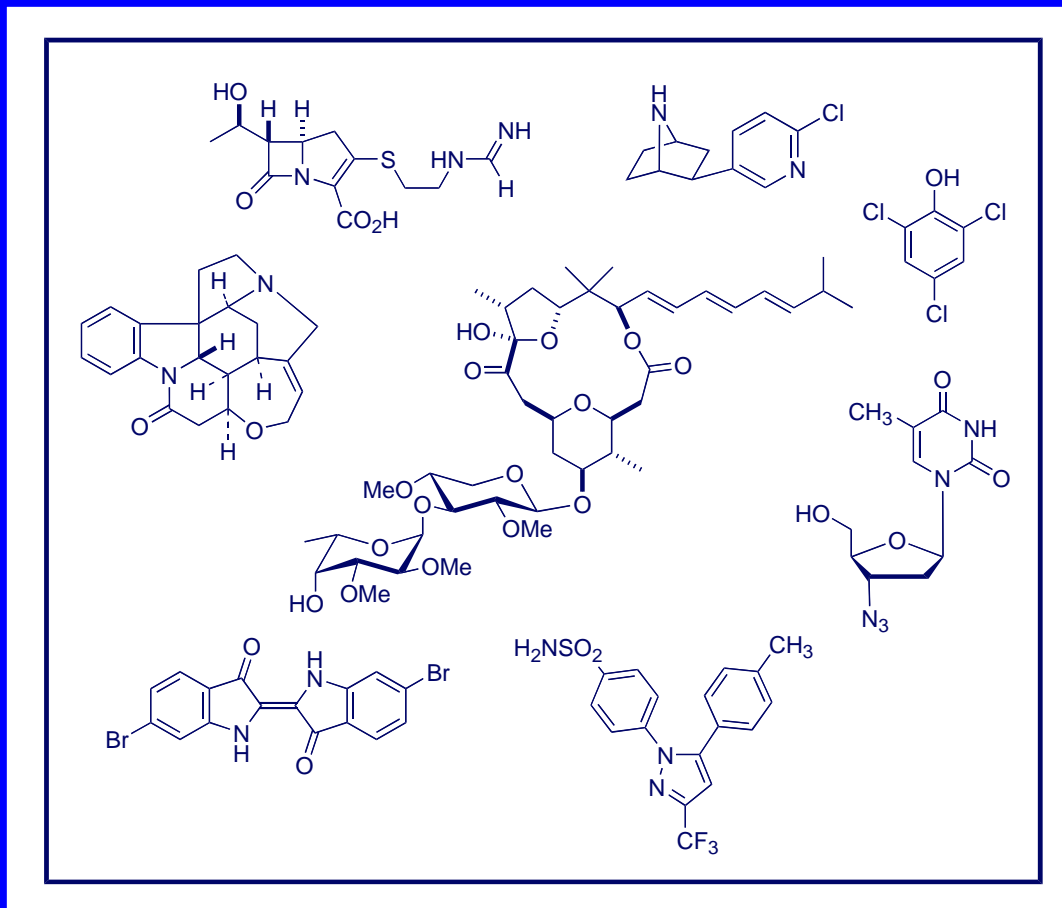


Chem 234 Organic Chemistry II

Professor Duncan J. Wardrop

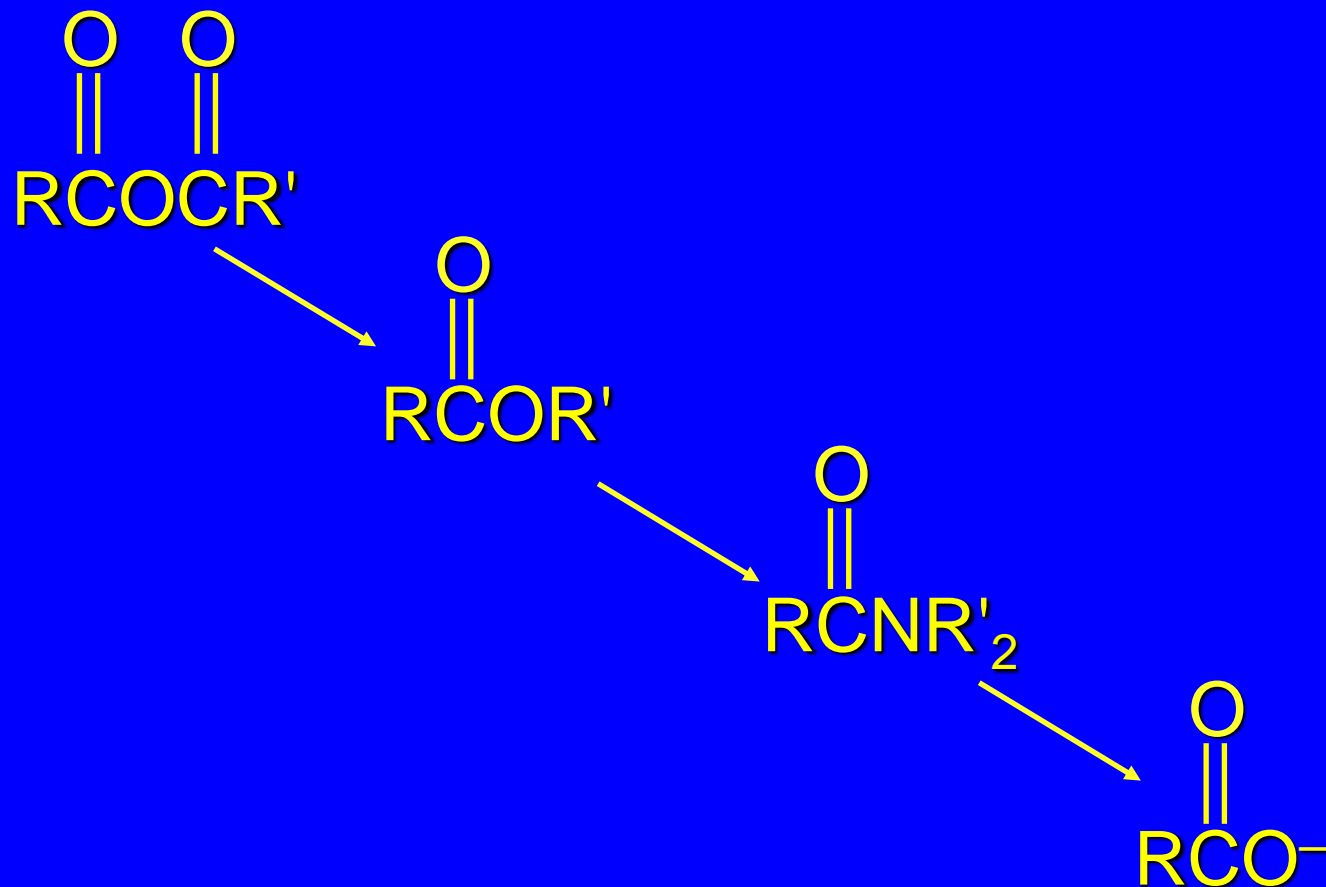


Spring 2004

University of Illinois at Chicago

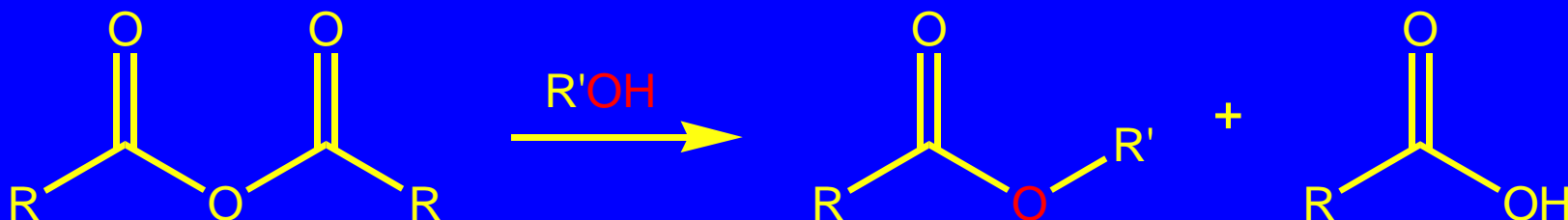
20.6
Reactions of
Carboxylic Acid Anhydrides

Reactions of Anhydrides



Reactions of Anhydrides

Carboxylic acid anhydrides react with alcohols to give esters:

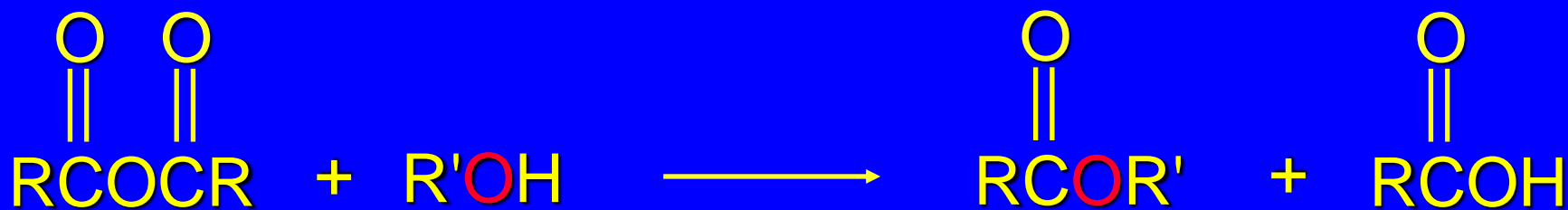


normally, symmetrical anhydrides are used
(both R groups the same)

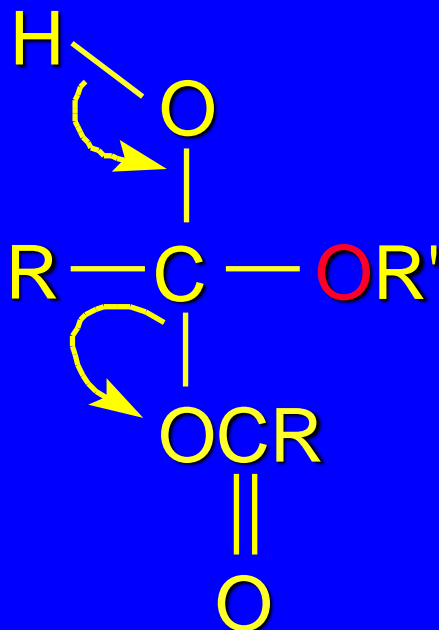
reaction can be carried out in presence of
pyridine (a base) or it can be catalyzed by acids

Reactions of Anhydrides

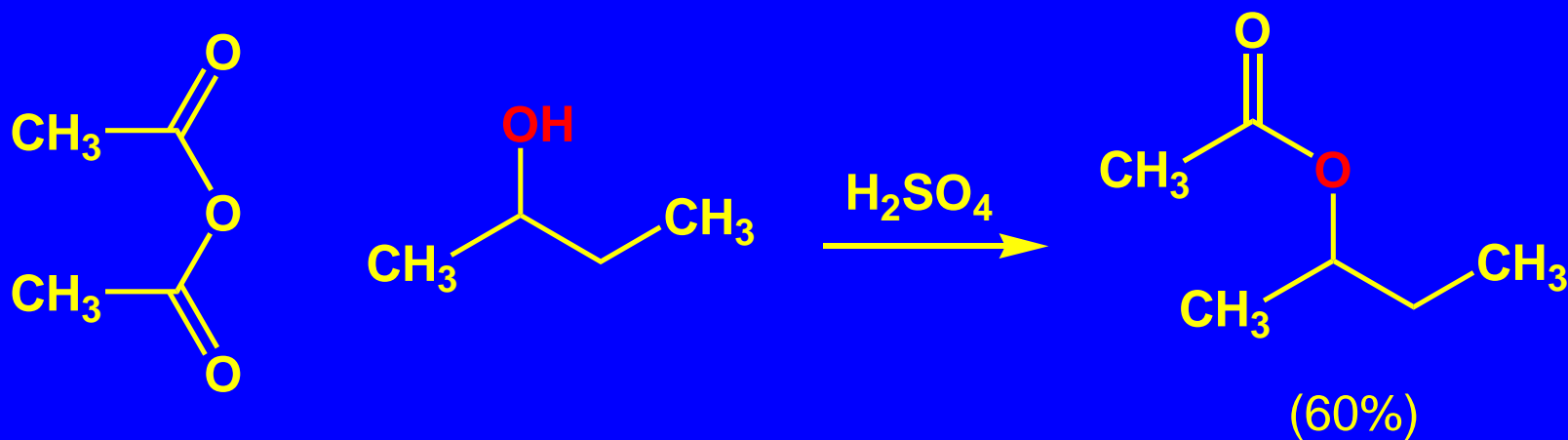
Carboxylic acid anhydrides react with alcohols to give esters:



via:

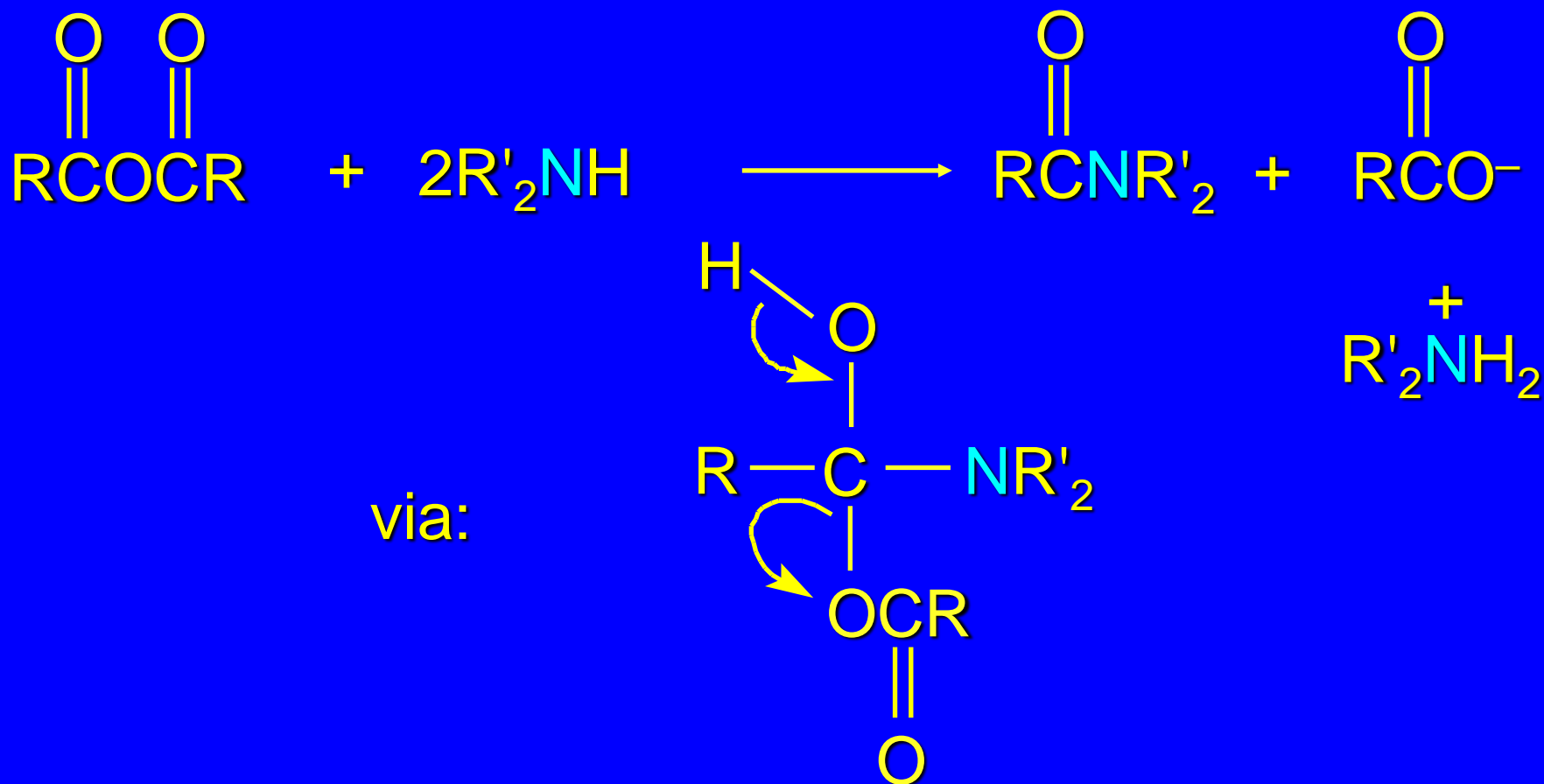


Reactions of Anhydrides- Examples

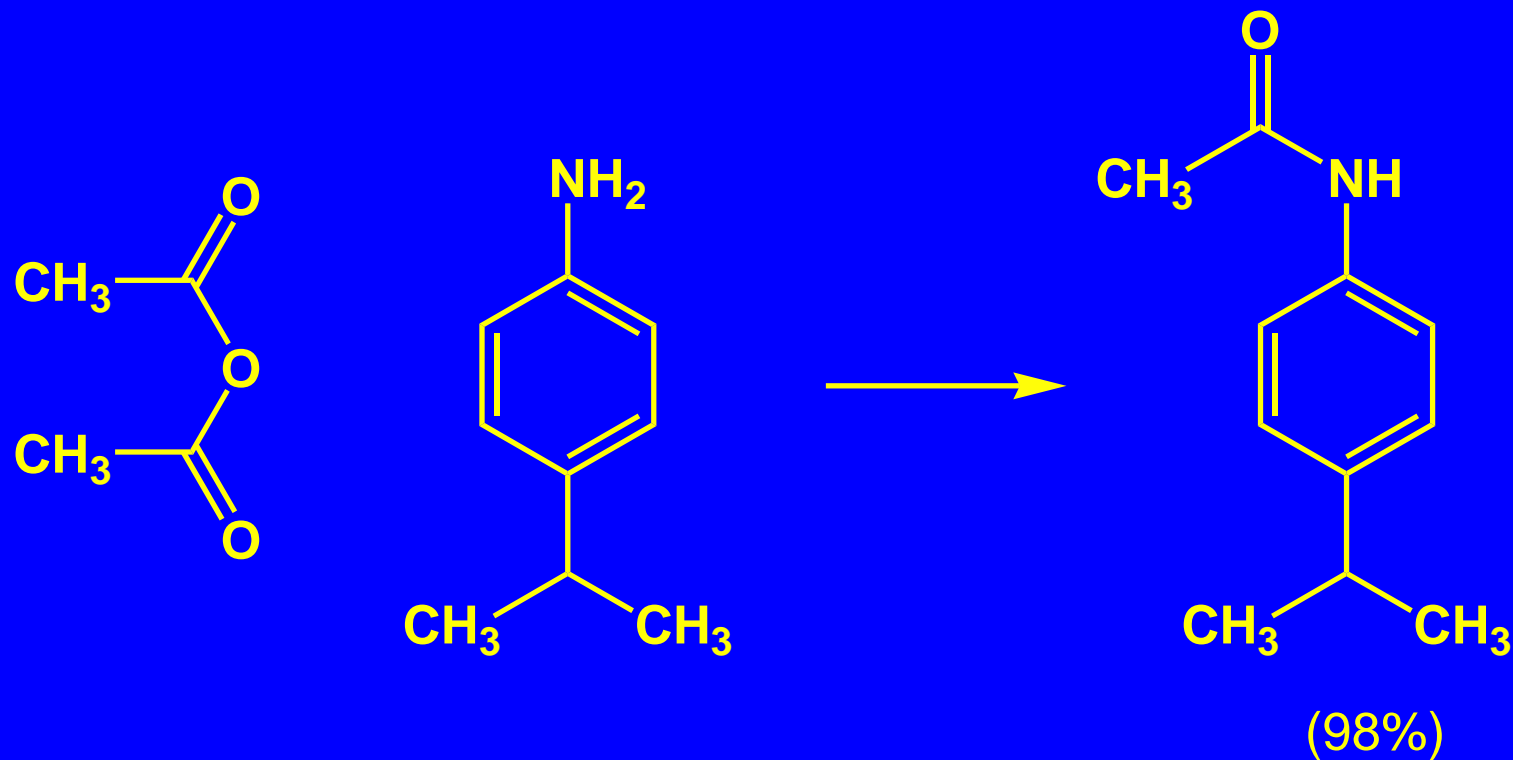


Reactions of Anhydrides with Amines

Acid anhydrides react with ammonia and amines to give amides:

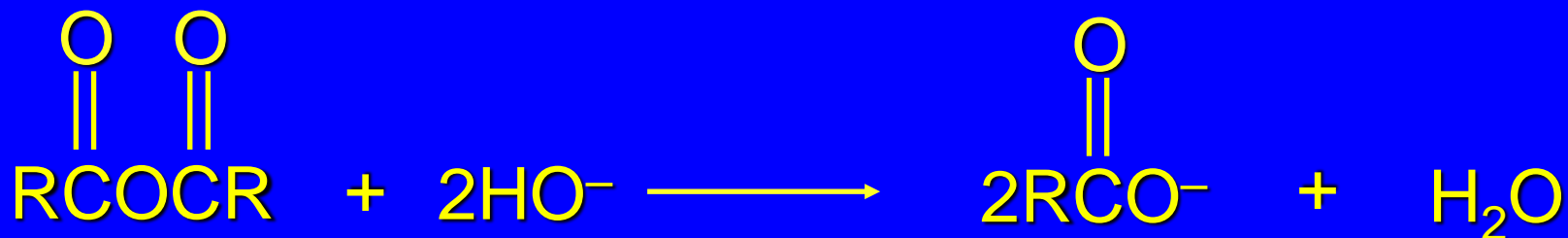
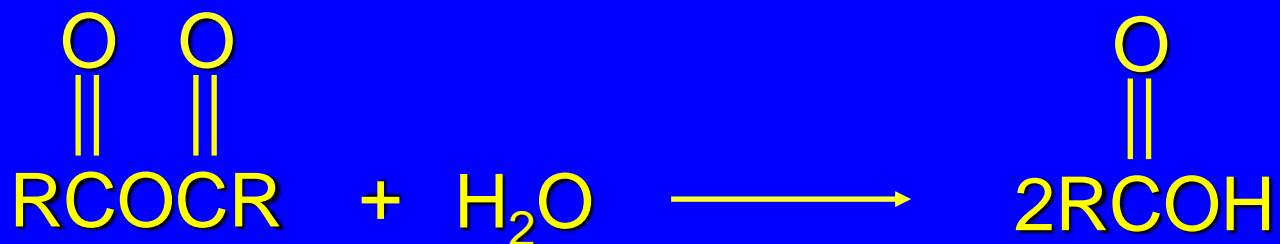


Reactions of Anhydrides with Amines- Example



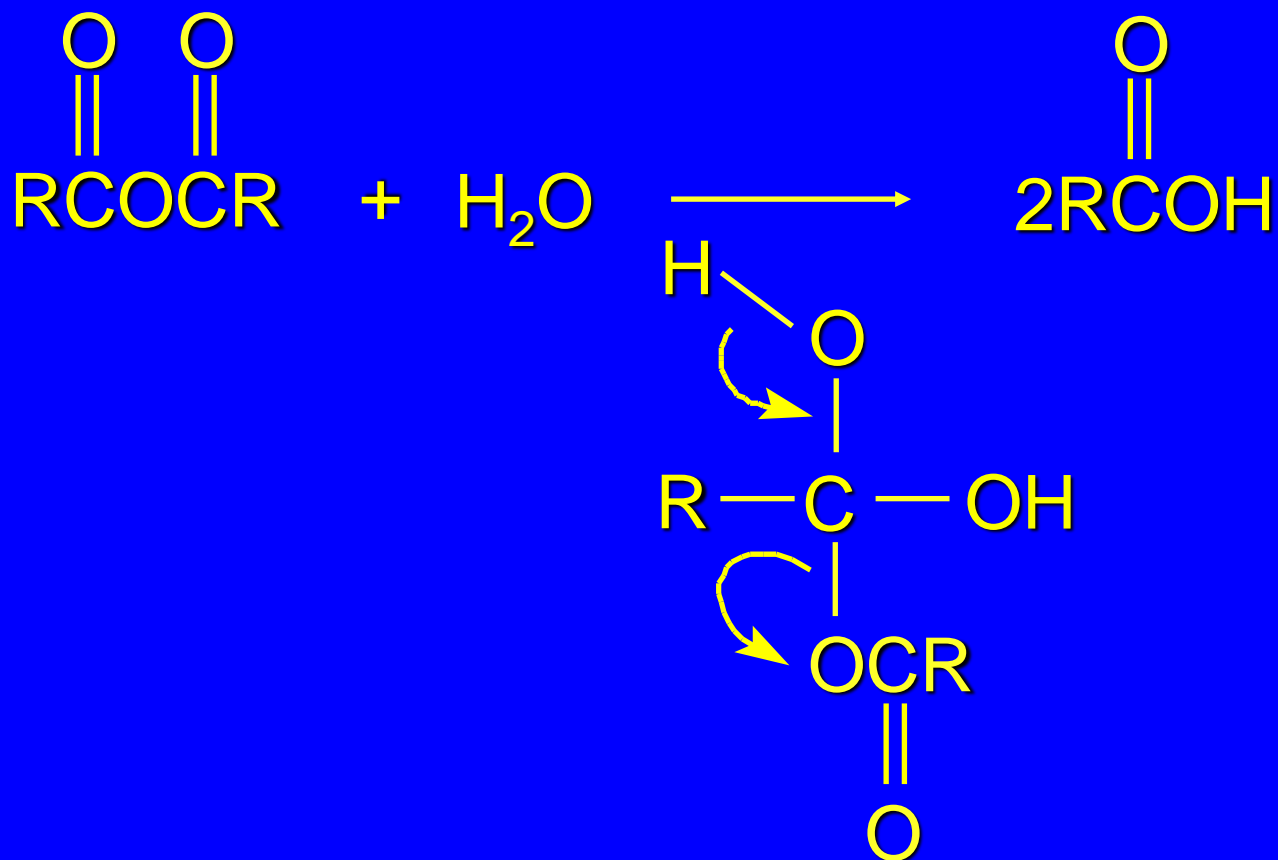
Reactions of Anhydrides with Water

Acid anhydrides react with water to give carboxylic acids (carboxylate ion in base):

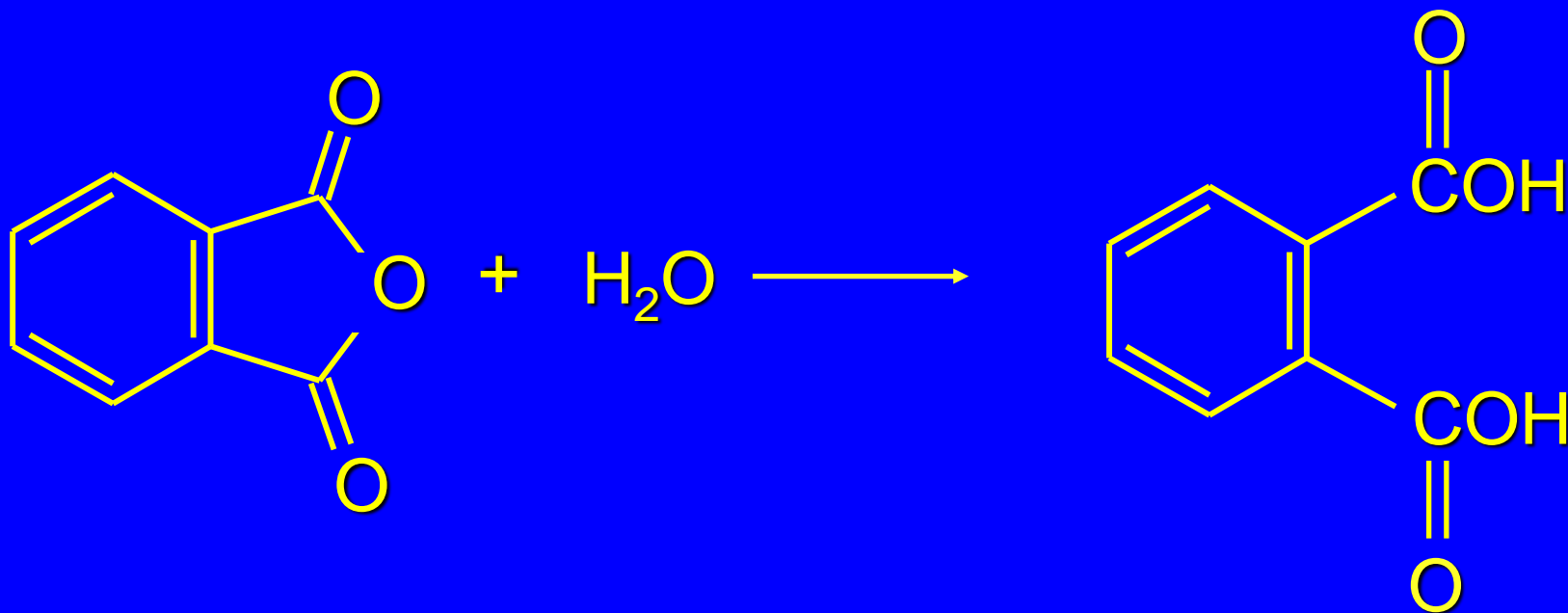


Reactions of Anhydrides with Water

Acid anhydrides react with water to give carboxylic acids (carboxylate ion in base):



