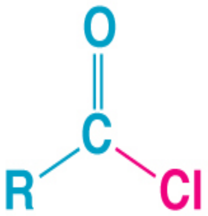
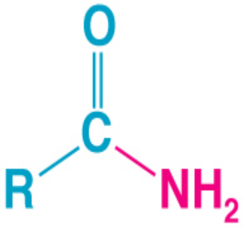
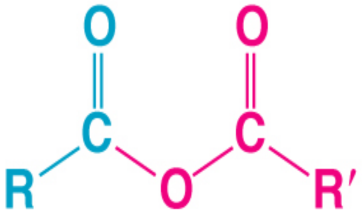
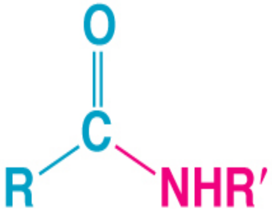
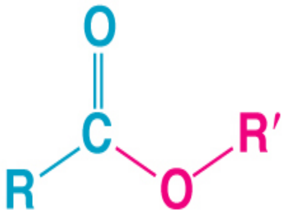
## Chapter 15

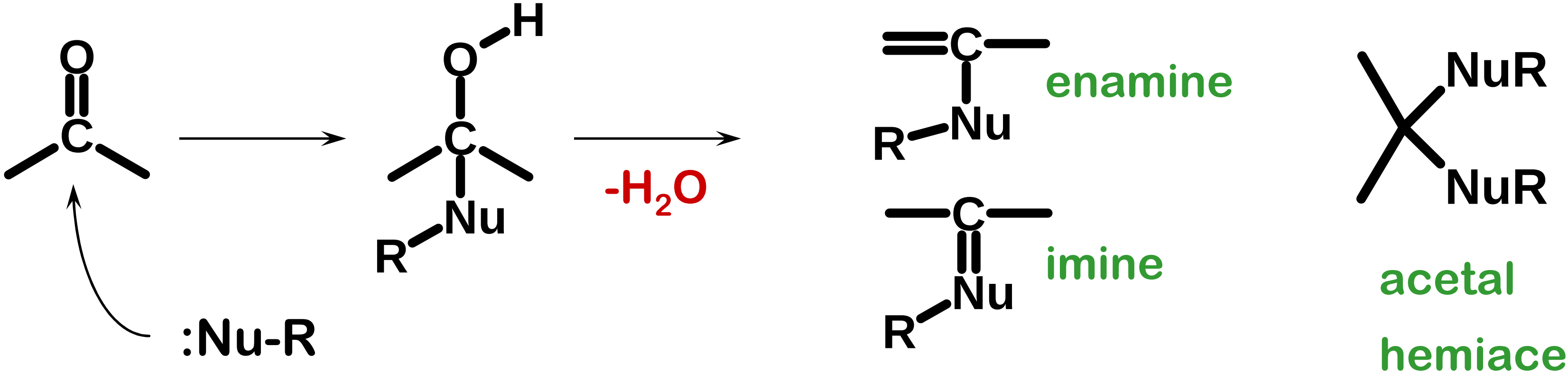
# Derivatives Of Carboxylic Acids

- **Derivative Of Carboxylic Acid is a compound that yields a carboxylic acid upon reaction with water**

| Structure | Name | Structure | Name |
|---|---|---|---|
|  | Acyl (or acid) chloride |  | Amide |
|  | Acid anhydride |  | |
|  | Ester |  | |
| $R-C\equiv N$ | Nitrile | | |

# COMPARISON OF CARBONYL COMPOUNDS

The typical reaction of an **aldehyde or ketone** is addition, or an addition followed by loss of water.



enamine

imine

acetal

hemiacetal

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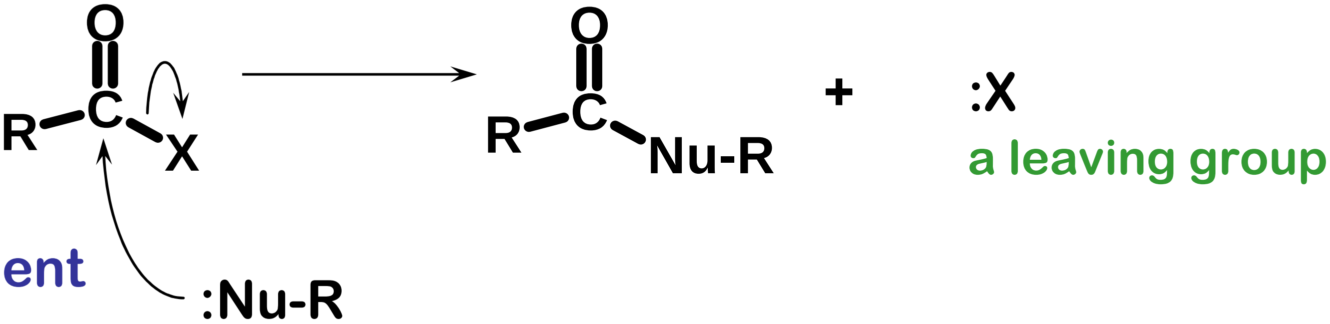
**Acid derivatives** (acyl compounds) undergo substitution reactions.



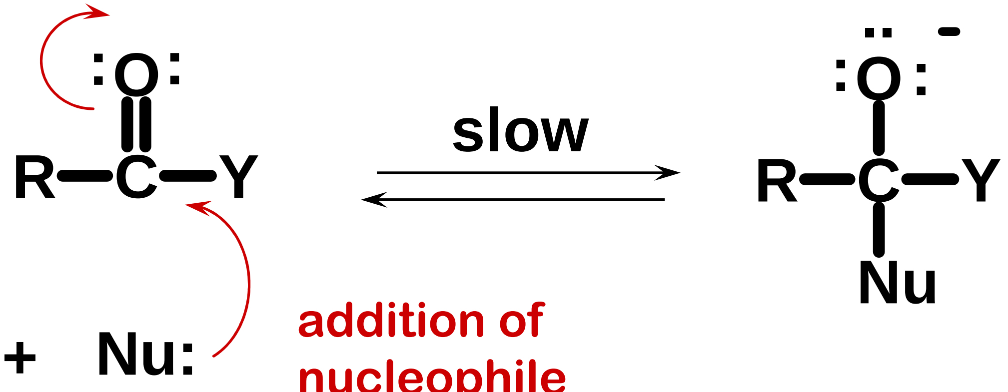
a leaving group

displacement

# Nucleophilic Acyl Substitution

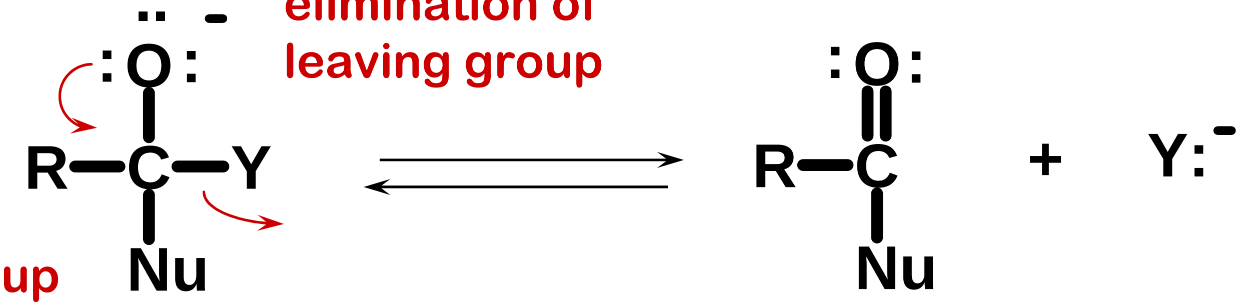
## SIMPLIFIED VIEW

1)



addition of
nucleophile

2)



elimination of
leaving group

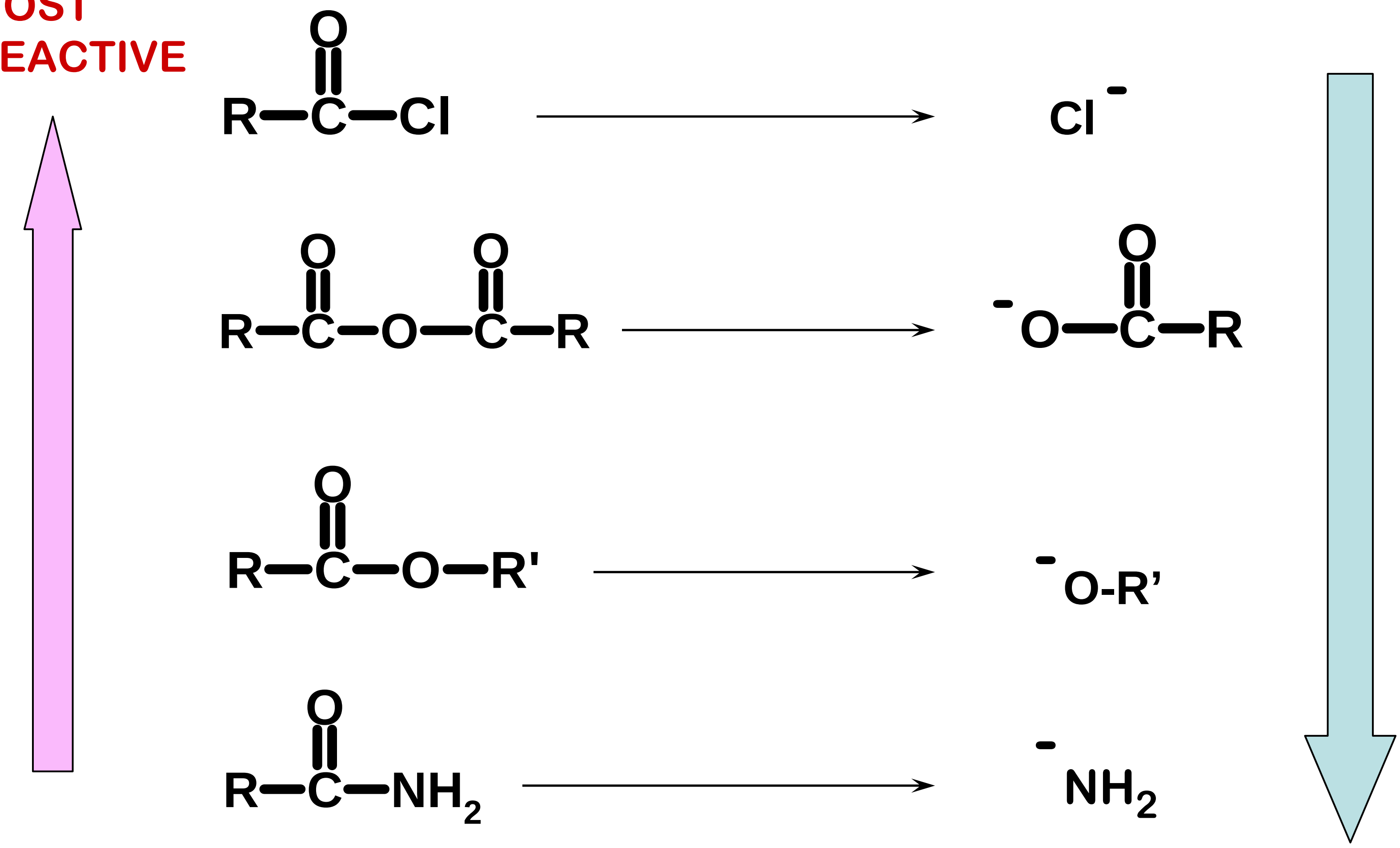
carbonyl group
forms again

most aren't this simple, proton
transfers are usually required

# REACTIVITY IS ALSO REFLECTED IN THE STABILITY OF THE LEAVING GROUP

(not considering acid catalysis)

**MOST REACTIVE**



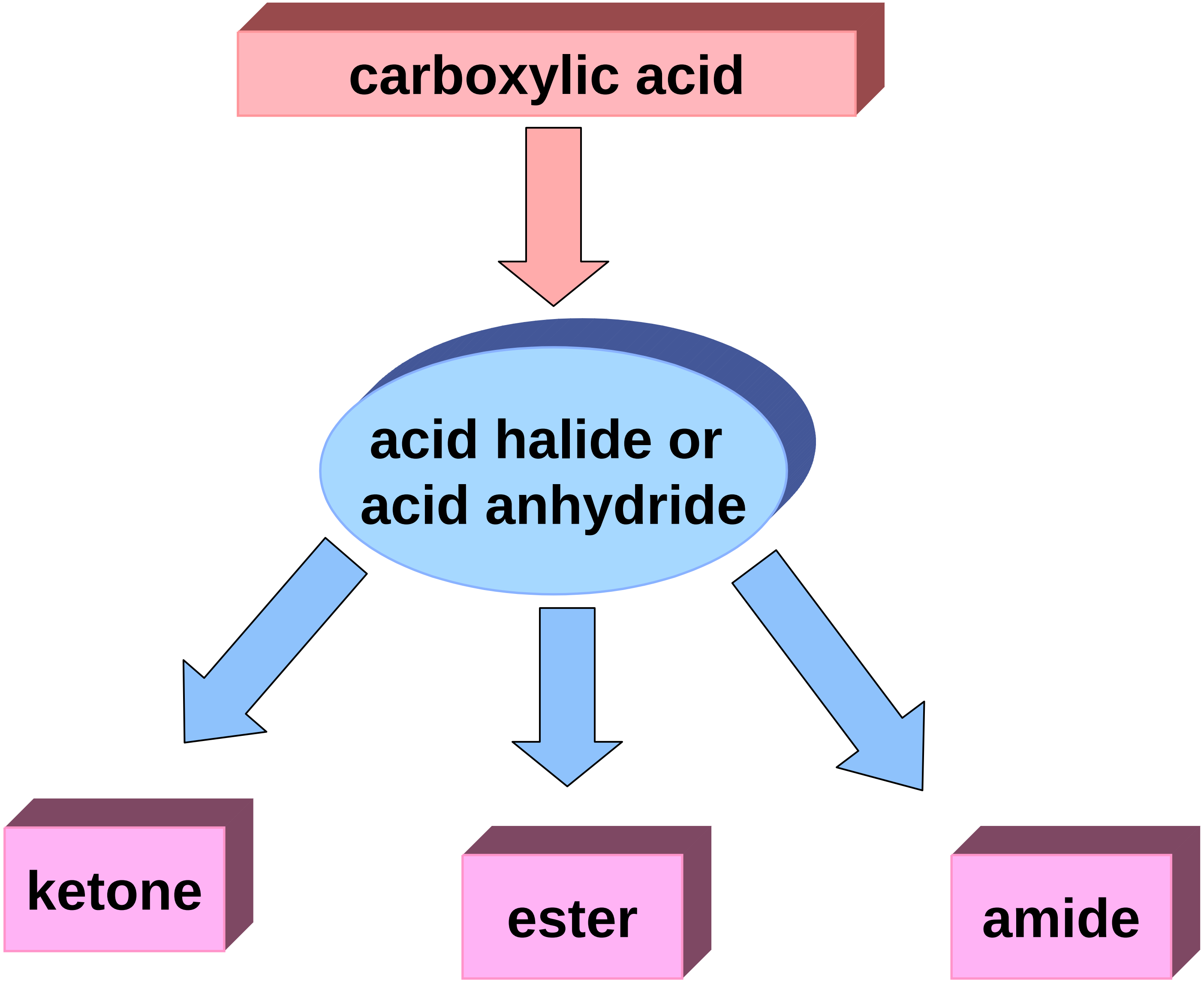
$$R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl \longrightarrow Cl^-$$

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{\overset{\displaystyle O}{\|}}{C}-R \longrightarrow {}^-O-\overset{\overset{\displaystyle O}{\|}}{C}-R$$

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-R' \longrightarrow {}^-O\text{-}R'$$

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \longrightarrow {}^-NH_2$$

**STRONGEST BASE**



carboxylic acid

acid halide or
acid anhydride

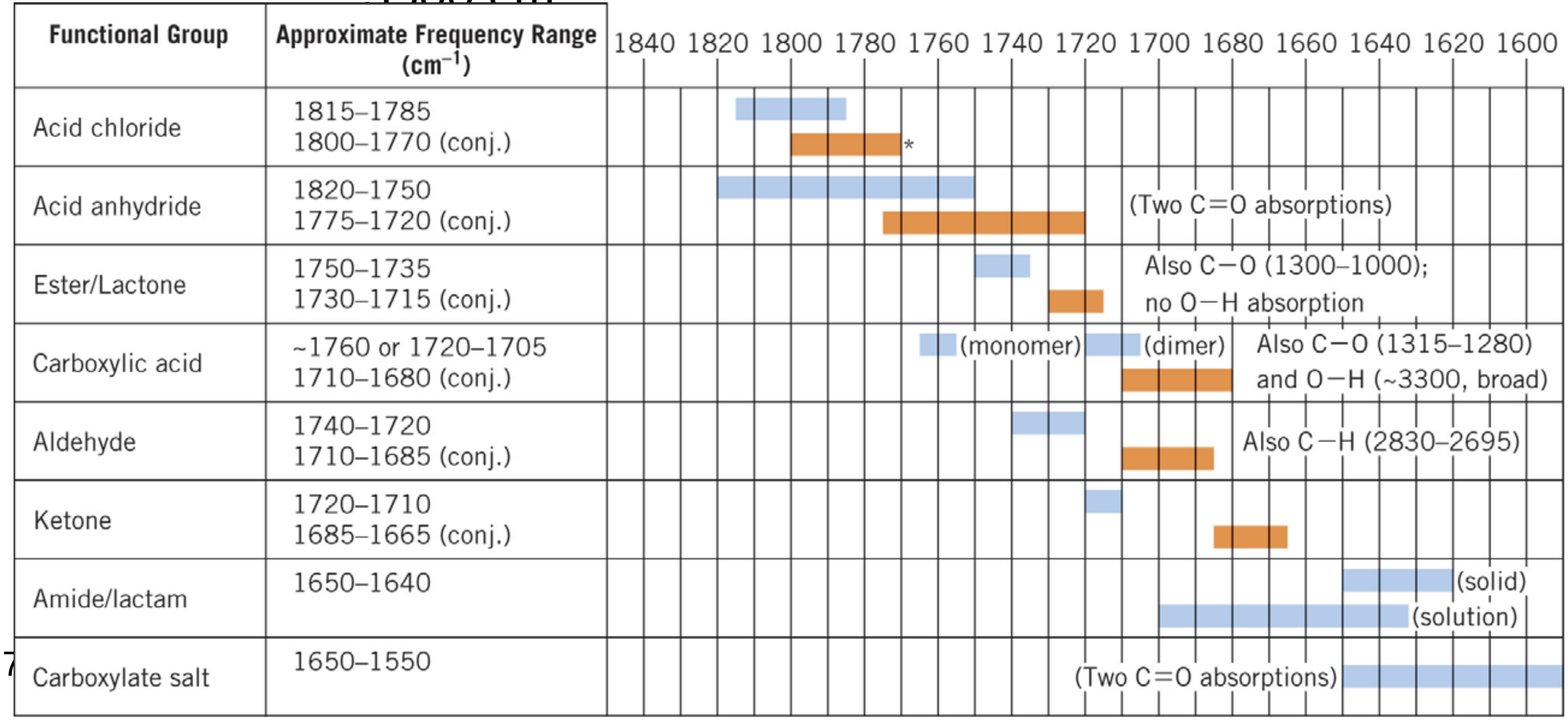
ketone

ester

amide

# Spectroscopic Properties of Acid derivatives

- IR Spectra
  - The carbonyl stretching frequency varies according to the type of carboxylic acid derivative present
  - O-H stretching vibrations of the carboxylic acid give a broad band at 2500-3100 cm$^{-1}$
  - N-H stretching vibrations of amides appear at 3140-3500 cm$^{-1}$

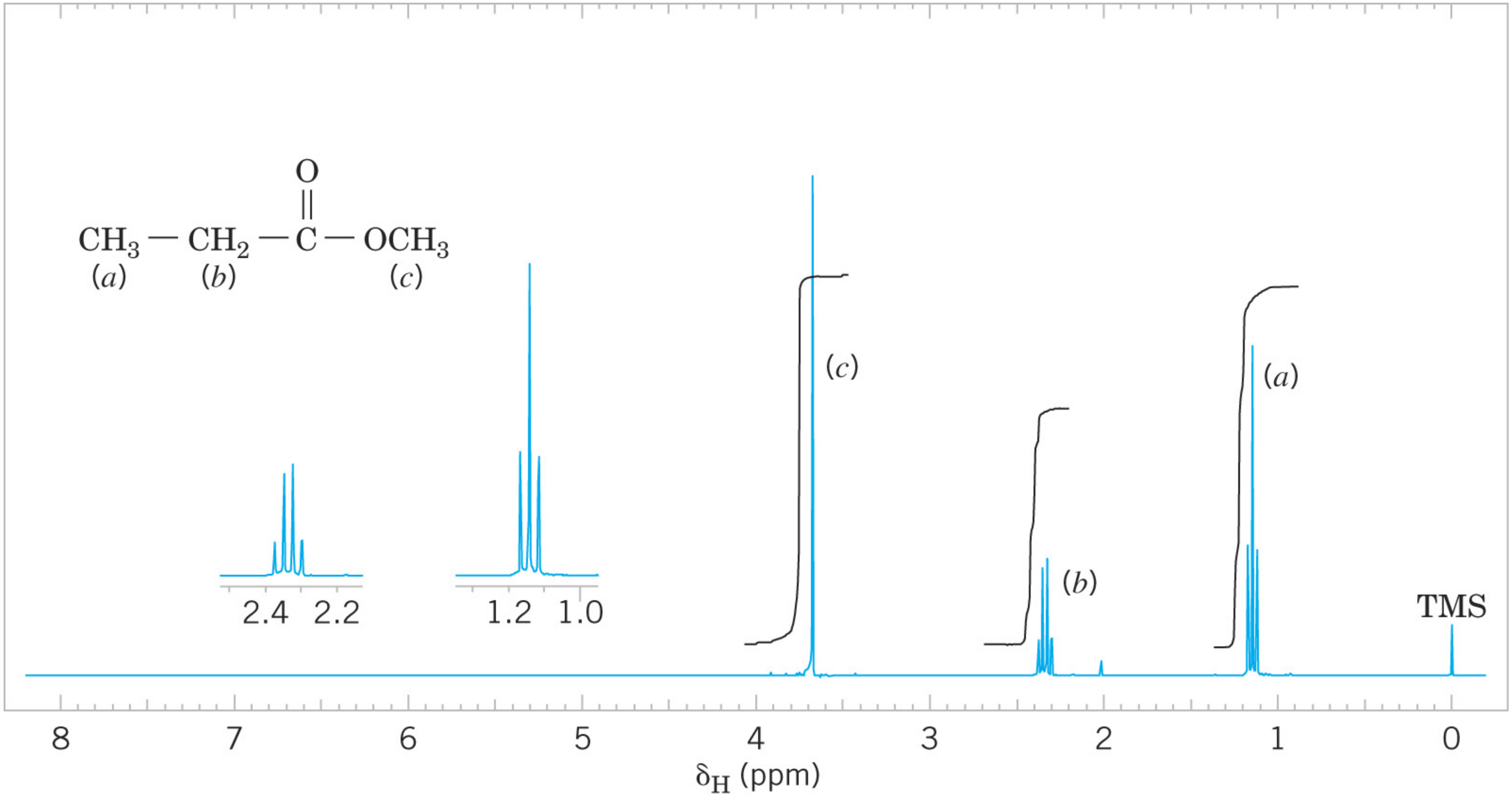


| Functional Group | Approximate Frequency Range (cm$^{-1}$) | |
|---|---|---|
| Acid chloride | 1815–1785<br>1800–1770 (conj.) | |
| Acid anhydride | 1820–1750<br>1775–1720 (conj.) | (Two C=O absorptions) |
| Ester/Lactone | 1750–1735<br>1730–1715 (conj.) | Also C—O (1300–1000); no O—H absorption |
| Carboxylic acid | ~1760 or 1720–1705<br>1710–1680 (conj.) | (monomer) (dimer) Also C—O (1315–1280) and O—H (~3300, broad) |
| Aldehyde | 1740–1720<br>1710–1685 (conj.) | Also C—H (2830–2695) |
| Ketone | 1720–1710<br>1685–1665 (conj.) | |
| Amide/lactam | 1650–1640 | (solid)<br>(solution) |
| Carboxylate salt | 1650–1550 | (Two C=O absorptions) |

*Orange bars represent absorption ranges for conjugated species.

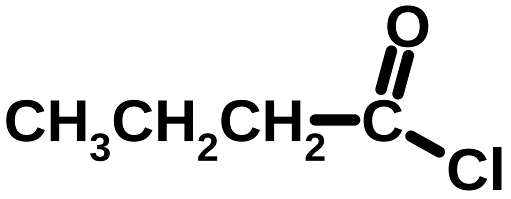
# 1H NMR Spectra

- The α hydrogens of carboxylic acids and their derivatives appear at δ 2.0-2.5
- The carboxyl group proton appears downfield at δ 10-12



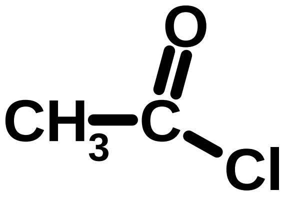
# Nomenclature Of Acid Chloride

- Acid chlorides are named by dropping the *-ic acid* from the name of the carboxylic acid and adding *-yl chloride*



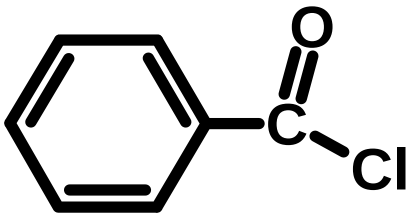
**butanoyl chloride**

**butyryl chloride**



**ethanoyl chloride**

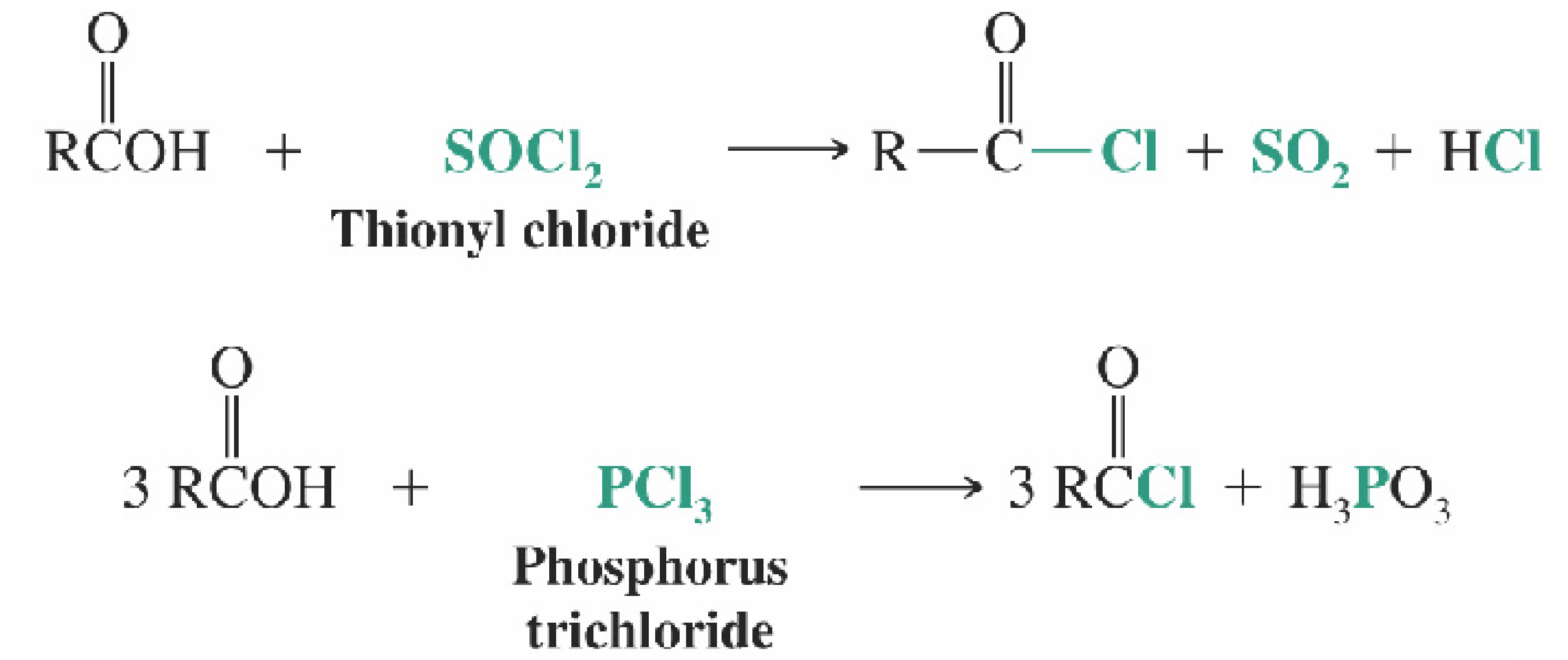
**acetyl chloride**



**benzoyl chloride**

# PREPARATION OF ACID CHLORIDES

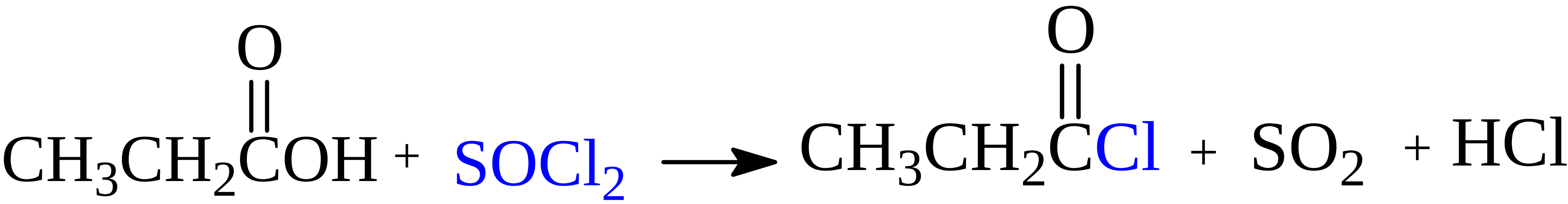
- Acid chlorides are made from carboxylic acids by reaction with thionyl chloride, or phosphorus trichloride.



$$\mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}OH} + \mathrm{SOCl_2} \longrightarrow \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Cl} + \mathrm{SO_2} + \mathrm{HCl}$$

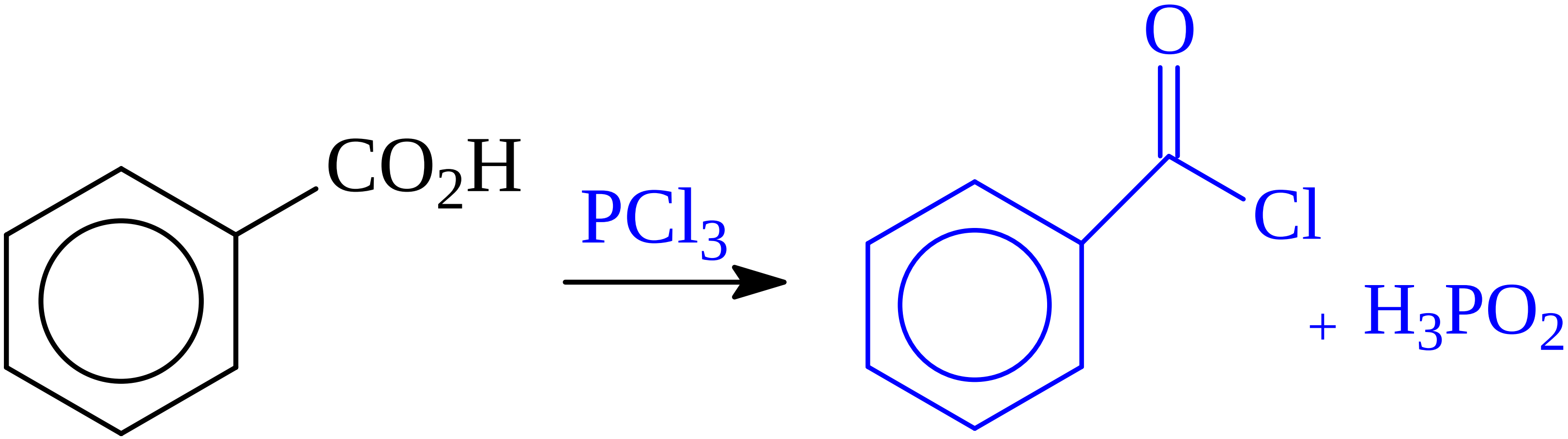
$$3\,\mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}OH} + \mathrm{PCl_3} \longrightarrow 3\,\mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}Cl} + \mathrm{H_3PO_3}$$

# Examples



$$CH_3CH_2\overset{\overset{O}{\|}}{C}OH + SOCl_2 \longrightarrow CH_3CH_2\overset{\overset{O}{\|}}{C}Cl + SO_2 + HCl$$

Propanoyl chloride

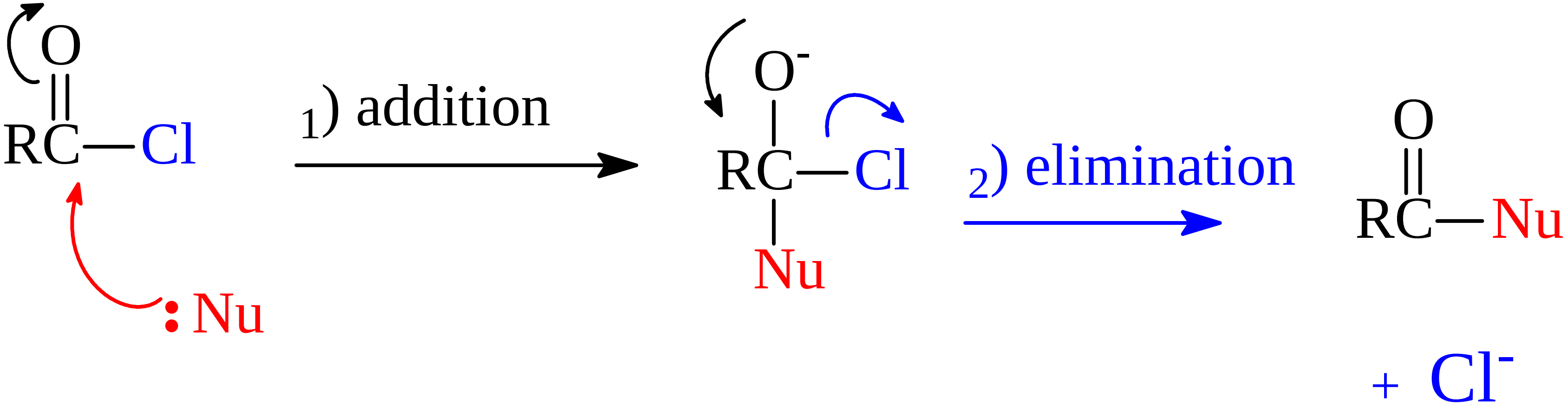


Benzoyl chloride

# REACTIONS OF ACID CHLORIDES

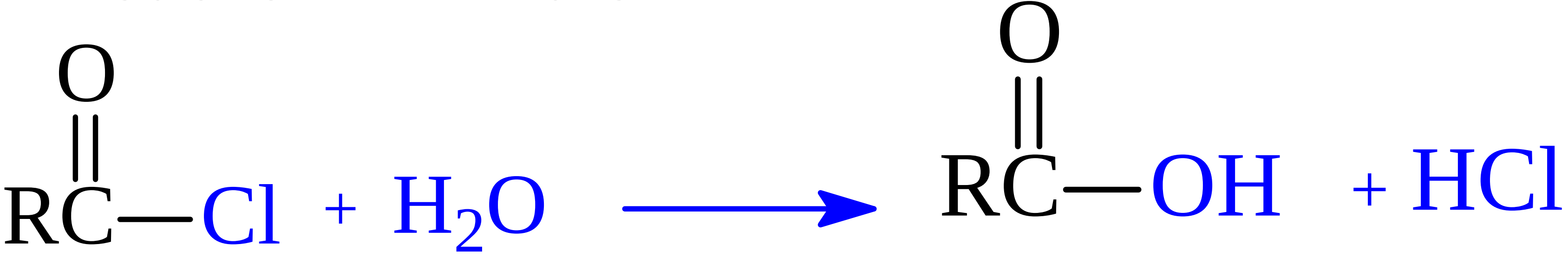
# Nucleophilic Acyl Substitution

Simplified Mechanism



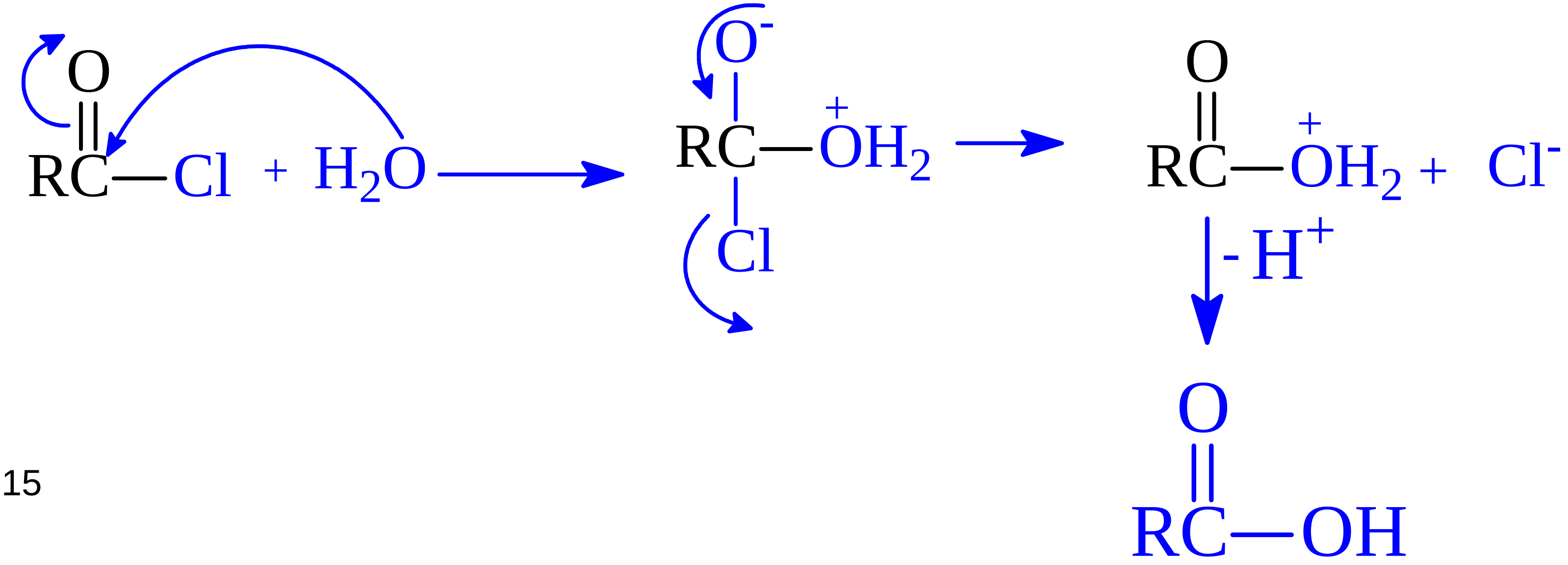
# 1) Hydrolysis

- Reaction with water



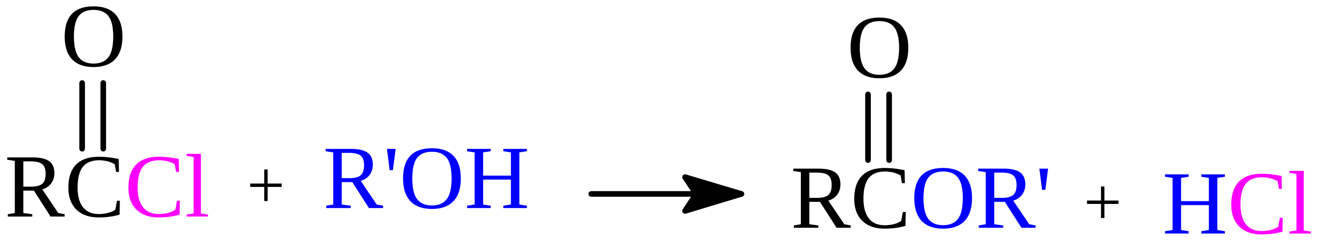
$$RCOCl + H_2O \longrightarrow RCOOH + HCl$$

