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# Halogenoalkanes: substitution and elimination reactions

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## Answers to worked examples

### WE 20.1 Allylic halogenations (on p. 918 in *Chemistry*<sup>3</sup>)

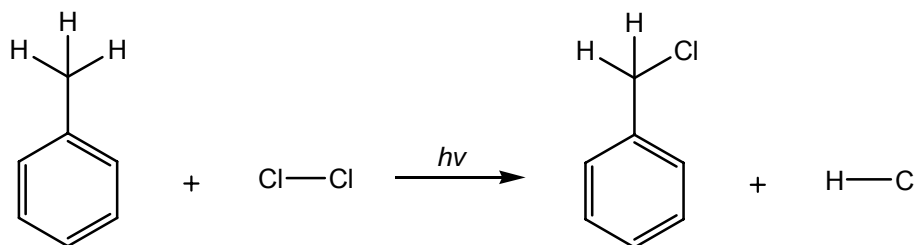
1-(Chloromethyl)benzene (benzyl chloride, PhCH<sub>2</sub>Cl) is made on a large scale in industry by reacting methylbenzene (toluene, PhCH<sub>3</sub>) with chlorine in the presence of UV radiation. Suggest a mechanism to explain the formation of 1-(chloromethyl)benzene from methylbenzene.

#### Strategy

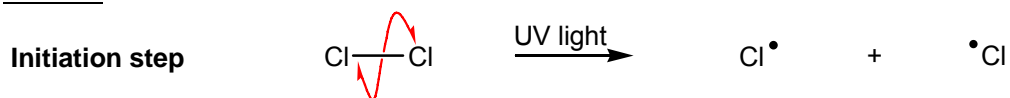
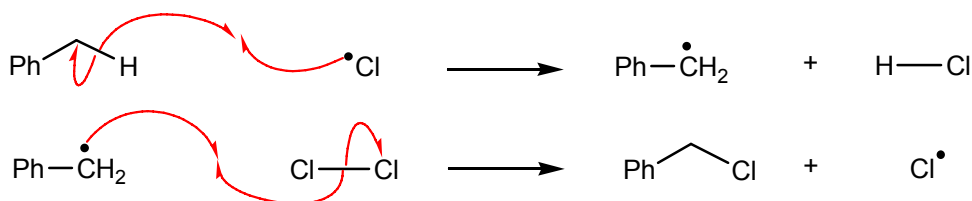
Draw out a balanced chemical equation for this reaction, and work out what the driving force for this process is. This reaction is more than likely a radical process as it requires UV radiation. If this is the case, most radical reactions occur in 3 stages; initiation, propagation and termination.

#### Solution

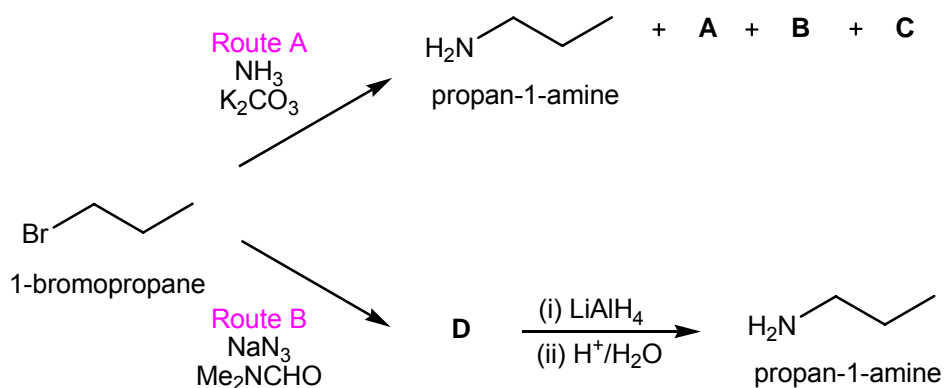
The balanced equation for this reaction is shown below. The driving force of this reaction must be the cleavage of the weak Cl-Cl bond and formation of strong H-Cl and C-Cl bonds.



This reaction must be a radical reaction. The initiation step involves photochemical cleavage of the weak Cl-Cl bond of molecular chlorine (Cl<sub>2</sub>) 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<sub>2</sub>•) and the required byproduct H-Cl. Capture of this benzyl radical (PhCH<sub>2</sub>•) 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. 971 in *Chemistry*<sup>3</sup>.

Answer**Propagation steps****WE 20.3 Predicting substitution pathways (on p. 935 in *Chemistry*<sup>3</sup>)**

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.



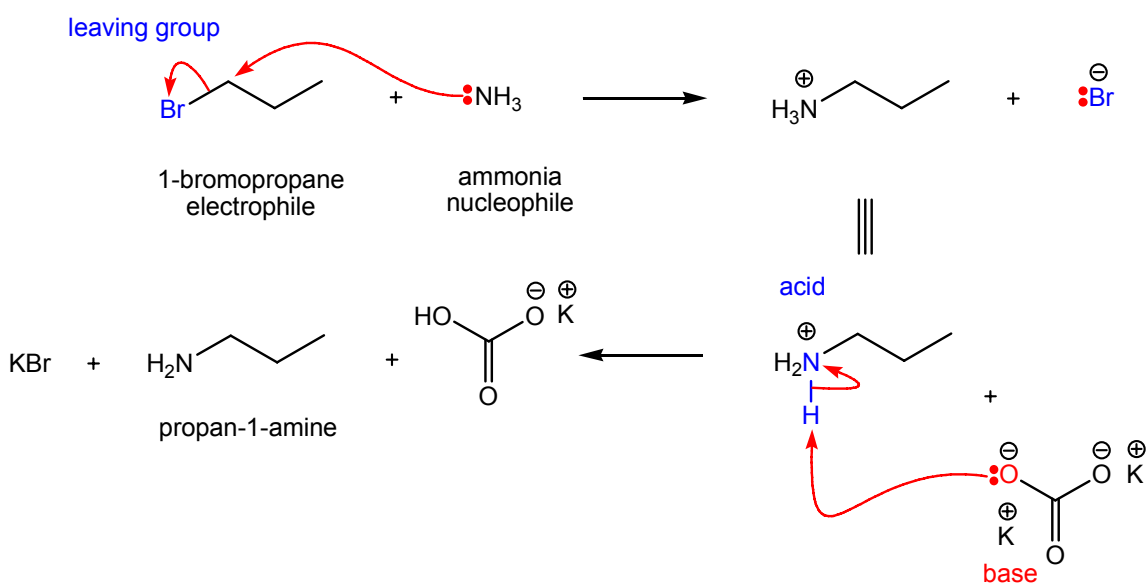
- (a) In route A, 1-bromopropane reacts with ammonia, in the presence of a base such as potassium carbonate, to give propan-1-amine in low yield and three additional organic compounds (**A**, **B**, and **C**).
- (i) Propose a mechanism to explain the formation of propan-1-amine from 1-bromopropane and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

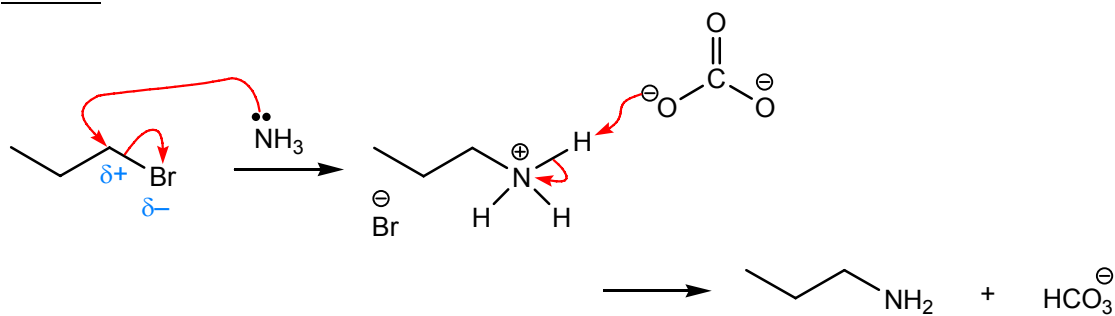
### Strategy

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 ( $\rightarrow$ ) 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

