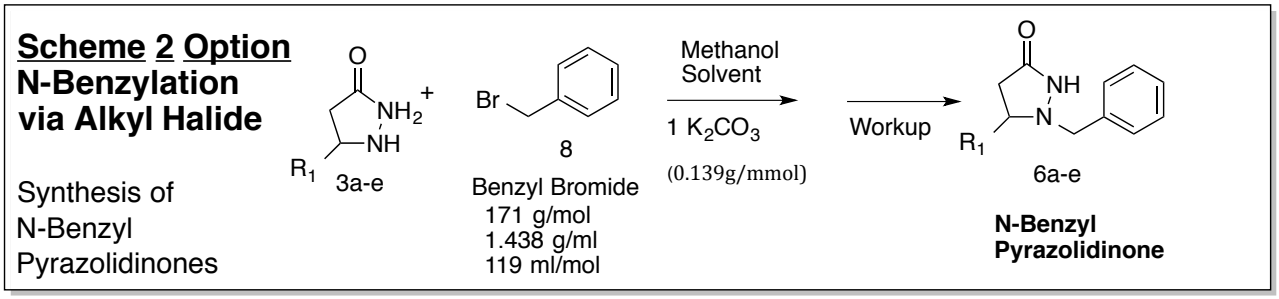


Scheme 2 Part A: Redissolve in Methanol

1. Turn hot plate to 5.
2. To the flask with your product 3 from Scheme 1, attach a condener with gentle water flow.
3. Add 15 mL of methanol.
   - For 4-methoxy compoud **3c**, you may need to add 20 mL of methanol, since the 4-methoxy substrates is probably less soluble.
4. Heat the mixture on the hot plate with the stirrer at 6 until the material dissolves and becomes completely homogeneous. Once it's dissolved, reduce the hot plate setting to 4.
   - If the stir bar isn't coming free even after several minutes, you may wish to detach the condenser and poke the stir-bar free with a spatula
   - Make sure that there aren't chunks or blobs of undissolved material on the outside. Everything needs to be dissolved.
5. Calculate 0.9 equivalents of benzyl bromide. Calculate how many mL of benzyl bromide (119 mL/mol) you need to add 0.90 mmol benzyl bromide per mmol of 3. In other words, if you have 20.0 mmol of 3c, how many mL of benzaldehyde will it take to provide 18.0 mmol?
   - You need to know how many mmol of reactant **3** you are working with. To do that, you needed to know your structure, your molar mass, and your actual number of grams. You should have recorded and saved all of this information at the end of Scheme 1.
   - The reason we're using less than an equal amount of benzyl bromide is because excess benzyl bromide leads to side products, and probably at least 10% (if not more) of your mass of reactant **3** is junk or side products or unreacted alkene **1** or something.
   - If time permits, also calculate how many grams of K_2CO_3 (0.139g/mmol) will be required to add 20 mmol of potassium carbonate.

Scheme 2 Part B: Addition and reaction of Benzyl Bromide

6. **Add K_2CO_3**: Add 20 mmol of potassium carbonate powder. (K_2CO_3, 0.139g/mmol) through a powder funnel.
   - You'll need to detach the reflux condenser while you do this. If your benzyl bromide is ready, you can immediately add that too. If not, reapply the reflux condenser.
   - Because the potassium carbonate is ionic, it won't dissolve in the methanol.
   - The function of the potassium carbonate is to deprotonate the proton that is originally on the nitrogen, but that gets replaced by the benzyl group
7. **Carefully/slowly add 0.90 equivalents of benzyl bromide** by syringe.
   - Benzyl bromide 0.1188 mL/mmol.
   - There may be some initial foaming; add slowly enough so that it doesn't foam up and foam over the flask.
   - Replace reflux condenser as soon as all the benzyl bromide has been added
   - Benzyl bromide smells bad and is a lachrymator. Avoid getting it on your hands or spilling any. The benzyl bromide should be returned to the main dispensing hood as soon as your are done adding it to your reaction.

8. Let the benzyl bromide reaction continue for **15 minutes**, with stirring (setting 3) and heat (setting 4). After the 15 minutes remove the hot plate.

