



Synthetic Pathways in Organic Chemistry

To succeed in this topic you need to understand:

- the chemical properties of organic functional groups
- how to choose suitable reagents and conditions for organic transformations
- how to calculate % yield and % atom economy
- the various techniques used in organic chemistry, for example reflux and distillation

After working through this FactSheet you will be able to:

- describe synthetic pathways between a range of simple organic compounds
- choose an appropriate synthetic pathway for a given organic compound

Choosing a Synthetic Pathway

The job of a synthetic organic chemist is to make a target molecule from readily available starting materials. The target molecule might be a drug, dye, flavouring or detergent, or have other useful properties. There will almost certainly be more than one route to any given target molecule, and so chemists have to choose the best, by which we mean the most *economically* and *environmentally viable*. When choosing a synthetic pathway, we need to balance a range of factors (Table 1).

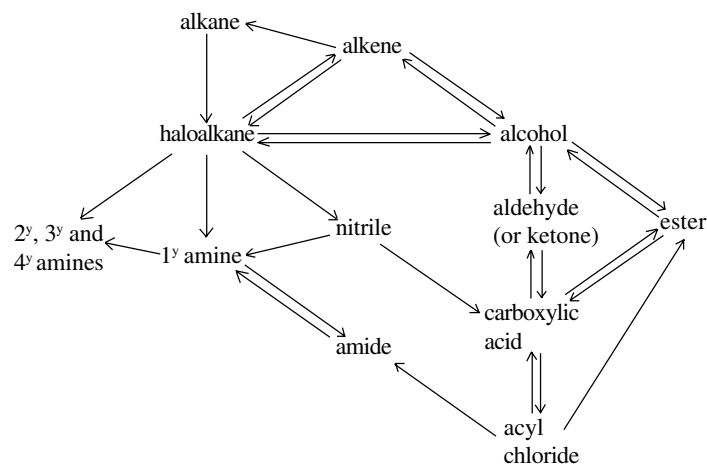
Table 1: Factors to be considered when choosing a synthetic pathway

| Factor to be considered | Notes |
|--|---|
| The number of steps | Each step in a synthetic pathway will involve at least a small loss of material, so, in general, the fewer steps, the better. |
| % Yield of each step | Reactions with yields of about 80% or higher are generally considered to be worth carrying out. |
| % Atom economy of each step | An addition reaction, with 100% atom economy, may well be a better option than a substitution reaction, which has a much lower atom economy. |
| The reagents needed | Some reactions require expensive metal catalysts or hazardous reagents such as chlorine. |
| How long the reactions take | A reaction that takes only a couple of hours is probably a better option than one which has to be left for 48 hours. Time is money! |
| The temperature needed for the reactions | A high temperature requires energy and therefore costs more. However a low temperature may slow the reaction down. The development and use of appropriate catalysts is vital to allow faster reactions at lower temperatures. |
| The cost and availability of starting materials | Starting materials from renewable sources (ethanol from fermentation, for example) may be preferable to those derived from non-renewable crude oil. |
| How easy it is to separate the target molecule from the other products | It can be time-consuming and tricky to purify the products of an organic reaction, so the easier the separation, the better. This is especially important when dealing with pharmaceutical drugs where a very high degree of purity is essential. |
| How the pathway may affect any other functional groups in the compound | Organic compounds may contain more than one functional group and often chiral centres. It is important to make sure that these are not destroyed inadvertently. |

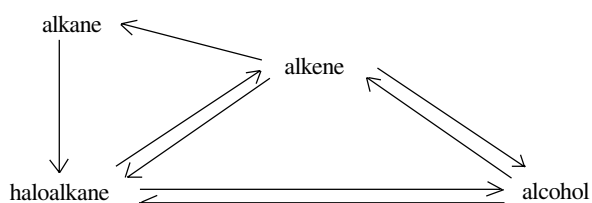
The best synthetic pathway from one molecule to another is likely to be the one with fewest steps, but remember that the choice of pathway will always be a balance of the factors in Table 1. For example, a reaction which needs an expensive platinum catalyst may have a high yield, and therefore provide a better option than a reaction with cheaper reagents but a lower yield. For more help on tackling exam questions on this topic, see FactSheet 35, Answering Questions on Organic Pathways and Conversions.

