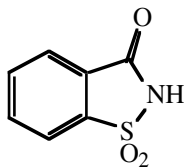


Chapters 17-18. Benzene and Aromaticity.

1. Naming Benzenoid Compounds. "Arenes".
 - a) One small substituent.
 - i) Nitro, bromo, propyl, isopropyl, etc.
 - ii) Trivial names. toluene, phenol, aniline. benzaldehyde, benzoic acid, benzonitrile.
 - b) Large substituents. Phenyl-xxx (Ph). Aryl-xxx (Ar). Benzyl.
 - c) Two substituents. ortho, meta, para.
 - d) Two or more substituents. Numbering.
2. Structure of benzene. Fact: All bonds equivalent.
 - a) Resonance description. Toilet bowl description.
 - b) Molecular orbital description. Six AOs, therefore six MOs.
 - i) butadiene -- acyclic -- 0, 1, 2, 3 nodes. Hexadiene -- acyclic -- 0 to 5 nodes.
 - ii) benzene -- cyclic -- can't have one, three, or five nodes. Two possibilities for two nodes or four nodes, one for none or six. Thus six energy levels, of which two pairs are *degenerate*. Frost mnemonic.
3. Reactivity of benzene. Fact: Not a triene.
 - a) Only substitution, not addition. Hard to hydrogenate. Unusually unreactive.
 - b) Hückel rule: Odd number of pairs of electrons in continuously overlapping cyclic system is unusually stable. Even number of pairs of electrons is unusually unstable.
 - c) Examples of aromatic compounds.
 - i) benzene, pyridine.
 - ii) cyclopentadienyl anion. cycloheptatrienyl cation.
 - iii) *not* cyclopentadiene itself. *not* hexatriene.
 - iv) furan, pyrrole.
 - v) naphthalene, anthracene, C₆₀.
 - d) Examples of anti-aromatic compounds.
 - i) cyclobutadiene. Elongates the bonds. Not isolable.
 - ii) cyclopentadienyl cation.
 - iii) cyclopentadienone.
 - iv) cyclooctatetraene. Folds to avoid overlap.
 - e) Energy of aromaticity.
 - i) Extremely hard to hydrogenate benzene. Doesn't do Diels-Alder reactions. Ca. 30 kcal/mol more stable than expected.
 - ii) cyclopentadiene 20 orders of magnitude more acidic than pentadiene.
 - iii) can buy cycloheptatrienyl cation.
 - iv) some more aromatic than others. Anthracene, furan do Diels-Alder reactions. C₆₀ does addition reactions.

Chapter 14. Chemistry of Arenes. Electrophilic Aromatic Substitution.

- Reactivity of Benzene.
 - Relatively unreactive!!!
 - Substitution of electrophiles, not addition. Typical alkene reactions like hydrogenation, hydroboration, dihydroxylation are difficult or don't go at all.
 - Nucleophile!!!
- Bromination and other halogenation reactions.
 - $C_6H_6 + Br_2 \rightarrow NR$, but $FeBr_3$ promotes reaction, gives C_6H_5Br .
 - Mechanism. Addition of electrophile gives cation. Br^- deprotonates cation to reestablish aromaticity. Doesn't add!
 - Polybromination can occur if xs Br_2 is used.
 - $Cl_2 + FeCl_3$ reacts same way. $I_2 + CuCl_2$ reacts same way.
 - Use: Can convert to Grignards, which can react with all sorts of electrophiles, especially π bond electrophiles.
- Sulfonation.
 - $C_6H_6 + H_2SO_4$ or SO_3 (oil of vitriol) \rightarrow gives $C_6H_5SO_3H$.
 - Mechanism. Nature of S=O bonds.



- Use: Sulfa drugs, Saccharin
- Nitration.
 - $C_6H_6 + HNO_3 \rightarrow$ gives $C_6H_5NO_2$.
 - Mechanism. Active species is NO_2^+ .
 - Not reversible. Second nitration is a lot harder. Why?
 - Use: TNT, to make anilines (will discuss later).
 - Friedel-Crafts alkylation.
 - $C_6H_6 + RX \rightarrow$ gives C_6H_5R . Requires catalytic amount of strong Lewis acid $AlCl_3$ to make reaction go.
 - Mechanism. Active species is R^+ .
 - Limitations.
 - Second alkylation is *easier*. Why? To control, use excess of arene, esp. as solvent. Sterics sometimes prevents second alkylation. (E.g., anisole + *t*-BuCl gives mostly one product.)
 - Works only with $C(sp^3)-X$. Aryl and vinyl halides don't work.
 - Works best with 3° halides, doesn't work well for 1° halides. n -PrCl \rightarrow cumene, n -BuCl \rightarrow s -BuC₆H₅ (65%) + n -BuC₆H₅ (35%), neopentyl chloride \rightarrow 1,1-dimethylpropylbenzene

only.

