

Week 8
CHE 3332 - Organic Chemistry 2

Hello and Welcome to the weekly resources for CHE 3332 – Organic Chemistry 2!

This week is Week 8 of class, and typically in this week of the semester your professors are covering these topics below. If you do not see the topics your particular section of class is learning this week, please take a look at other weekly resources listed on our website for additional topics throughout the semester.

We also invite you to **look at the group tutoring chart on our website to see if this course has a group tutoring session offered this semester.** If you have any questions about these study guides, group tutoring sessions, private 30 minute tutoring appointments, the Baylor Tutoring YouTube channel or any tutoring services we offer, please visit our website www.baylor.edu/tutoring or call our drop in center during open business hours. M-Th 9am-8pm on class days 254-710-4135.

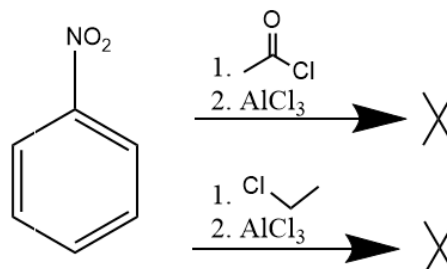
Keywords: Activating & Deactivating, Blocking Group, Nucleophilic Aromatic Substitution

TOPIC OF THE WEEK: Aromatic Substitution Reactions

Reaction	Reagent	Product
Halogenation	FeBr ₃ or AlBr ₃ (for bromine) AlCl ₃ (for chlorine)	Addition of a halogen on the benzene ring
Sulfonation	“Fuming” H ₂ SO ₄ (concentrated)	Addition of a HSO ₃ group on the benzene, can be reversed using dilute H ₂ SO ₄
Nitration	1. HNO ₃ 2. H ₂ SO ₄	Addition of a NO ₂ (nitro) group on the benzene
Reduction of Nitro Groups	1. Fe or Zn, HCl 2. NaOH	The nitro group gets reduced to an amine
Friedel-Crafts Alkylation	1. Halocarbon (w/ chlorine) 2. AlCl ₃	The carbon chain is added to the benzene ring
Friedel-Crafts Acylation	1. Acid Chloride 2. AlCl ₃	The acyl group (from the acid chloride) is added to the

		benzene ring
Clemmensen Reduction	1. ZnHg 2. HCl, Heat	Reduces the ketone group of a previously performed Friedel-Crafts Acylation

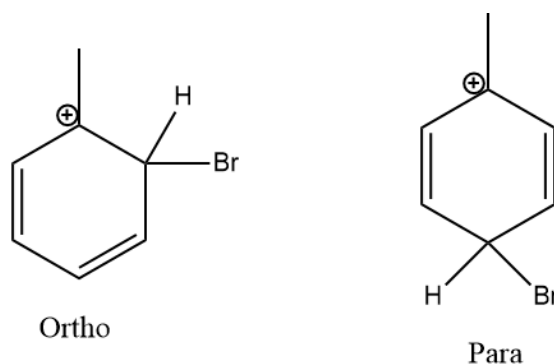
Something useful to know for synthesis problems is that both Friedel-Crafts Alkylation and Acylation are unable to be performed if the benzene ring has an electron withdrawing group attached. So it is best to perform these reactions first, and then add electron withdrawing substituents later.



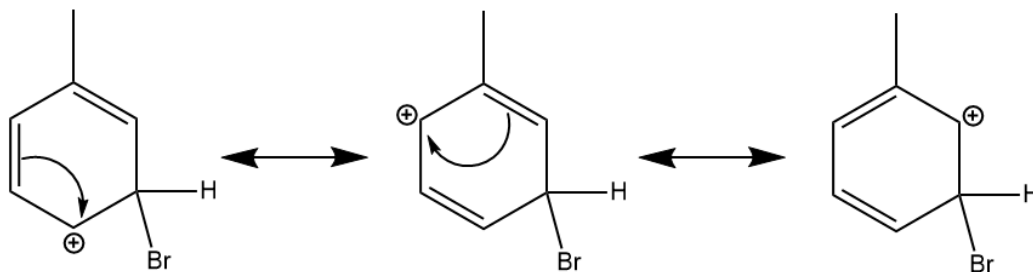
Activating and Deactivating Groups:

Earlier on when talking about aromatic compounds, there is a good chance that you have heard about electron donating and withdrawing groups. As the names suggest, when these groups are added to a benzene ring, they will either donate or take away electron density from the ring. Once they are added, we can then refer to them as **activating** or **deactivating** groups, because they now will affect how likely the benzene ring will undergo substitution again. For almost all substituents, activating groups are electron **donating** and deactivating groups are electron **withdrawing**. Additionally, these two types of groups also have a great effect on directing whether substituents will be placed on an ortho, para, or meta position.

