

CH 310 N

T TH 2-3:30

LECTURE 17

Textbook Assignment: Chapter 19

Homework (for credit): POW 8 posted

Today's Topics: Enolates & Enamines

Notice & Announcements:

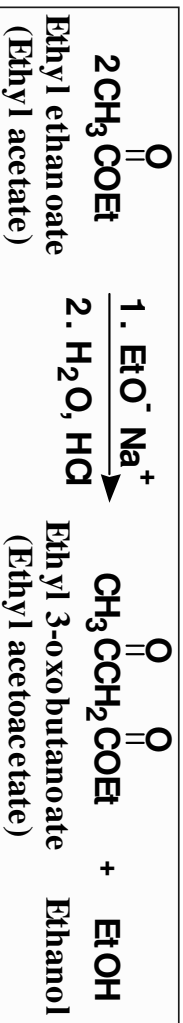
Exam II: Grades Posted to BB

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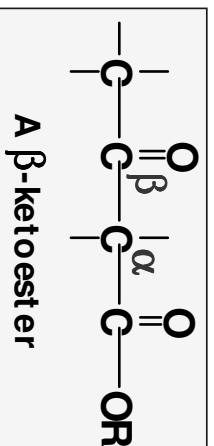
Enolate Anions and Enamines

Claisen Condensation

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



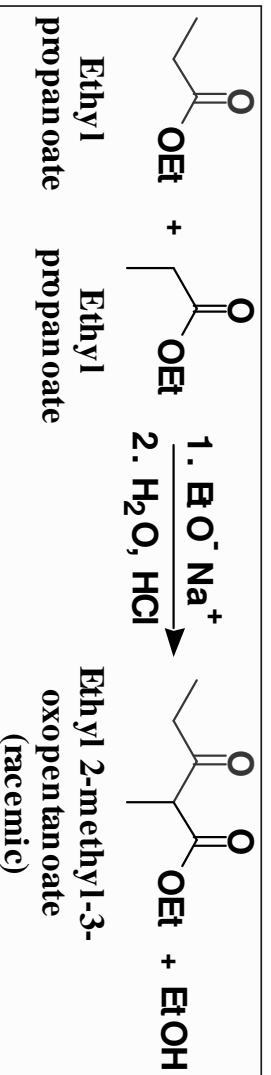
the product of a Claisen condensation is a β -ketoester



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Claisen Condensation

- Claisen condensation of ethyl propanoate gives this β -ketoester

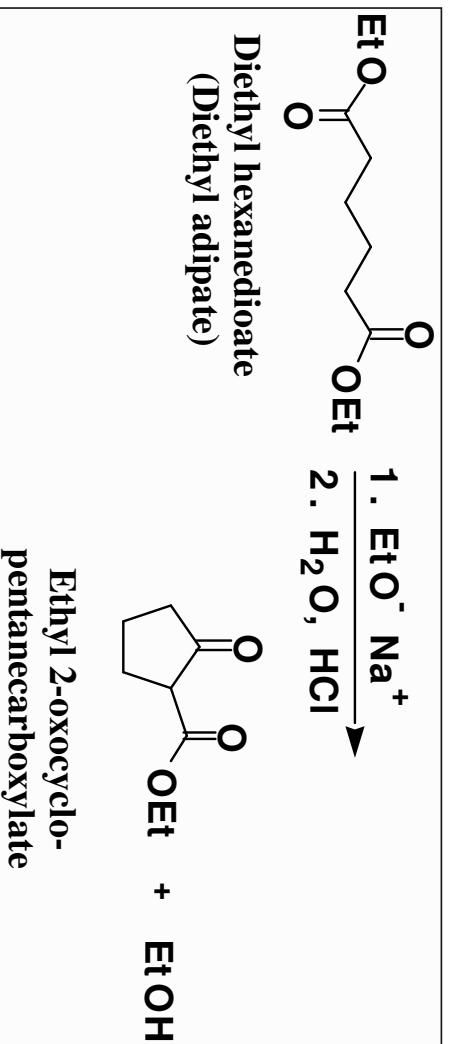


Nota bene: the base should be the alkoxide of the ester group
(This will overcome trans-esterification.)

