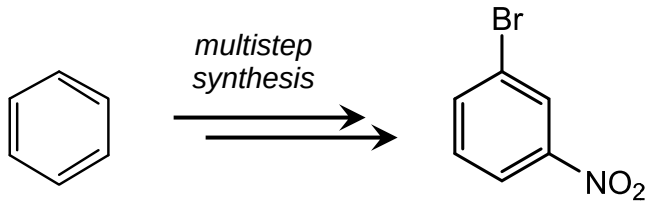
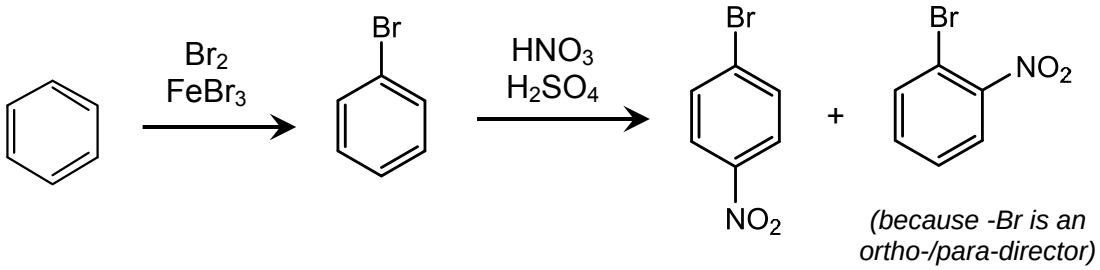
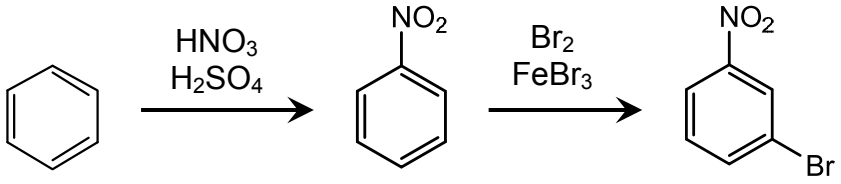
Chemistry 2302

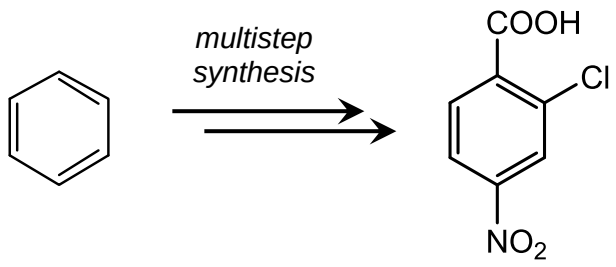
In-Class Exercise Solutions
Multistep Synthesis of Aromatic Molecules



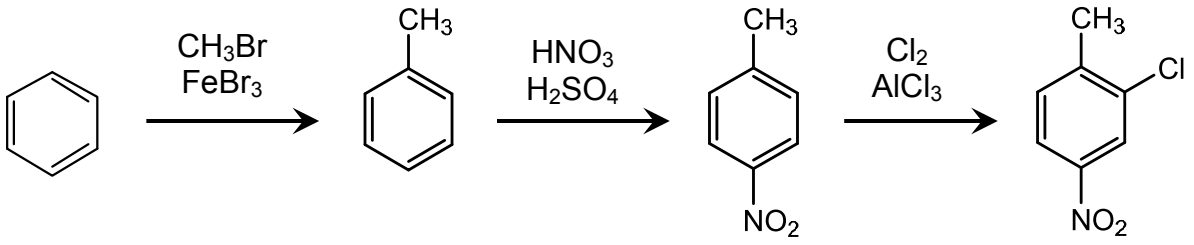
Of the three problems, hopefully this one was the easiest for you. Our product has two functional groups, and each of them can be introduced directly via electrophilic aromatic substitution—the -Br using $Br_2/FeBr_3$, and the $-NO_2$ using HNO_3/H_2SO_4. But I think the order matters, because -Br and $-NO_2$ have different directing effects:

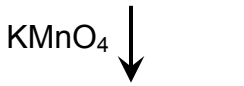


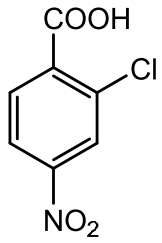




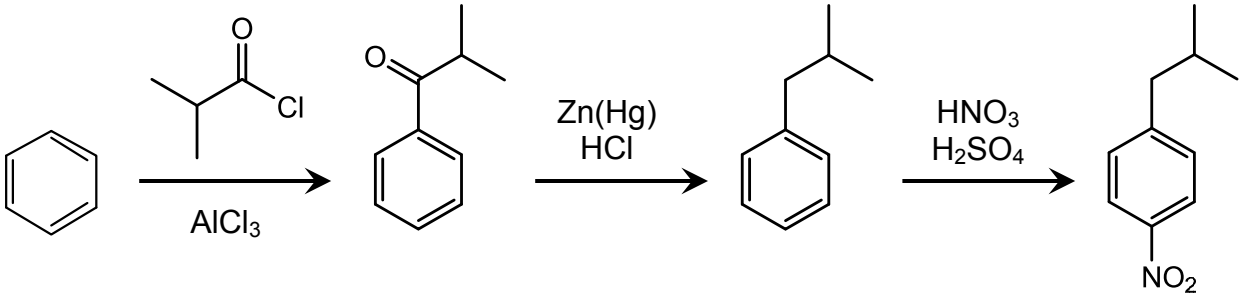
Okay, this problem is harder. Two the three functional groups in our product can be introduced by electrophilic aromatic substitution (-Cl and -NO_2), but the -COOH group has to be incorporated indirectly, via functional group transformation. (I have seen students propose to introduce it via Friedel-Crafts acylation, using Cl-(C=O)OH/$AlCl_3$. Friedel-Crafts acylation works with Cl-(C=O)R, where R is an alkyl group. OH isn't an alkyl group, so this wouldn't work.) -COOH groups can be generated by $KMnO_4$ oxidation at benzylic carbons. So, a synthetic route we might propose:

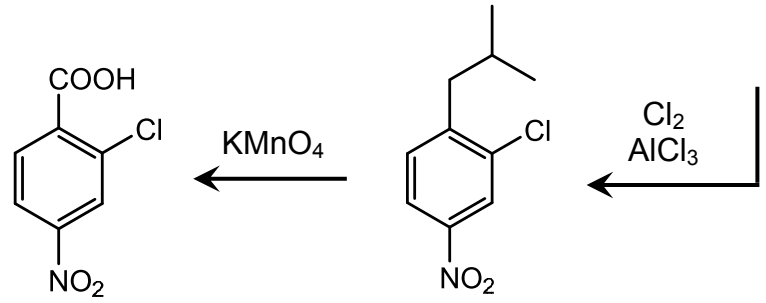


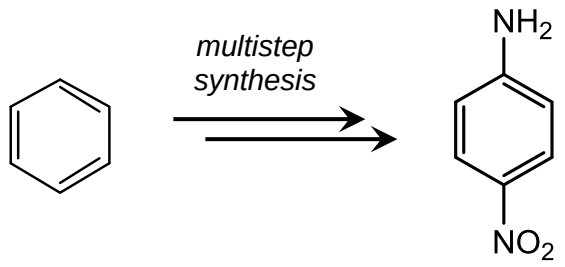




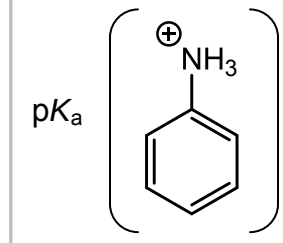
I like this synthesis, but it isn't perfect. The first step is a Friedel-Crafts alkylation, and we said in class that Friedel-Crafts alkylations are often complicated by over-alkylation; after adding the first alkyl group, the aromatic ring becomes even more reactive, and adds additional alkyl groups. So we might not be able to stop at just one methyl. And then, I show the second reaction making the *para*-product, but I'd also expect *ortho*-addition as well. I bet we could turn that off, however, if the alkyl group were a lot larger—sterics might then favor *para*-additon over *ortho*-addition. So a better synthesis might be:



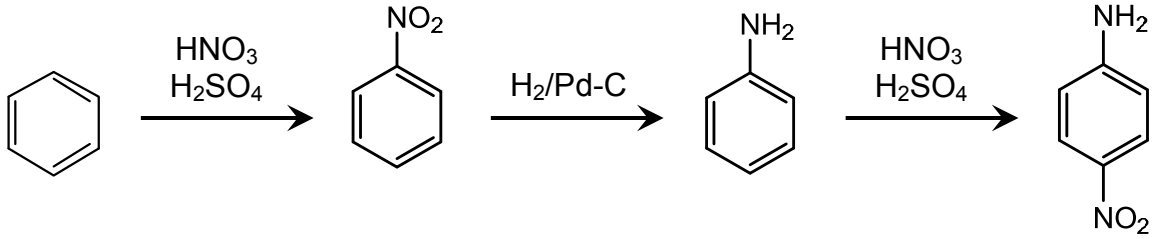




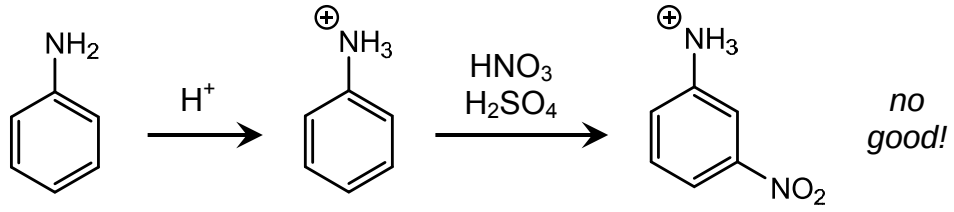
Potential issue in this problem:



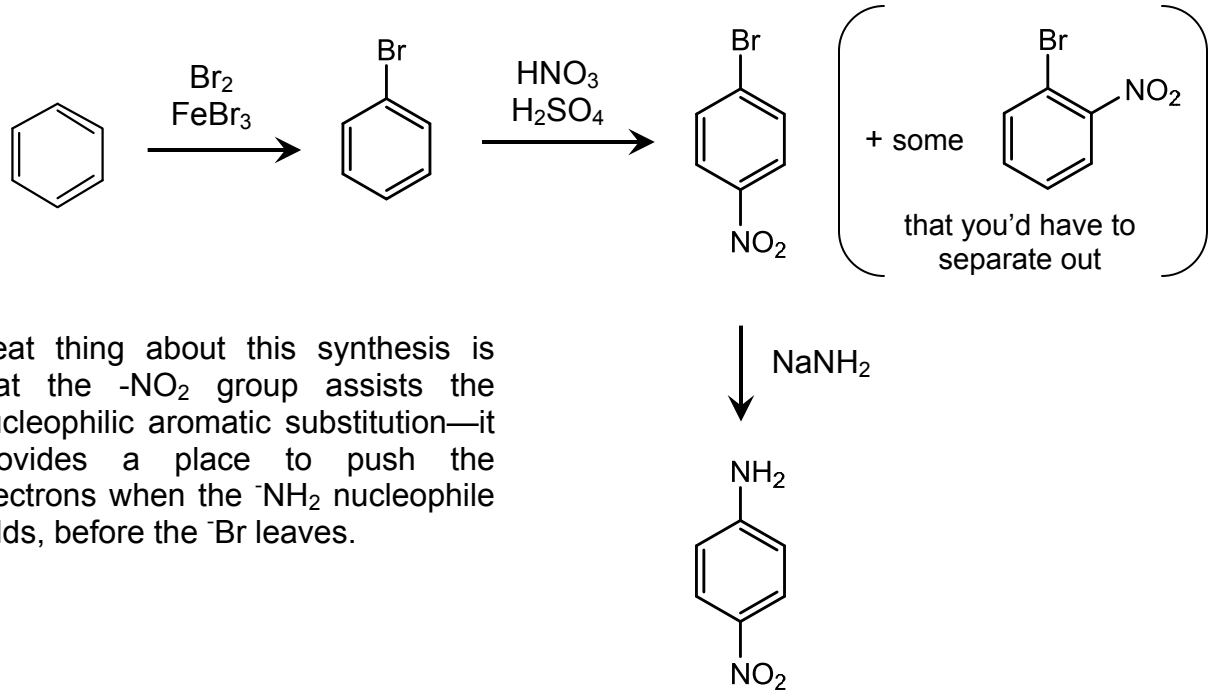
At first glance, this problem looks pretty straightforward: the -NH_2 group can be introduced via reduction of an -NO_2 group, followed by another -NO_2:



The problem is in the last step. Aniline (aminobenzene) is slightly basic, and will pick up a proton below the pH corresponding to the pKa of its conjugate acid. (So, because pK_a[anilinium ion] = 4, half of the aniline molecules will be protonated at pH = 4.) The reagents used in that last step are both really strong acids, so I would expect aniline to protonate, and our *para*-directing amine to turn into a *meta*-directing ammonium:



So how else will we do this synthesis? I think there are a couple of ways, but my favorite uses nucleophilic aromatic substitution:



Neat thing about this synthesis is that the -NO_2 group assists the nucleophilic aromatic substitution—it provides a place to push the electrons when the $^{-}NH_2$ nucleophile adds, before the $^{-}$Br leaves.