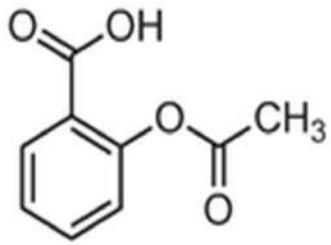
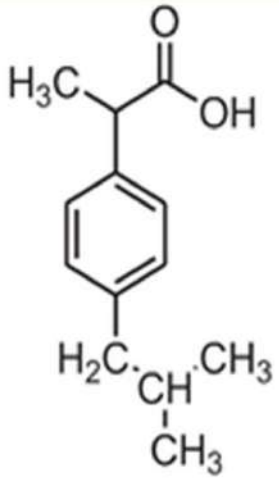
Part 1
Carboxylic acid

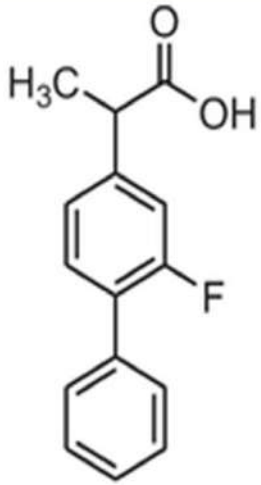
Some carboxylic acid containing Drugs



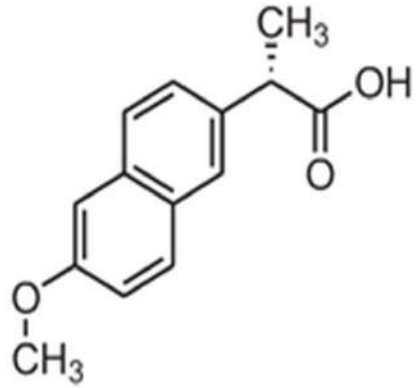
Aspirin



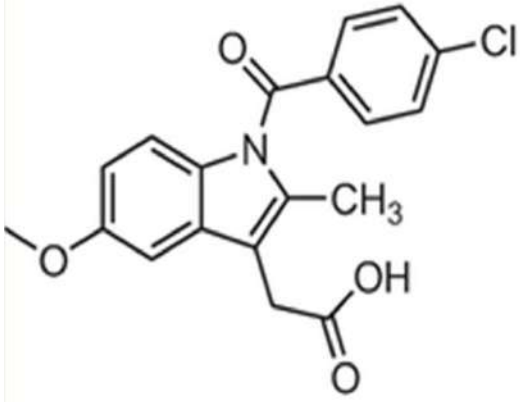
Ibuprofen



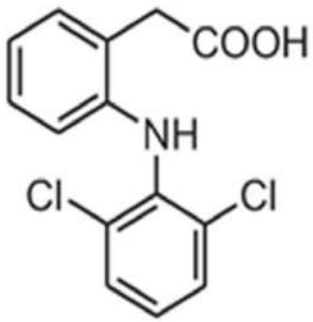
Flurbiprofen



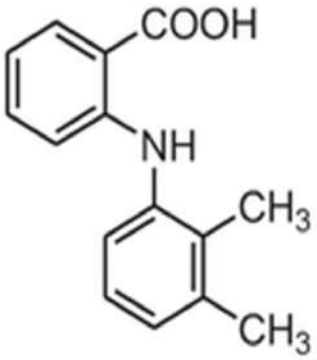
Naproxen



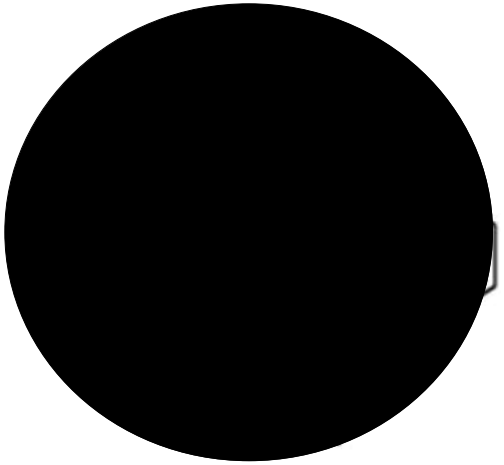
Indomethacin

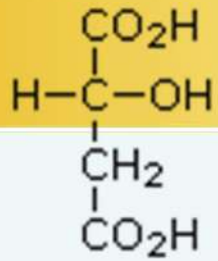


Diclofenac

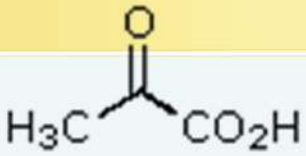


Mefenamic acid

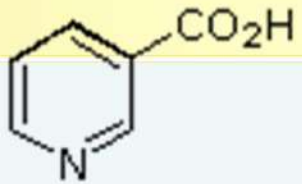




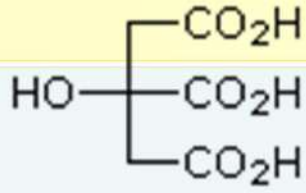
malic acid
(various fruits)



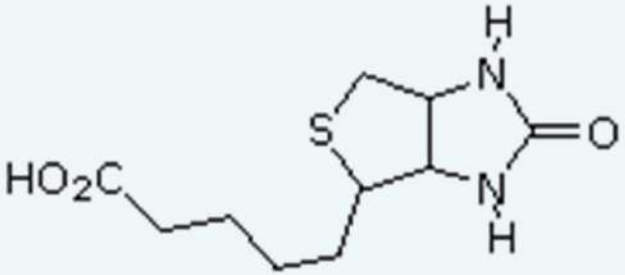
pyruvic acid
(a metabolic intermediate)



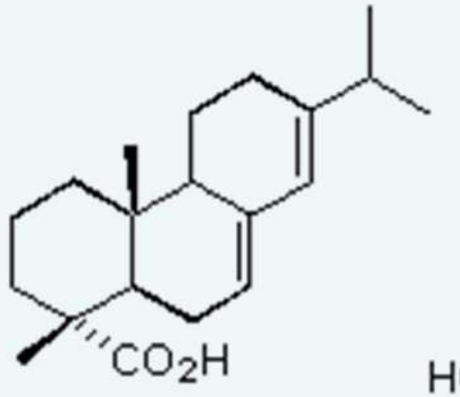
niacin
a vitamin



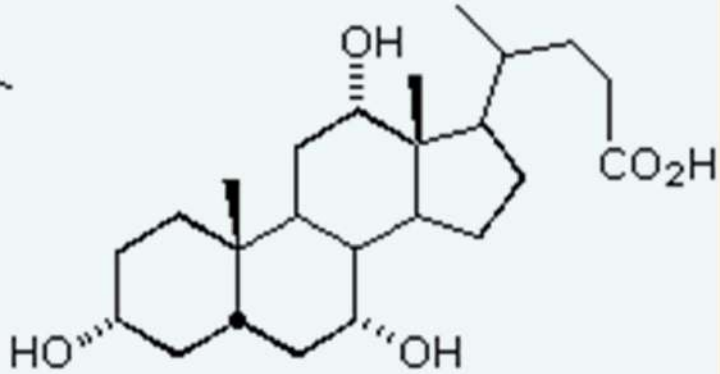
citric acid
(from citrus fruits)



biotin
(a cell growth factor)

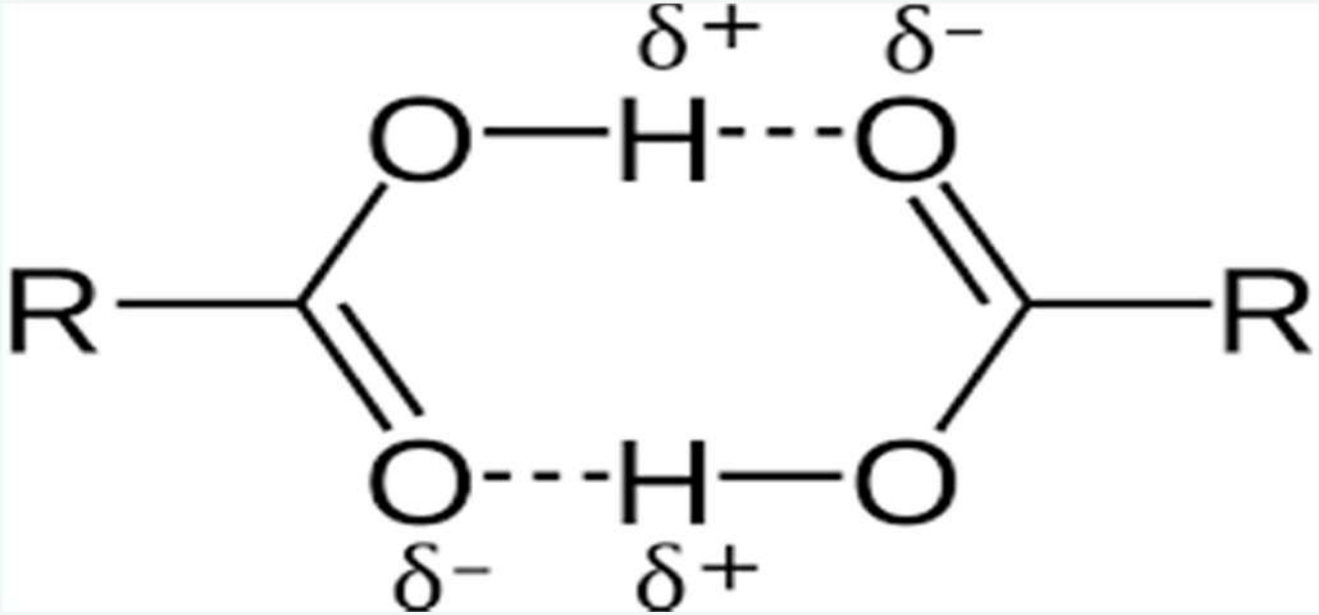


abietic acid
(pine resin)



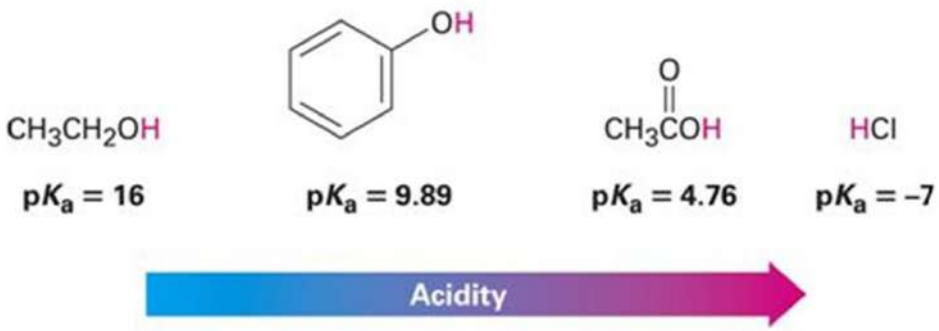
cholic acid
(from bile)

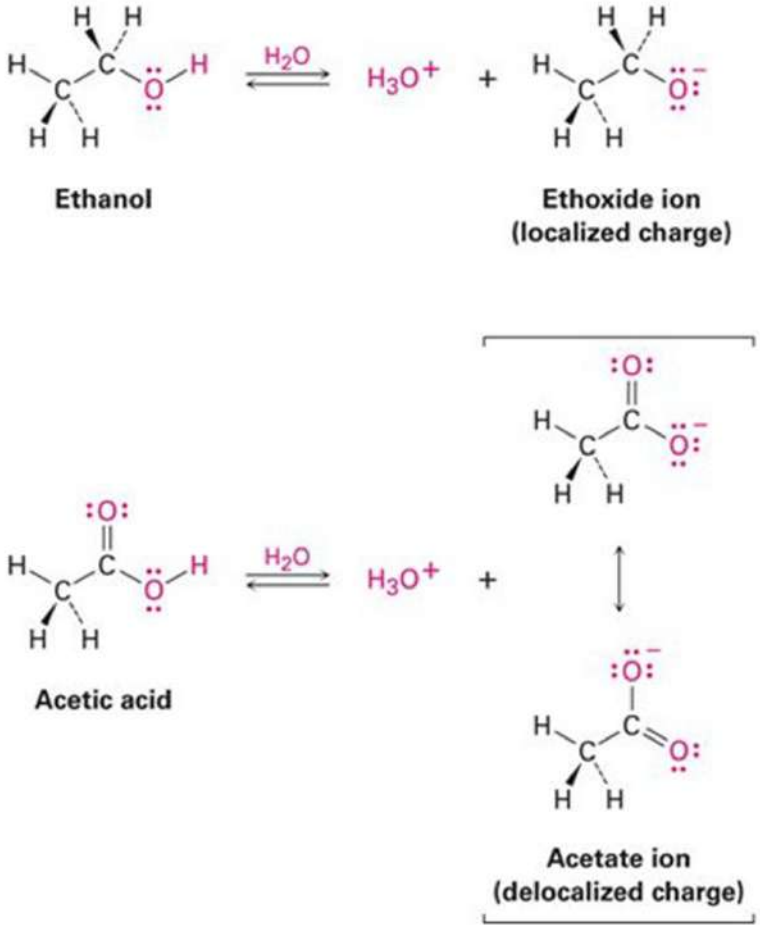
Structure and Properties of Carboxylic Acids



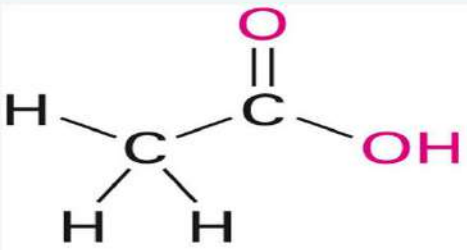
III. Acidity of Carboxylic Acids

- Weak acids (pK_a ~ 4-5)
- Stronger than alcohols because conjugate base is resonance-stabilized

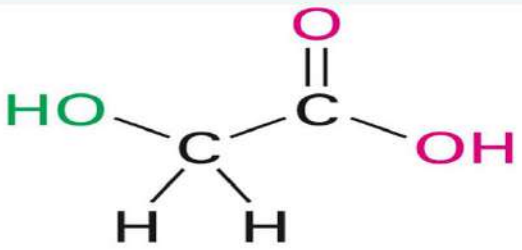




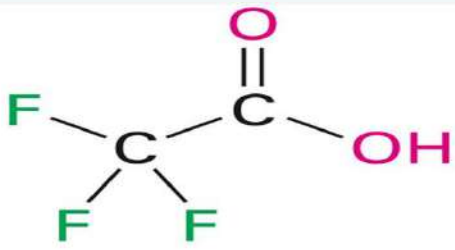
Substituent Effects on Acidity



$pK_a = 4.76$

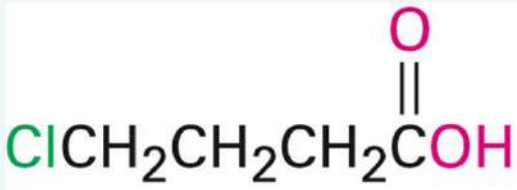


$pK_a = 3.83$



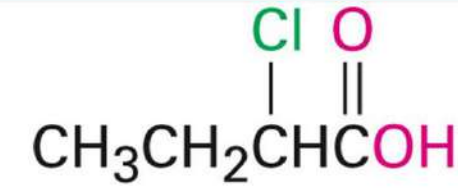
$pK_a = -0.23$

Acidity



$pK_a = 4.52$

$pK_a = 4.05$

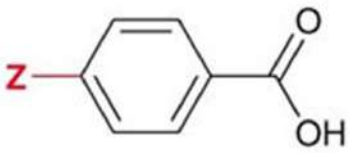


$pK_a = 2.86$

Acidity

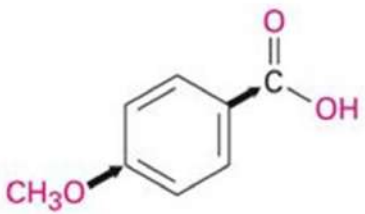
III. Acidity of Carboxylic Acids

- Substituted benzoic acids

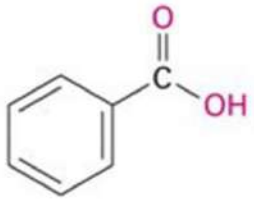


Z	—NO_2	—CHO	—Cl	—H	—CH_3	—OH
pK_a	3.4	3.8	4.0	4.2	4.3	4.5

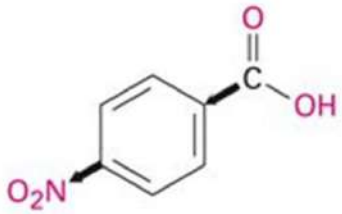
- If Z = electron-donating group, acid is weaker
- If Z = electron-withdrawing group, acid is stronger



p-Methoxybenzoic acid
(pK_a = 4.46)

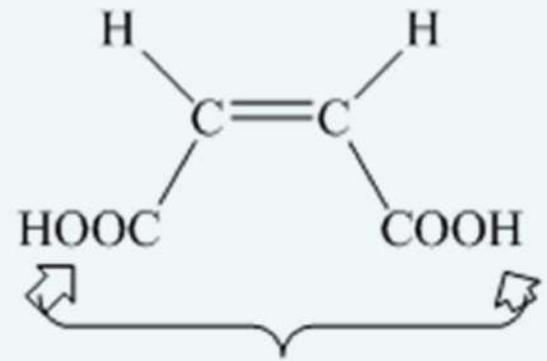


Benzoic acid
(pK_a = 4.19)



p-Nitrobenzoic acid
(pK_a = 3.41)

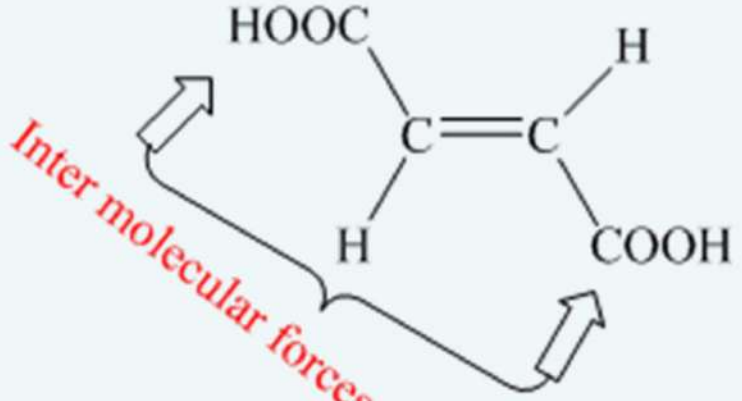
Effect of intramolecular hydrogen bonding on pKa1 and pKa2 in Dicarboxylic acid



Intra molecular forces are more

Maleic acid

mp = 130°C

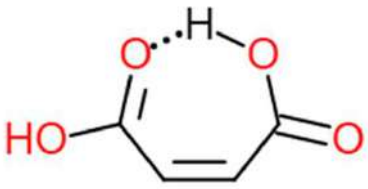


Inter molecular forces are more

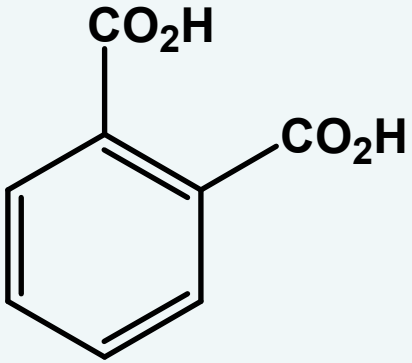
Fumaric acid

mp = 286°C

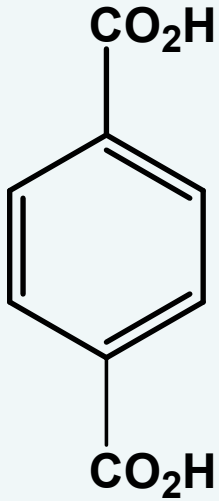
pKa1	**1.9**	**3.0**
pKa2	**6.5**	**4.5**



Discuss the values of pKa1 and pKa2 for the following two isomeric dicarboxylic acids



Phthalic acid

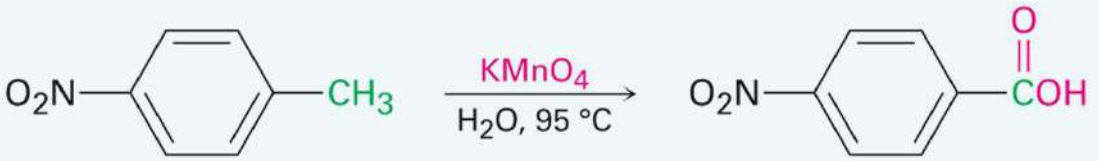


Terephthalic acid

pKa1	2.9	3.5
pKa2	5.4	4.3

Preparing Carboxylic Acids

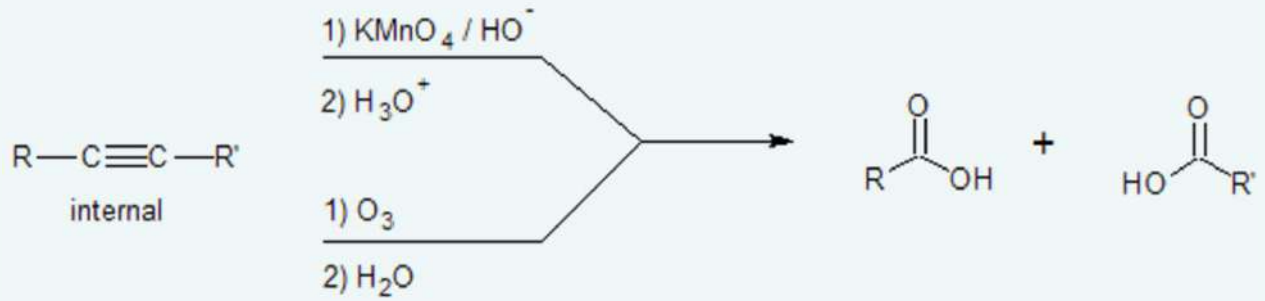
1- Oxidation of benzylic C-H

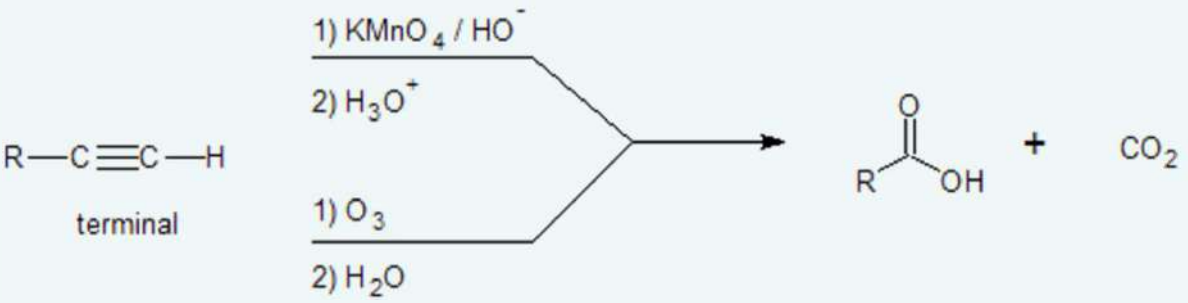


p-Nitrotoluene

p-Nitrobenzoic acid (88%)

