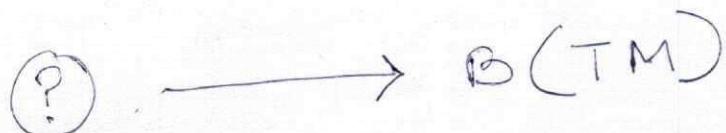
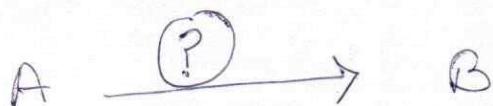
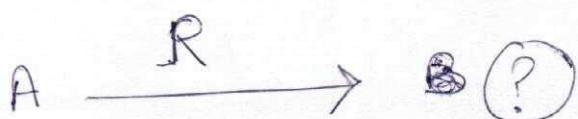
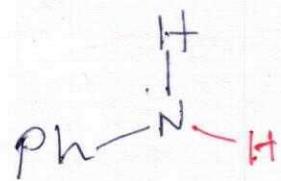
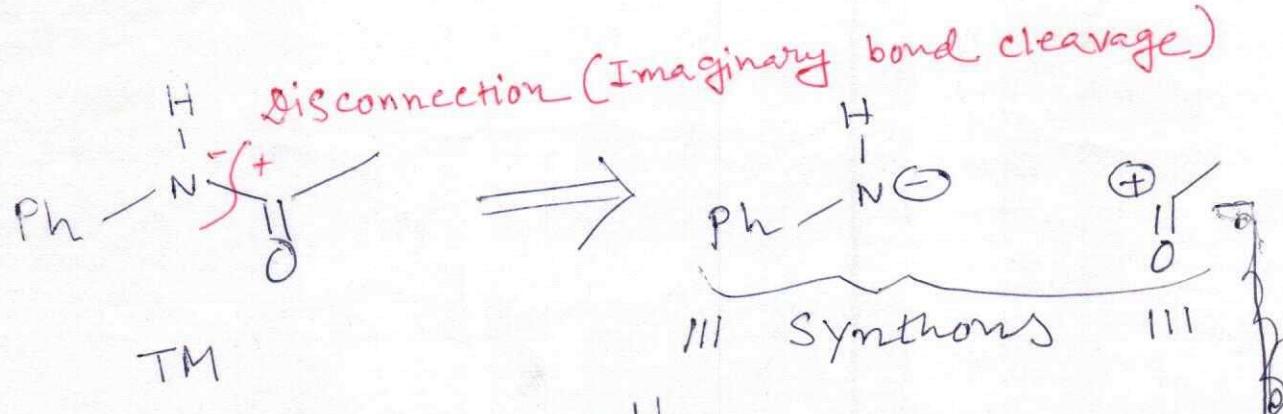


# ①

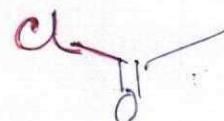
Retrosynthesis Analysis: Synthesis Backwards



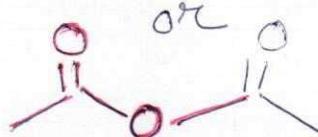
TM  $\longrightarrow$  SM [Retrosynthesis]  
 Retrosynthetic arrow (implies arrow)



Synthetic equivalent



synthetic equivalent / equivalent reagent

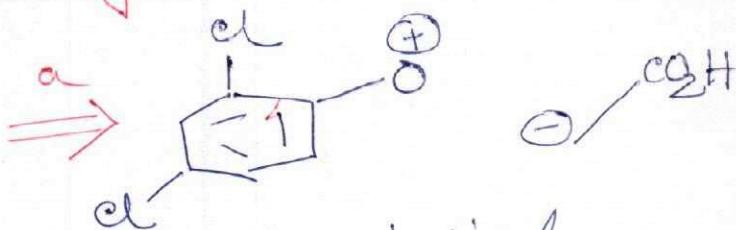
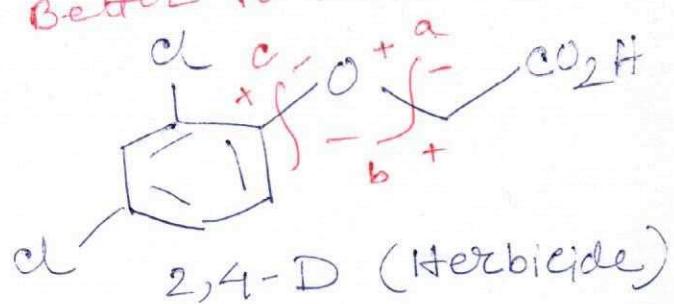


## choosing Disconnection:

(2)

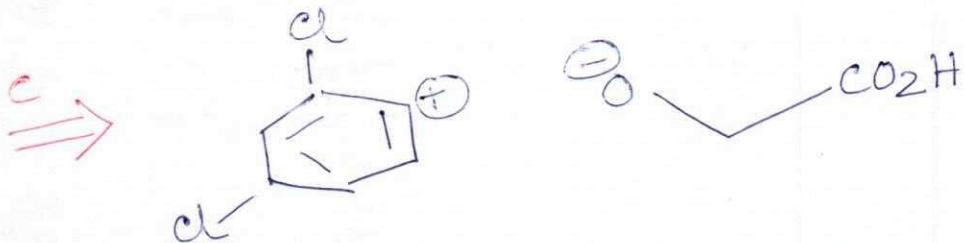
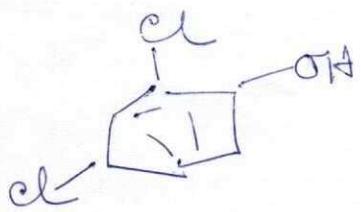
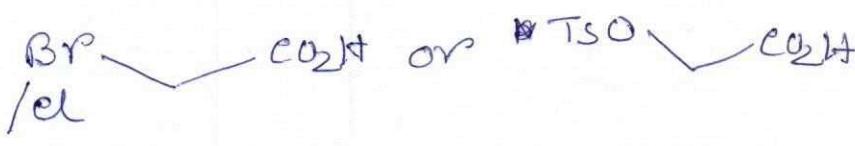
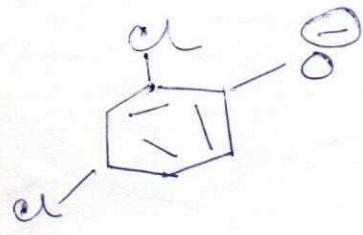
Guideline: Disconnection must produce logical

synthons and corresponds to reliable reactions  
 → Better to imagine <sup>more</sup> electro negative atom as the end



Not a logical synthon

(Bad choice of disconnection)



No reliable (Bad choice of disconnection)  
 reaction

Guideline: For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom. ③

~~previous X~~  
~~GL~~

a

b

c

cl

s

cl

c

III

cl

cl

s

+

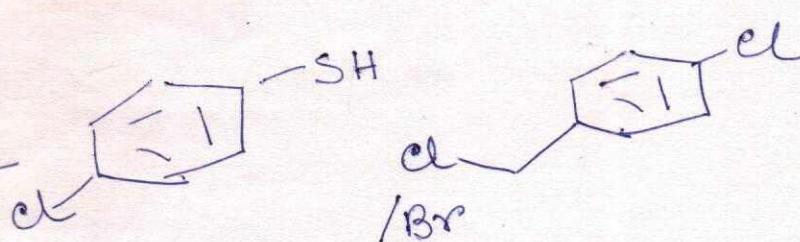
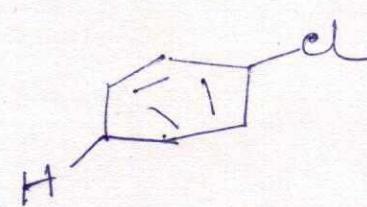
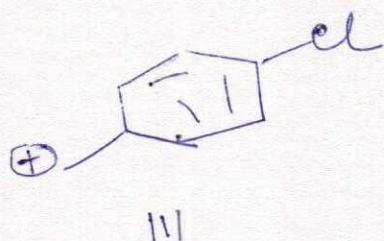
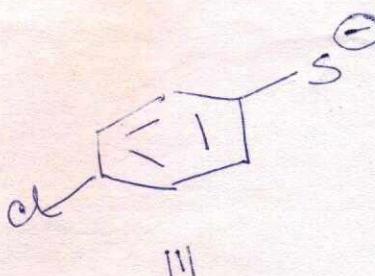
cl

chlorbenside

(Kill ticks & mites)

