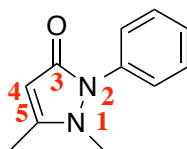


Structure Interpretation Key:

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

Big Picture Concept:

1. Pirfenidone is a medicine used to treat **pulmonary fibrosis**
 - It's not very good
 - It is not a life-saver
 - It isn't very good in terms of **potency, efficacy, toxicity** (or expense)
 - Its mechanism of operation is not understood
2. Five qualities for a drug
 - The Big Three:
 - a. Potency
 - b. Efficacy
 - c. Toxicity
 - Two Practicals:
 - a. Delivery
 - b. Cost
3. An extensive "**chemical library**" study has found **antipyrine** as a "**lead chemical**", comparable to pirfenidone
4. Group goal: Make as many **analogs** of antipyrine as we can, **in hopes that we can make something better** yet
5. The Drug Improvement Loop: (and the need for Chemical Synthesis)
 - Library study => initial lead
 - Make analogs (new library) => test again => secondary leads (**synthetic chemistry needed**)
 - Make further refinements (new library) => test again => 3rd-round lead (**more synthesis**)
 - **Lock+Key (Structure-Activity Relationships)**: We don't know what biochemical "lock" pirfenidone fits into, so we don't really know how to shape the "key". (3D volume; rigid vs flexible; hydrophobic vs hydrophilic.) Analogs help to map.

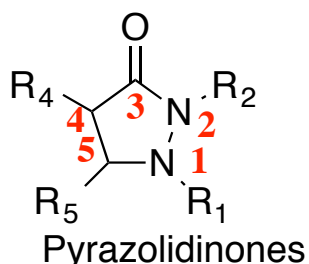
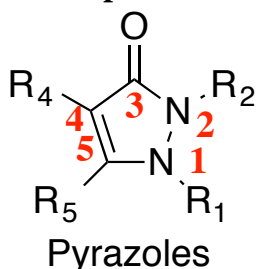


Our Project: Make a Library of Chemical Analogs to Antipyrine.

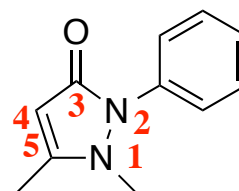
*Vary at Positions 1, 2, 4, + 5

*Including the presence or absence of C4=C5 double bond (pyrazoles vs pyrazolidinones)

*"R" represents some variable attachment



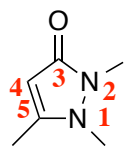
Antipyrine and its Numbering System Lead Drug Candidate



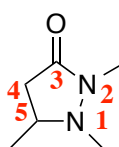
Terminology and Numbering:

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

Pyrazolone vs Pyrazolidinone Rings

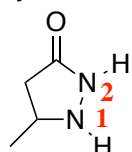


Pyrazolone



Pyrazolidinone

Hybridization and Reactivity in Pyrazolidinone Rings



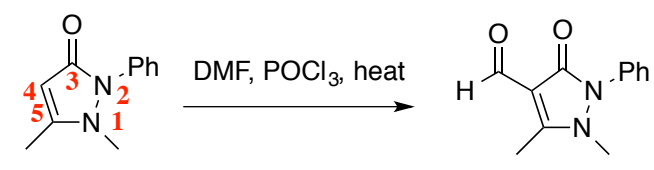
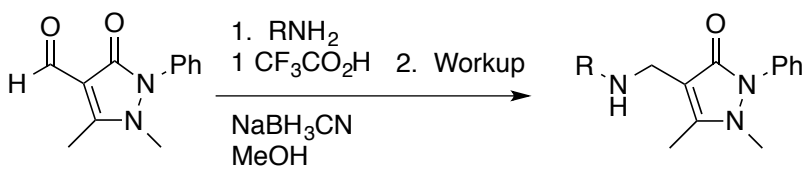
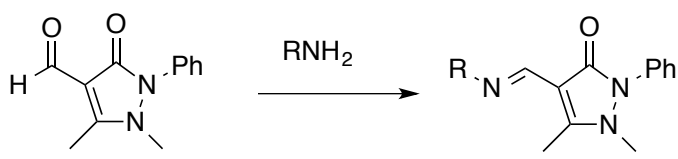
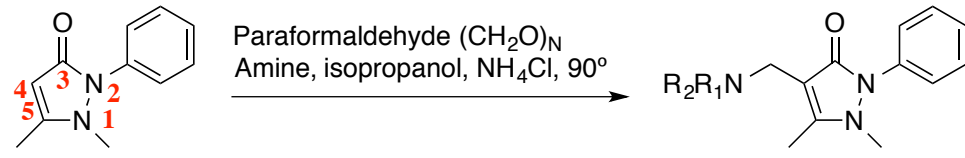
Pyrazolidinone

