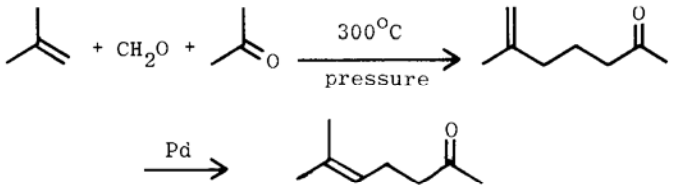
CHAPTER 1

The Disconnection Approach

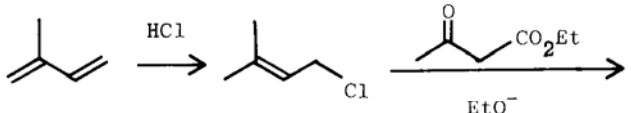
This book is to help you design your own syntheses rather than tell you about those devised by others. It still contains many examples of other people's work since learning by example is as important here as elsewhere. This chapter sets the scene for what follows so that the details of the syntheses need not concern you as much as the general approach.

The ketone **(1)** is an important industrial compound made by the ton from cheap starting materials[2] and used to make vitamin A and some flavouring and perfumery compounds.

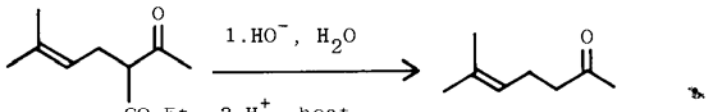


(1)

High pressure and temperatures are inconvenient in the laboratory where a simpler, though longer, route[3] uses **(2)** as an intermediate. This is still quite short, uses cheap starting materials, and gives high yields in each step.



(2)

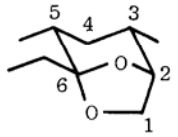


(1)

How did the workers choose these routes? The approaches to this simple molecule **(1)** containing only eight carbon atoms probably owed more to a comprehensive knowledge of reliable chemical reactions and reaction

mechanisms than to any step by step analysis. Even with the analytical approach these are still of vital importance as synthesis is largely about applying known reactions to unknown molecules.

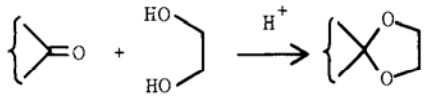
The synthesis of the next target molecule **(3)** could hardly be devised in a similar way. Its greater complexity demands a more sophisticated approach.



(3)

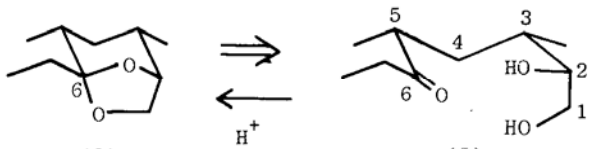
Multistriatin **(3)** is one of the pheromones of the elm bark beetle, a volatile compound released by a virgin female beetle when she has found a good source of food—an elm tree. Male beetles, which carry the fungus causing Dutch elm disease, are attracted by the pheromone, the tree becomes infected and soon dies.

Multistriatin could be used to trap the beetles and so prevent the spread of the disease but there is no prospect of isolating useful amounts from the beetles. It must be synthesised. In analysing the problem we notice that C-6 has two single bonds to oxygen atoms. We therefore *recognise* an acetal *functional group*. Acetals **(4)** can be made by a reliable reaction from carbonyl compounds and alcohols.



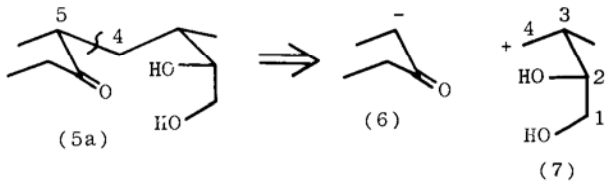
(4)

Working backwards, we *disconnect* the acetal, using ⇒ to indicate the reverse of a synthetic step, and discover **(5)** as the intermediate from which the required acetal **(3)** could be made.

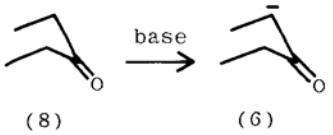


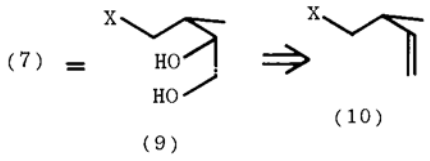
(3) (5)

To make **(5)** we shall doubtless join two simpler fragments together by forming a C–C single bond. But which one? Bond C4–C5 is a good choice because it joins a symmetrical ketone **(6)** to the rest of the molecule. We can therefore disconnect this bond (5a), writing ~ across the bond and using our symbol ⇒. Before writing the fragments, we consider the synthetic step corresponding to this disconnection. The ketone group in **(6)** could stabilise an anion, so **(7)** should be a cation for an ionic reaction to take place.



Anion **(6)** can be made from ketone **(8)** with base, but there is no simple way to make a cation at C4 of **(7)**. The solution is to attach a good leaving group to C4 giving **(9)** (X = Br, etc.) as the complete fragment.

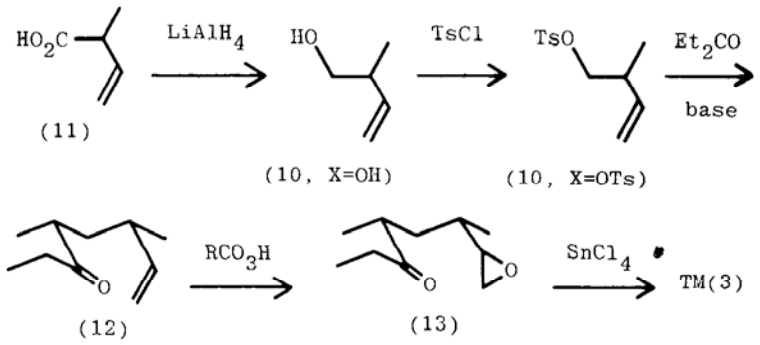




The ketone **(8)** is available, but **(9)** must be made. Once again we must recognise that **(9)** contains the 1,2-diol *functional group*, made by the hydroxylation of an alkene **(10)**, a known and reliable reaction.

One group of workers[4] planning this synthesis decided to use the alcohol **(10)** (X = OH) as it had already been made from the acid **(11)** and to use tosylate (= toluene-*p*-sulphonate) as a leaving group. This synthesis can now be written in a forward direction. In carrying out the synthesis, they hydroxylated **(12)** with a per-acid and found that the epoxide **(13)** gave multistriatin directly on treatment with a Lewis acid.

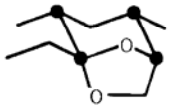
Synthesis



Routine for Designing a Synthesis

1. *Analysis*
   (a) recognise the functional groups in the target molecule.
   (b) disconnect by methods corresponding to known and reliable reactions.
   (c) repeat as necessary to reach available starting materials.
2. *Synthesis*
   (a) write out the plan according to the analysis, adding reagents and conditions.
   (b) modify the plan according to unexpected failures or successes in the laboratory.

