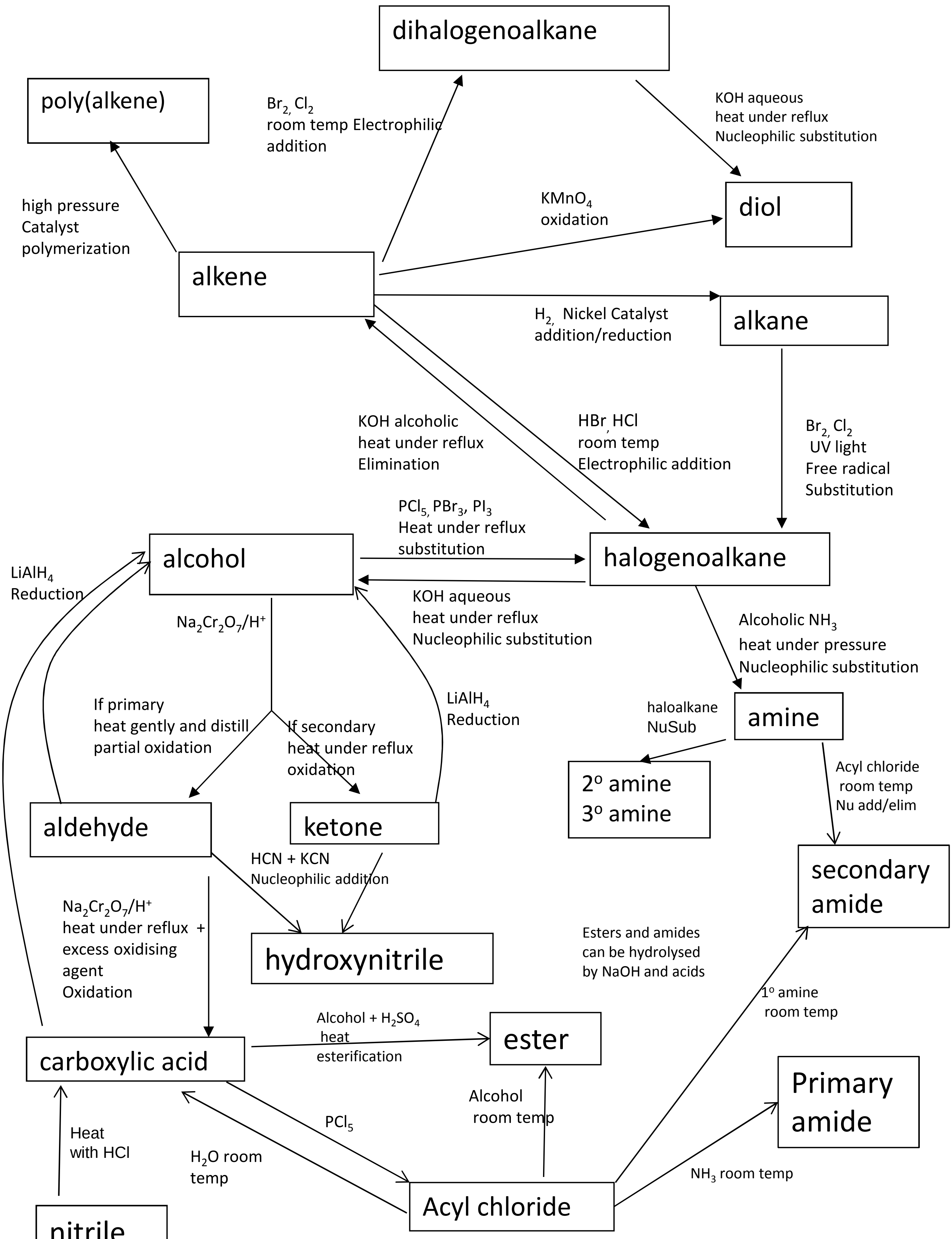
