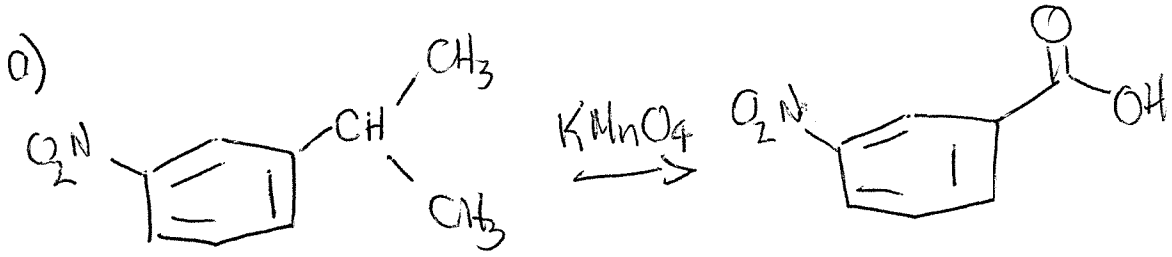
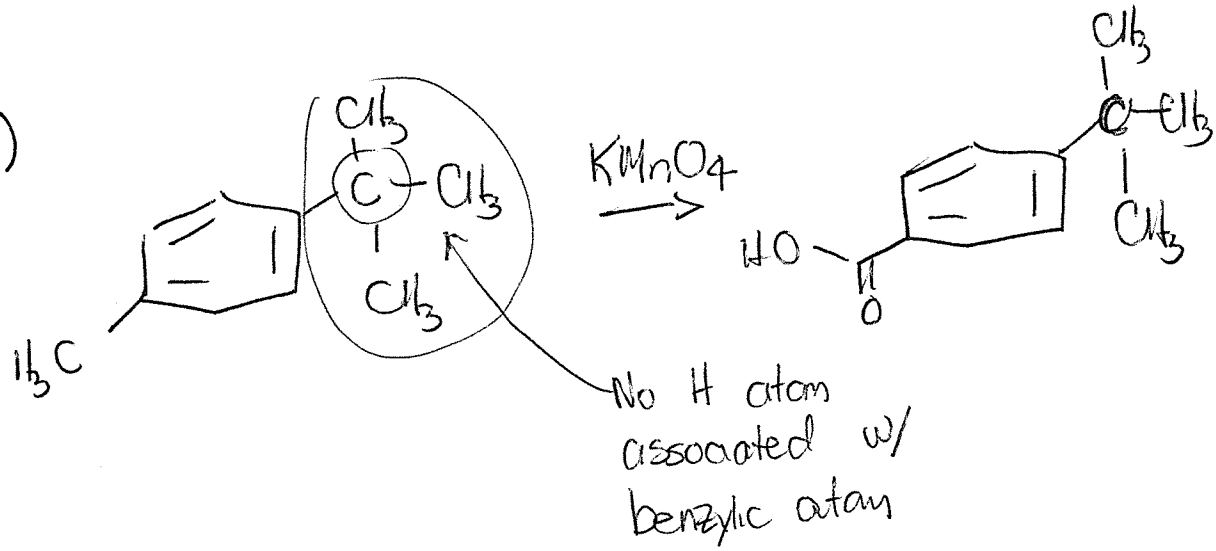
16.18. Oxidation of sp^3 benzylic carbons (that have at least 1 hydrogen atom) with $KMnO_4$ gives a carboxylic acid (benzoic acid) regardless of the length of the C substituent associated w/ the benzylic carbon (i.e. isopropyl or methyl)

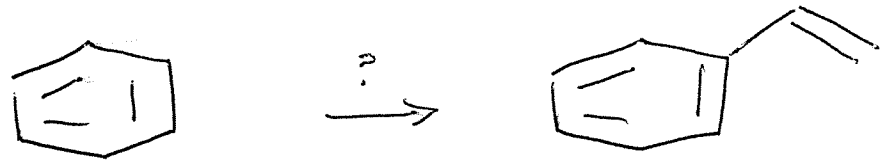
a)

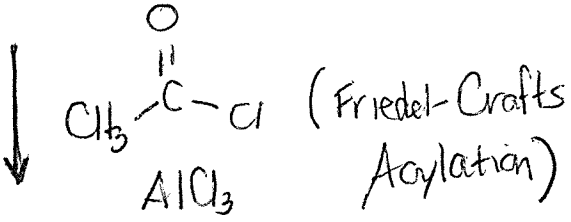


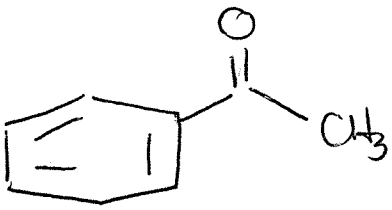
b)



16.20



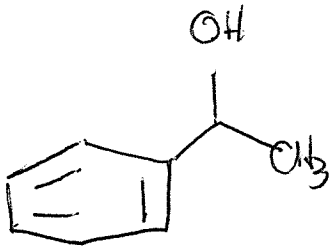




$NaBH_4$

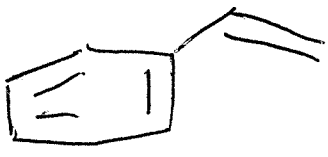
CH_3OH

(Sodium borohydride reduction of Ketones (lab)

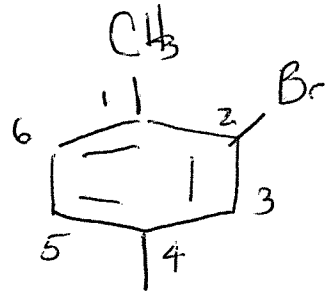


H_3PO_4

(E1 elimination (lab)



16.47

a)  ⟶ 

2-bromo-4-nitrotoluene

There are three substituents associated with the target product. First identify methods/reactions that can be used to introduce these substituents to the ring.

