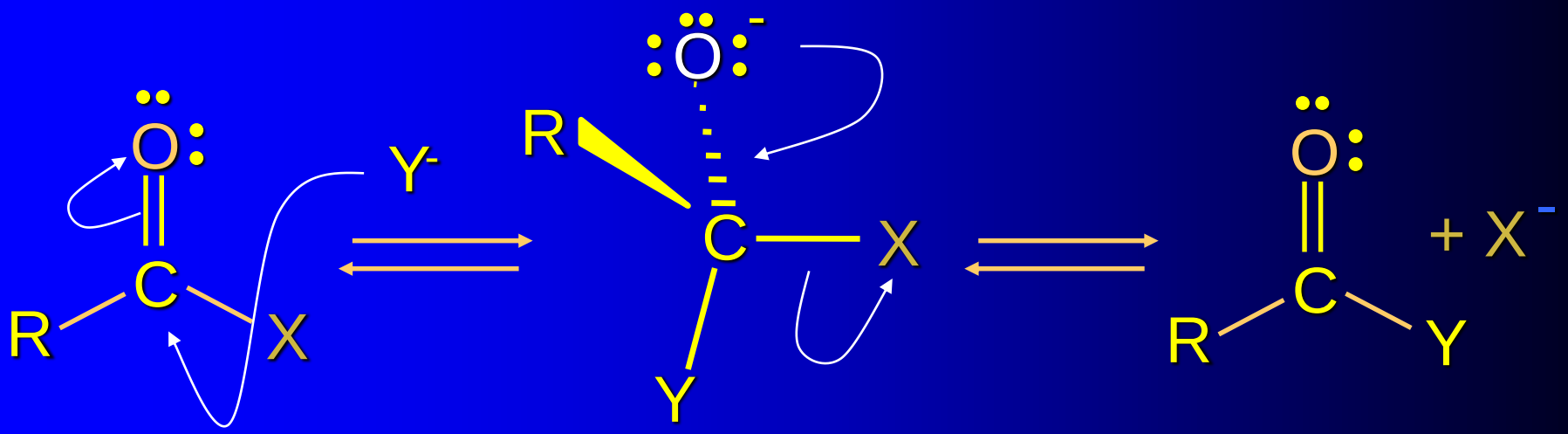
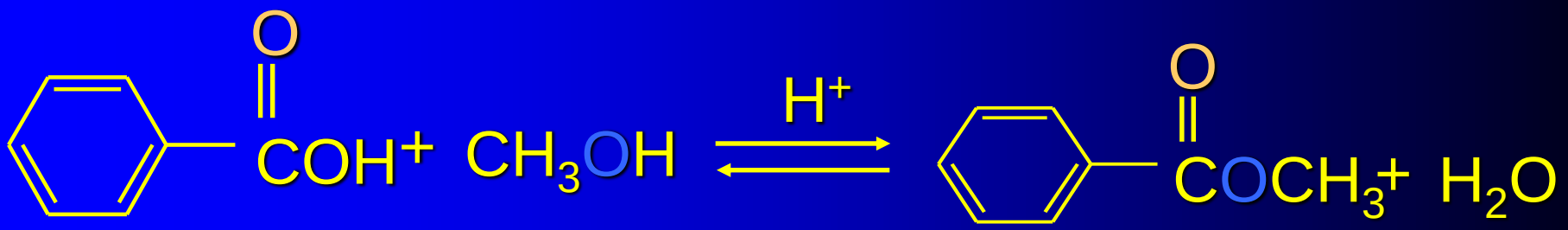
Lecture 19

Nucleophilic Acyl Substitution



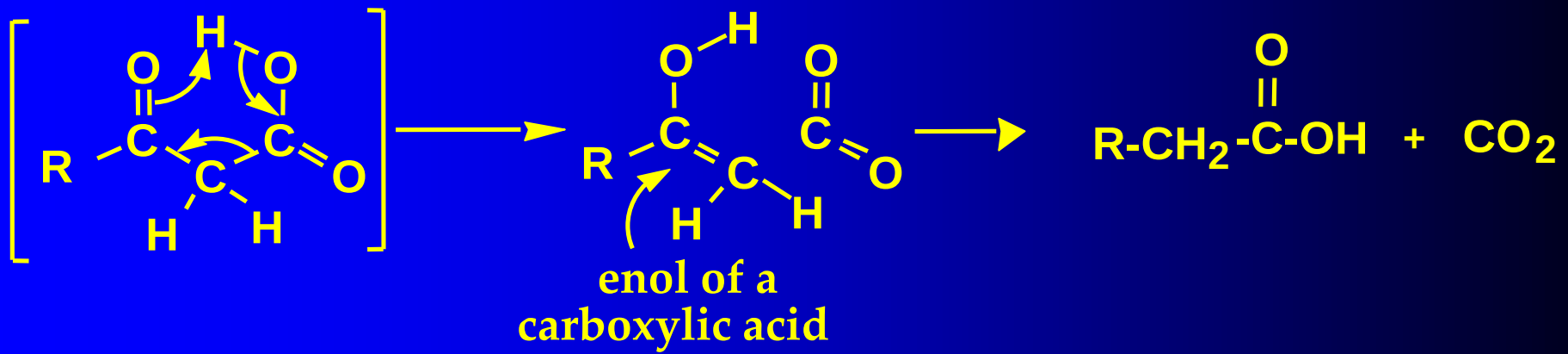
Acid-catalyzed Esterification

(also called Fischer esterification)



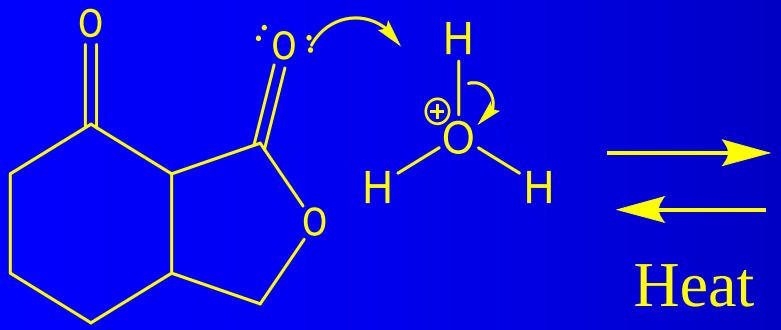
Please study the mechanism

Decarboxylation of β-keto acids

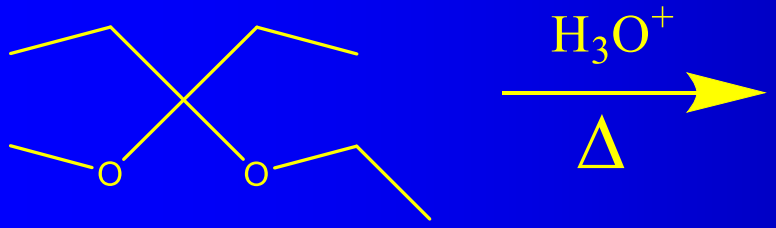


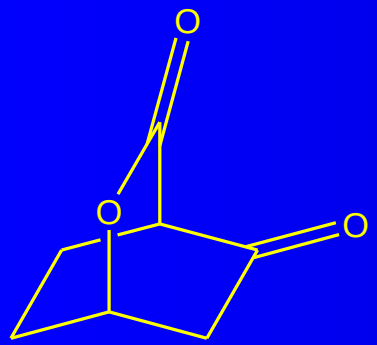
Please study the mechanism too

Practice



Practice these at home

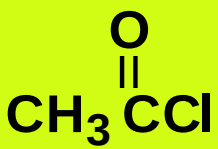




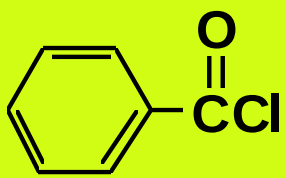
Acid Chlorides

- The functional group is a carbonyl bonded to a chlorine atom
- Name derived from the parent acid by dropping –ic acid and adding yl chloride