- d) Useful to make C–C bonds!
6. Friedel-Crafts acylation.
- $C_6H_6 + RCOX \rightarrow$ gives C_6H_5COR . Requires at least two equivalents of strong Lewis acid $AlCl_3$ to make reaction go.
 - Mechanism. Active species is RCO^+ . Stabilized cation.
 - Acylation always *stops* after occurring once.
 - Useful to make C–C bonds!
 - Can be reduced with Zn/H^+ or N_2H_4 , then KOH and Δ to give 1° alkylbenzenes.
7. Regiochemistry and reactivity of electrophilic aromatic substitution.
- o,p*-directing, activating groups: MeO , R_2N , alkyl.
 - m*-directing, deactivating groups: COX , SO_3H , CN , NO_2 , $\overset{+}{N}R_3$.
 - o,p*-directing, deactivating groups: Hal.
 - strongly acidic conditions of F–C reactions turns NH_2 (*o,p*-director) into NH_3^+ (*m*-director); do *p*-substitution by acetylating N first with Ac_2O , remove the Ac group with aq. $NaOH$.
8. Electrophilic aromatic substitution of heteroarenes.
- Pyridine reacts at C(3), “meta” to the N atom.
 - Furan and pyrrole react at C(2), next to the heteroatom.
 - All can be explained by looking at the relative stability of the different carbocationic intermediates and their resonance structures.
9. Further transformations of aromatic substituents.
- Diazonium ions.
 - $C_6H_5NO_2 + H_2, Pd/C \rightarrow C_6H_5NH_2 + NaNO_2, HCl \rightarrow C_6H_5N_2^+$
 - $C_6H_5N_2^+ + CuCl \rightarrow C_6H_5Cl$
 - $C_6H_5N_2^+ + CuBr \rightarrow C_6H_5Br$
 - $C_6H_5N_2^+ + KI \rightarrow C_6H_5I$
 - $C_6H_5N_2^+ + H_3PO_2 \rightarrow C_6H_6$
 - $C_6H_5N_2^+ + CuCN \rightarrow C_6H_5CN$ (Useful to make C–C bonds!)
 - CN can be converted to CO_2H with aq. $NaOH$
 - $C_6H_5N_2^+ + H_2O, CuO \rightarrow C_6H_5OH$
 - $C_6H_5N_2^+ + HBF_4 \rightarrow C_6H_5F$
 - Metal-catalyzed couplings.
 - C–C bond-forming reactions
 - $ArCl + RMgCl + \text{cat. } (Ph_3P)_2NiCl_2 \rightarrow ArR$ (Kumada coupling)
 - $ArX + RM + \text{cat. } Pd(0) + \text{phosphine ligand} \rightarrow ArR$ ($M = SnBu_3$ or $SnMe_3, B(OH)_2, ZnCl$) (Stille, Suzuki, Negishi couplings)
 - $ArX + CO + MeOH + \text{base} + \text{cat. } Pd(0) + \text{phosphine ligand} \rightarrow ArCO_2Me$

- d) $\text{ArX} + \text{RC}\equiv\text{CH} + \text{base} + \text{cat. CuI} + \text{cat. Pd(0)} + \text{phosphine ligand} \rightarrow \text{ArC}\equiv\text{CR}$
(Sonogashira coupling)
- e) use $\text{C}(\text{sp}^2)$ with $\text{B}(\text{OH})_2$, $\text{C}(\text{sp}^2)$ or $\text{C}(\text{sp}^3)$ with Sn or Zn. $\text{C}(\text{sp}^3)$ can be primary, secondary, or tertiary — no rearrangements, unlike F–C chemistry!
- f) most widely used methods these days for attaching $\text{C}(\text{sp}^3)$ and $\text{C}(\text{sp}^2)$ to aromatic rings
- g) Disconnection: $\text{Ar-R} \Rightarrow \text{Ar-Br} + \text{R-M}$.
- (1) If R is $\text{C}\equiv\text{C}$, M = H is best.
 - (2) If R is $\text{C}=\text{C}$, M = $\text{B}(\text{OH})_2$ is best.
 - (3) If R is C-C , M = ZnCl or SnMe_3 is best. F–C alkylation is also an option (watch for rearrangements when working forward!).
 - (4) If in doubt, M = SnMe_3 , which works with all kinds of C.
 - (5) If R is C=O , use F–C acylation!

