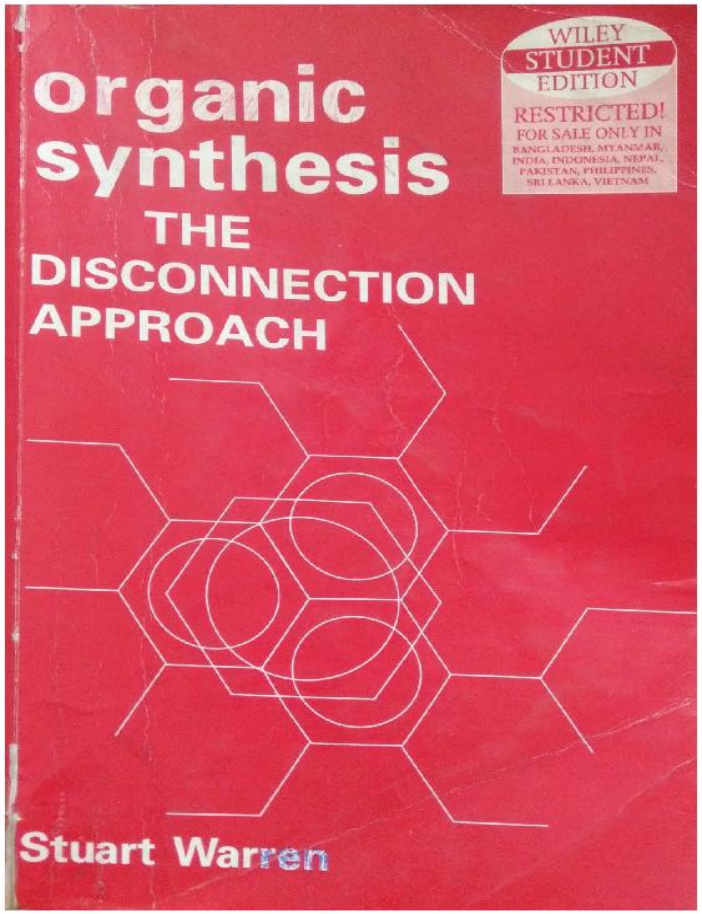
Disconnection approach

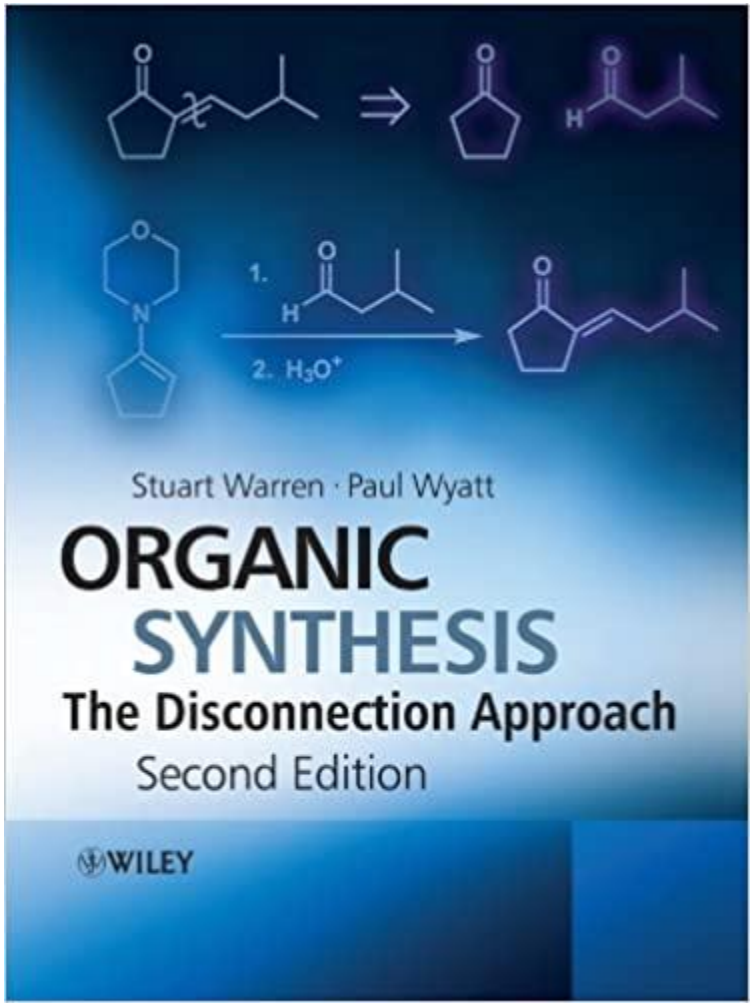
or

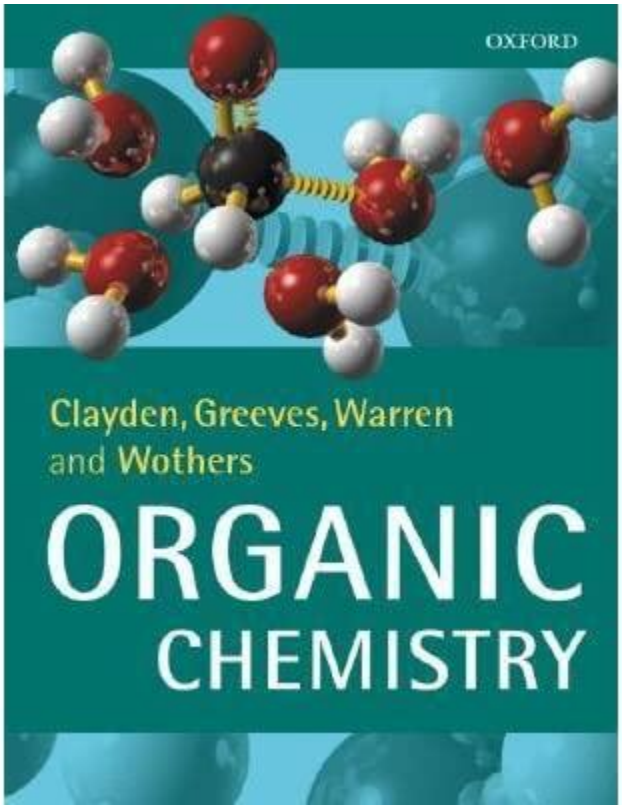
synthon approach

or

Reterosynthetic approach


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organic synthesis
THE DISCONNECTION APPROACH
Stuart Warren

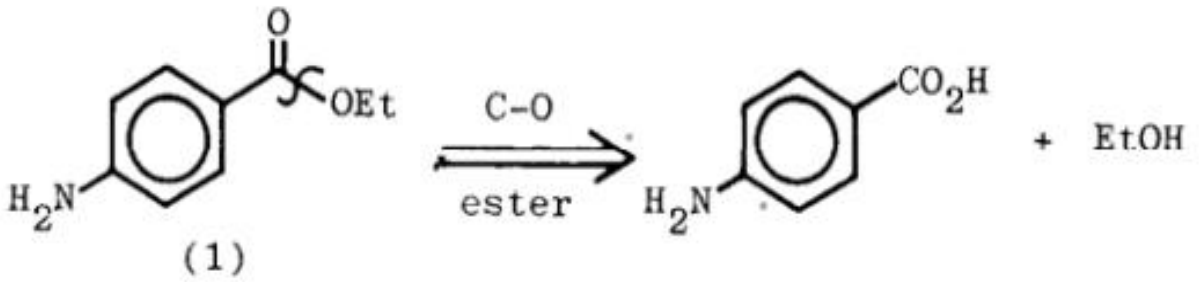

1.
2. H3O+
Stuart Warren · Paul Wyatt
ORGANIC SYNTHESIS
The Disconnection Approach
Second Edition
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OXFORD
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and Wothers
ORGANIC
CHEMISTRY

Disconnection: Reverse of synthetic reactions or steps

- We disconnect only when we have some reliable reaction in mind
- We disconnect to know the various steps of reaction and to get simplest starting material
- Disconnection is indicated by double line arrow or retrosynthetic arrow
- Site of disconnection is indicated by wiggly line which shows imaginary breaking of molecules

Benzocaine



(1)

Technical Terms

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.

