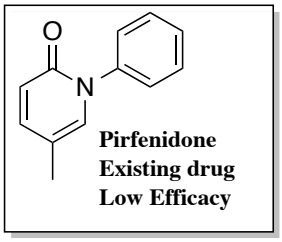
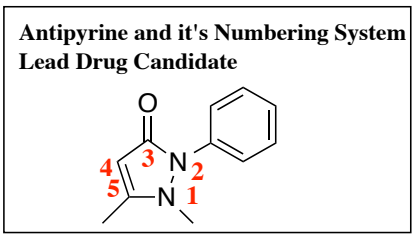
Research Idiopathic Pulmonary Fibrosis AntiPyrine Analog Library Synthesis Update 1/23/2020

("Idiopathic": "relating to or denoting any disease or condition which arises spontaneously or for which the cause is unknown.")

https://err.ersjournals.com/content/26/145/170053




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:**

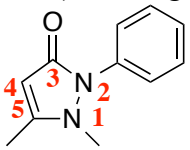
1. Pirfenidone is the FDA-approved (2017) medicine used to treat pulmonary fibrosis
   - It is not a life-saver
   - It isn't very good in terms of potency, efficacy, toxicity (or expense)
   - Its mechanism of operation is not understood
   - Some recommended dosage and price details:
     a. Daily, with 3 doses per day
     b. 801-mg per dose. (very large). 3 x 801mg >2 grams/day!
     c. Wholesale price: $131/tablet
     d. $131 x 3 = $393/day x 365 days = $143,445/year. In other words, Expensive!
     e. Research price: Sigma-Aldrich has it $107/10mg; TCI-America $67/100mg or $396/gram
     f. Antipyrine: $81/100g. So pirfenidone is ~500 times more expensive!!!
     g. Nintenadib: 2014 approved, 2 x 150mg/day, $209/capsule, $418/day => $153K/year

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

3. Extensive "chemical library" study identified antipyrine as a "lead chemical", comparable to pirfenidone

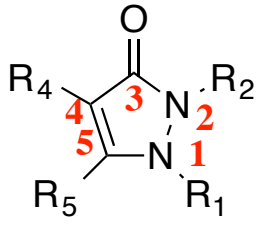
4. Jasperse research group goal: Make as many analogs of antipyrine as we can, in hopes that we can make something better yet

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.

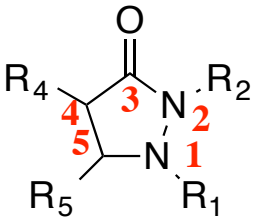


## Jasperse Synthetic Group Goal:

**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**

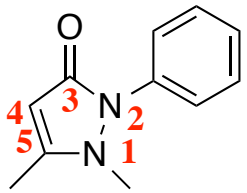


Pyrazoles



Pyrazolidinones

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




## Molecular Biology: Develop a procedural assay to evaluate different synthetic analogs.

## SAR questions: (Structure-Activity-Relationship Questions)

1. How/where does the drug bind?
2. Where is there spatial capacity for 3D-drug enlargement? Between the four quadrants, where are spatial enlargements tolerable or beneficial?
    a. Southeast Quadrant (N1)
    b. Northeast Quadrant (N2)
    c. Northwest Quadrant (C4)
    d. Southwest Quadrant (C5)
3. How does adding hydrophobic vs hydrophilic character impact drug performance?
4. Again, this question applies independently for each of the four quadrants
5. How does flexible (acyclic) vs rigid (rings, especially flat aromatics)?

https://www.google.com/search?q=ipf+orphan+disease&oq=IPF+orphan+disease&aqs=chrome.0.0.6725j0j4&sourceid=chrome&ie=UTF-8

"Idiopathic pulmonary fibrosis (**IPF**) is a non-neoplastic pulmonary **disease** that is characterized by the formation of scar tissue within the lungs in the absence of any known provocation. **IPF** is a rare **disease** which affects approximately 5 million persons worldwide."

There is currently no cure for **pulmonary fibrosis** but treatments and therapies are improving all the time. The average **life expectancy** of **someone with pulmonary fibrosis** is three to five years but if it's caught early, treatment can help slow down the progression of the disease.Jun 16, 2017

"Summary: Idiopathic **pulmonary fibrosis** is a little-known disease that kills as many people each year as breast cancer. ... A diagnosis of idiopathic **pulmonary fibrosis** is not much better than a **death sentence**, given a survival rate averaging 4 to 6 years as the disease robs its victim of the ability to breathe.Nov 11, 2010"
"

https://www.google.com/search?q=How+many+people+have+IPF+in+the+United+States%3F&oq=How+many+people+have+IPF+in+the+United+States%3F&aqs=chrome..69i57.10192j0j4&sourceid=chrome&ie=UTF-8
According to the National Institutes of Health, about **100,000 people** in the United States have IPF, and approximately **30,000** to **40,000** new cases are found each year. Worldwide, IPF affects **13** to 20 out of every **100,000 people**.Dec 13, 2016 (US population:

https://err.ersjournals.com/content/errev/26/145/170053.full.pdf (2017 article)
ABSTRACT Idiopathic pulmonary fibrosis (IPF) is characterised by progressive changes of the lung architecture causing cough and dyspnoea and ultimately leading to lung failure and death. Today, for the first time, two drugs that may reduce the inexorable progression of the disease are available, suggesting that treatment with specific drugs for IPF should be started as soon as diagnosis is made. This applies to any disease and particularly to IPF, which is marked by a 5-year survival comparable or even worse than many cancers. However, despite common sense and even worse, in spite of scientific data coming from clinical trials, post hoc analysis, long-term safety studies and real-life experiences, the question of when to start and when to stop treatment with antifibrotics is still debated. In IPF, particularly when the disease is diagnosed at an early stage, "wait and watch" behaviour is not rare to observe. This is largely due to the lack of awareness of both patients and clinicians regarding the progression of the disease and its prognosis. Another important issue is when treatment should be stopped. In general, there are two main reasons to stop a therapy: unbearable side-effects and/or lack of efficacy. According to current (although preliminary) evidence, antifibrotic drugs should not be discontinued except for safety issues.
**Introduction** Idiopathic pulmonary fibrosis (IPF) is a chronic progressive lung disease of unknown cause, which is limited to the lungs and associated with the radiological and/or histological pattern of usual interstitial pneumonia. The disease is characterised by progressive morphological changes of the lung architecture, causing cough and worsening dyspnoea and ultimately leading to lung failure and death. Several risk factors have been described to contribute to IPF onset and, despite the recent advances in our understanding of the pathogenesis, the real cause of the disease remains to be determined. IPF is a disease characterised by a very poor prognosis, with a median survival time of 3–5 years from diagnosis. Furthermore, the clinical course is unpredictable, marked in some cases by a relatively slow and gradual progression but in other cases by a rapid and often dramatic clinical evolution [1, 2]….
**Conclusion** IPF is a dreadful disease. Many efforts have been made in understanding its pathogenesis, but despite recent advances in research, this disease still represents a dilemma. Today, for the first time, we can use two effective drugs able to reduce the inexorable progression of the disease. … It is currently estimated that only 54% of patients with an IPF diagnosis in Europe receive antifibrotic treatment with an approved drug. It is desirable, when faced with evidence of a disease that is not cancer, but looks like a cancer in its behaviour, …

https://www.google.com/search?q=What+does+it+mean+to+be+an+%22orphan+drug%22%3F&oq=What+does+it+mean+to+be+an+%22orphan+drug%22%3F&aqs=chrome..69i57j0l2.9726j1j7&sourceid=chrome&ie=UTF-8
https://en.wikipedia.org/wiki/Orphan_drug

Orphan Drug/Orphan Disease: What does it mean to be an "Orphan Drug"?
An **orphan drug is** a pharmaceutical agent developed to treat medical conditions which, because they are so rare, **would** not be profitable to produce without government assistance. The conditions are referred to as orphan diseases.

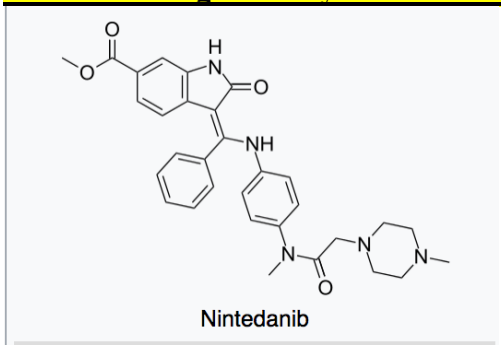
The assignment of **orphan status** to a disease and to drugs developed to treat it is a matter of public policy in many countries and has yielded medical breakthroughs that might not otherwise have been achieved, due to the economics of drug research and development.[1]

In the U.S. and the EU, it is easier to gain marketing approval for an orphan drug. There may be other financial incentives, such as an extended period of exclusivity, during which the producer has sole rights to market the drug. All are intended to encourage development of drugs which would otherwise lack sufficient profit motive to attract corporate research budgets and personnel.[2][3]

According to the US Food and Drug Administration (FDA), an orphan drug is defined as one "intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200,000 persons in the United States."[4][5]

~0.03% in US. About 3 out of 10,000 people.

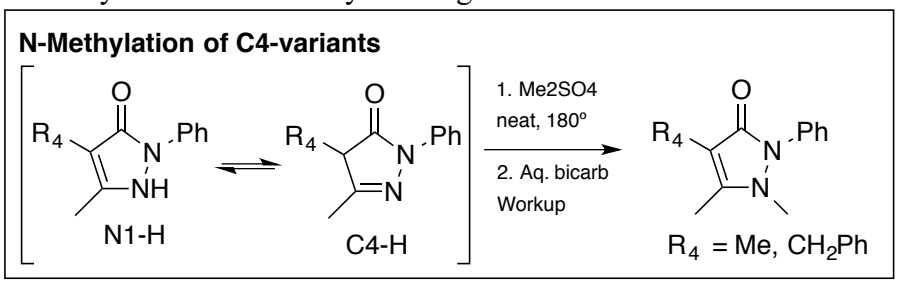
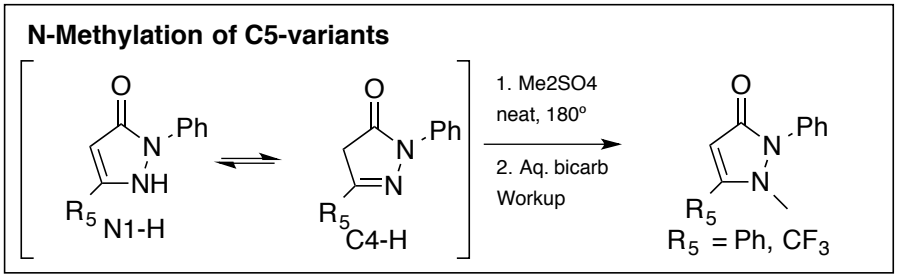
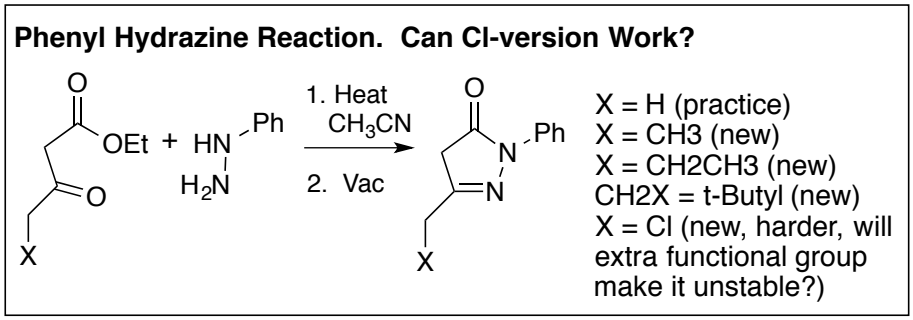
**The other drug: Totally different structure from pirfenidone**



Nintedanib

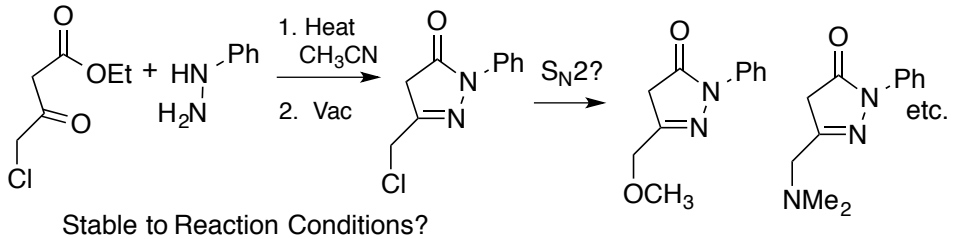
Table of Project Ideas, Fall 2021:

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

| | | |
|---|---|---|
| 1. | N-Methylation of Desmethyl Analogs<br>  <br><br>Can practice using the R4=H variant.<br>How hot do we need?<br>Can we clean up and purify at the end? Via digestion? Combiflash?<br>Have POP (proof-of-principle) precedent that the reaction works. It's the optimization (how long, how hot, what stoichiometry? How to best clean up afterwards?) that's to be processed.<br><br>  <br><br>Very much similar to above project, so same student could potentially attack both. | |
| 2. | **Phenyl Hydrazine addition to KetoEsters to make Des-Methyl Core with C5-Variations**<br>  <br><br>The "X = H" variant has been done and works.<br>The extra methyl and extra ethyl should work too.<br>The t-butyl one, sterics way different, so hard to know…. Maybe fine, maybe less so?<br>The Cl-one, that could be interesting. It might not be stable, too reactive. But *IF* we could make it, we could then substitute for it….<br>Difficulty: Low, other than the chloride version | |

3.

**Phenyl Hydrazine Reaction. Can Cl-version Work?**



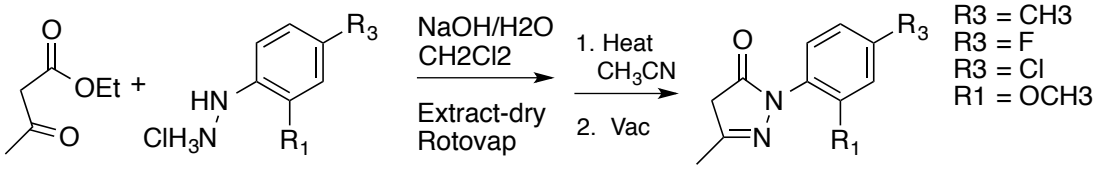

Stable to Reaction Conditions?

The Cl-one, that could be interesting.

- It might not be stable, too reactive.
- Should know within one or two experiments. Either it works, or it doesn't.
- But *IF* we could make it, we could then substitute for it….
- That would basically be an allyic 1º alkyl halide, so SN2 substitution with other things could make new analogs with Oxygen or Nitrogen

4.

**Variation at N2-Aryls By Variation of Aryl Hydrazine. Order. Deprotonate HCl Salt**

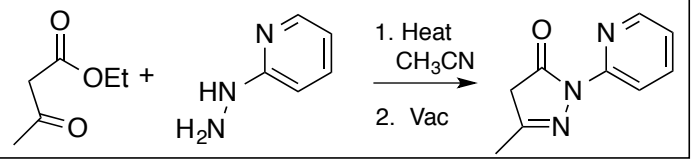



A POP experiment with the toluene version looked promising.

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

5.

**Can 2-Hydrazinopyridinine work?**



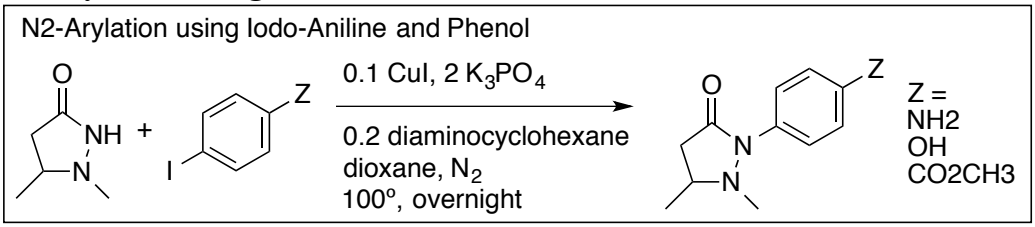

This one, *IF* the pyridine reagent is actually stable and healthy, might be fun.

- Basically replace the antipyrine phenyl with the nitrogenated pyridine instead, with differing solubility and H-bonding capacity.
- The pyridine hydrazine is expensive and may not be super stable. Should be a pretty quick check; either it's good, or it isn't.

**Area B:**

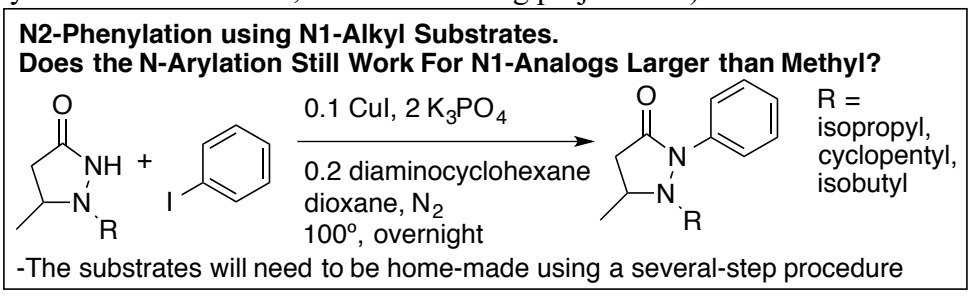
- **N2-Arylation with Functionalized Arenes**
- **N2-Phenylation with Larger-than-methyl R-groups on N1**
- **Preparation of precursors with Larger-than-Methyl-R-groups on N1**
- **Preparation of C5-Ethyl-instead-of-methyl analogs**

6. **N2-Arylation Using some Functionalized Substituents: NH2, OH, CO2CH3**



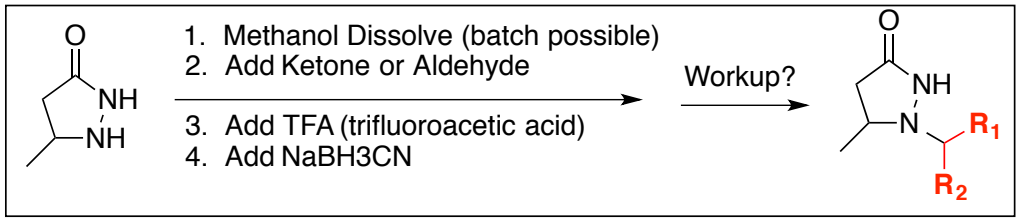

Focus on a couple of challenge ones that were NOT done in student labs…
Practice First on a Sure one (Z = H or CH3)
Then do the ones with the NH2 and CO2CH3 and OH functional groups
The OH one might be tougher; Does the amine base or the phosphate base deprotonate the phenol? Even if it does work, will need to convert to a less-basic extraction workup.

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

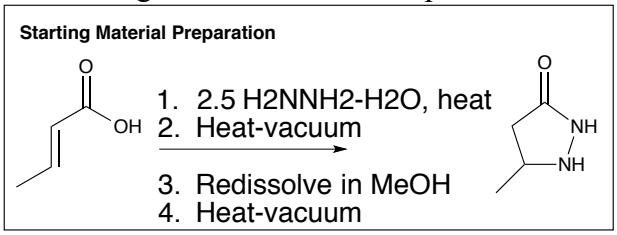



WE know this works awesomely well with the N1-R group = methyl.
But *IF* we size that up, does it still succeed? Or does more steric obstruction make it fail?
I need to check whether we have enough starting material made to test this. It might make better sense to make one of them yourself, see below…

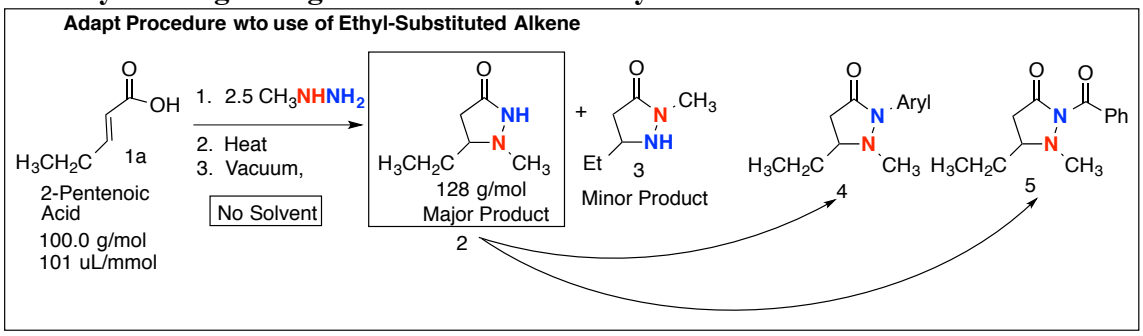
8.




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



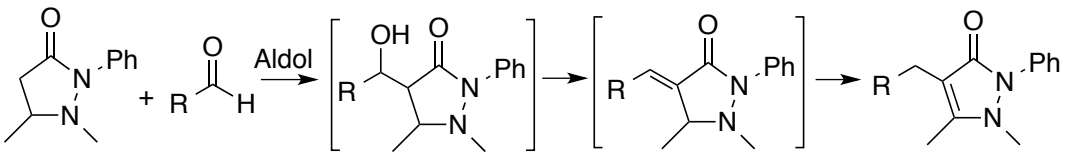
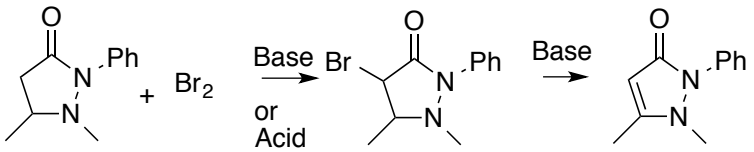
9. **C5-Ethyl Analogs using Pentenoic Acid: N-Arylation**




POP experiment has shown that this works.
The success with the methyl rather than ethyl is well established from spring Chem365 lab
NMR's won't be as clean and simple.
Difficulty: Low

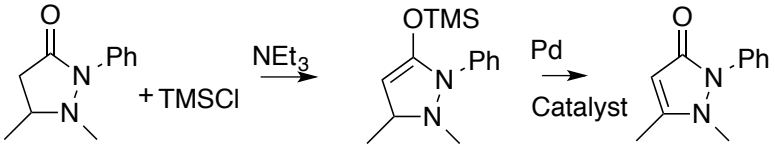
**Area C: Oxidation of product rings to convert to double-bond versions?**

- Context: Antipyrine has a C=C double bond.
- We have some really powerful ways to access a broad scope of the single-bonded analogs (se Area B above, for example).
- It would be nice if we had an efficient way to convert single-bonded pyrazolidinones into double-bonded pyrazolones. And it would be cool if we could test them against each other; does the double bond make any difference anyway in terms of pulmonary-fibrosis performance?
- Area C has some ideas for seeing whether we can convert single-bonded substrates into the double-bonded analogs.

| | | |
|---|---|---|
| 10. | **C4-Alkylation/Oxidation via Aldol Condensation + Alkene Isomerization. Introduction of C4-Substitutents with Otherwise Full-Antipyrine Core**<br>Aldol Condensation + Alkene Isomerization?<br>  <br>This project has NOT been started or have any proof-of-principled.<br>• POP experiments needed. (POP = Proof-of-Principle)<br>• We have an excellent process for preparing the starting material shown, and variants thereof, from last spring's Organic Chem Research Module.<br>• The products of that have single-bond, not double, unlike Antipyrine itself.<br>• The goal here would be to attach something new onto C4, but then to also be able to walk a double-bond into the ring.<br>• Aldol reaction options:<br>o Acid-catalyzed, maybe using EDDA?<br>o Maybe base-catalyzed, using organic lab process? (NaOH/H2O/Ethanol)<br>o Maybe just using NaOMe/MeOH?<br>o Maybe use LDA?<br>-Might want to make a largish stock of the starting material?<br>-Or maybe use a toluyl-version instead of phenyl?<br>-Could it work using just formaldehyde? *IF* a one-pot formaldehyde version worked, then we could make the whole family of Ph-variants. | |
| 11. | Oxidation via Bromination and then Dehydrobromination?<br>  <br>1. No group precedent that we can do this.<br>2. Base options for phase 1: NaOMe, NaOtBu, LDA, NEt3<br>3. Base options for Phase 2: NEt3, (iPr)2NEt, DBU, NaOMe, NaOtBu, LDA, NEt3<br>4. Do it on this one, because the product is antipyrine itself.<br>5. If we can find practical, convenient process, then we could to it on other aryl analogs<br>This project has NOT been started or proof-of-principled.<br>Expected difficulty: High.<br>Expected success rate: Low<br>Impact *if* a good process was developed: High | |

12.

Oxidation via Silyl Ether



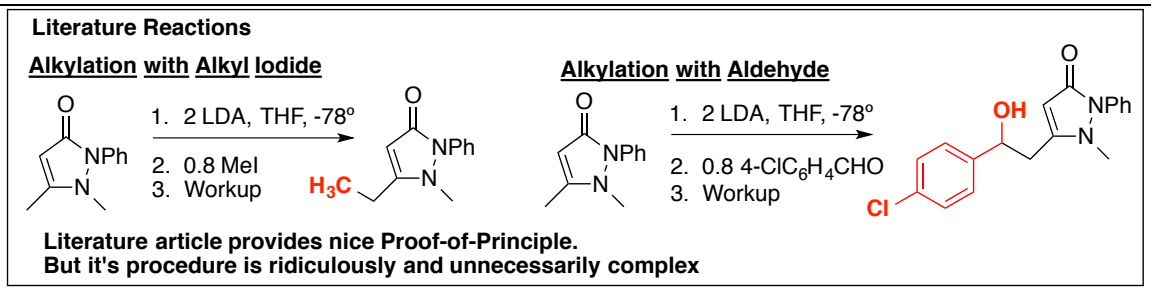

1. No group precedent that we can do this.
4. Do it on this one, because the product is antipyrine itself.
5. If we can find practical, convenient process, then we could to it on other aryl analogs

Saegusa Oxidation
Saegusa-Larock oxidation
Reference: Google Silyl Enol Ethers an Overview
And/or Oxidation Adjacent to C=X Bonds by S. S. Stahl
Pd Catalyst is typically Pd(OAc)2, in combination with O2 or something.
There is some literature for this type of process using ketones. But our molecules have a lot of functional complexity.

**Area D: LDA-based Reactions at C5?**

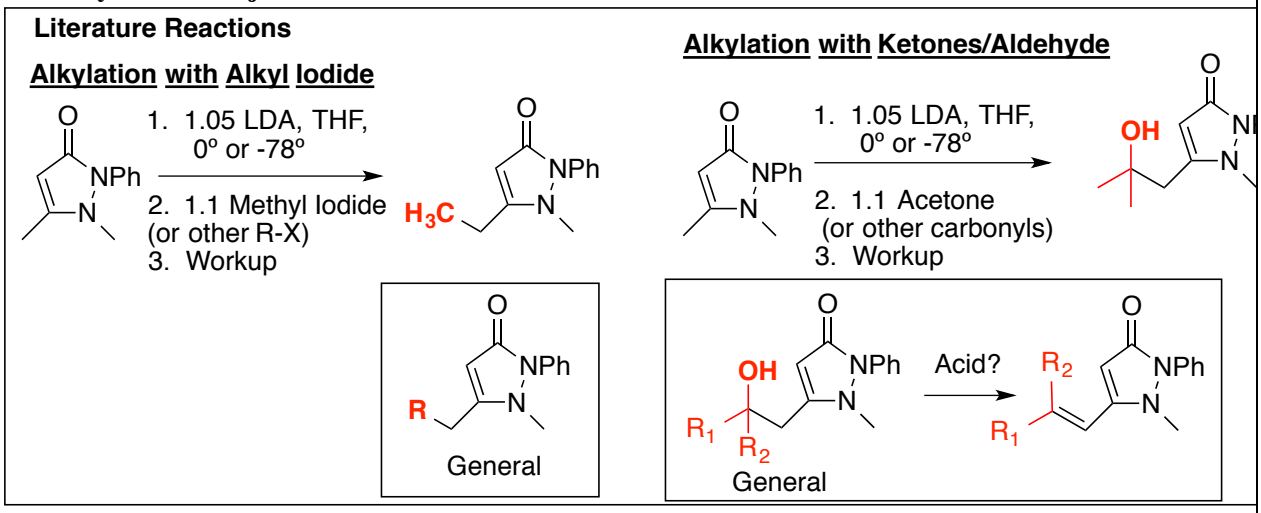
- There are technical challenges with these, because the LDA is very air- and moisture-sensitive.
- I have done POP experiments confirming that this absolutely works.

13.




The description above is in the literature. Their conditions are lousy and not efficient whatsoever! This is just context for project below.

14. **C5-Alkylation Project**

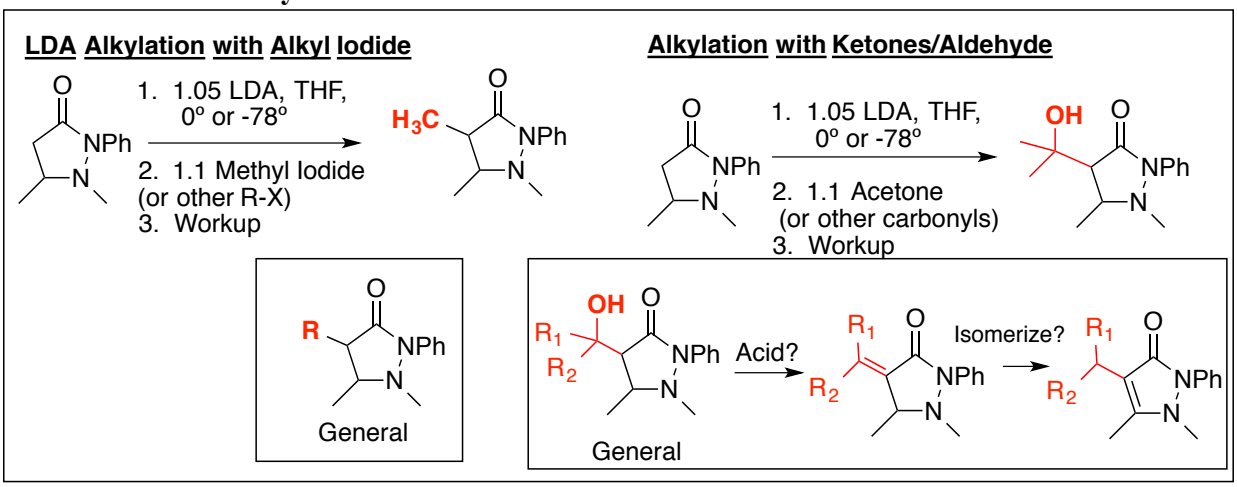



Some questions/notes:

- Jasperse has done POP experments using MeI that work very well.
- It's somewhat technically demanding; need to handle things with care due to air/water sensitivity of the LDA and the anion
- Stoichiometric precision is important. Some inconsistencies resulted from using too much LDA. Don't want that.
- Want electrophile to equal/exceed the amount of LDA. (Some inconsistencies resulted from not doing this….)
- I love this project in part because it has tons of scope, and also because it sources from cheap, accessible antipyrine itself. So, you'll NEVER need to worry about running out of a limitless stock of clean, pure starting material. No hesitation about scaleup or anything, or time spend preparing your starting material. ☺☺
- Some questions include:
- 1. Is -78º important versus just 0ºC? Way easier to get things done and way more time-convenient to just whip them through at 0º!!!
- 2. Works great with iodomethane. Will it work as well for other alkyl iodides?
- 3. Will alkylation with alkyl bromides also work? (one POP experiment suggests yes….)

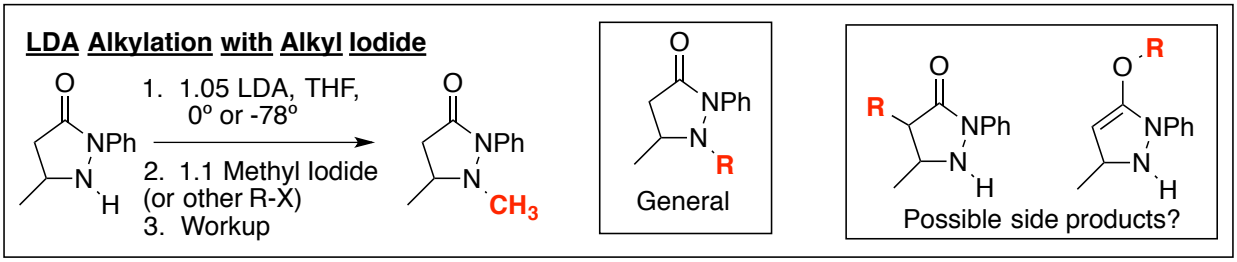
- 4. In POP experiment, product formed in ~90% yield, but there were traces of di-methylated product and starting material accompanying. Can we develop a convenient and practical digestion procedure to purify products?
- 5. Will products be solids or oils?
- 6. Will it work well for carbonyls?
- 7. If so, can we control whether we isolate alcohol versus alkene? (Elimination to the alkene will produce a conjugated alkene, so this might not be difficult.).
- 8. For asymmetric alkenes, will E/Z mixtures result?
- 9. For carbonyls, will the reaction be regiospecific? Exclusively at C5, as opposed to reacting at C4? If not clear, will temperature matter? (0º versus -78º?)
- 10. Use of acyl chlorides, to make ketones?

15. **LDA Process for Alkylation at C4?**




- If we have mastered LDA processes in the above process, it would be fun to apply the same types of procedural skills for alkylating at C4 for single-bonded analogs.
- Having a goodly stock of the starting material prepared would help for this.

16. **N1-Alkylation with LDA**

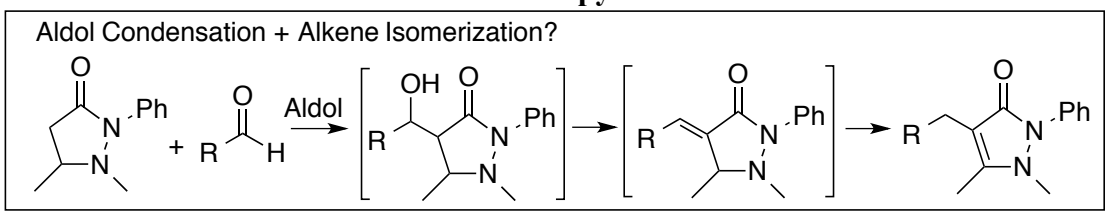



The common theme here is the use of LDA.
No POP experiments have tested this.

- But *IF* somebody gets to be proficient with handling LDA, this would be a nice and easy experiment to attempt.
- *IF* it works, great.
- If it doesn't, we could assess that quickly.
- The question is whether the N1-nitrogen would be ionized and act as the nucleophile, or whether instead the enolate might form leading to either or both of the possible side products displayed?
- Easier to try an experiment or two than to speculate!

**Area E: Alkylation Ideas Miscellaneous**

17. **C4-Alkylation/Oxidation via Aldol Condensation + Alkene Isomerization. Introduction of C4-Substitutents with Otherwise Full-Antipyrine Core**



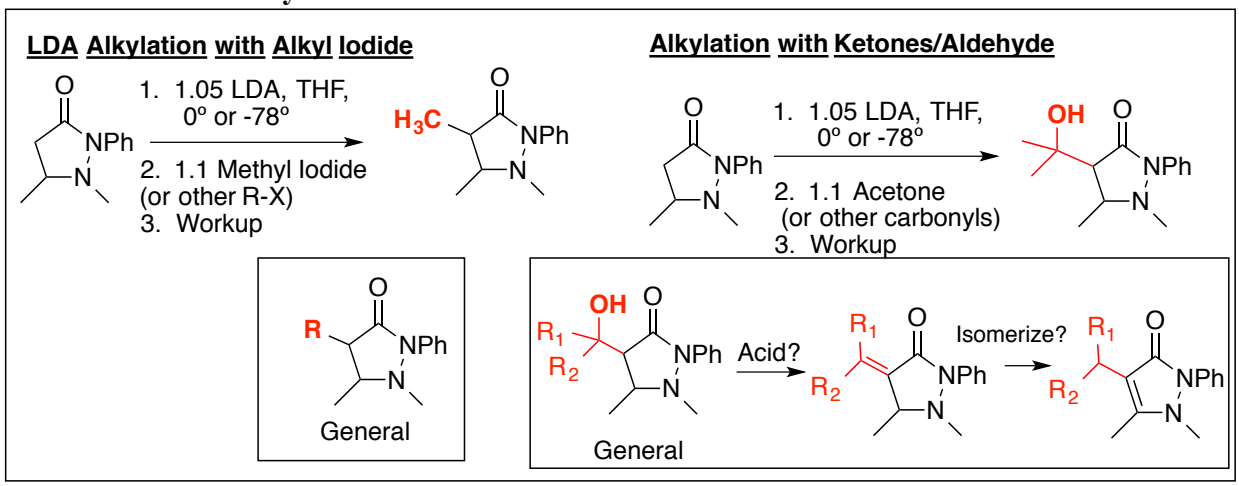

This project has NOT been started or have any proof-of-principled.