We shall be using this routine throughout the book.



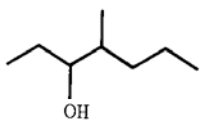
(14)

The synthesis of multistriatin just described has one great fault: no attempt was made to control the stereochemistry at the four chiral centres (• in **14**) and a mixture of stereoisomers was the result. Only the natural isomer **(14)** attracts the beetle and a stereoselective synthesis of multistriatin has now been devised (see Chapter 12). We must therefore add stereochemistry to the list of essential background knowledge an organic chemist must have to design syntheses effectively. The list is now:

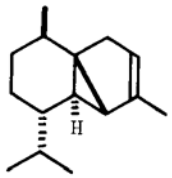
1. an understanding of reaction mechanisms.
2. a working knowledge of reliable reactions.
3. an appreciation that some compounds are readily available.
4. an understanding of stereochemistry.

This book will show you how to apply this background knowledge to organic syntheses using the basic scheme set out above. Don't be concerned if you feel that your background knowledge is weak. In each chapter all four aspects (1–4 above) will be discussed, if appropriate, and your background knowledge should be progressively strengthened.

The elm bark beetle releases three compounds in its pheromone mixture: multistriatin **(14)**, the alcohol **(15)**, and α-cubebene **(16)**. At first we shall be looking at simple molecules such as **(15)**. We shall progress to natural multistriatin, and finally, by the end of the book, to molecules as complex as α-cubebene.



(15)



(16)

The compounds we have met in this chapter, the ketone **(1)** and multistriatin **(3)**, have been made many times by different methods. Synthesis is a creative science and there is no 'right' or 'best' synthesis for any molecule. I shall usually give one synthesis only for each target molecule in the book: you may be able to devise shorter, more stereochemically controlled, higher yielding, more versatile—in short better—syntheses than those already published. If so, you are using the book to advantage.

CHAPTER 2

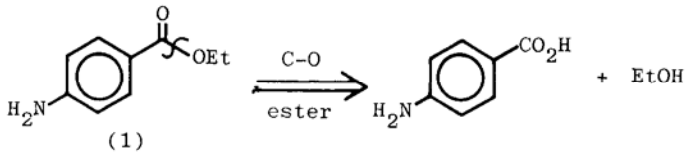
Basic Principles: Synthesis of Aromatic Compounds

We start with aromatic compounds because the bond to be disconnected is almost always the bond joining the aromatic ring to the rest of the molecule: all we have to decide is when to make the disconnection and exactly which starting materials to use. We shall use the technical terms disconnection, functional group interconversion (FGI), and synthon in this chapter.

Disconnection and FGI

Disconnections are the reverse of synthetic steps or *reactions* and we disconnect only when we have a reliable reaction in mind. In designing a synthesis of the local anaesthetic benzocaine **(1)** we know that esters are made from alcohols and acids so we can write a C–O disconnection. Usually, disconnections will be labelled to show the reason for making them.

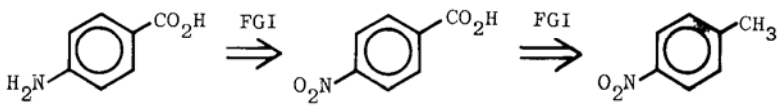
Benzocaine: *Analysis 1*



(1)

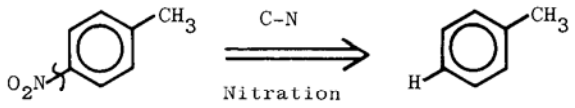
We should now like to disconnect either CO_2H or NH_2 from the aromatic ring but we know of no good reactions corresponding to these disconnections. We must therefore first do *functional group interconversion* (FGI) to change these functional groups into others which can be disconnected. Aromatic acids can be made by the oxidation of methyl groups and amino groups by the reduction of nitro groups. We can write these as follows.

Analysis 2



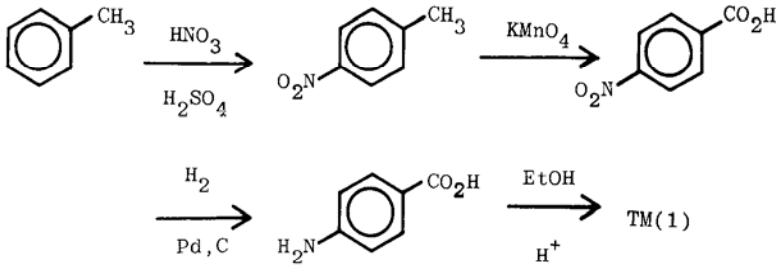
Now, disconnection of the nitro group is rational because we know that nitration of toluene occurs easily, and toluene is available.

Analysis 3



This completes the analysis and we should now write out the synthesis with suggested reagents. You should not expect to predict exact reagents and conditions and indeed no sensible organic chemist would without a thorough literature search. It is sufficient to be aware of the type of reagent needed and I shall give actual reagents and conditions to help broaden that awareness, emphasising any essential conditions.

Synthesis[5]

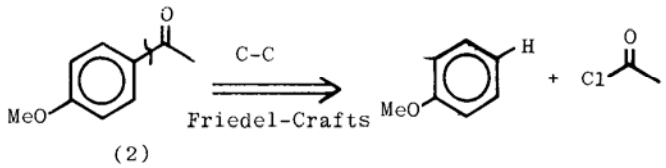


It might be possible to carry out these steps in a different order (e.g. reverse the order of the last two); decisions of this sort form part of *strategy* and are discussed in Chapter 3.

Synthons

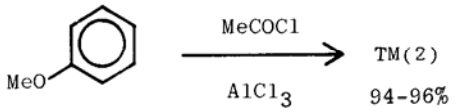
Another useful aromatic disconnection corresponds to the Friedel-Crafts reaction which would be used in the synthesis of the hawthorn blossom perfume compound **(2)**. The synthesis is one step from an available ether.

Analysis

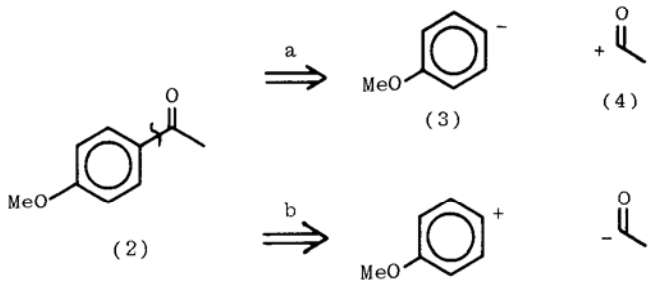


(2)

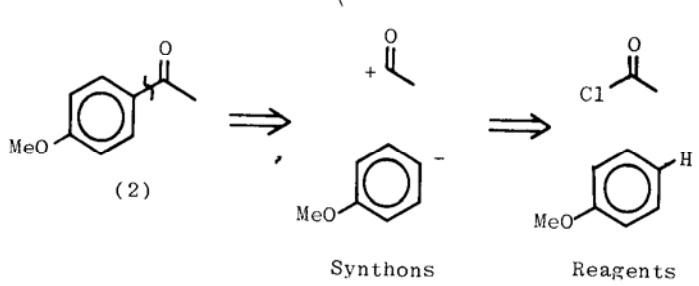
Synthesis[6]



In both this reaction, and in the nitration we used to make benzocaine, the reagent which carries out the attack on the benzene ring is a cation, $MeCO^+$ for the Friedel–Crafts, NO_2^+ for the nitration. When we disconnect a bond to an aromatic ring we normally expect this type of reaction and so we can choose not only which bond to break but which way, electronically, to break it. Here we write (a) and not (b) because the aromatic ring behaves as the nucleophile and the acid chloride as the electrophile.

