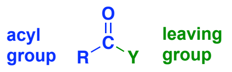
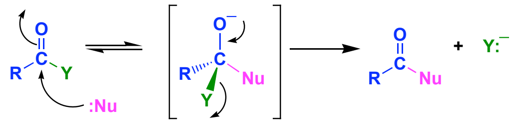
Chapter 21. Carboxylic Acid Derivatives and Nucleophilic Acyl Substitution Reactions

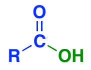


General mechanism:



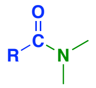
Carboxylic acid derivatives:

Increasing reactivity →

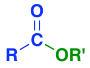


carboxylic acid

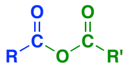
parent function group



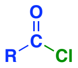
amide



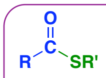
ester



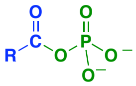
acid anhydride



acid chloride



thioester



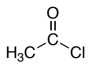
acyl phosphate

Chapter 21.8 please read

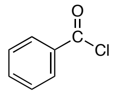
21.1 Naming Carboxylic Acid Derivatives: (Please read)

Acid Chlorides:

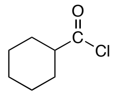
Derived from the carboxylic acid name by replacing the *-ic acid* ending with *-yl choride* or replacing the *-carboxylic acid* ending with *-carbonyl chloride*



acetyl chloride
(from acetic acid)



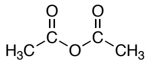
benzoyl chloride
(from benzoic acid)



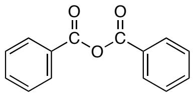
Cyclohexancarbonyl chloride
(from cyclohexane carboxylic acid)

Acid Anhydrides:

Name symmetrical anhydrides as the carboxylic acid except the word *acid* is replaced with *anhydride*



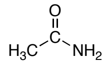
acetic anhydride



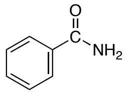
benzoic anhydride

Amides:

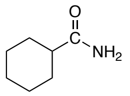
Primary amides ($RCONH_2$) are named as the carboxylic acid except the -*ic acid* ending is replaced with -*amide* or the -*carboxylic acid* ending is replaced with -*carboxamide.*



acetamide
(from acetic acid)

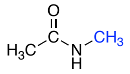


benzamide
(from benzoic acid)

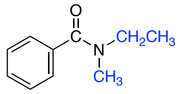


Cyclohexancarboxamide
(from cyclohexane carboxylic acid)

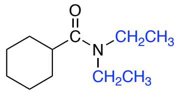
Substituted amides are named by first identifying the substituent(s) with an *N*- in front of it, then naming the parent amide



N-methylacetamide



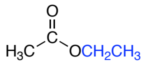
N-ethyl-*N*-methylbenzamide



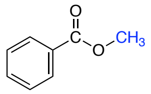
N,N-diethylcyclohexancarboxamide

Esters:

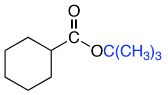
Esters are named by first identify the group on the carboxylate oxygen, then identifying the carboxylic acids and replacing the -*oic acid* with -*ate*.



ethyl acetate

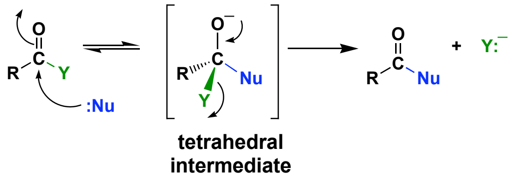


methyl benzoate



tert-butylcyclohexancarboxylate

21.2 Nucleophilic acyl substitution reactions



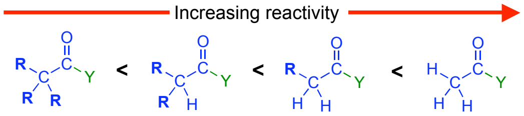
Y = a leaving group
-OH, -OR’, $-NR_2$, -Cl,
$-O_2CR'$, -SR’,$-OPO_3^{2-}$

Relative reactivity of carboxylic acid derivatives:

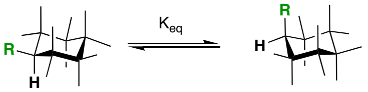
The mechanism of nucleophilic acyl substitution involves two critical steps that can influence the rate of the overall reaction: 1) the initial addition to the carbonyl groups, and 2) the elimination of the leaving group.

