Edexcel Chemistry A-Level

Topic 18: Organic Chemistry III

Detailed Notes

Topic 18A: Arenes - Benzene

Bonding in Aromatic Compounds

Arenes are aromatic compounds that **contain a benzene ring as part of their structure**. They have **high melting points** due to the high stability of the delocalised benzene ring, but **low boiling points** as they are **non-polar** molecules and generally **cannot be dissolved** in water. Benzene is an **arene** consisting of a ring of **six carbon atoms** each bonded to **one hydrogen atom**, giving it the molecular formula C_6H_6. This structure means benzene has a ring of **delocalised electrons**:

Example: Displayed and skeletal formula of benzene

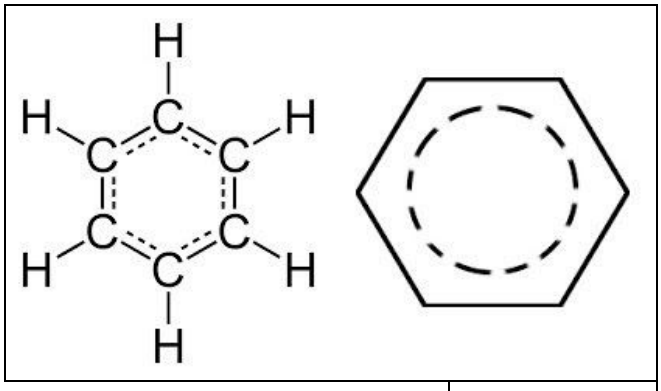


Image courtesy of Quora

The outer electron from the **p-orbital** of each carbon atom is **delocalised** into the centre to form the central ring. This overlap of electrons results in the formation of **π-bonds**.

The delocalised ring structure makes benzene **very stable** compared to other molecules of a similar size.

Evidence for Benzene's structure

When benzene was first discovered its structure was unknown. It was predicted from empirical measurements that it had a structure similar to that of **cyclohexatriene**, with three double bonds and three single bonds. However, chemical evidence and experiments suggested benzene actually had the structure given above.

Example: Displayed formula of cyclohexatriene

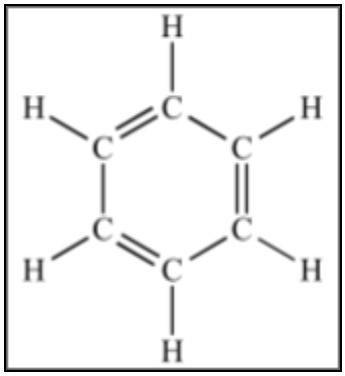


Image courtesy of www.chem.ucla.edu

Thermochemical - Cyclohexatriene vs. Benzene

Based on the structure of cyclohexatriene, the enthalpy change of hydrogenation for benzene was **predicted to be -360 kJmol^{-1}**, three times the enthalpy change of cyclohexene.

Example:

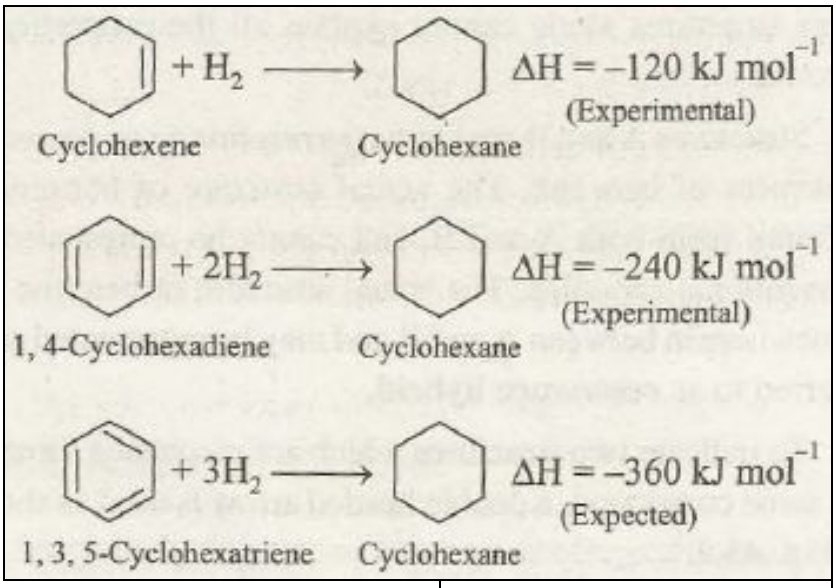


Image courtesy of chemistry-assignment.com

It was later discovered that the enthalpy change of hydrogenation of benzene was **actually -208 kJmol^{-1},** leading to the conclusion that its **structure** was **different** to that of **cyclohexatriene**. The enthalpy change of hydrogenation was **less negative than expected** (less exothermic), indicating that benzene is more stable than the suggested cyclohexatriene structure predicts.

X-ray Diffraction and Infrared Data

X-ray diffraction experiments have shown that **all** the bond lengths between carbon atoms in benzene are **the same**. If the cyclohexatriene structure was correct, three of the bond lengths would be the length of a **single** carbon bond and three would be the length of a **double** carbon bond. In reality, each bond in the benzene ring has an **intermediate length** in between that of a double and single bond.

The cyclohexatriene structure also did not explain **infrared data** collected from benzene molecules.

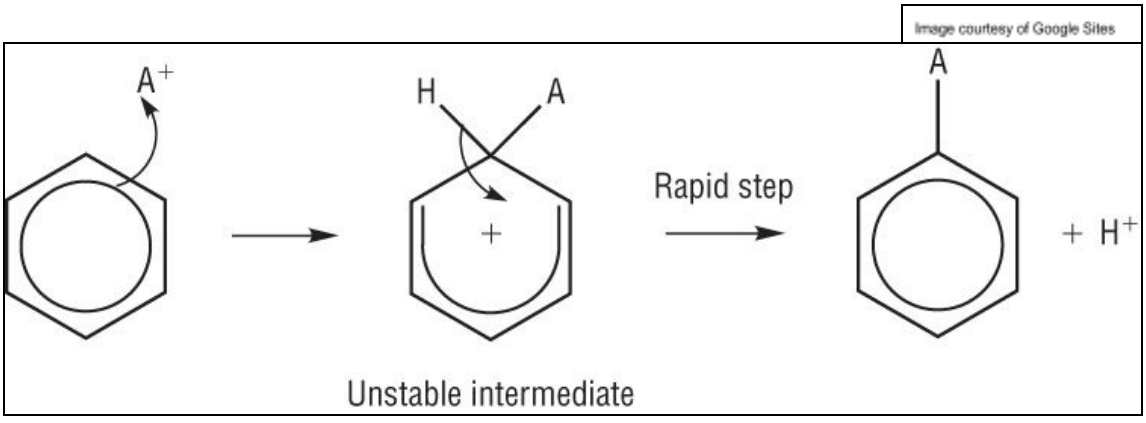
Reactions of Benzene

Benzene is resistant to **electrophilic addition** reactions, such as bromination, which other compounds with carbon-carbon double bonds, such as **alkenes**, readily undergo. Benzene does not undergo electrophilic addition since this would involve breaking up the **stable** delocalised ring of electrons, it instead undergoes **electrophilic substitution** reactions.

