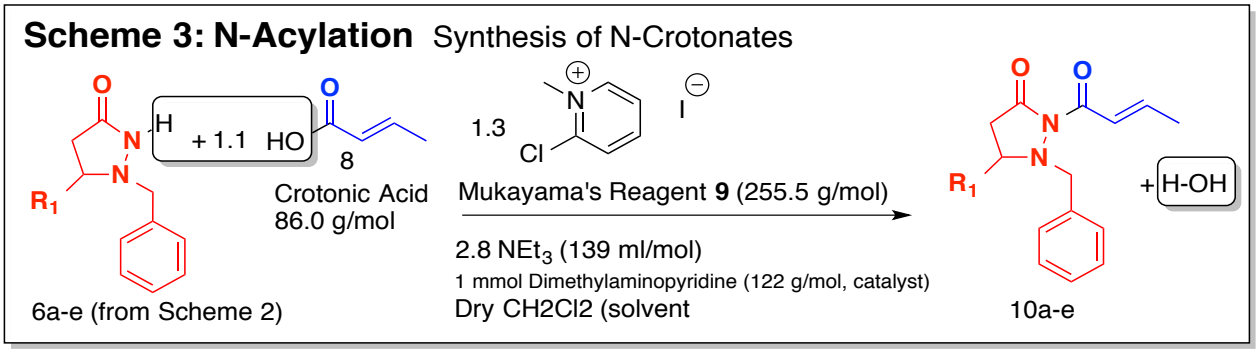

Scheme 3 Procedure: N-Acylation of N-Benzyl Pyrazolidinone (6a-e) Using Crotonic Acid (8) and Mukayama's Reagent (9)

- Start new Scheme 3 lab report here

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**, at the end of Scheme 2.
   - 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 and stir. (The correct bottle will have "molecular sieves" pellets to sponge up any water, and the label should say "Anhydrous" or "dry".)
   - Add a rubber septum to exclude air (and the water that it's in the air), if you aren't ready to continue with following steps very quickly.
   - 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.
3. Add 1.1 equivalents of solid crotonic acid **8** (86.0 g/mol). (Based on how many mmol of pyrazolidinone **6** you have.) (The crotonic acid should be by one of the balances.)
   - In other words, if you have 10 mmol of **6**, add 11 mmol of **8.**
4. 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.
5. 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 subsequent users will have problems.
   - Mukayama's reagent functions to stimulate and absorb loss of H-OH from reactants **6** and **8**.
   - The "excess" is to absorb any trace water on the glassware, from the air, or in the solvent.
6. Record all of your observations. (Is the mixture homogeneous or heterogeneous, etc.)
7. Syringe in 2.8 equivalents of triethylamine (139 mL/mol).
   - This will get the reaction started.
8. 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.
10. **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.**

- 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. Add 50 mL of aqueous NH_4Cl/water solution (already prepared, in the hood).
12. Get about 45 mL of ether (possible labeled as ether "ether" or "diethyl 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 250-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 did the Scheme 3 reaction in, and whose mass you have previously recorded. 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 250-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 pile 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.
    - If you can't tell which layer is which, and if your sep funnel has space, add in either an extra 20 mL of brine and/or an extra 20mL of ether to try to help clarify.
22. Carefully drain the organic solution onto the filter column, evenly so that the surface of the column doesn't get all pitted. (Pitting may compromise the effective length/function.)
    - 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.
23. Carefully/gradually open up the vacuum so that liquid gets pulled through without boiling out and getting sucked into the vacuum tube.
24. Pour the aqueous phase back into the separatory funnel.
25. 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.
26. Pour off the aqueous layer back into the same beaker (this will get thrown away)
27. Drain the organic phase through the filter column. Purpose: this extra rinse of the filter column should remove more of the desired product otherwise still absorbed on the silica.

- Waste handling: all of the solid silica and sodium sulfate in your filter column should go into a solid-waste container in the hood. Bulk may NOT go into the sink or garbage. (Trace amounts stuck on wall may.)

28. **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/carefully 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.
29. 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.
30. 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.
31. **NMR-Sample Preparation**: 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.
32. Add 1.0 mL of $CDCl_3$ as solvent to your NMR sample.
    - We won't run a GC on this one. The product is so big that it doesn't vaporize well.
33. Submit your NMR-**10** to the NMR queue.
34. **Mass/Yield**: 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 **10**. 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….)
35. **Yield Analysis**: Calculate the % yield for both the final step (Scheme 3), but also for the overall process. (If every step of the synthesis had worked perfectly, you'd end up with 17 mmol of product. So 17 mmol is your theoretical number of moles overall.)

Scheme 3 Part Three: Cleaning Up and Pooling Products into the Collection Jars

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 an additional 10mL of 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

3. 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. ☺
4. BE SURE THAT YOU'RE PUTTING YOUR PRODUCT INTO THE CORRECT CONTAINER. WE DON'T WANT ANY **10a** GOING INTO THE **10b** CONTAINER, ETC.

NMR Analysis/Interpretation. Concepts and expectations are similar to the Scheme 1 report.