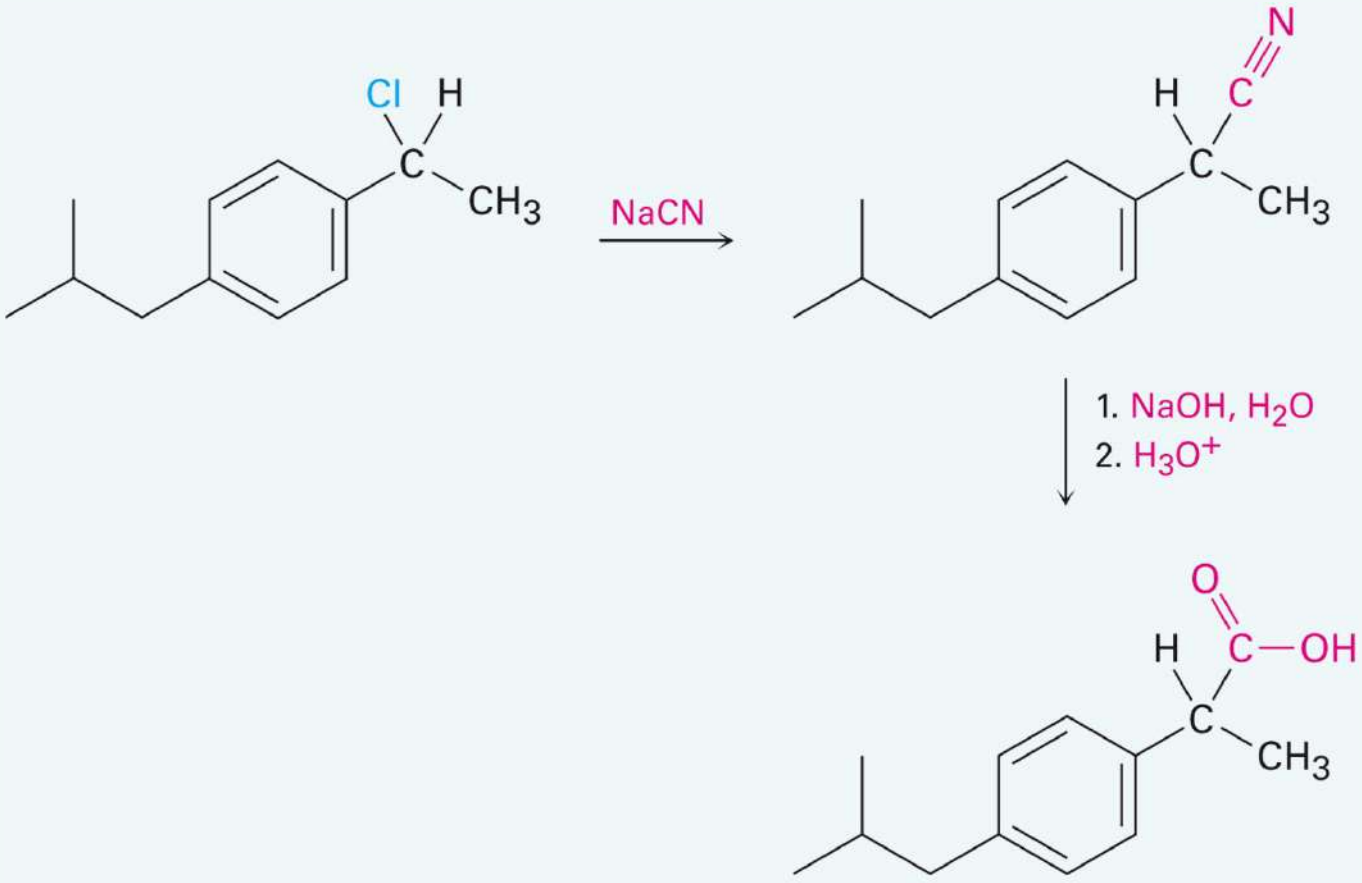
2- Oxidative cleavage of alkynes





Preparing Carboxylic Acids

3- Acidic or alkaline hydrolysis of nitriles



Ibuprofen

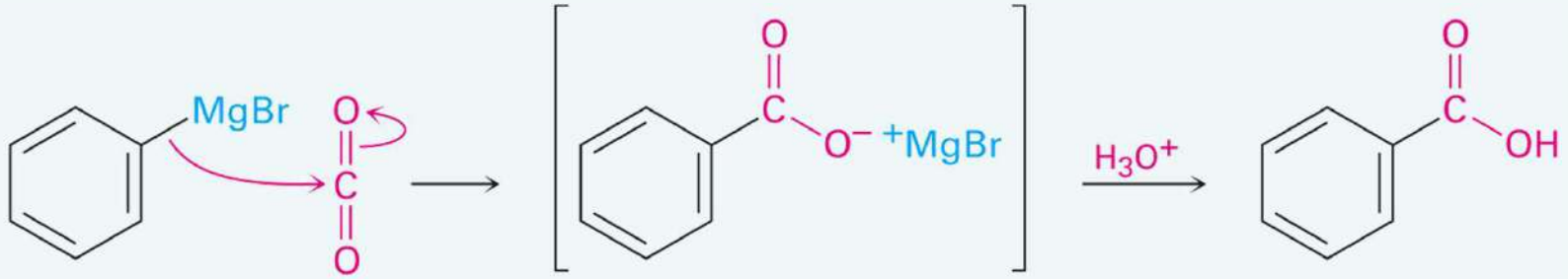
Preparing Carboxylic Acids

5- Oxidation of a primary alcohol or an aldehyde yields a carboxylic acid

4-Methyl-1-pentanol **4-Methylpentanoic acid**

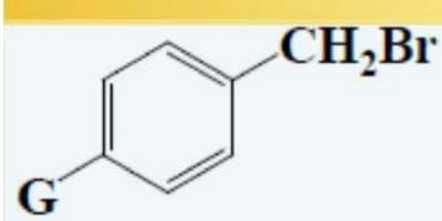
Hexanal **Hexanoic acid**

5- Carboxylation of Grignard Reagents



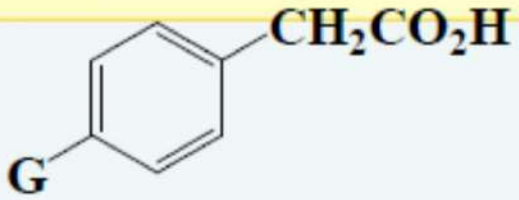
Phenylmagnesium bromide **Benzoic acid**

Limitation of Grignard Reagents

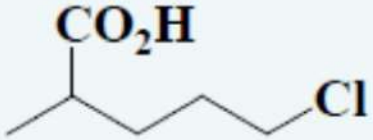


1) Mg(dry ether)
2) CO_2
3) H_3O^+
X

1) NaCN
2) H_3O^+
✓

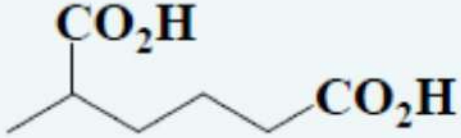


G = Acidic group such; SO_3H, CO_2H, OH, SH



1) Mg(dry ether)
2) CO_2
3) H_3O^+
X

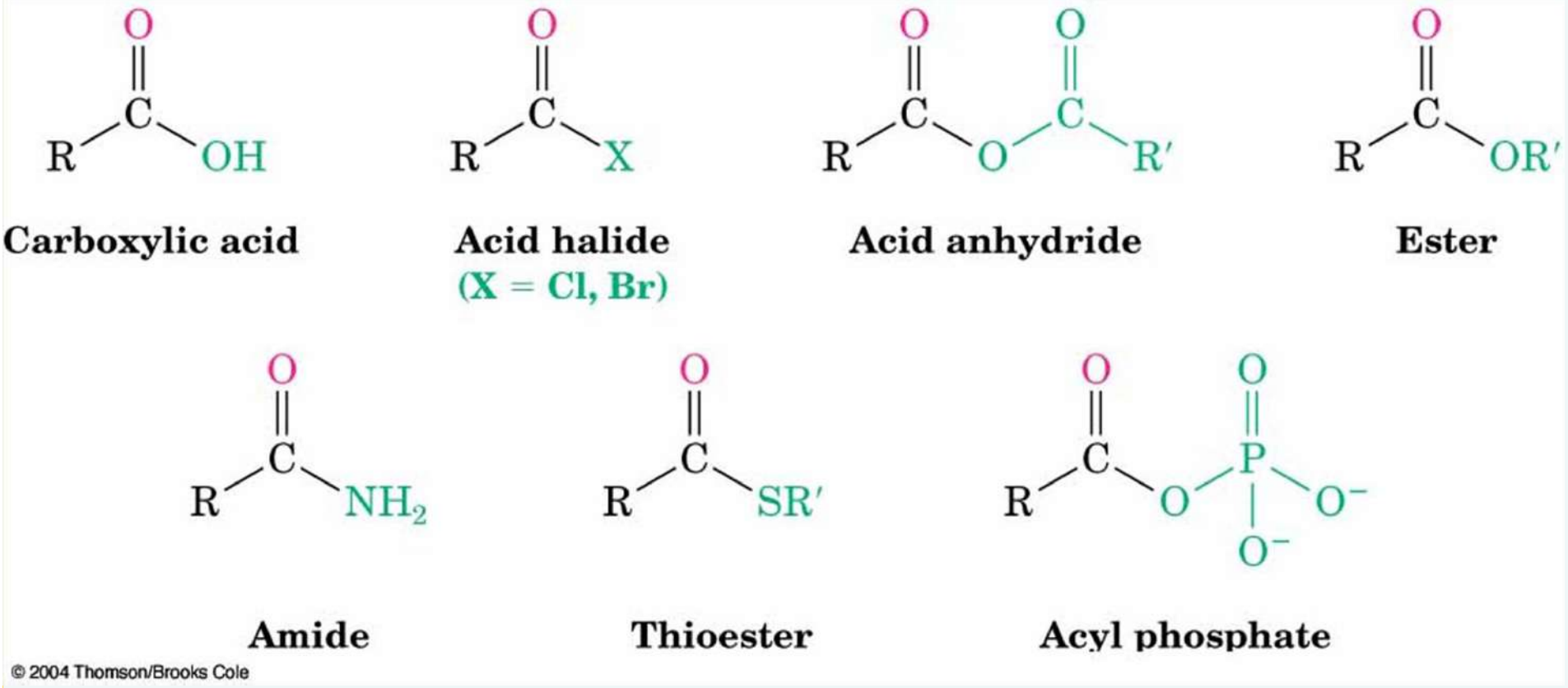
1) NaCN
2) H_3O^+
✓

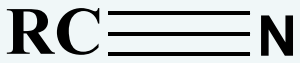


Part 2
Derivatives of Carboxylic Acid

1- Acid halide

Carboxylic Acid Derivatives



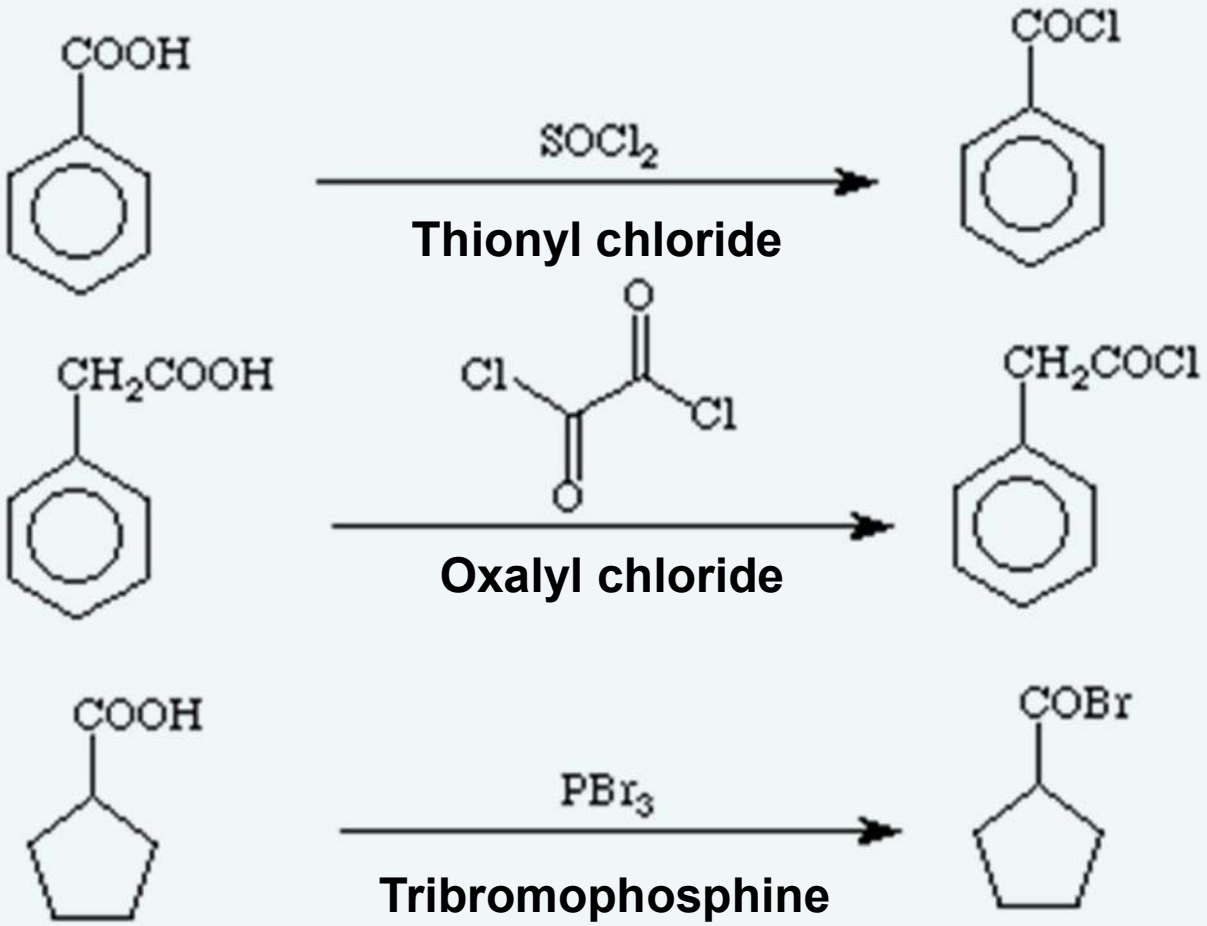


Nitrile

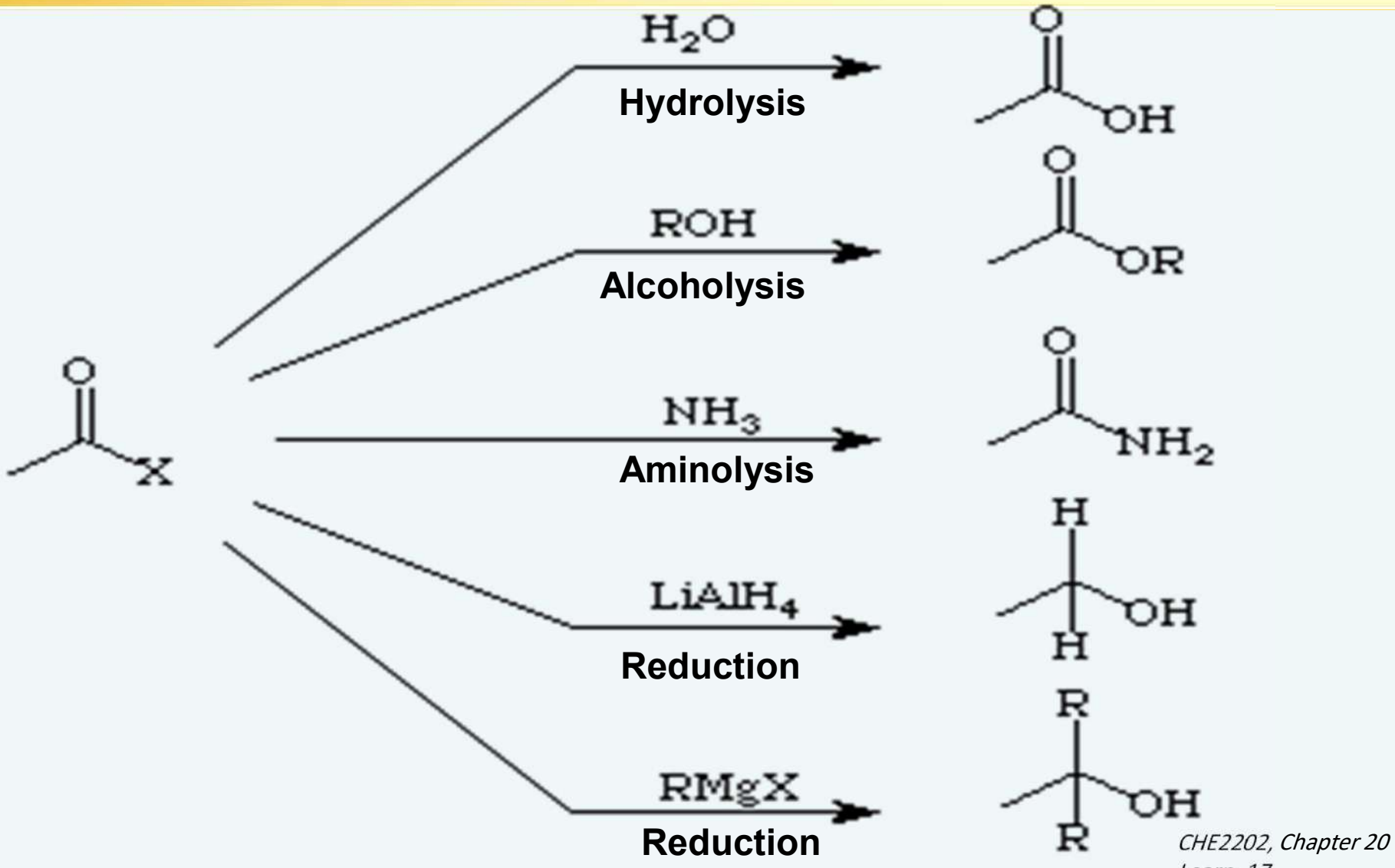
Carboxylic acid derivatives

1-Chemistry of Acid halides

There are three main methods to prepare acid halide

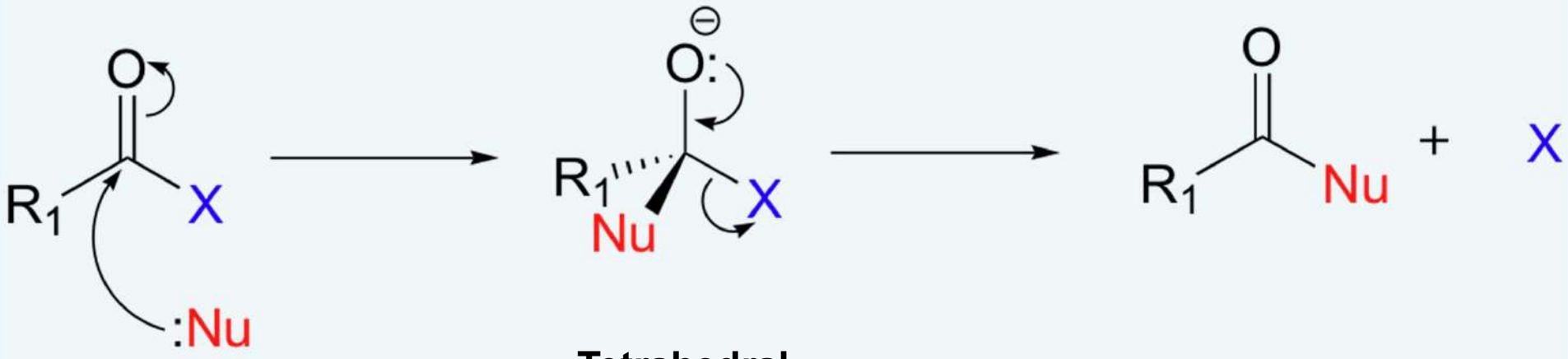


Reaction of acid halide
(common reactions for all derivatives”



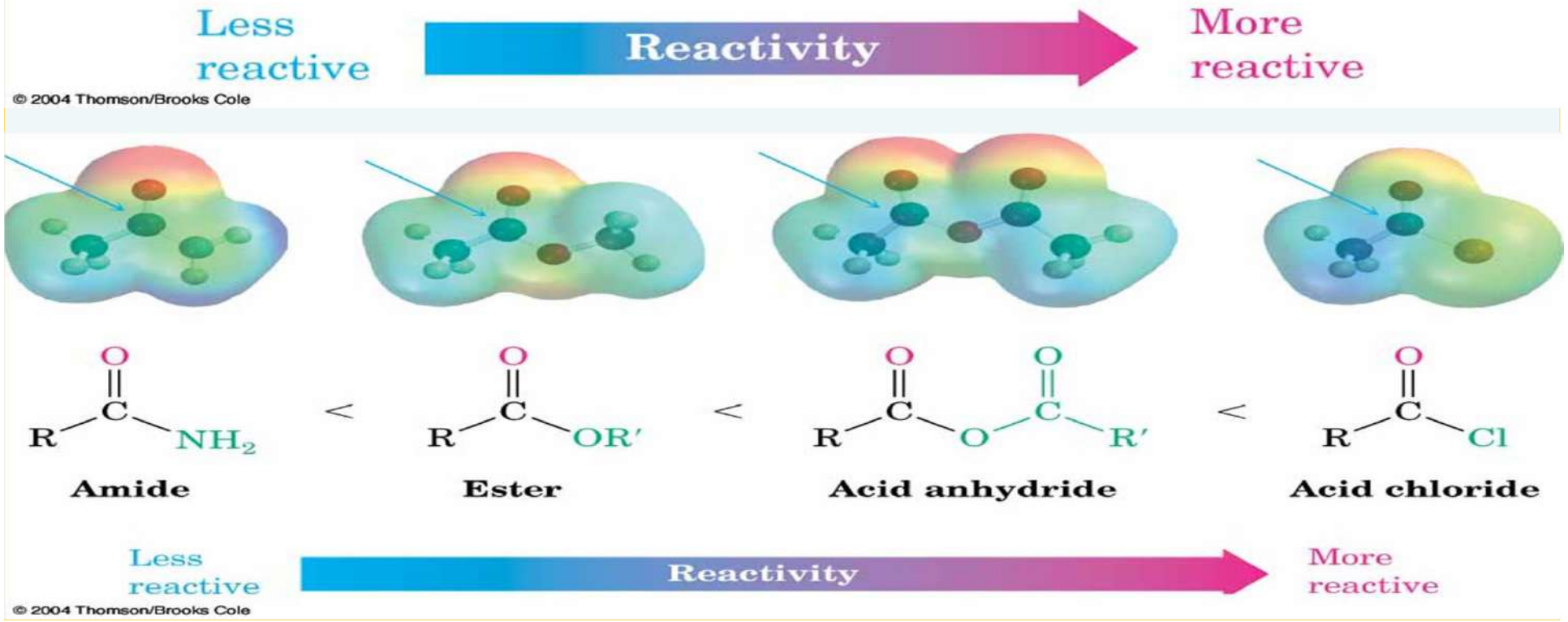
Nucleophilic Acyl Substitution

- **General mechanism of Nucleophilic Acyl Substitution**

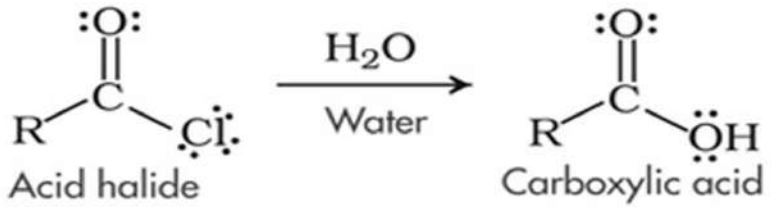


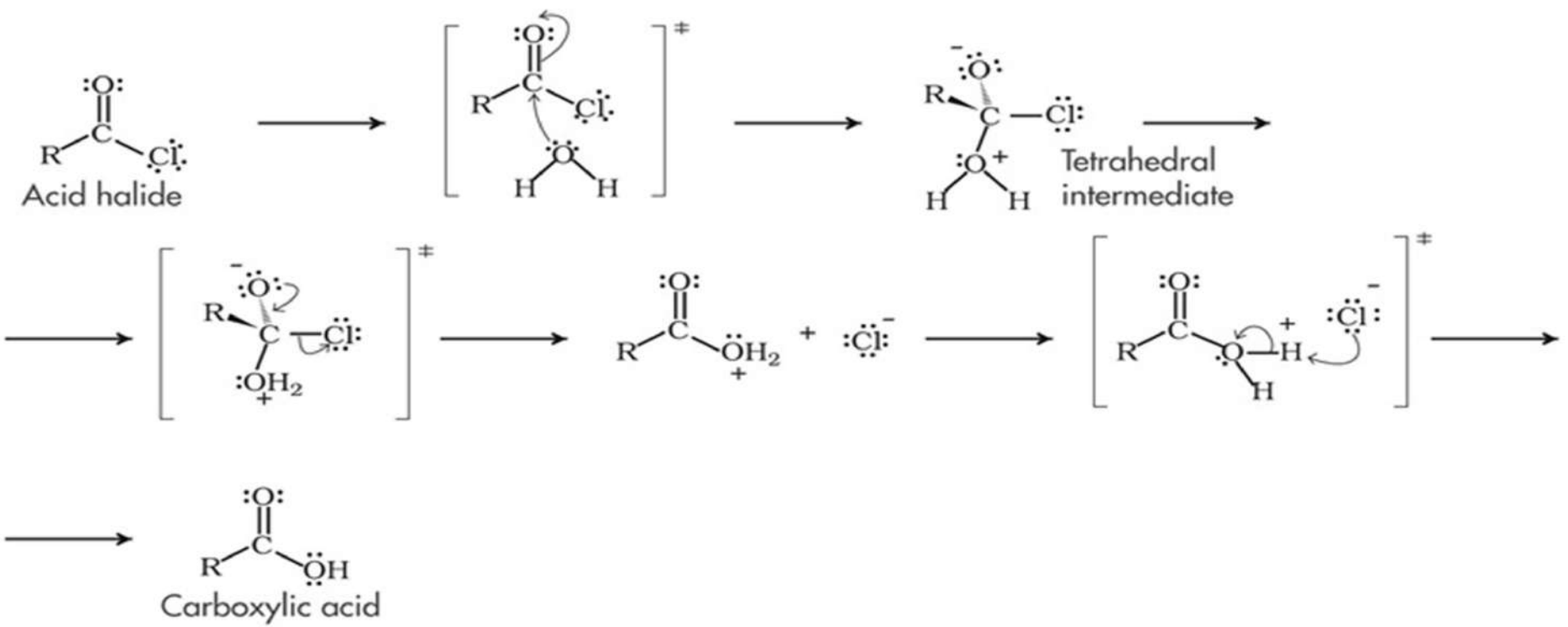
Tetrahedral intermediate

Relative Reactivity of Carboxylic Acid Derivatives toward Nu Acyl Sub

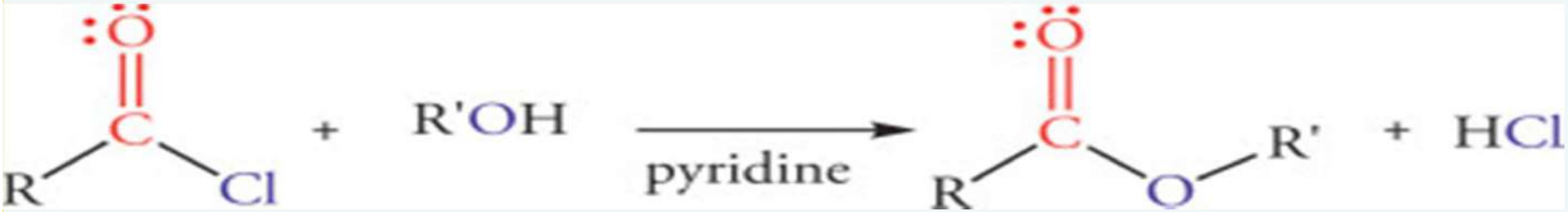


1] Hydrolysis of acid halides
“yields carboxylic acid”

