Chem Factsheet

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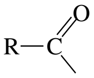
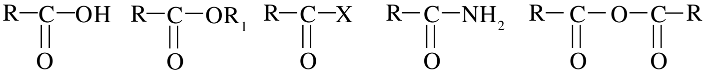
Acylation

Acylation is the introduction of an acyl group into a molecule.



An **acyl group** is an alkyl group, R, [e.g. methyl (CH_3-), ethyl (CH_3CH_2-)] or aryl group [e.g. phenyl (C_6H_5-)] bonded to a carbon atom which is doubly bonded to an oxygen atom. The carbon atom is called an *acyl carbon atom*.

The organic compounds containing acyl groups include carboxylic acids and their derivatives as shown below.

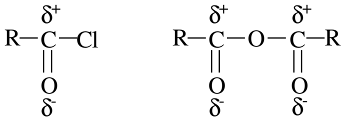


$$R-\underset{\underset{O}{\|}}{C}-OH \qquad R-\underset{\underset{O}{\|}}{C}-OR_1 \qquad R-\underset{\underset{O}{\|}}{C}-X \qquad R-\underset{\underset{O}{\|}}{C}-NH_2 \qquad R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R$$

Carboxylic acids | Esters | Acyl halides (X = halogen) | Amides | Acid anhydrides

An **acylating agent** is a compound used to introduce an acyl group into another molecule.

The most common acylating agents are *acyl chlorides* and *acid anhydrides*.



$$R-\overset{\delta^+}{\underset{\underset{\underset{\delta^-}{O}}{\|}}{C}}-Cl \qquad R-\overset{\delta^+}{\underset{\underset{\underset{\delta^-}{O}}{\|}}{C}}-O-\overset{\delta^+}{\underset{\underset{\underset{\delta^-}{O}}{\|}}{C}}-R$$

Both of these acylating agents have electron deficient (δ^+) acyl carbon atoms due to being bonded to electron withdrawing atoms / groups (O and Cl). Hence this carbon atom is susceptible to attack by a *nucleophile*.

Why acylations are important?.
Due to the high chemical reactivities of acylating agents, acyl groups are readily introduced into many different types of molecule and the products can then be converted into further types of molecule. Thus acylation reactions are an important step in *synthesis*. (See later.)

1. Preparation of acyl chlorides from carboxylic acids

Acyl chlorides may be prepared by adding phosphorus(V) chloride (phosphorus pentachloride) to the appropriate carboxylic acid at room temperature. Faint white fumes due to the evolution of hydrogen chloride are seen.

$$RCOOH(l) + PCl_5(s) \rightarrow RCOCl(l) + POCl_3(s) + HCl(g)$$

e.g. Ethanoyl chloride may be prepared from ethanoic acid.

$$CH_3COOH(l) + PCl_5(s) \rightarrow CH_3COCl(l) + POCl_3(s) + HCl(g)$$

2. Chemical reactions of acyl chlorides that produce compounds containing acyl groups.

Acyl chlorides react very rapidly at room temperature with water, alcohols, concentrated ammonia and amines forming carboxylic acids, esters, amides and N-substituted amides respectively.

> Note: The "*N*" in *N*-substituted amides denotes the fact that a hydrocarbon group (R_2) is bonded to the nitrogen atom of the amide.
> Amide = R_1CONH_2 but *N*-substituted amide = R_1CONHR_2

In each case a hydrogen atom on the reacting molecule (the nucleophile) is replaced by an acyl group (RCO-). Thus, overall, substitution has occurred and, because an acyl group has been introduced, the reaction is called acylation with the acyl chloride acting as the acylating agent.

> Note: Even though this is a substitution reaction overall and involves a nucleophile, the mechanism **is not** referred to as a nucleophilic substitution! It is called *nucleophilic addition-elimination* since experiment shows it to be a nucleophilic-addition followed by elimination. (See below.)

