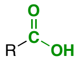
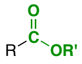
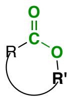
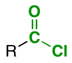
Chapter 20: Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution

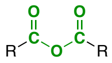
20.1: Nomenclature of Carboxylic Acid Derivatives (please read)

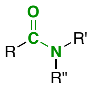

carboxylic acid
-oic acid

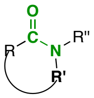

ester
-oate

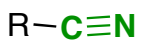

lactone
cyclic ester


acid chloride
-oyl chloride


acid anhydride
-oic anhydride

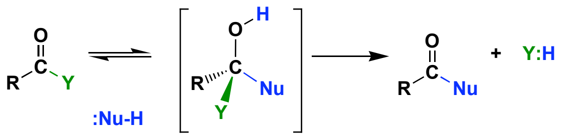

amide
-amide


lactam
cyclic amide


nitrile
-nitrile

20.3: General Mechanism for Nucleophilic Acyl Substitution

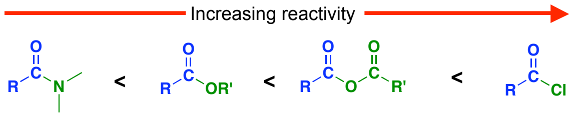
Mechanism occurs in two stages. The first is addition of the nucleophile to the carbonyl carbon to form a tetrahedral intermediate. The second stage in collapse of the tetrahedral intermediate to reform a carbonyl with expulsion of a leaving group (Y). There is overall substitution of the leaving group (Y) of the acid derivative with the nucleophile.



tetrahedral intermediate

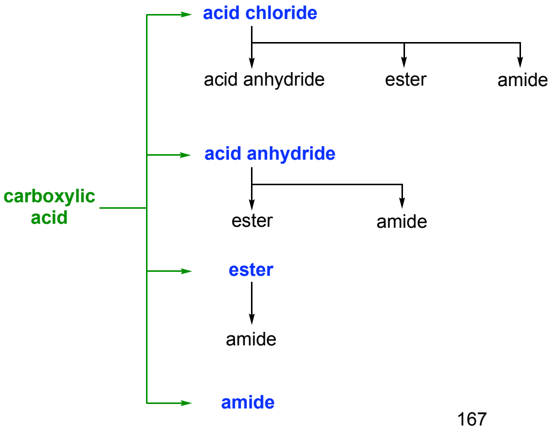
Y = a leaving group
-Cl, $-O_2CR'$, -OR', -OH, $-NR_2$,

20.2: Structure and Reactivity of Carboxylic Acid Derivatives

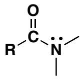


amide ester acid anhydride acid chloride

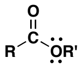
All acyl derivatives are prepared directly from the carboxylic acid. Less reactive acyl derivative (amides and esters) are more readily prepared from more reactive acyl derivatives (acid chlorides and anhydrides)



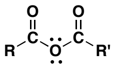
The reactivity of the acid derivative is related to it resonance stabilization. The C-N bond of amides is significantly stabilized through resonance and is consequently, the least reactive acid derivative. The C-Cl bond of acid chlorides is the least stabilized by resonance and is the most reactive acid derivative



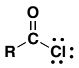
amide



ester



acid anhydride

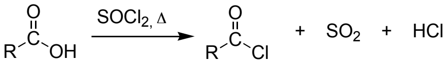


acid chloride

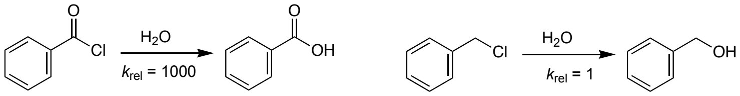
20.4: Nucleophilic Acyl Substitution in Acyl Chlorides

Preparation of acid chlorides from carboxylic acids

Reagent: **$SOCl_2$** (thionyl chloride)