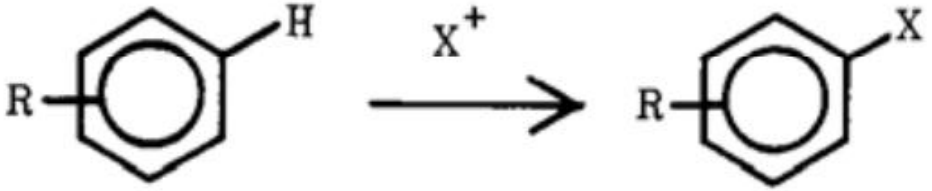
Disconnection: the reverse operation to a reaction. The imagined cleavage of a bond to 'break' the molecule into possible starting materials.

⇒: 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.

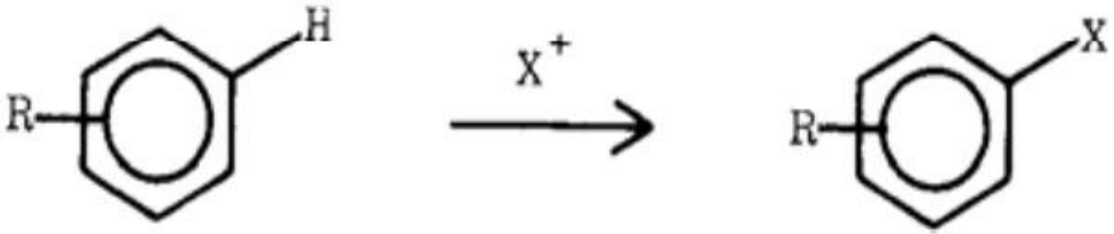
Reagent[a]: compound used in practice for a synthon. Thus MeI is the reagent for the Me^+ synthon.

One-carbon electrophiles for aromatic synthesis



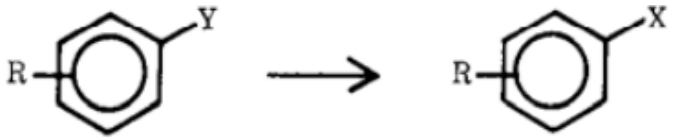
X	Reagent	Reaction
CH_2Cl	$CH_2O + HCl + ZnCl_2$	Chloromethylation
CHO	$CHCl_3 + HO^-$	Reimer–Tiemann[b]
	$Me_2N{=}CH{-}OPOCl_2$	Vilsmeier–Haack
	$(Me_2NCHO + POCl_3)$	Formylation
	$CO + HCl + AlCl_3$	
	$Zn(CN)_2 + HCl$	

Reagents for aromatic electrophilic substitution



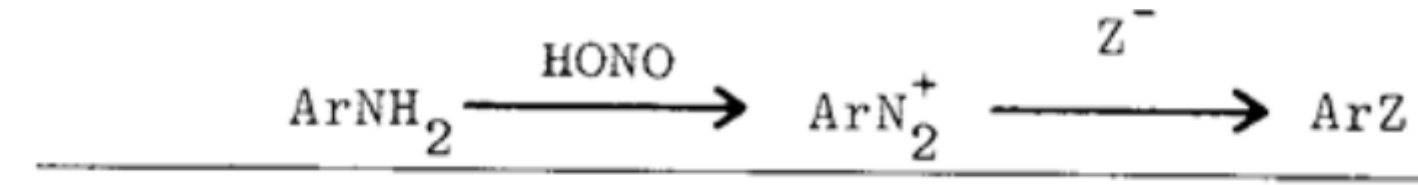
Synthon	Reagent	Reaction
R^+	$RBr + AlCl_3$ $ROH + H^+$ $Alkene + H^+$	Friedel–Crafts alkylation
RCO^+	$RCOCl + AlCl_3$	Friedel–Crafts acylation
NO_2^+	$HNO_3 + H_2SO_4$	Nitration
Cl^+	$Cl_2 + FeCl_3$	Chlorination
Br^+	$Br_2 + Fe$	Bromination
$^+SO_2OH$	H_2SO_4	Sulphonation
$^+SO_2Cl$	$ClSO_2OH$	Chlorosulphonation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

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
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

Aromatic compounds made by nucleophilic displacement of diazonium salts



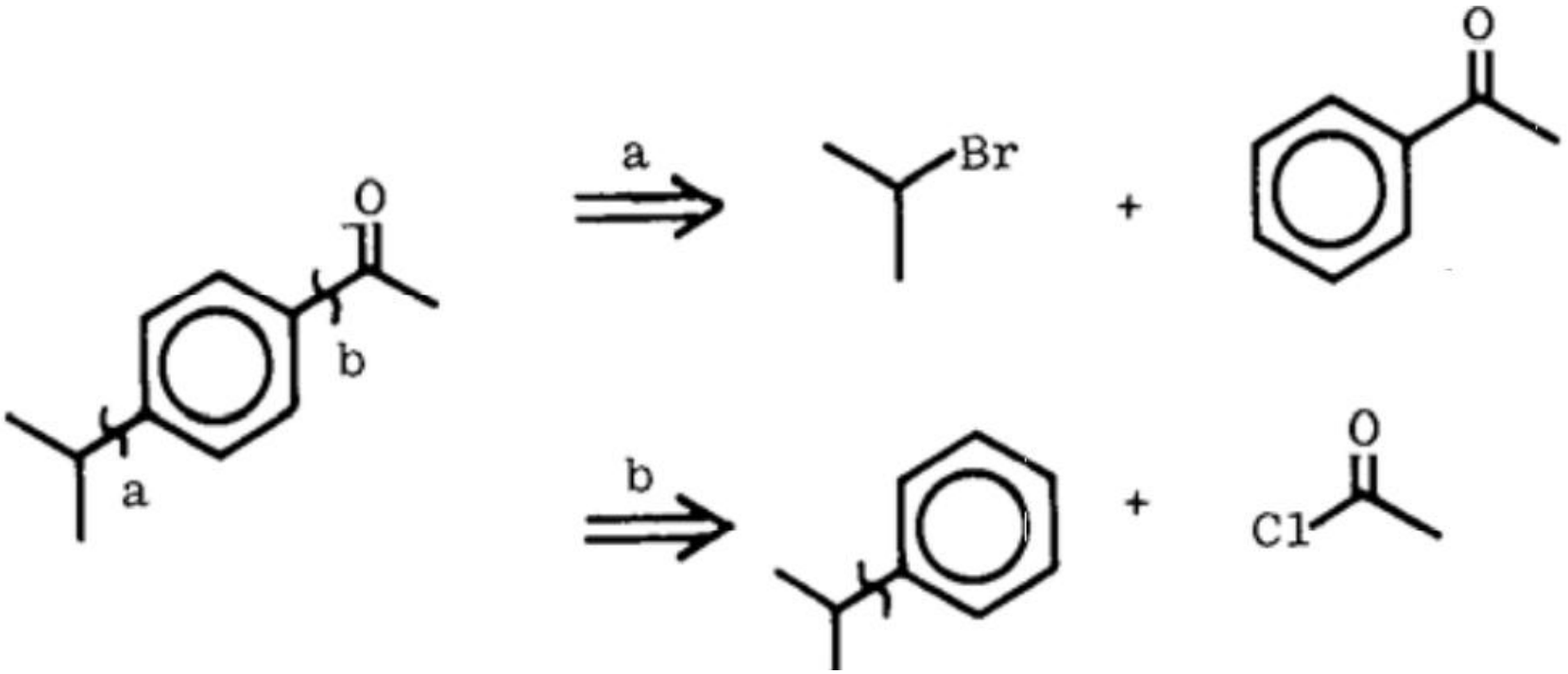
Z	Reagent
HO	H_2O
RO	ROH
CN	Cu(I)CN
Cl	Cu(I)Cl
Br	Cu(I)Br
I	KI
Ar	ArH
H	H_3PO_2 or $EtOH/H^+$

