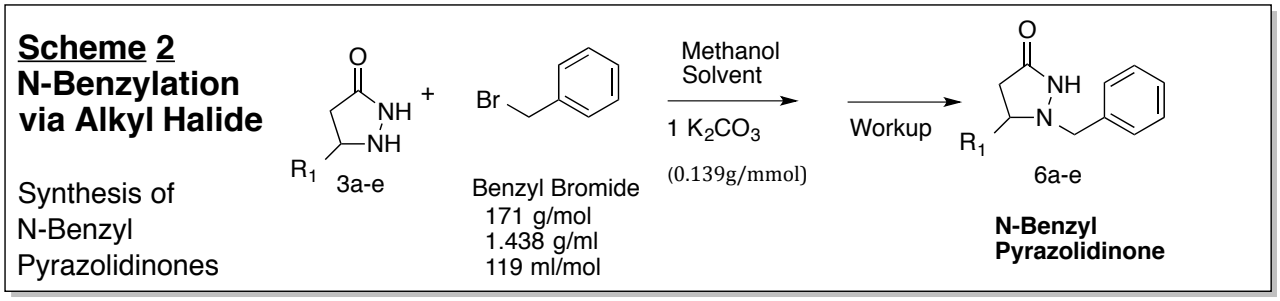

Scheme 2 Part A: Redissolve in Methanol

1. Turn hot plate to 5.
2. To the flask with your product 3 from Scheme 1, attach a condenser with gentle water flow.
3. Add 15 mL of methanol for **3a**, **3b**, **3d**, or **3e**. Add 35 mL of methanol for **3c**.
   - More methanol is needed for 4-methoxy compoud **3c** because it is less soluble.
4. 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.
5. Once your material is largely dissolved, reduce the hot plate setting to 4.

Scheme 2 Part B: Addition and reaction of Benzyl Bromide

6. **Add K_2CO_3**: Add 20 mmol of potassium carbonate powder (K_2CO_3, 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
7. **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.
8. **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: Workup Using Separatory Funnel and Chromatography

10. Add 20 mL of dichloromethane.
11. 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…
12. Pour the mixture into a separatory funnel.
13. Rinse the original reaction flask with an additional 10 mL dichloromethane and add to the separatory funnel.
14. 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).
15. 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!
16. 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.
17. Add 50 mL of ether to the same Erlenmeyer that already has the dichloromethane extracts.
18. Preweigh a 250-mL groundglass Erlenmeyer with a clean long stir bar already inside.
19. 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.
20. Add 15 grams of silica gel (approximately) to the fritted filter funnel.
21. Add 20 grams of sodium sulfate to the fritted funnel, on top of the silica gel layer.
22. 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.
23. 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.)
24. 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 helps to boost the yield

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Scheme 2 Part D: Concentration

25. 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.
26. 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.
27. 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.
28. 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).
29. 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.
30. 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. Attach a septum to block air from your hot sample as soon as possible.
31. Add 1.2-mL of $CDCl_3$ 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.
32. 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.)

33. 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.
34. 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.
35. 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.
36. 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.
37. 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 → 3 → 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 3-operation sequence, if each step is 80% (good), you'd end up 51% overall.

38. 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.

39. 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 **6b, 6c,** and **6e?**
    - Does your product look reasonably pure?
40. **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.)
41. **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.
42. **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 **6e**.
    - **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!**
43. 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 aromatic hydrogens. (There are so many overlapping aromatic H's that they aren't interpretively useful in this case.)
44. **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**.
45. **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 **6a-6d** should show up around the low 4's. For the β-hydrogen in **6e**, 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.
46. **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**

47. **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**?
48. **GC-MS:** Clearly label each page of each GC/MS printout.
49. 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 **6** 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 (PhCH2+ = 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.