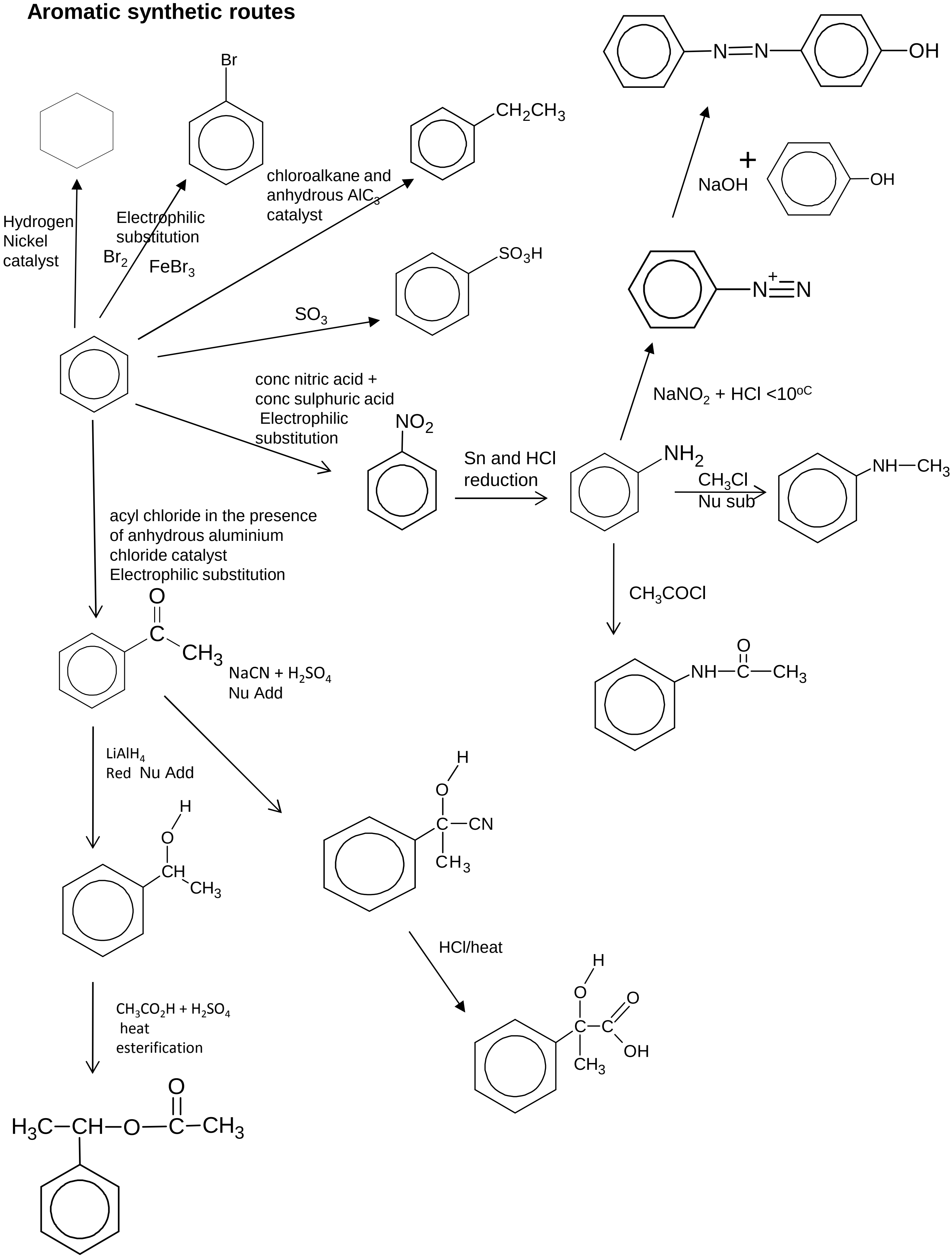
5. Synthetic Routes



