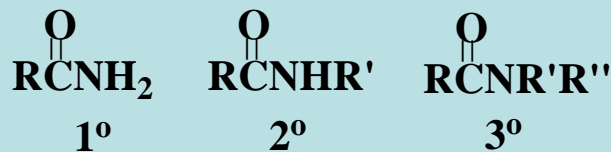


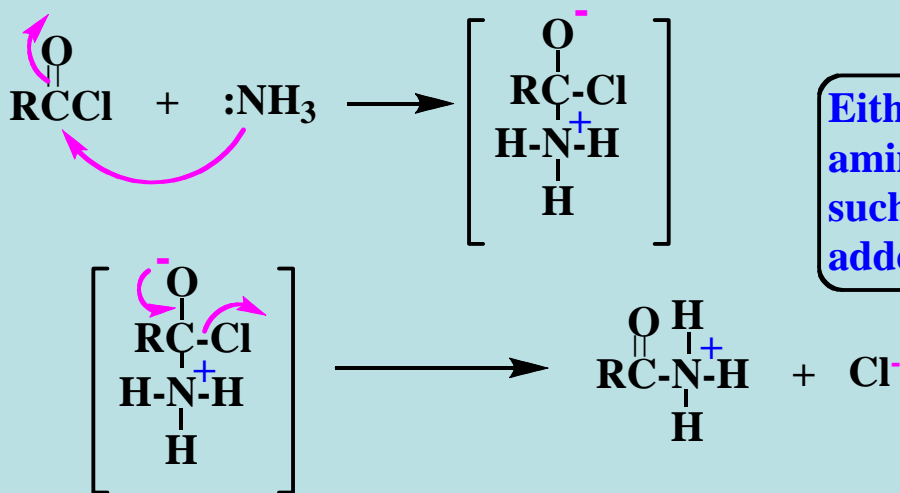
# Amides

Amides like amines are classified according to the number of substituents on the ammonia-type nitrogen:

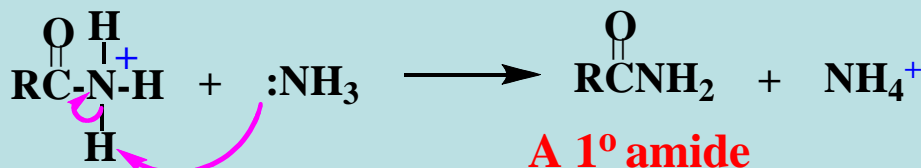


## Synthesis of Amides from Acyl Chlorides

The nucleophiles ammonia and primary and secondary amines all react rapidly with acyl chlorides to produce amides. For complete reaction, the byproduct HCl must be neutralized.



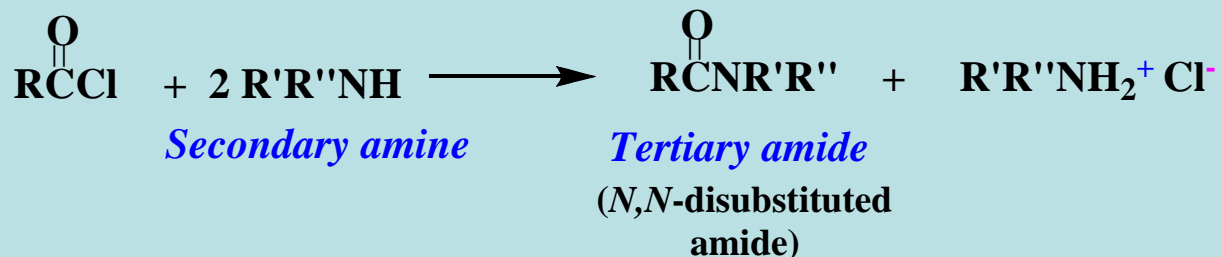
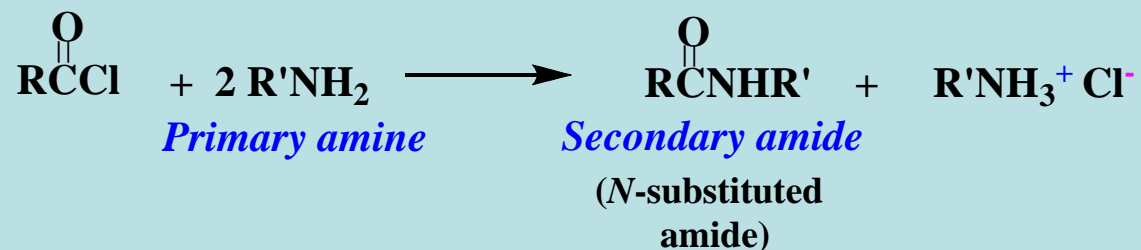
Either excess ammonia or amine, or a tertiary amine such as triethylamine, is added to neutralize the HCl.



A 1<sup>o</sup> amide

## Secondary and Tertiary Amides

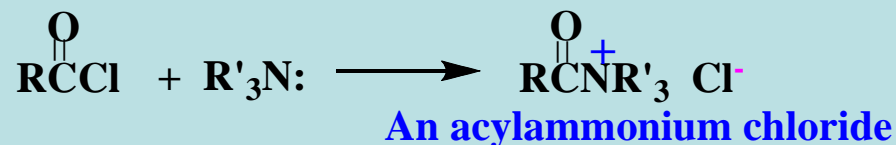
The reaction of acyl chlorides with primary and secondary amines yields secondary and tertiary amides, respectively.



Note: Two equivalents of the **amine** are required for complete reaction.

