20

Halogenoalkanes:substitution and elimination reactions

Answers to worked examples

WE 20.1 Allylic halogenations (on p. 922 in *Chemistry*^{3})

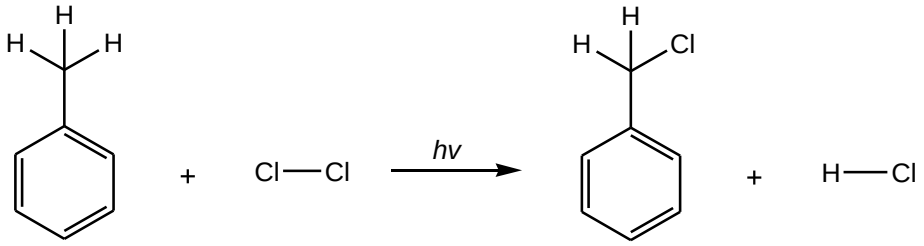
1-(Chloromethyl)benzene (benzyl chloride, $PhCH_2Cl$) is made on a large scale in industry by reacting methylbenzene (toluene, $PhCH_3$) with chlorine in the presence of UV radiation. Suggest a mechanism to explain the formation of 1-(chloromethyl)benzene from methylbenzene.

Strategy

Draw out a balanced chemical equation for this reaction, and work out what the driving force for this process is. This reaction is more than likely a radical process as it requires UV radiation. If this is the case, most radical reactions occur in 3 stages; initiation, propagation and termination.

Solution

The balanced equation for this reaction is shown below. The driving force of this reaction must be the cleavage of the weak Cl-Cl bond and formation of strong H-Cl and C-Cl bonds.

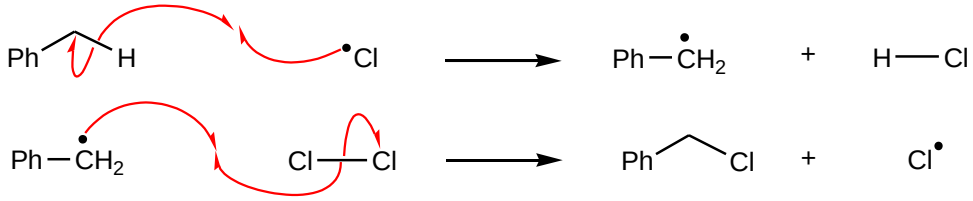


This reaction must be a radical reaction. The initiation step involves photochemical cleavage of the weak Cl-Cl bond of molecular chlorine (Cl_2) to give two Cl▪ radicals. As the byproduct of this reaction is H-Cl, H-abstraction (from toluene) using one of these Cl▪ radicals would give the benzyl radical ($PhCH_2$▪) and the required byproduct H-Cl. Capture of this benzyl radical ($PhCH_2$▪) with Cl-Cl (termination) or Cl▪ (propagation) would lead to the required product, 1-(chloromethyl)benzene. The termination step of this process is discussed on p. 969 in *Chemistry*[3].

Answer

Initiation step

Propagation steps



WE 20.2 Activation of alcohols (on p. 928 in *Chemistry*[3])

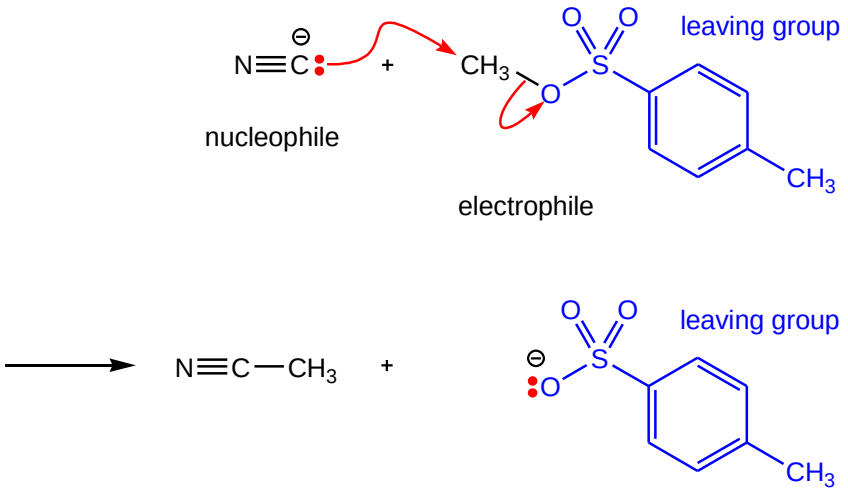
The 4-toluenesulfonate ion (TsO^-) is such a good leaving group that tosylates react with a wide variety of nucleophiles (in addition to halide ions). For the substitution reaction illustrated here, suggest structures for products **A** and **B**, and propose a mechanism for their formation.

Strategy

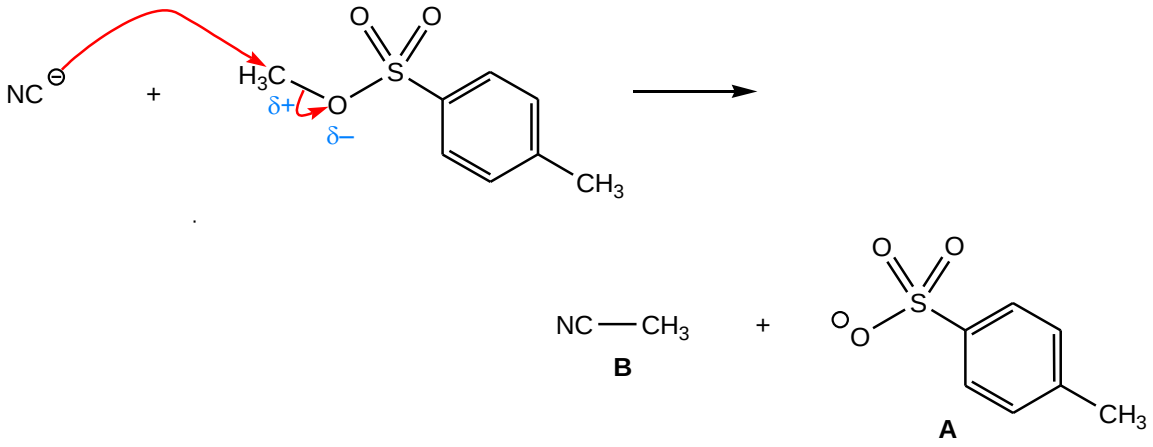
Work out which reagent is the nucleophile and electrophile. [Remember, the "curly arrow" flows from the nucleophile (→) to the electrophile.] Nucleophiles contain non-bonded electrons (which sometimes can be depicted by negative charge) and electrophiles have low-lying empty orbitals (which often contain a leaving group). In this particular case, this electrophile contains a good quality-leaving group, 4-toluenesulfonate ion; highlight this substructure on the given electrophile as this will aid you in drawing the mechanism of this reaction.

Solution

The cyanide anion is the nucleophile (as it has a pair of non-bonded electrons on its carbon atom) and methyl 4-toluenesulfonate is the electrophile (as it contains the leaving group). This reaction is a bimolecular nucleophilic substitution (S_N2) process in which the methyl group is transferred from electrophile to the *pro*-nucleophile. The mechanism is shown below.



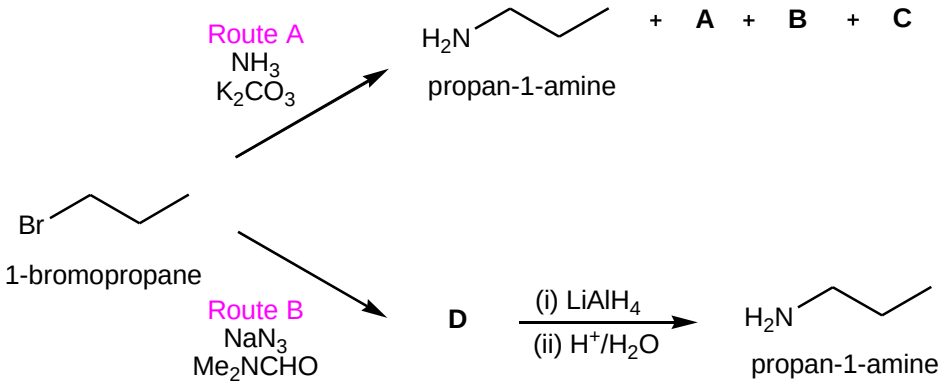
Answer



WE 20.3 Predicting substitution pathways (on p. 939 in *Chemistry*[3])

Ammonia reacts with halogenoalkanes in substitution reactions. The reactions usually produce a mixture of amine products. It is difficult to obtain good yields of primary amines because these react further to produce secondary amines, tertiary amines, and

quaternary ammonium salts. The reaction scheme below shows the preparation of propan-1-amine from 1-bromopropane by two routes.



(a) In route A, 1-bromopropane reacts with ammonia, in the presence of a base such as potassium carbonate, to give propan-1-amine in low yield and three additional organic compounds (**A**, **B**, and **C**).

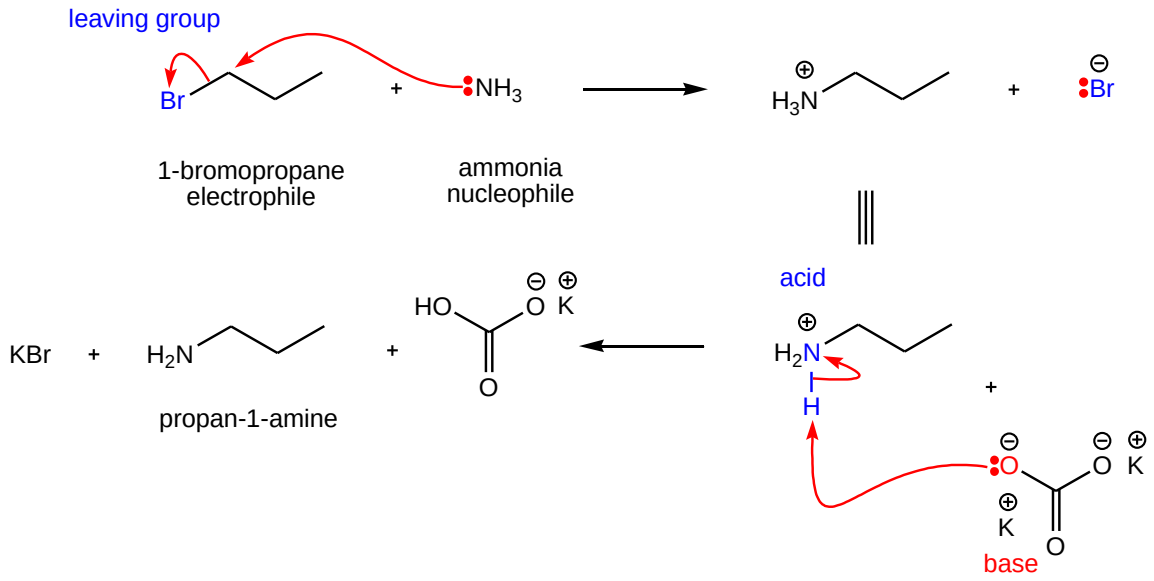
(i) Propose a mechanism to explain the formation of propan-1-amine from 1-bromopropane and ammonia.

Strategy

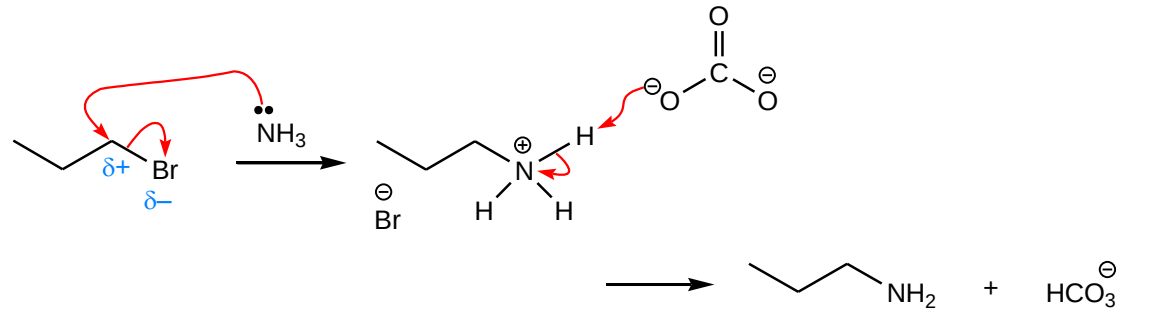
Draw out a balance chemical equation for the formation of propan-1-amine from 1-bromopropane and ammonia. Work out which reagent is the nucleophile and electrophile. [Remember, the "curly arrow" flows from the nucleophile (→) to the electrophile.] Nucleophiles contain non-bonded electrons (which sometimes can be depicted by negative charge) and electrophiles have low-lying empty orbitals (which often contain a leaving group).

Solution

1-Bromopropane is the electrophile, ammonia is the nucleophile, and bromide is the leaving group. The mechanism for this reaction is shown below. As potassium carbonate, K_2CO_3, is a weak base; deprotonation occurs post-nucleophilic substitution (S_N2) as the intermediate ammonium ion (pK_a = 9) is significantly more acidic than ammonia (pK_a = 33).



Answer



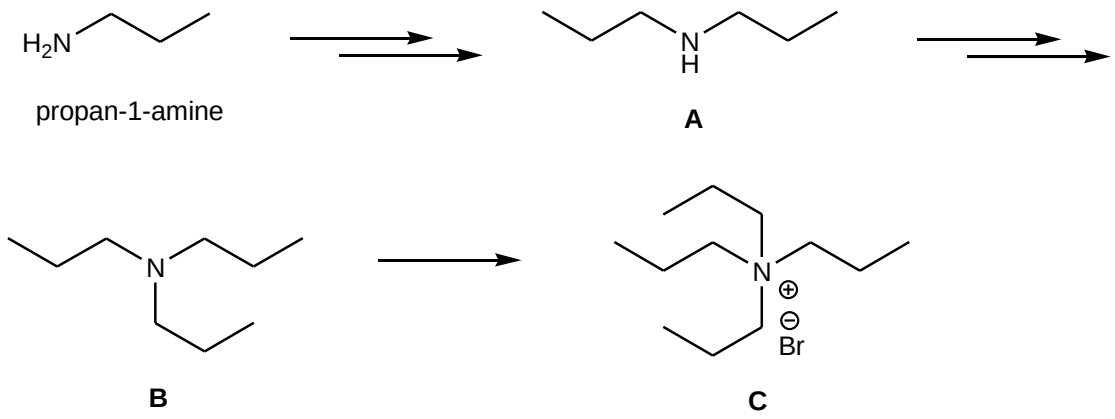
(ii) Suggest structures for the three compounds **A**, **B**, and **C**.