Scheme 2 Part C: Taking an NMR Analysis of the Mixture

9. Use a long-stemmed pipet to draw out 1 inch of solution (2-3 cm) into the skinny end of a long-stemmed pipet, and add this to an NMR tube. Rinse the pipet into the tube with 0.8-1.0 mL of $CDCl_3$.
   - The volume of solution removed should go about half way up the skinny part of the pipet.
   - It doesn't matter if some solid K_2CO_3 gets carried along, but if you can try to draw from the liquid and not the suspended solid it will be preferable.
   - Most of the solution is methanol, not product. That's why we're using more solution, but we'll also need to do something so that the methanol doesn't just dominate the spectrum.
10. Submit the sample for NMR, using an experiment procedure referred to as "Suppress Methanol"

Scheme 2 Part D: Workup: DABCO and Separatory Funnel

11. Add 2 mmol of solid "DABCO" (diazabicycyloundecane) to the mixture, turn the heat off, and stir for **5 minutes**.
    - The purpose is to destroy any possible unreacted benzyl bromide.
12. Add 30 mL of a mixed solution that is 2/1 ether/dichloromethane.
    - For the 4-methoxy product **6b**, use 30 mL of dichloromethane instead of ether/dichloro. There may otherwise be some solubility problems with the methoxy substrate.
13. Add 20 mL of water, and stir vigorously for 30 seconds.
14. Pour the mixture into a separatory funnel.
15. Rinse the original reaction flask with an additional 10 mL of ether/dichloromethane, and add to the separatory funnel.
16. Wash the original reaction flask and stir bar with some water and then acetone. Let dry so it's ready to re-use soon.
17. After the separatory funnel layers have settled, separate the aqueous layer, which can be poured down the drain.
    - The product should remain in the colored organic layer.
    - It is important to drain out almost all of the water.
    - NOTE, for the 4-methoxy product **6b**, the dichloromethane layer should be on the bottom rather than the top. Otherwise the organic layer should float on top.
    - You may be wise NOT to pour anything down the drain right away, just in case you goof up and throw the organic layer away by mistake! You probably don't want to go back and start over from Scheme 1 again!
18. To the separatory funnel containing the organic solution, add 20 mL of ammonium chloride-water, shake gently, let settle, and separate again.
    - It is important to drain out almost all of the water.
19. Find your fritted filter funnel (the unit that has a 6-inch column, a white filter disk, a ground-glass joint on the bottom, and a vacuum vent.) Attach this to the Erlenmeyer flask with stir-bar.
20. Add 7 grams of silica gel (approximately) to the fritted filter funnel.
21. Add 20 grams of sodium sulfate to the fritted funnel, on top of the silica gel layer.
22. Pour your organic solution directly onto the sodium sulfate/silica filter.
    - If you have the methoxy compound **6b**, you can still directly pour your lower dichloromethane layer directly into the filter funnel, as long as you're careful to stop before the water layer comes.
23. Carefully open the vacuum so that it pulls the solution through the filter pack into the Erlenmeyer without causing excessive foaming or getting material sucked back up into the tube.

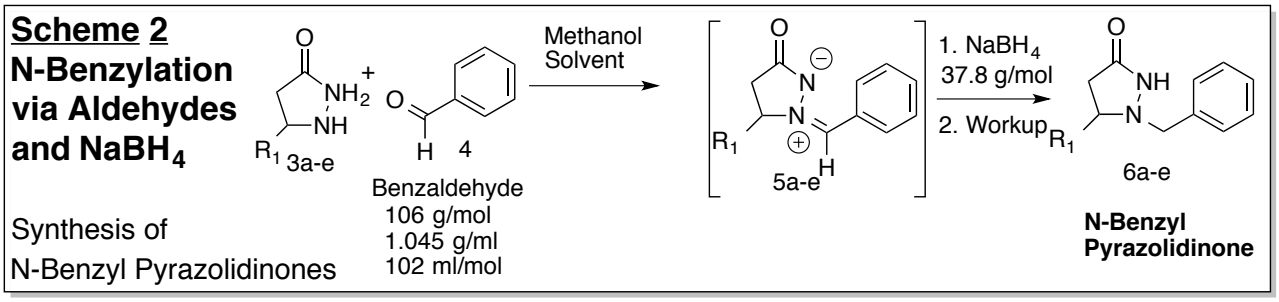
24. Get an additional 20-mL of the ether/dichloromethane mixture, and add 3 mL of methanol to that.
25. Pour this mixture into your separatory funnel (this will function as a rinse), and then drain it onto the filter column to rinse the filter pack as well.
    - This should ensure that all/most of the desired product comes through, so that your yield can be good.
    - Water and highly polar side products (including some containing boron) should stick to the column.
26. If you have methoxy 6b, add an extra dose of 10-mL dichloromethane and pour it into the separatory funnel without shaking. Then you can pour this second portion of organic solvent onto the filter funnel.