1. An **abbreviated summary report** process will again be required. Draw the structure and label the different carbons. Then make a table with the chemical shifts for the actual **non-aromatic, non-alkenyl C-H's**, and by each one write the letter of the carbon to which it is attached. This will demonstrate that you have analyzed and understand your spectrum.
   - **Also include integration**.
   - But you do not need to analyze/report the splitting (although you may do so.)
   - Which signal is from the β-H, which from the α-H's, which are the benzyl H's, and which the crotonate methyl?
   - Which signals are the methyls or methoxy signals in **3b, 3c,** and **3e?**
   - Does your product look reasonably pure?
2. **Does your NMR confirm that the reaction, and the solvent-removal basically worked**?
   - Does it look like your starting reactant **6** is still present, or gone?
   - Does it look like there is significant amount of solvent left? (Dichloromethane leaves a singlet at about 5.3 ppm.)
3. **The Crotonate Methyl Doublet:** If the reaction worked and you attached the new crotonate portion, that should introduce a new methyl group into your NMR that was not present in **6**. Because the new CH_3 group is attached to an alkene, and there is one H on the neighboring alkene, **the new methyl group should be a 3H doublet. It's allylic, but it's chemical shift will typically be around 1.9 ppm (just underneath 2).**
   - The present of the methyl doublet is the clearest signature for formation of product **10**
   - Ideally there will be one pretty clean doublet around 1.9. Extra doublets in that area reflect impurities. (Other contaminants may also have been "crotonated".)
4. **Chirality, H-non-equivalency, and chemical shift**: The chirality of the β-carbon makes the two β-H's and the two hydrogens on the benzyl carbon nonequivalent.
5. **Chirality, H-non-equivalency, and splitting**:
   - Each of the two α-hydrogens will usually appear as a four-line "doublet of doublets".
   - The β-H will typically also look like a 4-line "doublet of doublets", unless further split by the methyl group in **3e**.
   - The two benzyl H's are each split by each other, so each should look like a doublet.
6. For some of the samples **10**, you will see some **surprising changes in the splitting for the α- and β-hydrogens**. In some 5-membered rings, hydrogens which are trans to each other don't actually split. So it's possible that your β-hydrogen will be a doublet rather than a doublet-of-doublets, because it's split by the cis α-hydrogen but not by the trans α-hydrogen. Likewise it may be that one of the α-hydrogens will be 4-line doublet-of-doublets (the cis α-hydrogen, which is split by the β-hydrogen and the other α-hydrogen.) But the other α-hydrogen might be a simple doublet, split only by the other α-hydrogen but not by the β-hydrogen.
7. For your reports, **account for all and only the hydrogens connected to sp^3 carbons.** You don't need to discuss/present N-H hydrogens **or alkenyl hydrogens** or aromatic hydrogens . (There are so many overlapping aromatic H's that they aren't interpretively useful in this case.)
8. **Signature signals**: As mentioned above, inclusion of a new allylic methyl doublet around 1.9 ppm is diagnostic of product formation. All of the samples **10** will also have the interesting α- and β-hydrogens, and the benzyl hydrogens (5 hydrogens combined, in addition do the 3H crotonate methyl.) But there will be other additional signature methyl peaks for **6c**; **6b**; and **6e**.
9. **Signal Movement**: Notice that the α- and β-hydrogens, and the benzylic hydrogens have moved again. The chemical environment may be similar to in previous structures **3** and **6**, but the environments are not identical, so the chemicals shifts move to varying extent.
10. **Chemical shift logic**:

- The α-hydrogens, being next to a carbonyl, but being also β to nitrogen and perhaps also an aromatic, should fall in the high 2's or perhaps the low 3's.
- The β-hydrogen in **3a-3d** should show up around the low 4's. For the β-hydrogen in **3e**, we'd anticipate the β-hydrogen to show up in the 3's.
- For the benzyl hydrogens, they are on a carbon that has both a nitrogen (+2) and a benzene (+1) attached, so we'd expect them to come around the low 4's or high 3's as well.
- The crotonate methyl doublet is allylic, so you might expect it in the 2's. In reality, it is likely to "overlap" into the 1.8-2.0ppm region.

11. **The two alkene hydrogens** should actually appear probably in the high 6's, or perhaps even overlapping with the aromatic signals in the 7's. The electronic impact of the strongly electron-withdrawing carbonyl group on the alkene has a strong deshielding impact. You can ignore these in your simplified summary report.
12. **Impurities/contamination**: Recognizing which signals come from the desired product and which do not is again significant.
    - Remember that there should be a logical integration ratio for the main H's in product **10**
    - Between carry-over contaminants, the dimethylaminopyridine, the large excess of triethylamine, and the excess of Mukayama's reagent, there were a lot of other chemicals in your Scheme 3 mixture. It won't be surprising if the cleanup procedure didn't remove all of them. So your mix could be fairly contaminated at this point.
13. **Likely contaminants**:
    a. Unconverted starting material **6**.
    b. Residual solvents that didn't all boil off.
        a. Dichloromethane gives a singlet at around 5.28 ppm.
        b. Ether gives a quartet in the 3's and a triplet in the low 1's.
        c. Triethylamine, which gives a triplet in the low 1's and a quartet in the upper 2's.
    c. Carry-over contaminants that were already in reactant **6**. (Garbage in, garbage out).
    d. Material from the Mukayama reagent **9**. The intent is that the silica will have retained all of that, but maybe not entirely?

