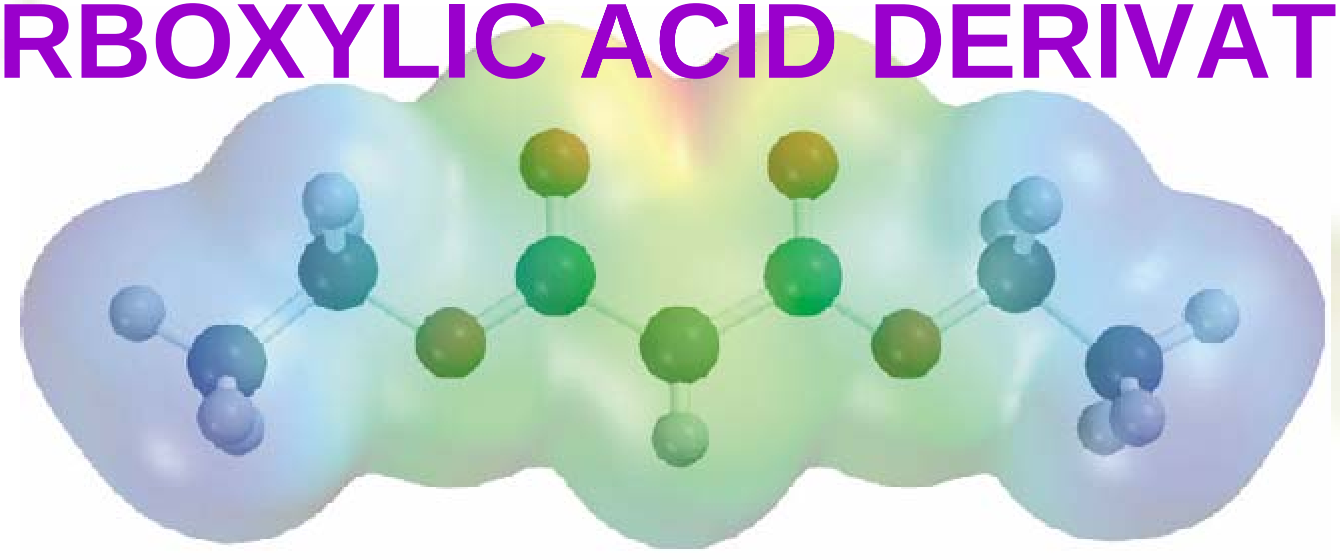
CHAPTER 13

CARBOXYLIC ACID DERIVATIVES



教学目的

1. 掌握羧酸衍生物的命名。
2. 掌握酰卤、酸酐、酯和酰胺的化学性质。
3. 掌握酯的水解历程($B_{Ac}2$、$A_{Ac}2$和$A_{Al}1$)。
4. 掌握乙酰乙酸乙酯和丙二酸二乙酯在有机合成中的应用。
5. 了解碳酸衍生物的种类和主要性质。
6. 熟悉有机合成的技巧并灵活使用。

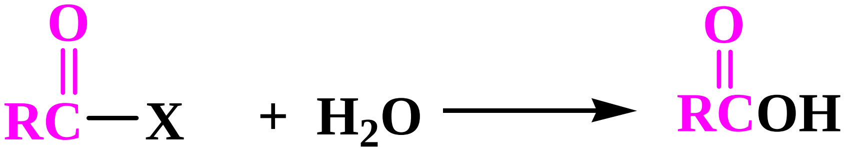
Contents

13.1 CARBOXYLIC ACID DERIVATIVES

13.1.1 NOMENCLATURE AND CLASSIFICATION

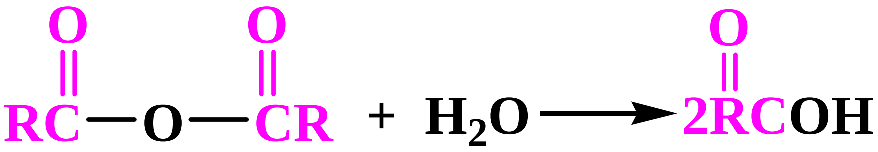
This chapter differs from preceding ones in that it deals with several related classes of compounds rather than just one. Although the compounds may encompass several functional group types, they share the common feature of yielding carboxylic acids on hydrolysis and , for this reason, are called carboxylic acid derivatives.

Acyl halide:



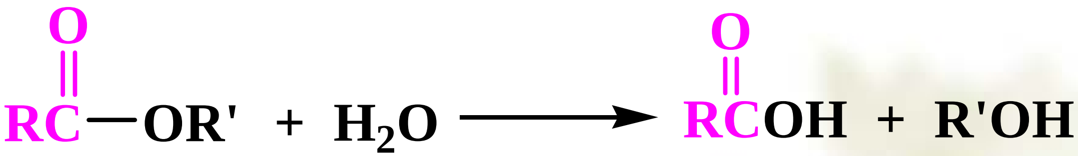
$$\mathrm{R\overset{\overset{O}{\|}}{C}-X + H_2O \longrightarrow R\overset{\overset{O}{\|}}{C}OH}$$

Carboxylic acid anhydride:



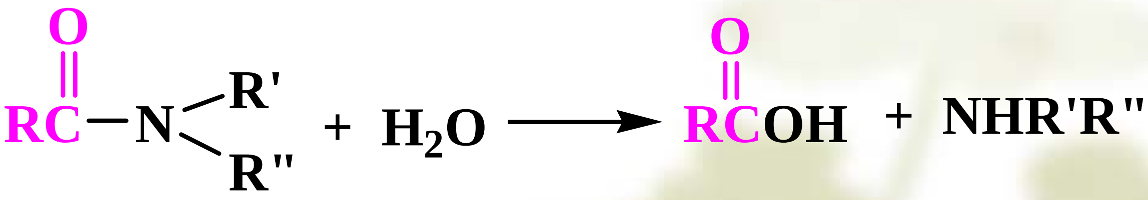
$$\mathrm{R\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}R + H_2O \longrightarrow 2R\overset{\overset{O}{\|}}{C}OH}$$

Ester:



$$\mathrm{R\overset{\overset{O}{\|}}{C}-OR' + H_2O \longrightarrow R\overset{\overset{O}{\|}}{C}OH + R'OH}$$

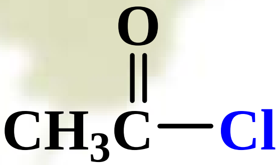
Amide:



$$\mathrm{R\overset{\overset{O}{\|}}{C}-N\begin{smallmatrix}\diagup R'\\ \diagdown R''\end{smallmatrix} + H_2O \longrightarrow R\overset{\overset{O}{\|}}{C}OH + NHR'R''}$$

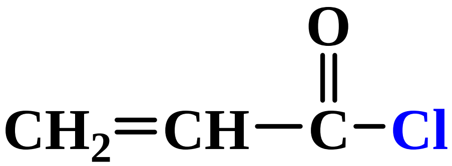
Naming:

Acyl halide:



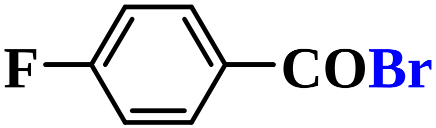
$CH_3\overset{\overset{O}{\|}}{C}-Cl$

Acetyl chloride



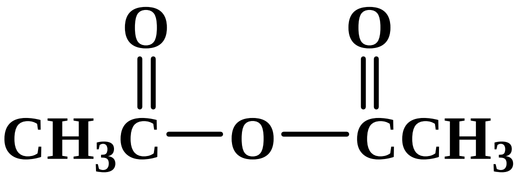
$CH_2=CH-\overset{\overset{O}{\|}}{C}-Cl$

Acryloyl chloride



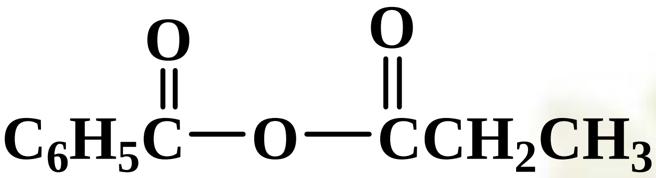
p-Fluorobenzoyl bromide

Carboxylic acid anhydride:



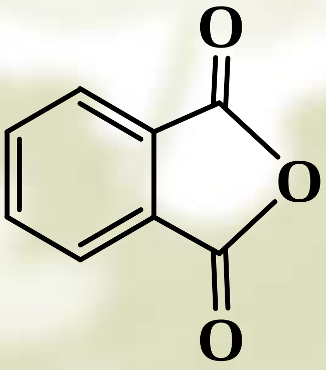
$CH_3\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}CH_3$

Acetic anhydride



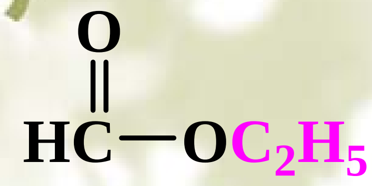
$C_6H_5\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}CH_2CH_3$

Benzoic propionic anhydride



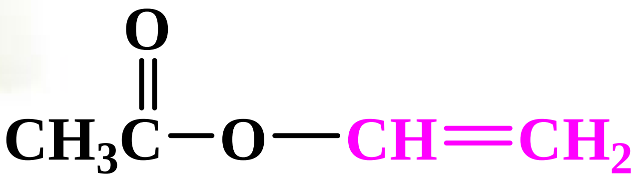
Phthalic anhydride

Esters:



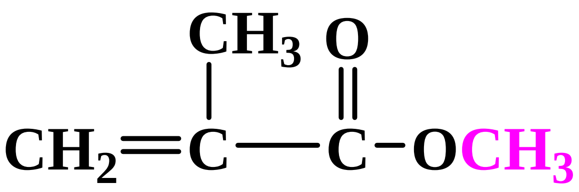
$H\overset{\overset{O}{\|}}{C}-OC_2H_5$

Ethyl formate



$CH_3\overset{\overset{O}{\|}}{C}-O-CH=CH_2$

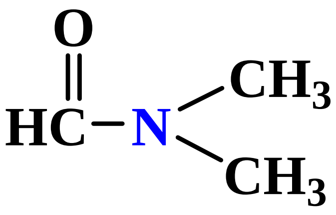
Vinyl acetate



$CH_2=\overset{\overset{CH_3}{|}}{C}-\overset{\overset{O}{\|}}{C}-OCH_3$

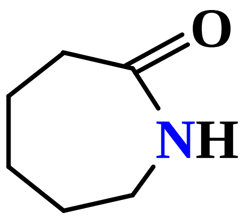
Methyl α -methacrylate

Amides:



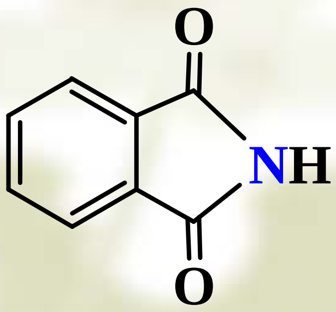
N,N-Dimethylformamide

(DMF)



ε -Caprolactam

(used to prepare a type of nylon-6)

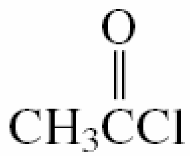


Phthalic imidine

13.1.2 SPECTROSCOPY

Infrared: **Infrared spectroscopy is quite useful in identifying carboxylic acid derivatives. The carbonyl stretching vibration is very strong, and its position is sensitive to the nature of the carbonyl group.**

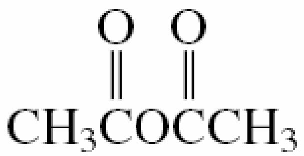
In general, electron donation from the substituent decreases the double-bond character of the bond between carbon and oxygen and decreases the stretching frequency.



$CH_3\overset{\overset{O}{\|}}{C}Cl$

Acetyl chloride

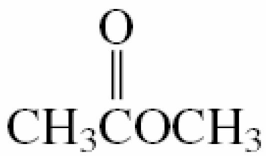
$\nu_{C=O} = 1822\ cm^{-1}$



$CH_3\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}CH_3$

Acetic anhydride

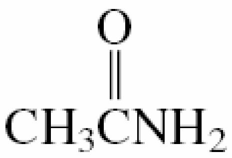
$\nu_{C=O} = 1748\ cm^{-1}$ and $1815\ cm^{-1}$



$CH_3\overset{\overset{O}{\|}}{C}OCH_3$

Methyl acetate

$\nu_{C=O} = 1736\ cm^{-1}$



$CH_3\overset{\overset{O}{\|}}{C}NH_2$

Acetamide

$\nu_{C=O} = 1694\ cm^{-1}$

Two distinct absorptions are observed for the symmetric and antisymmetrical stretching vibrations of the anhydride function.

Additional:

Carboxylic acid anhydrides:

$\nu_{C-O} = 1045\text{-}1300\ cm^{-1}$.

Esters: no O—H stretching vibration;

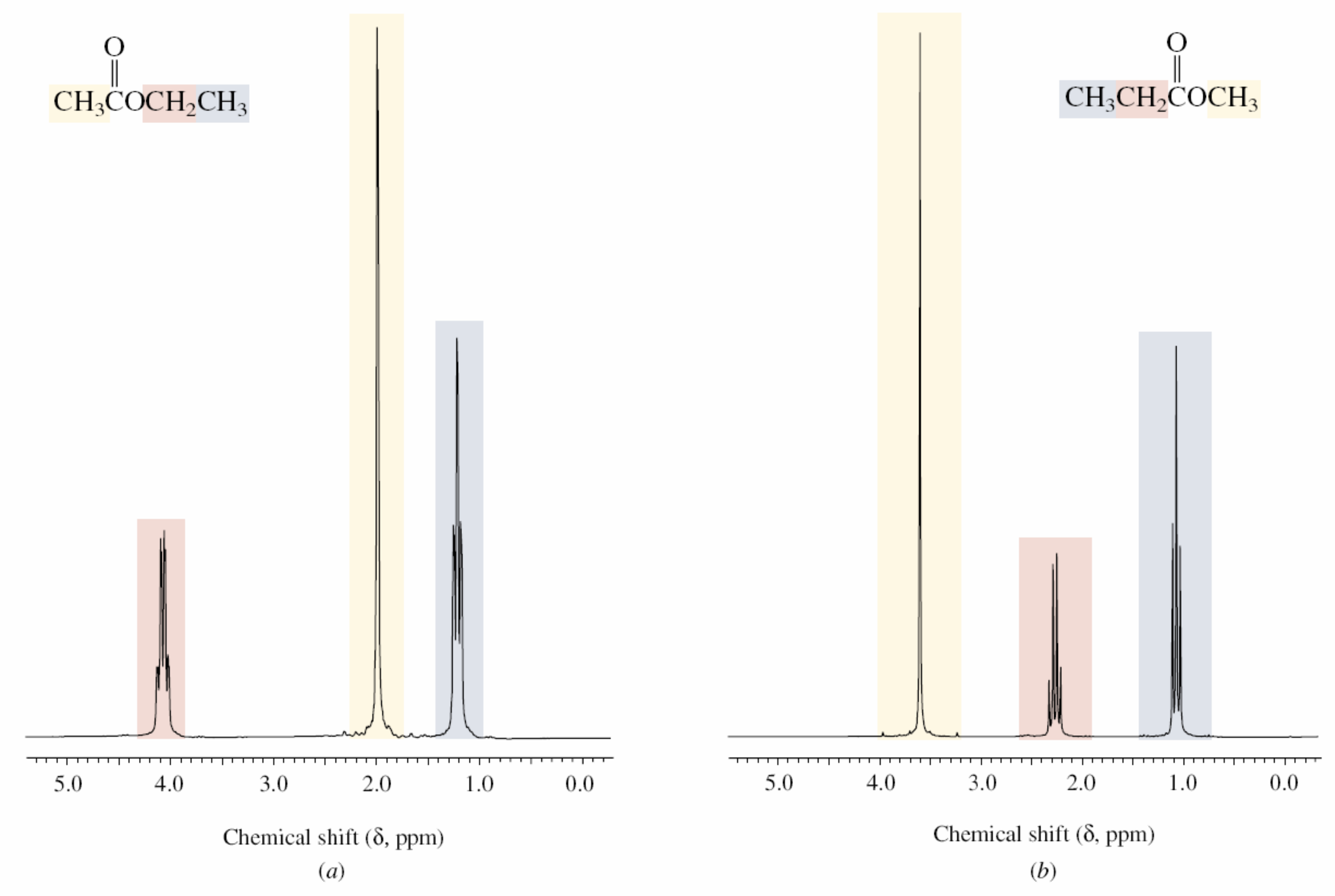
$\nu_{C-O} = 1050\text{-}1300\ cm^{-1}$.

Amides: $\nu_{N-H} = 3050\text{-}3550\ cm^{-1}$.

^{1}H NMR: **Chemical-shift differences in their ^{1}H NMR spectra aid the structure determination of esters.**

Ex: Ethyl acetate and methyl propionate

As Figure shows, the number of signals and their multiplicities are the same for both esters. Both have a methyl singlet and a triplet–quartet pattern for their ethyl group.



Esters: $\delta_{\text{alkoxyl H}} > \delta_{\text{acyloxy H}}$

The chemical shift of the **N-H** proton of amides appears in the range δ 5-8. It is often a very **broad peak**; sometimes it is so broad that it does not rise much over the baseline and can be lost in the background noise.

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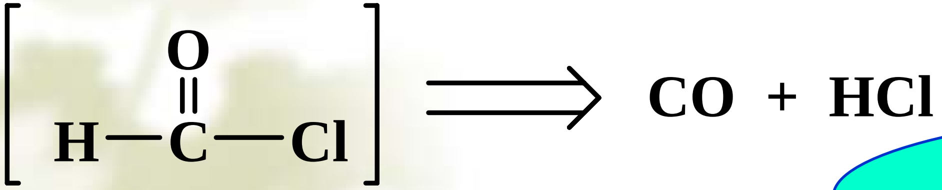
13.2 ACYL HALIDES AND CARBOXYLIC ACID ANHYDRIDES

13.2.1 ACYL HALIDES

Acyl chlorides are the most important acyl halides. They are readily prepared from carboxylic acids by reaction with $SOCl_2$, PCl_3, and PCl_5 (Section 12.3.2.2).



$$\left[H-\overset{O}{\overset{\|}{C}}-Cl \right] \Longrightarrow CO + HCl$$

Formyl chloride
(unstable)

Vigorous exothermal reaction

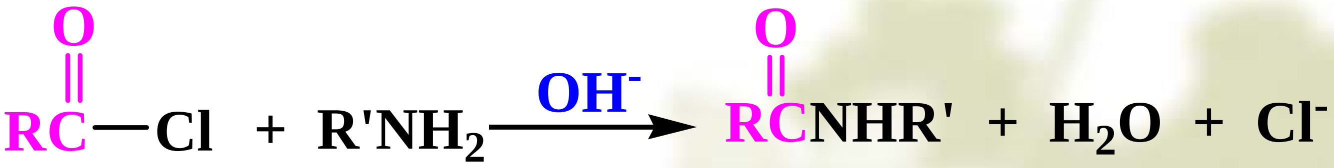
Hydrolysis:

$$R\overset{O}{\overset{\|}{C}}-Cl + H_2O \xrightarrow{\text{Pyridine}} R\overset{O}{\overset{\|}{C}}OH + HCl$$

Alcoholysis:

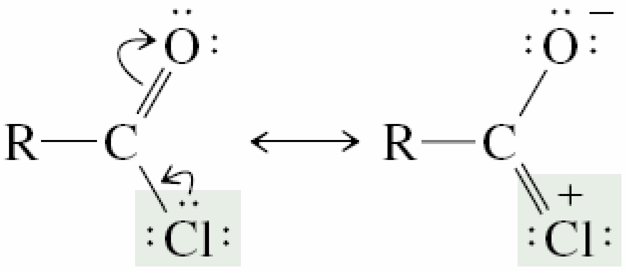
$$R\overset{O}{\overset{\|}{C}}-Cl + R'OH \xrightarrow{\text{Pyridine}} R\overset{O}{\overset{\|}{C}}OR' + HCl$$

Aminolysis:



$$R\overset{O}{\overset{\|}{C}}-Cl + R'NH_2 \xrightarrow{OH^-} R\overset{O}{\overset{\|}{C}}NHR' + H_2O + Cl^-$$

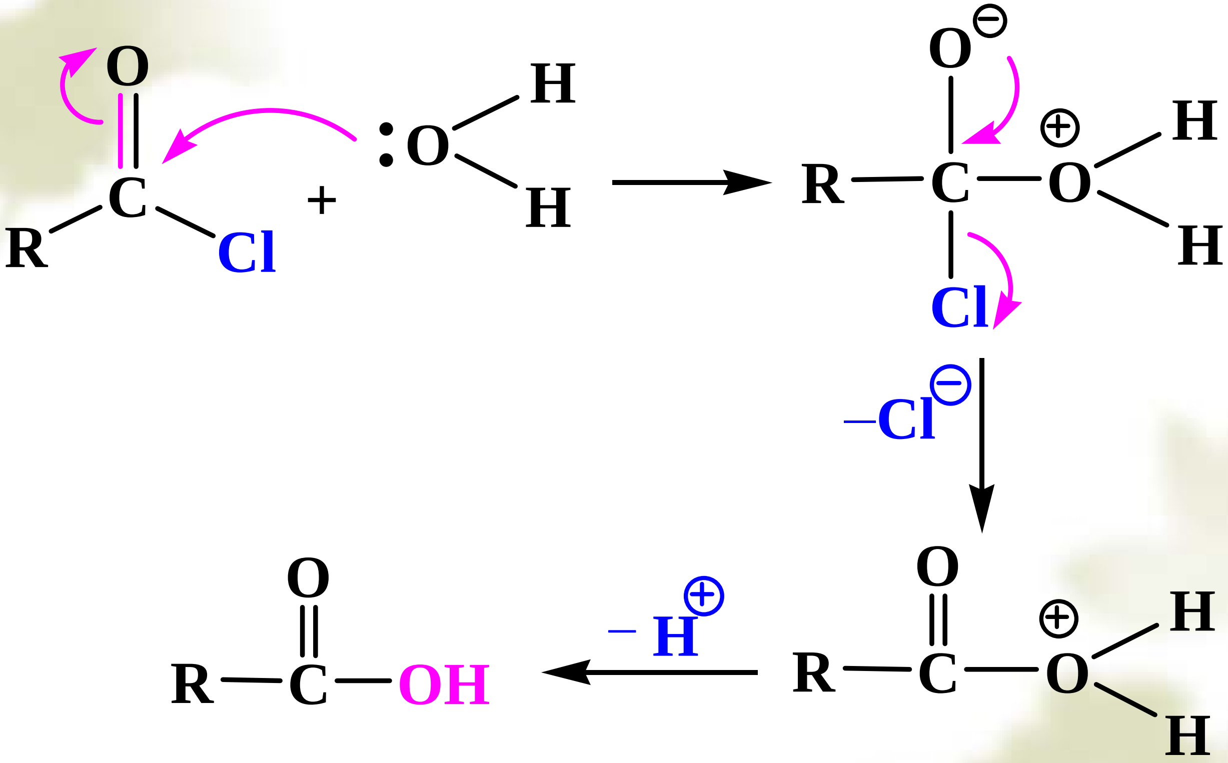
White solid



Weak resonance stabilization

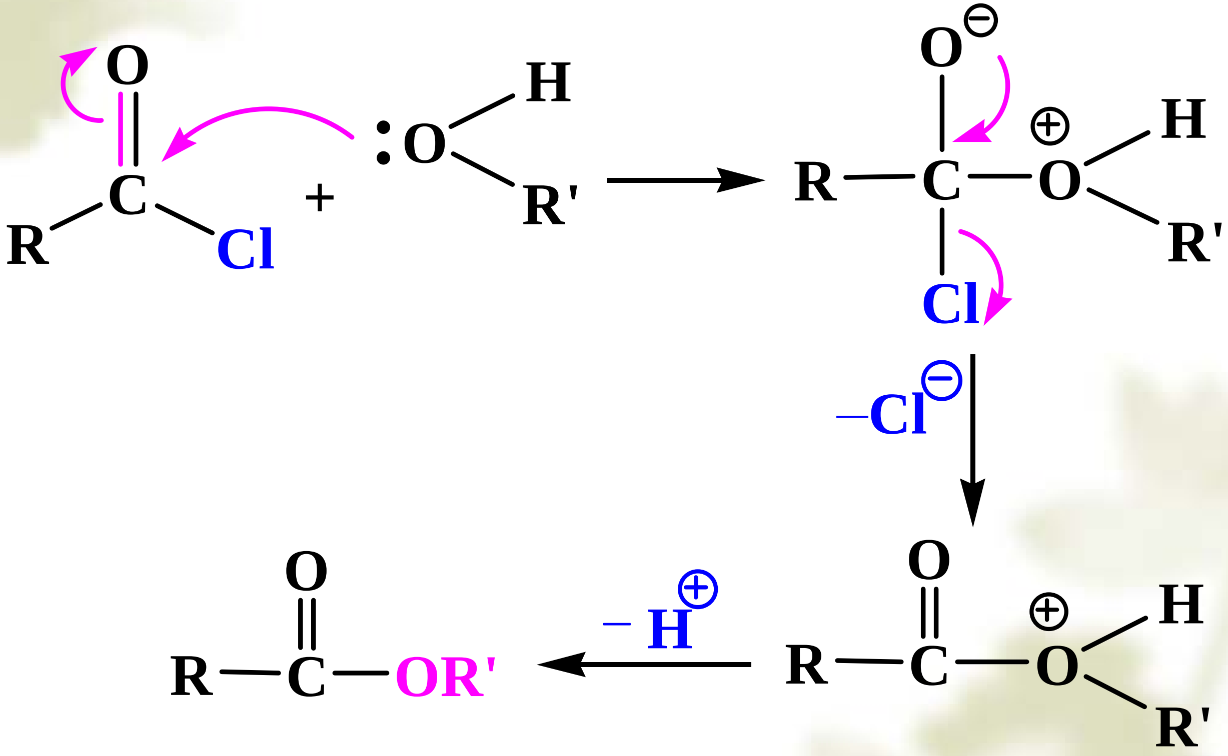
The carbonyl group of an acyl chloride feels the normal electron-withdrawing inductive effect of a chlorine substituent without much compensating electron donation by resonance. This *destabilizes* the carbonyl group and makes it *more reactive* to be attacked by nucleophiles.

Mechanism of Hydrolysis:

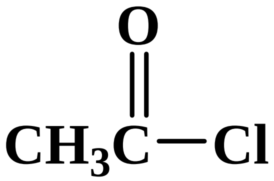


Problem: **Please give a reasonable explanation for the alcoholysis of acyl chloride.**

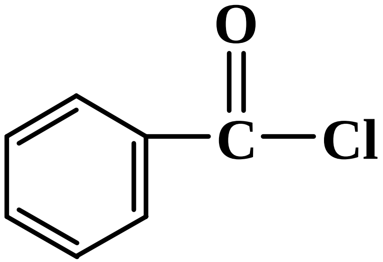
Sample solution: mechanism of alcoholysis



Example: **Rank the compounds in the following group in order of decreasing activity of hydrolysis, alcoholysis, and aminolysis:**

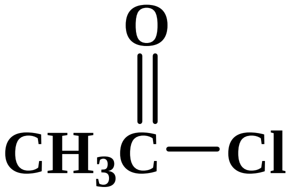


$\mathrm{CH_3}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}-\mathrm{Cl}$



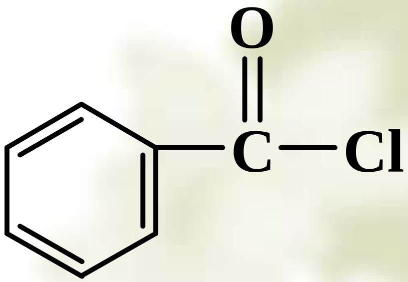
① Which reaction？ ② Stereo-electronic effect

Sample solution:



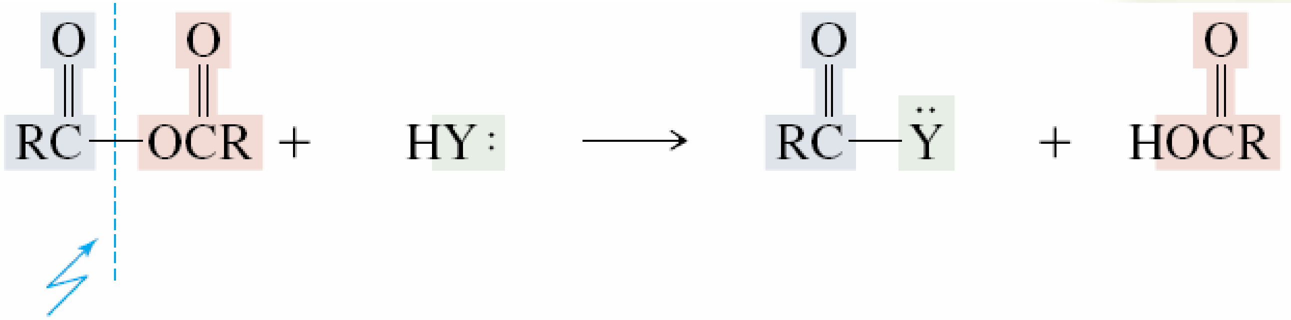
$\mathrm{CH_3}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}-\mathrm{Cl}$

$>$



13.2.2 CARBOXYLIC ACID ANHYDRIDES

Nucleophilic acyl substitution in acid anhydrides involves cleavage of a bond between oxygen and one of the carbonyl groups. One acyl group is transferred to an attacking nucleophile; the other retains its single bond to oxygen and becomes the acyl group of a carboxylic acid.



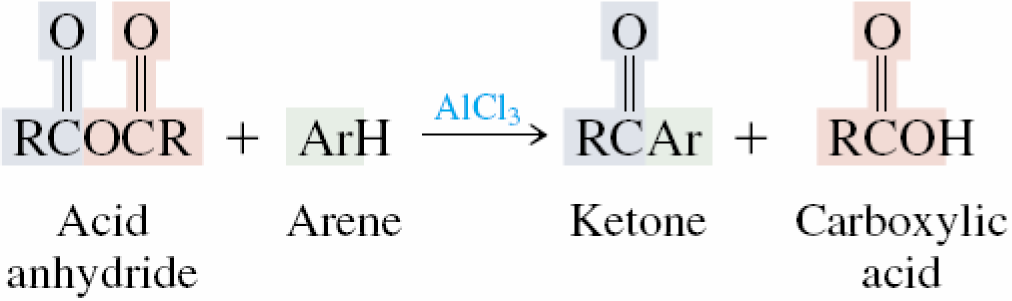
$$R\overset{\overset{O}{\|}}{C}-O\overset{\overset{O}{\|}}{C}R + HY\!: \longrightarrow R\overset{\overset{O}{\|}}{C}-\ddot{Y} + HO\overset{\overset{O}{\|}}{C}R$$

Bond cleavage occurs here in an acid anhydride.

Nucleophile

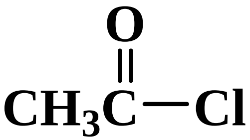
Product of nucleophilic acyl substitution

Carboxylic acid



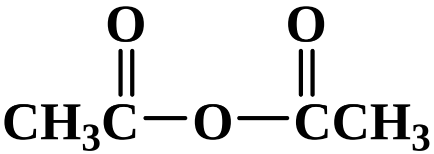
$$R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R + ArH \xrightarrow{AlCl_3} R\overset{O}{\overset{\|}{C}}Ar + R\overset{O}{\overset{\|}{C}}OH$$

Friedel-Crafts acylation reagents:



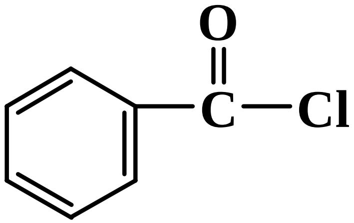
$$CH_3\overset{O}{\overset{\|}{C}}-Cl$$

Acetyl chloride

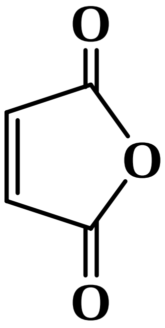


$$CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CH_3$$

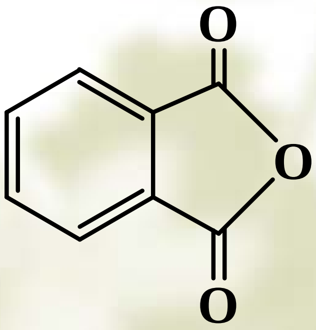
Acetic anhydride



Benzoyl chloride

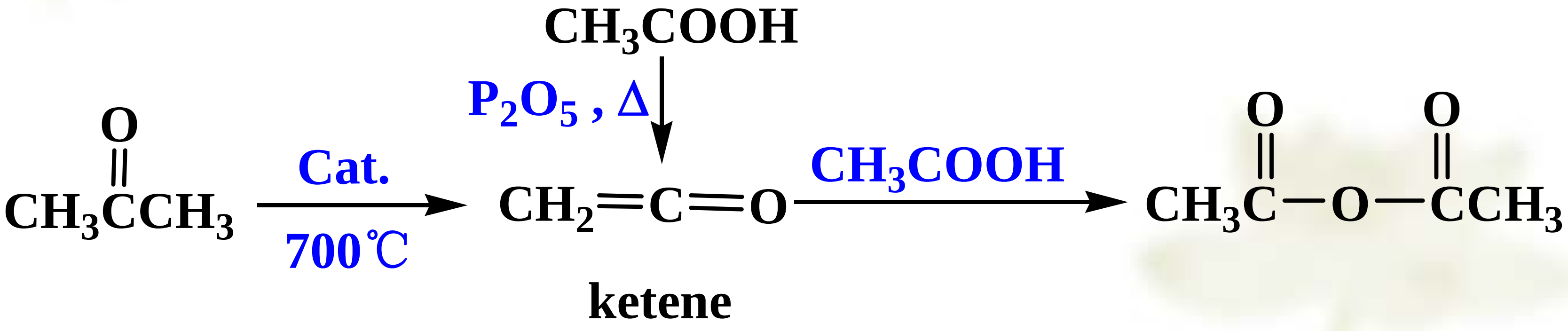


Maleic anhydride



Phthalic anhydride

An new method for the commercial production of acetic anhydride is shown as follows:



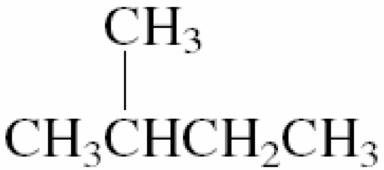
$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[700℃]{Cat.} \underset{ketene}{CH_2{=}\overset{\overset{CH_3COOH}{P_2O_5\ ,\ \Delta\ \downarrow}}{C}{=}O} \xrightarrow{CH_3COOH} CH_3\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}CH_3}$$

Contents

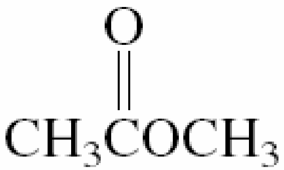
13.3 ESTERS

13.3.1 PHYSICAL PROPERTIES

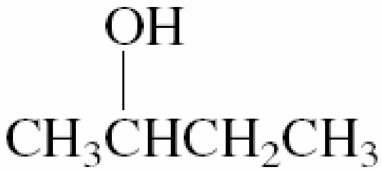
Esters are moderately polar. Dipole–dipole attractive forces give esters higher boiling points than hydrocarbons of similar shape and molecular weight. Because they lack hydroxyl groups, however, ester molecules cannot form hydrogen bonds to each other; consequently, esters have lower boiling points than alcohols of comparable molecular weight.


$CH_3CH(CH_3)CH_2CH_3$

2-Methylbutane:
mol wt 72, bp 28°C


$CH_3C(=O)OCH_3$

Methyl acetate:
mol wt 74, bp 57°C


$CH_3CH(OH)CH_2CH_3$

2-Butanol:
mol wt 74, bp 99°C

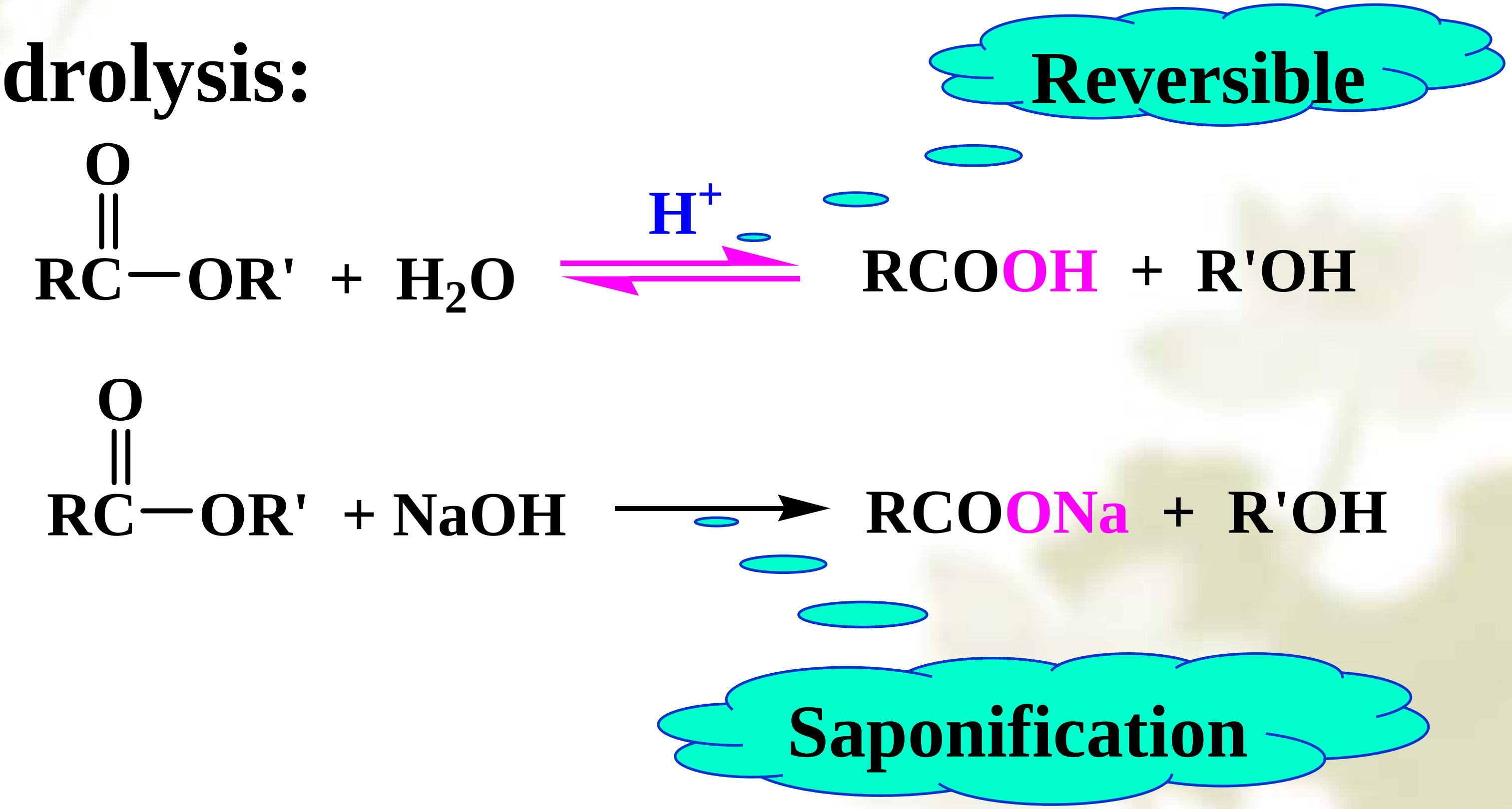
Esters can participate in hydrogen bonds with substances that contain hydroxyl groups (water, alcohols, carboxylic acids). This confers some measure of water solubility on low-molecular-weight esters; methyl acetate, for example, dissolves in water to the extent of 33 g/100 mL.