- POP experiments needed. (POP = Proof-of-Principle)
- We have an excellent process for preparing the starting material shown, and variants thereof, from last spring's Organic Chem Research Module.
- The products of that have single-bond, not double, unlike Antipyrine itself.
- The goal here would be to attach something new onto C4, but then to also be able to walk a double-bond into the ring.
- Aldol reaction options:
  - Acid-catalyzed, maybe using EDDA?
  - Maybe base-catalyzed, using organic lab process? (NaOH/H2O/Ethanol)
  - Maybe just using NaOMe/MeOH?
  - Maybe use LDA?
  - LDA should surely work; there may be technically easier approaches.

-Might want to make a largish stock of the starting material?
-Or maybe use a toluyl-version instead of phenyl?
-Could it work using just formaldehyde? *IF* a one-pot formaldehyde version worked, then we could make the whole family of Ph-variants.

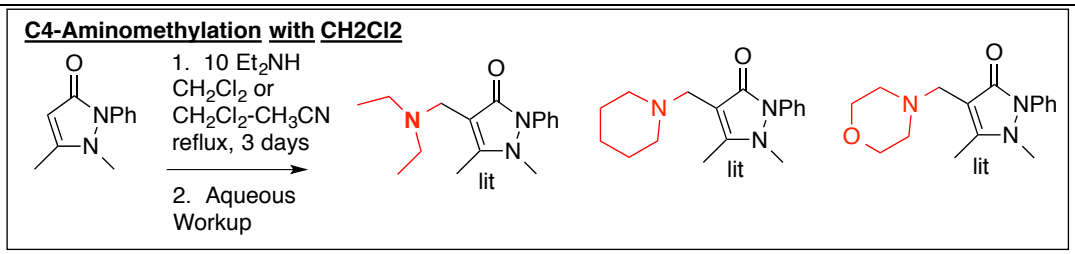
- 

18. **LDA Process for Alkylation at C4?**




- If we have mastered LDA processes in the above process, it would be fun to apply the same types of procedural skills for alkylating at C4 for single-bonded analogs.
- Having a goodly stock of the starting material prepared would help for this.

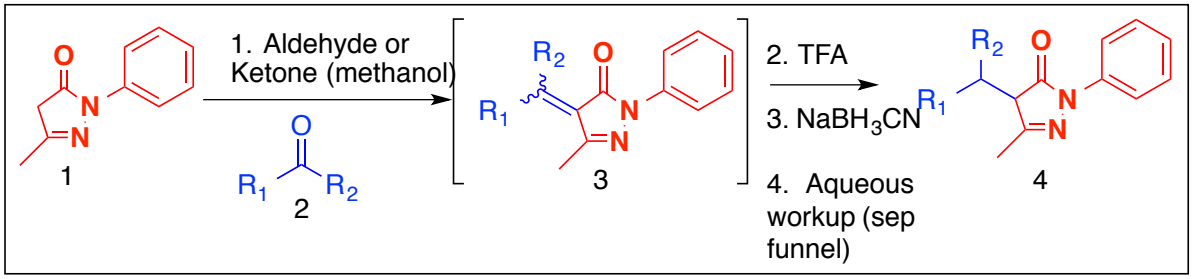
19.




Literature procedure for this.

- A student did a POP experiment that seemed to work, but I don't think she worked it up correctly.
- A really nice thing here is that the starting material is antipyrine, which we can buy in high purity and limitless quantities.
- And the amines and solvent are easy to handle, too.
- So this could assemble some interesting new functionalized products in a quick way.

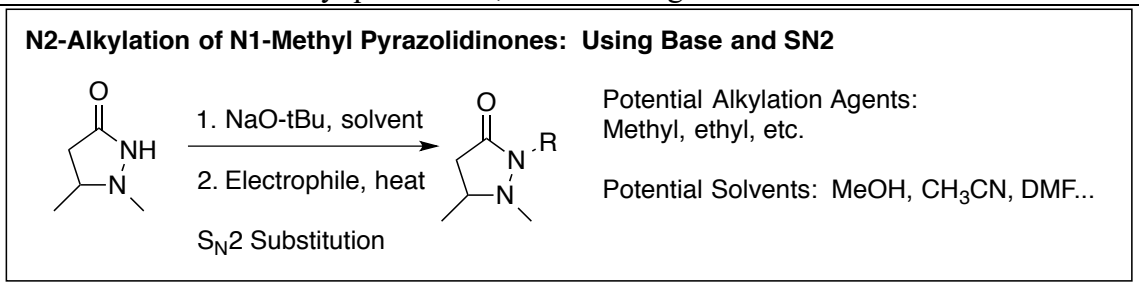
20.




Logan Spooner ?

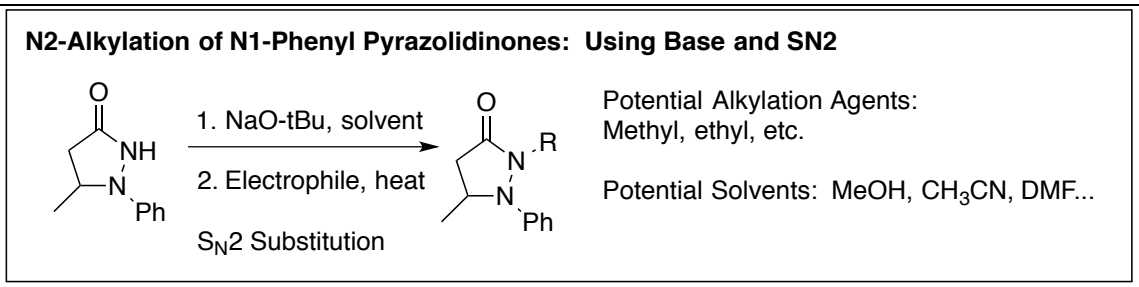
Proof of principle on this has been done.
Yields weren't necessarily quantitative, some starting material recovered.

21.




Craig Try

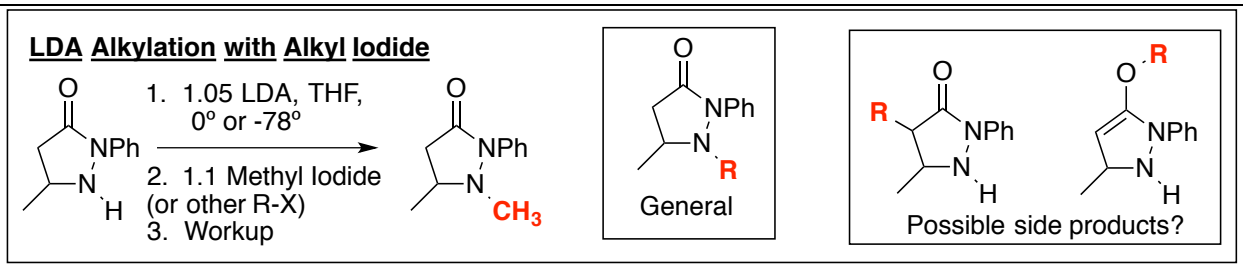
22.




Craig Try to make SM

This would be kind of fun, basically would flip the Ph and the R group relative to what we made in Chem 365 lab.
There is a procedure for making lots of the starting material. Might want to make a batch.
It's a little tricky, so this might be something for Jasperse to execute and try to diagnose as it happens?

23. **N1-Alkylation with LDA**

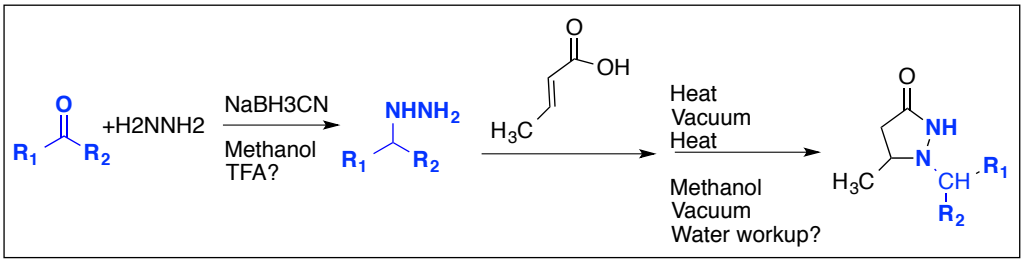



The common theme here is the use of LDA.
No POP experiments have tested this.

- But *IF* somebody gets to be proficient with handling LDA, this would be a nice and easy experiment to attempt.
- *IF* it works, great.
- If it doesn't, we could assess that quickly.
- The question is whether the N1-nitrogen would be ionized and act as the nucleophile, or whether instead the enolate might form leading to either or both of the possible side products displayed?

Easier to try an experiment or two than to speculate!

24.



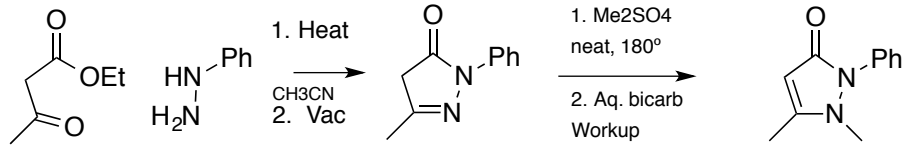

Is it work testing?
Might it work with NaBH4 instead of the cyanoborohydride?

Craig Try POP on this

**Variation at N1-Aryl group. Full Dihydro (double bonded) analogs?**
**N2-Aryl Ring Variation, Pyrazolones. Using alternate Arylhydrazines.**

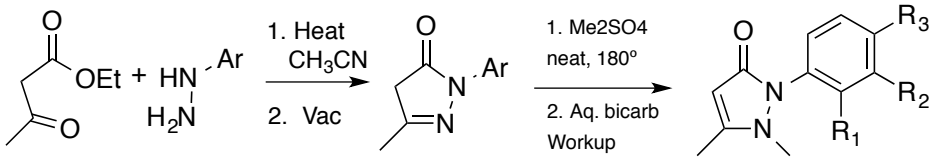
**Demonstrated POP reaction:**

**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 (5g, 109.1) (stability??) | Sigma/Aldrich: $86/5, $292/25 |
| o-Tol | 635-26-7 | o-Tolylhydrazine hydrochloride (5g), 158.6 | Sigma/Aldrich: $39/5 |
| p-Cl | 1073-70-7 | 4-Chlorophenylhydrazine hydrochloride (5g), 170.05 | Sigma/Aldrich: $29/5, $97/25 |
| 2-MeO | 6971-45-5 | 2-Methoxyphenylhydrazine hydrochloride (5g), 174.63 | |
| p-Tol | 637-60-5 | 4-Methylphenyl hydrazine hydrochloride | VWR-AA, $35.59/5g |
| p-F | 823-85-8 | 4-Fluorophenylhydrazine hydrochloride | Sigma/Aldrich: $67/10, |
| p-CN | 2863-98-1 | 4-Cyanophenylhydrazine hydrochloride | Sigma/Aldrich: $57/5 |
| m-Cl | 2312-23-4 | 3-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $97/25 |
| o-Cl | 41052-75-9 | 2-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $80/25 |
| 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) |

Keto-Esters, for reaction with Phenylhydrazine:

Some other accessible C5 variants: The following search will fine lots.
https://www.alfa.com/en/search/?q=acetoacetate

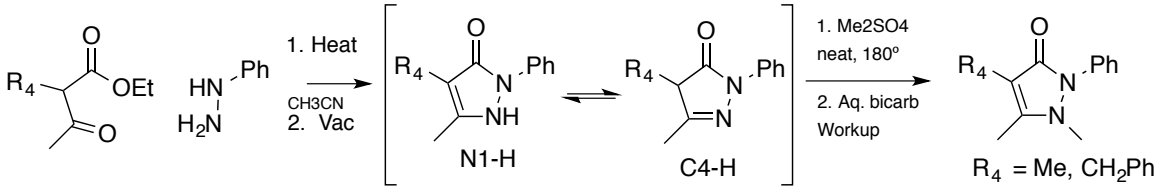
| Ethyl 2-X-acetoacetate | | |
|---|---|---|
| 2-Me | | $38 – 25g |
| 2-benzyl | | |
| 2-Chloro Ethyl 2-chloroacetoacetate, 96% | 609-15-4 | $30 – 100g |
| 2-ethyl | | $90 – 25g |
| 2-n-butyl | | $46 – 5g |
| 2-CN | | $50 – 2g |
| 2-Ph Ethyl 2-phenylacetoacetate, 97% | | |
| Ethyl 2-X-acetoacetate | | |
| 4,4,4-Trifluoro | 372-31-6 | $35 – 10g |
| 4-Chloro | 638-07-3 | $35 – 50g |

## Phenylhydrazine Addition to Keto-Esters.

- Difficulty estimate: Low
- Discovery level: Modest. POP discovered previously.
- Odds it will work: High. POP proof.
- Odds for some pretty quick success results: Good
- Operational difficulty: Low for ring formation.
- Access for time-controlled lab blocks: Low. Experiments probably take long blocks of time.?
- I think we've got a modest stock of the starting material

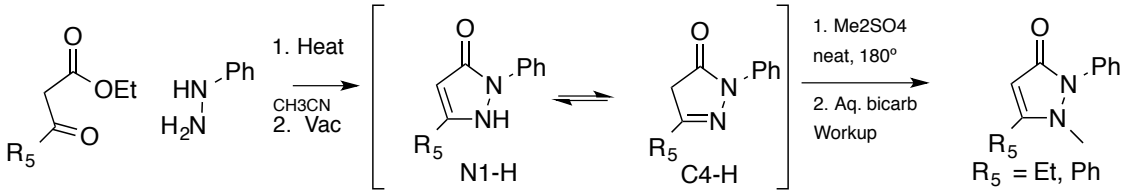
| | |
|---|---|
| Ethyl benzoylacetate, 50grams | PhCOCH2CO2Et |
| Ethyl propionylacetate, 5grams | CH3CH2COCH2CO2Et |
| Ethyl 2-benzylacetoacetate, 25grams | CH3COCH(CH2Ph)CO2Et |
| Ethyl 2-methylacetoacetate, 25grams | CH3COCH(CH3)CO2Et |

**Scheme 1: Variataion at C4:**




**Update: Taysir. Proof of Principle,, but very small scale**

**Scheme 2: Variataion at C5:**




**Update: Works. Taysir. Proof of Principle, but very small scale.**

POP experiments have already been executed, successful, but small scale.
Could scale up and batch-size a series of these.

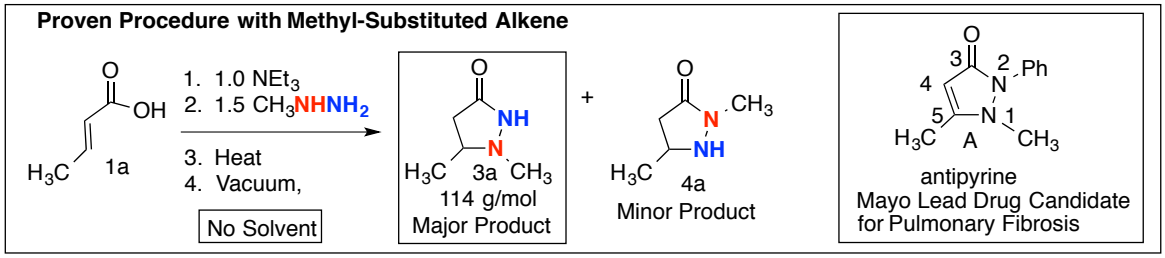
A variation: Could try ethyl tosylate instead of methyl tosylate for one of them. Can we make the N1-ethyl analogs, too?

I like this project. It will work, we just need somebody to get after it.

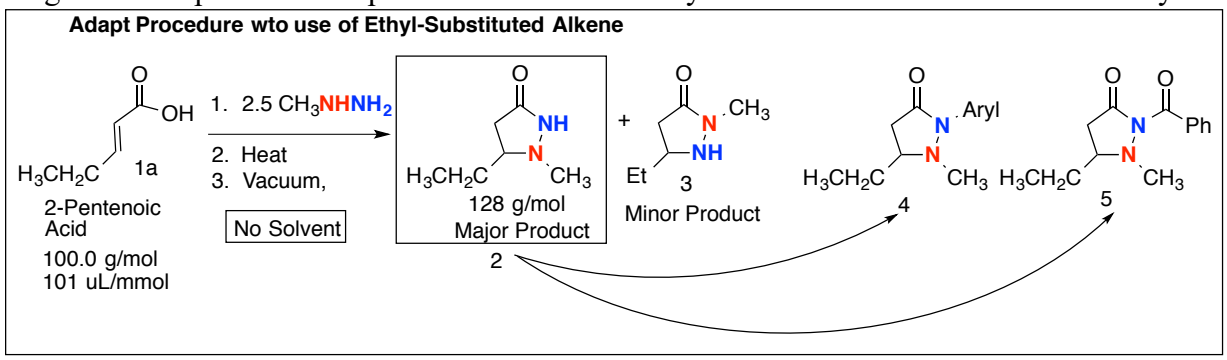
## 2-Pentenoic Acid project. C5-ethyl to replace 5-methyl

- Difficulty estimate: Low
- Odds for some successful results: High
- Odds for some pretty quick success results: Decent
- Access for time-controlled lab blocks: Uncertain, maybe good?

Proven procedure using methyl-substituted Reactant




Target: to Adapt the Above procedure to Use the Ethyl-substited alkene to make the 5-ethyl analog.




Some of the practical questions, and notes:

- Will the procedure that was developed for the methyl alkene ("crotonic acid"), translate to the ethyl alkene ("pentenoic acid")?
- Might be more steric hindrance, so higher temps or longer times may be required?
- May need to be tested and optimized.
- Will the major/minor product ratio be compromised, sterics? With crotonic, was ~8-10:1.
- Can triethylamine usage work with pentenoic, the way it did with crotonic?
- Note: NMR will be more complex. The C5-methyl in the crotonic acid product gives a nice doublet. The ethyl group will be considerably more complex.
- GC-MS should provide a measure of the major product 2, relative to the minor product 3.
- NMR may also do that, *if* the N-methyl singlets stand out from other signals.
- Will the product be water soluble, or can we do organic-water separatory-funnel treatment?

Approach:

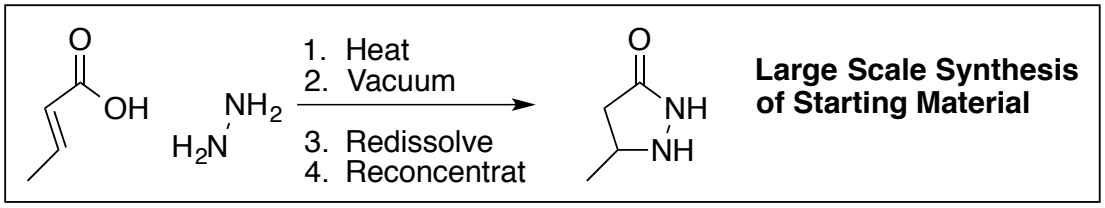
- Do small-scale experiment to develop successful conditions, (and do control with crotonic)
- Then would like to do a large-scale, and make a biggish batch of the 5-ethyl product 2.

Application:

- Try Logan's procedure for N-arylation to produce N-aryl product **4.**
- This can be Mayo-tested against the C5-methyl analog (ethyl vs methyl); and against antipyrine itself (is the C4=C5 double bond important?
- Try organic-lab procedure for N-acylation to product N-acyl products 5.
- This can be tested against N-methyl analogs.

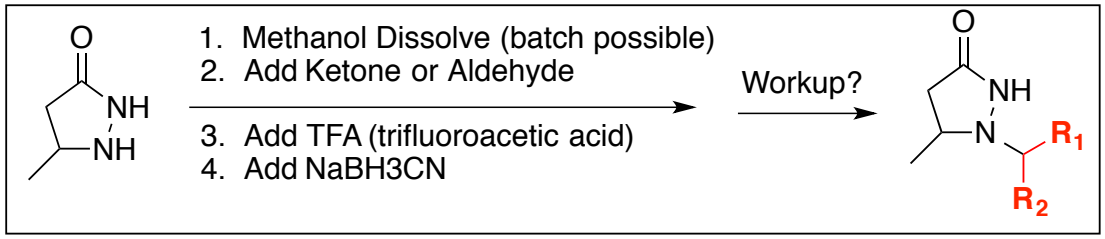
## N1-Alkylation via Reductive Alkylation

- Difficulty estimate: Low
- Discovery level: High.
- Odds it will work: High.
- Odds for some pretty quick success results: High
- Operational difficulty: Low.
- Access for time-controlled lab blocks: High. Experiments probably short.
- I think we've got a modest stock of the starting material? Purity of Starting material is important.



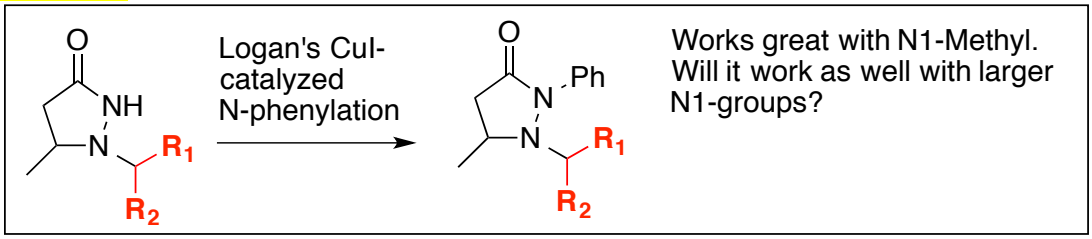

Making a good-sized batch of the starting material is key.
Can we actually try to distill it? It's an oil, not super big, so could perhaps be distilled?

Reactions, IF we had starting material in quality batch:




- No POP on this substrate.
- But reaction seemed to work very well on the C5-phenyl analog, although never totally confirmed.
- We have a broad access of different ketones, from smaller to larger; alkyl; aryl; cyclic.
- Could make a broad family.
- Can batch these: Make a solution of the substrate, then dose it out with a syringe, then measure carefully the specific ketone.
- None of these molecules has been made.
- For analog, see Jasperse 2018-172 or 272…

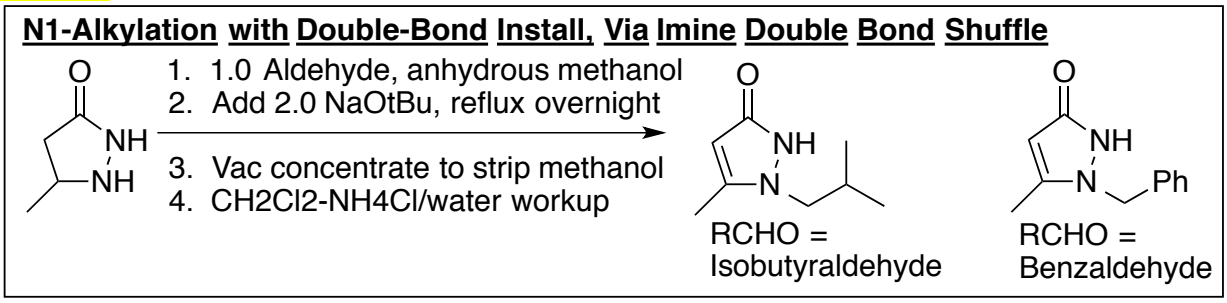
Followup:



## N1-Alkylation via Imine-Isomerization

- Difficulty estimate: High
- Discovery level: High.
- Odds it will work: Low.
- Odds for some pretty quick success results: Low
- Operational difficulty: High.
- Access for time-controlled lab blocks: Low, Overnight heatings required.
- I think we've got a modest stock of the starting material? Purity of Starting material is important.

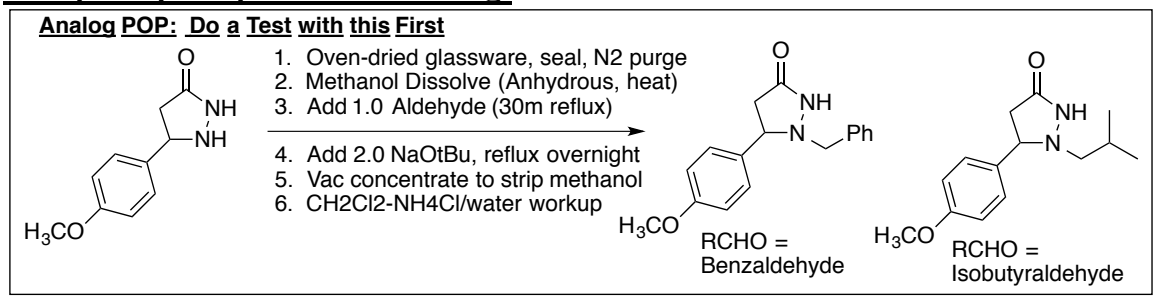
## Concept




Install N1-substituents while also installing double bond.

1. POP has worked for the C5 = aryl, but not the C5-methyl. It might make a world of difference (conjugation versus not).
2. This will probably take a couple of tests to prove either way.
    a. Prove effectiveness on aryl substituent, using isobutyraldehyde.
    b. Then carefully apply it to methyl substrate, and see if it works or fails.
3. *IF* it works, then we can optimize conditions, and generalize.
    a. If it works on non-conjugated iPr aldehyde, will it work on conjugated Ph aldehyde?
    b. Will it work on ketones?
    c. Taysir did strong conditions to give every chance for success; do we need the steps and the time and the temp? Or can we compress the process?
    d. Oil or crystal?
4. *IF* it worked, followup Q: can we N2-phenylate, using Brent/Logan's CuI procedure?
5. -Notebooks: Jasperse, 2019-2020 book, p 170-171
6. -Taysir Bader book, p49-75

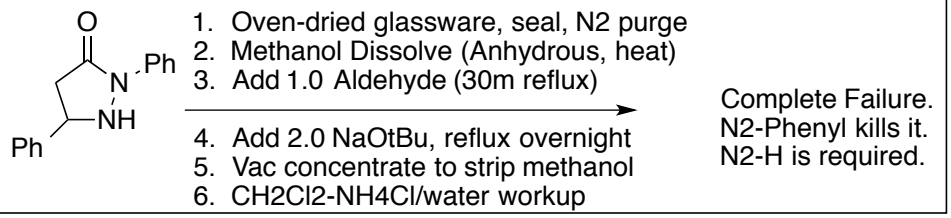
## POP principle experiment on analog:




-worked great on BOTH aromatic aldehyde (benzaldehyde) AND isobutyralided
-Fairly careful conditions were used; no actual tests were done on whether the times used were needed.
-Notebooks: Jasperse, 2019-2020 book, p 170-171
-Taysir Bader book, p49-75

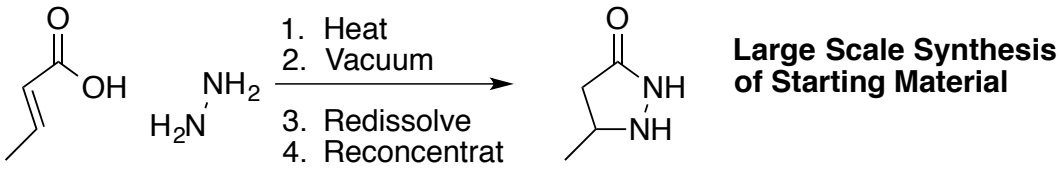
**Definite Fail:**

**Definite Fail with N2-Phenyl**




-Taysir used his aleady optimized conditions with the N-phenyl case. Total bust. The N2-H is essential, don't give any more thought to trying to use pre-alkylated stuff.

**Starting Material Prep (may have adequate stuff around)**

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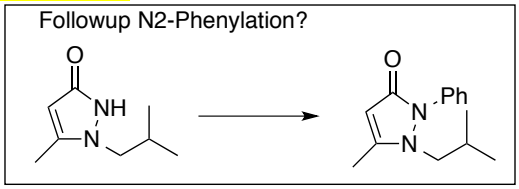
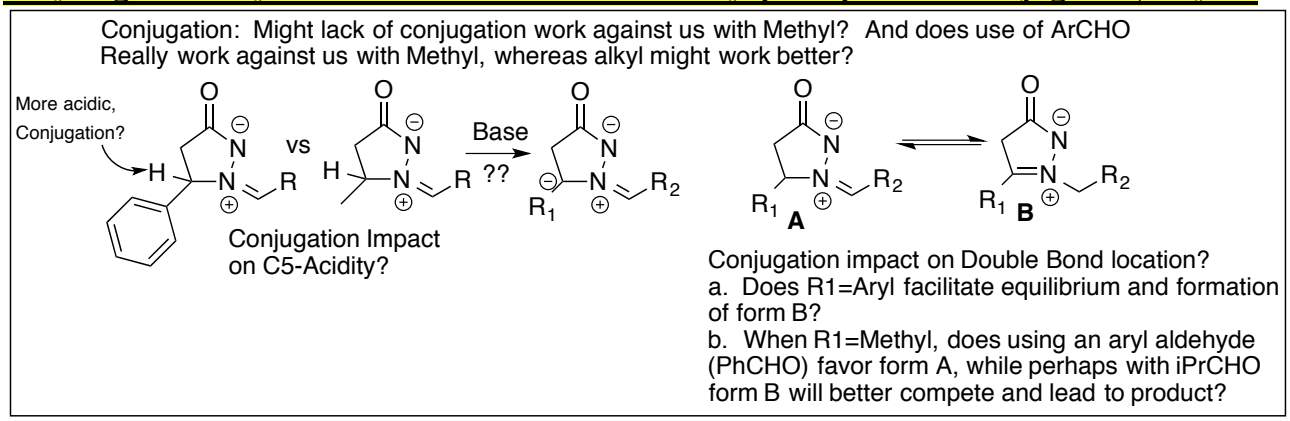
Can we actually try to distill it? It's an oil, not super big, so could perhaps be distilled?

Followup:




**Why might the Aryl POP have Worked but the Methyl perhaps Fail? Conjugation, maybe?**

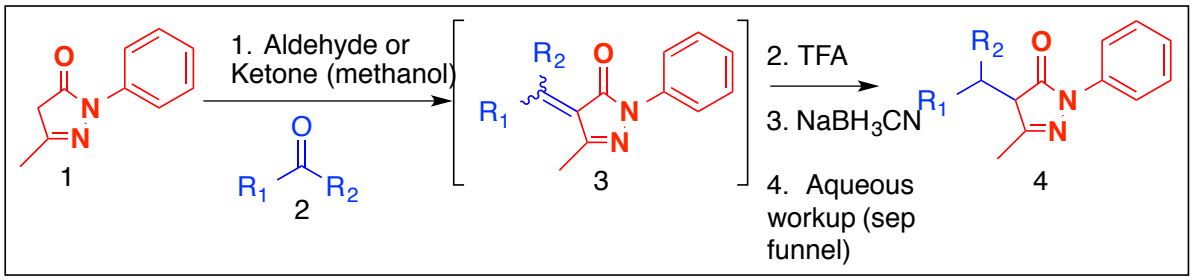



- Practical; Check methyl case with iPrCHO, not just PhCHO.
- It might work better with alkyl (no conjugation) than aryl.
- But *IF* the C5-aryl works, but the C5-methyl doesn't, probably the conjugation factor would have to be the reason.
- Hopefully that's not necessary.
- Note: In Taysir's POP work, he started with methyl (not very clean); he didn't have optimized conditions; and he only tested with PhCHO; and he didn't use dry, anhydrous methanol at first. And, I'm not sure whether it really worked or failed. So, even if it didn't work great, perhaps with optimized, anhydrous conditions, AND with two equivalents of base, AND with alkyl aldehyde, success will come for the C5-methyls, too!

**C4-Alkylation via Aldehyde or Ketone, followed by NaBH3CN (Abby POP)**

Difficulty estimate: Modest
Odds for some successful results: Good
Odds for some pretty quick success results: Good
Access for time-controlled lab blocks: good

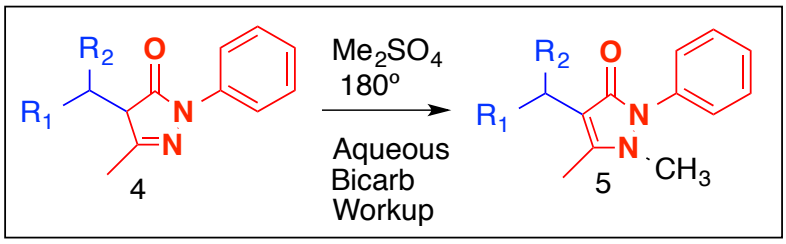
This sequence would provide a versatile way to have 4-alkyl variations relative to Antipyrine.



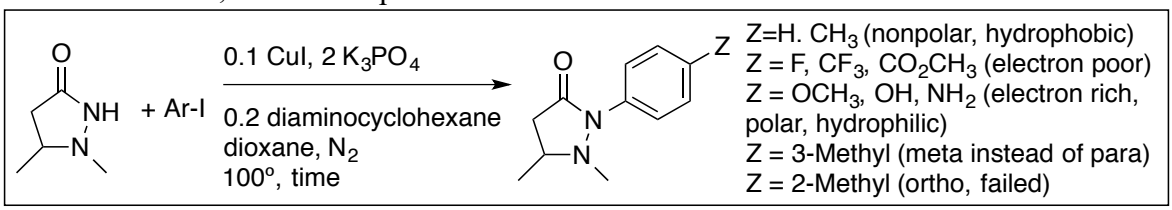

- Abby did some preliminary POP experiments on this.
- I believe it worked on both aldehyde and some simple ketones; failed for larger aryl ketone.
- At the moment trying to access the procedural details. Need to dig up the procedure.
- This sequence would provide a versatile way to have 4-alkyl variations relative to Antipyrine.

Notes:

1. Have a reasonable stock of starting solid 1.
    - More can be remade if needed.
2. This would involve a several-step but one-pot reaction. Or, maybe everything can all be thrown in right at the beginning, and equilibrium process will make everything work?
3. Could be executed in one lab period.
4. Workup could perhaps be saved for later.
5. Could be working batch? (Several at a time?).
6. Or, could be working where one day you're reacting a new one; during the stir-times you'd be working up and analyzing the one you'd run the previous lab period?
7. Would like to develop procedure on modest scale.
8. But would then like to do scaleup to make batch sizes.
9. Would like enough scale to take some of product 4 on toward N1-methyl products 5?
10. We need to get procedure and review from Abby, so as to best know where to start.
11. Unclear on need or procedure for purification. (Acceptable as is? Crystalline, so recrystallizable? Oil, so perhaps need chromatographic cleanup? Is there a quick-run chromatography to clean it up?)
12. Not sure what side products might perhaps form. RCH(OCH3)2 acetal, maybe?
13. Shown below is a potential alkylation procedure.



Copper(I) Iodide catalyzed arylation of 1,5-dimethylpyrazolidione using Aryl Iodides only. Logan S project: Want to continue, and scale-up and isolate?