ii) C–N and C–O bond-forming reactions (Buchwald–Hartwig couplings)

- a) $\text{ArX} + \text{ROH} + \text{base} + \text{cat. Pd(0)} + \text{phosphine ligand} \rightarrow \text{ArOR}$
- b) $\text{ArX} + \text{R}_2\text{NH} + \text{base} + \text{cat. Pd(0)} + \text{phosphine ligand} \rightarrow \text{ArNR}_2$
- c) *Cannot* do these reactions by $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$!

c) Comparison of diazonium ions vs, cross-couplings.

- i) Diazonium ion chemistry starts with $\text{H} \rightarrow \text{NO}_2 \rightarrow \text{NH}_2 \rightarrow \text{N}_2^+$, whereas metal-catalyzed reactions start with $\text{H} \rightarrow \text{halogen}$. Diazonium chemistry has a meta director intervene before ortho–para director: can be useful for synthesis. (E.g., *m*-bromotoluene.)
- ii) Metal-catalyzed route is much shorter; can often buy aryl halides.
- iii) Metal-catalyzed reaction is much more versatile for making C–C bonds. Very mild conditions. Nonaqueous, so more compatible with organic reagents.
- iv) Diazonium chemistry can replace NO_2 with F or OH; neither easy to do with metal-catalyzed couplings.
- v) Two methods can complement one another: e.g., 1,3,5-tributylbenzene.

10. Nucleophilic aromatic substitution. Trinitrochlorobenzene + $\text{HO}^- \rightarrow$ picric acid.

- a) Can't be $\text{S}_{\text{N}}2$ because backside attack can't occur. Can't be $\text{S}_{\text{N}}1$ because aryl cations are way unstable. Can't be electrophilic substitution because HO^- is a nucleophile.
- b) The nitro groups make benzene π bonds *electrophilic*. Negative charge upon attack of HO^- is stabilized by NO_2 groups. What other electrophilic π bonds do we know about?
- c) For aromatic ring to be electrophilic enough to react at room temperature, need at least one, preferably two NO_2 groups or other strong electron-withdrawing groups.

11. Aromatic side chain oxidation.

- a) KMnO_4 converts alkyl chains attached to benzene rings into CO_2H groups.
- b) All alkyl side chains that contain benzylic H atoms are oxidized.

12. Birch reduction.

- a) Li, liquid NH_3 converts benzene into 1,4-cyclohexadiene.
- b) Alkyl and alkoxy groups prefer to end up on the $\text{C}(\text{sp}^2)$ of the cyclohexadiene product.
- c) CO_2H group prefers to end up on the $\text{C}(\text{sp}^3)$ of the cyclohexadiene product.

13. Note: Many ways to make ArCO_2H .

- a) $\text{ArH} + \text{X}_2 + \text{Lewis acid} \rightarrow \text{ArX} + \text{Mg} \rightarrow \text{ArMgX} + \text{CO}_2 \rightarrow \text{ArCO}_2\text{H}$.
- b) $\text{ArH} + \text{X}_2 + \text{Lewis acid} \rightarrow \text{ArX} + \text{CuCN} \rightarrow \text{ArCN} + \text{aq. NaOH} \rightarrow \text{ArCO}_2\text{H}$.
- c) $\text{ArH} + \text{X}_2 + \text{Lewis acid} \rightarrow \text{ArX} + \text{CO} + \text{MeOH} + \text{cat. Pd(0)} + \text{phosphine ligand} \rightarrow \text{ArCO}_2\text{Me}$.
- d) $\text{ArH} + \text{CH}_3\text{Cl} + \text{AlCl}_3 \rightarrow \text{ArCH}_3 + \text{KMnO}_4 \rightarrow \text{ArCO}_2\text{H}$.

14. Note: ACE does not ask "design a synthesis" questions. Do the book homework.