

October CUME

Organic Chemistry

Department of Chemistry, University of Missouri—Columbia

Saturday, October 10, 1998, @Nine O'Clock, 1251 Chemistry

Dr. Rainer Glaser

Announced Reading: “Aromatic Substitution”

Question 1. Aromatic Electrophilic Substitution Chemistry. (30 points)

R Franklin P. DeHaan et al. (some 13 co-authors), *Electrophilic Aromatic Substitution. 13. Kinetics and Spectroscopy of the Chloromethylation of Benzene and Toluene with Methoxyacetyl Chloride or Chloromethyl Methyl Ether and Aluminum Chloride in Nitromethane or Tin Tetrachloride in Dichloromethane. The Journal of Organic Chemistry* **1997**, 62, 2694-2703.

(a) Chloromethylation means that the substituent $-\text{CH}_2\text{-Cl}$ is introduced to the aromatic ring. One reagent that is employed for this purpose is chloromethyl methyl ether (CMME), $\text{H}_3\text{C-O-CH}_2\text{-Cl}$. The reaction is carried out in the presence of the Lewis acid AlCl_3 . In the chloromethylation of benzene, two different electrophiles have been discussed; some consider the electrophile to be the chloromethyl cation while others have argued for the methoxymethyl cation as the reactive electrophile. For both of these options, explain the formation of $\text{Ph-CH}_2\text{-Cl}$. Which one of the two possible electrophiles do you consider more "stable", that is having the lower hydride affinity, and why? (15 points)

Chloromethyl Cation Mechanism:

Methoxy Methyl Cation Mechanism:

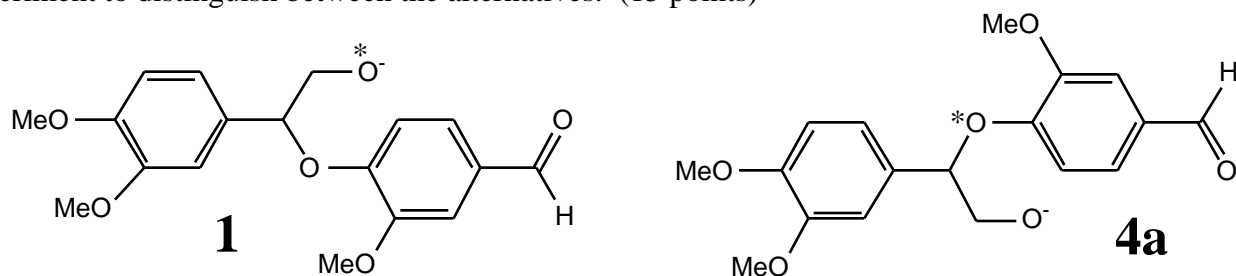
Stabilities of Chloromethyl Cation vs. Methoxy Methyl Cation?

(b) Chloromethylation also can be carried out with methoxyacetyl chloride (MAC) and AlCl_3 . Using structural formulas, show how the reactive electrophile is being generated from MAC. (5 points)

(c) Chloromethylation follows a third-order rate law of the form $\text{rate} = \{k_3[\text{AlCl}_3]^2[\text{MAC}]\}/[\text{AlCl}_3]_0$. Note that the rate is second-order in AlCl_3 . The term $[\text{AlCl}_3]_0$ is the initial concentration of AlCl_3 and for present purposes just a constant. Now, provide a mechanism for the electrophile generation that accounts for this second-order dependence on AlCl_3 . [Hint: Prof. Osamura discussed a related issue in his lecture in last week's colloquium.] (10 points)

Question 2. Aromatic Nucleophilic Substitution Chemistry. (30 points)

(a) Dexter L. Criss, Leonard L. Ingram, Jr., Tor P. Schultz, Thomas H. Fisher, and Debbie B. Saebo, *A Low-Temperature Internal Nucleophilic Aromatic Substitution Reaction on a -O-4 Lignin Model Dimer*, *Journal of Organic Chemistry* **1997**, 62, 7885-7887. The compound **1** was found to rearrange to compound **4a** (note that **1** and **4a** are in fact identical so long as the O-atoms are not labeled) and this rearrangement could in principle be accomplished (1) by an internal nucleophilic substitution or (2) by formation of a pair between a phenolate and an epoxide. Draw the pertinent intermediate for each of these pathways. Explain (in words, no structures needed) how one can employ a $^{17}/^{18}\text{O}$ label experiment to distinguish between the alternatives. (15 points)



Internal Arom. Nucl. Subst. Intermediate:

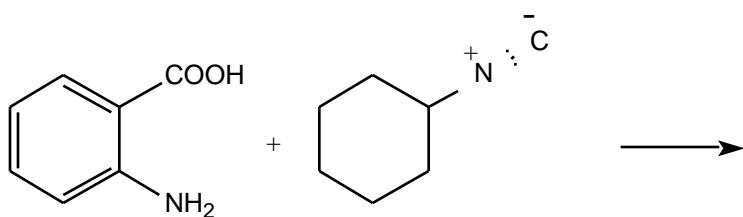
Epoxide Intermediate:

Describe a labeling experiment to distinguish between the alternative:

(b) J. Jens Wolff, Andreas Zietsch, Thomas Oeser, and Ion Bolocan, *Rate Increase in Consecutive Nucleophilic Aromatic Substitution Reactions of Trichlorotrinitrobenzene: The Synthesis of 1-(Alkylamino)-3,5-dichloro-2,4,6-trinitrobenzenes*, *Journal of Organic Chemistry* **1998**, 63, 5164-5168. The authors have studied the aromatic nucleophilic substitution reactions of trichlorotrinitrobenzene by ammonia and various primary and secondary amines. If multiple nucleophilic aromatic substitution via Meisenheimer complexes are possible with an electron-deficient arene, the rate of reaction is expected to decrease with the introduction of each donor substituent. For example, reaction of ammonia with 1,3-dinitro-2,4,6-trifluorobenzene or tetrafluoro-1,3-dinitrobenzene gives monosubstitution product in high yields. In contrast, however, trinitrotrichlorobenzene is found to react with ammonia all the way to the triaminotrinitrobenzene. No monoamino or diamino products were found. Explain this result in detail and using carefully drawn structures that reflect proper conformations. [Hint: The X-ray structure of trinitrotrichlorobenzene is known and it shows the nitro groups to be nearly perpendicular to the benzene ring.] (15 points)

Question 3. Benzyne Chemistry. (40 points)

(a) James H. Rigby* and Stéphane Laurent, *Addition of Alkyl and Aryl Isocyanides to Benzyne*, *Journal of Organic Chemistry* **1998**, *63*, 6742-6744: The authors have recently shown that isocyanides can behave as charge-reversed equivalents to isocyanates in reactions with benzyne electrophiles. For example, treatment of anthranilic acid with excess cyclohexylisocyanide in the presence of *tert*-butyl nitrite and water in refluxing 1,2-dichloroethane/dioxane afforded a benzamide in ca. 60% yield. Provide a mechanism for this reaction using Lewis structural formula for all starting materials, intermediates, and products. (10 points)



(b) William F. Bailey* and Sarah C. Longstaff, *Generation and Cyclization of a Benzyne-Tethered Alkylolithium: Preparation of 4-Substituted Indans*, *Journal of Organic Chemistry* **1998**; 63, 432-433. The authors describe a synthesis of indans by way of benzyne. 2-fluoro-1-(3-iodopropyl)benzene [yes, -F and -CH₂-CH₂-CH₂-I in *ortho* positions] is reacted with (more than 2 equivalents of) *t*-BuLi in pentane/THF at -78 degree Celsius. The mixture is allowed to warm up and an electrophilic reagent "E⁺" is then added to form the "4-substituted indane". For example, if E⁺ = H⁺ (e.g. addition of water), then the parent indane is formed. (i) Provide a mechanism for this reaction for the case E⁺ = H⁺ using Lewis structural formula for all starting materials, intermediates, and products. (ii) Suggest an electrophilic reagent that would result in the introduction of -Br in the 4-position. (iii) Suggest an electrophilic reagent that would result in the introduction of -CHPh(OH) in the 4-position. (16 points)

-Br in 4-position:	-CHPh(OH) in 4-position:

(c) A. Cobas, E. Guitian, and L. Castedo, *An Interesting Benzyne-Mediated Annulation Leading to Benzo[a]pyrene*, *Journal of Organic Chemistry* **1997**, 62, 4896-4897. The "dehydro Diels-Alder Reaction", or DDAR for short, involves the reaction of a conjugated enyne with a dienophile and leads through an allene intermediate to the formation of a cyclohexadiene system. Task 1: Show the mechanism of this reaction between $\text{H}_2\text{C}=\text{CH}-\text{C}\equiv\text{CH}$ and the parent benzyne (as the dienophile) assuming a concerted mechanism. It turns out that the $\text{H}_2\text{C}=\text{CH}-\text{C}\equiv\text{CH}$ moiety can be part of an aromatic system; e.g. Ph-C $\equiv\text{CH}$ is a suitable "enyne". The reaction of a naphthalene that carries -C $\equiv\text{CH}$ groups in the positions 1 and 8 with benzyne undergoes a DDAR and the ultimate product is a pyrene derivative. Task 2: Show all intermediate of this reaction again assuming a concerted DDAR. (14 pts)

Generic Mechanism:

Pyrene Formation Mechanism:

