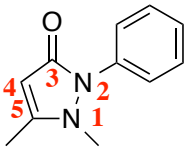
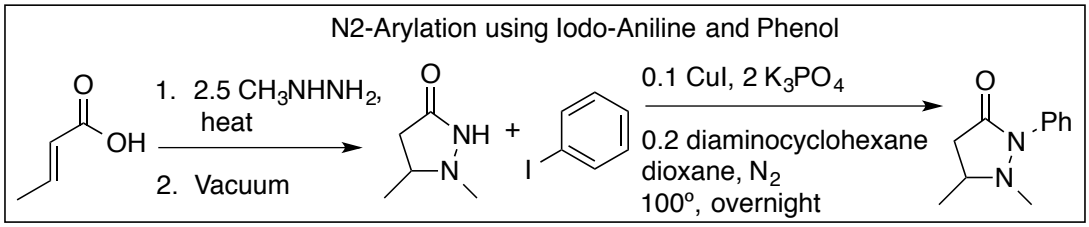
Document Beginning: 9/3/2021. Kudzi Chisveto

Context:

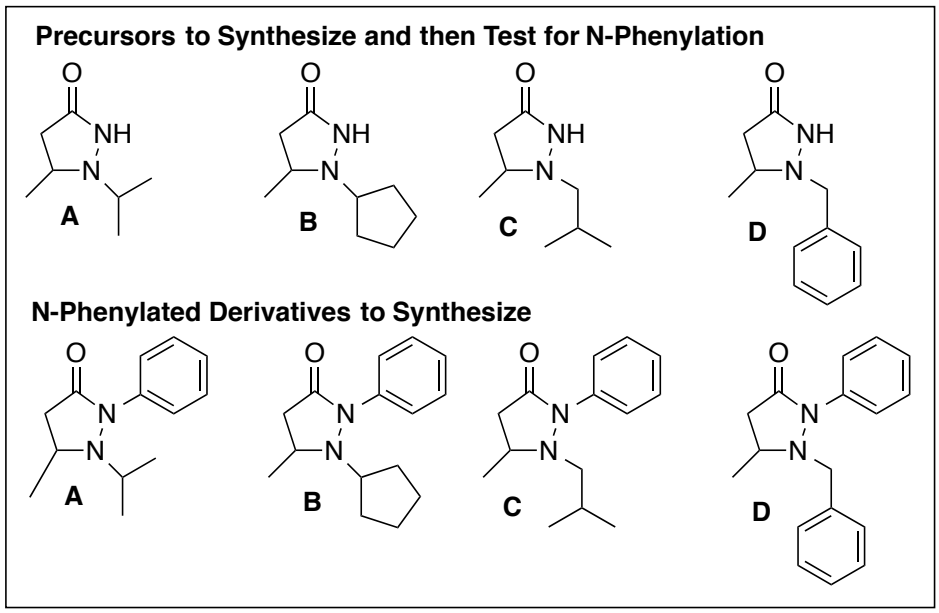
Antipyrine Itself:



Existing Process for Preparing Single-Bonded Analog:



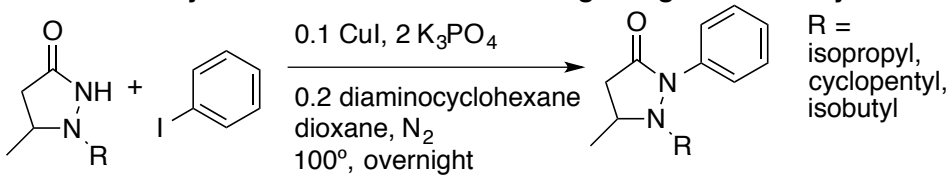
1. Analogs using aryl iodides with other substituents have also been made successfully, in Spring 2021 Chem 365 lab.
2. Pragya will be attempting to make some more, with more complex heteroatom substituents attached (NH2, OH, CO2CH3)
3. In this project, we want to try the phenylation on substrates in which the N1-methyl group is replaced by something bigger.
4. Unfortunately the phenylation precursors will need to be synthesized first, and each preparation will be somewhat more complex than preparation of the N1-methyl substrate shown above.
5. So the project will consist of two aspects:
    a. Trying to make the precursors
    b. Testing the N-phenylation of the precursors to see if the reaction still works.



