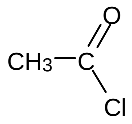
Carboxylic acid derivatives: Acyl Chlorides and Acid Anhydrides

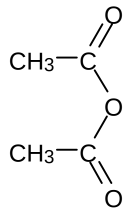
Acyl Chlorides



ethanoyl chloride

Acyl chlorides are much more reactive than carboxylic acids

Acid Anhydrides



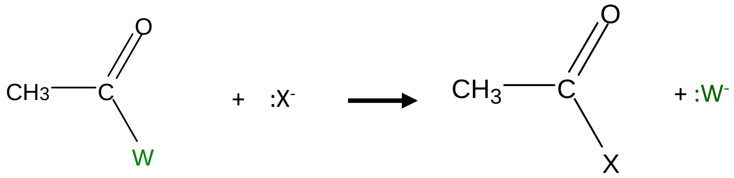
ethanoic anhydride.

Acid anhydrides have a similar reactivity to acyl chlorides and therefore bring about the same changes in functional groups.

The main difference is the by-products. Acyl chlorides mostly give off HCl. Acid anhydrides give off RCOOH

Explaining reactivity

Many of the reactions of the carboxylic acid derivatives follow the pattern below with an attack by an nucleophile.



Where –W: and :W⁻ can be –Cl and Cl^- (acyl chlorides)

or -OCH_3 and OCH_3^- (esters)

\`or -NH_2 and NH_2^- (amides)

On a simplistic level, the stronger the electron attracting power of 'W', the more positive the carbon, and the more attractive the carbon is to nucleophiles.

> The relative attractive powers of the –W: are
> -Cl > -OH > -OCH_3 > -NH_2

Therefore in the case of hydrolysis reactions, acyl chlorides are highly reactive and will be hydrolysed by weak nucleophiles such as water.

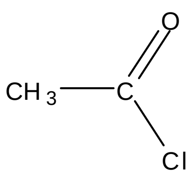
Amides and esters contain only weak electron attracting W groups and need strong nucleophiles such as hydroxide ions in NaOH to hydrolyse.

This difference in reactivity is caused by a combination of two factors

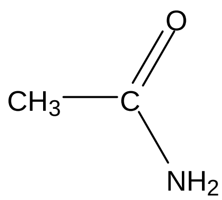
1. the electronegativity of the Cl's, N's and O's causing electron density to be withdrawn from the carbon making the carbon more positive and more attractive to nucleophiles- This factor makes them more reactive.
2. delocalisation of the lone pairs on these atoms into the carbonyl system which reduces the reactivity.

Comparing the reactivity of acyl chlorides to amides

Acyl Chloride



Amide



Acyl chloride are more reactive than amides

Cl and N have similar electronegativities and so should attract electron density from the carbon by similar amounts, making the carbons equally positive.

However, the lone pair on the nitrogen delocalises with the π bond in the carbonyl group which decreases its reactivity.

The Cl is too big (3p orbital rather than 2p orbital in N) to be able to delocalise. This difference in the ability to delocalise explains the difference in reactivity.

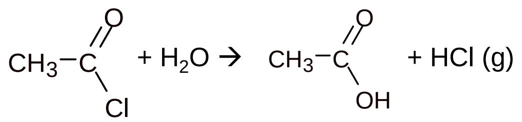
Reaction with water

Change in functional group: **acyl chloride → carboxylic acid**

Reagent: **water**

Conditions: **room temp.**

RCOCl (l) + H_2O → RCO_2H + HCl (g)



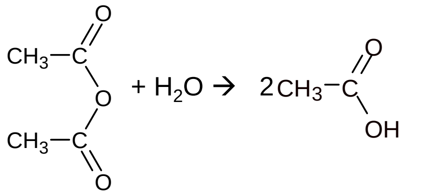
Observation: Steamy white fumes of HCl are given off