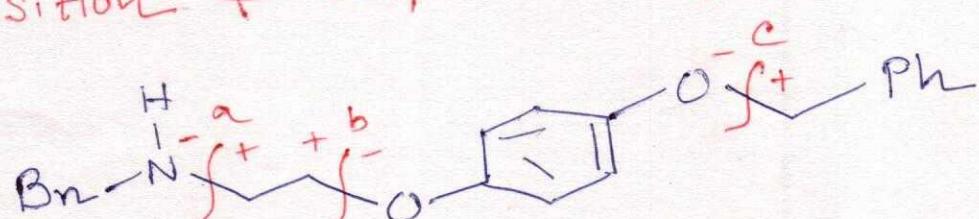
Etona

b ↓



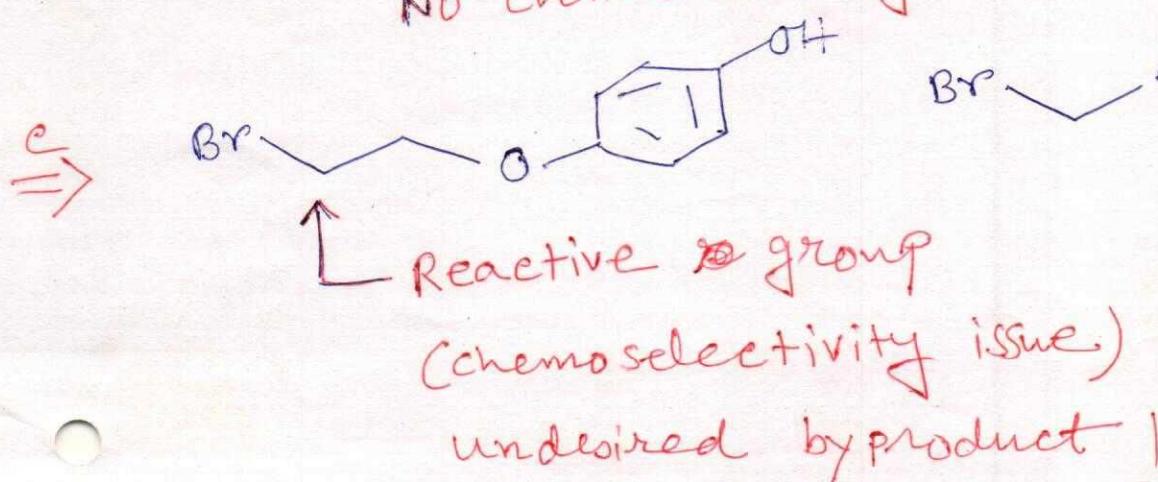
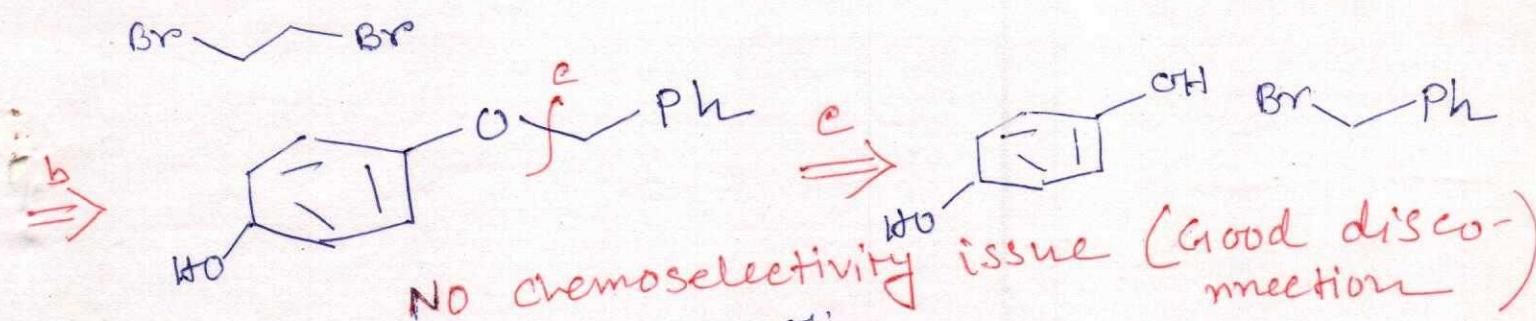
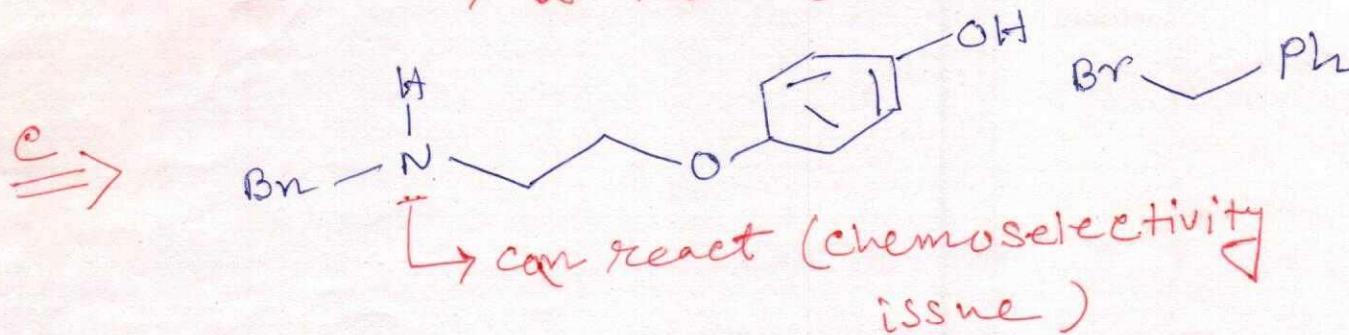
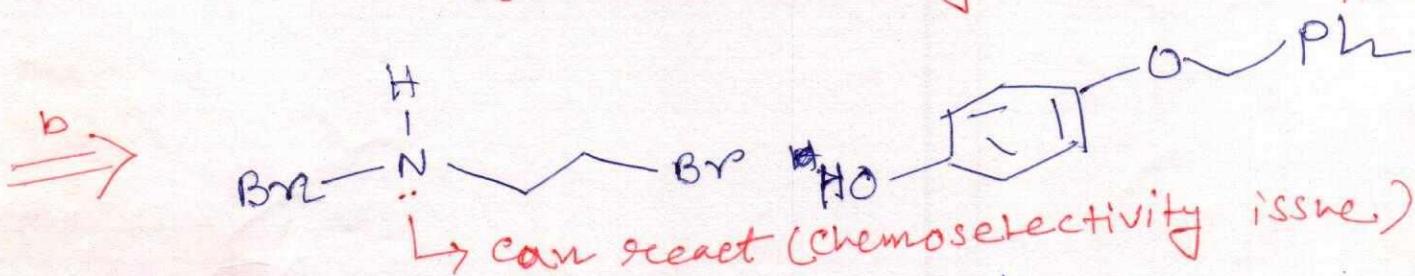
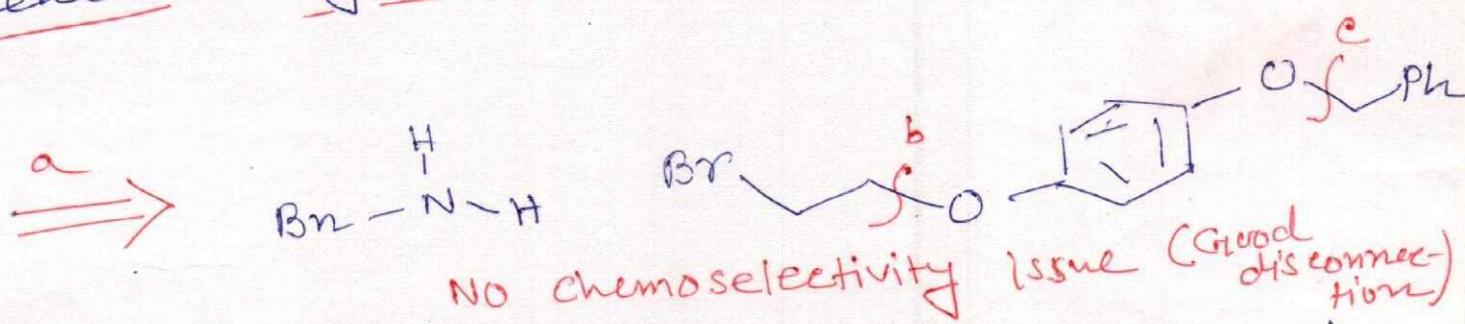
multiple step Synthesis :

⇒ Position & sequence of disconnection



Anti-obesity drug

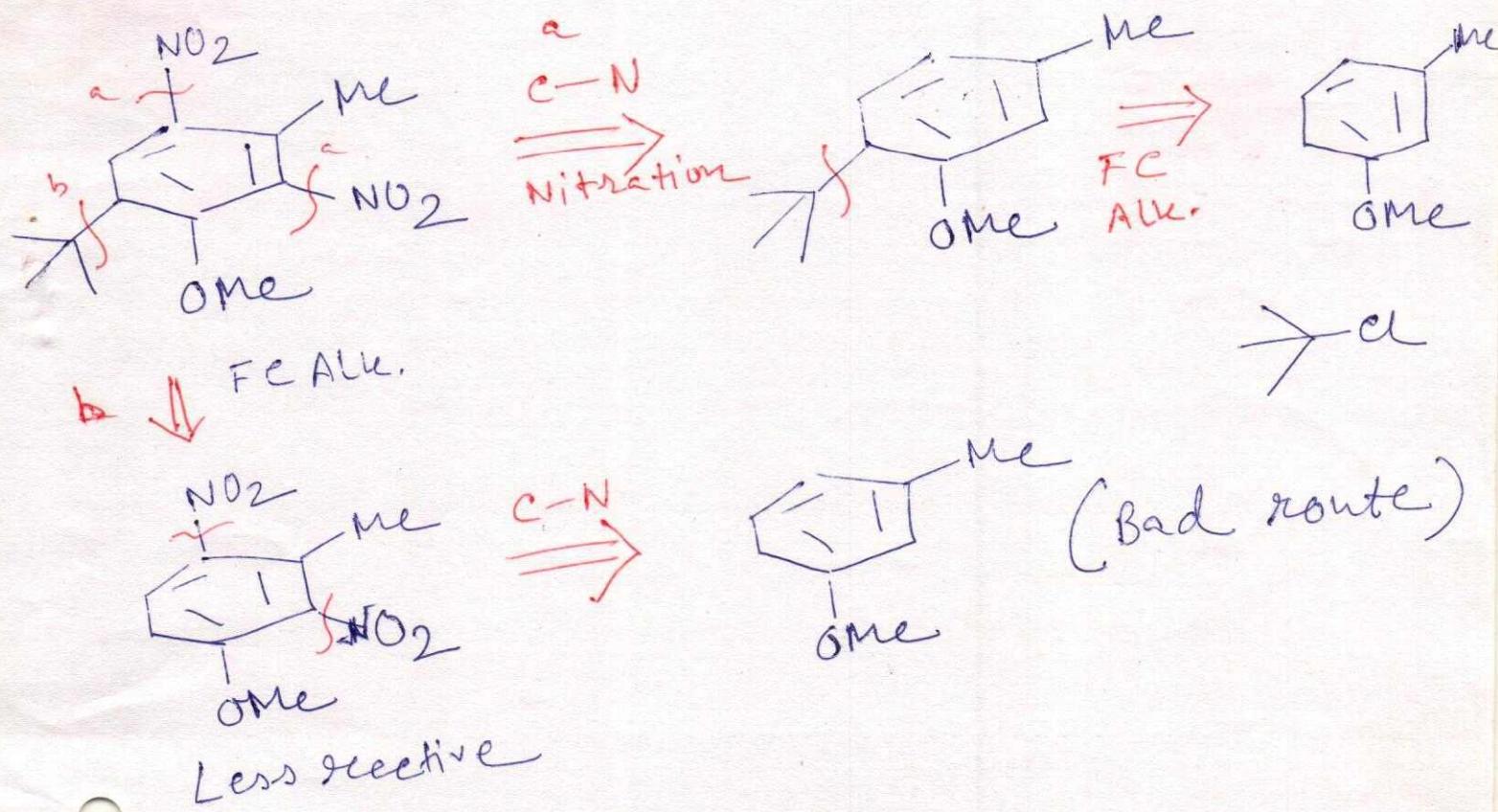
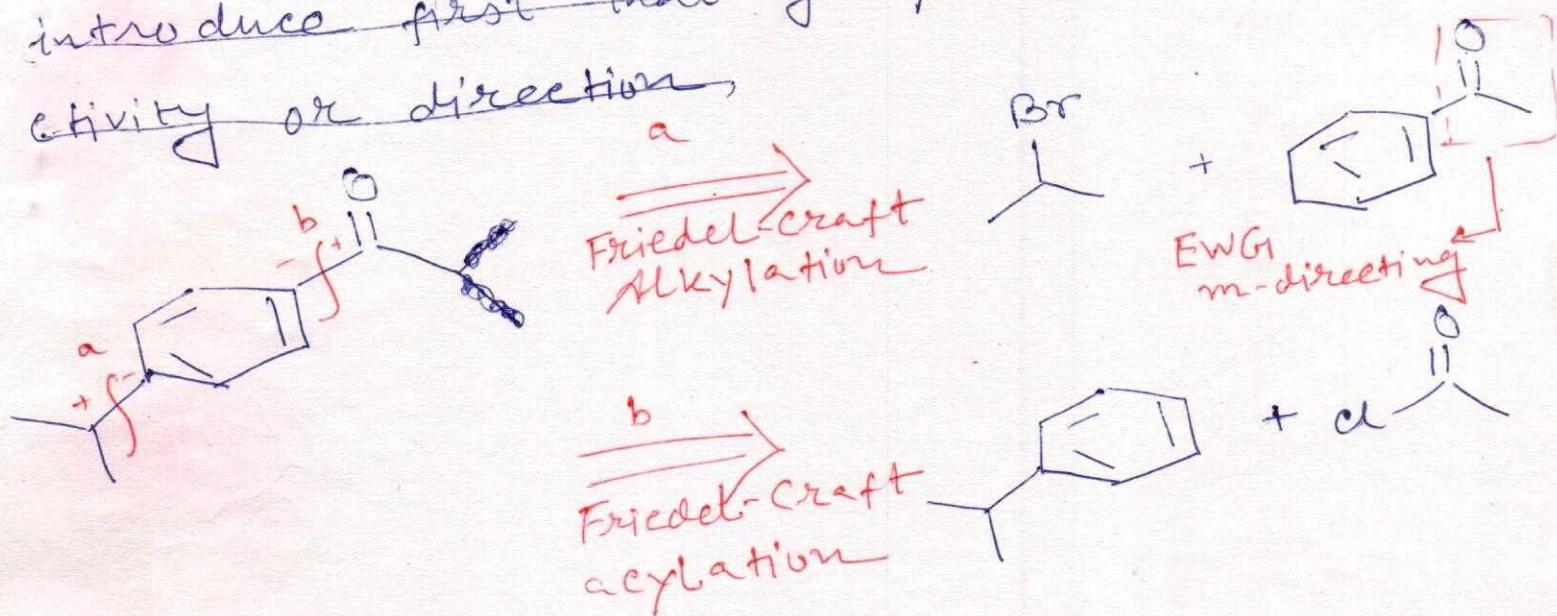
Guideline: Consider alternative disconnections & choose routes that avoid chemoselectivity problems - often this means disconnecting reactive groups first



## Retrosynthesis of Benzene derivatives

(5)

Guideline: Consider the effect of each function group on the others. Add first (i.e. disconnect last) the one that will increase reactivity in a helpful way. So, for aromatic compounds introduce first that group that helps, by reactivity or directions.

