

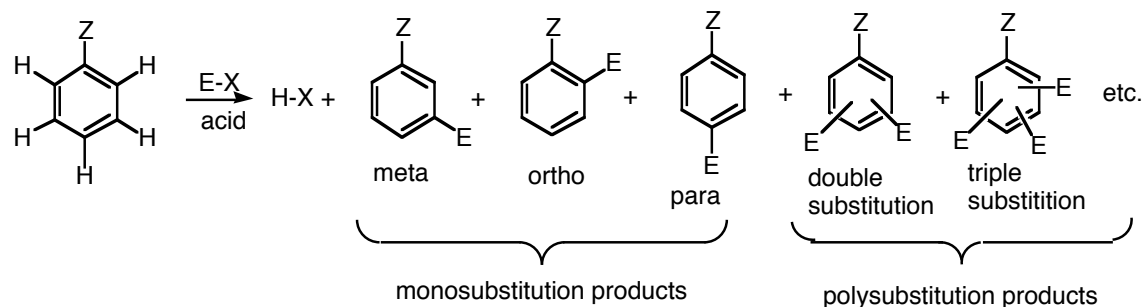
NITRATION OF METHYL BENZOATE

General Issues with Electrophilic Aromatic Substitution Reactions:

Aromatic substitution reactions involve the substitution of one (or more) aromatic hydrogens with electrophiles. Two major synthetic issues are always involved.

1. Monosubstitution versus Polysubstitution

- Because there is more than one benzene hydrogen available, can the reaction be disciplined so that monosubstitution occurs rather than polysubstitution?
- Selective **monosubstitution** is possible only if the monosubstitution product is **less** reactive than the original reactant. If the reactivity of the monosubstitution product equals or exceeds that of the original reactant, the monosubstitution product(s) will proceed on to polysubstitution products.
- There are two reasons why a monosubstitution product might be less reactive:
 - **Electronic reasons.** If the “E group” that added is electron withdrawing, it will make the product aromatic ring less electron rich and subsequently less reactive toward subsequent electrophilic addition.
 - **Steric reasons.** Replacement of a small H with a larger “E group” will make the monosubstitution product more crowded, which may interfere with subsequent addition of additional electrophiles.

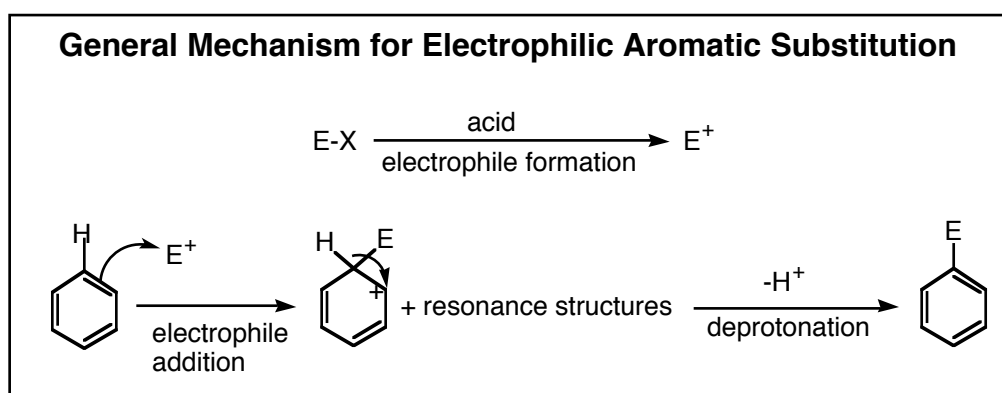
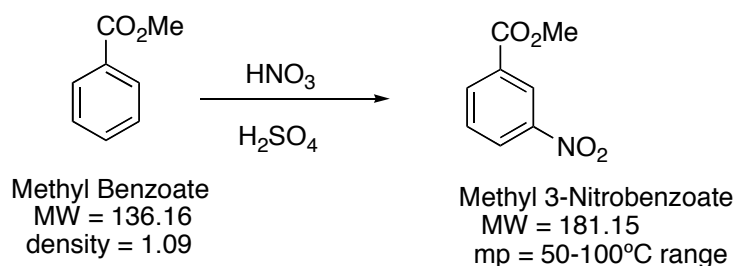


