TOPIC 2. REACTIONS OF AROMATIC COMPOUNDS (Chapters 15, parts of 20, and 21)

Add e.g. of SNAr, replace aniline example, turn BHT into and example

TOPIC 2. OTC PAIN KILLERS

OBJECTIVES

1. Describe the reactions between strong electrophiles and aromatic compounds (the nucleophilc component) which lead to substitution of a hydrogen atom on the aromatic ring.

2. Describe the reactions of anilines ($ArNH_2$) and phenols (ArOH) which take place on the nucleophilic ring or nucleophilic substituent.

3. Outline the mechanisms whereby aryl halides undergo nucleophilic substitution (*NOT* S_N1 or S_N2)

4. Describe various reactions of the side chain of aromatic compounds.

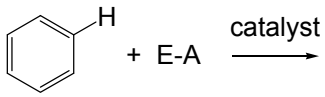
5. Use this knowledge to predict the products of these reactions and to be able to do single-step syntheses and multi-step syntheses using these reactions as well as the reactions previously studied.

ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

S:15.1-2
Review Prob: 15.28,30

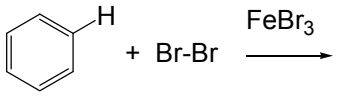
Electrophilic Substitution versus Addition

Arenes undergo *substitution* with strong electrophiles…

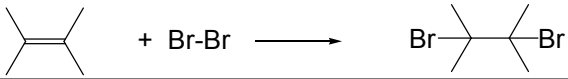


E=electrophile; A=anion or leaving group
E-A + catalyst ⇨ active electrophile

–E = –Cl, –Br
–NO_2
–SO_3H
–R
–C(=O)R

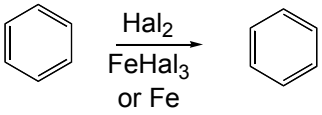


…whereas alkenes undergo *addition* reactions

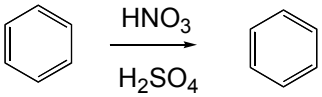


Electrophilic aromatic substitutions

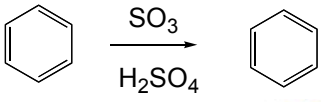
Halogenation



Nitration

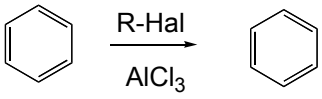


Sulfonation

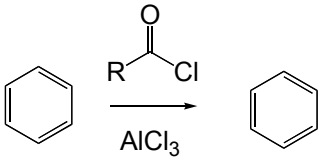


"fuming sulfuric acid"

Friedel-Crafts Alkylation

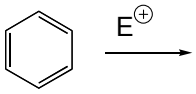


Friedel-Crafts Acylation

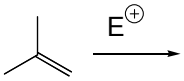


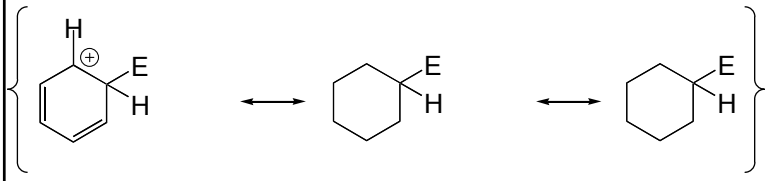
Mechanism

First step



Compare to:

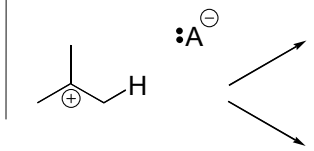


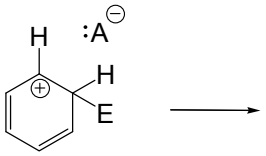


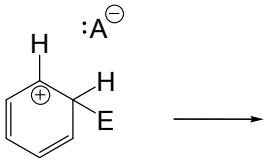
Second step

Consider two possibilities

Compare to:



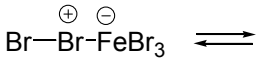


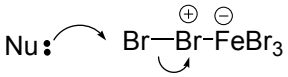


HALOGENATION OF BENZENE

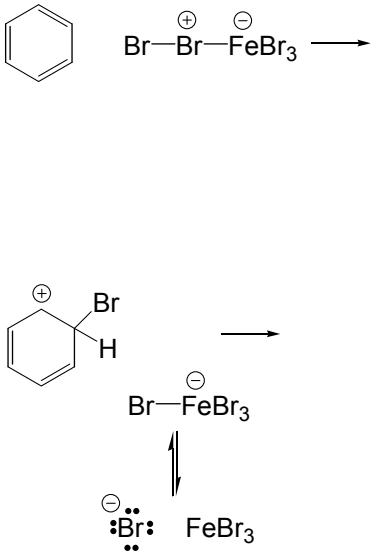
S:15.3

Role of the catalyst (bromine as example): Generation of Active Electrophile





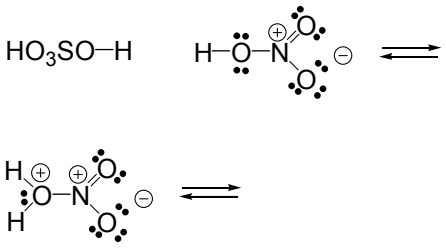
Mechanism of Substitution Step



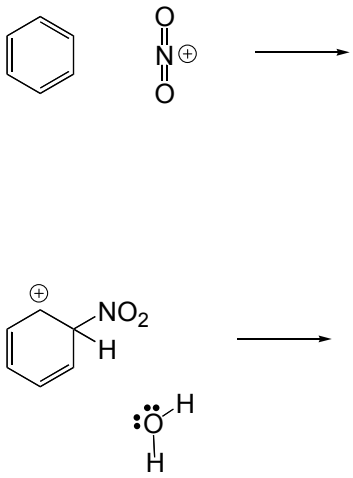
NITRATION OF BENZENE

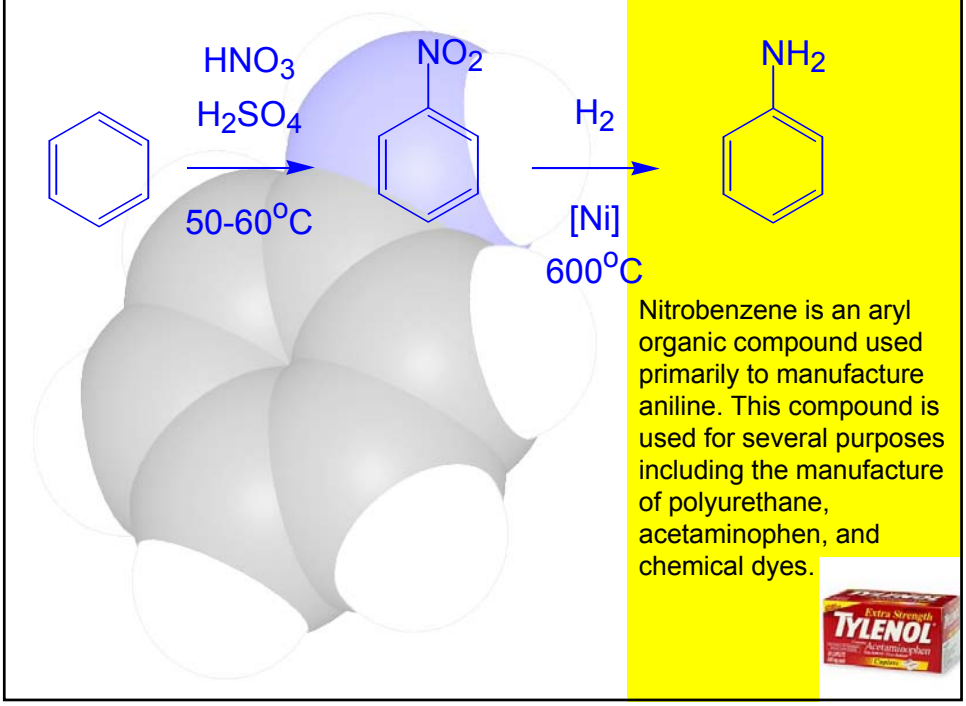
S:15.4

Role of the Catalyst: Generation of Active Electrophile



Mechanism of Substitution Step





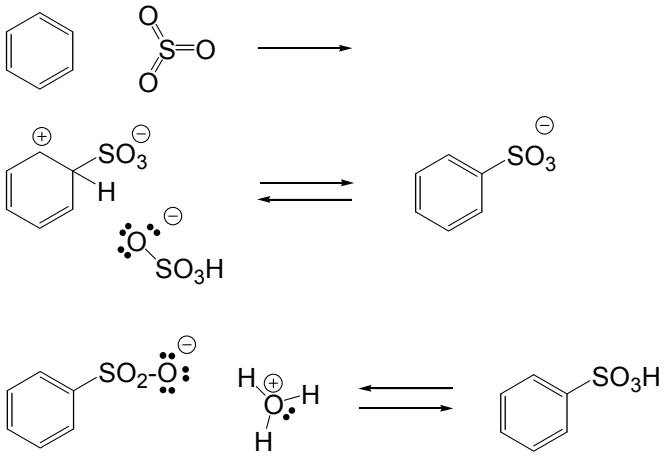
Nitrobenzene is an aryl organic compound used primarily to manufacture aniline. This compound is used for several purposes including the manufacture of polyurethane, acetaminophen, and chemical dyes.

SULFONATION OF BENZENE

Generation of Active Electrophile

H_2SO_4 

Mechanism of Substitution Step

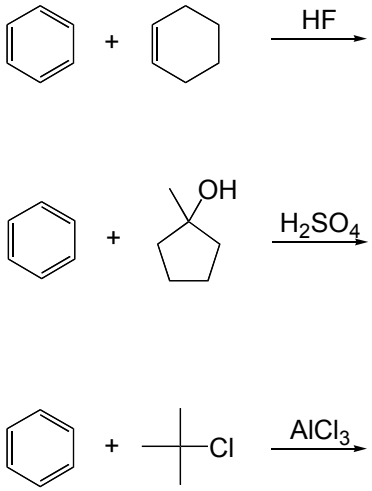


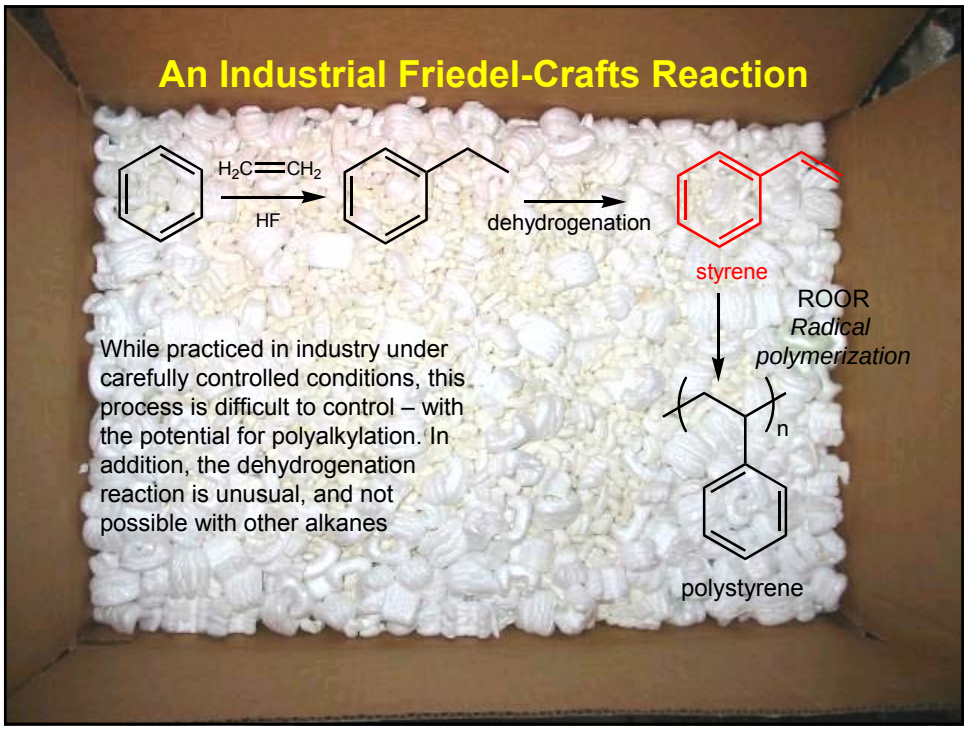
? *Prob: 15.18,30* ?

FRIEDEL-CRAFTS ALKYLATION

S:15.6
Prob: 15.29 a,b

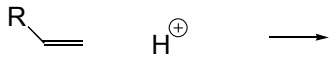
Examples



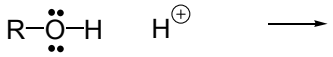


Role of the Catalyst: Generation of Active Electrophile

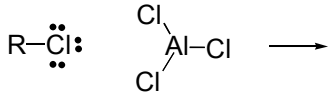
Alkene + strong acid



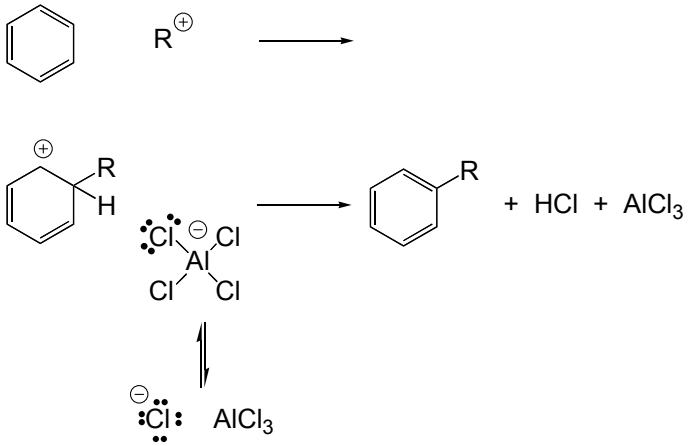
Alcohol + strong acid



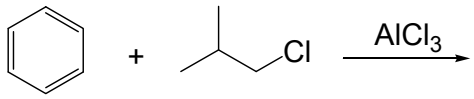
Alkyl chloride + Lewis acid



Mechanism of Substitution Step



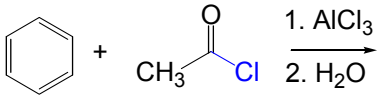
Rearrangement during Friedel-Crafts Alkylation

