

Cambridge (CIE) A Level Chemistry



Your notes

Organic Synthesis

Contents

- * Elucidating Organic Molecules
- * Multi-step Synthetic Routes
- * Analysis of Synthetic Routes



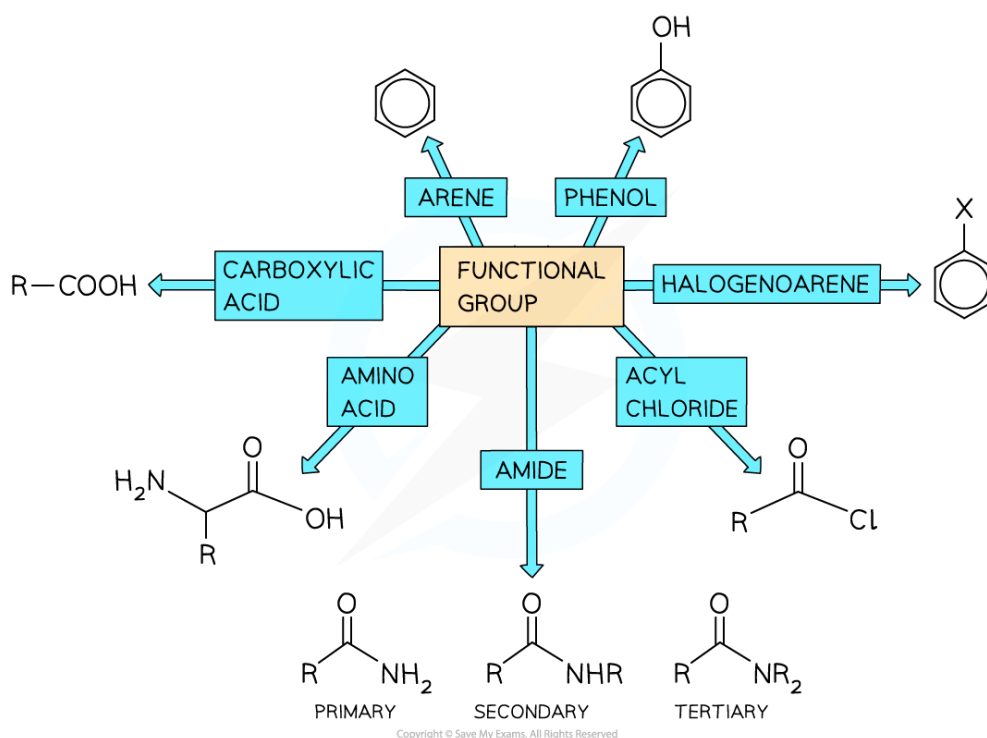
Elucidating Organic Molecules

- Students should be able to identify organic functional groups and recall their properties and the reactions that they undergo

Properties of functional groups

- In addition to the functional groups mentioned in the [AS course](#), students should also be familiar with additional functional groups and their properties including:
 - Arenes
 - Halogenoarenes
 - Carboxylic acids (and derivatives)
 - Phenols
 - Amides
 - Amino acids
 - Acyl chlorides

Overview of additional functional groups



These functional groups are extra to those already covered in [21.1 Organic Synthesis](#)

Reactions of functional groups



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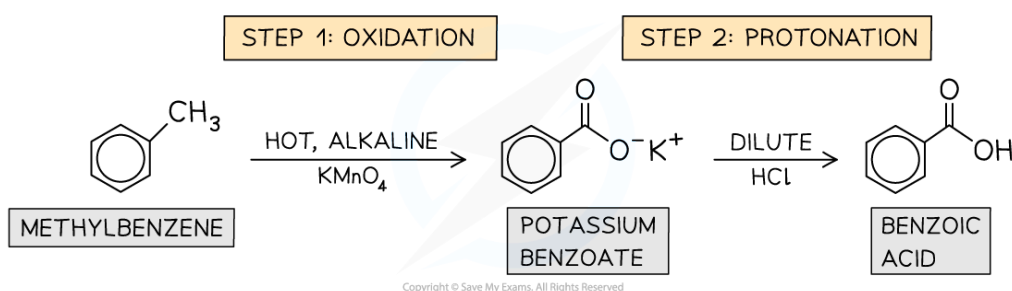
- Students should also be able to recall:
 - The reactions by which these functional groups can be produced including:
 - Benzoic acid
 - Acyl chlorides
 - Amides
 - The reactions that these functional groups undergo

