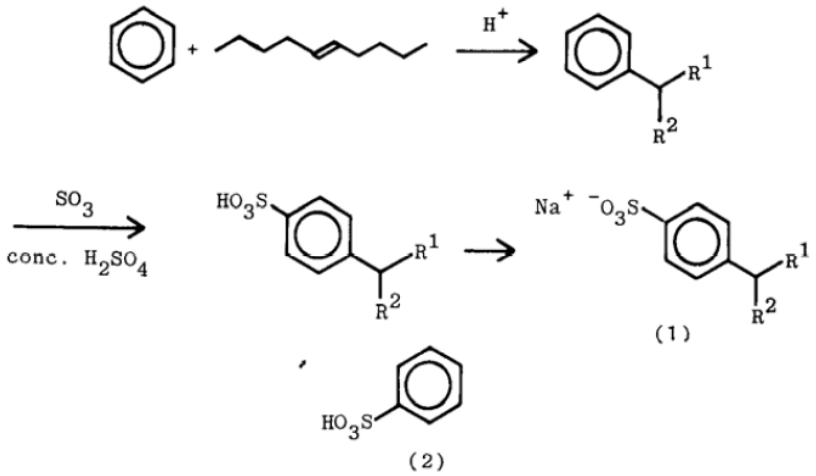
Lecture # 4

Strategy I: The Order of Events

In this chapter, using aromatic compounds as examples, we examine the question of the order in which reactions should be carried out.



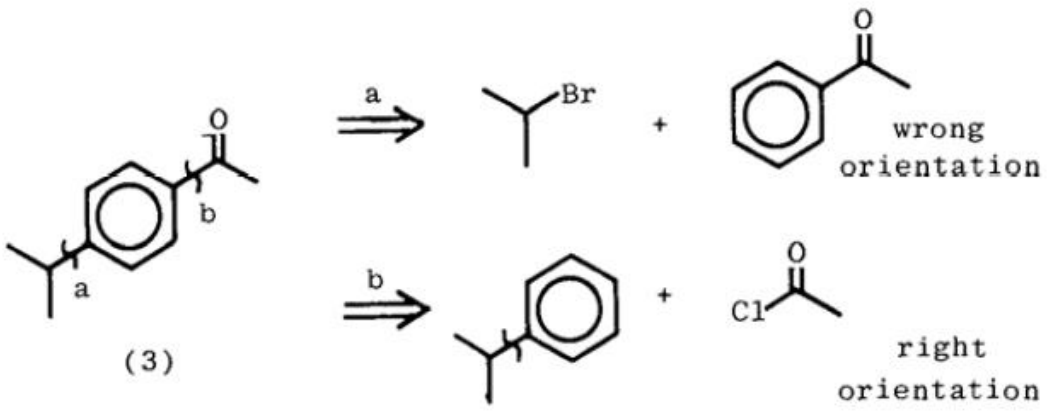
The detergents commonly used nowadays contain sodium salts of sulphonic acids such as **(1)**. They are made industrially[18] in two steps from benzene, a Friedel–Crafts reaction, and a sulphonation. The question is: why this order of events? Two factors influence the answer. The alkyl group is electron-donating 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.

Guideline 1

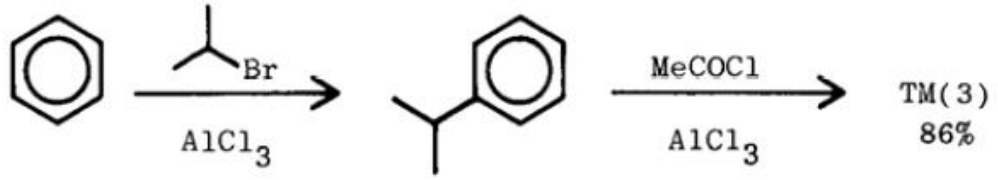
Examine the relationship between the groups, looking for groups which direct to the right position. The thorough way to do this is to disconnect all groups in turn and see if the reverse reaction would give the right orientation.