Water solubility *decreases* as the carbon content of the ester *increases*. Fats and oils, the glycerol esters (丙三醇酯) of long-chain carboxylic acids, are practically insoluble in water.

13.3.2 CHEMICAL PROPERTIES

13.3.2.1 NUCLEOPHILIC ACYL SUBSTITUTIONS

Hydrolysis:



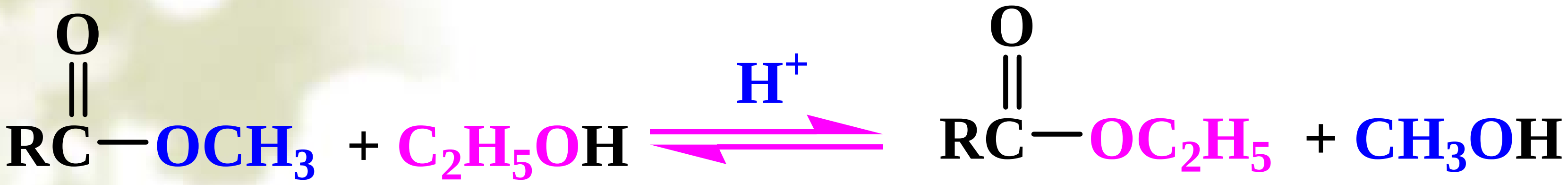
$$\mathrm{R}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}-\mathrm{OR'} + \mathrm{H_2O} \xrightleftharpoons{\mathrm{H^+}} \mathrm{RCOOH} + \mathrm{R'OH}$$

Reversible

$$\mathrm{R}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}-\mathrm{OR'} + \mathrm{NaOH} \longrightarrow \mathrm{RCOONa} + \mathrm{R'OH}$$

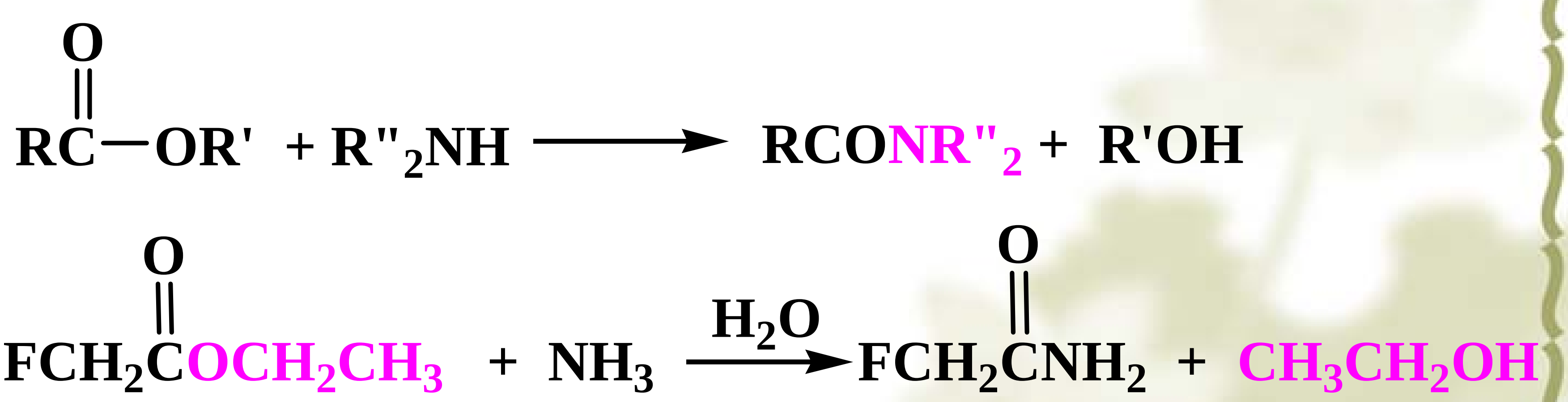
Saponification

Alcoholysis:



$$R\overset{\overset{O}{\|}}{C}-OCH_3 + C_2H_5OH \xrightleftharpoons{H^+} R\overset{\overset{O}{\|}}{C}-OC_2H_5 + CH_3OH$$

Aminolysis:

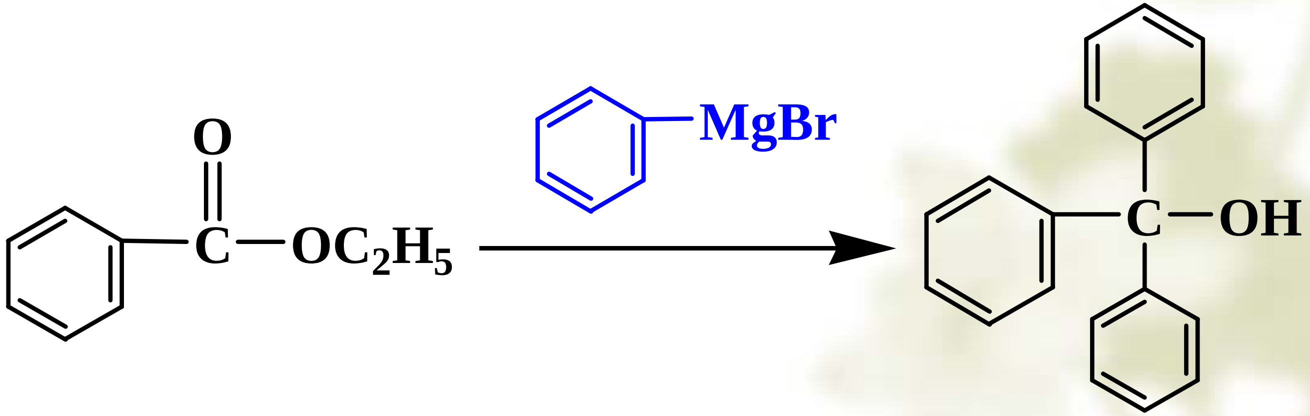


$$R\overset{\overset{O}{\|}}{C}-OR' + R''_2NH \longrightarrow RCONR''_2 + R'OH$$

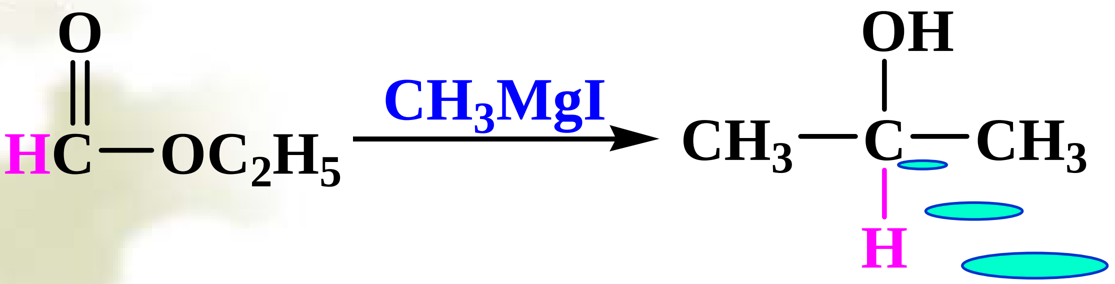
$$FCH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 + NH_3 \xrightarrow{H_2O} FCH_2\overset{\overset{O}{\|}}{C}NH_2 + CH_3CH_2OH$$

13.3.2.2 REACTION WITH GRIGNARD REAGENTS

Esters react with two equivalents of a Grignard reagent to produce tertiary alcohols. Two of the groups bonded to the carbon that bears the hydroxyl group in the tertiary alcohol are derived from the Grignard reagent.



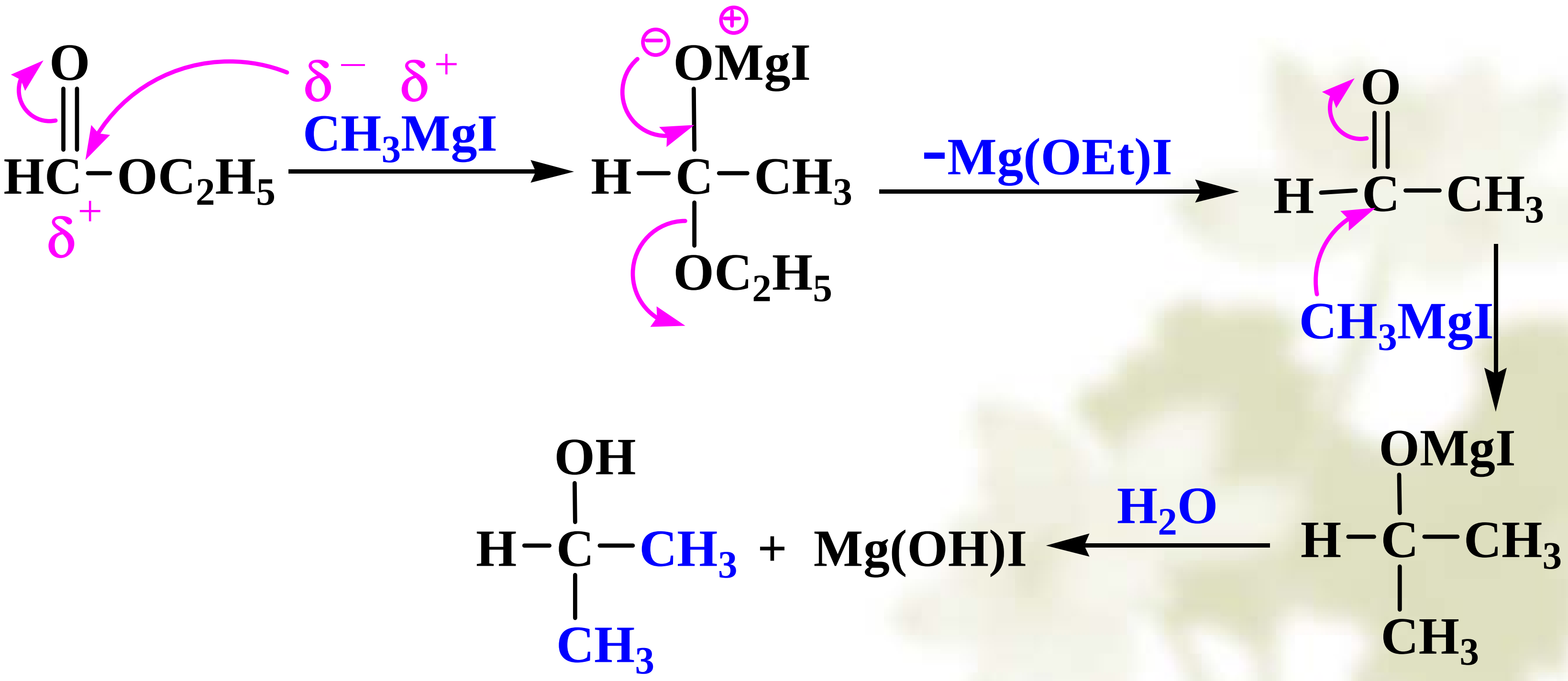
Ex1:



$$HCOOC_2H_5 \xrightarrow{CH_3MgI} CH_3-CH(OH)-CH_3$$

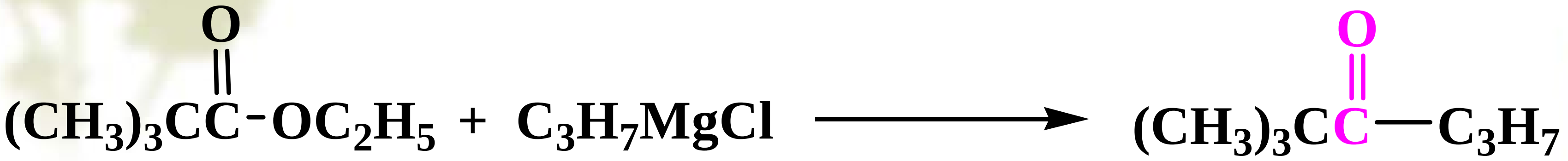
Secondary alcohol

Mechanism:



$$HC(=O)-OC_2H_5 \xrightarrow{CH_3MgI} H-C(OMgI)(OC_2H_5)-CH_3 \xrightarrow{-Mg(OEt)I} H-C(=O)-CH_3 \xrightarrow{CH_3MgI} H-C(OMgI)(CH_3)-CH_3 \xrightarrow{H_2O} H-C(OH)(CH_3)-CH_3 + Mg(OH)I$$

Ex2: Esters with steric substituents



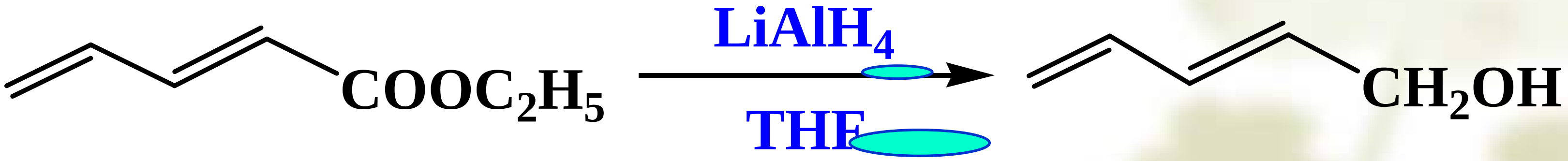
$$(CH_3)_3C\overset{O}{\overset{\|}{C}}-OC_2H_5 + C_3H_7MgCl \longrightarrow (CH_3)_3C\overset{O}{\overset{\|}{C}}-C_3H_7$$

13.3.2.3 REDUCTION

1. Catalytic hydrogenation:

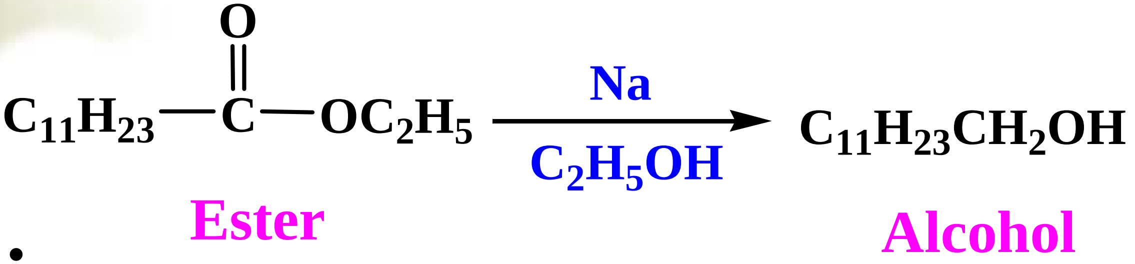
$$RCOOR' + H_2 \xrightarrow[250\ ^\circ\mathrm{C},\ 20\text{-}33\ \mathrm{MPa}]{CuO\text{-}Cr_2O_3} RCH_2OH + R'OH$$

2. Reduction with lithium aluminum hydride:



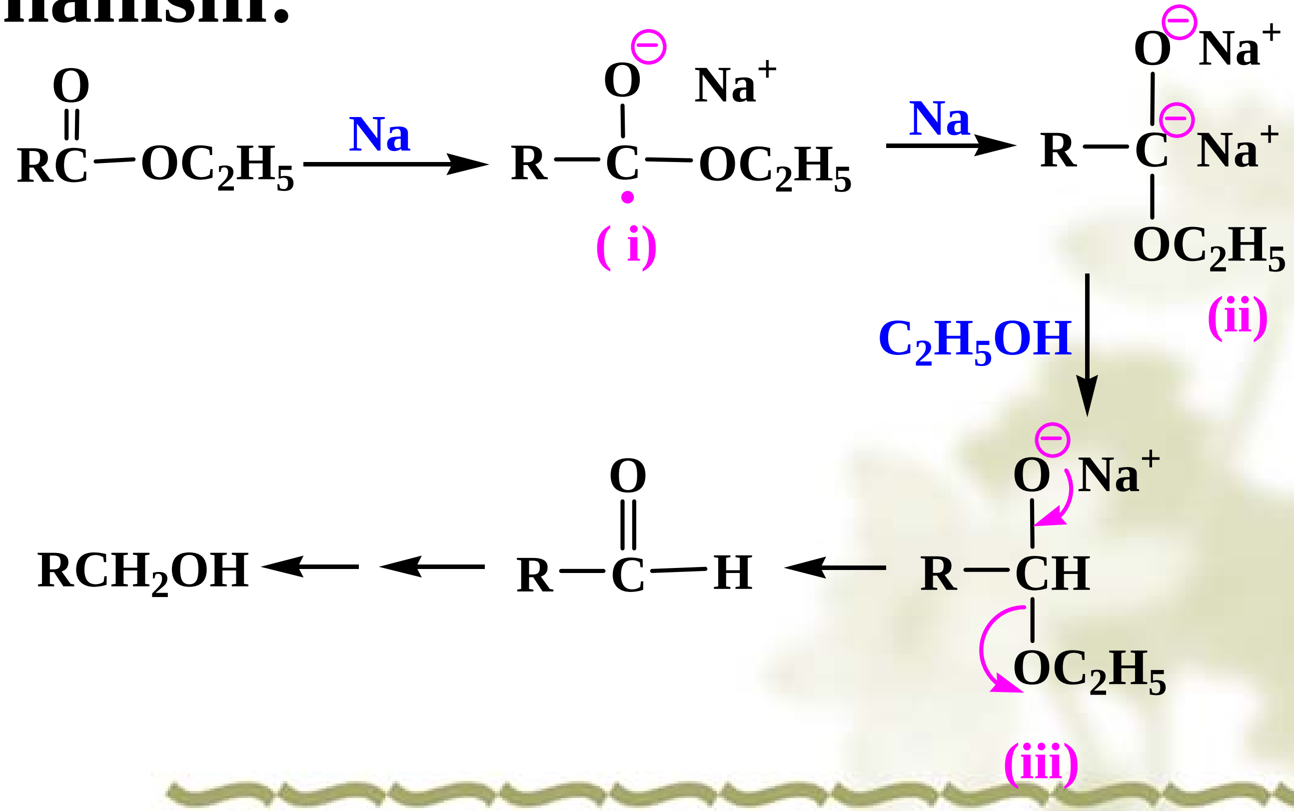
Selective reduction, C=C double bond retained

3. Reduction with sodium in protic solvent (alcohol):

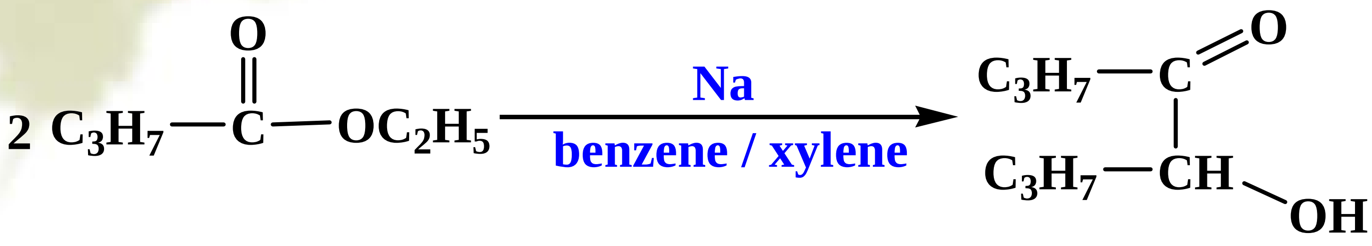


$$C_{11}H_{23}-\overset{\overset{O}{\parallel}}{C}-OC_2H_5 \xrightarrow[C_2H_5OH]{Na} C_{11}H_{23}CH_2OH$$

Mechanism:



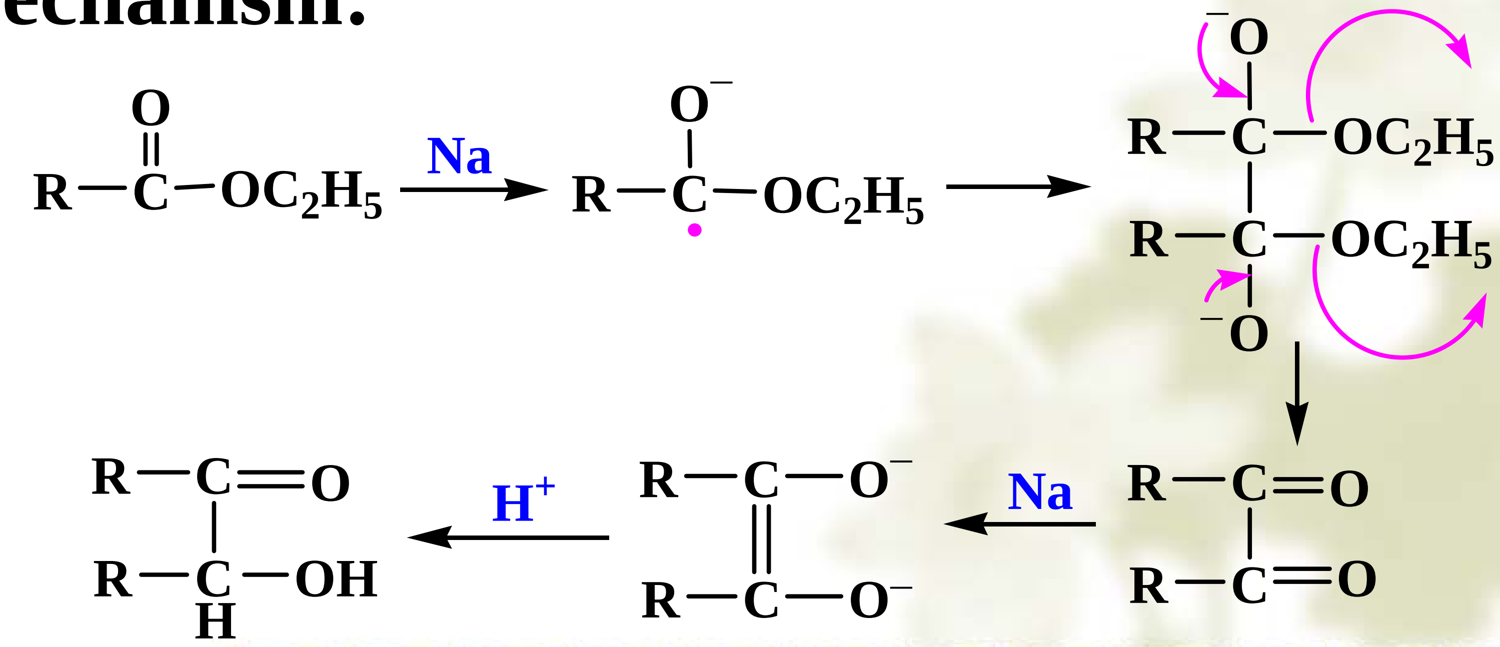
4. Reduction with sodium in aprotic solvent (benzene, toluene, xylene):



Ester

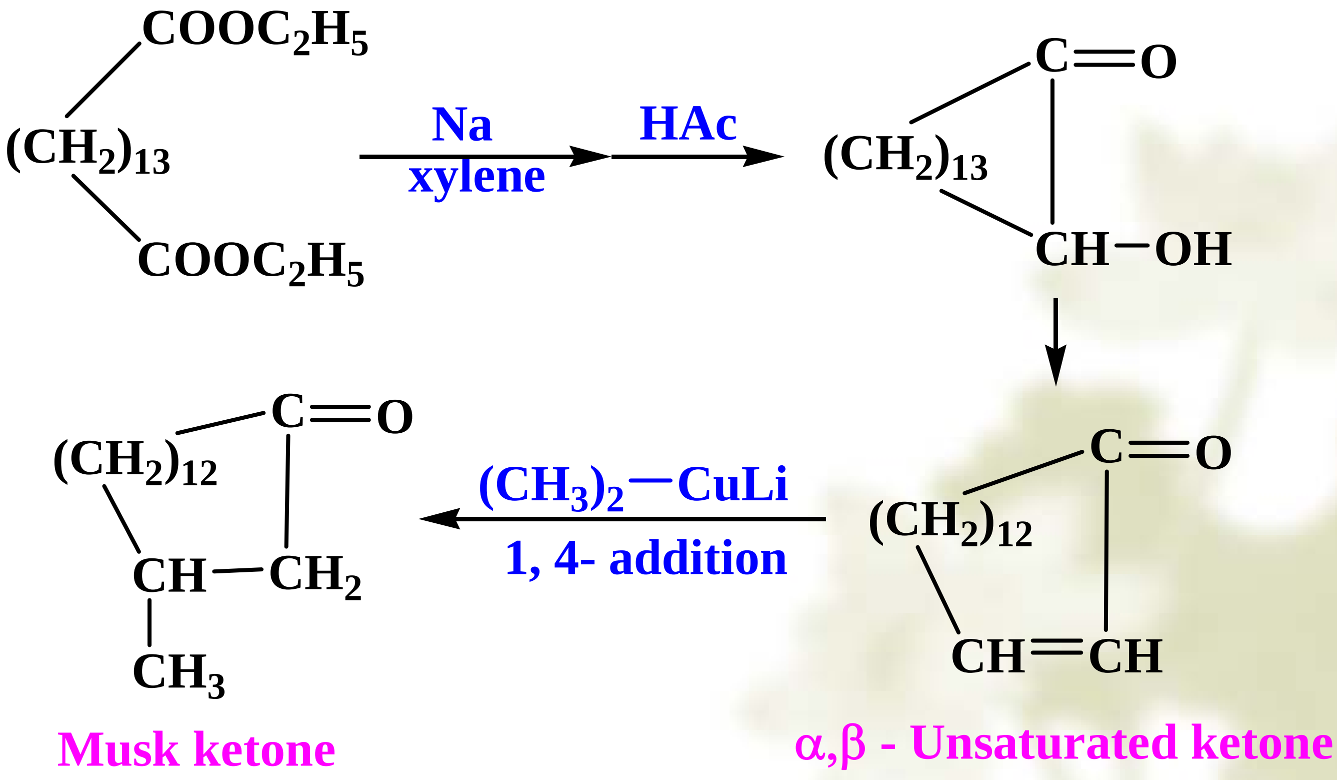
α–Hydroxy ketone

Mechanism:

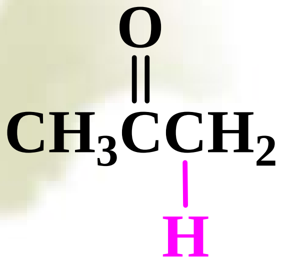


It is a useful method to synthesis macrocyclic compounds by reducing the diesters in good yields.

Ex:

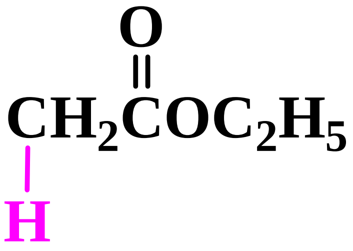


13.3.2.4 ESTER CONDENSATION



$CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{H}{|}}{CH_2}$

α -H *p*Ka = 20

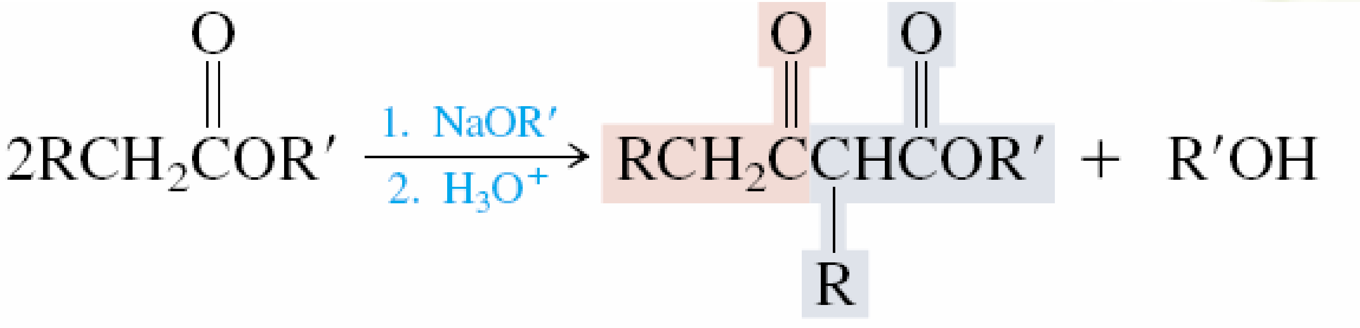


$\underset{\underset{H}{|}}{CH_2}\overset{\overset{O}{\|}}{C}OC_2H_5$

α -H *p*Ka = 24

Aldol condensation ***Claisen condensation***

1. Claisen condensation

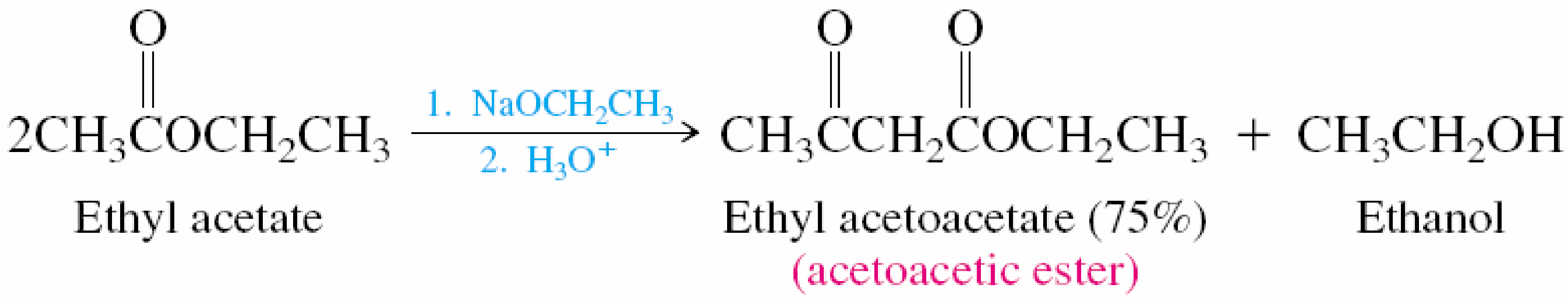


$$2RCH_2\overset{\overset{O}{\|}}{C}OR' \xrightarrow[2.\ H_3O^+]{1.\ NaOR'} RCH_2\overset{\overset{O}{\|}}{C}\underset{\underset{R}{|}}{C}H\overset{\overset{O}{\|}}{C}OR' + R'OH$$

Ester β-Keto ester Alcohol

On treatment with alkoxide bases, esters undergo self-condensation to give a β-keto ester and an alcohol.

Ethyl acetate, for example, undergoes a Claisen condensation on treatment with sodium ethoxide to give a β-keto ester known by its common name *ethyl acetoacetate*.



$$2CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2OH$$

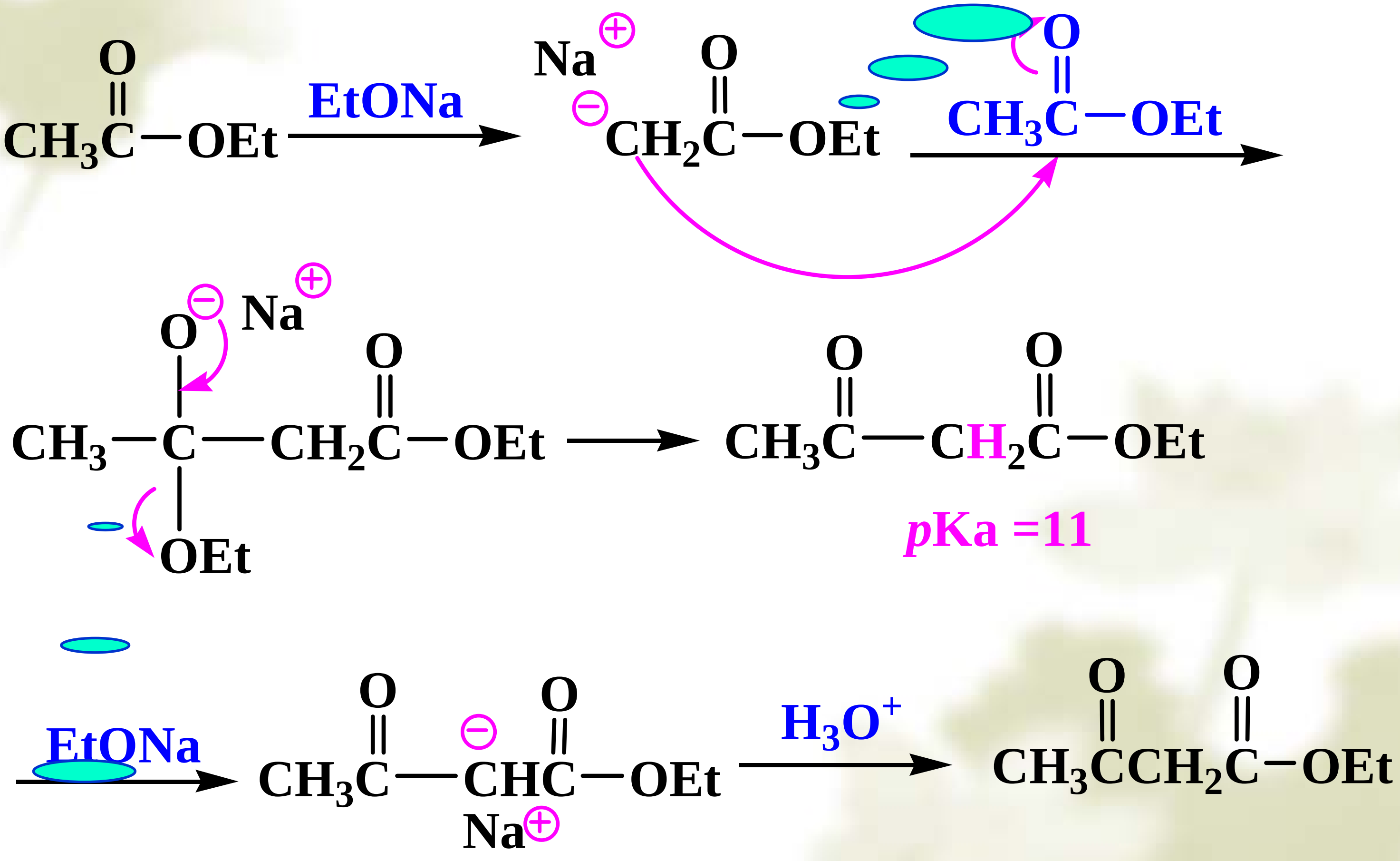
Ethyl acetate

Ethyl acetoacetate (75%)
(acetoacetic ester)

Ethanol

Mechanism:

Nucleophilic addition



$$CH_3\overset{O}{\overset{\|}{C}}-OEt \xrightarrow{EtONa} Na^{\oplus}\ {}^{\ominus}CH_2\overset{O}{\overset{\|}{C}}-OEt \xrightarrow{CH_3\overset{O}{\overset{\|}{C}}-OEt}$$

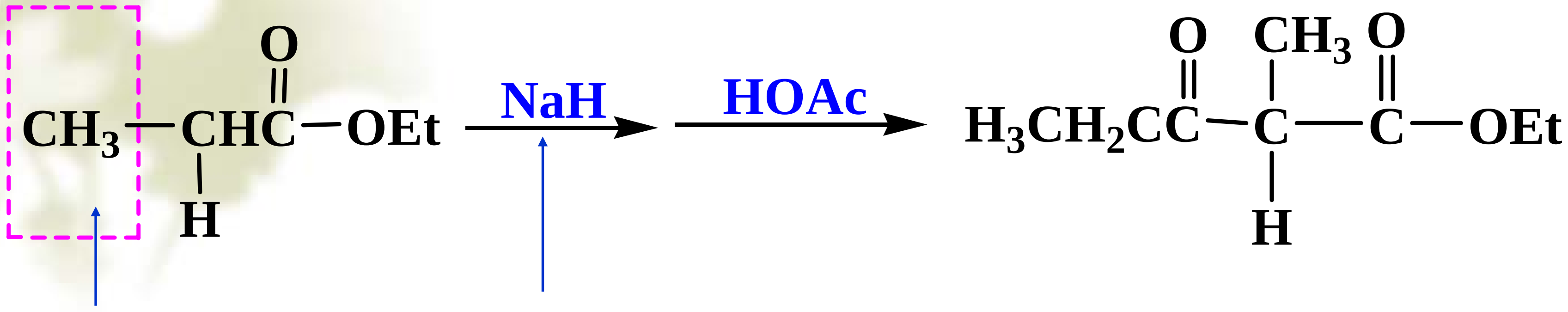
$$CH_3-\overset{O^{\ominus}\ Na^{\oplus}}{\overset{|}{\underset{\underset{OEt}{|}}{C}}}-CH_2\overset{O}{\overset{\|}{C}}-OEt \longrightarrow CH_3\overset{O}{\overset{\|}{C}}-CH_2\overset{O}{\overset{\|}{C}}-OEt$$

$pKa = 11$

$$\xrightarrow{EtONa} CH_3\overset{O}{\overset{\|}{C}}-\underset{Na^{\oplus}}{\overset{\ominus}{CH}}\overset{O}{\overset{\|}{C}}-OEt \xrightarrow{H_3O^+} CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}-OEt$$

Elimination

Ex:



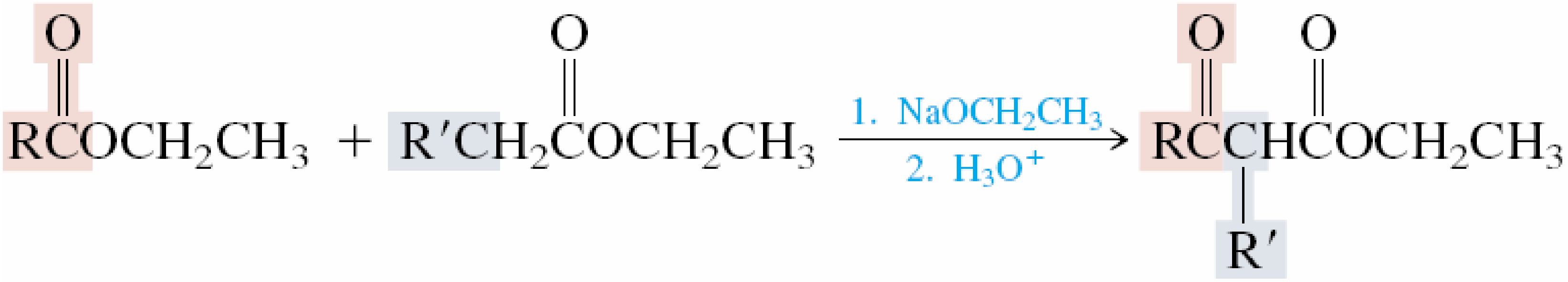
$$\mathrm{CH_3}-\underset{\mathrm{H}}{\mathrm{CH}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OEt} \xrightarrow{\mathrm{NaH}} \xrightarrow{\mathrm{HOAc}} \mathrm{H_3CH_2C}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{CH_3}}{\underset{\mathrm{H}}{\mathrm{C}}}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OEt}$$