Aliphatic (non-aromatic) Pathways

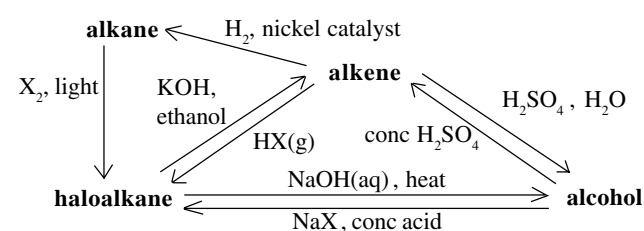
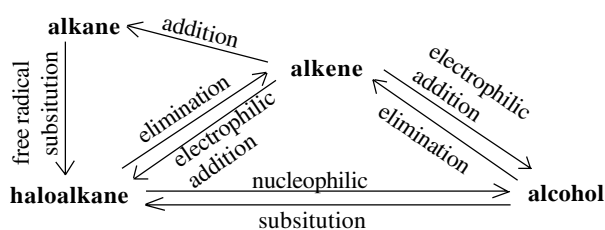
Fig 1 shows the connections between the non-aromatic functional groups you will meet at A level. It is important that you are confident in remembering these key synthetic pathways.

Fig 1 Synthetic pathways between functional groups

This is a lot to learn in one go, and a good way to tackle it might be to break the diagram down into smaller chunks. Fig 2, for example, shows the connections between alkanes, alkenes, haloalkanes and alcohols.

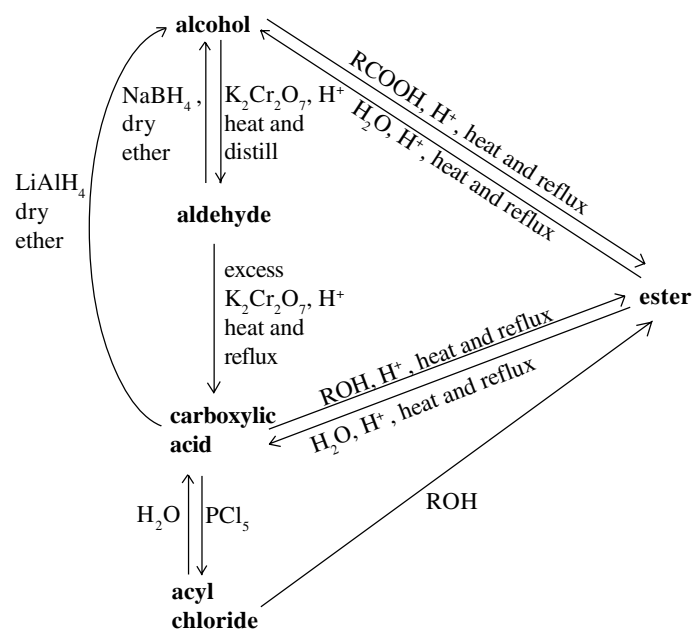
Fig 2. Synthetic pathways between simple functional groups

You should be able to label each of the arrows in these schemes with reagents, conditions and reaction types (see Figures 3 and 4).