    a. If your NMR-**10** looks highly contaminated by solvents, it's possible that another 5 minutes of vacuum at hot-plate setting of 5 while stirring vigorously might get rid of some of the contaminants.
14. **Comparison to Other NMR's**: It may be very interesting to look at how your NMR **6** looks compared to how other NMR's look.
    - How different is your **10** from the **6** that you began with in Scheme 3?
    - How different is your **10** compared to classmates who made different versions of **10**?
    - How clean is your NMR compared to that of classmates who made the same version of **10**?
15. **GC-MS: NOT REQUIRED.** None for product **10**. Some of the larger versions are getting so big so that it's hard to vaporize them, as needed for gas chromatography. And for some the injector needs to be so hot in order to vaporize them that they partially decompose under such hot temperatures, in which case the purity-measurement becomes confusing or misleading.

Scheme 3/Week 3 Lab Report + Overall Project Data Summary:

- For this week, I want both a synthesis-style lab report for Scheme 3, AND a summary report and collection of all of your NMR's/GC's.

1. Write a standard synthesis style lab report for your Scheme 3 reaction (**6 → 10**);
2. Make sure that all structures are drawn explicitly.
   - As always for a synthesis style report, you'll want to draw out the reactants and the products. In this case, be sure you draw your **actual** reactant **6** and product in your reaction.
   - None of your pictures should have an "R1": you should illustrate each structure with your actual R1 group drawn, whether that's methyl or phenyl or 4-methoxyphenyl or whatever.
3. Show all calculations. (Including any mole => mass for reactants or products)
4. When listing your chemicals/reactants and showing gram → mol calculations, make sure that you include your main reactant **6**!
5. Include procedural details.
6. For this report, you can skip the observations, just to keep the report shorter and since you've written up enough of these by now.
7. Calculate mass yields, and percent yields, etc., for product **10**.
8. Include your **NMR-10**, with clear labels, structures drawn, **and the abbreviated summary report** for non-aromatic and non-alkenyl C-H hydrogens for **NMR-10**. But assuming you hand in both your Scheme 3 report and your Data-Summary report at the same time, you could just include the NMR with the data-summary packet.
9. Include a results/data/discussion/analysis section. The analysis/discussion section needs to address what the yield information told you, and what the NMR data tells you about both the success and the efficiency of your reaction, and the purity of your product **10**.
   - The results/data/discussion/analysis section should summarize what the mass/yield/NMR data is, and what conclusions can be drawn from them. Just attaching the NMR without discussing or showing that you understand them will not be good. What is the summary for the key non-aromatic, non-alkenyl C-H hydrogens in your NMR? Does the NMR show that all of reactant **6** reacted, or is there still some reactant **6** left showing up in your NMR? Can you see how your carryover hydrogens, hydrogens that were already in reactant **6** and are still in product **10**, all have variably changed chemicals shifts? (The α- and β–hydrogens and the benzylic hydrogens). Does your product **10** look reasonably clean, or is it obviously significantly contaminated? Does it look cleaner or more contaminated than the reactant **6**? If it's less clean, is it much more contaminated, or only modestly more so? Was the yield respectable, or terrible?

Overall Project Data Summary:

1. Fill out the overall project data sheet on the following page.
2. Attach copies of all NMR's and GC-MS's.

Final Report Data Sheet.

1. Which Series Did You Make? (a,b,c,d,e..)_____ _____ _____

2. GC Results Table:

Substrate ID (ex **3a** or **3b…**)	Retention Time	Product Purity	Did the molecular ion show in the mass spec?	Retention Times and %'s for 3 Largest Impurities (if you have 3…)
3				
6				

- the molecular ion is the "molecular weight" ion, basically the unbroken molecule

3. Mass and % Yields Results Table:

Substrate ID	Molar Mass	Yield in grams	Yield in mmol	% yield
3				
6				
10				

4. NMR Results Table.

- Unless the header indicates otherwise, enter the chemical shifts.
- Some of the boxes will be blank, depending on the structure. For example, products **3** don't have any benzyl hydrogens yet. And only the "e" family has a methyl group attached to the β-carbon.

Substrate ID	β-H	α-H's (list both)	Benzyl H's (list both)	Methyl Doublet (in "e" series)	4-Methyl Singlet (in "b" series)	4-methoxy Singlet (in "c" series)	Crotonate Methyl group (only in product **10**)
3			-None				None
6							None
10							

5. Draw Structures for your Three Substrates: (may do on back if you want more space)

3 **6** **10**

6. Attach labeled NMR's and GC-MS's for products 3, 6, and 10. Include standard summary reports on the NMR's (unexpanded page only).