

Midterm 1 Review Packet Key

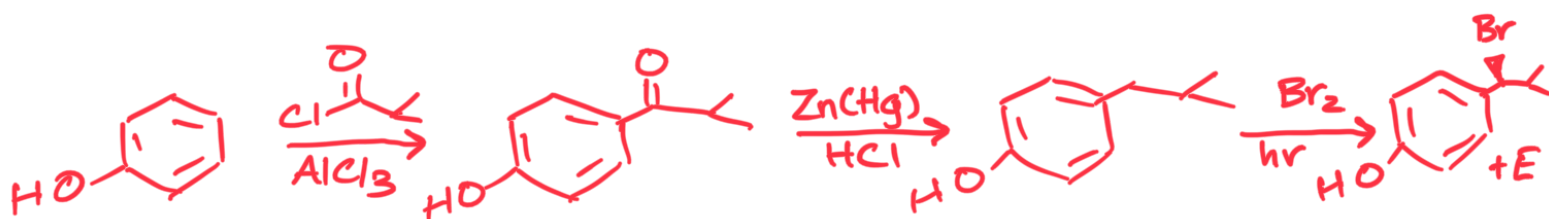
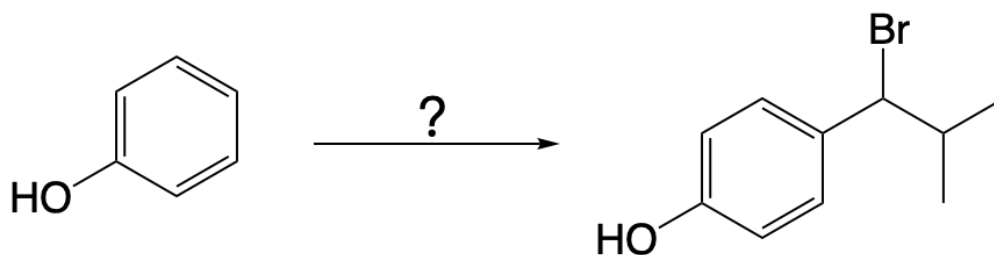
Concepts Covered:

- EAS

- Halogenation
- Nitration
- Sulfation
- Friedel-Crafts Alkylation/Acylation
 - Carbocation rearrangement

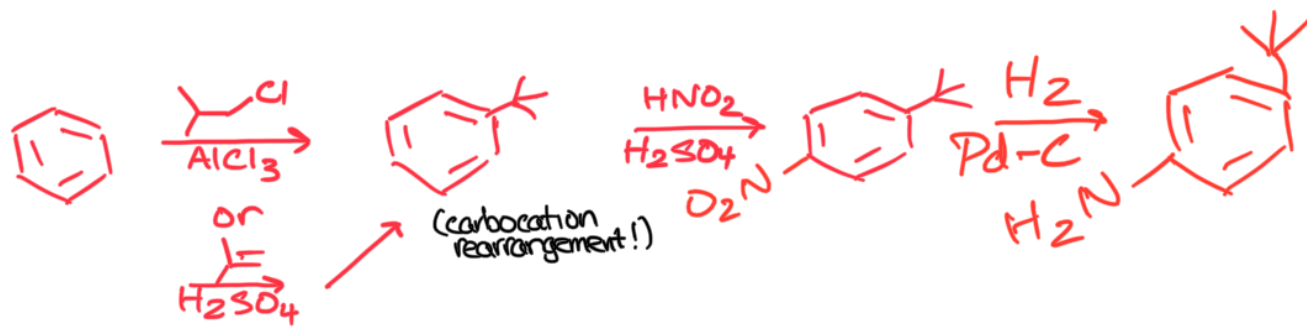
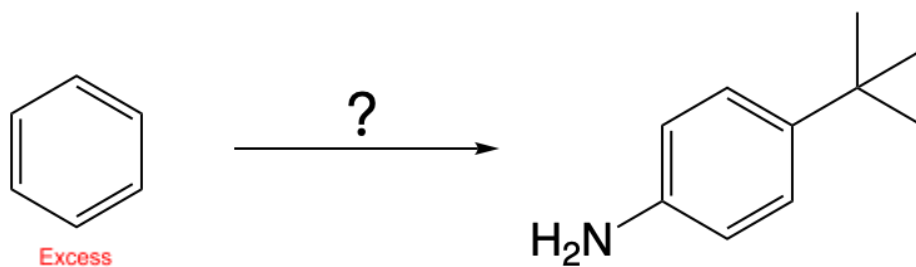
- Activating groups
 - Ortho/Para-directors
- Deactivating groups
 - Meta-directors
- Benzylic Bromination
- Reduction of ketones to CH_2
- Multistep synthesis
- **Nucleophilic Aromatic Substitution**
 - Benzyne Chemistry