Strategy

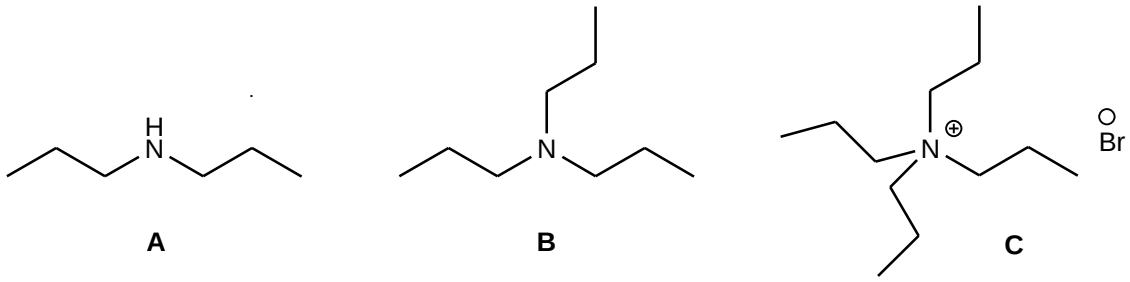
In order to form additional products, the initial product from the above reaction, propan-1-amine, must act as a competitive nucleophile. Alkylate this amine, using the same S_N2 mechanism outlined above, and so on.

Solution

Competitive alkylation of propan-1-amine with 1-bromopropane in the presence of potassium carbonate leads to formation of a secondary amine, **A**. This can be further alkylated to give the tertiary amine, **B**, and so on to give ammonium bromide, **C**.



Answer



(iii) Suggest an explanation as to why the reaction of 1-bromopropane with ammonia gives a mixture of products. (*Hint*: compare the nucleophilicity of ammonia and propan-1-amine.)

Strategy

Work out which amine, ammonia or propan-1-amine, is the more nucleophilic.

Solution

If ammonia was more nucleophilic than propan-1-amine, the formation of the product, propan-1-amine, would be faster than formation of the byproducts. Clearly, this cannot be the case as competitive formation of the secondary amine **A**, tertiary amine **B** and ammonium bromide **D** occurs. The primary amine, propan-1-amine, must be more nucleophilic than ammonia due to the electron donating (+I) propyl group increasing the availability of its non-bonded pair of electrons. The more *N*-alkyl substituents an amine contains, the more nucleophilic it becomes; therefore competitive alkylation of **A** and **B**

is faster than the parent amine, ammonia. The ammonium bromide is not a nucleophile as it has no non-bonded pair of electrons.

Answer

This is because ammonia and primary, secondary and tertiary amines all act as nucleophiles. As the number of electron donating alkyl groups bonded to nitrogen increases, the nucleophilicity of this amine also increases. For example, propan-1-amine (with one +I group) is slightly more nucleophilic than ammonia and so it reacts a little faster with 1-bromopropane than ammonia. This produces a secondary amine, which is also nucleophilic and so this amine can react with a further molecule of 1-bromopropane even more quickly.

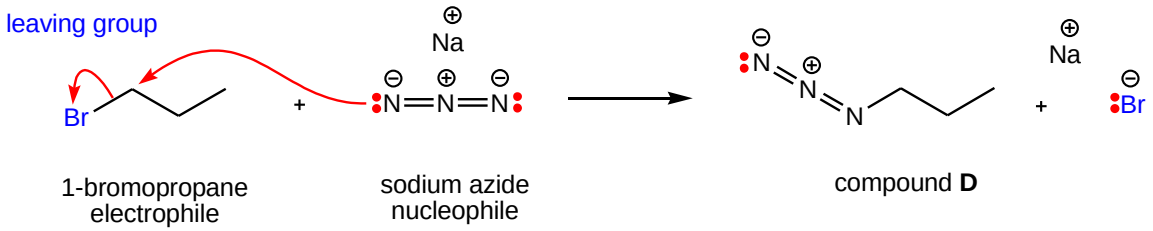
(b) In route B, propan-1-amine is prepared from 1-bromopropane in good yield by reaction with NaN_3 (in the solvent *N*,*N*-dimethylformamide) to give compound **D**, followed by reduction using $LiAlH_4$. Suggest a structure for compound **D** and propose a mechanism for its formation.

Strategy

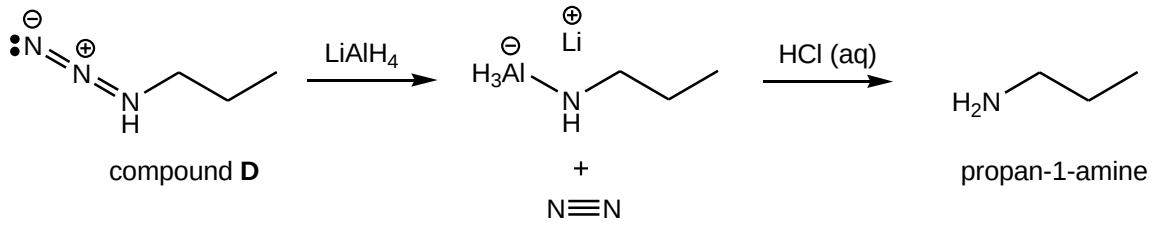
Draw out a balance chemical equation for the formation of compound **D** using 1-bromopropane and sodium azide (NaN_3). Work out which reagent is the nucleophile and electrophile. [Remember, the "curly arrow" flows from the nucleophile (→) to the electrophile.] Nucleophiles contain non-bonded electrons (which sometimes can be depicted by negative charge) and electrophiles have low-lying empty orbitals (which often contain a leaving group).

Solution

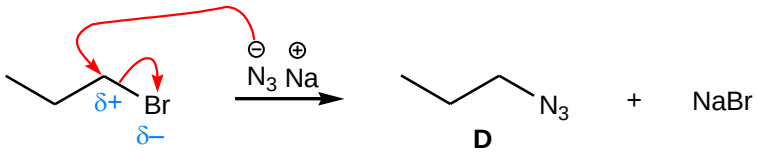
1-Bromopropane is the electrophile, azide is the nucleophile, and bromide is the leaving group. The mechanism for this reaction is shown below. Competitive alkylation of compound **D** with 1-bromopropane **does not** occur as the azide anion is an excellent nucleophile due to its high ground state energy and tri-charged structure.



$LiAlH_4$ reduction of compound **D** leads to propan-1-amine, as shown below.

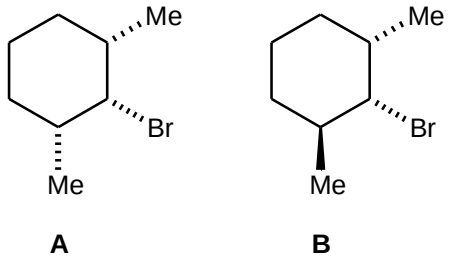


Answer



WE 20.4 Predicting elimination pathways (on p. 952 in *Chemistry*[3])

Diastereoisomer **A** reacts with sodium methoxide (in methanol) in an E2 reaction to form a racemic product. Under the same reaction conditions, diastereoisomer **B** reacts to form a single enantiomer of the product. Suggest an explanation for why **A** and **B** react differently.

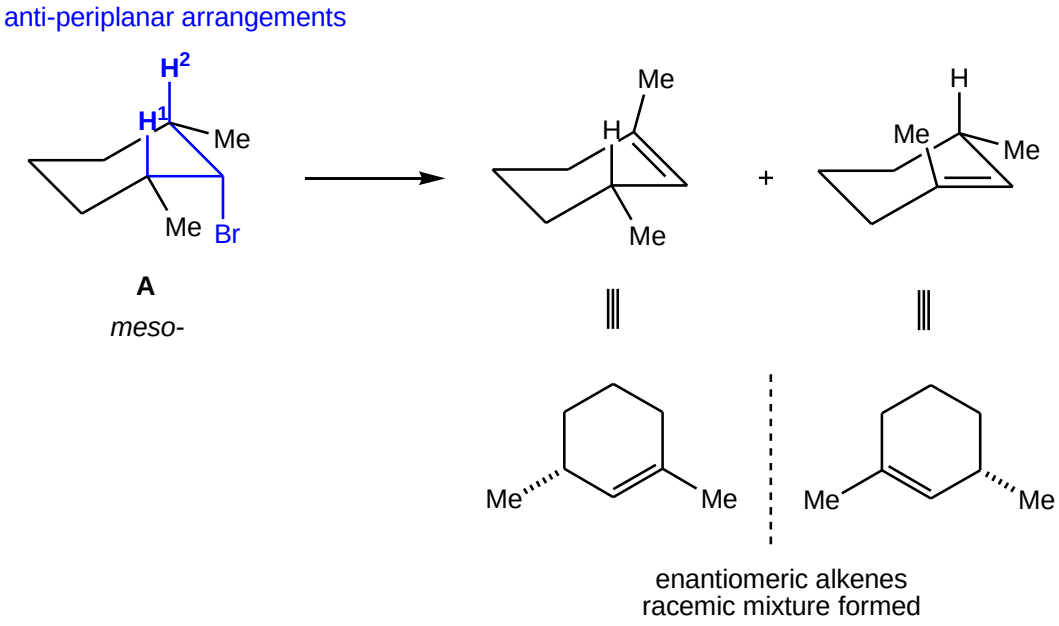


Strategy

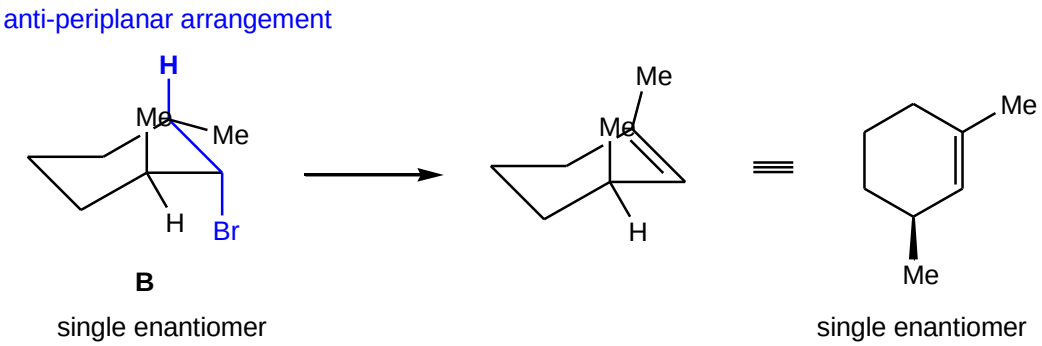
E2 elimination of HBr from aliphatic bromides to give alkenes occurs by anti-periplanar arrangement. Draw out both molecules, **A** and **B**, in a chair conformer, label any anti-periplanar β-hydrogen atoms, and use them to eliminate HBr. Work out the structure of these products (derived from E2 elimination), and consider their stereochemical relationship.

Solution

Diastereoisomer **A** is a *meso*-compound, and has two anti-periplanar β-hydrogen atom, H^1 and H^2. E2 elimination of H^1-Br and H^2-Br leads to two enantiomeric alkenes. As the starting material is *meso*-, and protons, H^1 and H^2, can be related to each other by a mirror plane; elimination of H^1-Br and H^2-Br is equally preferred leading to a racemic mixture of alkenes.

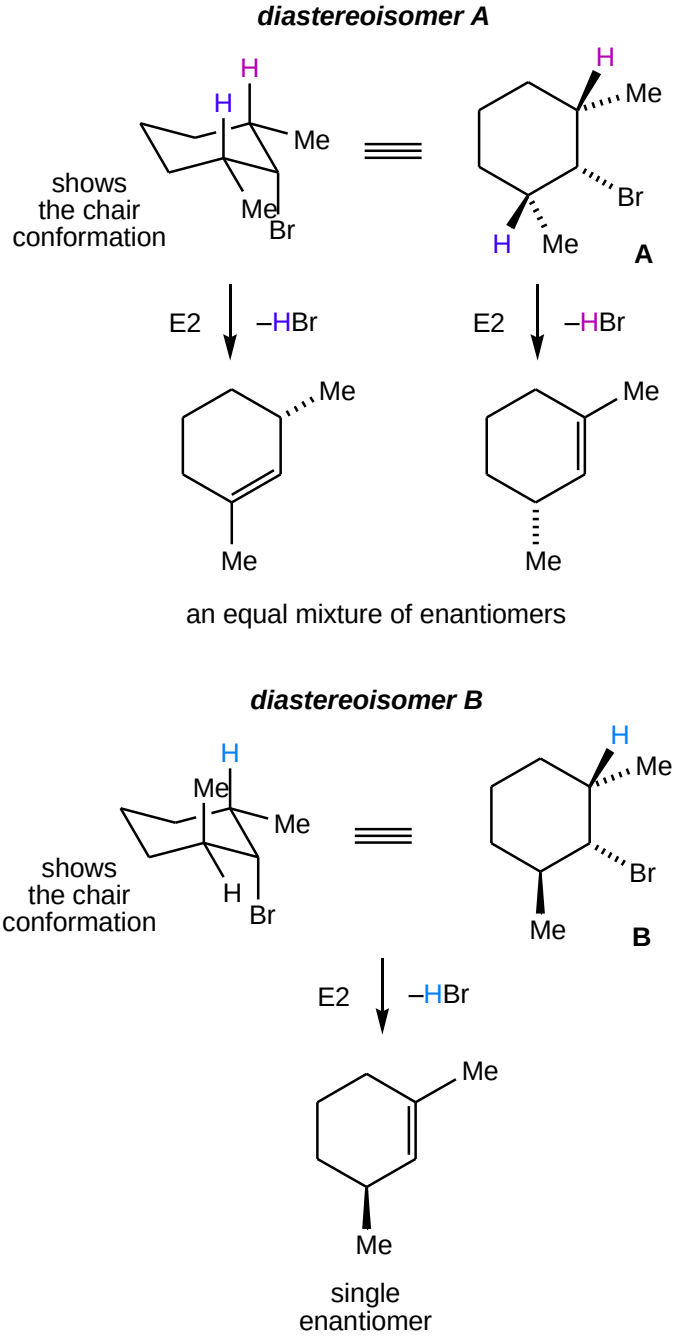


Diastereoisomer **B** is a single enantiomer, and contains one anti-periplanar β-hydrogen atom, H. E2 elimination of H-Br leads to a single enantiomeric alkene.