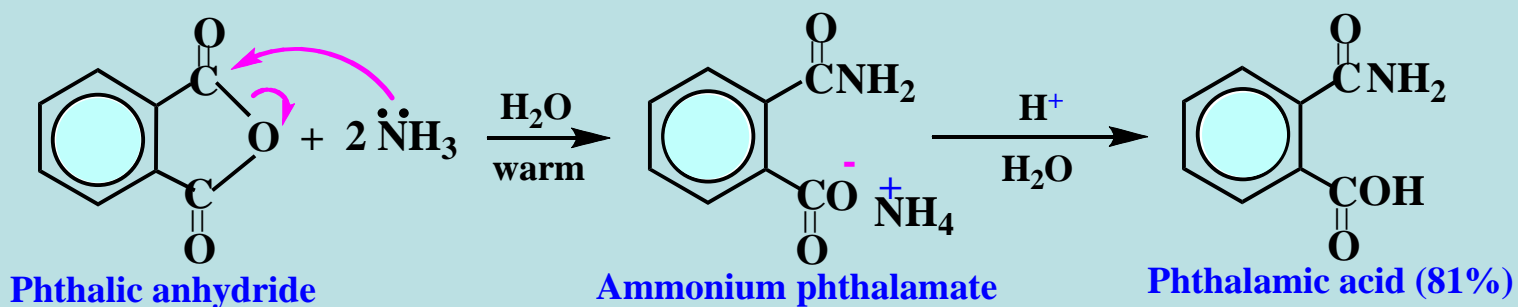
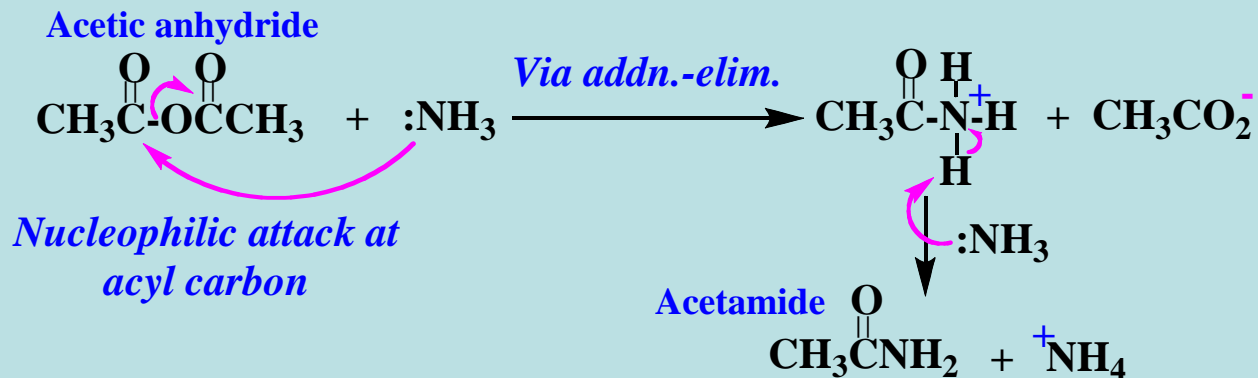
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Tertiary amines react with acyl chlorides to produce salts, not stable amide products.

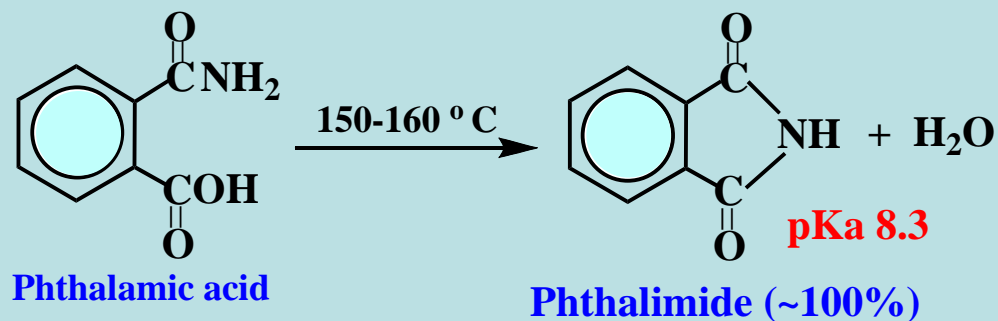


# Amides from Carboxylic Acid Anhydrides

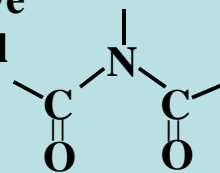
Analogous reactions occur between acid anhydrides and ammonia or amines.



Vigorous heating of phthamic acid results in dehydration and formation of **phthalimide**, which is used in a classic method of amine synthesis.

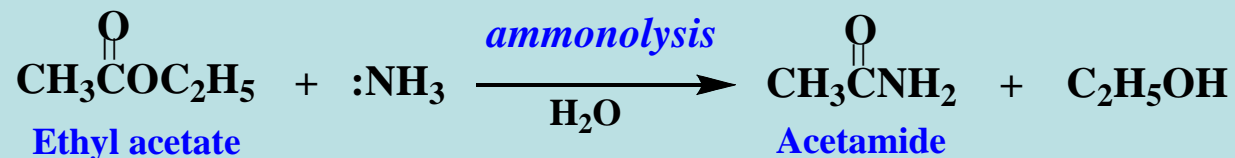


**Imides** have the general structure:



## Amides from Esters

Esters undergo nucleophilic addition-elimination at the acyl carbon with **nitrogen nucleophiles** such as ammonia (**ammonolysis**) or amines (**amination**).

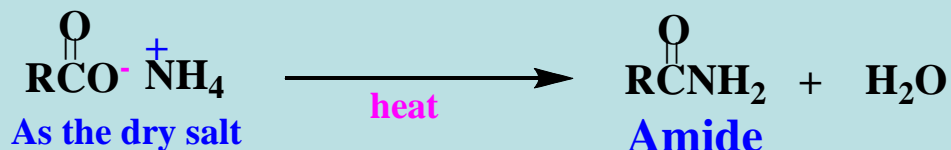


## Amides from Carboxylic Acids

Carboxylic acids react with aqueous ammonia to produce ammonium carboxylates in an acid-base reaction:



Recovery of the ammonium carboxylate and heating of the dry salt leads to dehydration and formation of the amide.