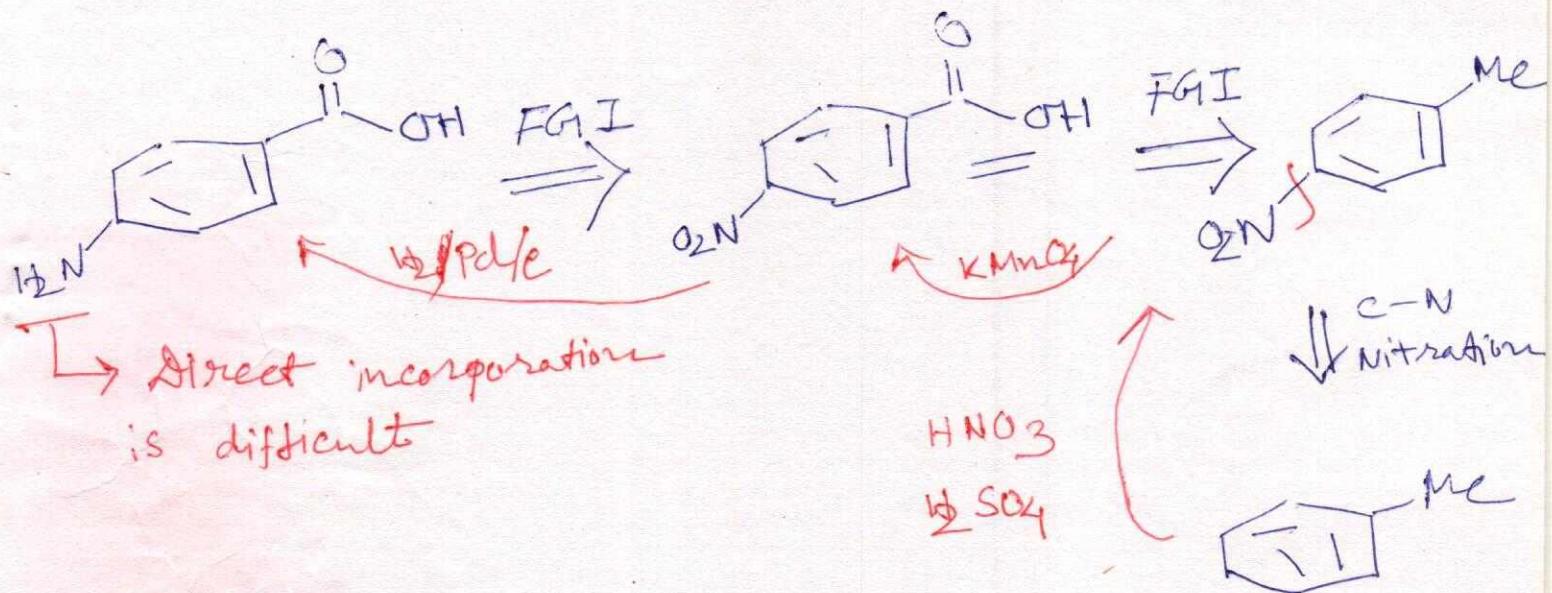


## Functional Group Interconversion (FGI): (6)

$\Rightarrow$  difficulty in <sup>direct</sup> incorporation of a FG  
 $\Rightarrow$  difficulty in reactivity

" regioselectivity "

$\Rightarrow$  "

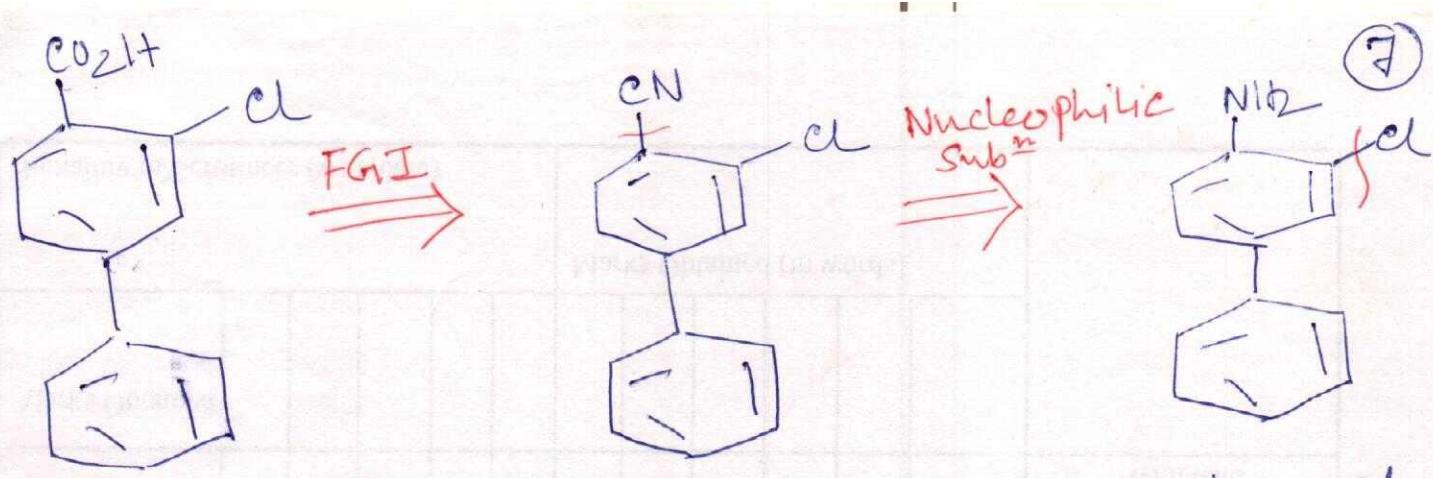


### use of diazonium salts :

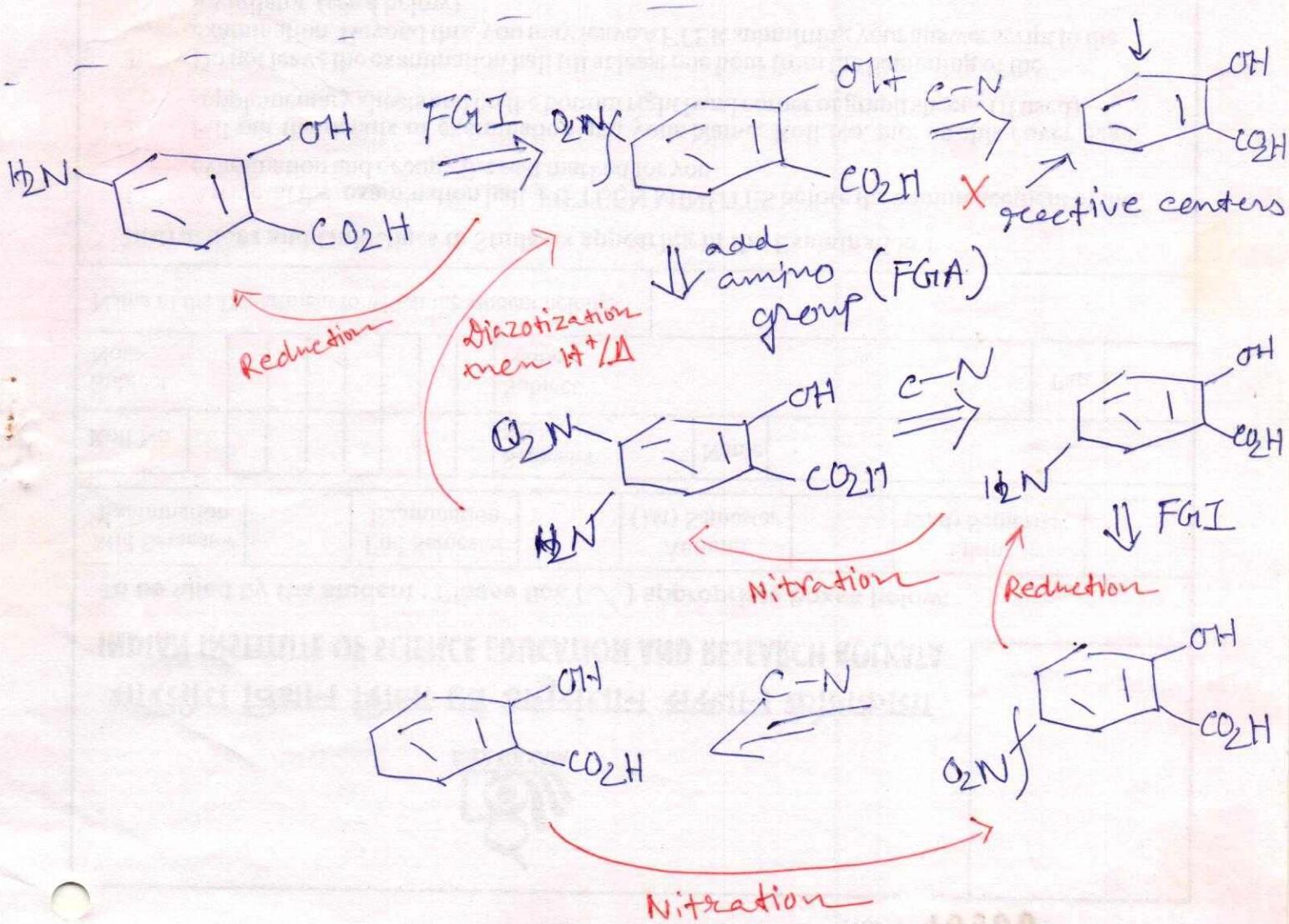
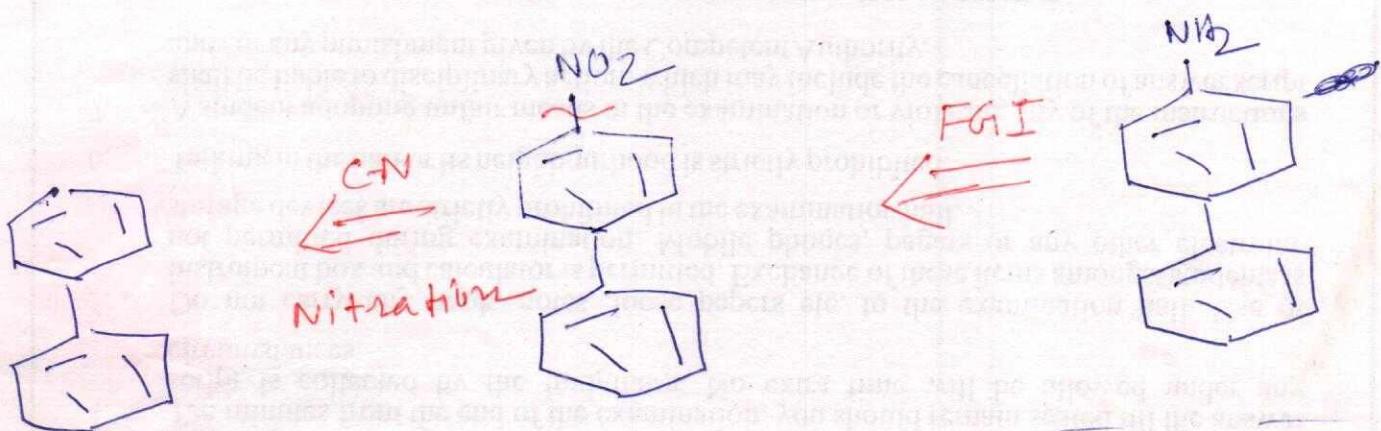
Guideline: Use die nucleophilic substitution  
on a diazonium salt made from amine.