Electrophilic Substitution

The delocalised ring in benzene is an **area of high electron density,** making it susceptible to attack from **electrophiles**. In an electrophilic substitution mechanism, electrophiles attack the electron ring, **partially destroying** it, before it is then restored to form the aromatic product. This mechanism allows **aromatic amines** and **nitrobenzene** to be produced from benzene.

Mechanism - general electrophilic substitution mechanism



The electrophile is shown as A^+.

Halogenation

Halogenation is a type of **electrophilic substitution reaction** in which benzene reacts with halogens in the presence of a **catalyst,** such as iron(III) bromide ($FeBr_3$). The catalyst is required to generate the electrophile, which then reacts as shown above.

Example: The iron(III) bromide polarises the bromine molecule. This makes it easier for the bromine bond to break so that the bromine atom can act as an electrophile.

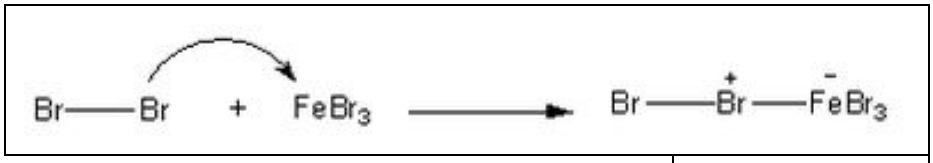


Image courtesy of wikipedia

Nitration

Nitration is a form of electrophilic substitution, where the electrophile is a **NO_2^+ ion**. This is a **reactive intermediate**, produced in the reaction of concentrated sulfuric acid (H_2SO_4) with concentrated nitric acid (HNO_3). Sulfuric acid behaves as a **catalyst** since it is not used up in the reaction.

Example: Formation of the electrophile

$$H_2SO_4 + HNO_3 \longrightarrow H_2NO_3^+ + HSO_4^-$$

$$H_2NO_3^+ \longrightarrow H_2O + NO_2^+$$

When heated with benzene, these reagents lead to the **substitution of the NO_2^+ electrophile** onto the benzene ring, **replacing a hydrogen** atom. The hydrogen ion released reacts with the HSO_4^- (produced above) to **reproduce** the sulfuric acid **catalyst**.

Mechanism

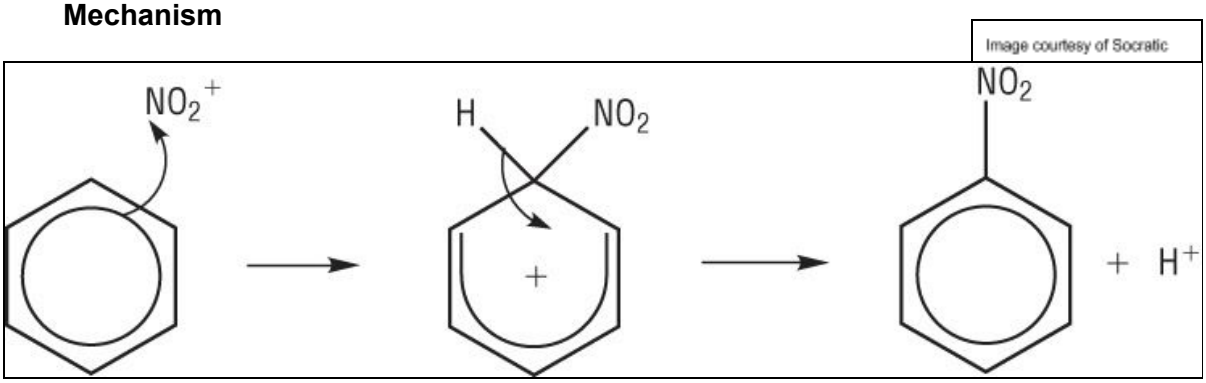


Image courtesy of Socratic

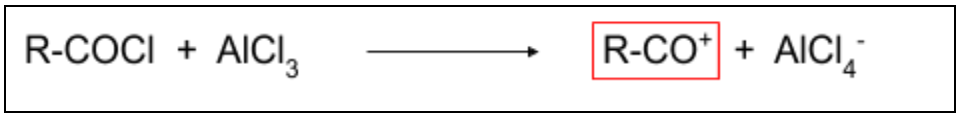
This reaction shows the **mono-substitution** of a single NO_2^+ electrophile, which takes place when the reaction temperature is **55°C**. At temperatures greater than this, multiple substitutions can occur on the benzene ring. It is vital that only one substitution occurs for the production of **aromatic amines**.

Friedel-Crafts Acylation

The delocalised electron ring in benzene can also act as a **nucleophile**, leading to their nucleophilic **attack on acyl chlorides**. This reaction is known as **Friedel-Crafts acylation**.

In order for the reaction to take place, a **reactive intermediate** must be produced from a reaction between the acyl chloride and an **aluminium chloride catalyst**.

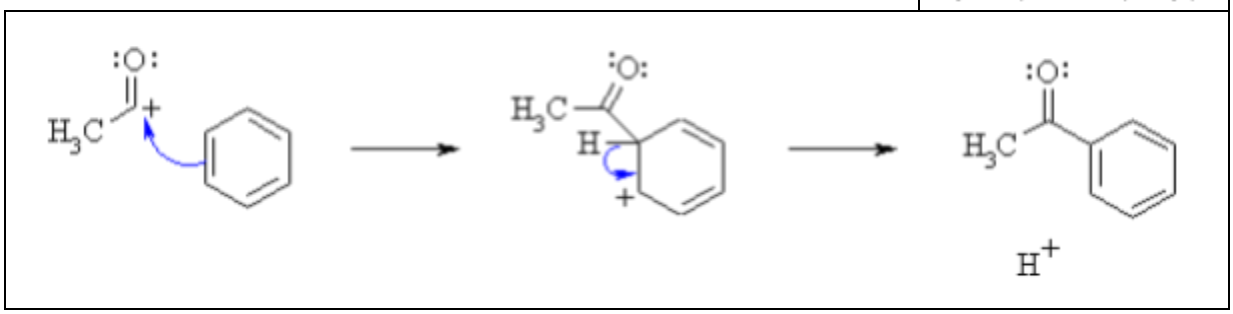
Example: Formation of the reactive intermediate



This reactive intermediate is then attacked by the benzene ring.

