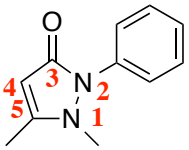
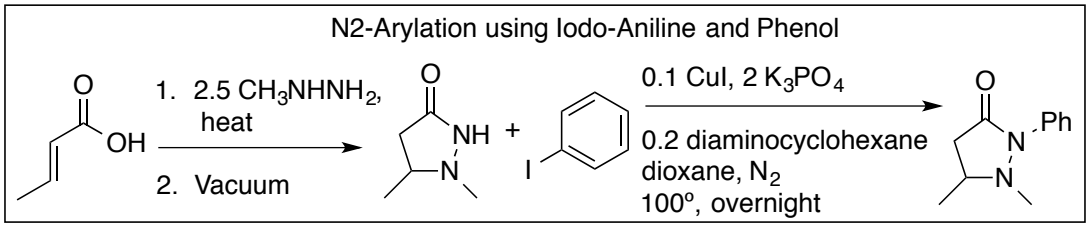
Document Beginning: 9/3/2021. Pragya Timalsina

Context:

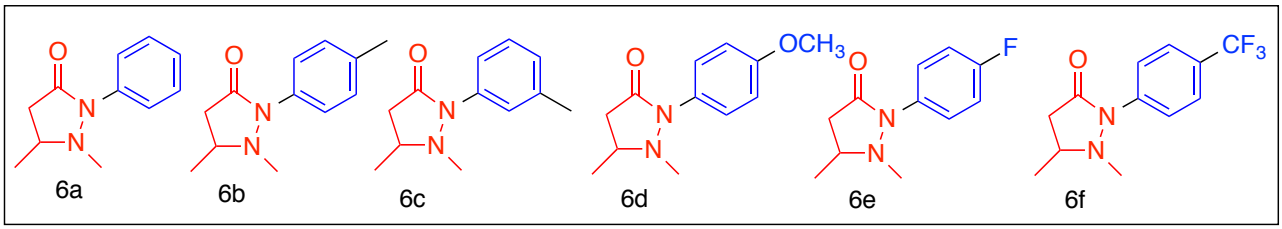
Antipyrine Itself:



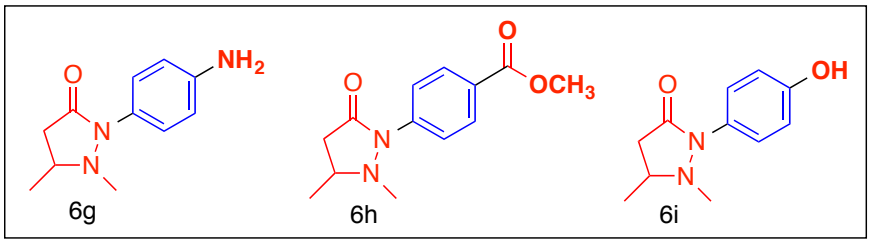
Existing Process for Preparing Single-Bonded Analog:



1. Analogs using aryl iodides with other substituents have also been made successfully, in Spring 2021 Chem 365 lab.

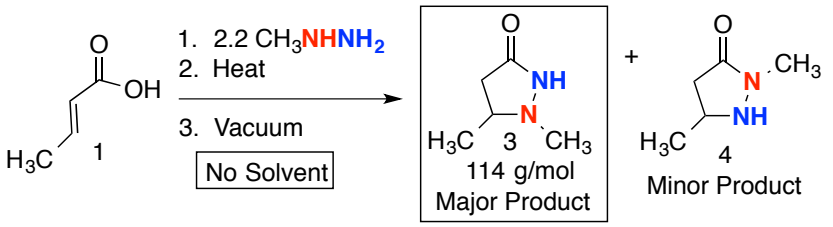


2. We this project, you will be attempting to make some more products, with more complex heteroatom substituents attached (NH2, OH, CO2CH3).
   - It's unclear how the extra functionality in the substituents might impact the reaction;
   - the possibility for side reactions;
   - and the process for isolating products if they do form effectively.
   - So, we'll try the reactions and see what happens!



3. Project plan:
   - Run a practice control reaction on one we did last spring. Just do the iodobenzene that we know works, and prove that you can do it.
   - Then try the amino candidate.
   - Then try the ester one.
   - Then do the phenol one last; that might be the most tricky, and require some modification in workup and/or in reaction base. (The normal phosphate base may be too strong and my deprotonate the phenol. Likewise the normal aqueous workup may need to be acidified to ensure that the phenol is in neutral, protonated form rather than in ionized form.