From the Overview Document as Displayed in the Video

1. **N2-Arylation Using N1-Alkyl variants Bigger than Methyl** (These will need to be synthesized in advance, see the following project box.)

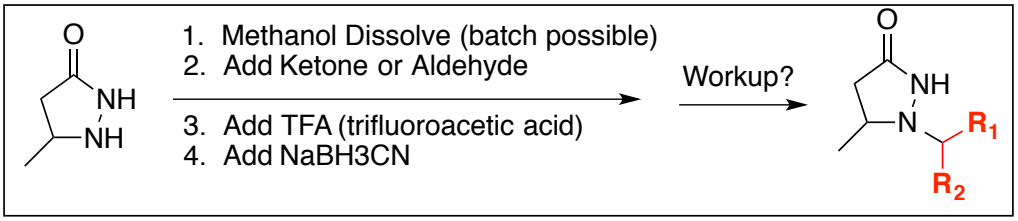
N2-Phenylation using N1-Alkyl Substrates.
Does the N-Arylation Still Work For N1-Analogs Larger than Methyl?



-The substrates will need to be home-made using a several-step procedure

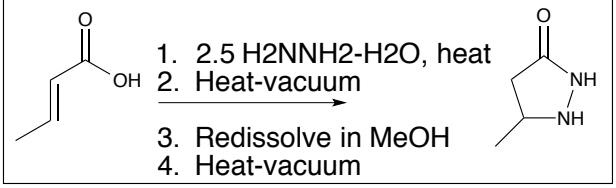
WE know this works awesomely well with the N1-R group = methyl.
But *IF* we size that up, does it still succeed? Or does more steric obstruction make it fail?
I need to check whether we have enough starting material made to test this. It might make better sense to make one of them yourself, see below…

2.



POP experiment suggests this works for small ketones (acetone, cyclopentanone), but not easily for aromatic ketone (PhCOCH3).
The starting material needs to be pre-made case-by-case

Starting Material Preparation



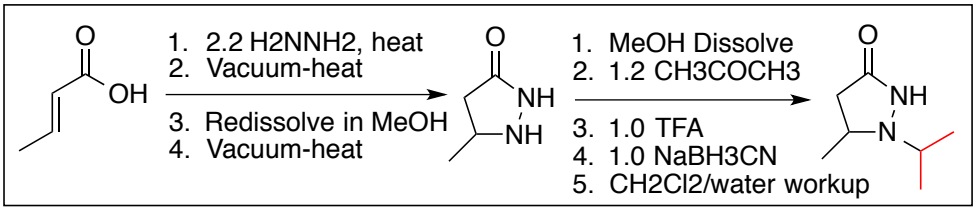
N1-Alkylation via Reductive Alkylation

- Difficulty estimate: Modest
- Discovery level: High.
- Odds it will work: High.
- Odds for some pretty quick success results: High
- Operational difficulty: Modest.
- Precision-and-detailed-care required: High
- Access for time-controlled lab blocks: Reasonable. Experiments occur in modest incremental time blocks.

N1-Phenylation

- Difficulty estimate: Modest
- Discovery level: High.
- Odds it will work: High.
- Odds for some pretty quick success results: High
- Operational difficulty: Low.
- Precision-and-detailed-care required: Modest
- Access for time-controlled lab blocks: Not great. Some ≥3-hour or overnight time blocks.

Specific First-Trial Proof-of-Principle and Procedure Optimization:



Reagents:

Crotonic acid: 20 mmol x 86 g/mol – 1.72 g
Hydrazine-hydrate: 44 mmol x 48 mL/mol = 2.1 mL
MeOH: 20 mL
Acetone: 28 mmol x 74 mL/mol = 2.1 mL
-note: for larger carbonyls, we'll want to use less, more like 24 mmol instead of 28.
Trifluoroacetic acid: 20 mmol x 77mL/mol = 1.54 mL
NaBH3CN: 20 mmol x 62.48 g/mol = 1.25 g
Workup: 10 mL water
CH2CL2: 3 x 20mL

Suggested Procedure, Part 1:

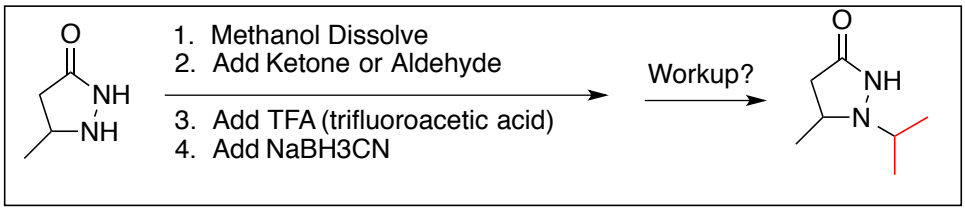
1. Put your hot-plate/stirrer on a jack, and turn your hot-plate heater to a setting of 6, so that by the time everything else is assembled the hot plate is good and hot.
2. Later on you'll need to be using a vacuum. Not all of the vacuums in the research lab work equally well, some have gotten partly plugged. So check with Jasperse regarding which one(s) is/are best to use.
3. Get a 125-mL ground-glass jointed Erlenmeyer, and add both a long stir-bar and a rubber septum. **Weigh the combination and record the mass.**
4. Add 1.72 g (0.0200 mol = 20 mmol) of crotonic acid.
5. Add 2.1 mL (0.044 mol = 44 mmol) of liquid hydrazine hydrate via syringe.
6. Attach a reflux condenser to your flask, with a gentle water flow.
7. Attach a septum on top with a syringe needle poking through it to serve as a pressure vent
8. Set the securely clamped flask with the condenser directly on the pre-heated hot plate (heat = 6) and stir for **10 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.
9. After the 10 minutes, remove the flask from the heat, AND reduce the hot-plate setting to 5, AND **let the solution and the hot-plate cool for 5 minutes**.
   - Getting the mix away from the heat could involve either sliding the jack/hot-plate out from underneath the flask, or else swinging the flask away from the hot plate, whichever seems easier
10. During any pause times, plan ahead.
    a. Find your vacuum adapter, and plug it into the vacuum hose.
    b. Get an empty distilling column. (in other words, without it being filled with water.).
    c. 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.

d. Get a glove for your left hand, so you can handle the hot glassware;
e. Note that the theoretical yield at this point should be 2.0 grams, given a 20.0 mmol scale.

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

11. After the 5 minutes of cooling is complete, remove the water-filled reflux condenser and immediately replace it with the empty reflux-condenser with the vacuum adaptor on top, and connect the vacuum hose. (No vacuum actually on yet, though…..).
    - These nitrogen-rich chemicals are subject to air oxidation, especially so when still hot. So limiting exposure to the air is important for yield and purity.
12. 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.
    - The first time you do this, you may wish to have Jasperse around for consulting?
13. The hot vacuum is intended to do several things:
    - Facilitate/complete ring closure (**2 → 3**).
    - Distill away water
    - Vacuum/distill away much of the extra hydrazine. Leftover hydrazine causes a problematic side-product in the, so we want to remove it.
    - Unfortunately this process will still leave a possibly problematic amount of hydrazine
14. Stir/heat/vacuum for **ten minutes.**
    - **Be very specific with the time, and record the times involved**.
    - This is the most sensitive part of the whole experiment. There are several challenges or problems that are involved:
        a. We need enough time/heat for the ring-closure to occur. Too little time, too little vacuum, too little heat, and the ring-closure will be incomplete
        b. We need enough time/heat/vacuum to remove most of the hydrazine-hydrate. We will certainly **not** get all of the hydrazine removed, and the residual may perhaps plague us later. But we need to get most of it. So again, too little time, too little vacuum, too little heat, and the hydrazine removal will be insufficient.
        c. **But we do NOT want too much time/heat/vacuum, or else some of the product will start to decompose**.
        d. So we think that ~10 minutes at HP=5 is kind of a sweet-spot best-case compromise.
15. After the 10 minutes of vacuum, a) **turn off the vacuum**, and b) remove the flask from the heat.
16. Let **cool** for ≥five minutes,
17. Then detach the vacuum adapter, and pull the distilling column off, and IMMEDIATELY plug the flask with your septum.
    - If the flask was still pretty hot, it may be helpful to wear a glove while handling it.
    - These nitrogen-rich chemicals are subject to air oxidation, especially so when still hot. So limiting exposure to the air is important for yield and purity.
18. Measure the mass for the flask+ product +stirbar+septum combination. By comparing this to the flask +stirbar + septum mass that you recorded at the beginning, what is your mass of product?
    - It should be ~2.0 grams. (2.0 grams is the theoretical yield at this point for a 20-mmol scale.)
    - If it's relatively close, like 1.9-2.15 grams, that's probably good.
    - If it exceeds 2.0 grams by much, that indicates the present of residual hydrazine. Not good.