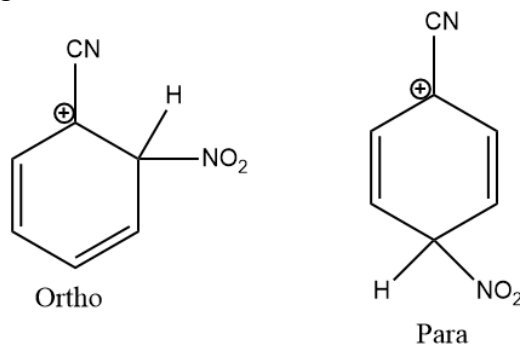
Let's take a look at how activating groups affect benzene first. We can start with toluene as alkyl groups are activators, and see what happens when we try to add bromine to the benzene ring. If the bromine happens to attach itself at an ortho or para position, these are two possible resonance structures we can get:



As can be seen, both structures have a positive charge on the carbon bonded to the toluene. Because of this, the positive charge at this location is greatly stabilized due to the toluene group adding electron density to the ring, which adds stability to the benzene. Now let's see what happens when the bromine is added at a meta position.

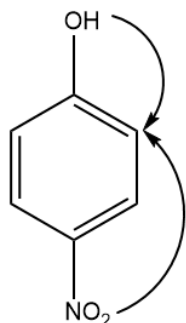


When the bromine is placed meta to the toluene, there is no resonance structure which places the positive charge next to the toluene. Because none of the structures have the extra increase in stability, the likelihood of the bromine being added at a meta position is very low. Thus, activating groups favor **ortho** and **para** positions over meta positions. Deactivating groups will then favor **meta** positions over ortho or para positions for a similar reason. Let's take a look at ortho and para addition using a deactivator:

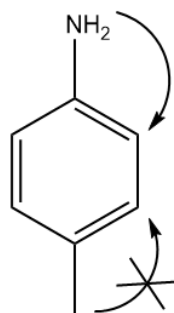


In this case, the positive charge being adjacent to the -CN group is actually bad for the stability of the ring. Unlike toluene, which adds electron density, the -CN group will take away electron density from the ring, which makes the positive charge extremely unstable at those positions. At meta positions, because we never have the positive charge placed next to the deactivating substituent, it is more stable, and will aid in the formation of the meta product. **Halogens** are the exception to this though. Despite being deactivators, they favor ortho and para products. Overall, there is a great table in chapter 18 of your book. Not only does it list each substituent and its directing effects, but it also lists them by strength.

While dealing with multiple substituents may seem daunting, they can be quite simple. For example, they may all direct towards the same position if over is an activator, and the other is a deactivator. If they are both activators, the strongest substituent will determine the location.

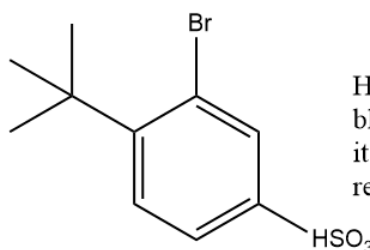
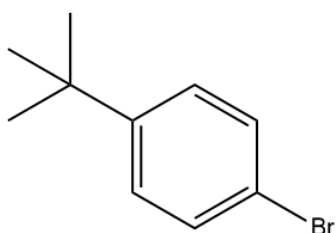


Because of their relative placement, these groups will direct a substituent to the same location.



Both substituents are ortho/para directors, but the amine group is stronger and determines the location.

While some activating groups do not have a great preference for either ortho or para locations, bulky substituents usually prefer para substitutions. However, if you need to have an ortho substituent next to something bulky, a **blocking group** can be used to force substitutions on the ortho location.



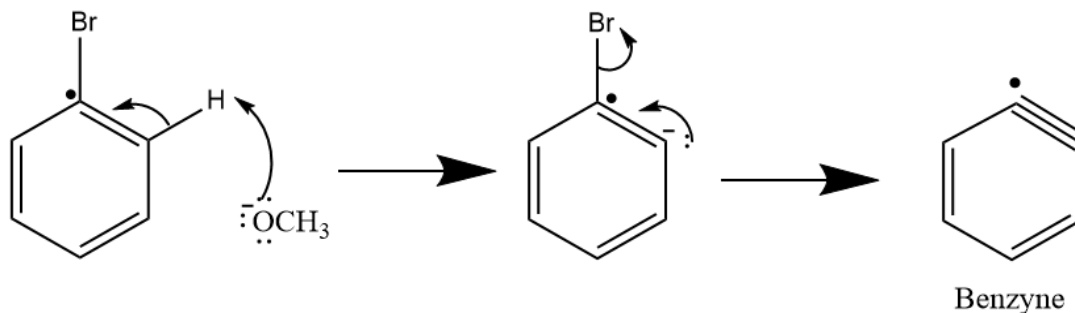
HSO_3 is a good blocking group because it is easily added and removed using H_2SO_4 .