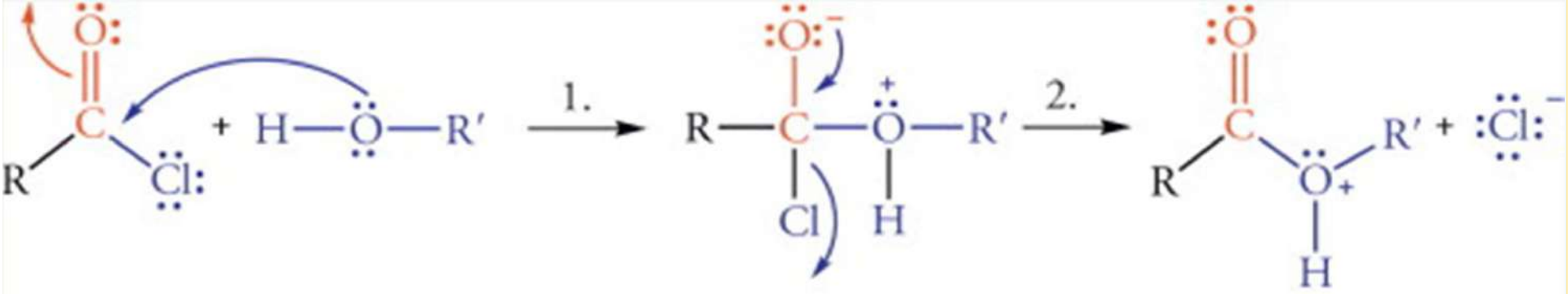


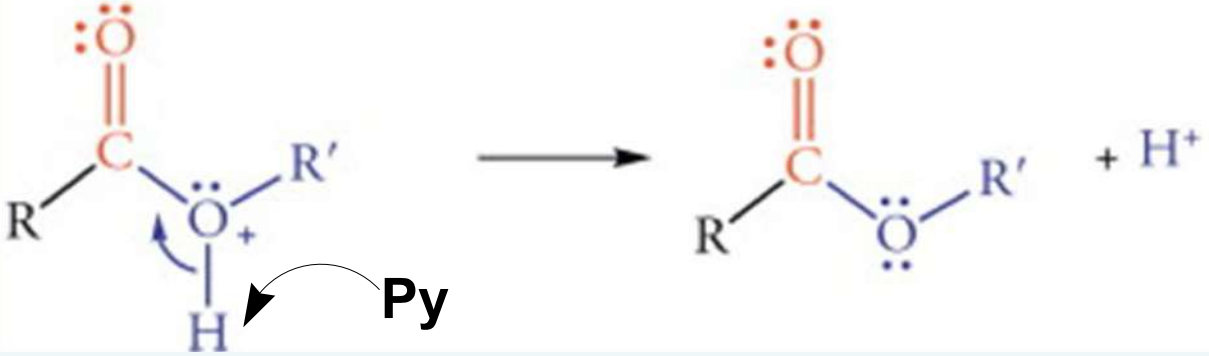


2] Alcoholysis of acid Halides “yields an ester”

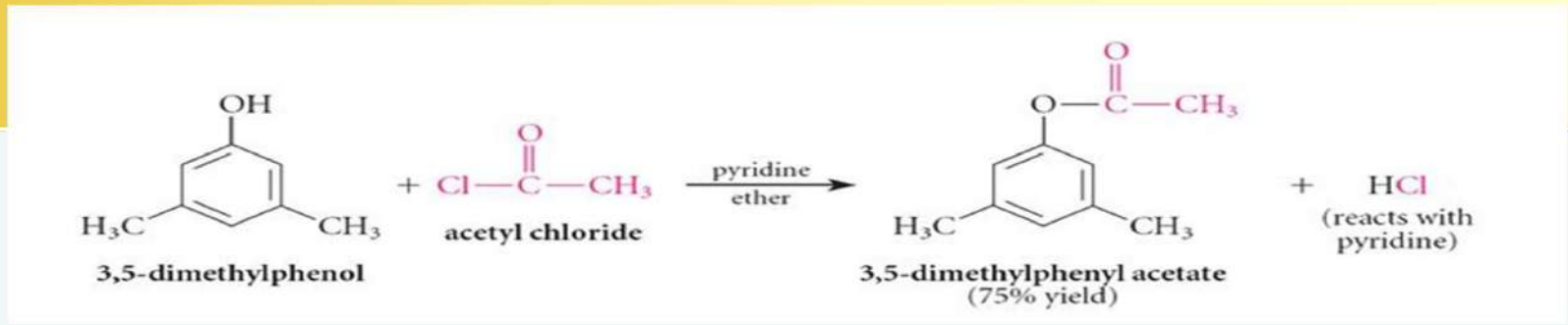


Mechanism of acloholysis of acid halide



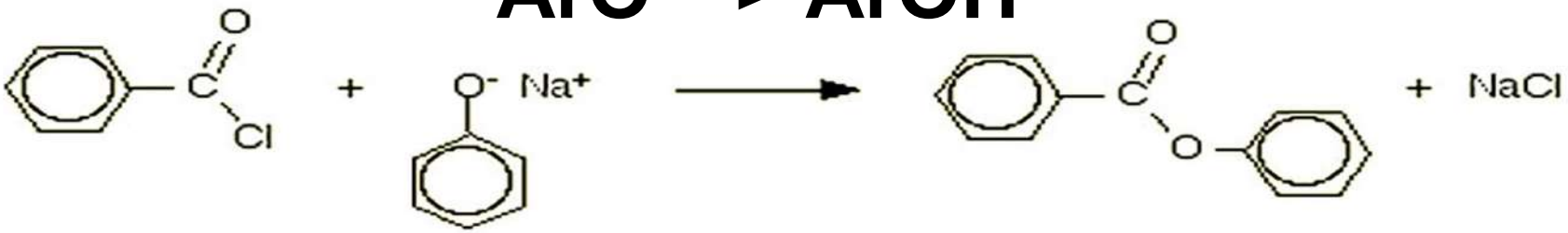


Phenolysis of acid halides

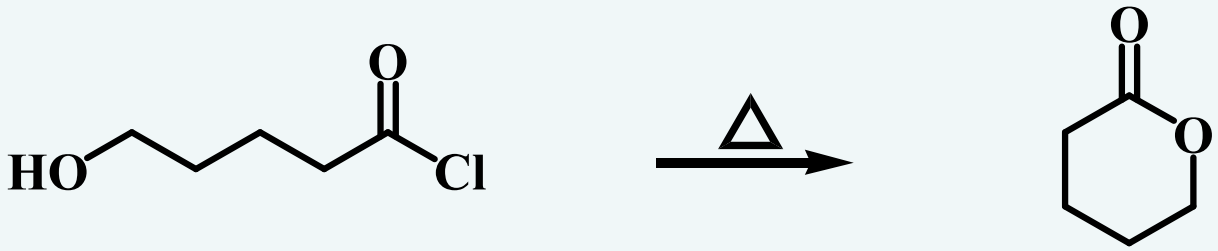


Phenoxide is stronger Nu Than the neutral form!!!!

$$ArO^- > ArOH$$

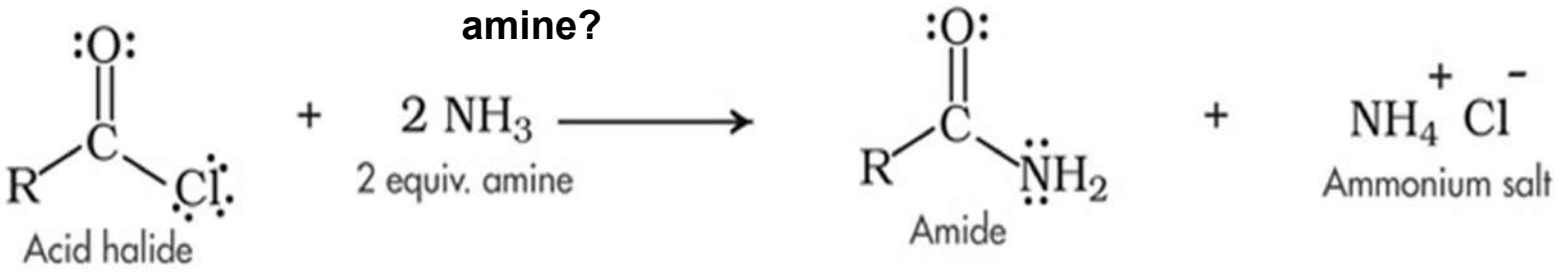


Intramolecular alcoholysis

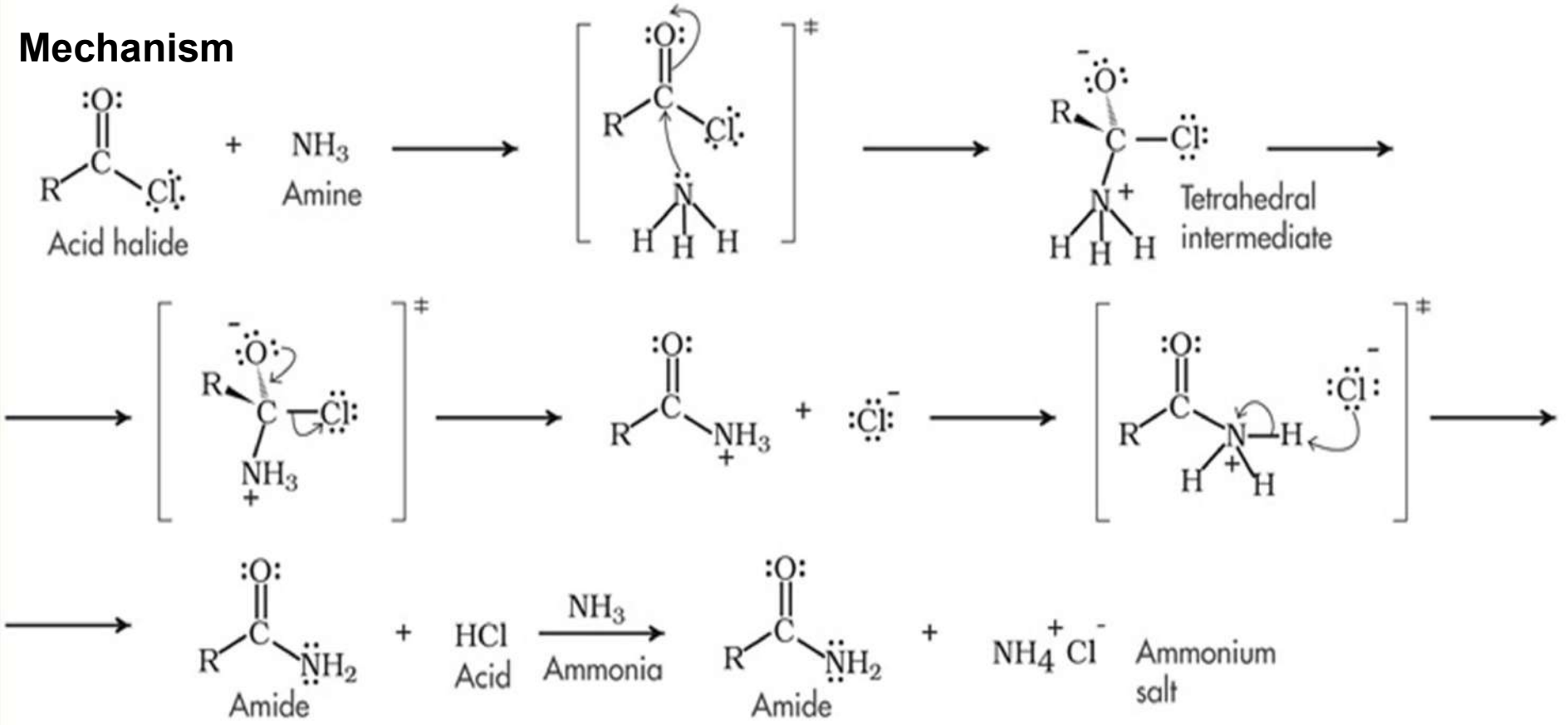


3] Aminolysis of acid halide
"yields an amide"

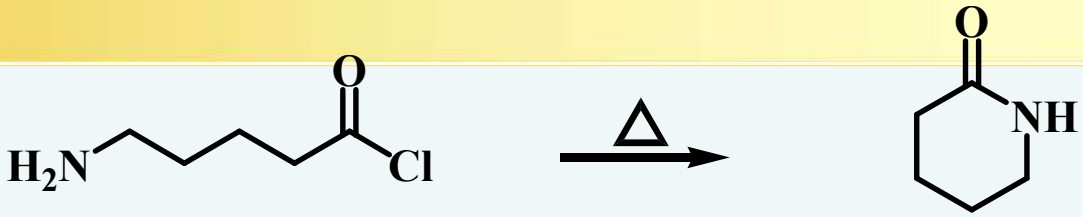
Why two moles of amine?



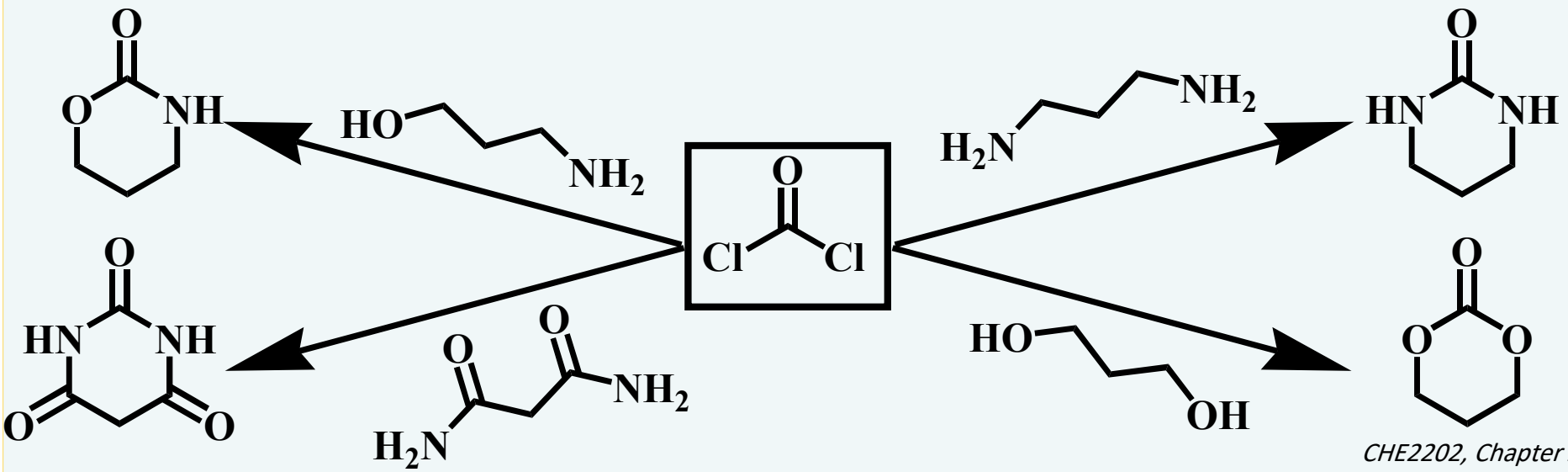
Mechanism



Intramolecular aminolysis affords Lactam

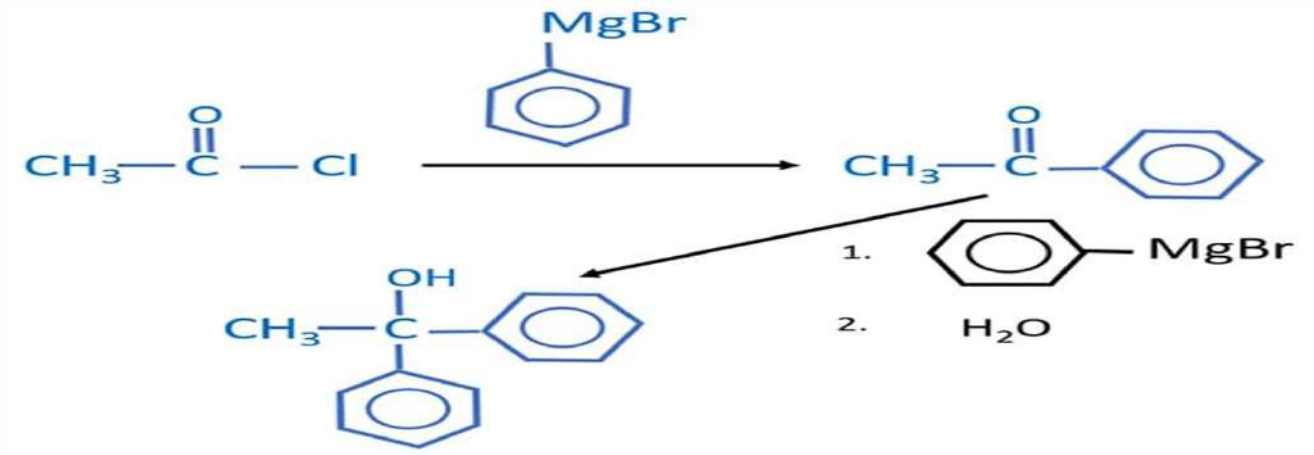


Some reactions related to phosgene

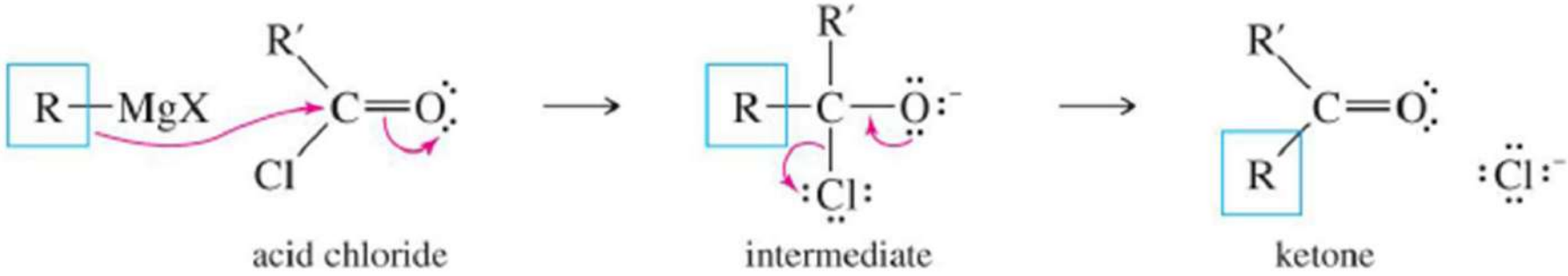


4] Reduction of acid haldies
"yields an alcohol"

a] Using Grignard reagent " yields ketone with one mole of GR and 3 alcohol with two moles":-



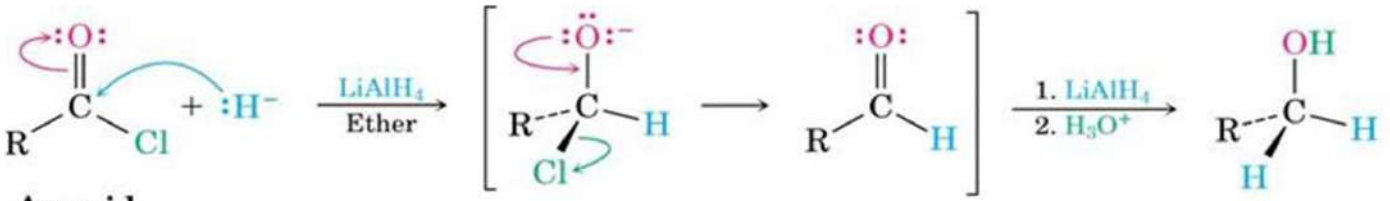
Mechanism



b] Reduction of acid halide using LiAlH4

iv. Reduction: Conversion of Acid Chlorides into **Alcohols**

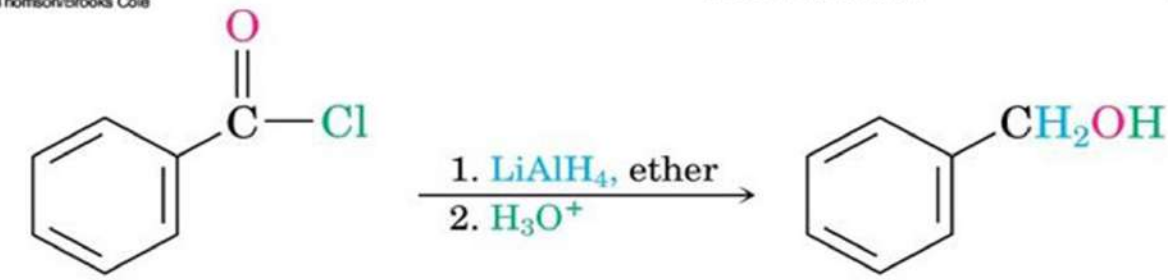
- $LiAlH_4$ reduces acid chlorides to yield aldehydes and then primary alcohols



An acid chloride

An aldehyde (*NOT isolated*)

A primary alcohol



Benzoyl chloride

Benzyl alcohol (96%)

Part 3
Derivatives of Carboxylic Acid

2- Acid anhydride

STRUCTURE OF ACID ANHYDRIDE

- The word 'anhydride' means without water.
- Contains two molecules of an acid, with loss of a molecule of water.
- Addition of water to an anhydride regenerates two molecules of the carboxylic acid.

two molecules of acid — acid anhydride

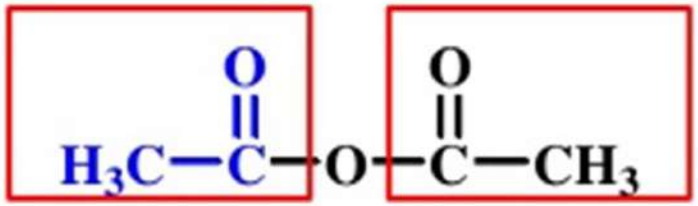
- General structure:

or $(RCO)_2O$

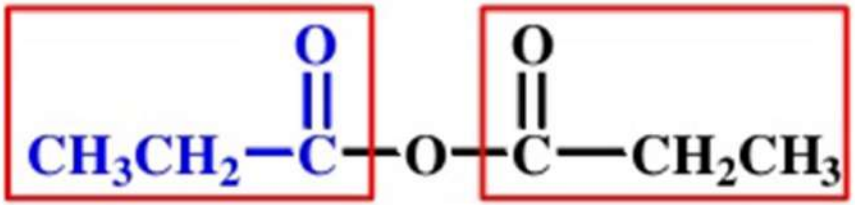
acid anhydride

NOMENCLATURE OF ACID ANHYDRIDE

- The word *'acid'* is changed to '*anhydride*' in both common name and the IUPAC name.
- Examples:
  - ethanoic *acid* → ethanoic *anhydride*
  - propanoic *acid* → propanoic *anhydride*



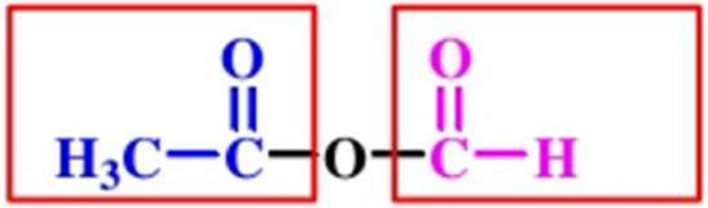
IUPAC : ethanoic anhydride
common: acetic anhydride



IUPAC : propanoic anhydride
common: propionic anhydride

NOMENCLATURE OF ACID ANHYDRIDE

- Anhydrides composed of two different acids are called *mixed anhydrides* and are named by using the names of the individual acids.