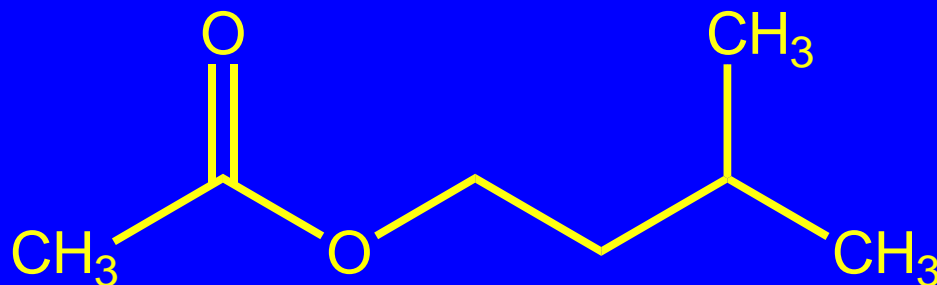
Reactions of Anhydrides with Water - Example



20.7

Sources of Esters

Esters are Commonly Found in Natural Products



3-methylbutyl acetate

also called "isopentyl acetate" and "isoamyl acetate"

contributes to characteristic odor of bananas

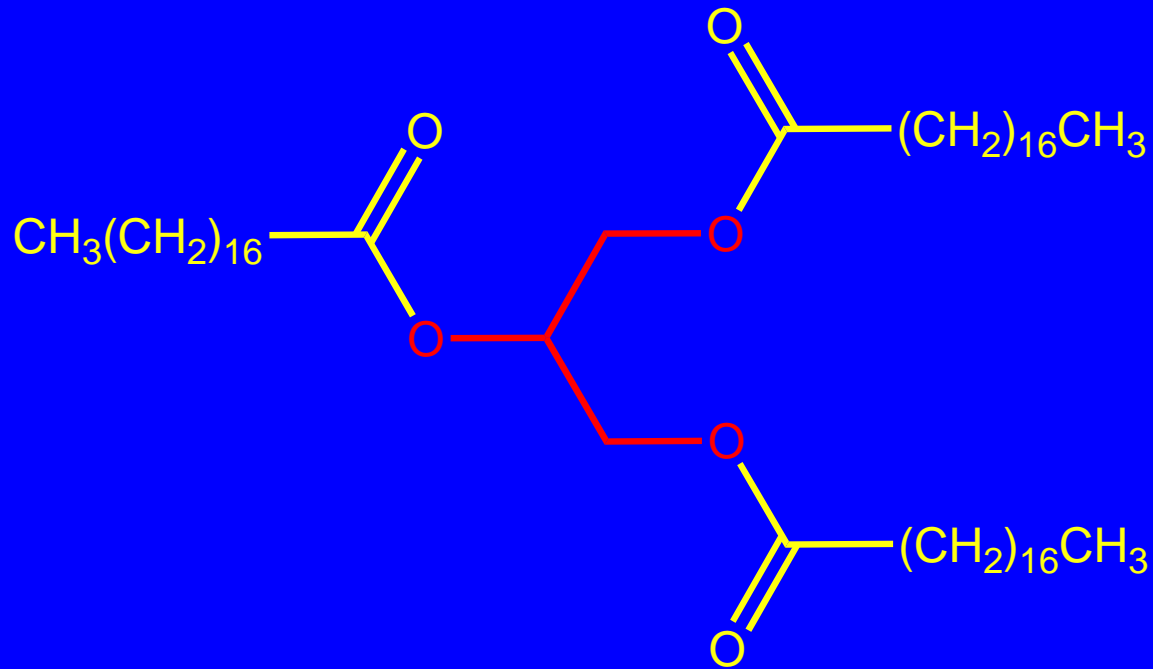
Esters of Glycerol



R, R', and R'' can be the same or different
called "triacylglycerols," "glyceryl triesters," or
"triglycerides"

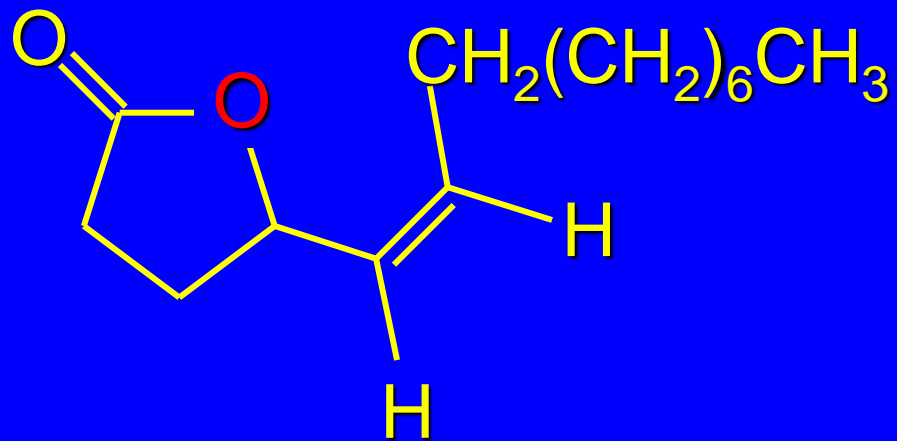
fats and oils are mixtures of glyceryl triesters

Fat & Oil are Mixtures of Glyceryl Triesters



Tristearin: found in many animal and vegetable fats

Lactones are Cyclic Esters



(Z)-5-Tetradecen-4-olide
(sex pheromone of female Japanese beetle)

Preparation of Lactones

1. Fischer esterification (Sections 15.8 and 19.14)
2. from acyl chlorides (Sections 15.8 and 20.4)
3. from carboxylic acid anhydrides (Sections 15.8 and 20.6)
4. Baeyer-Villiger oxidation of ketones (Section 17.16)

20.9
Reactions of Esters:
A Review and a Preview

Reactions of Esters

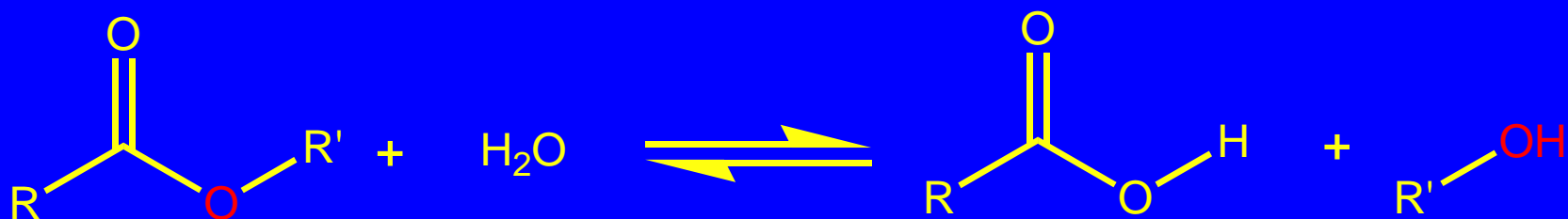
1. with Grignard reagents (Section 14.10)
2. reduction with LiAlH_4 (Section 15.3)
3. with ammonia and amines (Sections 20.12)
4. hydrolysis (Sections 20.10 and 20.11)

20.10

Acid-Catalyzed Ester Hydrolysis

Acid-Catalyzed Hydrolysis of Esters

Mechanism is just the reverse of Fischer esterification

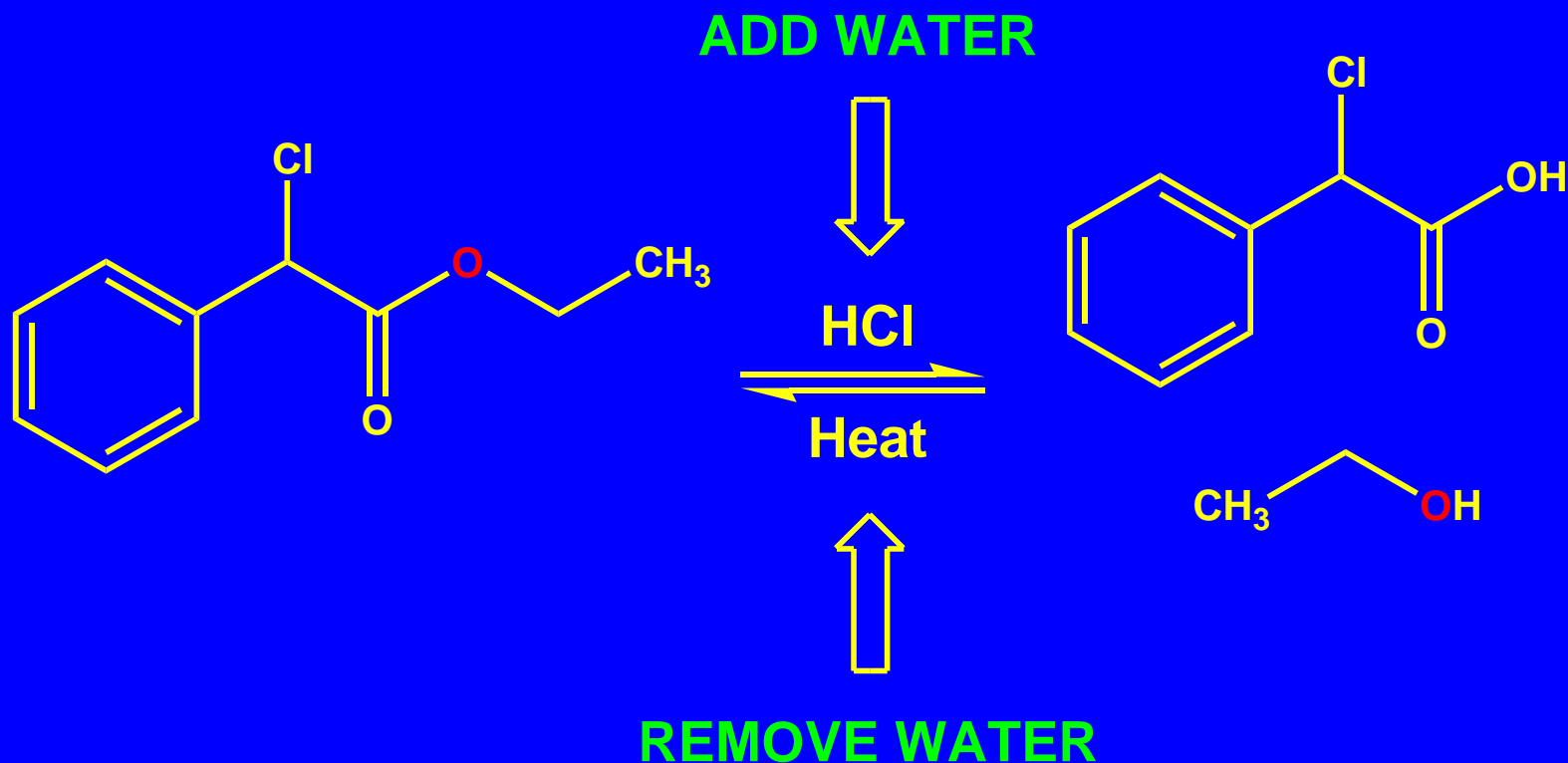


maximize conversion to ester by removing water

maximize ester hydrolysis by having large excess of water

equilibrium is closely balanced because carbonyl group of ester and of carboxylic acid are comparably stabilized

Acid-Catalyzed Hydrolysis of Esters - Example



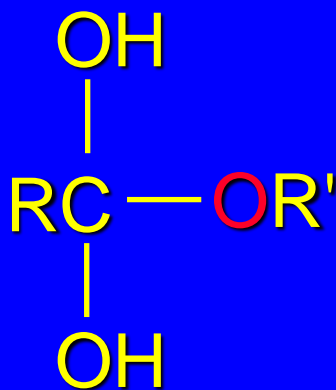
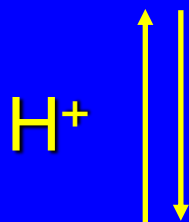
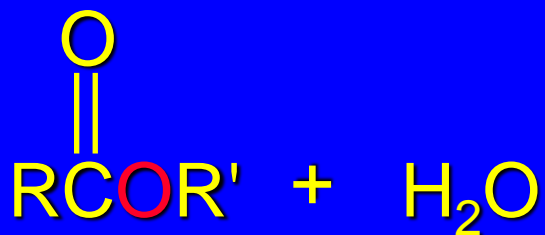
Acid-Catalyzed Hydrolysis of Esters - Mechanism

Is the reverse of the mechanism for acid-catalyzed esterification.

Like the mechanism of esterification, it involves two stages:

- 1) formation of tetrahedral intermediate
(3 steps)
- 2) dissociation of tetrahedral intermediate
(3 steps)

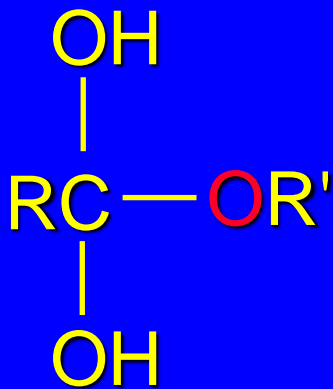
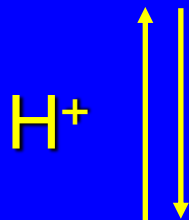
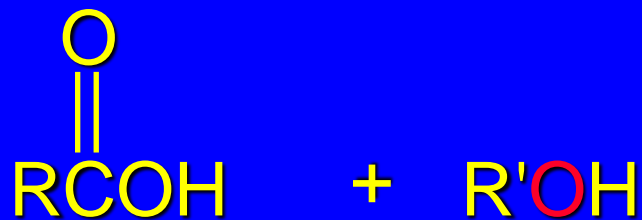
First stage: formation of tetrahedral intermediate



water adds to the carbonyl group of the ester

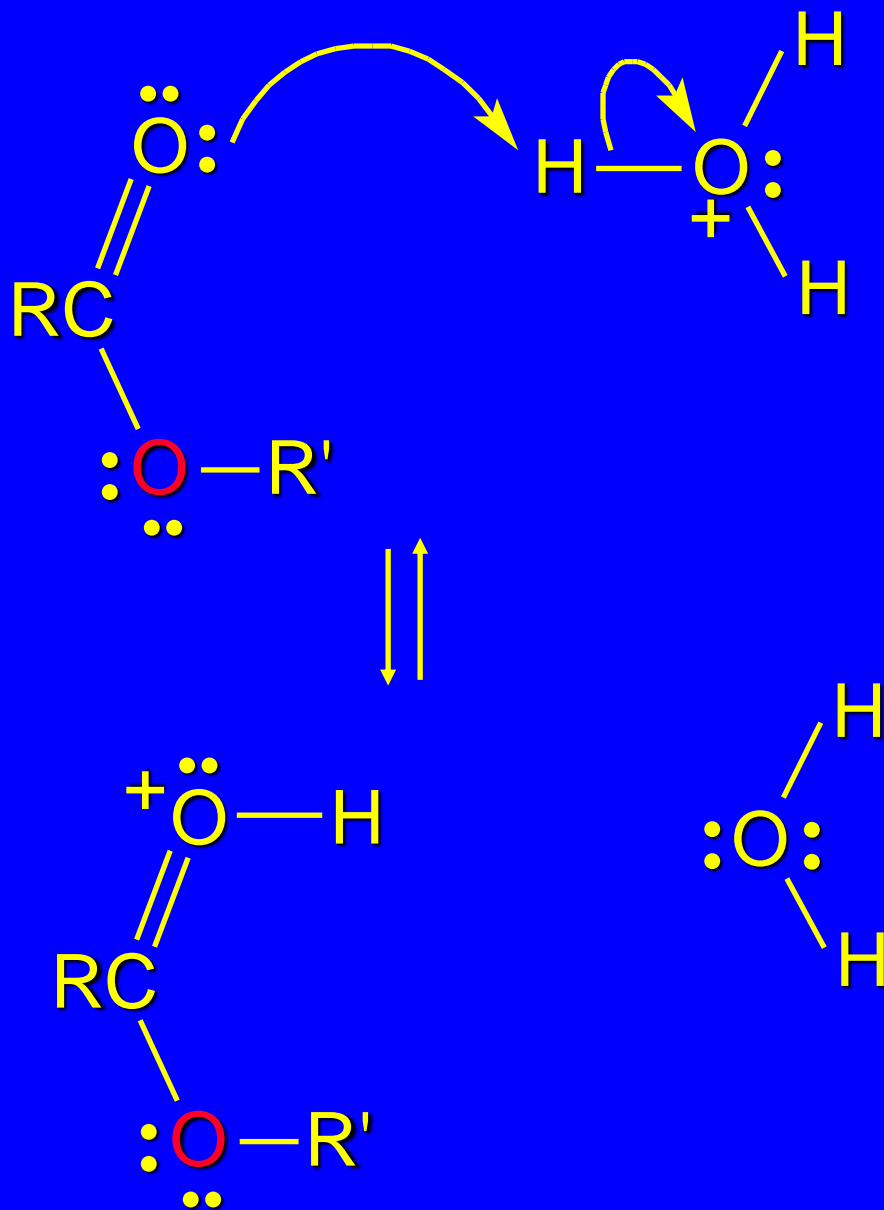
this stage is analogous to the acid-catalyzed addition of water to a ketone

Second stage: cleavage of tetrahedral intermediate

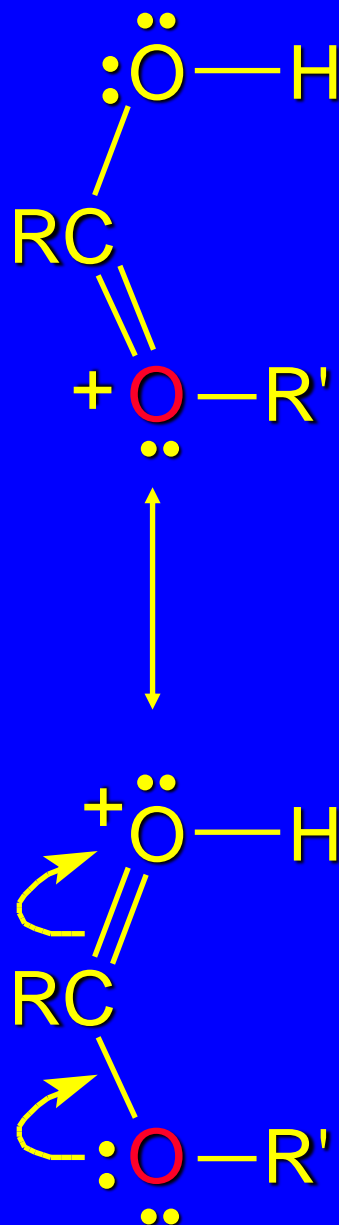


*Mechanism of formation
of
tetrahedral intermediate*

Step 1

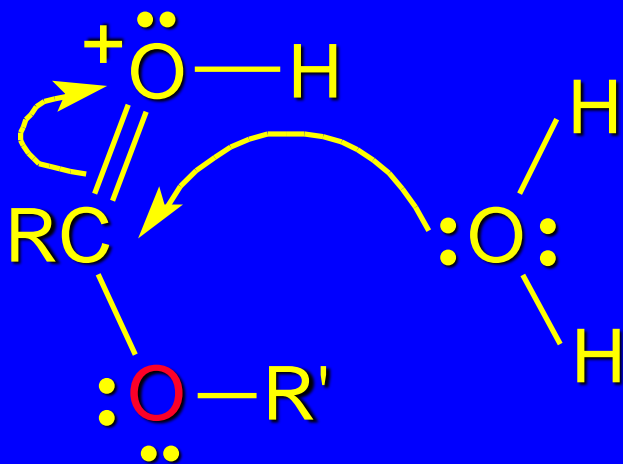
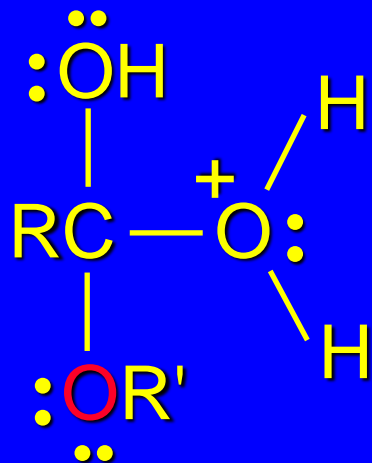


Step 1

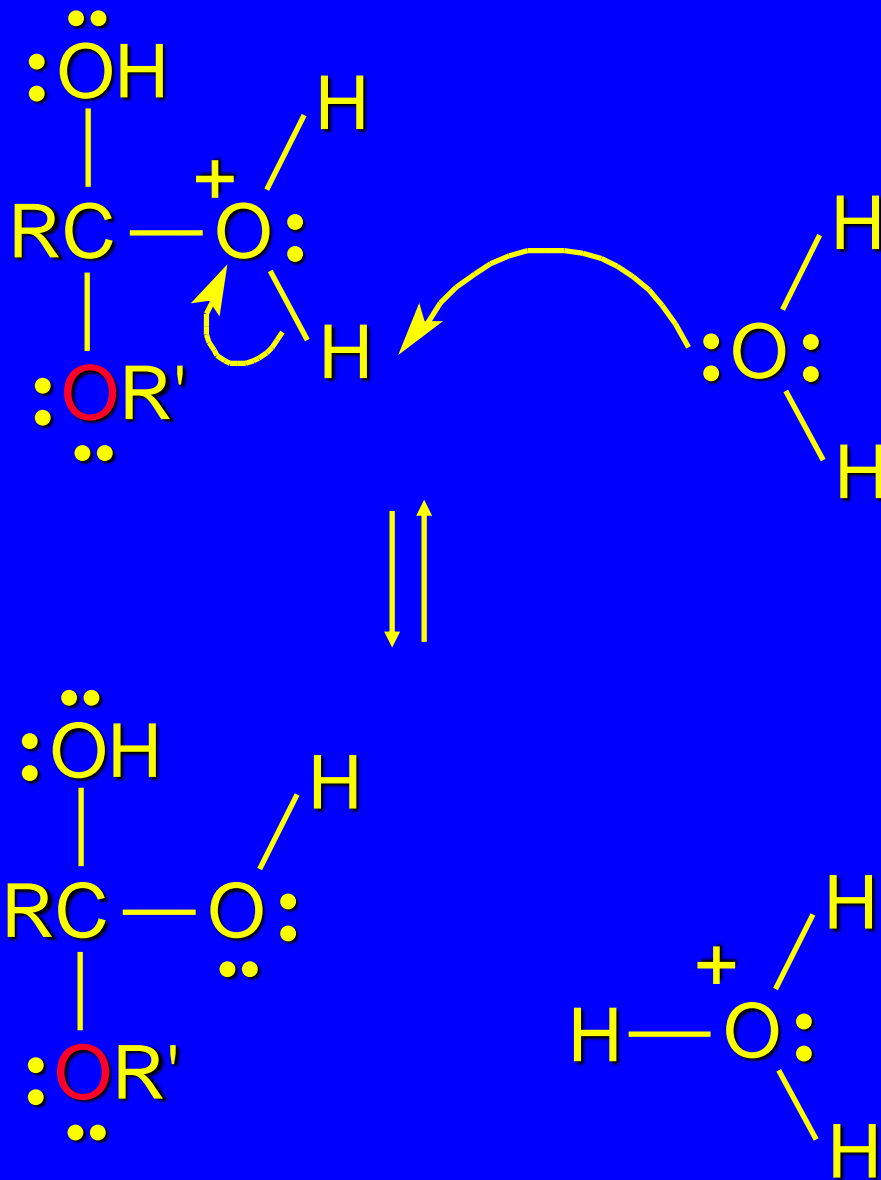


carbonyl oxygen is protonated because cation produced is stabilized by electron delocalization (resonance)