The nature of the acyl group:

The rate of addition to the carbonyl carbon is slower as the steric demands of the R group increase. Branching at the α-carbon has the largest effect.



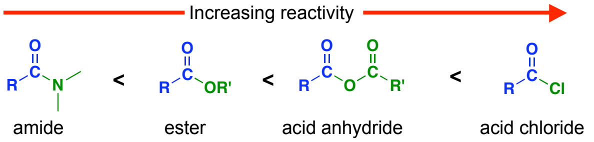
Recall from Chapter 4:



-CH_3	ΔG°=	7.6 KJ/mol
-CH_2CH_3		8.0
-$CH(CH_3)_2$		9.2
-$C(CH_3)_3$		> 18
-$CH_2C(CH_3)_3$		8.4
-C_6H_5		12.6

Nature of the leaving group (**Y**):

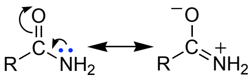
In general, the reactivity of acyl derivatives correlate with leaving group ability.



What makes a good leaving group?

	R'_2N-H	R'O-H	$R'CO_2$-H	Cl-H
pK_a:	30-40	16-18	4-5	-7

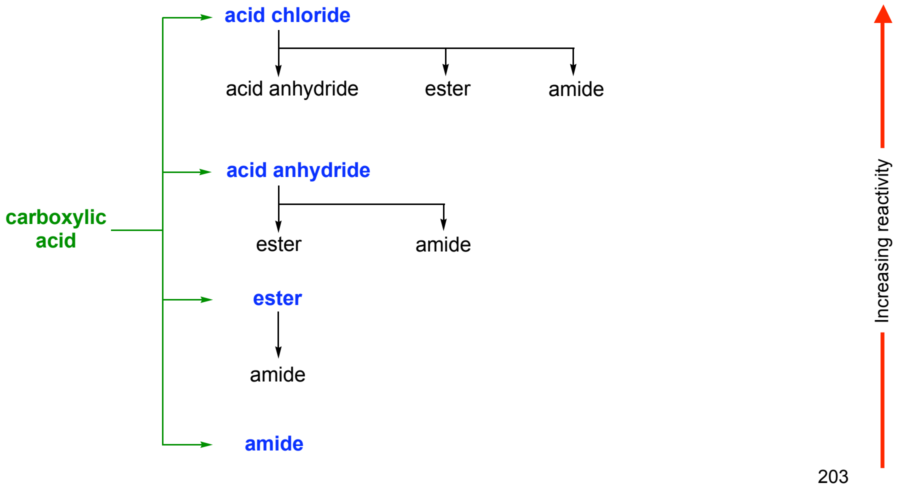
The reactivity of the acyl derivative inversely correlates with their resonance electron-donating ability



Resonance effect of the Y atom reduces the electrophilicity of the carbonyl carbon.
Partial double bond character of the C-N bond makes it harder to break.

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)



