

Chapter 12

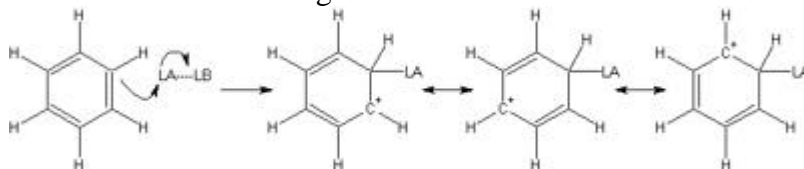
Reactions of Arenes: Electrophilic Aromatic Substitution

Chapter 12 suggested problems: 22, 23, 26, 27, 32, 33

Class Notes

I. Electrophilic aromatic substitution reactions

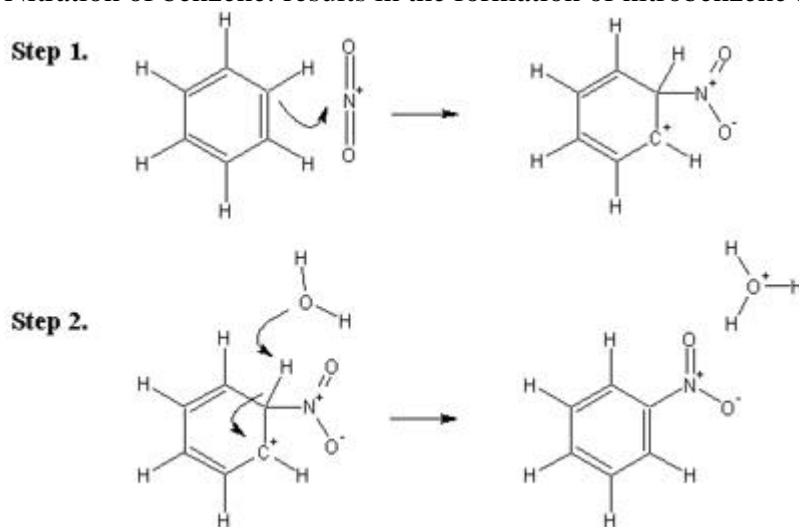
- A. The method by which substituted benzenes are synthesized
- B. General principles - roughly similar to SN1 reactions: a 2 step substitution reaction in which the rate-limiting is one in which a carbocation is formed



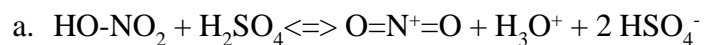
1. Attack by strong acid on pi electron system and formation of cyclohexadienyl carbocation (slow)
 - a. Cyclohexadienyl carbocation also called arenium ion
 - b. Allylic stabilization of carbocation
 - c. Cyclohexadienyl carbocation is not aromatic and not nearly as stable as benzene
 - d. The loss of aromatic stabilization is the reason for the relatively low reactivity of benzene
 - e. Due to the high activation energy associated with the first step, the electrophile must be very reactive
2. Removal of hydrogen by base (fast)

- a. Once the carbocation is formed it rapidly loses a proton and restores the aromatic character of the ring
- b. The hydrogen removed is usually allylic in one or more resonance forms

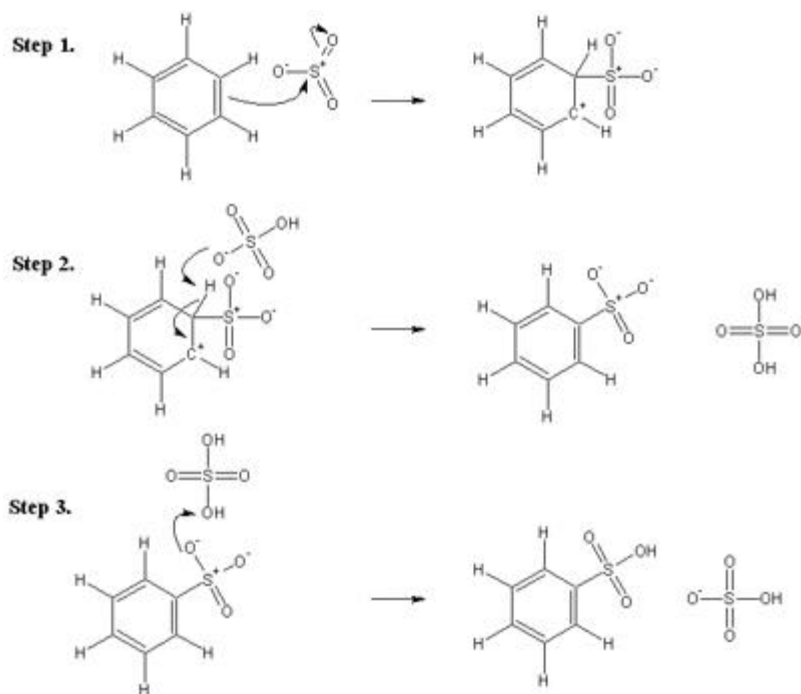
C. Nitration of benzene: results in the formation of nitrobenzene and water



