

CH 310 N

TH 2:3:30

LECTURE 14

**Textbook Assignment: Chapter 17**

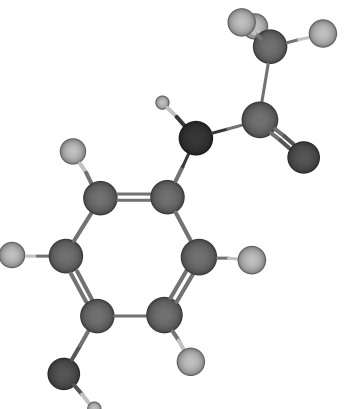
**Homework (for credit): POW 7 posted**

**Today's Topics: Derivatives of Carboxylic Acids**

*Notice & Announcements:*

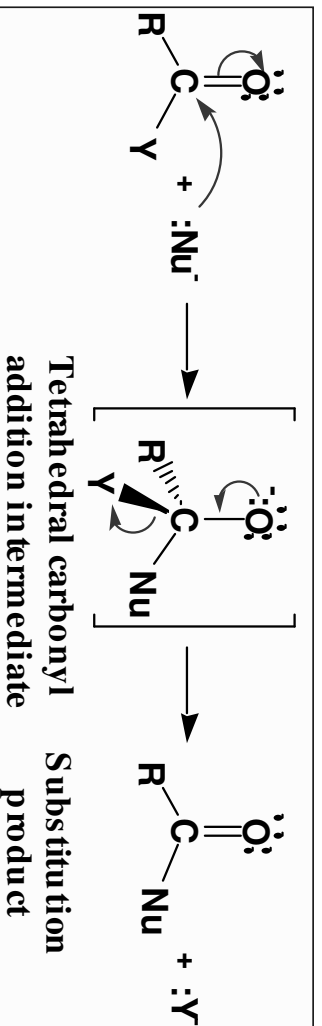
ORGANIC LECTURE SERIES

# **Functional Derivatives of Carboxylic Acids**



## Characteristic Reactions

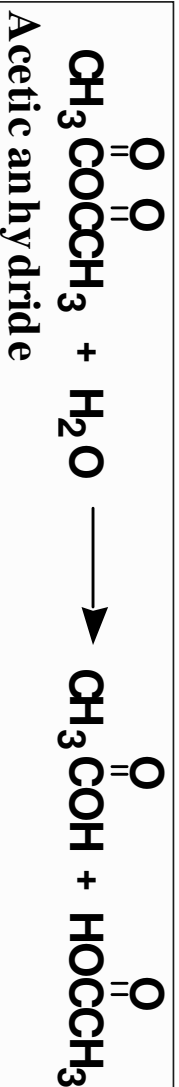
- **Nucleophilic acyl substitution:** an addition-elimination sequence resulting in substitution of one nucleophile for another



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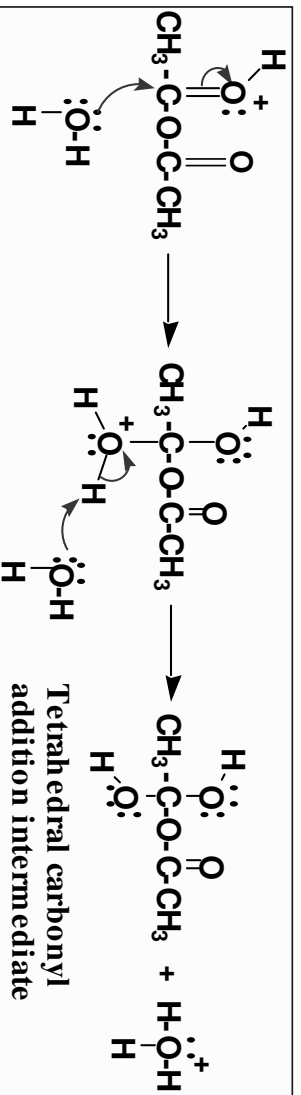
## Reaction with H<sub>2</sub>O - Anhydrides

- low-molecular-weight acid anhydrides react readily with water to give two molecules of carboxylic acid
- higher-molecular-weight acid anhydrides also react with water, but less readily

