

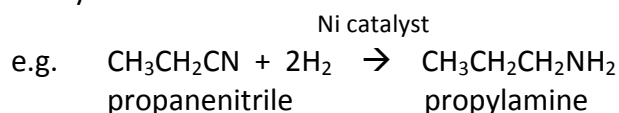


### Changing the nitrile group

The nitrile group is unlikely to be our target functional group. We therefore need a library of reactions for transforming functional groups from one kind to another, many of which we have already met. Firstly, we need to be able to change the nitrile group:

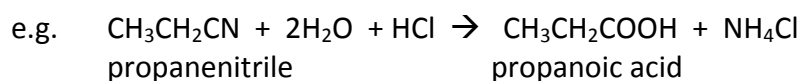
#### Reduction of nitriles

Nitriles are reduced to amines by reacting with hydrogen in the presence of a nickel catalyst.



#### Hydrolysis of nitriles

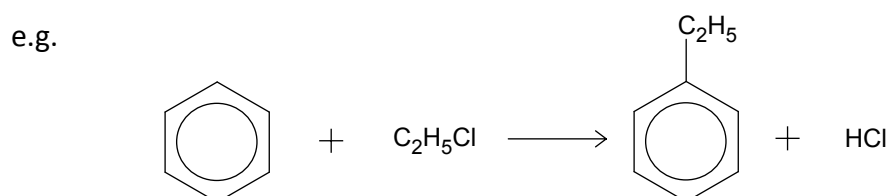
Nitriles also undergo hydrolysis to form carboxylic acids on heating with dilute acid (e.g.  $\text{HCl}_{(\text{aq})}$ )



### Adding a side-group to a benzene ring

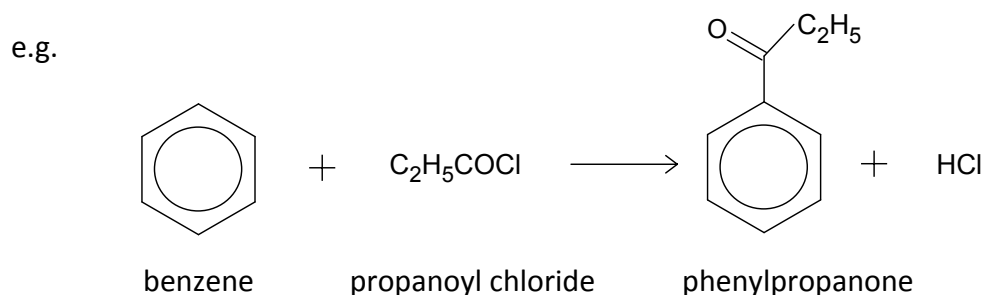
#### Adding an alkyl group

We have already met Friedel-Crafts alkylation, in which an alkyl group from a haloalkane is substituted onto a benzene ring. This reaction requires a halogen carrier such as aluminium chloride (assuming a chloroalkane is used).



#### Adding a carbonyl group

When benzene reacts with an acyl chloride in the presence of an aluminium chloride catalyst, a ketone is formed. This is known as **acylation**, and is a useful way of connecting a carbonyl group to a benzene ring.



### Introducing different functional groups

As well as modifying the carbon skeleton to that of our target molecule, it will also be necessary to change functional groups to get the ones required.

In developing a synthesis route, we work forwards from the raw material, as well as backwards from the target molecule. We therefore need to know what reactions we can do with each functional group, as well as what reactions can be used to form each functional group:

Functional Group	Reactions that can be done with functional group
None (alkane)	→ haloalkane (radical substitution with $X_2$ )
Alkene	→ alkane (electrophilic addition of $H_2$ ) → haloalkane (electrophilic addition of $HX$ ) → dihaloalkane (electrophilic addition of $X_2$ ) → alcohol (electrophilic addition of $H_2O_{(g)}$ ) → addition polymer
Alcohol	→ aldehyde (partial oxidation of primary alcohol) → carboxylic acid (full oxidation of primary alcohol) → ketone (oxidation of secondary alcohol) → alkene (dehydration) → haloalkane (nucleophilic substitution with $HX$ ) → ester (with carboxylic acid/acyl chloride/acid anhydride/amino acid) → polyester (condensation polymerization with carboxylic acid/acyl chloride)
Benzene ring	→ nitrobenzene (nucleophilic subs. with $c.HNO_3 + c.H_2SO_4$ ) → halobenzene (nucleophilic substitution with $X_2+AlX_3$ ) → alkylbenzene (nucleophilic substitution with $RX+AlX_3$ ) → acylbenzene (nucleophilic substitution with $RCOCl+AlCl_3$ )
Phenol	→ phenoxide salt (neutralisation) → brominated phenol → nitrated phenol → ester (with acyl chloride/acid anhydride)
Aldehyde	→ carboxylic acid (oxidation with Tollens or acidified $Cr_2O_7^{2-}$ ) → primary alcohol (reduction, nucleophilic addition $NaBH_{4(aq)}$ ) → hydroxynitrile (nucleophilic addition of $HCN$ )
Ketone	→ secondary alcohol (reduction, nucleophilic addition $NaBH_4$ ) → hydroxynitrile (nucleophilic addition of $HCN$ )
Ester	→ alcohol + carboxylic acid (acid hydrolysis) → alcohol + carboxylate salt (alkaline hydrolysis)
Amide	→ alkylammonium salt + carboxylic acid (acid hydrolysis) → amine + carboxylate salt (alkaline hydrolysis)
Carboxylic acid	→ acyl chloride (reaction with $SOCl_2$ ) → acid anhydride (dehydration/condensation) → carboxylate salt (neutralisation) → condensation polymer (with alcohols/amines)