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]

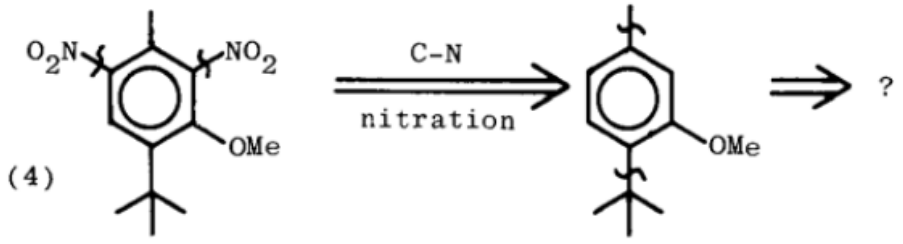


Guideline 2

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.

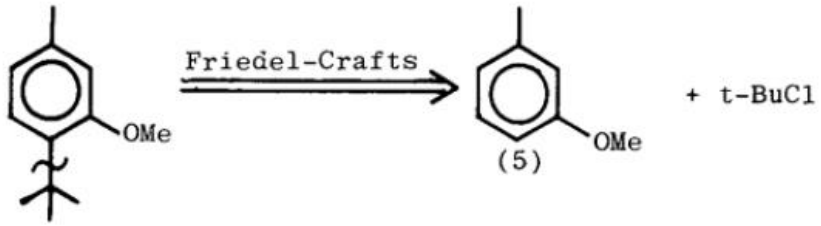
Musk ambrette **(4)**, a synthetic musk, essential in perfumes to enhance and retain the odour, is an aromatic compound with five substituents on the benzene ring. The nitro groups are by far the most electron-withdrawing so we can disconnect them first.

Musk ambrette: *Analysis 1*



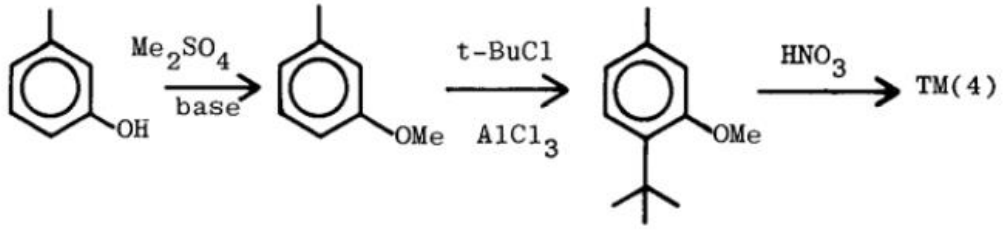
We could add either the Me or the *t*-Bu group by a Friedel–Crafts alkylation. The OMe group is strongly *o*,*p*-directing so only the *t*-Bu disconnection is reasonable (guideline 1).

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:

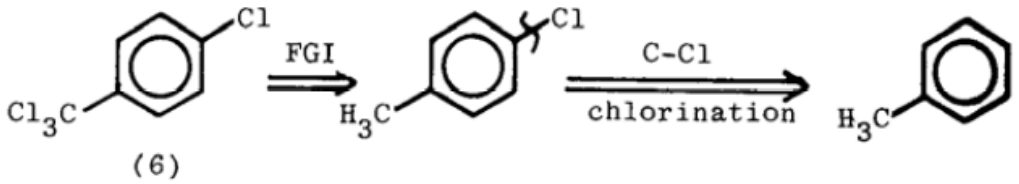
o,*p*-directing Me → CO_2H *m*-directing

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.

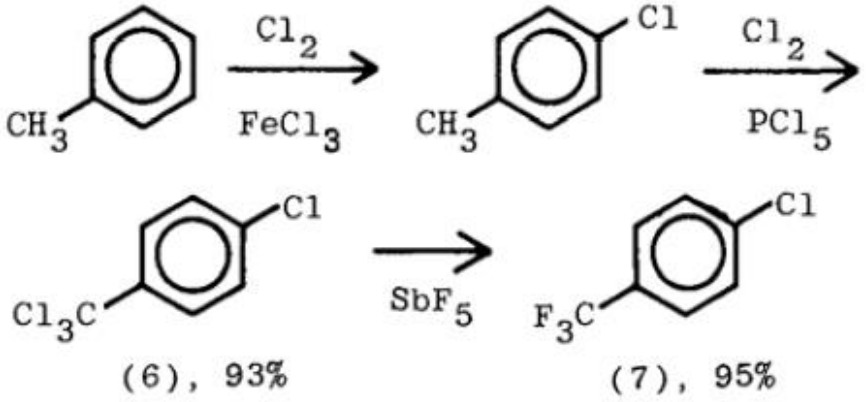
Analysis



(6)