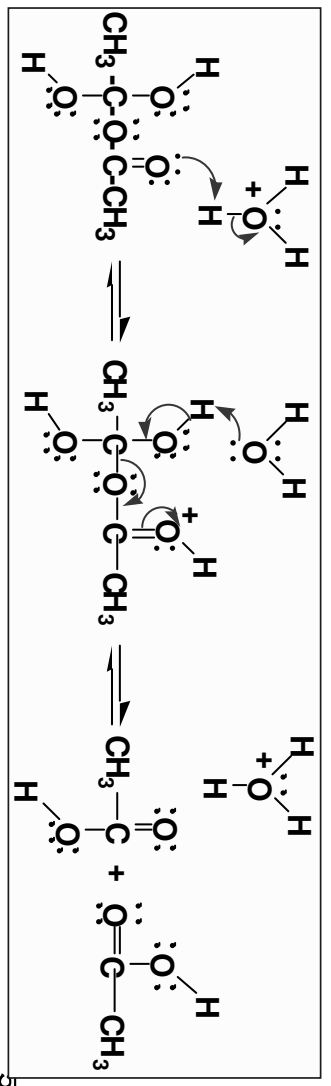


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– Step 1 : addition of H<sub>2</sub>O to give a TCAI



– Step 2: protonation followed collapse of the TCAI

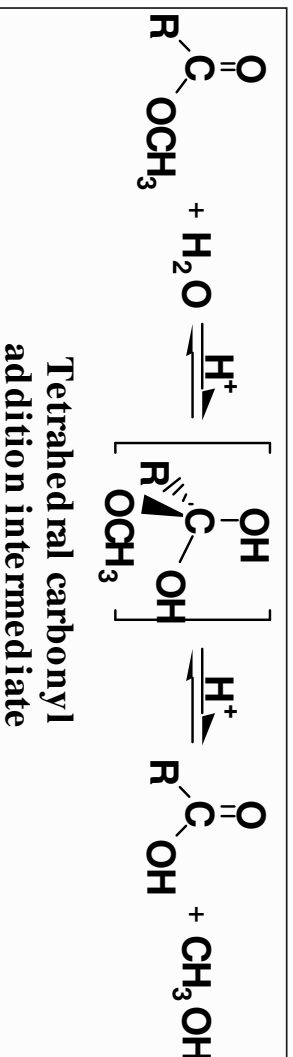


## Reaction with H<sub>2</sub>O - Esters

- Esters are hydrolyzed only slowly, even in boiling water
  - hydrolysis becomes more rapid if they are heated with either aqueous acid or base
- Hydrolysis in aqueous acid is the reverse of Fischer esterification
  - the role of the acid catalyst is to protonate the carbonyl oxygen and increase its electrophilic character toward attack by water (a weak nucleophile) to form a tetrahedral carbonyl addition intermediate
  - collapse of this intermediate gives the carboxylic acid and alcohol

## Reaction with H<sub>2</sub>O - Esters

- **Acid-catalyzed ester hydrolysis**



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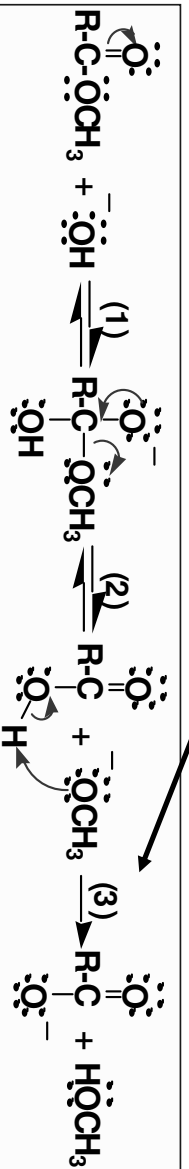
## Reaction with H<sub>2</sub>O - Esters

- Hydrolysis of an esters in aqueous base is often called **saponification**
    - each mole of ester hydrolyzed requires 1 mole of base
    - for this reason, ester hydrolysis in aqueous base is said to be base promoted
- $$\begin{array}{c}
 \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OCH}_3 + \text{NaOH} \xrightarrow{\text{H}_2\text{O}} \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}^- \text{Na}^+ + \text{CH}_3\text{OH}
 \end{array}$$
- hydrolysis of an ester in aqueous base involves formation of a tetrahedral carbonyl addition intermediate followed by its collapse and proton transfer