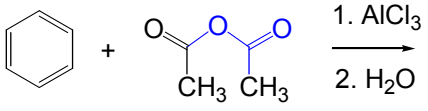


FRIEDEL-CRAFTS ACYLATION

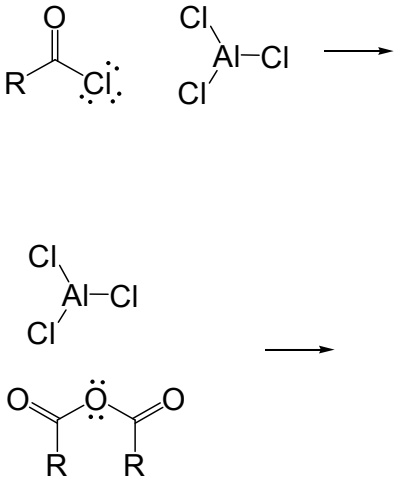
S:15.7

Examples

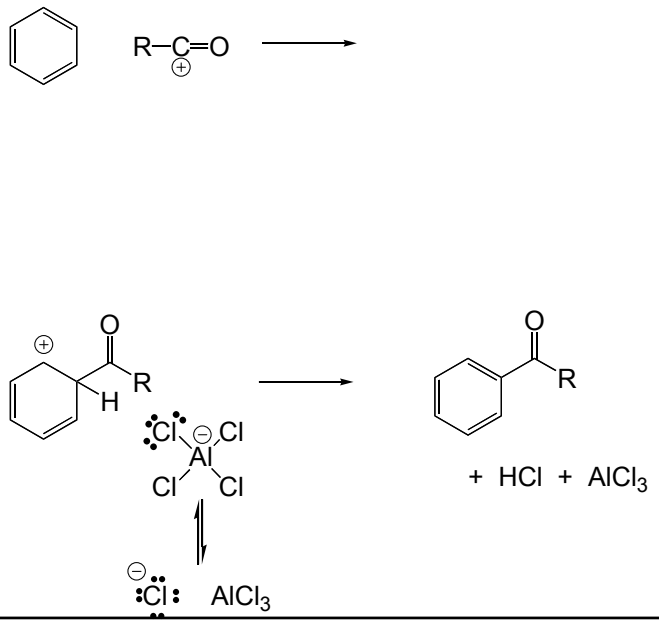




Role of the Catalyst: Generation of Active Electrophile



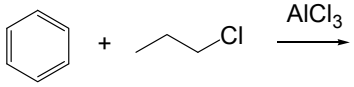
Mechanism of Substitution Step



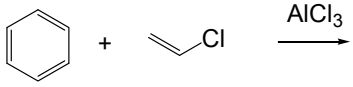
LIMITATIONS OF FRIEDEL-CRAFTS ALKYLATIONS AND ACYLATIONS

S:15.8,9
Prob:
15.29cd;33

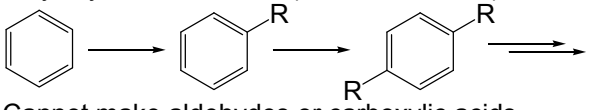
1. Rearrangements to more stable carbocations (1°→2° or 3°; 2°→3°)



2. Vinyl, alkynyl and aryl halides do not serve as electrophiles

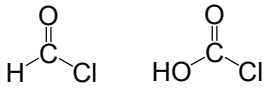


3. Polyalkyation can occur (will discuss later)

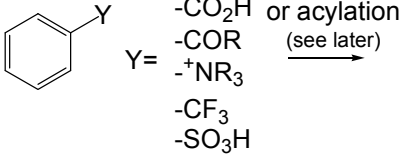


4. Cannot make aldehydes or carboxylic acids

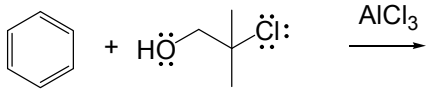
cannot use:

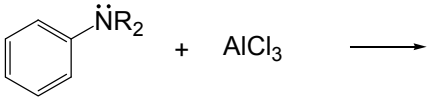


5. Benzene with electron withdrawing groups are poor nucleophiles

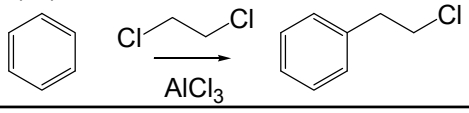


6. Lewis bases complex the Lewis acid and hinder reaction



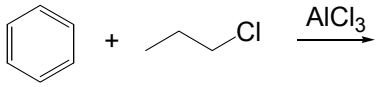


7. Di-, tri(…)-haloalkanes

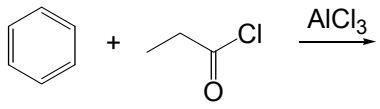


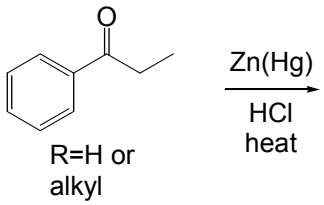
A Solution to the Problem of Rearrangements During Friedel-Crafts Alkylations

Problem: Rearrangement

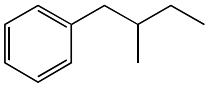


Solution: Acylation followed by Clemmensen Reduction



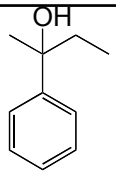


Problem: How would you prepare 1-phenyl-2-methylbutane?



?

Problem: How would you prepare 2-phenyl-2-butanol?



?

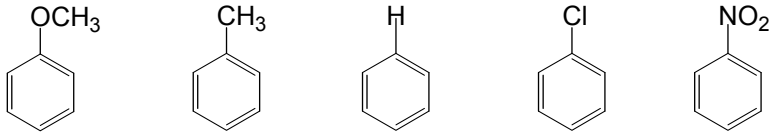
? *Prob: 15.29,33* ?

EFFECT OF SUBSTITUENTS ON REACTIVITY AND ORIENTATION

S:15.10
Prob:15.26,27, 31,32,34,35

Effect of Substituents on RATE of substitution

e.g. Relative rates for nitration



1000 25 1 0.03 0.001

Electron donating groups

Resonance donors
-Y: (except halogens), e.g. -OR and -NR_2

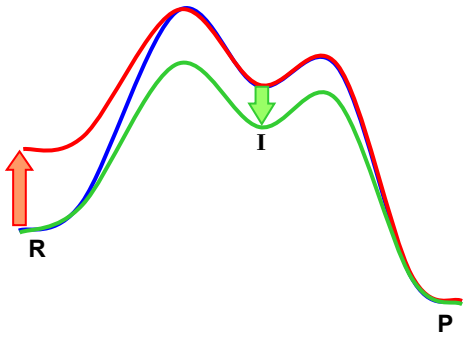
Inductive donors
-alkyl

Electron withdrawing groups

Resonance withdrawing
-X=Y

Inductive withdrawing
-Hal, -CF_3

Why do substituents effect the rate of S_EAr reactions?

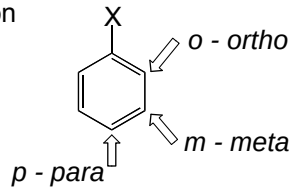


energy (reactivity) of *reactants* ↑ E_a ↓ rate ↑
EDG increase the nucleophilicity of the benzene ring – faster reaction
EWG decrease the nucleophilicity of the benzene ring – slower reaction

energy (reactivity) of *intermediates* ↓ E_a ↓ rate ↑
EDG decrease the energy of the carbocation intermediate – faster reaction
EWG increase the energy of the carbocation intermediate – slower reaction

Effect of Substituents on POSTION of substitution

Substituents direct the substitution reaction to different positions



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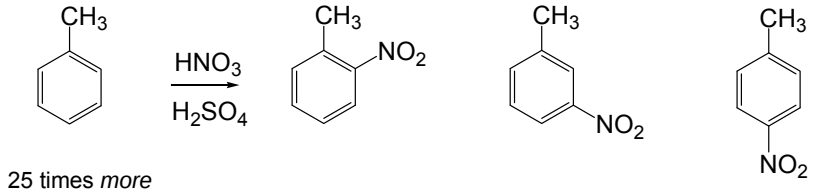
1. Activating ortho/para directors



25 times *more* reactive than benzene

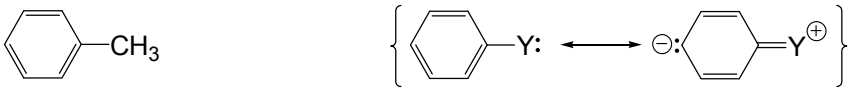
59 %

4 %

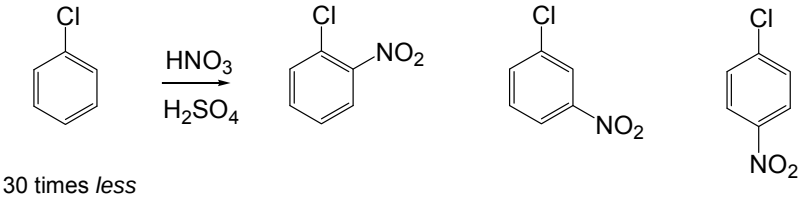
37 %

Type of substituents which are activating o/p directors:

-alkyl and -Y: (not halogen), e.g. -OR and -NR_2



2. Deactivating ortho-para directors



30 times *less* reactive than benzene

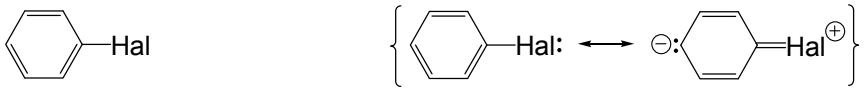
30 %

1%

69 %

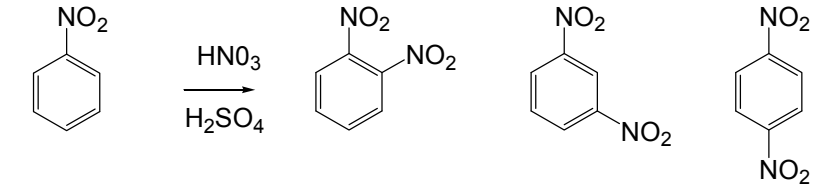
Type of substituents which are deactivating o/p directors:

-F, -Cl, -Br, -I



---

3. Deactivating meta directors



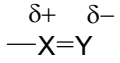
1000 times *less* reactive than benzene

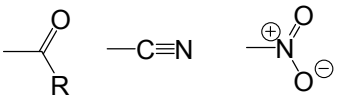
6 %

93%

1 %

Types of substituents which are deactivating m directors:

general  and 

e.g. 

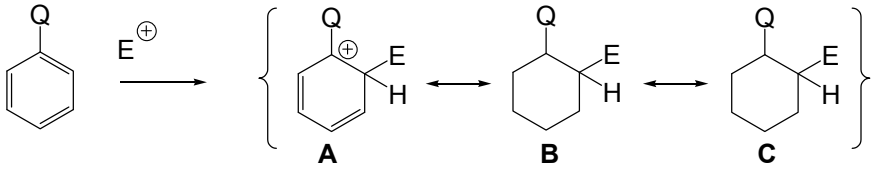
(there are no activating m directing substituents)

Understanding the Basis for Substituent Effects on Electrophilic Aromatic Substitution

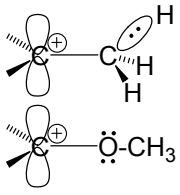
Analysis 1: Consider the effect of "Q" on the stability of the intermediate cyclohexadienyl cation.

ortho *meta* *para*

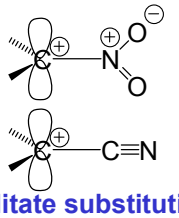
Resonance structures of cyclohexadienyl cation from ***ortho* attack**:



Resonance structure **A** is especially *stabilized* by electron *donating* substituents, increasing the rate of reaction at this position.

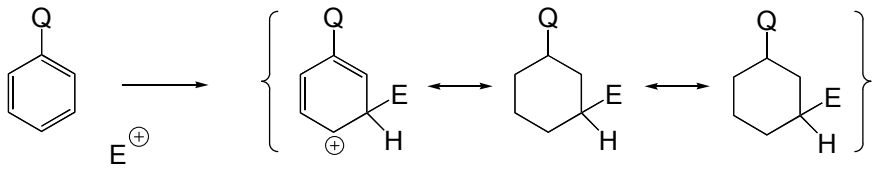


Resonance structure **A** is especially *destabilized* by electron *withdrawing* substituents, decreasing the rate of reaction at this position



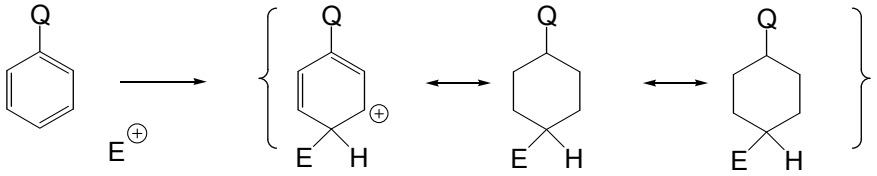
» Electron donating substituents facilitate substitution at the *ortho* positions.

Resonance structure of cyclohexadienyl cation from ***meta* attack**:



» Electron donating substituents do **not** facilitate substitution at the *meta* position.

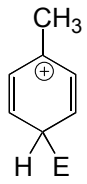
Resonance structures of cyclohexadienyl cation from ***para* attack**:



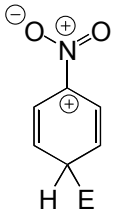
» Electron donating substituents facilitate substitution at the *para* position.

»» Electron donating groups are o/p- directing

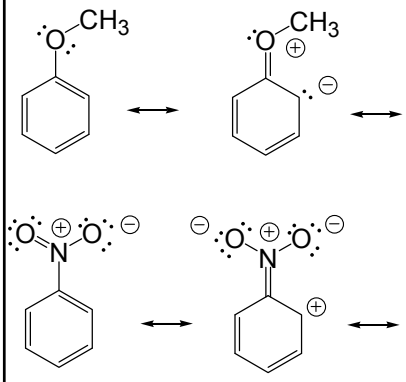
If the substituent is electron donating (*e.g.* alkyl [hyperconjugation] or oxygen (:O:) or nitrogen (N:) [resonance donating]), the resonance structures from *ortho* and *para* attack are stabilized compared to the *meta* position. This leads to a faster overall reaction, favoring substitution at the *ortho* and *para* positions.



If the substituent is electron withdrawing (*e.g.* -NO_2 or -COR [resonance] or -CF_3 [inductive]) the resonance structures from attack at all positions are destabilized. This leads a slower overall reaction. Those resonance structures from *ortho* and *para* attack are particularly destabilized. This disfavors substitution at these positions, leading to *meta* substitution.



Analysis 2: Consider the effect of the substituent on the electron distribution in the starting material

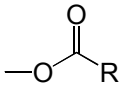
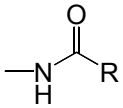


» Electron donating groups are *o*/*p*- directing
» Halogen substituents are *o*/*p*- directing
» Electron withdrawing groups are *m*- directing

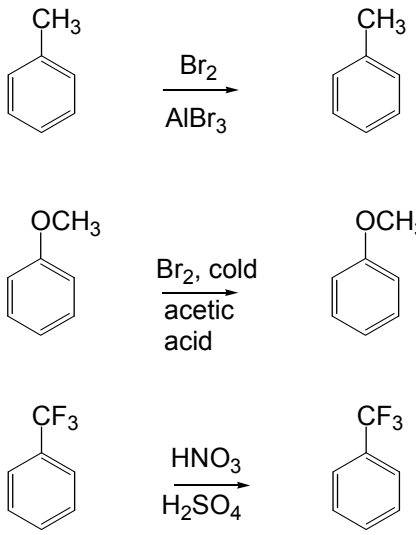
Summary of Activating and Directing Effects

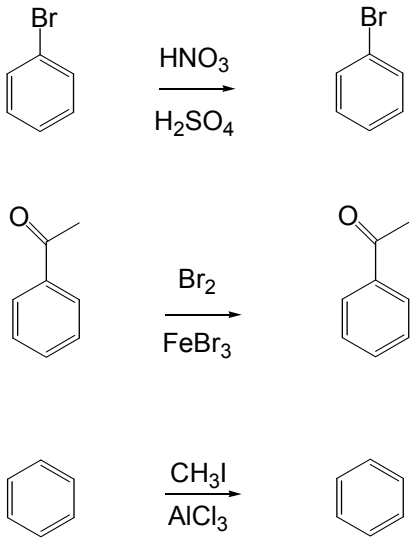
All *m*- directors are deactivators

All *o/p*- directors, except halogens, are activators

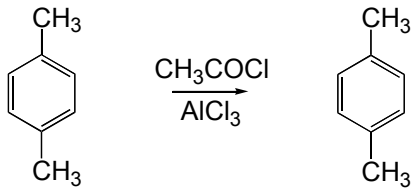
Strong electron withdrawing groups	*Weak electron withdrawing groups*	*Weak electron donating groups*	*Strong electron donating groups*
$-SO_3H$			-OR(H)
-CN			$-NR(H)_2$
$-NO_2$	-Hal		
-C(O)X (X=H,R,OH,OR)		-R	
$-CF_3$	*Inductive withdrawal ⇒ Deactivating*		
Deactivating meta-directing	*Resonance donation ⇒ ortho/para-directing*	*Activating ortho/para-directing*	*Activating ortho/para-directing*