Producing functional groups

Benzoic acid

- Benzoic acid is produced, from methylbenzene, in two steps:
 - An oxidation reaction by refluxing with hot alkaline KMnO_4 to form potassium benzoate
 - A protonation reaction with dilute HCl

Production of benzoic acid



Benzoic acid is produced from methylbenzene in 2 steps

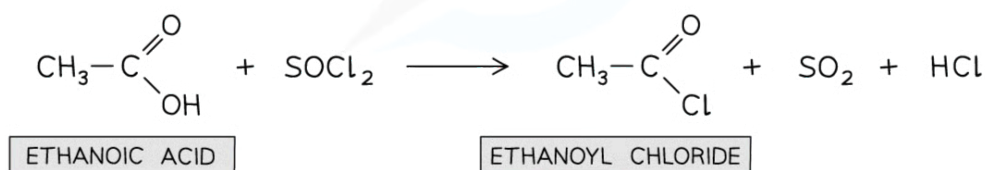
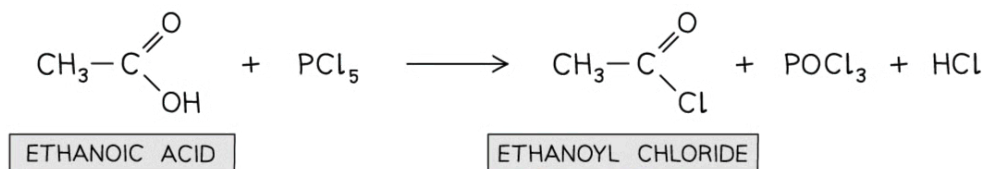
Acyl chlorides

- Acyl chlorides are formed by an electrophilic substitution reaction of the parent carboxylic acid
- There are various possible reagents:
 - Solid PCl_5 - producing the acyl chloride along with POCl_3 and HCl
 - Liquid PCl_3 and heat - producing the acyl chloride and H_3PO_3
 - Liquid SOCl_2 - producing the acyl chloride along with SO_2 and HCl

Production of acyl chlorides



Your notes



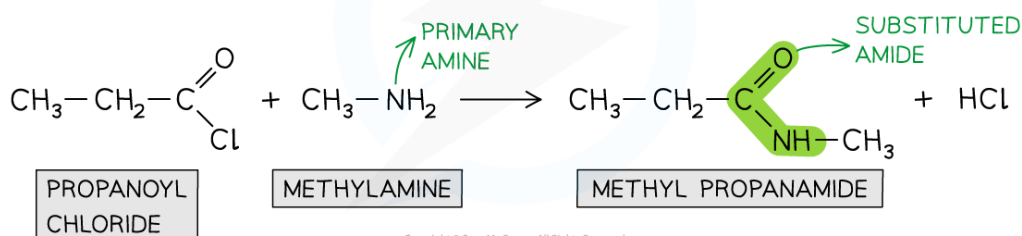
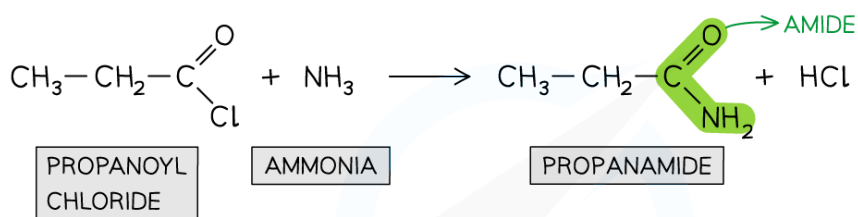
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Using ethanoic acid as an example, the reactions all produce acyl chlorides with different byproducts due to the different reagents

Amides

- Amides are formed by a condensation reaction, at room temperature, of an acyl chloride
- The possible amides that can be produced are substituted amides and non-substituted amides
 - Non-substituted amides are produced by the reaction with ammonia
 - Substituted amides are produced by the reaction with primary amines

Production of substituted and non-substituted amides



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Using propanoyl chloride as an example, the reaction with ammonia produces a non-substituted amide while the reaction with primary amines produces substituted amides