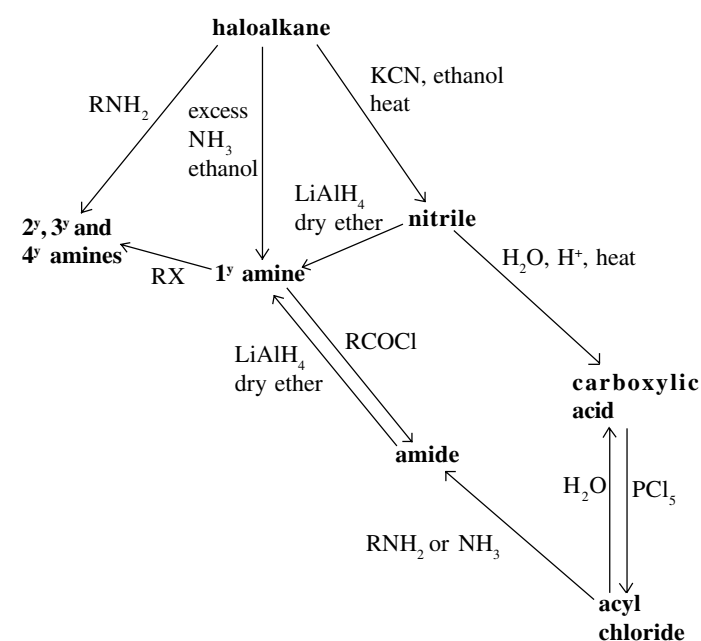
Fig 3. Reagents and conditions linking simple functional groups**Fig 4. Reaction types linking simple functional groups****Sample Question 1**

Using the schemes shown in Figure 3, describe: (a) a two-step synthetic pathway from bromoethane to ethane, (b) a three-step synthetic pathway from propane to propene. The answers are shown in Figures 12 and 13.

Another chunk of Fig 1 would show the links between oxygen-containing functional groups (Fig 5).

Fig 5. Synthetic pathways for oxygen-containing functional groups

Finally, Fig 6 shows the synthesis and reactions of nitrogen-containing groups.

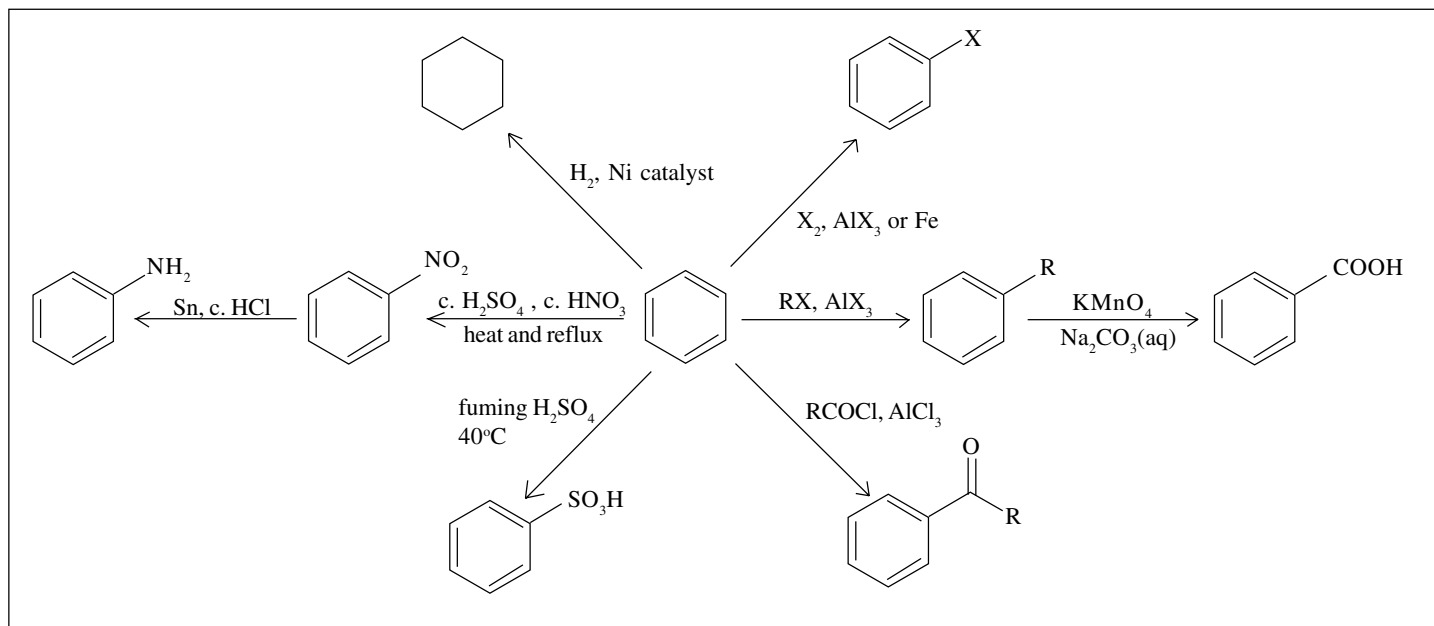
Fig 6. Synthesis and reactions of nitrogen-containing functional groups