Acyl chloride	<ul style="list-style-type: none"> <li>→ carboxylic acid (with water)</li> <li>→ ester (with phenol or alcohol)</li> <li>→ amide (with amine/ammonia)</li> <li>→ condensation polymer (with alcohols/amines)</li> </ul>
Acid anhydride	<ul style="list-style-type: none"> <li>→ carboxylic acid (with water)</li> <li>→ ester + carboxylic acid (with alcohol)</li> <li>→ amide (with amine/ammonia)</li> </ul>
Amine	<ul style="list-style-type: none"> <li>→ alkylammonium salt (neutralisation with acid)</li> <li>→ amide (with acyl chloride/acid anhydride)</li> <li>→ amine (primary to secondary, secondary to tertiary)</li> <li>→ polyamide (condensation polymerization with carboxylic acid/acyl chloride)</li> </ul>
Nitrobenzene	→ aromatic amine (reduction with Sn+conc.HCl)
Haloalkane	→ amine (nucleophilic substitution with ammonia/amine)
Nitrile	<ul style="list-style-type: none"> <li>→ amine (reduction with H<sub>2</sub> + Ni catalyst)</li> <li>→ carboxylic acid (hydrolysis with dilute acid)</li> </ul>
Amino acid	See reactions of amine and carboxylic acid functional groups

The same table can be rearranged to list each functional group and the reactions from which it can be made:

Functional Group	Reactions to make the functional group
Alcohol	<ul style="list-style-type: none"> <li>← electrophilic addition of H<sub>2</sub>O<sub>(g)</sub> to alkene</li> <li>← (primary) reduction of aldehyde with NaBH<sub>4(aq)</sub></li> <li>← (secondary) reduction of ketone with NaBH<sub>4(aq)</sub></li> <li>← acid or alkaline hydrolysis of ester</li> </ul>
Aldehyde	← partial oxidation of primary alcohol
Ketone	<ul style="list-style-type: none"> <li>← oxidation of secondary alcohol</li> <li>← acylation of benzene (nucl. subs. with RCOCl + AlCl<sub>3</sub>)</li> </ul>
Ester	<ul style="list-style-type: none"> <li>← esterification with alcohol and carboxylic acid/amino acid</li> <li>← reaction of alcohol with acyl chloride/acid anhydride</li> <li>← reaction of phenol with acyl chloride/acid anhydride</li> </ul>
Amide	<ul style="list-style-type: none"> <li>← reaction of acyl chloride with ammonia/amine</li> <li>← reaction of acid anhydride with ammonia/amine</li> <li>← condensation of amine and carboxylic acid</li> <li>← condensation of amine and acyl chloride</li> </ul>
Carboxylic acid	<ul style="list-style-type: none"> <li>← full oxidation of primary alcohol</li> <li>← oxidation of aldehyde (Tollens, or acidified dichromate)</li> <li>← acid hydrolysis of ester/polyester</li> <li>← acid hydrolysis of amide/polyamide</li> <li>← action of water on acid anhydride or acyl chloride</li> <li>← hydrolysis of nitrile with dilute acid</li> </ul>
Acyl chloride	← reaction of carboxylic acid with SOCl <sub>2</sub>
Acid anhydride	← dehydration (condensation) of carboxylic acids
Amine	<ul style="list-style-type: none"> <li>← (primary) nucleophilic subs. of haloalkane with ammonia</li> <li>← (secondary/tertiary) nucl. subs. of haloalkane with amine</li> <li>← (aromatic) reduction of nitrobenzene with Sn + conc.HCl</li> </ul>