Acid chlorides are much more reactive toward nucleophiles than alkyl chlorides



Nucleophilic acyl substitution reactions of acid halides

1. Anhydride formation; Acid chlorides react with carboxylic acids to give acid anhydrides

2. Alcoholysis: Acid chlorides react with alcohols to give esters. reactivity: 1° alcohols react faster than 2° alcohols, which react faster than 3° alcohols

3. Aminolysis: Reaction of acid chlorides with ammonia, 1° or 2° amines to afford amides.

4. Hydrolysis: Acid chlorides react with water to afford carboxylic acids

20.5: Nucleophilic Acyl Substitution in Acid Anhydrides
Prepared from acid chlorides and a carboxylic acid

Reactions of acid anhydrides
Acid anhydrides are slightly less reactive reactive that acid chlorides; however, the overall reactions are nearly identical and they can often be used interchangeably.

1. Alcoholysis to give esters
2. Aminolysis to give amides
3. Hydrolysis to give carboxylic acids

20.6: Sources of Esters
Preparation of esters (Table 20.3, p. 843)

1. Fischer Esterification (Ch. 15.8
2. Reaction of acid chlorides or acid anhydrides with alcohols
3. Baeyer-Villiger oxidation of ketones (Ch. 17.16)
4. SN2 reaction of carboxylate anions with alkyl halides

20.7: Physical Properties of Esters. (please read)
20.8: Reactions of Esters: A Review and a Preview.
Esters react with Grignard reagents to give tertiary alcohols.
two equivalents of the Grignard reagents adds to the carbonyl carbon. (Ch. 14.10)

Esters are reduced by $LiAlH_4$ (but not $NaBH_4$) to primary alcohols. (Ch. 15.3)

Nucleophilic acyl substitution reactions of esters (Table 20.5).
Esters are less reactive toward nucleophilic acyl substitution than Acid chlorides or acid anhydrides.

1. Aminolysis: Esters react with ammonia, 1° amd 2° amines to give amides

2. Hydrolysis: Esters can be hydrolyzed to carboxylic acids under basic conditions or acid-catalysis.

20.9: Acid-catalyzed Ester Hydrolysis. Reverse of the Fischer esterification reaction. Mechanism Fig. 20.3, p. 846-7

Protonation of the ester carbonyl accelerates nucleophic addition of water to give the tetrahedral intermediate. Protonation of The -OR’ group, then accelerates the expulsion of HOR.

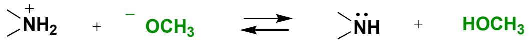
20.10: Ester Hydrolysis in Base: Saponification

Mechanism of the base-promoted hydrolysis, Fig. 20.4, p. 851

Why is the saponification of esters not base-catalyzed?

20.11: Reaction of Esters with Ammonia and Amines.

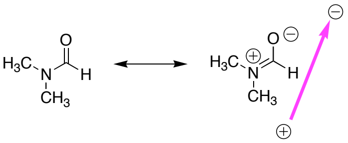
Esters react with ammonia, 1°, and 2° amines to give amides
Mechanism, Fig. 20.5, p. 853.



pK_a~ 10

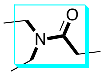
pK_a~ 16

20.12: Amides



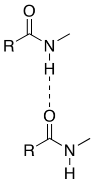
amide bond has a large
dipole moment ~ 3.5 Debye

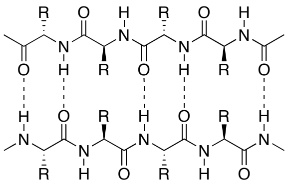
H_2O = 1.85 D
NH_3 = 1.5 D
H_3CNO_2 = 3.5