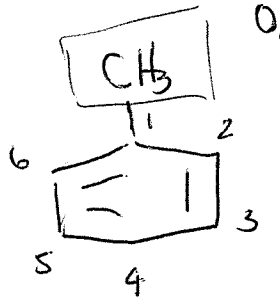
CH_3 (methyl)	Friedel-Crafts Alkylation	CH_3Cl, $AlCl_3$
Br	Bromination	Br_2, $FeBr_3$
NO_2	Nitration	HNO_3, H_2SO_4

Then, consider to <u>ORDER</u> for how to do the reactions. Keep in mind substituent effects (i.e. ortho-, para-directing versus meta directing)
THE ORDER <u>DOES</u> MATTER.

16.47 (cont'd)

a)

CH_3Cl
$AlCl_3$ →



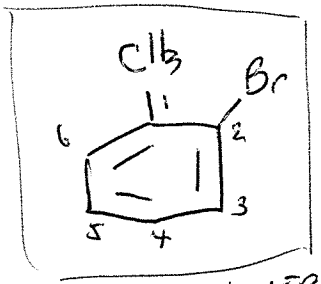
O, P-director

RXN FOLLOWS ACTIVATOR

CH_3: ACTIVATOR
O, P-director
C_4, C_6

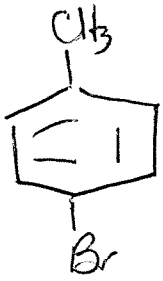
Br: DEACTIVATOR
O, P-director
C_3, C_5

↓ Br_2, $FeBr_3$



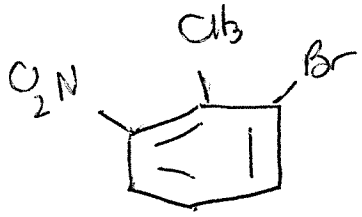
ORTHO ISOMER CAN BE USED TO CONTINUE W/ SYNTHESIS

+

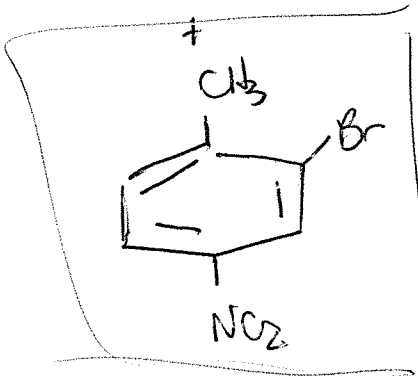


PARA product WILL NOT GIVE DESIRED PRODUCT

↓ HNO_3
H_2SO_4



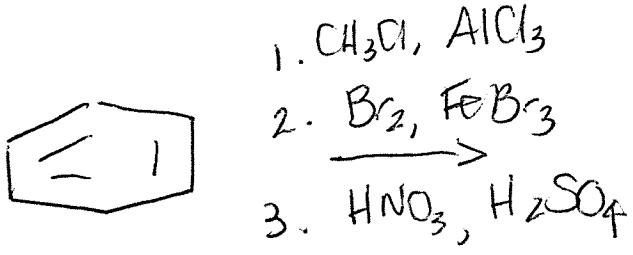
+



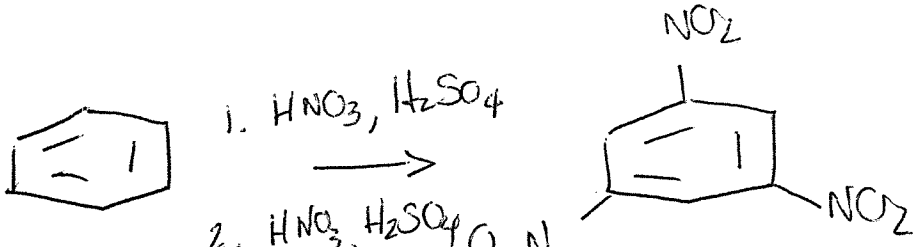
TARGET PRODUCT

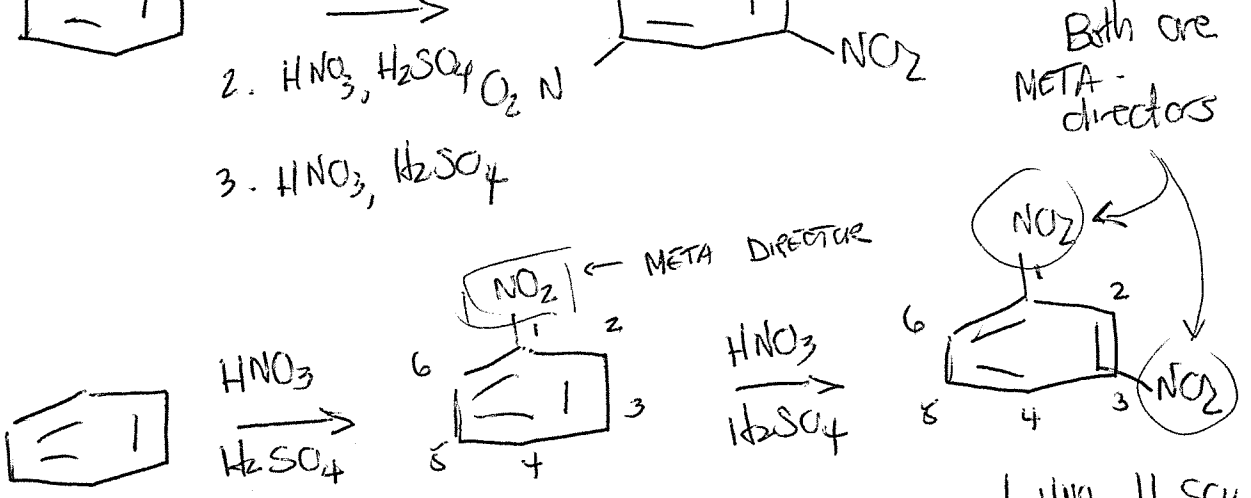
16.47 (cont'd)

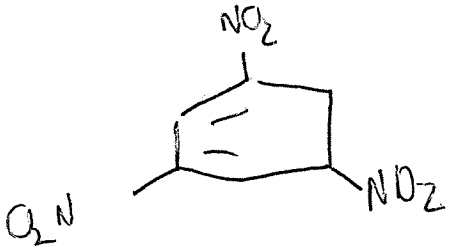
g) So the reaction scheme for this synthesis would be written as follows, indicating the specific order of reagents that give the target product.



b)