Functional group of an acid halide



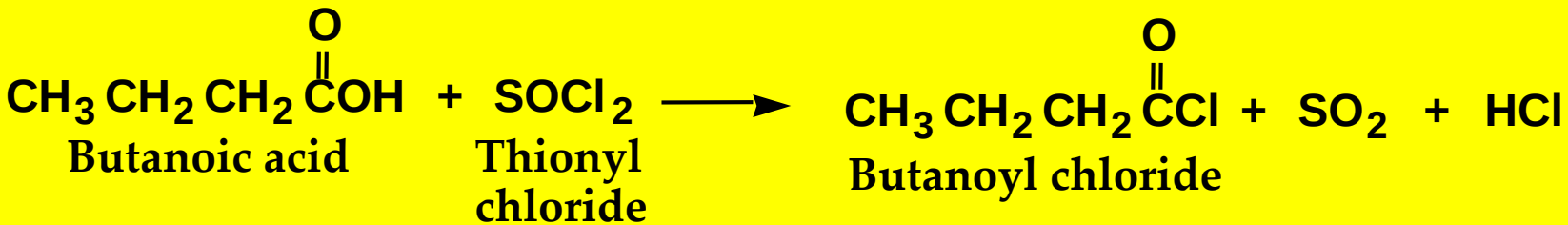
Acetyl chloride



Benzoyl chloride

Acid Chlorides

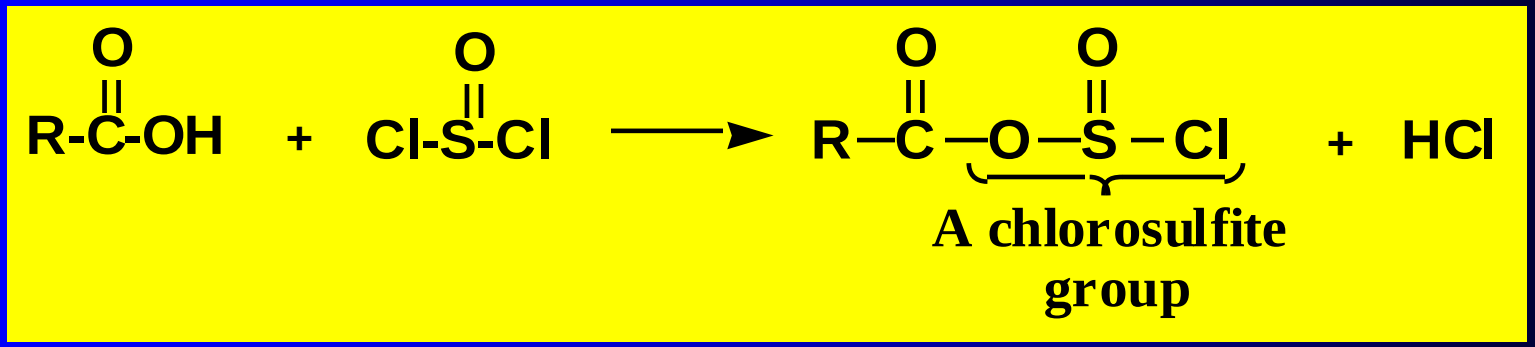
- Acid chlorides are most often prepared by treatment of a carboxylic acid with thionyl chloride - $SOCl_2$



Acid Chlorides

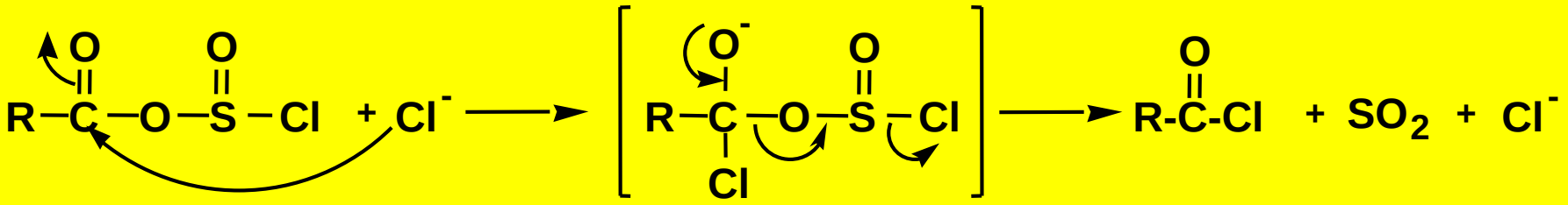
- **The mechanism divided into two steps.**

  Step 1: The -OH, is transformed into a chlorosulfite group, a great leaving group



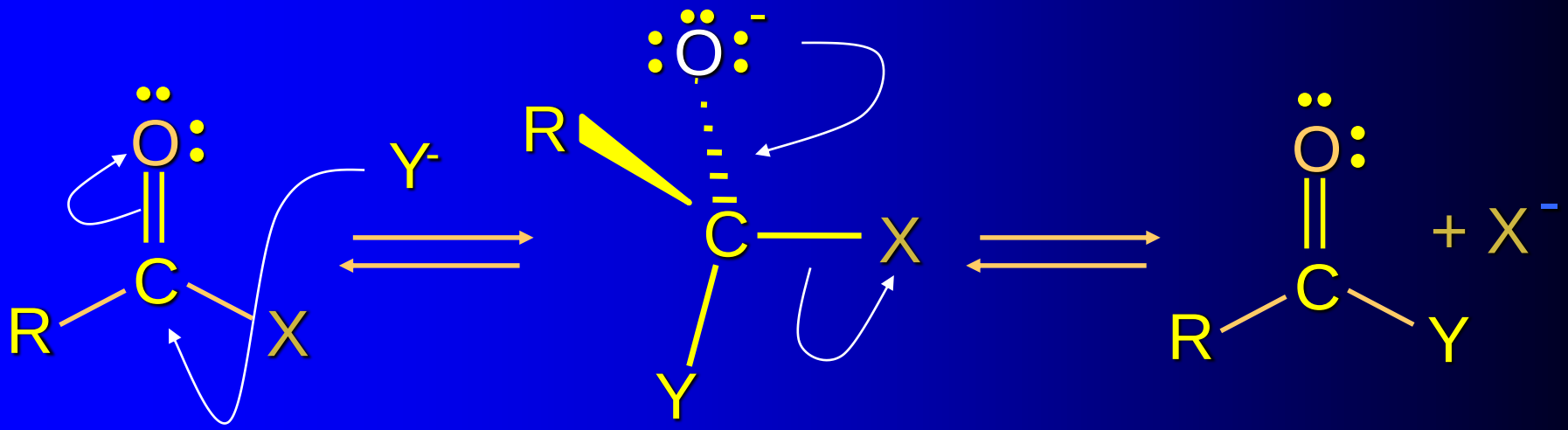
Acid Chlorides

Step 2: attack of chloride ion gives a tetrahedral carbonyl addition intermediate, which collapses to give the acid chloride



A tetrahedral carbonyl addition intermediate

Nucleophilic Acyl Substitution with an anion as nucleophile

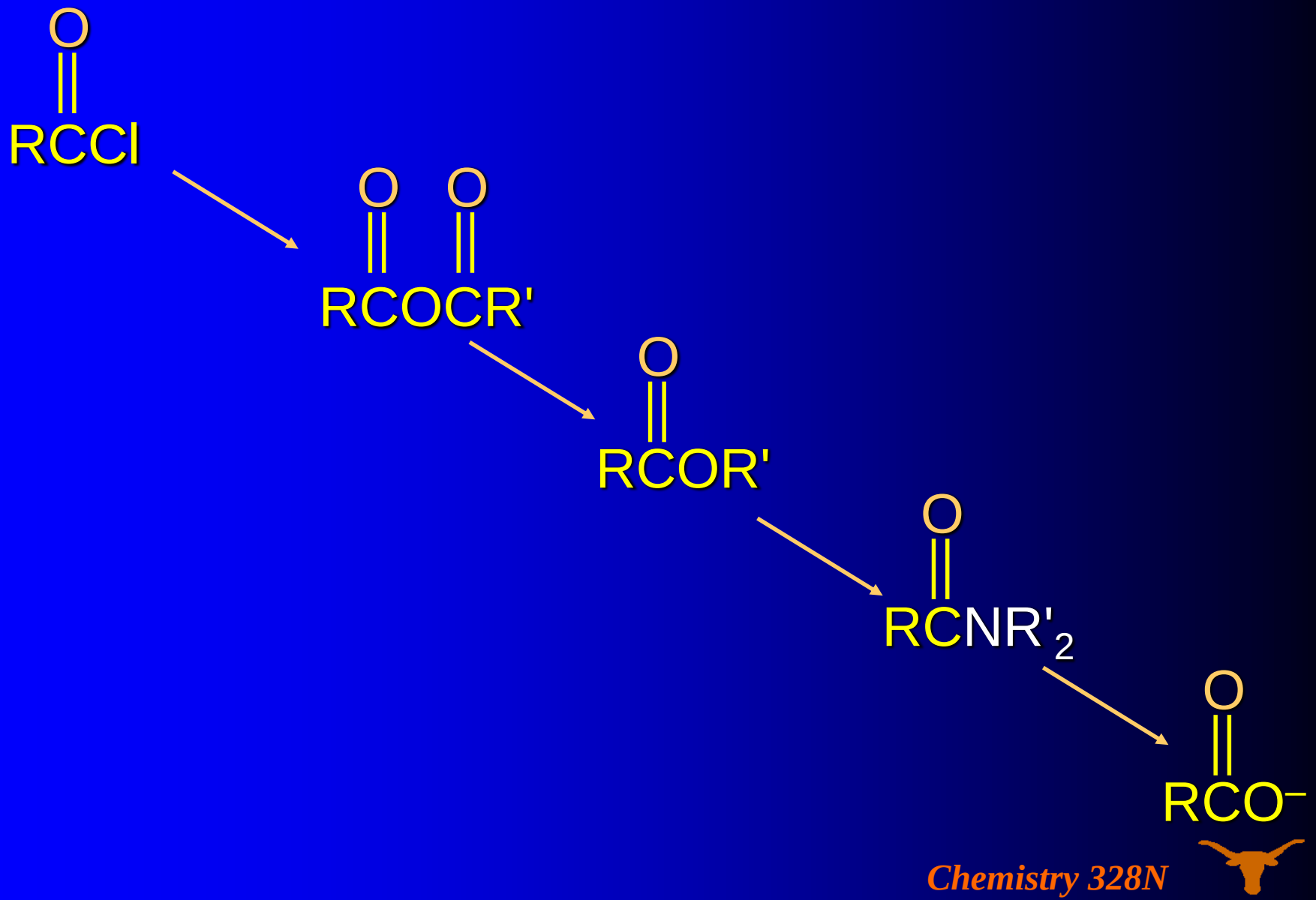


This is a very IMPORTANT general reaction. Understanding the mechanism allows one to explain and predict a large body of organic chemistry!

