Scheme 2: N2-Arylation using Aryl Iodides and CuI-Diaminocyclohexane Catalyst

- Note: While the next two pages are done week one, they should be included in your Scheme Two lab report.

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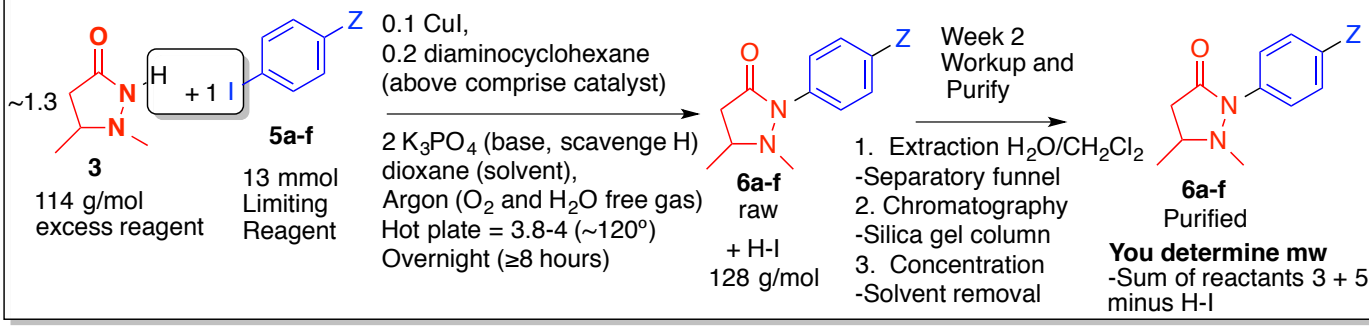
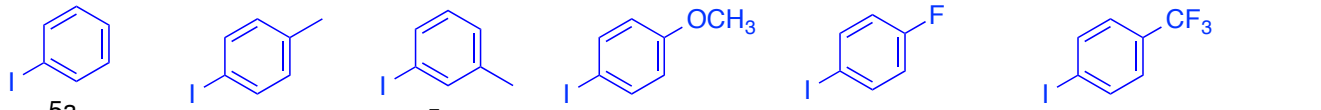
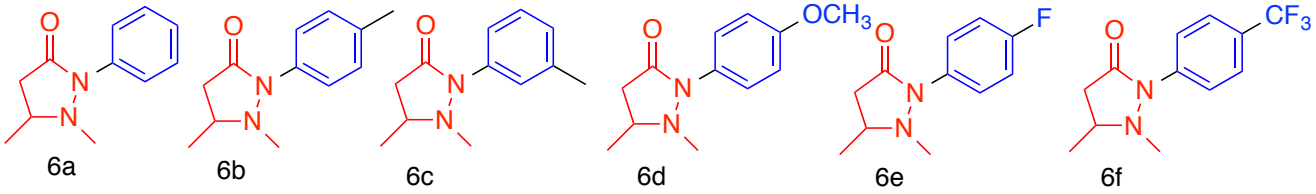


Reactant Aryl Iodides 5a-f and their Molecular Weights



5a	5b	5c	5d	5e	5f
Iodobenzene	4-Iodotoluene	3-Iodotoluene	4-Iodoanisole	1-Fluoro-4-Iodobenzene	4-Iodobenzotrifluoride
204 g/mol	218 g/mol	218 g/mol	234 g/mol	222 g/mol	272 g/mol
112 mL/mol		128.4 mL/mol		115.3 mL/mol	147 mL/mol
0.112 mL/mmol		0.1284 mL/mmol		0.1153 mL/mmol	0.147 mL/mmol

Desired Products



6a	6b	6c	6d	6e	6f

You determine the molecular weight of your product 6.
-But, it should be the sum of the molecular weights of reactants 3 + 5, minus the mass of H-I (128)

Reagents:

1. Pyrazolidinone **3**: Report how many grams and mmoles you actually produced at the end of Scheme. But it should be ≤20 mmol.
2. CuI: 2 mmol x 190 = 380mg
3. K3PO4: 20 mmol x 0.212 g/mmol = 4.2 g
4. Aryl iodide: 13 mmol. (you figure out how much of yours you need to add!
5. Dioxane (anhydrous): 20 mL
6. Diaminocyclohexane: 4 mmol x 0.120 mL/mmol = 0.48 mL
   - add only after air/argon gas replacement is completed
7. Argon atmosphere
   - Ask instructor help with this.

