23 Synthetic Routes

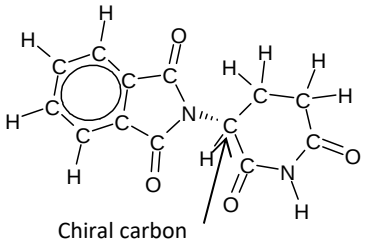
Chirality in pharmaceutical synthesis

The synthesis of pharmaceuticals often requires the production of a single optical isomer

Molecules prepared synthetically in the laboratory often contain a mixture of optical isomers, whereas molecules of the same compound produced naturally by enzymes in
living systems will often be present as one optical isomer only

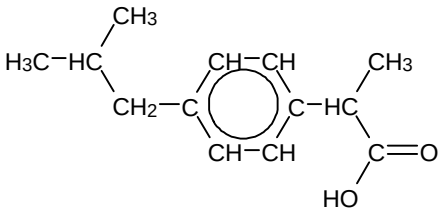
Drug action and optical isomers
Drug action may be determined by the stereochemistry of the molecule. Different optical isomers may have very different effects

Thalidomide



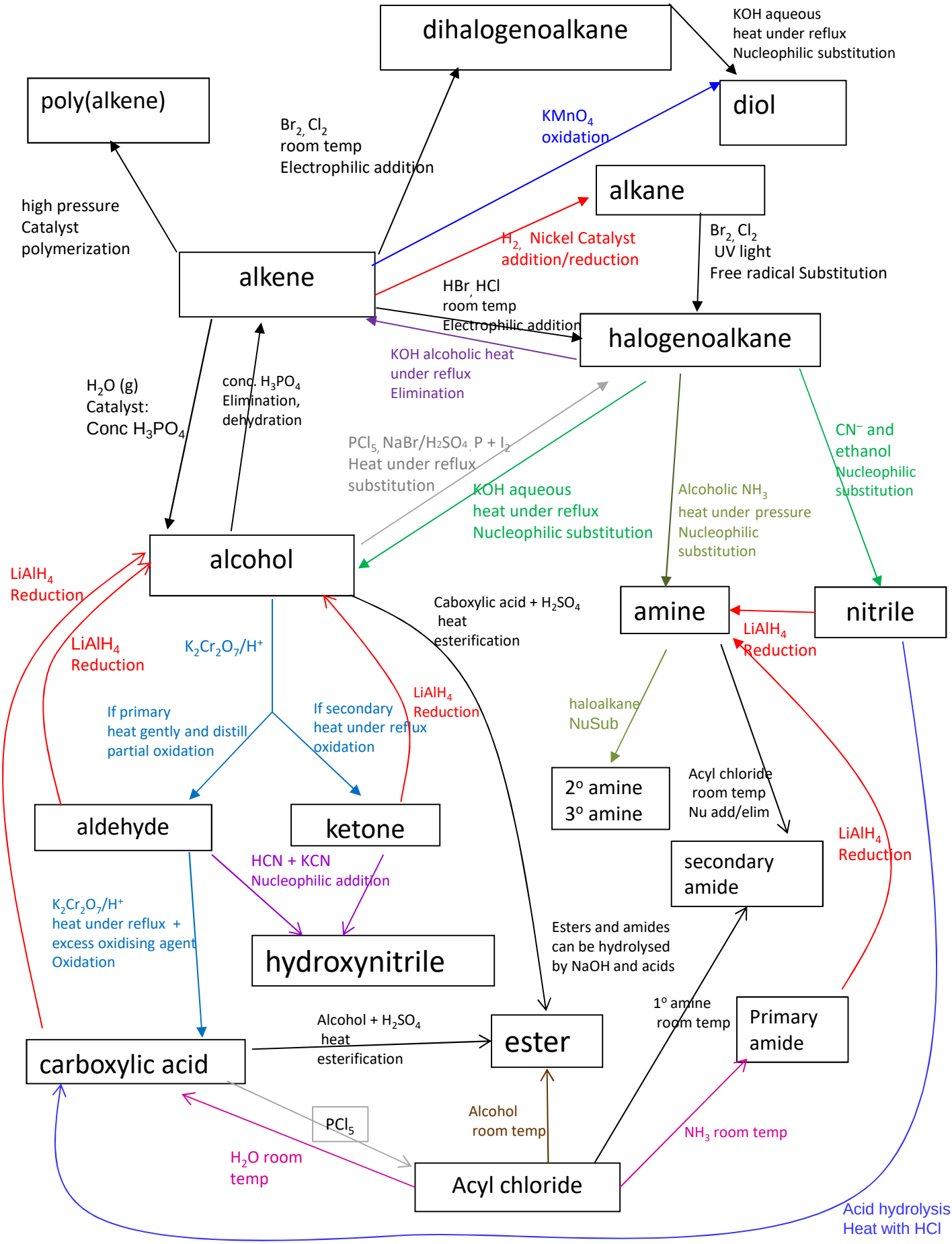
One enantiomer of thalidomide causes birth defects in unborn children whilst the other had useful sedative problems. Unfortunately it was given in a mixture of the two when first used.

