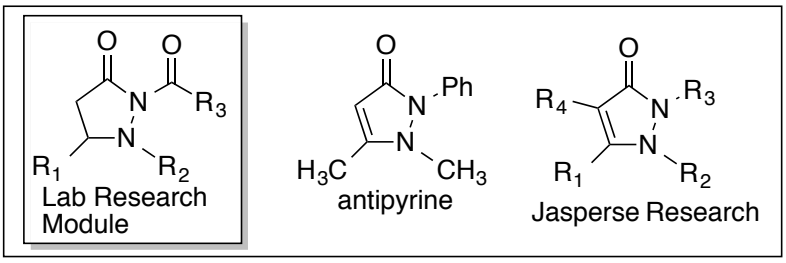
Chem 365 Lab Manual Part II

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" (see left-most "Lab Research Module" structure). The project will illustrate a variety of fundamental organic reactions and fundamental procedures. The acyl pyrazolidinones are of interest as medicinal candidates, as well as for use in further synthetic reactions. (The Jasperse research group is involved in making and bio-screening a diverse library of analogs for "antipyrine", a lead/best but very imperfect drug candidate for treating pulmonary fibrosis.)

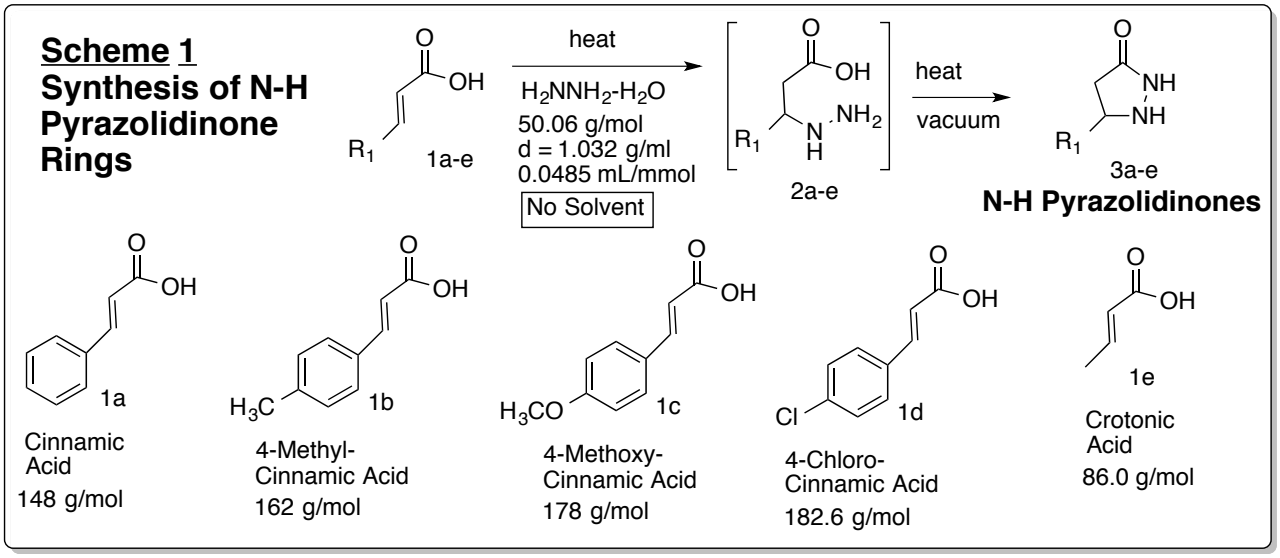


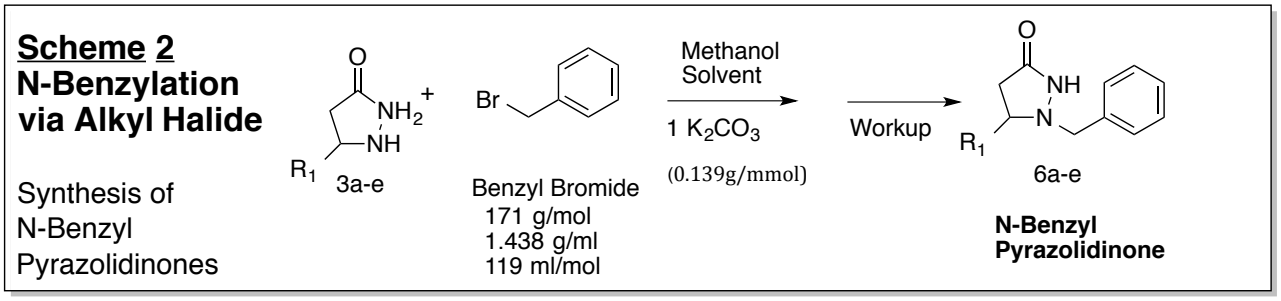
As shown in the "Lab Research Module" picture, there are three different variable R groups in the acyl pyrazolidinones. We will use five different R_1 groups; one, two, or three different R_2 groups; and for this year we'll use a single R_3 group. But imagine if we used five of each group; we could then produce a library of up to 5 x 5 x 5 = 125 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.)

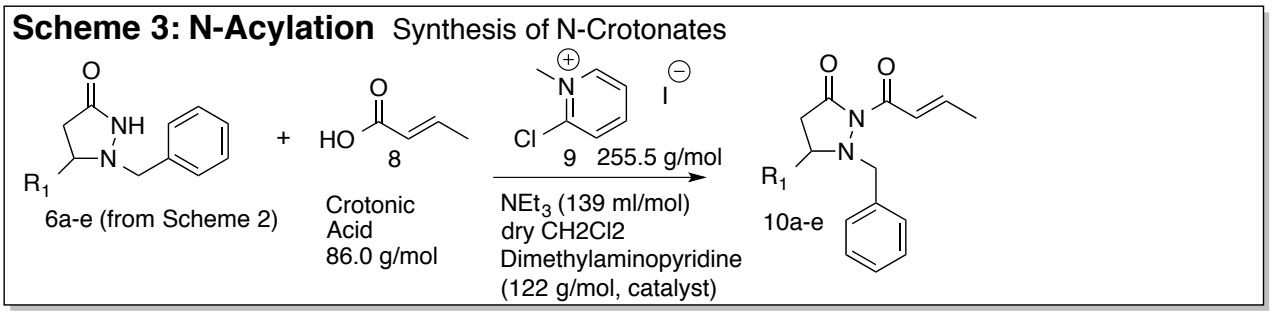
In the first stage, pyrazolidinone rings will be assembled with just one of the substituents attached, R_1, which is bound to the C5-carbon. (See Scheme 1, next page). In the pyrazolidinone ring numbering, the two nitrogens are #1 and #2, the carbonyl carbon is #3, etc.). An unsaturated acid will be 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 S_N2 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 S_N2 mechanism is that the nitrogen can perhaps alkylate twice, leading to a quaternary ammonium salt. Because of the S_N2 mechanism, the alkyl halide electrophile must be an S_N2-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.