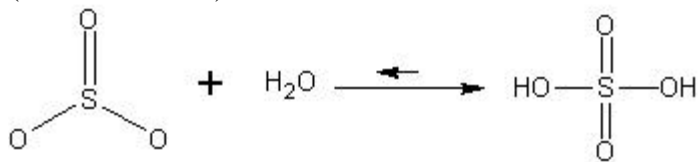
1. Nitronium ion is naturally in eqb. with nitric acid (AIC-C&W:430f)
2. Reaction of nitric acid and sulfuric acid results in formation of higher concentrations of nitronium ion



D. Sulfonation of benzene: reaction with sulfuric acid results in quantitative yields of benzenesulfonic acid

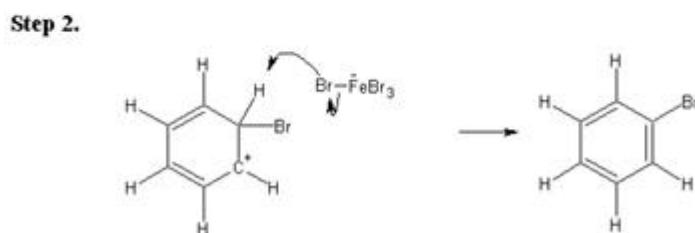
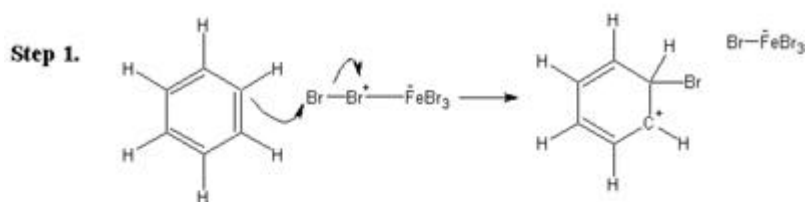


1. The active agent in sulfonation is probably sulfur trioxide
2. Sulfur trioxide - powerful oxidizing agent in eqb with sulfuric acid (AIC-C&W:529)



3. Polar S-O bonds and empty d orbitals result in a powerful Lewis acid (?)
4. Can react benzene with sulfur trioxide to push eqb. even more to product side

E. Halogenation of benzene: performed with halogen in the presence of iron



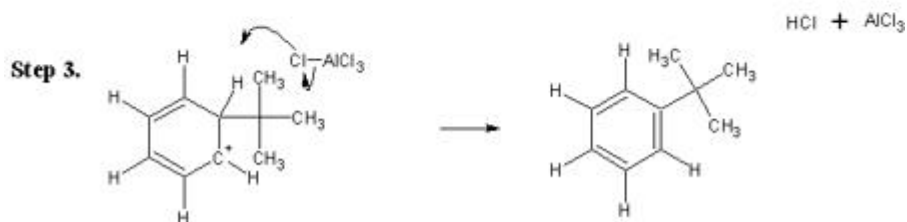
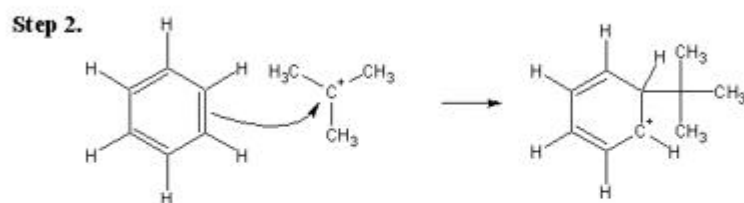
1. Halogen reacts with iron to form Lewis acid-base complex