Aromatic synthetic routes



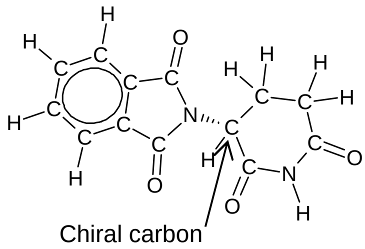
Drug action and optical isomers

Drug action may be determined by the stereochemistry of the molecule. Different optical isomers may have very different effects

Synthetic pathways for the manufacture of pharmaceuticals may require reactions that are highly stereospecific. This because receptors for the compound in the body are often stereospecific so only one stereoisomer is pharmacologically active and potentially the other isomer may be toxic

When a substance is chiral it will have enantiomers. If the mechanism leads to racemisation because it occurs via a planar molecule or carbocation then its production will lead to a mixture of enantiomers. This is will mean there is a need to separate the enantiomers and discard an unwanted enantiomer, leading to expense of separation and lower atom economy.

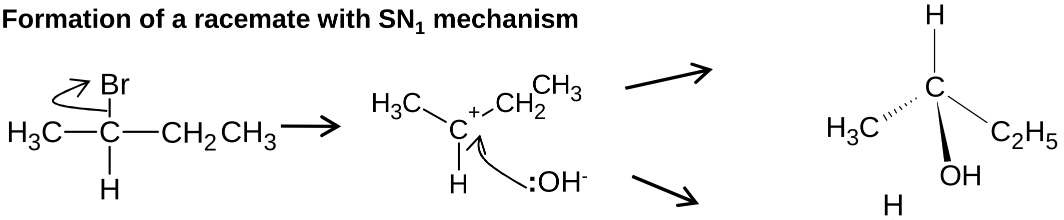
Thalidomide

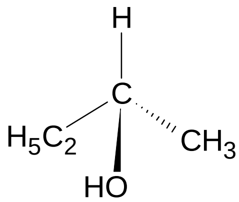


One enantiomer of thalidomide causes birth defects in unborn children whilst the other had useful sedative problems. Unfortunately it was given in a racemic mixture when first used.

Remember the two mechanisms below and how they can/cannot lead to racemic mixtures

Formation of a racemate with SN_1 mechanism





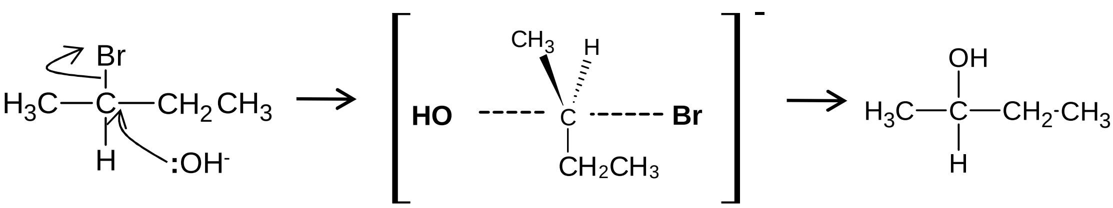
The Br first breaks away from the haloalkane to form a planar carbocation intermediate

The OH^- ion can then attack from either side resulting in different enantiomers and a **racemate forms**

Because a racemate forms there will be no optical activity in the products

Comparison with SN_2 mechanism

In the SN_2 mechanism no intermediates are formed and the reaction occurs via a transition state.



If the reactant was chiral then during the reaction the **opposite enantiomer would form**.
The product will rotate light in the opposite direction to the reactant

Combinatorial chemistry

Combinatorial chemistry is a modern method used in the pharmaceutical industry to synthesise many products quickly

Researchers attempting to optimize the activity profile of a compound will create a library of many different but related compounds