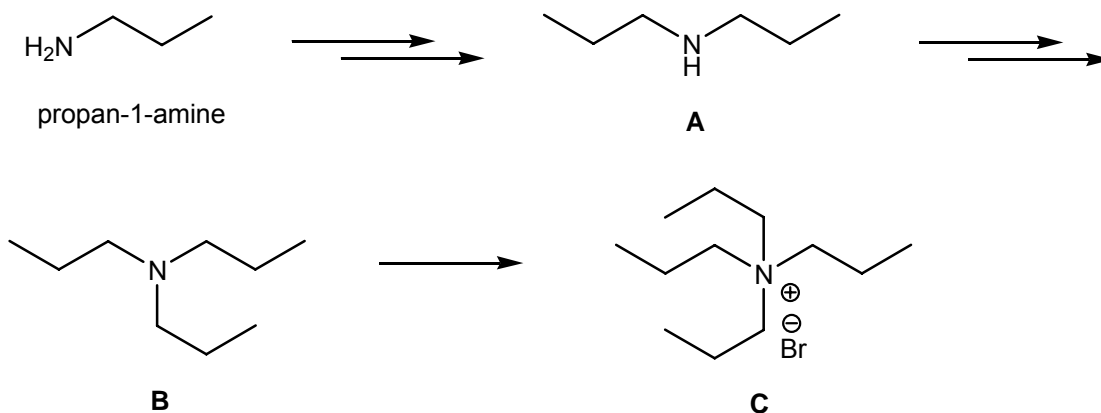
- (ii) Suggest structures for the three compounds
- A**
- ,
- B**
- , and
- C**
- .

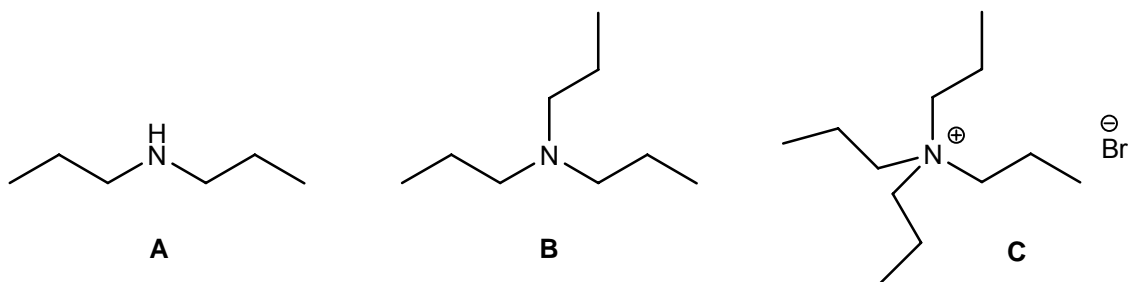
Strategy

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.

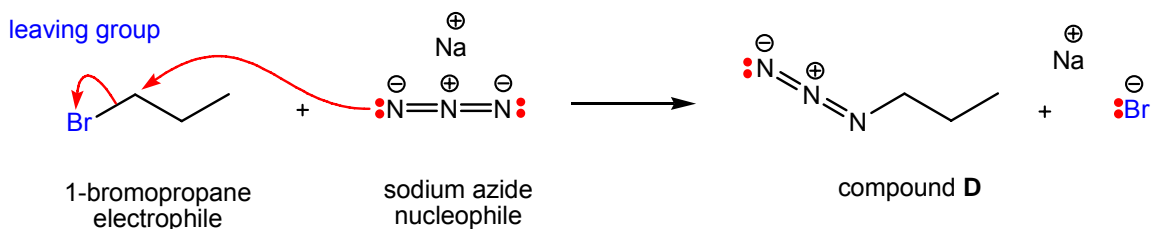
- (b) In route B, propan-1-amine is prepared from 1-bromopropane in good yield by reaction with  $\text{NaN}_3$  (in the solvent *N,N*-dimethylformamide) to give compound **D**, followed by reduction using  $\text{LiAlH}_4$ . Suggest a structure for compound **D** and propose a mechanism for its formation.

### Strategy

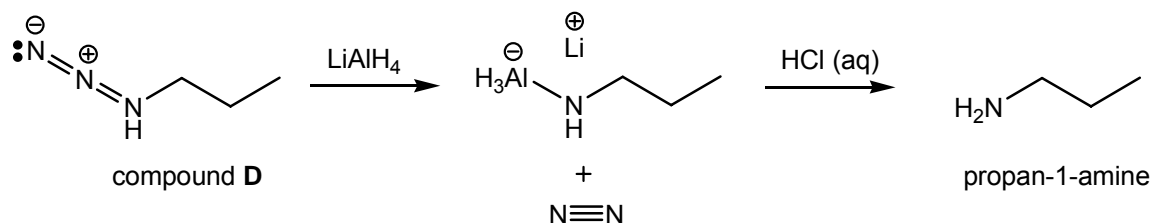
Draw out a balance chemical equation for the formation of compound **D** using 1-bromopropane and sodium azide ( $\text{NaN}_3$ ). Work out which reagent is the nucleophile and electrophile. [Remember, the “curly arrow” flows from the nucleophile ( $\rightarrow$ ) to the electrophile.] Nucleophiles contain 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

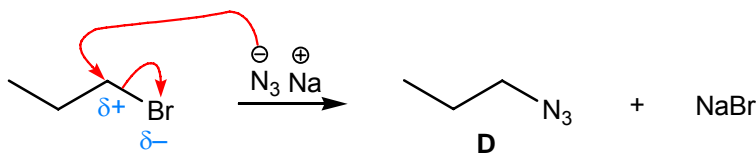
1-Bromopropane is the electrophile, azide is the nucleophile, and bromide is the leaving group. The mechanism for this reaction is shown below. Competitive alkylation of compound **D** with 1-bromopropane **does not** occur as the azide anion is an excellent nucleophile due to its high ground state energy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



$\text{LiAlH}_4$  reduction of compound **D** leads to propan-1-amine, as shown below.



### Answer

**WE 20.5 Assigning mechanisms to the formation of products (on p. 952 in *Chemistry*<sup>3</sup>)**

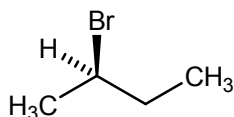
Suggest structures for the major substitution product and the major elimination product from reaction of (*R*)-2-bromobutane with ethoxide ion in acetonitrile.

Strategy

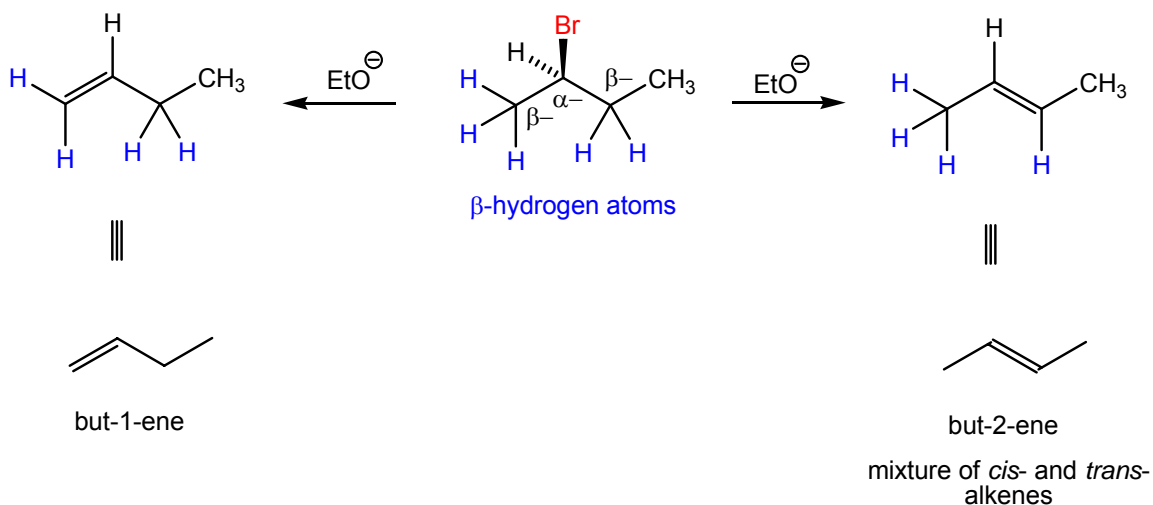
- Draw out the structure of (*R*)-2-bromobutane.
- For elimination, assign any  $\beta$ -hydrogen atoms. Primary and secondary bromides prefer E2 (anti-periplanar) elimination, and tertiary bromides prefer E1 elimination. Work out which mechanistic pathway is preferred. Draw the products from this elimination.
- 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