Mechanism

Image courtesy of the University of Calgary



At the end of the reaction, the **H^+ ion** removed from the ring reacts with the **$AlCl_4^-$ ion** to reform the aluminium chloride, indicating it to be a **catalyst**.

The product of this reaction is a **phenylketone**. In this case, the benzene group is called a **phenyl group**. These molecules are commonly used in the industrial production of dyes, pharmaceuticals and even explosives.

Bromine Water

Phenol, an aromatic compound with the formula **C_6H_5OH**, is produced in electrophilic substitution reactions with benzene. Phenol can react with bromine water via **multiple substitutions** to produce 2,4,6-tribromophenol which forms as a **white precipitate** with a distinct smell of antiseptic. This reaction decolourises bromine water.

Example: Formation of 2,4,6-tribromophenol

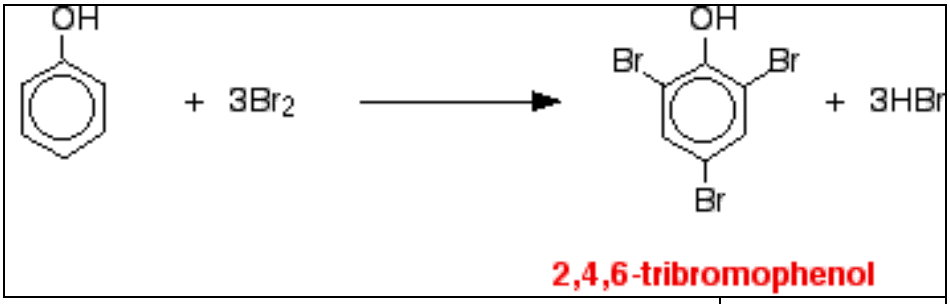


Image courtesy of ChemGuide

Benzene, on the other hand, cannot react with bromine water. The increased reactivity of phenol is due to the **lone pair of electrons on the oxygen atom,** which is delocalised into the benzene ring structure. This increases the **electron density** of the ring, making it less stable and thus **more susceptible to attack** from electrophiles.

Combustion

Benzene reacts with oxygen to produce carbon dioxide and water. This reaction produces a **smoky flame** due to the high carbon-content of benzene.

$$2C_6H_6 + 15O_2 \rightarrow 12CO_2 + 6H_2O$$

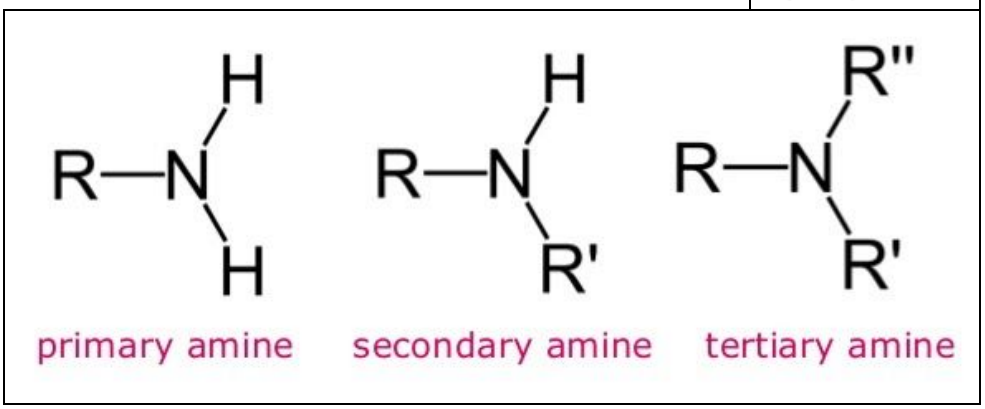
Topic 18B: Amines, Amides, Amino Acids and Proteins

Aliphatic Amines

Amines are produced when one or more of the hydrogen atoms in ammonia is **replaced with an alkyl group**. They can be classified as **primary, secondary or tertiary amines,** depending on how many alkyl groups are bonded to the nitrogen atom.

Example: Classification of amines

Image courtesy of SlideShare

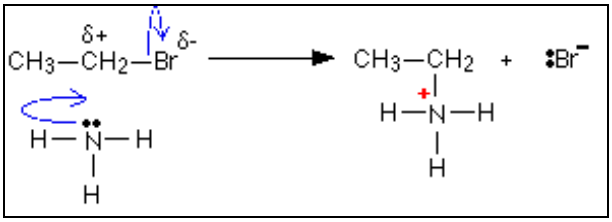


Amines can be produced by **nucleophilic substitution** or by the **reduction of nitriles**.

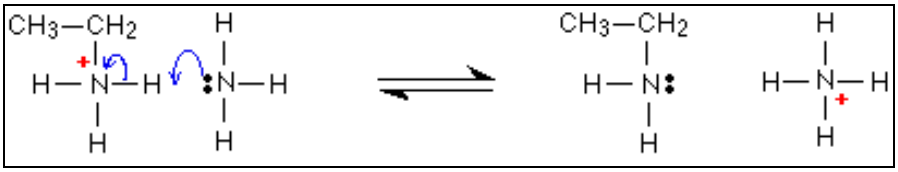
Nucleophilic Substitution

Amines can be produced from the nucleophilic substitution reaction between a **halogenoalkane with ammonia** in a sealed tube. One mole of halogenoalkane reacts with two moles of ammonia, producing a **primary amine** and an **ammonium salt (ammonium ion and halide ion)**.

Example: Nucleophilic substitution of bromoethane with ammonia



Images courtesy of chemguide.co.uk



This substitution reaction can continue until **all the hydrogen atoms have been replaced** with amine groups. Following this, an additional substitution can occur, producing a **quaternary ammonium salt**.

Example:

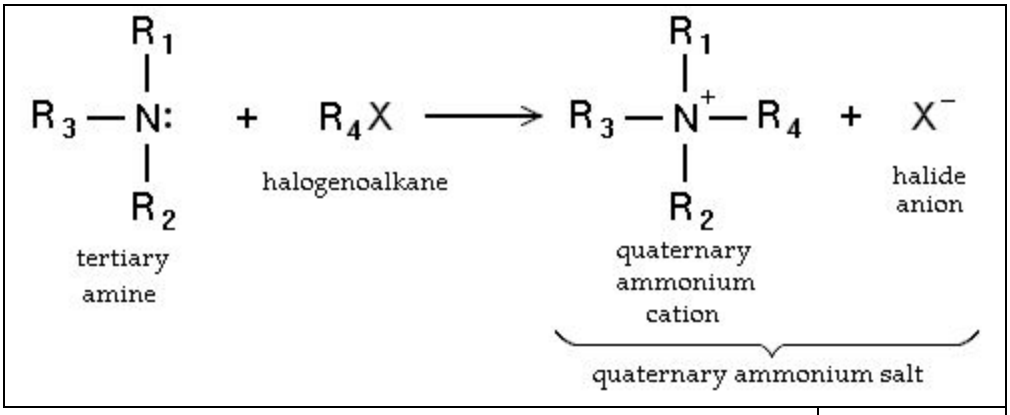


Image courtesy of Wikibooks

The multiple possible substitutions mean that a **mixture of products** is produced. Therefore, the reaction has **low efficiency** and the reaction **conditions** have to be changed so that only a single substitution occurs. Ammonia can be added **in excess** in order to form only the primary amine, or the mixture of products can be **separated using fractional distillation**.