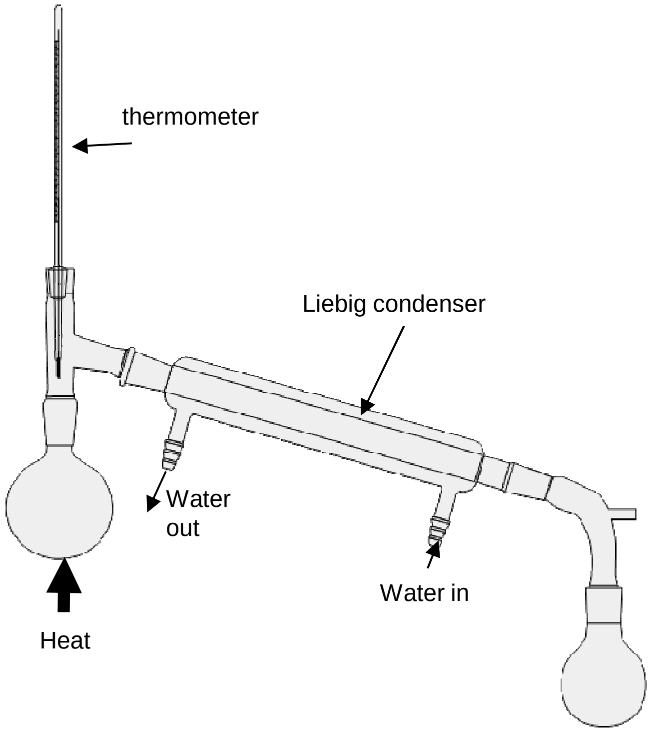
The principal advantage of combinatorial chemistry over traditional methods for developing pharmaceuticals is that many more compounds can be made in a given time.

Combinatorial chemistry involves initially attaching compounds firmly to polymer beads by covalent bonds, then different reagents are passed over them simultaneously synthesising a whole series of different substances

Organic techniques

Distillation

In general used as separation technique to separate an organic product from its reacting mixture. Need to collect the distillate of the approximate boiling point range of the desired liquid.

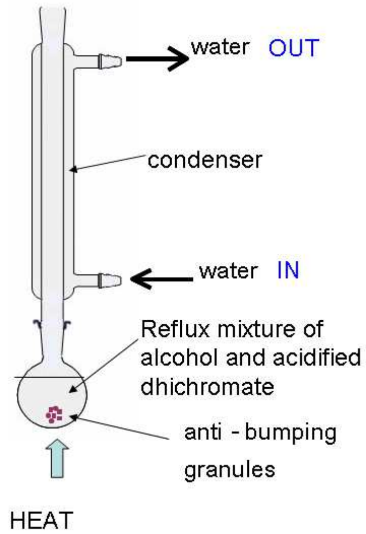


Classic AS reaction using distillation
Reaction: primary alcohol → aldehyde
Reagent: potassium dichromate (VI) solution and dilute sulphuric acid.
Conditions: use a limited amount of dichromate and **warm gently and distil** out the aldehyde as it forms [This prevents further oxidation to the carboxylic acid]
$CH_3CH_2CH_2OH + [O] \rightarrow CH_3CH_2CHO + H_2O$
Observation
Orange dichromate solution changes to green colour of Cr^{3+} ions

Reflux

Reflux is used when heating organic reaction mixtures for long periods to speed up the rates of reaction. The condenser prevents organic vapours from escaping by condensing them back to liquids.

Never seal the end of the condenser as the build up of gas pressure could cause the apparatus to explode. This is true of any apparatus where volatile liquids are heated



Classic AS reaction using reflux
Reaction: primary alcohol → carboxylic acid
Reagent: potassium dichromate(VI) solution and dilute sulphuric acid
Conditions: use an excess of dichromate, and **heat under reflux**: (distill off product after the reaction has finished using distillation set up)
$CH_3CH_2CH_2OH + 2[O] \rightarrow CH_3CH_2CO_2H + H_2O$
Observation
Orange dichromate solution changes to green colour of Cr^{3+} ions

Anti-bumping granules are added to the flask in both distillation and reflux to prevent vigorous, uneven boiling.

Purifying an organic liquid

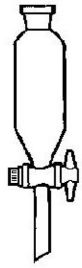
- Put the distillate of impure product into a separating funnel
- wash product by adding either
  - sodium hydrogencarbonate solution , shaking and releasing the pressure from CO_2 produced.
  - Saturated sodium chloride solution
- Allow the layers to separate in the funnel, and then run and discard the aqueous layer.
- Run the organic layer into a clean, dry conical flask and add three spatula loads of drying agent (anhydrous sodium sulphate) to dry the organic liquid.
- Carefully decant the liquid into the distillation flask
- Distill to collect pure product

Sodium hydrogencarbonate will neutralise any remaining reactant acid.

