Scheme 1
Synthesis of N-H Pyrazolidinone Rings

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 6, so that by the time everything else is assembled the hot plate is good and hot.
2. Check that the vacuum by your hood is turned off.
3. Get a 125-mL ground-glass jointed Erlenmeyer, and add a medium stir-bar. Weigh the combination and record the mass.
4. Calculate how much mass it will take to add 20.0 mmol (0.0200 mol) of whichever alkene acid 1a-1e (or alkene ester 1a-ester) that is assigned to you. Weigh that in a weighing boat.
5. Using a powder funnel, pour your material from the weighing boat into your Erlenmeyer flask. Wipe the ground-glass neck off with a paper towel. (Residual powder can make it difficult to make good glass-to-glass seals, and to detach other jointed glassware later.)
6. Calculate how much liquid hydrazine hydrate will be needed to add 36 mmol. (Hydrazine hydrate: 50.06 g/mol, d = 1.032 g/ml, 48.5 ml/mol, 0.0485 mL/mmol).
7. Use a syringe to inject the hydrazine hydrate into your flask.
8. Prepare a reflux condenser, get a gentle water flow running, and attach the condenser to your flask.
9. Clamp the flask securely. Set the flask with the condenser directly on the hot plate and stir for 20 minutes at spinner setting of 8.
   • Make sure that the flask is not tipped or 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, so 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.
10. During the 20 minutes, get prepared to work fast for what you will want to do after the 20 minutes is complete. During the 20 minutes, prepare the following:
    a. Get two long-stemmed pipets, each with a pipet bulb;
    b. Get two NMR tubes standing inside an empty Erlenmeyer, one with a green cap and one with a red cap;
    c. Find your vacuum adapter. This is about 1 inch long, with a 90-degree curve, a ground-glass joint on one end to plug into a reflux condenser, and a tapered end to plug into your vacuum hose.
d. Get a white rubber “septum” that will be able to get plugged into the neck of your flask

e. Get a glove for your left hand, so you can handle the hot glassware;

f. Double check that the vacuum is turned all the way off (to the right). IF SOMEBODY HAS THEIR VACUUM OPEN TO THE AIR, IT WILL KILL THE VACUUM AND WILL KILL EVERYBODY ELSE’S RESULTS for the next procedure. IF ONE VACUUM IS OPEN AND IS JUST PULLING AIR, THAT AIR LEAK WILL FEED EVERYBODY’S VACUUM AND NOBODY WILL GET THE LOW PRESSURE THEY NEED for the next procedure. Don’t let your hood be the one to ruin everybody’s experiment!

g. Draw the structure for the pyrazolidinone 3 that you should end up making (3a or 3b or 3c or whatever it should be), given the starting material 1a-1e that you used.

• The structure of your starting reactant dictates what the R1 group will be in your product 3.

h. 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)

i. Calculate what the theoretical yield for your 3 should be, given the 20.0 mmol scale.

j. Look ahead to Scheme 2, which you will do today and will start shortly after you complete Scheme 1.

11. After the 20 minutes of heating is complete, either swing the clamped array off of the hot plate or pull the hot plate out from under the flask.

12. With a glove for one hand (for the left hand if you’re right handed), hold the hot flask with the gloved hand, and twist the reflux condenser off with the other hand.

13. Using one of your long-stemmed pipets, draw up a tiny amount, maybe about one quarter-inch of solution (the length of one fingernail?) up into the skinny part of the pipet, and transfer it into an NMR tube. Leave the pipet in the NMR tube.

14. Get 1 mL of CDCl3, and inject it through the pipet into the NMR tube.

15. Cap the NMR tube with a green cap for later submission, and proceed with Scheme 1 Part B.

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

16. Attach the vacuum adapter 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. Turn the vacuum back off.

17. Attach the vacuum adapter to your flask.

18. Crack the vacuum open, really, really carefully and gently at first (so that it doesn’t cause everything to erupt and boil/foam over). Then turn it wide open as soon as possible (two full revolutions will more than suffice) as soon as the bubbling isn’t too wild.