Mechanism



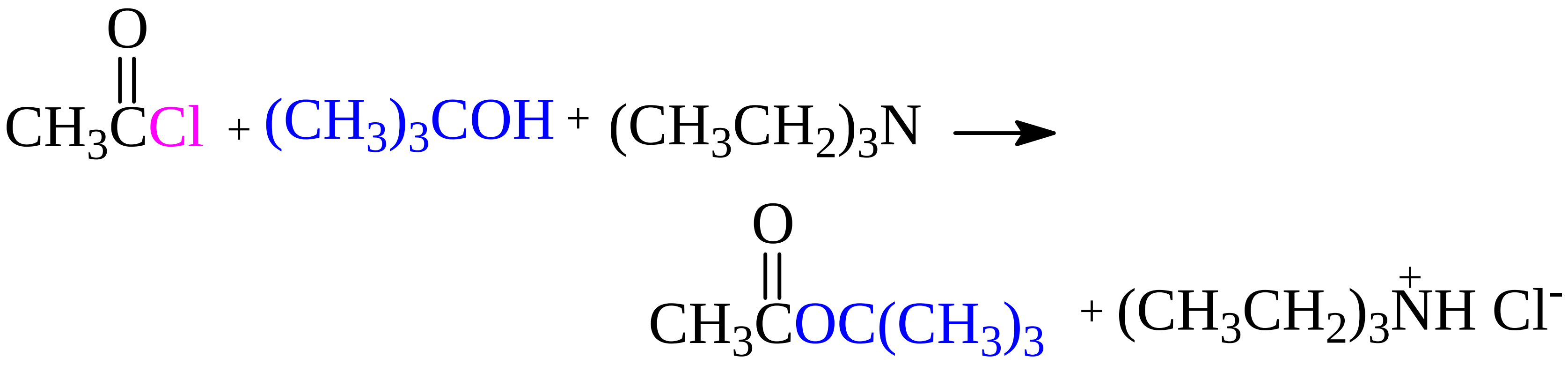
# 2- Reaction With Alcohols

General reaction➔ ESTER



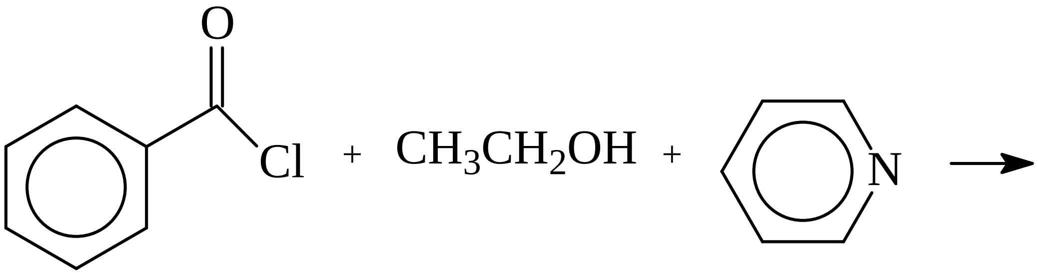
$$R\overset{\overset{O}{\|}}{C}Cl + R'OH \longrightarrow R\overset{\overset{O}{\|}}{C}OR' + HCl$$

**Usually HCl is removed using tertiary amine**

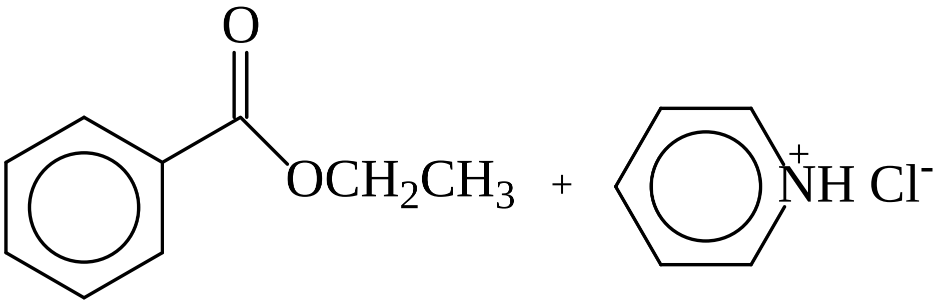


$$CH_3\overset{\overset{O}{\|}}{C}Cl + (CH_3)_3COH + (CH_3CH_2)_3N \longrightarrow CH_3\overset{\overset{O}{\|}}{C}OC(CH_3)_3 + (CH_3CH_2)_3\overset{+}{N}H\ Cl^-$$

# MORE EXAMPLES

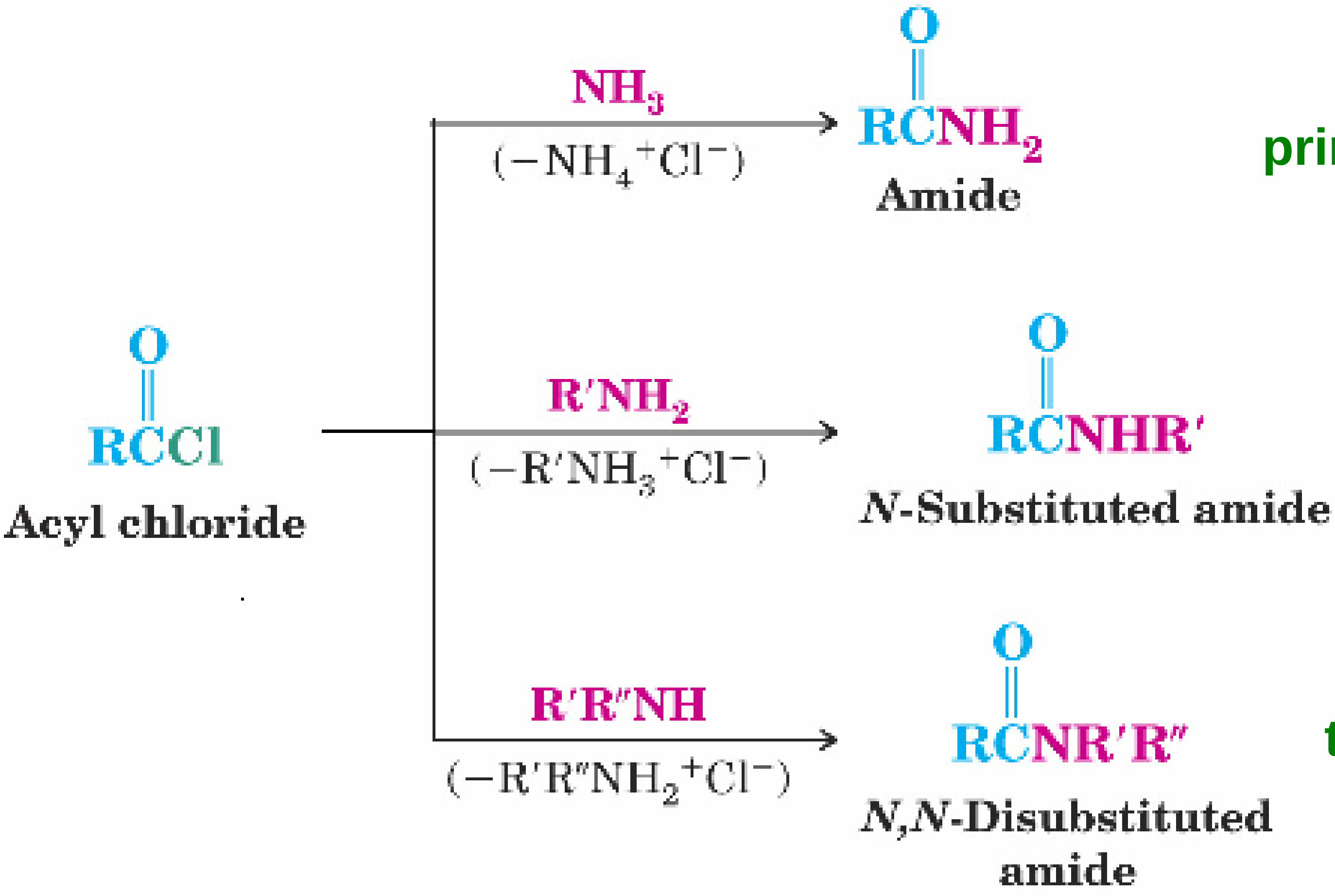


pyridine



**Ethyl benzoate**

# 3- Reaction with ammonia and amines

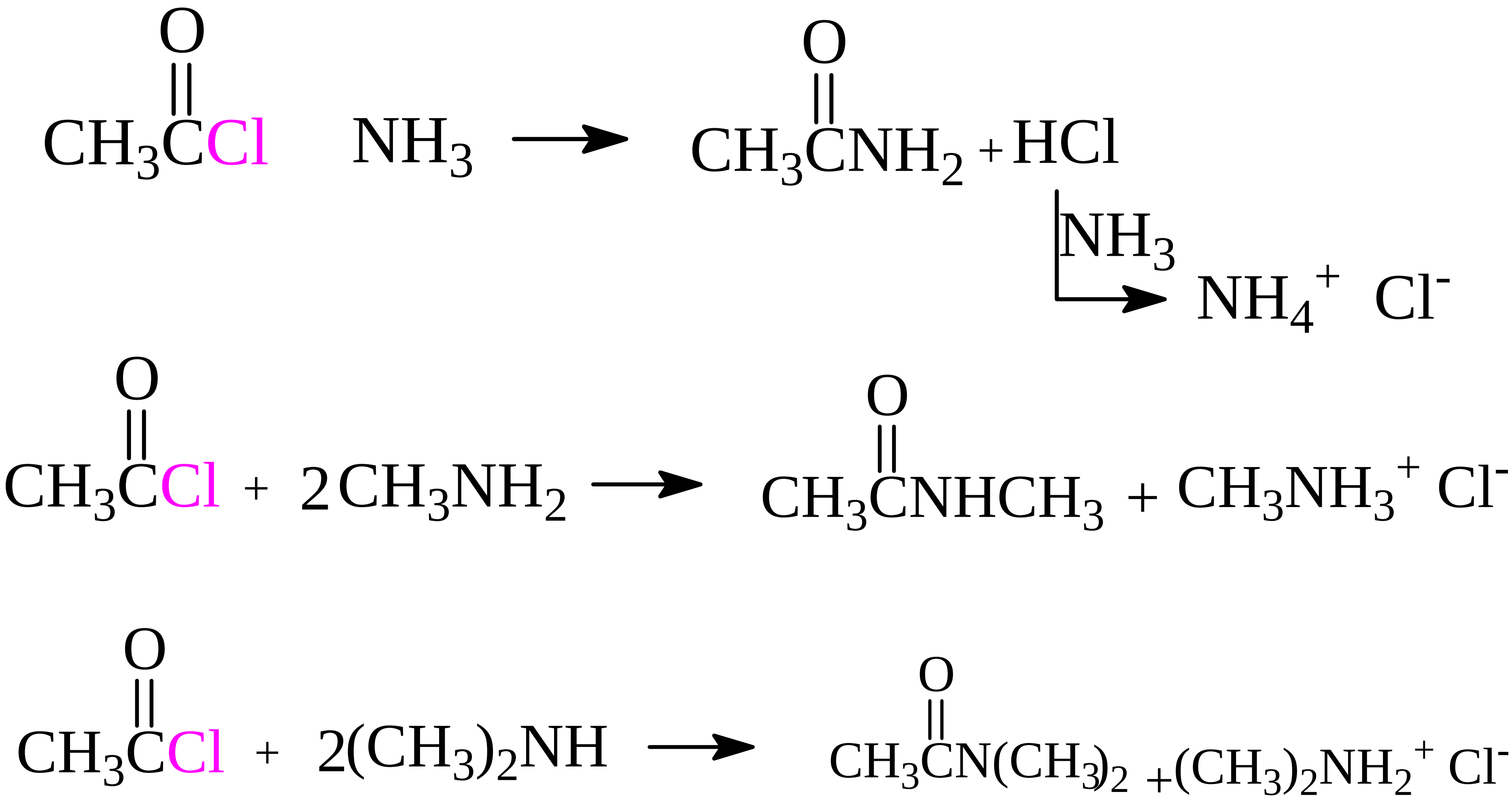


primary

secondary

tertiary

# Examples



$$CH_3\overset{\overset{O}{\|}}{C}Cl \quad NH_3 \longrightarrow CH_3\overset{\overset{O}{\|}}{C}NH_2 + HCl$$

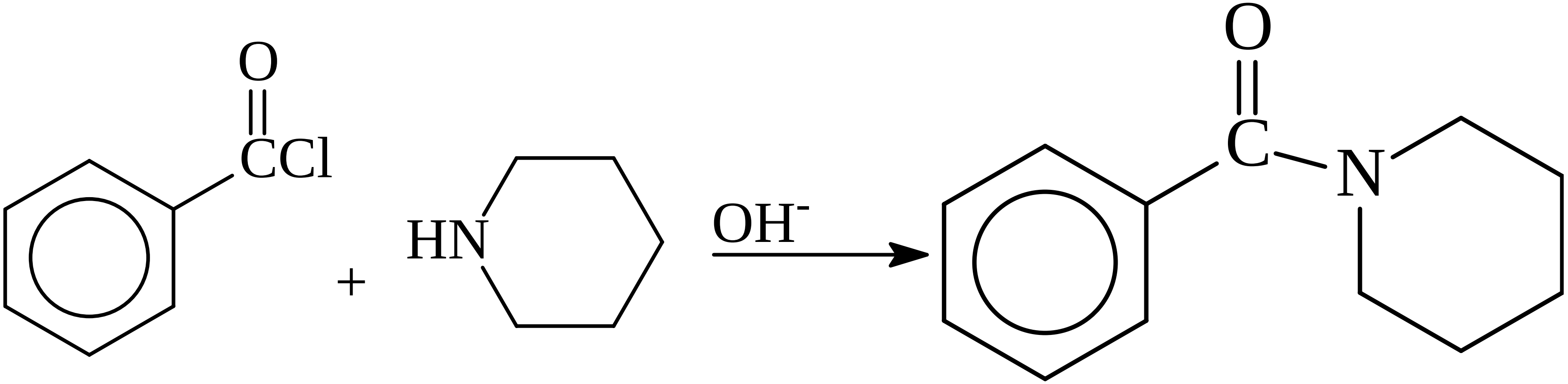
$$HCl \xrightarrow{NH_3} NH_4^+ \ Cl^-$$

$$CH_3\overset{\overset{O}{\|}}{C}Cl + 2CH_3NH_2 \longrightarrow CH_3\overset{\overset{O}{\|}}{C}NHCH_3 + CH_3NH_3^+ \ Cl^-$$

$$CH_3\overset{\overset{O}{\|}}{C}Cl + 2(CH_3)_2NH \longrightarrow CH_3\overset{\overset{O}{\|}}{C}N(CH_3)_2 + (CH_3)_2NH_2^+ \ Cl^-$$

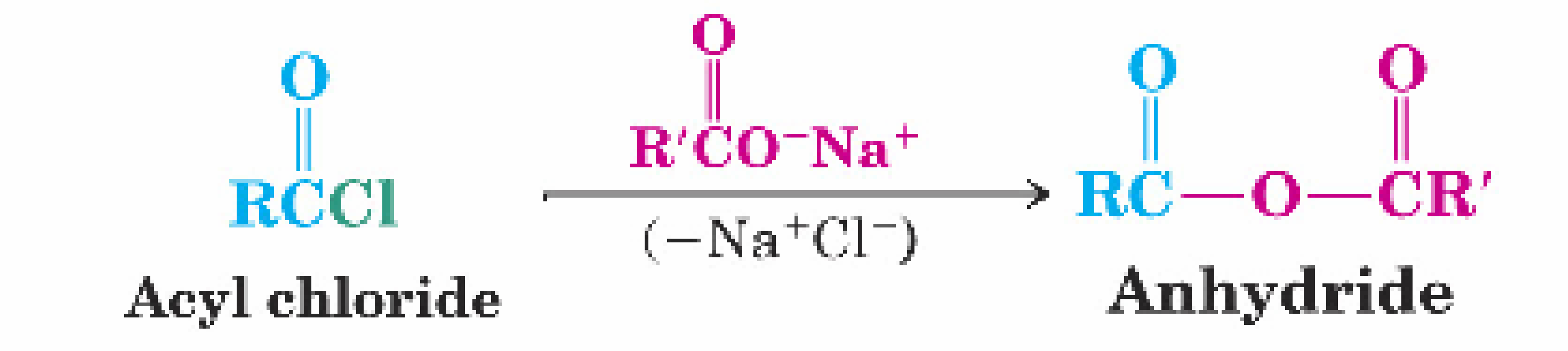
# Schotten-Baumann Reaction

- NaOH is added to remove HCl if the acid chloride is not very reactive



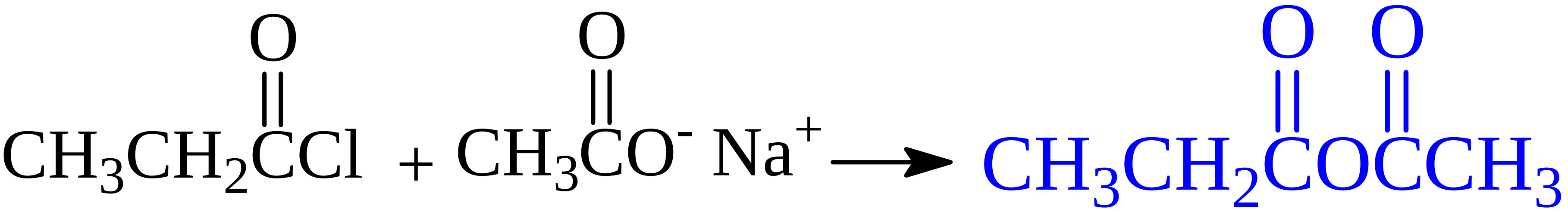
# 4- CONVERSION TO ANHYDRIDE

**Reaction with carboxylate ion**



$$R\overset{O}{\overset{\|}{C}}Cl \xrightarrow[(-Na^+Cl^-)]{R'\overset{O}{\overset{\|}{C}}O^-Na^+} R\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}R'$$

**Acyl chloride** **Anhydride**

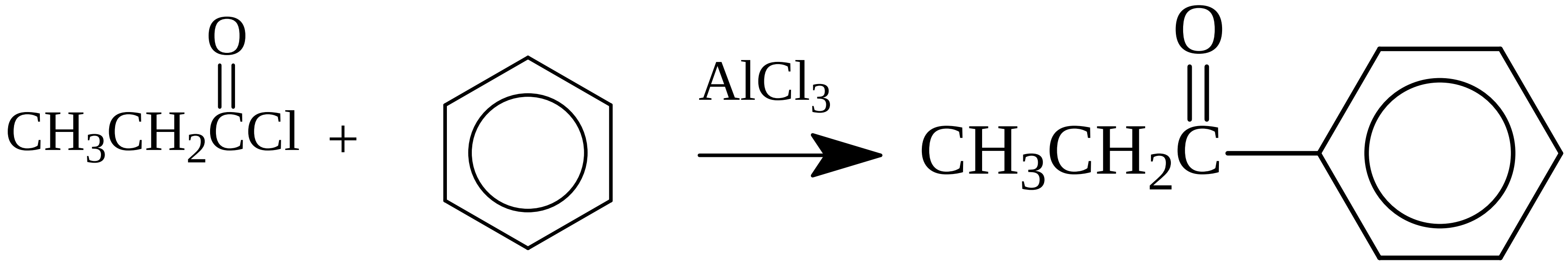


$$CH_3CH_2\overset{O}{\overset{\|}{C}}Cl + CH_3\overset{O}{\overset{\|}{C}}O^- Na^+ \longrightarrow CH_3CH_2\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3$$

**ethanoic propanoic anhydride**

# 5- Conversion to Aryl Ketone

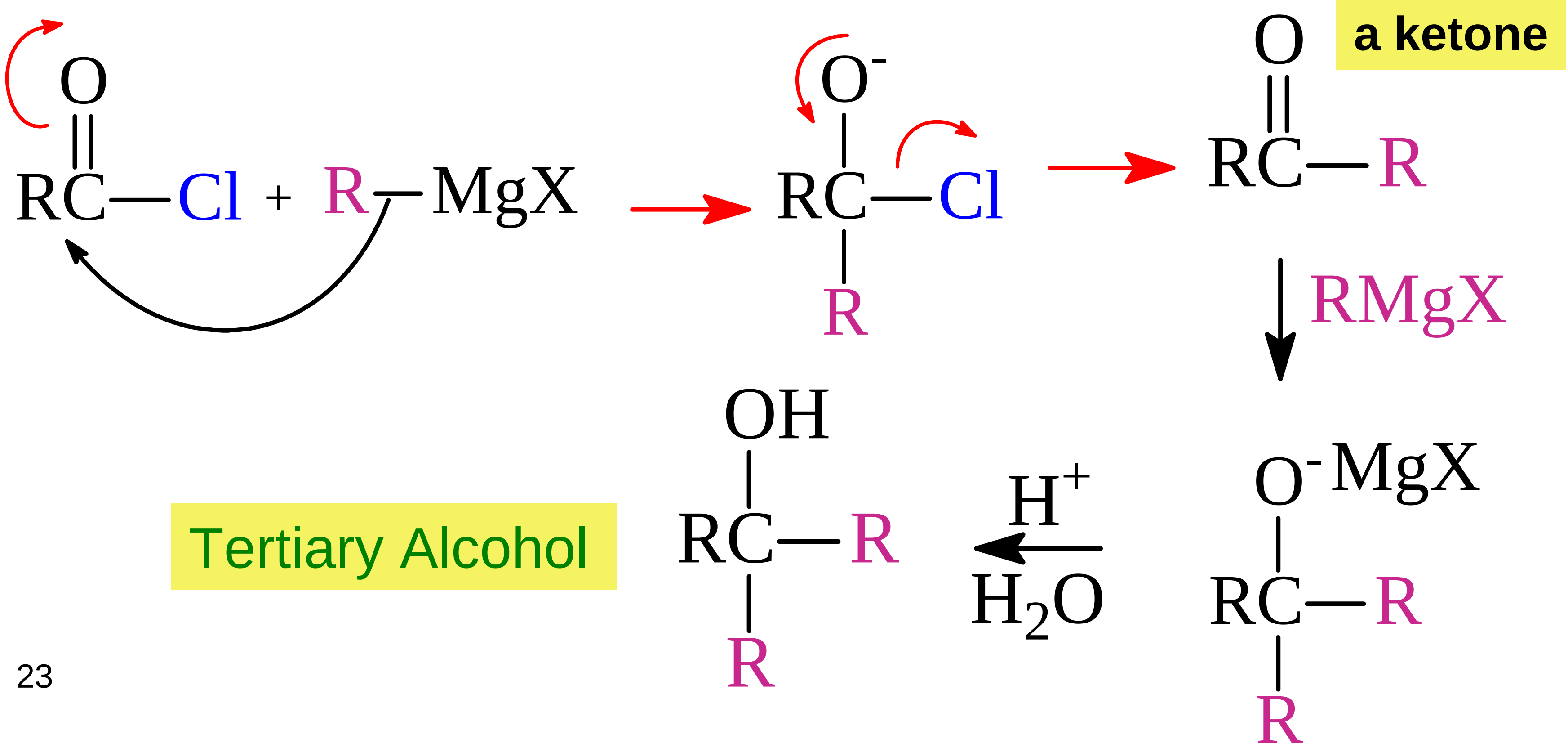
Friedel-Crafts acylation



**1-phenyl-1-propanone**

# 6- Reaction with Grignard Reagents

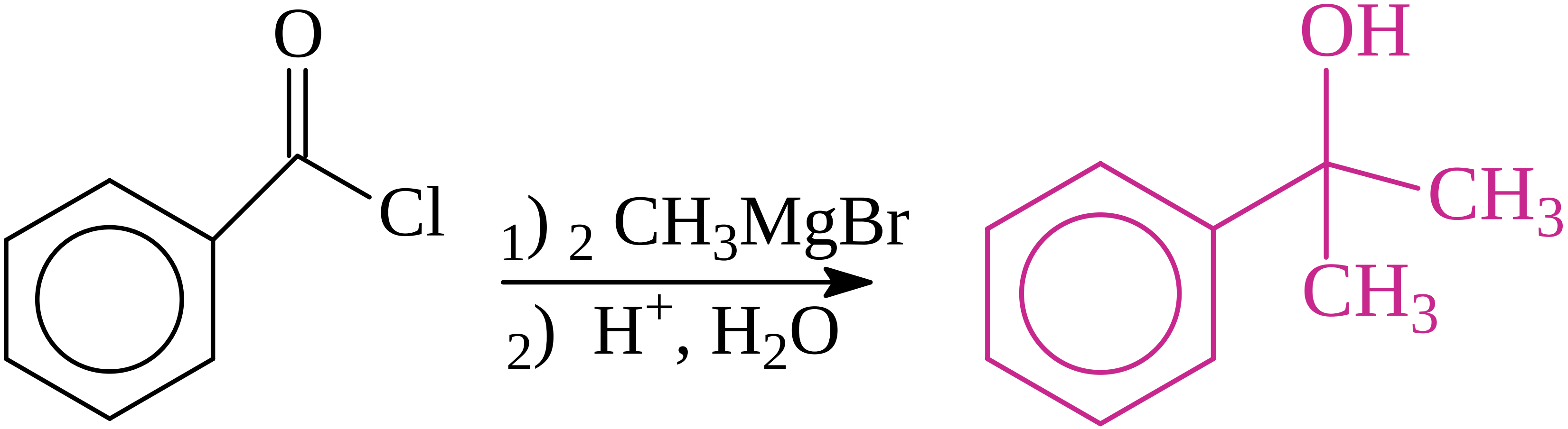
Acid chloride react with two moles of a Grignard reagent to yield a tertiary alcohol



a ketone

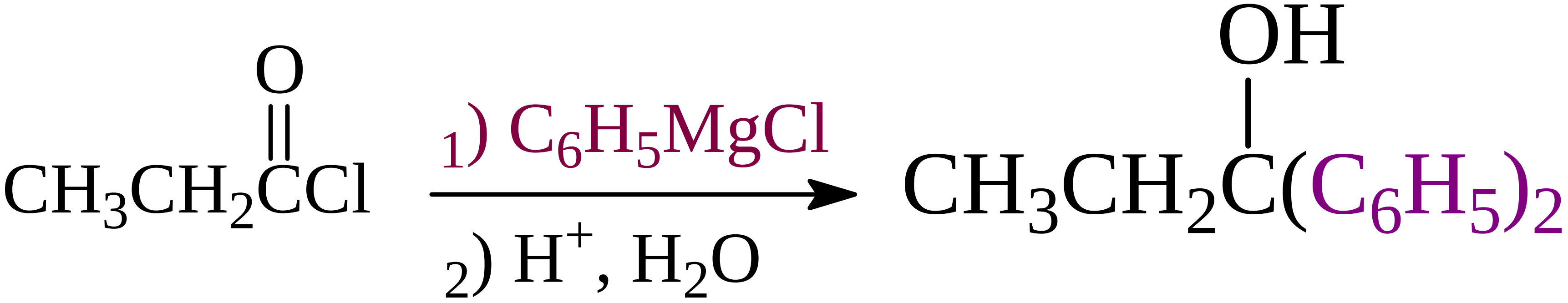
Tertiary Alcohol

# Examples



1) 2 $CH_3MgBr$

2) $H^+$, $H_2O$



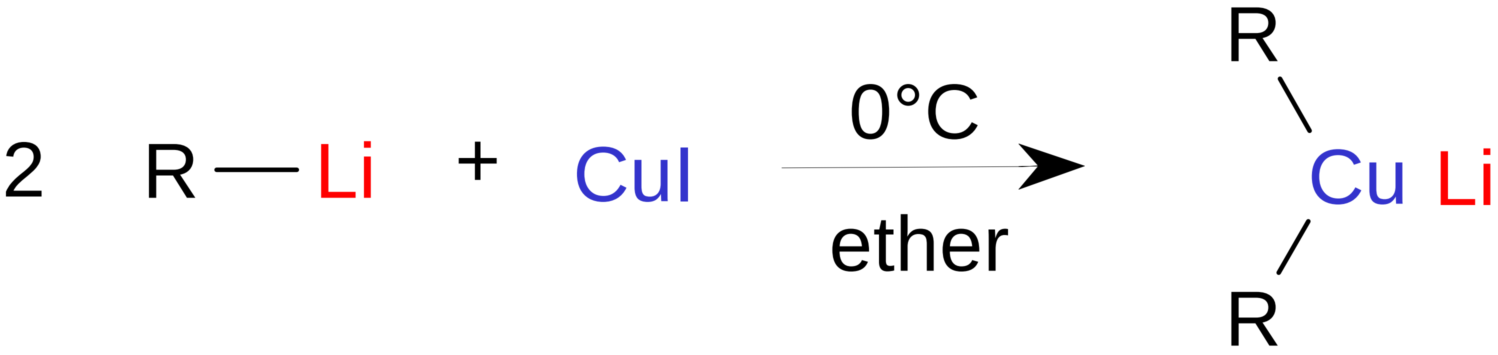
$$\mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}Cl} \xrightarrow[\text{2) H}^+\text{, H}_2\text{O}]{\text{1) C}_6\text{H}_5\text{MgCl}} \mathrm{CH_3CH_2\overset{\overset{OH}{|}}{C}(C_6H_5)_2}$$

# LITHIUM DIALKYLCUPRATES

**$R_2CuLi$**

**Made by treating an alkyllithium compound with copper (I) iodide.**

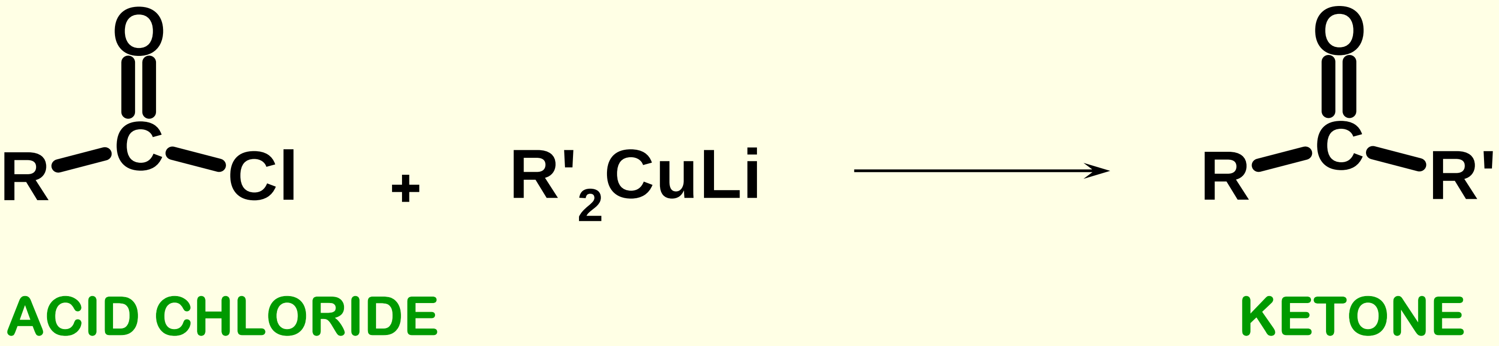
$$R{-}X \xrightarrow{Li} R{-}Li$$



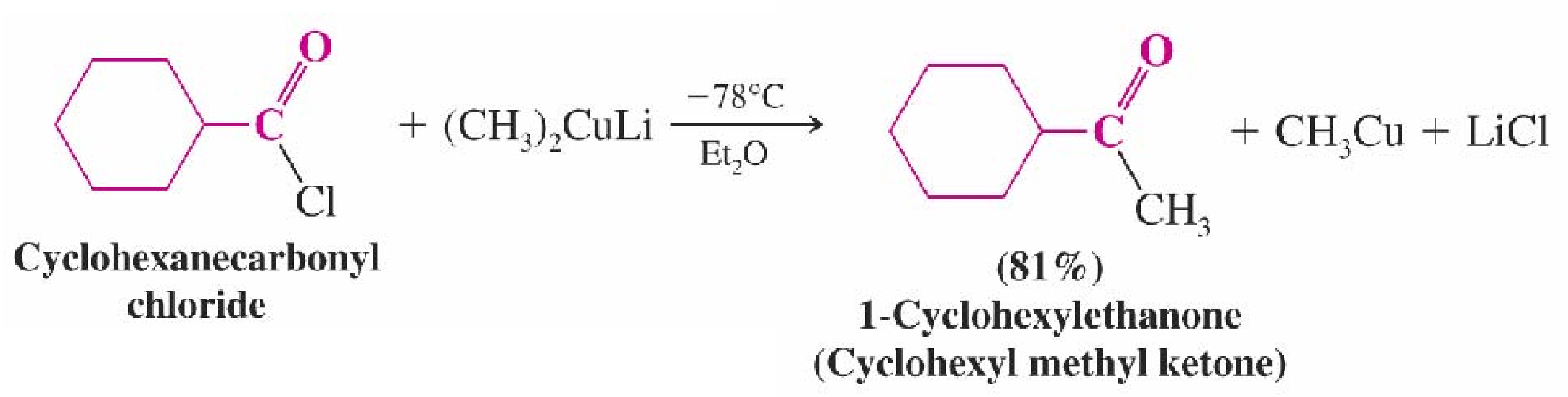
$$2\ R{-}Li + CuI \xrightarrow[\text{ether}]{0°C} R_2CuLi$$

# 7- Reaction with Cuprates

- An acid chloride can be coupled with a dialkylcuprate to yield a ketone

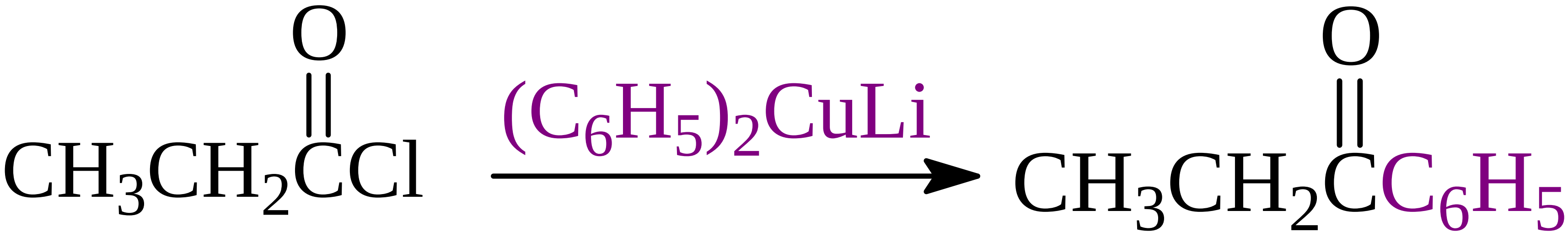


# Examples



**Cyclohexanecarbonyl chloride**

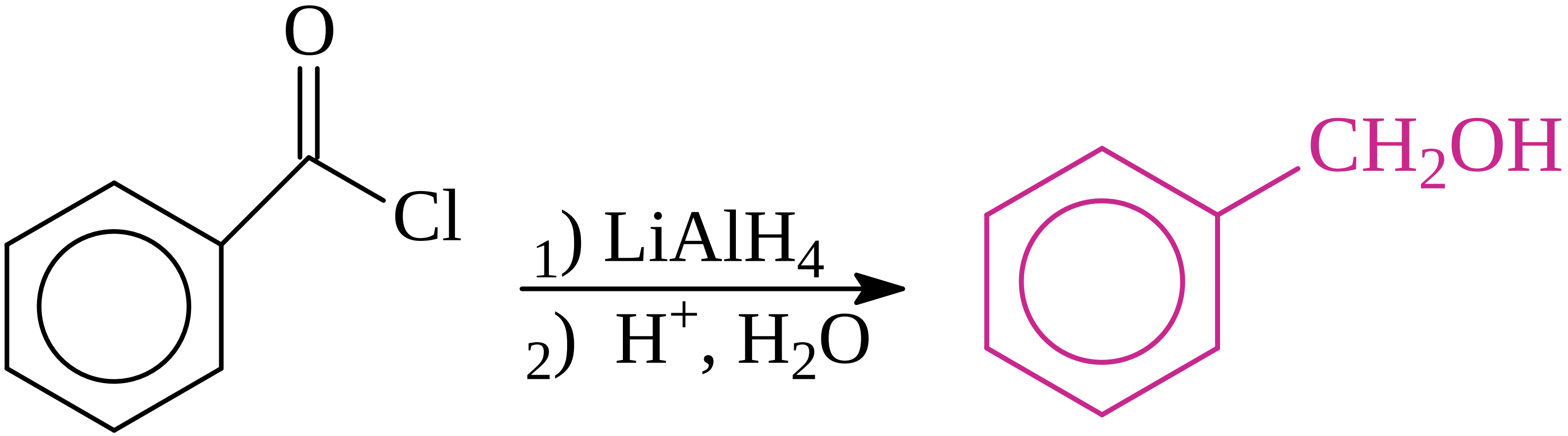
**(81%)**
**1-Cyclohexylethanone**
**(Cyclohexyl methyl ketone)**



