24. Electrophilic Aromatic Substitution

A. Introduction

Aromatic compounds are especially stable and despite having π-bonds do not react like typical alkenes. For example, the π-bond in 1-hexene is brominated to give 1,2-dibromohexane, while benzene does not react under similar conditions (figure 1).

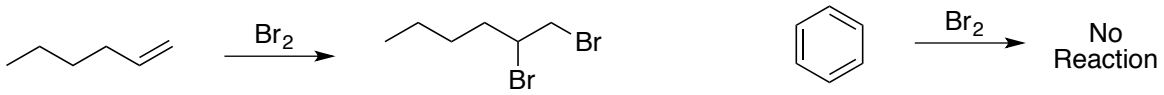
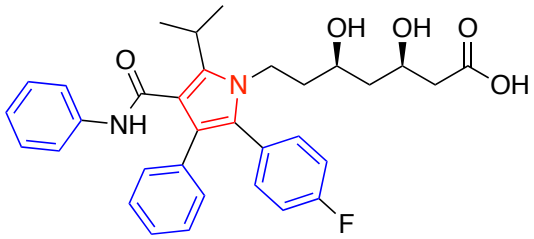
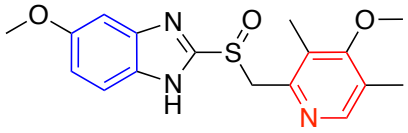


Figure 1. Bromination of Alkenes

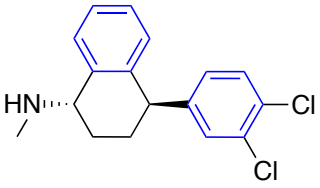
Aromatic compounds are extremely important for their industrial and pharmaceutical use. A few prescription drugs containing one or more aromatic rings are shown in figure 2. With their immense value as synthetic targets, it is necessary to have a way to tap into the chemistry of aromatic compounds allowing for their functionalization to form complex organic molecules. The focus of this experiment is on aromatic benzene rings (shown in blue in figure 2), however, a variety of other aromatic type rings do exist (this are shown in red in figure 2).



Lipitor
used for treating high cholesterol



Nexium
a proton pump inhibitor used to treat acid reflux



Zoloft
used for treating depression

Figure 2. Pharmaceutical Compounds Containing Benzene (blue) and Other Aromatic Functionality (red)

It was realized that by adding a Lewis acid ($FeBr_3$) to the reaction mixture, benzene could be mono-brominated in relatively high yield. The addition of the Lewis acid enhances the electrophilicity of the bromine to such a degree that one can overcome the low reactivity of benzene. The reaction mechanism first involves generation of the active electrophile by coordination of bromine with iron tribromide. This Lewis acid-base adduct provides an electrophilic source of the bromonium ion ($Br^{\oplus}$). The second part of the mechanism involves the reaction of the benzene π-bond with either the Lewis acid-base adduct (shown) or simply with

Br⊕ to provide a carbocation intermediate. Bromide (Br⊖), from $FeBr_4^-$ acts as a base to remove a proton from the ring, reestablishing aromaticity in the benzene ring. This overall process is referred to as an electrophilic aromatic substitution (EAS) because the hydrogen on an aromatic ring is substituted with an electrophile. (Figure 3)