In all these reactions hydrogen chloride gas is produced and, if this is released into the air [cases a) and b) below], faint white fumes are seen as the result of it reacting with water vapour in the air. However when a base is reacting with the acyl chloride [cases c) and d) below] a dense white smoke is formed. This is the salt of the base with HCl.

a) Acylation of water produces a *carboxylic acid*, RCOOH.
$RCO\mathbf{Cl} + \mathbf{H}OH \rightarrow RCOOH + \mathbf{HCl}$ (White fumes)

e.g. Ethanoyl chloride yields ethanoic acid.

$$CH_3CO\mathbf{Cl}(l) + \mathbf{H}OH(l) \rightarrow CH_3COOH(l) + \mathbf{HCl}(g)$$

Note. The CH_3CO- is an ethanoyl group. Hence the reaction may be called an *ethanoylation*.

b) Acylation of an alcohol produces a sweet smelling *ester*, R_1COOR_2.
$R_1CO\mathbf{Cl} + R_2O\mathbf{H} \rightarrow R_1COOR_2 + \mathbf{HCl}$ (White fumes)

e.g. Benzoyl chloride and ethanol produce ethyl benzoate.

$$C_6H_5CO\mathbf{Cl}(l) + CH_3CH_2O\mathbf{H}(l) \rightarrow C_6H_5COOCH_2CH_3(l) + \mathbf{HCl}(g)$$

Note. The C_6H_5CO- is a benzoyl group. Hence the reaction may be called a *benzoylation*.

c) Acylation of concentrated ammonia produces an *amide*, $RCONH_2$.
$RCO\mathbf{Cl} + \mathbf{H}NH_2 \rightarrow RCONH_2 + \mathbf{HCl}$

This is followed by: $HCl + NH_3 \rightarrow NH_4^+Cl^-(s)$ giving a dense white smoke.
e.g. Methanoyl chloride yields methanamide.

$$HCO\mathbf{Cl}(l) + \mathbf{H}NH_2(aq) \rightarrow HCONH_2(l) + \mathbf{HCl}(g)$$

d) Acylation of primary amine produces an *N-substituted amide* (a secondary amide).
$R_1CO\mathbf{Cl} + \mathbf{H}NHR_2 \rightarrow R_1CONHR_2 + \mathbf{HCl}$

Followed by: $HCl + R_2NH_2 \rightarrow [R_2NH_3^+]Cl^-(s)$ giving a dense white smoke.

e.g. 1. Propanoyl chloride and methylamine yield *N*-methylpropanamide.

$$C_2H_5CO\mathbf{Cl}(l) + \mathbf{H}NHCH_3(g) \rightarrow C_2H_5CONHCH_3(l) + \mathbf{HCl}(g)$$

e.g. 2. Ethanoyl chloride and phenylamine yield *N*-phenylethanamide.

$$CH_3CO\mathbf{Cl}(l) + \mathbf{H}NHC_6H_5(l) \rightarrow CH_3CONHC_6H_5(s) + \mathbf{HCl}(g)$$

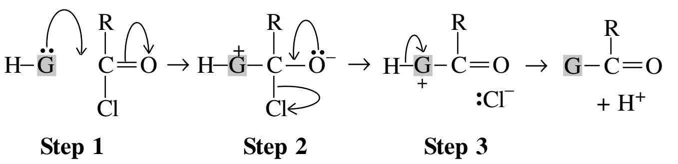
Summary
All these reactions fit the following general format
$RCO\mathbf{Cl} + \mathbf{HG} \rightarrow RCOG + \mathbf{HCl}$

where G = -OH in water, -OR in an alcohol, $-NH_2$ in ammonia and –NHR in an amine.

Note. The reactions are often done in the presence of a base such as NaOH (or pyridine) to remove the HCl. This prevents escape of the corrosive gas and also prevents it from causing side reactions.

3. The nucleophilic addition–elimination reaction mechanisms for acyl chlorides

Step 1: Nucleophilic *addition*.
The nucleophile (H-G where G = OH, OR, NH_2 or NHR) uses a lone pair of electrons to form a dative bond to the electron deficient carbon atom of the carbonyl group and one of the pairs of the electrons of the double bond (the π-electrons) moves on to the oxygen atom.



Step 2. Loss of Cl^- and reforming of the C=O bond

Step 3. Loss of H^+.

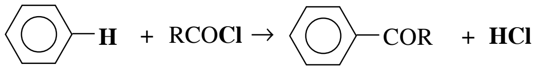
Steps 2 and 3 together are the *elimination* of hydrogen chloride.