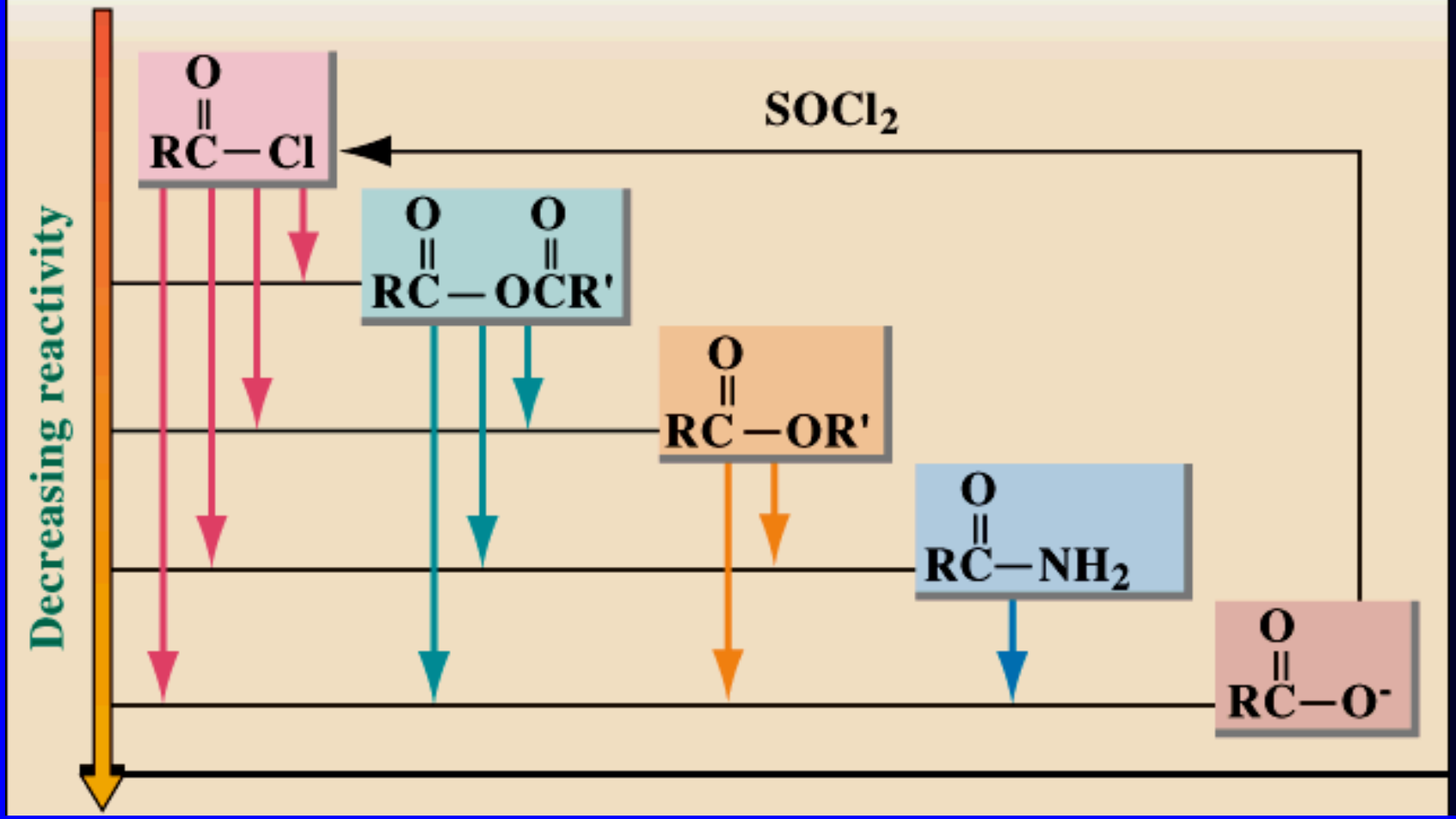
The best leaving group wins

- What makes a leaving group “good”
  - Stablility of the anion
  - The conjugate bases of strong acids are greatleaving groups.

Reactions of Acyl Chlorides

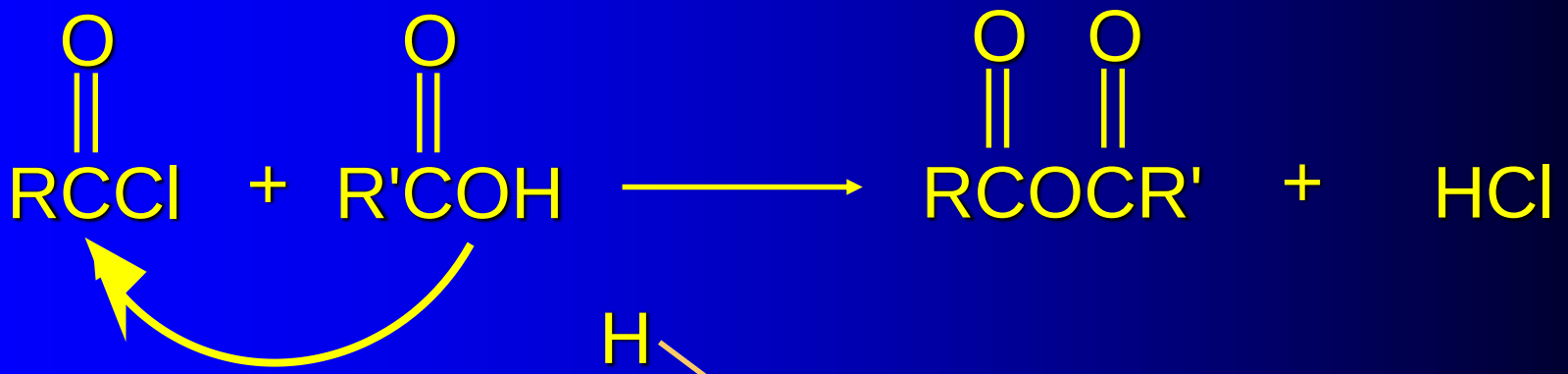


Relative reactivities of carboxyl derivatives

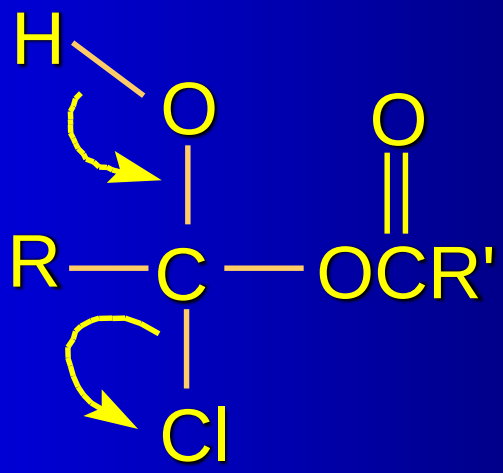


Reactions of Acyl Chlorides

Acyl chlorides react with carboxylic acids to give acid anhydrides:

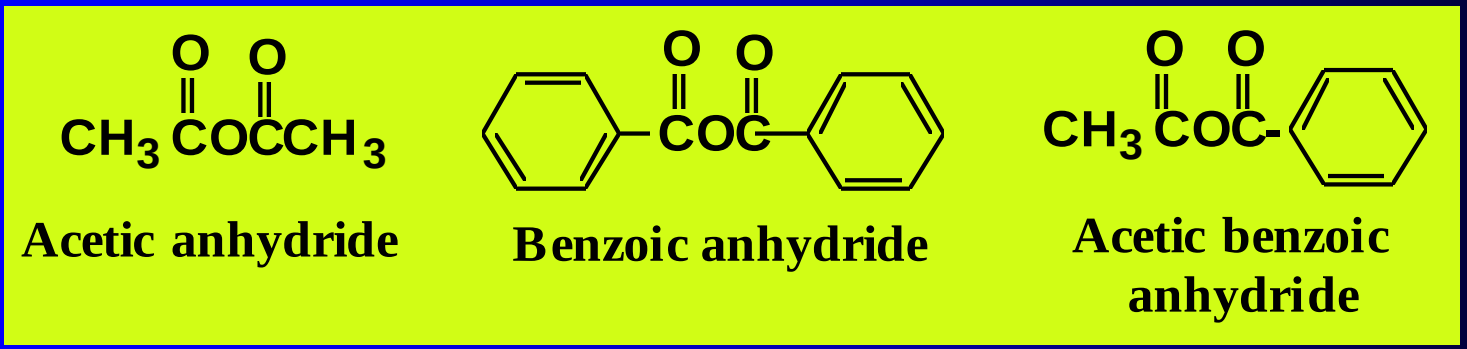


via:



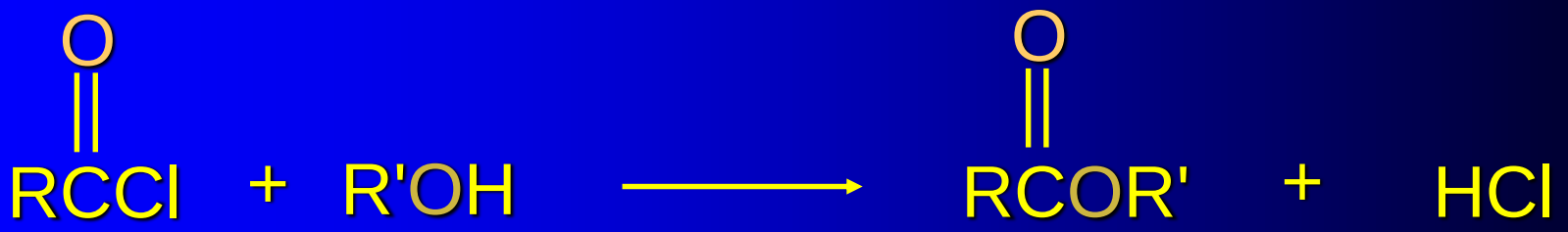
Acid Anhydrides

- The functional group of an acid anhydride is two acyl groups bonded to an oxygen atom
  - the anhydride may be symmetrical (two identical acyl groups) or mixed (two different acyl groups)
- To name, replace acid of the parent acid by anhydride



