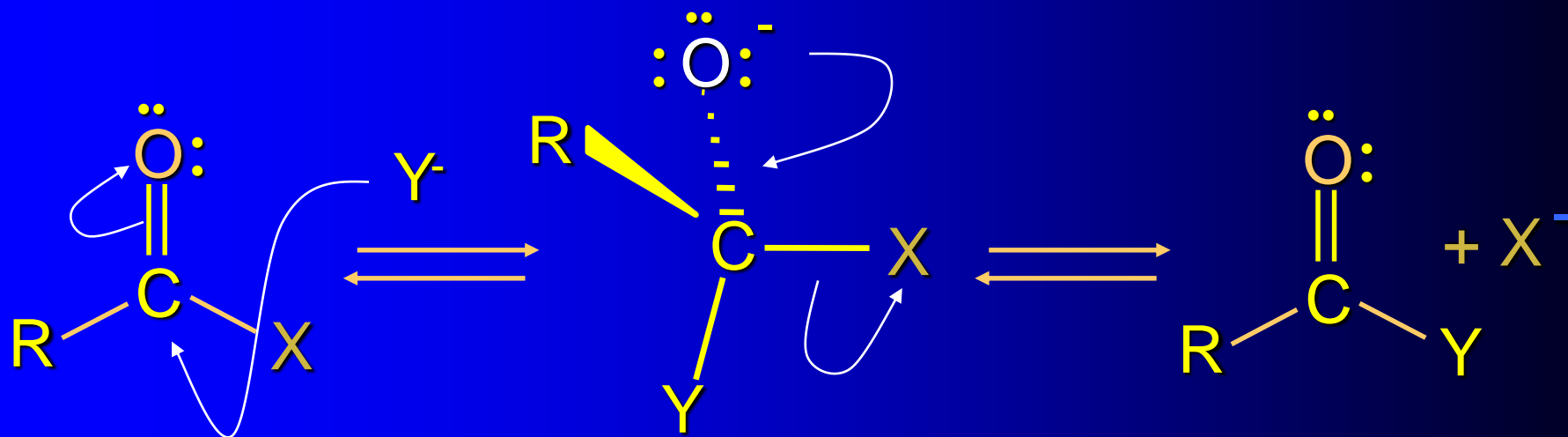


Lecture 17

More Carboxylic Acids



and... Nucleophilic Acyl Substitution
(or nucleophilic addition elimination)



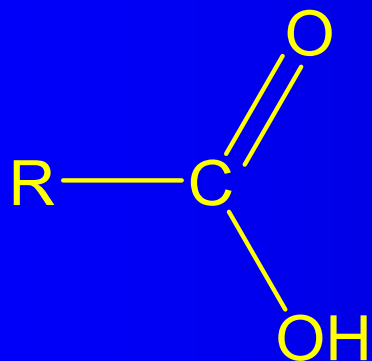
Important Information

● Midterm Exam II

- Wed March 30th
- 7:00-9:00 PM
- Room WEL 3.502
- Review Sessions:
 - Mon & Tue - 5-6 PM room TBA
- **Know the reactions (cards)**
- Review your homework and the old exams
- Practice synthesis problems
- Know the acetal mechanism
- Exam covers material through Thursday's lecture
- **Do a good job...please get an A!!**



Reactions of Carboxylic acids

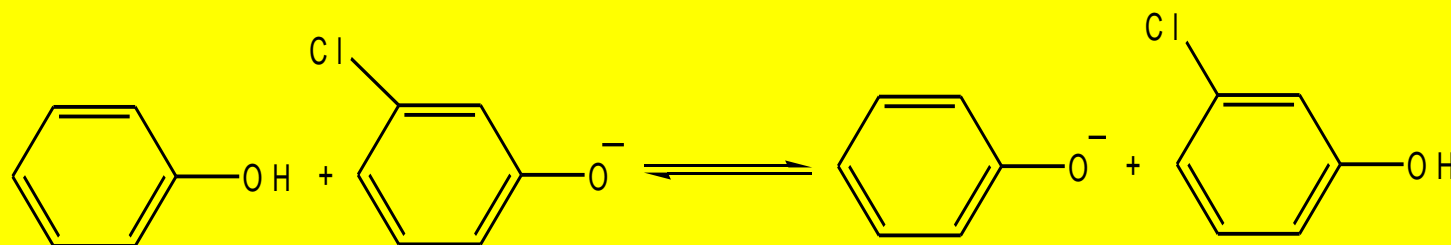


- Ionization
- Reduction
- Decarboxylation
- Esterification



Ionization

Be Sure to Study Trends in Acid Strength

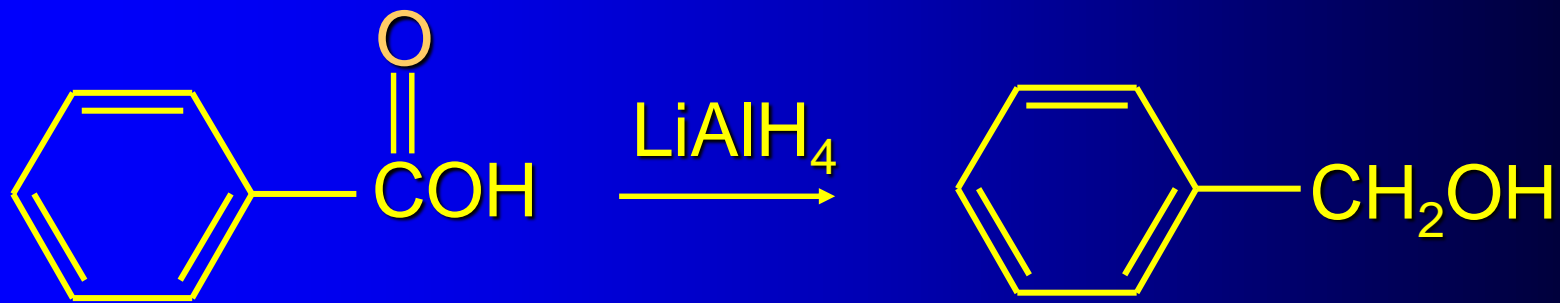


Which way does the equilibrium lie??