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Dieckman Condensation

- An intramolecular Claisen condensation



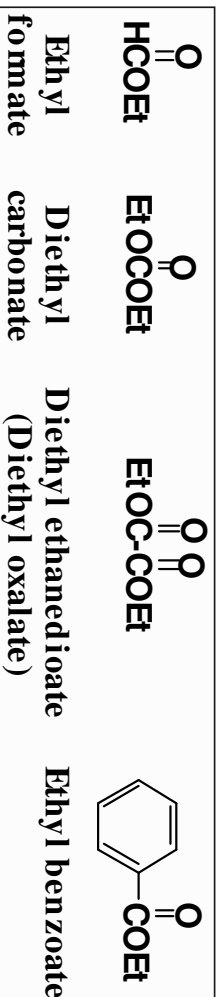
Psst...
He will ask
this

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Crossed Claisen Condensations

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

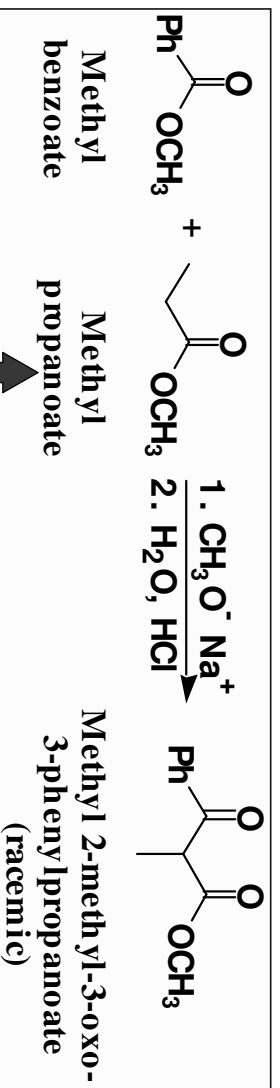
- crossed Claisen condensations are useful, if there is an appreciable difference in reactivity between the two esters; when one of them has no α -hydrogens



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Crossed Claisen Condensations

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

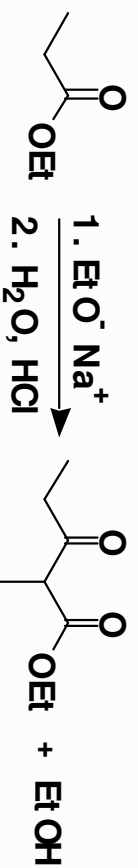


Only this enolate can be formed

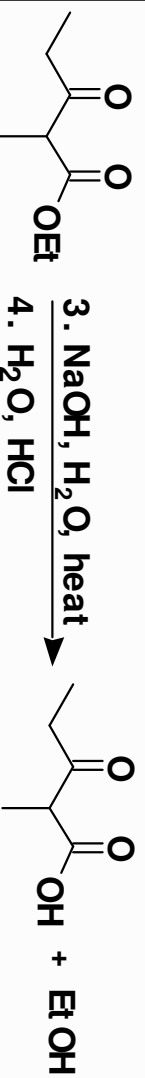
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Claisen condensations as routes to ketones

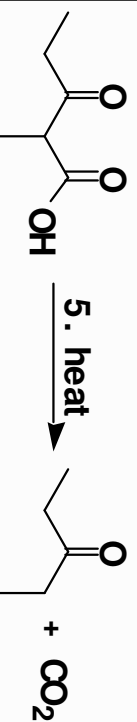
Reactions 1 & 2: Claisen condensation followed by acidification