Reactions of Acyl Chlorides

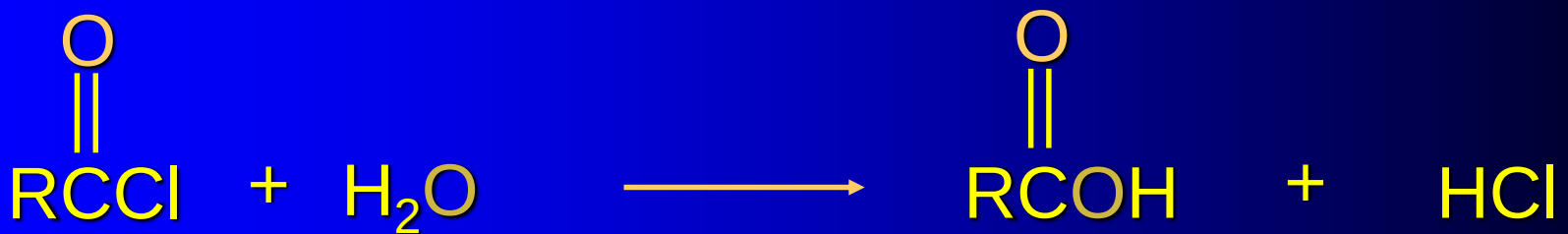
Acyl chlorides react with alcohols to give esters:

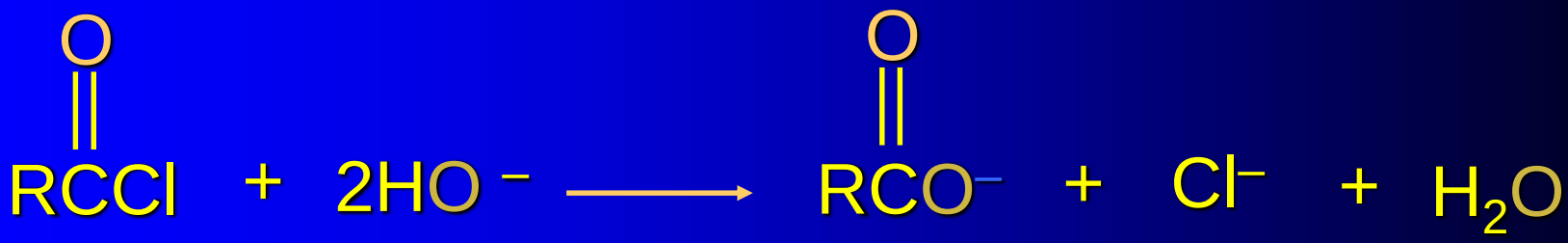


Please review the nomenclature of esters

Reactions of Acyl Chlorides

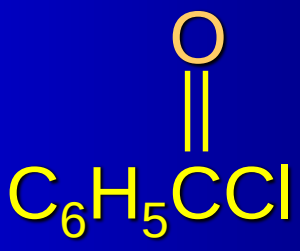
Acyl chlorides react with water (or base) to give carboxylic acids (carboxylate ion in base): **Hydrolysis**





Reactivity

- Acyl chlorides undergo nucleophilic acyl substitution much faster than the corresponding alkyl chlorides.



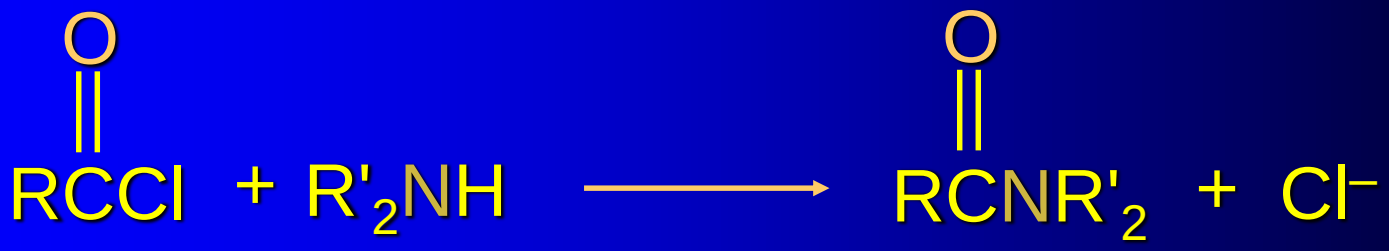
C_6H_5CCl

$C_6H_5CH_2Cl$

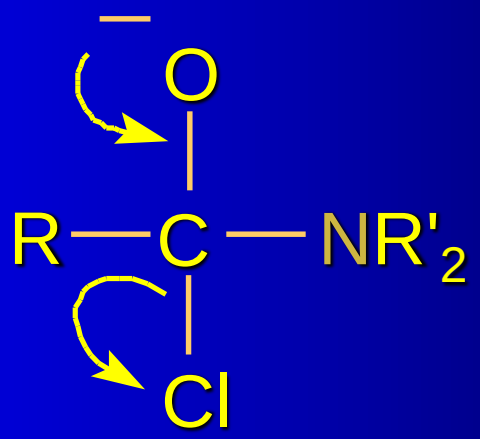
	C_6H_5CCl	$C_6H_5CH_2Cl$
Relative rates of hydrolysis (25°C)	1,000	1

Reactions of Acyl Chlorides

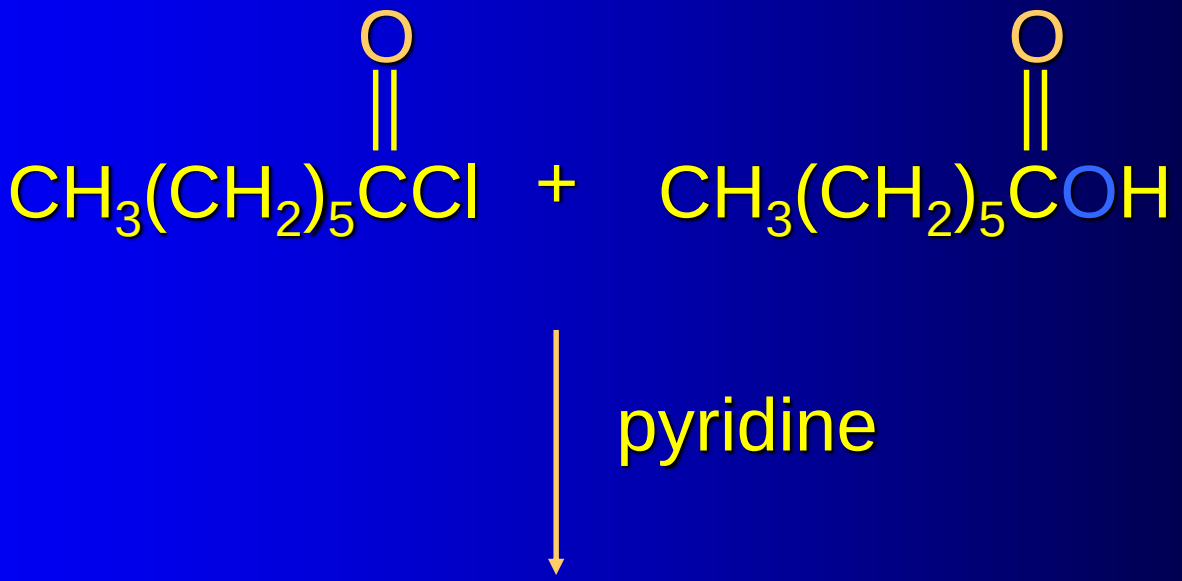
Acyl chlorides react with ammonia and amines to give amides:



via:



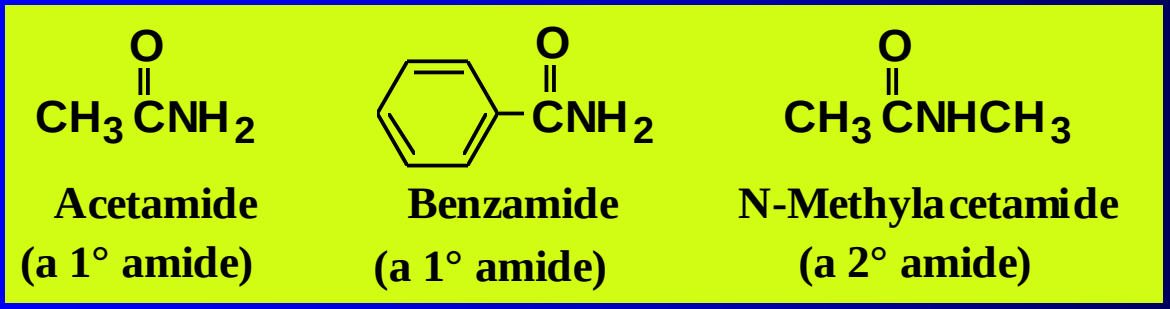
Example



Example of acyl chloride reaction with amines to make amides

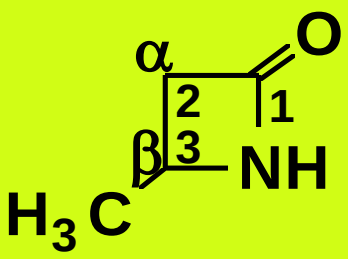
Amides

- The functional group of an amide is an acyl group bonded to a nitrogen atom
- IUPAC: drop -oic acid from the name of the parent acid and add -amide
- If the amide nitrogen is bonded to an alkyl or aryl group, name the group and show its location on nitrogen by N-