The Order of Events

- First we will discuss the question of order in which reactions should be carried out using aromatic compounds
- We start with aromatic compounds because the bond to be disconnected is almost always the one joining aromatic ring to rest of the molecule.
- It is based on some general guidelines.

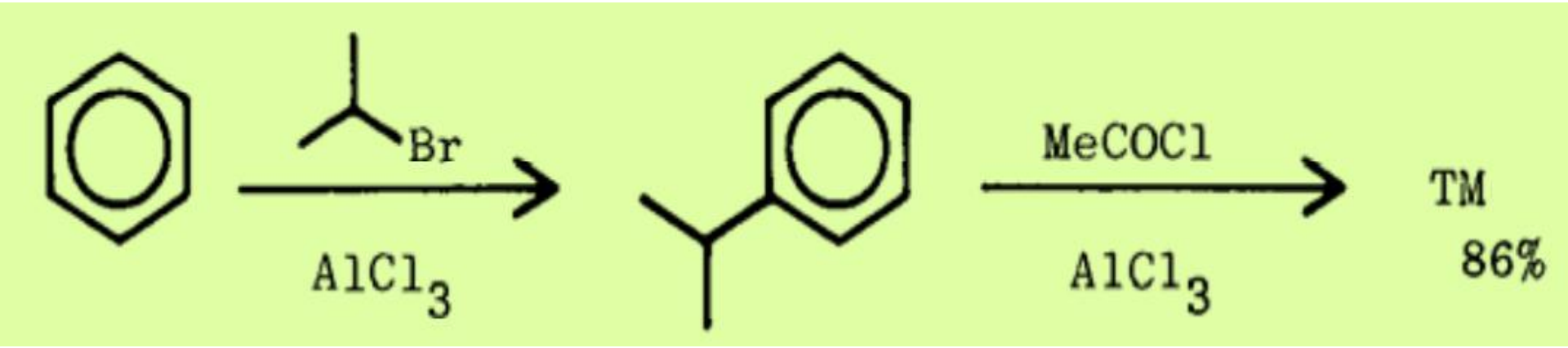
The Order of Events: Guideline 1

- Examine the relationship between the groups, look for the groups which direct to the right position



The Order of Events: Guideline 1

- Route b gives starting materials which would react in the right orientation since the keto group in a is meta directing

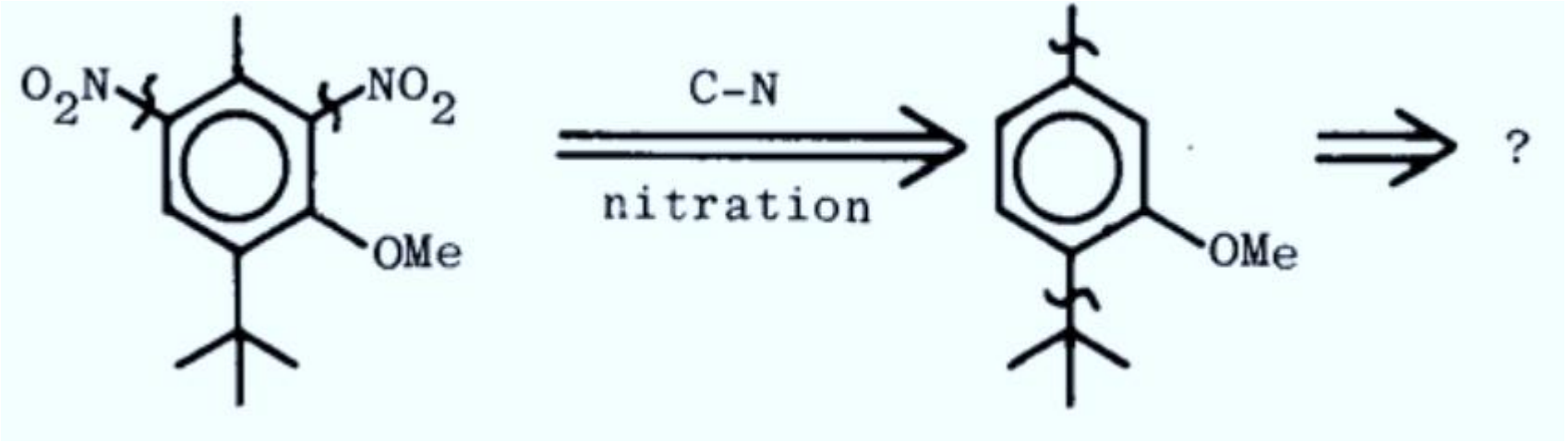


Direction and activation in aromatic electrophilic substitution

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	

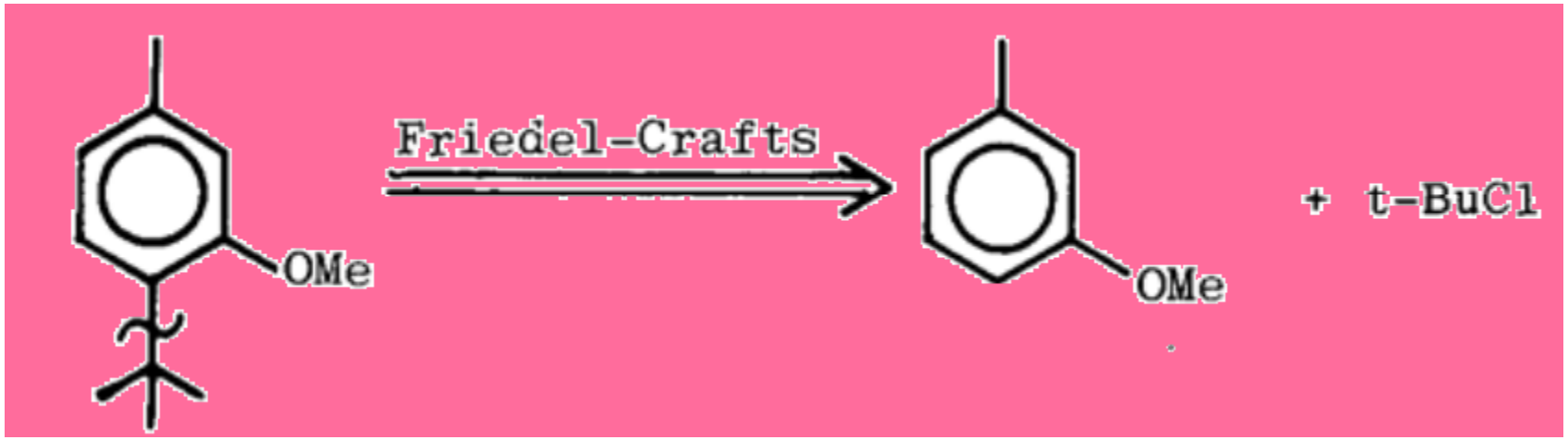
The Order of Events: Guideline 2

- If there is choice, disconnect first the most electron withdrawing substituent because the substituent will be deactivating and it may be difficult to add anything else once it is in.