4. Friedel-Crafts Acylation of Benzene using an Aluminium Chloride Catalyst

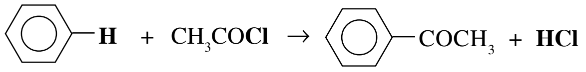
Charles Friedel (1832-1899) was born in Strasbourg, France. He was among the first to attempt to make synthetic diamonds.

James Mason Crafts (1839-1917) was born in Boston, Massachusetts, USA. He was the first professor of chemistry at Cornell University, but the winters were too cold for him so he went back

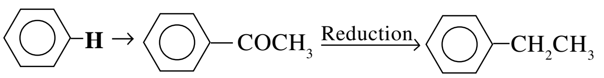
Here, an acyl chloride reacts with benzene at 40^{0}C in the presence of an *anhydrous* aluminium chloride catalyst to form a phenyl ketone and hydrogen chloride. i.e. an acyl group (RCO-) substitutes a hydrogen atom in benzene.

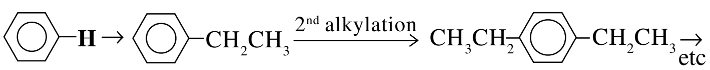


e.g. Ethanoyl chloride reacts to form phenylethanone (m.p.19-20^{0}C) and hydrogen chloride.



Note: Only one ethanoyl group enters the ring since the ketone formed is less reactive than benzene. Thus, to synthesis *ethyl benzene*, the two step sequence is better than the single step Friedel-Crafts alkylation because the former gives a single product whereas multiple alkylation *will* occur.

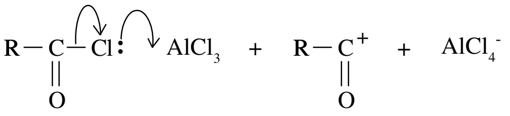




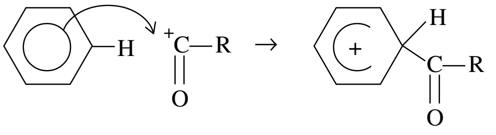
The Mechanism of a Friedel-Crafts Acylation

This is an *electrophilic substitution* which is typical of benzene.

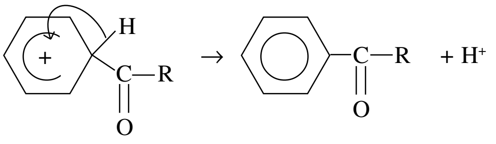
Step 1: Generation of the electrophile
The aluminium chloride acts as a Lewis acid since the aluminium atom can accept a pair of electrons from the chlorine atom in acyl chloride. This produces an acyl carbocation, the electrophile.



Step 2: The acyl carbocation accepts an electron pair from the benzene ring forming an positively-charged intermediate. This is the rate determining step.



Step 3. The intermediate rapidly loses a proton to form the ketone.



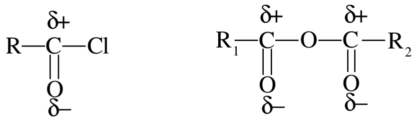
Step 4. The proton reacts with the $[AlCl_4]^-$ to regenerate the catalyst and release hydrogen chloride.

$$H^+ + AlCl_4^- \rightarrow AlCl_3 + HCl$$

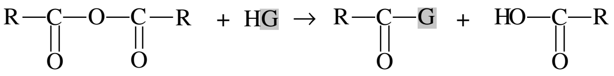
Friedel-Crafts acylations (and also alkylations) are important steps in organic synthesis. Not only is a single ketone formed but from this, other compounds can be made. (See Q4 and Q5)

5. Chemical reactions of acid anhydrides that produce compounds containing acyl groups

Compare the general structure of acid anhydrides with acyl chlorides



Remember, when acyl chlorides react with nucleophiles such as water, alcohols, ammonia or primary amines, a hydrogen atom of the hydroxyl (-OH) or amino group ($-NH_2$) is substituted by the acyl group (RCO-). Exactly the same happens with acid anhydrides. The reactions differ in the other product. With acyl chlorides this is hydrogen chloride (H-Cl) but with acid anhydrides it is a carboxylic acid (R_2COOH). The reactions with acid anhydrides are also *much less vigorous* than with acyl chlorides.


$$R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R + HG \rightarrow R-\underset{\underset{O}{\|}}{C}-G + HO-\underset{\underset{O}{\|}}{C}-R$$

where G = -OH in water, -OR in an alcohol, $-NH_2$ in ammonia and –NHR in an amine.