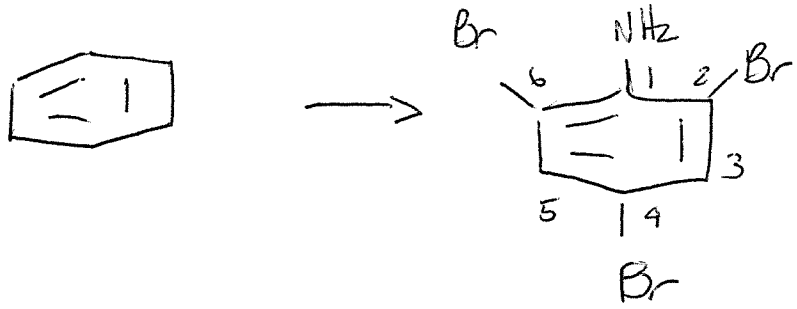


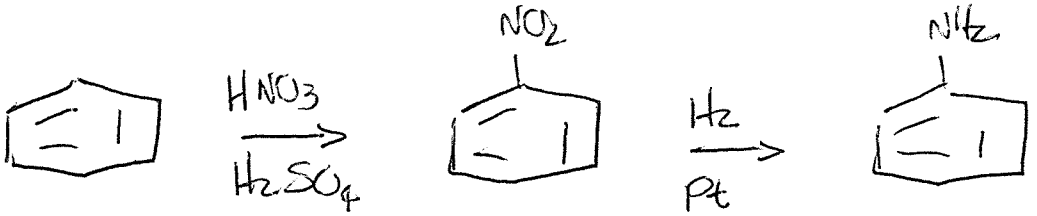




16.47 (cont'd)

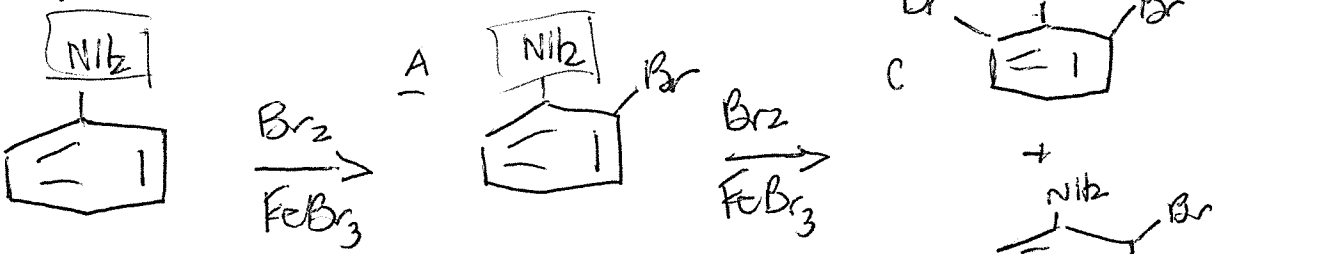
c)





There is no direct way to introduce NH_2 to ring. Must first do a nitration, then reduce the nitro group to an amino

