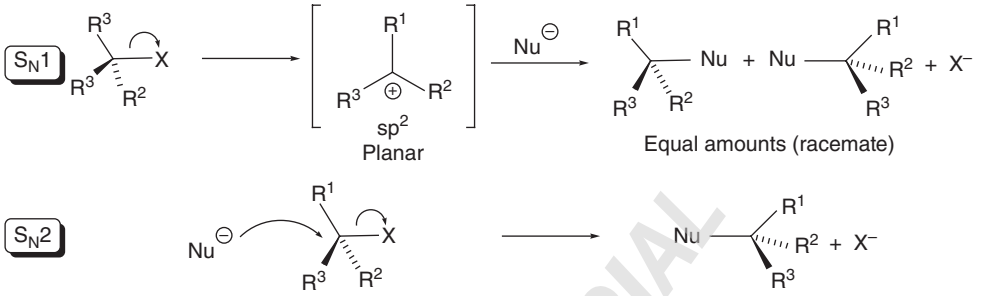
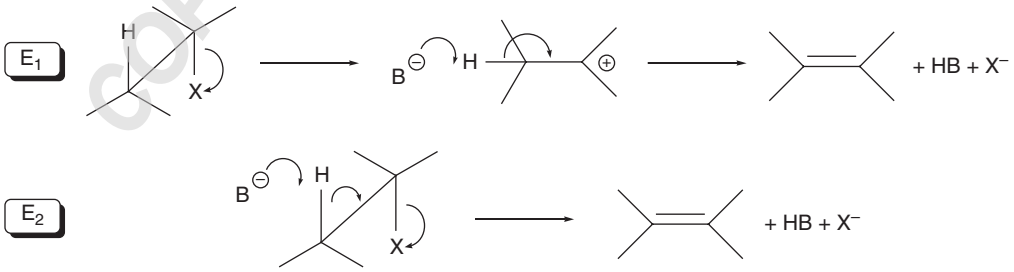
1 Nucleophilic substitution and elimination

Nucleophilic substitution: *S_N1 and S_N2 reactions*



- S_N1 is stepwise and unimolecular, proceeding through an intermediate carbocation, with a rate equation of Rate α $[R^3R^2R^1CX]$, that is, proportional only to the concentration of alkyl halide starting material. The order of stability of the carbocation depends on structure, $R_3C^+ > R_2CH^+ > RCH_2^+ > CH_3C^+ > H_3C^+$, and rearrangements, by either hydrogen or carbon migrations, are possible.
- S_N2 is bimolecular with simultaneous bond-making and bond-breaking steps, but does not proceed through an intermediate, with a rate equation of Rate α $[R^3R^2R^1CX][Nu^-]$, that is, the rate is reaction is proportional to both the concentration of alkyl halide starting material and the nucleophile.
- The nature of the substrate structure, nucleophile, leaving group, and solvent polarity can all alter the mechanistic course of the substitution.
- There are important stereochemical consequences of the S_N1 and S_N2 mechanisms (the former proceeds with racemisation and the latter with inversion).
- Steric effects are particularly important in the S_N2 reaction (neopentyl halides are unreactive).
- Neighbouring group participation in S_N1 reactions can be important.
- Special cases: (i) Allylic nucleophilic displacement: S_N1' and S_N2'; (ii) Aryl (PhX) and vinylic ($R_2C=CRX$) halides: these are generally unreactive towards nucleophilic displacement, although benzylic ($PhCH_2X$) and allylic ($RCH=CHCH_2X$) are more reactive.

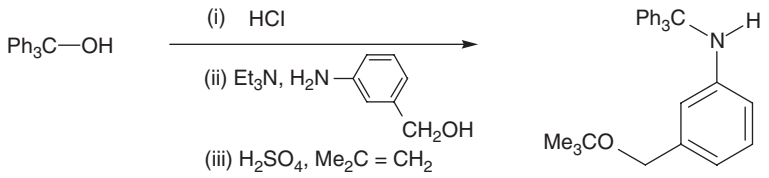
Elimination: E_1 and E_2 eliminations



- E_1 is stepwise and unimolecular, proceeding through an intermediate carbocation; E_2 is bimolecular with simultaneous bond-making and bond-breaking steps but does not proceed through an intermediate.
- The Saytzev's Rule and Hofmann's Rule can be used to predict the orientation of elimination, and the stereochemistry is preferentially antiperiplanar.
- Elimination and substitution are often competing reactions.

How to Solve Organic Reaction Mechanisms: A Stepwise Approach, First Edition. Mark G. Moloney.

1.1



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Alcohols are nucleophiles and bases, since the oxygen possesses lone pairs. HCl is a strong acid and fully ionised (pKa = –7). Triethylamine is a weak base and sulfuric acid is also a very strong acid.

Identify the most reactive sites, if more than one exists.

Aromatic rings can be protonated, but the alcohol is the most basic and nucleophilic site of Ph_3COH.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alcohols are easily protonated by strong acids, which converts the hydroxyl into a good *leaving group*, an *oxonium* ion, which is able to depart as water, leaving a carbocation intermediate.

Work through the mechanism leading to the intermediate product.

The leaving group departs to give a tertiary carbocation, which is also *resonance* stabilised, called the triphenylmethyl cation, which is then intercepted by chloride.

Repeat the above four steps.

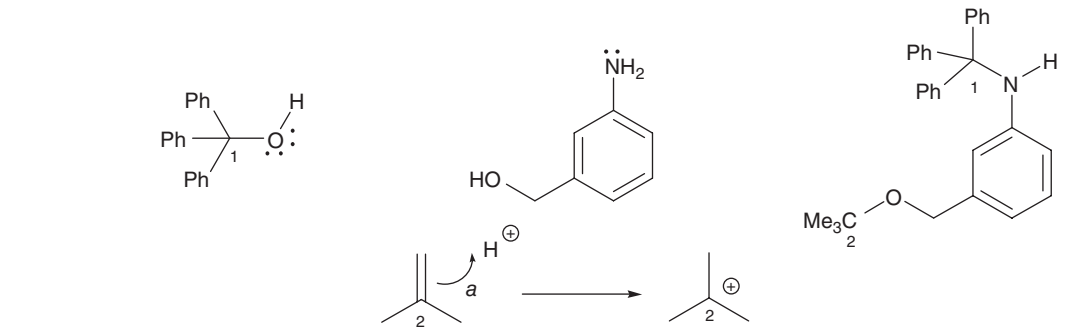
* Triphenylmethyl chloride readily undergoes S_N1 reactions; departure of the good *leaving group* (chloride) regenerates the triphenylmethyl carbocation, which is intercepted by the most nucleophilic functional group of the aniline reagent, that is, the amine group. A series of proton transfers then gives the product.

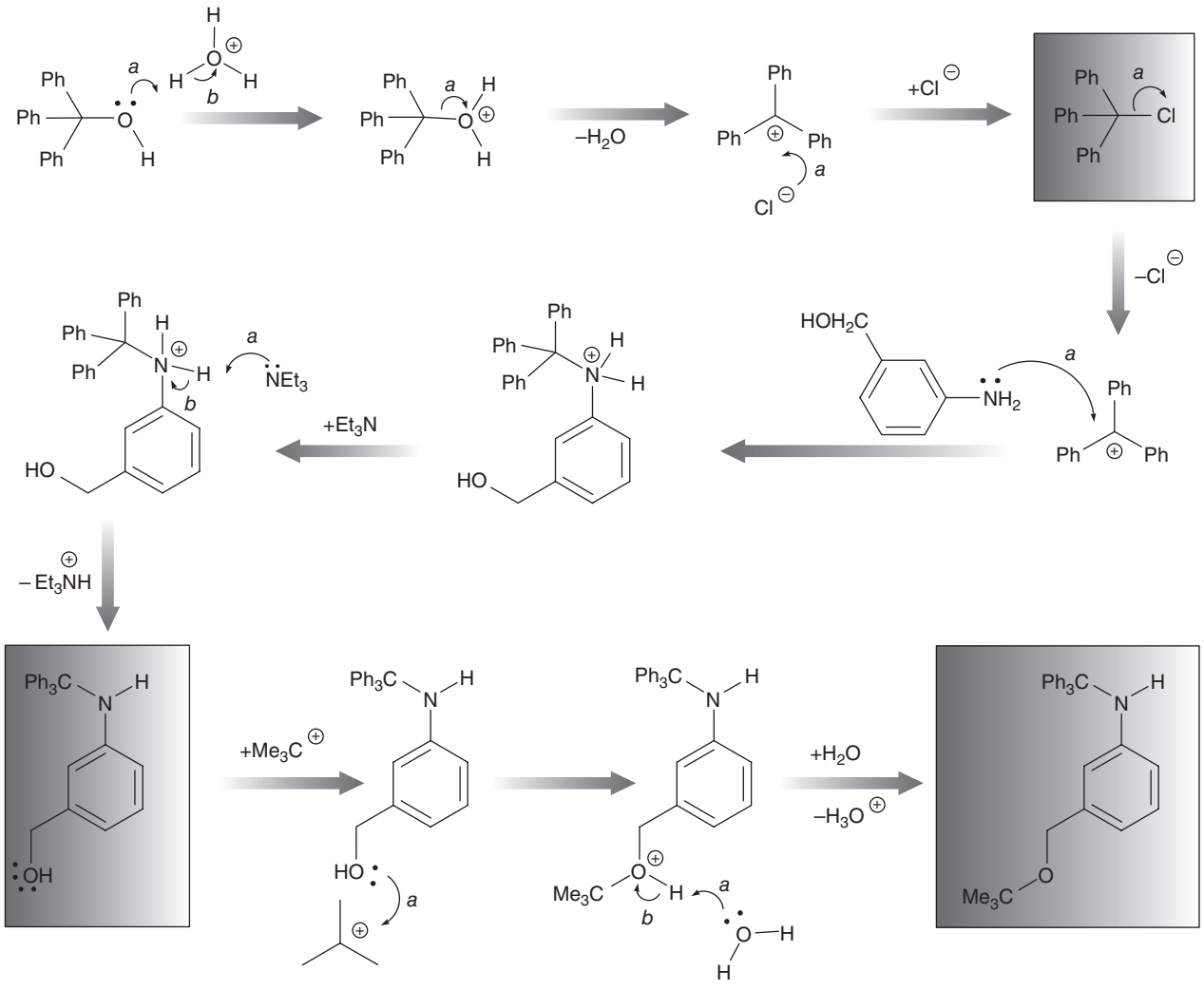
* Under stongly acidic conditions (H_2SO_4), isobutene is protonated (*Markovnikov* addition) to give a *t*-butyl cation; this is intercepted to give the ether product in its protonated form.

Recognise that this is not the final product, but is closely related to it.

Deprotonation of this *oxonium* cation gives the ether product.

Write down the structure of the final product.



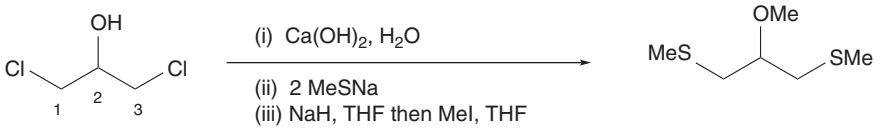


Summary: There are several examples of nucleophilic substitution (S_N1) reactions in this question:

$$Nu^{\ominus} + R\text{-}X \longrightarrow R\text{-}Nu + X^{\ominus}$$

Now try questions 1.8 and 1.9

1.2



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Alkyl chlorides are good electrophiles (chloride is a good leaving group and its electronegativity polarises the C-Cl bond). Alcohols are nucleophiles and weak acids. Calcium hydroxide is a weak base.