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

Synthesis[13]



(6), 93%

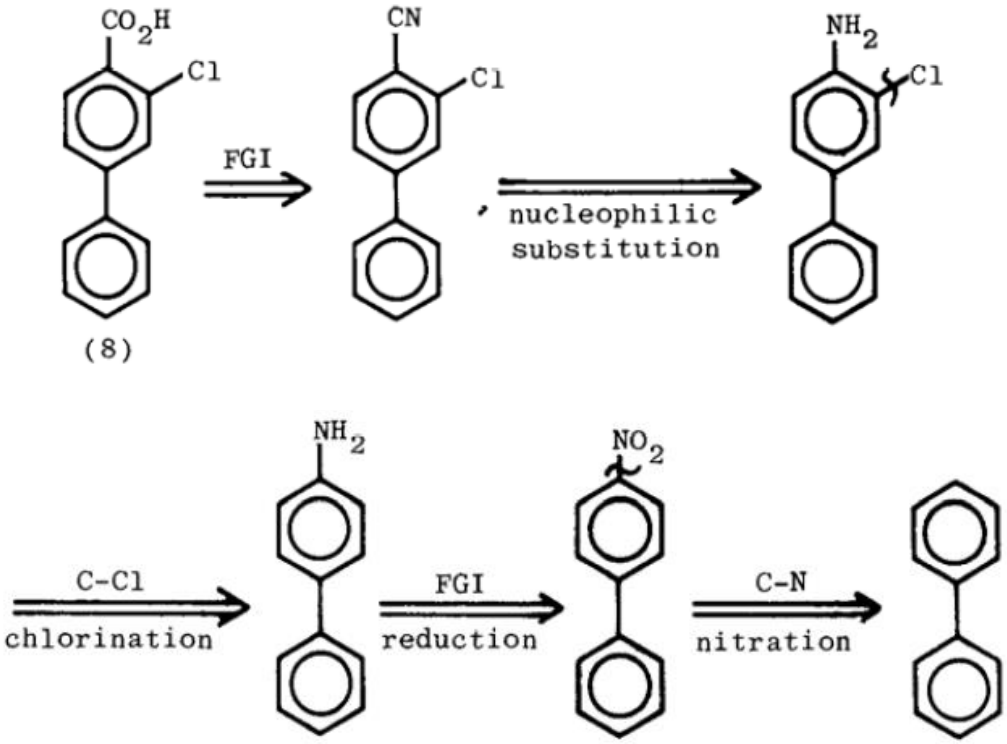
(7), 95%

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.