Sodium chloride will help separate the organic layer from the aqueous layer

The drying agent should
- be insoluble in the organic liquid
- not react with the organic liquid

Separating funnel



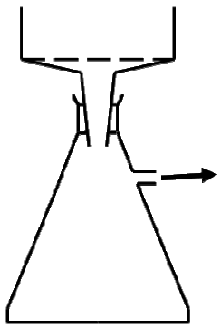
Purifying an organic solid: Recrystallisation

Used for purifying aspirin

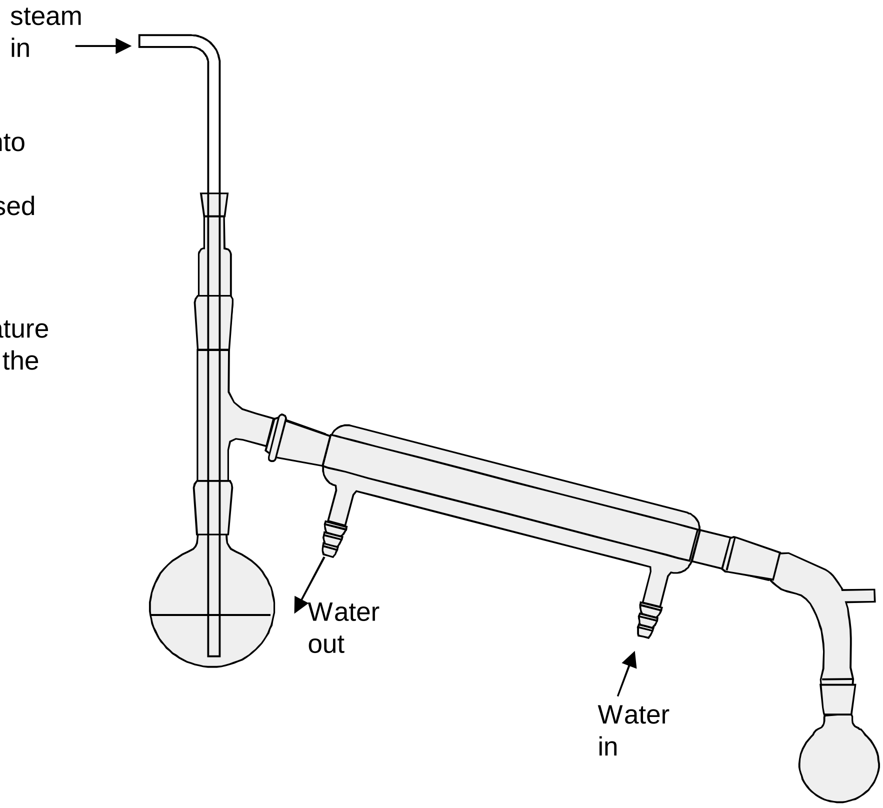
Step	Reason
1. Dissolve the impure compound in a **minimum volume** of **hot** (near boiling) **solvent**.	An appropriate solvent is one which will dissolve both compound and impurities when hot **and** one in which the compound itself does not dissolve well when cold. The minimum volume is used to obtain saturated solution and to enable crystallisation on cooling (If excess (solvent) is used, crystals might not form on cooling)
2. **Hot filter** solution through (fluted) filter paper quickly.	This step will remove any insoluble impurities and heat will prevent crystals reforming during filtration
3. **Cool** the filtered solution by inserting beaker **in ice**	Crystals will reform but soluble impurities will remain in solution form because they are present in small quantities so the solution is not saturated with the impurities. Ice will increase the yield of crystals
4**. Suction filtrate** with a buchner flask to separate out crystals	The water pump connected to the Buchner flask reduces the pressure and speeds up the filtration.
5 Wash the crystals with distilled water	To remove soluble impurities
6. Dry the crystals between absorbent paper	