carboxylic acid

acid chloride

acid anhydride

ester

amide

acid anhydride

ester

amide

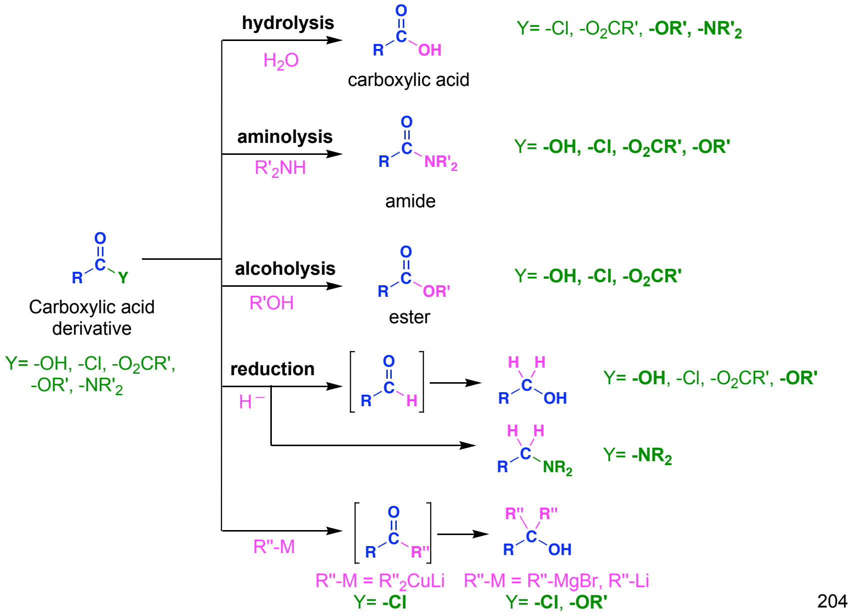
ester

amide

amide

Increasing reactivity

Nucleophilic acyl substitution reactions

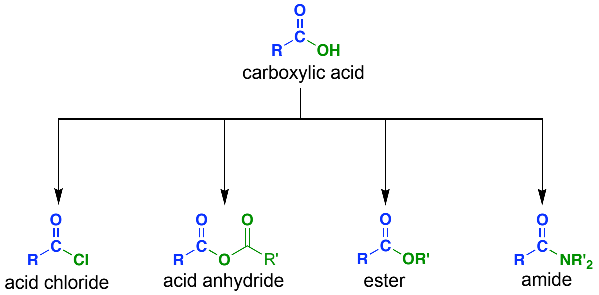


21.3 Nucleophilic acyl substitution reactions of carboxylic acids

Nucleophilic acyl substitution of carboxylic acids are slow because -OH is a poor leaving group

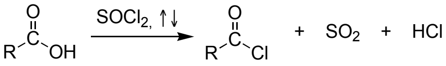
Reactivity is enhanced by converting the -OH into a better leaving groups

However, acid chlorides, anhydrides, esters and amides can be prepared directly from carboxylic acids



Conversion of carboxylic acids into acid chlorides

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



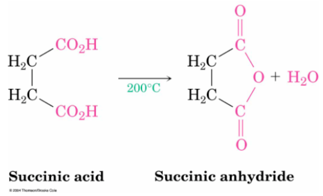
Recall the conversion of 1° and 2° alcohols to alkyl chlorides

Mechanism (p. 780), please read

Conversion of carboxylic acids into acid anhydrides (please read)

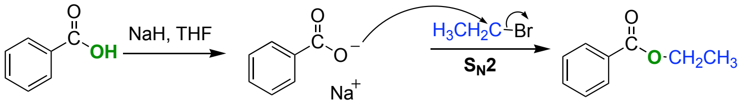
Reagent: heat

Reaction is best for the preparation of cyclic anhydrides from di-carboxylic acids



Conversion of carboxylic acids into esters

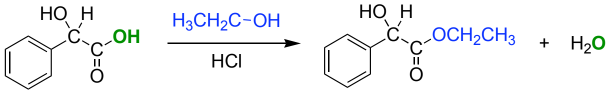
1. Reaction of a carboxylate salt with 1° ~~or 2°~~ alkyl halides
   Reagents: NaH, R'-X, THF



Note the similarity to the Williamson ether synthesis (Chapter 18.3)

Conversion of carboxylic acids into esters

2. Fisher esterification reaction: acid-catalyzed reaction of carboxylic acids with 1° or 2° alcohols to give esters
   Reagents: ROH (usually solvent), HCl (strong acid)



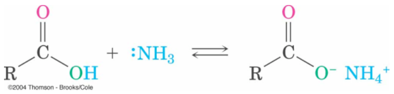
Mandelic acid

Ethyl mandelate

Mechanism: (Fig. 21.5, p. 782)

Conversion of carboxylic acids into amides
Not a particularly good reaction for the preparation of amides.