Reactions 3 & 4: Saponification and acidification



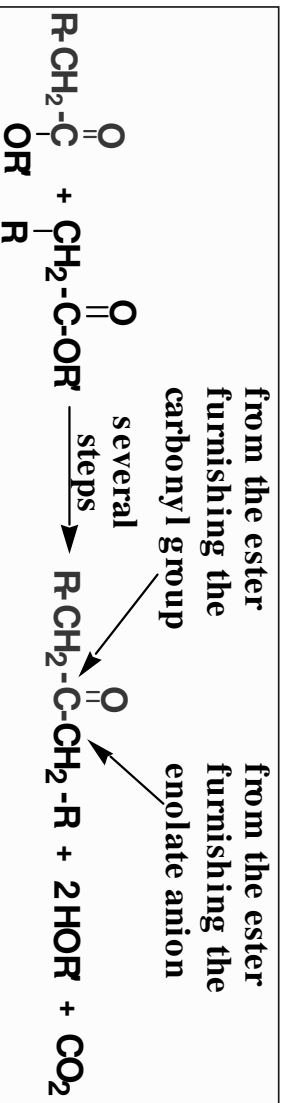
Reaction 5: thermal decarboxylation



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Claisen Condensations

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

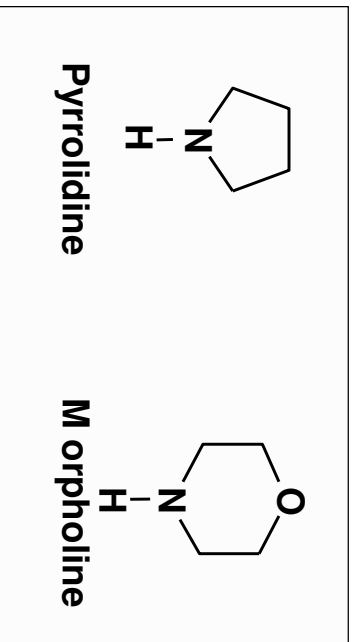


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Enamines

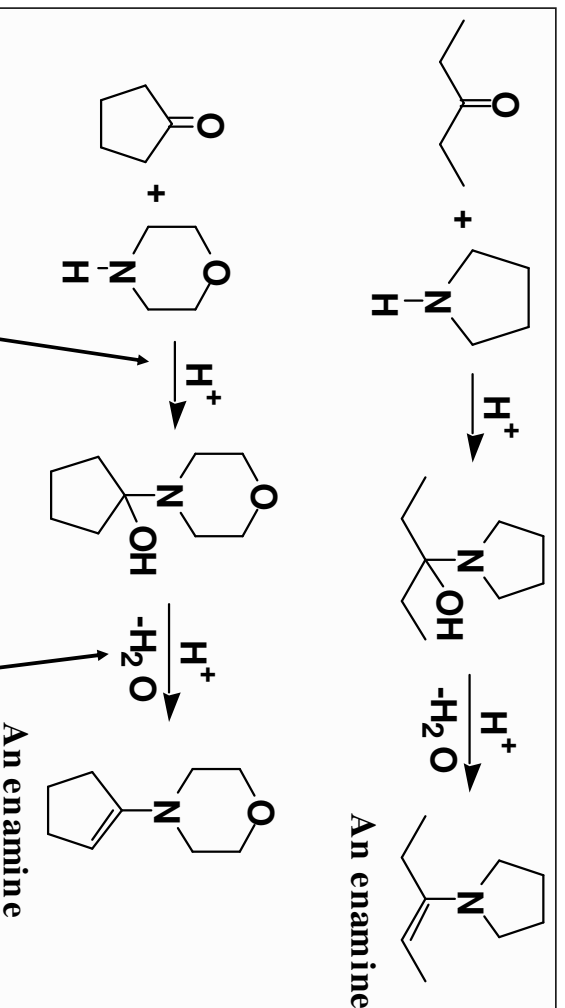
Enamines are formed by the reaction of a **2° amine with the carbonyl group of an aldehyde or ketone**

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



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Preparation of Enamines

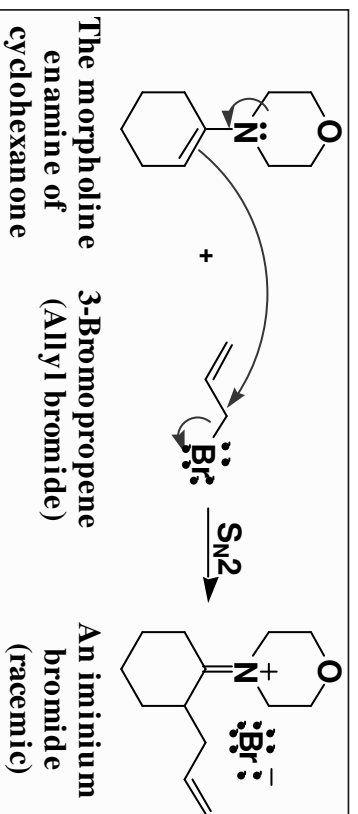


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Enamines-Alkylation

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

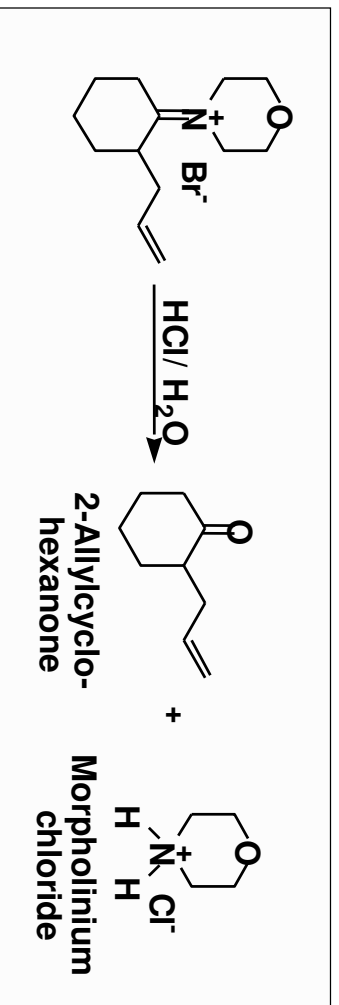
- enamines undergo S_N2 reactions with methyl and 1° haloalkanes, α -halo ketones, and α -haloesters
- treatment of the enamine with one equivalent of an alkylating agent gives an iminium halide