Identify the most reactive sites, if more than one exists.

Under the basic conditions of the reaction, the alcohol function is deprotonated to give an alkoxide anion which is very nucleophilic. The alkyl chloride is the most electrophilic site.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alkyl halides readily undergo nucleophilic substitution reactions with alkoxides to give ethers (the *Williamson ether synthesis*). In this case, the reaction would be an intramolecular one.

Work through the mechanism leading to the intermediate product.

The alkoxide undergoes an intramolecular *nucleophilic substitution* reaction with the alkyl chloride to give an epoxide.

Repeat the above four steps.

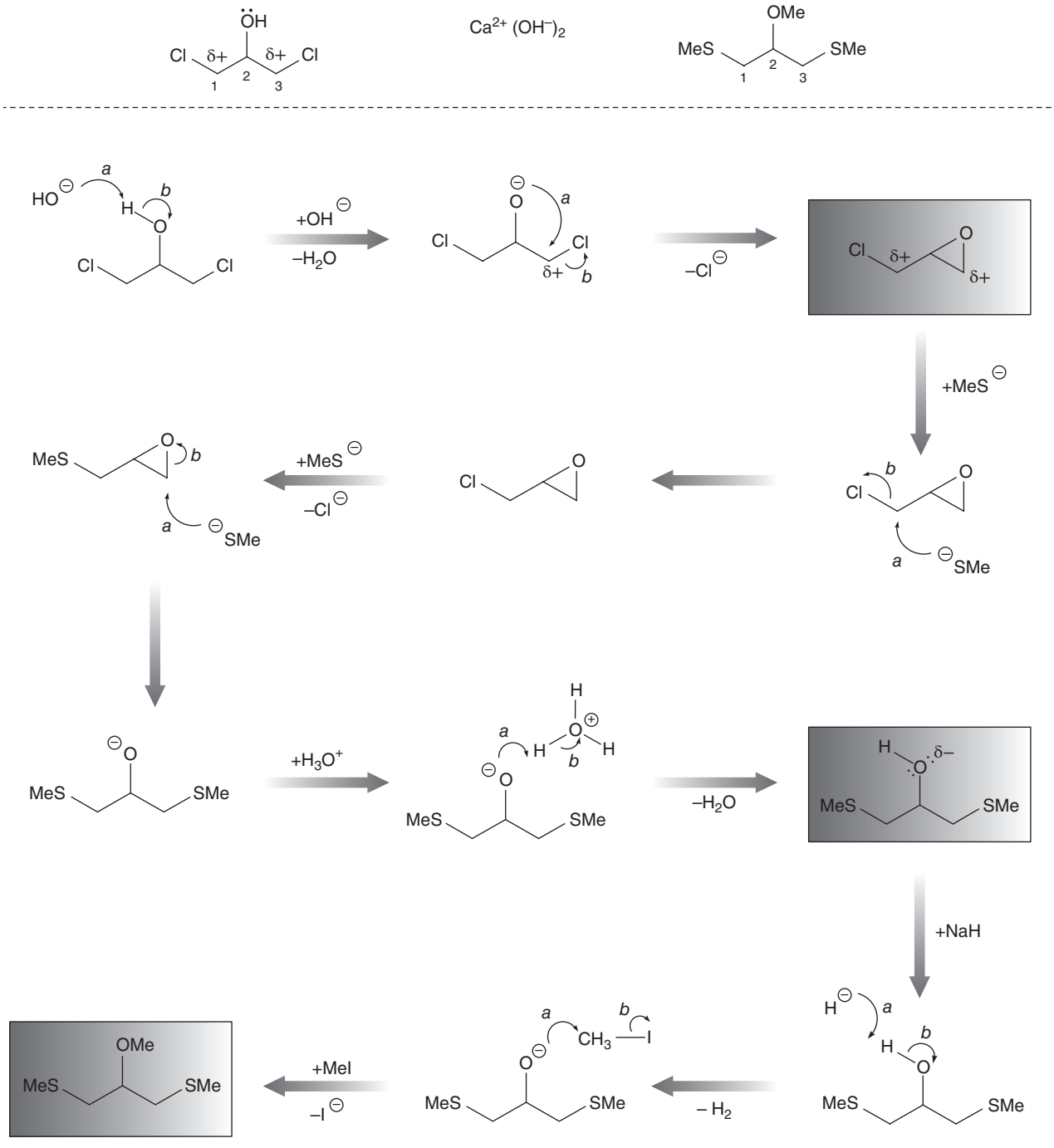
* Methanethiolate is a good nucleophile, and attacks both the C-Cl bond and the epoxide function (which has two electrophilic sites) at the less hindered end, to give the alkoxide product; this is protonated on work-up.

* Sodium hydride is a good base, and deprotonates the alcohol; *alkylation* with MeI, via a *nucleophilic substitution* mechanism, gives the final ether product (Williamson ether synthesis).

Recognise that this is not the final product, but is closely related to it.

Not needed here.

Write down the structure of the final product.

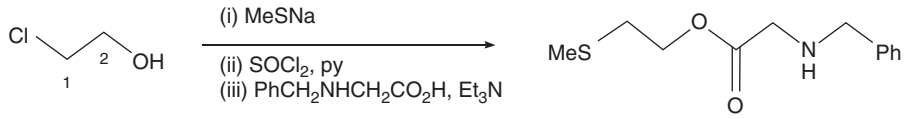


Summary: This question involves several examples of nucleophilic substitution (S_N2) reactions:

$$Nu^{\ominus} + R\text{-}X \longrightarrow R\text{-}Nu + X^{\ominus}$$

Now try questions 1.10 and 1.16

1.3



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Alkyl chlorides are good electrophiles (chloride is a good leaving group) and alcohols are good nucleophiles (the oxygen has two lone pairs). Methanethiolate is an excellent nucleophile (the sulfur is very polarisable and carries a negative charge).

Identify the most reactive sites, if more than one exists.

Since the reaction is with the highly nucleophilic reagent, MeS^-, the most reactive site is the alkyl chloride. An alcohol is not reactive with a nucleophilic reagent.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alkyl chlorides readily undergo *nucleophilic substitution* reactions, since they possess a leaving group, and are electrophilic by virtue of the electronegative halogen substituent.

Work through the mechanism leading to the intermediate product.

Since the reaction here is between a 1° alkyl chloride and a highly nucleophilic thiolate anion, an S_N2 mechanism is most likely.

Repeat the above four steps.

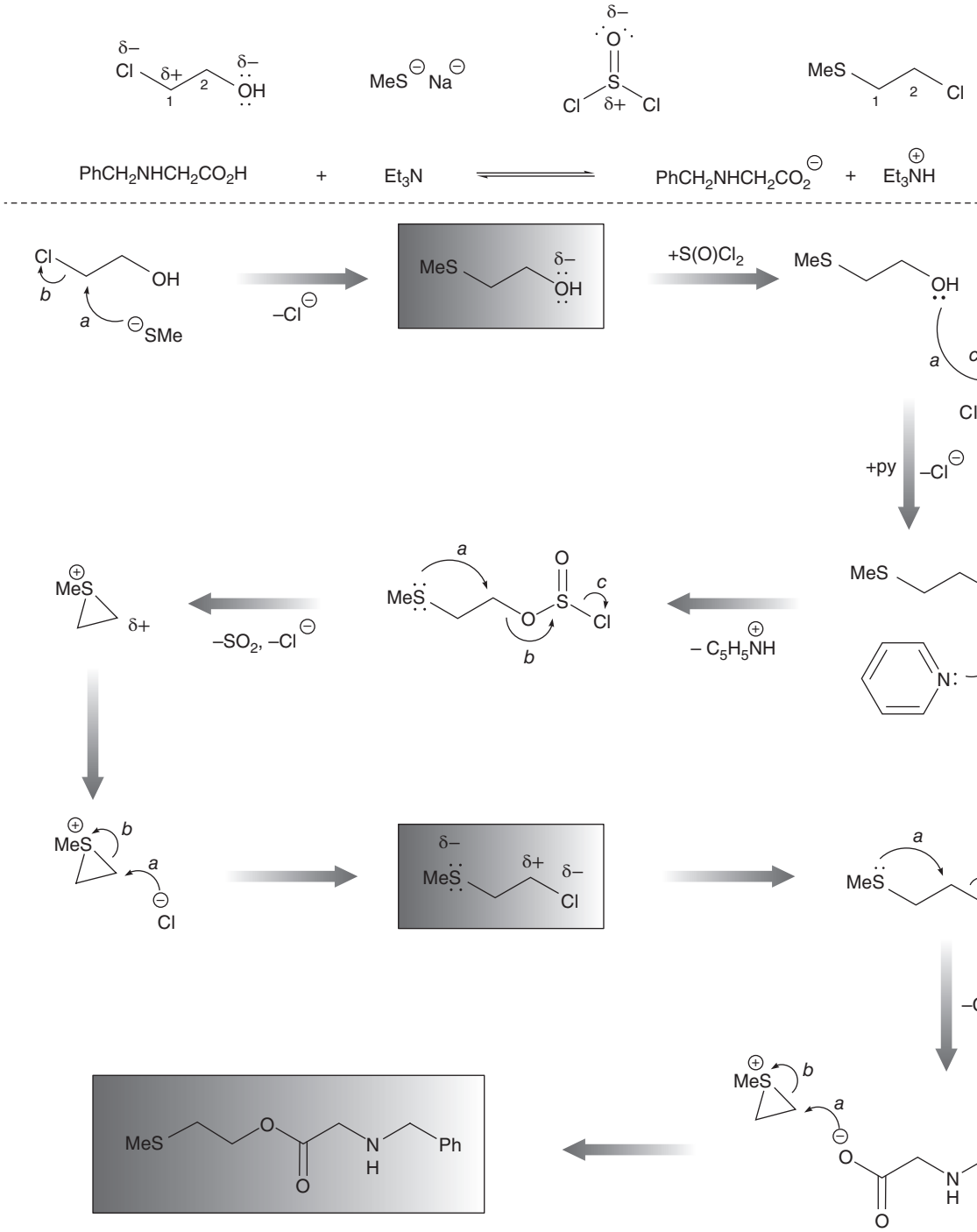
* Thionyl chloride is highly electrophilic, and converts the alcohol to the corresponding alkyl chloride *via* an *addition-elimination* process (with *neighbouring group* or *anchimeric* assistance of the SMe group).

* The nucleophilic hydroxyl oxygen of the carboxylic anion, generated by deprotonation of the carboxylic acid, undergoes a *nucleophilic substitution* reaction with the alkyl chloride formed in the previous step (with *anchimeric* assistance of the SMe group) to give the ester product.

Recognise that this is not the final product, but is closely related to it.

Not needed here.

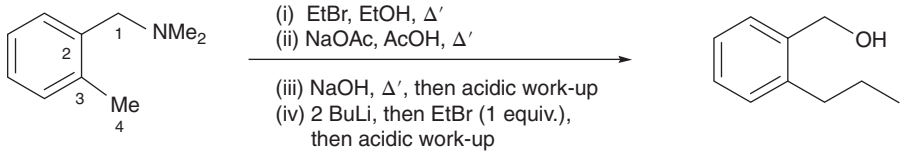
Write down the structure of the final product.



