

Textbook Assignment: Chapter 19

Homework (for credit): POW 9 posted

Today's Topics: Enolates-Enamines-Ring Anulations

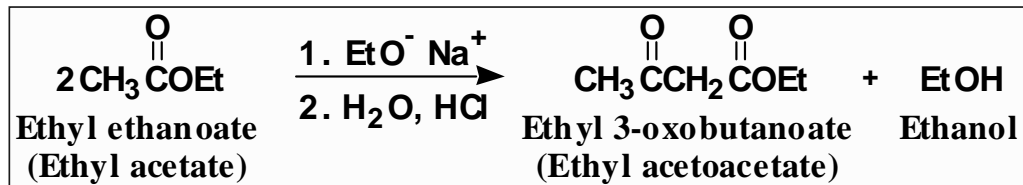
Notice & Announcements:

ORGANIC LECTURE SERIES

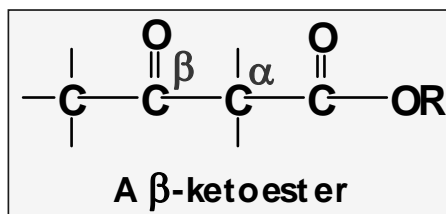
Enolate Anions and Enamines

Claisen Condensation

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



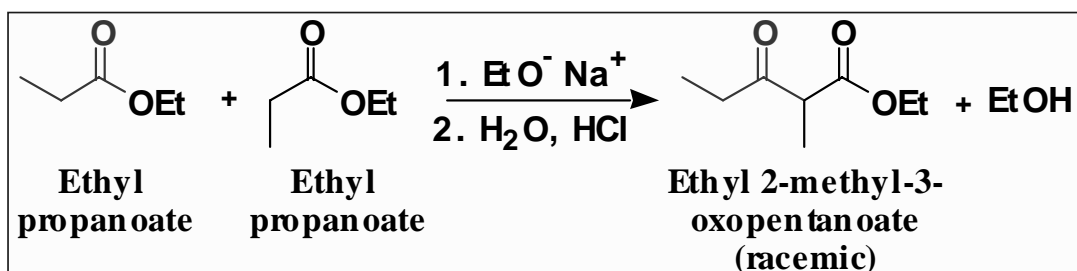
the product of a Claisen condensation is a β -ketoester



3

Claisen Condensation

– Claisen condensation of ethyl propanoate gives this β -ketoester

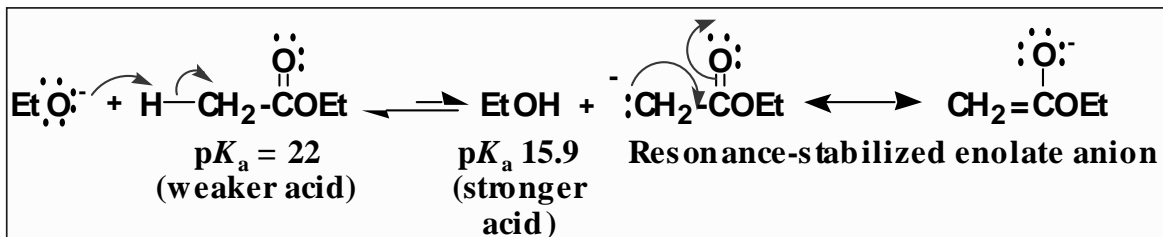


Nota bene: the base should be the alkoxide of the ester group
(This will overcome trans-esterification.)

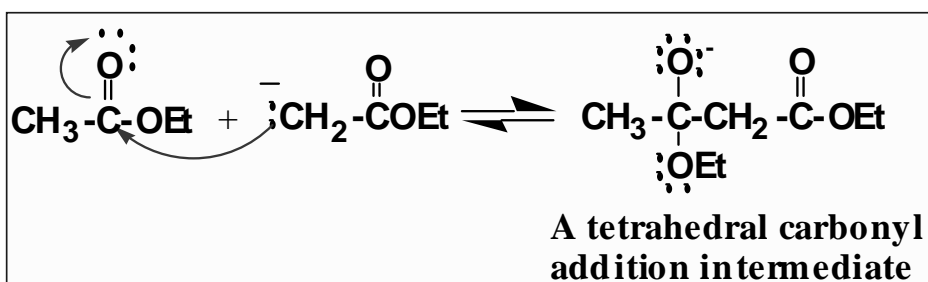
4

Claisen Condensation

Step 1: formation of an enolate anion



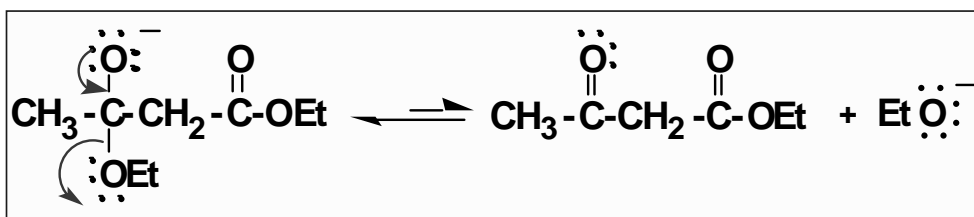
Step 2: attack of the enolate anion on a carbonyl carbon gives a TCAI



