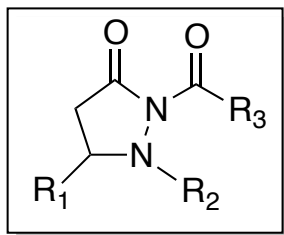


Chem 365 Lab Manual Part II

Multistep synthesis of an Acyl Pyrazolidinone**Introduction**

We will begin a multi-step semi-research sequence in which we make a library of different “acyl pyrazolidinones”. The project will illustrate a variety of fundamental organic reactions and fundamental procedures. The acyl pyrazolidinones are of interest as potential medicinal candidates, as well as for use in further synthetic reactions. (It’s possible that students in next year’s research module will use some of the products.)

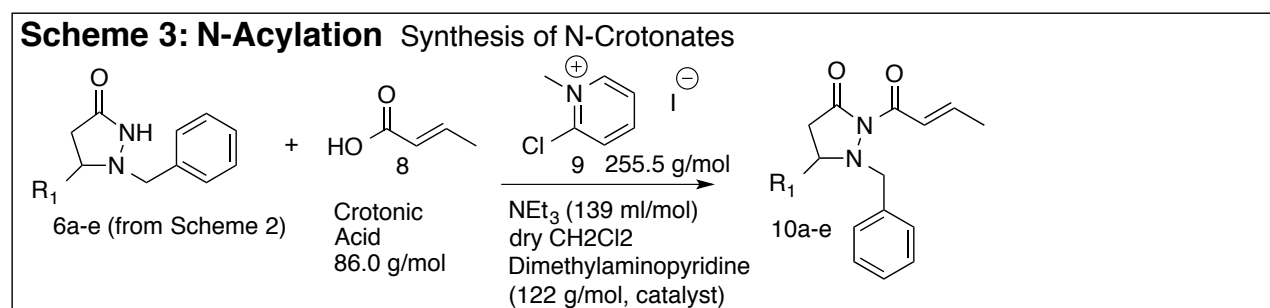
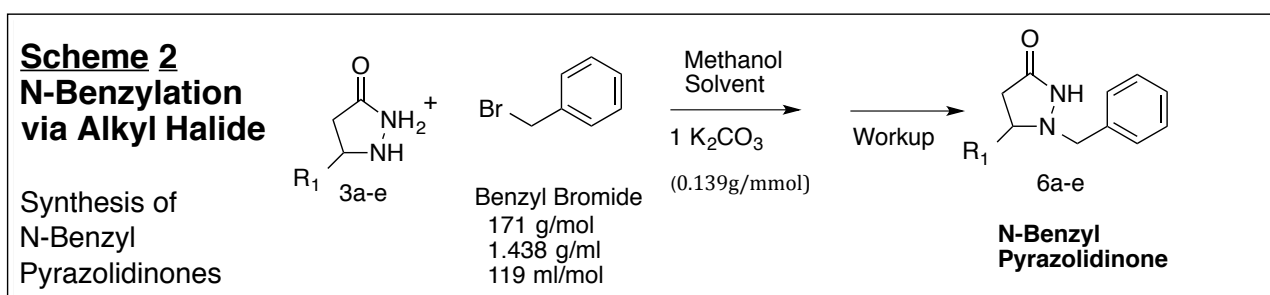
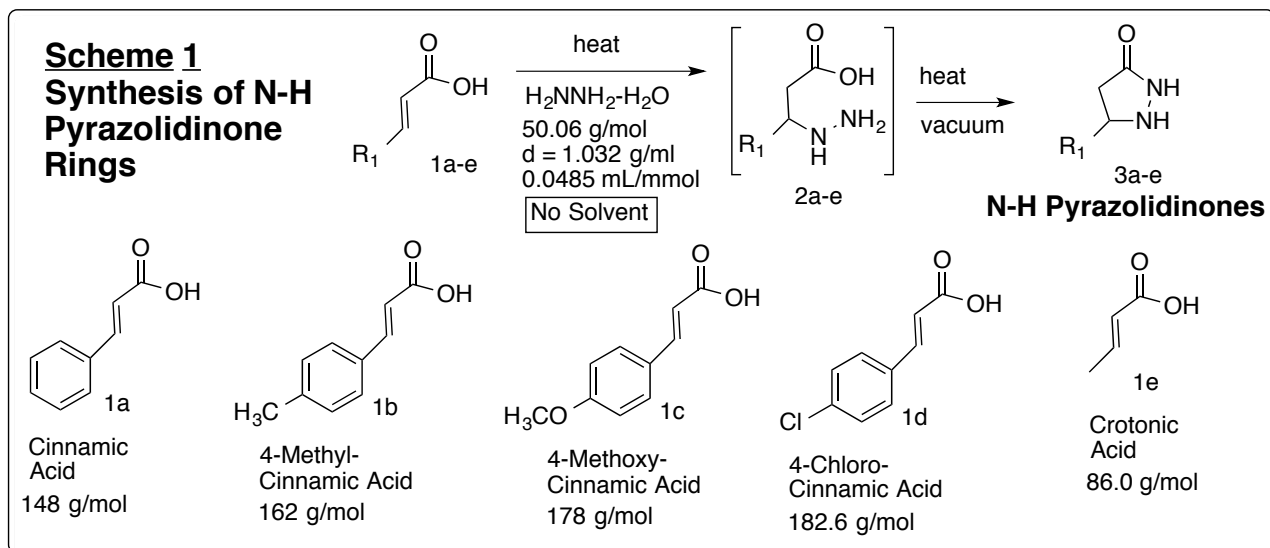


As shown in the picture, there are three different variable R groups. We will use five different R_1 groups; one, two, or three different R_2 groups; and for this year we’ll use a single R_3 group. But imagine if we used four of each group; we could then produce a library of up to $4 \times 4 \times 4 = 64$ different products. This kind of modular preparation of chemical libraries is routine in industry and medicinal chemistry. Subsequent biological testing can provide insights into the relationships between structure and activity. (Which parts of the molecule matter? Where does getting bigger or smaller help? Etc.)

In the first stage, pyrazolidinone rings **3** will be assembled with just one of the substituents attached, R_1 , which is bound to the C5-carbon. (See Scheme 1. In the pyrazolidinone ring numbering, the two nitrogens are #1 and #2, the carbonyl carbon is #3, etc.). An unsaturated acid will be treated with excess hydrazine hydrate. The nitrogen will initially add nucleophilically to the alkene, in a mechanism that can be viewed as involving either an enol or an enolate intermediate. This reaction is done in the absence of any solvent other than the hydrazine hydrate itself. Following addition, the product **2** undergoes loss of water and cyclic amide formation under high-temperature and vacuum, again with no solvent. The vacuum is important because it helps to distill off the water, whose hydrogen-bonding otherwise inhibits the ring closure. The pyrazolidinone rings **3** are often thick and gummy. The product (**3**) following the vacuum heating will need to be evaluated by NMR and GC-MS. Unfortunately getting rid of the excess hydrazine is hard, and it doesn’t display under either our NMR or GC conditions.

A second substituent (R_2) will be attached to N1, using Scheme 2. The bottom N1-nitrogen will effectively exchange a hydrogen for a new carbon substituent, CH_2Ph (which is called a “benzyl” group). This alkylation involves an $\text{S}_{\text{N}}2$ reaction, with the N1-nitrogen acting as nucleophile despite being neutral. The potassium carbonate serves to remove the proton after the nitrogen has become four-bonded with a formal plus charge. The risk in the $\text{S}_{\text{N}}2$ mechanism is that the nitrogen can perhaps alkylate twice, leading to a quaternary ammonium salt. Because of the $\text{S}_{\text{N}}2$ mechanism, the alkyl halide electrophile must be an $\text{S}_{\text{N}}2$ -eligible alkyl halide.

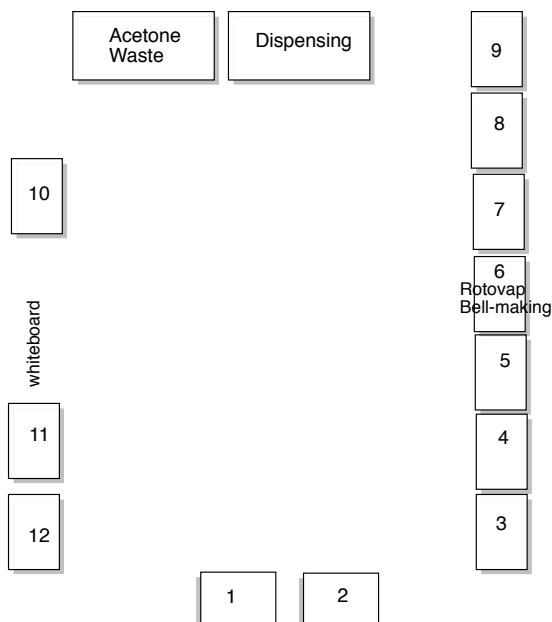
It is noteworthy that the two nitrogens in pyrazolidinones **3** behave very differently. The bottom nitrogen is sp^3 -hybridized and is basic/nucleophilic, essentially like an “amine” nitrogen. The top nitrogen is sp^2 -hybridized and is non-basic/non-nucleophilic because it is essentially an “amide” nitrogen, and is stabilized by conjugation to the carbonyl. Thus, as is typical when there are two functional groups of unequal reactivity, reaction proceeds selectively on the more reactive one.

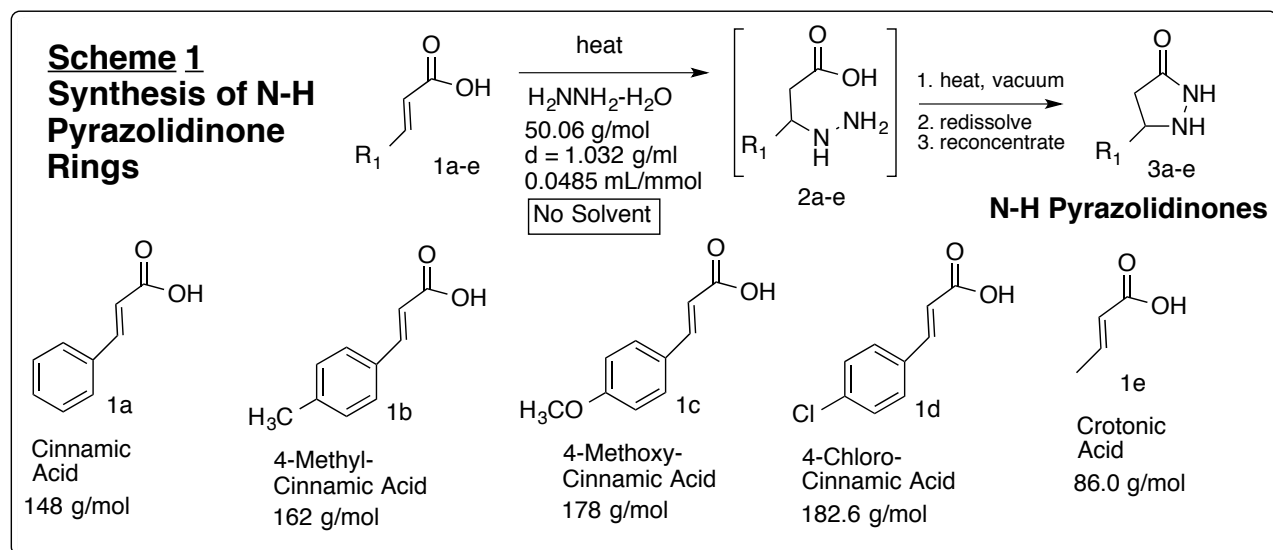


The last stage (Scheme 3) will involve acylation of the top amide nitrogen. The procedure has been invented and developed by MSUM students (most notably Amie Nowacki and Kris Brandvold). A water molecule effectively needs to be eliminated (H from the amide nitrogen in structure **6**, OH from the carboxylic acid **8**). The water oxygen gets absorbed by “Mukayama’s Reagent” **9**, and the two H’s end up getting absorbed by basic triethylamine. Dimethylaminopyridine functions as an essential catalyst. Since the function of **9** is to absorb water, the solvent needs to be dry, so that Mukayama’s agent acts on reactants **6** and **10** rather than getting destroyed by water in the solvent. This reaction takes several hours at least. So it will be desirable to start it at the end of the second lab period, and worked up during the third week. The risks in this reaction are various. First, if things are wet, it’s a problem. Second, if there are other NH or OH bonds present in residual contaminants, they will also be able to react to give new contaminants. The reaction should really work with any carboxylic acid, so if a student wanted to try something other than crotonic acid **8**, it should be possible.