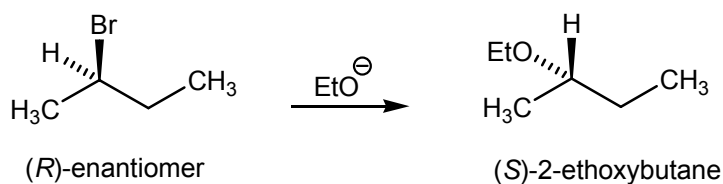
- The structure of (*R*)-2-bromobutane is given below.

(*R*)-2-bromobutane

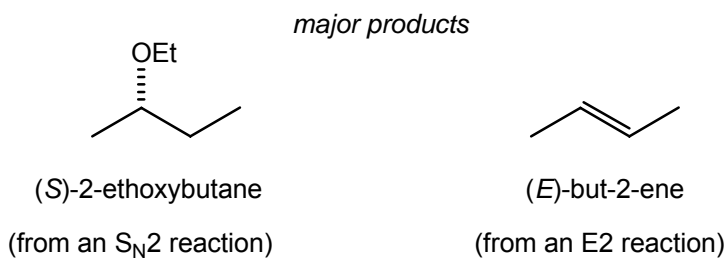
- (*R*)-2-bromobutane is a secondary bromide, and will prefer E2 elimination. As there are two sets of  $\beta$ -hydrogen atoms (from  $\text{CH}_3$  and  $\text{CH}_2$  groups); E2 elimination will lead to a mixture of but-1-ene and *cis*- and *trans*-but-2-enes. The major product will be *trans*-but-2-ene as E2 elimination to form the most stable alkene is preferred.



- (c) (*R*)-2-bromobutane is a secondary bromide, and will prefer  $\text{S}_{\text{N}}2$  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.



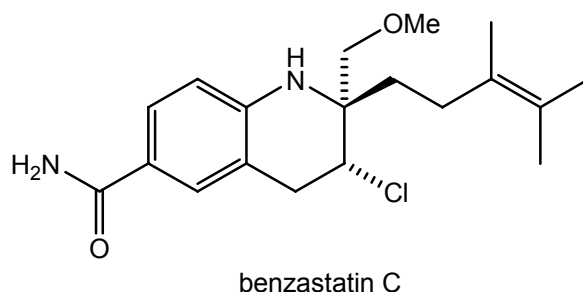
Answer



## Answers to boxes

### Box 20.1 Natural organohalogens (on p. 914 in *Chemistry*<sup>3</sup>)

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



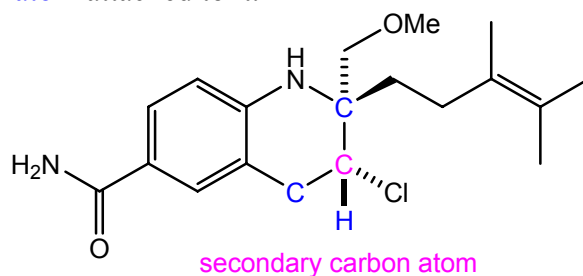
- (a) Is the chlorine atom in benzastatin C bonded to a primary, secondary, or tertiary carbon atom?

#### 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.



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 10.4 on p.480 in *Chemistry*<sup>3</sup>)

Strategy

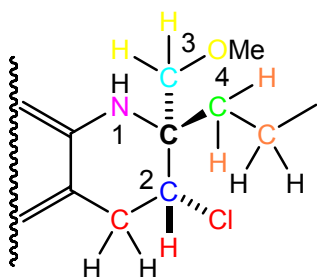
Work out where these two chiral centres are positioned in benzastatin C. Identify the two chiral centres in benzastatin C, and labelled them. Redraw this molecule in its condensed form, and work out the configurations at both chiral centres. It is easier to consider one centre at time. The (*R/S*)-stereochemistry is assigned using the Cahn-Ingold-Prelog rules (see p. 480 in *Chemistry*<sup>3</sup>).

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

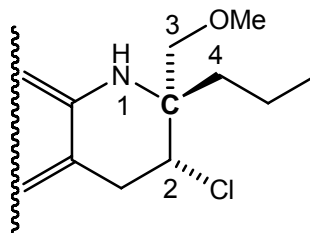
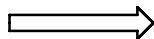
1 = N (-NHAr)

2 = C (-ClHCH<sub>2</sub>)

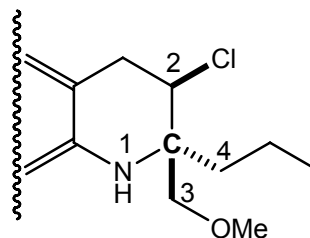
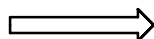
3 = C (-CH<sub>2</sub>OMe)

4 = C (-CH<sub>2</sub>CH<sub>2</sub>-)

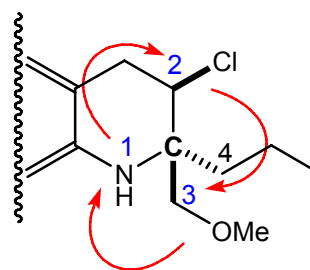
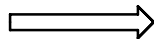
Group priorities at carbon-1



place the lowest  
priority at the rear

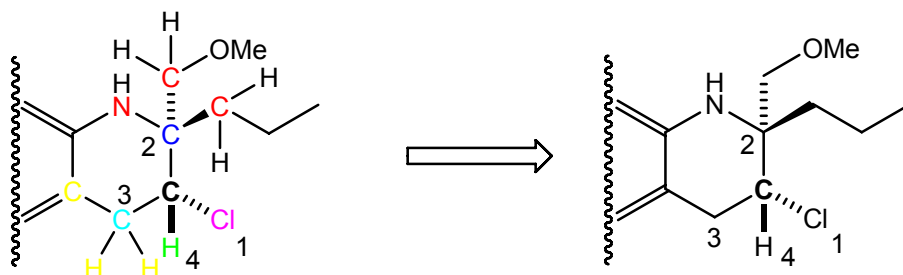


assign  
configuration



clockwise rotation = (R)-

Group priorities at carbon-2



CIP group priorities

1 = Cl (-Cl)

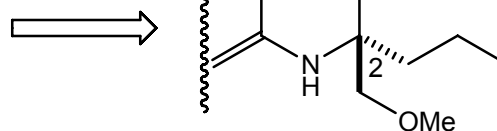
2 = C (-CNH(CH<sub>2</sub>-)(CH<sub>2</sub>-)

3 = C (-CH<sub>2</sub>C-)