2. Formation of halogen Lewis acid-base complex is required to make the halogens sufficiently reactive to interact with aromatic system

F. Friedel-Crafts alkylation of benzene: alkyl halides react in the presence of aluminum chloride to alkylate the ring

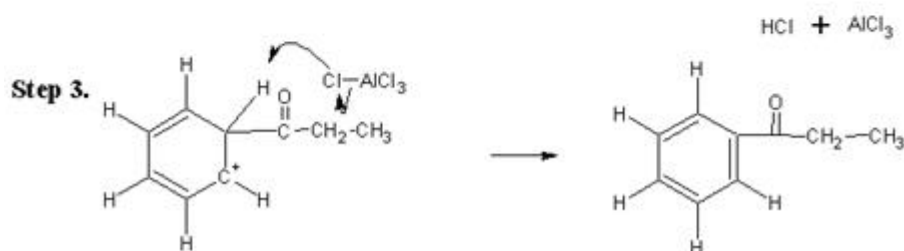
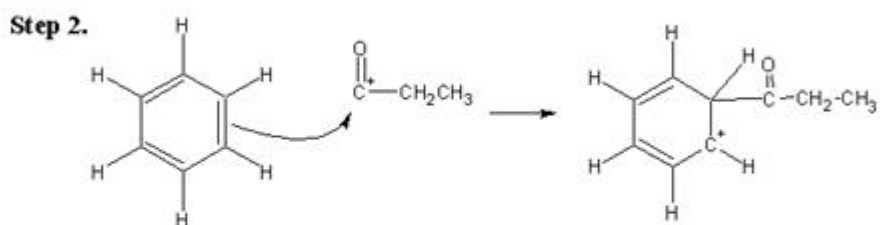
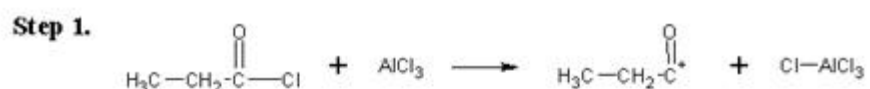
Step 1. reaction of alkyl halides with aluminum chloride to form carbocations or alkyl halide - aluminum chloride acid-base complexes



1. Secondary and tertiary alkyl halides form reactive carbocations
2. Primary and methyl alkyl halides form reactive Lewis acid-base complexes like the halogens (function of carbocation stability?)

3. Rearrangements can occur in alkyl groups
4. Other compounds that form carbocations (e.g., alkenes) can be used in addition to alkyl halides
5. Compounds that do not form carbocations on treatment with aluminum chloride cannot be used (vinylic and aryl halides)
6. Some substituted arenes cannot undergo Friedel-Crafts alkylation (if the substituents are ring-destabilizing)
7. Monoalkylation can be difficult to achieve, since adding an alkyl group to the ring makes it more reactive toward addition of extra alkyl groups

G. Friedel-Crafts acylation of benzene: acyl halides react in the presence of aluminum chloride to alkylate the ring



1. Acyl groups: R-CO-X
 - a. Nomenclature: suffix "oyl" + halogen name
 - b. Propanoyl chloride $\text{CH}_3\text{CH}_2\text{COCl}$
 - c. Readily formed by the reaction of carboxylic acids with thionyl chloride
2. Acyl halides react with aluminum chloride to acyl cations and aluminum chloride-halogen complexes

3. Carboxylic acid anhydrides can also serve as acylating agents in the presence of aluminum chloride
4. Acyl cations do not rearrange (as opposed to alkyl cations)
5. Acyl groups can be reduced to form alkyl groups