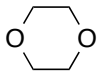
Workup materials:

8. Dichloromethane: ~80-90 mL
9. Water: 60 mL
10. silica: 10g
11. Sodium sulfate: 30grams
12. 5% methanol/Dichloromethane: ~20 mL

Procedure:

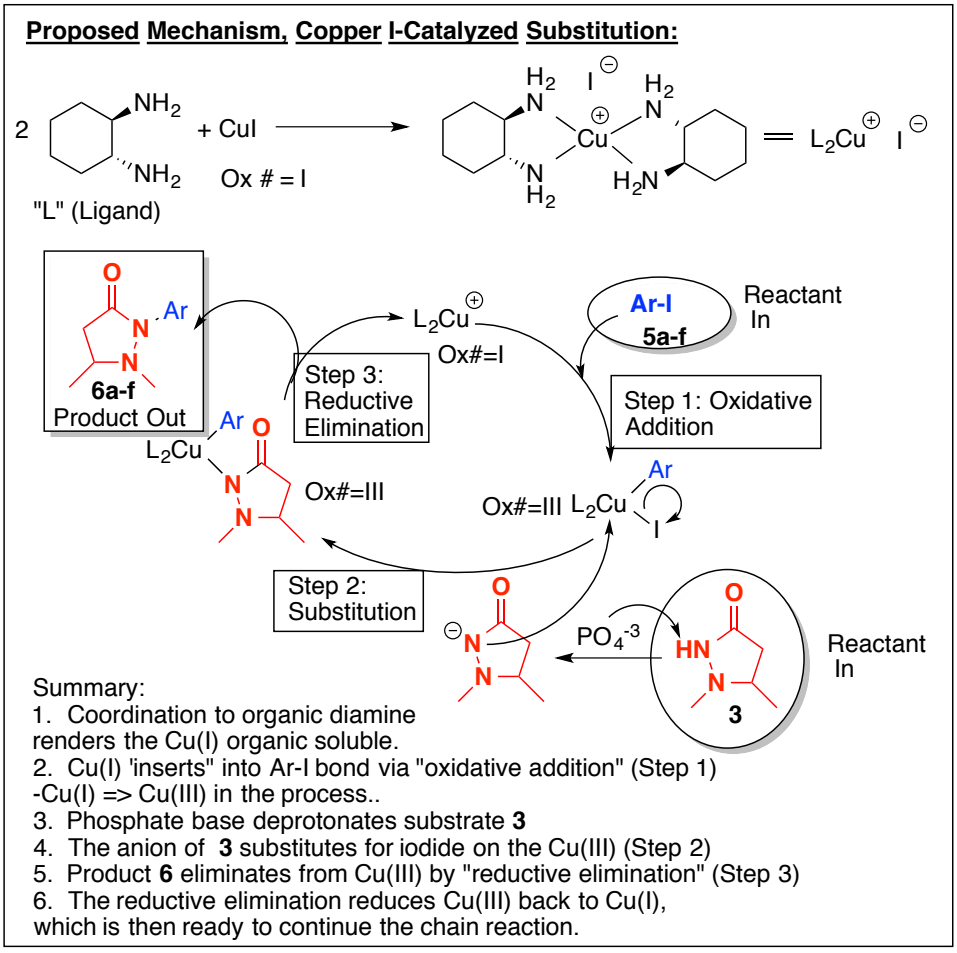
Part 1: Starting the Reaction for N-Arylation

1. Carry your flask with your reagent **3** in it, and the septum, to the balance, to weigh in any solids. Avoid air exposure, so pop the septum back in after each addition.
2. Add Copper iodide: 2 mmol x 190 = 380mg
3. Add Potasssium phosphate: 20 mmol x 0.212 g/mmol = 4.2
4. Add 13.0 mmol of your aryl iodide, whether it's a solid or a liquid.
    - Details for each one are listed on previous page.
    - For a solid, the molecular weight is used to determine how much mass to add.
    - For a liquid, use the mL/mmol value to calculate how much to add.
        - In either case, calculate for 13 mmol.
        - If uncertain, check with Dr. Jasperse.
5. Add ~20 mL of anhydrous dioxane.
    - The measurement doesn't need to be precise.
    - Get within 2 mL of 20mL, but better to act quickly than to be super precise! ☺
        - The dioxane is air/moisture sensitive. Because it a cyclic ether, it hydrogen bonds to water, so moisture from the air can dissolve in and contaminate the solvent.
        - We want it to stay as dry as possible for future users, so screw the cap back onto the dioxane bottle first, as soon as you've poured your 20mL out, before pouring your dioxane into your flask.
        - Then pour your 20-mL into your flask, and put the septum back in to exclude further air exposure.



Dioxane
1. Ether-type dissolving properties (only better)
2. Larger, so higher boiling point
   => hotter + faster reactions, but not too high-boiling to distill away at the end
3. Symmetry gives it a very simple NMR, so residual dioxane doesn't confuse spectra much

6. Purge three times with argon. The instructor will do this for you, at the purging station in the hood near the acetone waste hood.
    - The goal is to replace the air in your flask with inert argon gas, which has no water and no oxygen in it.
    - Residual oxygen is otherwise able to oxidize and destroy Cu(I)-oxidation-state catalyst. If all of your catalyst gets destroyed, the catalytic reaction will fail!
    - The instructor will execute the gas purge for you, but if you have a partner, make sure both come along to see how this is done.
7. Bring the flask back to your hood and stir vigorously for 1 minutes to get everything mixed.
8. Add diaminocyclohexane, via syringe by puncturing through the septum.
    - 4 mmol x 0.120 mL/mmol = 0.48 mL Dioxane (4 mL).
    - The order of addition of the other chemicals didn't really matter. But the diamine should be added last, and only after the argon purge is complete.
    - The diaminocyclohexane attaches to the copper to make the hopefully active catalyst.
    - It also serves to get the Cu(I) ion dissolved into the organic solution. (with two diamonocyclohexanes attached, the composite catalyst now has a lot of organic character.)
9. Stir vigorously on a hot plate.
    - Set hot-plate setting to ~3.8. (It's probably fine up to 4.0).
    - So I'd maybe just set to 100 and keep it simple, or find a hot plate and try something.
10. Stay for 15 minutes to watch and record color changes or other observations. After that, you are free to go! (But make sure your flask has your name labelled on it, so it won't get confused with other students in same hood!) **YOU ARE NOW DONE WITH THE WEEK ONE CHEMISTRY**! ☺
11. Let stir hot overnight. The instructor will come in the morning and turn the heat off.
12. The mixture will then wait till next week for workup, isolation, purification, and analysis! ☺



Proposed Hypothetical Mechanism for the Cu(I)-catalyzed arylation and discussion (for your interest): The mechanism is very interesting and is **very** different from anything you've seen before. In introduction to SN1 and SN2 reactions, for example, we couldn't use aryl iodides in either of those type mechanisms.

But something very different happens here with the Cu(I). Several low-oxidation-state transition metals [Cu(I) and Pd(0)] have a capacity to do "oxidative addition" into certain aryl-halide bonds. In Step I, Cu(I) inserts into the Ar-I bond, creating new Cu-I and Cu-Ar bonds. This is formally an oxidation-reduction reaction: copper is oxidized from Cu(I) => Cu(III). The iodide and carbon are reduced; they can be viewed as anions following Step 1. The mechanistic detail of how this oxidative addition proceeds is beyond the scope of this course!

