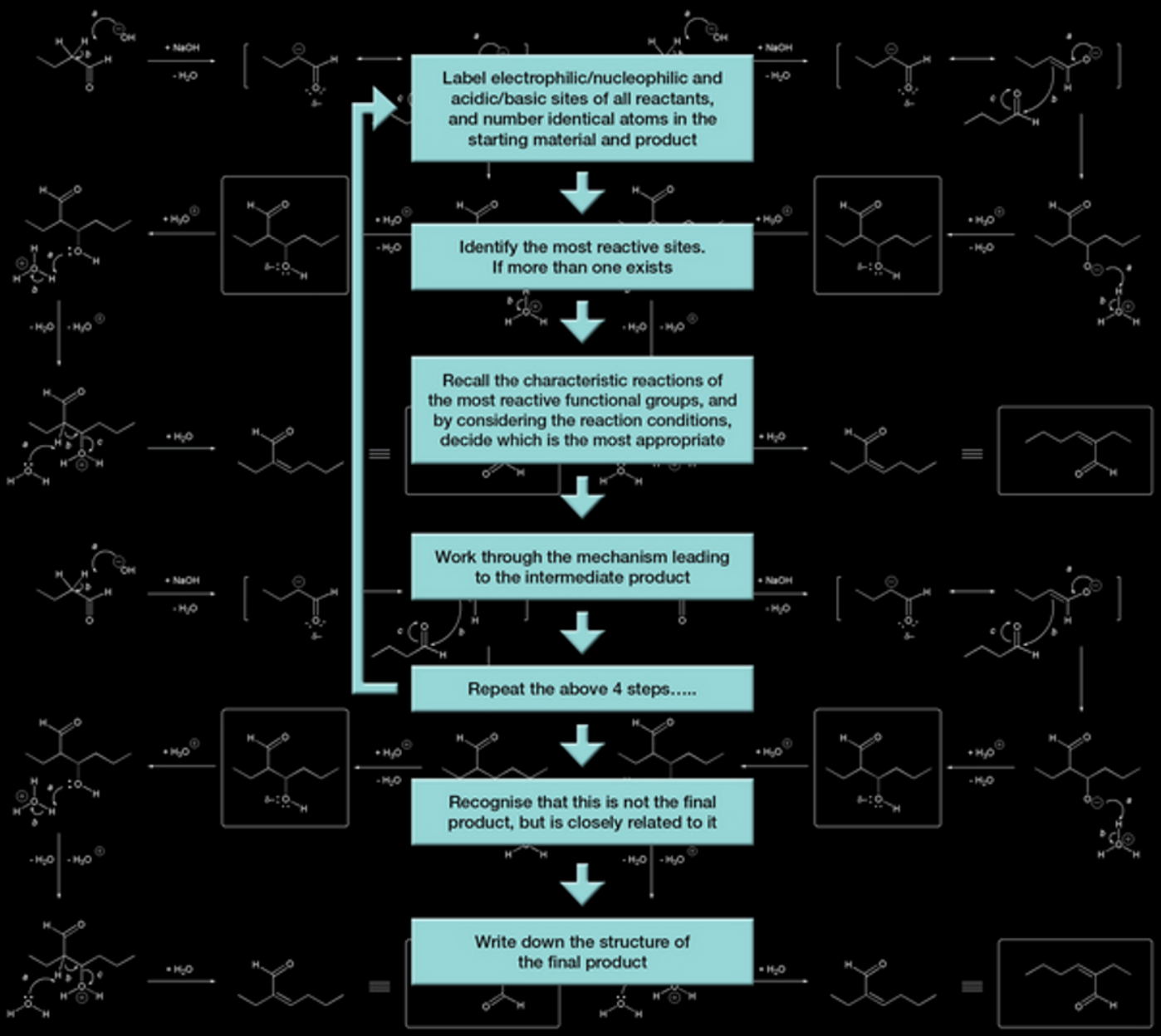
How To Solve Organic Reaction Mechanisms

A Stepwise Approach

MARK G. MOLONEY



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A Stepwise Approach

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Preface

This book is an upgraded version of *Reaction Mechanisms at a Glance*, first published in 2000. That book was an attempt to demonstrate that there is indeed an underlying set of rules suitable to working out plausible reaction mechanisms in organic chemistry and which can be grasped with a little effort. More importantly, the use of these rules in a systematic fashion substantially reduces the burden on memory! This version has an expanded set of fully worked problems and a new chapter which applies the problem-solving strategy to ligand-coupling reactions using transition metals. The latter is an addition which represents the exceptional growth and importance of this chemistry, and its widespread application in diverse areas of chemical science.

I would like to dedicate this book to my wife Julie and all the members of my family.

Mark Moloney
2014

Abbreviations

Ac	Acetyl ($CH_3C(O)$-)
cat.	catalytic
Δ	Heat
DMF	*N*,*N*-Dimethylformamide (Me_2NCHO)
MCPBA	meta-chloroperbenzoic acid
PPA	Polyphosphoric acid
THF	Tetrahydrofuran
p-TsCl	*p*-Toluenesulfonyl chloride (*p*-$MeC_6H_4SO_2Cl$)
p-TsOH	*p*-Toluenesulfonic acid (*p*-$MeC_6H_4SO_3H$)
py	Pyridine (C_5H_5N)
EWG	Electron withdrawing group
dil.	dilute
conc.	concentrated

About the companion website

This book is accompanied by a companion website:

www.wiley.com/go/moloney/mechanisms

The website includes worked supplementary questions.