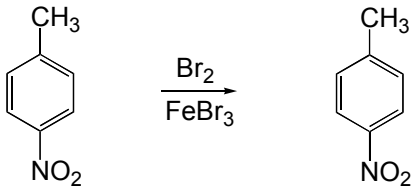
Directing effects on monosubstituted rings



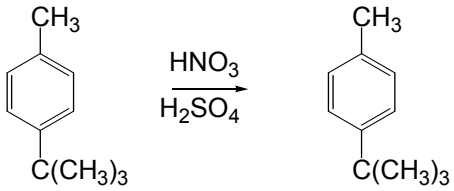


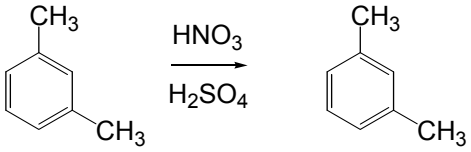
Directing Effects on Disubstituted Rings



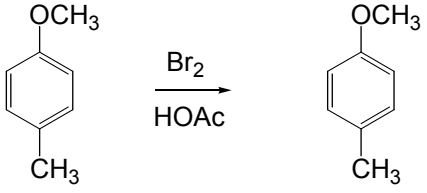


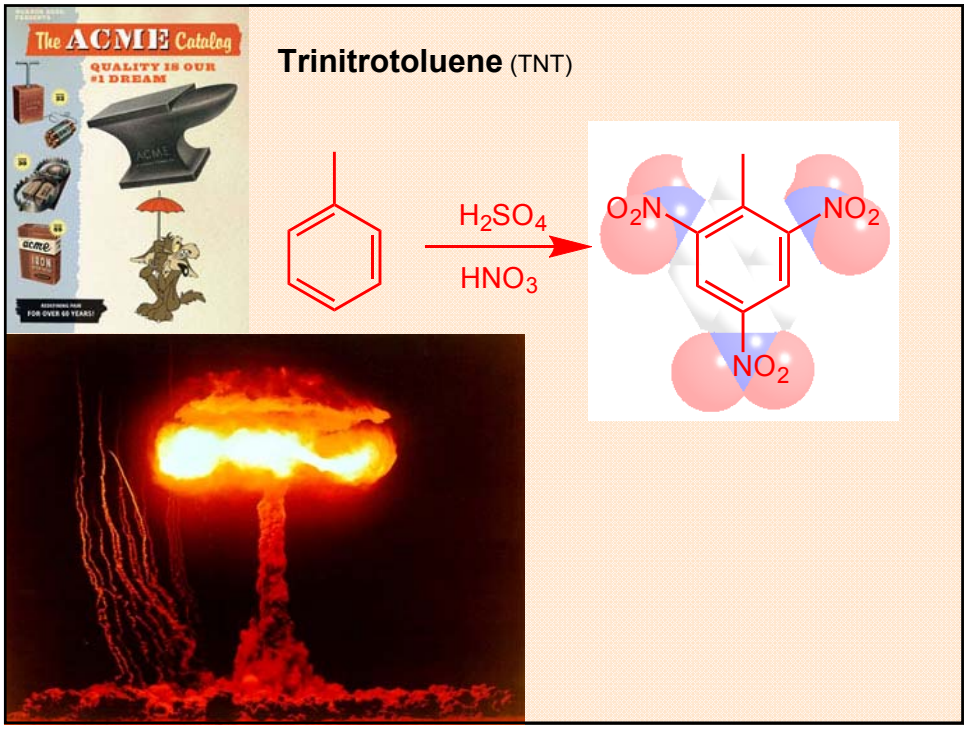
Steric effects

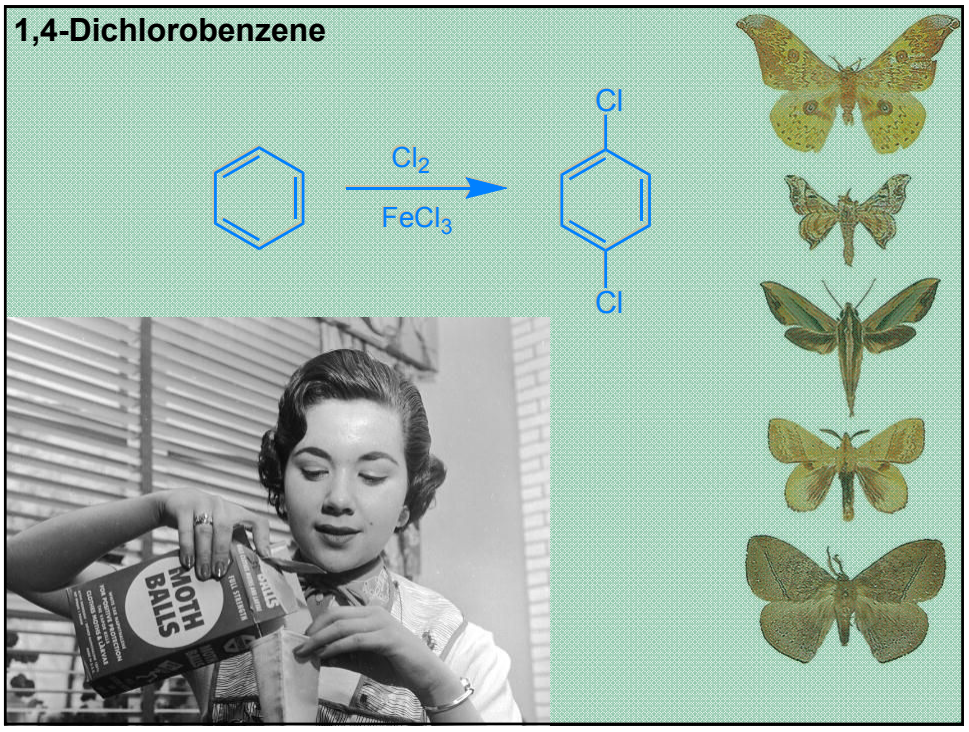




When directing effects are in competition with one another




The ACME Catalog
QUALITY IS OUR #1 DREAM
Trinitrotoluene (TNT)
H_2SO_4
HNO_3
O_2N
NO_2
NO_2


1,4-Dichlorobenzene
Cl_2
$FeCl_3$
Cl
Cl
MOTH BALLS

? *Prob: 15.26,27,31,32,34,35* ?

SYNTHETIC APPLICATIONS

S:15.14
Prob:15.29e-m, 38,41,43,45, 48,50,51,53

Consider how each substituent can be either:

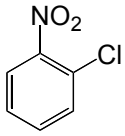
1. Introduced by electrophilic substitution
   -Hal, $-SO_3H$, $-NO_2$, -R, -COR

or 2. Prepared by modification of an existing substituent
   $-CO_2H$ from –R
   $-CH_2R$ from –COR
   $-CH_2Br$ from CH_3
   $-CH_2OH$ from CH_2Br

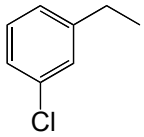
Consider whether reactions can really be performed:
   Directing effects of other substituents
   Effect of reagents/conditions on other substituents

Think RETROSYNTHETICALLY!

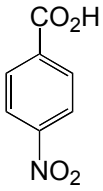
Problem [Solomons 15.29l) - How would you prepare 2-chloronitrobenzene?



Problem - 3-Chloroethylbenzene has two *o*/*p*-directors *meta* to one another. How can it be synthesized?