o,p- director



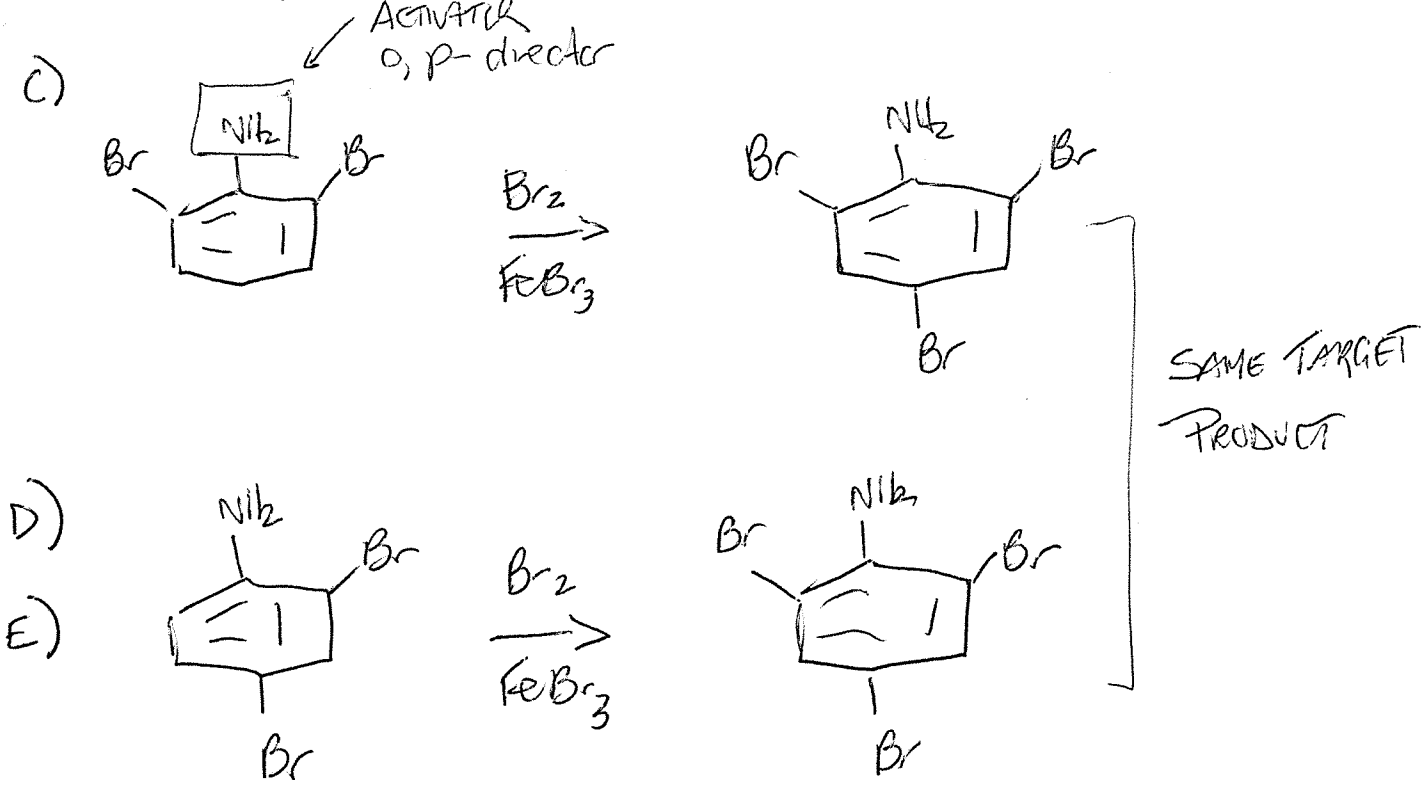
SAME PRODUCT

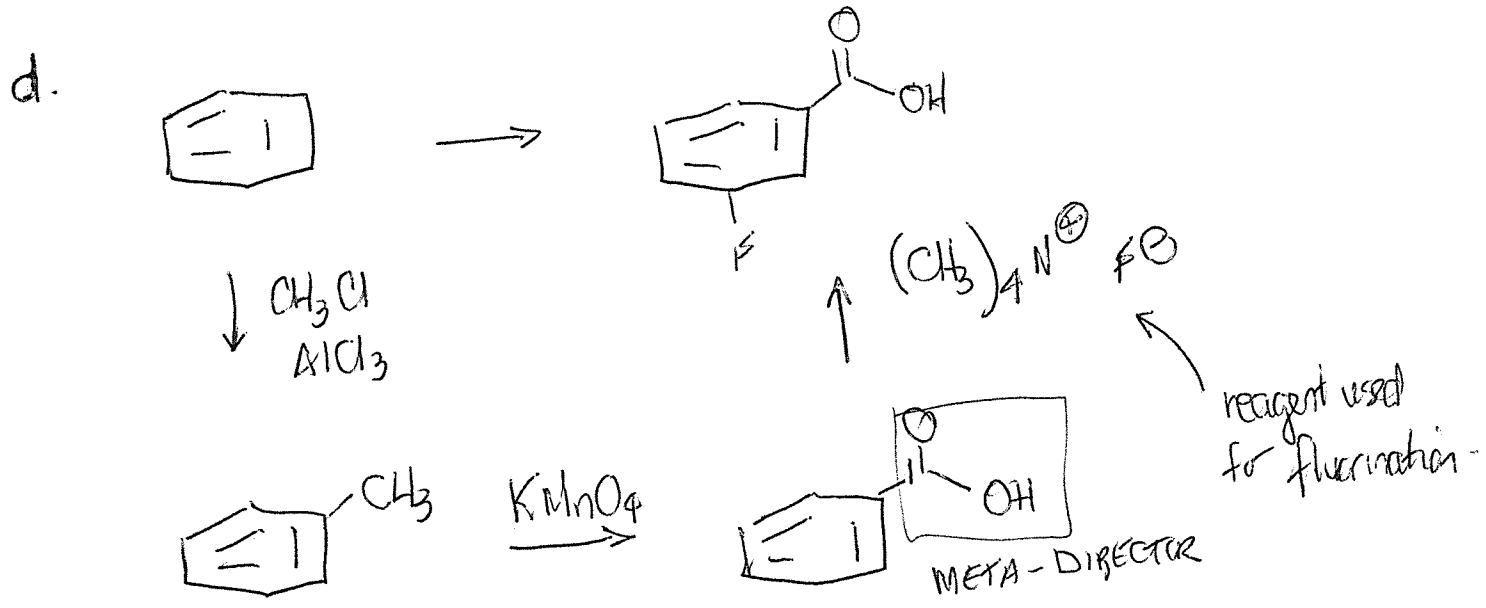
Bromination of aniline w/ Br_2, $FeBr_3$ gives products A and B (ortho/para products). A & B each react again to give products C, D, E

NH_2 IS ACTIVATOR
Br IS DEACTIVATOR

Rxn follows ACTIVATOR

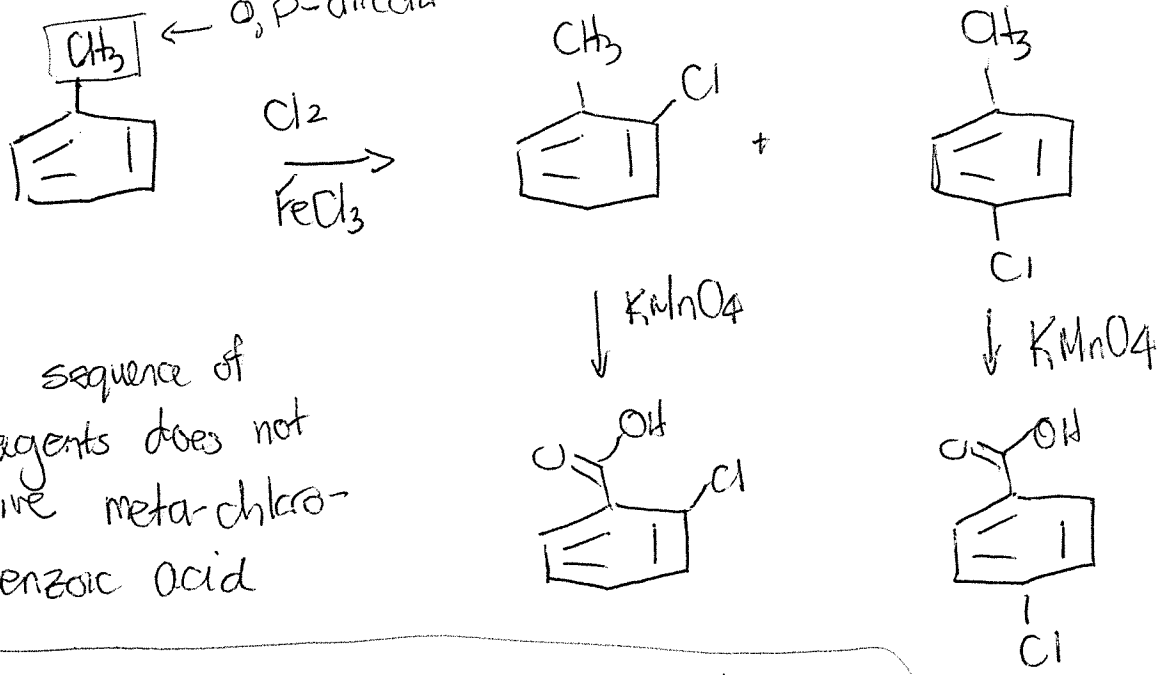
16.47 (cont'd)