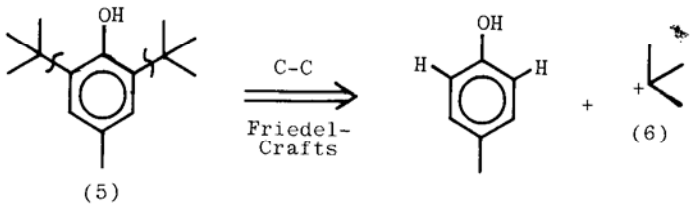


These fragments **(3)** and **(4)** are *synthons*—that is idealised fragments which may or may not be involved in the reaction but which help us to work out which reagents to use. Here, as it happens, **(4)**, but not **(3)**, is an intermediate in the synthesis. When the analysis is complete, the *synthons* must be replaced by *reagents* for practical use. For an anionic synthon, the reagent is often the corresponding hydrocarbon: for a cationic synthon the reagent is often the corresponding halide.



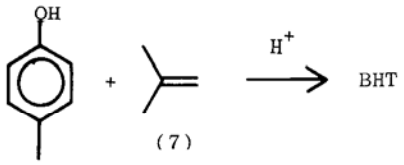
Friedel–Crafts alkylation is also a useful reaction, particularly with tertiary halides, so that the first disconnection on 'BHT' **(5)** (butylated hydroxytoluene —an antioxidant used in foods) can be of the tertiary butyl groups.

BHT: *Analysis*

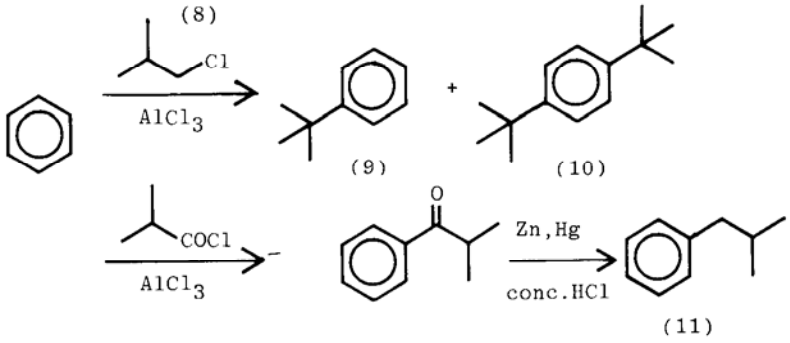


As reagents for the *t*-butyl cation **(6)** we can use either *t*-BuCl and $AlCl_3$, or the readily available alkene **(7)** and protic acid.

Synthesis[7]



Polyalkylation, an advantage here, can be a nuisance with Friedel–Crafts alkylations as can the rearrangement of primary alkyl halides. Thus, the alkyl halide **(8)** gives a mixture of **(9)** and **(10)** with benzene: and if we want to make compound **(11)** we must use the Friedel–Crafts acylation, which suffers from neither of these disadvantages, and then reduce the carbonyl group[8] (see Chapter 24).



If we wish to add just one carbon atom, as in the synthesis of aromatic aldehydes, we cannot use HCOCl since it does not exist. One of the most reliable methods is chloromethylation[9] with CH_2O and HCl giving a CH_2Cl group which can easily be oxidised to CHO (FGI). The important perfumery compound piperonal **(12)** can be made this way. Other methods of adding one carbon atom with a functional group are given in Table 2.1.

Piperonal: *Analysis*

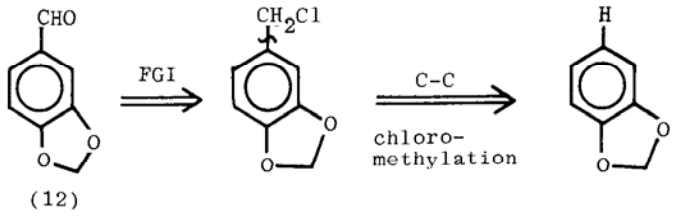
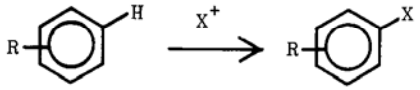


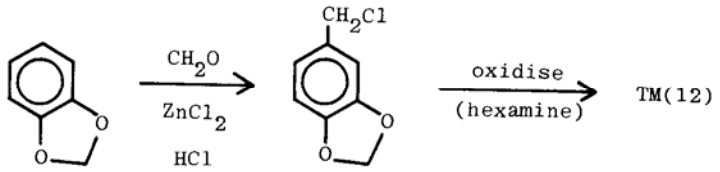
Table 2.1 One-carbon electrophiles[a] for aromatic synthesis



X	Reagent	Reaction
CH_2Cl	$CH_2O + HCl + ZnCl_2$	Chloromethylation
CHO	$CHCl_3 + HO^-$	Reimer–Tiemann[b]
	$Me_2N{=}CH{-}OPOCl_2$	Vilsmeier–Haack
	$(Me_2NCHO + POCl_3)$	Formylation
	$CO + HCl + AlCl_3$	
	$Zn(CN)_2 + HCl$	

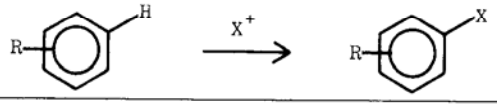
[a]See also Grignard reagents in Chapter 10.
[b]Only on phenol (R = OH): the *ortho* product is favoured.

Synthesis[10]



When heteroatoms are required, nitration gives the NO_2 group and halogenation puts in Cl or Br directly (OR and I are generally added by nucleophilic substitution, see page 12). Table 2.2 gives reliable reagents for these and some other synthons for aromatic synthesis.