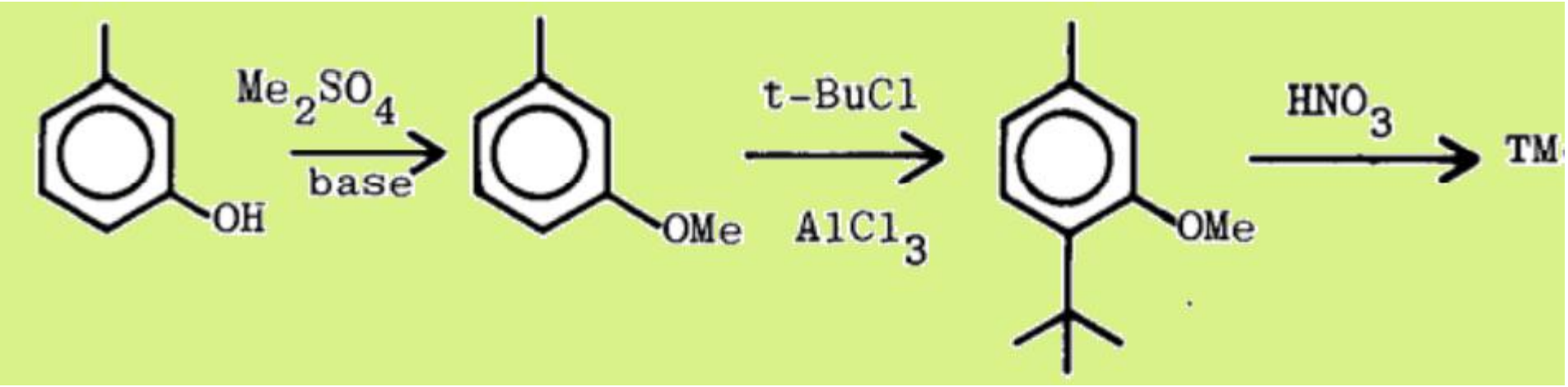
The Order of Events: Guideline 2

- We could add Me or *t*-Bu by Friedel-Crafts alkylation
- OMe is o,p-directing so only t-Bu disconnection is reasonable.



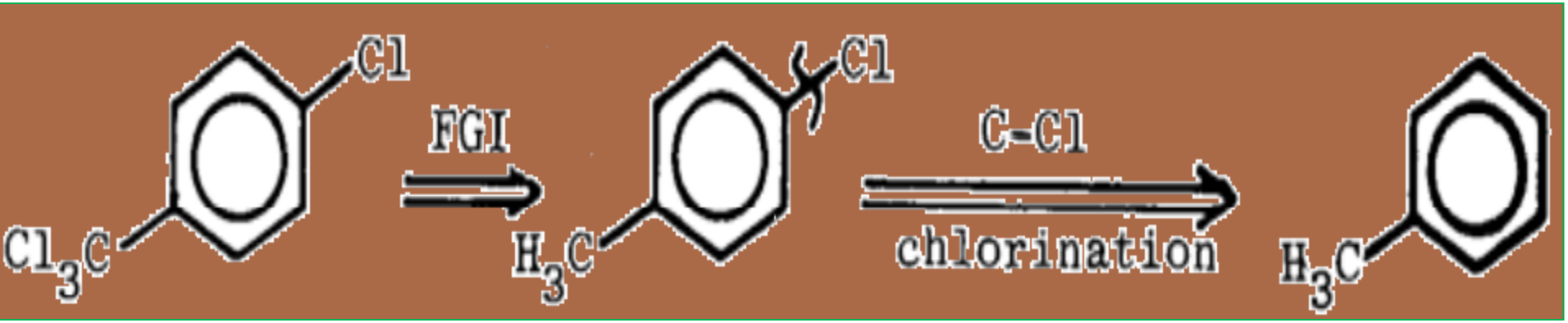
The Order of Events: Guideline 2

- SM is methyl ether of m-cresol which can be made with any methylating agent.

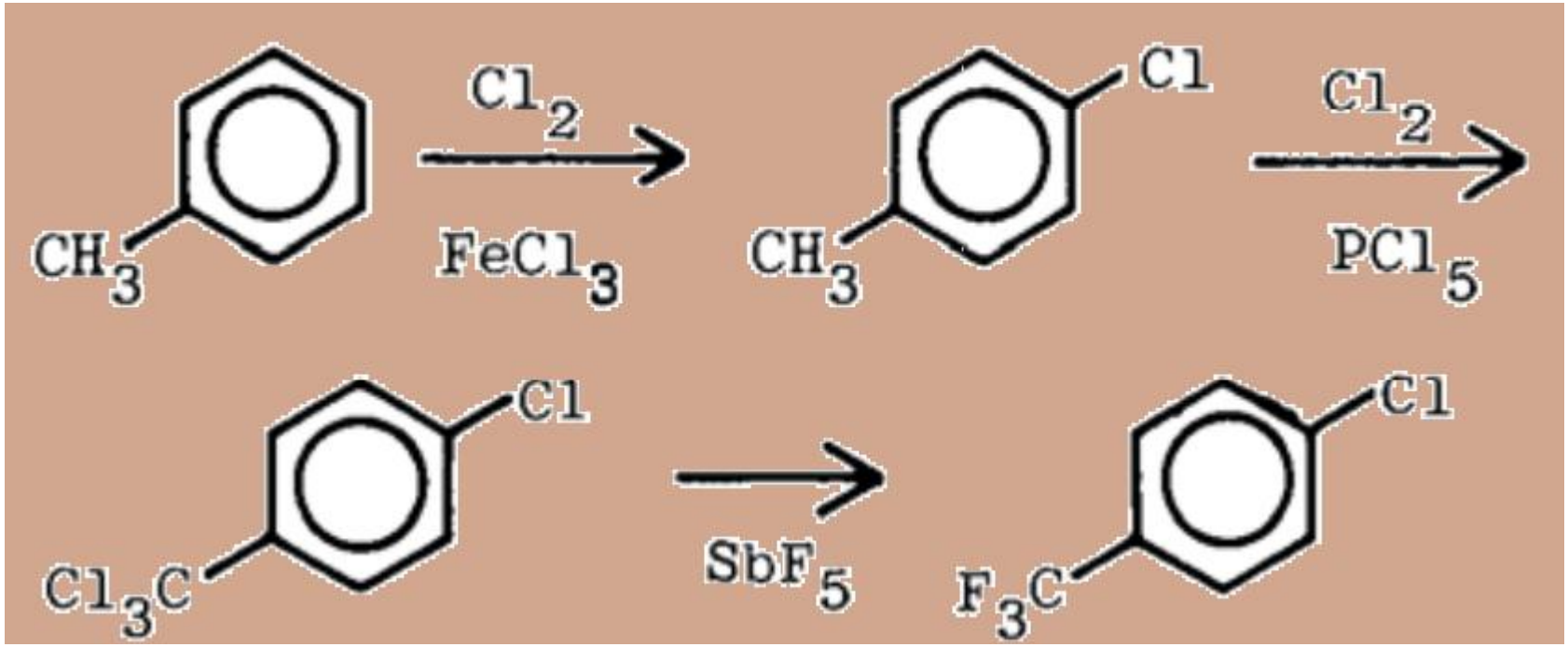


The Order of Events: Guideline 3

- If FGI is needed, other substituents may be added either before or after the FGI as it may well alter the directing effect of the group.



