

Edexcel IAL Chemistry A-level

Topic 20: Organic Synthesis

Detailed notes

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Why do we need organic synthesis?

Synthesis pathways are needed to convert starting materials into a **target product**. This can sometimes be achieved through single-step reactions, but other times **multistep pathways** that, for example, oxidize functional groups, lengthen the carbon chain and saturate double bonds, are required.

When designing a synthetic pathway a chemist must consider several factors:

- Product yield (related to Le Chatelier's principle)
- Reaction set up, including:
 - Catalysts
 - Reagents
 - Conditions - temperature, pressure, concentrations
- The process involved - batch or continuous
- Hazards
- Cost
- Formation of isomers - for example, many drug targets are enzymes that are stereospecific and react with one enantiomer only. The synthetic pathway designed for these drugs should, ideally, only produce this enantiomer and not a racemic mixture.

Experimental Techniques

Synthesis pathways involve a variety of **preparatory** and **purification** techniques that have been introduced throughout this course. These include:

- Reflux
- Distillation
- Melting point determination
- Boiling point determination
- Washing and drying
- Recrystallisation
- Solvent extraction

Functional Groups

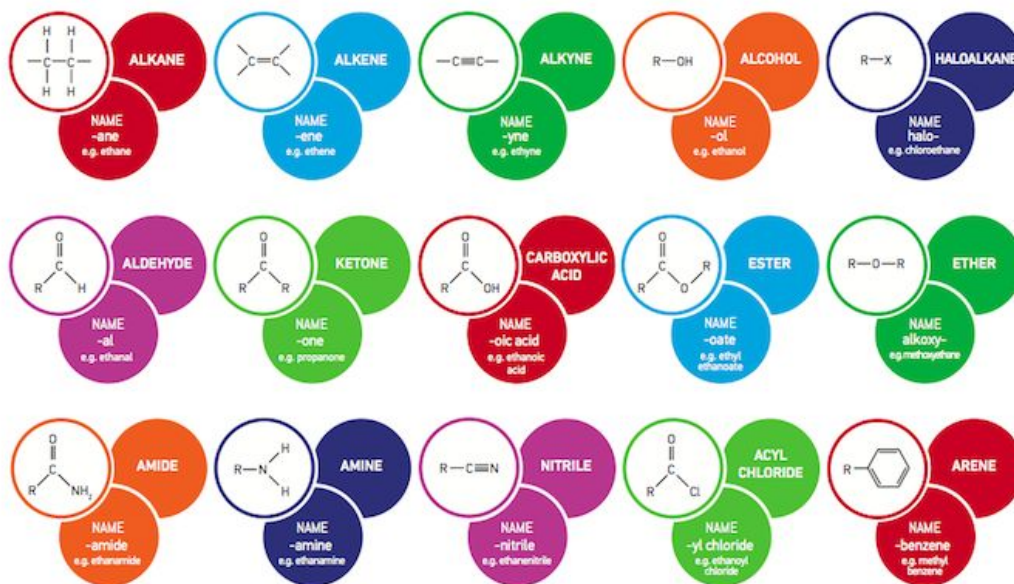
To best understand organic synthesis, you'll need to know the structures of all the functional groups relevant to the A-Level course.

Data from **NMR**, **element percentage composition**, experimental evidence of the presence of specific **functional groups**, **infrared** and **mass spectroscopy** can be used, often in combination with each other, to predict structures and formulae of organic compounds.



ORGANIC FUNCTIONAL GROUPS

FUNCTIONAL GROUPS ARE GROUPS OF ATOMS IN ORGANIC MOLECULES THAT ARE RESPONSIBLE FOR THE CHARACTERISTIC CHEMICAL REACTIONS OF THOSE MOLECULES
IN THE GENERAL FORMULAE BELOW, 'R' REPRESENTS A HYDROCARBON GROUP OR HYDROGEN, AND 'X' REPRESENTS ANY HALOGEN ATOM.



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Image courtesy of Compound Interest

The table below shows the typical reactions of different functional groups and how they can be identified.