Overall Format and Initial Assignments: You can work with a partner but don't need to. Each hood has a number above the top of it; see the lab map below. Assignments are based on which hood you are working in.

Hoods	Initial Reactant + Week 1	Week Two	Week Three	Chemical ID's
1 + 2	cinnamic acid 1a Execute Scheme 1. Product = 3a	Setup and execute Scheme 2 Workup and purify Product = 6a Begin Scheme 3.	Workup and Purify Product = 10a (Scheme 3)	1a, 2a, 3a, 5a, 6a, 10a
3 + 4	4-chlorocinnamic acid 1d Execute Scheme 1. Product = 3d	Setup and execute Scheme 2 Workup and purify Product = 6d Begin Scheme 3.	Workup and Purify Product = 10d (Scheme 3)	1d, 2d, 3d, 5d, 6d, 10d
5 + 7	crotonic acid 1e Execute Scheme 1. Product = 3e	Setup and execute Scheme 2 Workup and purify Product = 6e Begin Scheme 3.	Workup and Purify Product = 10e (Scheme 3)	1e, 2e, 3e, 5e, 6e, 10e
8, 9, 10	methylcinnamic acid 1b Execute Scheme 1. Product = 3b	Setup and execute Scheme 2 Workup and purify Product = 6b Begin Scheme 3.	Workup and Purify Product = 10b (Scheme 3)	1b, 2b, 3b, 5b, 6b, 10b
11, 12	methoxycinnamic acid 1c Product = 3c	Setup and execute Scheme 2 Workup and purify Product = 6c Begin Scheme 3.	Workup and Purify Product = 10c (Scheme 3)	1c, 2c, 3c, 5c, 6c, 10c





Scheme 1 Procedure: Formation of Pyrazolidinone Ring Using Hydrazine

Part A. Heating/Hydrazine Addition Phase

- Put your hot-plate/stirrer on a jack, and turn your hot-plate heater to a setting of 8, so that by the time everything else is assembled the hot plate is good and hot.
- Get a 125-mL ground-glass jointed Erlenmeyer, and add a long stir-bar. **Weigh the combination and record the mass.**
 - You'll need this mass both this week and in ensuing weeks, so record it somewhere where you'll be able to find the information next week.
- Add 20.0 mmol (0.0200 mol) of whichever alkene acid **1a-1e** is assigned to you.
 - Calculate how much mass it will take for your particular alkene acid **1a-1e**
 - Use a weighing boat.
 - Add through a powder funnel into your Erlenmeyer flask. (Record actual mass difference.)
- Add 50 mmol (0.050 mol) of liquid hydrazine hydrate via syringe.
 - Hydrazine hydrate: 0.0485 mL/mmol
- Attach a reflux condenser to your flask, with a gentle water flow.
- Set the securely clamped flask with the condenser directly on the pre-heated hot plate (heat = 8) and stir for 30 minutes at spinner = 3.
 - Make sure that the flask is not tipped and doesn't have any air-space between the hot-plate and the flask.
 - You need ideal, direct contact for the heat to do its work in the time given. If you leave space in between, or have a tipped flask without good thermal contact, the reaction might not complete correctly.
 - Within several minutes your solid should melt/dissolve, and boiling should proceed.
- During the 30 minutes, plan ahead. During the 30 minutes, prepare the following:
 - Find your vacuum adapter, and plug it into the vacuum hose. This is about 1 inch long, with a ground-glass joint on one end and a 90-degree curve. The ground-glass end will plug into a reflux condenser, the tapered end into your vacuum hose.
 - Familiarize yourself with your vacuum: With your vacuum attached to the vacuum hose, put your thumb over the end, and turn the vacuum counterclockwise to get an idea of how far you have to turn it before any vacuum actually starts to work. Then turn the vacuum back off.
 - A spike on the valve will typically need to be turned more than one quarter of a revolution, and sometimes considerably more, before the vacuum engages.

- You'll want to know this so that when you really need to apply the vacuum, you'll be able to get near the point where the vacuum engages, and then open it VERY cautiously and slightly at first.
 - c. Ensure that the vacuum is turned all the way off (to the right). IF SOMEBODY HAS THEIR VACUUM OPEN TO THE AIR, THAT AIR LEAK WILL COMPROMISE EVERYBODY'S VACUUM AND NOBODY WILL GET THE LOW PRESSURE THEY NEED for the next procedure. Don't let your hood's vacuum ruin everybody's experiment!
 - d. Get a glove for your left hand, so you can handle the hot glassware;
 - e. Draw the structure for the pyrazolidinone **3** that you should end up making, given the starting material **1a-1e** that you used. Will yours be **3a**, **3b**, **3c**, **3d**, or **3e**? What will it look like? What will it weigh, to the nearest whole number?
 - The structure of your starting reactant dictates what the R1 group will be in your product **3**.
 - Calculate what the molar mass of your product **3** should be, given its structure. (To the nearest whole number. You can round off the atomic masses: C=12, N=14, O=16, H=1)
 - f. Calculate what the theoretical yield for your **3** should be, given the 20.0 mmol scale.
 - g. Look ahead to both subsequent stages of Scheme 1, but also to Scheme 2, which you will do today and will start shortly after you complete Scheme 1....
 - h. Get an empty NMR tube and stand it inside an empty Erlenmeyer, with a red cap;
 - i. Get a long-stemmed pipet, with a pipet bulb to be used with NMR tube;
8. After the 30 minutes of heating is complete, a) slide the hot plate out from under your flask, b) **reduce the hot-plate setting to 5**, c) turn off your reflux condenser water, and d) detach the hose from the water source and redirect it into the drain so that most of the water in the condenser can drain out.
9. Let your solution (and the hot-plate) cool for at least **5 minutes** before starting Scheme 1 Part B.

Scheme 1 Part B: Heat/Vacuum/Ring-Closure/Amide Formation Phase

10. After the 5-minutes, attach the vacuum adapter to your reflux condenser, and then slide your hot plate back under the reaction flask. The hot plate should be set at 5 for heat and 3 for stirring.
- If you didn't turn your hot plate down to 5 earlier, do so now and wait five minutes.
11. Crack the vacuum open, really, really carefully and gently at first (so that it doesn't cause everything to erupt and boil/foam over). As soon as the vacuum is engaged but the bubbling isn't too wild, open the vacuum until it's wide open as soon as possible (two full revolutions will more than suffice). If the mixture splatters/bubbles a lot, it may help to lower the plate slightly.
12. Stir/heat/vacuum for **twelve minutes**, then a) **turn off the vacuum**, b) slide the hot plate out from under the flask, c) turn your condenser water back on, and d) detach the vacuum adaptor from your reflux condenser.
- Excess vacuum heating may result in some decomposition, so avoid excess time.
 - Notice that the volume should decrease and the solution should get thicker as the water and excess hydrazine boil off with the assistance of the vacuum.
 - The hot vacuum is intended to do several things:
 - a. Facilitate/complete ring closure (**2** → **3**).
 - b. Distill away water
 - c. Vacuum/distill away much of the extra hydrazine. Leftover hydrazine causes a problematic side-product in the Scheme 2 reaction, so we want to remove it.
 - d. Unfortunately this process will still leave a problematic amount of hydrazine behind, which is why we'll do parts C and D.
 - **NOTE: If you forget to turn your vacuum off, it will ruin things for everybody else!**

Scheme 1 Part C: Redissolve the mixture in methanol


13. Slowly/carefully add 10 mL of methanol down through the reflux condenser onto your mixture.
 - Pour it down one side of the condenser. Your product in the flask is very hot, enough so that the methanol will immediately boil on contact. So don't pour in all 10 mL fast down the middle or the boiling vapor will shoot out the top and carry liquid with it! Do it carefully by pouring down one side of the condenser slowly.
14. Reapply the hot plate/stir plate, with heat still at 5 and stirring still at 3. If the stir bar stirs freely and all of your material dissolves right away, proceed with Part D.
 - If not, heat/stir until you get a homogeneous solution. Turning the stirrer to 6 might help.
 - 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
 - For 4-methoxy compound **3c**, if at this stage your sample still doesn't partially dissolve and allow the stir bar to spin using only the 10 mL of methanol, you may need to add another 10 mL. The 4-methoxy substrate is probably less soluble than others.

Scheme 1 Part D: Reconcentration of the Methanol Solution

- **Purpose note:** Reconcentrating the methanol solution will help to remove much of the hydrazine that was not removed during the vacuum heating of Part B. This will prevent/limit problems and side-products in Scheme 2.
15. Reattach the vacuum adaptor to the reflux condenser.
 16. Turn the water flow to the condenser off, and detach the water-hose from the water source, quickly redirecting it into the sink/drain, so that most of the water in the condenser will drain out.
 17. **Hard, ask Jasperse if he's available:** Very cautiously/slowly open the vacuum.
 1. If you open too quickly the hot methanol will boil like crazy and all get sucked up the condenser and into the vacuum hose. So you need to be super careful.
 2. If the instructor is available, call him over to do this step.
 3. Crack open the vacuum as aggressively as you can get away without causing the mixture to foam over.
 4. If the mixture splatters/bubbles a lot, it may help to slightly lower the hot plate so the flask is not fully in contact with the hot surface, in order to reduce the bubbling/foaming. Gradual return of the hot plate until it's in full contact with the flask can sometimes help to moderate the foaming.
 18. Once the vacuum is wide open and the hot plate is actually touching the flask, heat/vacuum for 15 minutes (hot plate at 5, stirrer at 3).
 - It's possible that some of the material will foam up during this process; but don't stop. That will normally return to liquid form in time.
 19. After 15 minutes, a) slide the hot plate out from under your reaction mixture, b) **turn the vacuum off**, and c) detach the vacuum adaptor.
 - **NOTE: If you forget to turn your vacuum off, it will ruin things for everybody else because their vacuum won't work if yours is left open to the air.**
 - Pulling the vacuum adapter is easier if you grasp the hot flask with a GLOVED hand
 - Be prepared to rapidly/immediately continue with the next step while the solution is still hot and melted.

