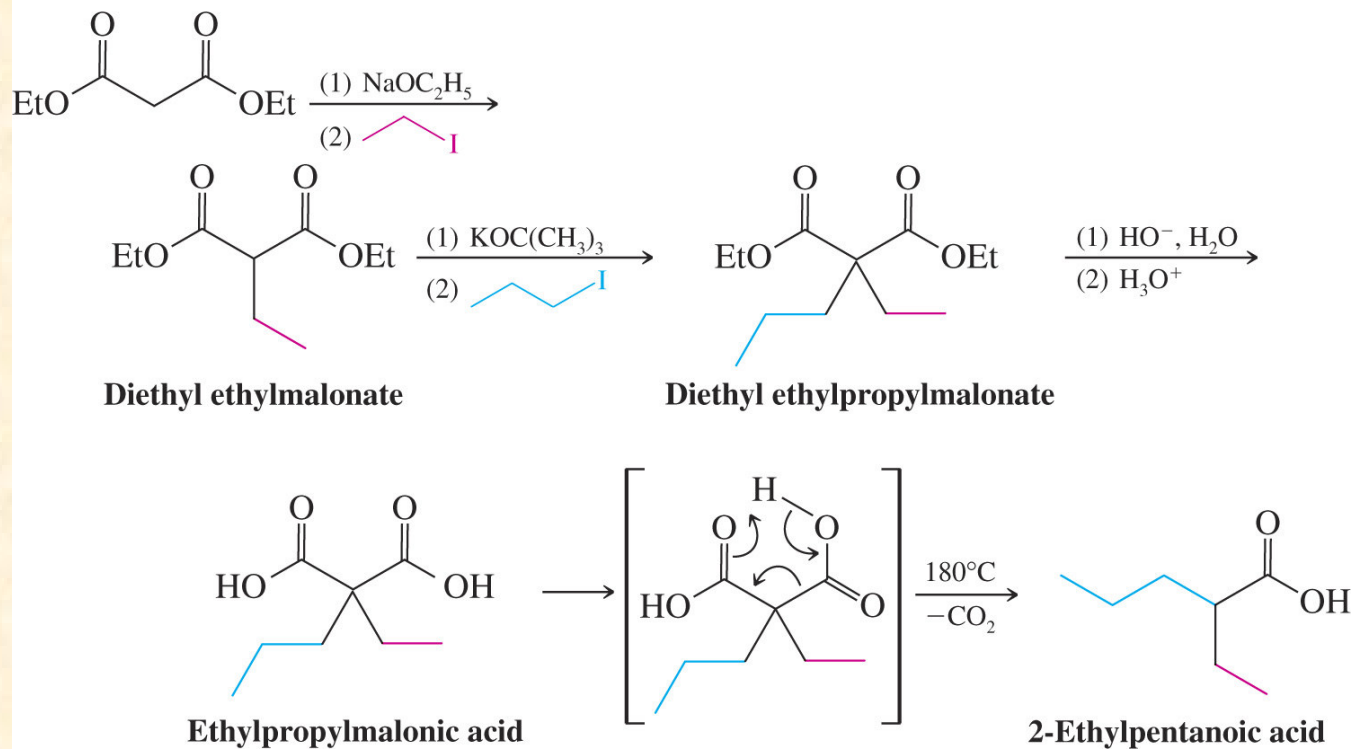
Reactions

- Examples

A Malonic Ester Synthesis of Hexanoic Acid

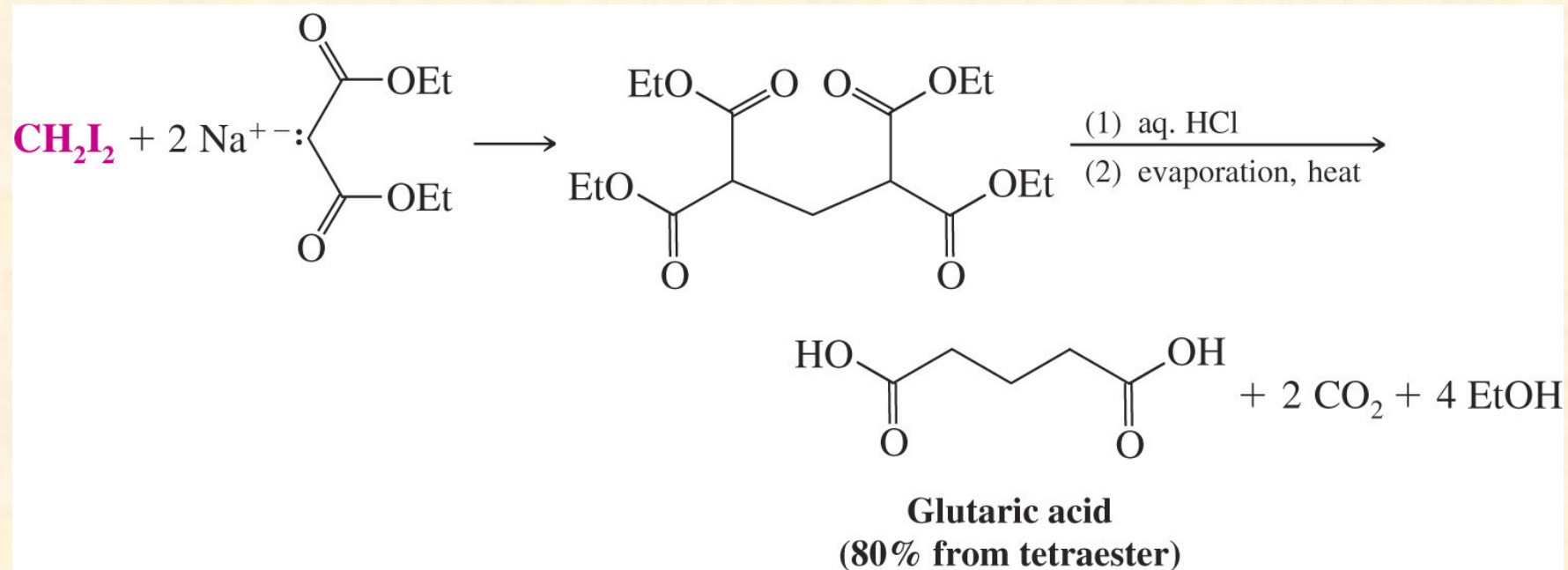


A Malonic Ester Synthesis of 2-Ethylpentanoic Acid



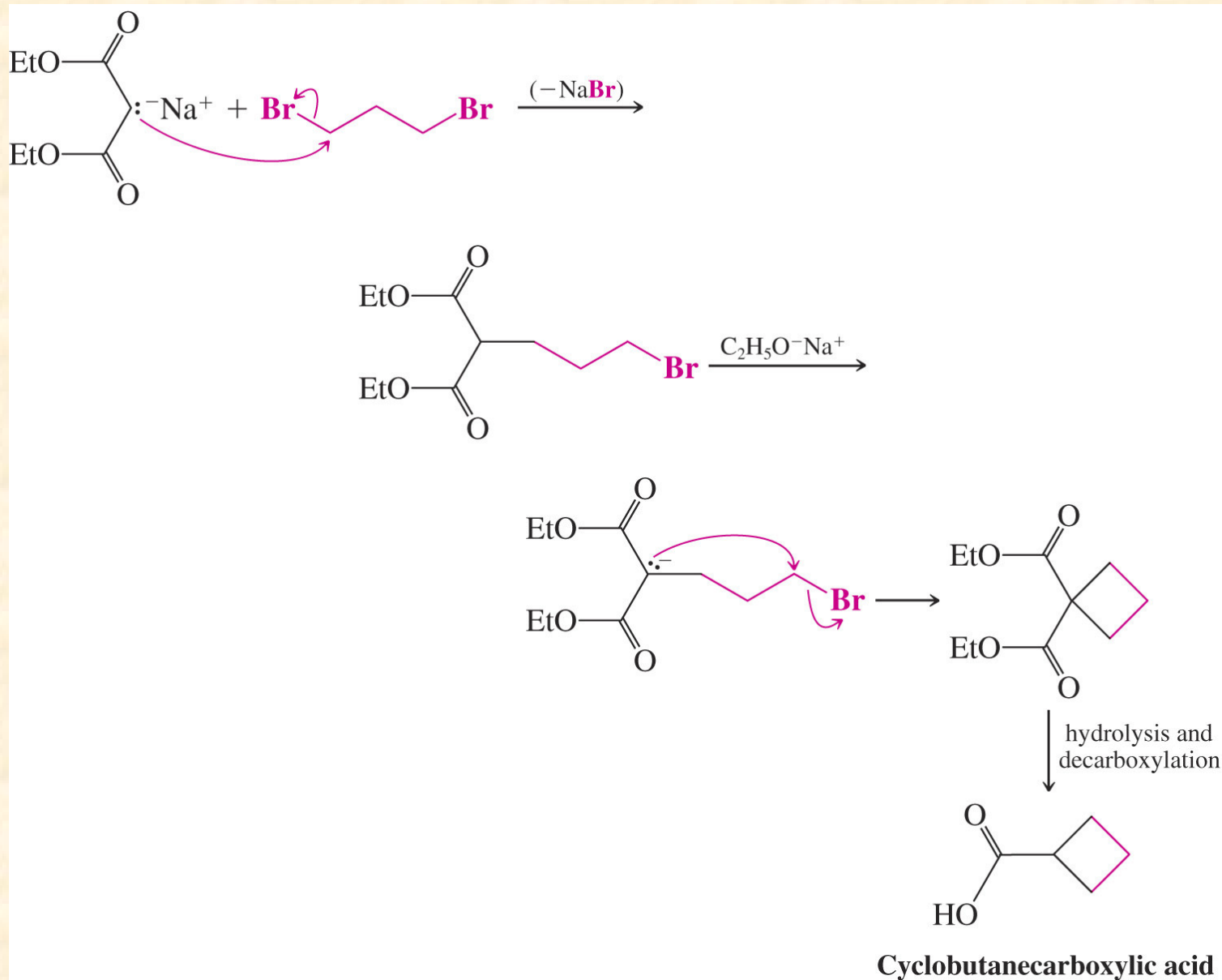
Reactions

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



Reactions

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

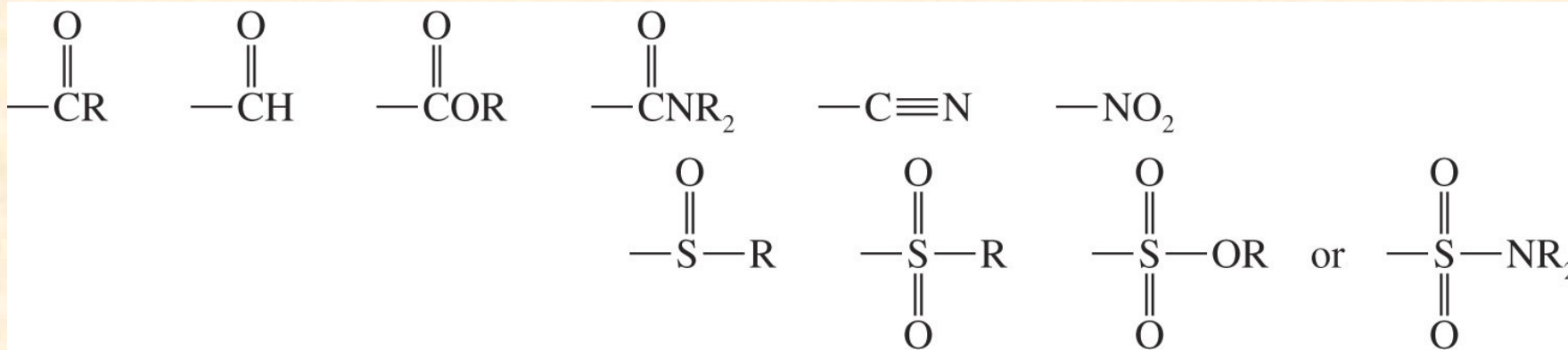