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Enamines-Alkylation

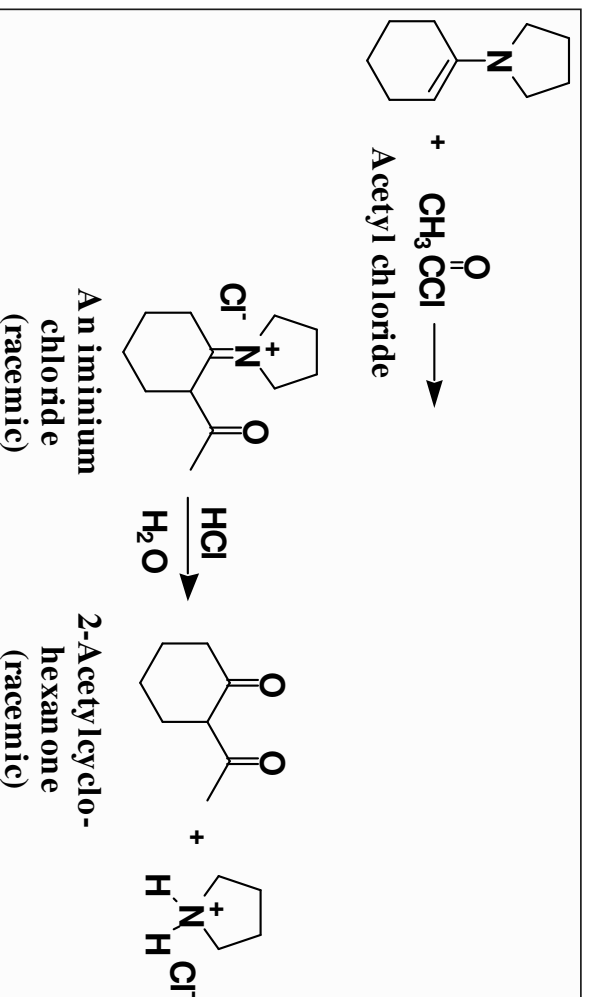
hydrolysis of the iminium halide (salt) gives
the alkylated aldehyde or ketone:



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Enamines-Acylation

enamines undergo acylation when treated
with acid chlorides and acid anhydrides



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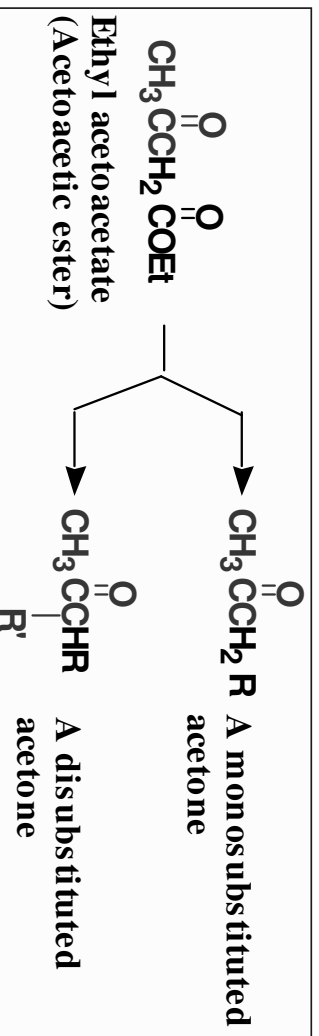
Synthetic Advantages of Enamines vs Enolates