ACTIVATOR
o, p- director
C)
NH2
Br
Br
Br2
FeBr3
NH2
Br
Br
Br
SAME TARGET PRODUCT
D)
E)
NH2
Br
Br
Br2
FeBr3
NH2
Br
Br
Br


d.
OH
F
CH3Cl
AlCl3
(CH3)4N⊕
F⊖
reagent used for fluorination
CH3
KMnO4
O
OH
META-DIRECTOR

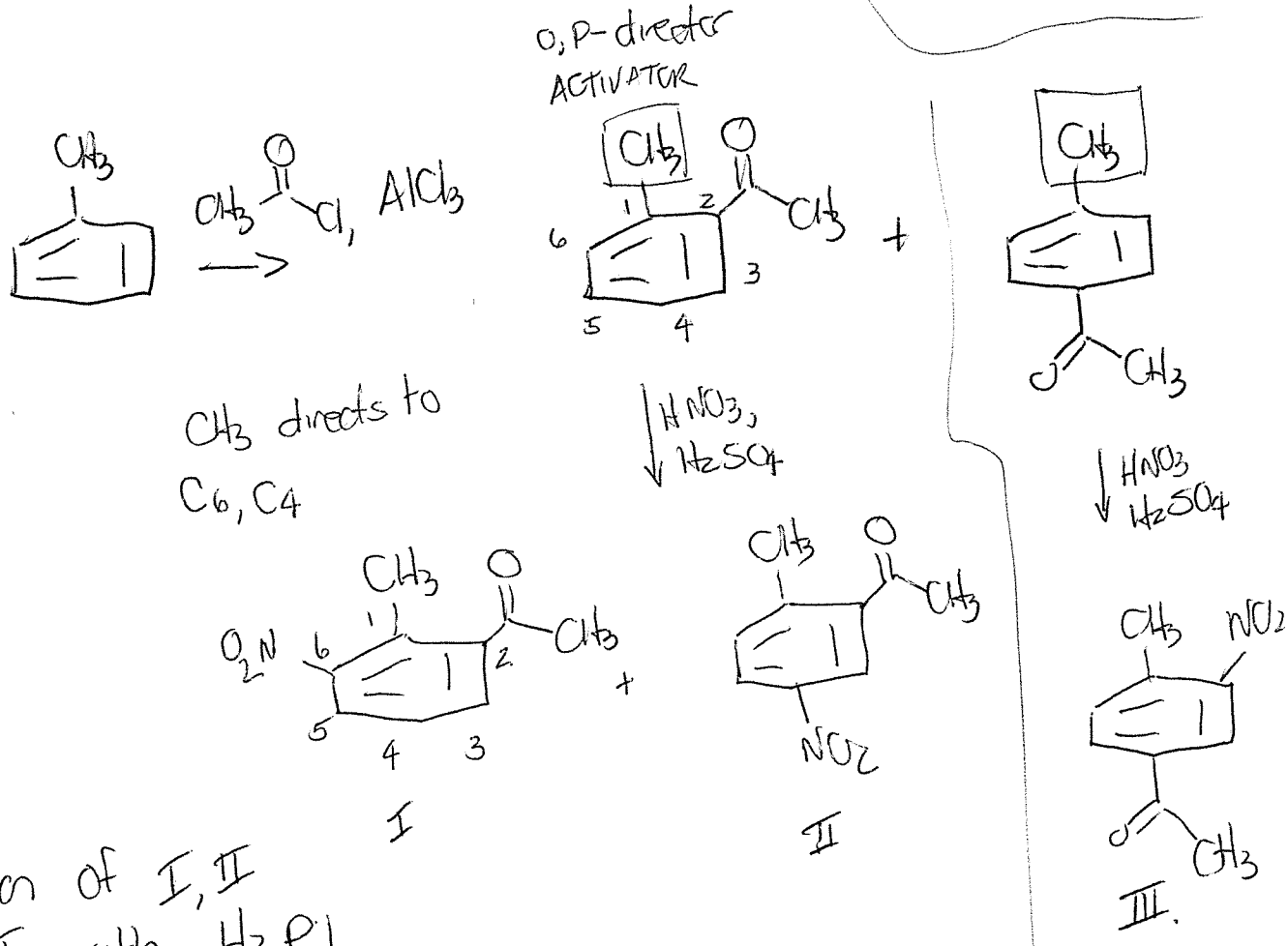
16.48

a)



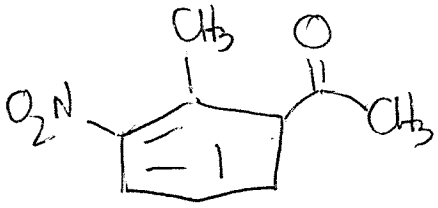
This sequence of reagents does not give meta-chloro-benzoic acid

c)



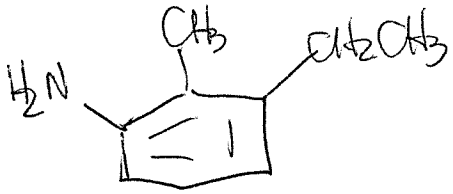
Reduction of I, II and III with H_2, Pd will reduce both the NO_2 and ketone.

c)