Summary: This is an example of *anchimeric assistance* (also called *neighbouring group participation*) in nucleophilic substitution reactions

Now try questions 1.11 and 1.17

1.4



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Amines are good nucleophiles (the nitrogen has a lone pair). Alkyl bromides are good electrophiles, since bromine is electronegative and bromide is a good leaving group.

Identify the most reactive sites, if more than one exists.

Although an aromatic ring is a possible nucleophile, the most nucleophilic site of this molecule is the dimethylamino group. The most reactive electrophile is ethyl bromide.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alkyl halides readily undergo *nucleophilic substitution* reaction, and in this case; the nucleophile is the dimethylamino function.

Work through the mechanism leading to the intermediate product.

Since bromoethane is a 1° alkyl halide, and amines are good nucleophiles, the reaction will proceed by an S_N2 process, to give a quaternary ammonium salt.

Repeat the above four steps.

* Quaternary ammonium groups are good (neutral) leaving groups, and are easily displaced by the nucleophile acetate, giving in this case an acetate ester.

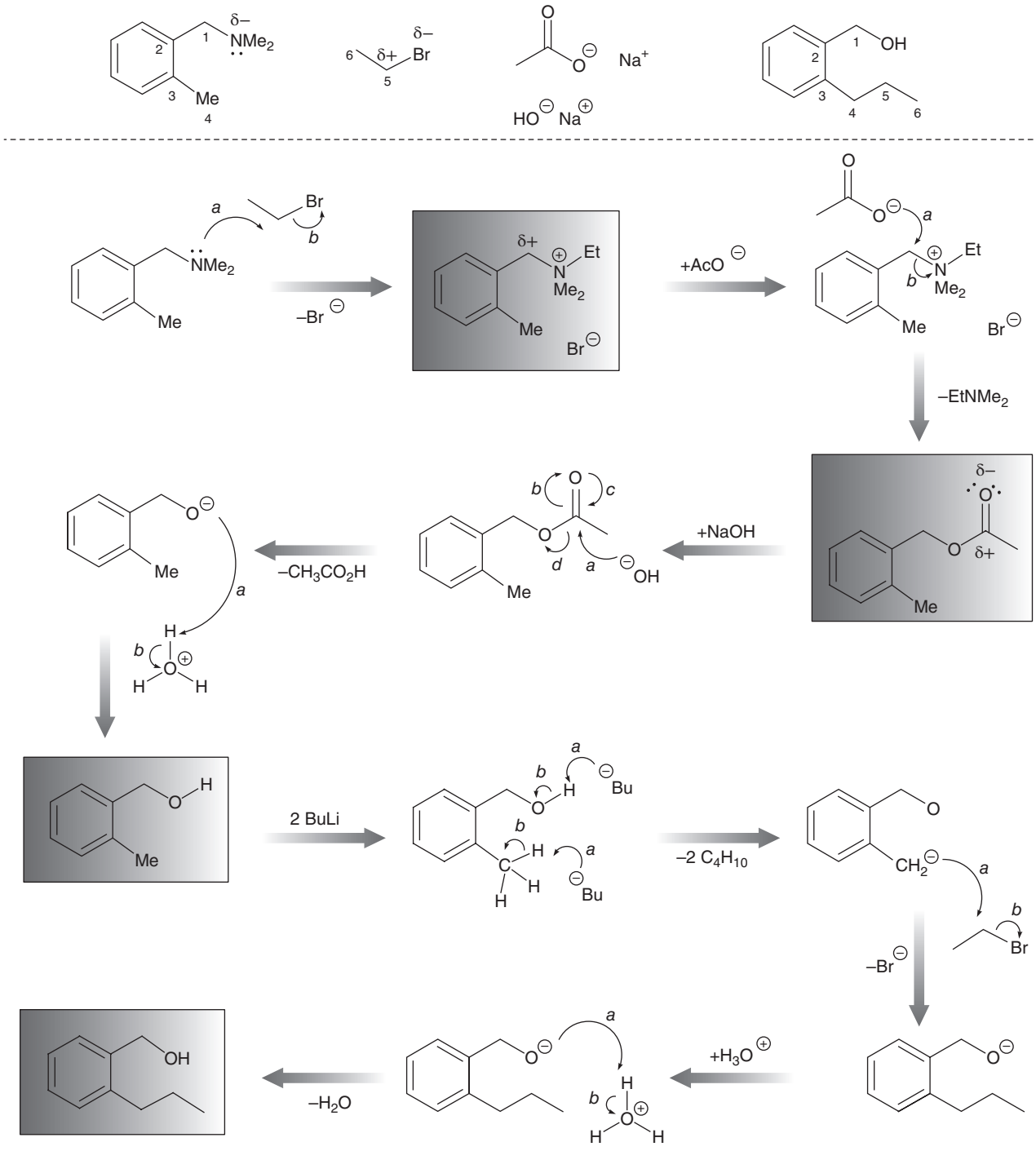
* Esters are easily hydrolysed under alkaline conditions (*addition-elimination mechanism*) to give the alcohol product upon acidic work-up.

* Reaction with butyllithium (a strong base) firstly deprotonates the more acidic alcohol, and only then deprotonates the benzylic methyl group to give a resonance stabilised carbanion; this nucleophilic carbanion is quenched with bromoethane (S_N2 reaction), but only the most reactive benzylic carbon centre reacts with the one equivalent of EtBr.

Recognise that this is not the final product, but is closely related to it.

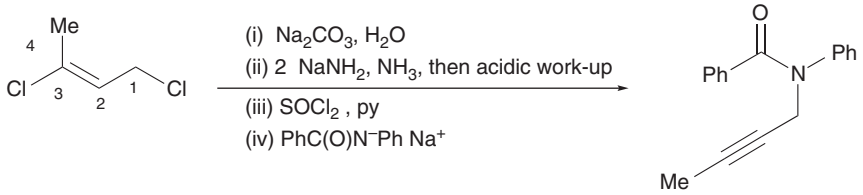
The alkoxide is protonated on acidic work-up to give the alcohol product.

Write down the structure of the final product.



Now try questions 1.12 and 1.18

1.5



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Alkyl chlorides are electrophiles, since chlorine is electronegative and chloride is a good leaving group. Sodium carbonate is a weak base; in aqueous solutions, hydroxide is generated which is a good base as well as a good nucleophile.

Identify the most reactive sites, if more than one exists.

The *allylic* chloride is the most electrophilic site (*vinylic* chlorides have a much stronger C-Cl bond and are not electrophilic). Hydroxide is the only available nucleophile.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Allylic chlorides are very susceptible to*nucleophilic substitution* reactions, which can be either by an S_N1 or S_N2 mechanism, depending on the substrate and solvent.

Work through the mechanism leading to the intermediate product.

Allylic chlorides easily undergo S_N1 reactions in polar solvents, proceeding via the highly *resonance* stabilised allyl cation; this is intercepted by hydroxide, which, after deprotonation, gives the allyl alcohol product.

Repeat the above four steps.

* Sodamide is a strong base; the first equivalent first deprotonates the alcohol function; the second then induces *elimination* of the vinylic chloride to give the alkyne product.

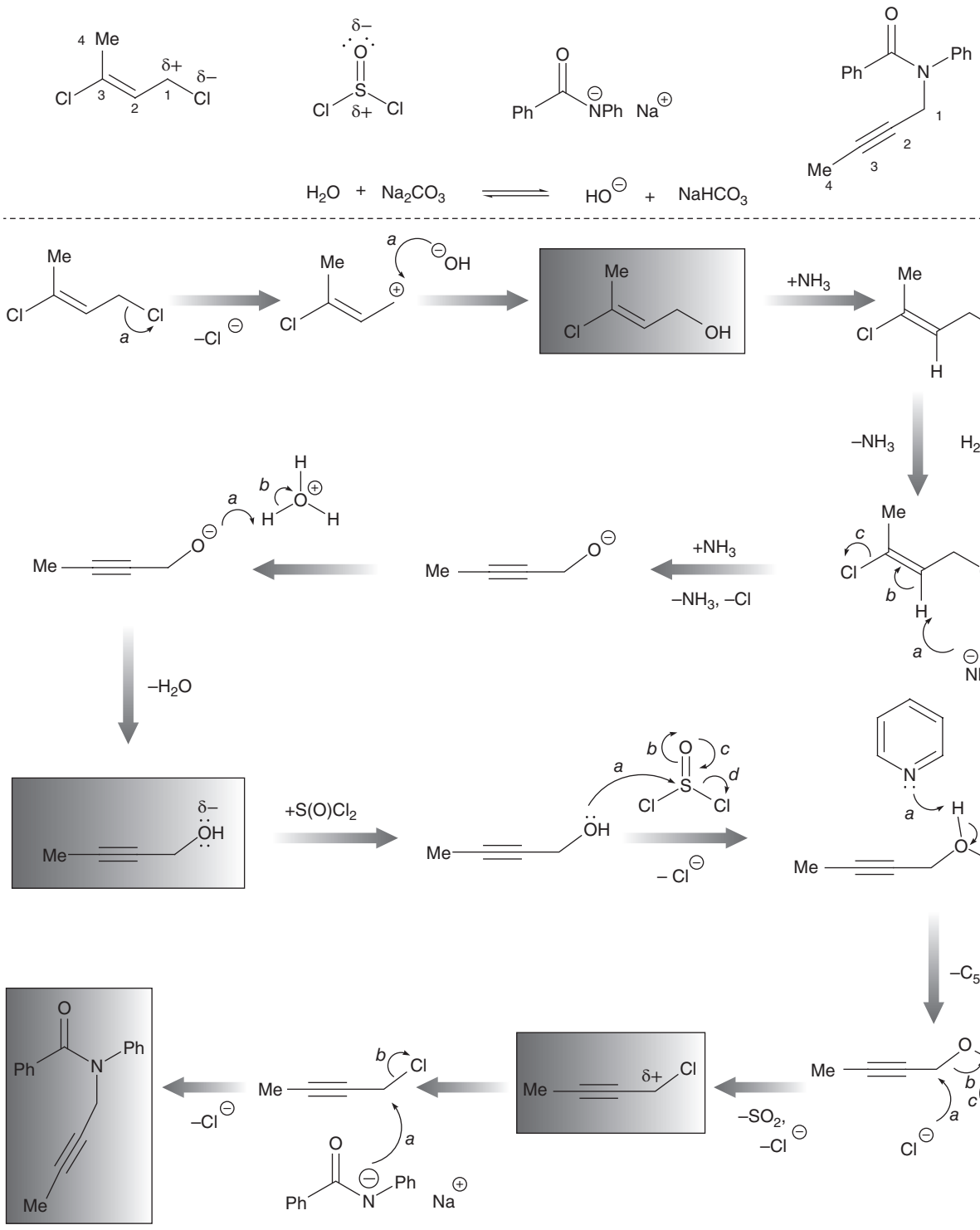
* Thionyl chloride is highly electrophilic, and converts the alcohol to the corresponding propargyl chloride *via* an *addition-elimination* process.

* *Nucleophilic substitution* by the sodium salt of PhC(O)NHPh (N more nucleophilic than O) gives the product directly.

Recognise that this is not the final product, but is closely related to it.

Not needed here.