Please Practice This Game

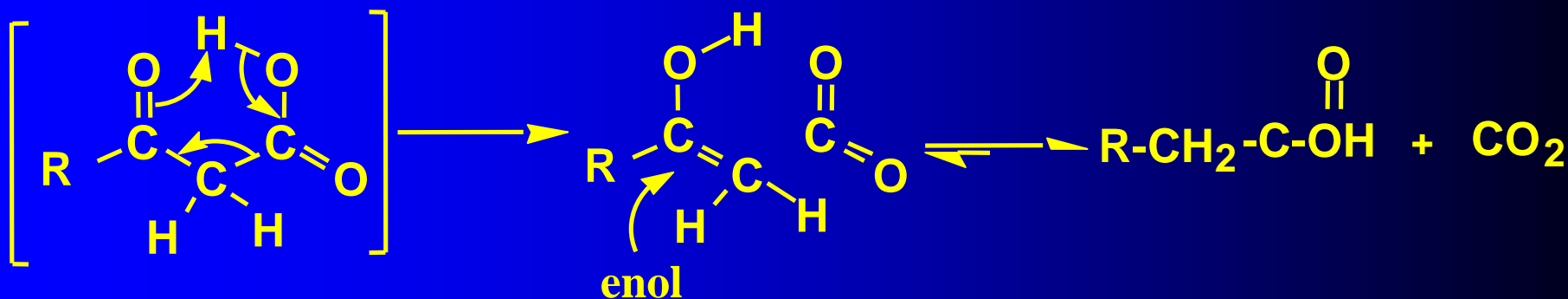


Reduction of Carboxylic Acids



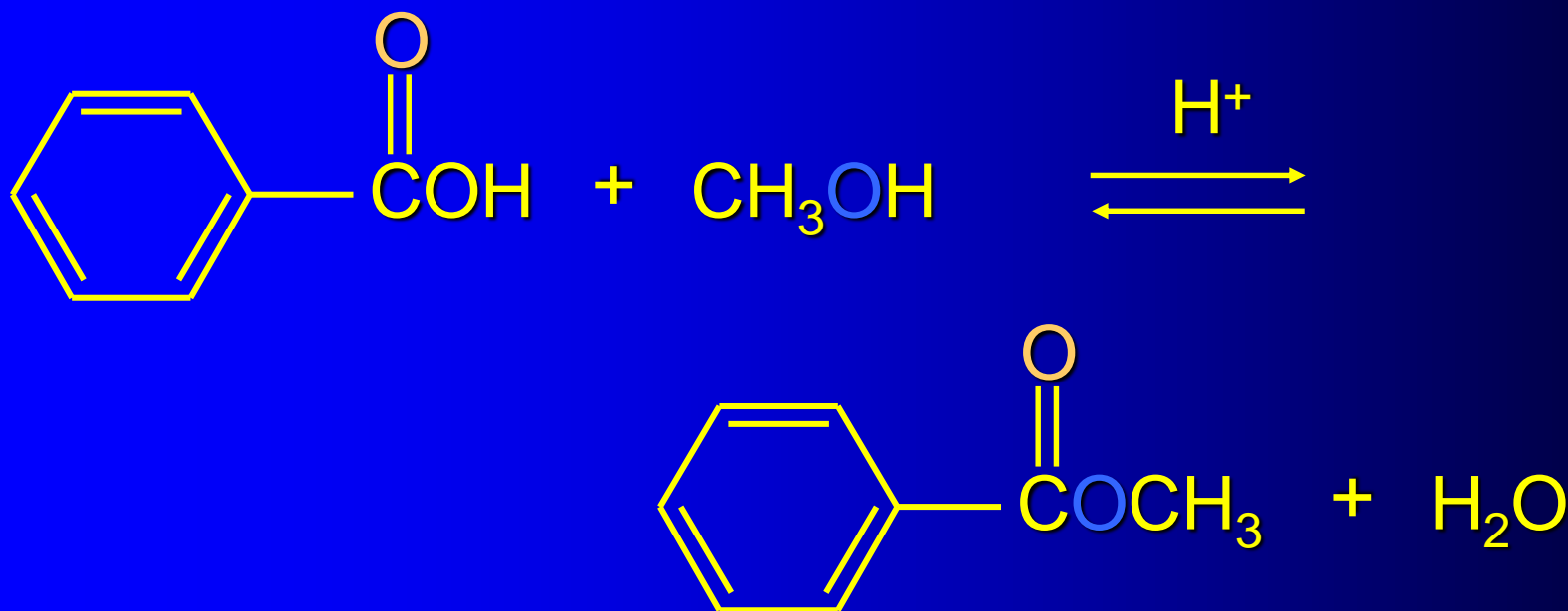
Decarboxylation

- Thermal decarboxylation of β -ketoacids involves rearrangement of six electrons in a cyclic six-membered transition state
- This class of compounds undergoes decarboxylation at relatively low temperatures



Acid-catalyzed Esterification

(also called Fischer esterification)