Answer

In the chair conformation of compound **A**, there are two β-hydrogen atoms that are antiperiplanar to the bromine atom and so the base, MeO^-, attacks equally well at both positions. In the chair conformation of compound **B**, there is only one β-hydrogen atom that is antiperiplanar to the bromine atom.



WE 20.5 Assigning mechanisms to the formation of products (on p. 955 in *Chemistry*^{3})

Suggest structures for the major substitution product and the major elimination product from reaction of (*R*)-2-bromobutane with ethoxide ion in acetonitrile.

Strategy

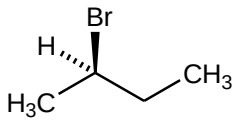
(a) Draw out the structure of (*R*)-2-bromobutane.

(b) For elimination, assign any β-hydrogen atoms. Primary and secondary bromides prefer E2 (anti-periplanar) elimination, and tertiary bromides prefer E1 elimination. Work out which mechanistic pathway is preferred. Draw the products from this elimination.

(c) For substitution: primary and secondary bromides prefer S_N2 substitution (with inversion of configuration), and tertiary bromides prefer S_N1 substitution. Work out which mechanistic pathway is preferred. Draw the products from this substitution.

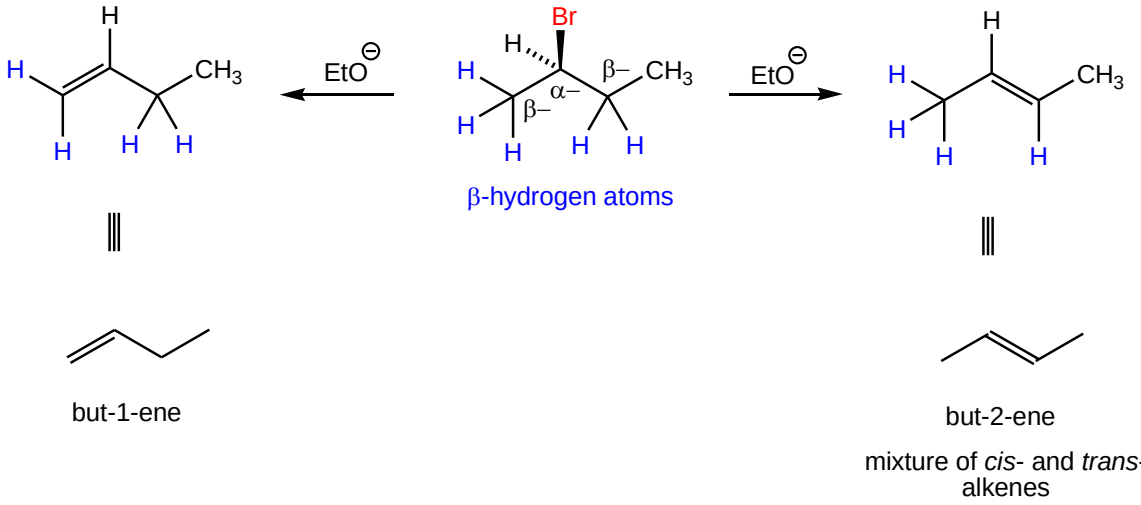
Solution

(a) The structure of (*R*)-2-bromobutane is given below.

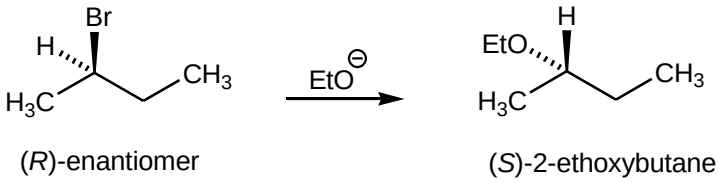


(*R*)-2-bromobutane

(b) (*R*)-2-bromobutane is a secondary bromide, and will prefer E2 elimination. As there are two sets of β-hydrogen atoms (from CH_3 and CH_2 groups); E2 elimination will lead to a mixture of but-1-ene and *cis*- and *trans*-but-2-enes. The major product will be *trans*-but-2-ene as E2 elimination to form the most stable alkene is preferred.

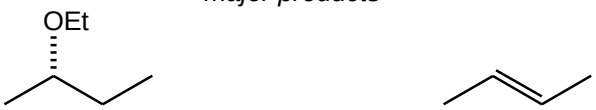


(c) (*R*)-2-bromobutane is a secondary bromide, and will prefer S_N2 substitution. This reaction will proceed with inversion of configuration; therefore only one product can be formed, namely (*S*)-2-ethoxybutane. However, under these reaction conditions, competitive E2 elimination of (*R*)-2-bromobutane is preferred.



Answer

major products



(*S*)-2-ethoxybutane

(from an S_N2 reaction)

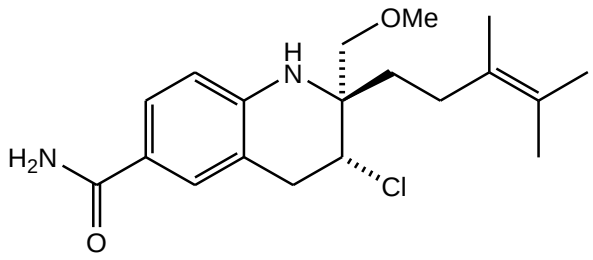
(*E*)-but-2-ene

(from an E2 reaction)

Answers to boxes

Box 20.1 Natural organohalogens (on p. 918 in *Chemistry*[3])

Benzastatin C is a member of a family of structurally similar compounds that are produced by a bacterium (*Streptomyces nitrosporeus*).



benzastatin C

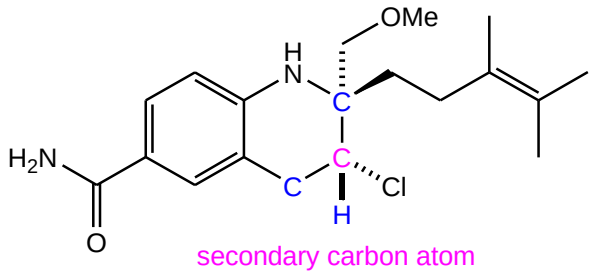
(a) Is the chlorine atom in benzastatin C bonded to a primary, secondary, or tertiary carbon atom?

Strategy

Draw out the structure of benzastatin C, and include all the principal atoms attached to the carbon bearing the chlorine atom. A tertiary carbon atom has three principal carbon atoms; a secondary carbon has two principal carbon atoms and a hydrogen atom; and a primary carbon atom has one principal carbon atom and two hydrogen atoms. From this information, it should be relatively straightforward to work out the substitution pattern of this carbon atom bonded to the chlorine atom.

Solution

This chlorine atom is attached to a secondary carbon atom, as it has two principal carbon atoms and a hydrogen atom attached to it.



secondary carbon atom

Answer

Secondary carbon atom

(b) What are the configurations [(*R*)- or (*S*)-] of the two chiral centres in benzastatin C? (For information on how to assign configurations; see section 18.4 on p.839 in *Chemistry*^{3})

Strategy

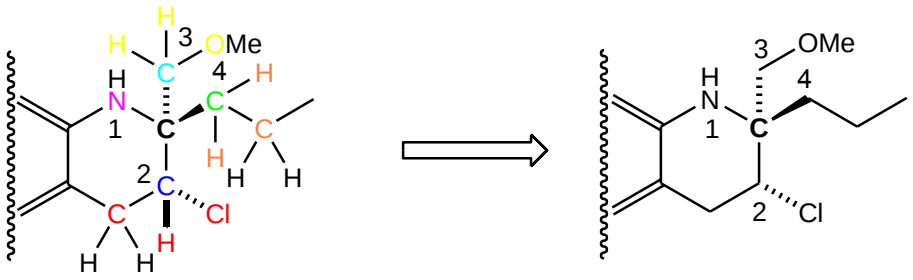
Work out where these two chiral centres are positioned in benzastatin C. Identify the two chiral centres in benzastatin C, and labelled them. Redraw this molecule in its condensed form, and work out the configurations at both chiral centres. It is easier to consider one centre at time. The (*R*/*S*)-stereochemistry is assigned using the Cahn-Ingold-Prelog rules (see p. 839 in *Chemistry*^{3}).

If required redrawing benzastatin C in its original arrangement, and label each chiral centre with their configuration. Check that your assignments are correct.

Solution

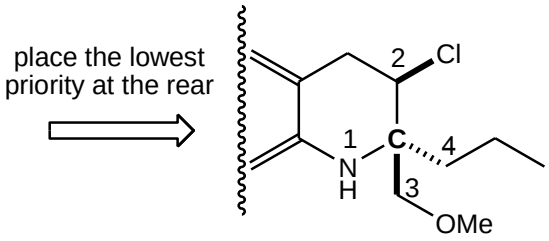
Chiral centres at carbons-1 and -2 have (*R*)-stereochemistry. A (*R*)-configuration is where the three highest priority groups (1, 2 and 3) on a particular conformation can be rotated clockwise (1→2→3), whilst the lowest priority group, 4, is at the rear of this conformer.

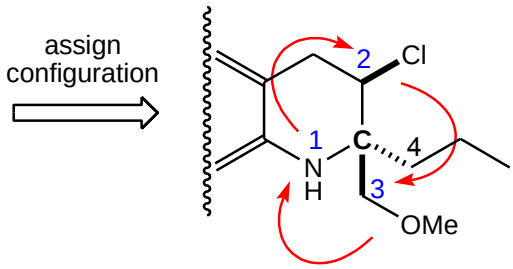
Group priorities at carbon-1



CIP group priorities
1 = N (-NHAr)
2 = C (-CClHCH$_2$)
3 = C (-CH$_2$OMe)
4 = C (-CH$_2$CH$_2$-)

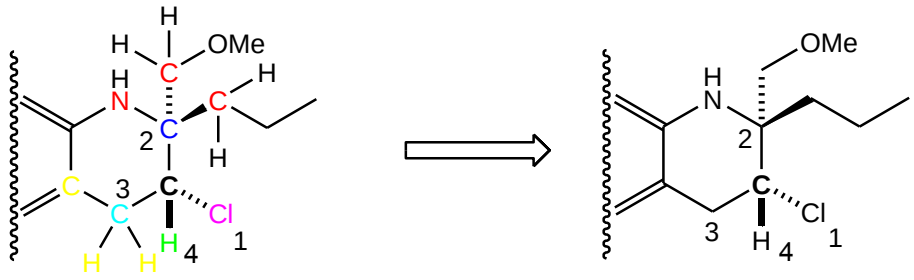
Group priorities at carbon-1





clockwise rotation = (*R*)-

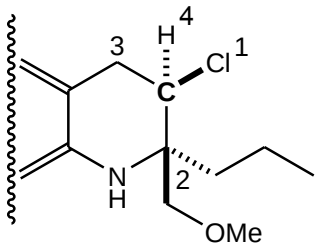
Group priorities at carbon-2



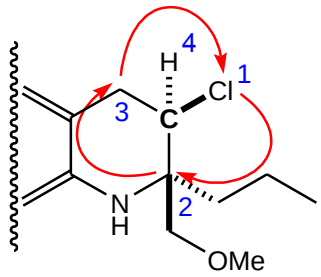
CIP group priorities
1 = Cl (-Cl)
2 = C (-CNH(CH_2-)(CH_2-)
3 = C (-CH_2C-)
4 = H (-H)

Group priorities at carbon-1

place the lowest priority at the rear

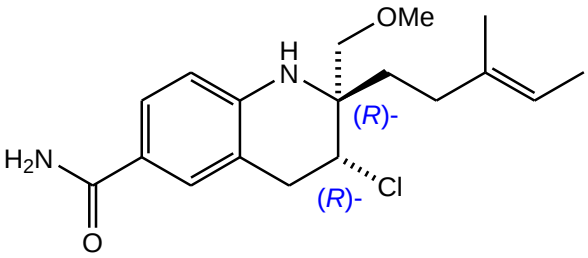


assign configuration



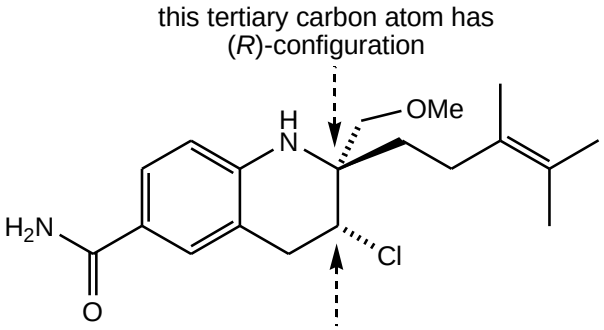
clockwise rotation = (*R*)-

Benzastatin C has two chiral centres with (*R*)-configurations.



benzastatin C

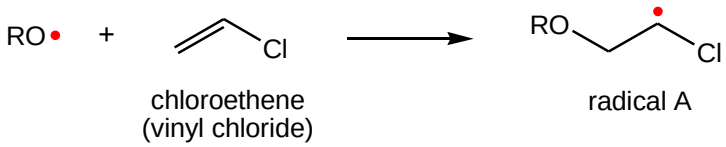
Answer



benzastatin C

Box 20.2 Teflon and radical polymerization (on p. 923 in *Chemistry*^{3})

The polymer PVC is prepared by heating chloroethene (vinyl chloride) with organic peroxide (ROOR). A key step in the mechanism is shown here.



chloroethene
(vinyl chloride)

radical A

(a) Suggest an explanation for the regioselective addition of RO▪ to the C=C bond (in your answer explain why the RO▪ radical adds to the less substituted carbon atom of the C=C bond).

Strategy

Draw out both intermediates from the addition of RO▪ to chloroethene. Look at the stability of these intermediate radicals, and deduce which one is more stable. As these radical processes are enthalpically controlled, the stability of these intermediates will influence the overall reaction pathway. [Remember, increasing the substitution of a radical increases its stability]

Solution

The secondary radical **A** is more stable than its isomeric primary radical **B** as it can conjugate with the chlorine atom (+M and –I) and has increased hyperconjugation from its alkyl substituent. This extra stability lowers the transition state energy leading to it, thus making this pathway more preferred.

radical A radical B

Answer

The RO▪ radical adds to the **less** hindered carbon atom of the C=C bond. [Remember, do not use the adverb "least" as this would refer to three or more carbon atoms].