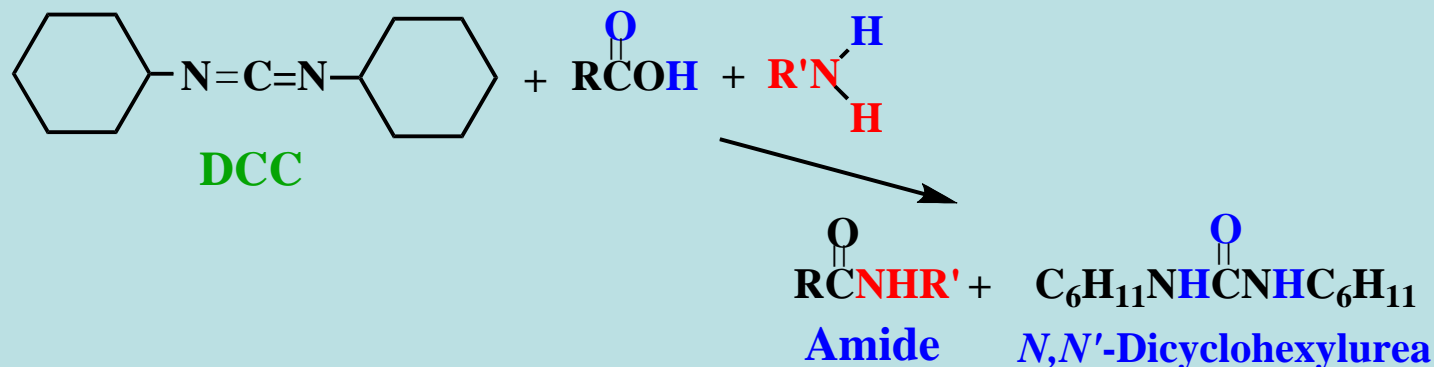


This method is generally not used in organic synthesis because the vigorous heating required will often decompose the sample.

## Amides by a Condensation Synthesis Using Dicyclohexylcarbodiimide (DCC)

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Amides may be prepared from carboxylic acids and amines in an indirect dehydration synthesis using **DCC**. This method was developed for synthesizing the amide bond in biological systems under very mild conditions.



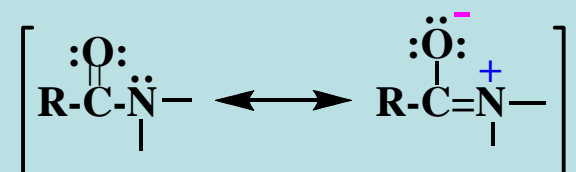
Note that the  $\text{H}_2\text{O}$  byproduct ends up hydrating the diimide function to an urea compound.

## Hydrolysis of Amides

---

Amides hydrolyze **much more slowly** than other acyl derivatives of carboxylic acids such as acyl chlorides, esters, or anhydrides. This decreased reactivity is associated with the **greater stability** of the amide functional group compared with the other acyl derivatives.

This enhanced stability is explained by **resonance theory** through these contributors to a hybrid structure:

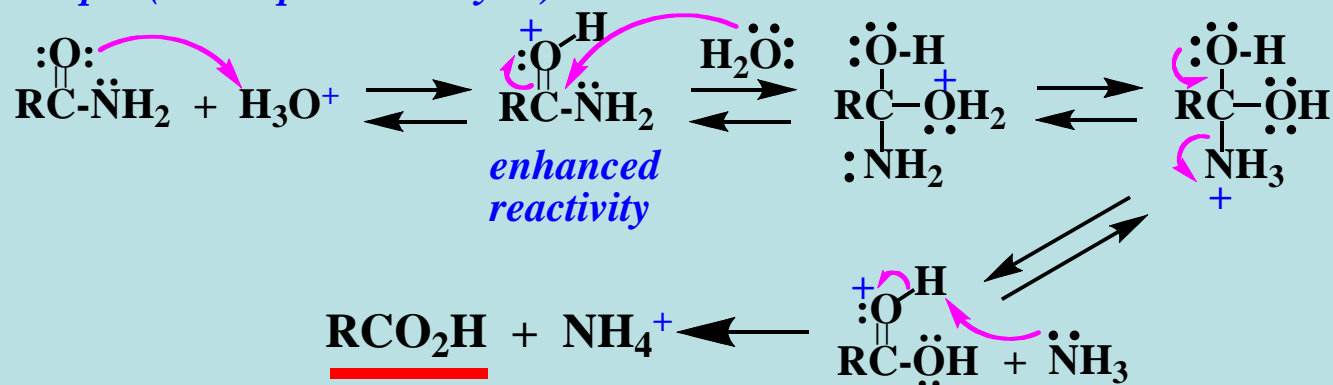


Amides are **neutral compounds** despite the presence of the amino-type nitrogen. Their decreased base strength compared with amines is also explained by the resonance stabilization of the amide function illustrated above, which much diminishes the electron density on the nitrogen. Much of this resonance stabilization is lost when the amide group is protonated.

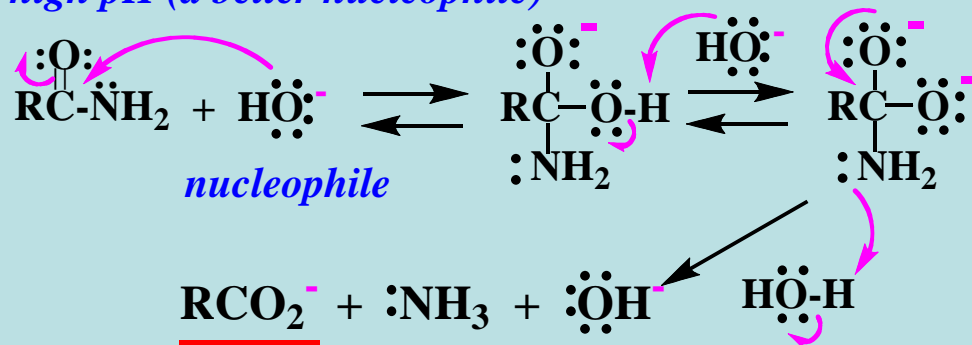
# Hydrolysis of Amides: Mechanisms

The rate of hydrolysis of amides is faster at lower or higher pH than at pH 7.

*At low pH (electrophilic catalysis)*



*At high pH (a better nucleophile)*

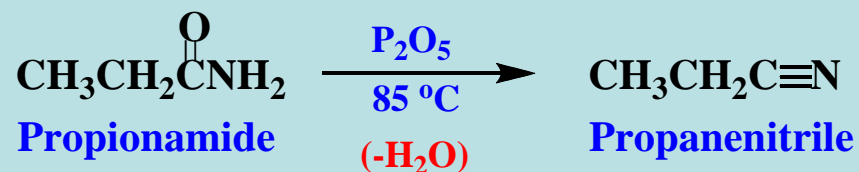


*N*-Substituted and *N,N*-disubstituted amides react similarly.