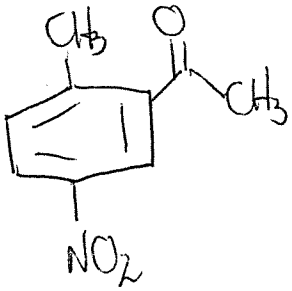


I

H_2/Pd →

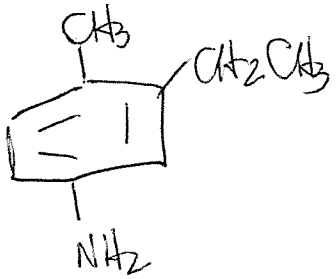


NOT PRODUCT SHOWN

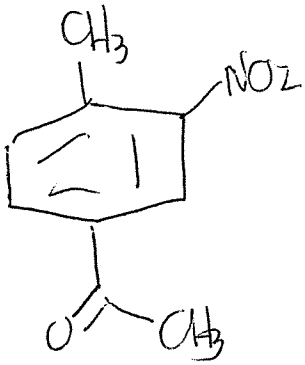


II

H_2/Pd →

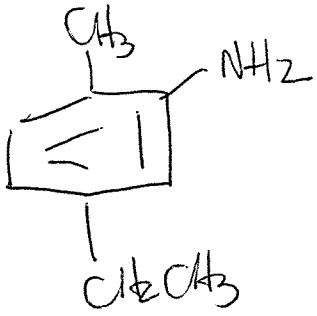


NOT PRODUCT SHOWN



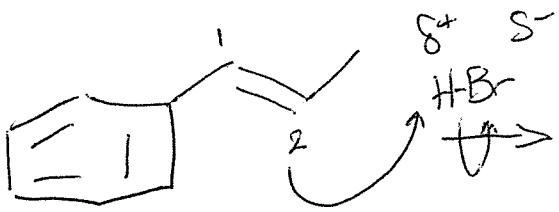
III

H_2/Pd →



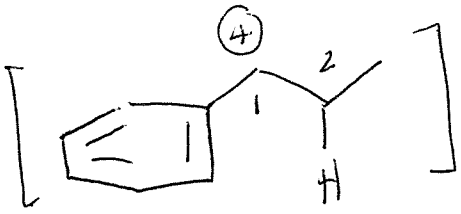
NOT PRODUCT SHOWN

16.51



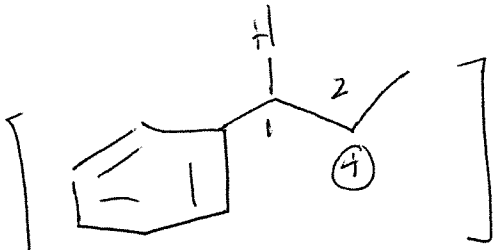
Reaction of H-Br with an alkene is an electrophilic addition. In general, reaction occurs to give two possible regioisomers

I.



2° BENZYLIC

II

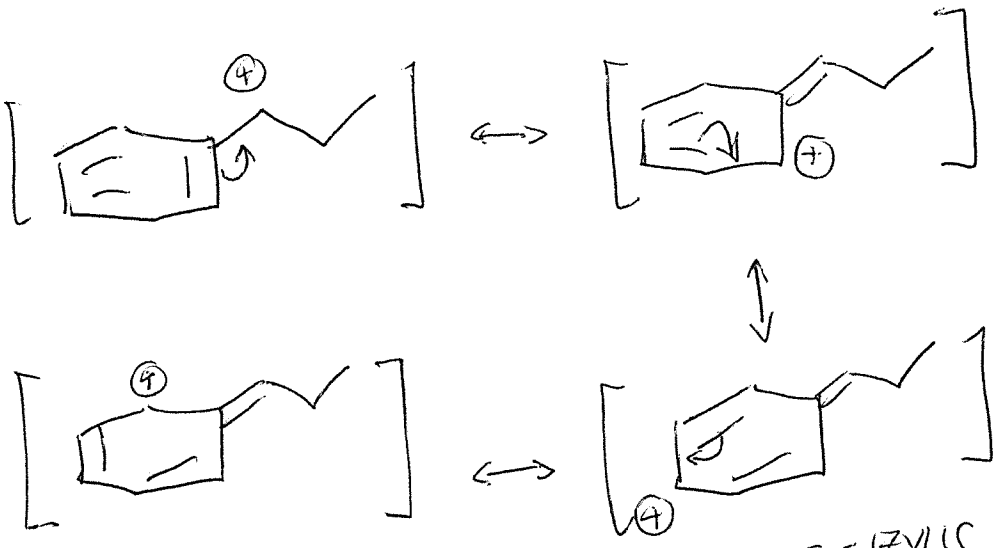


2° ALKYL

The H of H-Br can react w/ the π e⊖ of the alkene at C_1 leaving a carbocation @ C_2 (II) or the H can react at C_2 leaving a carbocation @ C_1 (I)

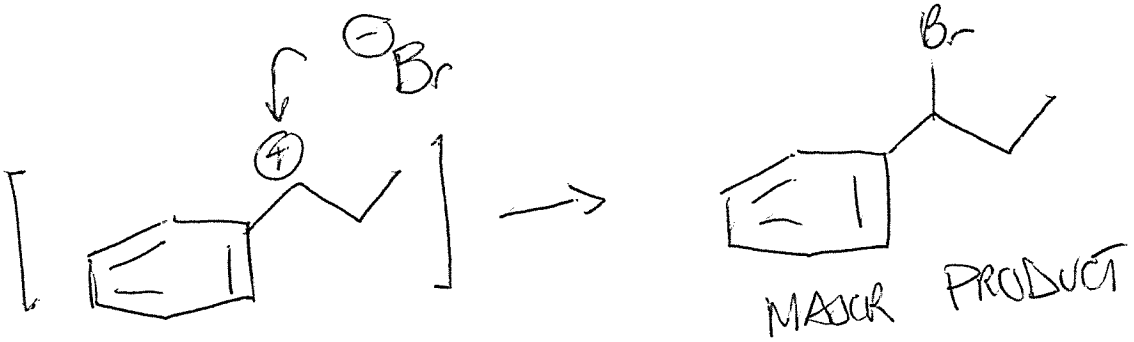
The 2° benzylic carbocation is significantly more stable than the 2° alkyl carbocation due to resonance stabilization associated with the benzylic carbocation.

