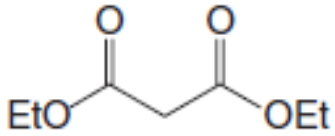
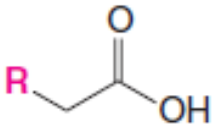
Synthesis of Substituted Acetic Acids: The Malonic Ester Synthesis

A useful counterpart of the acetoacetic ester synthesis—one that allows the synthesis of *mono*- and *disubstituted acetic acids*—is called the **malonic ester synthesis.** The starting compound is the diester of a β-dicarboxylic acid, called a malonic ester. The most commonly used malonic ester is diethyl malonate.



Diethyl malonate (a *β*-dicarboxylic acid ester)

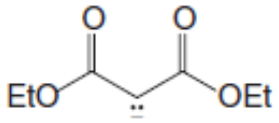
The malonic ester synthesis is a useful method for preparing mono- and dialkylacetic acids:



A monoalkylacetic acid

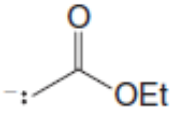
A dialkylacetic acid

Thus, the malonic ester synthesis provides us with a synthetic equivalent of an ester enolate of acetic acid or acetic acid dianion.

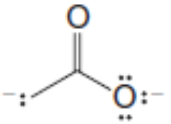


Diethyl malonate anion

is the synthetic equivalent of

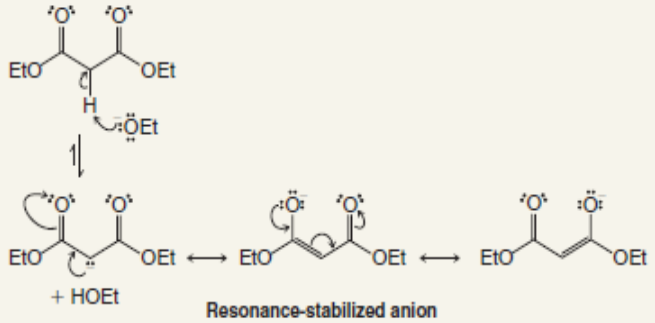


and



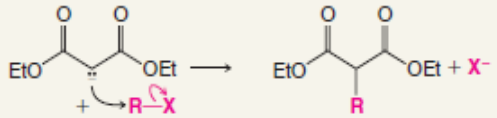
The Malonic Ester Synthesis of Substituted Acetic Acids:

Step 1 *Diethyl malonate, the starting compound, forms a relatively stable enolate:*



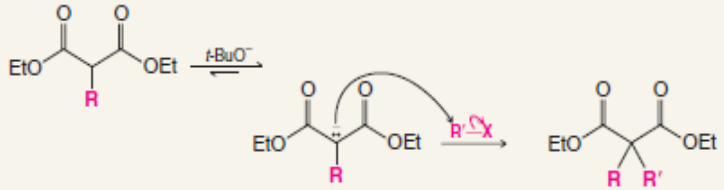
Resonance-stabilized anion

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



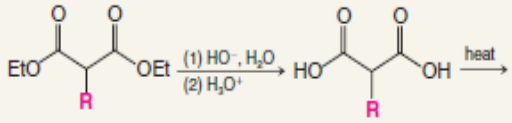
Enolate Monoalkylmalonic ester

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

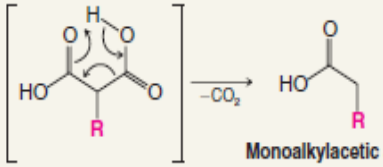


Dialkylmalonic ester

Step 3 *The mono- or dialkylmalonic ester can then be hydrolyzed to a mono- or dialkylmalonic acid, and substituted malonic acids decarboxylate readily. Decarboxylation gives a mono- or disubstituted acetic acid:*

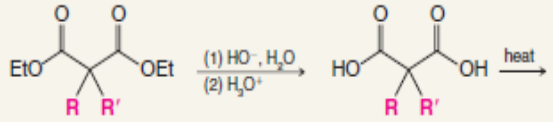


Monoalkylmalonic ester

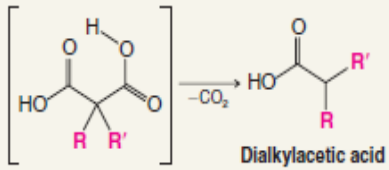


Monoalkylacetic acid

or after dialkylation,



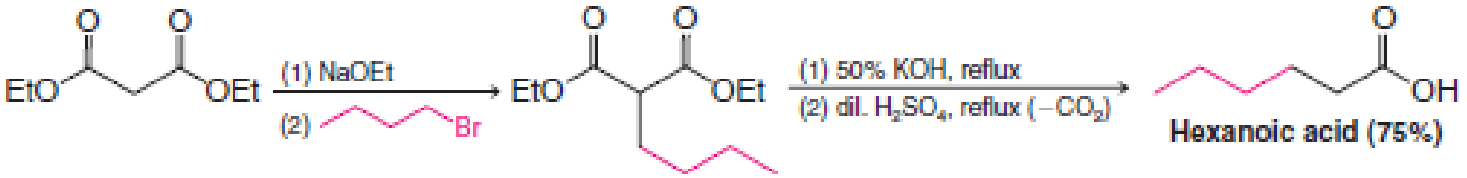
Dialkylmalonic ester



Dialkylacetic acid

Examples:

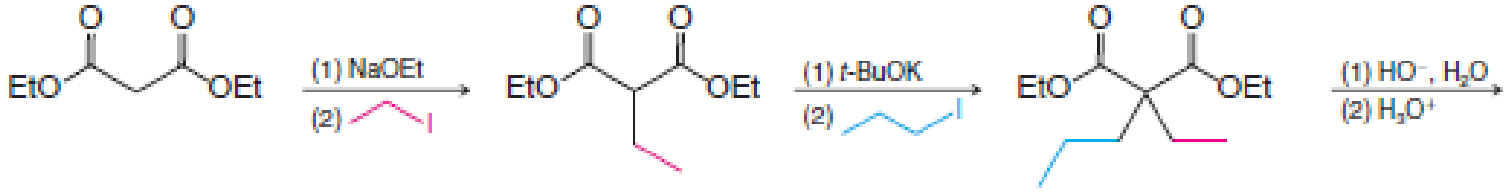
A Malonic Ester Synthesis of Hexanoic Acid



Diethyl butylmalonate (80–90%)