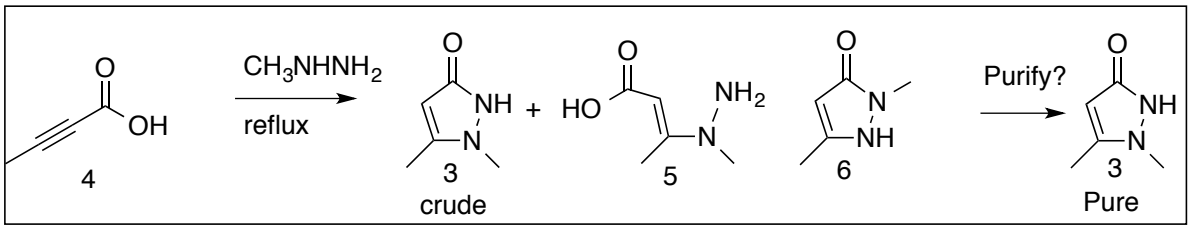

Logan S has worked through these POP-wise.
The procedure works **really** well for a wide variety of aryls.

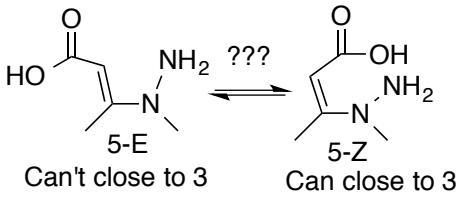
- However, scaleup and isolation was very limited.
- Logan, are you interested in reproducing process, scaling up, and isolating the products?

**Butynoic Acid Project: Possible Quick Access to 1,5-Dimethyl Pyrazole?**

- Difficulty estimate: Low
- Odds it will work: Iffy, but easy enough to check
- Odds for some pretty quick success results: Decent, but kinda yes-or-no
- Access for time-controlled lab blocks: Uncertain, maybe good?

Butynoic acid: kind of expensive, cheapest listing is $65/5g. (Through VWR). Most others are more expensive, Sigma, Alfa…: https://us.vwr.com/store/product?keyword=590-93-2&sortOrder=6

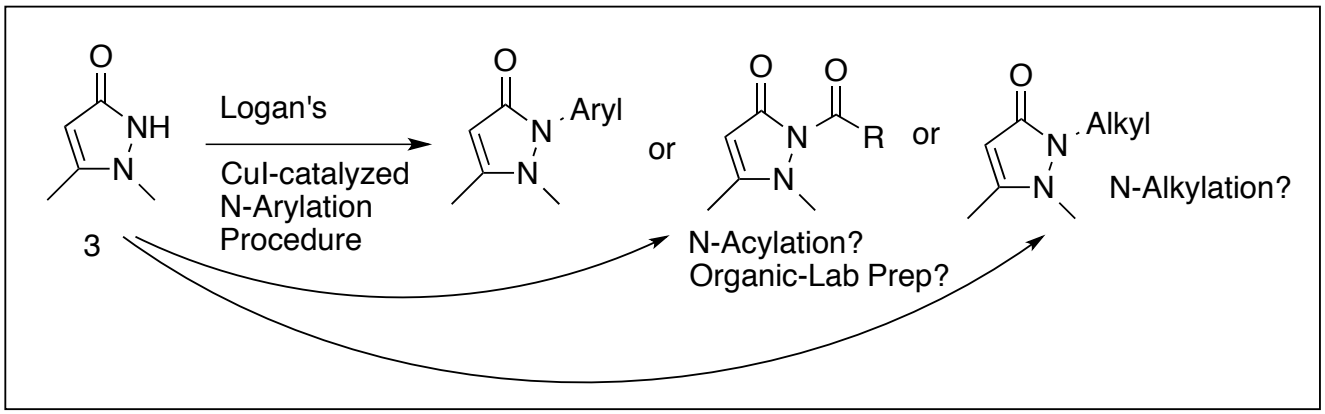



Questions:
1. Will the addition be as regiospecific as with the alkene?
2. Will the addition be E/Z stereospecific for or against us?
3. Under reaction conditions can the E/Z mixture isomerize, so that LeChatelier can allow irreversible closure, even if the kinetic E/Z mixture isn't in our favor?

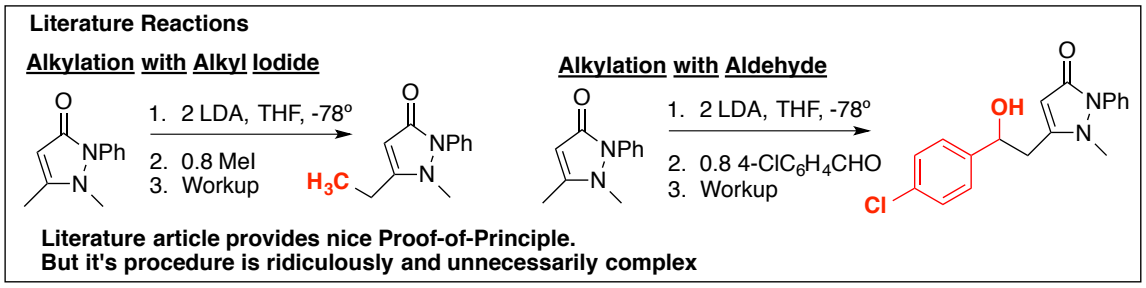
Notes:

1. WE know we can add methylhydrazine across crotonic acid (basically that's 4 but with a double instead of triple bond) with useful regioselectivity. (Meaning the methyl ends on N1 instead of N2). Will it work equally well and selectively on the alkyne?
2. Following addition to the alkyne, an alkene will be created. (See 5E and 5Z). The Z isomer can ring-close; the E one can't. So, when we add:
    a. Will our Z/E ratio be good enough to allow a good yield of 3?
    b. Or, can E/Z isomerize under the hot conditions, so that E/Z are in equilibrium and we can get good yield of 3 by LeChatelier's principle?
3. **IF** things work, it would be a nice one-step prep. If purification works, it's worth the money.
4. But, the starting alkyne 4 is not cheap. I found one list price at $65/5 grams, that's not terrible. But most suppliers charge lots more than that. (mw=84, so that's about 59 mmol.
5. Probably a pretty quick try-it-and-see experiment. If it works, awesome. If it doesn't, we'll be able to see within a couple of experiments.
6. **If it work, some followup derivatization questions. But we'd need to be able build a batch of 3 to have something to work with.**

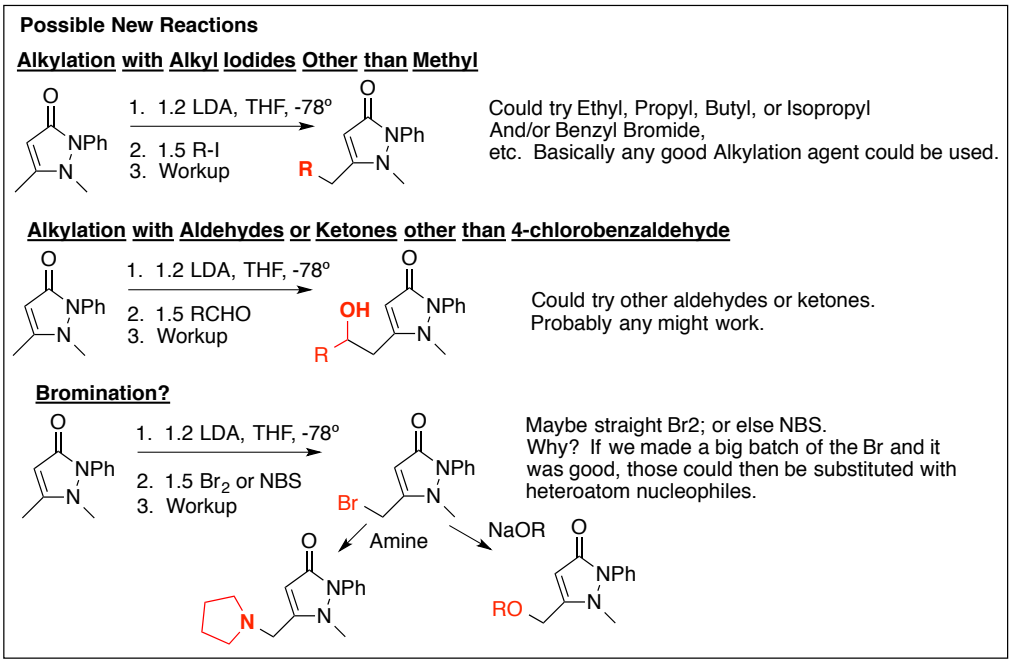


**C5-Alkylation, Using LDA and Anhydrous THF, Low Temp: Preliminary Attempts Confirm that this Can Work, at least for Methylation. Technically non-trivial. High Impact.**

- Difficulty estimate: Kinda demanding technically
- Odds for successful results: Excellent
- Odds for some pretty quick success results: Good
- Room for discovery and high impact: High
- Time management: Not super long time blocks required.




- 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!
- Article procedure is very poor.
- Preliminary POP experiments show that we can simplify.
- Some of the procedural mechanics require some level of physical strength and manual/mechanical dexterity.




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.

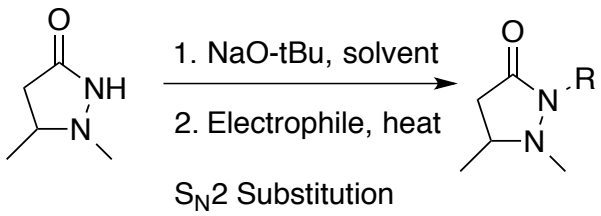
Reddy, K. R.; Roy, A.; Ila, H.; Juqjappa, H. *Tetrahedron*, 51, 40, p10941-10952, 1995. Regiospecific Generation and Application of 3-Lithiomethyl-2-methyl-1-phenylpyrazolinone as 1 ,3-Binucleophile in Aromatic Anuelation: A Novel Approach for Synthesis of 1,2-Disubstituted Indazolones and their Condensed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

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

**N2-Alkylation of N1-Methyl substrate. Analogs**

- Difficulty estimate: Low
- Discovery level: High
- Odds it will work: Pretty good for simple 1º electrophiles, unknown for 2º ones?
- Odds for some pretty quick success results: Good
- Access for time-controlled lab blocks: Excellent?
- I think we've got a good stock of the starting material

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




Potential Alkylation Agents:
Methyl, ethyl, etc.

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

Would ideally like this to work for not only 1º but also 2º substrates, including ideally cyclohexyl.

Expected best guess would be simplest: NaOtBu or NaOMe in methanol

- An alternative might be to use LDA in either THF or in methanol.

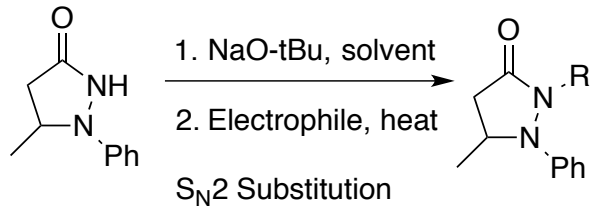
Possible side-products:

- O-Alkylation?
- Double alkylation? ($2^{nd}$ either on C4, or else on N1?).

**N2-Alkylation of N1-Phenyl substrate. "Phenyl Flip" Analogs**

- Difficulty estimate: Low
- Odds it will work: Good for simple 1° electrophiles, doubtful for 2° ones
- Odds for some pretty quick success results: Decent, but kinda yes-or-no
- Access for time-controlled lab blocks: Reasonable?
- Challenge: Not sure how much of the starting material is available.
- May need to try to synthesize the starting material, or have me take a day to try.

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

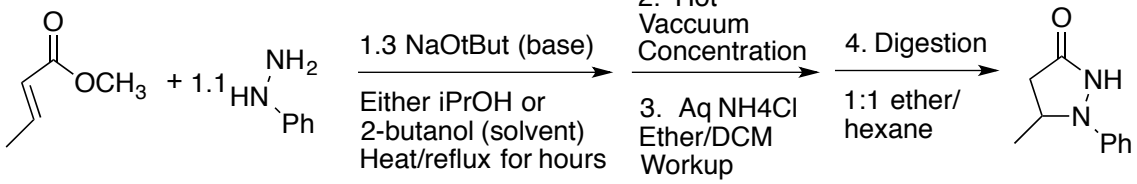



Potential Alkylation Agents:
Methyl, ethyl, etc.

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

Synthesis of the starting material: (This worked well in past for Hawau, but not so well when a student tried to reproduce it. Maybe a reaction I should try myself to see if it's reproducible, or if perhaps there is something wrong with the base or the solvent that prevents success?).
-Would want a good stock of SM for the above project.

**Starting Material Prep**

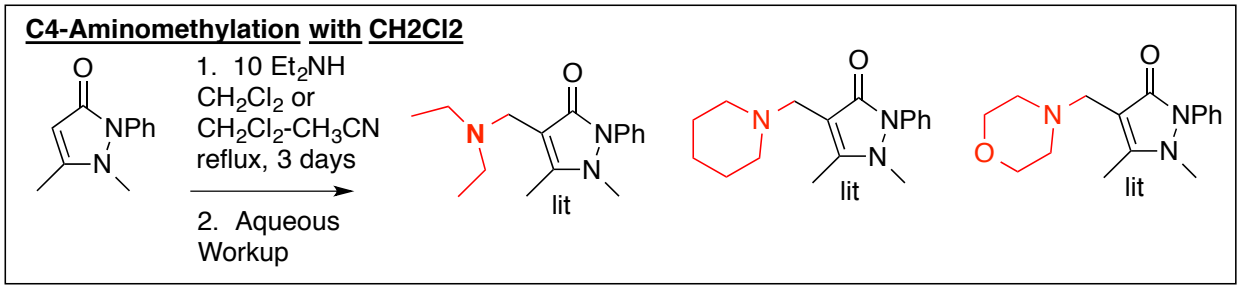



See Jasperse notebook, 2018, p267-273

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

Difficulty estimate: Modest
Odds for some successful results: Good
Odds for some pretty quick success results: Good

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?

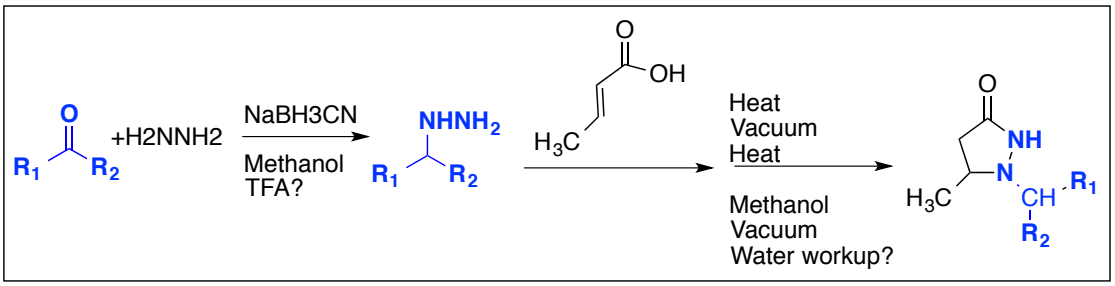
Chemicals and supplies:
We have antipyrine. And the solvents.
We have diethylamine
I have ordered piperidine (6-ring amine) and morpholine (6-ring amine with oxygen)
We have pyrrolidine (5-ring amine).

Notes from source paper:

1. Not sure they optimized the time at all. They said 3 days, but not sure needed.
2. Would be nice to monitor by NMR sample-checks periodically to get a feel for how long it actually takes?
3. NMR in-situ tests can work. Will need to do vertical-expansion, given the large excess of the amines.
4. Theirs suggested maybe better/cleaner/faster with acetonitrile solvent added, for other analogs. Worth testing for ours?
5. Workup: Water washes will be the key. That will take out the ammonium chloride side product, and each of these smallish amines are pretty soluble in water. So getting crude product shouldn't be too complicated.
6. Not sure whether further cleanup will be required? Recryst? Chromatography? I think the paper has suggestions.
7. Not sure whether 1° might also possibly work, even if the paper didn't show any such?

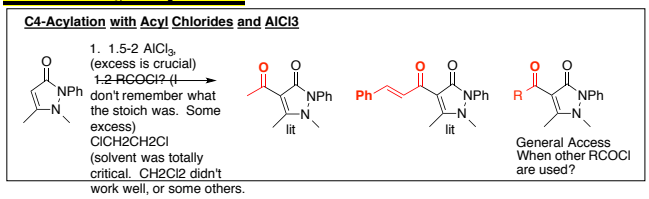
**In-Situ Hydrazine formation and one-pot N1-Alkyl product.**

- Difficulty estimate: Very high
- Discovery level: Super high.
- Odds it will work: Modest.
- Odds for some pretty quick success results: Modest
- Operational difficulty: Low.
- Access for time-controlled lab blocks: High. Experiments probably short.
- Really a remote kind of longish shot. But *IF* it actually works kinda decent, it would really be a convenient quick-stop way to make N1-variants from el-cheapo reactants.




**Craig Q's:**
**Would residual NaBH3CN mess up addition-cyclization? Or harmless?**
**Would we be able to wash the product, and clean it up?**
**Even if yield was modest, IF the product could be reasonably clean, it could be really nice.**

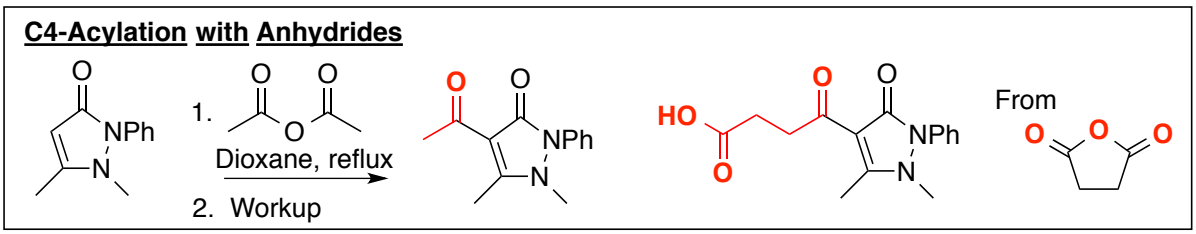
## C4-Acylation with Acyl Chlorides Abby. Solved? See Fall 2019 notebook Jasperse and Abby andAbby reports.




## 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

**C4-Acylation with Anhydrides. Logan Attempted. Did NOT Succeed. Fall 2019**




This did NOT work. No value, given the clean and practice success of the chloride way.

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.

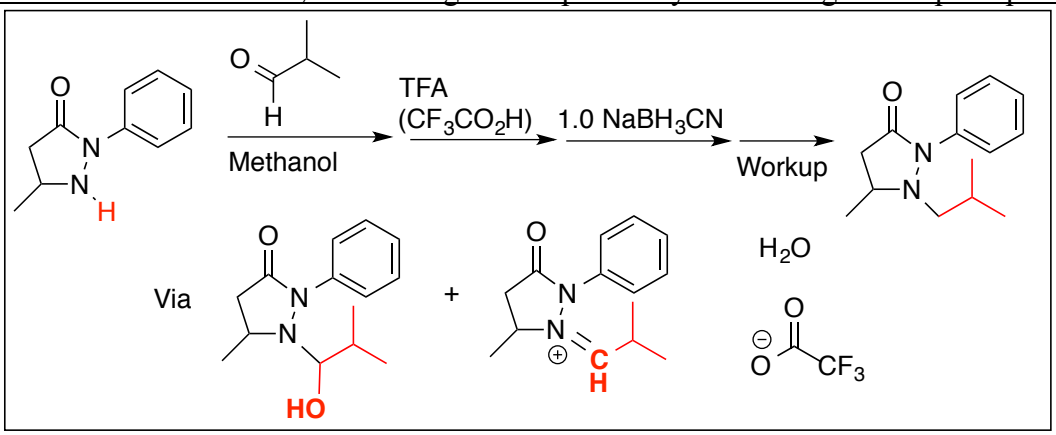
The following had no scifinder synthesis detailed. But it looks like antipyrine and maleic anhydride adduct….

Brent Schulte Research Project Plan Draft 2. Fall 2019

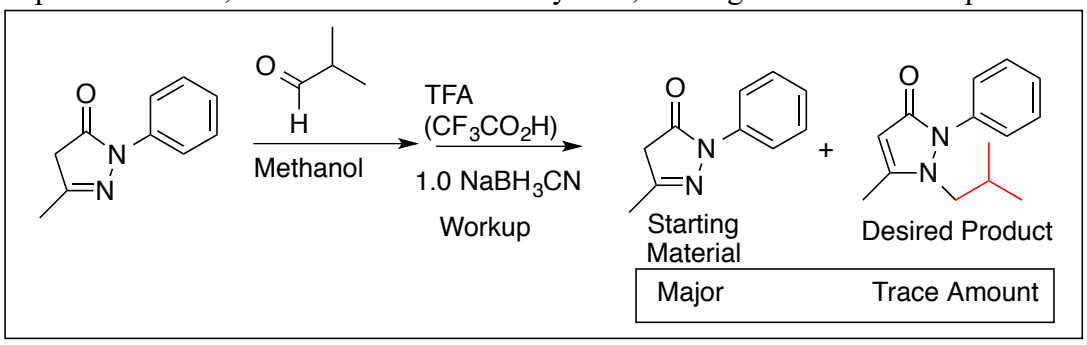
2019 Updates, Projects:

**"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?

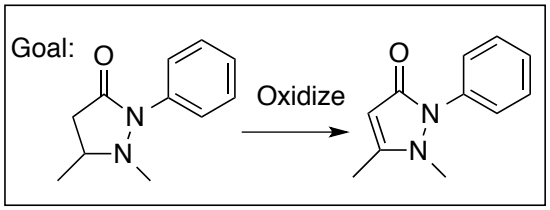
Maybe also try

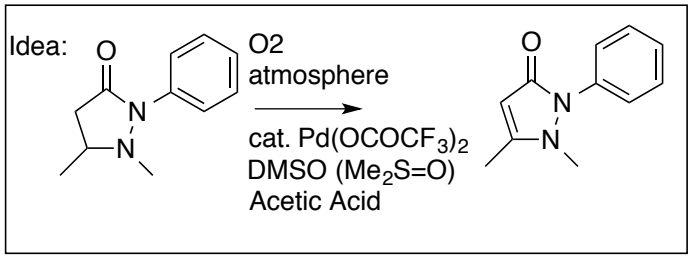
Also try: NaBH3CN on Jasperse substrate using acetic acid (CH3CO2H) instead of TFA (CF3CO2H). Maybe the borohydride will hold up better and accomplish more desirable stuff under milder conditions?

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.

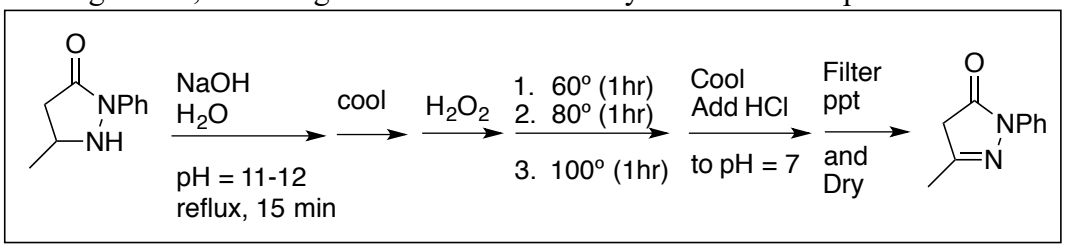



**References:**
**Diao, T; Stahl, S. S. J. Am. Chem. Soc, 2011, 133(37), pp 14566-14569**
**Stahl 2013 paper has more details.**
**Stahl also has a review paper.**

**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?

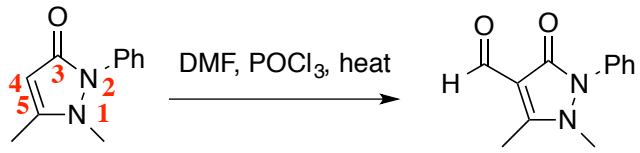
**Chromatographic Purification Project**: Mikayla will Try

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.

Specific project suggestions for Fall 2018

1.

**C4-Formylation.**

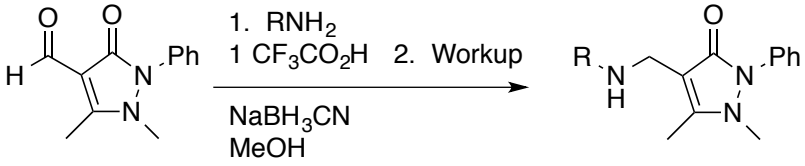



**Untried.**
**Pretty detailed literature procedure.**
**Want to try to do a large scaleup reaction, AND get it pretty clean.**
**To be done in combo with following two box.**

Matt Anderson

2.

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

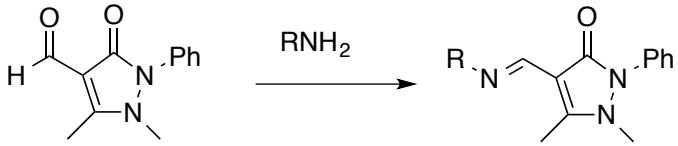



**Untried. No literature?**
**I don't have literature references, but haven't looked hardly at all…**
**Again, a range of different types and sizes and hybridization of amines could be screened?**

Matt Anderson

3.

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



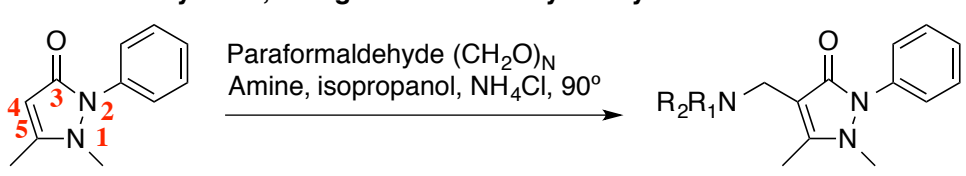

Lots of Examples, often with elaborate "R" groups

**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**

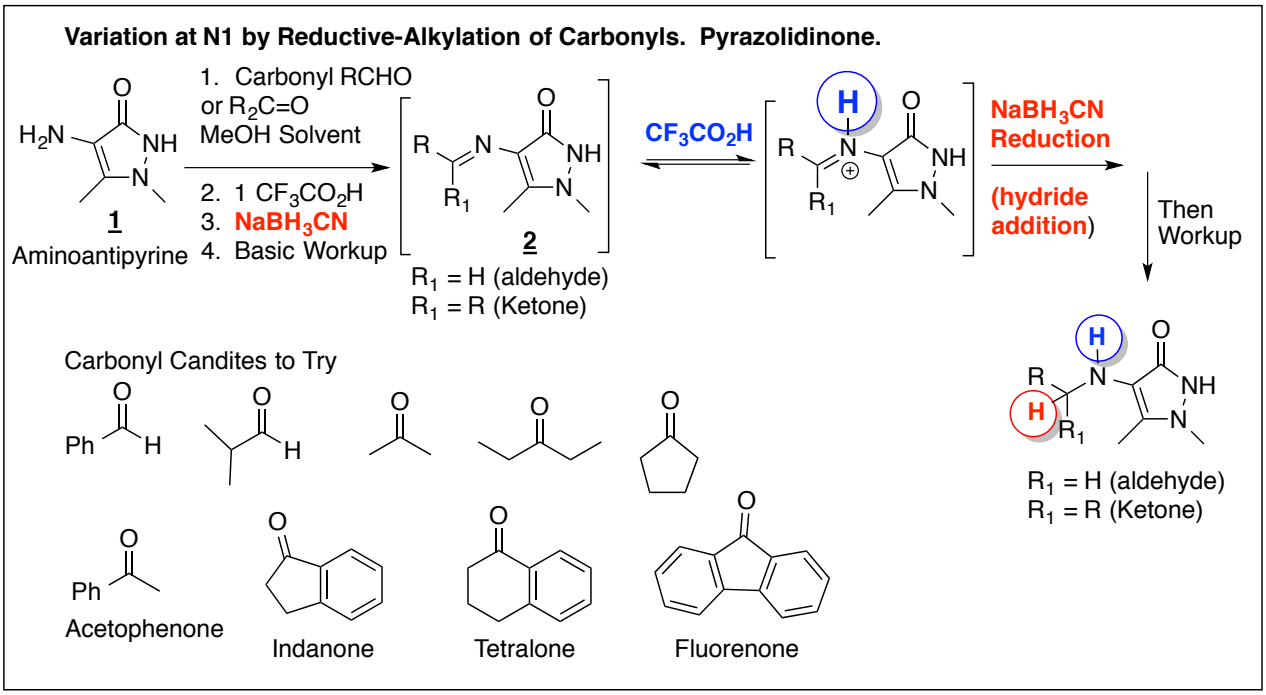



C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

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

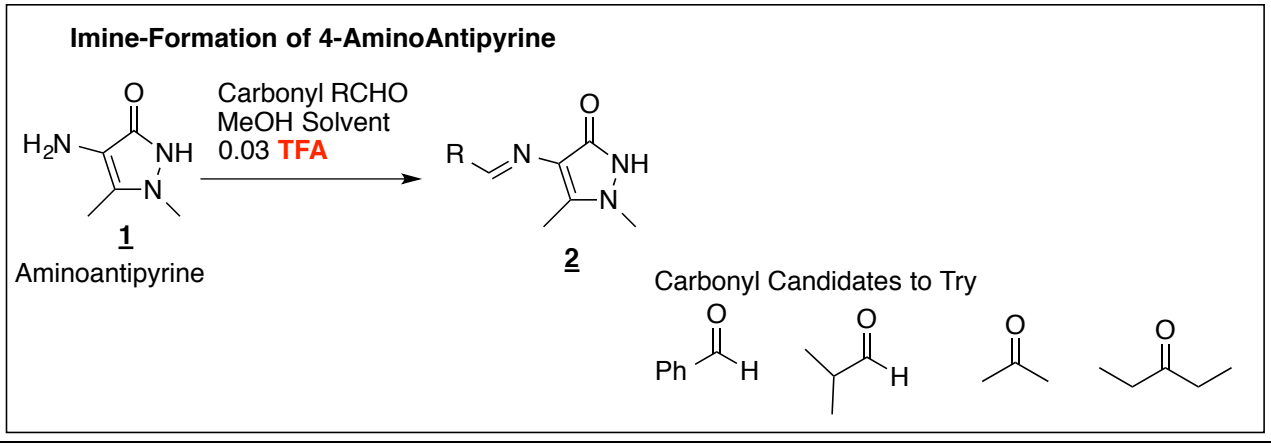
## Reductive Amination of Aminoantipyrine: Formation of 4-Alkylaminoantipyrine Analogs

5.



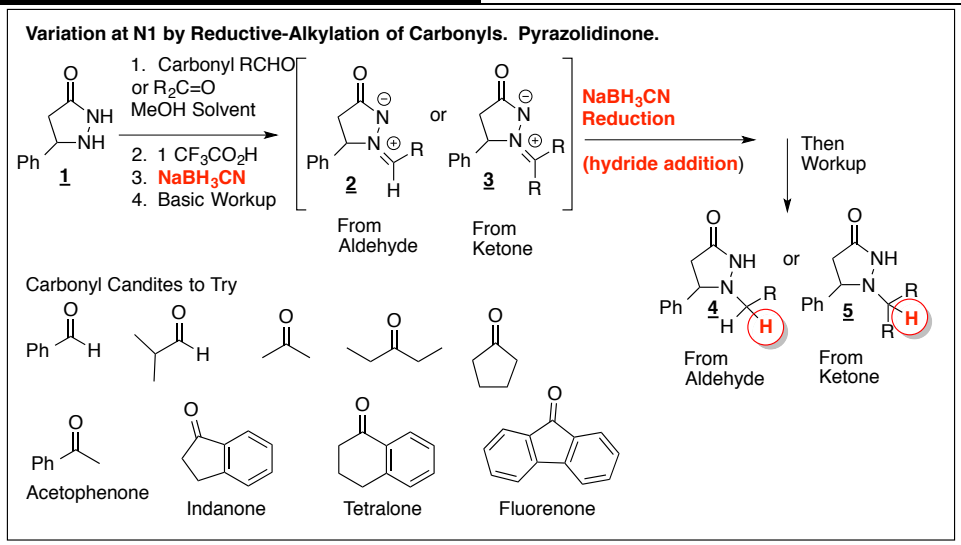

Jasperse has done small scale trial, proof-of-principle experiment; Ansu confirmed
Will it work for both aldehydes and ketones, or only aldehydes?
Will it work for ketones that get bigger
Will it work for conjugated ketones?
What might be a good workup procedure?
What is the best way to purify? Digestion?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

6.



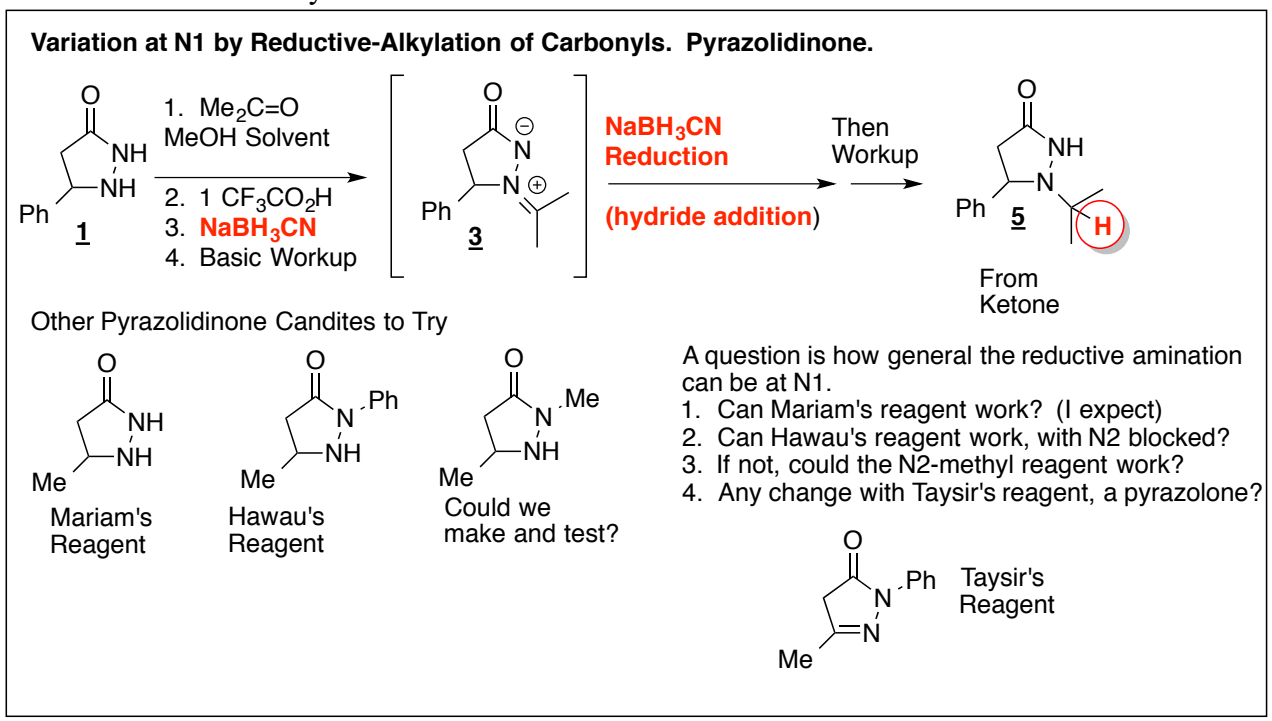
## Reductive Alklation at N1. N-Alkylation

7.