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

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

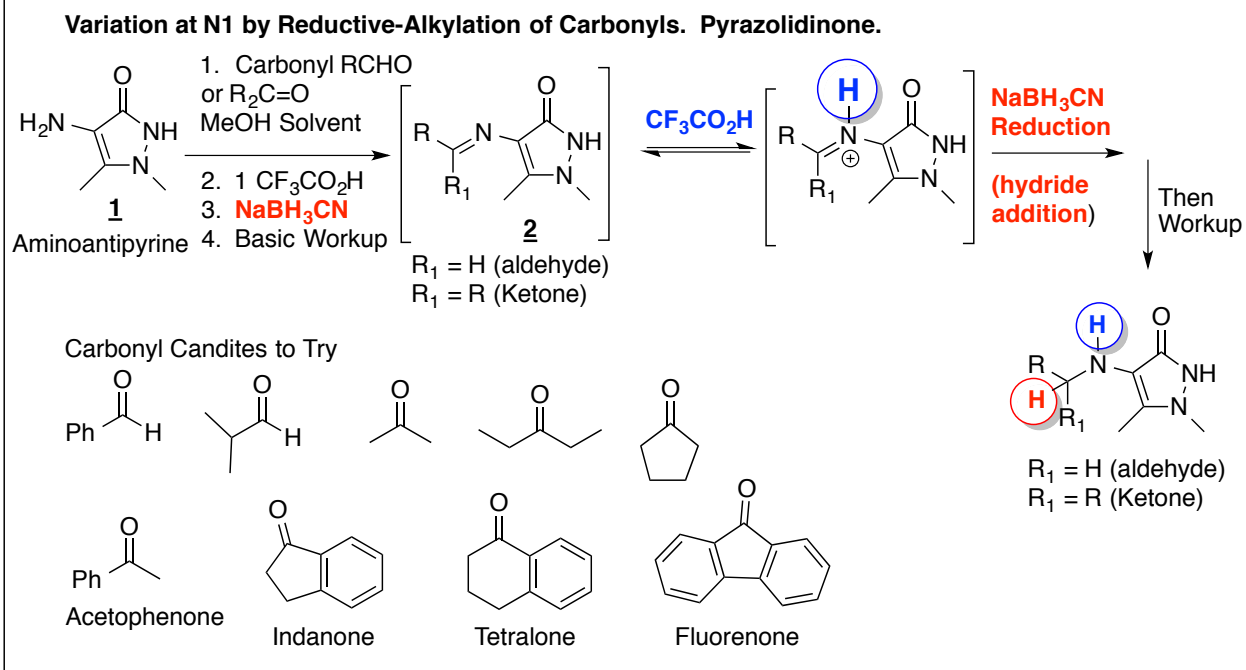
1. We like to build thing! ☺☺☺ Set up and run synthetic Reactions.
2. Decide when to shut them off: Analyze the reactions in progress
 - a. NMR, GC-MS.
 - b. Hoping HPLC-MS will be great for us!
3. Figure out how to work them up and isolate the product
4. Figure out how to purify the product
 - a. (My least favorite)
 - b. Much liquid-liquid extraction chemistry (sep funnel)
 - c. Much digestion/recrystallization chemistry (we often do digestion)
 - d. Much simple distillation (rotovap) for solvent removal.
5. Analyze the product
 - a. NMR
 - b. GC-MS
 - c. HPLC-MS?
6. Synthetic Methodology:
 - a. Optimizing a process.
 - b. Determining scope-and-limitation for a method: *****if*** a process works for one substrate, how far can we go (in the harder direction) before it will fail? (if ever)**
7. Reproducibility
8. Keeping Notebook, Keeping Organized! ☺☺☺
9. Time scheduling: Super Variable, high degree of independence allowed/encouraged (and required).
10. Space in Group: Yes.
11. Experience Required: First semester organic lab preferred (but not required, for a good, self-motivated, and ambitious student! ☺)