IUPAC : ethanoic methanoic anhydride
common: acetic formic anhydride

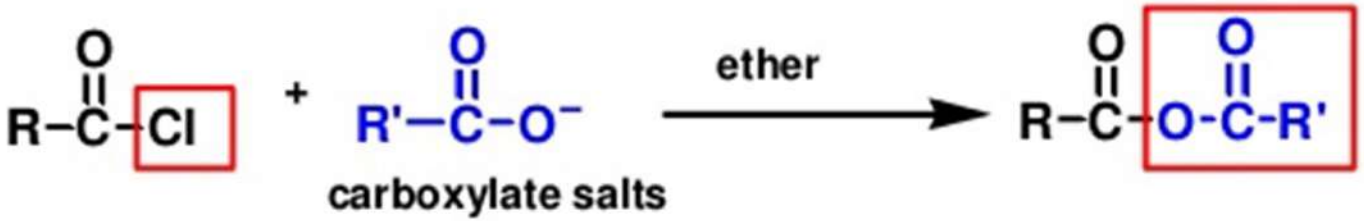
- Symmetrical anhydrides : change the word *acid* of the carboxylic acid to the word *anhydride*.
- Mixed anhydrides : alphabetizing the names for both acids and replacing the word *acid* with the word *anhydride*.

PREPARATION OF ACID ANHYDRIDES

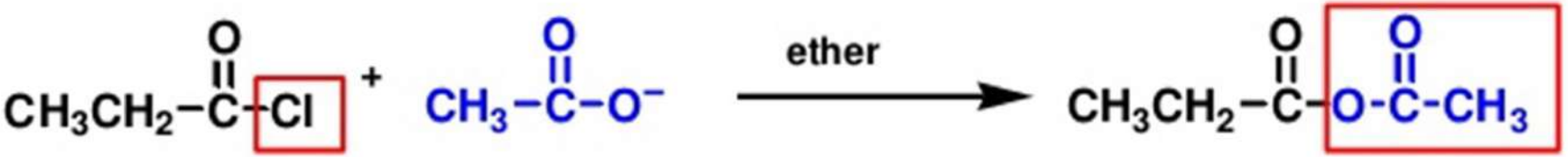
- Acid chloride and carboxylic acid
- Acid chloride and carboxylate salt
- Heating carboxylic acids with ZnO or P_2O_5
- Heating dicarboxylic acids

FROM ACYL CHLORIDES

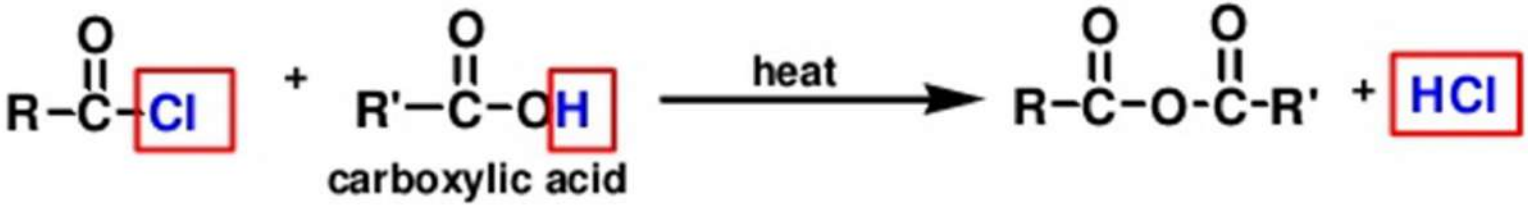
1) Acyl chlorides react with carboxylate salts to form acid anhydrides.
   - Can be used to prepare both symmetrical and unsymmetrical anhydrides



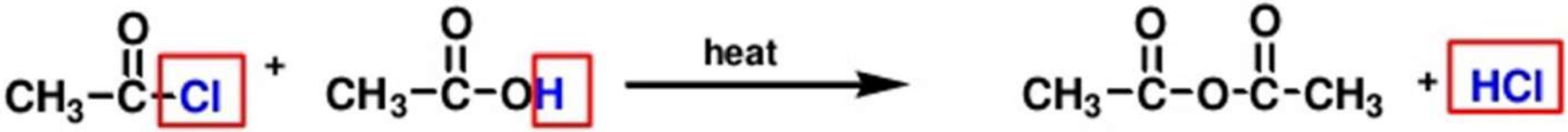
EXAMPLE



2) Acyl chlorides also reacts with carboxylic acid to give acid anhydride.

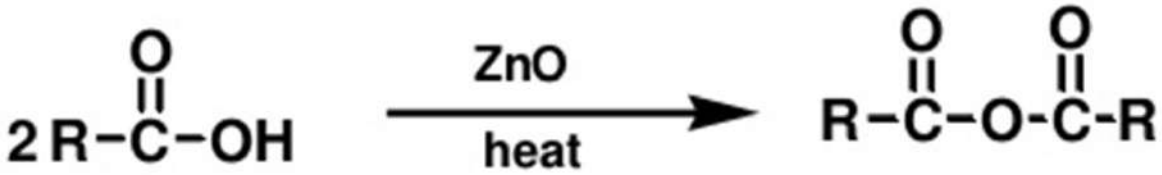


EXAMPLE

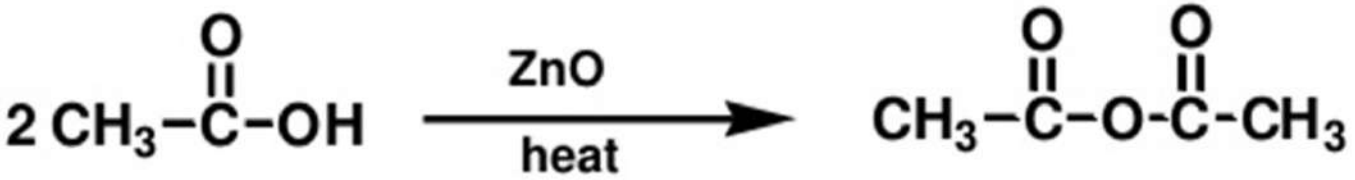


HEATING CARBOXYLIC ACIDS WITH ZnO or P2O5

Acid anhydride can be prepared from heating simple carboxylic acids with zinc oxide. **or P2O5**

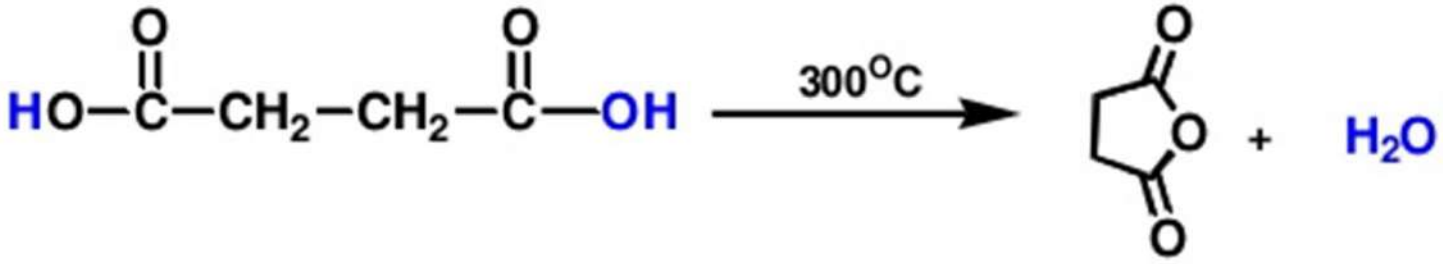


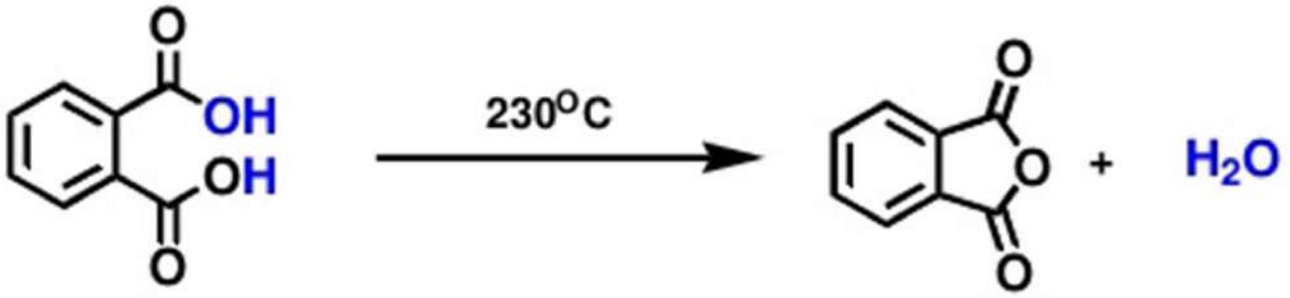
EXAMPLE



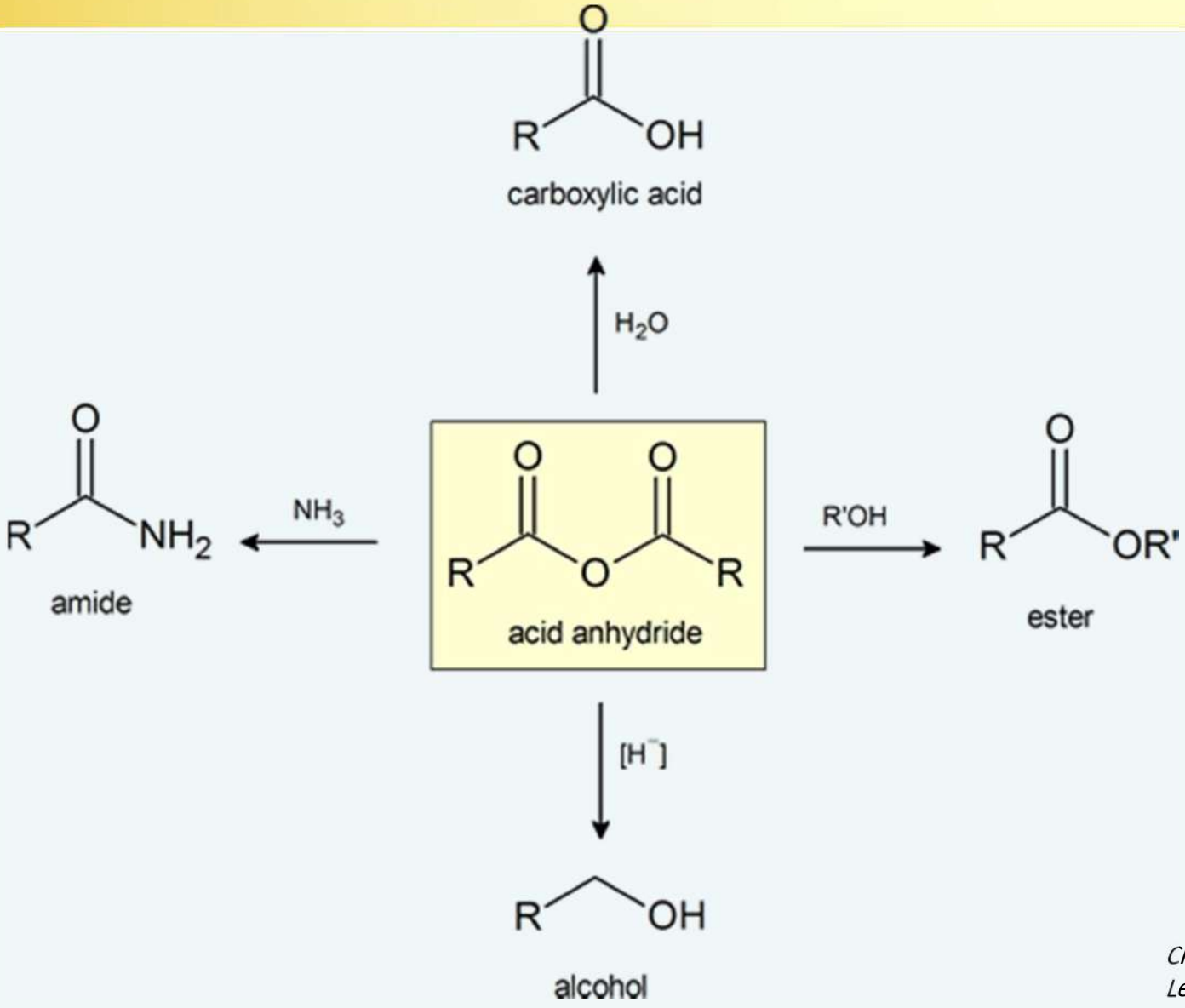
HEATING DICARBOXYLIC ACIDS

Certain cyclic anhydride can be prepared by heating dicarboxylic acid such as succinic and phthalic anhydride.



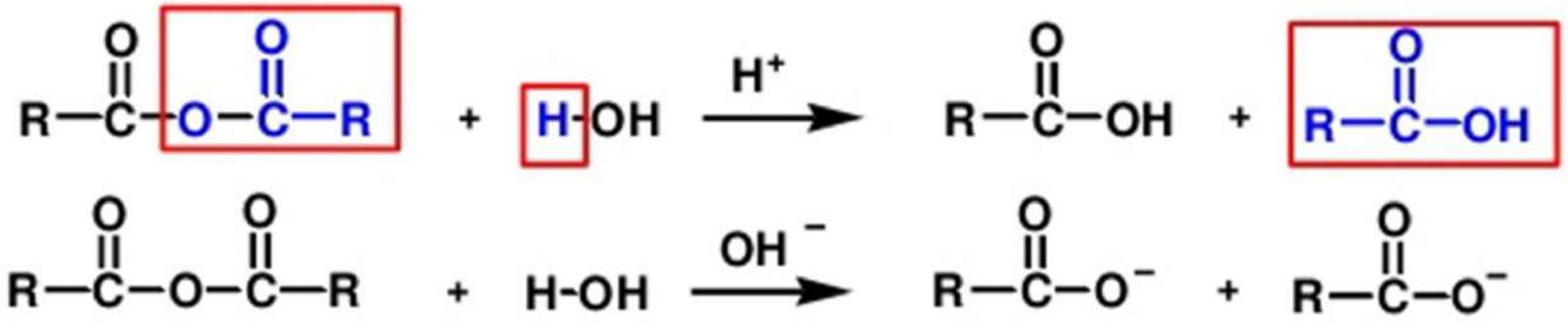


Reactions of acid anhydride

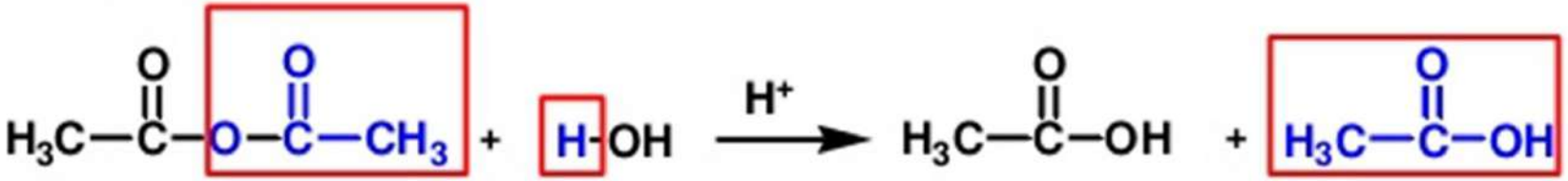


HYDROLYSIS

- Acid anhydrides undergoes hydrolysis to produce carboxylic acids.
- Can be carried out in acid or base.
- Carboxylate salts are formed if hydrolysis is done in basic solution.



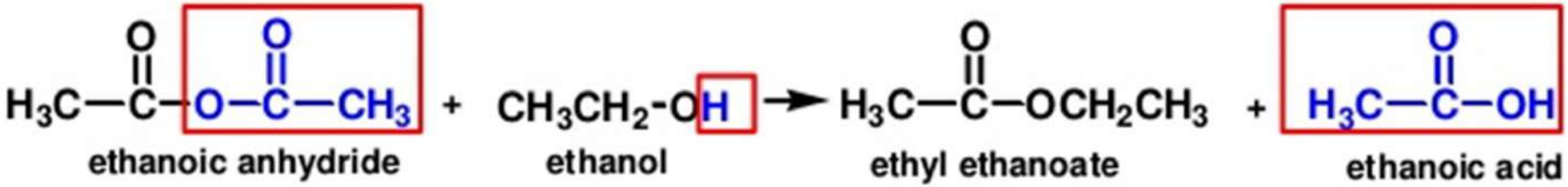
EXAMPLE

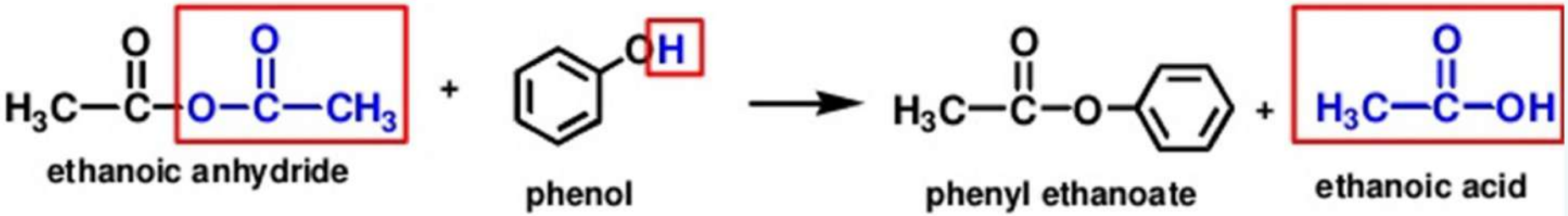


ALCOHOLYSIS

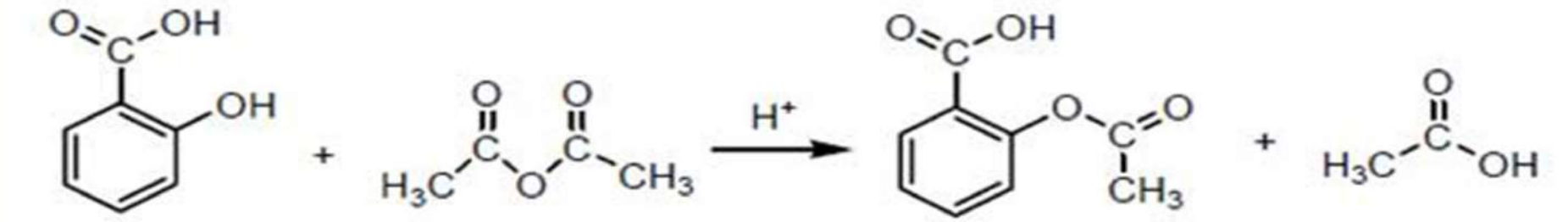
- Acid anhydrides react with alcohol to produce esters and carboxylic acids.
- Does not required catalyst, but still requires heating.