Homologous series	Typical reactions	Identification
Alkanes C-C	<p align="center"><i>Combustion</i></p> <p align="center"><i>Electrophilic substitution/free radical substitution</i> with Br₂ or Cl₂ (forms halogenoalkanes)</p> <p align="center"><i>Cracking</i> (forms short chain alkenes and alkanes)</p>	
Alkenes C=C	<p align="center"><i>Electrophilic addition:</i></p> <ul style="list-style-type: none"> - Steam (forms alcohols) - Hydrogen halides (forms halogenoalkanes) - Halogens (forms dihalogenoalkanes) - Hydrogen (forms alkanes) <p align="center"><i>Oxidation</i> with H⁺/MnO₄⁻ (forms diols)</p> <p align="center"><i>Addition polymerisation</i> (forms polymers)</p> <p align="center"><i>Combustion</i></p>	React with bromine water: Decolorises in the presence of C=C.
Haloalkanes C-F/ C-Cl/ C-Br/ C-I	<p align="center"><i>Nucleophilic substitution:</i></p> <ul style="list-style-type: none"> - Hydrolysis (forms alcohols) - Reaction with ethanolic cyanide (forms nitriles) 	React with AgNO₃(aq), test precipitate with NH₃(aq):



	<p>- Reaction with ammonia (forms primary amines)</p> <p><i>Elimination</i> of hydrogen halide using ethanolic hydroxide ions (forms alkenes)</p>	<p>AgCl - white ppt soluble in dilute $\text{NH}_3(\text{aq})$</p> <p>AgBr - cream ppt soluble in concentrated $\text{NH}_3(\text{aq})$</p> <p>AgI - yellow ppt insoluble in $\text{NH}_3(\text{aq})$</p>
<p>Alcohols -OH</p>	<p><i>Combustion</i></p> <p><i>Substitution</i> with halogenating agents (forms halogenoalkanes)</p> <p><i>Oxidation</i> with $\text{H}^+/\text{Cr}_2\text{O}_7^{2-}$ (forms carbonyls and carboxylic acids)</p> <p><i>Dehydration</i> using an acid catalyst (forms alkenes)</p> <p><i>Esterification</i> with carboxylic acids or acyl chlorides</p>	<p>React with $\text{H}^+/\text{Cr}_2\text{O}_7^{2-}$: Colour change from orange to green in the presence of primary and secondary alcohols (no change for tertiary alcohols).</p>
<p>Aldehydes -CHO</p>	<p><i>Oxidation</i> with $\text{H}^+/\text{Cr}_2\text{O}_7^{2-}$ (forms carboxylic acids)</p> <p><i>Reduction</i> using LiAlH_4 (forms primary alcohols)</p> <p><i>Nucleophilic addition</i> with HCN (forms hydroxynitriles)</p>	<p>React with 2,4-DNPH: A yellow-orange precipitate is formed in the presence of a carbonyl group.</p> <p>React with Tollens' reagent: A silver mirror is produced if an aldehyde is present.</p> <p>React with Fehling's reagent: The blue solution forms a brick red precipitate in the presence of an aldehyde.</p> <p>React with acidified potassium dichromate(VI): Orange solution turns green.</p>
<p>Ketones RCOR'</p>	<p><i>Reduction</i> using LiAlH_4 (forms secondary alcohols)</p> <p><i>Nucleophilic addition</i> with HCN (forms hydroxynitriles)</p>	<p>React with 2,4-DNPH: A yellow-orange precipitate is formed in the presence of a carbonyl group.</p>
<p>Carboxylic acids -COOH</p>	<p>Reaction with metals, alkalis or carbonates (forms a salt and inorganic products)</p> <p><i>Esterification</i> with alcohols</p> <p><i>Reduction</i> with LiAlH_4 (forms alcohols)</p>	<p>Test pH: pH less than 7 when measured using a pH probe.</p> <p>React with a carbonate: Effervescence as CO_2 is formed.</p>