Reduction of Nitriles

Amines can be produced by the reduction of nitriles by **hydrogenation.** This reduction requires the reducing agent **$LiAlH_4$**, and **acidic conditions,** or a combination of **hydrogen with a nickel catalyst** (catalytic hydrogenation).

Example:

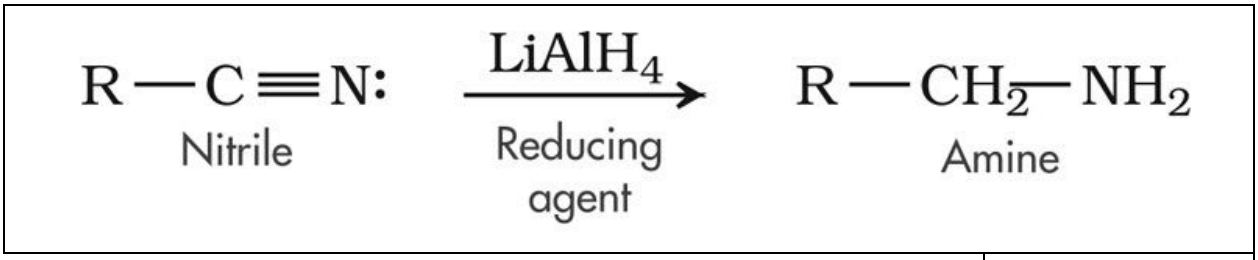


Image courtesy of Google Sites

Reactions of Primary Aliphatic Amines

Amines as Bases

Amines react with water to form an **alkaline solution**. The lone pair of electrons on the amine's nitrogen atom can **accept a hydrogen** from a water molecule, therefore acting as a base. This releases **OH^- ions** into the solution.

Example:

$$CH_3CH_2NH_2 + H_2O \rightarrow CH_3CH_2{}^+NH_3 + OH^-$$

To produce Salts

Amines react with acids to form an ammonium salt. Again, the amine acts as a base and accepts a proton to form a **quaternary ammonium salt**.

Example:

$$CH_3CH_2CH_2CH_2NH_2 + HCl \rightarrow CH_3CH_2CH_2CH_2{}^+NH_3\ Cl^-$$

Butylamine + hydrochloric acid → butylammonium chloride

Reaction with Copper(II) ions

In topic 15 we saw that ammonia can react with copper aqua ions to form an **octahedral complex.** Aliphatic amines can react in the same way. In solution, the copper ions will react with water to form a **copper aqua ion**. The amine then acts as a base to **accept protons** from the water ligands to give a **blue precipitate** of $Cu(OH)_2(H_2O)_4$ along with an ammonium salt.

Example:

$$[Cu(H_2O)_6]^{2+} + 2CH_3CH_2NH_2 \rightarrow [Cu(H_2O)_4(OH)_2] + 2CH_3CH_2NH_3{}^+$$

Amine Base Properties

Amines are **weak bases** because the **lone electron pair** on the nitrogen atom can accept protons. The base strength of amines depends on **how available** the electron pair is on the nitrogen atom. The more available the electron pair is, the more likely it is to accept a proton, meaning the amine is a stronger base.

The Inductive Effect

In an organic molecule, different functional groups can affect how available a lone electron pair is by changing the **electron density** around the molecule.

1. **Benzene rings** - draw electron density **away** from the nitrogen making the lone pair 'less available'

   Example:

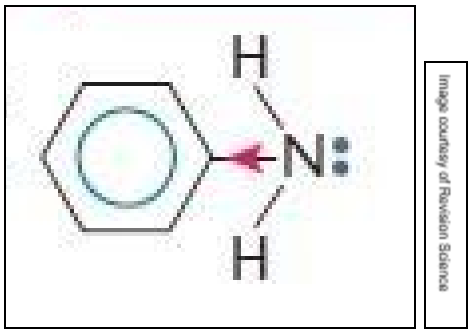


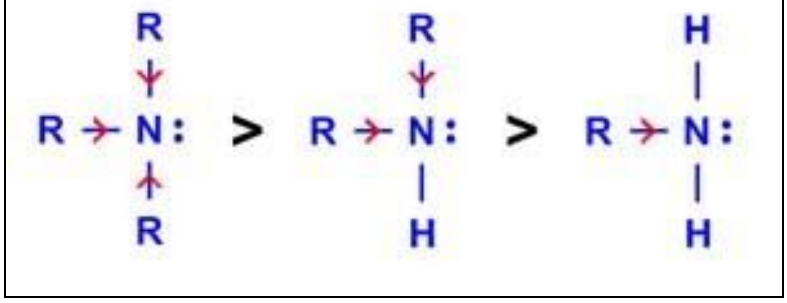
Image courtesy of Revision Science

Negative inductive effect

2. **Alkyl groups** - push electron density **towards** the nitrogen atom making the lone pair 'more available'. More alkyl groups means more 'pushing'.

   Example:

Image courtesy of Learnnext



Positive inductive effect

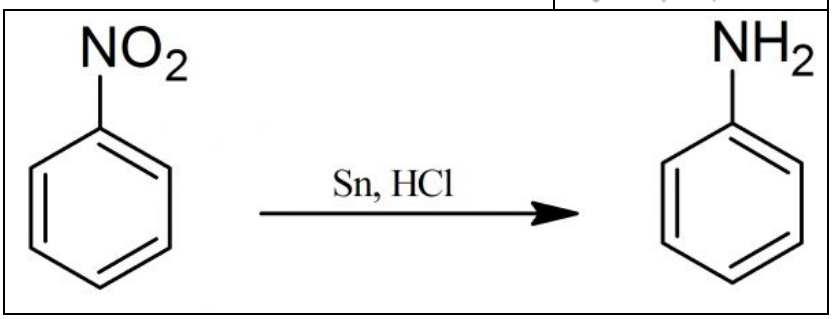
Therefore, **aliphatic amines are stronger** bases and **aromatic amines are weaker bases**.

Aromatic Amines

Aromatic amines can be produced from the **reduction of nitrobenzene** using **concentrated hydrochloric acid** (HCl) and a **tin catalyst**. Aromatic amines consist of an amine group and a benzene ring.