ERG **Stronger bases: PhLi, Ph_3CNa**

Attention: **At least two protons must be present at the carbon for the equilibrium to favor product formation. Claisen condensation is possible for esters of the type RCH_2CO_2R, but not for R_2CHCO_2R.**

2. Mixed Claisen condensation

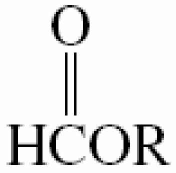
Analogous to mixed aldol condensations, mixed Claisen condensations involve carbon–carbon bond formation between the α-carbon atom of one ester and the carbonyl carbon of another.



$$R\overset{O}{\overset{\|}{C}}OCH_2CH_3 + R'CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} R\overset{O}{\overset{\|}{C}}\underset{R'}{\underset{|}{C}H}\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

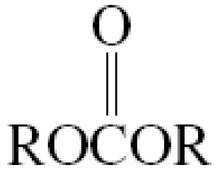
Ester Another ester β-Keto ester

The best results are obtained when one of the ester components is incapable of forming an enolate. Esters of this type include the following:



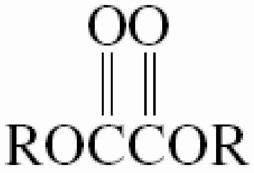
$H\overset{\overset{O}{\|}}{C}OR$

Formate esters



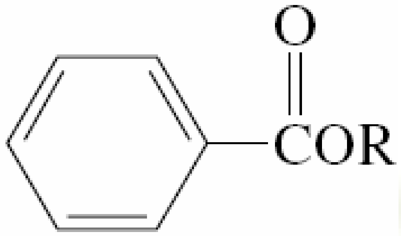
$RO\overset{\overset{O}{\|}}{C}OR$

Carbonate esters



$RO\overset{\overset{O}{\|}}{C}\overset{\overset{O}{\|}}{C}OR$

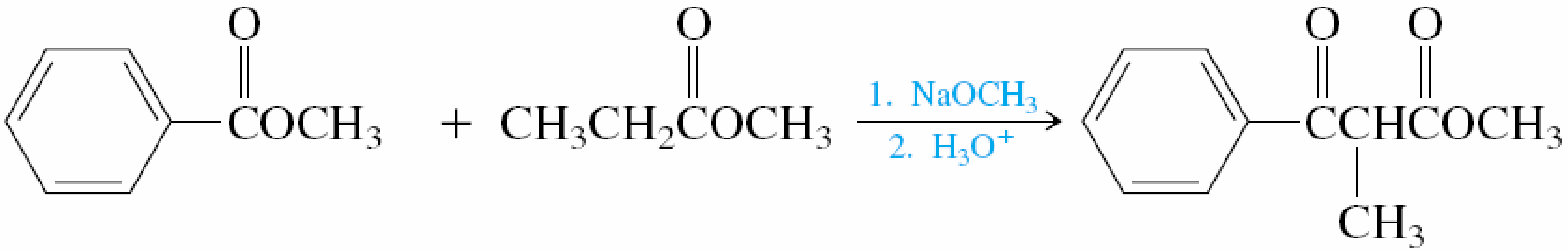
Oxalate esters



Benzoate esters

Lack of α-H atom

Ex 1: **The following equation shows an example of a mixed Claisen condensation in which a benzoate ester is used as the nonenolizable component:**

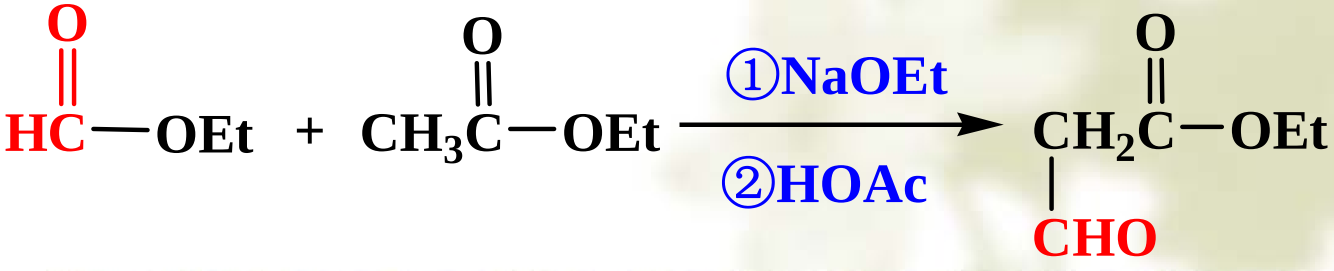


Methyl benzoate
(cannot form an enolate)

Methyl propanoate

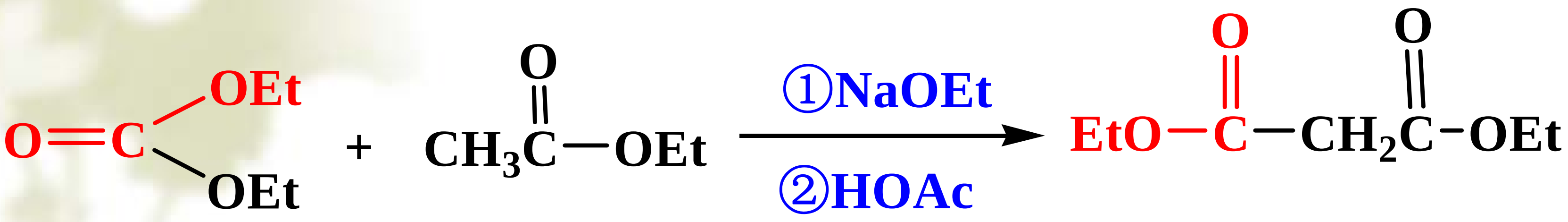
Methyl 2-methyl-3-oxo-3-phenylpropanoate (60%)

Ex 2:



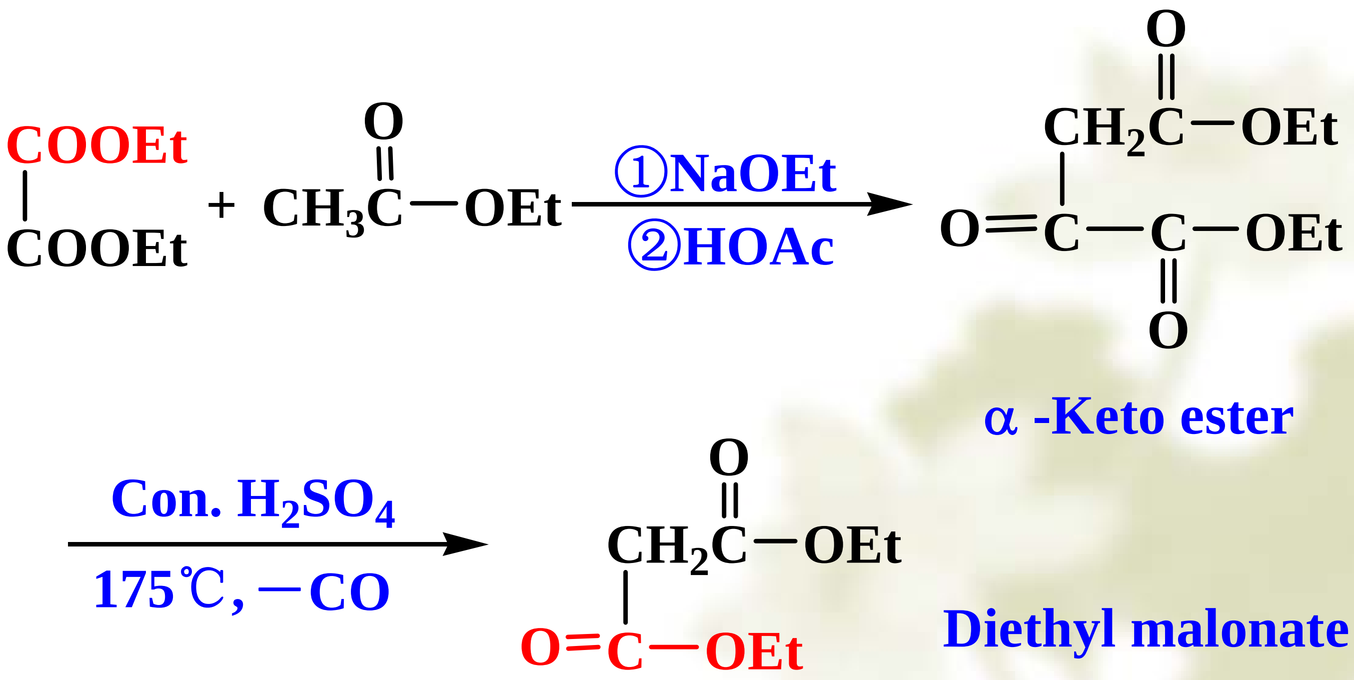
$$\overset{O}{\overset{\|}{HC}}-OEt + CH_3\overset{O}{\overset{\|}{C}}-OEt \xrightarrow[②HOAc]{①NaOEt} \underset{CHO}{\underset{|}{CH_2}}\overset{O}{\overset{\|}{C}}-OEt$$

Ex 3:



$$O{=}C(OEt)_2 + CH_3\overset{O}{\overset{\|}{C}}{-}OEt \xrightarrow[②HOAc]{①NaOEt} EtO{-}\overset{O}{\overset{\|}{C}}{-}CH_2\overset{O}{\overset{\|}{C}}{-}OEt$$

Ex 4:



$$\begin{array}{l}COOEt\\ |\\ COOEt\end{array} + CH_3\overset{O}{\overset{\|}{C}}{-}OEt \xrightarrow[②HOAc]{①NaOEt} O{=}C(CH_2COOEt){-}\overset{O}{\overset{\|}{C}}{-}OEt$$

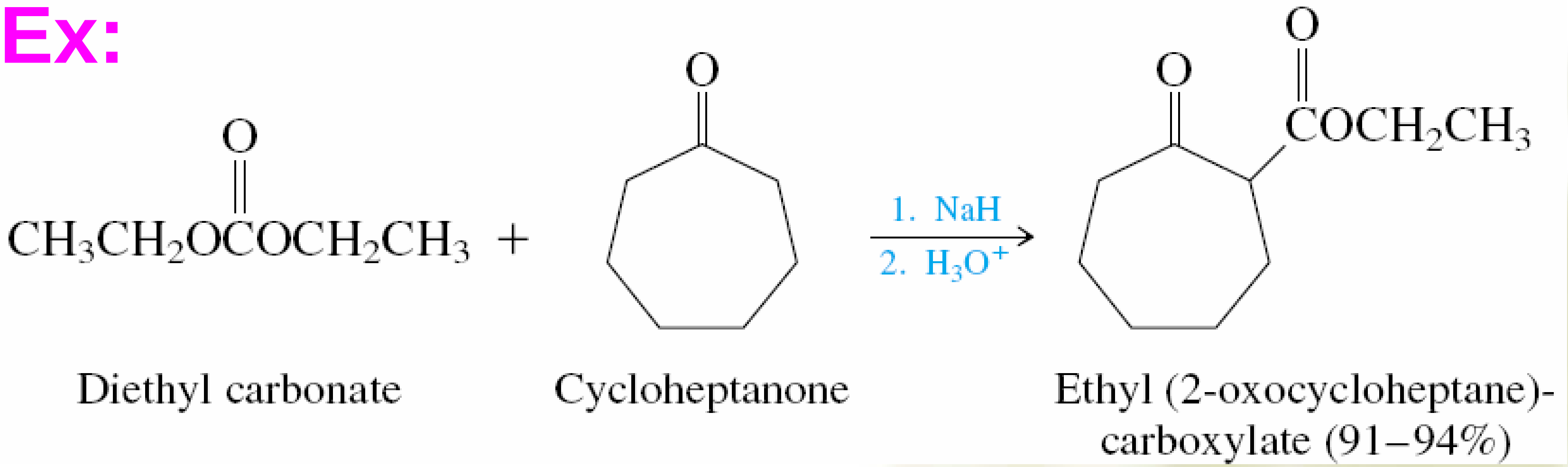
α -Keto ester

$$\xrightarrow[175℃,\ -CO]{Con.\ H_2SO_4} \begin{array}{l}CH_2\overset{O}{\overset{\|}{C}}{-}OEt\\ |\\ O{=}C{-}OEt\end{array}$$

Diethyl malonate

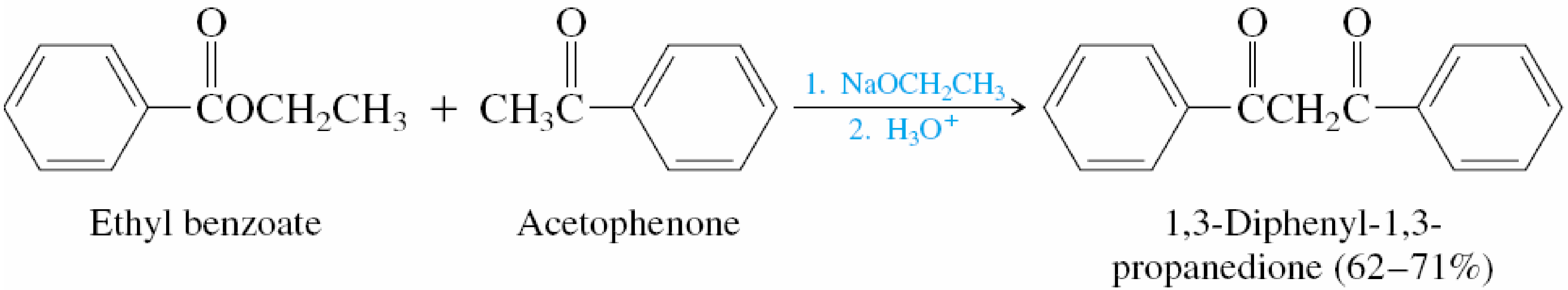
- **In a reaction related to the mixed Claisen condensation, nonenolizable esters are used as acylating agents for ketone enolates. Ketones (via their enolates) are converted to β-keto esters by reaction with diethyl carbonate.**

Ex:



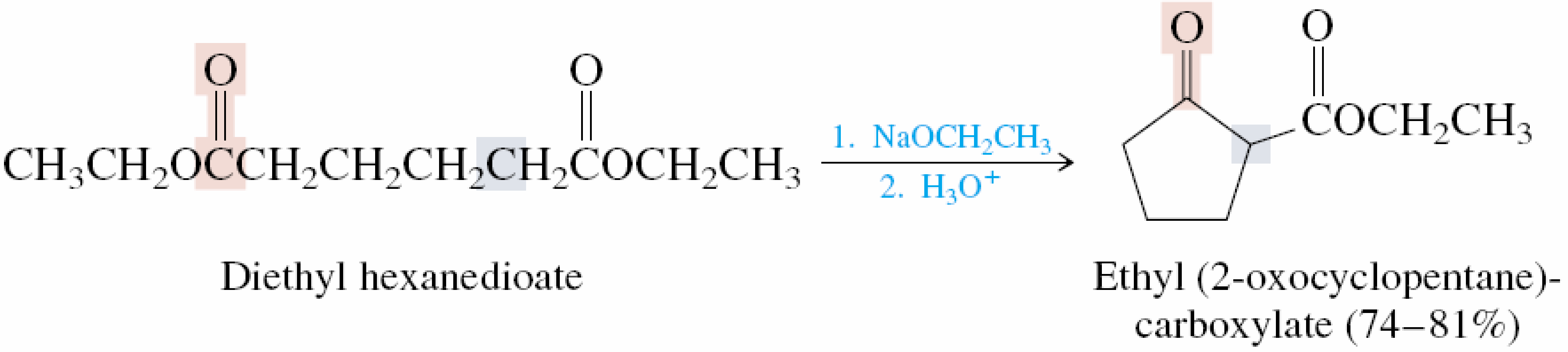
- Esters of nonenolizable monocarboxylic acids such as ethyl benzoate give β-diketones on reaction with ketone enolates:

Ex:



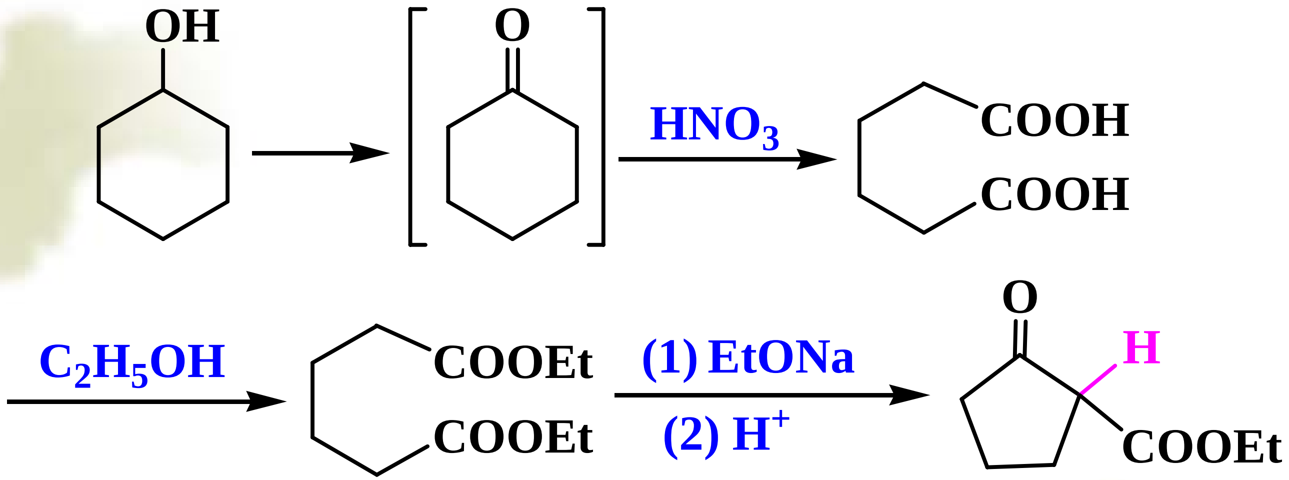
3. Intramolecular Claisen condensation

Esters of dicarboxylic acids undergo an *intramolecular* version of the Claisen condensation when a five- or six-membered ring can be formed.

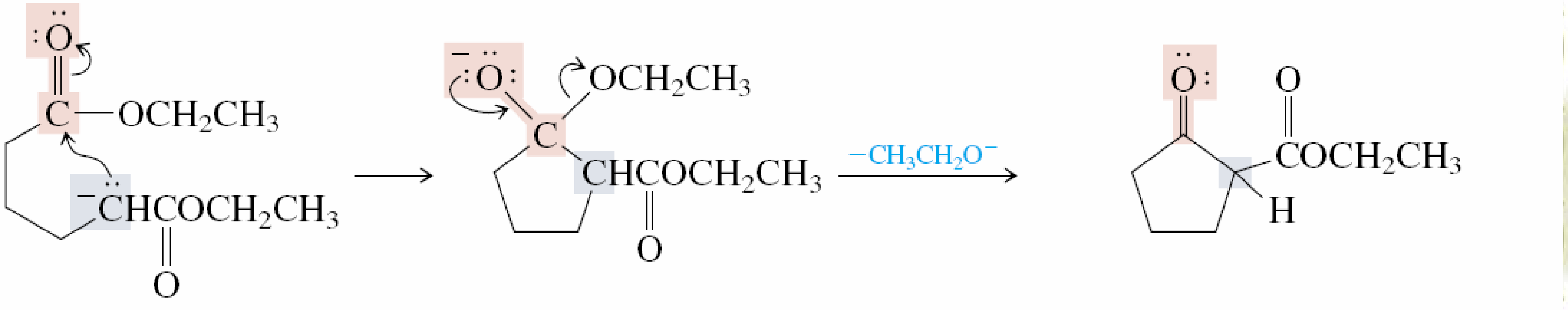


This reaction is an example of a Dieckmann cyclization.

Ex:



Mechanism:

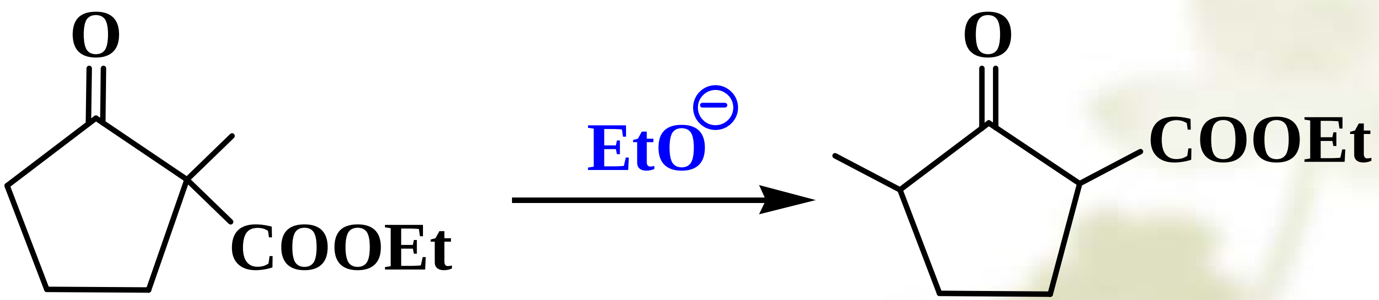


Enolate of diethyl
hexanedioate

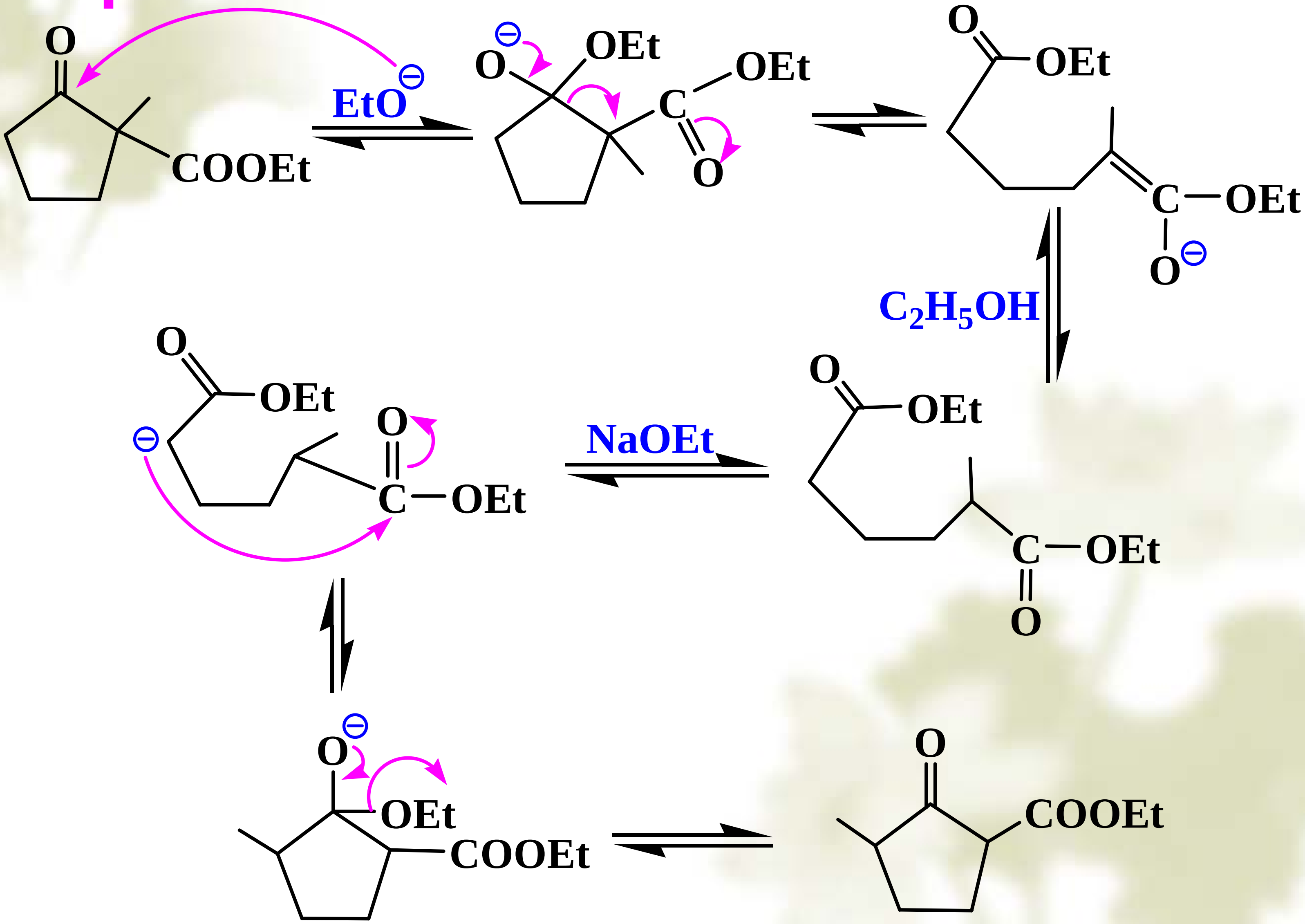
Ethyl (2-oxocyclopentane)carboxylate

This intramolecular Claisen condensation is a *reversible* reaction.

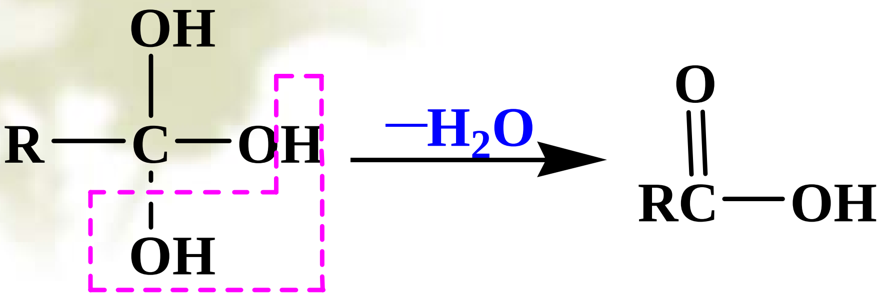
Example: **Give a reasonable explanation for the following process.**

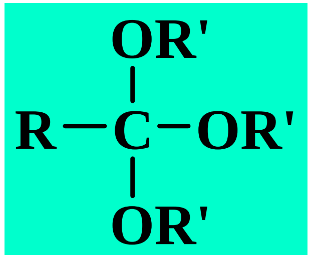


Sample Solution:



13.3.3 IMPORTANT COMPOUNDS

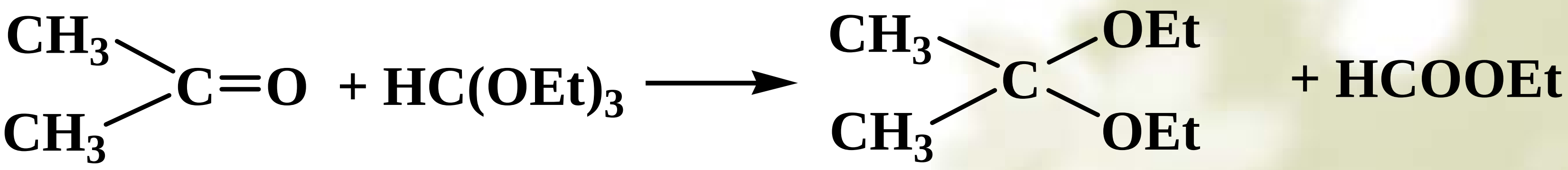




Orthoformic acid

Orthoformate

Acetals as protecting groups:



Ethyl orthoformate

Acetal

Contents

13.4 GREASE AND DETERGENT

13.4.1 GREASE

Oil — liquid; fat — solid

China wood oil (桐油): Eleostearate (桐酸酯)

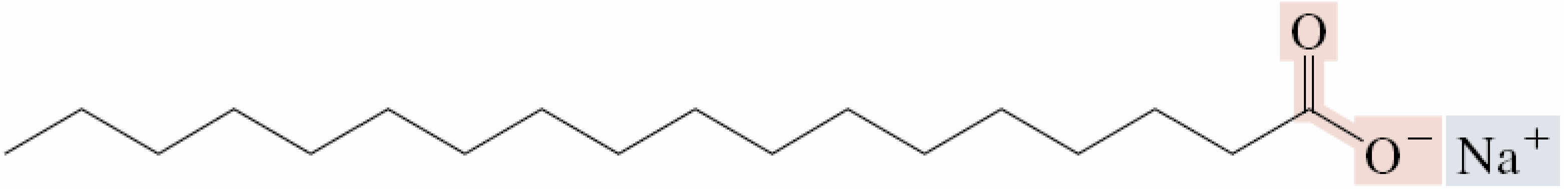
Eleostearic acid (桐酸 $C_{18}H_{30}O_2$):

$(CH_3(CH_2)_3(CH=CH)_3(CH_2)_7COOH$

13.4.2 SOAP AND DETERGENT

When the molecular weight isn’t too high, the sodium and potassium salts of carboxylic acids are soluble in water.

The solubility behavior of salts of carboxylic acids having 12–18 carbons is unusual and can be illustrated by considering sodium stearate:



Sodium stearate
(sodium octadecanoate)

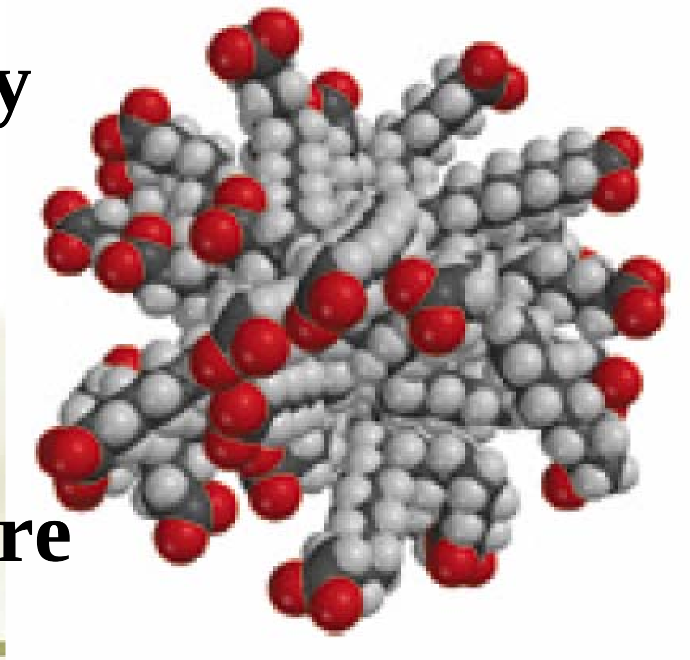
Sodium stearate has a polar carboxylate group at one end of a long hydrocarbon chain. The carboxylate group is hydrophilic (“water-loving”) and tends to confer water solubility on the molecule. The hydrocarbon chain is lipophilic (“fat-loving”) and tends to associate with other hydrocarbon chains.

When sodium stearate is placed in water, the hydrophilic carboxylate group encourages the formation of a solution; the lipophilic alkyl chain discourages it.

The compromise achieved is to form a colloidal dispersion of aggregates called micelles (胶束). Micelles form spontaneously when the carboxylate concentration exceeds a certain minimum value called the critical (临界) micelle concentration.

Each micelle is composed of 50–100 individual molecules, with the polar carboxylate groups directed toward its outside where they experience attractive forces with water and sodium ions. The nonpolar hydrocarbon chains are directed toward the interior of the micelle.

Micelles are approximately spherical because a sphere exposes the minimum surface for a given volume of material and disrupts the water structure least.

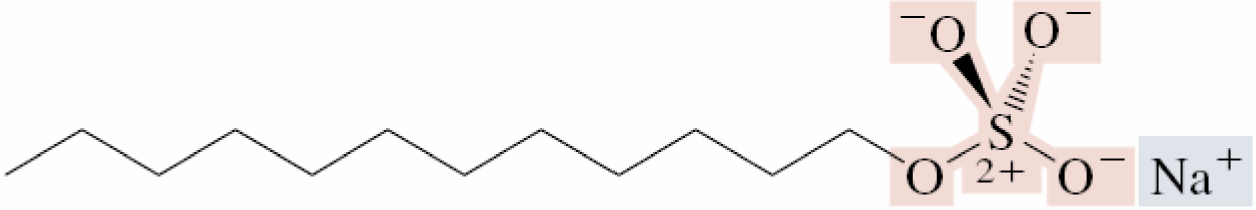


It is the formation of micelles and their properties that are responsible for the cleansing action of soaps.

Water that contains sodium stearate removes grease by enclosing it in the hydrocarbon-like interior of the micelles. The grease is washed away with the water, not because it dissolves in the water but because it dissolves in the micelles that are dispersed in the water.

Detergents are substances that cleanse by micellar action. A large number of synthetic detergents are known. One example is sodium lauryl (月桂醇) sulfate.

Sodium lauryl sulfate has a long hydrocarbon chain terminating in a polar sulfate ion and forms soap-like micelles in water.



Sodium lauryl sulfate
(sodium dodecyl sulfate)

Detergents are designed to be effective in hard water, meaning water containing calcium salts that form insoluble calcium carboxylates with soaps. These precipitates rob the soap of its cleansing power and form an unpleasant scum.

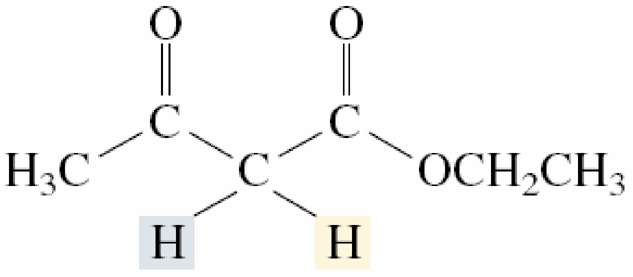
The calcium salts of synthetic detergents such as sodium lauryl sulfate, however, are soluble and retain their micelle-forming ability in water.

Contents

13.5 APPLICATIONS OF ETHYL ACETOACETATE AND DIETHYL MALONATE IN ORGANIC SYNTHESIS

13.5.1 ETHYL ACETOACETATE

1. Ester Enolates

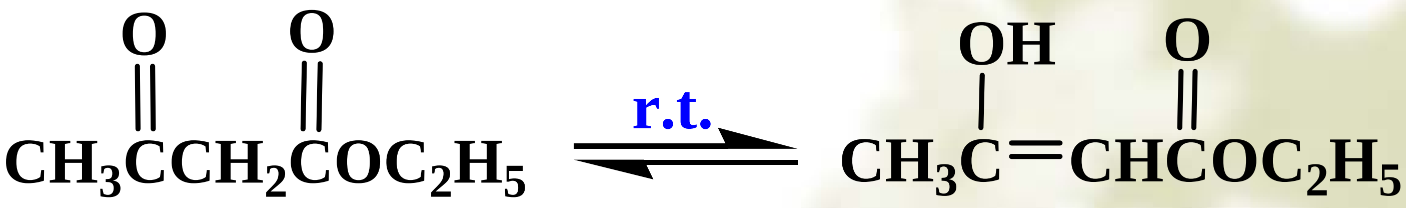


Ethyl acetoacetate

a. Reacts with sodium to yield H_2 ↑ ;

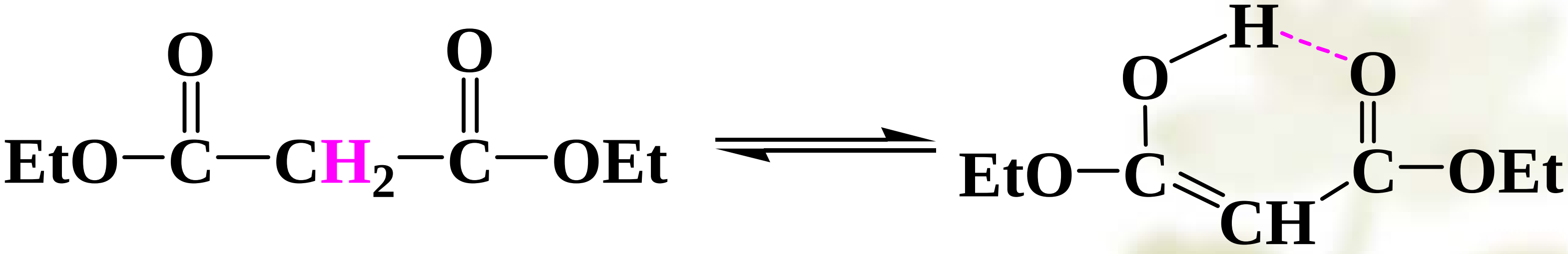
b. Depigmentize the Br_2/CCl_4 solution;

c. Reacts with $FeCl_3$ to yield a purple compound.