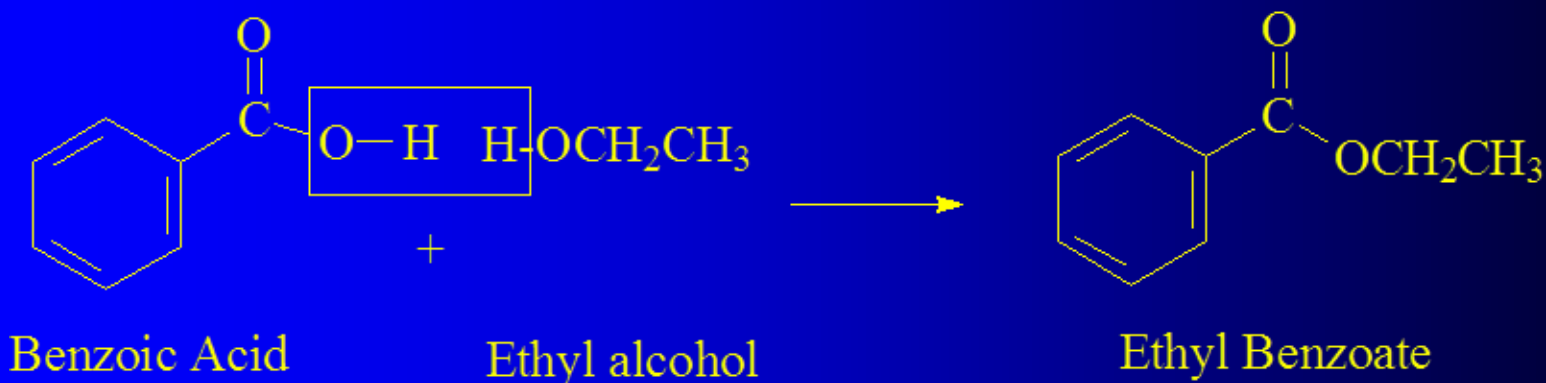


- Important fact: the oxygen of the alcohol is incorporated into the ester as shown.



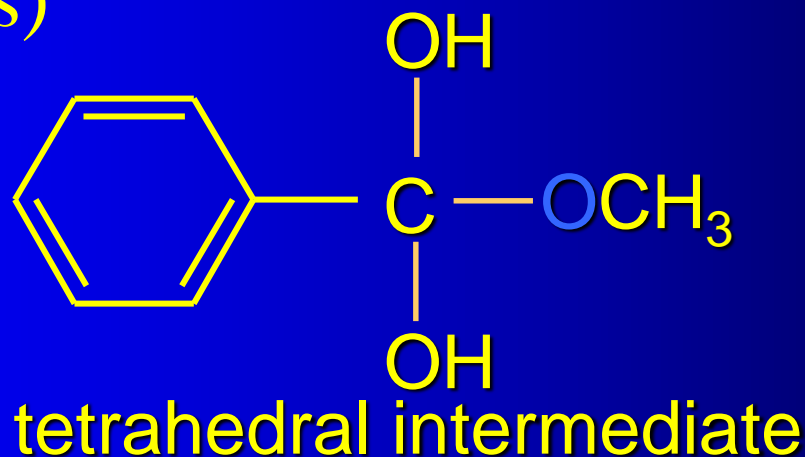
Nomenclature of Esters

The IUPAC name for esters is derived from the names of the parent carboxylic acids. The alkyl group bonded to oxygen is named first followed by the name of the acid in which the suffix **-ic** is replaced by the suffix **-ate**

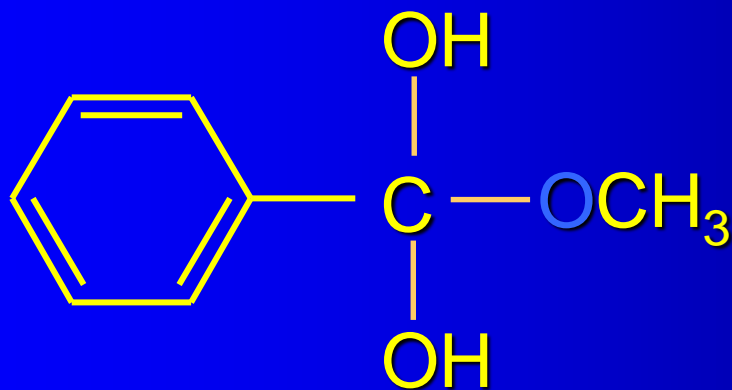
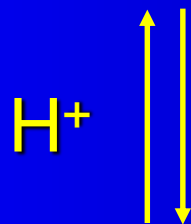
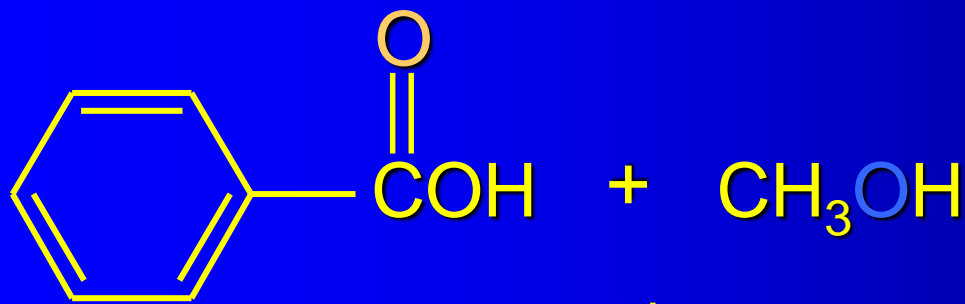


Mechanism of Fischer Esterification

- The mechanism involves two stages:
 - 1) formation of tetrahedral intermediate (3 steps)
 - 2) dissociation of tetrahedral intermediate (3 steps)