1. Provide the necessary reagents to produce the product with the given starting material



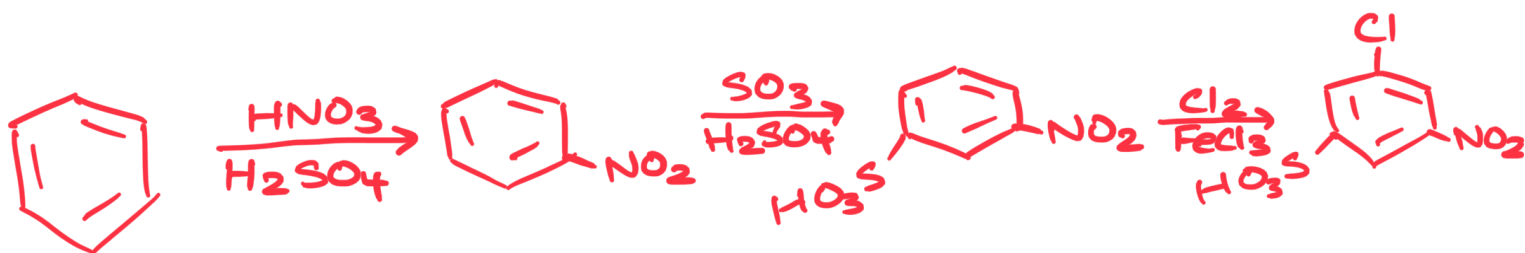
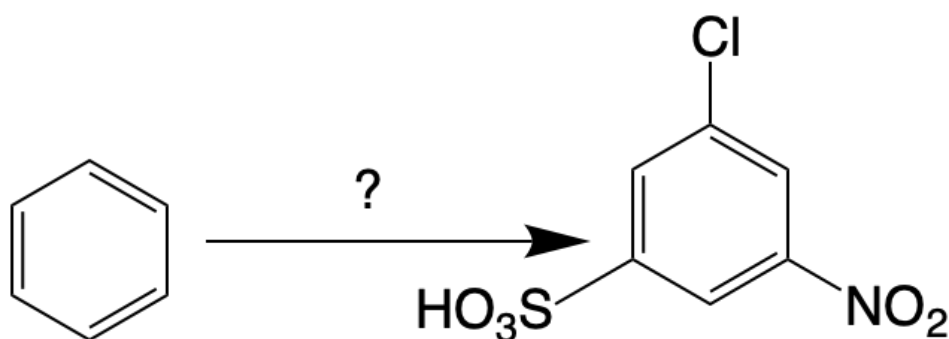
When comparing the starting material and product, there's a new alkyl chain with a bromine on the carbon adjacent to the benzene ring. In order to add new carbon-carbon bonds, you must use Friedel-crafts acylation or alkylation. In this situation, Friedel-crafts alkylation WILL NOT work due to carbocation rearrangement occurring. Therefore, using the recipe for acylation will add a ketone to the benzene. To add a bromine on the benzylic carbon, we must first reduce the C=O bond by either ($\text{H}_2\text{N-NH}_2$ / NaOH, heat) or Zn(Hg)/HCl. This will replace the C=O with two hydrogen atoms that are required (only one) for benzylic bromination to occur. Finally, Benzylic Bromination requires Br_2 & $h\nu$ (other recipes work as well but this is the easiest to remember). Note since the reaction produces a new stereogenic center, you must show stereochemistry (write +E to indicate stereoisomer).

B.



This question requires the use of nitration, Friedel-Crafts alkylation, and a reduction reaction. The main thing to figure out is the correct order. You've learned that Friedel-Crafts cannot occur with deactivating groups (halogens are an exception) as well as NR_2 ($\text{R} = \text{H}$ or alkyl). Given this information, Friedel-Crafts alkylation must occur first followed by nitration and then reducing it to NH_2 . Note that this question can use the mechanism of protonation of an alkene to generate the alkyl chain instead of the use of AlCl_3 (beware of this reagent on exams) Another note is that in Friedel-Crafts alkylation you must indicate **excess** benzene.