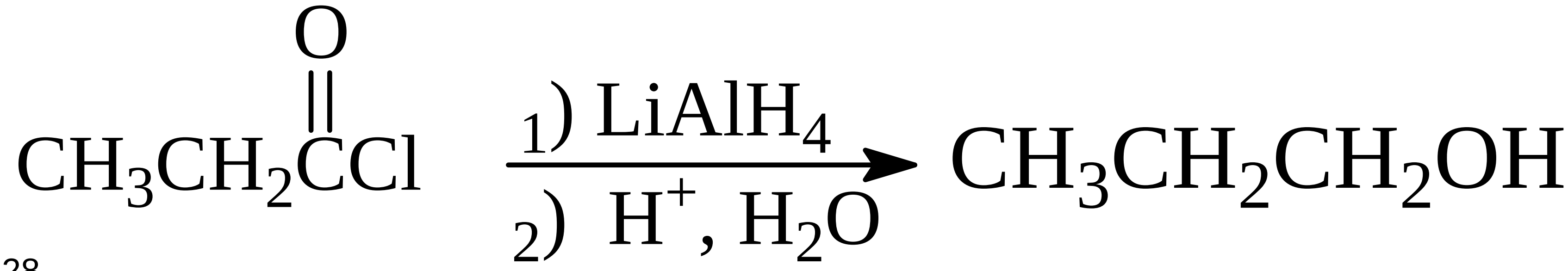
$$\mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}Cl} \xrightarrow{\mathrm{(C_6H_5)_2CuLi}} \mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}C_6H_5}$$

# 8a- Reduction with $LiAlH_4$

1) Acid chloride + $LiAlH_4$ ➔ primary alcohol



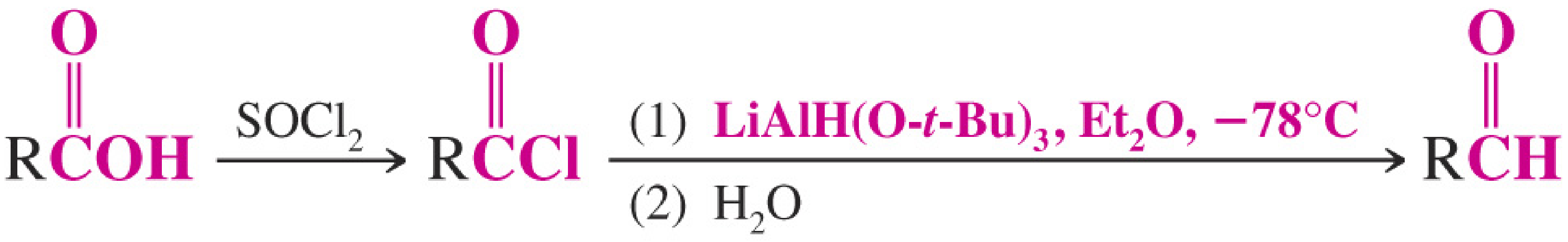
**Primary alcohol**



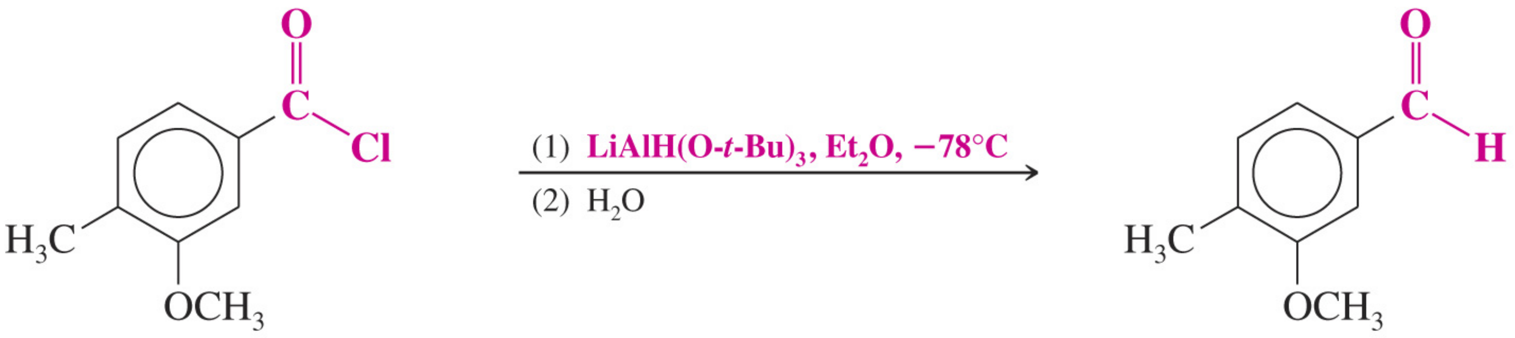
$$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}Cl \xrightarrow[\text{2) } H^+,\, H_2O]{\text{1) } LiAlH_4} CH_3CH_2CH_2OH$$

# 8b- Reduction with $LiAlH[OC(CH_3)_3]_3$

2) Acid chlorides react with lithium tri-*tert*-butoxyaluminum hydride to give aldehydes



$$\mathrm{R\overset{O}{\overset{\|}{C}}OH} \xrightarrow{\mathrm{SOCl_2}} \mathrm{R\overset{O}{\overset{\|}{C}}Cl} \xrightarrow[\text{(2) } \mathrm{H_2O}]{\text{(1) } \mathrm{LiAlH(O\text{-}}t\mathrm{\text{-}Bu)_3,\ Et_2O,\ -78^\circ C}} \mathrm{R\overset{O}{\overset{\|}{C}}H}$$

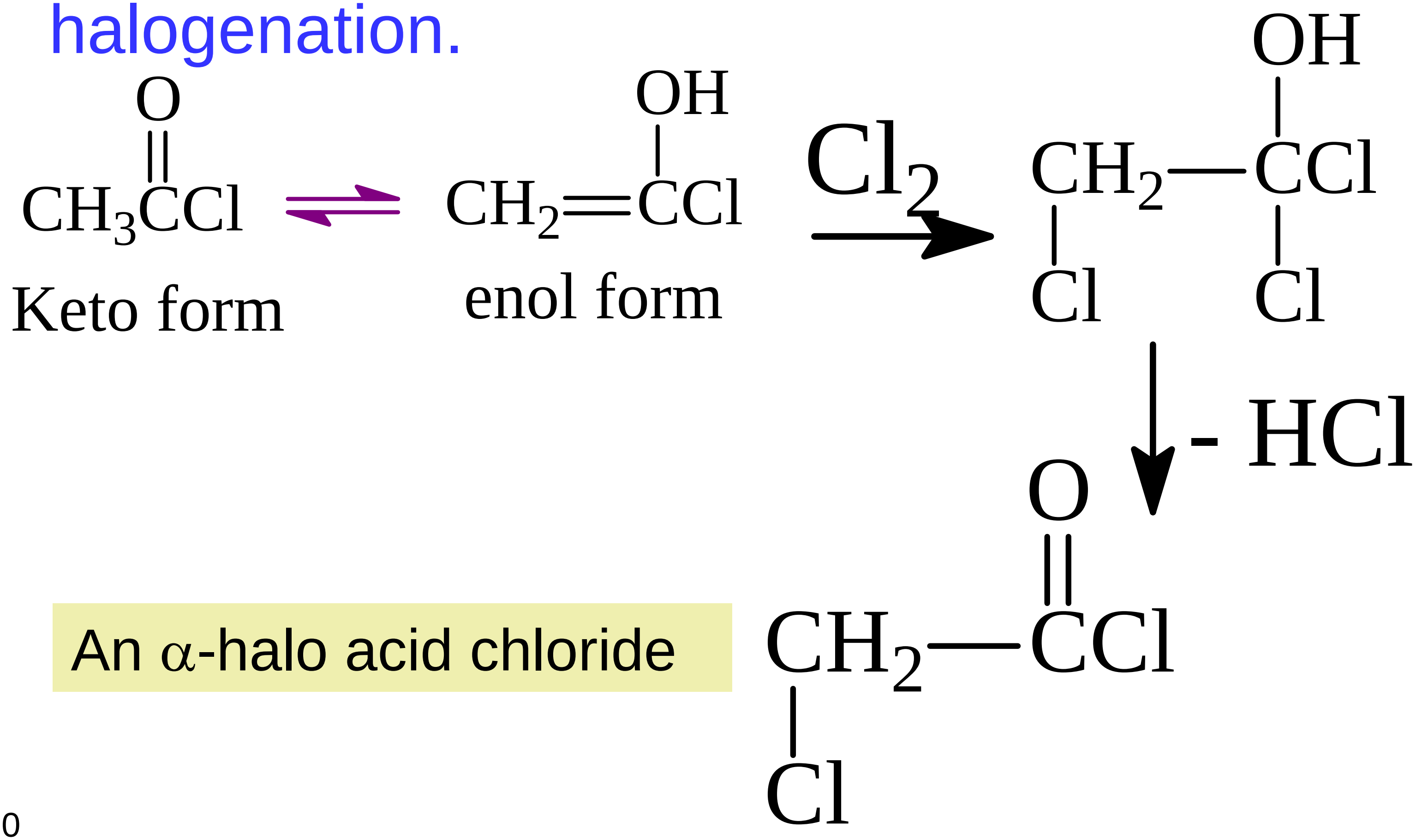


3-Methoxy-4-methylbenzoyl chloride

3-Methoxy-4-methylbenzaldehyde

# 9- Alpha halogenation

- Acid chloride undergo tautomerism ➔ alpha halogenation.



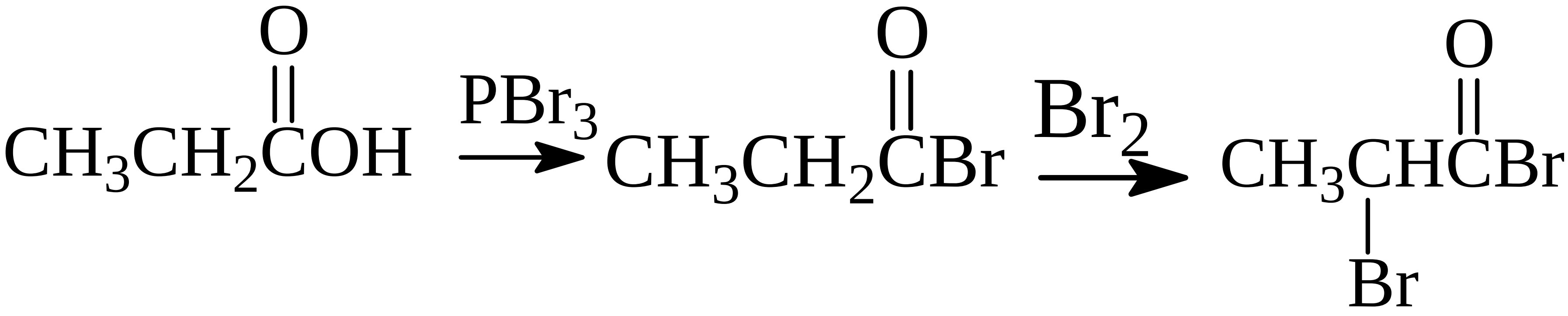
$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}Cl} \rightleftharpoons \mathrm{CH_2{=}\overset{\overset{OH}{|}}{C}Cl} \xrightarrow{\mathrm{Cl_2}} \mathrm{\underset{\underset{Cl}{|}}{CH_2}{-}\overset{\overset{OH}{|}}{\underset{\underset{Cl}{|}}{C}}Cl} \xrightarrow{\mathrm{-\,HCl}} \mathrm{\underset{\underset{Cl}{|}}{CH_2}{-}\overset{\overset{O}{\|}}{C}Cl}$$

Keto form

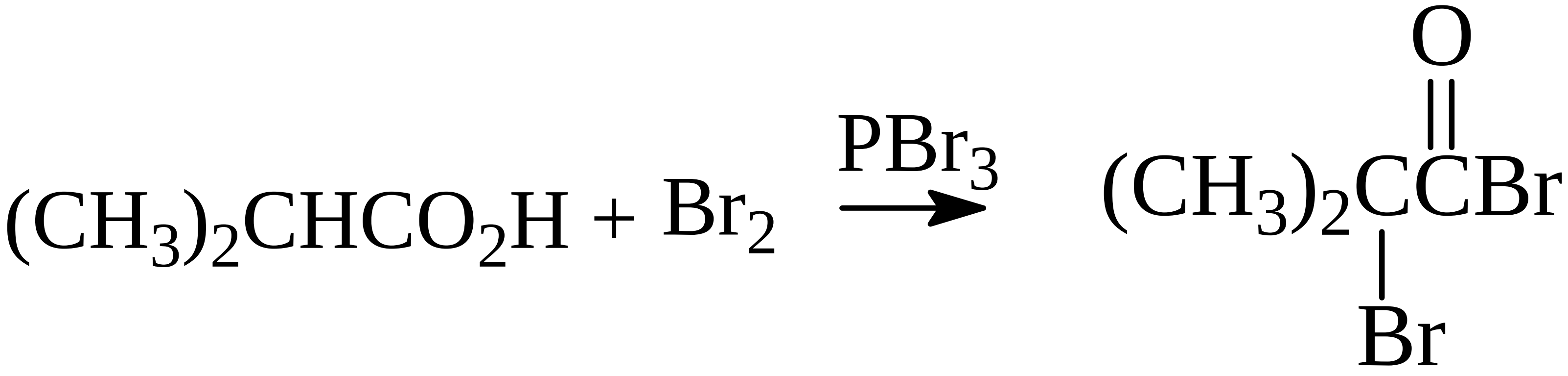
enol form

An $\alpha$-halo acid chloride

# Examples



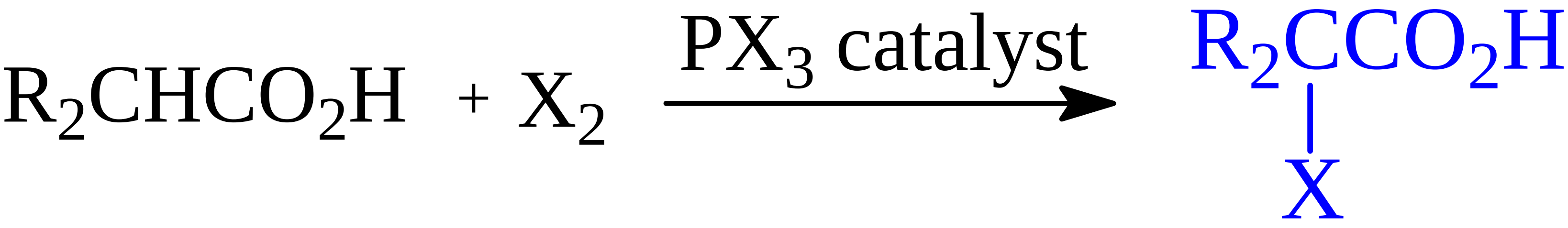
$$\mathrm{CH_3CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow{PBr_3} CH_3CH_2\overset{O}{\overset{\|}{C}}Br \xrightarrow{Br_2} CH_3\underset{\underset{Br}{|}}{CH}\overset{O}{\overset{\|}{C}}Br}$$



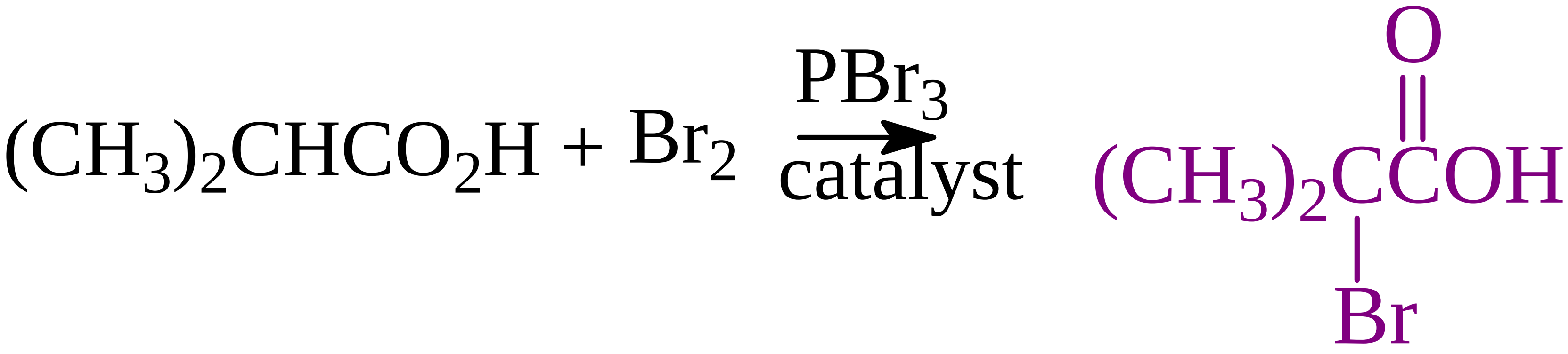
$$\mathrm{(CH_3)_2CHCO_2H + Br_2 \xrightarrow{PBr_3} (CH_3)_2\underset{\underset{Br}{|}}{C}\overset{O}{\overset{\|}{C}}Br}$$

# Hell-Volhard-Zelinesky Reaction

If $PBr_3$ is used as a catalyst, halogenation produce α-halo acid

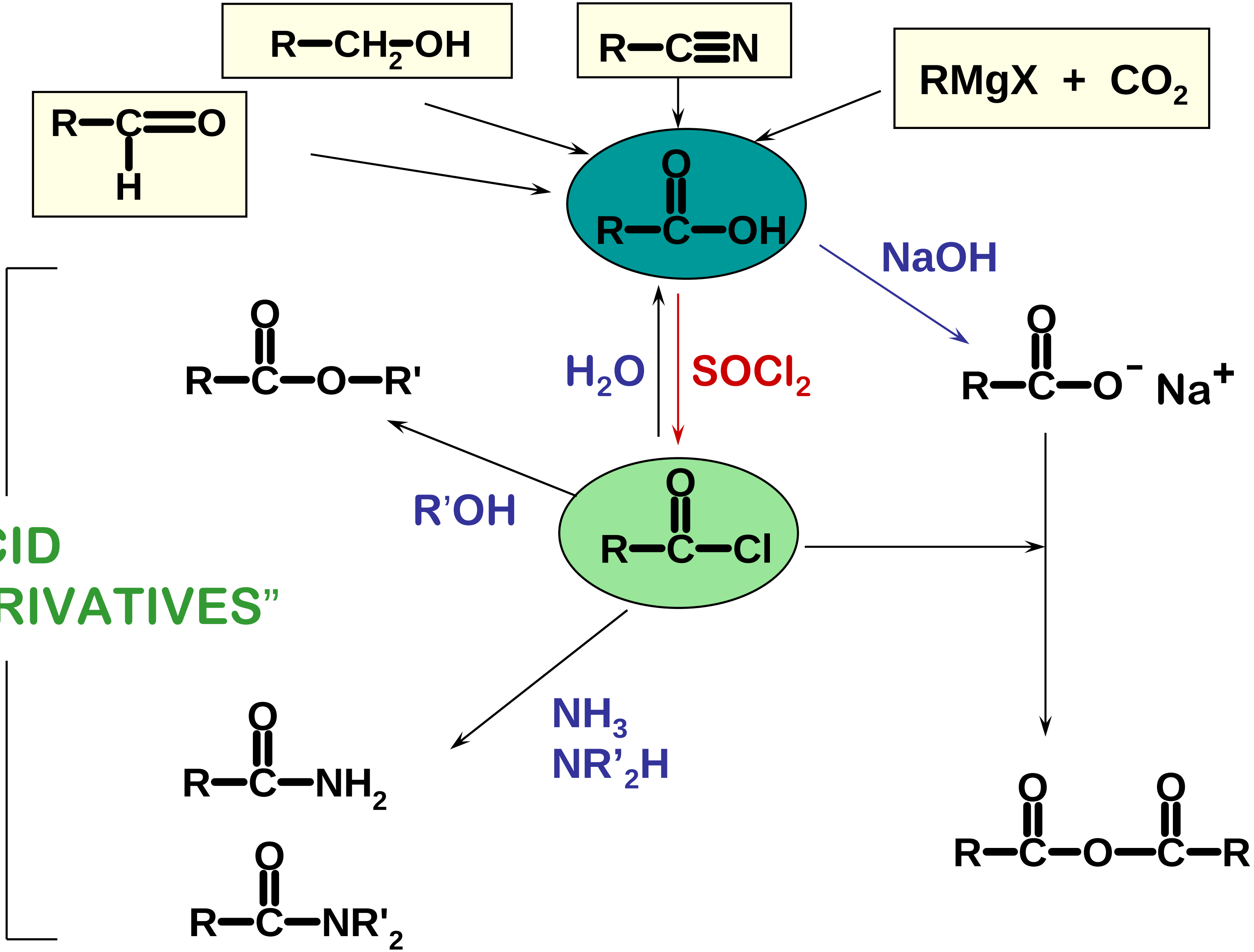


$$R_2CHCO_2H + X_2 \xrightarrow{PX_3\ \text{catalyst}} R_2\underset{\displaystyle X}{\underset{|}{C}}CO_2H$$



$$(CH_3)_2CHCO_2H + Br_2 \xrightarrow[\text{catalyst}]{PBr_3} (CH_3)_2\underset{\displaystyle Br}{\underset{|}{C}}\overset{\displaystyle O}{\overset{\|}{C}}OH$$

# EVERYTHING CAN BE MADE FROM THE ACID (CHLORIDE)



$R-CH_2-OH$

$R-C\equiv N$

$RMgX + CO_2$

NaOH

$H_2O$

$SOCl_2$

R'OH

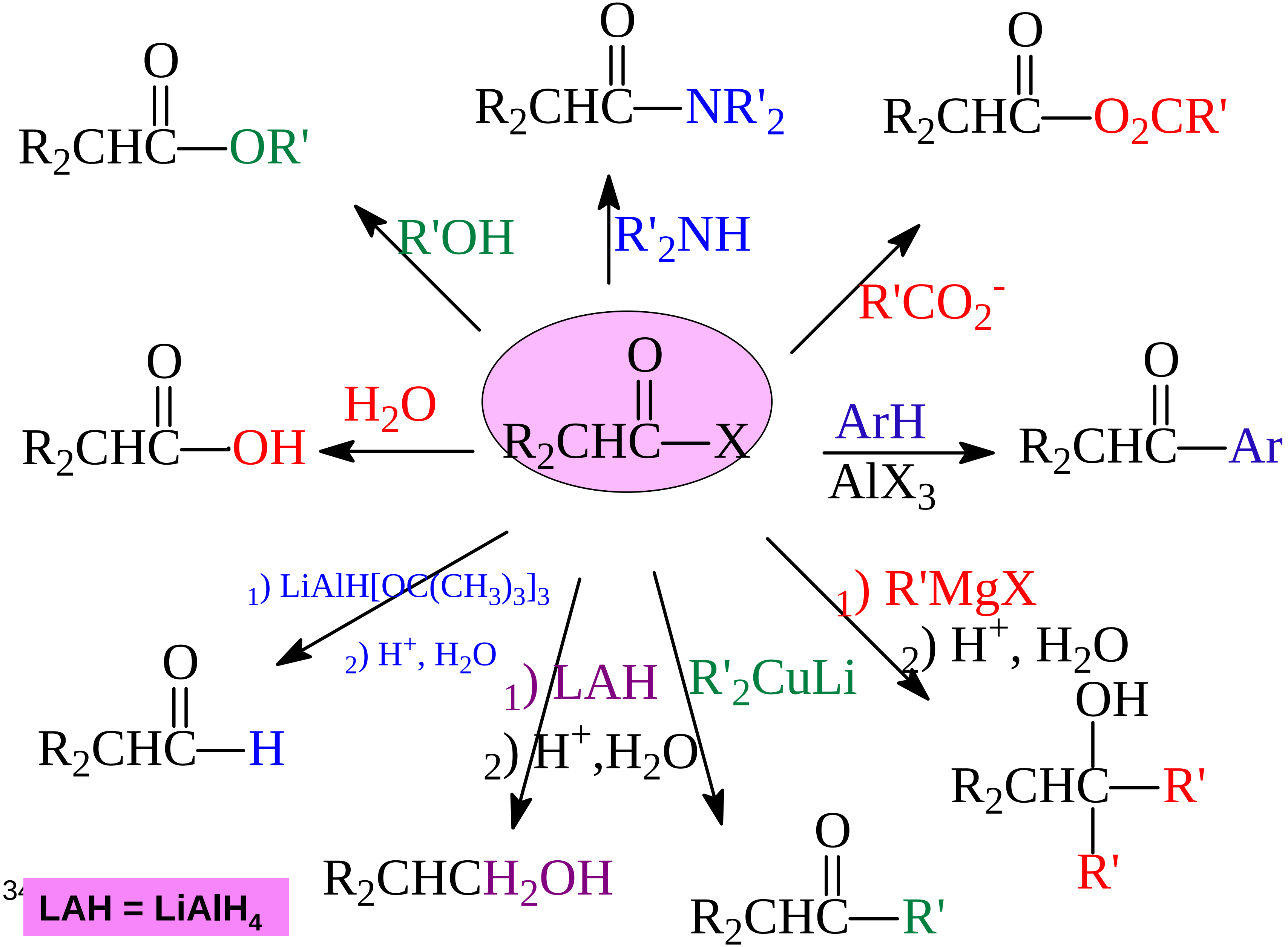
$NH_3$

$NR'_2H$

"ACID DERIVATIVES"

…. or the anhydride

# Acid Chloride Reactions ( summary)



$R_2CH\overset{O}{\overset{\|}{C}}-OR'$

$R_2CH\overset{O}{\overset{\|}{C}}-NR'_2$

$R_2CH\overset{O}{\overset{\|}{C}}-O_2CR'$

$R'OH$

$R'_2NH$

$R'CO_2^-$

$R_2CH\overset{O}{\overset{\|}{C}}-OH$

$H_2O$

$R_2CH\overset{O}{\overset{\|}{C}}-X$

$\xrightarrow[AlX_3]{ArH}$

$R_2CH\overset{O}{\overset{\|}{C}}-Ar$

1) $LiAlH[OC(CH_3)_3]_3$
2) $H^+$, $H_2O$

1) LAH
2) $H^+$,$H_2O$

$R'_2CuLi$

1) $R'MgX$
2) $H^+$, $H_2O$

$R_2CH\overset{O}{\overset{\|}{C}}-H$

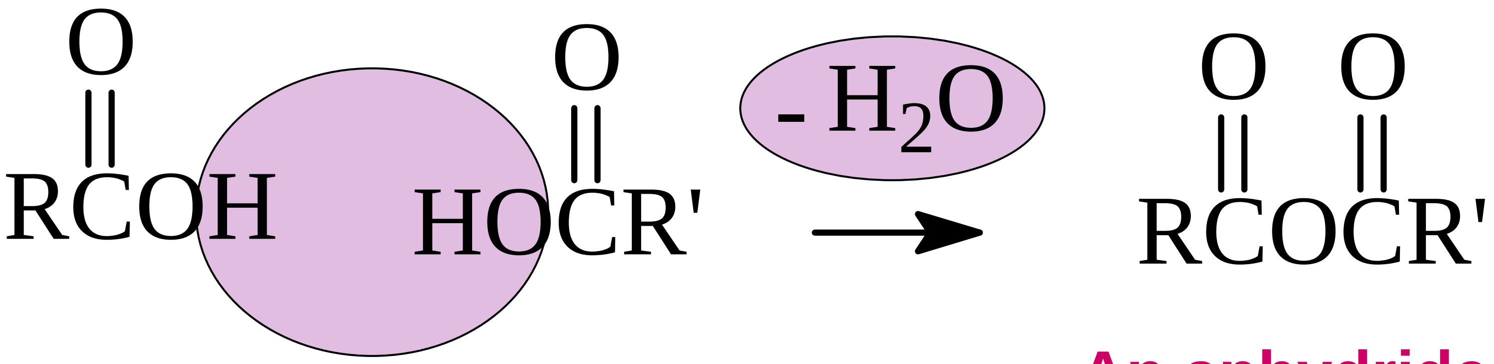
$R_2CHCH_2OH$

$R_2CH\overset{O}{\overset{\|}{C}}-R'$

$R_2CH\overset{OH}{\underset{R'}{\overset{|}{\underset{|}{C}}}}-R'$

**LAH = $LiAlH_4$**

# Anhydrides of Carboxylic Acids



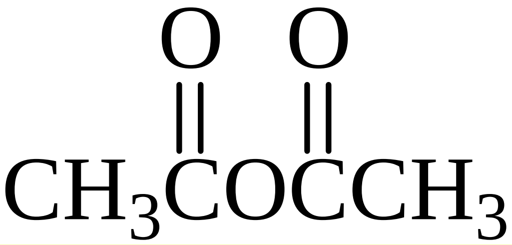
$$R\overset{\overset{O}{\|}}{C}OH \quad HO\overset{\overset{O}{\|}}{C}R' \xrightarrow{-H_2O} R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R'$$

**An anhydride**

***Anhydride*** **means “without water”**

# Nomenclature of anhydride

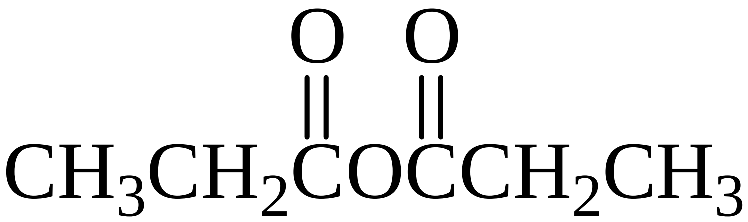
- Anhydrides are named after the parent carboxylic acid followed by the word anhydride



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

ethanoic anhydride (IUPAC)

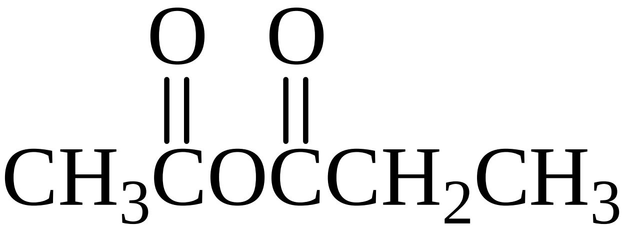
Acetic anhydride (trivial)



$$CH_3CH_2\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_2CH_3$$

**Propanoic anhydride (IUPAC)**

**Propionic anhydride (trivial**)



$$CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_2CH_3$$

ethanoic propanoic anhydride

# Preparation of Anhydride

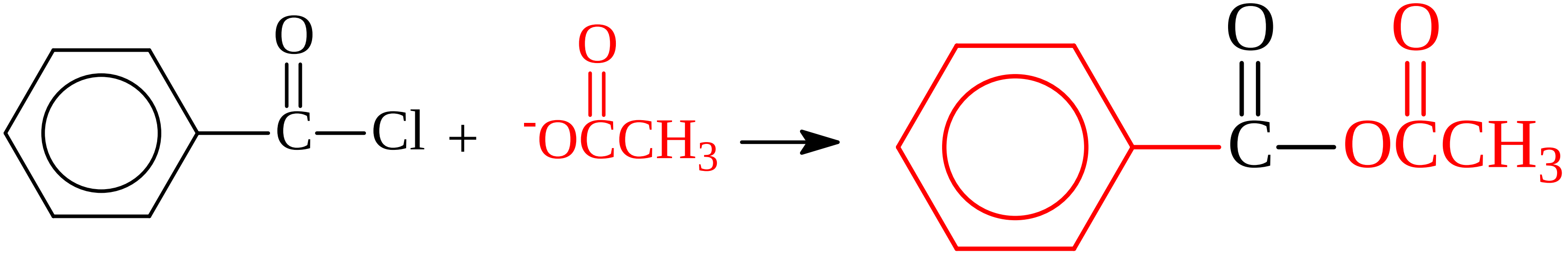
1. From acid chloride

$$R\overset{O}{\overset{\|}{C}}-Cl + {}^{-}O\overset{O}{\overset{\|}{C}}R' \longrightarrow R\overset{O}{\overset{\|}{C}}-O\overset{O}{\overset{\|}{C}}R'$$

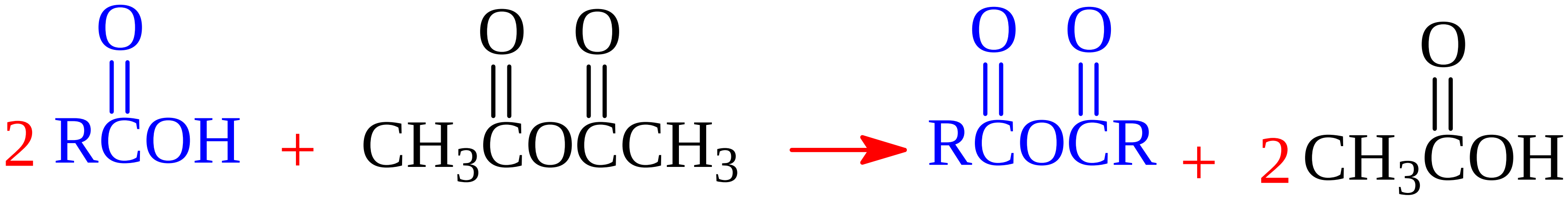
**An acid chloride**

**A carboxylate ion**

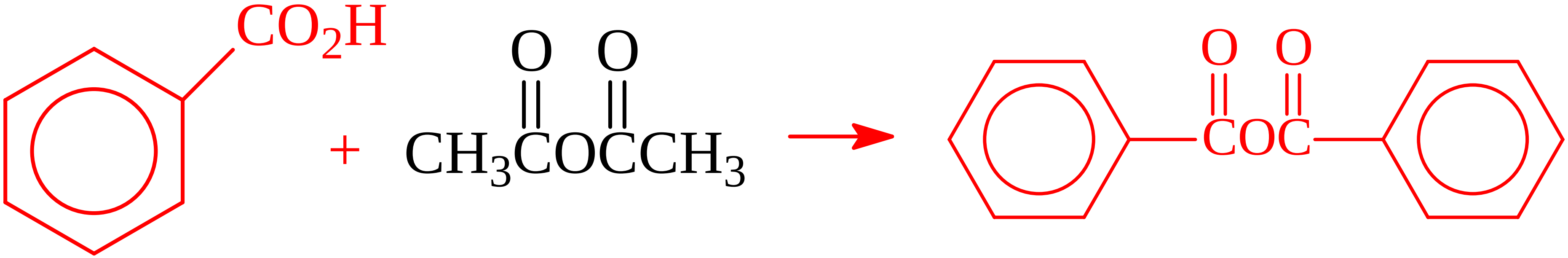
**An anhydride**



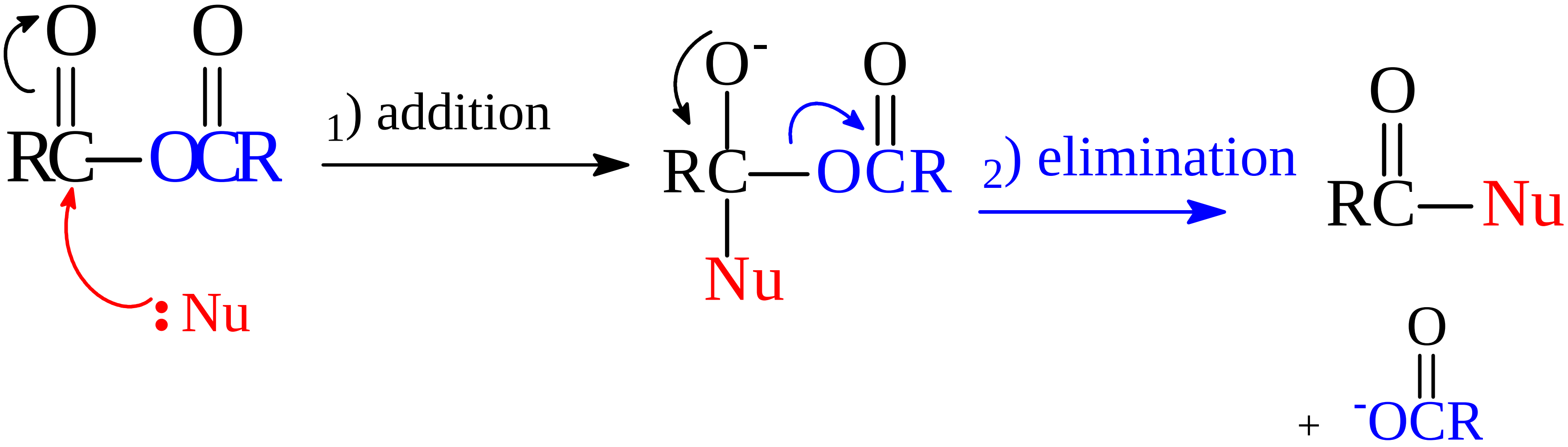
# 2-From carboxylic acids



$$2\,\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OH} + \mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{O}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH_3} \longrightarrow \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{O}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R} + 2\,\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OH}$$