Exam Hint:- Make sure that you understand what is required by the question. If it asks you to name reagents, be specific. H^+ , for example, is not acceptable. If you know that the reaction requires concentrated sulphuric acid or dilute hydrochloric acid, say so. If the question asks you for reaction conditions, it will probably not occur at room temperature. Again, be specific. If it needs heating for a while, then make sure you say heat and reflux.

Aromatic Pathways

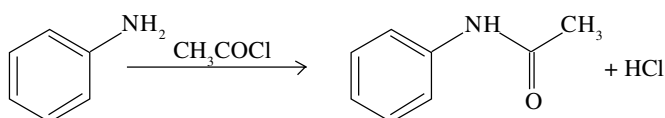
Fig 7. shows the pathways associated with aromatic compounds.

Fig 7. Aromatic pathways



Remember that the side chains on a benzene ring can undergo normal non-aromatic reactions such as formation of amides (Fig 8).

Fig 8. Reaction of a benzene side chain



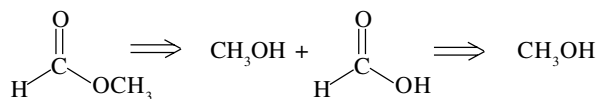
Sample Question 2

Devise a 3-step synthetic pathway from benzene to cyclohexene. The answer is shown in Figure 14.

More Tips and Hints

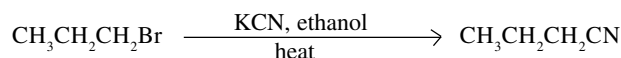
When devising a route, synthetic organic chemists use **retrosynthesis** (Fig 9). This means that they work backwards from their target molecule to the starting material. This is easy if you have the various synthetic pathways clear in front of you. When you meet a synthesis question in the exam, sketch out the synthetic pathways in the back of your answer booklet so that you can refer to them as you devise your route.

Fig 9. Retrosynthetic pathway from methyl methanoate to the starting material methanol



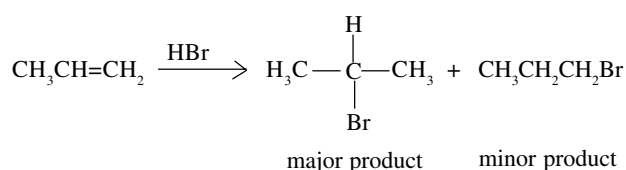
Check how many carbon atoms there are in the chains of the starting material and the target. If you need an extra carbon atom, the easiest way to do this is by the nucleophilic substitution by a CN^- ion. This reaction occurs readily with a bromoalkane (Figure 10), so you will need to synthesise the bromoalkane before substituting with the CN^- .

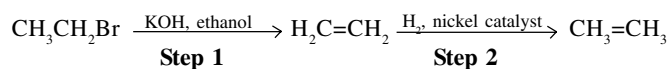
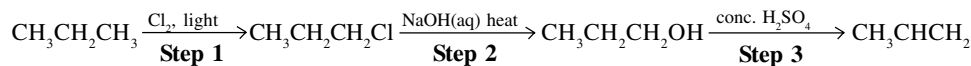
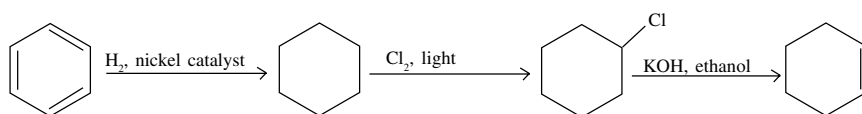
Fig 10. Adding an extra carbon atom by nucleophilic substitution with CN^-



Remember that many reactions give a mixture of products, but often one product will be favoured over another. Addition of a haloalkane to an unsymmetrical alkene is one example (Fig 11).