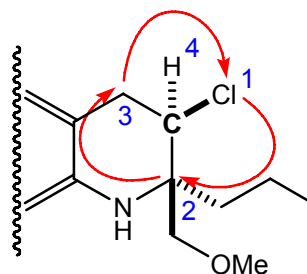
4 = H (-H)

place the lowest priority at the rear

Group priorities at carbon-1

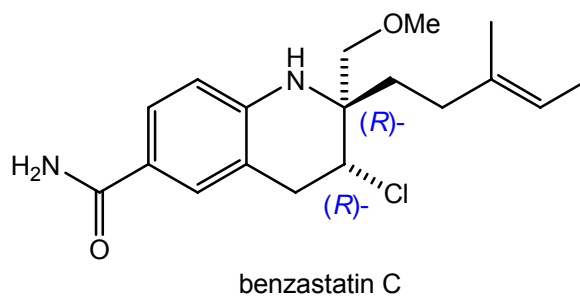


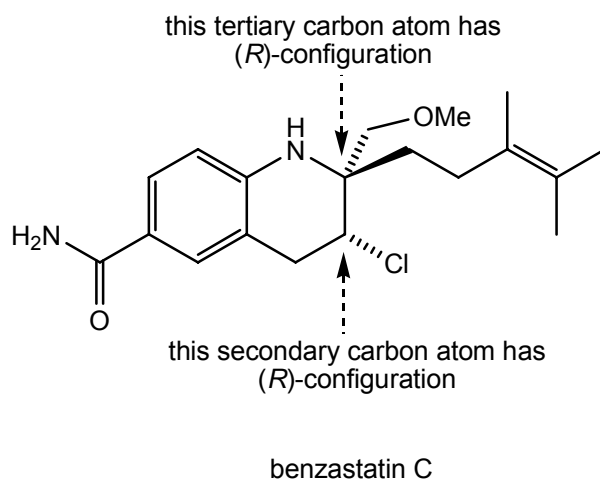
assign configuration



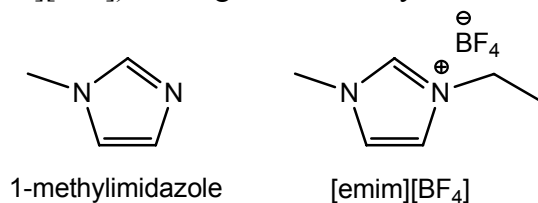
clockwise rotation = (R)-

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



Answer**Box 20.3 Designer solvents (on p. 928 in *Chemistry*<sup>3</sup>)**

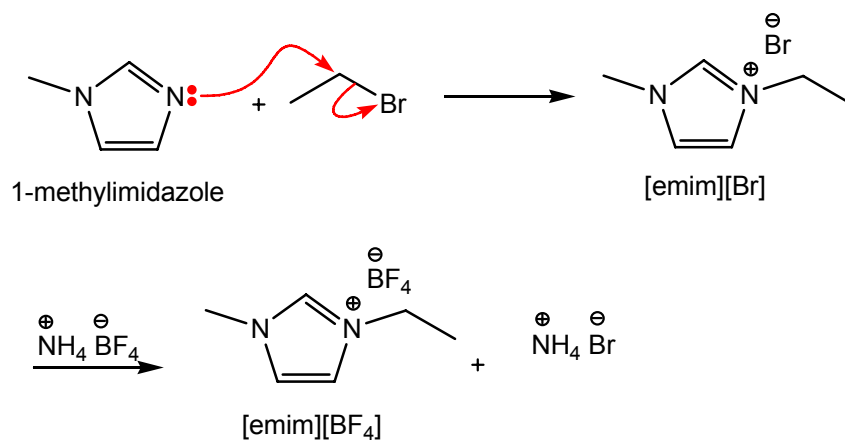
Suggest a two-step synthesis of the ionic liquid 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF<sub>4</sub>]) starting from 1-methylimidazole.

Strategy

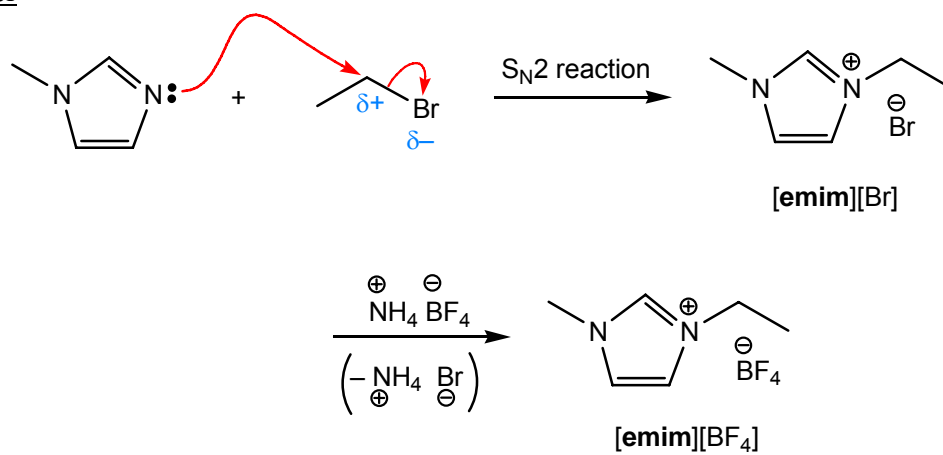
The strategy for this synthesis is similar to that outlined in Box 20.3 on p. 928 in *Chemistry*<sup>3</sup>. The first step must involve alkylation of 1-methylimidazole with an ethyl halide, and replacing the counter ion (the leaving group from the alkylation) with BF<sub>4</sub><sup>-</sup>.

Solution

Alkylation of 1-methylimidazole with ethyl bromide gives the intermediate imidazolium bromide, [emim]Br, by a S<sub>N</sub>2 mechanism. Anion exchange, using ammonium tetrafluoroborate [NH<sub>4</sub><sup>+</sup>BF<sub>4</sub><sup>-</sup>], gives the required 1-ethyl-3-methylimidazolium tetrafluoroborate, [emim]BF<sub>4</sub>. As this reaction is generally performed in acetone, the insoluble byproduct, ammonium bromide (NH<sub>4</sub><sup>+</sup>Br<sup>-</sup>), can be removed.

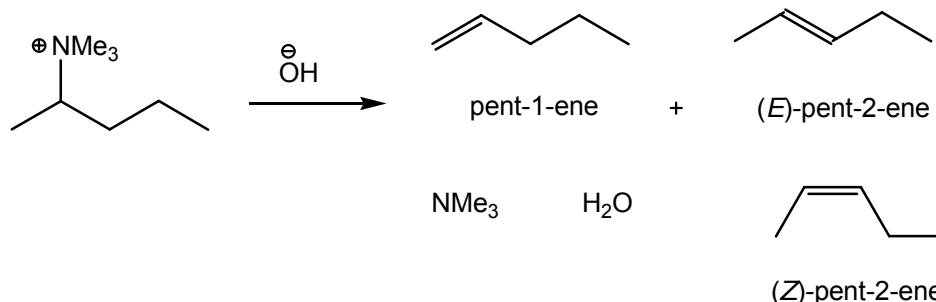


Answer



**Box 20.5 Muscle relaxants (on p. 943 in *Chemistry*<sup>3</sup>)**

An example of a Hofmann elimination is shown here.



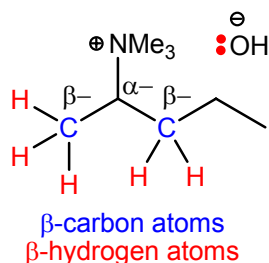
- (a) Suggest reaction mechanisms for the formation of pent-1-ene and (*E*)-pent-2-ene.