Scheme 2 Part E: Concentration

27. Attach a reflux condenser with a vacuum adaptor connected to a vacuum hose.
28. While stirring and with no heat turned on, very cautiously/slowly open the vacuum. Things will bubble a lot at first. Crack open the vacuum as aggressively as you can get away with without causing the mixture to foam over.
    - Within about 2 minutes you should be able to get the vacuum fully opened.
    - Notice the condensation (and perhaps ice) that forms on the outside of the flask.
    - This is a manifestation of how endothermic the vaporization process is.
29. Once the vacuum is wide open, turn the heat to 5 and vacuum for 15 minutes while stirring rapidly (set the stirrer to 6.)
    - Try to wipe off the frost from the walls as early as possible, this will make the solvent boiloff more efficient.
    - The mixture should be pretty thick and concentrated by the end, with limited bubbling.
    - In some cases, the material may foam up like cotton candy or taffy. This occurs when a limited amount of solvent is still present, but the mixture has gotten so thick that the solvent can't easily escape from its "shell" of non-volatile material. So when solvent molecules inside are vaporizing, but they can't escape easily, the volume puffs up as with cotton candy. With continued heating, though, usually any entrapped solvent does escape, and the material collapses back to a thick paste.
30. During the 20 minutes, do some calculations if you haven't before.
    - Draw out the structure of what your product **6** should be.
    - Given the structure, calculate what the molar mass of **6** should be, to the nearest whole number.
    - For atoms C, N, O, and H, you can just use their whole number masses in all calculations (in other words, C is 12, N is 14, O is 16, and H is 1. You don't need to use more detailed mass values than that, for example just use 1 rather than 1.0079 for H.)
    - For Cl, use 35.5, because that doesn't round off to a whole number so nicely as H/C/N/O.
    - Given the molar mass of your product, and given the mass and mmol of the reactant **3** that you started with, calculate what your theoretical yield in grams should be for product **6**.
    - The molar mass will also be needed for preparing your next reaction (Scheme 3).
31. After the vacuum-heating has completed, turn off your vacuum first, then turn off the heat, remove the flask from the heat, and detach the vacuum hose.
32. Immediately, while the mixture is still hot and hopefully liquid, dip in with a long-stem pipet and draw up a quarter inch of material. A glove to grip the not flask may help. Immediately place the pipet into an NMR tube. The material will probably harden/freeze as it cools.
33. Add 1.2-mL of CDCl3 into the pipet, then take the NMR tube with the pipet inside it over to the heat gun. With or without the instructor's assistance try to heat and melt your product so that

the solvent can flow into the NMR tube. Use a red cap for this one to remember that it's a priority sample.

34. Reach the long pipet in, and transfer the top quarter of NMR solution into a GC-MS vial. Submit this sample into the GC-MS queue. This should be labeled as "GC-6x" and refered to as "GC-6x" in your report. (Well, not really GC-6x, it should be 6a or 6b or 6c etc., depending on chemical you're really working with.)
35. Submit the NMR to the NMR queue for purity analysis.
36. The experiment will be called "proton 8".
37. Measure and record the mass of the flask. Given the original mass of the flask and stir bar, determine the yield of product in grams.
    - Record this on an extra sheet; save in your drawer. You'll need this for next week.
38. Given the structure of your product and the molar mass that you calculated earlier, determine the number of mmol of product that you made.
    - Record this on an extra sheet; save in your drawer. You'll need this for next week.
39. Calculate the percent yield, based on the number of millimoles you ended with and the number of millimoles that you began with in the overall 3 → 5 → 6 operation.
    - This is a record of the overall process: we started with 20 mmol of **3**; what percentage of that is now at **6**?
40. Also calculate the percent yield for Scheme 2, based on the number of millimoles of benzyl bromide you began with. Since we used 0.90 equivalents of benzyl bromide, that really can function as the limiting reactant.
    - This is a record of the Scheme 2 process.
41. Critical Note: Start the next reaction as described in Scheme 3 before week two is done. Before week two is completed, it is urgent that you get the final reaction started, see Scheme 3. This reaction takes at least several hours after it is begun, so you don't want to be trying to both start and finish it during the same lab period. Plus it requires time-consuming workup. So it is essential that it gets set up before the third lab period. If you don't get it started during the second lab period, you will want to/need to come in sometime at least a day before the final lab period to get it started.