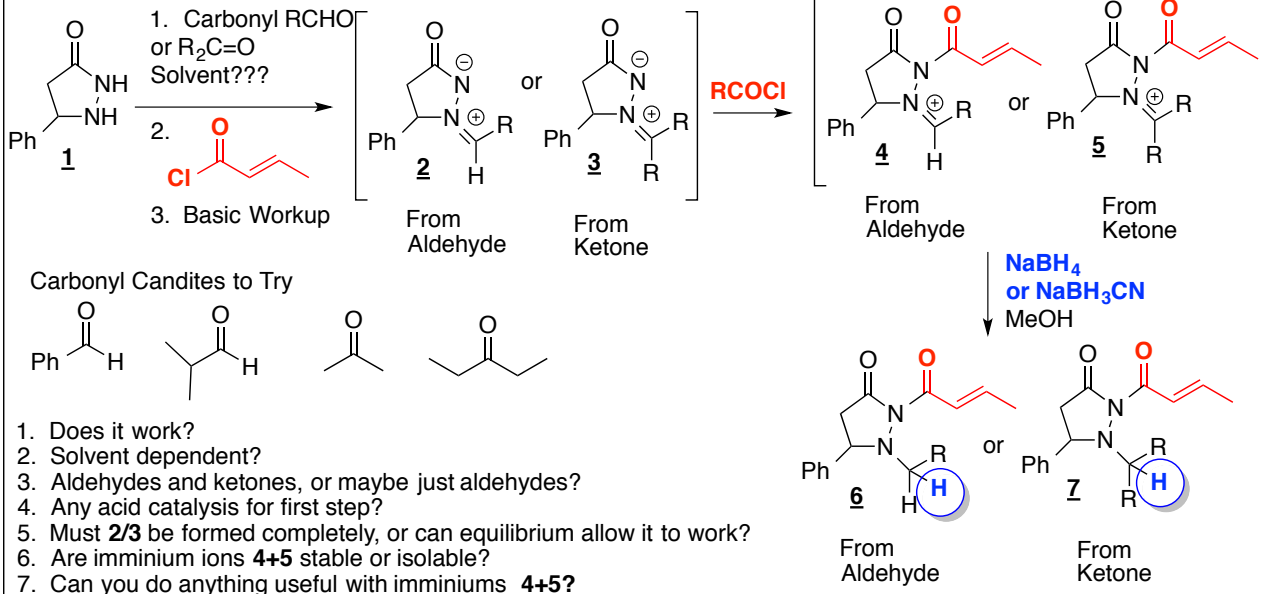

Jasperse has done small proof-of-principle using benzaldehyde and acetone; I think it works great! (But not sure…)

8 Does it work for other Pyrazolidinones?



9

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




Carbonyl Candites to Try

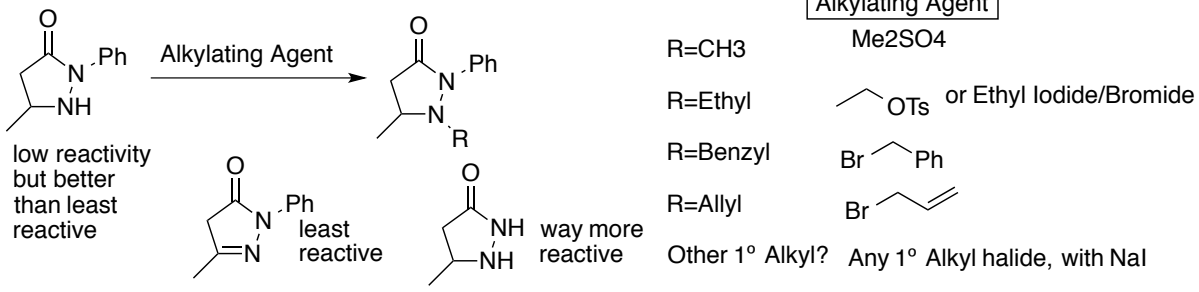


1. Does it work?
2. Solvent dependent?
3. Aldehydes and ketones, or maybe just aldehydes?
4. Any acid catalysis for first step?
5. Must **2/3** be formed completely, or can equilibrium allow it to work?
6. Are imminium ions **4+5** stable or isolable?
7. Can you do anything useful with imminiums **4+5?**

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

10

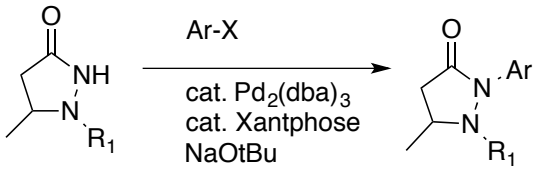
**Variation at N1 by N-Alkylation. Pyrazolidinone.**




**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

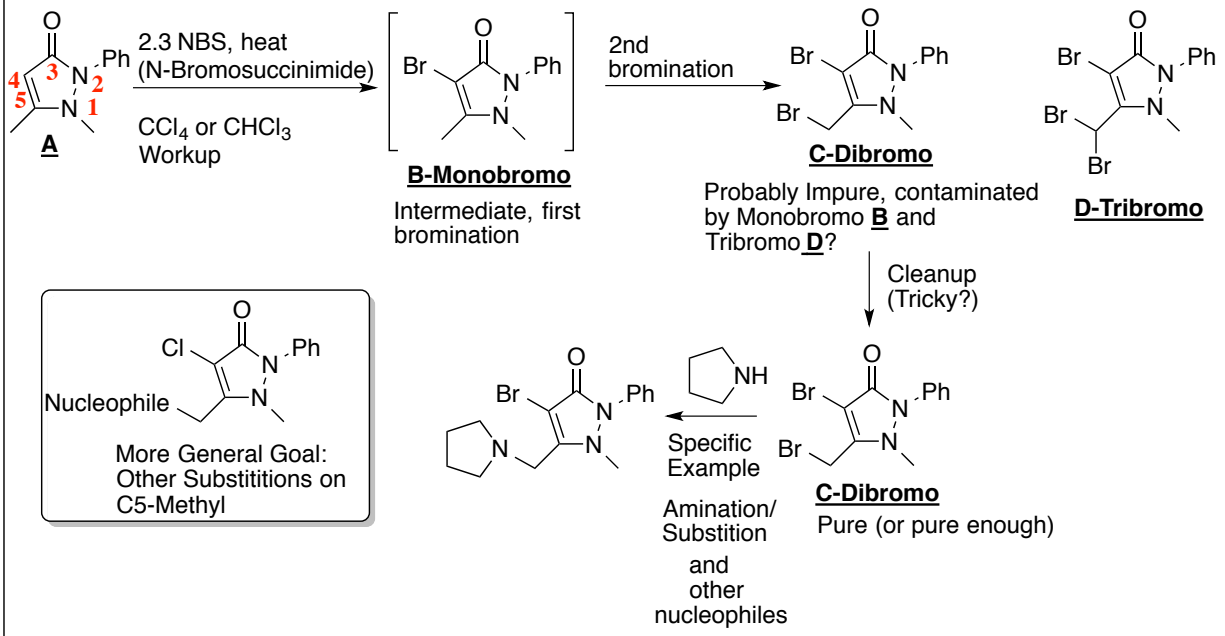
Antipyrine has N2-phenyl, so the opportunity to install variable aryl analogs from Hawau's Reagent would be really nice.... if it works.

**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**



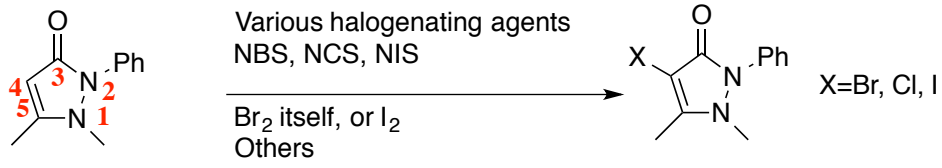

C4-Hetereo-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf

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**



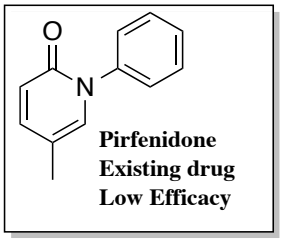

**C4-Hetereo-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf**

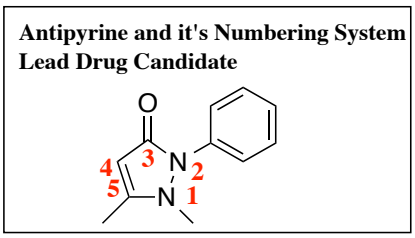
**Get and Print documents:**
Kaniel NCS General Procedure Suggestion.docx
NCS Procedure and Reference.pdf

Research Idiopathic Pulmonary Fibrosis AntiPyrine Analog Library Synthesis Update 1/23/2020

("Idiopathic": "relating to or denoting any disease or condition which arises spontaneously or for which the cause is unknown.")

https://err.ersjournals.com/content/26/145/170053




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:**

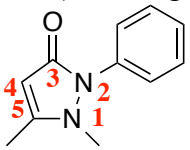
6. Pirfenidone is the FDA-approved (2017) medicine used to treat pulmonary fibrosis
   - It is not a life-saver
   - It isn't very good in terms of potency, efficacy, toxicity (or expense)
   - Its mechanism of operation is not understood
   - Some recommended dosage and price details:
     a. Daily, with 3 doses per day
     b. 801-mg per dose. (very large). 3 x 801mg >2 grams/day!
     c. Wholesale price: $131/tablet
     d. $131 x 3 = $393/day x 365 days = $143,445/year. In other words, Expensive!
     e. Research price: Sigma-Aldrich has it $107/10mg; TCI-America $67/100mg or $396/gram
     f. Antipyrine: $81/100g. So pirfenidone is ~500 times more expensive!!!
     g. Nintenadib: 2014 approved, 2 x 150mg/day, $209/capsule, $418/day => $153K/year

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

8. Extensive "chemical library" study identified antipyrine as a "lead chemical", comparable to pirfenidone

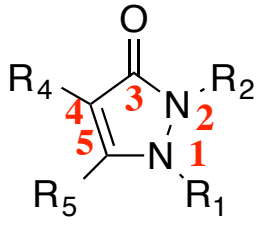
9. Jasperse research group goal: Make as many analogs of antipyrine as we can, in hopes that we can make something better yet

10. 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.

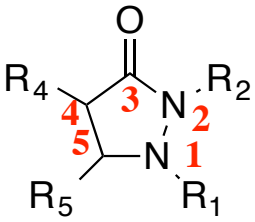


## Jasperse Synthetic Group Goal:

**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**

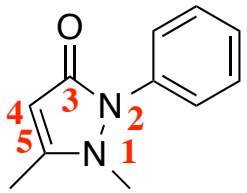


Pyrazoles



Pyrazolidinones

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




## Molecular Biology: Develop a procedural assay to evaluate different synthetic analogs.

## SAR questions: (Structure-Activity-Relationship Questions)

6. How/where does the drug bind?
7. Where is there spatial capacity for 3D-drug enlargement? Between the four quadrants, where are spatial enlargements tolerable or beneficial?
    a. Southeast Quadrant (N1)
    b. Northeast Quadrant (N2)
    c. Northwest Quadrant (C4)
    d. Southwest Quadrant (C5)
8. How does adding hydrophobic vs hydrophilic character impact drug performance?
9. Again, this question applies independently for each of the four quadrants
10. How does flexible (acyclic) vs rigid (rings, especially flat aromatics)?

https://www.google.com/search?q=ipf+orphan+disease&oq=IPF+orphan+disease&aqs=chrome.0.0.6725j0j4&sourceid=chrome&ie=UTF-8

"Idiopathic pulmonary fibrosis (**IPF**) is a non-neoplastic pulmonary **disease** that is characterized by the formation of scar tissue within the lungs in the absence of any known provocation. **IPF** is a rare **disease** which affects approximately 5 million persons worldwide."

There is currently no cure for **pulmonary fibrosis** but treatments and therapies are improving all the time. The average **life expectancy** of **someone with pulmonary fibrosis** is three to five years but if it's caught early, treatment can help slow down the progression of the disease.Jun 16, 2017

"Summary: Idiopathic **pulmonary fibrosis** is a little-known disease that kills as many people each year as breast cancer. ... A diagnosis of idiopathic **pulmonary fibrosis** is not much better than a **death sentence**, given a survival rate averaging 4 to 6 years as the disease robs its victim of the ability to breathe.Nov 11, 2010"
"

https://www.google.com/search?q=How+many+people+have+IPF+in+the+United+States%3F&oq=How+many+people+have+IPF+in+the+United+States%3F&aqs=chrome..69i57.10192j0j4&sourceid=chrome&ie=UTF-8
According to the National Institutes of Health, about **100,000 people** in the United States have IPF, and approximately **30,000** to **40,000** new cases are found each year. Worldwide, IPF affects **13** to 20 out of every **100,000 people**.Dec 13, 2016 (US population:

https://err.ersjournals.com/content/errev/26/145/170053.full.pdf (2017 article)
ABSTRACT Idiopathic pulmonary fibrosis (IPF) is characterised by progressive changes of the lung architecture causing cough and dyspnoea and ultimately leading to lung failure and death. Today, for the first time, two drugs that may reduce the inexorable progression of the disease are available, suggesting that treatment with specific drugs for IPF should be started as soon as diagnosis is made. This applies to any disease and particularly to IPF, which is marked by a 5-year survival comparable or even worse than many cancers. However, despite common sense and even worse, in spite of scientific data coming from clinical trials, post hoc analysis, long-term safety studies and real-life experiences, the question of when to start and when to stop treatment with antifibrotics is still debated. In IPF, particularly when the disease is diagnosed at an early stage, "wait and watch" behaviour is not rare to observe. This is largely due to the lack of awareness of both patients and clinicians regarding the progression of the disease and its prognosis. Another important issue is when treatment should be stopped. In general, there are two main reasons to stop a therapy: unbearable side-effects and/or lack of efficacy. According to current (although preliminary) evidence, antifibrotic drugs should not be discontinued except for safety issues.
**Introduction** Idiopathic pulmonary fibrosis (IPF) is a chronic progressive lung disease of unknown cause, which is limited to the lungs and associated with the radiological and/or histological pattern of usual interstitial pneumonia. The disease is characterised by progressive morphological changes of the lung architecture, causing cough and worsening dyspnoea and ultimately leading to lung failure and death. Several risk factors have been described to contribute to IPF onset and, despite the recent advances in our understanding of the pathogenesis, the real cause of the disease remains to be determined. IPF is a disease characterised by a very poor prognosis, with a median survival time of 3–5 years from diagnosis. Furthermore, the clinical course is unpredictable, marked in some cases by a relatively slow and gradual progression but in other cases by a rapid and often dramatic clinical evolution [1, 2]….
**Conclusion** IPF is a dreadful disease. Many efforts have been made in understanding its pathogenesis, but despite recent advances in research, this disease still represents a dilemma. Today, for the first time, we can use two effective drugs able to reduce the inexorable progression of the disease. … It is currently estimated that only 54% of patients with an IPF diagnosis in Europe receive antifibrotic treatment with an approved drug. It is desirable, when faced with evidence of a disease that is not cancer, but looks like a cancer in its behaviour, …

https://www.google.com/search?q=What+does+it+mean+to+be+an+%22orphan+drug%22%3F&oq=What+does+it+mean+to+be+an+%22orphan+drug%22%3F&aqs=chrome..69i57j0l2.9726j1j7&sourceid=chrome&ie=UTF-8
https://en.wikipedia.org/wiki/Orphan_drug

Orphan Drug/Orphan Disease: What does it mean to be an "Orphan Drug"?
An **orphan drug is** a pharmaceutical agent developed to treat medical conditions which, because they are so rare, **would** not be profitable to produce without government assistance. The conditions are referred to as orphan diseases.

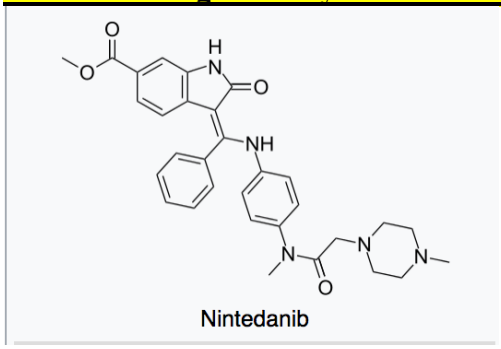
The assignment of **orphan status** to a disease and to drugs developed to treat it is a matter of public policy in many countries and has yielded medical breakthroughs that might not otherwise have been achieved, due to the economics of drug research and development.[1]

In the U.S. and the EU, it is easier to gain marketing approval for an orphan drug. There may be other financial incentives, such as an extended period of exclusivity, during which the producer has sole rights to market the drug. All are intended to encourage development of drugs which would otherwise lack sufficient profit motive to attract corporate research budgets and personnel.[2][3]

According to the US Food and Drug Administration (FDA), an orphan drug is defined as one "intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200,000 persons in the United States."[4][5]

~0.03% in US. About 3 out of 10,000 people.

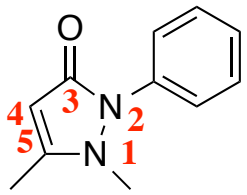
**The other drug: Totally different structure from pirfenidone**

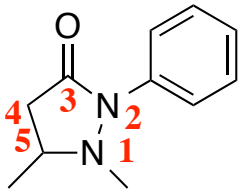
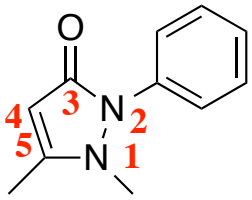
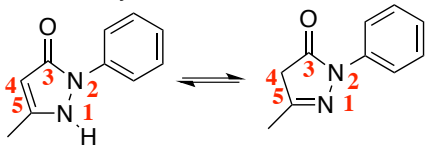
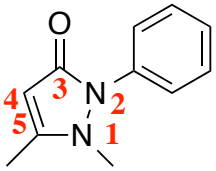


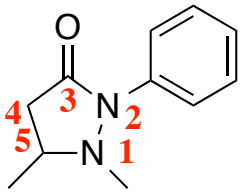
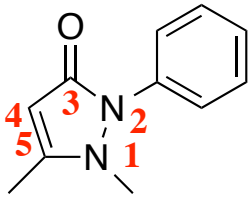
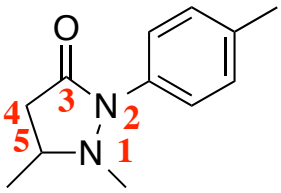
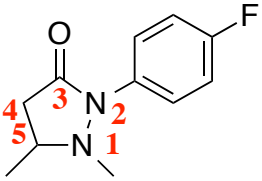
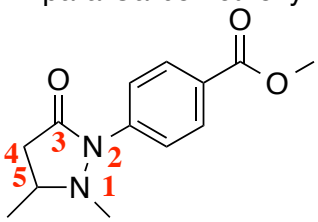
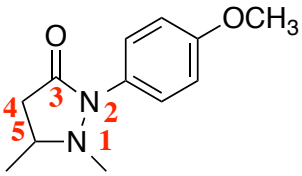
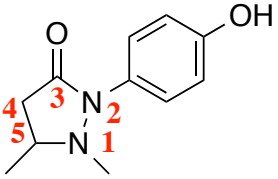
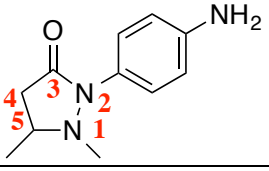
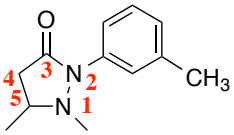
Nintedanib

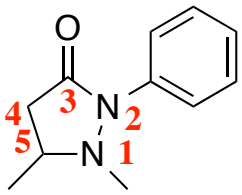
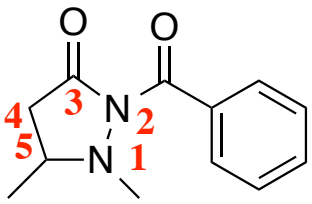
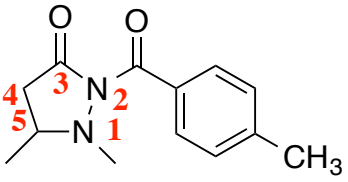
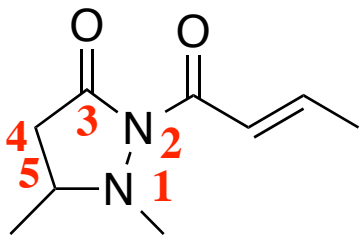
Some Structures we have made

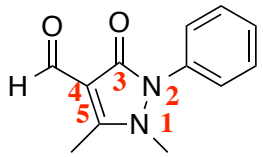
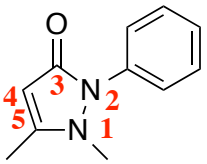
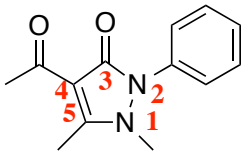
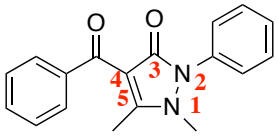
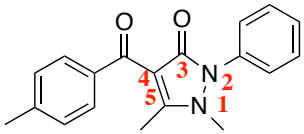
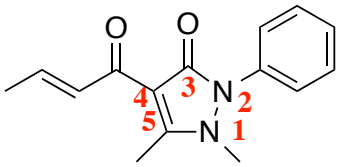
**Antipyrine and it's Numbering System**
**Lead Drug Candidate**

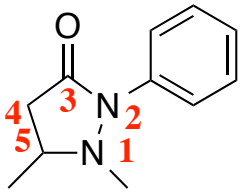
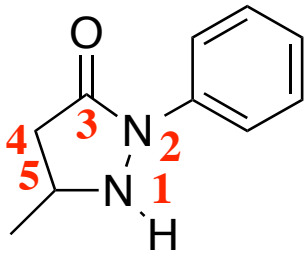
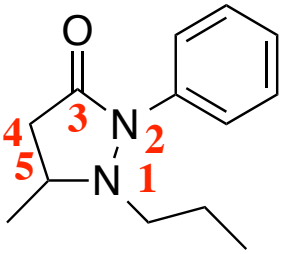
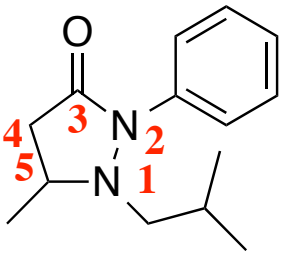
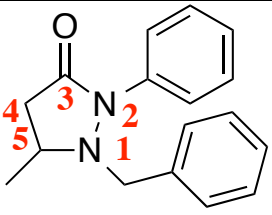


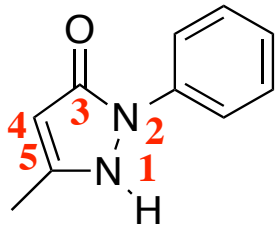
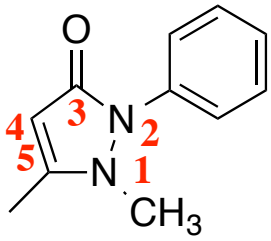
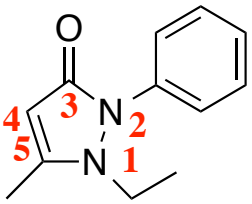
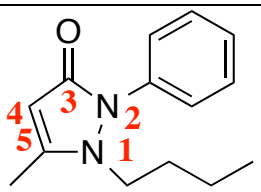

| | | | | |
|---|---|---|---|---|
| | The Dihydro-Double-Bond Question | | | Reference: |
| | **Dihydroantipyrine**<br>  | Is the 4-5 double bond necessary? (We can access a lot of analogs more easily without it) | | **Antipyrine Itself**<br>  |
| | | | | |
| | The Desmethyl Question: | | | |
| | 1-Desmethyl<br>  | Is the N-methyl group necessary? (We could quickly access several analogs without it) | | **Antipyrine Itself**<br>  |

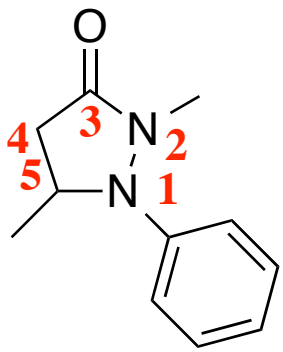
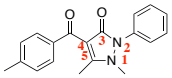
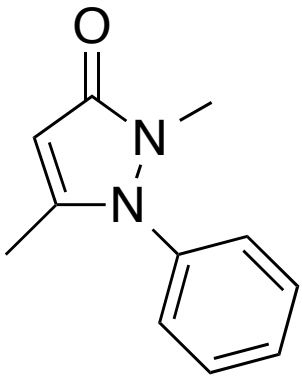
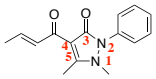
| | | | | |
|---|---|---|---|---|
| | The N2-Aryl Series | | | |
| | **Dihydroantipyrine**  | | | **Antipyrine Itself**  |
| | N2-para-Methyl  | Brent Schulte<br>Logan Spooner | | |
| | N2-para-Fluoro  | | | |
| | N2-para-Carbomethoxy  | | | |
| | N2-para-Methoxy  | | | |
| | N2-para-Hydroxy  | | | |
| | N2-para-Amino  | | | |
| | N2-meta-Methyl  | | | |

| | | | | |
|---|---|---|---|---|
| | The N2-Acyl Series | | | |
| | **Dihydroantipyrine**<br>  | The N2-Acyl series are all "dihydro" structures. Does inclusion of a carbonyl at N2 help or hurt? If not, lots of flex for other sizes and stuff. | | |
| | N2-Benzoyl<br>  | Spring 2019 Organic Chem Lab Has prepared all of these | | |
| | N2-Toluoyl<br>  | | | |
| | N2-Crotonyl<br>  | | | |

| | | | | |
|---|---|---|---|---|
| | **The C4-Acyl Series** | | | |
| | 4-Formyl  | Matt Anderson<br>Abby Bormann | | **Antipyrine Itself**  |
| | 4-Acetyl  | | | |
| | 4-Benzoyl  | | | |
| | 4-Toluyl  | | | |
| | 4-Crotonyl  | | | |

| | | | | |
|---|---|---|---|---|
| | The N1-Alkyl Series (The Dihydro version) | | | |
| | **Dihydroantipyrine**  | | | |
| | **N1-Desmethyl**  | | | |
| |  | | | |
| |  | | | |
| |  | | | |

| | | | | |
|---|---|---|---|---|
| | The N1-Alkyl Series (The Double-Bond version) | | | |
| | **N1-Desmethyl**<br>  | | | |
| | **Antipyrine**<br>  | | | |
| |  | Matt Anderson | | |
| |  | Matt Anderson | | |
| | | | | |

| | | | | |
|---|---|---|---|---|
| | The N1-Phenyl Flip | | | |
| | N1-Phenyl "Flip"<br>  | If this looks any good, we'd be able to make a bunch of N1 or N2 or C5 analogs.<br><br>Eric Gibbons? Hawau. | | 4-Toluyl<br>  |
| |  | Eric, this semester, not made yet….<br><br>If Eric's works, could add a bunch of variety to the N1-Phenyl group | | 4-Crotonyl<br>  |
| | If Eric's works, could add a bunch of variety to the N1-Phenyl group | | | |

**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

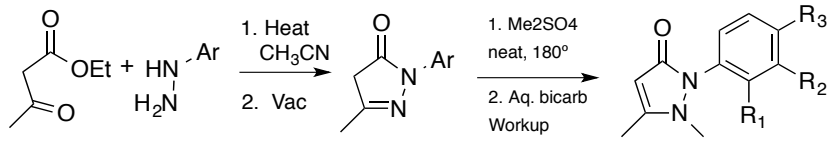
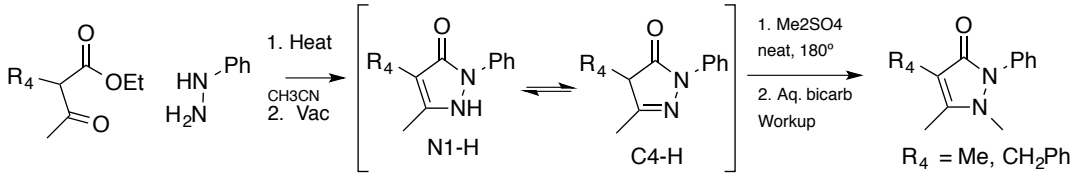
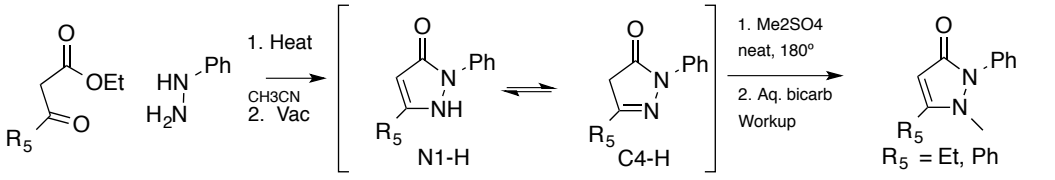
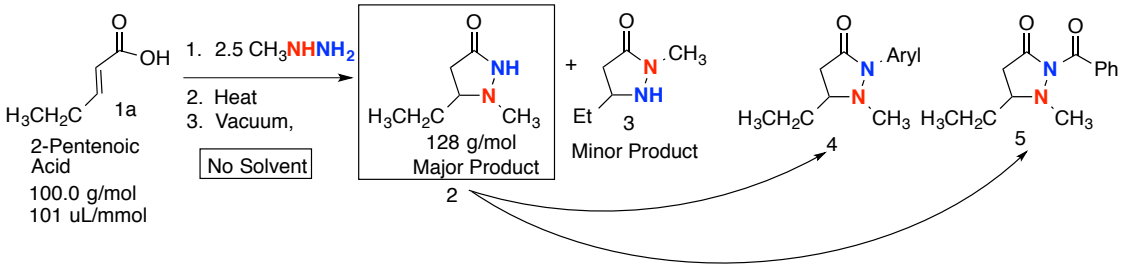
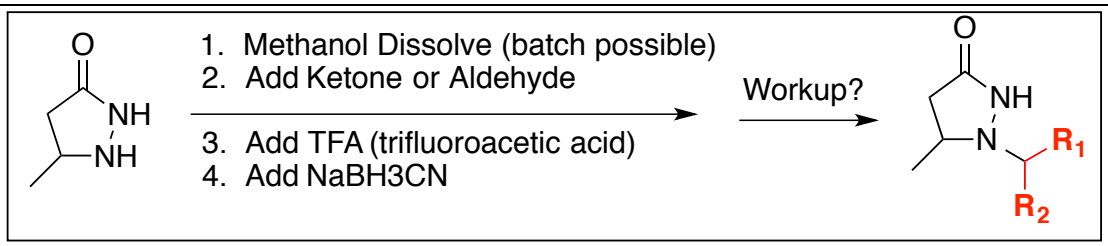
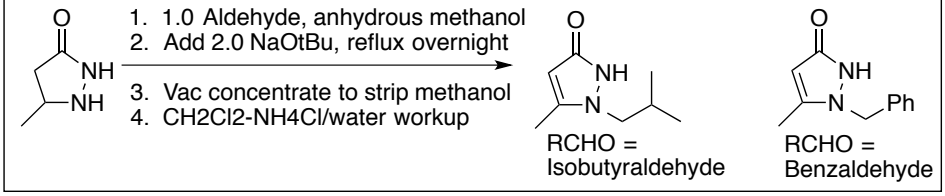
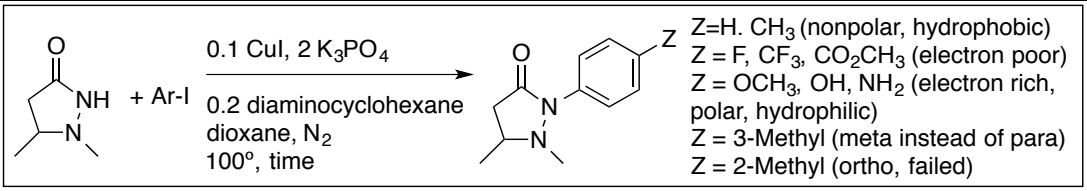
8. Keeping Notebook, Keeping Organized! ☺☺☺

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

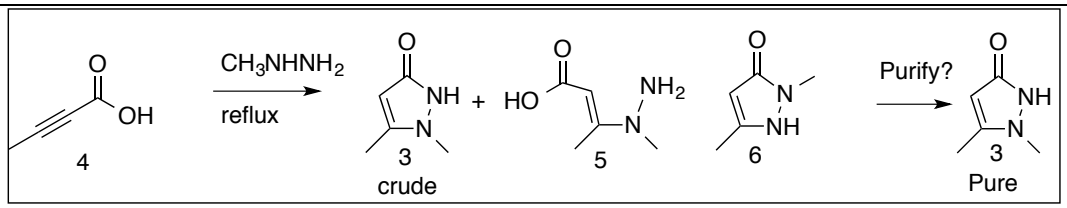
10. Space in Group: Yes.

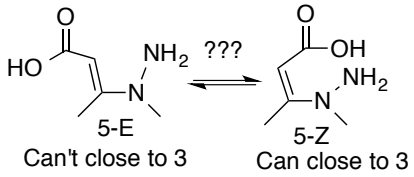
11. Experience Required: First semester organic lab preferred (but not required, for a good, self-motivated, and ambitious student! ☺

Table of Project Ideas, Fall 2020:

| | | |
|---|---|---|
| 25. | **Variation at N2-Aryls By Variation of Aryl Hydrazine. Order some, Grant $$**<br>  | Logan H |
| 26. | Continuation | |
| 27. | **Scheme 1: Variataion at C4:**<br>  <br>**Scheme 2: Variataion at C5:**<br>  | Logan H |
| 28. | **Adapt Procedure wto use of Ethyl-Substituted Alkene**<br>  | Hannah |
| 29. |  | Morgan |
| 30. | **N1-Alkylation with Double-Bond Install, Via Imine Double Bond Shuffle**<br>  | |
| 31. | Continuation | |
| 32. |  | Logan Spooner? |

33.



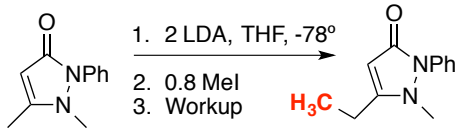




Questions:
1. Will the addition be as regiospecific as with the alkene?
2. Will the addition be E/Z stereospecific for or against us?
3. Under reaction conditions can the E/Z mixture isomerize, so that LeChatelier can allow irreversible closure, even if the kinetic E/Z mixture isn't in our favor?

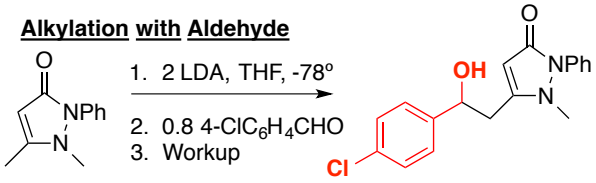
34.

**Literature Reactions**

**Alkylation with Alkyl Iodide**



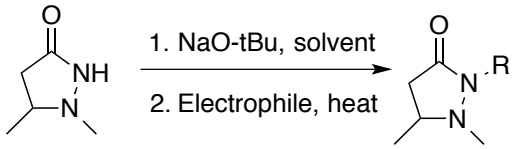

**Alkylation with Aldehyde**




**Literature article provides nice Proof-of-Principle.**
**But it's procedure is ridiculously and unnecessarily complex**

35.

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



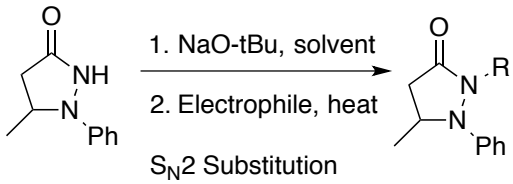

$S_N2$ Substitution

Potential Alkylation Agents:
Methyl, ethyl, etc.

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

36.

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



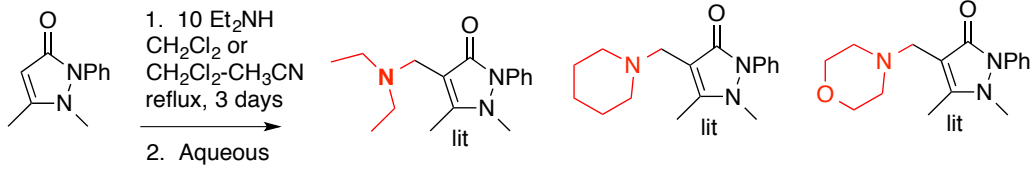

$S_N2$ Substitution

Potential Alkylation Agents:
Methyl, ethyl, etc.