Loss of yield in this process
- Crystals lost when filtering or washing
- Some product stays in solution after recrystallisation
- other side reactions occurring

buchner flask



Steam distillation



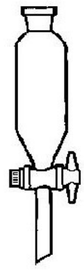
In steam distillation steam is passed into the mixture and the product vapour is distilled off with the water and condensed

Advantage of steam distillation:
The product distils at a lower temperature which can prevents decomposition of the product if it has a high boiling point

Solvent extraction

Mix organic solvent and oil-water mixture in a separating funnel then separate the oil layer.
Distil to separate oil from organic solvent
Add anhydrous $CaCl_2$ to clove oil to dry oil
Decant to remove $CaCl_2$

Separating funnel



Safety and hazards

A **hazard** is a substance or procedure that can has the potential to do harm.
Typical hazards are toxic/flammable /harmful/ irritant /corrosive /oxidizing/ carcinogenic

RISK: This is the probability or chance that harm will result from the use of a hazardous substance or a procedure

Irritant - dilute acid and alkalis- wear googles
Corrosive- stronger acids and alkalis wear goggles
Flammable – keep away from naked flames
Toxic – wear gloves- avoid skin contact- wash hands after use
Oxidising- Keep away from flammable / easily oxidised materials

Hazardous substances in low concentrations or amounts will not pose the same risks as the pure substance.

Measuring melting point

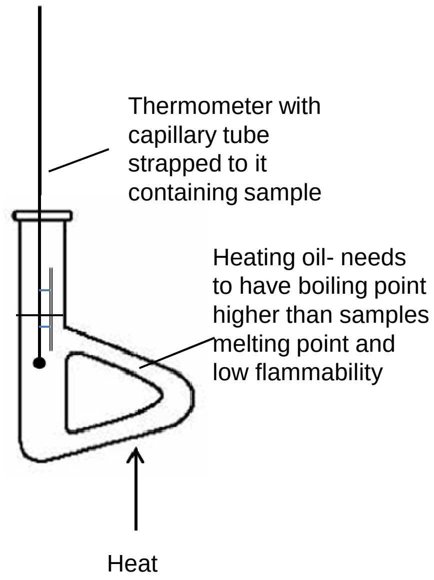
One way of testing for the degree of purity is to determine the melting "point", or melting range, of the sample.

If the sample is very pure then the melting point will be a sharp one, at the same value as quoted in data books.

If **impurities** are present (and this can include solvent from the recrystallisation process) the **melting point will be lowered** and the sample will **melt over a range** of several degrees Celsius

Melting point can be measured in an electronic melting point machine or by using a practical set up where the capillary tube is strapped to a thermometer immersed in some heating oil.

In both cases a small amount of the salt is put into a capillary tube.



Comparing an experimentally determined melting point value with one quoted in a data source will verify the degree of purity.

Sometimes an error may occur if the temperature on the thermometer is not the same as the temperature in the actual sample tube.

Measuring boiling point

Purity of liquid can be determined by measuring a boiling point. This can be done in a distillation set up or by simply boiling a tube of the sample in an heating oil bath.

Pressure should be noted as changing pressure can change the boiling point of a liquid

Measuring boiling point is not the most accurate method of identifying a substance as several substances may have the same boiling point.

To get a correct measure of boiling point the thermometer should be above the level of the surface of the boiling liquid and be measuring the temperature of the saturated vapour.

Combustion Analysis

0.328 g of a compound containing C,H and O was burnt completely in excess oxygen, producing 0.880 g of carbon dioxide and 0.216 g of water. Use these data to calculate the empirical formula of the compound.