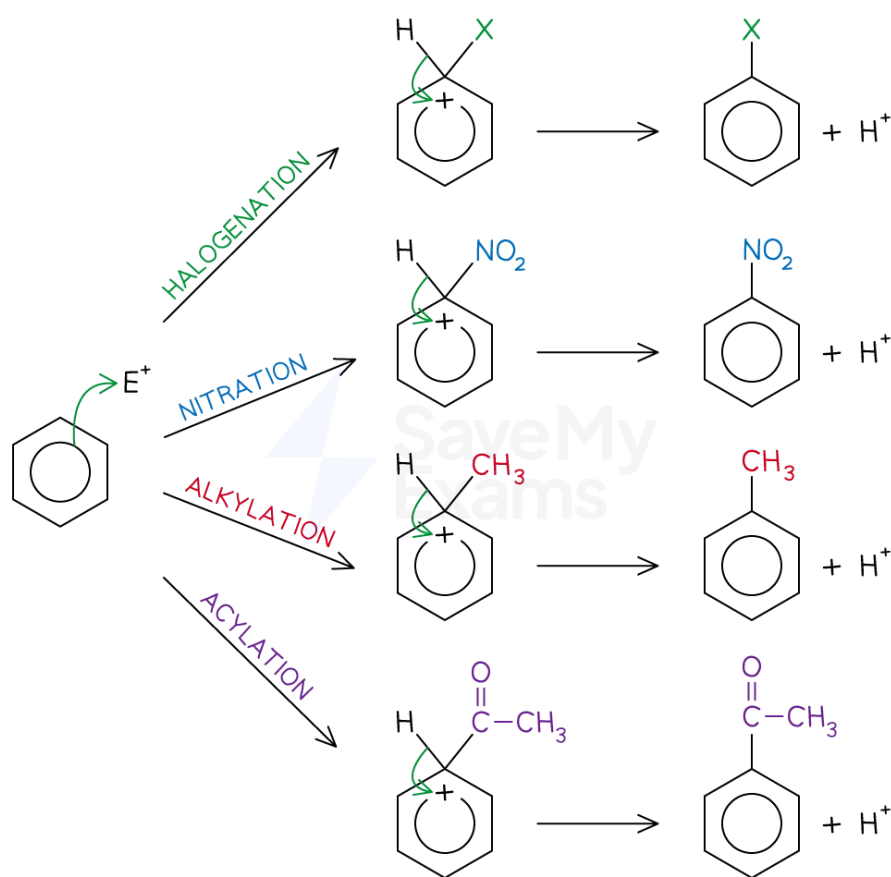
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Reacting functional groups

Electrophilic substitution reactions of arenes

- You should be able to provide the mechanisms for specific electrophilic substitution reactions of benzene:
 - The electrophile, E^+ , for a **halogenation** reaction, is a positive halogen ion, X^+
 - The electrophile, E^+ , for a **nitration** reaction, is the nitronium ion, NO_2^+
 - The electrophile, E^+ , for an **alkylation** reaction, is a carbocation, R^+
 - The electrophile, E^+ , for an **acylation** reaction, is an **acyl group**, RCO^+
 - An acyl group is an alkyl group containing a carbonyl, $C=O$ group

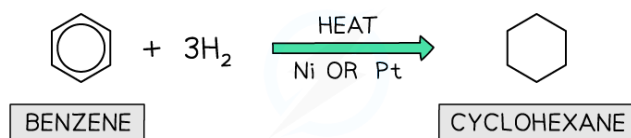
Specific electrophilic substitution reactions of arenes



Using different electrophiles, E^+ , the mechanisms for halogenation, nitration, alkylation and acylation are shown

Hydrogenation of arenes The hydrogenation of benzene is an **addition reaction**. Benzene is **heated** with **hydrogen gas** and a **nickel** or **platinum catalyst** to form **cyclohexane**.