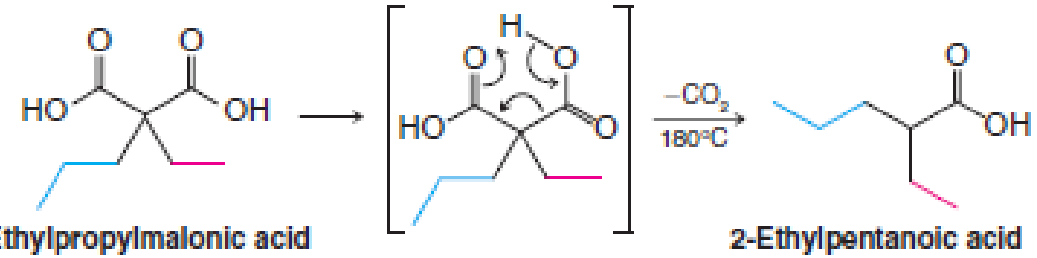
Hexanoic acid (75%)

A Malonic Ester Synthesis of 2-Ethylpentanoic Acid



Diethyl ethylmalonate

Diethyl ethylpropylmalonate

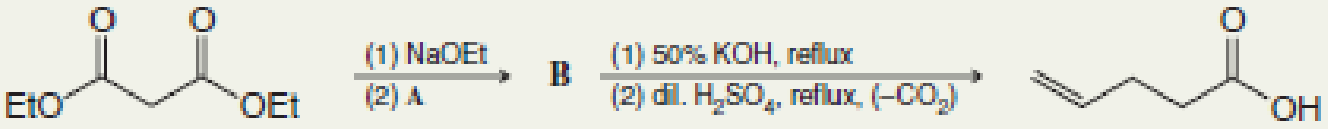


Ethylpropylmalonic acid

2-Ethylpentanoic acid

Problem:

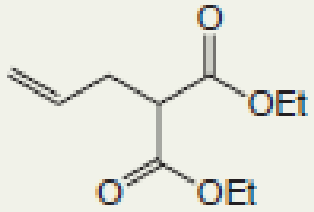
Provide structures for compounds **A** and **B** in the following synthesis.



ANSWER

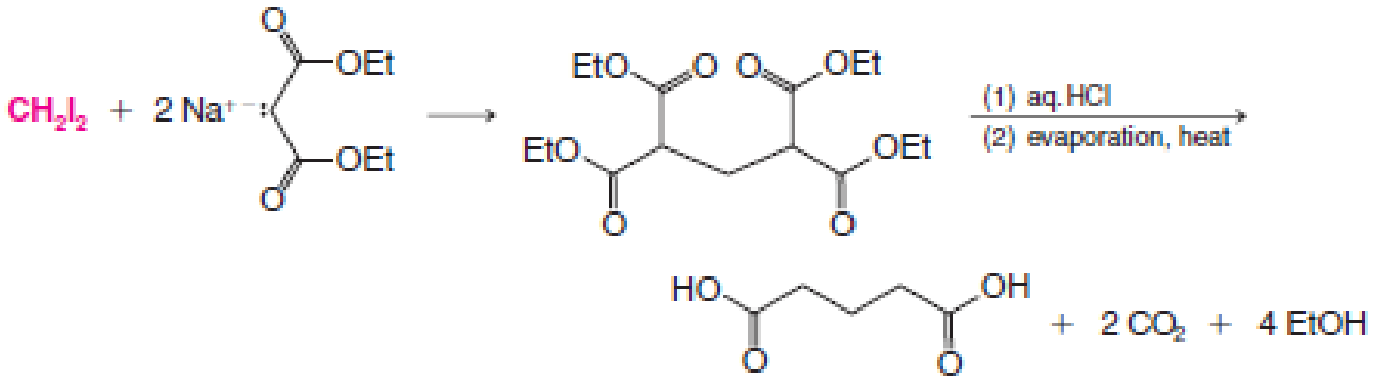
A =

B =



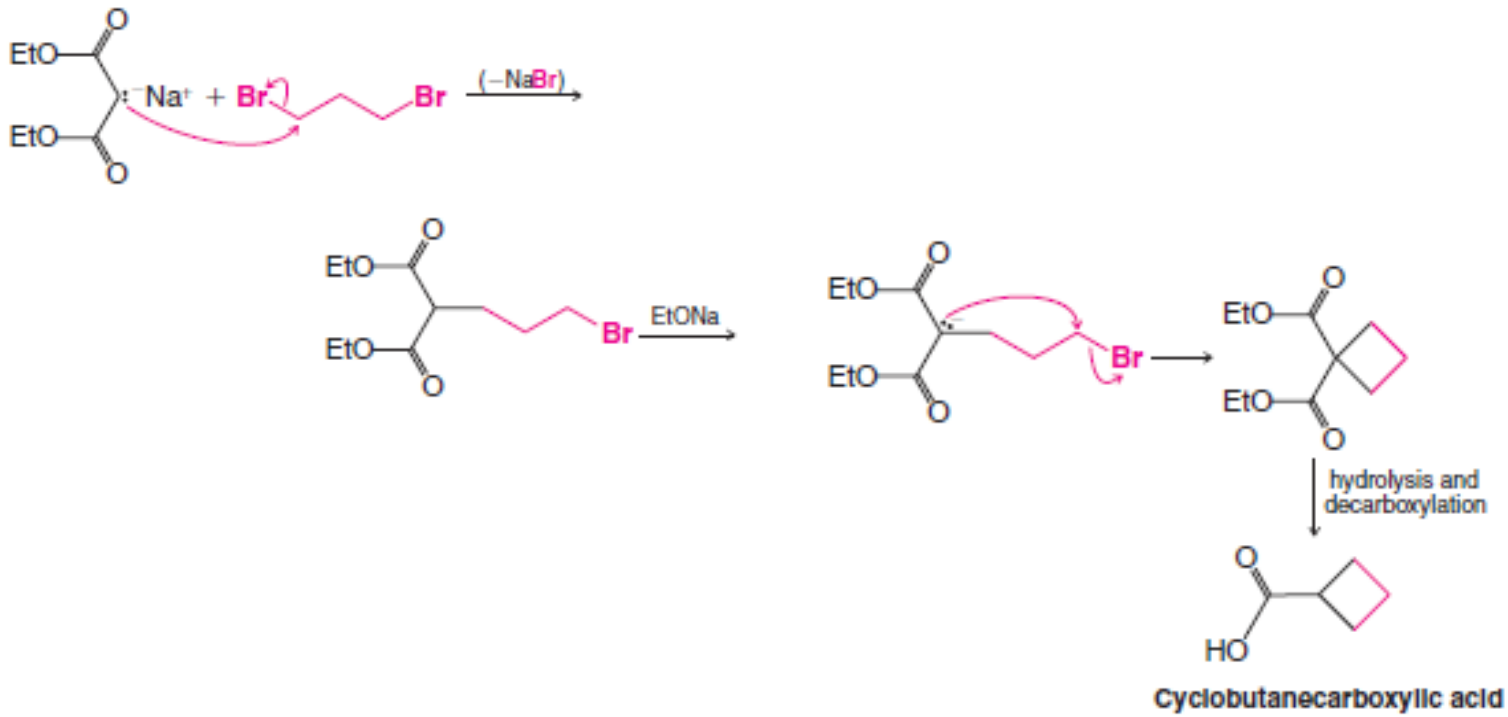
Two variations of the malonic ester synthesis make use of dihaloalkanes. In the first of these, two molar equivalents of sodiomalonic ester are allowed to react with a dihaloalkane.