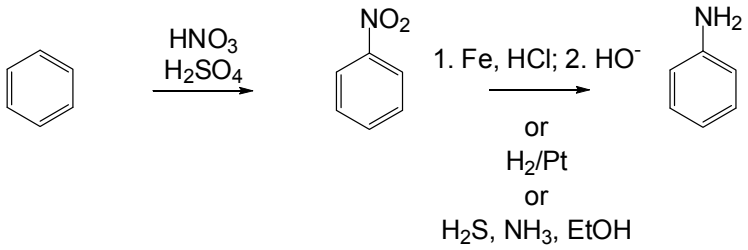
Problem - 4-Nitrobenzoic acid has two *m*-directors *para* to one another. How can it be synthesized?



? *Prob: 15.29e-m,38,41,43,45,48,51,53* ?

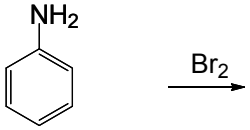
ANILINES: SYNTHESIS, BASICITY AND NUCLEOPHILICITY

Synthesis of Anilines: Reduction of Nitrobenzenes

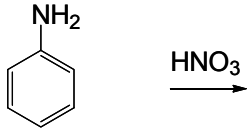


Challenges with Electrophilic Aromatic Substitutions of Anilines

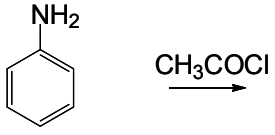
Attempts to Perform Friedel-Crafts Acylations



Attempts to Perform Nitrations



Attempts to Perform Halogenations

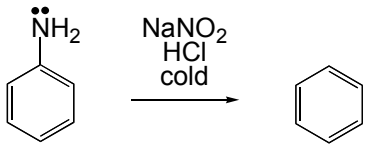


Using N-Acylation to Moderate Nucleophilicity of the Ring

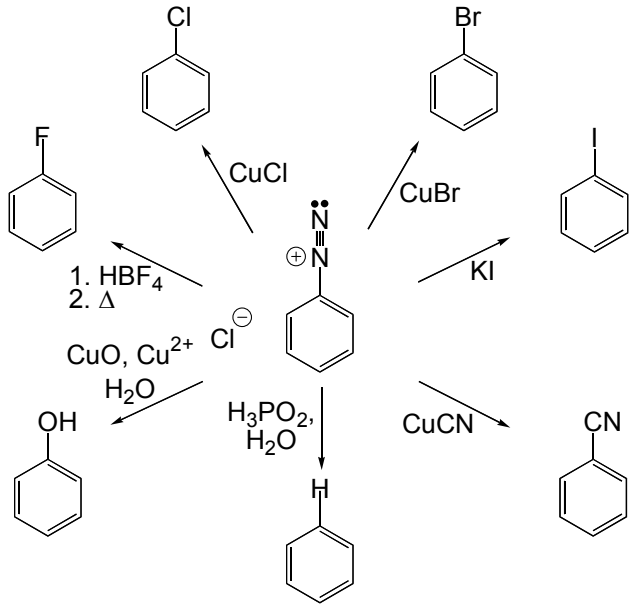
ARYLDIAZONIUM SALTS

S:20.5-8
Prob:20.26,31

Formation: Reaction of Anilines with Nitrous Acid

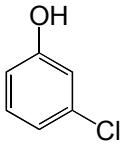


Substitution Reactions of Arene Diazonium Salts

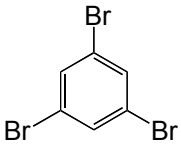


Designing Syntheses via Aromatic Diazonium Salts

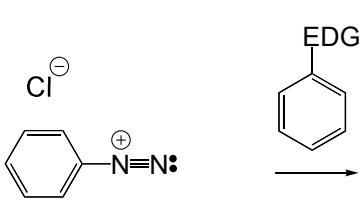
Problem - 3-Chlorophenol has two *o/p* directors *meta* to one another. Either substituent can be introduced by use of diazonium salts. The diazonium substituent is prepared from the nitro substituent (via the amine), which is a meta director. How can 3-chlorophenol be prepared?



Problem – 1,3,5-Tribromobenzene has three o/p directors meta to one another. How can 1,3,5-tribromobenzene be prepared?

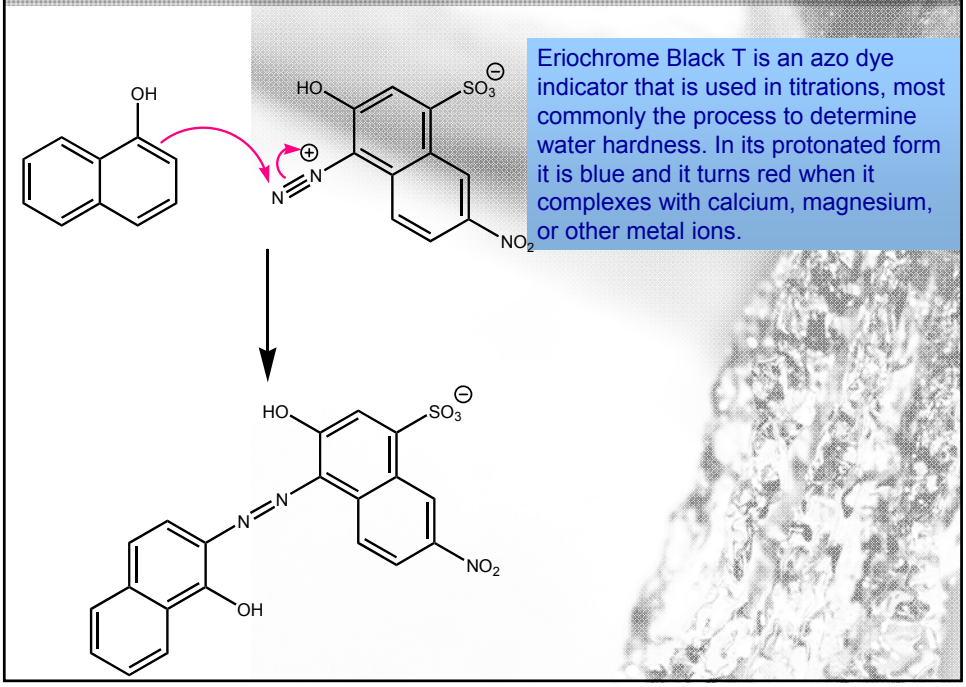


Diazo coupling of diazonium salts with electron-rich arenes



EDG= -$\ddot{X}$, not -Hal

Eriochrome Black T - Sodium (4Z)-4-[(1-hydroxynaphthalen-2-yl)hydrazinylidene]



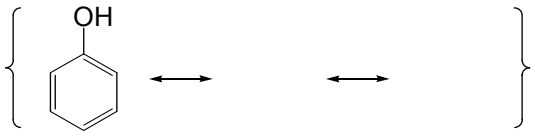
Eriochrome Black T is an azo dye indicator that is used in titrations, most commonly the process to determine water hardness. In its protonated form it is blue and it turns red when it complexes with calcium, magnesium, or other metal ions.

? *Prob: 15.26,31* ?