Introduction

There are many organic chemistry texts, old and new, which cover material from the fundamental to the advanced. Most texts, of course, are factually based, but students seem to find considerable difficulty in the application of this factual knowledge to the solution of problems, and all too often attempt to rely on memory alone. However, the sheer volume of material to be committed to memory presents a considerable burden, and the temptation to give up on the subject almost at the outset can be very strong. This book attempts to demonstrate that a general problem-solving strategy is indeed applicable to many of the common reactions of organic chemistry. It develops a checklist approach to problem-solving, using mechanistic organic chemistry as its basis, which is applicable in a wide variety of situations. It aims to show that logical and stepwise reasoning, in combination with a good understanding of the fundamentals, is a powerful tool to apply to the solution of problems.

Philosophy of the book

This book is not a 'fill in the box' text, nor does it have detailed explanations, but it does show how a problem can be worked through from beginning to the end. The principal aim is to develop deductive reasoning, which the student is then able to apply to unfamiliar situations, using as a basis a standard list of reactions and their associated mechanisms. This book is intended for First and Second Year students, but will not cover the fundamentals of the subject, which are more than adequately covered in a variety of texts already. A knowledge of electron accounting, such as the octet rule and Lewis structures, and the meaning of curly arrows and arrow pushing, is therefore assumed. However, this book will aim to reinforce and develop the use of these concepts by application of a generalised strategy to specific problems; this will be done using short multi-step reaction schemes. Note that because the emphasis is on the strategy of problem-solving, only a limited range of problems will be covered, and no attempt has been made to achieve a comprehensive list of all reactions. The aim is to demonstrate that this strategy is applicable to a wide variety of situations, and therefore an exhaustive list of problems is considered to be inappropriate; in fact, this would defeat the very purpose of this book.

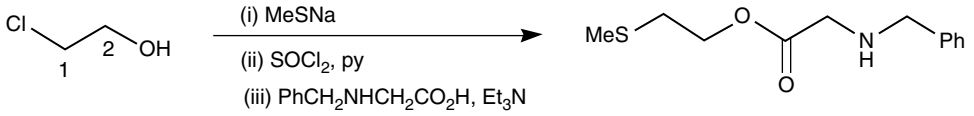
A novel layout is used, in which two facing pages will have the problem and answer. On the left page is the problem and the overall strategy; on the right side of this page are broad hints corresponding to each step. These hints are not intended to give a detailed explanation of the answer, but to provide a guide to the approach to arriving at the answer. The right hand page will have a complete worked solution. Placing a piece of A4 paper on the right hand page will both provide a working space and hide the full answer from view. The intention is that this will remove the temptation to look at the complete solution too early but still provide access both to the stepwise procedure for working through the problem and to the hints on the left page. Of course, maximum benefit from these problems will come only if they are worked through in their entirety before looking at the worked solution! The detailed answer will be as full as possible within the page constraints and will include, for example, proton transfers. A new innovation will be introduced regarding curly arrows; these are labelled in sequence thus (a,b,c,d), to clearly indicate to the student the starting point and the subsequent sequence of movement of electrons. It is hoped that the provision of both hints and worked solutions will cater for a variety of academic abilities.

However, it should be emphasised that no matter how well a strategy for problem-solving is developed, there is no substitute for a good knowledge of the subject. One might consider that learning organic chemistry is little different from learning a foreign language. The vocabulary of any language is very important and must be learnt, and for organic chemistry these are the standard reactions of the common functional groups. A checklist of the reactions which a student is expected to know, and which form the basis of the questions

in that chapter, are summarised before each set of problems. Little detail is included, however, since there are many excellent texts available which cover the required material. Mechanisms, which might be considered to be the grammar of organic chemistry, are covered in considerable detail in this book. Experience shows that mechanisms are best learnt by repeated practice in problem-solving.