Two consecutive alkylations occur, giving a tetraester; hydrolysis and decarboxylation of the tetraester yield a dicarboxylic acid. An example is the synthesis of glutaric acid:



Glutaric acid
(80% from tetraester)

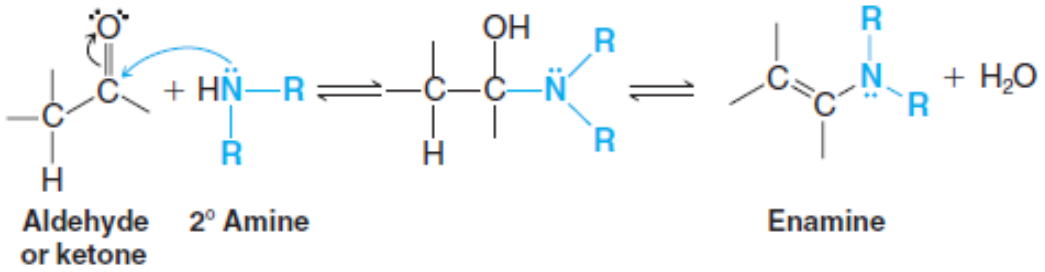
In a second variation, one molar equivalent of sodiomalonic ester is allowed to react with one molar equivalent of a dihaloalkane. This reaction gives a haloalkylmalonic ester, which, when treated with sodium ethoxide, undergoes an internal alkylation reaction. This method has been used to prepare three-, four-, five-, and six-membered rings. An example is the synthesis of cyclobutanecarboxylic acid:



Cyclobutanecarboxylic acid

Synthesis of Enamines: Stork Enamine Reactions

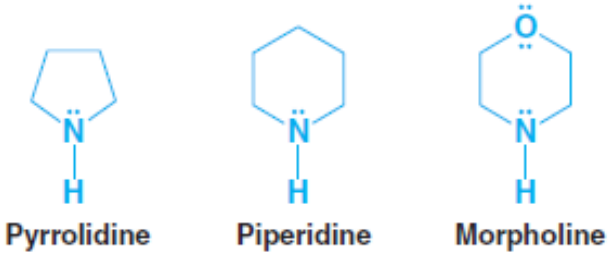
Aldehydes and ketones react with secondary amines to form compounds called **enamines.** The general reaction for enamine formation can be written as follows:

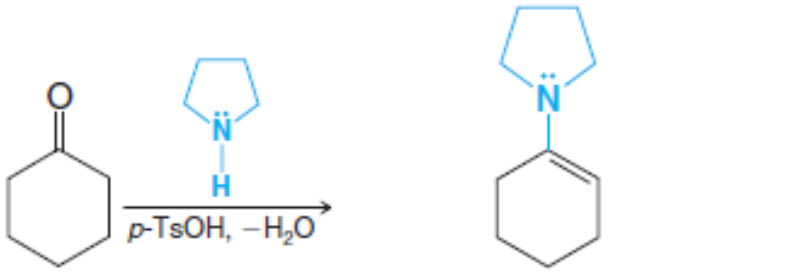


Since enamine formation requires the loss of a molecule of water, enamine preparations are usually carried out in a way that allows water to be removed as an azeotrope or by a drying agent. This removal of water drives the reversible reaction to completion.

Enamine formation is also catalyzed by the presence of a trace of an acid.

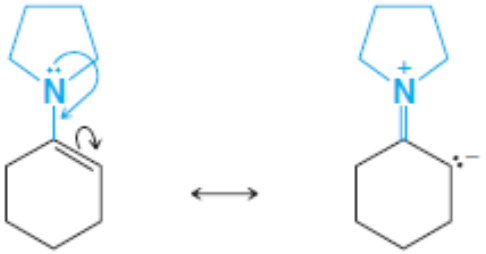
The secondary amines most commonly used to prepare enamines are cyclic amines such as pyrrolidine, piperidine, and morpholine:





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

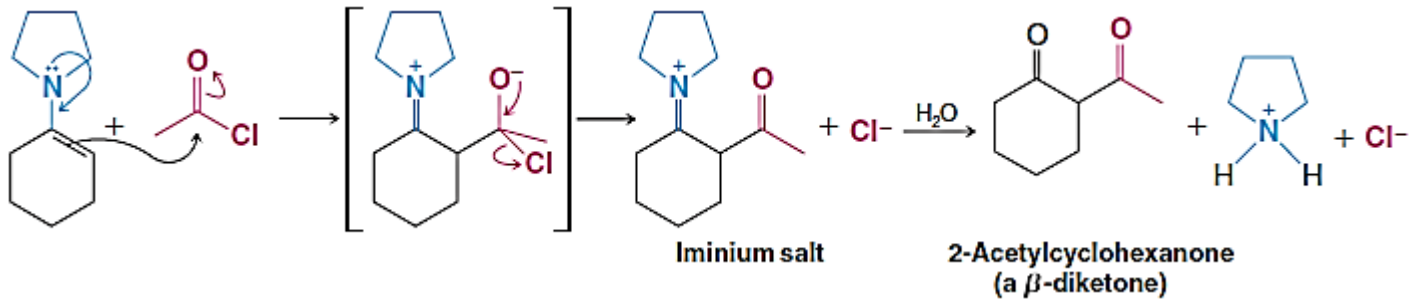
Enamines are good **nucleophiles**. Examination of the resonance structures that follow show that we should expect enamines to have both a nucleophilic nitrogen and a *nucleophilic carbon*.



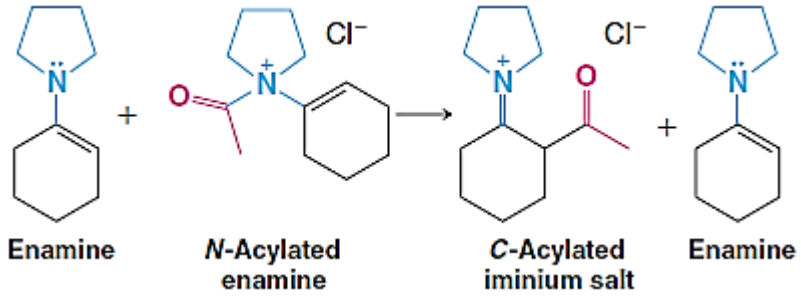
Contribution to the hybrid made by this structure confers nucleophilicity on nitrogen.