H. Synthesis of alkylbenzenes by acylation-reduction

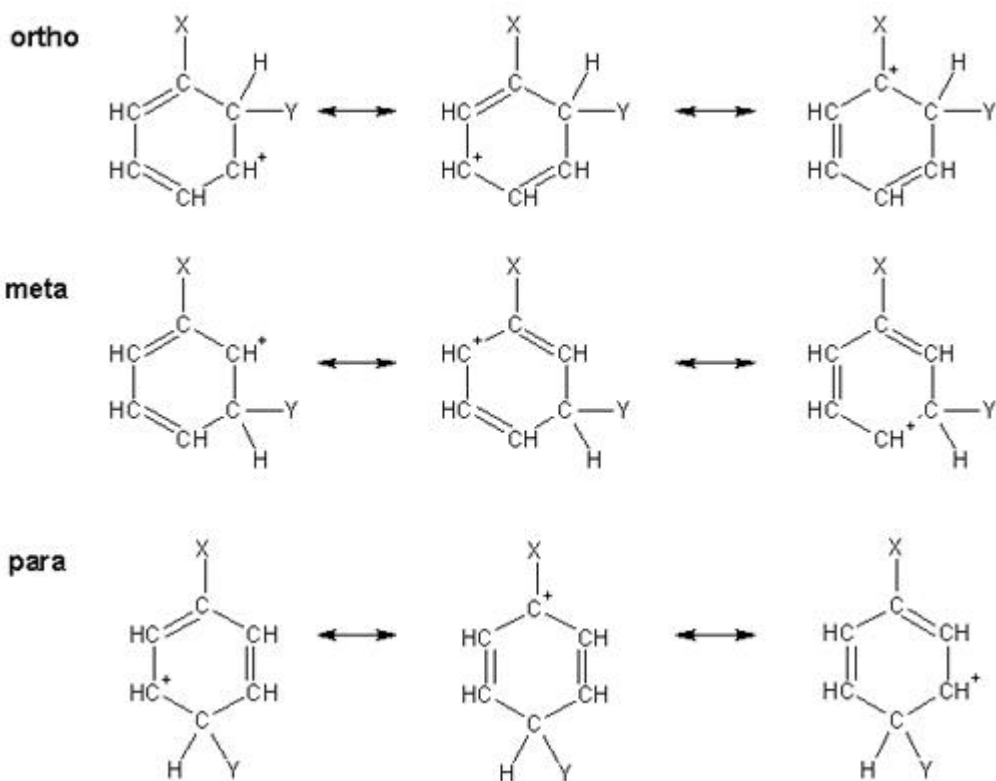
1. Two step reactions, Friedel-Crafts acylation followed by reduction using one of two methods
 - a. Clemmensen reduction: zinc-mercury amalgam in the presence of concentrated HCl
 - b. Wolf-Kishner reduction: heating an aldehyde/ketone in a high-boiling alcohol (e.g. triol) in the presence of hydrazine and sodium or potassium hydroxide converts to the carbonyl group to a methylene group

II. Reactions and mechanisms in substituted benzenes

A. Two questions

1. What is the effect of a substituent on the rate of EAS?
2. What is the effect of a substituent on the regioselectivity of EAS?
 - a. Regioselectivity: reactions that can proceed in more than one direction but in which one direction is preferred

B. Resonance forms and sites of substitution in monosubstituted benzenes



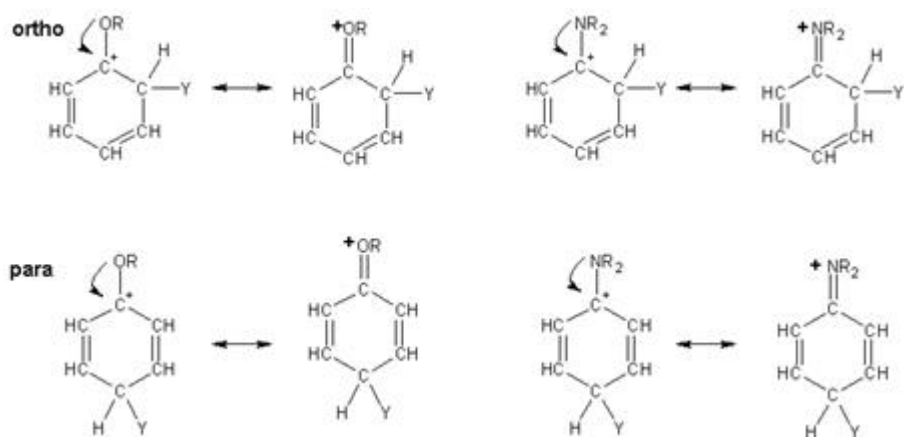
1. The stability of the carbocations will depend on X and its properties

