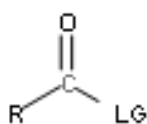


## Ch 21 Carboxylic Acid Derivatives and Nu Acyl Subst'n

### Acid Derivatives and their Names

- Acid Halides have a Cl or Br instead of OH.  
Replace "ic acid" with "yl halide", such as propionyl chloride (a common name) and propanoyl bromide (a systematic name).  
Replace "carboxylic acid" with "carbonyl halide", such as benzenecarbonyl chloride.
- Acid Anhydrides are two acid molecules condensed into one by dehydration.  
If the anhydride is symmetrical (both carbonyl groups are the same), replace "acid" with "anhydride", such as acetic anhydride.  
If unsymmetrical, put the two groups in alphabetical order, such as acetic benzoic anhydride.
- Esters have an alkoxy group (OR) instead of OH.  
The R is named as an alkyl group and is placed at the beginning as a separate word.  
The carbonyl group is named as a carboxylate.  
Examples include ethyl acetate, methyl propanoate, and cyclopropyl benzoate.
- Amides have an amino group, like NH<sub>2</sub>, instead of OH.  
Replace "ic acid" with "amide", such as acetamide and benzenecarboxamide.  
The N may have one or two R groups replacing H's.  
Place them at the beginning and precede them with "N-".  
Examples include N-ethylacetamide and N,N-diethylacetamide



Carboxylic Acid

LG = OH

Acid Halide

LG = Cl or Br

Acid Anhydride

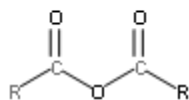
LG = O<sub>2</sub>CR (see below)

Ester

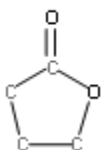
LG = OR (see also below)

Amide

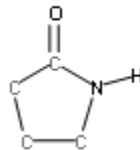
LG = NH<sub>2</sub>, NHR, or NR<sub>2</sub> (see also below)



acid anhydride



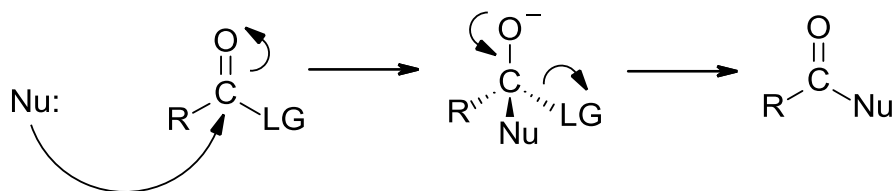
lactone  
(cyclic ester)



lactam  
(cyclic amide)

## Nu Acyl Substitution

- A bond between the carbonyl C and an atom with higher e/n (O, N, or halogen) can be broken easily. So, substituents bonded to the carbonyl C with an O, N, or halogen can act as LG's. The best LG's are stable molecules or anions.
- The first step creates an alkoxide anion and is identical to Nu addition. The Nu<sup>-</sup> attaches to the carbonyl C ( $\delta^+$ ) and changes it to sp<sup>3</sup> hybridization.
- The second step is different from Nu addition because of the leaving group. When the leaving group separates from the C, it takes the negative charge. The carbonyl  $\pi$  bond reforms at the same time, and the C reverts to sp<sup>2</sup>.
- Overall, the Nu replaces the LG.



