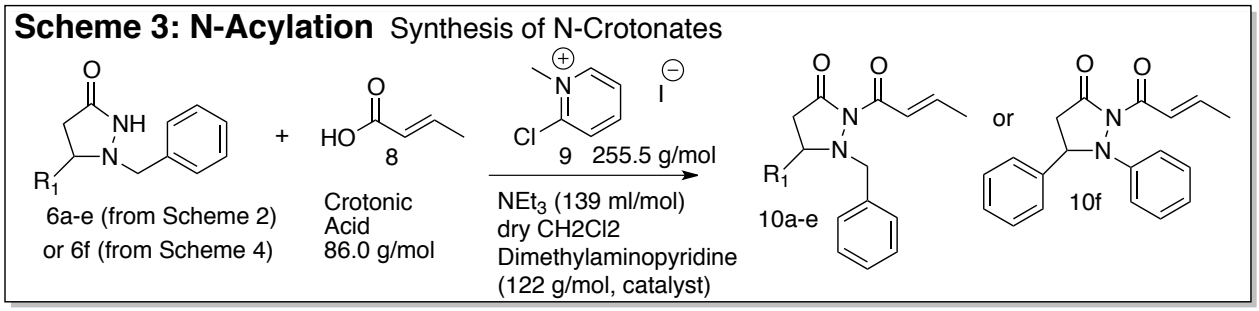

Scheme 3 Procedure: N-Acylation of Pyrazolidinone 6a-f Using Crotonic Acid and Mukayama's Reagent (9)

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 30 mL of dry anhydrous CH2Cl2
   - add a white rubber septum to exclude air, if you aren't ready to continue with following steps very quickly.
3. Based on how many mmol of pyrazolidinone **6** you have, add 1.2 equivalents of crotonic acid **8** (86 g/mol).
   - In other words, if you have 10 mmol of **6**, add 12 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 1.4 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.
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. Add a septum into your flask, and poke a syringe needle through it to serve as a pressure vent.
9. Stir for at least 5 minutes.

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. 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.
    - If you don't get it started at least a day before your week three lab period, it might be interesting to try to reflux it for one hour. But I'm not confident this will work very well. Otherwise, stir/react for at least two hours before you proceed with your workup.

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

11. Use your graduated cylinder to get about 25 mL of a mixed solution that is 2/1 ether/dichloromethane.
12. Pour the contents of your reaction flask into a separatory funnel.
13. Then to the original flask add the 25 mL of 2/1 ether/dichloromethane, and 60 mL of 1-M HCl/water. Shake and swirl, and add this rinse solution into the separatory funnel.
    - The purpose of the HCl/water wash is to convert the neutral triethylamine into ionic triethylamine-hydrochloride, which will extract into the aqueous layer.
14. Shake cautiously, with venting, then allow the mixture to settle.
    - The bottom layer will probably 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 to resolve this.
15. Prepare a clean 125-mL Erlenmeyer flask with a ground-glass joint, with a medium stir bar inside, and with the mass of the combination recorded.
16. Find a fritted filter funnel (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.)
17. Weigh out 18 g of silica, pour it into the filter funnel, and attach the filter funnel into the 150-mL Erlenmeyer.
18. Weigh out 30 g of sodium sulfate, and pour this on top of the silica bed.
    - The sodium sulfate will function to absorb water.
    - The silica layer is meant to absorb some polar, sticky byproduct from the Mukayama Reagent **9**. We are doing a crude but rapid "flash chromatography" to try to purify your product **10**.
19. Assuming the bottom layer in the separatory funnel is the organic phase, carefully drain the organic solution onto the filter column. (If the organic layer is on top, drain the lower aqueous layer into an Erlenmeyer and save it just in case, then drain the organic phase onto the filter column.
20. Carefully/gradually open up the vacuum so that liquid gets pulled through without boiling out and getting sucked into the vacuum tube.
21. Add an additional 25 mL of 2/1 ether/dichloromethane to your original Erlenmeyer, swirl that around, and pour/rinse it into your separatory funnel. Shake it up briefly. The organic layer will probably now 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.
22. **Concentrate this solution**. Attach a reflux condenser with no water hoses attached, 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.
        - This is a manifestation of how endothermic the vaporization process is.
23. 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 9) 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.

24. 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.
25. 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.
26. Weigh your flask, so that you can determine mass, millimoles, and percent yield.
27. Take a portion of your product **10** and transfer it into an NMR tube.
28. Add 1.0 mL of CDCl3, add a blue cap, and shake up the mixture.
29. Use a long pipet to pull as much solution out as you can reach, and transfer that into a GC-MS vial.
30. Submit your NMR-**10** to the NMR queue.
31. Submit your GC-**10** into the GC-MS queue. Your product has gotten quite large by now, so the retention times will be very long and the runs will take a long time. So you'll probably want to come back tomorrow to get your GC and to print your mass spectra.
    - Be sure to print the mass spectra for the major products and include them in your report.
32. See the section about NMR's and GC/MS's to review expectations in terms of data, analysis, and presentation.

Yield Analysis: Weigh the material, so that you can calculate your final mass and yield. 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!