Organic synthesis (A Level)

Reaction summaries for the A Level functional groups, identifying groups in multifunctional molecules, devising multi-step routes, and analysing routes in terms of reaction type, reagents and by-products.

36.1 Organic synthesis

At A Level the reactions of the AS Level are combined with those of arenes, phenols, acyl chlorides, amines, amides and amino acids.

Reaction map (additions at A Level)

Starting group	Reagents and conditions	Product
Benzene / arene	Br_2 or Cl_2, AlX_3	halogenoarene
Benzene	conc. HNO_3/H_2SO_4, 25–60 °C	nitrobenzene
Nitrobenzene	Sn, conc. HCl; then NaOH	phenylamine
Phenylamine	$NaNO_2$, HCl, below 10 °C	diazonium salt
Diazonium salt	warm with water	phenol
Diazonium salt + phenol in NaOH	below 10 °C	azo dye
Alkylbenzene	hot alkaline $KMnO_4$, then acid	benzoic acid
Carboxylic acid	PCl_5 or $SOCl_2$	acyl chloride
Acyl chloride	alcohol / phenol	ester
Acyl chloride	NH_3 / amine	amide / N-substituted amide
Amide	$LiAlH_4$	amine
Nitrile	$LiAlH_4$ or H_2/Ni	amine
Amide	dilute acid or alkali, heat	carboxylic acid (or salt)
Phenol	NaOH(aq)	phenoxide
Phenol	Br_2(aq)	2,4,6-tribromophenol

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Identifying functional groups

A molecule with several groups can give reactions of more than one: 4-hydroxybenzoic acid reacts with NaOH, gives CO_2 with carbonate through its acid group, and undergoes bromine-water substitution at the phenolic ring. Amines and amides differ greatly in basicity, but acid-solubility observations must be interpreted for the particular samples because some amides already dissolve in water. Use suitable distinguishing reactions alongside structural evidence.

Planning a route

1. **Work backwards** from the target to a starting material.
2. Decide the **order of steps**, which can matter greatly: the **directing effects** of the groups already on the ring decide the position of the next one.
3. **Protect** or avoid groups that would react with the reagent in a later step, and choose the right **strength of reducing or oxidising agent** (for example $LiAlH_4$ reduces C=O and nitriles, H_2/Ni can reduce a C=C and the ring).
4. Use **reagents, conditions and by-products** in the answer.

> **TRY IT**
>
> Suggest a route from benzene to 4-bromophenylamine. Which group goes on first?

$-NH_2$ is introduced last (from $-NO_2$), because $-NO_2$ directs to the 3-position, whereas bromine ($-Br$ directs 2- and 4-). Route: bromobenzene (Br_2, $FeBr_3$); nitrate (HNO_3/H_2SO_4) to give mainly 4-bromonitrobenzene; reduce (Sn/conc. HCl, then NaOH) to 4-bromophenylamine. The order is **halogenate first, then nitrate, then reduce**.

Analysing a route

For each step name the **type of reaction** (electrophilic substitution, nucleophilic substitution, addition–elimination, condensation, hydrolysis, reduction, oxidation), the reagents and conditions, and the likely **by-products** (such as the 2-isomer in electrophilic substitution, or a secondary amine in the reaction of a halogenoalkane with ammonia). Stereochemistry matters too: a route that forms a chiral centre from a planar group gives a **racemic mixture**.

Define the target precisely before choosing reagents

Mark ring positions, functional-group attachment and carbon count. $C_6H_5COOCH_3$ and $CH_3COOC_6H_5$ are different esters despite each containing an aromatic ring and ester linkage.

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$C_6H_5NHCH_3$ is an amine whereas $C_6H_5CONHCH_3$ is an amide. A route is correct only if it produces the target connectivity, not merely the right collection of functional-group names.

Worked example: methyl benzoate can be made by reacting benzoyl chloride with methanol. Phenyl ethanoate instead requires ethanoyl chloride with phenol or phenoxide. Reversing which fragment supplies the carbonyl produces a different compound. Drawing both fragments before selecting starting materials prevents this error.

Ring position makes reaction order important

An existing substituent changes where the next electrophile attacks. Oxidation of an alkyl side chain to COOH can change a 2/4-directing group into a 3-directing group. Nitro reduction can change a deactivating 3-director into an activating amino group. These operations change later substitution behaviour without moving substituents already installed.