Table 2.2 Reagents for aromatic electrophilic substitution



Synthon	Reagent	Reaction
R^+	$RBr + AlCl_3$	Friedel–Crafts[11] alkylation
	$ROH + H^+$	
	$Alkene + H^+$	
RCO^+	$RCOCl + AlCl_3$	Friedel–Crafts[12] acylation
NO_2^+	$HNO_3 + H_2SO_4$	Nitration
Cl^+	$Cl_2 + FeCl_3$	Chlorination
Br^+	$Br_2 + Fe$	Bromination
$^+SO_2OH$	H_2SO_4	Sulphonation
$^+SO_2Cl$	$ClSO_2OH$	Chlorosulphonation
ArN_2^+	ArN_2^+	Diazocoupling

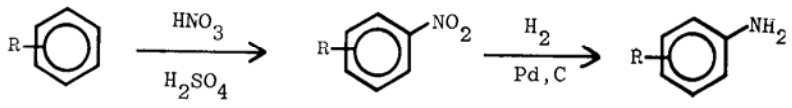
Other aromatic side chains are best added by FGI on these products. Table 2.3 gives some examples.

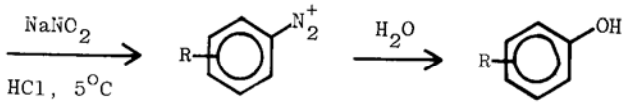
Table 2.3 Aromatic side chains by functional group interconversion

Y	X	Reagent
Reduction		
$-NO_2$	$-NH_2$	H_2, Pd, C Sn, conc. HCl
-COR	$-CH(OH)R$	$NaBH_4$
-COR	$-CH_2R$	e.g. Zn/Hg, conc. HCl see Table 24.1
Oxidation		
$-CH_2Cl$	-CHO	hexamine
$-CH_2R$	$-CO_2H$	$KMnO_4$
$-CH_3$		
-COR	-OCOR	$R'CO_3H$
Substitution		
$-CH_3$	$-CCl_3$	Cl_2, PCl_5 [13]
$-CCl_3$	$-CF_3$	SbF_5 [13]
-CN	$-CO_2H$	HO^-, H_2O

Nucleophilic Aromatic Substitution

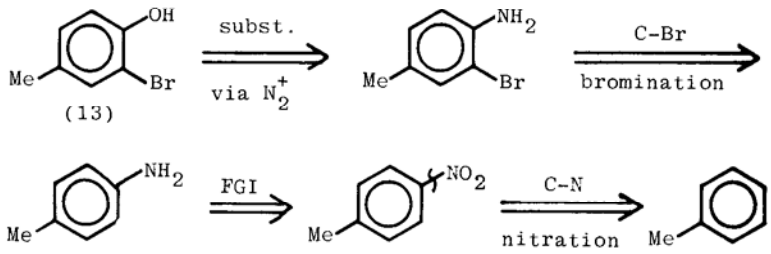
So far we have studied the addition of cationic synthons to the aromatic ring, but suitable reagents are not available for the synthon RO^+. If we wish to add an oxygen atom to an aromatic ring we must use the alternative approach, and add anionic reagents RO^- to an aromatic compound with a leaving group. This is nucleophilic aromatic substitution and works best when the leaving group is N_2 (diazonium salts). The synthetic sequence is nitration, diazotisation, and substitution.





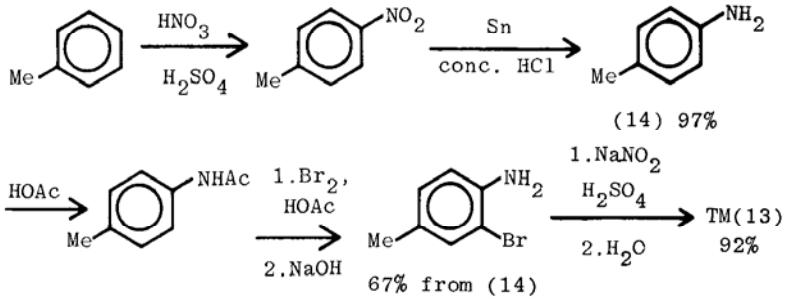
The synthesis of phenol (**13**) can be analysed in this way, the OH reverting to NO_2. The bromine could be added at the amine or the phenol stage, but the amine stage gives better control.

Analysis



In practice, the amine was protected as an amide to prevent the bromine adding to the other ortho position as well.

Synthesis[14]



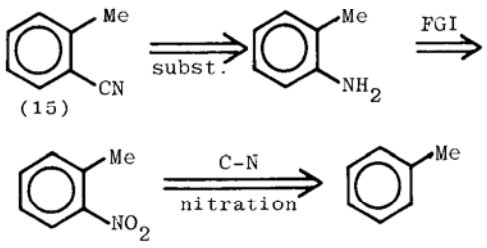
Some nucleophiles (CN^-, Cl^-, Br^- for example) are best added as Cu(I) derivatives: a list of these and others appears in Table 2.4. The aromatic cyanide **(15)** is most easily disconnected this way.

Table 2.4 Aromatic compounds made by nucleophilic displacement of diazonium salts

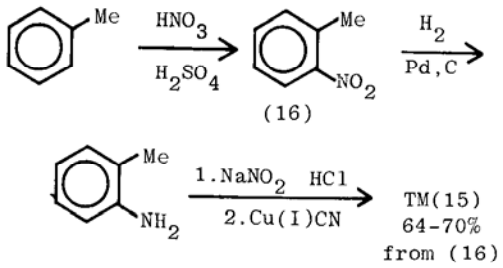
$$ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow{Z^-} ArZ$$

Z	Reagent
HO	H_2O
RO	ROH
CN	Cu(I)CN
Cl	Cu(I)Cl
Br	Cu(I)Br
I	KI
Ar	ArH
H	H_3PO_2 or EtOH/H^+

Analysis

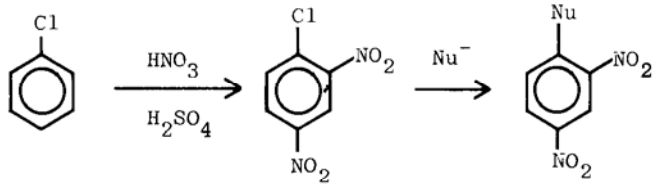


Synthesis[15]



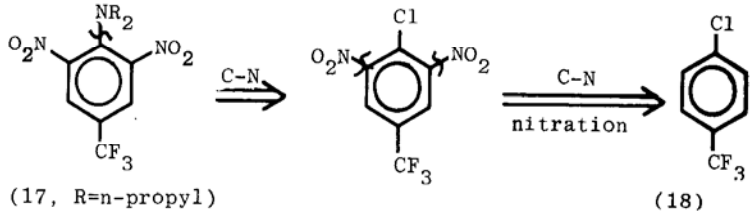
Nucleophilic Substitution of Halides

Direct displacement of halide from an aromatic ring is possible only if there are *ortho* and *para* nitro groups or similar electron-withdrawing groups. Fortunately these compounds are easily made by nitration:



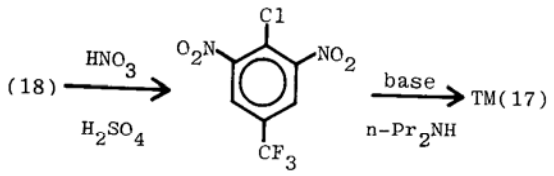
The Lilley Company's pre-emergent herbicides such as trifluralin B (**17**) are good candidates for this approach. The amino group can be added in this way and the two nitro groups put in by direct nitration. The synthesis of the starting material (**18**) is discussed in Chapter 3.