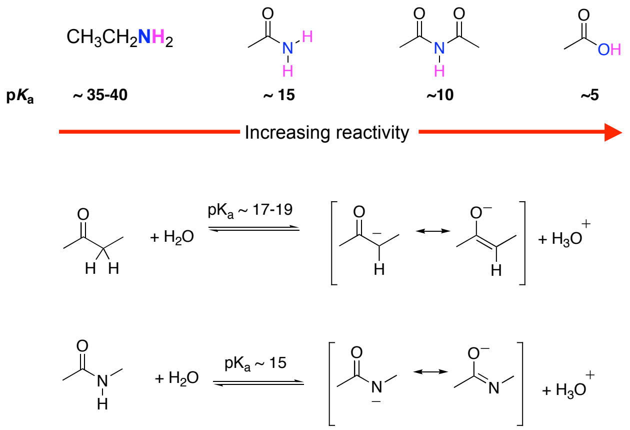
coplanar

The N-H bond of an amide is a good hydrogen bond donor and
The C=O is a good hydrogen bond acceptor.

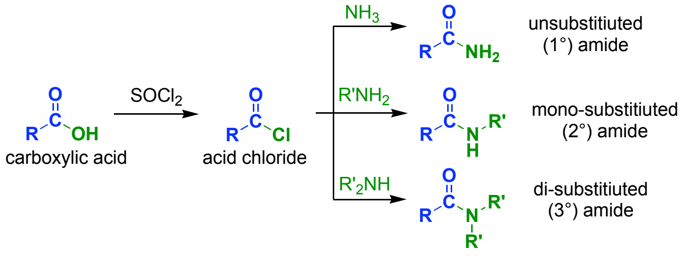




Acidity of Amides: The resulting negative charge from deprotonation of an amide N-H, is stabilized by the carbonyl

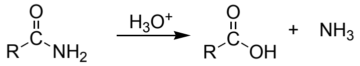


Synthesis of Amides: Amides are most commonly prepared from the reactions of ammonia, 1° or 2° amines with acids chlorides, acid anhydrides or esters. This is a nucleophilic acyl substitution reaction.

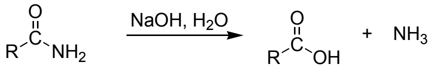


When an acid chloride or anhydride is used, a mol of acid (HCl or carboxylic acid) is produced. Since amines are bases, a second equivalent is required (or an equivalent of another base such as hydroxide or bicarbonate) is required to neutralize the acid

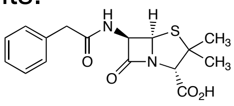
20.13: Hydrolysis of Amides. Amides are hydrolyzed to the carboxylic acids and amines
Acid-promoted mechanism (Fig. 20.6, p. 858-9)



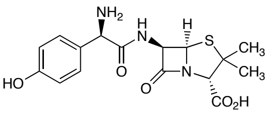
Base-promoted mechanism (Fig. 20.7, p. 860)



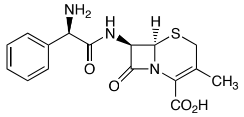
20.14: Lactams. (please read) cyclic amides
β-lactams (4-membered ring lactams) are important acti-bacterial agents.



Penicillin G



Amoxicillin



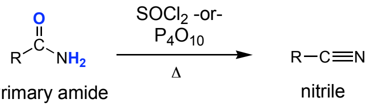
Cephalexin

20.15: Preparation of Nitriles

1. Reaction of cyanide ion with 1° and 2° alkyl halides- this is an S_N2 reaction. (see Ch. 19.12, 8.1, 8.12)

2. Cyanohydrins- reaction of cyanide ion with ketones and aldehydes. (Ch. 17.7)

3. Dehydration of primary amides with $SOCl_2$ (or P_4O_{10})

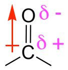


Dehydration: formal loss of H_2O from the substrate

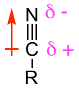
20.16: Hydrolysis of Nitriles. Nitriles are hydrolyzed in either aqueous acid or aqueous base to give carboxylic acids. The corresponding primary amide is an intermediate in the reaction.
Base-promoted mechanism (Fig. 20.8, p. 865)

Acid-promoted hydrolysis:

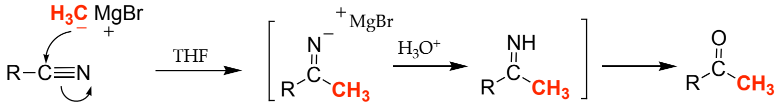
20.17: Addition of Grignard Reagents to Nitriles. One equiv. of a Grignard Reagent will add to a nitrile. After aqueous acid work-up, the product is a ketone.