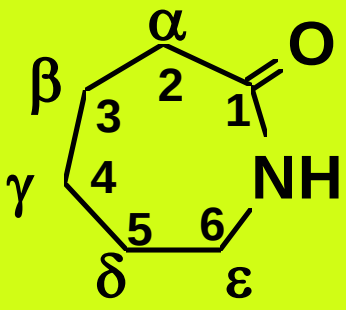


Amides

- Cyclic amides are called lactams
- Name the parent carboxylic acid, drop the suffix -ic acid, and add -lactam

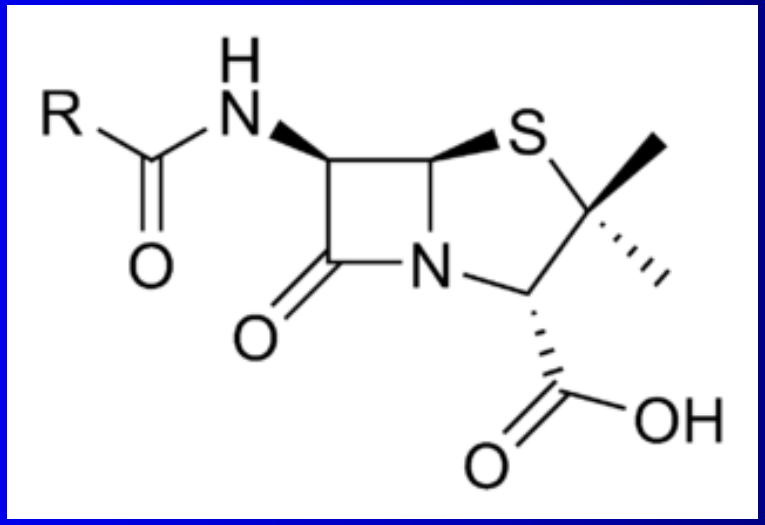


3-Butanolactam
(β-Butyrolactam)



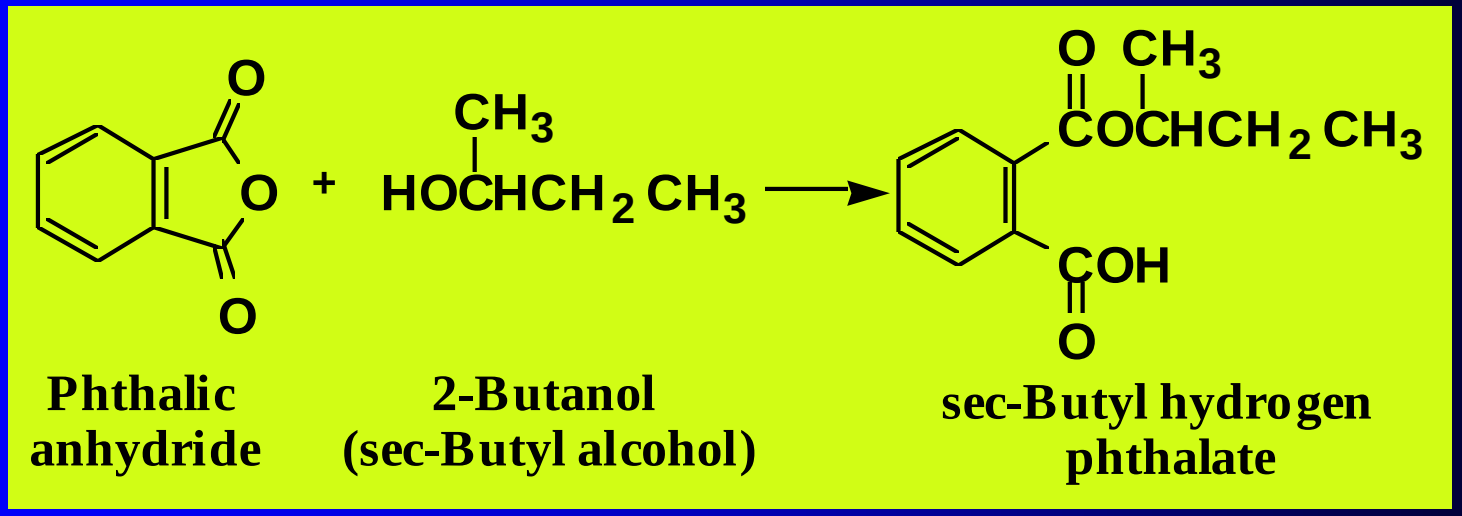
6-Hexanolactam
(ε-Caprolactam)

Lactam Antibiotics



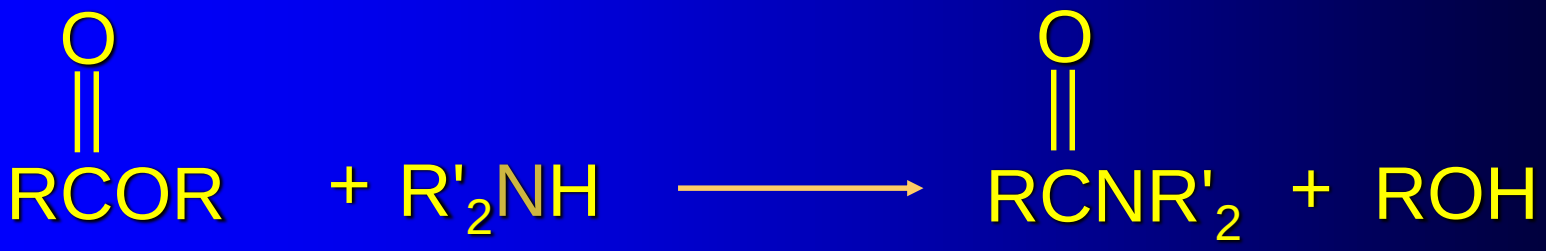
Reactions of Acid Anhydrides

- Acid anhydrides react with alcohols to give one mol of ester and one of carboxylic acid

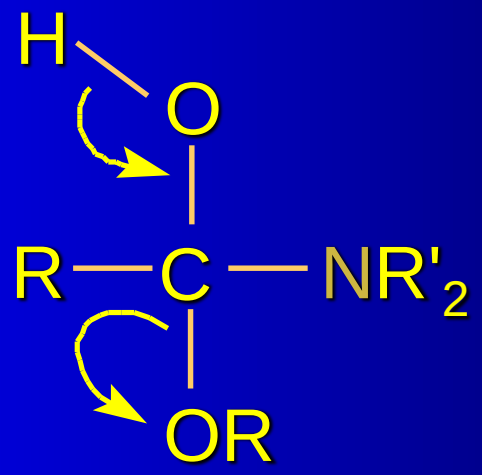


Reactions of Esters

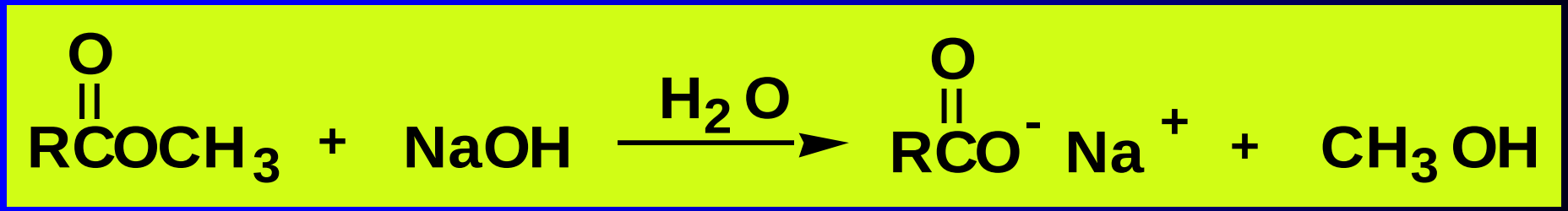
- Esters react with ammonia and amines to give amides:



via:

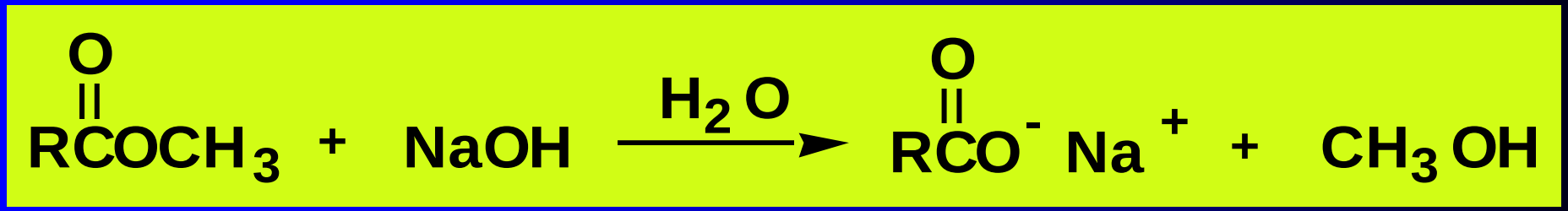


Reaction of Esters with Grignard Reagents



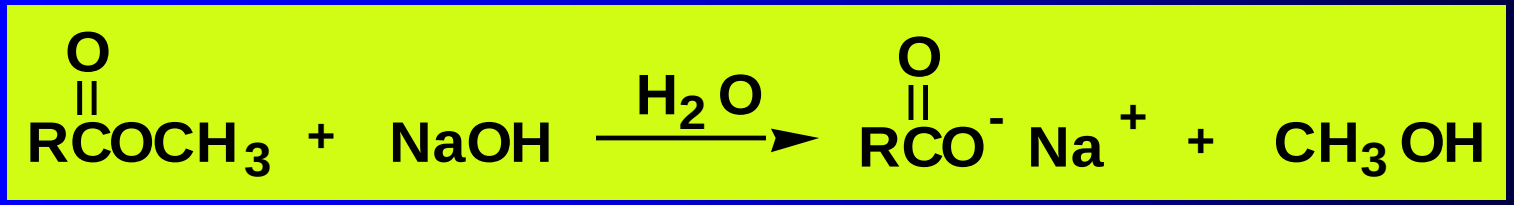
Reaction of Esters with OH^-

- Saponification



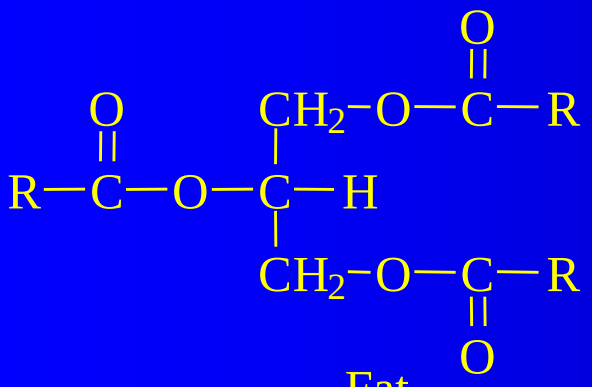
Saponification of Esters

- Hydrolysis of an esters is aqueous base is called saponification
- Each mol of ester hydrolyzed requires 1 mol of base; for this reason, ester hydrolysis in aqueous base is said to be "base-promoted" (not catalyzed)