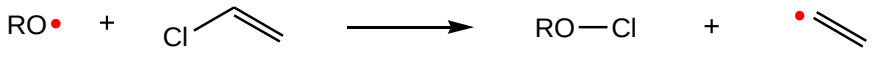
(b) Suggest an explanation for the chemoselectivity of the reaction (in your answer explain why the RO▪ radical adds to the C=C bond and not abstract a chlorine atom).

Strategy

Radical processes are enthalpically controlled; the relative stability of these intermediates will influence the overall reaction pathway.

Solution

Abstraction of the chlorine atom from chloroethene does not occur, as the resulting product RO-Cl is too unstable. This product is too reactive and would simply act as a chlorine radical donor, in the same way as molecular chlorine. For a radical reaction to efficiently proceed, the products must be more stable than the starting materials!



chloroethene
(vinyl chloride)

this process does not occur!

Addition of RO▪ to chloroethene leads to a more stable radical **A**. The enthalpic contribution of this reaction must be large enough to compensate for the negative entropy contribution in this addition reaction. Formation of a strong C-O bond at the expensive of a weak pi-bond (C=C) is the driving force of this reaction.

Answer

The RO▪ radical adds to the C=C bond and does not abstract a chlorine atom because this leads to the formation of the stronger bond – addition to the C=C bond forms the *stronger* C–O bond rather than the *weaker* O–Cl bond.

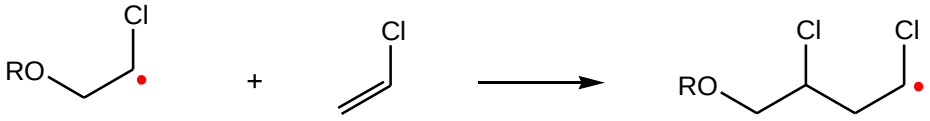
(c) Suggest a structure for the product formed from reaction of radical **A** with one molecule of chloroethene

Strategy

This reaction is a polymerisation process and these generally occur in a symmetrical manner. If the first radical addition occurs at the less hindered side of this alkene, chloroethane, subsequent additions in this polymerisation will more than likely occur in the same manner.

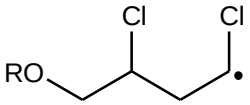
Solution

Addition of radical **A** to chloroethene will give the more stable and more substituted radical **C**.



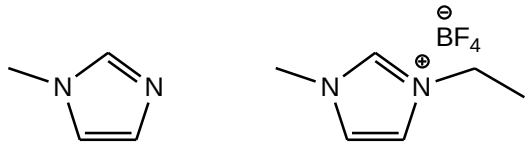
radical **A** | chloroethene (vinyl chloride) | radical **C**

Answer



Box 20.3 Designer solvents (on p. 932 in *Chemistry*^{3})

Suggest a two-step synthesis of the ionic liquid 1-ethyl-3-methylimidazolium tetrafluoroborate ([**emim**][BF_4]) starting from 1-methylimidazole.



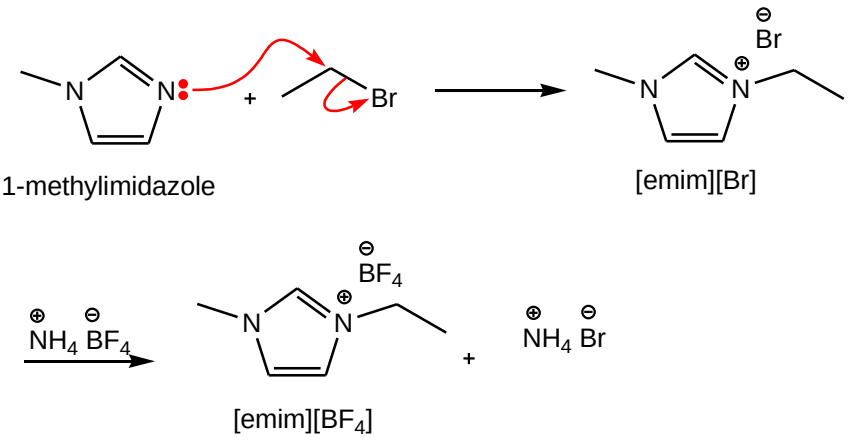
1-methylimidazole [emim][BF_4]

Strategy

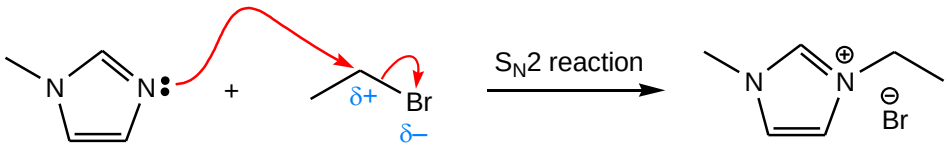
The strategy for this synthesis is similar to that outlined in Box 20.3 on p. 926 in *Chemistry*[3]. The first step must involve alkylation of 1-methylimidazole with an ethyl halide, and replacing the counter ion (the leaving group from the alkylation) with BF_4^-.

Solution

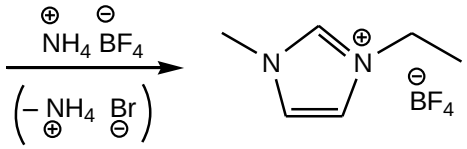
Alkylation of 1-methylimidazole with ethyl bromide gives the intermediate imidazolium bromide, [emim]Br, by a S_N2 mechanism. Anion exchange, using ammonium tetrafluoroborate [$NH_4^+BF_4^-$], gives the required 1-ethyl-3-methylimidazolium tetrafluoroborate, [emim]BF_4. As this reaction is generally performed in acetone, the insoluble byproduct, ammonium bromide ($NH_4^+Br^-$), can be removed.



Answer



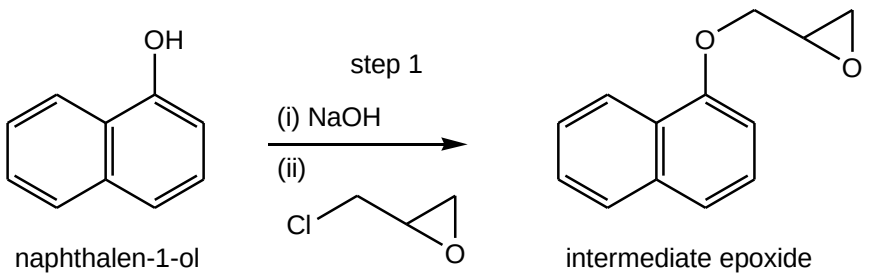
[**emim**][Br]



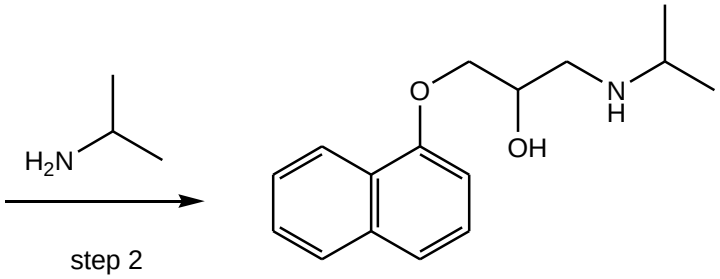
[**emim**][BF_4]

Box 20.4 Epoxy resins (on p. 940 in *Chemistry*[3])

Propanolol is a medicine that reduces blood pressure. It binds to and blocks β_1-receptors that control muscles in the heart, so it is called a beta-blocker. Propanolol is prepared in racemic form from naphthalen-1-ol as illustrated in the reaction scheme.



naphthalen-1-ol intermediate epoxide



propanolol

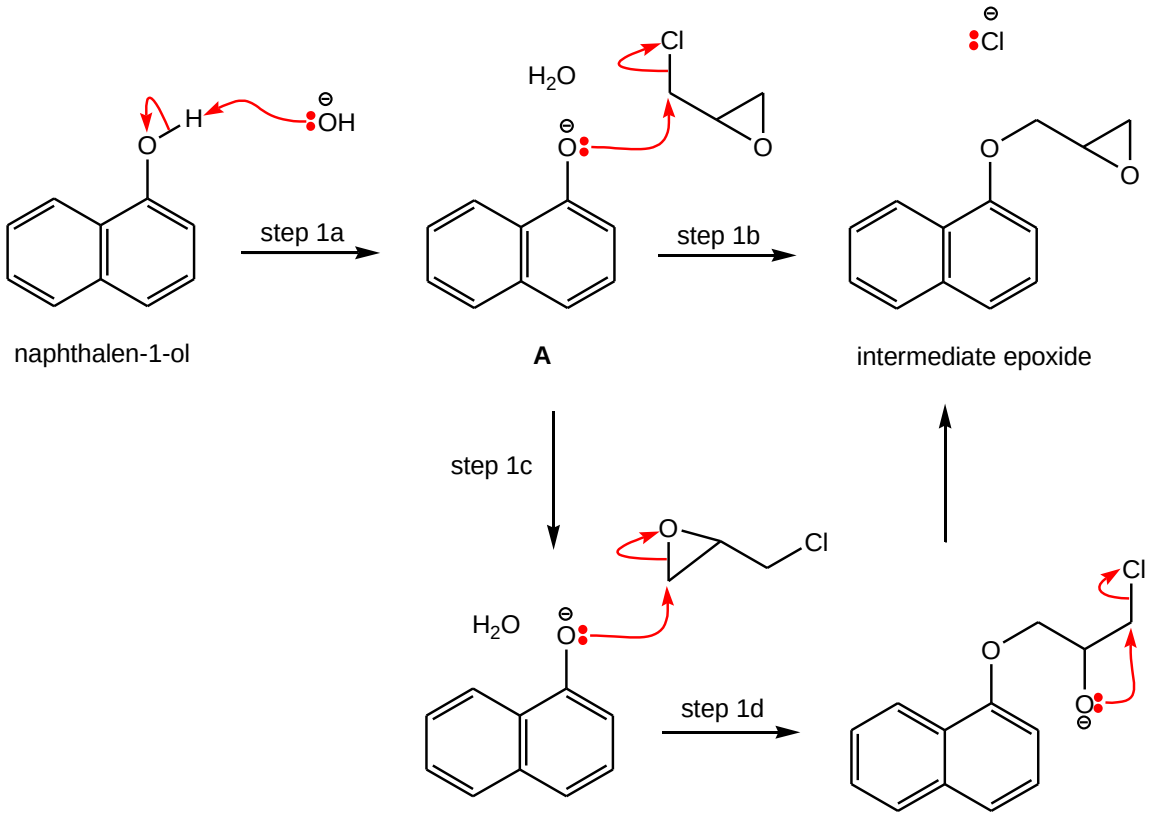
(a) Suggest reaction mechanisms for both steps in the above synthesis.

Strategy

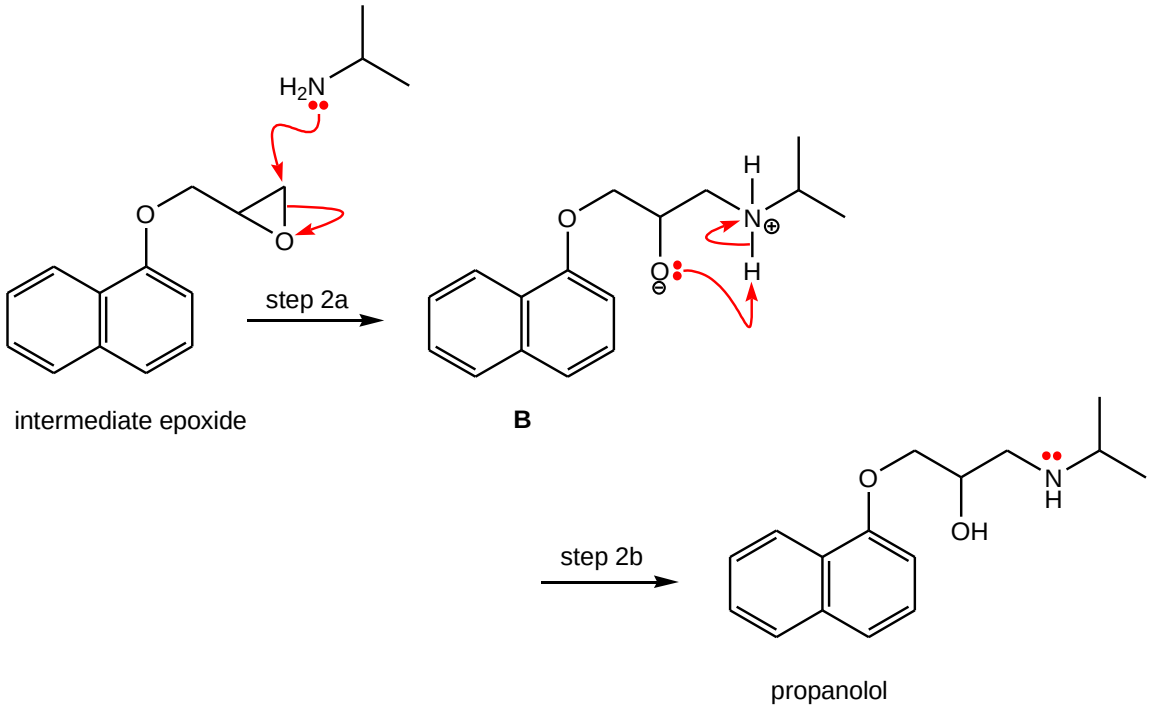
For each step (and sub-step), you will need to decide whether the reaction involves a electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making.