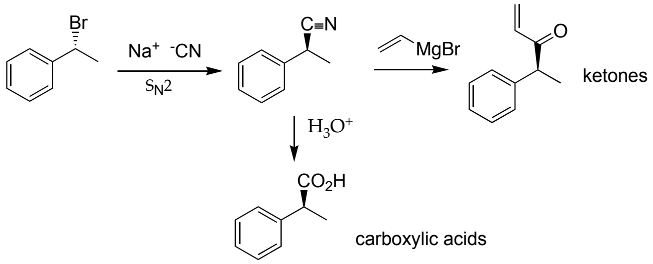
aldehydes
& ketones
μ~ 2.8 D



nitriles
μ ~ 3.9 D



Must consider functional group compatibility; there is wide flexibility in the choice of Grignard reagents.

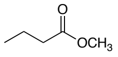


20.18: Spectroscopic Analysis of Carboxylic Acid Derivatives

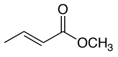
IR: typical C=O stretching frequencies for:

carboxylic acid:	1710 cm^{-1}
ester:	1735 cm^{-1}
amide:	1690 cm^{-1}
aldehyde:	1730 cm^{-1}
ketone	1715 cm^{-1}
anhydrides	1750 and 1815 cm^{-1}

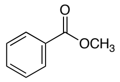
Conjugation (C=C π-bond or an aromatic ring) moves the C=O absorption to lower energy (right) by ~15 cm^{-1}



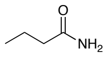
aliphatic ester
1735 cm^{-1}



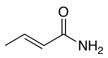
conjugated ester
1725 cm^{-1}



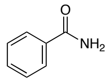
aromatic ester
1725 cm^{-1}



aliphatic amide
1690 cm^{-1}



conjugated amide
1675 cm^{-1}



aromatic amide
1675 cm^{-1}

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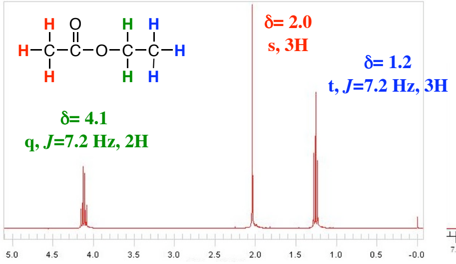
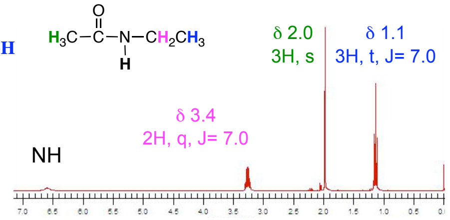
^1H NMR:

Protons on the α-carbon (next to the C=O) of esters and amides have a typical chemical shift range of δ 2.0 - 2.5 ppm

Proton on the carbon attached to the ester oxygen atom have a typical chemical shift range of δ 3.5 - 4.5 ppm

The chemical shift of an amide N-H proton is typically between 5-8 ppm. It is broad and often not observed.

