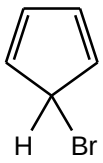
22

Benzene and other aromatic compounds: electrophilic substitution reactions

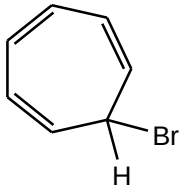
Answers to worked examples

WE 22.1 Aromatic and anti-aromatic compounds (on p. 1011 in *Chemistry*^{3})

5-Bromocyclopenta-1,3-diene is insoluble in water, whereas adding water to 7-bromocyclohepta-1,3,5-triene rapidly produces a water-soluble salt. Suggest an explanation for the different behaviour.



5-bromocyclopenta-1,3-diene



7-bromocyclohepta-1,3,5-triene

Strategy

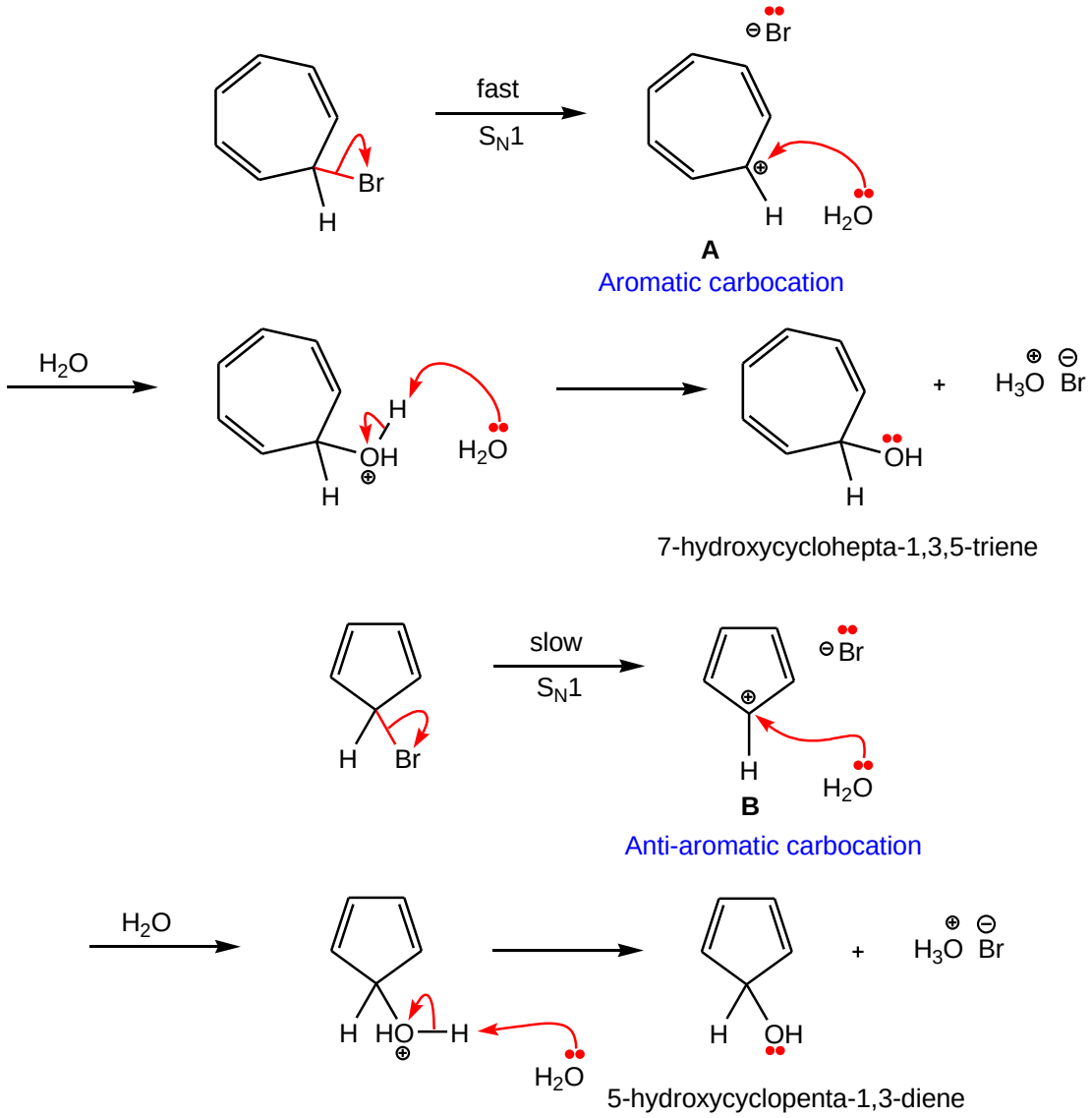
Both conjugated bromides are insoluble in water. 7-Bromocyclohepta-1,3,5-triene will dissolve in water by reacting with it. In essence, the rate of this bromide displacement must be faster for 7-bromocyclohepta-1,3,5-triene than 5-bromocyclopenta-1,3-diene as this does not dissolve in water.

Solution

7-Bromocyclohepta-1,3,5-triene readily reacts with water, by a S_N1 mechanism, to give the water-soluble 7-hydroxycyclohepta-1,3,5-triene. This reaction proceeds by formation of a stabilised **aromatic carbocation A**. By comparison, 5-bromocyclopenta-1,3-diene reacts much slower with water, by a S_N1 mechanism, to give its water-soluble product,

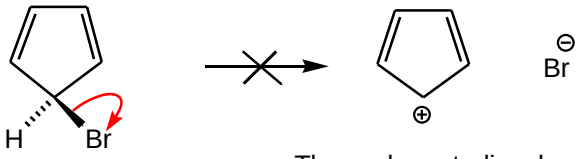
5-hydroxycyclopenta-1,3-diene, as its intermediate carbocation **B** is significantly less stable than **A** due to its **anti-aromatic** character.

[To recap: for a molecule to be (a) aromatic it must be cyclic, planar, have uninterrupted (continuous) conjugation, and (4*n* + 2)-pi-electrons; and (b) anti-aromatic it must be cyclic, planar, have uninterrupted (continuous) conjugation, and (4*n*)-pi-electrons.]

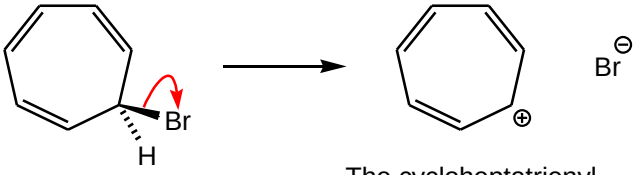


Answer

5-Bromocyclopenta-1,3-diene and 7-bromocyclohepta-1,3,5-triene react differently in water because their intermediate carbocations (formed by heterolytic cleavage of their corresponding C–Br bond) have different stabilities.



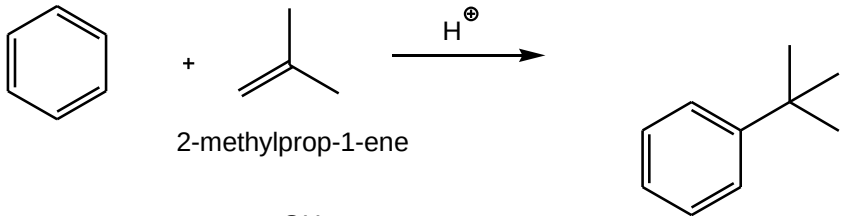
The cyclopentadienyl cation has four π-electrons and is **antiaromatic**



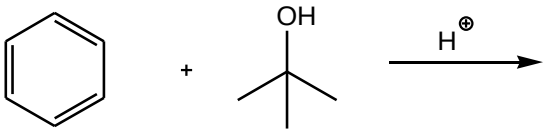
The cycloheptatrienyl cation has six π-electrons and is **aromatic**

WE 22.2 Alkylating benzene (on p. 1022 in *Chemistry*^{3})

Two alternative reactions for preparing *tert*-butylbenzene from benzene are shown below. Suggest mechanisms for both reactions. (*Hint*: in the first step of the reactions, react H^+ with the alkene or the alcohol.)



2-methylprop-1-ene



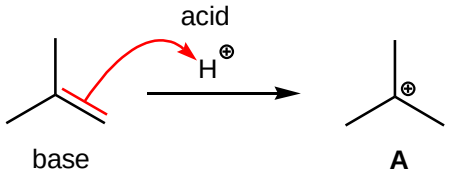
2-methylpropan-2-ol

Strategy

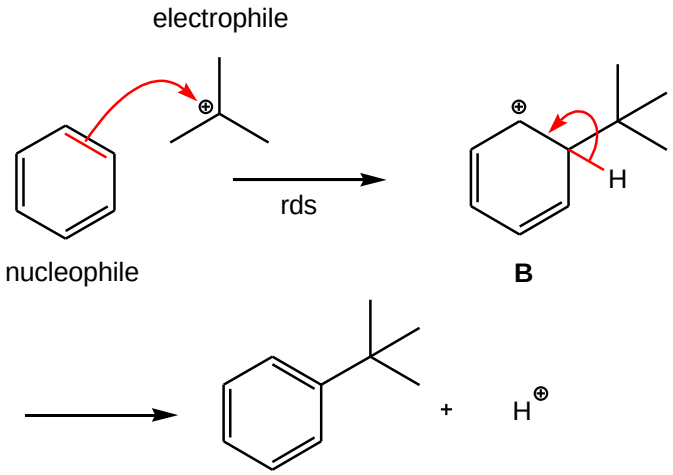
For each step, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (→). A related mechanism for this process is given on p. 1017 in *Chemistry*^{3}.

Solution

2-Methylprop-1-ene must act as a base and H^+ as an acid. Regioselective protonation of this alkene, 2-methylprop-1-ene, forms the more stable tertiary carbocation **A**.

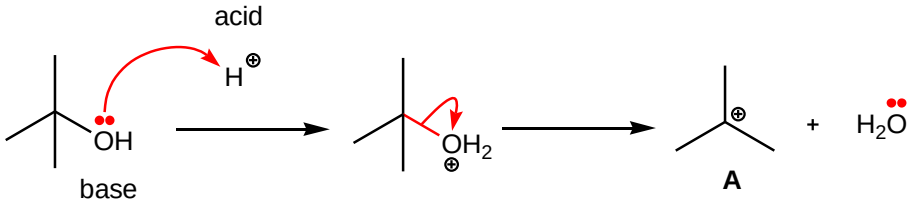


Electrophilic addition of the tertiary carbocation, **A**, to benzene gives the conjugated intermediate carbocation, **B**. Reformation of the aromatic ring occurs by deprotonating this intermediate carbocation, **B**, to give the required product, *t*-butylbenzene.

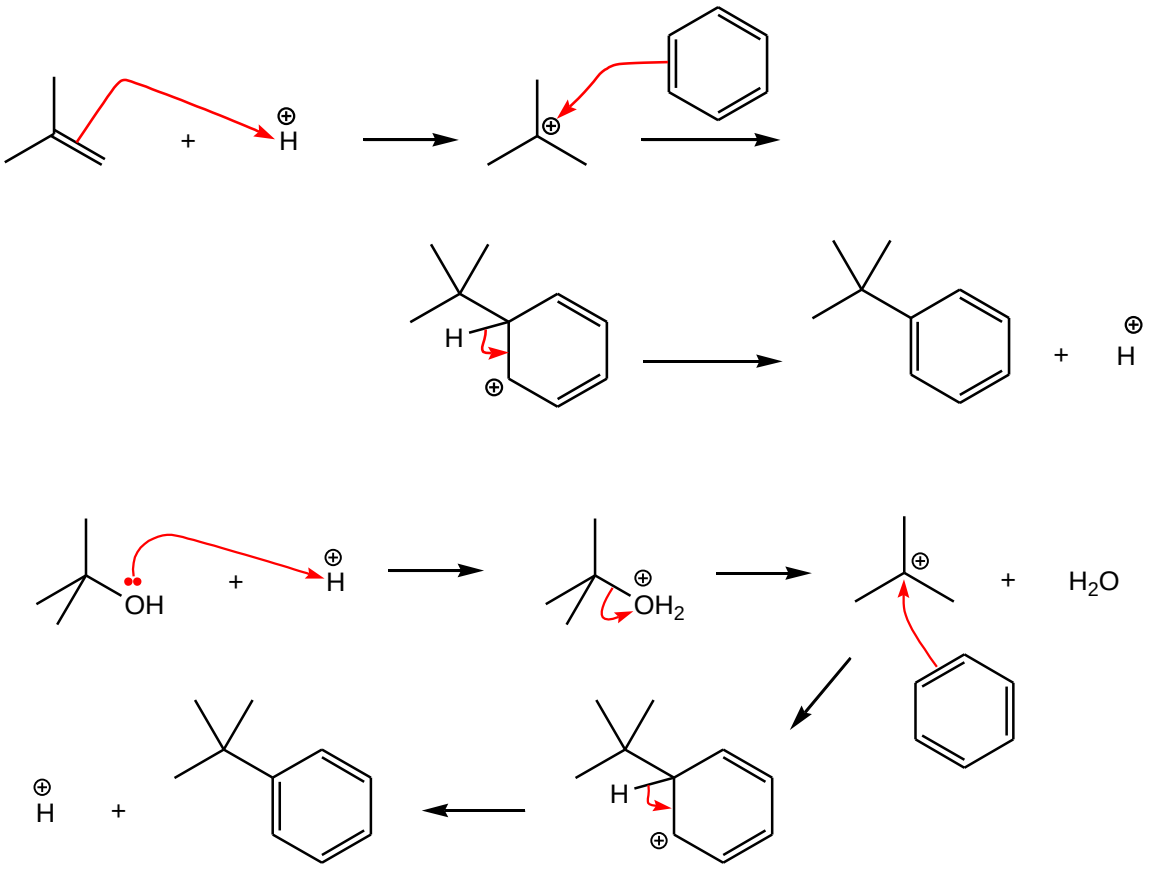


rds = rate determining step

For the complementary route involving 2-methylpropan-2-ol, this must occur by the same product-determining mechanism as both products are the same. 2-Methylpropan-2-ol must act as a base and H^+ as an acid. Protonation of 2-methylpropan-2-ol with H^+, followed by elimination of water gives the same tertiary carbocation, **A**, as described above. Both reactions involving 2-methylprop-1-ene and 2-methylpropan-2-ol generate a common intermediate tertiary carbocation, **A**.

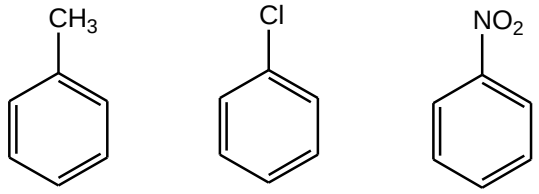


Answer



WE 22.3 The effect of existing substituents on electrophilic substitutions (on p. 1035 in *Chemistry*[3])

The following questions are based on the bromination of compounds **4**–**6** using Br_2 and $FeBr_3$ to give mono-brominated products.



4 **5** **6**

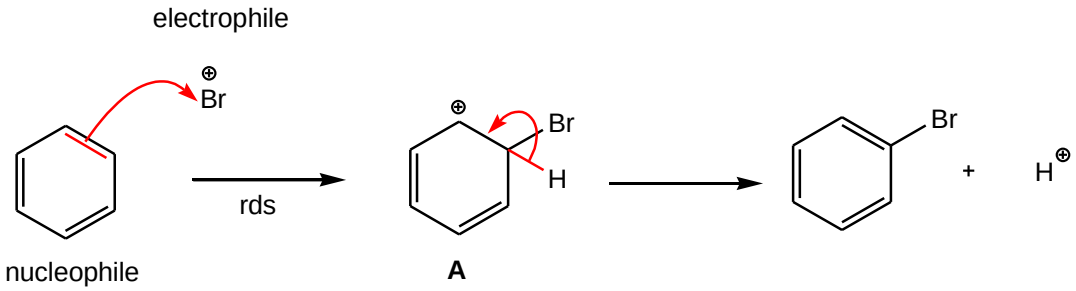
(a) Do compounds **4**–**6** react faster or slower than benzene with Br_2 and $FeBr_3$?

Strategy

The rate of these reactions will depend on the relative reactivity of these mono-substituted benzenes. In order to determine this, you must decide which components are the electrophile and nucleophile in this reaction, and what might be the rate-determining step in these bromination reactions.

Solution

This reaction is an electrophilic bromination; the Br^+ ion (or the Br_2-$FeBr_3$ complex) is the electrophile and benzene ring is the nucleophile. The rate-determining step is electrophilic addition of this bromonium ion, Br^+, to the benzene ring, to form an intermediate conjugated carbocation, **A**. Deprotonating this intermediate carbocation, **A**, reforms the aromatic ring to give the required product, bromobenzene.



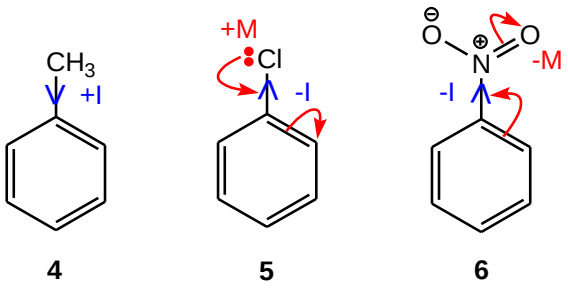
As the electrophile, Br^+, is common in all of these reactions, altering the nucleophilicity of the chosen nucleophile will alter the rate of electrophilic addition; the more nucleophilic the substituted benzene the faster the addition process.

Toluene, **4**, is more electron rich and a better nucleophile than benzene due to the electron-donating effect (+I effect) of its methyl group.

Chlorobenzene, **5**, is less electron rich and a poorer nucleophile than benzene due to the overall electon-withdrawing effect (-I effect > + M effect) of its chlorine substituent.

Nitrobenzene, **6**, is less electron rich and a poorer nucleophile than benzene due to the electon-withdrawing effect (-I effect and - M effect) of its nitro group.

Comparing these reactions, the relative rate of bromination is (fastest) toluene > benzene > chlorobenzene > nitrobenzene (slowest).



4 **5** **6**

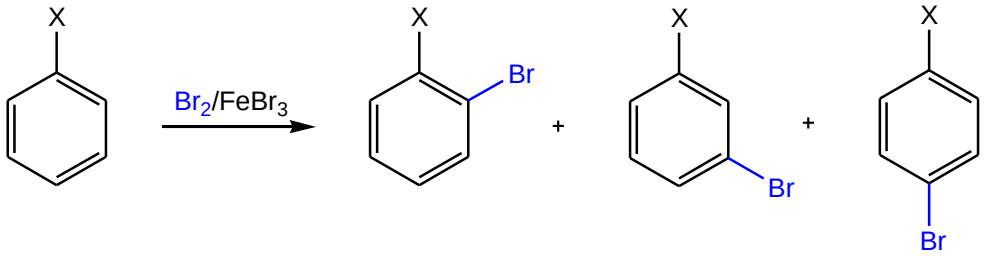
Answer

Compound **4** reacts faster than benzene (CH_3 is a 2,4-directing activator). Compound **5** reacts slower than benzene (Cl is a 2,4-directing deactivator). Compound **6** reacts slower than benzene (NO_2 is a 3-directing deactivator).

(b) Give the structure(s) of the major product(s) from reaction of **4**–**6** with Br_2 and $FeBr_3$

Strategy

Bromination of benzene leads to a single product because all the carbon atoms are identical. For mono-substituted benzenes, such as **A**, up to three products **B**, **C** and **D** are formed. Regioselective bromination will depend on which positions in this molecule are more nucleophilic, and thus better equipped at stabilising the intermediate conjugated carbocations.



