Enolate Anions and Enamines

Chapter 19

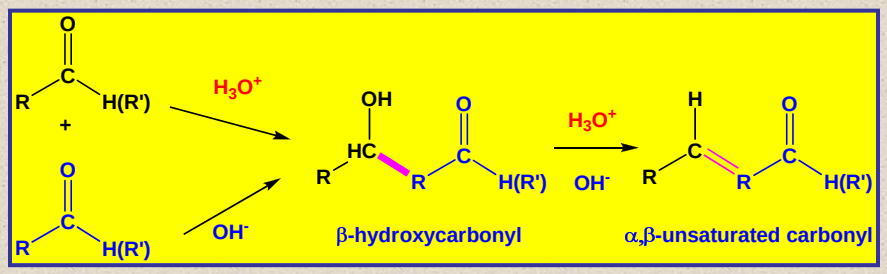
The Aldol Reaction

- The most important reaction of enolate anions is nucleophilic addition to the carbonyl group of another molecule of the same or different compound
  - although these reactions may be catalyzed by either acid or base, base catalysis is more common
  - **The reaction results in a new C—C bond**

The Aldol Reaction

The **product of an aldol** reaction is

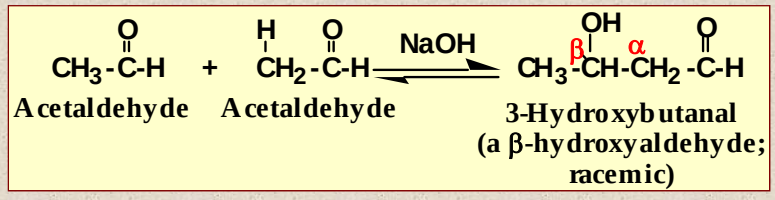
– a β-hydroxyaldehyde or a β-hydroxyketone



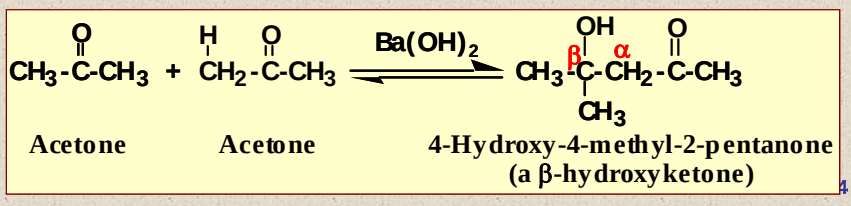
Frequently, there is a second, dehydration step

The Aldol Reaction

- The **product of an aldol** reaction is
  - a β-hydroxyaldehyde



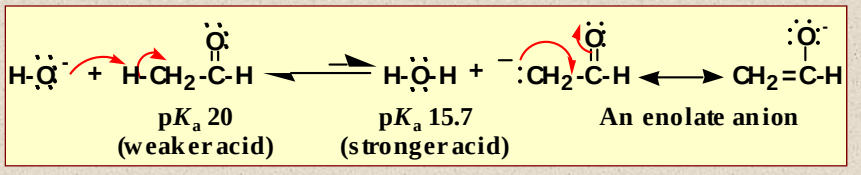
  - or a β-hydroxyketone



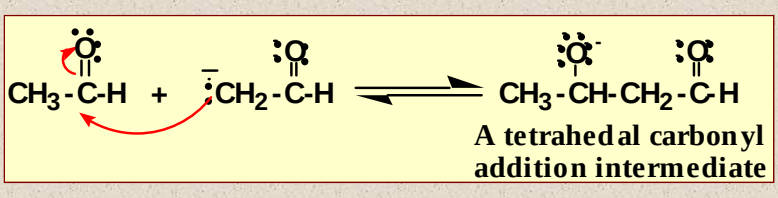
The Aldol Reaction

- **Base-catalyzed aldol reaction**

Step 1: formation of a resonance-stabilized enolate anion



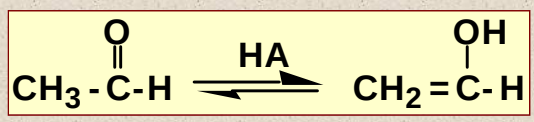
Step 2: carbonyl addition gives a TCAI



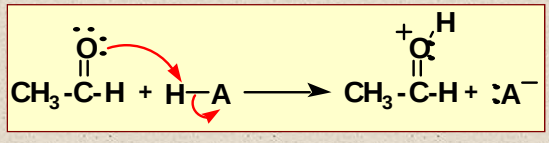
Step 3: proton transfer to O^- completes the aldol reaction

The Aldol Reaction-Acidic

- **Acid-catalyzed aldol reaction**
  - Step 1: acid-catalyzed equilibration of keto and enol forms

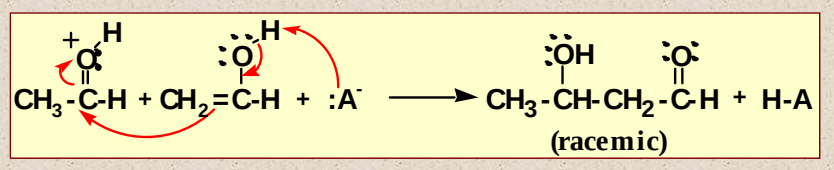


  - Step 2: proton transfer from HA to the carbonyl group of a second molecule of aldehyde or ketone



The Aldol Reaction-acidic

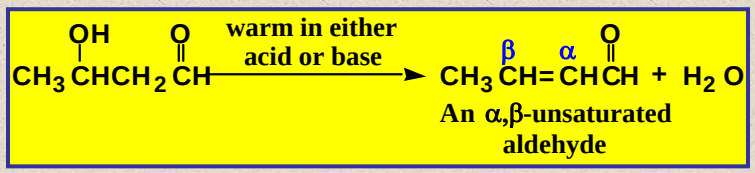
- Step 3: attack of the enol of one molecule on the protonated carbonyl group of another molecule
- Step 4: proton transfer to A^- completes the reaction



(Steps 3 & 4 are combined here)

The Aldol Products-H_2O

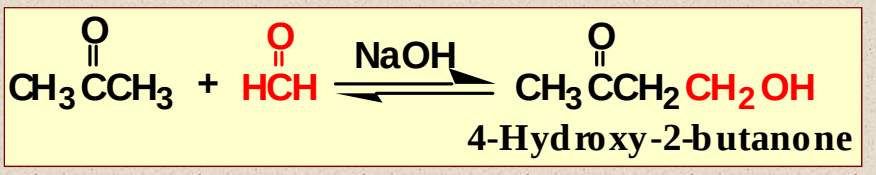
- aldol products are very easily dehydrated to α,β-unsaturated aldehydes or ketones



- aldol reactions are reversible and often little aldol present at equilibrium
- K_{eq} for dehydration is generally large
- if reaction conditions bring about dehydration, good yields of product can be obtained

Crossed Aldol Reaction

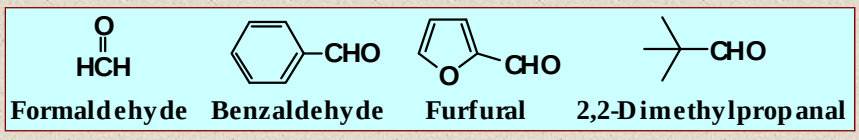
In a crossed aldol reaction, one kind of molecule provides the enolate anion and another kind provides the carbonyl group