Typical hydrolysis conditions involve extensive heating of the amide in 6 M HCl or 40% aqueous NaOH.

## Nitriles

One standard way of preparing a nitrile is by dehydration of the corresponding primary amide with reagents such as  $P_4O_{10}$  (usually called **phosphorus pentoxide**, from its empirical formula  $P_2O_5$ ) or refluxing **acetic anhydride**.

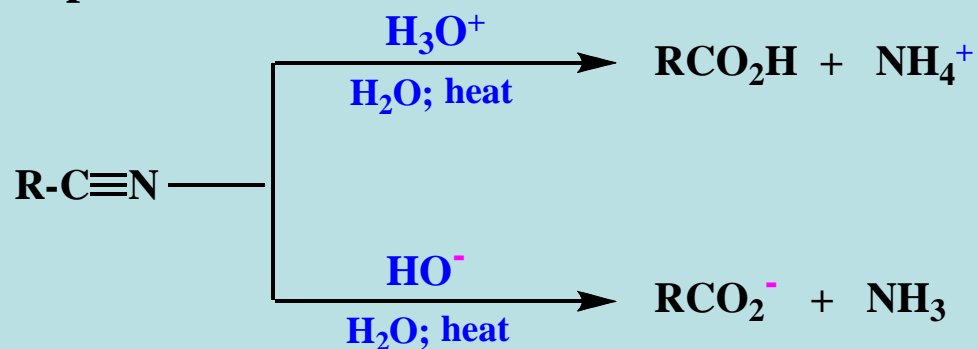


This synthesis is an alternative to the reaction of an alkyl halide with cyanide ion, which proceeds by an  $S_N2$  mechanism.

## Hydrolysis of Nitriles

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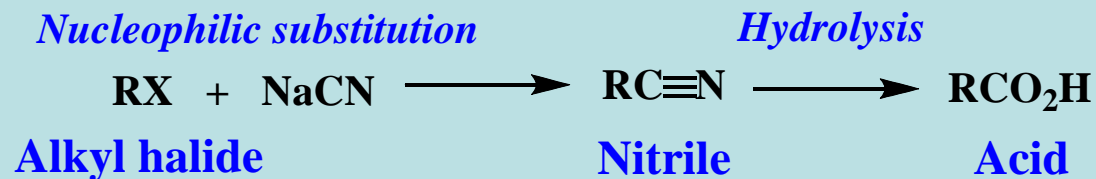
Nitriles are considered derivatives of carboxylic acids because hydrolysis of a nitrile produces an acid. As with amides, the rate of hydrolysis is faster under either acidic or basic conditions than at neutral pH.



## Use in a Synthetic Sequence

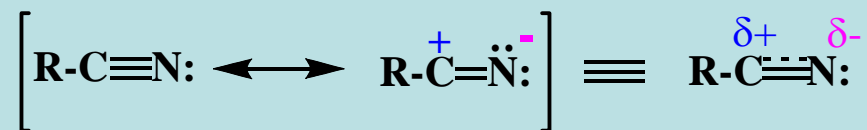
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The hydrolysis of nitriles to carboxylic acids is synthetically useful when linked with the readily available alkyl halides by the sequence:

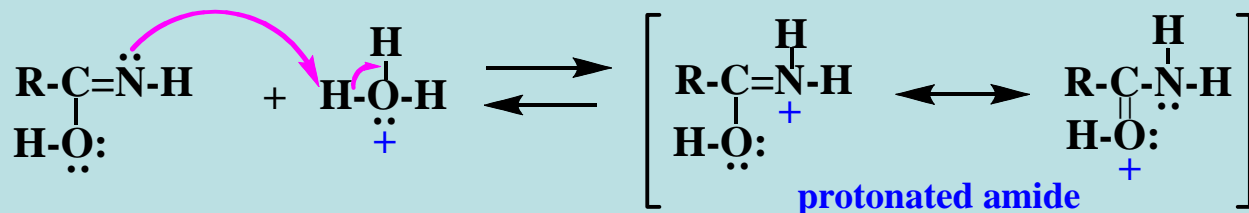
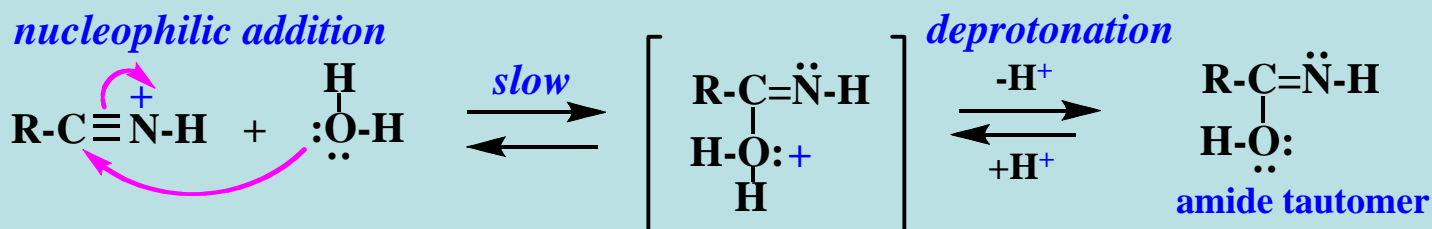
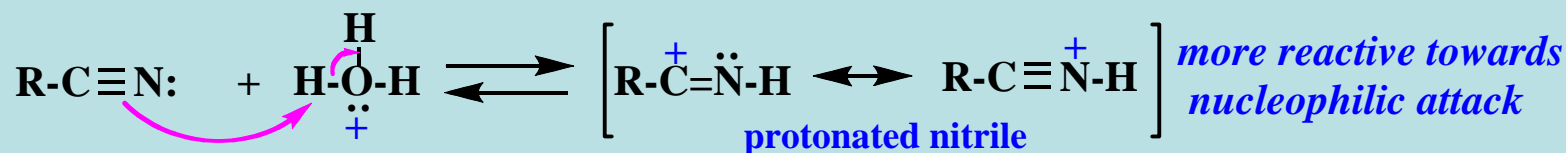