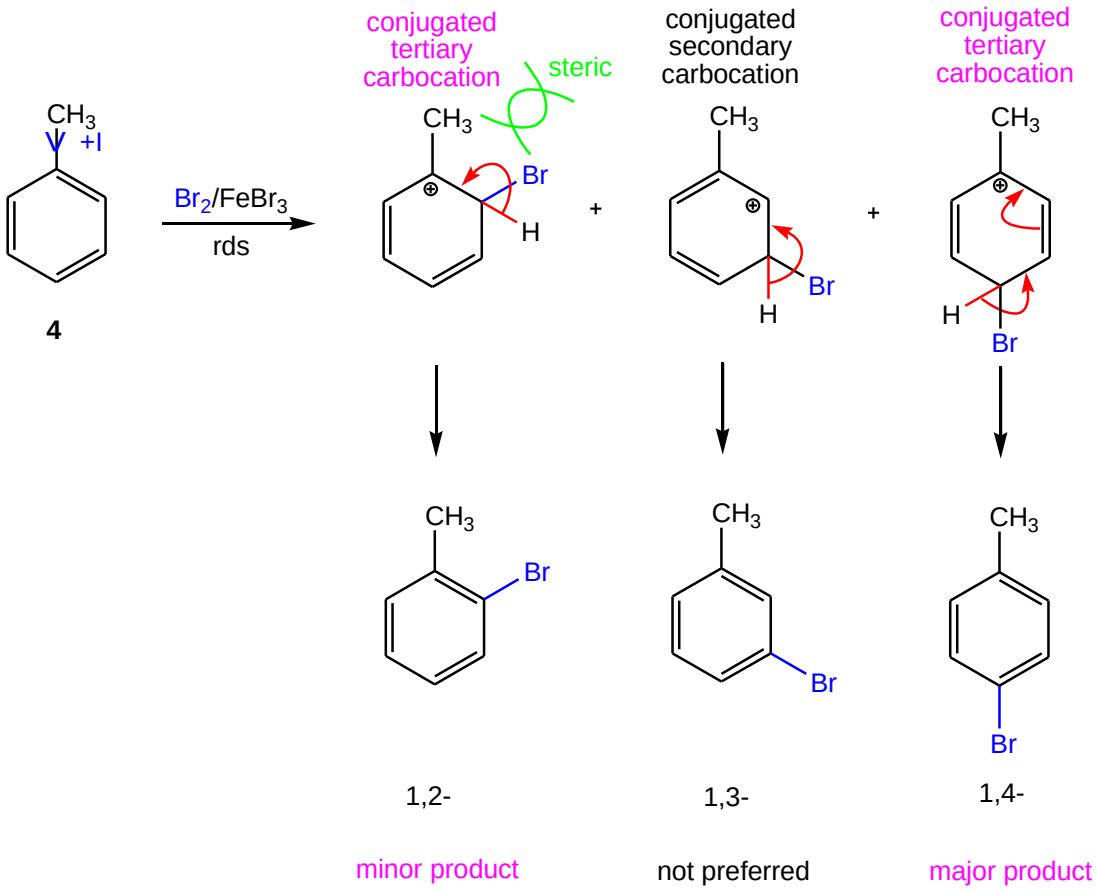
1,2- 1,3- 1,4-

A **B** **C** **D**

Draw out all potential products from the bromination of toluene (**4**), chlorobenzene (**5**) and nitrobenzene (**6**), and work out which carbon atoms in these molecules are the most nucleophilic.

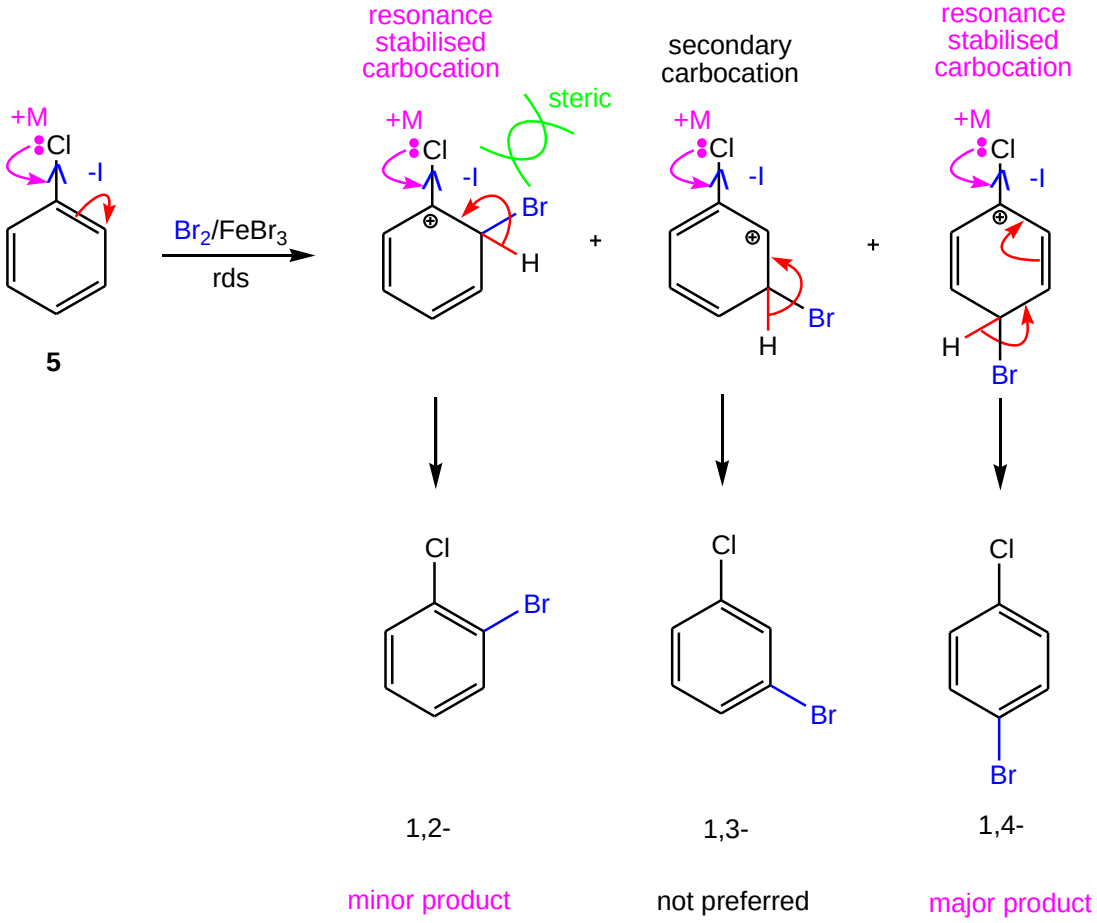
Solution

For toluene, **4**, only two of the three potential products are formed. The major and minor products are 4-bromotoluene and 2-bromotoluene, respectively. The remaining product, 3-bromotoluene is not formed. Bromination preferentially occurs on carbons-2 and -4 to give 2-bromotoluene and 4-bromotoluene as their intermediate tertiary carbocations are stabilised by the electron-donating methyl group (+I effect). However, bromination at carbon-2 is slightly less preferred due to steric congestion between the Br and Me groups. 3-Bromotoluene is not formed as its intermediate secondary carbocation is less stable.

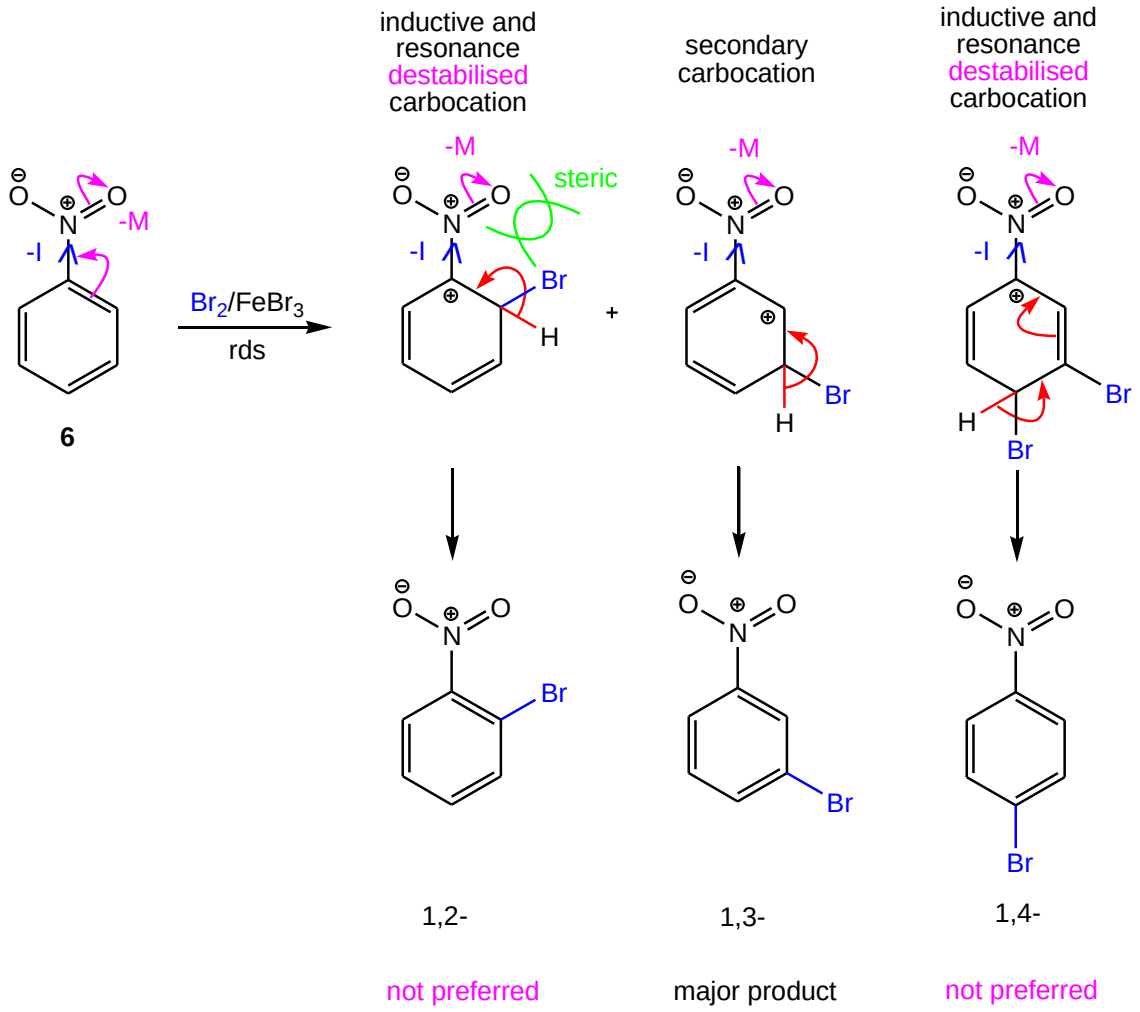


For chlorobenzene, **5**, only two of the three potential products are formed. The major and minor products are 1-bromo-4-chlorobenzene and 1-bromo-2-chlorobenzene, respectively. The remaining product, 1-bromo-3-chlorobenzene is not formed. Bromination preferentially occurs on carbons-2 and -4 to give 1-bromo-4-chlorobenzene and 1-bromo-2-chlorobenzene, respectively, as their intermediate carbocations are resonance stabilised by the electron-donating chlorine group (+M effect). However, bromination at carbon-2 is slightly less preferred due to steric congestion between the Cl and Me groups. 1-Bromo-3-

chlorobenzene is not formed as its intermediate secondary carbocation is less stable as it is not resonance stabilised by its chlorine substituent.



For nitrobenzene, **6**, only one of the three potential products is formed. The major product is 1-bromo-3-nitrobenzene. The remaining potential products, 1-bromo-2-nitrobenzene and 1-bromo-4-nitrobenzene are not formed. Bromination preferentially occurs on carbon-3 to give 1-bromo-3-nitrobenzene as its intermediate carbocation is **not destabilised** by the electron-withdrawing nitro group (-M and –I effects).



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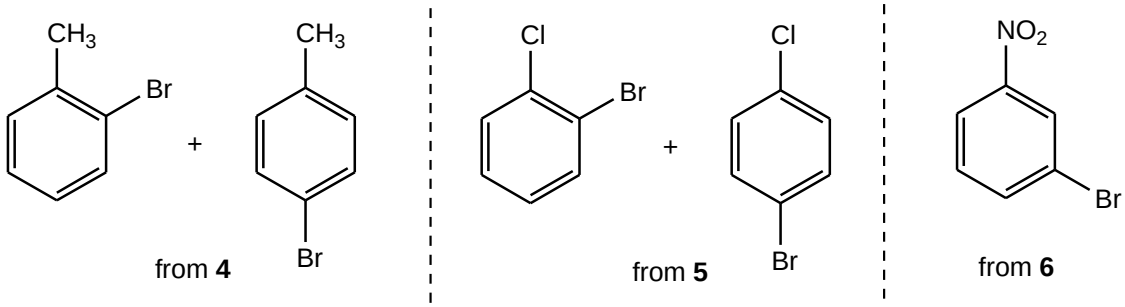
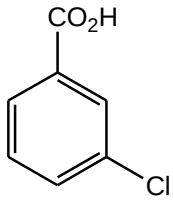


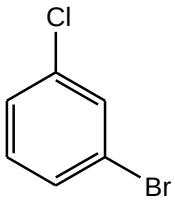
WE 22.4 Preparing substituted benzenes (on p. 1047 in *Chemistry*[3])

Propose efficient syntheses of compound **4**, starting from toluene (methylbenzene); compound **5**, starting from nitrobenzene; and compound **6** starting from phenol. Each synthesis requires more than one step.



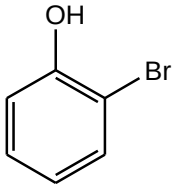
4

(from toluene)



5

(from nitrobenzene)



6

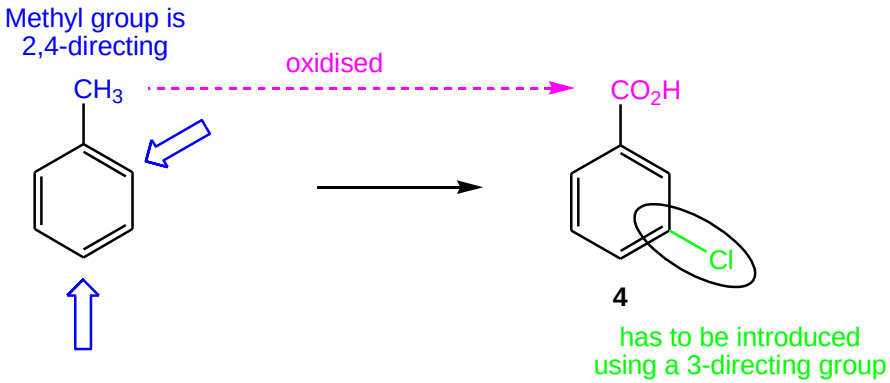
(from phenol)

Strategy

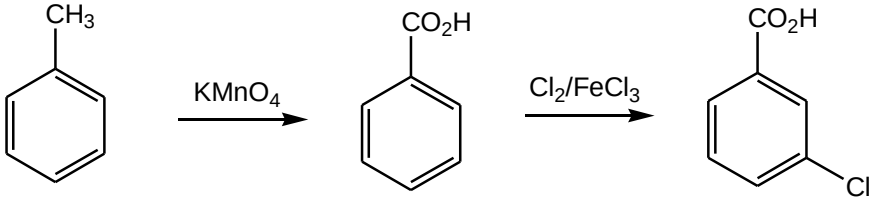
For each synthesis, draw out the starting material, label the substituent, and assign its directing effect. Work out if this directing effect and the newly introduced substituent is complementary. Suggest reagents for these required transformations.

Solution

*Proposed synthesis of compound **4** derived from toluene.*

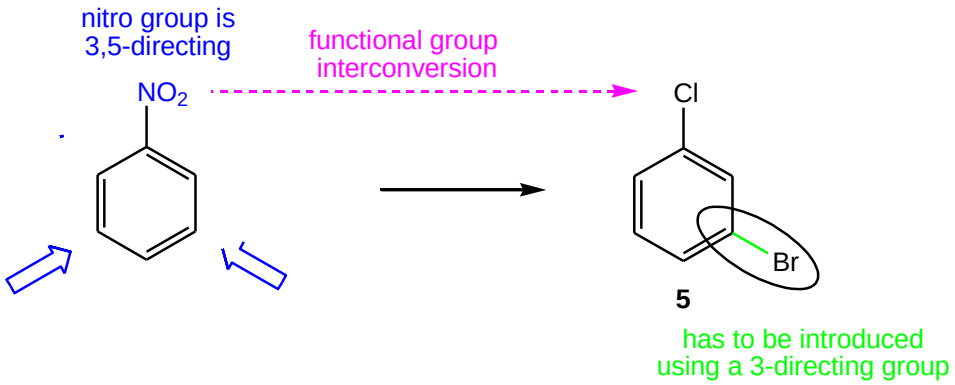


To convert toluene into 3-chlorobenzoic acid (**4**), the methyl group must be converted into the required carboxylic acid group (of benzoic acid) in order to change the directing effect of this substituent from 2,4-directing to 3-directing. The reagent for this step is $KMnO_4$; for an example of this reaction, see p. 1034 in *Chemistry*^{3}. Chlorination of benzoic acid using molecular chlorine (Cl_2) and a suitable promoter ($FeCl_3$), gives the required 3-chlorobenzoic acid **4** as the product. The proposed synthesis of 3-chlorobenzoic acid **4** derived from toluene is shown below.