19. Put your flask back onto the hot plate, still at setting 6, and again with direct and complete contact between the flask and the hot plate. Turn the spinner to setting 8 to get fast spinning.

20. Stir/heat/vacuum for eight minutes. Excess vacuum heating may result in both some decomposition, so do not let it stay on the hot plate under vacuum any longer than 10 minutes.

• The hot vacuum is intended to do several things:
  a. Facilitate/complete ring closure (2 \( \rightarrow \) 3).
  b. Distill away water
  c. Vacuum/distill away the 2\textsuperscript{nd} equivalent of hydrazine. Leftover hydrazine causes a problematic side-product in the Scheme 2 reaction, so we want to remove it.
  d. By purifying product 3, subsequent mass/mole calculations will be more accurate

• 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.

21. After the ten minutes, get your flask away from the hot plate. Either slide your hot plate out from under the flask, or use your clamp to swing the flask away from the hot plate.

• Immediately turn off the vacuum.
• If you forget to turn it off, it will ruin things for everybody else because their vacuum won’t work if yours is open to the air.
22. Reduce the hot-plate setting to 5. (You’ll want it at 5 for the next operation.)
23. With the vacuum turned off, detach the vacuum hose from the adapter first. Then grip the hot flask with a glove, and remove the adapter from your flask.
24. Immediately, while the material is still in a hot melted form, dip a long-stemmed pipet into the hot solution and draw up about a quarter inch sample (finger-nail length) of your hot mixture (from the skinny tip of your pipet), and put your pipet into an NMR tube. (If you wait too long and let things cool, the material will harden and make trouble.)
25. Add 1.0 mL of CDCl3 into the pipet, and attach a pipet bulb to the pipet. The sample will probably harden/freeze and prevent the solvent from running out the bottom. 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 same 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 flush solvent back and forth to help sample dissolve.
26. Using your 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
27. Attach a red cap to the NMR tube, shake it up, and submit it to the NMR queue.
  • The experiment that will be/should be run is “Proton 8”.
  • This sample should be given priority status. If you can get it quickly and it looks good, you’ll know you can being the N-benzylination reaction described in Scheme 2.
  • Consult instructor if necessary regarding how to submit NMR’s with priority status.
  • 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 working with the “b” series, then yours should be NMR-3c, etc.)
28. Dilute the GC-MS vial to around 0.5 mL with dichloromethane.
29. Submit your GC-MS sample to the GC-MS queue.
  • This will probably take a while. It is important data for your report, but we won’t wait to get this before starting Scheme 2.
  • In all of your reports, refer to this GC/MS as GC-3a-e. (Well, 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-3c, etc.)
30. Take your flask to the balance and measure the mass.
31. Subtract the original mass of the flask and stir bar in order to determine the mass of product.
32. 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 figure out what is correct for your specific product.
  • You will need a drawn-out structure of your product 3, with your actual R1 unit included, depending on which reactant 1 you started with.
  • 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)
33. Calculate the percent yield of your Scheme 1 reaction (1 → 3)
  • If your yield exceeds 100%, it probably means your heat/vacuum process was not sufficient to complete the ring closure and the boil-off of all of the hydrazine and water. Perhaps consult with the instructor. You’ll probably need to reconnect the vacuum and resume heating at hot-plate setting of 6 for an additional 5 minutes.
• If your yield is <100%, that’s a good indication that your heat/vacuum process has been successful, and that you can proceed with Scheme 2.

34. Timing note: You need to finish a lot of Scheme 2 today. But it would help if you could confirm that your ring closure from open intermediate 2 to closed product 3 is complete. The best tools to confirm are your NMR, and/or your percent yield. If your NMR is complete before you start Scheme 2, and if you can get the instructor’s attention, it might be a good thing to consult with the instructor to confirmation that it’s good to go forward with Scheme 2. But don’t wait.

35. Submit your green-capped NMR-2a-e into the queue. This should NOT be given priority status. This is needed for analysis and report purposes, but is not critical to deciding whether or not it’s good to proceed further with Scheme 2. You may need to come back and pick this up tomorrow or later, if it’s fairly far back in the line.