Ibuprofen

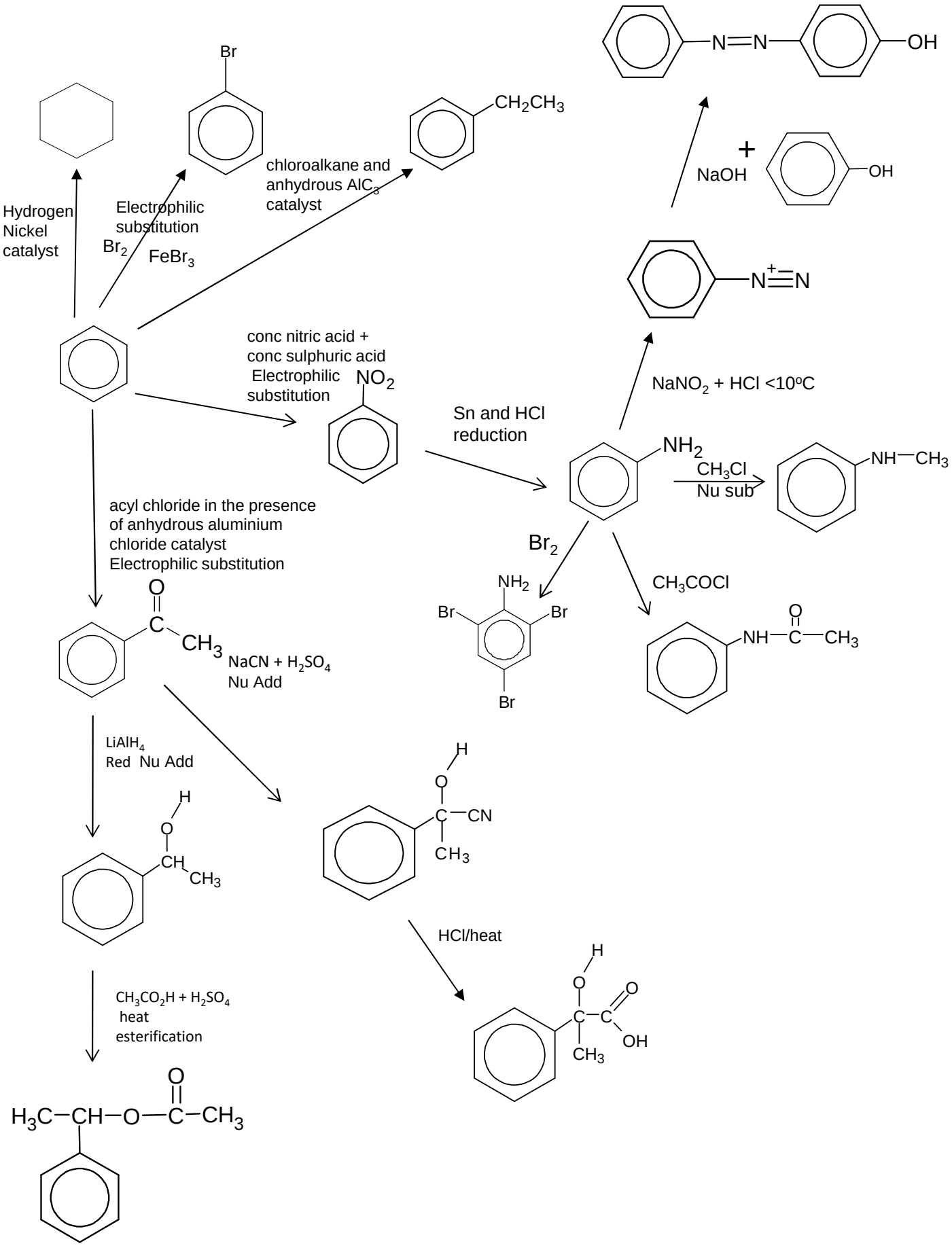


Synthesis of a pharmaceutical that is a single optical isomer is more expensive because separation of the single isomer is difficult.
However one of the isomers may be more pharmacologically active and one of the isomers might have adverse side effects .

Modern synthesis of a pharmaceutical with a single optical isomer is often carried out:
(i) using enzymes or bacteria which promote stereoselectivity,
(ii) using chemical chiral synthesis or chiral catalysts,
(iii) using natural chiral molecules, such as L-amino acids or sugars, as starting materials.


dihalogenoalkane
KOH aqueous
heat under reflux
Nucleophilic substitution
poly(alkene)
diol
Br_2, Cl_2
room temp
Electrophilic addition
$KMnO_4$
oxidation
high pressure
Catalyst
polymerization
alkane
H_2, Nickel Catalyst
addition/reduction
Br_2, Cl_2
UV light
Free radical Substitution
alkene
HBr, HCl
room temp
Electrophilic addition
halogenoalkane
KOH alcoholic heat
under reflux
Elimination
H_2O (g)
Catalyst:
Conc H_3PO_4
conc. H_3PO_4
Elimination,
dehydration
PCl_5, NaBr/H_2SO_4, P + I_2