The Order of Events: Guideline 3

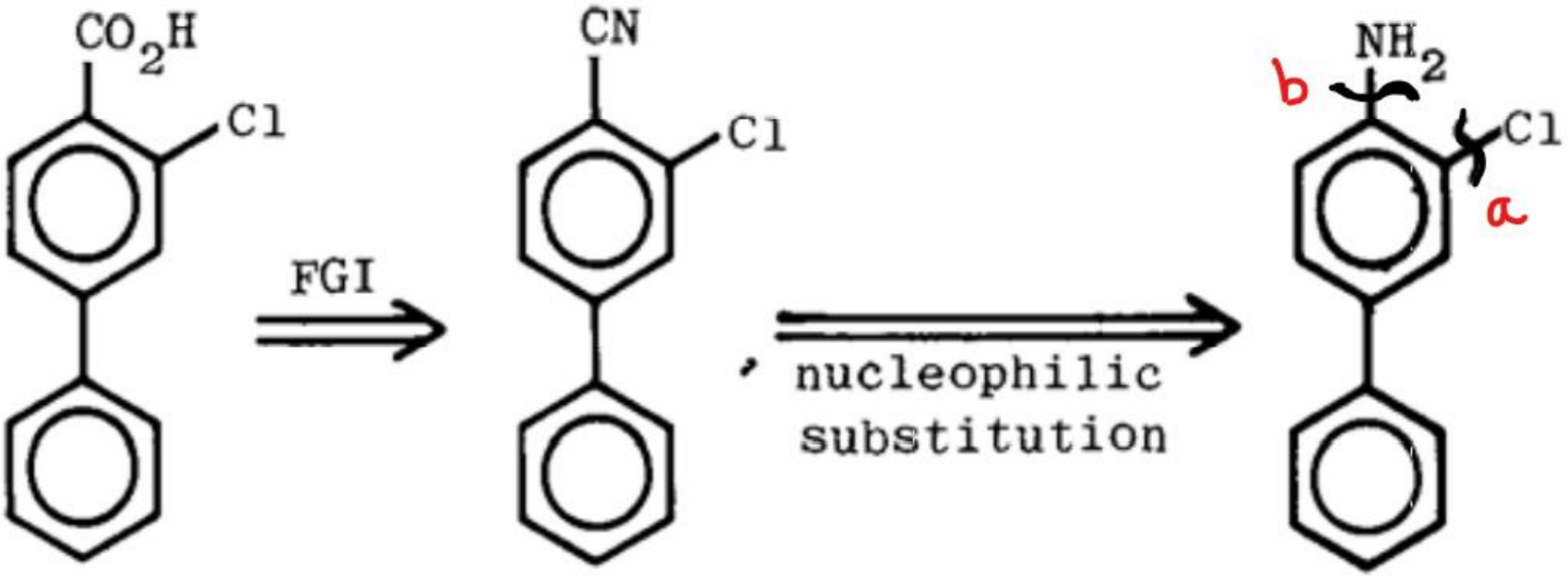


The Order of Events: Guideline 4

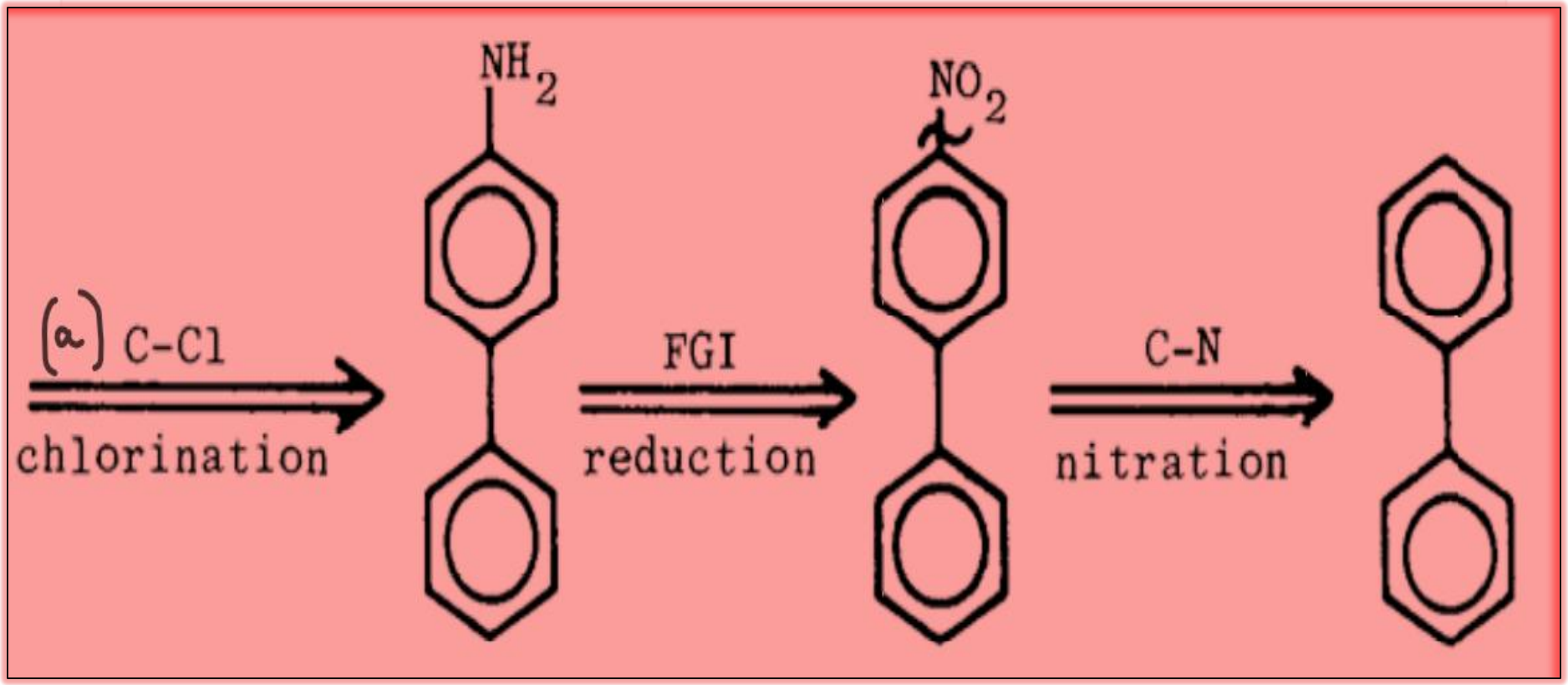
Groups may be added by nucleophilic substitution on diazonium salt made from aniline.

Adding other groups at amine stage may be advisable as the amino group is o,p-directing.