Solution

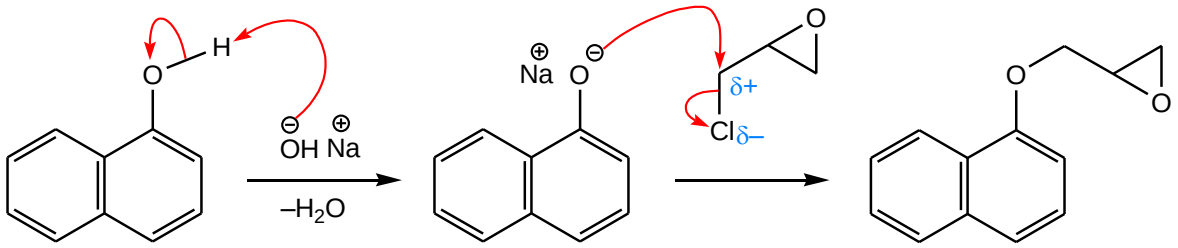
Step 1. There are two parts to this step. Step 1a involves an acid/base combination; deprotonation of naphthalen-1-ol (pK_a 9) with NaOH gives the resonance stabilised naphthoxide **A** and water (pK_a 16). Step 1b involves an electrophilic/nucleophilic combination; nucleophilic S_N2 substitution of the aliphatic chloride using naphthoxide **A** gives the required intermediate epoxide. The mechanisms involved in step 1 are shown below. Alternatively, this reaction could proceed by a S_N2'-type reaction involving nucleophilic addition to the epoxide (in step 1c), followed by elimination of chloride (in step 1d) with the newly formed intermediate alkoxide to give the required epoxide (as shown below).



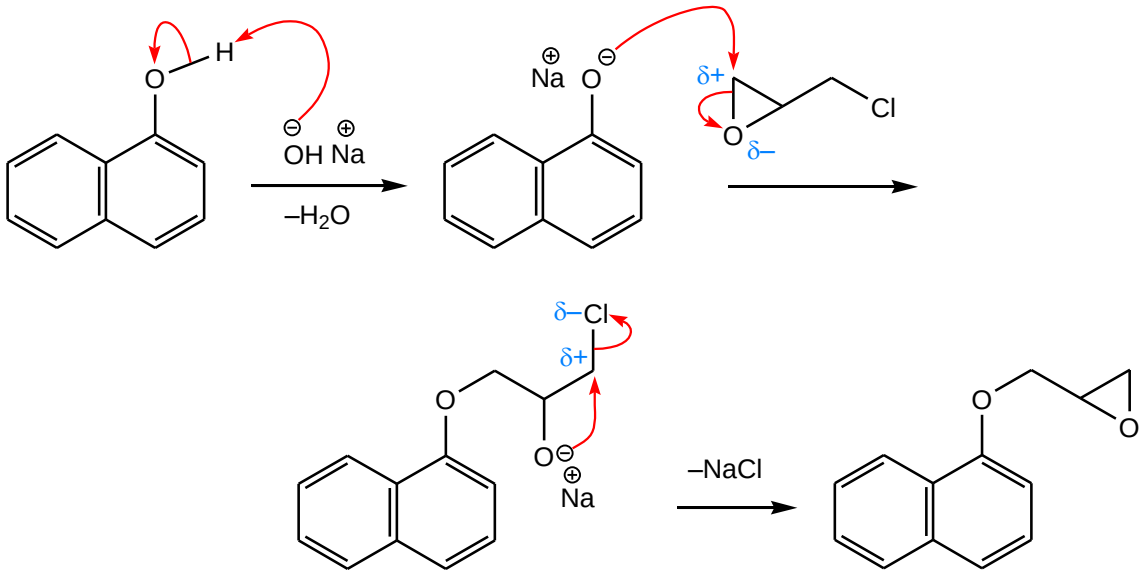
Step 2. There are two parts to this step. Step 2a involves an electrophilic/nucleophilic combination; nucleophilic addition of propan-2-amine to this intermediate epoxide gives the zwitterions **B**. This reaction can be thought of as an intramolecular S_N2-type reaction. Step 2b involves an acid/base combination; deprotonation of this intermediate ammonium ion (pK_a 9) with the internal alkoxide (pK_{Ha} 16), gives the required product, propanolol. The mechanisms involved in step 2 are shown below.



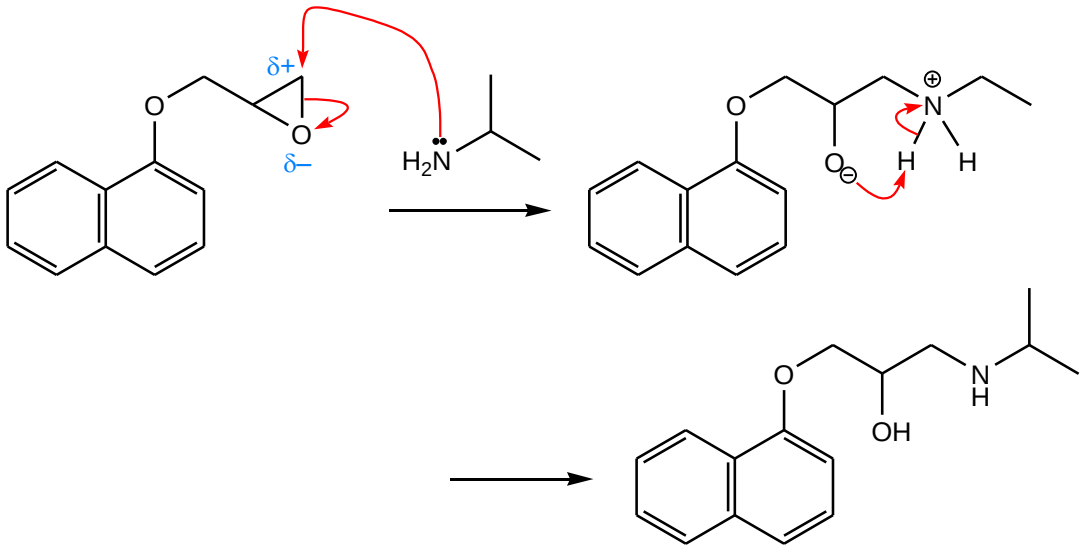
Answer



Alternatively,



Followed, by nucleophilic addition of the amine to the epoxide.



(b) Explain why the reaction of the intermediate epoxide with propan-2-amine is regioselective.

Strategy

The nucleophilic addition of propan-2-amine to the intermediate epoxide gives the zwitterions **B**. This reaction is an intermolecular S_N2-type reaction as the C-O bond (of the epoxide) is replaced with a new C-N bond (from the amine nucleophile). S_N2

substitution reactions are strongly influenced by the steric demanding nature of both the electrophile and nucleophile.

Solution

Nucleophilic S_N2 substitution of the epoxide intermediate with propan-2-amine occurs at its less hindered and less sterically demanding carbon atom to give the required product, propanolol.

Answer

Ring-opening of the epoxide is regioselective because the amine attacks the less substituted carbon atom in the ring – there is less steric hindrance at this carbon atom and therefore nucleophilic attack is favoured.

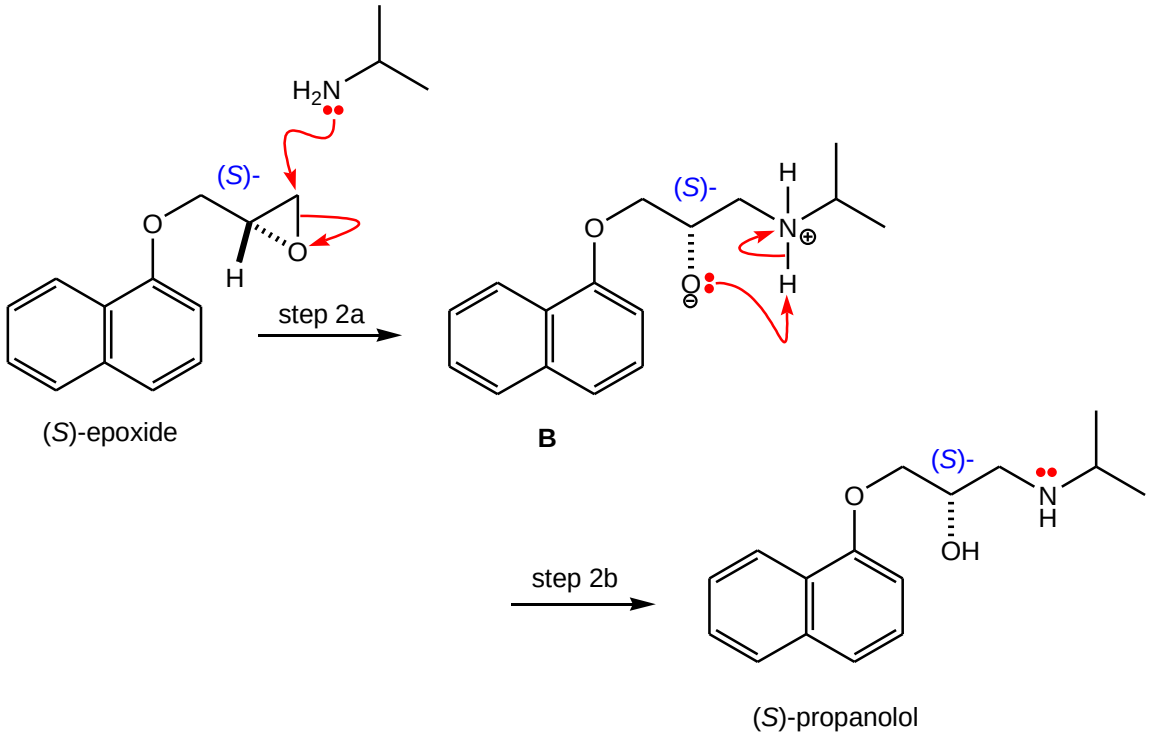
(c) Draw the structure of the product from reaction of the (*S*)-isomer of the intermediate epoxide with propan-2-amine.

Strategy

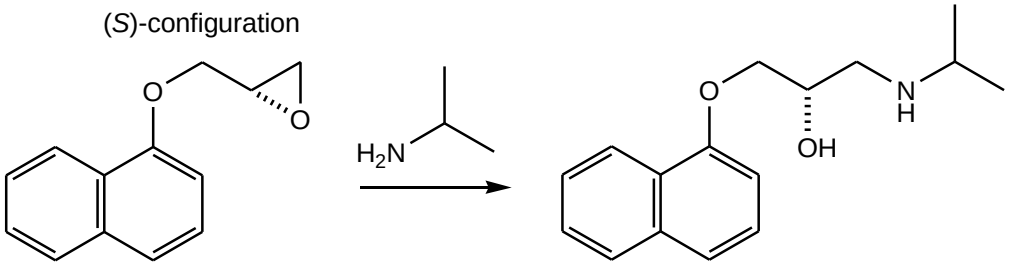
Draw out the (*S*)-isomer of this intermediate epoxide, and repeat the above intermolecular S_N2 reaction. If the reaction occurs at the chiral centre, then inversion of this chiral centre will occur; if it does not, the stereochemistry will remain unchanged (retention).

Solution

Nucleophilic addition of propan-2-amine to the (*S*)-enantiomer of this epoxide occurs at the non-chiral carbon atom; the product, (*S*)-propanolol, will have the same relative stereochemistry as the original (*S*)-epoxide. This reaction occurs with retention of configuration.

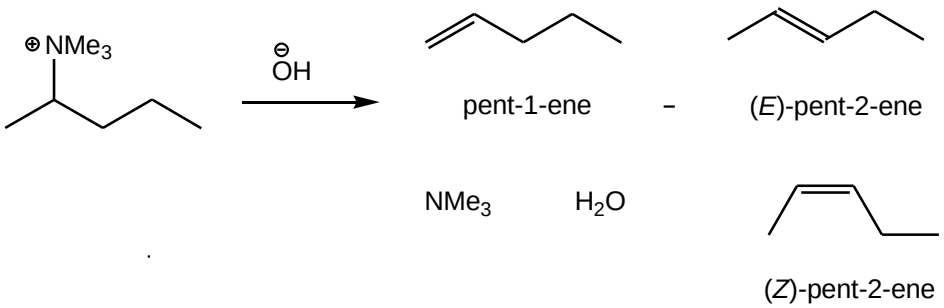


Answer



Box 20.5 Muscle relaxants (on p. 947 in *Chemistry*[3])

An example of a Hofmann elimination is shown here.



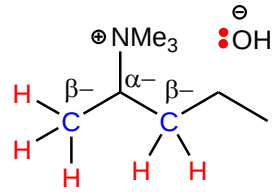
(a) Suggest reaction mechanisms for the formation of pent-1-ene and (*E*)-pent-2-ene.

Strategy

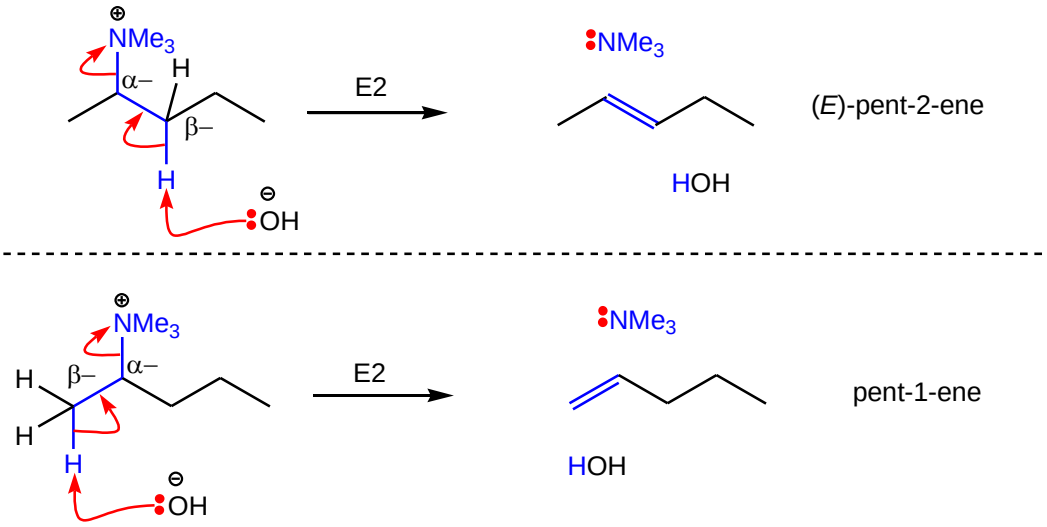
Elimination reactions involve acid/base combinations. Work out the substitution pattern of the starting material, and predict whether the reaction proceeds by an E1 or E2 elimination pathway. For E2 eliminations, start by drawing the first "curly arrow" from the non-bonded pair of electrons on the base, to the proton which is being removed (→), and so on.