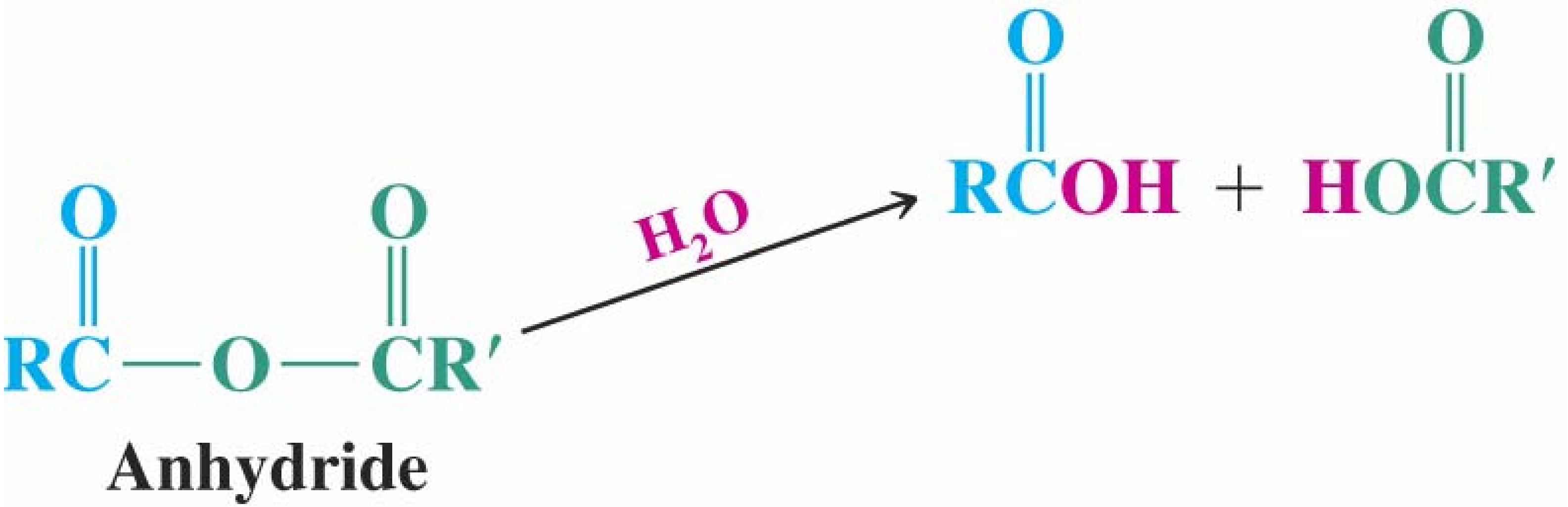


# Reactions of Anhydrides



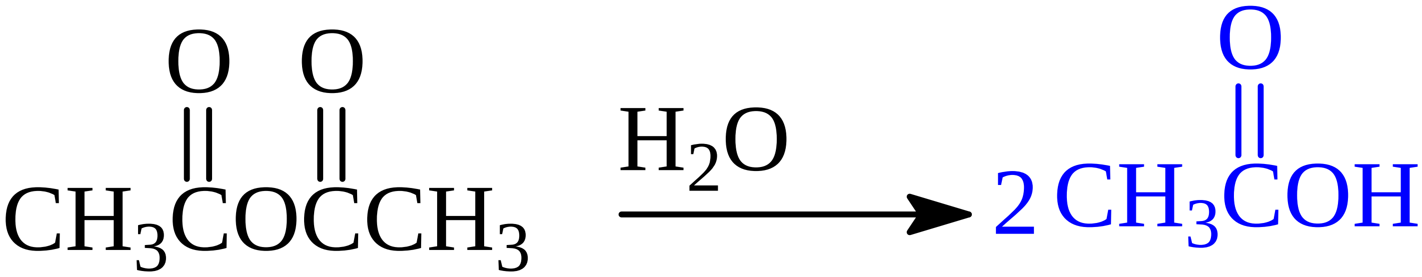
# 1- Hydrolysis

- Anhydrides react with water ➔ Carboxylic acid



$$R\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}R' \xrightarrow{H_2O} R\overset{O}{\overset{\|}{C}}OH + HO\overset{O}{\overset{\|}{C}}R'$$

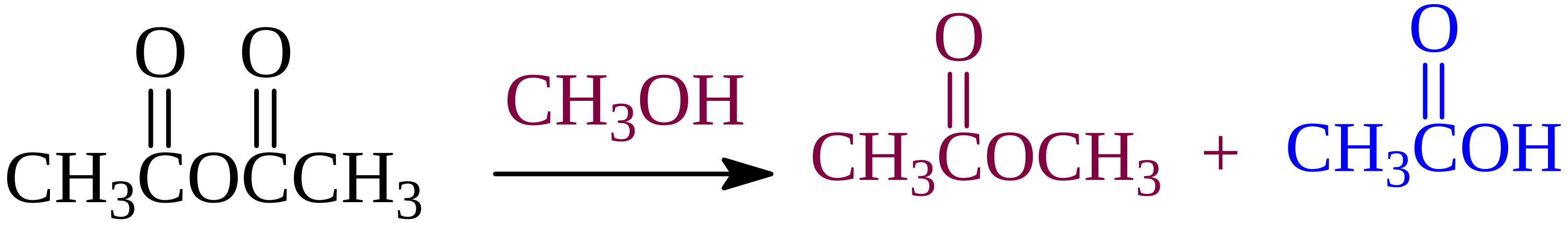
Anhydride



$$CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{H_2O} 2\,CH_3\overset{O}{\overset{\|}{C}}OH$$

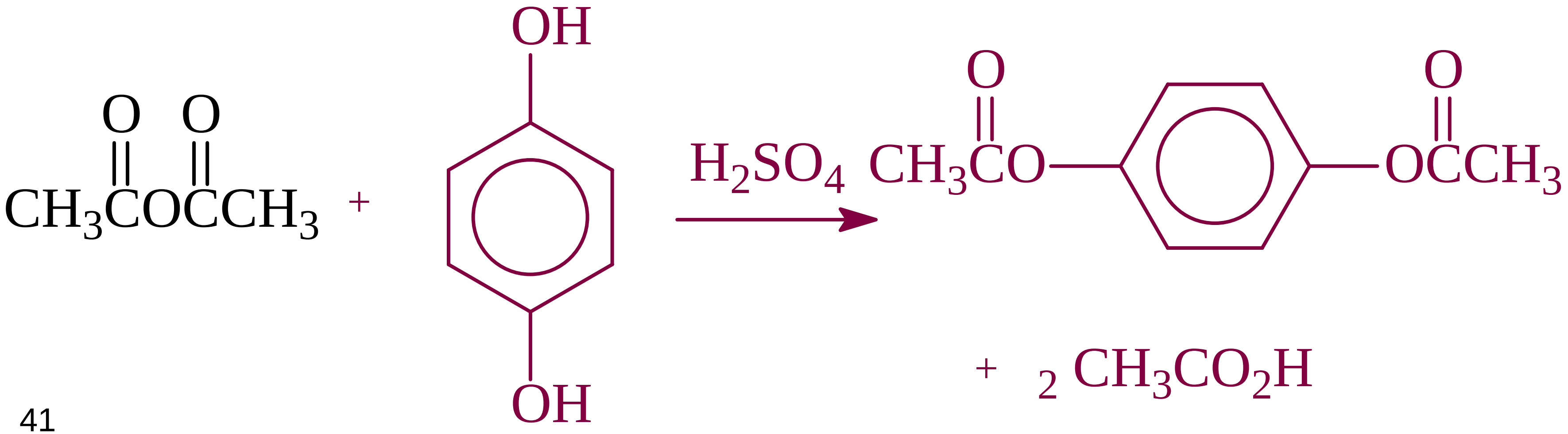
# 2- Reaction with Alcohols and Phenols

- Anhydride with alcohol or phenol in the presence oh acid ➔ Ester

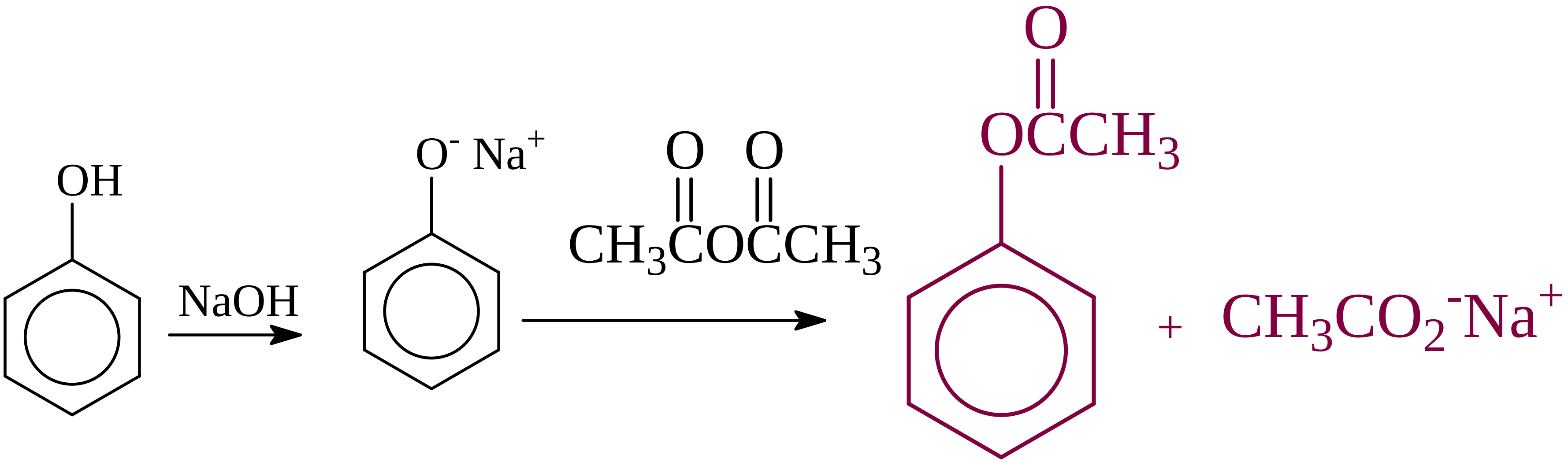


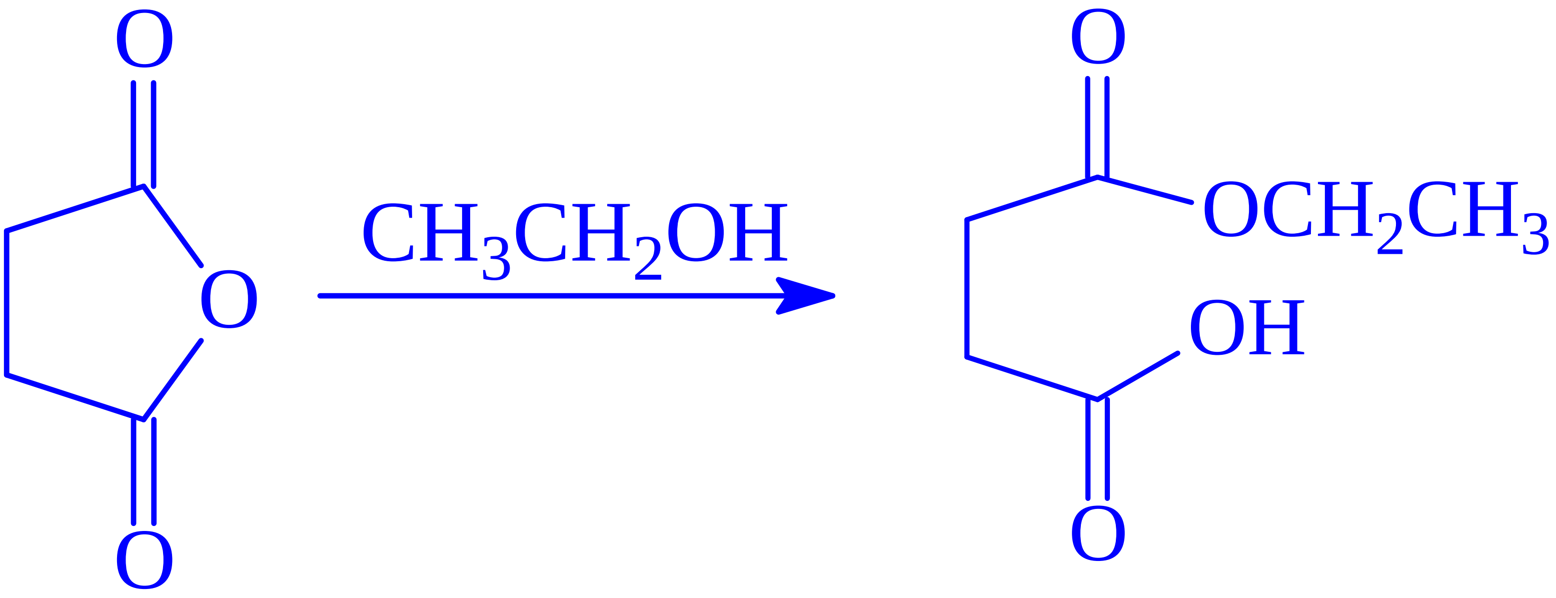
$$CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{CH_3OH} CH_3\overset{O}{\overset{\|}{C}}OCH_3 + CH_3\overset{O}{\overset{\|}{C}}OH$$

**An ester**

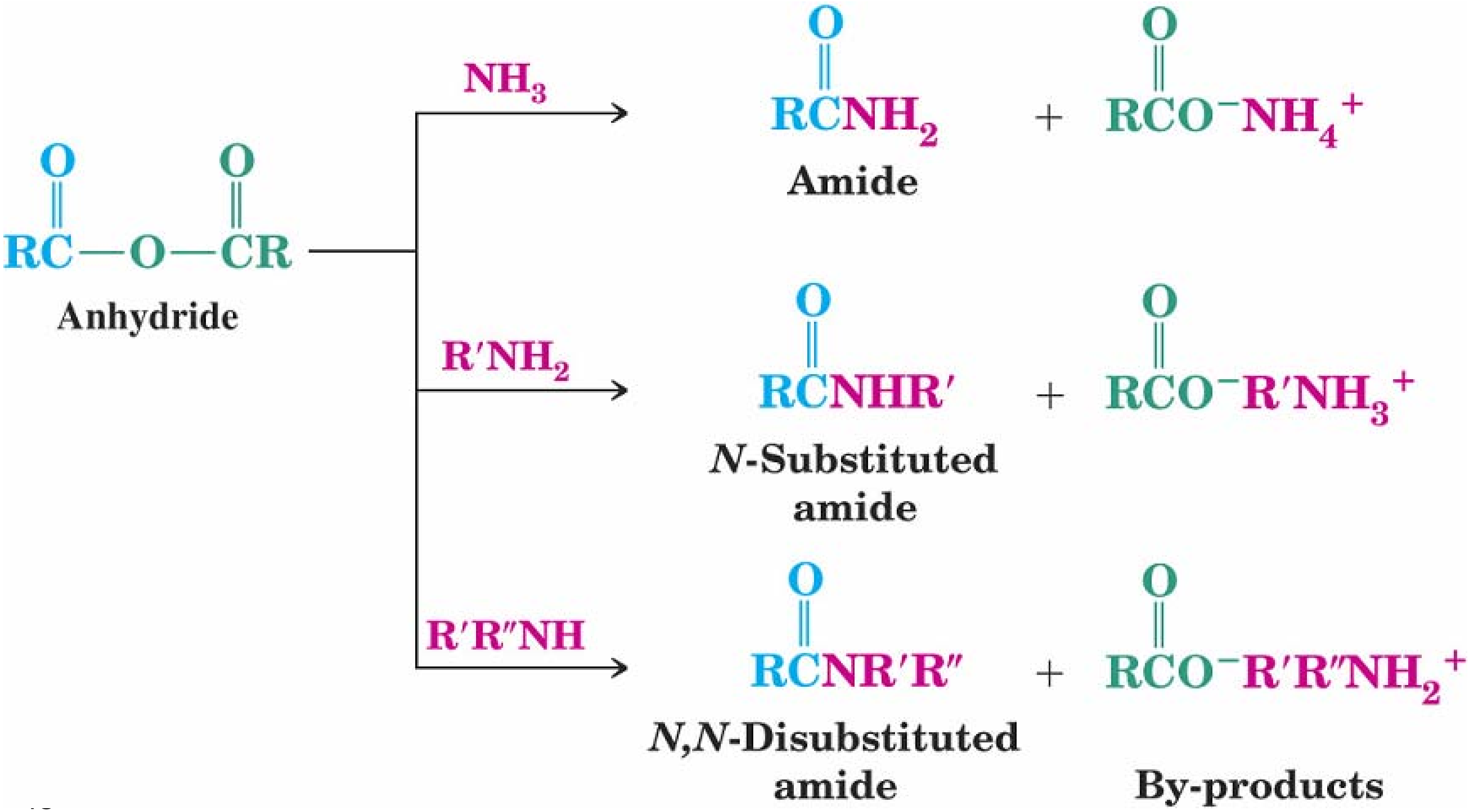


- Phenyl ester can prepared under basic conditions





# 3- Reaction with Ammonia and amines

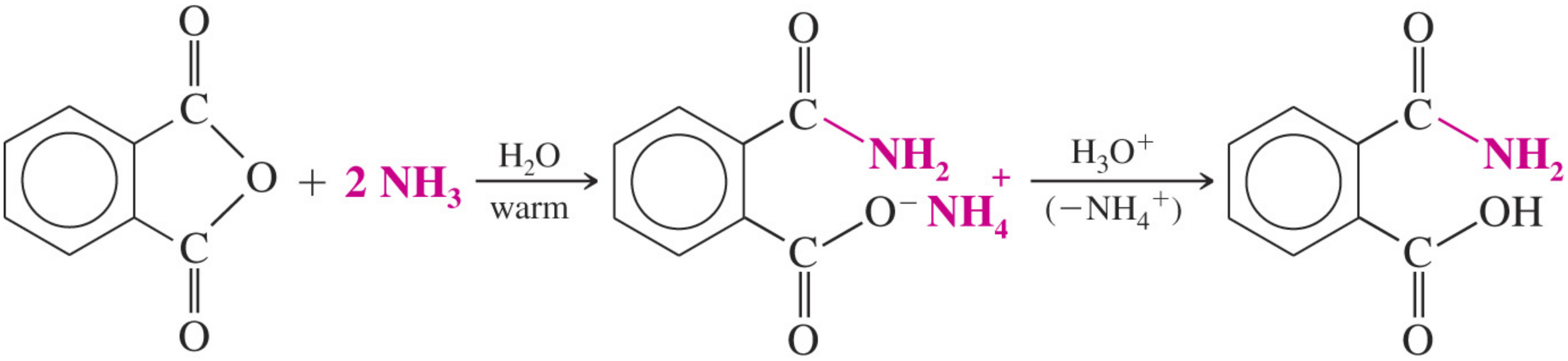


$$RC(=O)-O-C(=O)R \xrightarrow{NH_3} RC(=O)NH_2 + RC(=O)O^-NH_4^+$$

$$RC(=O)-O-C(=O)R \xrightarrow{R'NH_2} RC(=O)NHR' + RC(=O)O^-R'NH_3^+$$

$$RC(=O)-O-C(=O)R \xrightarrow{R'R''NH} RC(=O)NR'R'' + RC(=O)O^-R'R''NH_2^+$$

# Examples

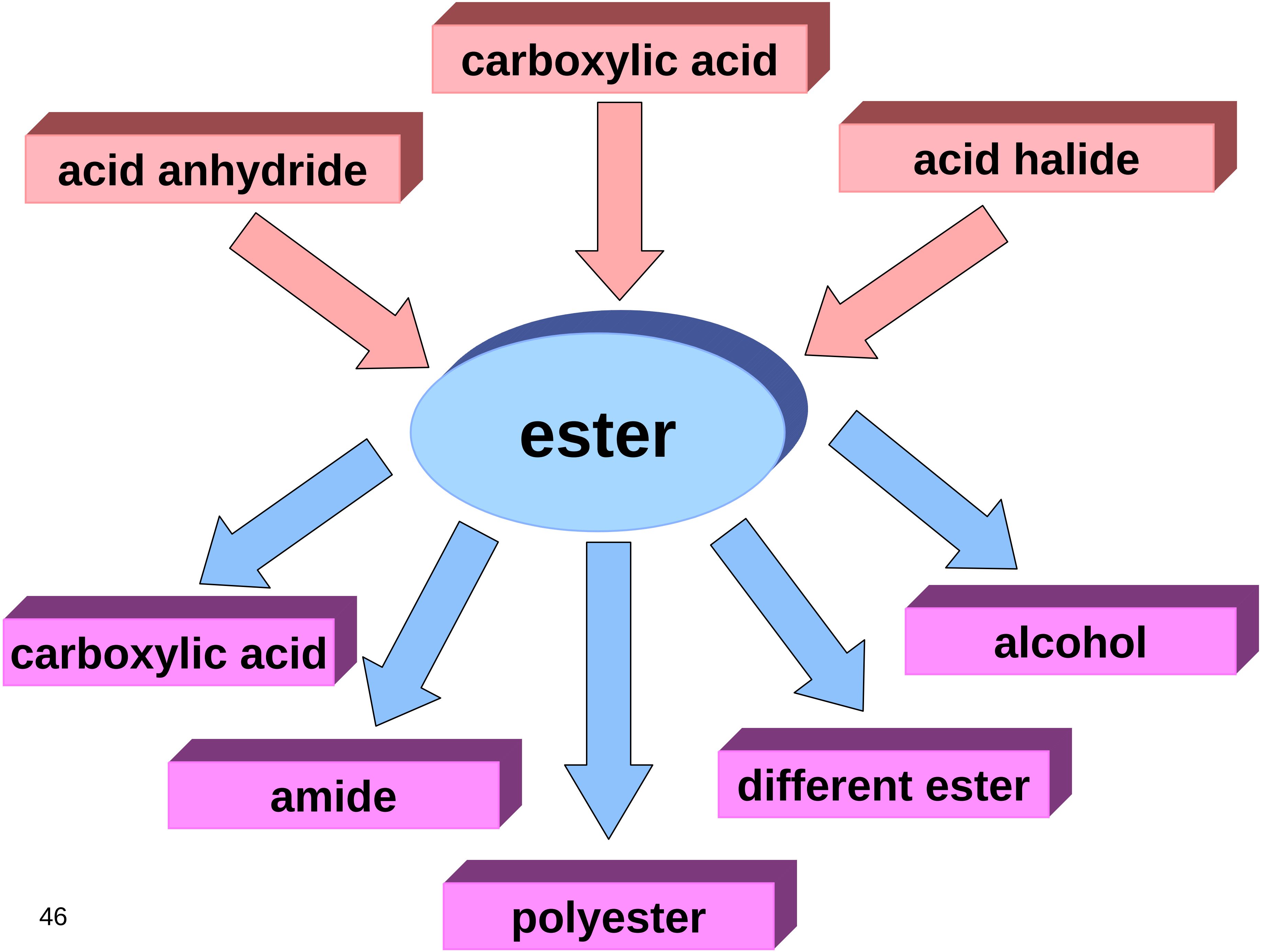


**Phthalic anhydride**

**Ammonium phthalamate (94%)**

**Phthalamic acid (81%)**

# Esters of carboxylic acids



carboxylic acid

acid anhydride

acid halide

**ester**

carboxylic acid

amide

polyester

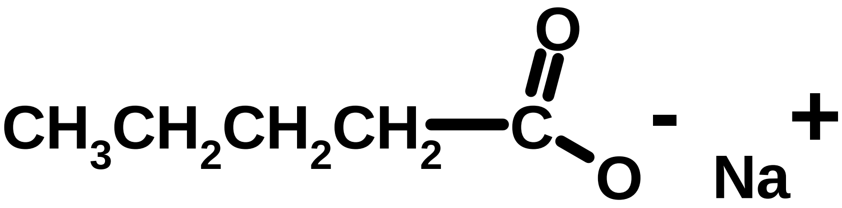
different ester

alcohol

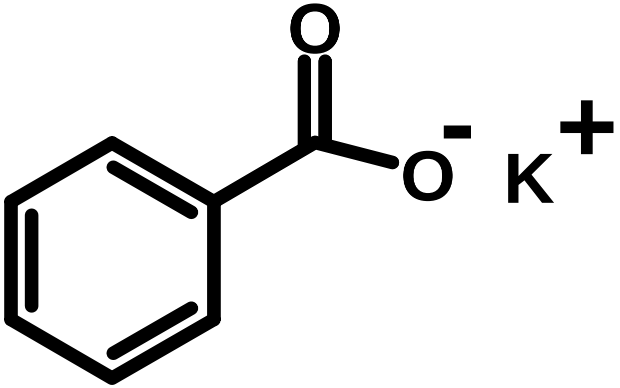
# Nomenclature of Esters

**Change -ic acid to -oate**

## SALTS OF ACIDS

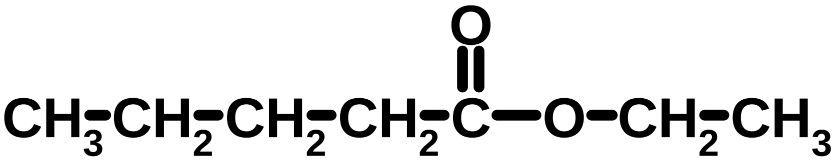


sodium pentanoate



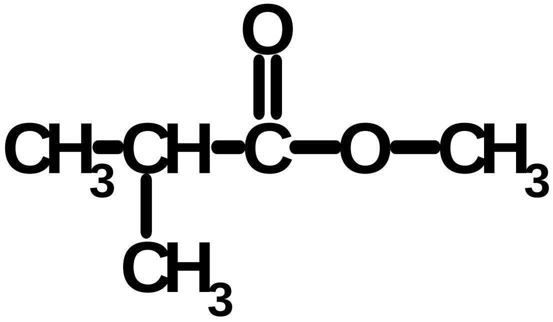
**potassium benzoate**

## ESTERS



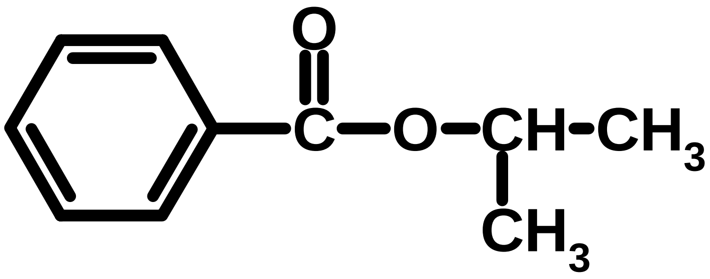
$CH_3-CH_2-CH_2-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2-CH_3$

**ethyl pentanoate**



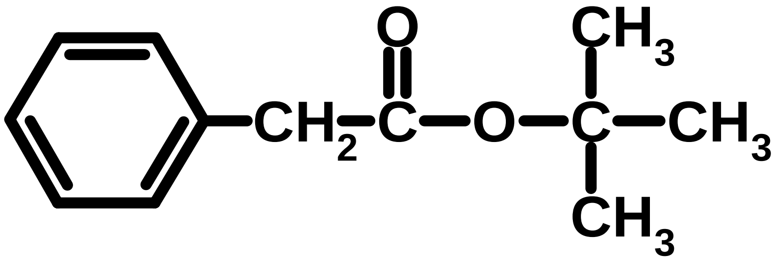
**methyl 2-methylpropanoate**
**methyl isobutyrate**

# ESTERS

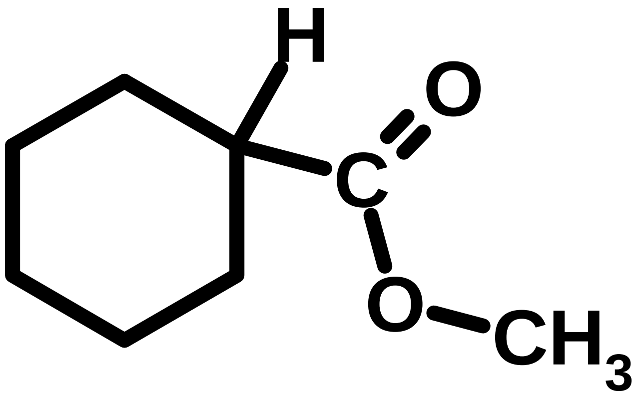


**isopropyl benzenecarboxylate**

**isopropyl benzoate**



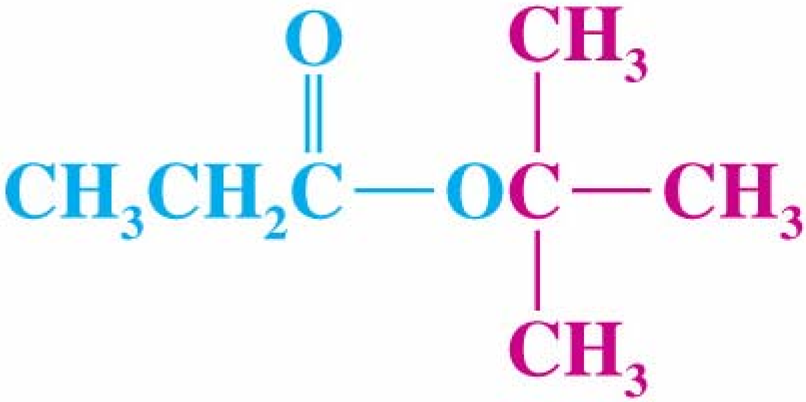
**tert-butyl phenylethanoate**



**methyl cyclohexanecarboxylate**

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

**Ethyl acetate** or
**ethyl ethanoate**



$$CH_3CH_2\overset{\overset{O}{\|}}{C}-O\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3$$

***tert*-Butyl propanoate**

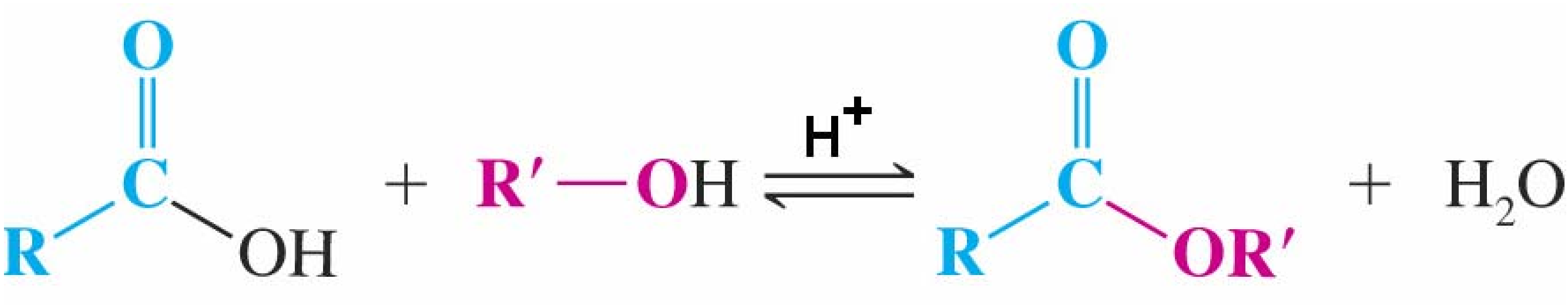
$$CH_3\overset{\overset{O}{\|}}{C}OCH{=}CH_2$$

**Vinyl acetate** or
**ethenyl ethanoate**

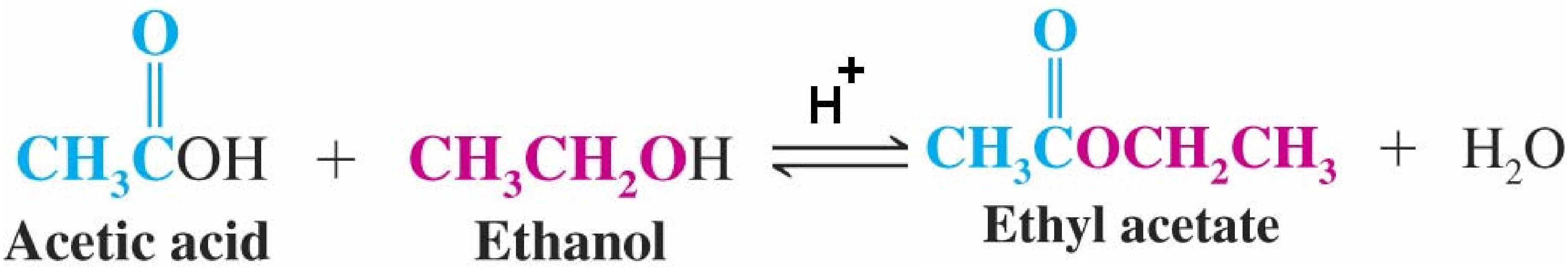
**Methyl *p*-chlorobenzoate**

# Preparation of Esters

## 1) From Carboxylic acids and Alcohols



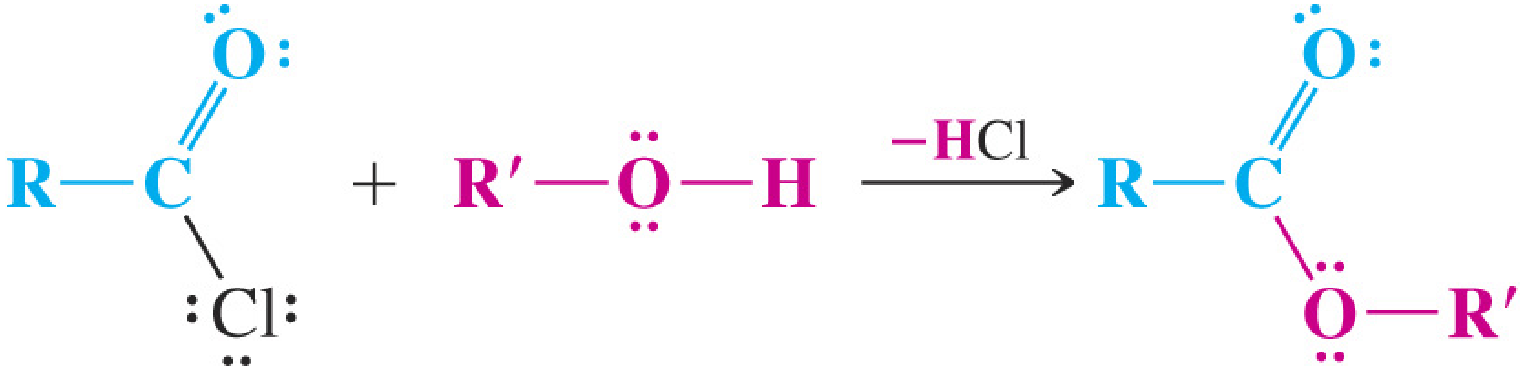
$$R\overset{\overset{O}{\|}}{C}OH + R'{-}OH \overset{H^+}{\rightleftharpoons} R\overset{\overset{O}{\|}}{C}OR' + H_2O$$

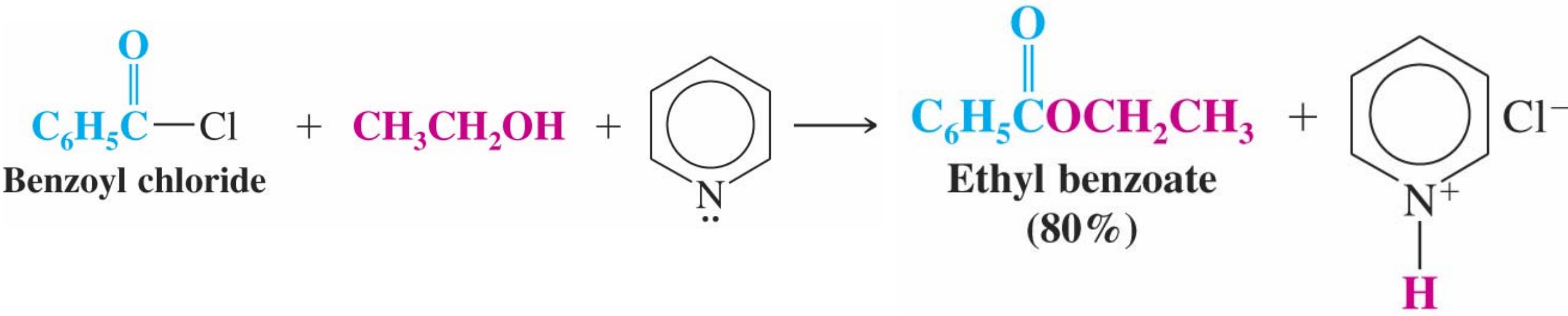


$$CH_3\overset{\overset{O}{\|}}{C}OH + CH_3CH_2OH \overset{H^+}{\rightleftharpoons} CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 + H_2O$$

Acetic acid Ethanol Ethyl acetate

# 2) Esters from Acid Chlorides and alcohols

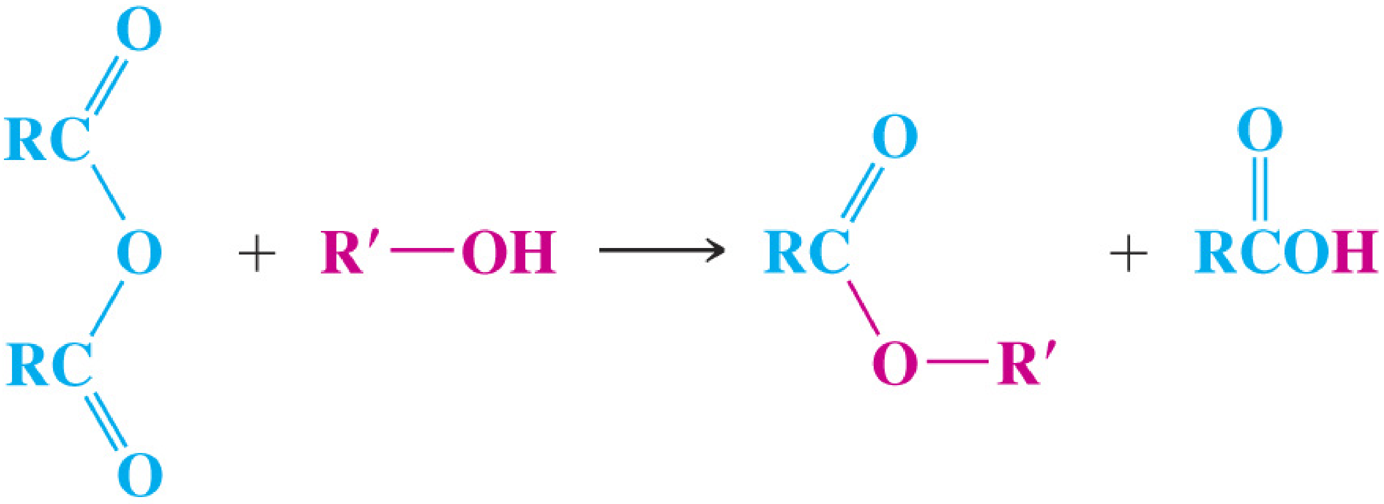


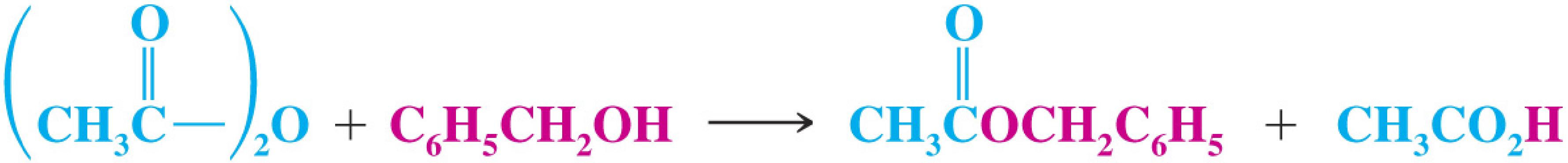


Benzoyl chloride

Ethyl benzoate (80%)