Amines are organic bases; the major reaction between a carboxylic acid and an amine is an acid-base reaction (proton transfer)



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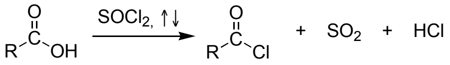
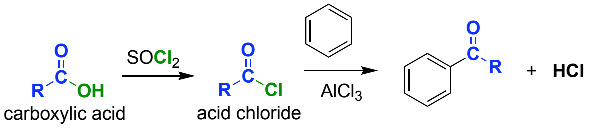
21.4: Chemistry of Acid Halides

Preparation of acid halides (Chapter 21.3)
Reaction of a carboxylic acid with thionyl chloride ($SOCl_2$)



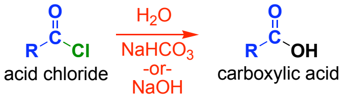
Reactions of acid halides

Friedel-Crafts acylation (Chapter 16.4): reaction of an acid chloride with a benzene derivative to give an aryl alkyl ketone.

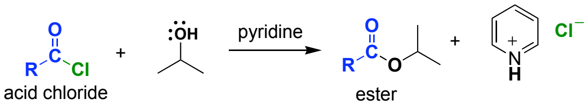


Nucleophilic acyl addition reactions of acid halides

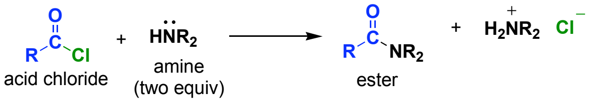
1. hydrolysis



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

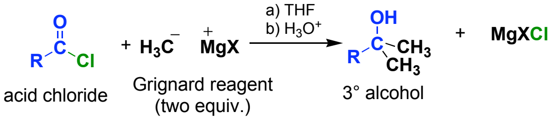


3. Aminolysis: Reaction of acid chlorides with ammonia, 1° or 2° amines gives amides.

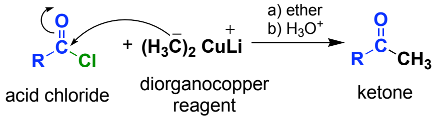


4. Reduction: Acid chlorides are reduced to primary alcohols with lithium aluminium hydride ($LiAlH_4$)

5. Reaction of acid chlorides with organometallic reagents: Reacts with two equivalents of a Grignard reagent to give a 3° alcohols (recall reaction with esters)

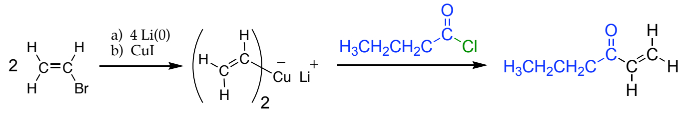


Reaction of acid halides with diorganocopper reagents

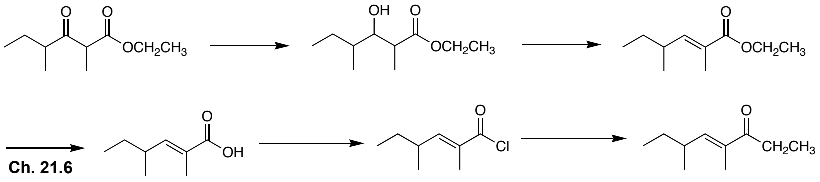


Mechanism (page 787), not typical, specific to diorganocopper reagents. please look it over if you like

Diorganocopper reagent can be alkyl, aryl or vinyl

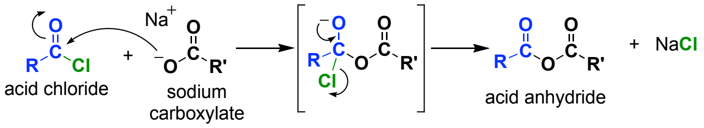


Fill in the reagents:



21.5 Chemistry of acid anhydrides

Preparation of acid anhydrides



Reactions of acid anhydrides

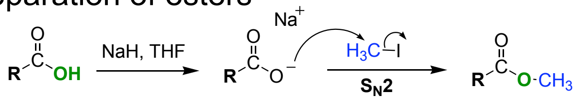
Acid anhydrides are slightly less reactive reactive that acid chlorides; however, the overall reactions are nearly identical and they can often be used interchangeably.