Solution

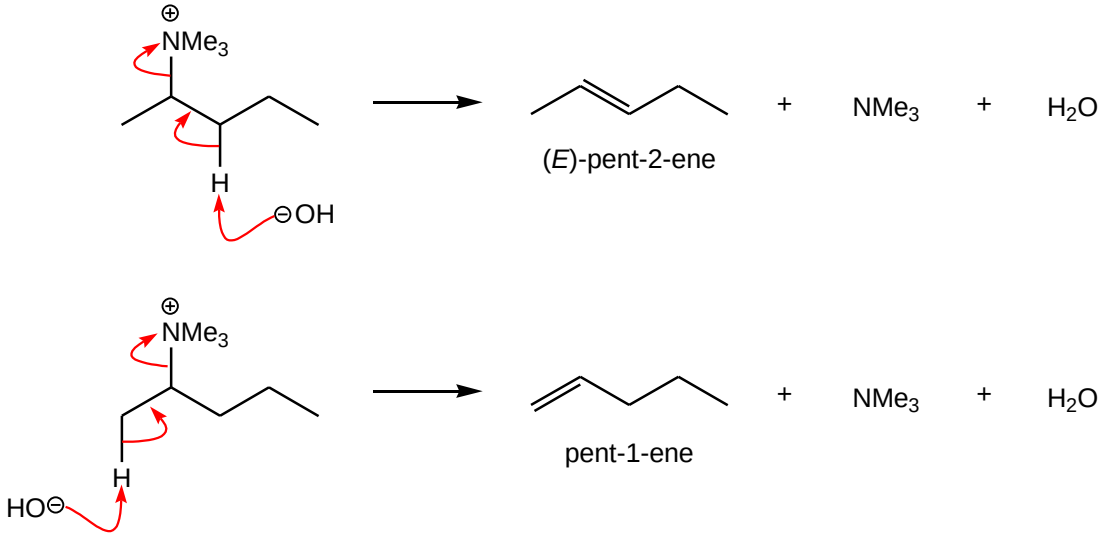
There are two β-carbon atoms in this ammonium ion; both contain hydrogen atoms which are capable of being removed by E2 elimination. Remove a proton from each β-carbon with concerted loss of trimethylamine (NMe_3) leads to the required isomeric alkenes, pent-1-ene and (*E*)-pent-2-ene.



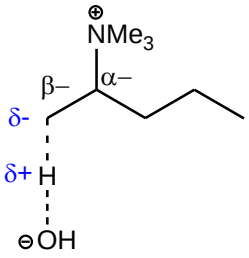
β-carbon atoms
β-hydrogen atoms



Answer



(b) The regioselective formation of the less substituted alkene is explained by the mechanism of the elimination. The C–H bond on the β-carbon starts to break before the C–N bond, so that the transition state has a carbanion-like structure. The transition state leading to pent-1-ene is shown here.



transition state leading to pent-1-ene

Draw the structure of the transition state that leads to (*E*)-pent-2-ene and suggest why the transition state that leads to pent-1-ene is lower in energy. (*Hint*: consider the relative stabilities of carbanions.)

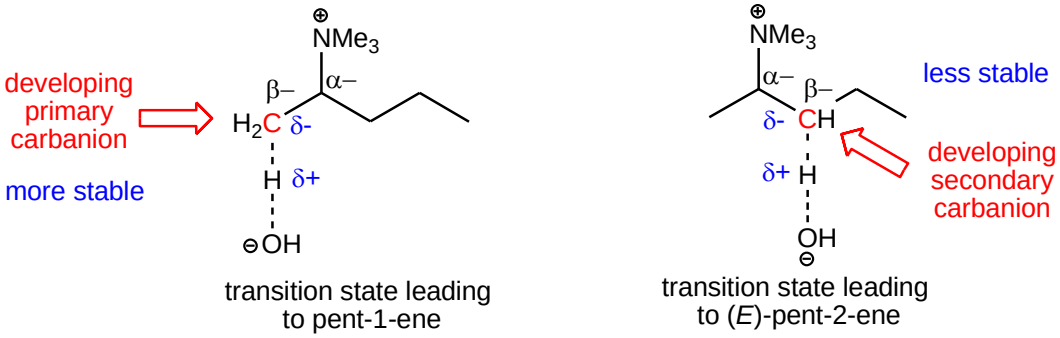
Strategy

The transition state for the formation of pent-1-ene is lower in energy than that of (*E*)-pent-2-ene. The major product will be the one which forms the faster; *i.e.*, the one with the lower activation barrier, pent-1-ene. The transition state leading to

(*E*)-pent-2-ene must be disfavoured relative to that of pent-1-ene. Simply re-draw the transition state for pent-1-ene, and ensure that the hydrogen atom on the other β-carbon is being removed.

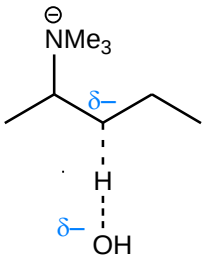
Solution

The transition state leading to (*E*)-pent-2-ene resembles a developing secondary carbanion. This carbanion is less stable (higher in energy) than the developing primary carbanion derived from E2 elimination of pent-1-ene. As the activation barrier leading to this transition state is less favoured, this reaction pathway will be less preferred and slower.



Answer

The transition state leading to the less substituted alkene resembles a primary carbanion whereas the transition state shown above resembles a secondary carbanion. As primary carbanions are more stable than secondary carbanions, the transition state leading to the less substituted alkene is of lower energy.



Answers to end of chapter questions (on p. 957 in *Chemistry*^{3})

1. Suggest a mechanism for the following reaction:

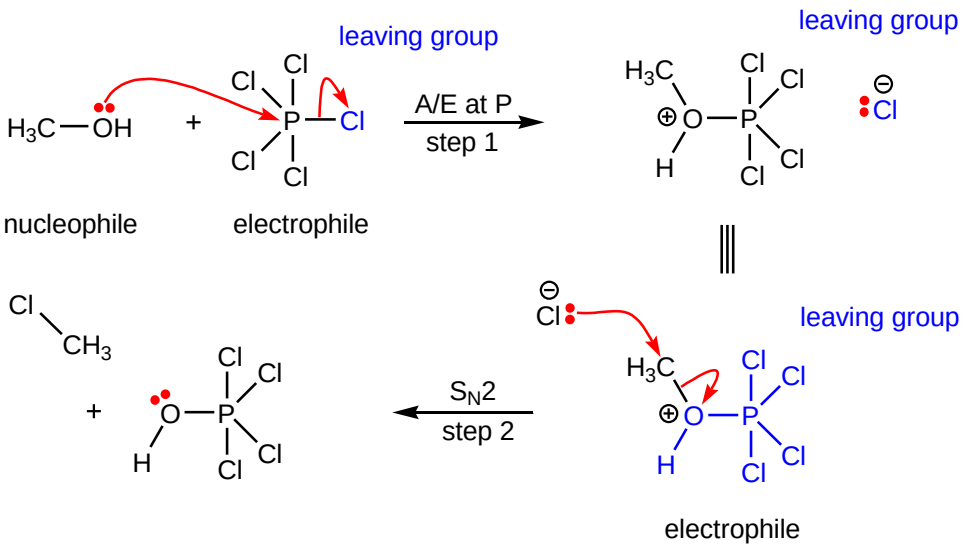
$$MeOH + PCl_5 \rightarrow MeCl + POCl_3 + HCl$$

Strategy

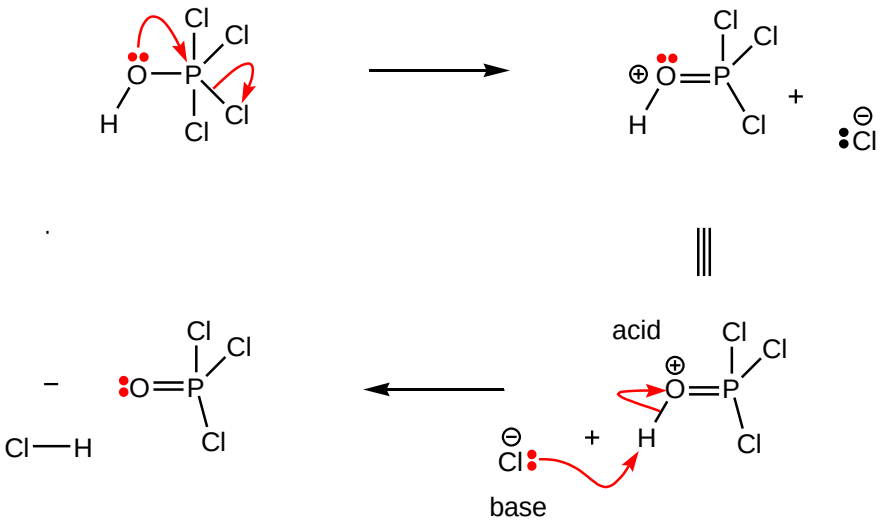
Work out which reagent is the nucleophile and electrophile. [Remember, the "curly arrow" flows from the nucleophile (→) to the electrophile.] Nucleophiles contain non-bonded electrons (which sometimes can be depicted by negative charge) and electrophiles have low-lying empty orbitals (which often contain a leaving group). In this particular case, this electrophile, PCl_5, contains good quality-leaving groups, chloride ions; highlight this substructure on the electrophile as this will aid you in drawing the mechanism of this reaction.

Solution

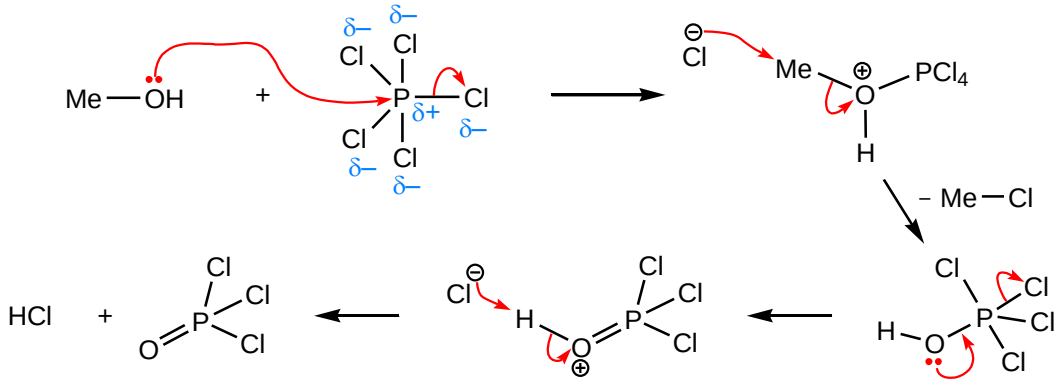
The driving force of this reaction is the formation of strong C-Cl and P=O bonds (in CH_3Cl and $POCl_3$, respectively) at the expense of two weaker P-Cl bonds (in PCl_5). Addition of methanol to PCl_5 leads to an intermediate oxonium chloride. S_N2 displacement of this oxonium ion using the chloride counter anion gives the required methyl chloride, CH_3Cl, and the byproduct PCl_4OH. This mechanism is shown below.



Fragmentation of this intermediate, PCl_4OH, to give the more stable $POCl_3$ and HCl is shown below.



Answer



2. The relative rates of solvolysis of 2-bromo-2-methylpropane in three solvents are shown below.

Solvent:	CH_3CO_2H	CH_3OH	H_2O
Relative rate of solvolysis:	1	4	150,000

Suggest an explanation for these observations.

Strategy

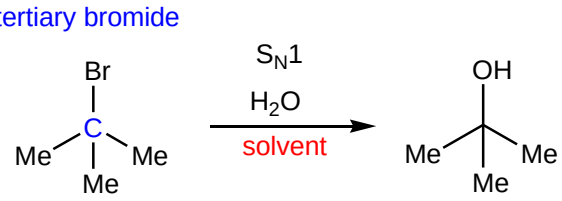
(a) Draw out the structure of 2-bromo-2-methylpropane, and work out whether it is a primary, secondary or tertiary bromide. From this, deduce whether the reaction mechanism is likely to be S_N1 or S_N2 substitution. If possible, draw the product from this reaction.

(b) Work out the relative polarity of these solvents.

(c) Account for the observations given in this question.

Solution

(a) 2-Bromo-2-methylpropane is a tertiary bromide. S_N1 substitution of 2-bromo-2-methylpropane using water as the nucleophile (*solvolysis*) leads to the corresponding tertiary alcohol, 2-hydroxy-2-methylpropane. [Remember, primary and secondary halides favour S_N2 substitution, and tertiary halides favour S_N1 substitution.]



2-bromo-2-methylpropane

(b) The most polar solvent is H_2O. The relative polarity of these solvents are H_2O > CH_3OH > CH_3CO_2H.

(c) As the polarity of these solvents increase, the rate of this S_N1 reaction increases. The rate-determining step involves the fragmentation of the C-Br bond, of 2-bromo-2-methylpropane, to give a tertiary carbocation and a bromide counter

anion. This polar carbocation is stabilised more efficiently using a more polar solvent. By stabilising this high-energy carbocation intermediate, will additionally lower the transition state energy leading to its formation, thus making this reaction faster.

Answer

In a solvolysis reaction, the solvent acts as a nucleophile in a substitution reaction. 2-Bromo-2-methylpropane is a tertiary halogenoalkane and undergoes S_N1 reactions with the three different solvents. The rate of the S_N1 reaction increases as the solvent is changed from CH_3CO_2H to CH_3OH to H_2O because the polarity of the solvent increases. Increasing the polarity of the solvent results in a significant increase in the rate of a S_N1 reaction because polar solvents can solvate (and stabilise) the intermediate carbocations that are produced in the first and rate determining step of this S_N1 reaction.

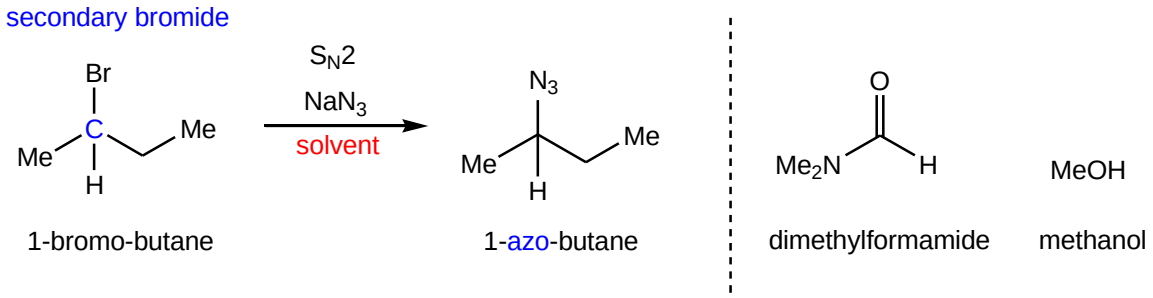
3. Explain why the relative rate of reaction of 1-bromobutane with azide ion (N_3^-) increases from 1 to 2800 on changing the solvent from methanol to dimethylformamide.