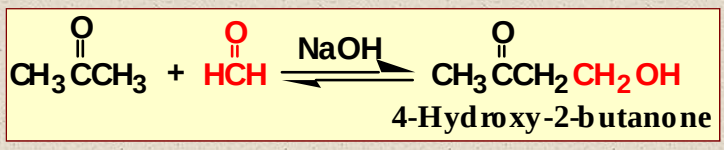


Crossed Aldol Reaction

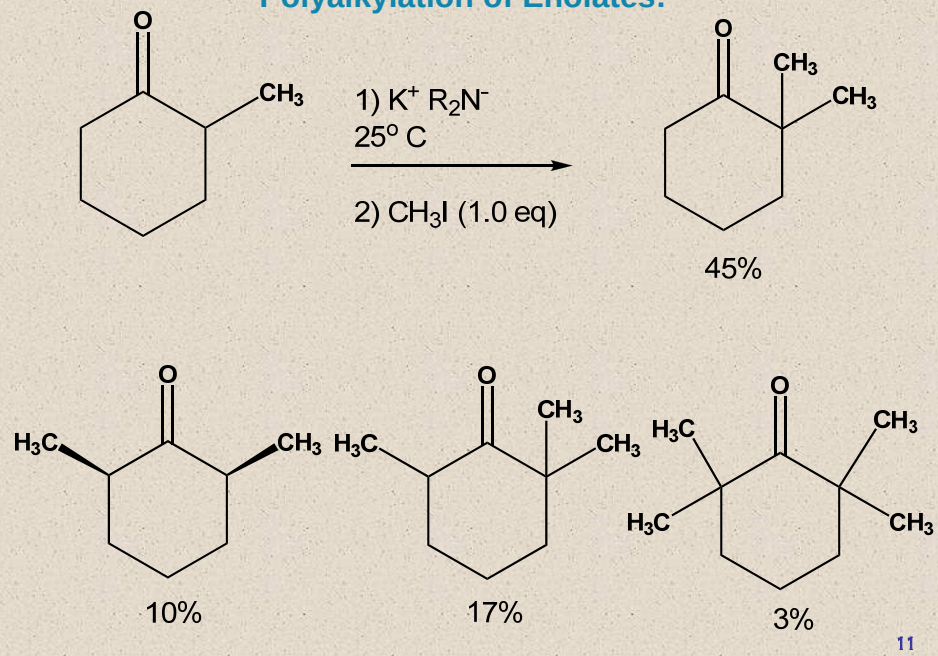
Crossed aldol reactions are successful if:

1. one of the reactants has no α-hydrogen and, therefore, cannot form an enolate anion and
2. the other reactant has a more reactive carbonyl group, namely an aldehyde

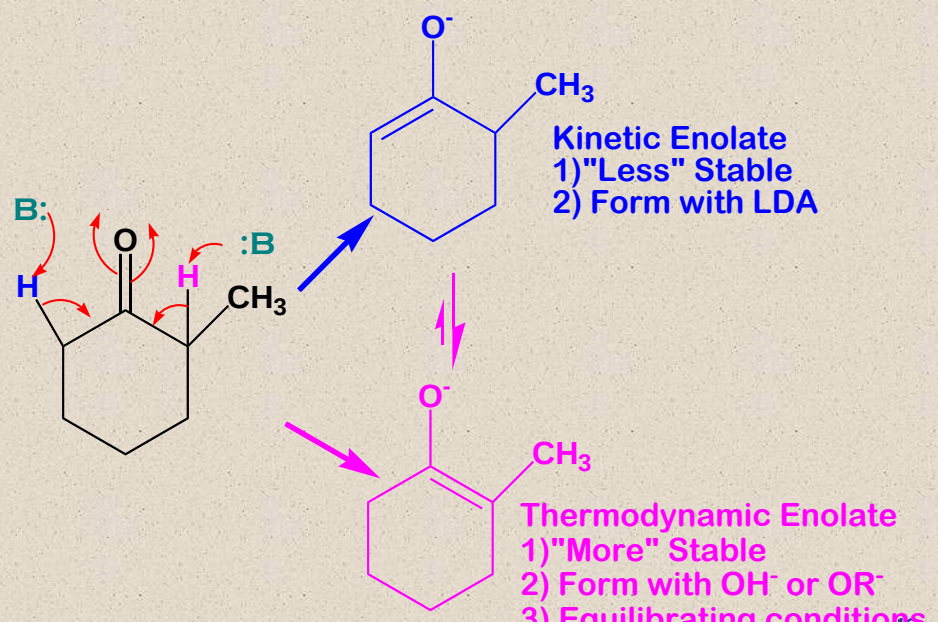




Polyalkylation of Enolates:



KINETIC VS THERMODYNAMIC ENOLATES



Crossed Enolate Reactions using LDA

- With a strong enough base, enolate anion formation can be driven to completion.
- The base most commonly used for this purpose is lithium diisopropylamide, LDA.
- LDA is prepared by dissolving diisopropylamine in THF and treating the solution with butyllithium.

$$[(CH_3)_2CH]_2NH + CH_3(CH_2)_3Li \longrightarrow [(CH_3)_2CH]_2N^-Li^+ + CH_3(CH_2)_2CH_3$$

Diisopropylamine	Butyllithium	Lithium diisopropylamde	Butane
(pK_a 40	(stronger base)	(weaker base)	pK_a 50
(stronger acid)			(weaker acid)

Crossed Enolate Reactions using LDA

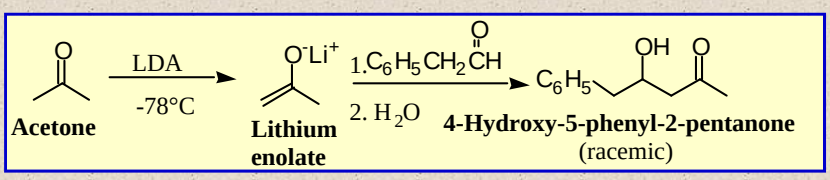
- Using a molar equivalent of LDA converts an aldehyde, ketone, or ester completely to its corresponding enolate anion.

$$CH_3\overset{O}{\overset{\|}{C}}OC_2H_5 + [(CH_3)_2CH]_2N^-Li^+ \longrightarrow CH_2{=}\overset{O^-\ Li^+}{\overset{|}{C}}OC_2H_5 + [(CH_3)_2CH]_2NH$$

Ethyl acetate	Lithium diisopropylamide	Lithium enolate	Diisopropylamine
pK_a 23	(stronger base)	(weaker base)	pK_a40
(stronger acid)			(weaker acid)

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 preform its enolate anion:



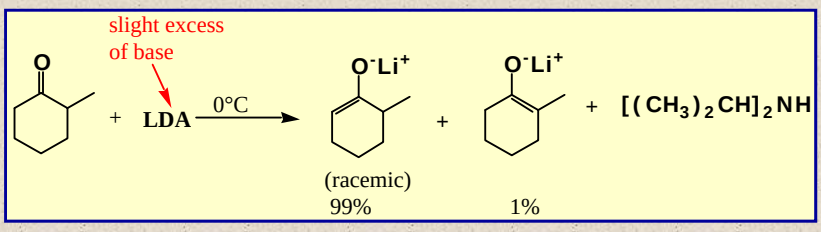
- which is then treated with the aldehyde.

Crossed Enolate Reactions using LDA

- For ketones with two sets of nonequivalent α-hydrogens, is formation of the enolate anion regioselective?
  - The answer is that a high degree of regioselectivity exists and that it depends on experimental conditions.

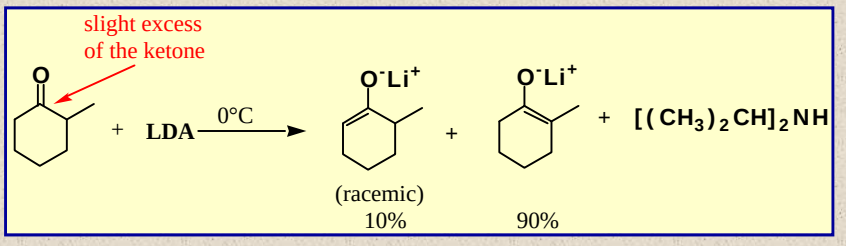
Crossed Enolate Reactions using LDA

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



Crossed Enolate Reactions using LDA

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

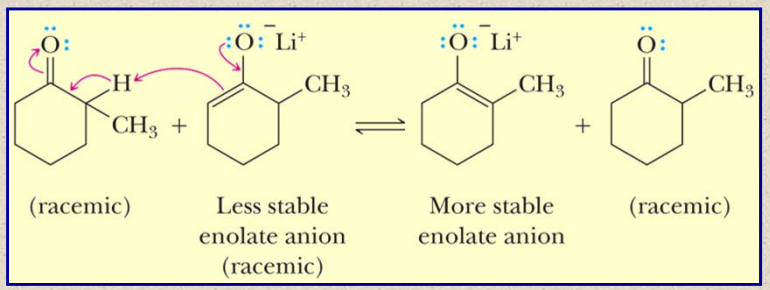


Crossed Enolate Reactions using LDA

- The most important factor determining the composition of the enolate anion mixture is whether the reaction is under kinetic (rate) or thermodynamic (equilibrium) control.
- **Thermodynamic Control**: Experimental conditions that permit establishment of equilibrium between two or more products of a reaction. The composition of the mixture is determined by the relative stabilities of the products.