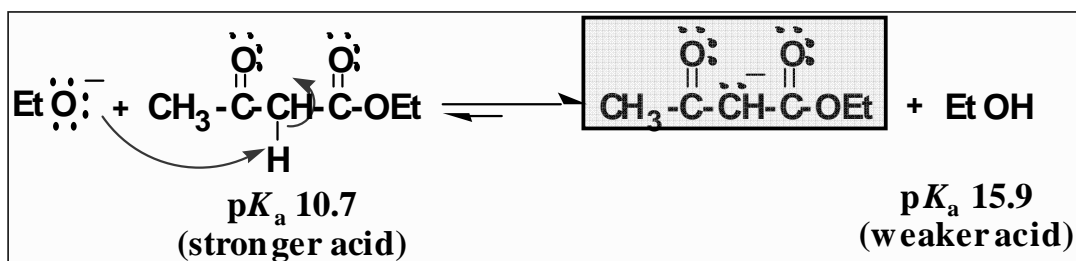
5

Claisen Condensation

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

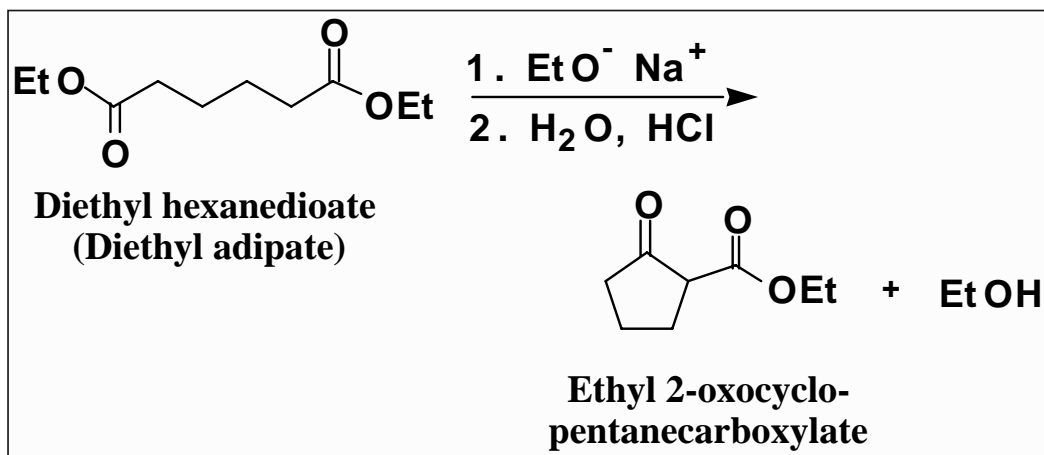


Step 4: an acid-base reaction drives the reaction to completion:



Dieckman Condensation

- An intramolecular Claisen condensation

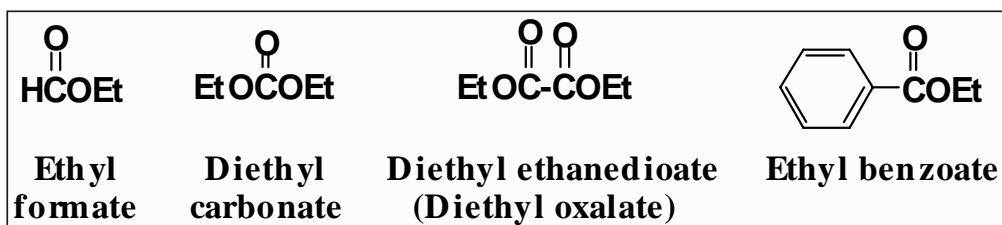


7

Crossed Claisen Condensations

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

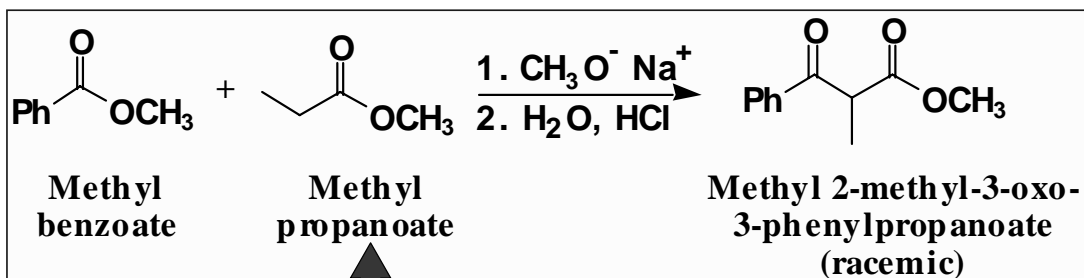
- crossed Claisen condensations are useful, if there is an appreciable difference in reactivity between the two esters; when one of them has no α -hydrogens



8

Crossed Claisen Condensations

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

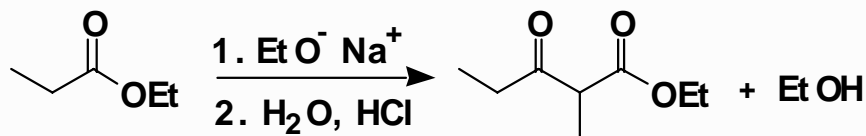


Only this enolate can be formed

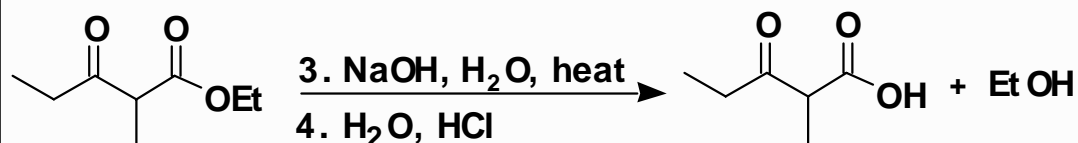
9

Claisen condensations as routes to ketones

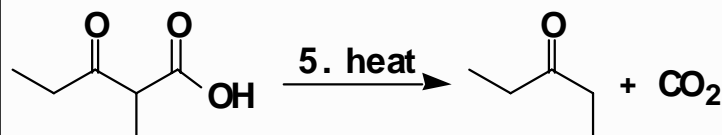
Reactions 1 & 2: Claisen condensation followed by acidification