Scheme 1: Synthesis of N1,C5-Dimethyl Pyrazolidinone



- See the following page for the hypothetical mechanism.

Reagents:

1. 20.0 mmol of Crotonic acid
   - Crotonic acid: 86.0 g/mol
2. 44 mmol of Methyl Hydrazine (52.4 ml/mol)
3. 125 mL Ground-Glass Erlenmeyer flask
4. Long sized stir bar
5. Hot plate
6. Reflux Condenser
7. Vacuum Condenser and Vacuum adaptor.

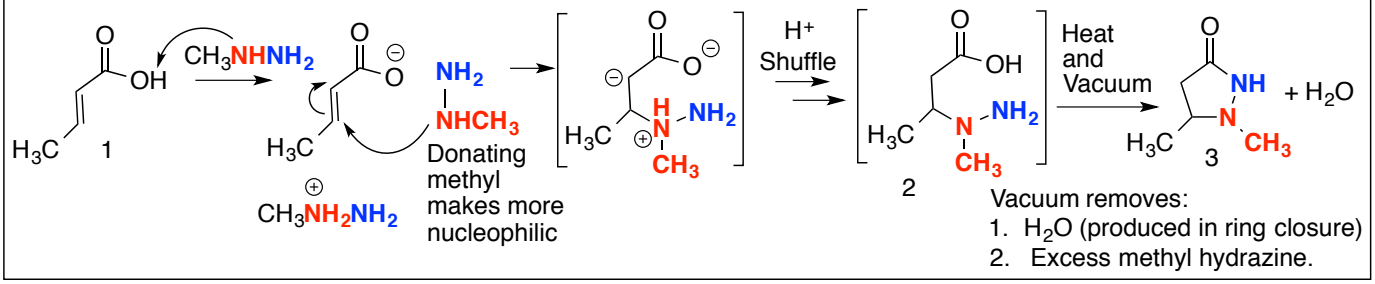
Scheme 1 Procedure: Formation of Pyrazolidinone Ring Using Hydrazine
Part A. Heating/Hydrazine Addition Phase

1. Get a 125-mL ground-glass-jointed Erlenmeyer, and add a long stir-bar. **Weigh the combination and record the mass.** Write your name(s) on the flask with your sharpie.
   - You'll need this mass to calculate your product yield, so record it somewhere!
2. Weigh out 20.0 mmols of "crotonic" (2-butenoic) acid:
   - Crotonic acid, 86.0 g/mol, is a solid. Add it using a powder funnel.
3. Add a rubber septum to the flask, and poke a syringe needle through it to vent any pressure buildup.
4. Add 44 mmol (0.042 mol) of liquid methylhydrazine (0.0524 ml/mmol) via syringe while stirring.
   - You can pull the septum out before injecting, and replace the septum following the addition.
5. Stir the mixture rapidly for 5 minutes at room temperature.
6. Add a reflux condenser, with a gentle flow of water running through it, and place the septum on top to prevent oxygen exposure. (Oxygen causes some oxidative decomposition.)
7. Turn the hot plate setting to 4, and stir vigorously for another 10 minutes.
   - Make sure that your Erlenmeyer and the hot plate are in contact.
   - Make sure that the flask is not tipped and doesn't have any air-space between the hot-plate and the flask. You need direct contact for the heat to do its work in the time given. If you leave space in between, or have a tipped flask without good thermal contact, the reaction might not complete.
8. After 10 minutes, turn your hot-plate setting up to 8, and continue stirring for an additional 30 minutes.
9. During the stirring time, prepare and run H-NMR and GC for your aryl iodide 5.
10. If it's a liquid, use a long-stemmed pipet and draw up about ½-inch of aryl iodide into the the skinny end section of the pipet; place into NMR tube; then pour in ~1.3mL of CDCl3 through the pipit. Shake.
11. During the stirring times, plan ahead. Prepare the following:
    a. Find your vacuum adapter, and plug it into the vacuum hose.

b. Familiarize yourself with your vacuum:

12. After the heating is complete, a) slide the hot plate out from under your flask, b) **reduce the hot-plate setting to 5**, c) turn off your reflux condenser water, and d) detach the hose from the water source and redirect it into the drain so that most of the water in the condenser can drain out.
13. Let your solution (and the hot-plate) cool for at least **5 minutes** before starting Scheme 1 Part B.