2. Position of Substitution: Ortho, Meta, or Para To a Pre-existing Substituent?

- Even if a reaction can be disciplined such that monosubstitution occurs to the exclusion of double or triple substitution, what happens when substitution occurs on a benzene that already has a substituent attached ($Z \neq H$)? Will ortho, meta, and para hydrogens be substituted with equal ease, so that a statistical mixture of ortho-, meta-, and para-disubstituted products form? Or will substitution be selective? Somewhat selective substitution is ordinarily possible based on two reasons:
 - **Electronic reasons.** Rate-determining addition of E^+ occurs with differing speeds because of the electronic impact of Z on the delocalized cationic charge. If Z is an electron donor, it will stabilize positive charge and facilitate ortho and para addition relative to meta addition. If Z is an electron withdrawer, it will destabilize positive charge and deactivate ortho and para addition relative to meta addition.
 - **Steric reasons.** Depending on the size of both Z and E, they will interact to varying degrees in the pathway leading to the ortho product. Thus the **ortho** product is normally destabilized for steric reasons relative to either the meta or the para products. Steric factors only impact when an electrophile adds ortho to a non-hydrogen. If an electrophile adds in between two non-hydrogens, steric problems are really awful.

General Mechanism for an Electrophilic Aromatic Substitution:

The general mechanism for all electrophilic aromatic substitutions is summarized below. First, a reactive electrophile E^+ must be generated by interaction of a reactant with acid (either a Lewis acid or a normal Bronsted acid). The mechanism for the E^+ formation depends on the electrophile. Once an active electrophile is available, it adds to an aromatic ring to give a cationic intermediate. The allylic nature of the cation means that it always has at least three meaningful resonance structures, and sometimes more. The positive charge is always distributed to the carbons that are ortho and para relative to the carbon to which the electrophile has added. Notice that the carbon to which addition occurs is temporarily tetrahedral, and that the ring temporarily loses its aromaticity when addition occurs. Once the cation has formed, subsequent deprotonation occurs (from the carbon onto which the electrophile has added), and aromaticity is restored. The two steps, electrophilic addition followed by loss of the proton, constitute a “substitution”; the electrophile takes the place of the hydrogen on the ring.

**Today's Actual Reaction:****Reaction Procedure:**

1. From a buret, add 6 mL of concentrated sulfuric acid directly to a 50-mL Erlenmeyer flask containing a stir bar. (If you don't have a very clean Erlenmeyer, do not wash now! The water will do more harm than any residue that may be present.)
2. Set an ice bath on a stir plate and cool the solution in an ice bath. Turn the stirrer on.
3. Measure out 2.00 mL of methyl benzoate via syringe from the reagent bottle, and inject it directly from the syringe into the cooled, stirring sulfuric acid solution.
4. From a buret, measure about 1.4 mL of concentrated nitric acid into your 10mL graduated cylinder. The accuracy does not need to be high. Then add the nitric acid dropwise, by long-stemmed pipet, over 3-4 minutes, to the methyl benzoate/sulfuric acid solution, which should still be kept cold in the ice bath and being continuously stirred. After completion stir for 5 more min.
5. Remove the cold bath and let the mixture stand at room temperature for 20 minutes, with continuous stirring.

Isolation of the Crude Product:

1. Transfer the solution (carefully) onto a pile of ice (about 20 g) in a small beaker (100 mL) by using a pipet. (The product will likely crystallize.)
2. Add another 10 mL of ice-cold water to the original Erlenmeyer, and clean your pipet that you used for the transfer by drawing up water and shooting it back out three times. Swirl the water around in the Erlenmeyer so that as much as possible of the original solution has a chance to go into the water.
3. Add another 20 mL of cold water. Pour the aqueous solution from the Erlenmeyer into the beaker, and swirl thoroughly.
4. Rinse the original Erlenmeyer with another portion of cold water.
5. By now the product should have crystallized. Isolate the crude crystals by suction filtration, using your medium-sized Buckner funnel. (Try to get the ice to melt first!) (Wet the filter with water.)
6. Wash once with about 20 mL of ice-cold water.
7. Do a second wash with about 10 mL of a methanol/water mixture (about 8/2 methanol/water ratio).
8. Measure the mass of the crude product.
9. Prepare a sample for GC/MS analysis. Do this by adding a spatula tip (0.010 g?) to a GC/MS vial, and add one pipet of methanol. Submit to the GC/MS queue.
10. Save a few of the crude crystals to get a crude melting point. (Save only enough for a melting point!)