Step 2

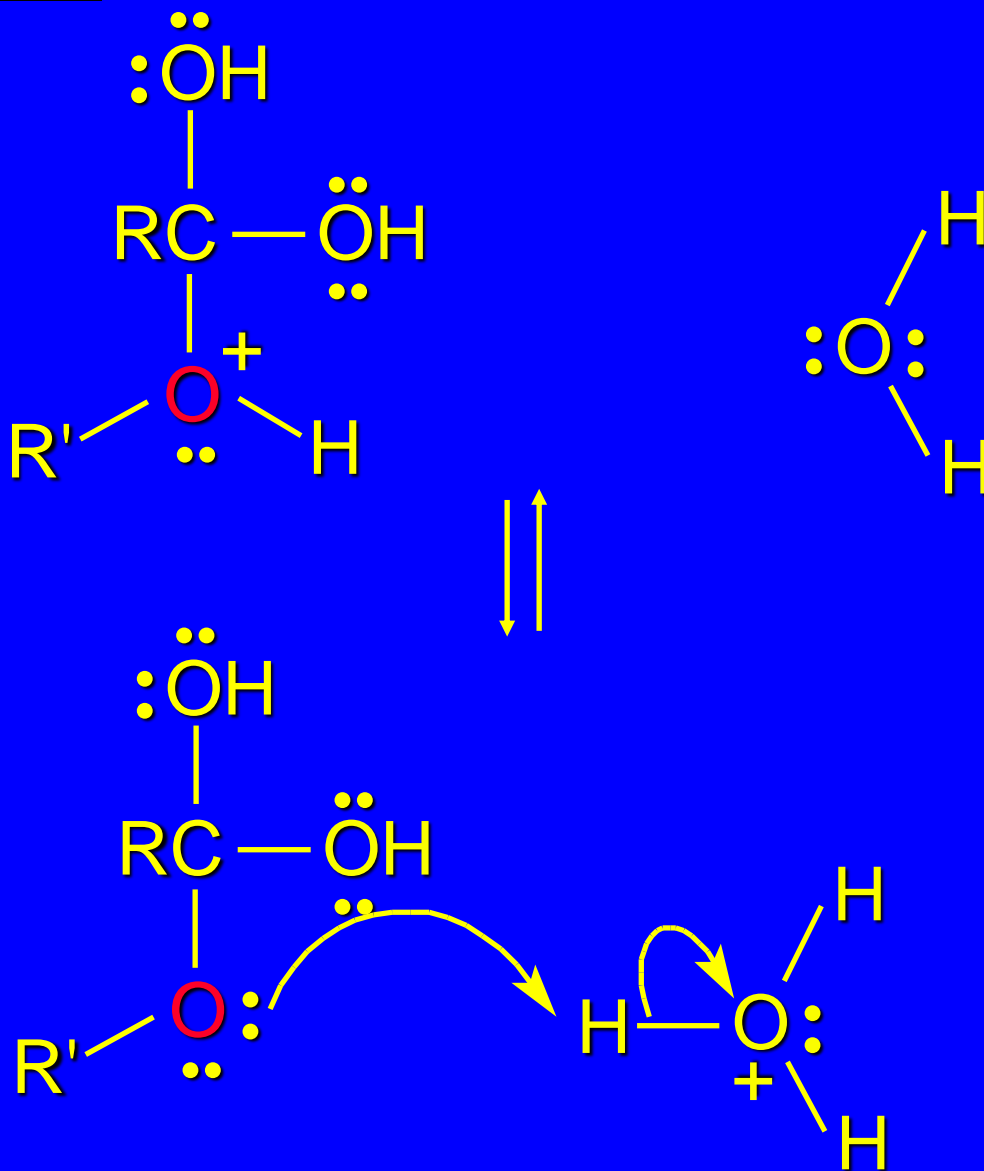


Step 3

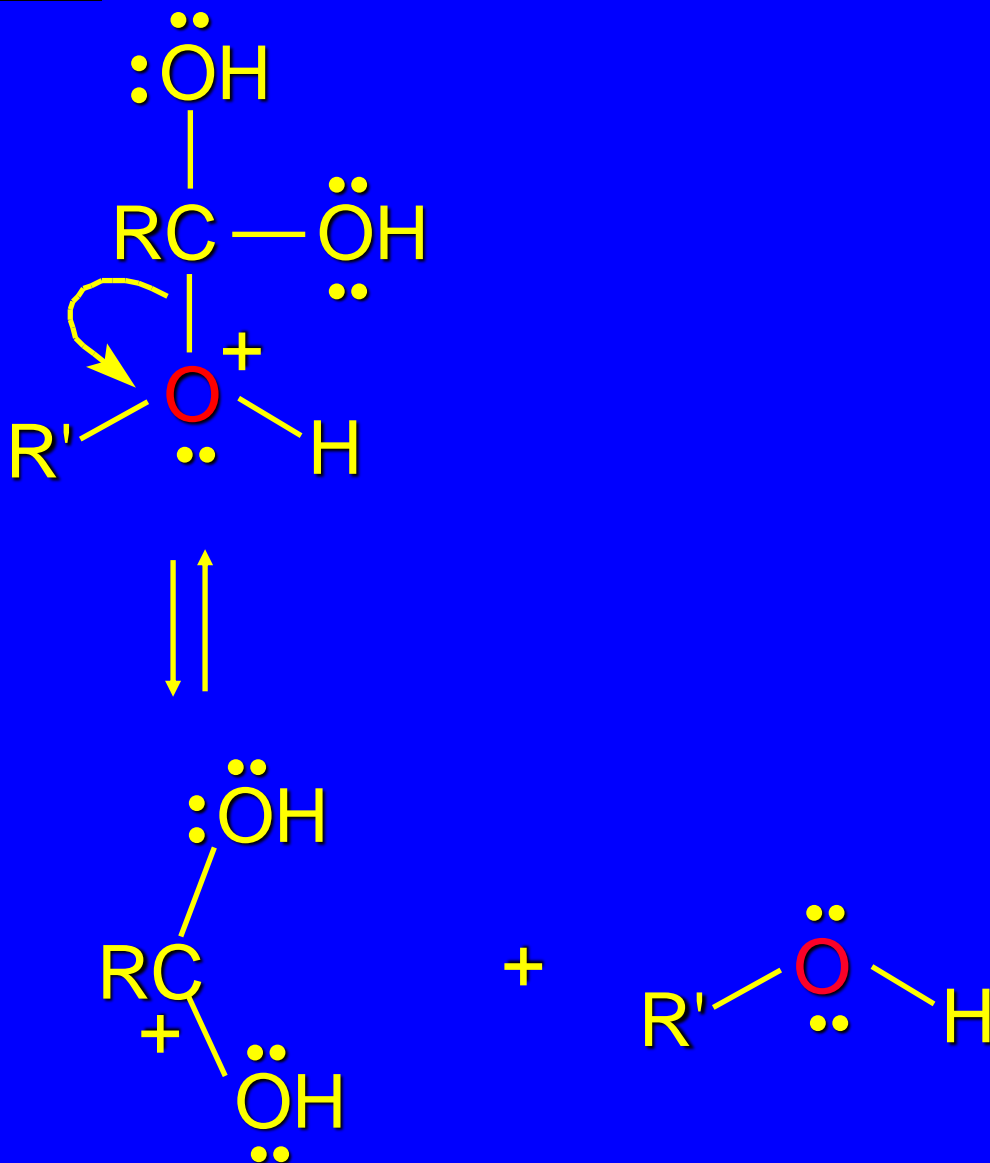


*Cleavage of tetrahedral
intermediate*

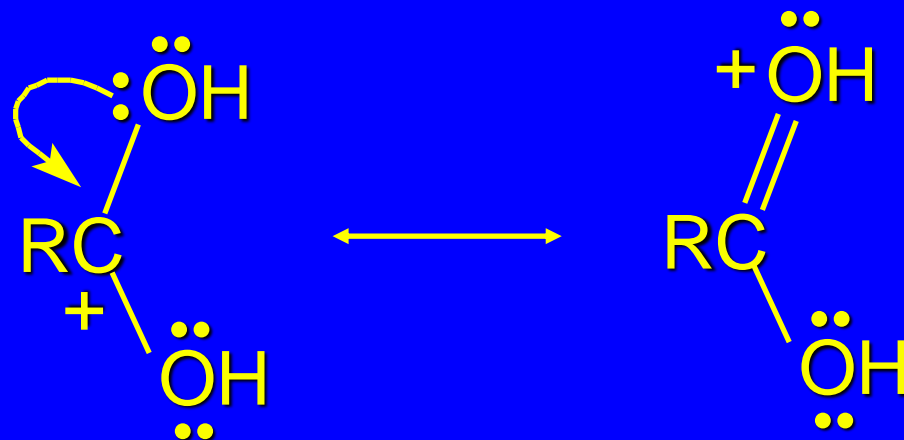
Step 4



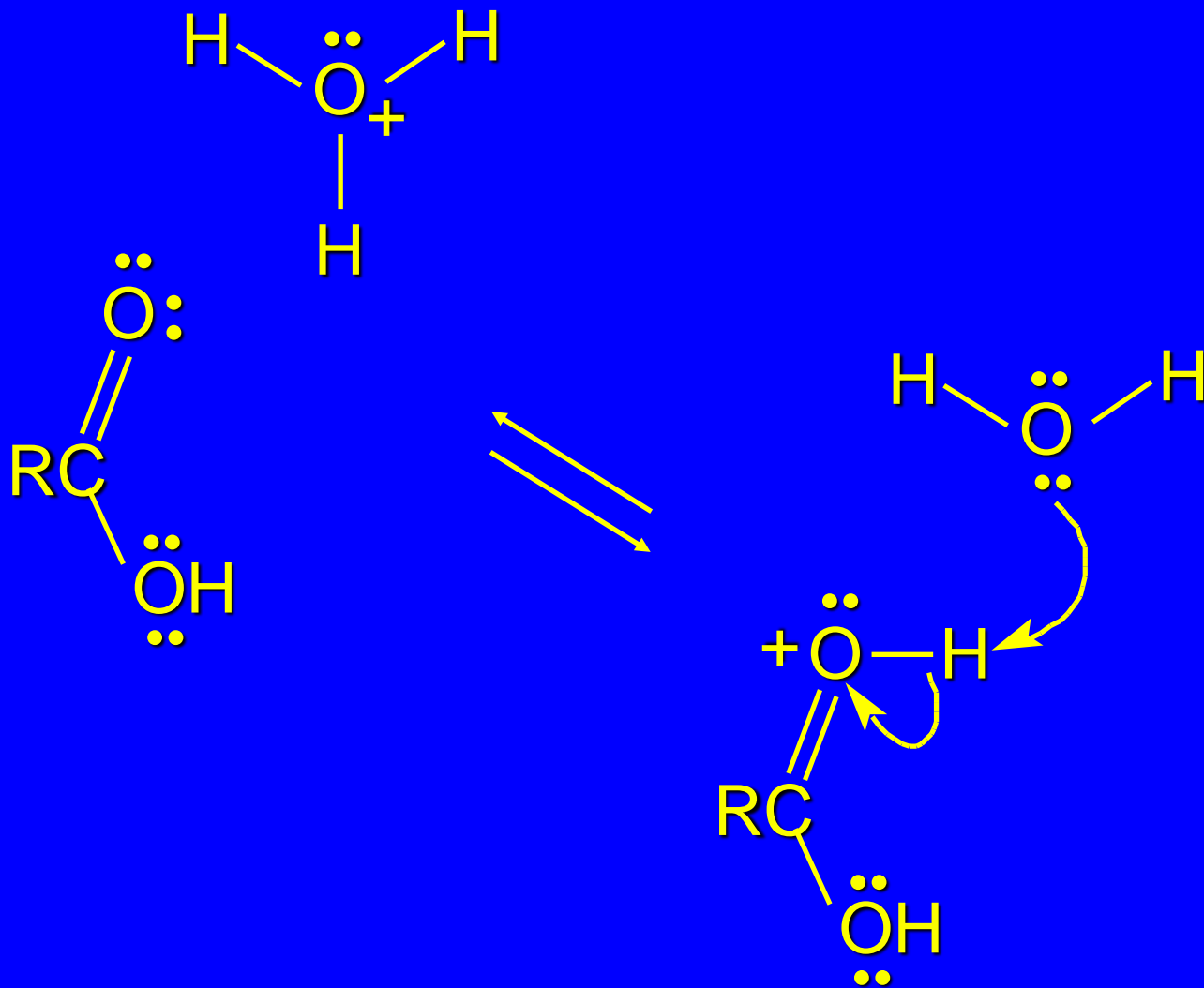
Step 5



Step 5



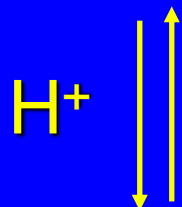
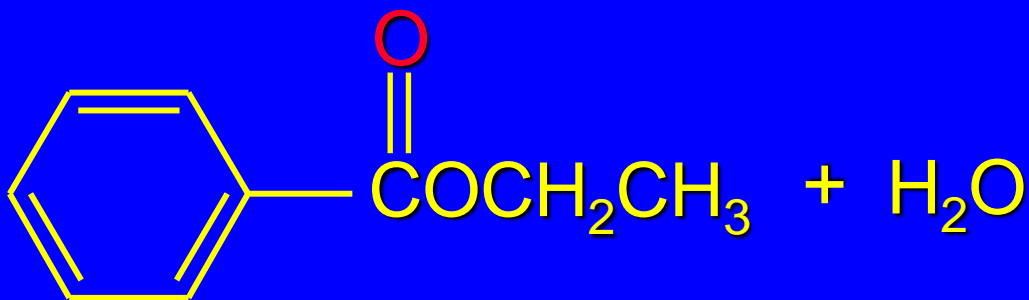
Step 6



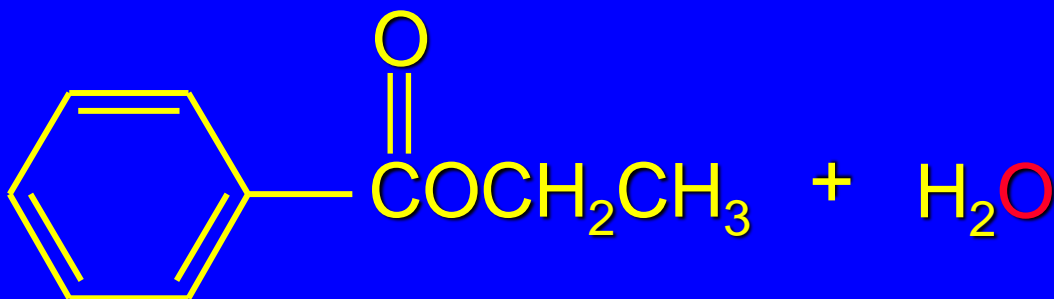
Key Features of Acid-Catalyzed Hydrolysis

1. Activation of carbonyl group by protonation of carbonyl oxygen
2. Nucleophilic addition of water to carbonyl group forms tetrahedral intermediate
3. Elimination of alcohol from tetrahedral intermediate restores carbonyl group

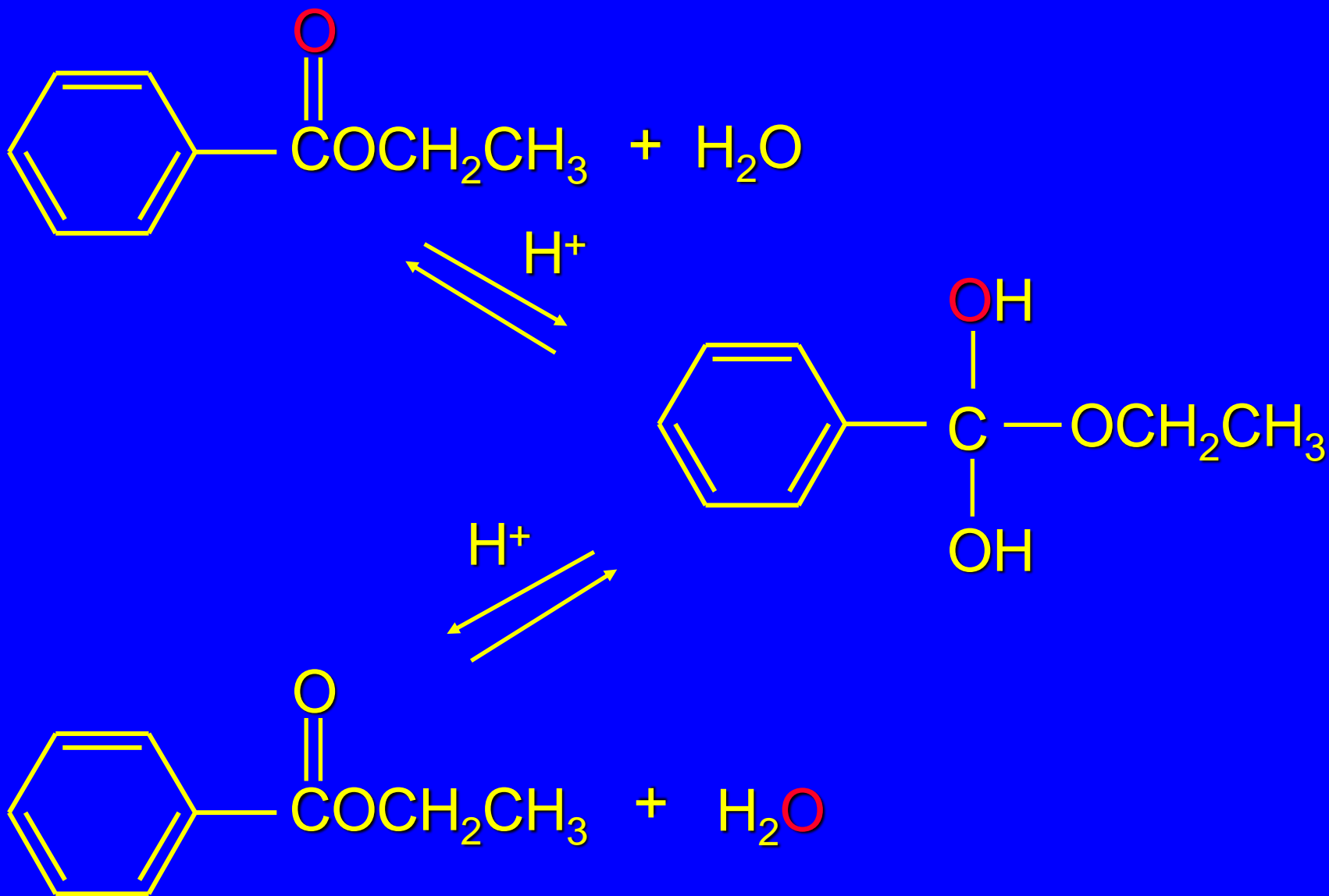
Investigation of Mechanism via ^{18}O Labeling Studies



1. Ethyl benzoate, labeled with ^{18}O at the carbonyl oxygen, was subjected to acid-catalyzed hydrolysis.
2. Ethyl benzoate, recovered before the reaction had gone to completion, had lost its ^{18}O label.
3. This observation is consistent with a tetrahedral intermediate.



Investigation of Mechanism via ^{18}O Labeling Studies



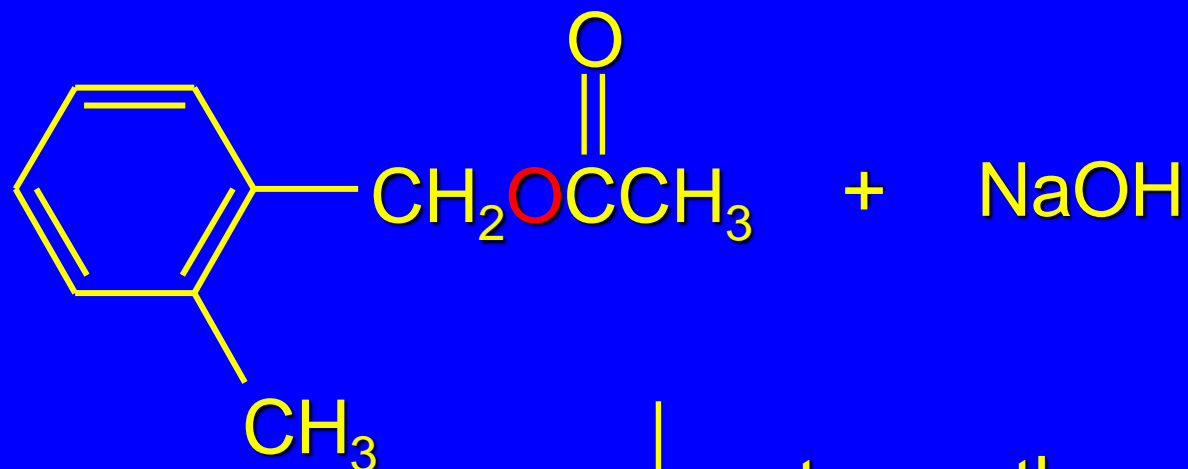
20.11
Ester Hydrolysis in Base:
Saponification

Ester Hydrolysis in Aqueous Base

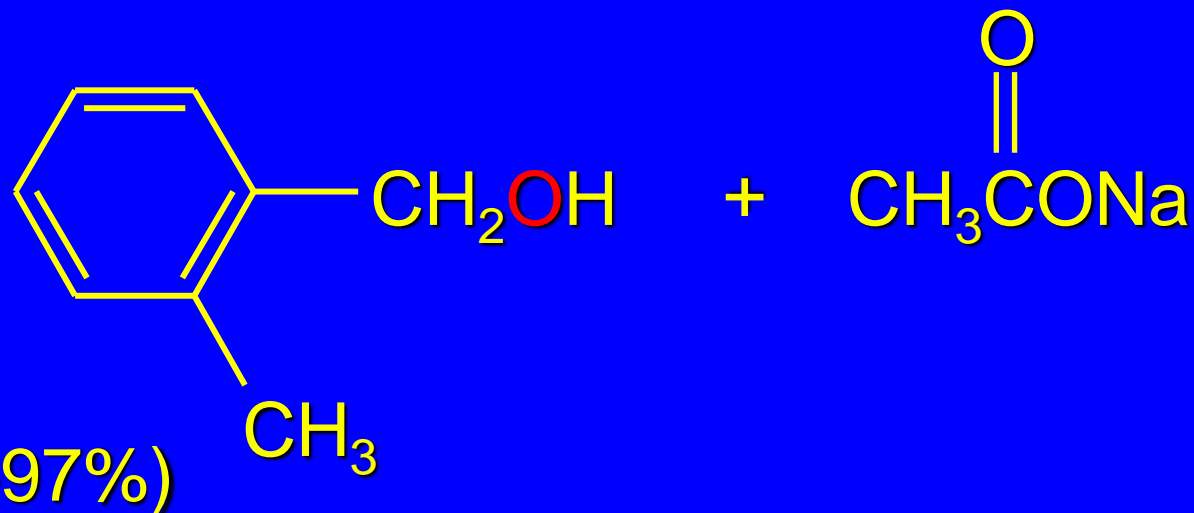


1. is called *saponification*
2. is irreversible, because of strong stabilization of carboxylate ion
3. if carboxylic acid is desired product, saponification is followed by a separate acidification step (simply a pH adjustment)

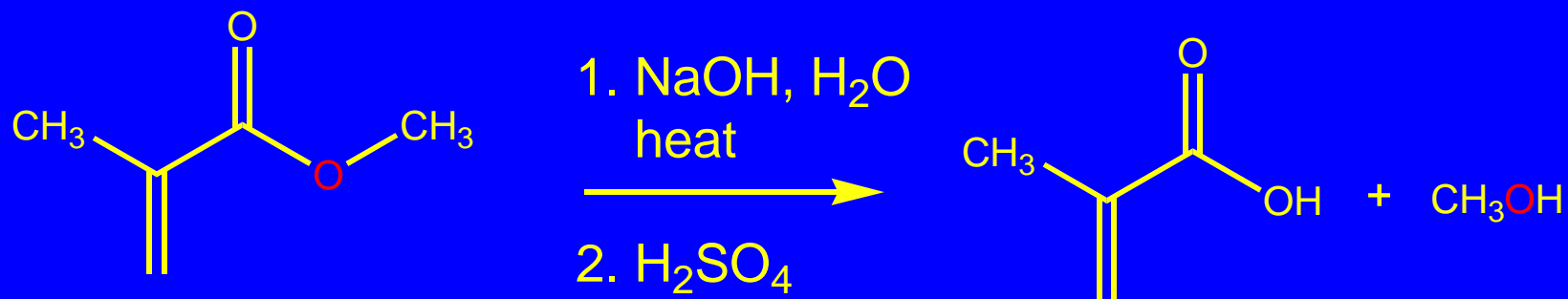
Ester Hydrolysis in Aqueous Base - Example 1



water-methanol, heat



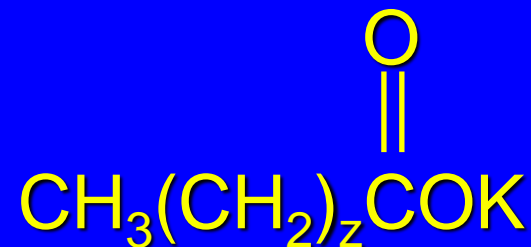
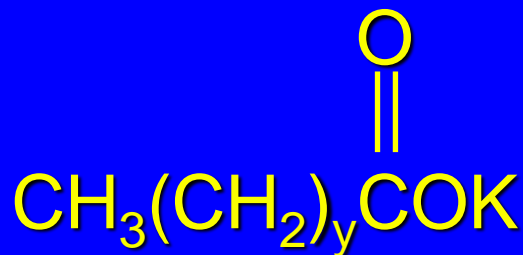
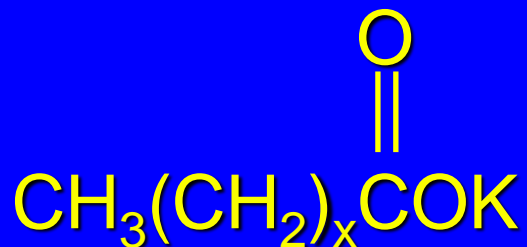
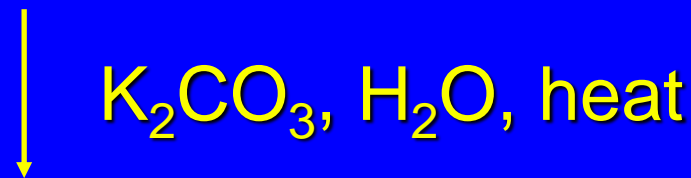
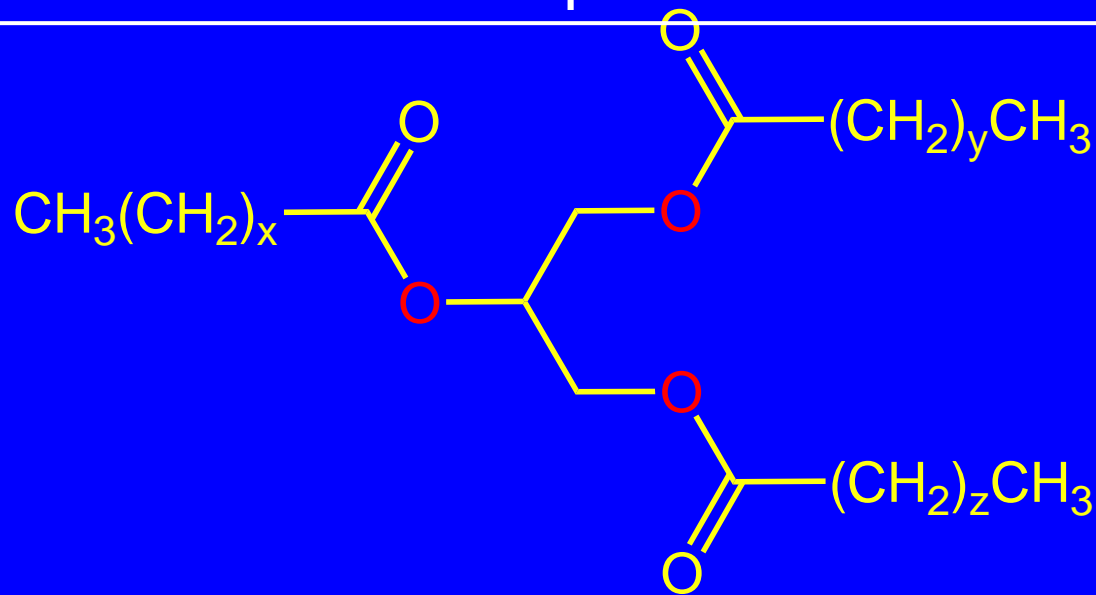
Ester Hydrolysis in Aqueous Base - Example 2



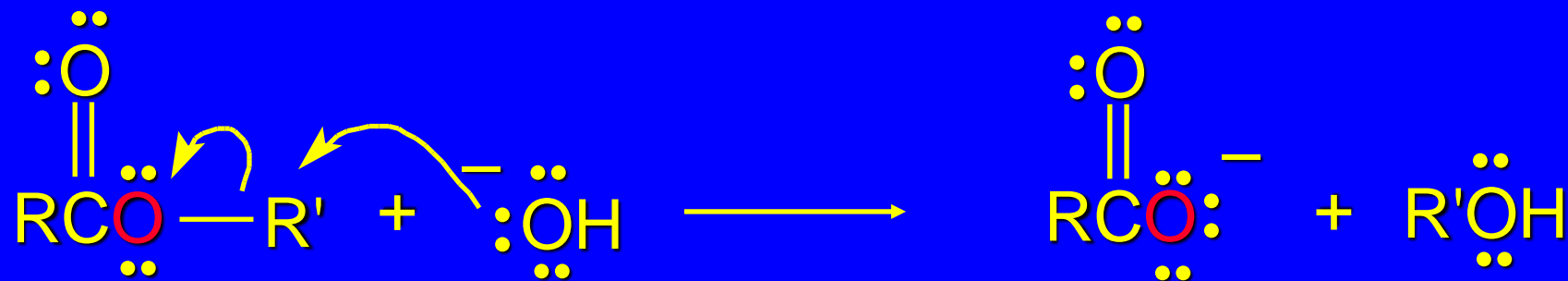
Manufacture of Soap

Basic hydrolysis of the glyceryl triesters (from fats and oils) gives salts of long-chain carboxylic acids.

These salts are soaps.



Is the Mechanism B_{AL}2 or B_{AC}2?



One possibility is an S_N2 attack by hydroxide on the alkyl group of the ester. Carboxylate is the leaving group.