16.51 (cont'd)



RESONANCE FORMS OF 2° BENZYLIC CARBOCATION

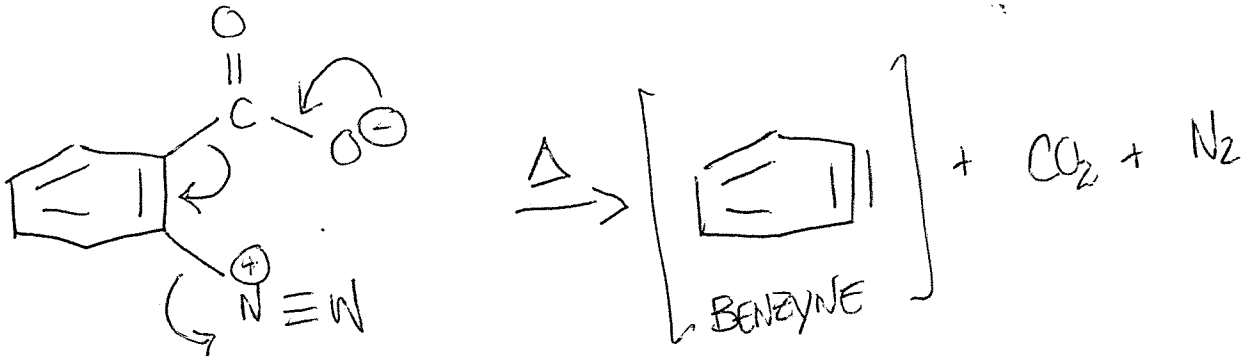
This stabilized carbocation forms much faster than the less stable 2° Alkyl carbocation. The major kinetic product is the one derived from the 2° benzylic carbocation.



MAJOR PRODUCT

The difference in stability between the possible carbocations is so great, essentially none of the product from the less stable 2° alkyl carbocation is formed.

16.58

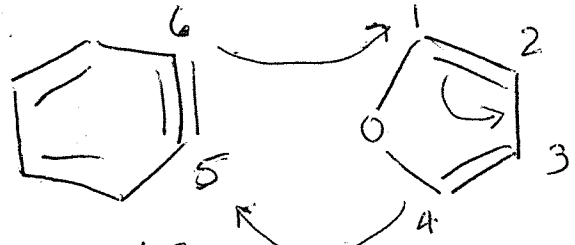


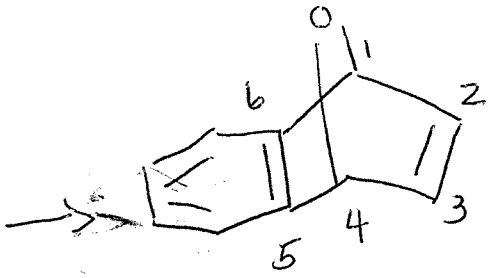
BENZENEDIAZONIUM CARBOXYLATE

(decomposes and forms benzyne)

N_2 gas and CO_2 gas.

The benzyne then serves as the dienophile in a Diels-Alder reaction with furan

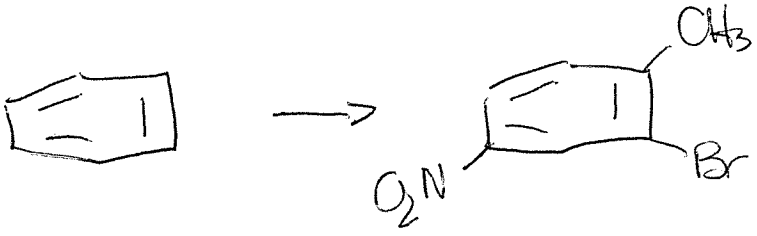




BENZYNE (serves as dienophile)

FURAN (serves as Diene)

16.68



Identify the three substituents in the product. and the methods used to introduce them to the ring.

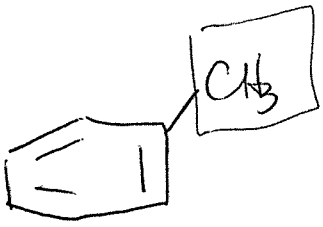
CH_3: CH_3Cl, $AlCl_3$

NO_2: HNO_3, H_2SO_4

Br: Br_2, $FeBr_3$

Next, the order that each group is introduced to the ring must be determined. The order is important since substituent effects play a role.

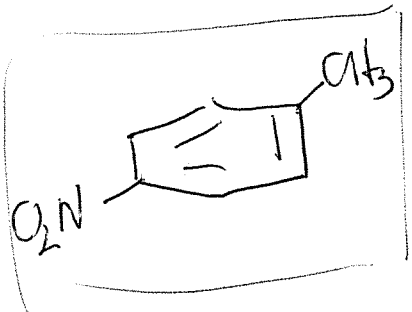
CH_3Cl, $AlCl_3$



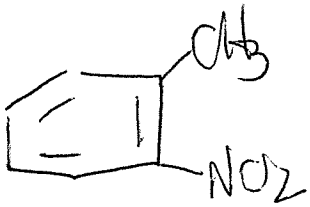
ACTIVATOR
O, P- DIRECTOR

↓ HNO_3, H_2SO_4

This sequence puts CH_3 and NO_2 is the right position (PARA)



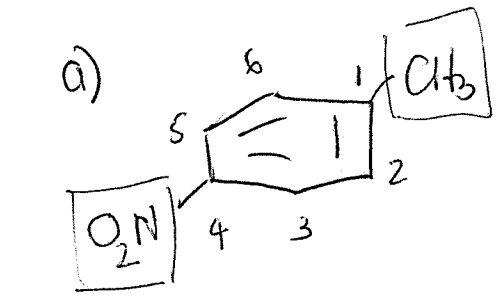
+



16.68 (cont'd)

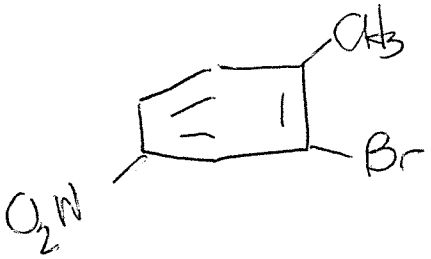
ACTIVATOR
↓ o, p-

a)



Deactivator
m-

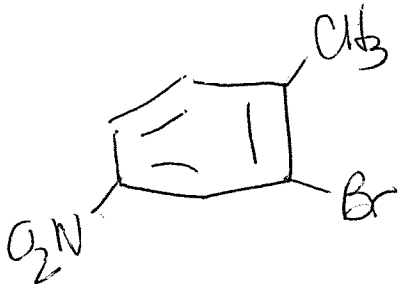
Br_2 / $FeBr_3$ →



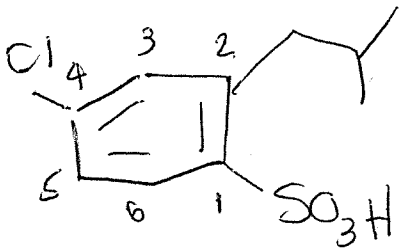
CH_3 group is an ACTIVATOR and directs the reaction to C_2 (or C_6) The NO_2 group directs to these same positions

Determining the order of the reagents is sometimes trial and error. Try a different order to show this product is not formed if the reagents are not put in the right order.