Change in functional group: **acid anhydride → carboxylic acid**

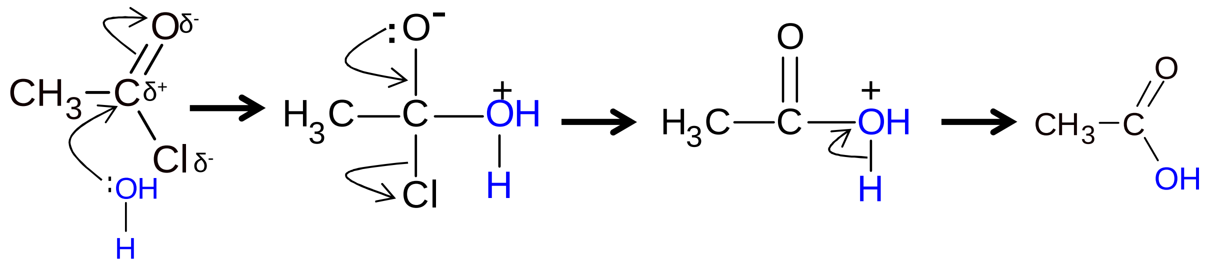
Reagent: **water**

Conditions: **room temp.**

$(RCO)_2O$ + H_2O → $2RCO_2H$



Nucleophilic Addition Elimination Mechanism



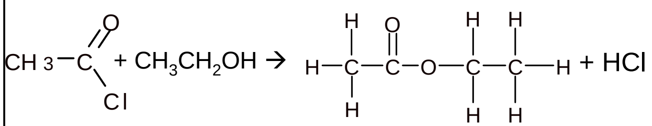
Reaction with alcohol

Change in functional group: **acyl chloride → ester**

Reagent: **alcohol**

Conditions: **room temp.**

RCOCl (l) + CH_3CH_2OH → $RCO_2CH_2CH_3$ + HCl (g)



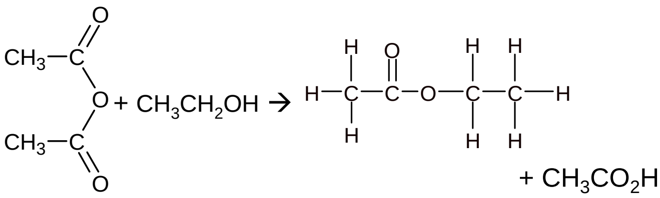
Observation: Steamy white fumes of HCl are given off

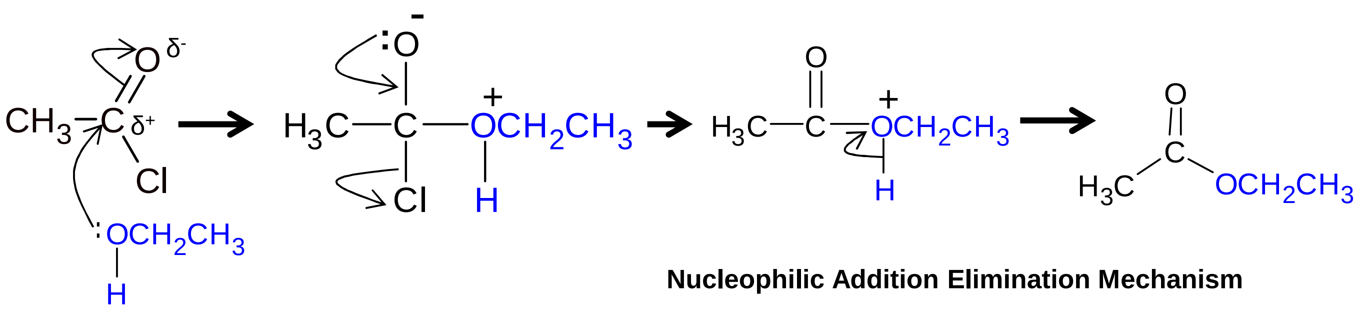
Change in functional group: **acid anhydride → ester**

Reagent: **alcohol**

Conditions: **room temp.**

$(RCO)_2O$ + CH_3CH_2OH → $RCO_2CH_2CH_3$ + RCO_2H





Nucleophilic Addition Elimination Mechanism

This reaction for making esters is much better than using carboxylic acids as the reaction is much quicker and it is not a reversible reaction.

