INTRODUCTION TO ORGANIC CHEMISTRY

UNIT 06: Synthesis

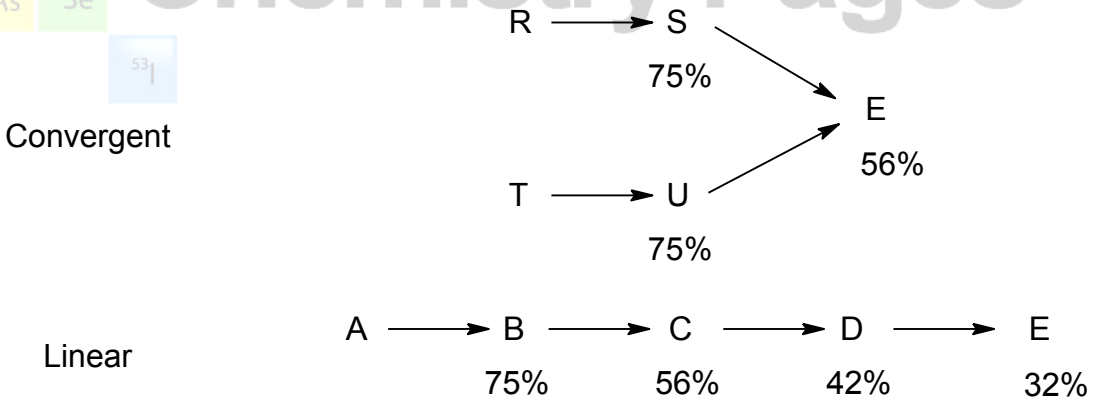
- **Suggesting routes for synthesis**

Retro-synthesis & disconnection

One of the most helpful methods is to turn the synthesis into a pictorial flowchart. Then start at the final product and work backwards (retro-synthesis), then try to recognize any compounds and/or reagents at all, and *then* begin to piece the evidence together. Disconnection is the process of breaking the target molecule up into recognizable building blocks. Disconnections are usually most helpful when they take place around functional groups.

If a synthesis offers a more open-ended approach, there may be several different routes to a particular product and a number of factors must be considered.

1. The number of steps involved. Too many steps mean a much lower final yield since a little is lost at each step. Convergent synthesis can help increase yields. Consider these two alternative routes with 75% yields at each step. Quite clearly the convergent route gives a better yield than the linear.



2. There may be competing reactions that also lead to a lower yield. The products from these other reactions may or may not be useful and may be difficult to separate from the reaction mixture. Equilibrium mixtures also reduce yield.
3. Availability and cost of the raw materials and the cost of the synthesis (plant etc.).
4. Consider the different problems between a small-scale (lab) synthesis and a large scale (industrial) one.

- **Planning and performing the experiment**

Multiple Aromatic Substitutions

Groups already attached to an aromatic ring have the effect of determining the position taken by a second, new substituent. For example, the nitration of ethylbenzene gives an approximate 50-50 mixture of the ortho and para nitrated isomers, with only a tiny percentage of the meta isomer.

Nitrobenzene on the other hand, gives the meta-nitrated isomer, with only a tiny percentage of the ortho and para isomers.

Below is a list of the directing effects of a few substituents.

Ortho-Para Directing	Meta
$-NH_2$	$-NO_2$
-OH	-CN
$-OCH_3$	-CHO
CH_3, C_2H_5	-COR
-F, -Cl, -Br, -I	-COOH

A consequence of the different directing effects of the substituents is the need to consider the sequence of aromatic substitution. For example, in an attempt to make chloronitrobenzene if chlorination takes place first followed by nitration, this will lead to the ortho and para isomers. If nitration is followed by chlorination the product is mainly the meta isomer.

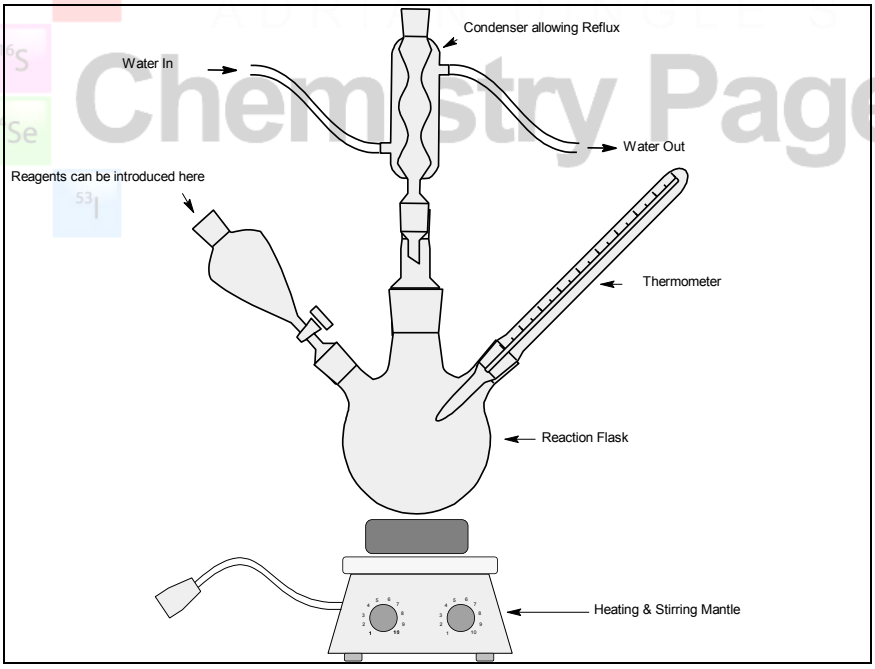
In order to achieve an ortho/para dominated mixture or a meta dominated di-substituted aromatic, always substitute with a group that will direct towards the final product, first.