Scheme 1 Part E: Product Analysis. NMR, GC/MS, and yield. And Deciding whether You Need to Heat and Vacuum Further.

- Hopefully everything has gone reasonably well. However, this isn't certain; perhaps the ring closure and water/hydrazine removal is not sufficiently complete, in which case you'll need to do some more vacuuming. (And in which case the yield will be too high, and the NMR will be contaminated.)
 - We don't want to do additional heat/vacuum time unless absolutely necessary, though, because doing so can cause some decomposition of your product.
 - So, in order to decide whether you're done, or whether you need to do more heating/vacuuming, you need a quick way to assess the situation. Both the NMR and/or the % yield can tell us. (See some of the following steps.) If the yield significantly exceeds 100%, that represents trouble. And if the NMR shows a lot more peaks than would be expected from the target, that also represents trouble.
20. **Immediately**, while the material is still in a hot melted form, dip a long-stemmed pipet into the hot residue and draw up about a quarter-inch (1 cm) sample (finger-nail length) of your hot mixture into the skinny tip of your pipet
 - Consult the instructor if he's available. You'll do this again in the next two weeks.
 - Sample should be small, both to give sharpest NMR and to minimize yield loss.
 21. Put your pipet with that small sample into an NMR tube. The material will probably harden (perhaps except for **3e**.)
 22. Put a septum into the top of your reaction flask to keep air out.
 - Air can cause some oxidation and decomposition of your product, particularly when it's hot.
 23. Add 1.2 mL of CDCl₃ into the same pipet that has the sample in it and is in the NMR tube, and attach a pipet bulb to the pipet.
 - The sample will have probably hardened/frozen and will probably prevent the solvent from running out the bottom.
 24. Take the NMR tube with the pipet inside it to the heat gun station. Use the heat gun to apply heat directly on the spot where the sample is hardened until the sample softens and the CDCl₃ is able to rinse through the pipet into the NMR tube.
 - Consult Dr. Jasperse for help with this if he's available.
 - Use your pipet bulb to flush solvent back and forth to help to dissolve any sample that is still stuck at the end of your pipet.
 25. Using the same long-stemmed pipet, draw out what solution it can reach and transfer it into a GC-MS vial.
 - There will still be enough solution for the NMR.
 - Basically the same solution will feed both NMR and GC-MS analyses
 26. Submit the NMR sample to the NMR queue.
 - Students will be using the NMR both for submitting, but also for processing (printing extra copies, doing horizontal expansions, etc.) So you may need to be able to work your way between "submit" and "spectrometer" modes.
 - If not in submit mode, click "New Study" to get into submit mode. The correct experiment should automatically load when you do so, if the software is working right.
 27. Submit your GC-MS sample to the GC-MS queue.
 - This will probably take a while to run.
 28. Take your flask to the balance and measure the mass.
 - Subtract the original mass of the flask and stir bar in order to determine the mass of product.
 29. If you have the NMR, or you have the mass and use that to calculate the % yield, those will provide the information needed to determine whether or not you're good, or need more vacuum.

30. **Make 3 extra copies of your NMR and put them in your drawer.** You'll need to have one as part of your lab report for Scheme 1, but you'll need to have another copy for comparison to derivative NMR's in Scheme 2, and you'll need one for inclusion in your final overall report following Week 3.
- Today's product **3** will be Scheme 2's reactant. As you go through Scheme 2, you'll want to be able to compare your NMR for product **6** to the NMR of the reactant **3** that you started with. After Scheme 3, you'll want to be able to compare/contrast NMR's of **3** to **6** to **10**.
 - NMR: If in submit mode, click "**Cancel**" to exit Submit mode in order to enter the spectrometer/processing mode for doing additional prints or horizontal expansions.
 - In "Spectrometer" mode, must have "Zones" map displayed (96 sample nodes show). Click on little circle icon () to the upper left of the spectra-display panel, if zones map not already open.
31. NMR labeling/reporting: In all of your reports, refer to this NMR as NMR-3a-e.
- (Well, don't actually refer to it as "a-e". If you're working with the "a" series, then yours should be NMR-3a. If you're the "b" series, then yours should be NMR-3b, etc.! ☺)
 - On the main NMR, rotate it 90° to the left, and write the label in the upper right-hand corner.
32. Calculate the percent yield of your Scheme 1 reaction (**1** → **3**)
- **If your yield exceeds 100%, it probably means your heat/vacuum process had problems. See instructor, in that case.**
33. Calculate how many mmol of product you have.
- Given your yield in grams, you could convert the grams into mmol if you knew the molar mass of your product. But the molar masses will be different for each of **3a**, **3b**, **3c**, **3d**, and **3e**. So you need to have drawn out your actual specific structure, and added up its molecular weight.
 - Hopefully you already had time to do all these drawings and calculations during the 30 minutes of heating earlier.
34. **Record the structure, molecular weight, mass in grams, and calculated number of millimoles on a sheet of paper and save it in your drawer. (Perhaps on an NMR you're saving?) You'll want all of that information next week, because your product 3 today will be your starting reactant next week, and your yield and stoichiometry calculations then will require that you know how many grams and millimoles you're starting with then.**
35. GC-MS labeling/reporting: In all of your reports, refer to this week's GC as GC-3a-e.
- (Don't actually refer to it as "a-e". If you're working with the "a" series, then yours should be GC-3a. If you're working with the "b" series, then yours should be GC-3b, etc.. ☺)
 - Write that label on the upper right-hand corner of every GC-MS sheet.
 - **Print two extra copies and leave in your drawer.**
36. Note: for analyzing/understanding/interpreting and reporting on your NMR and GC-MS data, see the section in the manual dedicated to that. The instructor also has a movie available from the Chem 365 website discussing the NMR details, and how to understand, report, and analyze these in your lab report.
37. Put a septum or stopper into your flask and store it for use next week. Once again, you'll need to know the mass of your flask/stir-bar next week; the mass of sample in your flask (it's next week's starting material); the molar mass; and the number of millimoles you'll be starting with.

NMR and GC-MS Data in the Research Module.

1. How to notate the spectra.	3. How to understand the Data.
2. How to report the data.	4. How to use your Mass Spectra for your main GC peak(s).

How to notate the spectra and refer to them in the reports.

Each NMR and each GC/MS will need to have a clear label that corresponds to the identity of the chemical. If the chemical is **3c**, then the NMR for that sample should be labeled as **NMR-3c**, and the GC/MS should be labeled as **GC/MS-3c**.

A labeling system like this is invaluable for synthesis reports. You can refer to **NMR-3c** in your procedure and in your data analysis sections, and you can label your actual NMR printouts (or GC-MS printouts) with the same labels.

These labels should be written on the upper right-hand corner of each spectra, relative to how a spectrum will be stapled into an actual report. Just as a page number is normally shown in the upper right-hand corner where it's easy to see as you page through a book, so too should spectra be labeled where it's easy to find the labels.

You MUST also draw the actual structure of your product on both your NMRs and your GC/MS's. (If you do several horizontal expansions, you don't need to redraw it on each page. But you should on the front page. And you should draw the label **3a-e** on every page.)

When discussing NMR's or GC/MS's in the reports, always do so by label. (For example, "GC-MS 3c was taken", or "as shown in NMR-3C, the product was very pure....")

NMR Analysis/Interpretation, General Considerations,

1. An **abbreviated summary report** process will be useful and required. Draw the structure and label the different carbons. Then make a table with the chemical shifts for the actual non-aromatic 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, and which signals are from the α -H's?
- Which signals are the methyls or methoxy signals in **3b**, **3c**, and **3e**?
- Does your product look pretty pure? If so, there should be a fairly limited number of non-aromatic signal sets.

2. **Does your NMR confirm that your heat-vacuum completed ring-closure, and removed water and hydrazine?** If your heat-vacuum concentration of product **3** was successful, you should NOT see a big broad lump that appears in the non-aromatic region. If you do have a big lump, that probably reflects residual water and/or hydrazine. Does it look like the hydrazine/water is gone?

3. **Chirality, H-non-equivalency, and chemical shift:** In your NMR, the β -carbon will be chiral. When you have a chiral carbon, it makes the two α -hydrogens (on the CH₂ group next to the carbonyl) unequal to each other. One α -H is cis and the other is trans to your β -H, so they are not in the same chemical environment. These unequal α -hydrogens usually (not always) come at different chemical shifts. (Depending on which **3** you made.)

4. **Chirality, H-non-equivalency, and splitting:** The non-equivalence of the two α -hydrogens also complicates the splitting. They now are split by each other, as well as by the neighboring β -H. Plus the splitting magnitudes are different because of the differing distances. (The "other" α -H is closer than the β -H, so they don't usually provide equivalent magnetic splitting, and don't usually provide a nice triplet.) In practice, each of the two α -hydrogens will usually appear as a four-line "doublet of doublets", and the two α -hydrogens should normally combine to show eight lines. The β -H will typically also look like a 4-line "doublet of doublets", unless

further split by the methyl group in **3e**. (In one of the **3**'s, the two α -hydrogens have almost exactly the same chemical shift and could look like just a simple doublet that integrates for 2H, in which case the β -H may look like a simple triplet.)

- N-H hydrogens**, like OH hydrogens, are typically broad and unpredictable. In many cases you won't be able to see them at all. Don't look for them or try to assign them
- For your reports, account for all the hydrogens connected to sp^3 carbons. You don't need to discuss/present N-H hydrogens or aromatic hydrogens. (There are so many overlapping aromatic H's that they aren't interpretively useful in this case.)
- Signature signals**: All of the samples will have the interesting α - and β -hydrogens. But there will be other signature peaks for other situations:
 - the para methoxy methyl in **3c**;
 - the para methyl group in **3b**;
 - the methyl doublet in the **3e**.
 - 3a** and **3d** won't have any non-aromatic C-H's other than the three on C- α and C- β .
- Nitrogen impact on chemical shift**: The impact of a nitrogen attachment on chemical shifts is similar to the impact of an oxygen attachment. In other words it has an addition factor of about +2. This will impact the chemical shift for hydrogen on the β -carbon (β relative to the carbonyl).
- Chemical shift logic**:
 - For the α -hydrogens in each of **3a-3e**, they are next to a carbonyl. So we'd expect them to come in the 2's. They are also β to nitrogen and perhaps also an aromatic, which further pushes them a bit downfield. So typically they should fall in the high 2's or perhaps slip into the low 3's.
 - For the β -hydrogen in **3a-3d**, the β -carbon has both a nitrogen (+2) and an aromatic (+1) attached, so normally we'd anticipate the β -hydrogen to show up in the 4's. For the β -hydrogen in **3e**, the β -carbon has a nitrogen (+2), so we'd anticipate the β -hydrogen to show up in the 3's.
- Impurities/contamination**: Real products often are accompanied by many impurities. The present of impurities, can complicate NMR interpretation. Recognizing which signals come from the desired product and which do not is significant. And qualitatively recognizing whether a spectrum is relatively clean or is pretty contaminated is important.
 - Remember that there should be a logical integration ratio for the main H's in your actual product **3**
 - Often there will be a variable amount of smaller signals in the baseline resulting from contaminants, side products, and product-decomposition. The less, the better.
 - In the cases of **3b** and **3c**, if you see "extra" methyl groups, those might result from side products or from starting reactants **1b** and **1c** that never reacted at all. Again, the less the better.
- Comparison to Other NMR's**: It may be very interesting to look at how your NMR looks compared to how NMR's of other students look.
 - How different is yours from different versions of **3**?
 - If you compare yours to somebody else who made the same version of **3**, how clean is yours compared to theirs?