Reactions – Other Active H Compounds

- Reactions of Other Active Hydrogen Compounds
 - Compounds in which the hydrogen atoms of a methylene (-CH₂-) group are made acidic by two attached electron-withdrawing groups are called *active hydrogen compounds* or *active methylene compounds*
 - A variety of electron-withdrawing groups can produce enhanced α hydrogen acidity

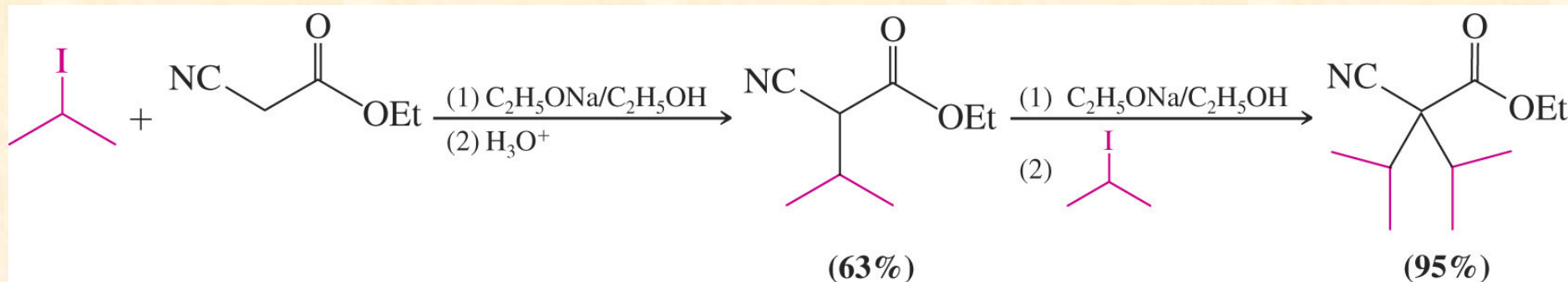
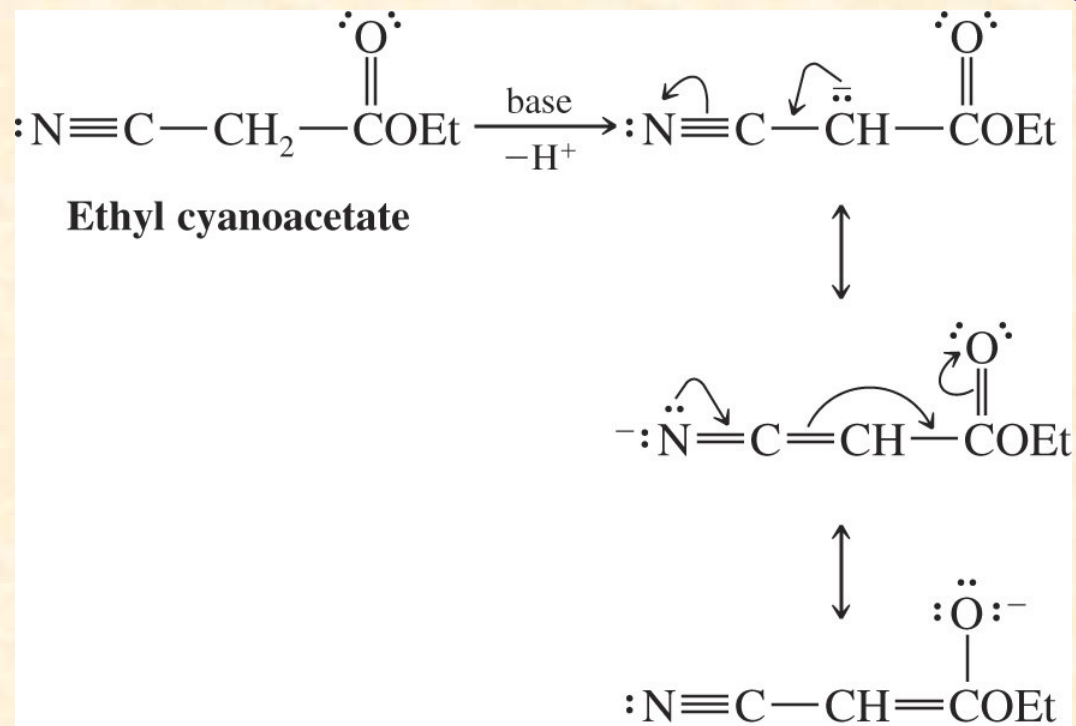