Worked route: methylbenzene to 3-nitrobenzoic acid requires side-chain oxidation first, then nitration. For a 4-nitrobenzoic-acid target, nitration while methyl is present can provide the 4-isomer, followed by oxidation. Such nitration normally also gives another positional isomer, so separation is part of a realistic route rather than assuming a completely pure para product.

Halogens illustrate why activation and direction are separate ideas: they deactivate the ring overall but direct ordinary further electrophilic substitution to 2/4 positions. Thus bromination before nitration can support a para-bromoamine route after nitro reduction. Direct bromination of phenylamine risks multiple substitutions, so "introduce NH_2 first because it is activating" need not give the desired monosubstituted product cleanly.

> **TRY IT**
>
> Why does nitrating benzene, then brominating, then reducing the nitro group tend towards a different positional product from brominating before nitration?

Answer: NO_2 present during bromination favours the 3-position; Br present during nitration directs to 2/4 positions. Reducing NO_2 afterwards changes the group but preserves its position.

Use work-up steps to obtain the named form

Hot Sn/HCl reduction ends with phenylammonium in an acidic medium; NaOH liberates phenylamine. Alkaline side-chain oxidation ends with benzoate; acidification gives benzoic acid. Alkaline ester/amide hydrolysis similarly leaves carboxylate salts. A correct reagent sequence should include the step that changes the ionic form to the actual target.

Worked sequence: methylbenzene, hot alkaline manganate(VII), then dilute acid gives benzoic acid. Treating that acid with an appropriate chlorinating reagent gives benzoyl chloride, which reacts with

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ammonia to give benzamide. Further reduction with $LiAlH_4$ gives phenylmethylamine, $C_6H_5CH_2NH_2$, **not phenylamine**: the carbonyl carbon becomes CH_2 and stays in the chain.

> **TRY IT**
>
> Why does benzamide reduction not give $C_6H_5NH_2$?

Answer: Amide reduction retains the acyl carbon and its C–N connection, replacing C=O by CH_2. Removing that carbon would require a different reaction, outside this ordinary route.

Multifunctional selectivity and distinguishing tests

Identify every potentially reacting group, then choose a reagent selective for the intended change. Sodium borohydride can reduce an aldehyde while preserving an ordinary carboxylic acid group; lithium aluminium hydride is less selective between those groups. Hydrogenation selectivity depends on catalyst and conditions, so a ring need not be reduced under every mild hydrogenation procedure.

Solubility is not a universal functional-group test. Amines can become more water-soluble on protonation, but some amides are already quite water-soluble. Therefore "dissolves in acid versus does not dissolve" is only useful for particular matched samples, not proof for all amines and amides. Hydrolysis products, basicity and structural/analytical evidence give a stronger combined argument.

Worked identification: a hydroxybenzoic acid can give carbonate effervescence from COOH and bromine-water substitution from the phenolic ring. Neutralisation with NaOH may consume both acidic groups under suitable conditions. A single positive reaction does not establish that only one functional group was present.

> **TRY IT**
>
> Why should separate portions be used when testing a compound for an aldehyde and a phenol?

Answer: The first reagent can alter the molecule and affect a later test. Independent portions allow observations to be attributed to the original sample rather than reaction products.

Stereochemistry, yield and route quality

Creating a chiral centre from an achiral planar carbonyl with achiral reagents usually gives a racemate if both faces are equally accessible. Retaining an existing centre or using a chiral reagent can change that conclusion. State where the stereogenic centre is and how the step affects it; do not label every multistep organic synthesis racemic automatically.

Worked calculation: three stages yield 80.0%, 70.0% and 90.0%. Overall fractional yield is $0.800(0.700)(0.900) = 0.504$, or 50.4%. If a 1 : 1 sequence starts with 0.0500 mol and final product

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molar mass is 150 g mol^{-1}, the expected isolated amount is $0.0500(0.504)(150) = 3.78$ g.

A stronger route balances correct structure, selectivity, number of stages, recovery and manageable by-products. An apparently shorter reaction that produces several hard-to-separate isomers may be less practical than a controlled longer sequence. Distinguish theoretical transformation from demonstrated isolated yield.

Chapter check: draw intermediates, specify work-ups and temperatures, justify directing-group order and verify retained carbons. Link final identity to **spectroscopic evidence**.

References and further reading

Scope follows section 36 of the **Cambridge 9701 syllabus for 2025–2027**. **Chemguide's Cambridge topic index** links to alternative explanations. The worked exercises and added diagrams are original teaching examples; numerical examples are illustrative unless a specific source is identified.

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