They do not react with diorganocopper reagents to give ketone

21.6 Chemistry of esters

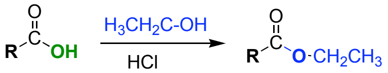
Preparation of esters

1.



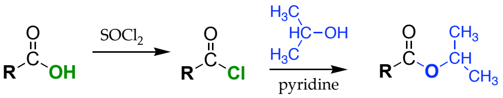
Limited to 1° alkyl halides
and tosylates

2.



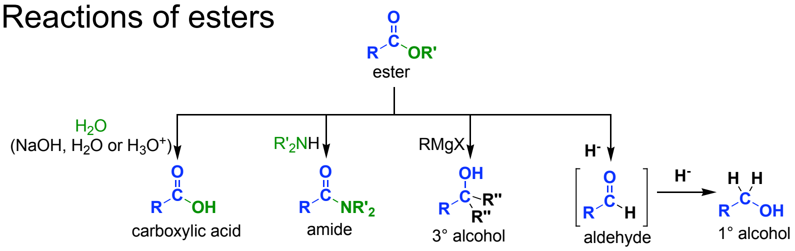
Limited to simple 1° and 2°
alcohols (used as solvent)

3.



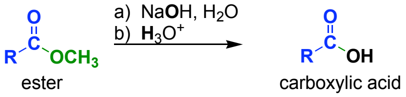
Very general method, 1°, 2° and
3° alcohols usually work fine

Reactions of esters

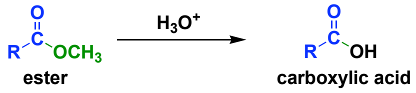


Hydrolysis of esters: esters can be hydrolyzed to the carboxylic acids with aqueous hydroxide (saponification) or aqueous acid.

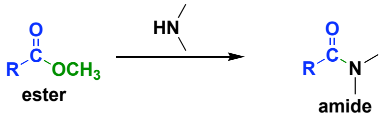
Mechanism of the base-promoted hydrolysis (Figure 21.9)



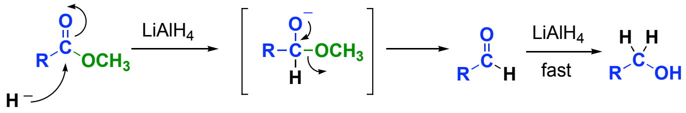
Acid-catalyzed hydrolysis of esters (Figure 21.10, p. 793)
(reverse of the Fischer esterification)



Aminolysis: Conversion of esters to amides

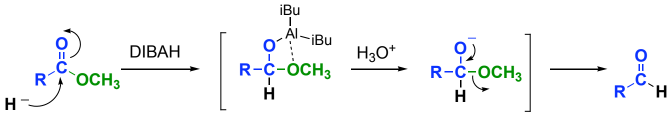


Reduction of esters
LiAlH$_4$ reduces esters to primary alcohols



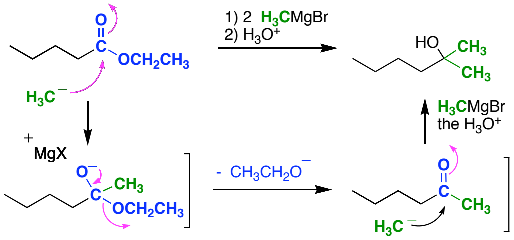
Reduction of esters

Diisobutylaluminium hydride (DIBAH) can reduce an ester to aldehyde



Esters do not react with $NaBH_4$ or BH_3

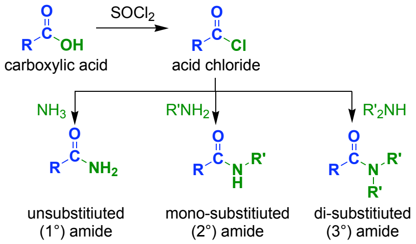
Reaction of esters with Grignard reagents: Esters will react with two equivalents of a Grignard reagent to give 3° alcohols



The Grignard reagent can be alkyl, vinyl or aryl

21.7 Chemistry of Amides

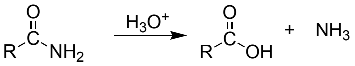
Preparation of amides: amides are prepared from the reaction of an acid chloride with ammonia, 1° or 2° amines



Reactions of amides: Amides bonds are very stable do to resonance between the nitrogen lone pair and the π-bond of the carbonyl

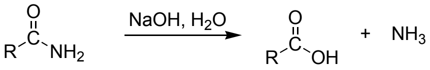
Hydrolysis- Amides are hydrolyzed to the carboxylic acids and amine with either aqueous acid or aqueous hydroxide.