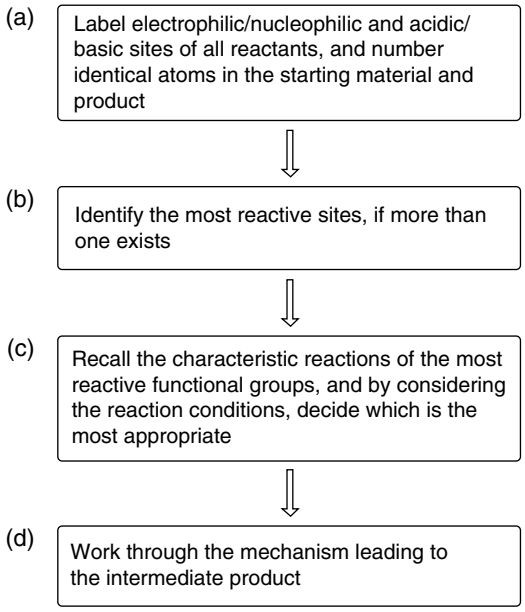
How to use the book

1. This text has been subdivided by functional groups, since this provides an instantly recognisable starting point, especially for the beginners. A key skill, therefore, which must be developed early, is the recognition of functional groups and recollection of their typical or characteristic reactions. This information is briefly summarised at the beginning of every chapter, but an important starting point is to prepare your own set of more detailed notes using your recommended texts and lecture notes as source material. There is no alternative but to commit this material to memory.
2. These characteristic reactions can be very often understood using some fundamental chemical principles; mechanisms provide a way of rationalising the conversion of starting materials to products. In order to devise plausible mechanisms (remember that the only way of verifying any postulate is by experiment), it is necessary first to be able to identify nucleophiles and electrophiles, Bronsted–Lowry and Lewis acids and bases, and leaving groups.
3. A further aid to problem-solving is to number the atoms in the starting material and the corresponding atoms in the product; this allows for effective atom 'book-keeping'.
4. In devising plausible mechanisms, it is usually most helpful to begin at an electron-rich centre (negative charge, lone pair, or carbon–carbon double or triple bond) and push electrons (i.e. begin an arrow thus:) from there.
5. Remember that a double-headed arrow ( ) refers to movement of two electrons and a single headed arrow ( ) to a single electron.
6. Each problem in this book is designed to illustrate a sequential strategy of thinking to solve a question of the type: 'Provide a plausible explanation of the following interconversion; in your answer, include mechanisms for each reaction step'. A typical example is:

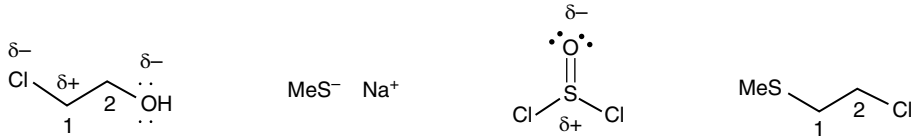


Note that numbering of each reagent, but not the product, is already given at this stage. Also the sequence of reagents drawn means that the intermediate product of step (i) is subsequently treated with the reagents of step (ii), whose product in turn is treated with the reagents of step (iii) to give the final product shown.

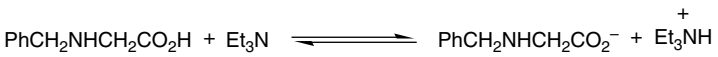
7. The general strategy is:



The first step (box (a)) is an important preparatory stage, and this information is given on the right hand answer page above the dotted line, thus:

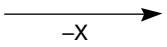


Also included in this section are any preliminary reactions necessary to generate reactive species, for example:



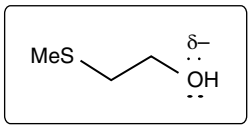
In order to solve a problem with multiple reaction sites, it is necessary to recognise which is the most reactive (box (b)). For the example shown, alkyl halides are electrophilic at the carbon adjacent to the halogen and alcohols are nucleophiles. Once the most reactive functional group has been identified, recollection of its characteristic reactions (box (c)) is a useful next step. In the example given, alkyl halides readily undergo nucleophilic substitution reactions. Once this is established, the next step (box (d)) can be deduced. To continue with this example, nucleophilic attack of thiolate, a potent nucleophile, at the alkyl halide generates the substitution product.

Fragments which are lost in the course of these steps (e.g. leaving groups, such as H_2O or Cl^-) are indicated as '–X' under the relevant reaction arrow, thus:



Two points are noteworthy: where possible, a series of unimolecular or bimolecular steps have been used; termolecular steps might make for a more concise answer but are kinetically much less favourable! It is important to remember that many reactions are in fact at equilibria, and that the overall transformation of starting materials to products often crucially depends on one or more irreversible steps in a reaction sequence; where space permits, this is indicated.

8. This process can be applied for as many iterations as are necessary in any given problem; when you have come to the end of one iterative cycle, the product (which could be an intermediate one or the final one of the question) is in a box, thus:



Once you have reached this stage, you will need to return to the beginning of the cycle (i.e. box (a)) and proceed through the sequence again. Note that the number of iterations required to reach the final product is different for each question; you will need to use your judgement accordingly. However, for a multi-step sequence like that in the example, you could expect to need at least the same number of iterations as there are steps, that is, in this case, three.

9. However, often a penultimate product is obtained which does not look like the desired product, but is in fact very close to it; this can be very misleading and needs to be watched for with care. Tautomerisation is a good example. Under these circumstances, the following step will be necessary:

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

Note that only general acidic or basic work-up conditions are indicated, and this implies that the final product can be obtained by protonation or deprotonation respectively. If base or acid reagents are specified for any reaction sequence, a reaction (other than simple protonation or deprotonation) is implied.

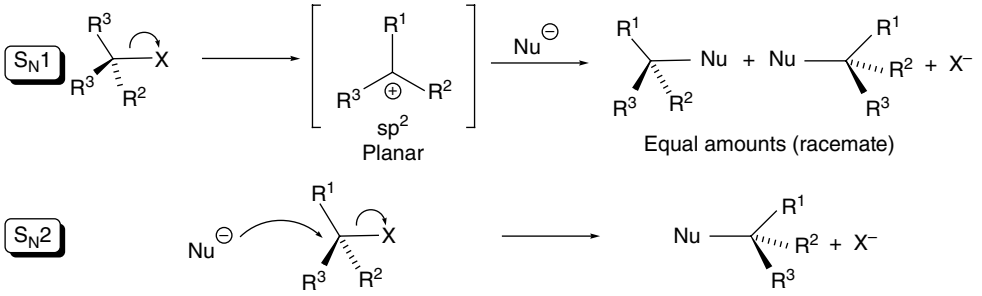
10. All going well, you should now be in a position to:

Write down the structure of the final product

11. Hints are provided adjacent to this general strategy; however, you may not need to use them, and if not, so much the better! Italicised terms should be familiar, but if not they can be checked in any suitable textbook.
12. The detailed answer is provided on the right hand page, allowing you to check your answer. Avoid the temptation to look at this until you have entirely finished the question!
13. There are 15 questions per chapter, designed to cover as many of the full range of characteristic reactions for each functional group as possible. On the website associated with the book, there are supplementary questions which are designed to reinforce the lessons of each detailed question.
14. Remember that this strategy is an aid to solving problems and is not always universally applicable; all problems are different, and slavish following of this approach is no guarantee to certain success. This strategy is no substitute for thinking!
15. There is one particularly important limitation to this strategy; it is designed specifically for mechanisms involving polar intermediates (hence the emphasis on electrophilic and nucleophilic processes). The strategy is not, however, directly applicable to radical reactions or pericyclic reactions, and reactions of this type have therefore been largely, although not exclusively, omitted. In any case, these types of reaction are considered to be too advanced for introductory organic chemistry.
16. Obviously, this approach is designed to develop your understanding of the subject, and in the short term, to be of use in those all-important examinations. The strategy is meant to make problem solving easier, and even fun! Enjoy them!

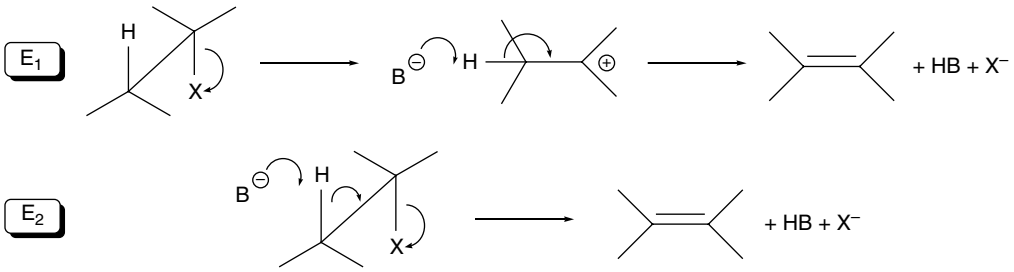
1 Nucleophilic substitution and elimination

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.

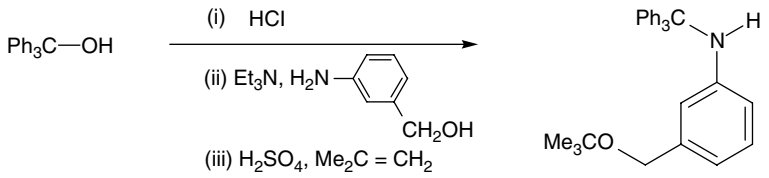
Elimination: E_1 and E_2 eliminations



- 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.

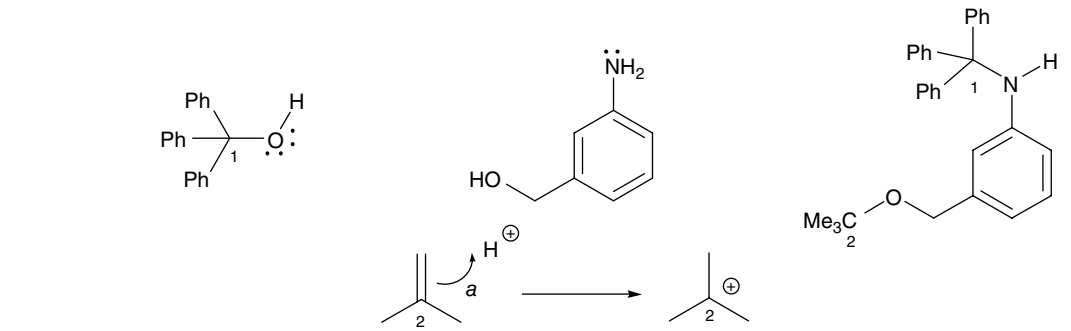
* Triphenylmethyl chloride readily undergoes S_N1 reactions; departure of the good *leaving group* (chloride) regenerates the triphenylmethyl carbocation, which is intercepted by the most nucleophilic functional group of the aniline reagent, that is, the amine group. A series of proton transfers then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