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

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Acetoacetic Ester Synthesis

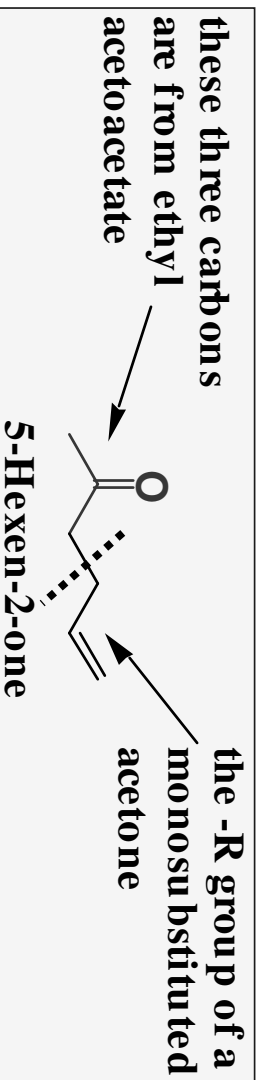
The acetoacetic ester (AAE) synthesis is useful for the preparation of mono- and disubstituted acetones of the following types



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Acetoacetic Ester Synthesis

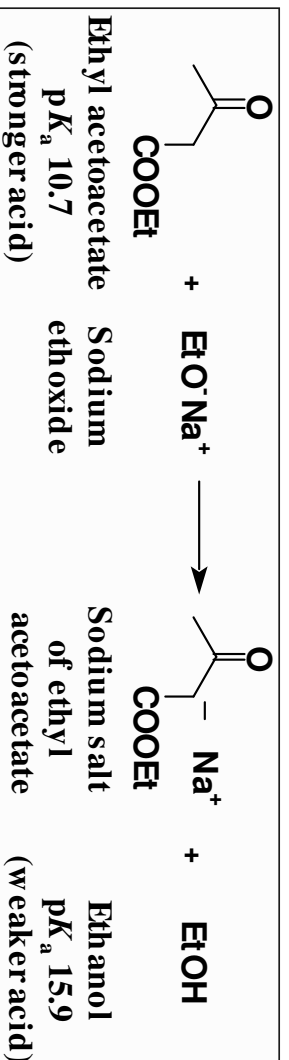
- consider the AAE synthesis of this target molecule, which is a monosubstituted acetone



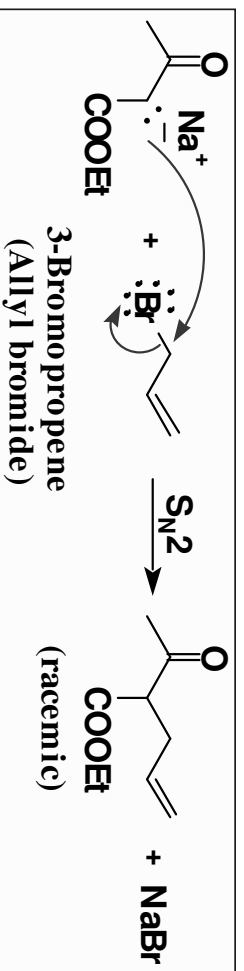
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Acetoacetic Ester Synthesis

- Step 1: formation of the enolate anion of AAE



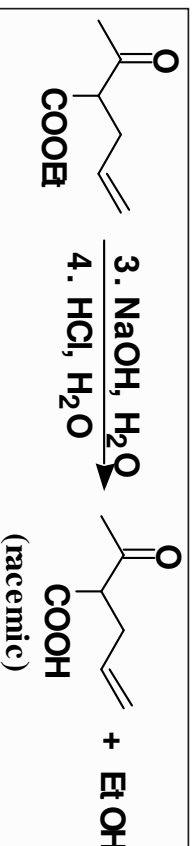
- Step 2: alkylation with allyl bromide



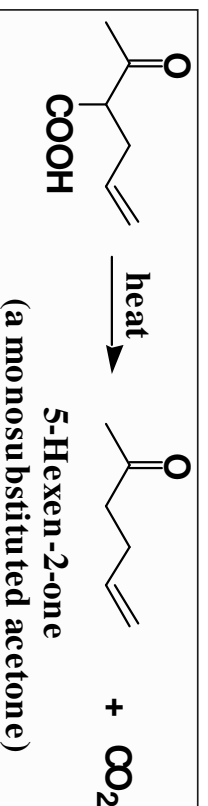
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Acetoacetic Ester Synthesis