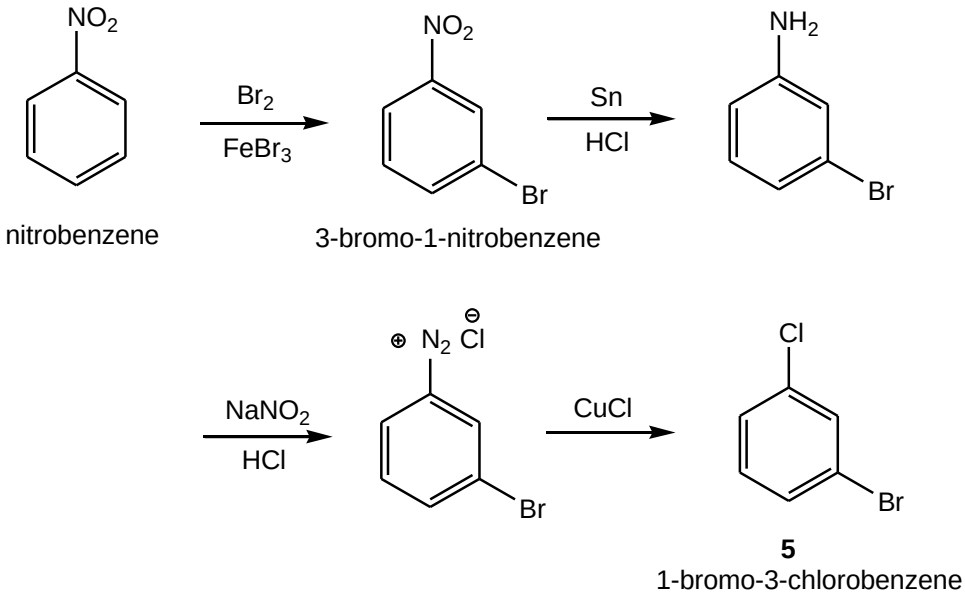


toluene benzoic acid **4**

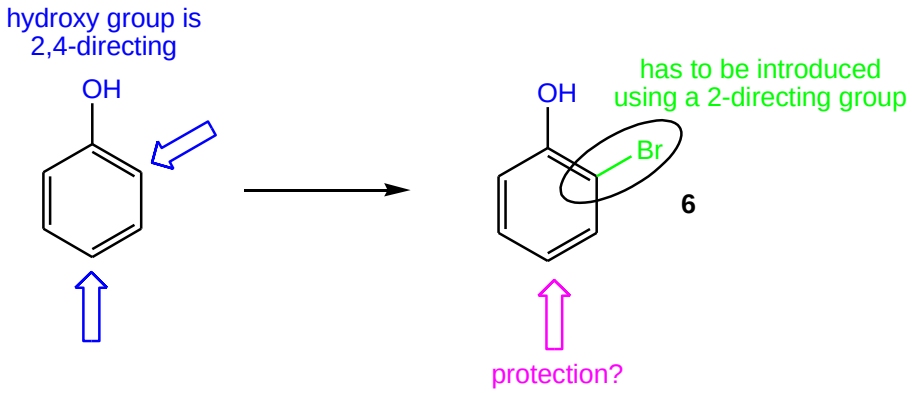
*Proposed synthesis of compound **5** derived from nitrobenzene.*



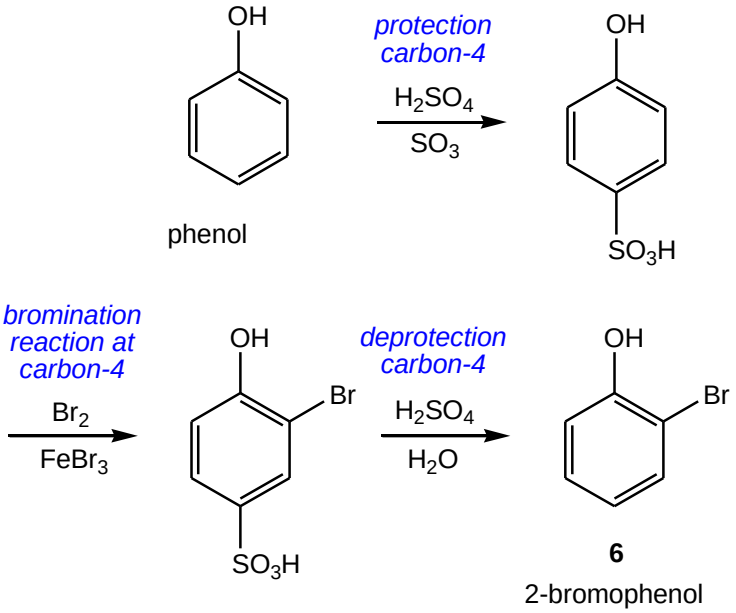
To convert nitrobenzene into 1-bromo-3-chlorobenzene (**5**), the bromine atom needs to be introduced at the beginning of this synthesis as the nitro- group has the correct 3-directing effect. It cannot be introduced after the chlorine substituent as this has the wrong 2,4-directing effect. This bromination is generally achieved using molecular bromine (Br_2) and a suitable promoter ($FeBr_3$), to give the intermediate 3-bromo-1-nitrobenzene. The remaining chlorine atom can be introduced by diazotisation of the amino ($-NH_2$) group (using Sn, HCl, followed by $NaNO_2$/HCl) and chlorine exchange (CuCl). Additional examples using these reactions can be found on p. 1036 in *Chemistry*[3]. The proposed synthesis of 1-bromo-3-chlorobenzene **5** derived from nitrobenzene is shown below.



*Proposed synthesis of compound **6** derived from phenol.*



To convert phenol into 2-bromophenol (**6**), the simplest route would introduce the bromine atom directly using classical electrophilic substitution conditions, such as Br_2 and $FeBr_3$. However, as the hydroxyl group in phenol has 2,4-directing ability, the major product will be the unwanted regioisomer 4-bromophenol as the 2-position is more sterically hindered. Bromination at carbon-2 can be achieved by introducing a temporary protecting group at the more nucleophilic carbon-4. Sulfonylation at carbon-4 using H_2SO_4/SO_3, followed by bromination at carbon-2 using $Br_2/FeBr_3$, followed by deprotection with H_2SO_4/H_2O, gives the required 2-bromophenol **6**. This sulfonylation reaction is an example of a reversible electrophilic aromatic substitution reaction; further information can be found on p. 1011 in *Chemistry*[3].



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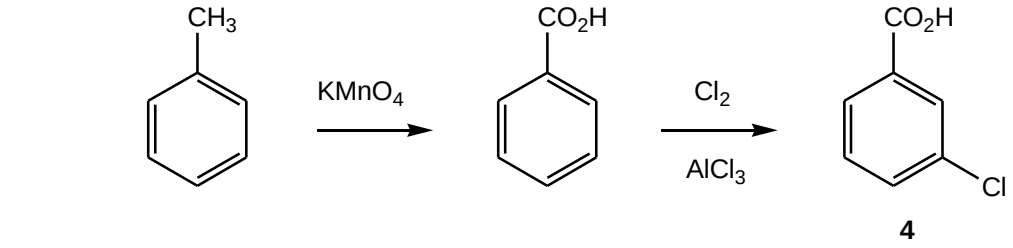

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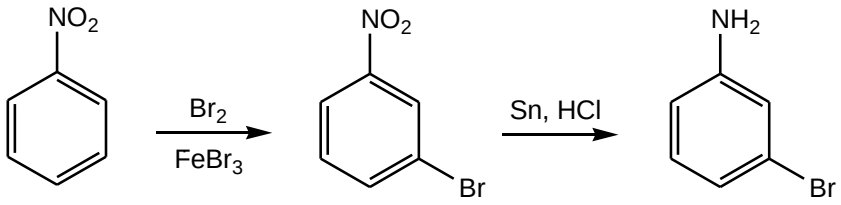
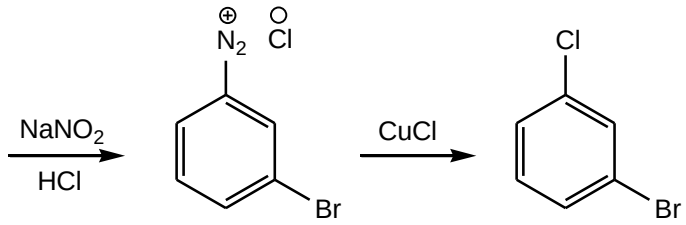
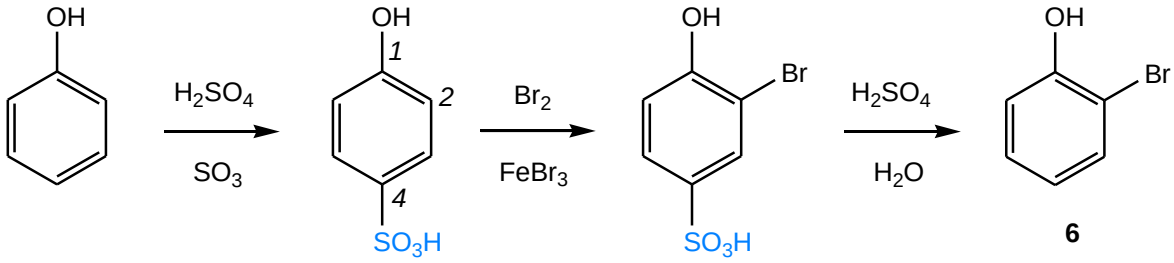




5



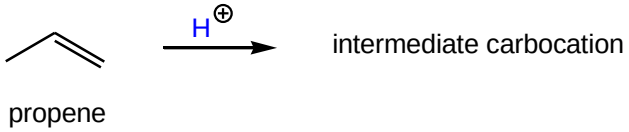
6

SO_3H is used as a temporary substituent to block the 4-position and direct Br^+ to the 2-position

Answers to boxes

Box 22.2 Making phenol from benzene (on p. 1007 in *Chemistry*^{3})

(a) In step 1, an intermediate carbocation is formed by regioselective addition of H^+ to propene. Draw the structure of the carbocation and explain why the addition is regioselective (*Hint*: see section 21.3 on p. 963 in *Chemistry*^{3}.)



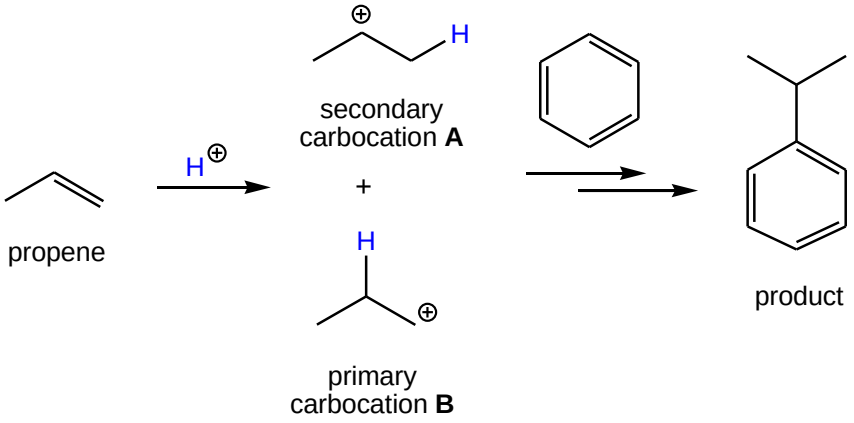
Strategy

Propene must be the base, as H^+ is the acid. As this alkene is unsymmetrical, protonation will give TWO carbocations. Work out the structure of these carbocations, and deduce which one is more stable. Using this information, explain the term *regioselective*.

Solution

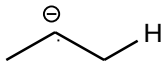
Protonation of propene leads to TWO carbocations **A** and **B**. The secondary carbocation, **A**, is more stable than primary carbocation, **B**, due to increased hyperconjugation (+I effect from the Me group). Electrophilic addition of benzene with the more stable carbocation **A** gives the required product. This protonation is regioselective, as both carbon atoms of the double (C=C) bond of propene are different, and therefore protonation will occur selectively on either carbon atom of this alkene to give potentially two carbocations **A** and **B**.

For a reaction to be regioselective, it must involve the formation of regioisomers (carbocations) and it must be selective; *i.e.*, **regioselective**. If there is a **choice** within its mechanism, then it will always be **selective**.

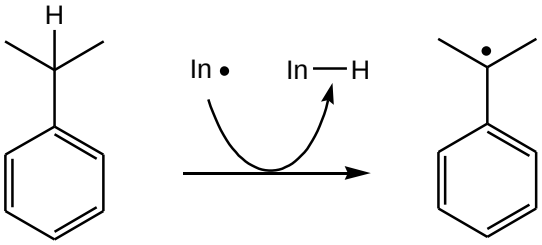


Answer

H^+ adds to the terminal carbon atom of the C=C bond to form the more stable carbocation.



(b) Explain why the radical initiator (In▪) selectively abstracts a hydrogen atom from the tertiary carbon atom of 1-methylethylbenzene in step 2.

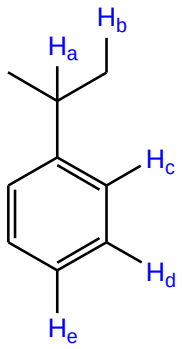


Strategy

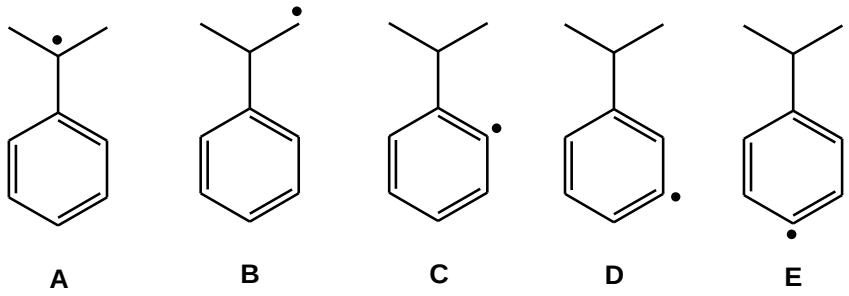
Radical reactions are generally under thermodynamic (stability) control, and as such, prefer the formation of stable radicals. Draw out all potential radicals, derived from hydrogen abstraction of isopropylbenzene, and deduce which one is the most stable.

Solution

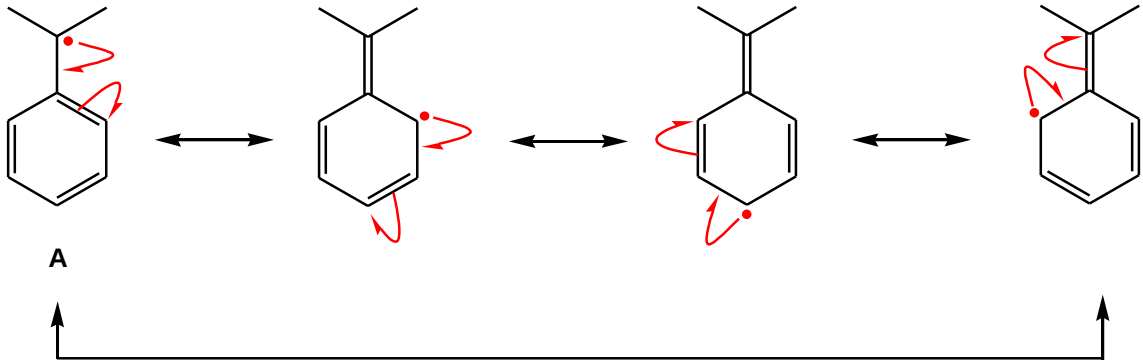
There are FIVE different hydrogen atoms, H_a-H_e, in isopropylbenzene. Alkyl groups contain weaker C-H bonds (H_a and H_b) than the alkenyl groups (H_c, H_d and H_e). The bond strengths for alkyl C-Hs are primary (strongest) > secondary > tertiary (weakest); therefore removal of H_a is the easiest as it has the weakest C-H bond. In addition, radical hydrogen abstraction of H_a with In▪ leads to the most stable (tertiary) radical, which is additionally stabilised through conjugation with its neighbouring phenyl ring.



five chemically
different hydrogen atoms

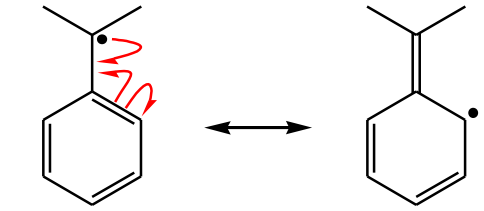


Resonance stabilised tertiary radical **A**.



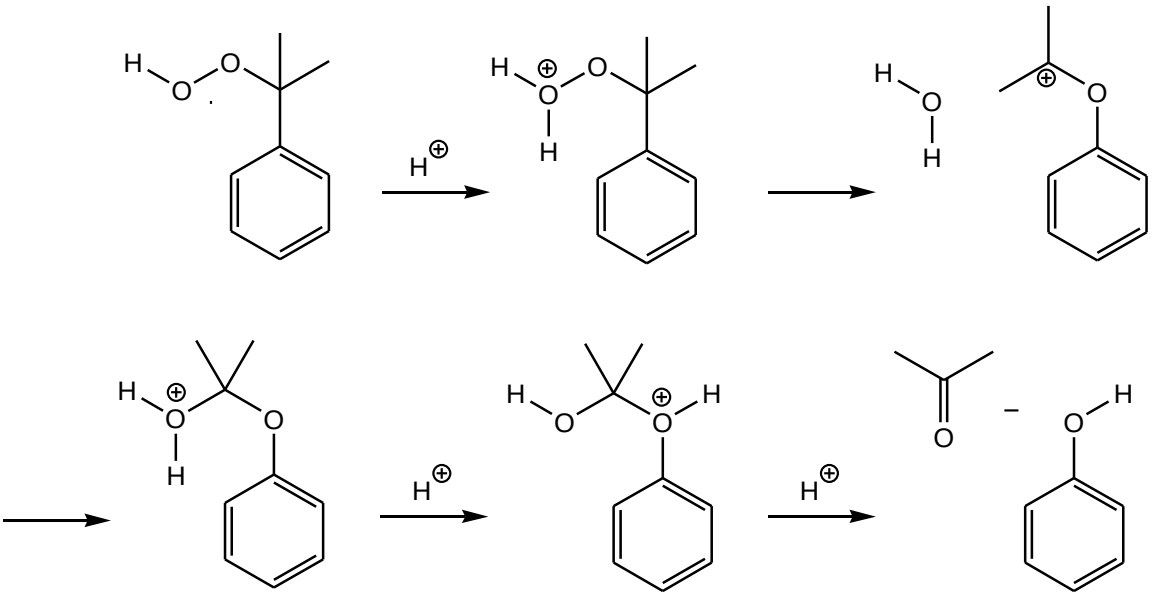
Answer

The radical initiator selectively abstracts a hydrogen atom from the tertiary carbon because the tertiary C–H bond is the weakest bond in 1-methylethylbenzene. It is the weakest C–H bond because abstraction of the hydrogen atom forms a relatively stable tertiary carbon radical, which is stabilised by resonance.



a tertiary carbon radical stabilised by resonance

(c) Suggest a reaction mechanism, using curly arrows, to explain how cumene hydroperoxide is converted into phenol and propanone in step 3. (Note: this mechanism involves ionic intermediates and not radical intermediates as in step 2.)

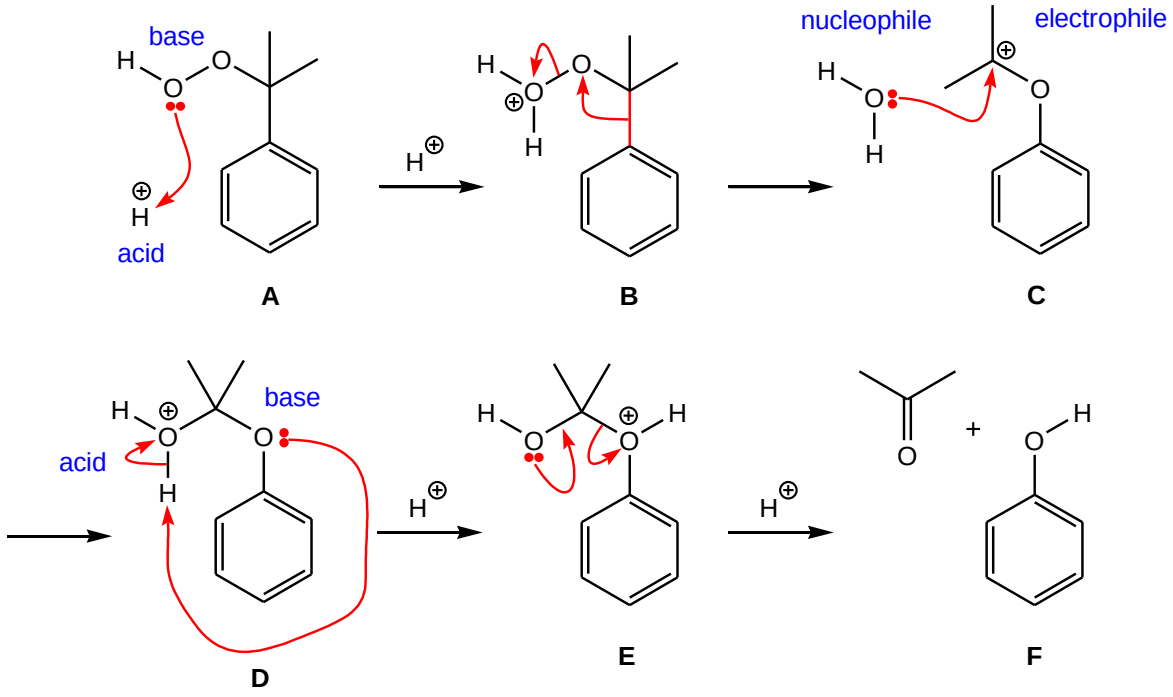


Strategy

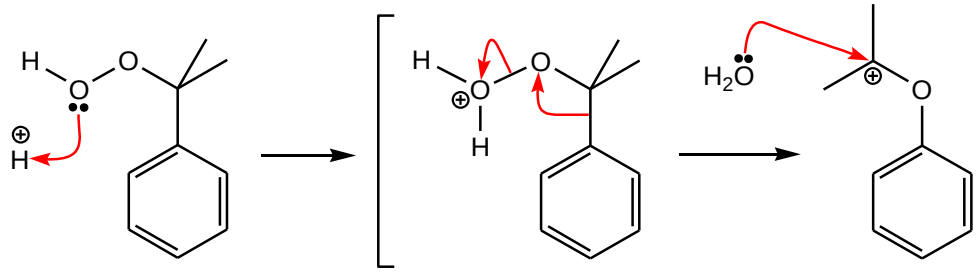
The intermediates in this mechanism are given above. You must first highlight on your scheme any non-bonded pairs of electrons. Secondly, for each step, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (→). When intermediates are formed, use nucleophile/base and electrophile/acid combinations to give more stable intermediates and/or products.