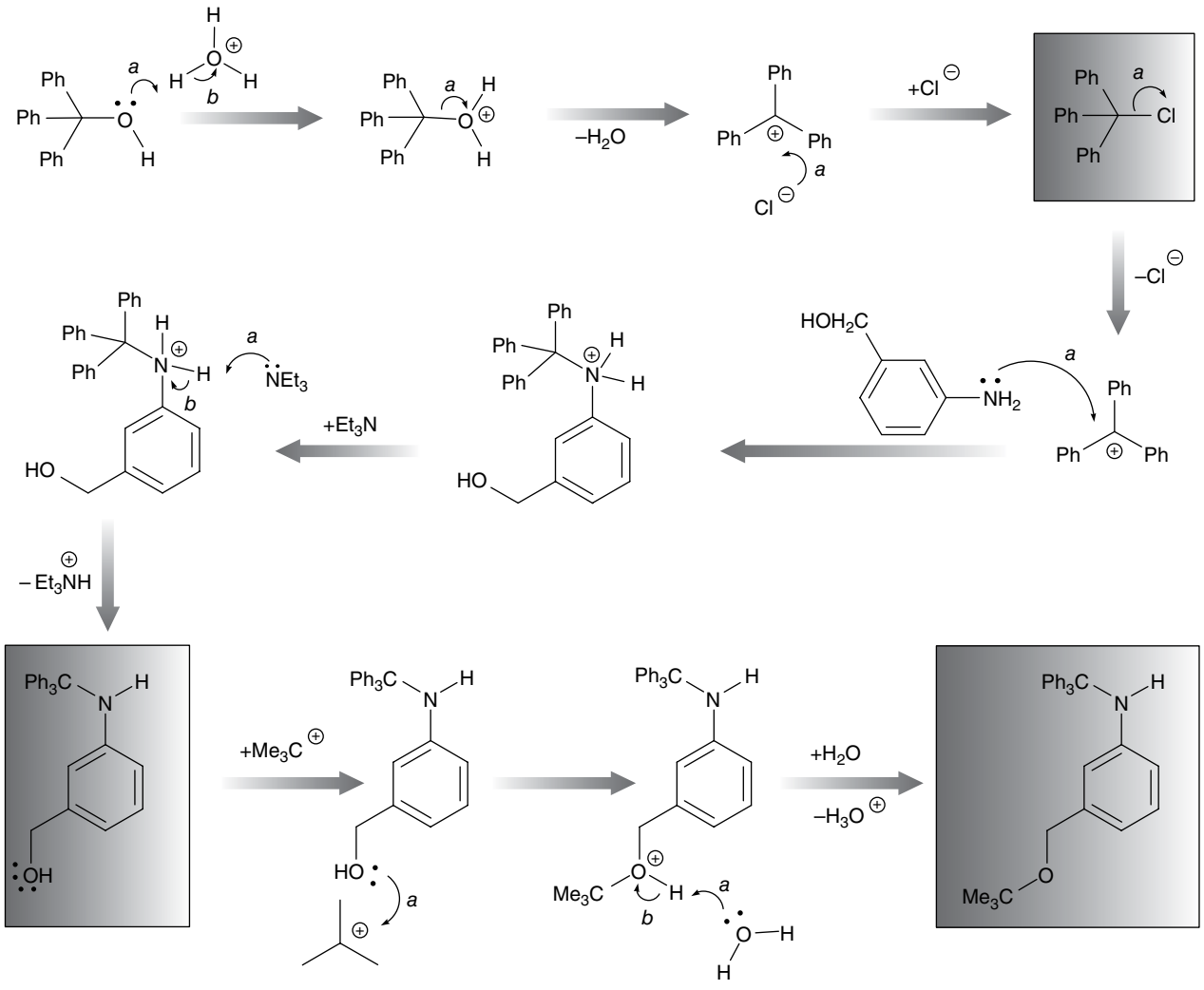
* Under stongly acidic conditions (H_2SO_4), isobutene is protonated (*Markovnikov* addition) to give a *t*-butyl cation; this is intercepted to give the ether product in its protonated form.

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.



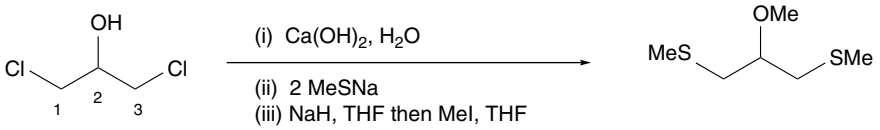


Summary: There are several examples of nucleophilic substitution (S_N1) reactions in this question:

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

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.