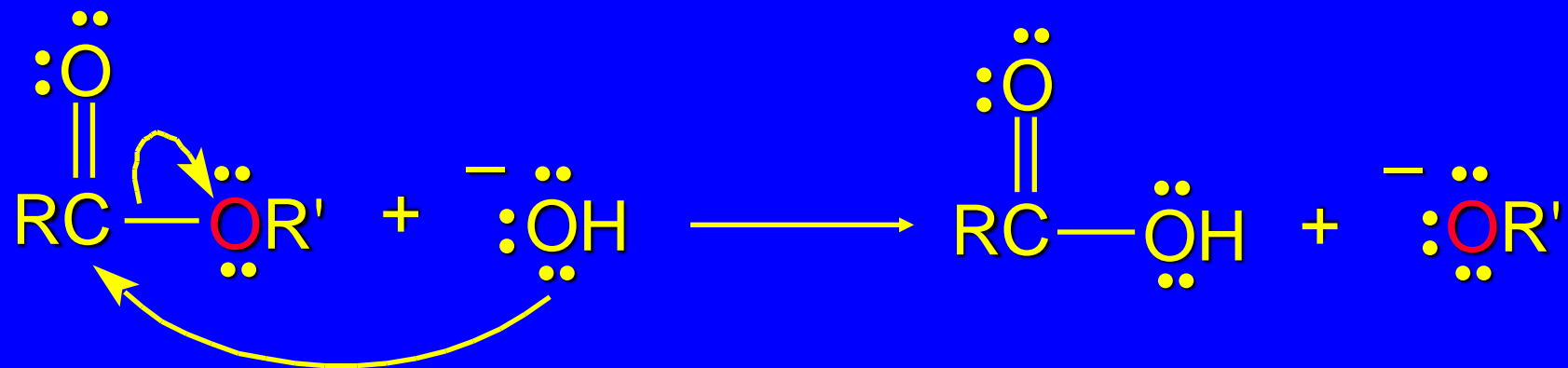
This mechanism would be designated B_{AL}2:

B (Basic conditions)

AL (Carbonyl-OAlkyl bond breaking in rate-determining step)

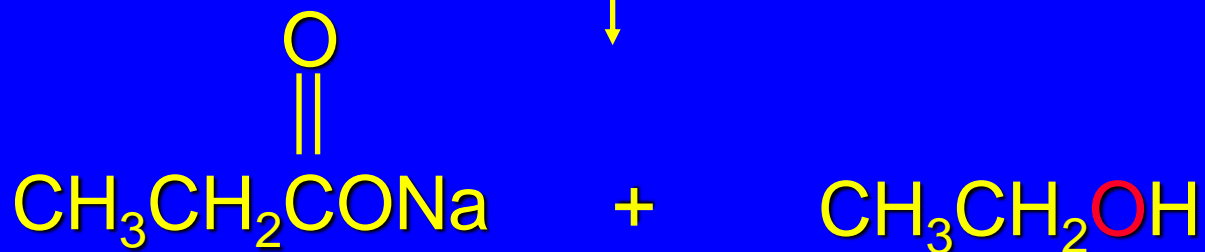
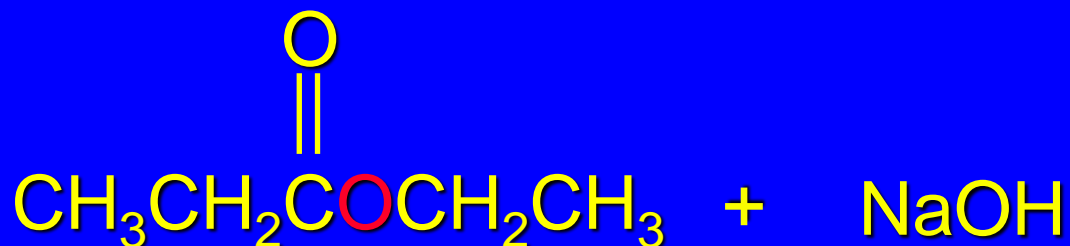
2 (Reaction is second order - rate = k[ester][hydroxide])

Is the Mechanism B_{AL}2 or B_{AC}2?



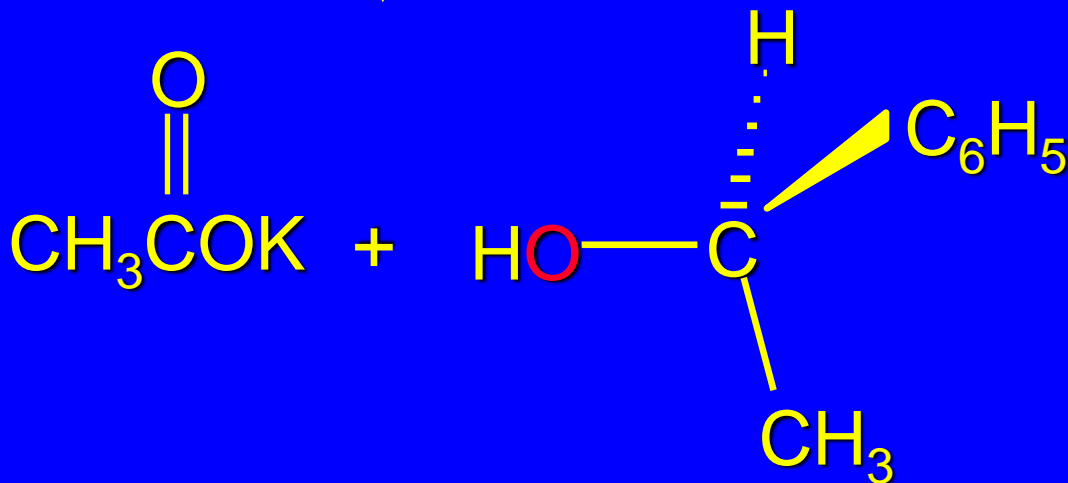
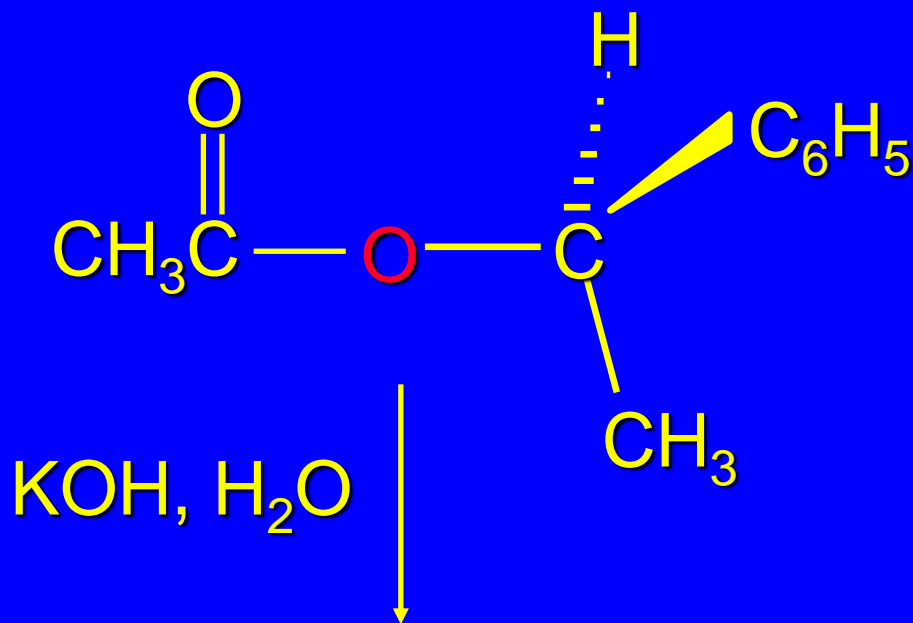
A second possibility is nucleophilic acyl substitution.

^{18}O Labeling gives the answer



^{18}O retained in alcohol, not carboxylate;
therefore nucleophilic acyl substitution.

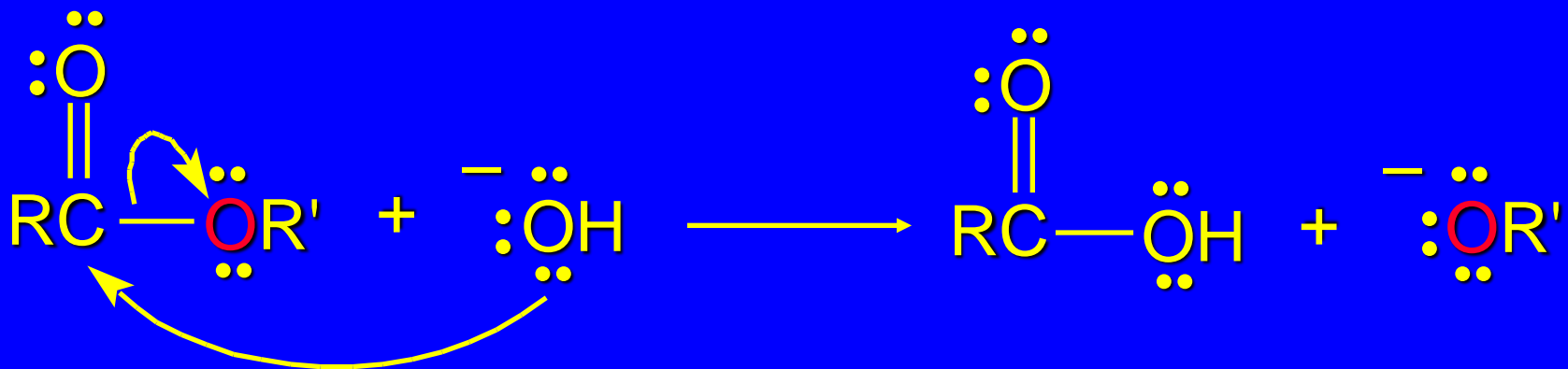
Stereochemistry gives the same answer



alcohol has same configuration at chirality center as ester; therefore, nucleophilic acyl substitution

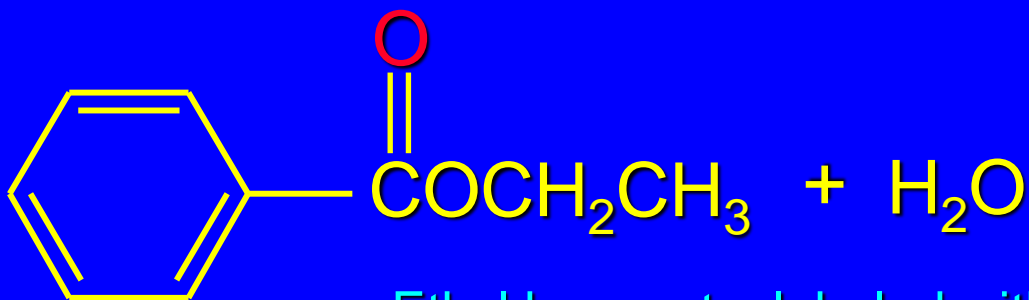
not $\text{S}_{\text{N}}2$

Does it proceed via a tetrahedral intermediate?



Does nucleophilic acyl substitution proceed in a single step, or is a tetrahedral intermediate involved?

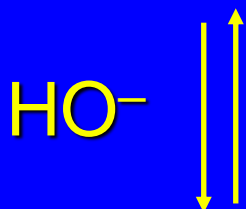
^{18}O Labeling Studies



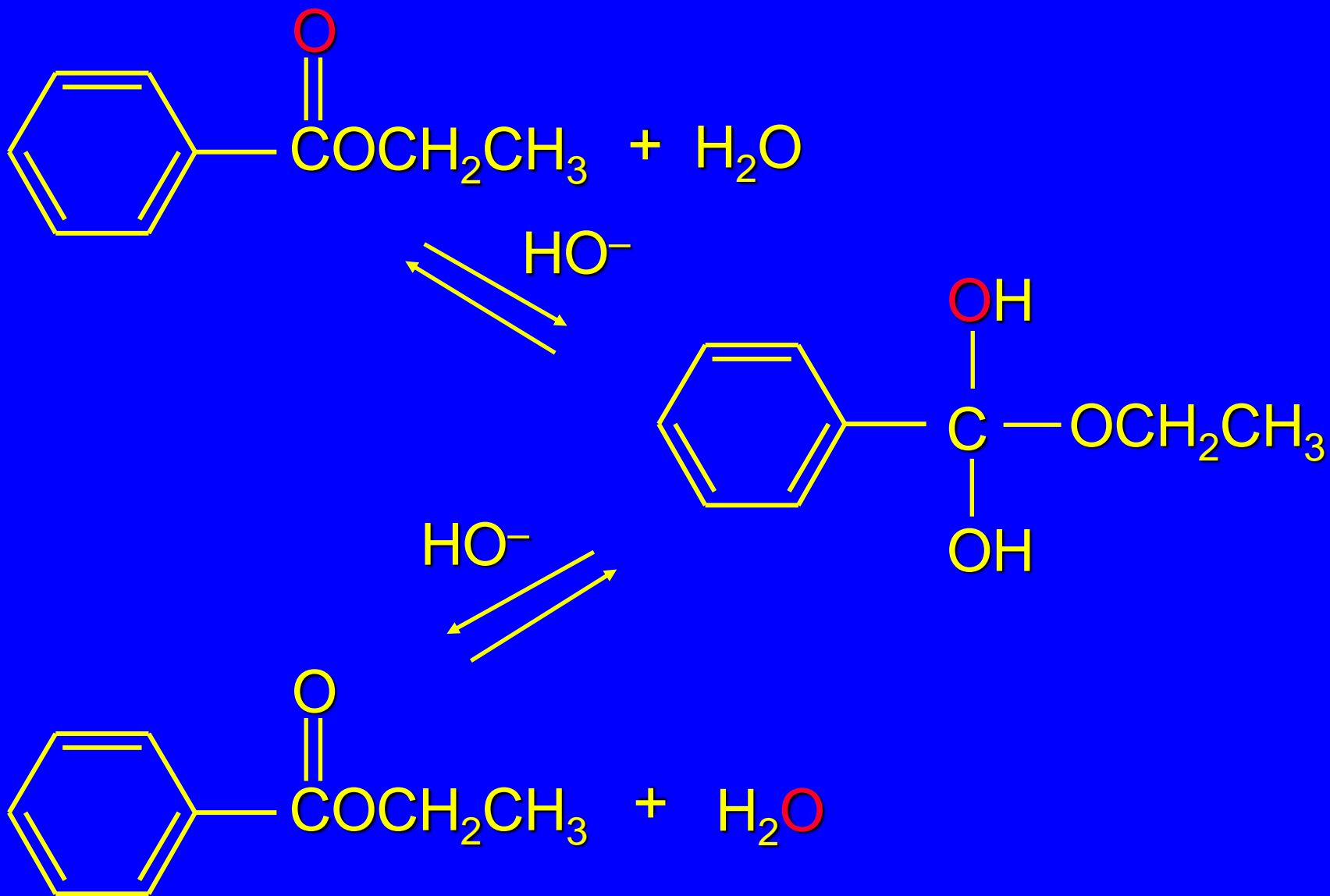
Ethyl benzoate, labeled with ^{18}O at the carbonyl oxygen, was subjected to hydrolysis in base.

Ethyl benzoate, recovered before the reaction had gone to completion, had lost its ^{18}O label.

This observation is consistent with a tetrahedral intermediate.



^{18}O Labeling Studies

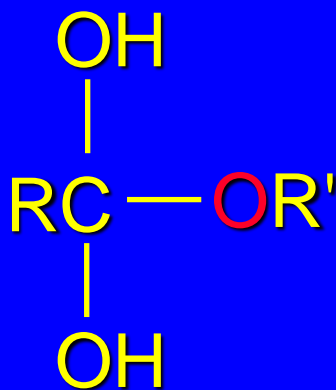
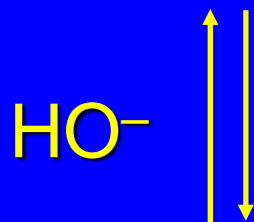
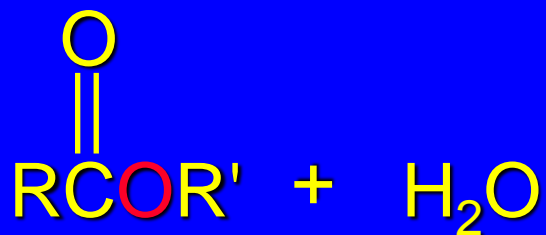


Mechanism of Ester Hydrolysis in Base

Involves two stages:

- 1) formation of tetrahedral intermediate
- 2) dissociation of tetrahedral intermediate

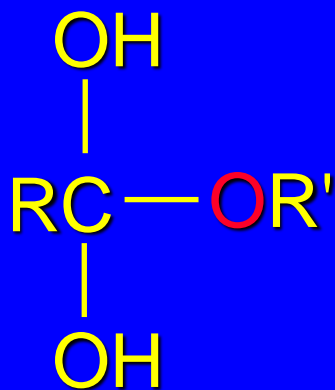
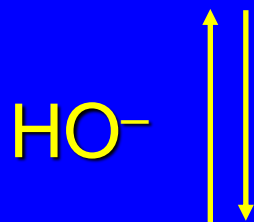
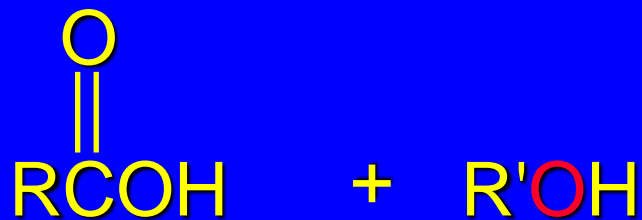
First stage: formation of tetrahedral intermediate



water adds to the carbonyl group of the ester

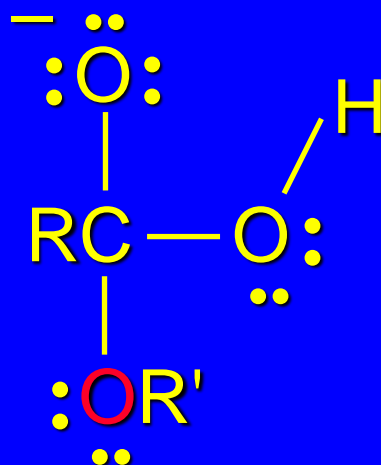
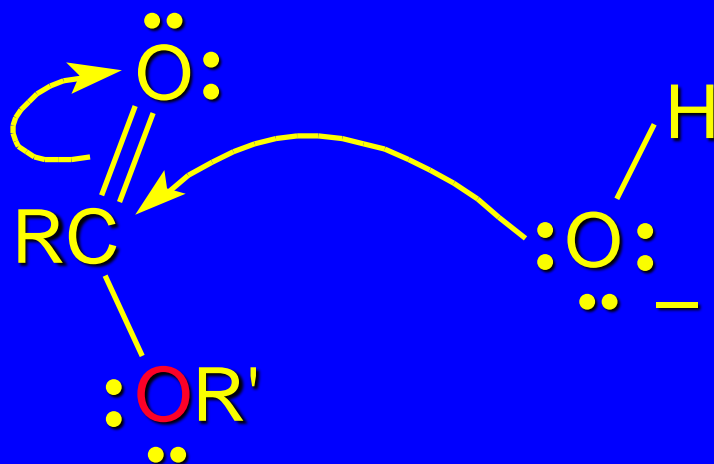
this stage is analogous to the base-catalyzed addition of water to a ketone

Second stage: cleavage of tetrahedral intermediate

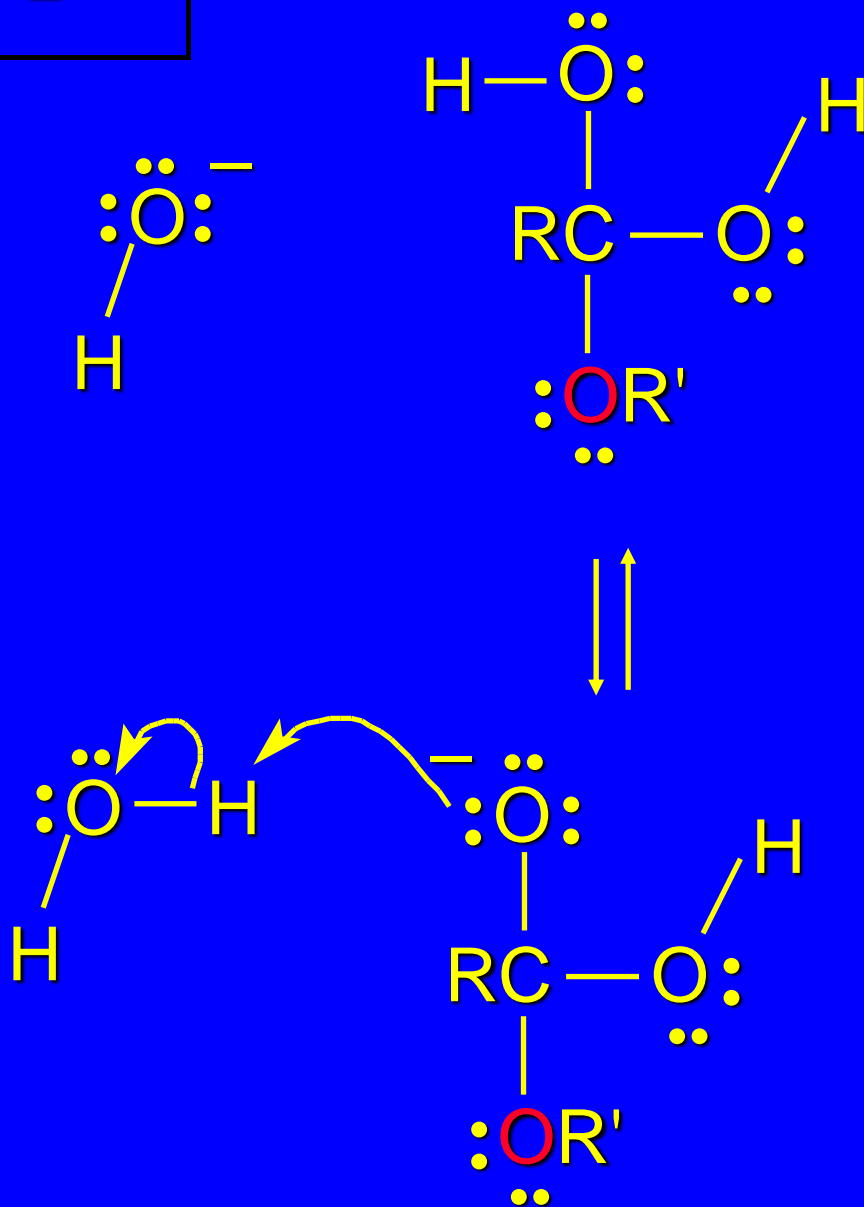


*Mechanism of formation
of
tetrahedral intermediate*

Step 1

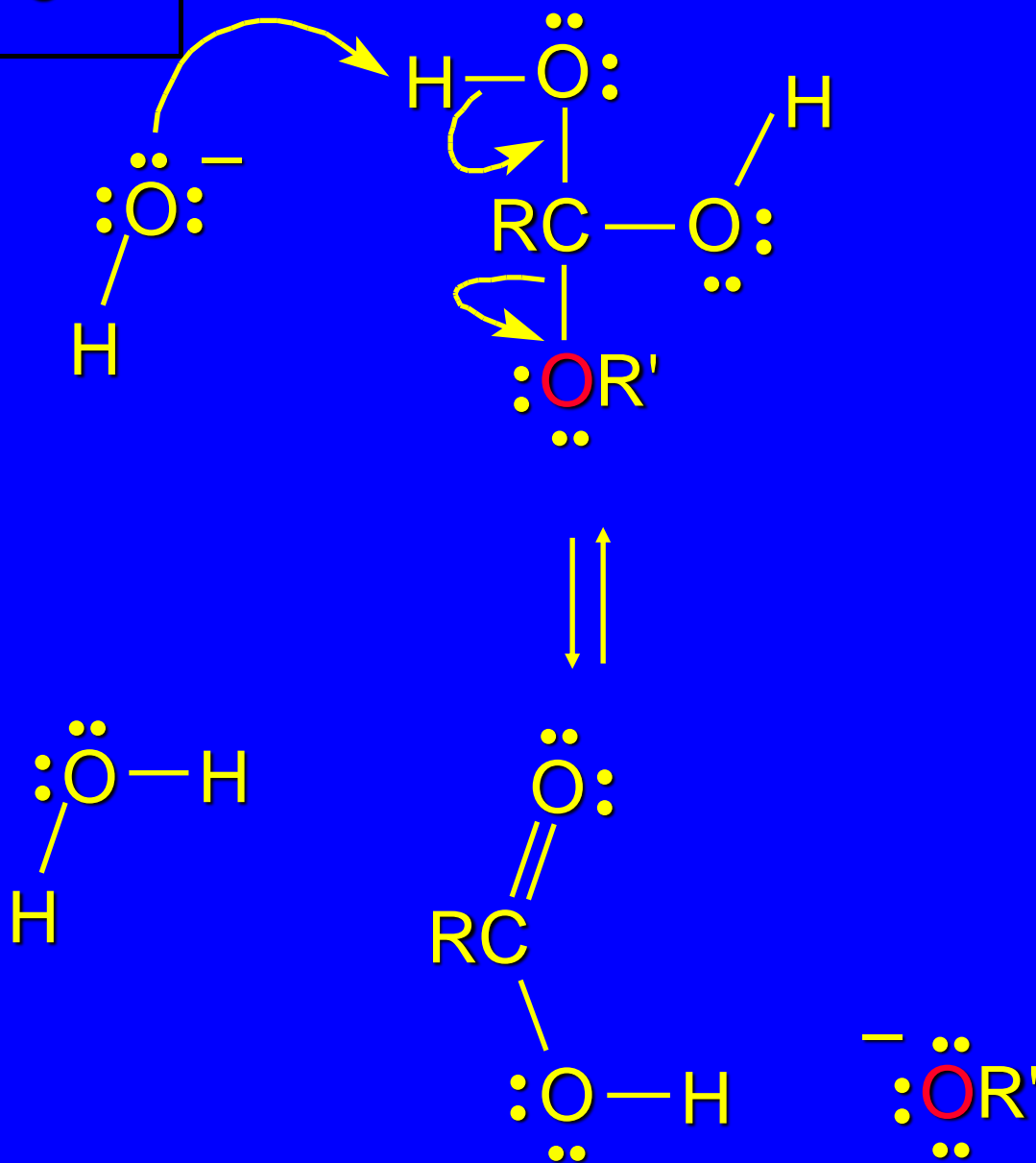


Step 2

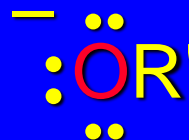
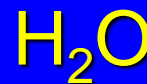
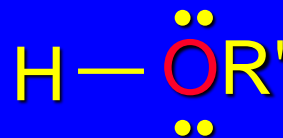
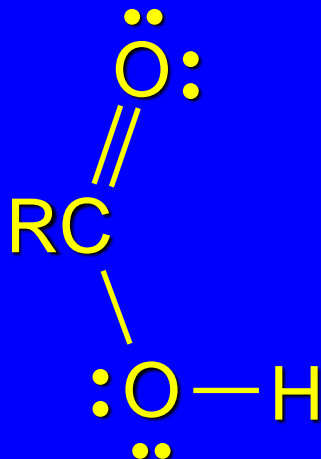
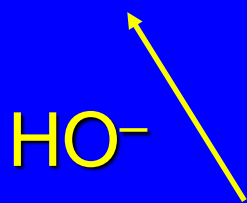
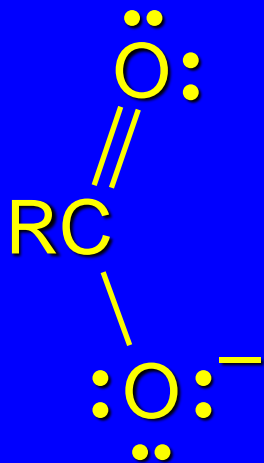