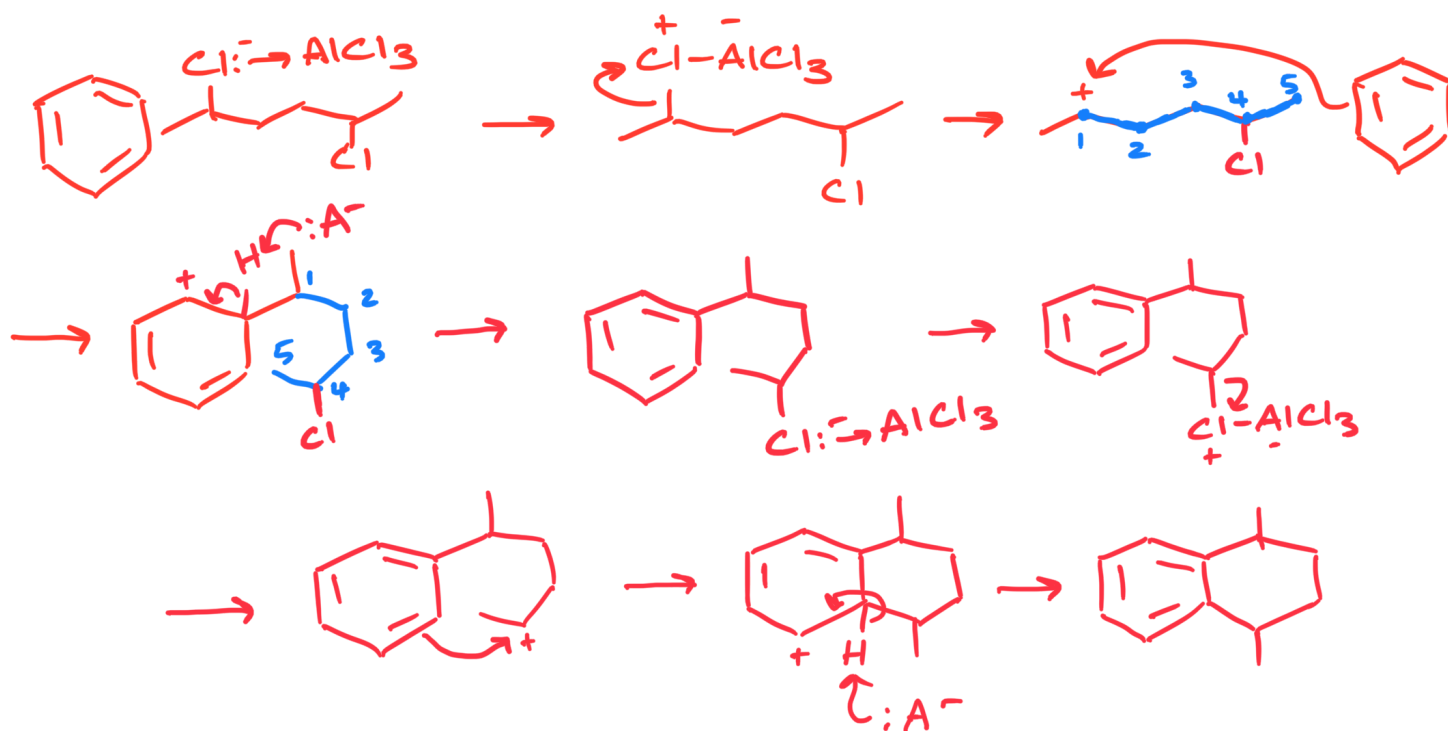
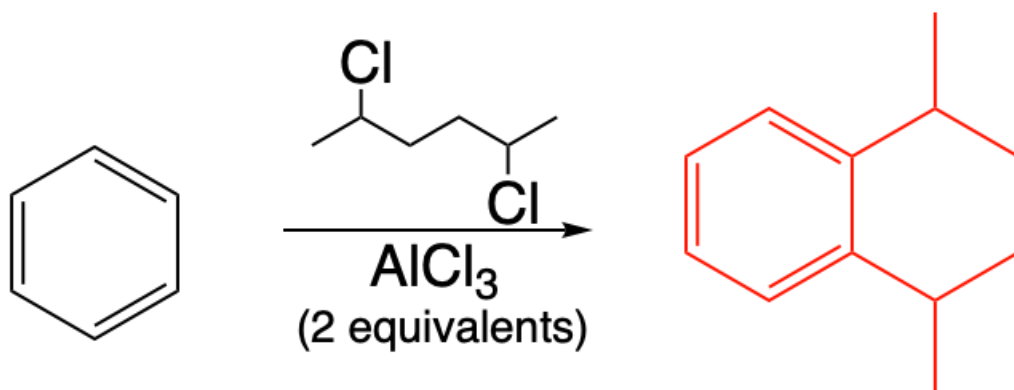
c.



Looking at the product, we see three deactivators all meta from each other which would at first glance indicate that the order of the reagents don't matter. However, even though halogens are deactivators, they are ortho/para directors which means we CANNOT add this first as the placement of the latter reagents will be incorrect. The order of the other two reagents produced by nitration & sulfation do not matter.