Active hydrogen compound
(Z and Z' are electron-withdrawing groups.)



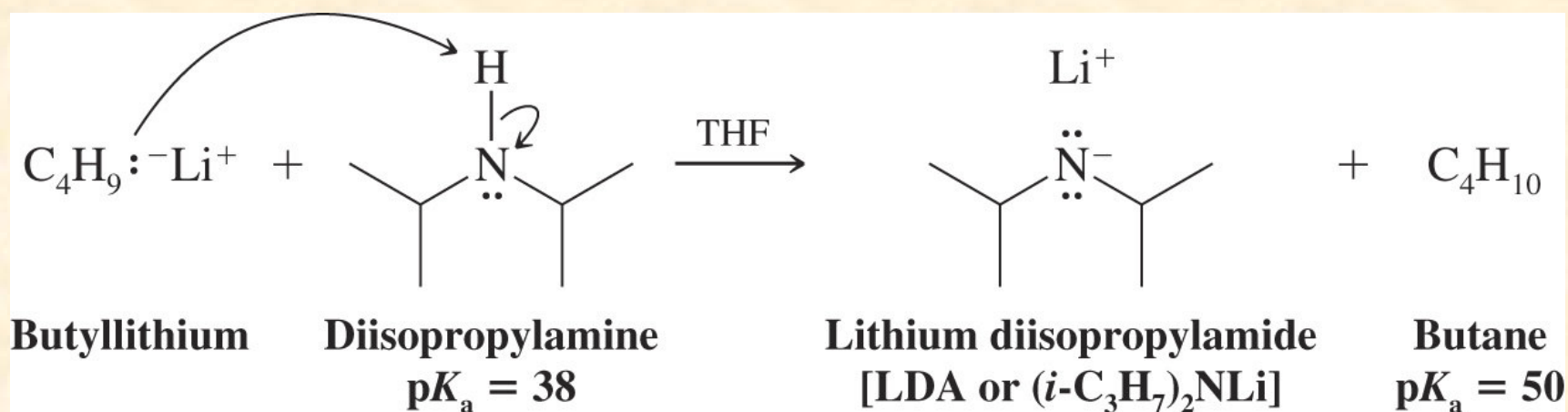
Reactions – Other Active H Compounds

- Example: Deprotonation of ethyl cyanoacetate forms a resonance-stabilized anion, which can then undergo alkylation

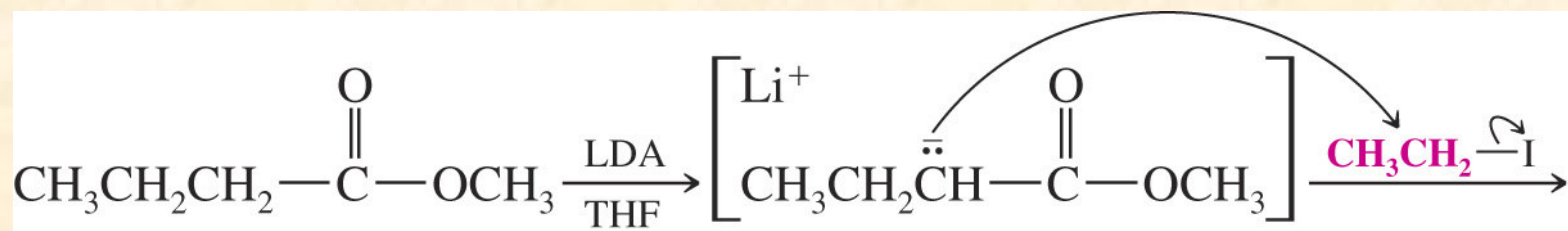


Reactions – Other Active H Compounds

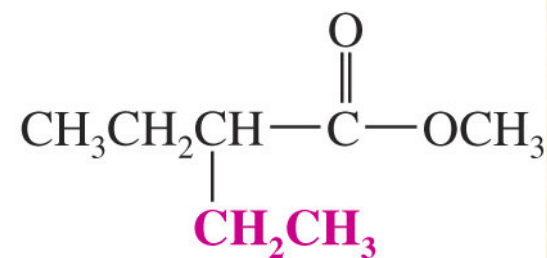
- Direct Alkylation of Esters and Nitriles
 - A strong and bulky base such as lithium diisopropyl amide (LDA) must be used to directly alkylate esters and nitriles
 - A strong base rapidly converts all of the ester or nitrile molecules into enolates so that they will not undergo Claisen condensation
 - A bulky base will not react as a nucleophile at the ester carbonyl or nitrile carbon



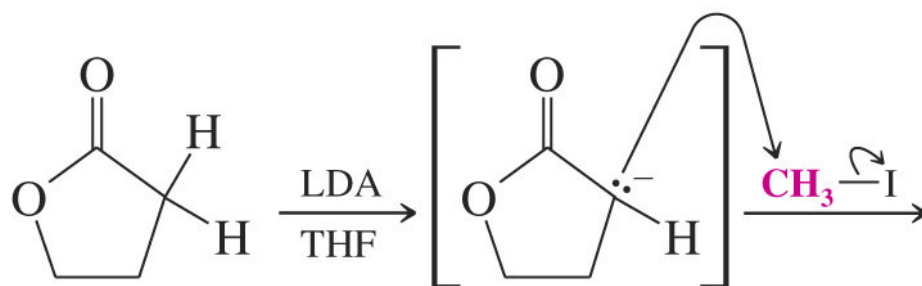
Reactions – Other Active H Compounds



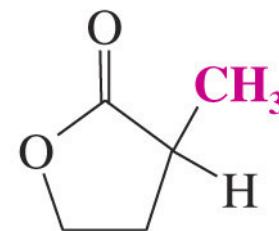
Methyl butanoate



Methyl 2-ethylbutanoate
(96%)



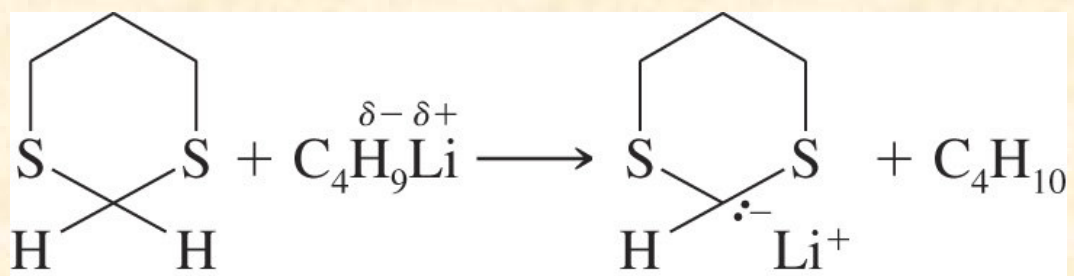
Butyrolactone



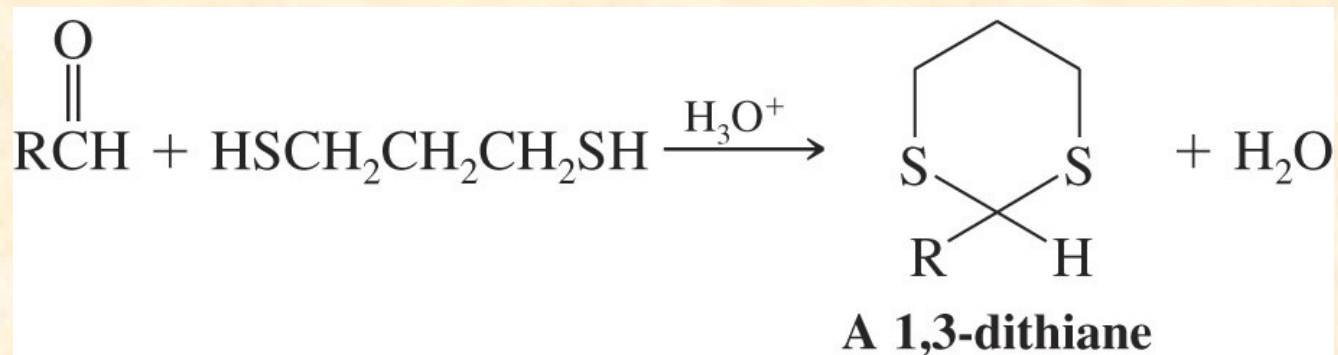
2-Methylbutyrolactone
(88%)

Reactions – Other Active H Compounds

- Alkylation of 1,3-Dithianes
 - Protons on the carbon between the sulfur atoms of a 1,3-dithiane are acidic
 - Strong bases convert the dithiane to its anion

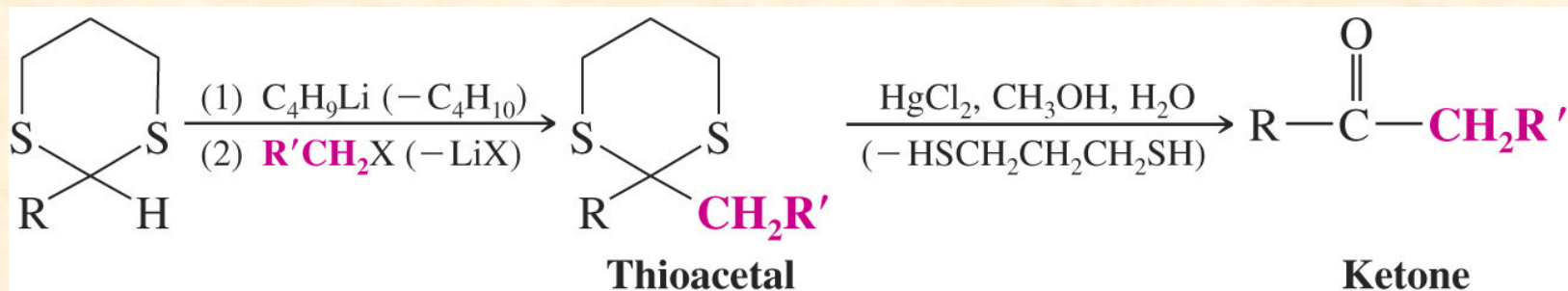


- Dithianes are 6-membered ring thioacetals
 - These can be prepared from an aldehyde and the 1,3- dithiol

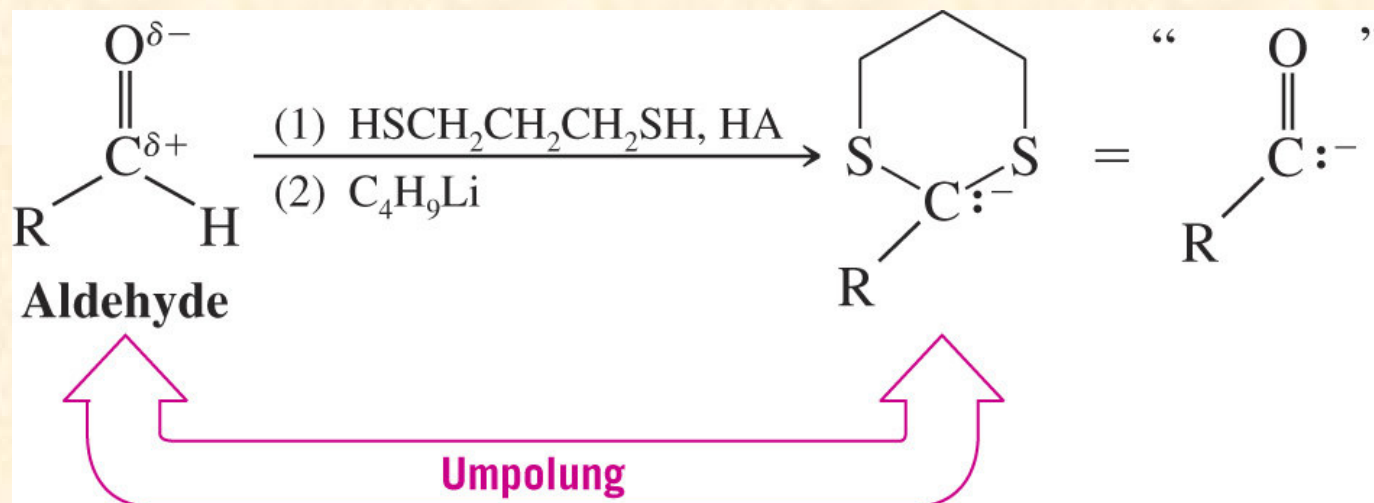


Reactions – Other Active H Compounds

- A dithioacetal anion is the synthetic equivalent of an aldehyde
 - An aldehyde can be converted to a ketone