*Dissociation of
tetrahedral intermediate*

Step 3



Step 4



Key Features of Mechanism

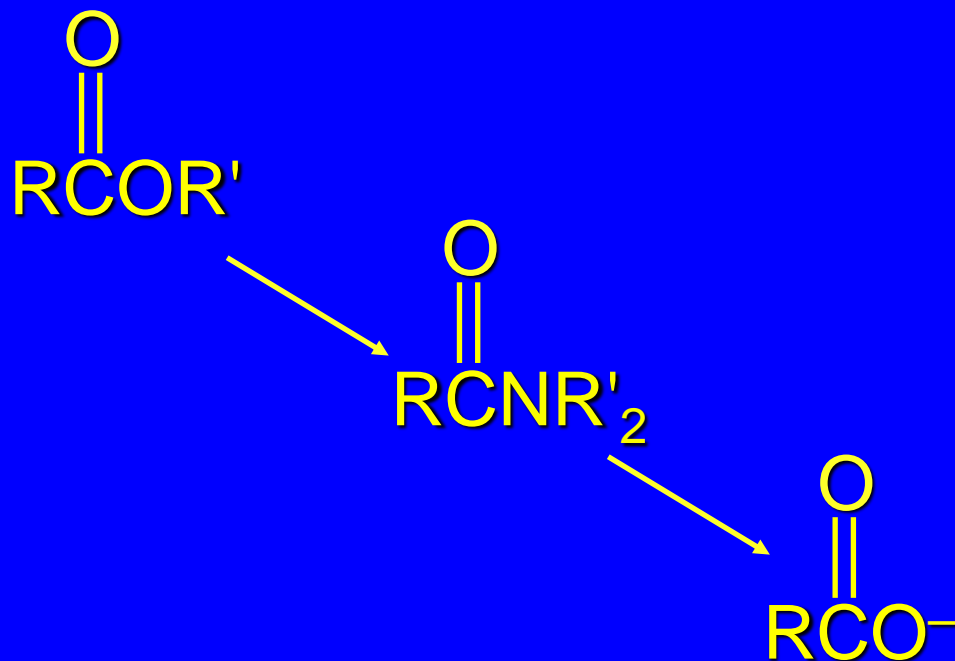
Nucleophilic addition of hydroxide ion to carbonyl group in first step

Tetrahedral intermediate formed in first stage

Hydroxide-induced dissociation of tetrahedral intermediate in second stage

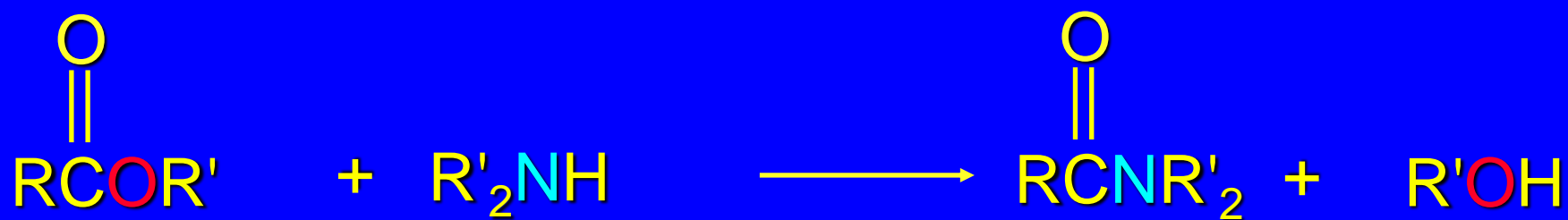
20.11
Reactions of Esters
with Ammonia and Amines

Reactions of Esters

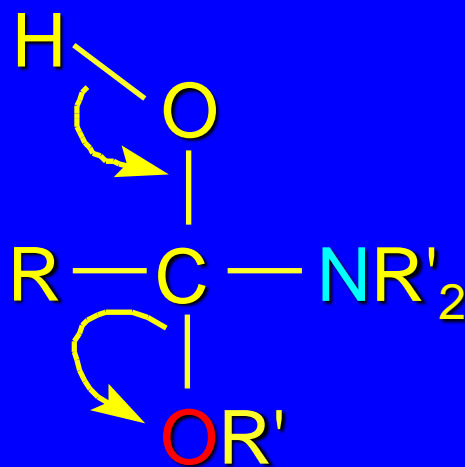


Reactions of Esters

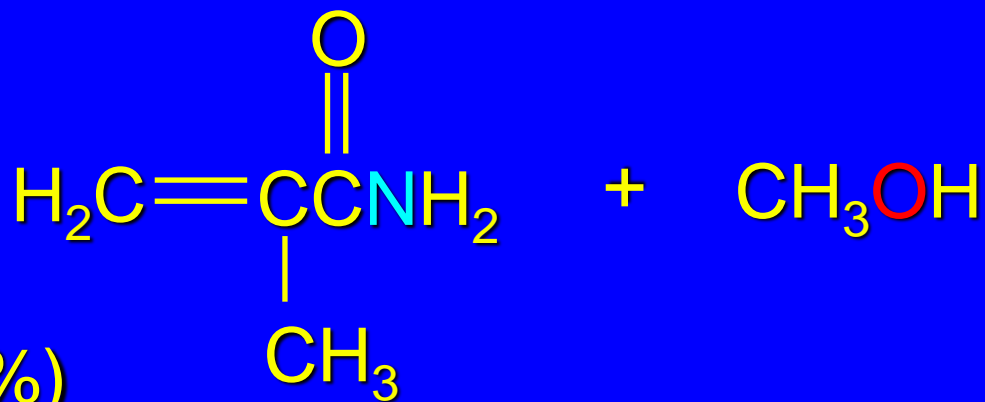
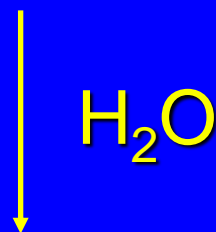
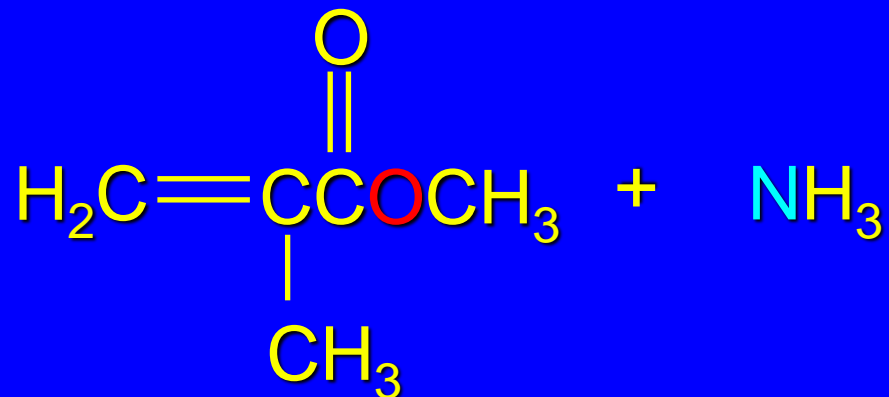
Esters react with ammonia and amines to give amides:



via:

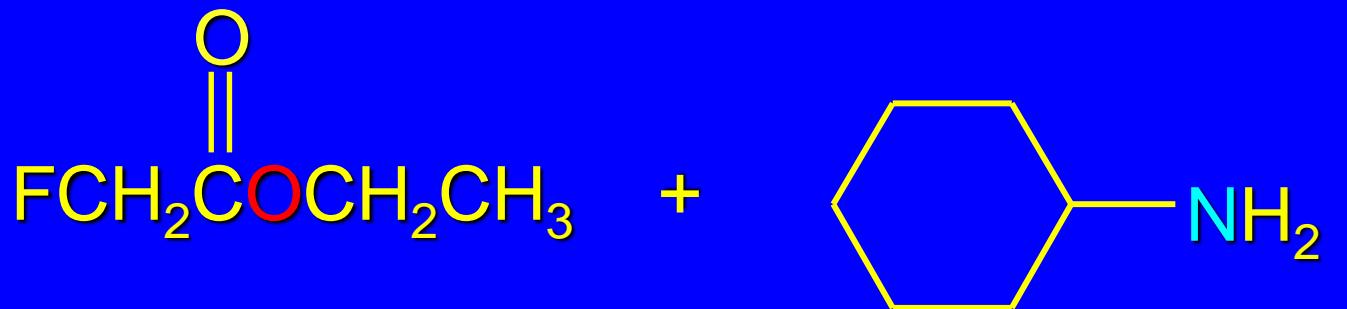


Example

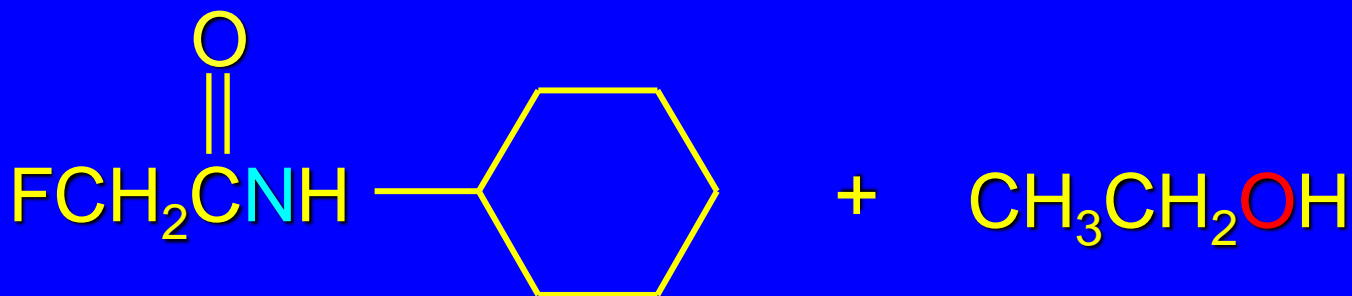


(75%)

Example



heat



(61%)

20.14

Preparation of Amides

Preparation of Amides

Amides are prepared from amines by acylation with:

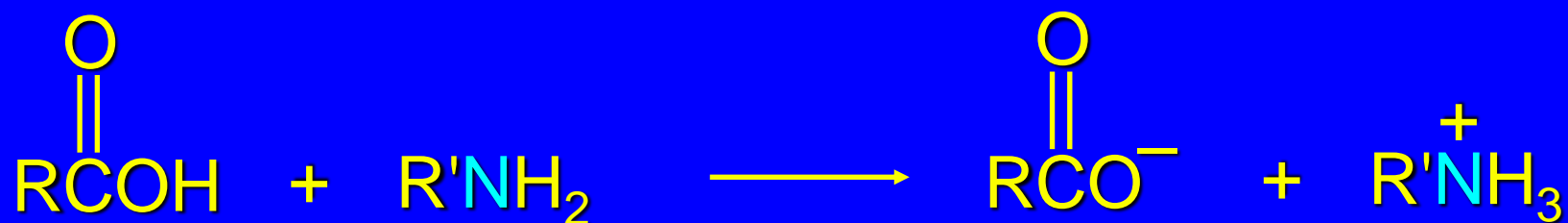
acyl chlorides (Table 20.1)

anhydrides (Table 20.2)

esters (Table 20.5)

Preparation of Amides

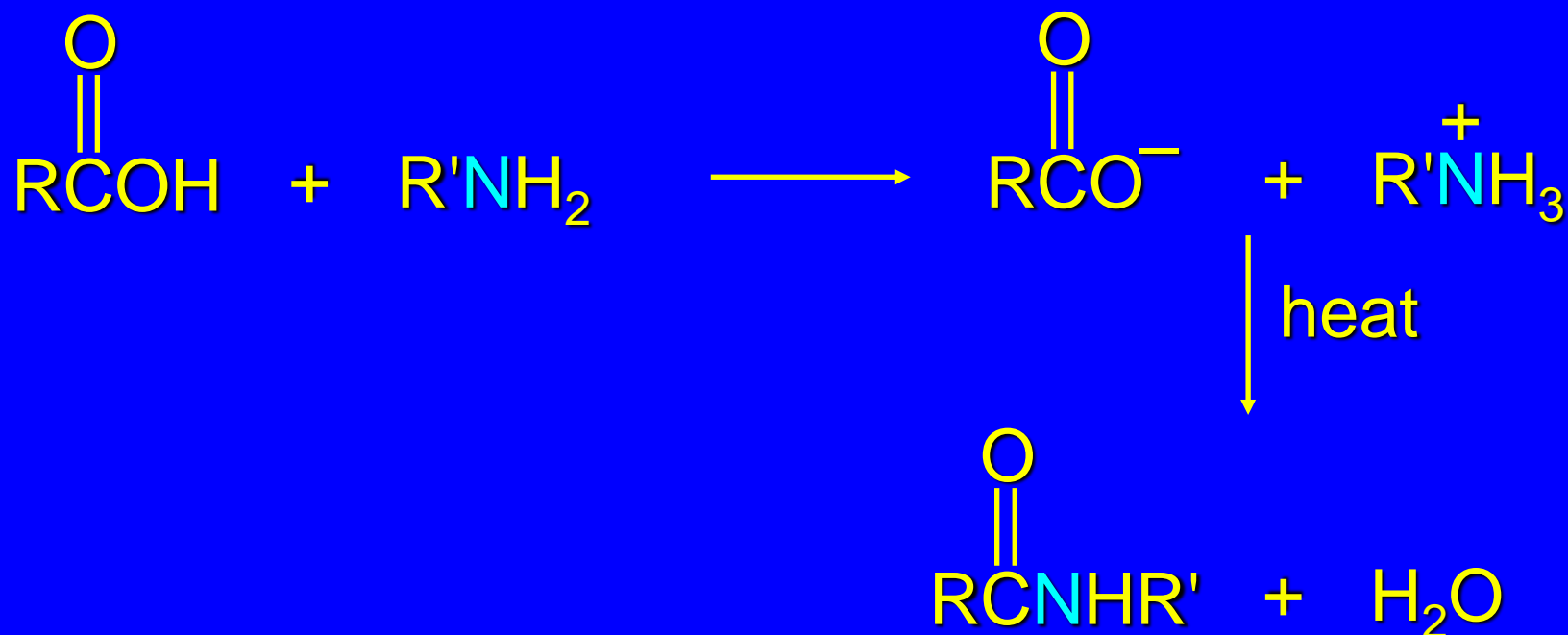
Amines do not react with carboxylic acids to give amides. The reaction that occurs is proton-transfer (acid-base).



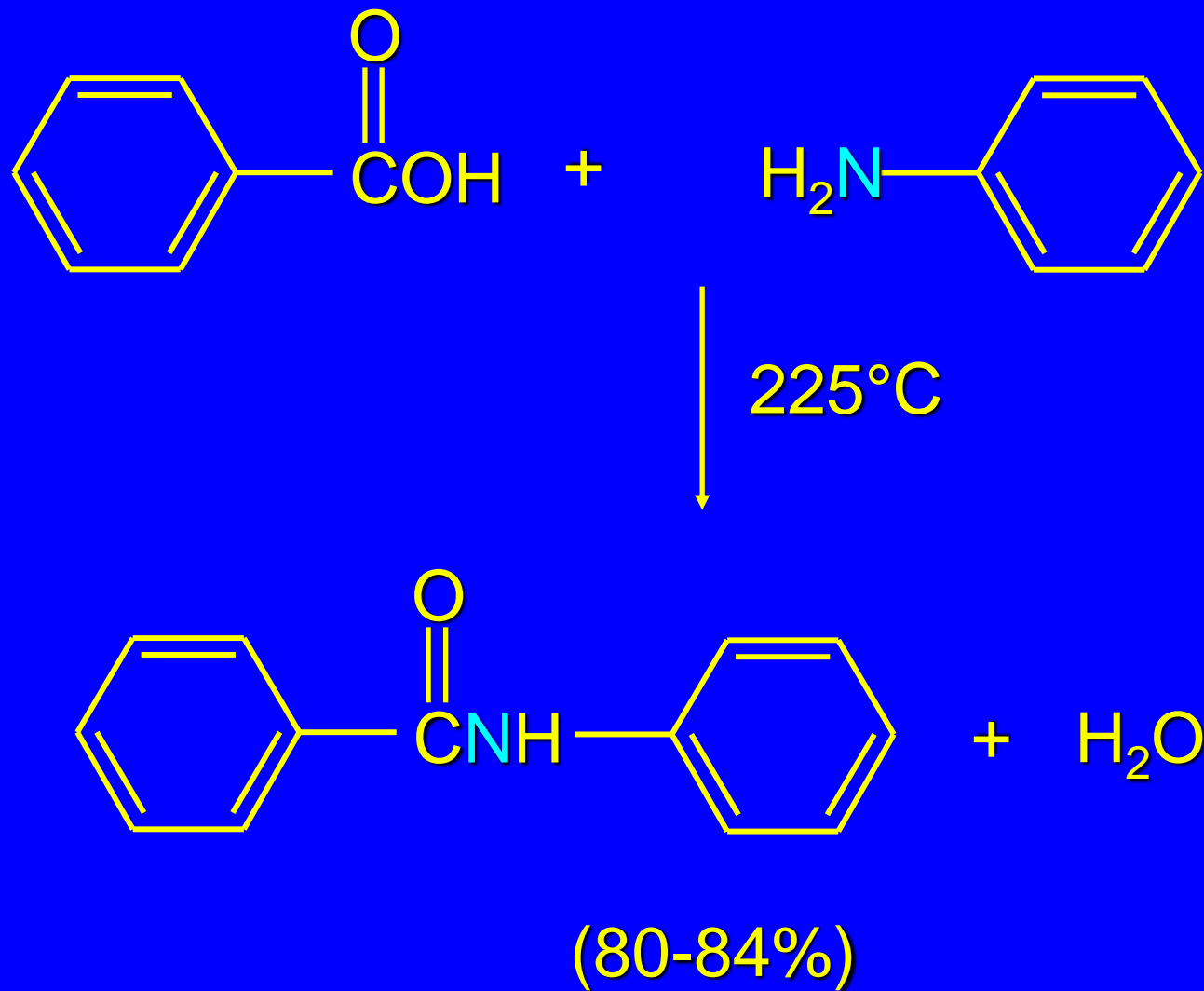
If no heat-sensitive groups are present, the resulting ammonium carboxylate salts can be converted to amides by heating.

Preparation of Amides

Amines do **not** react with carboxylic acids to give amides. The reaction that occurs is proton-transfer (acid-base).



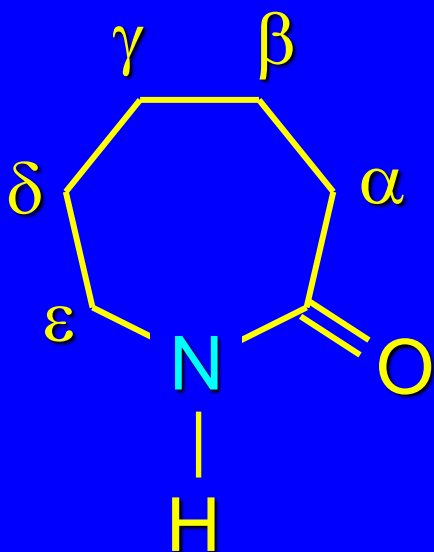
Example



20.15
Lactams

Lactams

Lactams are cyclic amides. Some are industrial chemicals, others occur naturally.

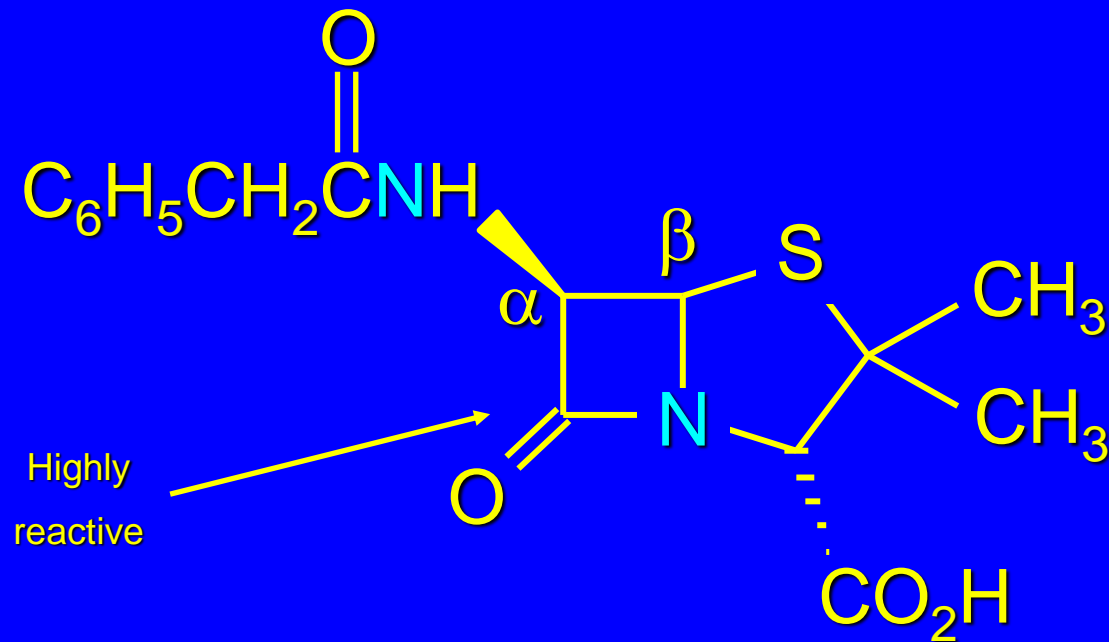


ϵ -Caprolactam*: used to prepare a type of nylon

*Caproic acid is the common name for hexanoic acid.

Lactams

Lactams are cyclic amides. Some are industrial chemicals, others occur naturally.



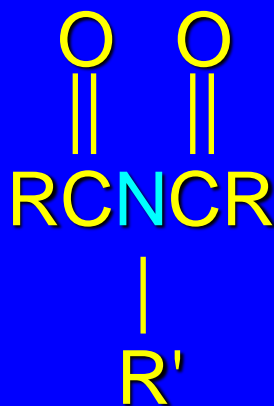
Penicillin G: a β -lactam antibiotic

20.16

Imides

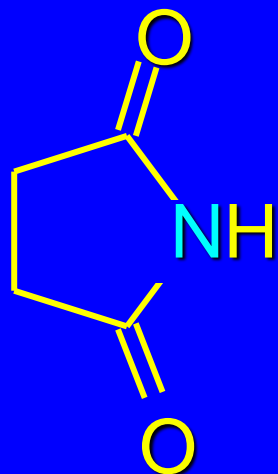
Imides

Imides have 2 acyl groups attached to the nitrogen.



Imides

The most common examples are cyclic imides.



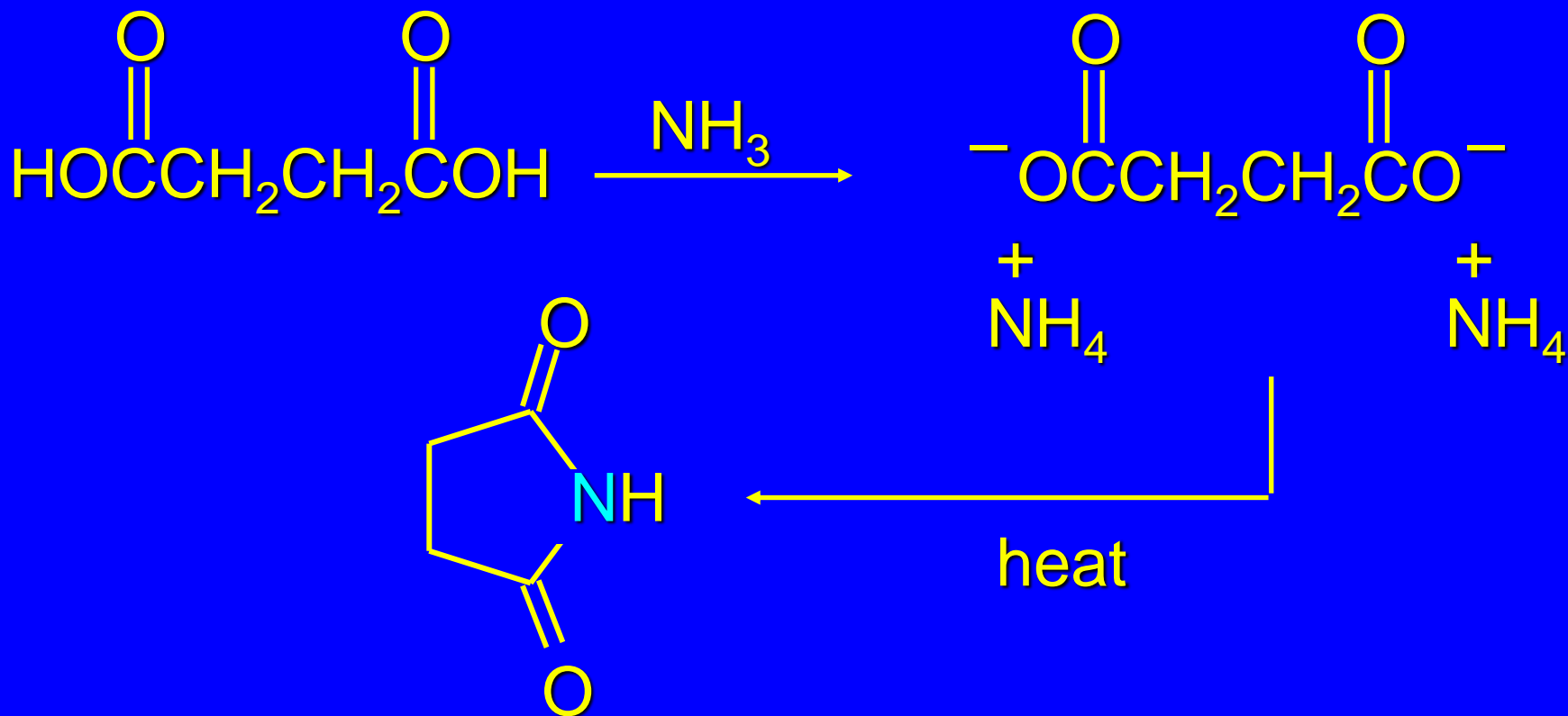
Succinimide



Phthalimide

Preparation of Imides

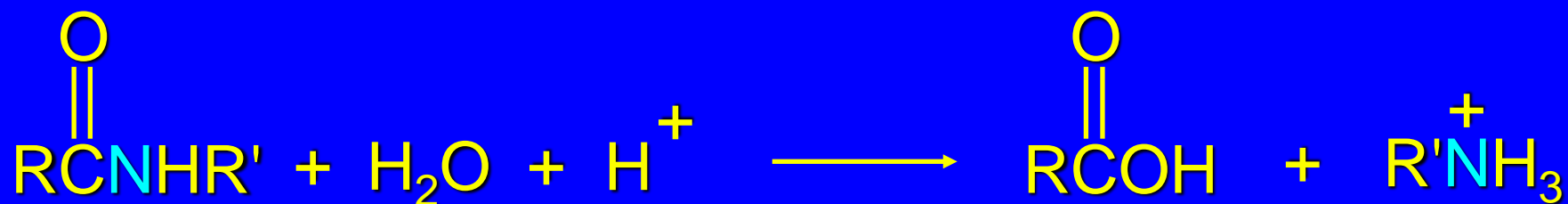
Cyclic imides are prepared by heating the ammonium salts of dicarboxylic acids.