# 3) **Esters from Carboxylic Acid Anhydrides and alcohols**





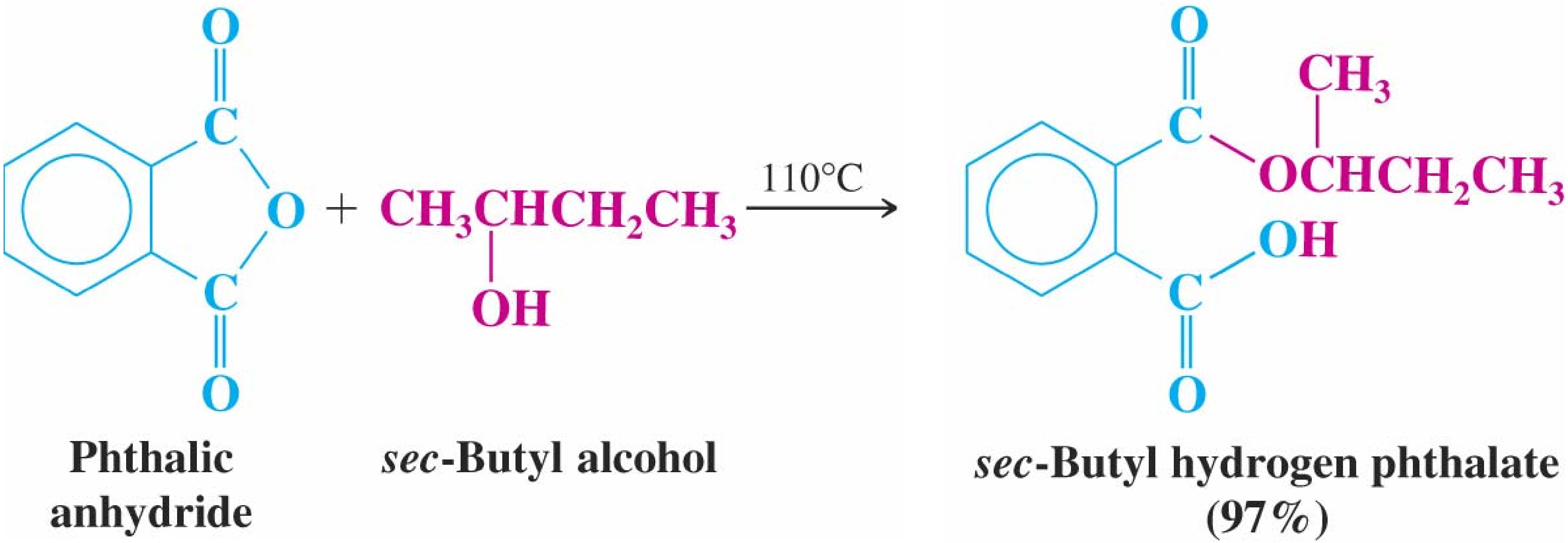
$$\left(CH_3\overset{O}{\overset{\|}{C}}-\right)_2O + C_6H_5CH_2OH \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OCH_2C_6H_5 + CH_3CO_2H$$

Acetic anhydride

Benzyl alcohol

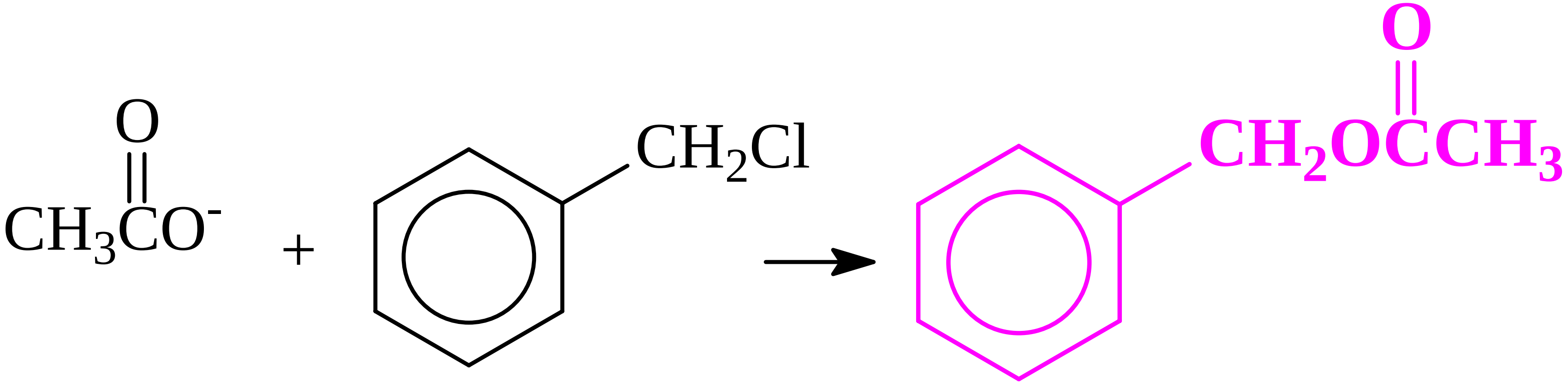
Benzyl acetate

# Example


O
C
O
C
O
+
$CH_3CHCH_2CH_3$
OH
110°C
O
C
$CH_3$
$OCHCH_2CH_3$
OH
C
O
Phthalic anhydride
*sec*-Butyl alcohol
*sec*-Butyl hydrogen phthalate (97%)

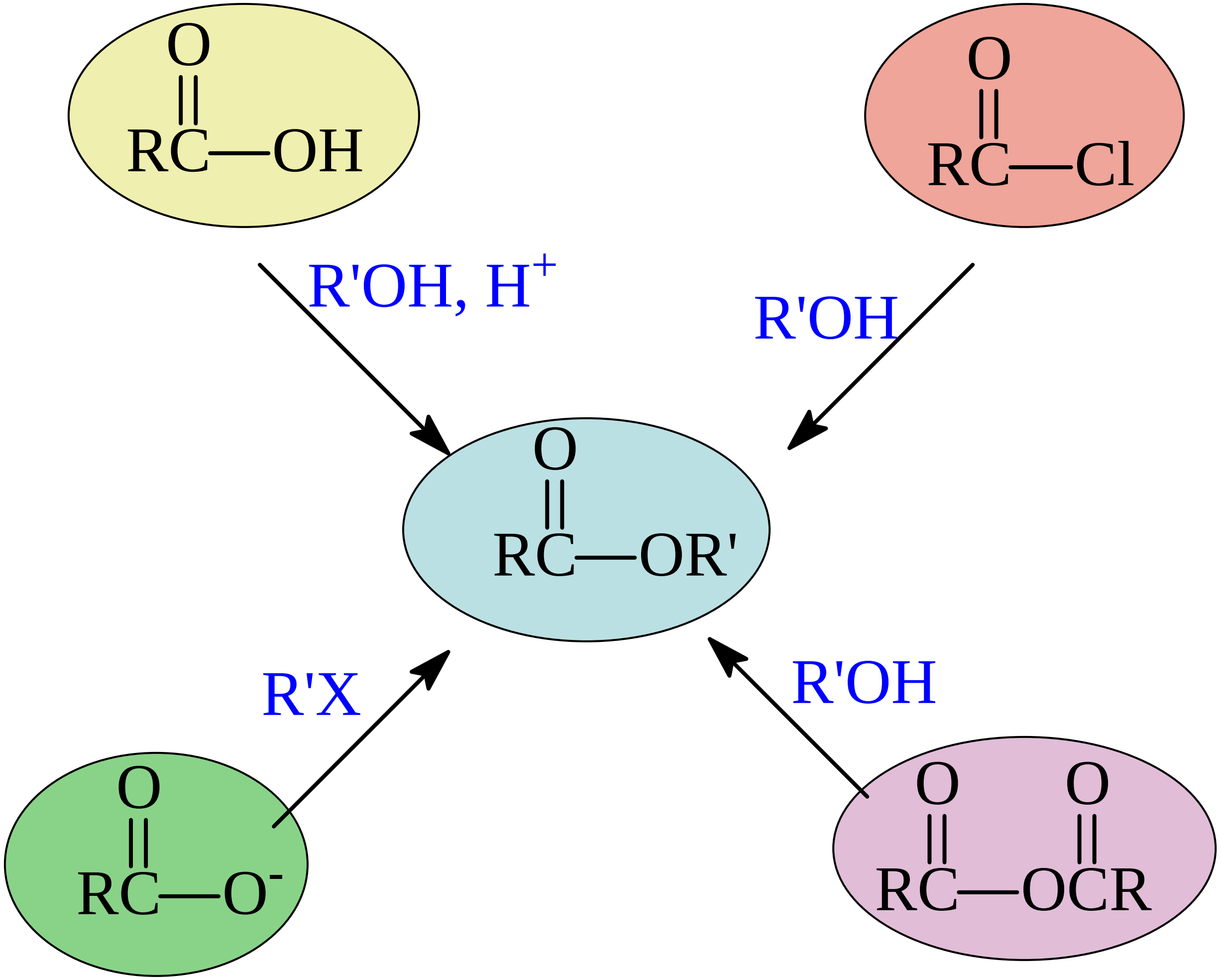
# 4) Esters from carboxylate ions and alkyl halide

$$RCO_2^- \quad + \quad R'\text{-}X \rightarrow \quad RCO_2R' + X^-$$



Benzyl acetate

# Summary of Ester Preparation



$R\overset{O}{\overset{\|}{C}}-OH \xrightarrow{R'OH,\ H^+} R\overset{O}{\overset{\|}{C}}-OR'$

$R\overset{O}{\overset{\|}{C}}-Cl \xrightarrow{R'OH} R\overset{O}{\overset{\|}{C}}-OR'$

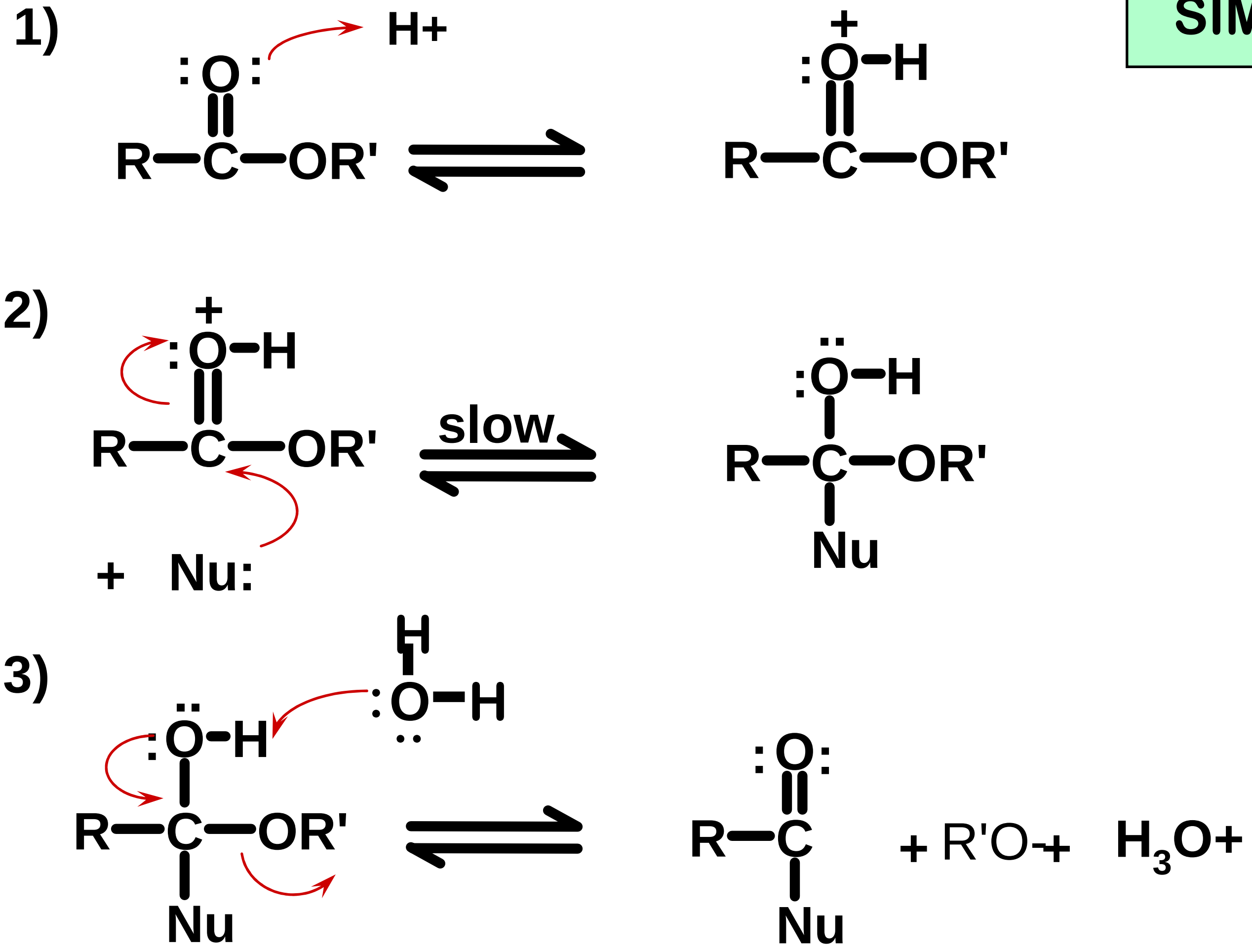
$R\overset{O}{\overset{\|}{C}}-O^- \xrightarrow{R'X} R\overset{O}{\overset{\|}{C}}-OR'$

$R\overset{O}{\overset{\|}{C}}-O\overset{O}{\overset{\|}{C}}R \xrightarrow{R'OH} R\overset{O}{\overset{\|}{C}}-OR'$

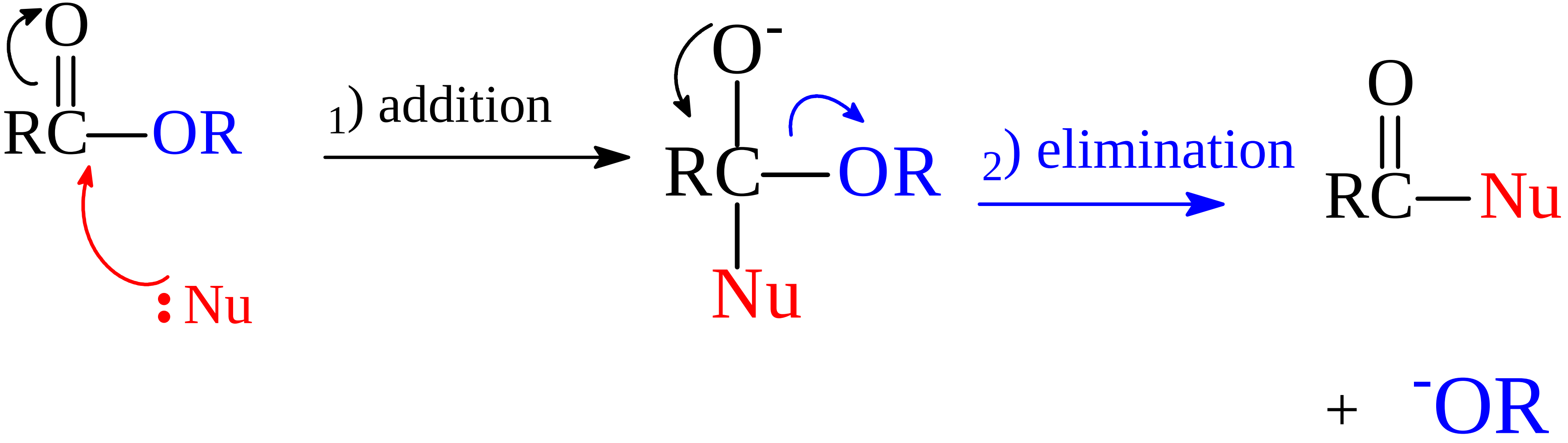
# Reactions of Esters

# Acid-Catalyzed Nucleophilic Acyl Substitution

**SIMPLIFIED**

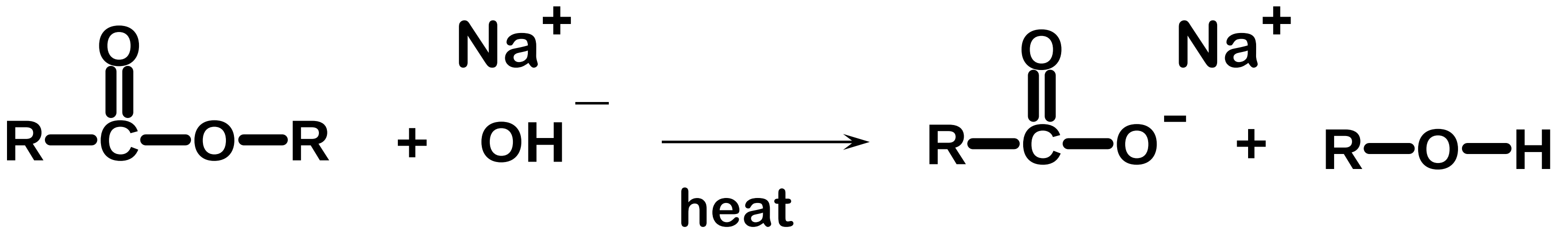


# Nucleophilic Acyl Sunstitution In Alkaline Conditions



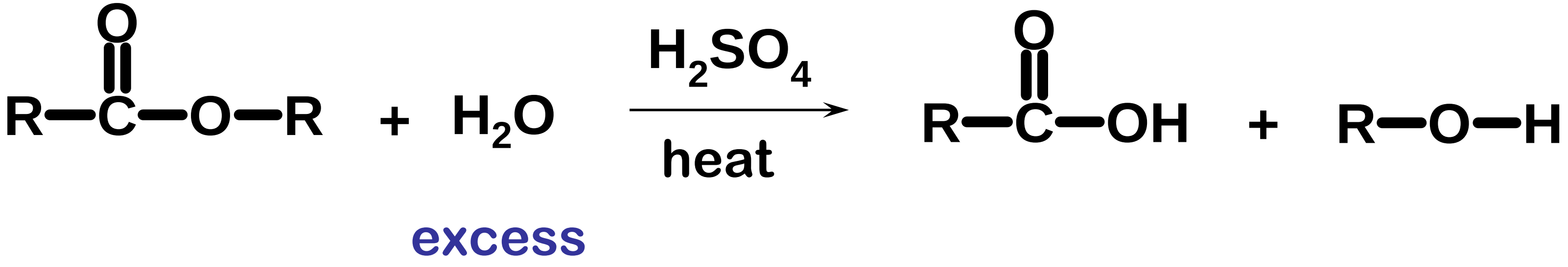
# 1- Hydrolysis of Esters

**Basic Solution**



$$R-\overset{O}{\overset{\|}{C}}-O-R \;+\; Na^{+}\ OH^{-} \xrightarrow[\text{heat}]{} R-\overset{O}{\overset{\|}{C}}-O^{-}\ Na^{+} \;+\; R-O-H$$

**Acidic Solution**



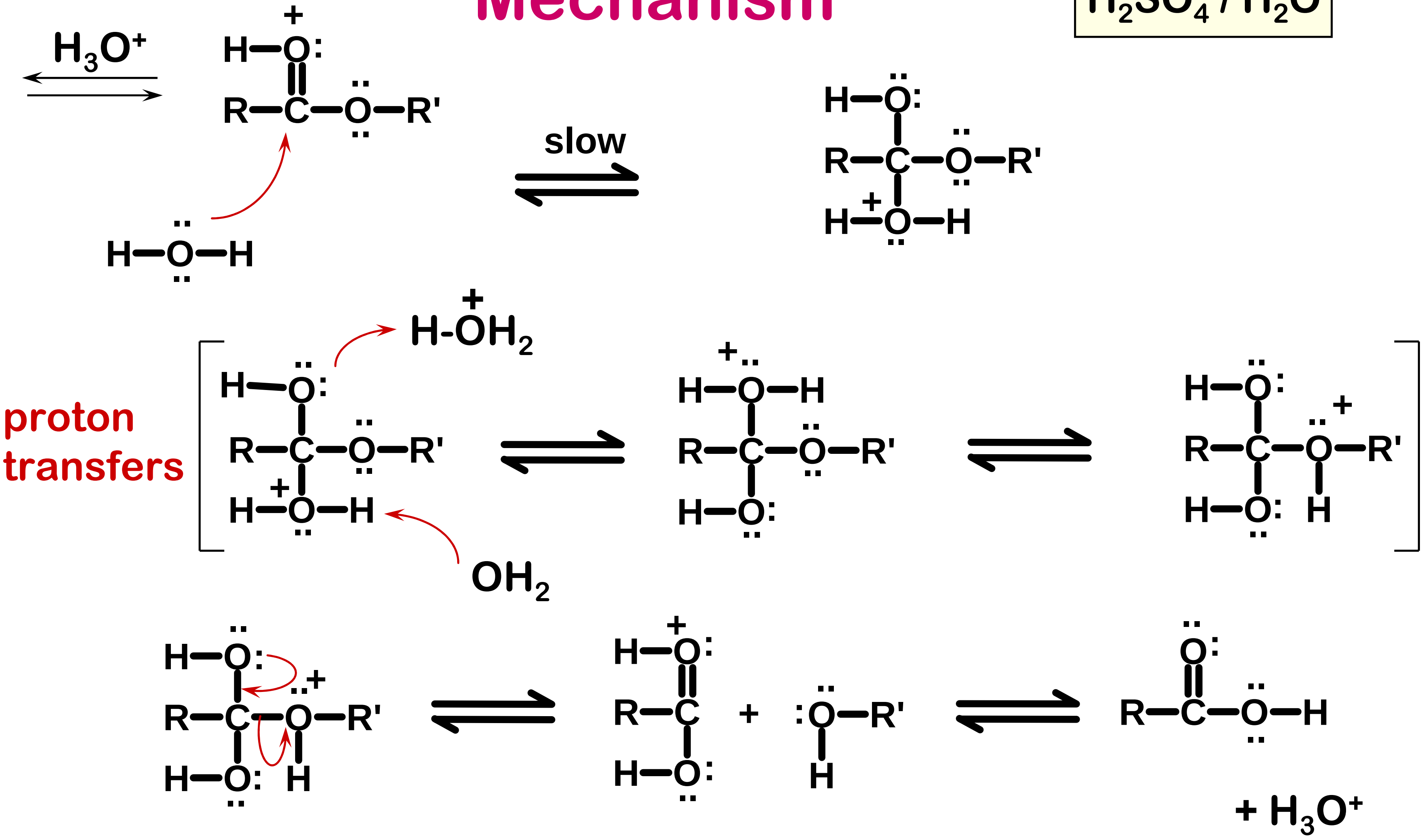
$$R-\overset{O}{\overset{\|}{C}}-O-R \;+\; \underset{\text{excess}}{H_2O} \xrightarrow[\text{heat}]{H_2SO_4} R-\overset{O}{\overset{\|}{C}}-OH \;+\; R-O-H$$

**Hydrolysis in acid is reversible ,but in base it is irreversible.**

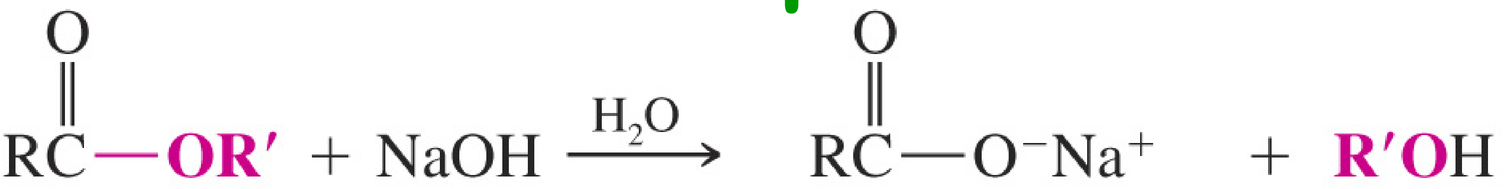
# Hydrolysis of an Ester in Acid

## Mechanism

$H_2SO_4$ / $H_2O$



# Base-Promoted Hydrolysis of Esters: Saponification



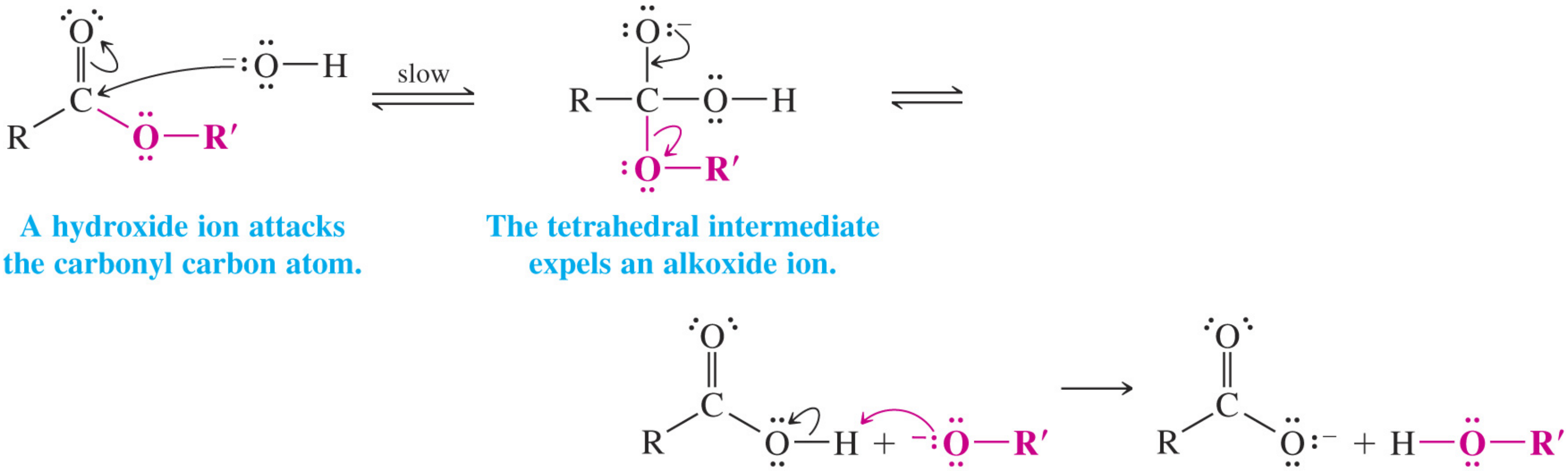
$$R\overset{\overset{\displaystyle O}{\|}}{C}-OR' + NaOH \xrightarrow{H_2O} R\overset{\overset{\displaystyle O}{\|}}{C}-O^-Na^+ + R'OH$$

Ester

Sodium carboxylate

Alcohol

## Mechanism

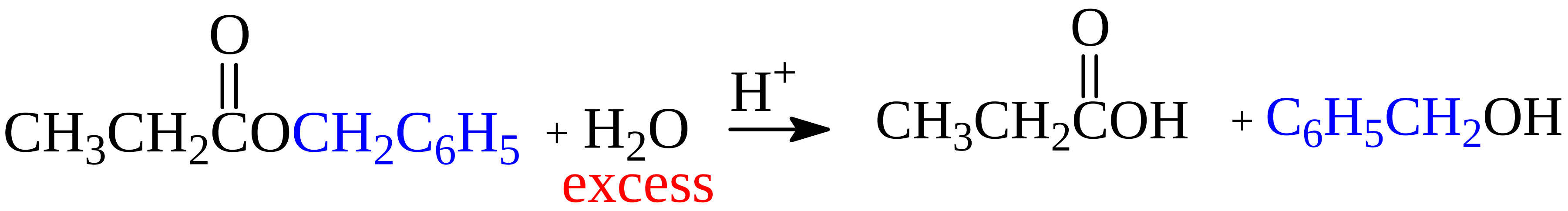


A hydroxide ion attacks the carbonyl carbon atom.

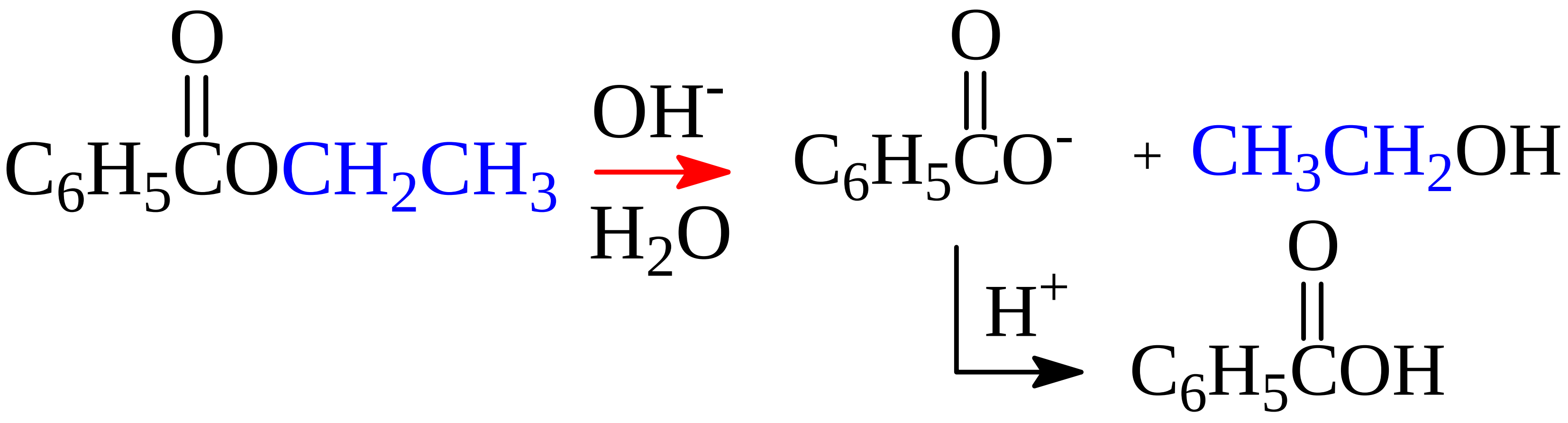
The tetrahedral intermediate expels an alkoxide ion.

Transfer of a proton leads to the products of the reaction.

# Examples

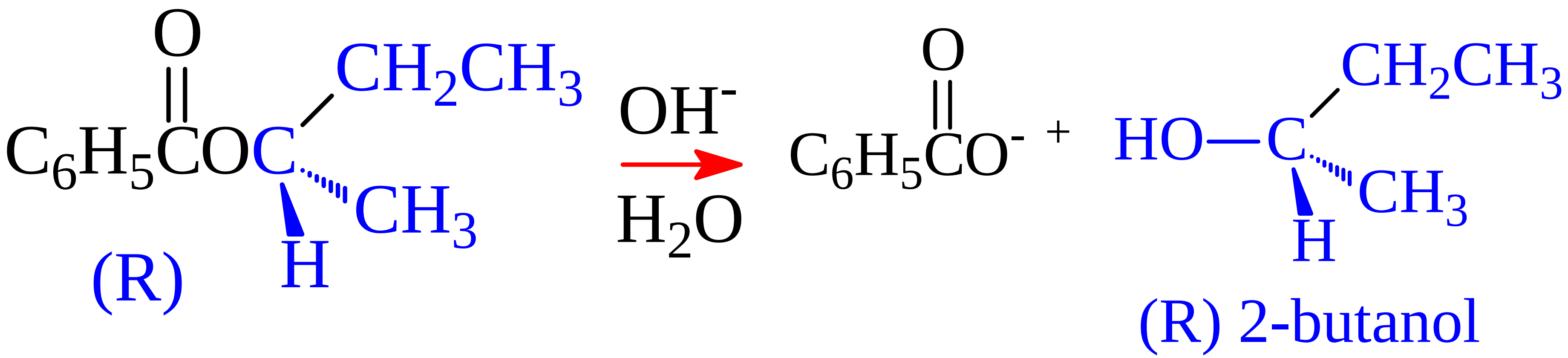


$$CH_3CH_2\overset{\overset{O}{\|}}{C}OCH_2C_6H_5 + \underset{\text{excess}}{H_2O} \xrightarrow{H^+} CH_3CH_2\overset{\overset{O}{\|}}{C}OH + C_6H_5CH_2OH$$



$$C_6H_5\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow[H_2O]{OH^-} C_6H_5\overset{\overset{O}{\|}}{C}O^- + CH_3CH_2OH$$

$$C_6H_5\overset{\overset{O}{\|}}{C}O^- \xrightarrow{H^+} C_6H_5\overset{\overset{O}{\|}}{C}OH$$

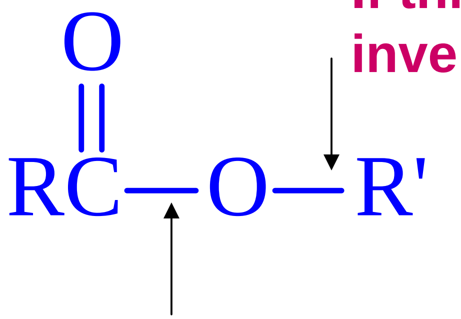


(R)

(R) 2-butanol

If this bond cleaved ➔ racemization or inversion of configuration is produced

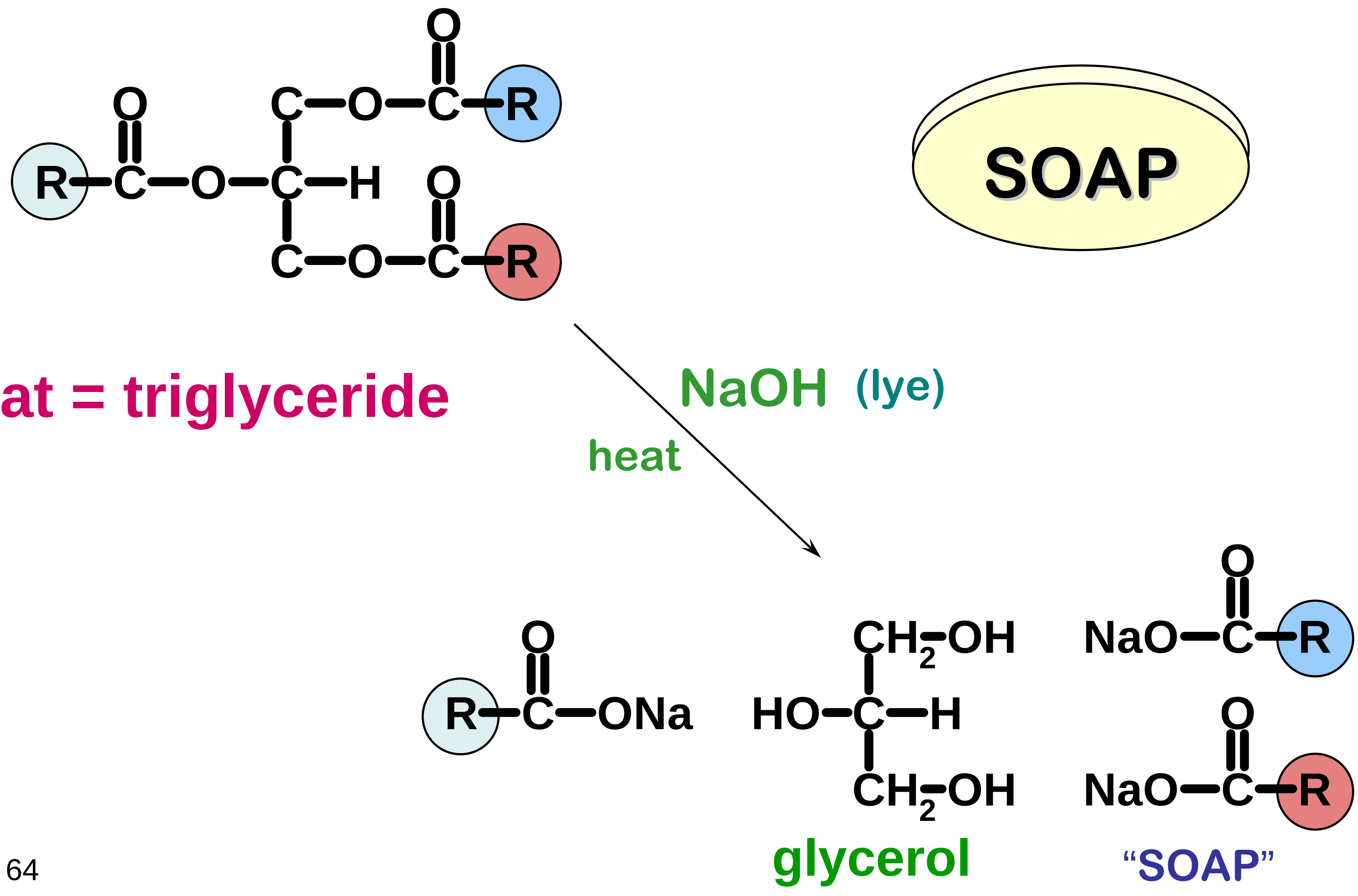
suggest:



$$R\overset{\overset{O}{\|}}{C}-O-R'$$

This bond is cleaved

# SAPONIFICATION



SOAP

fat = triglyceride

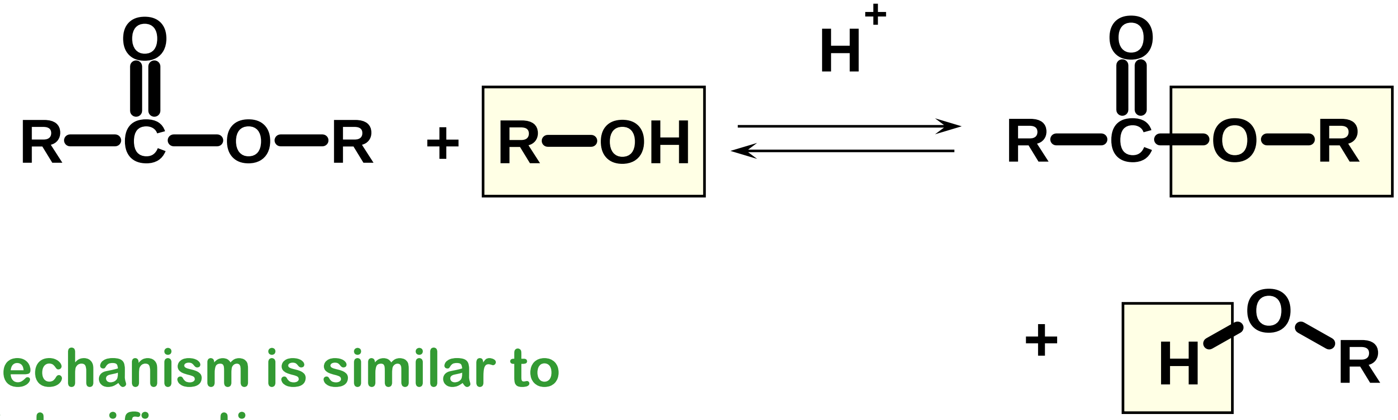
NaOH (lye)

heat

glycerol

“SOAP”