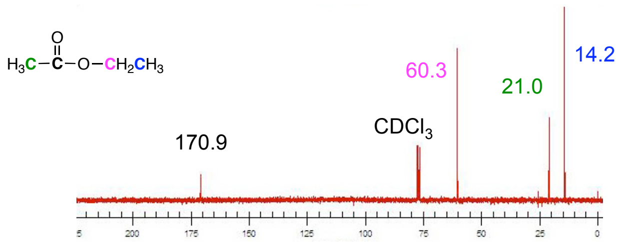


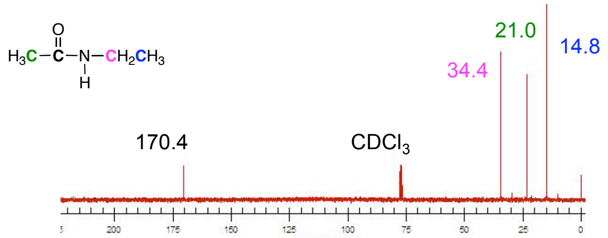


^{13}C NMR: very useful for determining the presence and nature of carbonyl groups. The typical chemical shift range for C=O carbon is δ160 - 220 ppm

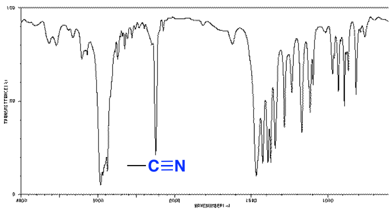
Aldehydes and ketones: δ 190 - 220 ppm

Carboxylic acids, esters and amides: δ 160 - 185 ppm

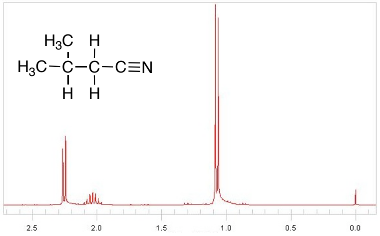




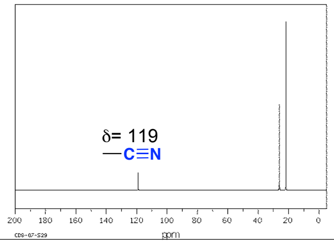
Nitriles have a sharp IR C≡N absorption near 2250 cm^{-1} for alkyl nitriles and 2230 cm^{-1} for aromatic and conjugated nitriles (highly diagnostic)