Example:

Image courtesy of PrepChem.com

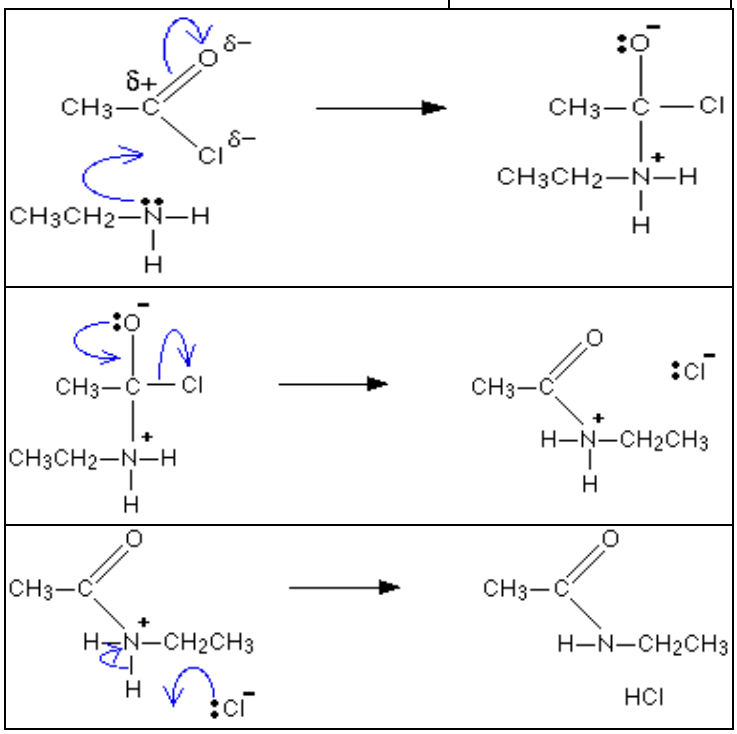


Amides

Amines can also undergo **nucleophilic addition-elimination** reactions with **acyl chlorides** to produce **amides** and **N-substituted amides**.

Mechanism

Images courtesy of chemguide.co.uk



N-substituted Amides

When **naming** N-substituted amides, they are treated in a similar way to **esters**. The **prefix** indicates the length of the carbon chain bonded to the **nitrogen** atom only and the **suffix** indicates the carbon chain which contains the **carbonyl** bond.

Example:

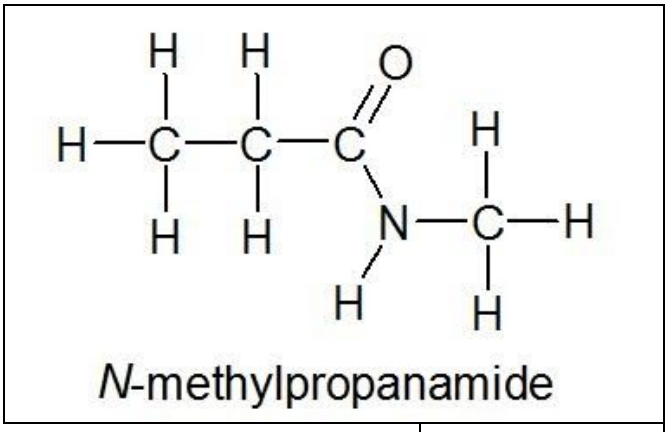


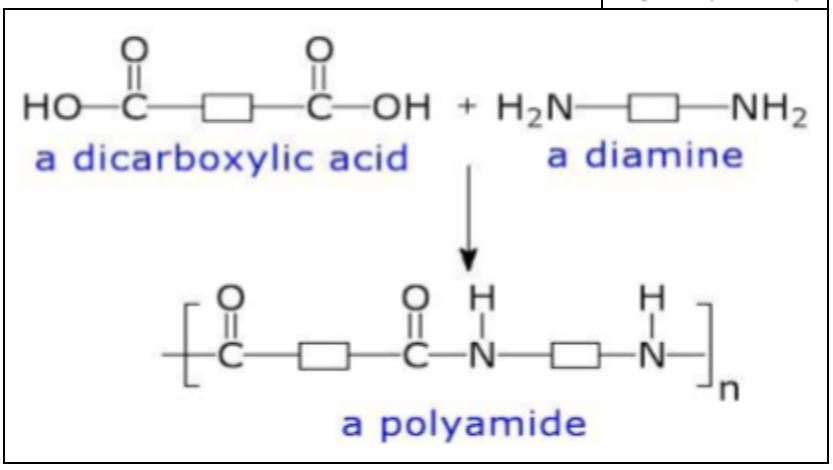
Image courtesy of callmedmob.com

Polyamides

Polyamides are condensation polymers generally formed in a reaction between a **dicarboxylic acid and a diamine**. A molecule of water is removed, leaving an **amide linkage**.

Example:

Image courtesy of QS Study



-CONH- is the amide linkage

Examples of polyamides include **nylon-6,6** made from 1,6-diaminohexane and hexanedioic acid.

Example: Repeat unit of nylon-6,6

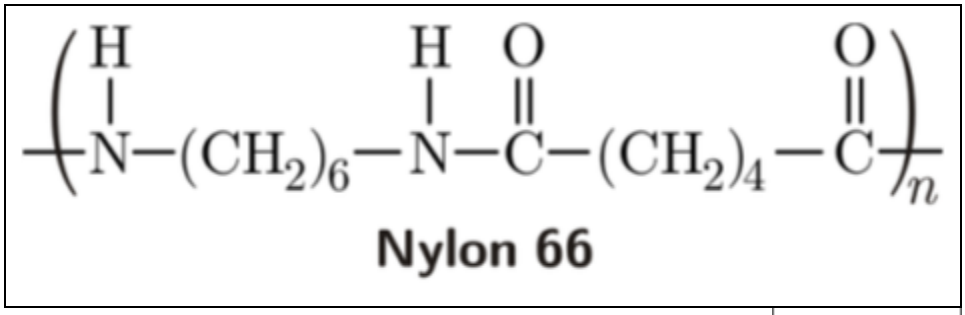


Image courtesy of Quora

Kevlar is another common polyamide made from benzene-1,4-dicarboxylic acid and 1,4-diaminobenzene.