Recrystallization of the Crude Product:

1. The main batch of crystals should be purified by recrystallization. (Prior to recrystallization, up to 20% may be ortho-, para-, or polynitrated material plus possible starting material).
2. Pour some hot tap water into a 100-mL beaker, and warm on a hot plate. (Note: if you pour hot water in in the first place, it doesn't take as long to heat up as if you start with cold water! Brilliant, huh?) You will subsequently warm a 25-mL Erlenmeyer in this water bath, so you probably don't need it to be more than 40-50 mL full. You will subsequently want to be mildly boiling methanol (bp = 64°C) in the water bath, so you'd like it to get hotter than 64° but you don't want it way hotter, in other words you don't want a hard boil.
3. Transfer the crystals from the filter paper into a 25-mL Erlenmeyer. Use a spatula to scrape.
4. Add 6 mL of methanol to the Erlenmeyer. (Use some of this to rinse off the filter paper and the spatula, if some crystals are sticking.)
5. Add a boiling stick, and then place the Erlenmeyer with the product/methanol mixture into the warm water bath to heat it to a gentle boil.
6. Depending on how much product you made and on how wet it may have been, the 6-mL of methanol may be more than plenty or may be too little. If your yield is either really good, or if your raw crystals are very wet with water, it may require more methanol. So once your solution has warmed to a boil, if the crystals don't dissolve within two minutes then add more methanol as needed until the crystals do dissolve. (But just barely. Remember that for a recrystallization, in order to get optimal yield you don't want to use an unnecessary excess of hot solvent....)
7. If appropriate, once the solution is homogeneous, if you think you have too much methanol, you may wish to add hot water dropwise to the hot solution to achieve saturation, just until the hot solution gets/stays slightly cloudy (standard mixed solvent technique).
8. Once you think you have optimized your solvent conditions for the recrystallization, remove the flask from the heat bath and let the solution cool slowly on a watch glass with a beaker over the top to prevent further solvent evaporation.
9. After cooling to room temperature, cool it on ice, and suction filter to get the purified product.

10. Be sure to rinse your crystals; what would be an appropriate wash solvent or solvent combination to use?
11. Prepare a sample for GC/MS analysis. Do this by adding a spatula tip (0.010 g?) to a GC/MS vial, and add one pipet of methanol. Submit to the GC/MS queue.
12. Let the crystals dry, then get the mass yield and take a melting point. When you take your melting point of the recrystallized material, also take a melting point of the crude material in order to compare so you can see whether recrystallizing actually helped.
13. Typical yields should be 40-80%. The melting point should fall somewhere in the 50-100° range, so don't heat too fast.
14. Summary of Required Data:
 - Mp, mass yield, GC/MS data, and % yield for both crude and purified material

NMR/IR: None required.

Caution: Safety Note: Both conc. sulfuric acid and conc. nitric acid are very potent and will dissolve you, your clothes, your papers, or anything else they touch! Avoid pouring; try to use burets/pipets exclusively, or as much as possible. Rinse your glassware and pipets thoroughly with water after usage.

Cleanup: If an aqueous acid waste bottle is out, put your original solution (following filtration) into that. If not, dilute the original solution with water, neutralize with sodium carbonate (expect it to fizz!), and pour down the drain.

Pour the methanol from the recrystallization into the organic waste container.

Questions:

1. Draw the mechanism for the reaction.
2. If you didn't already do so in your answer to question 1, draw out the three resonance structures for the carbocationic intermediate after NO₂ addition (prior to proton loss).
3. The para product is not formed to a significant extent. Draw the carbocationic intermediate that would be involved in the formation of the para product (had it actually formed), and its resonance structures. Explain why ortho product formation is much slower than meta-product formation. (Hint: is the CO₂Me substituent an electron donor or withdrawer? A cation stabilizer or destabilizer?) Circle the most problematic resonance of the three resonance structures.
4. In the experiment, an excess of nitric acid was used. Given that the nitro group is an electron-withdrawing group, explain why your reaction stopped with mostly only single nitration but didn't go on further to give lots of double nitration?

Lab Report:

Standard synthesis lab report format.