C. The effects of substituents on substitution

1. Note: these effects are a function of the substituent already on the ring and are not affected by the substituent trying to substitute onto the ring
2. Remember that inductive effects can be either positive (electron releasing) or negative (electron withdrawing)
3. All substituents can be divided into two classes, o,p-directors and m-directors

orientation of nitration of C ₆ H ₅ Y (M&B:340)				
Y	ortho	para	ortho + para	meta
-OH	50-55	45-50	100	trace
-NHCOCH ₃	19	79	98	2
-CH ₃	58	38	96	4
-F	12	88	100	trace
-Cl	30	70	100	trace
-Br	37	62	99	1
-I	38	60	98	2
-NO ₂	6.4	0.3	6.7	93.3
-N(CH ₃) ₃ ⁺	0	11	11	89
-CN	-	-	19	81
-COOH	19	1	20	80
-SO ₃ H	21	7	28	72
-CHO	-	-	28	72

4. Ring activating (ring stabilizing) substituents - make the ring more reactive than unsubstituted benzene
- Electron releasing (positive inductive effect) - alkyl groups
 - Relatively low electronegativity difference
 - Nonbonding pairs of electrons on the atom bonded to the ring can be delocalized into stabilization of the carbocation (amines, hydroxyl, acylamino, alkoxy) for ortho and para substitution



- d. These forms are also especially stable because every atom has an octet
 - e. Nonbonding pairs can not be used to stabilize any of the resonance forms of meta-substituted reactions
5. Ring deactivating (ring destabilizing) substituents - make the ring less reactive than unsubstituted benzene
- a. Electron withdrawing (negative inductive effect)
 - b. Relatively high electronegativity difference
 - c. Partial positive charge as a result of a polar bond
 - d. Positive formal charge on central atom of substituent
6. Rules
- a. All activating substituents are o,p-directors
 - b. Strongly deactivating substituents are m-directors
 - c. Halogens are slightly deactivating but are o,p-directors
7. Table of the effects of substituents (Carey: Table 12.2, p. 464)

effect on rate	substituent	effect on orientation
very strongly activating	amino (-NH ₂) alkylamino (-NHR) dialkylamino (-NR ₂) hydroxyl (-OH)	o,p-directing
strongly activating	acylamino (-NHCOR) alkoxy (-OR)	o,p-directing
activating	acyloxy (-OCOR) alkyl (-R) aryl (-Ph) alkenyl (-CH=CR ₂)	o,p-directing
standard of comparison	H	
deactivating	halogen (-X) halomethyl (-CH ₂ X)	o,p-directing
strongly deactivating	formyl (-CHO) acyl (-COR) carboxylic acid (-COOH) ester (-COOR) acyl chloride (-COCl) cyano (-CN) sulfonic acid (-SO ₃ H)	m-directing
very strongly deactivating	trifluoromethyl (-CF ₃) nitro (-NO ₂)	m-directing

8. Explanations

- Ring activating substituents are o,p-directing because they make the ortho and para positions react faster than the meta position (resonance forms with tertiary carbocations and in some cases delocalization of nonbonding electrons)
- Ring deactivating substituents are m-directing because the meta position is less unstable than the ortho and para positions and therefore reacts faster
- Halogens are slightly deactivating substituents because of their electronegativity, but are o,p-directors but of delocalization of their nonbonding electrons results in resonance forms like those of nitrogen and oxygen shown above

- d. "Reactivity is thus controlled by the stronger inductive effect, and orientation is controlled by the resonance effect, which, although weaker, seems to be more selective." (M&B:367)
9. Examples - starting with benzene, assume p-isomer can be separated from an o,p-mixture
- a. p-chloro isopropyl benzene
 - b. p-nitrotoluene
 - c. m-nitrotoluene
 - d. m-bromobenzenesulfonic acid
 - e. 3,5-dinitrobenzoic acid
 - f. 2-nitro-1,4-dichlorobenzene
 - g. 4-nitro-1,2-dibromobenzene

D. Multiple substituent effects

1. The more (most) activating substituent governs regioselectivity
2. Exception: alkyl groups vs. halogens
3. When two positions are comparably activated, substitution usually occurs at the less crowded site (steric effects)

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