Hydrogenation of benzene

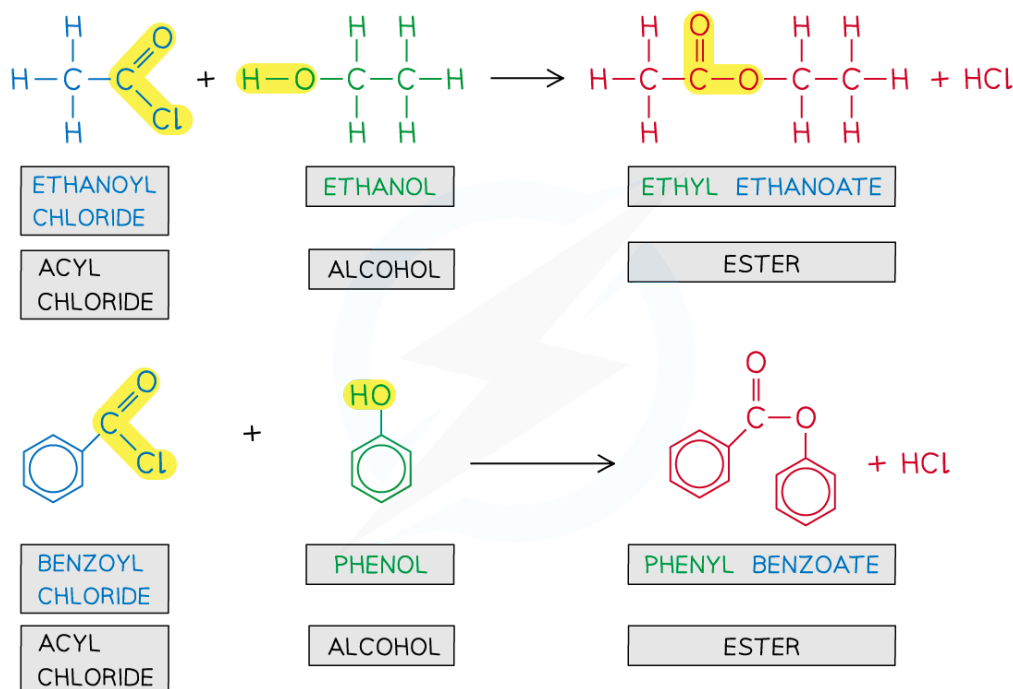


The hydrogenation of benzene causes a complete loss of aromaticity

Esterification of phenol

- The esterification reaction of carboxylic acids with phenol is slow, so acyl chlorides are used
- The reaction between ethanoyl chloride and phenol is similar to the reaction of ethanoyl chloride and ethanol, although it is not as vigorous
 - The products of this reaction are phenyl ethanoate and hydrogen chloride gas
- The reaction between benzoyl chloride and phenol is also similar to the reaction of ethanoyl chloride and ethanol
 - The products of this reaction are phenyl benzoate and hydrogen chloride gas

Formation of esters from the reaction of alcohols with acyl chlorides



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The first part of the ester name comes from the alcohol and the second part of the ester name comes from the acyl chloride

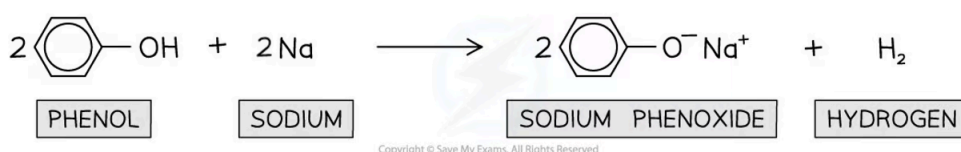


Your notes

- To make the reactions with acyl chlorides and aryl chlorides occur in a more timely fashion, phenol is converted into sodium phenoxide by heating with sodium hydroxide
 - This forms the phenoxide ion which is more reactive
 - The hydrogen chloride product is replaced by water and sodium chloride

Acid / base reactions of phenol

Phenols dissolve in alkaline solutions to undergo **acid-base** reactions with **bases** forming a **soluble salt** and **water**. **Molten phenols** also react **vigorously** with reactive metals such as **sodium (Na)** in an **acid-base** reaction forming a soluble salt and **hydrogen gas**. Acid / base reactions of phenol



Phenols behave as weak acids in alkaline conditions and molten phenols react vigorously with reactive metals to form a soluble salt and hydrogen gas