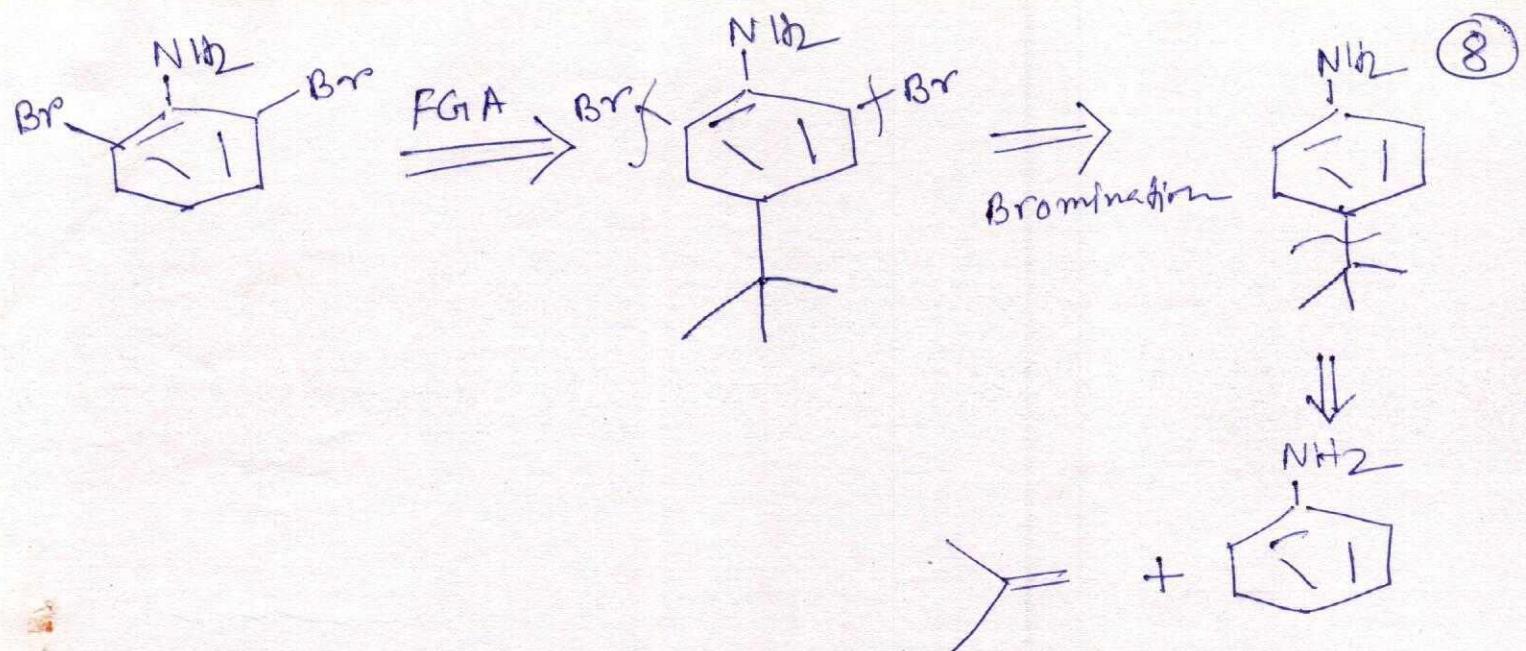
Guideline: In case of regioselectivity issues  
with existing FGs, use a 'dummy' ~~amino~~ group,  
which can be removed ~~through~~ diazotiza-  
~~tion & reduction~~ at the final stage.

FGA	Reagent
HO	H <sub>2</sub> O
RO	ROH
x (halogen) + CN	CuX
H	H <sub>3</sub> PO <sub>2</sub>