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 anion and an α-hydrogen of an unreacted ketone. Thus, equilibrium is established between alternative enolate anions.



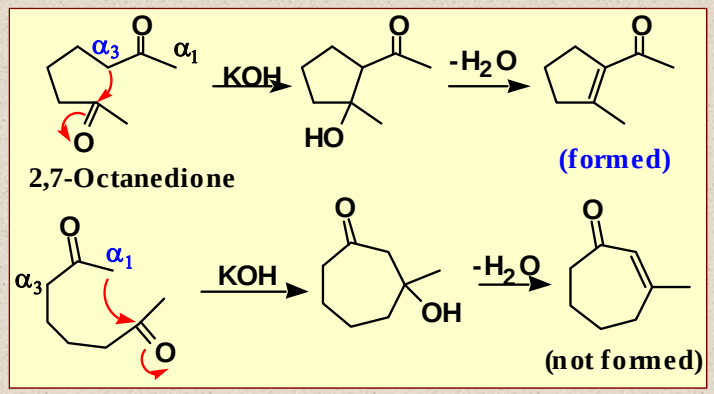
Crossed Enolate Reactions using LDA

- **Kinetic control:** Experimental conditions under which the composition of the product mixture is determined by the relative rates of formation of each product.
  - In the case of enolate anion formation, kinetic control refers to the relative rate of removal of alternative α-hydrogens.
  - With the use of a bulky base, the less hindered hydrogen is removed more rapidly, and the major product is the less substituted enolate anion.
  - No equilibrium among alternative structures is set up.

Intramolecular Aldol Reactions

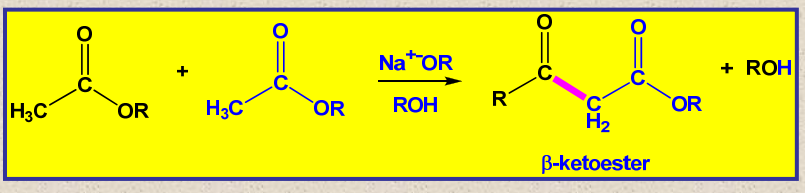
intramolecular aldol reactions are most successful for formation of five- and six-membered rings

consider 2,7-octadione, which has two α-carbons

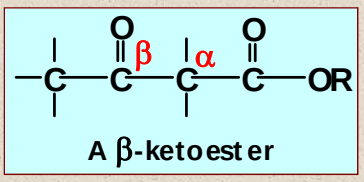


Claisen Condensation

- Esters also form enolate anions which participate in nucleophilic acyl substitution

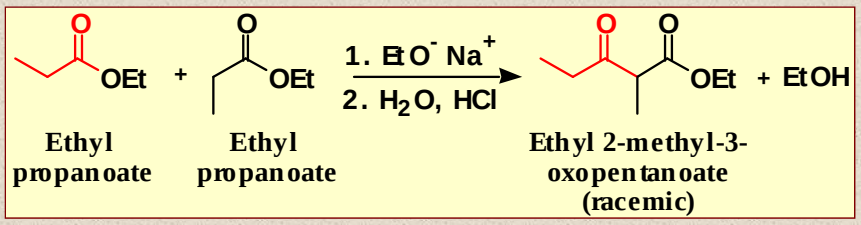


the product of a Claisen condensation is a β-ketoester:



Claisen Condensation

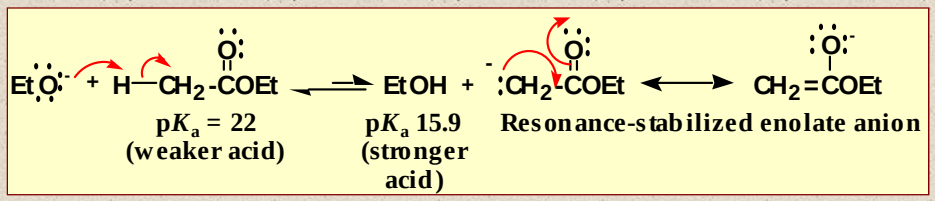
– Claisen condensation of ethyl propanoate gives this β-ketoester



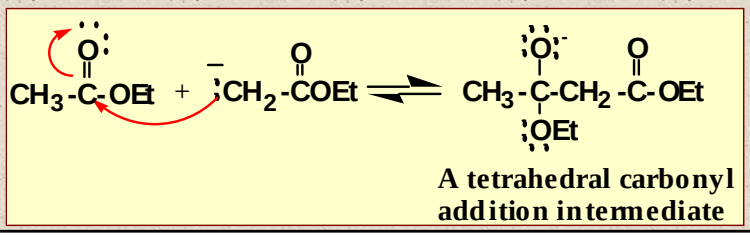
Nota bene: the base should be the alkoxide of the ester group (This will overcome trans-esterification.)

Claisen Condensation

Step 1: formation of an enolate anion

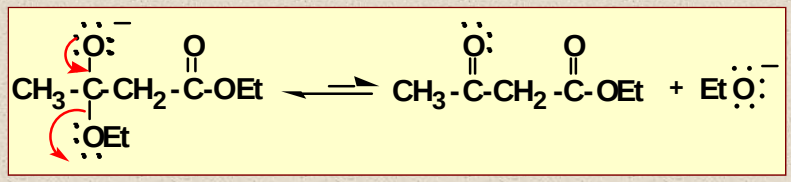


Step 2: attack of the enolate anion on a carbonyl carbon gives a TCAI

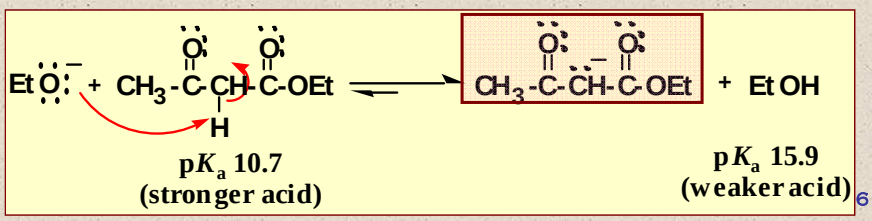


Claisen Condensation

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



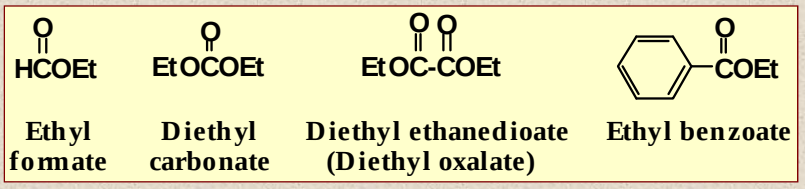
Step 4: an acid-base reaction drives the reaction to completion:



Crossed Claisen Condensations

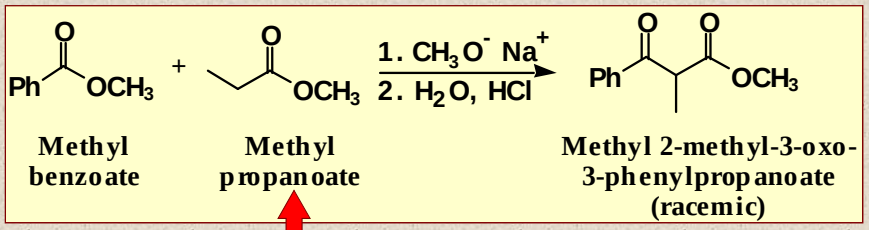
Crossed Claisen condensations between two different esters, each with α-hydrogens, give mixtures of products and are not useful

- crossed Claisen condensations are useful, if there is an appreciable difference in reactivity between the two esters; when one of them has no α-hydrogens



Crossed Claisen Condensations

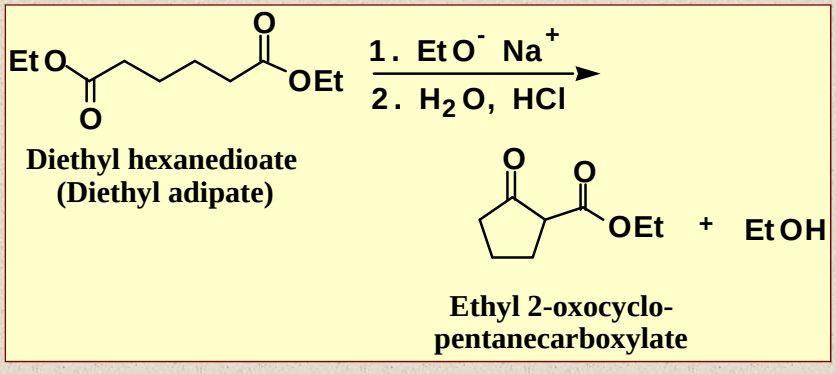
- the ester with no α-hydrogens is generally used in excess



Only this enolate can be formed

Dieckman Condensation

- An intramolecular Claisen condensation



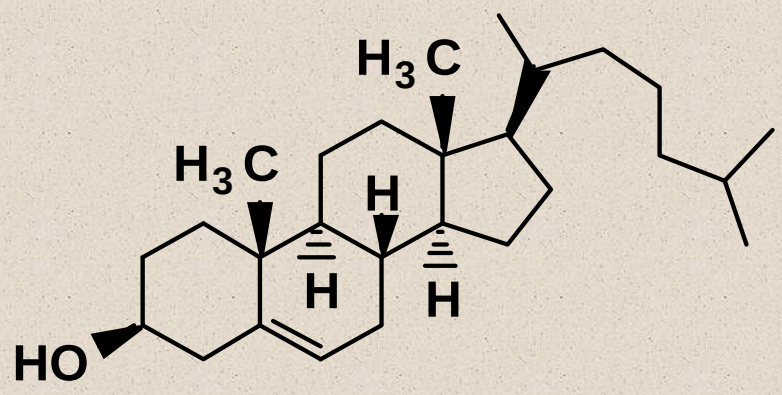
Diethyl hexanedioate (Diethyl adipate)

Ethyl 2-oxocyclo-pentanecarboxylate

Carbonyl Condensations in Biochemistry

- Carbonyl condensations are among the most widely used reactions in the biological world for the formation of new carbon-carbon bonds in such biomolecules as:
  - fatty acids.
  - cholesterol, bile acids, and steroid hormones.
  - terpenes.
- One source of carbon atoms for the synthesis of these biomolecules is acetyl coenzyme A (acetyl-CoA). Coenzyme A is a carrier of the two-carbon acetyl group, CH_3-CO-

Cholesterol



More details in Chap. 26

Biosynthesis of Steroids

The building block from which all carbon atoms of steroids are derived is the two carbon acetyl group of acetyl-CoA-

Stage 1: synthesis of isopentenyl pyrophosphate from three molecules of acetyl-CoA

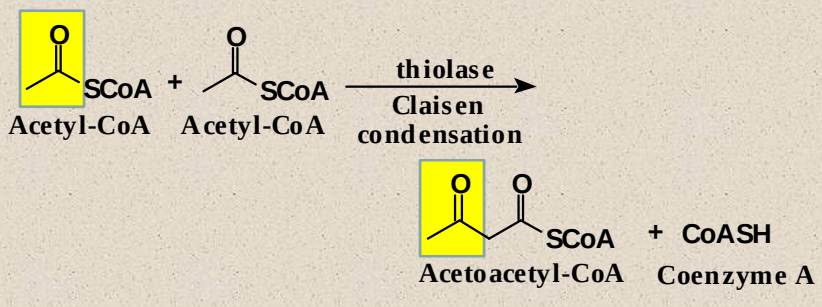
Stage 2: synthesis of cholesterol

Stage 3: conversion of cholesterol to other steroids

cholesterol →
- **bile acids (e.g., cholic acid)**
- **sex hormones (e.g., testosterone and estrone)**
- **mineralocorticoid hormones (e.g., aldosterone)**
- **glucocorticoid hormones (e.g., cortisone)**

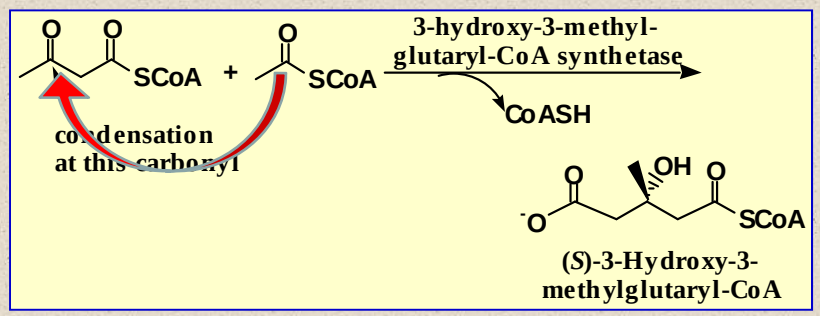
Acetyl-CoA in Biochemistry

– Claisen condensation of acetyl-CoA is catalyzed by the enzyme thiolase.



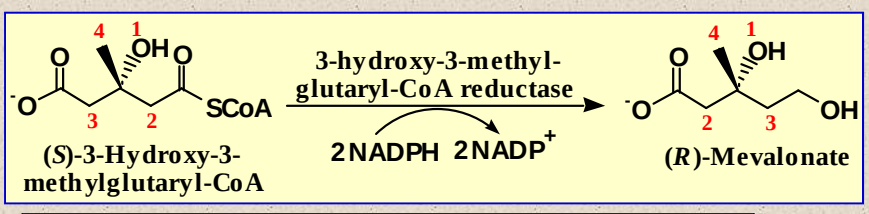
Acetyl-CoA in Biochemistry

– This is followed by an aldol reaction with a second molecule of acetyl-CoA. Note that this reaction is stereoselective and gives only the S enantiomer.

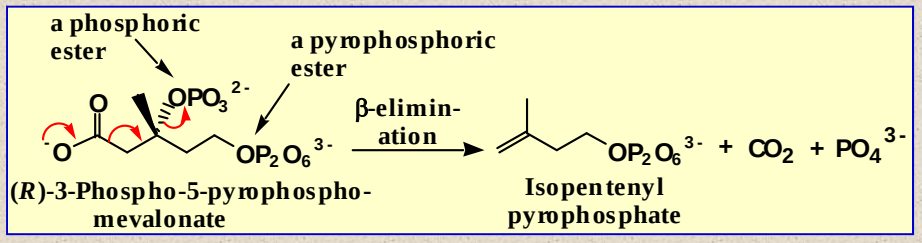


Acetyl-CoA in Biochemistry

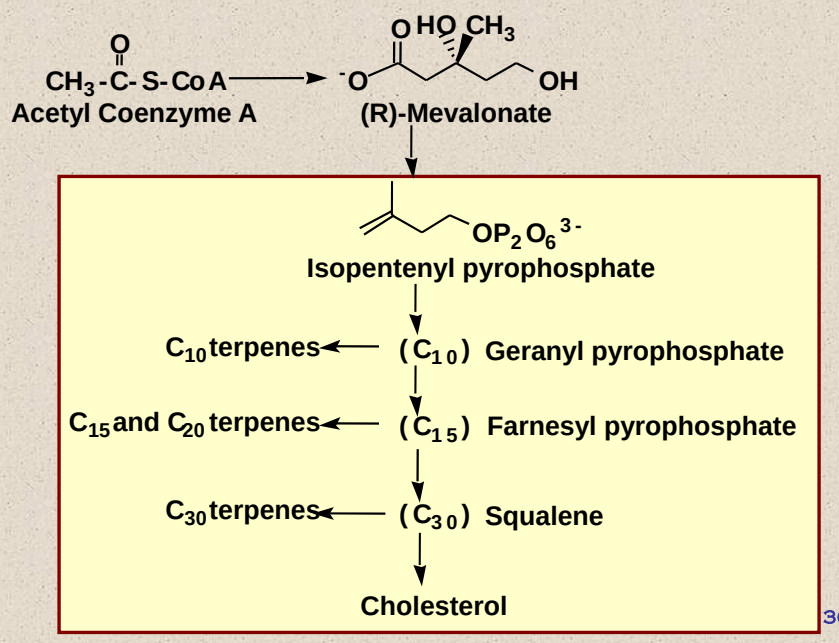
– Enzyme-catalyzed reduction by NADPH of the thioester group.



Phosphorylation by ATP followed by β-elimination.