The nitrogen then substitutes onto copper in Step 2. This can be viewed as a simple SN2-type substitution. The phosphate base is strong enough to generate the resonance-stabilized nitrogen anion under the high temperatures.

After both the nitrogen and aryl groups bond to the Cu(III), those two then hook together and detach from the copper (Step 3) to make product **6**. This is termed "reductive elimination" because the Cu(III) is reduced back to Cu(I). The aryl and nitrogen, formally anionic when coordinated to the copper, are oxidized back to neutral. The mechanistic detail of this reductive elimination is again beyond the scope of this course! ☺☺

The diaminocyclohexane serves two crucial roles. First, coordination to the Cu(I) makes the complex mostly "organic" so that it becomes soluble in the dioxane solvent. Solubility of the catalyst is essential. Second, coordination enriches the electron density of the Cu(I), which makes it more reactive as a reducing agent in Step 1. In the figure, "L" is a shorthand for "ligand", which is a general term for something coordinated to a metal. So "$L_2Cu(I)$" represents two diaminocyclohexane ligands coordinated to a Cu(I).

Notice how the $L_2Cu(I)$ catalyst, shown at the top of the loop, functions as a catalyst. Following the cycle of oxidative addition-substitution-reductive elimination (Steps 1-3), the original $L_2Cu(I)$ is regenerated and can repeat the chain. Thus a stoichiometric amount is not required.

Aryl-substituted nitrogens are prolific in nature and in medicinal reagents. The ability to use catalytic arylation to attach aryl groups onto nitrogen is very powerful and useful.

You probably noticed some color changes. If you saw some blue, that would be some Cu(II), probably resulting from trace oxygen oxidizing the catalyst. As the reaction proceeds (or when you return next week), you'll probably see a lot of red/purple. That is the color of iodine, resulting from oxidation of iodide product, either by adventitious oxygen leakage through the septa, or else by reduction of something else in the mixture.

Week Two: Scheme 2 Product Workup, Isolation, Purification, Concentration, and Analysis.

1. Remember that you will be submitting a lab report on ALL of Scheme 2. That includes the scheme 2 work and calculations and listings of chemicals and moles calculations that you did last week (page 7).

2. **Contaminants**: At this point you will have a LOT of different things in your solution mixture:
   a. **Product** (hopefully, and hopefully lots!)
   b. The dioxane solvent.
   c. Lots of potassium phosphate (or hydrogen phosphate, the conjugate acid)
   d. Iodide ions
   e. Excess reactant **3**
   f. Chemical **4**, the structural-isomer side-product from Scheme 1.
   g. Copper-iodide/diaminocyclohexane stuff.
      - These were combined to make the catalyst, so they should still be in there.
      - Some catalyst decomposition into who-knows-what occurs upon exposure to air and water.
      - I suspect that any insoluble junk (maybe a lot) is copper/diaminocyclohexane stuff?
   h. Some aryl iodide?
      - Hopefully not, because it's the limiting reagent.
      - But maybe the reaction didn't convert it all perfectly and completely?
   i. Carryover contaminants: Any junk that was present at the end of Scheme 1 is still in the soup.
   j. Contaminants in aryl iodides: the commercial aryl iodides weren't 100% pure to start with.
   k. Newly-formed contaminants = side products! (We hope not a lot, but there are probably some things other than just desired product forming.)
   - So, lots and lots of things we want to get our product away from!