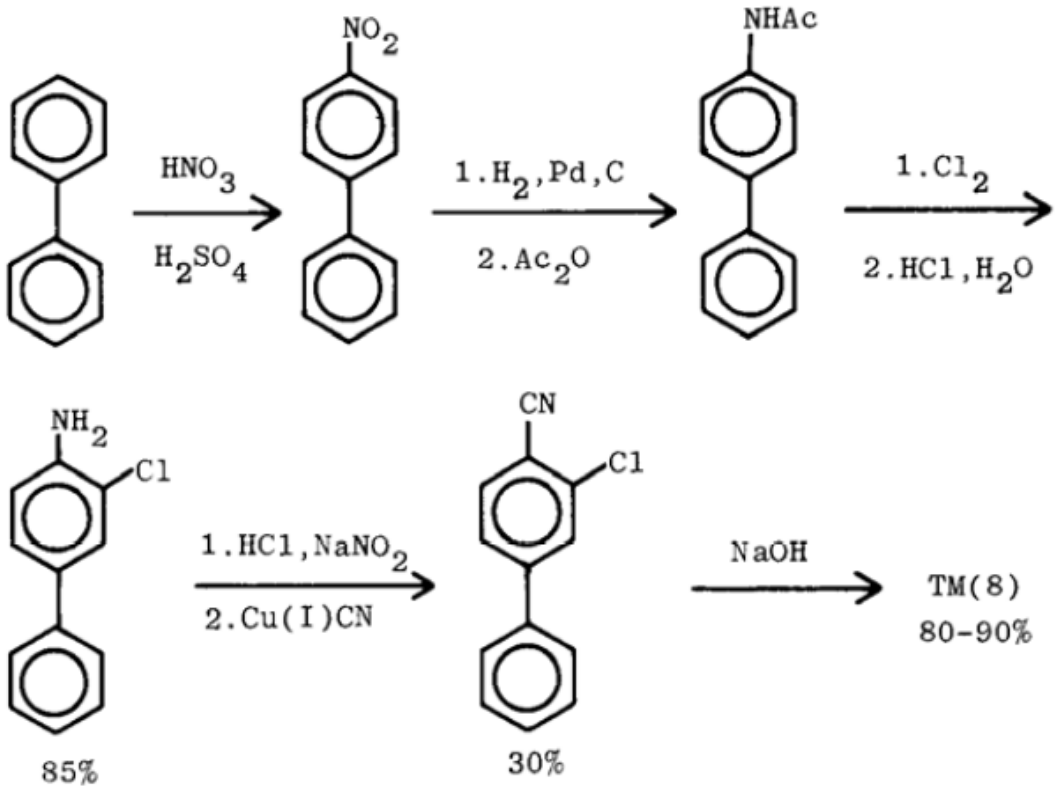
Acid **(8)** was needed at Hull University[22] to study its liquid crystal behaviour (liquid crystals are used in digital displays). The other benzene ring is *o*,*p*-directing, so to get the chlorine in we must replace the CO_2H group by a *more* *o*,*p*-directing group than Ph. Amino is the obvious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

Analysis



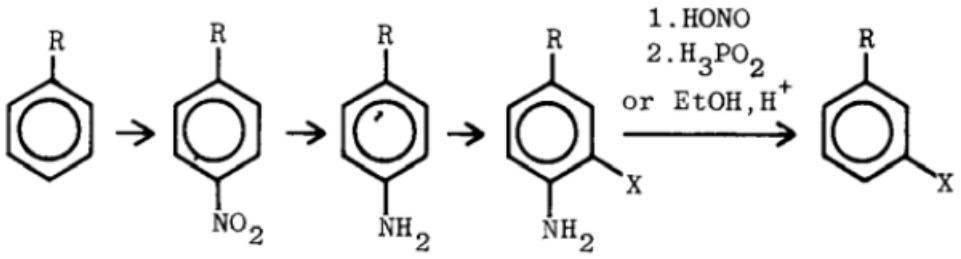
In the synthesis it will be necessary to acylate the amino group to prevent over-chlorination (cf. Chapter 2).

Synthesis[22,23]

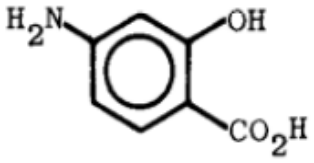


Guideline 5

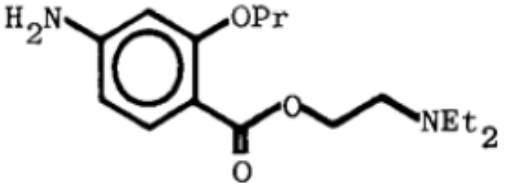
As a last resort, there is a trick to solve some difficult problems, such as adding two *o,p*-directing groups *meta* to each other. A 'dummy' amino group is added, used to set up the required relationship and then removed by diazotisation and reduction:



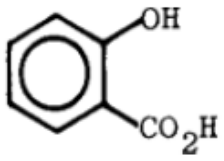
The acid **(9)** is used in the synthesis of a number of local anaesthetics[24] such as Propoxycaine **(10)**. The amino group cannot be put in by nitration of salicyclic acid **(11)** as the oxygen atom will direct *o,p* and give the wrong isomer. The problem can be solved by deliberately making the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



(9)