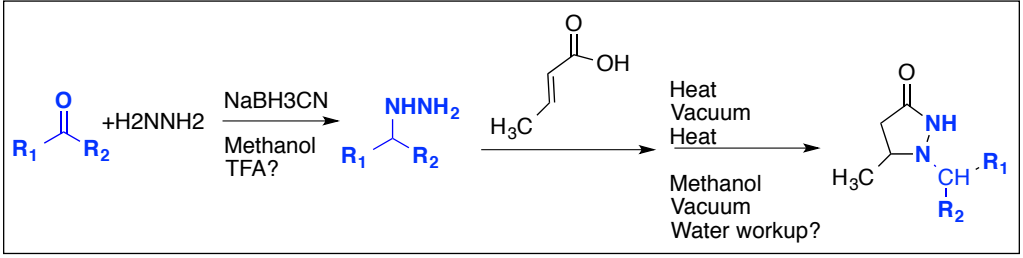
Potential Solvents: MeOH, $CH_3CN$, DMF...

37.

**C4-Aminomethylation with CH2Cl2**



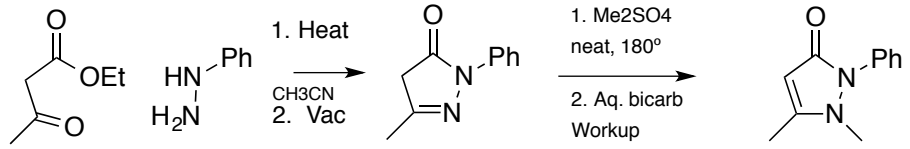

38.



**Variation at N1-Aryl group. Full Dihydro (double bonded) analogs?**
**N2-Aryl Ring Variation, Pyrazolones. Using alternate Arylhydrazines.**

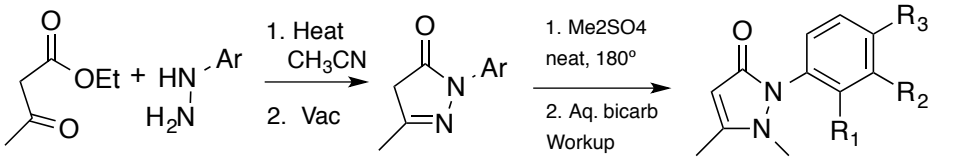
**Demonstrated POP reaction:**

**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 (5g, 109.1) (stability??) | Sigma/Aldrich: $86/5, $292/25 |
| o-Tol | 635-26-7 | o-Tolylhydrazine hydrochloride (5g), 158.6 | Sigma/Aldrich: $39/5 |
| p-Cl | 1073-70-7 | 4-Chlorophenylhydrazine hydrochloride (5g), 170.05 | Sigma/Aldrich: $29/5, $97/25 |
| 2-MeO | 6971-45-5 | 2-Methoxyphenylhydrazine hydrochloride (5g), 174.63 | |
| p-Tol | 637-60-5 | 4-Methylphenyl hydrazine hydrochloride | VWR-AA, $35.59/5g |
| p-F | 823-85-8 | 4-Fluorophenylhydrazine hydrochloride | Sigma/Aldrich: $67/10, |
| p-CN | 2863-98-1 | 4-Cyanophenylhydrazine hydrochloride | Sigma/Aldrich: $57/5 |
| m-Cl | 2312-23-4 | 3-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $97/25 |
| o-Cl | 41052-75-9 | 2-Chlorophenylhydrazine hydrochloride | Sigma/Aldrich: $80/25 |
| 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) |

Keto-Esters, for reaction with Phenylhydrazine:

Some other accessible C5 variants: The following search will fine lots.
https://www.alfa.com/en/search/?q=acetoacetate

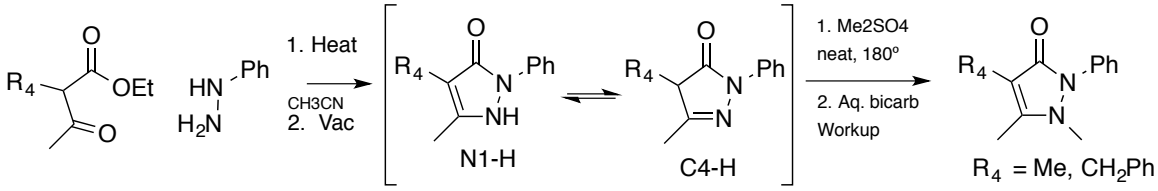
| Ethyl 2-X-acetoacetate | | |
|---|---|---|
| 2-Me | | $38 – 25g |
| 2-benzyl | | |
| 2-Chloro Ethyl 2-chloroacetoacetate, 96% | 609-15-4 | $30 – 100g |
| 2-ethyl | | $90 – 25g |
| 2-n-butyl | | $46 – 5g |
| 2-CN | | $50 – 2g |
| 2-Ph Ethyl 2-phenylacetoacetate, 97% | | |
| Ethyl 2-X-acetoacetate | | |
| 4,4,4-Trifluoro | 372-31-6 | $35 – 10g |
| 4-Chloro | 638-07-3 | $35 – 50g |

## Phenylhydrazine Addition to Keto-Esters.

- Difficulty estimate: Low
- Discovery level: Modest. POP discovered previously.
- Odds it will work: High. POP proof.
- Odds for some pretty quick success results: Good
- Operational difficulty: Low for ring formation.
- Access for time-controlled lab blocks: Low. Experiments probably take long blocks of time.?
- I think we've got a modest stock of the starting material

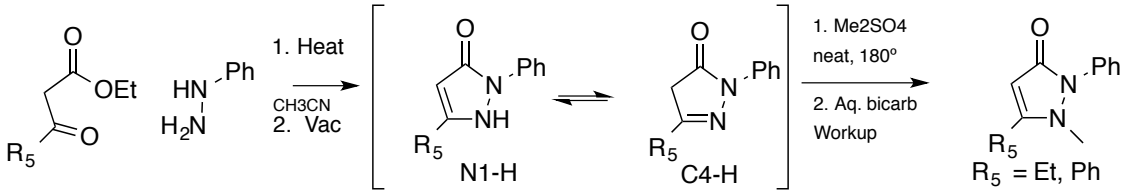
| | |
|---|---|
| Ethyl benzoylacetate, 50grams | PhCOCH2CO2Et |
| Ethyl propionylacetate, 5grams | CH3CH2COCH2CO2Et |
| Ethyl 2-benzylacetoacetate, 25grams | CH3COCH(CH2Ph)CO2Et |
| Ethyl 2-methylacetoacetate, 25grams | CH3COCH(CH3)CO2Et |

**Scheme 1: Variataion at C4:**




**Update: Taysir. Proof of Principle,, but very small scale**

**Scheme 2: Variataion at C5:**




**Update: Works. Taysir. Proof of Principle, but very small scale.**

POP experiments have already been executed, successful, but small scale.
Could scale up and batch-size a series of these.

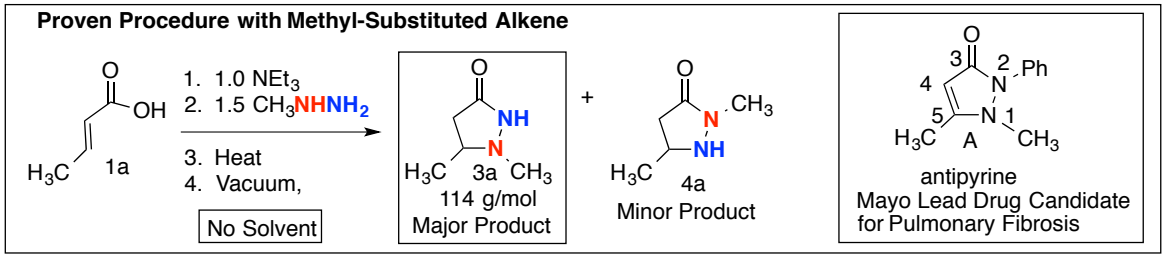
A variation: Could try ethyl tosylate instead of methyl tosylate for one of them. Can we make the N1-ethyl analogs, too?

I like this project. It will work, we just need somebody to get after it.

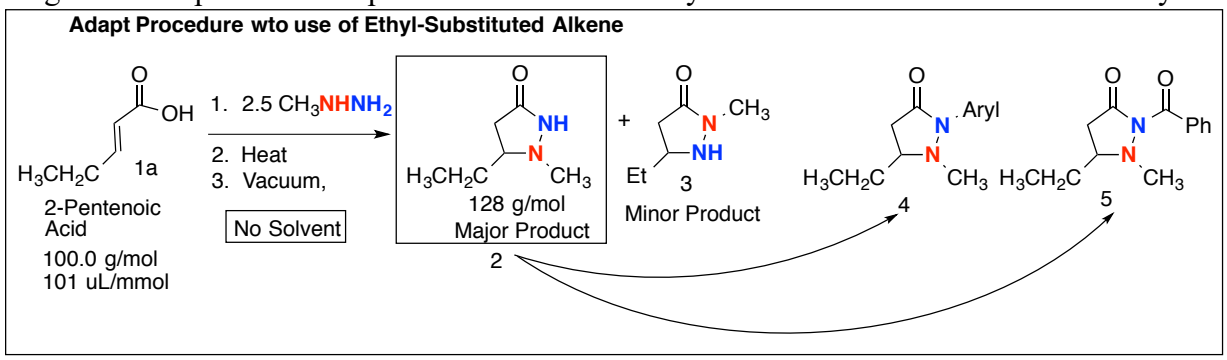
## 2-Pentenoic Acid project. C5-ethyl to replace 5-methyl

- Difficulty estimate: Low
- Odds for some successful results: High
- Odds for some pretty quick success results: Decent
- Access for time-controlled lab blocks: Uncertain, maybe good?

Proven procedure using methyl-substituted Reactant




Target: to Adapt the Above procedure to Use the Ethyl-substited alkene to make the 5-ethyl analog.




Some of the practical questions, and notes:

- Will the procedure that was developed for the methyl alkene ("crotonic acid"), translate to the ethyl alkene ("pentenoic acid")?
- Might be more steric hindrance, so higher temps or longer times may be required?
- May need to be tested and optimized.
- Will the major/minor product ratio be compromised, sterics? With crotonic, was ~8-10:1.
- Can triethylamine usage work with pentenoic, the way it did with crotonic?
- Note: NMR will be more complex. The C5-methyl in the crotonic acid product gives a nice doublet. The ethyl group will be considerably more complex.
- GC-MS should provide a measure of the major product 2, relative to the minor product 3.
- NMR may also do that, *if* the N-methyl singlets stand out from other signals.
- Will the product be water soluble, or can we do organic-water separatory-funnel treatment?

Approach:

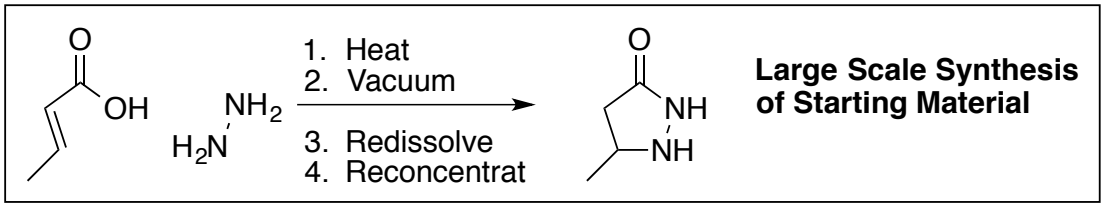
- Do small-scale experiment to develop successful conditions, (and do control with crotonic)
- Then would like to do a large-scale, and make a biggish batch of the 5-ethyl product 2.

Application:

- Try Logan's procedure for N-arylation to produce N-aryl product **4.**
- This can be Mayo-tested against the C5-methyl analog (ethyl vs methyl); and against antipyrine itself (is the C4=C5 double bond important?
- Try organic-lab procedure for N-acylation to product N-acyl products 5.
- This can be tested against N-methyl analogs.

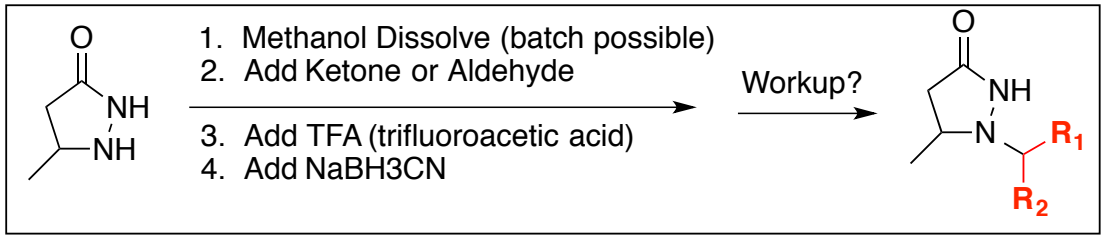
## N1-Alkylation via Reductive Alkylation

- Difficulty estimate: Low
- Discovery level: High.
- Odds it will work: High.
- Odds for some pretty quick success results: High
- Operational difficulty: Low.
- Access for time-controlled lab blocks: High. Experiments probably short.
- I think we've got a modest stock of the starting material? Purity of Starting material is important.



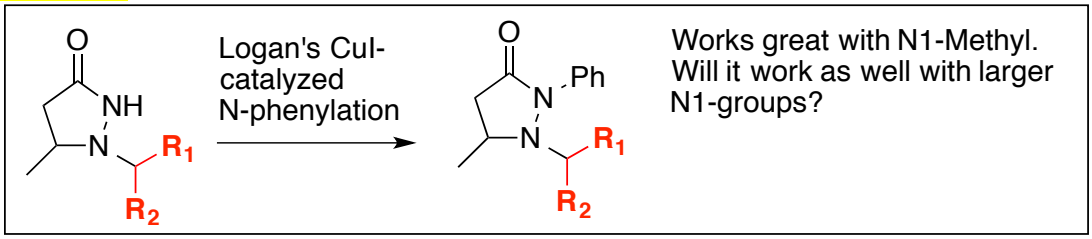

Making a good-sized batch of the starting material is key.
Can we actually try to distill it? It's an oil, not super big, so could perhaps be distilled?

Reactions, IF we had starting material in quality batch:




- No POP on this substrate.
- But reaction seemed to work very well on the C5-phenyl analog, although never totally confirmed.
- We have a broad access of different ketones, from smaller to larger; alkyl; aryl; cyclic.
- Could make a broad family.
- Can batch these: Make a solution of the substrate, then dose it out with a syringe, then measure carefully the specific ketone.
- None of these molecules has been made.
- For analog, see Jasperse 2018-172 or 272…

Followup:

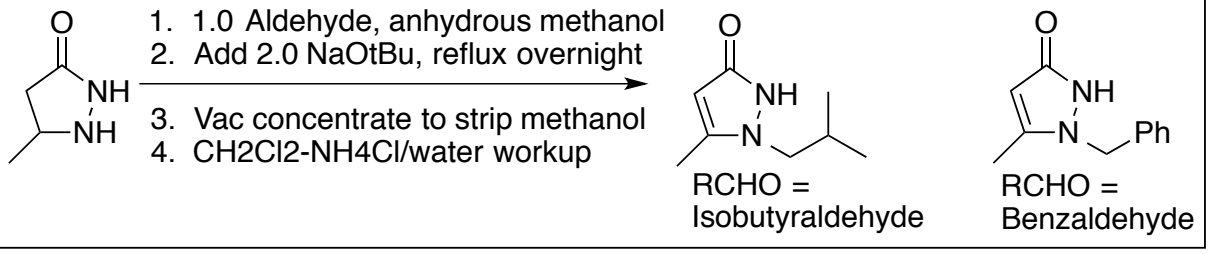


## N1-Alkylation via Imine-Isomerization

- Difficulty estimate: High
- Discovery level: High.
- Odds it will work: Low.
- Odds for some pretty quick success results: Low
- Operational difficulty: High.
- Access for time-controlled lab blocks: Low, Overnight heatings required.
- I think we've got a modest stock of the starting material? Purity of Starting material is important.

## Concept

**N1-Alkylation with Double-Bond Install, Via Imine Double Bond Shuffle**

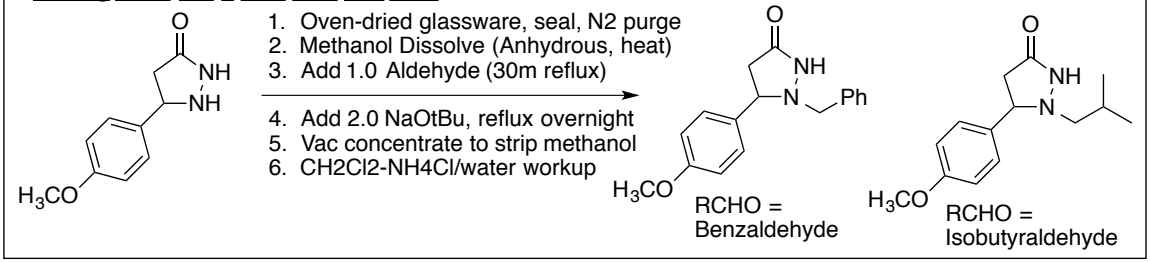



Install N1-substituents while also installing double bond.

7. POP has worked for the C5 = aryl, but not the C5-methyl. It might make a world of difference (conjugation versus not).
8. This will probably take a couple of tests to prove either way.
    a. Prove effectiveness on aryl substituent, using isobutyraldehyde.
    b. Then carefully apply it to methyl substrate, and see if it works or fails.
9. *IF* it works, then we can optimize conditions, and generalize.
    a. If it works on non-conjugated iPr aldehyde, will it work on conjugated Ph aldehyde?
    b. Will it work on ketones?
    c. Taysir did strong conditions to give every chance for success; do we need the steps and the time and the temp? Or can we compress the process?
    d. Oil or crystal?
10. *IF* it worked, followup Q: can we N2-phenylate, using Brent/Logan's CuI procedure?
11. -Notebooks: Jasperse, 2019-2020 book, p 170-171
12. -Taysir Bader book, p49-75

## POP principle experiment on analog:

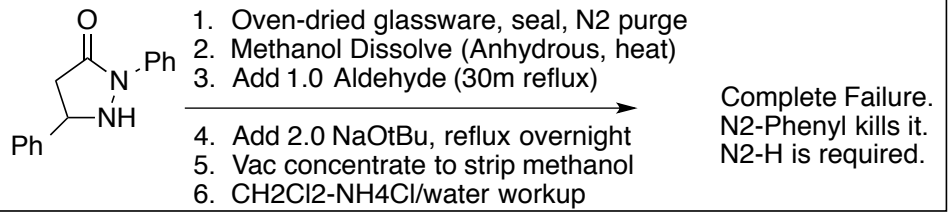
**Analog POP: Do a Test with this First**




-worked great on BOTH aromatic aldehyde (benzaldehyde) AND isobutyralided
-Fairly careful conditions were used; no actual tests were done on whether the times used were needed.
-Notebooks: Jasperse, 2019-2020 book, p 170-171
-Taysir Bader book, p49-75

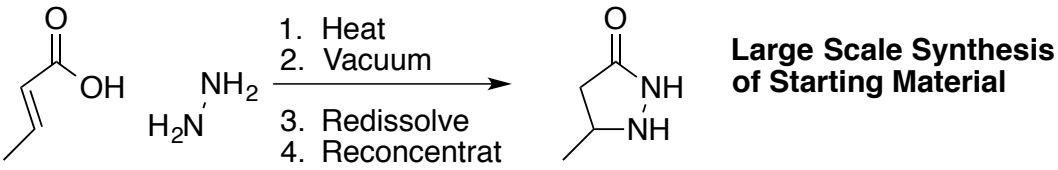
**Definite Fail:**

**Definite Fail with N2-Phenyl**



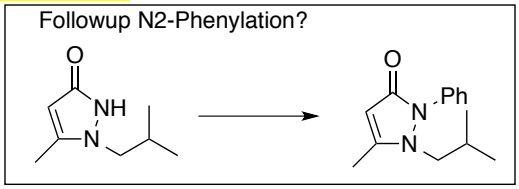

-Taysir used his aleady optimized conditions with the N-phenyl case. Total bust. The N2-H is essential, don't give any more thought to trying to use pre-alkylated stuff.

**Starting Material Prep (may have adequate stuff around)**




Making a good-sized batch of the starting material is key.
Can we actually try to distill it? It's an oil, not super big, so could perhaps be distilled?

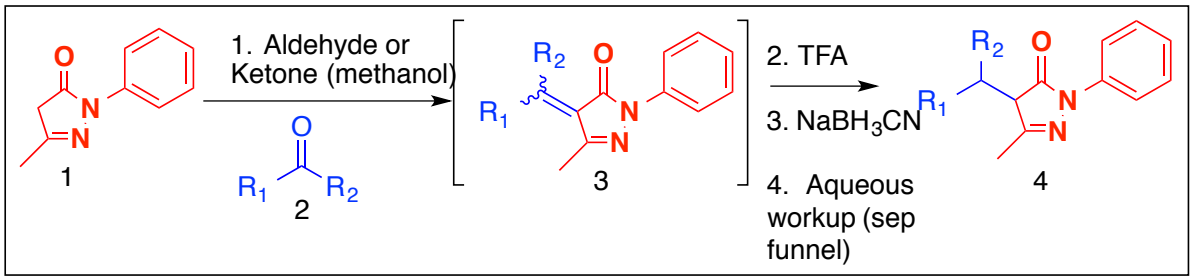
Followup:



**C4-Alkylation via Aldehyde or Ketone, followed by NaBH3CN (Abby POP)**

Difficulty estimate: Modest
Odds for some successful results: Good
Odds for some pretty quick success results: Good
Access for time-controlled lab blocks: good

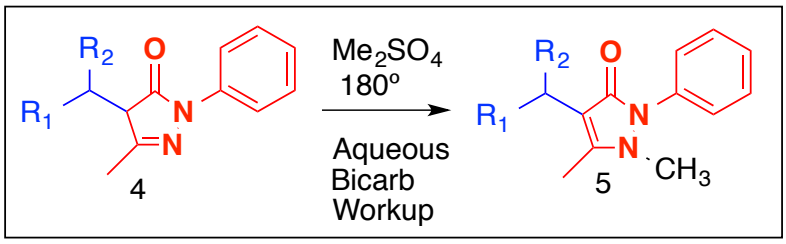
This sequence would provide a versatile way to have 4-alkyl variations relative to Antipyrine.



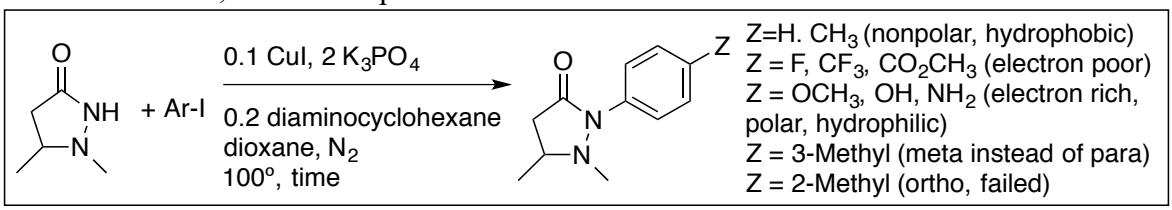

- Abby did some preliminary POP experiments on this.
- I believe it worked on both aldehyde and some simple ketones; failed for larger aryl ketone.
- At the moment trying to access the procedural details. Need to dig up the procedure.
- This sequence would provide a versatile way to have 4-alkyl variations relative to Antipyrine.

Notes:

14. Have a reasonable stock of starting solid 1.
    - More can be remade if needed.
15. This would involve a several-step but one-pot reaction. Or, maybe everything can all be thrown in right at the beginning, and equilibrium process will make everything work?
16. Could be executed in one lab period.
17. Workup could perhaps be saved for later.
18. Could be working batch? (Several at a time?).
19. Or, could be working where one day you're reacting a new one; during the stir-times you'd be working up and analyzing the one you'd run the previous lab period?
20. Would like to develop procedure on modest scale.
21. But would then like to do scaleup to make batch sizes.
22. Would like enough scale to take some of product 4 on toward N1-methyl products 5?
23. We need to get procedure and review from Abby, so as to best know where to start.
24. Unclear on need or procedure for purification. (Acceptable as is? Crystalline, so recrystallizable? Oil, so perhaps need chromatographic cleanup? Is there a quick-run chromatography to clean it up?)
25. Not sure what side products might perhaps form. RCH(OCH3)2 acetal, maybe?
26. Shown below is a potential alkylation procedure.



Copper(I) Iodide catalyzed arylation of 1,5-dimethylpyrazolidione using Aryl Iodides only. Logan S project: Want to continue, and scale-up and isolate?



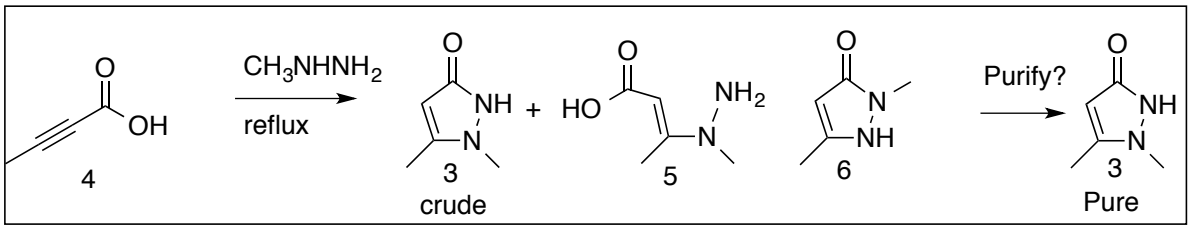

Logan S has worked through these POP-wise.
The procedure works **really** well for a wide variety of aryls.

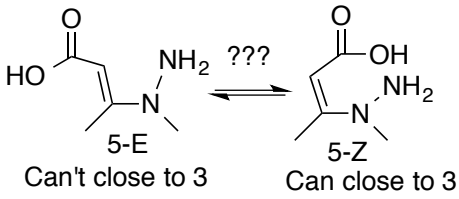
- However, scaleup and isolation was very limited.
- Logan, are you interested in reproducing process, scaling up, and isolating the products?

**Butynoic Acid Project: Possible Quick Access to 1,5-Dimethyl Pyrazole?**

- Difficulty estimate: Low
- Odds it will work: Iffy, but easy enough to check
- Odds for some pretty quick success results: Decent, but kinda yes-or-no
- Access for time-controlled lab blocks: Uncertain, maybe good?

Butynoic acid: kind of expensive, cheapest listing is $65/5g. (Through VWR). Most others are more expensive, Sigma, Alfa…: https://us.vwr.com/store/product?keyword=590-93-2&sortOrder=6

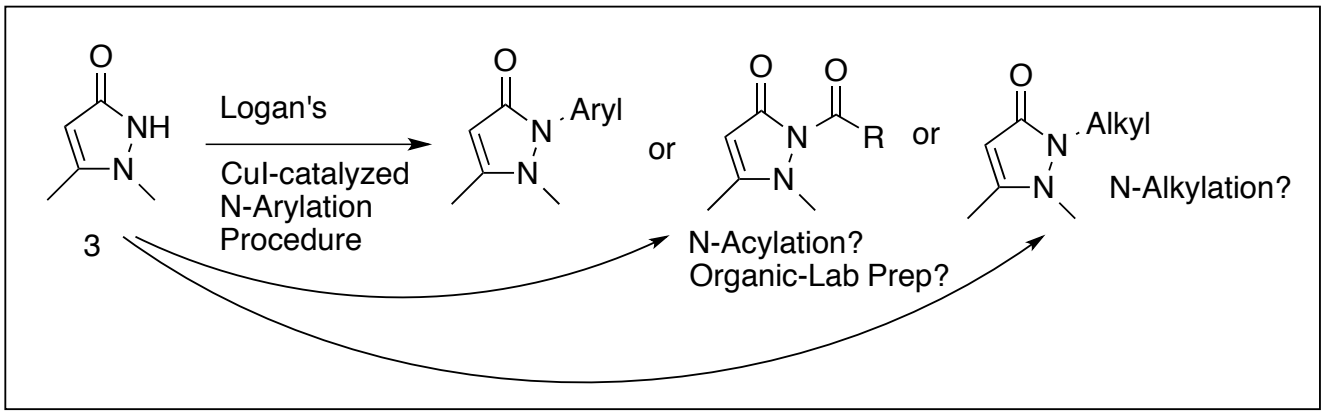



Questions:
1. Will the addition be as regiospecific as with the alkene?
2. Will the addition be E/Z stereospecific for or against us?
3. Under reaction conditions can the E/Z mixture isomerize, so that LeChatelier can allow irreversible closure, even if the kinetic E/Z mixture isn't in our favor?

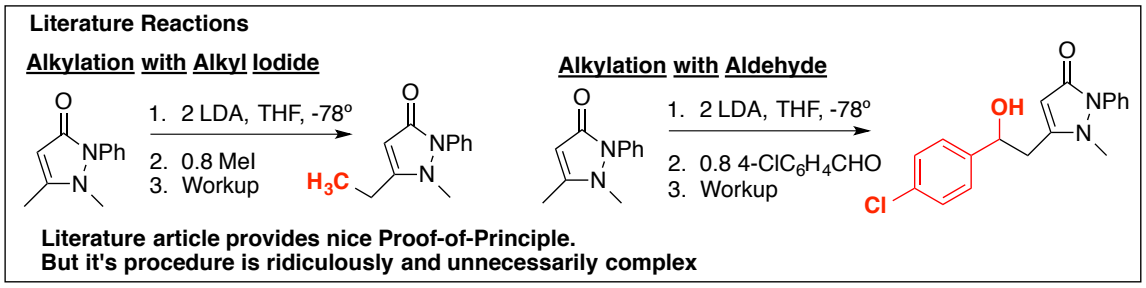
Notes:

7. WE know we can add methylhydrazine across crotonic acid (basically that's 4 but with a double instead of triple bond) with useful regioselectivity. (Meaning the methyl ends on N1 instead of N2). Will it work equally well and selectively on the alkyne?
8. Following addition to the alkyne, an alkene will be created. (See 5E and 5Z). The Z isomer can ring-close; the E one can't. So, when we add:
    a. Will our Z/E ratio be good enough to allow a good yield of 3?
    b. Or, can E/Z isomerize under the hot conditions, so that E/Z are in equilibrium and we can get good yield of 3 by LeChatelier's principle?
9. **IF** things work, it would be a nice one-step prep. If purification works, it's worth the money.
10. But, the starting alkyne 4 is not cheap. I found one list price at $65/5 grams, that's not terrible. But most suppliers charge lots more than that. (mw=84, so that's about 59 mmol.
11. Probably a pretty quick try-it-and-see experiment. If it works, awesome. If it doesn't, we'll be able to see within a couple of experiments.
12. **If it work, some followup derivatization questions. But we'd need to be able build a batch of 3 to have something to work with.**

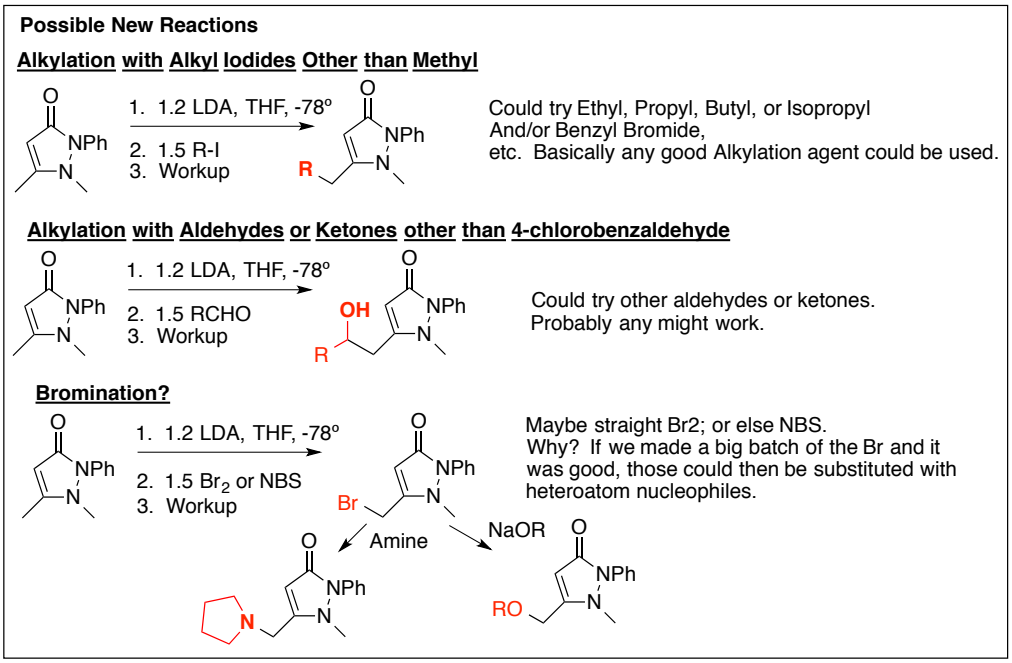


**C5-Alkylation, Using LDA and Anhydrous THF, Low Temp: Preliminary Attempts Confirm that this Can Work, at least for Methylation. Technically non-trivial. High Impact.**

- Difficulty estimate: Kinda demanding technically
- Odds for successful results: Excellent
- Odds for some pretty quick success results: Good
- Room for discovery and high impact: High
- Time management: Not super long time blocks required.




- 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!
- Article procedure is very poor.
- Preliminary POP experiments show that we can simplify.
- Some of the procedural mechanics require some level of physical strength and manual/mechanical dexterity.




Suggestions for us:

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

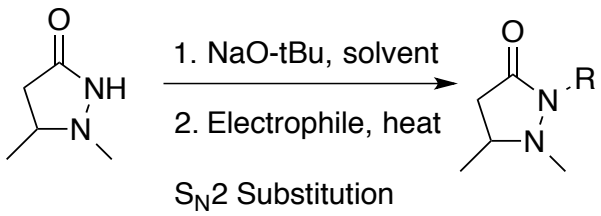
Reddy, K. R.; Roy, A.; Ila, H.; Juqjappa, H. *Tetrahedron*, 51, 40, p10941-10952, 1995. Regiospecific Generation and Application of 3-Lithiomethyl-2-methyl-1-phenylpyrazolinone as 1 ,3-Binucleophile in Aromatic Anuelation: A Novel Approach for Synthesis of 1,2-Disubstituted Indazolones and their Condensed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

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

**N2-Alkylation of N1-Methyl substrate. Analogs**

- Difficulty estimate: Low
- Discovery level: High
- Odds it will work: Pretty good for simple 1º electrophiles, unknown for 2º ones?
- Odds for some pretty quick success results: Good
- Access for time-controlled lab blocks: Excellent?
- I think we've got a good stock of the starting material

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




Potential Alkylation Agents:
Methyl, ethyl, etc.

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

Would ideally like this to work for not only 1º but also 2º substrates, including ideally cyclohexyl.

Expected best guess would be simplest: NaOtBu or NaOMe in methanol

- An alternative might be to use LDA in either THF or in methanol.

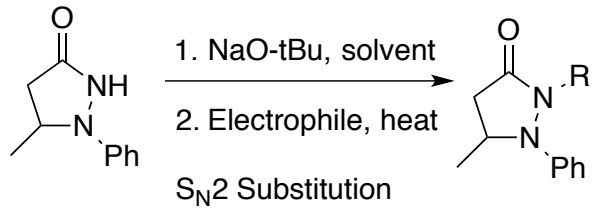
Possible side-products:

- O-Alkylation?
- Double alkylation? ($2^{nd}$ either on C4, or else on N1?).

**N2-Alkylation of N1-Phenyl substrate. "Phenyl Flip" Analogs**

- Difficulty estimate: Low
- Odds it will work: Good for simple 1° electrophiles, doubtful for 2° ones
- Odds for some pretty quick success results: Decent, but kinda yes-or-no
- Access for time-controlled lab blocks: Reasonable?
- Challenge: Not sure how much of the starting material is available.
- May need to try to synthesize the starting material, or have me take a day to try.