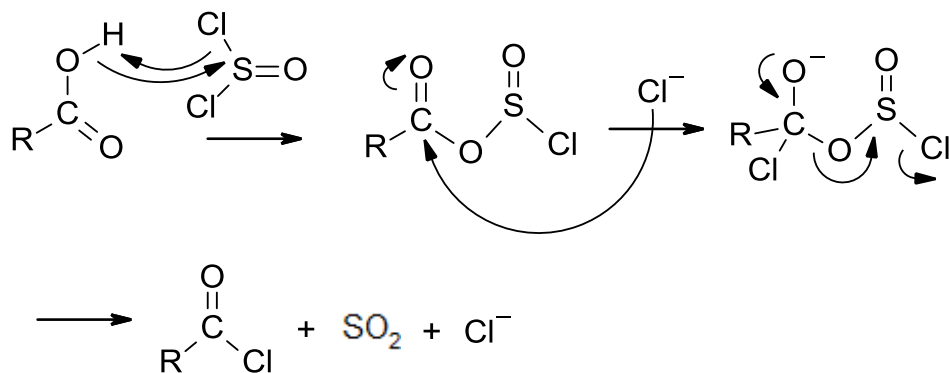
- Reactivity is highest if the LG withdraws the bonding e<sup>-</sup> pair between it and the C. This not only causes the LG to become a stable anion, but also makes the C more  $\delta^+$ , which makes the C more electrophilic. For example, acid chlorides are more reactive than amides.
- A more reactive Nu (like RO<sup>-</sup> and HO<sup>-</sup>) can replace a less reactive one (like Cl<sup>-</sup>), but not vice-versa. So, esters and amides are common in nature, but acid chlorides and anhydrides are not.

## Reactions

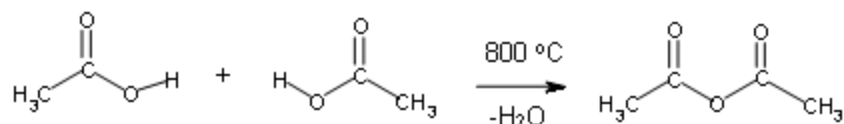
- Hydrolysis (with water) results in a carboxylic acid
- Alcoholysis (with an alcohol) results in an ester
- Aminolysis (with ammonia or an amine) results in an amide
- Reduction (with a hydride) results in an aldehyde
- Grignard (with a carbanion) results in a ketone

## Nu Acyl Substitution of Carboxylic Acids

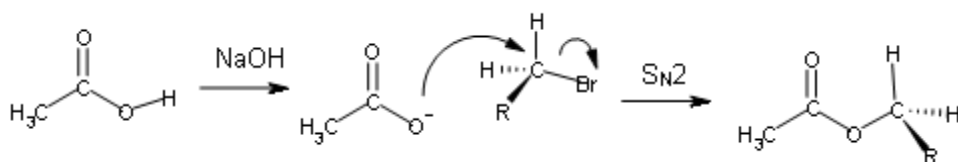
- Carboxylic acids do not undergo substitutions easily because OH is not a good LG.
- OH must often be transformed into a better LG first.
- Acids are converted to acid halides using SOCl<sub>2</sub> or PBr<sub>3</sub> to create the LG. Nu acyl substitution occurs after converting the -OH to -OSOCl or -OPBr<sub>2</sub>. (Similar to S<sub>N</sub>2 reactions of alcohols in ch 17)



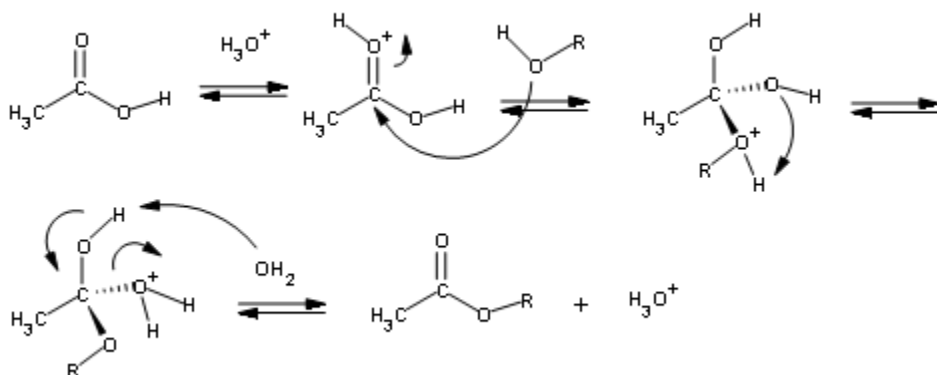
- Some acids (like acetic acid) can be dehydrated to anhydrides at 800 °C. Because of the very high temperatures though, this is not the best way to make anhydrides.