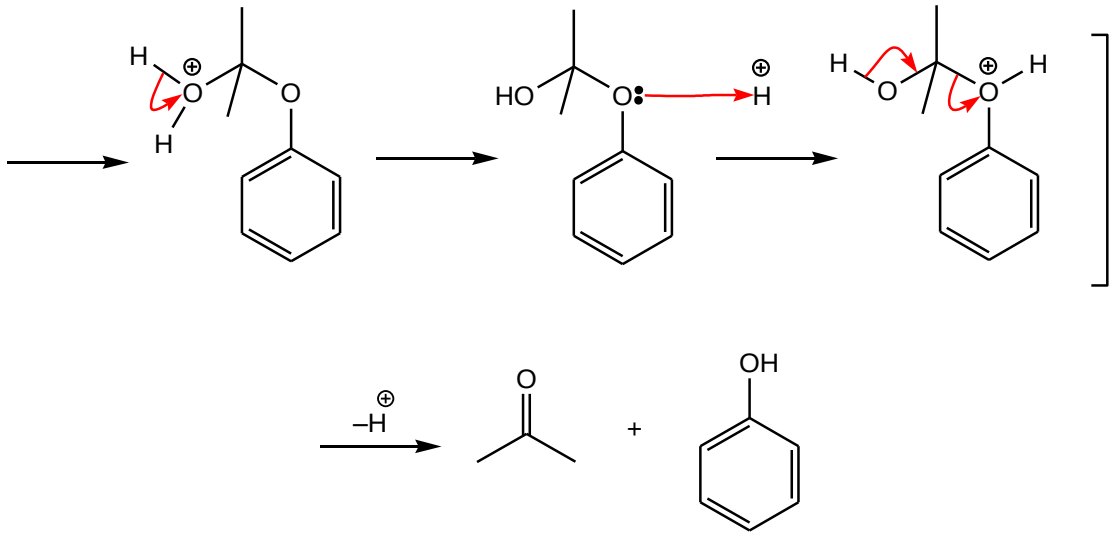
Solution

Converting the hydroperoxide **A**, which contains a very weak O-O bond into propanone (which has a strong C=O bond) and phenol **F** (which is resonance stabilised) is the driving force of this reaction. Protonation of hydroperoxide **A** with H^+ leads to the oxonium ion **B**. This oxonium ion, **B**, fragments by loss of water (H_2O) using a 1,2-phenyl shift to give the resonance-stabilised carbocation **C**. Nucleophilic addition of water (H_2O) to this carbocation **C** leads to the oxonium ion/hemiketal **D**. Internal proton exchange (in **D**), followed by loss of phenol **F** (in **E**) generates the important carbonyl (C=O) group in propanone. The mechanism for this rearrangement is shown below: the red components highlight the important movement of non-bonded and bonded electrons.



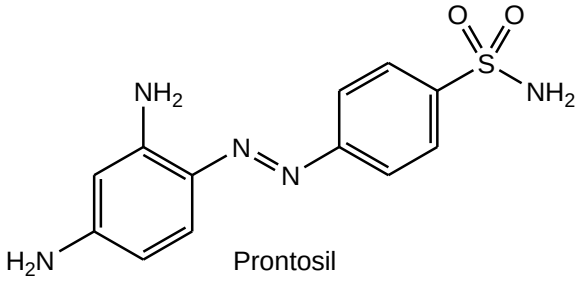
Answer





Box 22.3 From coal tar dyes to pharmaceuticals (on p. 1011 in *Chemistry*[3])

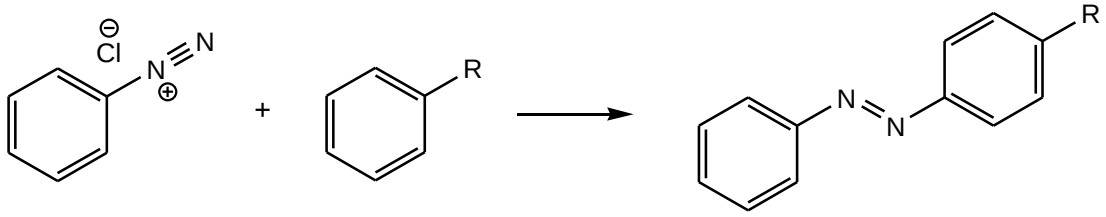
Suggest a diazonium salt and a coupling agent that could be used to prepare the azo dye, Prontosil.



Prontosil

Strategy

Azo dyes, likes **C**, are generally formed by coupling a diazonium salt, **A**, with a substituted benzene **B**. This reaction methodology has been discussed at length on p. 1037 in *Chemistry*[3].

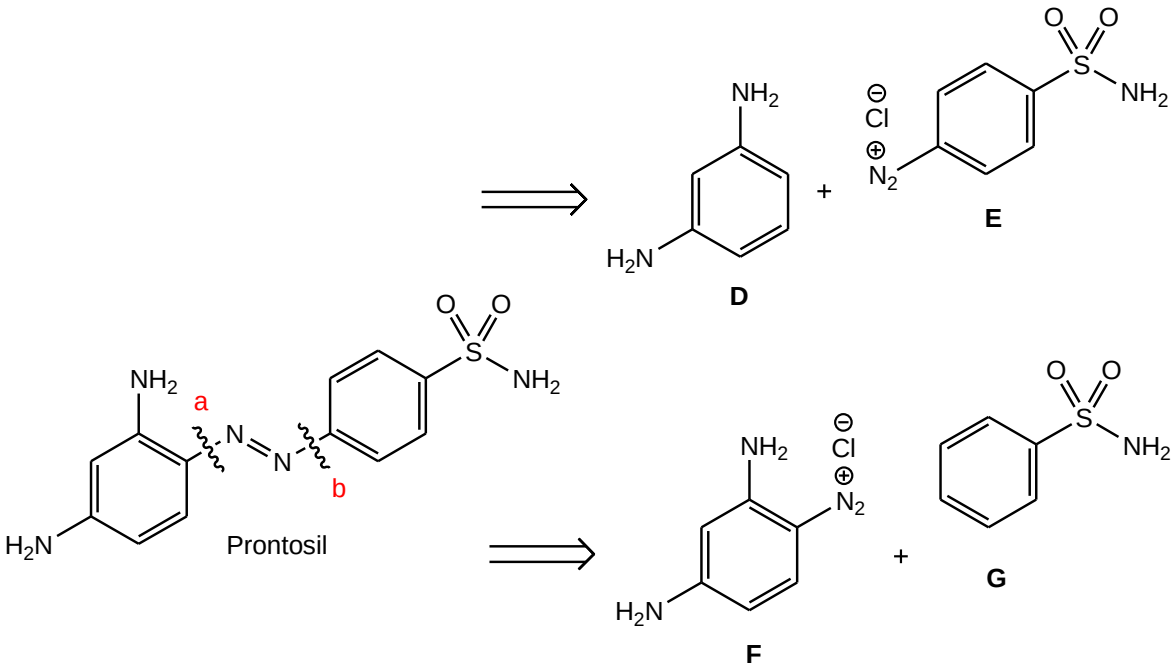


A **B** azo dye **C**

Using this azo dye synthesis, work out which reagent combinations are required to make Prontosil.

Solution

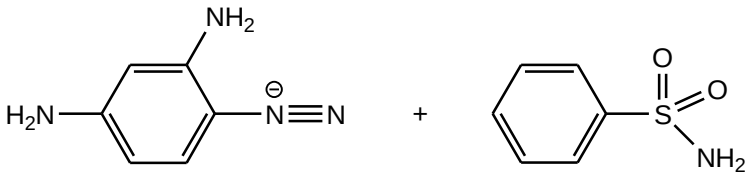
As this azo dye is unsymmetrical, there are two possible reagent combinations. Working backward from Prontosil; disconnecting bond (a) leads to the coupling reagent **D** and the corresponding diazonium salt **E**. Whereas, disconnecting bond (b) reveals the alternative coupling reagent **F** and diazonium salt **G**.



In this coupling reaction, the coupling reagent (**D** or **G**) is the nucleophile, and the diazonium salt (**E** or **F**) is the electrophile; using the more electron-rich coupling reagent **D** and the more electron-deficient diazonium salt **E** should be the better combination. In addition, formation of the diazonium salt **F** could be problematic, as selective diazotisation of one of the three amino groups in 2,4-diaminoaniline would be required.

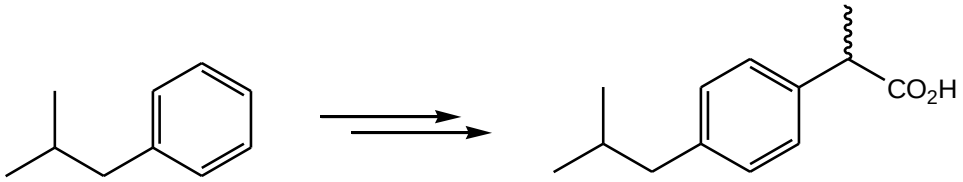
Answer

The required diazonium salt and coupling agent are shown below:



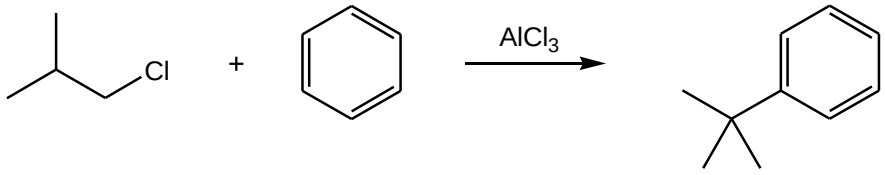
Box 22.4 Substituted benzenes in sport (on p. 1021 in *Chemistry*^{3})

Ibuprofen is an anti-inflammatory drug used by athletes to relieve minor aches and pains and to help reduce minor swelling. Ibuprofen is sold as a racemate (see box 18.7 on p. 842 in *Chemistry*^{3}) and is prepared on an industrial scale from isobutylbenzene.



isobutylbenzene ibuprofen

Isobutylbenzene is prepared in industry using a two-step sequence [Friedel–Crafts acylation followed by reduction of the C=O bond (see p. 1019 in *Chemistry*^{3})]. This is because attempts to prepare isobutylbenzene in a single step, by reacting benzene with 1-chloro-2-methylpropane and $AlCl_3$, gave *tert*-butylbenzene as the major product. Suggest a reaction mechanism to explain the formation of *tert*-butylbenzene, rather than isobutylbenzene, from the reaction below.



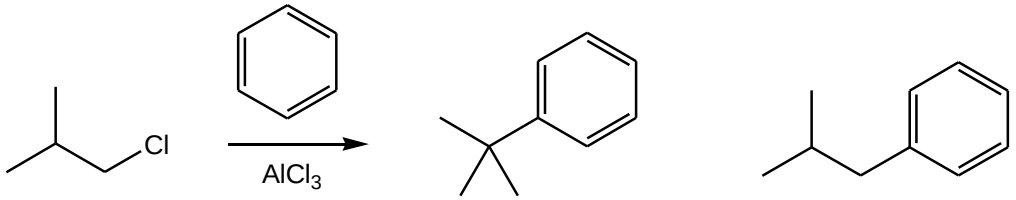
1-chloro-2-methylpropane *tert*-butylbenzene

Strategy

Draw out the reagents and a general scheme for this reaction. Work out which reagent is the nucleophile and electrophile. [Remember, the "curly arrow" flows from the nucleophile (→) to the electrophile.] Nucleophiles contain non-bonded electrons (which sometimes can be depicted by negative charge) and electrophiles have low-lying empty orbitals (which often contain a leaving group). Draw the mechanism of this reaction, and suggest why *tert*-butylbenzene, rather than isobutylbenzene is formed. A related mechanism for this reaction has been discussed on pages 965 and 1017 in *Chemistry*^{3}.

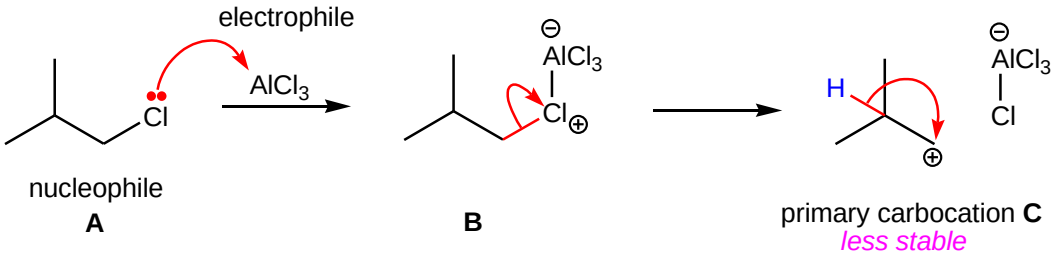
Solution

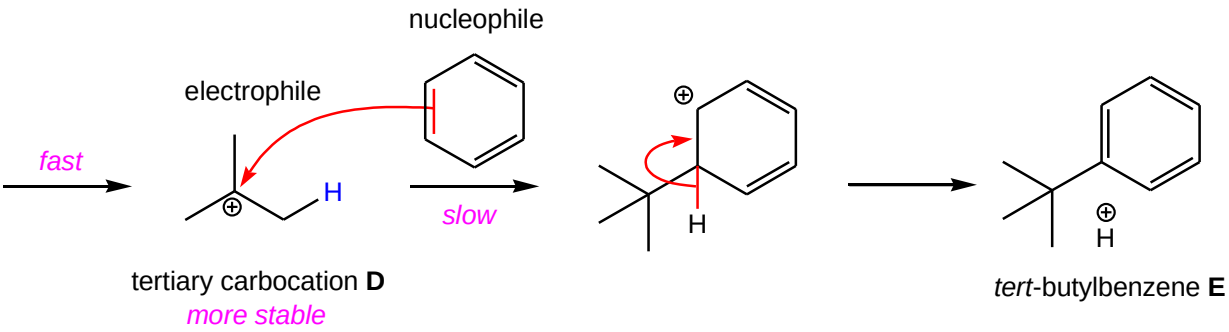
This reaction involves a Friedel–Crafts alkylation of benzene.



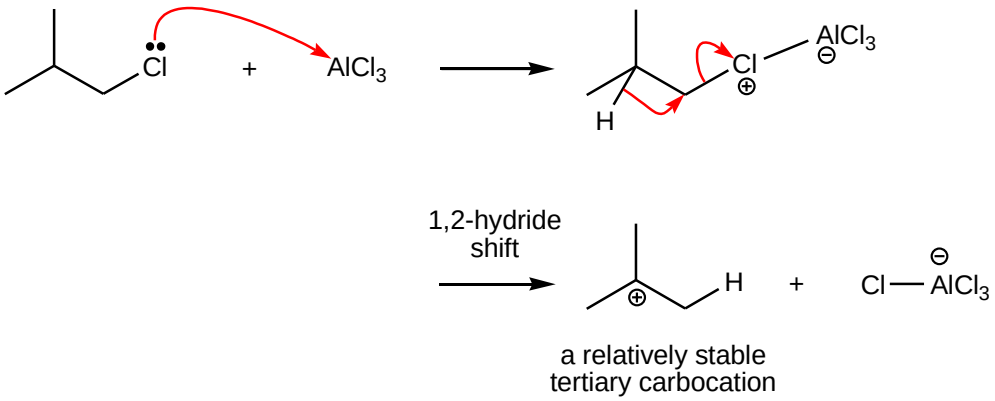
1-chloro-2-methylpropane — *tert*-butylbenzene — isobutylbenzene NOT FORMED

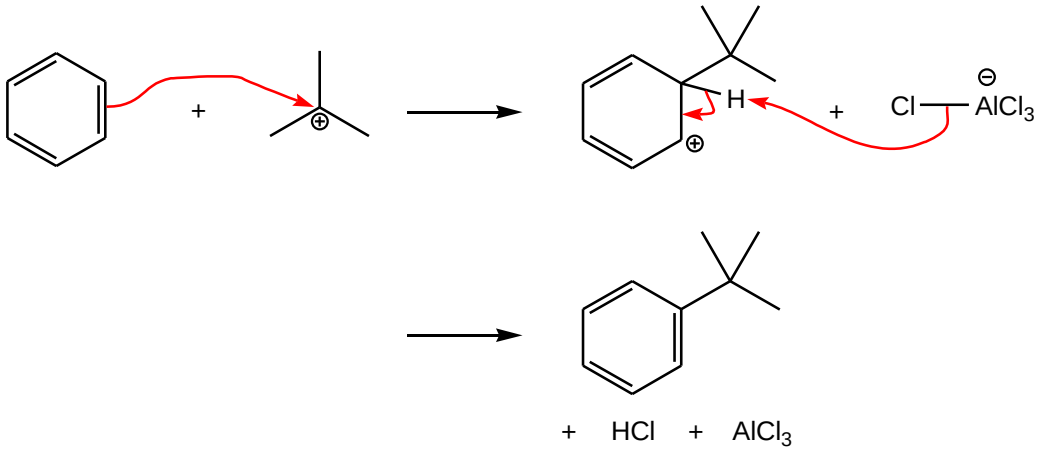
Activation of 1-chloro-2-methylpropane **A** with $AlCl_3$ (to give **B**), followed by loss of chlorine, forms the unstable primary carbocation **C** and $AlCl_4^-$. This primary carbocation, **C**, must rearrange to give the more stable tertiary carbocation **D** faster than electrophilic addition to benzene, as the product of this reaction, *tert*-butylbenzene **E**, is derived from this rearranged cation **D**.





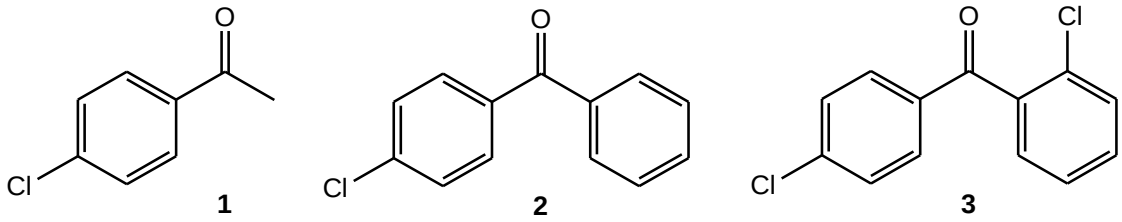
Answer





Box 22.5 Cleaning up the Friedel–Crafts acylation (on p. 1025 in *Chemistry*^{3})

Ketones **1**–**3** are prepared industrially by Friedel–Crafts acylations of chlorobenzene using an Envirocat and a suitable acyl chloride. Suggest structures for the acyl chlorides that are used to produce **1**–**3**.