# 2- Transesterification

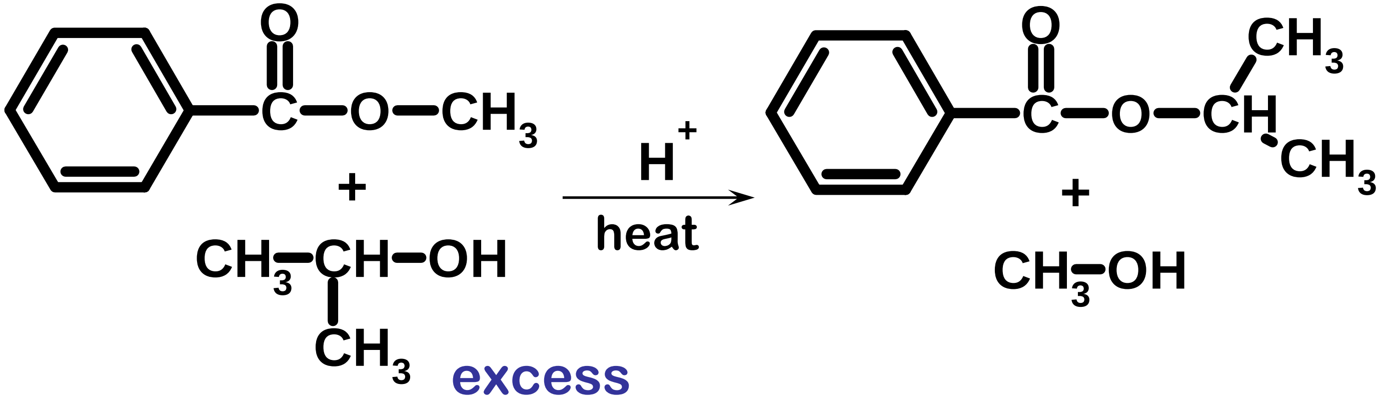


$$R-\overset{\overset{O}{\|}}{C}-O-R + \boxed{R-OH} \underset{}{\overset{H^+}{\rightleftharpoons}} R-\overset{\overset{O}{\|}}{C}-\boxed{O-R} + \boxed{H}-O-R$$

mechanism is similar to Esterification

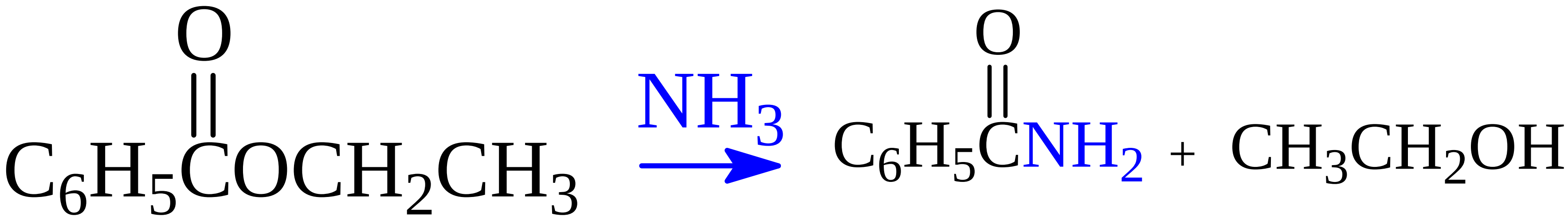
---

**EXAMPLE**

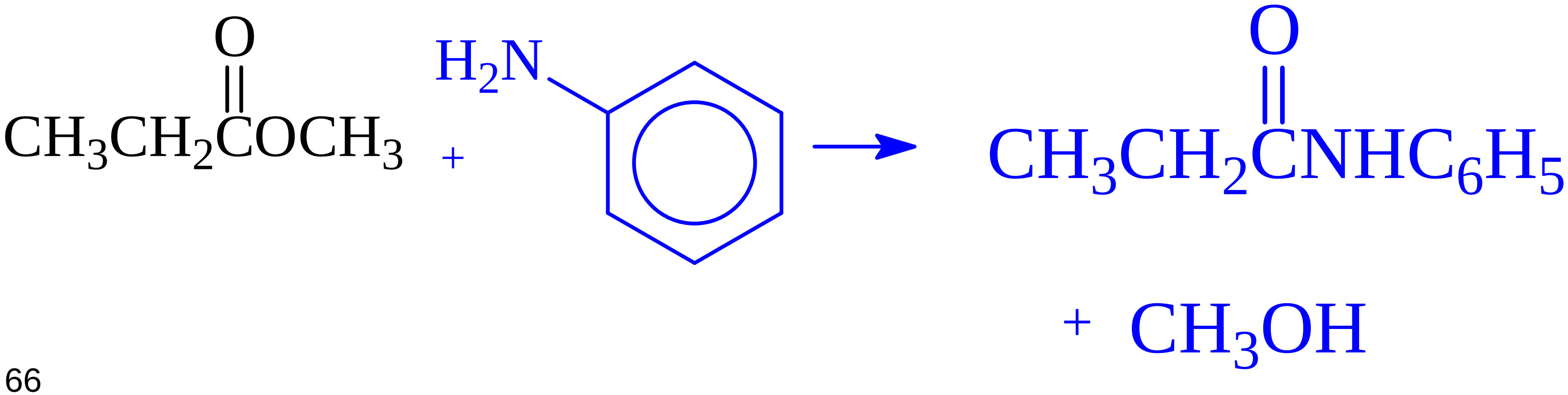


# 3- Reaction with Ammonia

- Esters + ammonia or amines ➔ amides

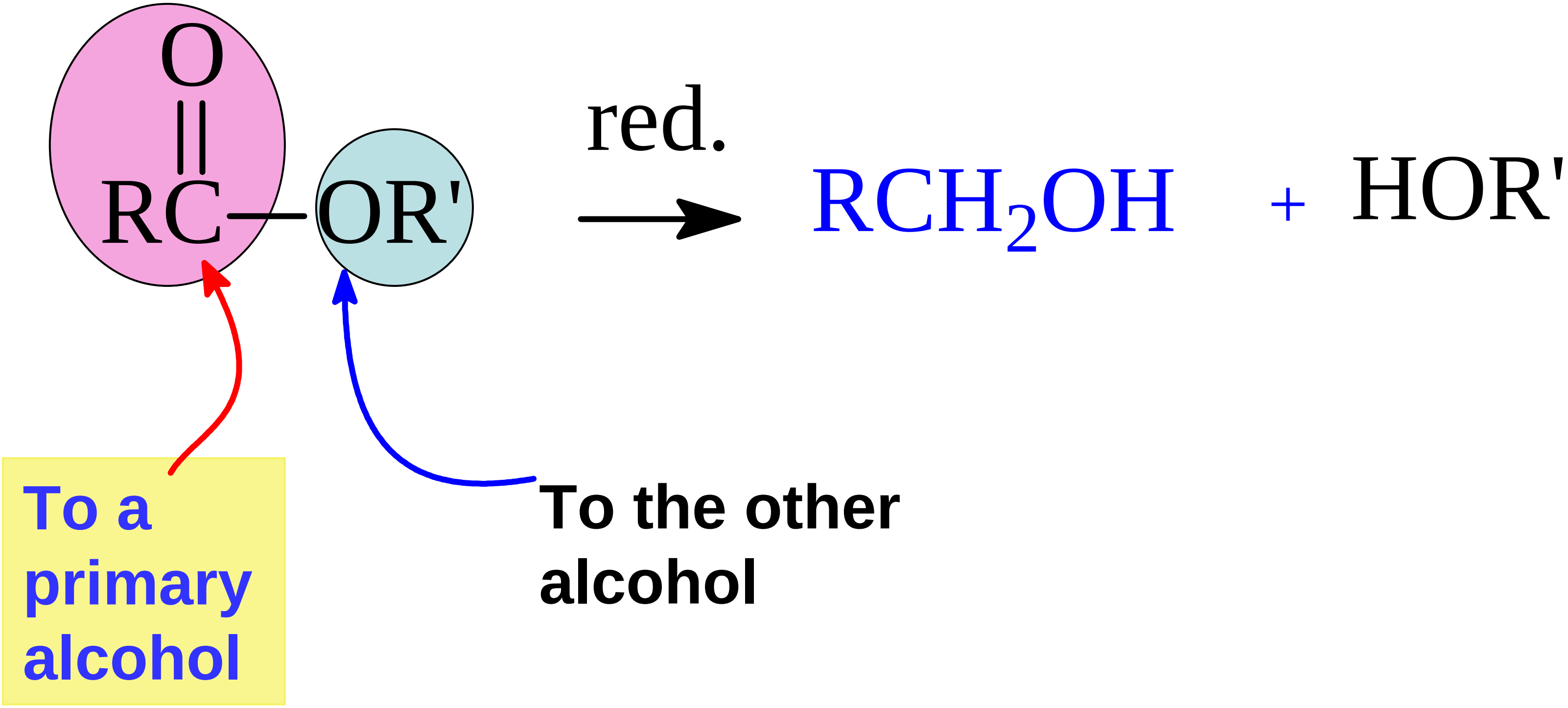


$$C_6H_5\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow{NH_3} C_6H_5\overset{\overset{O}{\|}}{C}NH_2 + CH_3CH_2OH$$



# 4- Reduction

- Esters are reduced to primary alcohols

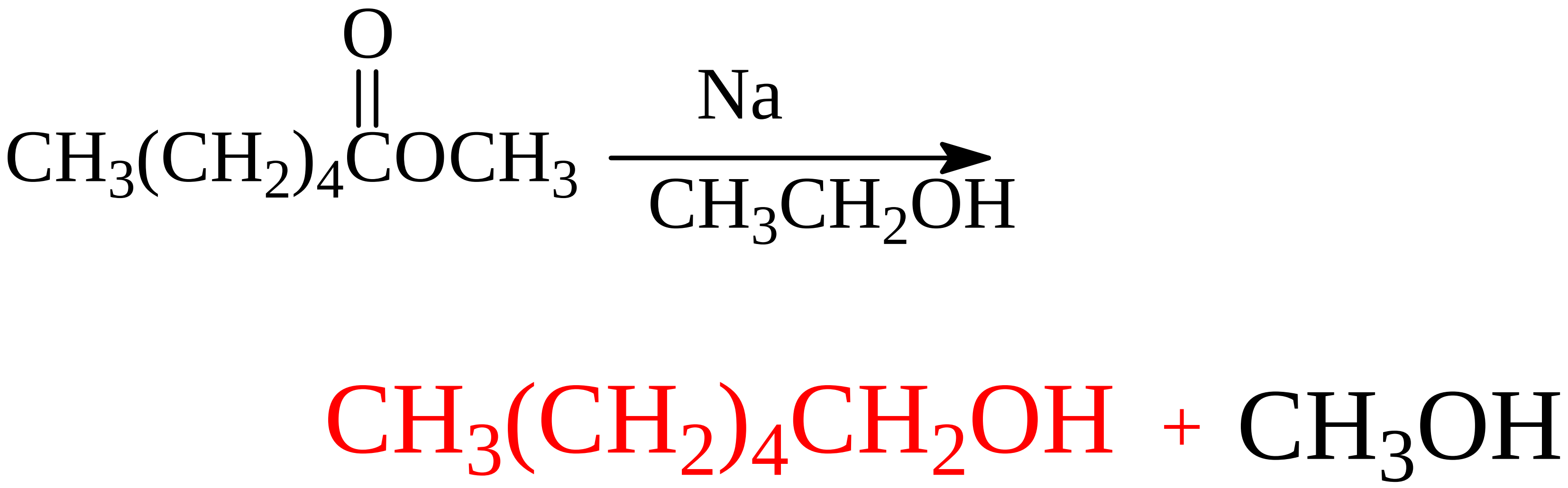


$$\overset{\displaystyle O}{\overset{\|}{RC}}-OR' \xrightarrow{\text{red.}} RCH_2OH + HOR'$$

**To a primary alcohol**

**To the other alcohol**

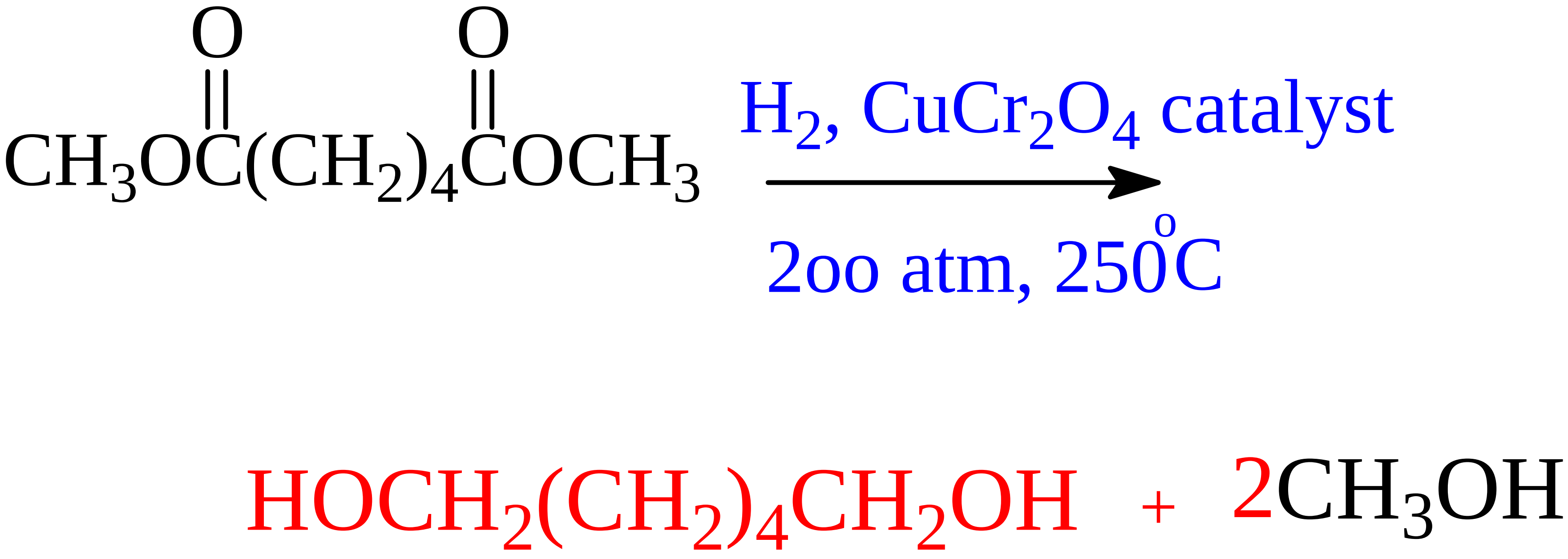
1) Reduction using sodium metal in ethanol.



$$CH_3(CH_2)_4\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow[CH_3CH_2OH]{Na}$$

$$CH_3(CH_2)_4CH_2OH + CH_3OH$$

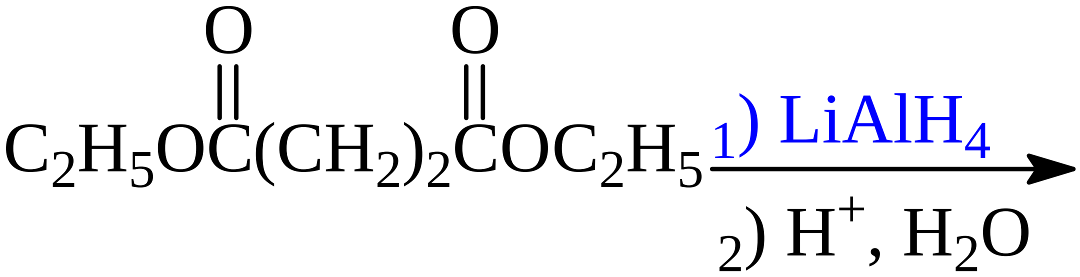
## 2) Reduction using catalytic Hydrogenation



$$CH_3O\overset{\overset{\displaystyle O}{\|}}{C}(CH_2)_4\overset{\overset{\displaystyle O}{\|}}{C}OCH_3 \xrightarrow[\text{2oo atm, 250}^{o}\text{C}]{H_2,\ CuCr_2O_4\ \text{catalyst}}$$

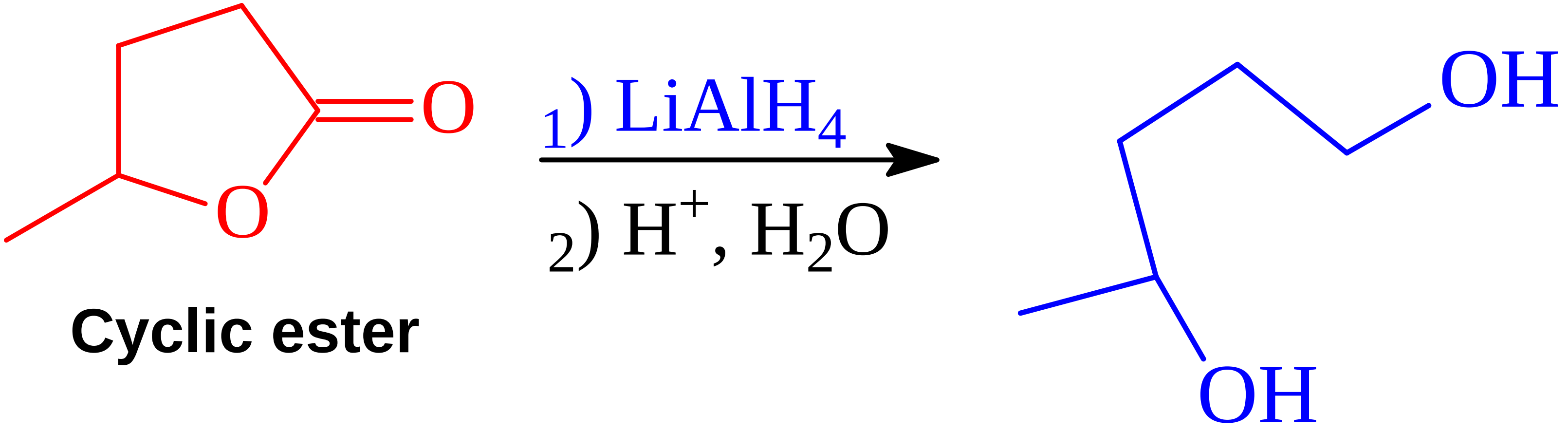
$$HOCH_2(CH_2)_4CH_2OH + 2CH_3OH$$

# 3) Reduction using $LiAlH_4$



$$C_2H_5O\overset{O}{\overset{\|}{C}}(CH_2)_2\overset{O}{\overset{\|}{C}}OC_2H_5 \xrightarrow[2)\ H^+,\ H_2O]{1)\ LiAlH_4}$$

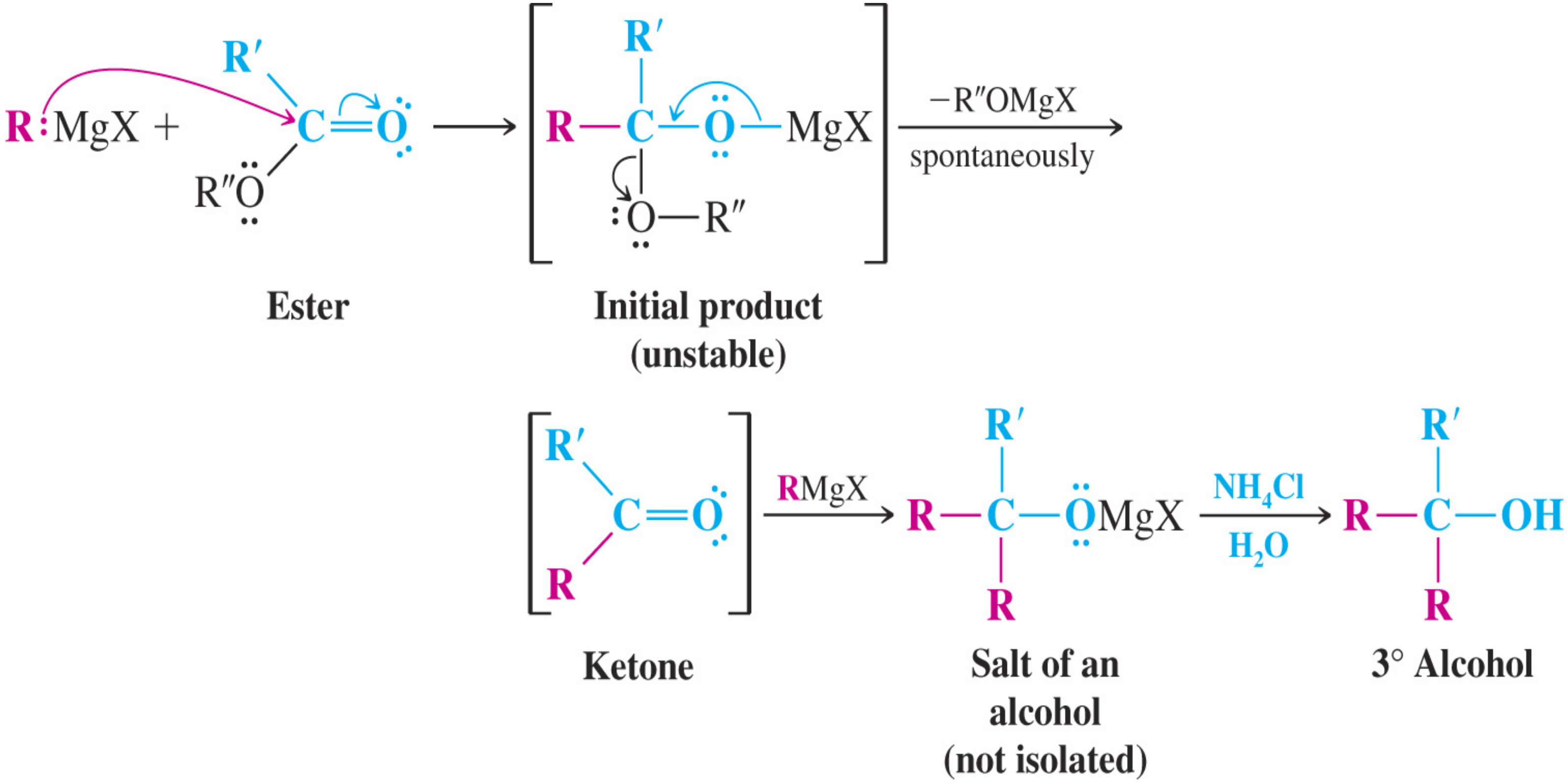
$$HOCH_2(CH_2)_2CH_2OH + 2C_2H_5OH$$



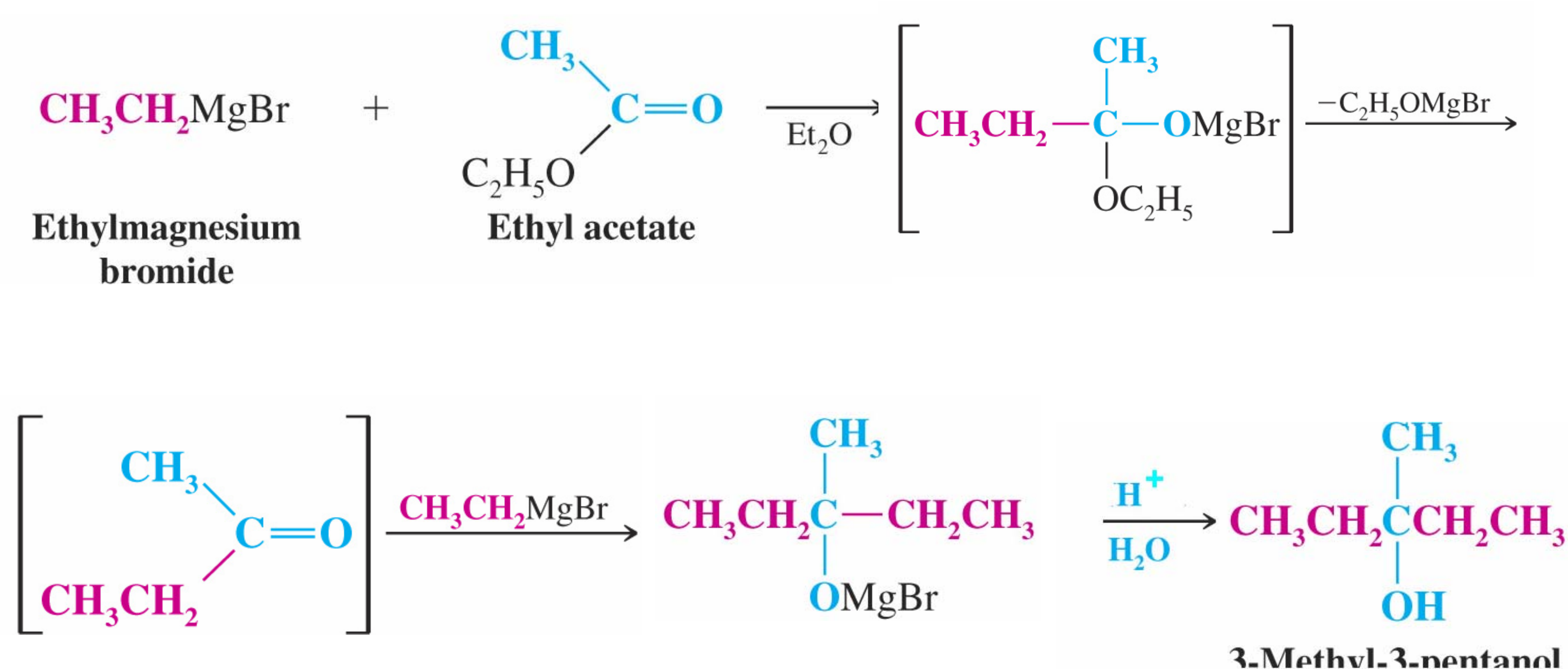
**Cyclic ester**

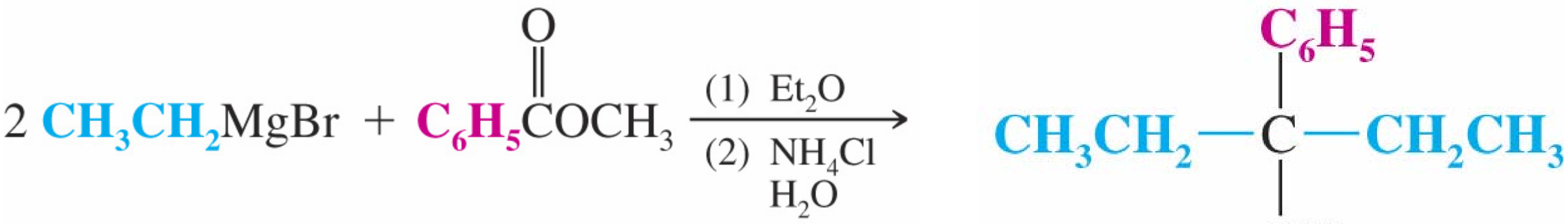
# 5- Reaction with Grignard Reagents

- Esters react with two moles of a Grignard reagent to yield a **tertiary alcohol**



# Example


CH3CH2MgBr
+
CH3
C=O
C2H5O
Ethylmagnesium bromide
Ethyl acetate
Et2O
CH3
CH3CH2—C—OMgBr
OC2H5
−C2H5OMgBr
CH3
C=O
CH3CH2
CH3CH2MgBr
CH3
CH3CH2C—CH2CH3
OMgBr
H+
H2O
CH3
CH3CH2CCH2CH3
OH
3-Methyl-3-pentanol

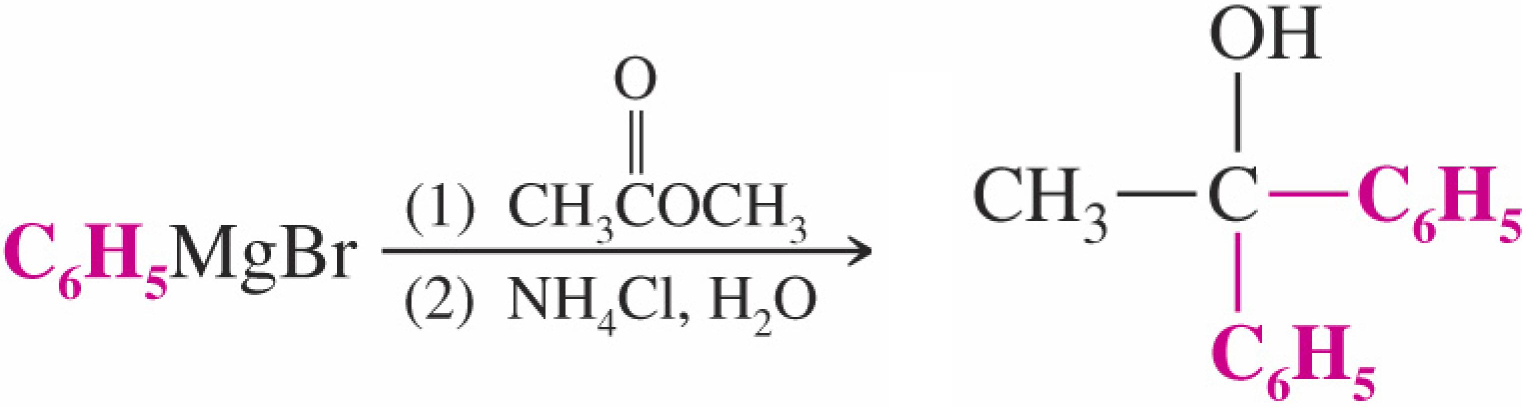


$$2\,CH_3CH_2MgBr + C_6H_5\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow[(2)\ NH_4Cl,\ H_2O]{(1)\ Et_2O} CH_3CH_2-\underset{OH}{\overset{C_6H_5}{C}}-CH_2CH_3$$

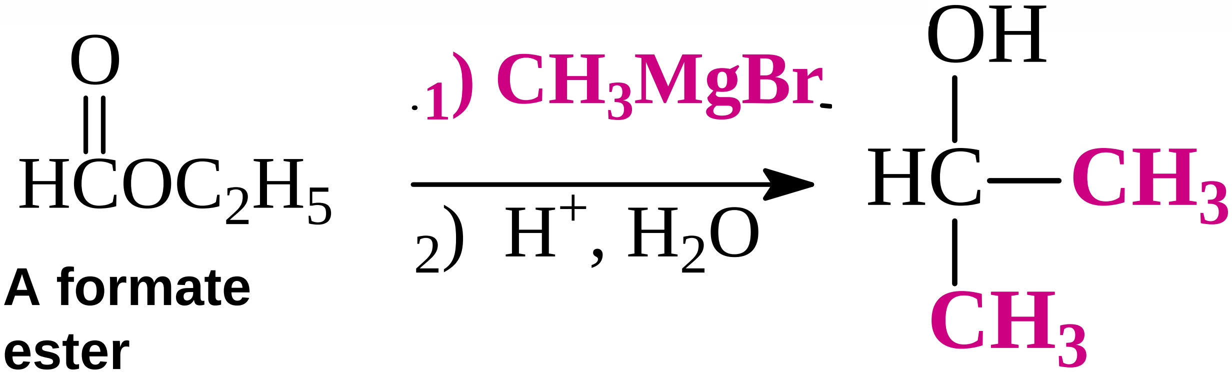
**Ethylmagnesium bromide**

**Methyl benzoate**

**3-Phenyl-3-pentanol**



$$C_6H_5MgBr \xrightarrow[(2)\ NH_4Cl,\ H_2O]{(1)\ CH_3\overset{O}{\overset{\|}{C}}CH_3} CH_3-\underset{C_6H_5}{\overset{OH}{C}}-C_6H_5$$



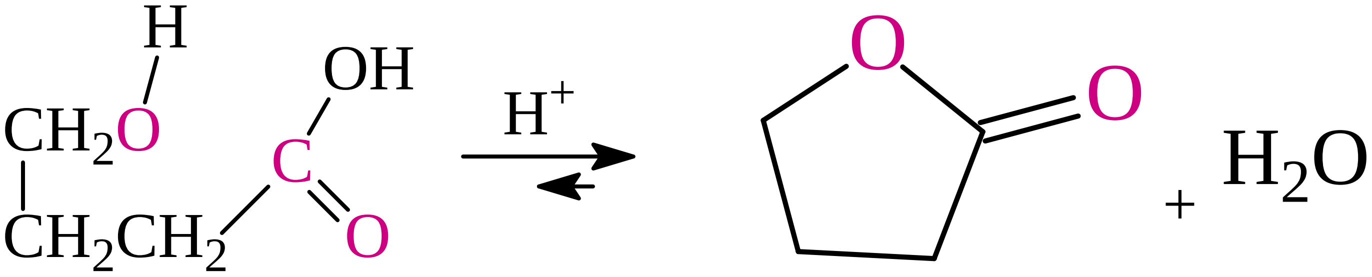
$$H\overset{O}{\overset{\|}{C}}OC_2H_5 \xrightarrow[2)\ H^+,\ H_2O]{1)\ CH_3MgBr} H\underset{CH_3}{\overset{OH}{C}}-CH_3$$

**A formate ester**

**Secondary alcohol**

# Lactones

γ- or δ-Hydroxyacids undergo acid catalyzed reaction to give cyclic esters known as γ**-** or δ-lactones, respectively

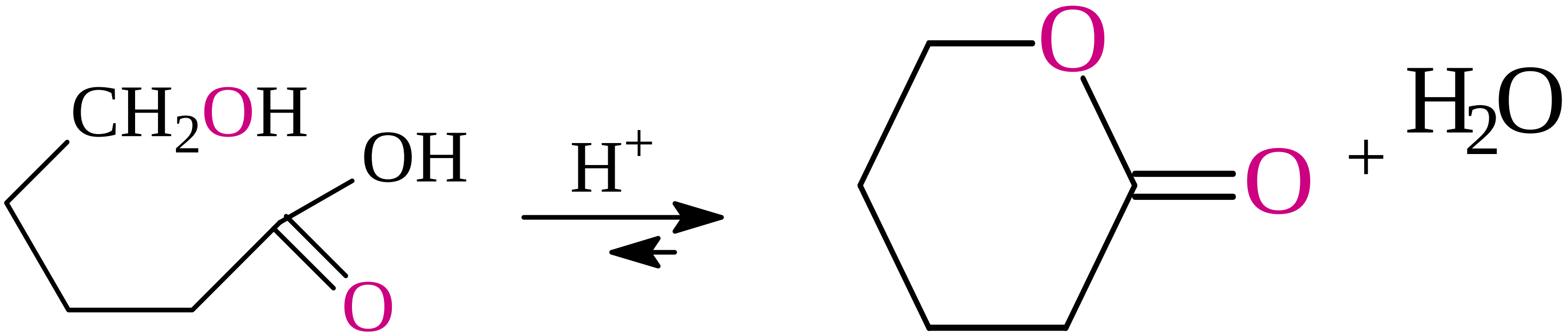


**4-hydroxybutanoic acid lactone**

**4-hydroxybutanoic acid**

**( γ-bytrolactone)**

**γ-hydroxy acid**



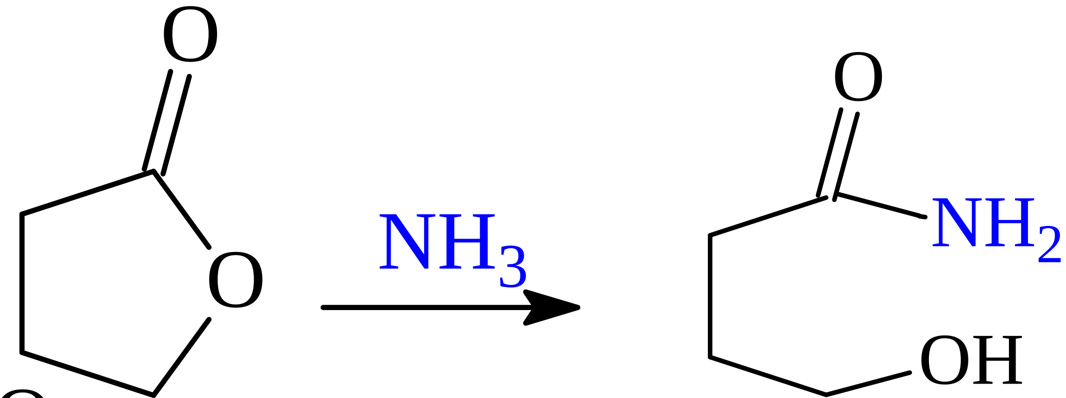
**5-hydroxypentanoic acid lactone**

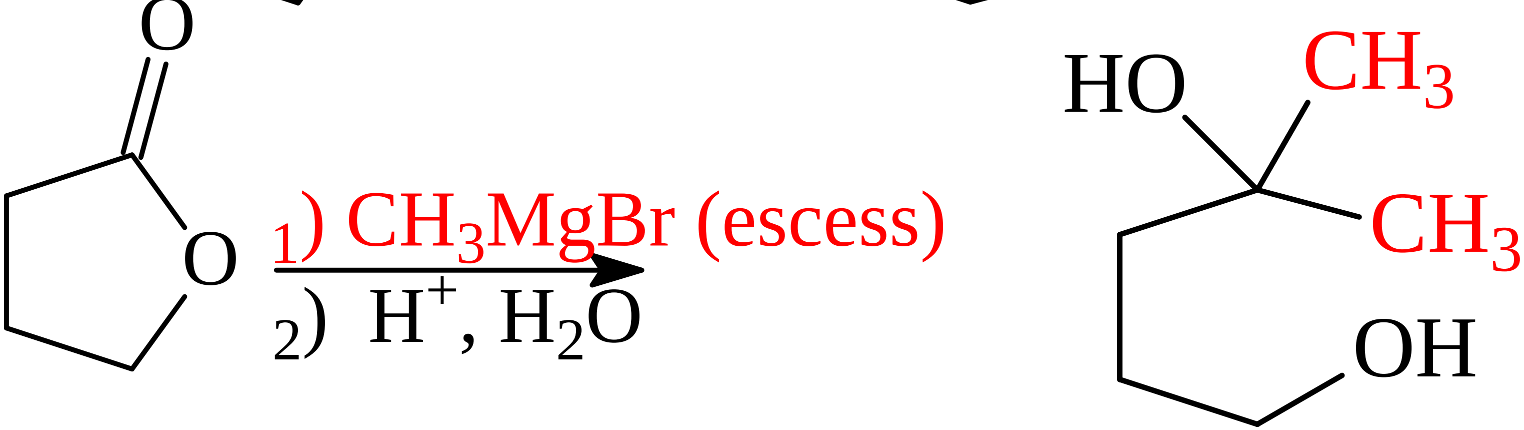
**5-hydroxypentanoic acid**

**δ-lactone**

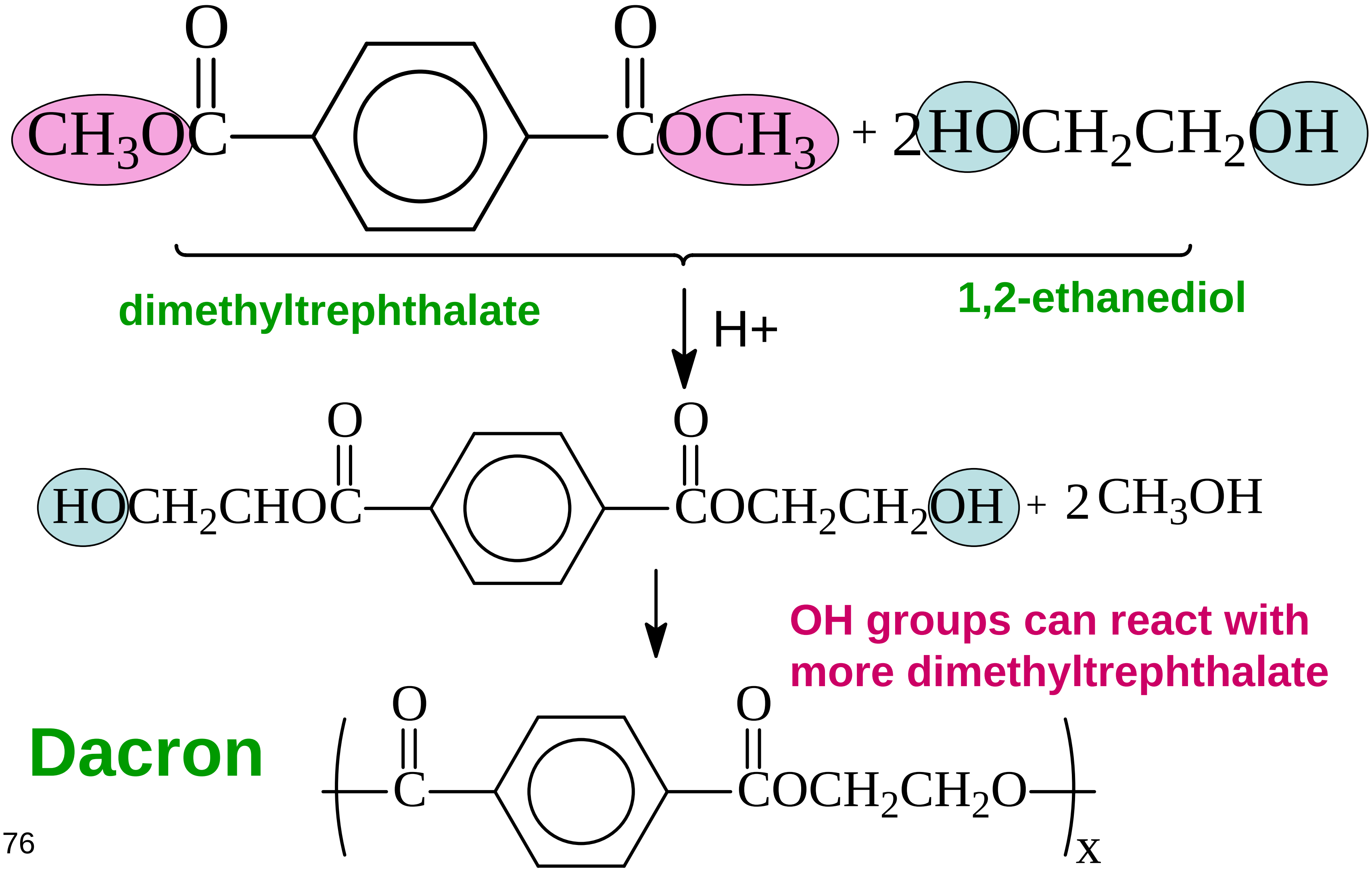
# Reactions of Lactones

- Lactones are cyclic esters and they undergo same reactions of esters





# Polyesters By Transesterification



**dimethyltrephthalate**

H+

**1,2-ethanediol**

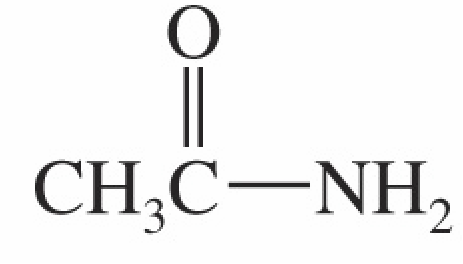
**OH groups can react with more dimethyltrephthalate**