- One way to convert an acid directly into an ester is with a 1° alkyl halide. Here, the carboxylate anion acts as a Nu in an S<sub>N</sub>2 reaction.



- In the Fischer Esterification, the carbonyl O is first protonated with HCl or H<sub>2</sub>SO<sub>4</sub>. This makes the carbonyl C electrophilic enough to react with an alcohol as the Nu. All of the steps are reversible, and equilibrium is made to favor the ester by removing the product, minimizing the presence of water, and using an excess of the alcohol.

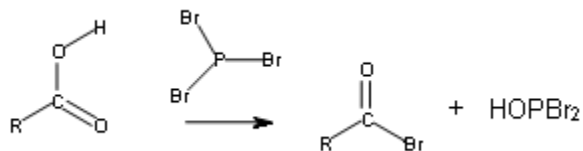


- Acids are not easily converted directly into amides because NH<sub>3</sub> and amines are bases, which deprotonate the acids. The result is an ammonium carboxylate salt, not an amide.

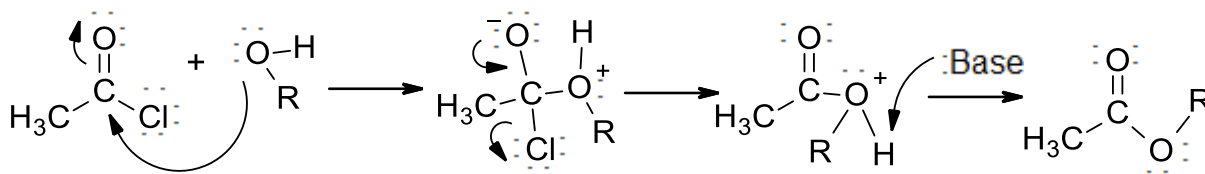


## Acid Halides

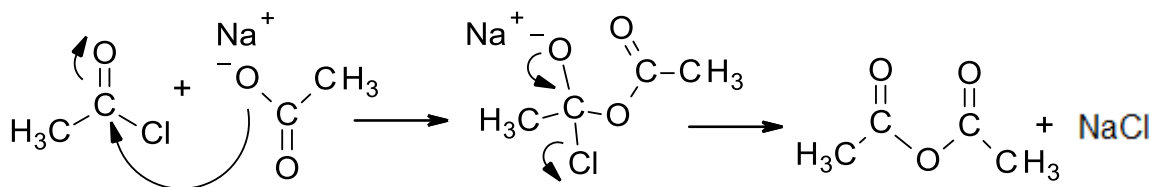
- An acid bromide can be made using  $\text{PBr}_3$ , similar to making an acid chloride with  $\text{SOCl}_2$ .