3. **Isolation/Purification Plan: The Overall Plan for the Day**
   a. Part 1: **Dichloromethane extraction from water in separatory funnel**:
      - The product **6** (neutral organic) should extract out into dichloromethane,
        - although several extractions will be needed to get it all out. (With two nitrogens and an oxygen, the solubility in water is non-trivial.)
      - Ionics should stay in the water. (Iodides, sodium phosphate, sodium hydrogenphosphate)
      - Starting substrate **3** will largely remain in the water. It turns out that excess reactant **3** and structural isomer **4**, which have two nitrogens and an oxygen versus only 5 carbons, are really strong hydrogen-bonders with water.
   b. **Chromatography**. The organic solution will be passed through silica gel and sodium sulfate.
      - Any insoluble junk will get stuck.
      - Any water in the organic solution will get physically absorbed on the sodium sulfate.
      - And starting substrate **3** that didn't stay in the water will absorb tightly to the polar silica gel.
      - Any other contaminants that are significantly more polar than the product will hopefully stay absorbed on the polar silica surface.
      - Organic contaminants that are not much more polar than the product will pass through, however.
   c. **Concentration (hot and with vacuum)** to remove all solvent
      - Following filtration, the solvent needs to be removed.
      - The solvent will include lots of dichloromethane, plus a lot of dioxane which has a much higher boiling point (~100ºC) than dichloromethane, plus some methanol.
      - The combination of vacuum and strong heating should be able to distill these away.
      - The product being much heavier and less volatile should remain behind!

Workup, Isolation, Purification, Concentration

1. Record observations of your solution.
2. Add 60 mL water (tap is fine)
3. Add 40 mL of dichloromethane ("DCM")
4. Stir very vigorously for ≥5 minutes to try to get the potassium phosphate solids dissolved up into the water layer.
5. Add a long stir-bar to a 250-mL ground-glass flask, and pre-weigh the combination
   - Your final yield will be determined by subtracting this mass from the flask+stir-bar+product mass.
6. Pour solution into a separatory funnel and allow it ≥2 minutes to settle.
7. Add another 10 mL of dichloromethane. Do not shake; this may help visualize the distinction between the aqueous layer on top versus the organic layer on the bottom.
8. Record obsevations.
9. Added fritted filter column to the 250-mL flask
10. Add 10 g silica to filter column
11. Add 30 g sodium sulfate to the filter column
12. Carefully drain the lower organic layer from your separatory funnel into the filter column, so that liquid gets pulled through without boiling out and getting sucked into the vacuum tube.
    - Don't worry if there is a lot of solid insoluble stuff at the interface between the two layers.
    - It isn't desired material; it is something copper-containing.
    - Whatever comes through will just get stuck on the sodium sulfate anyway.
13. If the solution flows slowly, you can assist by attaching a vacuum hose and gently vacuuming.
14. Avoid having any of the water layer drain out.
15. Add another 20 mL DCM to rinse the original flask
16. Pour this into the sep funnel, shake, let settle, and again drain the DCM layer through column
17. Repeat steps 26 and 27 (basically you're doing a 3rd extraction with DCM to make sure all of your product is extracted from the aqueous phase.
18. Take 15 mL of 5% methanol-dichloromethane (available in the hood), and rinse this directly and cautiously through the filter column.
    - Methanol is a stronger elution solvent than is DCM.
    - The purpose here is to make sure that all of your product is washed off of the silica, but hopefully without having a lot of dark-colored polar contaminants wash off besides. (They are impurities, and for Mayo testing, I'd rather have lower yields than contaminated products.)
    - As you do this last rinse, *if* it looks like a colored band is moving down the column and is going to come off, DO WHATEVER YOU CAN TO STOP BEFORE THAT COMES OFF!
      - Pull the vacuum hose off of the filter column,
      - Remove the filter column from the flask.
      - Turn off the vacuum.
      - I don't want dark colored bands flowing into the receiver flask, if possible!
19. What is happening with this silica chromatography/filtration?
    - The silica layer is meant to adsorb as many side-products as possible, while still allowing your product to pass through the column.
    - A quick and dirty chromatography like this won't do a perfect job; probably some side-products will leach through, and possibly some desired product may remain adsorbed to the silica and lost.
    - For medicinal screening at Mayo, we are more concerned with purity than with yield. So, 40-60% yield at >90% purity is much preferred to 75% yield at 75% purity, for example.
    - I'm hoping that your product **6** will be pure enough for direct drug testing. But this is research, so I don't know! ☺☺

- The amount of silica and the specific solvent is selected to hopefully allow most of the more-mobile product **6** to get through, while allowing relatively little of the side products to get through. But, it's research, so we'll see how well it does!
- As you might guess, expecting the silica to selectively bind ALL of the various side chemicals, while retaining NONE of the desired product **6**, seems somewhat unlikely!