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## Reaction with H<sub>2</sub>O - Esters

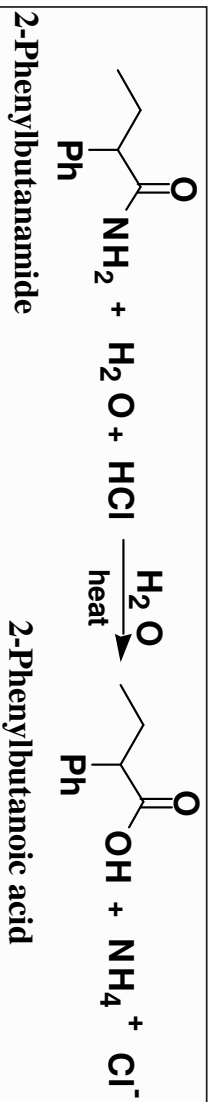
- Step 1 : attack of hydroxide ion (a nucleophile) on the carbonyl carbon (an electrophile)
- Step 2: collapse of the TCAI
- Step 3: proton transfer to the alkoxide ion; **this step is irreversible** and drives saponification to completion



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## Reaction with H<sub>2</sub>O - Amides

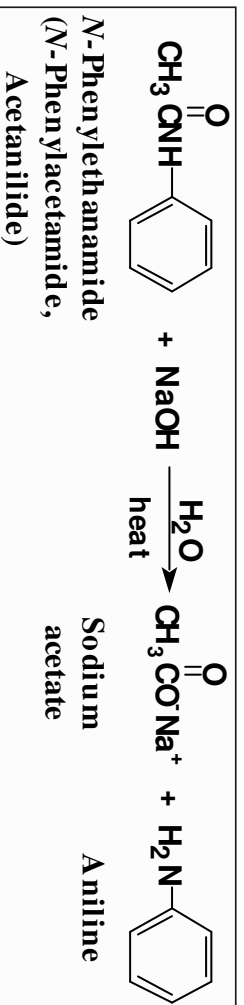
- Hydrolysis of an amide in aqueous acid requires 1 mole of acid per mole of amide
  - reaction is driven to completion by the acid-base reaction between the amine or ammonia and the acid



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## Reaction with H<sub>2</sub>O - Amides

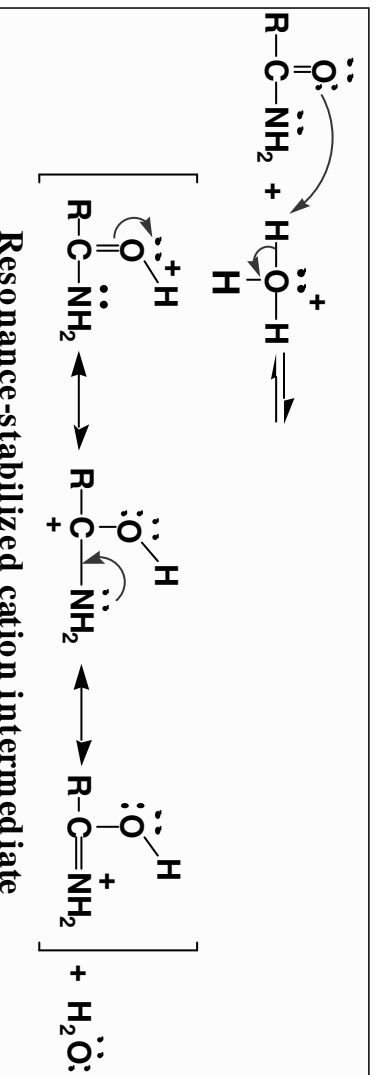
- Hydrolysis of an amide in aqueous base requires 1 mole of base per mole of amide
  - reaction is driven to completion by the irreversible formation of the carboxylate salt



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## Reaction with H<sub>2</sub>O - Amides