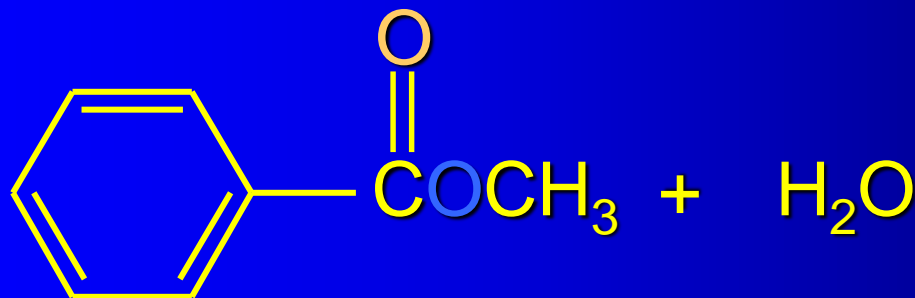
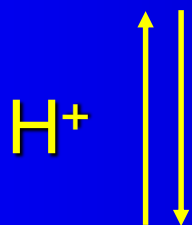
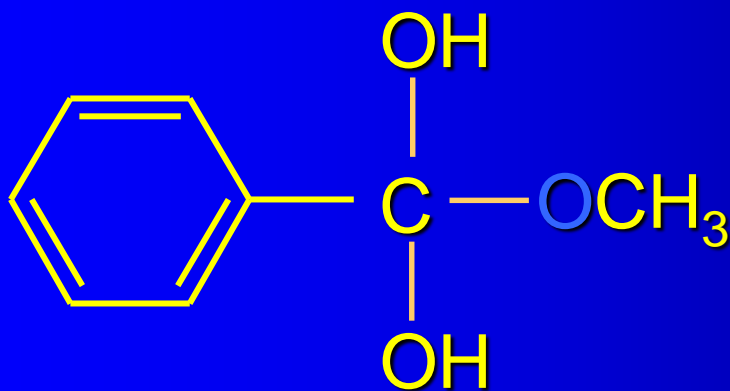
First stage: formation of tetrahedral intermediate



- methanol adds to the carbonyl group of the carboxylic acid
- the tetrahedral intermediate is analogous to a hemiacetal



Second stage: conversion of tetrahedral intermediate to ester



- this stage corresponds to an acid-catalyzed dehydration



Mechanism of Fischer esterification

1 Proton transfer from the acid catalyst to the carbonyl oxygen increases the electrophilicity of the carbonyl carbon...

2 which is then attacked by the nucleophilic oxygen atom of the alcohol...

3 to form an oxonium ion.

4 Proton transfer from the oxonium ion to a second molecule of alcohol...

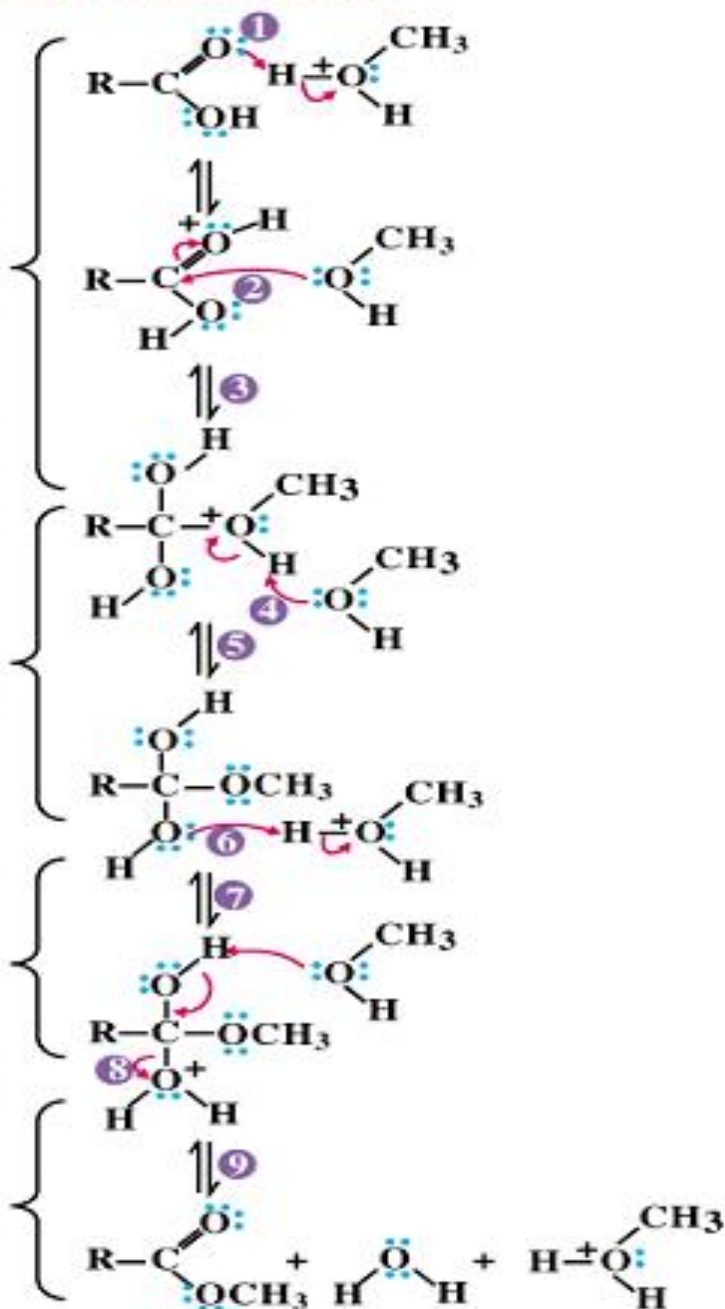
5 gives a tetrahedral carbonyl addition intermediate (TCAI).

6 Proton transfer to one of the —OH groups of the TCAI...

7 gives a new oxonium ion.