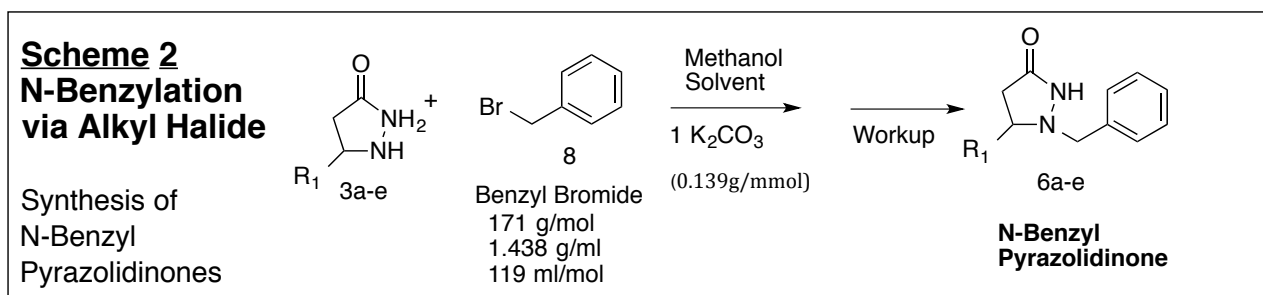
GC-MS Analysis/Interpretation

- Clearly label each page of each GC/MS printout with the appropriate GC/MS-**3a-e** label in the upper right corner.
- Draw the structure for your specific product on each GC-MS sheet, and write the molecular weight underneath the picture. (No "R" groups; write the specific structures.)

14. **Retention time?** What is the retention time for your **3**?
 - Bigger structures will have longer retention times. Next week, your product **6** should have a longer retention time than this week's **3**. Likewise this week heavier versions of **3** should have longer retention times than smaller versions.
15. **Purity:** How pure is your **3** by GC?
 - Many contaminants will NOT appear, since they come off fast during the solvent delay. So your purity reading will be deceptively high. NMR, which shows everything, is qualitatively more representative.
16. **Mass Spec and Molecular Ion:** For your major product **3**, check in the mass-spec whether there is a molecular ion peak that matches the molecular weight for your product.
17. **Lab report:** In your lab report, make sure that you have not only attached the labeled GC-MS information, but that you also discuss/present the retention time and purity in your data/results/discussion section.

Scheme 1/Week 1 Lab Report:

1. Write a standard synthesis style lab report for your Scheme 1 reaction (**1** → **3**).
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 the **actual** reactant 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 mass ⇒ mole for products)
4. Include procedural details and observations as usual.
5. Calculate mass yields, and percent yields, etc., for product **3**.
6. Include your NMR-**3** (**3a** or **3b** or **3c** or **3d** or **3e**, as your case may be).
 - This must be clearly labeled.
 - Be sure to draw your structure, and then provide an abbreviated summary report. This should include a listing of chemical shifts for **non-aromatic C-H hydrogens**, integrations for them, and a matchup-assignment between signals and hydrogens in the molecule.
 - **Note: you do not need to include aromatic H's, N-H's, or impurities/solvents/contaminants in the abbreviated NMR summary report.** There are so many overlapping aromatic H's that they are not really interpretively useful.
7. By putting definite labels on your NMR (for example, **NMR-3b...**), you will be able to easily refer to that that NMR in your report. (For example, "NMR-3b was submitted at this point." Or "NMR-3b shows considerable product, but it is clearly not clean. There is extensive solvent visible...".)
8. Include your GC-MS-**3**, and **print and attach mass spectra**.
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 and GC-MS data tells you about both the success and the efficiency of your reaction, and the purity of your product **3**.
10. The results/data/discussion/analysis section should summarize what the mass/yield/NMR/GC-MS data is, and what conclusions can be drawn from them. Just attaching the NMR's and GC-MS's without discussing or showing that you understand them will not be good. What is the summary for the key non-aromatic C-H hydrogens in your NMR? What is your GC-retention time? Between the NMR and the GC, did it look like the product **3** was formed successfully, and does it look reasonably clean? Or is it obviously significantly contaminated?
11. Note: Keep two extra copies of your NMR and your GC-MS's. Pyrazolidinone **3** functions as the product in week one report, but it is the reactant in the week two report. So when writing up and analyzing Scheme 2, you'll need information about mass, molecular weight, structure, and mmol of your reactant **3**. You'll also need to have NMR and GC for **3** so that you'll be able to compare your product **6** to reactant **3** and tell whether the reaction really worked. You'll also want copies of **3** for your Final Report after week 3.

**Scheme 2 Part A: Redissolve in Methanol**

- Turn hot plate to 5.
- To the flask with your product 3 from Scheme 1, attach a condenser with gentle water flow.
- Add 15 mL of methanol.
 - For 4-methoxy compound **3c**, you may need to add an additional 20 mL of methanol, since the 4-methoxy substrates are less soluble.
- Heat the mixture on the hot plate with the stirrer at 5 until the material dissolves and becomes completely homogeneous.
 - If the stir bar isn't coming free even after several minutes, detach the condenser and try to poke the stir-bar free with a spatula
 - Make sure that there aren't big chunks or blobs of undissolved material on the outside. Everything needs to be dissolved or else in as small of particles as possible.
 - While you are heating/dissolving/waiting, calculate the amounts and find the potassium carbonate and benzyl bromide that will be used in the next steps.
- Once your material is largely dissolved, reduce the hot plate setting to 4.

Scheme 2 Part B: Addition and reaction of Benzyl Bromide

- Add K₂CO₃:** Add 20 mmol of potassium carbonate powder (K₂CO₃, 0.139g/mmol) through a powder funnel. (It's a white solid, and will be next to one of the balances.)
 - 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 until benzyl bromide time.
 - 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
- Calculate 0.85 equivalents of benzyl bromide.** Calculate how many mL of benzyl bromide (119 mL/mol) you need to add 0.85 mmol benzyl bromide per each mmol of 3. In other words, if you have 20.0 mmol of **3**, how many mL of benzyl bromide will it take to add 17.0 mmol?
 - Calculation: Benzyl bromide 0.119 mL/mmol.
 - You need to know how many mmol of reactant **3** you are working with. To do that, you need to know your structure, your molar mass, and your actual number of grams that you began with today. 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. Probably at least 10-15% (if not more) of your mass of reactant **3** is probably junk or side products or unreacted alkene **1** or something.
- Carefully/slowly add the 0.85 equivalents of benzyl bromide** (119 mL/mol) by syringe. (It's a smelly liquid in the hood. You can temporarily carry the entire bottle over to your hood, so long as you return it as soon as you've finished adding it. 😊)
 - In order to add it, first detach the reflux condenser so that you can drip the benzyl bromide straight into the reaction flask. Reattach the reflux condenser as soon as addition is done.

- There may be some initial foaming; add slowly enough so that it doesn't foam up uncontrollably and foam over the flask.
 - Replace the 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 you are done adding it to your reaction.
9. 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 Sample of the Mixture

10. 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.
11. Save this sample in your drawer, we won't run it now or unless we need to. If your product **6** at the end of Scheme 2 is fine, we'll not run this. But if we do end up with some problem at the end, by going back and taking this NMR it may provide some insights about why.

Scheme 2 Part D: Workup Using Separatory Funnel and Chromatography

12. Add 20 mL of dichloromethane.
13. Add 30 mL of water and stir cautiously, then vigorously, for 30 seconds.
- Hopefully the two layers will be relatively homogeneous, with most of the solids dissolved either in the organic or aqueous phase. For methoxy substrate **6c**, that may not be so true...
14. Pour the mixture into a separatory funnel.
15. Rinse the original reaction flask with an additional 10 mL dichloromethane and add to the separatory funnel.
16. After the separatory funnel layers have settled, drain off the dichloromethane phase (lower layer, presumably) into a 250-mL Erlenmeyer (not the ground glass one).
- While the layers are settling, wash the original reaction flask and stir bar with some water and then with acetone. Let it dry so it's ready to re-use soon.
17. Then add another 15mL of dichloromethane into the separatory funnel, shake, let settle, and again drain off the lower dichloromethane layer into the same Erlenmeyer with the first extract
- The liquid left in the separatory funnel should be aqueous, with nothing we want. But you may want to save it for a while, just in case your layers got mixed up by mistake! You probably don't want to go back and start over from Scheme 1 again!
18. Take a drop of water from the aqueous phase (can use a pipet or a boiling stick or something) and add it to a piece of pH paper. Record the approximate pH in your lab report.
- Hopefully the pH is somewhere in the 4-10 range. Let Dr. Jasperse know if it isn't.
19. Add 50 mL of ether to the same Erlenmeyer that already has the dichloromethane extracts.
20. Preweigh a 250-mL groundglass Erlenmeyer with a clean long stir bar already inside.
21. 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 250-mL Erlenmeyer flask with stir-bar.
22. Add 15 grams of silica gel (approximately) to the fritted filter funnel.
23. Add 20 grams of sodium sulfate to the fritted funnel, on top of the silica gel layer.

24. Filter your organic solution. Pour your organic solution directly onto the sodium sulfate/silica filter. 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.
25. Water and highly polar side products will hopefully be retained on the polar silica column, while the desired product will hopefully wash through. (Side products that will hopefully be retained might include any double-alkylation side product; any residual hydrazine-derived side products; any unreacted pyrazolidinone **3** that may not have been converted in Scheme 2; and original carboxylic acid **1** that may not have been converted in Scheme 1.)
26. Pour 25-mL of a 2:1 ether/dichloromethane mixture in a graduated cylinder, and add 3 mL of methanol to that. Rinse this through your filter column. (For **6e**, do an additional 25-mL rinse.)
 - This should ensure that all/most of the desired product comes through, so that your yield can be reasonable. Hopefully without also washing off many of the polar side products that we want to stay on the silica.
 - Substrate **3e** binds more tightly to the silica than **3a-d**, so some extra rinsing may help to boost the yield

Scheme 2 Part E: Concentration

27. To your 250-mL flask with the long stir bar and the organic solution, attach a reflux condenser, at first with water running through it, 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 2-5 minutes you should be able to get the vacuum fully opened. (This may depend on how much solvent is in your 250-mL ground-glass Erlenmeyer.)
 - 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 condenser water off, detach the hose from the water source and quickly direct it into the drain so that most of the water runs out. Turn the hotplate heat to 5 and vacuum for 25 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 many cases, foaming may be a problem. 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 25 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 hot flask may help. Immediately place the pipet into an NMR tube. The material will probably harden/freeze as it cools. Attach a septum to block air from your hot sample as soon as possible.
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.
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 referred to as "GC-6x" in your report. (Well, not really GC-6x, it should be 6a or 6b or 6c etc., depending on which chemical you're really working with.)
35. Submit the NMR to the NMR queue for purity analysis.
 - Students will be using the NMR both for submitting, but also for processing (printing extra copies, doing horizontal expansions, etc.) So you may need to be able to work your way between "submit" and "spectrometer" modes.
 - If not in submit mode, click "New Study" to get into submit mode. The correct experiment should automatically load when you do so, if the software is working right.
 - Each partner will want two copies of the NMR printouts. One for inclusion in your Week 2 lab report, but the second both for comparison purposes when you complete Scheme 3, and also to include in your final data report.
36. 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 data for Scheme 3.
37. Calculate the percent yield for Scheme 2, based on the number of millimoles of benzyl bromide you began with. Since we used 0.85 equivalents of benzyl bromide, that functions as the limiting reactant for Scheme 2.
 - This is a record of the Scheme 2 process.
 - Note: Yields will probably be modest, especially for 6e. But we've gone through a lot of processes, there have been a lot of competing side reactions that cut into actual yield, plus probably some of our desired material was lost to solvents or silica while trying to remove side products.
38. Given the structure of your product and the molar mass that you calculated earlier, determine the number of mmol of product 6 that you made.
 - Record this on an extra sheet; save in your drawer. You'll need this for calculations involved in Scheme 3.
39. Also, just for interest, calculate the overall percent yield from the beginning, based on the number of grams/mmol that you ended with, for the **overall 1 → 2 → 3 → 5 → 6** operations thus far.
 - From the 20 mmol of 1 that we started with, what percentage of that is now at 6?
 - Context: For a 4-operation sequence, if each step is 80% (good), you'd end up 40% overall.
- 40. 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 Part F: NMR and GC-MS.