1. **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 may bubble a lot at first. Crack open the vacuum as aggressively as you can get away with without causing the mixture to foam over.
   - You may want to request the instructor to come over to get this started.
   - 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.
2. Once you've been able to safely open the vacuum fully, turn the hot plate on at a setting of 6, and heat/boil/vacuum the mixture while continuing to stir for 30 minutes.
   - Try to wipe off the frost from the walls as early as possible.
   - The mixture may be pretty thick and concentrated by the end, with limited bubbling.
   - In some cases, the material may perhaps foam up like cotton candy or taffy. With continued heating, though, usually the entrapped solvent will escape, and the material will collapses back to an oil.
3. During this time, prepare and run an H-NMR on the starting aryl iodide, if you haven't previously.
   - You'll want to be able to compare the NMR for your final product to both the starting material **3** from last week, and for the starting aryl iodide **5**.
4. If you haven't previously calculated your theoretical yield, do so now.
5. 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.
6. Measure the mass of the flask with the product.
   - Subtract the original mass of the flask and stir bar in order to determine the mass of product.
   - Record the mass of product.
7. If your yield exceeds 100%, more hot vacuum is required.

8. **NMR-Sample Preparation**: Dip in with a long-stem pipet and draw up a half-to-one inch of material. Immediately place the pipet into an NMR tube, and put the septum back into the flask.
9. Add 1.2 mL of $CDCl_3$ as solvent to your NMR sample/pipet.
10. **GC Prep**: Using the same long-stemmed pipet, draw out what solution it can reach from your NMR tube, and transfer it directly 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
11. **Submit the NMR sample**. (Print an extra copy of the un-zoomed to give to instructor!)
    - Will want to do horizontal expansion in the 1-4 and 6-8 ranges.
    - The 1-4 analysis will show whether alkyl signals from substrate have been converted to new product signals, and if cleanly or junky.
    - Will want to do horizontal expansion in the 6.5-8.5 kind of range. This should be able to illustrate whether starting aryl iodide has been converted, and if so whether cleanly or not.
12. **Submit your GC-MS sample to the GC-MS queue**. (Print an extra copy to give to instructor!)
    - This will probably take a while to run. Turnover time will be about 10-12 minutes?
    - To analyze this simply, you'll need to review what your retention time was for substrate 3.
    - You should also have a reference GC on the starting aryl iodide
    - The product should have a longer retention time than either substrate or iodobenzene.
    - You want to know the molecular weight of the product, so you can check to see whether a significant peak with matching molecular weight will be the dominant new peak.

Scheme 3 Part Three: Cleaning Up and Collecting Products into the Collection Vials

1. Using a pipet, transfer as much of your final product into a 20-mL vial with a black cap.
2. Write your sample name (**6a** or **6b** or **6c** or whatever) **and** your **student name(s)** on the vial with a sharpie.
3. Place the vial into a product-collection beaker with the correct **6a** or **6b** or **6c** or whatever
4. Place an extra copy of your NMR printout (no zooms required) and your GC printout next to the product-collection beakers. (I can sort them later.)
   - I'll want to look through the spectra to find the most pure samples, that are hopefully pure enough for Mayo submission! ☺☺.
5. BE SURE THAT YOU'RE PUTTING YOUR PRODUCT INTO THE CORRECT CONTAINER. WE DON'T WANT ANY **6ba** GOING INTO A **6aa** CONTAINER, ETC.

Silica Waste handling: all of the solid silica and sodium sulfate in your filter column should go into a solid-waste container in the hood. Bulk may NOT go into the sink or garbage. (Trace amounts stuck on wall may.)

Otherwise glassware should be washable with water and acetone.

Scheme 2/Week 2 Lab Report: The same principles as described for Scheme 1 report apply.