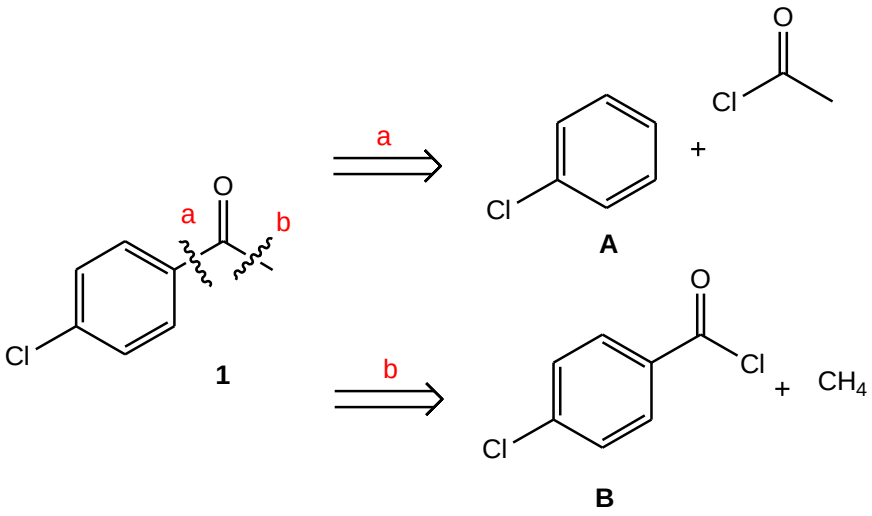
Strategy

These ketones **1-3** are prepared from the corresponding chlorobenzene and a suitable acid chloride. As these ketones are unsymmetrical, there will be two possible nucleophilic and electrophilic combinations for each ketone. Using the clue in the question "a chlorobenzene" is used; deduce which combination is the industrial method.

Solution

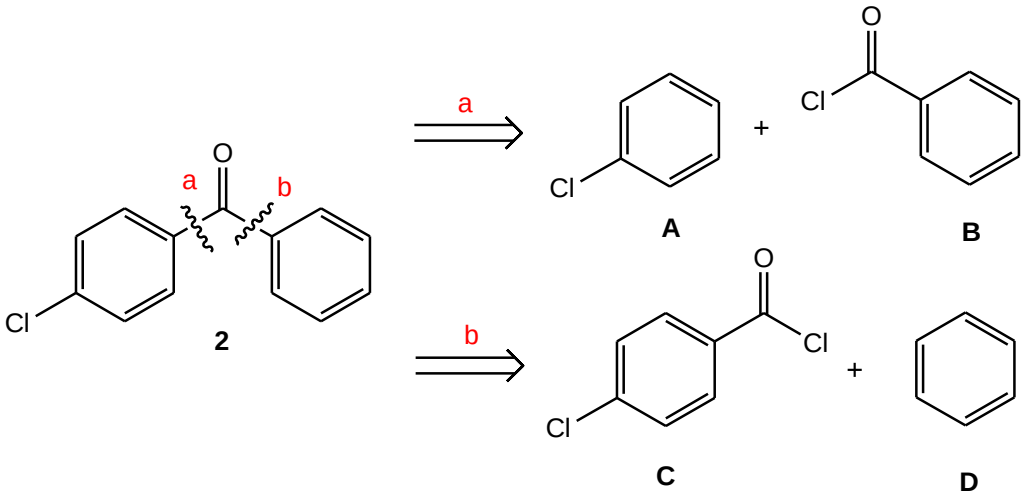
*Proposed synthesis of ketone **1**.*

Working backwards, disconnection of bonds (a) and (b), in ketone **1**, leads to two combinations of reagents; route (a) chlorobenzene **A** and acetyl chloride, and route (b) 4-chlorobenzoyl chloride **B** and methane. Using the clue in this question, the industrial procedure must use route (a) chlorobenzene **A** and acetyl chloride. Route (b) is NOT synthetically useful, as methane is not a nucleophile.



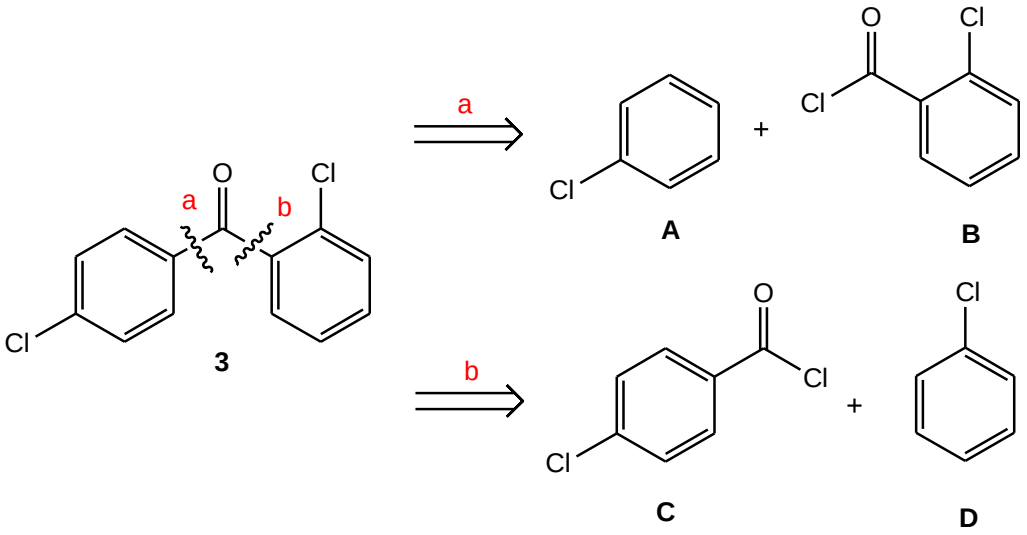
*Proposed synthesis of ketone **2**.*

Disconnection of bonds (a) and (b), in ketone **2**, leads to two combinations of reagents; route (a) chlorobenzene **A** and benzoyl chloride **B**, and route (b) 4-chlorobenzoyl chloride **C** and benzene **D**. Using the clue in this question, the industrial procedure must use route (a) chlorobenzene **A** and benzoyl chloride **B**. Route (b) is still synthetically useful, and would lead to the required ketone **2** under these reaction conditions.

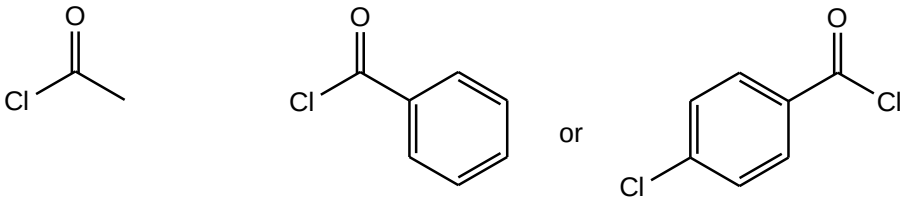


*Proposed synthesis of ketone **3**.*

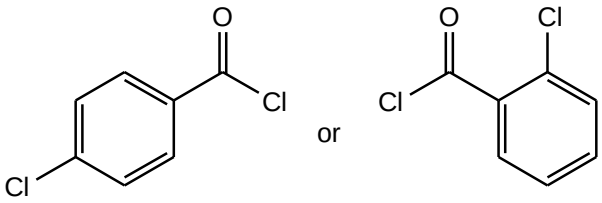
Disconnection of bonds (a) and (b), in ketone **3**, leads to two combinations of reagents; route (a) chlorobenzene **A** and 2-chlorobenzoyl chloride **B**, and route (b) 4-chlorobenzoyl chloride **C** and chlorobenzene **D**. Using the clue in this question, the industrial procedure can be either be route (a) chlorobenzene **A** and 2-chlorobenzoyl chloride **B**, or route (b) 4-chlorobenzoyl chloride **C** and chlorobenzene **D**. However, route (a) is better as the more difficult 2-chloro-substituent has already been introduced in the acyl chloride **B**. Route (b) would favour formation of the unwanted ketone, 4,4'-dichlorobenzophenone.



Answer



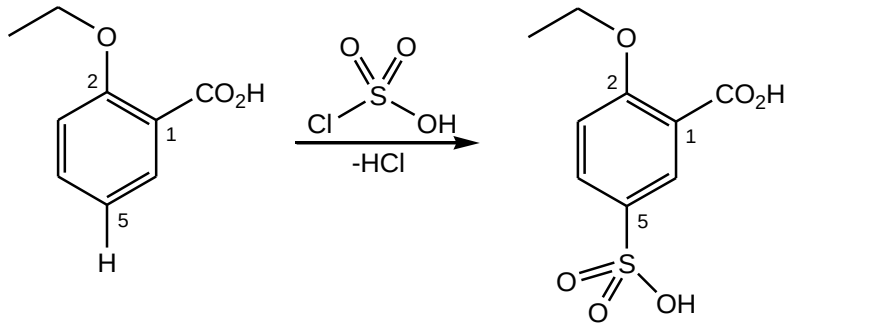
for **1** for **2**



for **3**

Box 22.6 The biological action and synthesis of Viagra (on p. 1039 in *Chemistry*[3])

(a) Suggest a mechanism for the formation of 2-ethoxy-5-sulfobenzoic acid from 2-ethoxybenzoic acid and chlorosulfonic acid.



2-ethyoxybenzoic acid 2-ethyoxy-5-sulfobenzoic acid

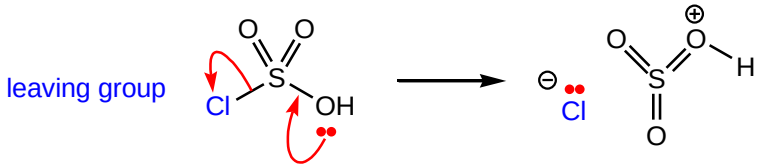
Strategy

Draw out the reagents and a general scheme for this reaction. Work out which reagent is the nucleophile and electrophile. [Remember, the "curly arrow" flows from the nucleophile (→) to the electrophile.] Nucleophiles contain non-bonded electrons (which sometimes can be depicted by negative charge) and electrophiles have low-lying empty orbitals (which often contain a leaving group).

Chlorosulfonic acid is a sulfonating agent, which can cleave to form SO_3 and HCl.
Draw the mechanism for this cleavage and the addition of SO_3/HCl to 2-ethoxybenzoic acid to give 2-ethoxy-5-sulfobenzoic acid. A related sulfonation mechanism is discussed on p. 1011 in *Chemistry*[3].

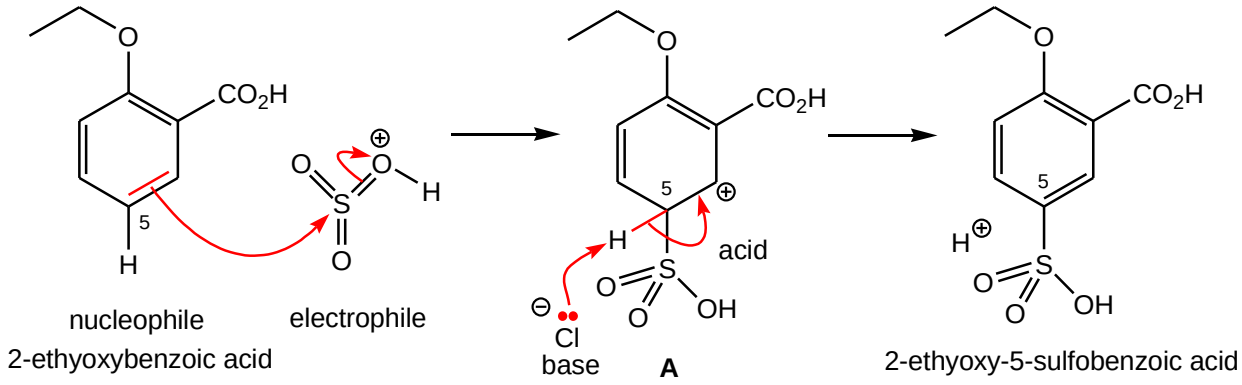
Solution

Elimination of chloride from chlorosulfonic acid gives the active electrophile, SO_3H^+. This electrophile is synonymous with aromatic sulfonylation, is made traditionally insitu by protonating sulfur trioxide (SO_3) with sulfuric acid (H_2SO_4).

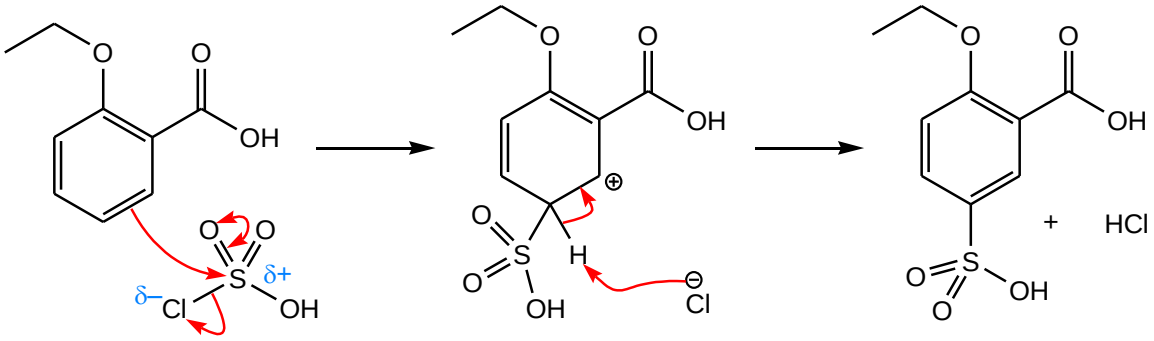


chlorosulfonic acid

Regioselective addition of this electrophile, SO_3H^+, to carbon-5 of 2-ethoxybenzoic acid forms to the intermediate conjugated carbocation, **A**; simple deprotonation with chloride gives the more stable aromatic 2-ethoxy-5-sulfobenzoic acid.



Answer



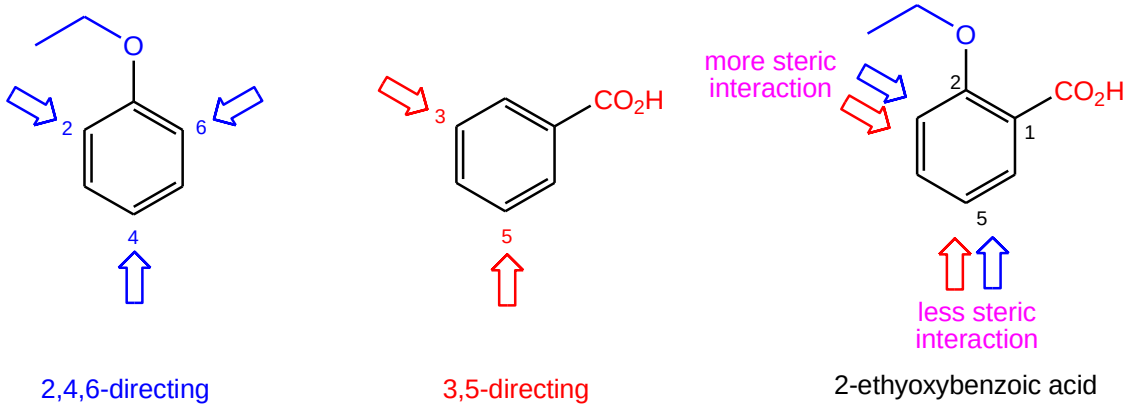
(b) In 2-ethoxybenzoic acid, the EtO and CO_2H groups direct an incoming electrophile to the 3- and 5-positions of the ring. Suggest an explanation as to why the SO_3H group is selectively introduced at the 5-position, rather than the 3-position, of this ring.

Strategy

Work out if the reaction involves electrophilic or nucleophilic substitution. Identify each substituent, and work out its directing ability. Determine the cumulative directing effect of these substituents. Explain why the sulfonic acid group is selectively introduced at carbon-5, rather than the carbon-3 of 2-ethoxybenzoic acid.

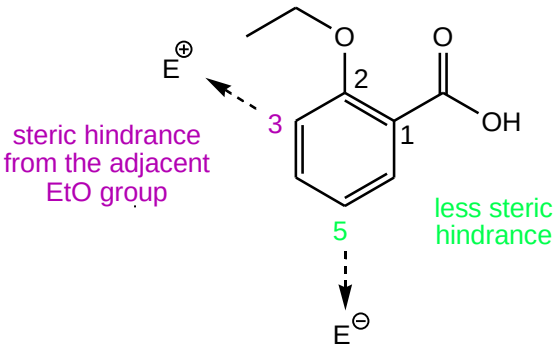
Solution

This reaction involves electrophilic substitution of 2-ethoxybenzoic acid (nucleophile) using SO_3H^+ as the electrophile; carbon-5 of this aromatic ring appears to be the most nucleophilic carbon atom. The ethoxy (EtO) group is 2,4,6-directing, and the carboxylic (CO_2H) acid is 3,5-directing; cumulatively, the more nucleophilic positions are carbons-3 and -5 of 2-ethoxybenzoic acid as shown below. However, carbon-5 is more reactive than carbon-3 as it is less steric demanding (lower steric hindrance).



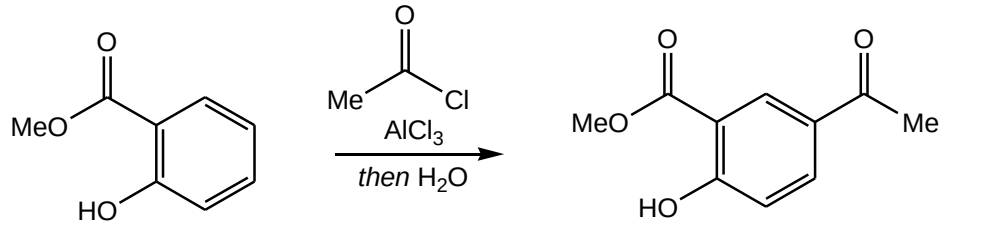
2,4,6-directing 3,5-directing 2-ethyoxybenzoic acid

Answers



Box 22.8 The biological action and synthesis of salbutamol (on p. 1049 in *Chemistry*[3])

(a) Suggest a mechanism for the formation of methyl 5-ethanoyl-2-hydroxybenzoate from methyl 2-hydroxybenzoate, $AlCl_3$, and CH_3COCl.



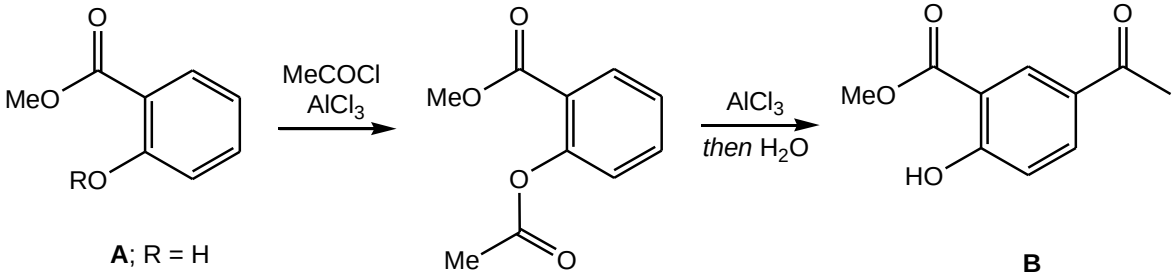
methyl 2-hydroxybenzoate

methyl 5-ethanoyl-2-hydroxybenzoate

Strategy

For each step, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (→).

There may be an additional intermediate, acetate **A**; R = Ac, in this reaction. However, this will not complicate the reaction mechanism.