Acid promoted mechanism:



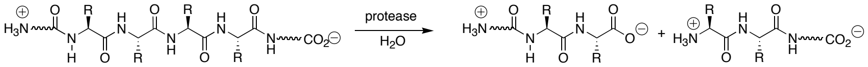
$$R\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{H_3O^+} R\overset{O}{\overset{\|}{C}}OH + NH_3$$

Base promoted mechanism



$$R\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{NaOH,\ H_2O} R\overset{O}{\overset{\|}{C}}OH + NH_3$$

Proteases: catalyzes the hydrolysis of amide bonds of peptides



Asp–Arg–Val–Tyr–Ile–His–Pro–Phe–His–Leu–Val–Ile–His–Asn

angiotensinogen

aspartyl protease ↓ renin

Asp–Arg–Val–Tyr–Ile–His–Pro–Phe–His–Leu

angiotensin I

(little biological activity)

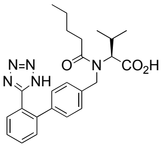
Zn^{2+} protease ↓ angiotensin converting enzyme (ACE)

Asp–Arg–Val–Tyr–Ile–His–Pro–Phe

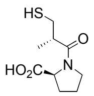
angiotensin II

(vasoconstriction → high blood pressure)

ACE inhibitors



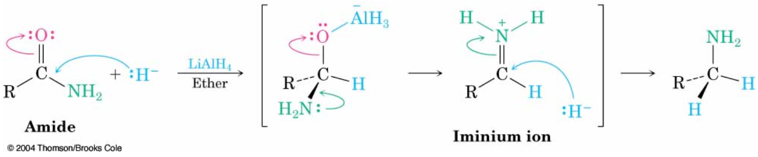
Diovan



Captopril

Reduction of amides to primary amines: amides can be reduced by $LiAlH_4$ or BH_3 (but not $NaBH_4$) to give primary amines

Mechanism:



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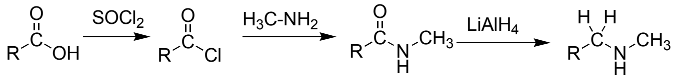


21.8 Thioesters and Acyl Phosphates: Biological Carboxylic AcidDerivatives (please read)

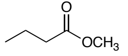
21.9 Polyamides and Polyesters: Step-Growth Polymers (please read)

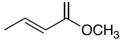
21.10 Spectroscopy of Carboxylic Acid Derivatives

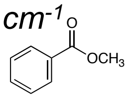
IR: typical C=O stretching frequencies for:

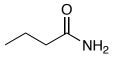
carboxylic acid: 1710 cm^{-1}
ester: 1735 cm^{-1}
amide: 1690 cm^{-1}
aldehyde: 1730 cm^{-1}
ketone 1715 cm^{-1}

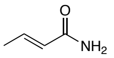
Conjugation (C=C π-bond or an aromatic ring) moves the C=O absorption to lower energy (right) by ~15 cm^{-1}