36. Note: for analyzing and reporting on your NMR and GC-MS data, see the section in the manual dedicated to that. The instructor may also have 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. Start Scheme 2. It is urgent that you get pretty far into Scheme 2 during Week One.
**Scheme 2 Procedure: N-Alkylation Using Aldehyde**

**Scheme 2 Part One: Reactant 3 ➔ Intermediate 5**

1. To the flask with your product 3 from Scheme 1, add 10 mL of anhydrous methanol.
   - For 4-methoxy compound 3c, add 20 mL of methanol, since the 4-methoxy substrates is probably less soluble.
2. Attach a condenser with gentle water flow, and heat the mixture on the hot plate at a setting of 5 with the stirrer at 8 until either the material dissolves or for five minutes, whichever comes first.
   - 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
   - During this time the material will hopefully become homogeneous.
3. Calculate how many mL of benzaldehyde (102 mL/mol) you need to add 1.0 mmol benzaldehyde per mmol of 3. In other words, if you have 18.4 mmol of 3c, how many mL of benzaldehyde will it take to provide 18.4 mmol?
   - This will require that you have already calculated how many mmol of reactant 3 you are working with. To do that, you needed to know your structure, your molar mass, and your actual number of grams. You should have done all this earlier, but if not do it now.
   - If time permits, also calculate how many grams of NaBH4 (37.8 g/mol) will be required to add 0.5 mmol of sodium borohydride per mmol of 3.
     - For example, if you calculate 18 mmol of 3, you would add 9 mmol of NaBH4.
     - Note: if you calculate more than 0.5 gram, you’ve made a calculation error.
4. After the material has dissolved, reduce the hot-plate setting to 4.
5. Use the syringe to directly add the benzaldehyde to your reaction mixture while stirring. You’ll want to detach the condenser first so that it’s easier to inject.
6. Immediately add 0.050 mL (= 50 uL) of trifluoracetic acid catalyst.
   - This is very little.
     - If using one of the Hamilton syringes, it should be about half full, to the 50 mark.
     - It’s just a catalyst, of course, so it doesn’t matter if you’ve got a little more than that or don’t measure it precisely.
   - Trifluoroacetic acid, CF$_3$CO$_2$H, is a nice acid for several reasons:
     - It’s soluble in non-aqueous organic solvents. (HCl is usually used in water...)
     - It’s a pure liquid that can be measured precisely by syringe. (Pure HCl is a gas...)
7. Reattach the reflux condenser, and stir for 5 minutes.
8. Turn the heat off, and add an ice-water bath (use one of the metal pans) to cool your sample for at least two minutes.
9. While it’s cooling, remove the condenser, use a long-stem pipet, and carefully draw up about 1/2 inch of sample into the skinny part of the pipet. Transfer it to an NMR tube, and add 1.0 mL of CDCl3.
   - Cap it with a blue cap, to indicate that it is not a priority sample.
• Do not run a GC on this.
• This can be submitted for a proton NMR as soon as possible and certainly before you leave today, but no urgency now. If the NMR is open, do it now, but if it’s busy, submit it later.
• The NMR experiment to run is called “Suppress-Methanol”, and is found under the UserStudies experiment folder. It will actually produce two NMR printouts for you. The first one will be dominated by methanol, since you have more of that than of your actual product, and can be thrown away. But the second NMR will have “suppressed” the methanol and will give you a more meaningful NMR.
• If you compare your NMR-4x with your NMR-3x, do you see signals where 3 gave signals? If not, it proves that your reactant 3 has completely converted to intermediate 5.
• Do not wait to check the NMR before proceeding ahead with the next operation, the intended conversion of 5 \(\rightarrow\) 6.

10. Note: You definitely want to get through step 14 if possible, which will take another 5-10 minutes. But if you are really struggling with time, you could stop at this point. If so, you could just stick a septum into your flask and stash it in your hood till next week.