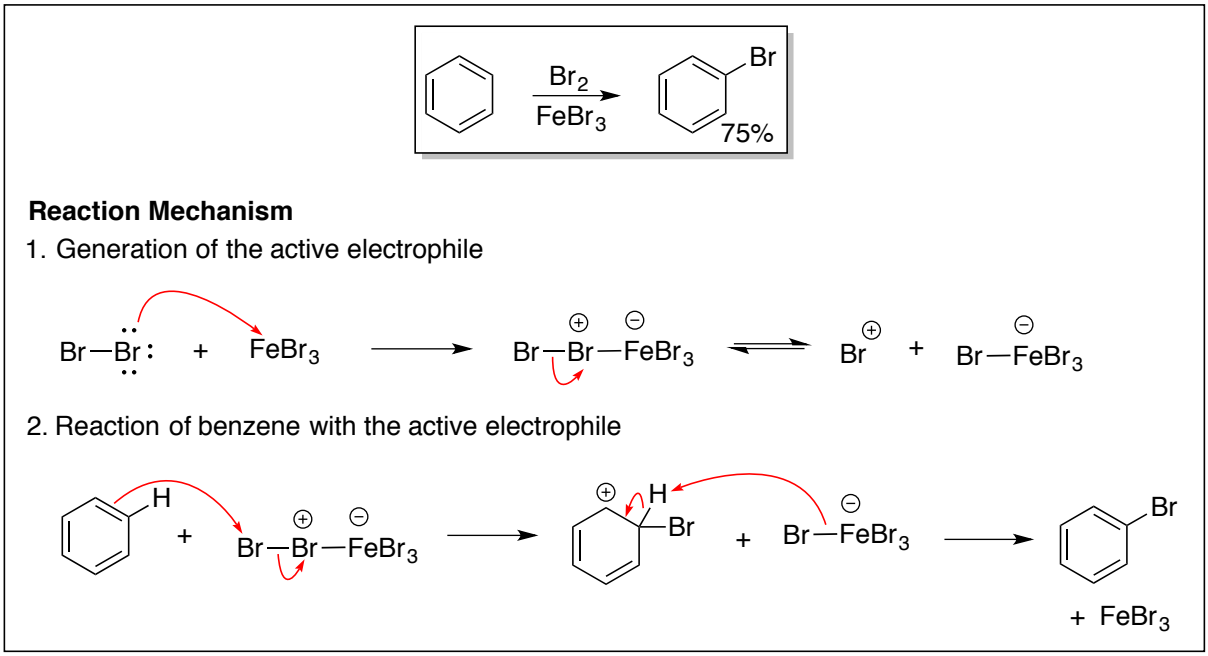


Figure 3. Electrophilic Bromination of Benzene

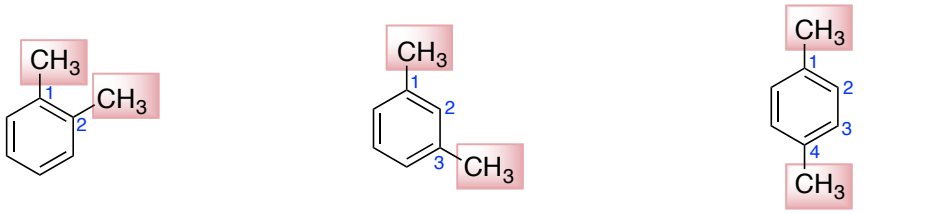
A variety of different conditions can be employed to obtain severed different mono-substituted aromatic rings. Table 1 lists the five most common electrophilic aromatic substitution reactions.

	Conditions	Product	Active Electrophile
Ph—H	$\xrightarrow[FeBr_3]{Br_2}$	Ph—Br	$Br^{\oplus}$
Ph—H	$\xrightarrow[FeCl_3]{Cl_2}$	Ph—Cl	$Cl^{\oplus}$
Ph—H	$\xrightarrow[H_2SO_4]{HNO_3}$	$Ph—NO_2$	$NO_2^{\oplus}$
Ph—H	$\xrightarrow[H_2SO_4]{SO_3}$	$Ph—SO_3H$	$SO_3H^{\oplus}$
Ph—H	$\xrightarrow[AlCl_3]{R\text{-}Cl}$	Ph—R	$R^{\oplus}$

Table 1. Typical Conditions for Electrophilic Aromatic Substitution

Disubstituted Benzene Terminology

The terms *ortho*, *meta*, and *para* are frequently used to describe the locational relationship between two substituents on an aromatic ring. When two substituents are in a 1,2 relationship, they are said to be *ortho*. When two substituents are in a 1,3 relationship, they are said to be *meta*. When two substituents are in a 1,4 relationship, they are said to be *para*. (Figure 4)



1,2-dimethylbenzene
ortho-diemthylbenzene

1,3-dimethylbenzene
meta-diemthylbenzene

1,4-dimethylbenzene
para-diemthylbenzene

Figure 4. Ortho, Meta, and Para Terminology

Directing Group Effects

When an aromatic ring is substituted with a substituent, that substituent affects the nucleophilicity and therefore reactivity of the aromatic ring. Some substituents activate the ring, making it more reactive than benzene alone. Other substituents deactivate the ring, making it less reactive than benzene. Figure 5 lists some common activating and deactivating groups. These groups can be generalized as follows. Activating groups typically contain a lone pair on the atom that is directly attached to the aromatic ring. Alkyl groups are one exception, however, alkyls are only weakly activating. Deactivating groups on the other hand have a halogen or electron withdrawing group, such as C=O, directly attached to the aromatic ring.