20.17
Hydrolysis of Amides

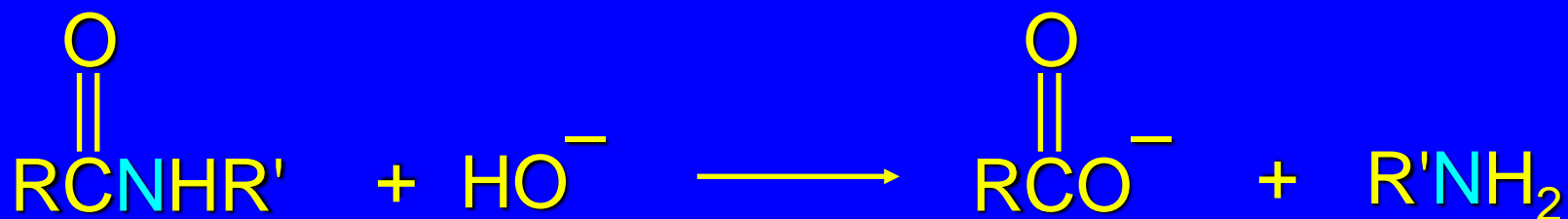
Hydrolysis of Amides

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

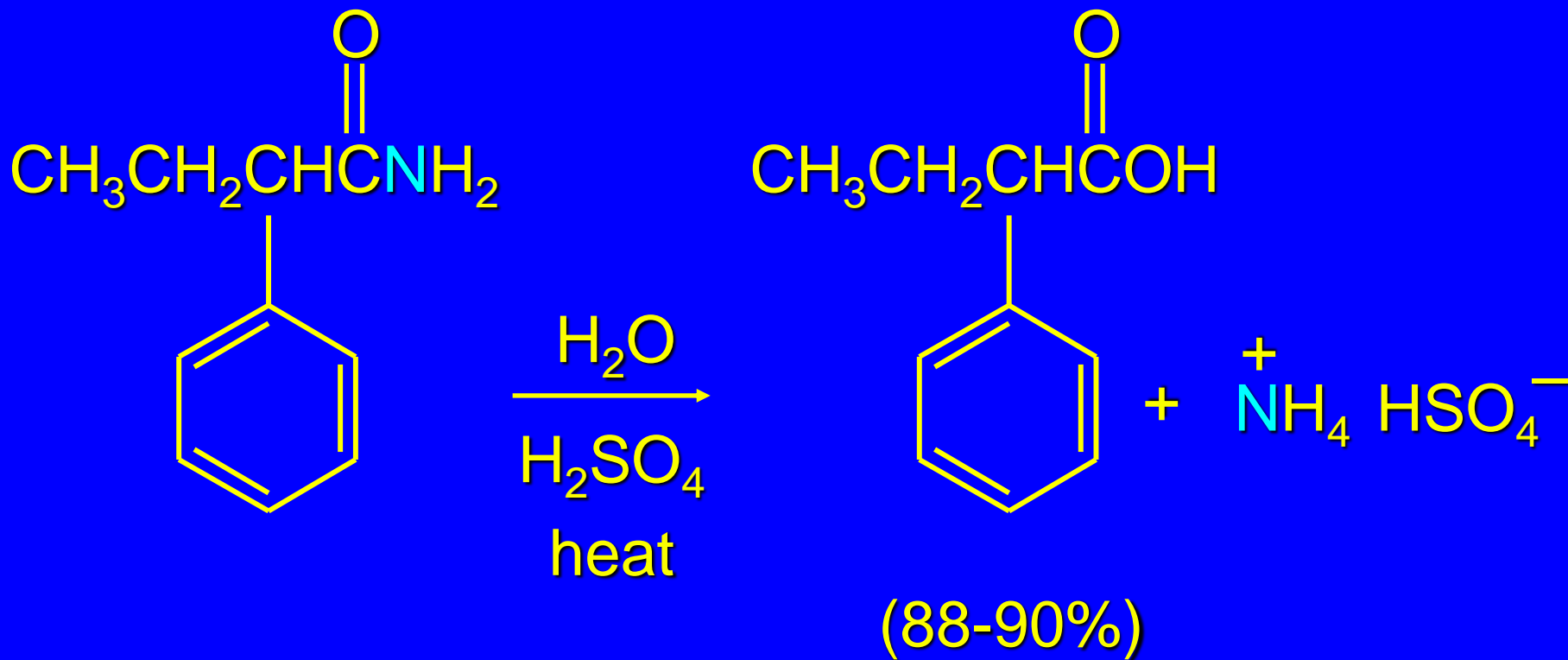


Hydrolysis of Amides

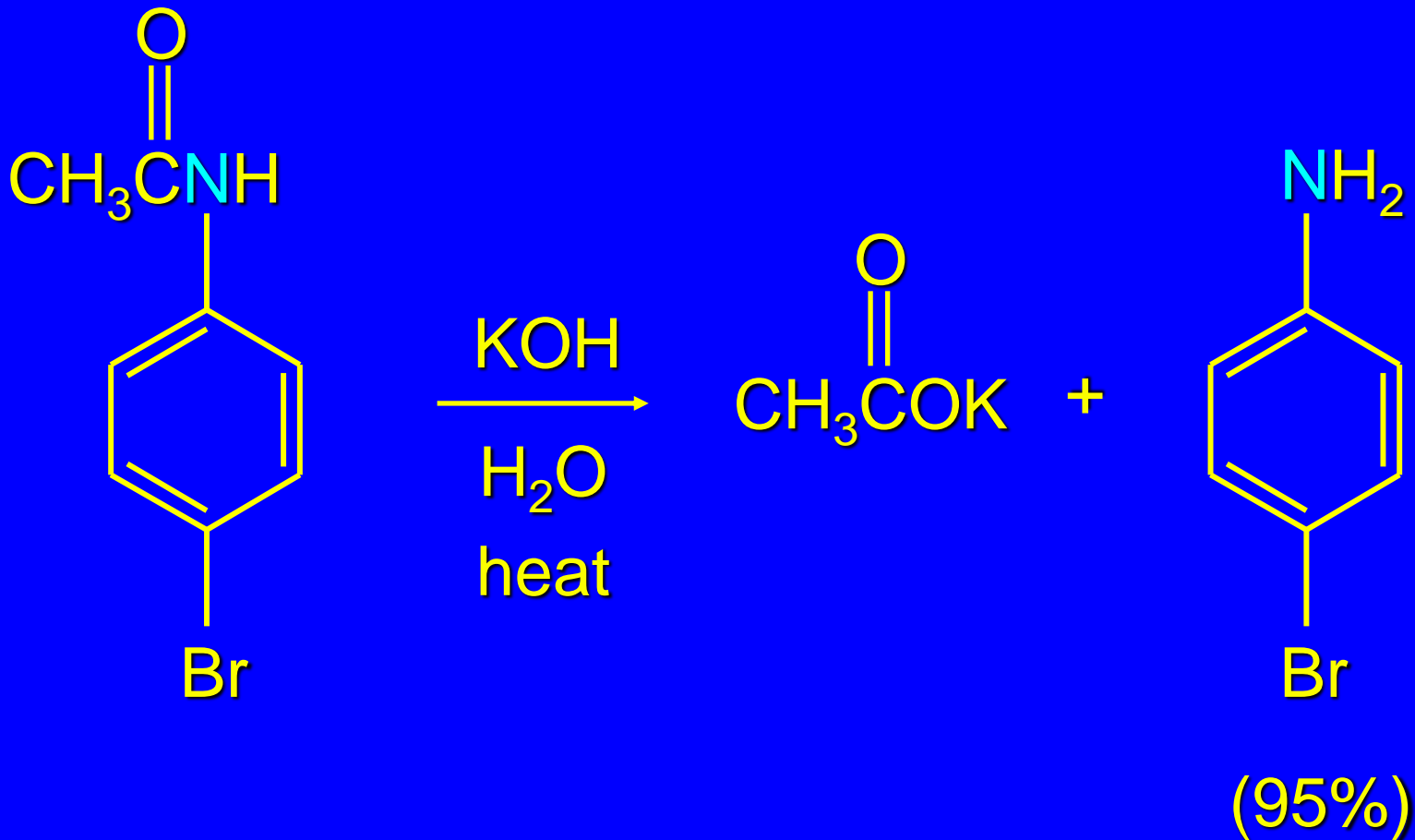
In basic solution the carboxylic acid product is deprotonated to give a carboxylate ion.



Example: Acid Hydrolysis



Example: Basic Hydrolysis

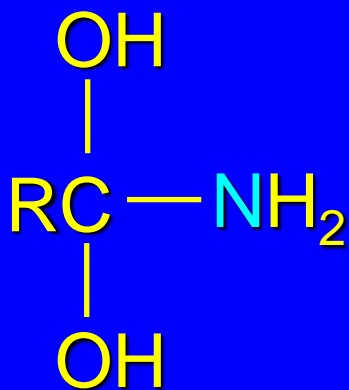
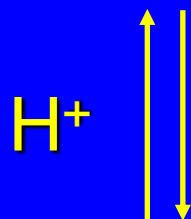
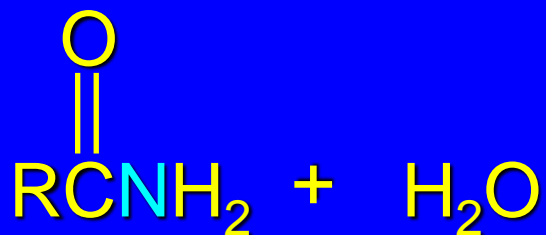


Mechanism of Acid-Catalyzed Amide Hydrolysis

Acid-catalyzed amide hydrolysis proceeds via the customary two stages:

- 1) formation of tetrahedral intermediate
- 2) dissociation of tetrahedral intermediate

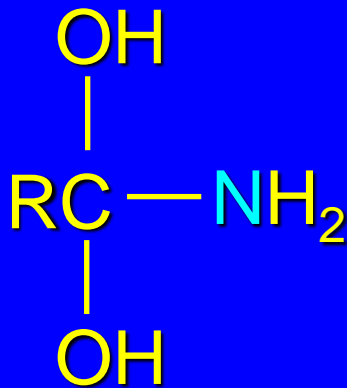
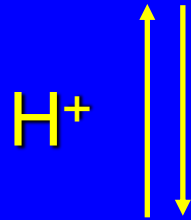
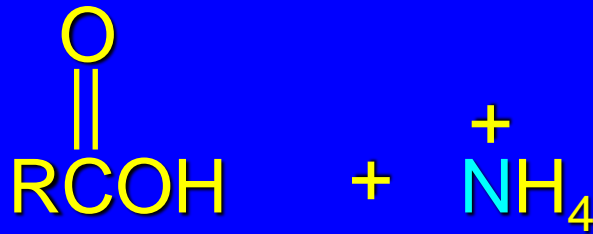
First stage: formation of tetrahedral intermediate



water adds to the carbonyl group of the amide

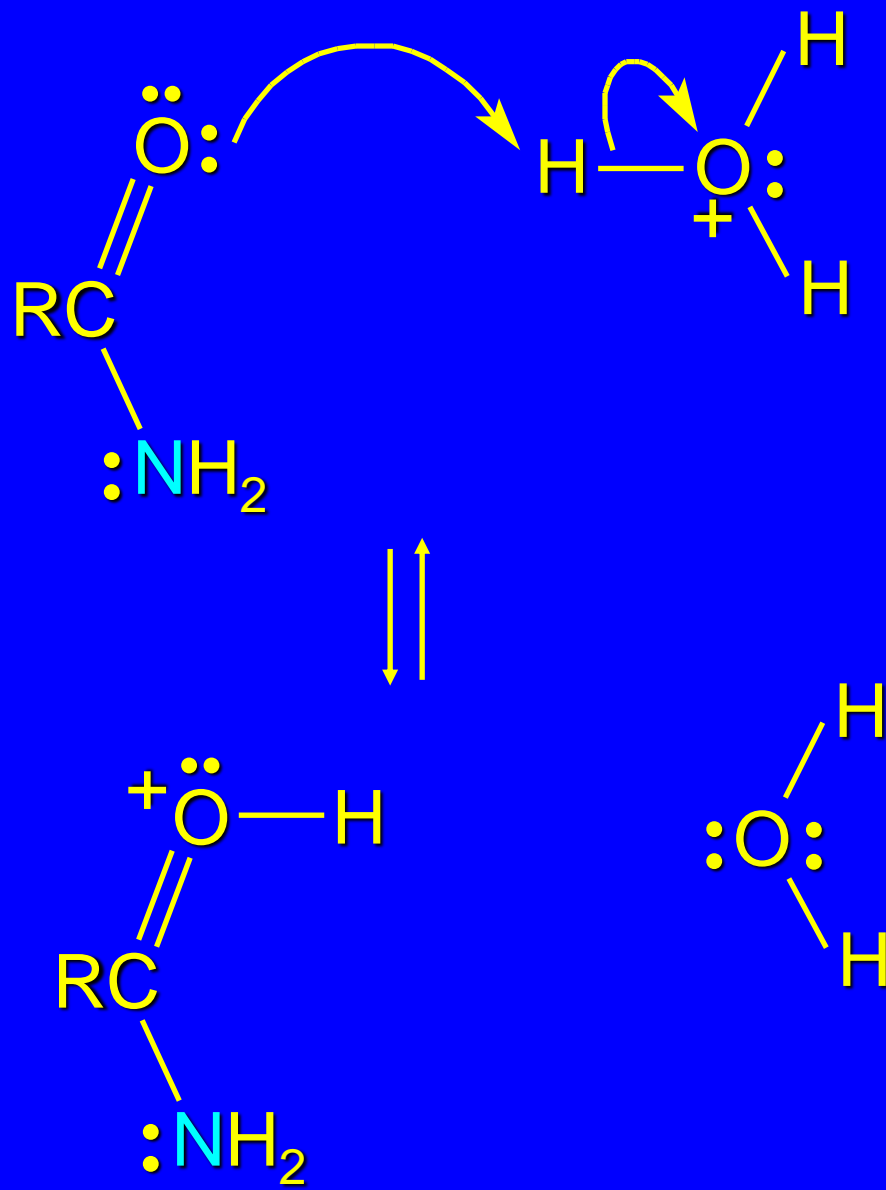
this stage is analogous to the acid-catalyzed addition of water to a ketone

Second stage: cleavage of tetrahedral intermediate

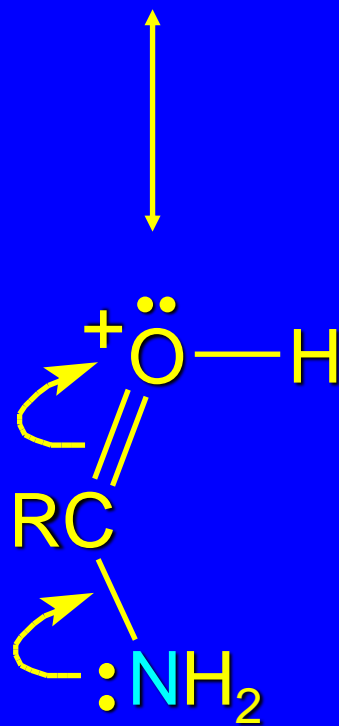
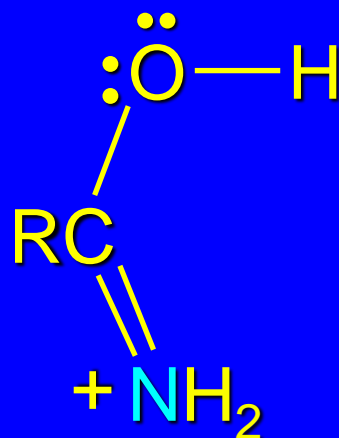


*Mechanism of formation
of
tetrahedral intermediate*

Step 1

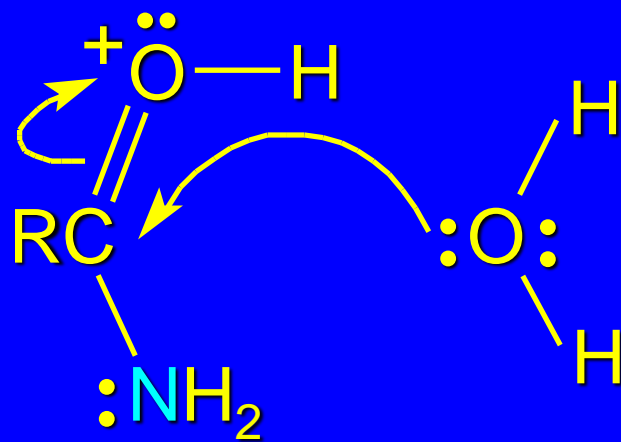
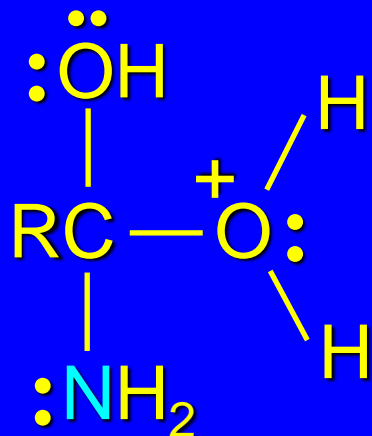


Step 1

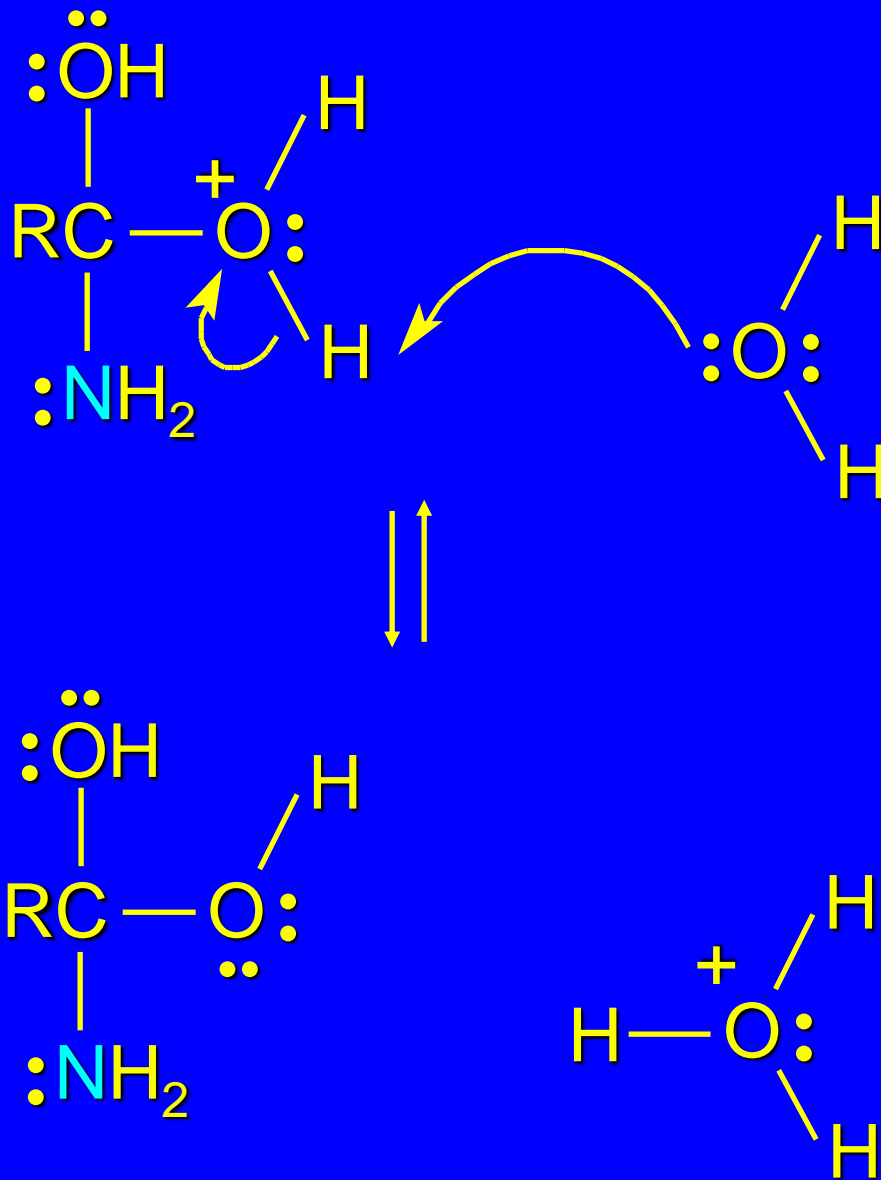


carbonyl oxygen is protonated because cation produced is stabilized by electron delocalization (resonance)

Step 2

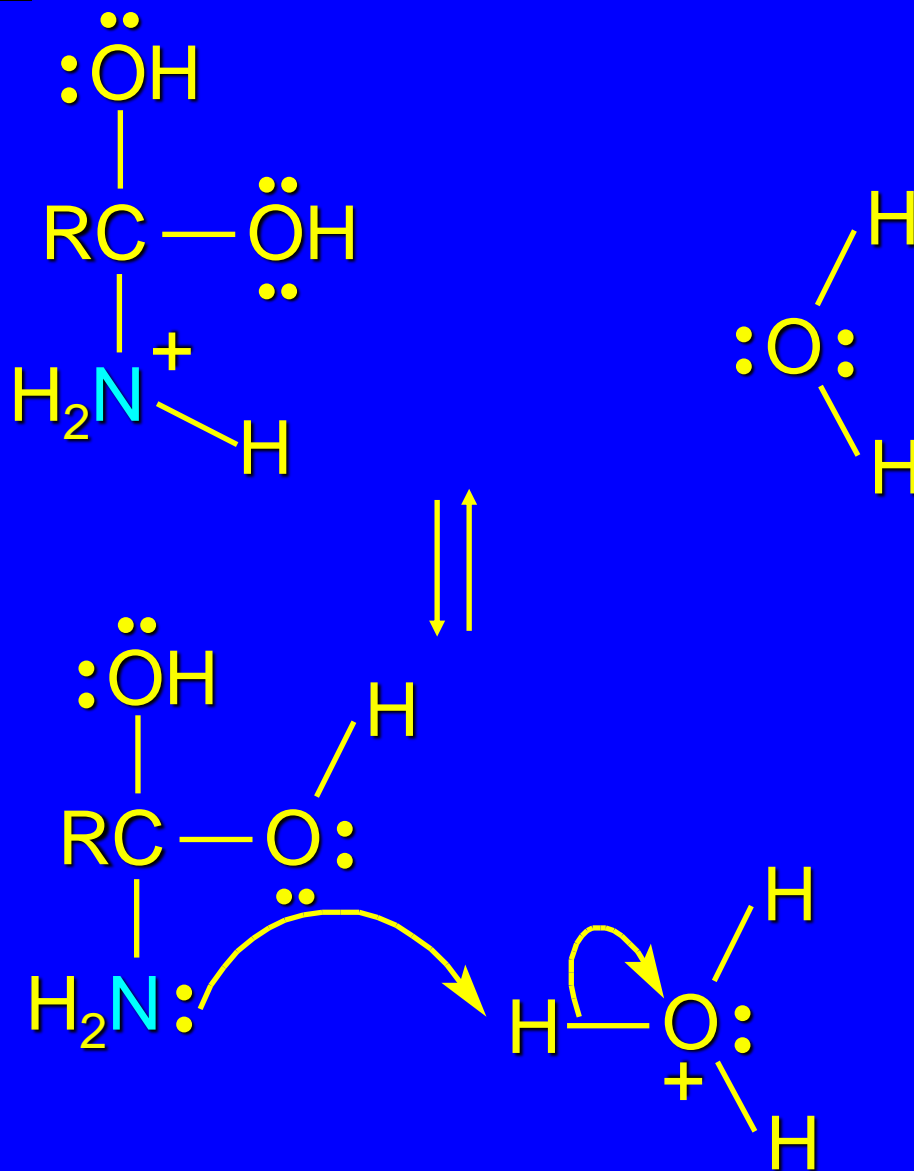


Step 3

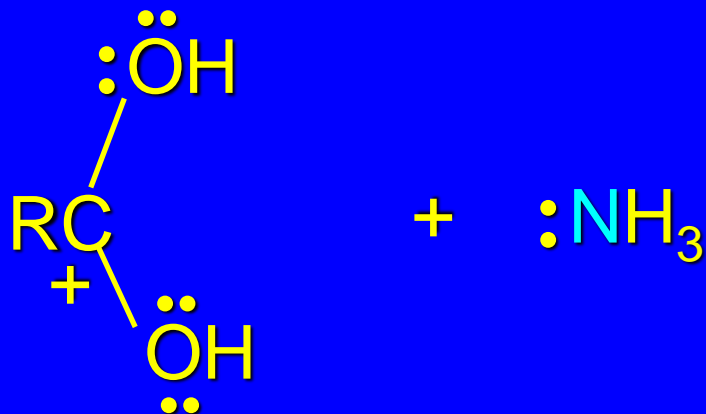
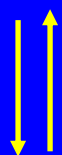
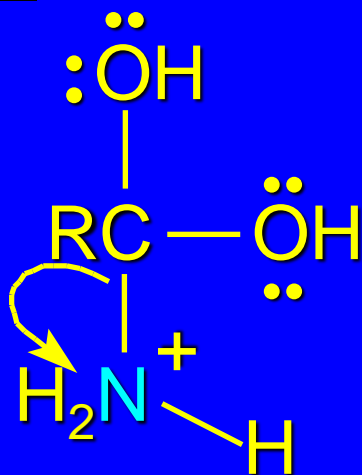


*Cleavage of tetrahedral
intermediate*

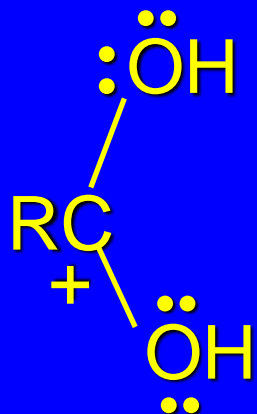
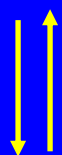
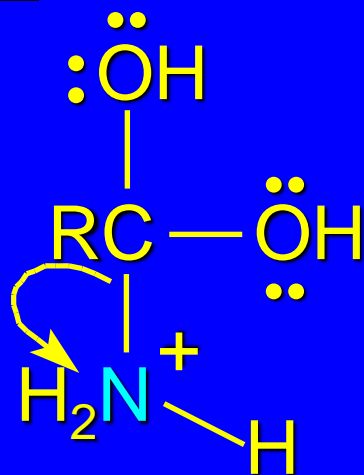
Step 4