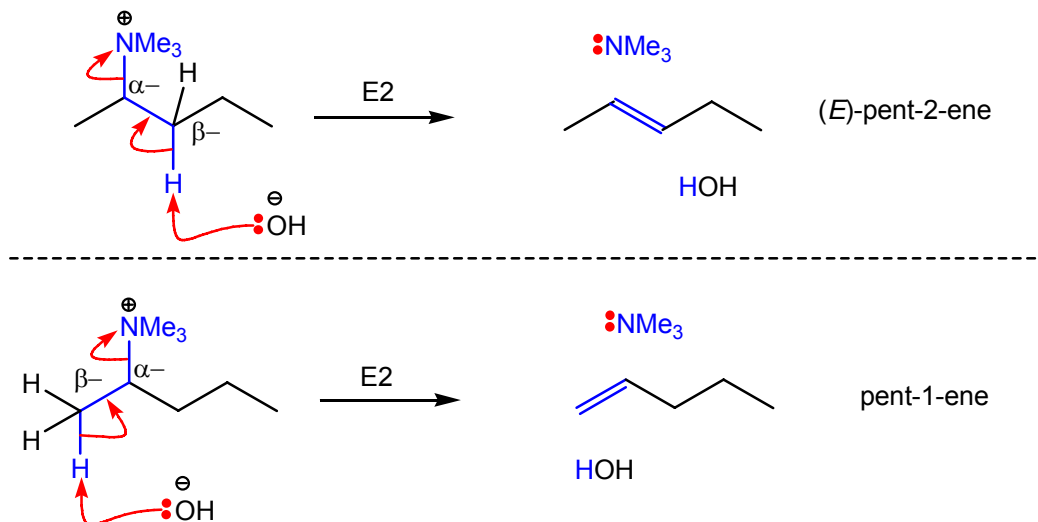
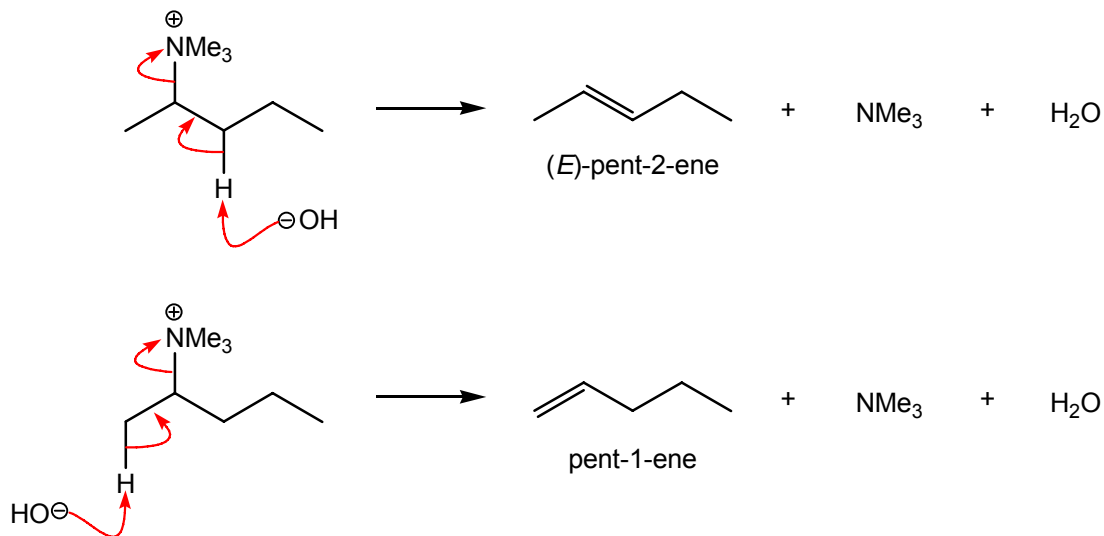
Strategy

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 ( $\rightarrow$ ), and so on.

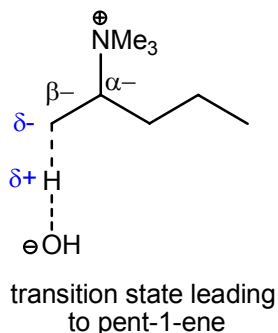
Solution

There are two  $\beta$ -carbon atoms in this ammonium ion; both contain hydrogen atoms which are capable of being removed by E2 elimination. Remove a proton from each  $\beta$ -carbon with concerted loss of trimethylamine (NMe<sub>3</sub>) leads to the required isomeric alkenes, pent-1-ene and (*E*)-pent-2-ene.



Answer

- (b) The regioselective formation of the less substituted alkene is explained by the mechanism of the elimination. The C–H bond on the  $\beta$ -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.



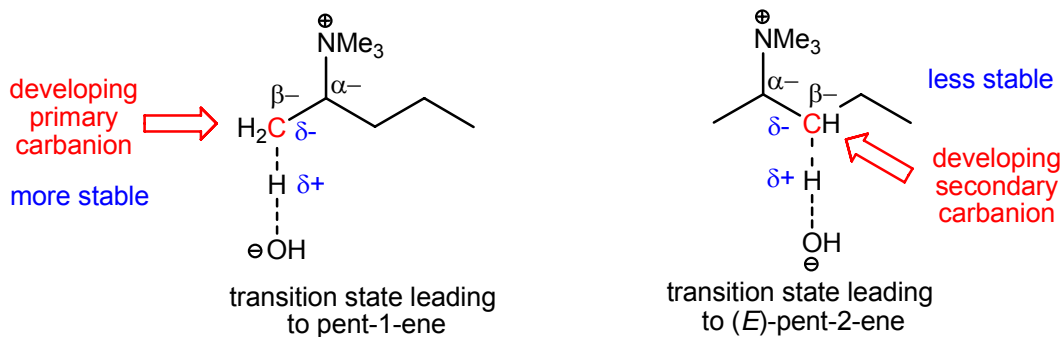
Draw the structure of the transition state that leads to (*E*)-pent-2-ene and suggest why the transition state that leads to pent-1-ene is lower in energy. (*Hint*: consider the relative stabilities of carbanions.)

### 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.

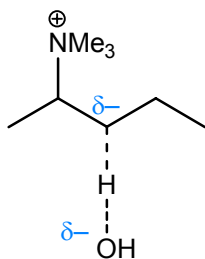
### Solution

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. 954 in *Chemistry*<sup>3</sup>)**

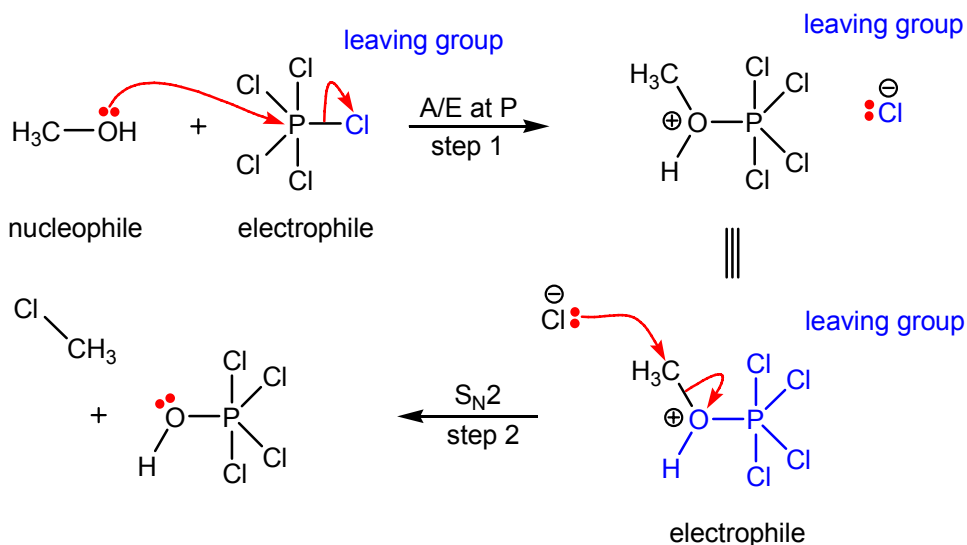
1. Suggest a mechanism for the following reaction:

Strategy

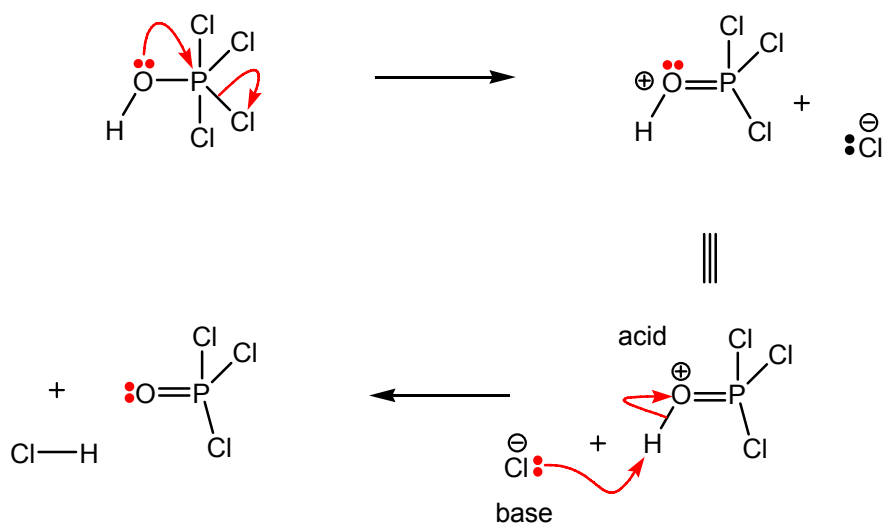
Work out which reagent is the nucleophile and electrophile. [Remember, the “curly arrow” flows from the nucleophile ( $\rightarrow$ ) to the electrophile.] Nucleophiles contain non-bonded electrons (which sometimes can be depicted by negative charge) and electrophiles have low-lying empty orbitals (which often contain a leaving group). In this particular case, this electrophile,  $\text{PCl}_5$ , 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

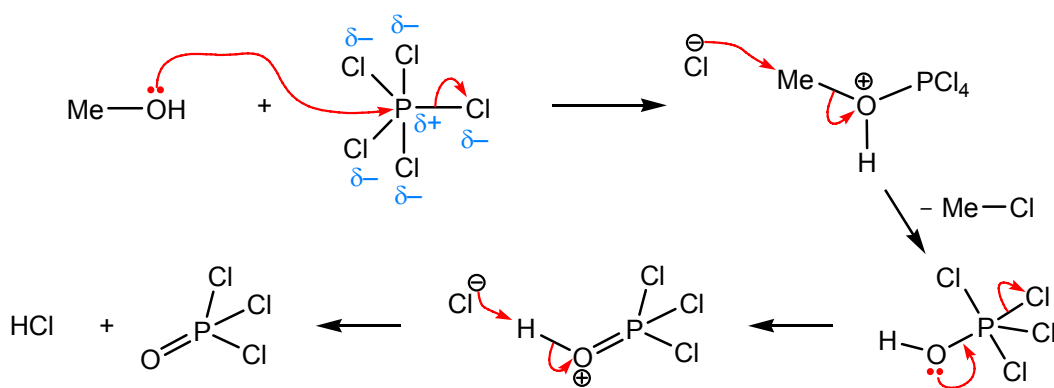
The driving force of this reaction is the formation of strong C-Cl and P=O bonds (in  $\text{CH}_3\text{Cl}$  and  $\text{POCl}_3$ , respectively) at the expense of two weaker P-Cl bonds (in  $\text{PCl}_5$ ). Addition of methanol to  $\text{PCl}_5$  leads to an intermediate oxonium chloride.  $\text{S}_{\text{N}}2$  displacement of this oxonium ion using the chloride counter anion gives the required methyl chloride,  $\text{CH}_3\text{Cl}$ , and the byproduct  $\text{PCl}_4\text{OH}$ . This mechanism is shown below.



Fragmentation of this intermediate,  $\text{PCl}_4\text{OH}$ , to give the more stable  $\text{POCl}_3$  and  $\text{HCl}$  is shown below.



Answer



3. Explain why the relative rate of reaction of 1-bromobutane with azide ion ( $\text{N}_3^-$ ) increases from 1 to 2800 on changing the solvent from methanol to dimethylformamide.

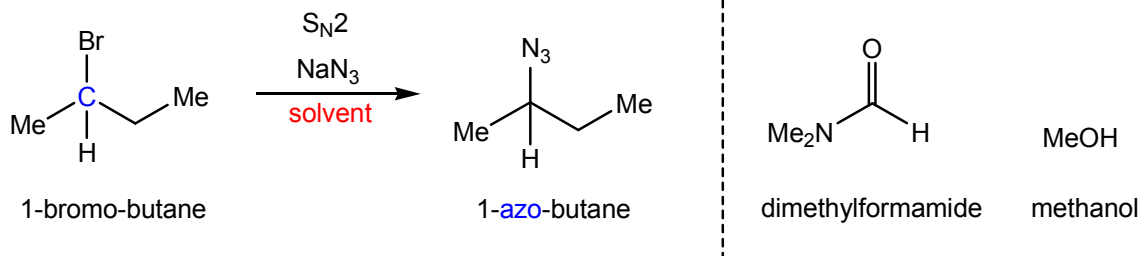
### Strategy

- (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  $\text{S}_{\text{N}}1$  or  $\text{S}_{\text{N}}2$  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.  $\text{S}_{\text{N}}2$  substitution of 1-bromobutane using sodium azide as the nucleophile leads to the corresponding product, 1-azobutane. [Remember, primary and secondary halides favour  $\text{S}_{\text{N}}2$  substitution, and tertiary halides favour  $\text{S}_{\text{N}}1$  substitution.]

secondary bromide

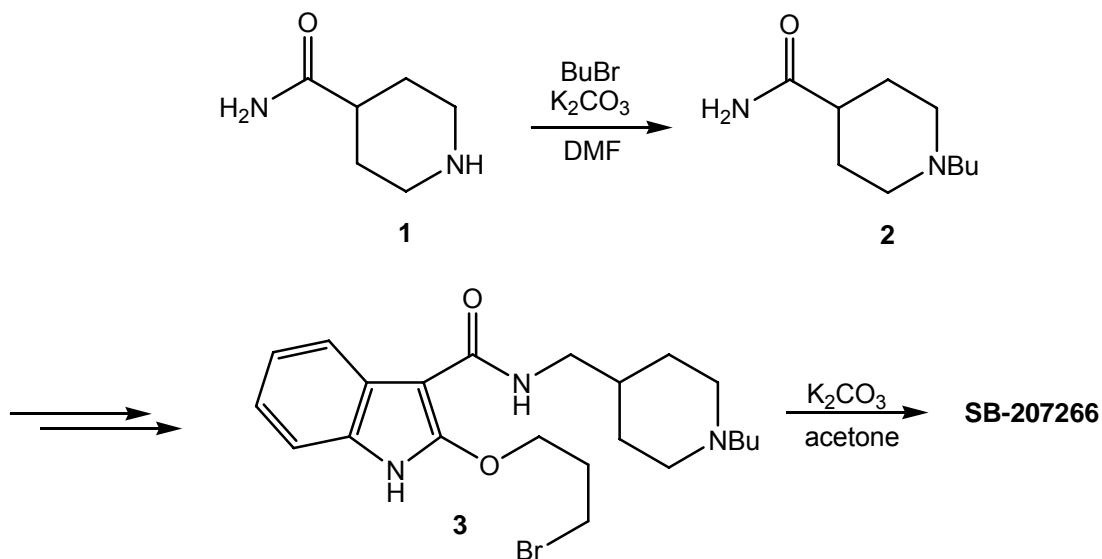


- (b) The more polar solvent is methanol (MeOH). However, this solvent is protic (which is capable of acting as a hydrogen bonding donor), whereas, dimethylformamide (DMF) is aprotic. Both solvents are polar solvents.
- (c) This  $\text{S}_{\text{N}}2$  displacement is faster in an aprotic polar solvent (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 ( $\text{N}_3^-$ ) nucleophile, which consequently lowers its nucleophilicity. [Remember, high-energy nucleophiles are more nucleophilic than low-energy nucleophiles.]