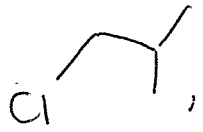
1. CH_3Cl, $AlCl_3$
2. HNO_3, H_2SO_4
3. Br_2, $FeBr_3$



16.68

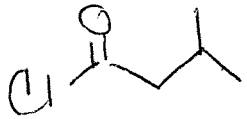
b) 

Cl: Cl_2, $FeCl_3$

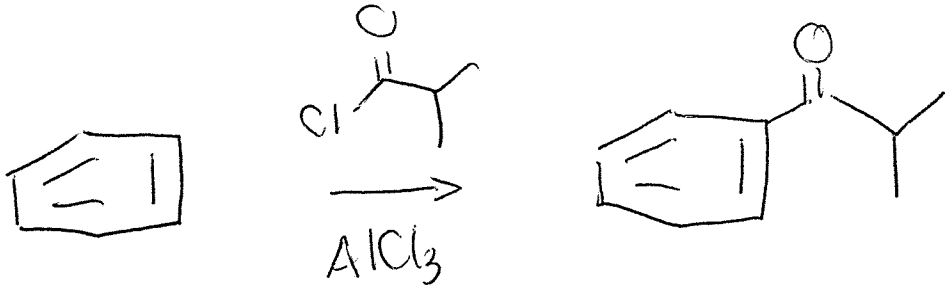
$-CH_2CH(CH_3)_2$: 

$-SO_3H$: H_2SO_4, SO_3

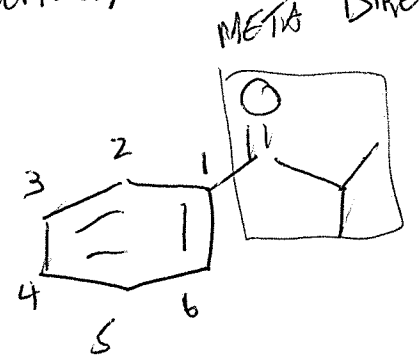
The isobutyl group at C_2 cannot be used directly because the Cl is not o- or p- but meta.

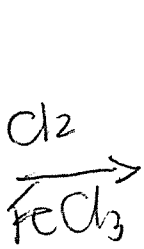
If the acid chloride (i.e. 

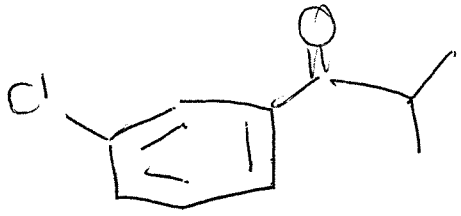
is used instead, it will be a META- director and will set the relative position between the Cl and the isobutyl group. The resulting ketone can be reduced to the alkyl w/ H_2/Pd.



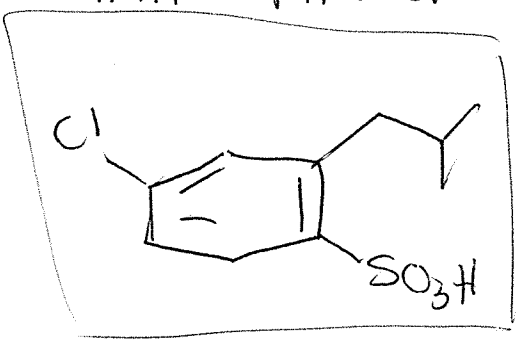
16.68 (cont'd)



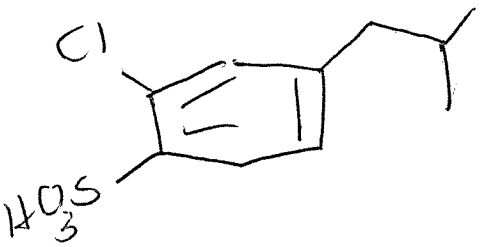


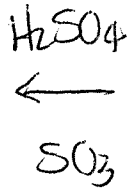


TARGET PRODUCT



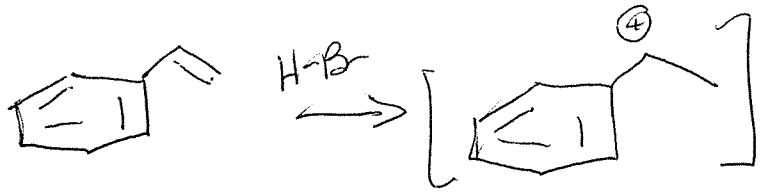
+

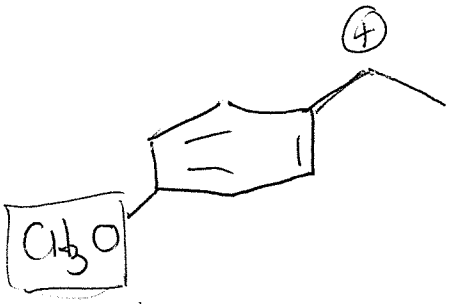




The meta director is converted to an alkyl which is an o-, p- director

16.69

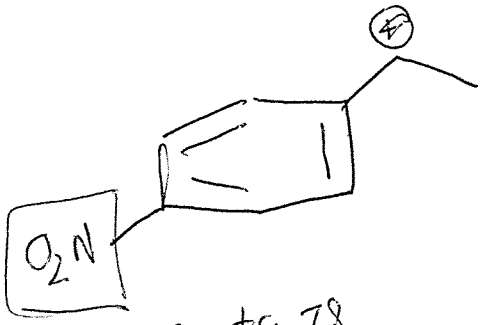




EDG by resonance

$\sigma_p = -0.27$

STABILIZES the carbocation formed in the rate-determining step (FASTER)



EWG $\sigma_p = +0.78$

DESTABILIZES carbocation (SLOWER)