The Order of Events: Guideline 4

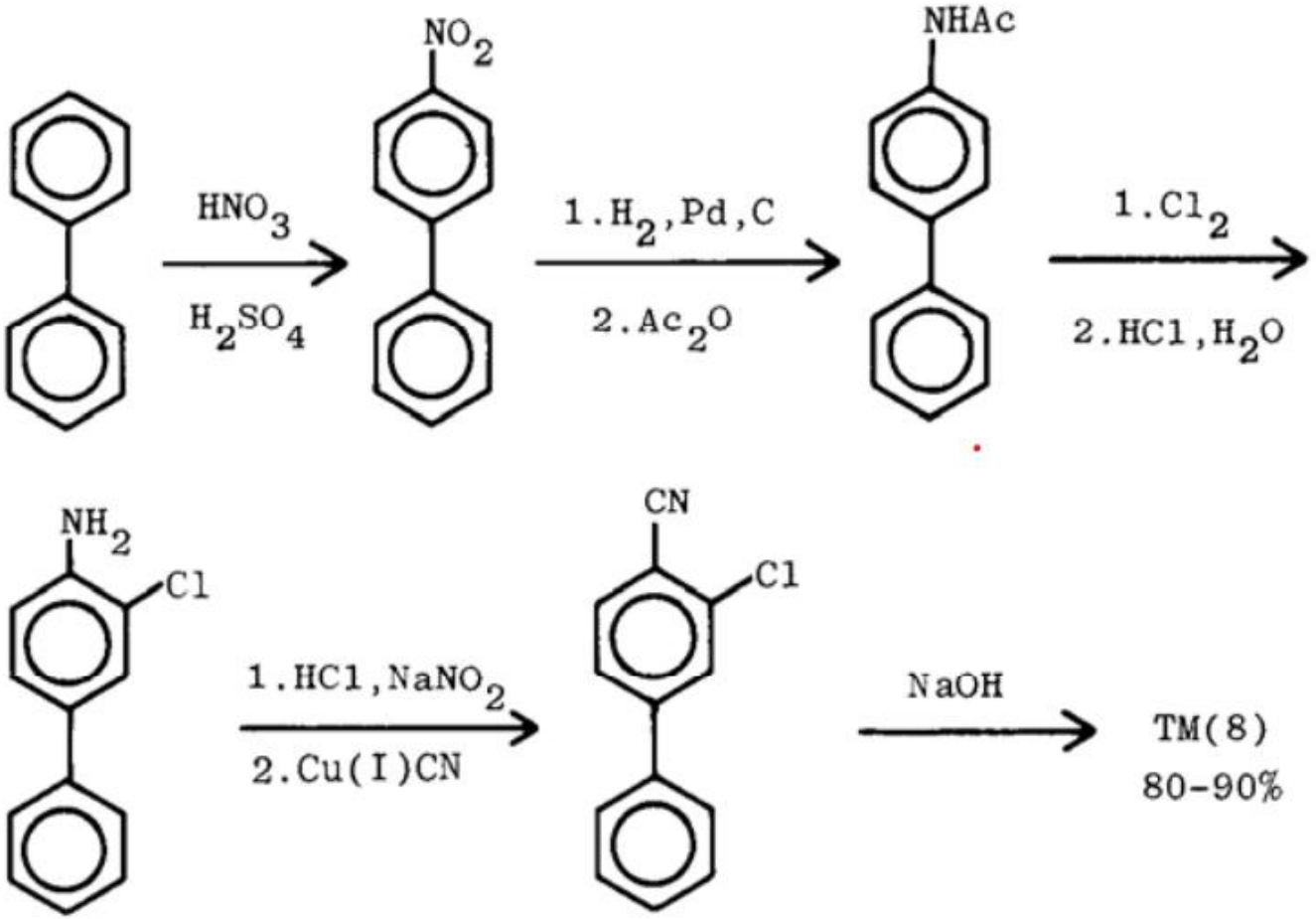


The Order of Events: Guideline 4



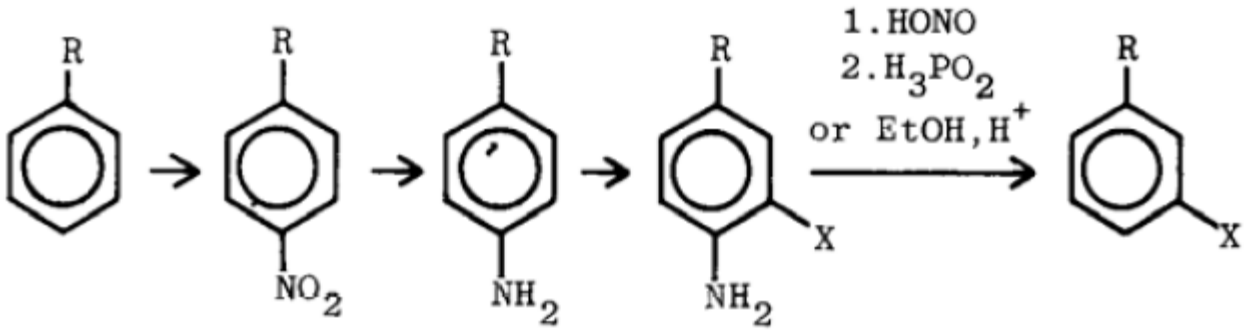
The Order of Events: Guideline 4

Synthesis

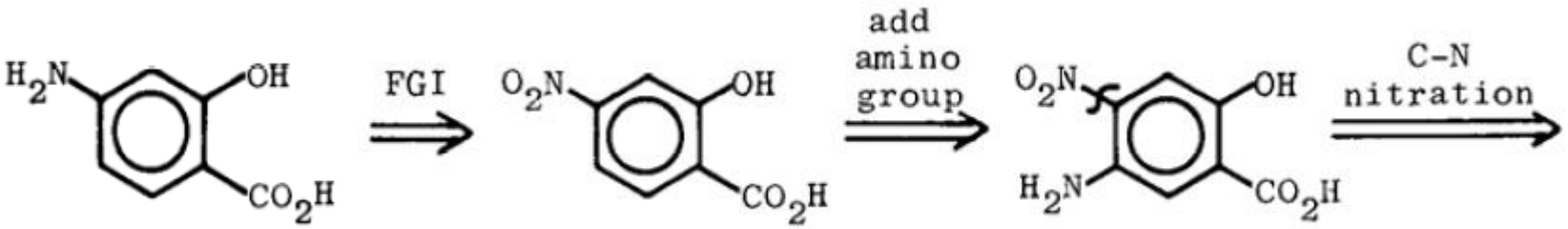


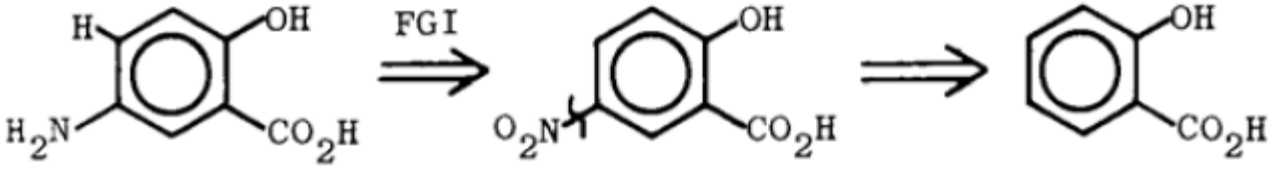
The Order of Events: Guideline 5

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 diazotization and reduction.