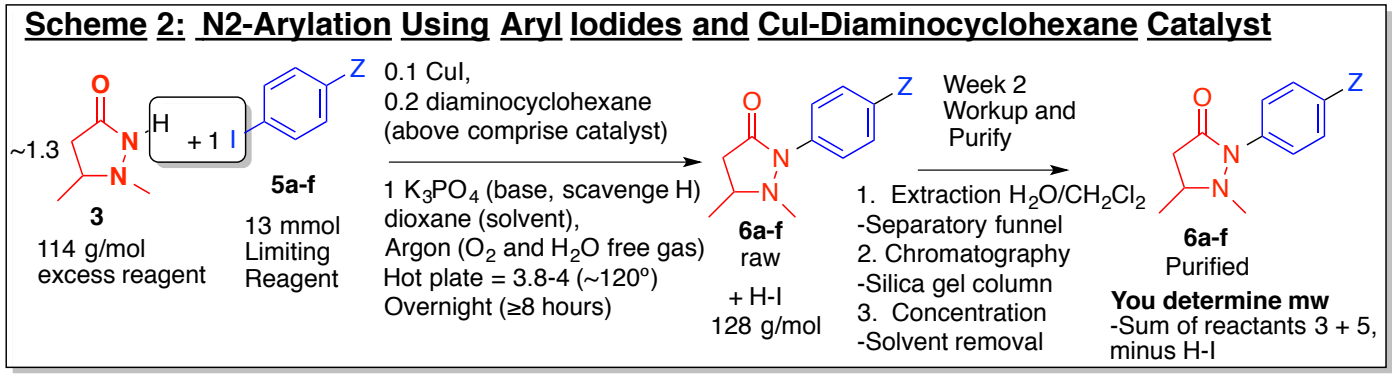
Hypothetical Mechanism



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

14. After the 5-minutes, attach the vacuum adapter to your reflux condenser, and then slide your hot plate back under the reaction flask. The hot plate should be set at 5 for heat. (And maybe 3-5 for stirring?)
    - If you didn't turn your hot plate down to 5 earlier, do so now and wait five minutes.
15. 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.
16. Stir/heat/vacuum for **25 minutes**. (Measured from when the vacuum was first fully open.)
17. After the 25 minutes, slide the hot plate out from under your reaction mixture.
18. After the flask cools a little, **turn the vacuum off**, and detach the vacuum adapter.
19. Prepare an NMR sample. *IF* the NMR is working run it; if not, label and get it to Jasperse for when I go to NDSU to run samples.

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



Reagents:

1. Pyrazolidinone **3**: Report how many grams and mmoles you actually produced at the end of Scheme 1. 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.

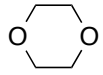
Workup materials:

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 iodobenzene.. (If uncertain, check your calculation with Jasperse)
5. Add ~20 mL of anhydrous dioxane.



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. Jasperse will show you the process for the first time.
   - 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.
7. Add diaminocyclohexane, via syringe by puncturing through the septum.
   - 4 mmol x 0.120 mL/mmol = 0.48 mL diaminocyclohexan
   - 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.)

8. Stir vigorously on a hot plate.
   - Set hot-plate setting to ~3.9. (It's probably fine up to 4.0).
9. Stay for 15 minutes to watch and record color changes or other observations. After that, you are free to go!
10. Let stir hot for either at least 3 hours, or else overnight. *IF* you want to run it overnight, but aren't going to be right in on the following morning, talk to Jasperse and arrange; I can make sure I turn the heat off in the moring.
11. The mixture can wait for a while for workup, isolation, purification, and analysis! ☺

Week Two: Scheme 2 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 **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!

2. **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.

12. If the solution flows slowly, you can assist by attaching a vacuum hose and gently vacuuming.
13. Avoid having any of the water layer drain out.
14. Add another 20 mL DCM to rinse the original flask
15. Pour this into the sep funnel, shake, let settle, and again drain the DCM layer through column
16. 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.
17. 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.)