Specific project suggestions for Fall 2018

1.	<p>C4-Formylation.</p>  <p>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.</p> <p>Matt Anderson</p>
2.	<p>4-Alkylaminomethyl Analogs, from 4-Formyl. Try NaBH₃CN?</p>  <p>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?</p> <p>Matt Anderson</p>
3.	<p>4-Iminomethyl Analogs, from 4-Formyl</p>  <p>Lots of Examples, often with elaborate "R" groups</p> <p>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...</p> <p>Matt Anderson</p>
4.	<p>C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone</p>  <p>C. Pe'gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228-4231</p> <p>Untried/slightly tried. Craig got one to work; Amanda tried 1° that didn't? 2° Should work, literature.</p>

Reductive Amination of Aminoantipyrene: Formation of 4-Alkylaminoantipyrene 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?

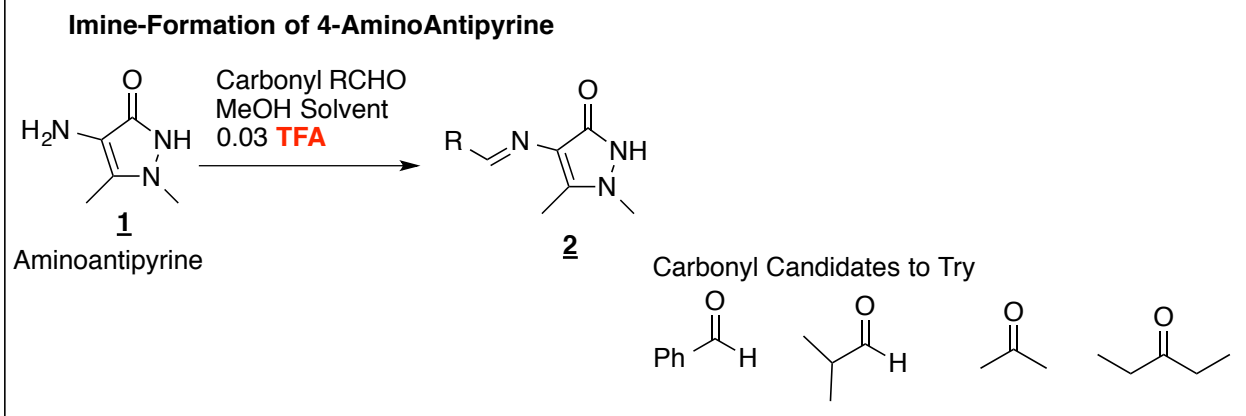
What is the best way to purify? Digestion? Crystallization? ???

Control: NaBH₄? LiAlH₄?

Control: Solvent variation?

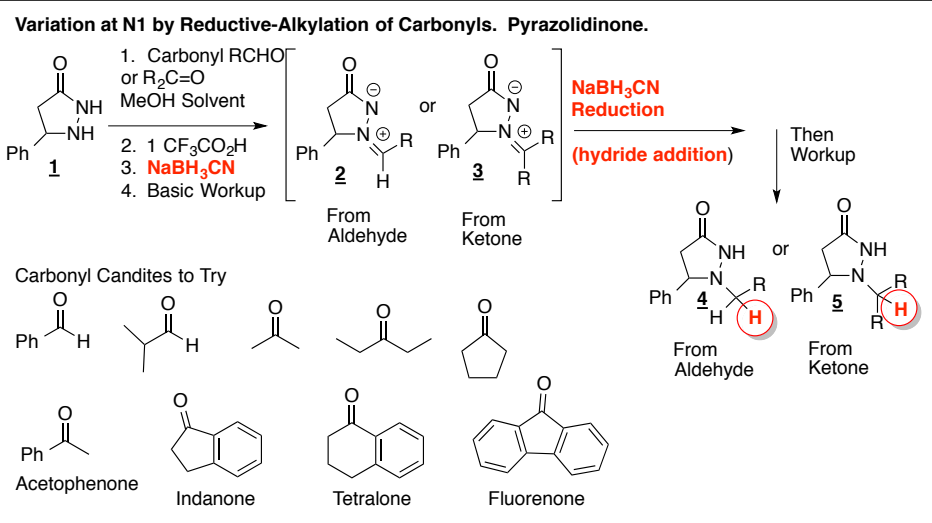
Control: Run without acid?

6.



Reductive Alkylation at N1. N-Alkylation

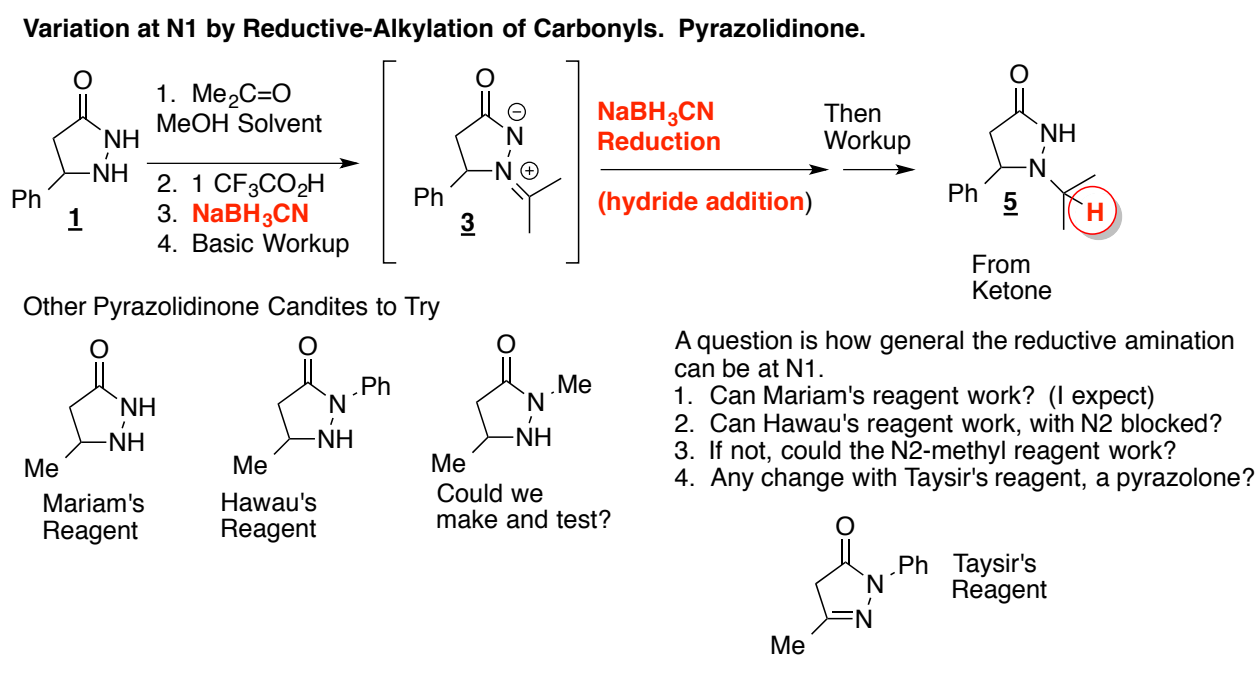
7.