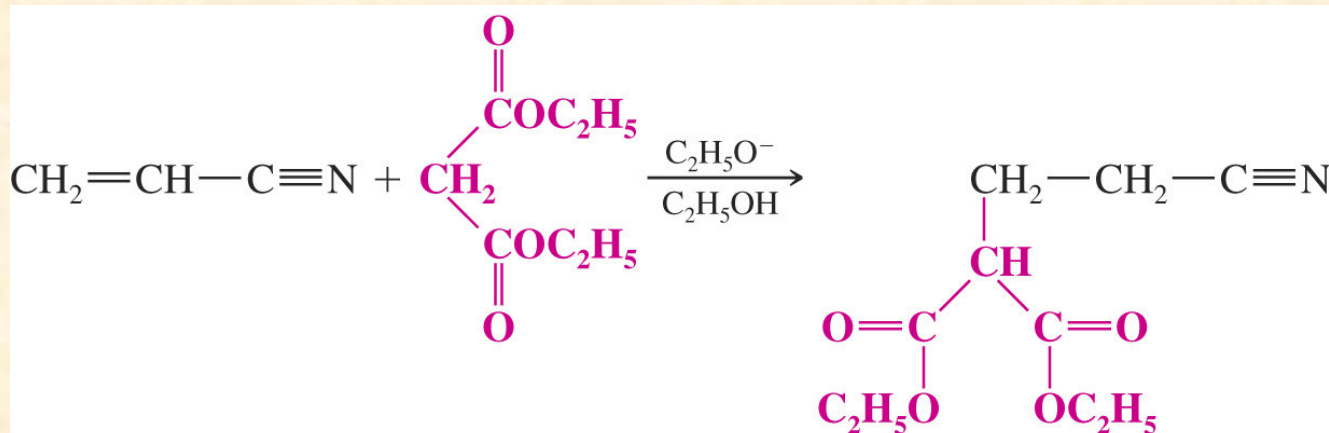
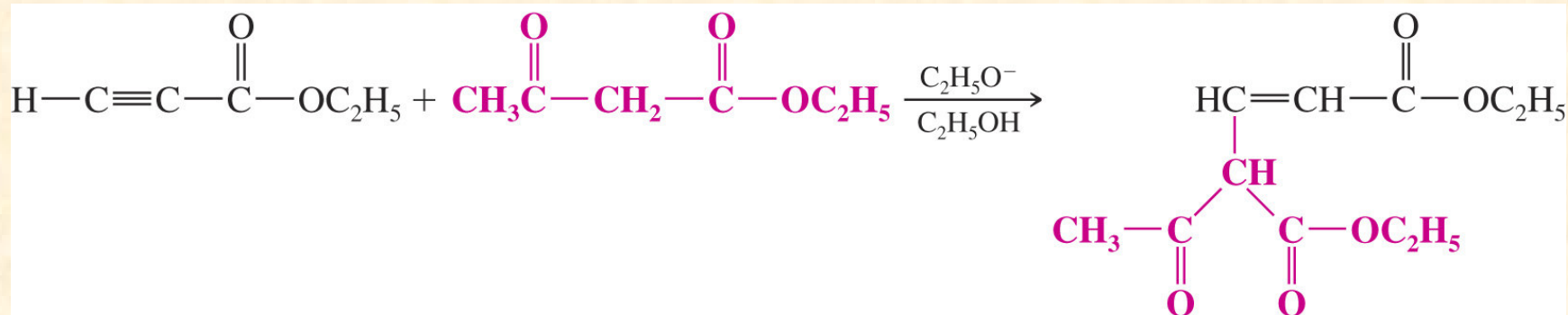
- The reversal of the polarity of the carbonyl carbon in this series of reactions is called *umpolung*
 - An aldehyde carbonyl carbon normally $\delta+$ and is electrophilic
 - In dithioacetal alkylation, the equivalent of the aldehyde carbon is nucleophilic



Reactions

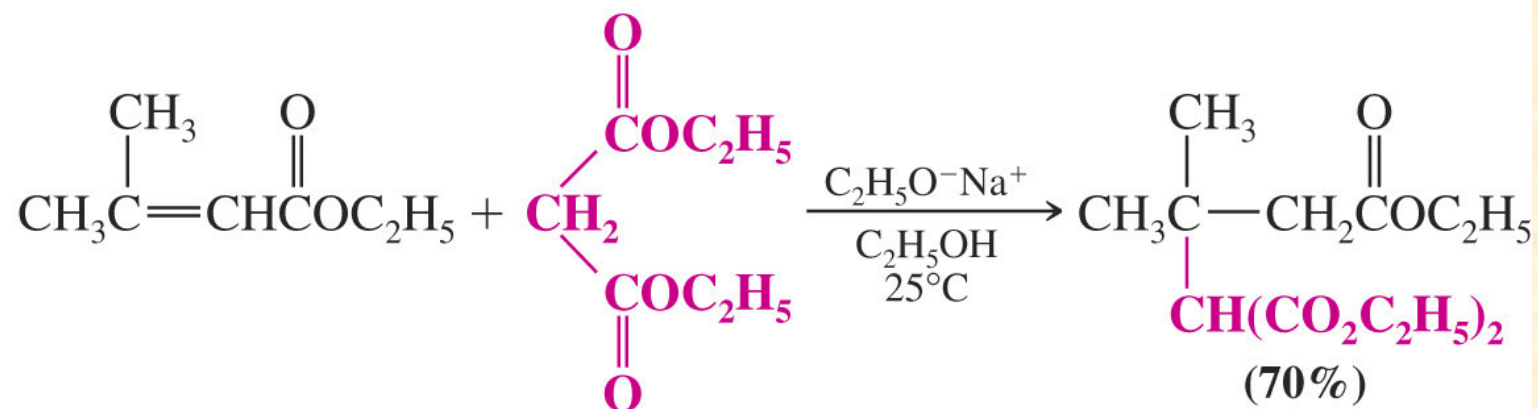
Michael Additions

- 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 (see next slide)
- Michael additions take place with a wide variety of α,β -unsaturated compounds



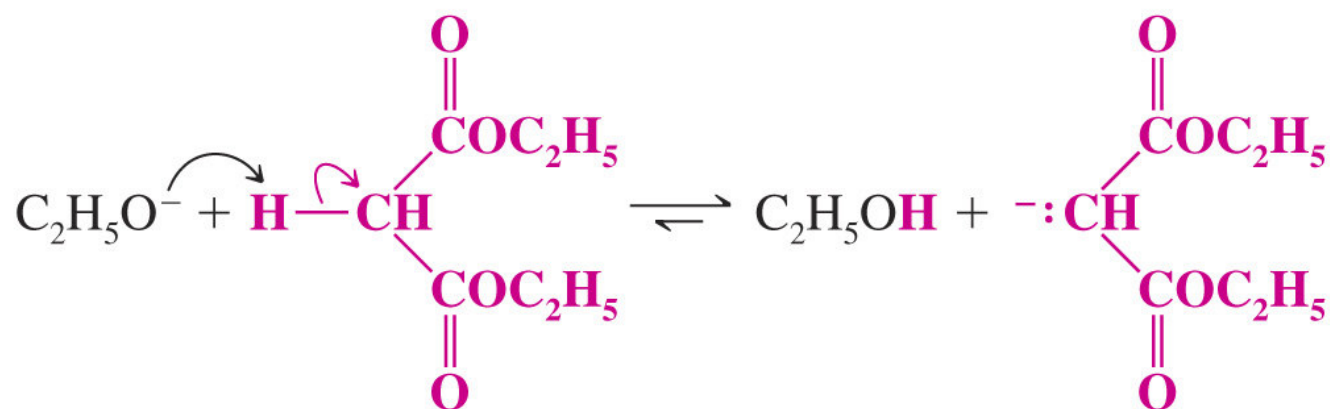
Reactions

Overall Reaction:



Mechanism:

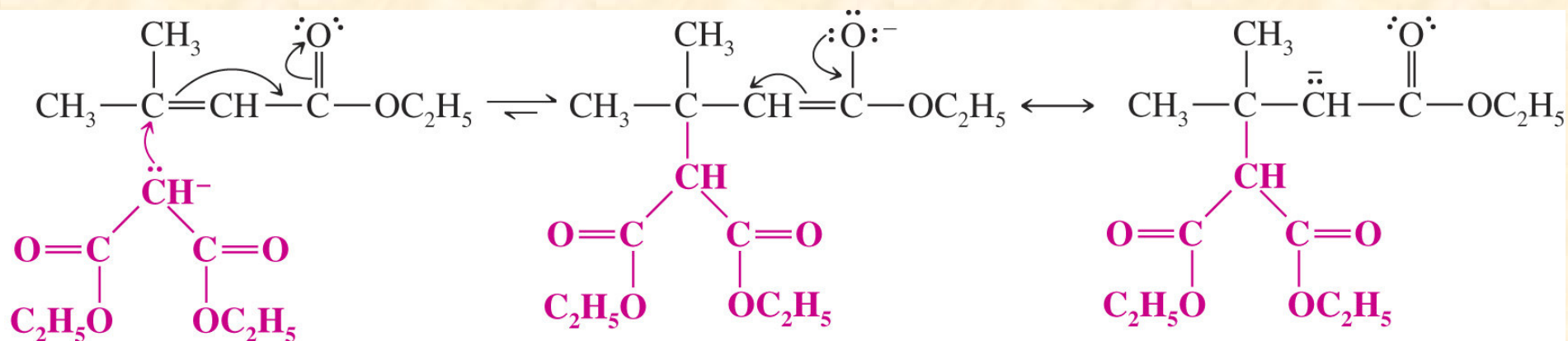
Step 1



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

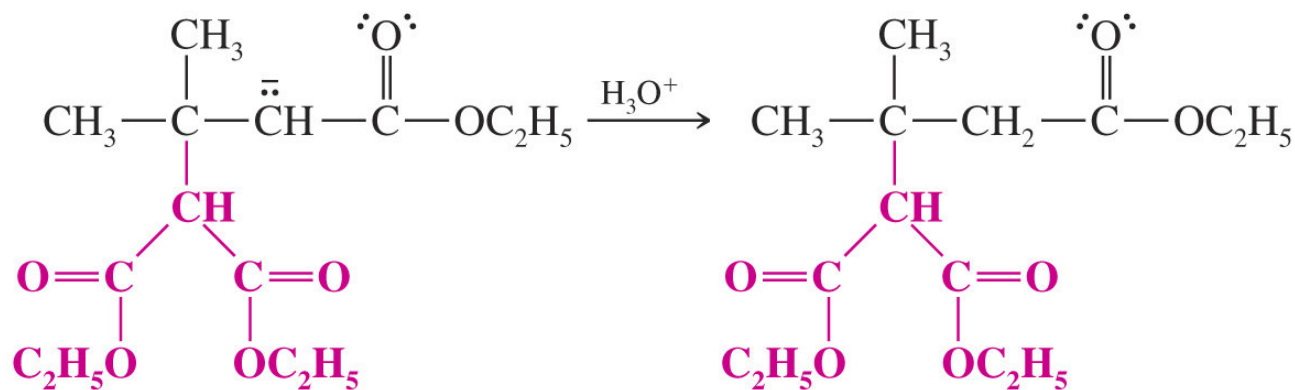
Reactions

Step 2



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

Step 3

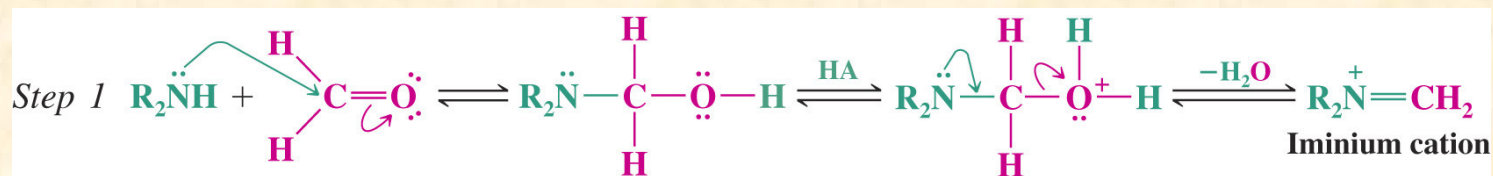
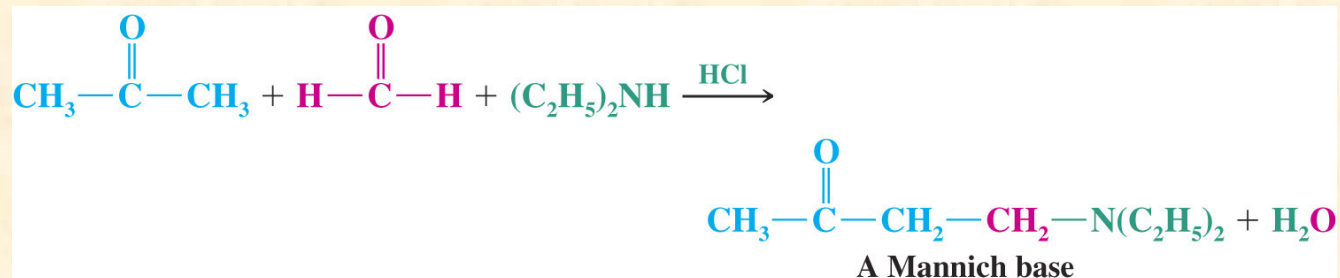


The enolate anion is protonated by an acid during the workup of the reaction.

Reactions

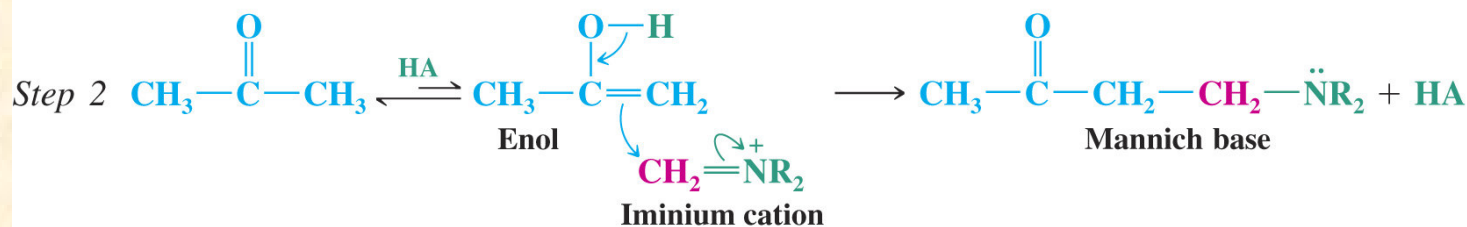
- The Mannich Reaction

- Compounds which can form enols react with imines or iminium ions derived from formaldehyde
 - Primary or secondary amines can be used to form the corresponding formaldehyde imines or iminium ions



Reaction of the secondary amine with the aldehyde forms a hemiaminal.

The hemiaminal loses a molecule of water to form an iminium cation.

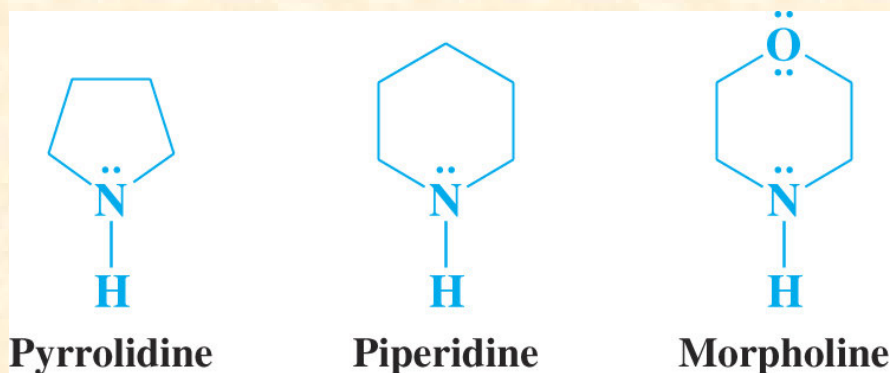
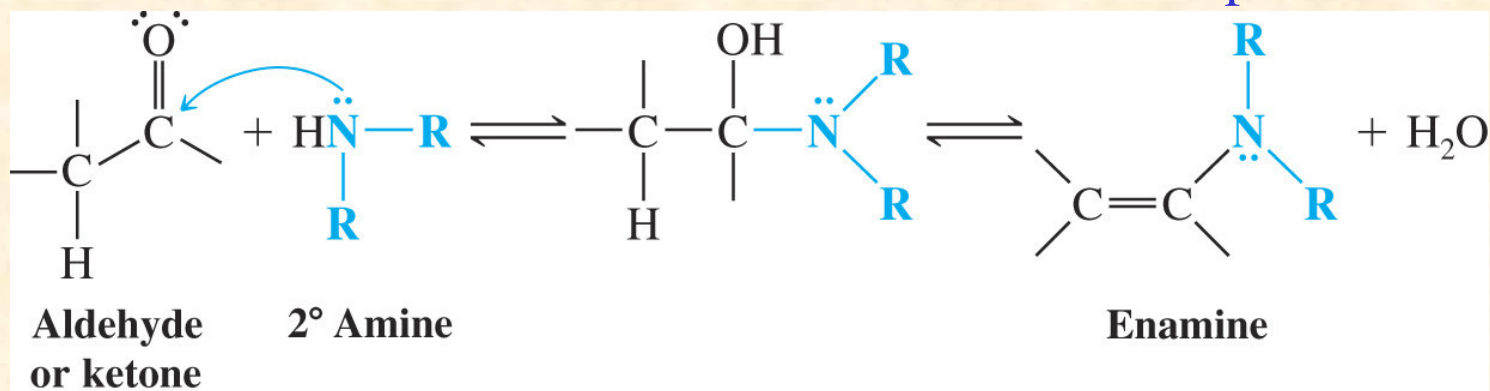