- Steps 3 & 4 saponification followed by acidification



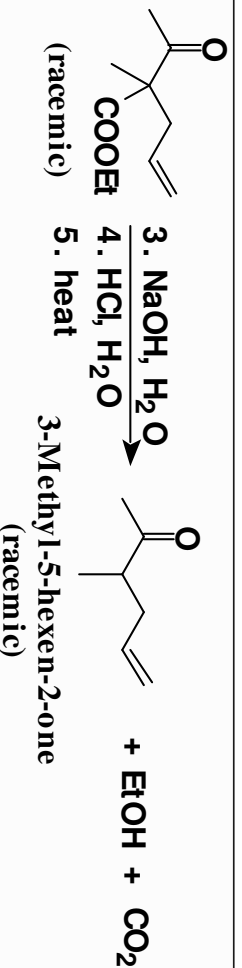
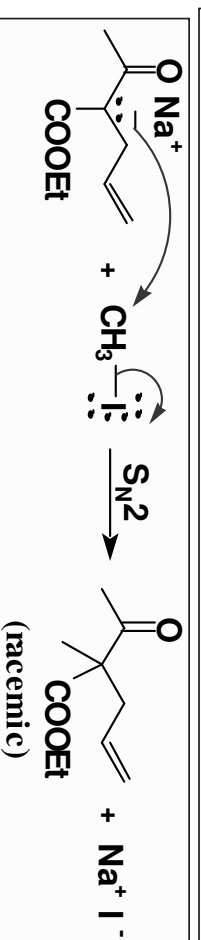
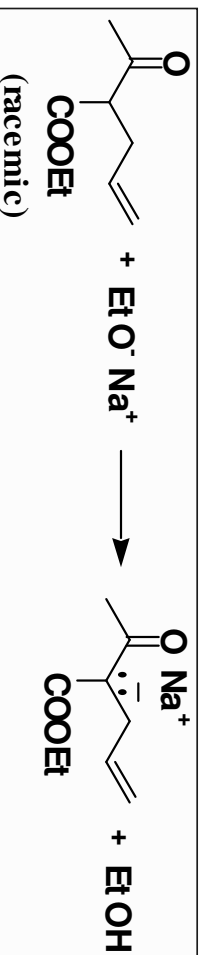
- Step 5: thermal decarboxylation



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Acetoacetic Ester Synthesis

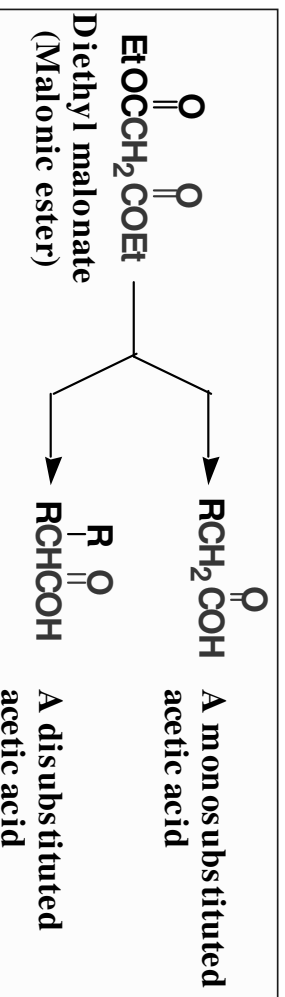
- to prepare a **disubstituted acetone**, treat the monoalkylated AAE with a second mole of base, etc



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Malonic Ester Synthesis

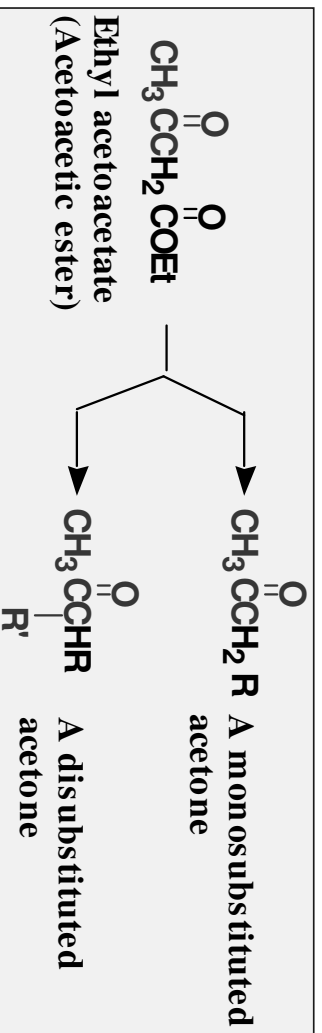
- The strategy of a malonic ester (ME) synthesis is identical to that of an acetoacetic ester synthesis, except that the starting material is a β -diester rather than a β -ketoester



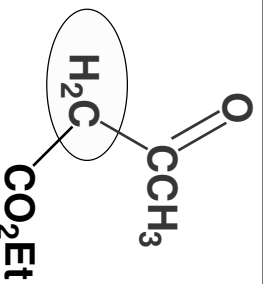
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Acetoacetic Ester Synthesis