Fig 11. Addition of HBr to an unsymmetrical alkene



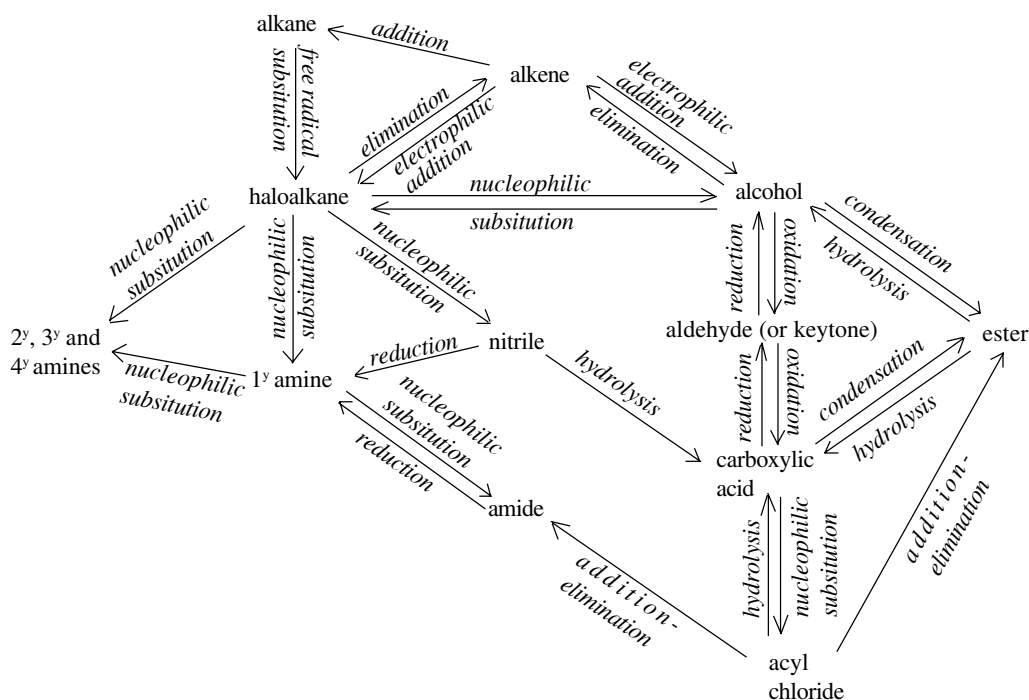
Answers to Sample Questions**Question 1****Fig 12. A two-step pathway from bromoethane to ethane****Fig 13. A three-step pathway from propane to propene****Question 2****Fig 14. Pathway from benzene to cyclohexene****Practice Questions**

- From each of the following pairs of synthetic pathways, choose the more commercially viable one.
 - (i) One step with a 50% yield, or
(ii) two steps, each with a yield of 80%.
 - (i) A reaction which takes ten minutes at 60°C, or
(ii) one which takes four hours at 30°C.
 - (i) A reaction which starts from ethanoic acid, or
(ii) a reaction which uses hexane as its starting material.
 - (i) A reaction which requires refluxing for two hours with concentrated sulphuric acid, or
(ii) a reaction which takes place at room temperature with dilute hydrochloric acid.
 - (i) A reaction which is catalysed by an enzyme derived from bacteria, or
(ii) one which is catalysed by finely divided platinum.
 - (i) A reaction which produces a mixture of water soluble products, or
(ii) one which produces a single solid product.
- Make a copy of Fig 1 and fill in the names of each type of reaction.
- Look back at the two synthetic pathways shown in Figures 12 and 13.
 - If the yield for each of the reactions in Figure 12 is 75% what is the overall yield of ethane from bromoethane?
 - Which of the two steps in Figure 12 has the higher % atom economy? Explain your answer.
 - In Fig 13, the first step is the free radical substitution of propane to make chloropropane. What economic and environmental issues are there with this reaction?
- Use Figure 5 to describe a synthetic pathway from methyl ethanoate to ethanal.
- Devise pathways for each of the following syntheses:
 - Propanoic acid from 1-chloropropane
 - Butanoic acid from 1-bromopropane
 - Propanone from propene
 - Propyl propanoate from propan-1-ol
 - 4-Aminomethylbenzene from benzene