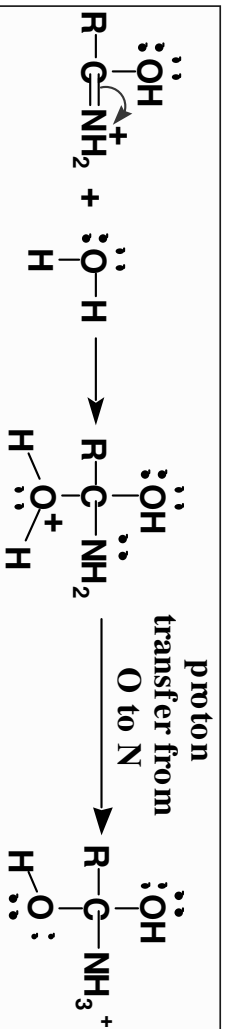
- Step1 : protonation of the carbonyl oxygen gives a resonance-stabilized cation intermediate



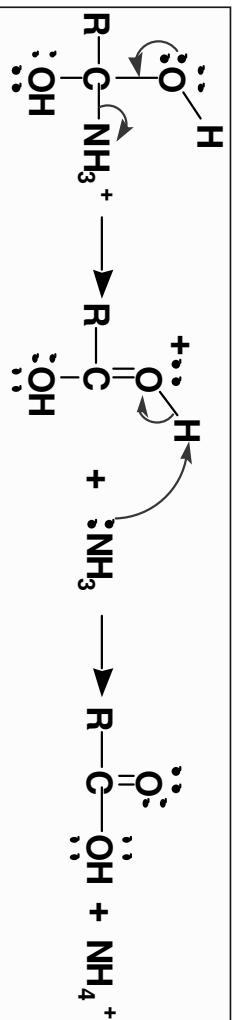
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## Reaction with H<sub>2</sub>O - Amides

- Step 2: addition of water (a nucleophile) to the carbonyl carbon (an electrophile) followed by proton transfer gives a TCAI



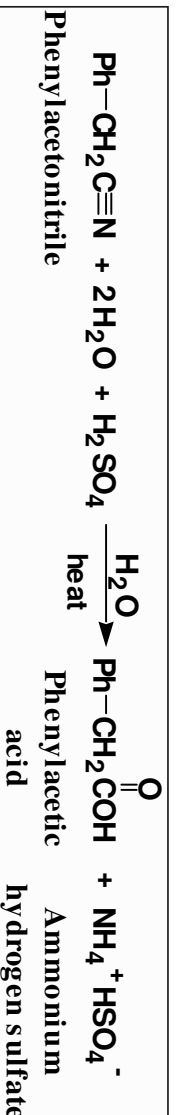
- Step 3: collapse of the TCAI and proton transfer



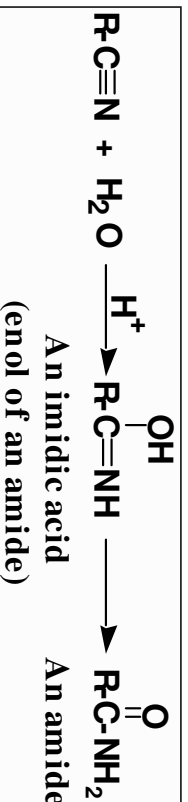
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## Reaction with H<sub>2</sub>O - Nitriles

- The cyano group is hydrolyzed in aqueous acid to a carboxyl group and ammonium ion



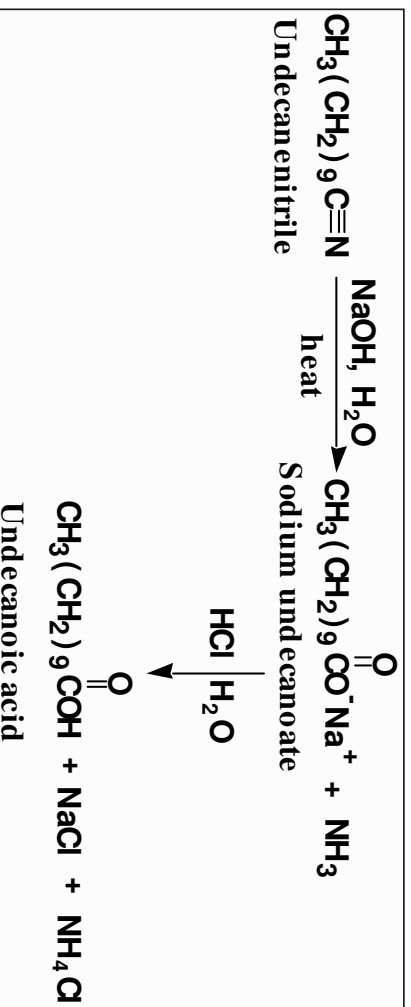
- protonation of the cyano nitrogen gives a cation that reacts with water to give an imidic acid
- keto-enol tautomerism gives the amide