Scheme 2 Procedure: N-Alkylation Using Aldehyde

Scheme 2 Part One: Reactant 3 → Intermediate 5

1. Turn hot plate to 5.
2. To the flask with your product **3** from Scheme 1, attach a condener with gentle water flow.
3. Add 10 mL of methanol.
   - For 4-methoxy compoud **3c**, you may need to add 20 mL of methanol, since the 4-methoxy substrates is probably less soluble.
4. Heat the mixture on the hot plate with the stirrer at 6 until the material dissolves and becomes completely homogeneous.
   - If the stir bar isn't coming free even after several minutes, you may wish to detach the condenser and poke the stir-bar free with a spatula
   - Make sure that there aren't chunks or blobs of undissolved material on the outside. Everything needs to be dissolved.
5. Calculate 0.9 equivalents of benzaldehyde. Calculate how many mL of benzaldehyde (102 mL/mol) you need to add 0.90 mmol benzaldehyde per mmol of **3**. In other words, if you have 20.0 mmol of **3c**, how many mL of benzaldehyde will it take to provide 18.0 mmol?
   - This will require that you have already calculated how many mmol of reactant **3** you are working with. To do that, you needed to know your structure, your molar mass, and your actual number of grams. You should have done all this earlier, but if not do it now.
   - The reason we're using less than an equal amount of benzaldehyde is because excess benzaldehyde leads to side products, and probably at least 10% (if not more) of your mass of reactant **3** is junk or side products or unreacted alkene **1** or something.
   - If time permits, also calculate how many grams of NaBH4 (37.8 g/mol) will be required to add 0.5 mmol of sodium borohydride per mmol of **3**.
     - For example, if you calculate 18 mmol of **3,** you would add 9 mmol of $NaBH_4$.
     - Note: if you calculate more than 0.5 gram, you've made a calculation error.
6. After the material has dissolved, reduce the hot-plate setting to 4.
7. Use the syringe to directly add the benzaldehyde to your reaction mixture while stirring.
   - You'll want to detach the condenser first in order to inject.
8. Reattach the reflux condenser, and stir for 15 minutes.
9. Turn the heat off, and add an ice-water bath (use one of the metal pans) to cool your sample for at least two minutes.
10. While it's cooling, remove the condenser, use a long-stem pipet, and carefully draw up about 1/2 inch (2 cm) of sample into the skinny part of the pipet. Transfer it to an NMR tube, and add 1 mL of CDCl3.
    - Do not run a GC on this.
    - This can be submitted for a proton NMR as soon as possible.
    - The NMR experiment to run is called "Suppress-Methanol", and is found under the UserStudies experiment folder. It will actually produce two NMR printouts for you. The first one will be dominated by methanol, since you have more of that than of your actual

product, and can be thrown away. But the second NMR will have "suppressed" the methanol and will give you a more meaningful NMR.

- If you compare your **NMR-5x** with your **NMR-3x**, do you see signals where **3** gave signals? If not, it proves that your reactant **3** has completely converted to intermediate **5**.
- In structure **5**, the beta-hydrogen is now next to a nitrogen that is cationic and is doubled bonded. The beta-hydrogen should now move further downfield than it was before. Usually it will be a 4-line "doublet-of-doublets" signal. (For more discussion on the NMR's, see later section in the manual and see the movie.)
- Do not wait to check the NMR before proceeding ahead with the next operation, the intended conversion of **5 → 6**

Scheme 2 Part Two, using NaBH4: Intermediate **5** → N-Benzyl Product **6** via Sodium Borohydride Reduction Reaction

11. If you haven't already done so, based on the calculated number of mmols that you used for your chemical **3**, calculate how many grams of sodium borohydride (37.8 g/mol) you need to add 0.5 mmol sodium borohydride per mmol of **3**.
    - For example, if you calculate 18 mmol of **3,** you would add 9 mmol of $NaBH_4$.
    - Note: if you calculate more than 0.5 gram, you've made a calculation error.
    - NaBH4 has four hydrides, that's why you don't need very many moles.
12. Weigh the sodium borohydride out on a small boat.
    - If there are any big chunks, use another boat, place it on top of your NaBH4 boat, and press down to crush and break up the chunks.
13. Put a powder funnel into the neck of your beaker.
14. Carefully add the sodium borohydride to your stirring solution.
    - Add about half of your $NaBH_4$ first, and stir for 15 seconds or so while the foaming settles a bit, and then add the rest.
    - Some hydrogen gas is produced as a side reaction, and causes the bubbling/foaming. When a hydride reacts with a proton it produces H2.
15. Attach a reflux condenser with gently flowing water, turn the hot plate to 5, and stir (setting 3).
16. Watch for when the mixture gets hot enough to begin boiling, and stir for 10 more minutes after that.
17. Cool your flask for 2 minutes in an icewater bath before continuing with the next workup/isolation.