Nucleophilic Aromatic Substitution (NAS):

Many of the previous reactions involved electrophiles attacking the benzene, however there are instances where we can have a nucleophilic attack. To do so a few requirements must be met:

- There must be a good leaving group (like a halogen or H_2O)
- There must be an electron withdrawing (deactivating) group
- Both groups must either be ortho or para to each other

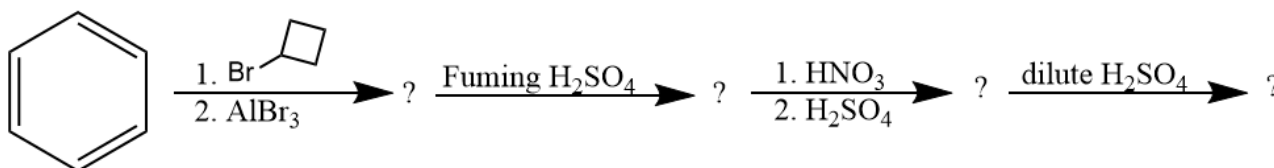
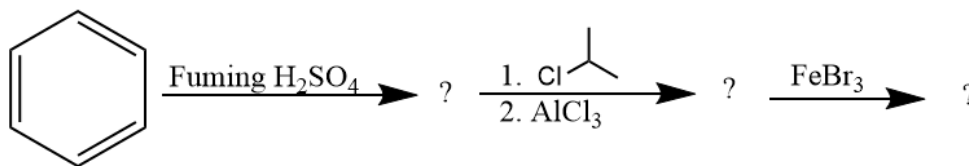
During NAS, there is an important intermediate complex (that you should know) called a **Meisenheimer complex** that is formed after our nucleophile attacks at the position of the leaving group. For example, using the molecule below we can get one of these intermediates to form:



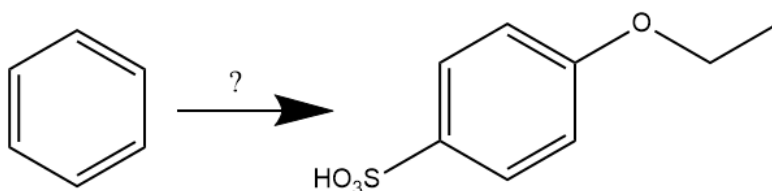
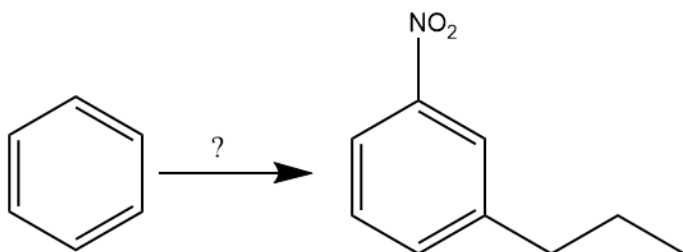
In the case of elimination addition, as the leaving group is pulled off, a hydrogen atom leaves with it, leaving a benzene ring with a triple bond, known as a benzyne. At the triple bond location, our nucleophile can attack at either end, leading to two products being formed.

CHECK YOUR LEARNING:

Predict the product and intermediates for these reactions:



Provide a synthesis for the following reactions:



THINGS YOU MAY STRUGGLE WITH:

- If you have not already done so by now, memorizing what common functional groups are electron donating, and which are electron withdrawing is a great idea. This chapter is heavily based on that material, and chapter 17 material, so it is important to keep all the information in the back of your head.
- Additionally there are few exceptions to the rules that occur in this chapter, such as not being able to perform Friedel-Crafts Acylation on a highly deactivated benzene ring. These can certainly be tricky, especially on a test, so you should certainly be familiar with them

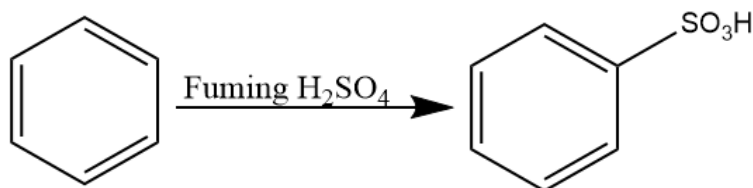
- Some of the more obscure reactions, like NAS mentioned above, may fly under your radar during your studying, since they are not talked about at length. This doesn't mean they aren't important however, so make sure not to forget them!