Part 2: The N-Alkylation Reaction

1. Add 20 mL of methanol. (Remove septum, but immediately replace the septum)
2. Place on a hot plate set to 4, add a syringe needle through the septum as a vent, and heat/stir until the solution dissolves up and becomes homogeneous.
3. As soon as it becomes soluble, turn the hot plate off.
4. Add the acetone. (28 mmol for acetone; maybe try 24 mmol for other larger carbonyls later?).
5. Stir for 5 minutes.
6. Add the trifluoroacetic acid. It's fine to pull the septum out, inject directly into the flask, and then to replace the septum right away. But it should still have it's venting-needle inserted.
    a. Note: This is a strong acid. So avoid touching or spilling.
    b. After use, rinse the syringe and syringe needle right away, first with water and then with acetone.
    c. Needles will corrode, rust, and plug up if you don't.
7. Stir for 5 minutes.
8. Pull out the septum, and add in the NaBH3CN by doses, so that nothing foams over. But add it as quickly as the foaming allows. This shouldn't take real long, the sooner the better.
9. Put the septum with the venting needle back in. (preferably a pink one
10. Stir for 15 min.

Workup:

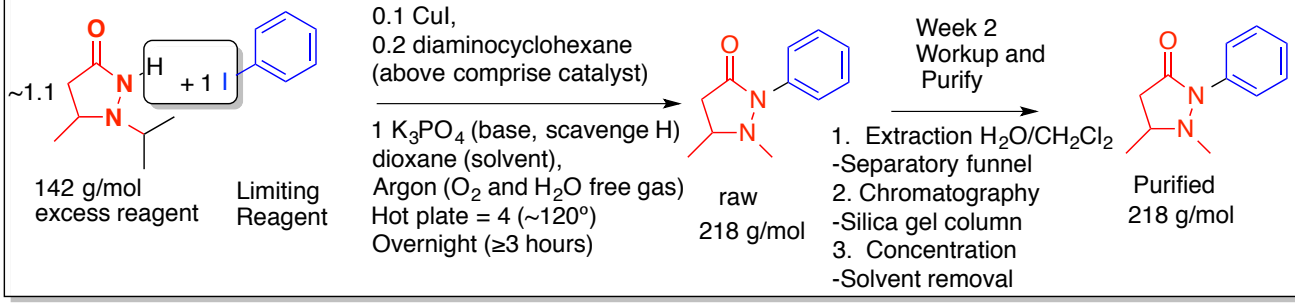
11. Add 20 mL of dichloromethane, and 10 mL of water. (Avoid using much surplus water.)
12. Stir vigorously to get everything dissolved.
13. Pour two-phase solution into a separatory funnel.
14. Rinse the separatory funnel with an additional ~10mL of dichloromethane.
15. Prepare a 125-mL ground-glass flask with a long-stir-bar.
    a. This could be a new one, if that's easiest.
    b. Or you could take your original one, rinse it with water and then acetone, then dry it with a quick blow-it-dry flow of air.
16. Add a ground-glass filter column, and add ~30g stack of sodium sulfate (about 1 inch high).
17. Carefully pour the lower CH2Cl2 layer of the separatory funnel over the sodium sulfate and pull it into the flask. Be careful to avoid pouring any of the water layer out.
18. Extraction 2: Add an additional 20 mL of dichloromethane to the separatory funnel, shake it up, let it settle, and pour the lower CH2Cl2 layer through the sodium sulfate into the flask that already has the first extract. Again be careful to avoid pouring any of the water layer out.
19. Extraction 3, repeats extraction 2. Add an additional 20 mL of dichloromethane to the separatory funnel, shake it up, let it settle, and pour the lower CH2Cl2 layer through the sodium sulfate into the flask that already has the first and second extracts. Again be careful to avoid pouring any of the water layer out.
    a. Note: Why all the extractions, and so little water?
    b. The product with two nitrogens and a carbonyl has significant polar character and hydrogen-bonding affinity to water.

   c. Depending on which carbonyl you used, the product may not have a huge number of alkyl carbons. (6, in the case of acetone.).
   d. So in order to thoroughly extract the organic product, we need some repetitive extraction.
20. Concentrate to remove the dichloromethane solvent. This could be done using either the rotary evaporator, or using the house vacuum
   a. If using the vacuum, attach an empty condenser, attach a vacuum adaptor, and VERY cautiously gently crack open the vacuum a little bit until boiling ensues.
   b. Be very careful on this, though, because dichloromethane is VERY volatile, and can boil up and over really easily.
   c. Do not have any heat turned on while starting this.
   d. If/when the boiling settles down, crack open the vacuum as quickly as you can and eventually get to fully-wide-open.
   e. There will probably be lots of coldness/condensation/frost on the outside of the flask, because it gets so cold.
   f. Turn the hot plate up to 2 and vacuum for however long it takes for the solvent to mostly seem to be gone. (10-15 minute will probably be plenty.)
   g. Turn off the vacuum, and replace the vacuum adapter with a septum to block air.
21. Make sure the septum is on!
22. Record/measure mass, and calculate the % yield.
   a. For the acetone product, the molecular weight is 142, and the theoretical yield at 20 mmol would be 2.84 grams.
   b. Given that the molecular weight is 142 (for the acetone product), how many millimoles did you recover?
23. Analysis: *IF* the NMR is running, run both an NMR and a GC.
24. *IF* the NMR is NOT working, prepare and label an NMR sample and get it to Jasperse to run at NDSU.
25. Either way, prepare and run a GC-MS.
26. And make sure you have a clear record of how much mass and how many mmol of product you have (if you assume all the mass is product, which of course may not necessarily be true.).

N-Arylation Reaction

Note: This is basically the same process we did in lab last spring, just adjusted for having the different starting material, and adjusting depending on how much starting material we made.

Scheme 2: N2-Arylation Using Phenyl Iodide and CuI-Diaminocyclohexane Catalyst

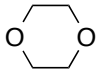


Reagents:

1. Substrate: Calculate how many mmoles you think you had..
2. Copper iodide: 2 mmol x 190 = 380mg
3. Potasssium phosphate: 20 mmol x 0.212 g/mmol = 4.2g
4. Iodobenzene: 112 mL/mol = .112 mL/mmol.
   - Add 0.9 equivalents relative to your mmol of substrate.
   - In other words, if you have 20 mmol of subtrate, add 18 mmol of PhI, etc.
   - Basically for 0.9 times "X" mmol of substrate, then times 0.112 mL/mmol.
5. Dioxane: 20 mL
6. Diaminocyclohexane: 4 mmol x 0.120 mL/mmol = 0.48 mL diaminocyclohexane

Part 1: Starting the Reaction for N-Arylation

7. Carry your flask to the balance. Avoid air exposure, so pop the septum back in after each addition.
8. Add Copper iodide: 2 mmol x 190 = 380mg
9. Add Potasssium phosphate: 20 mmol x 0.212 g/mmol = 4.2
10. Add the appropriate amount of iodobenzene
    - Add 0.9 equivalents relative to your mmol of substrate.
    - In other words, if you have 20 mmol of subtrate, add 18 mmol of PhI, etc.
    - Basically for 0.9 times "X" mmol of substrate, then times 0.112 mL/mmol.
    - If uncertain, check with Dr. Jasperse.
11. Add ~20 mL of anhydrous dioxane.
    - The measurement doesn't need to be precise.
    - Get within 5 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

12. Purge three times with argon.
    - Consult with Jasperse on how to do this.
    - 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!
13. Bring the flask back to your hood and stir vigorously for 1 minutes to get everything mixed.
14. Add diaminocyclohexane, via syringe by puncturing through the septum.
    - 4 mmol x 0.120 mL/mmol = 0.48 mL diaminocyclohexan
    - 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.)
15. Stir vigorously on a hot plate.
    - Set hot-plate setting to ~3.9. (It's probably fine up to 4.0).
16. Stir hot for either ≥3 hours or else for overnight. *IF* you are doing an overnight, make sure that either you'll be in tomorrow morning to turn the heat off; or else arrange with Dr. Jasperse and remind me. I can definitely do that turn-off, and then you can complete the workup when your next lab-work day arrives. It's OK to stand.

Part Two: Product Workup, Isolation, Purification, Concentration, and Analysis.

1. **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
   f. 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?
   g. Some aryl iodide?
      - Hopefully not, because it's the limiting reagent.
      - But maybe the reaction didn't convert it all perfectly and completely?
   h. Carryover contaminants: Any junk that was present at the end of Scheme 1 is still in the soup.
   i. Any side-things that originated from un-removed hydrazine, etc..
   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!