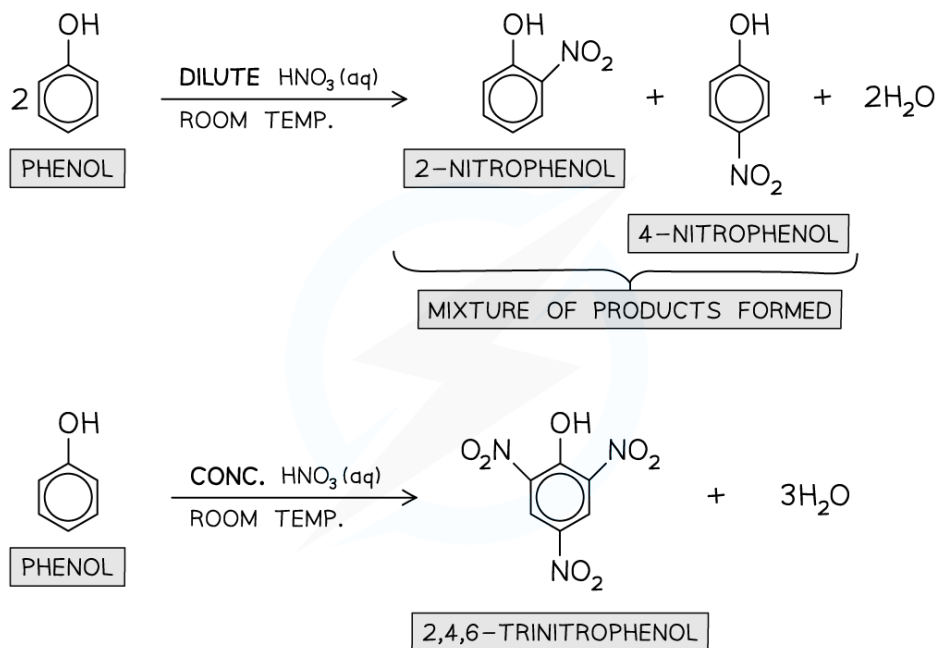
Nitration of phenol

Phenols undergo **electrophilic substitution** reactions with **dilute nitric acid** (HNO_3) at **room temperature** to give a mixture of **2-nitrophenol** and **4-nitrophenol**. When **concentrated HNO_3** is used, the product will be 2,4,6-trinitrophenol instead.

Nitration of phenol



Your notes

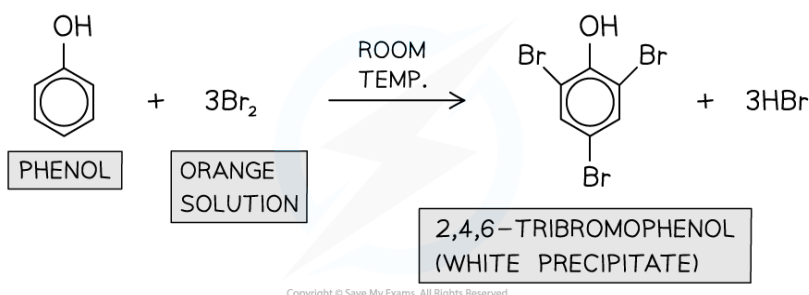


Phenols undergo nitration when reacted with dilute HNO_3 at room temperature

Bromination of phenol

Phenols undergo **electrophilic substitution** with **bromine water** at **room temperature** forming a **white precipitate** of 2,4,6-tribromophenol

Phenol in bromination reactions



Phenols undergo bromination when reacted with bromine water at room temperature



Multi-Step Synthetic Routes

- A large number of organic products are made from a few starting compounds using appropriate reagents and conditions
- Knowing how organic functional groups are related to each other is key to the synthesis of a given molecule
- The main functional groups you need to know are
 - Alkanes
 - Alkenes
 - Haloalkanes
 - Nitriles
 - Amines
 - Alcohols
 - Carbonyls (aldehydes & ketones)
 - Hydroxynitriles
 - Carboxylic acids
 - Esters
 - Acyl chlorides
 - Primary and secondary amides



Examiner Tips and Tricks

You also need to be able to identify the functional groups of these chemicals in structures that are given to you

Aliphatic Reaction Pathways

- The key interconversions between functional groups are summarised here:

Aliphatic Reactions Table

Reactant	Product	Reagents	Reaction
Alkene	Haloalkane	Hydrogen halide	Electrophilic addition

Alkene	Alcohol	Hydration	Steam + H_2SO_4 / heat
Alkene	Alkane	Hydrogen + Ni catalyst / 150°C	Electrophilic addition / hydrogenation
Alcohol	Alkene	Al_2O_3 or conc. acid / heat	Elimination / dehydration
Alcohol	Haloalkane	$\text{NaX} + \text{H}_2\text{SO}_4$ / heat under reflux	Nucleophilic substitution
Haloalkane	Alcohol	$\text{NaOH}(\text{aq})$ / heat under reflux	Nucleophilic substitution
Alkane	Haloalkane	Halogen / UV light	Free radical substitution
Primary alcohol	Aldehyde	Oxidation	$\text{K}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4$ / Distillation
Secondary alcohol	Ketone	Oxidation	Heat
Primary alcohol	Carboxylic acid	Oxidation	Heat under reflux
Aldehyde	Primary alcohol	$\text{NaBH}_4 / \text{H}_2\text{O}$	Reduction
Ketone	Secondary alcohol	$\text{NaBH}_4 / \text{H}_2\text{O}$, NaCN	Reduction
Haloalkane	Nitrile	Nucleophilic substitution	
Haloalkane	Amine	NH_3 / ethanol	Nucleophilic substitution
Nitrile	Carboxylic acid	$\text{H}_2\text{O} / \text{HCl}$	Hydrolysis
Aldehyde	Hydroxynitrile	NaCN / H^+	Nucleophilic addition
Alcohol	Ester	Esterification	Carboxylic acid / H_2SO_4
Carboxylic acid	Ester	Alcohol / H_2SO_4	Esterification