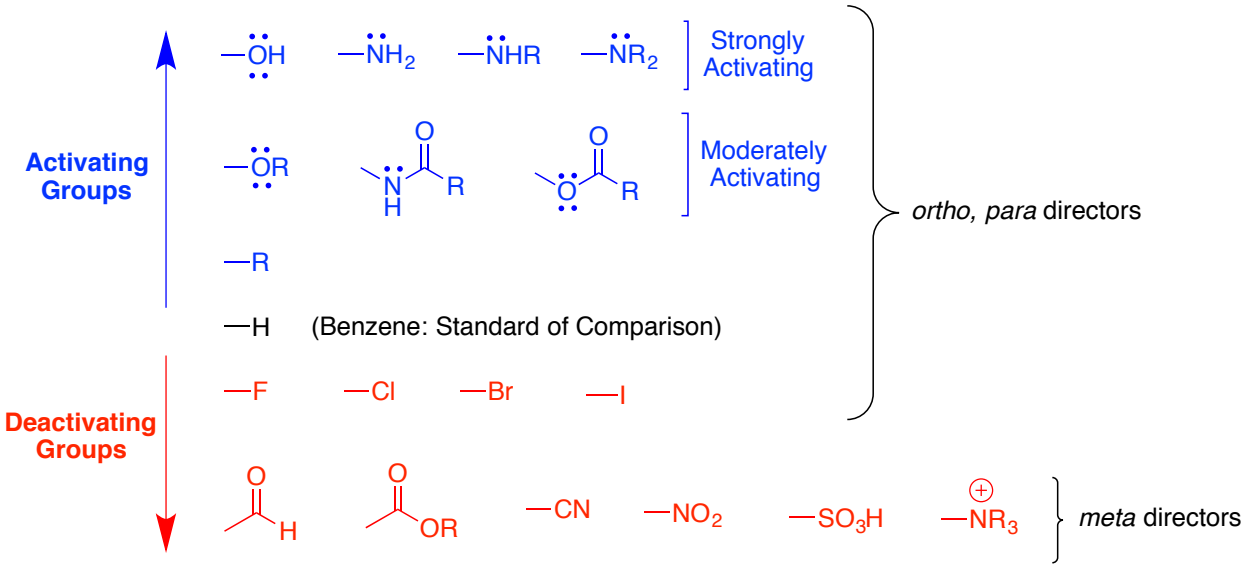
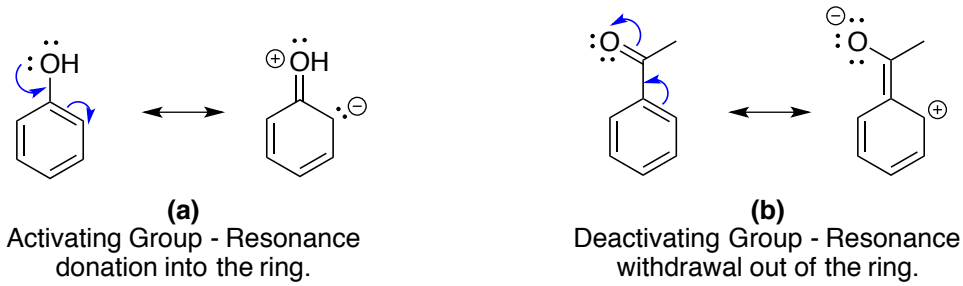


Figure 5. Common Activating and Deactivating Groups

Activating groups enhance the nucleophilicity and reactivity of the ring by resonance donation as shown in figure 6a. Deactivating groups on the other hand, decrease the nucleophilicity and reactivity of the ring by resonance and/or inductive withdraw of electron density from the aromatic ring as shown in figure 6b.

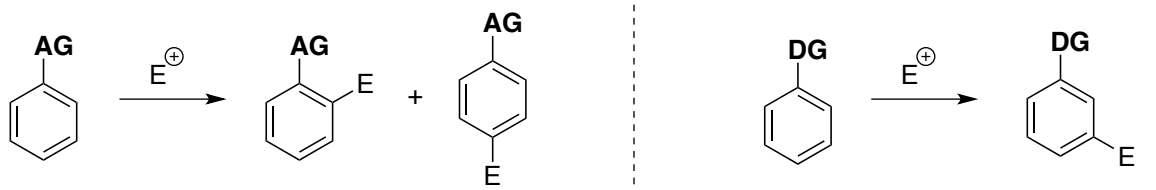


(a)
Activating Group - Resonance donation into the ring.