Scheme 2 Part Three: Workup/Isolation of N-Benzyl Product 6 (Week Two Begins Here)

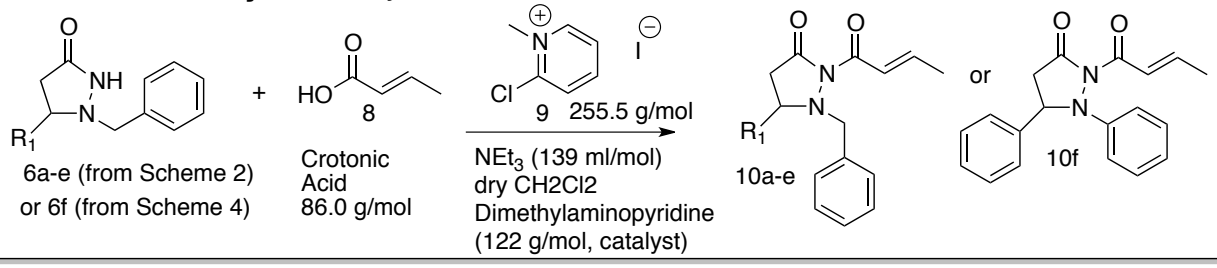
18. Add 30 mL of dichloromethane.
19. Add 20 mL of brine (NaCl/water) and 20 mL of water.
20. Stir vigorously for five minutes.
21. Pour the mixture into a separatory funnel, and allow the layers to settle.
22. Add an additional 10 mL of dichloromethane to the original reaction flask, and an additional 10 mL of brine, and add the mixture into the separatory funnel. This should rinse out any residual material.
23. After the layers have settled, the product should be in the colored bottom organic layer.
24. There may be a bunch of solid material that doesn't dissolve in either layer. This is probably unwanted contaminant, and it's not a problem so long as it doesn't obscure recognition of the layers, or obstruct the flow of the bottom organic layer out the stopcock later on.
    - However, if there is too much solid material to proceed, then one solution is to pre-filter the whole mixture through a large Buchner funnel with filter paper, directly into a filter flask. (Like you would for a regular recrystallizaion filtration.) Then pour the filtrate back into the separatory funnel and proceed. If you do this, tell the instructor; he might be interested in seeing how much solid is present, and perhaps trying to analyze to see what it actually is!
25. Clean the flask/stirbar you've been using. To re-use, rinse the flask with water, scrub quickly with a brush, and then rinse with acetone. If you want you can quickly semi-dry it by blowing air into it. But it won't hurt if there is still acetone.
26. Find your fritted filter column (the unit that has a 6-inch column, a white filter disk, a ground-glass joint on the bottom, and a vacuum vent.) Attach this to the Erlenmeyer.
27. Weigh out 10 grams of silica, and pour this into the fritted filter column.
    - The weight here does not need to be super precise.
28. Weigh out 20 grams of sodium sulfate, and pour this into the fritted column on top of the silica gel layer.
29. Carefully pour your organic layer from the separatory funnel directly onto the sodium sulfate filter. Be careful to stop before the water layer comes.
    - Try to do this without badly pitting the filter layers, especially the lower silica layer.
    - If you have too much "undissolved" junk in your mixture, and it's settling into the bottom and plugging your separatory funnel, it may help to poke it or stir it up with a long pipet.
30. Carefully open the vacuum so that it pulls the solution through the filter pack into the Erlenmeyer without causing excessive foaming or getting material sucked back up into the tube.
31. Get an additional 20-mL of a 2:1 ether/dichloromethane mixture, and add 3 mL of methanol to that.
32. Pour this mixture into your separatory funnel (this will function as a rinse), and shake things up again. The organic layer should now be the top layer, with water on the bottom.
33. Drain the aqueous layer out into a beaker. (This will later be thrown away, but don't throw anything yet, just in case a mistake was made.)
34. Then drain the ether/dichloromethane/methanol layer onto the filter column to rinse the filter pack as well.
    - This should ensure that all/most of the desired product comes through, so that your yield can be good.
    - Water and highly polar side products (including some containing boron) should hopefully stick to the column.