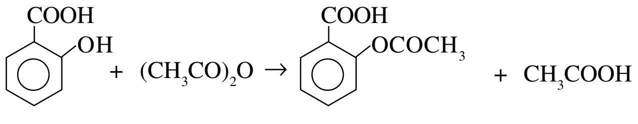
Note. A mixed acid anhydride would ***not*** be used for acylation since there are two different acyl groups and hence two different products would be formed. Thus for acylation purposes $R_1 = R_2$ with $R_1 = R_2 = CH_3$ being the most common case.

Question 1
Name the products and write an equation for the reaction occurring when:

a) Propanoic anhydride reacts with water
b) Ethanoic anhydride reacts with ethanol
c) Methanoic anhydride reacts with ammonia
d) Ethanoic anhydride reacts with aminomethane (methyl amine).

6. The industrial advantages of ethanoic anhydride over ethanoyl chloride in the manufacture of the drug aspirin.

2-hydroxybenzenecarboxylic acid is heated with ethanoic anhydride to give the ester, aspirin

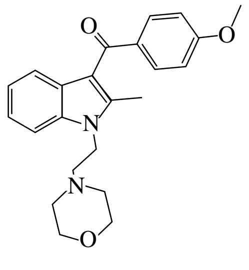


The anhydride is used rather than the acyl chloride because:
(1) the reaction is less dangerous
(2) no HCl (poisonous and corrosive) is produced
(3) the reaction is much less exothermic and easier to control
(4) it is a cheaper reagent (produced by the dehydration of ethanoic acid)

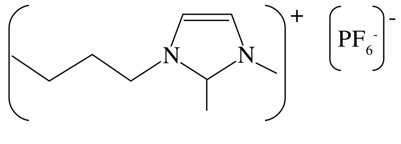
7 HSW : Friedel-Crafts acylations using "ionic liquids"

Since Friedel and Crafts developed their reaction over a 100 years ago many developments have occurred to make the reactions more efficient, less energy demanding and "greener". One of these is the development of so-called "*ionic liquids*" (compounds composed of large, irregular shaped ions which do not pack close together and form a "normal" high melting point lattice) as solvents where the need for a catalyst is removed. This saves a lot in terms of removing waste metal products after reaction.

e.g. the non-steroidal, anti-inflammatory drug, *Pravadoline* (show below) is



synthesised by a Friedel-Crafts acylation in the ionic liquid "[bdmim]$^+$[PF$_6$]$^-$" ; [C$_9$N$_2$H$_{15}$]$^+$ [PF$_6$]$^-$.



Such ionic liquids, as well as being better catalysts (giving higher yield even at room temperature) than AlCl$_3$, also act as the solvent for the reaction. They have the advantages over traditional solvents of being non-volatile and non-flammable. However, their toxicity must be assessed! Nevertheless, they have great potential as clean, green solvents.

Question 2
Draw a ring around the part of the Pravadoline molecule which is introduced by a Friedel-Crafts acylation?

Answers to in text questions

1 a) $(CH_3CH_2CO)_2O + H_2O \rightarrow 2CH_3CH_2COOH$
Propanoic acid

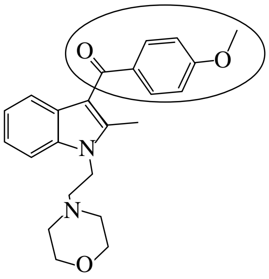
b) $(CH_3CO)_2O + CH_3CH_2OH(l) \rightarrow CH_3COOCH_2CH_3 + CH_3COOH$
Ethyl ethanoate, Ethanoic acid

c) $(HCO)_2O + NH_3 \rightarrow HCONH_2 + HCOOH$
Methanamide, Methanoic acid

Note : This is followed by salt formation:
$HCOOH + NH_3 \rightarrow [NH_4]^+[HCOO]^-$

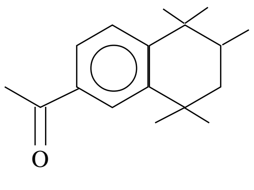
d) $(CH_3CO)_2O + CH_3NH_2 \rightarrow CH_3CONHCH_3 + CH_3COOH$
N-methylethanamide, Ethanoic acid

2.