EXAMPLE





Phenolysis of acid anhydride "yields ester"

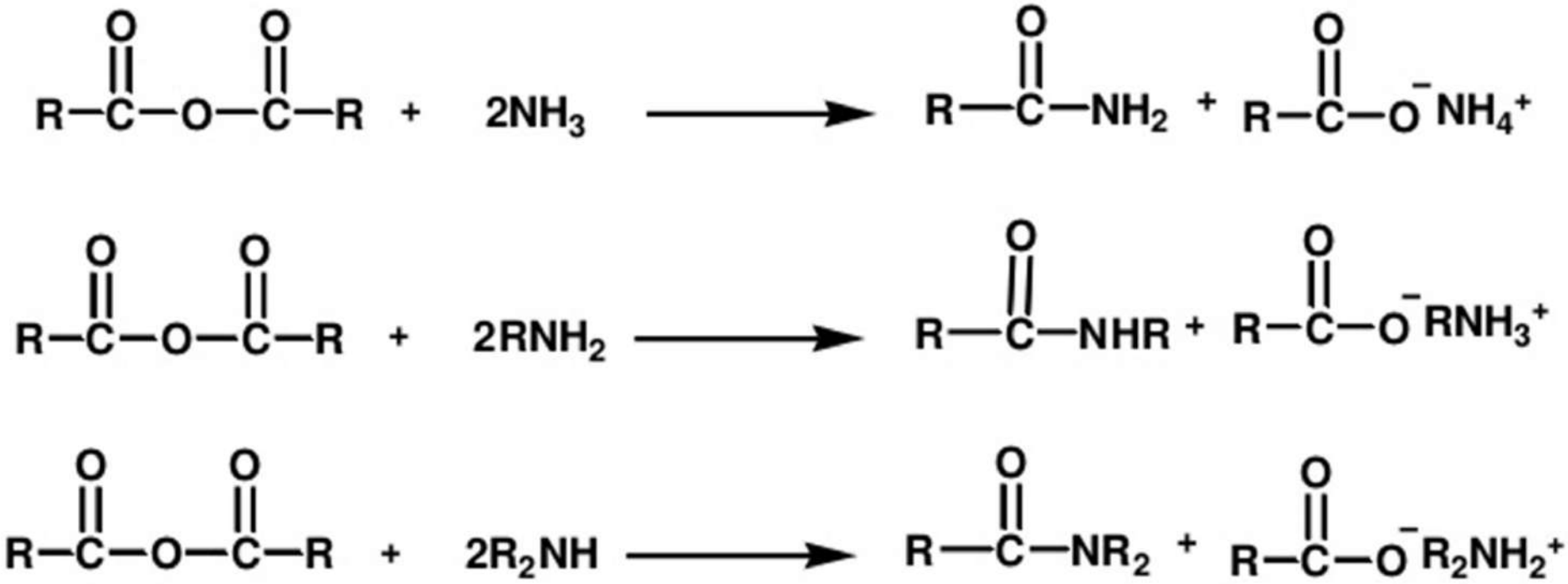


Salicylic Acid | Acetic anhydride | Acetylsalicylic acid (aspirin) | Acetic acid

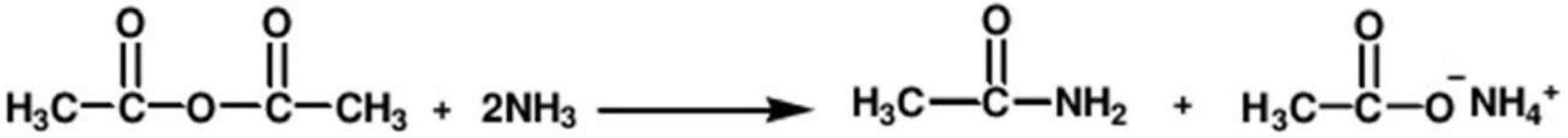
Notes:- the reaction can be accelerated through activation either the acid anhydride (through adding few drops of conc. acid) or activating the phenol (through adding NaOH)

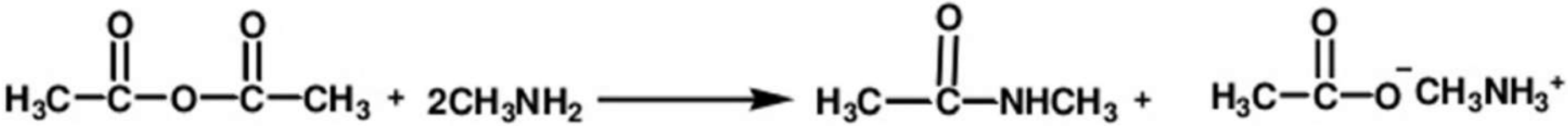
AMMONOLYSIS

- Amide can be prepared through ammonolysis of acid anhydrides with ammonia, primary and secondary amines.



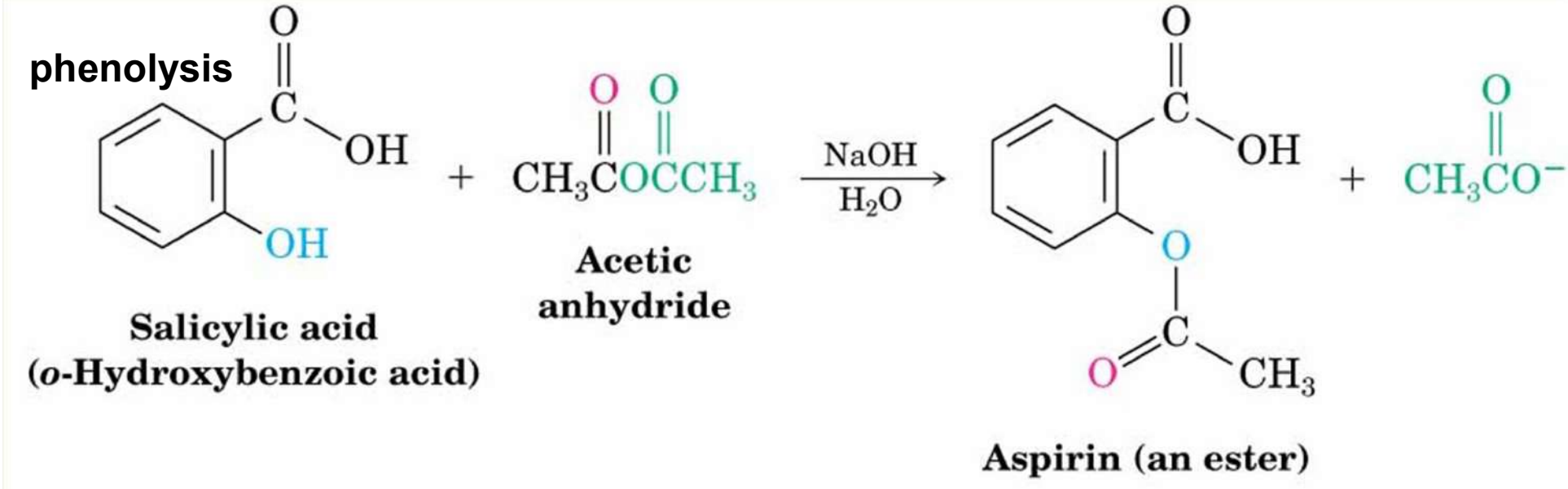
EXAMPLES:


H3C–C(=O)–O–C(=O)–CH3 + 2NH3
H3C–C(=O)–NH2 + H3C–C(=O)–O⁻ NH4⁺


H3C–C(=O)–O–C(=O)–CH3 + 2CH3NH2
H3C–C(=O)–NHCH3 + H3C–C(=O)–O⁻ CH3NH3⁺

The last step in both aspirin and paracetamol synthesis

phenolysis



Part 4
Derivatives of Carboxylic Acid

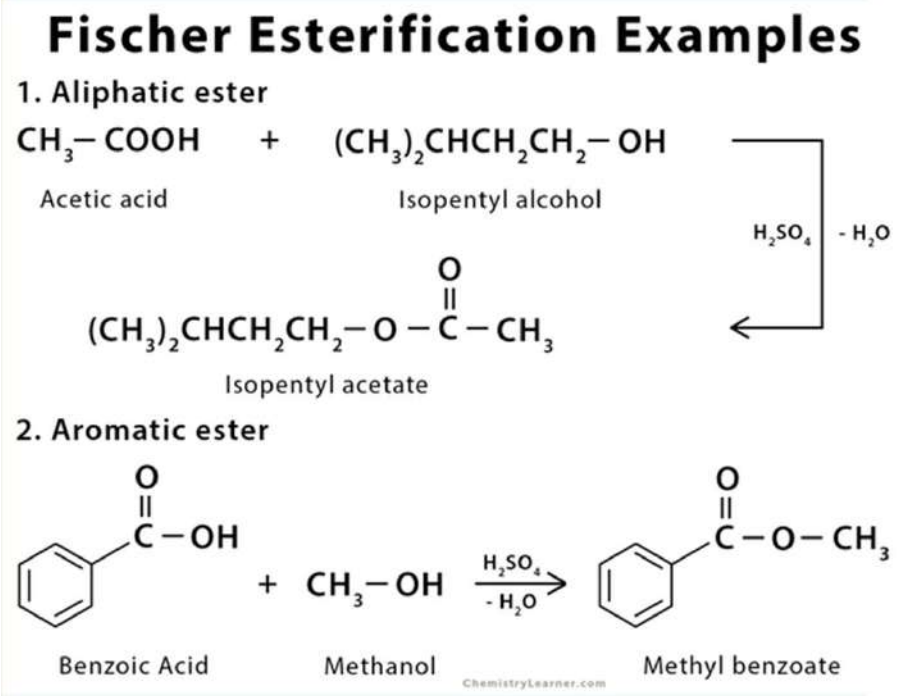
3- Ester

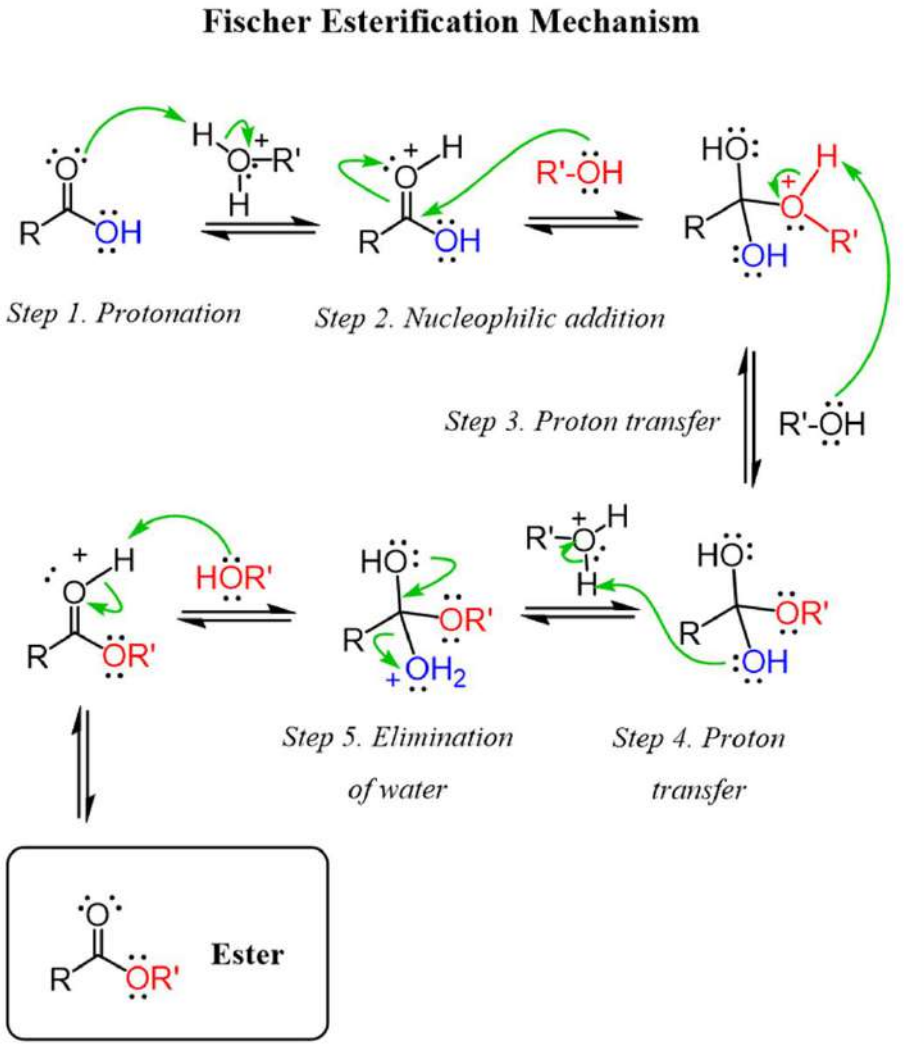
3) Chemistry of ester

Preparations of Ester

1] all alcoholysis and phenolysis of acid halide or acid anhydride. " studied before"

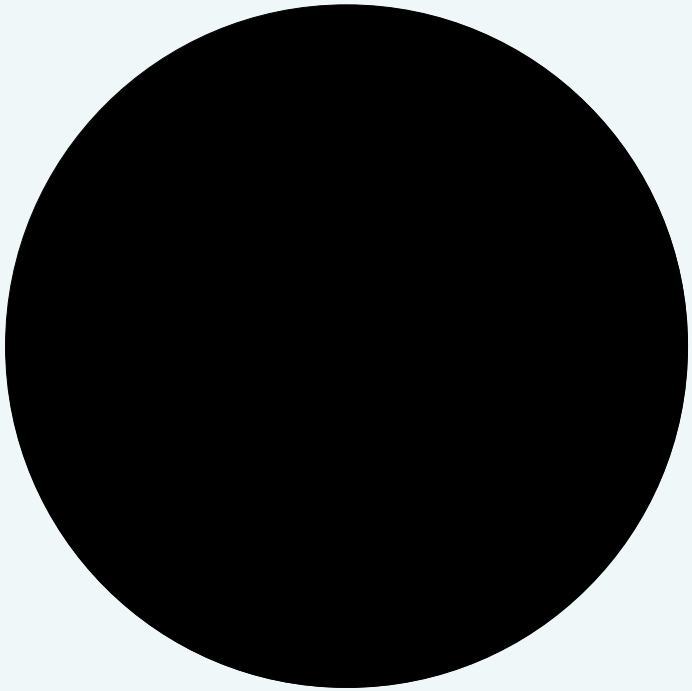
2] Fischer esterification

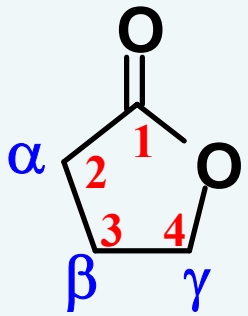




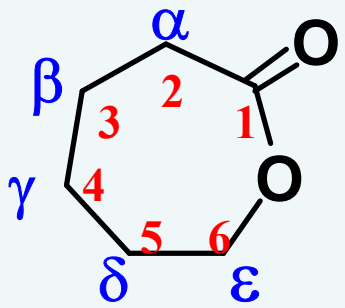
Esters

- Lactone: A cyclic ester.
  - name the parent carboxylic acid, drop the suffix -ic acid and add -olactone.



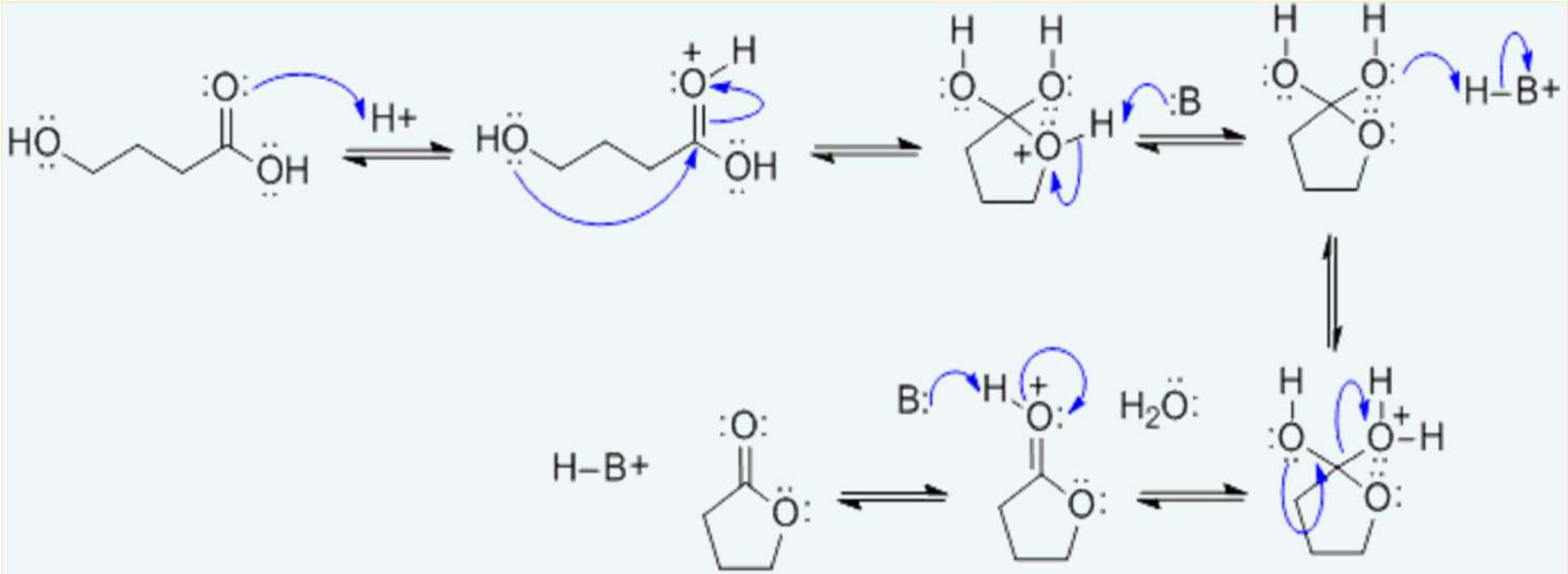


4-Butanolactone
(γ-Butyrolactone)

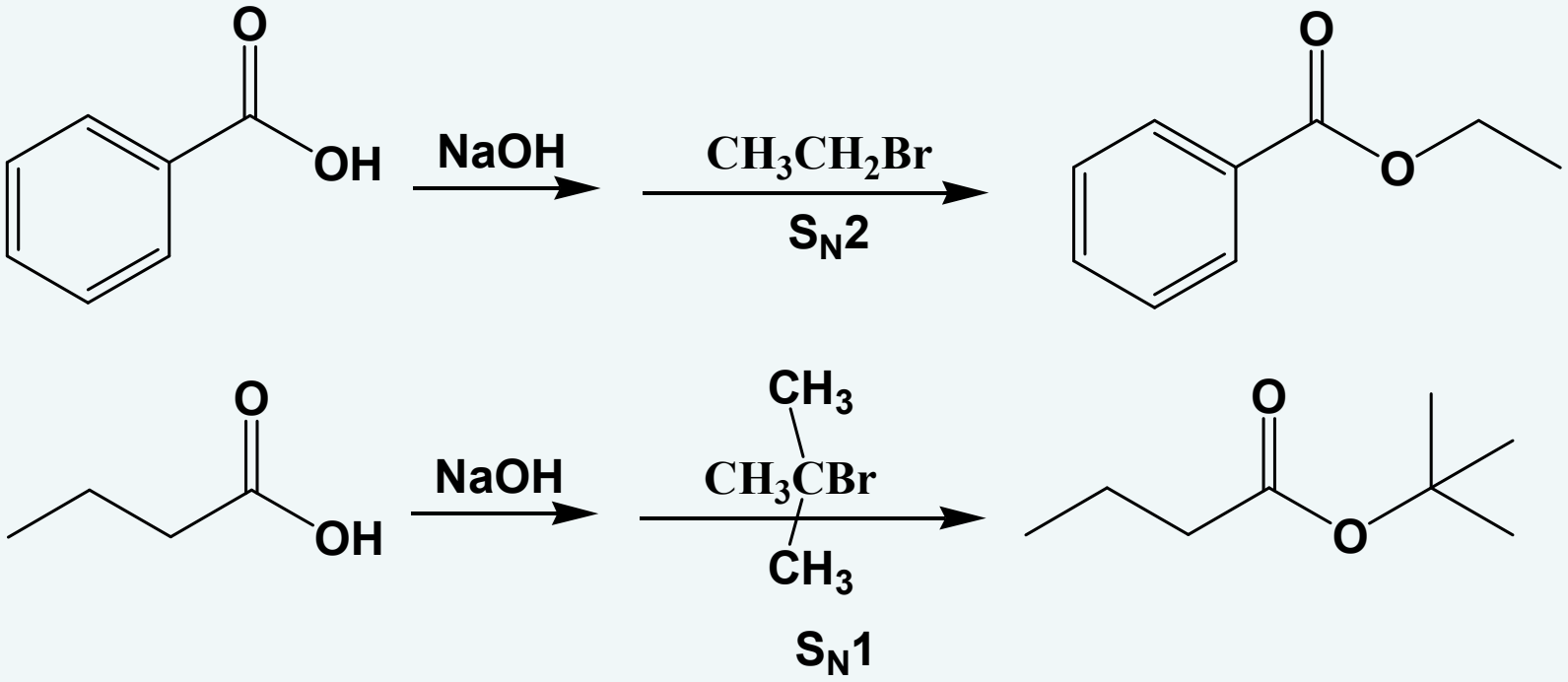


6-Hexanolactone
(ε-Caprolactone)

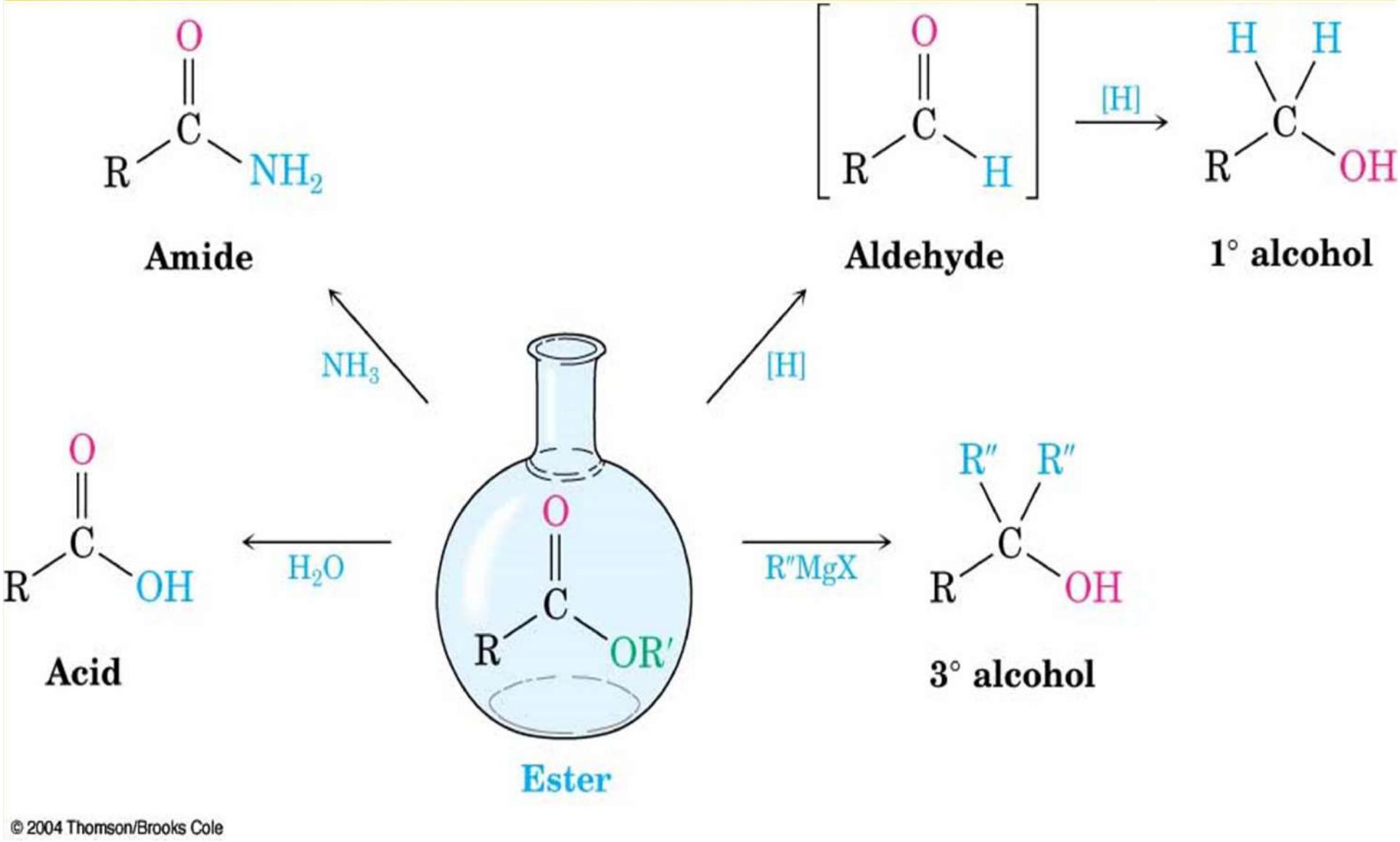
Intramolecular Fisher Esterification leads to form Lactone ctone