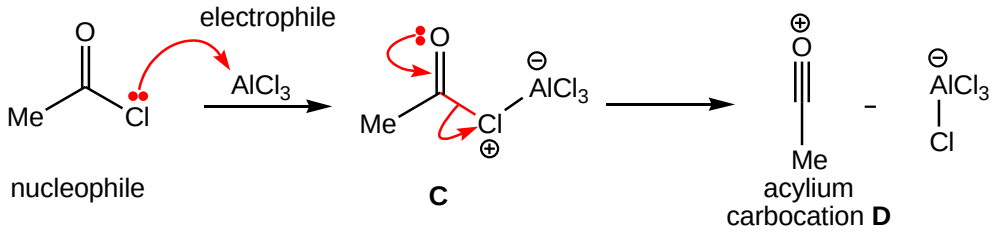
A; R = H

intermediate acetate
A; R = Ac

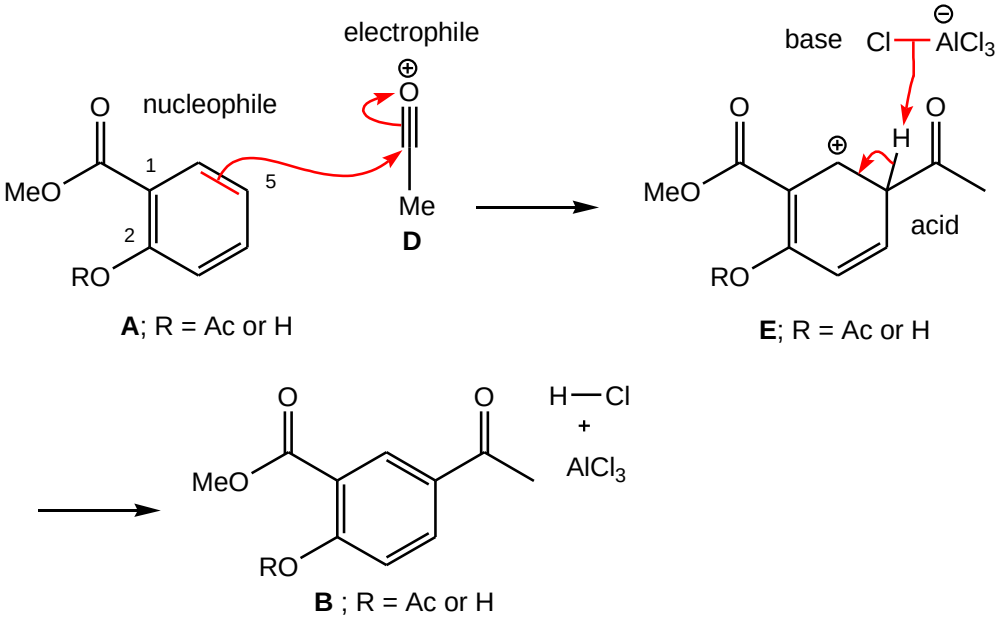
B

Solution

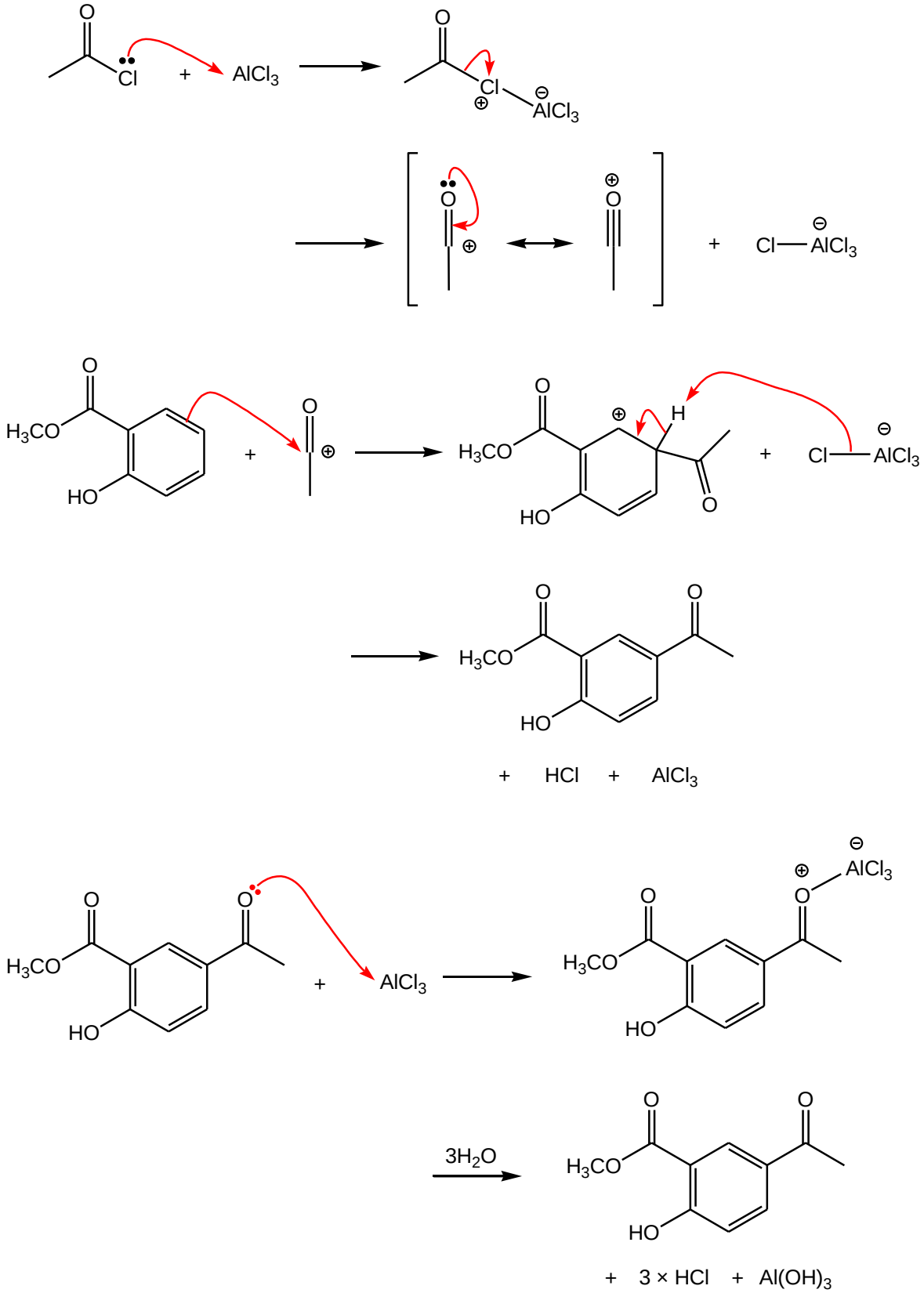
The active electrophile in this reaction is the acylium carbocation, **D**. This is formed in-situ by nucleophilic addition (of the chlorine atom) of the acetyl chloride to the electrophile, $AlCl_3$. Subsequent, fragmentation of the C-Cl bond, by participation of the non-bonded pairs of electrons on the carbonyl oxygen atom in **C**, gives the acylium ion **D** and $AlCl_4^-$.



Electrophilic addition of the acylium ion **D** to carbon-5 of **A**; R = H or Ac, gives the conjugated secondary carbocation **E**; R=H or Ac. Simple deprotonation of **E**; R=H or Ac using the sigma C-Cl bond of $AlCl_4^-$, gives the required acylated product **B**; R = H or Ac. Quenching this reaction mixture with water (H_2O), converts the $AlCl_3$ to $Al(OH)_3$, and hydrolyses the resulting ester **B**; R= Ac, into the required phenol **B**; R= H. This process is a simplified *Fries reaction*.



Answer



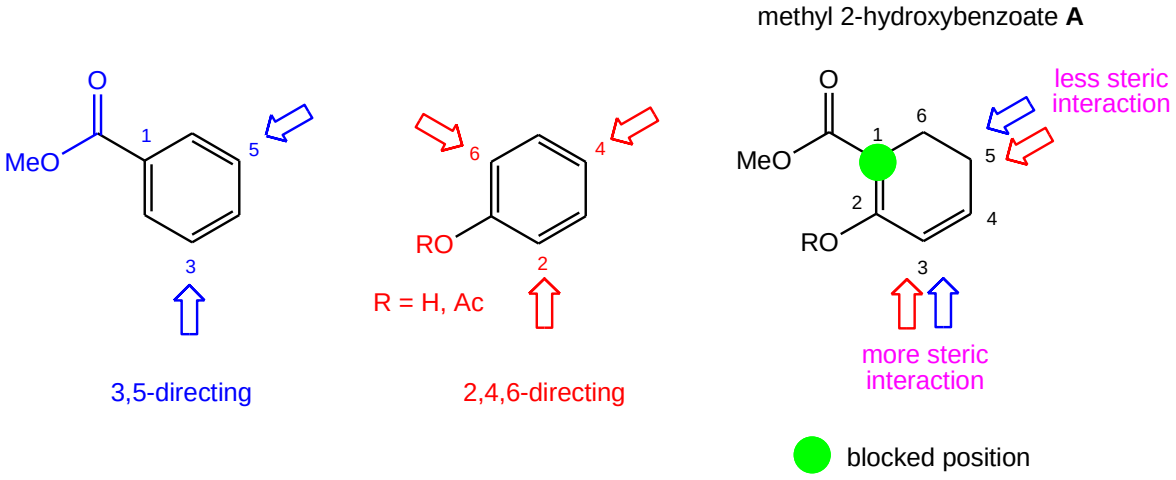
(b) Suggest why the $COCH_3$ group is selectively introduced at the 5-position of the ring.

Strategy

Work out if the reaction involves electrophilic or nucleophilic substitution. Identify each substituent, and work out its directing ability. Determine the cumulative directing effect of these substituents. Explain why the acetylation is selectively introduced at carbon-5 of methyl 2-hydroxybenzoate.

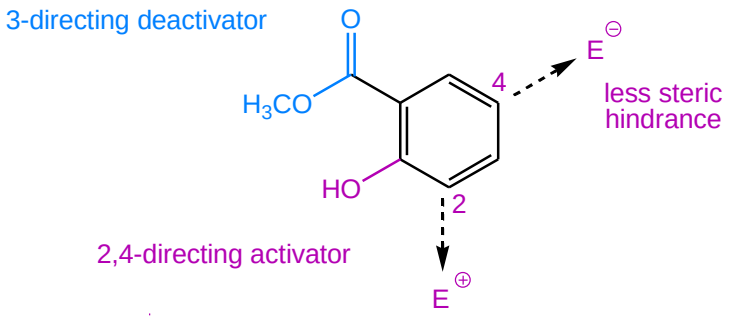
Solution

This reaction involves electrophilic substitution of methyl 2-hydroxybenzoate **A** (nucleophile) using the acylium ion **D** as the electrophile; carbon-5 of this aromatic ring appears to be the most nucleophilic carbon atom. The methyl ester (MeO_2C-) group is 3,5-directing, and the phenol (OH or OR) is 2,4,6-directing; cumulatively, the more nucleophilic positions are carbons-3 and -5 of methyl 2-hydroxybenzoate **A** as shown below. However, carbon-5 is more reactive than carbon-3 as it is less steric demanding (lower steric hindrance).

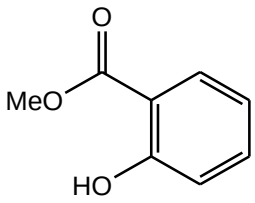


Answer

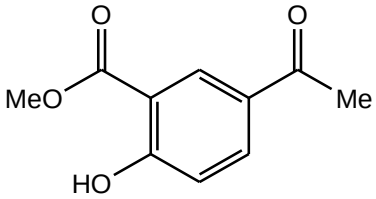
The most powerful activating group on the ring is the OH group and this controls the position of attack by the electrophile. The electrophile selectively reacts with the 4-position of the ring, rather than the 2-position, because there is less steric hindrance (the electrophile also approaches the opposite side of the ring to avoid the bulky HO and CO_2CH_3 groups). The CO_2CH_3 group is 3-directing, which means that this group also directs the electrophile to the same position of the ring as the OH group.



(c) Would you expect methyl 5-ethanoyl-2-hydroxybenzoate or methyl 2-hydroxybenzoate to react more quickly with electrophiles in electrophilic substitution reactions?



methyl 2-hydroxybenzoate **A**



methyl 5-ethanoyl-2-hydroxybenzoate **B**

Strategy

Work out if the reaction involves electrophilic or nucleophilic substitution. For each compound, methyl 5-ethanoyl-2-hydroxybenzoate and methyl 2-hydroxybenzoate, rationalise which is more or less nucleophilic (or electrophilic). Predict which compound would react faster with the acylium ion **D**. [Note: this answer is already hidden in the question!]

Solution

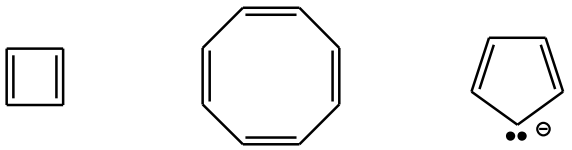
These reactions involve electrophilic addition of the acylium ion **D** to the benzene rings of methyl 2-hydroxybenzoate **A** and methyl 5-ethanoyl-2-hydroxybenzoate **B**. Methyl 2-hydroxybenzoate **A** reacts more readily than methyl 5-ethanoyl-2-hydroxybenzoate **B** as it is more nucleophilic (electron-rich) due the absence of an additional electron-withdrawing (-M effect) acetyl ($COCH_3$) group. Clearly, this reaction, **A**→**B**, must be faster than the conversion of **B**→to something else, otherwise a different product would have been formed.

Answer

Methyl 5-ethanoyl-2-hydroxybenzoate reacts more slowly with electrophiles than methyl 2-hydroxybenzoate. The extra $COCH_3$ group in methyl 5-ethanoyl-2-hydroxybenzoate is electron withdrawing and deactivates the benzene ring to electrophilic substitution.

Answers to end of chapter questions (on p. 1052 in *Chemistry*^{3})

1. State Hückel's rule, and use it to predict which of the compounds **1**–**3** are aromatic.



1 **2** **3**

Strategy

In order to determine whether these molecules are aromatic using Hückel's rule, you must work out if these molecules are cyclic, planar, contains uninterrupted (continuous) conjugation, and $(4n + 2)$ π-electrons. In some cases, it is a good idea to make a model to see if they are planar.

Solution

Hückel's rule states that a molecule is aromatic if it is cyclic, planar, contains uninterrupted (continuous) conjugation and $(4n + 2)$ π-electrons.

Cyclobutadiene **1** is not aromatic, as it does not obey the $(4n + 2)$ π-electron rule. It is **anti-aromatic** as it is cyclic, planar, contains uninterrupted (continuous) conjugation and has $4n$ π-electrons (where $n = 1$).

Cyclooctatetraene is not aromatic, as it is not planar (make a **model** to convince yourself), does not have uninterrupted (continuous) conjugation, and does not obey the $(4n + 2)$ π-electron rule. It is neither anti-aromatic even though it appears to have 8 π-electrons, as it is not planar and has no uninterrupted (continuous) conjugation. It is simply a tetraalkene.

Cyclopentadienyl anion is aromatic, as it is cyclic, planar, has uninterrupted (continuous) conjugation and contains $(4n + 2)$ π-electrons (where $n = 1 \rightarrow 6$ π-electrons).

Answer

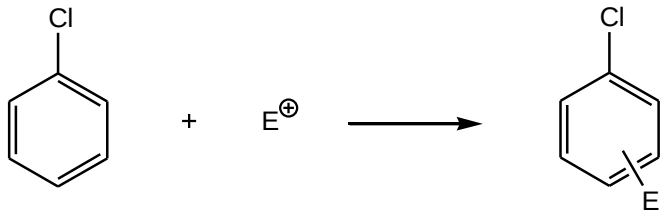
Hückel's rule states that aromatic compounds are monocyclic, planar and have an uninterrupted ring of $4n + 2$ π electrons (where $n = 1, 2, 3$ etc).

Compound **1** is monocyclic, planar and has an uninterrupted ring of 4 π electrons. It does not obey Hückel's rule and so it is not aromatic (it is anti-aromatic).

Compound **2** is monocyclic and has an uninterrupted ring of 8 π electrons. It does not obey Hückel's rule and it is not aromatic. (It is actually non-planar and non-aromatic, although this is not obvious from the structure drawn).
Compound **3** is monocyclic, planar and has an uninterrupted ring of 6 π electrons (n = 1). It obeys Hückel's rule and so it is aromatic.

2. The following table gives the results of four electrophilic substitution reactions of chlorobenzene.

(a) Draw the structure of the major product of the sulfonation reaction.



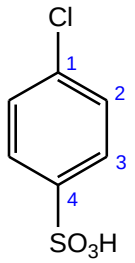
Reaction	% 2-substitution	% 3-substitution	% 4-substitution
Chlorination	39	6	55
Nitration	30	0	70
Bromination	11	2	87
Sulfonation	1	0	99

Strategy

Identify which row on the above table corresponds to sulfonation; the largest percentage corresponds to the major product. Looking up this column, you will be able to identify the major product. [Remember, sulfonylation introduces a sulfonic acid (-SO_3H) group.]
Draw the structure of this major product.

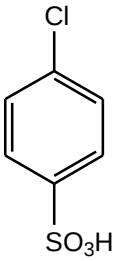
Solution

The bottom row is sulfonation; the major product consists of 99% of the 4-sulfonylated product. The structure of this major product is shown below.



4-chlorobenzenesulfonic acid

Answer



(b) Draw the structure of the minor product of the nitration reaction.

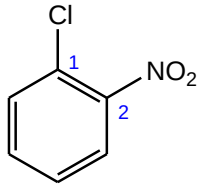
Strategy

Identify which row on the above table corresponds to nitration; the **lowest percentage** corresponds to the minor product. [A zero means there is no product]. Looking up this column, you will be able to identify the minor product. [Remember, nitration introduces a nitro (-NO_2) group.]

Draw the structure of this minor product.

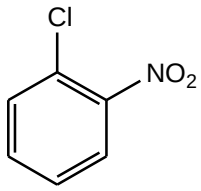
Solution

The second row is nitration; the minor product consists of 33% of the 2-nitrated product. The structure of this minor product is shown below.



2-nitro-1-chlorobenzene

Answer

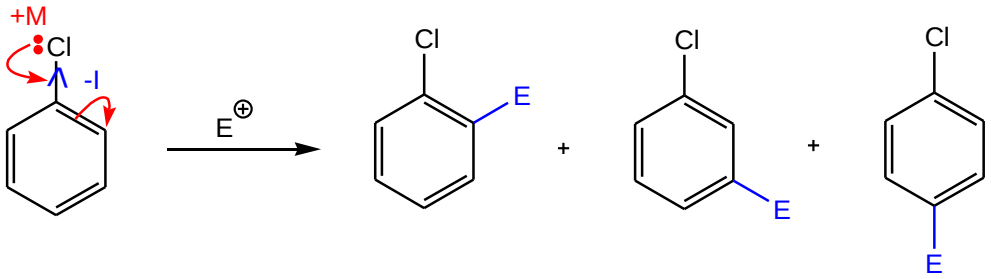


(c) Explain, with reference to the stabilities of the reaction intermediates, why 2-substituted and 4-substituted products are favoured in all four reactions.

Attack at the 2- and 4-positions produces the most stable carbocations, which have an additional resonance form because the chlorine atom stabilises the carbocations by exerting a weak +M effect.

Strategy

Electrophilic substitution of benzene leads to a single product because all the carbon atoms are identical. For mono-substituted benzenes, such as chlorobenzene **A**, up to three products **B**, **C** and **D** are formed. Regioselective addition of E^+ will depend on which positions in this molecule are more nucleophilic, and thus better equipped at stabilising the intermediate conjugated carbocations.