**Dacron**

# Amides

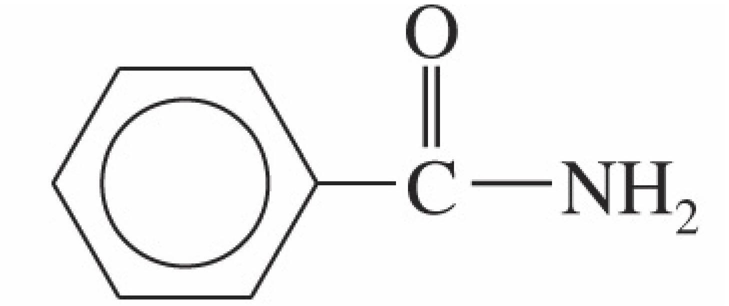
# Nomenclature of Amides

- Amides with no substituents on nitrogen are named by replacing ***-ic acid*** or **–oic acid** in the name with **amide.**

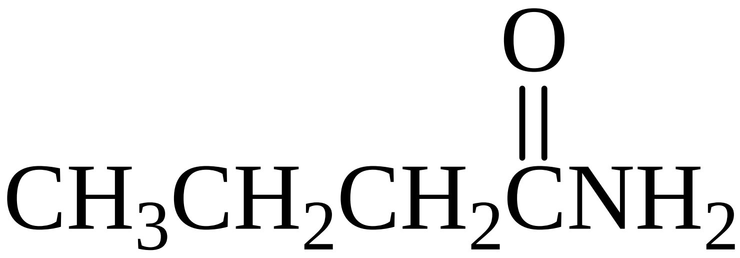


$$CH_3\overset{\overset{\Large O}{\|}}{C}{-}NH_2$$

**Acetamide**
**(ethanamide)**



**Benzamide**



$$CH_3CH_2CH_2\overset{\overset{\Large O}{\|}}{C}NH_2$$

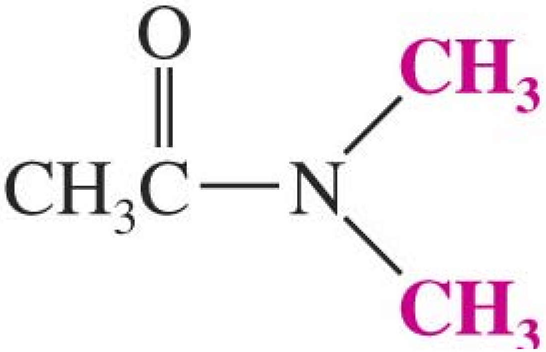
Butanamide

- Groups on the nitrogen are named as substitutents and are given the prefix *N*- or *N*,*N*-

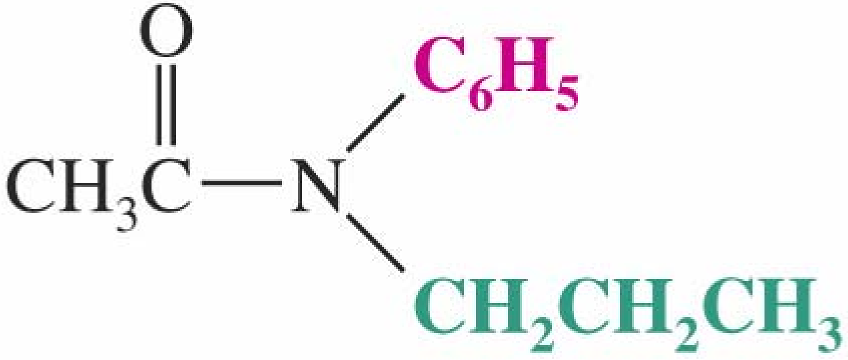
$CH_3\overset{O}{\overset{\|}{C}}{-}NHC_2H_5$

***N*-Ethylacetamide**

**N-Ethylethanamide**

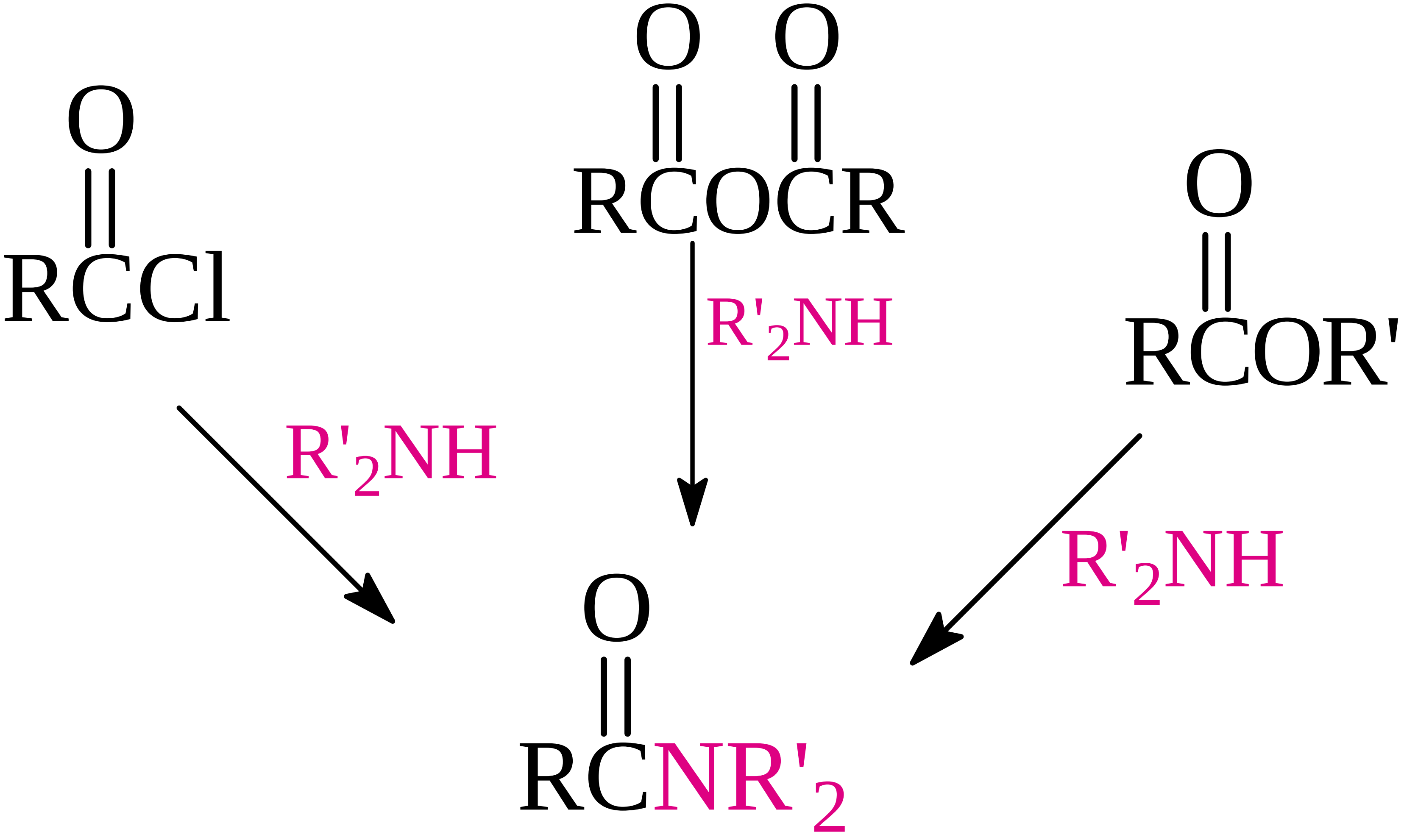


***N*,*N*-Dimethylacetamide**



***N*-Phenyl-*N*-propylacetamide**

# Preparation of amides



$$\mathrm{R\overset{O}{\overset{\|}{C}}Cl} \xrightarrow{R'_2NH} \mathrm{R\overset{O}{\overset{\|}{C}}NR'_2}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R} \xrightarrow{R'_2NH} \mathrm{R\overset{O}{\overset{\|}{C}}NR'_2}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}OR'} \xrightarrow{R'_2NH} \mathrm{R\overset{O}{\overset{\|}{C}}NR'_2}$$

**Amide**

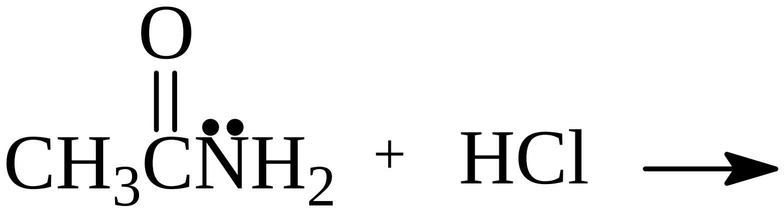
# Reactions of Amides

- Amides are not basic.

$CH_3NH_2 \ + \ HCl \rightarrow \ CH_3NH_3^+Cl^-$

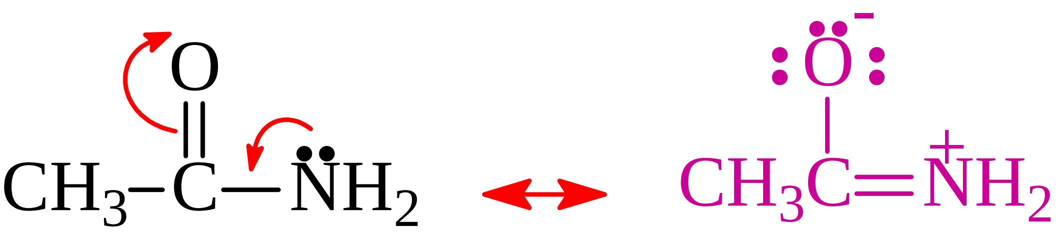
**Methyl amine**

**Methylammonium chloride ( salt)**



$CH_3\overset{\overset{O}{\|}}{C}\ddot{N}H_2 \ + \ HCl \longrightarrow$ **No reaction**

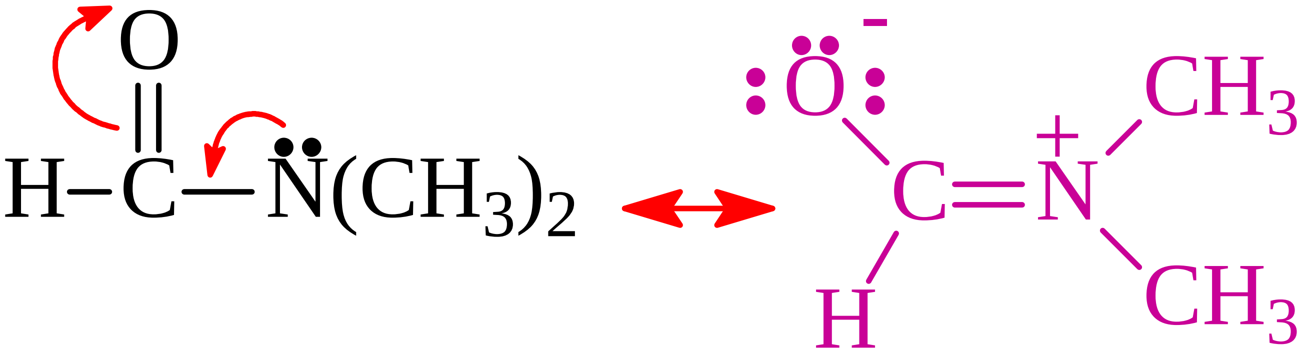
**Due to resonance**



$CH_3-\overset{\overset{O}{\|}}{C}-\ddot{N}H_2 \longleftrightarrow CH_3\overset{\overset{:\ddot{O}:^-}{|}}{C}=\overset{+}{N}H_2$

**Positive N → not basic**

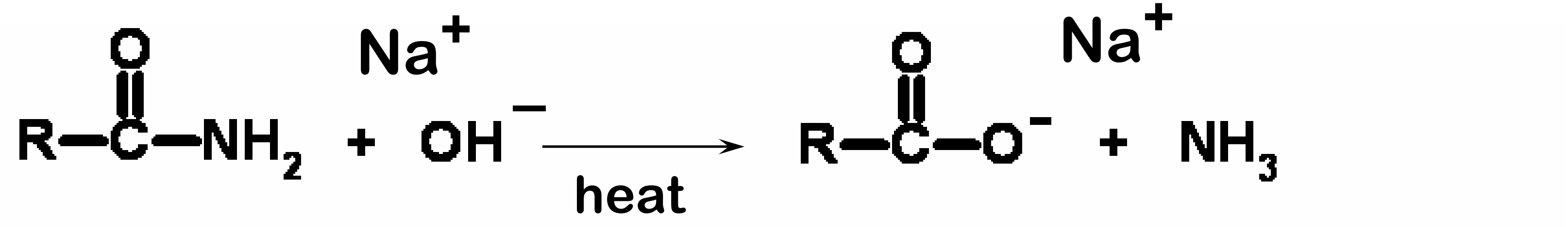
# Evidence for resonance participation



**The two methyl groups are not equivalent → NMR shows two singlets**

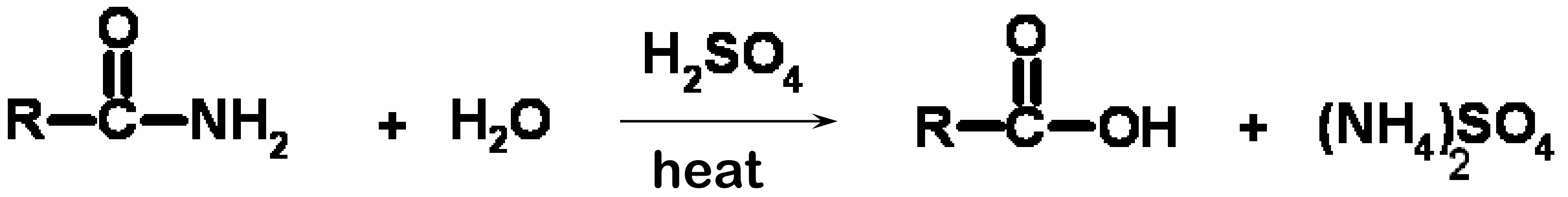
# 1- Hydrolysis of Amides

**Basic Solution**



$$R-\overset{O}{\overset{\Vert}{C}}-NH_2 + \overset{Na^+}{OH^-} \xrightarrow[heat]{} R-\overset{O}{\overset{\Vert}{C}}-\overset{Na^+}{O^-} + NH_3$$

**Acidic Solution**



$$R-\overset{O}{\overset{\Vert}{C}}-NH_2 + \underset{excess}{H_2O} \xrightarrow[heat]{H_2SO_4} R-\overset{O}{\overset{\Vert}{C}}-OH + (NH_4)_2SO_4$$

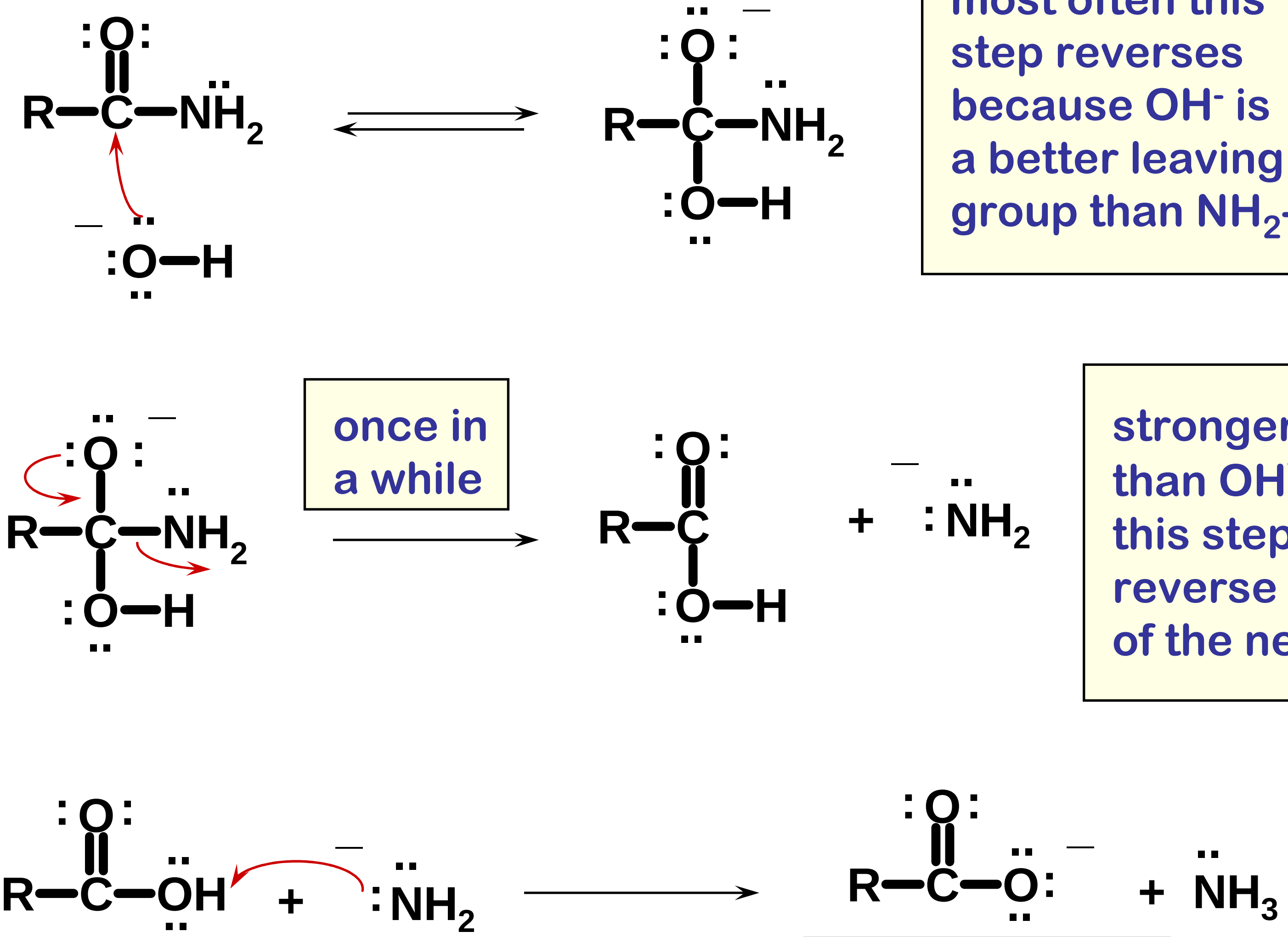
excess

**Hydrolysis requires strong acid or base and heating under reflux.**

# Base-Promoted Hydrolysis of a Amide

## MECHANISM

**NaOH**



most often this step reverses because $OH^-$ is a better leaving group than $NH_2^-$

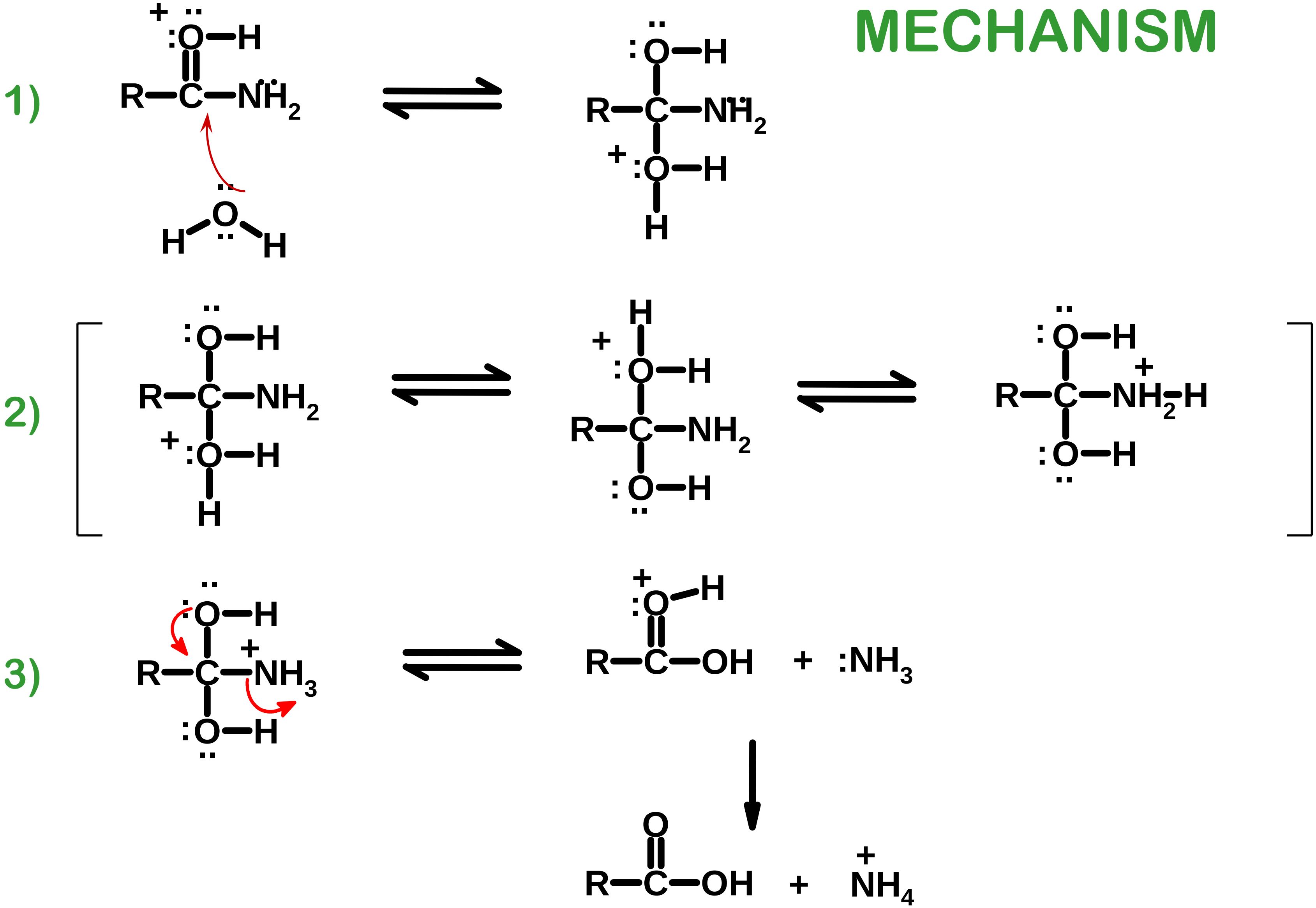
once in a while

stronger base than $OH^-$, but this step doesn't reverse because of the next one

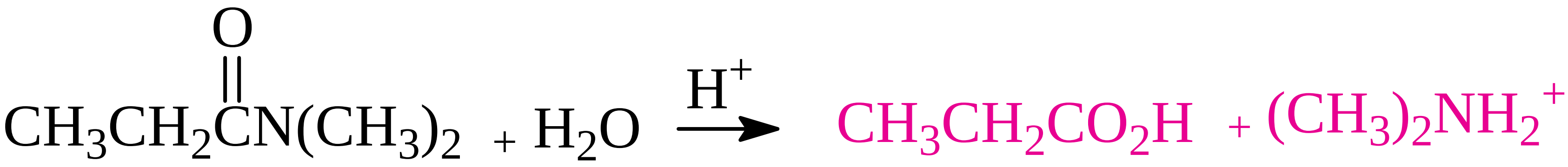
accumulates

# Acid-catalyzed Hydrolysis of a Amide

**MECHANISM**



# Examples

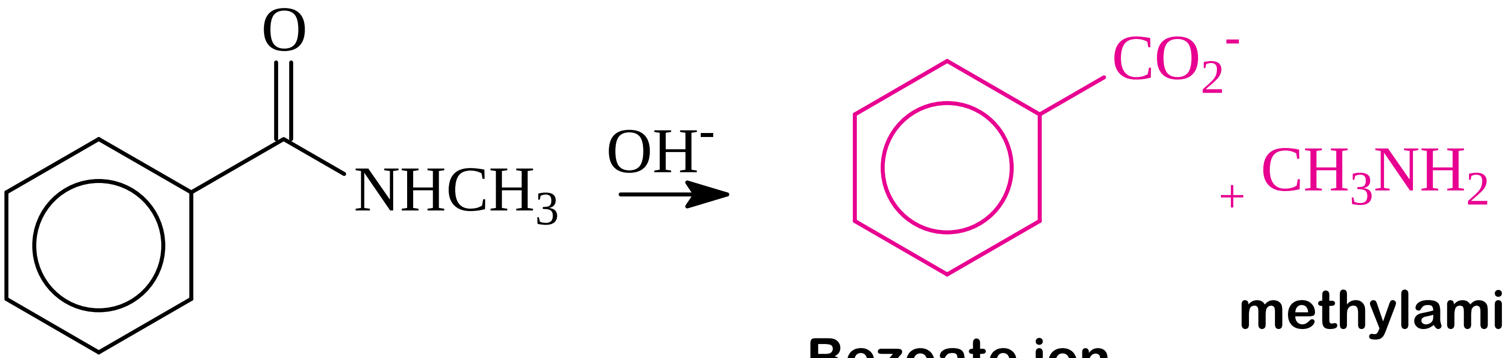


$$\mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}N(CH_3)_2 + H_2O \xrightarrow{H^+} CH_3CH_2CO_2H + (CH_3)_2NH_2^+}$$

**N,N-dimethylpropanamide**

**Propanoic acid**

**Dimethyl ammonium ion**



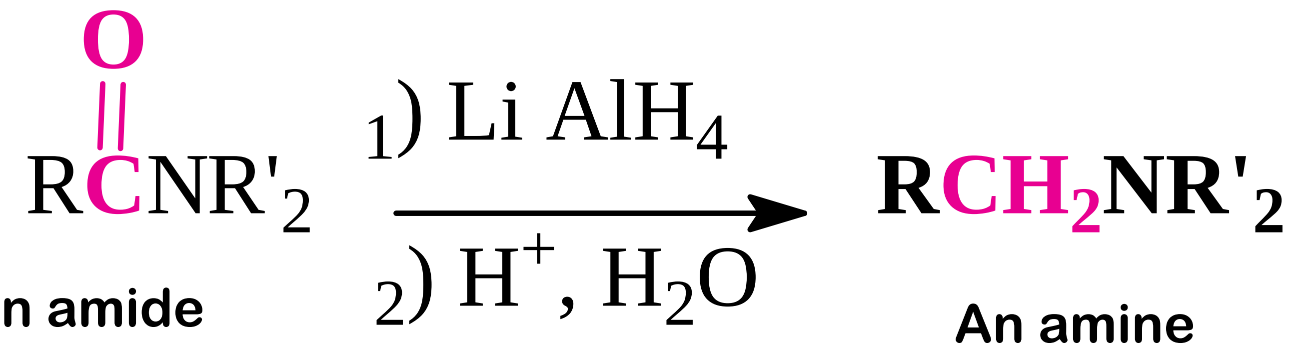
**Bezoate ion**

**methylamine**

**N-methylbenzamide**

# Reduction

**General**

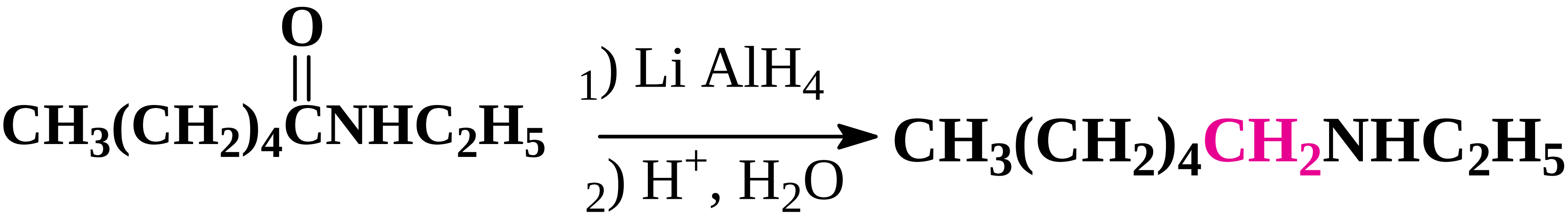


$$R\overset{\overset{O}{\|}}{C}NR'_2 \xrightarrow[2)\ H^+,\ H_2O]{1)\ Li\ AlH_4} RCH_2NR'_2$$

**An amide**

**An amine**

**example**

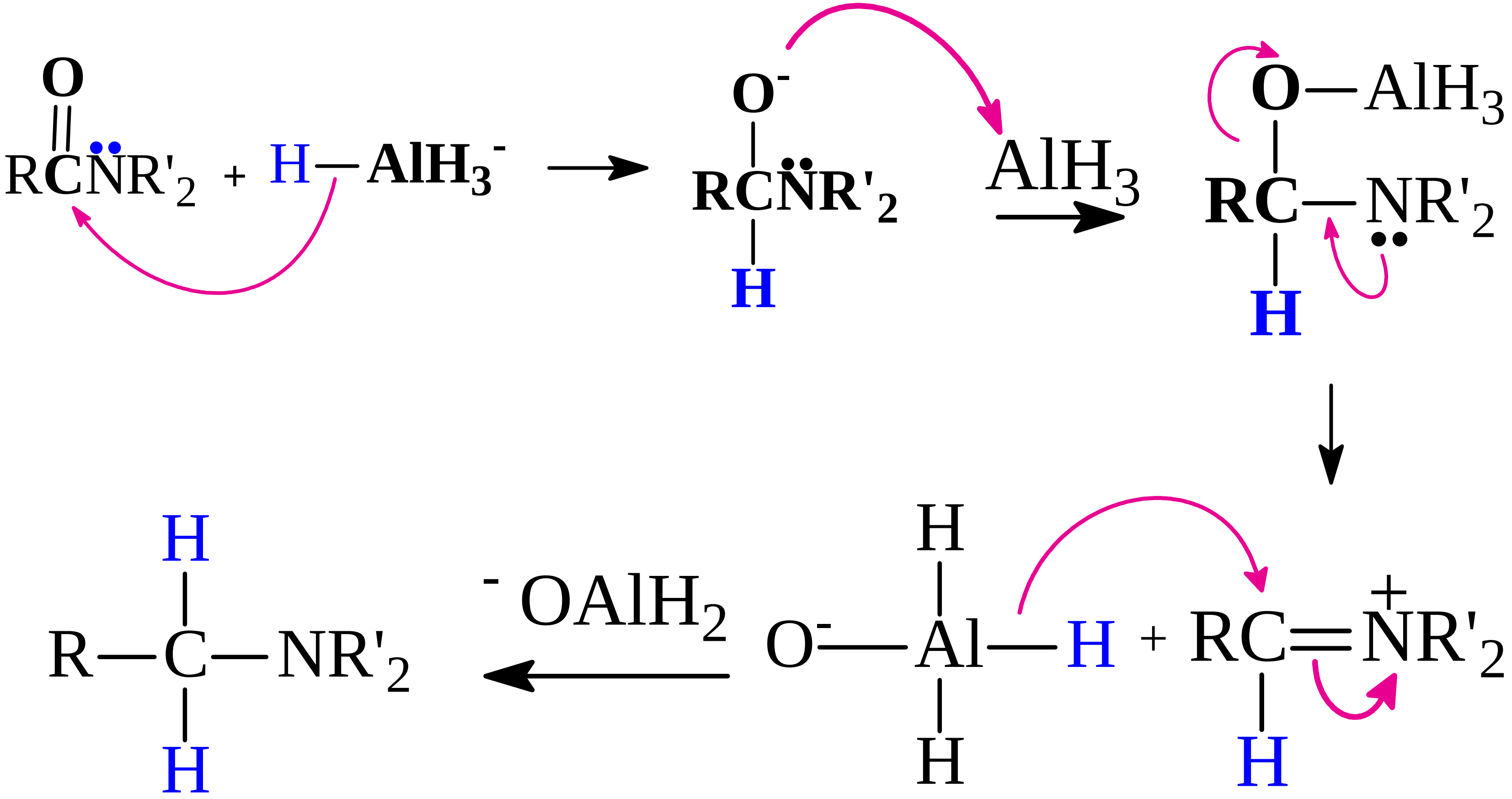


$$CH_3(CH_2)_4\overset{\overset{O}{\|}}{C}NHC_2H_5 \xrightarrow[2)\ H^+,\ H_2O]{1)\ Li\ AlH_4} CH_3(CH_2)_4CH_2NHC_2H_5$$

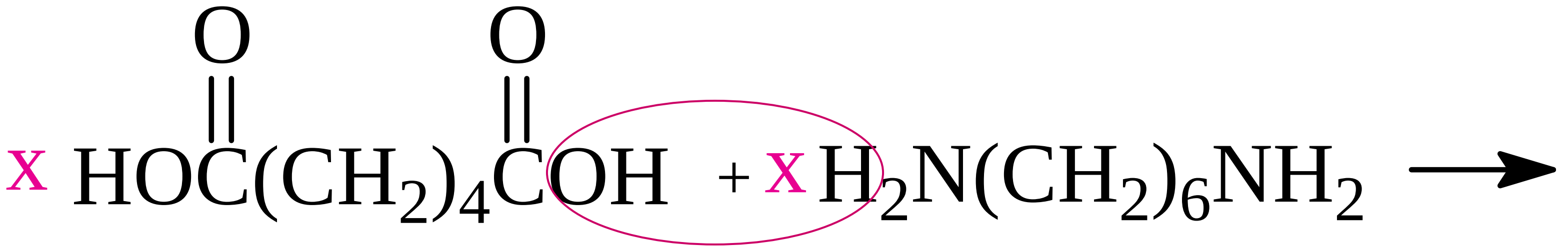
**N-ethylhexanamide**

**N-ethyl hexylamine**

# Reduction Mechanism



# Polyamides



$$x\ \mathrm{HO}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}(\mathrm{CH_2})_4\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OH} + x\ \mathrm{H_2N(CH_2)_6NH_2} \longrightarrow$$