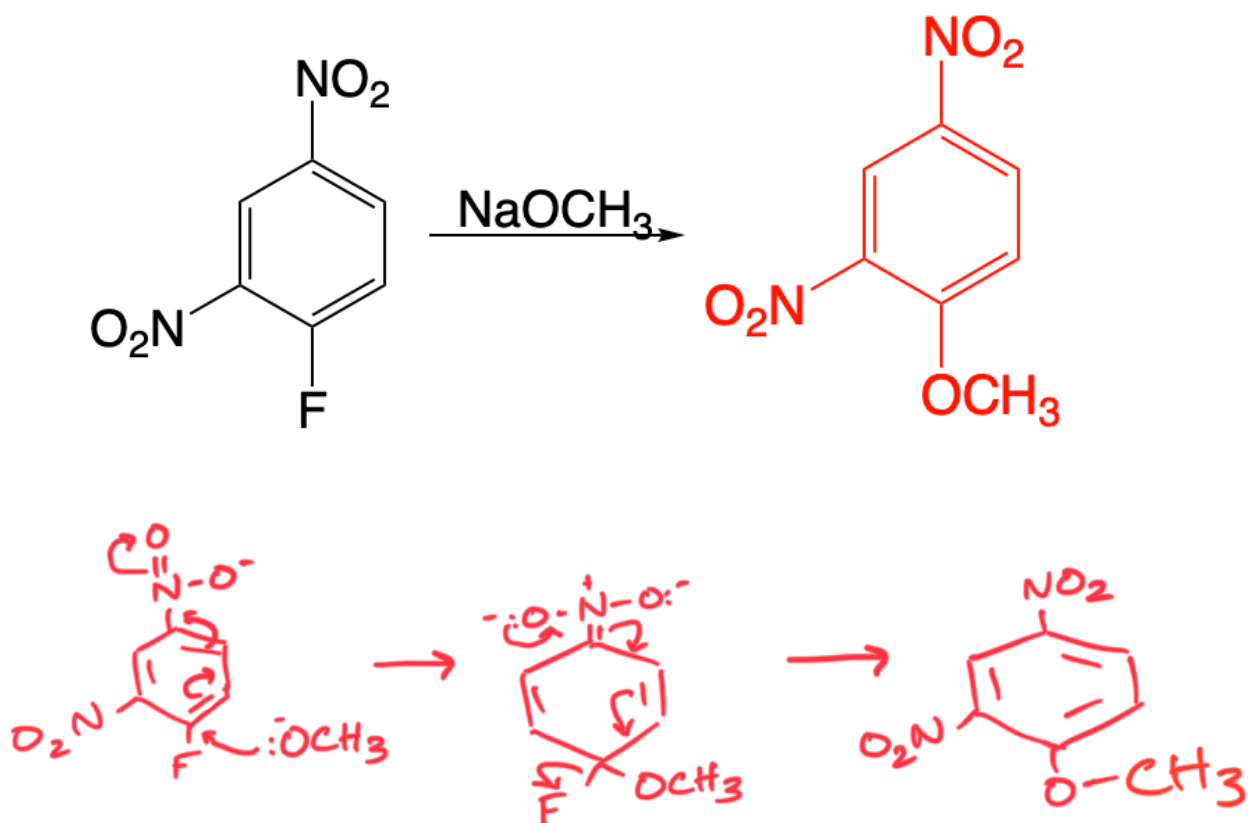
2. Provide the product produced by each of the following reactions

A.



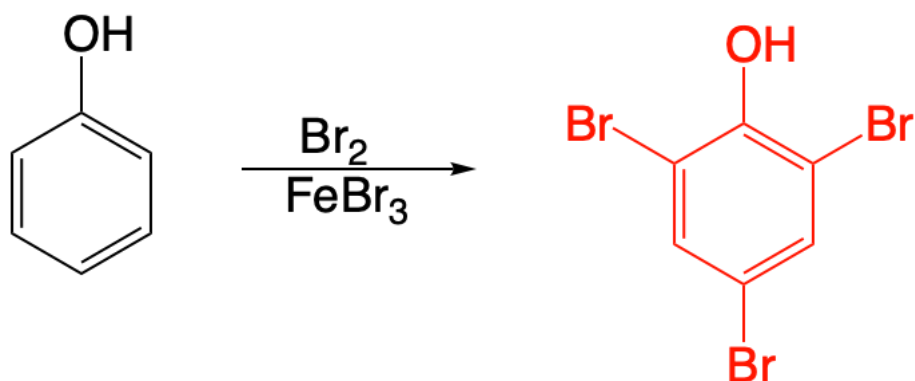
This is an example of intramolecular Friedel-Crafts alkylation where the reaction will occur twice due to the two equivalents of AlCl_3 . After the initial reaction, the second chlorine atom will attack the Lewis acid (again same mechanism steps as before) and leave to form a carbocation. The benzene ring attacks the carbocation forming a new bond and thus creating a cyclic structure.