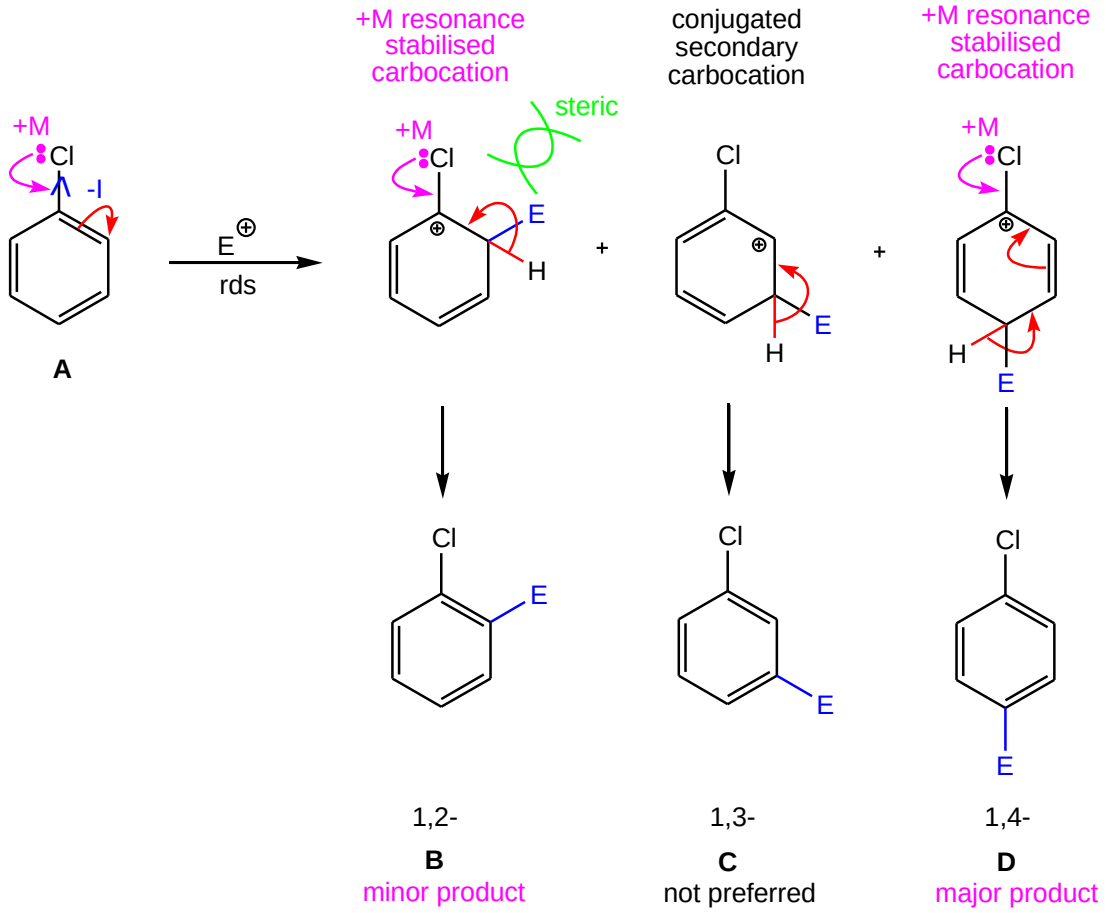


Draw out all potential products from the addition of E^+ to chlorobenzene **A**, and work out which carbon atom is the most nucleophilic.

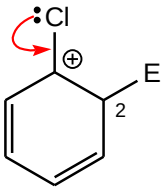
Solution

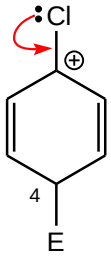
For chlorobenzene, only two of the three potential products are generally formed. The major and minor products are 1-chloro-2-substituted benzene and 1-chloro-4-substituted benzene, respectively. The remaining product, 1-chloro-3-substituted benzene, is either not formed, or formed in a negligible amount (<5%). Electrophilic substitution preferentially

occurs on carbons-2 and -4 to give 1-chloro-2-substituted benzene and 1-chloro-4-substituted benzene, respectively, as their intermediate carbocations are resonance stabilised by the electron-donating chlorine group (weak +M effect). However, electrophilic substitution at carbon-2 is slightly less preferred due to steric congestion between the Cl and the incoming electrophile, E^+. 1-Chloro-3-substituted benzene is generally not formed, as its intermediate secondary carbocation is less stable as it cannot be resonance stabilised by its chlorine substituent.

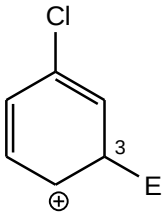


Answer





attack at the 2- and 4-positions produces a carbocation that is stabilised by the +M effect of the halogen



attack at the 3-position produces a carbocation that cannot be stabilised by the +M effect of the halogen

(d) Suggest why the four reactions give different ratios of 2-substituted:4-substituted products.

Strategy

Electrophilic substitution preferentially occurs on carbons-2 and -4 to give 1-chloro-2-substituted benzene and 1-chloro-4-substituted benzene, respectively, as their intermediate carbocations are resonance stabilised by the electron-donating chlorine group (weak +M effect). However, electrophilic substitution at carbon-2 is slightly less preferred due to steric congestion between the Cl atom and the incoming electrophile, E^+.

Consider the kinetic and thermodynamic effects of these electrophilic additions, and the size and reactivity of the incoming electrophiles.

Solution

Large electrophiles favour formation of the 4-substituted products, as this position is less sterically demanding (*e.g.* bromination versus chlorination). Small electrophiles, with high-charge density, favour formation of 2-substituted products (*e.g.* nitration).

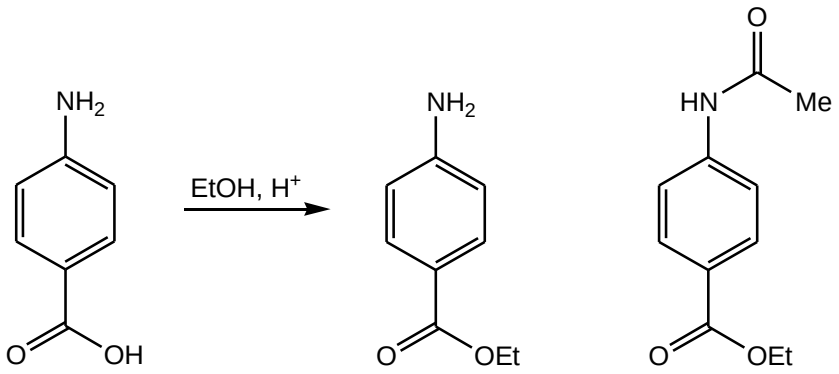
For electrophilic additions which are reversible, the more stable 4-substituted product is preferred (*e.g.*, sulfonation).

The kinetic product is generally the 2-substituted product, and the thermodynamic product is the 4-substituted product.

Answer

The different ratios of 2-substituted:4-substituted products depends on the size and reactivity of the electrophile. Large electrophiles show a higher selectivity for attack at the 4-position because this position is less sterically hindered. The ratio of the three structural isomers also depends on the reactivity of the electrophile. Weak electrophiles (e.g. $Br_2/FeBr_3$) react more slowly and more selectively than strong electrophiles (e.g. HNO_3/H_2SO_4).

3. Benzocaine **5** is a local anaesthetic, which is formed from 4-aminobenzoic acid **4**.



4 4-aminobenzoic acid

5 benzocaine

6

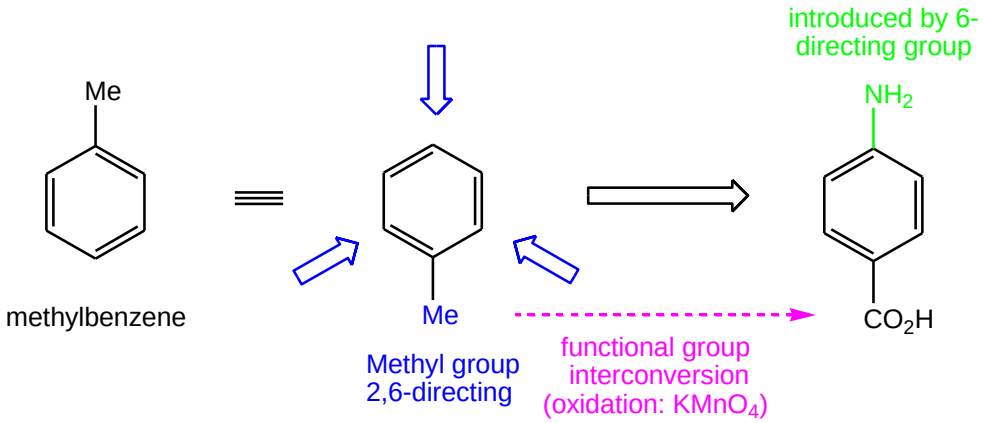
(a) Suggest a three-step synthesis of **4** starting from methylbenzene. Comment on the regioselectivity of any electrophilic substitution reactions.

Strategy

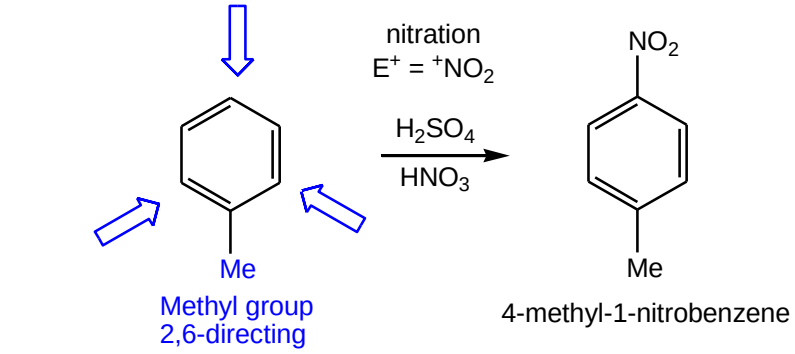
For each synthesis, draw out the starting material, label the substituent, and assign its directing effect. Work out if this directing effect and the newly introduced substituent is complementary. Suggest reagents for these required transformations.

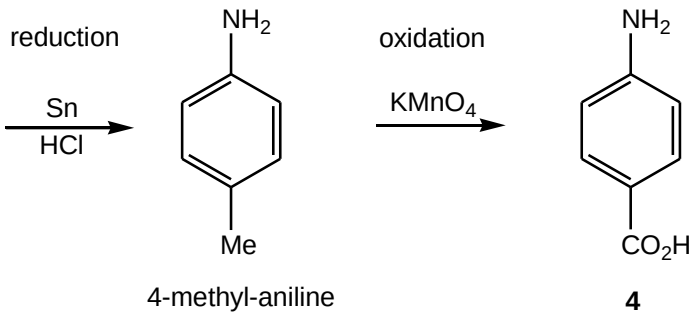
Solution

*Proposed synthesis of compound **4** derived from methylbenzene.*

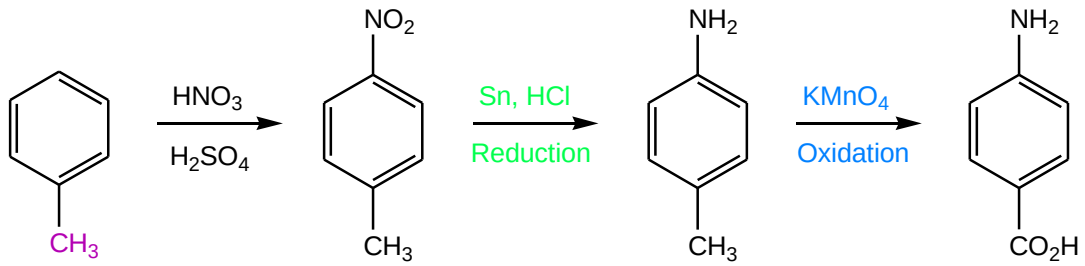


In order to convert methylbenzene into compound **4**, the amino (-NH_2) group must be introduced into this molecule, before the methyl (Me) group is converted into the 3,5-directing carboxylic acid group. This amino group is introduced by nitration of methylbenzene (H_2SO_4/HNO_3) to give 4-methyl-1-nitrobenzene, followed by reduction (Sn/HCl) to give 4-methylaniline. Conversion of the methyl (Me) group (in 4-methylaniline) into the carboxylic acid (CO_2H) group (in **4**) can be achieved by oxidation using $KMnO_4$. The proposed synthesis of compound **4**, starting from methylbenzene, is shown below.





Answer



2-/4-directing but selective attack at the 4-position for steric reasons

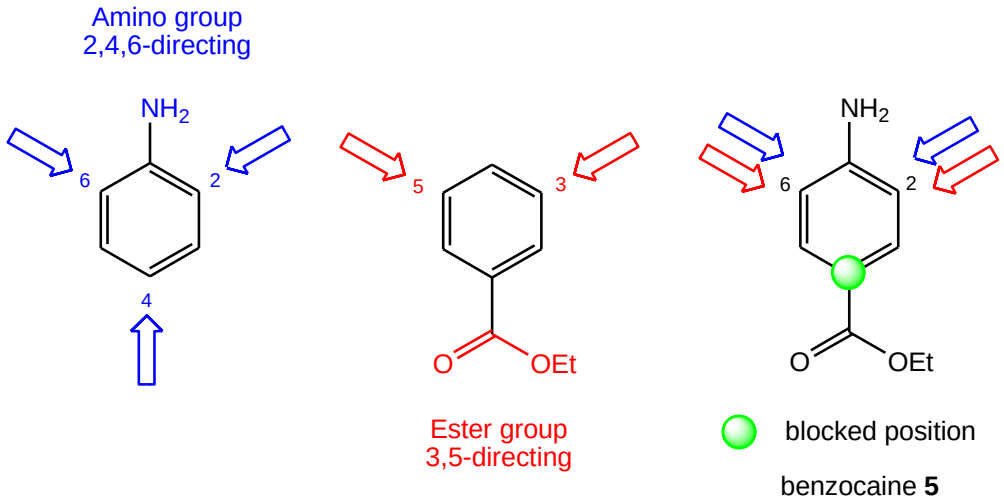
(b) Which position of the ring in benzocaine **5** is most reactive towards an electrophile (E^+)? Explain your reasoning by drawing resonance forms of the carbocation reaction intermediates.

Strategy

Work out if the reaction involves electrophilic or nucleophilic substitution. Identify each substituent, and work out its directing ability. Determine the cumulative directing effect of these substituents. Explain your reasoning by drawing resonance forms of the carbocation reaction intermediates.

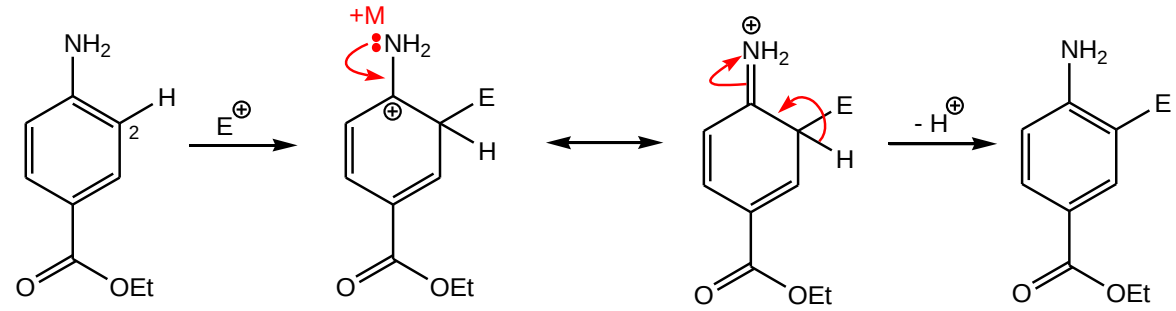
Solution

The proposed reaction involves electrophilic substitution of benzocaine **4** (nucleophile) using an electrophile, E^+; carbons-2 and -6 of this aromatic ring appears to be the most nucleophilic carbon atom. The amino ($-NH_2$) group is 2,4,6-directing, and the ethyl ester (EtO_2C-) group is 3,5-directing; cumulatively, the more nucleophilic positions are carbons-2 and -6 of benzocaine **5** as shown below.



benzocaine **5**

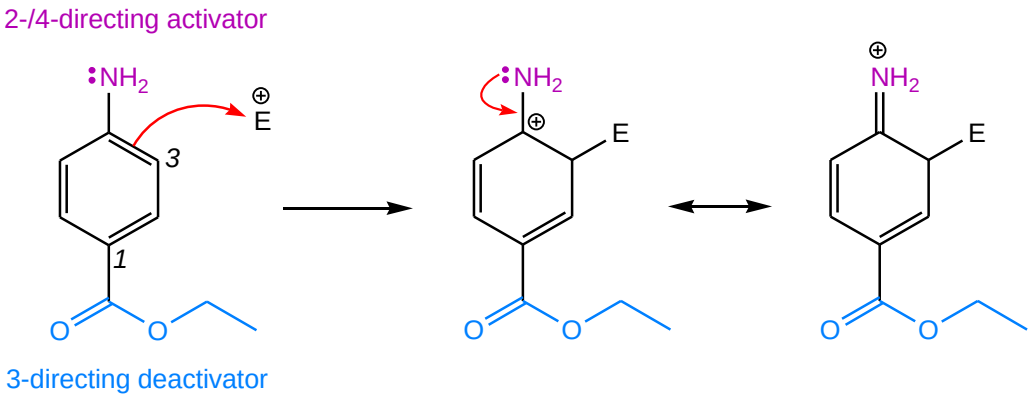
Electrophilic addition of E^+ to carbon-2 of benzocaine gives the intermediate conjugated carbocation **A**. This carbocation **A** can be resonance stabilised by the non-bonded pair of electrons on the neighbouring amino ($-NH_2$) group (to give the canonical structure **B**). Reformation of the more stable aromatic ring through deprotonation of **B** gives the 2-substituted benzocaine as the major product. The mechanism of this process is shown below.



benzocaine **5** **A** **B** product **C**

Answer

Both the NH_2 and CO_2Et substituents direct the electrophile to the 3-position of the ring numbered below. Attack at the 3-position produces a carbocation, which is stabilised by the +M effect of the NH_2 substituent.



(c) Would you expect benzocaine **4** or compound **6** to react more rapidly with an electrophile? Explain your reasoning.

Strategy

Work out if the reaction involves electrophilic or nucleophilic substitution. For each compound, benzocaine **4** and compound **6**, rationalise which is more or less nucleophilic (or electrophilic). Predict which compound would react faster with the given reagent (in this case, assume it is E^+).

Solution

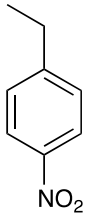
These proposed reactions involve electrophilic addition of E^+ to the benzene rings of benzocaine **4** and compound **6**. Benzocaine **4** reacts more readily than compound **6**, as it is more nucleophilic (electron-rich) as the amino (NH_2-) group (in **4**) has a stronger electron donating (+M) effect than the amide (-NHCOMe) group (in **6**).

Answer

Benzocaine **5** reacts more rapidly with electrophiles than compound **6**. The amino (NH_2-) substituent is a stronger activating group than the $NHCOCH_3$ substituent, and it is also smaller, so electrophiles can more easily attack the 3-position of the ring.

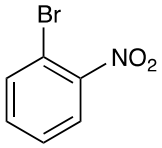
4. Suggest efficient syntheses of compounds **7**–**10** from benzene (more than one step is required in each case). Comment on the regioselectivity of any electrophilic substitution reactions.

(a)



7

(b)



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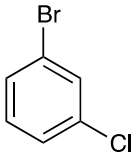
(c)



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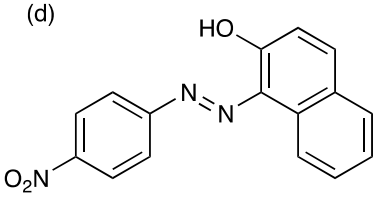
(d)



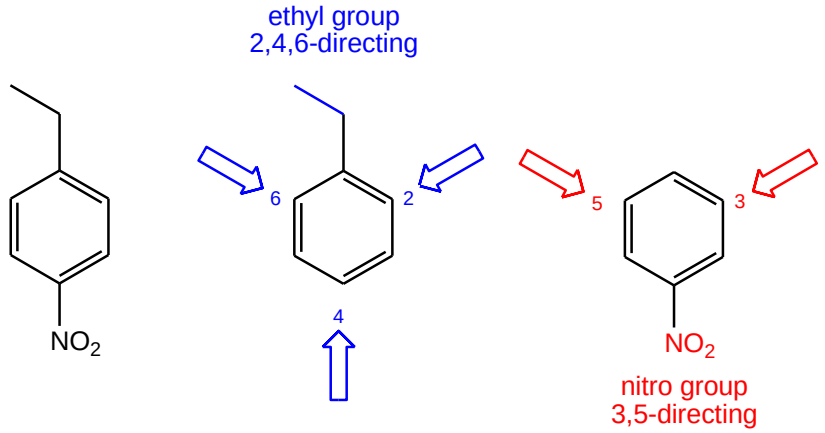
10

Strategy

As these products **7**-**10** are disubstituted benzenes, you will need to decide which substituent (or masked variant) has to be introduced first. For each synthesis, draw out the starting material, introduce the first substituent, and assign their directing effect. Work out if this directing effect allows the second substituent to be introduced in the correct position. If not, swap the order in which these substituents are introduced. Suggest reagents for these required transformations.