# A Mechanism for the Acidic Hydrolysis of Nitriles

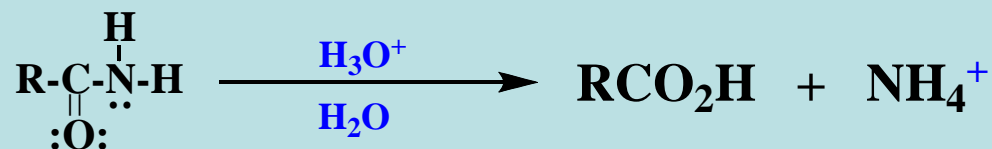
The nitrile is a polar functional group similar to a carbonyl:



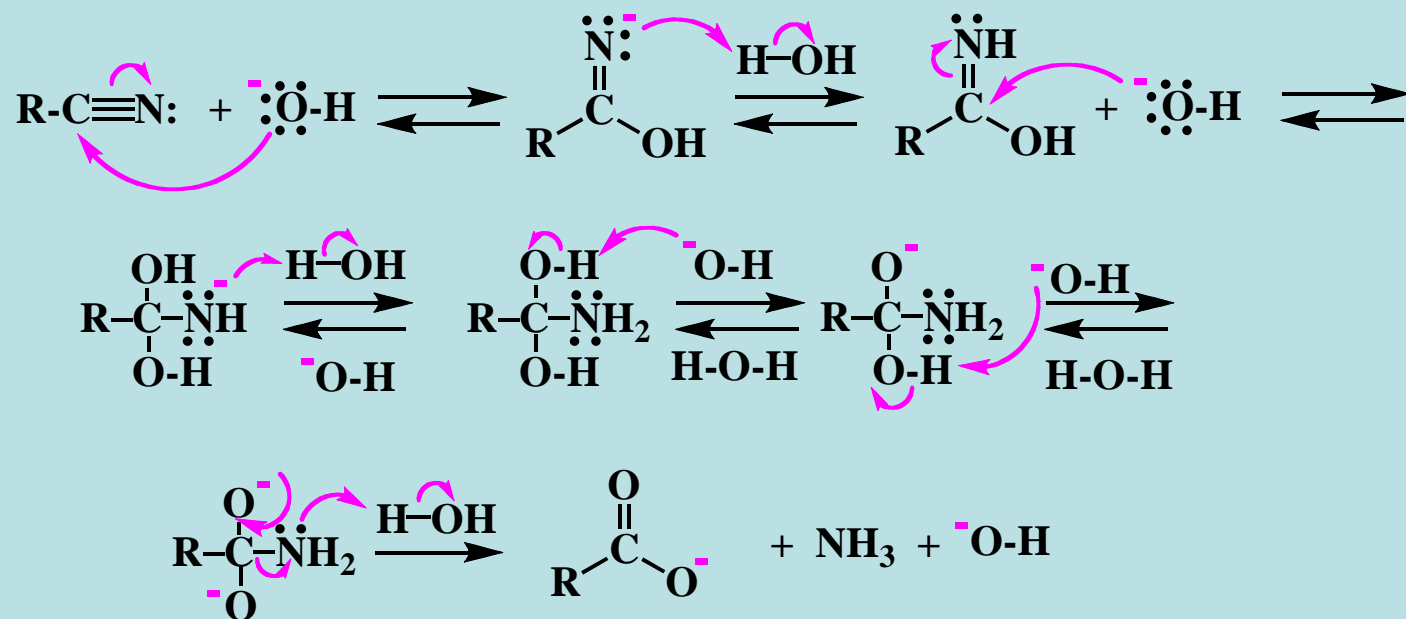
Stage 1: Hydrolysis of nitrile to amide



Stage 2: Continued hydrolysis yields carboxylic acid

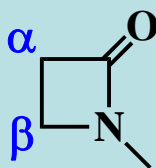


## A Mechanism for the Basic Hydrolysis of Nitriles



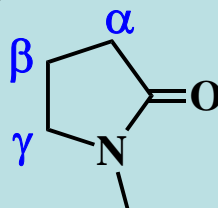
## Lactams: Cyclic Amides

Cyclic amides are called **lactams**. The size of the ring is given by a Greek letter that indicates the relative positions of the carbonyl and amino functions.



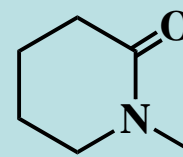
a  $\beta$  lactam

**Highly reactive;**  
ring opens easily  
on nucleophilic  
attack because of  
bond-angle strain.



a  $\gamma$  lactam

**Stable; often form spontaneously**  
from  $\gamma$ - and  $\delta$ -amino acids.



a  $\delta$  lactam

## Decarboxylation of Carboxylic Acids

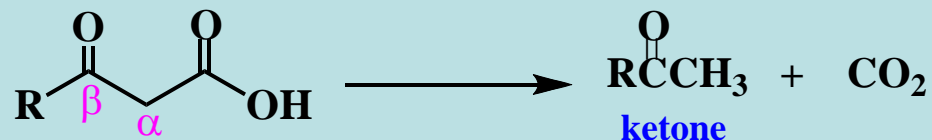
The loss of CO<sub>2</sub> from a carboxylic acid is called **decarboxylation**.



Although the loss of CO<sub>2</sub> is usually exothermic (because of the stability of CO<sub>2</sub>), the reaction is **kinetically slow**. However, certain structural features promote decarboxylation.