Reactions 3 & 4: Saponification and acidification



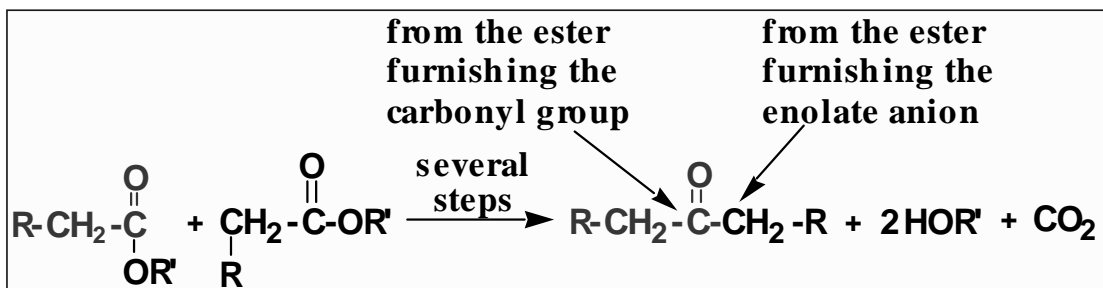
Reaction 5: thermal decarboxylation



10

Claisen Condensations

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

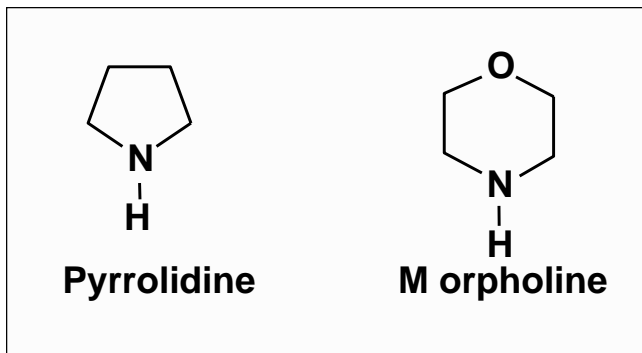


11

Enamines

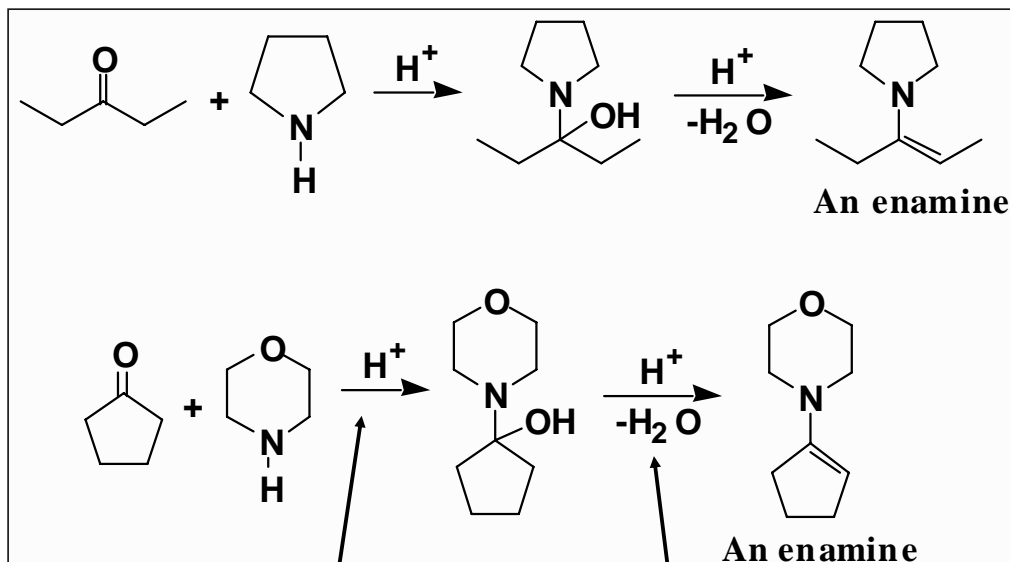
Enamines are formed by the reaction of a **2° amine with the carbonyl group of an aldehyde or ketone**

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



12

Preparation of Enamines



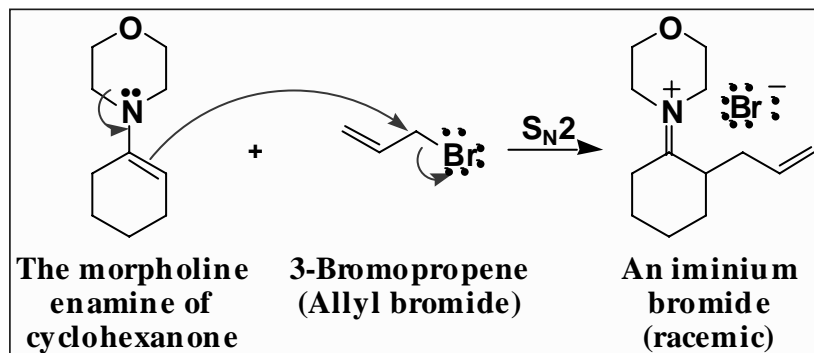
Acid catalyst is usually TsOH; azeotropic removal of H₂O.

13

Enamines-Alkylation

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

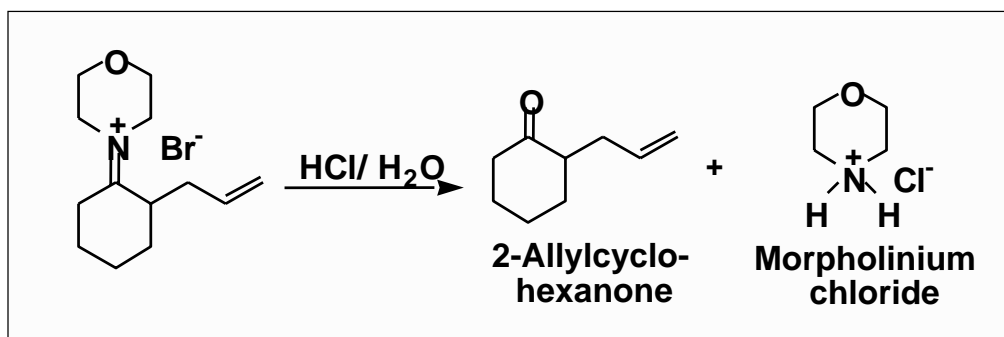
- enamines undergo S_N2 reactions with methyl and 1° haloalkanes, α -haloketones, and α -haloesters
- treatment of the enamine with one equivalent of an alkylating agent gives an iminium halide