B.



This is an example of nucleophilic aromatic substitution by addition-elimination where a powerful nucleophile (in this case OCH_3^-) will replace the halogen. This occurs in a two step process where addition of the nucleophile to form a resonance-stabilized carbanion is the first step. The second step is the elimination of the halogen leaving group. For this reaction to occur, anion stabilizing groups (in this case NO_2) are required at ortho and/or para positions. The reason for this has to do with their ability to delocalize the negative charge of the intermediate carbanion (cannot be done if they were in the meta position)

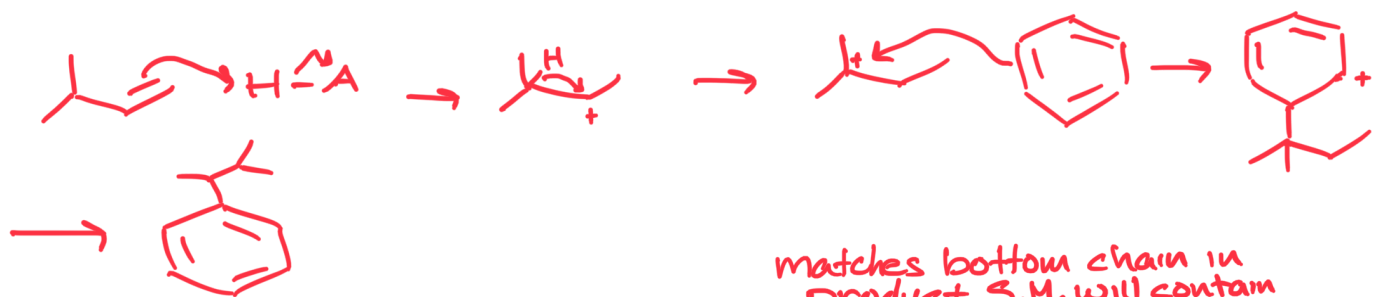
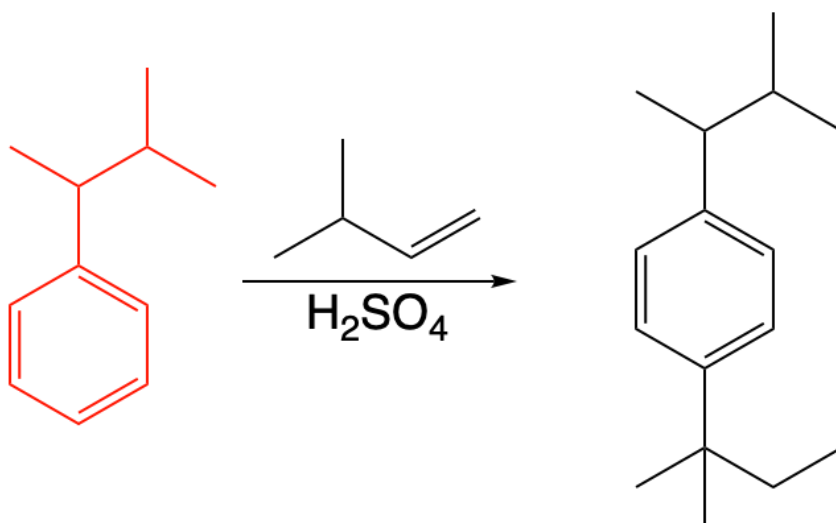
C.



This is a simple bromination mechanism with the slight twist being that phenols over-halogenate when the lewis acid catalyst is added. This results in bromine being added to all positions- ortho/para. If you only want a single bromine atom to be added, you would omit the lewis acid. Aniline also over-halogenates no matter what unless one of the R groups bonded to the nitrogen is a carbonyl.

3. Provide the starting material for each of the following reactions

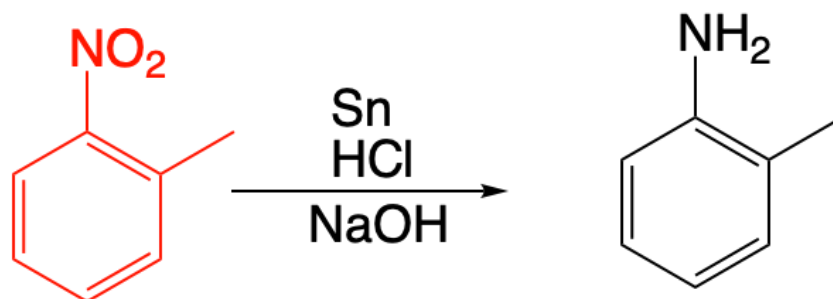
A.



matches bottom chain in product, S.M. will contain top chain.