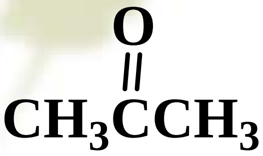


$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 \xrightleftharpoons{r.t.} CH_3\overset{OH}{\overset{|}{C}}=CH\overset{O}{\overset{\|}{C}}OC_2H_5$$

The stability of an enolate of a keto ester lies on the hydrogen bonding of the six-membered cyclic ring, for example,

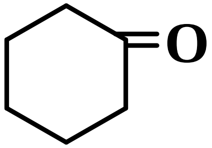


Problem: **Identify the following structures to figure out the most stable enolate.**

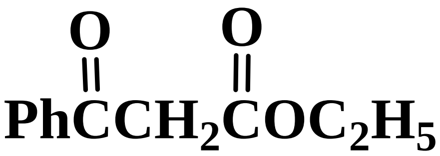


$CH_3\overset{\overset{O}{\|}}{C}CH_3$

Acetone



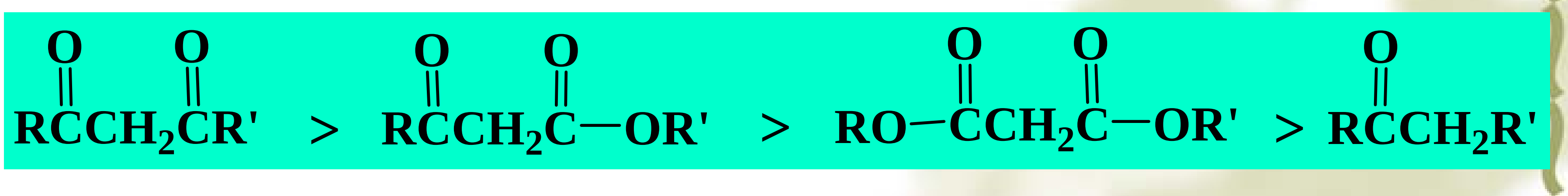
Cyclohexanone



$Ph\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OC_2H_5$

Ethyl benzoacetate

The sequence of the following structures in order of decreasing content of enloate is:



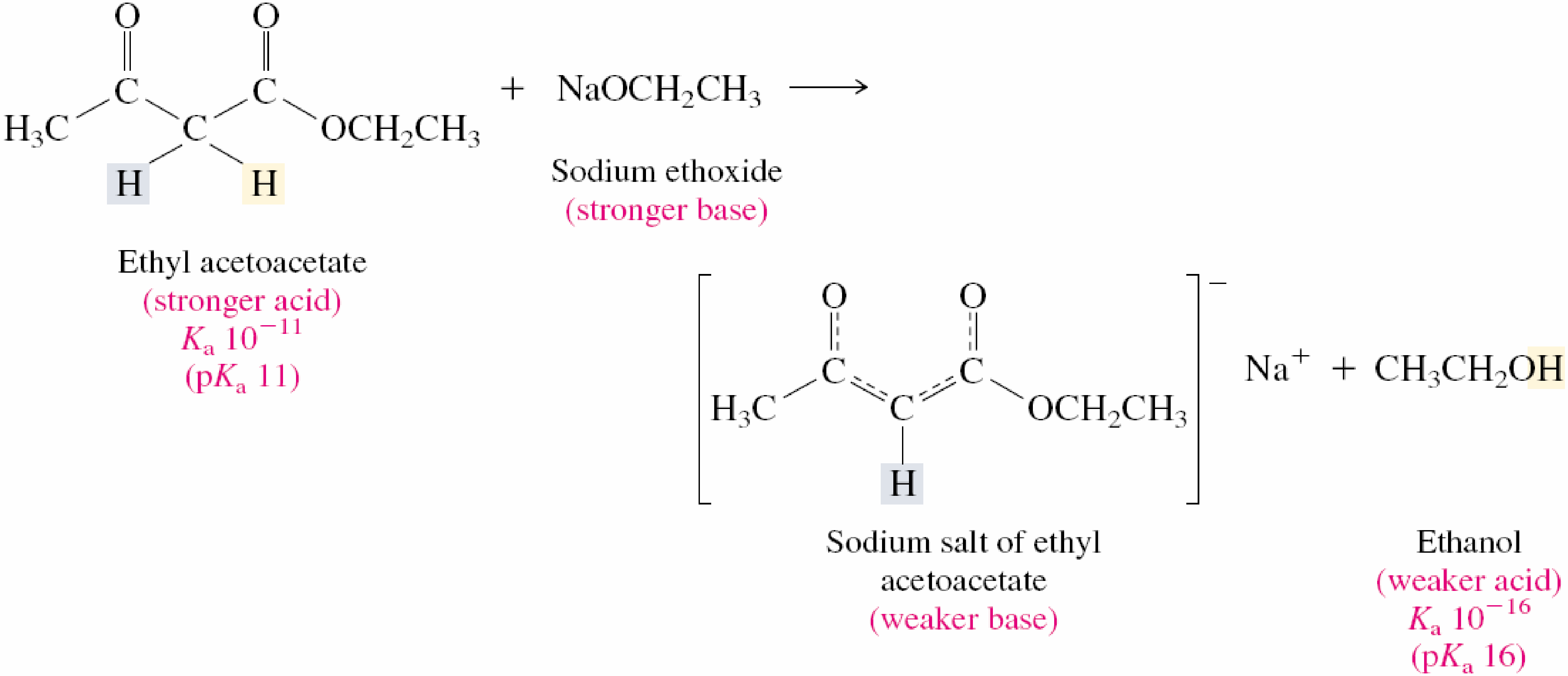
$$R\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}R' > R\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}-OR' > RO-\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}-OR' > R\overset{\overset{O}{\|}}{C}CH_2R'$$

2. Ethyl Acetoacetate

Ethyl acetoacetate (acetoacetic ester), available by the Claisen condensation of ethyl acetate, has properties that make it a useful starting material for the preparation of ketones. These properties are

- **The acidity of the α-hydrogen;**
- **The ease with which acetoacetic acid undergoes thermal decarboxylation.**

Ethyl acetoacetate is a stronger acid than ethanol and is quantitatively converted to its anion on treatment with sodium ethoxide in ethanol.



Ethyl acetoacetate
(stronger acid)
K_a 10^{-11}
(pK_a 11)

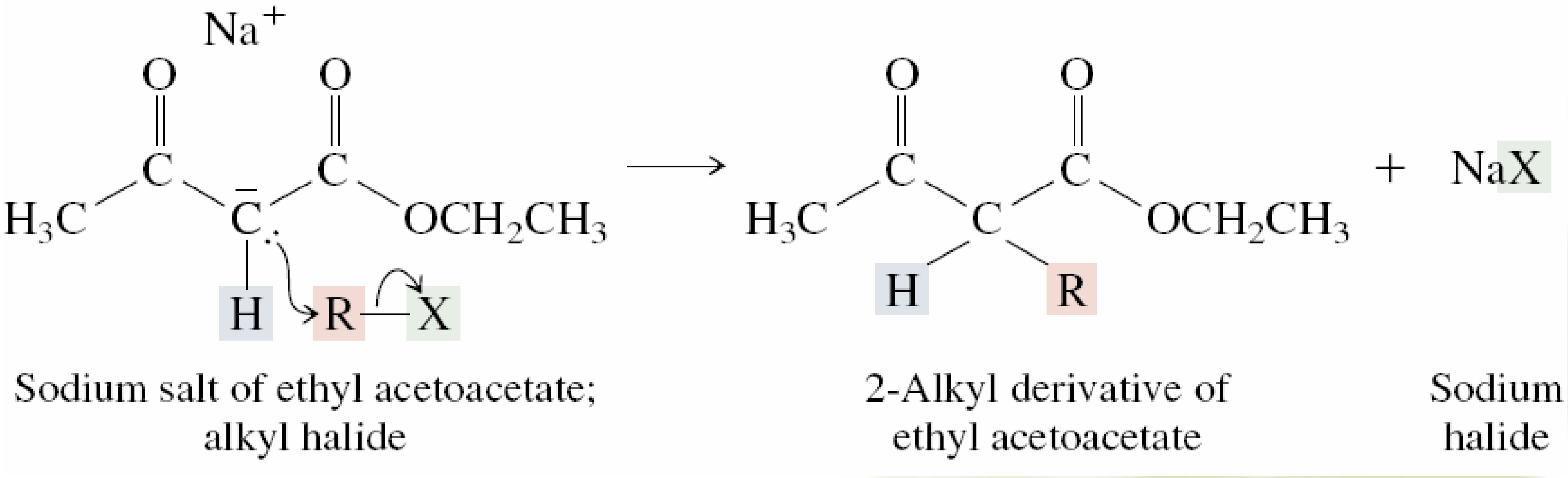
Sodium ethoxide
(stronger base)

Sodium salt of ethyl acetoacetate
(weaker base)

Ethanol
(weaker acid)
K_a 10^{-16}
(pK_a 16)

The anion produced by proton abstraction from ethyl acetoacetate is **nucleophilic**.

Adding an alkyl halide to a solution of the sodium salt of ethyl acetoacetate leads to alkylation of the carbon.



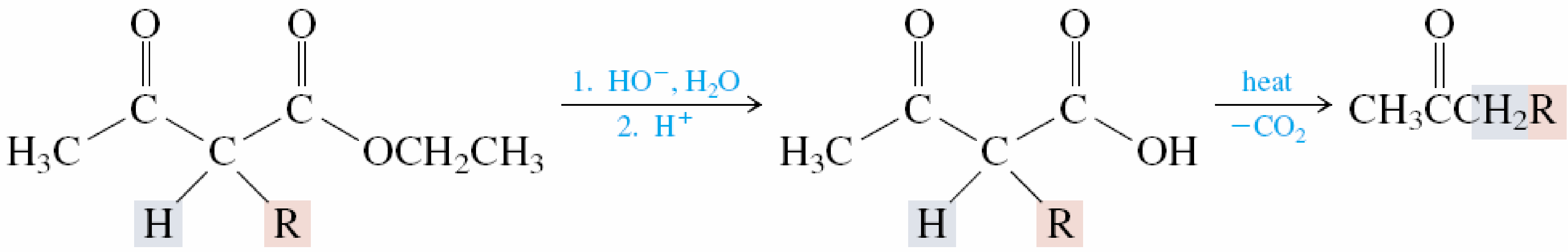
Sodium salt of ethyl acetoacetate; alkyl halide

2-Alkyl derivative of ethyl acetoacetate

Sodium halide

The new carbon–carbon bond is formed by an S_N2-type reaction. The alkyl halide must therefore be one that is not sterically hindered. Methyl and primary alkyl halides work best; secondary alkyl halides give lower yields. Tertiary alkyl halides react only by elimination, not substitution.

Saponification and decarboxylation of the alkylated derivative of ethyl acetoacetate yields a ketone.



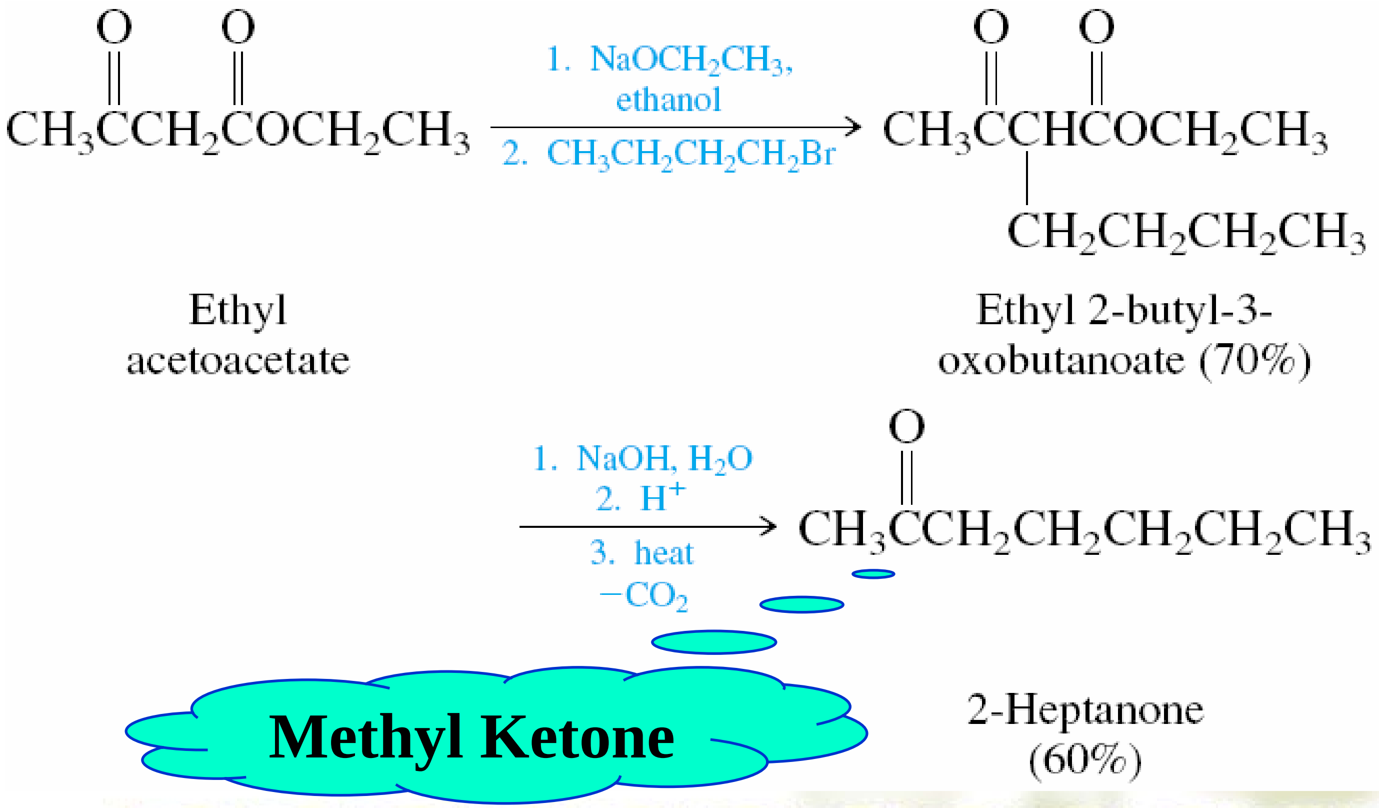
2-Alkyl derivative of ethyl acetoacetate

2-Alkyl derivative of acetoacetic acid

Ketone

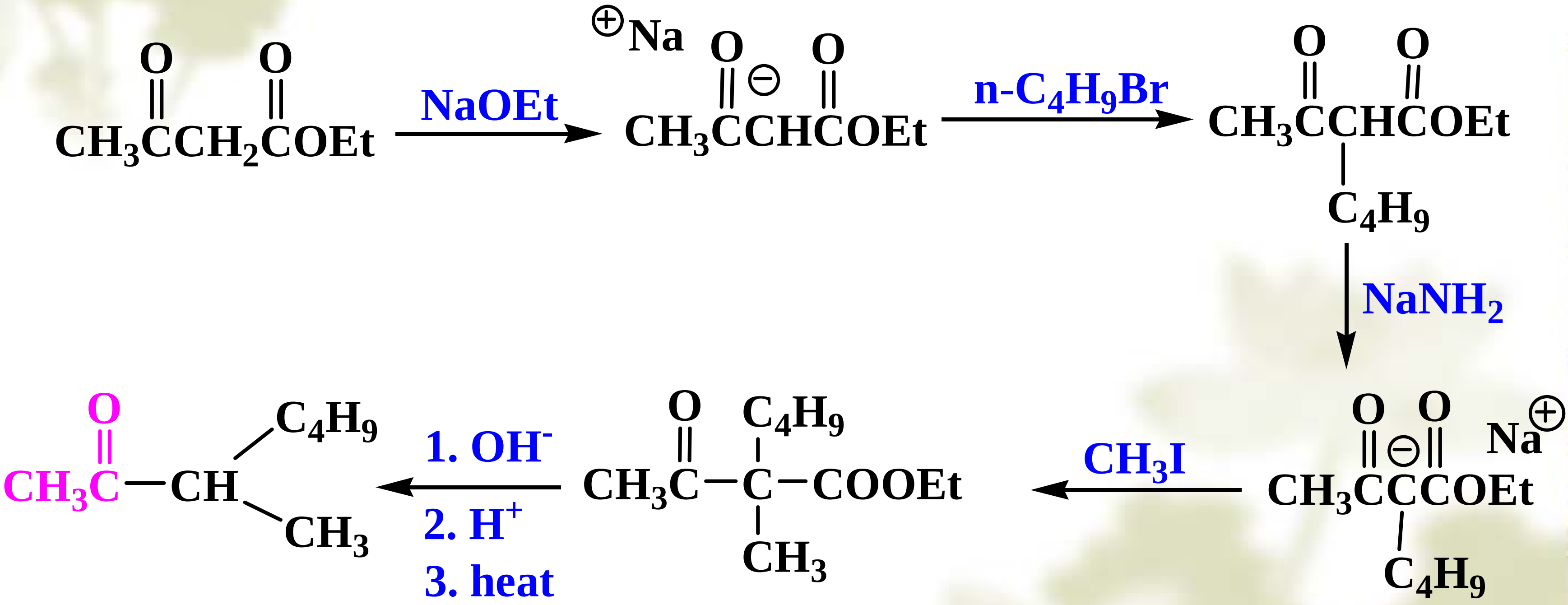
This reaction sequence is called the **acetoacetic ester (AAE) synthesis**. It is a standard procedure for the preparation of ketones from alkyl halides.

Ex1:



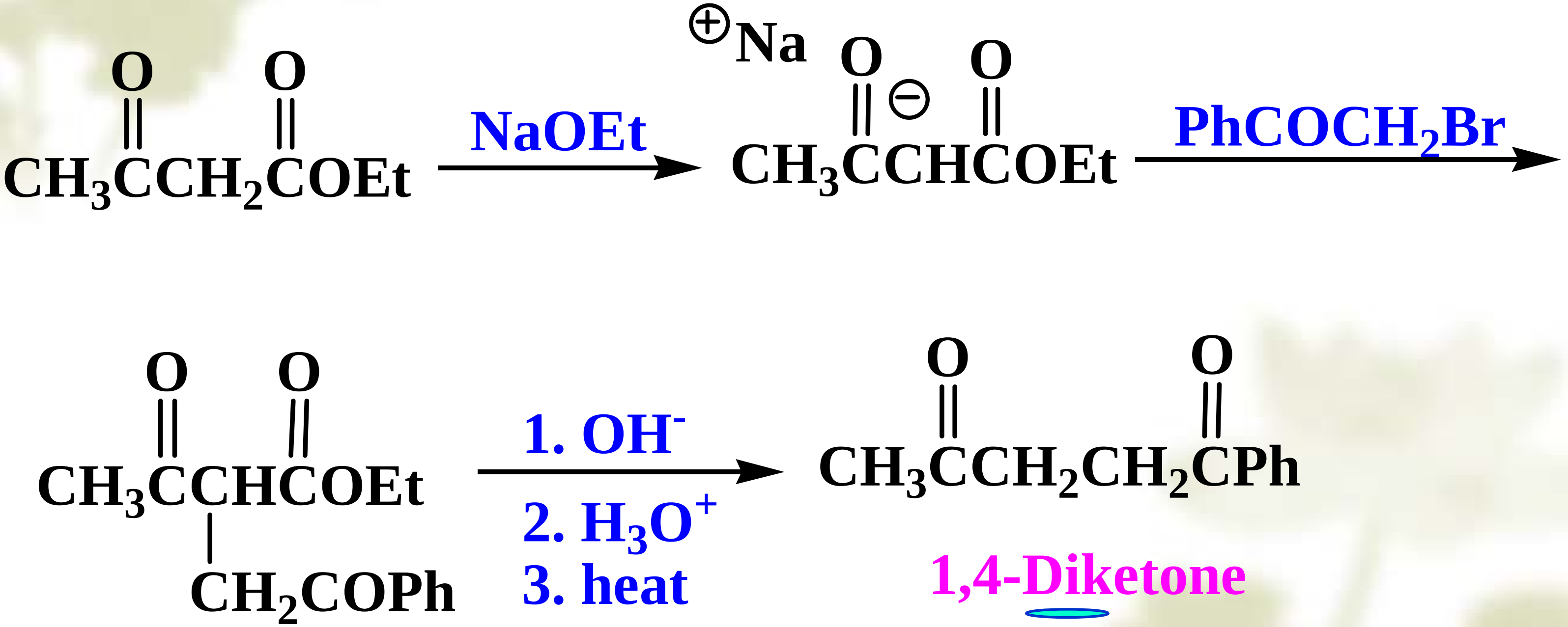
Methyl Ketone

Ex 2: Ethyl acetoacetate reacts with alkyl halides



Methyl ketone

Ex 3: Ethyl acetoacetate reacts with α-halo ketones



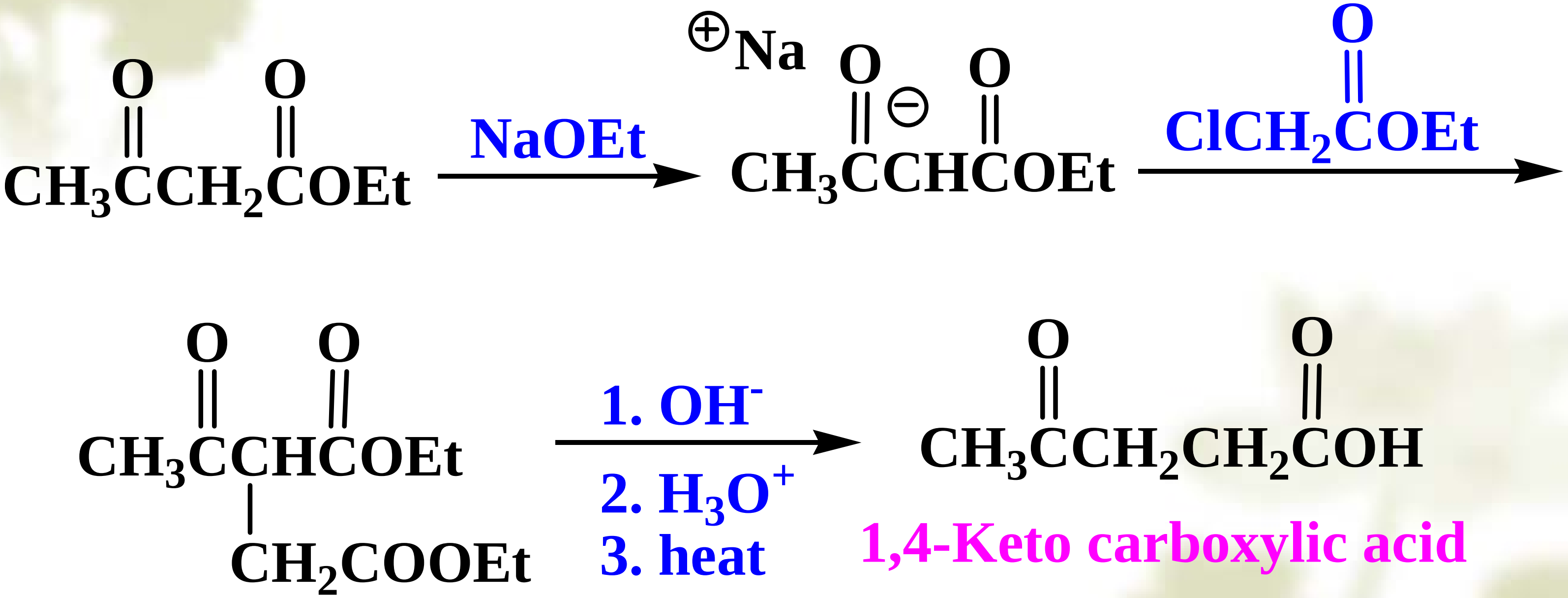
$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt \xrightarrow{NaOEt} {}^{\oplus}Na\ CH_3\overset{O}{\overset{\|}{C}}\overset{\ominus}{C}H\overset{O}{\overset{\|}{C}}OEt \xrightarrow{PhCOCH_2Br}$$

$$CH_3\overset{O}{\overset{\|}{C}}\underset{\overset{|}{CH_2COPh}}{CH}\overset{O}{\overset{\|}{C}}OEt \xrightarrow[\substack{2.\ H_3O^+\\ 3.\ heat}]{1.\ OH^-} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}Ph$$

1,4-Diketone

Intramolecular aldol reaction

Ex 4: Ethyl acetoacetate reacts with α-halo esters

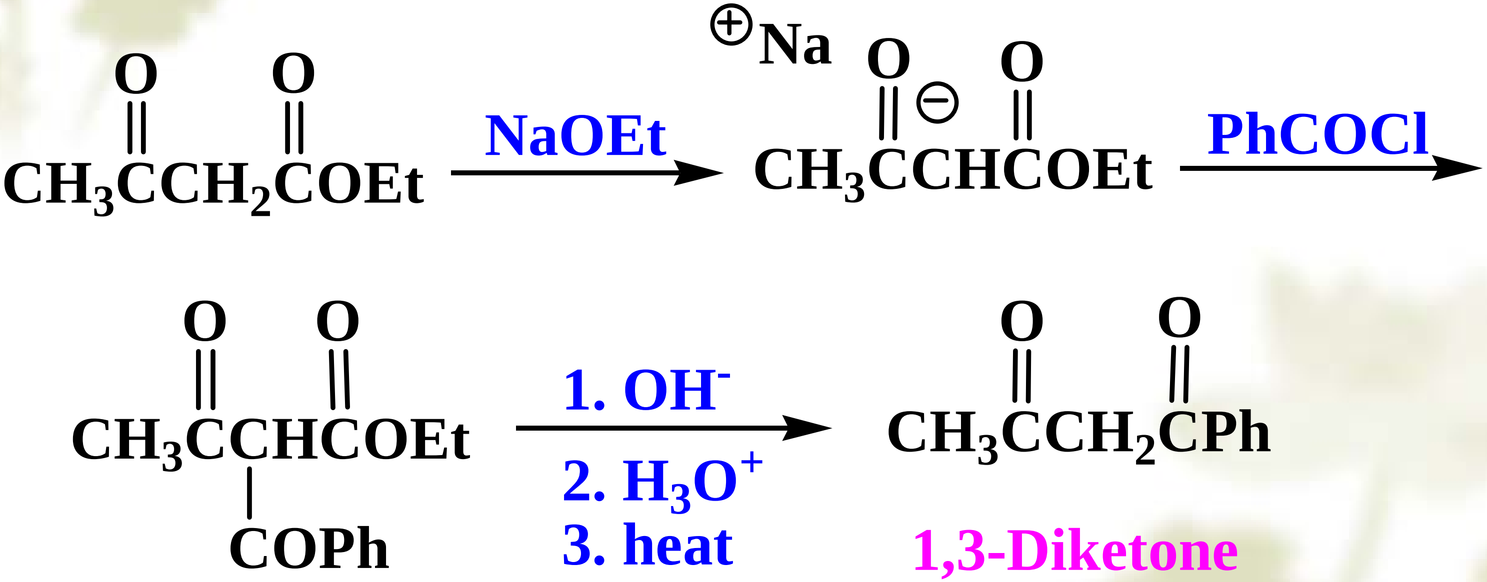


$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt \xrightarrow{NaOEt} {}^{\oplus}Na\ CH_3\overset{O}{\overset{\|}{C}}\overset{\ominus}{C}H\overset{O}{\overset{\|}{C}}OEt \xrightarrow{ClCH_2\overset{O}{\overset{\|}{C}}OEt}$$

$$CH_3\overset{O}{\overset{\|}{C}}\underset{CH_2COOEt}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OEt \xrightarrow[\text{2. } H_3O^+ \text{ 3. heat}]{\text{1. } OH^-} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OH$$

1,4-Keto carboxylic acid

Ex 5: Ethyl acetoacetate reacts with acyl halide

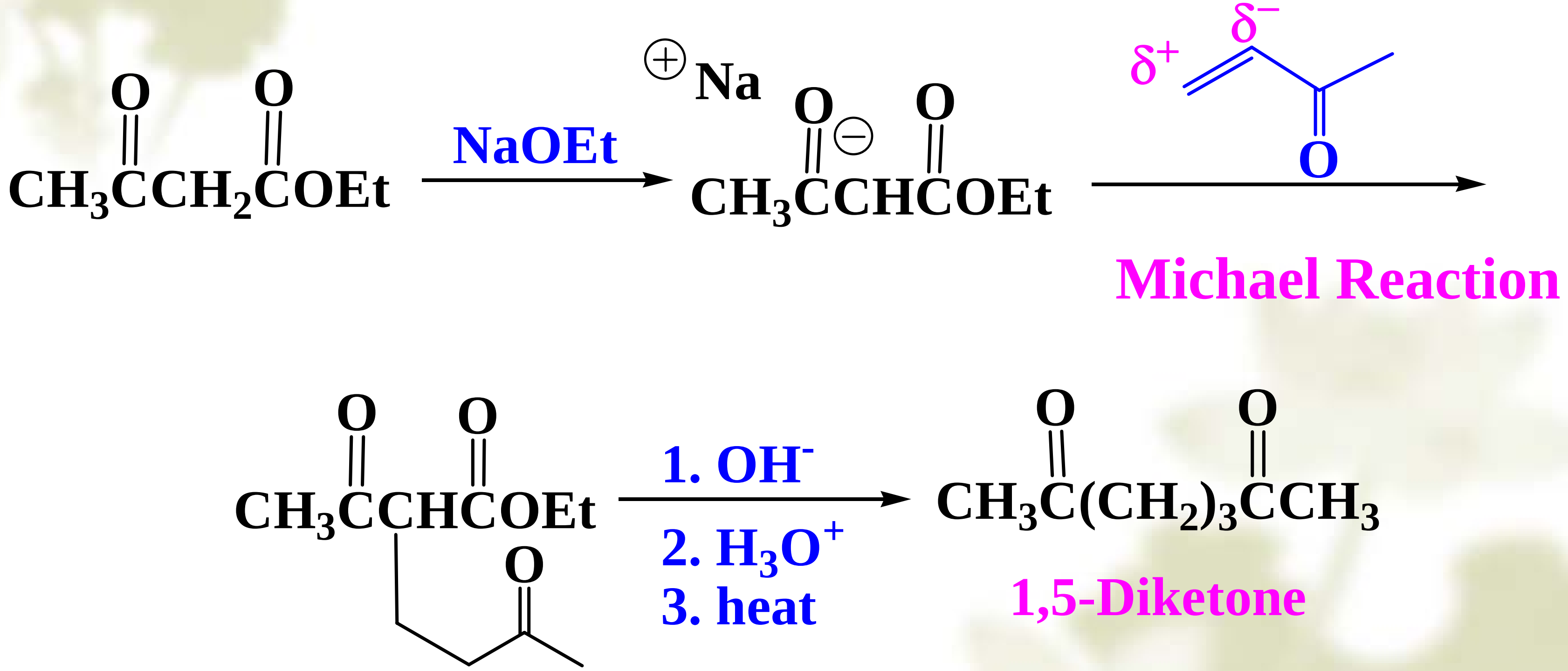


$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt \xrightarrow{NaOEt} \overset{\oplus}{Na}\; CH_3\overset{O}{\overset{\|}{C}}\overset{\ominus}{C}H\overset{O}{\overset{\|}{C}}OEt \xrightarrow{PhCOCl}$$

$$CH_3\overset{O}{\overset{\|}{C}}\underset{\underset{COPh}{|}}{C}H\overset{O}{\overset{\|}{C}}OEt \xrightarrow[\text{2. } H_3O^+ \text{ 3. heat}]{\text{1. } OH^-} CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}Ph$$

1,3-Diketone

Ex 6: Ethyl acetoacetate reacts with α, β-unsaturated ketone

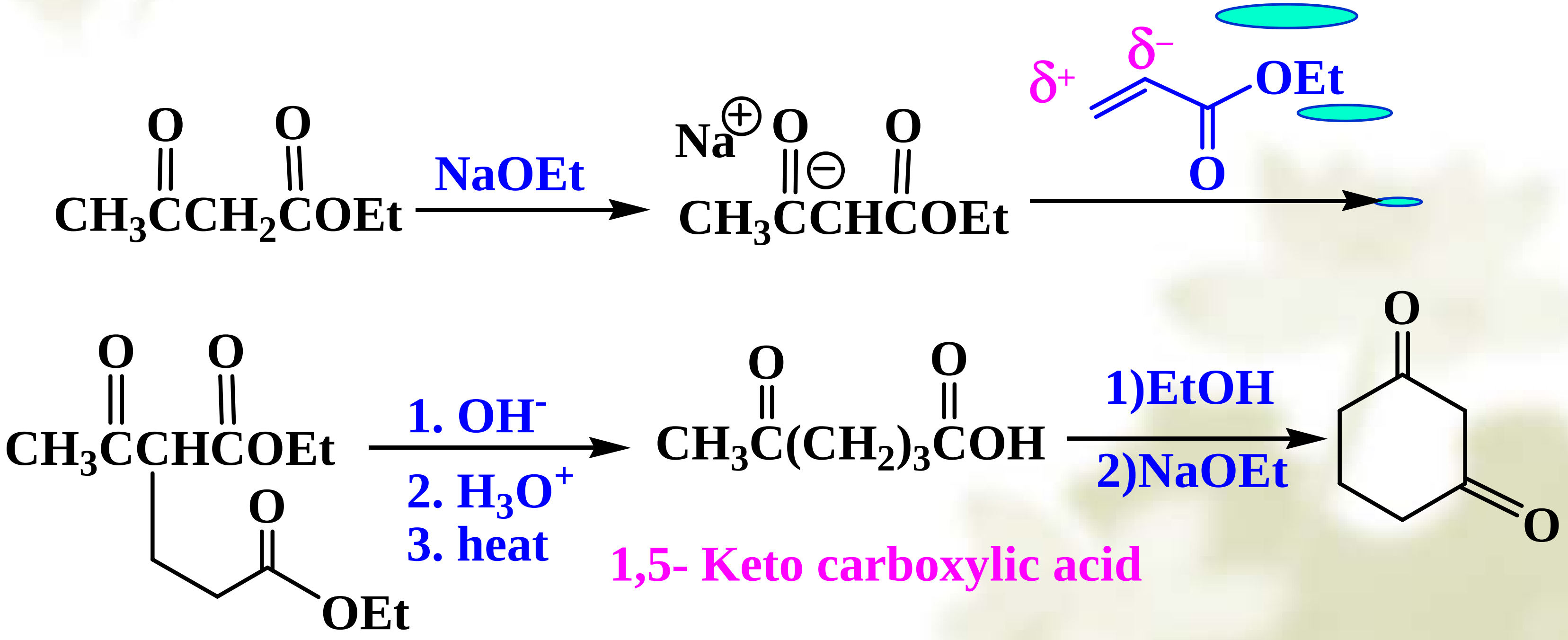


Michael Reaction

1,5-Diketone

Ex 7: Ethyl acetoacetate reacts with α,β-unsaturated esters

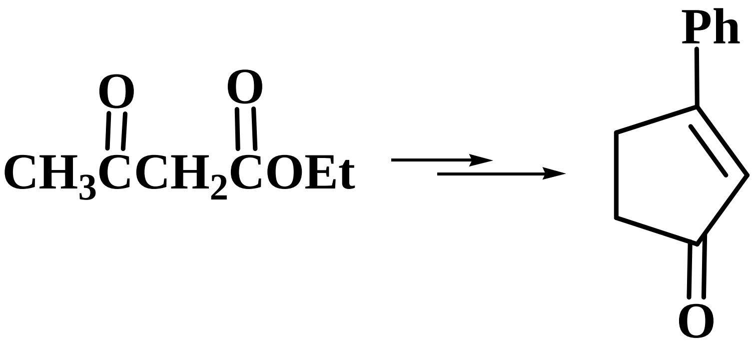
Michael addition



1,5- Keto carboxylic acid

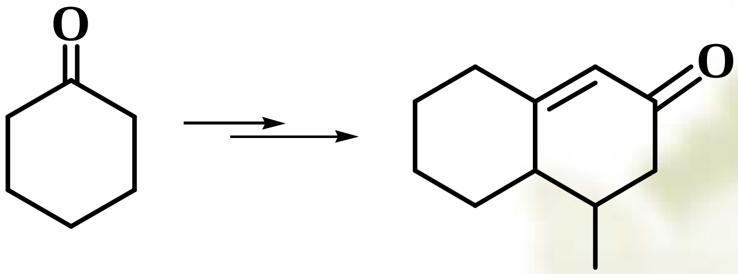
Problem: **Show how you could prepare each of the following compounds by using the starting materials:**

1.

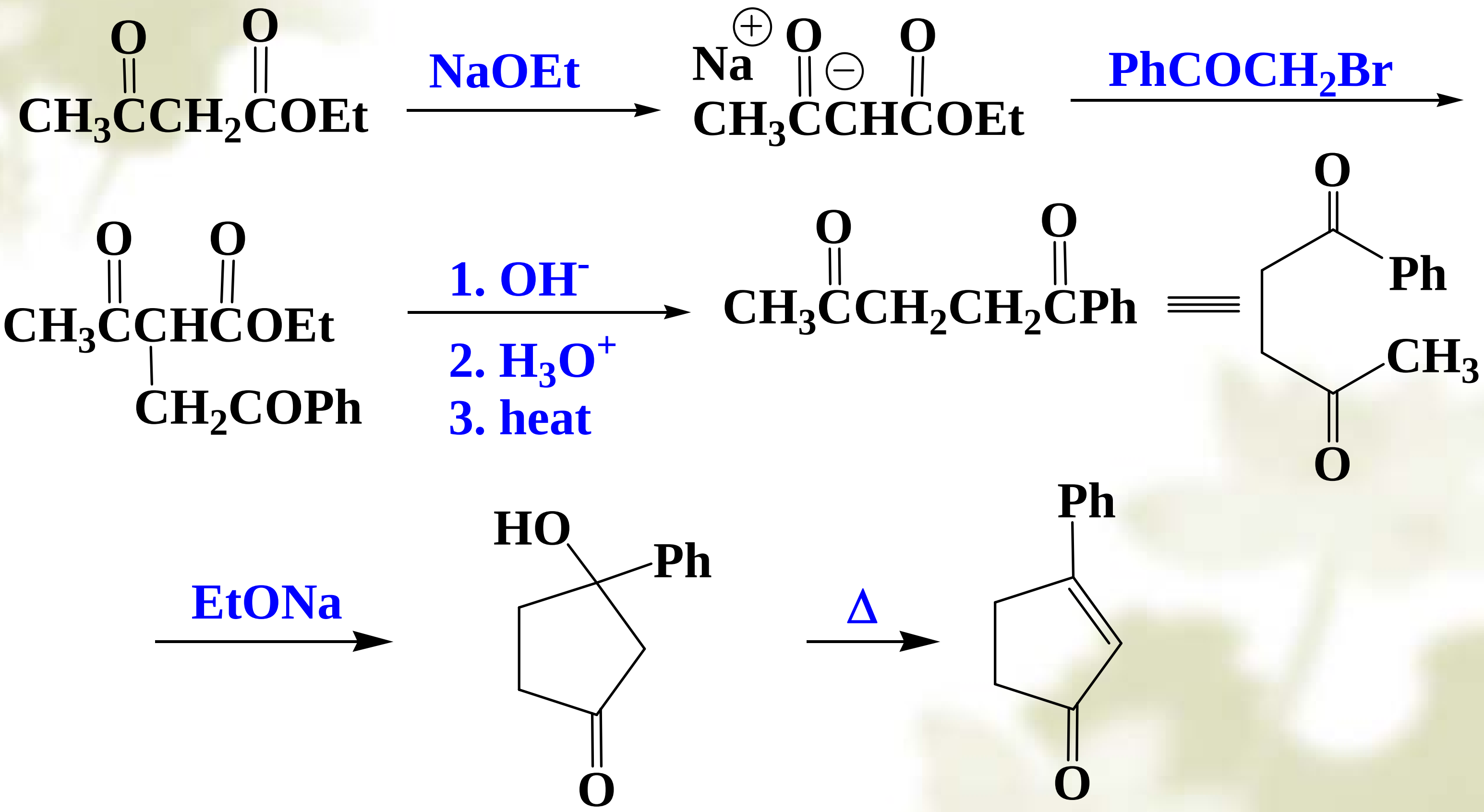


$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt$

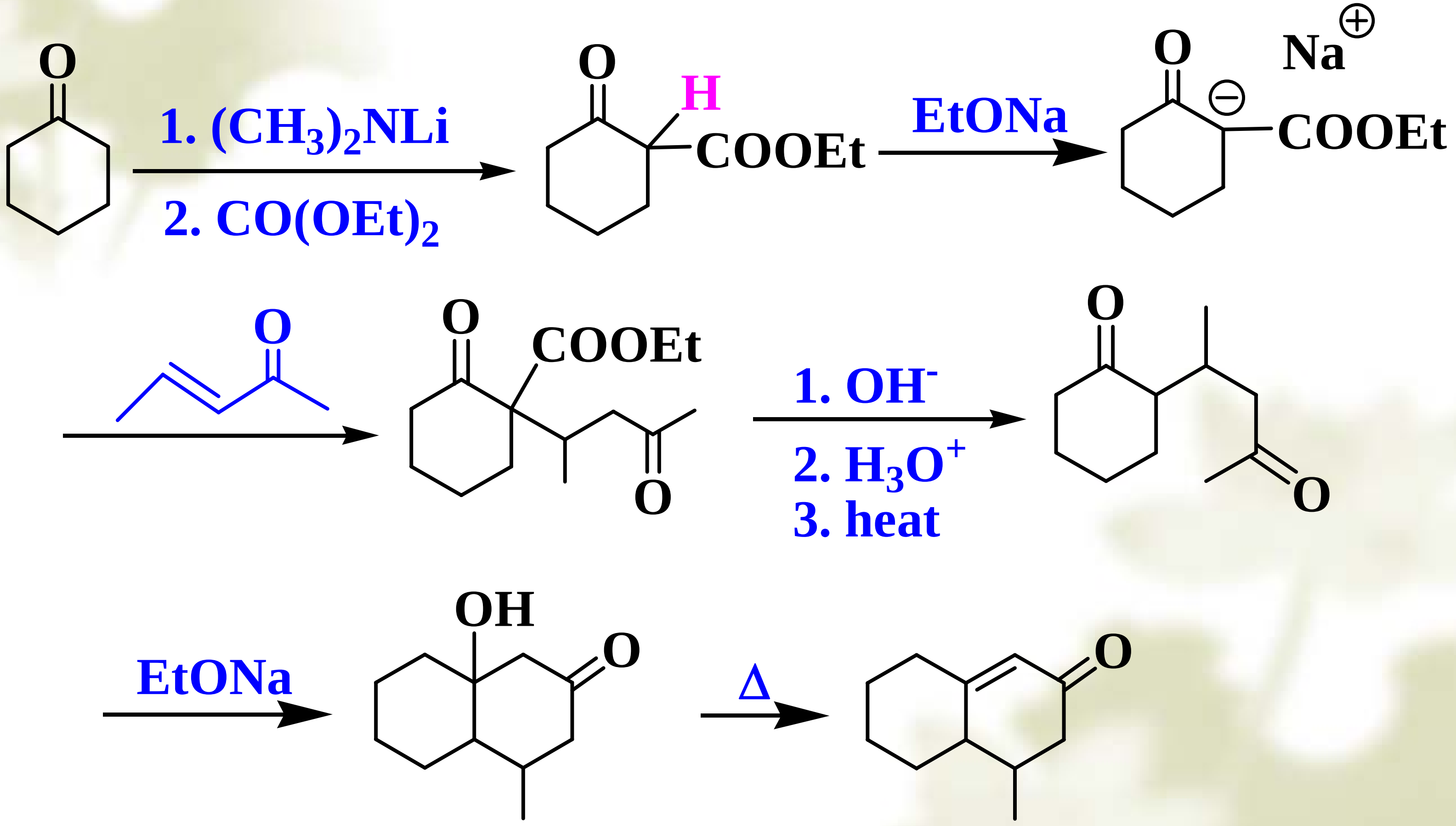
2.