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



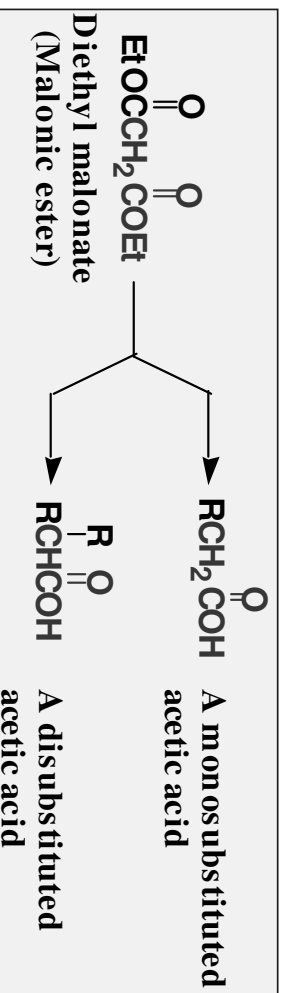
These types of reactions involve active (i.e. acidic) methylene units as the nucleophilic component.



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Malonic Ester Synthesis

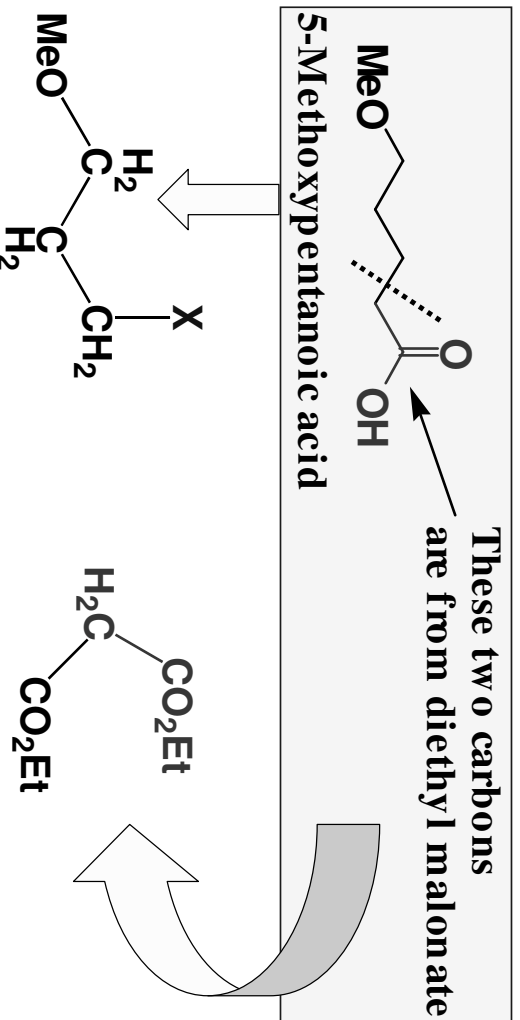
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Malonic Ester Synthesis

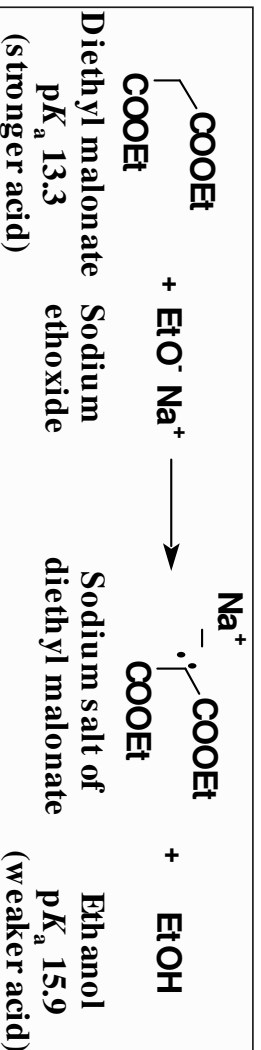
Consider the synthesis of this target molecule



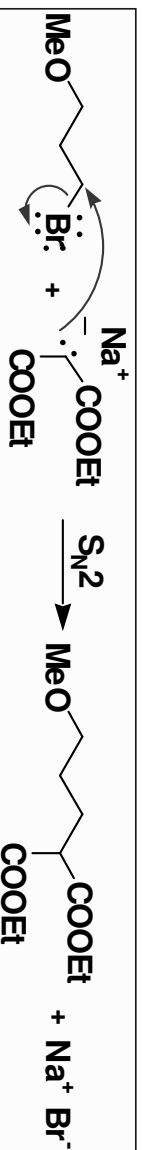
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Malonic Ester Synthesis