Trifluralin B: *Analysis*



(17, R=n-propyl) (18)

Synthesis[16]

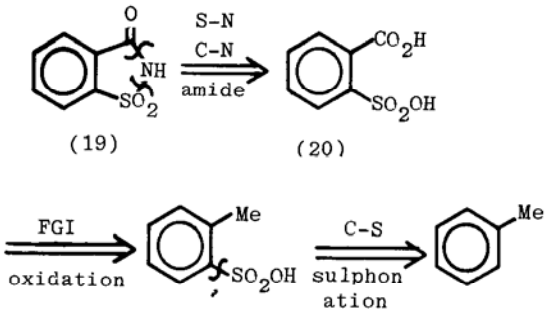


Ortho and *Para* Product Mixtures

We used the same reaction—the nitration of toluene—to make both the *ortho* **(10)** and *para* (for **14**) nitrotoluenes. In practice, a mixture is formed and must be separated to give the required isomer. In other circumstances, reactions which give mixtures of products are best avoided but aromatic substitution is so easy to carry out that separation is acceptable, particularly if it is at the first stage in a sequence. The reaction is then carried out on a large scale to get enough of the right isomer and a use sought for the other.

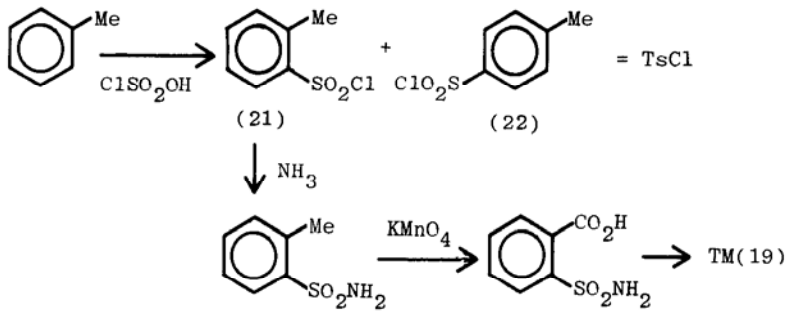
Saccharine **(19)** is made this way. Disconnection of the imide gives the diacid **(20)** which can be made by FGI from toluene-*ortho*-sulphonic acid.

Saccharine: *Analysis*



In practice it is quicker to make the sulphonyl chloride **(21)** directly and separate it from the *para* compound. The rest of the synthesis is routine.

Synthesis[17]



Saccharine is made on a large scale so there is plenty of toluene-*p*-sulphonyl chloride spare and it is cheap. This is one reason why the tosyl group is such a popular leaving group with organic chemists (see Chapter 4).

The question of *ortho–para* mixtures and other similar strategic questions in aromatic syntheses are the subject of the next chapter.

Technical Terms for the Disconnection Approach

Target Molecule (TM): the molecule to be synthesised.

Analysis or *Retrosynthetic Analysis*: the process of breaking down a TM into available starting materials by FGI and disconnection.

FGI (Functional Group Interconversion): the process of converting one functional group into another by substitution, addition, elimination, oxidation, or reduction, and the reverse operation used in analysis.

Disconnection: the reverse operation to a reaction. The imagined cleavage of a bond to 'break' the molecule into possible starting materials.

⇒: symbol for disconnection or FGI.

Synthon[a]: an idealised fragment, usually a cation or an anion, resulting from a disconnection. May or may not be an intermediate in the corresponding reaction.

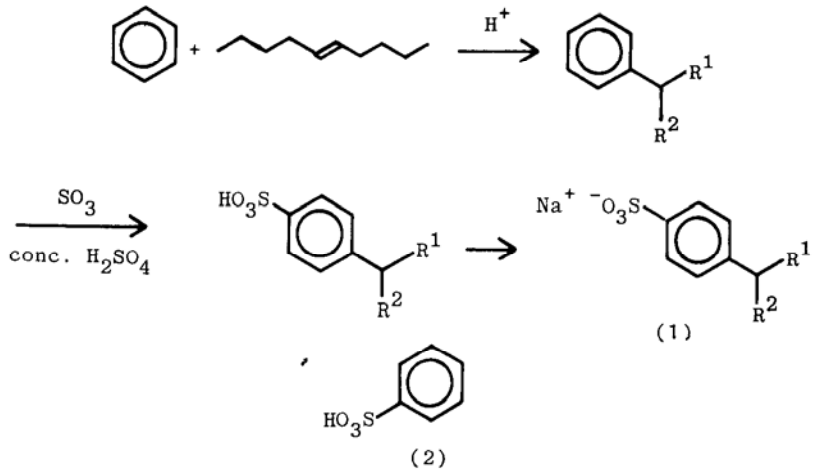
Reagent[a]: compound used in practice for a synthon. Thus MeI is the reagent for the Me^+ synthon.

[a]Some chemists use 'synthon' to mean a useful reagent in organic synthesis.

CHAPTER 3

Strategy I: The Order of Events

Alternating with instructional chapters, like the last one, will be strategy chapters, like this one, in which some point relevant more to the overall plan than to some individual reaction is examined. In this chapter, using aromatic compounds as examples, we examine the question of the order in which reactions should be carried out.



The detergents commonly used nowadays contain sodium salts of sulphonic acids such as **(1)**. They are made industrially[18] in two steps from benzene, a Friedel–Crafts reaction, and a sulphonation. The question is: why this order of events? Two factors influence the answer. The alkyl group is electron-donating and makes the sulphonation easier. The alternative sequence via the sulphonic acid **(2)** would be very difficult as the SO_2OH group is strongly electron-withdrawing and therefore deactivating. The second point is that the electron-donating alkyl group is *o,p*-directing (it gives only *para* product because of its size). The SO_2OH group is *meta* directing and would give a different product.

In choosing the order of events we must take both these related aspects into consideration (they are summarised in Table 3.1) and we can lay down some general guidelines based on them.

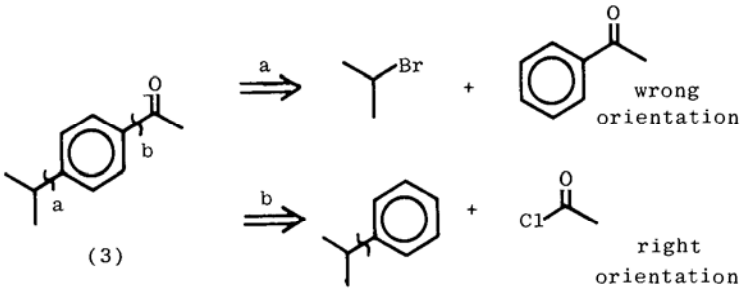
Guidelines for the Order of Events

Guideline 1

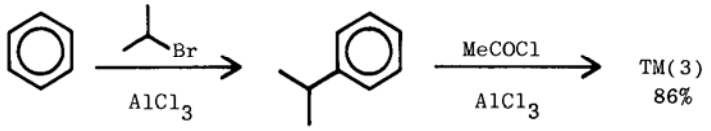
Examine the relationship between the groups, looking for groups which direct to the right position. The thorough way to do this is to disconnect all groups in turn and see if the reverse reaction would give the right orientation.