(b)
Deactivating Group - Resonance withdrawal out of the ring.

Figure 6. Resonance Effect of Activating and Deactivating Groups

It is also important to note that when an electrophilic aromatic substitution reaction is performed on a mono-substituted benzene ring containing an activating group, the new electrophile will add to the *ortho* and the *para* positions of the ring (figure 7a). In the case of most deactivating groups on the ring, the electrophile will add to the *meta* position (figure 7b). The origin of this selectivity will be discussed in the next section.



AG = Activating Group

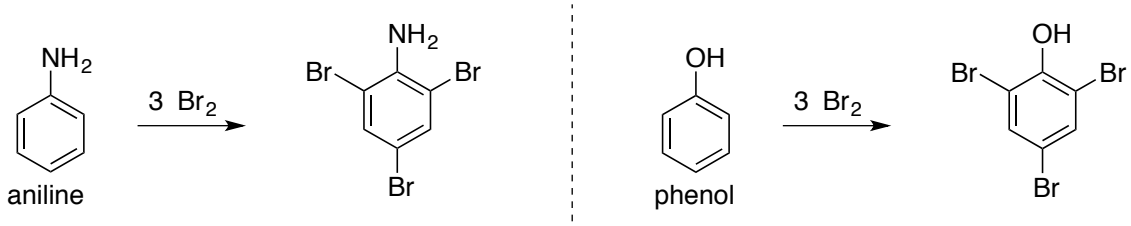
(a)
Electrophilic Aromatic Substitution with an Activating Group on the Ring

DG = Deactivating Group

(b)
Electrophilic Aromatic Substitution with a Deactivating Group on the Ring

Figure 7. Directing Group Effects in Electrophilic Aromatic Substitution

Aromatic rings containing very strongly activating groups such as –OH (phenol) and $–NH_2$ (aniline) can actually be halogenated in the absence of a Lewis acid catalyst. In fact, these strongly activated aromatic rings are so highly activated that it is difficult to stop at mono-halogenation. When three equivalents of bromine are used, the compound is tri-halogenated at both *ortho* positions and the *para* position as shown in figure 8. In the first part of the laboratory experiment, you will perform a bromination of phenol to produce tribromophenol.



aniline

phenol

Figure 8. Halogenation of a Strongly Activated Aromatic Ring

In the second part of the laboratory experiment you will perform an electrophilic nitration on two substituted benzene derivatives. Like bromination, the first step of nitration involves generation of the active electrophile, which is a nitronium ion ($NO_2^{\oplus}$). The aromatic compound then reacts with this electrophile. You will investigate the relative reactivities of methyl benzoate and

acetanilide under electrophilic nitration conditions to determine experimentally which substrate is more reactive. (Figure 9)