Nu Sub of alkyl halide by carboxylate salt



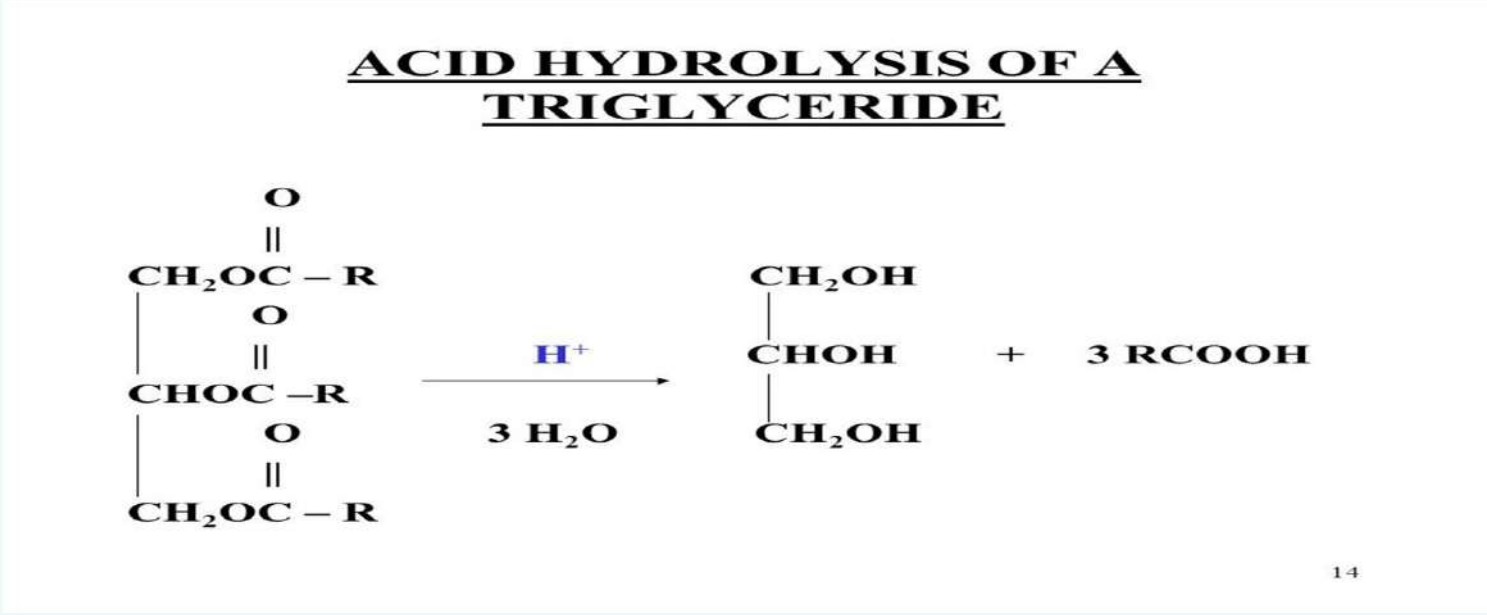
Reactions of Esters

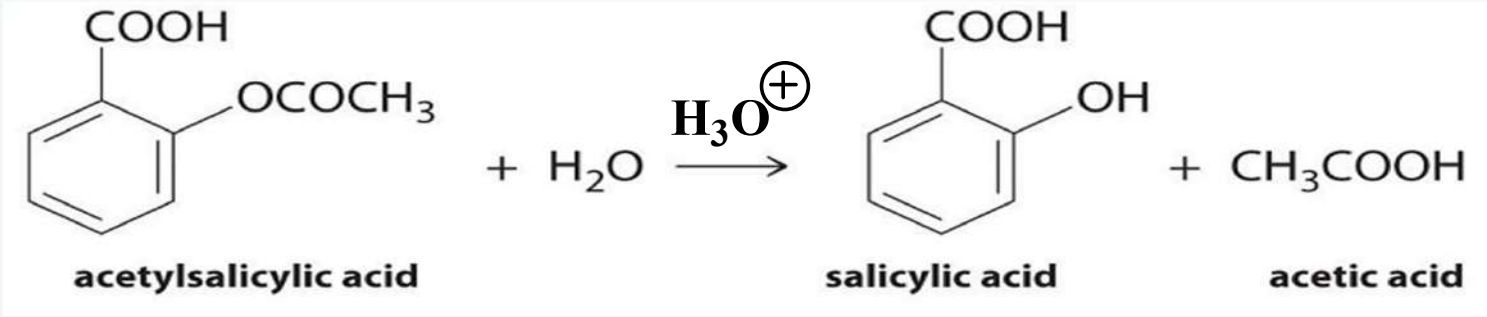


Reaction of ester

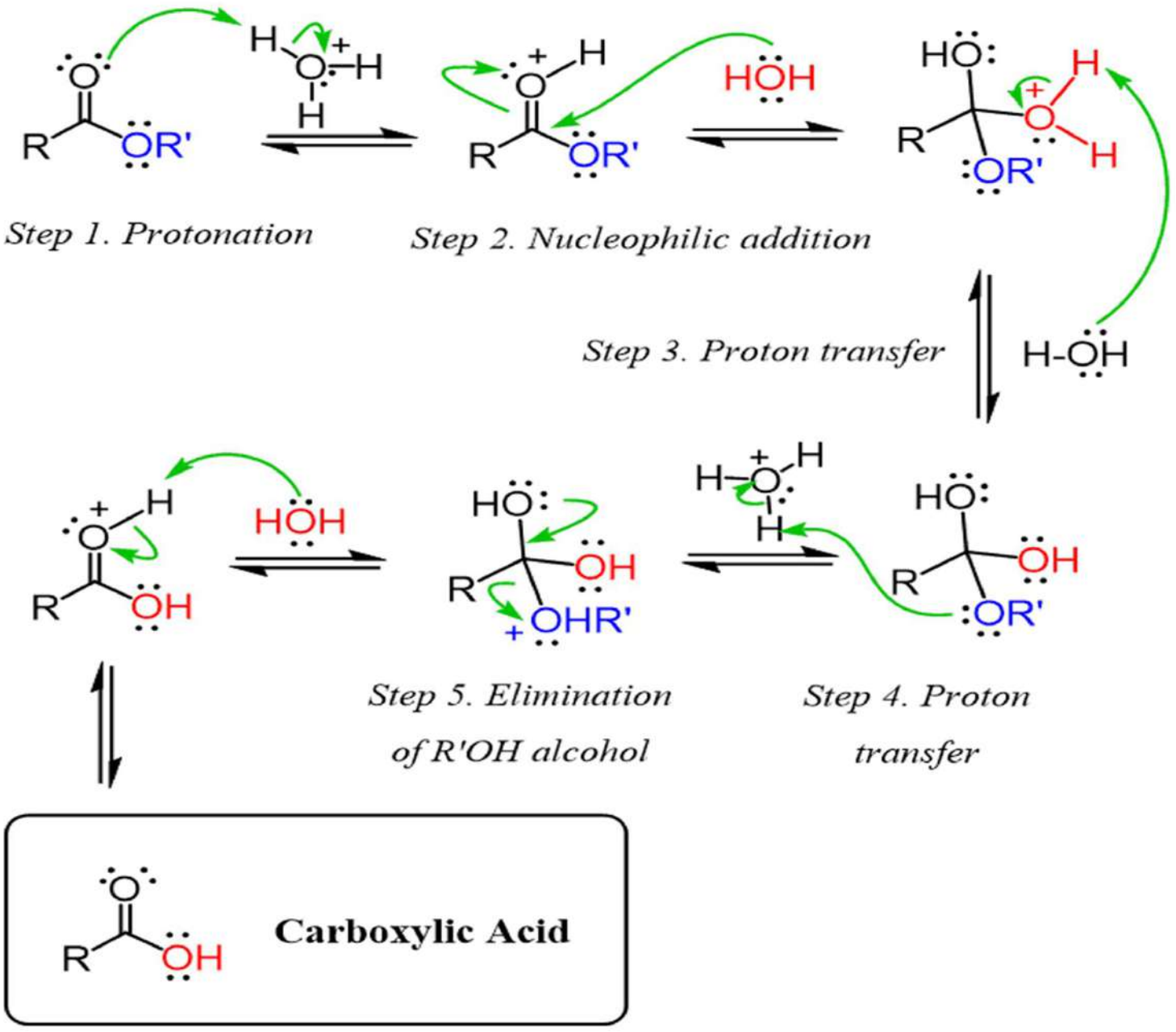
1- Hydrolysis of ester:-

a] acidic hydrolysis

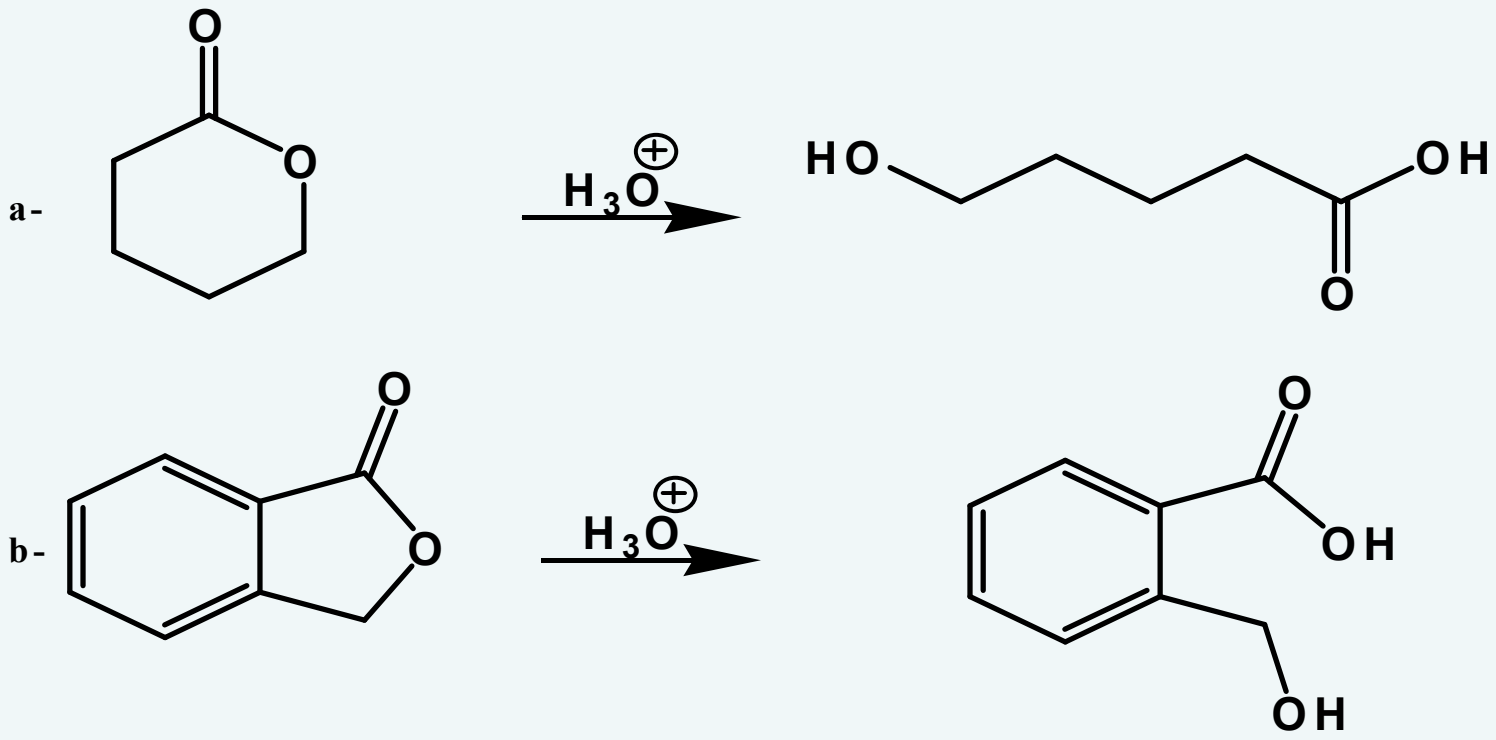




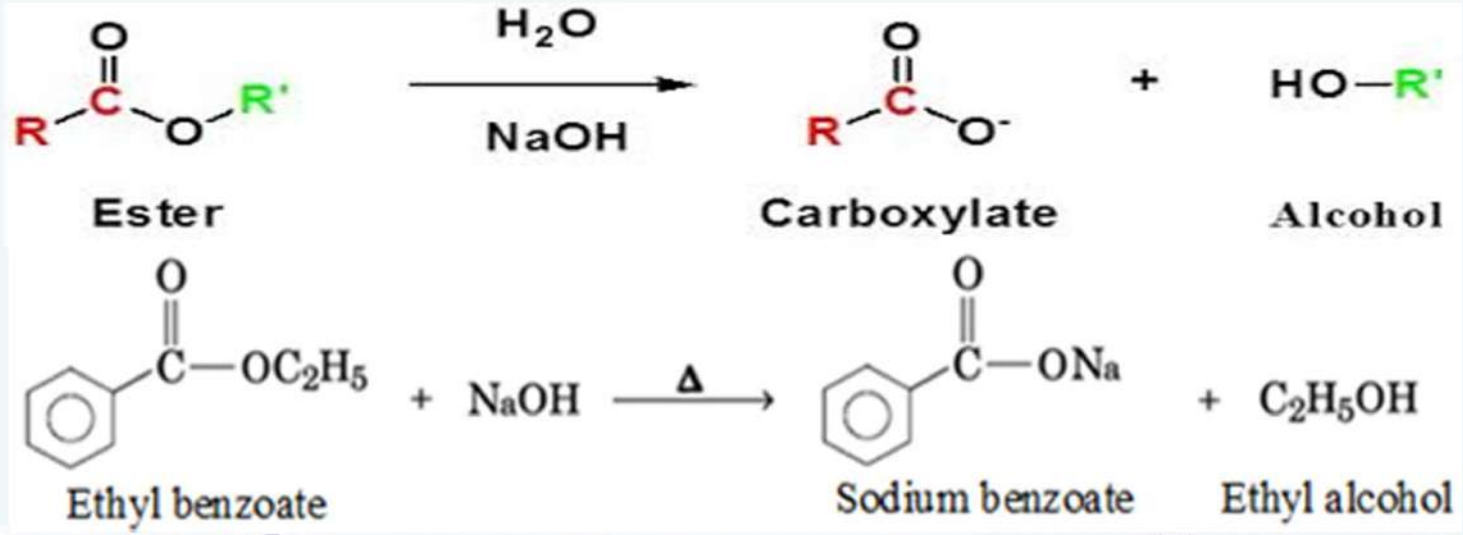
Mechanism of Acid-Catalyzed Esters Hydrolysis

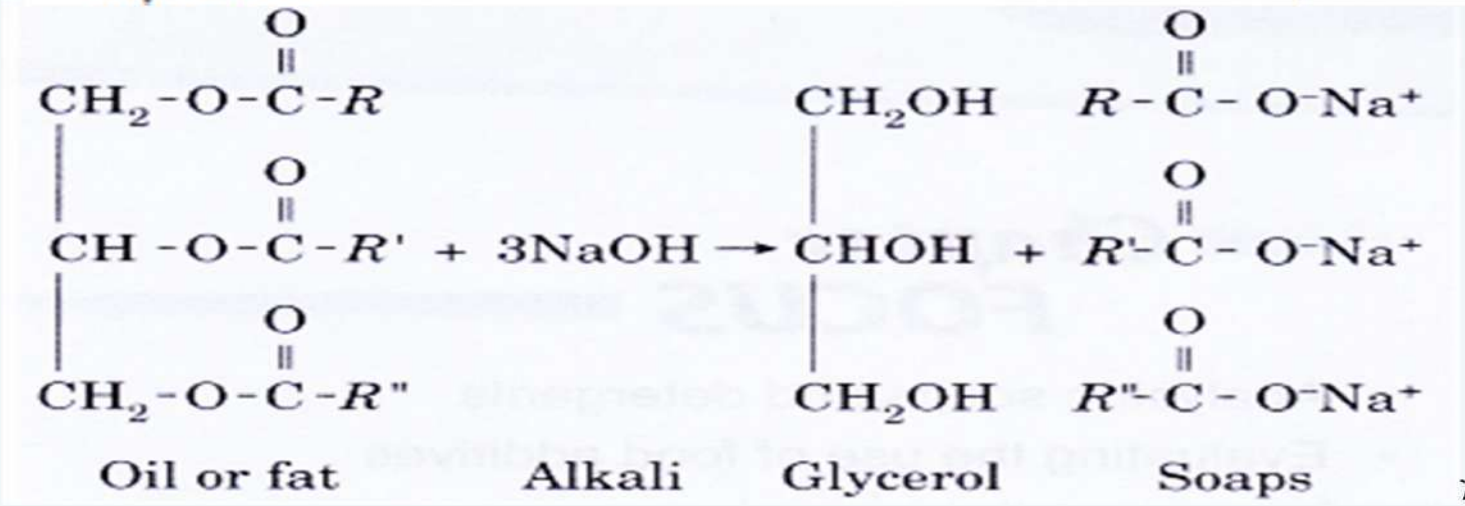


Lactone “cyclic ester” acidic hydrolysis



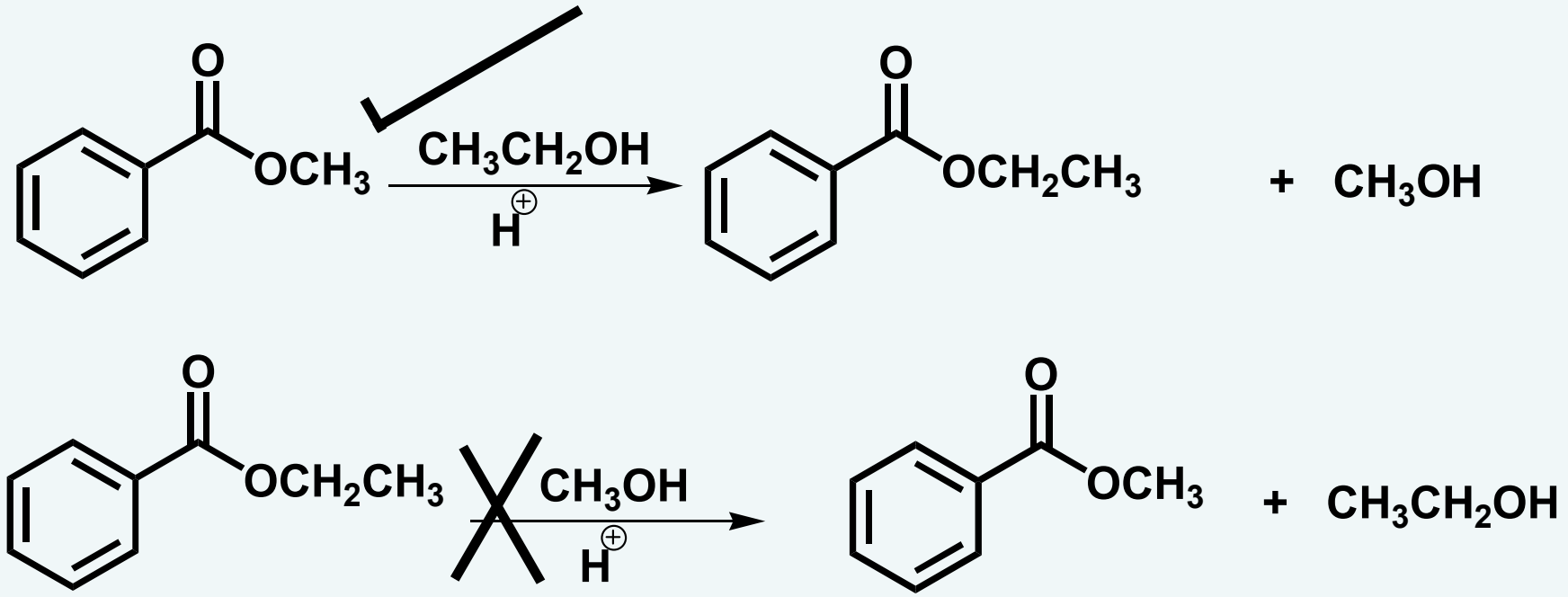
b] Alkaline hydrolysis of ester "Saponification"



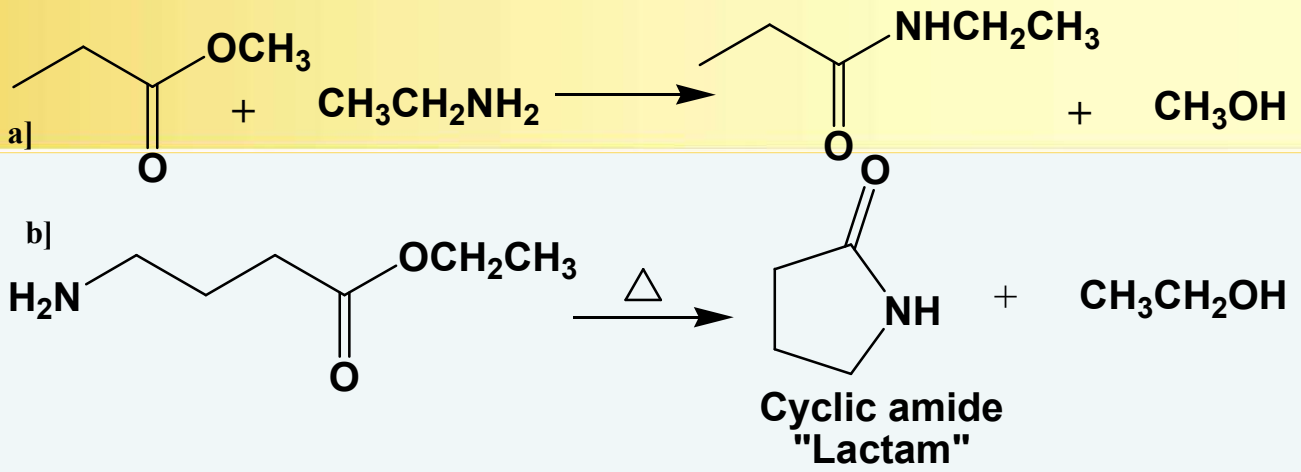


3] Alcoholysis of ester Trans-esterification

Easter conversion to different ester through changing the original alcohol

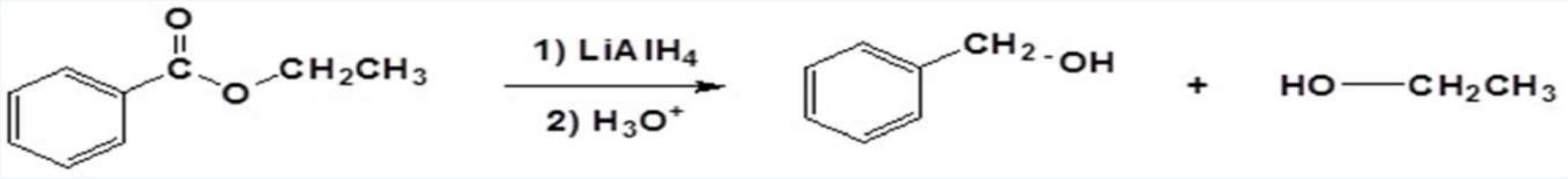


4] Aminolysis of Esters“ amide & Lactam synthesis”