The analysis of the orris odour ketone **(3)** could be tackled by two possible first disconnections. One (b) gives starting materials which would react in the right orientation since the ketone group in (a) is *meta* directing. The order of events in the synthesis follows.

Analysis



Synthesis[19]

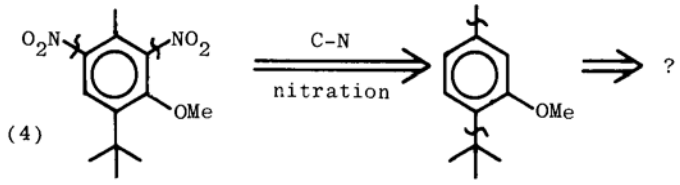


Guideline 2

If there is a choice, disconnect *first* (that is add last) the most electron-withdrawing substituent. This substituent will be deactivating so it may be difficult to add anything else once it is in.

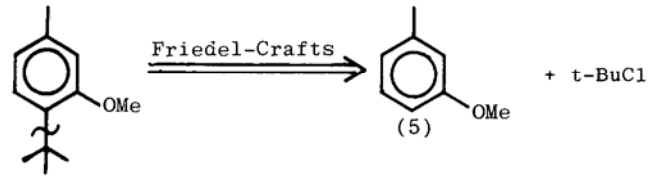
Musk ambrette **(4)**, a synthetic musk, essential in perfumes to enhance and retain the odour, is an aromatic compound with five substituents on the benzene ring. The nitro groups are by far the most electron-withdrawing so we can disconnect them first.

Musk ambrette: *Analysis 1*



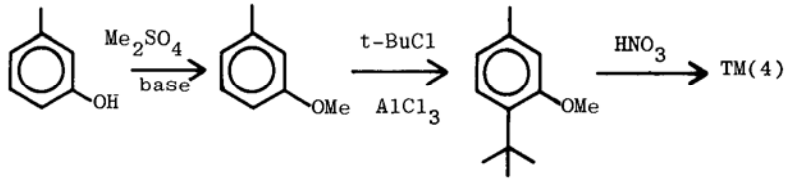
We could add either the Me or the *t*-Bu group by a Friedel–Crafts alkylation. The OMe group is strongly *o,p*-directing so only the *t*-Bu disconnection is reasonable (guideline 1).

Analysis 2



The starting material **(5)** is the methyl ether of readily available *meta*-cresol, and can be made with any methylating agent. Dimethyl sulphate is often used.

Synthesis[20, 21]



Only experience would show whether the Friedel–Crafts alkylation puts the *t*-butyl group *ortho* or *para* to the methoxy group.

Guideline 3

If FGI is needed during the synthesis, it may well alter the directing effect of the group and the other substituents may therefore be added either before or after the FGI. Some examples are:

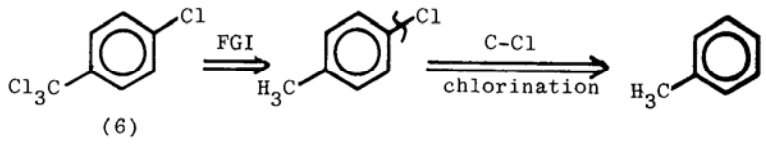
o,p-directing Me → CO_2H m-directing

Me → CCl_3/CF_3

m-directing NO_2 → NH_2 o,p-directing

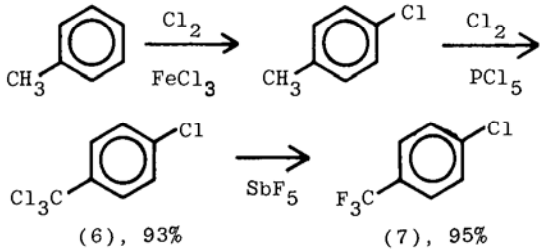
The synthesis of **(6)** obviously involves chlorination of both the ring and a methyl group (FGI). CCl_3 is *m*-directing so we must reverse the FGI before we disconnect the aryl chloride.

Analysis



The synthesis, used to make **(7)**, goes in excellent yield.

Synthesis[13]



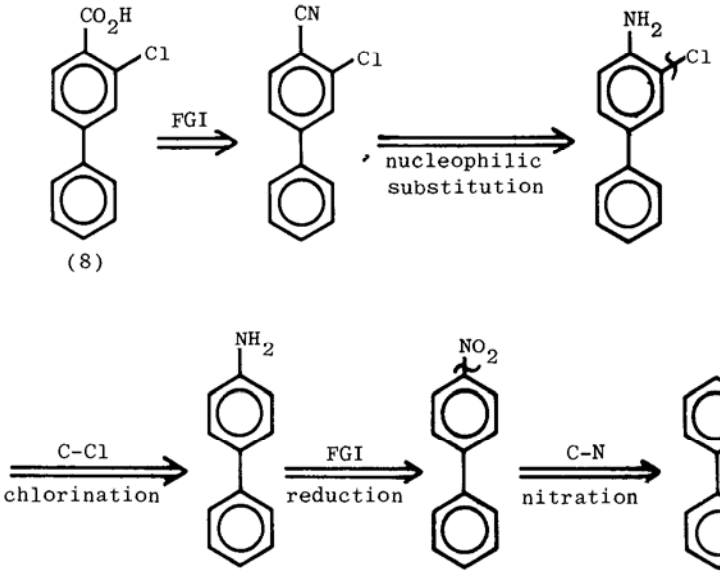
(6), 93% (7), 95%

Guideline 4

Many groups can be added by *nucleophilic* substitution on a diazonium salt (see Chapter 2), made from an amine. Adding other groups at the amine stage may be advisable as the amino group is strongly *o,p*-directing.

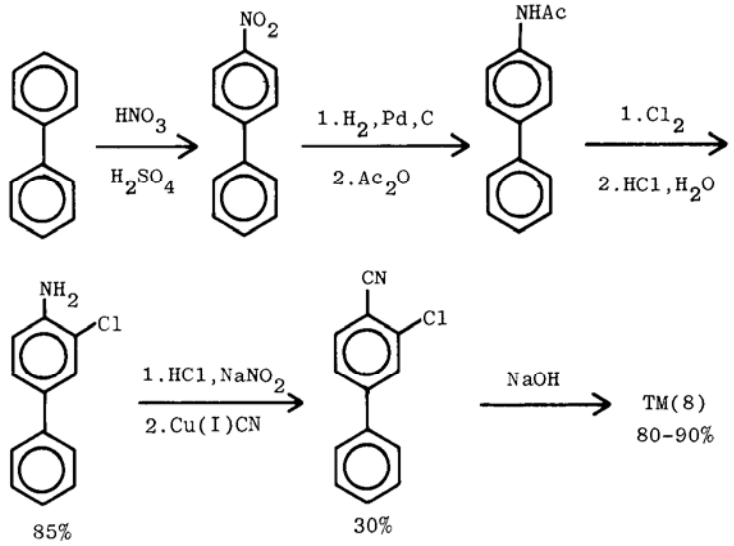
Acid **(8)** was needed at Hull University[22] to study its liquid crystal behaviour (liquid crystals are used in digital displays). The other benzene ring is *o,p*-directing, so to get the chlorine in we must replace the CO_2H group by a *more* *o,p*-directing group than Ph. Amino is the obvious choice.