- Checking your NMR prior to starting Scheme 3 is wise.
- Each NMR and each GC/MS will again need to have a clear label that corresponds to the identity of the chemical.
- You **MUST** again draw actual structures of your product on both NMRs and GC/MS's.
- When discussing NMR's or GC/MS's in the reports, always do so by label. (For example, "GC-MS-6c was taken", or "as shown in NMR-6C, the product was very pure....")

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

41. 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 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 are from the α -H's, and which are the benzyl H's?
- Which signals are the methyls or methoxy signals in **3b**, **3c**, and **3e**?
- Does your product look reasonably pure?

42. **Does your NMR confirm that the reaction, and the solvent-removal basically worked?**

- Does it look like your starting reactant **3** 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.)

43. **Chirality, H-non-equivalency, and chemical shift:** The chirality of the β -carbon not only makes the two β -H's non-equivalent, but also makes the two hydrogens on the newly attached CH₂ carbon nonequivalent. The two benzyl hydrogens should each appear as two doublets.

44. **Chirality, H-non-equivalency, and splitting:** As in product **3**, the non-equivalence of the two α -hydrogens, and now the two benzyl hydrogens, complicates their 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.**
- **The appearance of these two new doublets is very diagnostic for product 6 formation!**

45. For your reports, **account for all and only the hydrogens connected to sp³ carbons.** You don't need to discuss/present N-H hydrogens or aromatic hydrogens. (There are so many overlapping aromatic H's that they aren't interpretively useful in this case.)

46. **Signature signals:** All of the samples will have the interesting α - and β -hydrogens, and the benzyl hydrogens (5 hydrogens combined). But there will be other additional signature methyl peaks for **6c**; **6b**; and **6e**.

47. **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.

48. **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 **6**

49. **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 **6** from the **3** that you began with in Scheme 2?
- How different is your **6** compared to classmates who made different versions of **6**?
- How clean is your NMR compared to that of classmates who made the same version of **6**?

50. **GC-MS:** Clearly label each page of each GC/MS printout.

51. Draw the structure and molecular weight for your specific product on each GC-MS sheet.

18. **Retention time?** What is the retention time for your **6**? How much longer is it than **3**?

19. **Purity:** How pure is your **3** by GC?

20. **Mass Spec and Molecular Ion:** For your major product **3**, check in the mass-spec whether there is a molecular ion peak that matches the molecular weight for your product.

21. **Mass Spec and Fragmentation:** The weakest break-point is at the N-benzyl bond. You should be able to see a benzyl fragment ($\text{PhCH}_2^+ = 99$) and a fragment that it molecular weight - 99. Do you see both of those fragments?

22. **Lab report:** In your lab report, make sure that you have not only attached the labeled GC-MS information, but that you also discuss/present the retention time and purity.

Scheme 2/Week 2 Lab Report:

1. Write a standard synthesis style lab report for your Scheme 1 reaction (**3** → **6**).

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 **3** 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 **3**!

5. Include procedural details and observations as usual.

6. Calculate mass yields, and percent yields, etc., for product **6**.

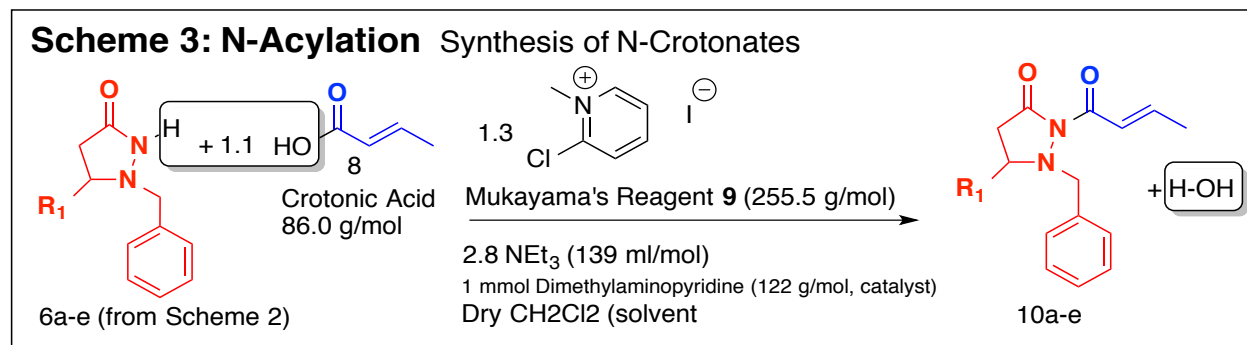
7. Include your **NMR-6** and **GC-MS-6**, with clear labels, structures drawn, **and the abbreviated summary report** for non-aromatic C-H hydrogens for **NMR-6**.

8. Print and attach mass spectra for **GC-MS-6**.

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 and GC-MS data tells you about both the success and the efficiency of your reaction, and the purity of your product **6**.

10. The results/data/discussion/analysis section should summarize what the mass/yield/NMR/GC-MS data is, and what conclusions can be drawn from them. Just attaching the NMR's and GC-MS's without discussing or showing that you understand them will not be good. What is the summary for the key non-aromatic C-H hydrogens in your NMR? What is your GC-retention time? Between the NMR and the GC, did it look like the react **3** was successfully converted to product **6**, and does your product **6** look reasonably clean? Or is it obviously significantly contaminated? Was the yield respectable, or terrible?

11. Note: Keep extra copies of your NMR and your GC-MS's. Pyrazolidinone **6** functions as the product in week two report, but it is the reactant in the Schemd 3/Week 3 report. So when writing up and analyzing Scheme 3, you'll need information about mass, molecular weight, structure, and mmol of your reactant **6**. You'll also need to have NMR and GC for **6** so that you'll be able to compare your product **10** to reactant **6** and tell whether the reaction really worked. You'll also want copies of **6** for your Final Report after week 3.



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

- 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.
 - Add 25 mL of dry anhydrous CH₂Cl₂ 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.
 - 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**.
 - 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.
 - 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.
 - Record all of your observations. (Is the mixture homogeneous or heterogeneous, etc.)
 - 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?
 - 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.**
- 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 already prepared, if so use 50mL.
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 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.

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 CDCl₃ 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
- | |
|---|
| <ol style="list-style-type: none">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 chemical 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 benzylic 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)	Benzylic 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).**

Amine Unknowns

Overview:

You will receive an amine as an unknown. Your job will be to both identify your compound and prepare a derivative. Several pieces of information will be useful:

- Water solubility tests (big or small? Aromatic or not?)
- Solubility in acid-water. (Many basic amines ionize and dissolve in acid-water.)
- Boiling point or melting point of starting material.
- The melting point of the derivative.
- H-NMR information on the starting material.

Classifying Tests

1. Water Solubility Test (Helpful, but not always decisive or clear-cut.)

- Add 15 drops of water to a small test tube, and then add 2 drops of sample. Shake vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
- Interpretation:
 - a. Amines with <6 carbons always dissolve.
 - b. Amines with >10 carbons have $\leq 5\%$ solubility (never dissolve)
 - c. Amines with 6-9 C's may or may not dissolve.
 - a. Amines are more soluble than alcohols; no 7-carbon alcohols would dissolve.
 - b. Water solubility depends on basicity. Amines in which the nitrogen lone pair is sp^3 hybridized tend to dissolve much better than if the lone-pair is p.
 - c. For basic sp^3 -hybridized amines, the solution takes on a cloudy look when they dissolve. This is due to the basicity and the formation of ammonium hydroxide.

2. HCl/Water Solubility Test

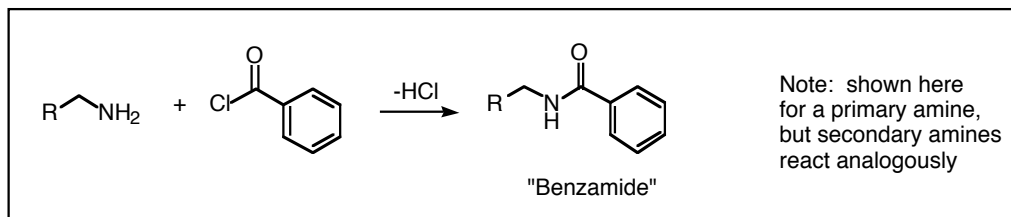
- Same procedure as above, except use a large test tube, use acid-water, add a stir-bar, and use 25 drops of acid-water instead of 15. Use magnetic stirring.
- Interpretation: Most amines with normal basicity will be protonated and become soluble. If you had a sample that didn't dissolve in water, but does dissolve easily in acid-water, it is likely to be an amine. Caution: solid amines sometimes take a while to ionize and dissolve, and amines in which the nitrogen is conjugated and has the nitrogen lone-pair in a p orbital may be relatively nonbasic and may not dissolve.

3. Amines Smell Variably Rancid. Liquids with sp^3 lone pairs smell worse than solids (less volatile).

4. Many Amines are Solids

5. NMR:

- Splitting: The N-H hydrogens in an amine experience hydrogen bonding. So like alcohol hydrogens, they tend to be a little broad and normally don't participate in splitting.
- NH or NH₂ signals can integrate for 1H or 2H, and typically show in the 1-3 ppm range.
- Chemical shift: hydrogens on a nitrogen-bearing carbon are not moved as far as when the carbon is oxygenated, but more than when it's allylic. Typically the additivity factor is about 1.5 ppm, and for a typical CH₂ group connected to an amine nitrogen, the CH₂ group would show up around 2.7 ppm.
- On an aniline (ArNH₂), the hydrogens ortho to the nitrogen are typically pushed upfield, into the 6 ppm window. This is because an amino group is a strong electron donor, so it makes the ortho carbons more electron rich and "shields" the ortho hydrogen, pushing them upfield.

