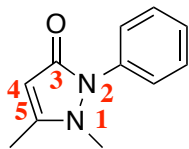
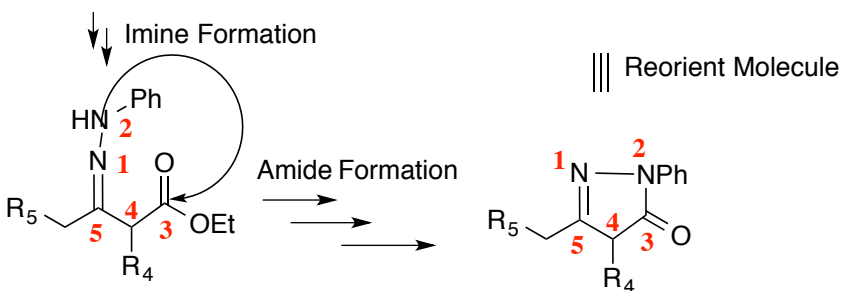
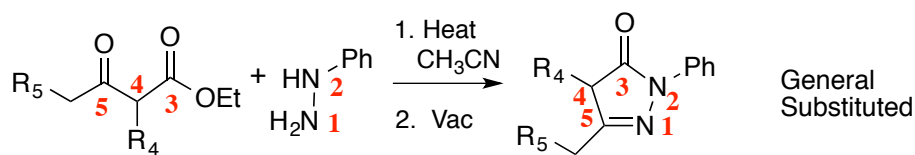
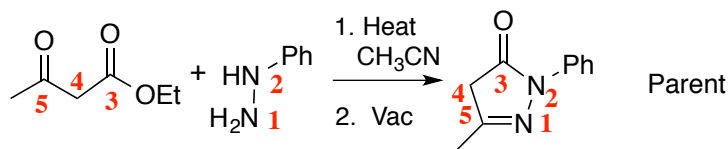


Document Beginning: 9/3/2021. Gael Shama

Antipyrine Itself:



General Access to Antipyrine Analogs Missing the N1-Methyl

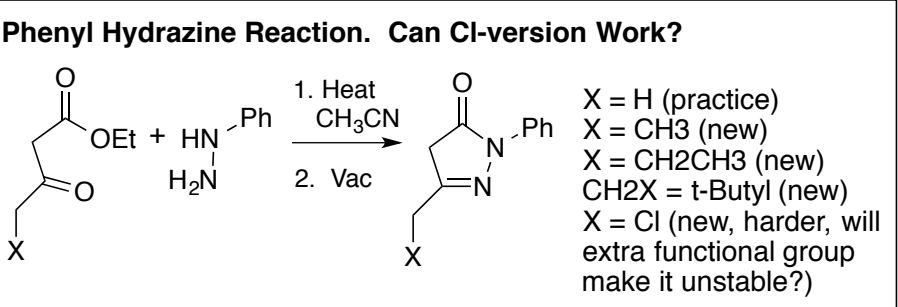
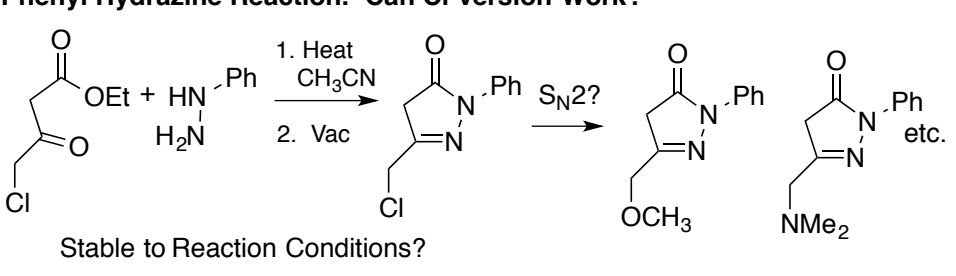
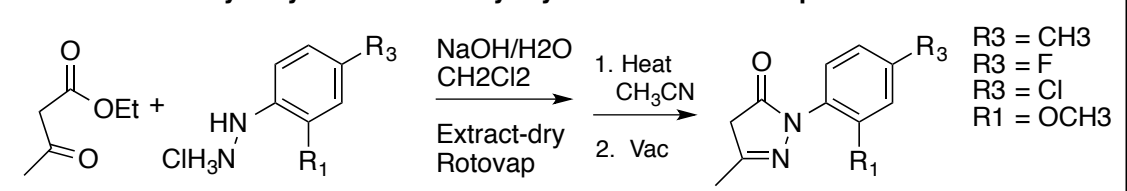