Analysis



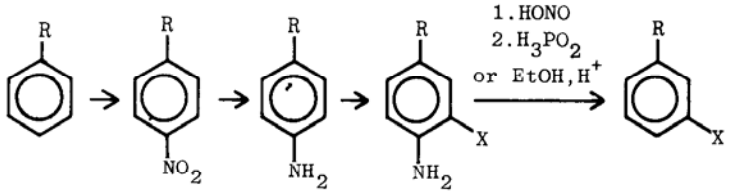
In the synthesis it will be necessary to acylate the amino group to prevent over-chlorination (cf. Chapter 2).

Synthesis[22,23]

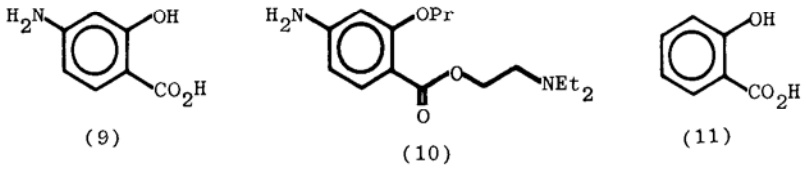


Guideline 5

As a last resort, there is a trick to solve some difficult problems, such as adding two *o,p*-directing groups *meta* to each other. A 'dummy' amino group is added, used to set up the required relationship and then removed by diazotisation and reduction:

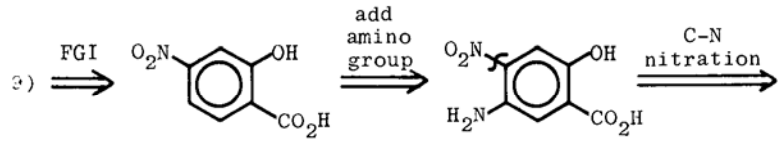


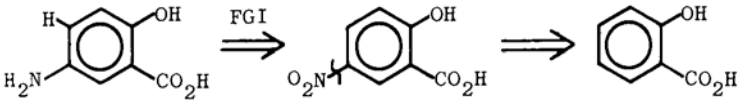
The acid **(9)** is used in the synthesis of a number of local anaesthetics[24] such as Propoxycaine **(10)**. The amino group cannot be put in by nitration of salicyclic acid **(11)** as the oxygen atom will direct *o,p* and give the wrong isomer. The problem can be solved by deliberately making the wrong isomer and nitrating that.



(9) (10) (11)

Analysis

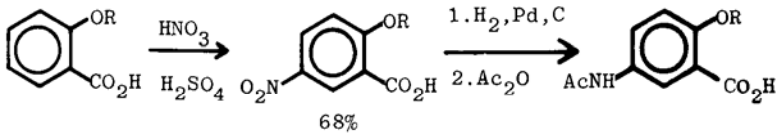


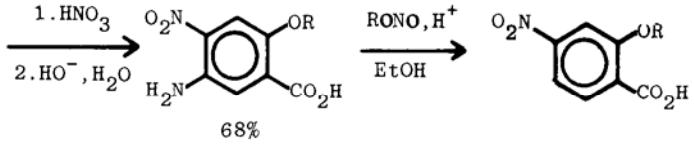


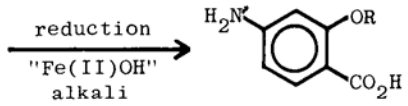
(11)

In practice it is wise to add the alkyl group at the start to protect the hydroxyl group.

Synthesis[25]







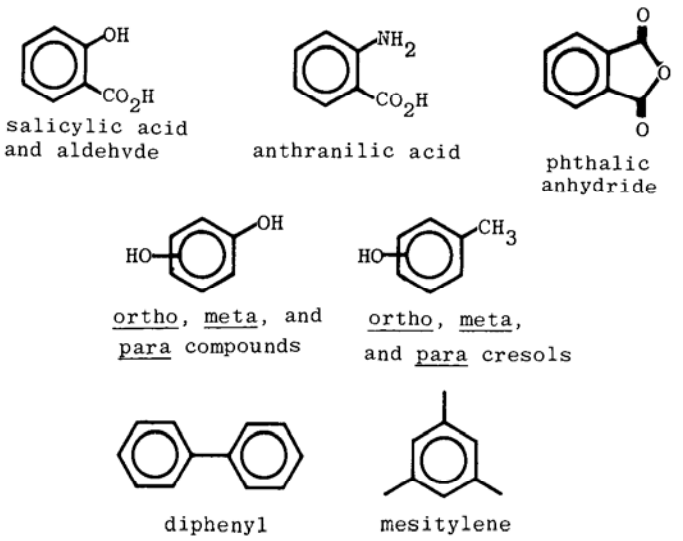
Guideline 6

Look for substituents which are difficult to add. It is often good strategy not to disconnect these at all but to use a starting material containing the substituent. OH and OR are examples. We have already used this guideline for compound **(4)** (substituent OMe) and for compound **(8)** (substituent Ph).

Guideline 7

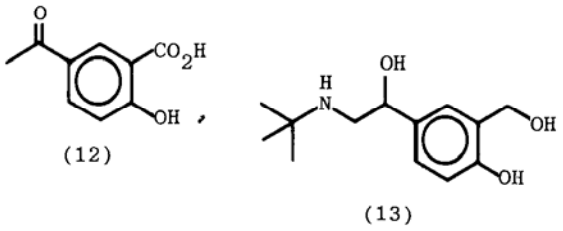
This is an extension of guideline 6. Look for a combination of substituents present in the TM and in a readily available starting material, particularly if it would be a difficult combination to set up.

Examples are:



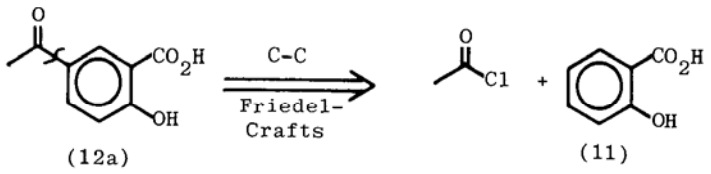
We have already used this guideline in syntheses of compounds **(4)** (from *m*-cresol), **(8)** (from biphenyl), and **(9)** (from salicyclic acid).