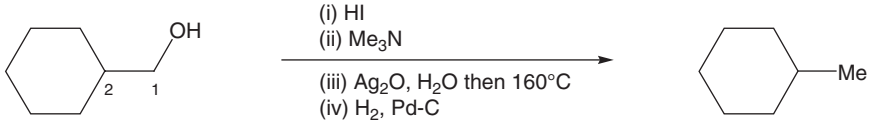
Write down the structure of the final product.



Summary: This question gives more examples of nucleophilic substitution and elimination reactions:

Now try questions 1.13 and 1.19

1.6



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Alcohols are nucleophiles and bases, since the oxygen possesses lone pairs. HI is a strong acid, and fully ionised ($pK_a = -10$).

Identify the most reactive sites, if more than one exists.

The alcohol is the only basic and nucleophilic site in this molecule, and HI the most electrophilic reagent.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alcohols are readily protonated by acids, thereby converting the hydroxyl group into an *oxonium* ion, which is able to depart as water; they therefore readily undergo *nucleophilic substitution* reactions under acidic conditions with suitable nucleophiles.

Work through the mechanism leading to the intermediate product.

The *oxonium* ion is a good leaving group, and is easily displaced by the good nucleophile, iodide, in an S_N2 process (1° substrate, good nucleophile).

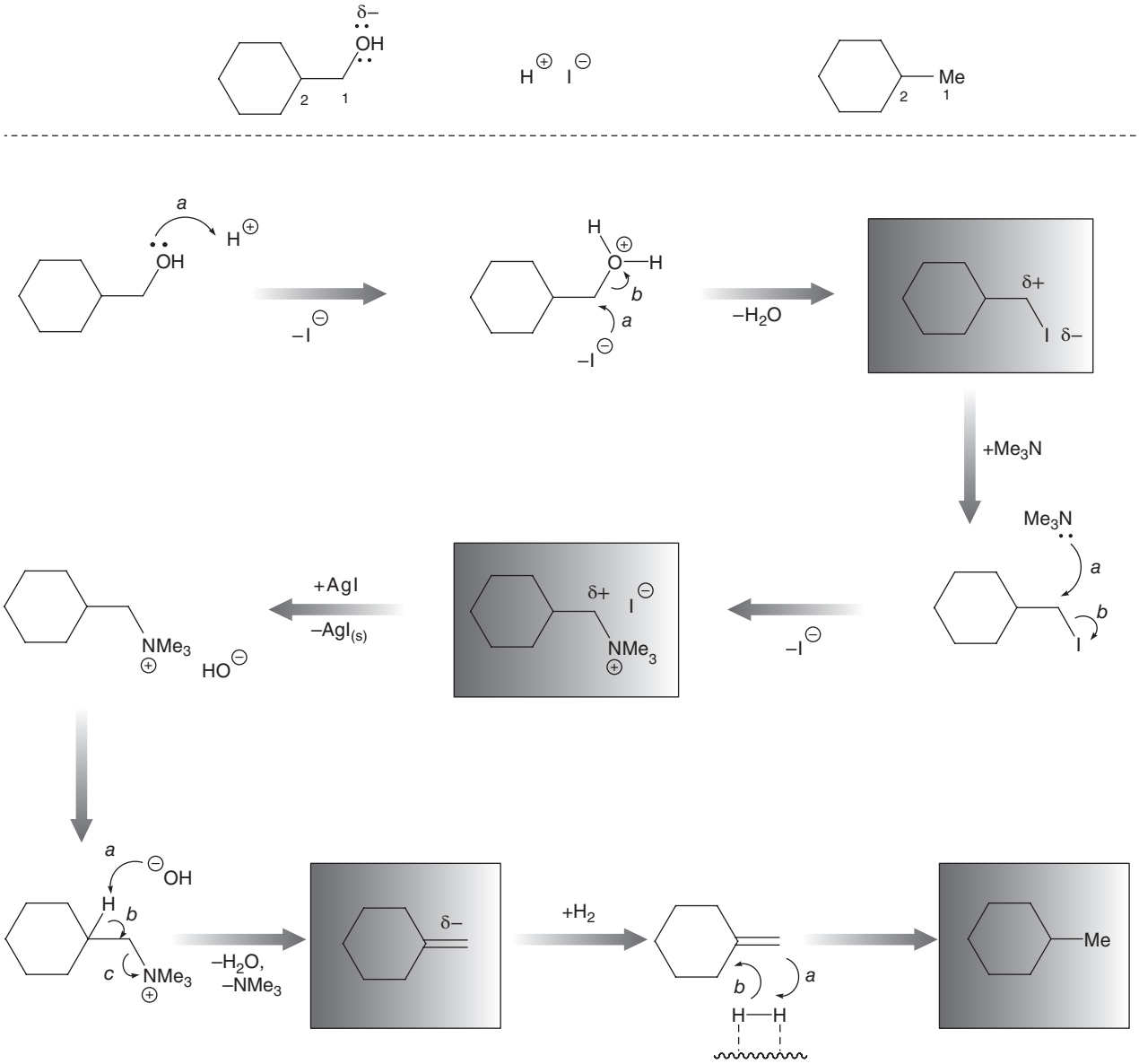
Repeat the above four steps.

* Trimethylamine is a good base and nucleophile. Alkyl iodides are also reactive to S_N2 reactions, and the iodide is easily displaced to give a quaternary ammonium iodide.
* Treatment with silver oxide converts the iodide salt to the hydroxide salt (driven by the precipitation of AgI); heating of this salt causes an *elimination* reaction (*Hofmann elimination*) to give the corresponding alkene.
* Hydrogenation of the alkene using Pd supported on charcoal as catalyst gives the alkane (*syn*- addition of H_2).

Recognise that this is not the final product, but is closely related to it.

Not needed here.

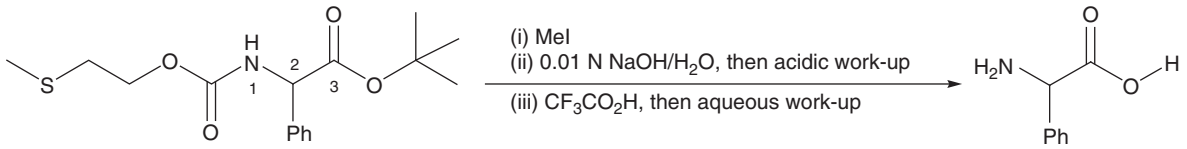
Write down the structure of the final product.



Summary: This is an example of the Hofmann elimination reaction of quaternary ammonium iodides:

Now try questions 1.14 and 1.20

1.7



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Sulfur, oxygen and nitrogen are all nucleophilic, since all possess lone pairs. Methyl iodide is a good electrophile, since iodine is electronegative and iodide is a good leaving group.

Identify the most reactive sites, if more than one exists.

Sulfur is the most nucleophilic heteroatom, since it is the least electronegative of O, N and S. Methyl iodide is the most reactive electrophile.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alkyl halides readily undergo *nucleophilic substitution* reactions, the nucleophile in this case being the sulfur atom.

Work through the mechanism leading to the intermediate product.

The nucleophilic sulfur undergoes a *nucleophilic substitution* reaction with methyl iodide (S_N2) to generate a *sulfonium* cation.

Repeat the above four steps.

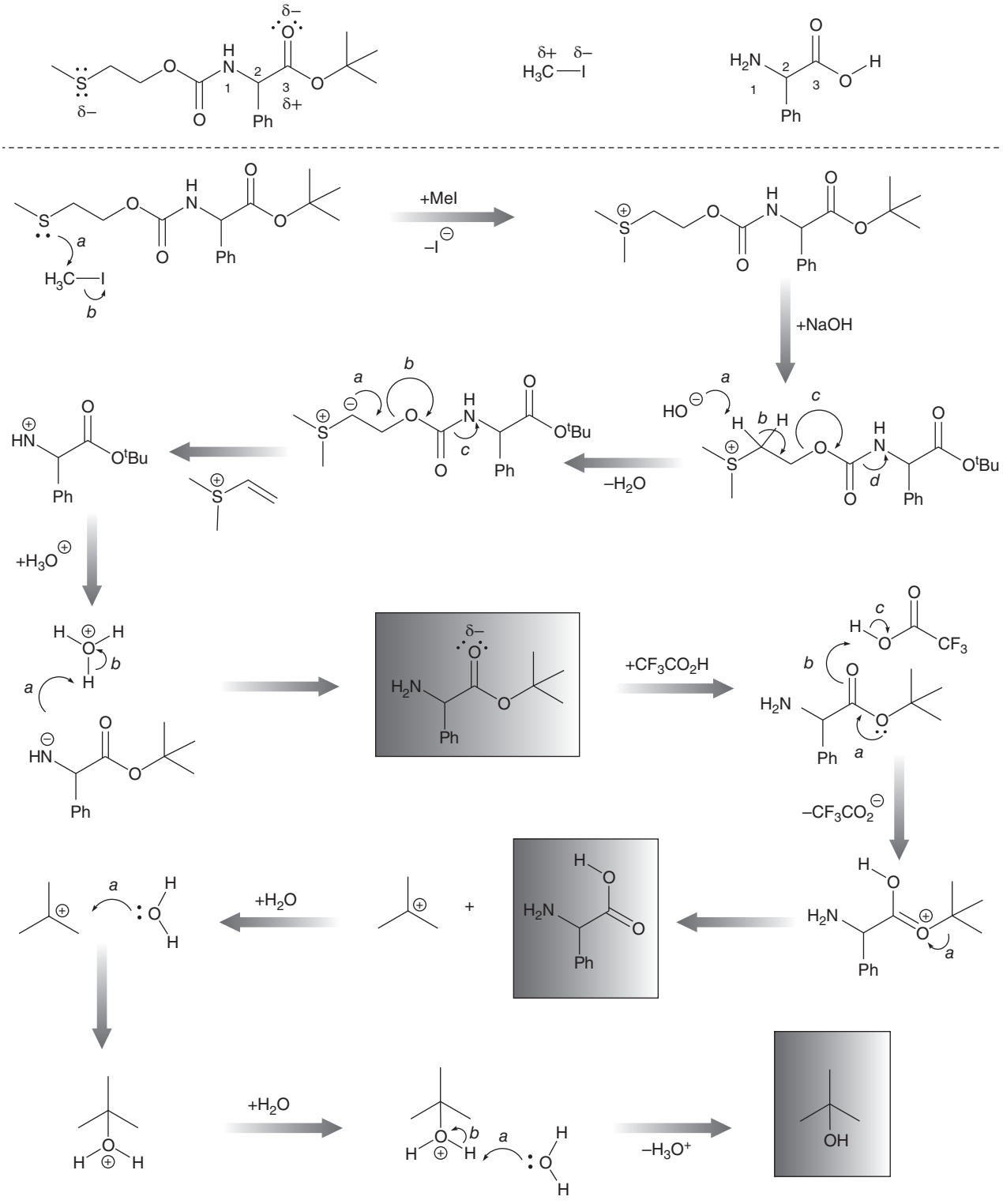
* The α-protons of the sulfonium cation are very acidic (highly stabilised conjugate base), and only weak base is required for deprotonation; this induces an *elimination* (E1CB) reaction.

* Esters can be protonated on the carbonyl oxygen by strong acids (e.g. CF_3CO_2H); the ester alkyl group departs in an E_1 process, to give the amino acid product and a *t*-butyl cation. The cation is intercepted by water, to give an *oxonium* cation.

Recognise that this is not the final product, but is closely related to it.