Derivatives: Benzamide Derivatives

1. Place a small stir-bar and 2 mL of aqueous sodium hydroxide solution into a large test tube.
2. Add the amine, about 15 drops if it's a liquid, about 0.20 g if it's a solid.
3. Stir the solution vigorously, and add about 15 drops of benzoyl chloride.
4. Stir vigorously for 5 minutes.
5. Then acidify with aqueous HCl (this helps the amide to crystallize), while continuing to stir vigorously. (Use pH paper to confirm that the pH is lower than 7. This can be done by touching a boiling stick or something else into the mixture, then touching it onto a strip of pH-paper. An acidic solution should turn the paper red.) There is no risk in making it too acidic.
6. Cool on ice for one minute.
7. Filter the lumpy product through the Hirsch funnel, using vacuum. **Pulverize/crush any chunks.**
 - If material is chunky, transfer to a small weighing boat. Place a second empty boat on top, and then grind down on the top boat to crush/grind/pulverize the solid material between the two boats. Then return the material to your Hirsch funnel.
 - Chunks/blocks are a problem because contaminants (either amine or benzoyl chloride derivatives) may be entrapped and may not have any exposure/contact with the subsequent acid-water or base-water rinses that are intended to ionize and extract those impurities.
8. Wash repeatedly: with 3 x 5 mL of cold water, then 2 x 3 mL of HCl/water (to wash off unreacted amine), then 2 x 3 mL of NaOH/water (to wash off unreacted benzoyl chloride), then wash again with HCl/water (to make sure there is no ionic PhCO₂Na present).
9. **Recrystallize**, perhaps adding ethanol or water as necessary. A suggested starting point is 3mL of ethanol and 10 drops of water. But the solubilities will vary greatly from unknown to unknown, so you need to make whatever adjustments are appropriate for your particular sample. You shouldn't need these anymore, but several recrystallization reminders (read):
 - Use a small Erlenmeyer (25 or 50-mL), not a beaker, to reduce solvent evaporation.
 - Make all your adjustment decisions while the solution is boiling hot.
 - Heating your Erlenmeyer in a hot-water beaker (150-mL) is convenient, to provide more even heating and to avoid overheating on the hot-plate surface.
 - You and your hood partner should also warm up some ethanol in case you need to add some
 - Other than when you're just starting, don't add cold solvents.
 - During cooling, cover flask to avoid evaporation of the hot solvent.
 - If no crystals form even after slowly cooling and then icing, try adding ice chip(s).
 - If after chilling you seem to have no solvent, add some cold ethanol. You need solvent for the impurities to have a place to swim!
 - Your rinse should be pretty similar to what you think your actual solvent blend is. But avoid water if possible so that your crystals will dry better.

Micro-Boiling Points in the Melting Point Apparatus

A microscale boiling point can be taken in a melting point tube that has an inverted "bell" in it. Add about 7 uL of liquid via syringe and tapping. Pre-boiling bubbling will often occur as the air inside the bell heats and expands and gets displaced by sample evaporation. When the boiling point is reached, the liquid level should begin to drop (slowly at first, more rapidly the more "above" the boiling point you are.) Sometimes more rapid bubbling often takes place, but not always. Keep heating somewhat beyond the point

where you think boiling has occurred, because you may not be experienced enough to distinguish “pre-boiling” bubbles from real boiling bubbles. And in some cases, you’ll never see bubbles. Even so, at or somewhat beyond the boiling point, vaporization should accelerate such that the liquid level will drop. Watch for this.

These boiling points will not be very accurate, especially for an inexperienced user. Don't trust them to be accurate better than to about 10 degrees. While the observed boiling points are imprecise, they still greatly shorten the list of candidates.

Amine Candidates

Bp of Starting Amines (Liquids)	Unknown	mp of Benzamide Derivative
48	Propylamine	84
55	Diethylamine	42
78	Butylamine	42
159	Dibutylamine (Bu ₂ NH)	oil
182-185	Benzylamine (PhCH ₂ NH ₂)	105
184	Aniline	163
185	PhCH(CH ₃)NH ₂	120
196	N-Methylaniline (PhNHCH ₃)	63
200	2-Methylaniline	144
204	3-Methylaniline	125
208	2-Chloroaniline	99
210	2-Ethylaniline	147
216	2,6-Dimethylaniline	168
218	2,4-Dimethylaniline	192
218	2,5-Dimethylaniline	140
225	2-Methoxyaniline	60
230	3-Chloroaniline	120

Mp of Starting Amines (Solids)	Unknown	mp of Benzamide Derivative
35-38	PhCH ₂ NHPh	107
41-48	4-methylaniline	158
49-51	2,5-dichloroaniline	120
52-55	Diphenylamine (Ph ₂ NH)	180
57-60	4-methoxyaniline	158
57-60	2-aminopyridine	165
58-66	4-bromoaniline	204
71-73	2-Nitroaniline	110
112-114	3-nitroaniline	157
115-116	4-methyl-2-nitroaniline	148
138-140	2-methoxy-4-Nitroaniline	149
148-149	4-Nitroaniline	199

Note: amines are hydrophilic, and tend to absorb some water from the air. Some of the starting amines may also have trace isomeric impurities. The result of moisture and/or impurities means that some of the starting materials may have melting points that are a little bit depressed.

Unknown No. _____ Name _____

1. Physical Examination of Starting Material

a) Physical State _____ b) Color _____ c) Odor _____

2. Solubility Tests on Starting Material

Solubility in Water: _____ If Insoluble, Does it Float or Sink?

Solubility in HCl/Water: _____

3. Boiling point or melting point for starting material:

“Literature” value:
(list, previous page)

4. Recrystallized Derivative

observed mp

literature mp

5. H-NMR (attach, with assignments/interpretation.)

- **On the proton spectrum, create a standard summary table of your H-NMR data, detailing chemical shifts, integrations, and splittings.**
- Draw the structure of your molecule, with identifiers by each carbon (a, b, c...).
- Then on your standard summary table add a column in which you explain which hydrogens (a, b, or c, etc...) are responsible for which signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic.
- Do analyze aromatic H's for solid solid samples. For liquid samples with aromatics, the aromatic H's will have overlapping so won't be useful to detail.

6. What is My Actual Unknown? (Letter, Structure and Name)

7. Comments, difficulties, complaints, etc..

CARBOXYLIC ACID UNKNOWN

A. Solubility Tests: Water, NaHCO₃, and NaOH

Test the solubility of your acid first in neutral water, in NaOH/H₂O, and in NaHCO₃. For each test, add 15 drops of aqueous solution to a small test tube, and then add 2 drops of sample if it is a liquid, or a little spatula quantity if you have a solid. If you do have a solid, double your NaOH/H₂O to 30 drops. Swirl/mix well. Use of small stir bar helps.

- Water Test: Only acids with small numbers of carbons should be soluble.
- NaOH/H₂O: Carboxylic acids are ionized by NaOH, and the resulting sodium carboxylates are usually soluble (with some exceptions, if there are too many carbons present...).
 - Note 1: if it is so small that it dissolves in neutral water, then dissolving in NaOH/H₂O tells nothing extra.
 - Note 2: Solubility of solid acids is often quite slow, because the hydroxide may only be able to “attack” the acid at the surface. Trying this test in a large test tube with a stir-bar is sometimes helpful. But be sure to check after five or ten minutes have passed, not just initially. Also, sometimes it helps if you double your NaOH/H₂O to 30 drops, because if you put in more acid than you realized, and the hydroxide runs out, you won't get full dissolving.
- NaHCO₃/H₂O: An acid-base reaction should lead to solution, but the other unique thing is that acid-base protonation of bicarbonate leads to CO₂ bubbles. If the solubility is poor the bubbles are small and slow, but even with a solid you can often see little bubbles forming. As with the NaOH/H₂O, solubility is often quite slow; often benefits from a larger portion of NaHCO₃/H₂O; and often benefits from stirring with a stir bar.
 - Note: If you see the bubbles, it's a firm proof of acid. But the failure to see bubbles isn't proof to the contrary, that you don't have an acid. Sometimes the bubbles are too small, or too slow, or you just can't see them for whatever reason.

B. Melting Point/Boiling Point

If your carboxylic acid is a solid, take its melting point. If it is a liquid, take its micro-boiling point.

C. Titration/Neutralization Equivalence → Molecular Weight Determination

Weigh, as accurately as possible, around 200 mg (0.200g) of your acid into a 125 mL Erlenmeyer flask. You want 3-4 significant figures after the decimal for this, so the usual balances are unacceptable. Whether you have 200 mg or 220 or 180 doesn't matter, so long as you know exactly what your original mass is. If you have a liquid, add drops until you get to about the same mass. Dissolve your material in around 25 mL of ethanol. [Logic: It is vital that the solution be homogeneous, so you need ethanol to keep it dissolved. But the indicator needs water to work right.] Add 2 drops of phenolphthalein indicator solution. Titrate the solution with _____ M NaOH. (Copy the concentration down from the bottle!)

Summary of titration logic: Molecular weight (or "formula weight", FW) is the ratio of mass per mole. Having weighed your acid, you know the mass very precisely; but how do you know how many moles? By titrating against the precisely standardized base! From the precisely known volume of base and the molarity of the base, you can determine the # of moles of base used. Since the mole/mole stoichiometry is 1 mole of base per 1 mole of acid, the # of moles of base tells the # of moles of acid. Knowing mass of acid and moles of acid, the ratio gives you the formula weight.

Note: Do your titration once, and check the molecular weight value with me. If you get within 5 g/mol, I'll tell you and you won't need to repeat. If you don't get within 5 g/mol, then you'll need to do it again. (Normally several repeats for reproducibility would be in order.)

Molecular weight calculations like this are not perfectly reliable (even if you calculate right!). In general an error of up to five grams/mole is acceptable. Logical reasons for errors are shown below:

- Reason 1: If you don't see the color change right away and "overshoot" the amount of NaOH added, you will have added more moles of NaOH than necessary. The calculation assumes that the number of moles of acid is exactly the same as the number of moles of NaOH added; but if you overshoot the NaOH, this won't actually be true. Your moles of acid will actually be slightly less than the number of moles of base. So when you are dividing mass of acid by moles of acid, you will have a slightly exaggerated number for the denominator. This will result in an underestimation of the grams/mole ratio, and will underestimate the actual molecular weight.
- Reason 2: Not all of the acids are perfectly pure. For example, if the solid sample is only 95% pure, this will cause an error in the calculation! Since acids are somewhat hydrophilic, it's not uncommon for acids to be somewhat wet and to give somewhat exaggerated molecular weight numbers.

Example of Molecular Weight Calculation:

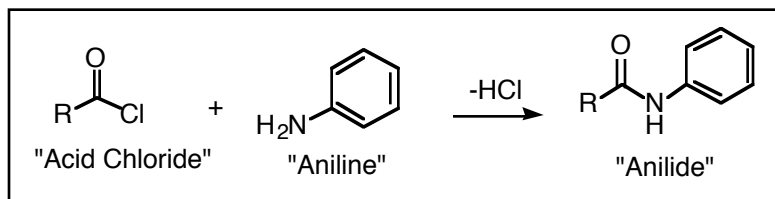
Measured data:

- Weight of acid: 0.2015 g
- Molarity of NaOH: 0.1005 M
- Volume of NaOH to reach the titration end-point: 14.50 mL

Mathematical Calculation of Molecular Weight:

- Moles of NaOH = $(14.50\text{mL})\left(\frac{1\text{L}}{1000\text{mL}}\right)\left(\frac{.1005\text{mol}}{1\text{L}}\right) = 0.001457 \text{ mol NaOH}$
- Moles of acid = moles of base = 0.001457 mol acid
- Molecular weight of acid = $\frac{0.2015\text{g}}{0.001457\text{mol}} = 138.3 \text{ g/mol}$

D. Anilide Derivative



Place 10 drops (or 0.10 grams, if it's a solid) of the acid chloride into a large test tube. Add a stir bar, and add 1 pipet of ether. To this solution add 20 drops of aniline, dropwise (may spatter if you add it all at once) and stir for 5 minutes if it's not already solid. The primary precipitate that forms is the aniline hydrochloride salt. If your reaction is so exothermic that the ether boils away and you end up with an unstirrable solid, then add another pipet of ether. After the five minutes is up, add 2 pipets of aqueous NaOH, and continue stirring for an additional five minutes. If some precipitate remains it is the derivative itself. Use a long pipet to remove the aqueous layer from the bottom of the test tube. (Any unreacted acid chloride should be removed by the basic water.) Then add 2 pipets of aqueous HCl, and stir vigorously. Use a long pipet to remove the aqueous layer. (The aniline should be removed in the process.) Cool your solution in an ice-bath.