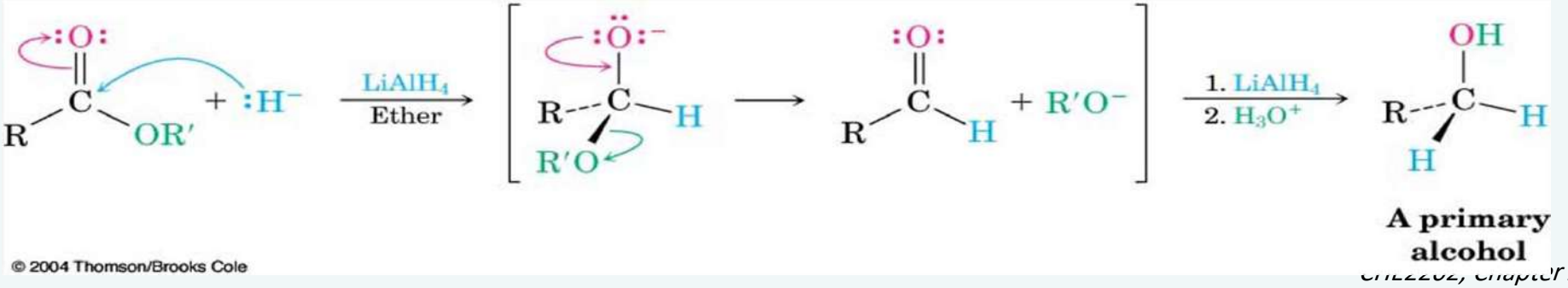


5] Reduction: Conversion of Esters into Alcohols

1] Using $LiAlH_4$ yields primary alcohols

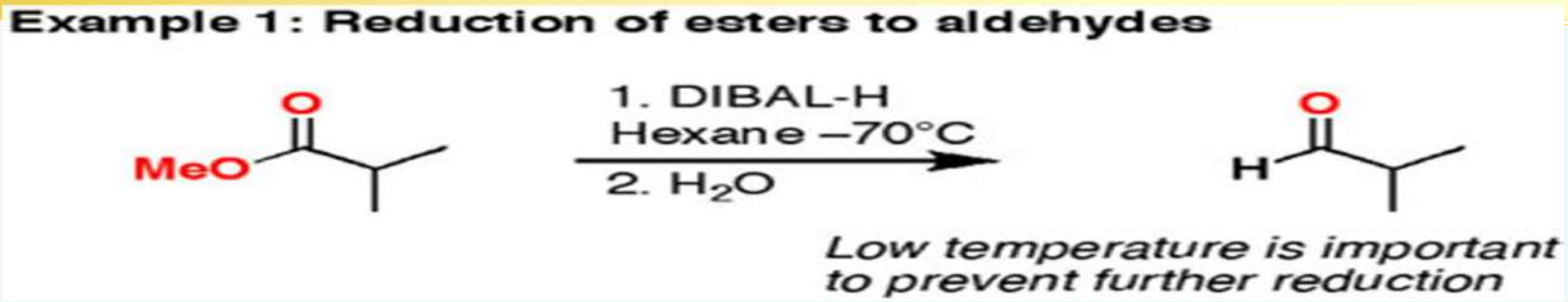


Mechanism

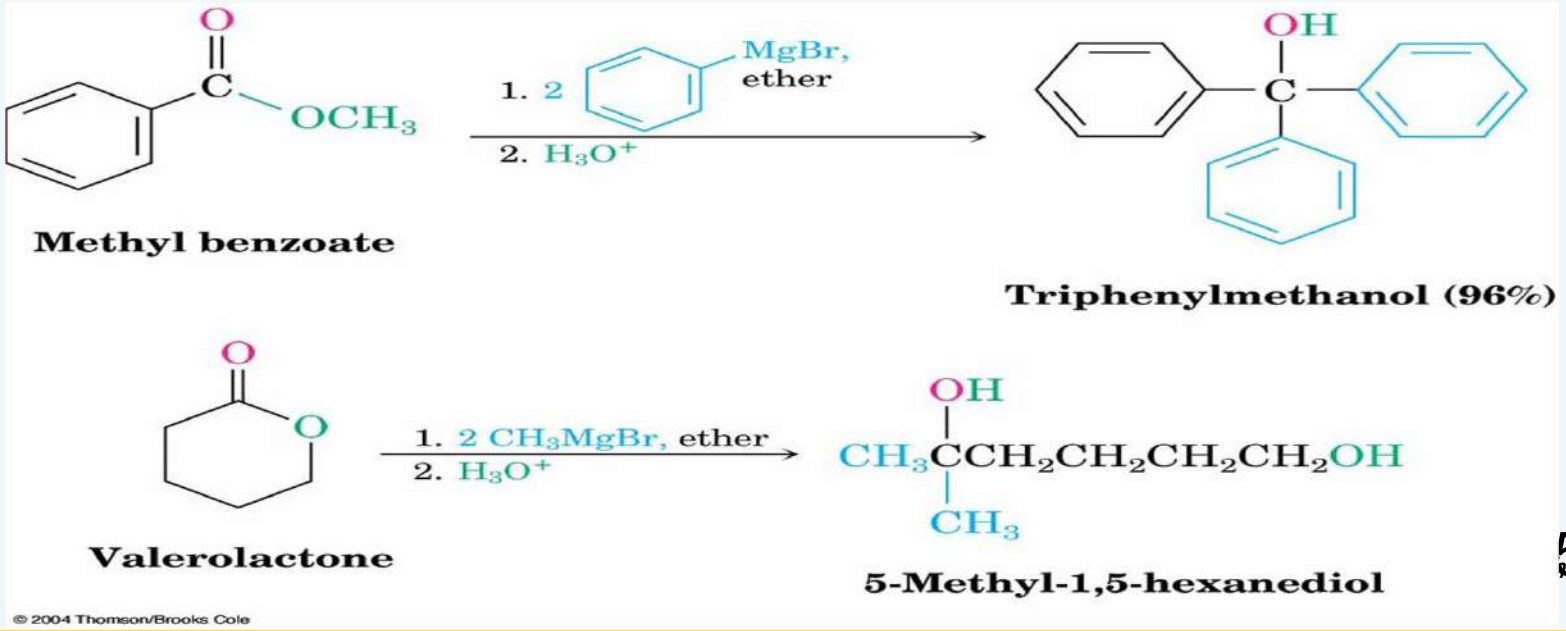


Partial Reduction of ester

2] Using DIBAH (DIBAL) yields Aldehyde



3] Using RMgX yields ketone then alcohol when React with 2 equivalents of a Grignard reagent to yield a tertiary alcohol

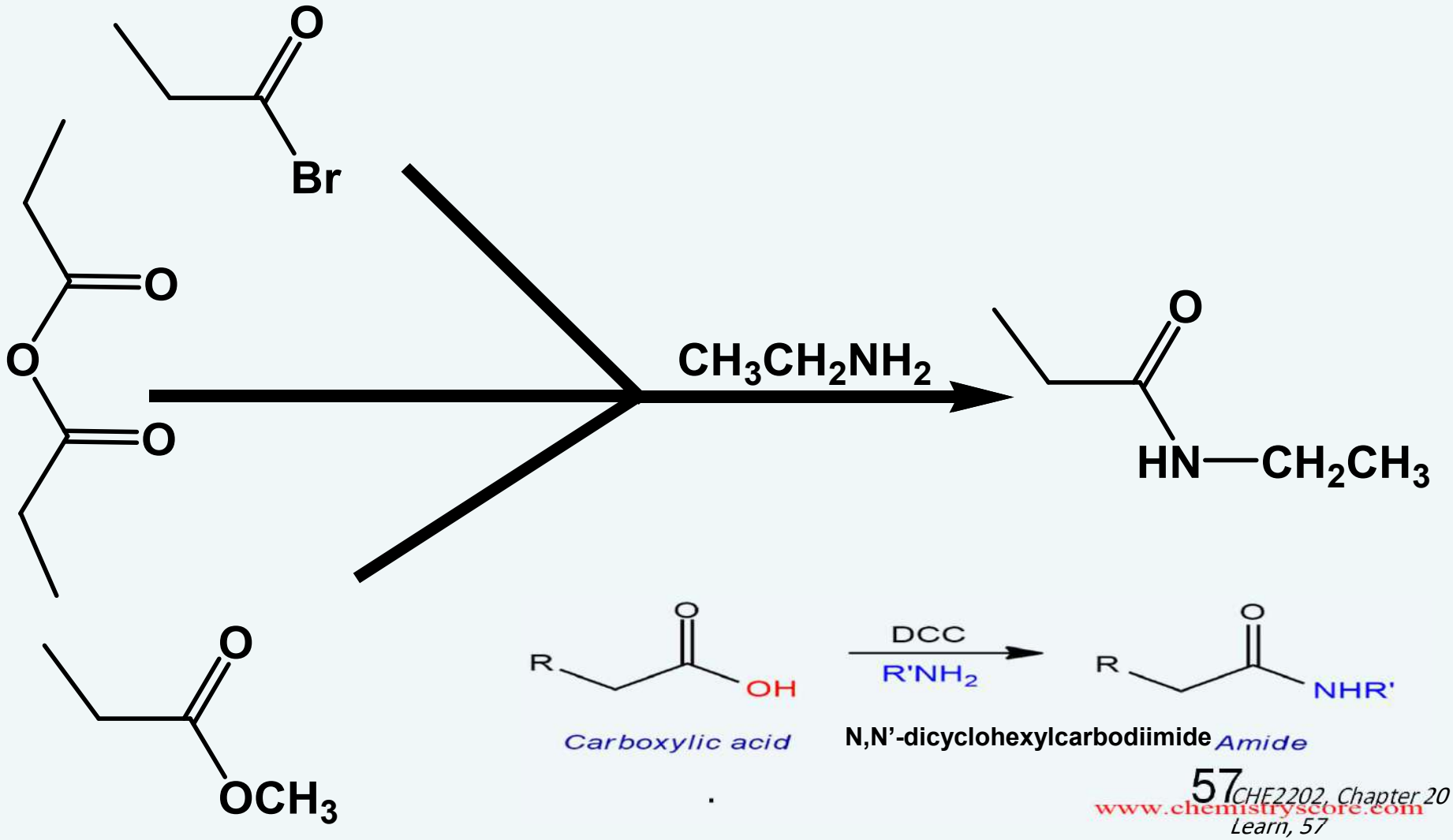


Part 5
Derivatives of Carboxylic Acid

4-Amide
5-Nitrile

4) Chemistry of Amides
Preparation :-

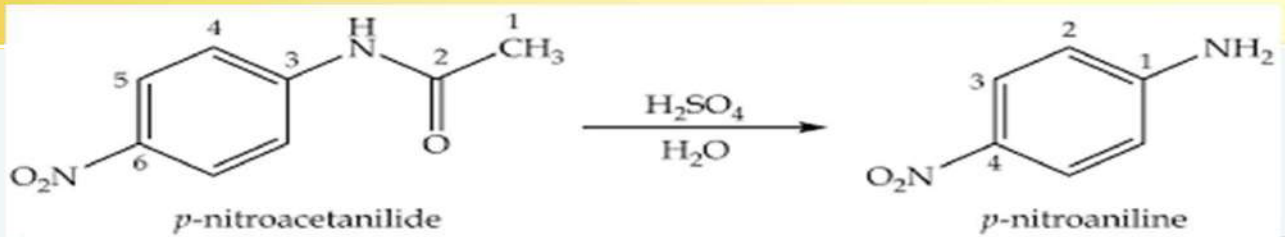
Aminolysis of acid halide, acid anhydride and ester

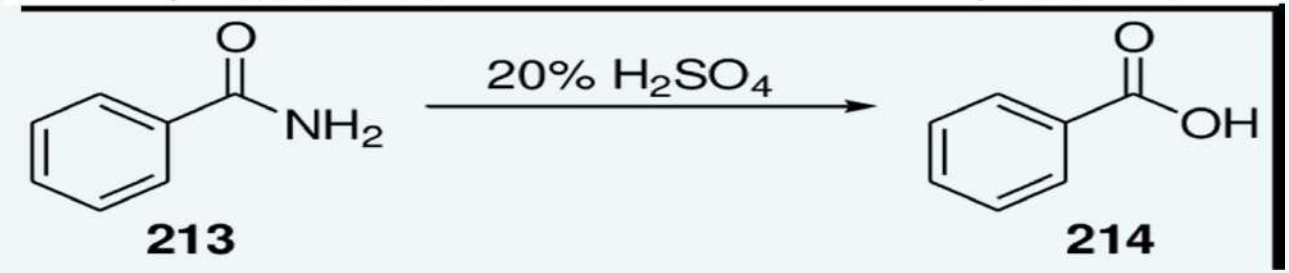


Carboxylic acid **N,N'-dicyclohexylcarbodiimide** *Amide*

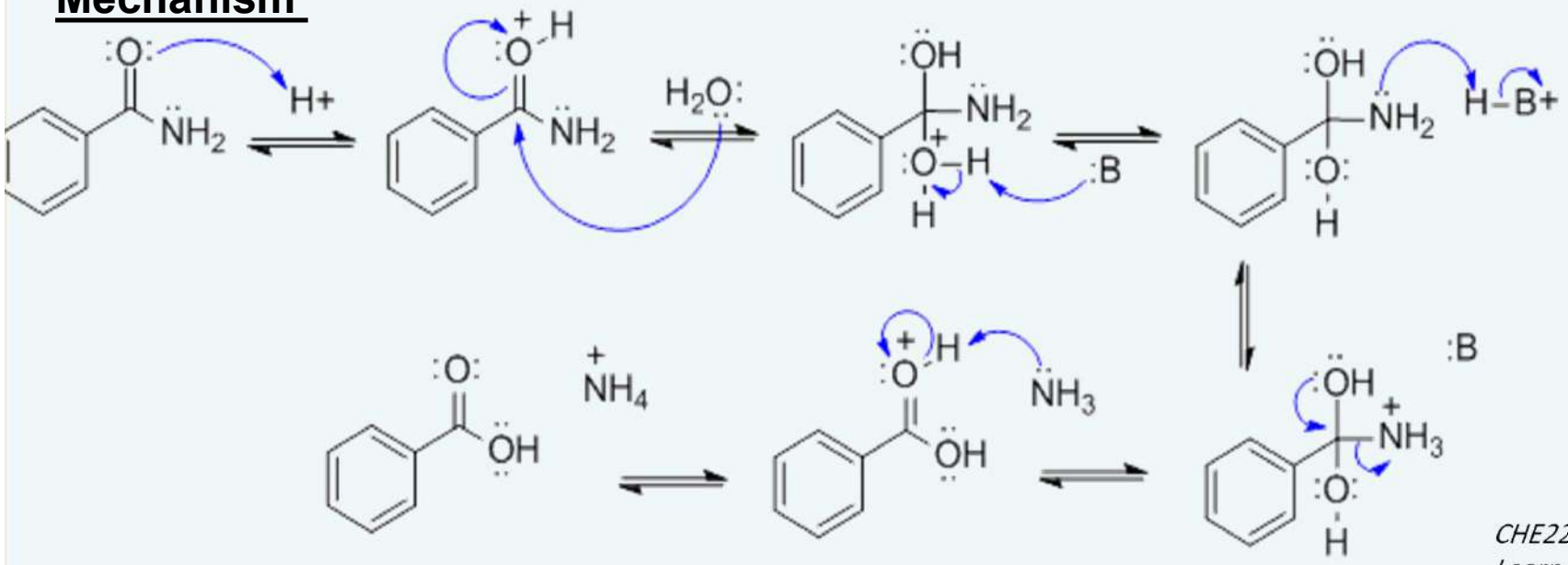
3] Reaction of amides

a- Acidic Hydrolysis

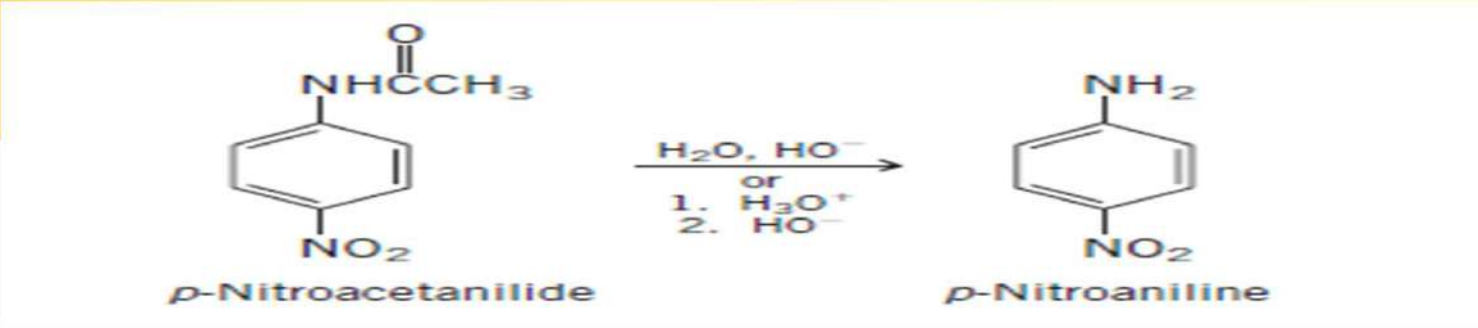




Mechanism

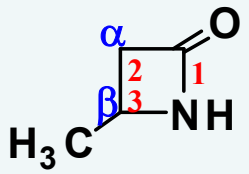


b- Alkaline Hydrolysis

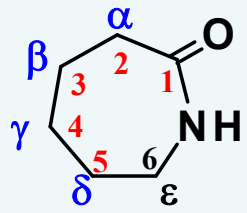


Name the parent carboxylic acid, drop the suffix -ic acid and add -lactam.

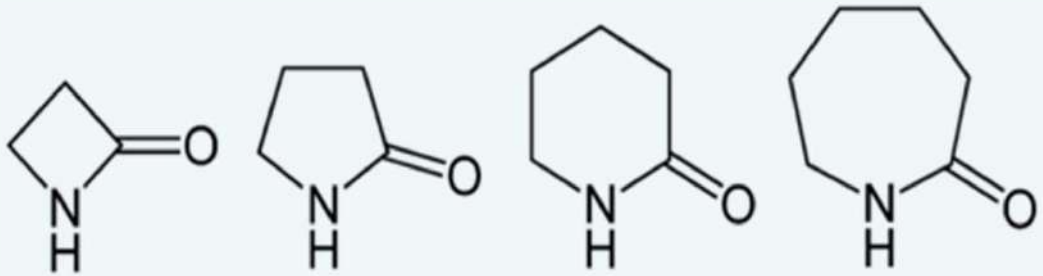
Lactam



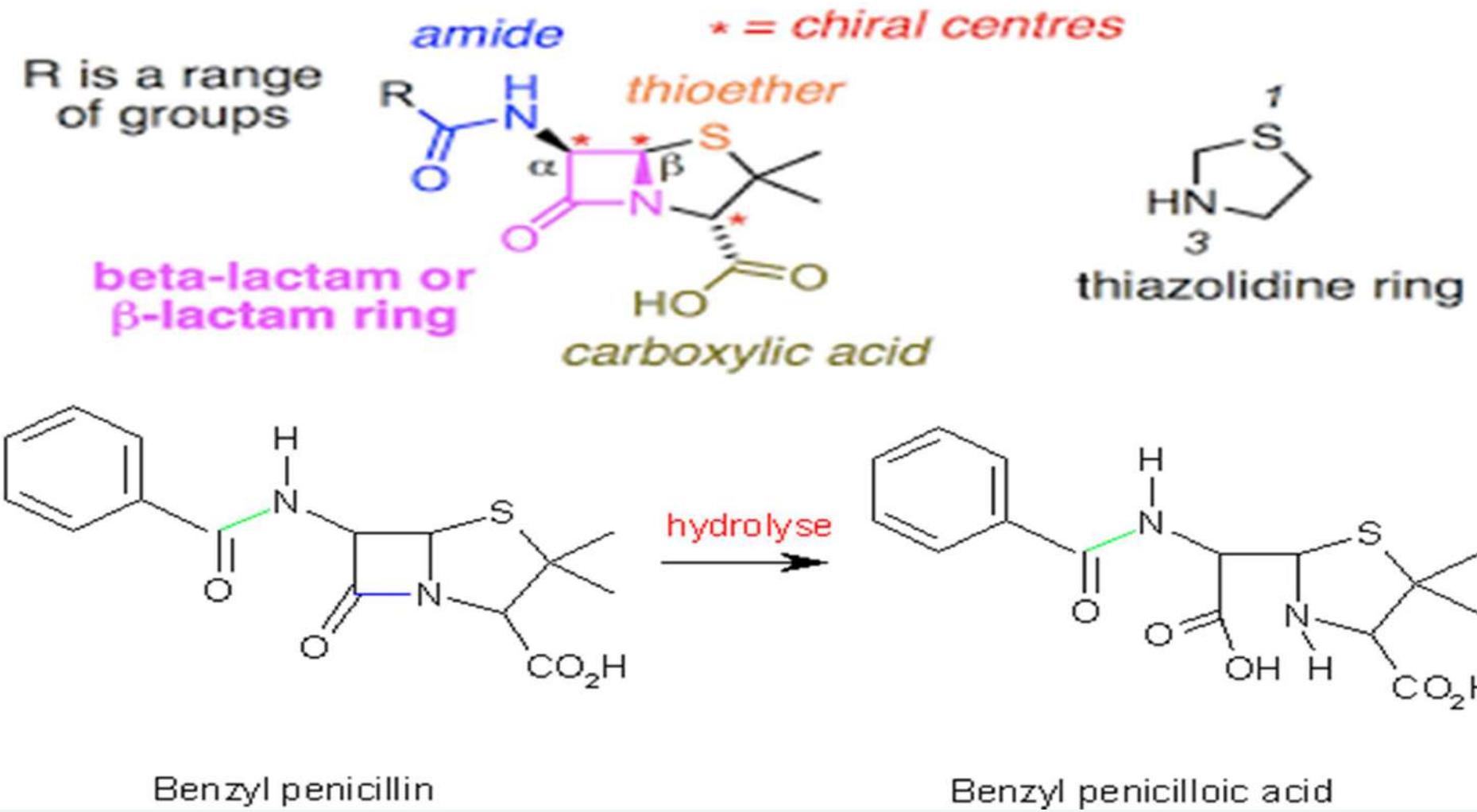
3-Butanolactam
(β-Butyrolactam)



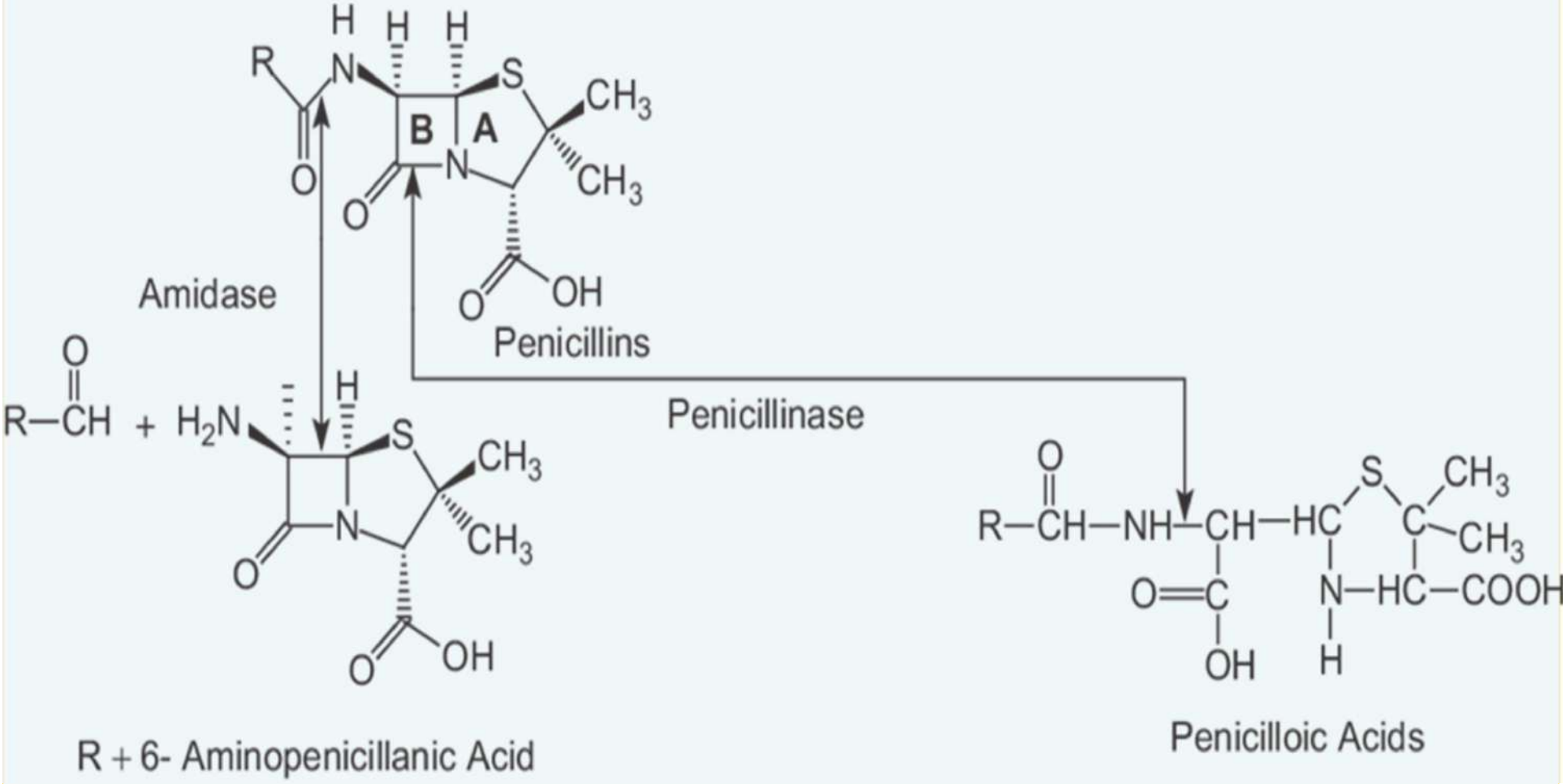
6-Hexanolactam
(ε-Caprolactam)