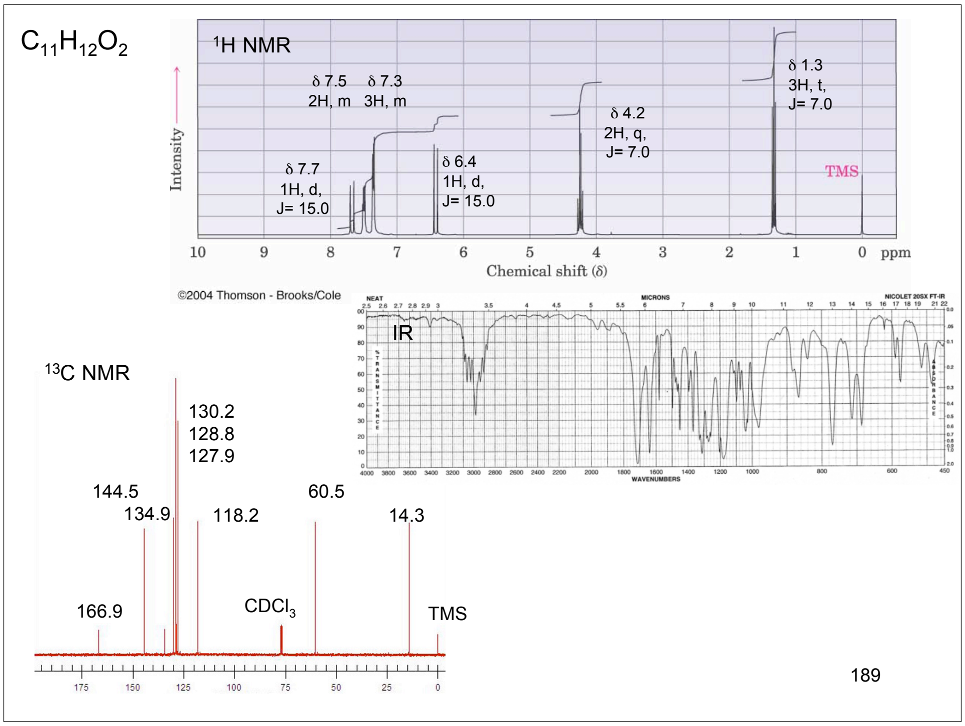


The nitrile function group is invisible in the ^{1}H NMR. The effect of a nitrile on the chemical shift of the protons on the α-carbon is similar to that of a ketone.



The chemical shift of the nitrile carbon in the ^{13}C spectrum is in the range of ~115-130 (significant overlap with the aromatic region).





$C_{11}H_{12}O_2$

^{1}H NMR

δ 7.7
1H, d,
J= 15.0

δ 7.5
2H, m

δ 7.3
3H, m

δ 6.4
1H, d,
J= 15.0

δ 4.2
2H, q,
J= 7.0

δ 1.3
3H, t,
J= 7.0

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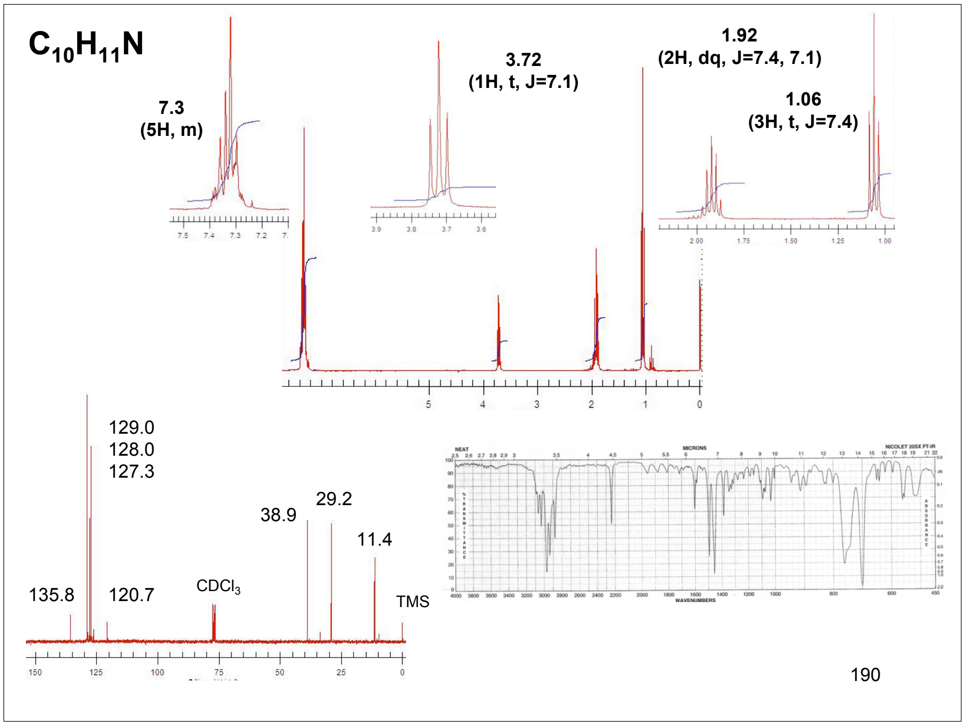
IR

^{13}C NMR

144.5
134.9
130.2
128.8
127.9
118.2
60.5
14.3
166.9
$CDCl_3$
TMS



$C_{10}H_{11}N$

**7.3
(5H, m)**

**3.72
(1H, t, J=7.1)**

**1.92
(2H, dq, J=7.4, 7.1)**

**1.06
(3H, t, J=7.4)**

129.0
128.0
127.3
38.9
29.2
11.4
135.8
120.7
$CDCl_3$
TMS