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## Reaction with H<sub>2</sub>O - Nitriles

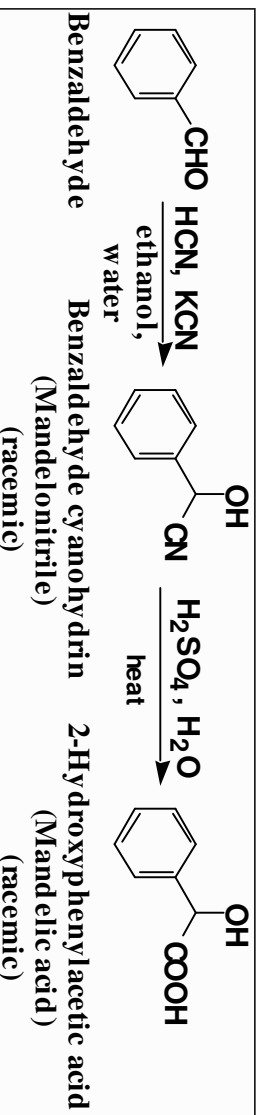
– hydrolysis of a cyano group in aqueous base gives a carboxylic anion and ammonia; acidification converts the carboxylic anion to the carboxylic acid



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## Reaction with H<sub>2</sub>O - Nitriles

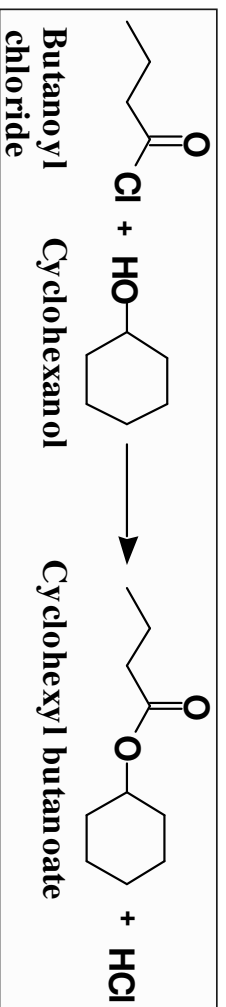
– hydrolysis of nitriles is a valuable route to carboxylic acids



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## Reaction with Alcohols

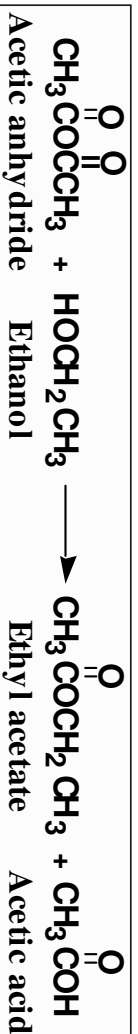
- Acid halides react with alcohols to give esters
  - acid halides are so reactive toward even weak nucleophiles such as alcohols that no catalyst is necessary
  - where the alcohol or resulting ester is sensitive to HCl, reaction is carried out in the presence of a 3° amine to neutralize the acid



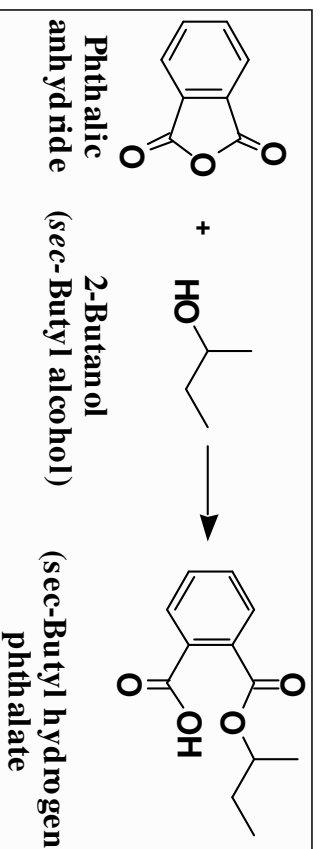
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## Reaction with Alcohols