Ester	NaOH(aq)	Alkaline hydrolysis	Carboxylate salt and alcohol
Ester	Carboxylic acid	Dilute acid	Acid hydrolysis
Carboxylic acid	Acyl chloride	SOCl ₂	Chlorination
Acyl chloride	Carboxylic acid	H ₂ O	Hydrolysis
Acyl chloride	Primary amide	NH ₃	Nucleophilic addition elimination
Acyl chloride	Secondary amide	Primary amine	Nucleophilic addition elimination

Aromatic Reaction Pathways

- The key aromatic reactions are summarised here:

Aromatic Reactions Table

Reactant	Product	Reagents	Reaction
Benzene	Methylbenzene	CH ₃ Cl / AlCl ₃	Alkylation / Electrophilic substitution
Benzene	Bromobenzene	Br ₂ / FeBr ₃	Bromination / Electrophilic substitution
Benzene	Chlorobenzene	Cl ₂ / AlCl ₃	Chlorination / Electrophilic substitution
Benzene	Nitrobenzene	HNO ₃ / H ₂ SO ₄	Nitration / Electrophilic substitution
Nitrobenzene	Aminobenzene / phenylamine / aniline	Sn / HCl	Reduction
Aminobenzene	2,4,6-tribromoaminobenzene / 2,4,6-tribromoaniline	Bromine	Electrophilic substitution

Benzene	Phenylethanone	$\text{CH}_3\text{COCl} / \text{AlCl}_3$	Acylation / Electrophilic substitution
Phenylethanone	1-Phenylethanol	NaBH_4	Reduction



Your notes

Designing a Reaction Pathway

- The given molecule is usually called the **target molecule** and chemists try to design a synthesis as efficiently as possible
- Designing a reaction pathway starts by drawing the structures of the **target molecule** and the **starting molecule**
- Determine if they have the **same number** of carbon atoms
 - If you need to lengthen the carbon chain you will need to put on a **nitrile group** by nucleophilic substitution
- Work out all the compounds that can be made from the starting molecule and all the molecules that can be made into the target molecule
 - Match the groups they have in common and work out the reagents and conditions needed



Worked Example

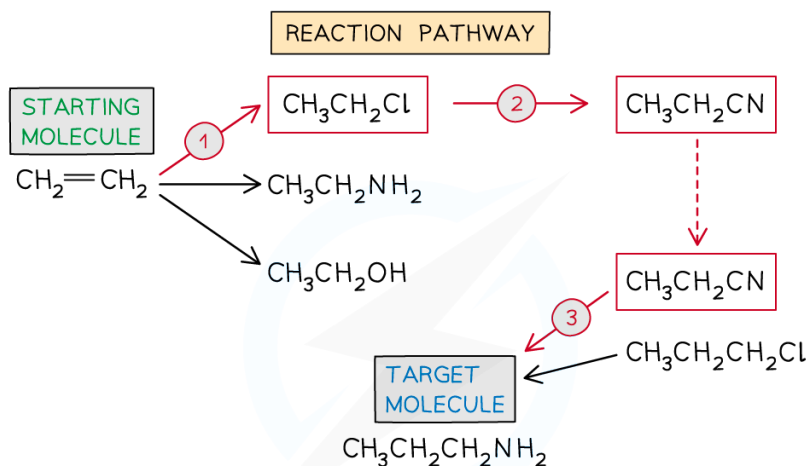
Suggest how the following synthesis could be carried out:

Ethene to 1-aminopropane

Answer



Your notes



- 1 REACT WITH HCl AT ROOM TEMPERATURE
- 2 REACT WITH KCN IN ETHANOL + HEAT UNDER REFLUX
- 3 REDUCE WITH LiAlH_4 IN DRY ETHER + HEAT