Thanks for checking out these weekly resources!

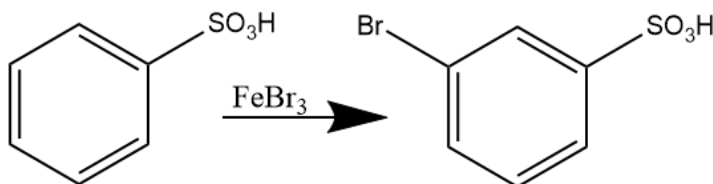
Don't forget to check out our website for group tutoring times, video tutorials and lots of other resources: www.baylor.edu/tutoring! Answers to check your learning questions are below!

ANSWERS FOR THE PRACTICE PROBLEMS:

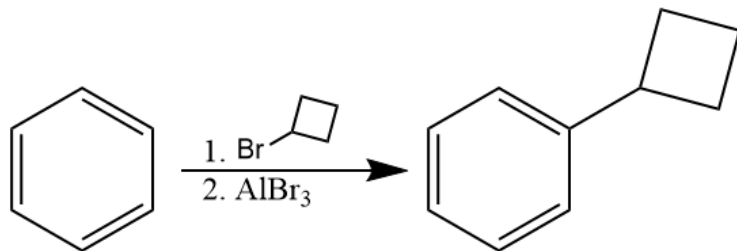
Our first set of reactions starts out quite simple, by putting a sulfite group on the benzene ring.



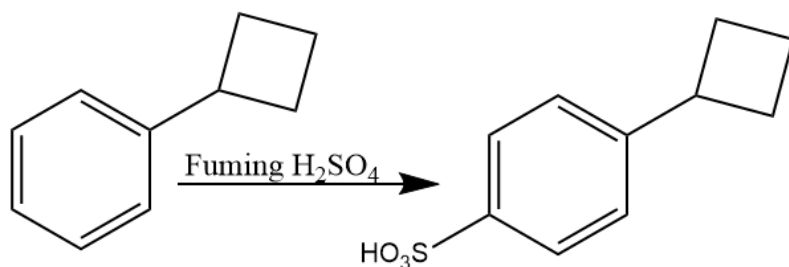
Now, because we have put an EWG group on the benzene ring, we are unable to use a Friedel-Crafts reaction. Thus, our second reaction would not proceed. This means we can go straight to the halogenation step, which will be added to a meta position.



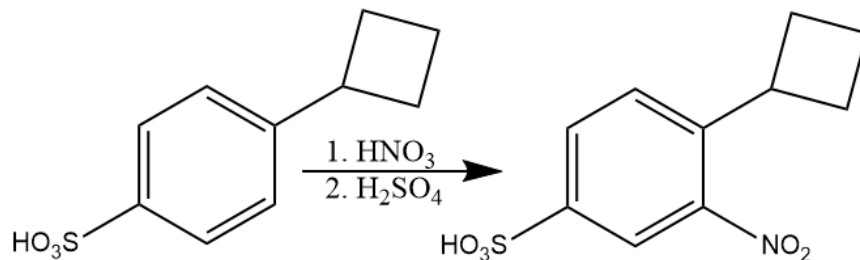
For the second set of reactions, we first have an alkylation.



Next up we have the addition of fuming sulfuric acid. Can you guess what this may be important for?



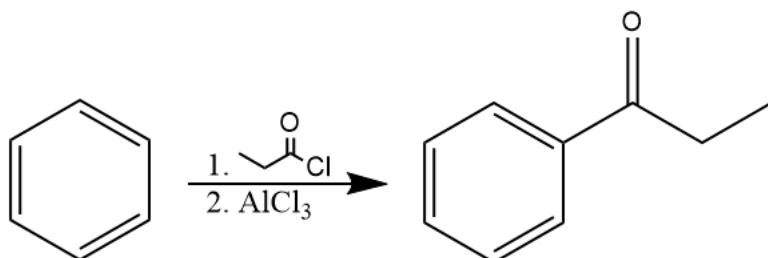
Now we can add a nitro group to our benzene ring. Because we have a sulfite group (a blocking group), the nitro group will be added ortho to the bulky alkyl substituent.