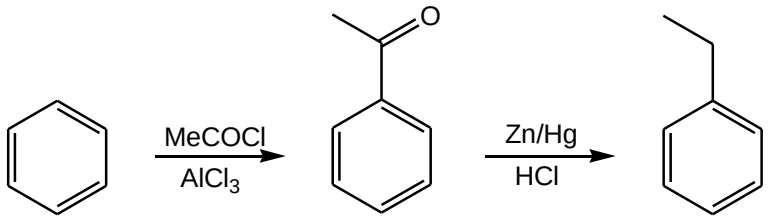
Solution

(a) The ethyl (Et-) substituent must be introduced before the nitro (-NO_2) group as this has the necessary 4-directing ability. The nitro group in **B** will favour unwanted 3- and 3,5-substitution.



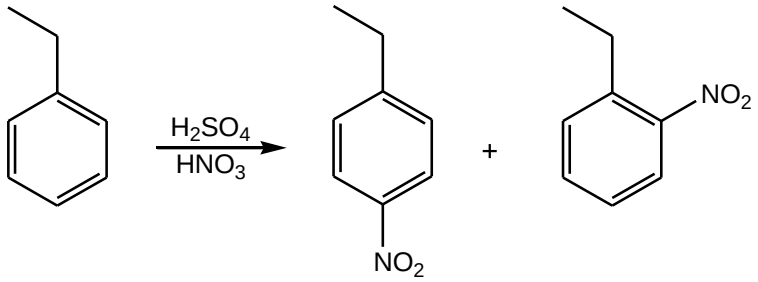
7 **A** **B**

Ethylbenzene **A** can be synthesised in two steps from benzene. Friedal Crafts acylation of benzene, followed by a Clemmenson reduction (Zn/Hg in HCl) leads to the required ethylbenzene. This two step procedure is more efficient than using the related Friedel Crafts alkylation involving EtCl and $AlCl_3$ (see pages 1013, 1018 and 1019 in *Chemistry*^{3}).



A

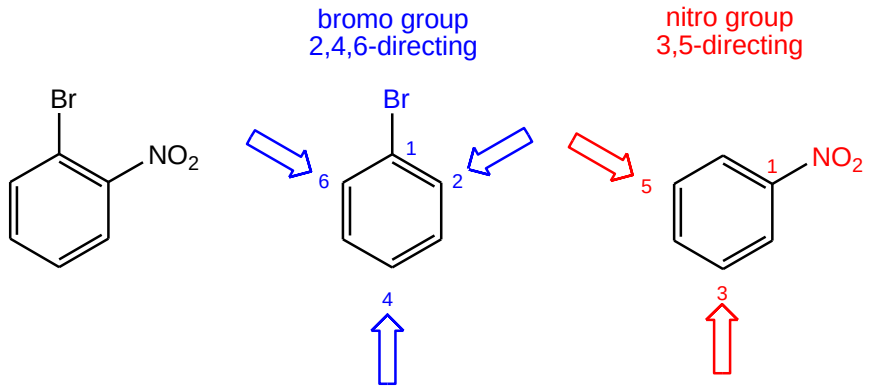
The remaining nitro ($-NO_2$) substituent can be introduced in the 2- and 4-positions by electrophilic nitration (H_2SO_4/HNO_3). The major product is 4-nitroethylbenzene as nitration at the less sterically demanding position-4 is preferred; the minor product, 2-nitroethylbenzene, can be removed on purification (*e.g.*, through distillation).



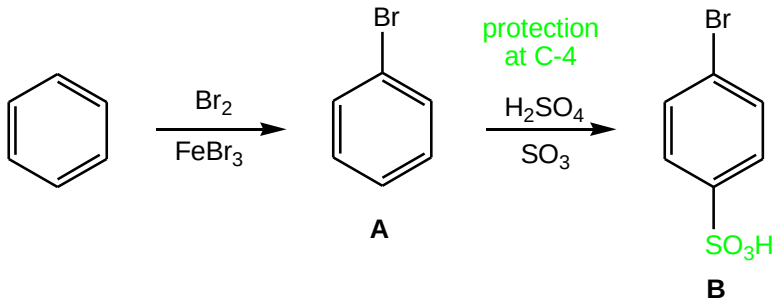
A major minor

7

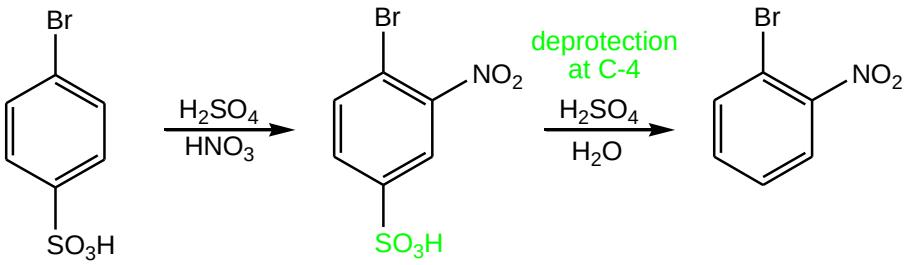
(b) The bromine (Br-) substituent must be introduced before the nitro (-NO_2) group as this has the necessary 2-directing ability. However, competitive electrophilic addition at the less steric demanding position-4 will be more efficient. Whereas, the nitro group in **X** will favour unwanted 3- and 3,5-substitution.



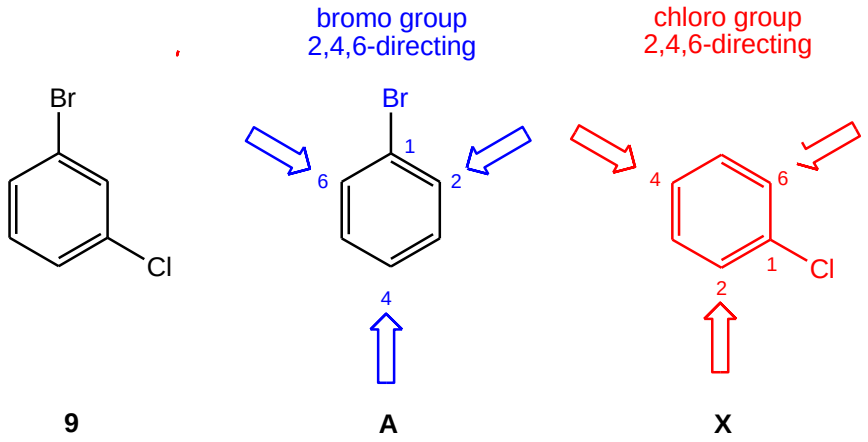
Bromobenzene **A** can be synthesised in one step from benzene using Br_2 and $FeBr_3$. Nitration of bromobenzene **A** at this stage will lead to predominantly 4-nitro-1-bromobenzene and a small quantity of the wanted 2-nitro-1-bromobenzene.



Nitration at position-2 can be achieved by introducing a temporary protecting group at the more nucelophilic and less steric demanding position-4. Sulfonation at position-4, using H_2SO_4/SO_3 to give **B**, and nitration at position-2, using H_2SO_4/HNO_3 gives **C**. Removal of the sulfonic acid group in **C** (deprotection) with H_2SO_4/H_2O, gives the required 2-nitro-1-bromobenzene **8**. This sulfonation reaction is an example of a reversible electrophilic aromatic substitution reaction; further information can be found on p. 1011 in *Chemistry*[3].



(c) Neither the bromine (Br-) substituent nor the chlorine (Cl-) substituent has the ability to direct the second electrophilic substitution to the required position-3 of the benzene ring. Therefore, the first alogen will have to be introduced indirectly as a nitro (NO_2-) group. The most common way of indirectly introducing an alogen is to use the Sandmeyer reaction (for additional information, see p. 1036 in *Chemistry*[3]).

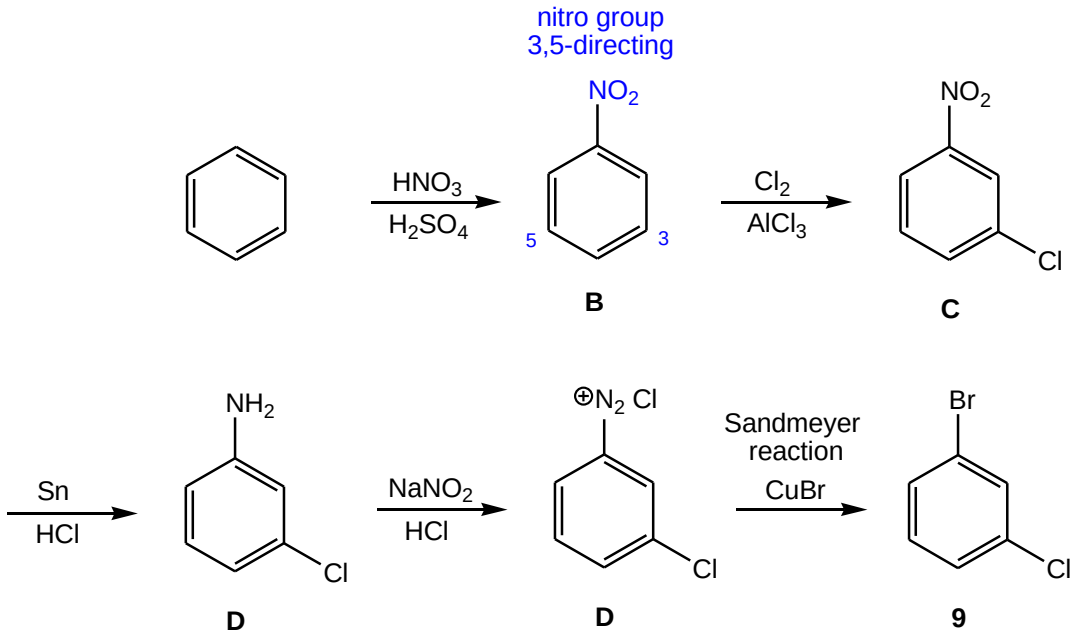


Nitrobenzene **B** can be synthesised easily from benzene using traditional nitration conditions, HNO_3 and H_2SO_4. Chlorination of nitrobenzene **B** at this stage allows the 1,3-regiochemistry (present in the product **8**) to be controlled. Treatment of nitrobenzene **B** with Cl_2 and $AlCl_3$ gives predominantly 3-chloro-1-nitrobenzene **C** as the product due to strong 3-directing ability of its nitro (-NO_2) group. Conversion of this nitro (-NO_2) group into the required bromine (-Br) substituent can be achieved in three short steps;

(i) Reduction with Sn and HCl to give the amino group in **D**.

(ii) Diazotisation of the amino group with HNO_2 (formed from $NaNO_2$ and HCl) to give the diazonium salt **E**.

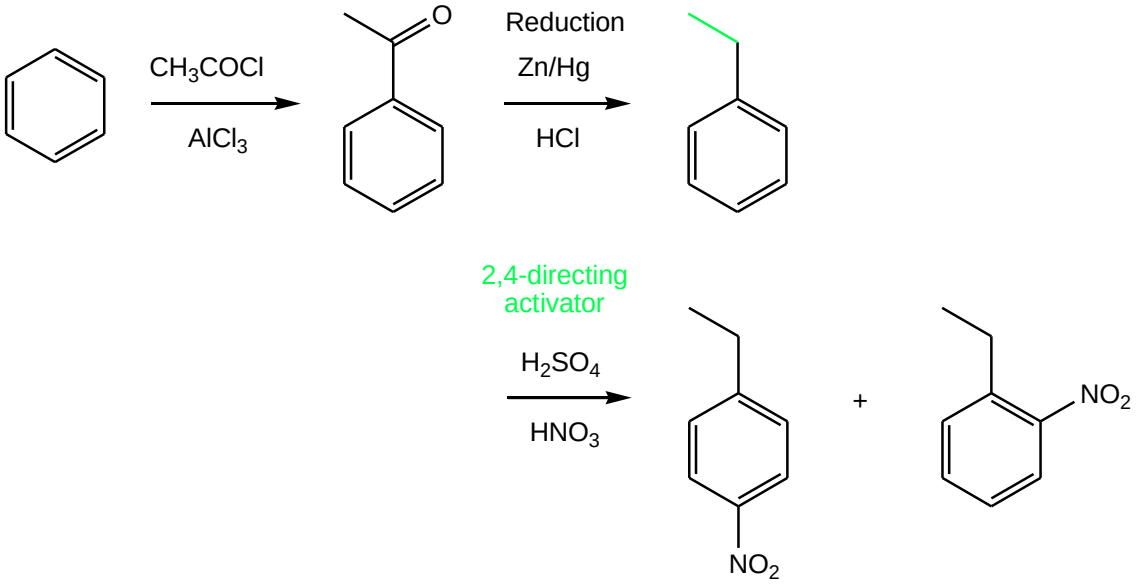
(iii) Conversion of this diazonium salt, in **D**, to the bromine (-Br) substituent, in **8**, using a CuBr mediated Sandmeyer reaction.



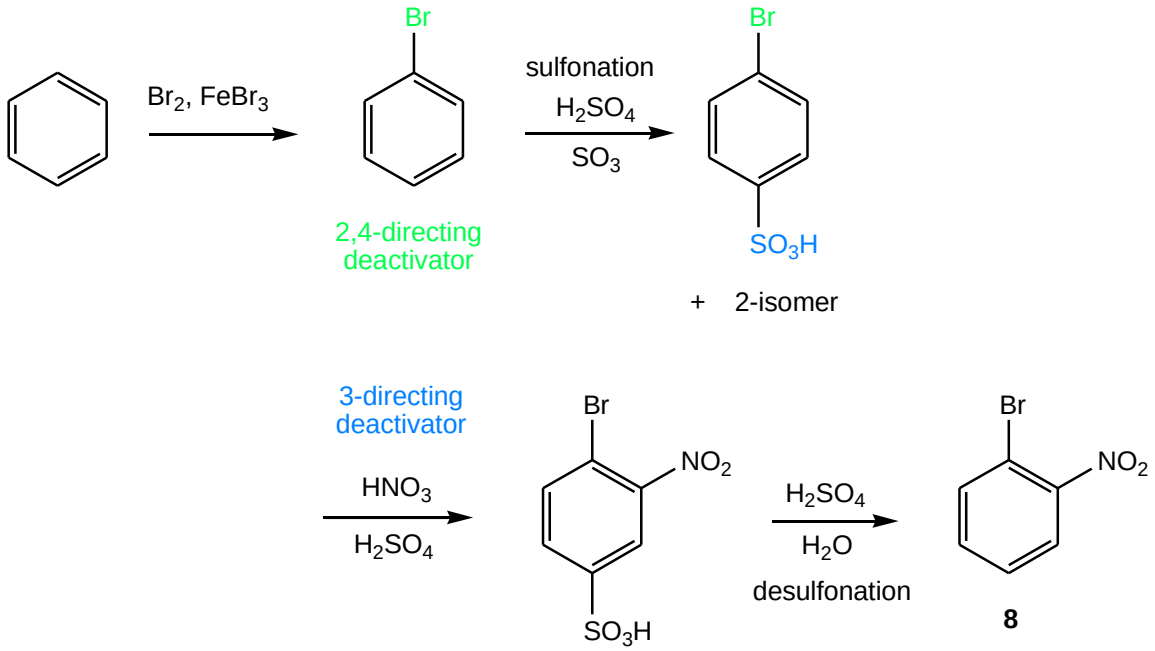
(d)

Answer

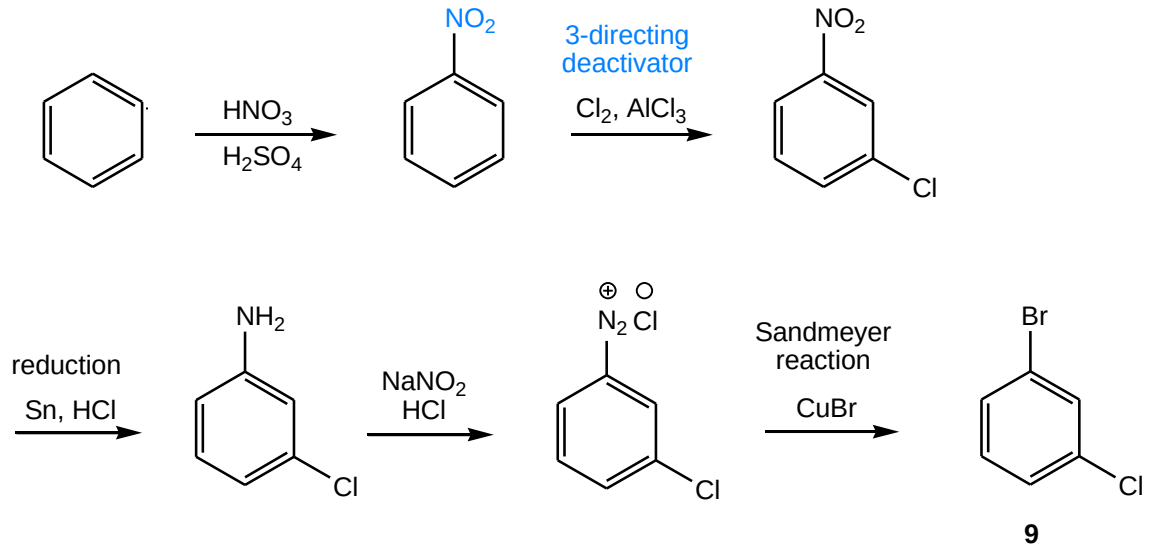
(a)



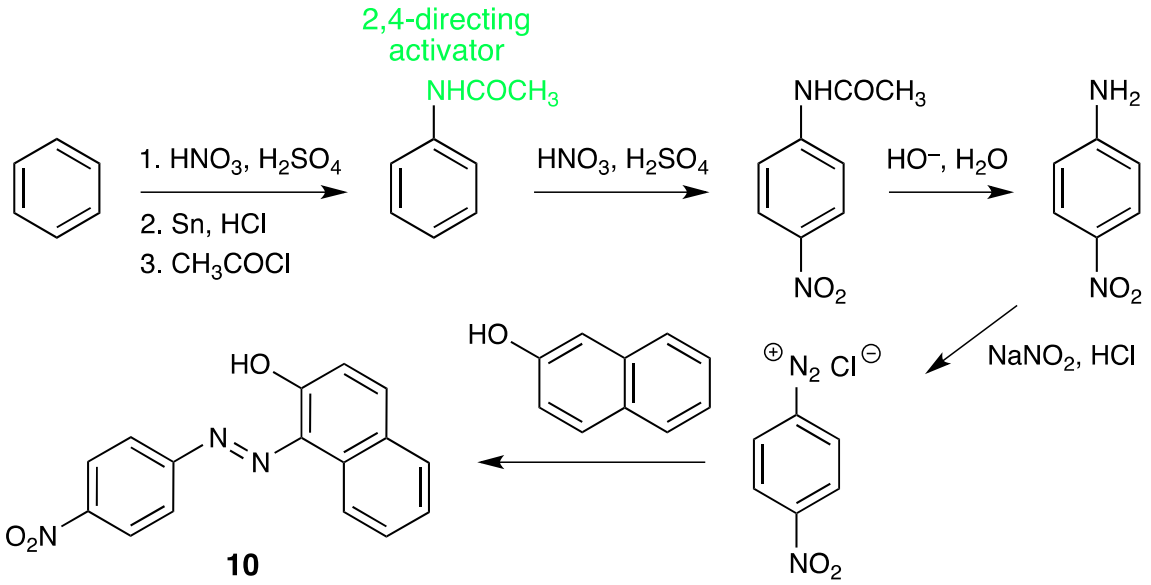
(b)



(c)



(d)



Solutions provided by J. Eames (j.eames@hull.ac.uk)