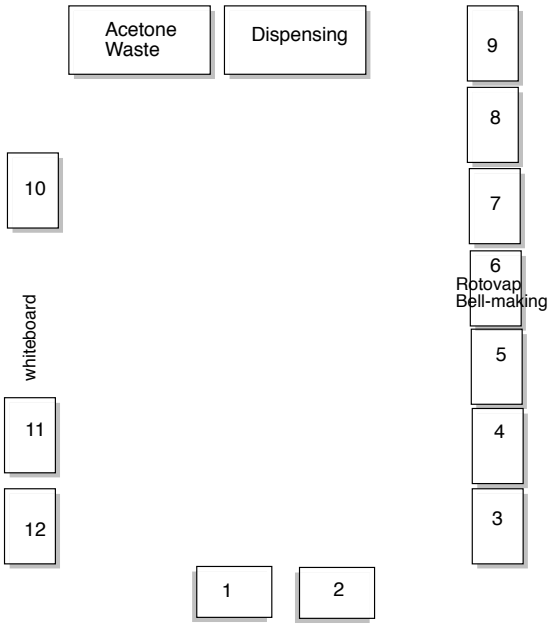


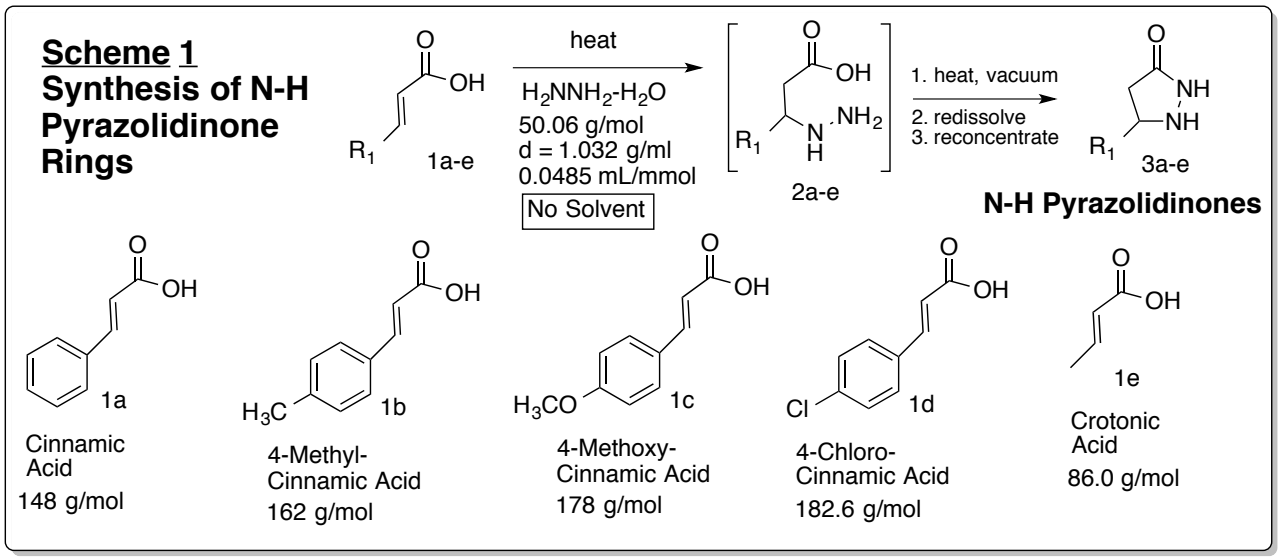


The last stage (Scheme 3) will involve acylation of the top amide nitrogen. The procedure has been invented and developed by MSUM students (most notably Amie Nowacki and Kris Brandvold). A water molecule effectively needs to be eliminated (H from the amide nitrogen in structure **6**, OH from the carboxylic 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 take 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

1. 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.
2. 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.
3. 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.)
4. Add 50 mmol (0.050 mol) of liquid hydrazine hydrate via syringe.
   - Hydazine hydrate: 0.0485 mL/mmol
5. Attach a reflux condenser to your flask, with a gentle water flow.
6. Set the securely clamped flask with the condenser directly on the pre-heated hot plate (heat = 8) and stir for 60 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.
7. During the 60 minutes, plan ahead. During the 60 minutes, prepare the following:
   a. 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.
   b. 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 60 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 (for **3a, 3b**, or **3e**) or 20 mL of methanol (for **3c** or **3d**) 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.
    - The 4-methoxy and 4-chloro compouds **3c** and **3d** are less soluble than the others, so need more methanol to get them relatively dissolved.
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 **3c** and **3d**, if most of the material is dissolved and the stir-bar is stirring, it's OK if there are a few undissolved particles.

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 adapter.
    - **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 $CDCl_3$ 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 $CDCl_3$ 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 90º 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 our your actual specific structure, and added up it's 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.)

5. **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
6. 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.)
7. **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.
8. **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).
9. **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.
10. **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.
11. **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

12. Clearly label each page of each GC/MS printout with the appropriate GC/MS-**3a-e** label in the upper right corner.
13. 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.