14

Enamines-Alkylation

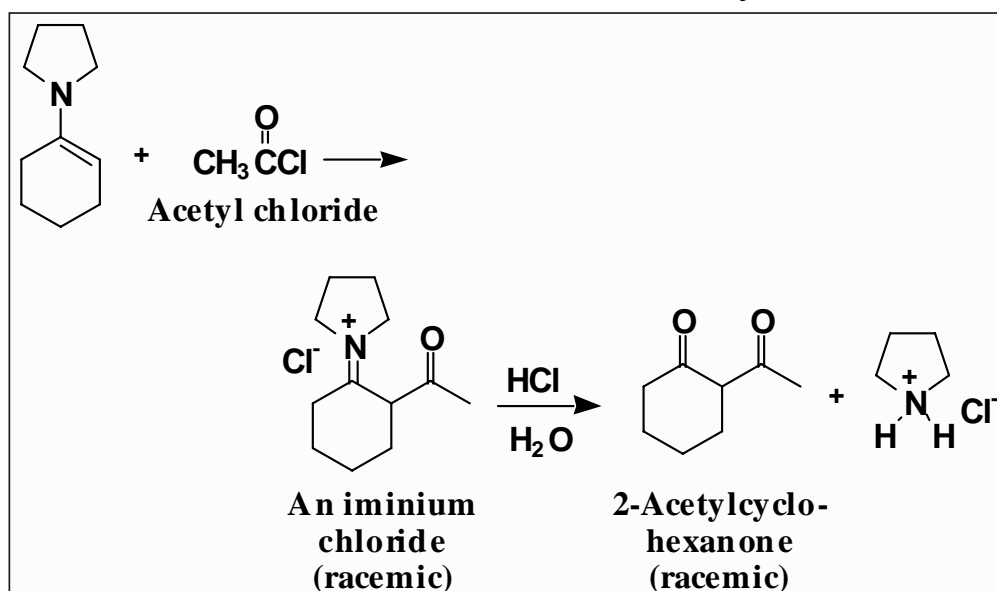
hydrolysis of the iminium halide (salt) gives the alkylated aldehyde or ketone:



15

Enamines-Acylation

enamines undergo acylation when treated with acid chlorides and acid anhydrides



16

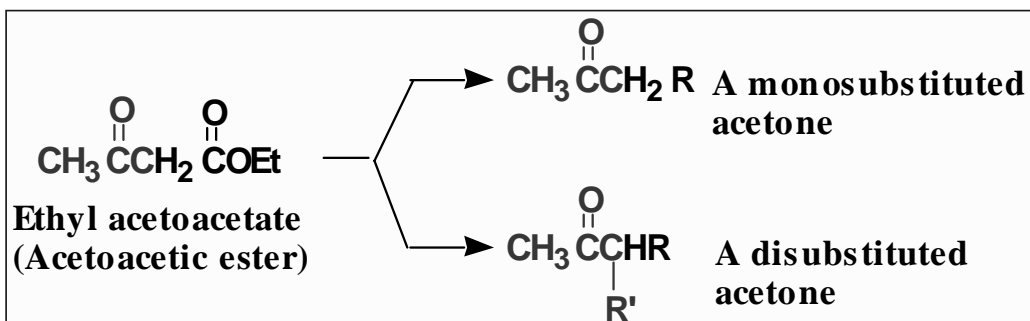
Synthetic Advantages of Enamines vs Enolates

- 1) Avoids proton transfer.
- 2) Regiochemistry of alkylation can be controlled. (For un-symmetric ketones)
- 3) Avoids polyalkylation.
- 4) Avoids O-alkylation.

17

Acetoacetic Ester Synthesis

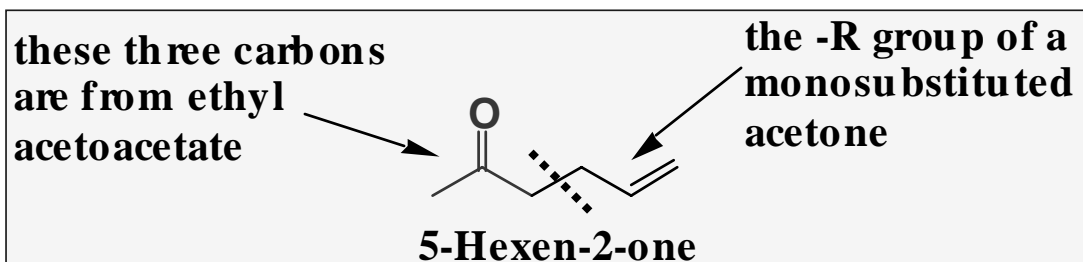
The acetoacetic ester (AAE) synthesis is useful for the preparation of mono- and disubstituted acetones of the following types



18

Acetoacetic Ester Synthesis

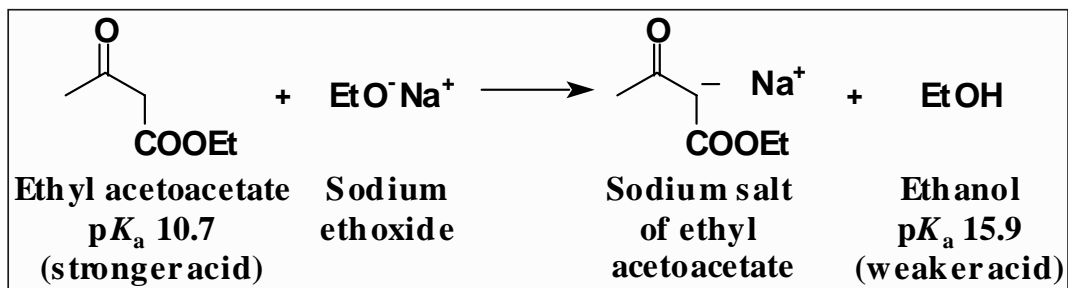
- consider the AAE synthesis of this target molecule, which is a monosubstituted acetone