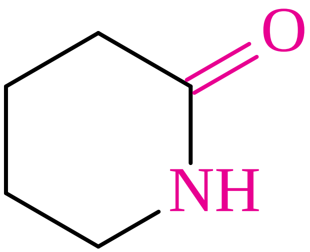
**Hexanedioic acid** **1,6-hexanediamine**

$$-\!\!\left[\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}(\mathrm{CH_2})_4\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{NH(CH_2)_6NH}\right]_x\!\!-$$

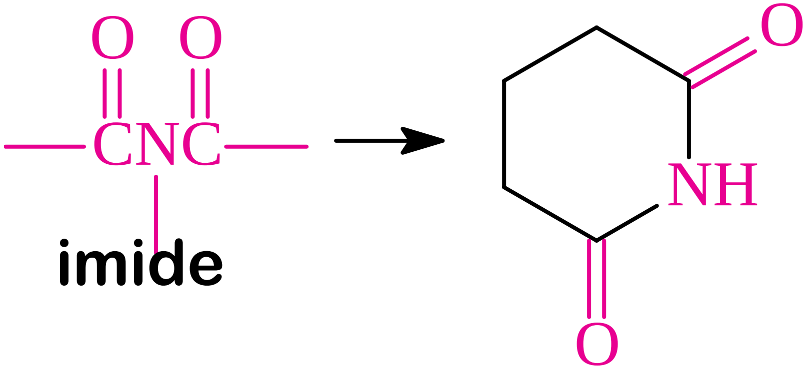
**nylon 6,6**

polyamide

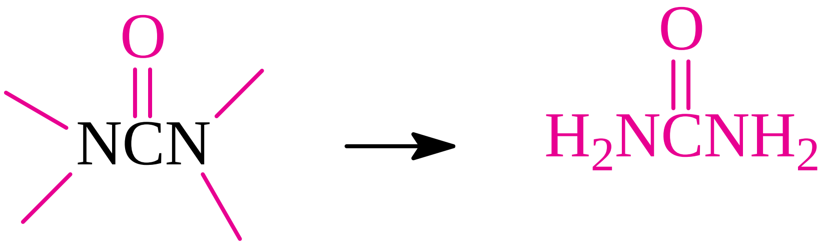
# Compounds Related to amides



**Lactam = cyclic amide**

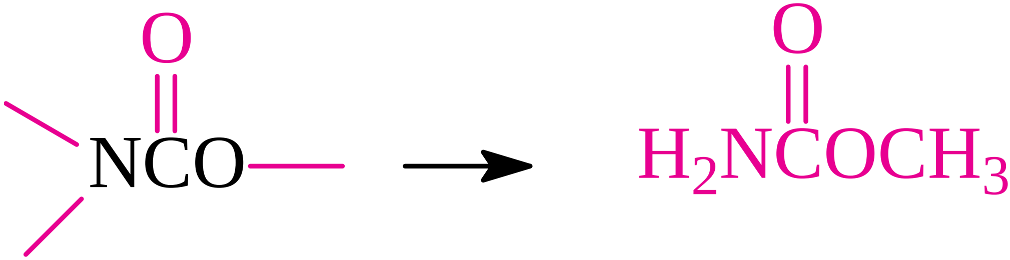


**imide**



$H_2N\overset{O}{\overset{\|}{C}}NH_2$

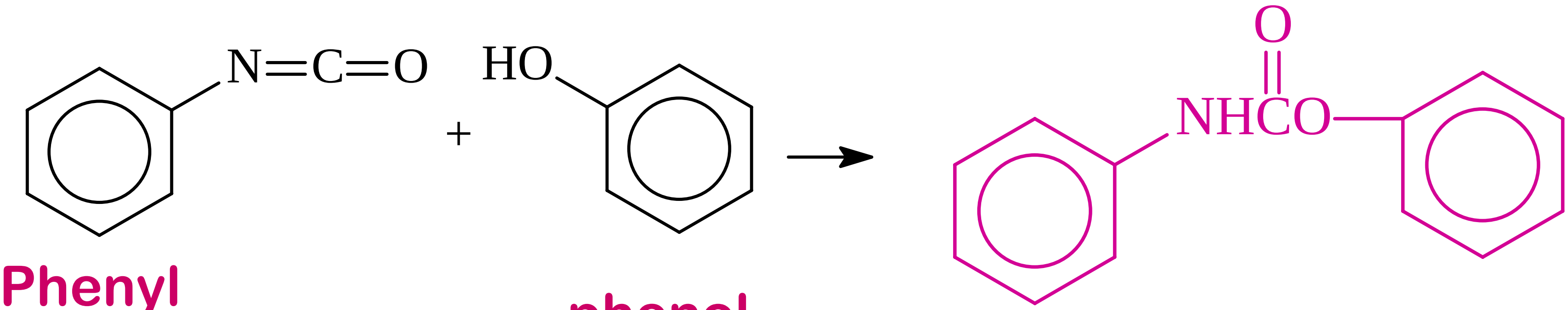
**UREA**



$H_2N\overset{O}{\overset{\|}{C}}OCH_3$

**Carbamate, or urethane**

# Carbamates are prepared from isocyanates and alcohols

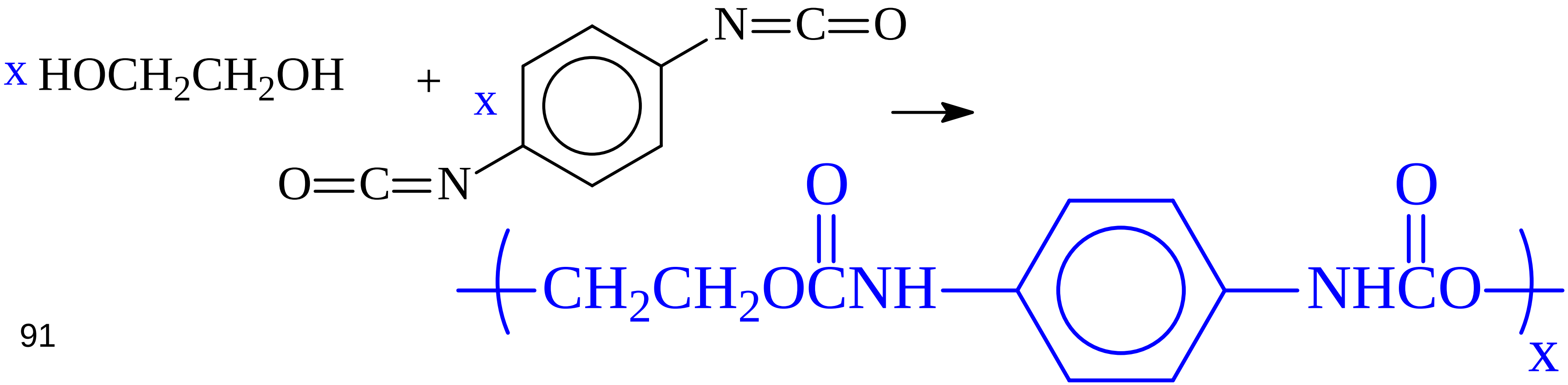


**Phenyl isocyanate**

**phenol**

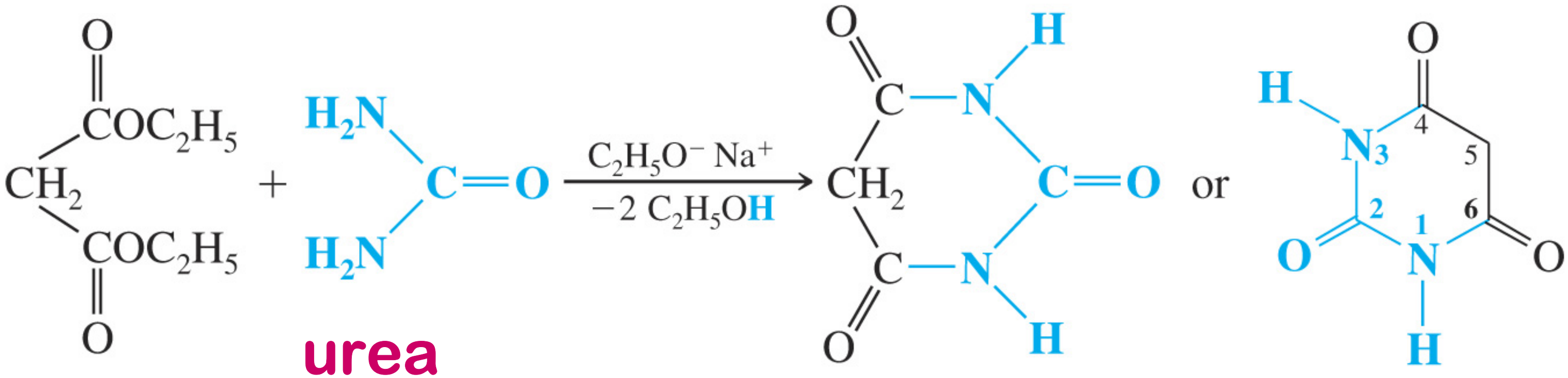
**Phenyl N-phenyl carbamate**

**polyurethanes**



# Barbiturates

- Reaction of diethyl malonate with urea in the presence of sodium ethoxide produces barbituric acid

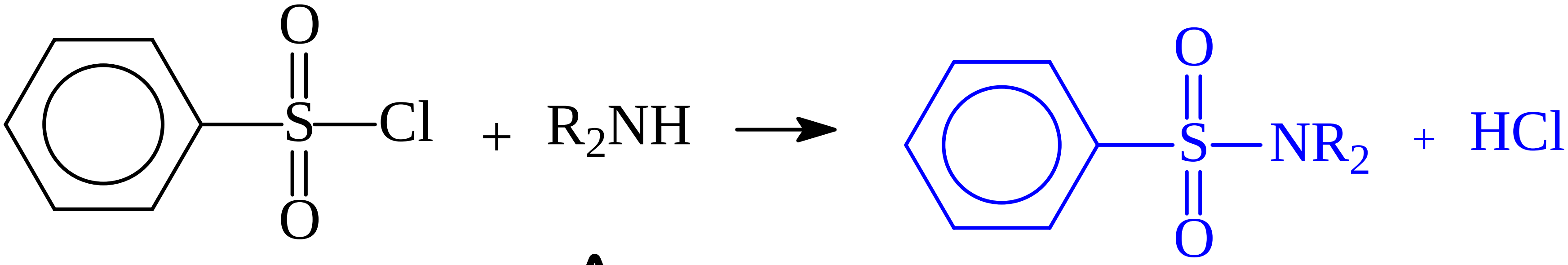


urea

Barbituric acid

Used as sedatives

# Sulfonamides or Sulfa drugs



**Benzenesulfonyl chloride**

**An amine**

**a sulfonamide**

**Nitrogen is attached to sulfonyl group**

# NITRILES

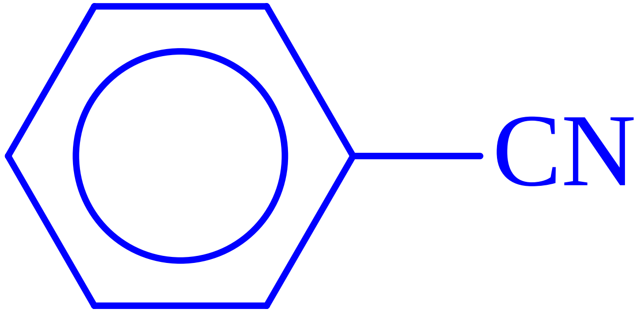
# Nomenclature

**IUPAC:** The alkane name is suffixed with nitrile

$CH_3C{\equiv}N$

ethanenitrile

Trivial:
acetonitrile



benzenecarbonitrile

Trivial: benzonitrile

# Preparation of Nitriles

## 1) $S_N2$ Reaction

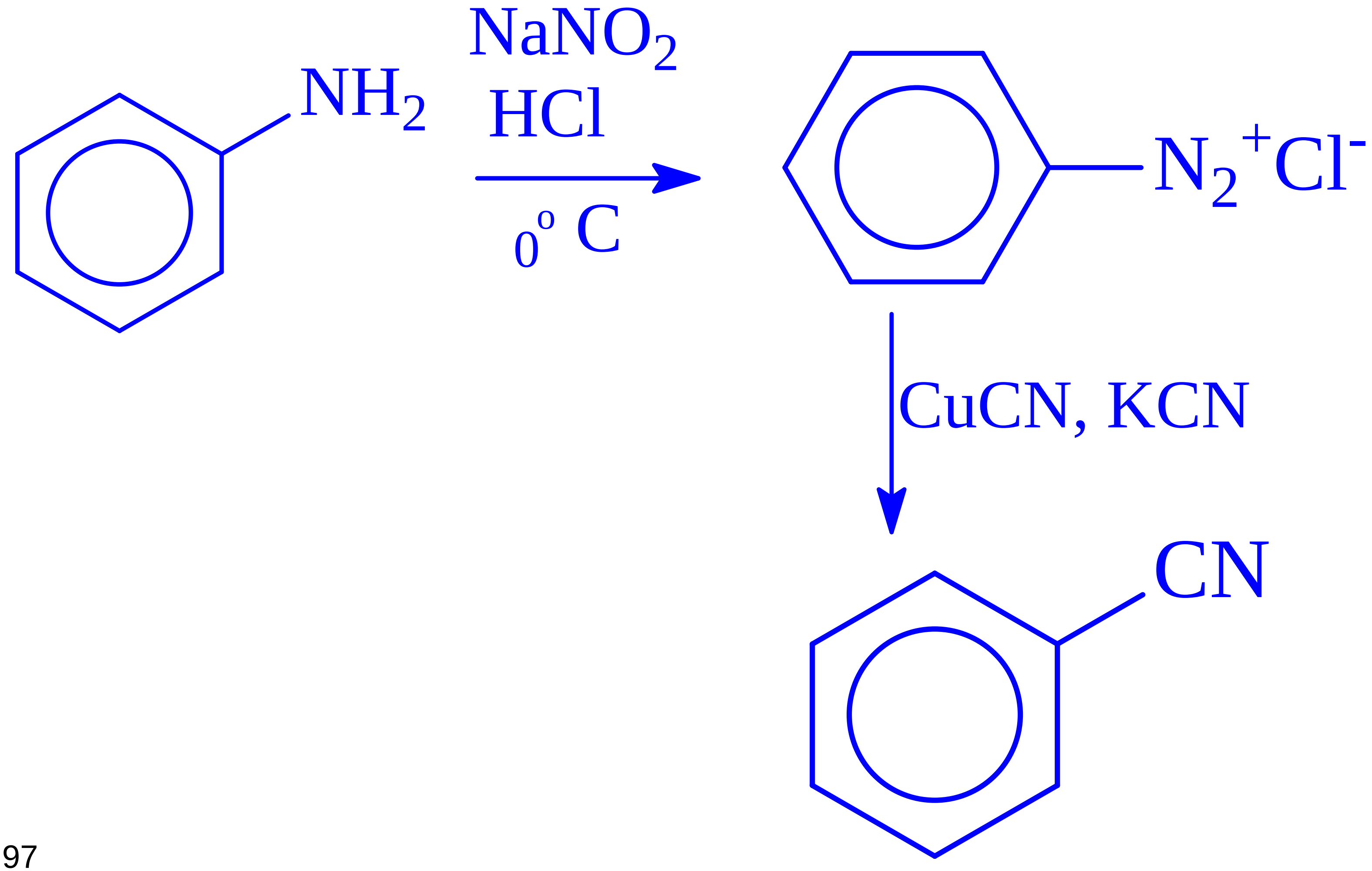
$$R-CH_2-Cl + :\overset{-}{C}\equiv N: \longrightarrow R-CH_2-C\equiv N: + Cl^-$$

$$HOCH_2CH_2Cl \xrightarrow{NaCN} HOCH_2CH_2CN$$

**3-Hydroxy-propanenitrile**

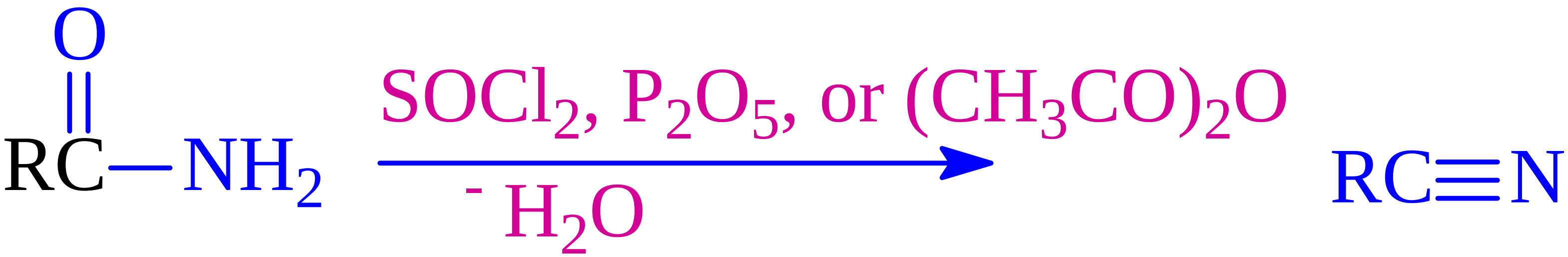
$$BrCH_2CH_2CH_2Br \xrightarrow{NaCN} NCCH_2CH_2CH_2CN$$

# 2) Aryl nitriles from diazonium salts



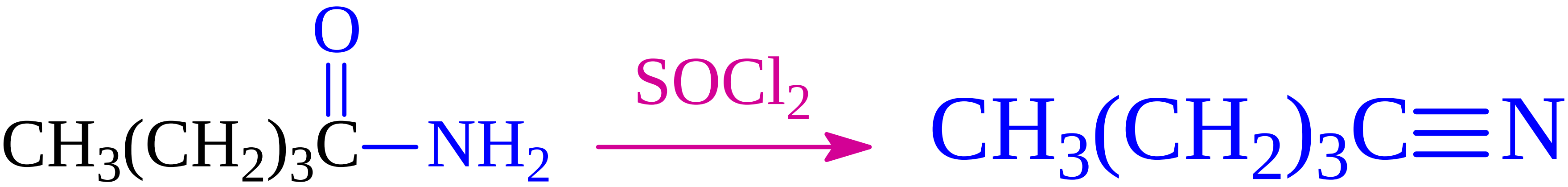
# 3) Nitriles from the Dehydration of Amides

Anitrile can be formed by reaction of an amide with $SOCl_2$ ,phosphorous pentoxide ($P_2O_5$)or boiling acetic anhydride



$$R\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \xrightarrow[-\,H_2O]{SOCl_2,\ P_2O_5,\text{ or }(CH_3CO)_2O} RC\equiv N$$

**A nitrile**



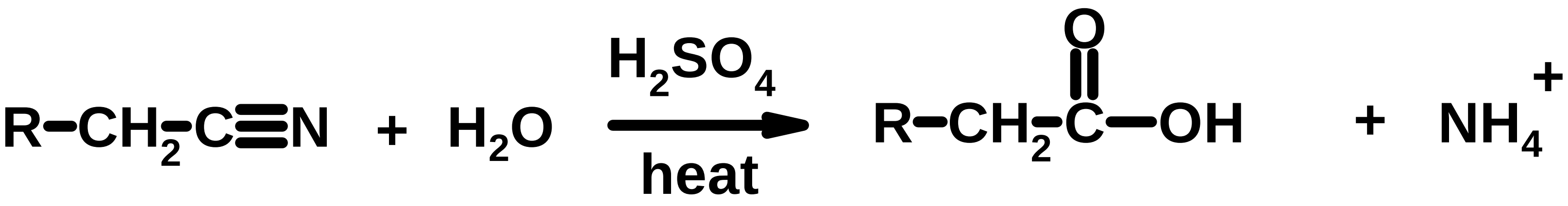
$$CH_3(CH_2)_3\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \xrightarrow{SOCl_2} CH_3(CH_2)_3C\equiv N$$

**pentanenitrile**

# Reactions of Nitriles

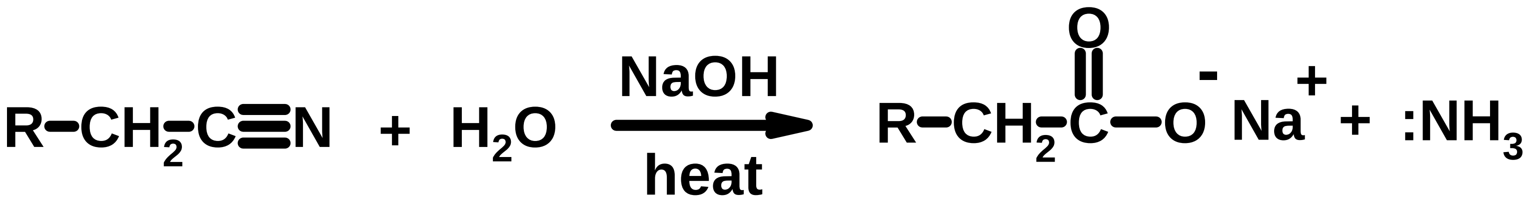
# 1) Hydrolysis of Nitriles

**ACID SOLUTION**



$$R{-}CH_2{-}C{\equiv}N \;+\; H_2O \xrightarrow[\text{heat}]{H_2SO_4} R{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}OH \;+\; NH_4^+$$

**BASIC SOLUTION**

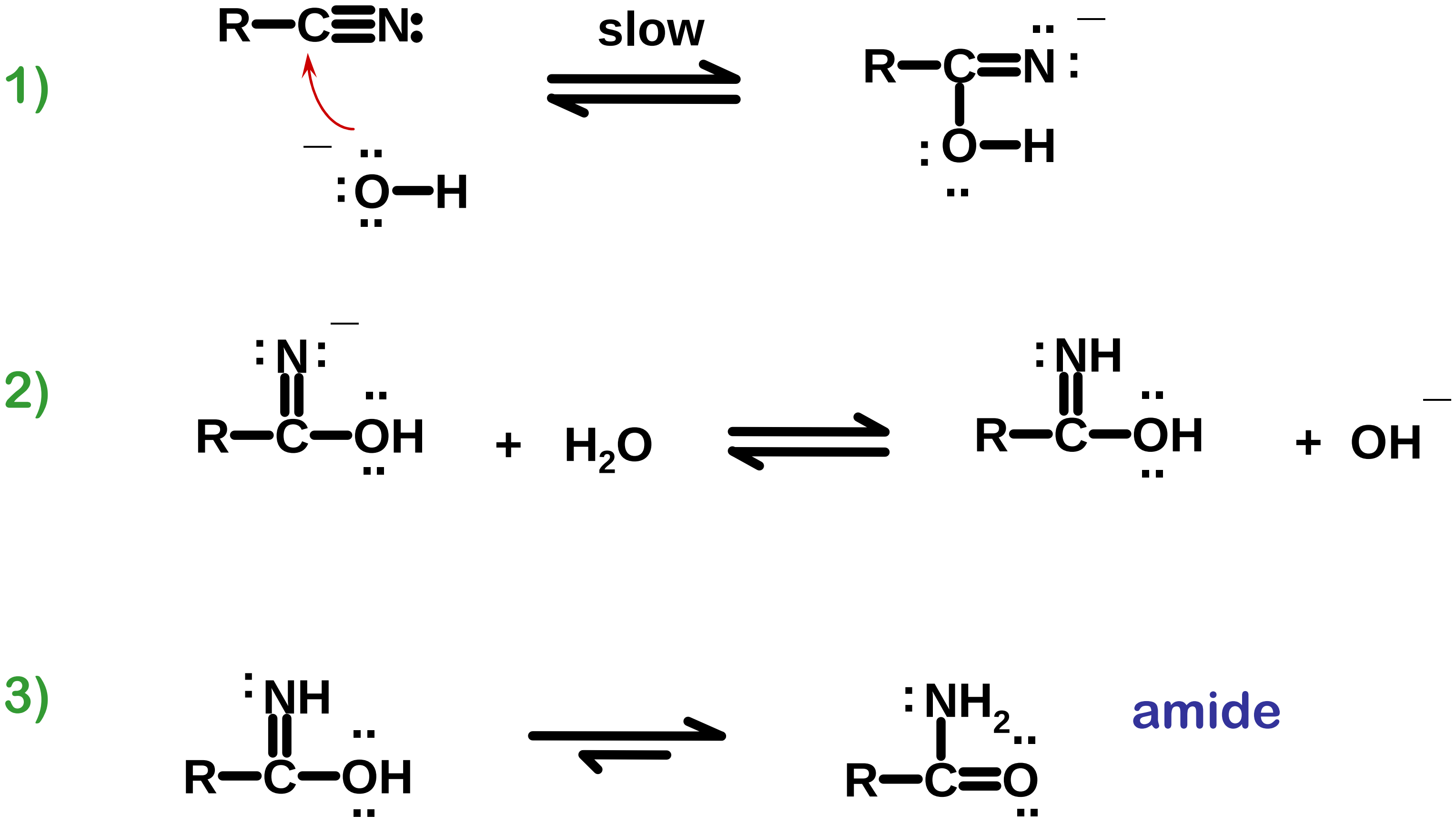


$$R{-}CH_2{-}C{\equiv}N \;+\; H_2O \xrightarrow[\text{heat}]{NaOH} R{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}O^- \; Na^+ \;+\; :NH_3$$

# Base-Promoted Hydrolysis of a Nitrile

## MECHANISM

**NaOH**



amide

Tautomerism

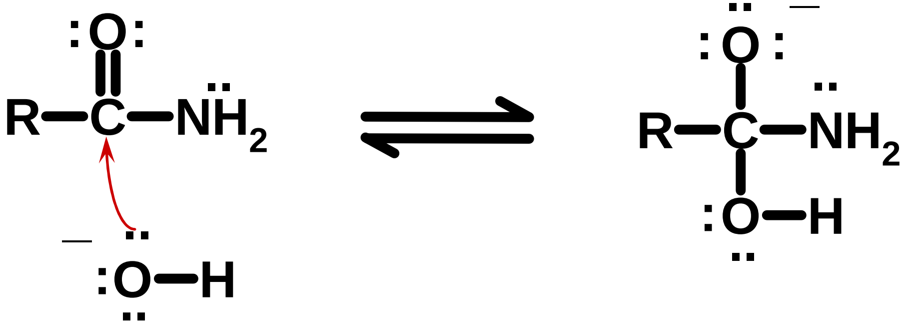
….. continued

# Base-Promoted Hydrolysis of a Amide

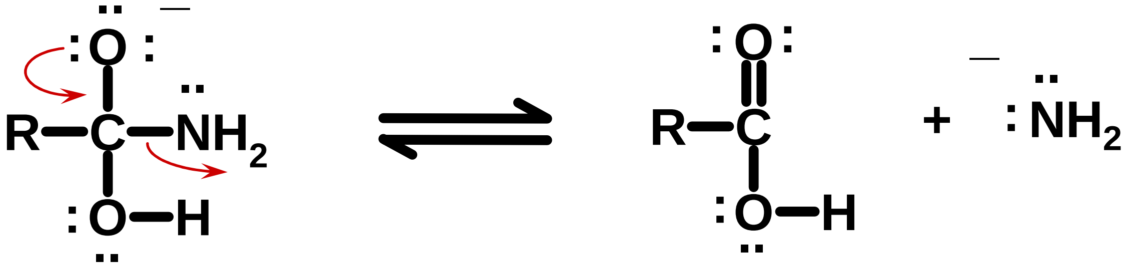
## MECHANISM

**NaOH**

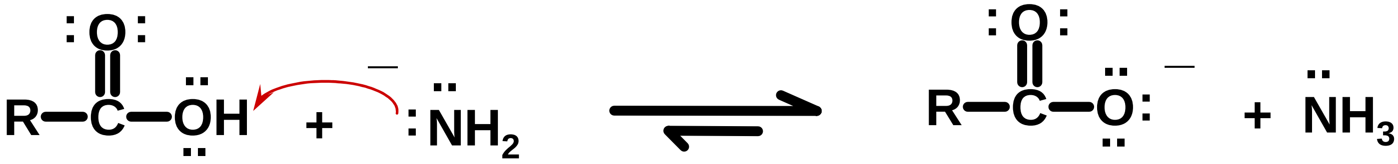
4)



5)

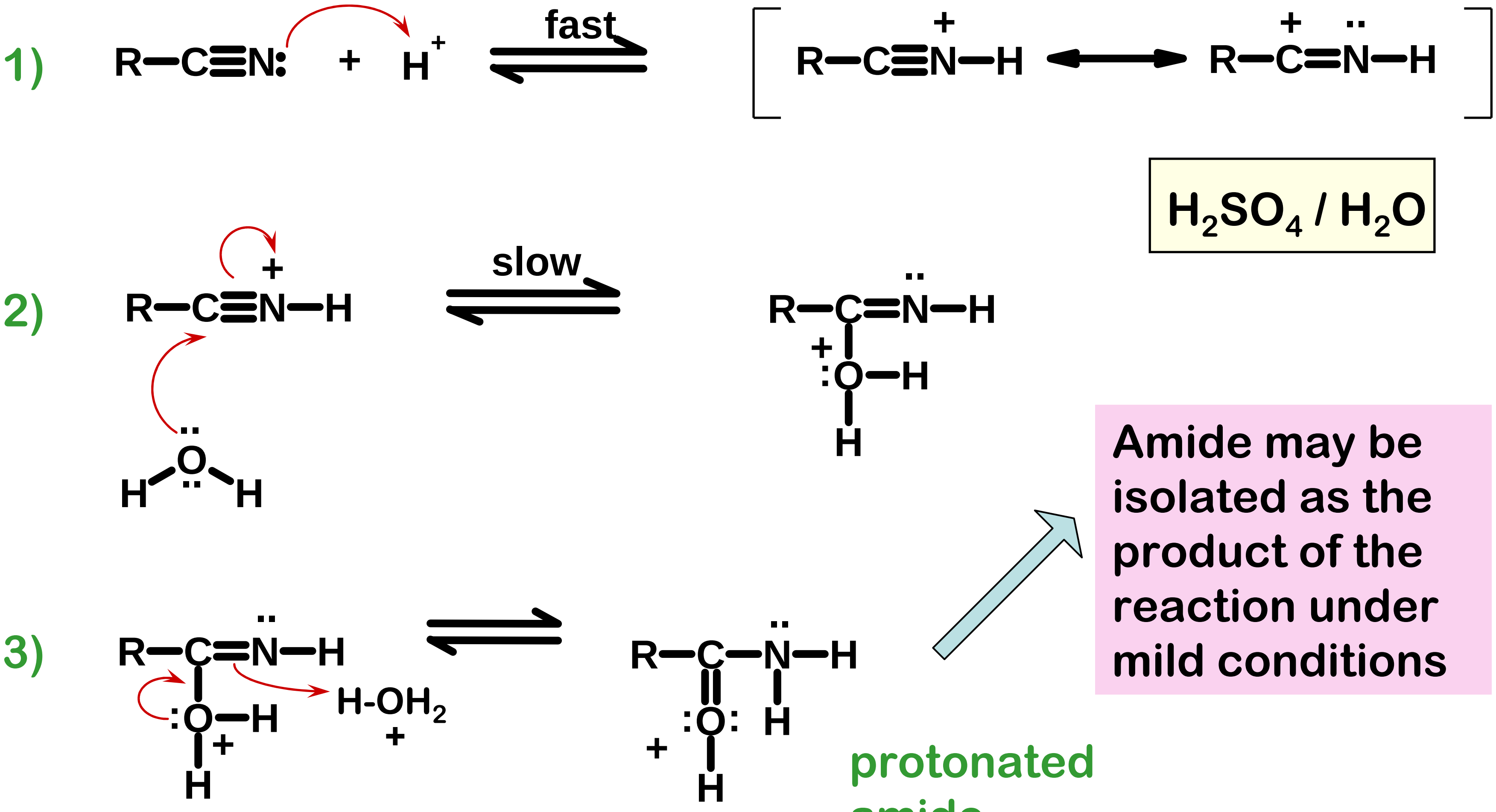


6)



# Acid-catalyzed Hydrolysis of a Nitrile

## MECHANISM



$H_2SO_4$ / $H_2O$

Amide may be isolated as the product of the reaction under mild conditions

protonated amide

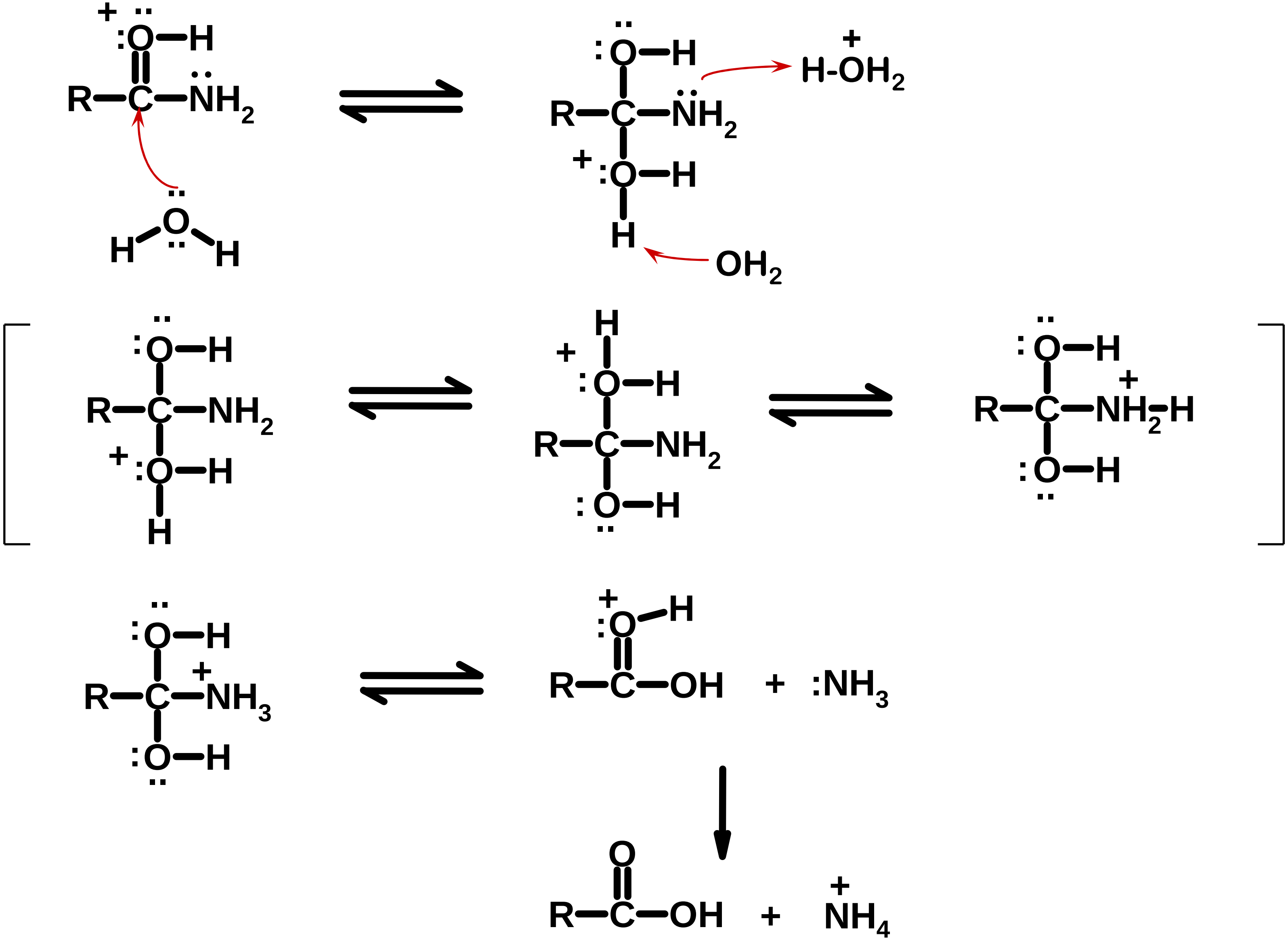
….. continued

# Acid-catalyzed Hydrolysis of a Amide

4)

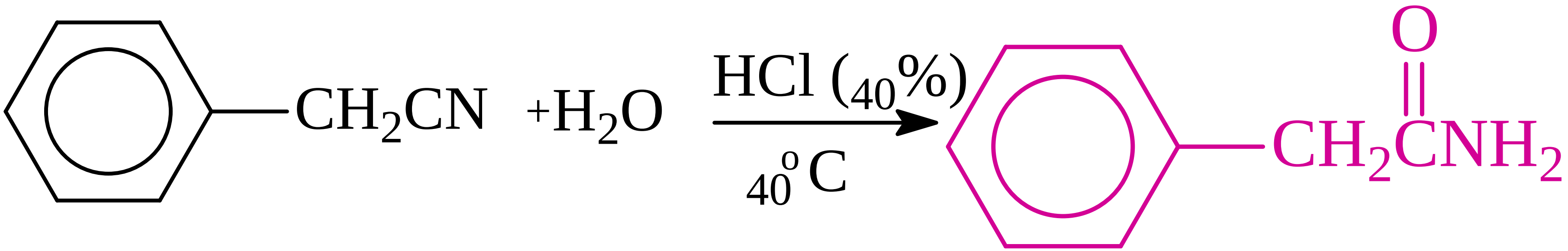
5)

6)



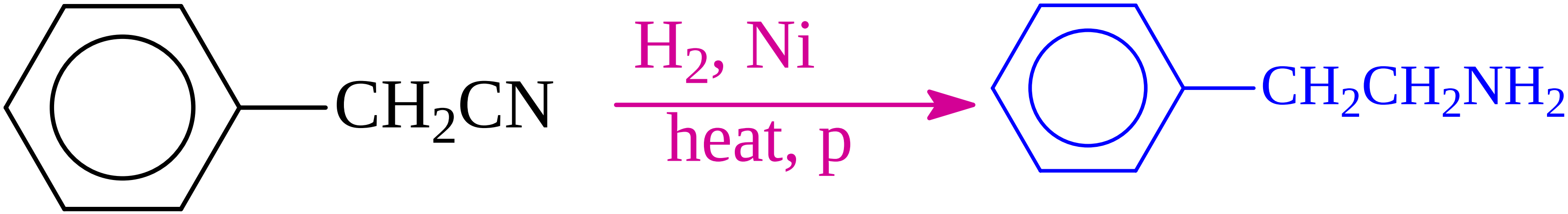
# Examples


CH2CN
+H2O
H2SO4 (40%)
reflux
O
CH2COH


CH2CN
+H2O
HCl (40%)
40o C
O
CH2CNH2

# 2) Reduction

- Nitriles can be reduced to primary amines ($RCH_2NH_2$ ) by Hydrogenation or $LiAlH_4$



$$CH_3CH_2CH_2C\equiv N \xrightarrow[2)\ H^+,\ H_2O]{1)\ LiAlH_4} CH_3CH_2CH_2CH_2NH_2$$