If you have a significant amount of precipitate at this point, it is the desired derivative. Filter directly over a Hirsch funnel. Rinse with some HCl/water and then some water to get your

crude derivative. If you don't have a significant amount of precipitate, skip down to the instructions in bold.

Recrystallize the crude derivative from ethanol. Ideal volumes will vary depending on your unknown, but a suggested starting point is 2mL of ethanol and 10 drops of water. But the solubilities will vary greatly from unknown to unknown, so you need to make whatever adjustments are appropriate for your particular sample. You shouldn't need these anymore, but several recrystallization reminders:

- Use a small Erlenmeyer, not a beaker, to reduce solvent evaporation.
- Make all your adjustment decisions while the solution is boiling hot.
- Heating your Erlenmeyer in a hot-water beaker is convenient, to provide more even heating than if you just stand it on a hot plate, and to avoid overheating on the hot-plate surface.
- You and your hood partner should also warm up some ethanol in case you need to add some
- Other than when you're just starting, never add cold solvents.
- During cooling, cover the flask to avoid evaporation of the hot solvent.
- Supersaturation is quite common. If you think you're 50% water, probably stop and cool and see whether crystals will form.
- If no crystals form even after slowly cooling and then icing, try adding ice chip(s).
- Your rinse should be pretty similar to what you think your actual solvent blend is.

If following the acid wash you do not have a precipitate (or don't have very much precipitate), then much/all of the derivative is dissolved in the ether. Add a boiling stick and heat your test-tube to boil off the ether, either with a heat gun or in a hot-water bath. place it in an ice-bath. (Maybe consult with the instructor for fast help.) The residue will probably then crystallize. If not, try to add an ice chip and scrape it with a rough stick. Whether it actually crystallized or not, just recrystallize right in the large test tube. Start with around 1 mL of water. Heat it up in a hot water bath, and add as much hot ethanol as it takes to just barely get the product to just barely dissolve. Cool slowly, and perhaps stimulate crystal formation with an ice chip if necessary. Then harvest your crystals. Your wash solvent should probably be at least 50% water.

E. NMR ^1H will be useful. Don't bother with a ^{13}C NMR, since solubility will probably be too low to get anything worthwhile. The OH hydrogen is often very broad, due to H-bonding, sometimes so broad that you won't see it at all.

- Aromatic hydrogens ortho to a carbonyl are typically pushed downfield, toward 8 ppm. This is because a carbonyl group is a strong electron withdrawer, so it makes the ortho carbons more electron poor, which "deshields" the ortho hydrogens.
- A carboxylic acid hydrogen will normally be invisible, so don't look for it. They are so broadened by hydrogen-bonding that they often just blend into the baseline. Even if you could see them, they appear down at 11-14 ppm, which is off-scale from our plots.
- Some solid carboxylic acids will have low solubility in CDCl_3 . If your sample is not completely soluble, you can run it anyway. But sometimes when there isn't that much sample dissolved, background lines from components in the CDCl_3 solvent can be misinterpreted for real sample lines. The two most common candidates are a line at 0.00 ppm (tetramethylsilane) and a singlet at 7.26 (CHCl_3). These two components are always present when you use CDCl_3 solvent, but their height in a printed spectrum looks much taller relative to other signals if the real sample is very dilute versus if the real sample is more concentrated.

Carboxylic Acid Candidates

<u>Liquid Acid Unknowns</u>	bp of Acid	mw of Acid (g/mol)	mp of Anilide Derivative
Ethanoic Acid	118	60	47
Propanoic Acid	141	74	103
Butanoic Acid	162	88	95
Pentanoic Acid	185	102	63
2,2-Dichloroethanoic Acid	194	129	118
Hexanoic Acid	202	116	95
Octanoic Acid	237	140	57

<u>Solid Acid Unknowns</u>	mp of Acid	mw of Acid (g/mol)	mp of Anilide Derivative
Decanoic Acid	31-32	164	70
Bromoethanoic Acid	47-49	139	131
3-Phenylpropanoic Acid	47-49	150	92-98
2,2,2-Trichloroethanoic Acid	54-58	163.4	97
2-Chloroethanoic Acid	61-62	94.5	137
2-Butenoic Acid ($\text{CH}_3\text{CH}=\text{CHCO}_2\text{H}$)	71-73	86	118
2-Phenylethanoic Acid	76-79	136	118
3-Methylbenzoic Acid	108-110	136	126
Benzoic Acid	122-123	122	163
2-Benzoylbenzoic Acid ($\text{PhCOC}_6\text{H}_4\text{CO}_2\text{H}$)	127-128	226	195
Cinnamic Acid ($\text{PhCH}=\text{CHCO}_2\text{H}$)	133-135	148	153
2-Chlorobenzoic Acid	138-142	156.5	118
3-Nitrobenzoic Acid	140-142	167	155
2,2-Diphenylethanoic Acid	147-149	212	180
2-Bromobenzoic Acid	150	201	141
2,2-Dimethylpropanoic Acid	163-164	102	127
3,4-Dimethoxybenzoic Acid	179-182	182	154
4-Methylbenzoic Acid	180-182	136	145
4-Methoxybenzoic Acid	182-185	152	169-171
3-Hydroxybenzoic Acid	201-203	138	157
3,5-Dinitrobenzoic Acid	203-206	212	234
4-Nitrobenzoic Acid	239-241	167	211-217

- Note: Carboxylic acids are hydrophilic, and tend to absorb some water from the air. Some of the starting amines may also have trace isomeric impurities. The result of moisture and/or impurities means that some of the starting materials may have melting points that are a little bit depressed.

Unknown Report Sheet- **Carboxylic Acid**

Unknown No.

Name

1. Physical Examination of Starting Material

a) Physical State _____ b) Color _____

2. Solubility Tests on Starting Material

Solvent:	Water	If Insoluble in Water, Does it Float or Sink?	Aq NaOH	Aq NaHCO
----------	-------	--	---------	----------

Solubility:	_____	_____	_____	_____
-------------	-------	-------	-------	-------

3. Melting point or boiling point for starting material:

List value:

4. What is the approximate molecular weight (mw) of my sample, based on my titration?

_____ g/mol. (Attach a separate sheet that details your weights, calculation!)
*Beware of ridiculous significant figures.

5. Derivative

observed mpliterature mp

Crude (optional)

Recrystallized

6. H-NMR (attach, with assignments/interpretation. Do analyze aromatic H's)

- **On the proton spectrum, create a standard summary table of your H-NMR data, detailing chemical shifts, integrations, and splittings.**
- Draw the structure of your molecule, with identifiers by each carbon (a, b, c...).
- Then on your standard summary table add a column in which you explain which hydrogens (a, b, or c, etc...) are responsible for which signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic.
- Do analyze aromatic H's for solid samples. For liquid samples with aromatics, the aromatic H's will have overlapping so won't be useful to detail.

7. What is My Actual Unknown? (Letter and Structure)

8. Comments, difficulties, complaints, etc..

User's Guide to NMR: General

- For help, see Dr. Jasperse, Hagen 407J, phone 477-2230
- Draft 10/28/15

1. Add sample to a Spinner/Turbine**2. Adjust depth by placing the turbine into the golden depth finder****3. Load sample/turbine into autosampler.**

- Press the round white **Access Request Button** on the panel below the sample trays/doors
- **Wait until "status" light turns to a solid yellow, and the message panel reads "door unlocked"**

4. Opening Program on Computer: Usually already open, and usually to correct "operator"

- If not open: Operator: Should be your class or research group Password: none.
- To switch operator, click **Logout** from submit mode and select the correct operator

5. "Submit" vs "Spectrometer" modes: New Study/Submit Queue to submit; Spectrometer to print/view

- Click "**New Study**" button (lower left) to jump from Spectrometer to Submit mode
- Click "**Cancel**" button (lower left) to exit Submit queue and go to Spectrometer:

6. Experiment Selection (from within Submit mode). Usually preselected for organic labs.

- If not already in New Sample/submit queue mode, push **New Study** button on lower left
- **Proton8** is the normal H-NMR experiment, under the "UserStudies" folder
- For some classes/operators, **Proton8** has been set to open by default, since most NMR's are regular H-NMR's
- Add experiments as needed from the Experiment Selector.
- To **edit or delete**: **right click** on experiment and select "Open Experiment" or "Delete Experiment"

7. 3 Step Submission (assuming the experiment already specified, and still/already in Submit mode).

- a. **Fill Sample Name** (for both computer filing and printout recognition)
 - b. **Click Sample Spot**: Click on the button showing your sample site. (Remember/record! ☺)
 - c. **Submit**: clicking the **red Submit** button on the lower left side.
- **Note**: Can repeat this 3-step sequence for new samples/new students, if running same experiment
 - **Comment box**: (can add comments for the paper printout). (Control C to cut and Control K to paste)
- Other submission options** of possible use for advanced labs, research, or offsite Concordia users: **Solvent**; **Autoplot** (offsite Concordia users should turn this off); **Email**; **Email Address** (offsite Concordia users should set this correctly!☺); **Lock**: (with non-deuterated solvent run unlocked), **Shim** (with non-deuterated solvent run 1H PFG); **Tune**

8. Opening Completed Samples for Printing and Processing. ("Spectrometer Mode" required)




- Must be in "Spectrometer" mode, not "Submit" mode.
 - If in submit mode, "Submit" button will display (lower left). Click "**Cancel**" to exit Submit mode.
 - In "Spectrometer" mode, must **have "Zones" map displayed** (96 sample nodes show). Click on little circle icon (🔍) to the upper left of the spectra-display panel, if zones map not already open.
- a. **Right click on sample number**
 - b. Click "Show Study"
 - c. **Click on file folder name located on the left**
 - d. Then **double click on spectrum** you want to view to load it into the spectra-display viewscreen.
 - e. Process > **Auto Plot or Print**. See next page for more detailed printing and processing instructions.
- Re-click the little circle icon (🔍) to get back to zone map in order to open other files
 - To return to "Submission" mode in order to run more samples, click "New study"

9. Logout: Click "Logout**" button underneath spectrum-display from Submit Mode.**


10. Plotting (when wanting non-automatic plots)

- Must be in the process mode. (Highlight “Process” beneath the spectrum display)
- a. Click “Auto Plot” or “Print” button, way on lower right corner of page.
- b. Re-click if you want to print additional copies for the other students
 - Note to offline Concordia users: this “plot” command will print to MSUM NMR-room printer. ☺
 - For advanced labs or research groups, additional plot preferences are available in the process mode by clicking “Plot (Beneath spectrum display, 2nd from bottom underneath “Start”)

11. Horizontal Expansions

- With spectrum displayed on screen, use a panel of display icons on the far right.
- a. Click on the magnifying glass icon (6th icon down, )
- b. Move your cursor to the left end of the zone you want to expand, then **hold down left mouse button** and slide it to the other end of the zone you want to expand.
 - To return to the full display, you can either click on the 3rd icon () or the 5th icon ()
 - If the lines aren't tall enough, type “vsadj” (vertical scale adjust) on the command line.