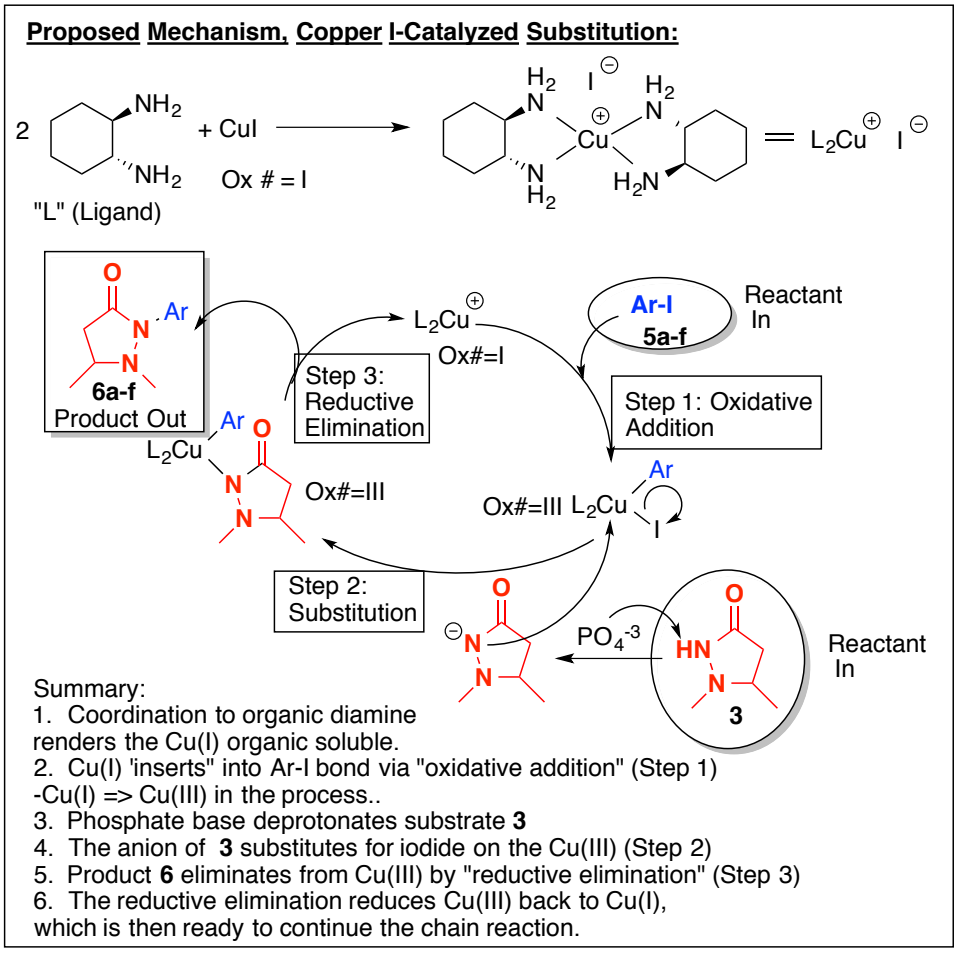
- As you do this last rinse, *if* it looks like a colored band is moving down the column and is going to come off, DO WHATEVER YOU CAN TO STOP BEFORE THAT COMES OFF!
    - Pull the vacuum hose off of the filter column,
    - Remove the filter column from the flask.
    - Turn off the vacuum.
    - I don't want dark colored bands flowing into the receiver flask, if possible!

18. 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. **<u>Concentrate this solution</u>**. 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. **<u>Prepare NMR sample, and run it if NMR is fixed. Get to Jasperse to run at NDSU if not.</u>**
9. Run GC-MS.

Thoughts/Suggestions for when doing the Phenol One

1. As we know, phenol OH's are somewhat acidic.
2. It's possible that under the experiment itself, that perhaps the phosphate base will simply deprotonate the phenol? If so, maybe it won't react at all. Or if so, perhaps it will fall out of the dioxane solvent and be unavailable for reaction.
3. So *IF* we try it on the phenol and it does NOT work very well, we may consider trying to do the reaction with a milder, weaker base?
4. The other factor is the workup. Normally we work it up just with tap water; but with all of the phosphate present the resulting aqueous solution is pretty basic. So I think for sure if/when we try the phenol reaction, we'll want to add enough HCl to neutralize the aqueous solution, and get it's pH to around 7. That might better enable us to extract the product from the aqueous phase.



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.