Example: Repeat unit of kevlar

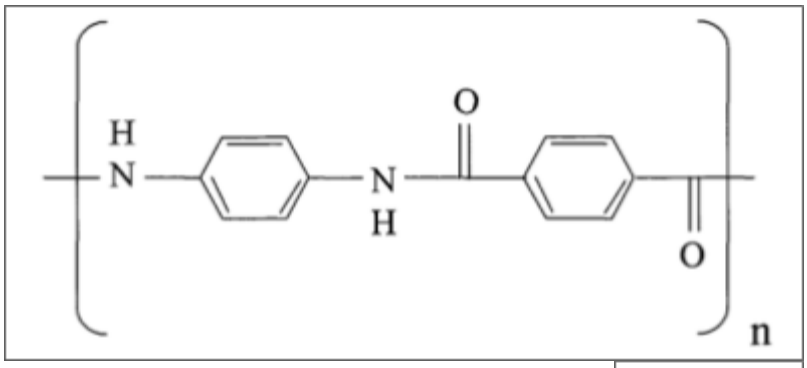


Image courtesy of Quora

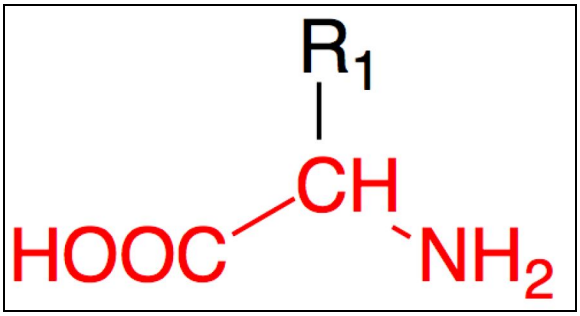
Polyamides are commonly formed from **long-chain molecules** which makes them **strong**.

Other polymers can be formed by condensation reactions. For example, **polyesters** are formed from the reaction between **dicarboxylic acids** and **diols.**

Amino Acids

Chirality

α-amino acids are organic molecules containing a **carboxylic acid group** and an **amine group** bonded to the same carbon atom. Their general structure is shown below, where different amino acids have different chemical groups as the 'R' side chain.



All amino acids, except **glycine**, contain a **chiral carbon** atom bonded to four separate groups. The R group on aminoethanoic acid (glycine) is just a hydrogen atom so the carbon is not bonded to four separate groups.

Since all other amino acids are chiral, they are **optically active**, so a solution of amino acids will **rotate plane-polarised monochromatic light**.

Zwitterions

The two functional groups within a single molecule mean that amino acids can **react as both acids and bases** depending on the conditions of the reaction.

In **acidic conditions (low pH)**, the COO^- group is more likely to accept a hydrogen ion, producing a **positive (acidic) end** to the molecule.

Example:

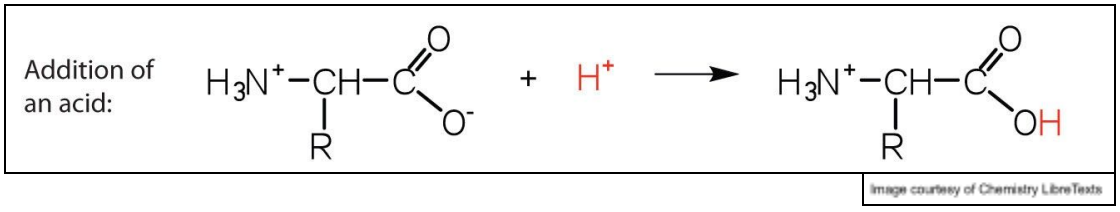
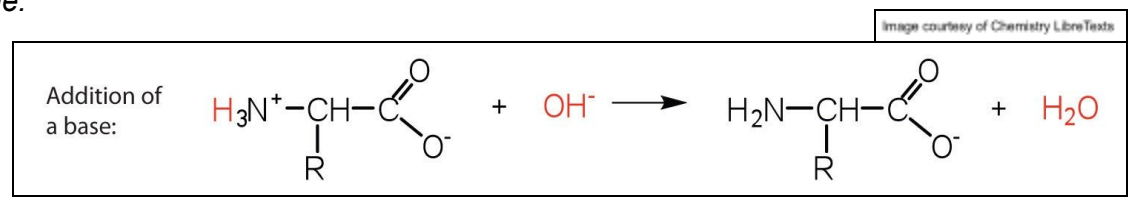


Image courtesy of Chemistry LibreTexts

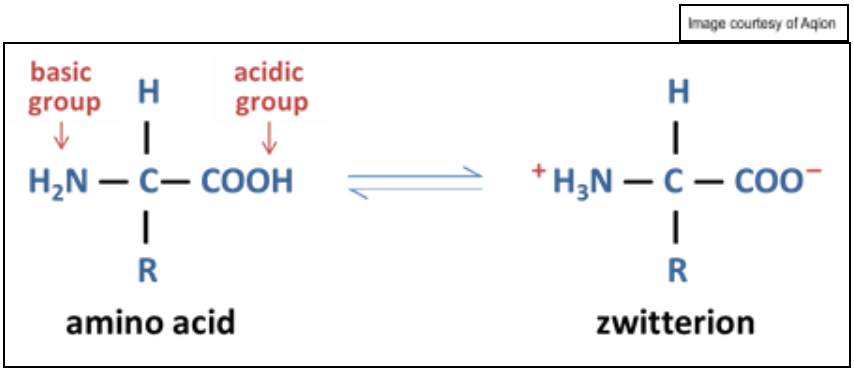
In **basic conditions (high pH)**, the hydrogen ion in the NH_3^+ group is more likely to be lost, producing a **negative (basic) end** to the molecule.

Example:



Zwitterions form at the **isoelectric** point, which is the pH at which the overall charge of the molecule is **zero**.

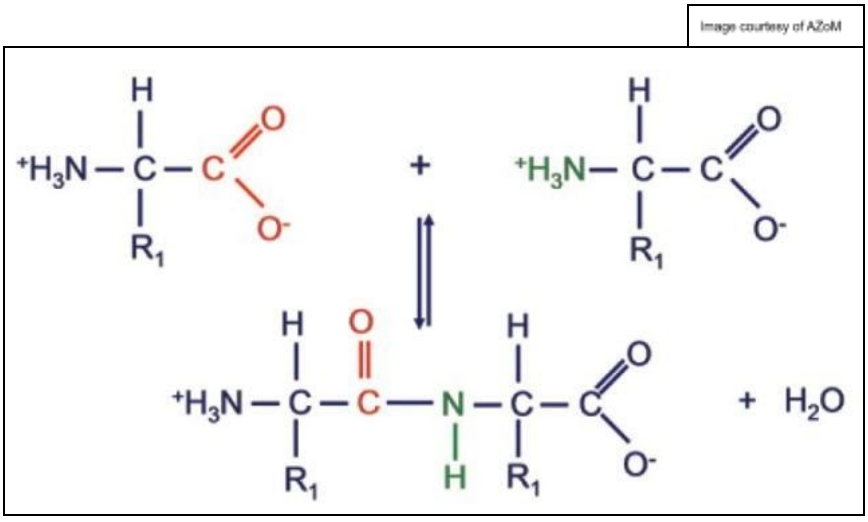
Example:



Proteins

Proteins are another form of condensation polymer formed from sequences of amino acids joined together by **peptide bonds**. Proteins can be **hydrolysed** into their constituent amino acids, which can then be separated and identified by **thin-layer chromatography**.