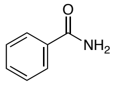

aliphatic ester
1735 cm^{-1}


conjugated ester
1725 cm^{-1}


aromatic ester
1725 cm^{-1}


aliphatic amide
1690 cm^{-1}

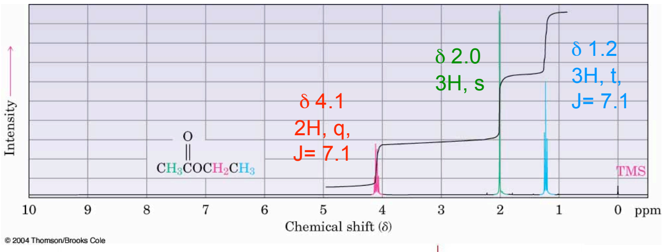

conjugated amide
1675 cm^{-1}


aromatic amide
1675 cm^{-1}

^{1}H 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



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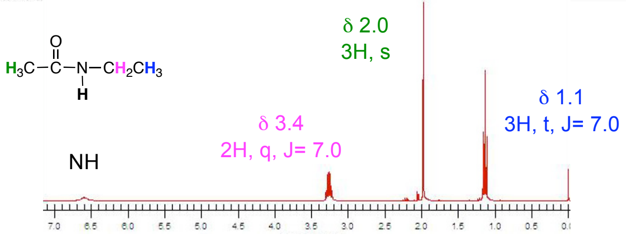
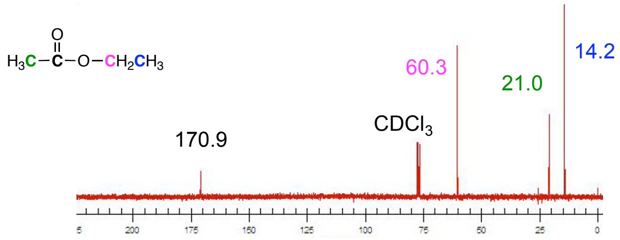
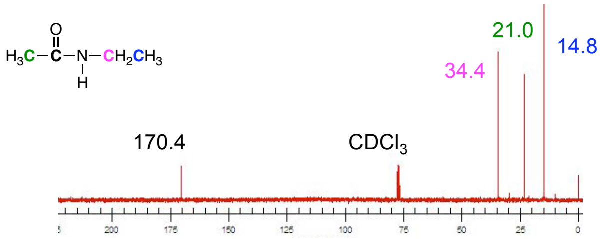


^{13}C NMR: very useful for determining the presence and nature of carbonyl groups. The typical chemical shift range for C=O carbon is δ160 - 220 ppm

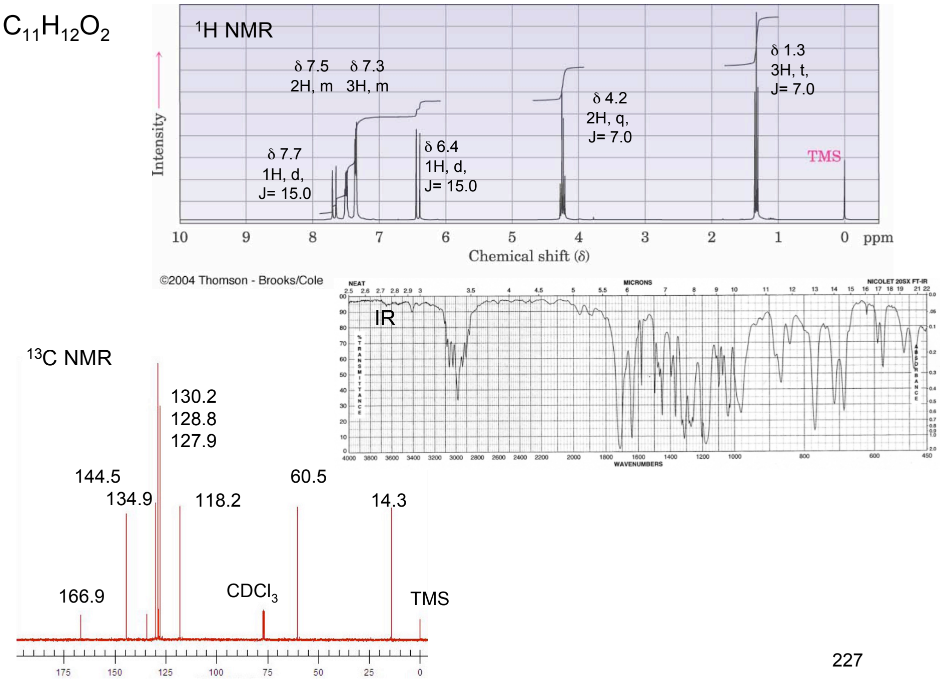
Aldehydes and ketones: δ 190 - 220 ppm

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





$C_{11}H_{12}O_2$



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