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



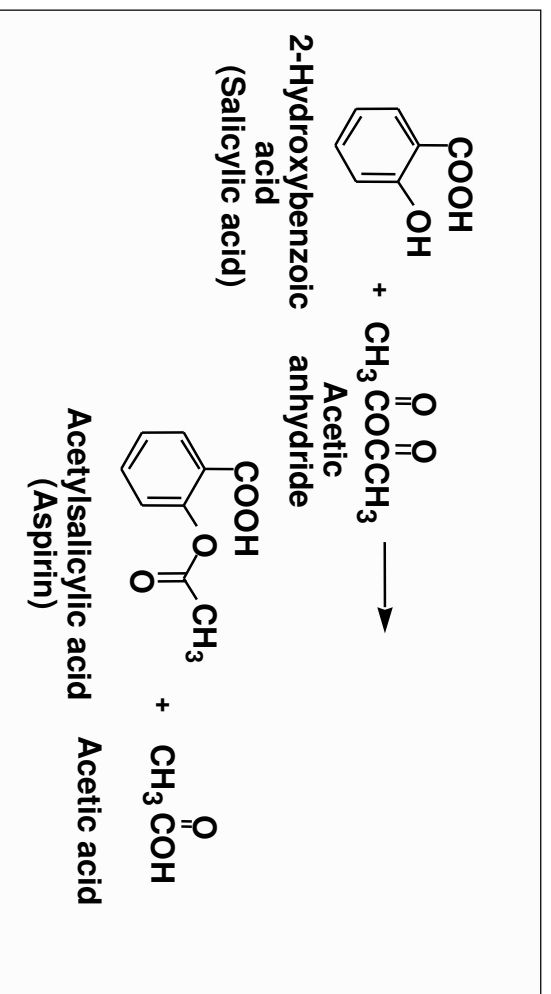
- cyclic anhydrides react with alcohols to give one ester group and one carboxyl group



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## Use in Practice

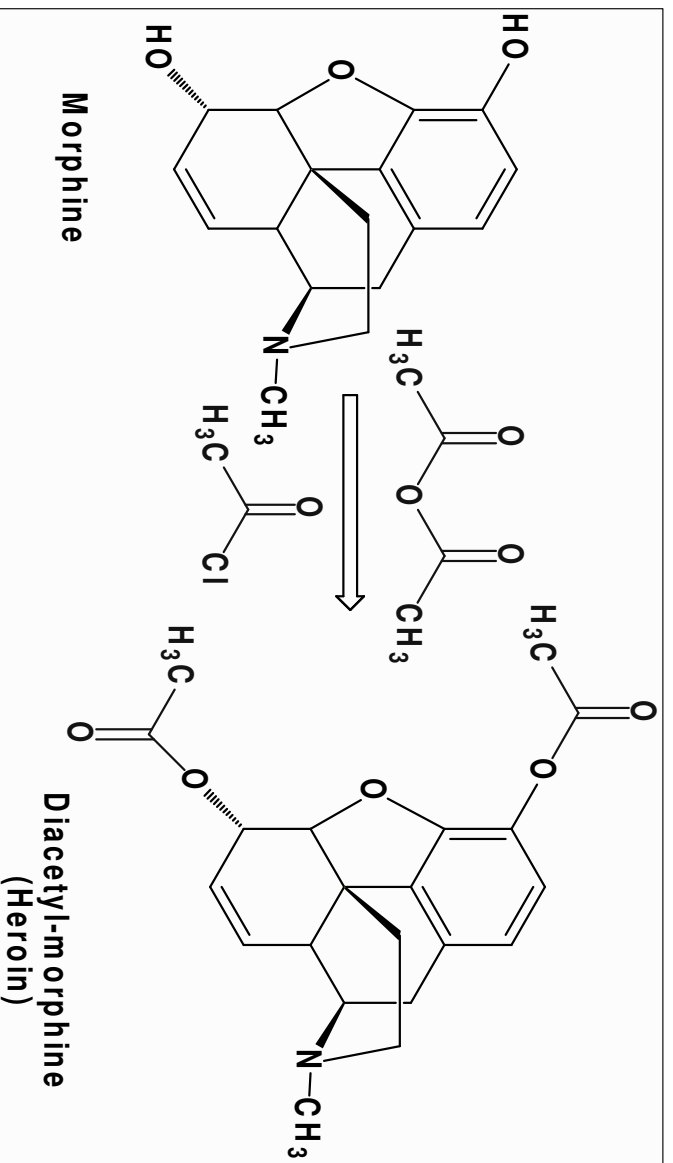
– aspirin is synthesized by treating salicylic acid with acetic anhydride