Example:



-CONH- is the peptide bond/amide linkage

Topic 18C: Organic Synthesis

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.

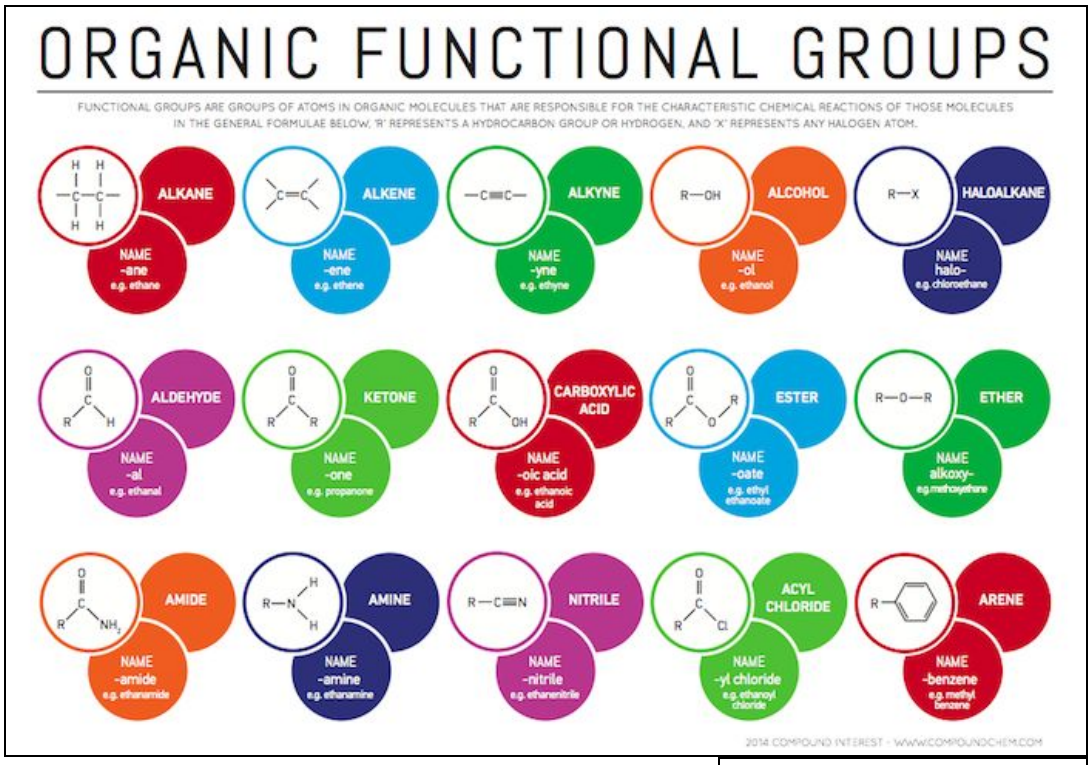


Image courtesy of Compound Interest

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	*Combustion* *Electrophilic substitution/free radical substitution* with Br_2 or Cl_2 (forms halogenoalkanes) *Cracking* (forms short chain alkenes and alkanes)	
Alkenes C=C	*Electrophilic addition:* - Steam (forms alcohols) - Hydrogen halides (forms halogenoalkanes) - Halogens (forms di-halogenoalkanes) - Hydrogen (forms alkanes) *Oxidation* with H^+/MnO_4^- (forms diols) *Addition polymerisation* (forms polymers) *Combustion*	**React with bromine water:** Decolorises in the presence of C=C.

Haloalkanes **C-F/ C-Cl/ C-Br/ C-I**	*Nucleophilic substitution:* - Hydrolysis (forms alcohols) - Reaction with ethanolic cyanide (forms nitriles) - Reaction with ammonia (forms primary amines) *Elimination* of hydrogen halide using ethanolic hydroxide ions (forms alkenes)	**React with $AgNO_3(aq)$, test precipitate with $NH_3(aq)$:** **AgCl** - white ppt soluble in dilute $NH_3(aq)$ **AgBr** - cream ppt soluble in concentrated $NH_3(aq)$ **AgI** - yellow ppt insoluble in $NH_3(aq)$
Alcohols **-OH**	*Combustion* *Substitution* with halogenating agents (forms halogenoalkanes) *Oxidation* with $H^+/Cr_2O_7^{2-}$ (forms carbonyls and carboxylic acids) *Dehydration* using an acid catalyst (forms alkenes) *Esterification* with carboxylic acids or acyl chlorides	**React with $H^+/Cr_2O_7^{2-}$:** Colour change from **orange** to **green** in the presence of primary and secondary alcohols (no change for tertiary alcohols).
Aldehydes **-CHO**	*Oxidation* with $H^+/Cr_2O_7^{2-}$ (forms carboxylic acids) *Reduction* using $LiAlH_4$ (forms primary alcohols) *Nucleophilic addition* with HCN (forms hydroxynitriles)	**React with 2,4-DNPH**: A yellow-orange precipitate is formed in the presence of a carbonyl group. **React with Tollens' reagent:** A silver mirror is produced if an aldehyde is present. **React with Fehling's reagent:** The blue solution forms a brick red precipitate in the presence of an aldehyde. **React with acidified potassium dichromate(VI):** Orange solution turns green.
Ketones **RCOR'**	*Reduction* using $LiAlH_4$ (forms secondary alcohols) *Nucleophilic addition* with HCN (forms hydroxynitriles)	**React with 2,4-DNPH**: A yellow-orange precipitate is formed in the presence of a carbonyl group.
Carboxylic acids **-COOH**	Reaction with metals, alkalis or carbonates (forms a salt and inorganic products) *Esterification* with alcohols *Reduction* with $LiAlH_4$ (forms alcohols)	**Test pH:** pH less than 7 when measured using a pH probe. **React with a carbonate**: Effervescence as CO_2 is formed.