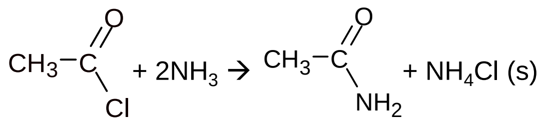
Reaction with ammonia

Change in functional group**: acyl chloride → primary amide**

Reagent: **ammonia**

Conditions: **room temp.**

$RCOCl\ (l) + 2NH_3 \rightarrow RCONH_2 + NH_4Cl\ (s)$



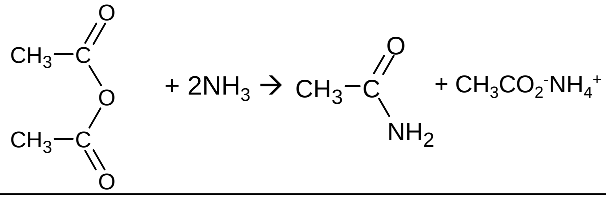
Observation: white smoke of NH_4Cl is given off

Change in functional group**: acid anhydride → primary amide**

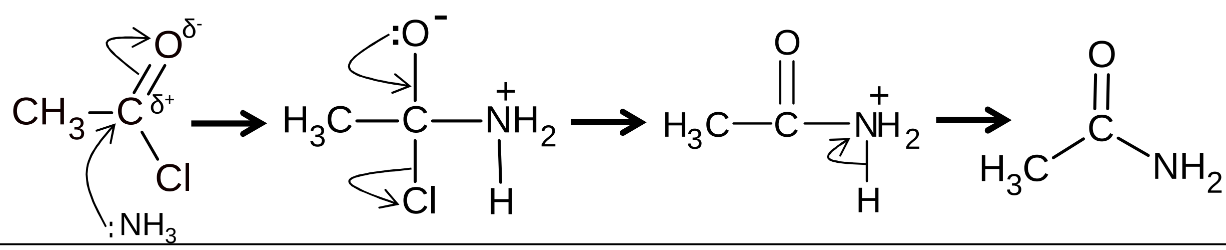
Reagent: **ammonia**

Conditions: **room temp.**

$(RCO)_2O + 2NH_3 \rightarrow RCONH_2 + RCO_2^-NH_4^+$



Nucleophilic Addition Elimination Mechanism



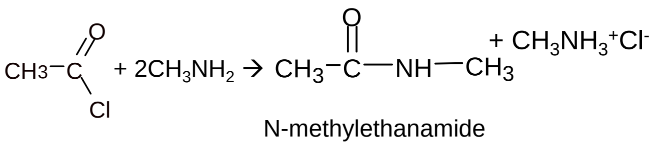
Reaction with primary amines

Change in functional group**: acyl chloride → secondary amide**

Reagent: **primary amine**

Conditions: **room temp.**

$RCOCl + 2CH_3NH_2 \rightarrow RCONHCH_3 + CH_3NH_3^+Cl^-$



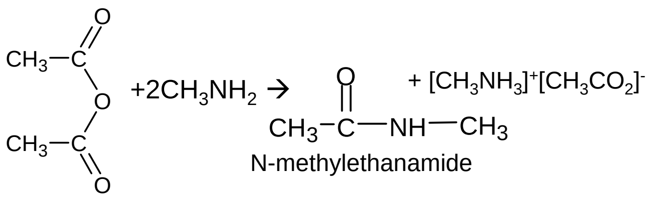
N-methylethanamide

Change in functional group**: acid anhydride → secondary amide**