Heating and the Reflux technique

It is often necessary to heat organic compounds together in order for them to react. Since most of these compounds are rather volatile, heating them leads to their vaporization, and if they were held in an open container they would escape. In a reflux apparatus the reactants are placed in a flask and a condenser attached to the top of the flask. The reactants can then be repeatedly heated and condensed over a period of time allowing them to react at a high temperature with them being lost.

The heat source may vary. Bunsen burners with naked flames present the danger of fire so one of two methods is usually employed, a water bath (100°C) or paraffin bath (220°C), or an electric heater. If the reaction is highly exothermic then it may be necessary to cool the reaction mixture by immersing the flask in water, iced water, or a mixture of carbon dioxide in ethanol.

N.B. refluxing is simply the technique of condensing volatile substances; it does not necessarily imply heating. If you wish to heat a compound with refluxing say HEAT UNDER REFLUX. Do not assume that heat is being applied.



- **Mixing and stirring the reactants**

Careful mixing of the reactants is often required and this is achieved by using multi-necked flasks and dropping funnels. It may be necessary if the reaction is particularly vigorous or, for example, in the oxidation of ethanol, different products can be produced.

Stirring helps the reactants mix together and allows the heat to be distributed evenly throughout the mixture. Even heating can be aided by the addition of anti-bumping granules.

Organic compounds are often volatile and flammable and many are toxic, so potential hazards must be borne in mind when planning and performing the experiments. Such hazards can be minimized by working in a fume hood, away from naked flames, with all the appropriate safety clothing and goggles being worn. It is important not to generalize too much about safety so avoid comments like "wear goggles and lab coat" and try to be more specific, relating specific hazards to specific chemicals. On a small scale the apparatus usually consists of "Kwik Fit" glassware with ground glass, lighted greased joints. In industry large stainless steel vessels are often used.

- **Separation of the crude product and purification**

Having obtained the crude product it is necessary to separate it from any unused reactants, by-products, solvents or catalysts and purify it. Some purification techniques are shown below.

Technique	What it separates	Notes
Distillation	A liquid from a dissolved non-volatile solid or liquids with very different boiling points	Heating the mixture allows one of the components to boil and be collected by condensation before the other component reaches its boiling point
Fractional distillation	Liquids with similar boiling points	As above
Filtering	An insoluble solid from a liquid	Simple filtration process
Steam distillation	A high boiling point liquid from a non-volatile solid	Steam is passed through the hot mixture and the distillate collected. On standing the distillate forms two layers. Any product can be removed by solvent extraction from the aqueous layer
Solvent extraction	A solid or liquid from its solution	Crude product is shaken with a small quantity of volatile solvent in which only the product is soluble. Transferring to a separating funnel produces two layers; keep the layer that contains the product (the extract). Small amounts of water remaining can be removed by drying that involves shaking with an anhydrous salt such as magnesium sulfate. Drying usually takes a few hours, after which time the by now hydrated salt can be filtered off
Re-crystallization	A solid from other solid impurities	Choose a solvent in which the solid dissolves readily when hot but not when cold, and in which the impurities do not dissolve. After dissolving the mixture in the minimum amount of hot solvent any insoluble impurities can be filtered out immediately. As the filtrate cools the pure product will crystallize out. The crystals can be vacuum filtered using a Buchner funnel to allow rapid filtration and some drying. The final drying can be carried out in a desiccator or oven. The test the purity (see below)
Chromatography	A mixtures of solids, volatile liquids or gases	Gas-liquid chromatography (GLC) used to separate mixtures of gases and volatile liquids. Thin-layer chromatography (TLC) used to separate mixtures of solids. The mixture is dissolved in a solvent that is carried along a stationary phase, e.g. Al_2O_3. In time, the components will have travelled different distances and separation will have occurred. Chromatography allows separation of very complex mixtures, even when the components are present in very small amounts

- **Testing the purity**

In a simple laboratory, the purity of a substance is usually measured by taking a melting point or boiling point. Comparison of the value with a data book will give an indication of the purity that has been achieved.

- **Percentage yield calculations**

In all organic syntheses the yield of the product will be less than 100%. The % yield is given as,

$$\% \text{ Yield} = \frac{\text{Actual yield}}{\text{Theoretical yield}} \times 100$$

The yield is always less than 100% since the reactants are often not pure, some of the product is lost during purification and/or side reactions may give unwanted by-products.

Task 6a

1. ***5.9 g of aspirin, $C_9H_8O_4$, is prepared from 5.0 g of 2-hydroxybenzoic acid, $C_7H_6O_3$, and 7.5 g of ethanoic anhydride, $C_4H_6O_3$. The reactants react in a 1:1 ratio to form 1.0 mole of aspirin. Calculate the percentage yield of aspirin.***

2. ***When 6.2 g of anhydrous 2-methylpropan-2-ol are treated with excess concentrated hydrochloric acid at room temperature, 6.2 g of 2-chloro-2-methylpropane are formed, according to the equation,***

$$CH_3C(OH)(CH_3)CH_3 + HCl \rightarrow CH_3C(Cl)(CH_3)CH_3 + H_2O$$

Calculate the percentage yield of the product.