Deprotonation of the *oxonium* cation on work-up gives the product, *t*-butyl alcohol.

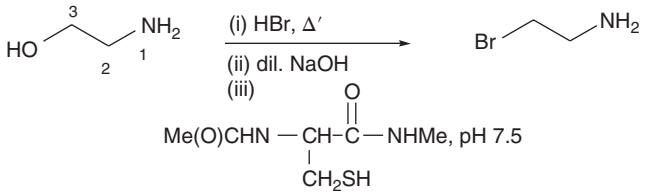
Write down the structure of the final product.



Summary: This is an example of a base catalysed β-elimination and acid-catalysed ester hydrolysis.

Now try questions 1.15, 1.21 and 1.9

1.8



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Amines and alcohols are both basic, since they both possess non-bonded electron pairs. HBr is a strong acid, and fully ionised ($pK_a = -8$).

Identify the most reactive sites, if more than one exists.

Although amines and alcohols are both basic, amines are more so (nitrogen is less electronegative than oxygen). HBr is the strongest acid present.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Amines are easily protonated by hydrogen bromide, but so too are alcohols.

Work through the mechanism leading to the intermediate product.

The amine function is initially protonated by the hydrogen bromide. Protonation of the amine generates bromide anion.

Repeat the above four steps.

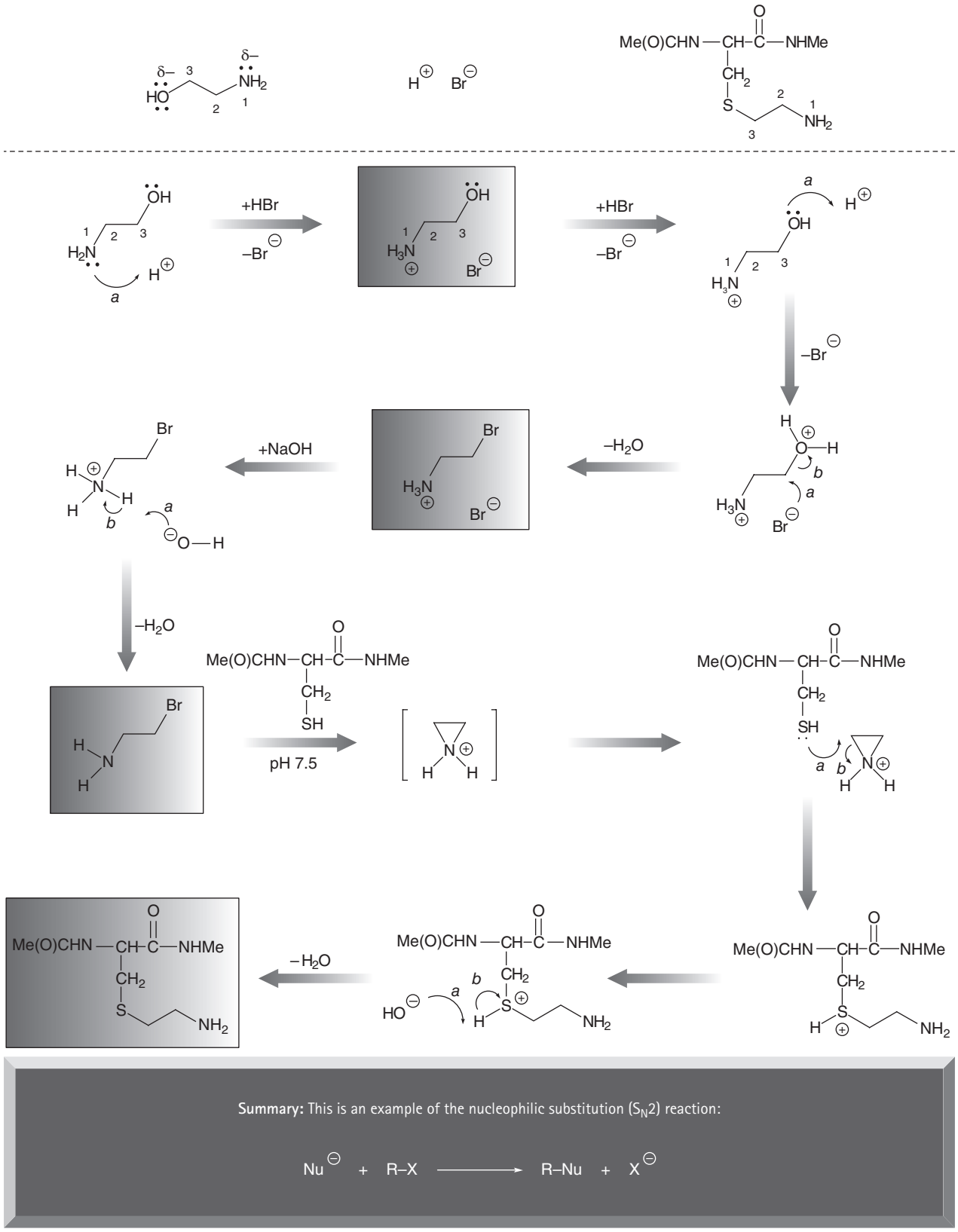
* HBr is a strong acid, easily capable of protonating the remaining alcohol. This converts the alcohol into an excellent hydroxonium leaving group, which can depart as water, if a suitable nucleophile attacks, which in this case would be bromide anion. Deprotonation on basic work-up generates the amine product.

* Reaction with a cysteine derivative occurs by attack of the most nucleophilic sulfur atom on the bromide (with *anchimeric* assistance of the NH_2 group) to give the protonated form of the thioether product.

Recognise that this is not the final product, but is closely related to it.

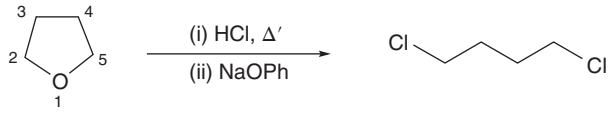
Deprotonation on work-up generates the thioether product.

Write down the structure of the final product.



Now try question 1.9

1.9



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Ethers have oxygen nucleophiles, since the oxygen possesses lone pairs, and HCl is a strong acid and fully ionised ($pK_a = -7$).

Identify the most reactive sites, if more than one exists.

The ether function is the only reactive group in this molecule, and HCl is the strongest acid.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Ethers are generally unreactive to most reagents, but may be cleaved by strong acids like HCl, to generate alkyl halides.

Work through the mechanism leading to the intermediate product.

The ether function can be protonated by the HCl, to generate an oxonium cation. This cation provides an excellent leaving group (water), which may be displaced by the weak nucleophile, chloride anion. This generates an alkyl halide product.

Repeat the above four steps.

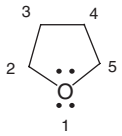
* The alchoholic group simultaneously generated may react as before; protonation by the strong acid HCl gives the corresponding oxonium ion. This oxonium cation provides an excellent leaving group, which may be displaced by the weak nucleophile, chloride anion. This generates an alkyl halide product, and the dichloro product is thus formed.

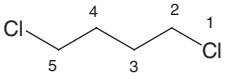
* Reaction of the dichloride with sodium phenoxide gives the product from double displacement of halogen by nucleophilic substitution.

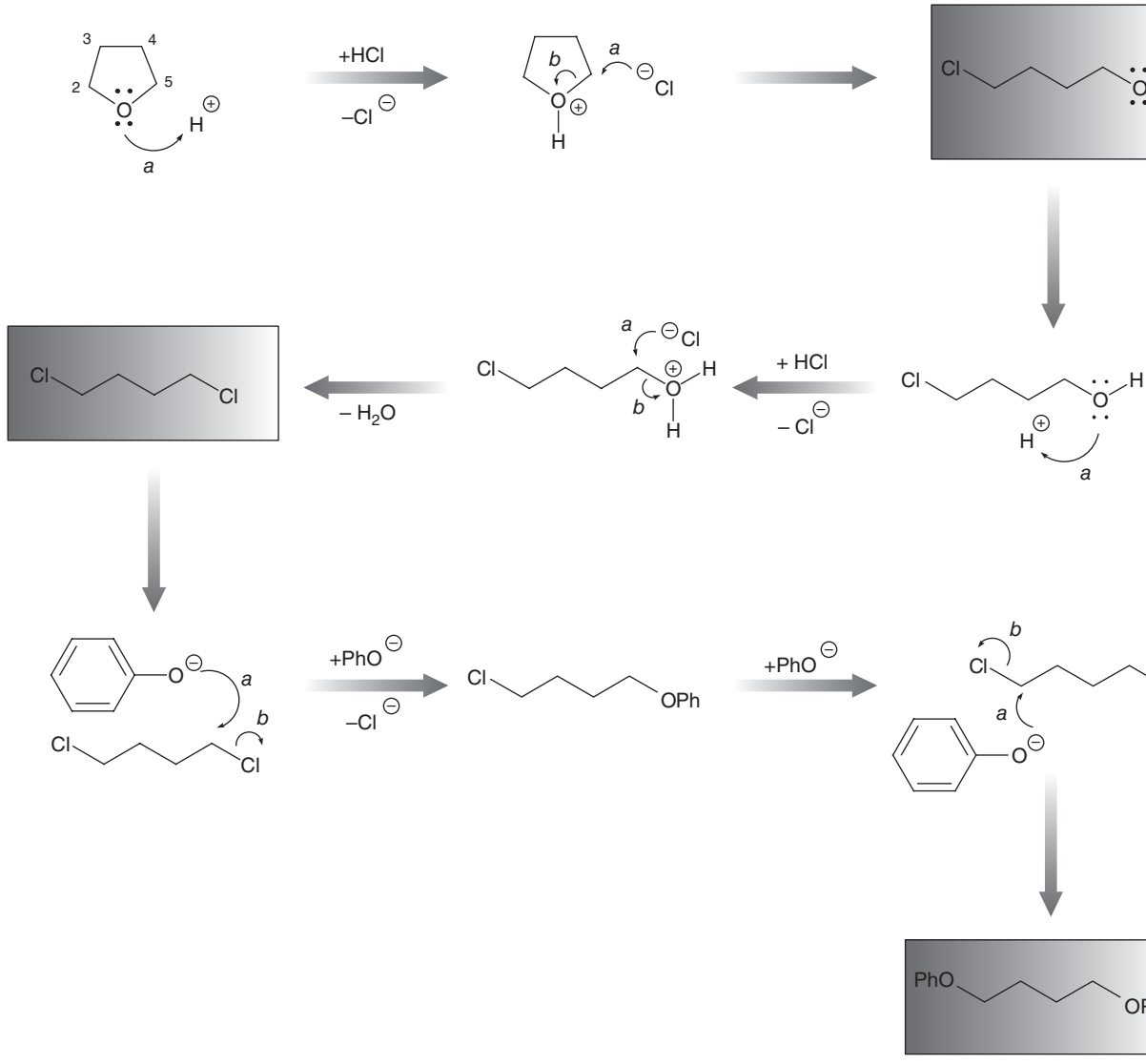
Recognise that this is not the final product, but is closely related to it.

Not needed here.

Write down the structure of the final product.