Reagent: **primary amine**

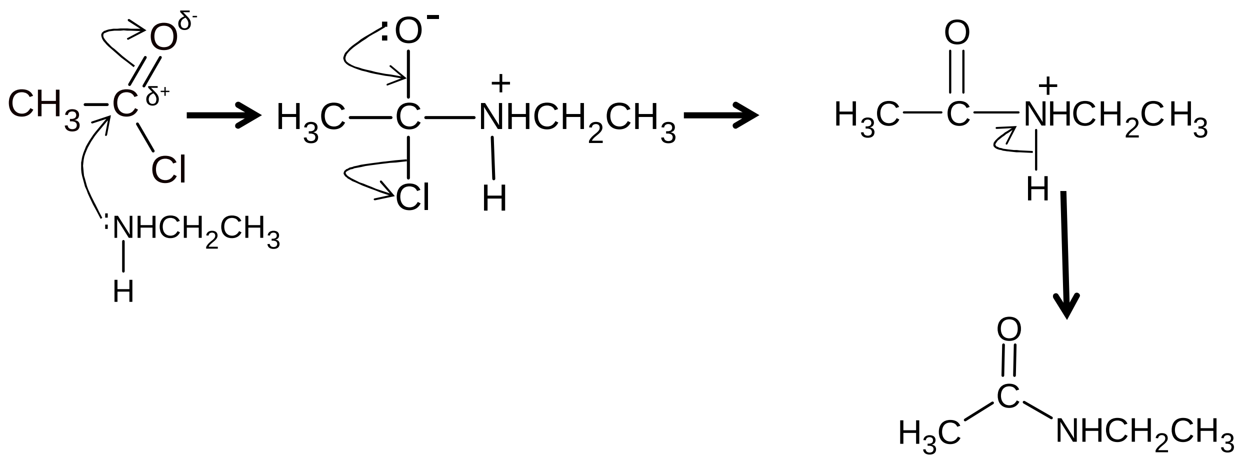
Conditions: **room temp.**

$(RCO)_2O + 2CH_3NH_2 \rightarrow RCONHCH_3 + [CH_3NH_3]^+[RCO_2]^-$



N-methylethanamide

Nucleophilic Addition Elimination Mechanism

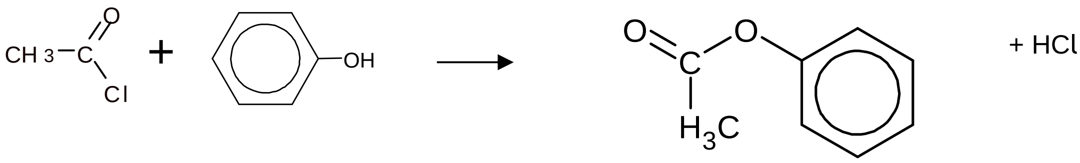


Reaction with phenol

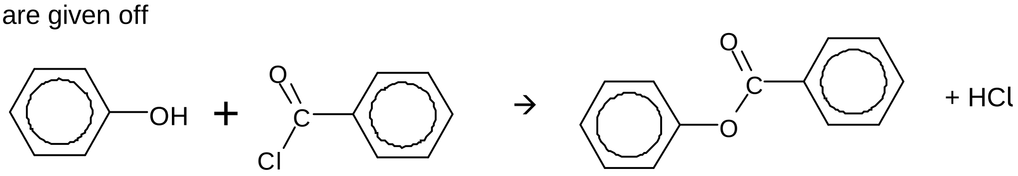
Change in functional group**: acyl chloride → ester**
Reagent: **phenol**
Conditions: **room temp.**

Phenols do not easily form esters with carboxylic acids but do so readily with acyl chlorides.

RCOCl (l) + C_6H_5OH → $RCO_2C_6H_5$ + HCl (g)



Observation: Steamy white fumes of HCl are given off



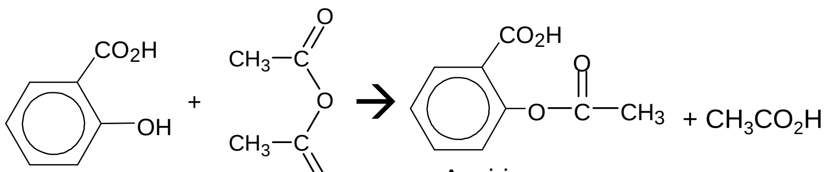
phenol

Benzoyl chloride

Phenyl benzoate

Making Aspirin

Aspirin is made from 2-hydroxybenzoic acid which contains a phenol group. In the reaction the phenol group is turned into an ester by reacting it with the reactive ethanoic anhydride.