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

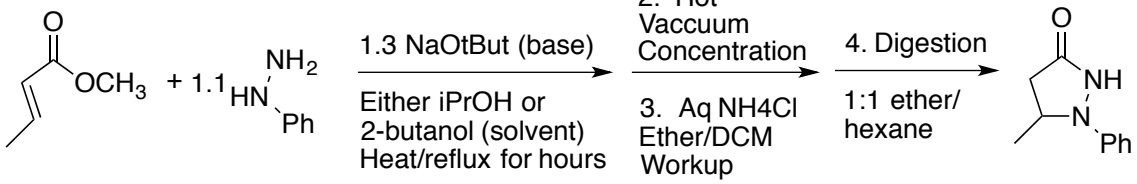



Potential Alkylation Agents:
Methyl, ethyl, etc.

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

Synthesis of the starting material: (This worked well in past for Hawau, but not so well when a student tried to reproduce it. Maybe a reaction I should try myself to see if it's reproducible, or if perhaps there is something wrong with the base or the solvent that prevents success?).
-Would want a good stock of SM for the above project.

**Starting Material Prep**

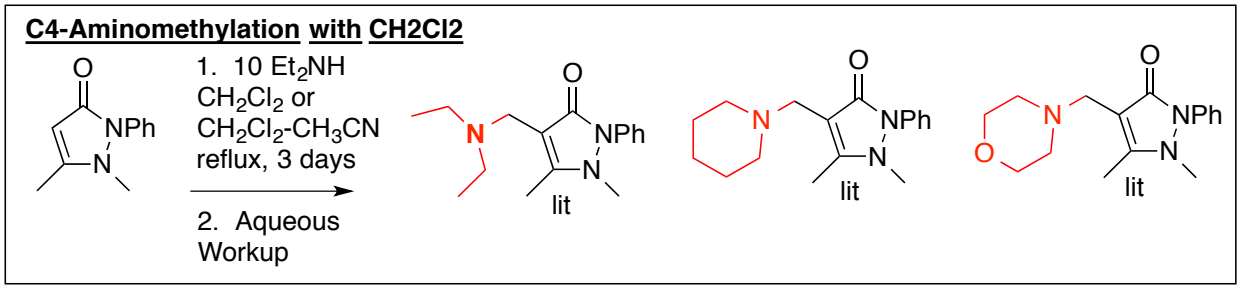



See Jasperse notebook, 2018, p267-273

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

Difficulty estimate: Modest
Odds for some successful results: Good
Odds for some pretty quick success results: Good

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?

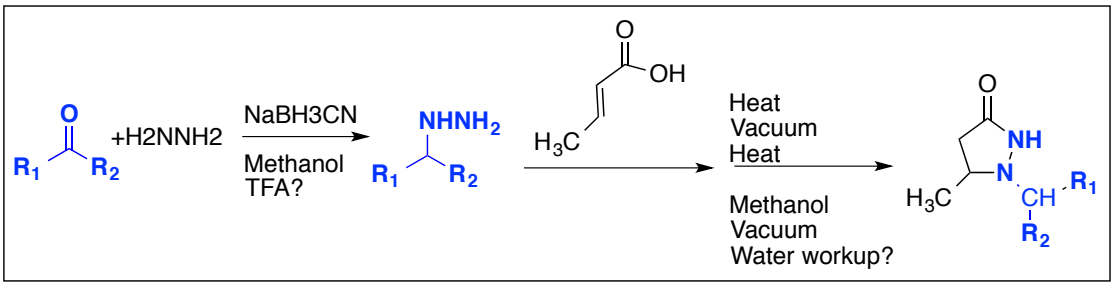
Chemicals and supplies:
We have antipyrine. And the solvents.
We have diethylamine
I have ordered piperidine (6-ring amine) and morpholine (6-ring amine with oxygen)
We have pyrrolidine (5-ring amine).

Notes from source paper:

8. Not sure they optimized the time at all. They said 3 days, but not sure needed.
9. Would be nice to monitor by NMR sample-checks periodically to get a feel for how long it actually takes?
10. NMR in-situ tests can work. Will need to do vertical-expansion, given the large excess of the amines.
11. Theirs suggested maybe better/cleaner/faster with acetonitrile solvent added, for other analogs. Worth testing for ours?
12. Workup: Water washes will be the key. That will take out the ammonium chloride side product, and each of these smallish amines are pretty soluble in water. So getting crude product shouldn't be too complicated.
13. Not sure whether further cleanup will be required? Recryst? Chromatography? I think the paper has suggestions.
14. Not sure whether 1° might also possibly work, even if the paper didn't show any such?

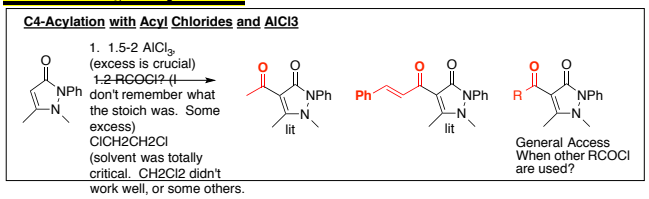
**In-Situ Hydrazine formation and one-pot N1-Alkyl product.**

- Difficulty estimate: Very high
- Discovery level: Super high.
- Odds it will work: Modest.
- Odds for some pretty quick success results: Modest
- Operational difficulty: Low.
- Access for time-controlled lab blocks: High. Experiments probably short.
- Really a remote kind of longish shot. But *IF* it actually works kinda decent, it would really be a convenient quick-stop way to make N1-variants from el-cheapo reactants.




**Craig Q's:**
**Would residual NaBH3CN mess up addition-cyclization? Or harmless?**
**Would we be able to wash the product, and clean it up?**
**Even if yield was modest, IF the product could be reasonably clean, it could be really nice.**

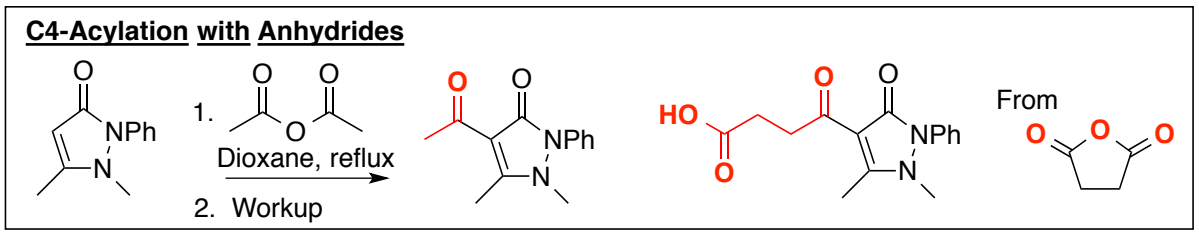
# C4-Acylation with Acyl Chlorides Abby. Solved? See Fall 2019 notebook Jasperse and Abby andAbby reports.




## References, PDF's:


5. "Acetyl Chloride Antipyrine Acylation 1962 Article" (jasperse pdf)
6. "Acetyl Chloride Article; English translation" (jasperse pdf)
7. 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"
8. Stach, K. Archiv der Pharmazie und Berichte der Deutschen Pharmazeutischen Gesellschaft, 295(11), 853-9; 1962 Substituted derivatives of pyrazolone. I. Pyrazonyl carbinole

**C4-Acylation with Anhydrides. Logan Attempted. Did NOT Succeed. Fall 2019**




This did NOT work. No value, given the clean and practice success of the chloride way.

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….

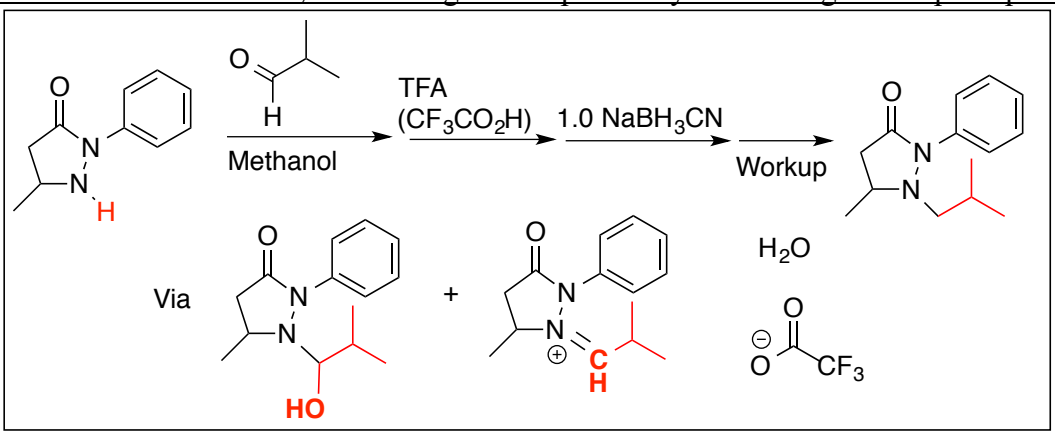
Brent Schulte Research Project Plan Draft 2. Fall 2019

2019 Updates, Projects:

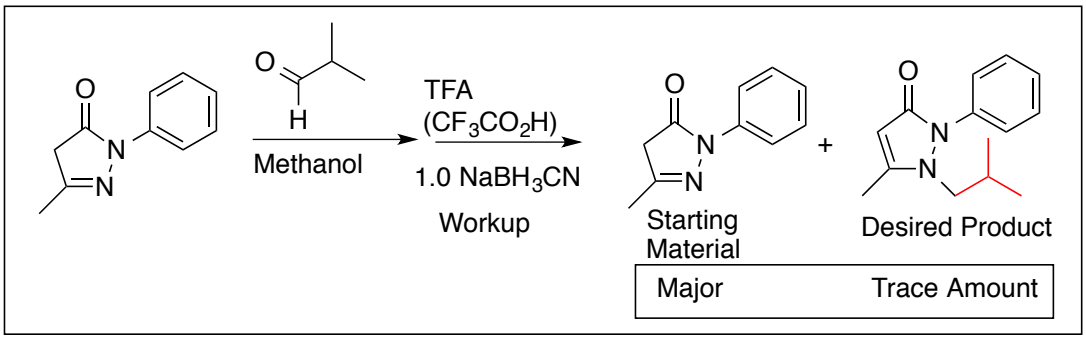
**"STAB" Use for Reductive Alkylation. Might STAB work better than NaBH3CN? Or might NaBH3CN work better with milder CH3CO2H instead of CF3CO2H**

**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?**

6. Control: Same NaBH3CN/TFA that you did last spring (control)
7. 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?)
8. TFA vs STAB test: NaBH(OAc)3/TFA methanol. (Basically do same, but replace NaBH3CN with STAB?
9. NaBH(OAc)3/Acetic acid in ClCH2CH2Cl test.
10. 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?

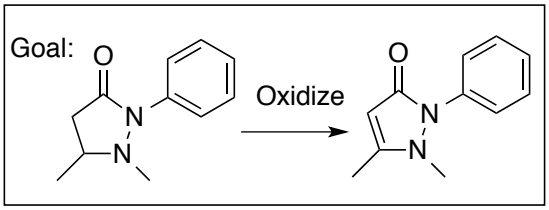
Reference:

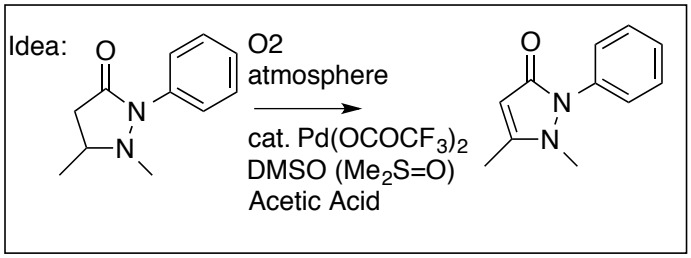

3. **"Sodium triacetoxyborohydride – Wikipedia"** https://en.wikipedia.org/wiki/Sodium_triacetoxyborohydride
4. "Sodium Triacetoxyborohydride - Gribble - - Major Reference Works - Wiley Online Library"

**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.



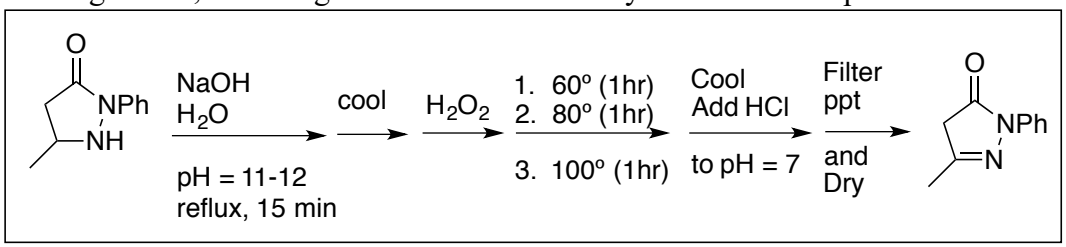




**References:**

**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?

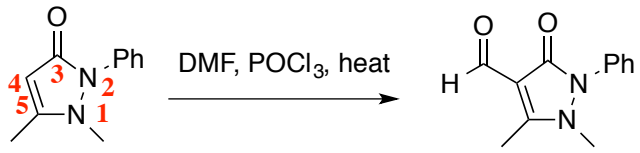
**Chromatographic Purification Project**: Mikayla will Try

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.

Specific project suggestions for Fall 2018

8.

**C4-Formylation.**

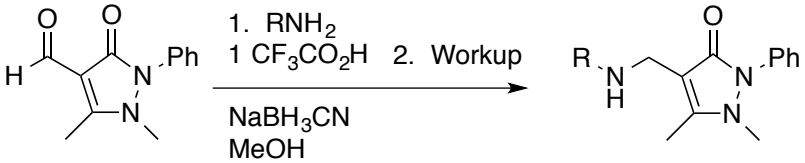



**Untried.**
**Pretty detailed literature procedure.**
**Want to try to do a large scaleup reaction, AND get it pretty clean.**
**To be done in combo with following two box.**

Matt Anderson

9.

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

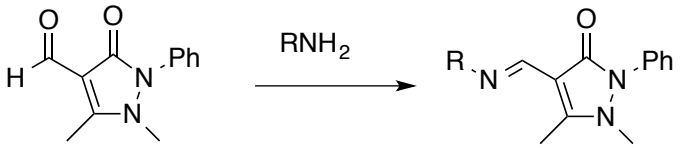



**Untried. No literature?**
**I don't have literature references, but haven't looked hardly at all…**
**Again, a range of different types and sizes and hybridization of amines could be screened?**

Matt Anderson

10.

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



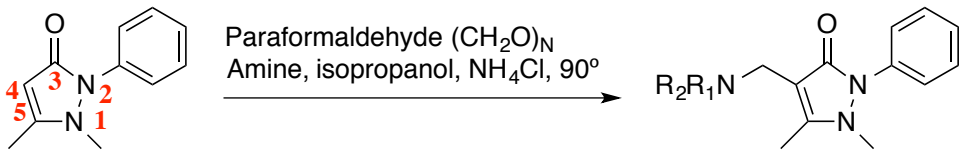

Lots of Examples, often with elaborate "R" groups

**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

11.

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

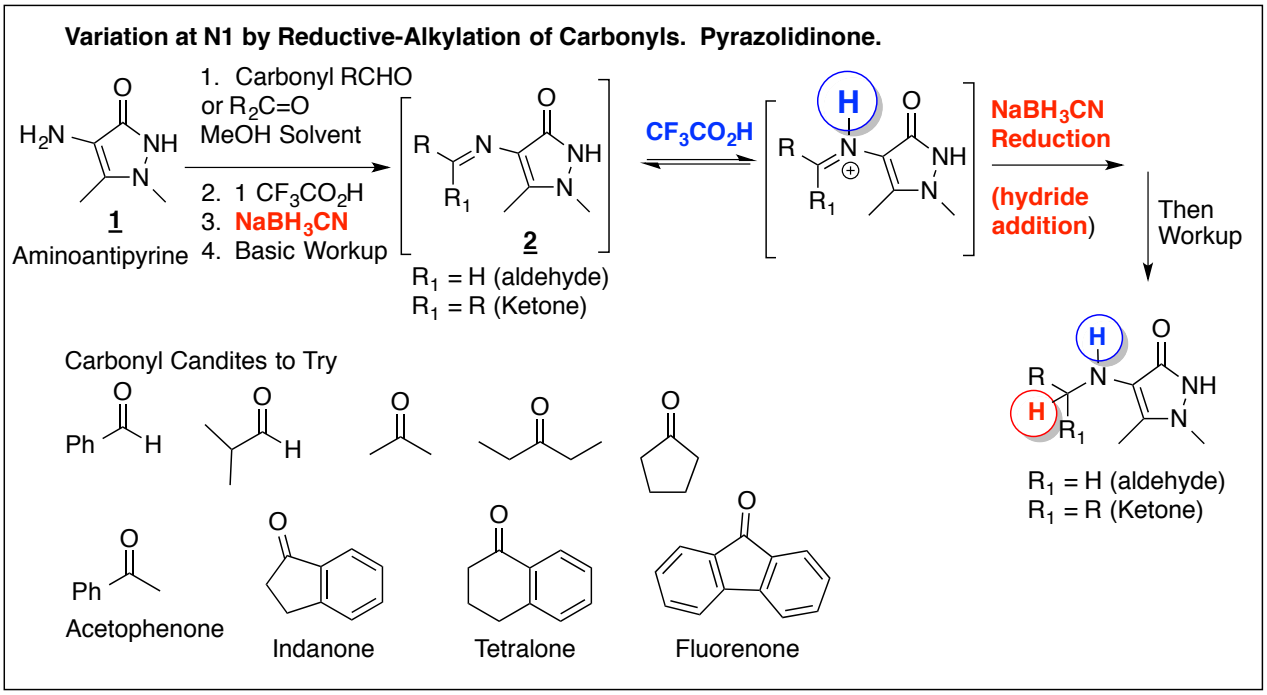



C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

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

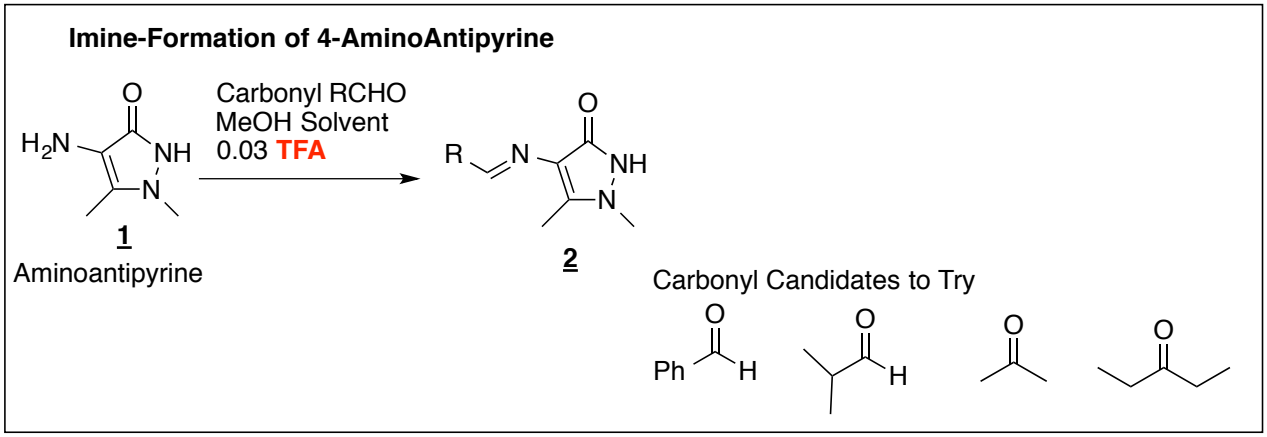
## Reductive Amination of Aminoantipyrine: Formation of 4-Alkylaminoantipyrine Analogs

12.



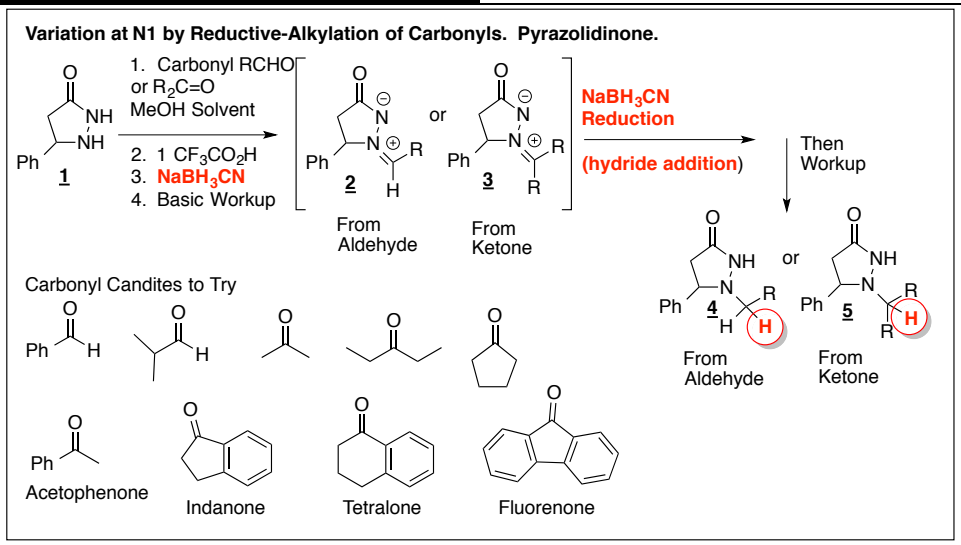

Jasperse has done small scale trial, proof-of-principle experiment; Ansu confirmed
Will it work for both aldehydes and ketones, or only aldehydes?
Will it work for ketones that get bigger
Will it work for conjugated ketones?
What might be a good workup procedure?
What is the best way to purify? Digestion?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

13.



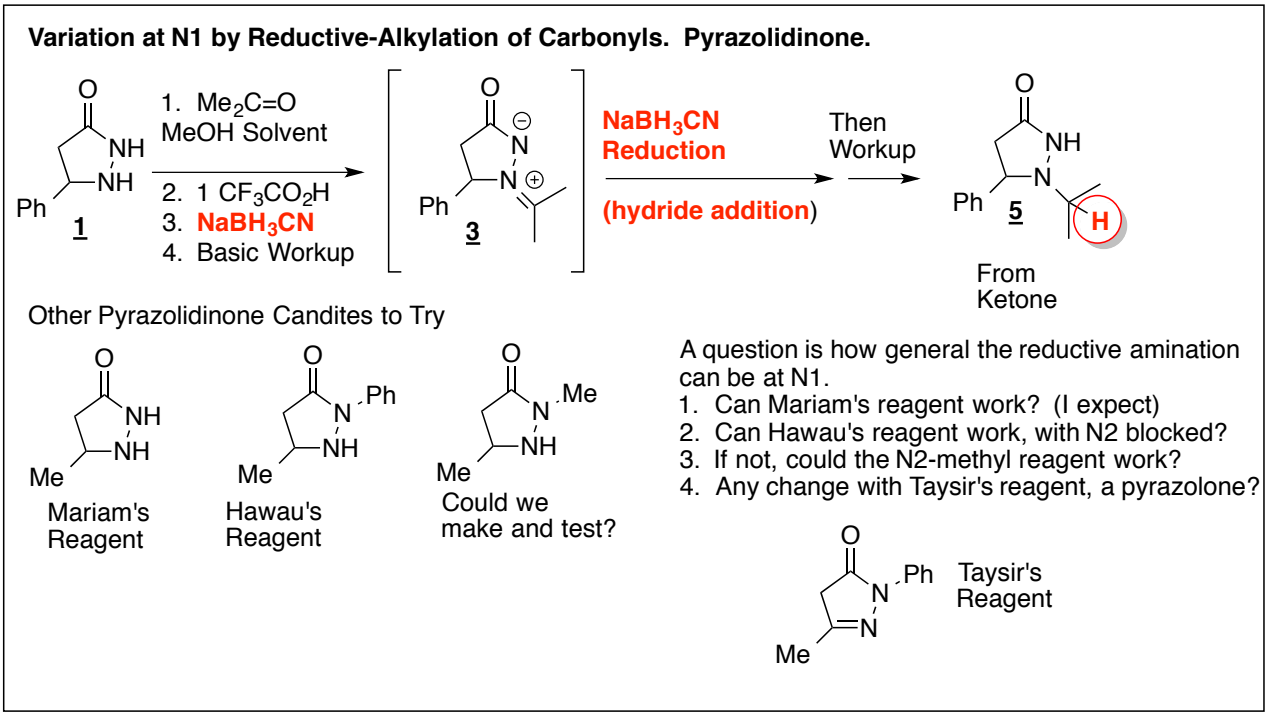
## Reductive Alklation at N1. N-Alkylation

14.



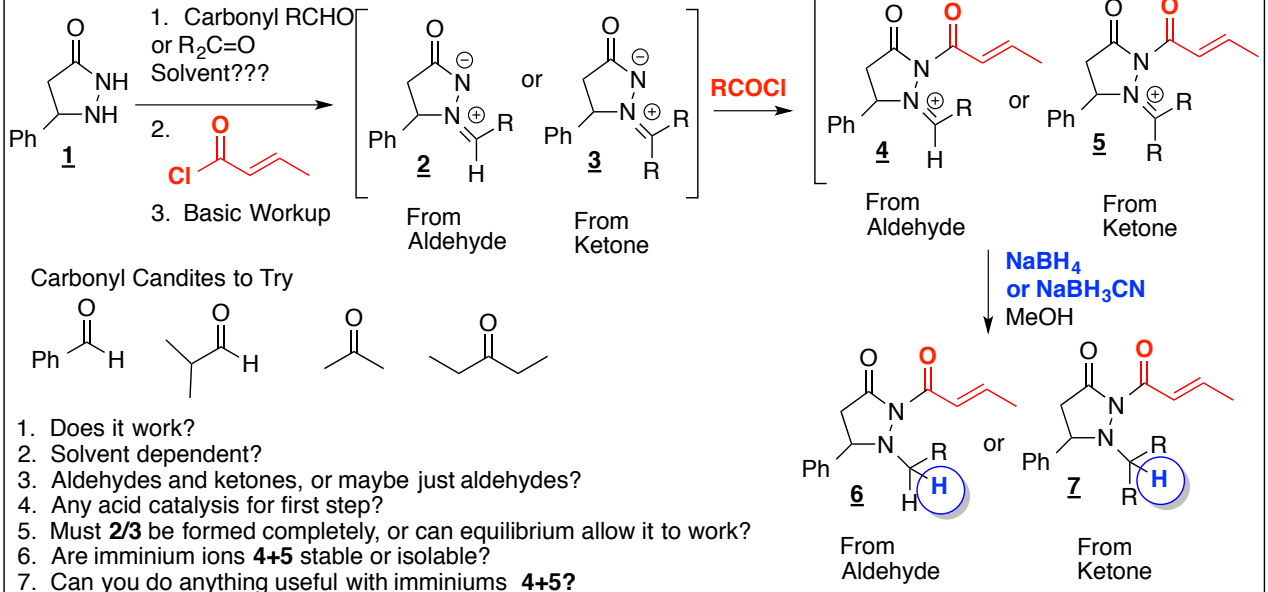

Jasperse has done small proof-of-principle using benzaldehyde and acetone; I think it works great! (But not sure…)

14 Does it work for other Pyrazolidinones?



15

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




Carbonyl Candites to Try

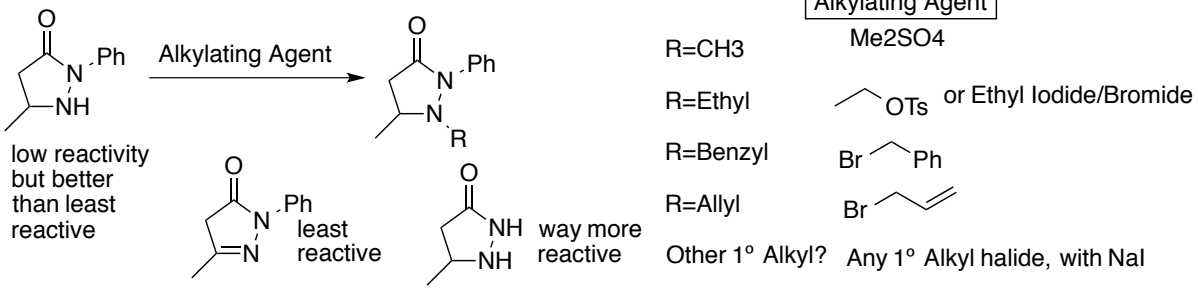


1. Does it work?
2. Solvent dependent?
3. Aldehydes and ketones, or maybe just aldehydes?
4. Any acid catalysis for first step?
5. Must **2/3** be formed completely, or can equilibrium allow it to work?
6. Are imminium ions **4+5** stable or isolable?
7. Can you do anything useful with imminiums **4+5?**

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

16

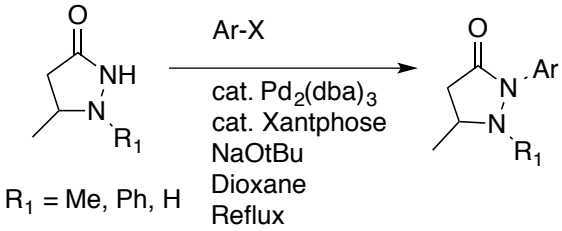
**Variation at N1 by N-Alkylation. Pyrazolidinone.**




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

17

**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

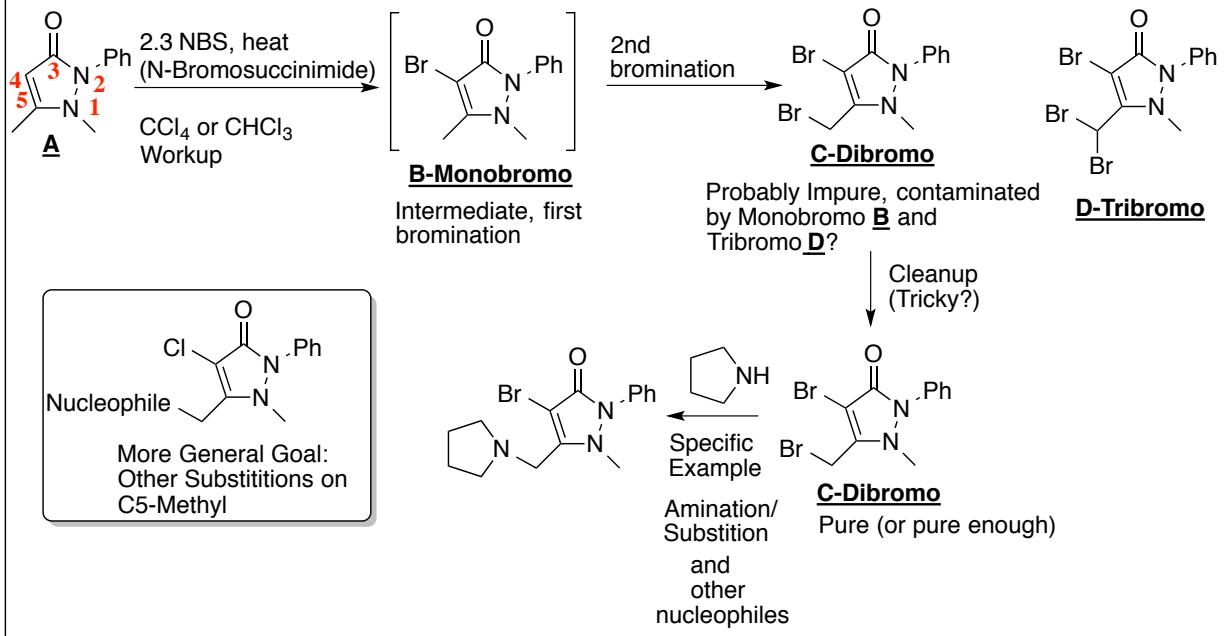
Antipyrine has N2-phenyl, so the opportunity to install variable aryl analogs from Hawau's Reagent would be really nice.... if it works.

**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…

18

**C4,C5-Dibromination**




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

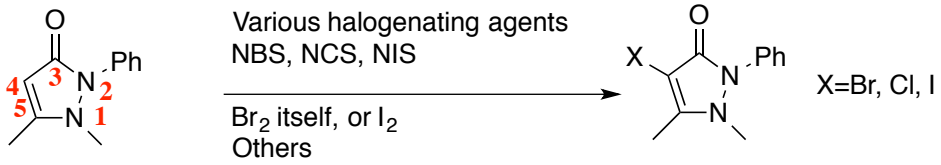
A preliminary proof-of-concept reaction by Kaniel and Bishnu demonstrates that this kind of works.

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.

19

**C4-Bromination/Chlorination/Iodination**




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

**Get and Print documents:**

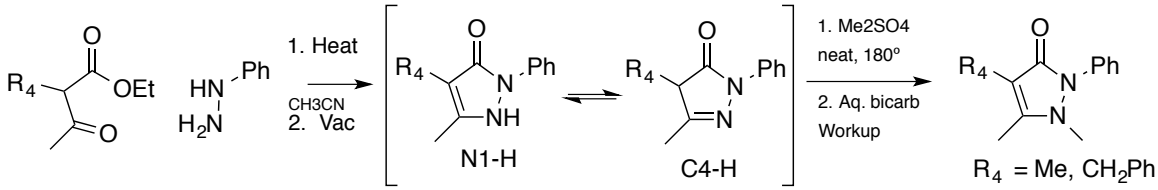
Kaniel NCS General Procedure Suggestion.docx
NCS Procedure and Reference.pdf

Table of Contents Update10/5/16 1/12/16 9/6/17 1/12/18


| | |
|---|---|
| 1. | Table of Contents |
| 7 | Intro; Terminology; Numbering; Relative Reactivity; Synthesis of Parent |
| 8 | **Stock of Home-Made (or Store-Bought) Ready-to-Use Chemicals:** |


9

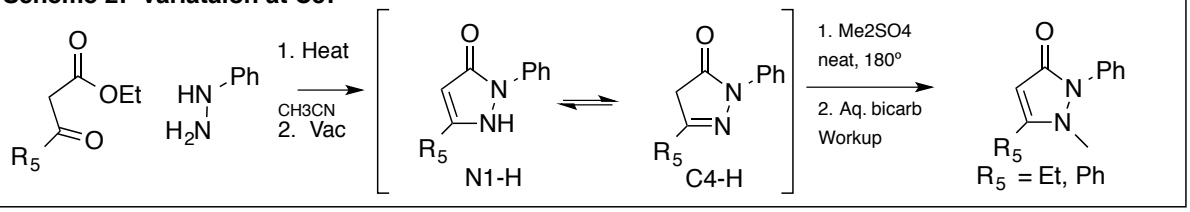
**Scheme 1: Variataion at C4:**




Update: Checked. Works. Taysir. Proof of Principle. (limited examples)

10

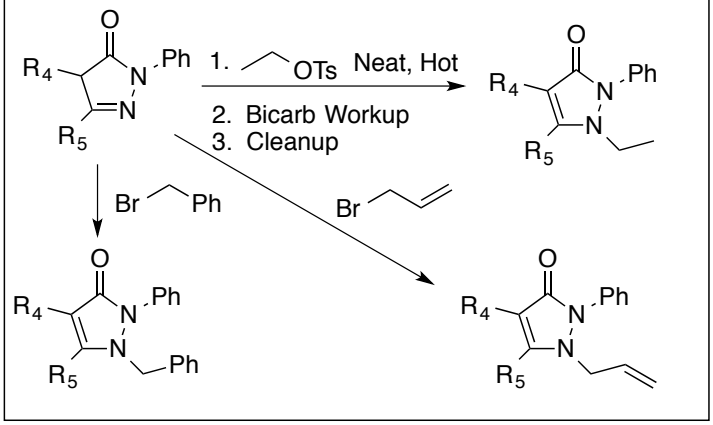
**Scheme 2: Variataion at C5:**




Update: Checked. Works. Taysir. Proof of Principle. (limited examples)

11

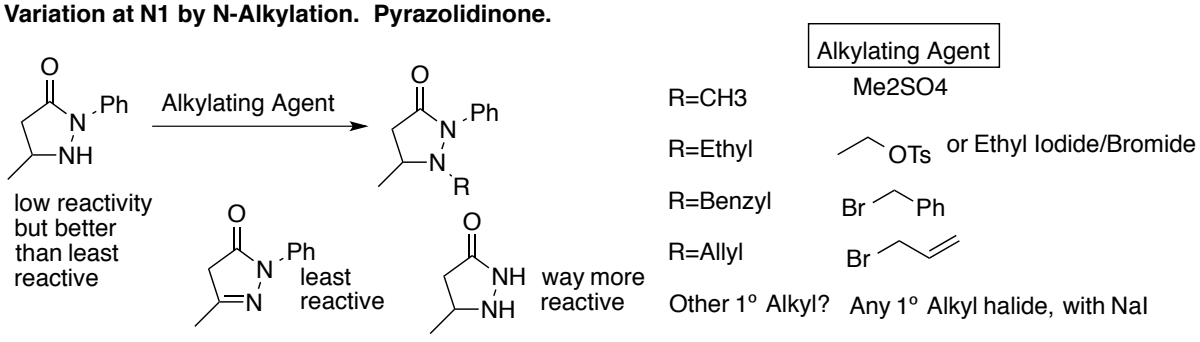
**Scheme 3: Variataion at N1 by N-Alkylation:**




Update: Checked. Works, somewhat. Craig, Erhiga. Proof of Principle. (limited examples, Me, Et.)