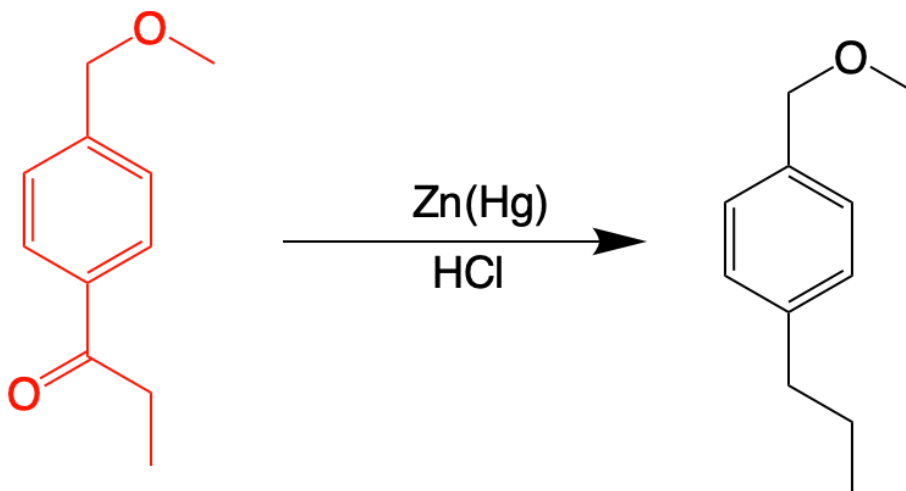
This is an example of forming a carbocation by protonation of an alkene rather than forming it using the AlCl_3 lewis acid. The final product contains two very similar alkyl chains so if the reagent forms the chain on the bottom, the initial product will contain the top chain and vice versa. Protonation of this alkene will cause a carbocation rearrangement (if you forget this step, you will get the wrong alkyl chain!) After adding the chain to the benzene, you can see it matches the chain on the bottom and therefore the initial product will contain the top alkyl chain.

B.



This problem is testing your ability to identify reduction reagents and determining whether it's the reduction of a C=O or the reduction of NO₂. These reagents (can also use H₂/Pd-C) are used to reduce NO₂ to NH₂ so the starting material will contain the nitro group.

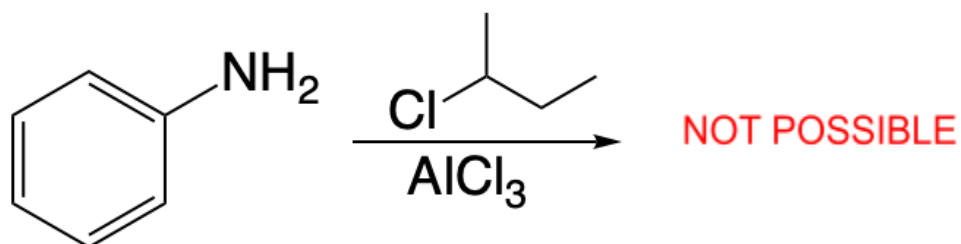
C.



Like the previous example, this is also identifying reduction reagents but this time, you are reducing a ketone to an alkyl chain. So now the question is which chain will contain the carbonyl group. It's important to remember that these reagents do not work on esters or amides! Adding the C=O to the top chain will create an ester and that is not the correct answer.

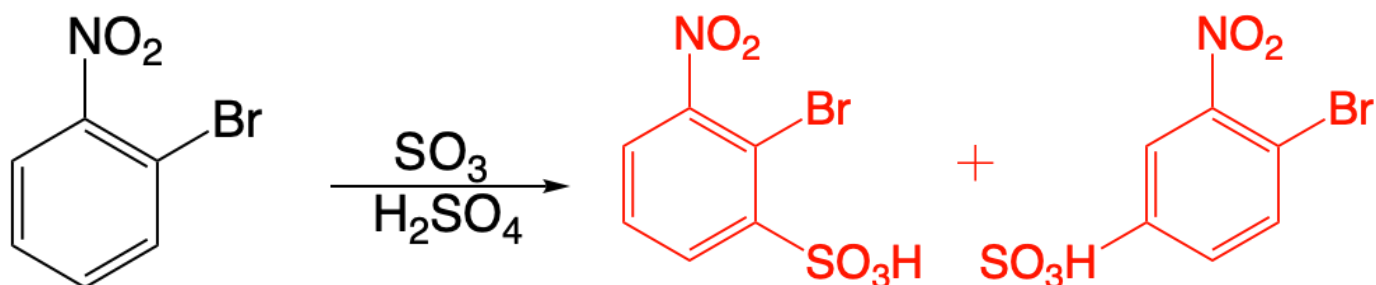
4. Determine whether the reactant will add ortho/para or meta and draw the product

A.



