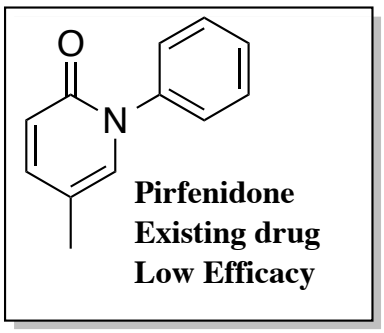
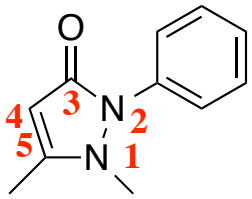
Research Pulmonary Fibrosis AntiPyrine Analog Library Synthesis Update 9/4/2019




**Antipyrine and it's Numbering System**
**Lead Drug Candidate**




Structure Interpretation Key:
1. Each "vertex" represents a carbon atom
2. Hydrogen atoms are not drawn, but each carbon has enough attached hydrogens to give it four bonds

**Big Picture Concept:**

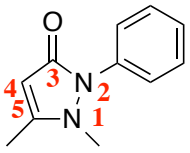
1. Pirfenidone is a medicine used to treat pulmonary fibrosis
   - It's not very good
   - It is not a life-saver
   - It isn't very good in terms of potency, efficacy, toxicity (or expense)
   - Its mechanism of operation is not understood

2. Five qualities for a drug
   - The Big Three:
     a. Potency
     b. Efficacy
     c. Toxicity
   - Two Practicals:
     a. Delivery
     b. Cost

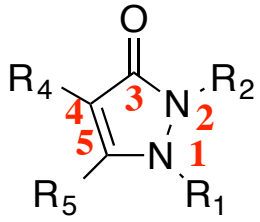
3. An extensive "chemical library" study has found antipyrine as a "lead chemical", comparable to pirfenidone

4. Group goal: Make as many analogs of antipyrine as we can, in hopes that we can make something better yet

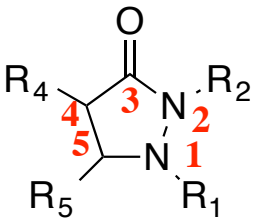
5. The Drug Improvement Loop: (and the need for Chemical Synthesis …..)
   - Library study => initial lead
   - Make analogs (new library) => test again => secondary leads (synthetic chemistry needed)
   - Make further refinements (new library) => test again => 3rd-round lead (more synthesis)
     - Lock+Key (Structure-Activity Relationships): We don't know what biochemical "lock" pirfenidone fits into, so we don't really know how to shape the "key". (3D volume; rigid vs flexible; hydrophobic vs hydrophilic.) Analogs help to map.



**Our Project: Make a Library of Chemical Analogs to Antipyrine.**
***Vary at Positions 1, 2, 4, + 5**
***Including the presence or absence of C4=C5 double bond (pyrazoles vs pyrazolidinones)**
***"R" represents some variable attachment**

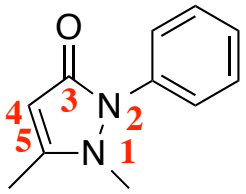


Pyrazoles



Pyrazolidinones

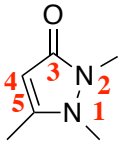
**Antipyrine and it's Numbering System Lead Drug Candidate**



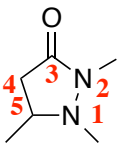

**Terminology and Numbering:**

- "Pyrazolone" (has double bond) versus
- "Pyrazolidinone" (no double bonds in ring)
- Numbering: The two nitrogens are #'s 1 and 2, with the carbonyl #3
  - Number logic: The two nitrogens naturally win over the 3 carbons, so they've got to be 1 and 2.
  - Of the 3 carbons, the carbonyl is highest priority.
  - So, by starting with N1 on the bottom, it leads to the carbonyl being #3.
    - If the top N had been #1, then the carbonyl would have been #5.
- In the pyrazolidinones, N1 is tetrahedral/$sp^3$, and the conjugated N2 is $sp^2$.
  - N1 is thus more nucleophilic (reactant stability/reactivity principle)
  - N2 is more acidic (product stability/reactivity principle)

Pyrazolone vs Pyrazolidinone Rings

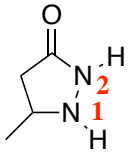


**Pyrazolone**



**Pyrazolidinone**

Hybridization and Reactivity in Pyrazolidione Rings



**Pyrazolidinone**

N2: Conjugated, $sp^2$, more stable
-more acidic, since resulting anion would be stabilized
N1: Non-conjugated, $sp^3$, less stable
-more basic/nucleophilic

**What Kind of Activities Do My Students Do? Generic aspects:**

1. We like to build thing! ☺☺☺ Set up and run synthetic Reactions.

2. Decide when to shut them off: Analyze the reactions in progress
   a. NMR, GC-MS.
   b. Hoping HPLC-MS will be great for us!

3. Figure out how to work them up and isolate the product

4. Figure out how to purify the product
   a. (My least favorite)
   b. Much liquid-liquid extraction chemistry (sep funnel)
   c. Much digestion/recrystallization chemistry (we often do digestion)
   d. Much simple distillation (rotovap) for solvent removal.

5. Analyze the product
   a. NMR
   b. GC-MS
   c. HPLC-MS?

6. Synthetic Methodology:
   a. Optimizing a process.
   b. Determining scope-and-limitation for a method: ***if*** **a process works for one substrate, how far can we go (in the harder direction) before it will fail? (if ever)**

7. Reproducibility

8. Keeping Notebook, Keeping Organized! ☺☺☺

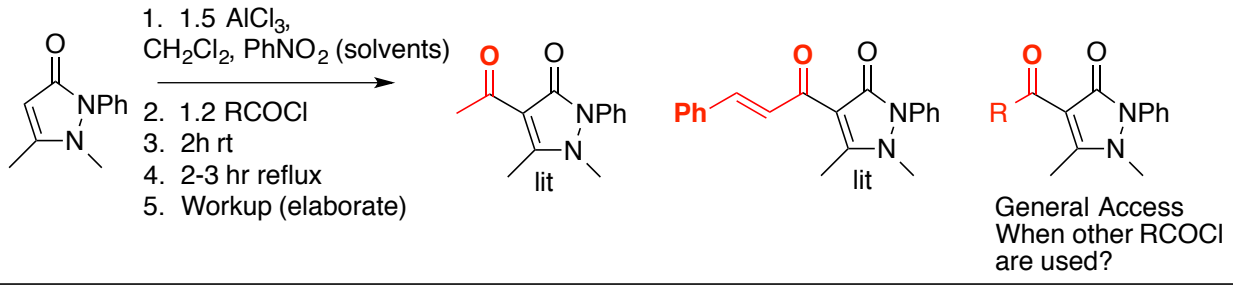
9. Time scheduling: Super Variable, high degree of independence allowed/encouraged (and required).

10. Space in Group: Yes.

11. Experience Required: First semester organic lab preferred (but not required, for a good, self-motivated, and ambitious student! ☺

## C4-Acylation with Acyl Chlorides Abby and Logan?

**C4-Acylation with Acyl Chlorides and AlCl3**




## References, PDF's:

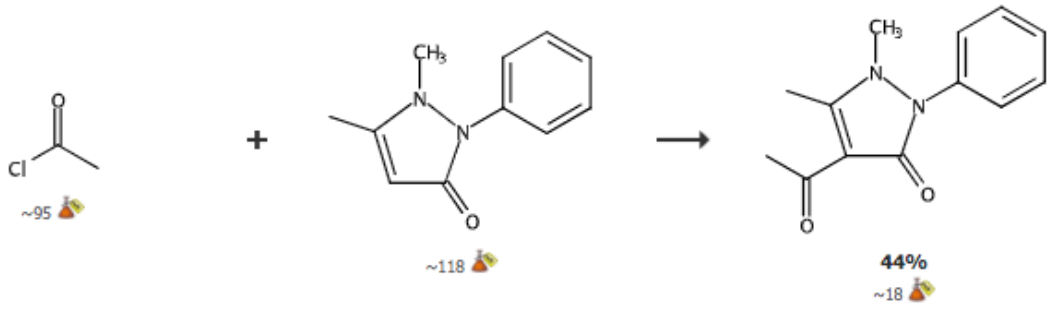
1. "Acetyl Chloride Antipyrine Acylation 1962 Article" (jasperse pdf)
2. "Acetyl Chloride Article; English translation" (jasperse pdf)
3. Ibrahim, A. E-S; Kandil, A.; El-Moghayar, M. H.; Archiv der Pharmazie, 1983, 316(1), p76-82."Reactions with 3-pyrazolin-5-ones: Synthesis of some 4-substituted 2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones"
4. Stach, K. Archiv der Pharmazie und Berichte der Deutschen Pharmazeutischen Gesellschaft, 295(11), 853-9; 1962 Substituted derivatives of pyrazolone. I. Pyrazonyl carbinole

**Chemical Abstrate procedure, very detailed!**

Under agitation, 200 g. (1.5 mol) $AlCl_3$ are added portionwise to 188 g. (1.0 mol) 1-phenyl-2,3-dimethyl-5-pyrazolone, 1000 ml. $CS_2$, and 300 ml. nitrobenzene at 15-20°. Acid chloride (1.2 moles) dissolved in an equal vol. $CS_2$ is added to the soln. After addn., the mixt. is held 2 hrs. at room temp. and thereafter boiled 2 hrs. After cooling, the $CS_2$ layer is sepd. and shaken with 200 ml. 5N HCl. After sepn. of $CS_2$, 800-1000 ml. 5N HCl is added to the product under cooling and agitation. The combined aq. acid soln. is extd. with ether and, under cooling and agitation, made alk. by addn. of concd. NaOH soln. until the pptd. $Al(OH)_3$ is dissolved. The crystal slurry is extd. with chloroform. The combined exts. are washed with concd. NaCl soln. until neutral and dried with $Na_2SO_4$ and the chloroform evapd. in vacuo. The residue is washed with Skellysolve and ether and dried in vacuo at 40-50°. The obtained crude pyrazolonyl ketone usually does not require addnl. purification. M.p. of recrystd. pyrazolonyl ketones were: acetyl, 175°; propionyl, 177°; butyl, 180°; isobutyl, 224°.

Notes: The literature uses Carbon disulfide as solvent, but that is smelly and is not good to clean up. It might not work exactly the same, but we would try it in anhydrous CH2Cl2 in it's place.
The nitrobenzene is able to dissolve AlCl3. I bought a solution.
So, we'd need some improvising a little bit.
May need to boil longer? Replacement of CS2 with CH2CL2, the boiling point is about 10º cooler, so we'd want some extra boiling time to be equivalent, probably? I'm not sure I'm totally tracking what is going where at each step; we'd probably want to try one and figure things out as we go. Smaller scale => easier!

The following is a procedure for taking the ketone, and doing RMgBr additions to make Alcohols.
(For prepn. of pyrazonyl carbinols, 0.2 mole of a pyrazonyl ketone is dissolved in 800-1000 ml. tetrahydrofuran and, under agitation, added dropwise to 15-20° to 0.6 mole of an alkylmagnesium compd., $R_2MgX$, dissolved in 600 ml. anhyd. ether. After addn. the mixt. is held 1 hr. at 20-5° and thereafter 3 hrs. at 30-5°. Concd. $NH_4Cl$ soln. is added at 15-20° and the org. layer washed with concd. NaCl soln., dried with $Na_2SO_4$, and evapd. at 30-5° in vacuo. The product can be recrystd. from ethyl acetate. The products prepd. were: (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)dimethylcarbinol, 55-60%, m. 124-6°; (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)-methylpropylcarbinol, 65-70%, m. 103-5°; (1-phenyl-2,3-di-methyl-5-pyrazolon-4-yl)methylbutylcarbinol, 35-40%, m. 71-3°; (1-phenyl-2,3- dimethyl- 5- pyrazolon- 4- yl)methylphenylcarbinol, 70-5%, m. 116-18°; (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)diethylcarbinol, 65-70%, m. 107-9°; (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)dipropylcarbinol, 75-80%, 87-9°; (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)methylpropylcarbinol, 70-5%, m. 103-5°; (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)methylisopropylcarbinol, 70-5%, m. 104-6°; (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl(propylcarbinol, 50-5%, m. 71-4°; (1-phenyl-2,3-dimethyl-5-pyrazolone-4-yl)isopropylcarbinol, 60-5%, m. 113-15°; (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)butylcarbinol, 50-5%, 93-6°; (1-phenyl-2,3-dimethyl-5-pyrazolone-4-yl)-sec-butyl-carbinol, 60-5%, m. 95-8°; (1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)cyclohexylcarbinol, 50-5%, m. 150-2°.)




**Overview**

**Steps/Stages**

1.1

**Notes**

Reactants: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

**References**

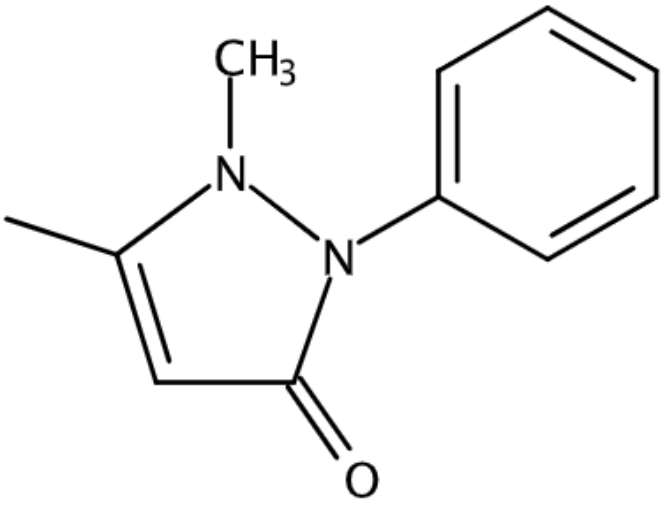
Synthesis and properties of 4-acetylantipyrine
Quick View  Other Sources
By Chen, Kaixun et al
From Huaxue Shiji, 14(6), 373, 324; 1992

**Synthesis and properties of 4-acetylantipyrine**
Other Sources
By Chen, Kaixun; Liu, Lin; Tang, Zongxun
From Huaxue Shiji (1992), 14(6), 373, 324. | Language: Chinese, Database: CAPLUS

Refluxing powd. antipyrine with AcCl for 3-4 h gave 44.3% 4-acetylantipyrine (I). The UV, IR, and mass spectra of I were reported.

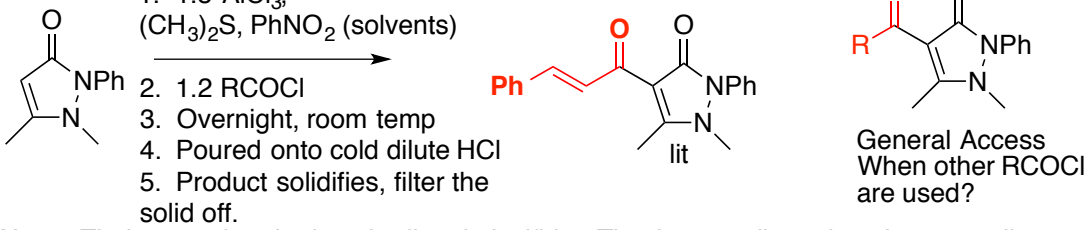
**Substance Images**

60-80-0 Antipyrine  1 2 3 of 3



Simpler procedure using paper in English, 1983:
They did this using a single acyl chloride, cinnamoyl chloride, which we do have.

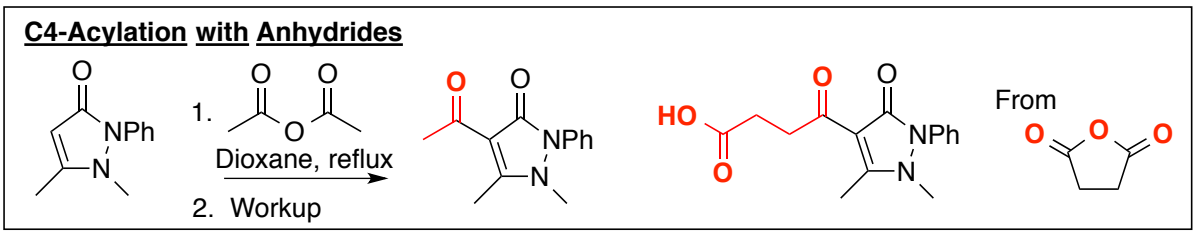
**C4-Acylation with Acyl Chlorides and AlCl3. 1983 Article**




General Access
When other RCOCl are used?

Note: Their procedure is done in dimethylsulfide. That is a smelly and environmentally bad solvent. I'd like to try to repeat this using dichloromethane in stead.
Not sure how or whether that would impact the reactivity, or the ability of the product to come out of the solution upon pouring onto the HCl.
Might perhaps pour it onto the HCl, then let the dichloromethane evaporate to facilitate crystallization?

**C4-Acylation with Anhydrides. Logan?**

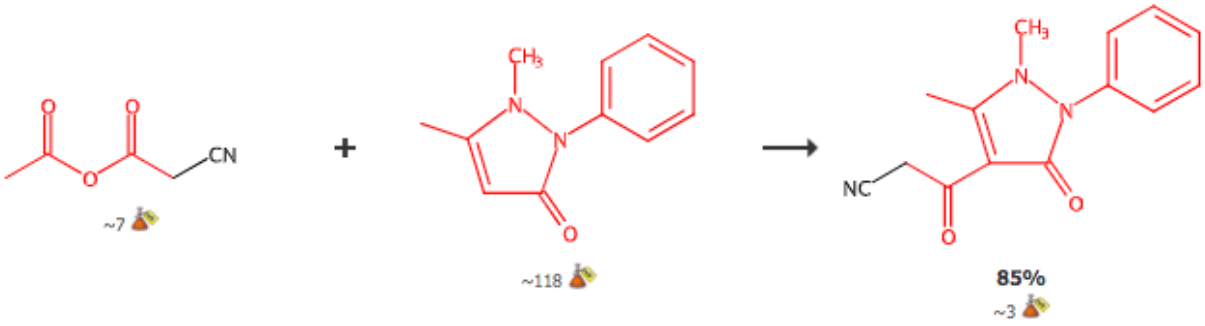



Might be simpler operationally than the AlCl3 reaction, if we don't need to get rid of the AlCl3?

Difficulty estimate: Unknown.
Odds for some successful results: Medium
Odds for some pretty quick success results: Good
Novelty and necessity for extensive innovation and self-discovery: Medium
Notes: May want to do true column chromatography as opposed to combiflash? Or perhaps could be a good opportunity to practice and experience combiflash, too?

Lots of cheap anhydrides available: acetic, propionic, butyric, isobutyric, maleic, phthalic

Ref:
Studies on 3-oxoalkanenitriles: novel rearrangement reactions observed in studies of the chemistry of 3-heteroaroyl-3-oxoalkanenitriles as novel routes to 2-dialkylaminopyridines
Quick ViewOther Sources
By Al-Matar, Hamad M. et al
From Molecules, 17, 897-909; 2012



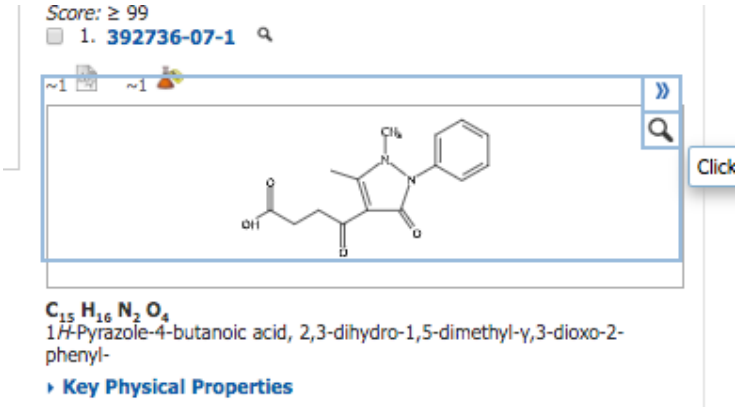

Experimental: "*3.3. Cyanoacetylation Reactions of* **1a–d** *with Acetic 2-Cyanoacetic Anhydride* (**2**) A mixture of pre-prepared acetic 2-cyanoacetic anhydride (**2**, 1.27 g, 10.0 mmol), the starting aromatic or heteroaromatic compound (10.0 mmol), and indium trichloride (0.12 g, 10% wt.) in case of 1-methylimidazole (**1c**) and 1-methylbenzimidazole (**1d**), in dry dioxane (15 mL) was stirred at reflux for 1 h. The reaction mixture was then poured into water. The formed solid product was then collected by filtration, washed with water and crystallized from ethanol. Cyanoacetylation of benzimidazole **1d** afforded one isolable products **5** as the major product. The product was isolated by column chromatography using ethyl acetate-*n*-hexane (1:3) as eluent and its structure confirmed by X-ray determination.:

- Jasperse notes: We should anticipate heating beyond the 1h, since without the cyano regular acetic anhydride could be less reactive. I'd check via NMR check, and/or GC analysis.
- Their procedure makes reference to using indium trichloride; they did NOT use that for antipyrine. But putting that or something else in as an activator might be an option if our reactivity is too slow?
- I'd think we'd also have a good chance to have the product solidify upon pouring into water, but we

have a different product, so who knows?

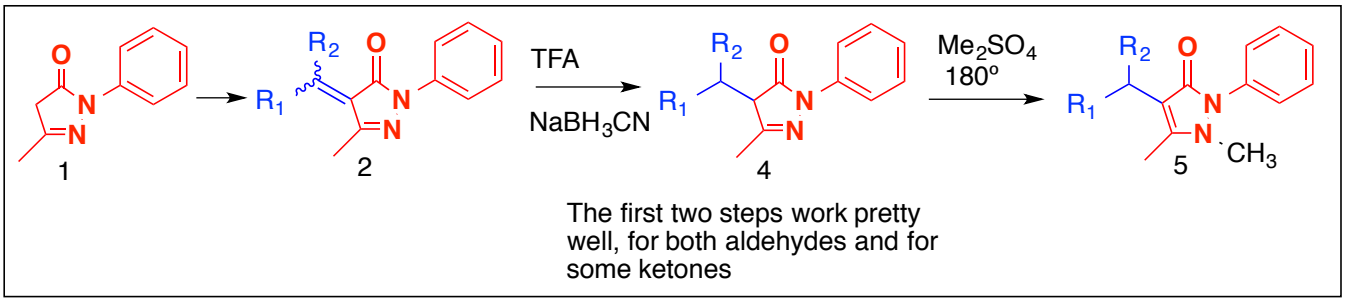
- The dioxane solvent gives a big singlet in the NMR. But we ought to be able to take direct aliquot samples and do NMR analysis to track progress..
- I am ordering a couple of additional anhydrides.