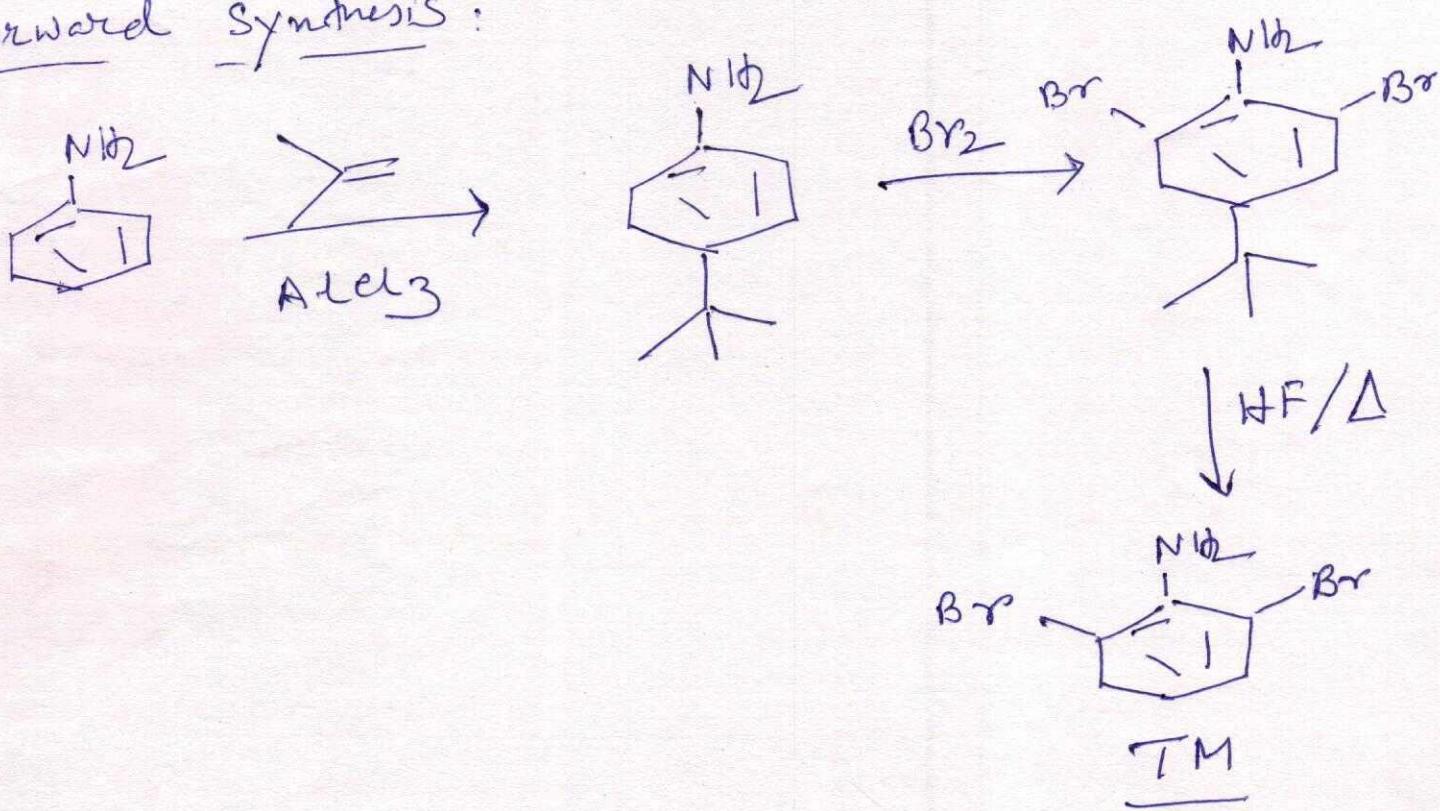


Chlorination  $\downarrow$  c-cl



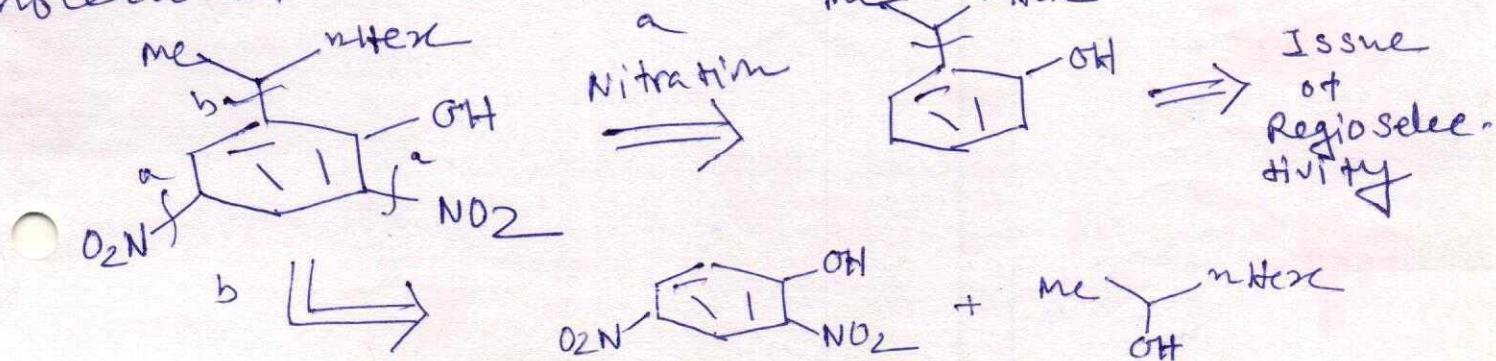


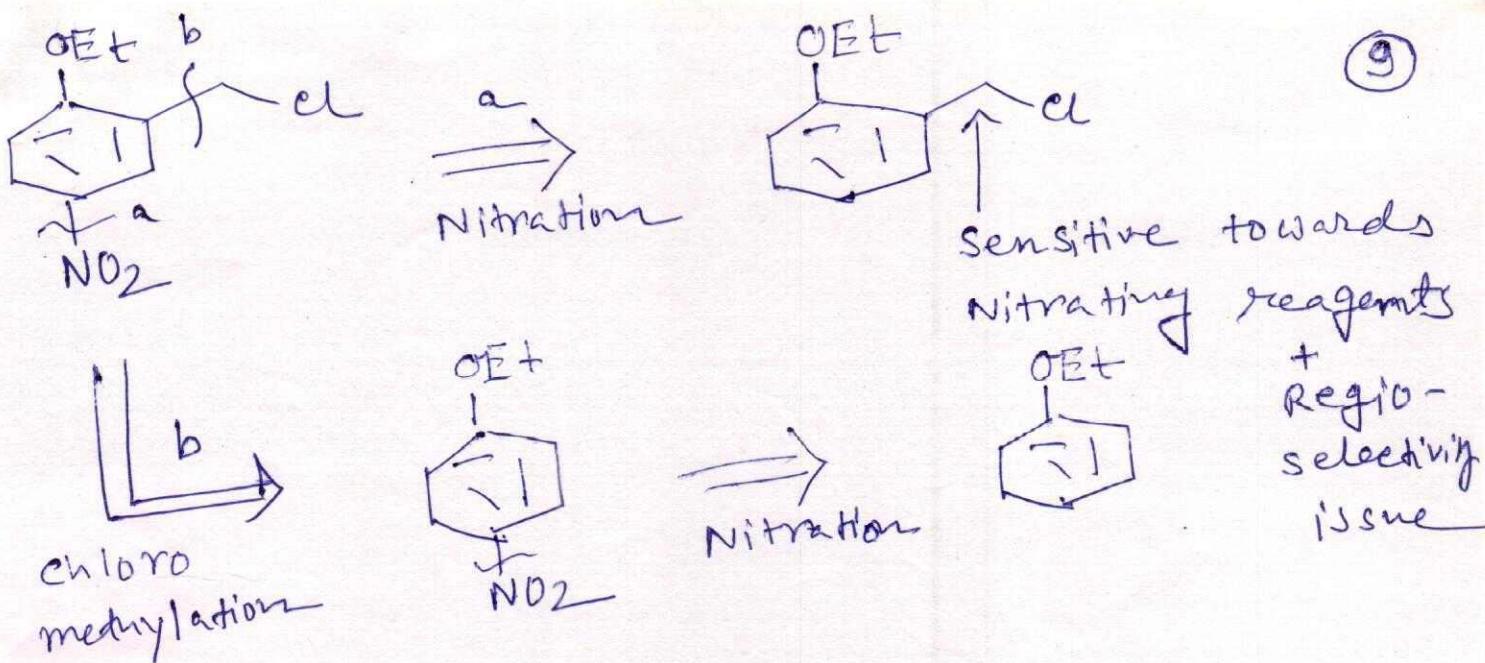
### Forward Synthesis:



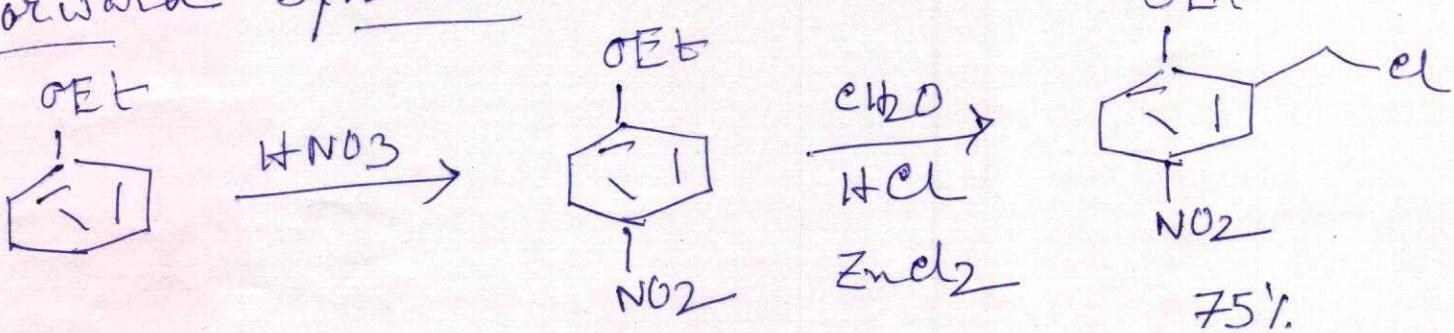
### Exceptions:

Guideline: Avoid sequences which may lead to issues of regioselectivity & to unwanted reactions at ~~the~~ other sites in the molecule.



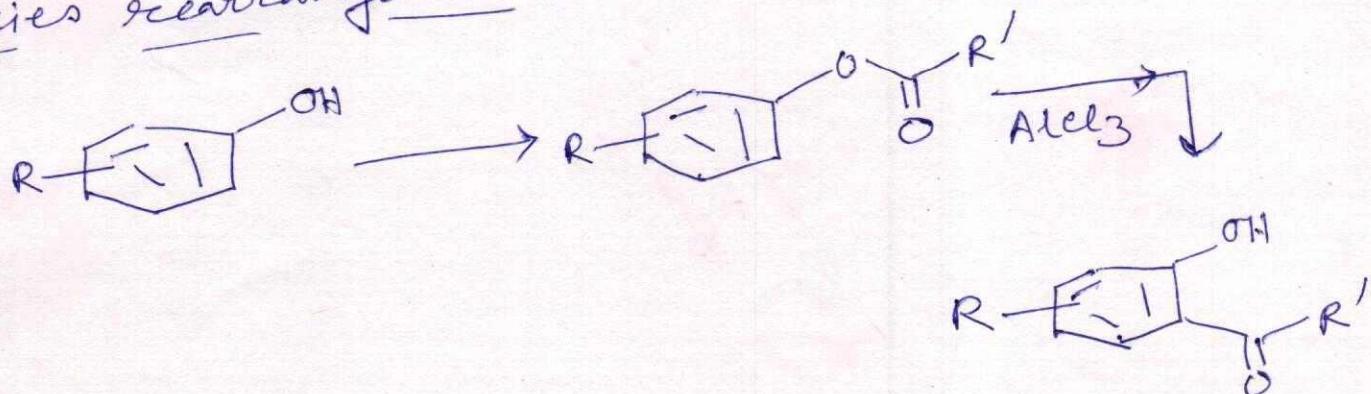


### Forward Synthesis:

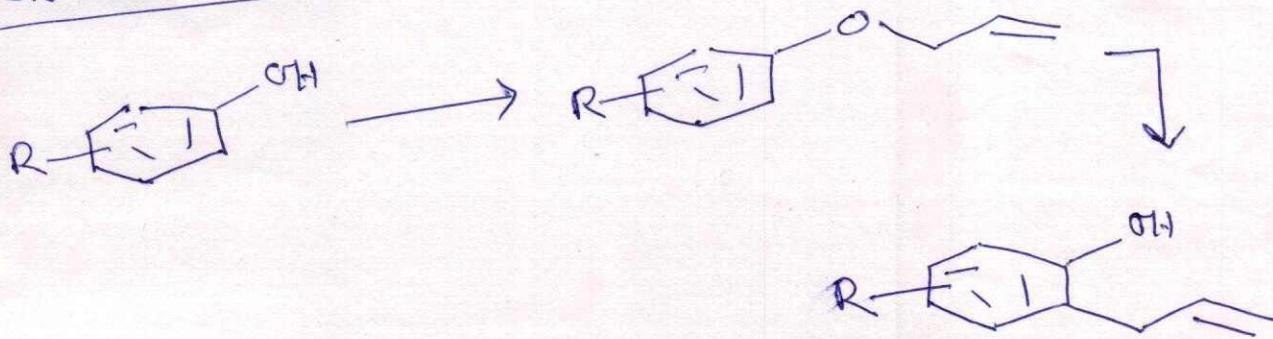


### Reactions to produce ortho-sub. products:

#### Fries rearrangement:

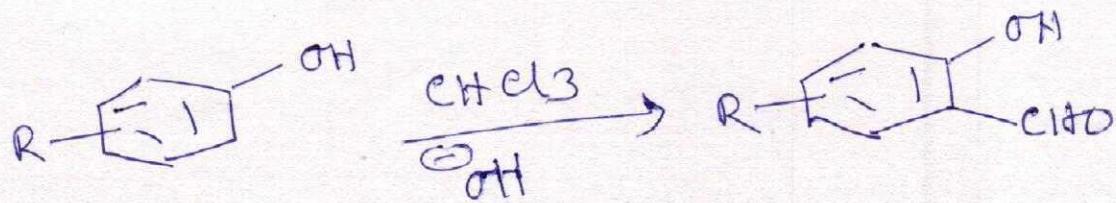


#### Claisen rearrangement:



# Reimer-Tiemann Reac<sup>n</sup>:

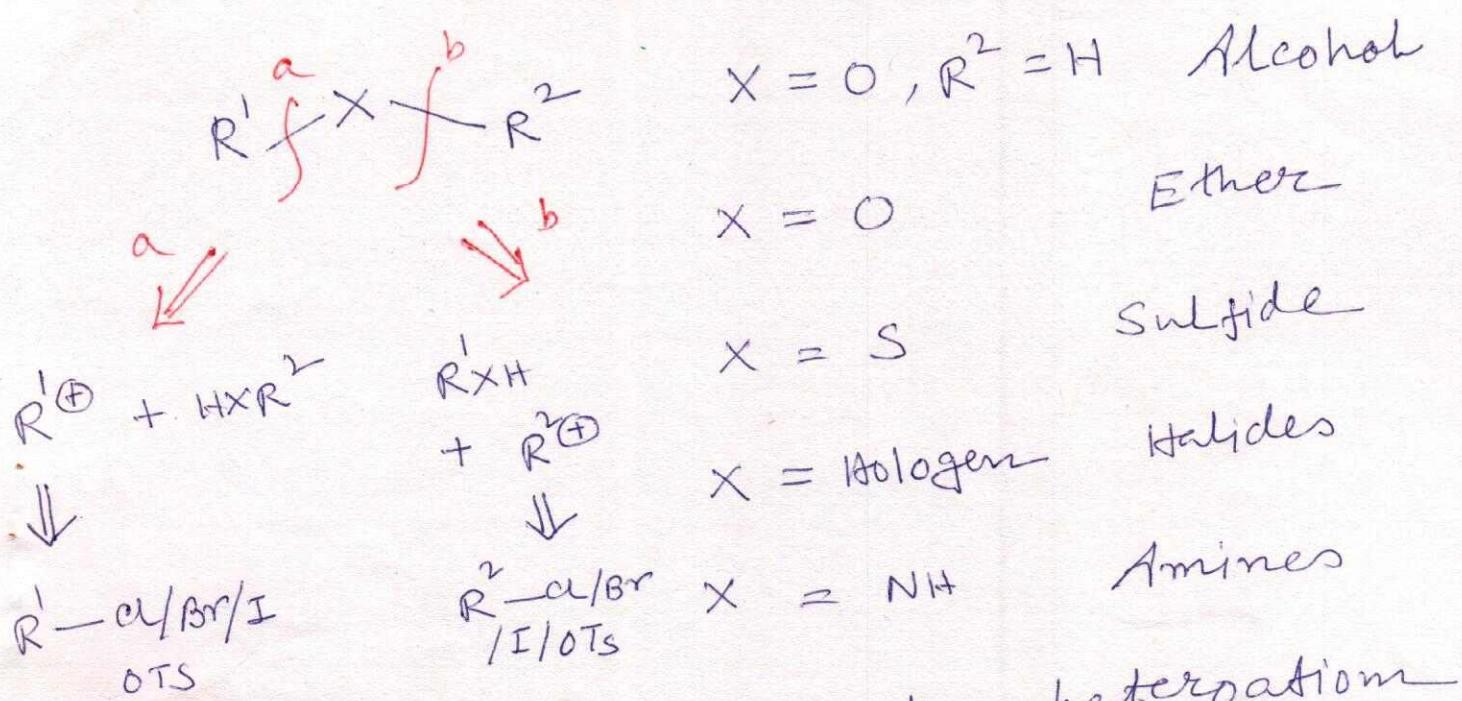
(10)