Heat under reflux
substitution
KOH aqueous
heat under reflux
Nucleophilic substitution
Alcoholic NH_3
heat under pressure
Nucleophilic
substitution
CN^- and
ethanol
Nucleophilic
substitution
alcohol
$LiAlH_4$
Reduction
Caboxylic acid + H_2SO_4
heat
esterification
amine
nitrile
$LiAlH_4$
Reduction
$LiAlH_4$
Reduction
$K_2Cr_2O_7/H^+$
If primary
heat gently and distill
partial oxidation
If secondary
heat under reflux
oxidation
$LiAlH_4$
Reduction
haloalkane
NuSub
2º amine
3º amine
Acyl chloride
room temp
Nu add/elim
$LiAlH_4$
Reduction
aldehyde
ketone
secondary
amide
HCN + KCN
Nucleophilic addition
$K_2Cr_2O_7/H^+$
heat under reflux +
excess oxidising agent
Oxidation
hydroxynitrile
Esters and amides
can be hydrolysed
by NaOH and acids
1º amine
room temp
Primary
amide
Alcohol + H_2SO_4
heat
esterification
carboxylic acid
ester
PCl_5
Alcohol
room temp
NH_3 room temp
H_2O room
temp
Acyl chloride
Acid hydrolysis
Heat with HCl

Aromatic synthetic routes



Organic techniques

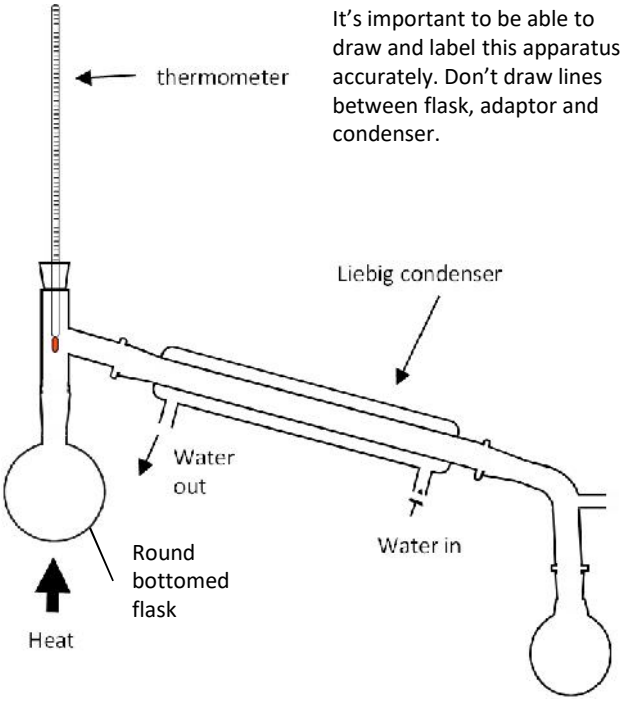
Distillation

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.