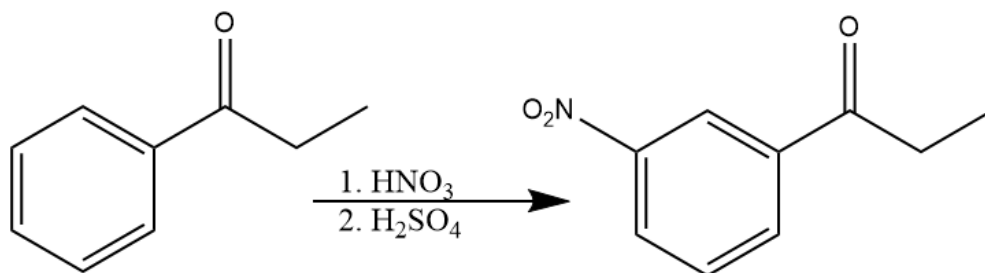
Now, we can just remove the sulfite group.. This can be easily done using a bit of dilute H_2SO_4 .



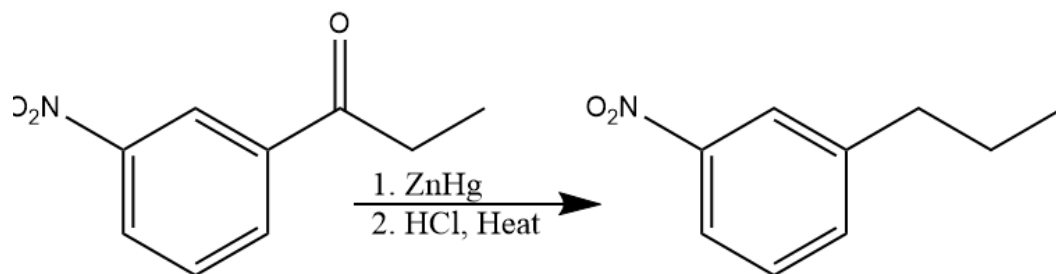
For the first synthesis problem, we have a nitro group, and an alkyl group. Using the information in the beginning of the resource, we know that we cannot alkylate after an EWG is placed, so there must be a way to add the alkyl group first. Additionally, note how the two groups are oriented (meta) towards each other. While adding an alkyl group first may not give us this directing force, if we were to add a carbonyl (through a ketone), this would give us a meta-directing functional group.



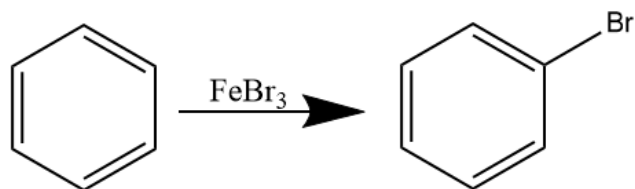
Now that we have our carbonyl (which is an EWG), we can now add our nitro group.



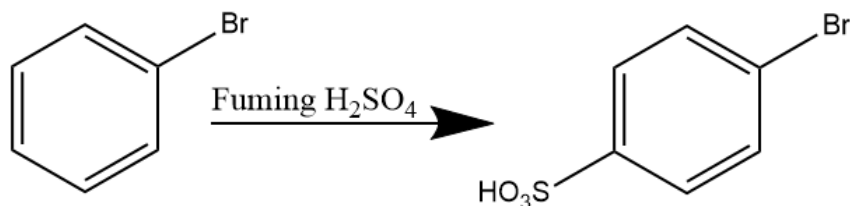
Now that we have done that, our intermediate looks close to our product, however our product does not have a ketone on it. Using the table at the beginning of this resource, we can see that we can reduce a ketone completely using a Clemmensen Reduction.



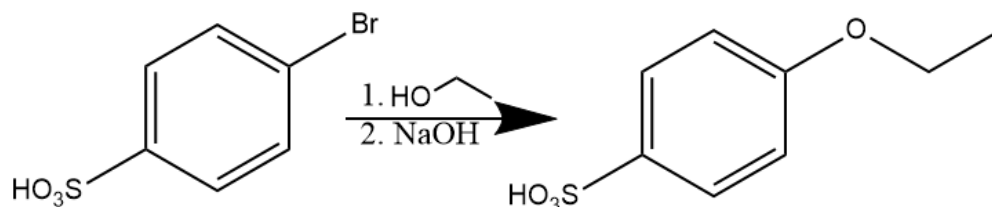
For the second synthesis problem, we can see that there is an EWG, and an ether component to the ring. While we did not cover a way to add an ether directly to a benzene using a normal substitution reaction, we can use NAS instead. Thus we should put a halogen on.



Next, we can add the SO_3 group on as normal.



Now our benzene ring is looking close to our product, and we just need to swap our bromine for the ether, using NAS.



All tables are courtesy of Organic Chemistry by David Klein. All drawings of molecules and mechanisms are made by me.