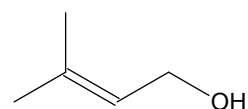
Nitrobenzene	← nucleophilic substitution of benzene with c.HNO <sub>3</sub> + c.H <sub>2</sub> SO <sub>4</sub> ← reduction of nitrile with H <sub>2</sub> and Ni catalyst
Haloalkane	← radical substitution of alkane with X <sub>2</sub> ← electrophilic addition of X <sub>2</sub> /HX to alkene ← nucleophilic substitution of alcohol with HX
None (alkane)	← hydrogenation of alkene with H <sub>2</sub> + Ni catalyst ← addition polymerization of alkene
Alkene	← dehydration of alcohol (with H-C adjacent to C-OH)
Halobenzene	← nucleophilic substitution of benzene with X <sub>2</sub> and AlX <sub>3</sub>
Alkylbenzene	← alkylation of benzene with RX and AlX <sub>3</sub>
Phenoxide salt	← neutralisation of phenol with alkali
Bromophenol	← bromination of phenol with Br <sub>2</sub>
Nitrophenol	← nitration of phenol with dil. HNO <sub>3</sub>
Hydroxynitrile	← nucleophilic addition of HCN to aldehyde or ketone
Carboxylate salt	← alkaline hydrolysis of ester/polyester ← alkaline hydrolysis of amide/polyamide ← neutralisation of carboxylic acid with alkali
Alkylammonium salt	← acid hydrolysis of amide/polyamide ← neutralisation of amine with acid

### Synthesis with unfamiliar molecules

We will constantly meet unfamiliar molecules, but they will contain functional groups that we know. The reactions of these functional groups are the same in complicated molecules as in simple ones: we should practise analyzing unfamiliar molecules so that we can predict their properties:

e.g. prenol             $(\text{CH}_3)_2\text{CCHCH}_2\text{OH}$             found naturally in many fruits,  
widely used in synthesis

i) draw the molecule to visualize functional groups  
(skeletal is best)



ii) tabulate the physical and chemical properties that the functional groups confer

Physical properties	Reactions of alkene gp.	Reactions of alcohol gp.
-OH group will form hydrogen bonds with water, so expect to be soluble.	→ alkane → haloalkane → alcohol → addition polymer	→ alkene → haloalkane → aldehyde → carboxylic acid → ester

Now you can predict how this molecule might fit into a series of synthesis steps.

### Synthesis with unfamiliar reactions

We are also expected to be able to apply the principles we have encountered in organic chemistry to unfamiliar reactions, where information is provided, and to be able to apply these unfamiliar reactions as part of synthesis. Synthetic chemists



- Heating using a mantle heater avoids naked flames and the risk of ignition. ( A water bath or oil bath could also be used if the required temperature is not too high)

#### Filtration under reduced pressure

- Uses a Buchner flask and funnel
- Speeds up filtration compared to gravity filtration with folded/fluted filter paper
- Rinse all solid from reaction vessel into Buchner funnel using reaction solvent
- Rinse in funnel with more solvent, and allow to dry under suction for a few minutes

#### Recrystallisation

Impure product obtained by filtering is purified by recrystallization. A solvent is chosen in which the impurities are soluble and in which the product is soluble when hot, but much less soluble when cold.

- The chosen solvent is heated (using a water bath if the solvent is flammable)
- The impure solid product is placed in a flask and the minimum amount of hot solvent added to dissolve the solid
- The solution is allowed to cool so crystals of the product form, leaving the impurities in solution
- When no more crystal form (cooling in ice can complete the process), filter under reduced pressure to obtain the dry crystalline product

#### Separation techniques

- Many organic liquids are immiscible with water, meaning that two liquid layers will form: one containing water and water-soluble components, and one containing organics not soluble in water. These can be separated using a Separating Funnel to run off one layer, then the other, and discard the one containing the impurities. For example, water-soluble impurities can be removed from an insoluble product by washing the product with successive portions of water and discarding the aqueous layers from the Separating funnel.
- After distillation, the product may still contain impurities with boiling points close to that of the product. Using clean, dry distillation apparatus to perform a second distillation and collecting only the fraction that is distilled over at the boiling point of the desired product allows further purification.
- Organic liquids can appear cloudy when there are traces of water present. Removing these traces of water can be done by adding a drying agent – an anhydrous salt that readily takes up water such as  $\text{CaCl}_2$ ,  $\text{CaSO}_4$  or  $\text{MgSO}_4$ . The organic liquid is swirled with the drying agent, left for a few minutes, then the drying agent removed by i) decanting the liquid or ii) filtering through cotton wool. If the drying agent sticks together in a lump, more needs to be added until it remains as a fine powder. If the organic liquid is dry it should be clear.

#### Melting point determination

Pure organic substances have a sharp melting range over 1-2°C. If the product contains impurities, the solid melts over a wider range of temperature. Melting point

measurement therefore allows the identity of a product to be confirmed (by comparison to published values) and its purity assessed.

- Sample should be dry
- Approaching the melting point, the rate of heating the sample must be very slow so that the sample is at the same temperature as the heater and thermometer, to reduce measurement errors
- Repeat to confirm results