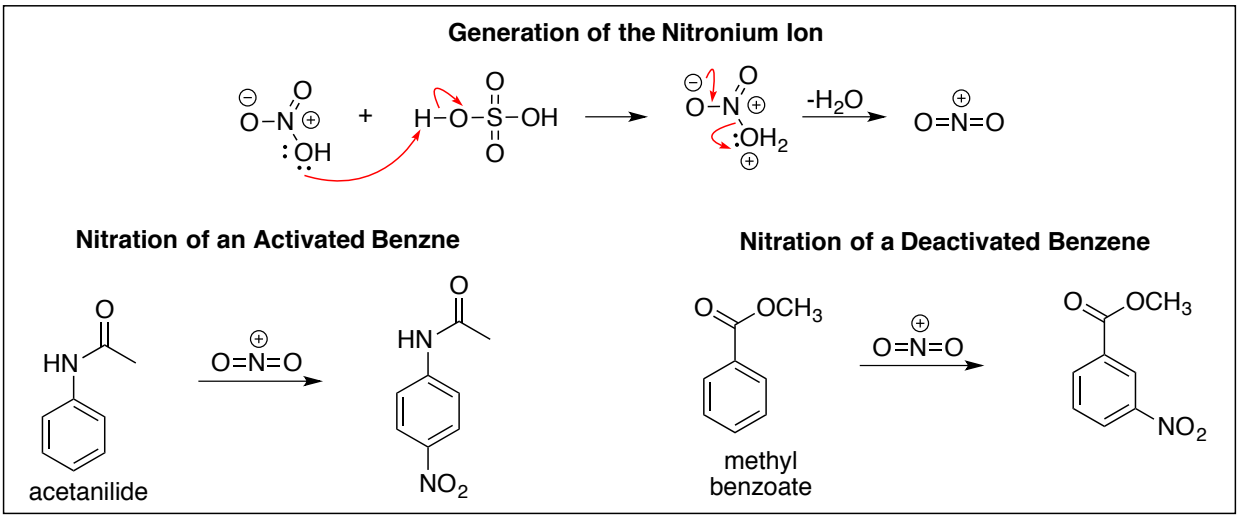


Figure 9. Nitration of an Aromatic Ring

***Ortho/Para* Selectivity with an Activating Group**

When an activating group is present on the benzene ring, electrophilic aromatic substitution occurs such that the new group adds *ortho* and/or *para* to the activating group. This selectivity can be rationalized by investigating the reaction mechanism. In both *ortho* and *para* additions of the electrophile, aromaticity is temporarily broken and a carbocation resides on the ring. This carbocation can be delocalized over the ring's π-system (blue arrows, figure 10). Additionally, the lone pair on the activating group can delocalize (green arrows, figure 10) giving a fourth resonance structure which is a major contributor to the resonance hybrid due to all atoms in this resonance structure having an octet of electrons. *Para* addition is analogous, giving four similar resonance structures. You will explore the mechanism for para addition in pre-lab question 3.

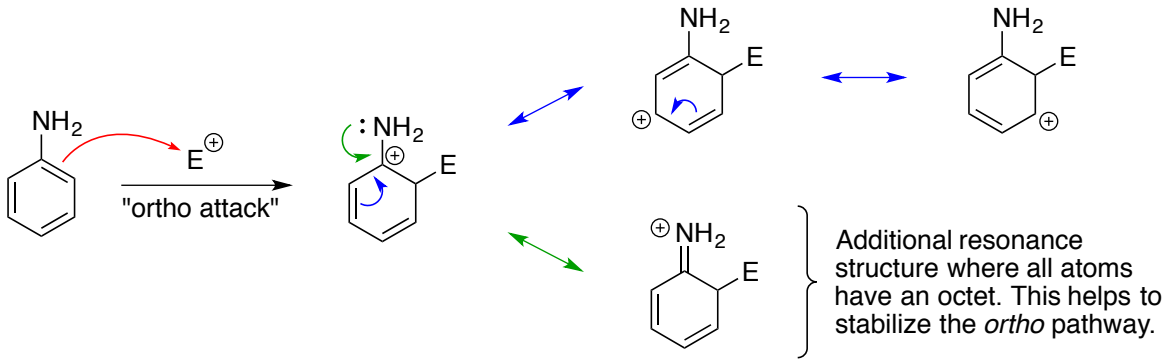


Figure 10. Ortho Addition of an Electrophile to an Activated Aromatic Ring

While there is nothing especially bad about *meta* addition to an activated aromatic ring, it is simply a much slower process due to the mechanistic pathway being higher in energy than *ortho/para* addition pathway. The *meta* addition pathway (figure 11), has only three resonance structures stabilizing the intermediate carbocation. In comparison, the *ortho/para* pathway has four resonance structures.

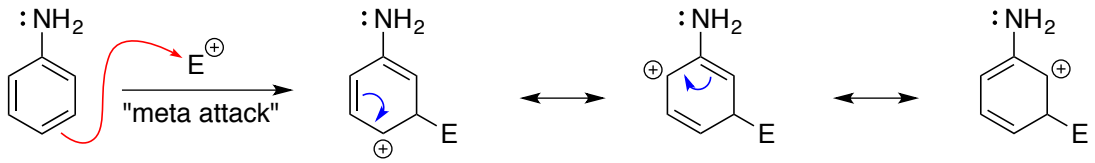


Figure 11. Meta Addition of an Electrophile to an Activated Aromatic Ring

Mechanistically, the pathways for both *ortho* and *para* nitration of acetanilide are essentially equivalent, yet when the reaction is performed, the *para* product is obtained selectively. This selectivity is du to the substrate having a large and bulky activating group which sterically hinders (blocks) the *ortho* sites, making *para* addition preferred. (Figure 12)