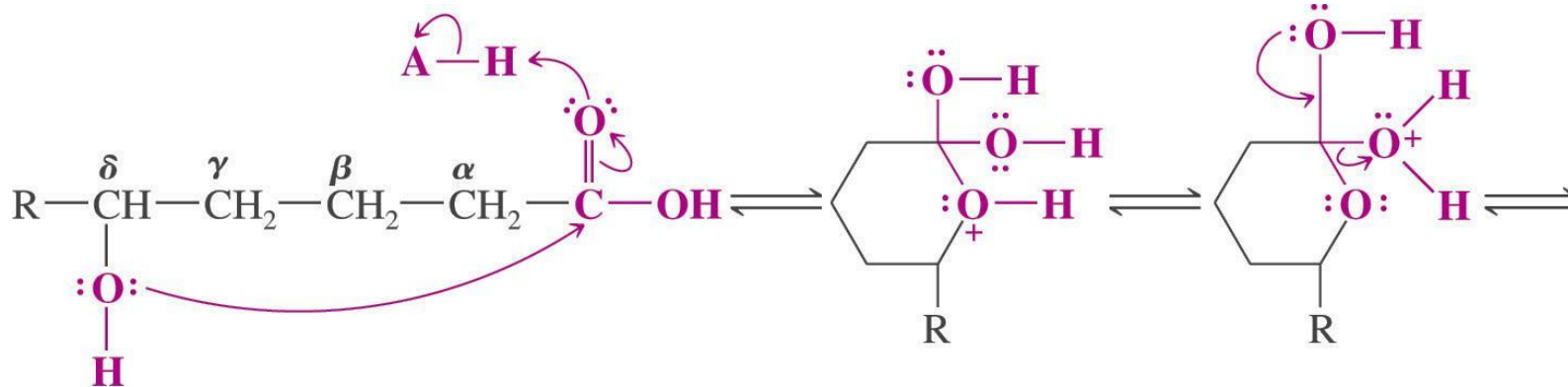
8 Loss of water from this oxonium ion...

9 gives the ester and water.

