

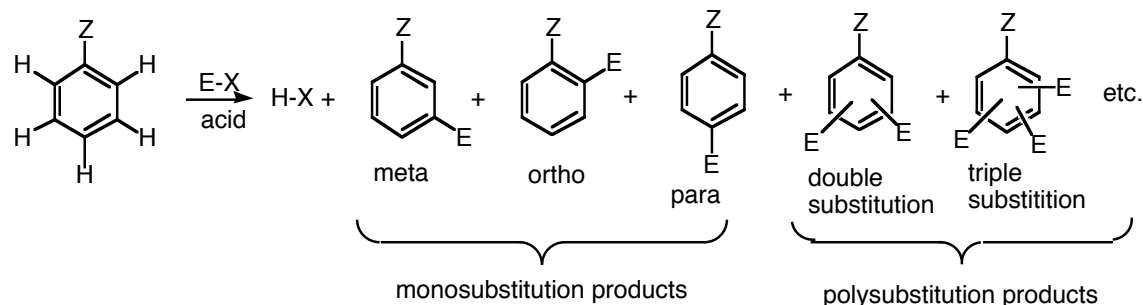
NITRATION OF METHYL BENZOATE

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.

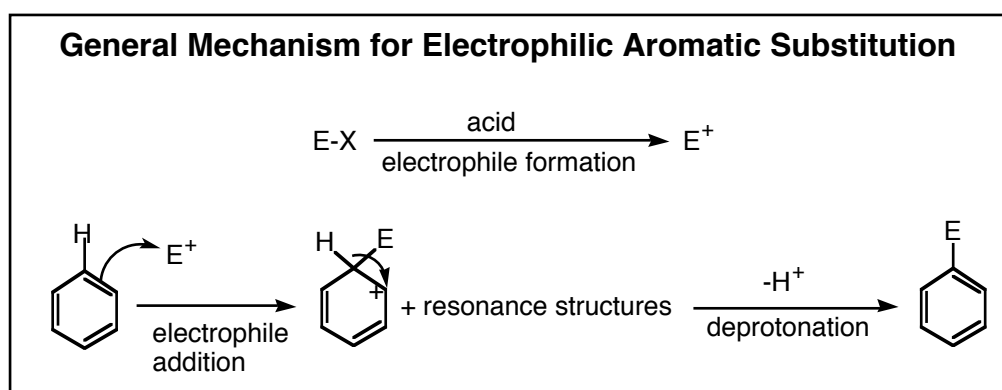
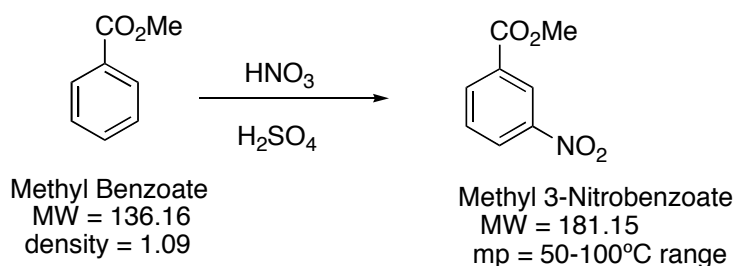


2. Position of Substitution: Ortho, Meta, or Para To a Pre-existing Substituent?

- 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 ($Z \neq \text{H}$)? 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 (150 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. (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 20-30% may be ortho-, para-, or polynitrated material plus possible starting material).
2. Pour some hot tap water into a 150-mL beaker, and warm on a hot plate. (Setting 4 is probably good). (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. 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.
8. After cooling to room temperature, cool it on ice, and suction filter to get the purified product.
9. Be sure to rinse your crystals; what would be an appropriate wash solvent or combination to use?
10. 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.

11. 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.
12. Typical yields should be 50-75%. The melting point should fall somewhere in the 50-100° range, so don't heat too fast. (Power setting of 4 would probably be good.)
13. Summary of Required Data:
 - Mp, mass yield, GC/MS data, and % yield for both crude and purified material.
 - No NMR or TLC 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 para 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. Make sure to follow that to get full credit!
- Make sure you remember to answer the above questions, and staple those answers to the back of your report.
- This lab report will need much more discussion/analysis than the previous report. In particular, you need to present/discuss/analyze the differences between the crude material (pre-recrystallization) and the purified material (following recrystallization). A four-column table, with the second column for the "Crude" and the third column for the "Purified" would be good. A first column should include the retention times for the three different structural isomers, and in the fourth column you should indicate which GC peaks were the ortho, meta, and para products.) The mass/yield changed; the melting range changed; and the GC purity changed dramatically. Why did they change? Should they have changed? Where did the "lost mass" go, and was it appropriate or was it a failure on your part that the mass decreased as it did? Present the data in an organized way, and discuss at least a little bit.

Basic GC-MS Operation Compressed Draft 3 For Chem 355 Organic Unknowns Lab

Note: The following assumes that the hydrogen and compressed air gases have been turned on; that the machine has been warmed up; that the gc/ms program has been opened; that an appropriate “method” and “sequence” have been selected; and that Jasperse will shut things down.

Sequenced Data Acquisition: Using the Autosampler to Sequence Runs Automatically

Note: this assumes that Jasperse has already prepared and started a “sequence” (“Grignard..” for example, but you are trying to add your sample to the lineup. If you’re first in line, get Jasperse to come and help.

1. **Add your sample to the back of the line in the autosampler.**
 - Do NOT leave any open holes (unless the sample belonging in that hole is being sampled.)
 - Filling a “sample-is-in-the-injector-tray” hole will cause a system freeze.
2. **Open “edit sequence” by clicking the “edit” icon on the yellow panel** low on the computer screen.
 - This will open a spreadsheet that you can edit.
 - Add your names in the “name” box that goes with your vial number.
 - **Click OK.** Note: if you don’t click “OK”, the machine will freeze at the end of the current run. NEVER leave the spreadsheet page open unless somebody behind you is going to close it.

Data Processing/Analysis: Getting and Printing the GC Graph, % Report, and/or Mass Spec.

- Note: data analysis can be done while acquisition is ongoing.
 - Note: this assumes that the “**gems data analysis**” software and appropriate analysis method are opened. In the data analysis page, check on the top blue line to see if it says “Enhanced data analysis-ADEFAULT-RTE.M...”, or “Grignards”, or something that fits the experiment for the week. If not, check with Jasperse or open it. (ex, Method > Load Method > Yes > ADefault-RTE.M > OK.)
3. **Open a data file** using the left mouse button to double click.
 - Your data file should be within the folder Organic Lab within the Data folder.
 - Data file will have the names “Vial-1” or “Vial-2”, so **remember which vial was yours.**
 4. **Printing GC Graph, % report, and retention times: Click Method>Run Method**
 - Repeat as many times as needed to provide prints for each student in your group.
 5. **Printing Mass Specs: Click the 2nd Hammer icon.**
 - Click the 2nd hammer icon as many times as needed to provide prints for each student in group.
 - Note: You don’t need to wait for a print to finish before clicking the hammer again. If you’ve got 5 partners, just click the hammer five times and the prints will come out one by one....

Library Matching: With a data file open (as described in #3 above):

6. **Right mouse double-click on a peak in the top window** to get its individual mass spectrum to appear in the lower window.
7. **Right mouse double-click on the mass spectrum to get a library search results**
 - Note: the library searches aren’t perfect and don’t always find the very best structure match.

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