35. **Concentrate of the solution**. Attach a reflux condenser with a vacuum adaptor on top, but with no water flowing. While stirring and with no heat turned on, very cautiously/slowly open the vacuum. Things will bubble a lot at first. Crack open the vacuum as aggressively as you can get away with without causing the mixture to foam over.
    - Within about 2 minutes you should be able to get the vacuum fully opened. Continue to vacuum with the condenser attached for two more minutes.
    - Notice the condensation (and perhaps ice) that forms on the outside of the flask.
        - This is a manifestation of how endothermic the vaporization process is. Rotary evaporation can be used, or if the rotovap is occupied you can try to just distill off the solvent in your hood.
36. After two minutes with the vacuum wide open, turn the vacuum off, and detach the vacuum hose from the vacuum adapter. Remove the condenser, reattach the vacuum hose to the adapter, and connect the adapter directly to the flask. Again while stirring, carefully crack open the vacuum until it is wide open. Once you've been able to safely open the vacuum fully, turn the hot plate on at a setting of 5, and heat/boil/vacuum the mixture while stirring rapidly (set the stirrer to 6.)
37. Plan this distillation for 30 minutes. As it goes, watch for when most of the solvent is gone, and perhaps where you can wipe the frost off without having any more form, and make an estimate in your lab report. Essentially at least 15 minutes where it's really hot should be enough to boil off most of the benzyl alcohol side product and all of the benzaldehyde dimethyl acetal. But if it's still cold after 20 minutes, then the 30 minutes will probably be insufficient.
    - Try to wipe off the frost from the walls as early as possible, this will make the solvent boiloff more efficient.
    - The mixture should be pretty thick and concentrated by the end, with limited bubbling.
    - In some cases, the material may foam up like cotton candy or taffy. This occurs when a limited amount of solvent is still present, but the mixture has gotten so thick that the volatiles can't easily escape from the "shell" of non-volatile material. So when molecules inside are vaporizing, but they can't escape easily, the volume puffs up as with cotton candy. With continued heating, though, usually any entrapped vapor does escape, and the material collapses back to a thick paste.
38. During the 30 minutes, do some calculations if you haven't before. (You may have done this earlier.)
    - Draw out the structure of what your product **6** should be.
    - Given the structure, calculate what the molar mass of **6** should be, to the nearest whole number.
    - For atoms C, N, O, and H, you can just use their whole number masses in all calculations (in other words, C is 12, N is 14, O is 16, and H is 1. You don't need to use more detailed mass values than that, for example just use 1 rather than 1.0079 for H.)
    - For Cl, use 35.5, because that doesn't round off to a whole number so nicely as H/C/N/O.
    - Given the molar mass of your product, and given the mass and mmol of the reactant **3** that you started with, calculate what your theoretical yield in grams should be for product **6**.
    - The molar mass will also be needed for preparing your next reaction (Scheme 3).
39. After the vacuum-heating has completed, turn off your vacuum first, then turn off the heat, remove the flask from the heat, and detach the vacuum hose.
40. Immediately, while the mixture is still hot and hopefully liquid, dip in with a long-stem pipet and draw up a quarter inch of material. A glove to grip the not flask may help. Immediately place the pipet into an NMR tube. The material will probably harden/freeze as it cools.

41. Add 1.2-mL of CDCl3 into the pipet, then take the NMR tube with the pipet inside it over to the heat gun. With or without the instructor's assistance try to heat and melt your product so that the solvent can flow into the NMR tube. Use a green cap for this one.
42. Reach the long pipet in, and transfer the top quarter of NMR solution into a GC-MS vial. Submit this sample into the GC-MS queue. This should be labeled as "GC-6x" and refered to as "GC-6x" in your report. (Well, not really GC-6x, it should be 6a or 6b or 6c etc., depending on chemical you're really working with.)
43. Submit the NMR to the NMR queue for purity analysis.
    - The experiment will be called "proton 8", but this should be available by default, if a previous student left the NMR in "submit" mode, or it will be called up automatically if you click "New Study" to enter the "submit" mode.
44. Measure and record the mass of the flask. Given the original mass of the flask and stir bar, determine the yield of product in grams.
45. Given the structure of your product and the molar mass that you calculated earlier, determine the number of mmol of product that you made. You will need this for Scheme 3.
46. Calculate the percent yield, based on the number of grams you ended with compared to your theoretical yield in grams.
47. **Critical Note**: **Start the next reaction as described in Scheme 3 before week two is done**. Before week two is completed, it is urgent that you get the final reaction started, see Scheme 3. This reaction takes at least several hours after it is begun, so you don't want to be trying to both start and finish it during the same lab period. Plus it requires time-consuming workup. So it is essential that it gets set up **before** the third lab period. If you don't get it started during the second lab period, you will want to/need to come in sometime at least a day before the final lab period to get it started.

Notes: Benzaldehyde acetal boils off pretty thoroughly in the 20 minutes at HP=5
Benzyl alcohol boils off significantly, but not completely. Alyssa and Nicole had a bunch, heated it for another 10 minutes, and most but not all was gone. So extra time would help.