## Few Examples:

- 1)
- 2)
- 3)
- 4)

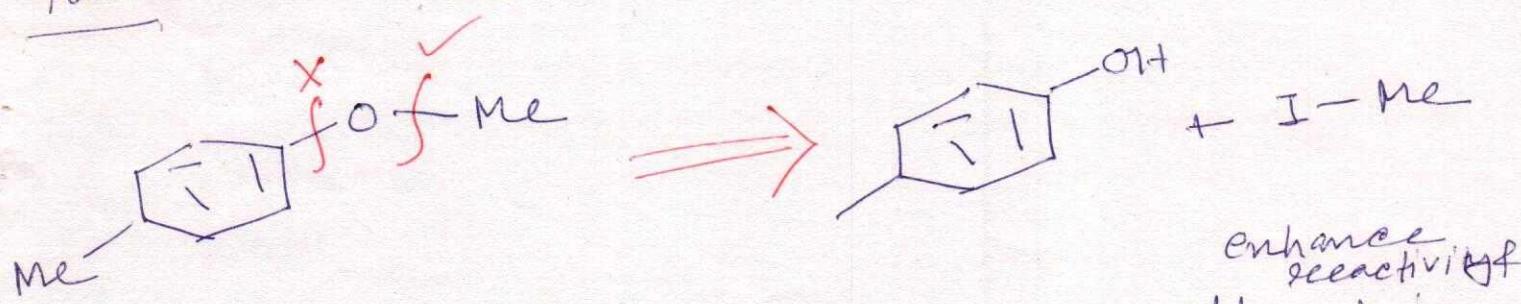
## One group C-X disconnections:



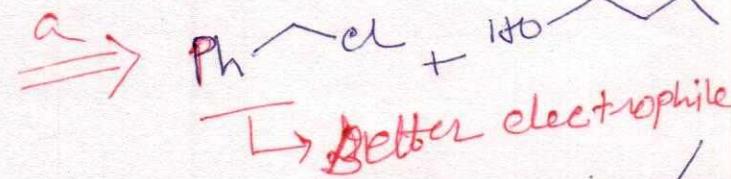
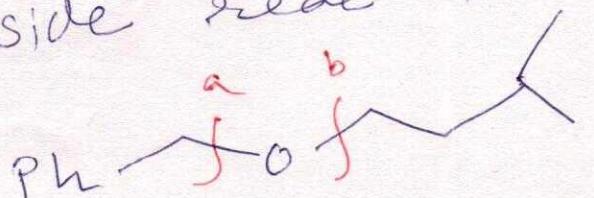
$\Rightarrow$  Disconnect next to the heteroatom

$\Rightarrow$  C-X disconnection leads to nucleophilic  
 $-XH$  & electrophilic carbon species.

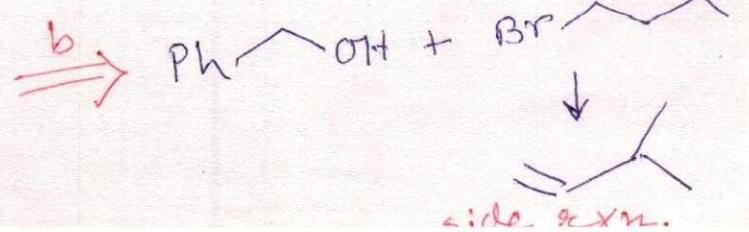
## Position of disconnection:

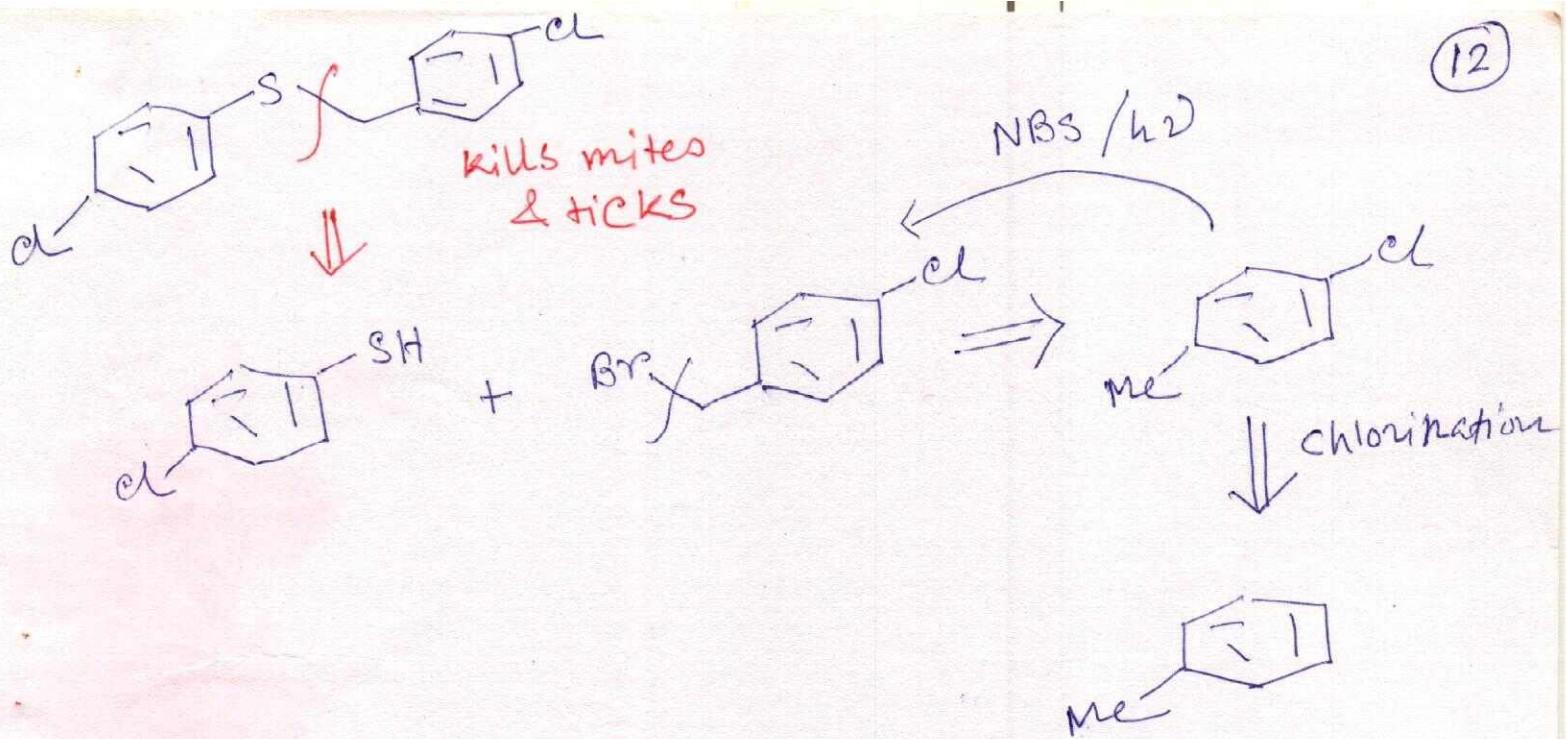


$\Rightarrow$  choose the route which will minimize side reac<sup>n</sup>.

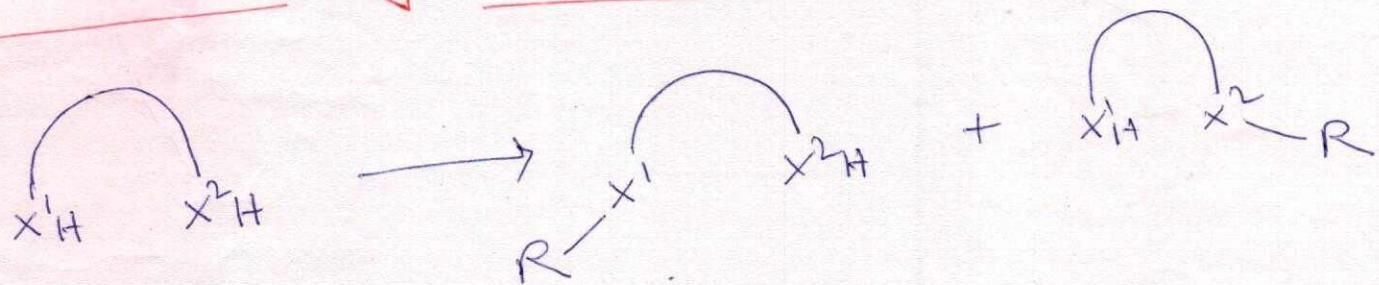


Gardenia perfume

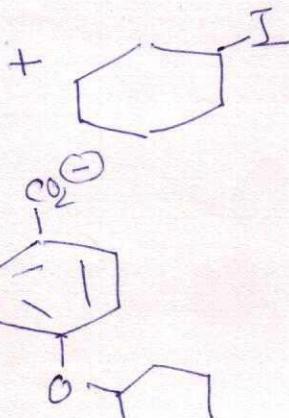
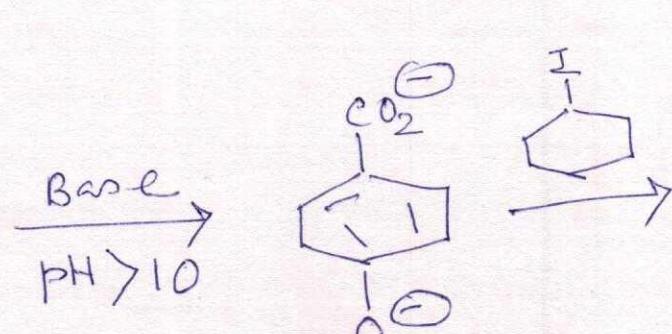
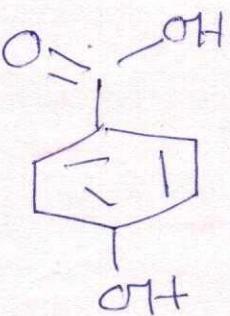
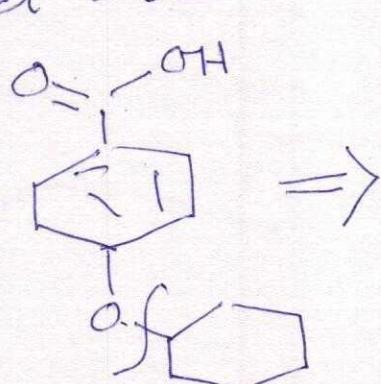
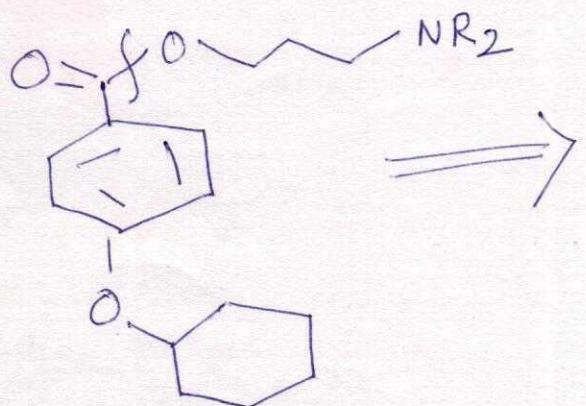