12

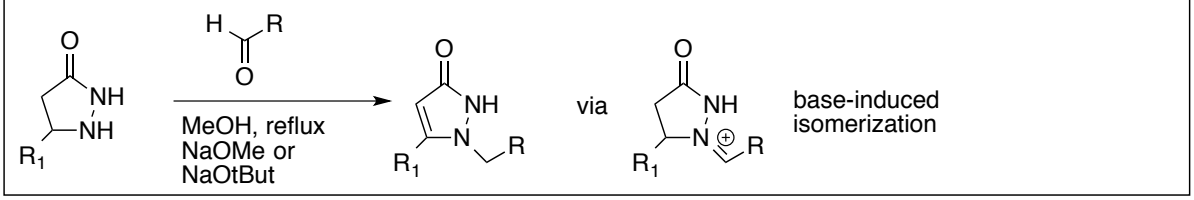
**Variation at N1 by N-Alkylation. Pyrazolidinone.**




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

13

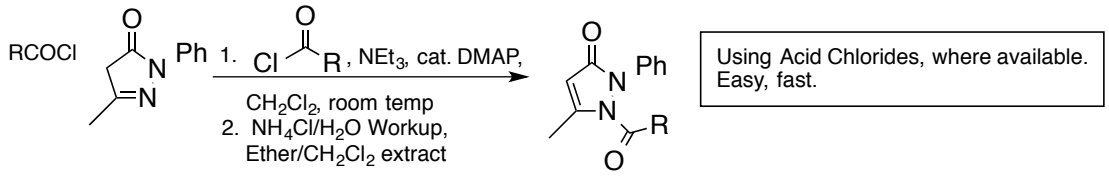
**Variation at N1 by N-Aldehyde Reaction, then Alkoxide Isomerization. Pyrazolidinone to Pyrazolone**



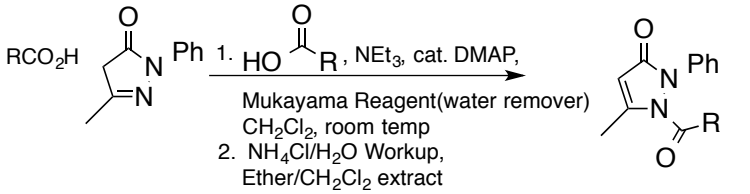

Update: Checked. Works with Aldehydes. Proof of Principle. Fails if N2 is substituted. Ketones Unchecked. (Taysir)

14

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




Using Acid Chlorides, where available. Easy, fast.

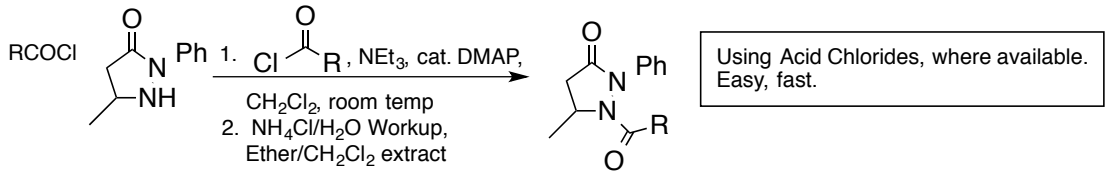



Using Carboxylic Acids, which are often more accessible than the acid chlorides.

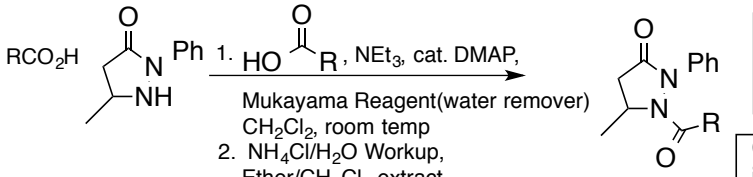
**Update: Works with Acid Chloride. (Andrea). Easy. Didn't Try with Acid/Mukayama..**

15

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




Using Acid Chlorides, where available. Easy, fast.



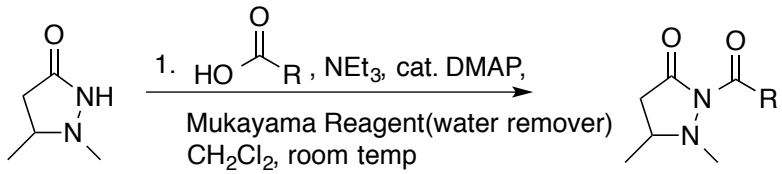

Using Carboxylic Acids, which are often more accessible than the acid chlorides.

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.**

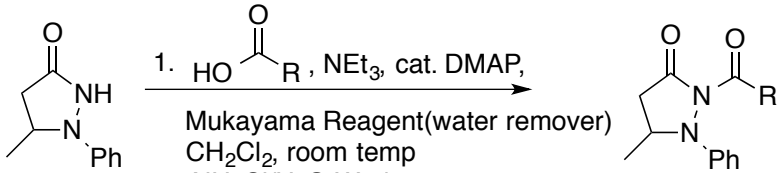



Using Carboxylic Acids, which are proven. Doubtful if RCOCl work

**Untried on dimethyl Should work.**

17

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

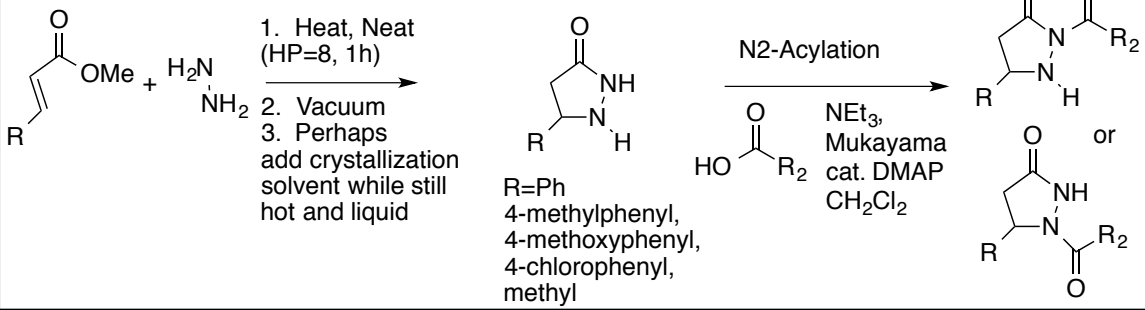



Using Carboxylic Acids, which are proven. Doubtful if RCOCl work

**Untried. Should work.**

18

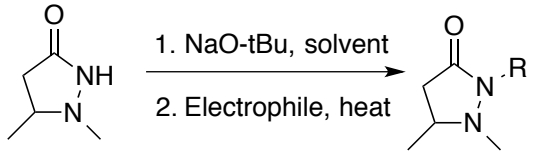
Reactions/Acylation of the "Classic" Hydrazine-Derived Pyrazolidinones. When N1 and N2 were both NH




**Untried.**

19

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



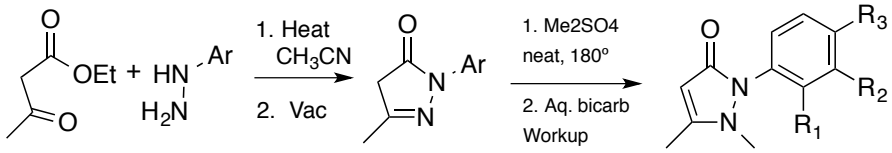

Potential Alkylation Agents:
$Me_2SO_4$, Ethyl tosylate or iodide,
Benzyl or Allyl bromide, etc.

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 $$**

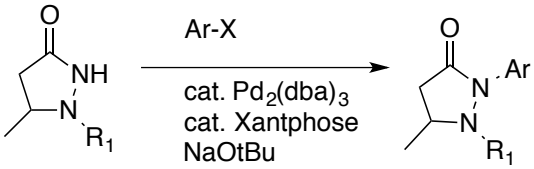



2-Pyridine $86/5
4-CN $57/5
4-Me $36/5
2-Me $40/5
4-Cl $29/5
3-Cl $97/25
2-Cl $80/25
4-F $67/10
2-F $70/5
========
4-Br $132/10
4-OCH3 $200/10
4-CF3 $70/5

**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.**




CHEMReview 2016
Stephen L. Buchwald and Paula Ruiz-Castillo

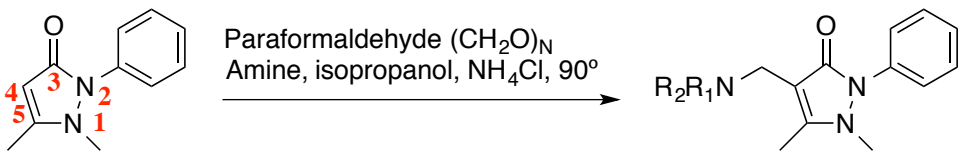
Might be hard. Detailed correct handling of the Pd catalyst and the diphosphorus ligand may be crucial

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**

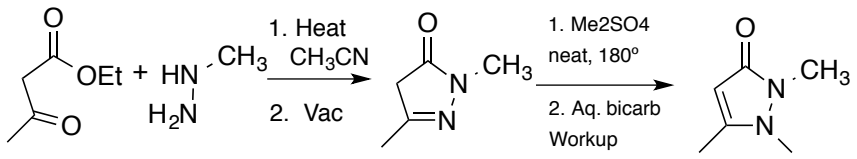



C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

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

23

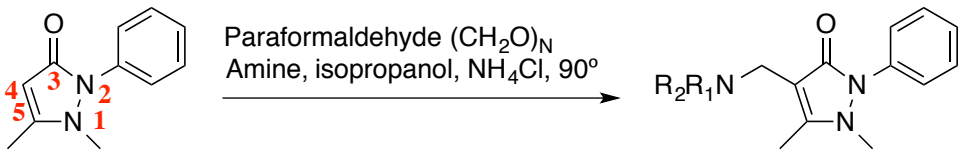
**Scheme 4: Variataion at N2 By Use of MethylHydrazine:**




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

24

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

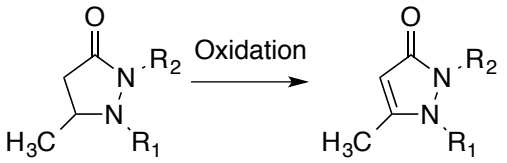



C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

**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.**

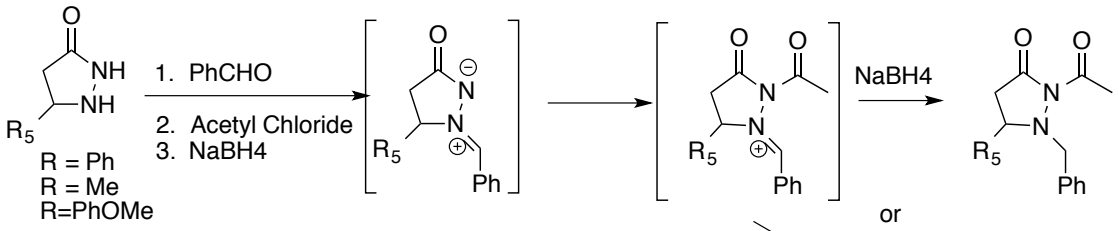
26 Continuation of Page 21, Oxidation

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.**

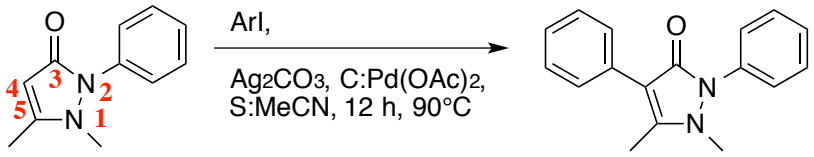



Other aldehydes might also be used.
N2-alkylating agents might possibly be used, also.

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

30

**C4-Arylation. Pyrazolone**

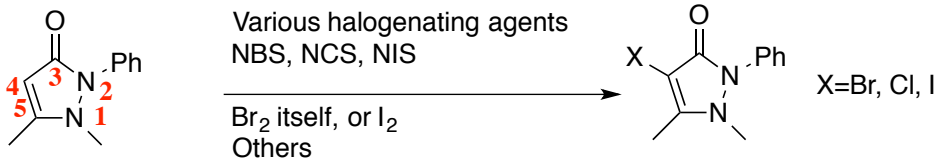



4-Arylation of Antipyrine-Good using PdOAc2 + AgOAc.pdf
Gong, Hao et al From Beilstein Journal of Organic Chemistry, 9, 2033-2039, 7 pp.; 2013

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

31

**C4-Bromination/Chlorination/Iodination**

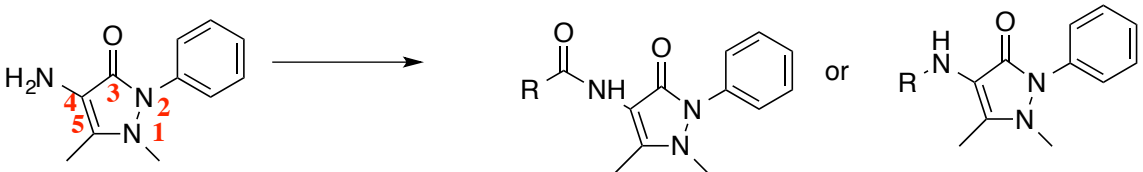



**C4-Hetereo-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf**

**Kaniel is trying.**

32

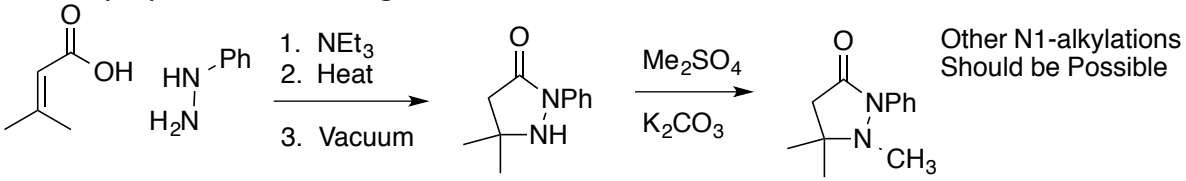
**C4-Nitrogen Varients. Pyrazolone. "Analgin" Derivatives**




**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

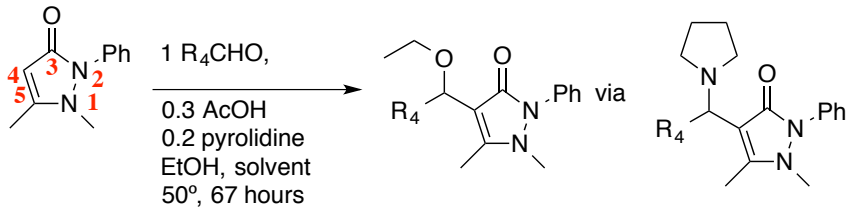
**5,5-Dimethyl Pyrazolidinone Analog**




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

34

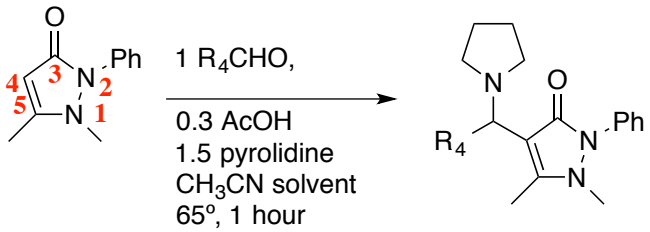
**C4-Aldehyde Reaction**




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

35

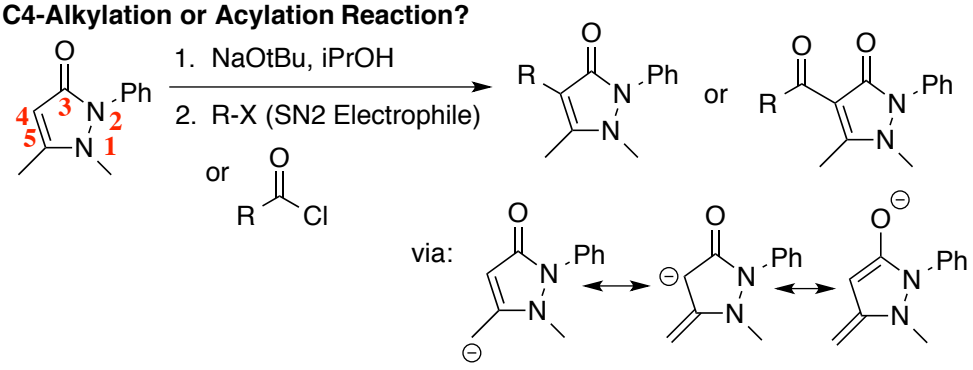
**C4-Aldehyde Reaction**




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

36

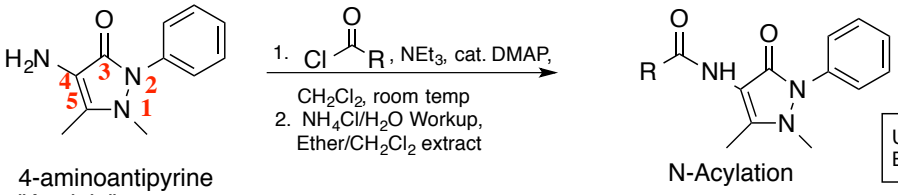
**C4-Alkylation or Acylation Reaction?**




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

37

**Acylation of Aminoantipyrine Using Acid Chlorides**

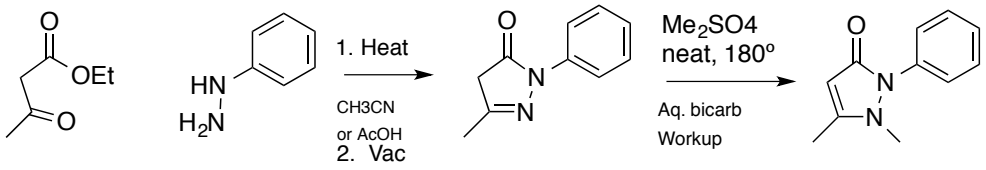



4-aminoantipyrine
"Analgin"
Commercially Available, Alfa-Aeser

Using Acid Chlorides, where available. Easy, fast.

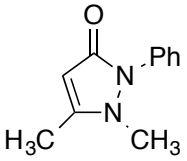
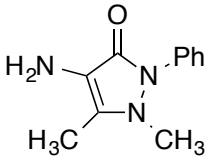
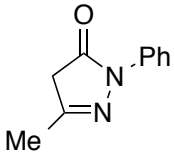
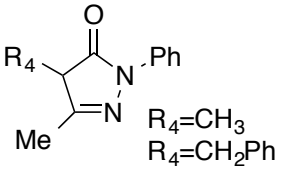
**Literature extensive for acylation.**
**Ansu worked several of these. They worked very well. Easy to Crystallize and purify..**
Ansu had one success with CH3PhCOCl. Not so good with crotonyl, benzoyl.
Check RCOCl, NMR's, etc; maybe do control? Find some others that are good/clean?
Ansu has established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

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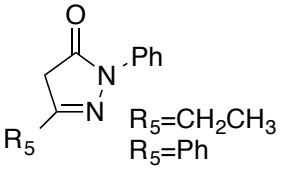
<td>  </td>
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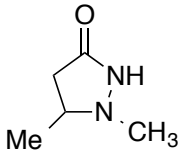
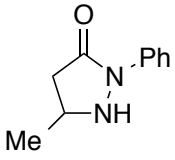
<td>  Hawau’s N1-Methyl Reagent</td>
<td>  Hawau’s N2-Phenyl Reagent</td>
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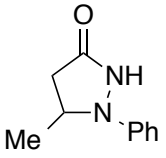
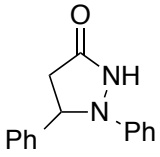
<td>  Sunny’s Reagent</td>
<td>  Jasperse Diphenyl Reagent</td>
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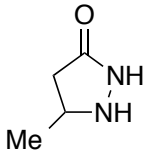
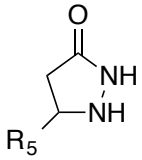
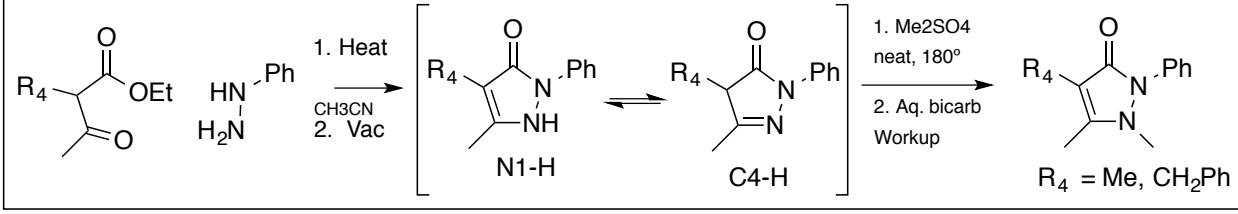
<td>  Mariam’s Reagent</td>
<td>  Trinh’s Reagents</td>
</tr>
</table>

## C4-Variation (Alkyl/Benzyl)

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

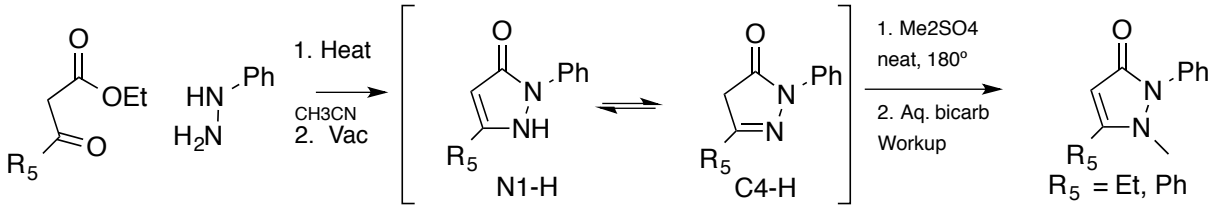
**Scheme 1: Variataion at C4:**




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:**



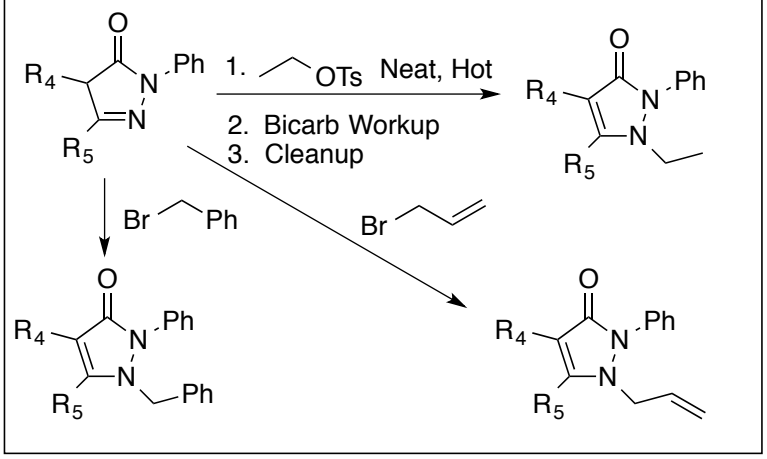

CAS ID:

| $R_5$ | 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:**



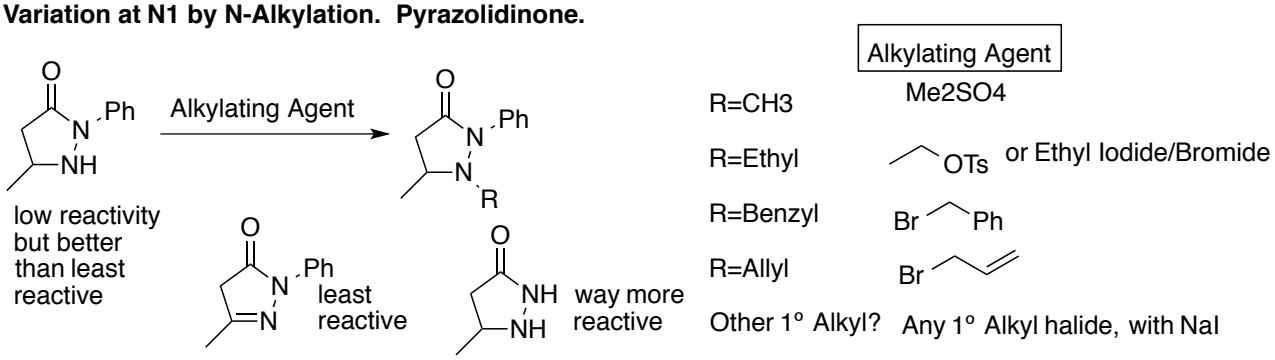

1. Alkylation is pretty slow
2. Preliminary results: Works well with dimethylsulfate hot/neat (see scheme 1)
3. Tried ethyl iodide, and that works, slowly, but partially/incomplete. Seemed very clean, just didn't go to completion in preliminary attempt.
   - Problem is getting hot enough without having 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

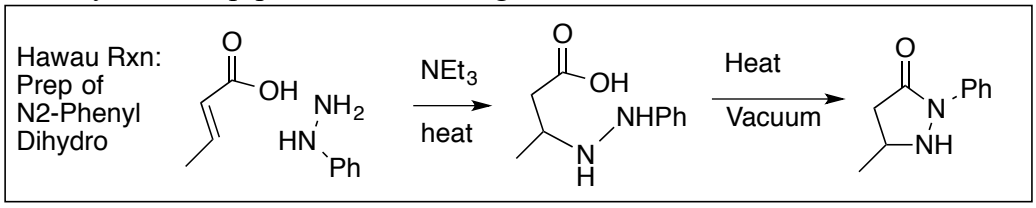
| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| | 80-40-0 | Ethyl Tosylate | Sigma/Aldrich: $26/50g |
| | | No other tosylates commercial. | Sigma/Aldrich: $26/50g |

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

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

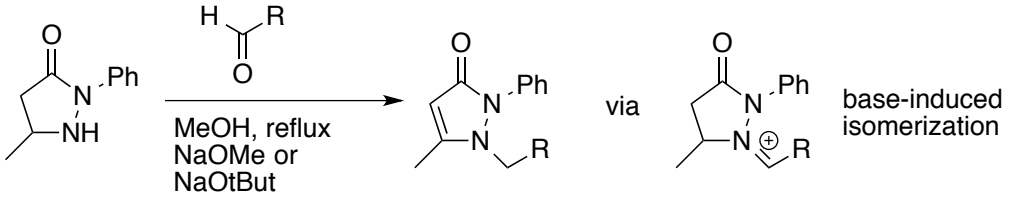



1. This would be a natural match project (Alkylations Projects) with page-3, which involves N1-alkylation of the double-bonded analog shown on the bottom.
   - See discussion and observations from the Page 3/Scheme 3 alkylations
   - The same alkylating agents that work there should work here (only better/easier 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.



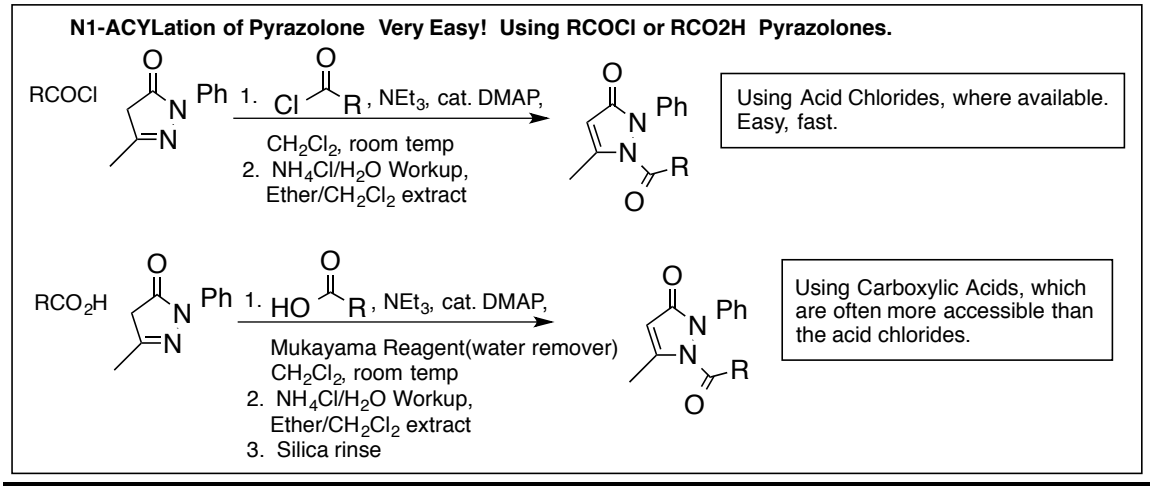
**Variation at N1 Pyrazolones. By Reaction of Hawau Phenyl-Pyrazolidinone with Aldehyde, followed by NaOR/ROH isomerization. Pyrazolidinone => Pyrazolone**

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

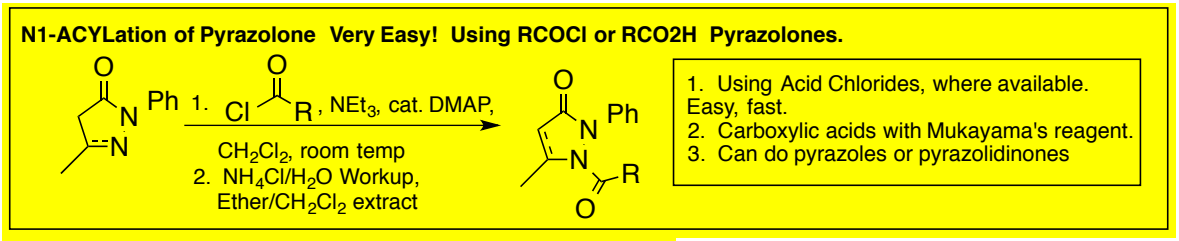



1. Kangasmetsa, Jussi J. et al From PCT Int. Appl., 2013096501, 27 Jun
2. N1-Aldehyde use, followed by NaOMe/MeOH isomerization: N1 plus Aldehyde, then NaOMe/MeOH reflux to isomerize
   - … 35 mmol… 5-methypyrazolidin-3-one. This oil was dissolved in MeOH (20 mL), cooled to 0°C under N2 atmosphere and 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).

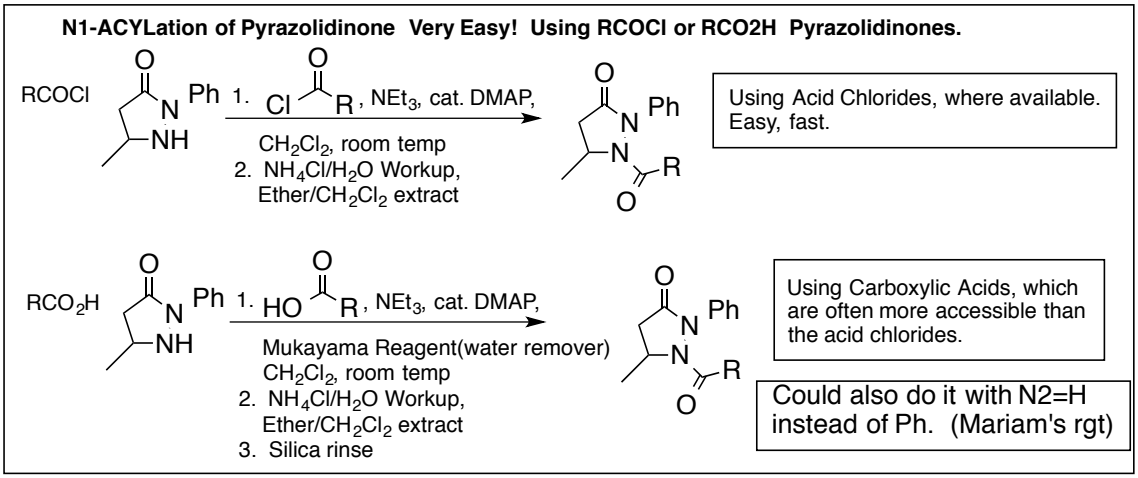



1. Super Easy and flexible
2. Preliminary result using 4-toluyl chloride appears to complete within minutes at room temp, and was easy to work up.
3. Preliminary experiment using crotonic acid also appeared to proceed very quickly and easily.
4. Antipyrine of course does not have the carbonyl attachment 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

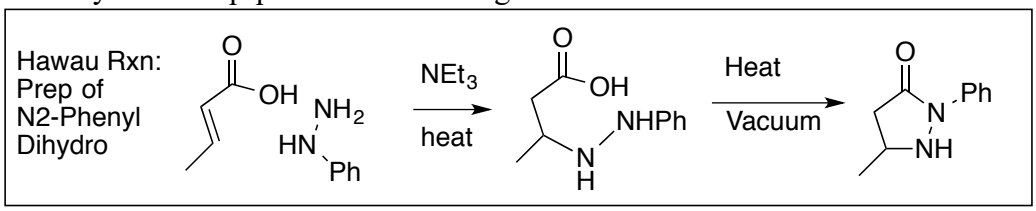



Use General Thing for pyrazolone or pyrazolidinone

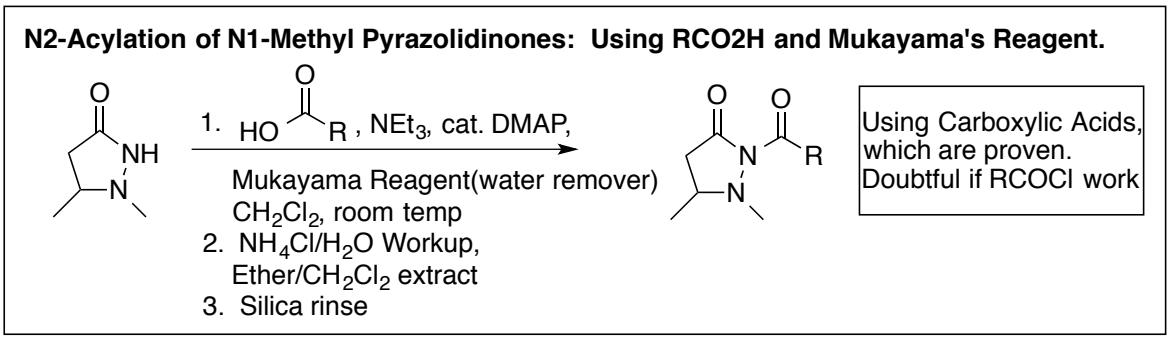
## N1-ACYLation of Pyrazolidinones.