Contribution to the hybrid made by this structure confers nucleophilicity on carbon and decreases the nucleophilicity of nitrogen.

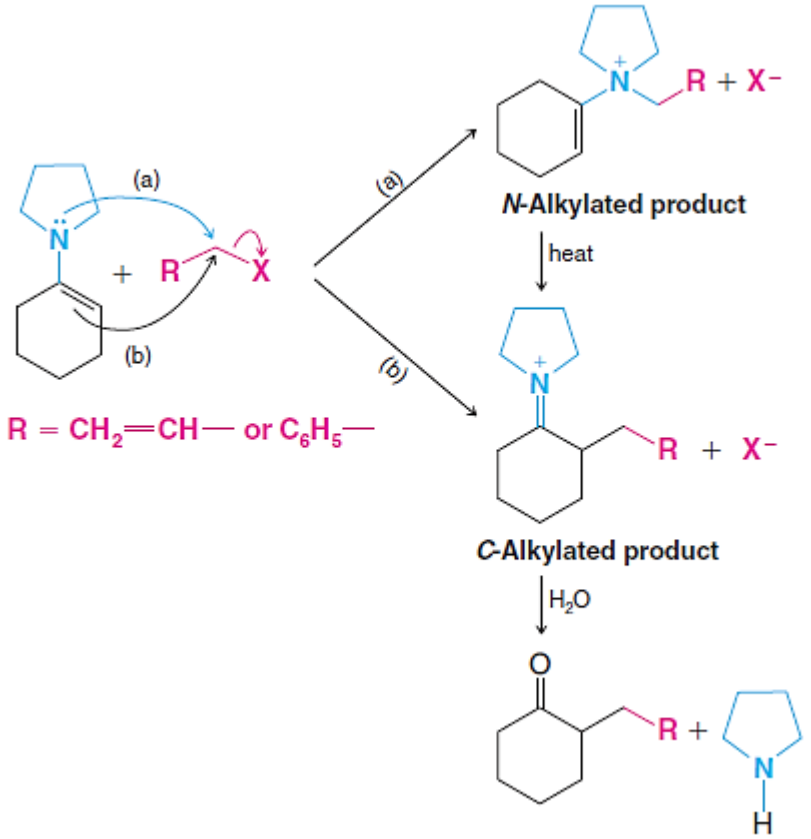
Enamines are the synthetic equivalents of aldehyde and ketone enolates



Although *N*-acylation may occur in this synthesis, the *N*-acyl product is unstable and can act as an acylating agent itself. As a consequence, the yields of *C*-acylated products are generally high.:

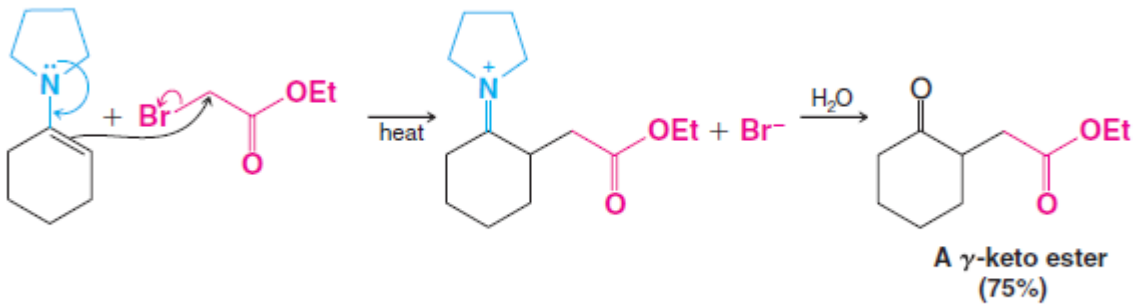


Enamines can be alkylated as well as acylated. Although alkylation may lead to the formation of a considerable amount of *N*-alkylated product, heating the *N*-alkylated product often converts it to a *C*-alkyl compound. This rearrangement is particularly favored when the alkyl halide is an allylic halide, benzylic halide, or a-haloacetic ester:



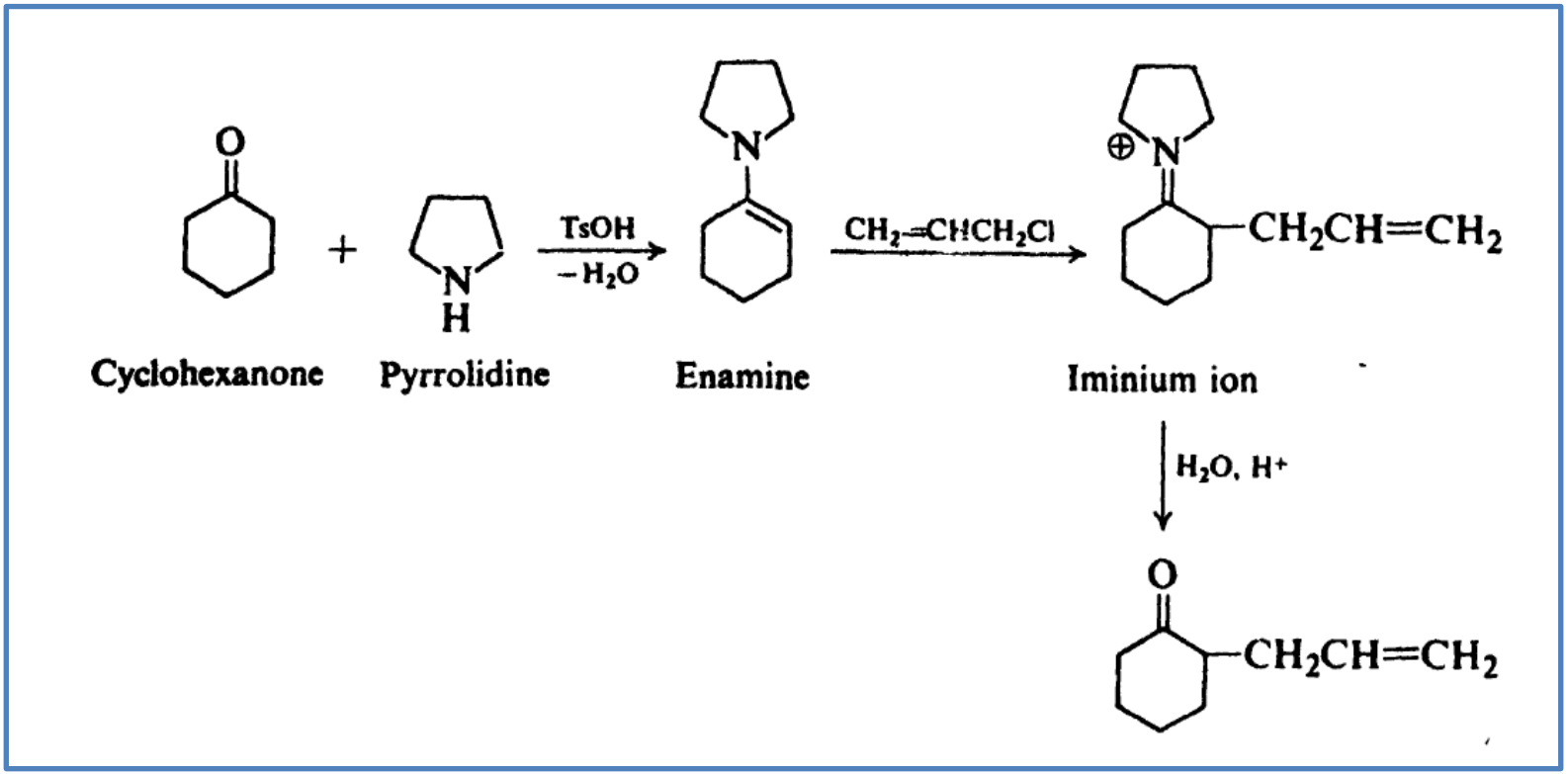
Enamine alkylations are SN2 reactions; therefore, when we choose our alkylating agents, we are usually restricted to the use of methyl, primary, allylic, and benzylic halides.