Practice Questions

1. What do you see when a few drops of butanoyl chloride are added to a few cm^3 of the following liquids: a) methanol, b) concentrated ammonia, c) water, d) ethyl amine. Name the products and write balanced equations for each reaction.
2. In the acylation mechanisms why are the molecules that react with the acyl chloride called "nucleophiles"?
3. Name the type of mechanism for the reaction between propanoyl chloride and ammonia. Using curly arrows illustrate this mechanism. Name the type of product produced.
4. Friedel-Crafts acylations are important steps in organic synthesis. Which acyl chloride would be used in the first step to produce
   a) 1-phenylpropanone,
   b) 1-phenylethan-1-ol,
   c) benzoic acid from benzene?
5. Outline how 2-hydroxy-2-phenylpropanoic acid could be prepared from benzene.
6. Showing all atoms and bonds, draw the structure of the acyl chloride use to prepare the molecule shown below, Tonalid®.



7. Acylium ions are particular stable. When ethanoyl chloride and propanoic anhydride are subjected to mass spectrometry suggest the mass:charge ratios of the peaks with the highest relative abundance?

Answers

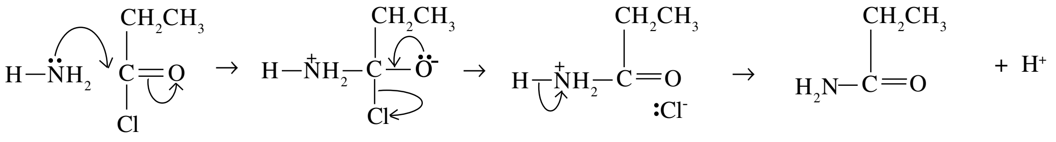
1. Observations:
   a) and c) (Faint) white fumes,
   b) and d) White smoke.

   Names: a) methyl butanoate b) butanamide c) butanoic acid d) <u>N</u>-ethyl butanamide.

Equations:
a) $CH_3CH_2CH_2COCl + CH_3OH \rightarrow CH_3CH_2CH_2COOCH_3 + HCl$
b) $CH_3CH_2CH_2COCl + NH_3 \rightarrow CH_3CH_2CH_2CONH_2 + HCl$
c) $CH_3CH_2CH_2COCl + H_2O \rightarrow CH_3CH_2CH_2COOH + HCl$
d) $CH_3CH_2CH_2COCl + H_2NCH_2CH_3 \rightarrow CH_3CH_2CH_2CONHCH_2CH_3$

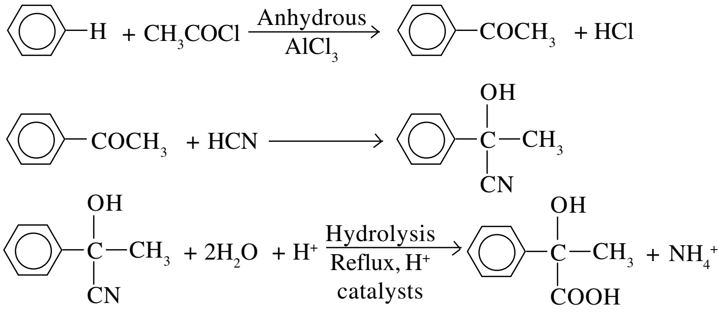
2. The molecules are lone pair donors. (Donating a lone pair to the electron deficient carbon atom of the acyl group and forming a dative bond.)

3. Mechanism = Addition-elimination. Type of product = Amide.

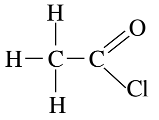


4. a) propanoyl chloride
   b) ethanoyl chloride
   c) methanoyl chloride.

5.



6.



Ethanoyl chloride

7. Ethanoyl chloride at m:z 43 due to $[CH_3CO]^+$. Propanoic anhydride at m:z 57 due to $[CH_3CH_2CO]^+$.

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