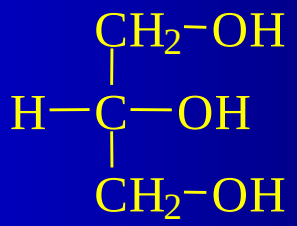


- Hydrolysis of an ester in aqueous base involves Nucleophilic acyl substitution

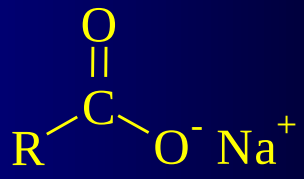
Saponification of Fat



Fat



glycerol



Fatty Acid Salt
"Soap"

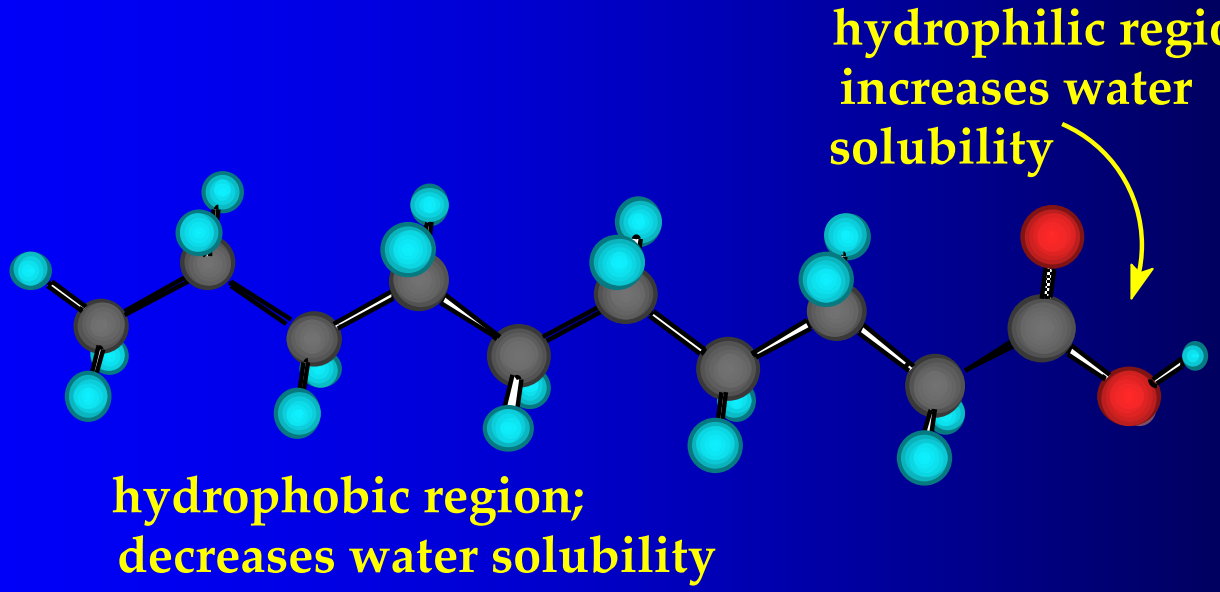
R = $CH_3(CH_2)_{16}COOH$ Stearic Acid

$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$ Oleic acid

etc.

Physical Properties

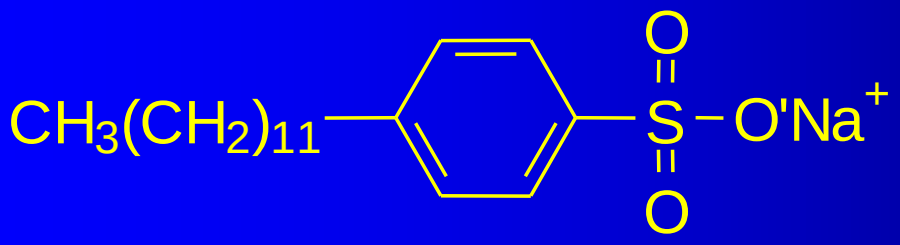
- Water solubility decreases as the relative size of the hydrophobic portion of the molecule increases