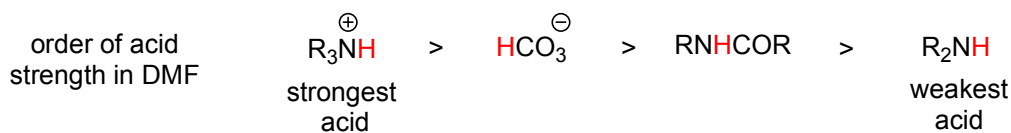
### Answer

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.

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.



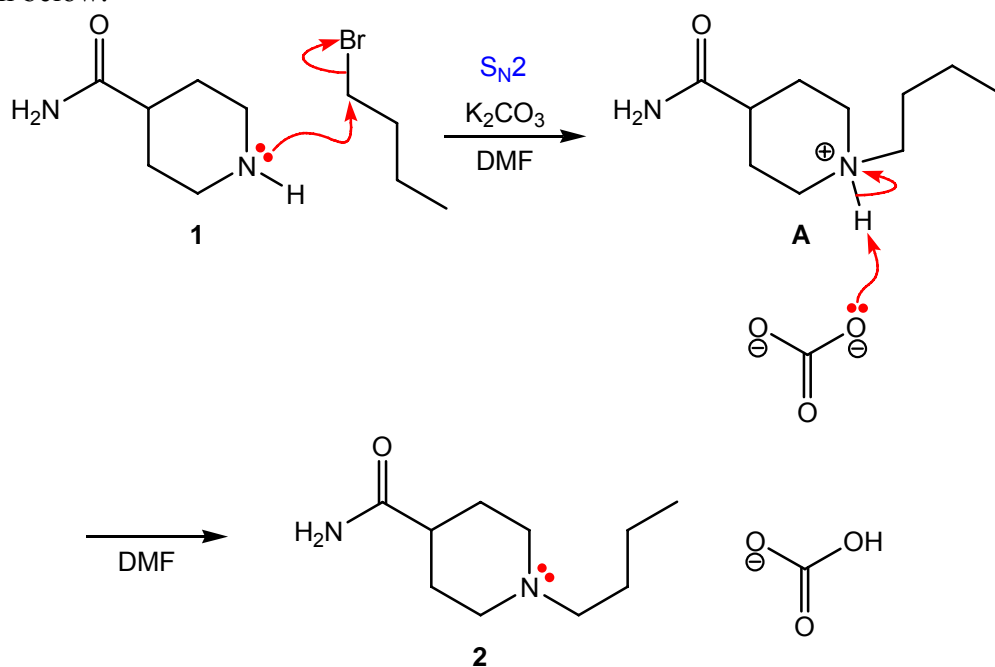
### Strategy

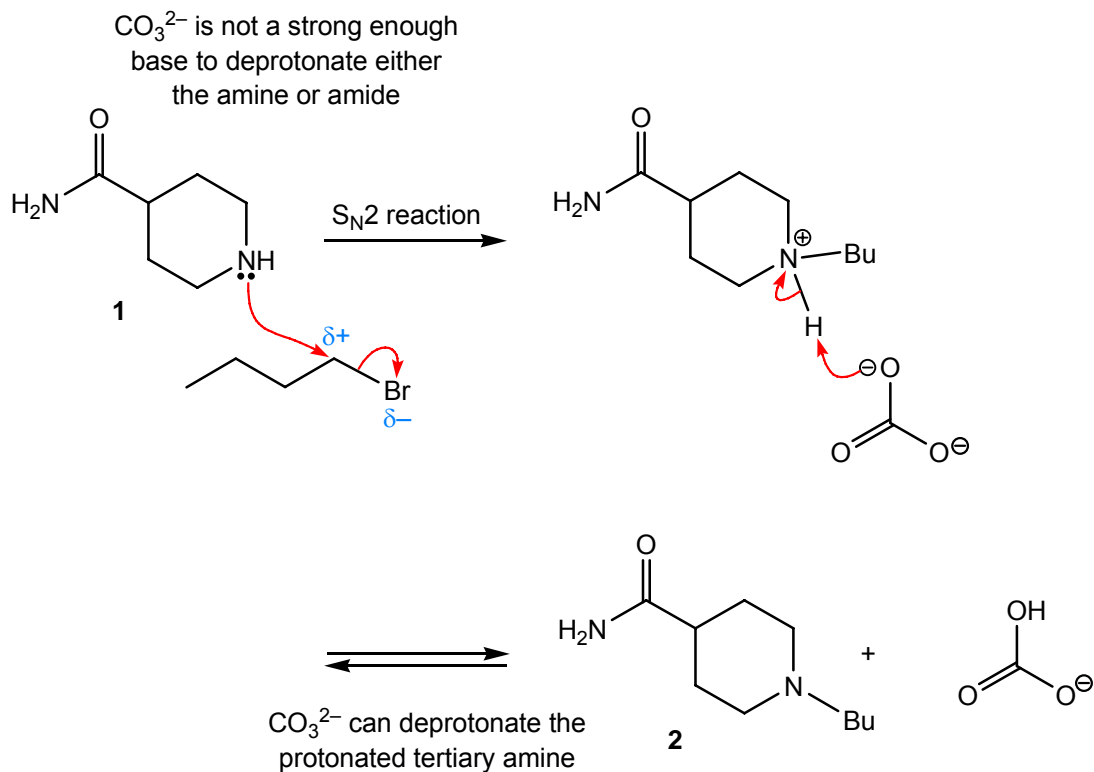
This reaction is a nucleophilic substitution, where the N-H group of compound **1** is being replaced with the N-Bu in compound **2**. There are two reagents; the electrophile, BuBr, and the base, potassium carbonate ( $K_2CO_3$ ). [The solvent for this reaction is DMF.]

Using the above acidity data, work out if this reaction proceeds by initial deprotonation (followed by alkylation), or by alkylation (followed by deprotonation).

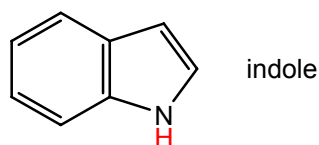
### Solution

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

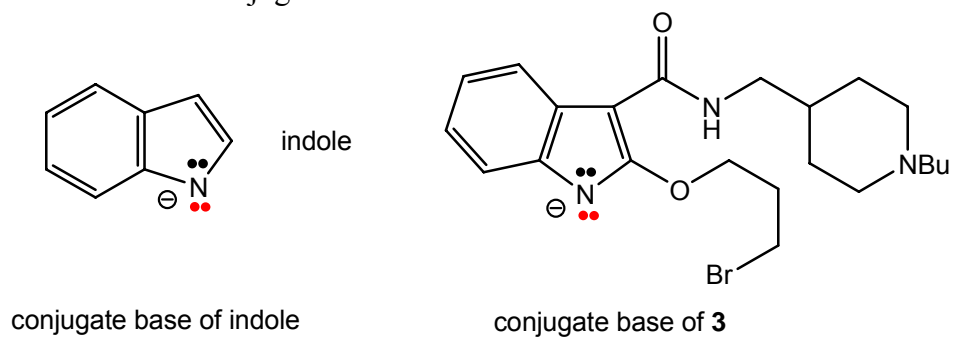
- (b) Although the  $\text{CO}_3^{2-}$  ion is not a sufficiently strong base to deprotonate the NH group in indole itself (see below), it is able to deprotonate the NH group in the indole ring of compound **3**. Suggest an explanation for the different acidities of these two indole rings.