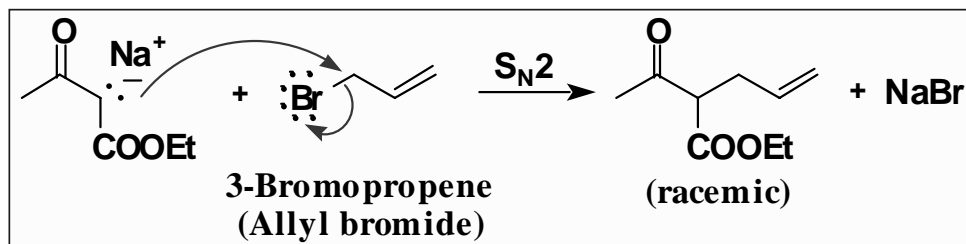
19

Acetoacetic Ester Synthesis

- Step 1: formation of the enolate anion of AAE



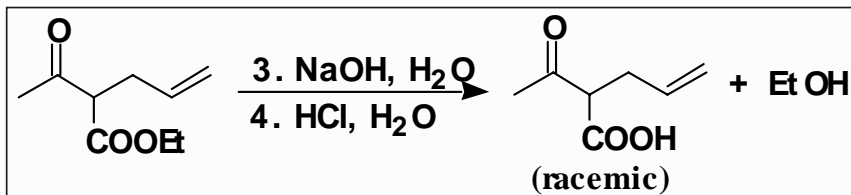
- Step 2: alkylation with allyl bromide



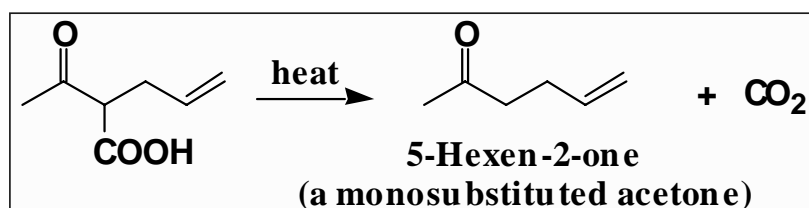
20

Acetoacetic Ester Synthesis

- Steps 3 & 4 saponification followed by acidification



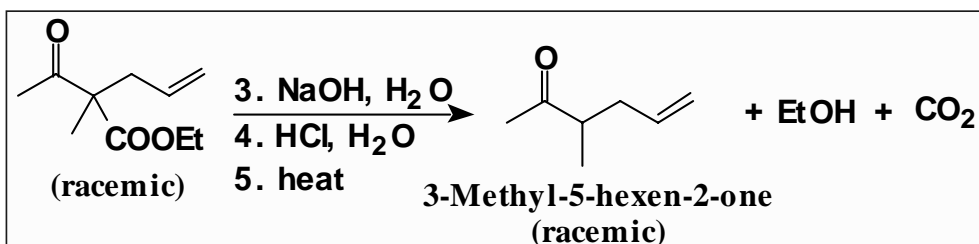
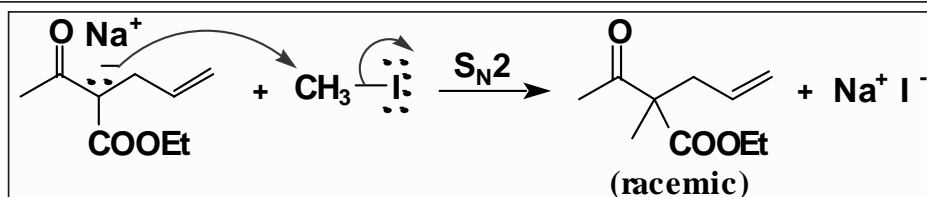
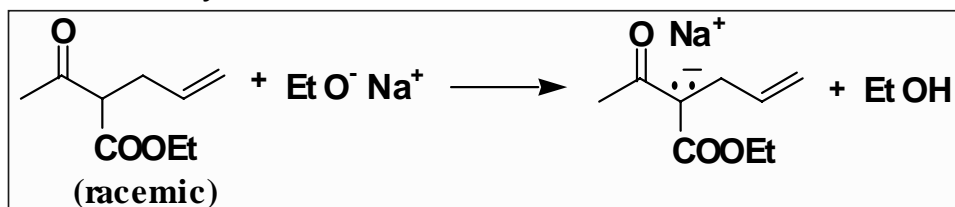
- Step 5: thermal decarboxylation



21

Acetoacetic Ester Synthesis

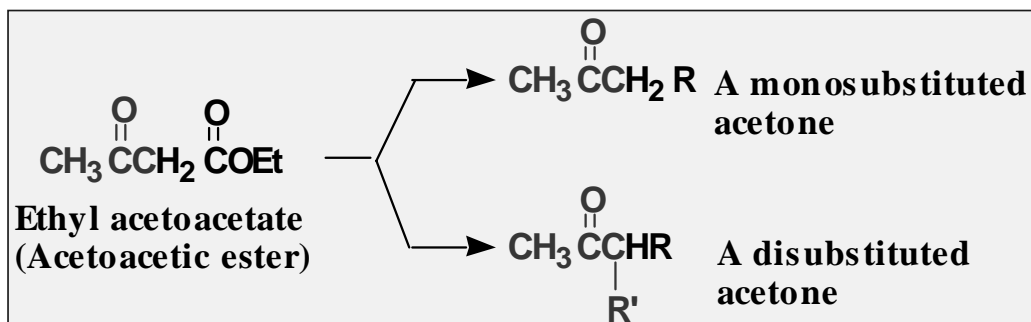
- to prepare a **disubstituted acetone**, treat the monoalkylated AAE with a second mole of base, etc