B-Lactam ring hydrolysis

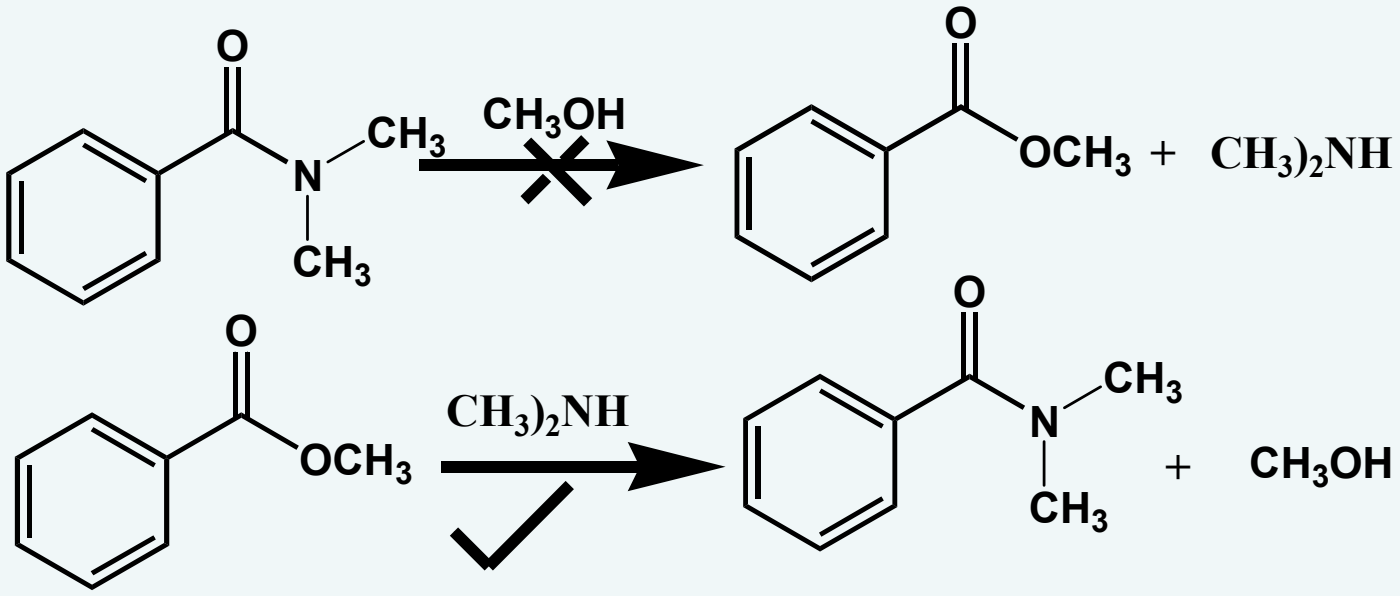


Penicillin hydrolysis



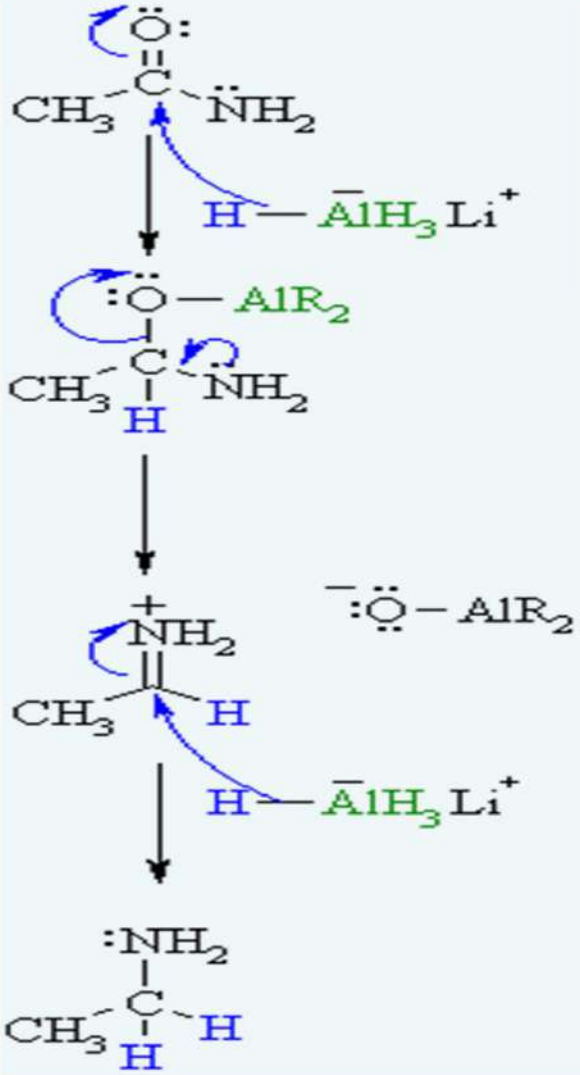
3] Alcoholysis of amide

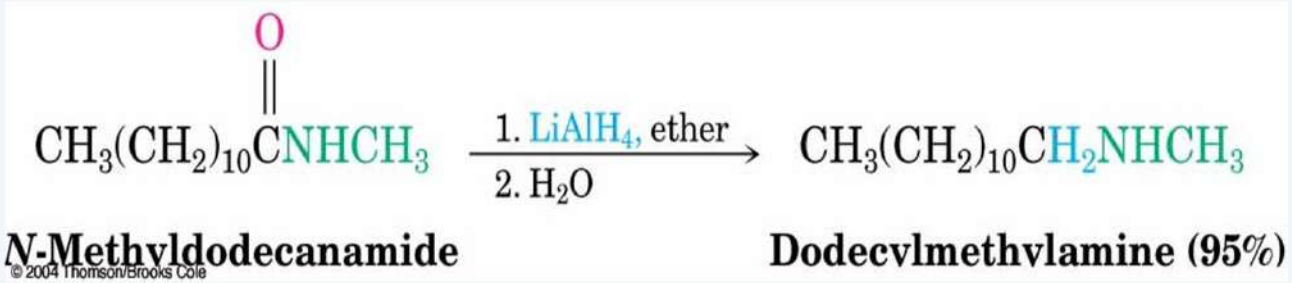
Aminolysis of an ester can be done; while Alcoholysis of amide can not be achieved directly ?

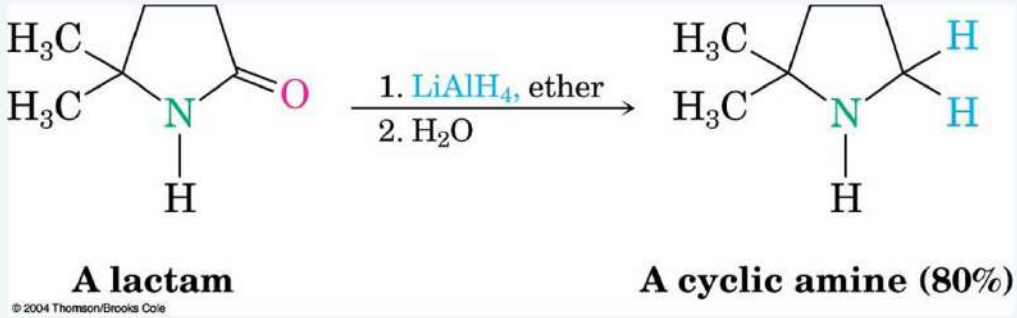


4- Reduction: Conversion of Amides into Amines using LiAlH4

- **Reduced by $LiAlH_4$ to an amine rather than an alcohol**
- **Converts C=O → CH_2** *(Looks-like wolf-kischnner and Clemmenson"*

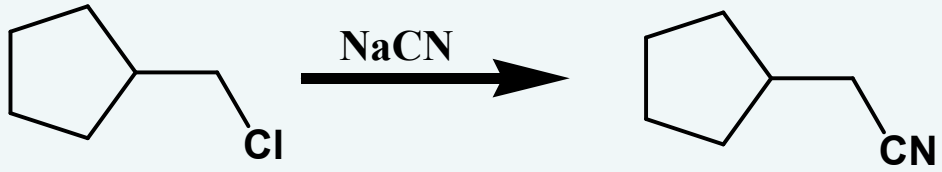




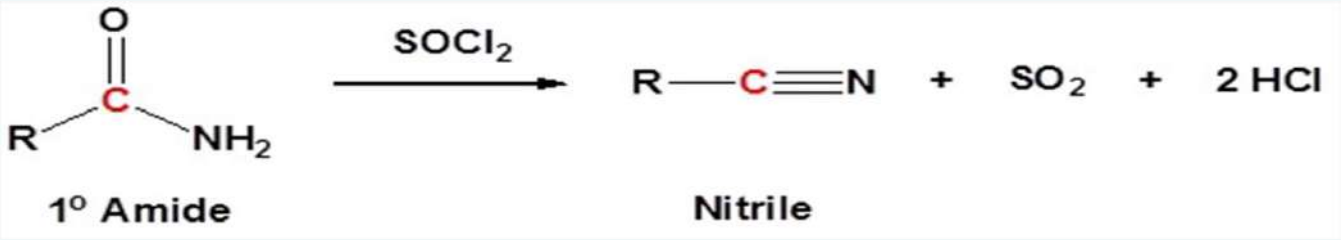


5- Chemistry of Nitriles

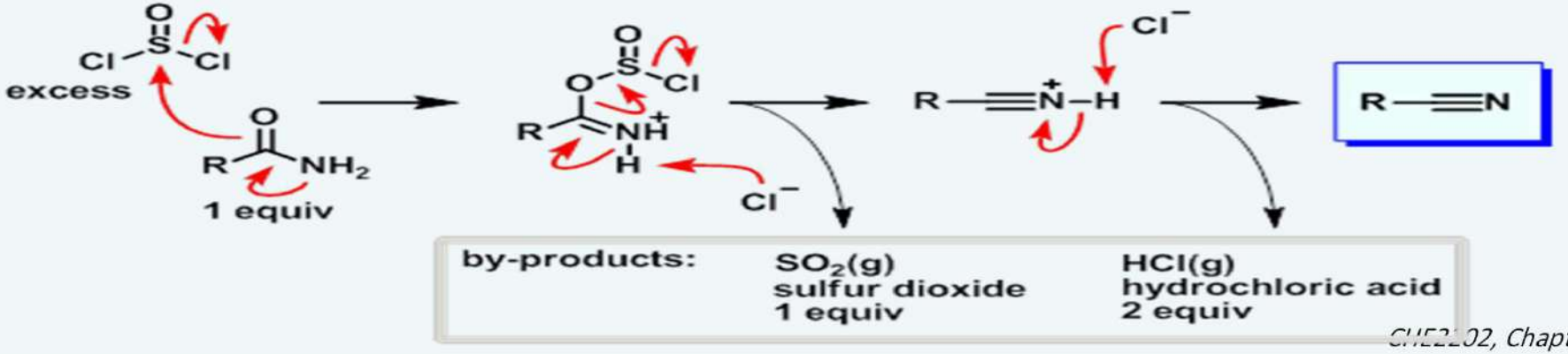
1- Nu Sub of alkyl halide using cyanide salt via SN1 or SN2



2- Reaction of primary amide with thionyl chloride



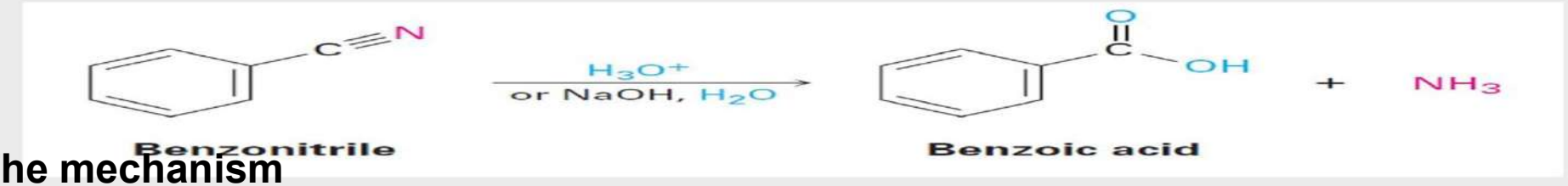
The mechanism



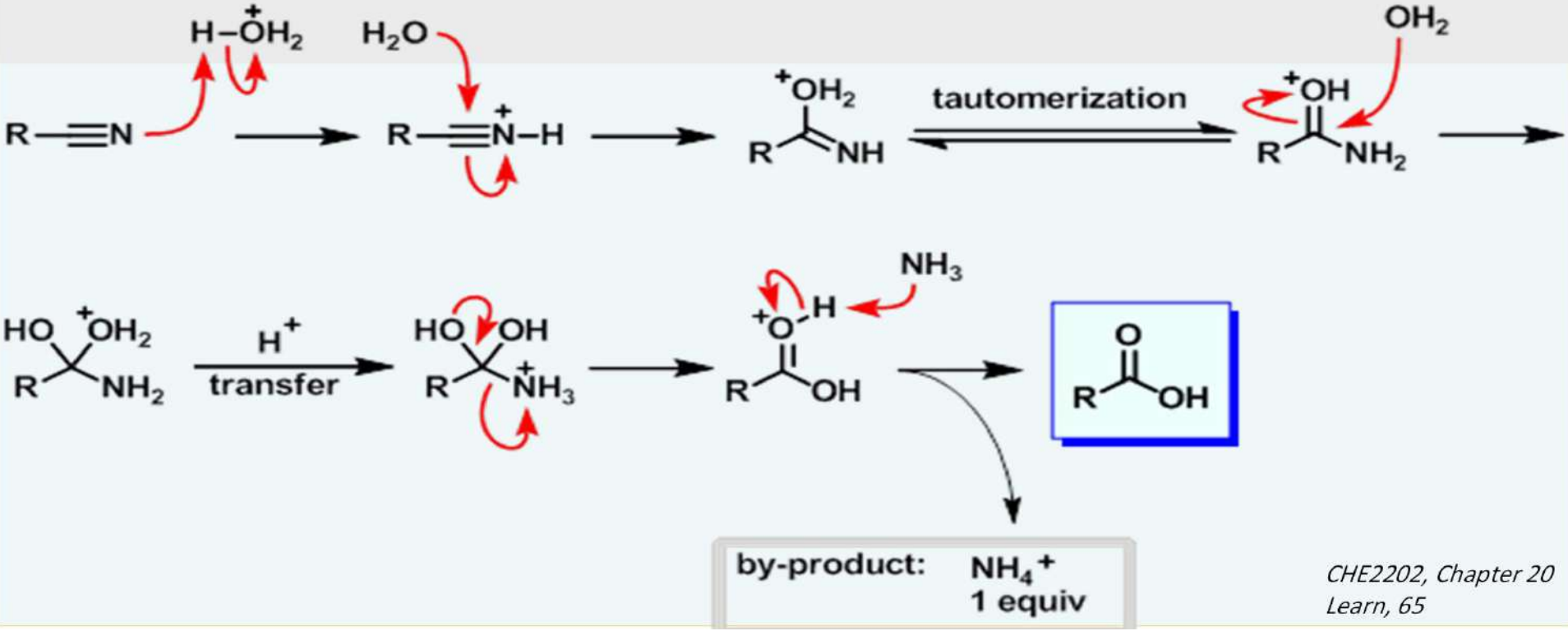
Reactions of Nitriles

Hydrolysis: Conversion of Nitriles into Carboxylic Acids

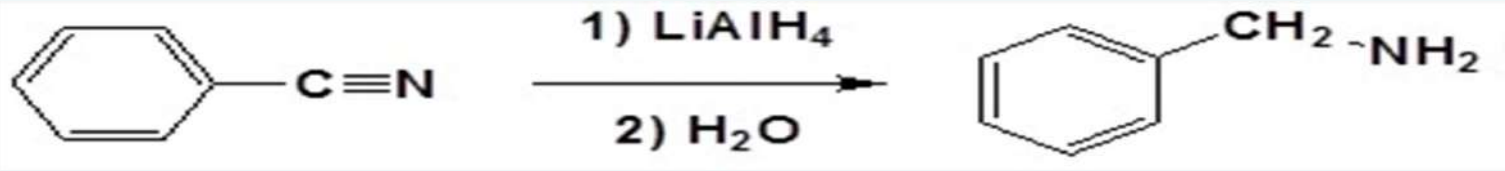
- Hydrolyzed in with acid or base catalysis to a carboxylic acid and ammonia (or an amine)



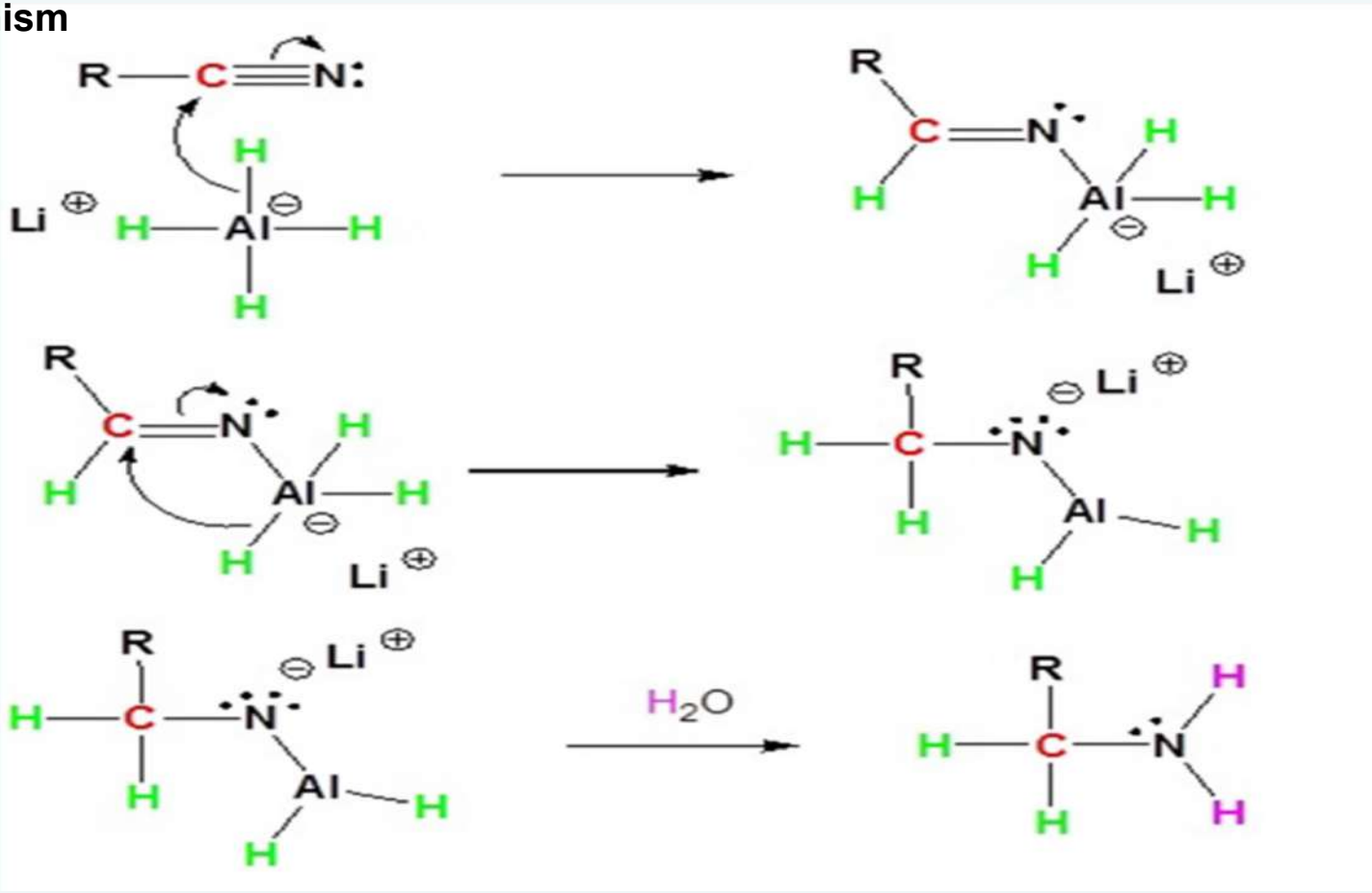
The mechanism



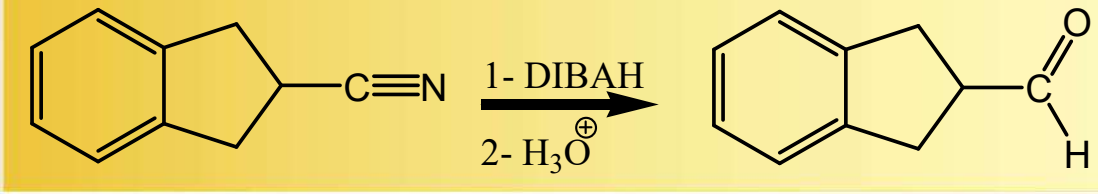
2] Reduction of nitrile
a- Using LiAlH4 (yields amine)



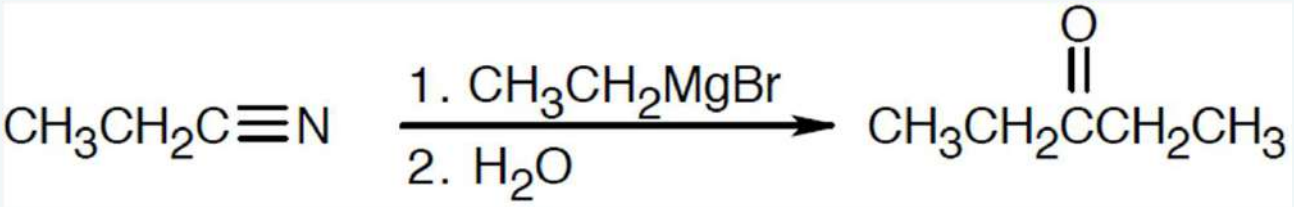
The mechanism

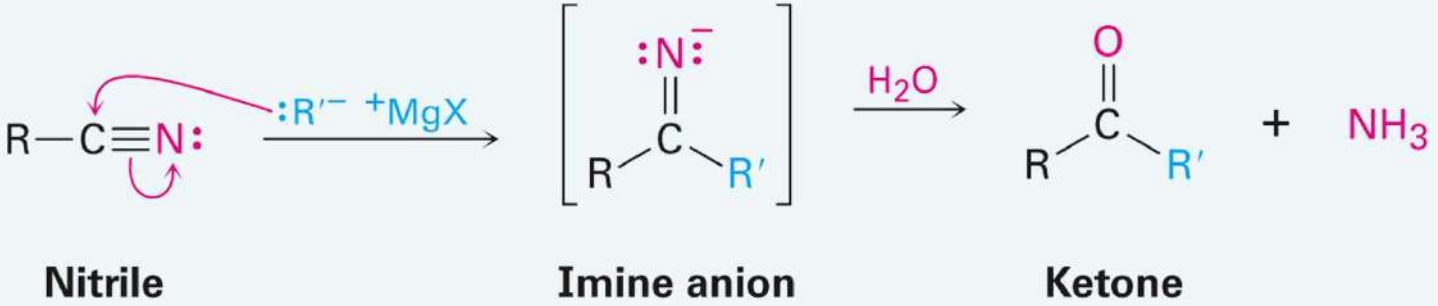


b- Using DIBAL (yields aldehyde)



c- Using Grignard reagent (yields ketone)





d- Using H2/Ni (yields amine)