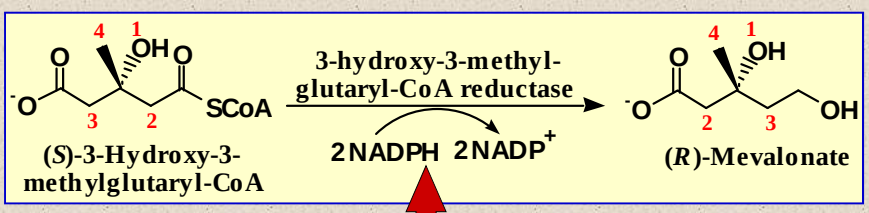


Biosynthesis of Cholesterol

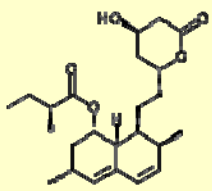


Acetyl-CoA in Biochemistry

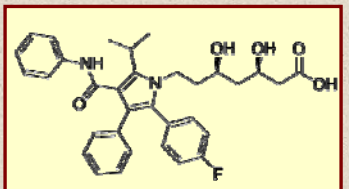
– Enzyme-catalyzed reduction by NADPH of the thioester group.



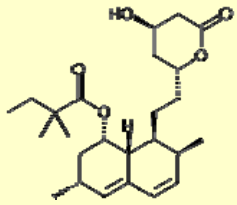
The "Statin" drugs inhibit HMGCoA Reductase and exert their action in this step



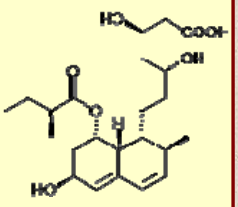
Lovastatin
Mevacor



Atorvastatin
Lipitor



Simvastatin
Zocor

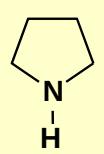


Pravastatin
Pravacol

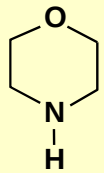
Enamines

Enamines are formed by the reaction of a **2° amine with the carbonyl group of an aldehyde or ketone**

the 2° amines most commonly used to prepare enamines are pyrrolidine and morpholine:

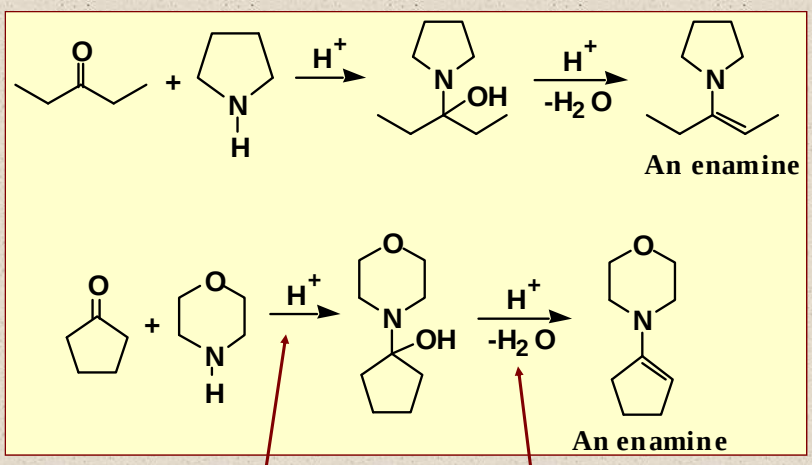


Pyrrolidine



M orpholine

Preparation of Enamines



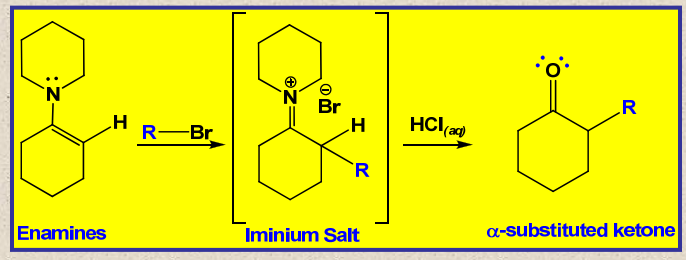
Acid catalyst is usually TsOH; azeotropic removal of H_2O.

See Chapter 16 for details

Enamines-Alkylation

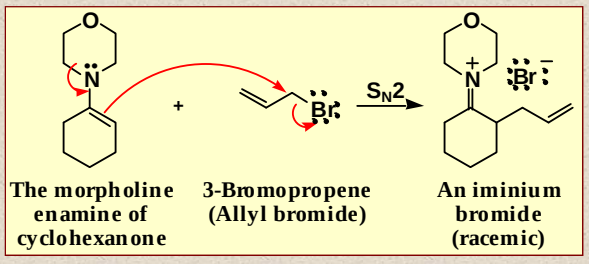
The value of enamines is that the β-carbon is nucleophilic (**same C that was α to carbonyl**)

– enamines undergo S_N2 reactions with methyl and 1° haloalkanes, α-haloketones, and α-haloesters

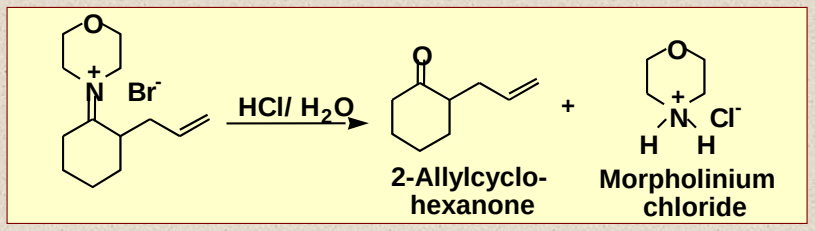


Enamines-Alkylation

treatment of the enamine with 1 eq of an alkylating agent gives an iminium halide:

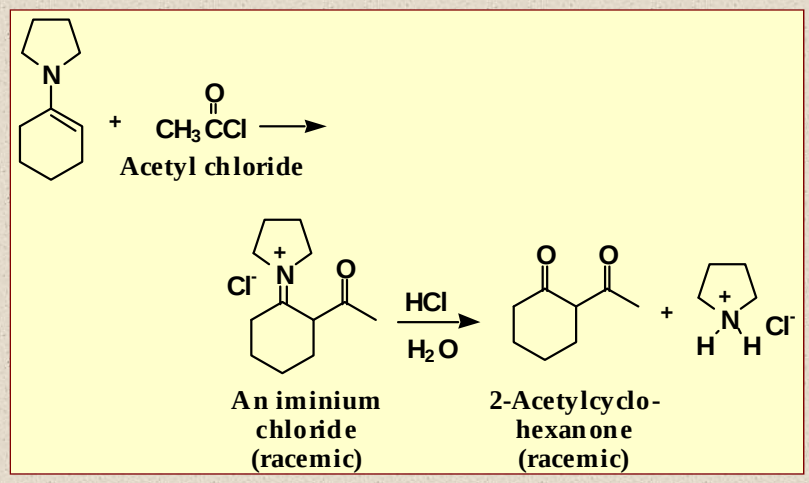


hydrolysis of the iminium halide (salt) gives the alkylated aldehyde or ketone:



Enamines-Acylation

enamines undergo acylation when treated with acid chlorides and acid anhydrides



Synthetic Advantages of Enamines vs Enolates

1) Avoids proton transfer.

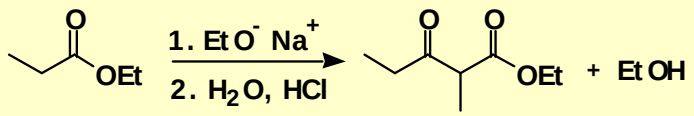
2) Regiochemistry of alkylation can be controlled. (For un-symmetric ketones)

3) Avoids polyalkylation.

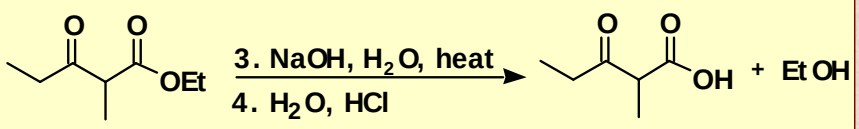
4) Avoids O-alkylation.