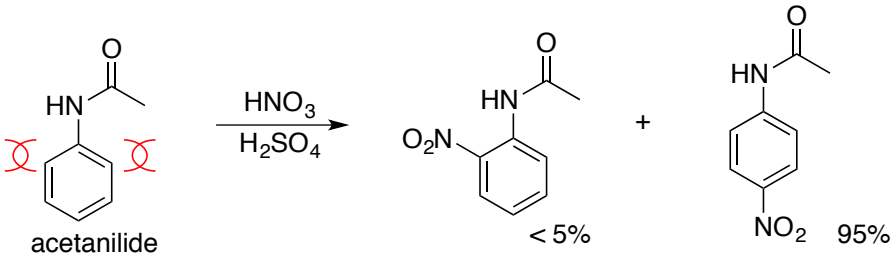


Figure 12. Electrophilic Nitration of Acetanilide

***Meta* Selectivity with a Deactivating Group**

When a deactivating group is present on the aromatic ring, the electrophilic aromatic substitution takes place at a much slower rate than with an activating group. Additionally, most deactivating groups direct the incoming electrophile to the *meta* position. While there is nothing especially good about the *meta* pathway, it is relatively lower in energy than the *ortho/para* pathways. As shown in figure 13, the *ortho/para* addition will give a resonance structure that puts the carbocation adjacent to a partially positive charged atom. This is a high energy structure that is not favored. *Meta* addition does not give this high-energy resonance structure, resulting in this being the preferred pathway when a deactivating group is on the ring.

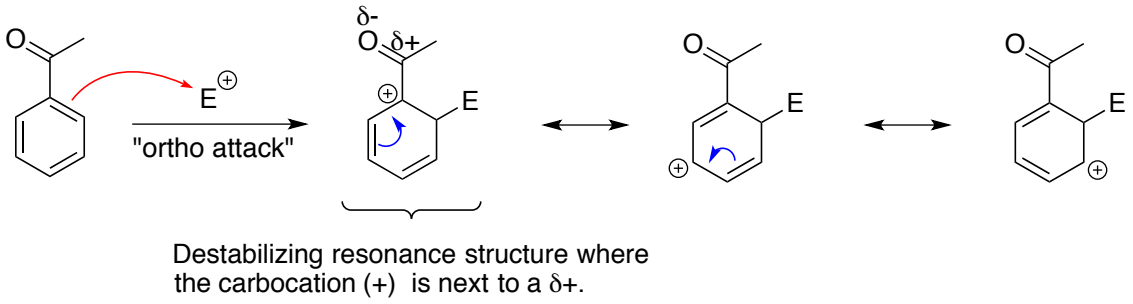


Figure 13. Ortho Addition of an Electrophile to a Deactivated Aromatic Ring

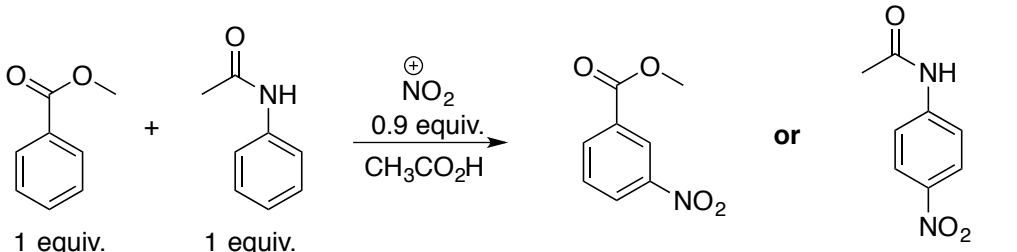
B. Experimental Procedure

1. Tribromination of Phenol

Measure 50. mg of phenol into a a small test tube supported in a 100 mL beaker. Add 5 mL of water to dissolve the phenol. Next add 20% Br_2 in AcOH dropwise mixing thoroughly throughout the addition. Bromine addition should be ceased once a permanent red/brown color persists. At this point, bromination is complete. Add 5-10 drops of aqueous $NaHSO_3$ with thorough mixing to destroy the excess bromine. Collect the solid product via Hirsch filtration, washing the solid with 2-3 mL of cold water. After briefly air drying the solid, transfer it to a Craig tube and dissolve it in a minimum amount of hot ethanol. Allow the solution to cool slowly to room temperature at which time crystals should begin to form. Place the mixture in an ice bath to complete crystallization. Collect the solid product by centrifugation. Record the yield, melting point, and an IR spectrum of the dry product. *While waiting on the crystallization, you should begin experiment 2.*

2. Competitive Nitration

In this experiment you will investigate the relative reactivities of acetanilide and methyl benzoate toward electrophilic nitration. Based on the results of the experiment, you will be able to provide experimental evidence to support your theoretical hypothesis as to which one of the two aromatic compounds is more reactive in electrophilic aromatic substitution.