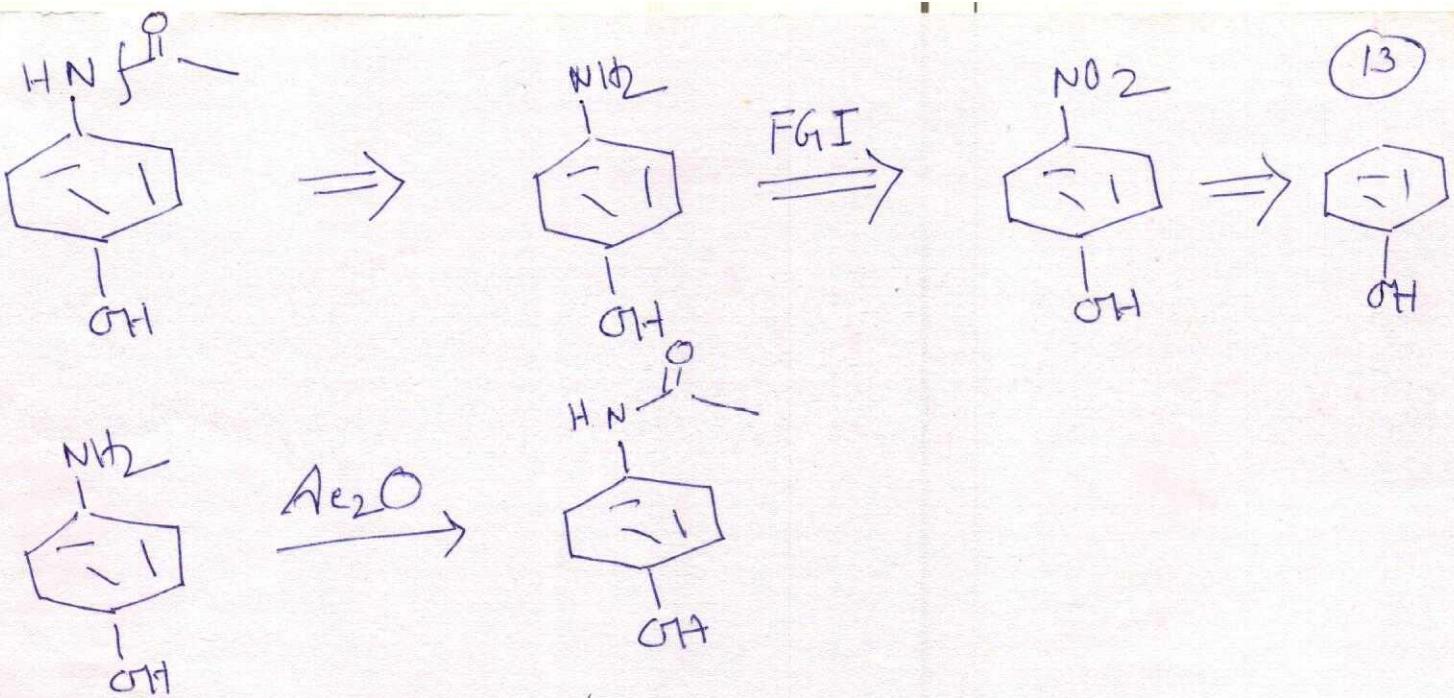


## Chemosselectivity      Issues:

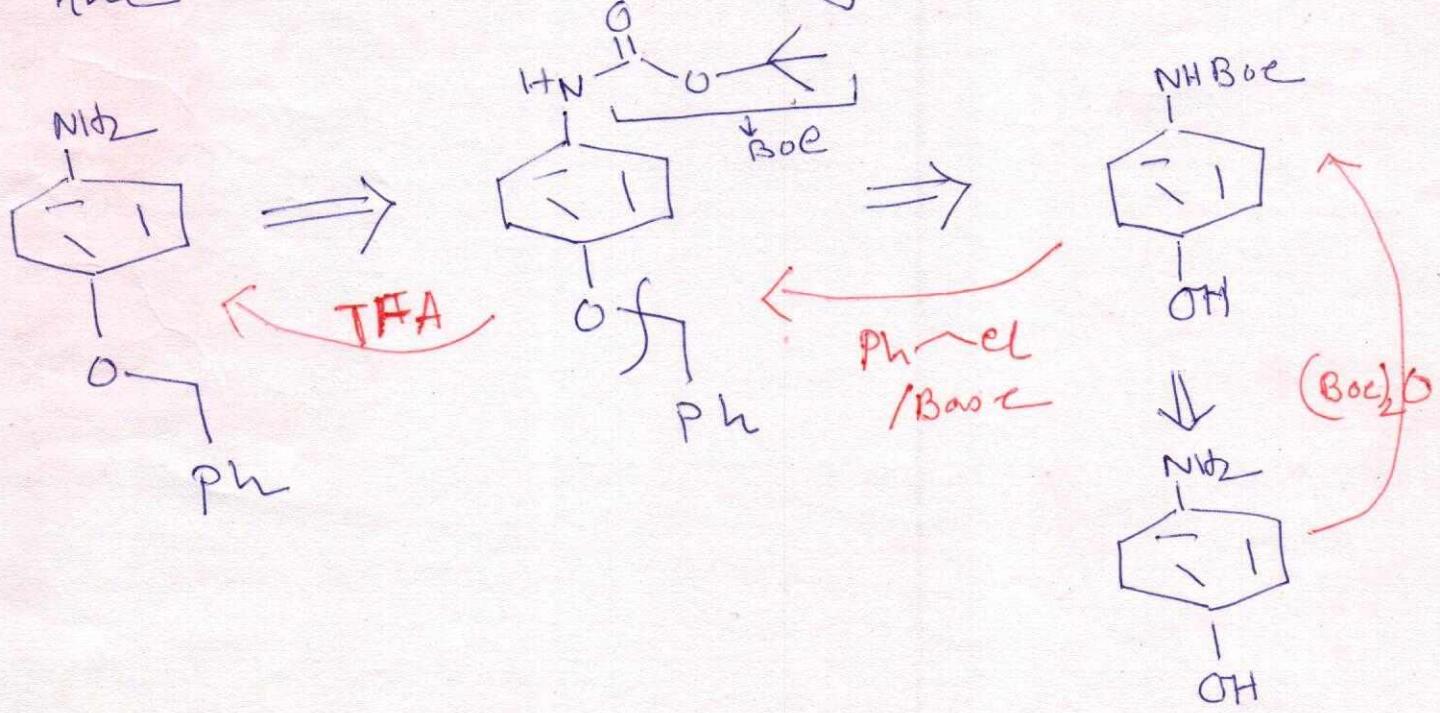


Guideline: With two functional groups of unequal reactivity, the more reactive one can be made to react alone.

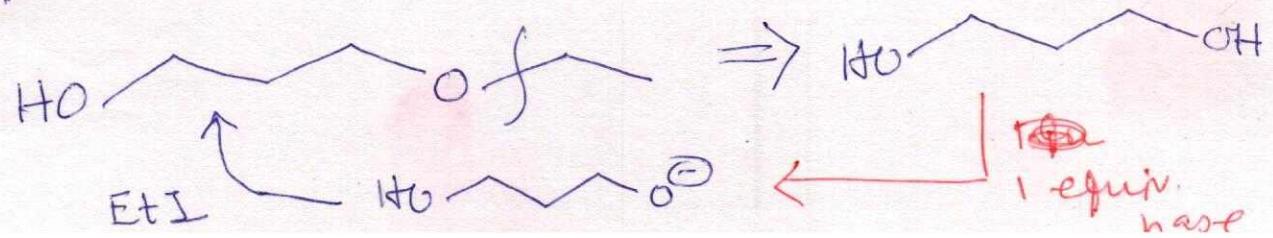




Guideline: unfavourable cases may be solved by the use of protecting groups.



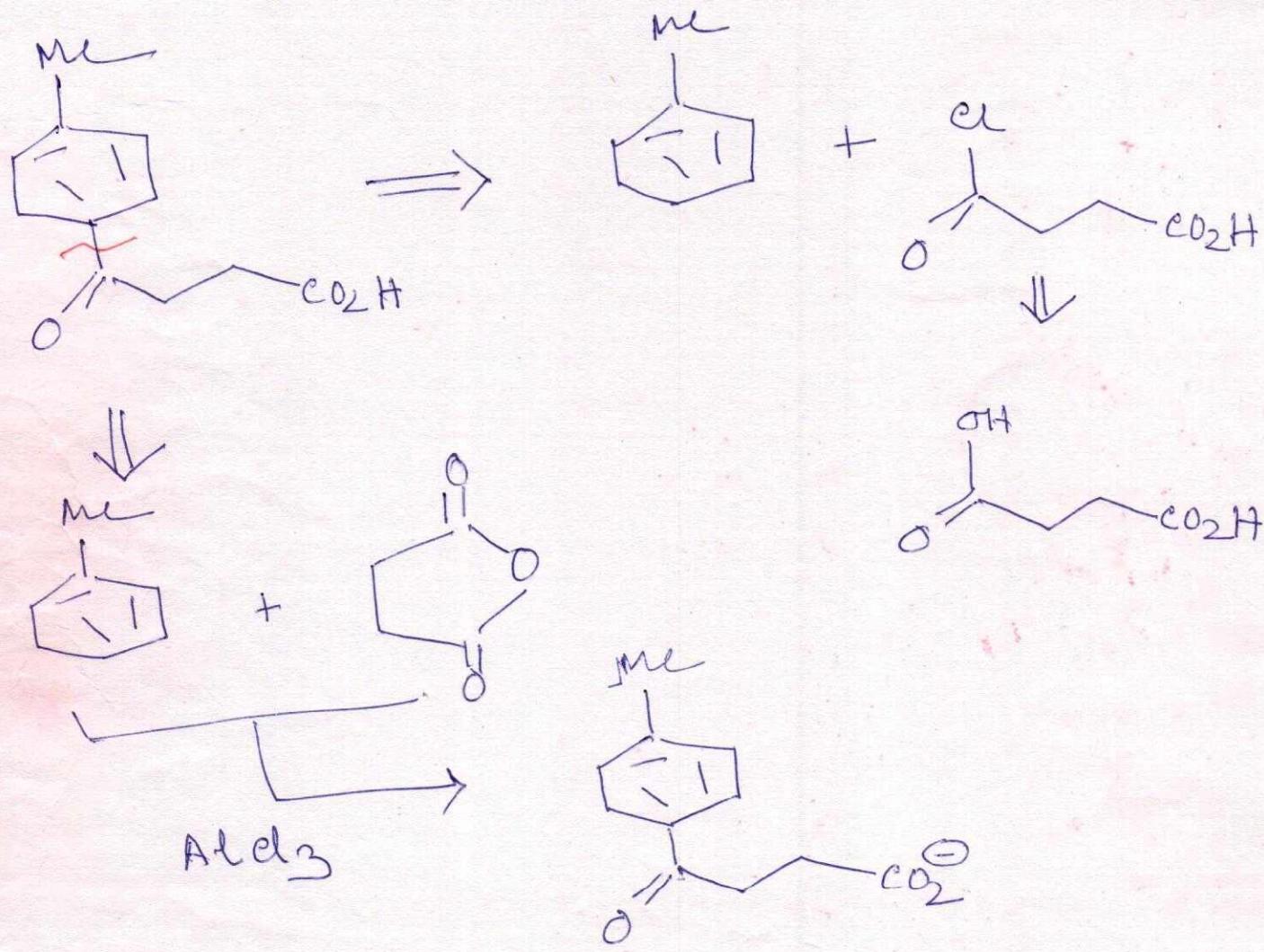
Guideline: One of two FGIs may react with one equiv. of reagent using statistical effect.