PHENOLS

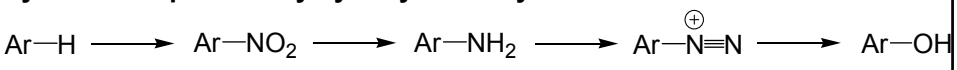
S:21.1-5
rob: 21.17

Introduction

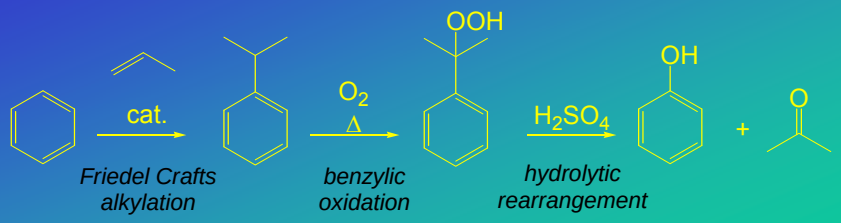


oxygen: nucleophilic
ring (o-,p- positions): nucleophilic

Synthesis of phenols by hydrolysis of aryldiazonium salts

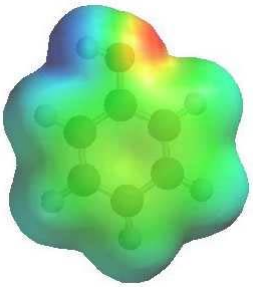


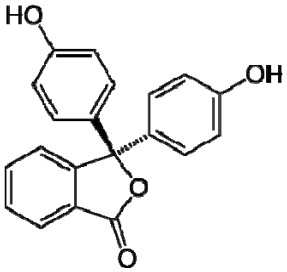
Industrial preparation of phenol and acetone



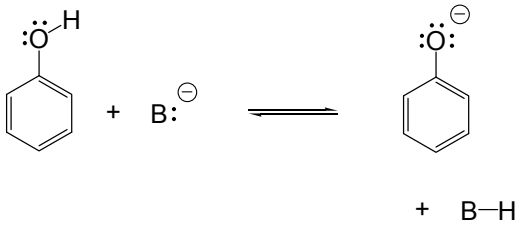
Friedel Crafts alkylation — *benzylic oxidation* — *hydrolytic rearrangement*

benzene cumene phenol acetone





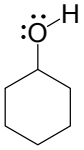
Acidity of Phenols



+ B—H

pK_a = 9.9

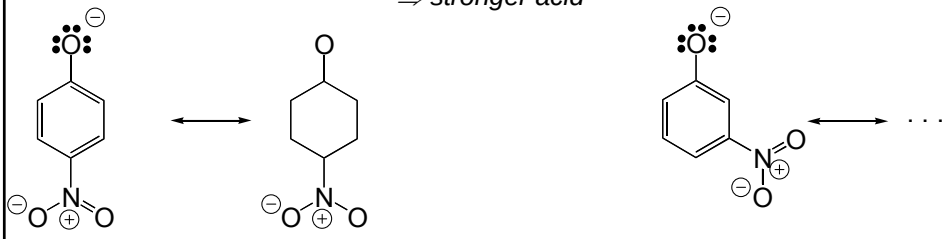
Compare to cyclohexanol: pK_a = 18



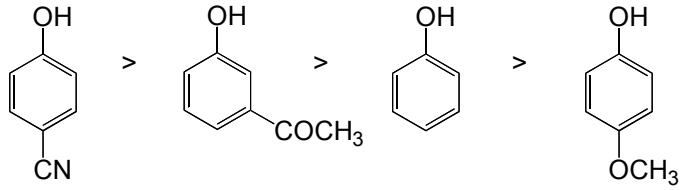
Electron withdrawing groups, -X=Y:

stabilize the conjugate base

⇒ *stronger acid*



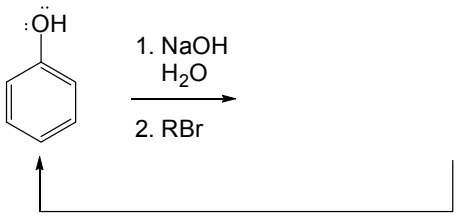
Acid strength



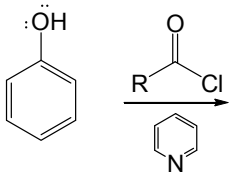
o- or *p*-EWG *m*-EWG *o*- or *p*-EDG

REACTIONS OF PHENOL: NUCLEOPHILIC OXYGEN

S:21.6,7
Prob 21.14



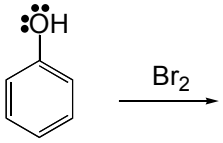
Williamson ether synthesis

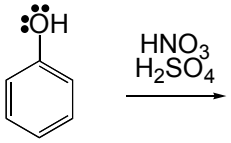


Esterification: see later

REACTIONS OF PHENOL: NUCLEOPHILIC RING

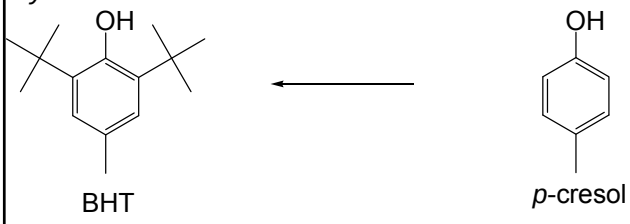
S:21.8



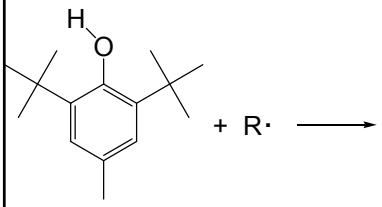


BHT - Butylated Hydroxy Toluene

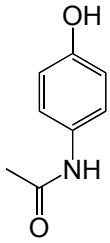
Synthesis



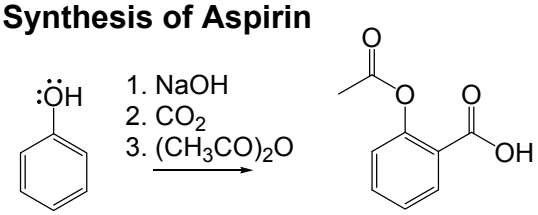
Anti-oxidative action



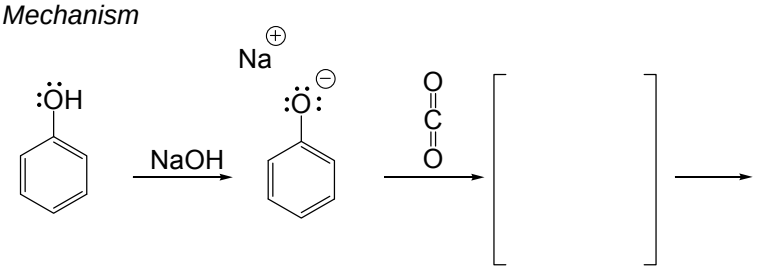
Tylenol - Acetaminophen



Synthesis of Aspirin

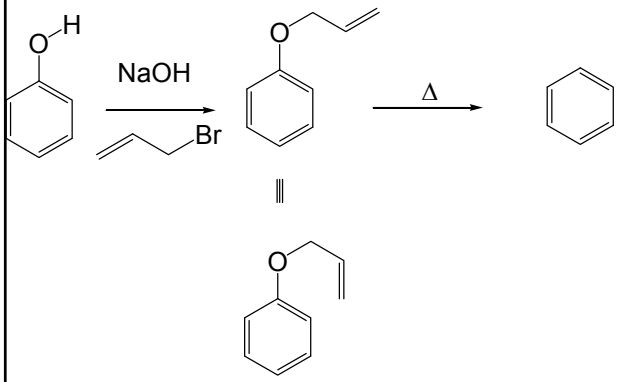


Mechanism



THE CLAISEN REARRANGEMENT

S:21.9



? *Prob: 21.13,16* ?