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

11. If you haven’t already done so, based on the calculated number of mmols that you used for your chemical 3, calculate how many grams of sodium borohydride (37.8 g/mol) you need to add 0.5 mmol sodium borohydride per mmol of 3.
   • For example, if you calculate 18 mmol of 3, you would add 9 mmol of NaBH4.
   • Note: if you calculate more than 0.5 gram, you’ve made a calculation error.
   • NaBH4 has four hydrides, that’s why you don’t need very many moles.

12. Weigh the sodium borohydride out on a small boat.
   • If there are any big chunks, use another boat, place it on top of your NaBH4 boat, and press down to crush and break up the chunks.

13. Put a powder funnel into the neck of your beaker.

14. Carefully add the sodium borohydride to your stirring solution.
   • Add about half of your NaBH4 first, and stir for 15 seconds or so while the foaming settles a bit, and then add the rest.
   • Some hydrogen gas is produced as a side reaction, and causes the bubbling/foaming. When a hydride reacts with a proton it produces H2.

**THIS IS AN IDEAL PLACE TO STOP AT THE END OF WEEK ONE. LET THINGS STIR FOR 5 MINUTES, THEN ADD A SEPTUM TO YOUR FLASK, POKE A SYRINGE THROUGH THE SEPTUM TO RELEASE ANY HYDROGEN PRESSURE, AND STASH IT IN YOUR DRAWER TILL NEXT WEEK.**

15. If you did not complete steps 11-14 during week one, and are trying to pick up here during week two, then attach a reflux condenser with gently flowing water, turn the hot plate to 5, and stir. Watch for when the mixture gets hot enough to begin boiling, and stir for 5 more minutes after that. Turn the hot plate off after the 5 minutes of boiling. Then cool your flask for 2 minutes in an icewater bath before continuing with the next workup/isolation.
Scheme 2 Part Three: Workup/Isolation of N-Benzyl Product 6 (Week Two Begins Here)

16. Add 30 mL of a mixed solution that is 2/1 ether/dichloromethane.
   • For the 4-methoxy product 6b, use 30 mL of dichloromethane instead of ether/dichloro.
     There may otherwise be some solubility problems with the methoxy substrate.
17. Add 20 mL of brine (NaCl/water) and 20 mL of water.
18. Stir vigorously for five minutes.
19. Pour the mixture into a separatory funnel, and allow the layers to settle.
20. Add an additional 10 mL of ether/dichloromethane (or dichloromethane for the 4-methoxy product 6b) to the original reaction flask, and an additional 10 mL of brine, and add the mixture into the separatory funnel. This should rinse out any residual material.
21. After the layers have settled, drain off the lower aqueous layer, which can be poured down the drain.
   • The product should remain in the colored organic layer on top.
   • It is important to drain out almost all of the water.
   • NOTE, for the 4-methoxy product 6b, it will be in the dichloromethane layer, which should be on the bottom rather than the top.
22. Prepare a clean 125-mL Erlenmeyer flask with a ground-glass joint, with a medium stir bar inside, and with the mass of the combination recorded.
   • This could be same flask/stirbar you’ve been using and which you already weighed earlier.
     To re-use, rinse the flask with water, scrub quickly with a brush, and then rinse with acetone. If you want you can quickly semi-dry it by blowing air into it. But it won’t hurt if there is still acetone.
23. Find your fritted filter funnel (the unit that has a 6-inch column, a white filter disk, a ground-glass joint on the bottom, and a vacuum vent.) Attach this to the Erlenmeyer.
24. Weigh out 7 grams of silica gel, and pour this into the fritted filter funnel.
   • The weight here does not need to be precise.
25. Weight out 20 grams of sodium sulfate, and pour this into the fritted funnel on top of the silica gel layer.
26. Pour your organic solution from the separatory funnel directly onto the sodium sulfate filter.
   • If you have the methoxy compound 6b, you can still directly pour your lower dichloromethane layer directly into the filter funnel, as long as you’re careful to stop before the water layer comes.
27. 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.
28. Get an additional 20-mL of the ether/dichloromethane mixture, and add 3 mL of methanol to that.
29. Pour this mixture into your separatory funnel (this will function as a rinse), and then drain it onto the filter column to rinse the filter pack as well.
   • This should ensure that all/most of the desired product comes through, so that your yield can be good.
   • Water and highly polar side products (including some containing boron) should stick to the column.
30. If you have methoxy 6b, add an extra dose of 10-mL dichloromethane and pour it into the separatory funnel without shaking. Then you can pour this second portion of organic solvent onto the filter funnel. Then pour out the water from the separatory funnel, and do steps 28+29, the rinse of the filter flask with ether/dichloromethane/methanol.
31. **Concentrate of the solution.** Attach a reflux condenser with no water hoses attached, and with a vacuum adaptor on top. While stirring and with no heat turned on, very cautiously/slowly open the vacuum. Things will bubble a lot at first. Crack open the vacuum as aggressively as you can get away with without causing the mixture to foam over.