### β-Keto Acids

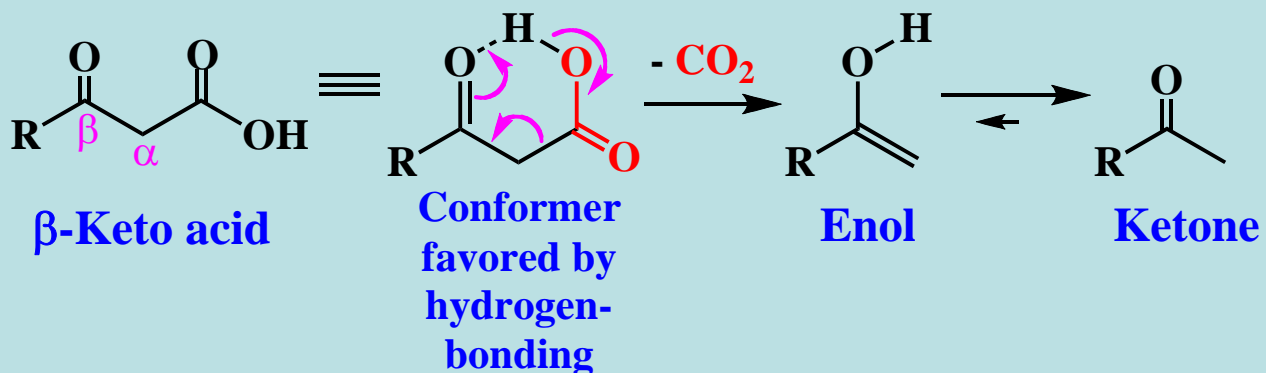
**β-Keto acids** decarboxylate rapidly when heated to 100-150 °C.



The decarboxylation reaction occurs with either the acid or its carboxylate salt.

## Decarboxylation of the Acid

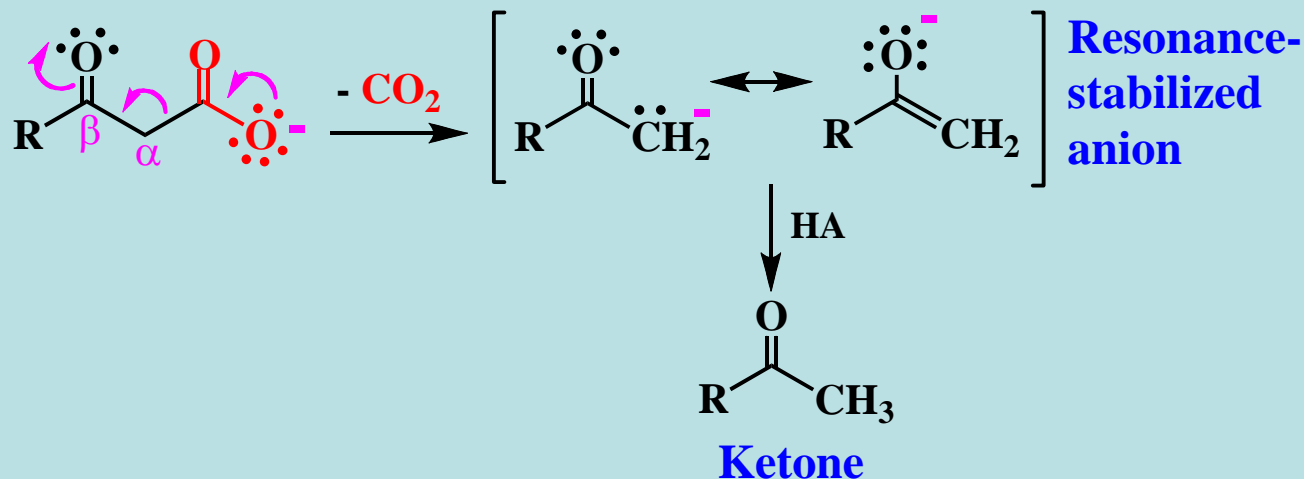
This reaction of the acid involves a six-membered cyclic transition state that initially produces the **enol** of the ketone product.



This decarboxylation reaction proceeds well because of a mechanism that avoids high energy intermediates. It is believed that bond-making and bond-breaking in the cyclic transition state proceed more or less at the same rate, producing an enol product that subsequently isomerizes to the more stable ketone.

## Decarboxylation of the Carboxylate Salt

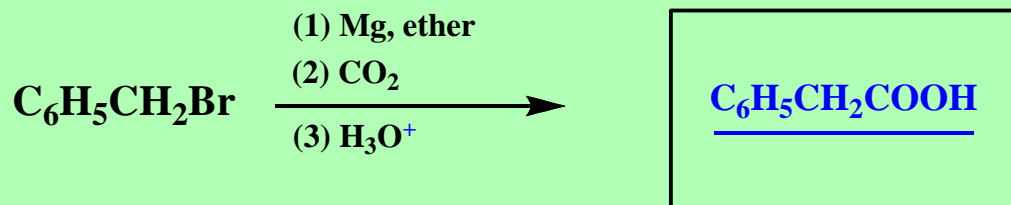
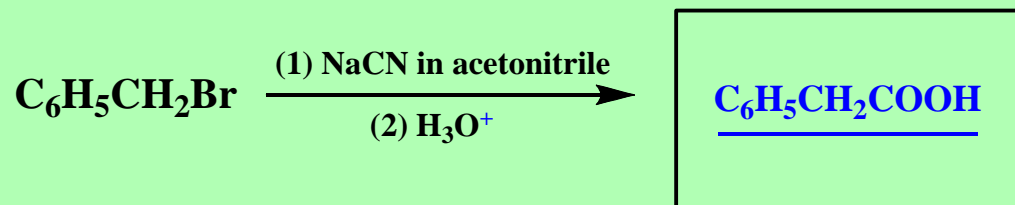
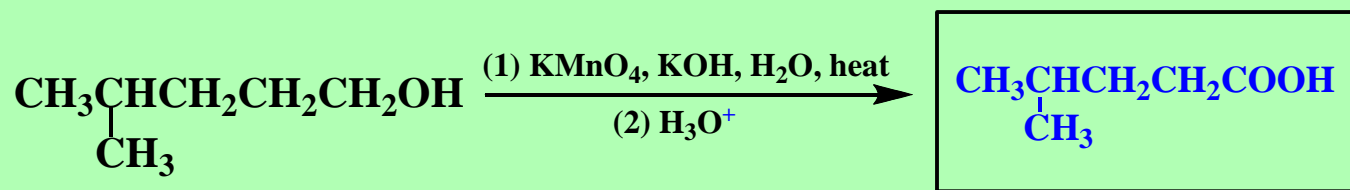
Decarboxylation of the carboxylate anion produces a resonance stabilized enolate anion:



This decarboxylation reaction proceeds well because a resonance stabilized enolate anion is formed in contrast to a high energy carbanion, the result of decarboxylation of a simple carboxylic acid.