Another example is compound **(12)** needed for the synthesis of the anti-asthma drug Salbutamol **(13)**. The acid **(12)** can obviously be made by a Friedel-Crafts reaction on salicyclic acid.



(12) (13)

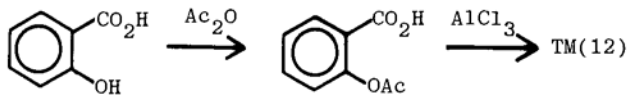
Analysis



(12a) (11)

The synthesis is easier than it may seem since Friedel-Crafts acylation of phenols is best done by first making the phenolic ester and rearranging this with $AlCl_3$. In this case, the ester needed is **(14)** which hardly needs to be made since it is aspirin. No doubt this Salbutamol synthesis was planned with this cheap starting material in mind.

Synthesis[26]

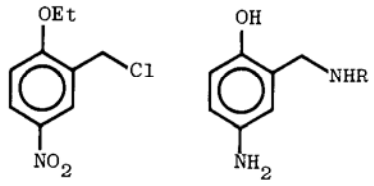


(14)

Guideline 8

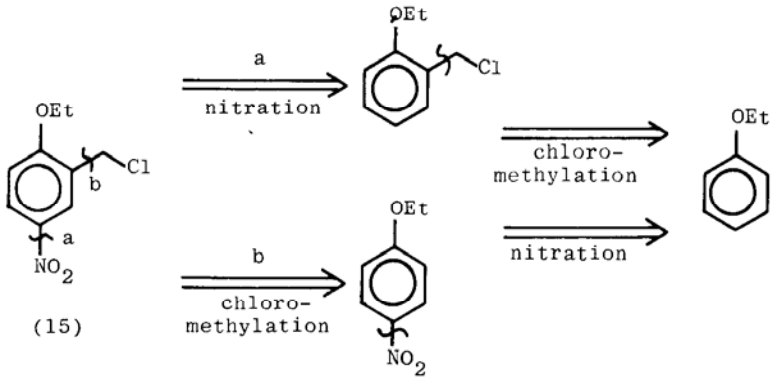
Avoid sequences which may lead to unwanted reactions at other sites in the molecule. Thus nitration of benzaldehyde gives only 50% *m*-nitrobenzaldehyde since the nitric acid oxidises CHO to CO_2H. One way round this particular problem is to nitrate benzoic acid and reduce CO_2H to CHO.

A more interesting example is compound **(15)**, needed to make amines such as **(16)** for trial as antimalarial drugs.[27] The OEt group is best left to appear in the starting material (guideline 6) so we have two strategies differing only in the order of events.



(15) (16)

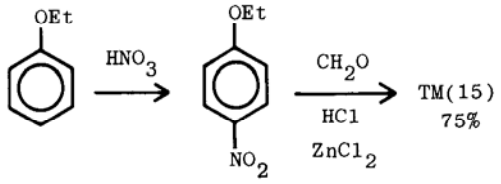
Analysis



(15)

Both strategies fit the substitution pattern (OEt is more electron-donating than CH_2Cl) and strategy (a) also meets guideline (2). But CH_2Cl is oxidised easily (see Chapter 2) so nitrating conditions may destroy it. Strategy (b) gives good yields.

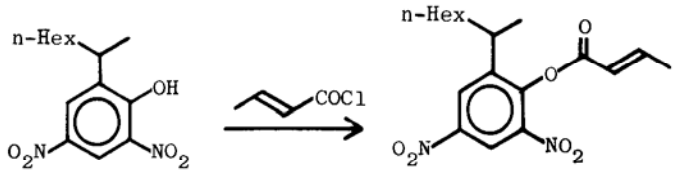
Synthesis[27]



Guideline 9

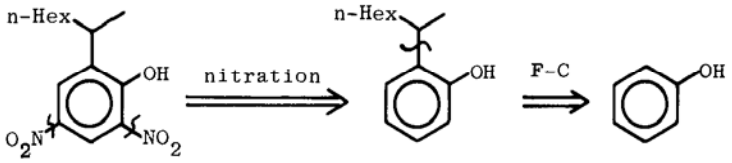
If *o,p*-substitution is involved, one strategy may avoid separation of isomers in that the other position becomes blocked.

Esters of phenol **(17)** are used as garden fungicides,[28] e.g. **(18)** is Dinocap. We can disconnect the nitro group first (guideline 2) but the Friedel-Crafts reaction required would surely give mostly *para* product as the electrophile is so large.



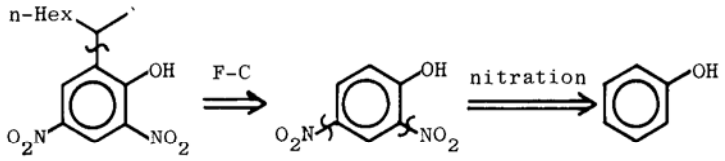
(17) (18)

Analysis 1



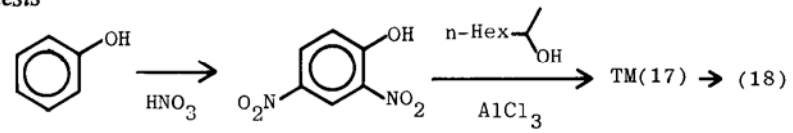
The alternative order of events, disconnecting the Friedel-Crafts first, is unusual but sensible here since the *para* position is blocked.

Analysis 2

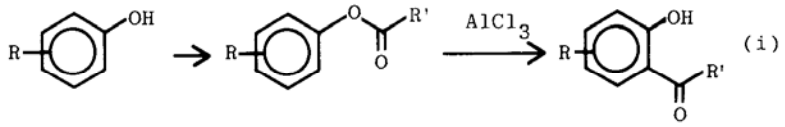


Dinocap is manufactured by the second route.

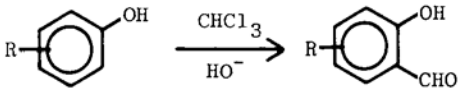
Synthesis[28]



There are two reactions which can give unusually large amounts of *ortho* product: the Fries rearrangement[29] (i) (see page 22), and the Reimer–Tiemann reaction[30] (ii) These can be used to set up *ortho* substituents with other substituents present but one OH group is needed in the molecule.



(i)



(ii)

Not all these nine guidelines apply to any one case—indeed some may well contradict others. It is a matter of judgement—as well as a laboratory trial and error—to select a good route. As always, several strategies may be successful.

Table 3.1 Direction and activation in aromatic electrophilic substitution. The most activating groups are at the top of the list. In general, the more activating group dominates the less activating* and the selectivity will be greater the more the difference between them

Direction	Group	Activation
o,p	R_2N, NH_2	Activating (electron-donating)
	RO, OH	
	Alkenyl	
	Aryl	
	Alkyl	
	CO_2^-, H	Electronically neutral
	Halide	
m	CX_3	
	(X=F, Cl etc)	
	CO_2H	Deactivating (electron-withdrawing)
	COR, CHO	
	SO_3H	
	NO_2	

*Ignoring steric effects.