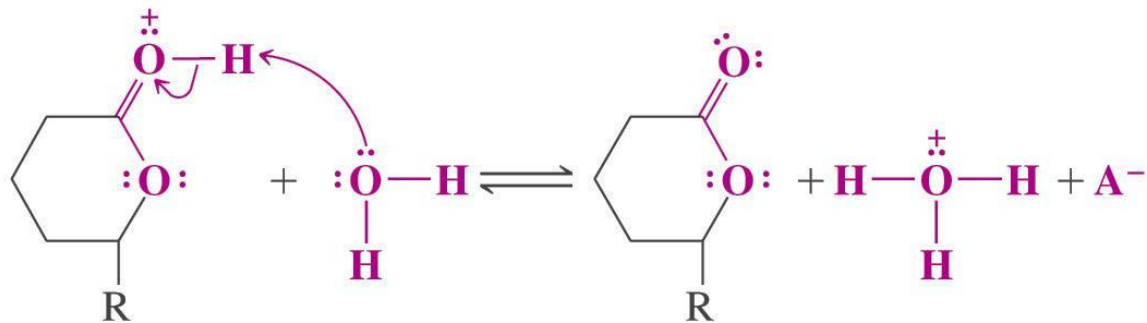


– Lactones

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

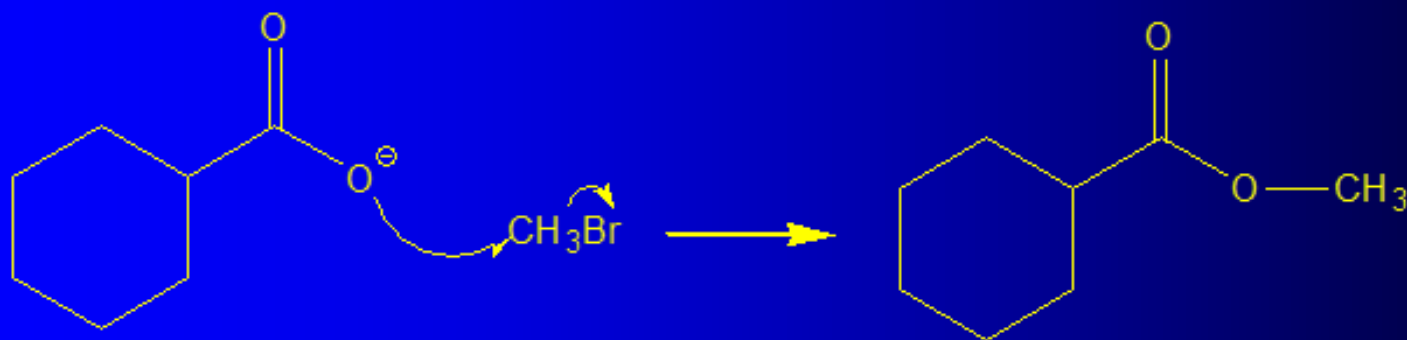


A δ -hydroxy acid

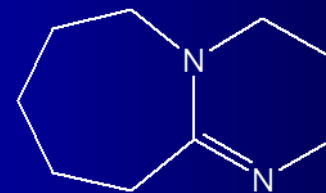


A δ -lactone

Synthesis of Esters by S_N2



- Fischer Esterification
- Diazomethane
- Via Acyl chloride

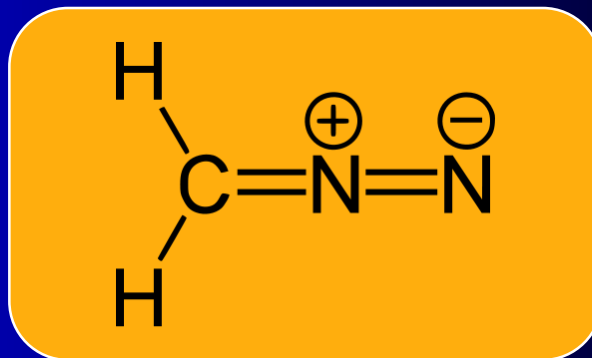


1,8-Diazabicyclo[5.4.0]undec-7-ene

DBU

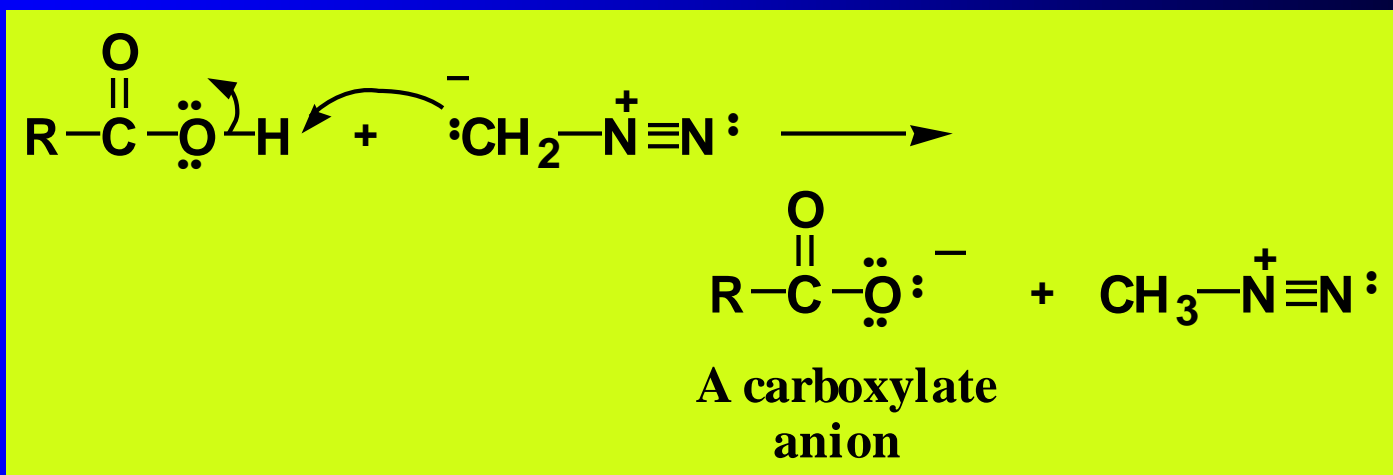


Diazomethane



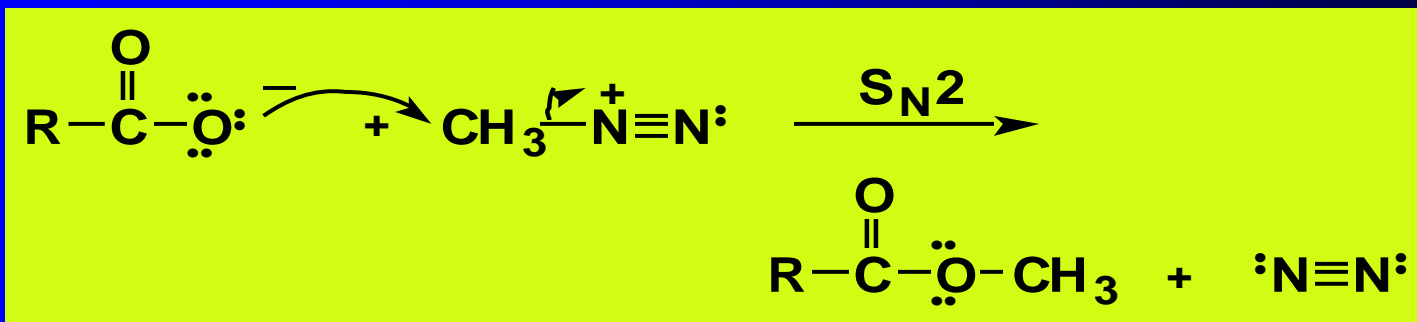
- Esterification occurs in two steps

Step 1: proton transfer from the carboxyl group to diazomethane



Diazomethane

Step 2: nucleophilic displacement (S_N2) of N_2 , an extraordinarily good leaving group, by the carboxylate anion



Diazomethane

Diazomethane is toxic by inhalation or by contact with the skin. Symptoms include chest discomfort, headache, weakness and, in severe cases, collapse. Symptoms may be delayed. In one instance a laboratory worker consumed a hamburger near a fumehood where he was generating a large quantity of diazomethane, and died four days later from fulminating pneumonia. Like any other alkylating agents it is expected to be carcinogenic, but such concerns are overshadowed by its serious acute toxicity.

CH₂N₂ may explode in contact with sharp edges, such as ground-glass joints, even scratches in glassware¹ Glassware should be inspected before use and preparation should take place behind a blast shield. Specialized kits to prepare diazomethane with flame-polished joints are commercially available. ***The compound explodes when heated beyond 100 °C, exposed to intense light, alkali metals, or calcium sulfate. Use of a blast shield is highly recommended while using this compound.***



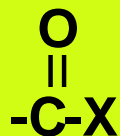
Explosive response to safer chemistry

Chemists in Switzerland have devised a neat chemical trick that allows them to use the highly explosive reagent, diazomethane, in their reactions without risk to life or limb. Bill Morandi and Erick Carreira at ETH Zurich have shown that it is possible to use a precursor and a simple iron porphyrin catalyst to carry out cyclopropanations of styrenes, enynes and dienes in strong aqueous potassium hydroxide solution. Diazomethane can be used in aziridination, carbonyl homologation, cyclopropanation, dipolar cycloaddition, epoxidation, esterification reactions and more but its toxicity and explosive nature often precludes its use. Carreira's work opens up a new approach in which the gas is generated and consumed by the reaction in situ. Nature Chemistry Volume: 4, Page:431