– treat malonic ester with an alkali metal alkoxide



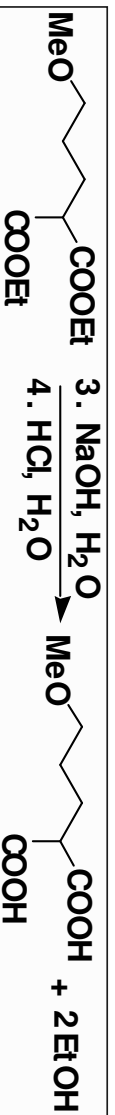
– alkylate with 1-bromo-3-methoxy propane



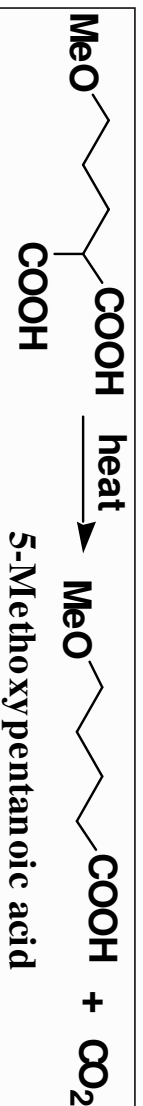
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Malonic Ester Synthesis

– saponify and acidify



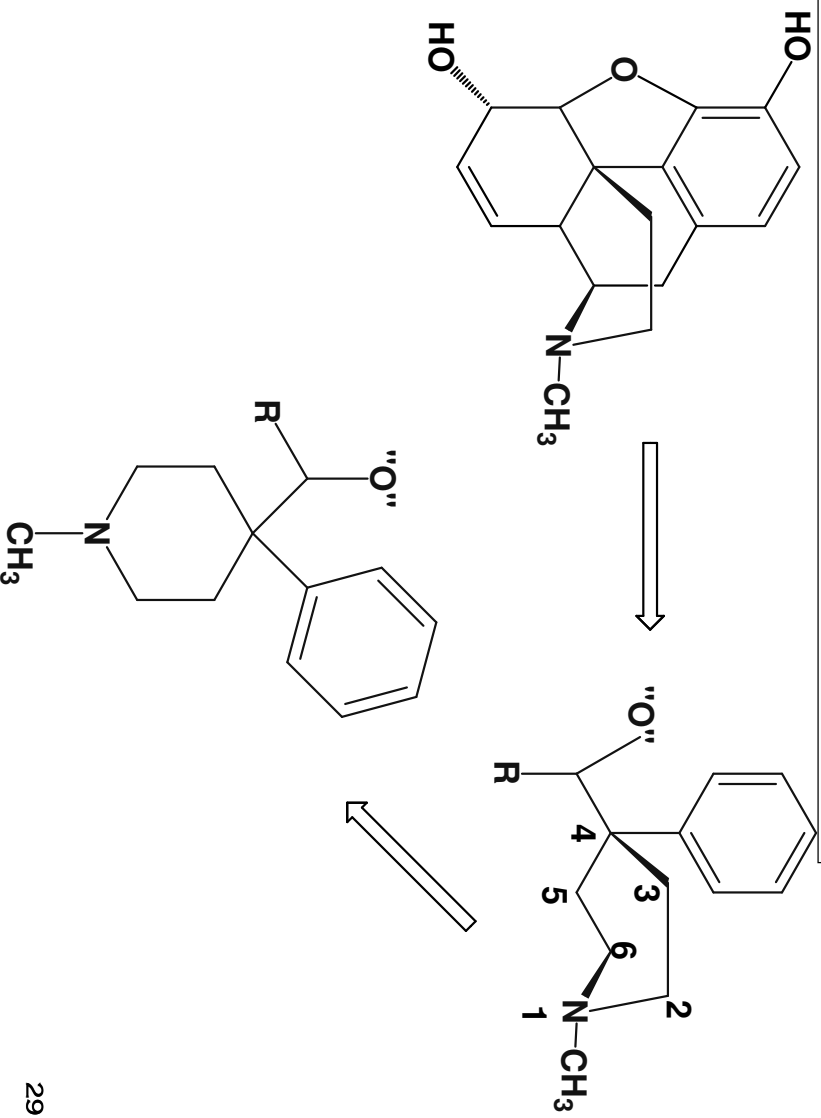
– decarboxylation



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Application: Synthesis of 4,4-Disubstituted Piperidines

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Application: Synthesis of 4,4-Disubstituted Piperidines

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