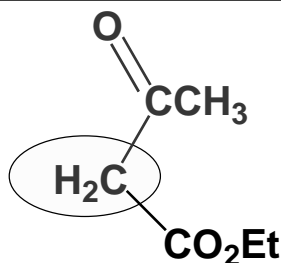
22

Acetoacetic Ester Synthesis

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



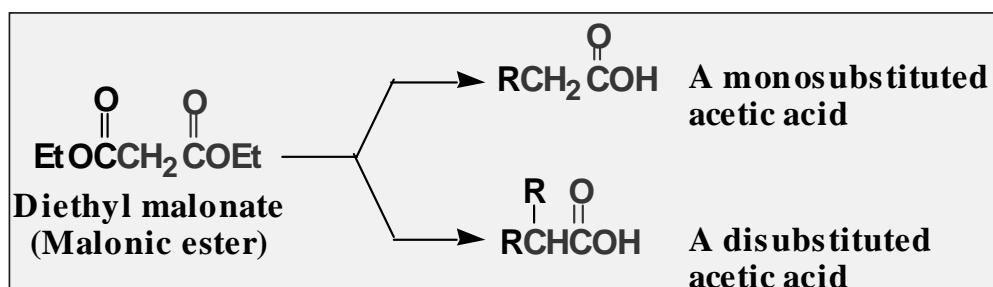
These types of reactions involve active (i.e. acidic) methylene units as the nucleophilic component.



23

Malonic Ester Synthesis

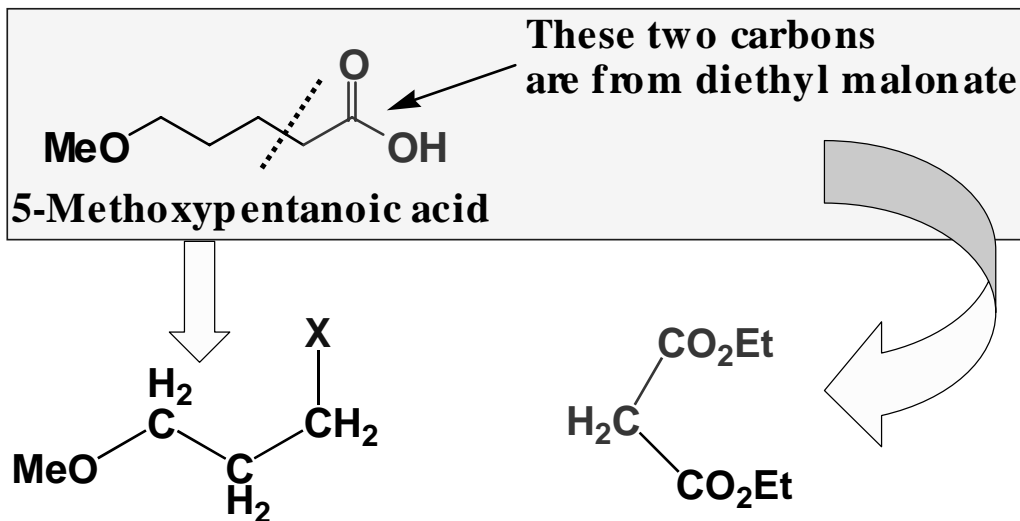
- The strategy of a malonic ester (ME) synthesis is identical to that of an acetoacetic ester synthesis, except that the starting material is a β -diester rather than a β -ketoester



24

Malonic Ester Synthesis

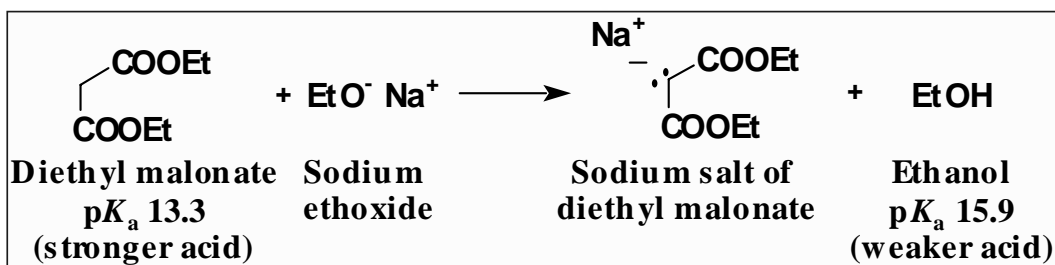
Consider the synthesis of this target molecule



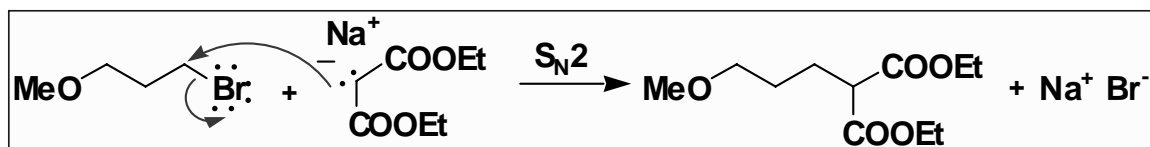
25

Malonic Ester Synthesis

– treat malonic ester with an alkali metal alkoxide



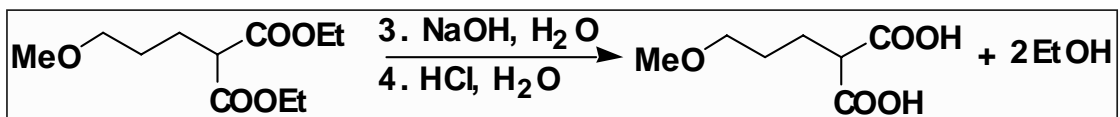
– alkylate with 1-bromo-3-methoxy propane