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**



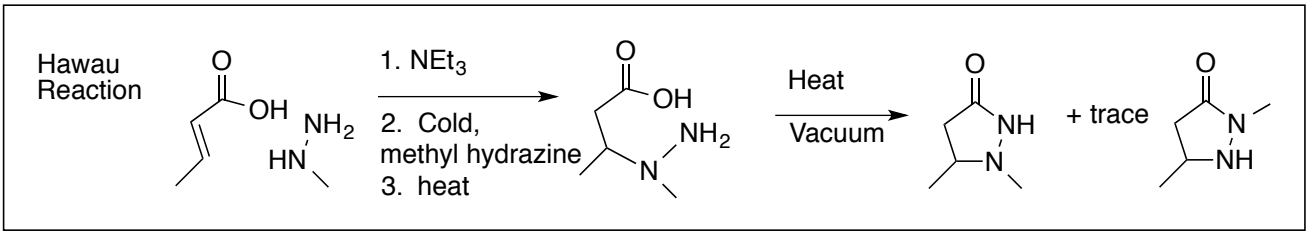

1. Starting chemical synthesis nicely developed by Hawau
2. Starting material isn't completely clean; contaminated by modest amount of N2-methyl isomer
3. The simplest to make here would be R=Ph
4. Antipyrine of course does not have the carbonyl attachment on at N2. So who knows what assay-impact this 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:

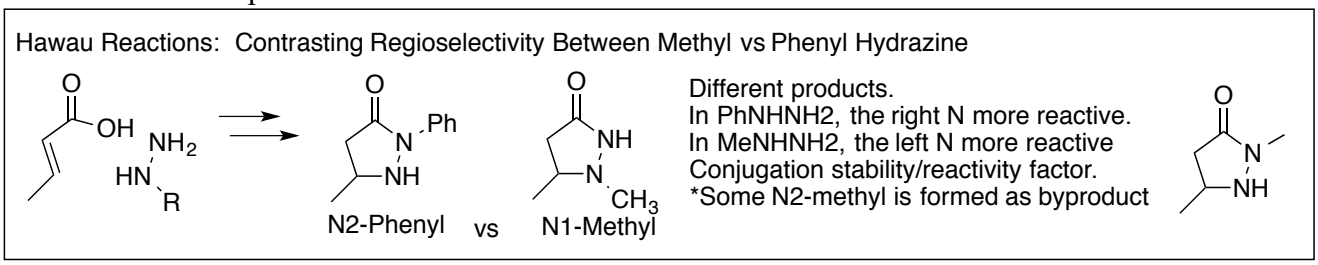
| | CAS | One Name variant | Supplier, Price |
|---|---|---|---|
| Me | 60-34-4 | Methyl hydrazine | Sigma/Aldrich: $308/25 |

Note: Aldrich is cheapest here, and good.

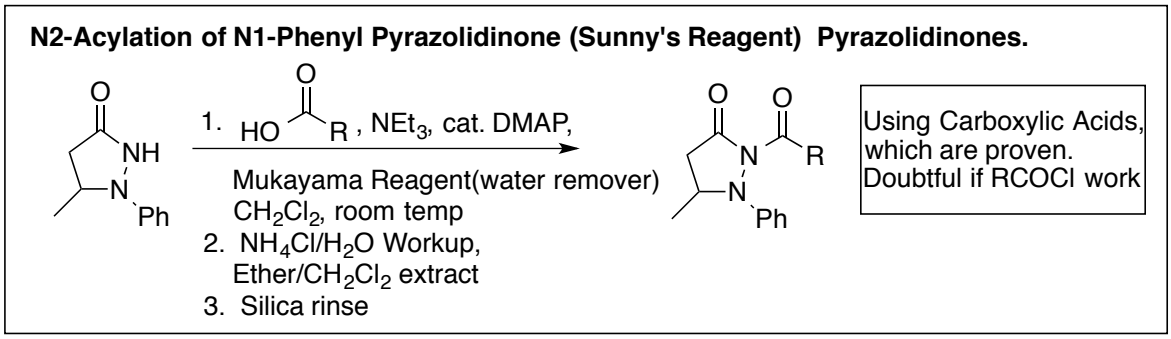
- Price looks worse than it is, because it's so small. So you get a lot of moles per gram.
- INCLUDE IN GRANT TO BUY A BUNCH
- Note: In the Hawau reaction, starting ice-cold and doing a lot of low-temp improves the selectivity for the N1-Me product. So, if you need more, don't just mix and heat!




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.

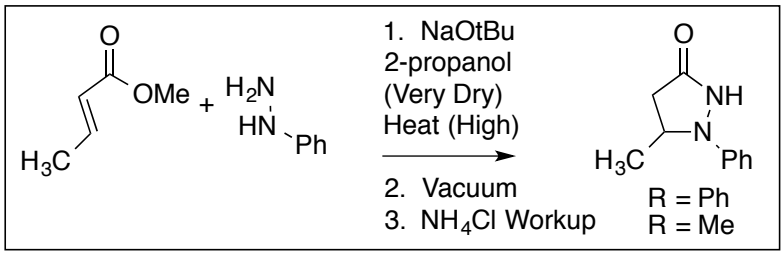


**N2-Acylation of N1-Phenyl Pyrazolidinone, Using Sunny's Phenyl Reagent:**

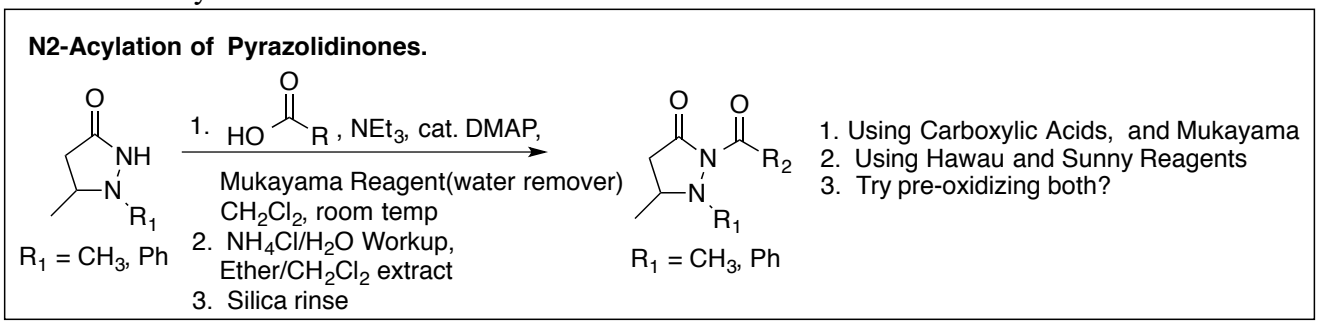



1. The N2-acylation using carboxylic acid and Mukayama reagent works to make derivative
2. This will function as an "Antipyrine-Twist" analog. If three core components of antipyrine are the aromatic ring, the 5-ring, and the carbonyl, this will effectively push the carbonyl over relative to the arene.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

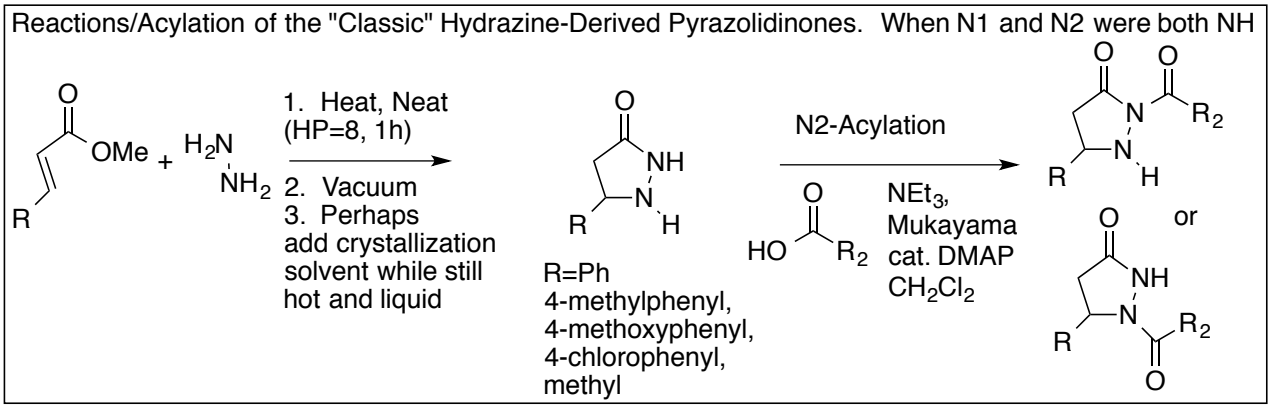
Prep of Sunny's Reagent:




General N2-Acylation



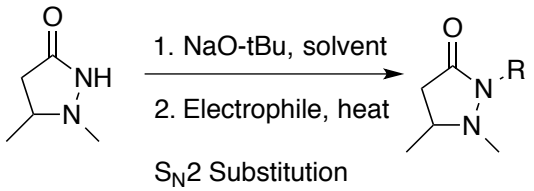
**N2-Acylation of N1-H Rings, Using Trinh's Reagents:**
**Acylation Using Acids and Mukayama's Reagent: Di-Hydro Rings**
**(Actually, I'm not sure what will happen here. Maybe just some exploring to check.)**




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**



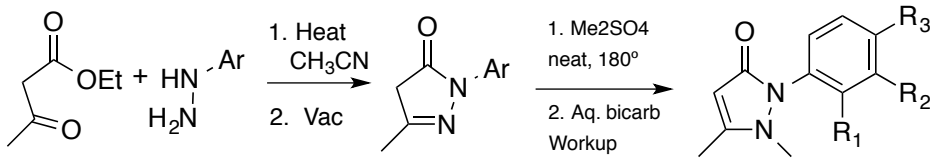

Potential Alkylation Agents:
$Me_2SO_4$, Ethyl tosylate or iodide,
Benzyl or Allyl bromide, etc.

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

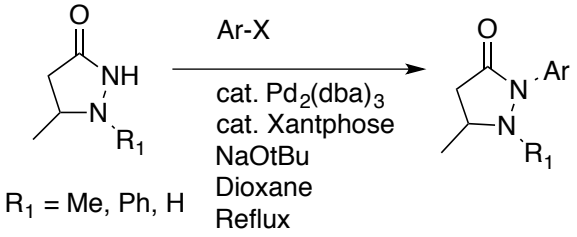
Notes:

- 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

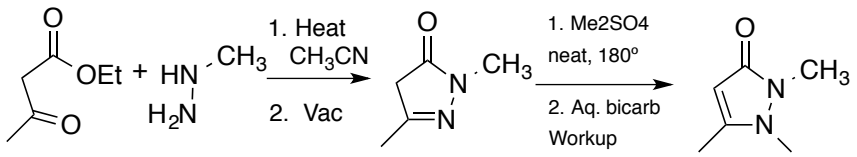
Might be hard. Detailed correct handling of the Pd catalyst and the diphosphorus ligand may be crucial

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:**

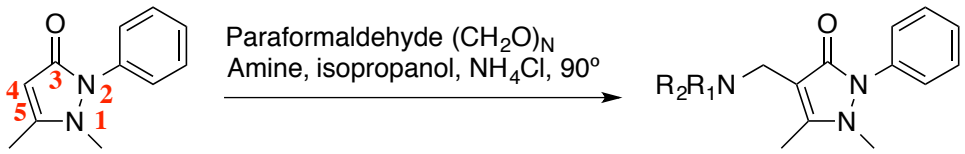



Notes:

- 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.

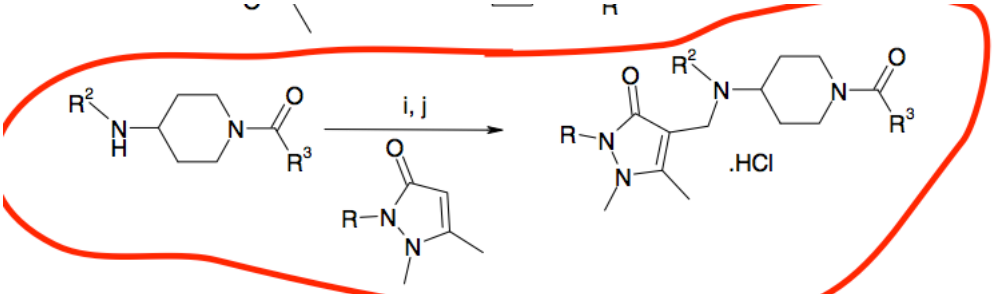
## C4-Aminomethyl Analogs

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



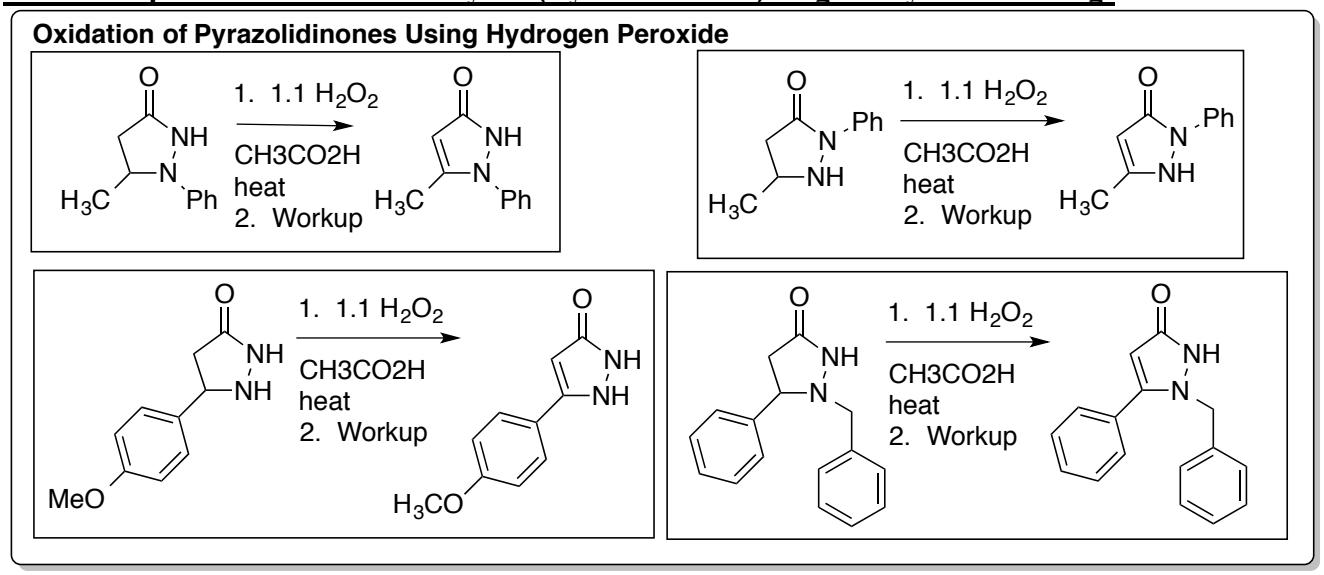

C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231

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**

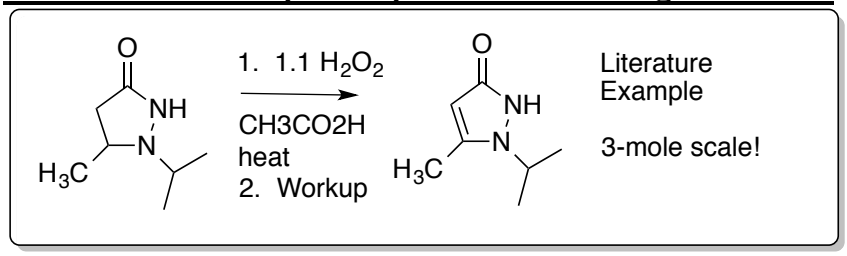



Suggest First Experiment to Try

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.

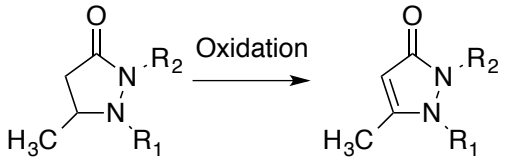
**The literature example and procedure I'm using as a model:**




- 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**

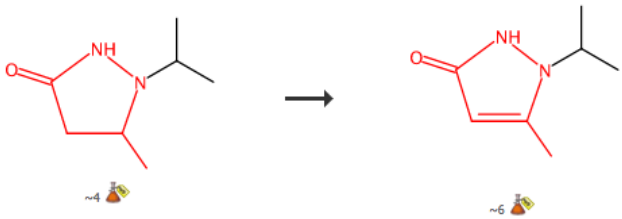
**Oxidation of Pyrazolidinones to Pyrazolones**

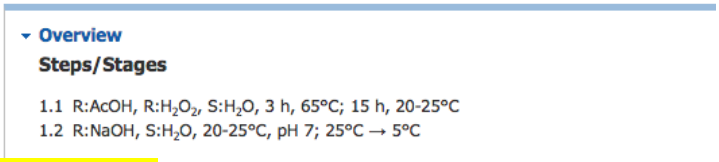



Oxidizing agent candidates:
1. $H_2O_2$, $CH_3CO_2H$
2. $O_2$, cat. $FeCl_3$
3. $K_2S_2O_8$
4. NBS

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.



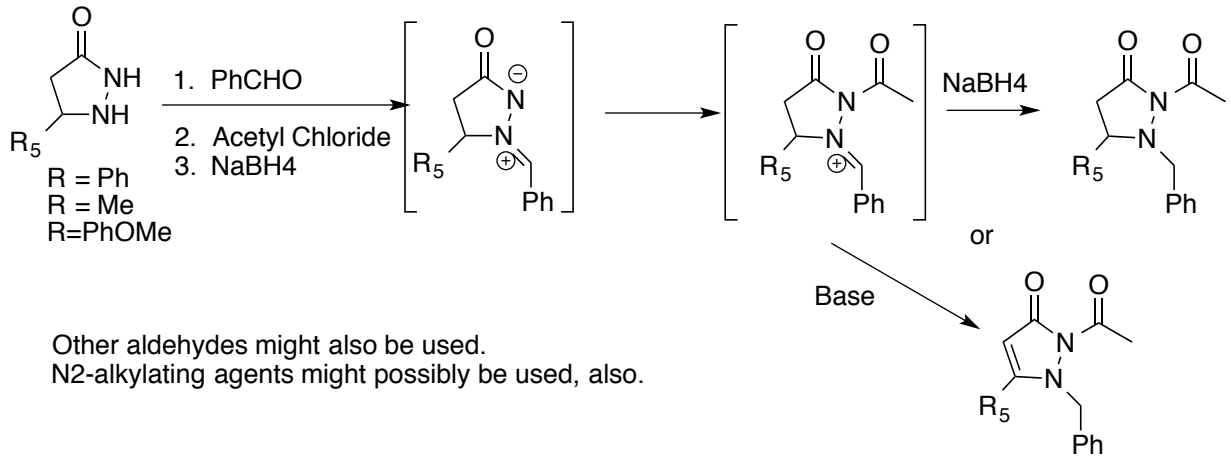

8. Peracetic Acid: Pfrengle, Waldemar From PCT Int. Appl., 2007010015, 25 Jan 2007 To the latter is added 50 mL acetic acid and the mixture is cooled to approx. 3°C. 66.9 g of peracetic acid is added together with 12.5 mL acetic acid. The mixture is stirred at 3°C for approx. 1h. 325 mL of water is then 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.**

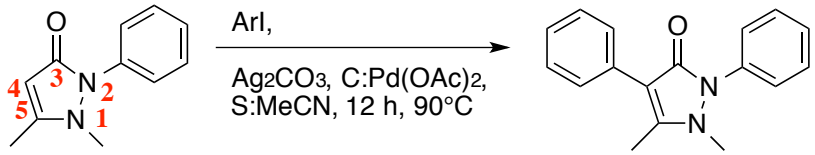
**Sequential Concept: Sequential alkylation-acylation-reduction for N1-alkylation and N2-acylation. Alternative to the NaBH4 might perhaps be the use of base, to produce pyrazolone.**




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**



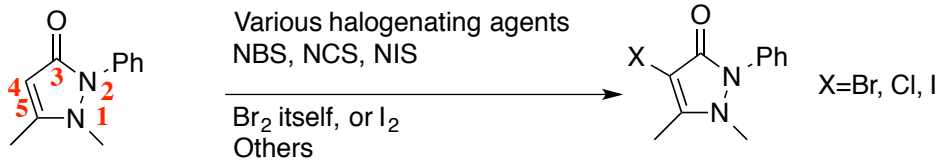

4-Arylation of Antipyrine-Good using PdOAc2 + AgOAc.pdf

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

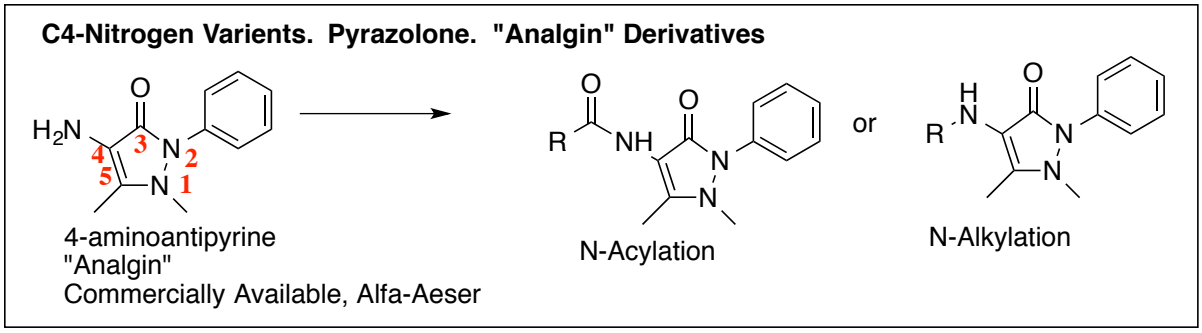
**C4-Bromination/Chlorination/Iodination**




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

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.

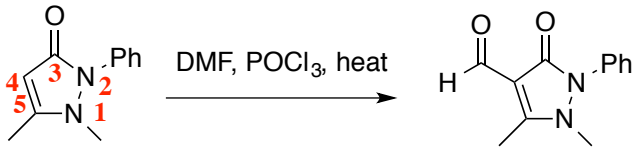
**4-Acylamino and Alkylamino Analogs. Analgin Reactions. C4-Aminoantipyrine to Amides or alkyl amines. Pyrazolones.**




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

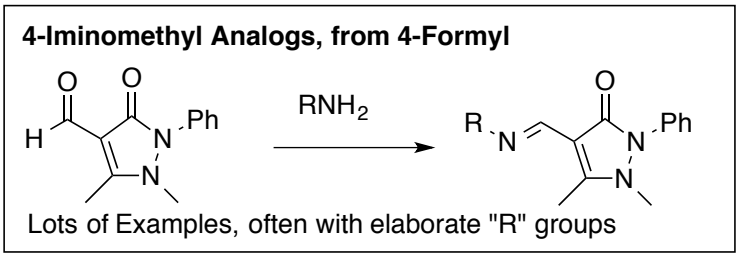
## C4-Formylation

**C4-Formylation.**




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

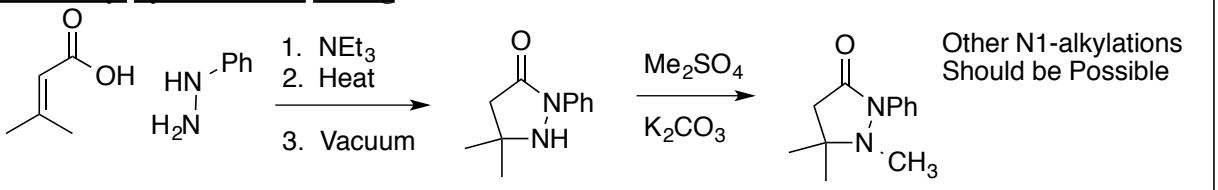
**C4-Iminomethyl Analogs. From the Formyl Derivative. Lots of examples with elaborate "R" groups**




- Easy Sci-Finder Search

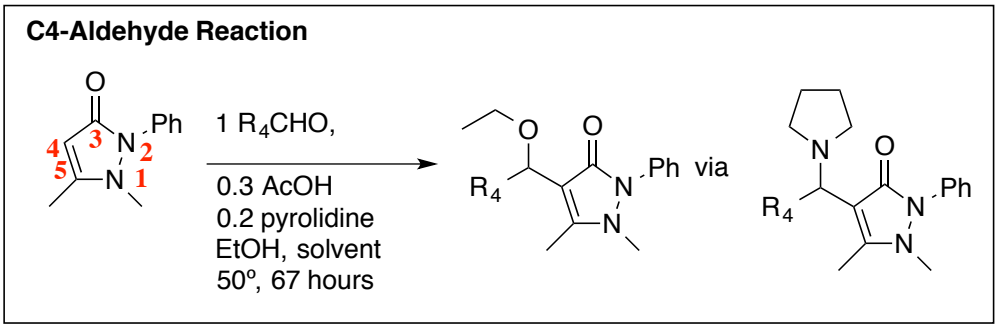
## 5,5-Dimethyl Pyrazolidinone

**5,5-Dimethyl Pyrazolidinone Analog**



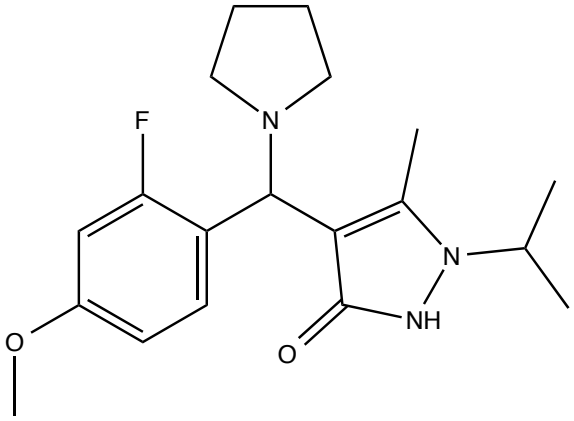

1. This one is interesting in that with the 5,5-dimethyl, there is no way the ring can be oxidized to the pyrazolone form. It's pyrazolidinone, and no redox is going to change that, whether in lab or in the cell
2. The first reaction hasn't been tried yet.
3. Based on earlier Hawau reactions, it would 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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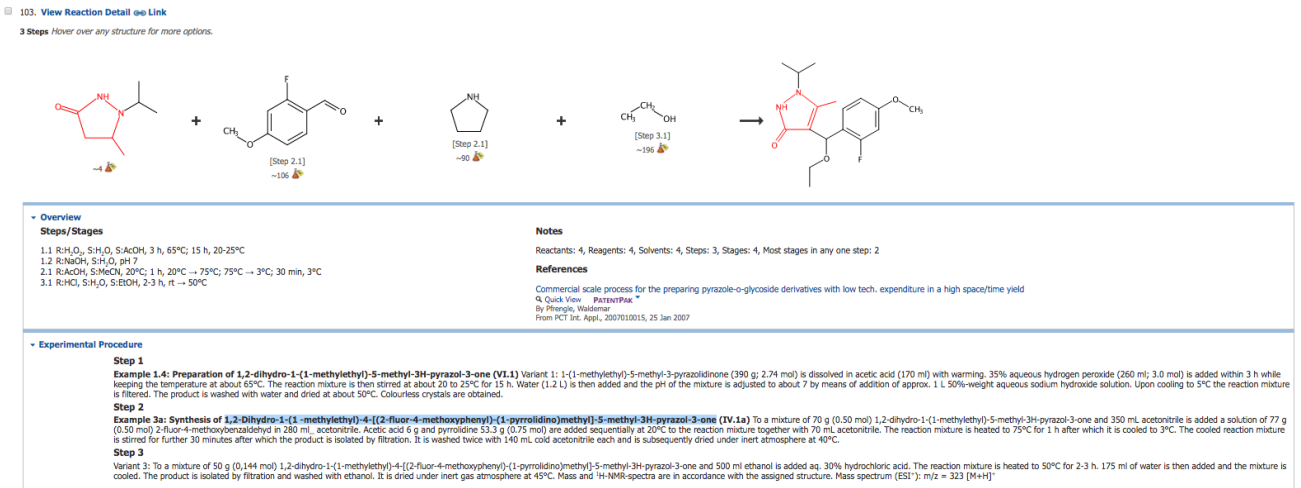


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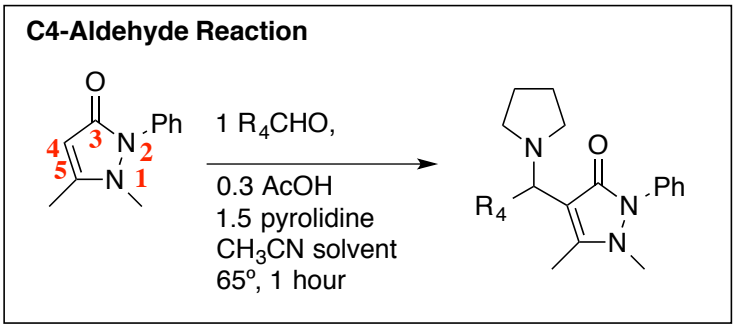
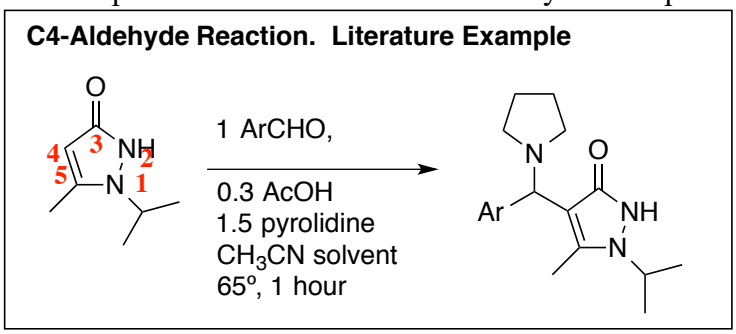
Oxidation to Pyrazolones using Hydrogen Peroxide.pdf
C4 Reaction with Aldehdye and amine.pdf

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



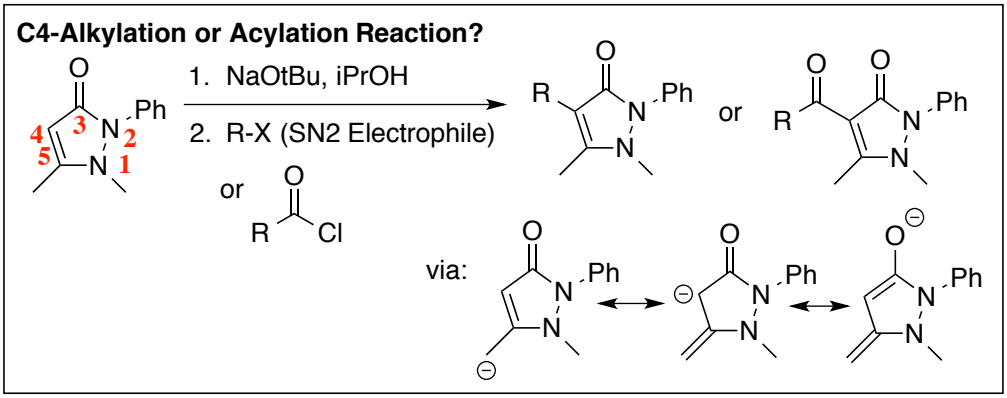

Example 3a: Synthesis of 1,2-Dihydro-1-(1 -methylethyl)-4-[(2-fluor-4-methoxyphenyl)-(1-pyrrolidino)methyl]-5-methyl-3H-pyrazol-3-one (IV.1a) To a mixture of 70 g (0.50 mol) 1,2-dihydro-1-(1-methylethyl)-5-methyl-3H-pyrazol-3-one and 350 mL acetonitrile is added a solution of 77 g (0.50 mol) 2-fluor-4-methoxybenzaldehyd 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?



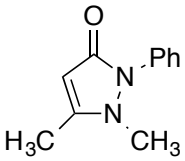
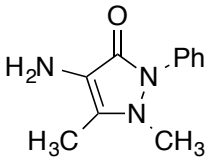
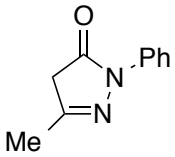
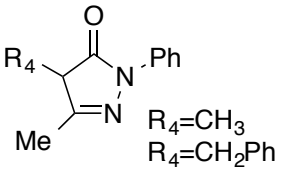
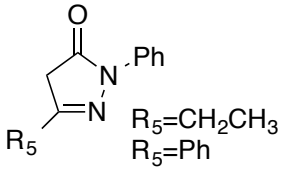
**C4-Alkylation or Acylation via Anion/Enolate?**

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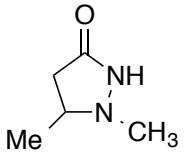
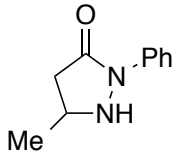
<td>  Hawau’s N1-Methyl Reagent</td>
<td>  Hawau’s N2-Phenyl Reagent</td>
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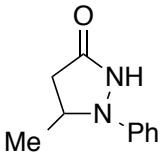
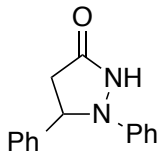
<td>  Sunny’s Reagent</td>
<td>  </td>
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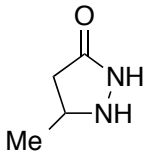
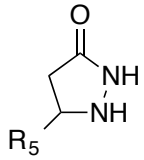
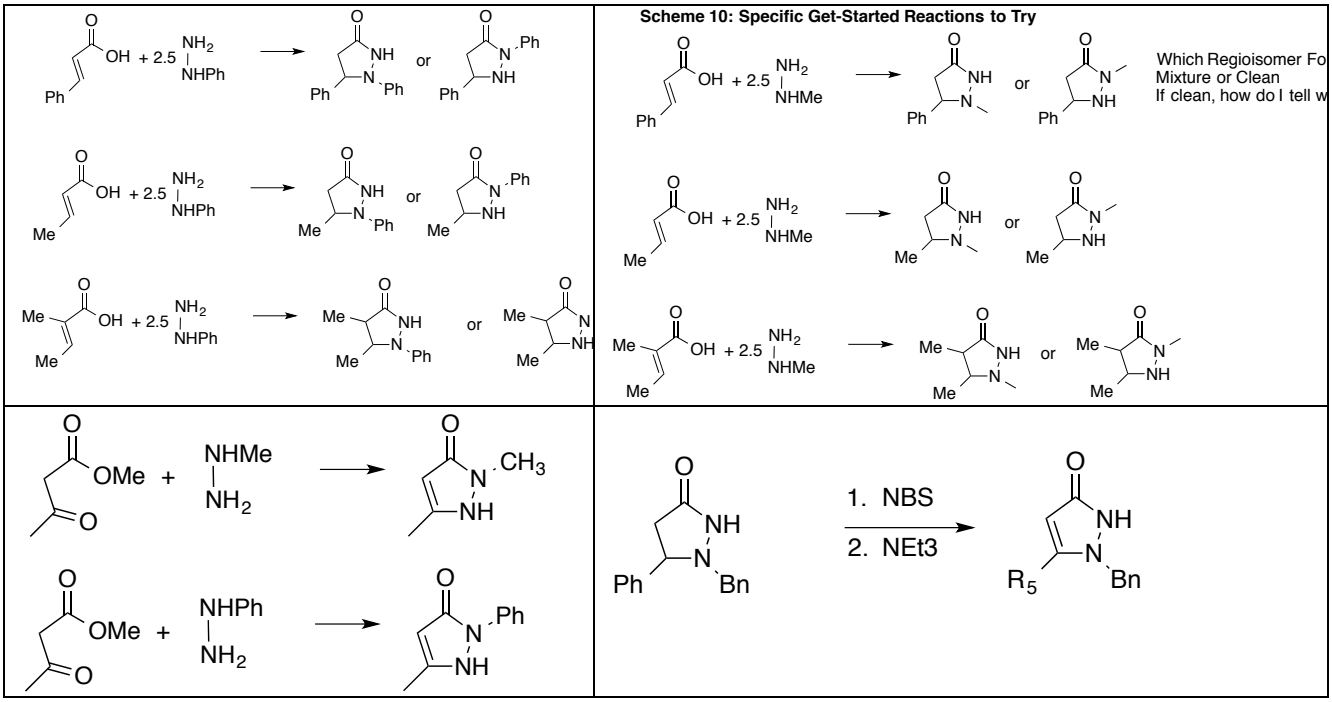
<td>  Mariam’s Reagent</td>
<td>  Trinh’s Reagents</td>
</tr>
</table>

**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 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 |
| | | | |
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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 |
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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 |
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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 |