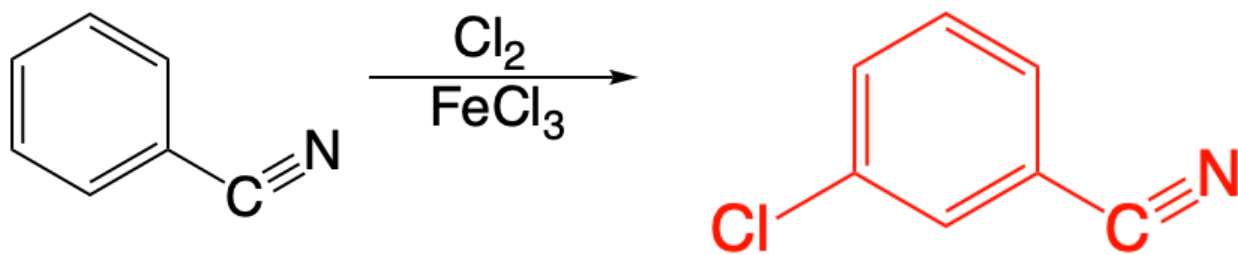
NH₂ activating group is the one exception that you cannot do Friedel-Crafts with! NH₂ is a Lewis base and the lone pair electrons would react with the Lewis acid AlCl₃. This places a positive charge next to the benzene ring, which is so strongly activating that the Friedel-Crafts reaction cannot occur.

B.



Both NO₂ and Br are deactivators, however NO₂ is a meta director and Br is an ortho/para director. If the directing effects of two groups oppose each other, the more powerful activator "wins out." Since Br is higher on the list, it will control the regioselectivity and SO₃H will add ortho/para to Br.

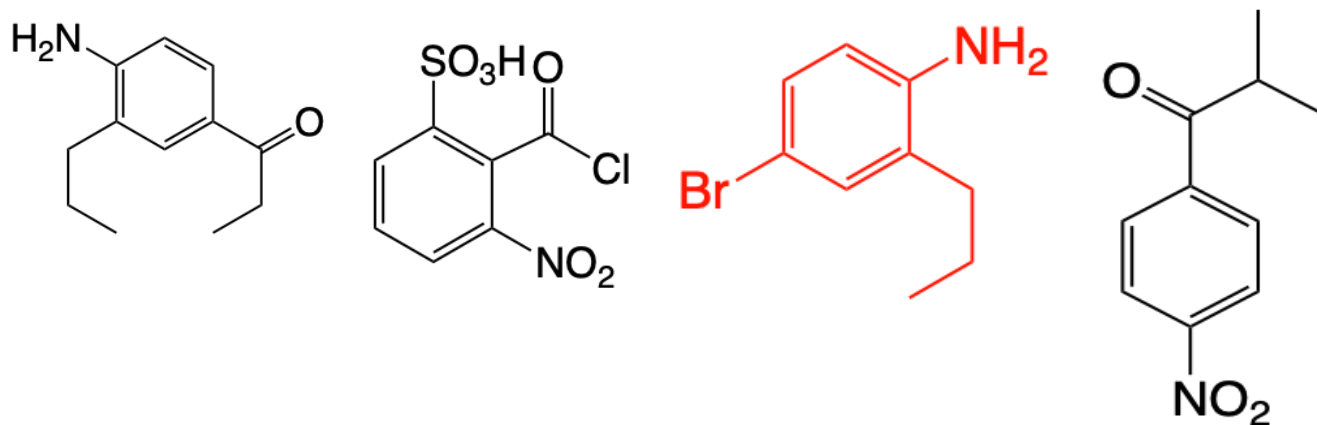
C.



This is a halogenation reaction that will add a Cl atom to the benzene ring. To determine which position it will attach to, you have to identify whether cyanide is an ortho/para or meta director.

Cyanide is a deactivating group and meta director so therefore the Cl will be added meta to this group.