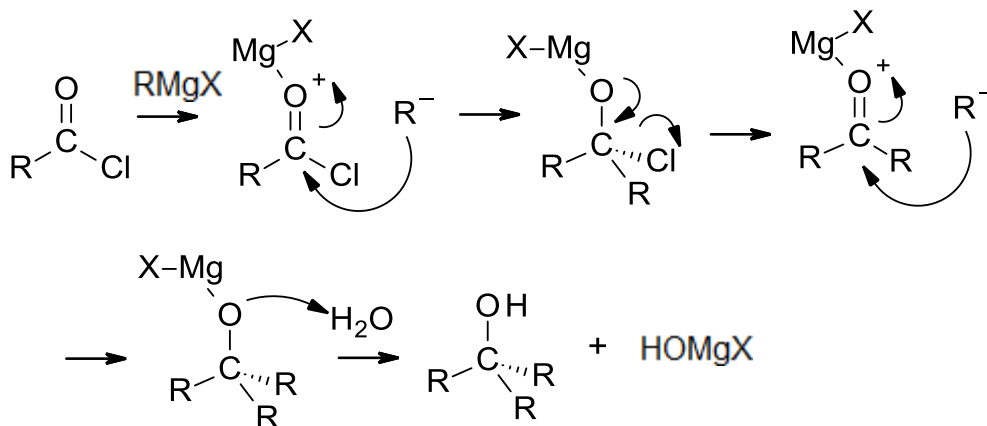
- Friedel-Crafts acylations use an acid chloride to add an acyl group ( $\text{RC=O}$ ) to an aromatic ring by Electrophilic Aromatic Substitution (ch 16). It is not exactly Nu Acyl Substitution because the  $\text{Cl}^-$  is removed first. An acyl cation ( $\text{RC}^+=\text{O} \leftrightarrow \text{RC}\equiv\text{O}^{+1}$ ) is the  $\text{E}^+$ , created from acid chloride with  $\text{AlCl}_3$ .
- Acid halides are the most reactive of acid derivatives, and undergo most Nu acyl substitution reactions easily. Hydrolysis (with water) results in a carboxylic acid, alcoholysis (with an alcohol) results in an ester, and aminolysis (with ammonia or an amine) results in an amide.



- Acid halides also undergo Nu acyl substitution with carboxylate anions to form anhydrides. This is a more efficient way to create anhydrides.



- Acid chlorides undergo reduction (violently) to  $1^\circ$  alcohols with  $\text{LiAlH}_4$  followed by  $\text{H}_3\text{O}^+$ . The first step is Nu acyl substitution to aldehyde ( $\text{H}^-$  replaces  $\text{Cl}^-$ ). Then the aldehyde quickly undergoes Nu addition (of  $\text{H}^-$ ) to form an alkoxide. Finally, the acid protonates the alkoxide to create the  $1^\circ$  alcohol.
- Acid chlorides undergo similar reactions with Grignard reagents (followed by  $\text{H}_3\text{O}^+$ ). These reactions form  $3^\circ$  alcohols. The first step, again, is Nu acyl substitution, where  $\text{R}^-$  replaces  $\text{Cl}^-$  to form a ketone. The ketone then undergoes Nu addition (of another  $\text{R}^-$ ) to form an alkoxide. Finally, acid protonates the alkoxide to create the  $3^\circ$  alcohol.

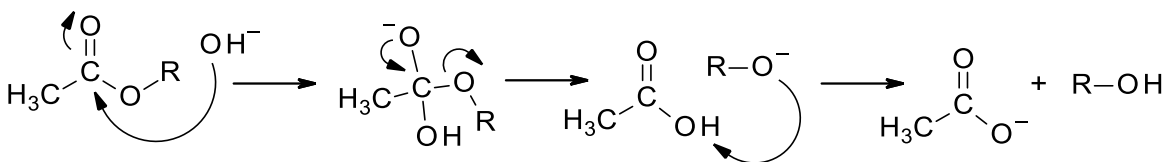


## Acid Anhydrides

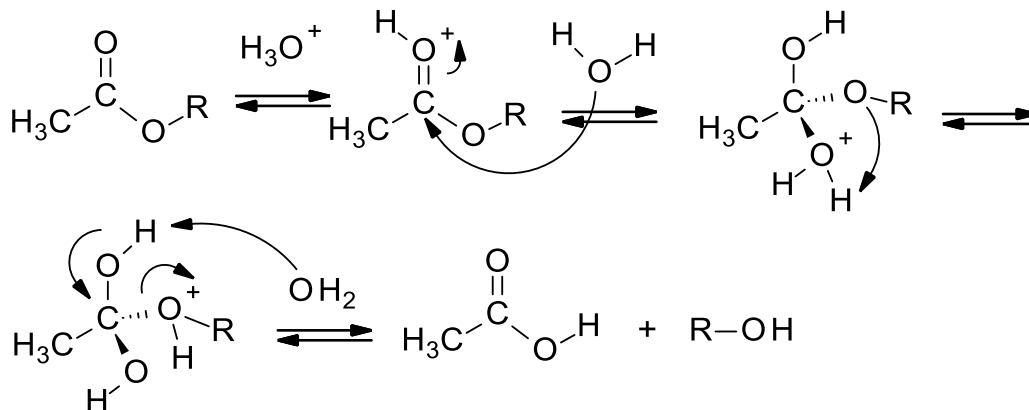
- As discussed in the acid halide section, the more efficient way to make an anhydride is with an acid chloride and a carboxylate anion. Unsymmetrical products such as acetic formic anhydride and acetic benzoic anhydride can easily be created with this method.
- The Nu acyl substitution reactions are similar to those of acid halides, only somewhat slower. Carboxylate anions are the LG's, and anhydrides can be used to create acids, esters, and amides.

