Organic synthesis

Deducing structures from combined data, lengthening carbon chains with cyanide and Grignard reagents, planning multi-step routes, and techniques for preparing and purifying organic solids (aspirin).

Deducing a structure from data

Use all the evidence together.

1. **Combustion analysis or percentage composition** gives the **empirical formula**.
2. The **molecular ion** in the mass spectrum gives M_r and the **molecular formula**.
3. **Chemical tests** give functional groups: bromine water (C=C), 2,4-DNPH (C=O), Benedict's or Tollens' (aldehyde), iodoform (CH_3CO-), sodium carbonate (COOH), PCl_5 (OH).
4. **Infrared** confirms the groups (C=O near 1700, broad O–H).
5. ^{13}C **NMR** gives the number of carbon environments and their types.
6. **Proton NMR** gives the number of proton environments, their ratio, and (from splitting) neighbours.

> **TRY IT**
>
> A compound $C_4H_8O_2$ has IR peaks at 1740 cm^{-1} and no broad O–H. The proton NMR shows a singlet (3H) at δ 2.0, a quartet (2H) at δ 4.1 and a triplet (3H) at δ 1.2. Identify it.

The C=O at 1740 without O–H suggests an ester. A $CH_3-C=O$ singlet at 2.0, an $-O-CH_2-$ quartet next to a CH_3 triplet: ethyl ethanoate, $CH_3COOCH_2CH_3$.

Increasing the length of the carbon chain

Method	Reagents	Product
Nitrile route	Halogenoalkane with KCN in ethanol, reflux	**Nitrile** (+1 carbon); then hydrolyse (acid, reflux) to a carboxylic acid or reduce ($LiAlH_4$) to an amine
Hydroxynitrile	Aldehyde or ketone with HCN/KCN	**Hydroxynitrile** (+1 carbon)
Grignard reagent	Halogenoalkane with **magnesium in dry ether**	$RMgX$ (a source of R^-, a nucleophile)

Grignard reagents

$$CH_3CH_2Br + Mg \rightarrow CH_3CH_2MgBr$$

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The reaction must be in **dry (anhydrous) ether**, because the Grignard reagent reacts with water to give an alkane, $RMgBr + H_2O \rightarrow RH + Mg(OH)Br$.

The reagent acts as a **nucleophile** (carbon with partial negative charge) towards $\delta+$ carbons.

- With **carbon dioxide**, then dilute acid: a **carboxylic acid** (one more carbon): $RMgBr + CO_2 \rightarrow RCOO^-MgBr^+ \xrightarrow{H^+} RCOOH$
- With **aldehydes**, then dilute acid: a **secondary alcohol** (methanal gives a primary alcohol)
- With **ketones**, then dilute acid: a **tertiary alcohol**

Planning a synthesis

Retrosynthesis: start with the target, ask what it can be made from, and work back. Combine the reactions in this specification (up to four steps).

Main functional-group conversions:

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From → To	Reagents
Alkane → halogenoalkane	Cl_2 or Br_2, UV
Alkene → halogenoalkane	HX
Alkene → alcohol	Steam, acid catalyst
Alkene → diol	Cold acidified $KMnO_4$
Halogenoalkane → alcohol	Aqueous NaOH, reflux
Halogenoalkane → alkene	Ethanolic NaOH
Halogenoalkane → nitrile	KCN in ethanol
Halogenoalkane → amine	Excess NH_3 in ethanol, pressure
Alcohol → halogenoalkane	PCl_5; KBr + 50% H_2SO_4; red P and I_2
Alcohol → alkene	Concentrated H_3PO_4
Primary alcohol → aldehyde	$K_2Cr_2O_7/H^+$, distil
Primary alcohol → carboxylic acid	$K_2Cr_2O_7/H^+$, reflux
Secondary alcohol → ketone	$K_2Cr_2O_7/H^+$
Aldehyde or ketone → alcohol	$LiAlH_4$ in dry ether
Aldehyde or ketone → hydroxynitrile	HCN, KCN
Carboxylic acid → ester	Alcohol, concentrated H_2SO_4
Carboxylic acid → acyl chloride	PCl_5
Acyl chloride → ester, amide	Alcohol; NH_3 or an amine
Nitrile → carboxylic acid	Dilute acid, reflux
Nitrile → amine	$LiAlH_4$ in dry ether or H_2/Ni
Benzene → nitrobenzene	Conc. HNO_3 + conc. H_2SO_4
Nitrobenzene → phenylamine	Sn + conc. HCl, then NaOH
Phenylamine → diazonium salt	$NaNO_2$ + HCl, below 5 °C

Name the reagent and the condition for each step (reflux, dry ether, UV, temperature), and say whether a solvent is aqueous or ethanolic. Chemical routes that give mixtures should be

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avoided, so check that each step is selective.

In an exam you may also need to **select a practical procedure**, **predict properties** of unfamiliar compounds by recognising the functional groups, and **identify control measures** from hazard data.

Preparing and purifying an organic solid

Technique	Purpose
Heating under reflux	Carry out the reaction without losing volatile reactants
Washing (with water or sodium carbonate solution)	Remove soluble impurities and acid, in a separating funnel
Solvent extraction	Separate the product into an organic solvent
Recrystallisation	Purify a solid
Drying (anhydrous salt for liquids; air or desiccator for solids)	Remove water
Distillation and **steam distillation**	Purify a liquid; steam distillation for a compound that is immiscible with water and would decompose at its own boiling temperature (e.g. limonene from orange peel)
Melting temperature determination	A **pure** solid melts at a sharp, specific temperature; **impurities lower** and **broaden** the melting range
Boiling temperature determination	Check purity of a liquid

Recrystallisation

1. Dissolve the impure solid in the **minimum volume of hot solvent**.
2. **Filter while hot** (through a heated funnel) to remove insoluble impurities.
3. Cool slowly. **Pure crystals form** and the soluble impurities stay in the solution because their concentration is low.
4. **Filter** under reduced pressure (Buchner funnel), **wash** with a small volume of cold solvent, and **dry**.

Using too much solvent lowers the yield.

Core Practical 16: the preparation of aspirin

Aspirin (2-ethanoyloxybenzoic acid) is made by **esterifying 2-hydroxybenzoic acid** (salicylic acid) with **ethanoic anhydride** and a few drops of concentrated sulfuric (or phosphoric) acid as the catalyst.

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1. **Warm** the mixture in a water bath for about 15 minutes.
2. Add **cold water** to destroy the excess ethanoic anhydride and precipitate the crude aspirin.
3. **Filter under reduced pressure** and **wash** with cold water.
4. **Recrystallise** from a minimum of hot ethanol or water.
5. Dry the crystals, **weigh** them to find the **percentage yield**, and measure the **melting temperature**.

NOTE

Purity is shown by a sharp melting temperature close to the literature value (about 135 °C). A test with iron(III) chloride gives a **purple colour** if unreacted 2-hydroxybenzoic acid (a phenol) remains.

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