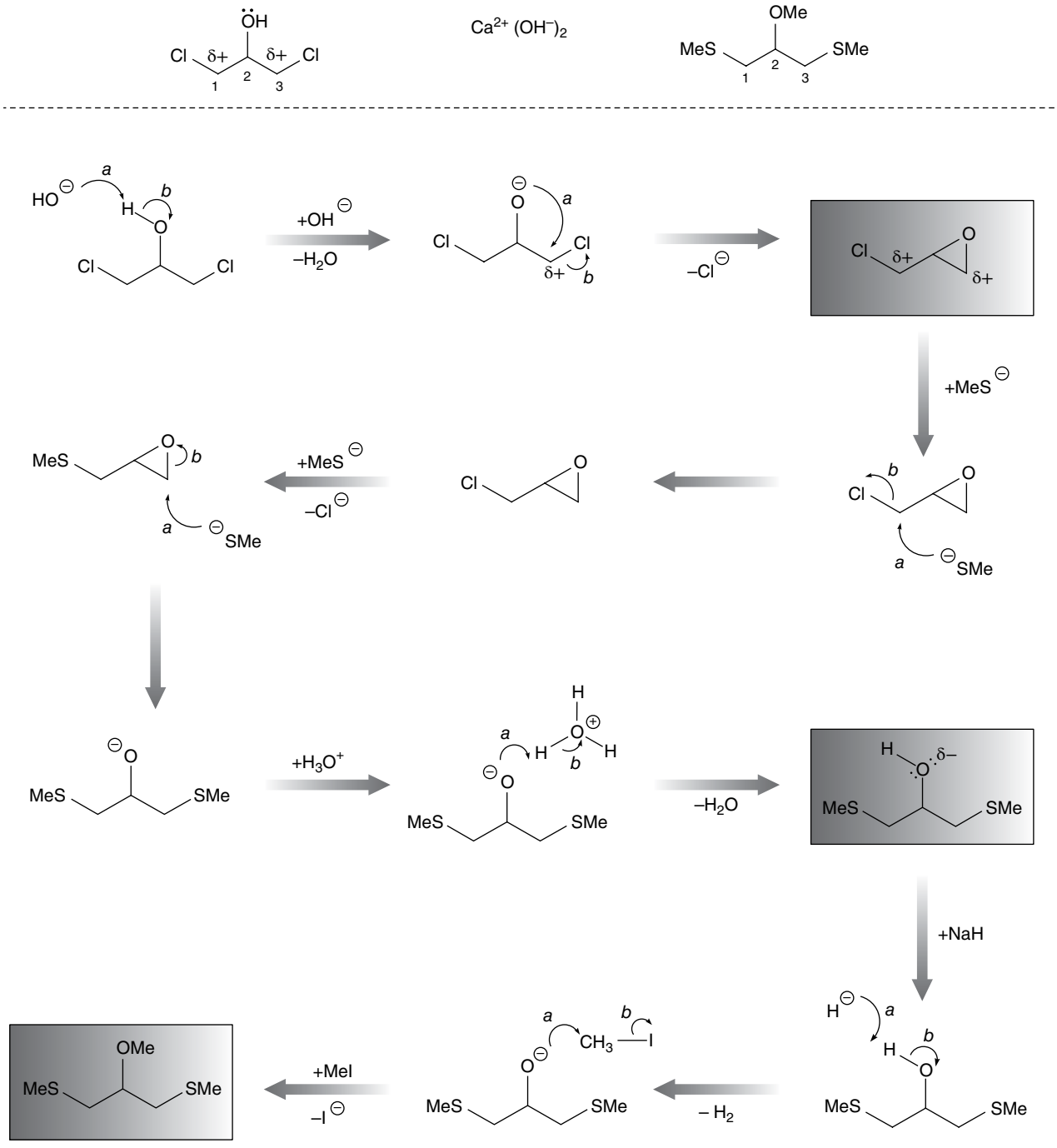
* Methanethiolate is a good nucleophile, and attacks both the C-Cl bond and the epoxide function (which has two electrophilic sites) at the less hindered end, to give the alkoxide product; this is protonated on work-up.

* 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.

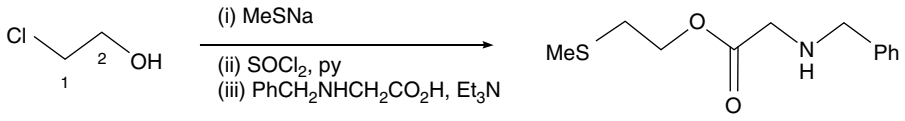


Summary: This question involves several examples of nucleophilic substitution (S_N2) reactions:

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

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.

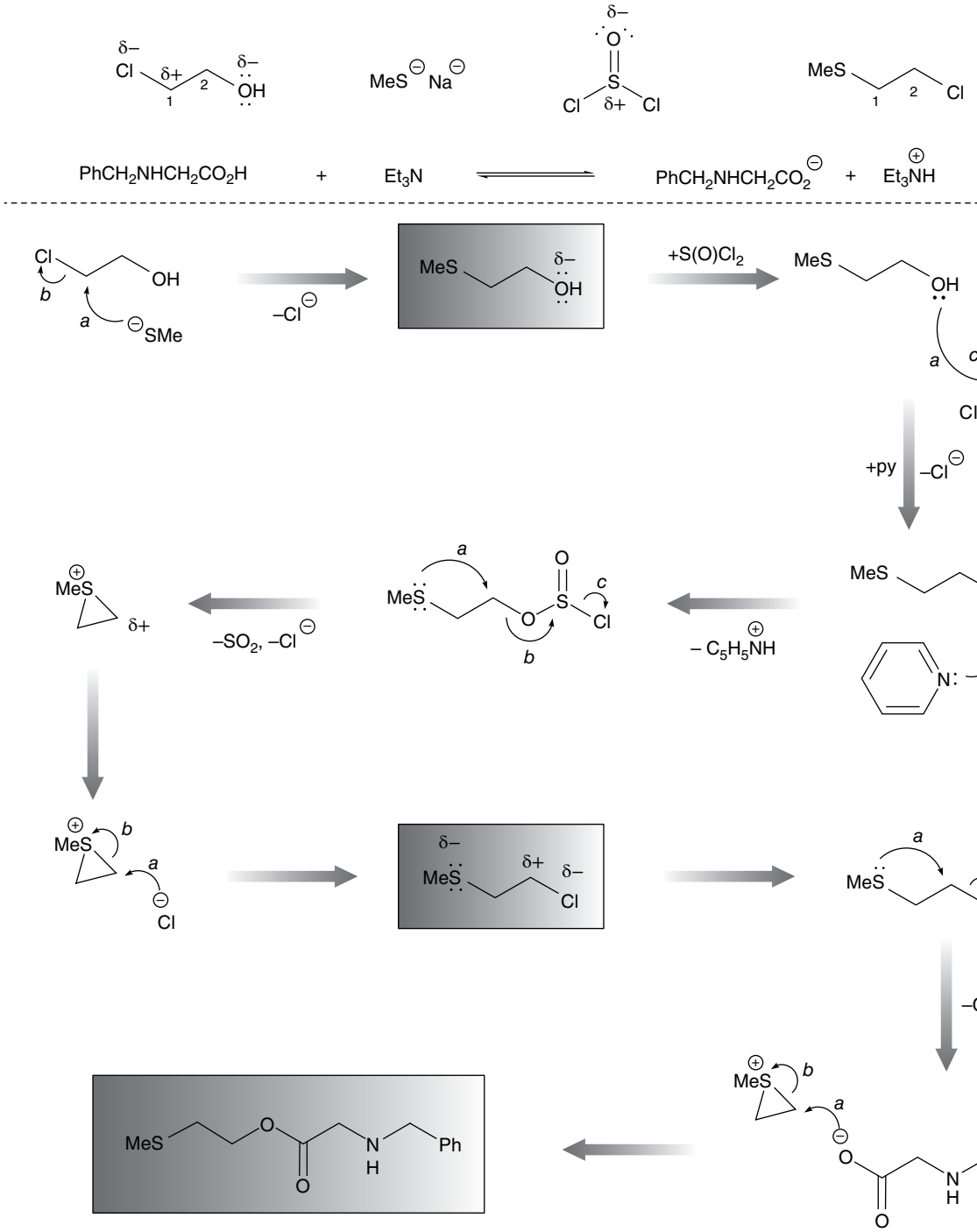
* Thionyl chloride is highly electrophilic, and converts the alcohol to the corresponding alkyl chloride *via* an *addition-elimination* process (with *neighbouring group* or *anchimeric* assistance of the SMe group).