The following had no scifinder synthesis detailed. But it looks like antipyrine and maleic anhydride adduct….



**Abby: Project 2. Some continuation from this Summer's successful alkylation-reduction.**

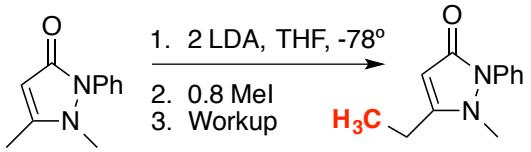
This sequence would provide a versatile way to have 4-alkyl variations relative to Antipyrine.



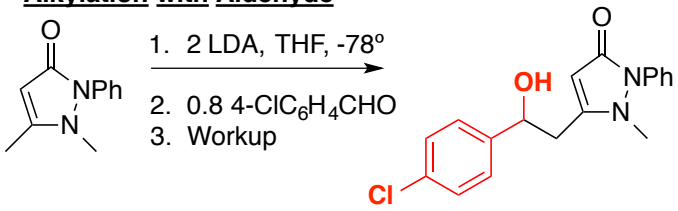
# C5-Alkylation, Using LDA and Anhydrous THF, Low Temp: Eric Gibbons will Try

**Literature Reactions**

**Alkylation with Alkyl Iodide**




**Alkylation with Aldehyde**

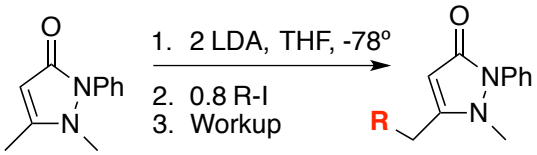



**LDA Preparation** 2.8 $(iPr)_2NH$ —(2.0 BuLi, THF, 0°C)→ 2.0 (iPr)2NLi (LDA)

Awesome article! LDA in THF at -78, get alkylation on C5-methyl, with alkyl halide or with aldehyde! Direct protocol for varying the C5-methyl group!

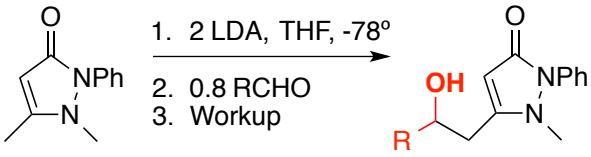
**Possible New Reactions**

**Alkylation with Alkyl Iodides Other than Methyl**



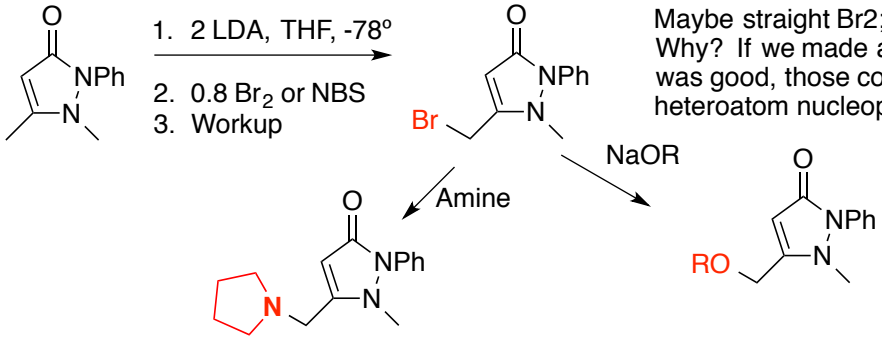

Could try Ethyl, Propyl, Butyl, or Isopropyl
And/or Benzyl Bromide,
etc. Basically any good Alkylation agent could be used.

**Alkylation with Aldehydes or Ketones other than 4-chlorobenzaldehyde**




Could try other aldehydes or ketones.
Probably any might work.

**Bromination?**




Maybe straight Br2; or else NBS.
Why? If we made a big batch of the Br and it was good, those could then be substituted with heteroatom nucleophiles.

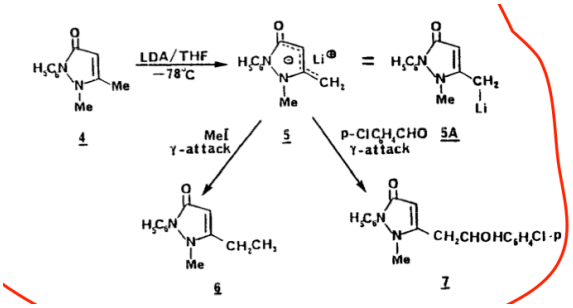
Suggestions for us:

1. Do exactly those same two reactions. See if we can reproduce them. They'll have exact NMR and workup/chromatography details for us.
2. If we can get them to work, then we could expand and do some variants.

Reddy, K. R.; Roy, A.; Ila, H.; Juqjappa, H. *Tetrahedron*, 51, 40, p10941-10952, 1995. Regiospecific Generation and Application of 3-Lithiomethyl-2-methyl-1-phenylpyrazolinone as 1 ,3-Binucleophile in Aromatic Anuelation: A Novel Approach for Synthesis of 1,2-Disubstituted Indazolones and their Condensed Analogs

- PDF Article on Jasperse Computer, in Chem397 folder: "Ref 66 Reddy Direct LDA C5-Methyl-Alkylation"

"We began our investigation by first studying the specificity of lithiation of I-phenyl-2,3-dimethylpyrazolin-5-one (Antipyrine) 4 (Scheme 2). Treatment of a solution of Antipyrine in THF with LDA at -78"C, followed by quenching of the enolate 5 with methyl iodide and work-up produced exclusively the y-methylated derivative 6 in almost quantitative yield. The product 6 was found to be identical with that reported in the literature.' Similarly when the enolate 5 was quenched with 4-chlorobenzaldehyde, a good yield of the corresponding y-secondary alcohol 7 was obtained. Thus the enolate 5 displays exclusive y-selectivity in its reaction. (Scheme 1)."




All anhydrous, low temperature reactions were carried out in oven dried (120°C) glassware under a stream of dry argon/nitrogen. Transfer of anhydrous solvents or mixtures was accomplished with oven dried (120°C) syringes using standard syringe-septum technique. Analytical thin layer chromatography (tic) was performed on glass plates (18x6 and 18x4 cm) coated with Acme's silica gel containing 13% calcium sulfate as binder and various combinations of ethyl acetate-hexane and ethyl acetate-benzene were used as eluents. Chromatograms were developed either with iodine vapour or potassium permanganate.

**General procedure for the generation and reaction of 3-lithiomethyl 2-methyl-1-phenylpyrazolone 5A with electrophiles (iodomethane and 4-chlorobenzaldehyde): Synthesis of 3-ethyl-2-methyl-1-phenylpyrazolone 6 and 1,2-Dihydro-5-[2-(4-chlorophenyl)-hydroxyethyl]-1-methyl-2-phenyl-3H-pyrazol-3-one 7.**

To a solution of diisopropylamine 2 ml (14 mmol) in sodium dried tetrahydrofuran (THF) 10 ml under dry and inert atmosphere was added 10 mmol of n-BuLi in ether with stirring for 20 min and temperature control at 0°C with an ice bath. To the resulting solution of lithium diisopropylamide (LDA) at -78°C was added a solution of 0.9g (5 mmol) of antipyrine in 25 ml dry THF, the reaction mixture was stirred at the same termperature for 30-40 min. To the resulting enolate solution at -78°C was added 4 mmol of electrophile in 15 ml dry THF dropwise and stirred for 30-45 min.(-78°C) and then allowed to warm to room temperature (monitored by tlc). The mixture was quenched with aqueous saturated ammonium chloride solution (100 ml) and extracted with chloroform (3x25 ml). The combined extracts were washed with water (3x25 ml), dried (sodium sulphate) and then evaporated to give the crude product, which was purified by column chromatography over silica gel using ethyl acetate-hexane (3:7) as eluent.

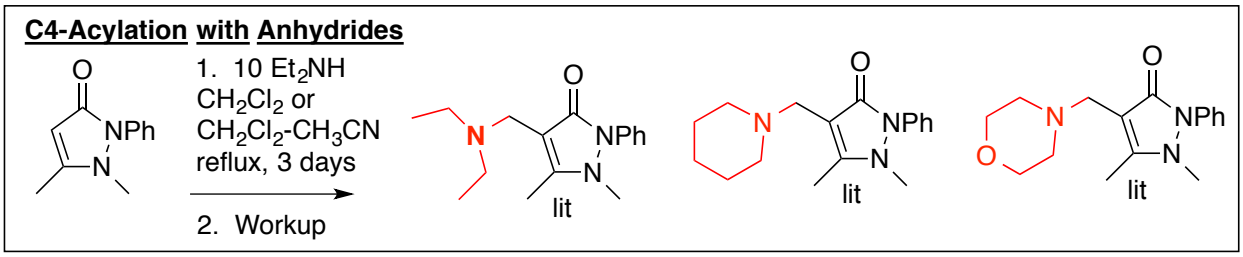
**1,2-Dihydro-5-ethyl-1-methyl-2-phenyl-3H-pyrazol-3-one 6**:
Light brown viscous liquid; yield 0.83g (82%); $R_f$ 0.5 EtOAc/benzene (9:4). IR (KBr): $\nu$max = 3417, 2963, 1642 (CO), 1298, 757 $cm^{-1}$. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ = 1.25 (t, 3H, J = 7Hz, $CH_3$); 2.49 (q, 2H, J=7Hz, $CH_2$); 2.99 (s, 3H, $CH_3$); 5.33 (s, 1H, vinylic); 7.25-7.60 (m, 5H, ArH). Anal: Calc. for $C_{12}H_{14}N_2O$ (202.246): C 71.26; H 6.98; N 13.85. Found C 71.50; H 6.95; N 13.90%.

**1,2-Dihydro-5-[2-(4-chlorophenyl)-hydroxyethyl]-1-methyl-2-phenyl-3H-pyrazol-3-one 7**:
Colourless crystals; yield 1.46g (86%); mp 160-163°C (chloroform-hexane); $R_f$ 0.29 EtOAc/benzene (6:4). IR (KBr): $\nu$max = 3095, 1622 (CO), 1478, 1064, 762 $cm^{-1}$. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 2.75 (d, 2H, J = 9Hz, $CH_2$); 2.90 (s, 3H, $NCH_3$); 3.35 (brs, 1H, OH exchangeable with $D_2O$); 4.88 (t, 1H, J = 9Hz, benzylic); 5.00 (s, 1H, vinylic); 7.24-7.58(m, 9H, ArH). Anal. Calc. for $C_{18}H_{17}ClO_2N_2$ (328.993): C 65.75; H 5.21; N 8.52. Found C 66.70; H 5.22; N 8.54%.

Yaa Pokua Fall 2019

**C4-Aminomethylation using Methylene Chloride and Amine Yaa?**

Lit: Souquet, F.; Martens, T.; Fleury, M.-B. Synthetic Communications, 23(6), 817-828, (1993)




Operational procedure appears to be quite simple. All three were crystalline following chromatographic purification.

Might be a nice, easy experiment to try. Could reproduce 2 or 3 of the literature examples with listed melting points and stuff. Maybe add in pyrollidine, the 5-member ring amine.

If you want, you could then move on to another project; or if you wanted to you could check for greater generality and try another amine or two to make something completely new.

Difficulty estimate: Modest
Odds for some successful results: Good
Odds for some pretty quick success results: Good
Novelty and necessity for extensive innovation and self-discovery: Modest
Notes: May want to do true column chromatography as opposed to combiflash? Or perhaps could be a good opportunity to practice and experience combiflash, too?

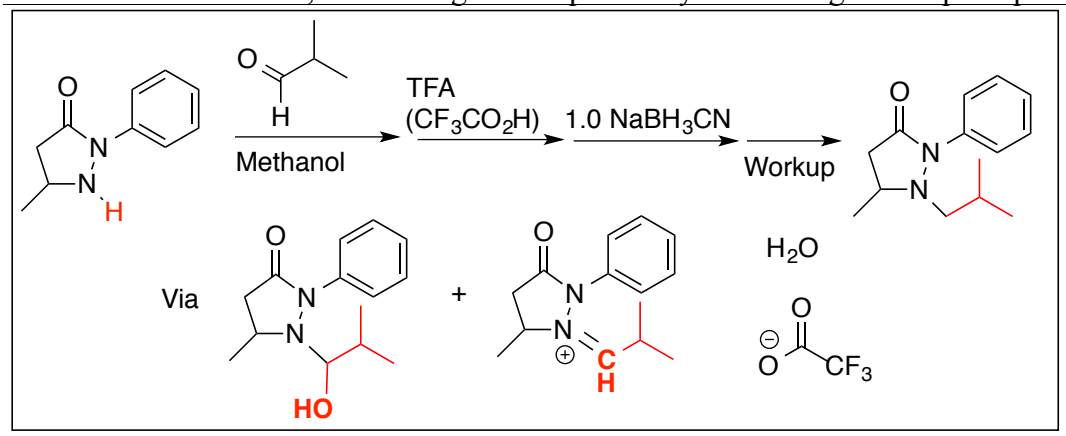
Chemicals and supplies:
We have antipyrine. And the solvents.
We have diethylamine
I have ordered piperidine (6-ring amine) and morpholine (6-ring amine with oxygen)
We have pyrrolidine (5-ring amine).

Brent Schulte Research Project Plan Draft 2. Fall 2019

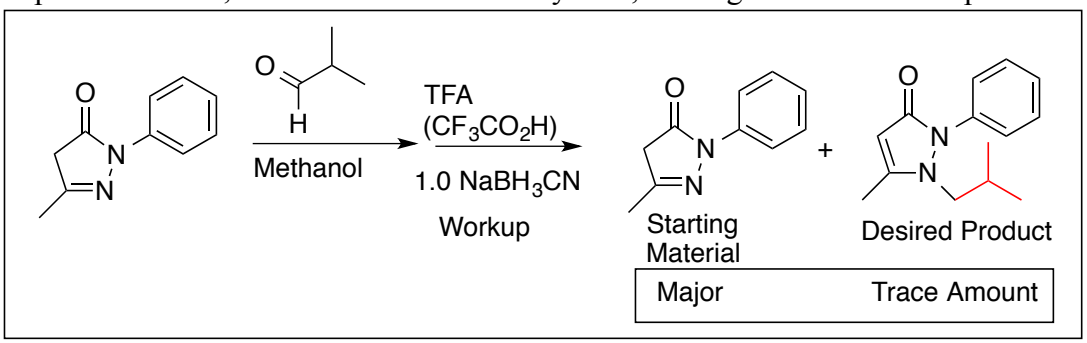
2019 Updates, Projects:

**"STAB" Use for Reductive Alkylation. Might STAB work better than NaBH3CN?**
**Or might NaBH3CN work better with milder CH3CO2H instead of CF3CO2H**
**Brent will Try:**

Review: These worked, but didn't give complete alkylation. Might Stab perhaps work better?




Jasperse tried this, and it DIDN'T work very well, although there was ~5% product




**STAB: Sodium TriAcetocy Borane, $NaBH(OCOCH_3)_3$**
Alternative to NaBH3CN. STAB is thought to be:

- Unstable in methanol (too bad)
- Less reactive than NaBH3CN
- That would slow it's reactions, but perhaps also slow it's decomposition or inadvertent reaction with aldehydes or with TFA.
- Idea is to use milder CH3CO2H as acid, and use a different solvent, and see if we can get better results.
    - On reaction(s) you did: Might conversion be cleaner and more complete?
    - On the reaction that I tried that gave only trace conversion. (I think the NaBH3CN just reacted with the aldehyde/TFA combination.

**Ideas:**

A. Do ~5 trials on your existing reaction**: Proof of Principle test?**

1. Control: Same NaBH3CN/TFA that you did last spring (control)
2. TFA/Acetic-acid test: Same, except replace TFA with Acetic acid. (does milder acid help, by extending lifetime of the borohydride? Or hurt, by being less acidic does the acid-catalyzed desired process get retarded?)
3. TFA vs STAB test: NaBH(OAc)3/TFA methanol. (Basically do same, but replace NaBH3CN with STAB?
4. NaBH(OAc)3/Acetic acid in ClCH2CH2Cl test.
5. NaBH(OAc)3/Acetic acid in THF test.

Purpose/question: Can you do things better with STAB than with NaBH3CN?
If not, maybe forget about STAB. But **if** it helps, maybe we could try the least successful ones from the spring?

**IF** it helps, maybe try on the Jasperse substrate in figure above?

Maybe also try

Also try: NaBH3CN on Jasperse substrate using acetic acid (CH3CO2H) instead of TFA (CF3CO2H). Maybe the borohydride will hold up better and accomplish more desirable stuff under milder conditions?

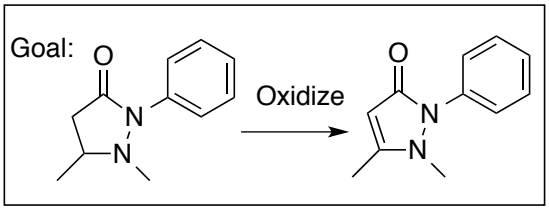
Reference:

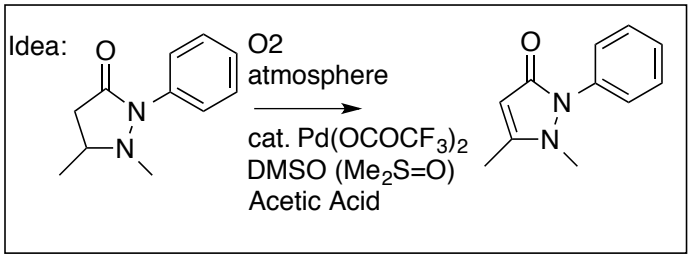
1. **"Sodium triacetoxyborohydride – Wikipedia"** https://en.wikipedia.org/wiki/Sodium_triacetoxyborohydride
2. "Sodium Triacetoxyborohydride - Gribble - - Major Reference Works - Wiley Online Library"

**Oxidation of pyrazolidinones with O2/Pd(TFA)2/DMSO??? Brent?**

**Notes:**

You've already made a batch of the starting material.
And you also have the analog with the N-Me replaced by N-H.
So you've got the perfect chemicals for testing oxidation chemistry out on.



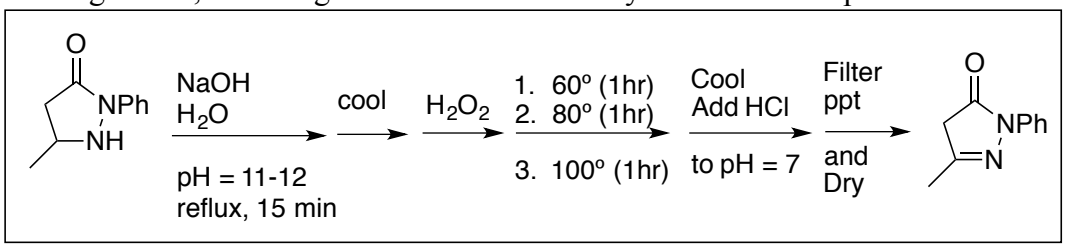




**References:**

**Diao, T; Stahl, S. S. J. Am. Chem. Soc, 2011, 133(37), pp 14566-14569**
**Stahl 2013 paper has more details.**
**Stahl also has a review paper.**

**Control: Use some simpler ketone that was used in the paper.**
**See if we can reproduce reaction.**
**If so, then try to apply to our pyrazolidinone.**

Also try the hydrogen peroxide patent thing. (That was quite different.)
Fleming Patent, "Fleming Oxidation Patent for Pyrazolones 1978.pdf"

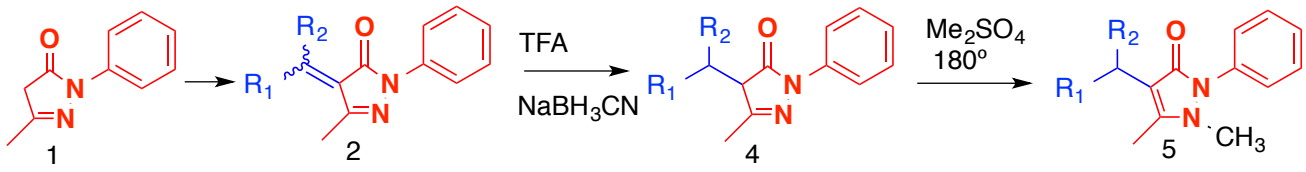



Operationally uncomplicated
Question: Is it limited to pyrazolidinones with N1 = NH? Or might it also work with N1 being already methylated or substituted in other ways?

**Chromatographic Purification Project**: Mikayla will Try

Goals:
Learn how to prepare and run regular combiflash.
Try using regular silica
Try using regular silica with some amine
Try using expensive amine-packed column
Try using a traditional column chromatography, with some amine in the solvent.

Some continuation from Abby's Summer's successful alkylation-reduction. Abby?
This sequence would provide a versatile way to have 4-alkyl variations relative to Antipyrine.

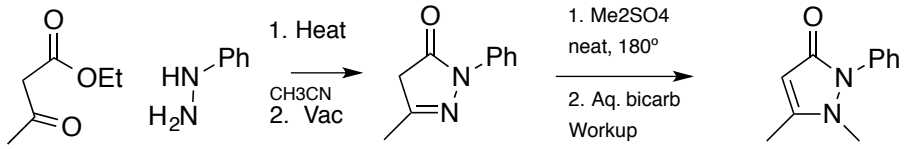



The first two steps work pretty well, for both aldehydes and for some ketones

**Other Aryl hydrazines. Nobody available to try, yet?**

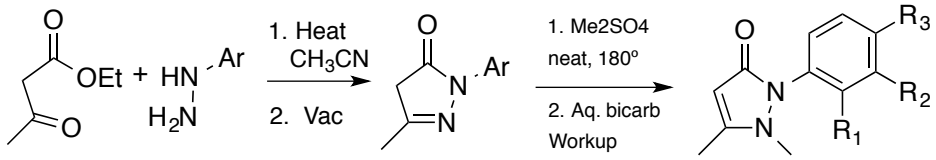
**N2-Aryl Ring Variation, Pyrazolones. Using alternate Arylhydrazines.**

**Scheme 1: Variation at N2.**
**Known experiment.**




**High Priority, Have Bought a couple of the Varients?**

**Variation at N2-Aryls By Variation of Aryl Hydrazine. Order some, Grant $$**




2-Pyridine $86/5
4-CN $57/5
4-Me $36/5
2-Me $40/5
4-Cl $29/5
3-Cl $97/25
2-Cl $80/25
4-F $67/10
2-F $70/5
========
4-Br $132/10
4-OCH3 $200/10
4-CF3 $70/5

Notes:

- Many of these hydrazines are variably affordable
- Probably try 2 or 3, and try to have tested.
- Include in grant proposal budget for buying more
- Most come as HCl salts.
- May be able to directly follow the Scheme 1 process, but solubility may perhaps alter that?
- Or perhaps the HCl will actual simplify and help things, not sure.
- Did we already buy the 4-methyl one, perhaps?
- If I was to target 2 or 3, I'd probably start with
  - the pyridine (does a heteroatom make any difference?)
  - and either 4-Methyl or 4-cyano (or both.)
- Note: If we can figue out how to do the Pd-catalyzed arylation, that could greatly open other variations on N2-Aryl
- If one of these looks advantageous, and we see other advantages at N1, C4, or C5, could move towards multiple-substituent combinations. But for the beginning, just start with one at a time

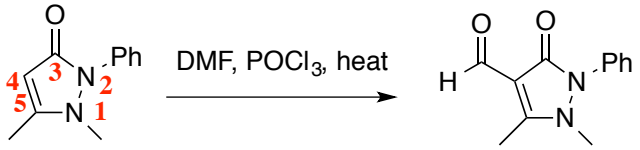
| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Pyridine | 4930-98-7 | 2-Hydrazinopyridine | Sigma/Aldrich: $86/5, $292/25 |
| p-CN | 2863-98-1 | 4-Cyanophenylhydrazine hydrochloride | Sigma/Aldrich: $57/5 |
| p-Tol | 637-60-5 | 4-Methylphenyl hydrazine | VWR-AA, $35.59/5g |
| o-Tol | 635-26-7 | o-Tolylhydrazine hydrochloride | Sigma/Aldrich: $39/5 |
| p-Cl | 1073-70-7 | 4-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $29/5, $97/25 |
| m-Cl | 2312-23-4 | 3-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $97/25 |
| o-Cl | 41052-75-9 | 2-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $80/25 |
| p-F | 823-85-8 | 4-Fluorophenylhydrazine hydrochloride | Sigma/Aldrich: $67/10, |
| 2-F | 2924-15-4 | 2-Fluorophenylhydrazine hydrochloride | Sigma/Aldrich: $70/5 |

| | | | |
|---|---|---|---|
| | | **TOO EXPENSIVE** | |
| p-Br | 622-88-8 | 4-Bromophenylhydrazine hydrochloride | Sigma/Aldrich: $132/10 (expensive) |
| p-OCH3 | 19501-58-7 | 4-Methoxyphenylhydrazine hydrochloride | Sigma/Aldrich: $200/10 (expensive) |
| p-CF3 | 368-90-1 | 4-(Trifluoromethyl)phenylhydrazine | Sigma/Aldrich: $125/5 (Too expensive) |

Specific project suggestions for Fall 2018

1.

**C4-Formylation.**

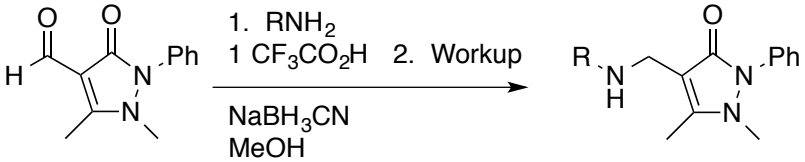



**Untried.**
**Pretty detailed literature procedure.**
**Want to try to do a large scaleup reaction, AND get it pretty clean.**
**To be done in combo with following two box.**

Matt Anderson

2.

**4-Alkylaminomethyl Analogs, from 4-Formyl. Try $NaBH_3CN$?**

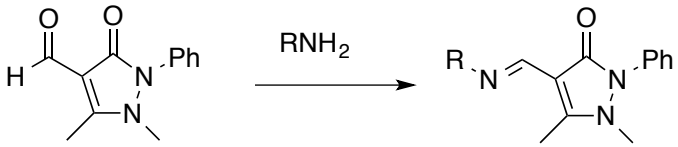



**Untried. No literature?**
**I don't have literature references, but haven't looked hardly at all…**
**Again, a range of different types and sizes and hybridization of amines could be screened?**

Matt Anderson

3.

**4-Iminomethyl Analogs, from 4-Formyl**



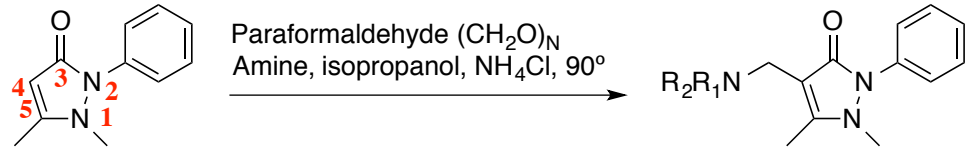

Lots of Examples, often with elaborate "R" groups

**Untried. Extensive literature, but seemingly with large, extended aromatic amines that probably crystallize irreversibly?**
**Not sure how well this might work with regular amines?**
**Sp3 Amines versus ArNH2 amines may be different…**

Matt Anderson

4.

**C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone**



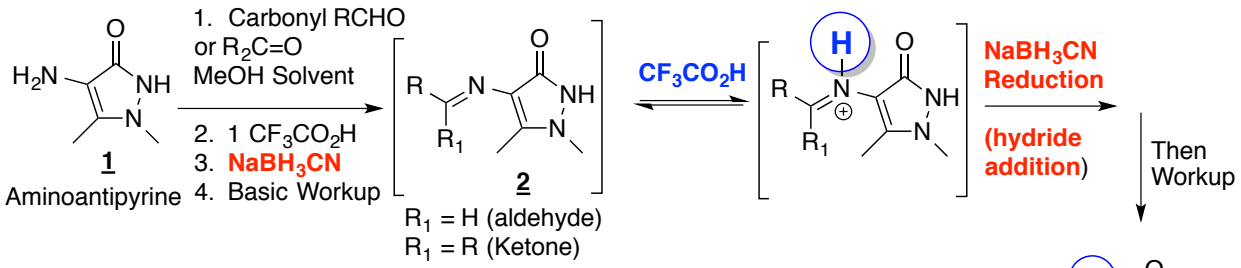

C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

**Untried/slightly tried. Craig got one to work; Amanda tried 1° that didn't? 2° Should work, literature.**

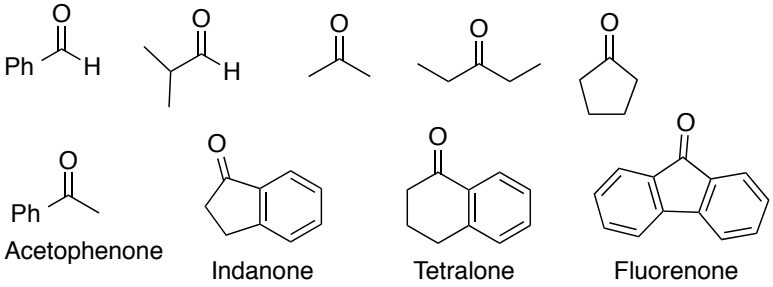
## Reductive Amination of Aminoantipyrine: Formation of 4-Alkylaminoantipyrine Analogs

5.

**Variation at N1 by Reductive-Alkylation of Carbonyls. Pyrazolidinone.**

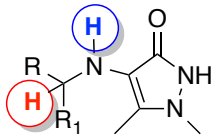



Carbonyl Candites to Try





Acetophenone, Indanone, Tetralone, Fluorenone

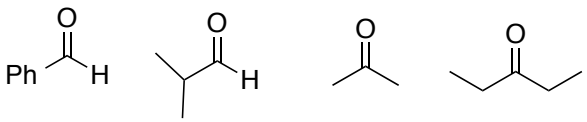



Jasperse has done small scale trial, proof-of-principle experiment; Ansu confirmed
Will it work for both aldehydes and ketones, or only aldehydes?
Will it work for ketones that get bigger
Will it work for conjugated ketones?
What might be a good workup procedure?
What is the best way to purify? Digestion? Crystallization? ???
Control: $NaBH_4$? $LiAlH_4$?
Control: Solvent variation?
Control: Run without acid?

6.

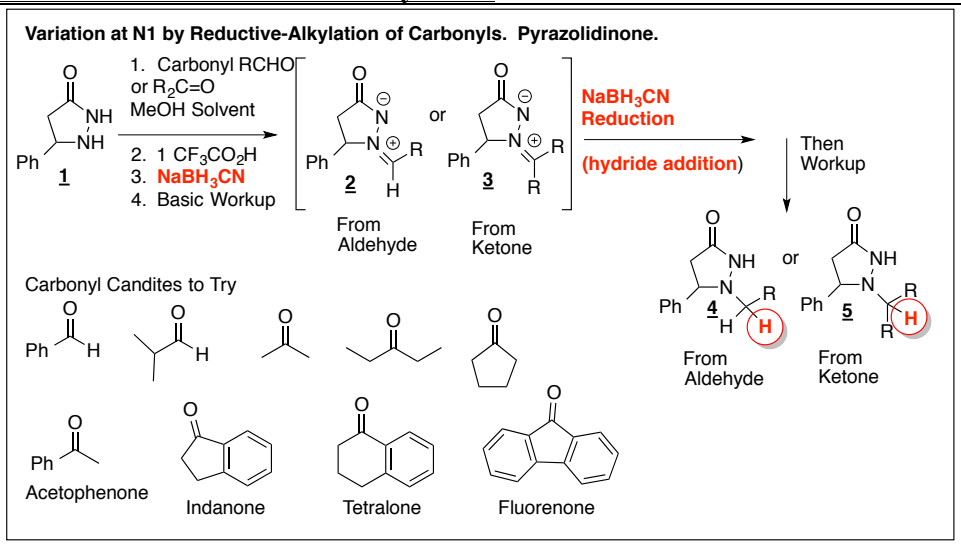
**Imine-Formation of 4-AminoAntipyrine**


Carbonyl Candidates to Try



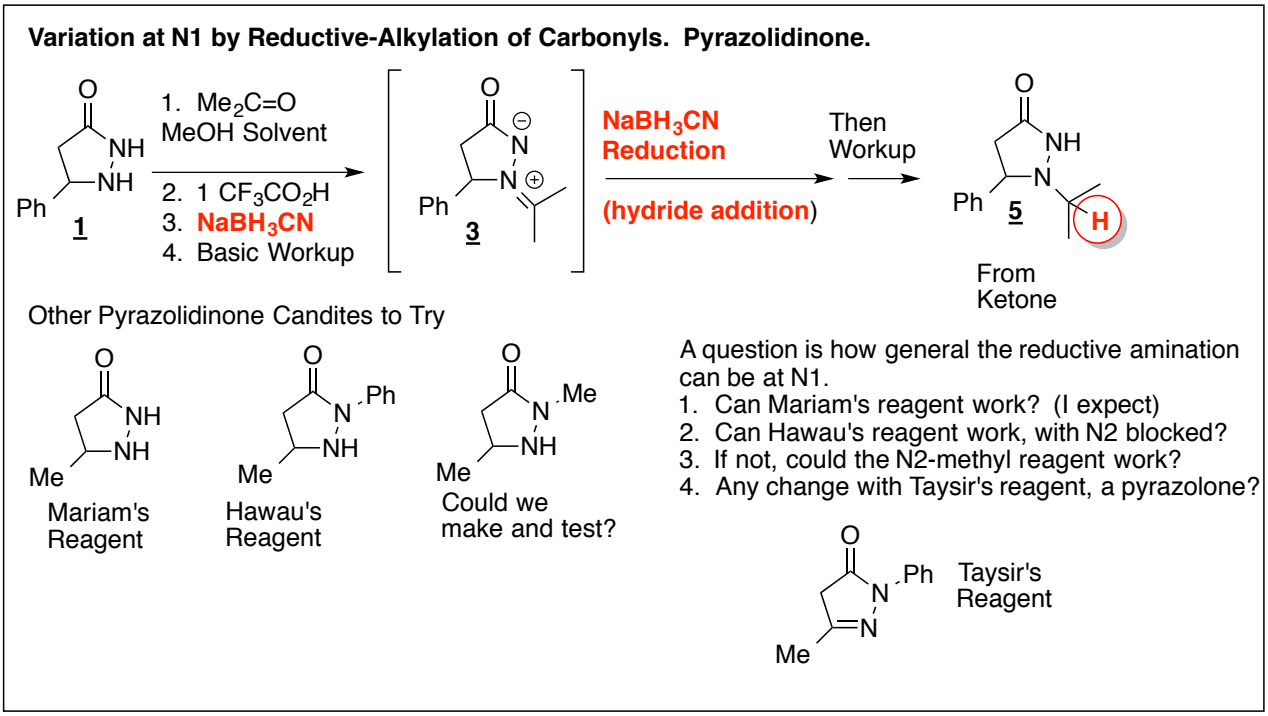
## Reductive Alklation at N1. N-Alkylation

7.



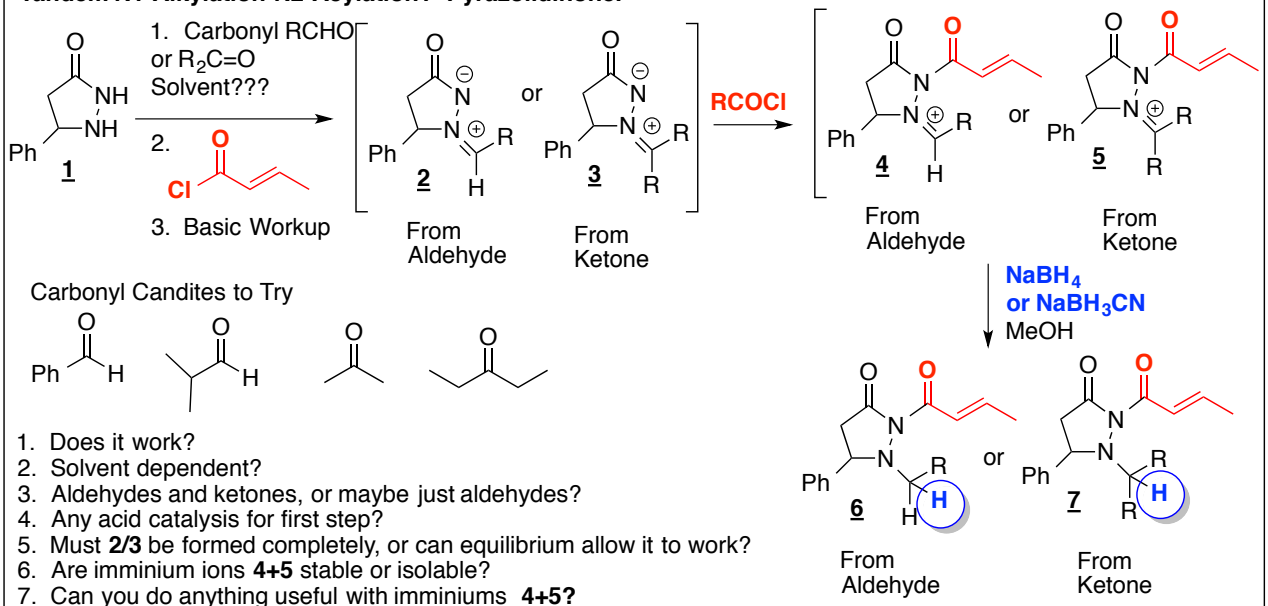

Jasperse has done small proof-of-principle using benzaldehyde and acetone; I think it works great! (But not sure…)

8 Does it work for other Pyrazolidinones?



9

**Tandem N1-Alkylation-N2-Acylation? Pyrazolidinone.**




Carbonyl Candites to Try

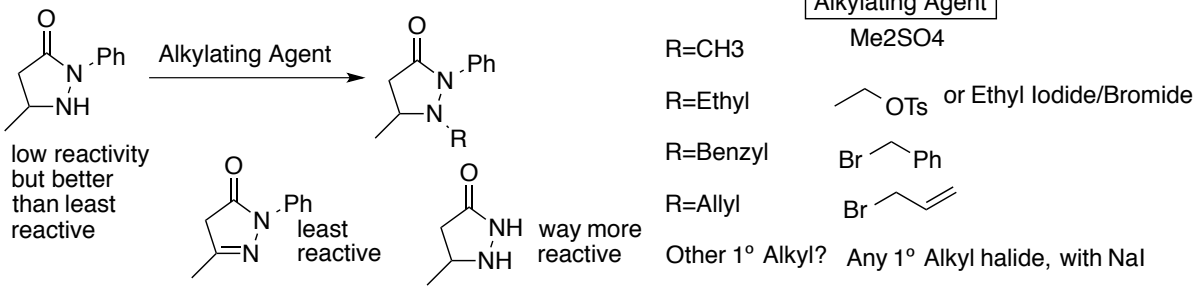


1. Does it work?
2. Solvent dependent?
3. Aldehydes and ketones, or maybe just aldehydes?
4. Any acid catalysis for first step?
5. Must **2/3** be formed completely, or can equilibrium allow it to work?
6. Are imminium ions **4+5** stable or isolable?
7. Can you do anything useful with imminiums **4+5?**

(Example shows reduction, but could you isomerize, or perhaps alkylate with something nucleophile or something?

10

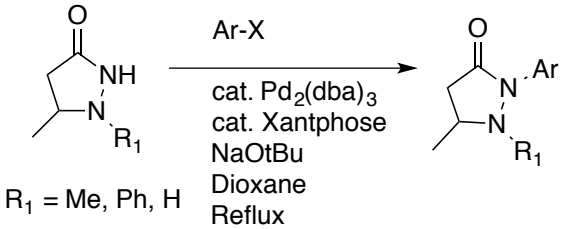
**Variation at N1 by N-Alkylation. Pyrazolidinone.**




**Update: Checked. Works, more easily than Scheme 3. Proof of Principle. (Limited examples, Me, Et.)**

11

**N2-Arylation of Pyrazolidinone, Pd-catalyzed. Might be Harder Project, But High-Impact if we could Figure it Out.**




CHEMReview 2016
Stephen L. Buchwald and Paula Ruiz-Castillo

Might be hard. Detailed correct handling of the Pd catalyst and the diphosphorus ligand may be crucial

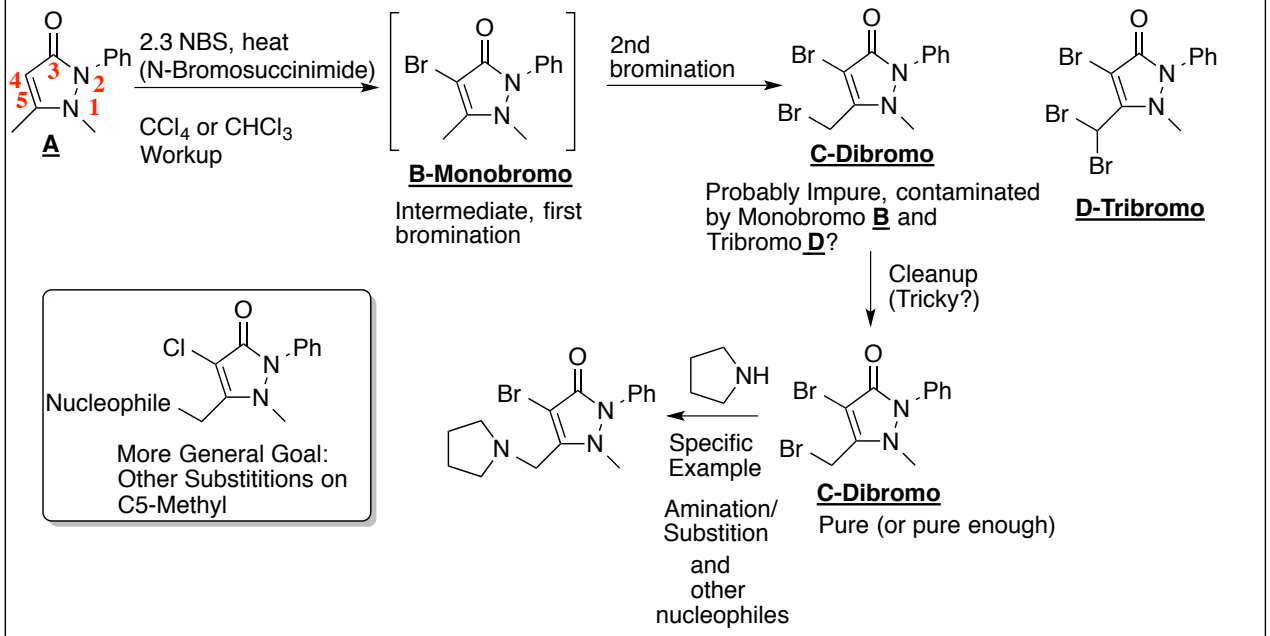
Antipyrine has N2-phenyl, so the opportunity to install variable aryl analogs from Hawau's Reagent would be really nice.... if it works.

**Untried. Taysir did procedure on oxazolidinone, but not pyrazolidinone. Make Buchwald JACS air-stable catalyst!**

Variations at C5: Bromomethyl, and SN2 substitutions. (5-Alkylaminomethyl; 5-Alkoxymethyl…

12

**C4,C5-Dibromination**



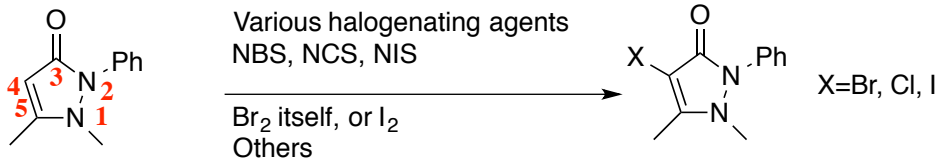

C4-Hetereo-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf

A preliminary proof-of-concept reaction by Kaniel and Bishnu demonstrates that this kind of works.
There seemed to be a kinetics challenge, so that would get mixture of monobromo **B** and tribromo **D** mixing in with target dibromo **C**. (It seemed that NBS-bromination of B wasn't that much faster than NBS-bromination of target **C**. Think **D** is much more chromatography mobile, so may be removable, and that if little **B** is left, hope to digest-it free.

If stock of **C** could be made, then could do substitutions.
Amines, oxygen things, etc.

13

**C4-Bromination/Chlorination/Iodination**




**C4-Hetereo-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf**

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**Get and Print documents:**

Kaniel NCS General Procedure Suggestion.docx
NCS Procedure and Reference.pdf

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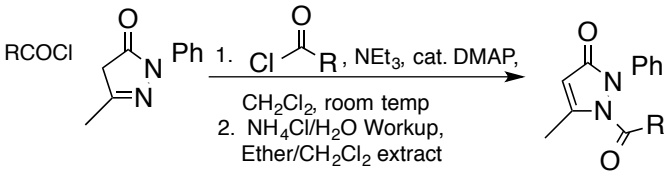
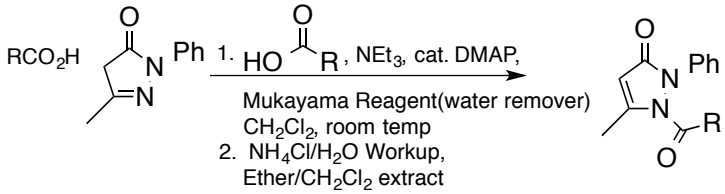
**N1-ACYLation of Pyrazolone Very Easy! Using RCOCl or RCO2H Pyrazolones.**




Using Acid Chlorides, where available. Easy, fast.

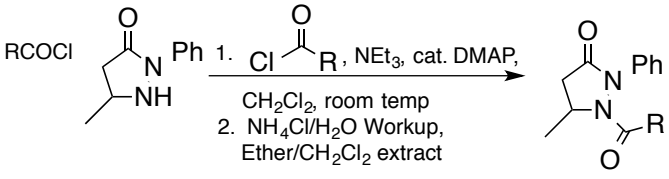



Using Carboxylic Acids, which are often more accessible than the acid chlorides.

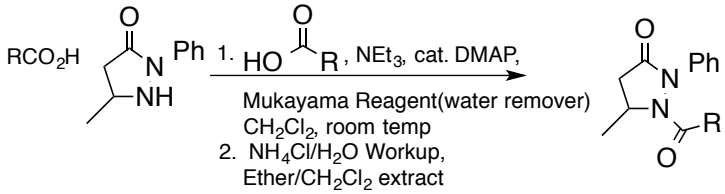
**Update: Works with Acid Chloride. (Andrea). Easy. Didn't Try with Acid/Mukayama..**

15

**N1-ACYLation of Pyrazolidinone Very Easy! Using RCOCl or RCO2H Pyrazolidinones.**




Using Acid Chlorides, where available. Easy, fast.



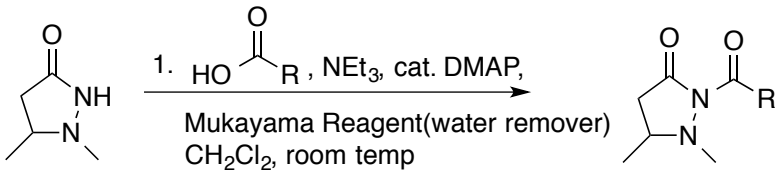

Using Carboxylic Acids, which are often more accessible than the acid chlorides.

Could also do it with N2=H instead of Ph. (Mariam's rgt)

**Update: Works with Acid Chloride, although not Super Clean. (Val). Easy. Didn't Try with Acid/Mukayama..**

16

**N2-Acylation of N1-Methyl Pyrazolidinones: Using RCO2H and Mukayama's Reagent.**

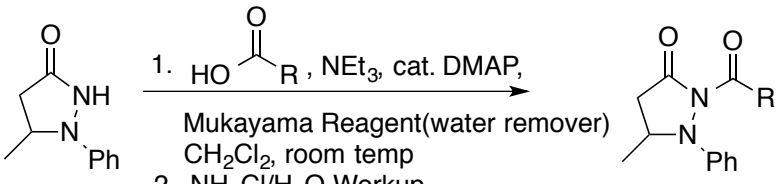



Using Carboxylic Acids, which are proven. Doubtful if RCOCl work

**Untried on dimethyl Should work.**

17

**N2-Acylation of N1-Phenyl Pyrazolidinone (Sunny's Reagent) Pyrazolidinones.**

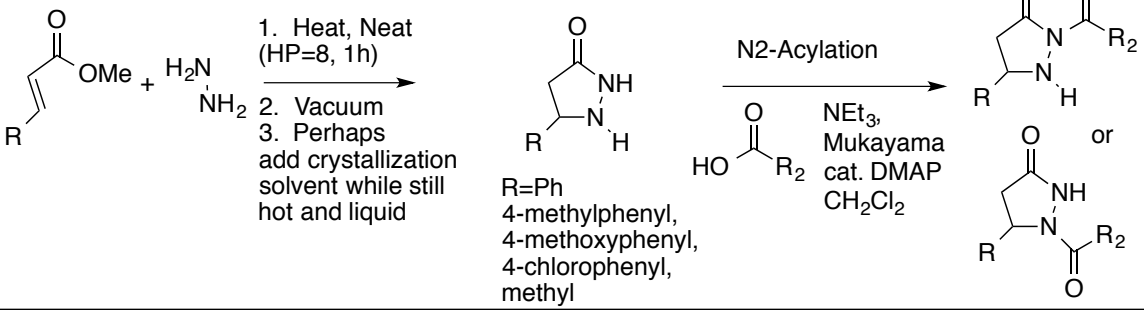



Using Carboxylic Acids, which are proven. Doubtful if RCOCl work

**Untried. Should work.**

18

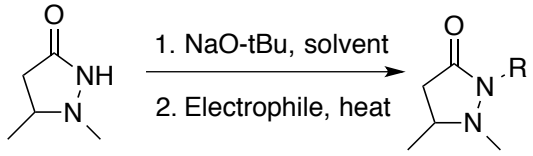
Reactions/Acylation of the "Classic" Hydrazine-Derived Pyrazolidinones. When N1 and N2 were both NH




**Untried.**

19

**N2-Alkylation of N1-Methyl Pyrazolidinones: Using Base and SN2**



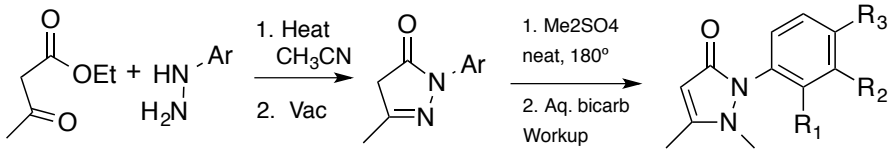

Potential Alkylation Agents:
$Me_2SO_4$, Ethyl tosylate or iodide,
Benzyl or Allyl bromide, etc.

Potential Solvents: MeOH, $CH_3CN$, DMF...

**Untried on dimethyl. Worked with phenyl analog (Hawau)**

20

**Variation at N2-Aryls By Variation of Aryl Hydrazine. Order some, Grant $$**

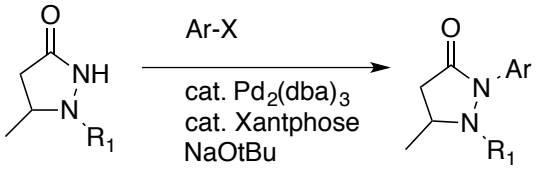



2-Pyridine $86/5
4-CN $57/5
4-Me $36/5
2-Me $40/5
4-Cl $29/5
3-Cl $97/25
2-Cl $80/25
4-F $67/10
2-F $70/5
========
4-Br $132/10
4-OCH3 $200/10
4-CF3 $70/5

**Untried, but should work. (Boring? May be great for medicinal eval; but no new synthetic methodology principle)**

21

**N2-Arylation of Pyrazolidinone, Pd-catalyzed. Might be Harder Project, But High-Impact if we could Figure it Out.**




$R_1$ = Me, Ph, H

CHEMReview 2016
Stephen L. Buchwald and Paula Ruiz-Castillo

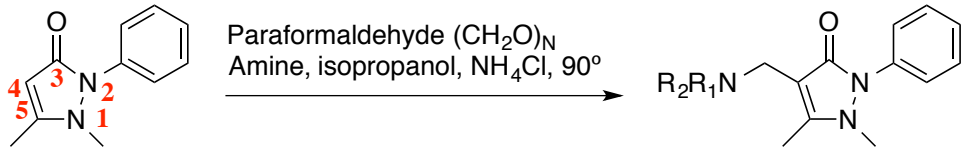
Might be hard. Detailed correct handling of the Pd catalyst and the diphosphorus ligand may be crucial

Antipyrine has N2-phenyl, so the opportunity to install variable aryl analogs from Hawau's Reagent would be really nice.... if it works.

**Untried. Taysir did procedure on oxazolidinone, but not pyrazolidinone. Make Buchwald JACS air-stable catalyst!**

22

**C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone**

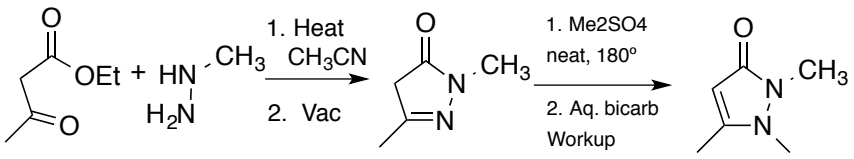



C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

**Untried/slightly tried. Craig got one to work; Amanda tried 1° that didn't? 2° Should work, literature.**

23

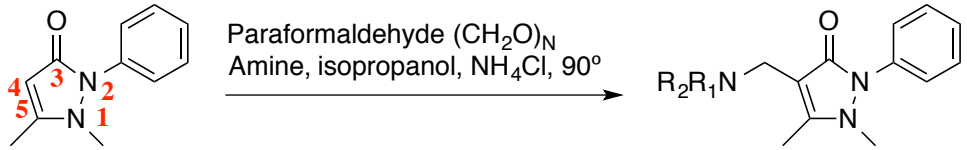
**Scheme 4: Variataion at N2 By Use of MethylHydrazine:**




**Untried. Would enable N2-methyl analogs.**

24

**C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone**

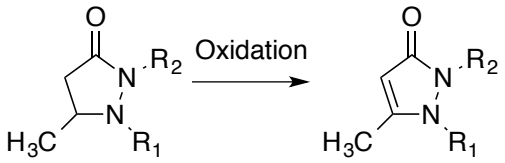



C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

**Untried/slightly tried. Craig got one to work; Amanda tried 1° that didn't? 2° Should work, literature.**

25

**Oxidation of Pyrazolidinones to Pyrazolones**




Oxidizing agent candidates:
1. $H_2O_2$, $CH_3CO_2H$
2. $O_2$, cat. $FeCl_3$
3. $K_2S_2O_8$
4. NBS
etc.

**Somewhat tried. mCPBA looked good for one or two, failed other (Hawau); oxone, NBS, K2S2O8, and H2O2/CH3CO3H looked bad. mCPBA worked for one; failed for another. Want to screen it, and NMR tests could work well.**

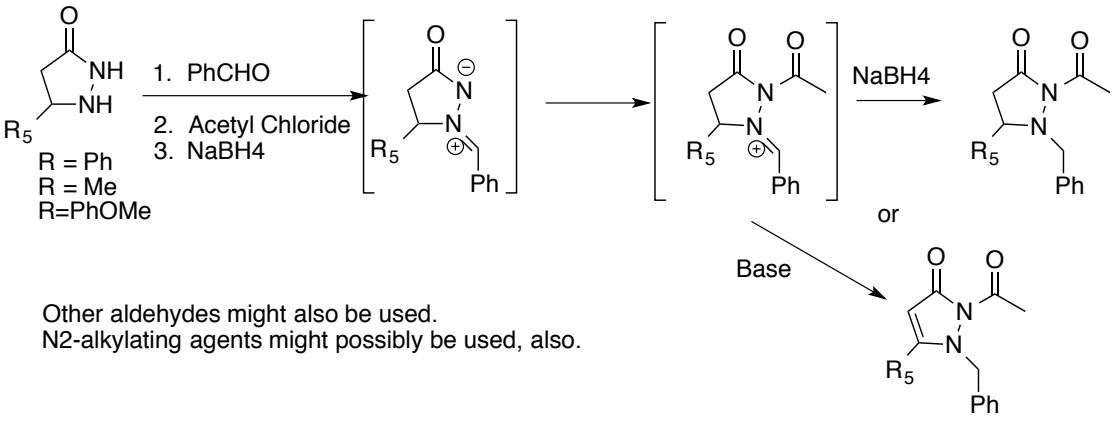
26 Continuation of Page 21, Oxidation

27 Continuation of Page 21, Oxidation

28 Continuation of Page 21, Oxidation

29

**Sequential Concept: Sequential alkylation-acylation-reduction for N1-alkylation and N2-acylation. Alternative to the NaBH4 might perhaps be the use of base, to produce pyrazolone.**

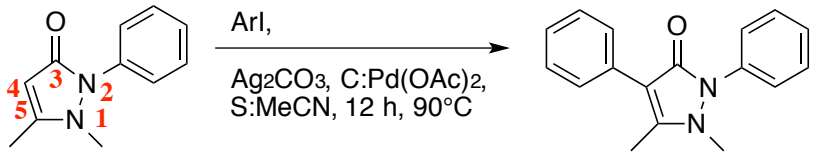



Other aldehydes might also be used.
N2-alkylating agents might possibly be used, also.

**Untried. Tandem alkylation/acylation would be cool, if it worked.**

30

**C4-Arylation. Pyrazolone**

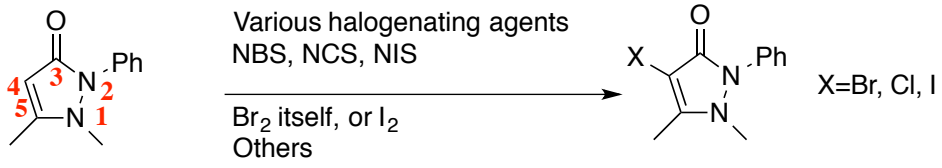



4-Arylation of Antipyrine-Good using PdOAc2 + AgOAc.pdf
Gong, Hao et al From Beilstein Journal of Organic Chemistry, 9, 2033-2039, 7 pp.; 2013

**Untried. Have chems.**
**Might be good to try the Buchwald catalyst, once made?.**

31

**C4-Bromination/Chlorination/Iodination**

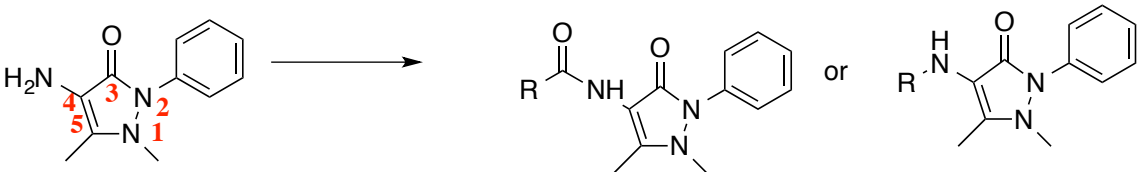



**C4-Hetereo-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf**

**Kaniel is trying.**

32

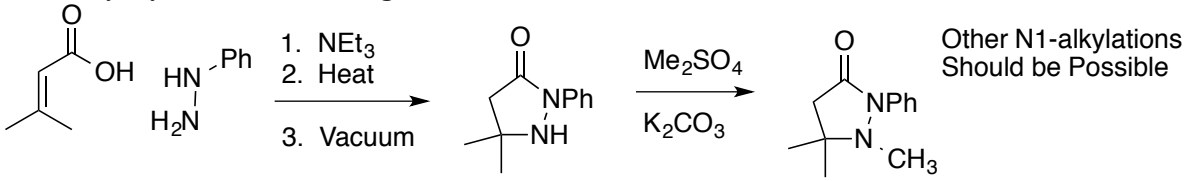
**C4-Nitrogen Varients. Pyrazolone. "Analgin" Derivatives**




**Untried. Literature extensive for acylation, only one example for alkylation.**
**I think alkylation may be good with better base/solvent conditions than single literature example.**

33

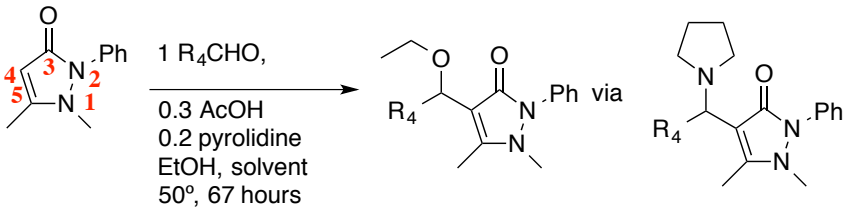
**5,5-Dimethyl Pyrazolidinone Analog**




**Update. Slow; Joshua got small scale and crystalline. Methylation small scale worked, kind of. Proof of principle. Scaleup.**

34

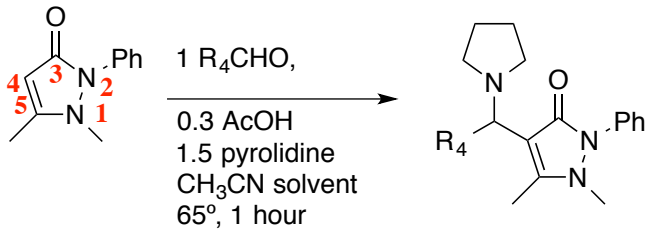
**C4-Aldehyde Reaction**




**Untried. One literature example, iffy. Combo with 35.**

35

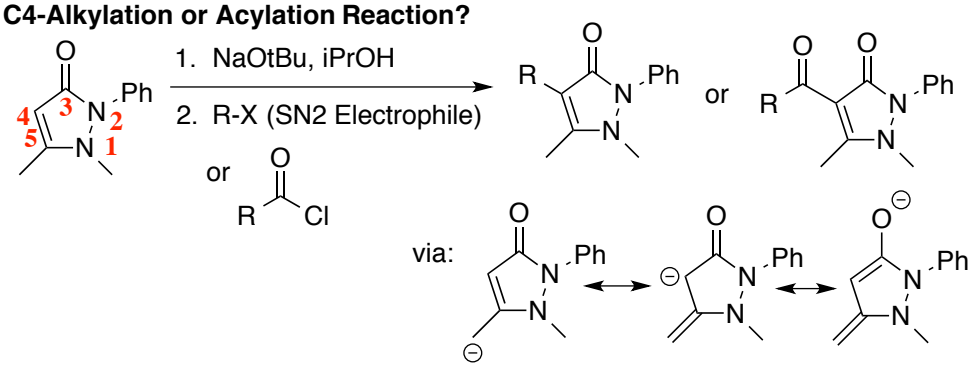
**C4-Aldehyde Reaction**




**Untried. One literature example, iffy. Combo with 34.**

36

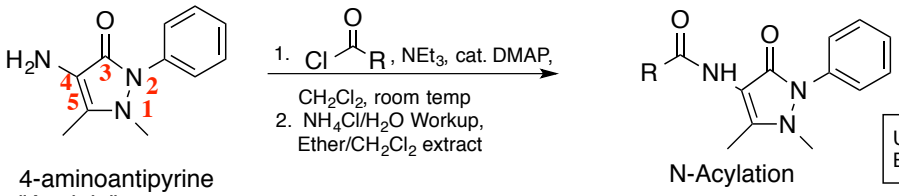
**C4-Alkylation or Acylation Reaction?**




**Untried. Zero literature example, but pKa estimate suggests anion should be accessible.**

37

**Acylation of Aminoantipyrine Using Acid Chlorides**



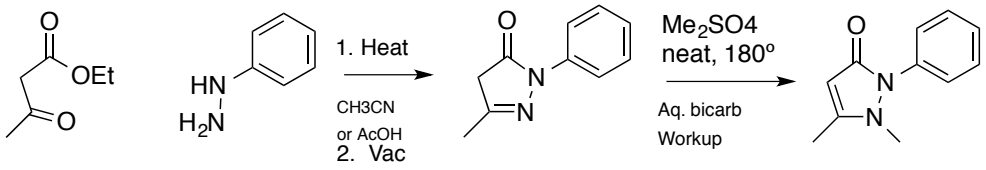

4-aminoantipyrine
"Analgin"
Commercially Available, Alfa-Aeser

N-Acylation

Using Acid Chlorides, where available. Easy, fast.

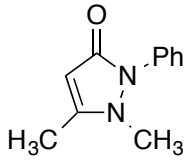
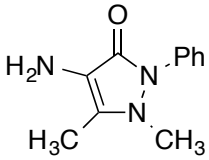
**Literature extensive for acylation,**
**Ansu worked several of these. They worked very well. Easy to Crystallize and purify..**
Ansu had one success with CH3PhCOCl. Not so good with crotonyl, benzoyl.
Check RCOCl, NMR's, etc; maybe do control? Find some others that are good/clean?
Ansu has established strong proof of principle and has made several of these.

## Home-made synthesis:




- Have worked out procedure for this home-made synthesis of antipyrine parent
- Antipyrine itself is commercial and inexpensive, so no actual need for us to make it.

## Stock of Home-Made (or Store-Bought) Ready-to-Use Chemicals:

<table>
<tr>
<td>  Antipyrine. $$.</td>
<td>  4-aminoantipyrine = “Analgin”. $$</td>
</tr>
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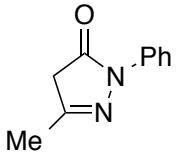
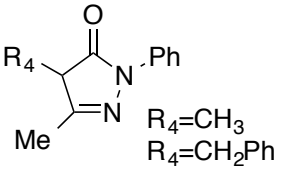
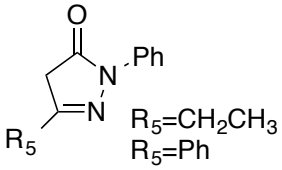
<td>  Taysir’s Reagent.</td>
<td>  </td>
<td>  </td>
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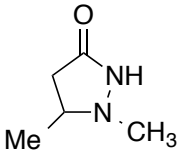
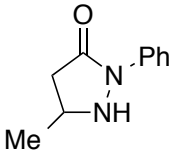
<td>  Hawau’s N1-Methyl Reagent</td>
<td>  Hawau’s N2-Phenyl Reagent</td>
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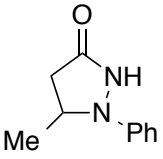
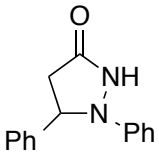
<td>  Sunny’s Reagent</td>
<td>  Jasperse Diphenyl Reagent</td>
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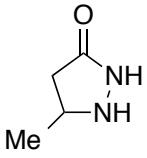
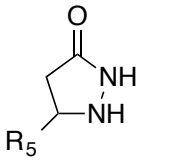
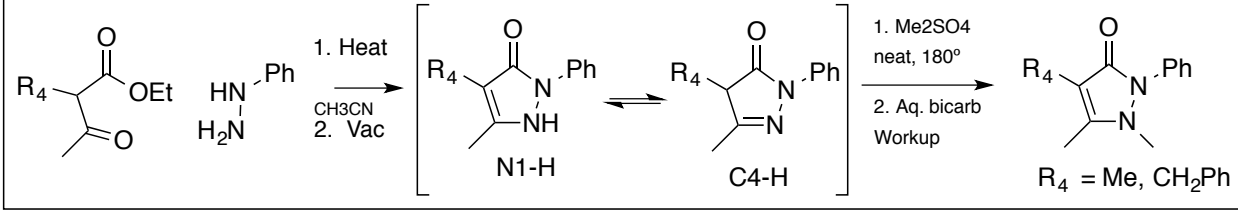
<td>  Mariam’s Reagent</td>
<td>  </td>
</tr>
</table>

## C4-Variation (Alkyl/Benzyl)

**Update: Checked. Works. Taysir. (limited examples)**

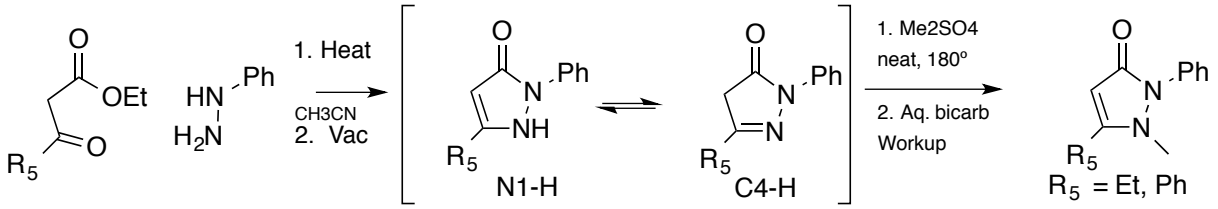
**Scheme 1: Variataion at C4:**




1. Commercially available R4: Me, Bn, also
   - Named as either: Ethyl 2-methylacetoacetate, Ethyl 2-ethylacetoacetate, Ethyl 2-benzylacetoacetate, etc.
   - Or Ethyl 2-acetylbutanoate, Ethyl 2-acetylpentanoate,
2. Notes: Not sure how easy step one is. E/Z issues with the hydrazine? NOT A PROBLEM
3. Preliminary data: Small-scale prep of both R4=Me, CH2Ph.
4. Seems very accessible process.
5. Targets/To-Do:
   a. Scaleup/ Reproduce b. Cleanup c. Test
6. Puzzle with form of intermediate. Mixture of structural isomers.
   a. Acid-base sensitive. Upon treatment with acid, it presents in the N-H form.
   b. Under bicarb conditions, appears to be substantially in the C4-H form.
   c. Which at biological pH?
   d. Once formed, is either stable enough to survive, or will they simply bio-equilibrate?
   e. Do they differ meaningfully in their reactivity?
   f. Do they interchange and equilibrate under the high-temp methylation?
7. Note: should be able to submit the N1-Me, N1-H, and C4-H analogs for testing.
8. I/we did step one in CH3CN. Reference did so in acetic acid. Does the acetic acid work cleaner, or produce the N1-H analog more specifically? Would doing that help in the alkylation?

| | CAS | One Name variant | Commercial? | Supplier, Price |
|---|---|---|---|---|
| Me | 609-14-3 | Ethyl 2-methylacetoacetate | | Bought it |
| Et | 607-97-6 | Ethyl 2-ethylacetoacetate | | Could buy |
| Pr | 1540-28-9 | Ethyl 2-acetylpentanoate | | Super expensive, NO |
| iPr | 1522-46-9 | Ethyl 2-isopropylacetoacetate | | Could buy |
| Bn | 620-79-1 | Ethyl 2-benzylacetoacetate | | Bought it |

**Scheme 2: Variataion at C5:**



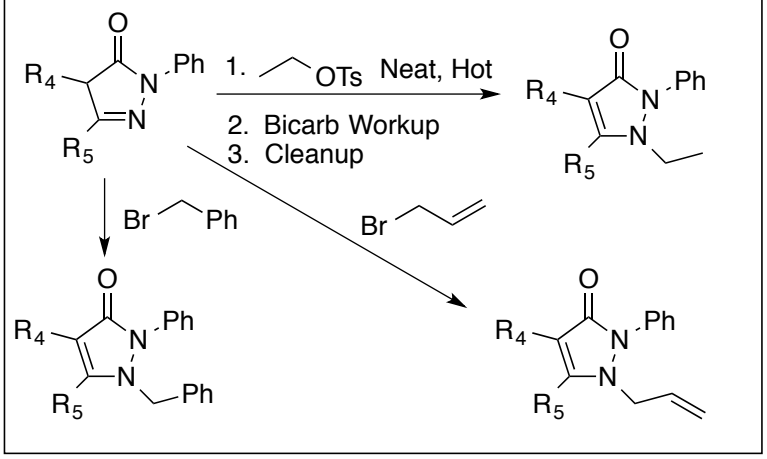

CAS ID:

| $R_5$ | CAS | One Name variant | Commercial? | Supplier, Price |
|---|---|---|---|---|
| Et | 4949-44-4 | Ethyl 3-oxopentanoate | | |
| Ph | 94-02-0 | Benzenepropanoic acid, β-oxo-, ethyl ester | | |

1. Many of the issues match with previous page.
2. The layout tends to be more the C4-H coming out of the acetonitrile process.
3. Have already done small-scale on R5=Et, Ph, with good success
4. Probably other analogs available or commercial, I haven't checked.
5. One of the references seemed to have $Me_2SO_4$/MeOH/CaO, but that didn't seem to work well
6. Targets/To-Do:
    a. Scaleup/ Reproduce  b. Cleanup  c. Test

## N1-Variation: Alkylation of Double-Bonded Rings (Pyrazoles)

**Scheme 3: Variataion at N1 by N-Alkylation:**

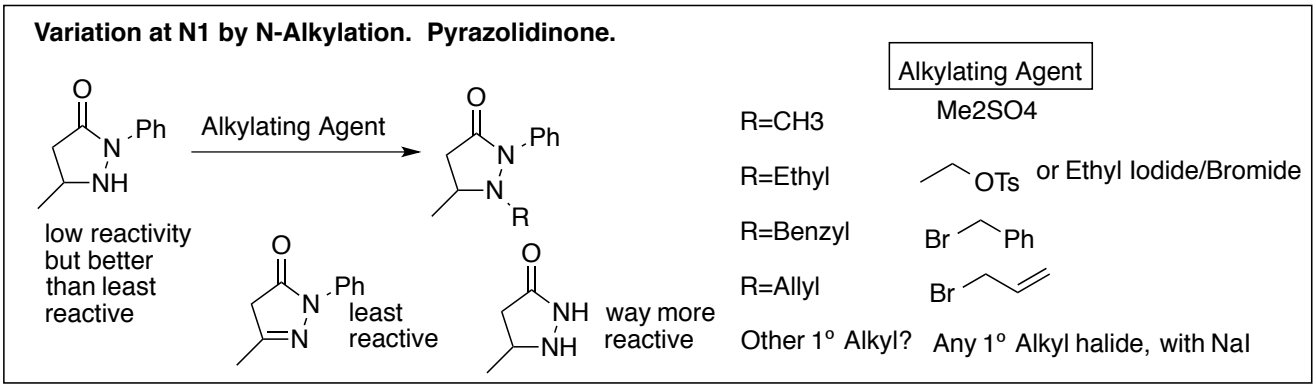



1. Alkylation is pretty slow
2. Preliminary results: Works well with dimethylsulfate hot/neat (see scheme 1)
3. Tried ethyl iodide, and that works, slowly, but partially/incomplete. Seemed very clean, just didn't go to completion in preliminary attempt.
   - Problem is getting hot enough without having the ethyl bromide or iodide boil away, I think? Perhaps with scaleup and reflux condenser that would be better and easily resolved?
4. A likely alternative, untried thus far, would be to use ethyl tosylate.
   - That's cheap, and being bigger it would allow more convenient stoichiometric heating.
5. Ethyl will provide a check on modest extension of N1-chain (Methyl to Ethyl)
6. Preliminary results with benzyl bromide, an activated SN2 electrophile, show that reaction is quite fast.
   - The reaction does seem somewhat touchy.
   - In methanol, it seems to not work well and give side products.
   - In some other solvents, upon overheating, there seems to be some double-reaction (giving AB quartet of some kind; double benzlation, perhaps?)
7. Neat, with stoichiometry control, and with limited time, it appears to work mostly well.
8. But may not be super clean, so may require a recrystallization or chromatography to clean it up.
9. No preliminary chromatography results thus far.
10. Don't remember whether having base present (K2CO3) was helpful or not.
11. Allyl bromide should be plenty reactive
12. Ethyl tosylate seems to be about the only commercial tosylate (other than methyl).
13. Update: Try the ethyl tosylate under the dimethyl-sulfate conditins. Does it work?
14. 
15. Try a semi-scaleup with benzyl bromide, and then do some workup. Maybe a combiflash? Should be massively UV-active, so should be VERY easy to track on combiflash.
16. In fact, getting comfortable with combiflash might be a great way to clean many of these types of products up.

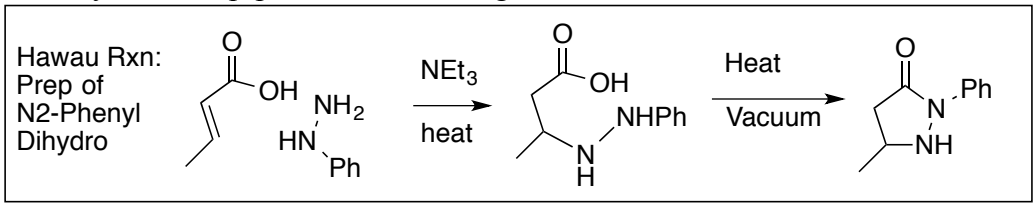
N-Ethylation Reagents and Catalysts

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| | 80-40-0 | Ethyl Tosylate | Sigma/Aldrich: $26/50g |
| | | No other tosylates commercial. | Sigma/Aldrich: $26/50g |

## N1-Alkylation of Pyrazolidinone Rings (Pyrazolidinones) Safe, Easy

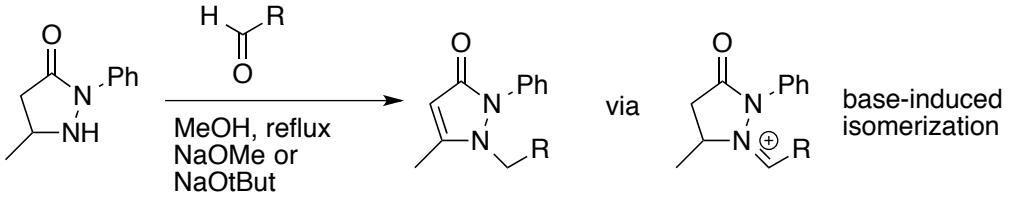



1. This would be a natural match project (Alkylations Projects) with page-3, which involves N1-alkylation of the double-bonded analog shown on the bottom.
   - See discussion and observations from the Page 3/Scheme 3 alkylations
   - The same alkylating agents that work there should work here (only better/easier here)
   - So, high temp and neat and stuff like that will apply here, depending on the alkylating agent.
2. Preliminary data: This worked well for ethyl iodide, but was slow.
3. The reactivity of the dihydro is better than for the double-bonded one.
   - But the N2-Phenyl group really reduces the reactivity compared to N2-H analogs.
4. This alkylation will likely be cleaner and simpler. There is no question about where alkylation will occur; it will be on the N1-nitrogen, plane and simple. No competition from O-alkylation or anything.
5. In preliminary ethyl experiment, there was no problem using solvent (refluxing acetonitrile, but neater and hotter naturally went faster.
6. Hawau's starting material is really clean, so not complications from that.
7. Hawau's preparation is shown below, it is very clean and she has a nice process for producing nice, clean, crystalline material.
8. Easy to scaleup-produce the starting material if stock runs low.



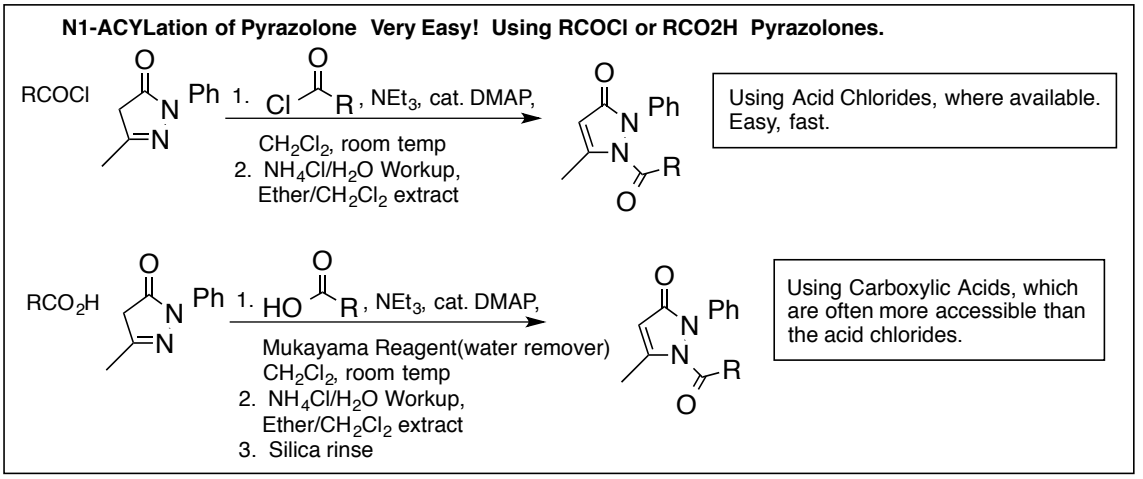
**Variation at N1 Pyrazolones. By Reaction of Hawau Phenyl-Pyrazolidinone with Aldehyde, followed by NaOR/ROH isomerization. Pyrazolidinone => Pyrazolone**

**Variation at N1 by N-Aldehyde Reaction, then Alkoxide Isomerization. Pyrazolidinone to Pyrazolone**

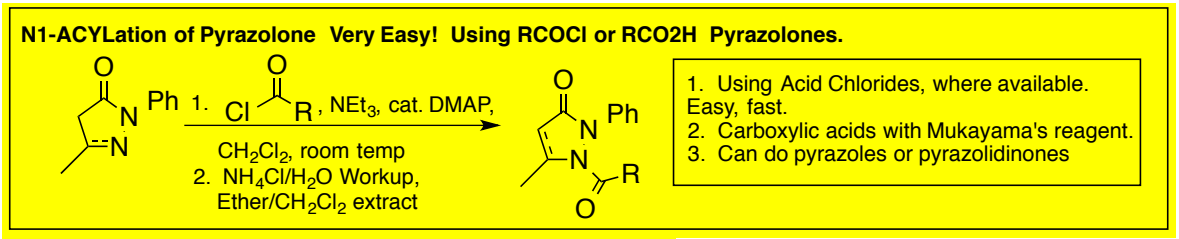



1. Kangasmetsa, Jussi J. et al From PCT Int. Appl., 2013096501, 27 Jun
2. N1-Aldehyde use, followed by NaOMe/MeOH isomerization: N1 plus Aldehyde, then NaOMe/MeOH reflux to isomerize
   - … 35 mmol… 5-methypyrazolidin-3-one. This oil was dissolved in MeOH (20 mL), cooled to 0°C under N2 atmosphere and sodium methoxide in MeOH (2 ml of 4.4M) was added. After 10 minutes 2-Benzyloxy-5-bromo-benzaldehyde, 6, (7.66g, 31mmol) in MeOH (100 mL) was added and the mixture was stirred at RT for 1 hour. Sodium methoxide in MeOH (7 ml of 4.4M) was added and the mixture was refluxed for 16 hours. The volatiles were removed in vacuo and the residue was portioned between EtOAc and HCl (aq., 2M). A yellow solid was collected and triturated with diethyl ether to yield a cream coloured solid which was dried under vacuum to yield 1-(2-Benzyloxy-5-chloro-benzyl)-5-methylH-pyrazo3-
3. N1-Aldehyde use, followed by NaOMe/MeOH isomerization: N1 plus Aldehyde to make imminium, with some base-isomerization, then base isomerization.
4. No preliminary data.
5. Some potential advantages:
   a. Aldehydes are more reactive than alkyl halides, etc., so this could be much easier than SN2 alkylation
   b. There are a lot of aldehydes available.
   c. This gets directly to the double-bond pyrazole rather than the di-hydro pyrazolidinone

## N1-Acylation of Pyrazolones: Using Acid Chlorides or Acids (with Mukayama's Reagent).

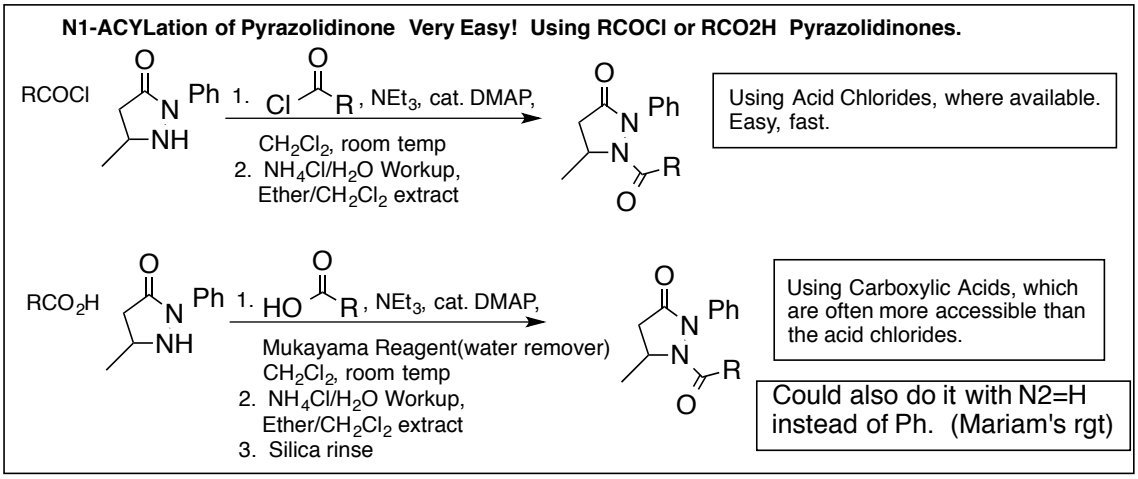



1. Super Easy and flexible
2. Preliminary result using 4-toluyl chloride appears to complete within minutes at room temp, and was easy to work up.
3. Preliminary experiment using crotonic acid also appeared to proceed very quickly and easily.
4. Antipyrine of course does not have the carbonyl attachment on at N1. So who knows what assay-impact this might have.
5. Probably start by making a couple of these (R = Me, Ph, Toluyl) and getting them assayed
6. The R=Me one would be the closest analog to Antipyrine: Basically just a carbonyl slipped in

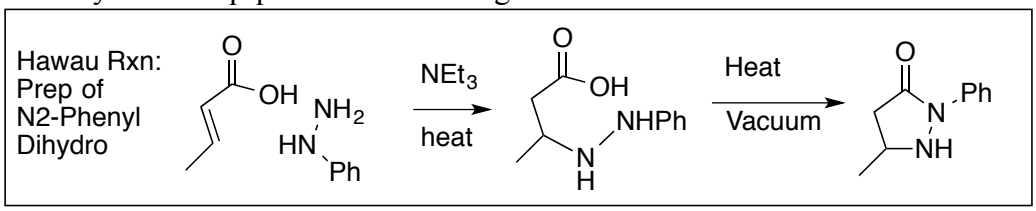



Use General Thing for pyrazolone or pyrazolidinone

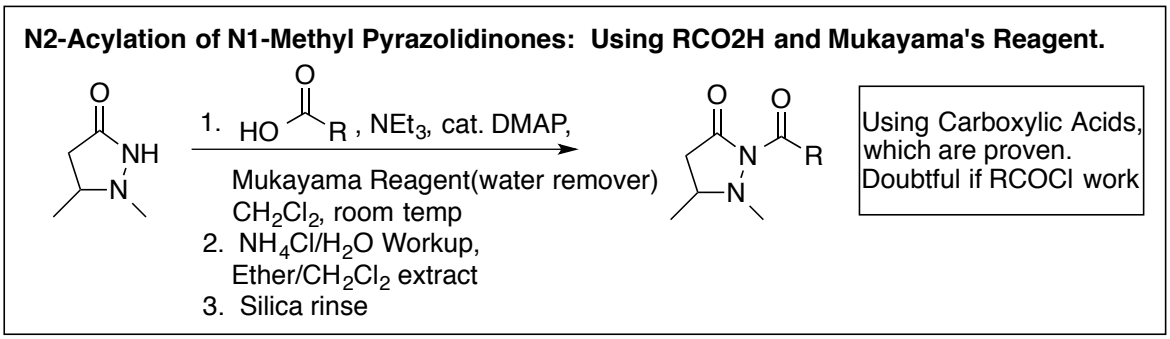
## N1-ACYLation of Pyrazolidinones.




1. This would be a natural match project (Alkylations Projects) with page-3, which involves N1-alkylation of the double-bonded analog shown on the bottom.
   - See discussion and observations from the Page 3/Scheme 3 alkylations
   - The same alkylating agents that work there should work here (only better/easier here)
   - So, high temp and neat and stuff like that will apply here, depending on the alkylating agent.
2. Preliminary data: This worked well for ethyl iodide, but was slow.
3. The reactivity of the dihydro is better than for the double-bonded one.
   - But the N2-Phenyl group really reduces the reactivity compared to N2-H analogs.
4. This alkylation will likely be cleaner and simpler. There is no question about where alkylation will occur; it will be on the N1-nitrogen, plane and simple. No competition from O-alkylation or anything.
5. In preliminary ethyl experiment, there was no problem using solvent (refluxing acetonitrile, but neater and hotter naturally went faster.
6. Hawau's starting material is really clean, so not complications from that.
7. Hawau's preparation is shown below, it is very clean and she has a nice process for producing nice, clean, crystalline material.
8. Easy to scaleup-produce the starting material if stock runs low.



**N2-Acylation of N1-Methyl Pyrazolidinone, Using Hawau's Methyl Reagent: Acylation Using Acids and Mukayama's Reagent: Pyrazolidinone**



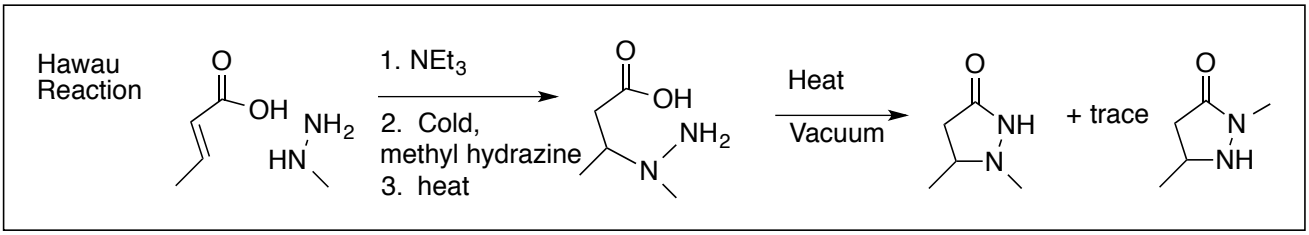

1. Starting chemical synthesis nicely developed by Hawau
2. Starting material isn't completely clean; contaminated by modest amount of N2-methyl isomer
3. The simplest to make here would be R=Ph
4. Antipyrine of course does not have the carbonyl attachment on at N2. So who knows what assay-impact this might have.
5. Antipyrine is also pyrazolone; this will be pyrazolidinone
6. Probably start by making a couple of these (R = Me, Ph, Toluyl) and getting them assayed
7. The R=Ph one would be the closest analog to Antipyrine: Basically just a carbonyl slipped in

Methyl Hydrazine Process:

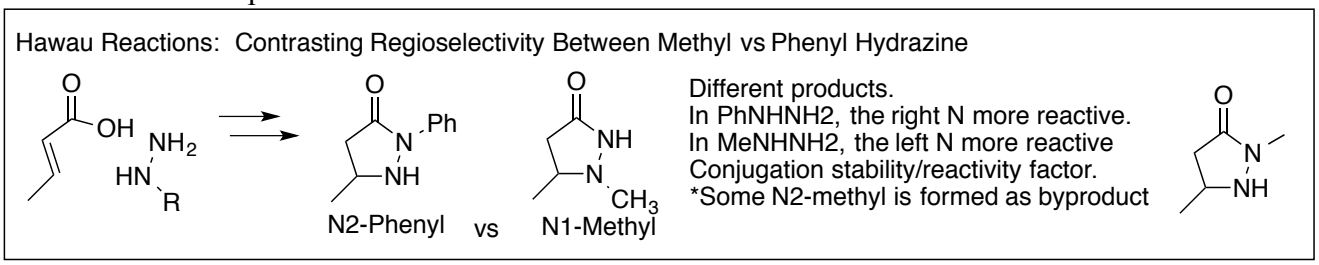
| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Me | 60-34-4 | Methyl hydrazine | Sigma/Aldrich: $308/25 |

Note: Aldrich is cheapest here, and good.

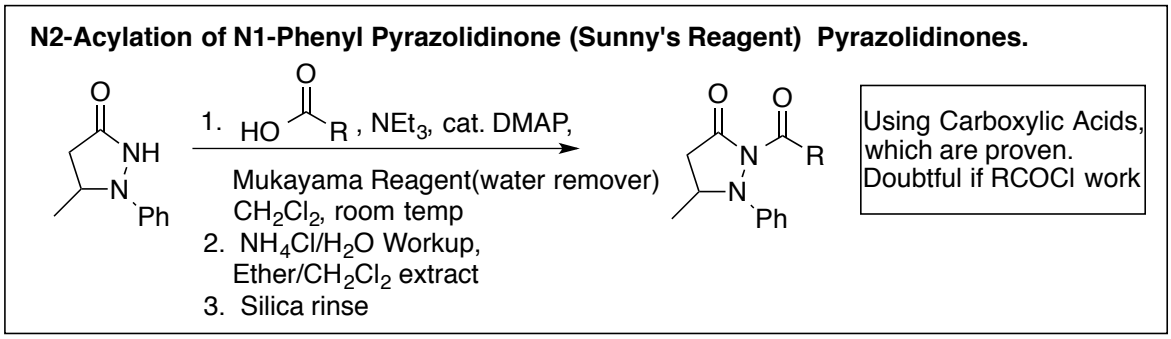
- Price looks worse than it is, because it's so small. So you get a lot of moles per gram.
- INCLUDE IN GRANT TO BUY A BUNCH
- Note: In the Hawau reaction, starting ice-cold and doing a lot of low-temp improves the selectivity for the N1-Me product. So, if you need more, don't just mix and heat!




Note the interesting contrast between Hawau reactions, depending on whether or not the hydrazine is or is not conjugated. In methyl hydrazine, the methyl-substituted nitrogen is more electron rich and more reactive nucleophile. In phenyl hydrazine, the phenyl-substituted nitrogen is conjugated ans is less reactive nucleophile.

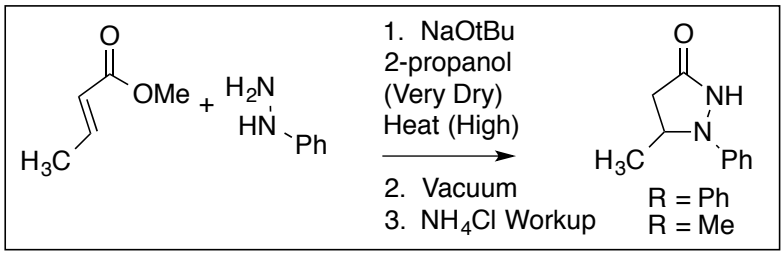


**N2-Acylation of N1-Phenyl Pyrazolidinone, Using Sunny's Phenyl Reagent:**

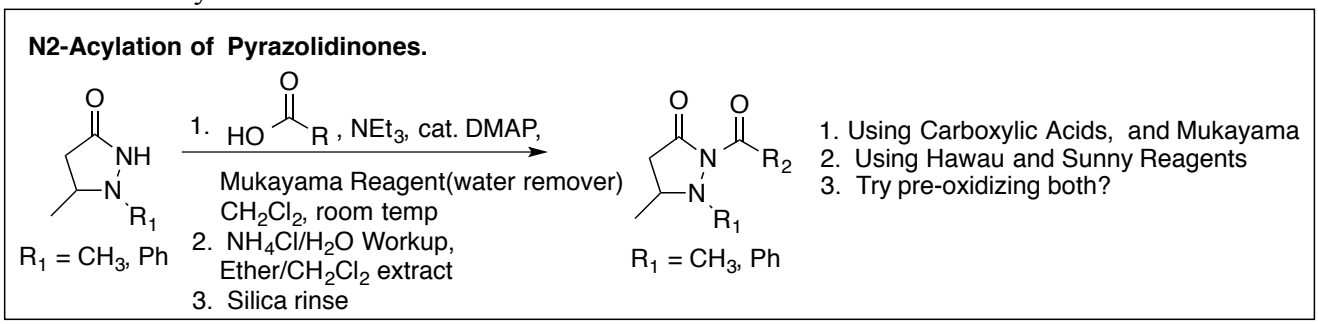



1. The N2-acylation using carboxylic acid and Mukayama reagent works to make derivative
2. This will function as an "Antipyrine-Twist" analog. If three core components of antipyrine are the aromatic ring, the 5-ring, and the carbonyl, this will effectively push the carbonyl over relative to the arene.
3. We also have a batch of the N1, C5-diphenyl analog

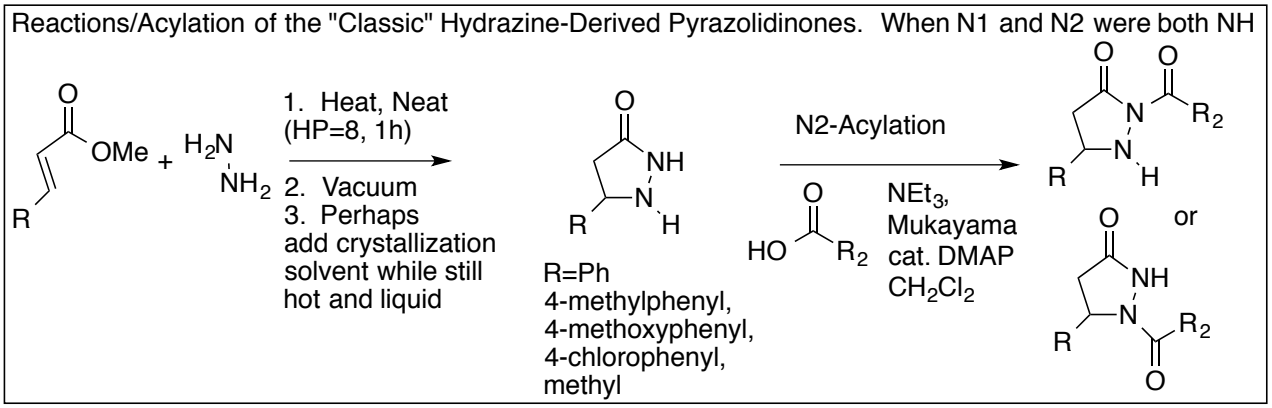
Prep of Sunny's Reagent:




General N2-Acylation



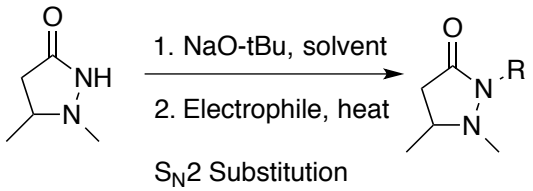
**N2-Acylation of N1-H Rings, Using Trinh's Reagents:**
**Acylation Using Acids and Mukayama's Reagent: Di-Hydro Rings**
**(Actually, I'm not sure what will happen here. Maybe just some exploring to check.)**




1. The initial products are well available
2. The extra time and crystallization procedure is good, other than for the 5-methyl case.
3. The N2-acylation using carboxylic acid and Mukayama reagent works to make derivative
4. The benzoyl case (R2=Ph) would be the natural target, to be closest to antipyrine
5. For antipyrine, the N1=H analog works about as well as the N1=Me. So fair chance that the N-H is pretty reasonable candidate. If so, these are really easy to make.

**N2-Alkylation of Hawau's N1-Methyl Pyrazolidinone, Using Base and $S_N2$ Reaction:**

**N2-Alkylation of N1-Methyl Pyrazolidinones: Using Base and SN2**



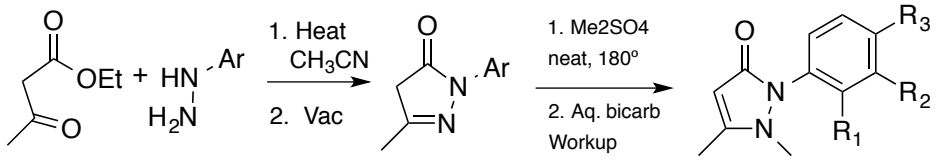

Potential Alkylation Agents:
$Me_2SO_4$, Ethyl tosylate or iodide,
Benzyl or Allyl bromide, etc.

Potential Solvents: MeOH, $CH_3CN$, DMF...

1 This could also be attempted using Sunny's N1-Phenyl or Mariam's N1-H pyrazolidinones
2 No preliminary results done on this.
3 SciFinder search looks promising: "Amide N-Methylation of 5-Ring Amide.PDF"
4 However, unclear how the N1-nitrogen impacts the reactivity of the N2-anion. (SciFinder was done on the 5-membered amide, pyrrolidinone. So with the adjacent N1-nitrogen versus CH2, that might stabilize the amide anion and make it less reactive? Also, the adjacent N-methyl group might produce some steric deactivation.
5 But, perhaps those things will be no problem, and it will work just fine and very well.
6 Unclear on solvent; one example was in methanol, so I think I'd probably go with methanol or isopropanol first. Another example used acetonitrile, that might be very convenient too.
7 Additional SciFinder literature makes this look very well demonstrated and very doable. Lots of examples.
    - N1-Alkylation of N2-Methyl Pyrazolidinone.pdf
    - N1-Alkylation of N2-Phenyl Pyrazolidinone.pdf
    - N1-Alkylation of N2-Unspecified Pyrazolidinones Selected

**N2-Aryl Ring Variation, Pyrazolones. Using alternate Arylhydrazines.**
**High Priority, But May need some Grant Money to Buy the Varients?**

**Variation at N2-Aryls By Variation of Aryl Hydrazine. Order some, Grant $$**




2-Pyridine $86/5
4-CN $57/5
4-Me $36/5
2-Me $40/5
4-Cl $29/5
3-Cl $97/25
2-Cl $80/25
4-F $67/10
2-F $70/5
========
4-Br $132/10
4-OCH3 $200/10
4-CF3 $70/5

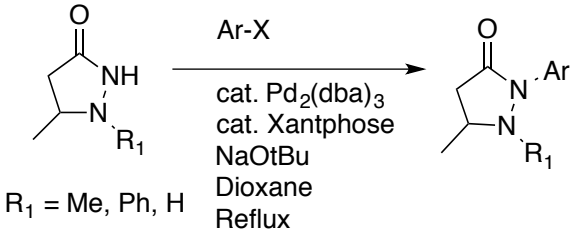
Notes:

- Many of these hydrazines are variably affordable
- Probably try 2 or 3, and try to have tested.
- Include in grant proposal budget for buying more
- Most come as HCl salts.
- May be able to directly follow the Scheme 1 process, but solubility may perhaps alter that?
- Or perhaps the HCl will actual simplify and help things, not sure.
- Did we already buy the 4-methyl one, perhaps?
- If I was to target 2 or 3, I'd probably start with
  - the pyridine (does a heteroatom make any difference?)
  - and either 4-Methyl or 4-cyano (or both.)
- Note: If we can figue out how to do the Pd-catalyzed arylation, that could greatly open other variations on N2-Aryl
- If one of these looks advantageous, and we see other advantages at N1, C4, or C5, could move towards multiple-substituent combinations. But for the beginning, just start with one at a time

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Pyridine | 4930-98-7 | 2-Hydrazinopyridine | Sigma/Aldrich: $86/5, $292/25 |
| p-CN | 2863-98-1 | 4-Cyanophenylhydrazine hydrochloride | Sigma/Aldrich: $57/5 |
| p-Tol | 637-60-5 | 4-Methylphenyl hydrazine | VWR-AA, $35.59/5g |
| o-Tol | 635-26-7 | o-Tolylhydrazine hydrochloride | Sigma/Aldrich: $39/5 |
| p-Cl | 1073-70-7 | 4-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $29/5, $97/25 |
| m-Cl | 2312-23-4 | 3-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $97/25 |
| o-Cl | 41052-75-9 | 2-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $80/25 |
| p-F | 823-85-8 | 4-Fluorophenylhydrazine hydrochloride | Sigma/Aldrich: $67/10, |
| 2-F | 2924-15-4 | 2-Fluorophenylhydrazine hydrochloride | Sigma/Aldrich: $70/5 |
| | | **TOO EXPENSIVE** | |
| p-Br | 622-88-8 | 4-Bromophenylhydrazine hydrochloride | Sigma/Aldrich: $132/10 (expensive) |
| p-OCH3 | 19501-58-7 | 4-Methoxyphenylhydrazine hydrochloride | Sigma/Aldrich: $200/10 (expensive) |
| p-CF3 | 368-90-1 | 4-(Trifluoromethyl)phenylhydrazine | Sigma/Aldrich: $125/5 (Too expensive) |

**N2-Arylation using Aryl bromides/iodides, Base, and Pd catalysis**

**N2-Arylation of Pyrazolidinone, Pd-catalyzed. Might be Harder Project, But High-Impact if we could Figure it Out.**




$R_1$ = Me, Ph, H

CHEMReview 2016
Stephen L. Buchwald and Paula Ruiz-Castillo

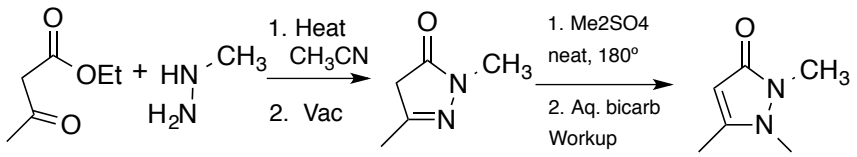
Might be hard. Detailed correct handling of the Pd catalyst and the diphosphorus ligand may be crucial

Antipyrine has N2-phenyl, so the opportunity to install variable aryl analogs from Hawau's Reagent would be really nice.... if it works.

1 Both the Pd catalyst and the diphosphine ligand are expensive and sensitive
2 I tried one preliminary experiment myself, but it did NOT work. Not sure why.
3 I haven't done much reading to get a really good super-detailed procedure, I just tried to wing it

**N2-Methyl Pyrazole, using Methyl Hydrazine to make the pyrazole.**

**Scheme 4: Variataion at N2 By Use of MethylHydrazine:**

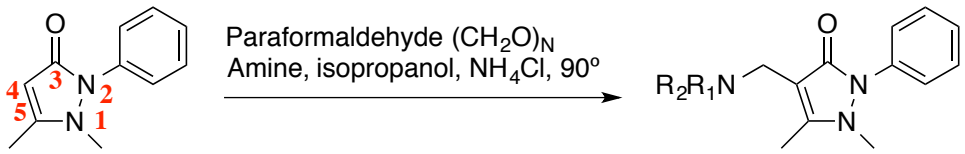



Notes:

- Haven't tried this yet, but if it works with the phenylhydrazine, should likely work with the methyl hydrazine also?
- Initial product might not allow for strong vacuum; don't want to distill it away.
- Low priority, but would be an interesting analog of antipyrine.

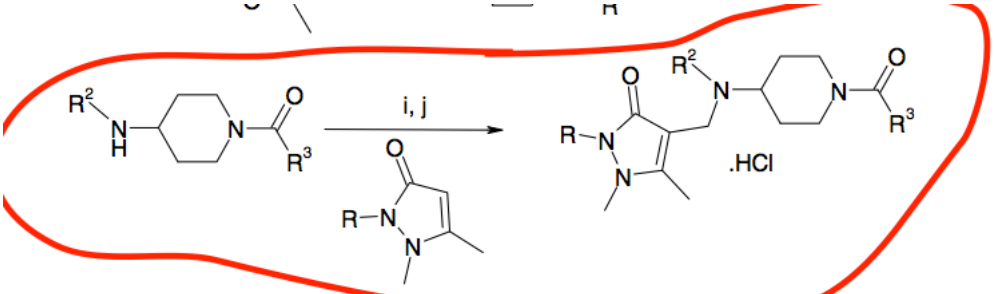
## C4-Aminomethyl Analogs

**C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone**



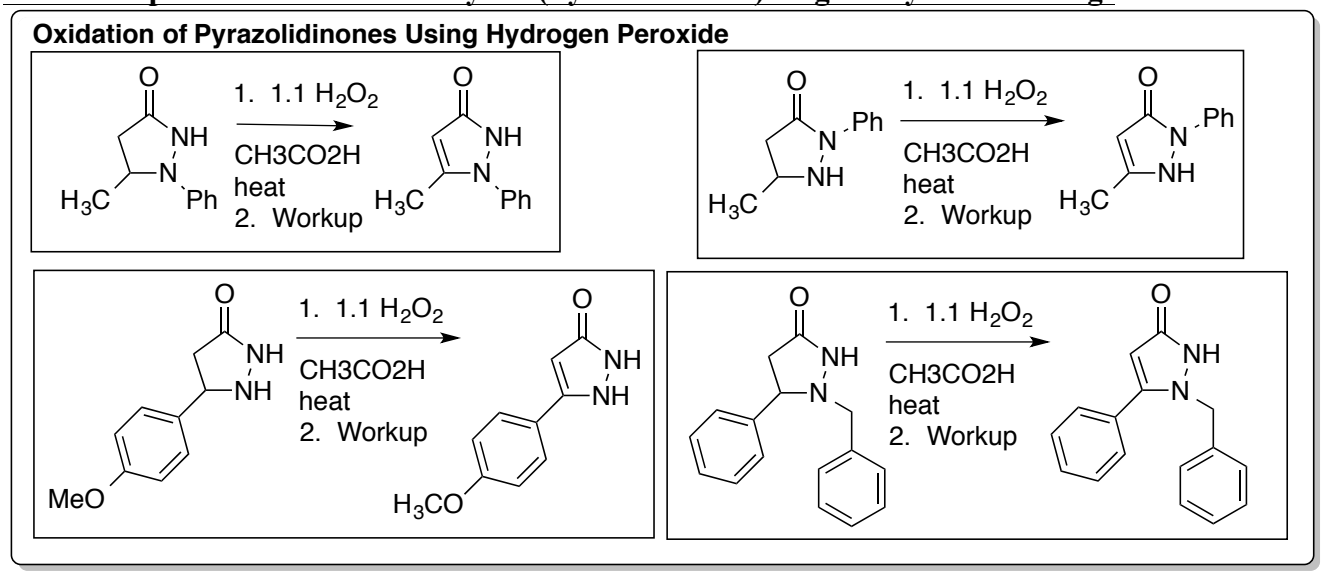

C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

1. C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231
2. Reference shows reaction, but provides zero experimental details
3. We haven't done any preliminary work on this, so not sure on stoichiometry, length, yields, etc..
4. Order: Paraformaldehyde (or borrow from Sibi)
5. We have lots of amines to try
6. C4-Aminomethyl analog has looked good in Dr. Haak's initial screening. Could be a promising area to build on.
7. If the reaction is general and straightforward, limitless library of amines that could be tagged on.
8. I have the one Bioorg Med Chem Lett reference; but have not done extended SciFinder search or other literature or citation search to see if there is a more detailed experimental for something like this.
9. I haven't found an email or anything to contact the author, either.
10. Could probably just try to wing it; maybe it's as easy as it looks? Would be great if we found it so.




**Scheme 2.** Medicinal chemistry procedure. Reagents and conditions: (a) $SnCl_2$, conc. HCl, EtOH, (b) $NaNO_2$, conc. HCl; (c) $SnCl_2$, conc. HCl; (d) methyl acetoacetate, $CH_3CN$, reflux; (e) $Me_2SO_4$, CaO, MeOH; (f) TFA, DCM; (g) $R^3COCl$, NEt, DCM; (h) $R^2NH_2$, $NaBH(OAc)_3$, DCE, AcOH, molecular sieves; (i) paraformaldehyde, iPrOH, $NH_4Cl$, 90 °C; (j) methanolic HCl, ether.

**Oxidation protocol to convert Dihydro (Pyrazolidinone) rings to Pyrazolone rings**

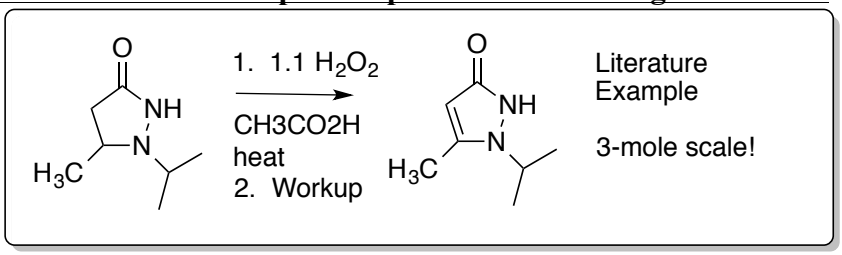



Suggest First Experiment to Try

1. Use a dry 20-mL vial with stir bar
2. Add 2.0 mmol of substrate
3. Add 1 mL of acetic acid and stir, perhaps with warming on a hot-plate, to try to dissolve. (Hot-plate = 4, maybe?). If it doesn't dissolve, more heating or perhaps additional acetic acid could help. If neither works, adding a little methanol might help?
4. Add 2.2 mmol of 35% hydrogen peroxide. (87 ml/mol). Note whether you feel any exotherm.
5. Seal very tightly; some Teflon tape around the rim, and a tightly snugged cap is good. Then place a septum over that. (For a larger scale, we would use a reflux condenser.)
6. Heat on hot plate with stirring, at hot-plate = 3.5 maybe?
7. Heat for 3 hours. (No idea whether this is way more than necessary, or inadequate in some cases, or what.
8. If you don't already have one, prepare and run an NMR for your starting pyrazolidinone.
9. Workup: Add 8 mL of 2:1 ether/dichloromethane. ("ether/DCM")
10. Pour into an Erlenmeyer or beaker, rinsing with additional 2:1 ether/DCM
11. Add 10 mL water and a larger stir bar.
12. Adjust the pH to ~neutral by adding ~6mL of 2.5M NaOH to try to neutralize the acetic acid. (This will need to be more if we used more than 1 mL of acetic acid). (Note: this might be very exothermic? So, maybe putting some ice in first, or adding the NaOH gradually, would be wise?) Note: just throwing in around 15-20 mmol worth of NaOH or KOH solid should work fine, too.
13. Test the pH with pH paper. If the water is not strongly acidic or basic, add ~6mL of aqueous bicarbonate (to ensure relative neutrality).
14. Pour into sep funnel, rinse with a little extra 2:1 ether/DCM to make sure all of your organic product gets there.
15. I assume the water layer will be on the bottom and the organic layer on top. If not sure, add more water and see which layer grows. If the layers don't settle out very well, adding NaCl/water ("brine") or more straight either may help?
16. Pour off the water layer.
17. Dry the organic layer by passage through Na2SO4 into a preweighed ground-glass flask.
18. Rinse the sep funnel and the Na2SO4 filter with more 2:1 ether/DCM.
19. Concentrate the organic solution on rotovap. (At only 2-mmol scale, we're only expecting a couple tenths of a gram of product.)
20. Record mass, and calculate percent yield.
21. Prepare and run NMR sample.

22. If Jasperse is around, come over and tell him mass, % yield, and show NMR. Is he's not around, email mass, % yield, and what spot your NMR was in. (Like spot 32 or spot 12 or whatever, so I can view your NMR myself, even if from home or wherever.)
23. To evaluate the NMR, compare your product to the starting NMR for your pyrazolidinone. Are signature signals from your starting material gone? For example, for the samples that have C5=methyl, the starting material should have had a 3H doublet in the 1's; the product that should have vanished, and you should now have a 3H singlet in the low 2's. For the methoxyphenyl compound, the multiplets in the 2-4.5 region should be gone. For all of the target products, there should be a new 1H singlet somewhere in the 5.4-6.3 area, for the C4-H which should be a vinyl-H in the product.

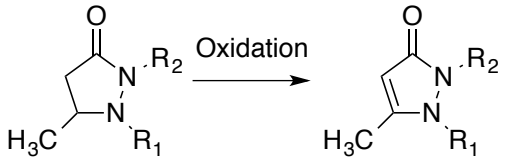
**The literature example and procedure I'm using as a model:**




- Example: (N1-isopropyl, C5-methyl example) Preparation of 1,2-dihydro-1-(1-methylethyl)-5-methyl-3H-pyrazol-3-one (VI.1) 1-(1-methylethyl)-5-methyl-3-pyrazolidinone (390 g; 2.74 mol) is dissolved in acetic acid (170 ml) with warming. 35% aqueous hydrogen peroxide (260 ml; 3.0 mol) is added within 3 h while keeping the temperature at about 65°C. The reaction mixture is then stirred at about 20 to 25°C for 15 h. Water (1.2 L) is then added and the pH of the mixture is adjusted to about 7 by means of addition of approx. 1 L 50%-weight aqueous sodium hydroxide solution. Upon cooling to 5°C the reaction mixture is filtered. The product is washed with water and dried at about 50°C. Colourless crystals are obtained.

**Oxidation protocol to convert Dihydro (Pyrazolidinone) rings to Pyrazzole rings**

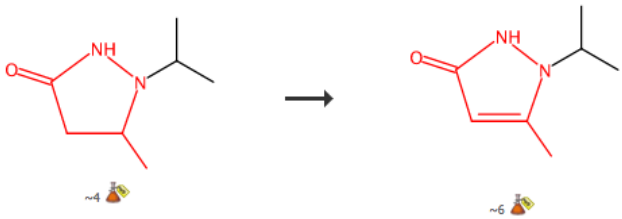
**Oxidation of Pyrazolidinones to Pyrazolones**

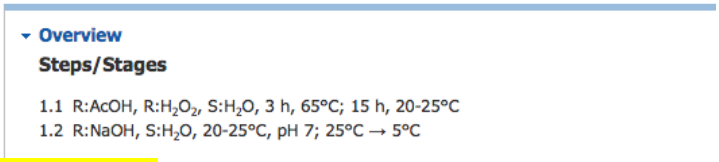



Oxidizing agent candidates:
1. $H_2O_2$, $CH_3CO_2H$
2. $O_2$, cat. $FeCl_3$
3. $K_2S_2O_8$
4. NBS

etc.

1. No preliminary results on these yet.
2. A couple of SciFinder references.
    d. One used FeCl3 and oxygen
    e. The other uses a sulfur reagent.
    f. Third used hydrogen peroxide
    g. Some experimental, although a bit vague.
    h. See PDF file called: Pyrazolidinone Oxidation to Pyrazolinone sciFinder.pdf
6. The value here is that we have a lot of ways to make the pyrazolidinones. If we had a convenient way to convert them into pyrazoles, that would be great and would double the volume of testable chemicals.
7. H2O2: Kraemer, Gerd et al From PCT Int. Appl., 2007080170, 19 Jul 2007
    - 1.1R:AcOH, R:H2O2, S:H2O, 3 h, 65°C; 15 h, 20-25°C
    - 1.2R:NaOH, S:H2O, 20-25°C, pH 7; 25°C => 5°C
    - Example: (N1-isopropyl, C5-methyl example) Preparation of 1,2-dihydro-1-(1-methylethyl)-5-methyl-3H-pyrazol-3-one (VI.1) 1-(1-methylethyl)-5-methyl-3-pyrazolidinone (390 g; 2.74 mol) is dissolved in acetic acid (170 ml) with warming. 35% aqueous hydrogen peroxide (260 ml; 3.0 mol) is added within 3 h while keeping the temperature at about 65°C. The reaction mixture is then stirred at about 20 to 25°C for 15 h. Water (1.2 L) is then added and the pH of the mixture is adjusted to about 7 by means of addition of approx. 1 L 50%-weight aqueous sodium hydroxide solution. Upon cooling to 5°C the reaction mixture is filtered. The product is washed with water and dried at about 50°C. Colourless crystals are obtained.



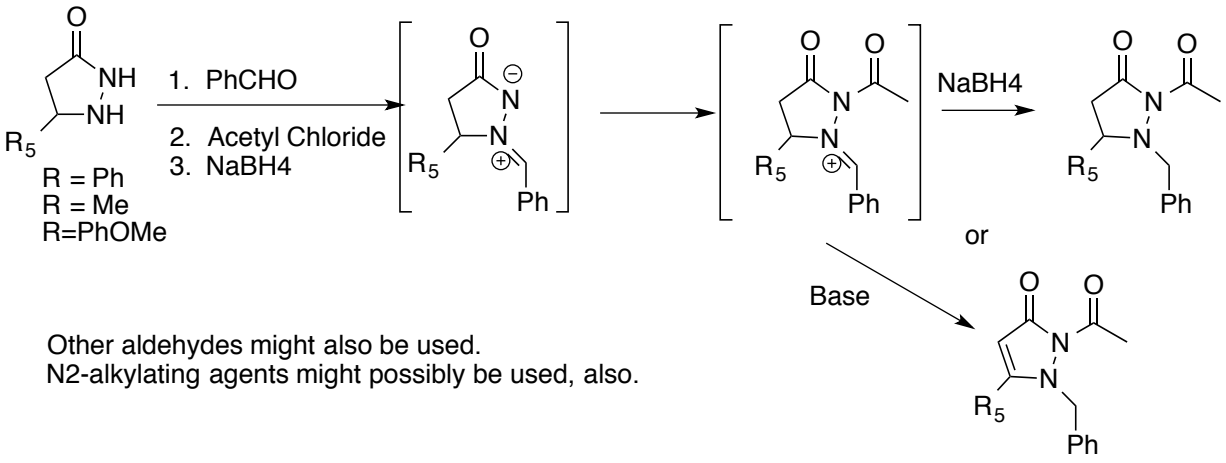

8. Peracetic Acid: Pfrengle, Waldemar From PCT Int. Appl., 2007010015, 25 Jan 2007 To the latter is added 50 mL acetic acid and the mixture is cooled to approx. 3°C. 66.9 g of peracetic acid is added together with 12.5 mL acetic acid. The mixture is stirred at 3°C for approx. 1h. 325 mL of water is then added and the pH of the solution is adjusted to 6.6 -7.0 by means of addition of 50% aqueous sodium hydroxide. The resulting suspension is stirred for 30 min. at 10°C after which it is filtered. The product is washed with water and dried at 45°C. or
9. 1-(1-methylethyl)-5-methyl-3-pyrazolidinone (390 g; 2.74 mol) is dissolved in acetic acid (170 ml) with warming. 35% aqueous hydrogen peroxide (260 ml; 3.0 mol) is added within 3 h while keeping the temperature at about 65°C. The reaction mixture is then stirred at about 20 to 25°C for 15 h. Water (1.2 L) is then added and the pH of the mixture is adjusted to about 7 by means of

addition of approx. 1 L 50%-weight aqueous sodium hydroxide solution. Upon cooling to 5°C the reaction mixture is filtered.

10. K2(S2O8): 1.1C:H2SO4, S:MeCN, 5 min 1.2R:K2(S2O8), 5 h, reflux
    - Mao, Wutao et al From Faming Zhuanli Shenqing, 105175336, 23 Dec 2015
    - Potassium Persulfate SL311 12-A Two containers. Also an ammonium persulfate
    - This seemed to be applied to C5-Aryl or C5-carbonyl cases
    - Synthetic procedure: To a solution of 2-(3-chloro-pyridin-2-yl)-5-oxo-pyrazolidine-3-carboxylic acid ethyl ester (9) (10 g, 37 mmol) in acetonitrile (150 mL) was added sulfuric acid (98 %, 7.2 g, 74 mmol). After being stirred for several minutes, the reaction mixture was treated with $K_2S_2O_8$ (15 g, 56 mmol) and was refluxed for 4.5 h. After being cooled to 60 °C, the mixture was filtered to remove a fine filter cake which was washed with acetonitrile (30 mL). The filtrate was concentrated and poured into ice water (200 mL). The aqueous layer was extracted with dichloromethane (3 × 150 mL). The organic layer was washed with water (3 × 100 mL) and dried over anhydrous sodium sulfate. Then, the ethyl acetate was concentrated. The residue was purified by column chromatography over silica gel using petroleum
    - ether (60-90 °C) and ethyl acetate as the eluent. (Yields around 60-70)
11. FeCl3/O2 1.1R:O2, C:FeCl3, S:DMF, 2 h, 80°C; 20 h, 30°C
    - By Liu, Yuanyuan et al, From Journal of Heterocyclic Chemistry, 47(4), 897-902; 2010
    - This one seemed to be applied only to "cinnamates" (C5-aryl)
12. N1-Aldehyde use, followed by NaOMe/MeOH isomerization: N1 plus Aldehyde, then NaOMe/MeOH reflux to isomerize
    - … 35 mmol… 5-methypyrazolidin-3-one. This oil was dissolved in MeOH (20 mL), cooled to 0°C under N2 atmosphere and sodium methoxide in MeOH (2 ml of 4.4M) was added. After 10 minutes 2-Benzyloxy-5-bromo-benzaldehyde, 6, (7.66g, 31mmol) in MeOH (100 mL) was added and the mixture was stirred at RT for 1 hour. Sodium methoxide in MeOH (7 ml of 4.4M) was added and the mixture was refluxed for 16 hours. The volatiles were removed in vacuo and the residue was portioned between EtOAc and HCl (aq., 2M). A yellow solid was collected and triturated with diethyl ether to yield a cream coloured solid which was dried under vacuum to yield 1-(2-Benzyloxy-5-chloro-benzyl)-5-methylH-pyrazo3-
13. Oxone To a solution of D (9.35 g, 0.03 mol) in acetonitrile (100 ml) is added oxone (11.7 g, 0.019 mol) portion-wise with good stirring. The reaction mixture is then heated to 90°C and stirred at this temperature overnight. After cooling to ambient temperature, the reaction mixture is filtered and the solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate, washed with water, salt solution and the organic layer dried and evaporated. The crude product E is re-crystallised using a mixture of ethyl acetate and pentane to give E as a solid.
14. NBS would seem a very convenient, simple oxidant for us that might work.
    a. Easy to track via NMR, for initial screening
    b. If it brominates alpha to the carbonyl, that should work following elimination.
    c. If it brominates the Nitrogen, elimination should then work.
    d. The benzyl might be an issue; might be better on the N1-phenyls
    e. Treatment with base should put it easily into success mode.
    f. Concept: Prepare solution in anhydrous methanol. Add 1 equivalent of NBS and stir for 10 min. Add 2 or 3 equivalents of NaOR base and reflux for a while.
    g. Workup with bicarb and 2:1 ether/DCM.

**Sequential N1-N2 Alkylation/Acylation using Aldehydes first, then perhaps acylating the azomethine imine. Perhaps with Base. Perhaps Alkylation/Alkylation might also work.**

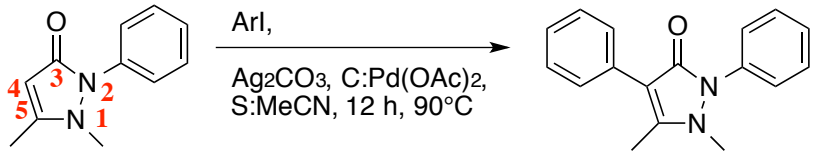
**Sequential Concept: Sequential alkylation-acylation-reduction for N1-alkylation and N2-acylation. Alternative to the NaBH4 might perhaps be the use of base, to produce pyrazolone.**




1. Lot of steps involved: Might be really efficient!
2. Might the imminium rearrange, perhaps with base, into the pyrazolone?
3. That would be super cool
4. Would direct acyl chloride work?
5. Would Mukayama and acid work?
6. Would N2-alkylation (methylation, allylation, benzylation, for example)
7. Would I need to add base to or following the aldehyde?
8. I have several alkyl aldehydes available in the fridge.
9. No preliminary data or experiments providing that this would work. Just a cool, short concept.
10. Test: Do simple test in NMR tube.

## C4-Arylation. C4-Aryl Analogs

**C4-Arylation. Pyrazolone**

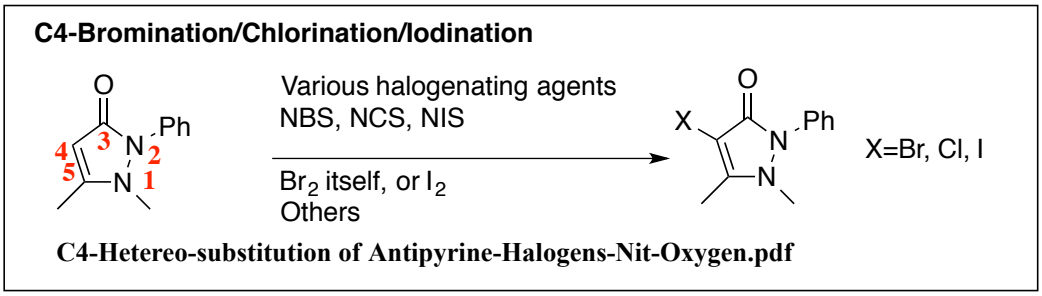



4-Arylation of Antipyrine-Good using PdOAc2 + AgOAc.pdf

Gong, Hao et al From Beilstein Journal of Organic Chemistry, 9, 2033-2039, 7 pp.; 2013

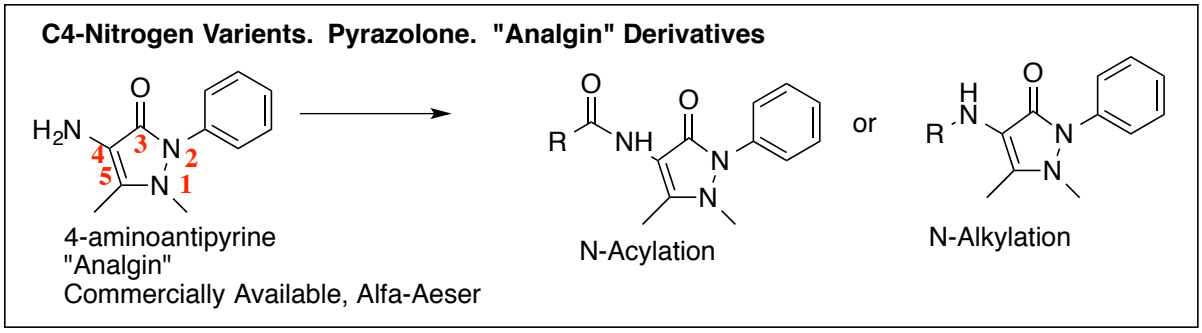
11. Gong, Hao et al From Beilstein Journal of Organic Chemistry, 9, 2033-2039, 7 pp.; 2013
12. We haven't done any preliminary work on this, so not sure on stoichiometry, length, yields, etc..
13. 4-Arylation of Antipyrine-Good using PdOAc2 + AgOAc.pdf
14. Looks very straightforward. Not sure how new/good our Ag salt is, or our Pd catalyt

## C4-Bromination/Chlorination/Iodination




1. C4-Hetereo-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf
2. These have all been reported in high yields
3. Seems like simple NBS/NCS works well
4. I have good NBS. Have some NIS? Don't think we have any NCS. Sibi might?
5. $Br_2$ seems to work fine, too.
6. Some fancier halogenation agents have also been used.
7. Very simple SciFinder search to do, since we can be super specific.

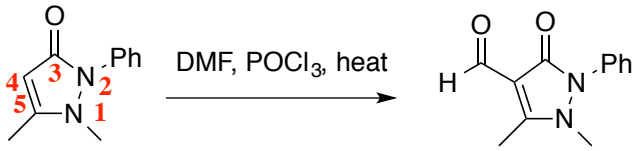
**4-Acylamino and Alkylamino Analogs. Analgin Reactions. C4-Aminoantipyrine to Amides or alkyl amines. Pyrazolones.**




1. 4-Aminoantipyrine is called “Analgin”, it’s a commercial drug (that was banned for a while)
2. It is cheap and commercially available from Alfa-Aeser.
3. Should be able to do amine reactions to make analogs.
4. It’s a conjugated nitrogen, so it’s not super reactive, maybe.
5. But should be easy to acylate it (make amides)
6. May be possible to alkylate it (“N-Alkylation”)
7. No preliminary experiments done yet.
8. Haven’t done SciFinder Search yet, either.
9. Analgin 4-aminoantipyrine CAS 83-07-8.pdf
10. Amino Antipyrine Alfa-Aeser Cheap.pdf

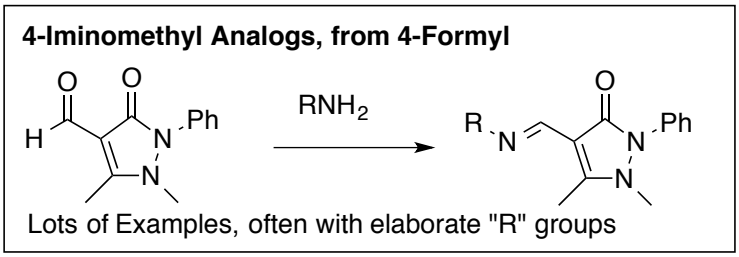
## C4-Formylation

**C4-Formylation.**




- C4-Formylation of Antipyrine.pdf
- The aldehyde provides a functional group that can then be converted into lots of other stuff

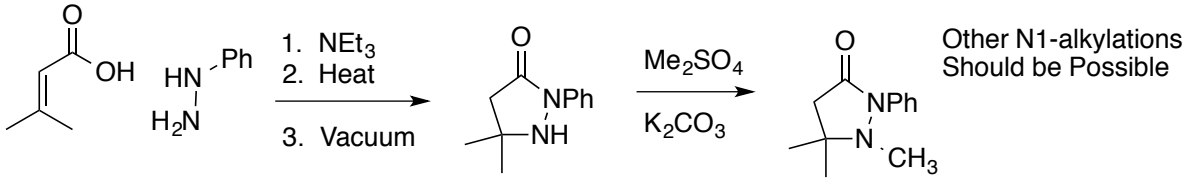
**C4-Iminomethyl Analogs. From the Formyl Derivative. Lots of examples with elaborate "R" groups**




- Easy Sci-Finder Search

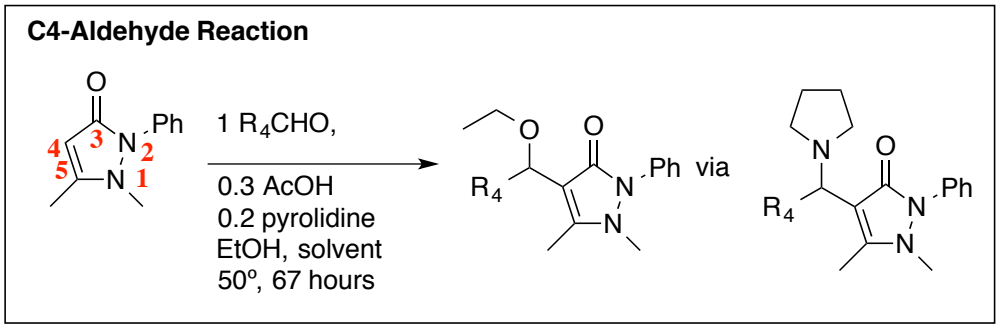
## 5,5-Dimethyl Pyrazolidinone

**5,5-Dimethyl Pyrazolidinone Analog**



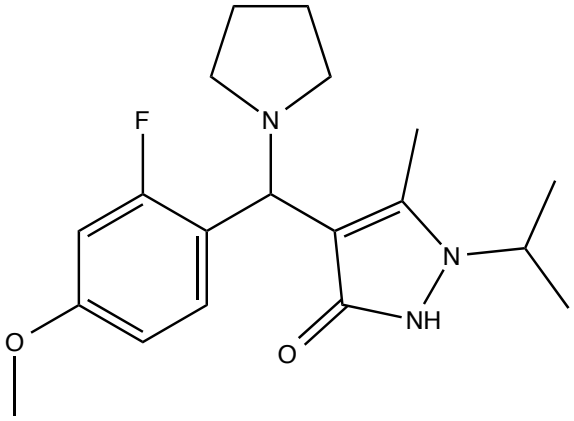

1. This one is interesting in that with the 5,5-dimethyl, there is no way the ring can be oxidized to the pyrazolone form. It's pyrazolidinone, and no redox is going to change that, whether in lab or in the cell
2. The first reaction hasn't been tried yet.
3. Based on earlier Hawau reactions, it would be surprising if it didn't succeed, but the reaction may be a little slow.
4. The methylation may also require stronger conditions than other pyrazolidinones;.
5. The capacity to make the N1-methyl analog should be even easier (using methylhydrazine).

**C4-Reaction with Aldehydes and Amines.**




Example 1.5: 1,2-Dihydro-1-(1-methylethyl)-4-[(2-fluor-4-methoxyphenyl)-(ethoxy)methyl]-5-methyl-3H-pyrazol-3-one (IV.1) Pyrrolidine ( 21 ml; 0.257 mol) and acetic acid (22 ml; 0.385 mol) are added to a mixture of 1,2-dihydro-1-(1-methylethyl)-5-methyl-3H-pyrazol-3-one (180 g; 1.28 mol) and 2-fluoro-4-methoxybenzaldehyde (198 g; 1.28 mol) in ethanol (2.7 L). The suspension is heated to about 50°C for about 67 h. The reaction mixture is then cooled to approx. 17°C and filtered. The product is washed with diisopropyl ether (500 ml) and subsequently refluxed with THF (2.5 L). The obtained solution is filtered over a pad of Celite and charcoal. The filtrate is concentrated in vacuo and water (2 L) is added to the suspension which is cooled and filtered.

Note: The literature example has N2=H, not N2=Ph like we want. Might the phenyl deactivate somewhat?



1,2-Dihydro-1-(1 -methylethyl)-4-[(2-fluor-4-methoxyphenyl)-(1-pyrrolidino)methyl]-5-methyl-3H-pyrazol-3-one

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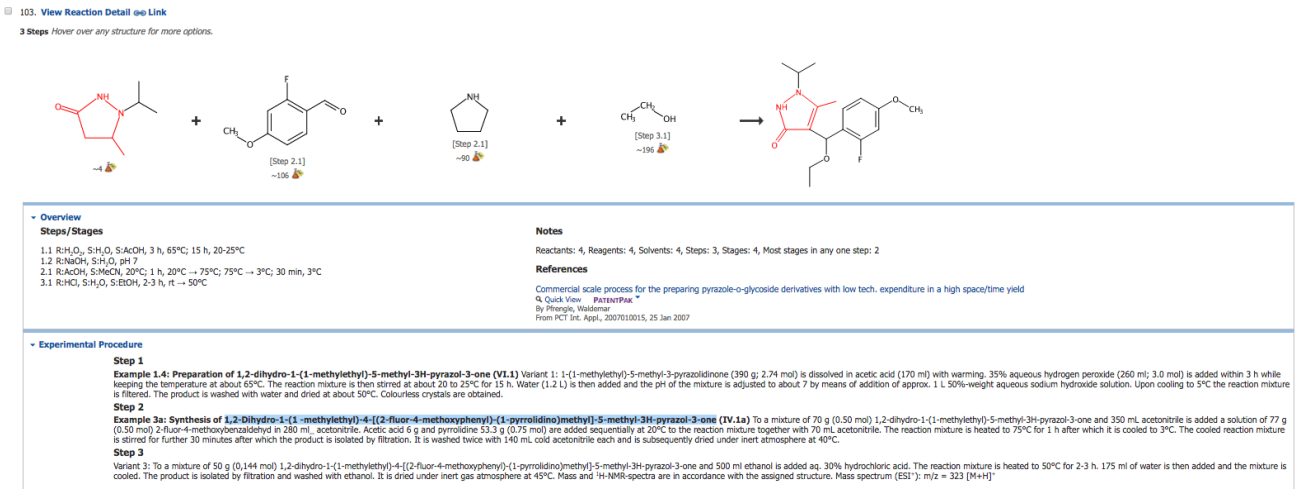


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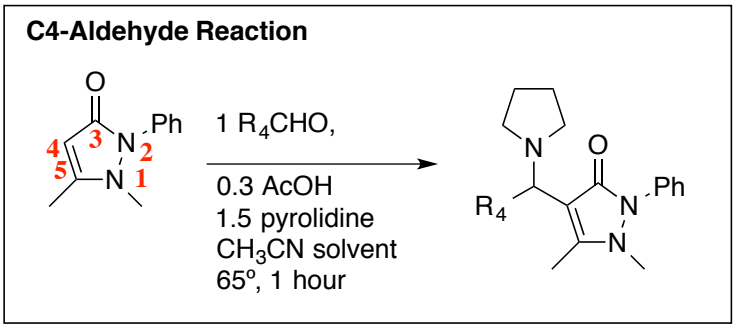
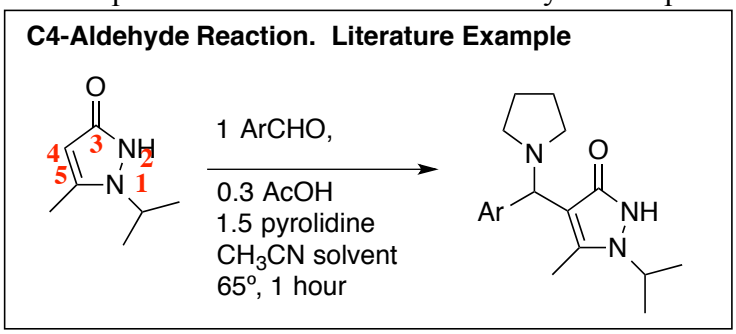
Oxidation to Pyrazolones using Hydrogen Peroxide.pdf
C4 Reaction with Aldehdye and amine.pdf

**C4-Aldehyde + Amine then Alcohol.pdf**



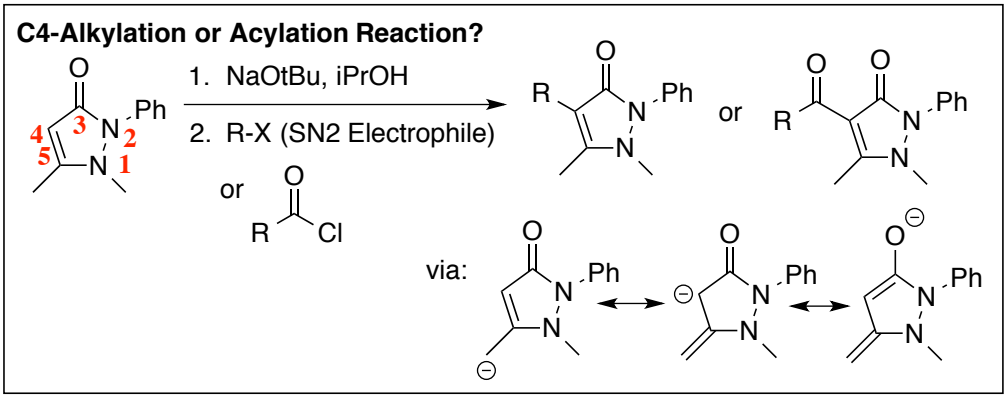

Example 3a: Synthesis of 1,2-Dihydro-1-(1 -methylethyl)-4-[(2-fluor-4-methoxyphenyl)-(1-pyrrolidino)methyl]-5-methyl-3H-pyrazol-3-one (IV.1a) To a mixture of 70 g (0.50 mol) 1,2-dihydro-1-(1-methylethyl)-5-methyl-3H-pyrazol-3-one and 350 mL acetonitrile is added a solution of 77 g (0.50 mol) 2-fluor-4-methoxybenzaldehyd in 280 ml_ acetonitrile. Acetic acid 6 g and pyrrolidine 53.3 g (0.75 mol) are added sequentially at 20°C to the reaction mixture together with 70 mL acetonitrile. The reaction mixture is heated to 75°C for 1 h after which it is cooled to 3°C. The cooled reaction mixture is stirred for further 30 minutes after which the product is isolated by filtration. It is washed twice with 140 mL cold acetonitrile each and is subsequently dried under inert atmosphere at 40°C.

Lit example: It doesn't have the N2-Phenyl. Perhaps the N2-phenyl is a bit of a deactivator?



**C4-Alkylation or Acylation via Anion/Enolate?**

- Scifinder search finds zero precedence. Maybe that means it can't work, but maybe it means nobody else has thought of it or had reason to try.
- I think it should be able to work; but whether DBU, NaOtBu, or LDA is needed as based, I don't know.
- There is also a question of whether electrophile addition will be regioselective, at C4, versus reacting to varying degree at the oxygen or the C4-methyl.




Zero literature precedence. Which is why it would be cool and more publishable if it worked! ☺
If so, could be a really convenient way to install new chunks onto antipyrine. Nice in that the starting material is cheap and clean and commercially available.

**Stock of Home-Made (or Store-Bought) Ready-to-Use Chemicals:**

<table>
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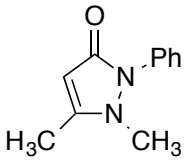
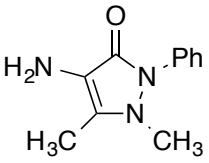
<td>  Antipyrine. $$.</td>
<td>  4-aminoantipyrine = “Analgin”. $$</td>
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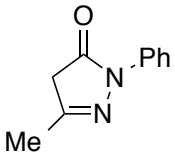
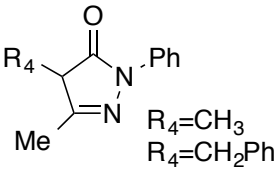
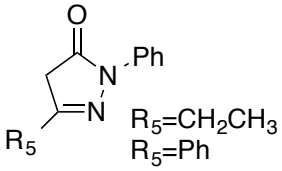
<td>  Taysir’s Reagent.</td>
<td>  </td>
<td>  </td>
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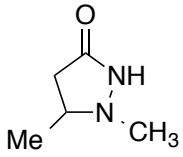
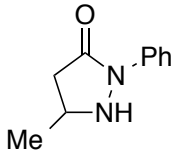
<td>  Hawau’s N1-Methyl Reagent</td>
<td>  Hawau’s N2-Phenyl Reagent</td>
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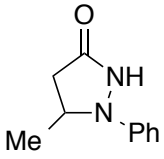
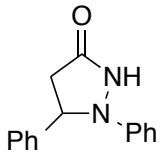
<td>  Sunny’s Reagent</td>
<td>  </td>
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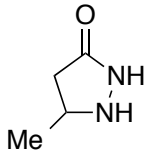
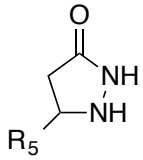
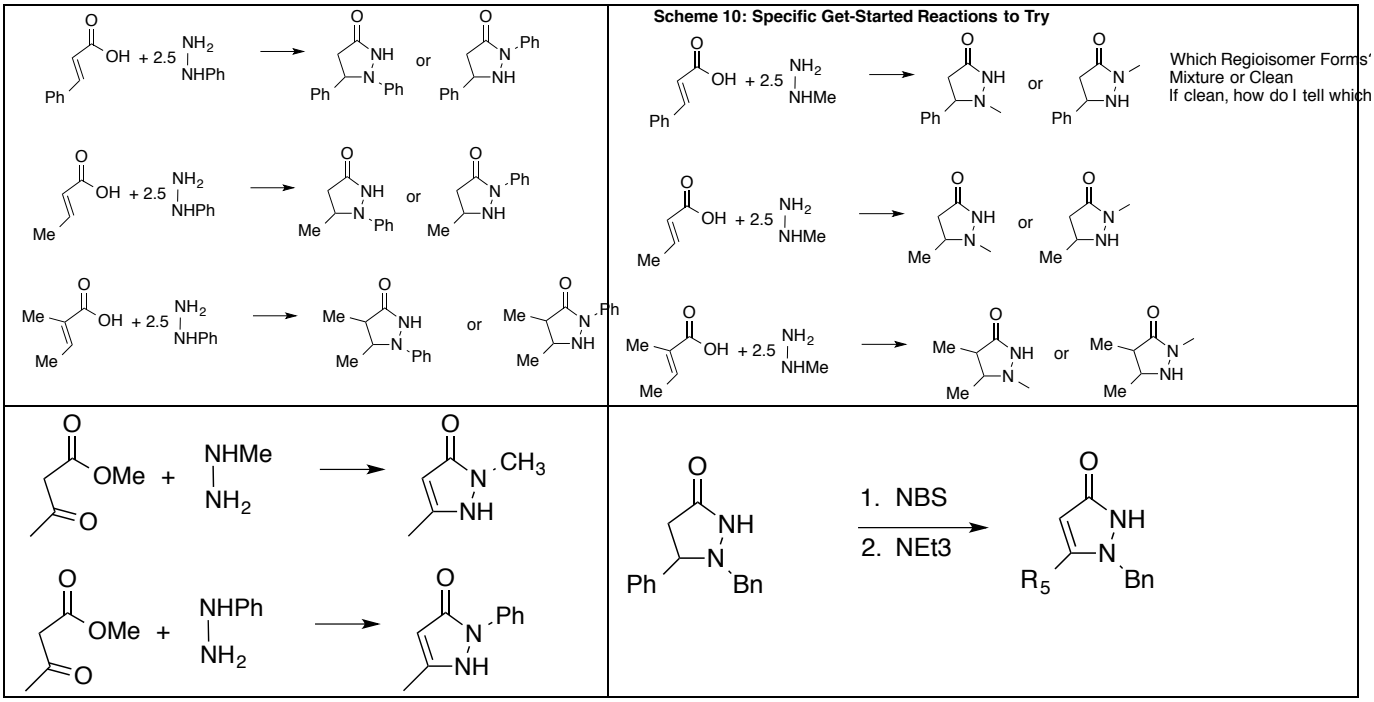
<tr>
<td>  Mariam’s Reagent</td>
<td>  Trinh’s Reagents</td>
</tr>
</table>

**Some Chemical Ordering info:**

Palladium coupling:

| CAS | One Name variant | Commercial? | Supplier, Price |
|---|---|---|---|
| 161265-03-8 | Xantphos | Not that bad | Strem, I think? ~$38/g |
| 51364-51-3 | Pd2(dba)3<br>Tris(dibenzylideneacetone)dipalladium(0) | Not that bad | 0.5g scales are best, Acros ~$40/0.5g |
| 534-17-8 | Cesium Carbonate | | |




Scheme 1: C4-Varients, Ethylacetoacetates.

| R4 | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| H | 141-97-9 | Ethyl acetoacetate | Stockroom probably has? Shelf 5-C |
| Me | 609-14-3 | Ethyl 2-methylacetoacetate | VWR-AA, $36.39/25g or 102.80/100g |
| Et | 607-97-6 | Ethyl 2-ethylacetoacetate | VWR-AA, $119.13/25g |
| Pr | 1540-28-9 | Ethyl 2-acetylpentanoate | VWR-Matrix Scientific, $236/1g |
| iPr | 1522-46-9 | Ethyl 2-isopropylacetoacetate | Sigma - 59280-25ML-F, $130.50/25mL |
| Bn | 620-79-1 | Ethyl 2-benzylacetoacetate | VWR-AA, $55.58/25g |

Scheme 2: C5-Varients, Ethylacetoacetates.

| $R_5$ | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Et | 4949-44-4 | Ethyl 3-oxopentanoate | VWR-AA, $73.40/5g |
| Ph | 94-02-0 | Benzenepropanoic acid, β-oxo-, ethyl ester | I probably still have some? VWR-AA, $27.46/50g |

Scheme 3, Scheme 4, Scheme 6: Different Hydrazines, N1 Varients and N2 Varients, whether with ethylacetoacetates, or with unsaturated acids.

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Me | 60-34-4 | Methyl hydrazine | WOW, VWR-Pfaltz & Bauer, $597.30/50 mL |
| Tol | 637-60-5 | 4-Methylphenyl hydrazine | VWR-AA, $35.59/5g |
| Et | 624-80-6 | Ethylhydrazine | Too Pricey? YES – Sigma ,$402.50/1g DO NOT BUY |

N-Arylation Reagents and Catalysts
Palladium coupling:

| CAS | One Name variant | Commercial? | Supplier, Price |
|---|---|---|---|
| 161265-03-8 | Xantphos | Not that bad | Strem, I think? ~$38/g |
| 51364-51-3 | Pd2(dba)3 Tris(dibenzylideneacetone)dipalladium(0) | Not that bad | 0.5g scales are best, Acros ~$40/0.5g |
| 534-17-8 | Cesium Carbonate | | |

Miscellaneous, that Stockroom Probably has (or me. Assuming so, perhaps mark where it's listed as being?)

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| | 128-08-5 | N-Bromosuccinimide | VWR-AA, $36.39/250g |
| | 591-50-4 | Iodobenzene | Strockroom probably has? Jasperse research area or stockroom shelf 8B |
| | 534-17-8 | Cesium Carbonate | Stockroom probably has? Stockroom shelf 16C |
| | | | |
| | | | |
| | | | |
| | | | |

Chems to Order, For Jasperse, Jan 7/2017
Antipyrine projects

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| | 80-40-0 | Ethyl Tosylate | Sigma/Aldrich: $26/50g |
| | 74-88-4 | Iodomethane, 99%, stab. with copper | Alfa Aesar $20/50g |
| | 30525-89-4 | Paraformaldehyde | Sigma/Aldrich: $45/100g 158127-100G |
| | 83-07-8 | 4-Aminoantipyrine, 97% | Alfa Aesar $43/100g |
| | | | |
| | | | |

Ignore these, these are for Research Grant.

| R4 | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Et | 607-97-6 | Ethyl 2-ethylacetoacetate | Sigma Aldrich, $108/25g |
| iPr | 1522-46-9 | Ethyl 2-isopropylacetoacetate | Sigma Aldrich, $130/25g |
| | 128-09-6 | N-Chlorosuccinimide, 98% | Alfa Aeser $15/50g |
| Me | 60-34-4 | Methyl hydrazine | Aldrich: $51/25g or $137/100g<br>Sigma/Aldrich: $71/50 |
| | 10025-87-3 | Phosphorus(V) oxychloride | Aldrich, 79582-25ML, 47.90 |
| | | | |
| | | | |

Aryl Hydrazines

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Pyridine | 4930-98-7 | 2-Hydrazinopyridine | Sigma/Aldrich: $86/5, $292/25 |
| p-CN | 2863-98-1 | 4-Cyanophenylhydrazine hydrochloride | Sigma/Aldrich: $57/5 |
| p-Tol | 637-60-5 | 4-Methylphenyl hydrazine | VWR-AA, $35.59/5g |
| o-Tol | 635-26-7 | o-Tolylhydrazine hydrochloride | Sigma/Aldrich: $39/5 |
| p-Cl | 1073-70-7 | 4-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $29/5, $97/25 |
| m-Cl | 2312-23-4 | 3-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $97/25 |
| o-Cl | 41052-75-9 | 2-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $80/25 |
| p-F | 823-85-8 | 4-Fluorophenylhydrazine hydrochloride | Sigma/Aldrich: $67/10, |
| 2-F | 2924-15-4 | 2-Fluorophenylhydrazine hydrochloride | Sigma/Aldrich: $70/5 |
| | | **TOO EXPENSIVE** | |
| p-Br | 622-88-8 | 4-Bromophenylhydrazine hydrochloride | Sigma/Aldrich: $132/10 (expensive) |
| p-OCH3 | 19501-58-7 | 4-Methoxyphenylhydrazine hydrochloride | Sigma/Aldrich: $200/10 (expensive) |
| p-CF3 | 368-90-1 | 4-(Trifluoromethyl)phenylhydrazine | Sigma/Aldrich: $125/5 (Too expensive) |

Ignore these, these were already bought October 2016

Scheme 1: C4-Varients, Ethylacetoacetates.

| R4 | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Me | 609-14-3 | Ethyl 2-methylacetoacetate | VWR-AA, $36.39/25g |
| Bn | 620-79-1 | Ethyl 2-benzylacetoacetate | VWR-AA, $55.58/25g |

| $R_5$ | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Et | 4949-44-4 | Ethyl 3-oxopentanoate | VWR-AA, $73.40/5g |
| Ph | 94-02-0 | Benzenepropanoic acid, β-oxo-, ethyl ester | VWR-AA, $27.46/50g |

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Tol | 637-60-5 | 4-Methylphenyl hydrazine | VWR-AA, $35.59/5g |

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| | 51364-51-3 | Pd2(dba)3 Tris(dibenzylideneacetone)dipalladium(0) | Catalyst, 1-2 grams is plenty VWR-Acros, $34.88/500mg |

| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| | 128-08-5 | N-Bromosuccinimide | VWR-AA, $36.39/250g |