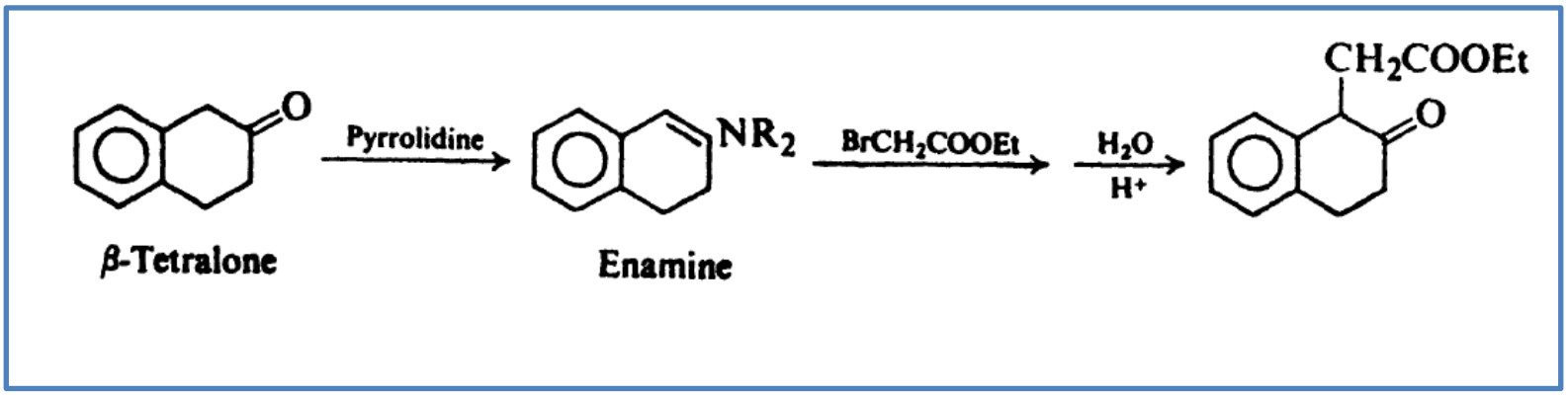
α-Halo esters can also be used as the alkylating agents, and this reaction provides a convenient synthesis
of γ-keto esters:

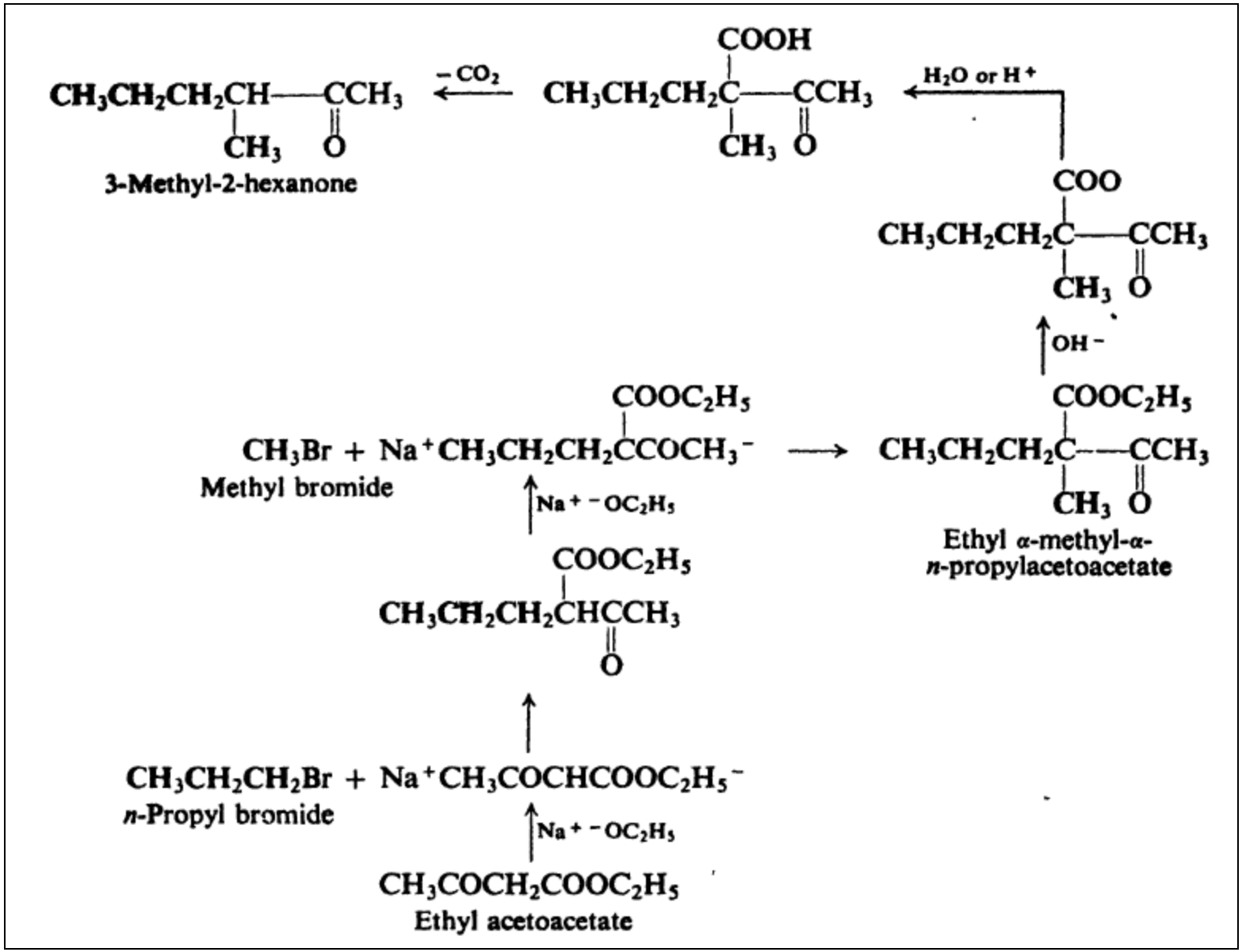


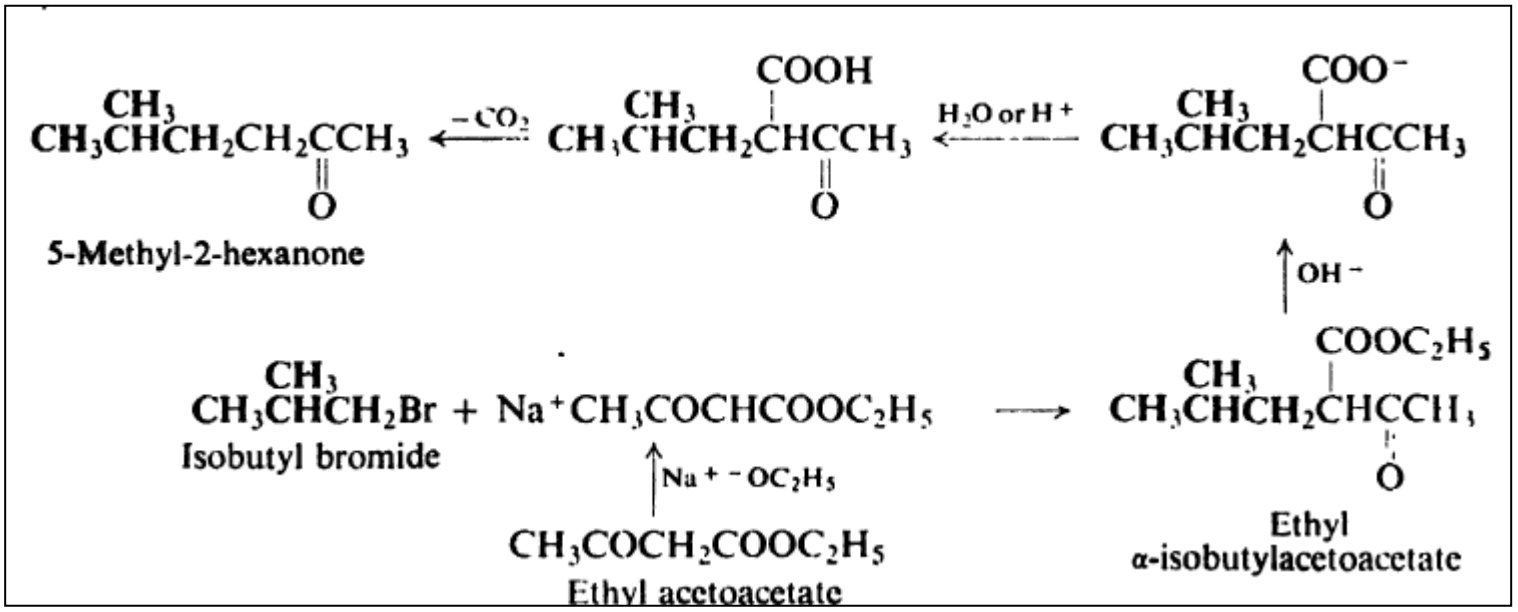
A γ-keto ester (75%)

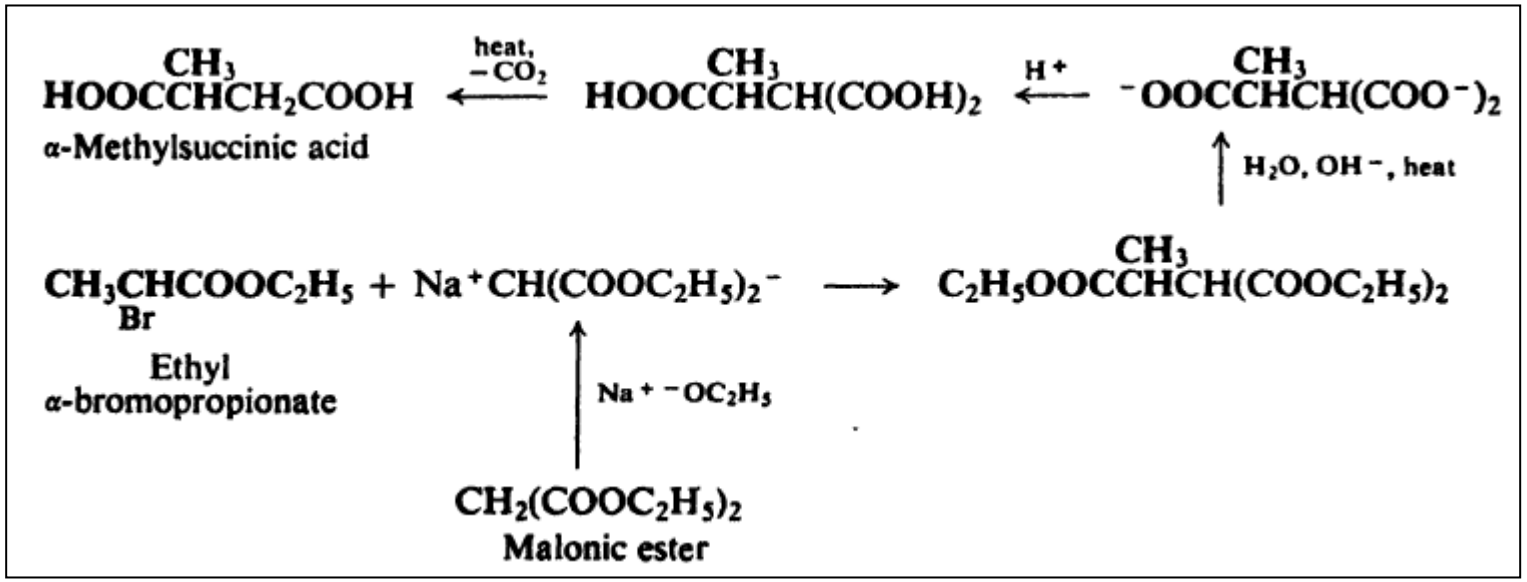
Examples:

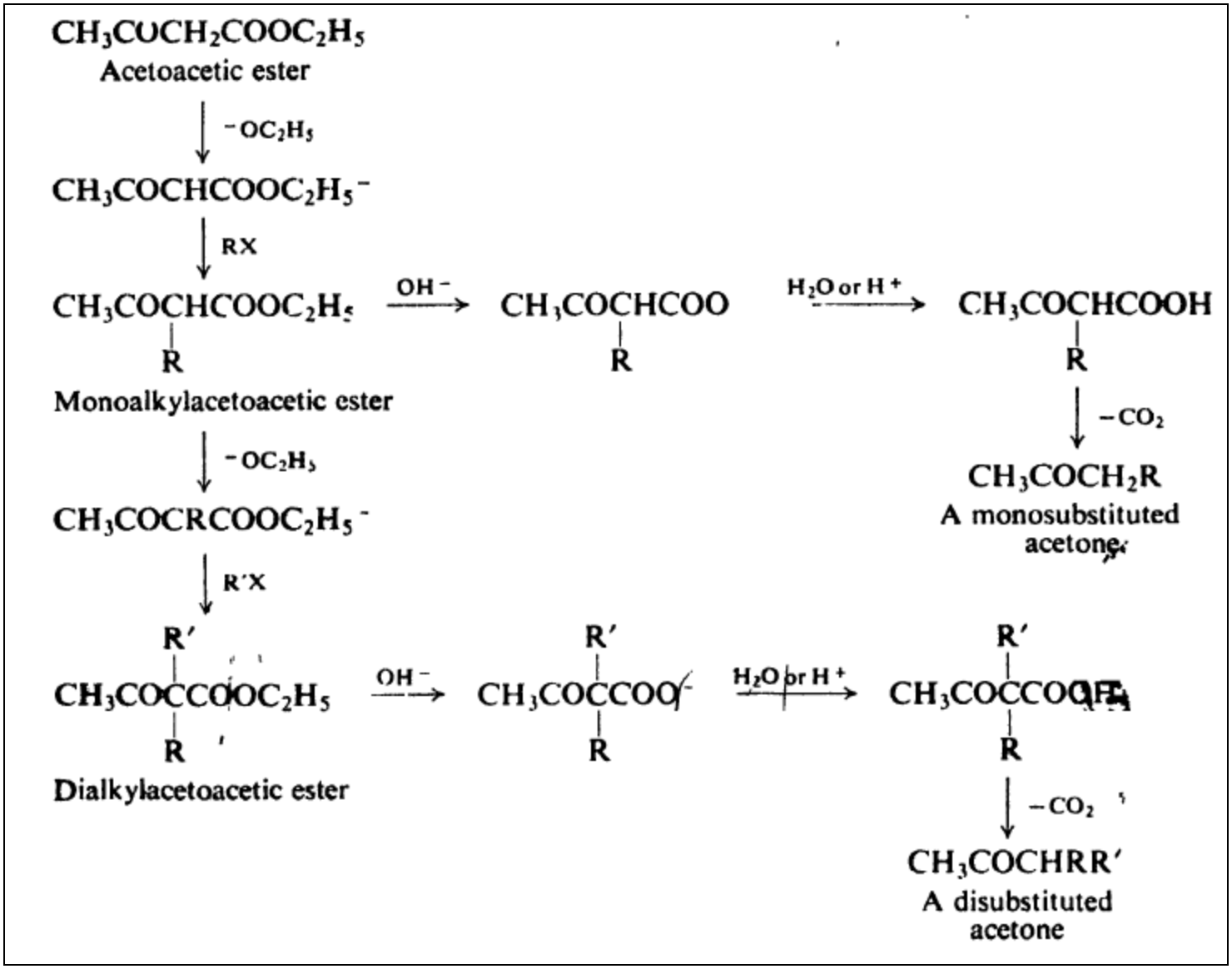

TsOH
$-H_2O$
$CH_2{=}CHCH_2Cl$
$CH_2CH{=}CH_2$
Cyclohexanone
Pyrrolidine
Enamine
Iminium ion
H_2O, H^+
$CH_2CH{=}CH_2$