* 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.

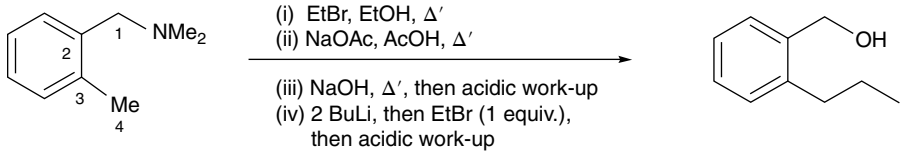
Write down the structure of the final product.



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.

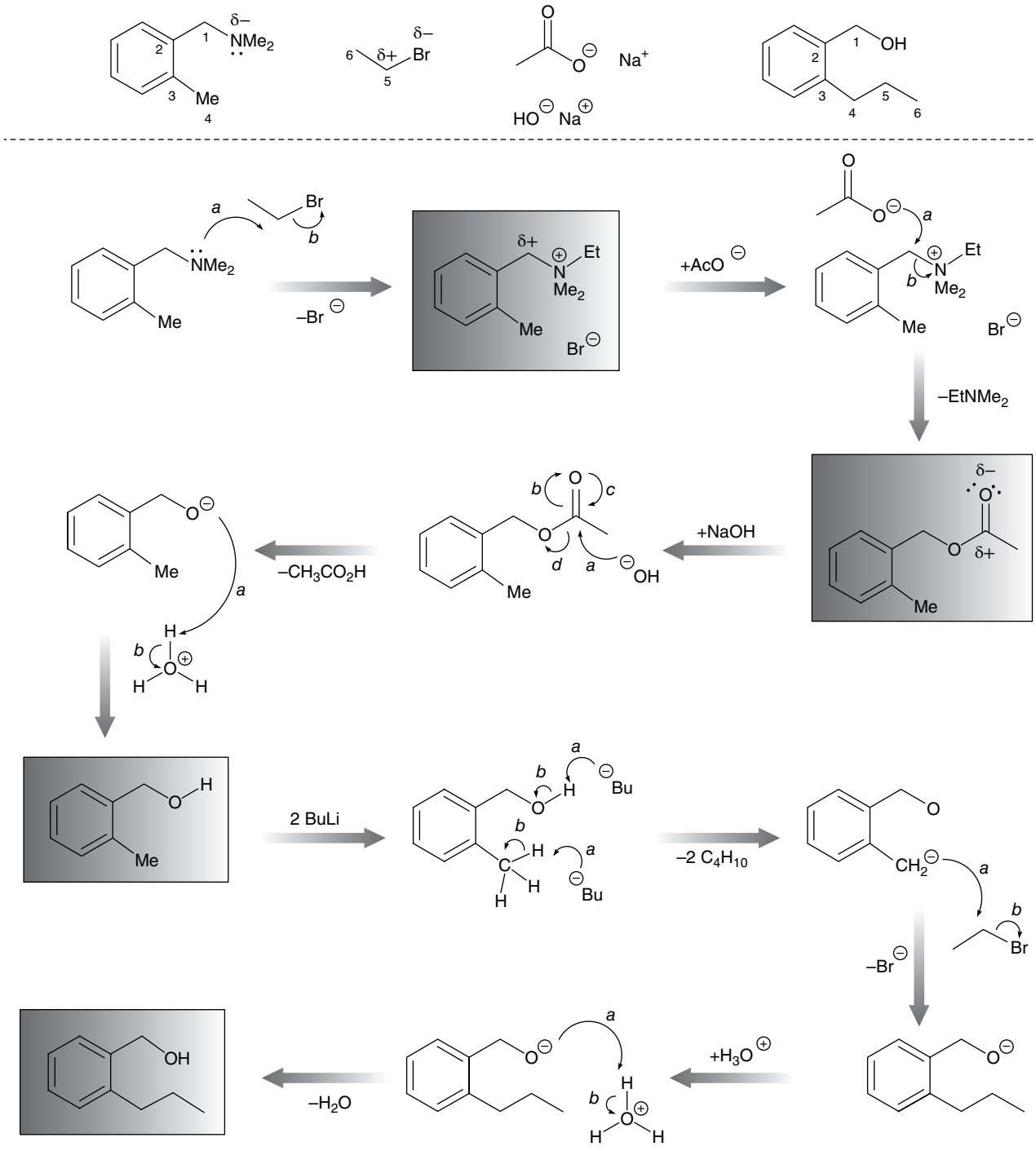
* Esters are easily hydrolysed under alkaline conditions (*addition-elimination mechanism*) to give the alcohol product upon acidic work-up.