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Examiner Tips and Tricks

Sound knowledge of all of the different reactions is beneficial as the A-level course simply states that you should be able to design a multistage synthesis

Past papers generally go to four steps in a multistep reaction although there is no clear limit stated



Analysis of Synthetic Routes

Analysis of Synthetic Routes

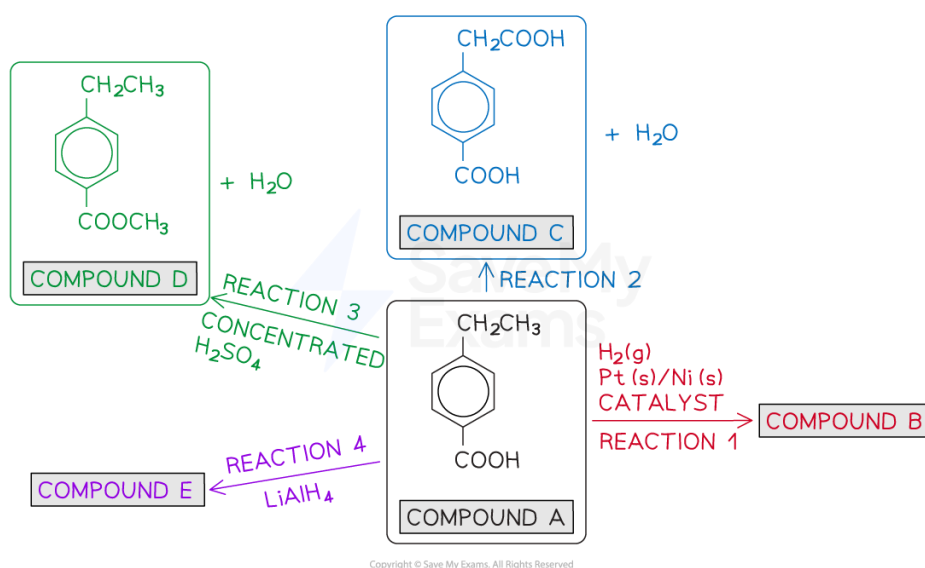
- Students should be able to apply their knowledge of functional groups and their reactions by critically analysing a given synthetic route in terms of:
 - The type of reaction
 - The reagents used for each step
 - Any possible by-products



Worked Example

Analysis of synthetic routes

Some reactions of compound **A**, are shown below

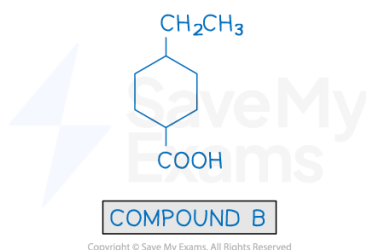


- Give the structure of compound **B** and state the type of reaction by which this compound is formed from compound **A**
- What are the suitable reagents for reaction 2?
- Suggest a more effective way to synthesise compound **D** from compound **A**
- What are the possible by-products of reaction 4?

Answer 1

- This is a hydrogenation reaction

- The benzene ring becomes hydrogenated to form a cyclohexane
- The structure of compound **B** is:



- The COOH group is unlikely to be reduced by H_2 , Pt (s) / Ni (s) in this case

Answer 2

- The ethyl ($-\text{CH}_2\text{CH}_3$) in compound **A** has been oxidised to a carboxylic acid ($-\text{CH}_2\text{COOH}$)
- The reagents for this oxidation to occur are alkaline KMnO_4 followed by dilute H_2SO_4

Answer 3

- Compound **D** contains an ester ($-\text{COOCH}_3$) group which is formed from the esterification reaction between compound **A** and methanol (CH_3OH)
- By carrying out an electrophilic substitution reaction of compound **A** with chlorine (Cl_2), the carboxylic acid ($-\text{COOH}$) group is converted into an acyl chloride ($-\text{COCl}$) group which is more reactive
- The reaction of this acyl chloride with methanol will cause the reaction to occur faster and will give a higher yield of the ester (compound **D**) as the reaction goes to completion

Answer 4

- Reaction **4** is a reduction of the carboxylic acid ($-\text{COOH}$) group in compound **A** to a primary alcohol ($\text{R}-\text{COH}$)
- The by-product of this reduction is water (H_2O)



Your notes