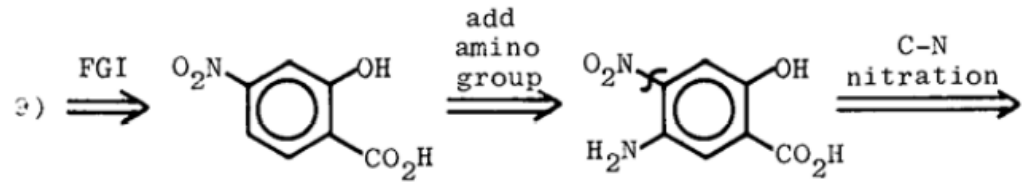


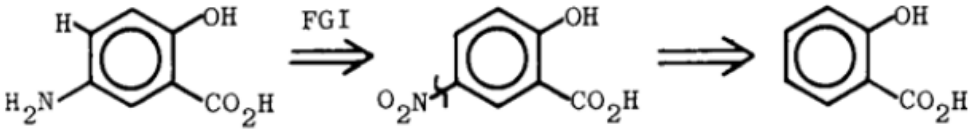
(10)



(11)

Analysis

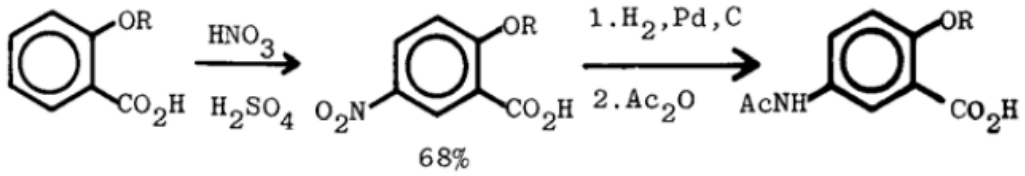


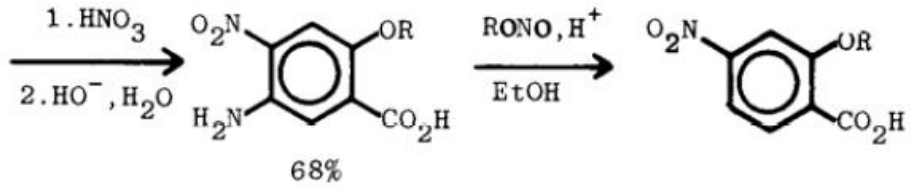


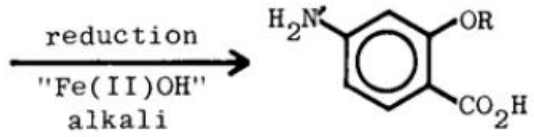
(11)

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

Synthesis[25]







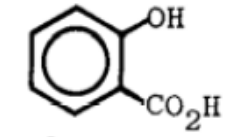
Guideline 6

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).

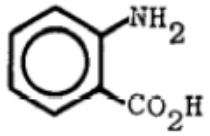
Guideline 7

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.

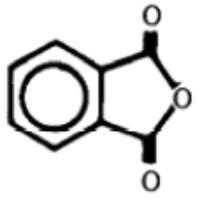
Examples are:



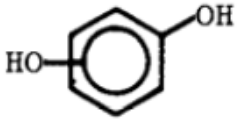
salicylic acid
and aldehyde



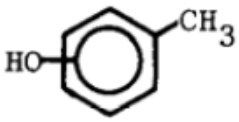
anthranilic acid



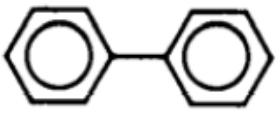
phthalic
anhydride



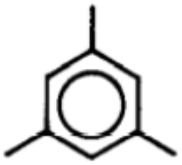
ortho, meta, and
para compounds



ortho, meta,
and para cresols



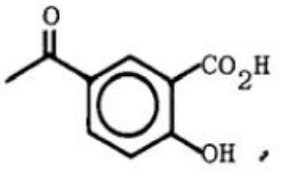
diphenyl



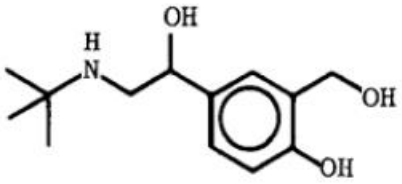
mesitylene

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.