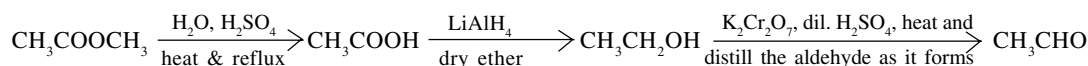
Answers

- (a) (ii) The two steps give a total yield over the two steps of 64%, higher than the 50% of the single step.
 - (b) (i) A reaction which takes ten minutes at 60°C, because it is quicker and requires proportionally less energy for heating.
 - (c) (i) A reaction which starts from ethanoic acid. Ethanoic acid can be derived from vinegar, which is easily obtained from plants. The most likely source of hexane, on the other hand, is non-renewable crude oil.
 - (d) (ii) The alternative, refluxing with concentrated sulphuric acid, involves very harsh conditions which may destroy other functional groups in the compound.
 - (e) (i) Enzymes from bacteria are relatively cheap to obtain, and are a renewable resource, whereas metal catalysts are expensive and non-renewable.
 - (f) (ii) The reaction which produces a single product will have a higher atom economy, and therefore involves less waste of resources. Since it is a solid, it is also easy to separate by filtering. However, it is possible that the other reaction may actually produce a higher yield of the desired product, even with taking into account the formation of two unwanted by-products and the difficulties of separation.

2.



- (a) Overall yield = $75/100 \times 75 = 56\%$
 - (b) Step 2 is an addition reaction and will therefore have an atom economy of 100%, because there is a single product. Step 1 is an elimination reaction which produces two products, so its atom economy will be much less than 100%.
 - (c) This free radical substitution reaction produces a mixture of chloroalkane products, which must be separated. This will use energy and time. It also requires the use of chlorine gas, which is toxic, so care must be taken to ensure no leakages occur.
- Note that it is not possible to easily reduce a carboxylic acid to an aldehyde because reduction through to the alcohol can also occur. Hence, the ethanoic acid must be reduced to the alcohol and then re-oxidised.



- (a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{NaOH, H}_2\text{O}} \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \xrightarrow[\text{heat and reflux}]{\text{K}_2\text{Cr}_2\text{O}_7, \text{dil. H}_2\text{SO}_4} \text{CH}_3\text{CH}_2\text{COOH}$
 - (b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \xrightarrow[\text{heat}]{\text{KCN, ethanol}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CN} \xrightarrow[\text{heat and reflux}]{\text{H}_2\text{O, dil. H}_2\text{SO}_4} \text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$
 - (c) $\text{CH}_3\text{CHCH}_2 \xrightarrow[\text{H}_2\text{O}]{\text{c. H}_2\text{SO}_4} \text{CH}_3\text{CH}(\text{OH})\text{CH}_3 \xrightarrow[\text{heat and reflux}]{\text{K}_2\text{Cr}_2\text{O}_7, \text{dil. H}_2\text{SO}_4} \text{CH}_3\text{COCH}_3$
 - (d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \xrightarrow[\text{heat and reflux}]{\text{K}_2\text{Cr}_2\text{O}_7, \text{dil. H}_2\text{SO}_4} \text{CH}_3\text{CH}_2\text{COOH} \xrightarrow[\text{heat and reflux}]{\text{CH}_3\text{CH}_2\text{CH}_2\text{OH, c. H}_2\text{SO}_4} \text{CH}_3\text{CH}_2\text{COOCH}_2\text{CH}_2\text{CH}_3$