The enol form of the active hydrogen compound reacts with the iminium cation to form a β -aminocarbonyl compound (a Mannich base).

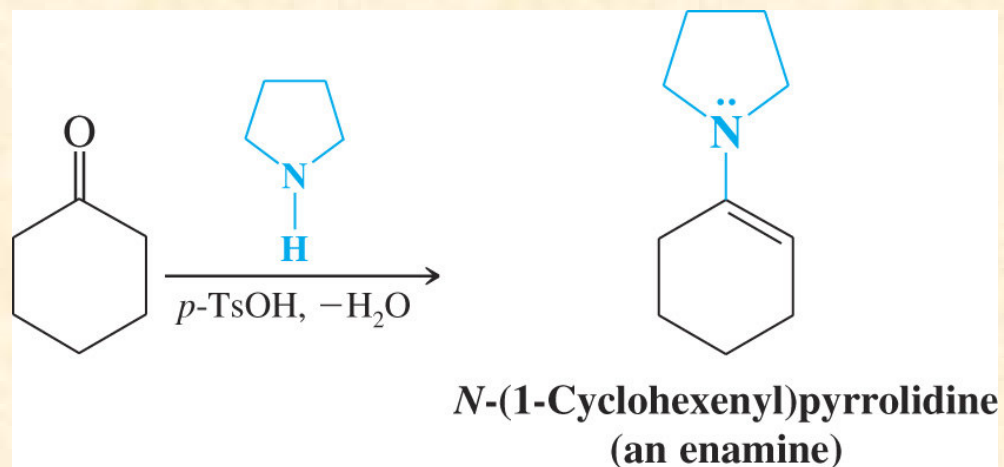
Reactions

Synthesis of Enamines: The Stork Enamine Reactions

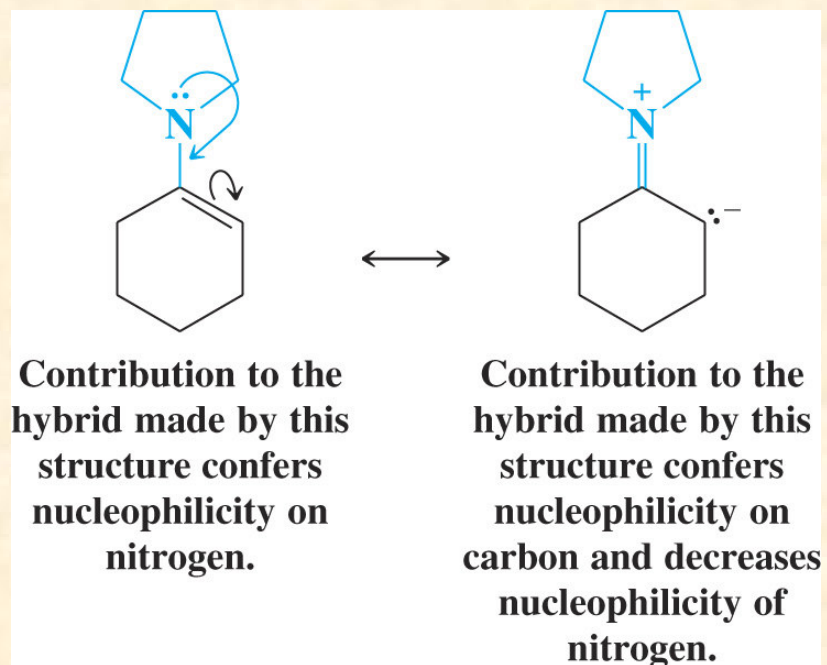
- Aldehydes and ketones react with secondary amines to form enamines (see Section 16.8C)
 - Cyclic amines are often used
 - The reaction is catalyzed by acid
 - Removal of water drives enamine formation to completion



Reactions

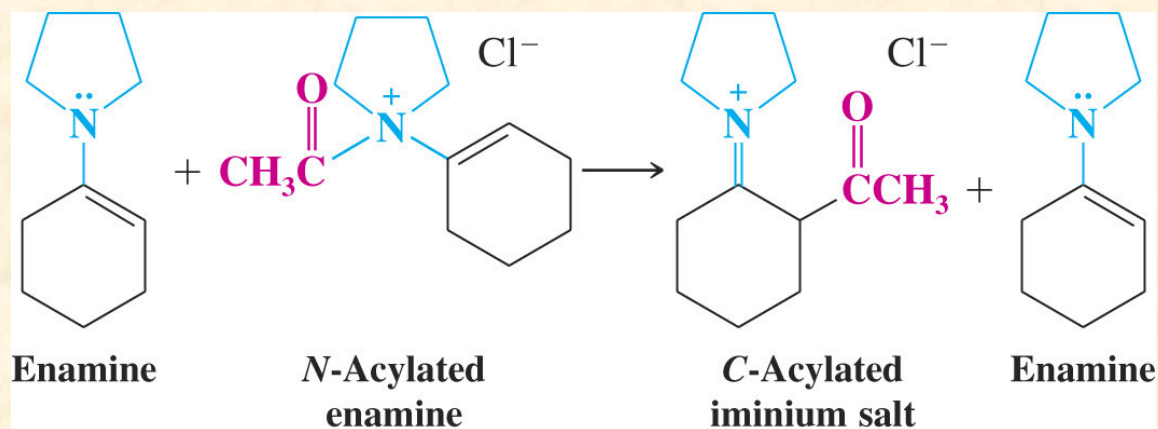
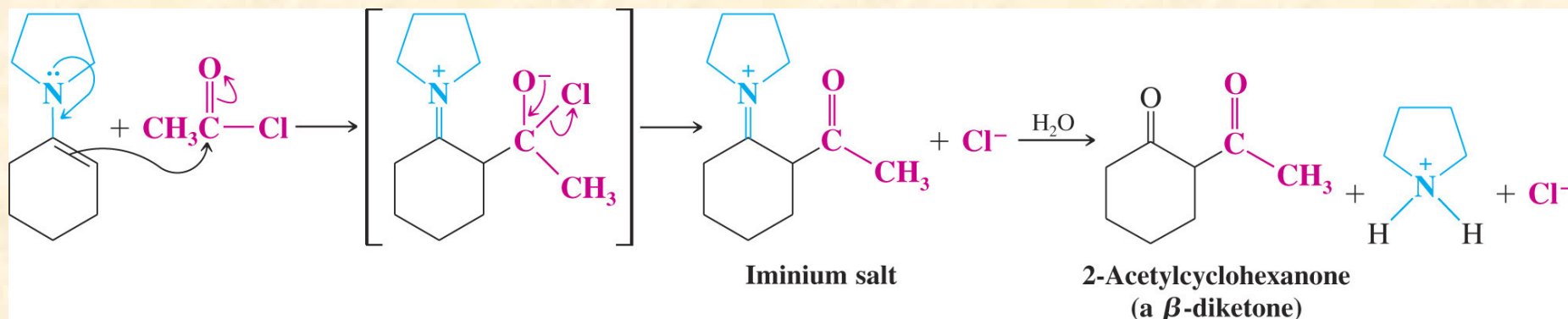