	Reaction with phosphorus(V) chloride (forms acyl chlorides) <i>Reduction</i> with LiAlH_4 (forms aldehydes and then primary alcohols)	
Esters RCOOR'	<i>Acid hydrolysis</i> (forms a carboxylic acid and an alcohol) <i>Alkali hydrolysis</i> (forms a carboxylate salt and an alcohol)	Generally have distinct sweet smells.
Amines $-\text{NH}_2$	Reaction with acids (forms a salt)	
Nitriles $\text{C}\equiv\text{N}$	<i>Acid hydrolysis</i> (forms a carboxylic acid and a salt) <i>Alkaline hydrolysis</i> (forms a carboxylate salt and ammonia) <i>Reduction</i> (forms primary aliphatic amines)	
Arenes $-\text{C}_6\text{H}_5$	<i>Electrophilic substitution:</i> <ul style="list-style-type: none"> - Halogen (forms chlorobenzene with Cl_2 and bromobenzene with Br_2) - Nitration (forms nitrobenzene) Friedel-Crafts <i>acylation</i> and <i>alkylation</i> <i>Hydrogenation</i> (forms cyclohexane)	
Phenol $\text{C}_6\text{H}_5\text{OH}$	Reactions with strong bases (not acidic enough to react with carbonates) <i>Electrophilic substitution:</i> <ul style="list-style-type: none"> - Bromination using Br_2 (forms bromophenol) 	
Acyl chlorides $-\text{COCl}$	<i>Hydrolysis</i> with water (forms carboxylic acids and HCl) <i>Hydrolysis</i> with sodium hydroxide (forms a carboxylate salt and water) <i>Esterification</i> with alcohols or phenol Reaction with ammonia (forms an amide and HCl) Reactions with primary amines (forms an N-substituted amide)	
Amides $-\text{CONH}_2$	<i>Acid hydrolysis</i> (forms a carboxylic acid and ammonium ions) <i>Alkali hydrolysis</i> (forms a carboxylate salt and ammonia or an amine) <i>Reduction</i> using LiAlH_4 (forms a primary amine)	

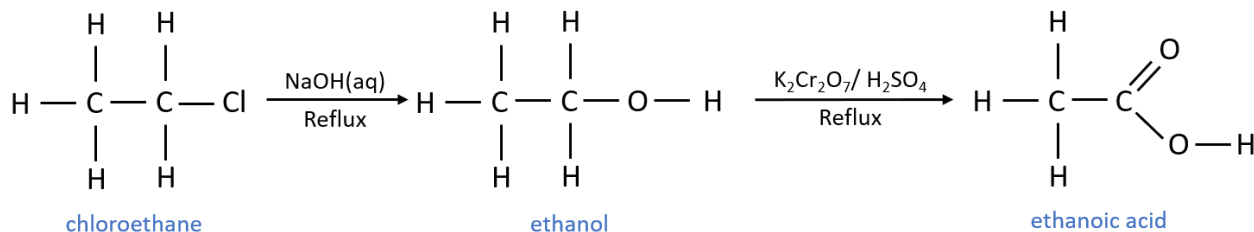


Multi-stage synthesis

Some organic molecules can be prepared using a **multi-stage synthesis**. Typically, this involves two stages: reactant → intermediate → product. It can cover more stages.

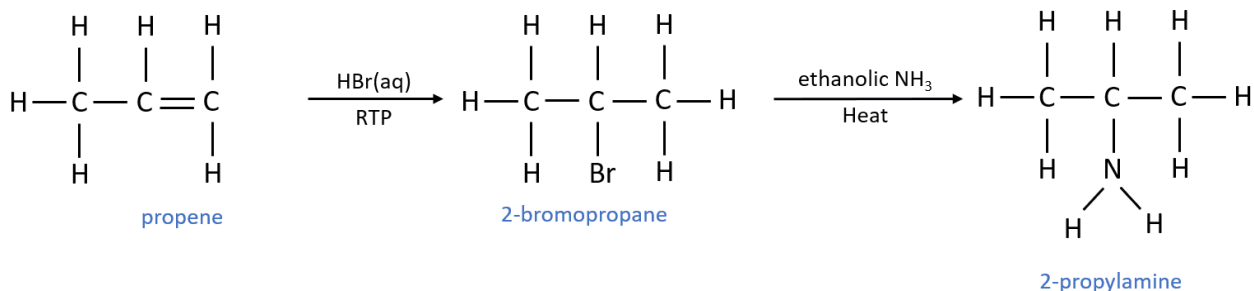
Example 1

Below is a diagram showing how ethanoic acid can be synthesised from chloroethane:



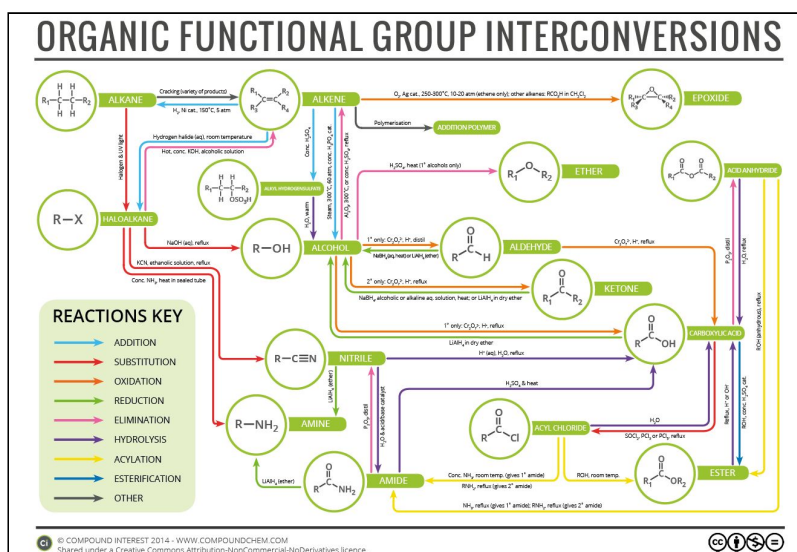
Example 2

2-propylamine can be formed from propene:



Synthesis Maps

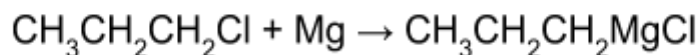
Synthesis maps provide a good **summary** of reactions in organic chemistry and show how multistep reactions can be used to get from one compound to another. Below is a good, detailed example of a synthesis map. Click on the link to view it in **full size**.



Grignard Reagents

Grignard reagents are molecules with the general formula **RMgX**, where X is a halogen and R is an alkyl or aryl group. They are prepared in a reflux setup by reacting a halogenoalkane with a small quantity of magnesium in **dry ether**.

Example:

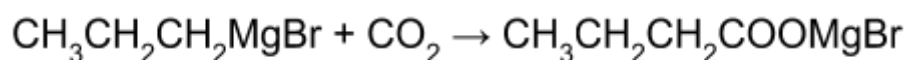


The produced Grignard reagent can be used to **lengthen the carbon chain** of another molecule/compound.

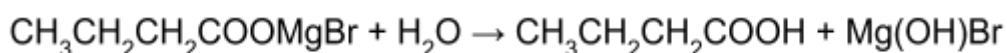
Reaction with Carbon Dioxide

Grignard reagents react with carbon dioxide. The product of this reaction is then **hydrolysed** to produce halides and **carboxylic acids**. The carboxylic acid has a carbon chain length of one more than the initial Grignard reagent.

Step 1: The reagent adds across the COO group.



Step 2: The product from step one is hydrolysed in dilute acid.

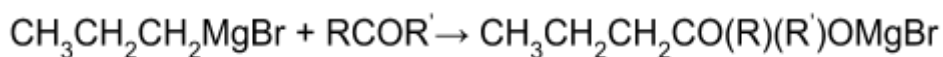


The second step is carried out in **dilute acid (H₃O⁺_(aq))**. The halide, in this case Mg(OH)Br, reacts with the acid to produce magnesium ions, bromide ions and water.

Reaction with Carbonyl Compounds

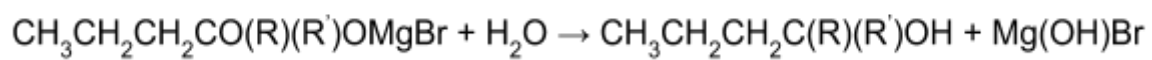
Grignard reagents react with carbonyl compounds in a similar way to their reaction with carbon dioxide. This reaction produces **alcohols**.

Step 1: The reagent adds across the C=O group.



Step 2: The product from step one is hydrolysed in dilute acid.





The identity of the alcohol product depends on the **R groups** of the initial carbonyl compound. Again, this reaction is useful for organic synthesis since it increases the **length of the carbon chain**.