The Order of Events: Guideline 5

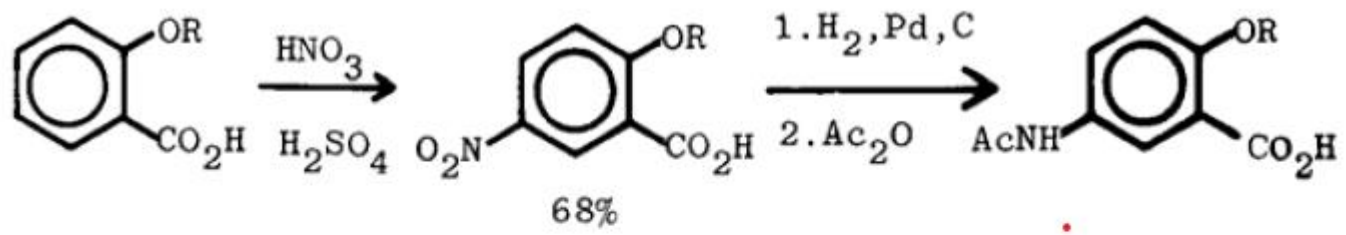


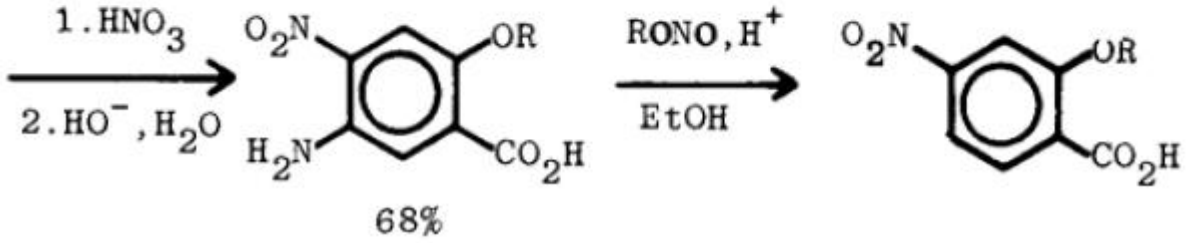


The Order of Events: Guideline 5

Synthesis

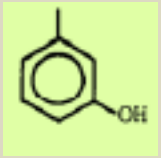
It is advisable to add alkyl to protect hydroxyl group

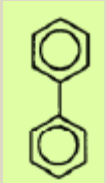




The Order of Events: Guideline 6

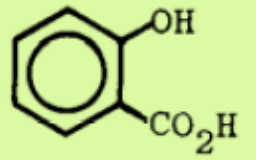
It is a good strategy not to disconnect the substituents which are difficult to add, but to use a starting material containing the substituent.



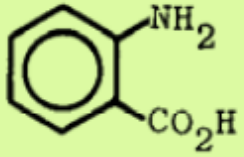


The Order of Events: Guideline 7

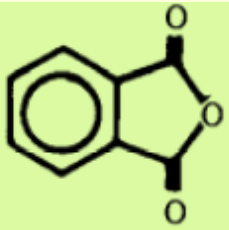
This is an extension of guideline 6. Look for a combination of substituents present in the TM and in a readily available starting material, particularly if it would be a difficult combination to set up.