Claisen condensations as routes to ketones

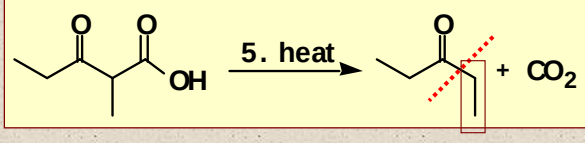
Reactions 1 & 2: Claisen condensation followed by acidification



Reactions 3 & 4: Saponification and acidification



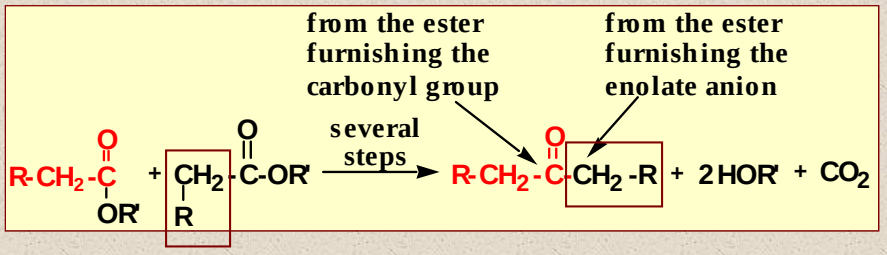
Reaction 5: thermal decarboxylation



This segment was added

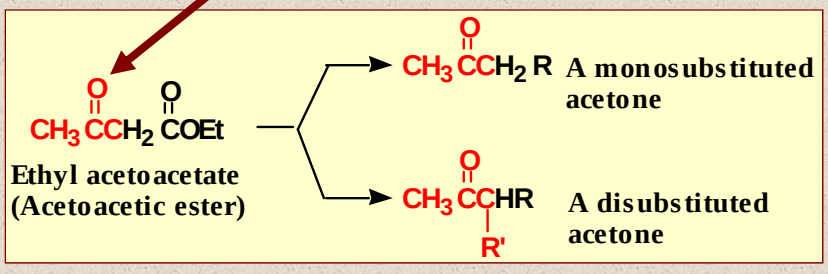
Claisen condensations as routes to ketones

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



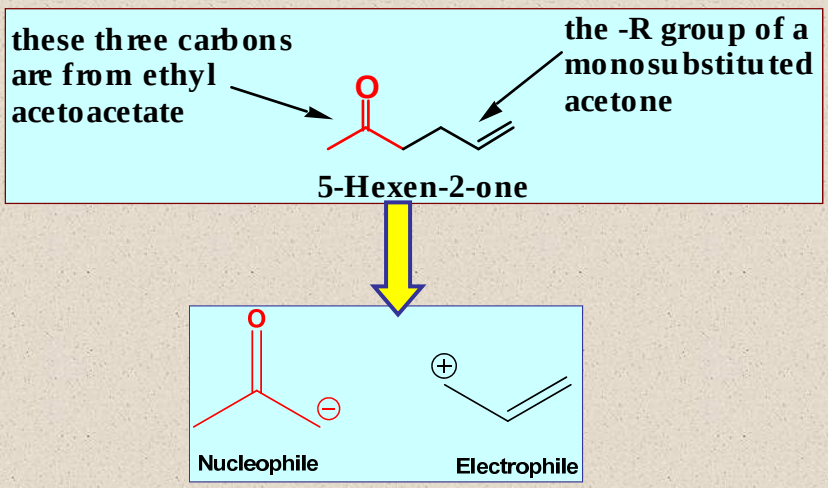
Acetoacetic Ester Synthesis

The acetoacetic ester (AAE) synthesis is useful for the preparation of mono- and disubstituted acetones of the following types



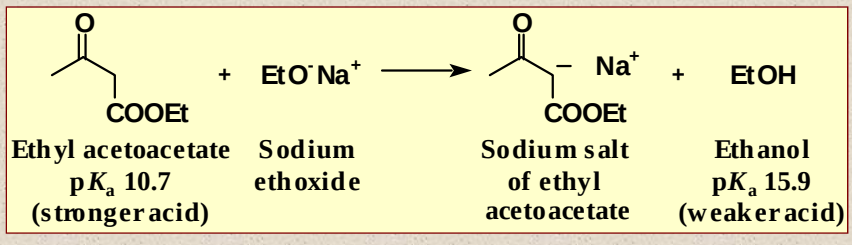
Acetoacetic Ester Synthesis

– consider the AAE synthesis of this target molecule, which is a monosubstituted acetone

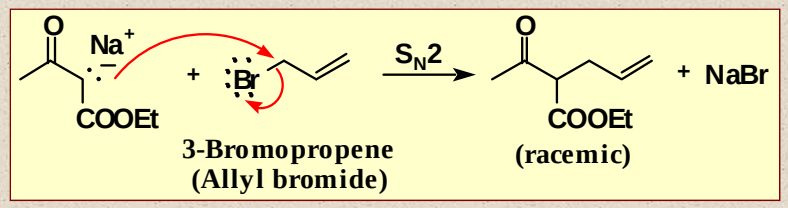


Acetoacetic Ester Synthesis

– Step 1: formation of the enolate anion of AAE

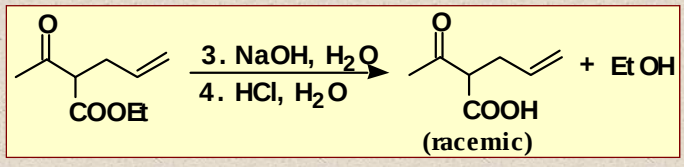


– Step 2: alkylation with allyl bromide

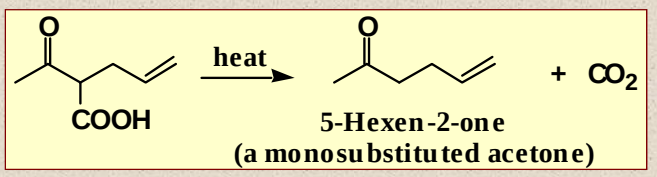


Acetoacetic Ester Synthesis

– Steps 3 & 4 saponification followed by acidification

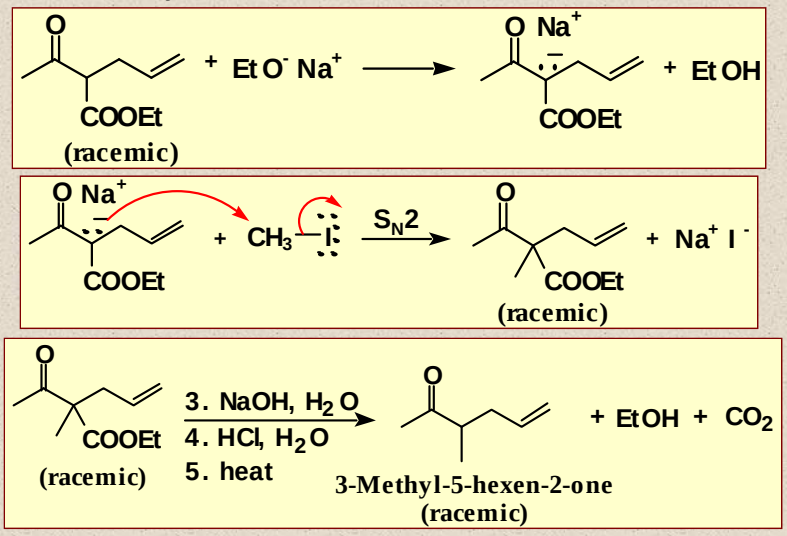


– Step 5: thermal decarboxylation



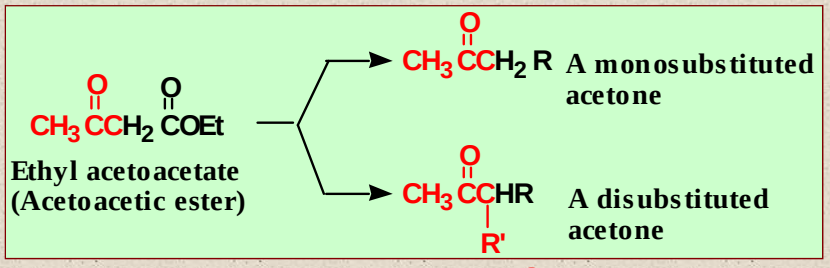
Acetoacetic Ester Synthesis

– to prepare a **disubstituted acetone**, treat the monoalkylated AAE with a second mole of base, etc