Note the bulb of the thermometer should be at the T junction connecting to the condenser to measure the correct boiling point

Note the water goes in the bottom of the condenser to go against gravity. This allows more efficient cooling and prevents back flow of water.

Electric heaters are often used to heat organic chemicals. This is because organic chemicals are normally highly flammable and could set on fire with a naked flame.



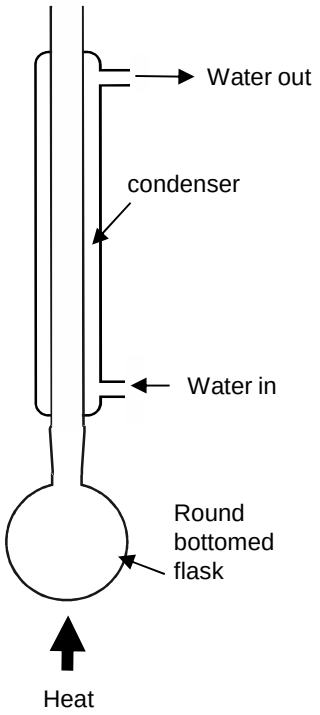
It's important to be able to draw and label this apparatus accurately. Don't draw lines between flask, adaptor and condenser.

Reflux

Reflux is used when heating organic reaction mixtures for long periods. 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 including the distillation set up

Anti-bumping granules are added to the flask in both distillation and reflux to prevent vigorous, uneven boiling by **making small bubbles** form instead of large bubbles

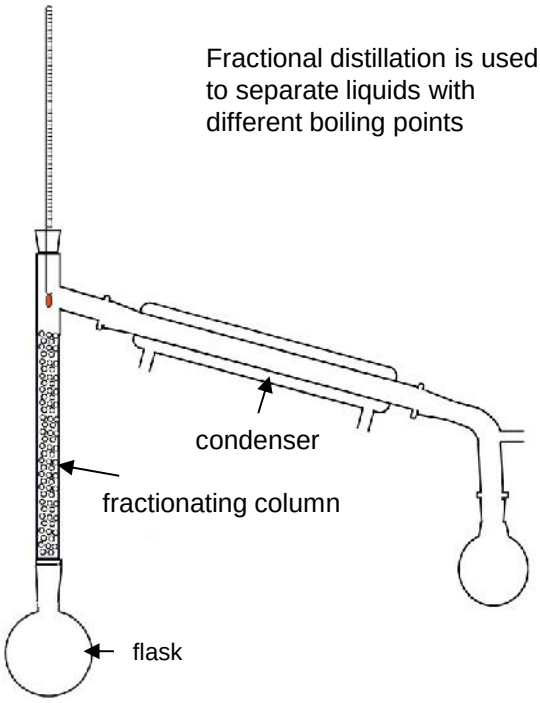


It's important to be able to draw and label this apparatus accurately.

- Don't draw lines between flask and condenser.
- Don't have top of condenser sealed
- Condenser must have outer tube for water that is sealed at top and bottom
- Condenser must have two openings for water in and out that are open

Fractional Distillation: In the laboratory

- Heat the flask, with a Bunsen burner or electric mantle
- This causes vapours of all the components in the mixture to be produced.
- Vapours pass up the fractionating column.
- The vapour of the substance with the lower boiling point reaches the top of the fractionating column first.
- The thermometer should be at or below the boiling point of the most volatile substance.
- The vapours with higher boiling points condense back into the flask.
- Only the most volatile vapour passes into the condenser.
- The condenser cools the vapours and condenses to a liquid and is collected.



Fractional distillation is used to separate liquids with different boiling points

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.