	Reaction with phosphorus(V) chloride (forms acyl chlorides) *Reduction* with $LiAlH_4$ (forms aldehydes and then primary alcohols)	
Esters RCOOR'	*Acid hydrolysis* (forms a carboxylic acid and an alcohol) *Alkali hydrolysis* (forms a carboxylate salt and an alcohol)	Generally have distinct sweet smells.
Amines $-NH_2$	Reaction with acids (forms a salt)	
Nitriles C≡N	*Acid hydrolysis* (forms a carboxylic acid and a salt) *Alkaline hydrolysis* (forms a carboxylate salt and ammonia) *Reduction* (forms primary aliphatic amines)	
Arenes $-C_6H_5$	*Electrophilic substitution:* - Halogen (forms chlorobenzene with Cl_2 and bromobenzene with Br_2) - Nitration (forms nitrobenzene) Friedel-Crafts *acylation* and *alkylation* *Hydrogenation* (forms cyclohexane)	
Phenol C_6H_5OH	Reactions with strong bases (not acidic enough to react with carbonates) *Electrophilic substitution:* - Bromination using Br_2 (forms bromophenol)	
Acyl chlorides -COCl	*Hydrolysis* with water (forms carboxylic acids and HCl) *Hydrolysis* with sodium hydroxide (forms a carboxylate salt and water) *Esterification* with alcohols or phenol Reaction with ammonia (forms an amide and HCl) Reactions with primary amines (forms an N-substituted amide)	

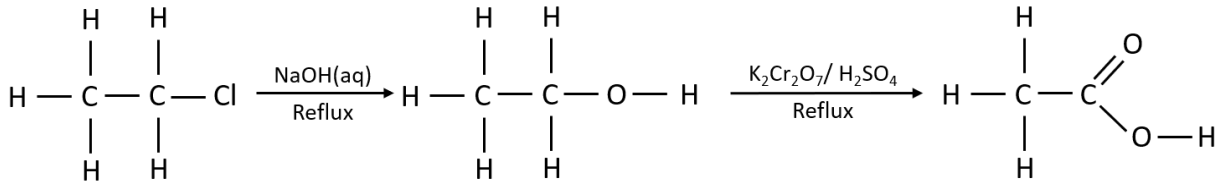
Amides -CONH$_2$	*Acid hydrolysis* (forms a carboxylic acid and ammonium ions) *Alkali hydrolysis* (forms a carboxylate salt and ammonia or an amine) *Reduction* using $LiAlH_4$ (forms a primary amine)	

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.

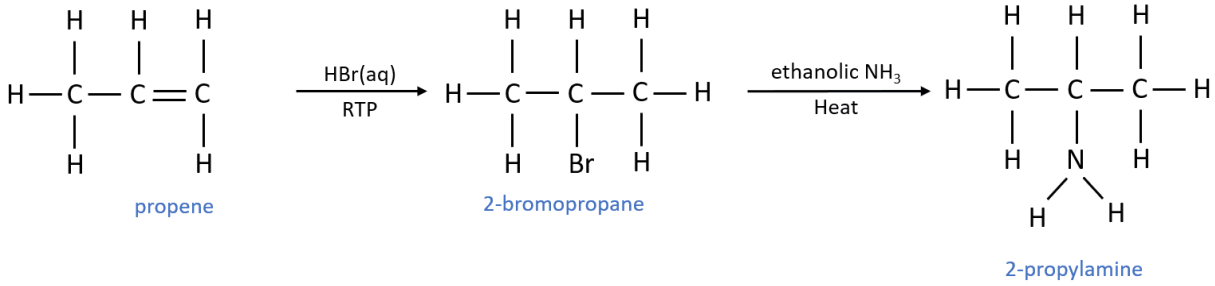
Example 1

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



Example 2

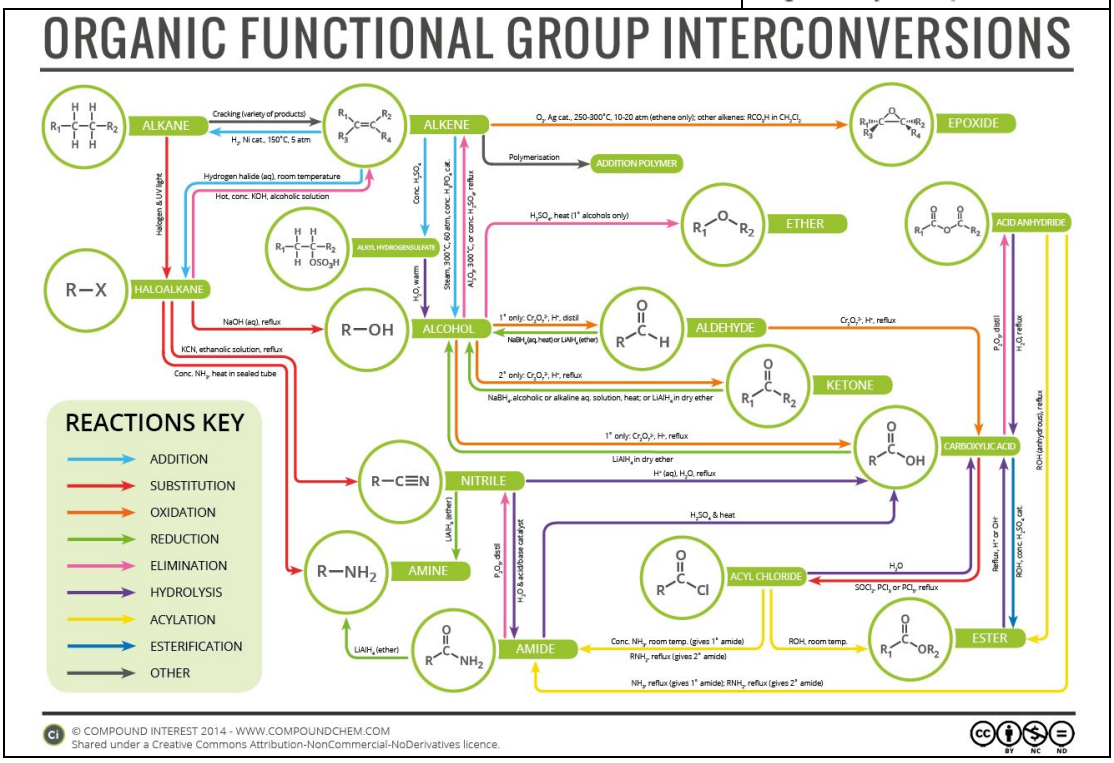
2-propylamine can be formed from propene:



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**.

Image courtesy of Compound Interest



(http://www.compoundchem.com/2014/02/17/organic-chemistry-reaction-map/)

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:

$$CH_3CH_2CH_2Cl + Mg \rightarrow CH_3CH_2CH_2MgCl$$

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.

$$CH_3CH_2CH_2MgBr + CO_2 \rightarrow CH_3CH_2CH_2COOMgBr$$

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

$$CH_3CH_2CH_2COOMgBr + H_2O \rightarrow CH_3CH_2CH_2COOH + Mg(OH)Br$$

The second step is carried out in **dilute acid ($H_3O^+_{(aq)}$)**. 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.

$$CH_3CH_2CH_2MgBr + RCOR' \rightarrow CH_3CH_2CH_2CO(R)(R')OMgBr$$

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

$$CH_3CH_2CH_2CO(R)(R')OMgBr + H_2O \rightarrow CH_3CH_2CH_2C(R)(R')OH + Mg(OH)Br$$

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**.