Sample solution 1:

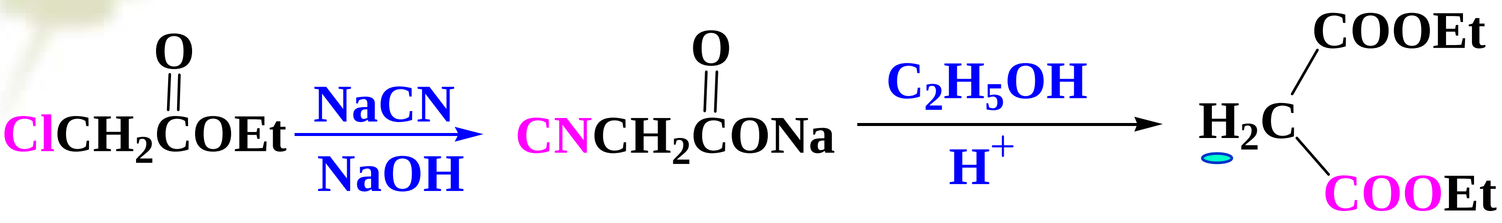


Sample solution 2:



13.5.2 MALONATES

1.Preparation of Malonates:

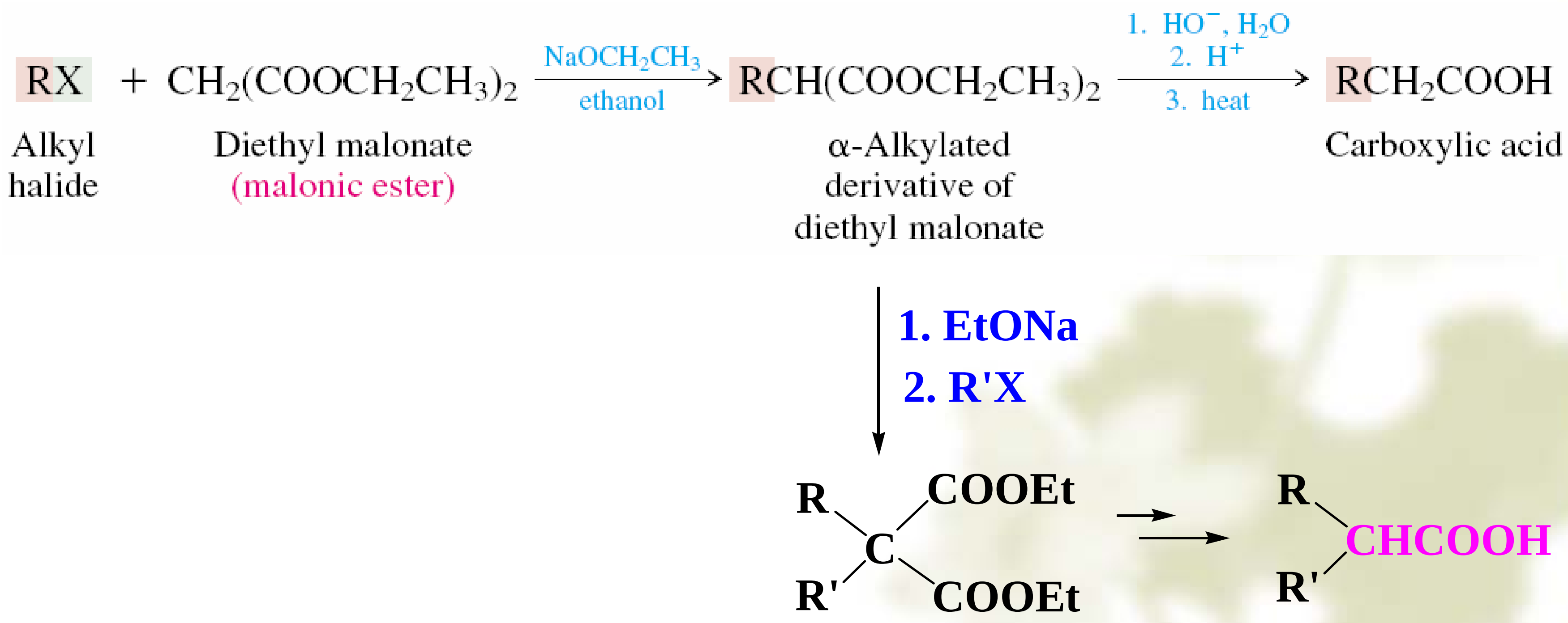


$$\mathrm{ClCH_2\overset{\overset{\displaystyle O}{\|}}{C}OEt} \xrightarrow[\mathrm{NaOH}]{\mathrm{NaCN}} \mathrm{CNCH_2\overset{\overset{\displaystyle O}{\|}}{C}ONa} \xrightarrow[\mathrm{H^+}]{\mathrm{C_2H_5OH}} \mathrm{H_2C}\begin{matrix}\mathrm{COOEt}\\ \mathrm{COOEt}\end{matrix}$$

*p*Ka=13

2. Application

The **malonic ester synthesis** is a method for the preparation of carboxylic acids and is represented by the general equation.



$$RX + CH_2(COOCH_2CH_3)_2 \xrightarrow[\text{ethanol}]{NaOCH_2CH_3} RCH(COOCH_2CH_3)_2 \xrightarrow[\text{3. heat}]{\text{1. } HO^-,\ H_2O \quad \text{2. } H^+} RCH_2COOH$$

Alkyl halide

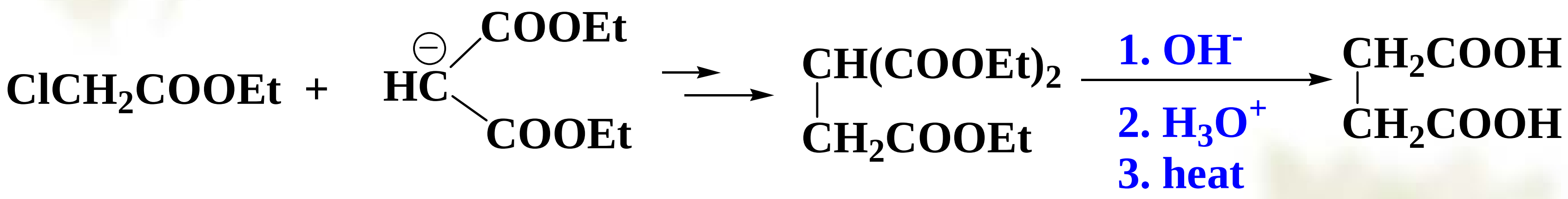
Diethyl malonate (malonic ester)

α-Alkylated derivative of diethyl malonate

Carboxylic acid

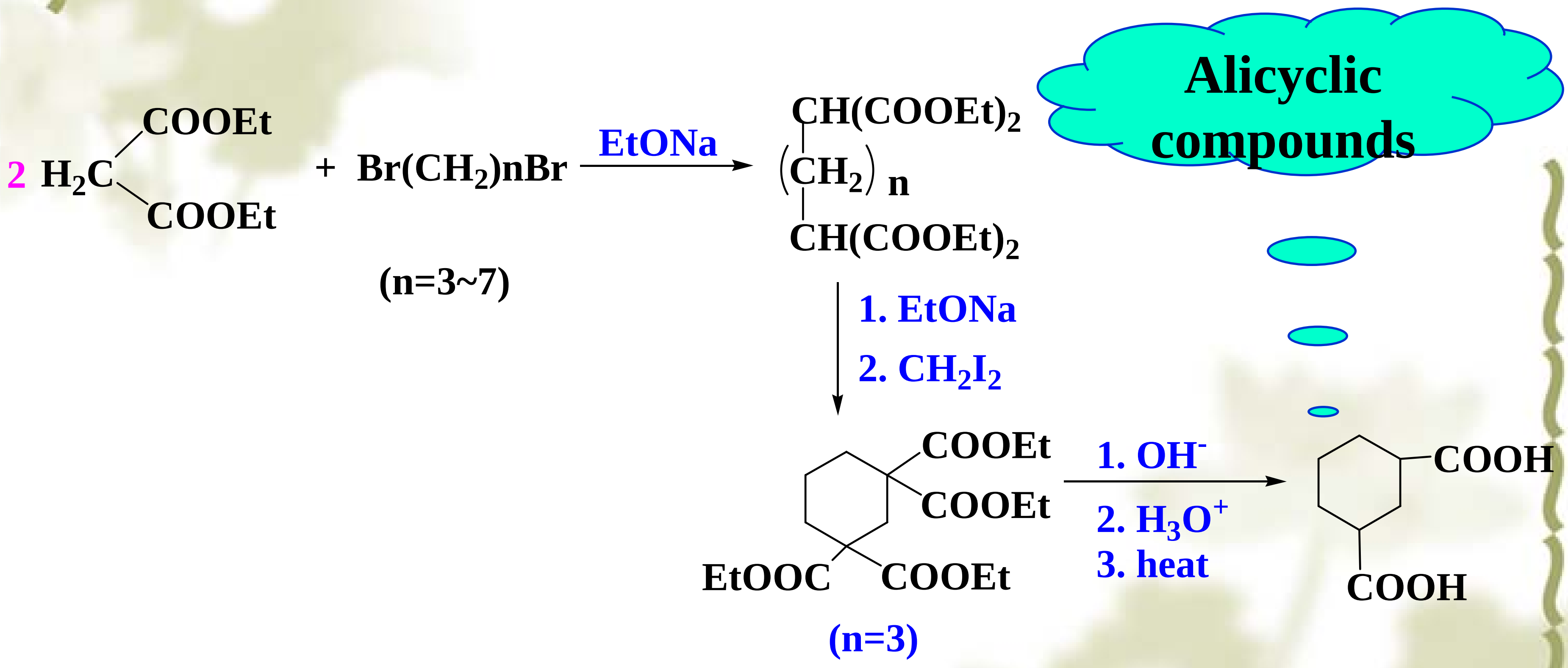
1. EtONa
2. R'X

Ex 1: Diethyl malonate reacts with halo carboxylic acids (esters)



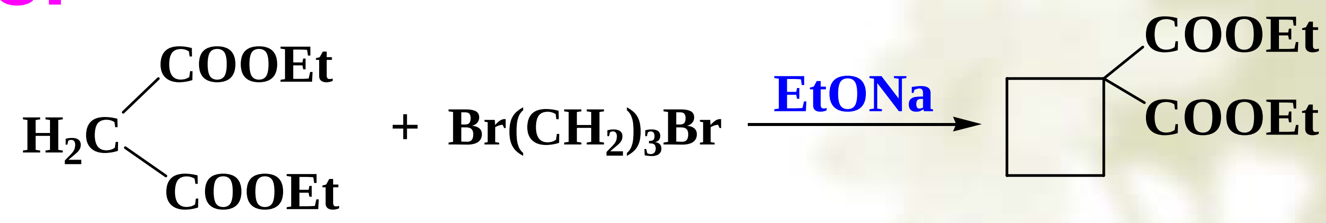
Dicarboxylic acid

Ex 2: Diethyl malonate reacts with dihalides

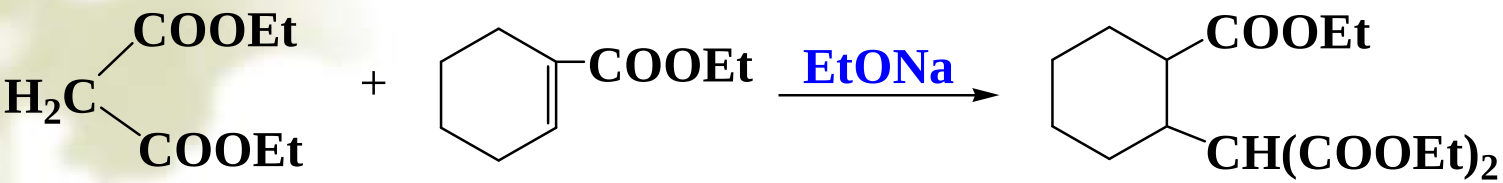


Alicyclic compounds

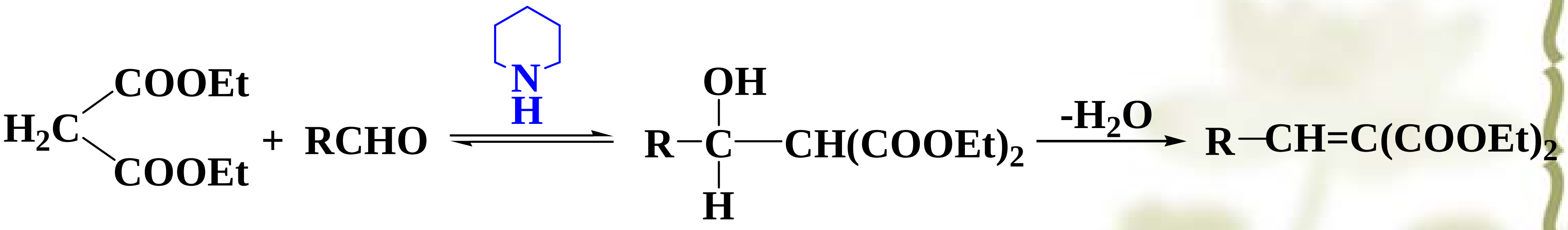
Ex 3:

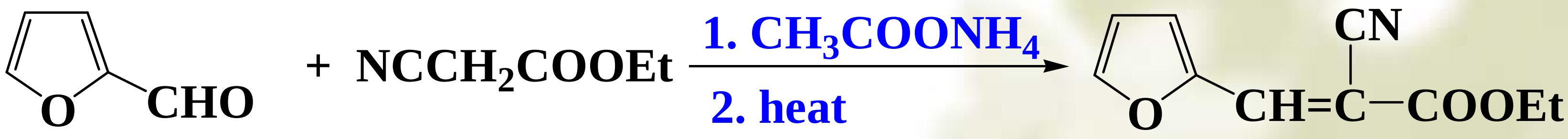


Ex 4: Michael addition

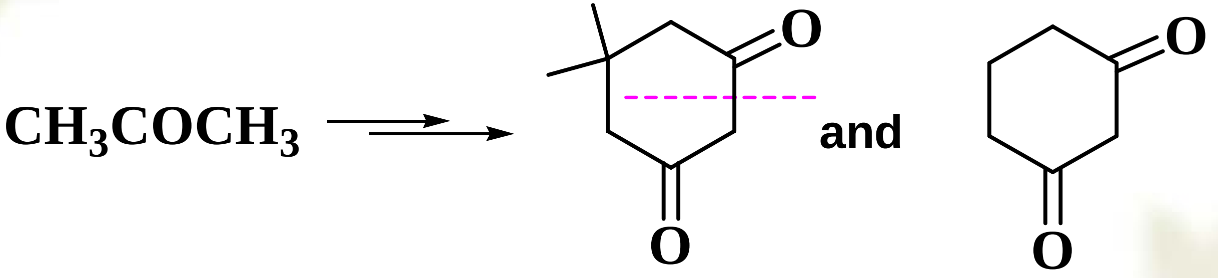


Ex 5: Knoevenagel reaction

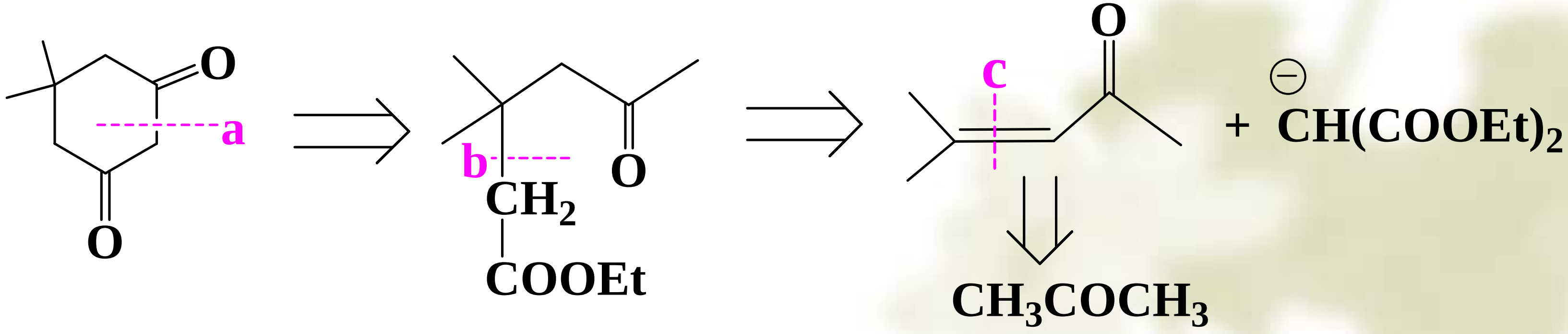




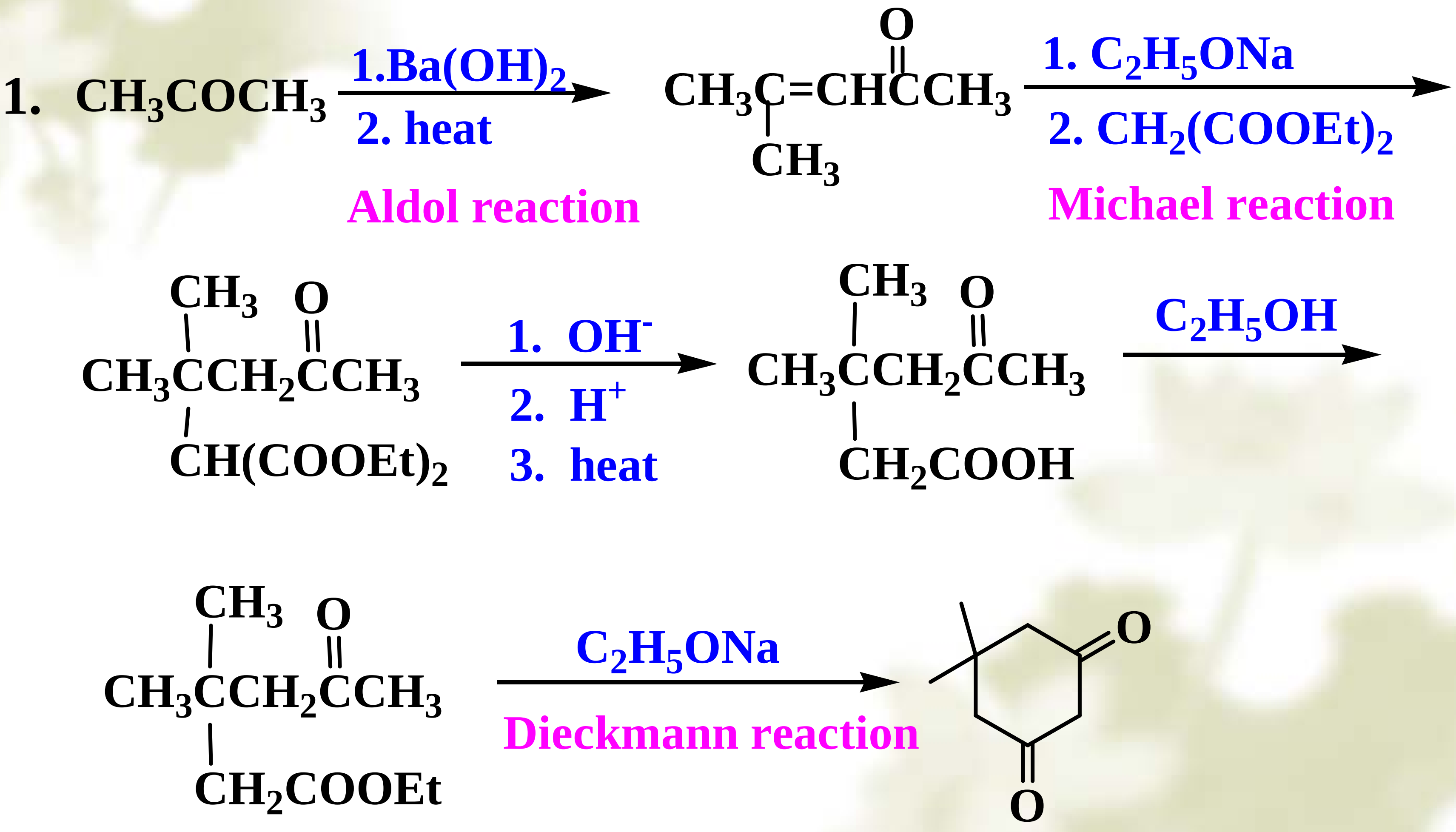
Problem: Show how you could prepare each of the following compounds by using the starting materials:



Retrosynthetic analysis:



Sample solution:



1. $CH_3COCH_3 \xrightarrow[\text{2. heat}]{\text{1.Ba(OH)}_2} \underset{\displaystyle CH_3}{\underset{|}{CH_3C}}{=}CH\overset{\displaystyle O}{\overset{\|}{C}}CH_3 \xrightarrow[\text{2. }CH_2(COOEt)_2]{\text{1. }C_2H_5ONa}$

Aldol reaction

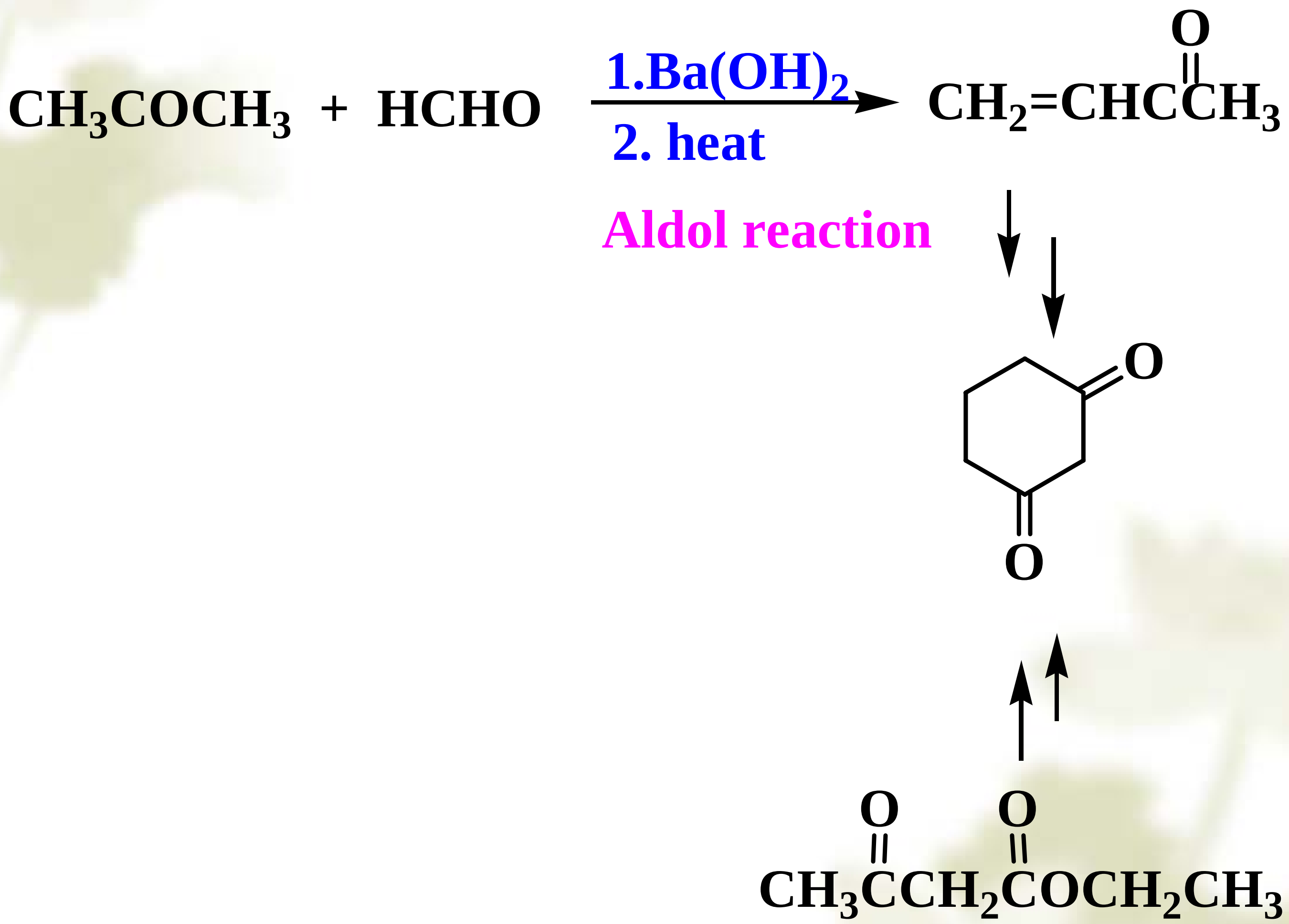
Michael reaction

$\underset{\displaystyle CH(COOEt)_2}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{CH_3C}}}}CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_3 \xrightarrow[\text{2. }H^+\text{ 3. heat}]{\text{1. }OH^-} \underset{\displaystyle CH_2COOH}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{CH_3C}}}}CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_3 \xrightarrow{C_2H_5OH}$

$\underset{\displaystyle CH_2COOEt}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{CH_3C}}}}CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_3 \xrightarrow{C_2H_5ONa}$

Dieckmann reaction

2.



$$CH_3COCH_3 + HCHO \xrightarrow[\text{2. heat}]{\text{1.Ba(OH)}_2} CH_2{=}CH\overset{\overset{O}{\|}}{C}CH_3$$

Aldol reaction

$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

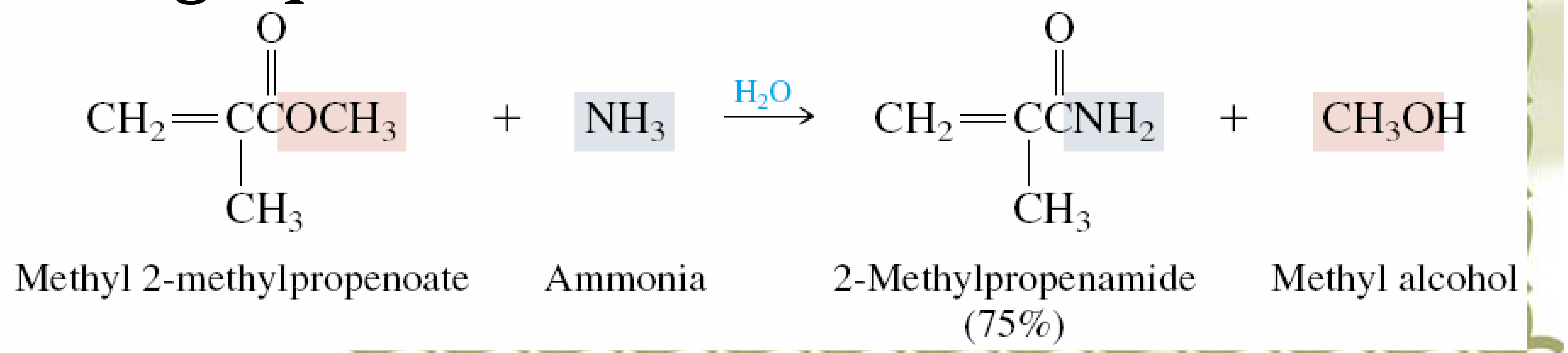
Contents

13.6 AMIDES

13.6.1 PREPARATION

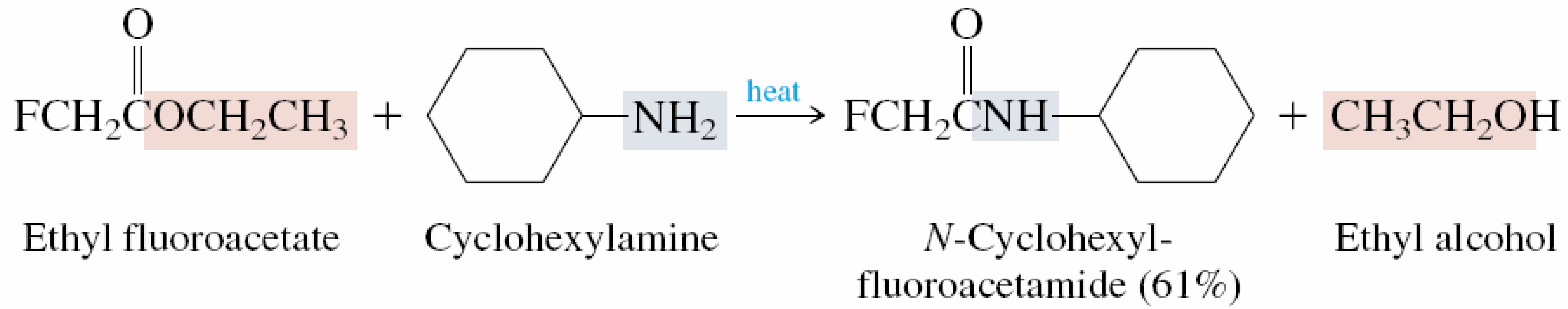
Amides are readily prepared by acylation of ammonia and amines with acyl chlorides, anhydrides, or esters.

Ammonia is more nucleophilic than water, making it possible to carry out this reaction using aqueous ammonia.



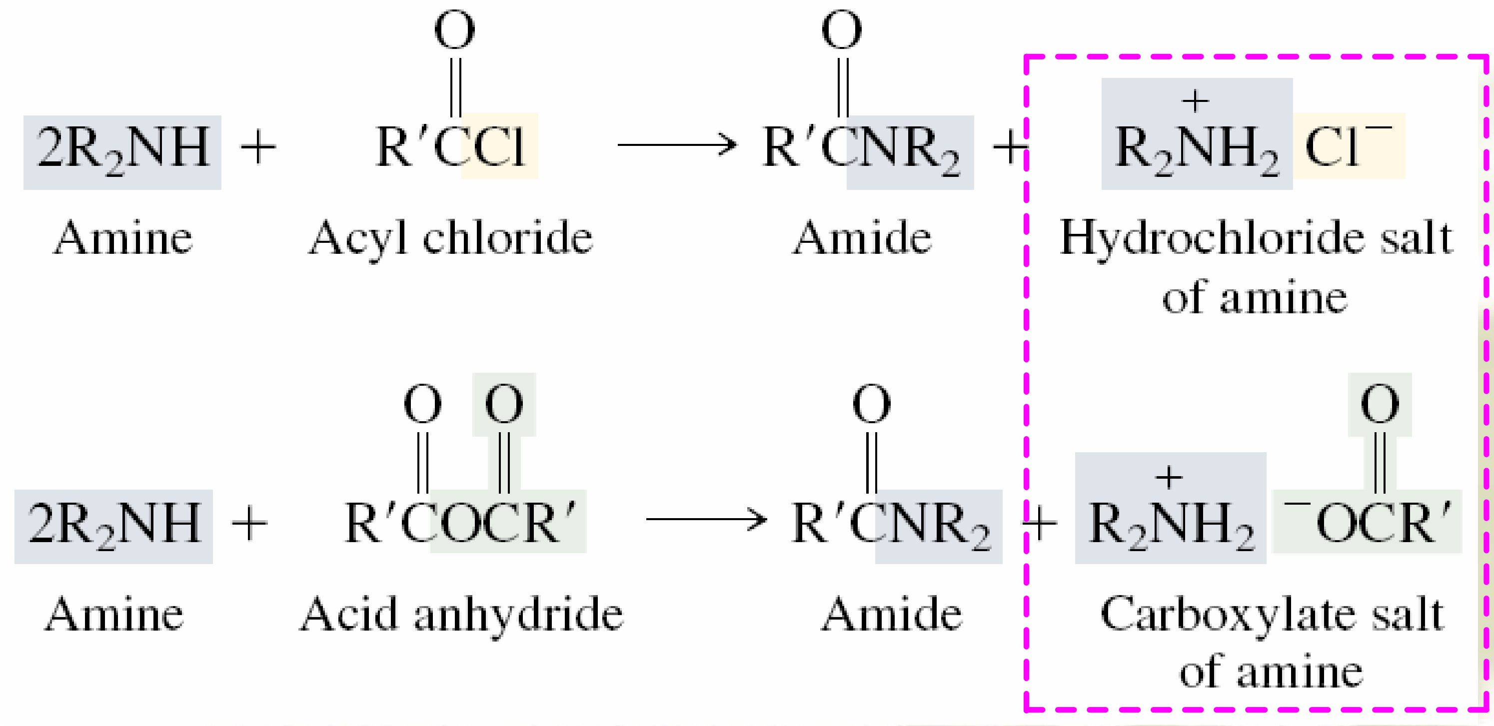
$$CH_2{=}C(CH_3)C({=}O)OCH_3 + NH_3 \xrightarrow{H_2O} CH_2{=}C(CH_3)C({=}O)NH_2 + CH_3OH$$

Amines, which are substituted derivatives of ammonia, react similarly:



The amine must be primary (RNH_2) or secondary (R_2NH). Tertiary amines (R_3N) cannot form amides, because they have no proton on nitrogen that can be replaced by an acyl group.

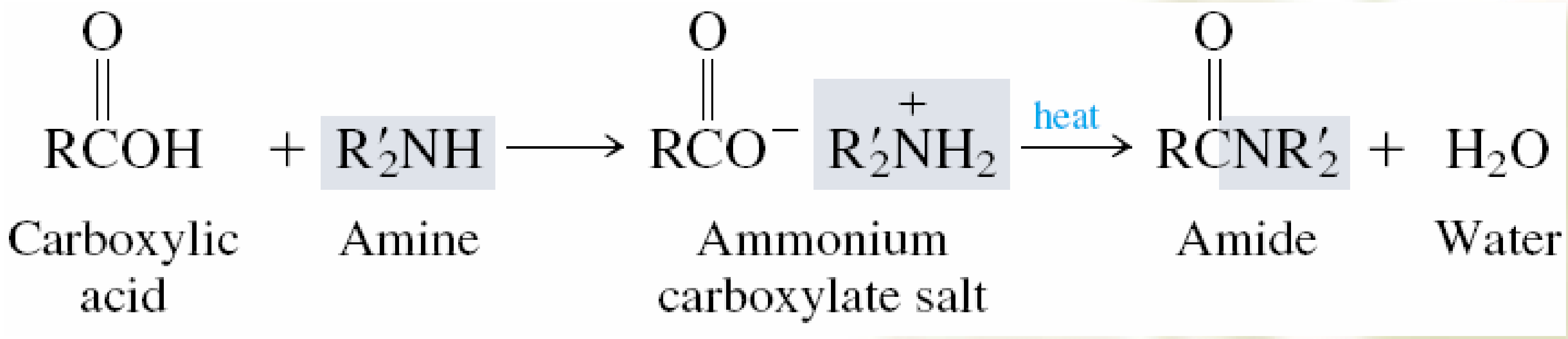
Two molar equivalents of amine are required in the reaction with acyl chlorides and acid anhydrides; one molecule of amine acts as a nucleophile, the second as a Brønsted base.



$$2R_2NH + R'\overset{\overset{O}{\|}}{C}Cl \longrightarrow R'\overset{\overset{O}{\|}}{C}NR_2 + R_2\overset{+}{N}H_2\ Cl^-$$

$$2R_2NH + R'\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R' \longrightarrow R'\overset{\overset{O}{\|}}{C}NR_2 + R_2\overset{+}{N}H_2\ {}^-O\overset{\overset{O}{\|}}{C}R'$$

Amides are sometimes prepared directly from carboxylic acids and amines by a two-step process. The first step is an acid–base reaction in which the acid and the amine combine to form an ammonium carboxylate salt. On heating, the ammonium carboxylate salt loses water to form an amide.



$$\mathrm{R\overset{O}{\overset{\|}{C}}OH} + \mathrm{R'_2NH} \longrightarrow \mathrm{R\overset{O}{\overset{\|}{C}}O^-}\ \mathrm{R'_2\overset{+}{N}H_2} \xrightarrow{\text{heat}} \mathrm{R\overset{O}{\overset{\|}{C}}NR'_2} + \mathrm{H_2O}$$

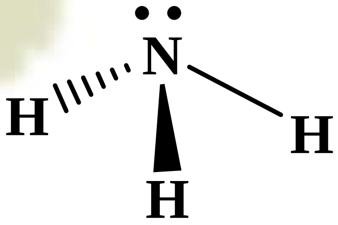
Notice： These thermal methods for preparing amides are limited in their generality. Most often amides are prepared in the laboratory from acyl chlorides, acid anhydrides, or esters, and these are the methods that you should apply to solving synthetic problems.