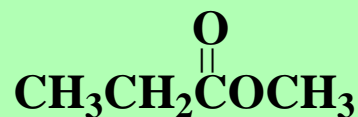
### Quiz 18.03

Draw the structures of the products of the following synthetic procedures.

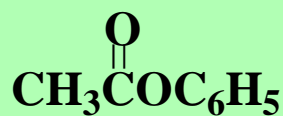


### Quiz 18.04

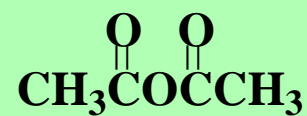
Provide IUPAC names for the following acid derivatives.



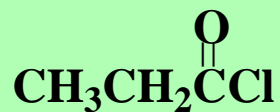
Methyl propanoate



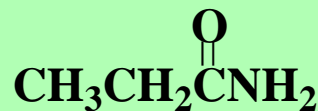
Phenyl ethanoate  
(phenyl acetate)



Ethanoic anhydride  
(acetic anhydride)



Propanoyl chloride



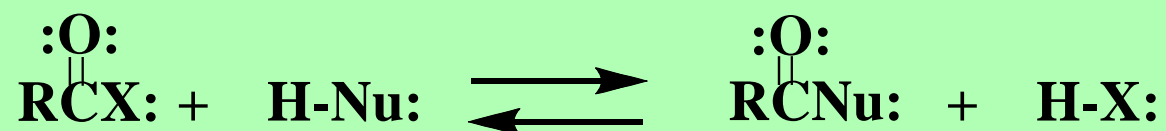
Propanamide



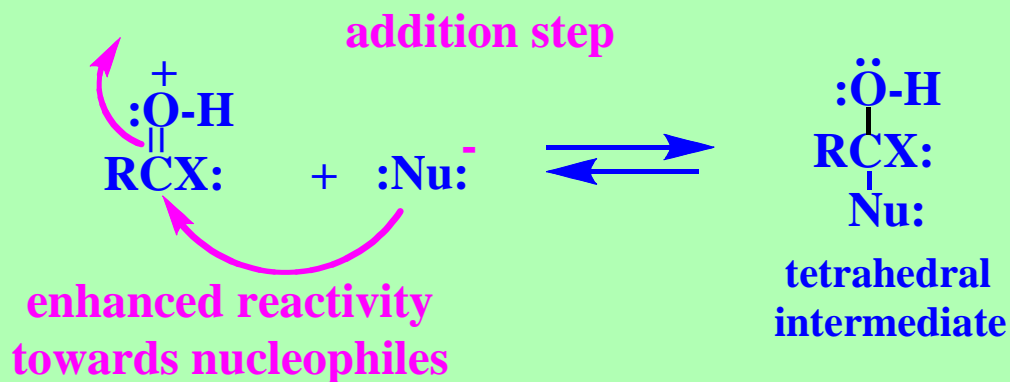
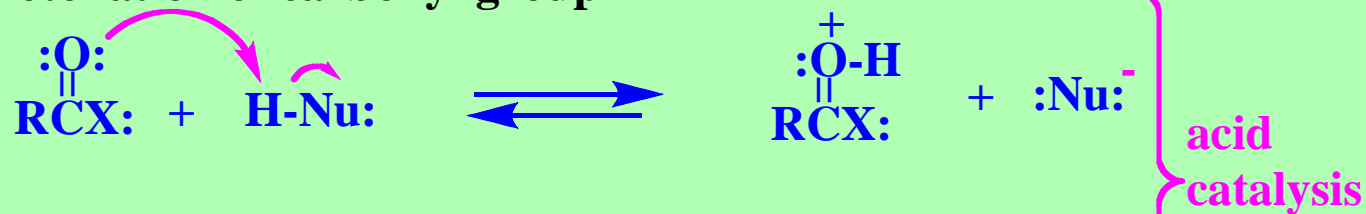
Propanenitrile

## Quiz 18.05

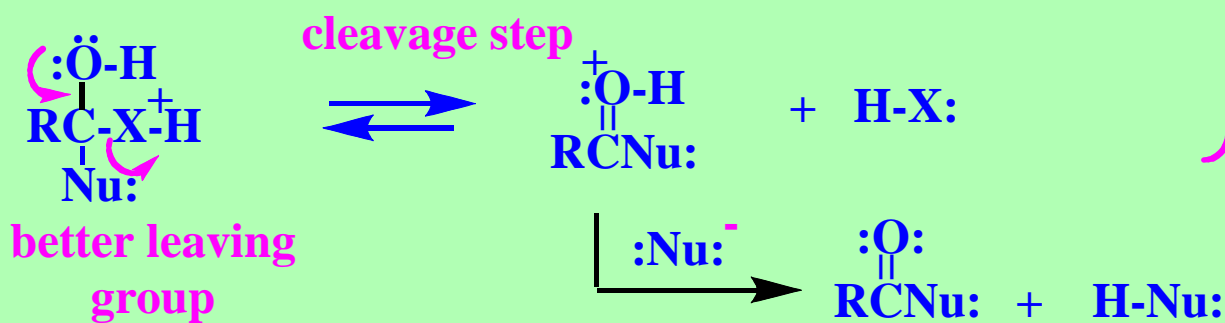
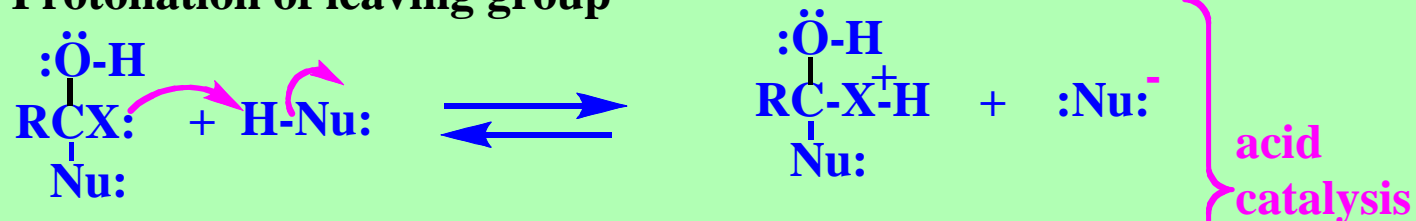
Acid catalysis is important in nucleophilic addition-elimination at acyl carbon. Sketch the general mechanism for this reaction, indicating where the catalysis occurs.