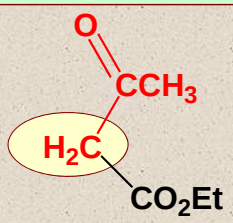


Acetoacetic Ester Synthesis

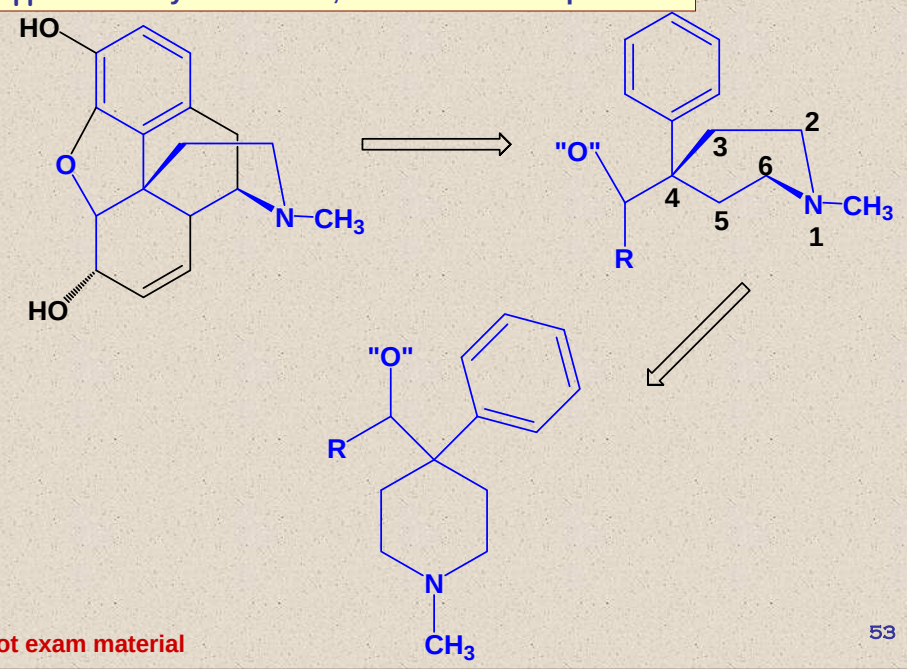
The acetoacetic ester (AAE) synthesis is useful for the preparation of mono- and disubstituted acetones of the following types



These types of reactions involve active (i.e. acidic) methylene units as the nucleophilic component.

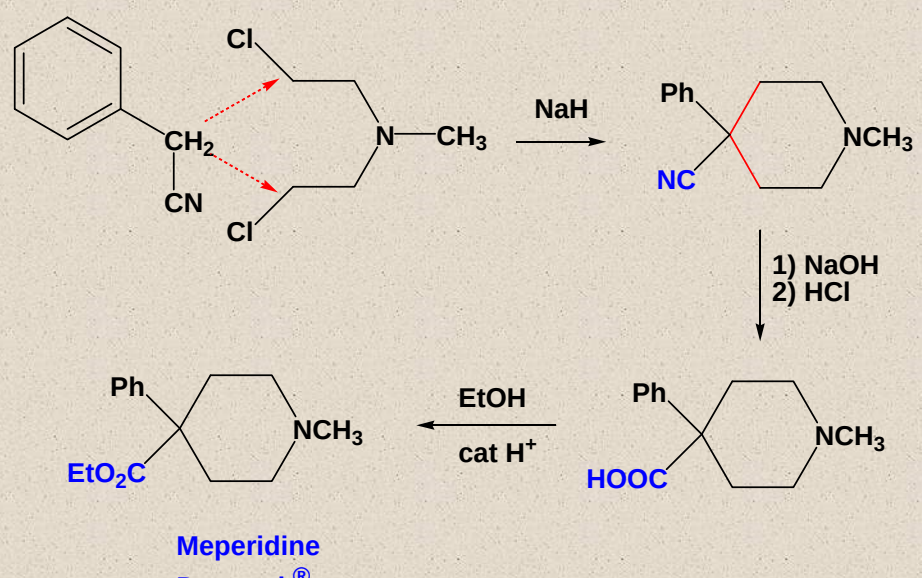


Application: Synthesis of 4,4-Disubstituted Piperidines



Not exam material

Application: Synthesis of 4,4-Disubstituted Piperidines



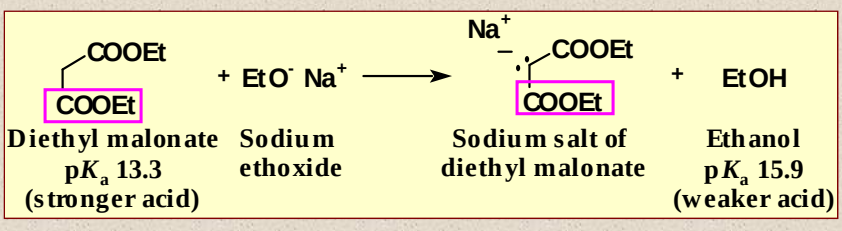
Meperidine

Demerol ®

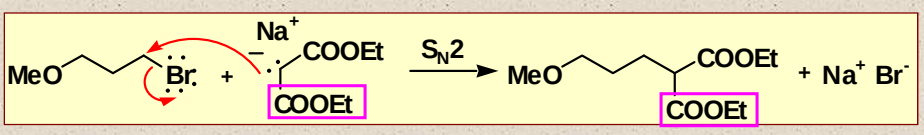
Not exam material

Malonic Ester Synthesis

– treat malonic ester with an alkali metal alkoxide

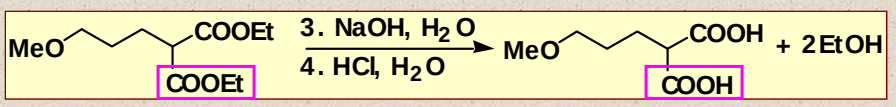


– alkylate with 1-bromo-3-methoxy propane

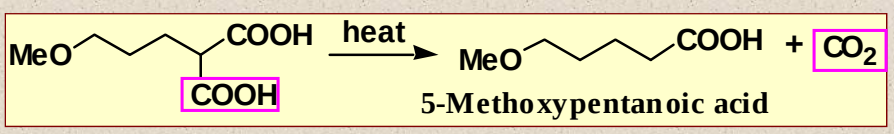


Malonic Ester Synthesis

– saponify and acidify



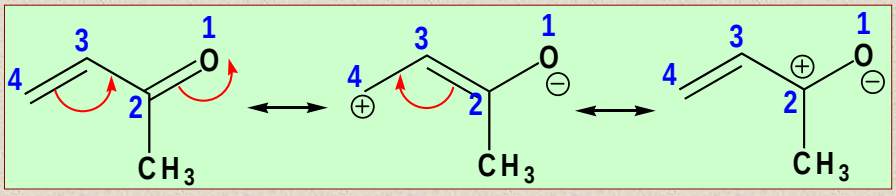
– decarboxylation

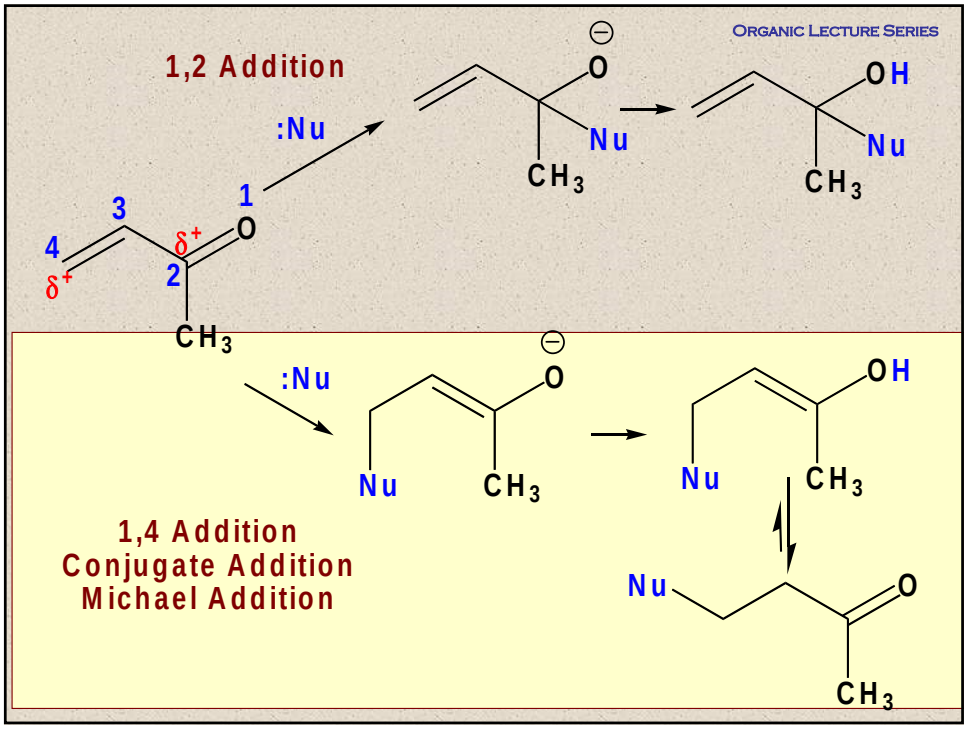


Addition to α,β-unsaturated Carbonyls

When the carbonyl group is conjugated with an alkene, the two groups can act in tandem to expand synthetic utility.