2. **Isolation/Purification Plan: The Overall Plan for the Day**
   a. Part 1: **Dichloromethane extraction from water in separatory funnel**:
      - The product 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)

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 unreacted starting substrate that didn't stay in the water may 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 observations.
9. Add 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.

17. If the solution flows slowly, you can assist by attaching a vacuum hose and gently vacuuming.
18. Avoid having any of the water layer drain out.
19. Add another 20 mL DCM to rinse the original flask
20. Pour this into the sep funnel, shake, let settle, and again drain the DCM layer through column
21. Add another 20 mL DCM into the sep funnel, let shake, and again drain the DCM layer through the column. (basically you're doing a 3rd extraction with DCM to make sure all of your product is extracted from the aqueous phase.
22. 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.

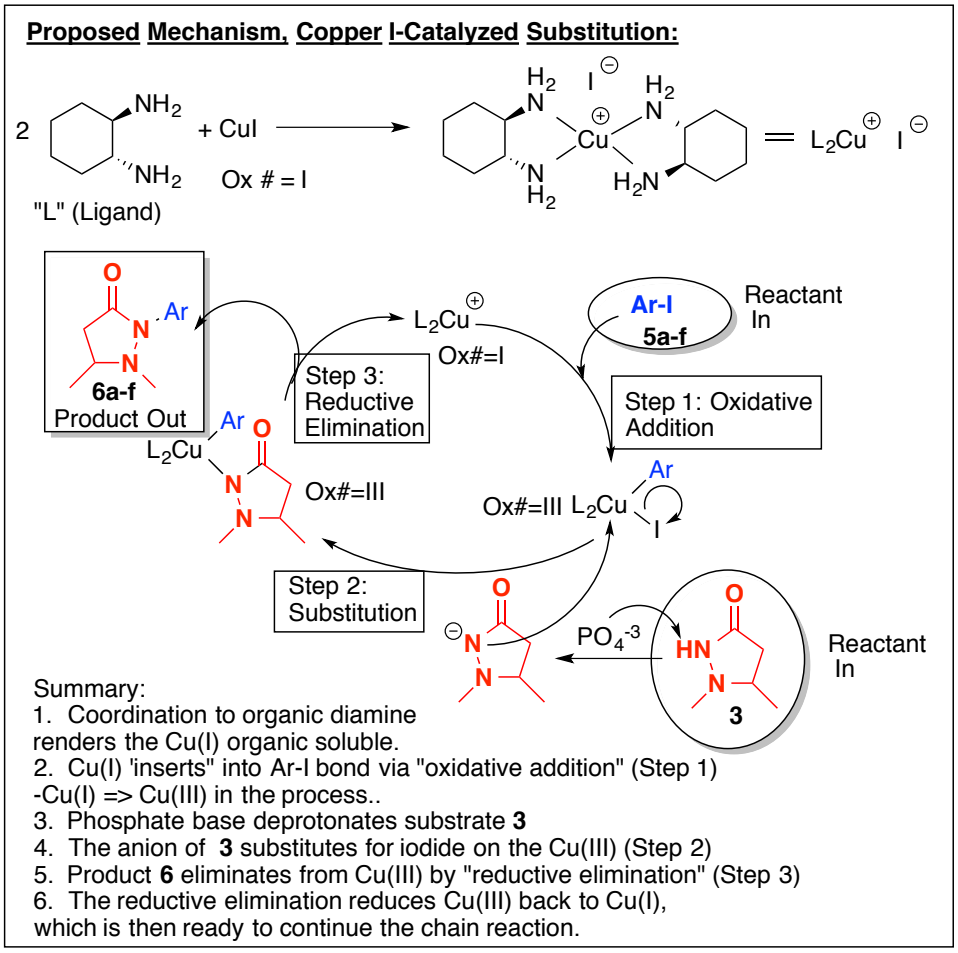
- A quick and dirty chromatography like this won't do a perfect job; probably some side-products will leach through, and possibly some desired product may remain adsorbed to the silica and lost.
- For medicinal screening at Mayo, we are more concerned with purity than with yield. So, 40-60% yield at >90% purity is much preferred to 75% yield at 75% purity, for example.
- I'm hoping that your product 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 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, 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.



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.