* 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.

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

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

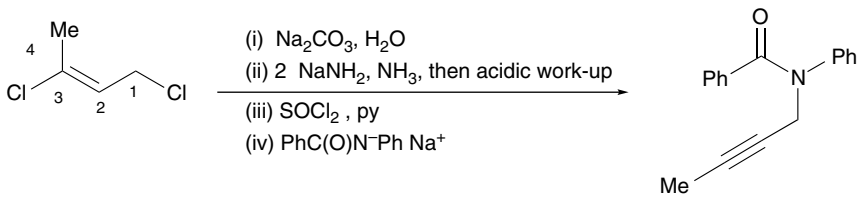
Write down the structure of the final product.



Summary: This question includes an example of nucleophilic attack at a benzylic position:

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.

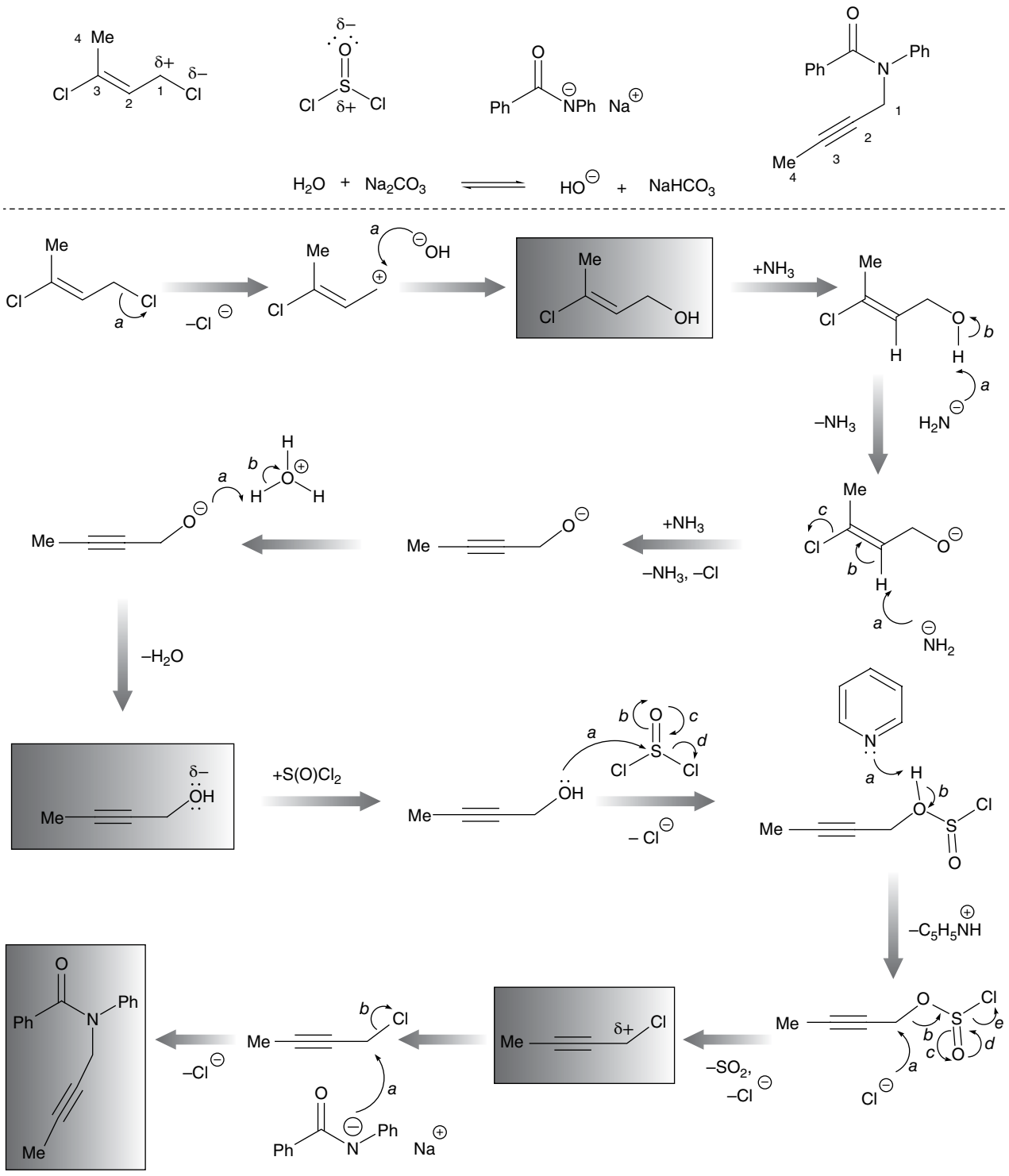
* Thionyl chloride is highly electrophilic, and converts the alcohol to the corresponding propargyl chloride *via* an *addition-elimination* process.

* *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