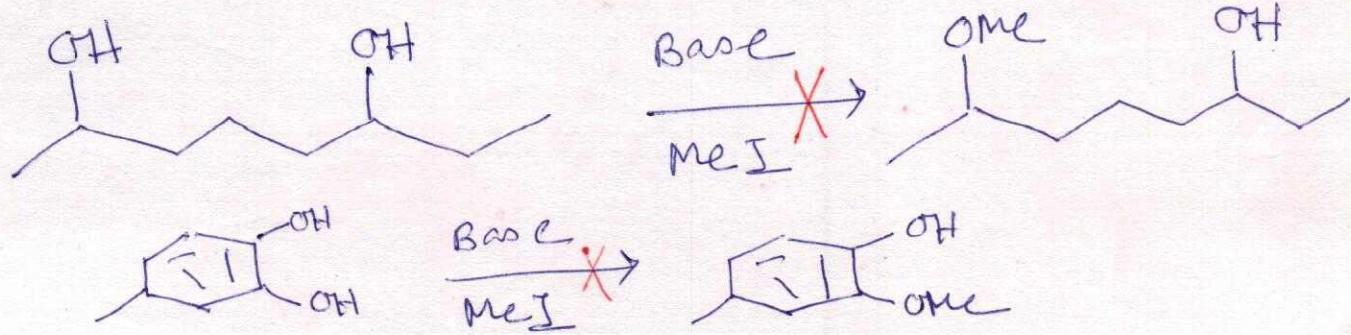
## Guideline :

(14)

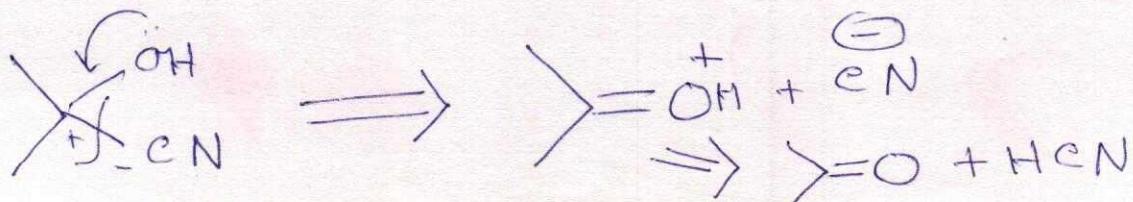
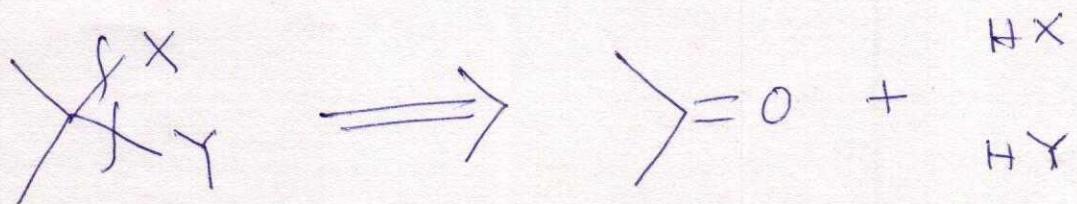
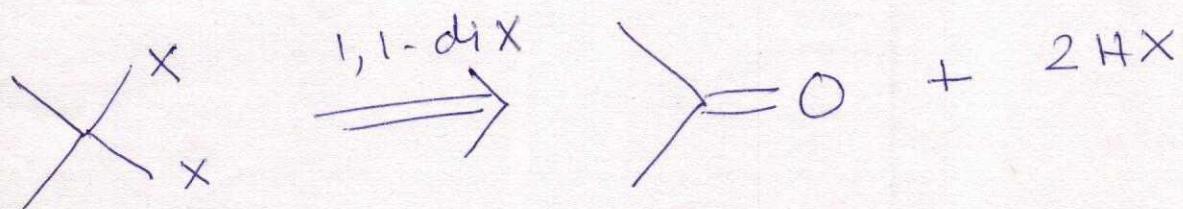
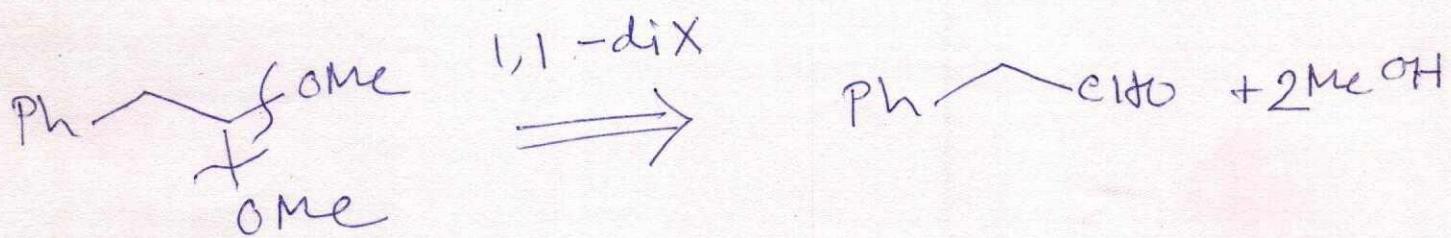
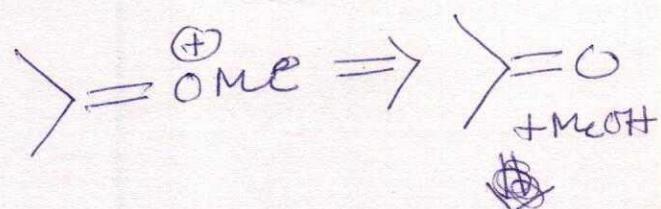
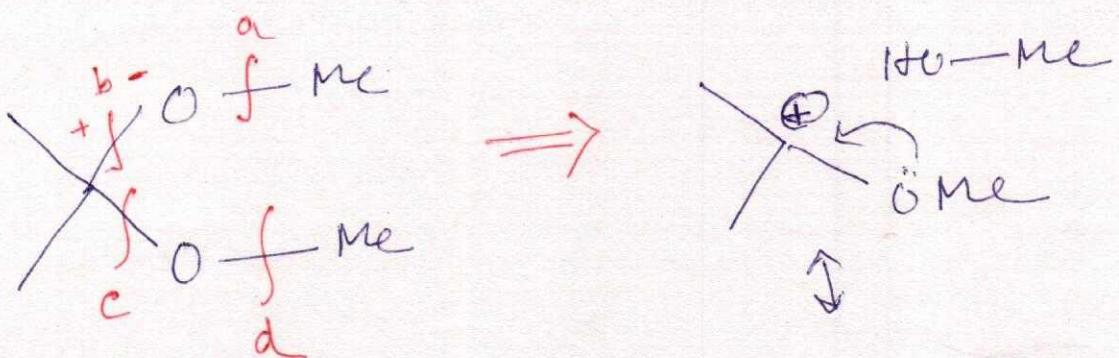
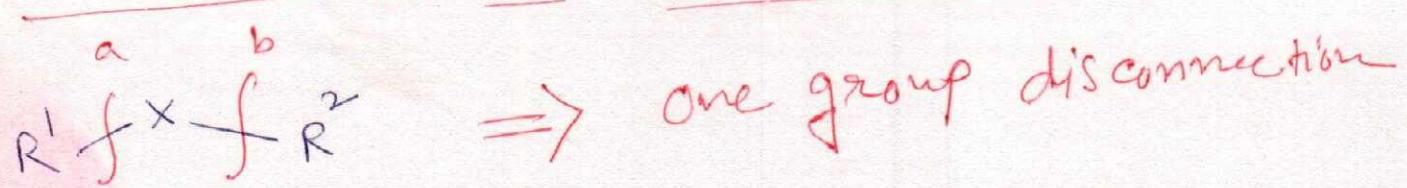
A more reliable method with two identical functional groups is to use a derivative which can react once only.



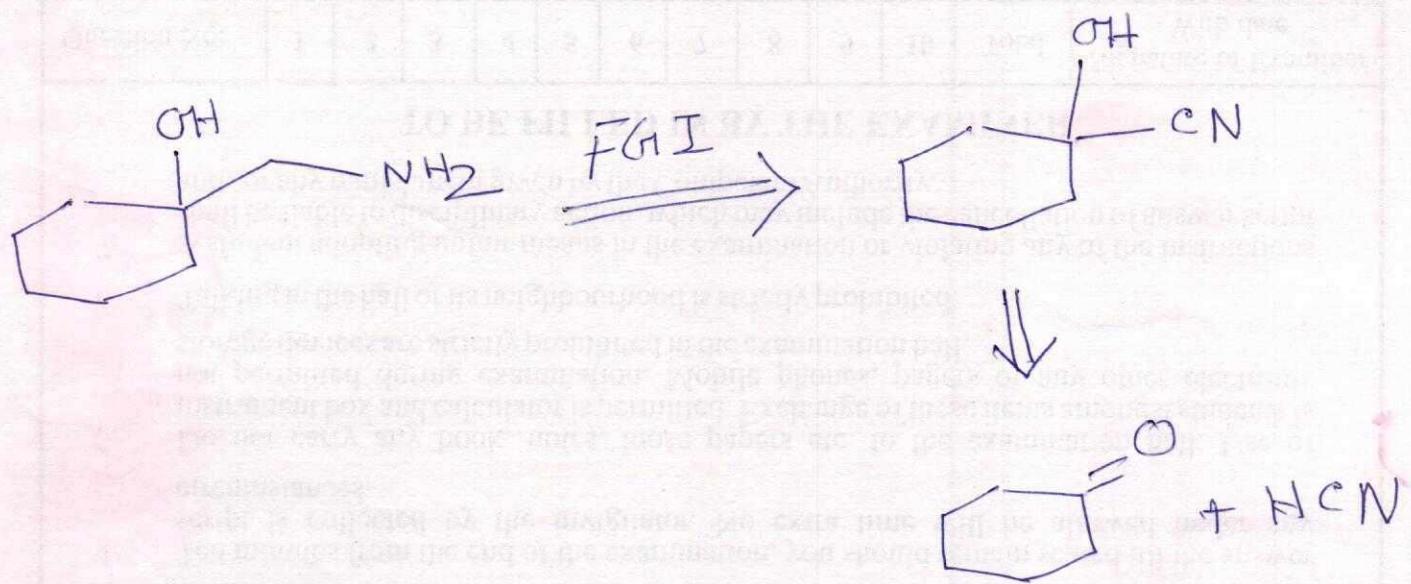
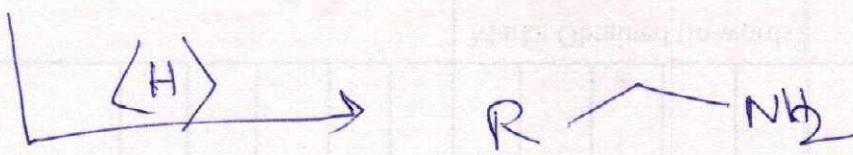
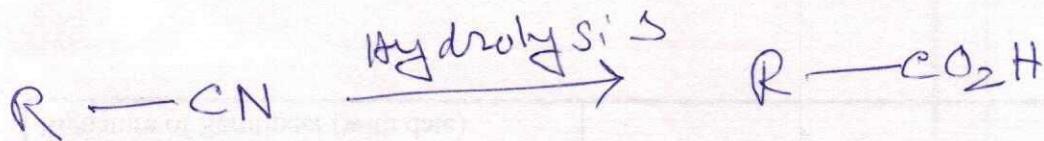
Guideline: When two groups are nearly but not quite identical, avoid attempts to make only one of them react.



TWO-Group C-X Disconnection



(16)



Synthesis of  $\alpha$ -amino acid:

