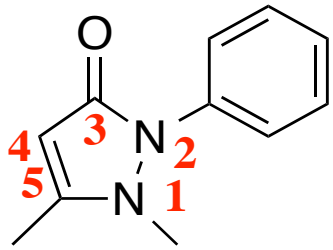
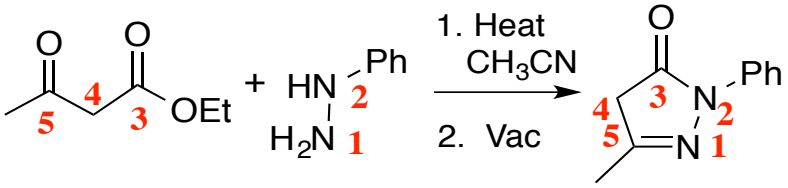
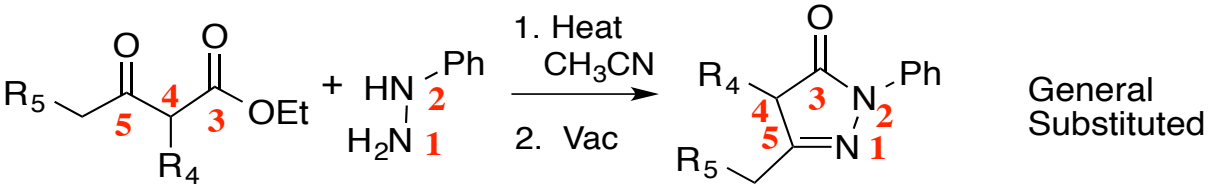
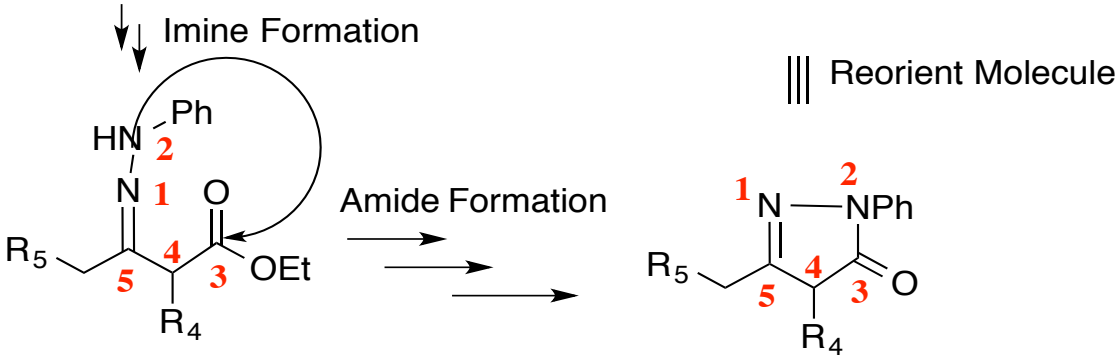
Antipyrine and it's Numbering System
Lead Drug Candidate



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?

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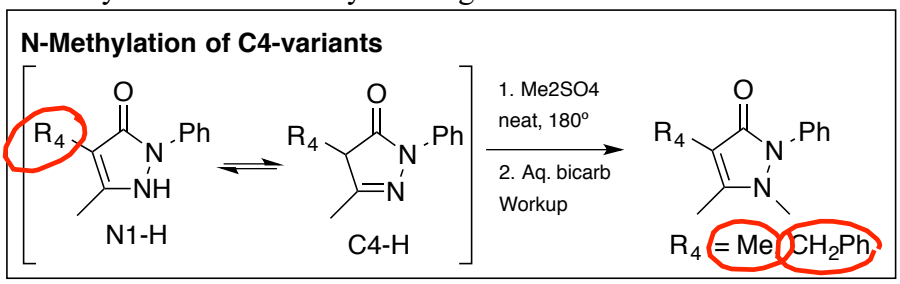
Table of Project Ideas, Fall 2021:

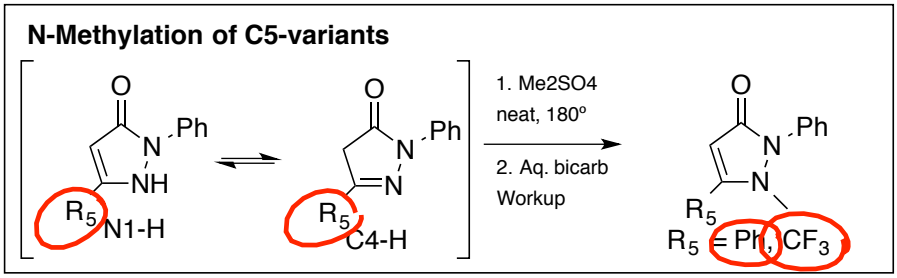
Area A: **N1-Desmethyl analogs by addition of hydrazines to ketoesters.**
Then Conversion to N1-Methyl Analogs by methylation

1. N-Methylation of Desmethyl Analogs



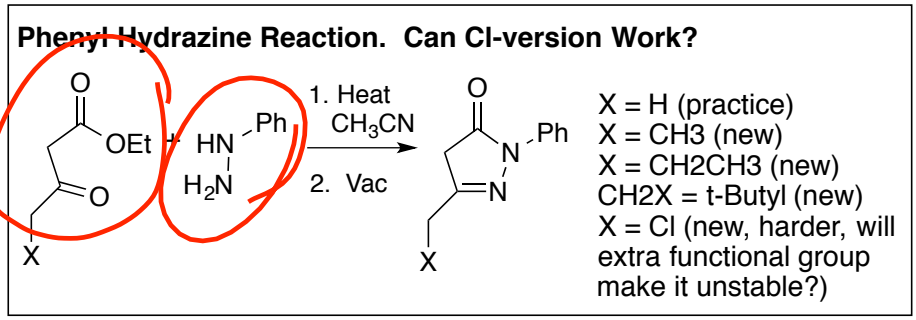
Lola?

Can practice using the R4=H variant.
How hot do we need?
Can we clean up and purify at the end? Via digestion? Combiflash?
Have POP (proof-of-principle) precedent that the reaction works. It's the optimization (how long, how hot, what stoichiometry? How to best clean up afterwards?) that's to be processed.



Very much similar to above project, so same student could potentially attack both.

2. **Phenyl Hydrazine addition to KetoEsters to make Des-Methyl Core with C5-Variations**

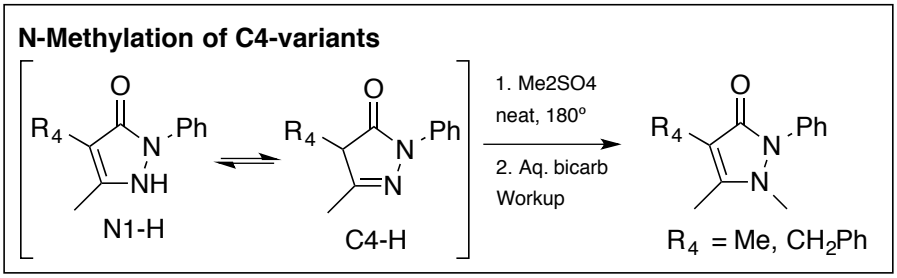


Gael?

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

Document Beginning: 9/1/2021. Lola Sibaud

1. N-Methylation of Desmethyl Analogs



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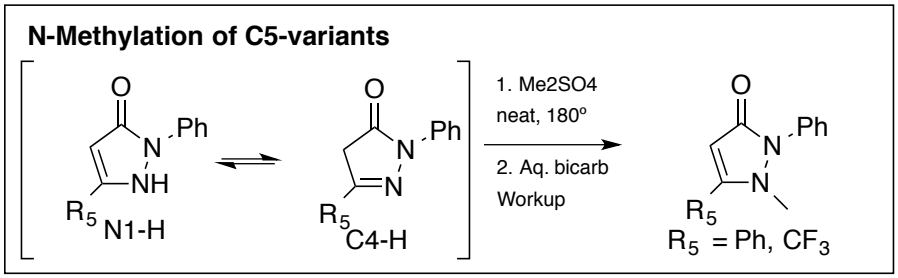

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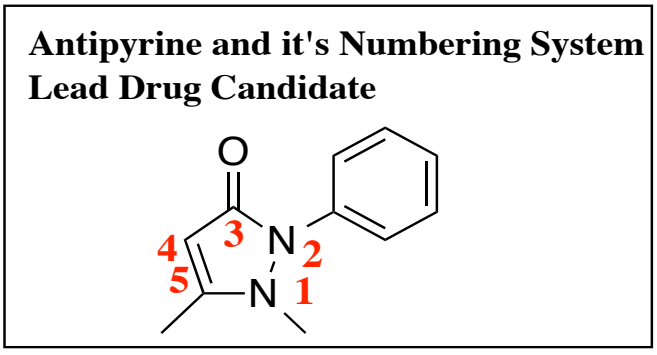
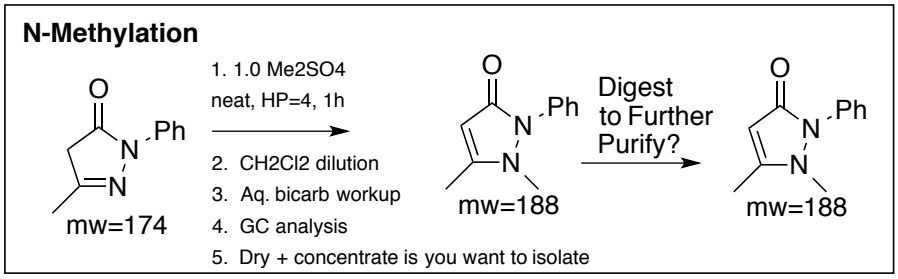


Specific First-Trial Proof-of-Principle and Procedure Optimization:



Substrate: 4.0 mmol
Dimethylsulfate: 4.0 mmol
Workup:
CH2Cl2: 10 mL
NaHCO3/water: ~10 mL

Suggested initial-attempt procedure:

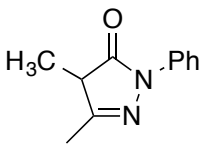
1. Weigh out 4.0 mmol of substrate into oven-dry 20-mL vial with stir bar.
2. Calculate and add in 4.0 mmol of Dimethylsulfate.
3. Cap the flask.
4. Place on hot plate set to HP=4.
   - Totally guessing here.
   - We know in a POP-test (proof-of-principle) that it works at HP = 6. But that extreme-heat seems unnecessarily excessive.
5. Suggestion: Stir gently for some time period (1 hour?).
   - Again, time-guessing. I'm thinking an hour will suffice, but perhaps that's longer than needed, or less than needed.
   - In the previous POP test, it was done for 3 hours at HP=6! Likely overkill, but that sufficed.
6. During the 1h, turn GC-MS on, and run a sample of the starting material if you haven't previously, so that you know it's retention time.
7. Aliquot analysis:
   - After 1 h, remove from hot plate with gloves.
   - Unscrew the cap
   - Take a pipet and pull out an ~2-3cm tiny sample in the skinny end of long pipet, and transfer if possible into a GC-vial.
   - Reattach the cap to the flask and return it to the hot plate for continued stirring.
   - Add ~.6mL CH2Cl2 to the pipet and try to flush the sample through, and to rinse the sample.
     - This is best done pretty quickly, while things are still in hot melted form. If we wait too long, the material will likely harden into a glass..
     - Good chance after drawing some up into pipet, that it will harden/freeze in there.
     - If so, place your plugged pipet into the clamped-down GC-vial, then try to use a heat gun to melt the plug.
     - Consult Jasperse if needed.).
   - Carefully add 0.5 mL of NaHCO3/water to the GC vial. (May be some bubbling.).
   - Try to mix it up thoroughly via pipet draw-and-flush.
   - Let settle, so that the CH2Cl2 layer sinks to the bottom.
   - Run GC.
   - GC thinking analysis, key processing questions:

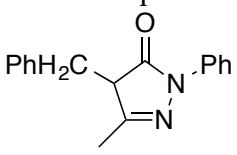
- Does the GC look reasonably clean, or grossly complex?
- What is the ratio of product (mw = 188) versus starting material (mw = 174)
- If the starting material is gone, then the reaction is complete and there is no need for further heating. If the starting material is largely still present, then there is reason to heat further and see if conversion progresses later.

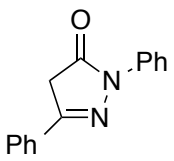
8. If the GC showed significant residual starting material, continue heating for a variably longer time.
9. If the GC showed completion, then it's time to workup the reaction mixture.
10. Workup: Reduce the HP = 3, lift the clamp a bit to add 1-2 cm space from hot plate, and quickly but carefully begin adding some CH2Cl2.
    - The goal is to dilute the solution, and to do so before the mixture hardens into a hard block.
    - So doing this before it cools is desirable; but some of the CH2Cl2 will just boil off at first, because the flask is too hot.
    - Would like to get the flask to be half filled with CH2Cl2, then return it to the HP=3 and try to stir to solubilize.
    - If it mostly seems solubilized and easy to stir, then turn off the hot plate.
    - Add ~5mL of K2CO3/H2O. If things are too hard or glass-ized, it may take some work to get it able to dissolve up. But hopefully between the organic and aqueous solvents, things will dissolve into one or the other. Stir vigorously for 1-2 minutes so that carbonate has a chance to neutralize all nitrogens.
11. Transfer to sep funnel, and dry organic phase over Na2SO4 through a ground-glass filter into a pre-weighed flask. (Consult Jasperse as needed). Probably a 50-mL flask?
12. Rinse out vial with 2nd dose of CH2Cl2, pour into sep funnel that still has the aqueous phase, shake, and pour the organic phase through the Na2SO4 into the flask with the organic solution.
13. Don't worry if there is some residual black sludge in the vial.
14. Add an additional 10 mL of CH2Cl2 to sep funnel, shake it up, and extract that too through the drying tower.
15. Rotovap off the combined organic phases.
16. Get mass and NMR, if the NMR is working.
17. Re-run a GC on the purified product.
18. NMR keys: A key is the present of a new vinyl singlet for the C4-H. Plus obviously the disappearance of your starting substrate, and hopefully a relatively clean methyl singlet for the C5-methyl.
19. Possible digestion?
    - Is the concentrated material solid or oil?
    - Try some solvent or solvent blend to stir it. Want it to NOT be able to fully dissolve the product at room temp, whether it's an oil or a solid either way. Idea would be to stir around, perhaps while heating, and then to let it cool and crystallize/oil out.

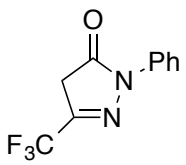
Suggestions for us:

1. Consider further scaleup? 10 mmol?
2. Apply to other analogs.
3. In each case, try to purify.
4. Each of these would produce novel substances.









Perhaps Others As They Are Made. These are currently in stock