Scheme 3: N-Acylation Synthesis of N-Crotonates



Scheme 3 Procedure: N-Acylation of Pyrazolidinone 6a-f Using Crotonic Acid and Mukayama's Reagent (9)

Scheme 3, Part 1: Starting the Reaction for N-Acylation, 6 → 10

1. Determine the number of mmol of pyrazolidione **6** that you have in your Erlenmeyer.
   - You should have calculated your mass yield, as well as the molar mass and the number of mmol for your version of **6**, during the previous Scheme.
   - Note: Your substrate **6** might be somewhat contaminated, so you may not actually have as many mmol of **6** as you calculated based on mass alone.
2. Add 25 mL of dry anhydrous CH_2Cl_2
   - add a white rubber septum to exclude air, if you aren't ready to continue with following steps very quickly.
3. Hopefully the sample will dissolve on it's own within a few minutes. If not, you may wish to add a reflux condenser and heat the mixture (hot plate 5) until it dissolves. If you did heat it, to facilitate dissolving, then turn the hot plate off as soon as things are dissolved, and take the flask away from the hot plate to cool for 5 minutes.
4. Based on how many mmol of pyrazolidinone **6** you have, add 1.1 equivalents of crotonic acid **8** (86.0 g/mol).
   - In other words, if you have 10 mmol of **6**, add 11 mmol of **8.**
5. Then add 1 mmol of dimethylaminopyridine (122.2 g/mol). This is a catalyst, so the exact amount isn't crucial, and we're using a lot less of this than of the other reactants.
6. Weigh out and add 1.3 equivalents of 2-chloro-1-methylpyridinium iodide (Mukayama's Reagent, **9,** 255.6 g/mol).
   - Immediately reclose the bottle from which you took reagent **9**, since it is moisture sensitive. If you leave it uncovered, it will go bad and everybody who uses it after you will have problems.
7. Record all of your observations. (Is the mixture homogeneous or heterogeneous, etc.)
8. Syringe in 2.8 equivalents of triethylamine (139 mL/mol).
   - This will get the reaction started.
   - Record observations. Does anything happen? Exotherm or anything? Color change? Solubility changes?
9. Add a septum into your flask, and poke a syringe needle through it to serve as a pressure vent.

THIS IS AN IDEAL PLACE TO STOP AT THE END OF WEEK TWO. LET THINGS STIR FOR 5 MINUTES, MAKE SURE THERE IS A SEPTUM TO YOUR FLASK WITH A SYRINGE NEEDLE POKING IN TO SERVE AS A PRESSURE VENT, AND STASH IT IN YOUR DRAWER TILL NEXT WEEK.

10. Emergency Note: If you don't get this far during week two, be sure that you come in and get the reaction set up at least a day before your lab period.

Scheme 3, Part Two: Workup/Isolation of Product 10 (Week Three Begins Here)

11. Weigh out 3 equivalents (relative to your reactant **6**) of solid ammonium chloride (0.0535 g/mmol), and dissolve it into 50 mL of tap water.
    - It's possible that there will be an NH_4Cl/water mixture already prepared.
12. Get about 45 mL of ether.
13. Pour about half of the ether and about half of the NH_4Cl/water into your reaction flask. Stir the mixture for a minute.
14. Pour the contents of your reaction flask into a separatory funnel.
15. Add the rest of the ether and NH_4Cl/water into your Erlenmeyer, rinse them around, and then add that to your separatory funnel.
    - The purpose of the NH_4Cl /water wash is to convert the neutral triethylamine into ionic triethylamine-hydrochloride, which will extract into the aqueous layer.
16. Shake cautiously, with venting, then allow the mixture to settle.
    - The organic layer will probably be more strongly colored
    - The top layer will normally be the organic layer, but if you aren't sure, add some extra water to see which layer gets bigger.
    - If the layers separate poorly, consult the instructor and we can improvise.
17. Prepare a clean 125-mL Erlenmeyer flask with a ground-glass joint, with a long stir bar inside, and with the mass of the combination recorded.
    - This could be the same flask/stirrer you've used and weighed before. If so, clean it by rinsing/brushing with water, then with acetone.
18. Find a fritted filter column (the one with the 6-inch column above a white fritted filter, with a ground-glass joint on the bottom, and with a vacuum connector on the side.)
19. Weigh out 20 g of silica, pour it into the filter funnel, and attach the filter funnel into the 150-mL Erlenmeyer.
    - This is a lot more silica than was used in Scheme 2. When the dry silica is poured into your fritted filter column, it should fill about half of the space from the frit to the top of the column. If not, consult instructor. If the column is too short, contaminants will get through.
    - The silica layer is meant to absorb some polar, sticky byproduct from the Mukayama Reagent **9**, and also any triethylamine hydrochloride that did not get removed by the separatory funnel treatment. We are doing a crude but rapid "flash chromatography" to try to partially purify your product **10**.
20. Weigh out 30 g of sodium sulfate, and pour this on top of the silica bed.
    - The sodium sulfate will function to absorb water.
21. Assuming the top layer in the separatory funnel is the organic phase, carefully drain out the lower aqueous layer into a beaker, and pour the organic solution onto the filter column.
    - Try to pour it carefully/evenly so that the surface of the column doesn't get all pitted. If pouring it in makes a big pit, the effective length may be compromised.
    - If you scissor-cut a piece of filter paper to kind of lay on top of the sodium sulfate, that can help to protect against pitting. Probably not needed.
22. Carefully/gradually open up the vacuum so that liquid gets pulled through without boiling out and getting sucked into the vacuum tube.
23. Pour the aqueous phase back into the separatory funnel. Add an additional 25 mL of 2/1 ether/dichloromethane, and shake it up briefly. The organic layer will probably again be the top layer. If so, pour off the aqueous layer into a beaker (this will get thrown away), and then pour the organic phase onto the filter column. Rinse this through the filter column to try to make sure that no desired product is left stuck on the silica.
24. **Concentrate this solution**. Attach a reflux condenser with no water flow, and with a vacuum adaptor on top. While stirring and with no heat turned on, slowly open the vacuum. Things