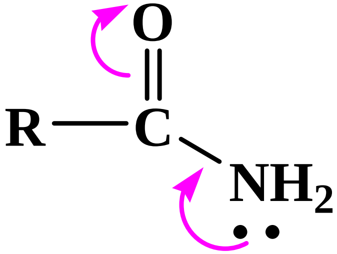
13.6.2 PHYSICAL PROPERTIES

- **Most often amides are white solids.**
- **Liquid amides used as solvents (such as DMF)**
- **High boiling point due to association**

13.6.3 CHEMICAL PROPERTIES

13.6.3.1 ACIDIC AND BASIC PROPERTIES

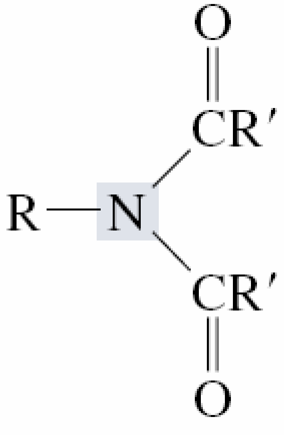




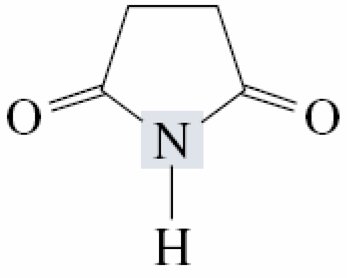
***p*-π conjugation**

Basic

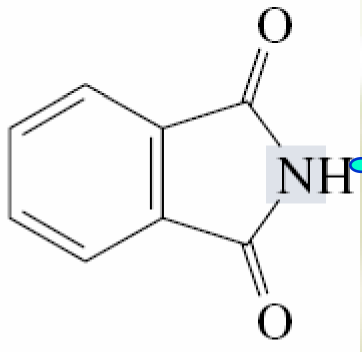
Neutral



Imide



Succinimide



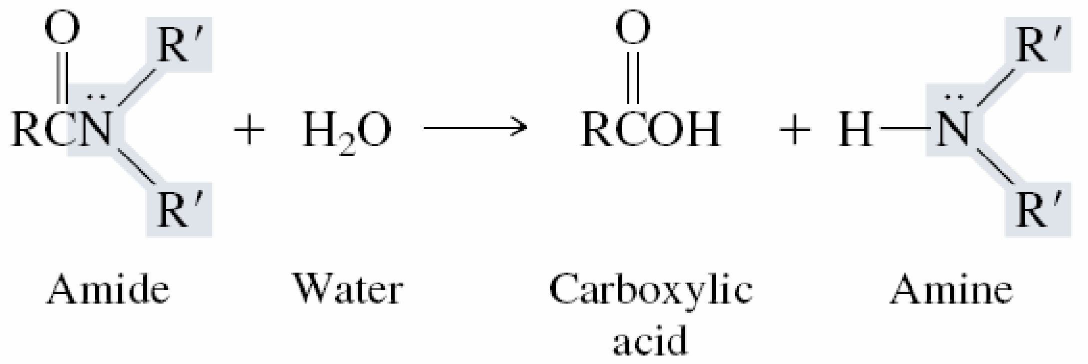
Phthalimide

Weak acidity

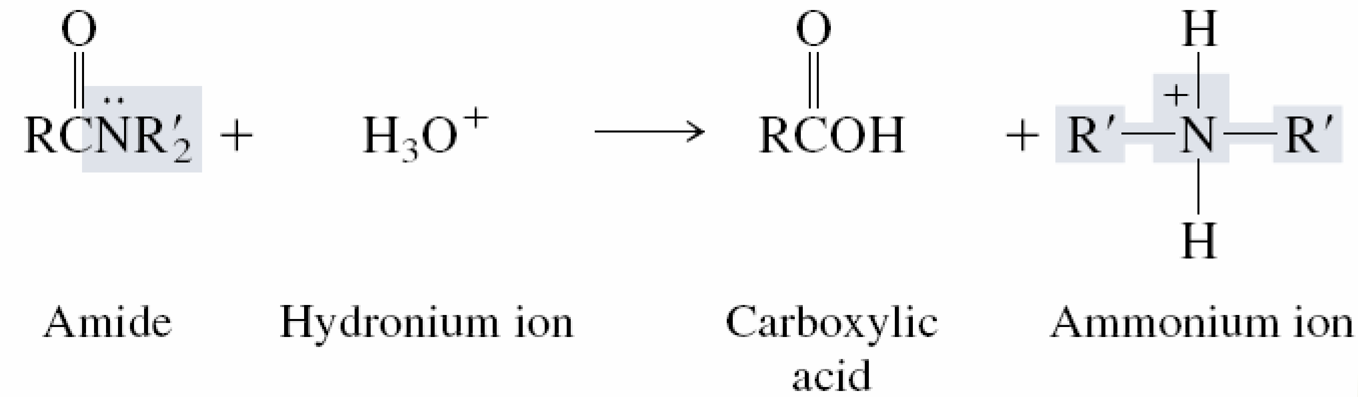
13.6.3.2 HYDROLYSIS OF AMIDES

Amides are the least reactive carboxylic acid derivative, and the only nucleophilic acyl substitution reaction they undergo is hydrolysis. Amides are fairly stable in water, but the amide bond is cleaved on heating in the presence of strong acids or bases.

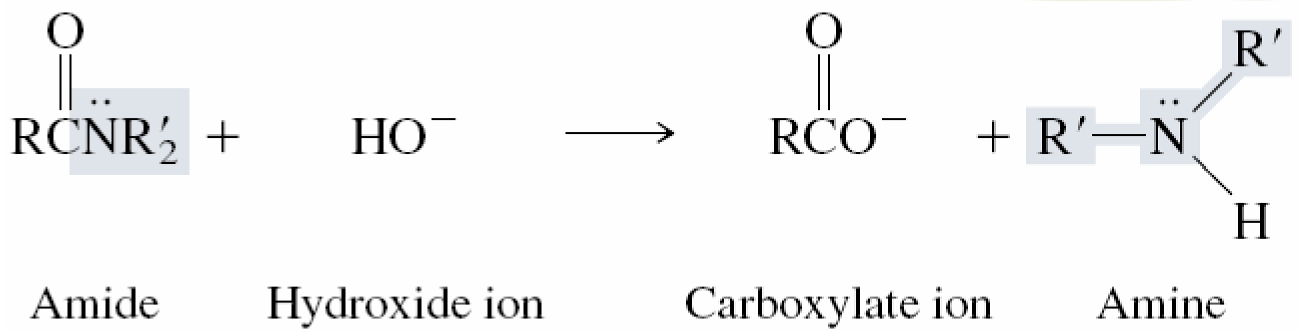
***Nominally*, this cleavage produces an amine and a carboxylic acid.**



In acid, however, the amine is protonated, giving an ammonium ion:

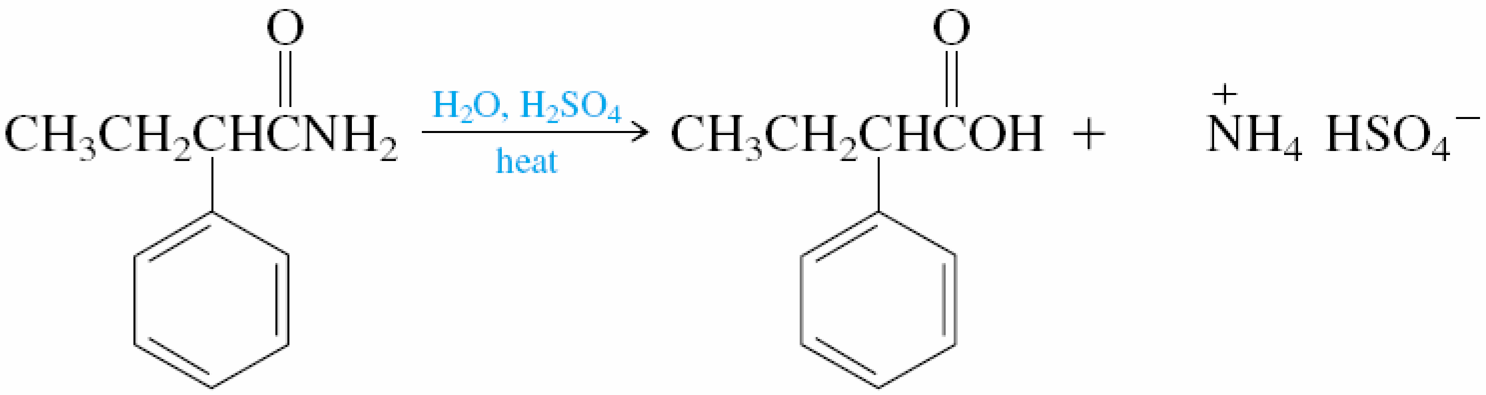


In base the carboxylic acid is deprotonated, giving a carboxylate ion:



The acid–base reactions that occur after the amide bond is broken make the overall hydrolysis irreversible in both cases. The amine product is protonated in acid; the carboxylic acid is deprotonated in base.

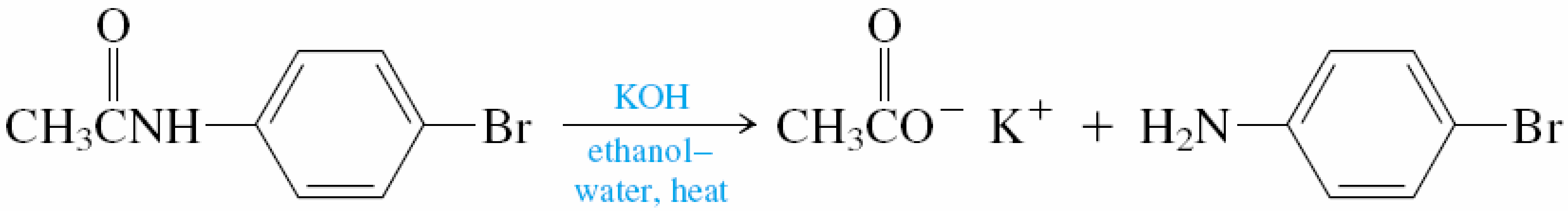
Ex:



2-Phenylbutanamide

2-Phenylbutanoic acid (88–90%)

Ammonium hydrogen sulfate



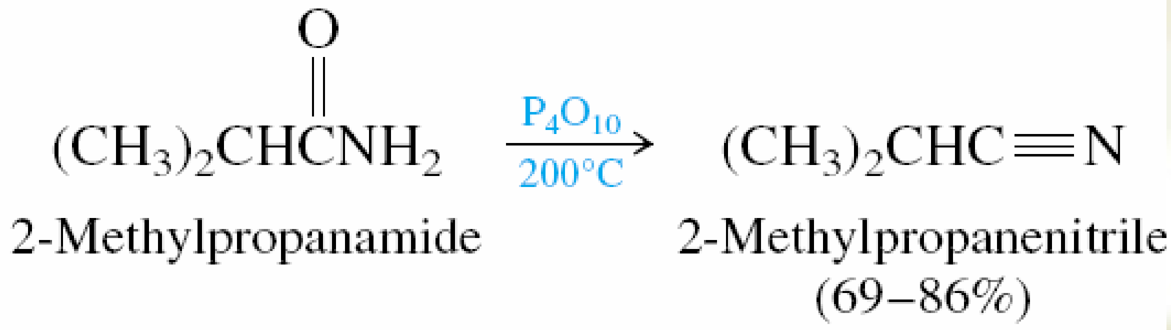
N-(4-Bromophenyl)acetamide (*p*-bromoacetanilide)

Potassium acetate

p-Bromoaniline (95%)

13.6.3.3 DEHYDRATION OF AMIDES

Among the reagents used to effect the dehydration of amides is the compound P_4O_{10} , known by the common name *phosphorus pentoxide* . Phosphorus pentoxide is used in a number of reactions requiring dehydrating agents.



$$(CH_3)_2CH\overset{\overset{\displaystyle O}{\|}}{C}NH_2 \xrightarrow[200°C]{P_4O_{10}} (CH_3)_2CHC{\equiv}N$$

2-Methylpropanamide

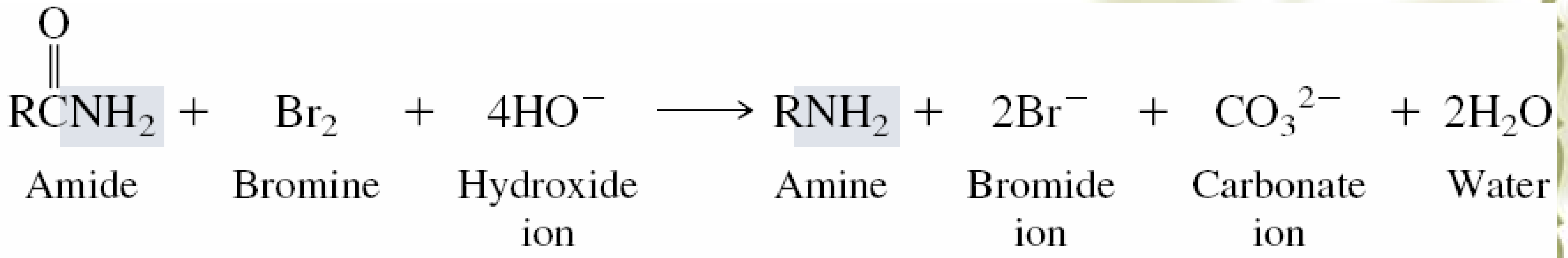
2-Methylpropanenitrile (69–86%)

Functional group transformation:

$$RCOOH \rightleftharpoons RCOONH_4 \overset{-H_2O}{\rightleftharpoons} RCONH_2 \overset{-H_2O}{\rightleftharpoons} RCN$$

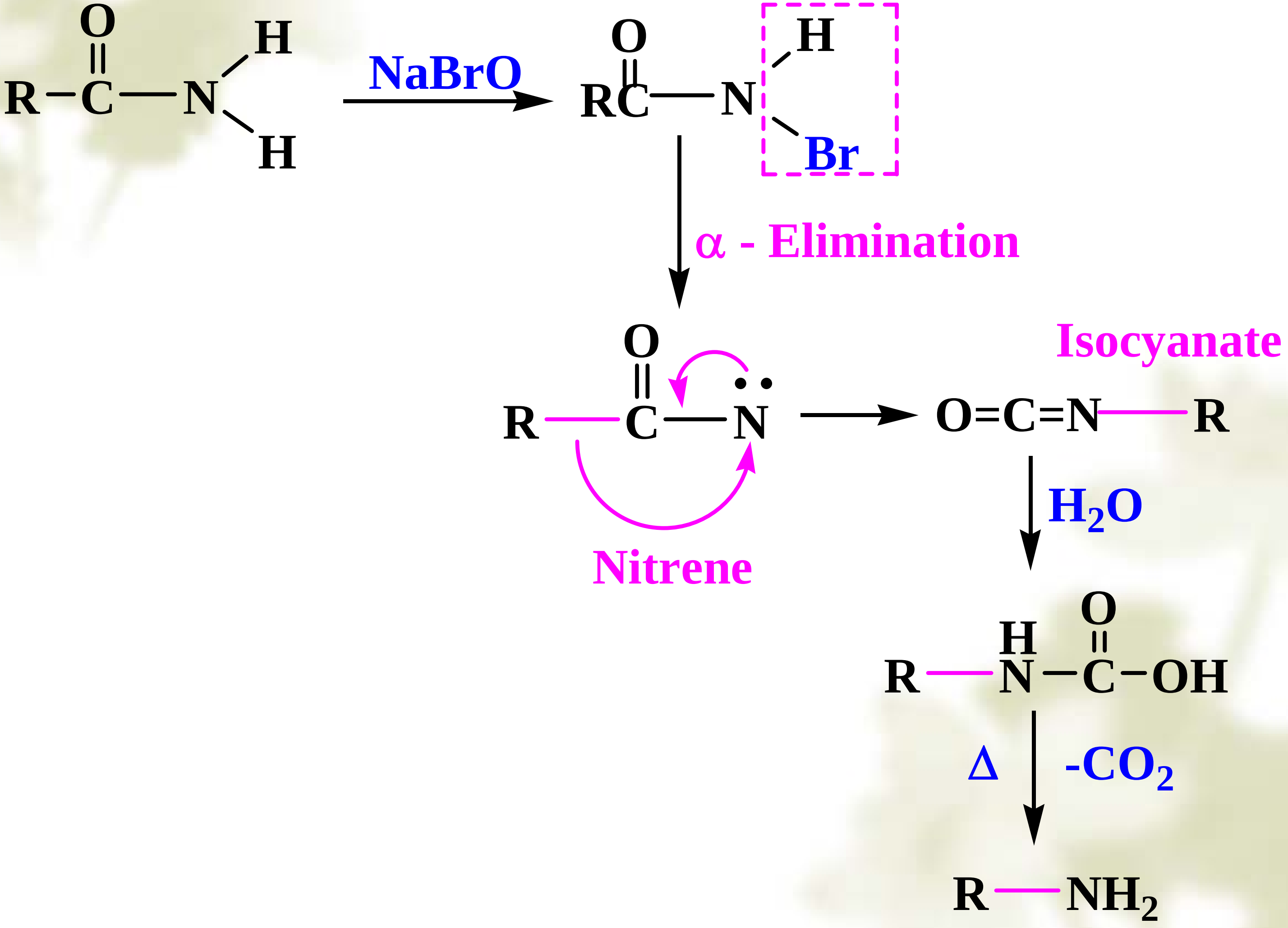
13.6.3.4 THE HOFMANN REARRANGEMENT

On treatment with bromine in basic solution, amides of the type $RCONH_2$ undergo an interesting reaction that leads to amines. This reaction was discovered by the 19th century German chemist August W. Hofmann and is called **the Hofmann rearrangement**.



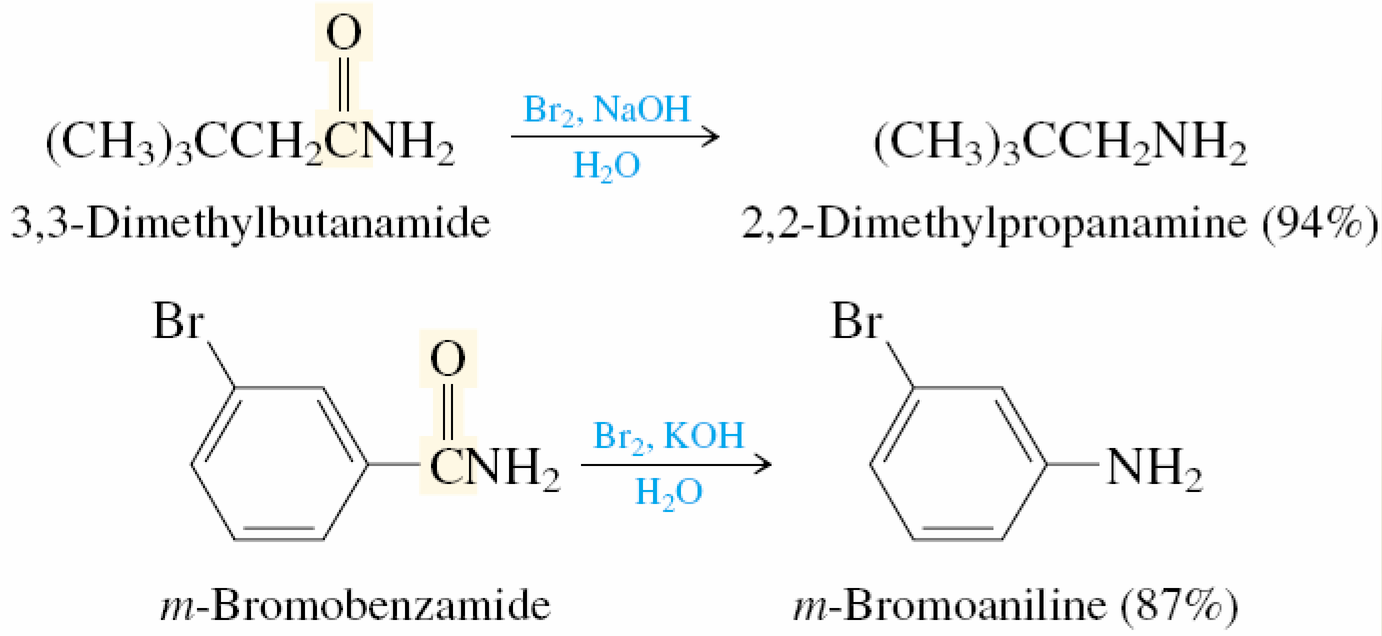
$$R\overset{\overset{O}{\|}}{C}NH_2 + Br_2 + 4HO^- \longrightarrow RNH_2 + 2Br^- + CO_3^{2-} + 2H_2O$$

Mechanism:


R–C(=O)–NH2
NaBrO
RC(=O)–N(H)Br
α - Elimination
R–C(=O)–N:
Nitrene
Isocyanate
O=C=N–R
H2O
R–NH–C(=O)–OH
Δ
-CO2
R–NH2

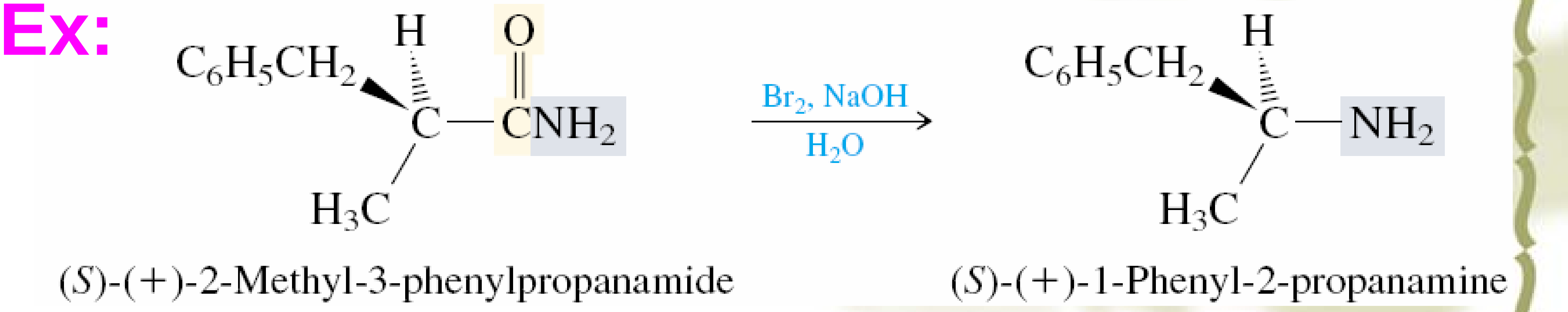
The overall reaction appears as if the carbonyl group had been plucked out of the amide, leaving behind a primary amine having one less carbon atom than the amide.

Ex:



Rearrangement proceeds with *retention of configuration* at the migrating group. The new carbon–nitrogen bond is formed at the same face of the migrating carbon as the bond that is broken. Presumably, carbon–nitrogen bond formation is concerted with carbon–carbon bond cleavage.

Ex:



(*S*)-(+)-2-Methyl-3-phenylpropanamide (*S*)-(+)-1-Phenyl-2-propanamine

Problem: $\mathrm{RCN} \rightrightarrows \mathrm{RNH_2}$

Sample solution:

$$\mathrm{RCN} \xrightarrow{\mathrm{H_3O^+}} \mathrm{RCOOH} \xrightarrow[\text{2. heat}]{\text{1. } \mathrm{NH_3}} \mathrm{RCONH_2}$$

$$\xrightarrow[\mathrm{H_2O}]{\mathrm{Br_2,\ NaOH}} \mathrm{RNH_2}$$

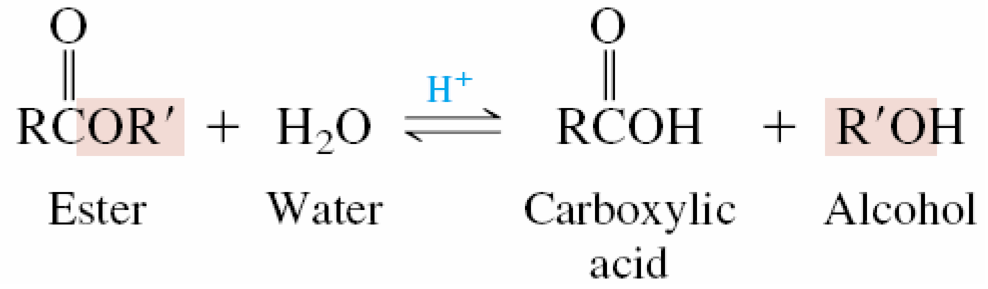
Contents

13.7 THE MECHANISM OF CARBOXYLIC ACID DERIVATIVES’ HYDROLYSIS, AMINOLYSIS AND ALCOHOLYSIS

13.7.1 ACID-CATALYZED ESTER HYDROLYSIS

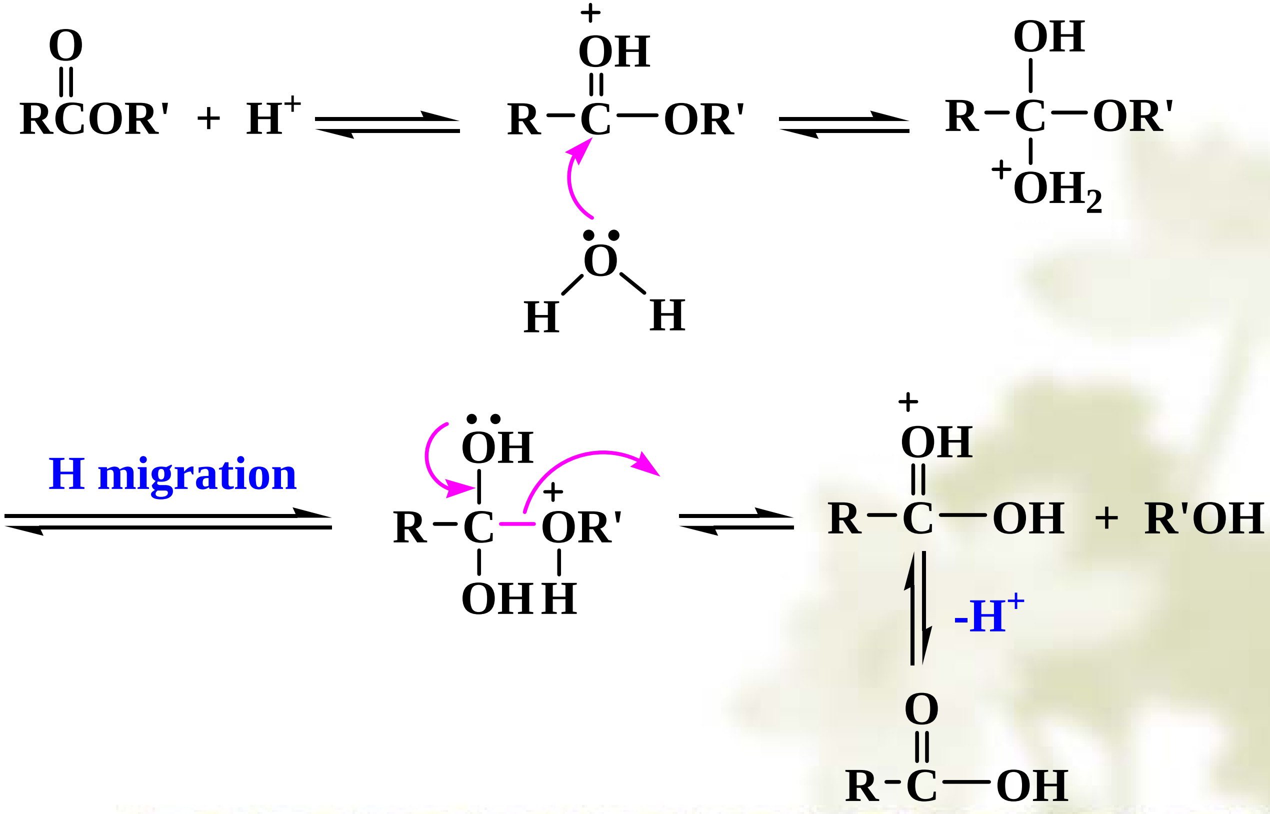
Ester hydrolysis is the most studied and best understood of all nucleophilic acyl substitutions. Esters are fairly stable in neutral aqueous media but are cleaved when heated with water in the presence of strong acids or bases. The hydrolysis of esters in dilute aqueous acid is the reverse of the Fischer esterification.

Overall reaction:

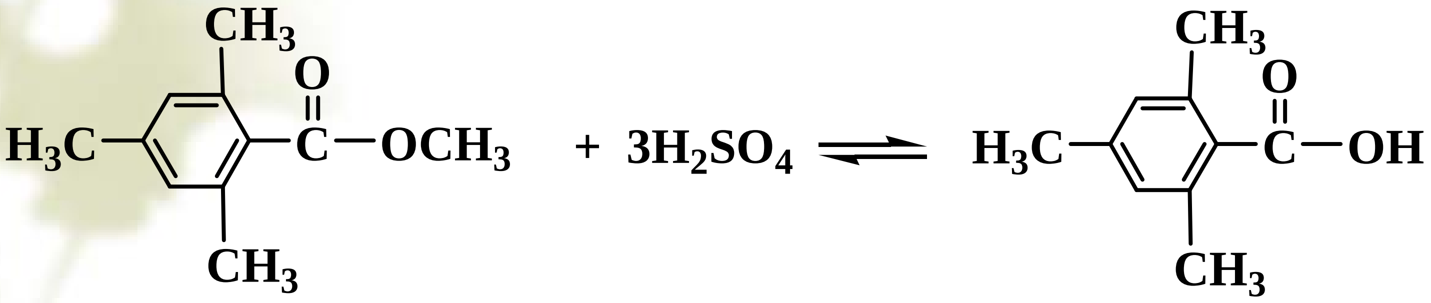


$$\mathrm{R\overset{O}{\overset{\|}{C}}OR' + H_2O \xrightleftharpoons{H^+} R\overset{O}{\overset{\|}{C}}OH + R'OH}$$

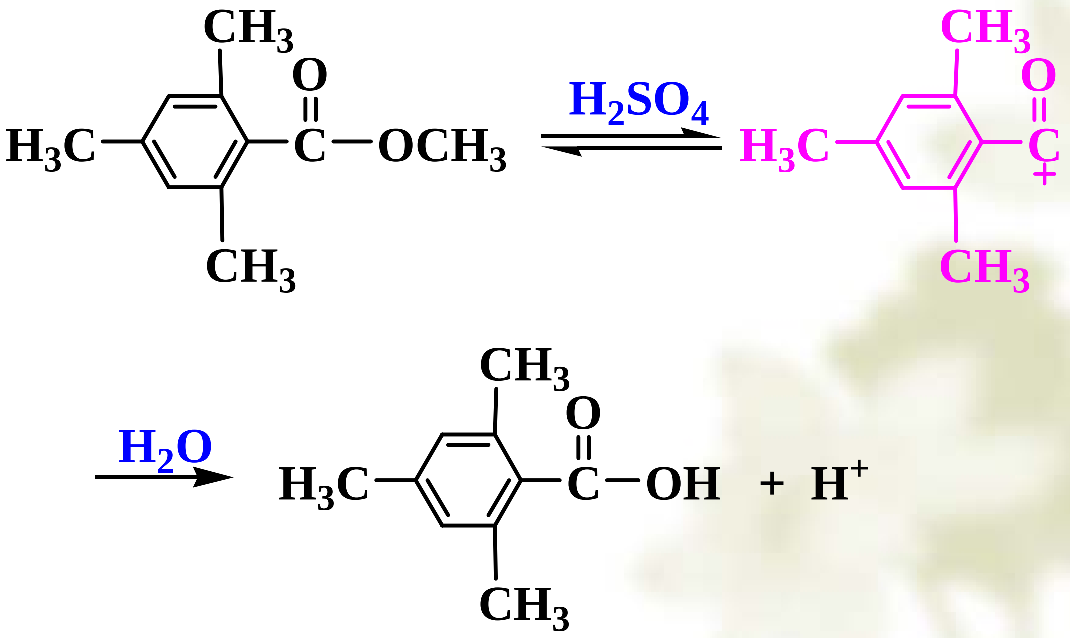
$A_{Ac}2$ Mechanism:



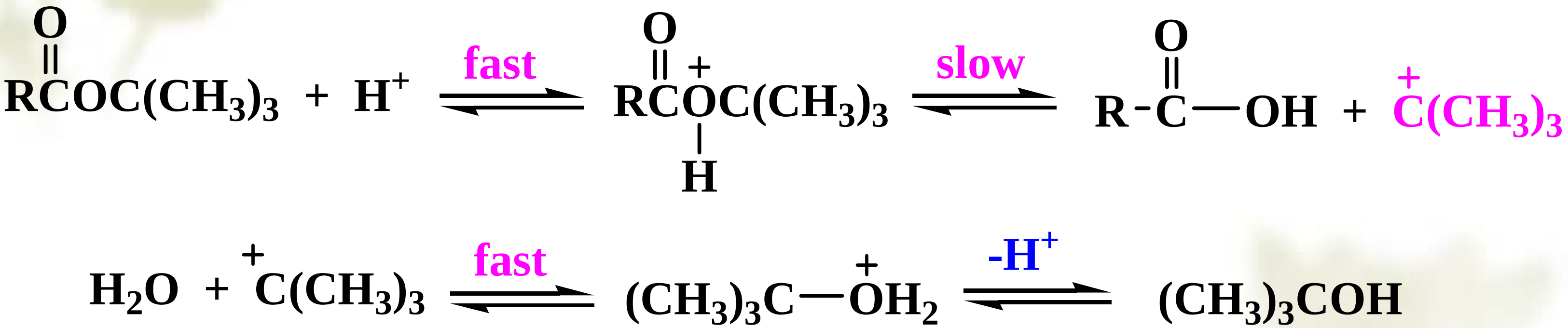
Overall reaction:



A_{Ac}1 Mechanism:



$A_{Al}1$ Mechanism:

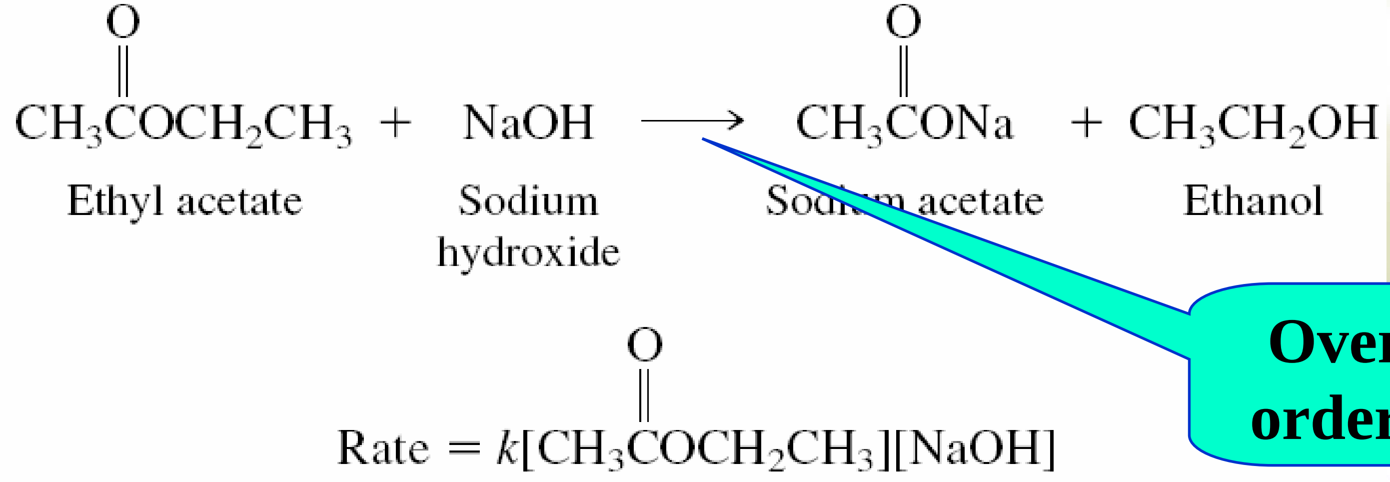


$$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OC(CH_3)_3} + \mathrm{H^+} \overset{\text{fast}}{\rightleftharpoons} \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\underset{\mathrm{H}}{\underset{|}{\overset{+}{\mathrm{O}}}}\mathrm{C(CH_3)_3} \overset{\text{slow}}{\rightleftharpoons} \mathrm{R-}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{-OH} + \overset{+}{\mathrm{C}}\mathrm{(CH_3)_3}$$

$$\mathrm{H_2O} + \overset{+}{\mathrm{C}}\mathrm{(CH_3)_3} \overset{\text{fast}}{\rightleftharpoons} \mathrm{(CH_3)_3C-}\overset{+}{\mathrm{O}}\mathrm{H_2} \overset{-\mathrm{H^+}}{\rightleftharpoons} \mathrm{(CH_3)_3COH}$$

13.7.2 ESTER HYDROLYSIS IN BASE: SAPONIFICATION

In one of the earliest kinetic studies of an organic reaction, carried out in the 19th century, the rate of hydrolysis of ethyl acetate in aqueous sodium hydroxide was found to be *first* order in ester and *first* order in base.



$$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 + NaOH \longrightarrow CH_3\overset{O}{\overset{\|}{C}}ONa + CH_3CH_2OH$$

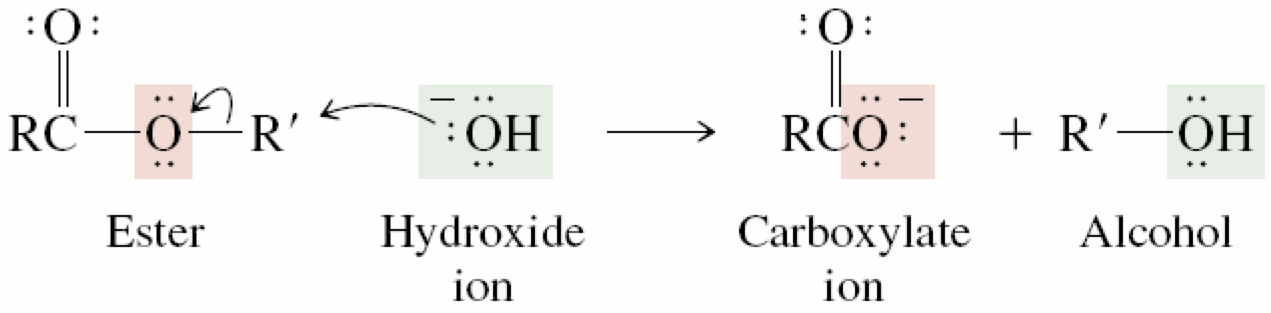
$$\text{Rate} = k[CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3][NaOH]$$

Overall: 2^{nd}-order kinetics

Two processes that are consistent with second-order kinetics both involve hydroxide ion as a nucleophile but differ in the site of nucleophilic attack.