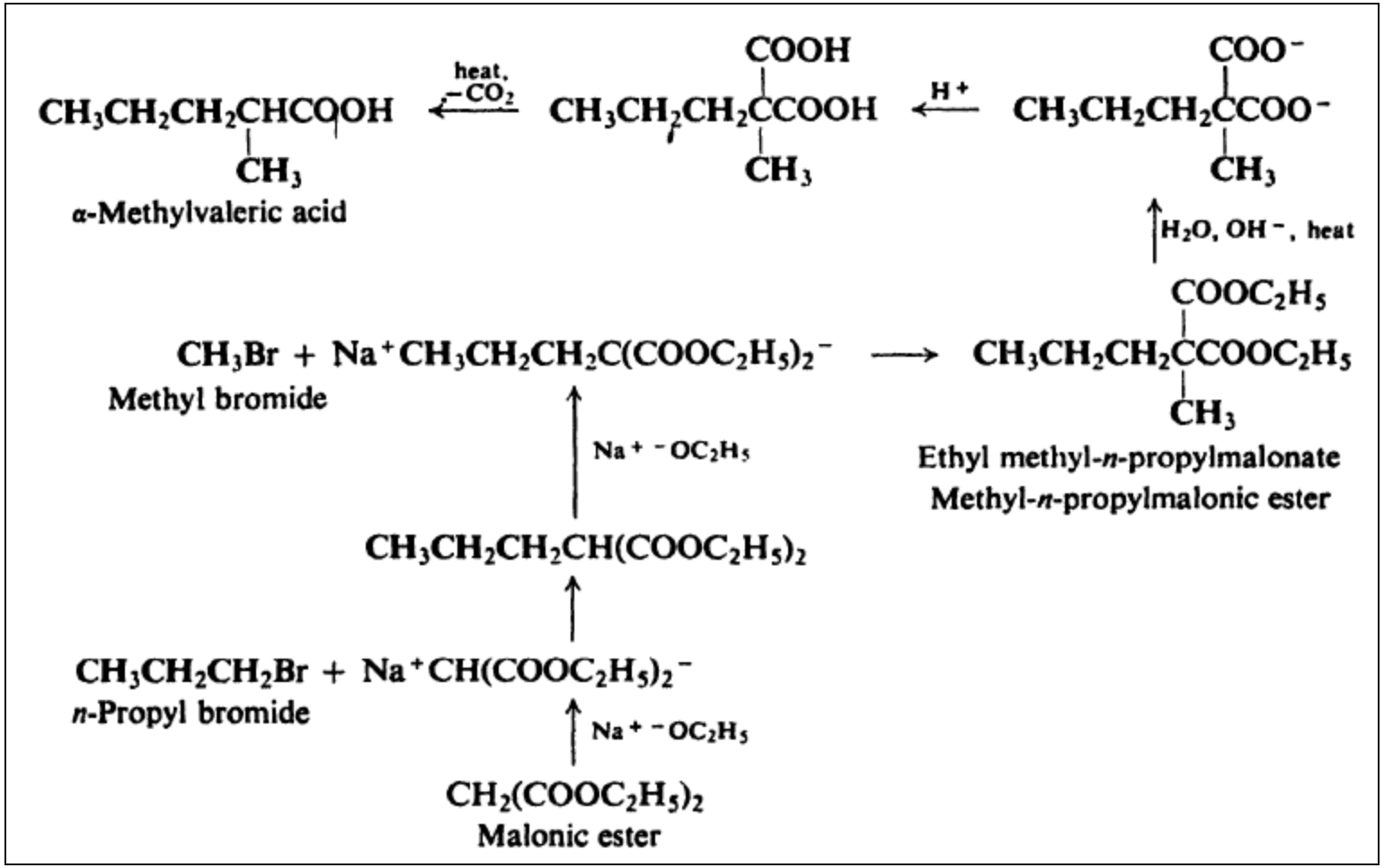

Pyrrolidine
NR_2
$BrCH_2COOEt$
H_2O
H^+
CH_2COOEt
β-Tetralone
Enamine

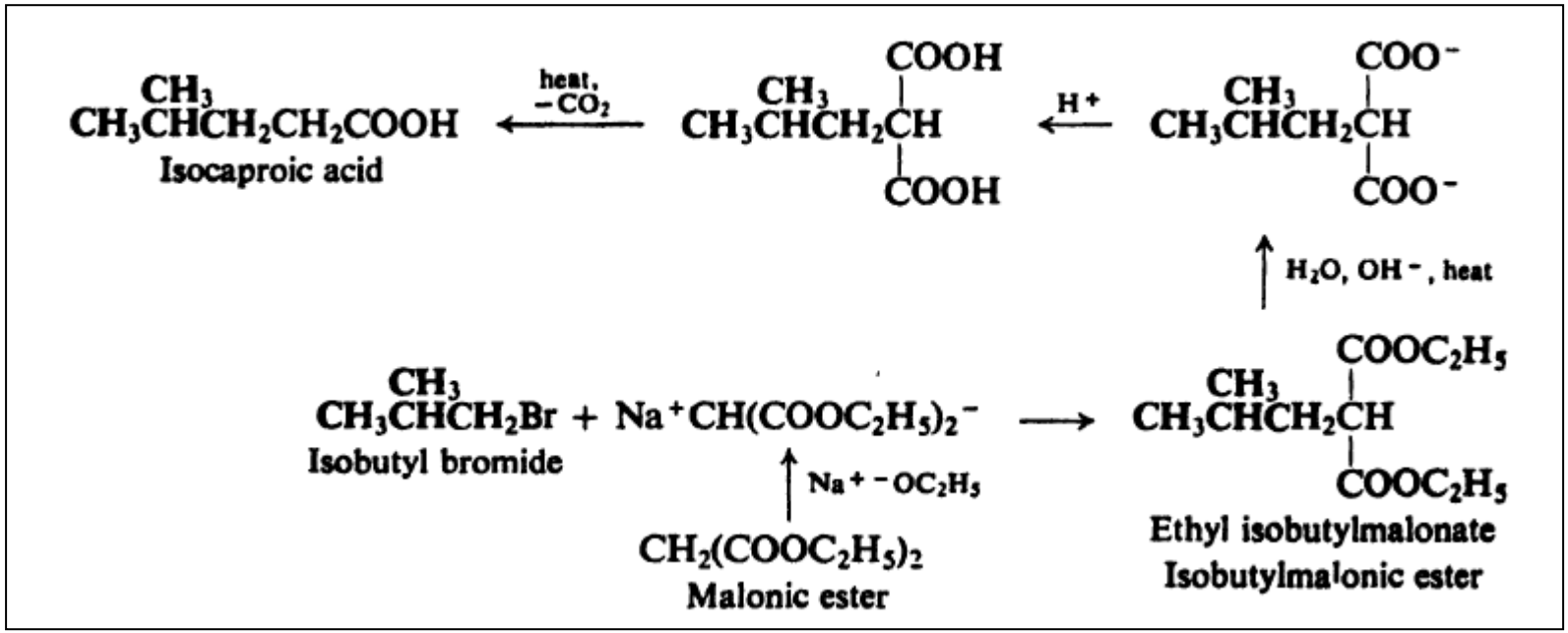

3-Methyl-2-hexanone
$-CO_2$
H_2O or H^+
OH^-
Methyl bromide
$Na^+ -OC_2H_5$
Ethyl α-methyl-α-n-propylacetoacetate
n-Propyl bromide
$Na^+ -OC_2H_5$
Ethyl acetoacetate


5-Methyl-2-hexanone
Isobutyl bromide
Ethyl acetoacetate
Ethyl α-isobutylacetoacetate


α-Methylsuccinic acid
Ethyl α-bromopropionate
Malonic ester


CH3COCH2COOC2H5
Acetoacetic ester
-OC2H5
CH3COCHCOOC2H5-
RX
CH3COCHCOOC2H5
R
OH-
CH3COCHCOO
R
H2O or H+
CH3COCHCOOH
R
-CO2
CH3COCH2R
A monosubstituted acetone
Monoalkylacetoacetic ester
-OC2H5
CH3COCRCOOC2H5-
R'X
R'
CH3COCCOOC2H5
R
OH-
R'
CH3COCCOO-
R
H2O or H+
R'
CH3COCCOOH
R
-CO2
CH3COCHRR'
A disubstituted acetone
Dialkylacetoacetic ester


CH3CH2CH2CHCOOH
CH3
α-Methylvaleric acid
heat, −CO2
COOH
CH3CH2CH2CCOOH
CH3
H+
COO−
CH3CH2CH2CCOO−
CH3
H2O, OH−, heat
COOC2H5
CH3CH2CH2CCOOC2H5
CH3
Ethyl methyl-n-propylmalonate
Methyl-n-propylmalonic ester
CH3Br + Na+CH3CH2CH2C(COOC2H5)2−
Methyl bromide
Na+ −OC2H5
CH3CH2CH2CH(COOC2H5)2
CH3CH2CH2Br + Na+CH(COOC2H5)2−
n-Propyl bromide
Na+ −OC2H5
CH2(COOC2H5)2
Malonic ester


CH3CHCH2CH2COOH
Isocaproic acid
heat, −CO2
CH3CHCH2CH
COOH
COOH
H+
COO−
COO−
H2O, OH−, heat
CH3CHCH2Br + Na+CH(COOC2H5)2−
Isobutyl bromide
Na+ −OC2H5
CH2(COOC2H5)2
Malonic ester
COOC2H5
COOC2H5
Ethyl isobutylmalonate
Isobutylmalonic ester