Purifying an organic liquid **General method**

• 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 (e.g. anhydrous sodium sulphate, calcium chloride) to dry the organic liquid. When dry the organic liquid should appear clear.

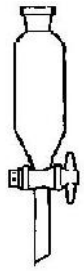
• Carefully decant the liquid into the distillation flask

•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 layer with lower density will be the upper layer. This is usually the organic layer



Separating funnel

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

Decant means carefully pour off organic liquid leaving the drying agent in the conical flask

Purifying an organic solid: Recrystallisation

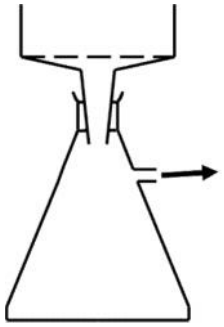
Used for purifying aspirin

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
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 solution is not saturated. 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

If the crystals are not dried properly the mass will be larger than expected which can lead to a percentage yield >100%

buchner flask

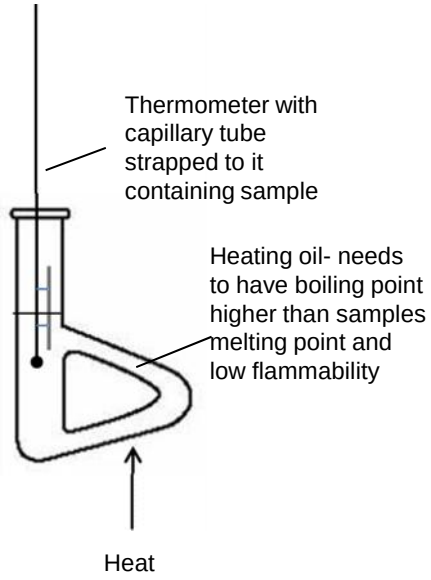


Measuring melting point

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 sample is put into a capillary tube. The tube is heated up and is **heated slowly near the melting point**

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.

Summary of Organic Analysis

Tests for alcohol, aldehyde, alkene and carboxylic acid

Functional group test for an Alkene
To 0.5 cm^3 of bromine water in a test tube add a few drops of the unknown and shake.
Observation: alkenes should decolourise bromine water

Reaction with 2,4-dinitro phenylhydrazine

2,4-DNP reacts with both aldehydes and ketones. The product is an orange precipitate, It can be used as a test for a carbonyl group in a compound.

Use 2,4-DNP to identify if the compound is a carbonyl. Then to differentiate an aldehyde from a ketone use Tollen's reagent.

The melting point of the crystal formed can be used to help identify which carbonyl was used. Take the melting point of orange crystals product from 2,4-DNP. Compare melting point with known values in database

Functional group tests for an Aldehyde

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.

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

Tollen's reagent method

Place 1 cm^3 of silver nitrate solution in each of two clean boiling tubes. Then add one drop of sodium hydroxide solution to form a precipitate of silver oxide. Add ammonia solution dropwise until a clear, colourless solution is formed. Add a few drops of the unknown and leave in the water bath for a few minutes.

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 (II) 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**

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

Fehling's solution method
Place 1 cm^3 of Fehling's A into each of two boiling tubes, and then add Fehling's B until the blue precipitate redissolves. Add a few drops of the unknown and leave in the water bath for a few minutes.

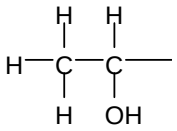
Reaction of carbonyls with iodine in presence of alkali

Reagents: Iodine and sodium hydroxide

Conditions: warm very gently

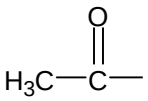
The product CHI_3 is a yellow crystalline precipitate with an antiseptic smell

Only alcohols with a methyl group next to the C-O -H bond will do this reaction.



This reaction is called the Iodoform test

Only carbonyls with a methyl group next to the C=O bond will do this reaction. Ethanal is the only aldehyde that reacts. More commonly is methyl ketones.



This reaction is called the Iodoform test

Functional group test for a Carboxylic acid

To 0.5 cm^3 of your unknown solution in a test tube add a small amount of sodium carbonate solid and observe.

Result carboxylic acids will fizz with sodium carbonate due to CO_2 produced

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

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

Summary of Identification of Functional Groups by test-tube reactions

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