Strategy

(a) Draw out the structure of 1-bromobutane, and work out whether it is a primary, secondary or tertiary bromide. From this, deduce whether the reaction mechanism is likely to be S_N1 or S_N2 substitution. If possible, draw the product from this reaction.
(b) Work out the relative polarity of these solvents.
(c) Account for the observation given in this question.

Solution

(a) 1-Bromobutane is a primary bromide. S_N2 substitution of 1-bromobutane using sodium azide as the nucleophile leads to the corresponding product, 1-azobutane. [Remember, primary and secondary halides favour S_N2 substitution, and tertiary halides favour S_N1 substitution.]



(b) The more polar solvent is methanol (MeOH). However, this solvent is protic (which is capable of acting as a hydrogen bonding donor), whereas, dimethylformamide (DMF) is aprotic. Both solvents are polar solvents.

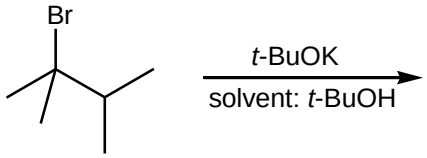
(c) This S_N2 displacement is faster in an aprotic polar solvent (DMF) than a protic polar solvent (MeOH). The decrease in rate for this protic solvent (MeOH) is due to the increased solvation (and thus stabilisation) of the azide (N_3^-) nucleophile, which consequently lowers its nucleophilicity. [Remember, high-energy nucleophiles are more nucleophilic than low-energy nucleophiles.]

Answer

1-Bromobutane is a primary halogenoalkane and undergoes S_N2 reactions with nucleophiles such as N_3^-. Changing from methanol (a polar protic solvent) to dimethylformamide (a polar aprotic solvent) increases the rate of a S_N2 reaction because polar aprotic solvents do not solvate negatively charged nucleophiles. The N_3^- ion is highly reactive in dimethylformamide and is free to approach and react with 1-bromobutane. In contrast, methanol solvates the N_3^- ion (by forming hydrogen bonds) and this reduces its reactivity.

4. Suggest structures for the major products formed in the following reactions and state whether these are formed by S_N1, S_N2, E1, or E2 mechanisms. Explain your reasoning.

(a)



Strategy

(a) Work out whether this aliphatic bromide it is a primary, secondary or tertiary. From this, deduce whether the reaction mechanism is S_N1/E1 or S_N2/E2.

(b) Work out if the reagent is a nucleophile or a base. [Remember, high-energy species such as alkoxides prefer to act as bases, and low-energy species like carboxylates prefer to act as nucleophiles.]

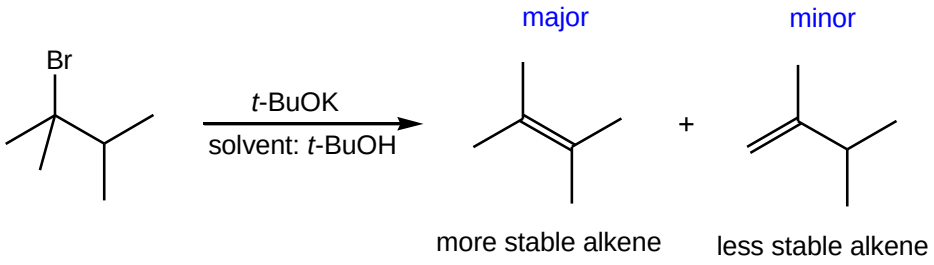
(c) Predict the likely reaction pathway, and draw the product derived from this reaction.

Solution

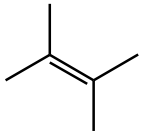
(a) This aliphatic bromide is a tertiary bromide. The preferred reaction pathways will be S_N1/E1. [Remember, primary and secondary halides favour S_N2 substitution/E2 elimination, and tertiary halides favour S_N1 substitution/E1 elimination.]

(b) Potassium *tert*-butoxide (*t*-BuOK) is a good quality base, as it is a high-energy charged species.

(c) The likely outcome of this reaction is E1 elimination. There are two potential products. The more substituted (and more stable) alkene is preferred.

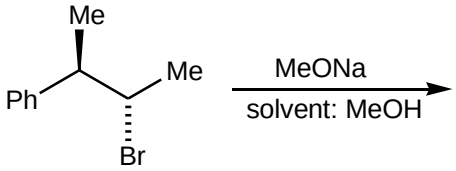


Answer



the tertiary bromoalkane undergoes an E1 reaction (*tert*-BuO^- is a strong, bulky base that removes a proton from the intermediate carbocation to form the more stable alkene)

(b)



Strategy

(a) Work out whether this aliphatic bromide it is a primary, secondary or tertiary. From this, deduce whether the reaction mechanism is S_N1/E1 or S_N2/E2.

(b) Work out if the reagent is a nucleophile or a base. [Remember, high-energy species such as alkoxides prefer to act as bases, and low-energy species like carboxylates prefer to act as nucleophiles.]

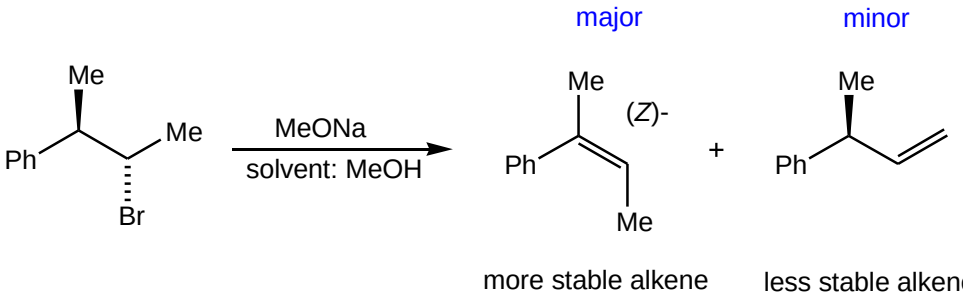
(c) Predict the likely reaction pathway, and draw the product derived from this reaction.

Solution

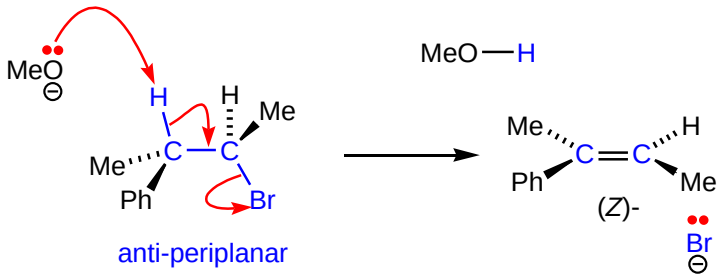
(a) This aliphatic bromide is a secondary bromide. The preferred reaction pathways will be S_N2/E2. [Remember, primary and secondary halides favour S_N2 substitution/E2 elimination, and tertiary halides favour S_N1 substitution/E1 elimination.]

(b) Sodium methoxide (MeONa) is a good quality base, as it is a high-energy charged species.

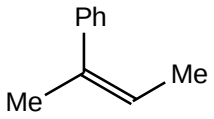
(c) The likely outcome of this reaction is E2 elimination. A special feature of this mechanism is its anti-periplanar elimination pathway. There are two potential products. The more substituted and conjugated (and more stable) (*Z*)-alkene is preferred as the transition state leading to this product will be lower in energy.



Anti-periplanar E2 elimination of this aliphatic bromide leads exclusively to the (Z)-alkene as shown below. Formation of its stereoisomeric (*E*)-alkene does not occur, as this would need to proceed via a disfavoured *syn*-periplanar elimination pathway.

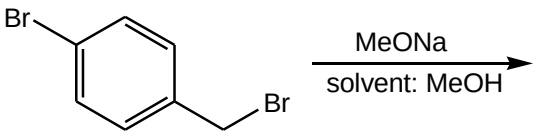


Answer



the secondary bromoalkane undergoes an E2 reaction (MeO^- is a strong base; elimination via an antiperiplanar transition state produces one isomer)

(c)



Strategy

(a) Work out whether this aliphatic bromide it is a primary, secondary or tertiary. From this, deduce whether the reaction mechanism is S_N1/E1 or S_N2/E2.

(b) Work out if the reagent is a nucleophile or a base. [Remember, high-energy species such as alkoxides prefer to act as bases, and low-energy species like carboxylates prefer to act as nucleophiles.]

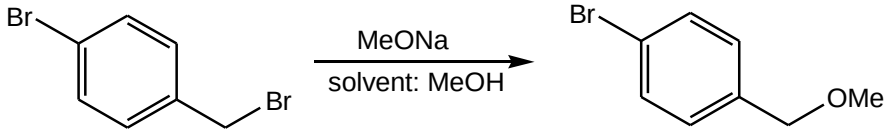
(c) Predict the likely reaction pathway, and draw the product derived from this reaction.

Solution

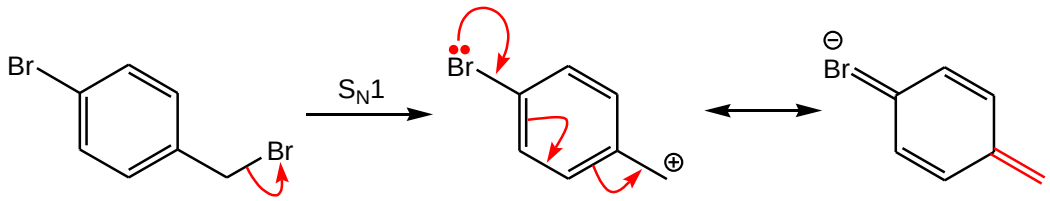
(a) This aliphatic bromide is a primary **benzylic** bromide. The preferred reaction pathways will be S_N2/E2. [Remember, primary and secondary halides favour S_N2 substitution/E2 elimination, and tertiary halides favour S_N1 substitution/E1 elimination.]

(b) Sodium methoxide (MeONa) is a good quality base, as it is a high-energy charged species.

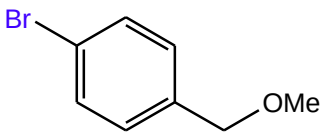
(c) The likely outcome of this reaction **would be** E2 elimination; however, this benzylic bromide has **no** β-hydrogen atoms for elimination! The only reaction pathway available is S_N2 substitution. The product from this reaction is shown below.



This product can **also** be formed by an S_N1 reaction, as the its intermediate carbocation (shown below) can be stabilised by conjugation involving its 4-bromophenyl ring. Either answer is correct just as long as it is justified.



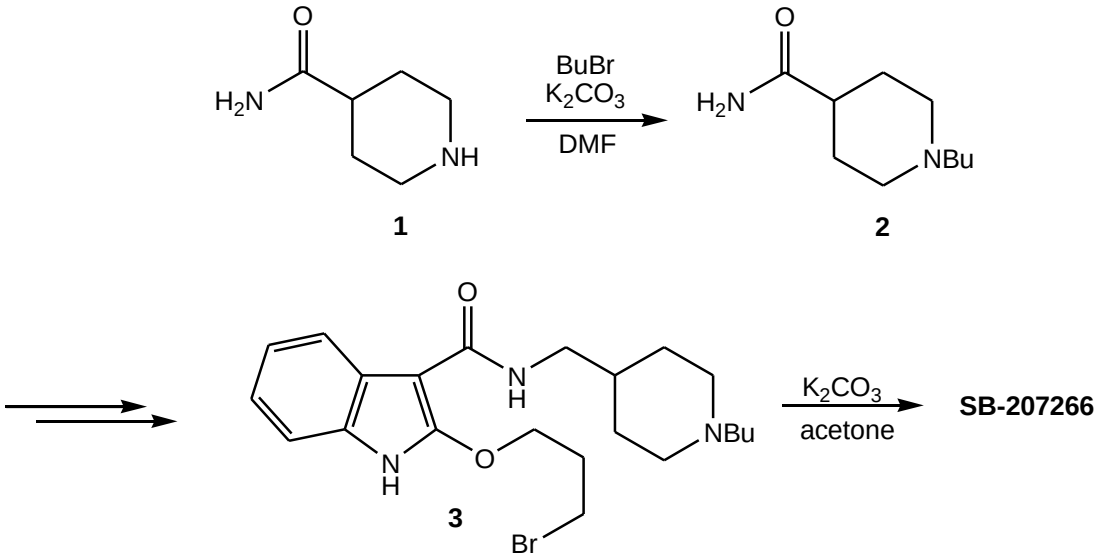
Answer



Aryl bromides cannot undergo S_N1 or S_N2 reactions

the primary benzylic bromide undergoes an S_N1 reaction (MeOH is a weak nucleophile; the intermediate carbocation is stabilised by resonance and by solvation, because MeOH is a polar protic solvent)

5. Compound SB-207266 is a medicine developed for the treatment of irritable bowel syndrome. An outline synthesis is shown below.