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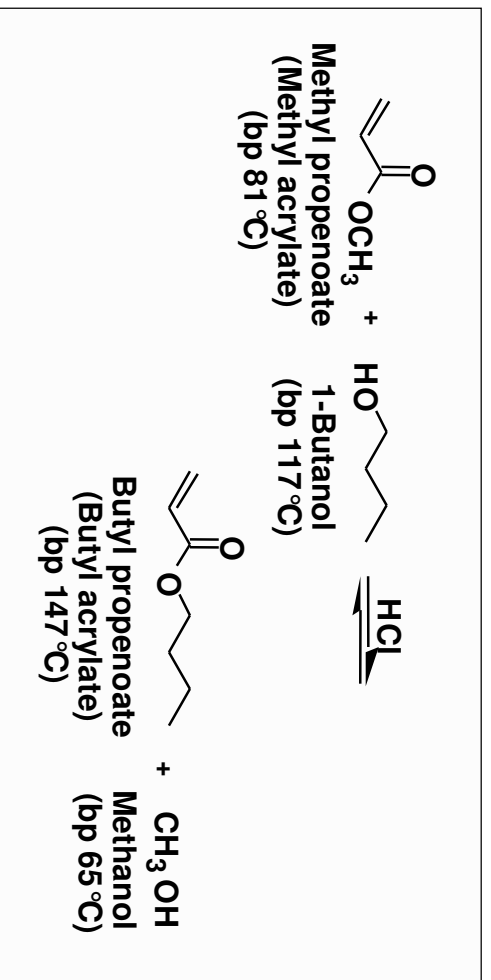
## Use in Practice

Both Acid anhydrides or acid chlorides can be used as acylating agents:



## Reaction with Alcohols

- Esters react with alcohols in the presence of an acid catalyst in an equilibrium reaction called **transesterification**

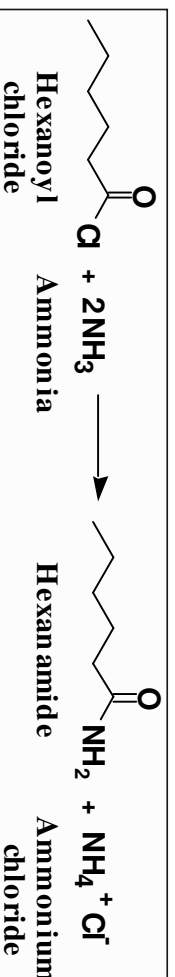


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## Reaction with Ammonia

Acid halides react with ammonia, 1° amines, and 2° amines to form amides

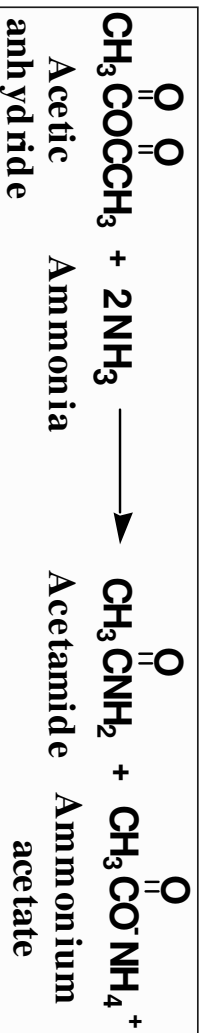
– 2 moles of the amine are required per mole of acid chloride



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## Reaction with Ammonia

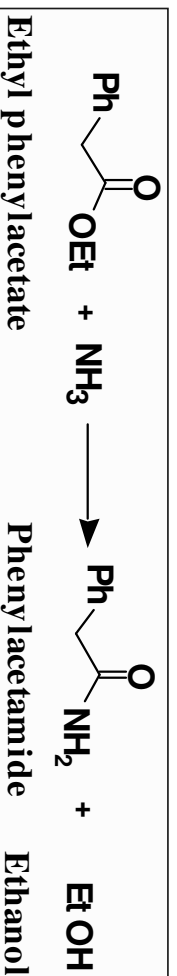
Acid anhydrides react with ammonia,  
and 1° and 2° amines to form amides  
– 2 moles of ammonia or amine are  
required