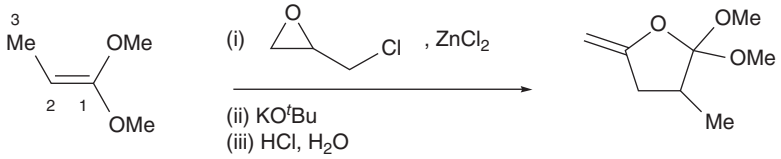






Summary: This question involves several examples of nucleophilic substitution (SN2) reactions:

1.10



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Alkenes are good nucleophiles. Alkyl chlorides are electrophiles, since chlorine is electronegative and chloride is a good leaving group. Epoxides are also electrophiles, since oxygen is electronegative and can be a good leaving group. Zinc chloride is an excellent Lewis acid. Potassium *t*-butoxide is a strong base.

Identify the most reactive sites, if more than one exists.

Once activated by the Lewis acid, the epoxide is the most electrophilic site.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Epoxides are very susceptible to *nucleophilic substitution* reactions, especially when activated by Lewis acids. Under these circumstances, the alkyl chloride is the less reactive group. Alkenes are weak nucleophiles.

Work through the mechanism leading to the intermediate product.

The zinc cation co-ordinates to the epoxide, and this group is then attacked by the alkene. This attack is promoted by the presence two methoxy groups which activate the alkene, leading to the formation of an *oxonium cation*. Ring closure of the released alkoxide onto this oxonium cation generates the ring closed product.

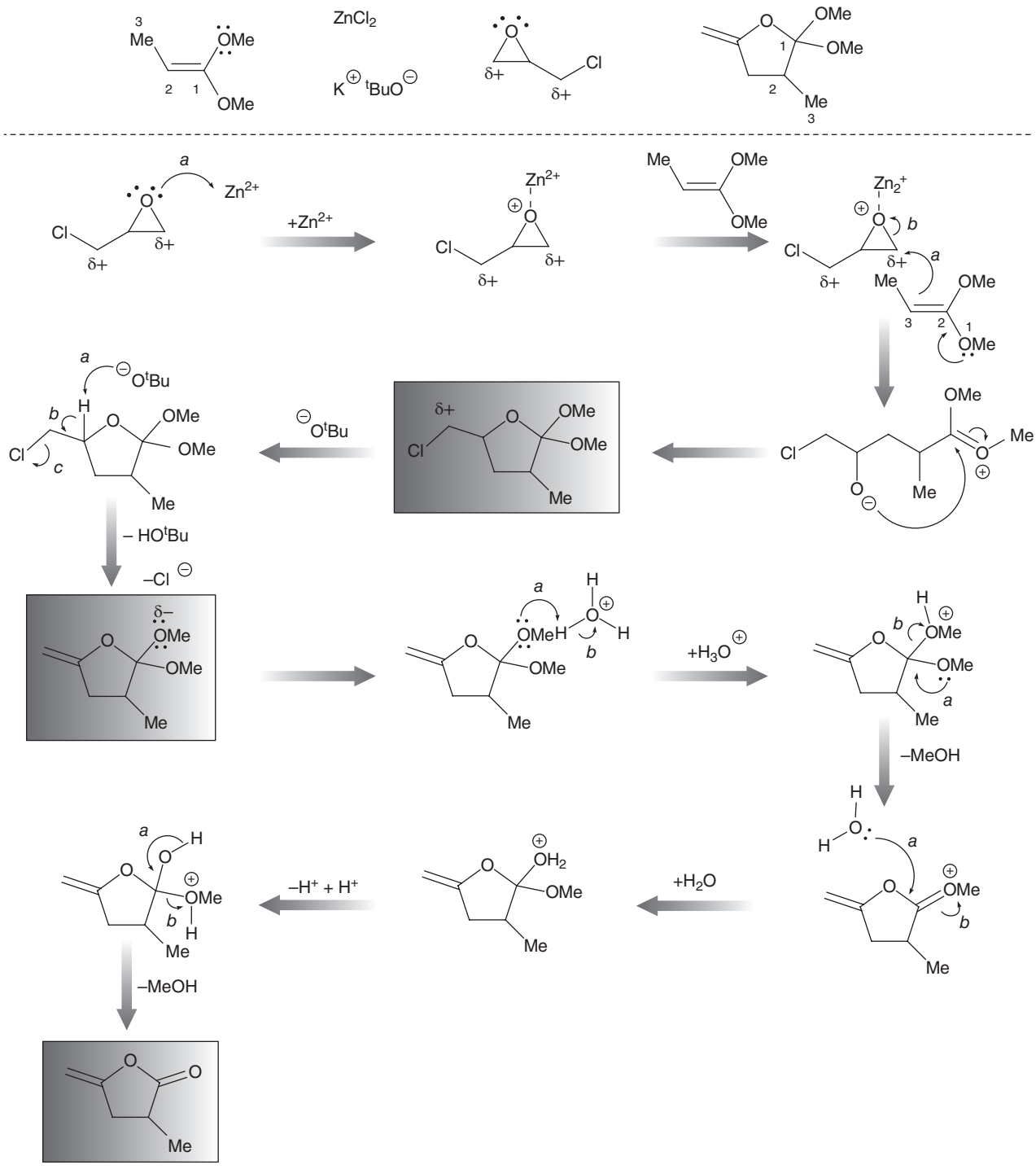
Repeat the above four steps.

* Potassium *t*-butoxide is a strong base; this induces *elimination* of the alkyl chloride to give the alkene product. This is most likely to proceed by an E_2 mechanism.
* Under aqueous acidic conditions, the acetal is readily *hydrolysed*, by the usual protonation–elimination–addition of water-elimination sequence for acetal hydrolysis.

Recognise that this is not the final product, but is closely related to it.

Not needed here.

Write down the structure of the final product.

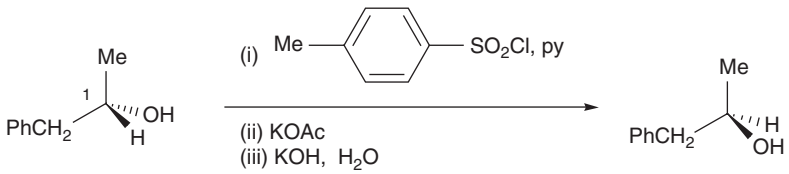


Summary: This question involves nucleophilic substitution and elimination reactions:

$$Nu^{\ominus} + R\text{-}X \longrightarrow R\text{-}Nu + X^{\ominus}$$

Now try question 1.16

1.11



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Alcohols are good nucleophiles (oxygen possesses lone pairs). *p*-TsCl is an acid chloride derived from a sulfonic acid, and is electrophilic due to the electronegative oxygen atoms with a chloride being a good leaving group. Potassium acetate is a weak base and good nucleophile.

Identify the most reactive sites, if more than one exists.

The alcohol is the only nucleophilic site, tosyl chloride is the only electrophile. Pyridine is a base.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alcohols are easily converted to esters by acid chlorides, in this case a sulfonyl chloride.

Work through the mechanism leading to the intermediate product.

The alcohol undergoes a *nucleophilic addition-elimination* reaction at the sulfonic acid group, with loss of chloride; this generates a protonated sulfonate ester. Deprotonation by pyridine generates the product.

Repeat the above four steps.

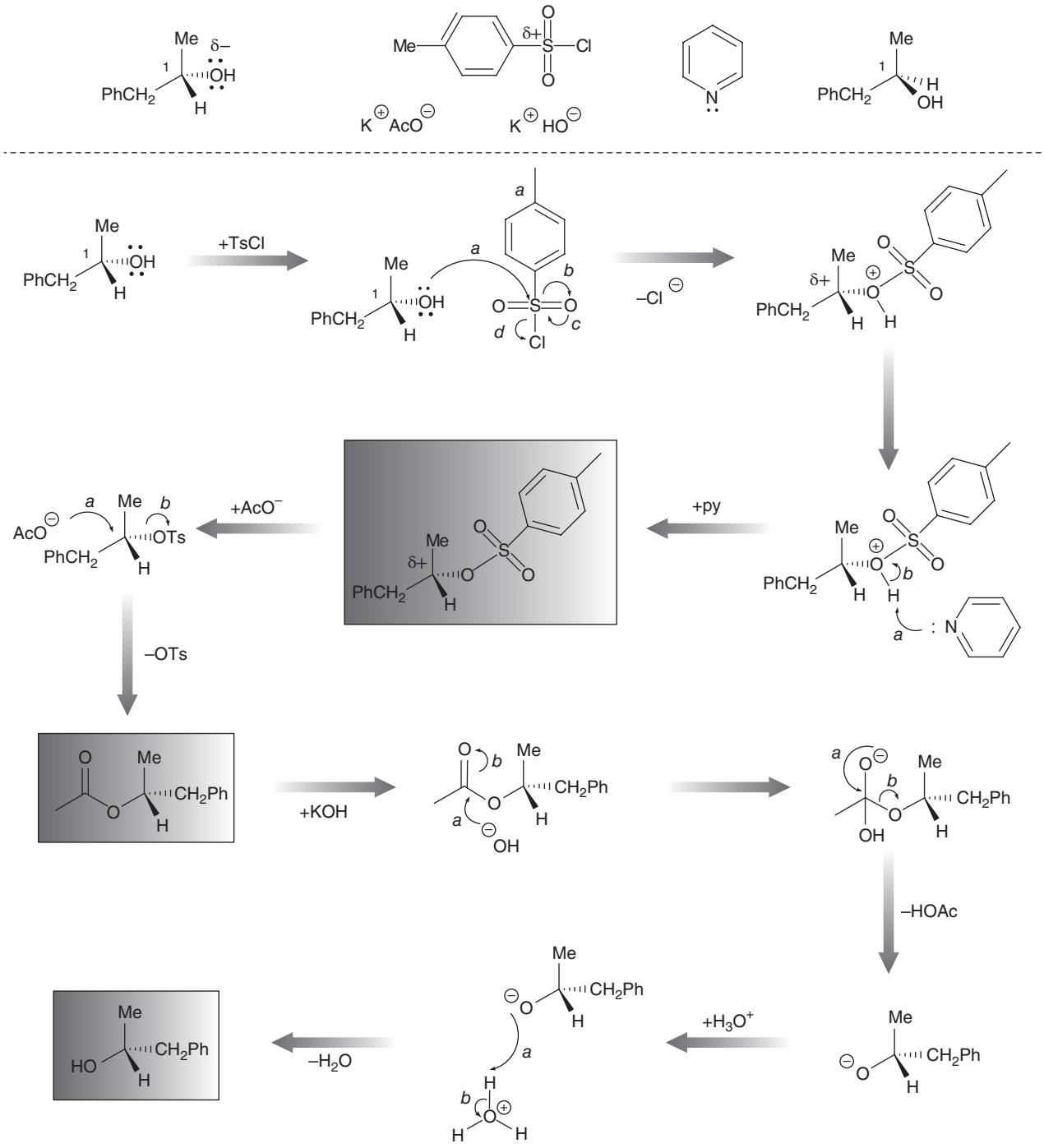
* The tosylate group is an excellent leaving group, and this system is especially activated towards S_N2 reactions by attack from the weak nucleophile, acetate. Such reaction leads to displacement of the tosylate giving an ester product but with stereochemical *inversion*.

* Hydroxide is highly nucleophilic, and hydrolyses the ester; this converts the ester to the alcoholate anion via an *addition-elimination* process.

Recognise that this is not the final product, but is closely related to it.

The basic conditions of this reaction gives an alcoholate product, which is reprotonated on acidic work-up.

Write down the structure of the final product.