Strategy

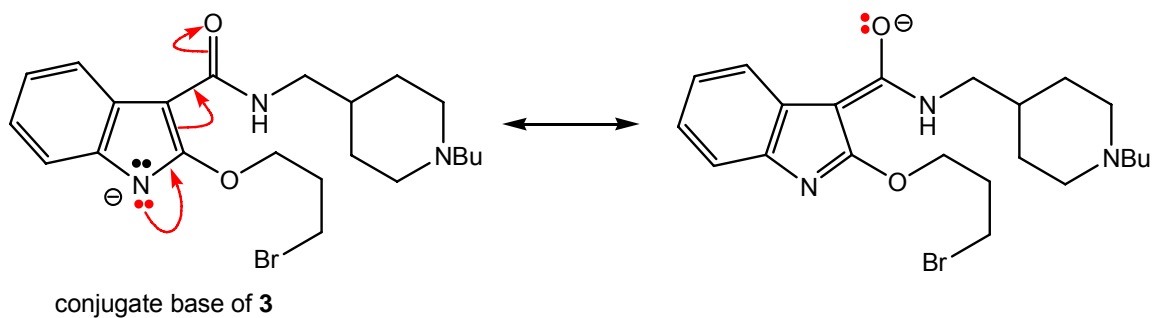
From the information given above, the NH bond of indole in compound **3** is more acidic than that of indole itself. Draw out the structure of both conjugate bases and work out where this extra stability (for the conjugate base of compound **3**) may come from.

Solution

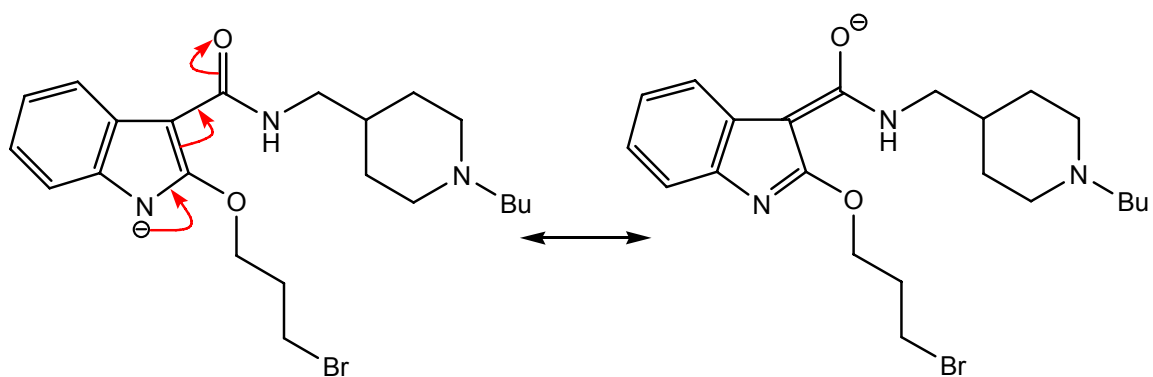
The structures of these conjugate bases are shown below.



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.



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

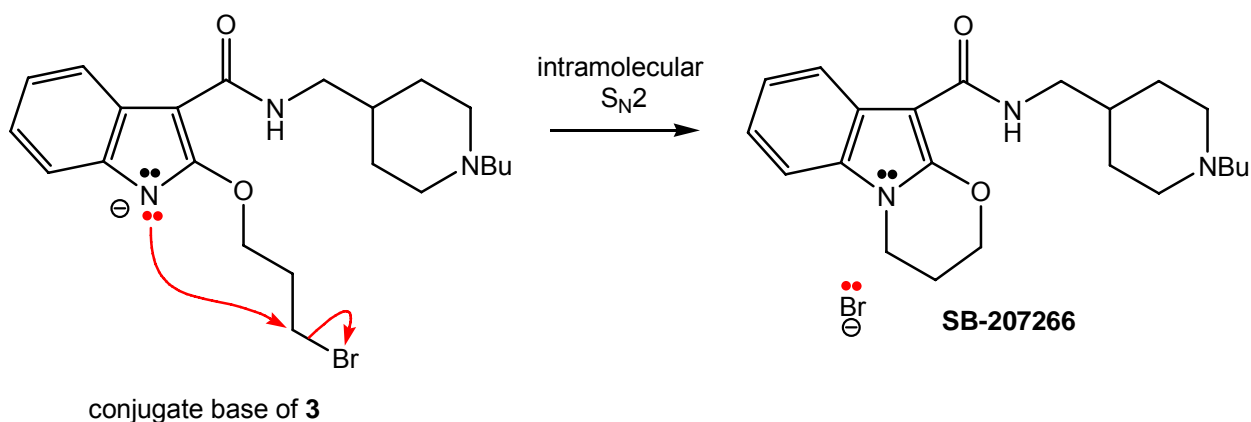
substitution reaction. Suggest a structure for SB-207266 and give a mechanism for its formation. Does the substitution involve an  $S_N1$  or  $S_N2$  mechanism?

### Strategy

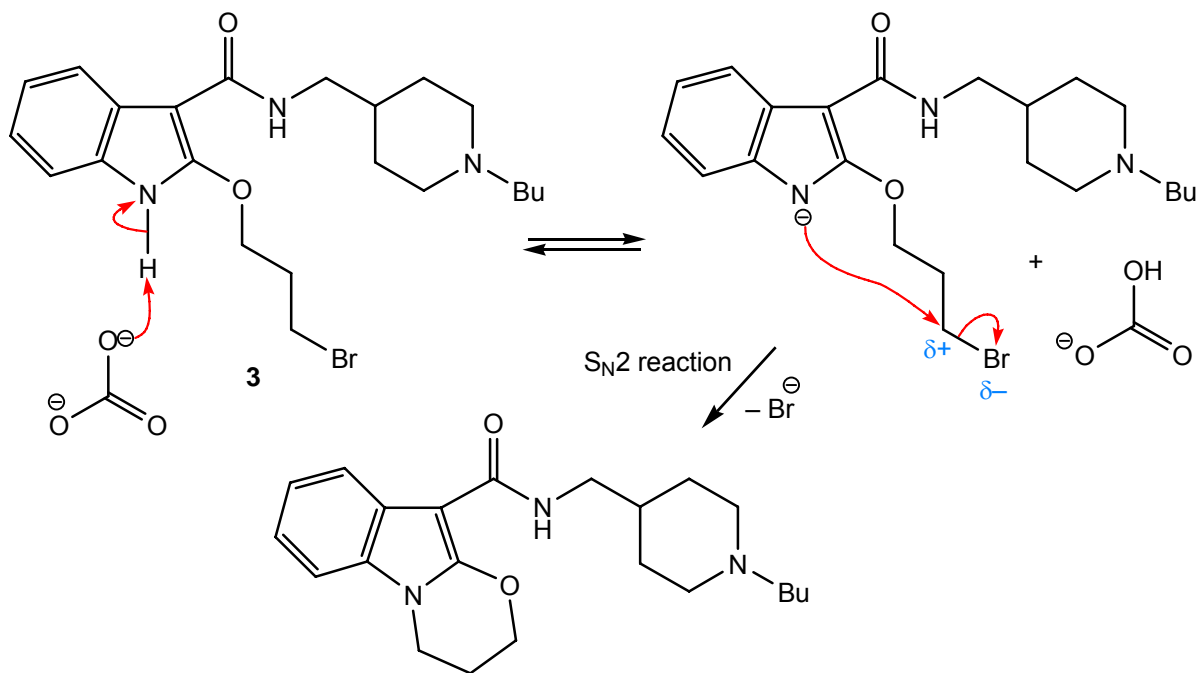
Draw out the conjugate base of compound **3**. The mechanism for this deprotonation step is similar to that shown above (in part a). From this question, we are told that this reaction proceeds *via* a nucleophilic substitution, and the nucleophile is the indole anion. From the structure of this conjugate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



Answer



SB-207266

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