### Protonation of carbonyl group

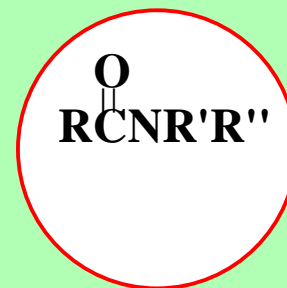


### Protonation of leaving group



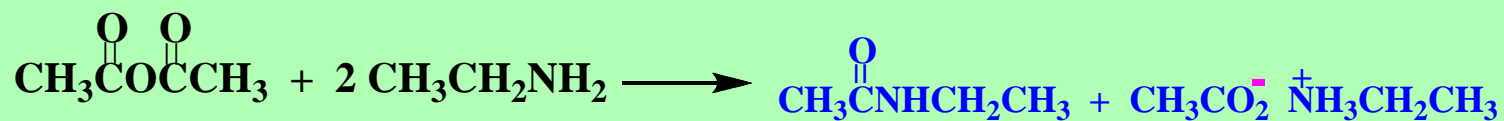
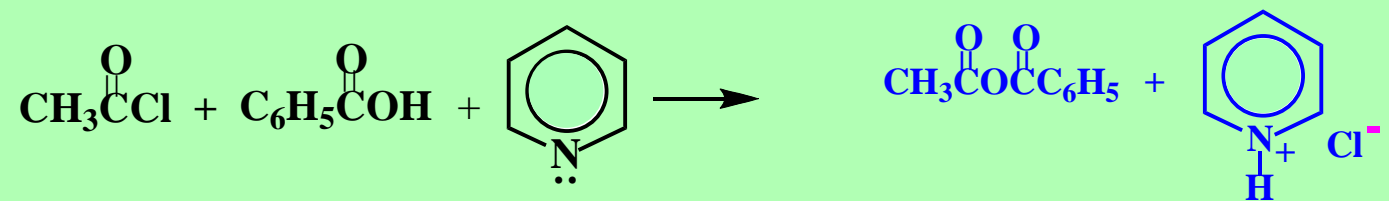
Quiz 18.06

Circle the least reactive acid derivative among those below.



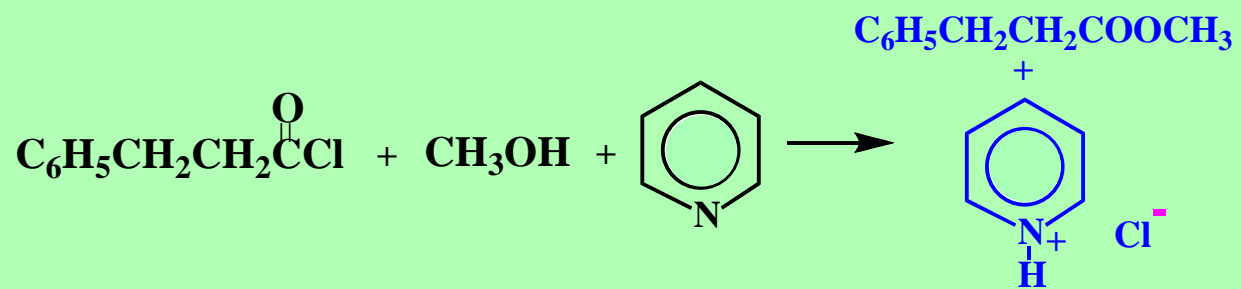
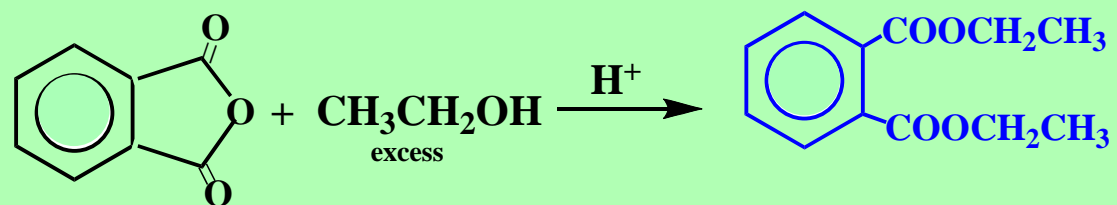
### Quiz 18.07

Draw the structures of the products of the following reactions.



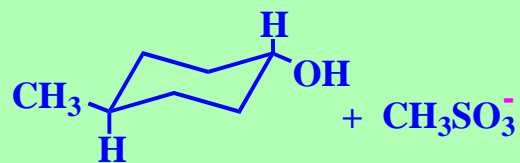
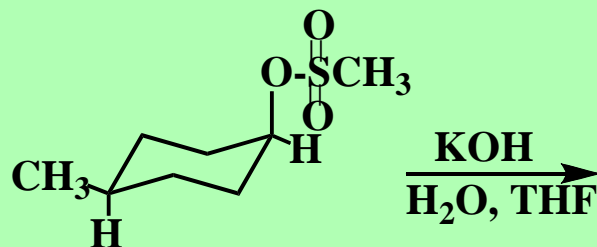
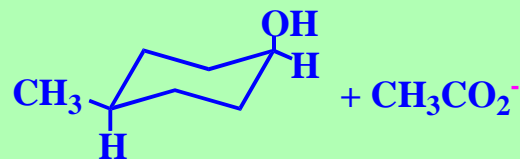
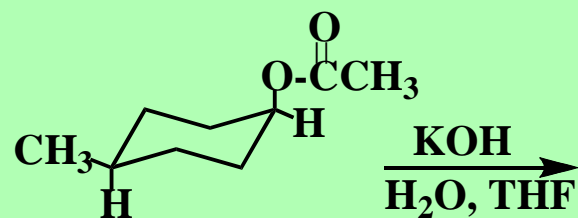
### Quiz 18.08

Draw the structures of the products of the following reactions.



### Quiz 18.09

Draw the structures of the products of the following alkaline hydrolysis reactions.



## Quiz 18.011

Design a two-step synthesis of (*R*)-2-methylbutanoic acid from (*S*)-2-bromobutane.