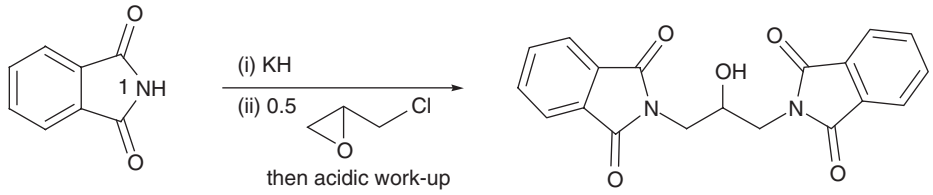


Summary: This question involves several examples of nucleophilic substitution (S_N2) reactions:

$$Nu^{\ominus} + R\text{-}X \longrightarrow R\text{-}Nu + X^{\ominus}$$

Now try question 1.17

1.12



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Phthalimide is acidic, and potassium hydride is a strong base. The epoxide has two electrophilic sites, at the less hindered end of the epoxide, and at the chloride-bearing carbon.

Identify the most reactive sites, if more than one exists.

The chloride is the most electrophilic site, and the N–H is the only acidic bond present.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alkyl chlorides are electrophiles and are very susceptible to *nucleophilic substitution* reactions, which can be either by an S_N1 or S_N2 mechanism, depending on the substrate and solvent.

Work through the mechanism leading to the intermediate product.

Phthalimide is easily deprotonated by potassium hydride, to give the corresponding anion. Alkyl chlorides easily undergo S_N2 reactions with good nucleophiles, such as the phthalimide anion, and give the amine product.

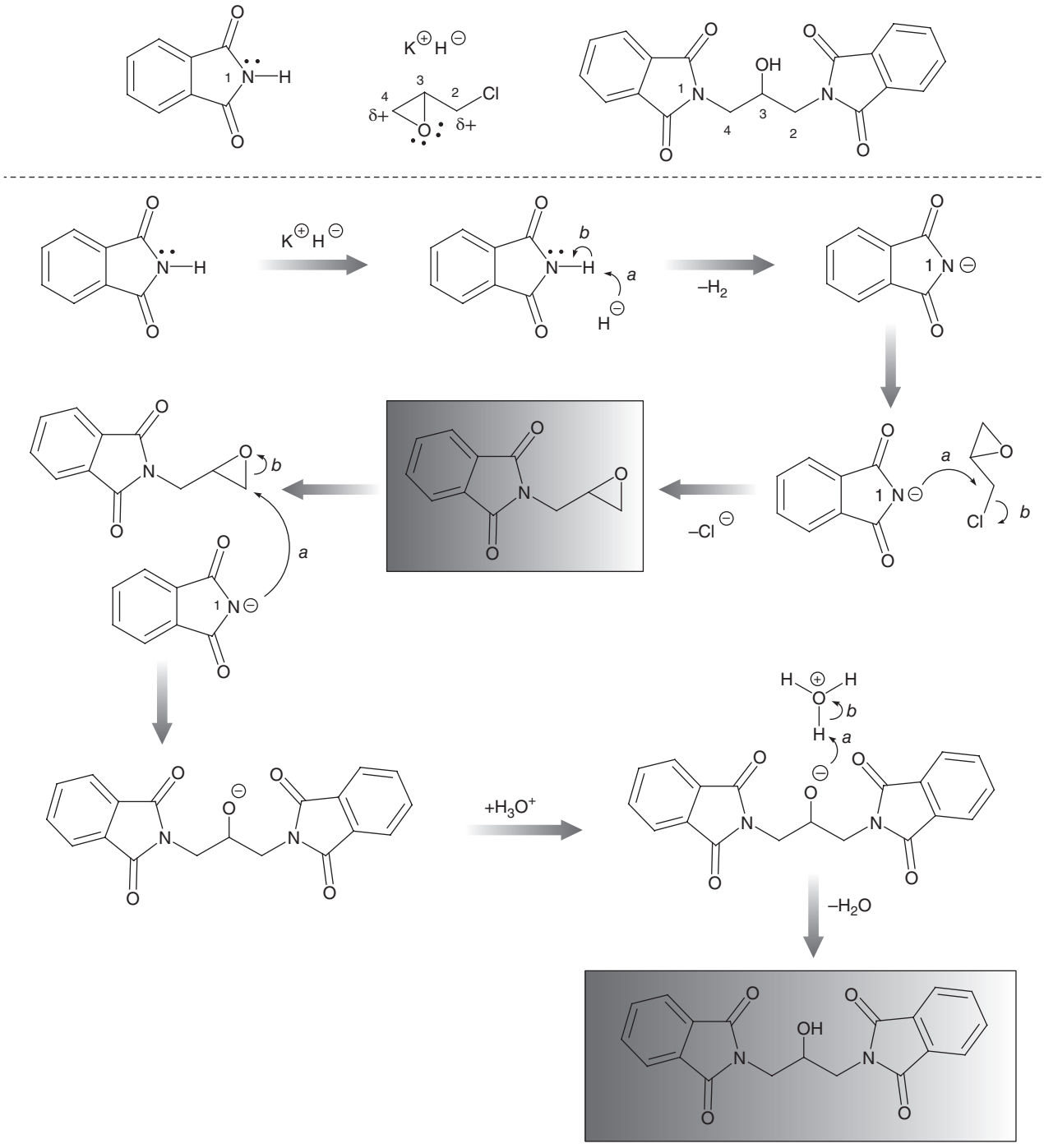
Repeat the above four steps.

Phthalimide anion is a strong nucleophile, and reacts further to open the epoxide at the least hindered end, to give an alkoxide product.

Recognise that this is not the final product, but is closely related to it.

The alkoxide product is protonated on acidic work-up to give the final product.

Write down the structure of the final product.

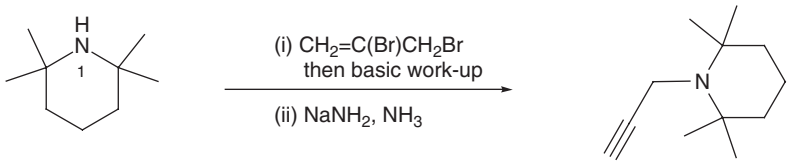


Summary: This question involves several examples of nucleophilic substitution (S_N2) reactions:

$$Nu^{\ominus} + R\text{-}X \longrightarrow R\text{-}Nu + X^{\ominus}$$

Now try questions 1.18

1.13



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Allyl bromides are excellent electrophiles, since bromine is electronegative and bromide is a good leaving group. Amines are weak bases and good nucleophiles. Sodamide is an excellent base.

Identify the most reactive sites, if more than one exists.

The *allylic* bromide is the most electrophilic site (*vinylic* bromides have a much stronger C-Br bond) and the amine is the only nucleophile present.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Allylic bromides are very susceptible to *nucleophilic substitution* reactions, which can be either by an S_N1 or S_N2 mechanism, depending on the solvent.

Work through the mechanism leading to the intermediate product.

Allylic bromides easily undergo nucleophilic substitution reactions, even with weak amine nucleophiles; the initially formed product is depronated on work-up, to give the allylic amine product.

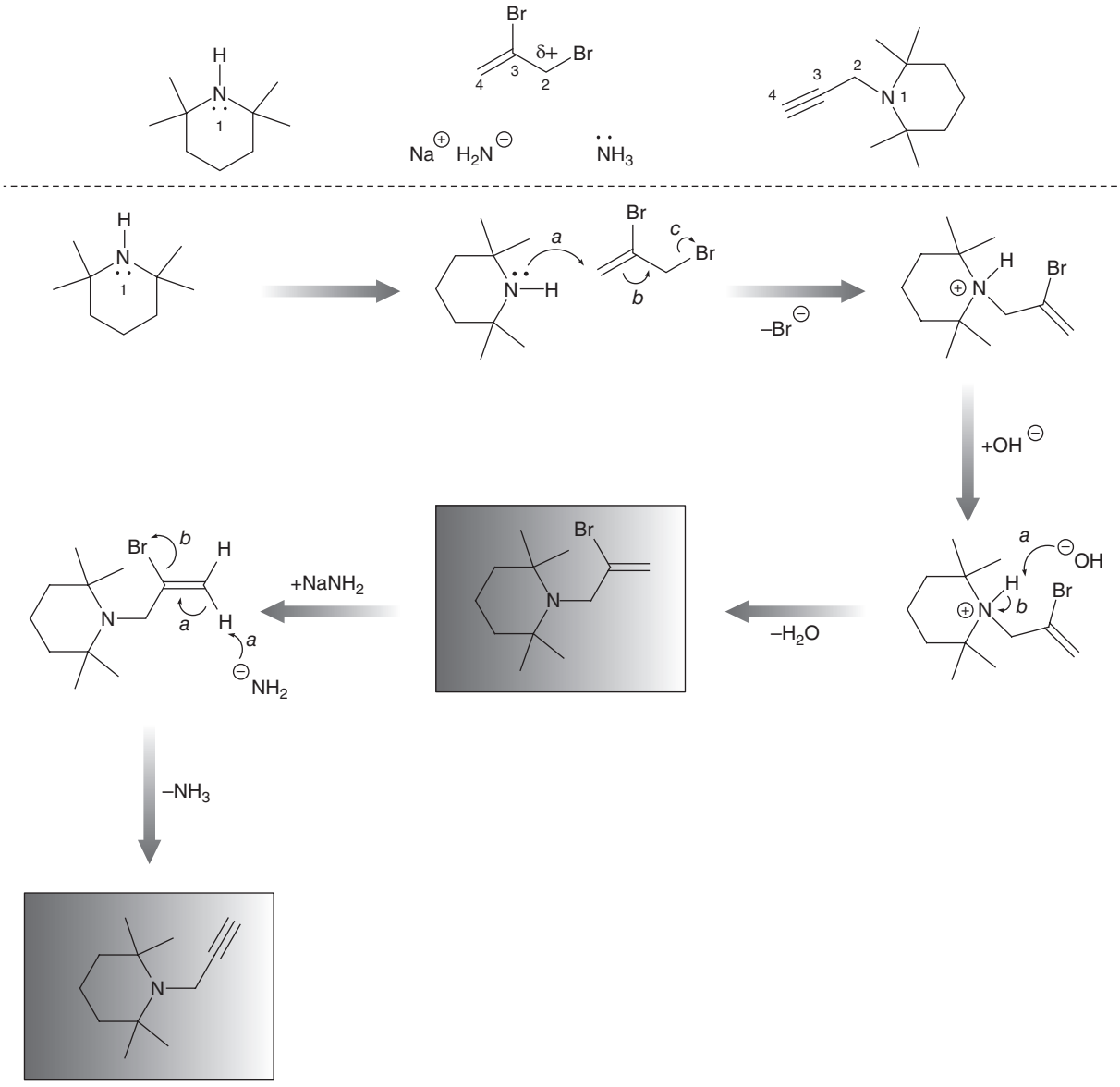
Repeat the above four steps.

Sodamide is a strong base; it induces *elimination* of the vinylic chloride to give the alkyne product.

Recognise that this is not the final product, but is closely related to it.

Not needed here.

Write down the structure of the final product.

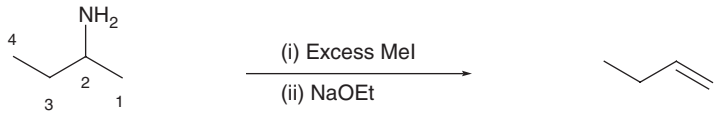


Summary: This question involves examples of nucleophilic substitution (S_N2) and elimination (E2) reactions:

$$Nu^{\ominus} + R\text{-}X \longrightarrow R\text{-}Nu + X^{\ominus}$$

Now try questions 1.19

1.14



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Alkyl iodides are electrophiles, since iodine is electronegative and iodide is a good leaving group. Amines are good nucleophiles, since the nitrogen possesses a lone pair. Sodium ethoxide is an excellent base.