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## Reaction with Ammonia

- Esters react with ammonia, and 1° and 2° amines to form amides
  - esters are less reactive than either acid halides or acid anhydrides



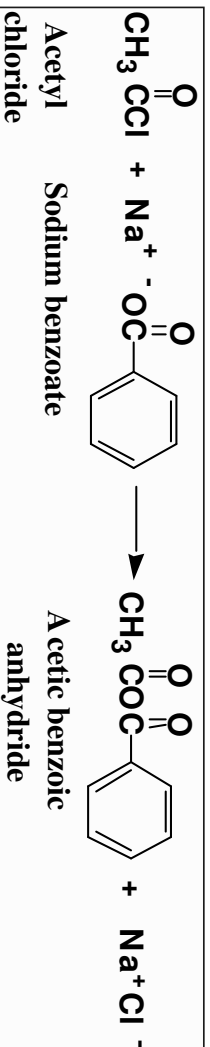
- Amides do not react with ammonia, or 1° or 2° amines

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## Acid Chlorides with Salts

Acid chlorides react with salts of carboxylic acids to give anhydrides

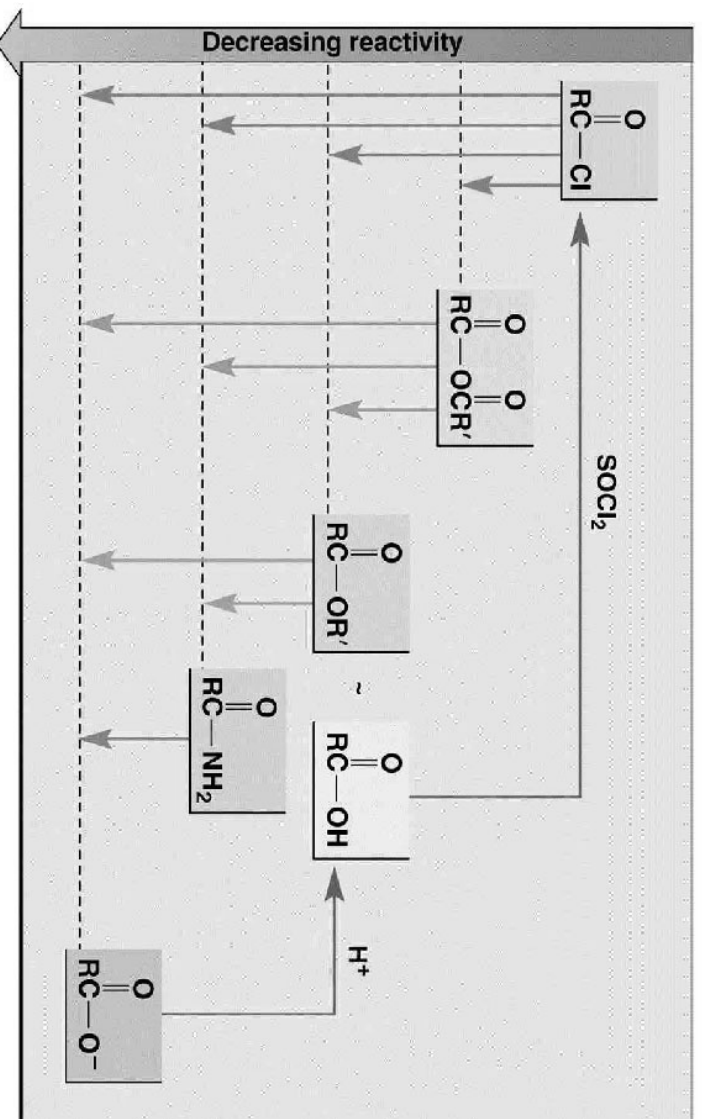
– most commonly used are sodium or potassium salts



This is a method to prepare mixed acid anhydrides

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## Interconversions



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