Work out moles of CO_2 = Mass of CO_2/Mr of CO_2
= 0.88/44
=0.02mol

Moles of C in compound = moles of CO_2
= 0.02 mol
→ Mass of C in compound = mol of C x 12
=0.02 x12
=0.24g

Work out moles of H_2O = Mass of H_2O /Mr of H_2O
= 0.216/18
=0.012mol

Moles of H in compound = 2 x moles of H_2O
= 0.024 mol
→ Mass of H in compound = mol of H x 1
=0.024 x1
=0.024g

Work out mass of O in compound = mass of compound – mass of C – mass of H
= 0.328 – 0.24 -0.024
=0.064

Work out moles of O in compound = Mass of O /Ar of O
= 0.064/16
= mol 0.004

Work out molar ratio of 3 elements (divide by smallest moles)

C = 0.02/0.004
=5

H = 0.024/0.004
=6

O = 0.004/0.004
= 1

empirical formula = C_5H_6O

See notes in module 4 on spectroscopy for mass spec, IR, and NMR

Bringing it all together

1. Work out empirical formula

Elemental analysis C 66.63% H 11.18% O 22.19%

C	H	O
66.63/12	11.18/1	22.19/16
=5.5525	=11.18	=1.386875
=4	=8	=1

2. Using molecular ion peak m/z value from mass spectrum calculate Molecular formula

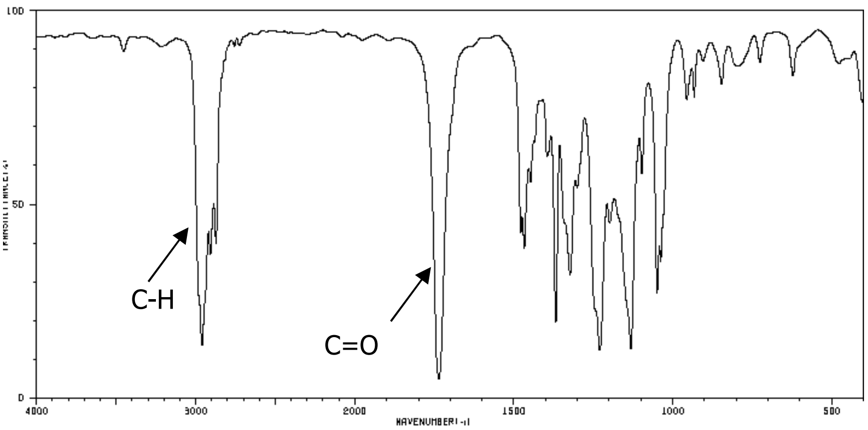
molecular ion peak m/z value= 144

Mr empirical formula C_4H_8O = 72

If Mr molecular formula 144 then compound is $C_8H_{16}O_2$

3. Use IR spectra or functional group chemical tests to identify main bonds/functional group

$C_8H_{16}O_2$ could be an ester, carboxylic acid or combination of alcohol and carbonyl. Look for IR spectra for C=O and O-H bonds

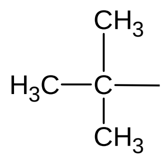


There is a C=O but no O-H absorptions, so must be an ester.

4. Use NMR spectra to give details of carbon chain

4 peaks – only 4 different environments.