(a) Using the order of acid strength shown below, propose a mechanism for the formation of compound **2** from compound **1**.

order of acid strength in DMF

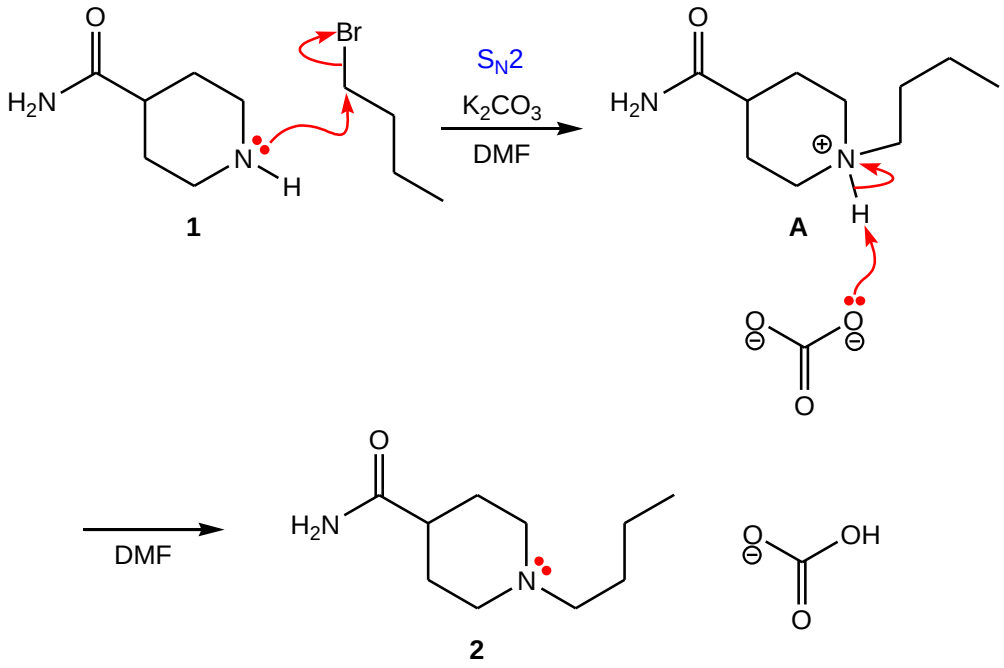
$\overset{\oplus}{R_3NH}$ (strongest acid) > $H\overset{\ominus}{C}O_3$ > RNHCOR > R_2NH (weakest acid)

Strategy

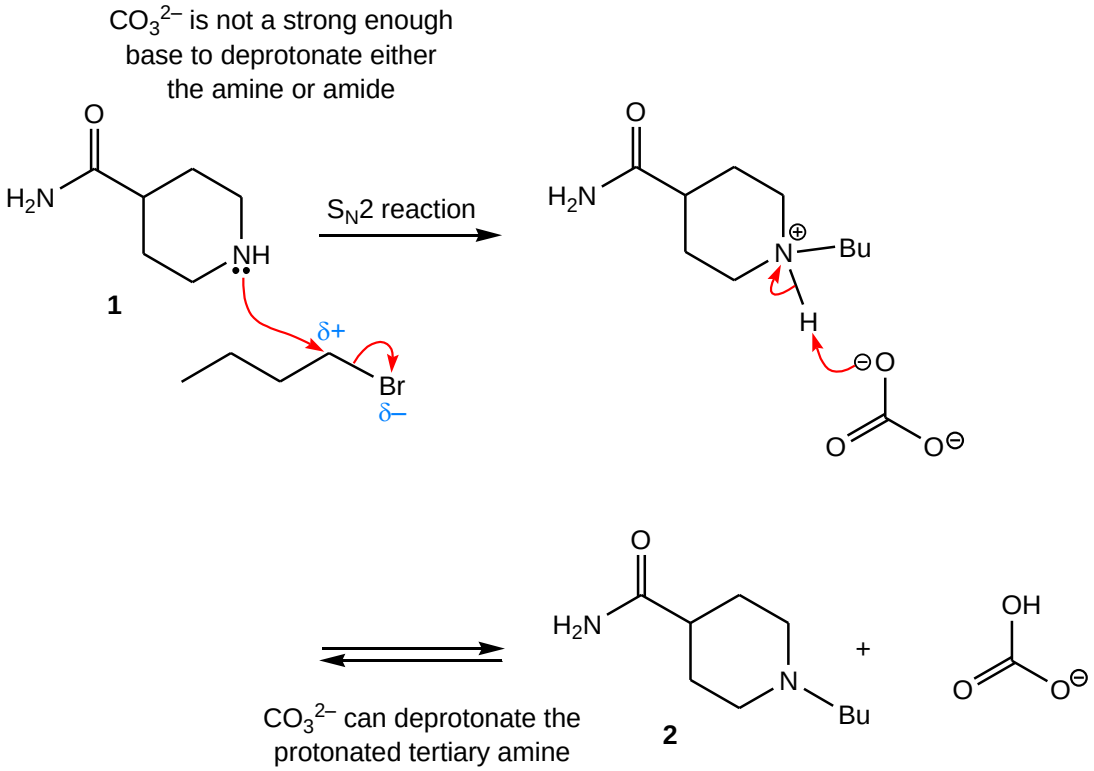
This reaction is a nucleophilic substitution, where the N-H group of compound **1** is being replaced with the N-Bu in compound **2**. There are two reagents; the electrophile, BuBr, and the base, potassium carbonate (K_2CO_3). [The solvent for this reaction is DMF.]
Using the above acidity data, work out if this reaction proceeds by initial deprotonation (followed by alkylation), or by alkylation (followed by deprotonation).

Solution

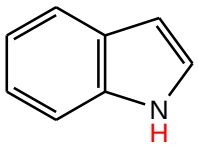
Potassium carbonate, K_2CO_3, is a weak base and therefore deprotonation of a very weak acid, such as the secondary amine (NH) in compound **1**, is negligible. Whereas, deprotonation of the more acidic ammonium ion (NH) (formed by initial alkylation of compound **1** with BuBr) is favourable. This reaction proceeds in two steps; alkylation of compound **1** (to give the ammonium ion **A**), followed by deprotonation (of this ammonium ion) to give the product, compound **2**. The mechanism of this reaction is shown below.



Answer



(b) Although the CO_3^{2-} ion is not a sufficiently strong base to deprotonate the NH group in indole itself (see below), it is able to deprotonate the NH group in the indole ring of compound **3**. Suggest an explanation for the different acidities of these two indole rings.



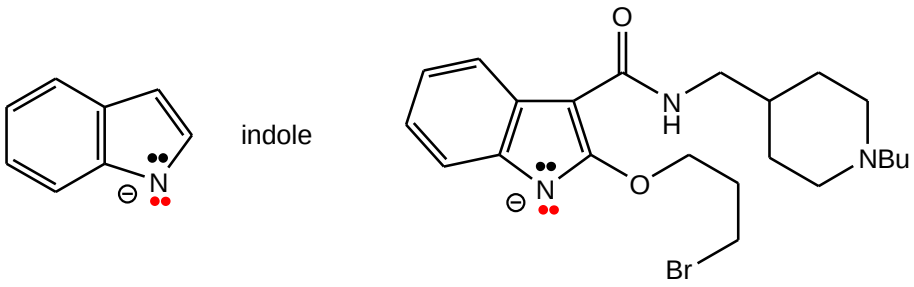
indole

Strategy

From the information given above, the NH bond of indole in compound **3** is more acidic than that of indole itself. Draw out the structure of both conjugate bases and work out where this extra stability (for the conjugate base of compound **3**) may come from.

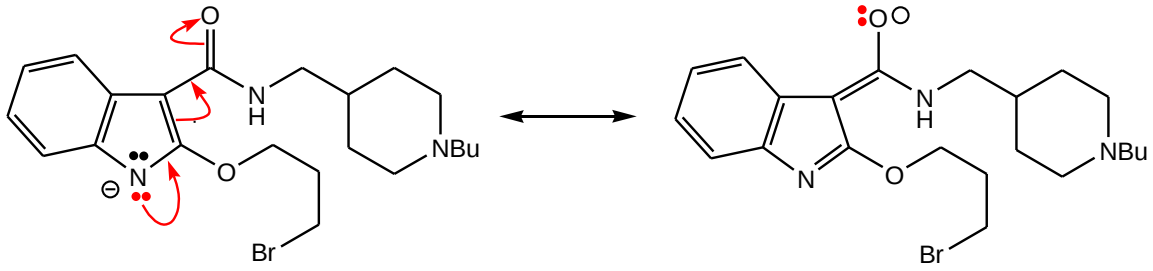
Solution

The structures of these conjugate bases are shown below.



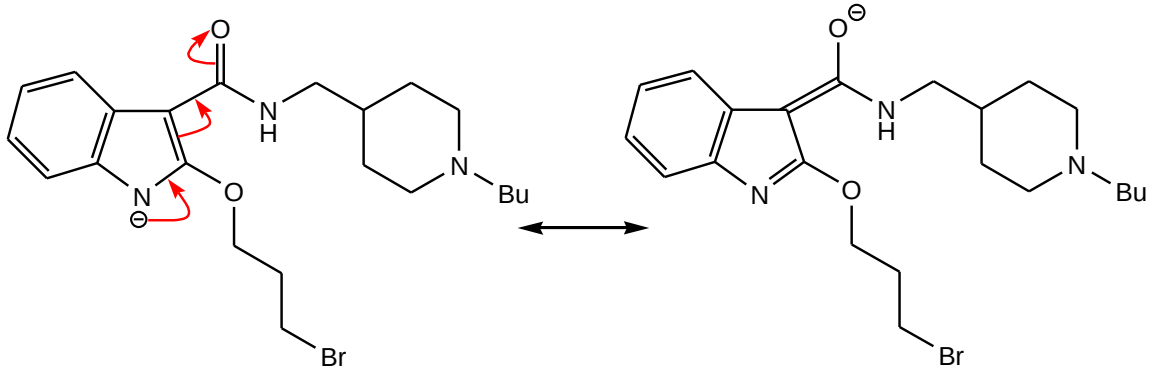
conjugate base of indole conjugate base of **3**

The conjugate base of compound **3** is more stable than the conjugate base of indole because of additional conjugation between the amide anion and its adjacent carbonyl (C=O) group, as shown below.



conjugate base of **3**

Answer



the conjugate base of **3** is stabilised by resonance – the negative charge can be moved on to the electron withdrawing amide group

(c) The formation of SB-207266 from compound **3** involves deprotonation of the indole ring to form an anion, which acts as a nucleophile in a nucleophilic

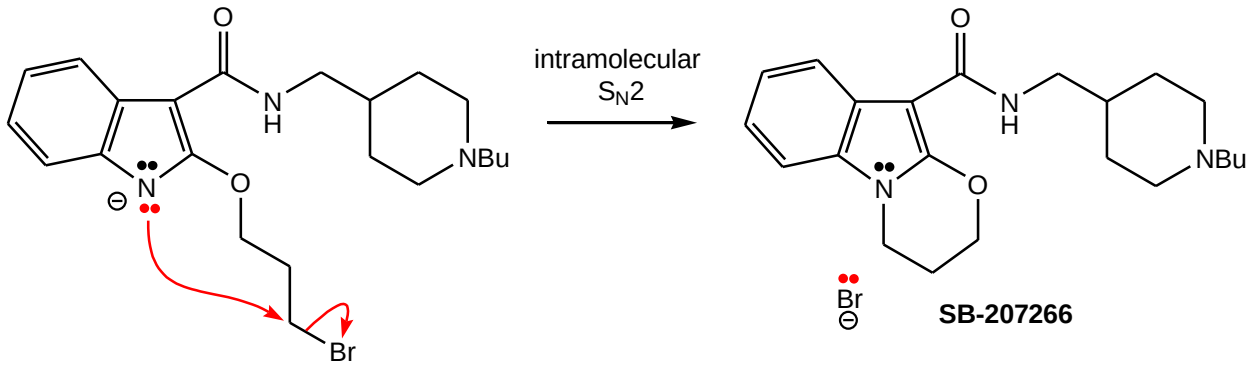
substitution reaction. Suggest a structure for SB-207266 and give a mechanism for its formation. Does the substitution involve an S_N1 or S_N2 mechanism?

Strategy

Draw out the conjugate base of compound **3**. The mechanism for this deprotonation step is similar to that shown above (in part a). From this question, we are told that this reaction proceeds *via* a nucleophilic substitution, and the nucleophile is the indole anion. From the structure of this conjugate base, work out the position of the potential **intramolecular** electrophile.

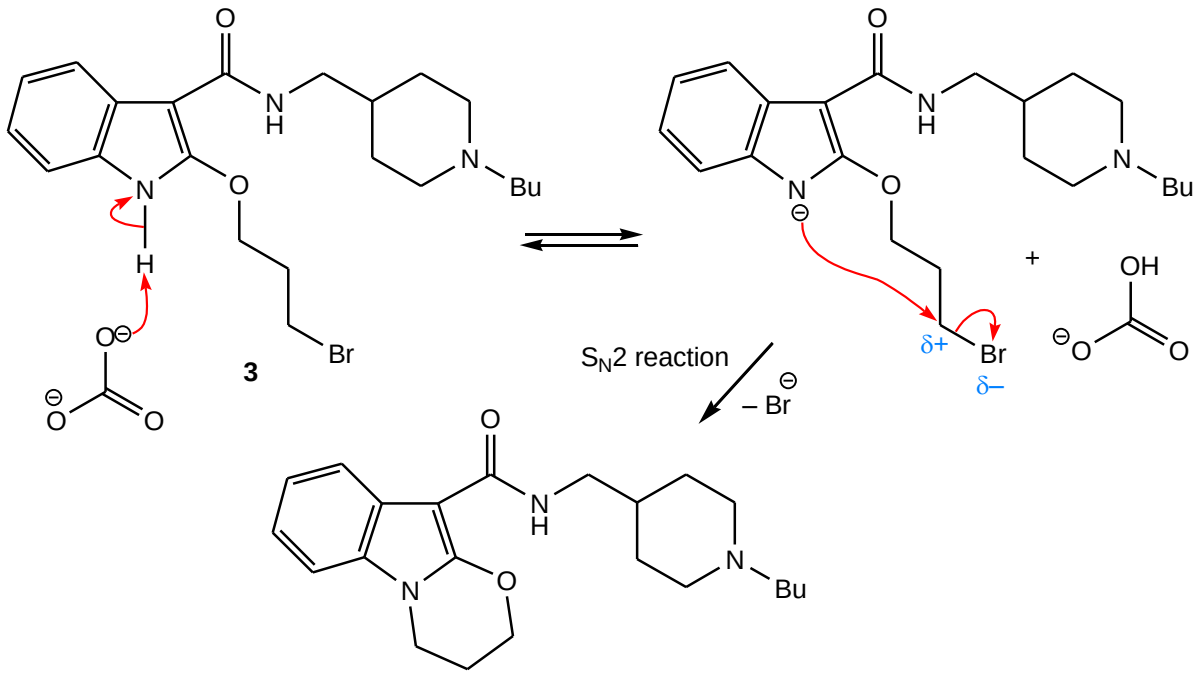
Solution

From surveying the structure of this conjugate base, the most likely electrophile is the aliphatic bromide. Displacement of the bromide anion (from this electrophilic aliphatic bromide side chain) using the non-bonded pair of electrons on the *N*-atom of the indole, leads to the formation of the six-membered heterocyclic ring in SB-207266. This reaction proceeds by an intramolecular S_N2 displacement. However, as this reaction is intramolecular, the reaction rate will only be proportional to the concentration of **3**.



conjugate base of **3**

Answer



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