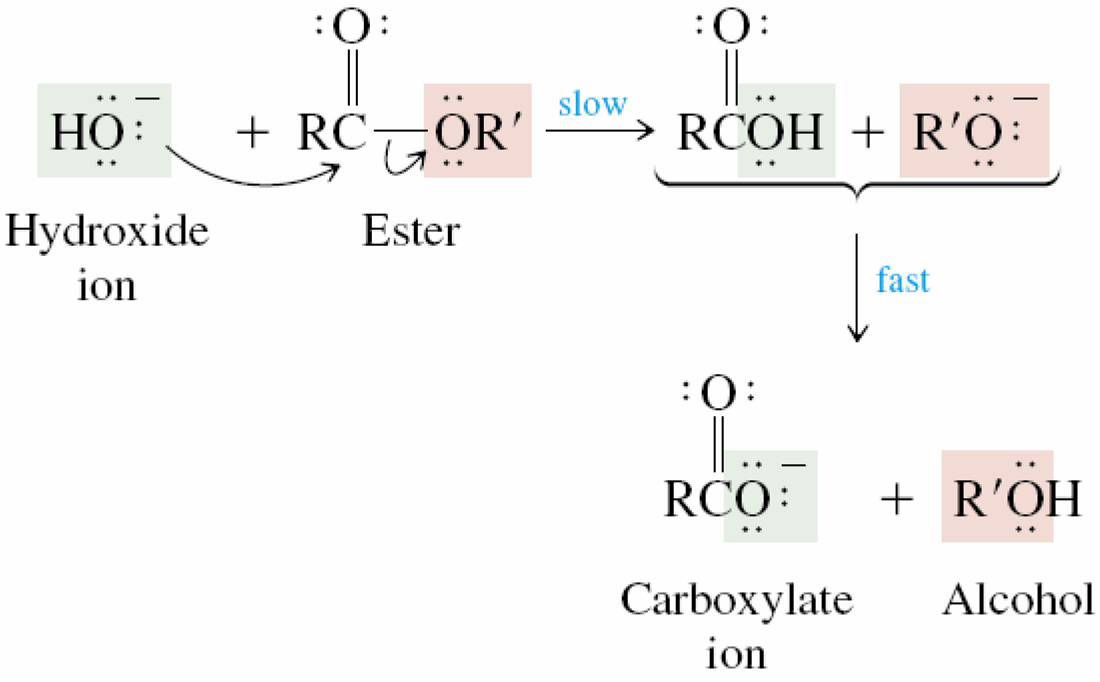
- **One of these processes is *alkyl-oxygen cleavage*, with hydroxide displacing carboxylate from the alkyl group of the ester.**

Alkyl–oxygen cleavage



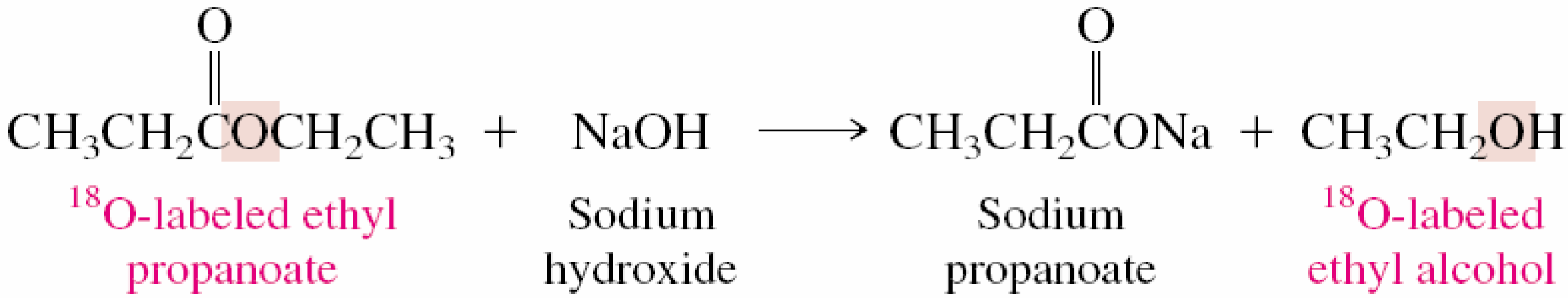
- The other process involves ***acyl–oxygen cleavage***, **with hydroxide attacking the carbonyl group.**

Acyl–oxygen cleavage



Convincing evidence that ester hydrolysis in base proceeds by the second of these two paths, namely, *acyl–oxygen cleavage*, has been obtained from several sources.

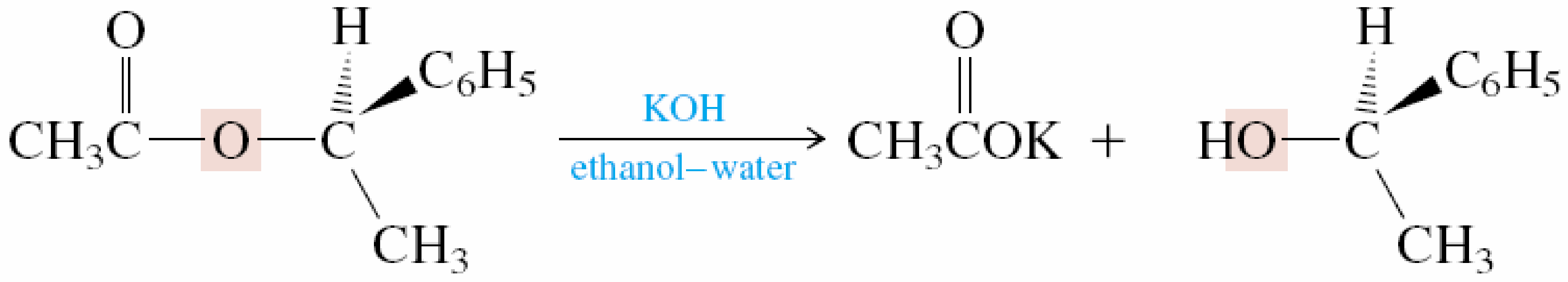
Ex:



$$CH_3CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + NaOH \longrightarrow CH_3CH_2\overset{O}{\overset{\|}{C}}ONa + CH_3CH_2OH$$

Identical conclusions in support of acyl–oxygen cleavage have been obtained from stereochemical studies. Saponification of esters of optically active alcohols proceeds with *retention of configuration*.

Ex:

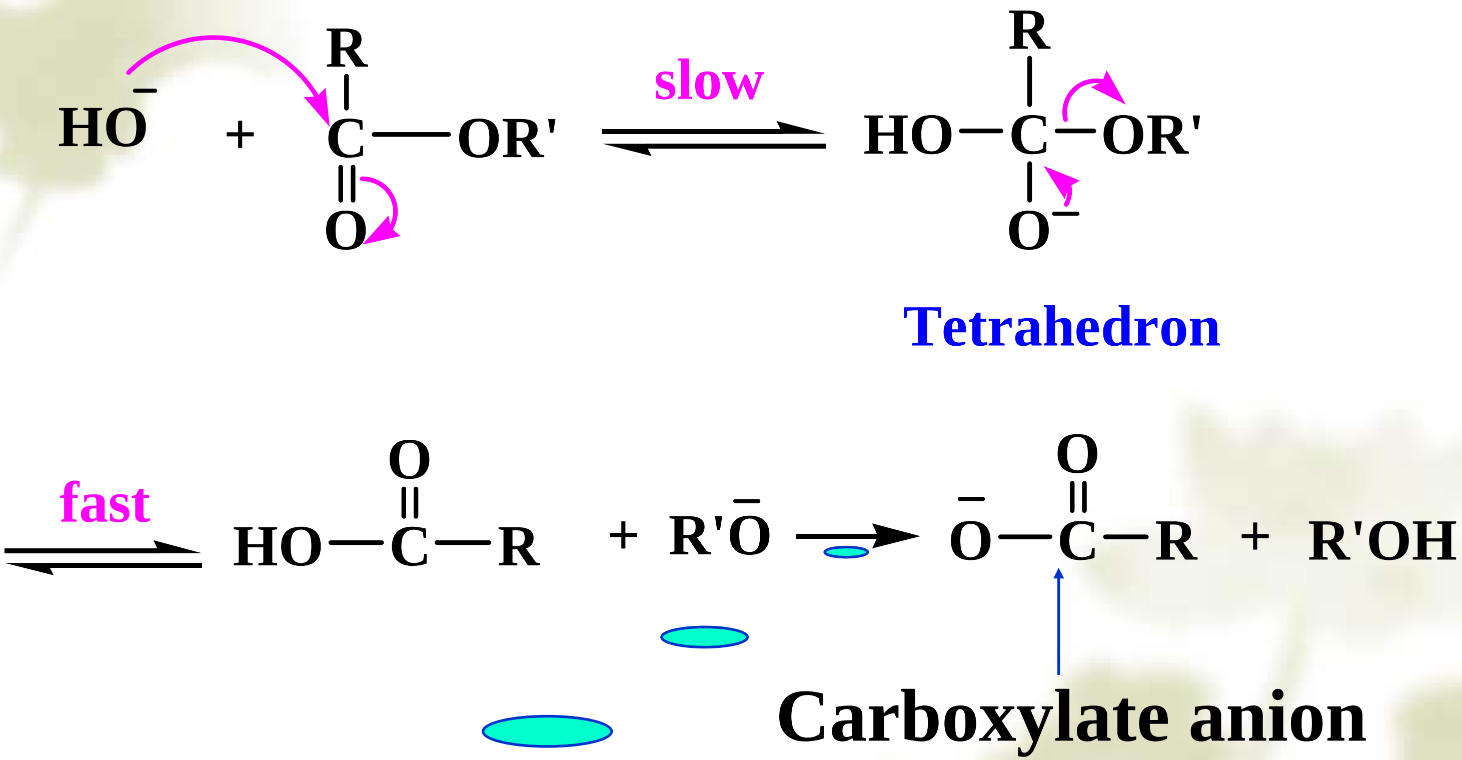


(*R*)-(+)-1-Phenylethyl acetate

Potassium acetate

(*R*)-(+)-1-Phenylethyl alcohol (80% yield; same optical purity as ester)

The mechanism of saponification:



$$HO^{-} + \underset{\underset{O}{\|}}{\overset{\overset{R}{|}}{C}}-OR' \underset{}{\overset{slow}{\rightleftharpoons}} HO-\underset{\underset{O^{-}}{|}}{\overset{\overset{R}{|}}{C}}-OR'$$

Tetrahedron

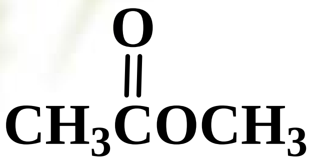
$$\overset{fast}{\rightleftharpoons} HO-\overset{\overset{O}{\|}}{C}-R + R'\bar{O} \longrightarrow \bar{O}-\overset{\overset{O}{\|}}{C}-R + R'OH$$

Carboxylate anion

Irreversible

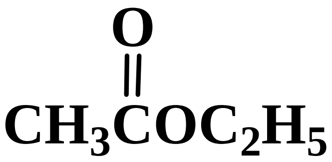
Problem 1: Rank the compounds in each of the following groups in order of decreasing reactivity toward saponification.

1.



$CH_3\overset{\overset{O}{\|}}{C}OCH_3$

a



$CH_3\overset{\overset{O}{\|}}{C}OC_2H_5$

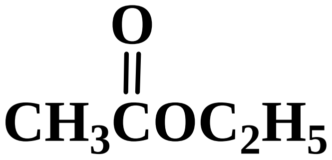
b

$CH_3\overset{\overset{O}{\|}}{C}OCH(CH_3)_2$

c

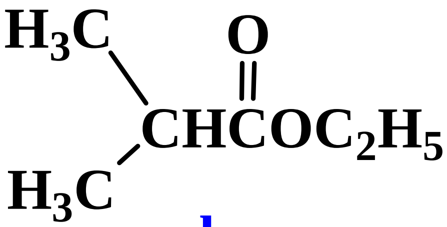
a > b > c

2.

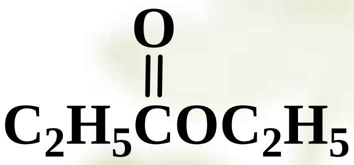


$CH_3\overset{\overset{O}{\|}}{C}OC_2H_5$

a



b



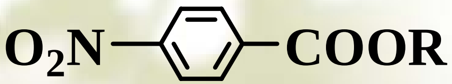
$C_2H_5\overset{\overset{O}{\|}}{C}OC_2H_5$

c

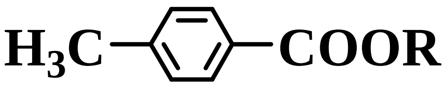
a > c > b

Steric effect

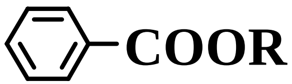
3.



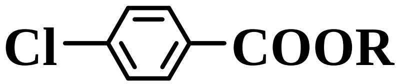
a



b



c



d

a > d > c > b

Electronic effect

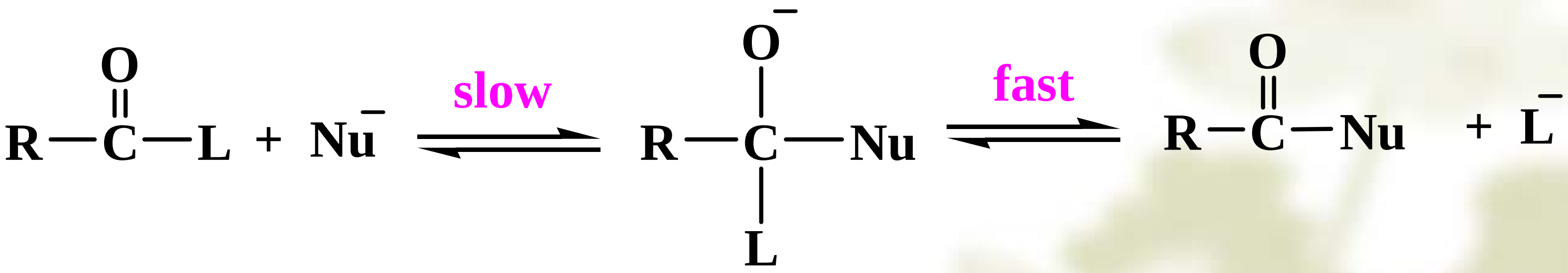
Problem 2: $CH_3COOC(CH_3)_3 > CH_3COOCH_3$

Hydrolysis rate: 1.15 1.0

Why?

13.7.3 CARBOXYLIC ACID DERIVATIVES' HYDROLYSIS AMINOLYSIS AND ALCOHOLYSIS

General mechanism for nucleophilic acyl substitution:



$$R-\overset{\overset{O}{\|}}{C}-L + Nu^- \xrightleftharpoons[]{\text{slow}} R-\underset{\underset{L}{|}}{\overset{\overset{O^-}{|}}{C}}-Nu \xrightleftharpoons[]{\text{fast}} R-\overset{\overset{O}{\|}}{C}-Nu + L^-$$

Tetrahedral intermediate

Acyl halides are the most reactive, amides the least reactive. The reactivity order,

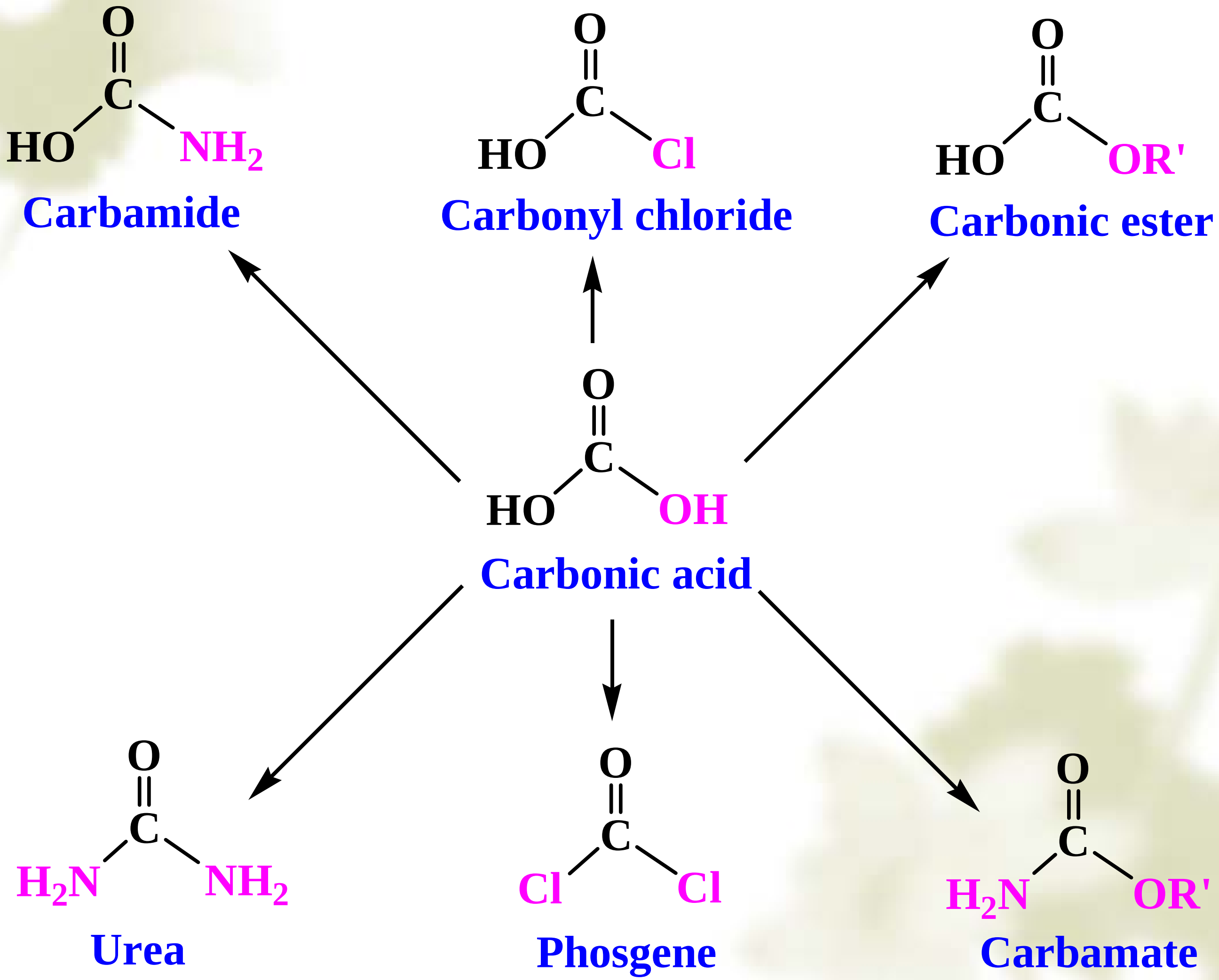
Acyl halide > anhydride > ester > amide

is general for nucleophilic acyl substitution and well worth remembering.

What structural features are responsible for the reactivity order of carboxylic acid derivatives?

Contents

13.8 DERIVATIVES OF CARBONIC ACID



Carbamide

Carbonyl chloride

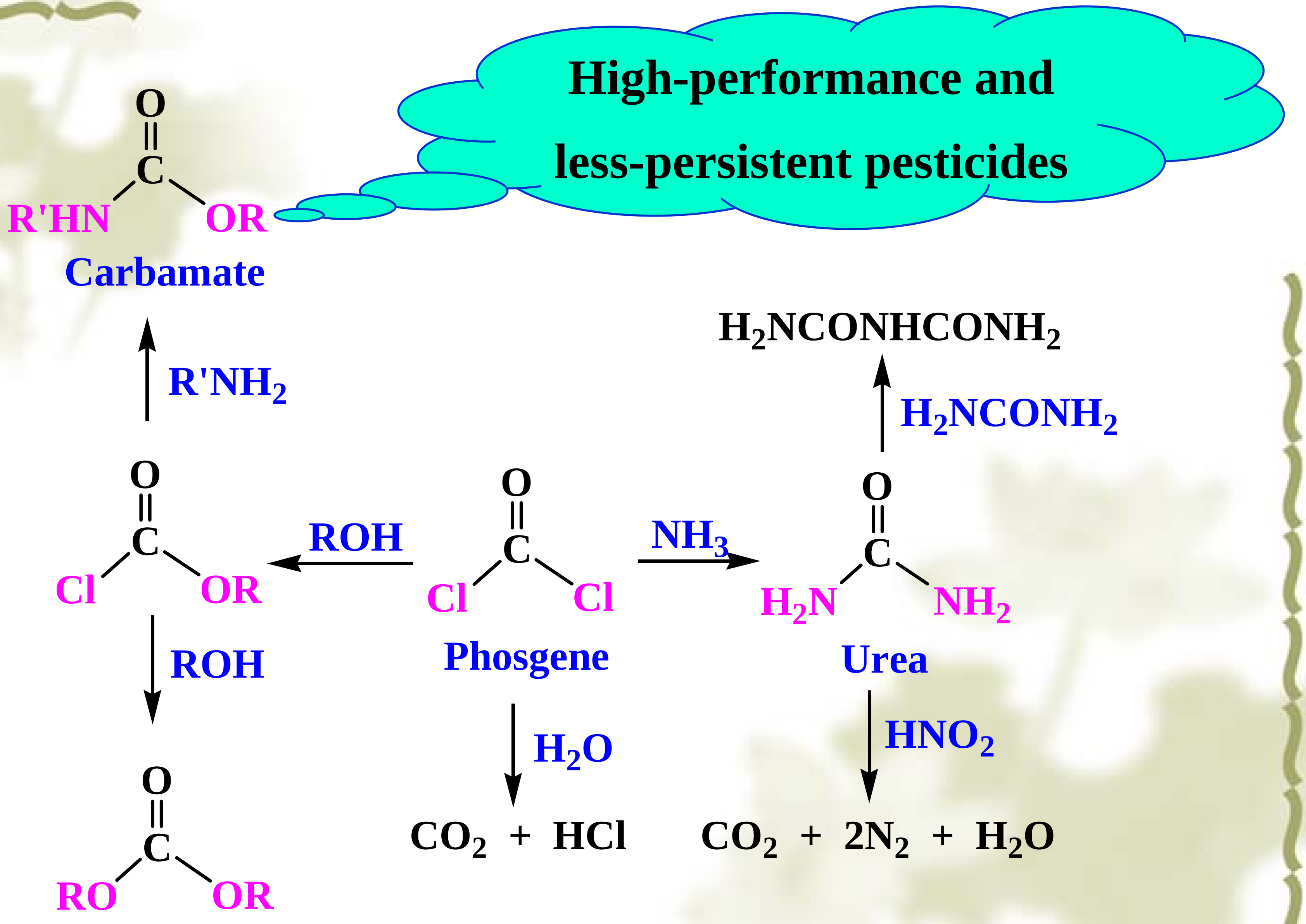
Carbonic ester

Carbonic acid

Urea

Phosgene

Carbamate

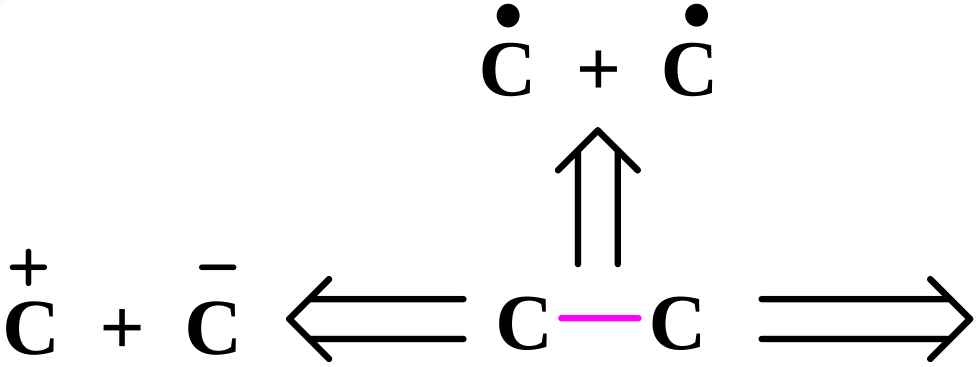


High-performance and less-persistent pesticides

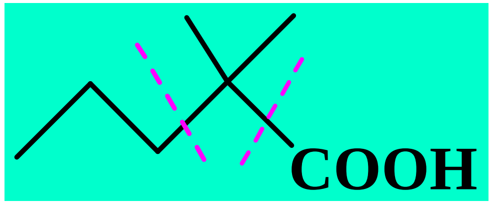
Contents

13.9 SYNTHETIC ROUTE

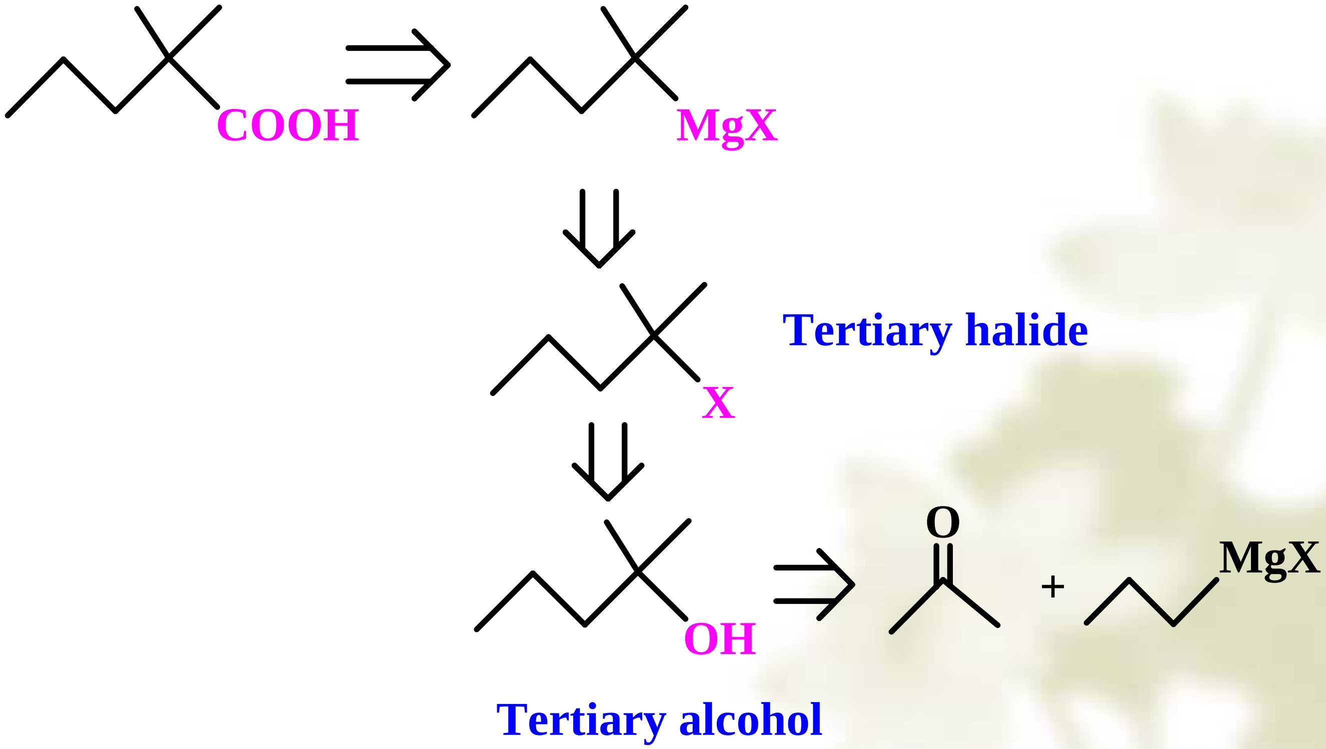
13.9.1 THE FORMATION OF C-C BOND



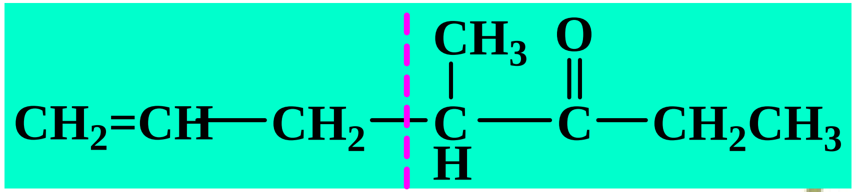
Ex 1: Synthesis the following compound by using the starting material which less than three carbon atoms.



Retrosynthesis:

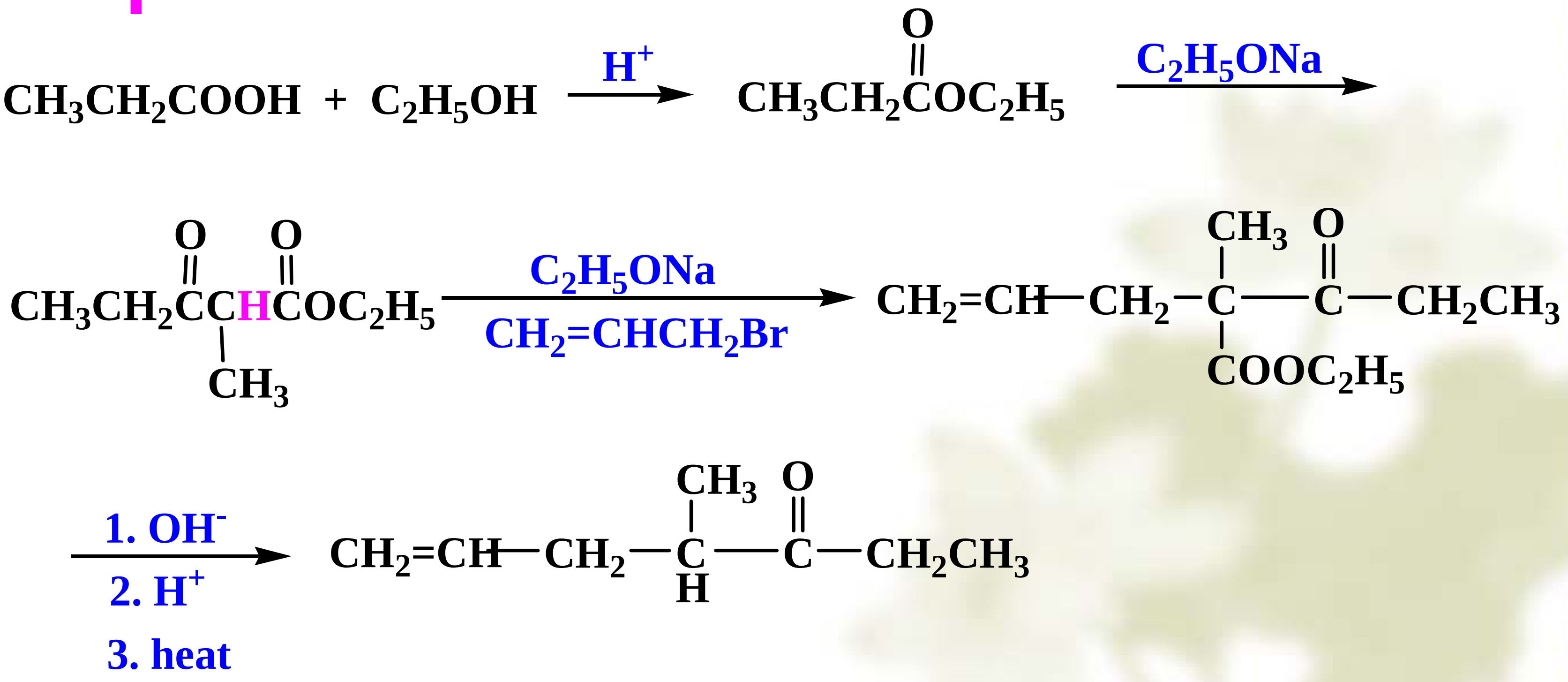


Ex 2: Synthesis the following compound by using the starting material which less than three carbon atoms.



$$CH_2{=}CH{-}CH_2{-}\overset{CH_3}{\underset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_3$$

Sample solution:

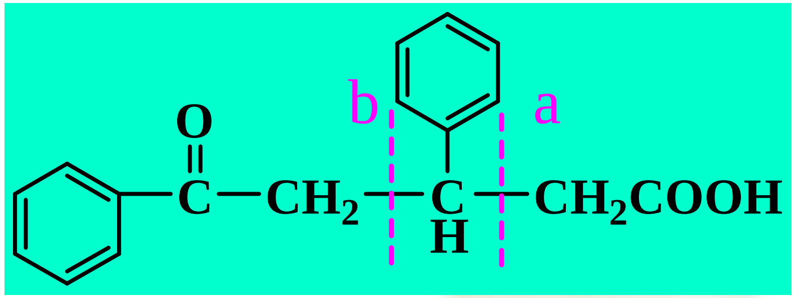


$$CH_3CH_2COOH + C_2H_5OH \xrightarrow{H^+} CH_3CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 \xrightarrow{C_2H_5ONa}$$

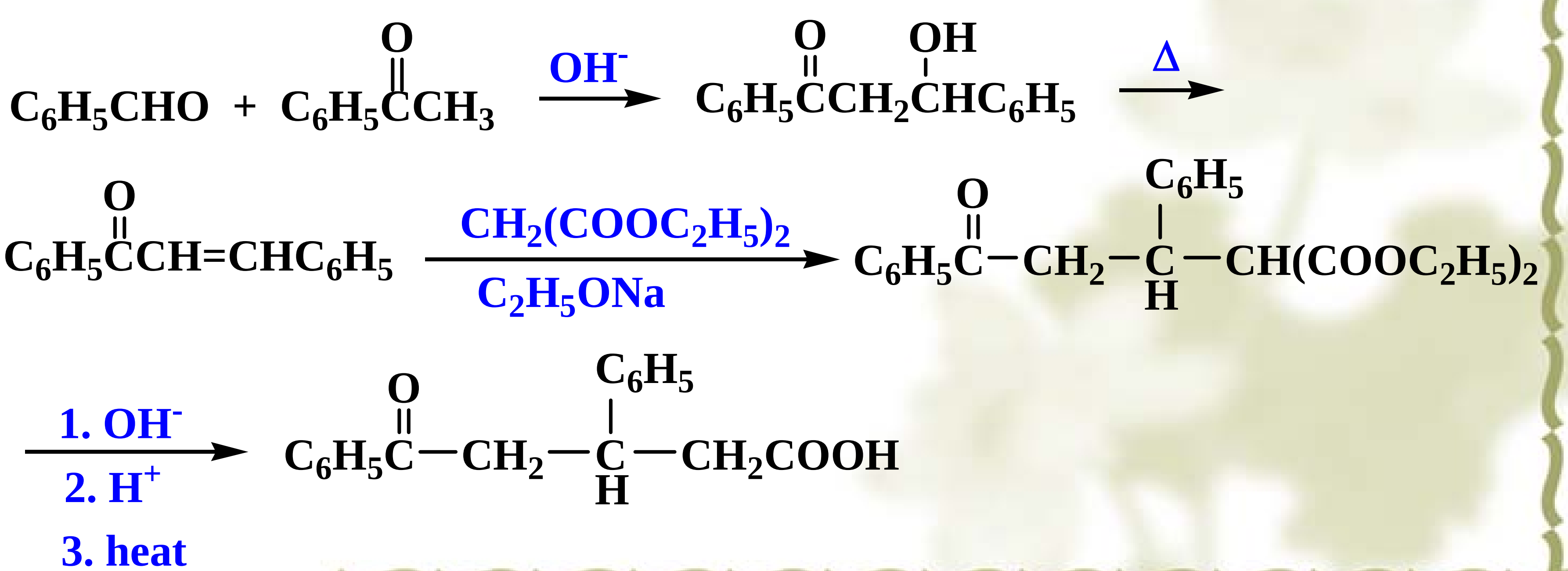
$$CH_3CH_2\overset{O}{\overset{\|}{C}}\underset{CH_3}{C}H\overset{O}{\overset{\|}{C}}OC_2H_5 \xrightarrow[CH_2=CHCH_2Br]{C_2H_5ONa} CH_2{=}CH{-}CH_2{-}\overset{CH_3}{\underset{COOC_2H_5}{C}}{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_3$$

$$\xrightarrow[\substack{2.\ H^+ \\ 3.\ heat}]{1.\ OH^-} CH_2{=}CH{-}CH_2{-}\overset{CH_3}{\underset{H}{C}}{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_3$$

Ex 3: Show how you could prepare the following compound using any necessary inorganic and organic reagents.



Sample solution:

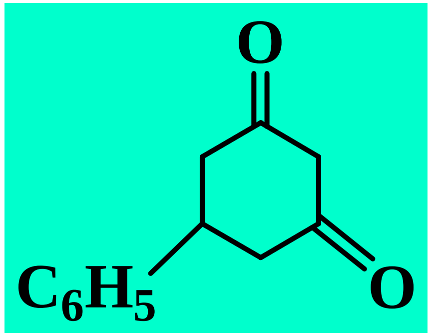


$$C_6H_5CHO + C_6H_5\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{OH^-} C_6H_5\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{OH}{|}}{C}HC_6H_5 \xrightarrow{\Delta}$$

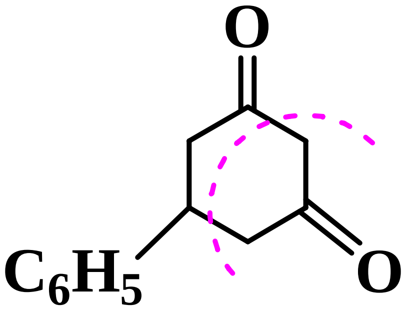
$$C_6H_5\overset{\overset{O}{\|}}{C}CH{=}CHC_6H_5 \xrightarrow[C_2H_5ONa]{CH_2(COOC_2H_5)_2} C_6H_5\overset{\overset{O}{\|}}{C}-CH_2-\underset{H}{\overset{\overset{C_6H_5}{|}}{C}}-CH(COOC_2H_5)_2$$

$$\xrightarrow[\substack{2.\ H^+ \\ 3.\ heat}]{1.\ OH^-} C_6H_5\overset{\overset{O}{\|}}{C}-CH_2-\underset{H}{\overset{\overset{C_6H_5}{|}}{C}}-CH_2COOH$$

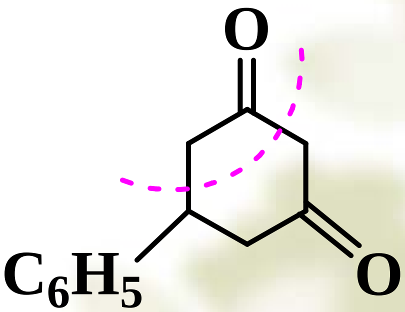
Ex 4: Prepare the following compound by using benzaldehyde and any necessary organic and inorganic reagents.