singlet of area 9
At δ =0.9
Means 3 CH_3 groups



Peak at δ 4 shows H–C–O

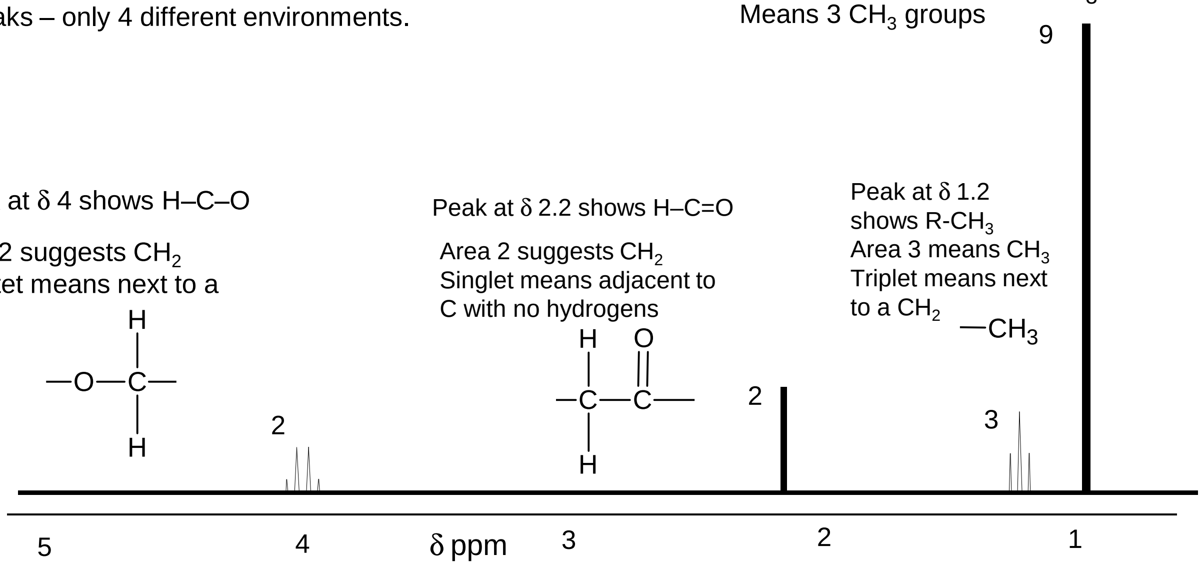
Area 2 suggests CH_2
Quartet means next to a CH_3

Peak at δ 2.2 shows H–C=O

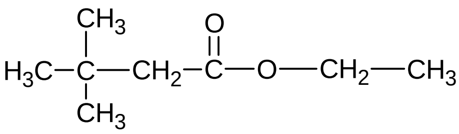
Area 2 suggests CH_2
Singlet means adjacent to C with no hydrogens

Peak at δ 1.2 shows R-CH_3
Area 3 means CH_3
Triplet means next to a CH_2

—CH_3



Put all together to give final structure



Testing for Organic Functional Groups

Functional group	Reagent	Result
Alkene	Bromine water	Orange colour decolourises
Alcohols + carboxylic acids	PCl_5	Misty fumes of HCl produced
Alcohols, phenols, carboxylic acids	Sodium metal	Efferevesence due to H_2 gas
Carbonyls	2,4,DNP	Orange/red crystals produced
Aldehyde	Fehlings solution	Blue solution to red precipitate
Aldehyde	Tollens Reagent	Silver mirror formed
Carboxylic acid	Sodium carbonate	Effervescence of CO_2 evolved
1^o 2^o alcohol and aldehyde	Sodium dichromate and sulphuric acid	Orange to green colour change
chloroalkane	Warm with silver nitrate	Slow formation of white precipitate of AgCl
Acyl chloride	Silver nitrate	Vigorous reaction- steamy fumes of HCl- rapid white precipitate of AgCl

Tollen's Reagent

Reagent: Tollen's Reagent formed by mixing aqueous ammonia and silver nitrate. The active substance is the complex ion of $[Ag(NH_3)_2]^+$.

Conditions: heat gently

Reaction: aldehydes only are oxidised by Tollen's reagent into a carboxylic acid and the silver(I) ions are reduced to silver atoms

Observation: with aldehydes, a silver mirror forms coating the inside of the test tube. Ketones result in no change.

$$CH_3CHO + 2Ag^+ + H_2O \rightarrow CH_3COOH + 2Ag + 2H^+$$

Fehling's solution

Reagent: Fehling's Solution containing blue Cu^{2+} ions.

Conditions: heat gently

Reaction: aldehydes only are oxidised by Fehling's Solution into a carboxylic acid and the copper ions are reduced to copper(I) oxide .

Observation: Aldehydes : Blue Cu^{2+} ions in solution change to a red precipitate of Cu_2O. **Ketones do not react**

$$CH_3CHO + 2Cu^{2+} + 2H_2O \rightarrow CH_3COOH + Cu_2O + 4H^+$$

The presence of a carboxylic acid can be tested by addition of **sodium carbonate.** It will fizz and produce carbon dioxide

$$2CH_3CO_2H + Na_2CO_3 \rightarrow 2CH_3CO_2^-Na^+ + H_2O + CO_2$$