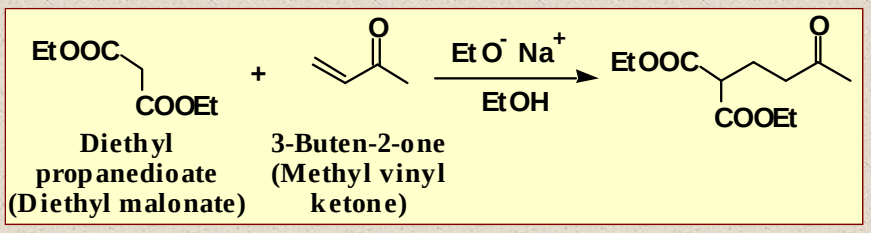
α,β-unsaturated carbonyl compounds can exhibit properties of both the carbonyl and alkene group:



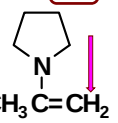


Michael Reaction

- Michael reaction: the nucleophilic addition of an enolate anion to an α,β-unsaturated carbonyl compound (1,4 addition)
  - Example:

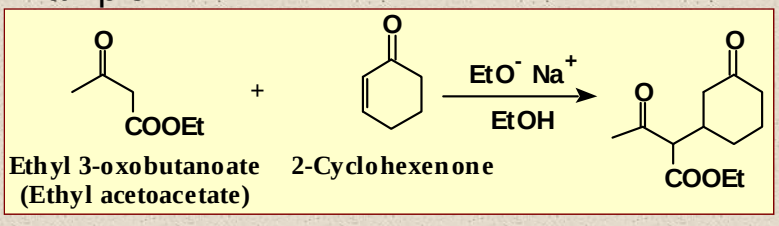


Michael Acceptors & Nucleophiles

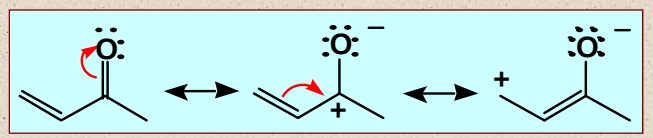
These Types of α,β-Unsaturated Compounds are Nucleophile Acceptors in Michael Reactions		These Types of Compounds Provide Effective Nucleophiles for Michael Reactions	
$CH_2{=}CH{-}C(=O)H$	Aldehyde	$CH_3C(=O)CH_2C(=O)CH_3$	β-Diketone
$CH_2{=}CH{-}C(=O)CH_3$	Ketone	$CH_3C(=O)CH_2C(=O)OEt$	β-Ketoester
$CH_2{=}CH{-}C(=O)OEt$	Ester	$CH_3C(=O)CH_2CN$	β-Ketonitrile
$CH_2{=}CH{-}C(=O)NH_2$	Amide	$EtOC(=O)CH_2C(=O)OEt$	β-Diester
$CH_2{=}CH{-}C{\equiv}N$	Nitrile		Enamine
$CH_2{=}CHNO_2$	Nitro compound		
		NH_3, RNH_2, R_2NH	Amine

Michael Reaction

Example:



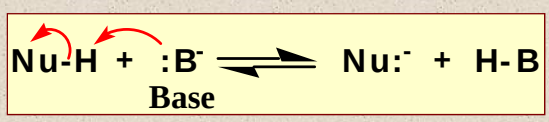
– the double bond of an α,β-unsaturated carbonyl compound is activated for nucleophilic attack:



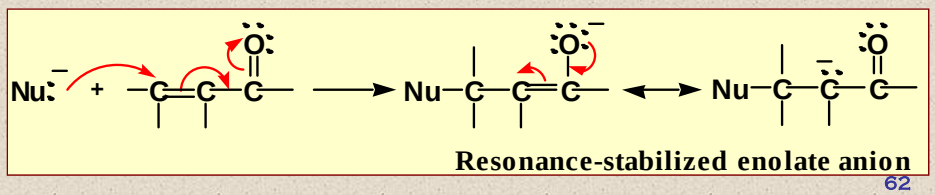
Michael Reaction

- Mechanism

Step 1: proton transfer to the base

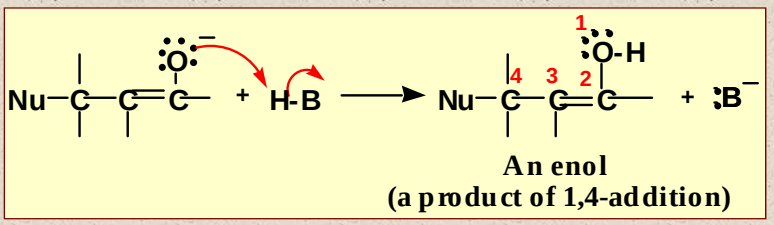


Step 2: addition of Nu:⁻ to the β carbon of the α,β-unsaturated carbonyl compound



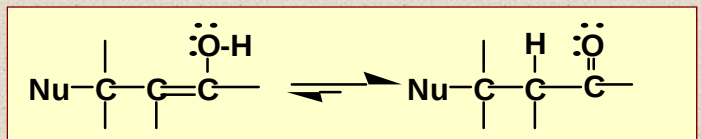
Michael Reaction

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



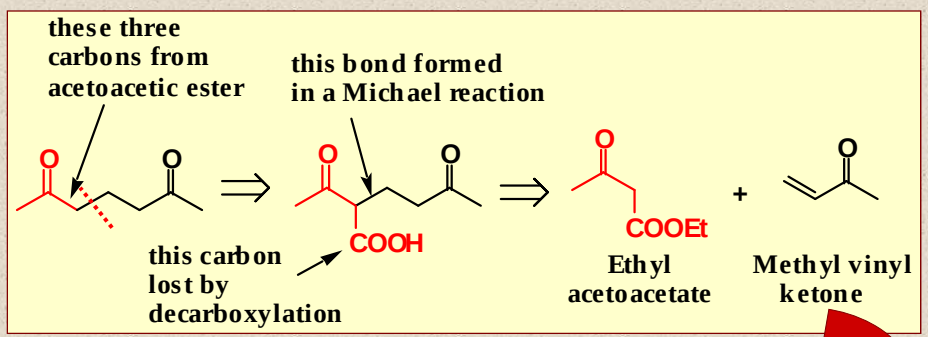
Less stable enol form More stable keto form

Michael Reaction

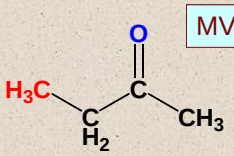
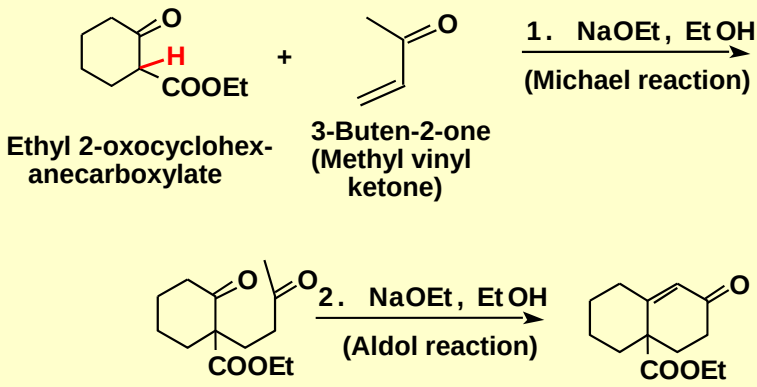
A final note about nucleophilic addition to α,β-unsaturated carbonyl compounds:

- resonance-stabilized enolate anions and enamines are **weak nucleophiles**,
- react slowly with α,β-unsaturated carbonyl compounds
- give 1,4-addition products

Retrosynthesis of 2,6-Heptadione



MVK is the reagent to add a 2-oxobutyl side chain



Michael-Aldol in Combination: The Robinson Ring Annulation