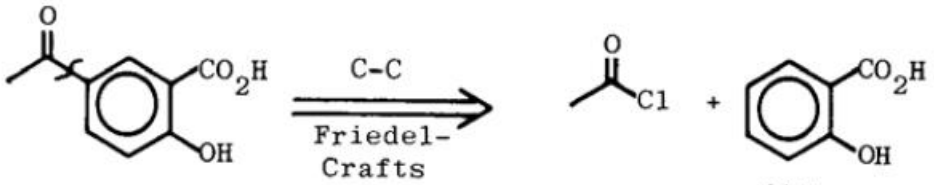


(12)



(13)

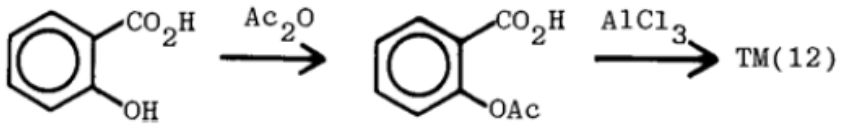
Analysis



(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]

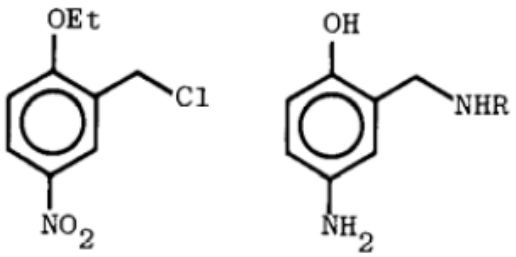


(14)

Guideline 8

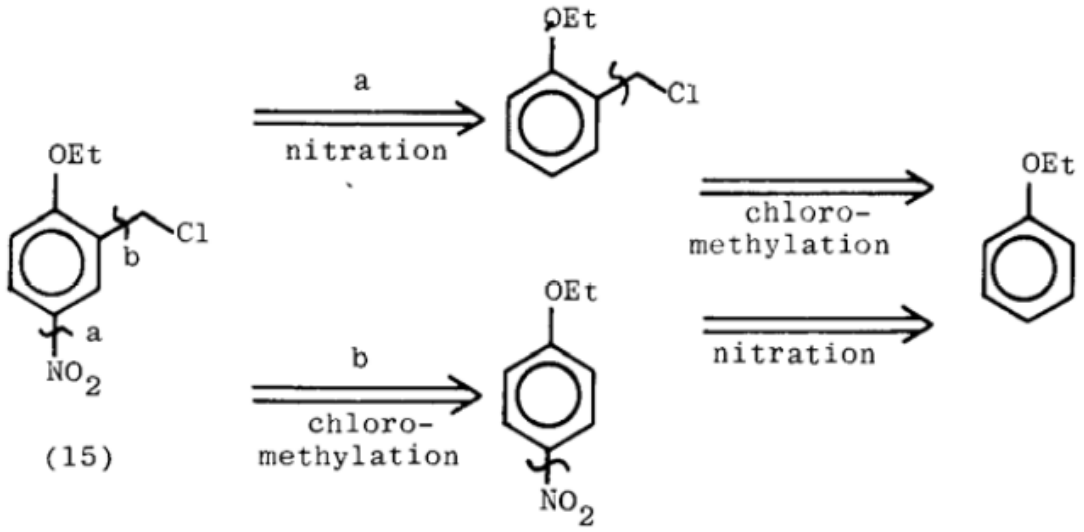
Avoid sequences which may lead to unwanted reactions at other sites in the molecule. Thus nitration of benzaldehyde gives only 50% *m*-nitrobenzaldehyde since the nitric acid oxidises CHO to CO_2H. One way round this particular problem is to nitrate benzoic acid and reduce CO_2H to CHO.

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.



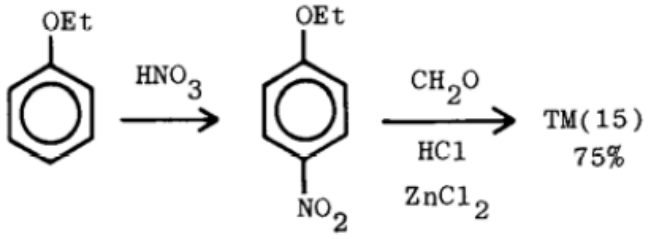
(15) (16)

Analysis



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.