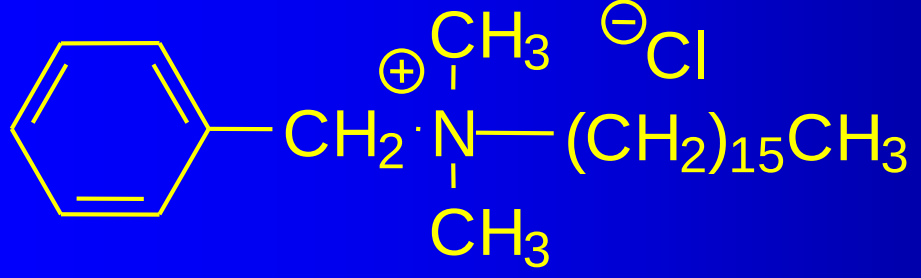
Soaps and Detergents

*Surf*ace *Act*ive Ag*ents* = surfactants

$CH_3(CH_2)_{16}COO^- Na^+$ Soap

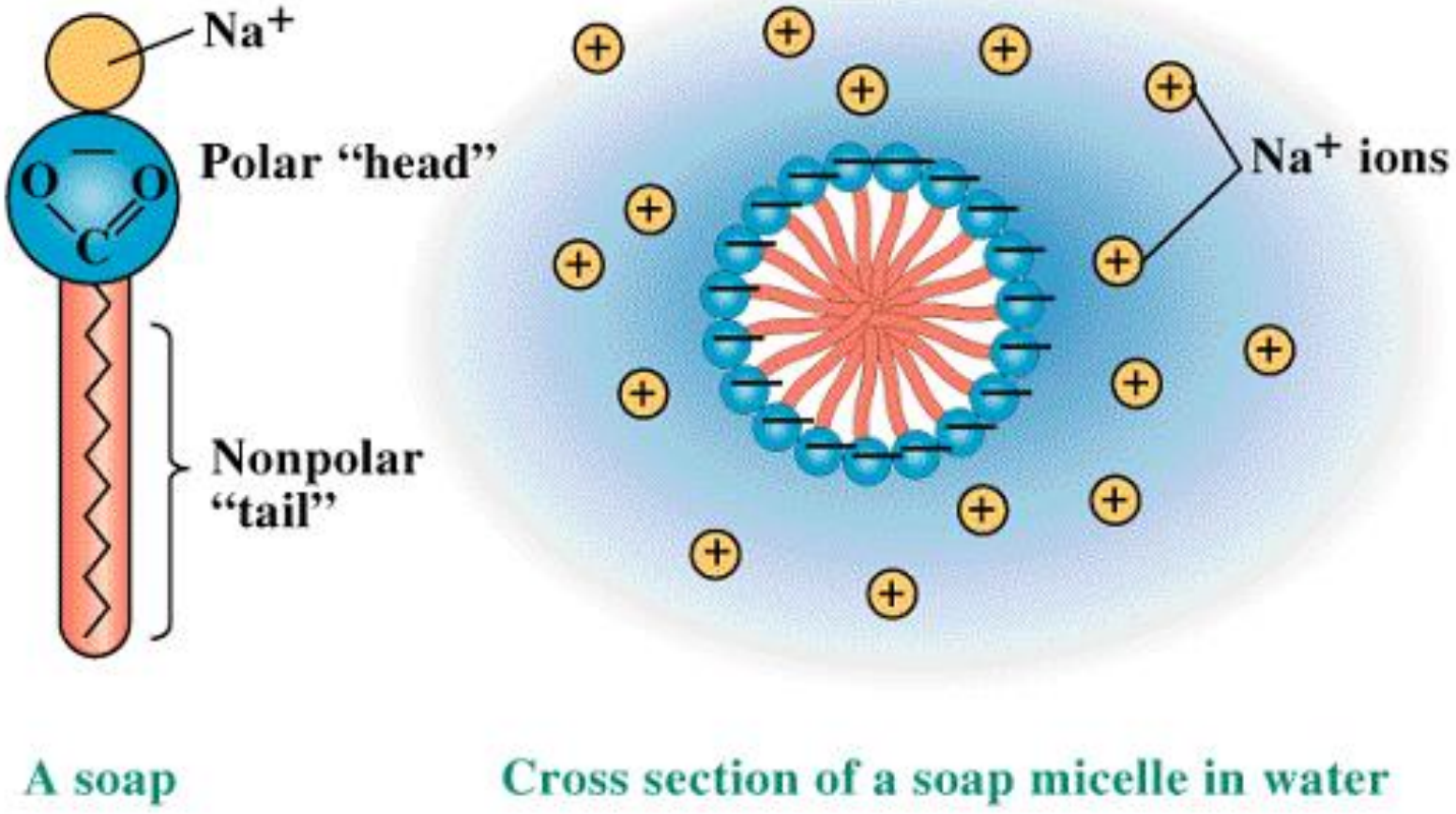


Anionic detergent

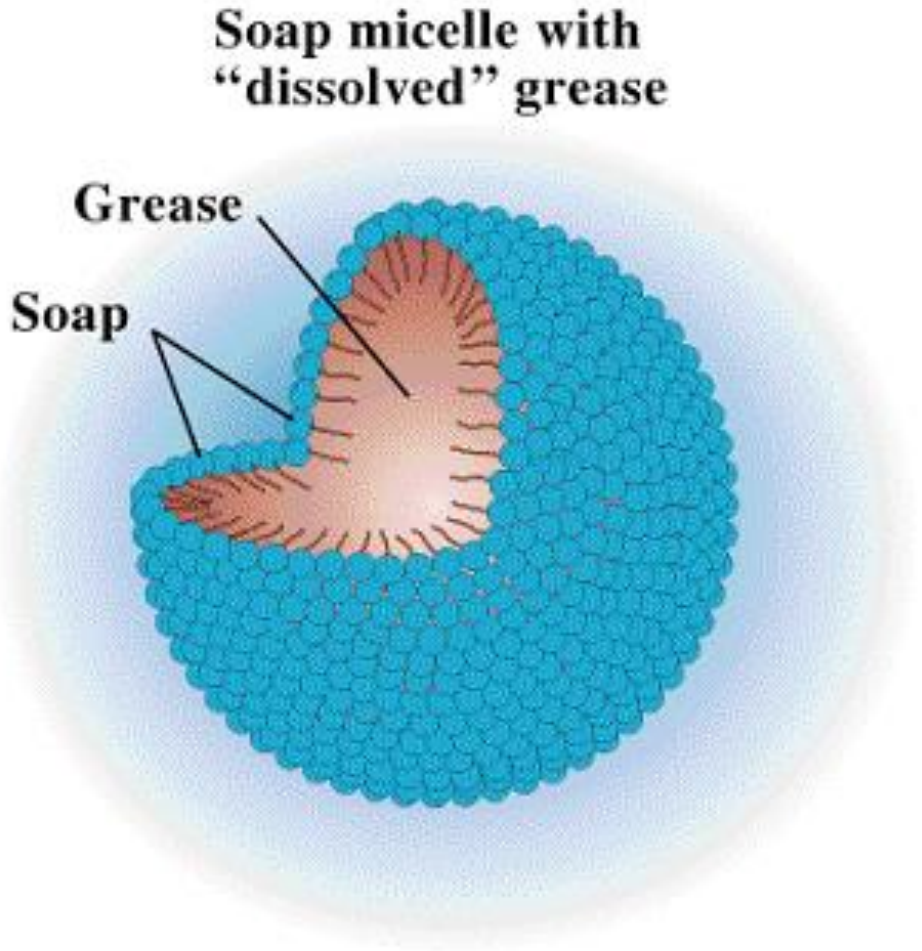


Cationic Detergent

Soap micelle

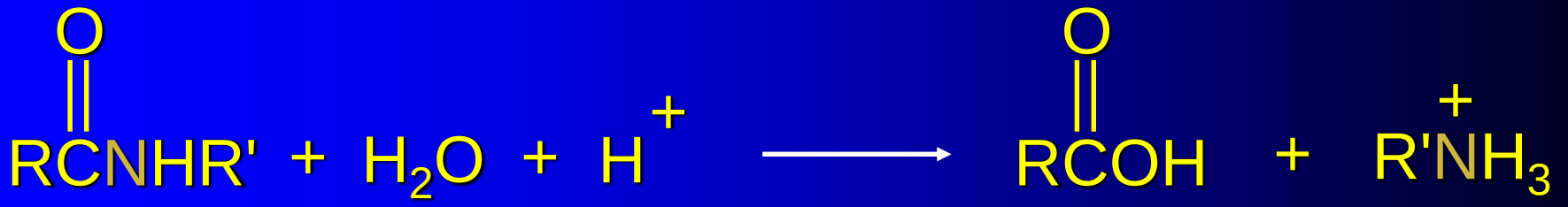


Soap micelle with a dissolved grease droplet



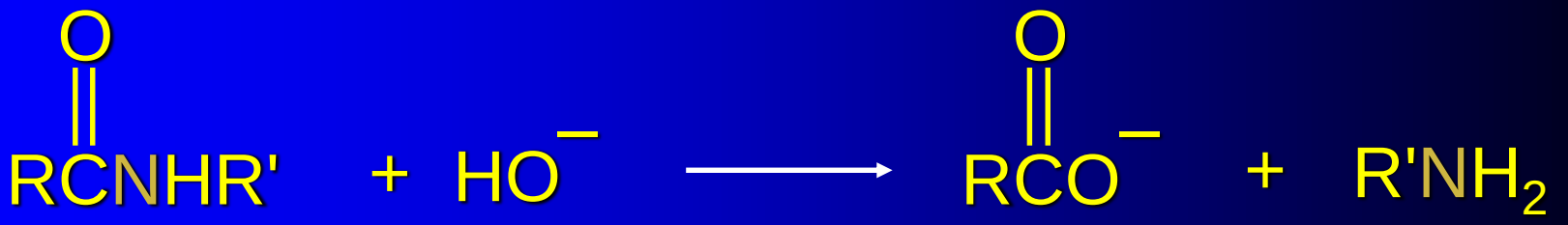
Hydrolysis of Amides

Hydrolysis of amides is also irreversible. In acid solution the amine product is protonated to give an ammonium salt.



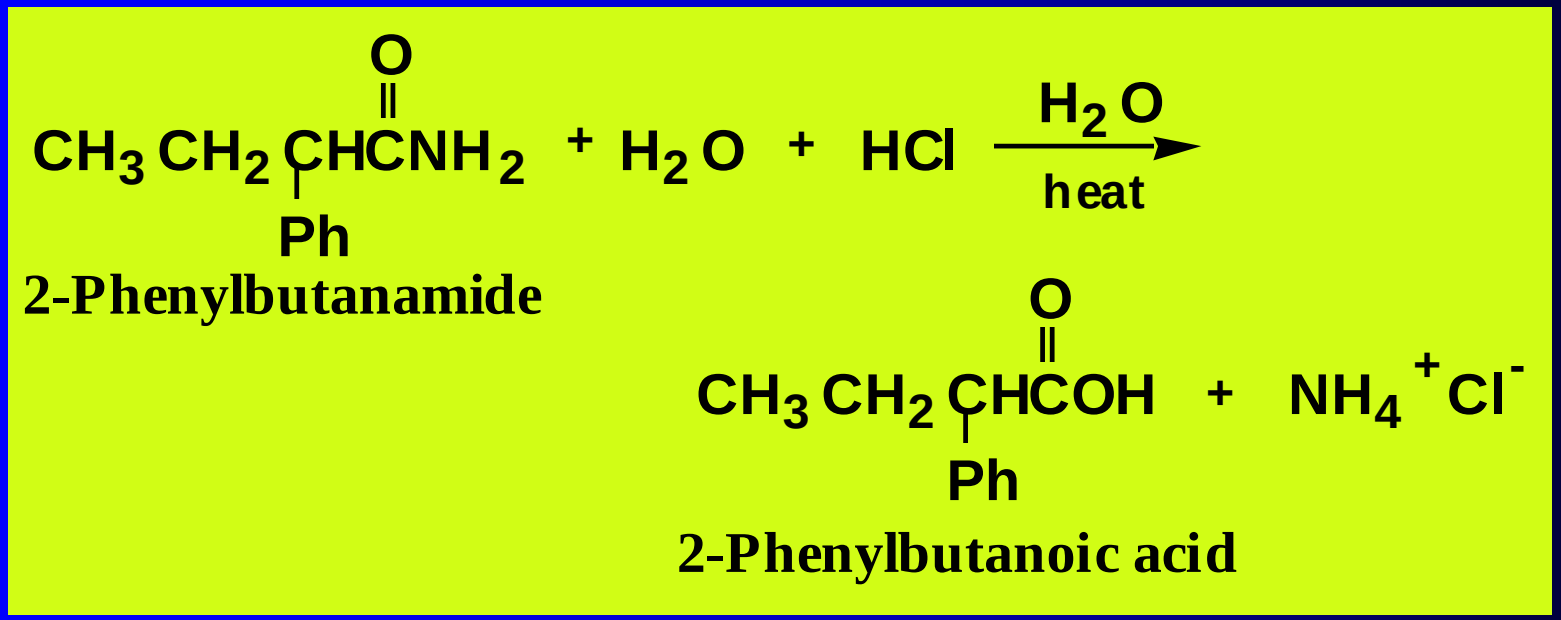
Hydrolysis of Amides

- In basic solution the carboxylic acid product is deprotonated to give a carboxylate ion.
- This makes the reaction irreversible!