- Within about 2 minutes you should be able to get the vacuum fully opened. Continue to vacuum with the condenser attached for two minutes.
- Notice the condensation (and perhaps ice) that forms on the outside of the flask.
  - This is a manifestation of how endothermic the vaporization process is. Rotary evaporation can be used, or if the rotovap is occupied you can try to just distill off the solvent in your hood.

32. After two minutes with the vacuum wide open, turn the vacuum off, and detach the vacuum hose from the vacuum adapter. Remove the condenser, reattach the vacuum hose to the adapter, and connect the adapter directly to the flask. Again while stirring, carefully crack open the vacuum until it is wide open. Once you’ve been able to safely open the vacuum fully, turn the hot plate on at a setting of 5, and heat/boil/vacuum the mixture for 20 minutes while stirring rapidly (set the stirrer to 8.)

- Try to wipe off the frost from the walls as early as possible, this will make the solvent boiloff more efficient.
- The mixture should be pretty thick and concentrated by the end, with limited bubbling.
- In some cases, the material may foam up like cotton candy or taffy. This occurs when a limited amount of solvent is still present, but the mixture has gotten so thick that the solvent can’t easily escape from its “shell” of non-volatile material. So when solvent molecules inside are vaporizing, but they can’t escape easily, the volume puffs up as with cotton candy. With continued heating, though, usually any entrapped solvent does escape, and the material collapses back to a thick paste.

33. During the 20 minutes, do some calculations if you haven’t before.

- Draw out the structure of what your product 6 should be.
- Given the structure, calculate what the molar mass of 6 should be, to the nearest whole number.
- For atoms C, N, O, and H, you can just use their whole number masses in all calculations (in other words, C is 12, N is 14, O is 16, and H is 1. You don’t need to use more detailed mass values than that, for example just use 1 rather than 1.0079 for H.)
- For Cl, use 35.5, because that doesn’t round off to a whole number so nicely as H/C/N/O.
- Given the molar mass of your product, and given the mass and mmol of the reactant 3 that you started with, calculate what your theoretical yield in grams should be for product 6.
- The molar mass will also be needed for preparing your next reaction (Scheme 3).

34. 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.

35. Immediately, while the mixture is still hot and hopefully liquid, dip in with a long-stem pipet and draw up a quarter inch of material. A glove to grip the not flask may help. Immediately place the pipet into an NMR tube. The material will probably harden/freeze as it cools.

36. Add 1-mL of CDCl3 into the pipet, then take the NMR tube with the pipet inside it over to the heat gun. With or without the instructor’s assistance try to heat and melt your product so that the solvent can flow into the NMR tube. Use a red cap for this one to remember that it’s a priority sample.

37. 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 chemical you’re really working with.)
38. Submit the NMR to the NMR queue for purity analysis.
   • The experiment will be called “proton 8”.
39. 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.
40. Given the structure of your product and the molar mass that you calculated earlier, determine the number of mmol of product that you made.
41. Calculate the percent yield, based on the number of millimoles you ended with and the number of millimoles that you began with in the overall $3 \rightarrow 5 \rightarrow 6$ operation.
42. **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.