1. Write a standard synthesis style lab report for your Scheme 2 reaction (**3** → **6**).
2. Show all calculations. (Including any mole => mass for reactants, or mass => mole for products)
3. Include procedural details and observations as usual.
4. Calculate mass yields, and percent yields, etc., for product ~~3~~ 6
5. Include your NMRs for **6**
   - Be sure to draw your structure, and then provide an abbreviated summary report. This should include a listing of chemical shifts, integrations, and a matchup-assignment between signals and hydrogens in the molecule.
   - You can perhaps ignore splittings for the alph and beta H's, since they will likely be rounded.
6. Note: For the Scheme 2 report, include both NMR's and GC's for product **6** but also for starting material **3** and for your aryl iodide **5** too, for comparison.
   - Comparing products to reactants helps show whether they converted or not, and whether unreacted starting materials are contaminating your product.

17. 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**.
18. This should have already been in your main lab report, but for my grading convenience, for the major product **6**, list the chemicals shifts for the following signal sets in major product 3a:
    - N-methyl:
    - C-methyl.
    - β-H:
    - α-H (one of them):
    - α-H (the other one):
    - Aryl H's
    - Any additional methyl groups (**6b,c,d** will all have an additional methyl group**)**

NMR and GC-MS Data in the Research Module Scheme 2.

1. An **abbreviated summary report** process will be required. Draw the structure and label the different carbons. Then make a table with the actual chemical shifts, integrations, and splittings (some hydrogens may have very rounded signals) for the actual spectra, 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 spectra. The two alpha-hydrogens will have difference chemical shifts

   - Include integration.
   - Do not need to analyze/report the splitting (although you may do so. But in several cases H's may be very broad and rounded.)
   - Which signal is from the β-H, and which signals are from the α-H's?
   - Does your product look pretty pure? If so, there should be a fairly limited number of contaminant signal sets.

2. **Scheme 2: Does your NMR confirm that your heat-vacuum process removed the solvent? Does it look like your product is relatively clean, or is there a lot of junk present? Does it confirm that you starting material 3 converted to new product 6**?
3. If you compare your NMR for product **6** versus for reactant **3**, you should be able to see whether reactant **3** is gone or is still present.
4. You should be able to recognize the presence of residual solvents. CH_2Cl_2 gives a singlet at ~5.28 ppm; dioxane in the high 3's, maybe ~3.8?
5. **Chirality, H non-equivalency, and chemical shift**. In your NMR for both products **3** and **6**, 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.
6. **Rounded H-signals in products 6:** 5-membered rings sometimes have energetically similar conformations that exchange at rates comparable to the NMR time scale. A result is that some of the ring-H's in products **6** will look really broad and rounded. The integrations and chemicals shifts should be appropriate, but the splitting may not be visible.
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:
   - There should be a nice methyl doublet in the 1's, and an N-methyl singlet in the 2's.
   - Samples **6b, 6c,** and **6c** should each an additional methyl singlet in the 2's or 3's.
   - Samples **6b,d-f** should all have a pair of 2H doublets in the aryl region, due to the para substitution.
8. **Nitrogen impact on chemical shift**: The impact of nitrogen on chemical shifts is somewhat similar to but weaker than the impact of an oxygen attachment (addition factor of about +1.5-2.)
9. **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.
10. **Comparison to Other NMRs**: It may be interesting to look at how your NMR looks compared to how NMRs of other students look. It will also be very important to see how your NMR changes from structure 3 (the product of the "Scheme 1" chemistry) versus product 6 (the product of the "Scheme 2").

GC-MS Analysis/Interpretation

14. Draw the structure and write the molecular weight underneath the picture.
15. **Retention time**? What is the retention time for your **6**?
    - Product **6** should have a longer retention time than product **3**, being bigger.
16. **Purity:** How pure is your **6** by GC?
17. **Mass Spec and Molecular Ion**: Check in the mass-spec whether there is a molecular ion peak that matches the molecular weight for your product.
18. **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.