## Esters

- Esters are very common, both in nature and in industry. In nature, they make up fruit and flower fragrances, as well as fats and waxy lipids. Industrially, they are frequently used as solvents and plastic additives.
- Three methods to make esters have been seen previously:
  - $S_N2$  reaction between a carboxylate anion (Nu) and a  $1^\circ$  alkyl halide
  - Fischer esterification using an acid, an alcohol, and a strong acid catalyst
  - Reaction between an acid halide and an alcohol
- Esters are less reactive than halides and anhydrides. However, they still undergo some Nu acyl substitution reactions.
- Esters undergo hydrolysis to carboxylic acids when catalyzed by acid or base. The base-catalyzed reaction has  $\text{OH}^-$  as the Nu and  $\text{OR}^-$  as the LG.



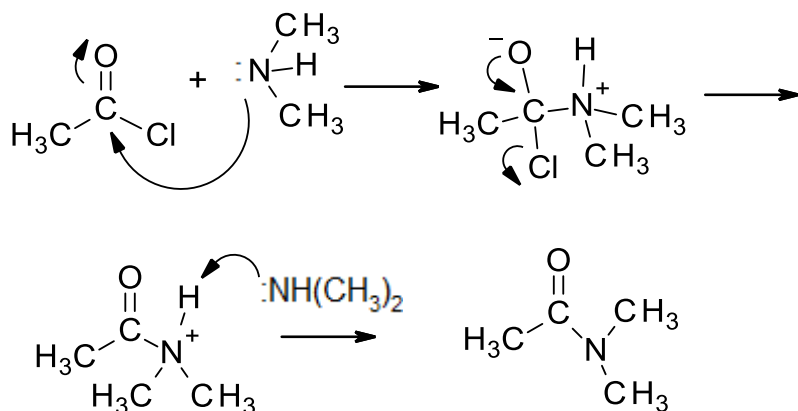
The acid-catalyzed reaction is the reverse of the Fischer esterification. It has water as the Nu and an alcohol as the LG.



- Esters undergo aminolysis to amides with  $\text{NH}_3$ ,  $\text{NH}_2\text{R}$  or  $\text{NHR}_2$  in ether.
- Esters undergo reduction to  $1^\circ$  alcohols with  $\text{LiAlH}_4$  followed by  $\text{H}_3\text{O}^+$ . Esters undergo reduction to aldehydes instead with DIBALH followed by  $\text{H}_3\text{O}^+$ .
- Esters undergo reactions with Grignard reagents (followed by  $\text{H}_3\text{O}^+$ ) to form  $3^\circ$  alcohols. As with acid halides, the intermediate is a ketone.

## Amides

- As discussed in the carboxylic acid section, amides cannot be made easily from carboxylic acids because the acids will protonate the amines, which are bases. Amides can be made much more easily from acid halides.



- Amides undergo hydrolysis to carboxylic acids when catalyzed by acid or base. The reactions are similar to the hydrolysis reactions of esters.
- Amides undergo reduction with  $\text{LiAlH}_4$  followed by  $\text{H}_3\text{O}^+$ . The products are  $1^\circ$  amines, not alcohols.