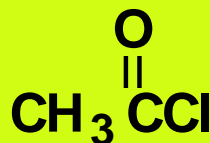


Acid Chlorides

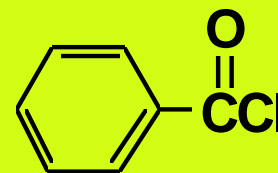
- The functional group is a carbonyl bonded to a chlorine atom
- Name derived from the parent acid by dropping **-ic acid** and adding **yl chloride**



**Functional group
of an acid halide**



Acetyl chloride

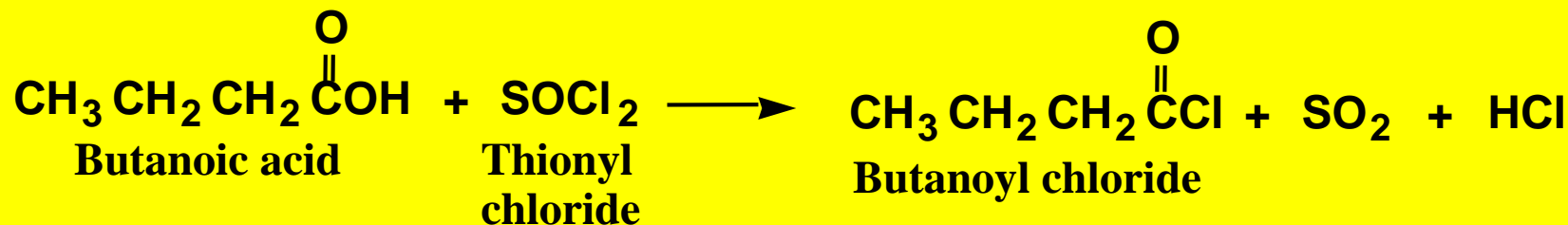


Benzoyl chloride



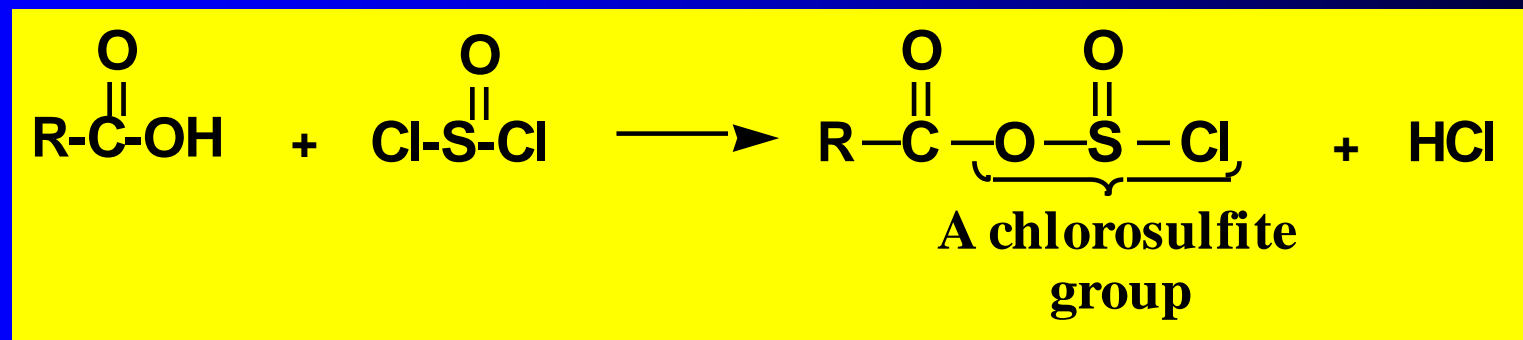
Acid Chlorides

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



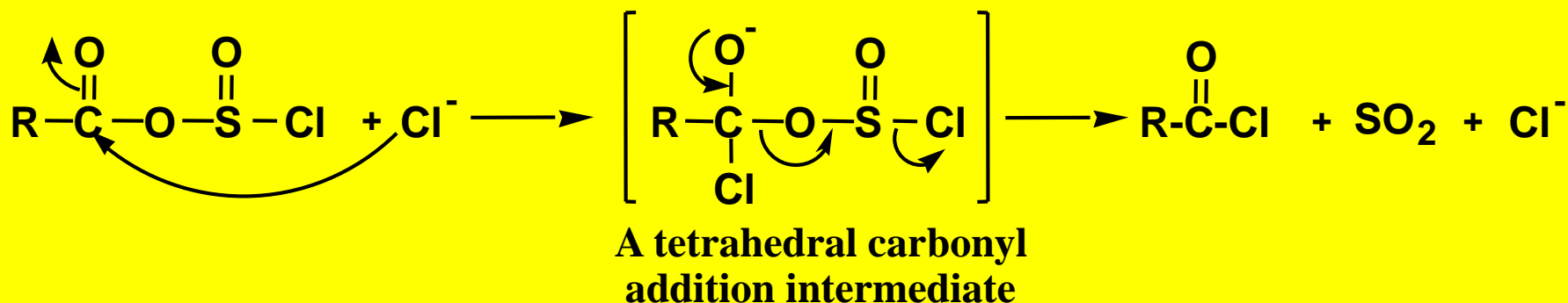
Acid Chlorides

- The mechanism divided into two steps.
Step 1: The -OH, is transformed into a chlorosulfite group, a great leaving group