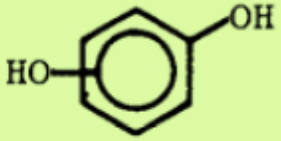
salicylic acid and aldehvde



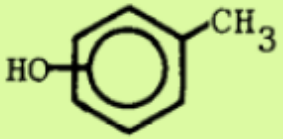
anthranilic acid



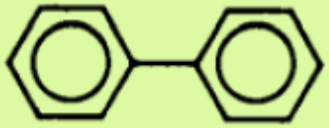
phthalic anhydride



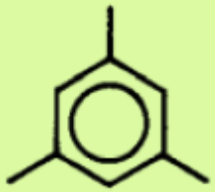
ortho, meta, and para compounds



ortho, meta, and para cresols



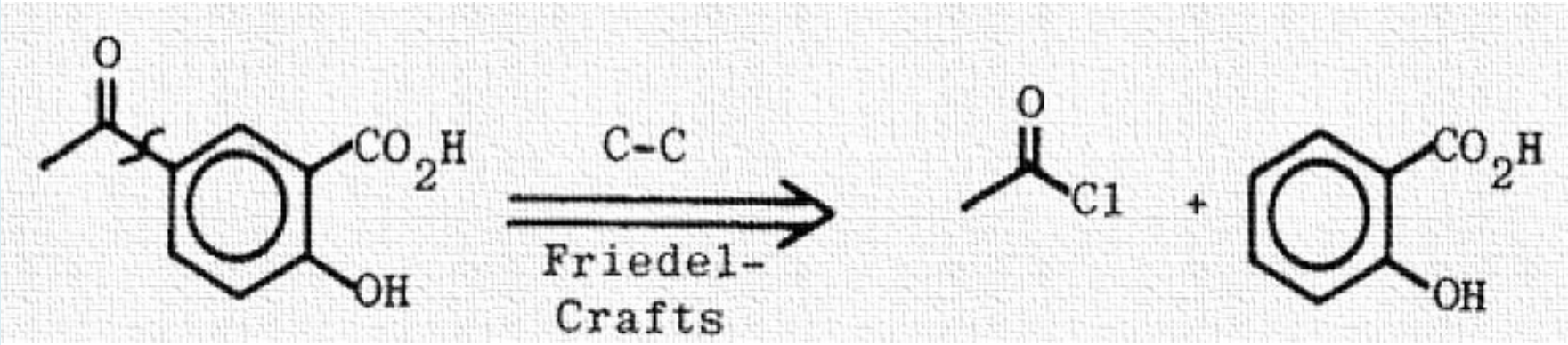
diphenyl



mesitylene

The Order of Events: Guideline 7

analysis



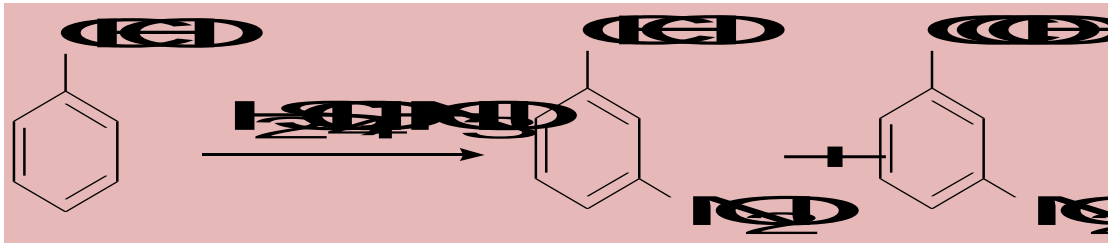
The Order of Events: Guideline 7

synthesis



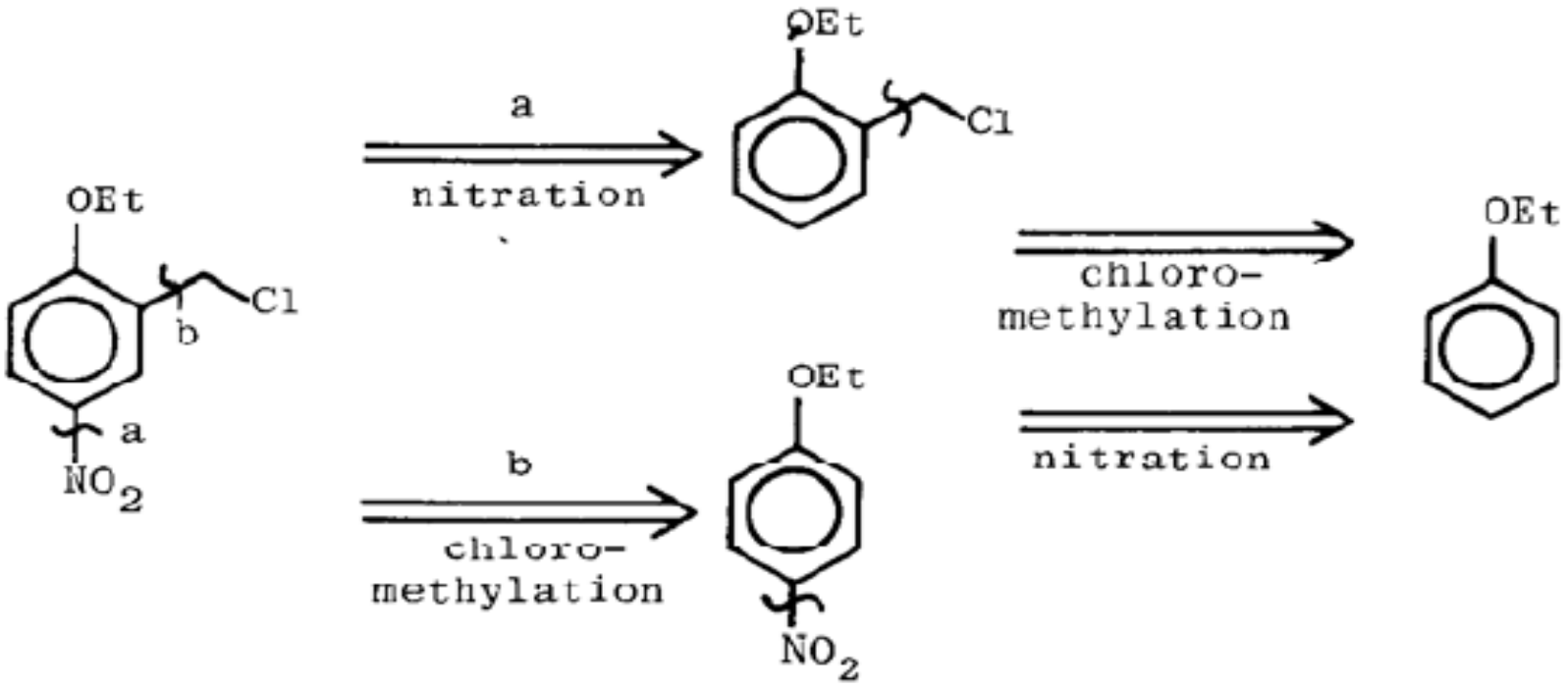
The Order of Events: Guideline 8

We must avoid sequences which may lead to unwanted reactions at other sites in the molecule



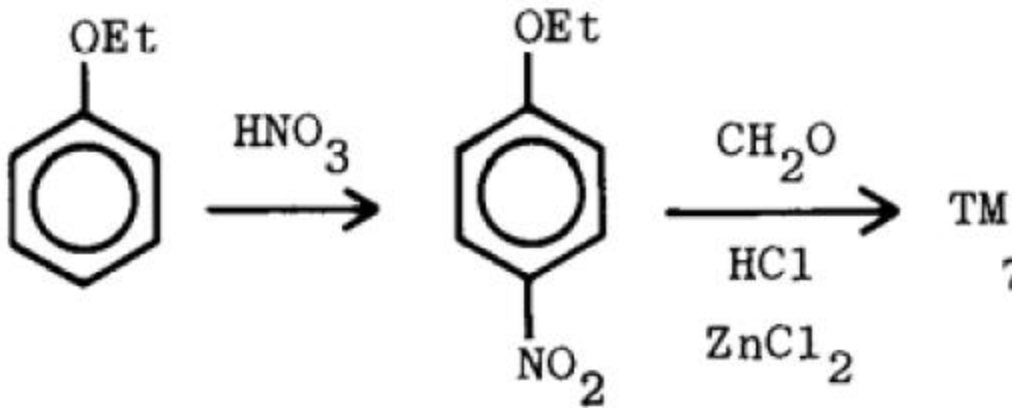
The Order of Events: Guideline 8

analysis



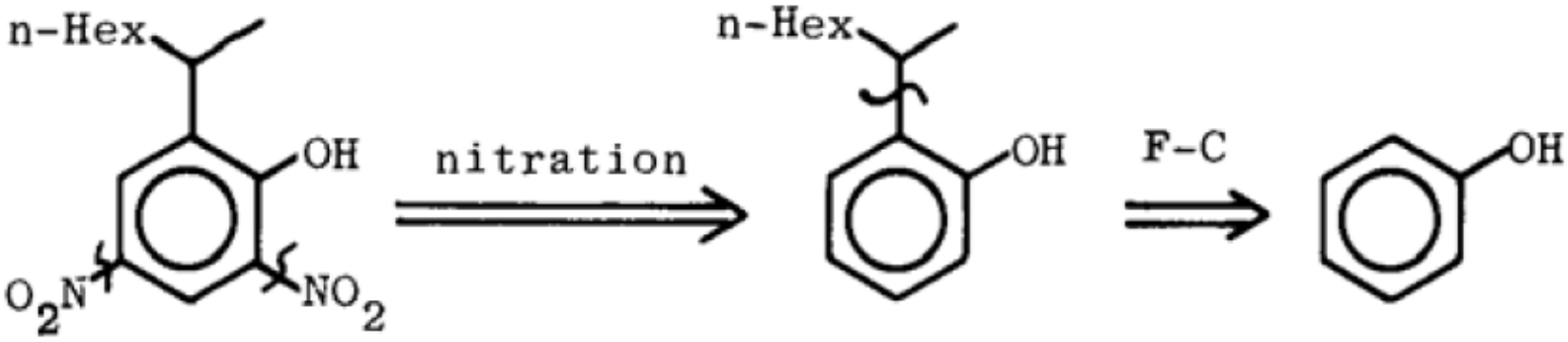
The Order of Events: Guideline 8

synthesis

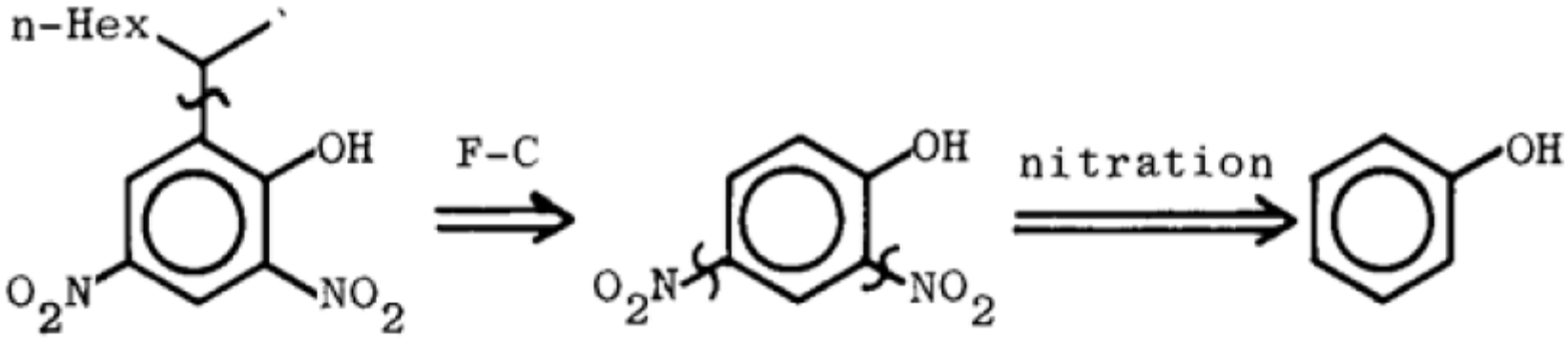


The Order of Events: Guideline 9

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



The Order of Events: Guideline 9



The Order of Events: Guideline 9

Synthesis