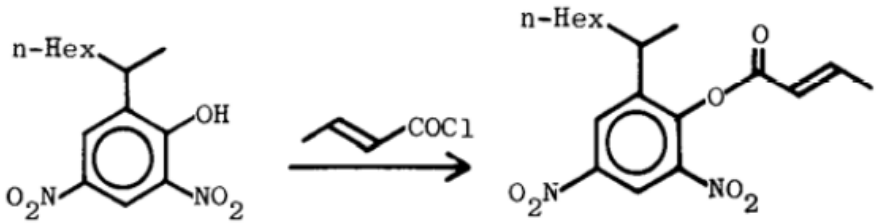
Synthesis[27]



Guideline 9

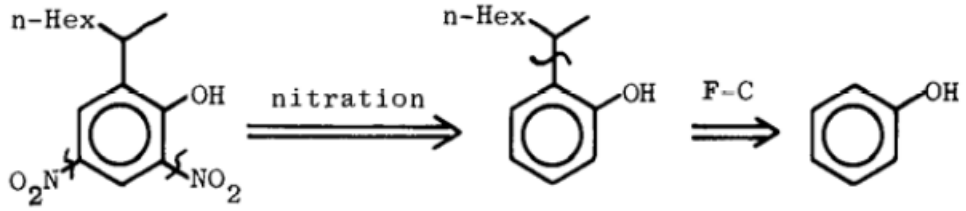
If *o*,*p*-substitution is involved, one strategy may avoid separation of isomers in that the other position becomes blocked.

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.



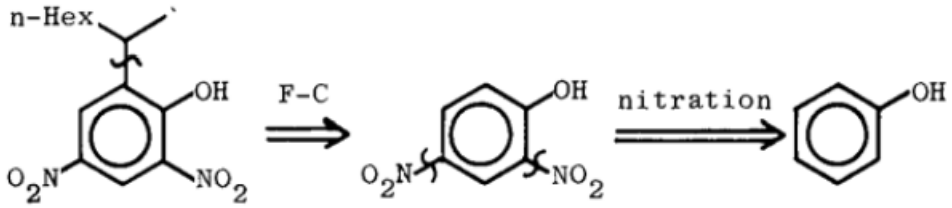
(17) (18)

Analysis 1



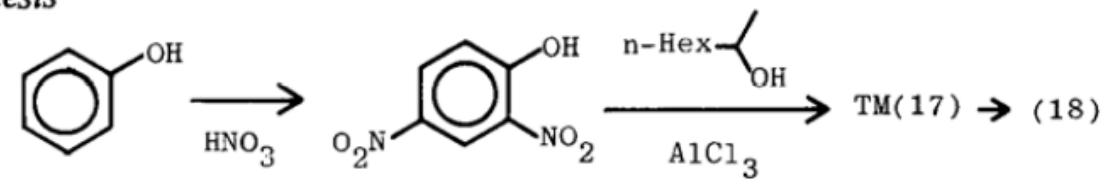
The alternative order of events, disconnecting the Friedel–Crafts first, is unusual but sensible here since the *para* position is blocked.

Analysis 2

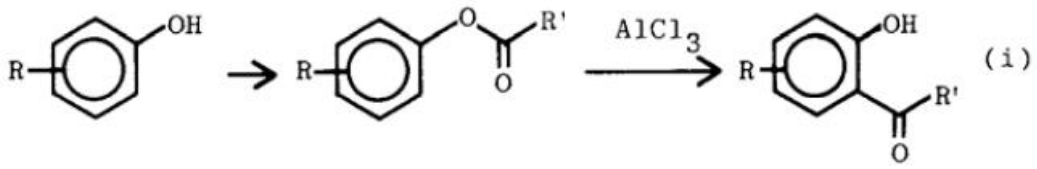


Dinocap is manufactured by the second route.

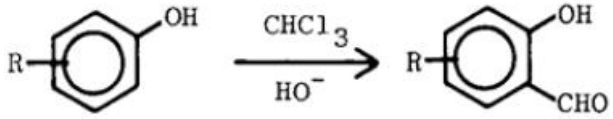
Synthesis[28]



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.