Identify the most reactive sites, if more than one exists.

The alkyl iodide is the only electrophilic site and the amine the only nucleophilic site.

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Alkyl iodides are very susceptible to *nucleophilic substitution* reactions, which can be either by an S_N1 or S_N2 mechanism, depending on the substrate.

Work through the mechanism leading to the intermediate product.

Methyl iodide easily undergoes S_N2 reactions since it is very unhindered; amines are weak nucleophiles, and reaction gives the ammonium intermediate which is deprotonated to give the methylamine product.

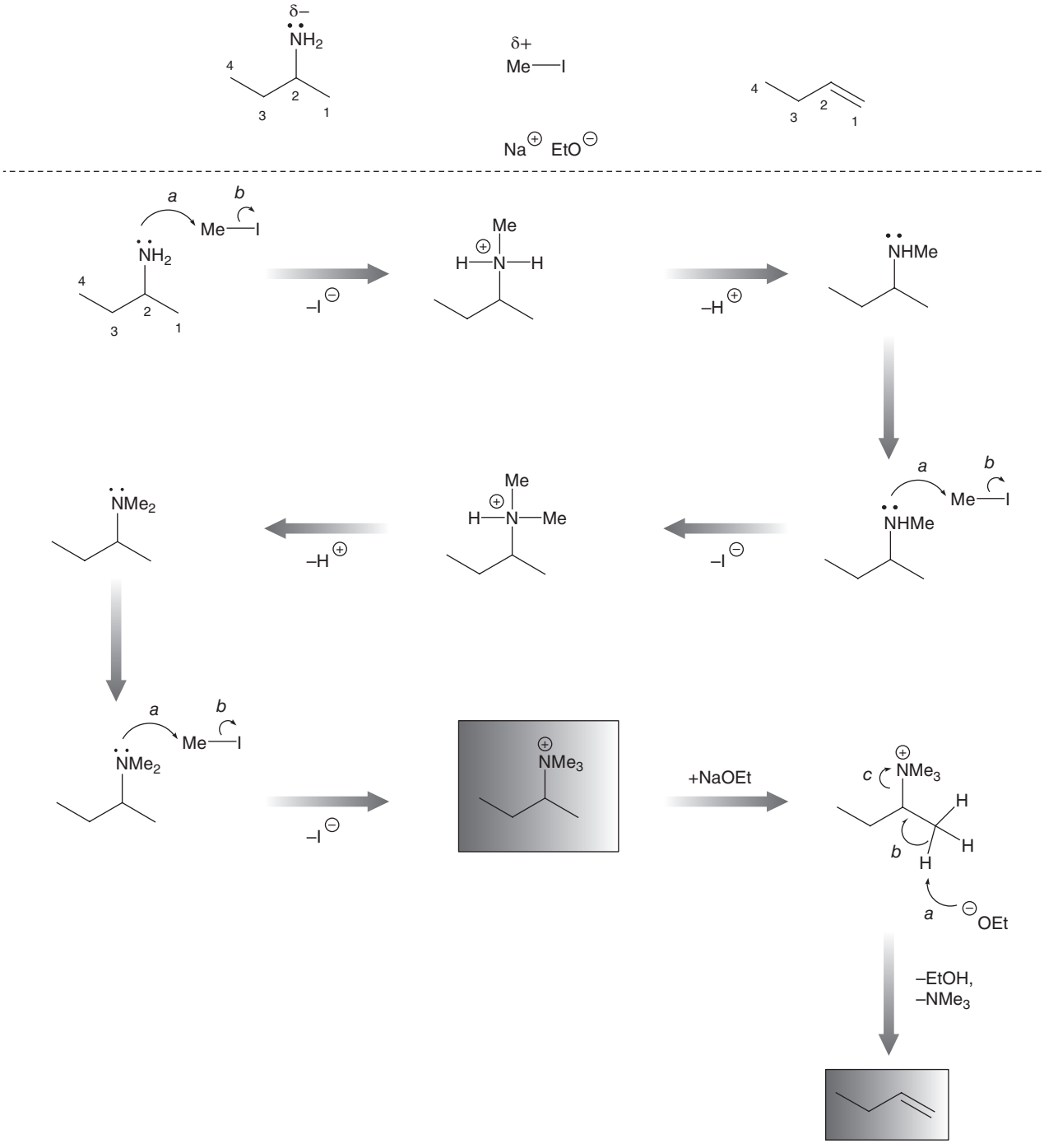
Repeat the above four steps.

* This methylamine product is a weak base and good nucleophile, better in fact than the starting material as a result of inductive electron release of the N substituents; the alkylation reaction therefore repeats to give the dimethylamine.
* This dimethylamine product is an even better nucleophile; the alkylation reaction therefore repeats to give the trimethylammonium product. This is called *exhaustive* methylation.
* Sodium ethoxide then induces *elimination* of the trimethylammonium groups to give the alkene product, in a reaction which is controlled kinetically, to give the less substituted alkene (*Hofmann* elimination).

Recognise that this is not the final product, but is closely related to it.

Not needed here.

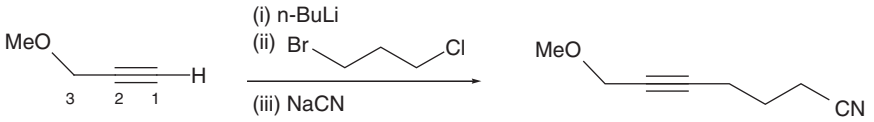
Write down the structure of the final product.



Summary: This is an example of the quarternisation of an amine followed by Hofmann elimination reaction:

Now try question 1.20

1.15



Label electrophilic/nucleophilic and acidic/basic sites of all reactants, and number identical atoms in the starting material and product.

Acetylenes are weakly acidic. *n*-BuLi is a excellent base. Alkyl chlorides and bromides are electrophiles, since chlorine and bromine are electronegative and both are good leaving groups. Sodium cyanide is a good nucleophile.

Identify the most reactive sites, if more than one exists.

The acetylenic hydrogen is the most acidic site, and alkyl bromides are more reactive to nucleophilic attack than alkyl chlorides (bromide is a better leaving group).

Recall the characteristic reactions of the most reactive functional groups; and by considering the reaction conditions, decide which is the most appropriate.

Acetylide anions are easily alkylated at the triple bond. Alkyl halides are very susceptible to *nucleophilic substitution* reactions, which can be either by an S_N1 or S_N2 mechanism, depending on the substrate and solvent.

Work through the mechanism leading to the intermediate product.

n-BuLi is a strong base; it first deprotonates the acetylenic function to give an acetylide anion. Alkyl bromides easily undergo S_N2 reactions, especially with good nucleophiles such as a carbanion.

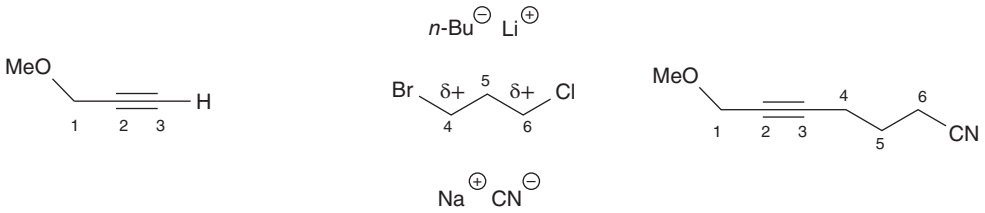
Repeat the above four steps.

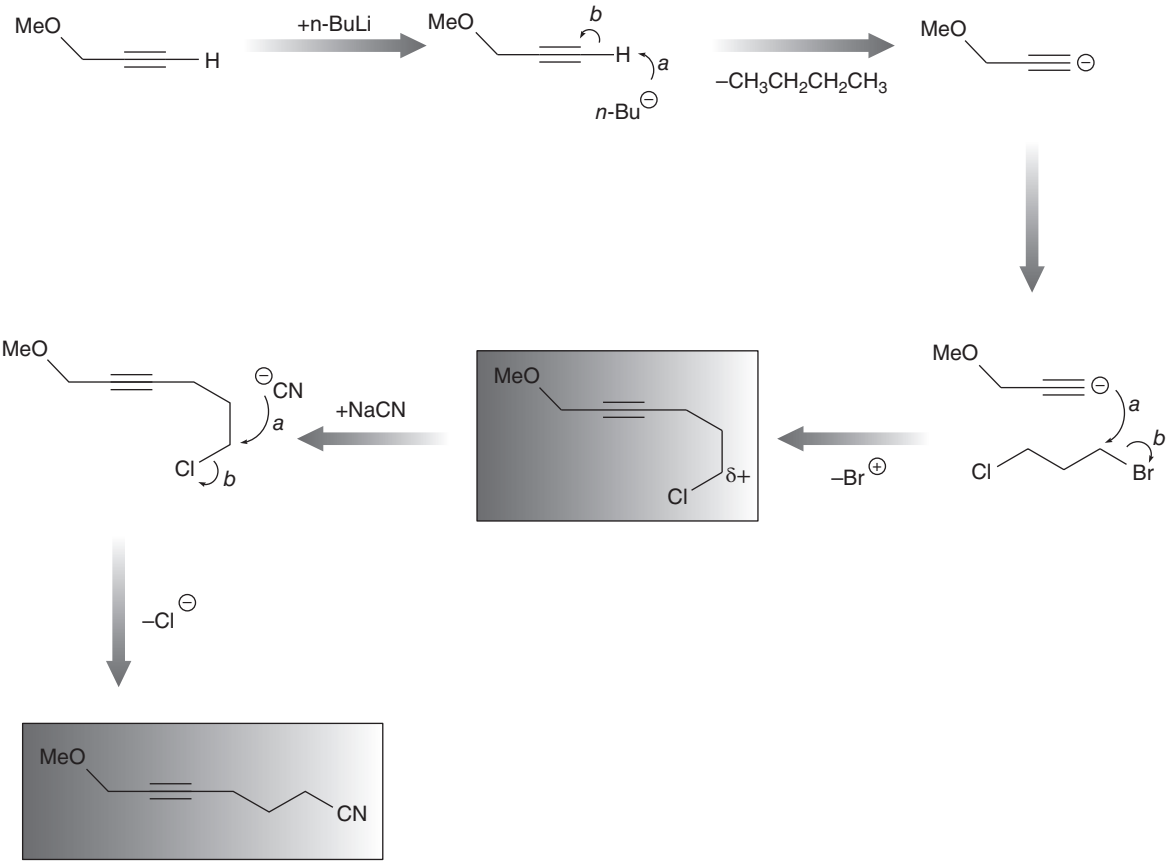
Alkyl chlorides easily undergo S_N2 reactions, especially with good nucleophiles such as cyanide.

Recognise that this is not the final product, but is closely related to it.

Not needed here.

Write down the structure of the final product.





Summary: This question involves several examples of nucleophilic substitution (S_N2) reactions:

$$Nu^{\ominus} + R\text{-}X \longrightarrow R\text{-}Nu + X^{\ominus}$$

Now try questions 1.21 and 1.22