will bubble a lot at first. Crack open the vacuum as aggressively as you can get away with without causing the mixture to foam over.
- Within about 2 minutes you should be able to get the vacuum fully opened.
- Notice the condensation (and perhaps ice) that forms on the outside of the flask.

25. Once you've been able to safely open the vacuum fully, turn the hot plate on at a setting of 5, and heat/boil/vacuum the mixture while continuing to stir (setting 6) for 20 minutes.
    - Try to wipe off the frost from the walls as early as possible.
    - The mixture should be pretty thick and concentrated by the end, with limited bubbling.
    - In some cases, the material will foam up like cotton candy or taffy. With continued heating, though, usually the entrapped solvent does escape, and the material collapses back to a thick paste.
26. After the vacuum-heating, turn off your vacuum first, then turn off the heat, remove the flask from the heat, detach the vacuum hose, and remove the condenser.
27. Immediately, while the mixture is still hot and hopefully liquid, dip in with a long-stem pipet and draw up a quarter inch of material. Immediately place the pipet into an NMR tube. The material will probably harden/freeze as soon as it cools.
28. Use 1.0 mL of CDCl3 to make up your NMR sample. Add a red cap to this one.
    - We won't run a GC on this one. The product is so big that it doesn't vaporize well.
29. Submit your NMR-**10** to the NMR queue.
30. See the section about NMR's to review expectations in terms of data, analysis, and presentation.
31. Weigh your flask, so that you can determine mass, millimoles, and percent yield.
    - It is well possible that your mass recovery will exceed your theoretical yield. That would be impossible if the material was all and only desired product **10x**. But there were a lot of side products, and solvents, to try to remove in a short purification sequence. If the yield exceeds 100%, perhaps by a lot, that's evidence that the purification/distillation was imperfect. (Perhaps badly so….)

Yield Analysis: Calculate the % yield for both the final step, but also for the overall process. (If every step of the synthesis had worked perfectly, you'd end up with 20 mmol of product. So 20 mmol is your theoretical number of moles.)

Scheme 3 Part Three: Cleaning Up and Pooling Products

1. BE SURE THAT YOU'RE PUTTING YOUR PRODUCT INTO THE CORRECT CONTAINER. WE DON'T WANT ANY **10a** GOING INTO THE **10b** CONTAINER, ETC.

2. IF POSSIBLE, AND IF YOU'VE GOTTEN AN NMR FOR YOUR PRODUCT, SHOW IT TO THE INSTRUCTOR BEFORE PUTTING YOUR PRODUCT INTO THE COLLECTION JAR. IF YOUR STUFF IS JUNK FOR SOME REASON, WE DON'T WANT IT TO BE CONTAMINATING THE GOOD PRODUCT CONTRIBUTED BY OTHER STUDENTS.

Process for transferring your product into the collection jar:

1. Add 10 mL of dichloromethane to your flask, and try to dissolve up all of your product with that. If that doesn't succeed, try heating the mixture on a hot plate for a few minutes to facilitate solubility, and/or perhaps add some additional dichloromethane.
2. Once the product is dissolved, simply pour the solution into the appropriately labeled collection jar.
    - Make sure you're putting your stuff into the correct jar!