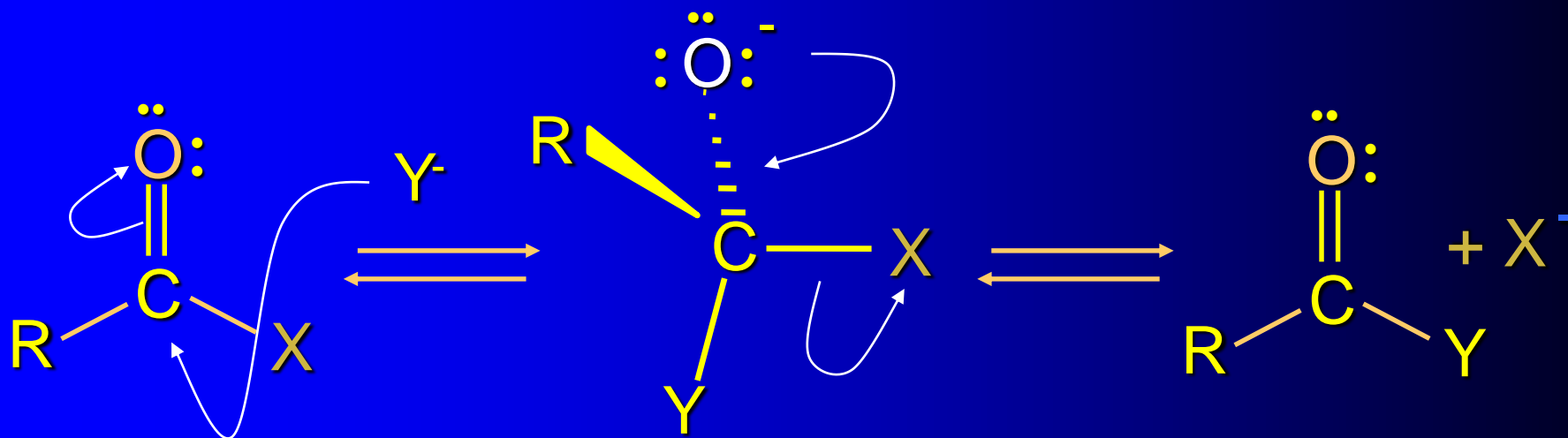


Acid Chlorides

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



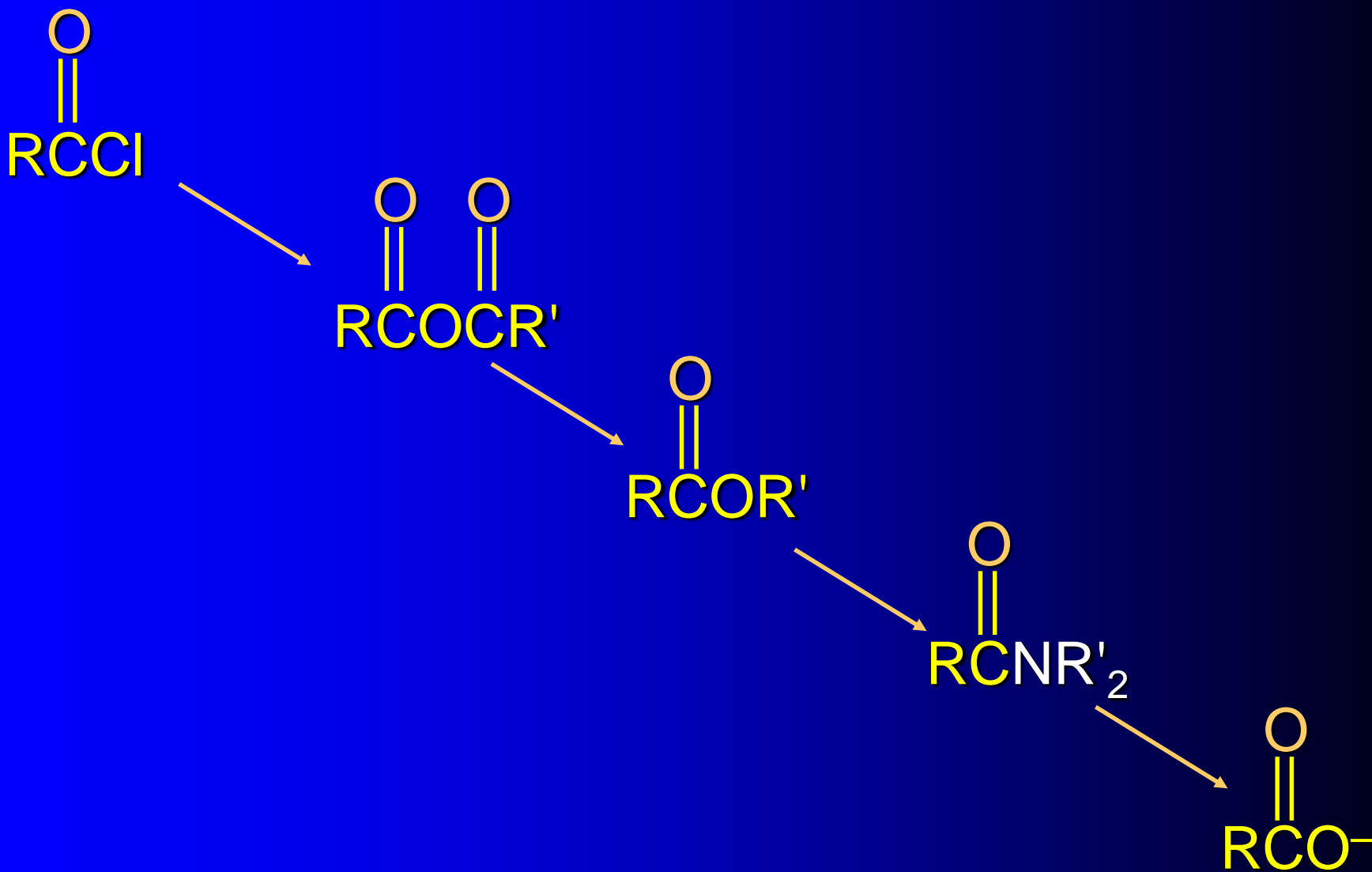
Nucleophilic Acyl Substitution with an anion as nucleophile



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



Reactions of Acyl Chlorides



Relative reactivities of carboxyl derivatives