26

Malonic Ester Synthesis

– saponify and acidify

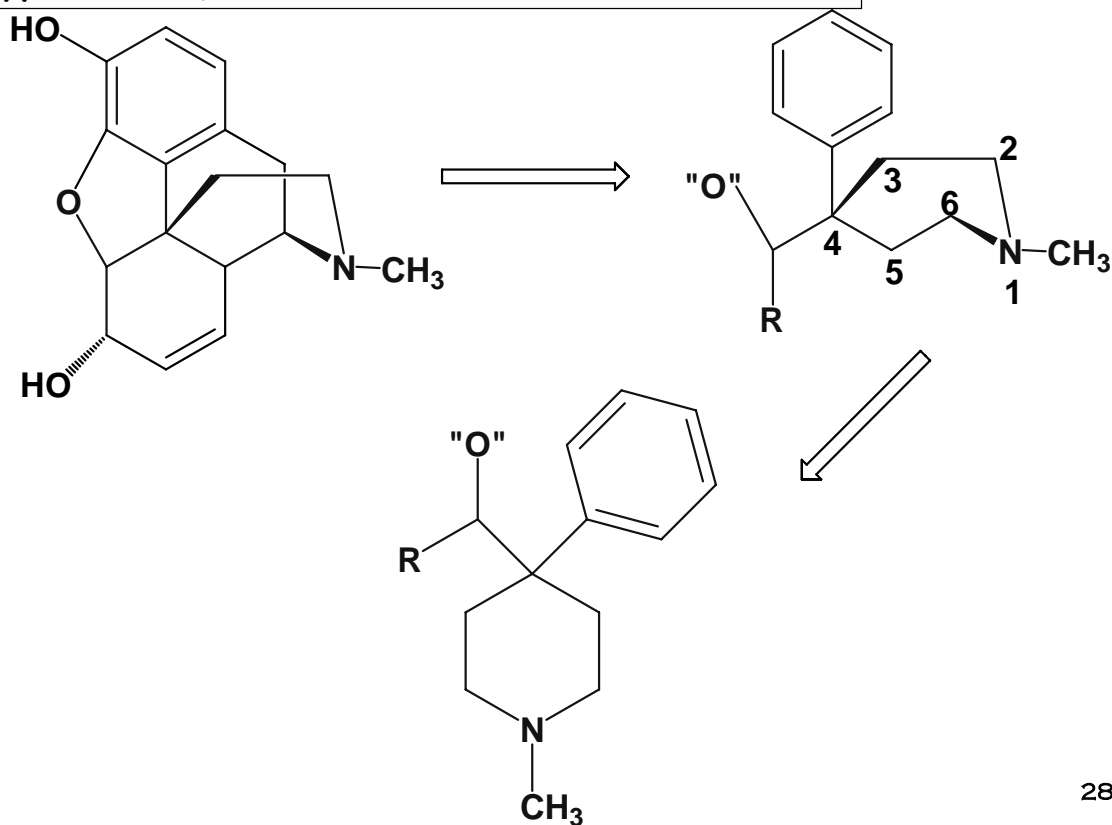


– decarboxylation

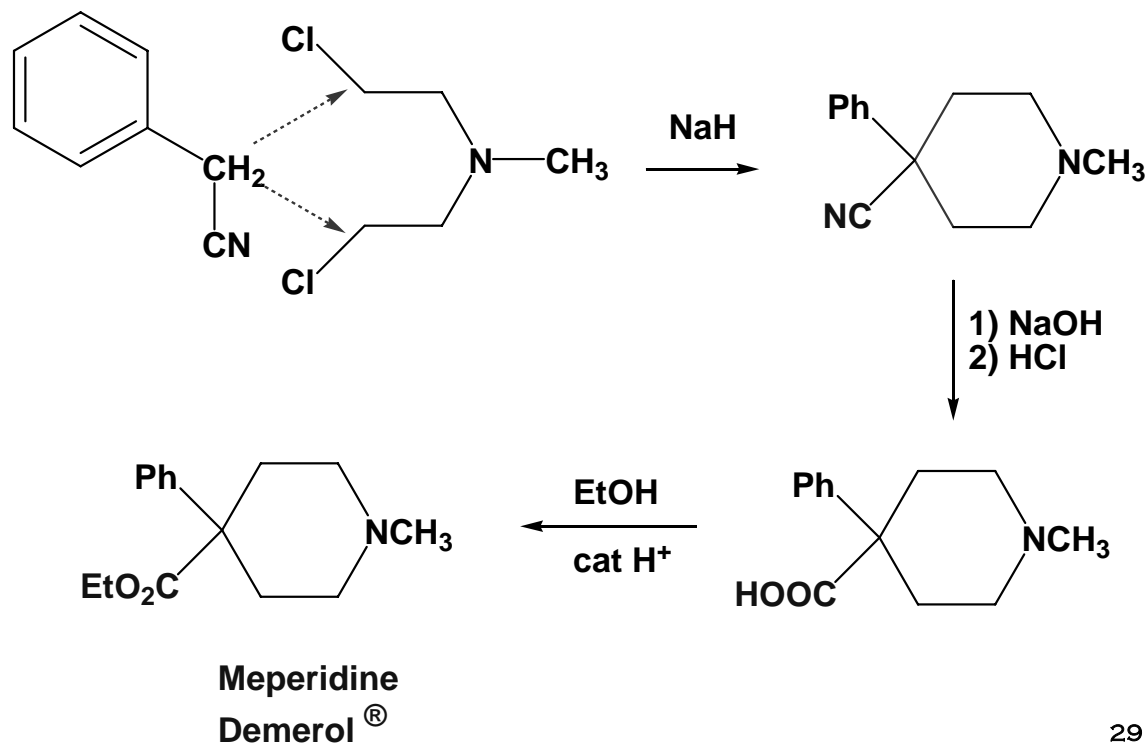


27

Application: Synthesis of 4,4-Disubstituted Piperidines



28

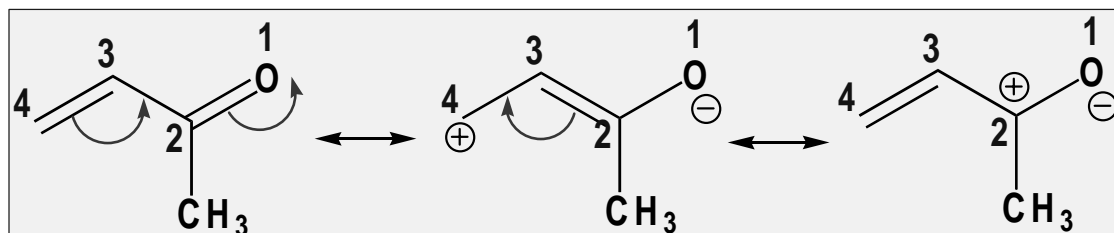


29

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.