1. Access to the "Desmethyl" substrates seems to be pretty general.
2. Phenyl Hydrazine is Cheap.
3. Several keto-esters are commercially available and not real expensive
4. Other Keto-esters could be synthesized
5. ***IF* we had a practical, reliable way to add the N-methyl, we could access antipyrine analogs differing from antipyrine only at R4 or R5.**
6. Comparing the methyl-on versus methyl-off pairs could also establish whether the N1-methyl is important or crucial. Does it make any difference?

More notes:

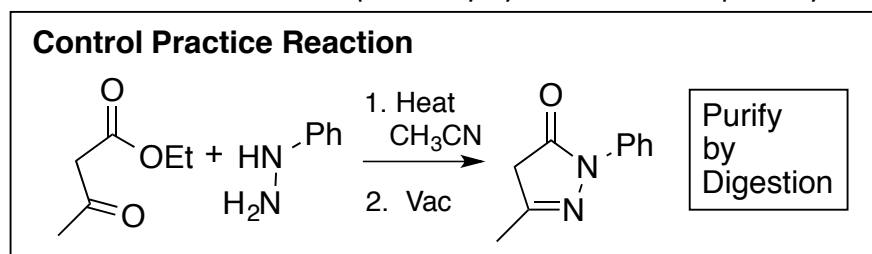
- Lola will be working on taking some of these and developing a method for N-methylating them.
- Logan Hooker did this reaction successfully on several keto-esters last fall. It worked really well.
- **The goal of this project will be to** apply the procedure to several more keto-esters to make some new novel products.
- Included will be a couple that should work; but also to test a couple that might be more challenging.
- One with a sterically challenging t-butyl group; does that get in the way?
- Another with an allylic chloride, which may be too reactive to survive?
- Then we'd also like to try modified aryl-hydrazines to modify the N-phenyl group.

The following is copied from the document shared earlier and discussed in the video.

2.	<p>Phenyl Hydrazine addition to KetoEsters to make Des-Methyl Core with C5-Variations</p> <div style="border: 1px solid black; padding: 10px;"> <p>Phenyl Hydrazine Reaction. Can Cl-version Work?</p>  <p>X = H (practice) X = CH3 (new) X = CH2CH3 (new) CH2X = t-Butyl (new) X = Cl (new, harder, will extra functional group make it unstable?)</p> </div> <p>The "X = H" variant has been done and works. The extra methyl and extra ethyl should work too. The t-butyl one, sterics way different, so hard to know.... Maybe fine, maybe less so? The Cl-one, that could be interesting. It might not be stable, too reactive. But *IF* we could make it, we could then substitute for it.... Difficulty: Low, other than the chloride version</p>	
3.	<div style="border: 1px solid black; padding: 10px;"> <p>Phenyl Hydrazine Reaction. Can Cl-version Work?</p>  <p>Stable to Reaction Conditions?</p> </div> <p>The Cl-one, that could be interesting.</p> <ul style="list-style-type: none"> • It might not be stable, too reactive. • Should know within one or two experiments. Either it works, or it doesn't. • But *IF* we could make it, we could then substitute for it.... • That would basically be an allyic 1° alkyl halide, so SN2 substitution with other things could make new analogs with Oxygen or Nitrogen 	
4.	<div style="border: 1px solid black; padding: 10px;"> <p>Variation at N2-Aryls By Variation of Aryl Hydrazine. Order. Deprotonate HCl Salt</p>  <p>R3 = CH3 R3 = F R3 = Cl R1 = OCH3</p> </div> <p>A POP experiment with the toluene version looked promising.</p> <ul style="list-style-type: none"> • This is similar to earlier project, but now instead of messing with the keto-ester, we'd vary the aryl hydrazine. • A factor for this is that the aryl hydrazines are few and expensive, and come usually as HCl salts. So, they'd need to be deprotonated first. 	

First Day:

Parent control reaction: Simple Phenylhydrazine with simple ethyl acetoacetate

**Suggested Initial procedure for reaction of neutral phenylhydrazine with the different ketoesters:**

Reagents: ketoester: 0.100 mol x 127.5 mL/mol = 12.75 mL

PhNHNH₂: 0.100 mol x 98.3 mL/mol = 9.83 mL

CH₃CN (anhydrous): 50 mL

Suggested Procedure

2. Get a dry 125-mL ground-glass flask with a long stir bar
3. Pre-weigh the combination.
4. Have a reflux condenser ready (should be able to use one already sitting in the hood)
5. Have a septum, with a venting syringe, ready.
6. Add in 100 mmol of the keto-ester.
7. Add in 50 mL of anhydrous acetonitrile solvent
8. Add in 100 mmol (1.0 equivalent) of phenylhydrazine.
 - a. Note: the sequence of addition of which adds 2nd or 3rd shouldn't matter for this substrate or most of the others.
 - b. But, for the Cl-containing molecules, we want to make absolutely sure the phenylhydrazine is added last, and probably with some care, possibly with some ice-water bath or something while the phenylhydrazine is added.
9. Attach the reflux condenser, with a septum on top with a pressure-venting syringe in it.
10. Heat the solution to reflux, with hot plate set to 5, and reflux for ≥overnight.
 - a. If it goes longer, that's probably fine and harmless.
 - b. So weekend reflux, or Monday-to-Wednesday reflux, or whatever, that's probably fine.

Workup:

11. Lift flask away from the hot plate, and replace the water-filled reflux condenser with an empty condenser.
12. Attach vacuum adapter (vacuum not on yet...). Get the flask within 2cm of the hot plate, but not directly on it.
13. With stirring on, gently open the vacuum (make sure it doesn't erupt and go crazy). Then get the vacuum wide open, and reconnect the hot-plate and the flask. (Hot plate is still at 5). (Basically want to get it wide open and on the hot plate as soon as it's safe, but without risking having things get sucked up.)
14. Concentrate for a while until the solvent is all gone. 10 minutes at HP=5 will probably be enough to remove much if not all of the solvent.
15. Turn the hot-plate up to 6, and vacuum for an additional 15 minutes, to try to complete ring closure.
16. Take off from hot plate and from the vacuum, and let cool. Is it solid?
17. Get mass so you can calculate the crude % yield.
18. Analysis: Take a portion and submit a crude-sample GC. If NMR is working, take a crude NMR.

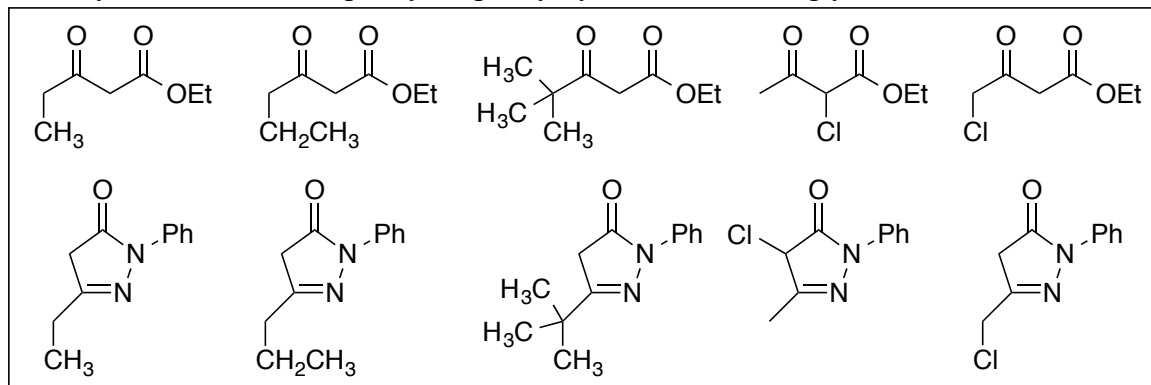
Purification/Digestion

19. Take the solid and crush/powder it.
 - a. Consult with Jasperse on how to perhaps do this...
 - b. Often pouring/cutting it out into a big weighing boat, then placing another weight boat on top of that, and crush/grind it with flask or vial.
20. Add 5mL ether/25mL hexane, and reflux for 30 minutes at hot-plate = 3.
21. Filter, rinsing with straight hexane.
22. **Make sure it's dried quite well.**
23. Remass, recalculate purified % yield, re-NMR if it's working

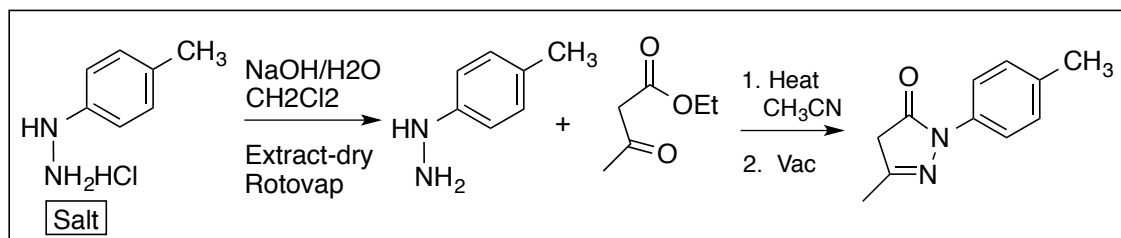
Store the hopefully solid product in a well-labelled vial.

Suggestions after establishing that you now how to do the reaction:

1. Apply to other analogs. (Depending on the cost, some of these might need to be scaled down a bit. (So, for example, if there is 5 mL of a ketoester and it's <<100 mmol, figure out how much you have, and then plan your phenylhydrazine accordingly.



Aryl Hydrazine Salt Reactions. Variation of the Aryl Hydrazine



A POP experiment with the toluene version looked promising.

- This is similar to earlier project, but now instead of messing with the keto-ester, we'd vary the aryl hydrazine.
- A factor for this is that the aryl hydrazines are few and expensive, and come usually as HCl salts. So, they'd need to be deprotonated first. And most other than toluene need to be small-scale.

Suggested Initial procedure for reaction of neutral phenylhydrazine with the different ketoesters:

Do 50-mmol scale.

CH₃PhNHNH₂-HCl: 0.050 mol x 158.6 g/mol = 7.93g

NaOH: want ~0.060 mL and ≥20 mL.

Two options:

From a pre-made solution.

- For example, if it's 3.0 M, then 20 mL x 3 mol/L = 0.060 mol

From solid NaOH and water:

- 0.060 mol x 40 g/mol = 2.4 g.
- H₂O: 20 mL

CH₂Cl₂: 30mL (plus more for additional extractions)

Ketoester (ethyl acetoacetate): 0.050 mol x 127.5 mL/mol = 6.37 mL

CH₃CN (anhydrous): 25 mL

Suggested Procedure

1. Get a dry 125-mL ground-glass flask with a long stir bar
2. Pre-weigh the combination.
3. Weigh in the solid toluene hydrazine hydrochloride salt
4. Add in 30mL of dichloromethane solvent and stir.
5. Add in 20 mL of 3M NaOH/water.
 - Do this with some care, and perhaps have some ice-water nearby. There is the possibility that there will be exothermic acid-base reaction that could cause the dichloromethane to start to boil.
6. Note: Aryl hydrazines are subject to air oxidation. So at all steps, try to limit the exposure to the air.
7. Stir vigorously for a while until all of the solid material has dissolved. Add a septum with a pink 18-gage syringe in it, to allow pressure release, but to minimize exposure to air.
8. Pour two-phase solution into a separatory funnel. Rinse the flask with an additional ~10mL of dichloromethane.
9. Prepare a 125-mL ground-glass flask with a long-stir-bar.
 - This could be a new one, if that's easiest.
 - 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.

10. Add a ground-glass filter column, and add ~30g stack of sodium sulfate (about 1 inch high).
11. Carefully pour the lower CH_2Cl_2 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.
12. Extraction 2: Add an additional 20 mL of dichloromethane to the separatory funnel, shake it up, let it settle, and pour the lower CH_2Cl_2 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.
13. 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 CH_2Cl_2 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.
14. Concentrate to remove the dichloromethane solvent. This could be done using either the rotary evaporator, or using the house vacuum
 - 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.
 - Be very careful on this, though, because dichloromethane is VERY volatile, and can boil up and over really easily.
 - Do not have any heat turned on while starting this.
 - If/when the boiling settles down, crack open the vacuum as quickly as you can and eventually get to fully-wide-open.
 - There will probably be lots of coldness/condensation/frost on the outside of the flask, because it gets so cold.
 - 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.)
 - Turn off the vacuum, and replace the vacuum adapter with a septum to block air.
15. Note: Aryl hydrazines are subject to air oxidation. So at all steps, try to limit the exposure to the air.
16. Record the mass of what's inside. 50 mmol of $\text{CH}_3\text{PhNHNH}_2$ (neutral) would weigh 6.1g. Are you kind of in that neighborhood?
 - If it's significantly less, that's probably not good!
 - If it's close to 6.1g, that's probably good.
 - If it's somewhat greater than 6.1g, that's probably OK. Having a little bit of residual dichloromethane solvent that maybe didn't completely boil away shouldn't be any problem.
17. Add the 25mL of anhydrous acetonitrile.
24. Add in the 50 mmol of the keto-ester.
25. From this point on, things should be as normal for the previous reactions with the phenyl hydrazine.
26. Attach the reflux condenser, with a septum on top with a pressure-venting syringe in it.
27. Heat the solution to reflux, with hot plate set to 5, and reflux for \geq overnight.
 - a. If it goes longer, that's probably fine and harmless.
 - b. So weekend reflux, or Monday-to-Wednesday reflux, or whatever, that's probably fine.

Workup:

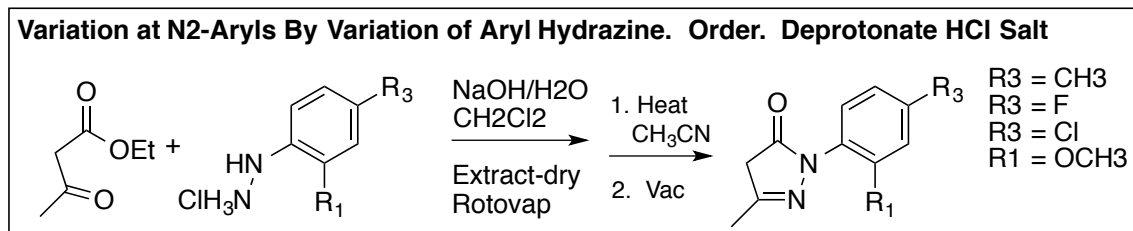
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30. With stirring on, gently open the vacuum (make sure it doesn't erupt and go crazy). Then get the vacuum wide open, and reconnect the hot-plate and the flask. (Hot plate is still at 5). (Basically want

to get it wide open and on the hot plate as soon as it's safe, but without risking having things get sucked up.)

31. Concentrate for a while until the solvent is all gone. 10 minutes at HP=5 will probably be enough to remove much if not all of the solvent.
32. Turn the hot-plate up to 6, and vacuum for an additional 20 minutes, to try to complete ring closure.
33. Take off from hot plate and from the vacuum, and let cool. Is it solid?
34. Get mass so you can calculate the crude % yield.
35. Analysis: Take a portion and submit a crude-sample GC. If NMR is working, take a crude NMR.

Purification/Digestion

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 - b. Often pouring/cutting it out into a big weighing boat, then placing another weight boat on top of that, and crush/grind it with flask or vial.
37. Add 5mL ether/25mL hexane, and reflux for 30 minutes at hot-plate = 3.
38. Filter, rinsing with straight hexane.
39. **Make sure it's dried quite well.**
40. Remass, recalculate purified % yield, re-NMR if it's working



We have several other salts. Most in small scales, like 5 grams. But *IF* the toluenehydrazine salt process works well, we could try to repeat it with some of the other salts, too, just in smaller scale.