Analysis:



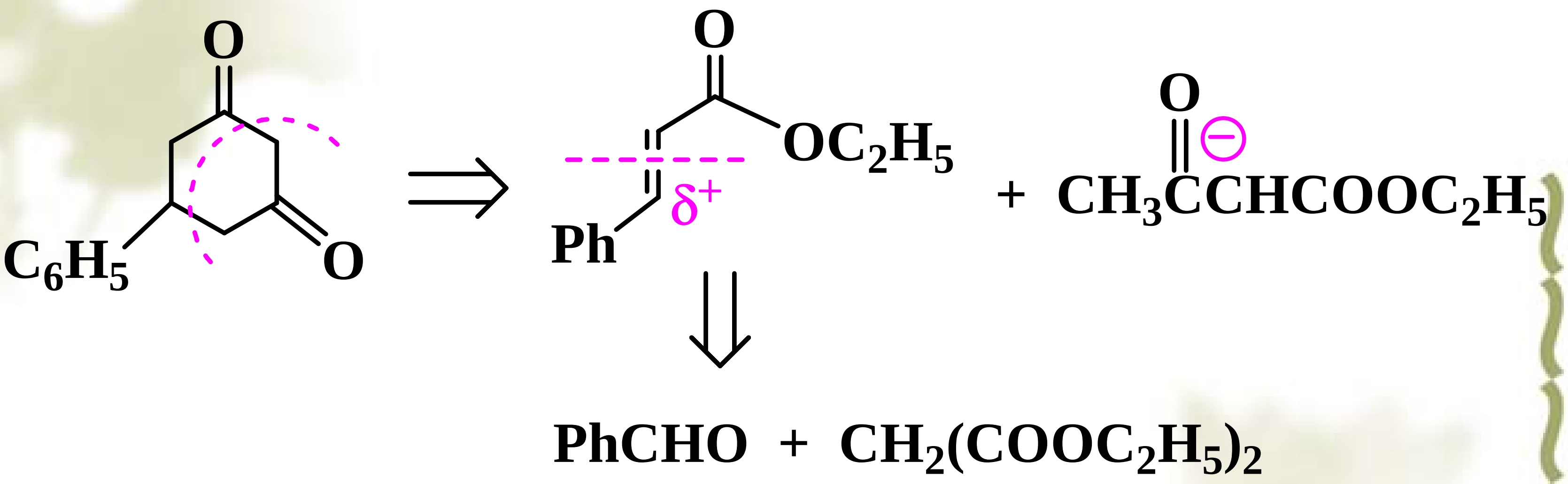
(1)



(2)

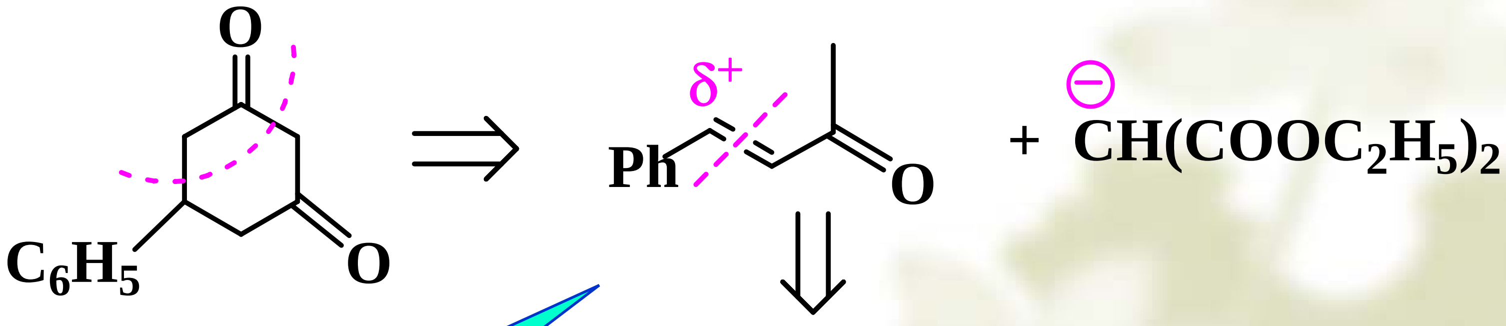
Retrosynthesis:

(1)



$PhCHO + CH_2(COOC_2H_5)_2$

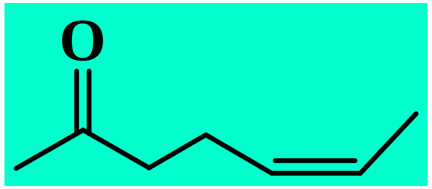
(2)



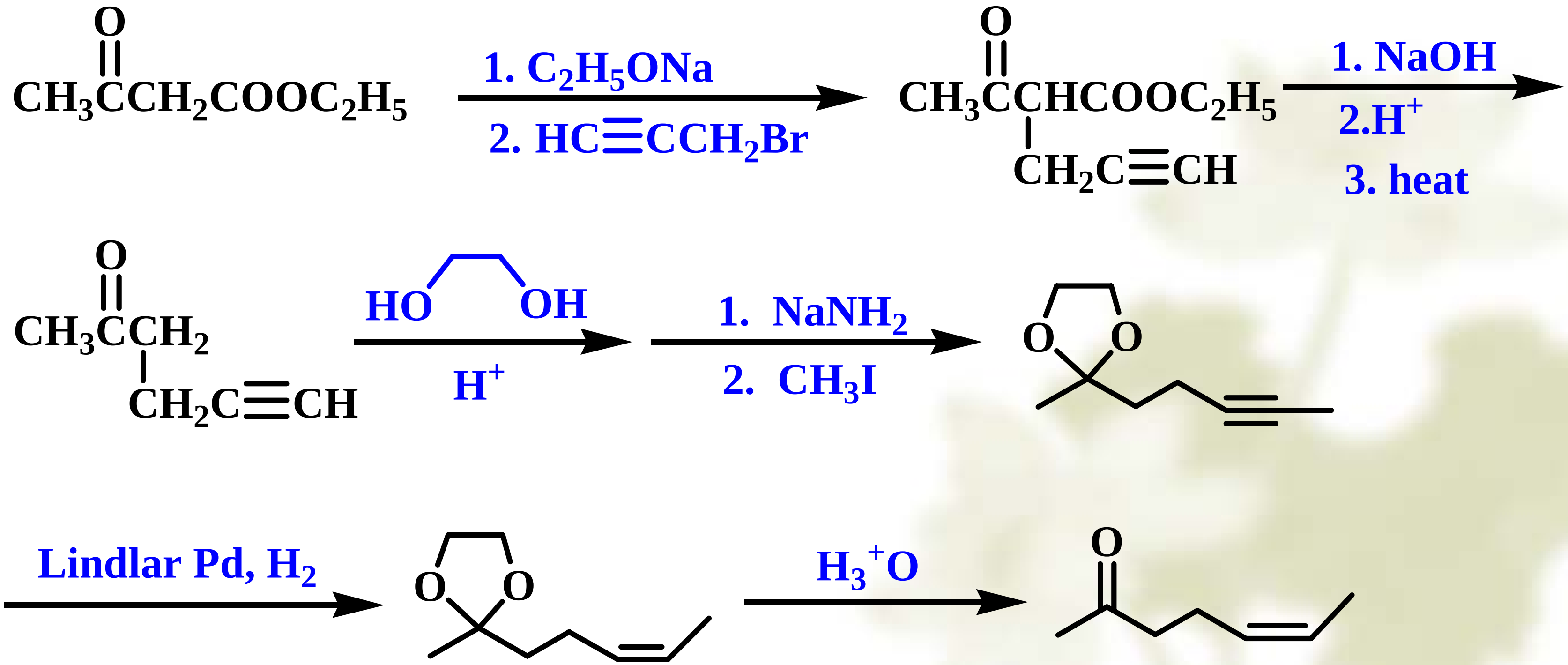
$PhCHO + CH_3COCH_3$

Convenient

Ex 5: Prepare the following compound by using ethyl acetoacetate and any necessary organic reagents with less than three carbon atoms.



Sample solution:



13.9.2 INTRODUCING AND TRANSFORMATION OF FUNCTIONAL GROUPS

Synthetic strategies:

a. Stereoselectivity and regioselectivity reaction

b. Protection and deprotection of the functional group

c. Activation of the necessary site

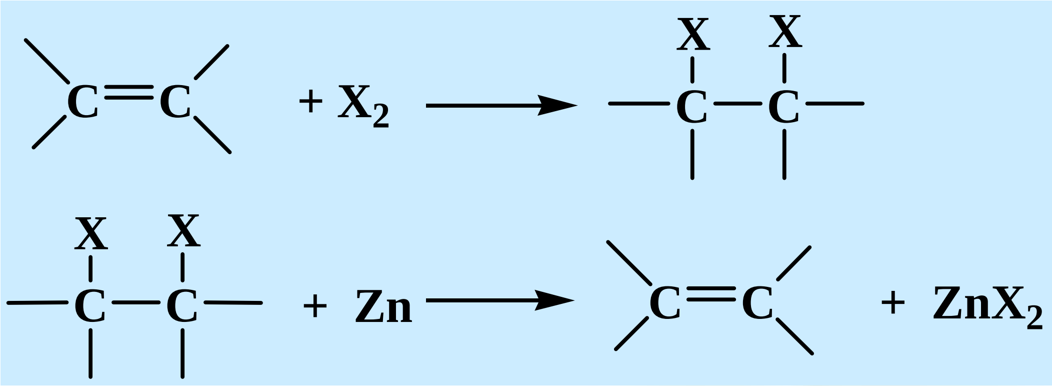
d. Introducing the orientating group

13.9.2.1 STEREOSELECTIVITY AND REGIOSELECTIVITY REACTIONS

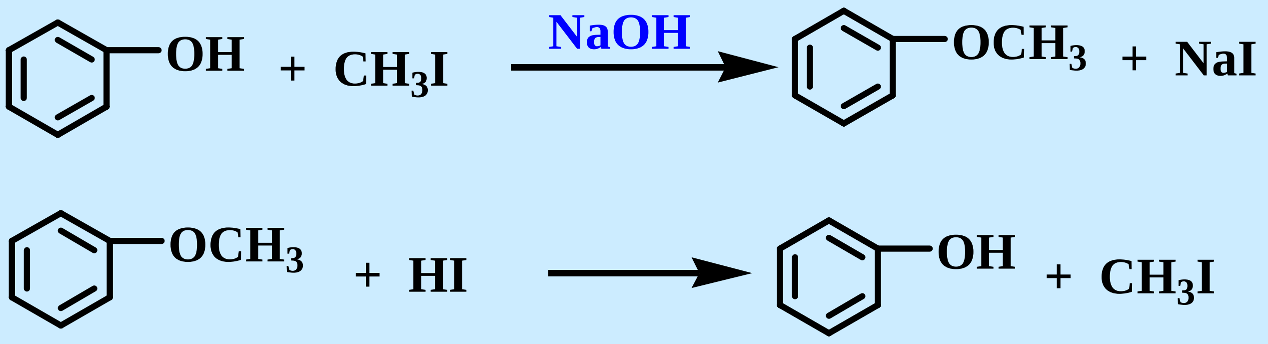
- **Asymmetric electrophilic addition－Markovnikov’s Rule；**
- **Elimination reactions－Zaitsev Rule；**
- **Electrophilic aromatic substitution ；**
- **Selectivity reduction of alkyne.**

13.9.2.2 PROTECTION AND DEPROTECTION OF THE FUNCTIONAL GROUPS

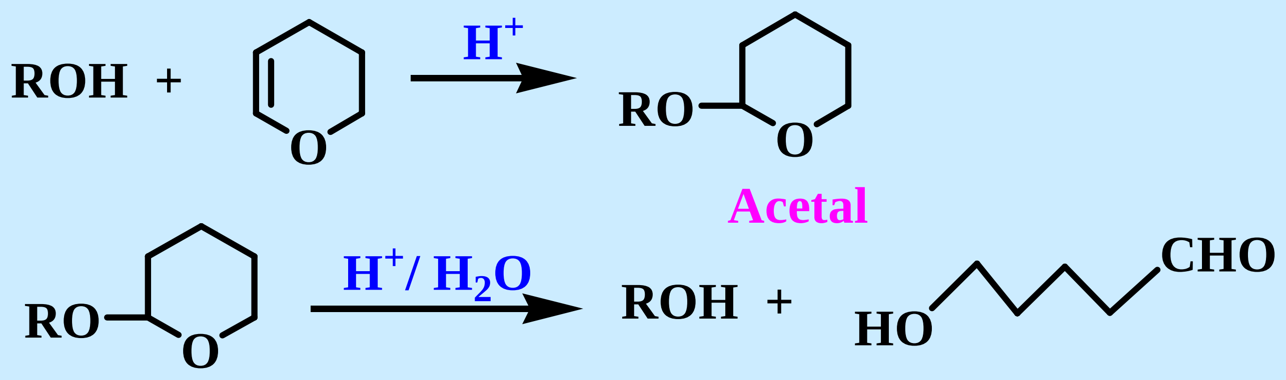
a. Carbon-carbon double bond



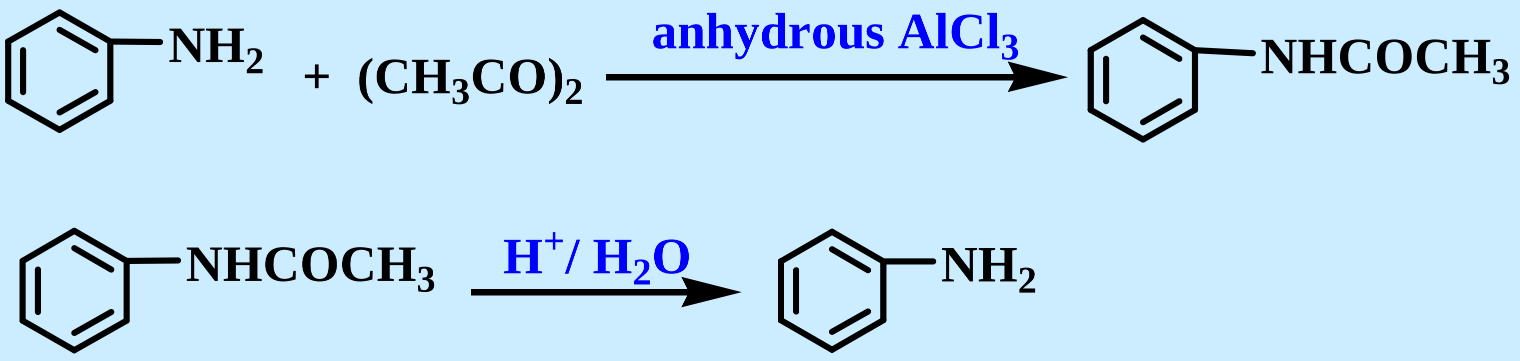
b. Hydroxyl group in phenols



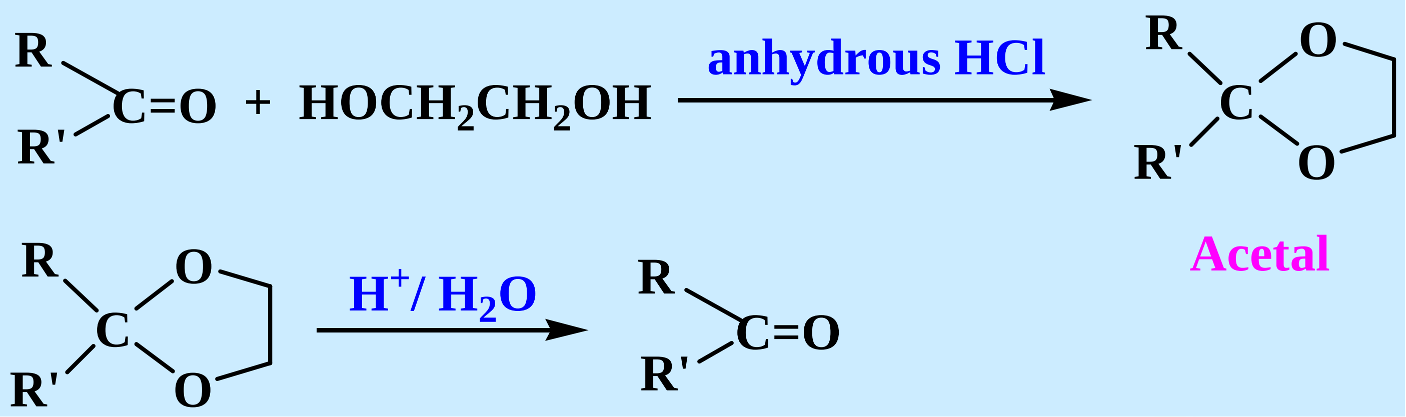
c. Hydroxyl group in alcohols



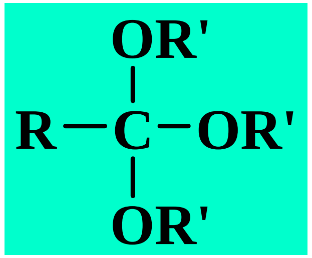
d. Amino group



e. Carbonyl group

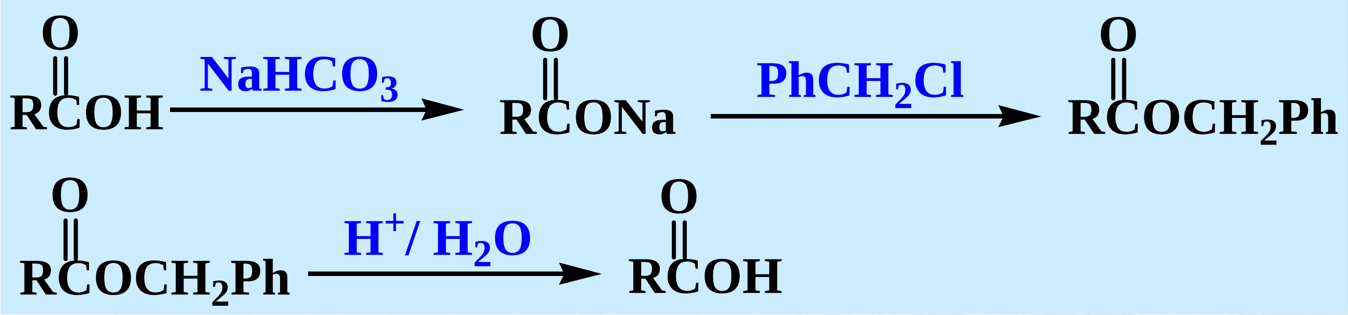


Orthoformate:



$$\mathrm{R-\underset{OR'}{\underset{|}{\overset{OR'}{\overset{|}{C}}}}-OR'}$$

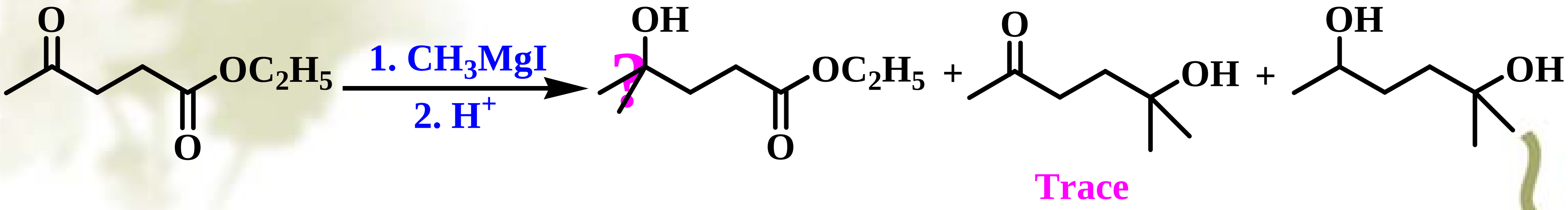
f. Carboxylic group



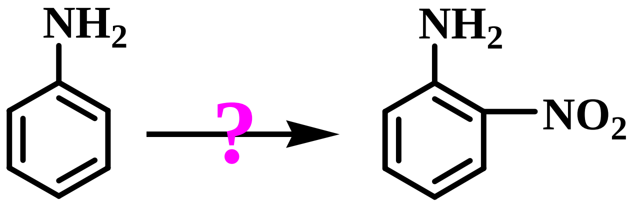
$$\mathrm{R\overset{O}{\overset{\|}{C}}OH \xrightarrow{NaHCO_3} R\overset{O}{\overset{\|}{C}}ONa \xrightarrow{PhCH_2Cl} R\overset{O}{\overset{\|}{C}}OCH_2Ph}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}OCH_2Ph \xrightarrow{H^+/\,H_2O} R\overset{O}{\overset{\|}{C}}OH}$$

Problem 1.

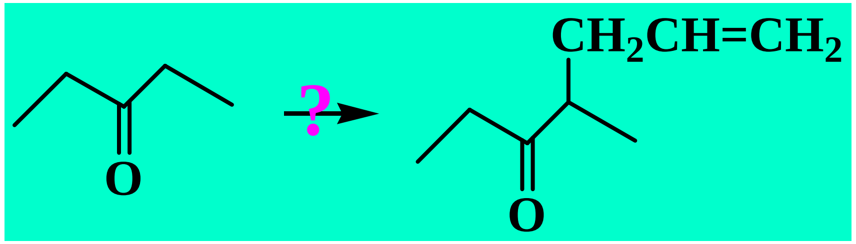


Problem 2.

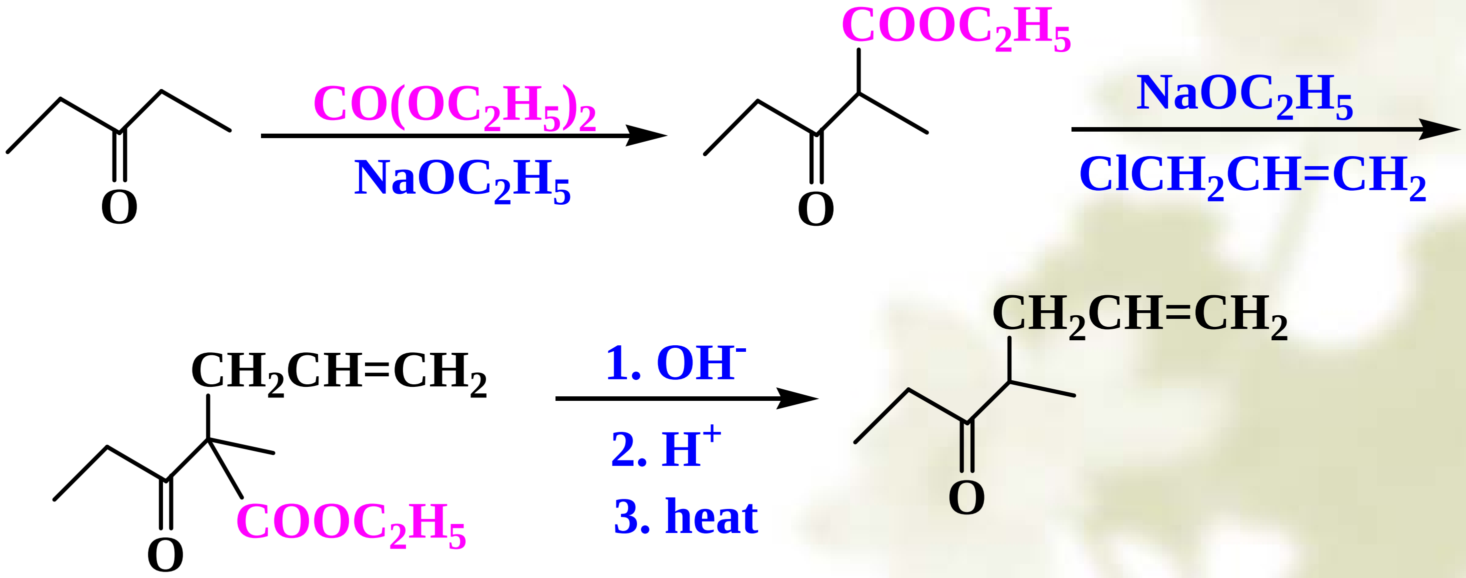


13.9.2.3 ACTIVATION OF THE NECESSARY SITE

Ex 6:

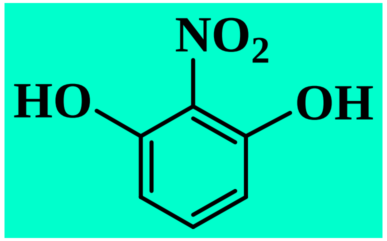


Sample solution:

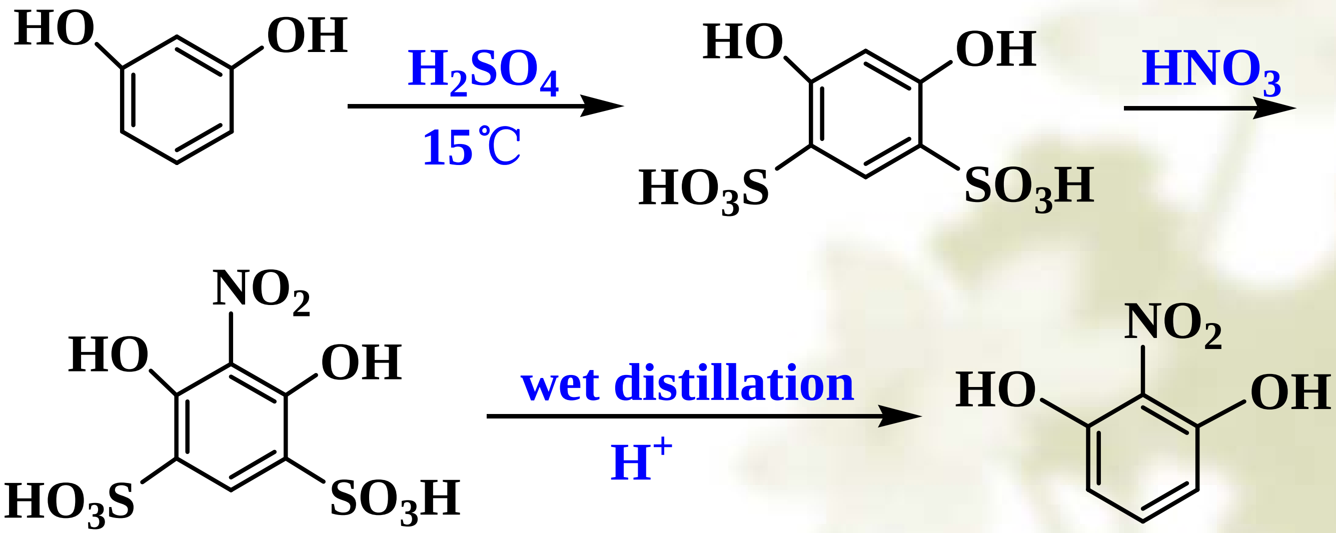


13.9.3.4 INTRODUCING THE ORIENTATING GROUP

Ex 7:



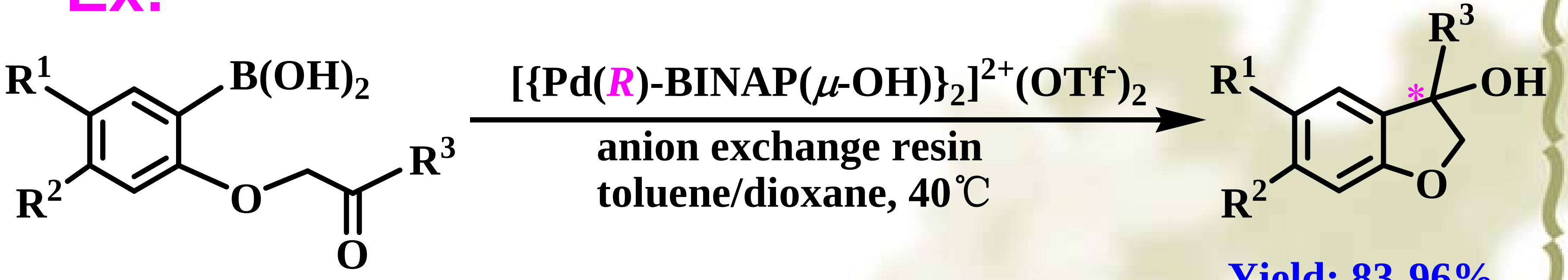
Sample solution:



13.9.3 MATCH WITH THE STERIC CONFIGURATION OF TARGET MOLECULES

The asymmetric factor we usually use in asymmetric synthesis involves asymmetric reactant, reagent; chiral solvent, medium; polarized light and so on.

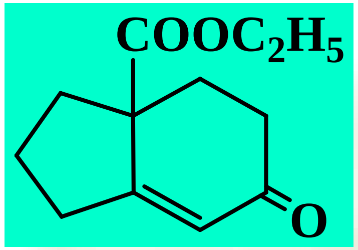
Ex:



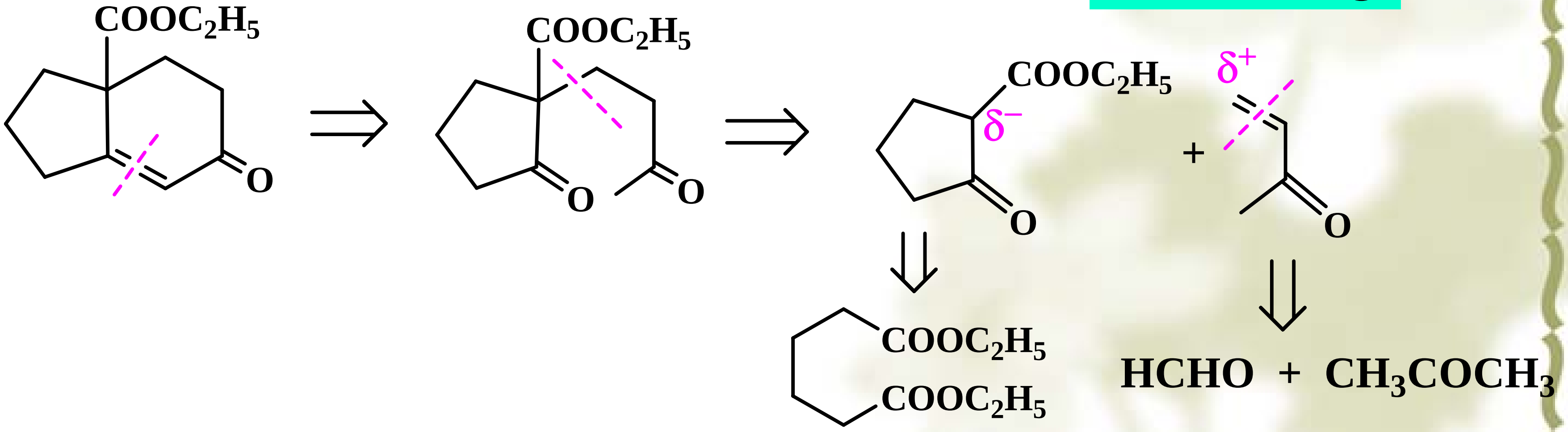
Yield: 83-96%
ee: 84-97%

13.9.4 THE SELECTIVE OF SYNTHETIC ROUTE

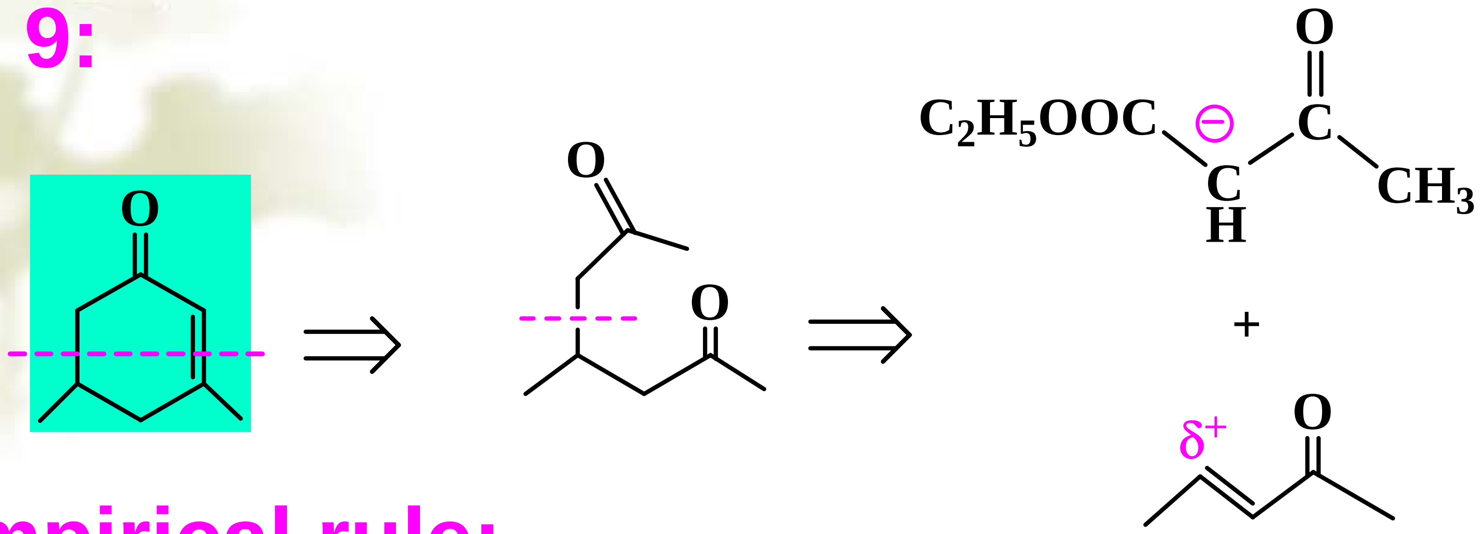
Ex 8: **Prepare the compound by using adipic acid and the organic reagents with less than three carbon atoms.**



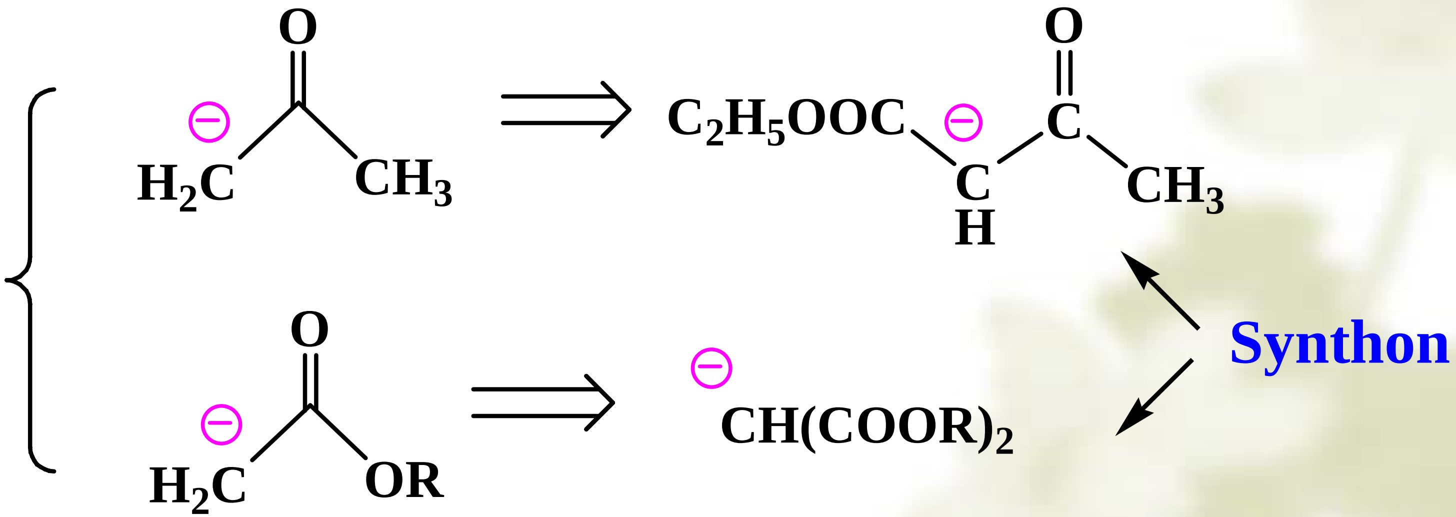
Retrosynthesis:



Ex 9:

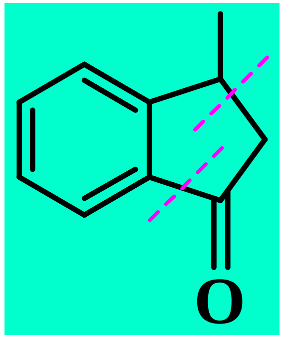


Empirical rule:

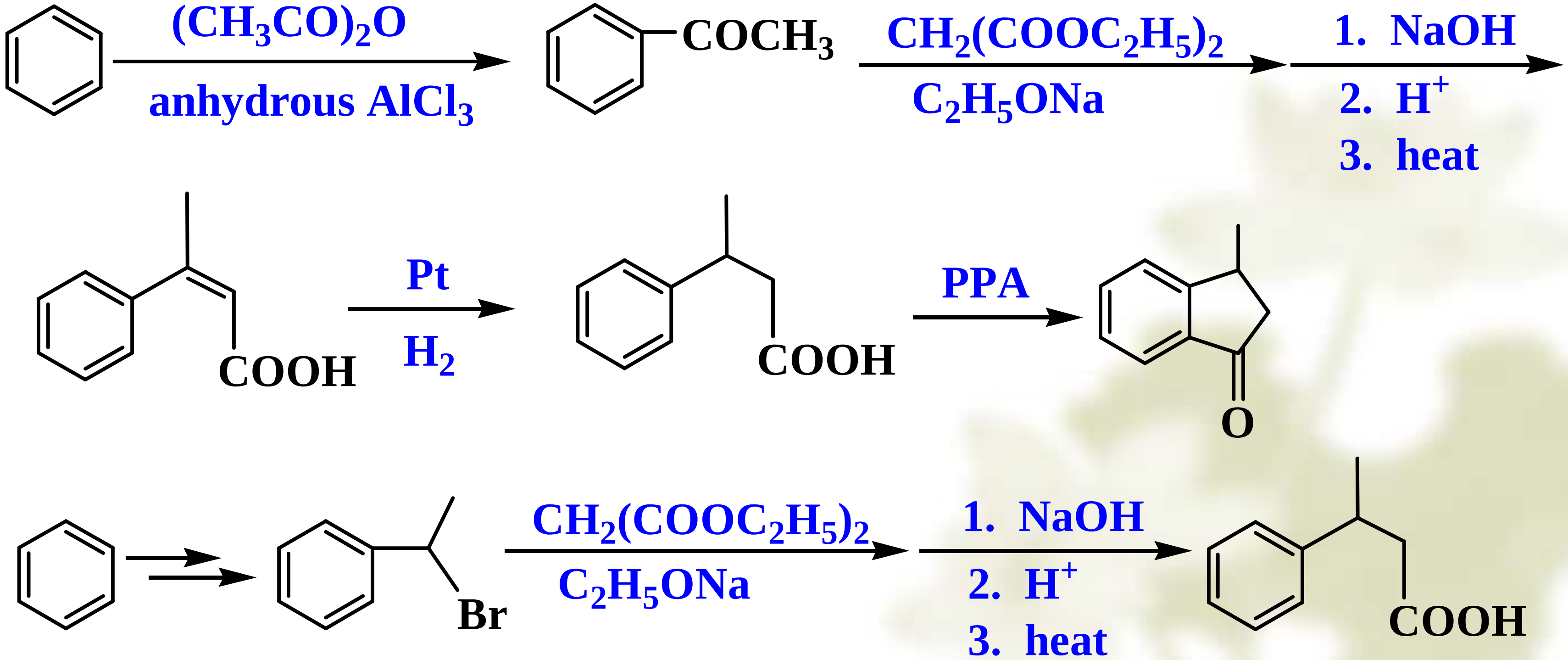


Synthon

Ex 10: Prepare the compound using benzene and other organic reagents.



Sample solution:



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