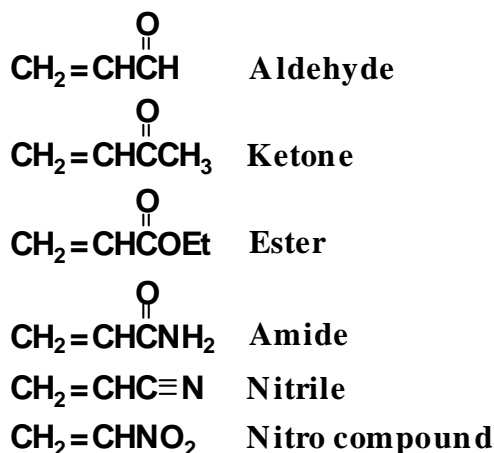
α,β -unsaturated carbonyl compounds can exhibit properties of both the carbonyl and alkene group:



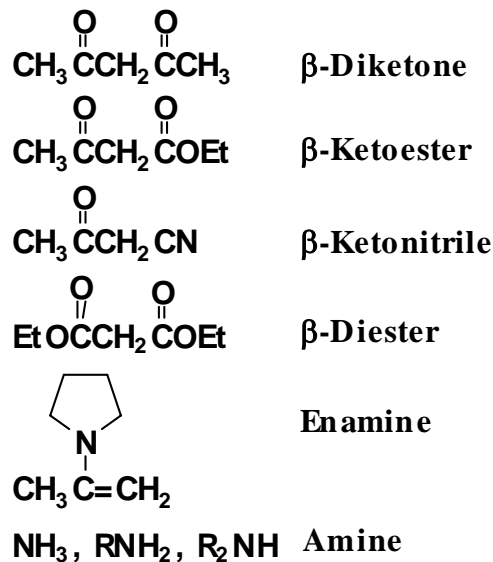
30

Michael Acceptors & Nucleophiles

These Types of α,β -Unsaturated Compounds are Nucleophile Acceptors in Michael Reactions

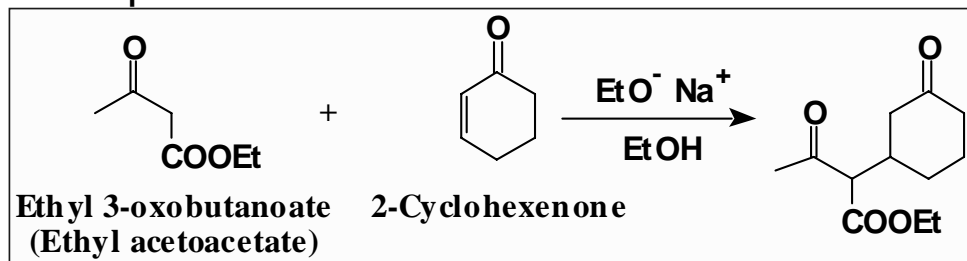


These Types of Compounds Provide Effective Nucleophiles for Michael Reactions

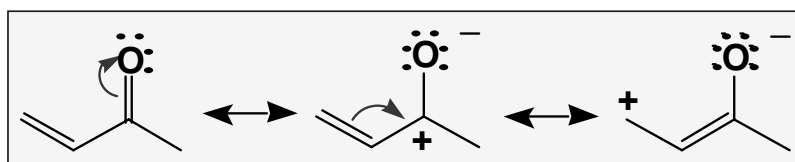


Michael Reaction

Example:



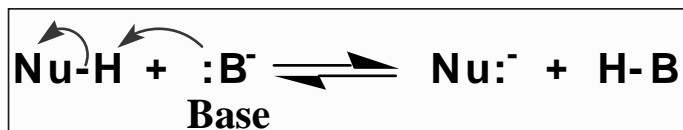
– the double bond of an α,β -unsaturated carbonyl compound is activated for nucleophilic attack:



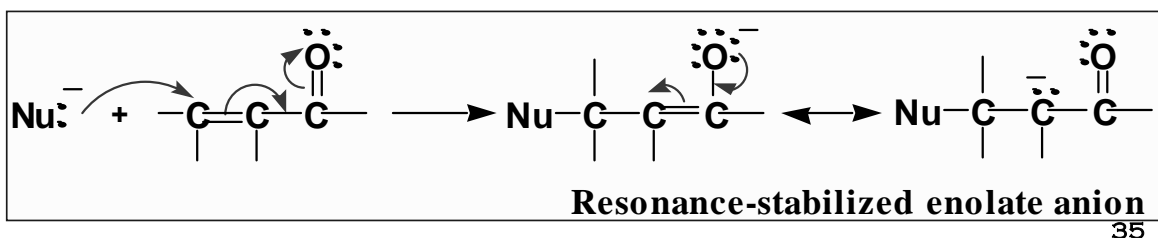
Michael Reaction

- Mechanism

Step 1: proton transfer to the base

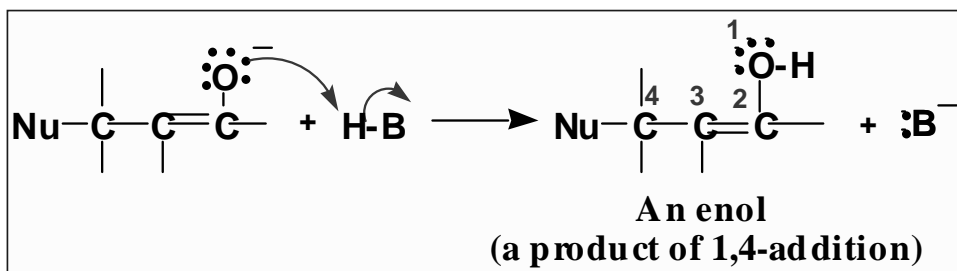


Step 2: addition of Nu:⁻ to the β carbon of the α,β-unsaturated carbonyl compound



Michael Reaction

Step 3: proton transfer to HB gives an enol



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