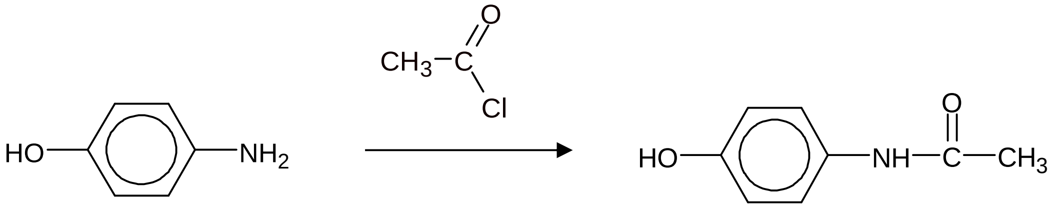


Aspirin

Ethanoic anhydride is used instead of acid chlorides because it is cheaper, less corrosive, less vulnerable to hydrolysis, and less dangerous to use.

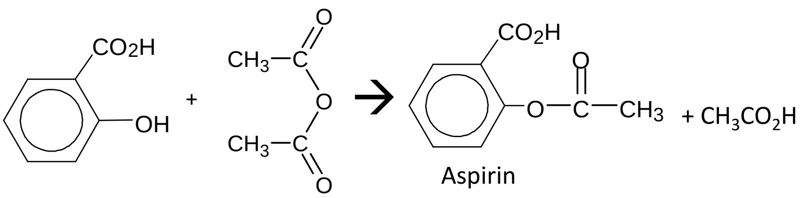
Making Paracetamol

Paracetamol is made by the reaction of an aromatic amine with an acyl chloride to produce an amide.



Paracetamol

Detailed method for Preparation of Aspirin



Aspirin is made from 2-hydroxybenzoic acid which contains a phenol group. In the reaction the phenol group is turned into an ester by reacting it with the reactive ethanoic anhydride

Ethanoic anhydride is used instead of acid chlorides because it is cheaper, less corrosive, less vulnerable to hydrolysis, and less dangerous to use.

Add to a 50 cm^3 pear-shaped flask 2.0 g of 2-hydroxybenzoic acid and 4 cm^3 of ethanoic anhydride.
To this mixture add 5 drops of 85% phosphoric(v) acid and swirl to mix, Fit the flask with a **reflux condenser** and heat the mixture on a boiling water bath for about 5 minutes. Without cooling the mixture, carefully add 2 **cm^3 of water** in one portion down the condenser.

The excess ethanoic anhydride will hydrolyse and the contents of the flask will boil.

When the vigorous reaction has ended, pour the mixture into 40 cm^3 of cold water in a 100 cm^3 beaker, stir and rub the sides of the beaker with a stirring rod necessary to induce crystallisation and, finally, allow the mixture to stand in ice bath to complete crystallisation.
Collect the product by suction filtration and wash it with a little water.

Purification stage: recrystallisation

Using a measuring cylinder, measure out 15 cm^3 of ethanol into a boiling tube.
Prepare a beaker half-filled with hot water from a kettle at a temperature of approximately 75 °C.
Use a spatula to add the crude aspirin to the boiling tube with ethanol and place the tube in the beaker of hot water.

Avoid naked flames due to flammability of ethanol

Stir the contents of the boiling tube until all of the aspirin dissolves into the ethanol.
Pour the hot solution containing dissolved aspirin through a **warmed filter funnel and fluted filter** paper to hot filter

This step will remove any insoluble impurities and heat will prevent crystals reforming during filtration

Then pour filtrate into 40 cm^3 of water in a conical flask.
Allow the conical flask to cool slowly and white needles of aspirin should separate.
Cool the whole mixture in an ice bath.
Filter off the purified solid under reduced pressure and allow it to dry on filter paper.
Record the mass of the dry purified solid

Soluble impurities will remain in solution form because they are present in small quantities so solution is not saturated. Ice will increase the yield of crystals