OXIDATION AND REDUCTION OF THE AROMATIC RINGS

S:15.16

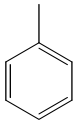
Reduction

H_2 / Ni

heat

pressure

+ 2Na + 2EtOH $\xrightarrow{NH_3}$

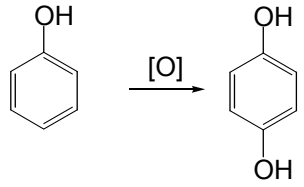


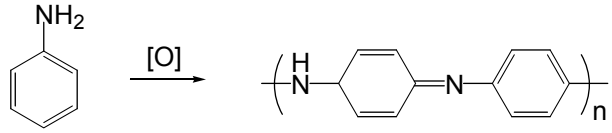
$\xrightarrow{NH_3}$

Na, EtOH

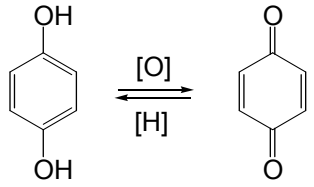
Oxidation

Electron Rich Arenes





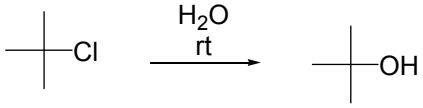
Hydroquinones and Quinones

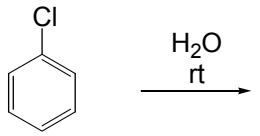


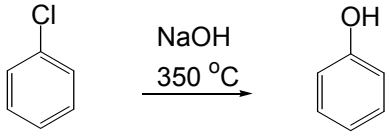
ARYL HALIDES AND NUCLEOPHILIC AROMATIC SUBSTITUTION

S.21.11

Comparison of Hydrolysis Reactions







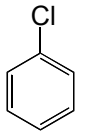
Nucleophilic Aromatic Substitution take place primarily in two cases:

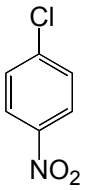
1. The presence of a strong electron withdrawing group o- or p- to the leaving group

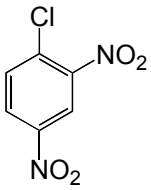
2. The presence of a strong base and a hydrogen adjacent to the leaving group

Scenario 1: Presence of Strong Electron Withdrawing Groups

Relative rates of hydrolysis – effect of o/p EWG



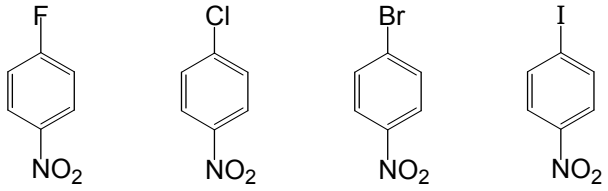




k_{rel}	1	7×10^{10}	2.4×10^{13}

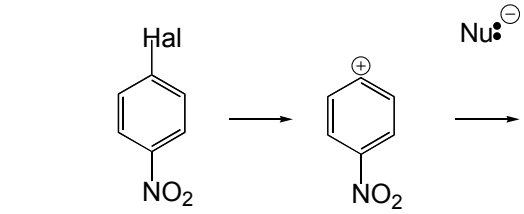
Rate = *k*[substrate][nucleophile]

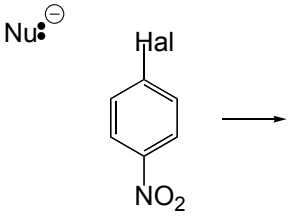
Relative rates of hydrolysis – effect of halide



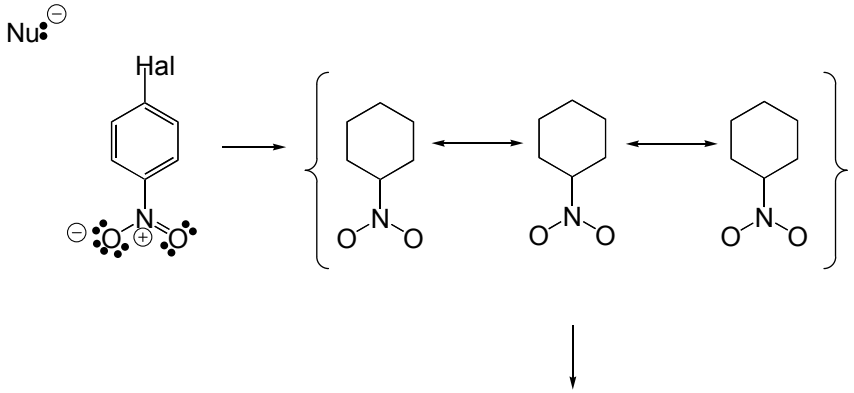
k_{rel}	312	1	0.8	0.4

Wrong Mechanisms – Disproven by Experimental Data



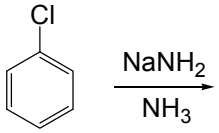


Mechanism – Consistent with Experimental Data

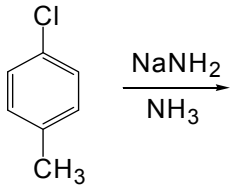


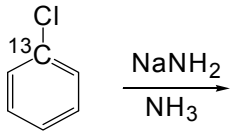
Scenario 2: Effect of a very strong base in the absence of EWG

Overall Reaction

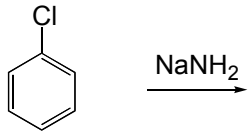


Other Experimental Observations

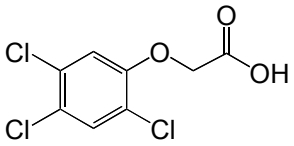




Mechanism - Consistent with Experimental Data



Problem: 2,4,5-Trichlorophenoxyacetic acid (4,5-T, Agent Orange). How could 2,4,5-T be prepared from 2,4,5-trichlorophenol?



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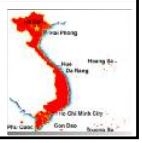
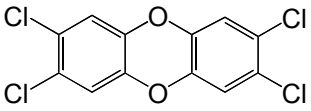


Problem: Dioxins are polychloroinated dibenzodioxanes. They are extremely toxic. 2,3,7,8-TCDD, a dioxin, is formed during the production of 2,4,5-T. Provide a mechanism for its formation.



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http://seawifs.gsfc.nasa.gov/OCEAN_PLANET/HTML/peril_toxins.html

REVIEW: ELECTROPHILIC AROMATIC SUBSTITUTION

Reactions

Halogenation
Nitration
Sulfonation
Friedel-Crafts alkylation
Frieldel-Crafts acylation

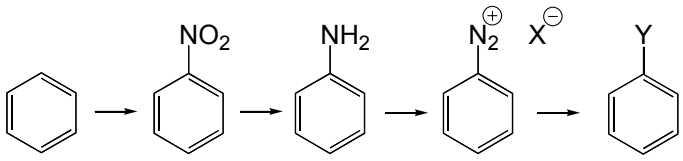
Activating/Deactivating and Directing effects

Deactivating meta-directing	*Deactivating ortho/para-directing*	*Activating ortho/para-directing*	*Activating ortho/para-directing*
-CN	-Hal	-R	-OH(R)
$-NO_2$			$-NH(R)_2$
-C(O)X (X=R,OH,OR)			
$-CF_3$			

Modification of Side chains

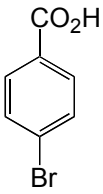
$-CO_2H$ from –R
$-CH_2R$ from –COR
$-CH_2Br$ from CH_3
$-CH_2OH$ from CH_2Br

Anilines in Synthesis



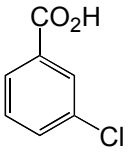
m-directing *o/p*-directing Y= Hal, OH, CN, H

Problem [Solomons 15.31d] - Propose a synthesis of 4-bromobenzoic acid from toluene



?

Problem [Solomons 15.31a] - Propose a synthesis of *m*-chlorobenzoic acid from toluene



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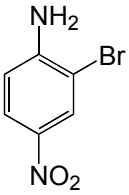
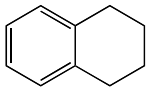
Problem [Solomons 15.32c] - Propose a synthesis of 2-bromo-4-nitroaniline from aniline.



?

Problem [Solomons 15.43a] - Propose a synthesis of the following molecule from benzene



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TOPIC 2 ON EXAM 2

Types of Questions

- Predict product of reactions – S_EAr, S_NAr, reactions of substituents, diazonium salts
- Mechanisms - S_EAr (incl. generation of electrophile), S_NAr (two pathways)
- The effect of substituents: rate of reactions, directing effects, relative acidity/basicity of phenols and anilines
- Design of multistep syntheses (including use of reactions from organic-I and earlier in semester)

Provide mechanistic rationale for experimental observations; use knowledge of mechanism to predict the outcome and pathways of reactions

Do the problems in the book; they are great examples of the types of problems on the exam!

Preparing for Exam 2

- Get up-to-date *NOW!*
- Work as many problems as possible. Do the problems first, then consult the solutions manual.
- Work in groups, discuss chemistry, teach and test each other.
- Do the "Learning Group Problem" at the end of the chapter.