12. Manual Integration: Defining Integrals Yourself (see #13 to also give nice integral numbers)

- With spectrum displayed, **must be in the process mode** (“Process” beneath the spectrum display)
- a. Choose “Integration” (Beneath spectrum display towards left, 2nd underneath “Start”)
- b. Hit “Clear Integrals” button (slightly further to the right and lower down from previous button)
- c. Hit “Interactive Resets” button (immediately above the “clear integrals” button) and define
 5. Move cursor beyond the left end of the signal you want to integrate.
 6. **Left-mouse click-and-release**
 7. Move the cursor to the right of the signal, and again click-and-release. Everything between the two “clicks” will be integrated.
 8. Repeat this for each area you want to integrate.
- d. Click very top cursor icon () to the right of the display screen to regain normal cursor function

13. Setting Nice Integral Numbers (While already in integration mode following steps a-d above)

- a. Click cursor on one of your integral regions
- b. Click “Normalize Area to” “Single Peak” below “Set Integral Area” panel underneath the display
- c. Set “integral area” to some nice whole number (1, 2, or 3, depending on your molecule)
- d. Click the “set integral value” button
 - If it says “cursor is outside of integral region”, then reset the cursor on an integral of choice, and re-click the “set integral value” button again.
 - Click “Auto Plot” (lower right) in order to print.


14. Other Processing Options for Advanced Users/Research Groups/2D-NMR

- | | | |
|---------------------|---------------------|--|
| 1. Peak Picking | 4. Insets | 6. Absolute Concentration Integration |
| 2. Vsadj | 5. Arraying spectra | 7. 2D NMR processing, including varying the signal intensity |
| 3. wp=2p sp=2p plot | | |

15. Opening Spectra From the Data Folders

- Click on the Folder icon and find your class or research professor's folder
- Double-click on the folder with your name.
- Double click on the experiment file
- To get the Folder icon to go back up a step, click on the Folder icon again, then click ONCE only on the little icon that shows an arrow up

16. Getting the last sample out and replacing with a Lock Sample (if auto-eject isn't turned on)

- a. In “Spectrometer” mode, display “zones” map ()
- b. Right click on sample 48 => select “Sample in Magnet” (3rd choice from the bottom) => OK.

17. Logout: Click “Logout” button underneath spectrum-display

Summary of ^1H -NMR Interpretation

I. Number of Signal Sets

II. "Chemical Shifts" of the Signal Sets

9's (9.0-10.0)	<u>Aldehyde</u> sp^2 hybridized C-H's
7's (6.5-8.4)	<u>Aromatic</u> sp^2 hybridized C-H's
5's (4.8-6.8)	<u>Alkene</u> sp^2 hybridized C-H's
3's (2.8-4.5)	<u>Oxygenated</u> or <u>Halogenated</u> sp^3 hybridized C-H's (halogenated and nitrogenated alkyl C-H's will also come in this window, although no candidates for today's lab). Oxygenated sp^3 -carbons are routinely present for the following functional groups that contain oxygen single bonds: a. <u>alcohols</u> , b. <u>ethers</u> , or c. <u>esters</u>
2's (1.8-2.8)	<u>Allylic</u> sp^3 hybridized C-H's (sp^3 hybridized C-H's that has a double bond attached to the sp^3 hybridized C). Allylic signals routinely appear when one of the following double-bonded functional groups is present: d. <u>carbonyls</u> , (ketones, esters, aldehydes, acids, amides) e. <u>alkenes</u> , or f. <u>aromatics</u>
1's (0.7-2.0)	sp^3 hybridized C-H's, with no attached Functional Groups g. <u>Note:</u> Many molecules with non-functional alkyl portions will give a lot of signal in this area.
0-12 (anywhere!)	<u>Alcohol/Acid</u> O-H hydrogens (N-H hydrogens likewise) h. <u>alcohols</u> , i. <u>carboxylic acids</u>

1. Check each of the zones. Each one gives you a yes or no answer about the presence of absence of the featured group.
2. End-Check: Check that the functional groups indicated by your chemical shift information match with the structure you believe you actually have! If not, structure needs correction!
3. The regions are somewhat approximate, and have some spillover.
4. For multi-functional complex molecules, there are more complex ways for a C-H to come in some of the above window. For example, an sp^3 -hybridized C-H with two attached oxygens can come in the 5's, or an sp^3 -hybridized C-H that is doubly allylic can come in the 3's. In other words, the impact of functional groups is roughly additive.

III. Integration These **must be simple whole-number ratios** (2:1, 3:1, 3:2, etc..)

IV. Splitting

- **N-1 Rule:** **N lines** \Rightarrow **N-1 neighbor H's** (H's directly attached to carbons attached to the C-H group causing the signal)
 - The N-1 Rule is useful when working from spectrum to actual structure
- **N+1 Rule:** **N neighbor H's** \Rightarrow **N+1 lines**
 - The N+1 Rule is useful when working from structure to actual spectrum

Note: OH hydrogens don't participate in splitting (normally)

Summary of C13-NMR Interpretation

- Count how many lines** you have. **This will tell you how many types of carbons** you have. (Symmetry equivalent carbons can at times cause the number of lines to be less than the number of carbons in your structure.)
 - Each "unique" carbon gives a separate line.
 - Symmetry duplicates give the same line.
 - If there are more carbons in your formula than there are lines in your spectrum, it means you have symmetry.
- Check diagnostic frequency windows** ("chemical shift windows") of the lines **to provide yes-or-no answers regarding the presence or absence of key functional groups** in your molecule.

220-160	C=O carbonyl carbons, sp ² hybridized
160-100	C alkene or aromatic carbons, sp ² hybridized
100-50	C-O oxygen-bearing carbons, single bonds only, sp ³ hybridized
50-0	C alkyl carbons, no oxygens attached, sp ³ hybridized

- Use DEPT and/or Coupled C13 NMR to Differentiate C, CH, CH₂, and CH₃ carbons.**

<u>Type of C</u>	<u>Name</u>	<u>DEPT-135</u>	<u>Coupled C13</u>
CH ₃	Methyl	Up	Quartert (q)
CH ₂	Methylene	Down	Triplet (t)
CH	Methane	Up	Doublet (d)
C (no attached hydrogens)	Quaternary	Absent	Singlet (s)

- Aromatics, Symmetry, and C-13 Signals.** Most aromatics have symmetry, and both the number of aromatic lines and the splitting of the aromatic lines can be indicative of the substitution pattern on a benzene. Mono- and para-disubstituted benzenes have symmetry.

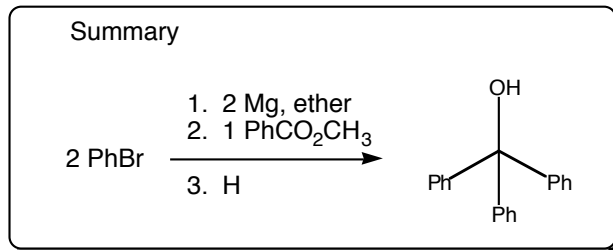
4 lines	s, d, d, d	Monosubstituted benzene. (Has symmetry)
4 lines	s, s, d, d	Para-disubstituted benzene. (Has symmetry)
6 lines	s, s, d, d, d, d	Ortho- or meta-disubstituted benzene. (Has no symmetry)

- Signal Height/Size**
 - Carbons without any attached H's are short. This is common for carbonyls (aldehydes are the only carbonyl carbons that have hydrogens attached) and for substituted carbons in a benzene ring.
 - Symmetry duplication multiplies signal height (if you have two copies of a carbon, the line will probably be taller than normal!)

Standard Synthesis Laboratory Report Format: The following layout is standard for a “synthesis reaction” report. Provide the parts and information in the sequence specified.

1. Title = Reaction Summary

For an organic reaction, there is no point in having a Worded Title: The chemical reaction is the best title summary of what you did!



2. Listing of all Chemicals Used

- This should include all chemicals used, including solvents.
- For each chemical, you should include the actual quantity used and measured. For example, with the methyl benzoate you measured a volume by syringe, rather than by weighing on a balance. So you should list the volume you actually used rather than just the weight.
- For reactants that might possibly be limiting reactants and might possibly factor into calculation of the theoretical yield, you must include more than just the quantity of chemical used. You should also include a conversion from what you measured into the number of moles used.
- In some cases, there may be considerable roundoff (you needn't keep precise record of the quantity of solvent that was used, for example, or of sodium sulfate drying agent...)
- If a person was later to repeat your experiment, they should be able to look at this list and know all the chemicals they'd need to have on hand and in what quantities, in order to complete the experiment.

3. Calculation of Theoretical Yield

- Specify which chemical is the limiting reactant
- Given moles of limiting reactant, calculate theoretical moles of product
- Given moles of product, calculate theoretical grams of product.
- Note: Why do this so early in report?
 - First, because it fits in near your mole calculations above.
 - Second, if calculated in advance. as with most research, you know which chemical is limiting and thus must be measured most carefully, but you also know which are in excess and thus need not be measured with equal precision.
 - Third, it's nice to know approximately how much material is expected, so you can recognize whether your actual results are reasonable or problematic.

4. Writeup of Actual Procedure.

- For this particular experiment, the “procedure” section will be by far the biggest portion of your report.
- This should be a concise but detailed description of things, including:
 - What you actually did (even if not recommended or not from recipe)
 - All observations should be included. These include all observed changes, such as:
 - Changes in **color**
 - Changes in **solubility** (formation of precipitate or cloudiness...)
 - Changes in **temperature** (like, reaction became hot...)
 - Formation of **bubbles**
 - Time and temperature details:
 - Whenever you heat something or cool something, the procedure should specify
 - Specify times. Whether you boiled for 5 minutes or 5 hours matters!
- Writing details: As a record of what actually happened, the report must be written in **past tense**, not **command tense**. (Rather than “Add this”, should read “I added this”, or “I dropped that...”)
- Use of personal pronouns is accepted in this class. You may use “I” or “we” to simplify writing.

5. Product Analysis

- Any NMR, mp, bp, TLC information. For this report, mp and TLC information must be included.
- Final yield and percent yield information.

6. Discussion/Summary. Need not be long, but any conclusions or excuses would go here...

7. Answers to any assigned Questions

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” has 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” (“Chem355 Unknowns..”, or “Nitration” or “Grignard..” or “Esters” for example), but you are trying to add your sample to the lineup.

3. If you’re first in line, get Jasperse to come and help.

- **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. When the machine tries to put the injection sample back, it will have no place to go.
- **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 “sample” 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 “**gcms 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.)

11. 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.**

12. 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.

13. 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):**14. Right mouse double-click on a peak in the top window to get its individual mass spectrum to appear in the lower window.****15. 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