- Enamines have a nucleophilic carbon and are the equivalent of ketone and aldehyde enolates
 - The nitrogen of enamines is also nucleophilic



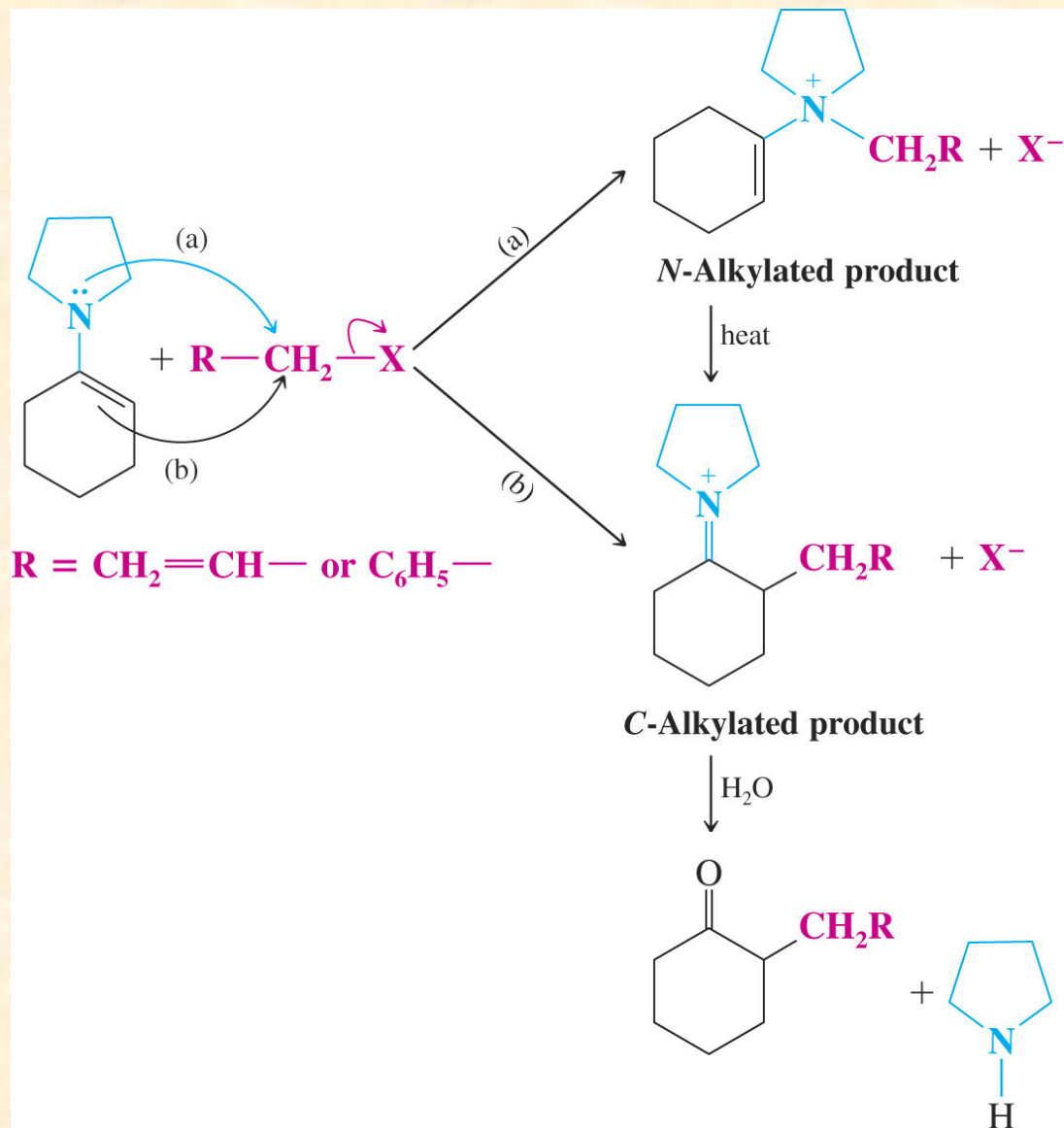
Reactions

- Enamines can be acylated, alkylated, and used in Michael reactions
 - The iminium intermediate is hydrolyzed when water is added
- C-Acylation leads to β -diketones
 - *N*-acylated products can be formed, but they are unstable and act as acylating agents themselves



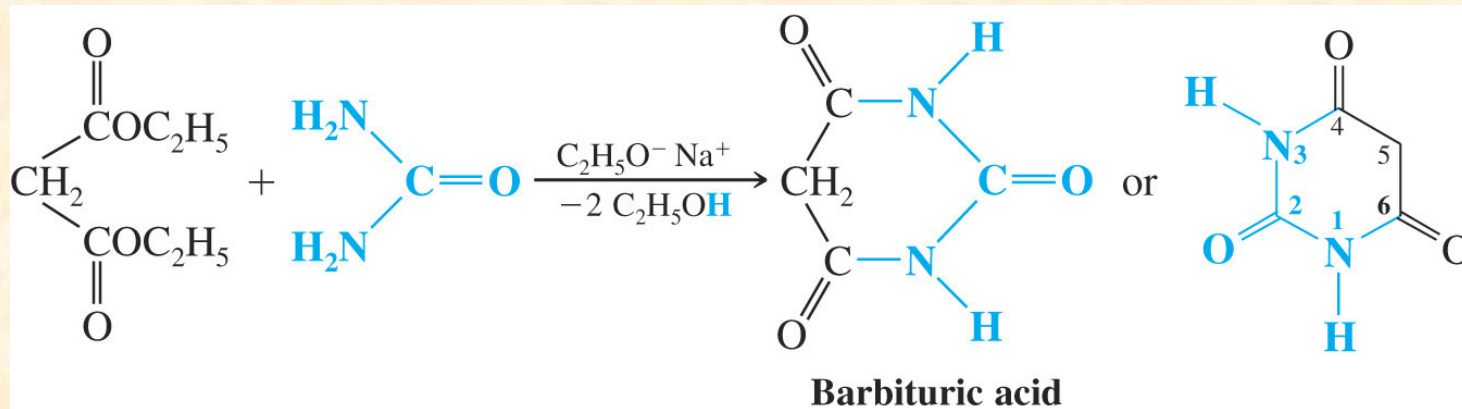
Reactions

- Alkylation of enamines can lead to some *N*-alkylation
 - The *N*-alkylated product can often be converted to the *C*-alkylated product by heating



Reactions

- Barbiturates
 - Reaction of diethyl malonate with urea in the presence of sodium ethoxide produces barbituric acid



- Barbiturates are substituted derivatives of barbituric acid
 - Barbiturates are used in medicine as soporifics (sleep inducers)