Hydrolysis of Amides in Acid

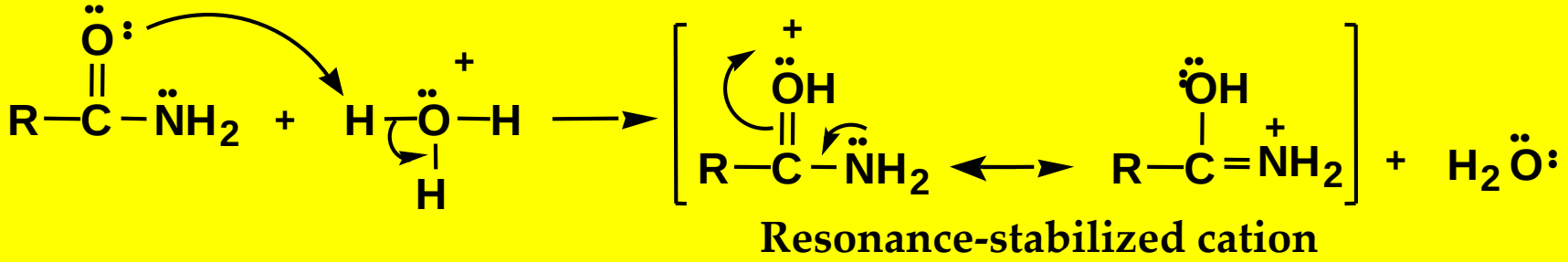
- Hydrolysis of amides in aqueous acid requires 1 mol of acid per mol of amide



Hydrolysis of Amides in Acid

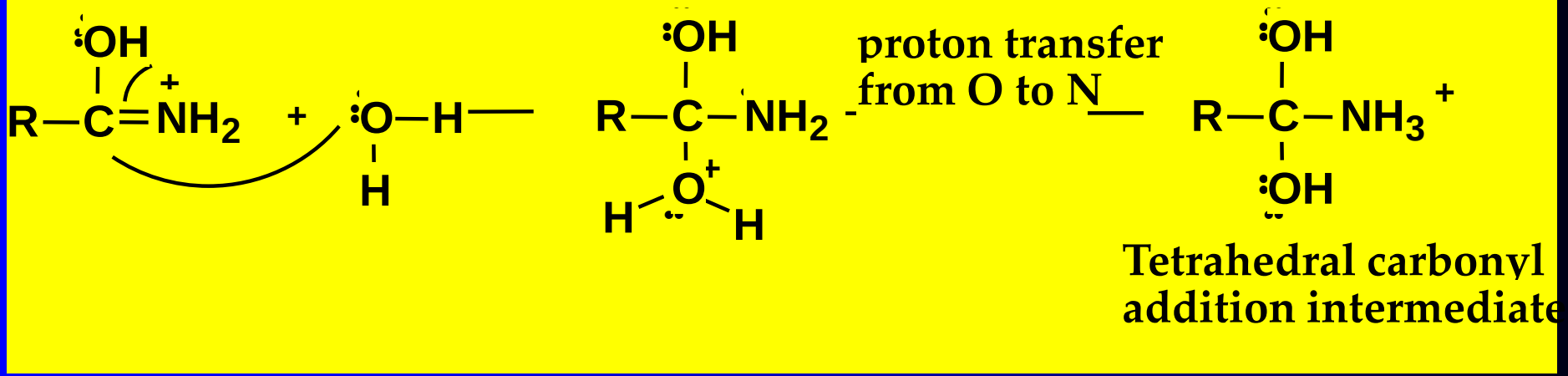
- Acid-catalyzed hydrolysis of an amide is divided into three steps

  Step 1: protonation of the carbonyl oxygen



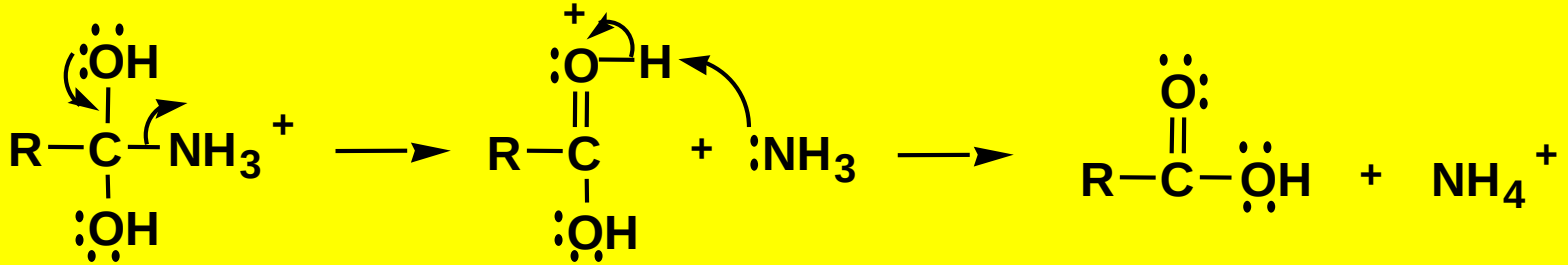
Hydrolysis of Amides in Acid

Step 2: addition of H_2O to the carbonyl carbon followed by proton transfer



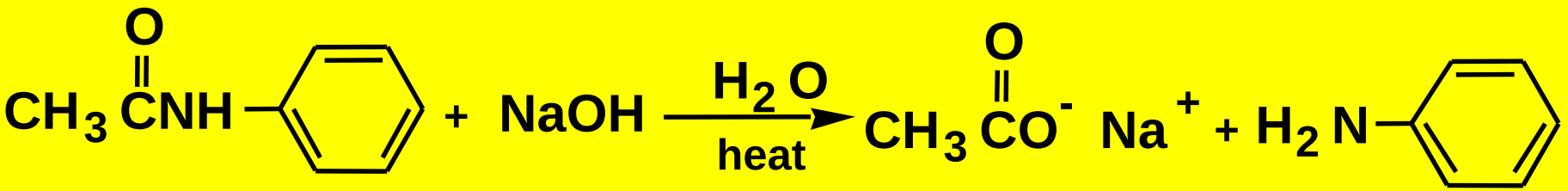
Hydrolysis of Amides in Acid

Step 3: collapse of the intermediate coupled with proton transfer to give the carboxylic acid and ammonium ion



Hydrolysis of Amides in Base

- **Hydrolysis of an amide in aqueous base requires 1 mole of base per mole of amide**

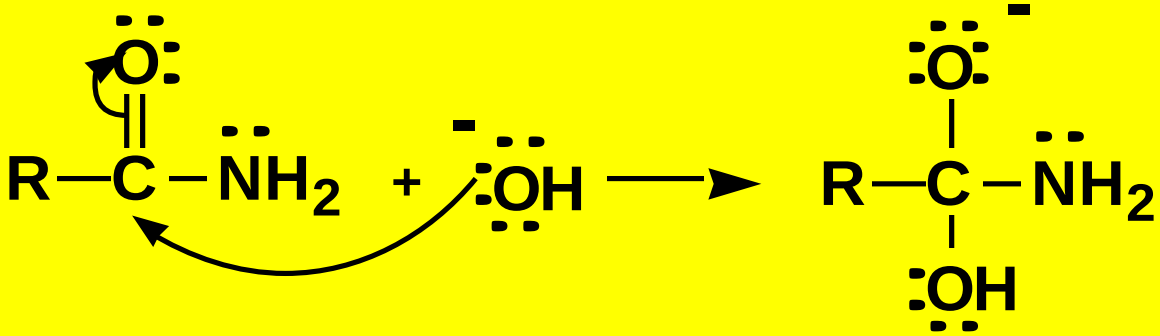


N-Phenylethanamide **Sodium acetate** **Aniline**

Hydrolysis of Amides in Base

- Hydrolysis of an amide in aqueous base is divided into three steps

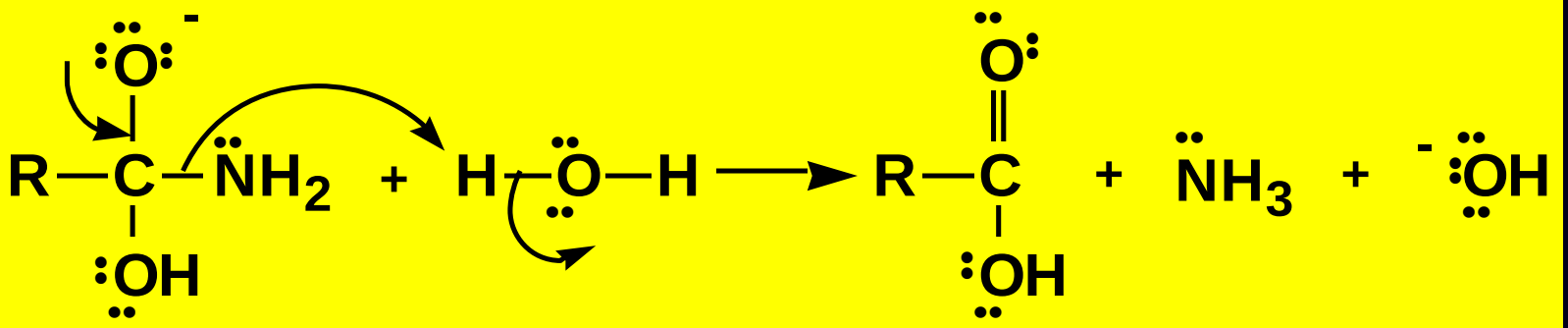
  Step 1: addition of hydroxide ion to the carbonyl carbon



Tetrahedral carbonyl addition intermediate

Hydrolysis of Amides in Base

Step 2: collapse of the intermediate to form a carboxylic acid and ammonia



Tetrahedral carbonyl addition intermediate

A very rare event… Why???

Hydrolysis of Amides in Base

Step 3: **proton transfer to form the carboxylate anion and water. Hydrolysis is driven to completion by this acid-base reaction**