The resulting product will come from the more reactive aromatic starting material (methyl benzoate or acetanilide)

When performing this experiment, it is imperative that a deficiency of nitric acid is used. Otherwise, once the more reactive aromatic compound has reacted away, the less reactive one will begin to react, skewing your results. The reagent table below is based on 50. mg of nitric acid, however, once you weigh out the nitric acid for the experiment, you will need to adjust the requires masses of acetanilide and methyl benzoate to use based on that amount of nitric acid.

				Sample Data		Actual Data	
Reagent	**Mol. Wt.**	**Equiv.**	**Density**	**Mass**	**Mmol**	**Mass**	**Mmol**
Methyl Benzoate	136 g/mol	1	--	68.0 mg	0.500		
Acetanilide	135 g/mol	1	--	67.5 mg	0.500		
HNO_3 (70%)	190 g/mol	0.9	1.5 g/mL	50.0 mg	0.555		

Measure approximately 50 mg of concentrated HNO_3 (70% aqueous solution) into a pre-weighed 3 mL conical reaction vial. Weigh the vial containing the acid to get an exact mass of HNO_3 used. *Note: Two drops of HNO_3 is approximately 50 mg*. Next add 10 drops of glacial acetic acid and 20 drops of concentrated H_2SO_4. Mix the solution thoroughly to generate the active electrophile *in situ*.

To a 5 mL conical reaction vial, add methyl benzoate and acetanilide (masses to use should be calculated above). Add 10 drops of glacial acetic acid and 20 drops of sulfuric acid. Insert a spin vane into the vial and mix until a clear solution is obtained. Place this vial into a cold water bath (~10 °C) prepared from ice and water in a small beaker. With rapid stirring, add the nitration solution dropwise via pipet over 5 min. Once addition is complete, remove the water bath and allow the mixture to stir at room temperature for 5 min. To the resulting solution, slowly add water with mixing to bring the total volume to 4 mL. Collect the solid precipitate via Hirsch filtration and wash the solid well with small volumes of cold water. Transfer the solid to the Craig tube and recrystallize from hot ethanol. Once the crystals have dried, record the yield, melting point, IR spectrum, and NMR spectrum. You will be able to identify the nitration product based on this data.

C. Pre-Lab Questions

1. Compare the reactivity of $PhNH_3^{\oplus}$ and $PhNH_2$ under bromination conditions. Classify each as an activating or deactivating group and explain your reasoning. *Hint: draw out the complete structure of each showing all lone pairs.*

2. Show all aniline resonance structures involving donation of the $-NH_2$ lone pair into the aromatic ring. Using these resonance structures, explain why $-NH_2$ is an *ortho, para* directing group.

3. The mechanism for the *ortho* substitution of aniline is shown in figure 10. Using acetanilide, which is an activating group like aniline, show the mechanism for *para* addition. Include all resonance structures. Explain why *para* addition, like *ortho* addition, is favored when an activating group is on the ring.

4. Based on the discussion of reactivity in the introduction, what do you hypothesize will be the major product of the competitive nitration reaction?

D. Post-Lab Questions

1. Had you performed the bromination of phenol with only one equivalent of Br_2, which product (*ortho* or *para*) do you think would predominate? *Hint: think about probability and statistics.*

2. What product did you obtain from the competitive nitration?
    a. Which particular IR absorptions led you to this conclusion?
    b. How can the NMR signals in the aromatic region be used to confirm the identity of your product?
    c. Look up the literature melting points for 4-nitroacetanilide and methyl 3-nitrobenzoate at www.sigmaaldrich.com. How does your experimental melting point compare?

3. Explain why the $-NHCOCH_3$ in acetanilide is only moderately activating while the $-NH_2$ group in aniline is strongly activating.