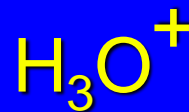
Step 5



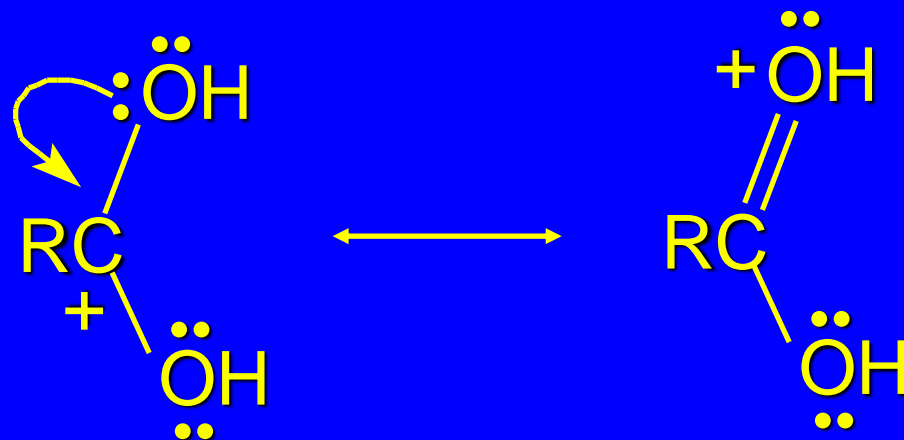
Step 6



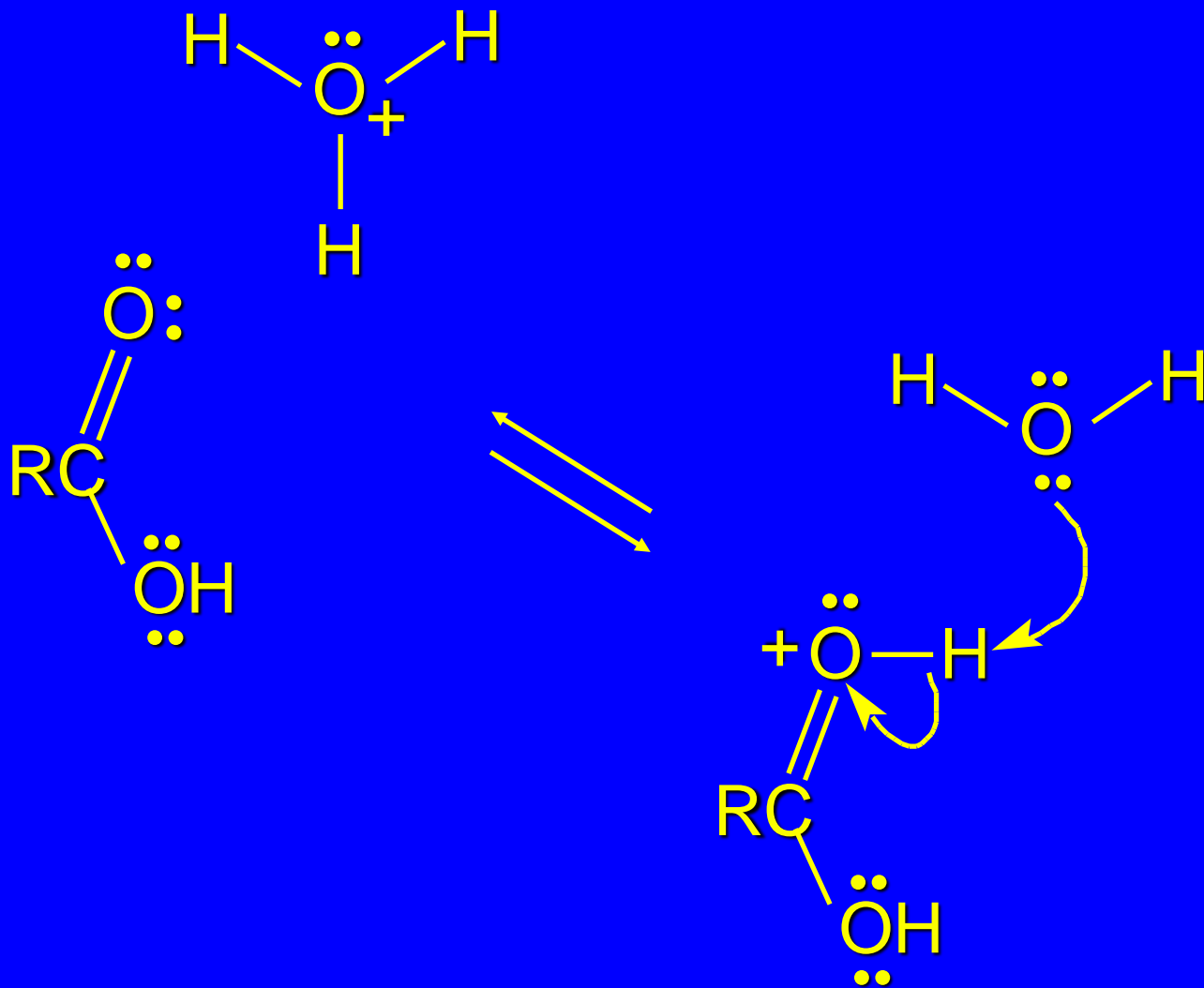
+



Step 6



Step 6

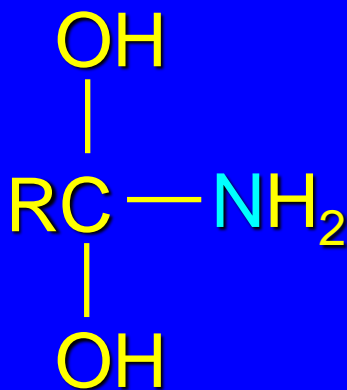
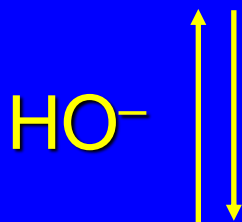
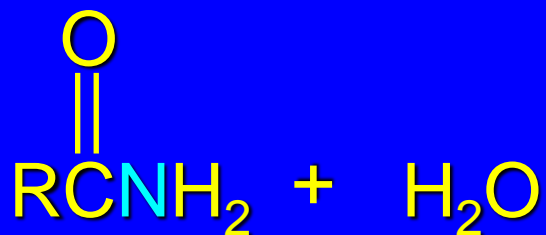


Mechanism of Amide Hydrolysis in Base

Involves two stages:

- 1) formation of tetrahedral intermediate
- 2) dissociation of tetrahedral intermediate

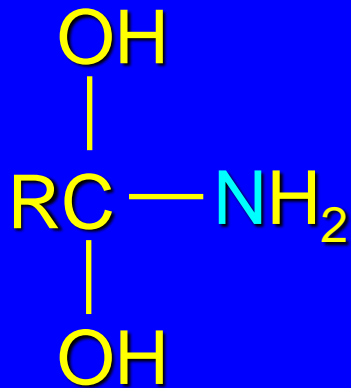
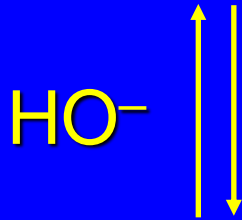
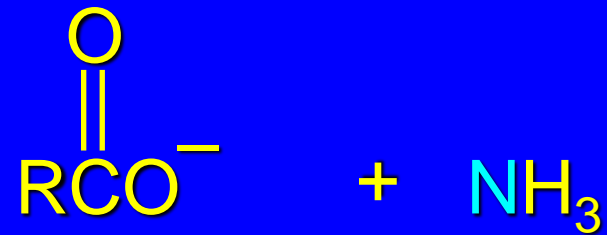
First stage: formation of tetrahedral intermediate



water adds to the carbonyl group of the amide

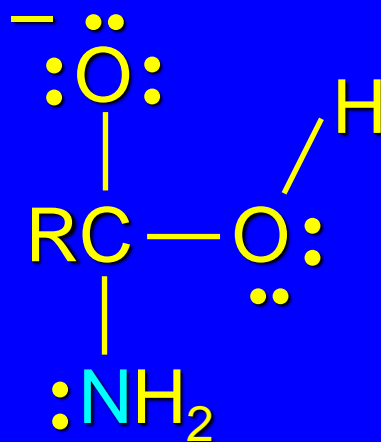
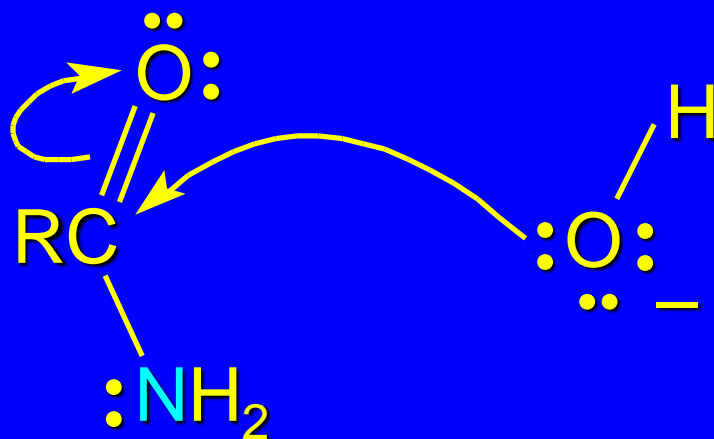
this stage is analogous to the base-catalyzed addition of water to a ketone

Second stage: cleavage of tetrahedral intermediate

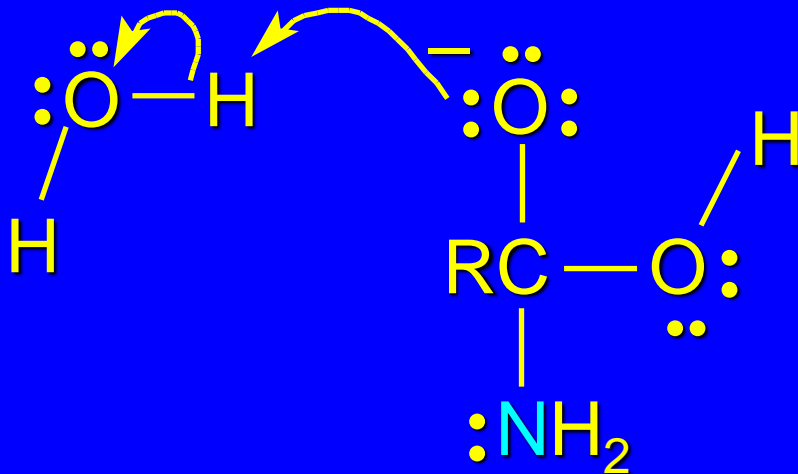
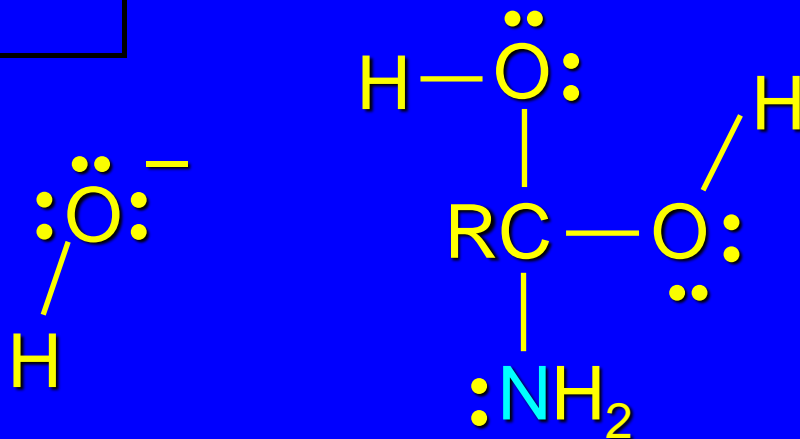


*Mechanism of formation
of
tetrahedral intermediate*

Step 1

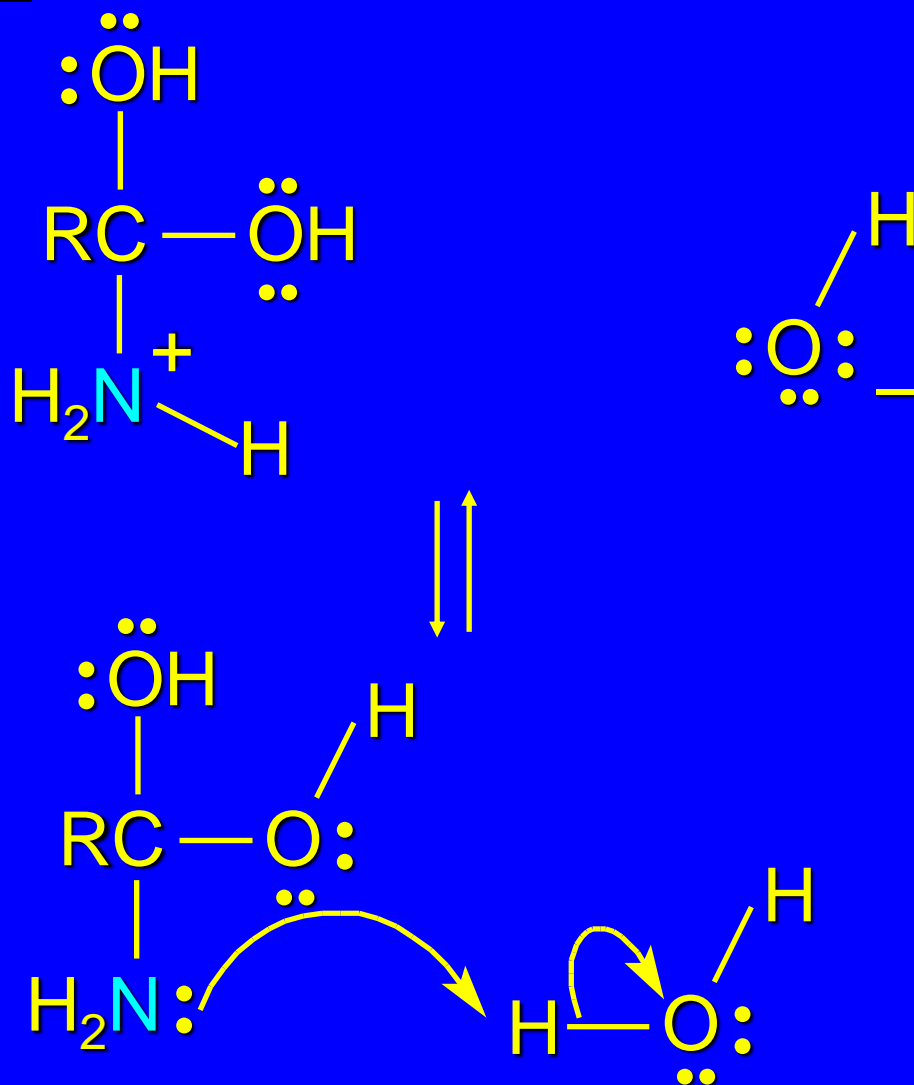


Step 2

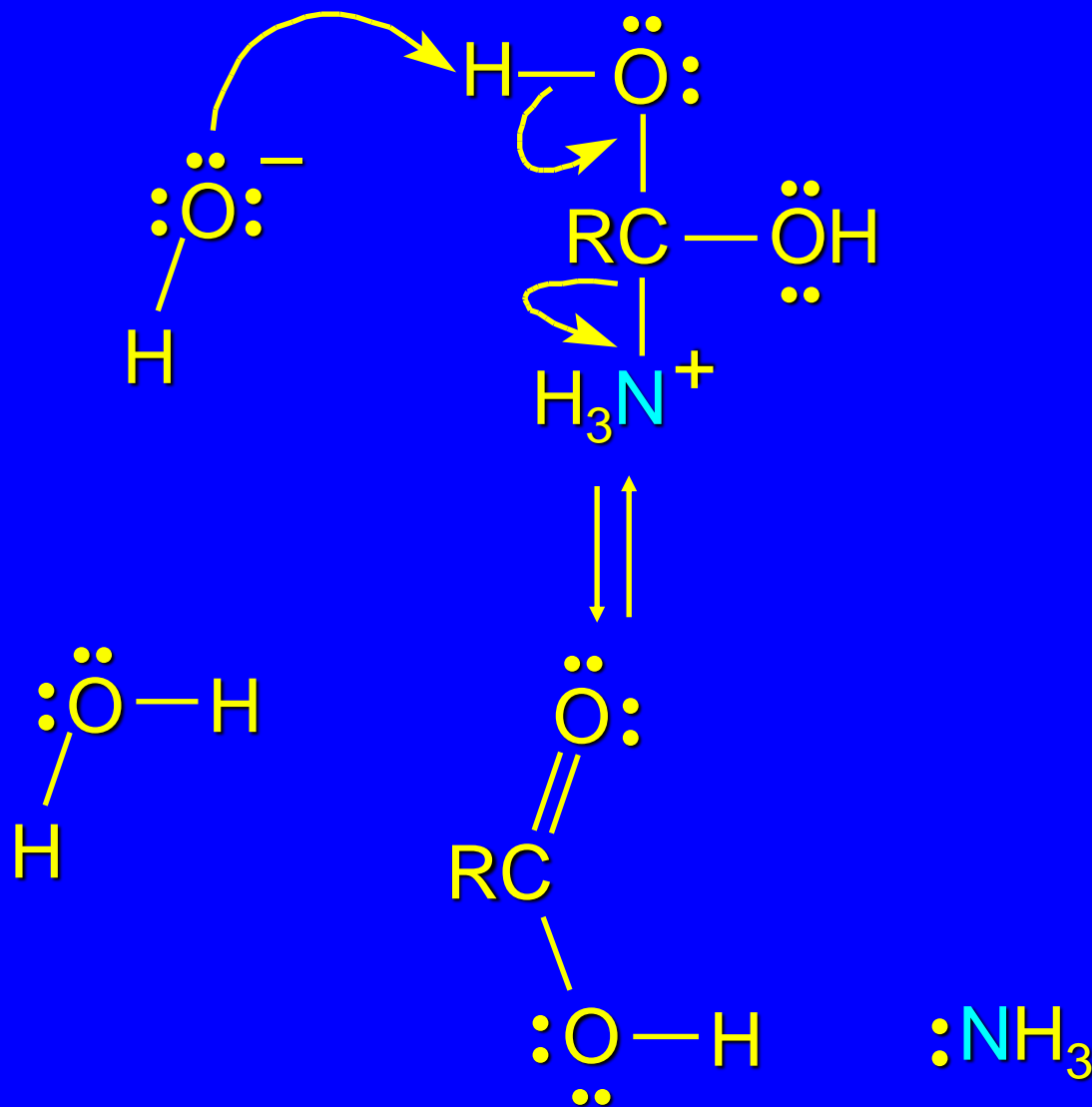


*Dissociation of
tetrahedral intermediate*

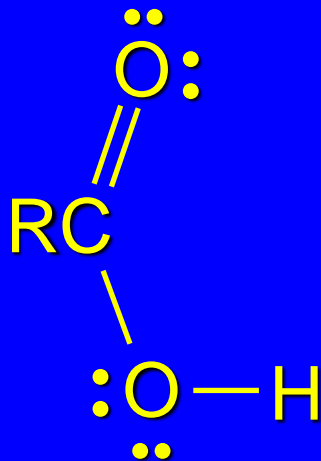
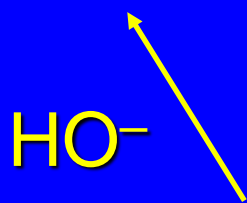
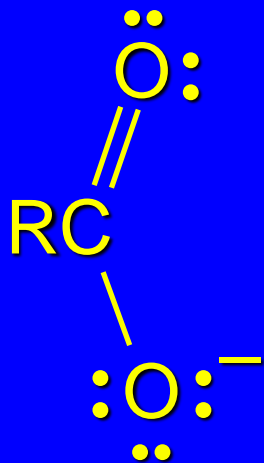
Step 3



Step 4



Step 5



20.18

Preparation of Nitriles

Preparation of Nitriles

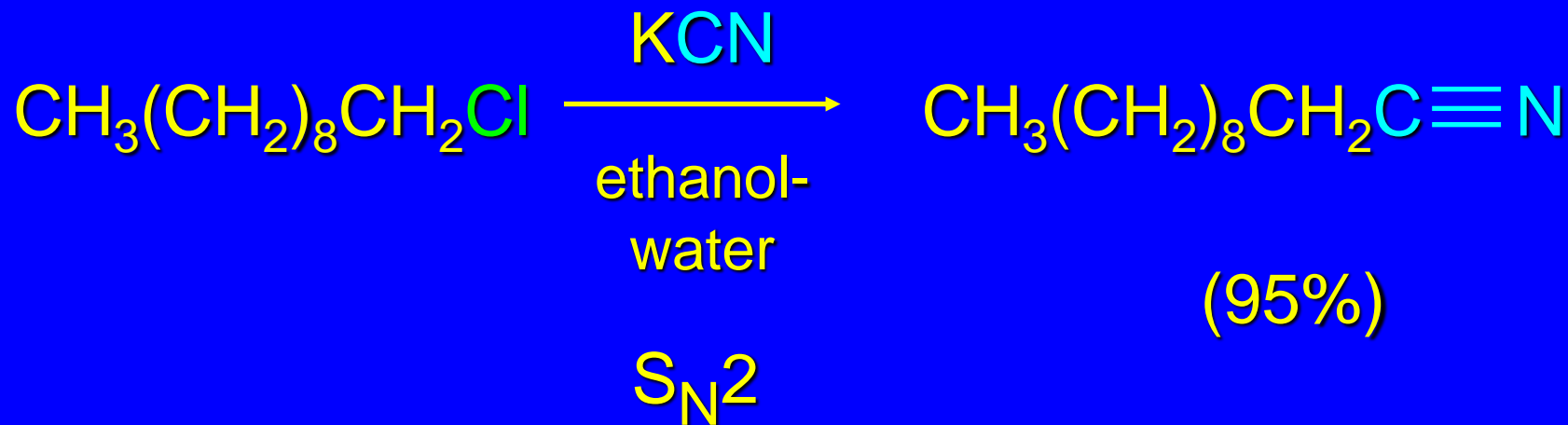
Nitriles are prepared by:

nucleophilic substitution by cyanide on alkyl halides (Sections 8.1 and 8.13)

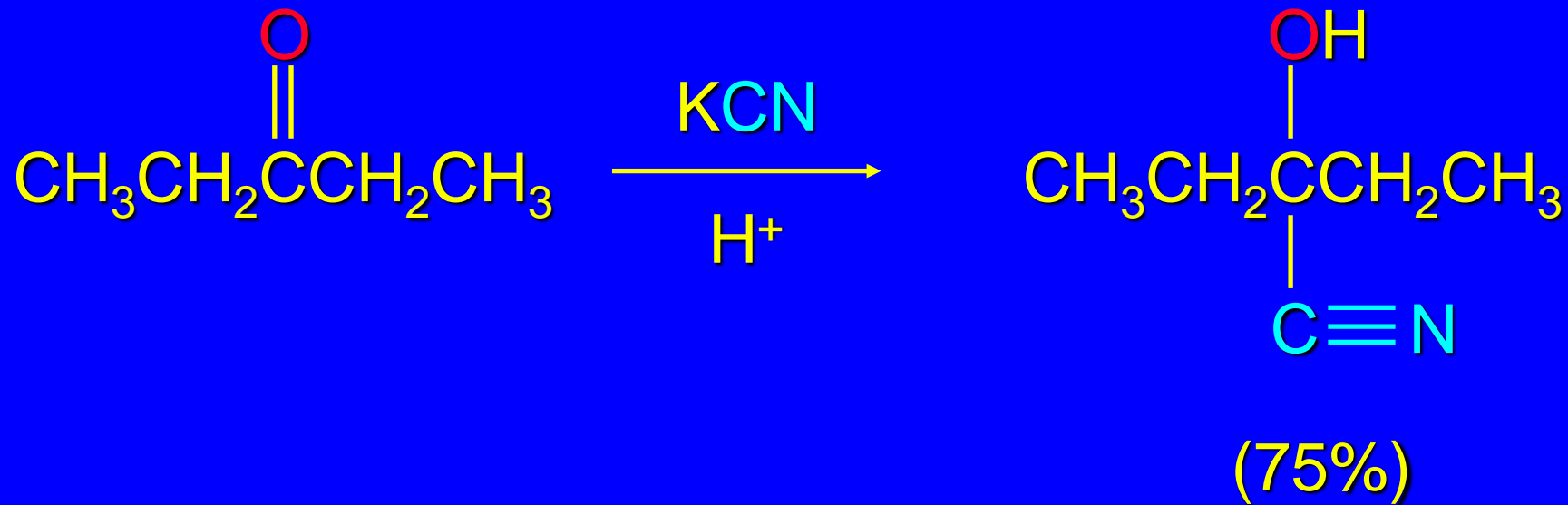
cyanohydrin formation (Section 17.7)

dehydration of amides

Example



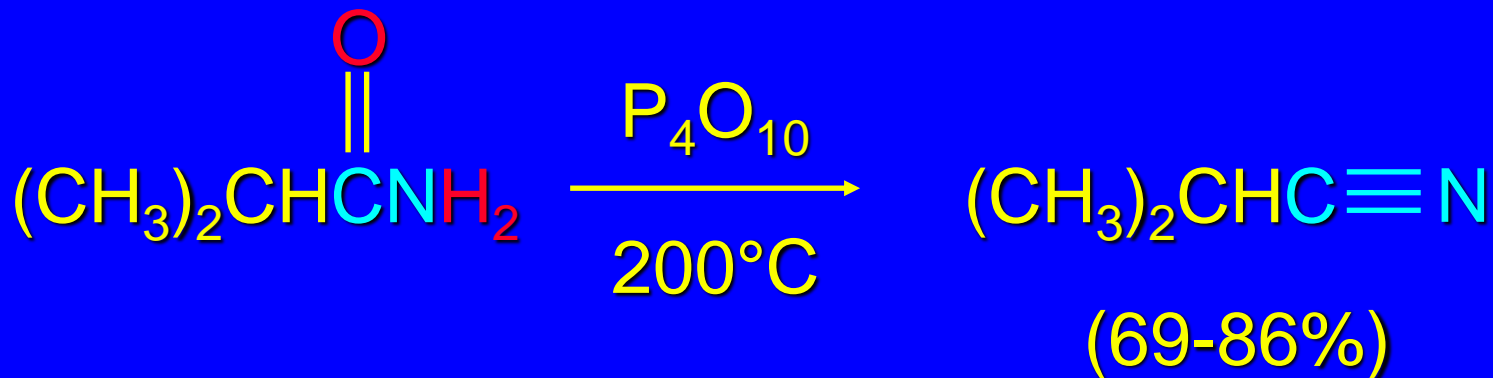
Example



Preparation of Nitriles

By dehydration of amides

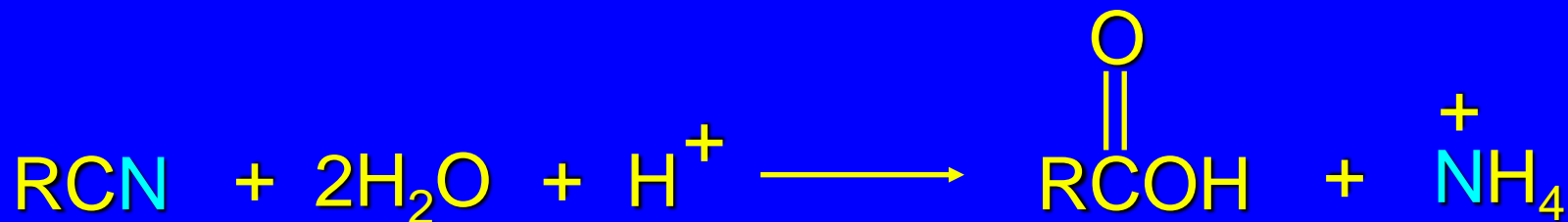
uses the reagent P_4O_{10} (often written as P_2O_5)



20.19

Hydrolysis of Nitriles

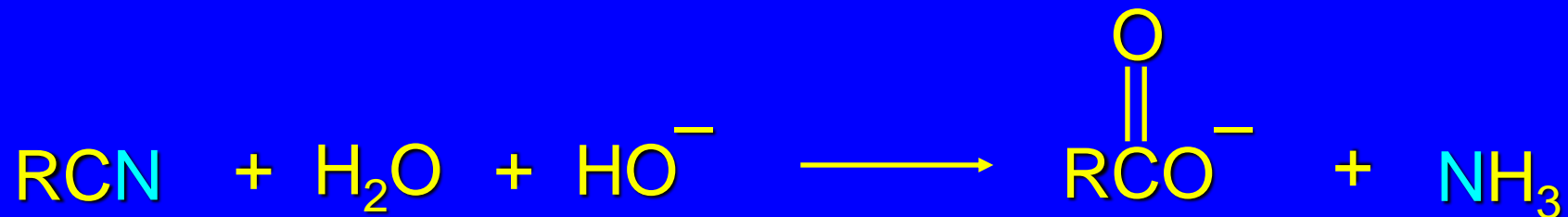
Hydrolysis of Nitriles



Hydrolysis of nitriles resembles the hydrolysis of amides. The reaction is irreversible.

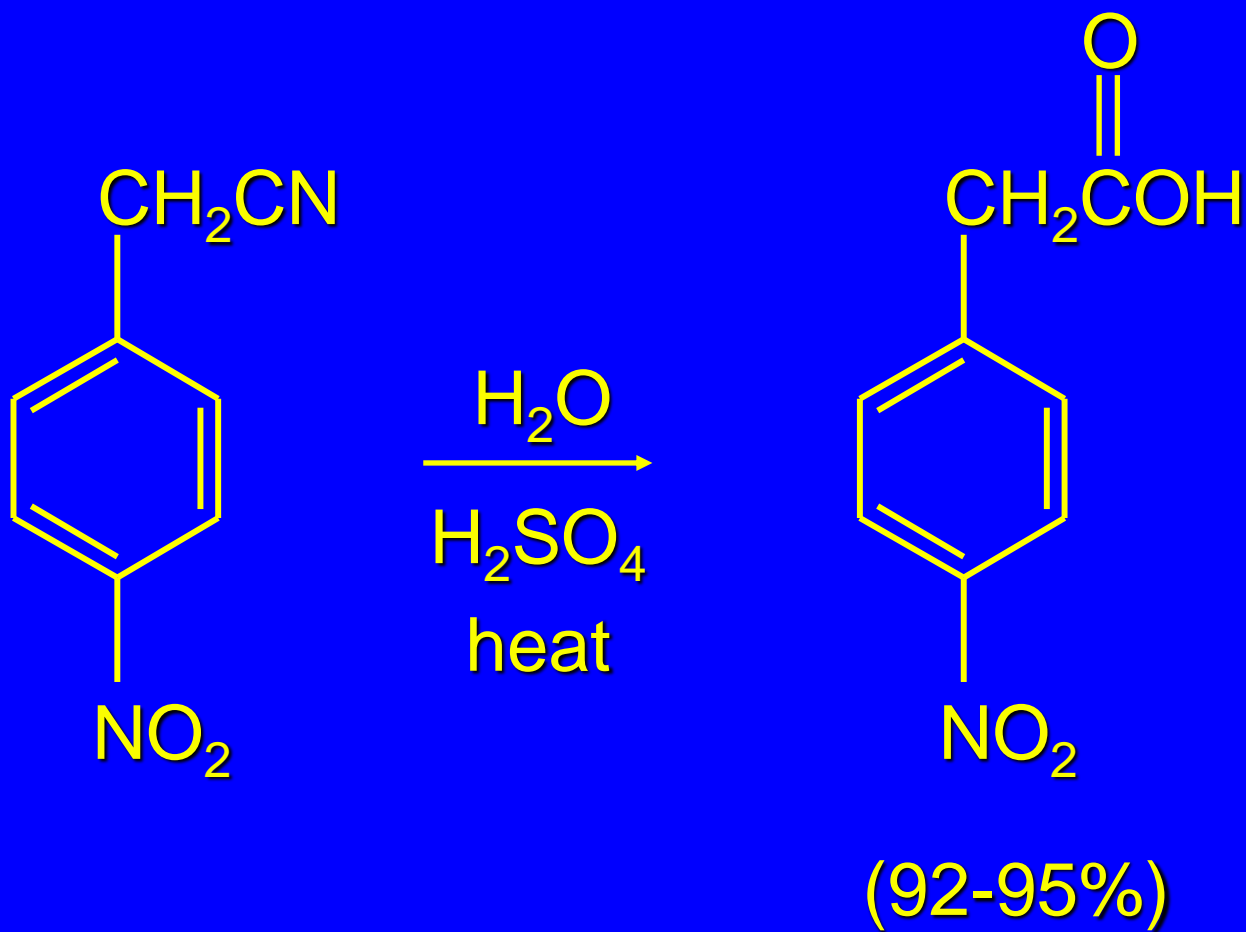
Ammonia is produced and is protonated to ammonium ion in acid solution.

Hydrolysis of Nitriles

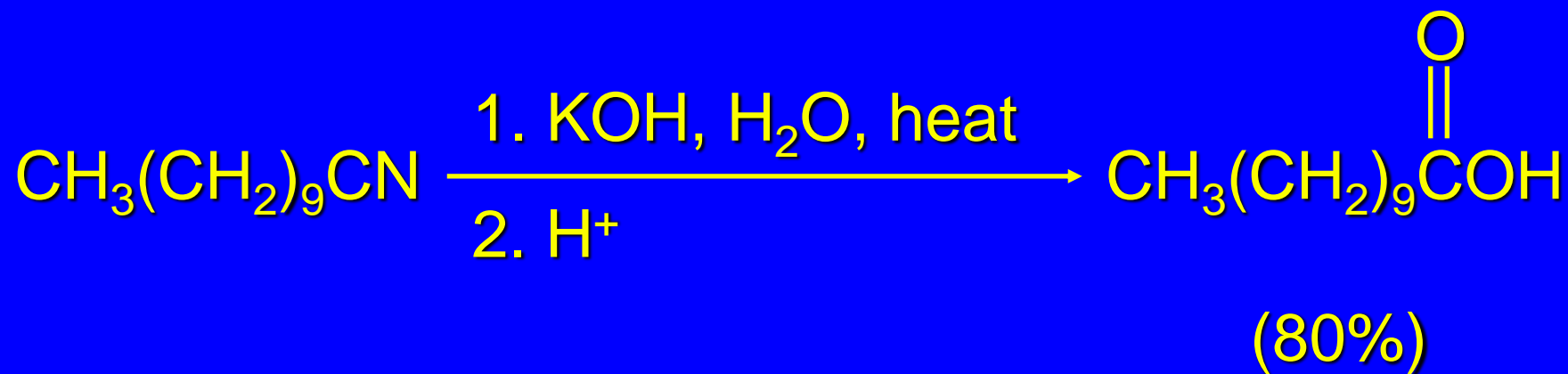


In basic solution the carboxylic acid product is deprotonated to give a carboxylate ion.

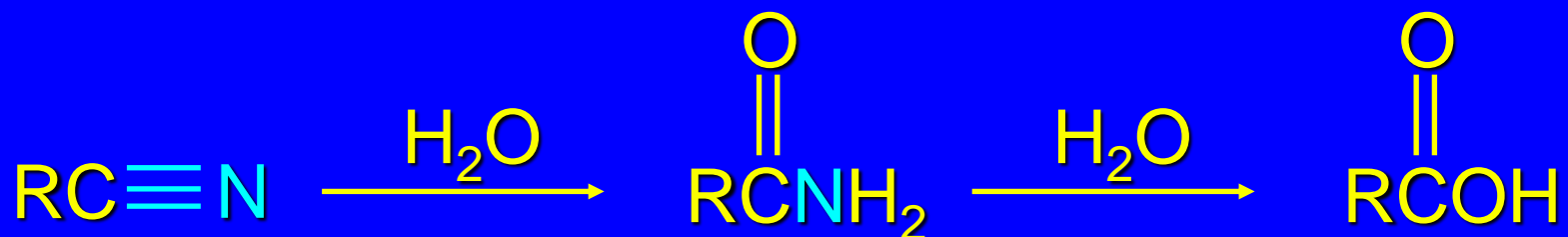
Example: Acid Hydrolysis



Example: Basic Hydrolysis



Mechanism of Hydrolysis of Nitriles

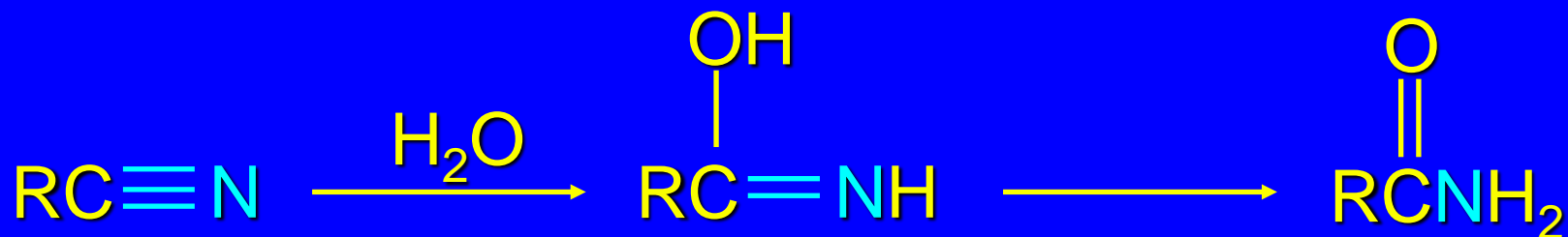


Hydrolysis of nitriles proceeds via the corresponding amide.

We already know the mechanism of amide hydrolysis.

Therefore, all we need to do is to see how amides are formed from nitriles under the conditions of hydrolysis.

Mechanism of Hydrolysis of Nitriles

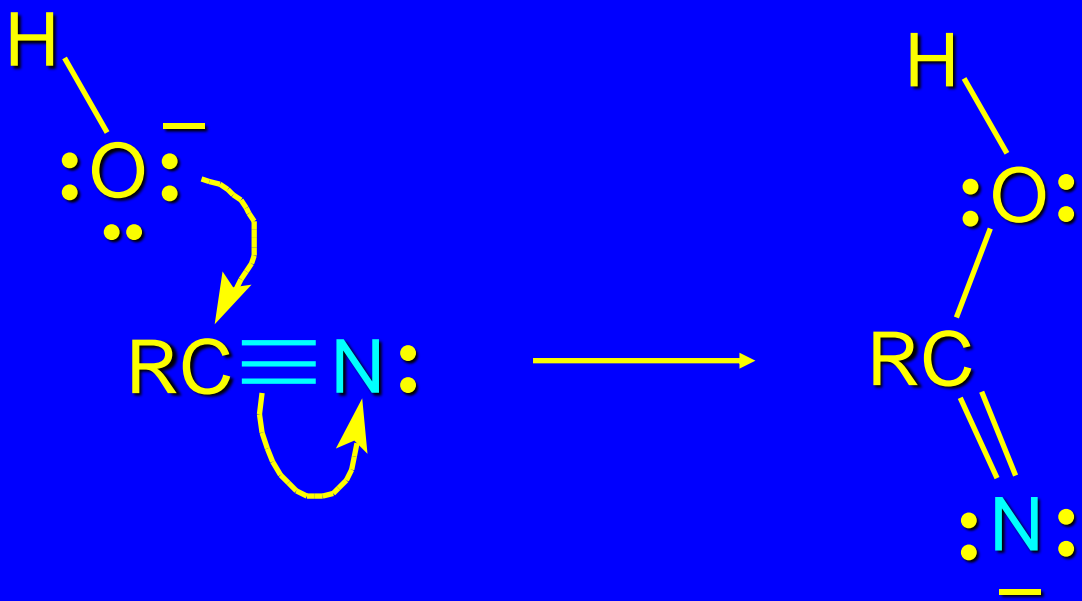


The mechanism of amide formation is analogous to that of conversion of alkynes to ketones.

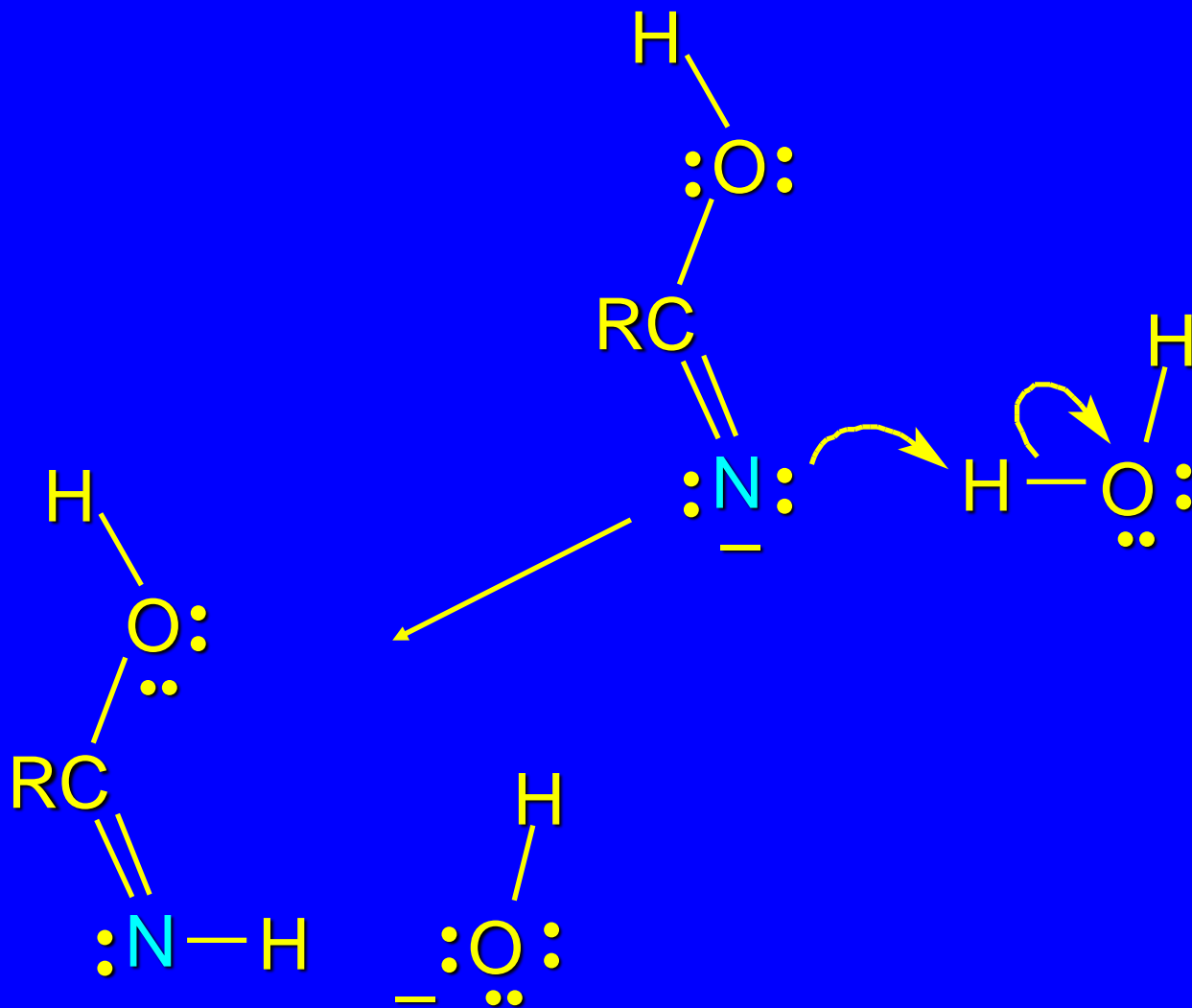
It begins with the addition of water across the carbon-nitrogen triple bond.

The product of this addition is the nitrogen analog of an enol. It is transformed to an amide under the reaction conditions.

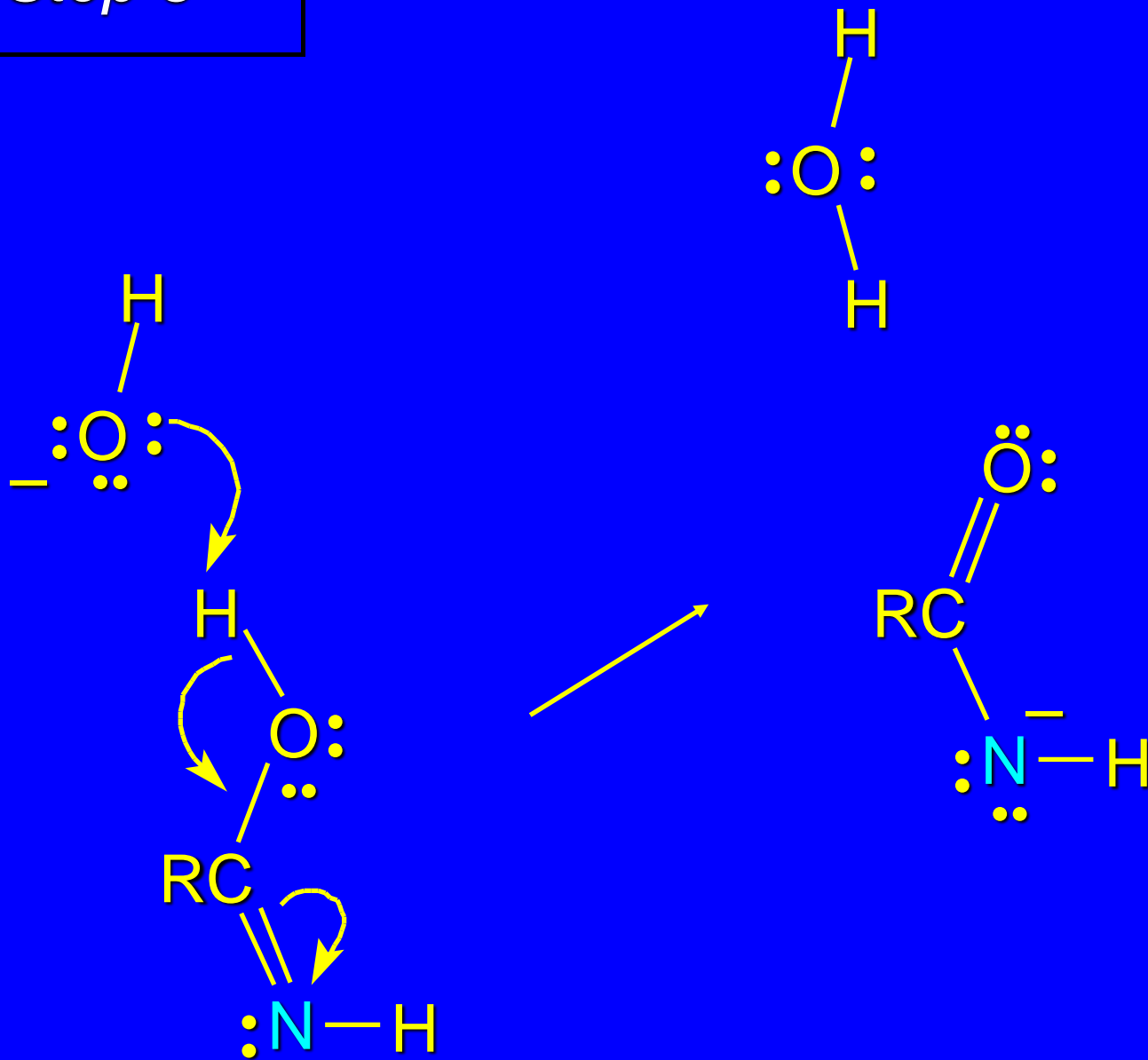
Step 1



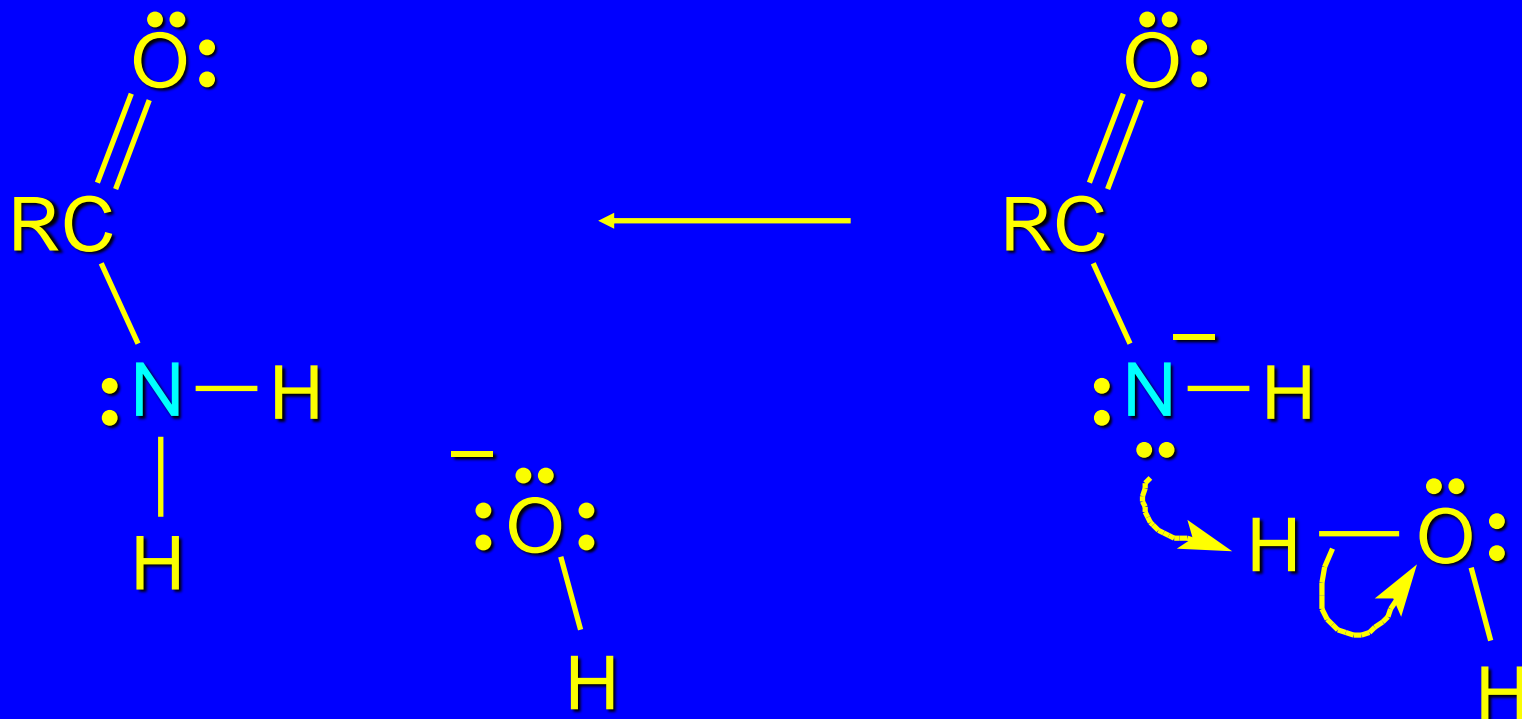
Step 2



Step 3



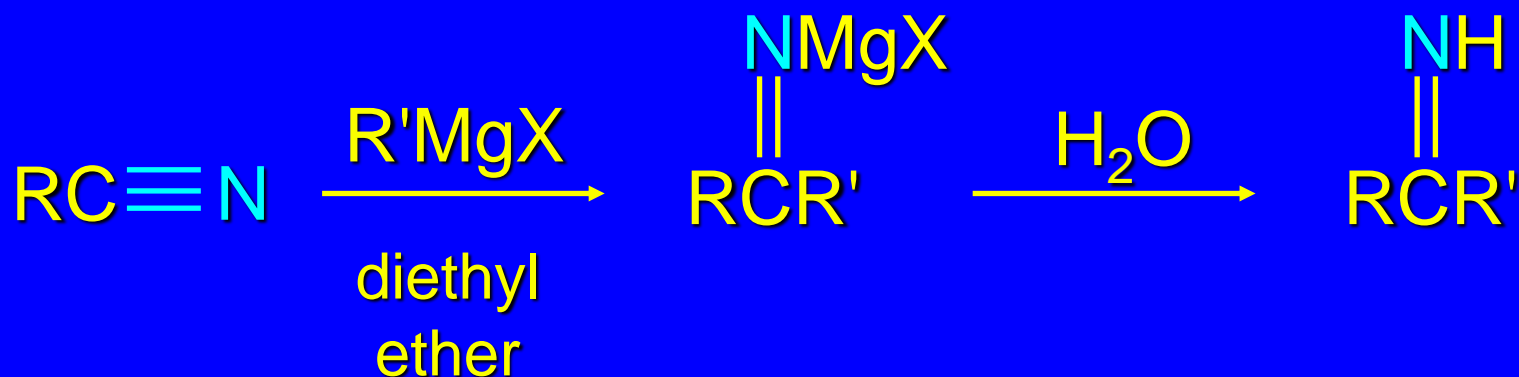
Step 4



20.20

**Addition of Grignard Reagents
to Nitriles**

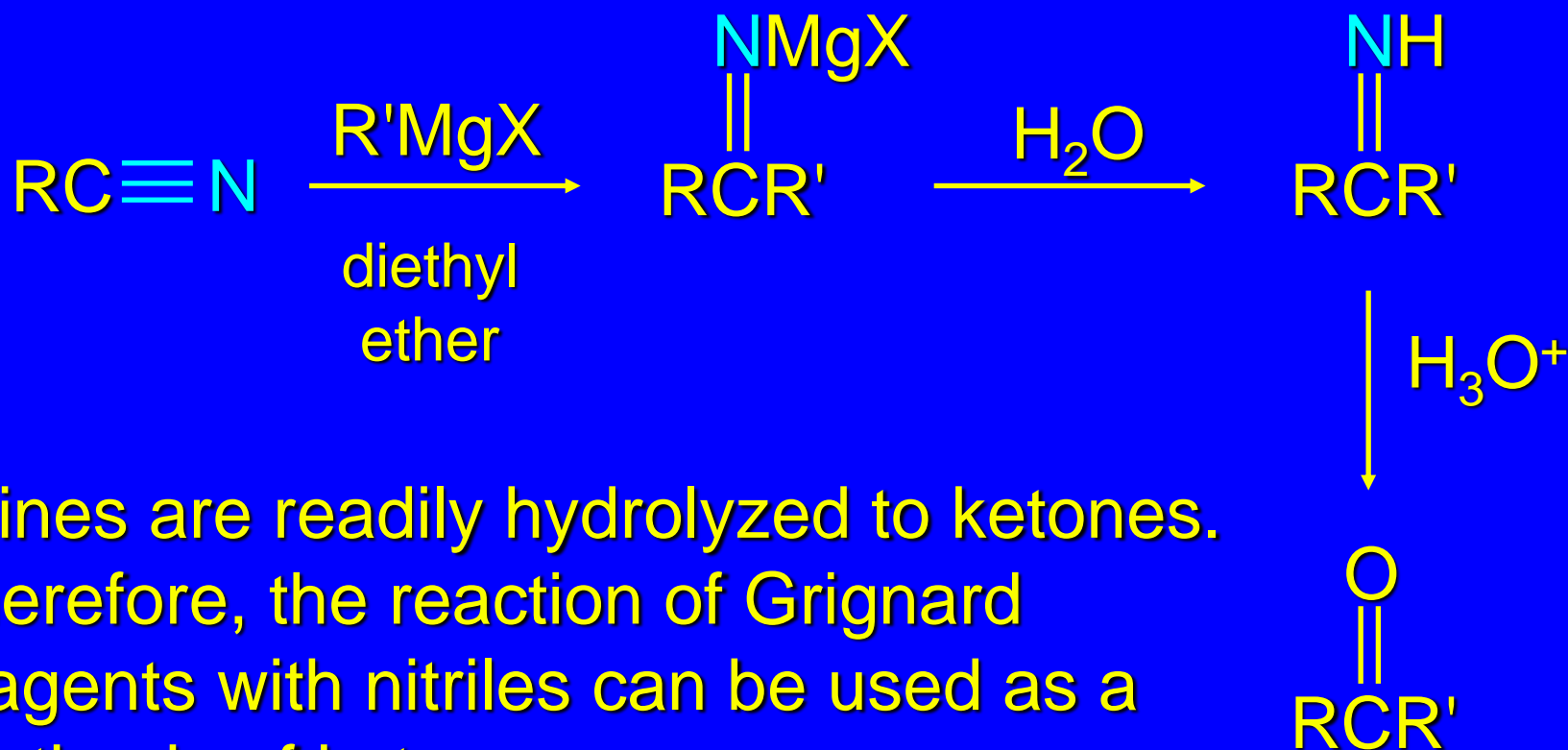
Addition of Grignard Reagents to Nitriles



Grignard reagents add to carbon-nitrogen triple bonds in the same way that they add to carbon-oxygen double bonds.

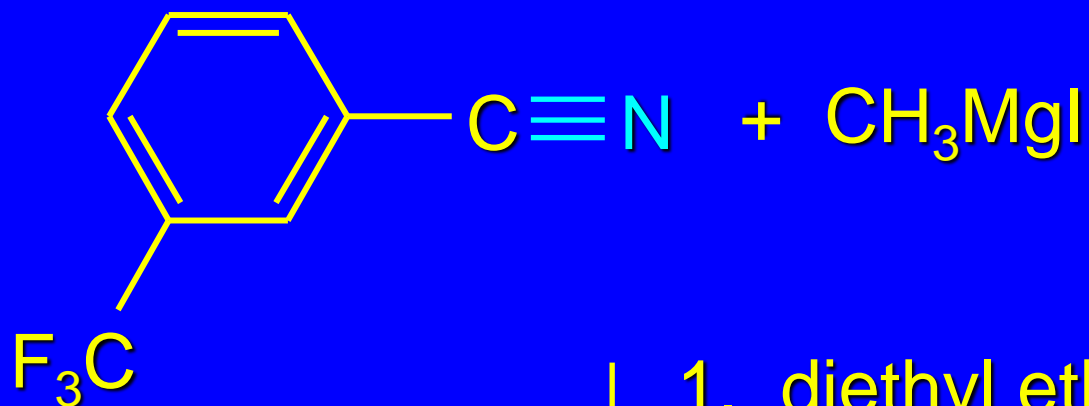
The product of the reaction is an imine.

Addition of Grignard Reagents to Nitriles



Imines are readily hydrolyzed to ketones. Therefore, the reaction of Grignard reagents with nitriles can be used as a synthesis of ketones.

Example



1. diethyl ether
2. H_3O^+ , heat



Information & Suggested Problems

Sample Available Posted on Website

Suggested Problems: 20.29-20.38

Office Hour: Thursday, 3.30 P.M., SES 4446
