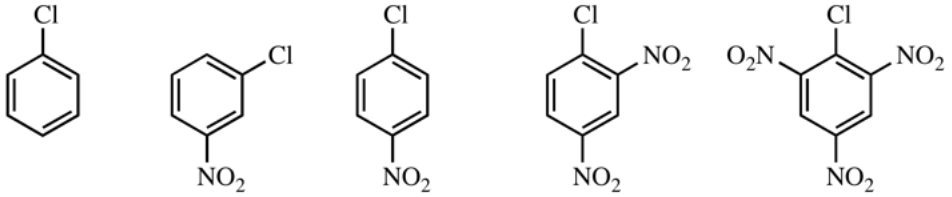
51C Review Problems
Spring 2019

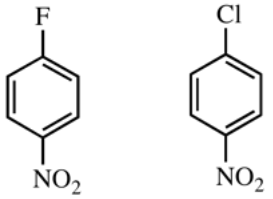
1. Nucleophilic aromatic substitution is very effective when there is a powerful electron withdrawing group (typically a nitro group) ortho or para to a leaving group. Additional powerful electron withdrawing groups make the reaction even more favorable. Compare the following rates of reaction and explain the differences:

Effect of Substitution:



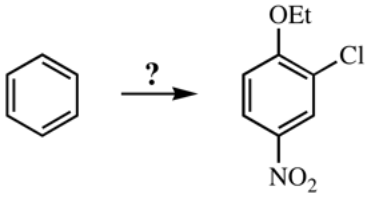
relative rate: 1 | 1 | 7×10^{10} | 2.4×10^{15} | too fast to measure

Effect of Leaving Group:

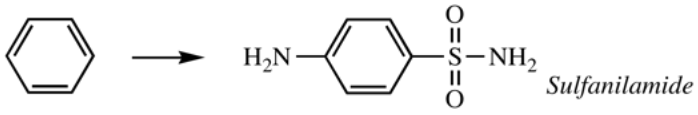


F is 312 times faster than Cl

Now, using nucleophilic aromatic substitution in one of the steps, synthesize the following compound starting from benzene:

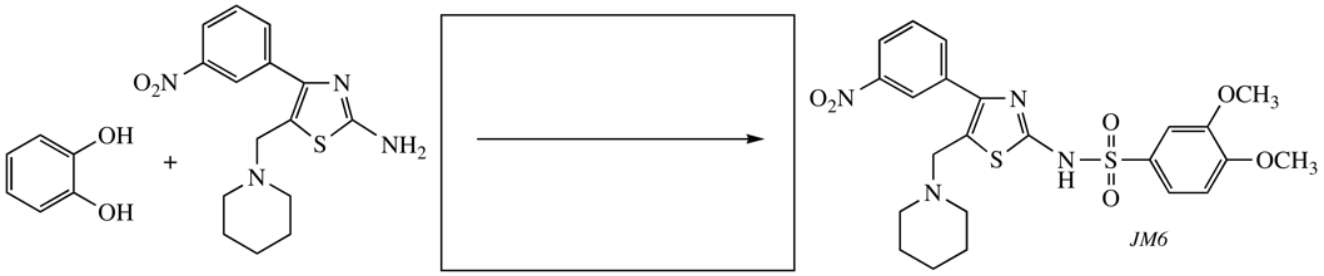


2. Sulfanilamide is a sulfonamide antibiotic used to treat upper respiratory infections and urinary tract infections. It functions by competitively inhibiting (i.e., by acting as a substrate analogue) enzymatic reactions involving para-aminobenzoic (PABA). PABA is needed in enzymatic reactions that produce folic acid, which acts as a coenzyme in the synthesis of purine, pyrimidine and other amino acids. Provide a synthesis of sulfanilimide from the given starting materials. You can use any other necessary reagents. Remember that R-SO_3H can be converted to RSO_2Cl with $SOCl_2$. SO_2Clcan be converted to SO_2NH_2 by using two equivalents NH_3 (just like making amides from acid chlorides).

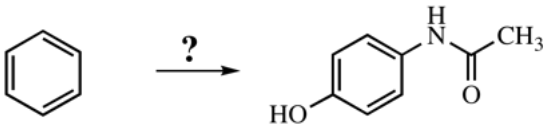


Sulfanilamide

3. JM6 is a compound that reverses and prevents symptoms of neurodegenerative diseases like Alzheimer's and Huntington's disease in animal models. Provide a synthesis of JM6 starting from the following compounds You can use any other necessary reagents. *Number individual steps*.

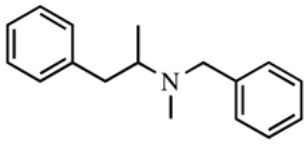


4. Provide a synthesis of acetaminophen starting from benzene:



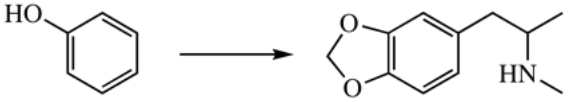
Acetaminophen
(Tylenol)

5. Provide a synthesis of benphetamine starting from benzene and any other necessary reagents, and using NH_3 as your only source of nitrogen.

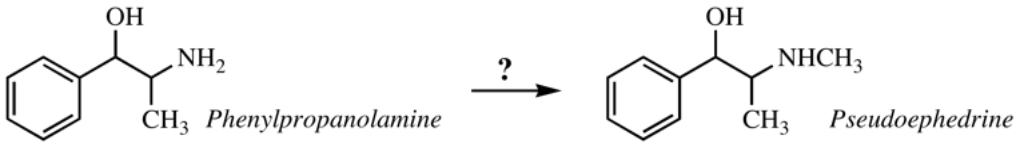


Benzphetamine (Didrex)
(antiobesity drug)

6. Provide a synthesis of ecstasy starting from phenol:

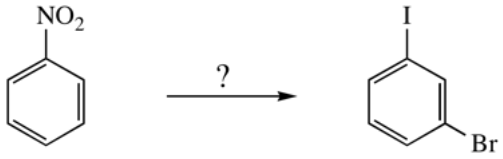


7. **Phenylpropanolamine** is a decongestant closely related to **pseudoephedrine** *(Sudafed)*. Phenylpropanolamine was recently removed from many over-the counter remedies because it has been shown to cause serious side effects (even death) when too much is taken, or when taken by patients with hypertension. How would you convert phenylpropanolamine to pseudoephedrine <u>*without overalkylation*</u>*?*

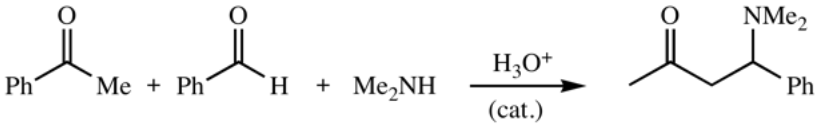


Phenylpropanolamine *Pseudoephedrine*

8. Provide reagents for the following transformations. If more than one step is required, number individual steps.



9. The process shown below is an example of a Mannich reaction. Nature uses this reaction to synthesize alkaloids (natural products that contain a basic nitrogen). Provide a mechanism for this reaction.



10. Challenge mechanism: Draw a detailed mechanism for the following reaction. Clearly show all lone pairs, charges, and curvy arrows, and show the mechanism in a stepwise manner. ***DO NOT*** combine two steps into one. (Try it – you can do it!)