5. Which of the following product(s) are possible from a starting benzene



(left to right: A,B,C,D)

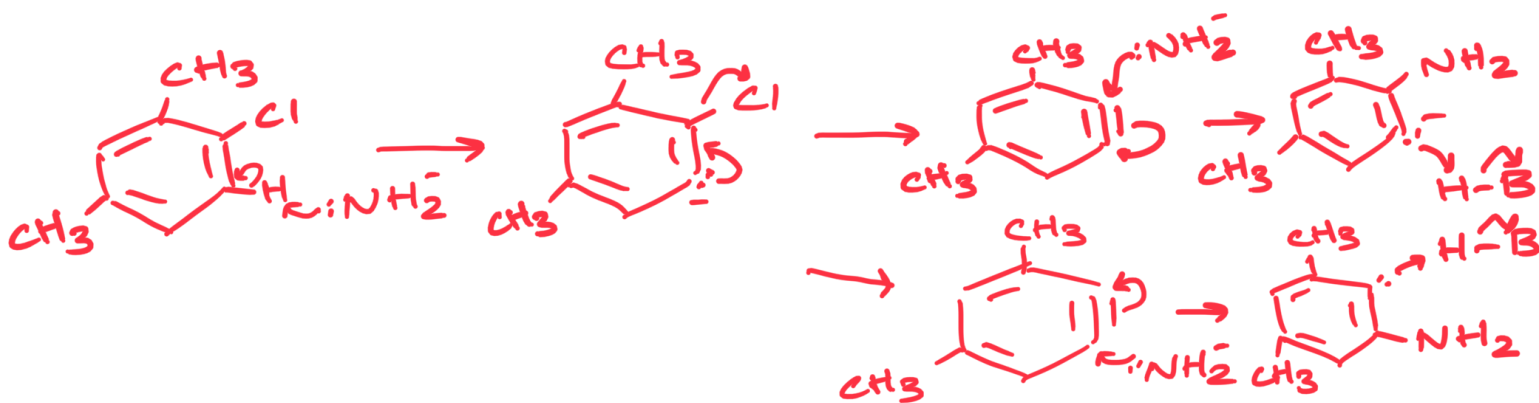
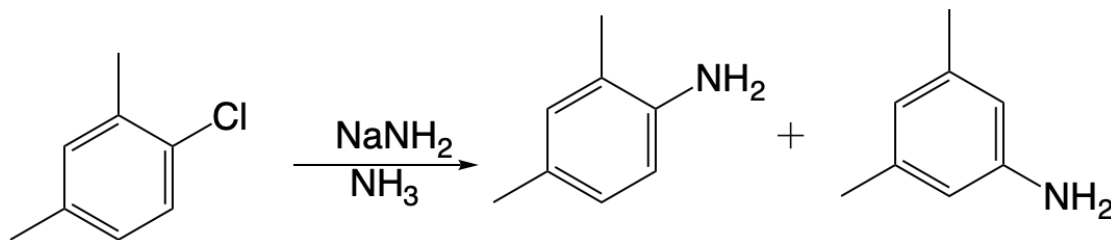
A: Product A is not possible because you are very limited in what your first step can be. Since the ring contains an NH_2 group and a ketone, you cannot perform Friedel-Crafts after adding those substituents. Therefore, the first step must be Friedel-Crafts acylation followed by reduction to produce the alkyl chain. Once this is produced, it will control the regioselectivity of the benzene ring (since it's the only substituent currently). Next, regardless of what you pick as the next substituent to add, it won't work. Adding an NH_2 won't allow Friedel-Crafts to add the ketone group. Adding the ketone group first would add ortho/para to the alkyl chain and not meta like it is shown in this case. Therefore, this product is not possible.

B: This product contains three deactivators which should add meta to each other but that is not seen here. We cannot perform substitution between meta-substituents.

C: This is the correct answer. Since there is an NH_2 (doesn't allow Friedel-Crafts), it cannot be the first step and now you have to determine whether halogenation or Friedel-Crafts comes first. Performing halogenation first would cause the next substituent to add ortho/para but we observe a meta substitution with respect to the bromine. Therefore, Friedel-Crafts will be the first step, followed by a reduction. Next, you have to determine whether halogenation or nitration (followed by reduction) comes first. Performing halogenation first, would result in it being substituted ortho/para to the alkyl chain but again it is seen as meta in this case. Performing nitration first would add ortho to the alkyl chain and then performing reduction to transform it into an activating group (NH_2) would allow the bromine to add para to it.

D: This product contains two meta directors but we observe them being ortho from each other which is not possible.

6. Show the mechanism for the following reaction



This is an example of Nucleophilic Aromatic Substitution via E1 conjugate base to generate a Benzyne intermediate. Step 1 of this reaction would be the elimination of H & X (halogen) from adjacent atoms to form a reactive intermediate. Step 2 is the nucleophilic attack and protonation. Note that the nucleophile can add to either side of the triple bond and therefore two products will be produced.