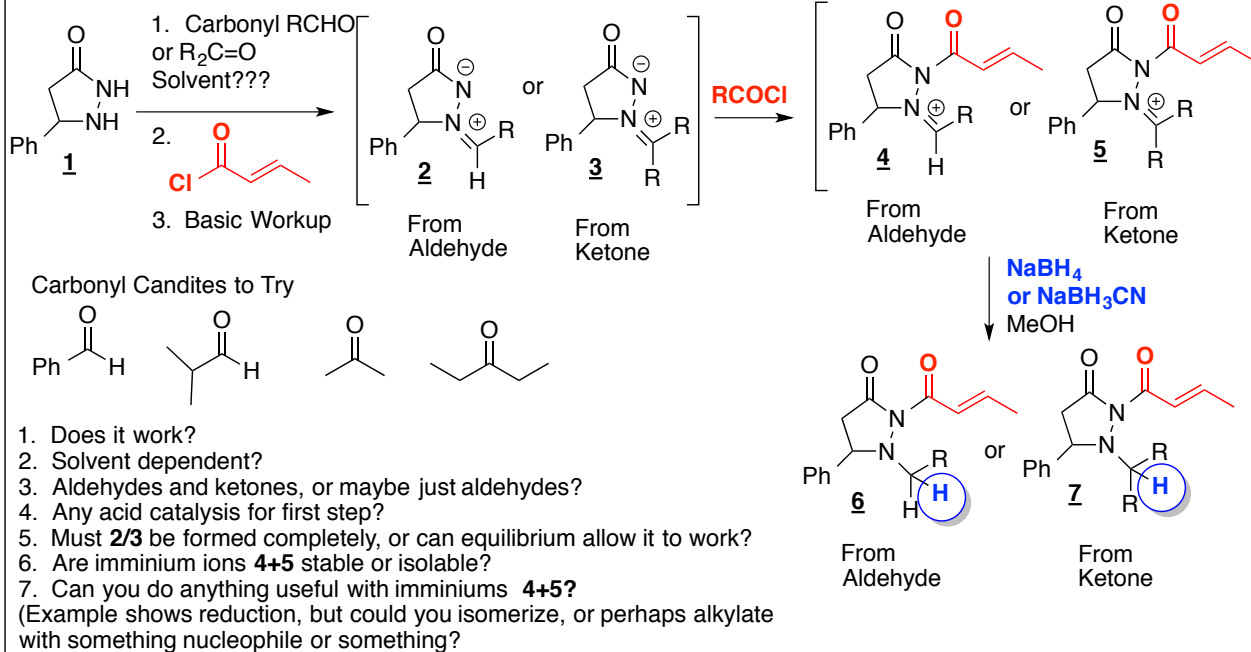
Jasperse has done small proof-of-principle using benzaldehyde and acetone; I think it works great!
(But not sure...)

8

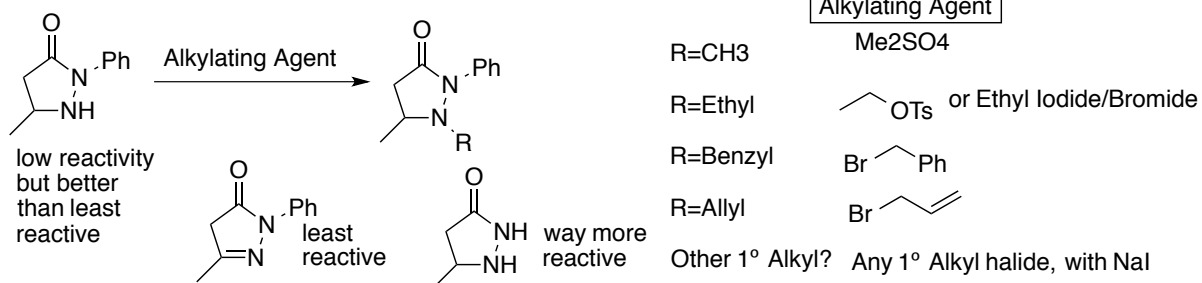
Does it work for other Pyrazolidinones?



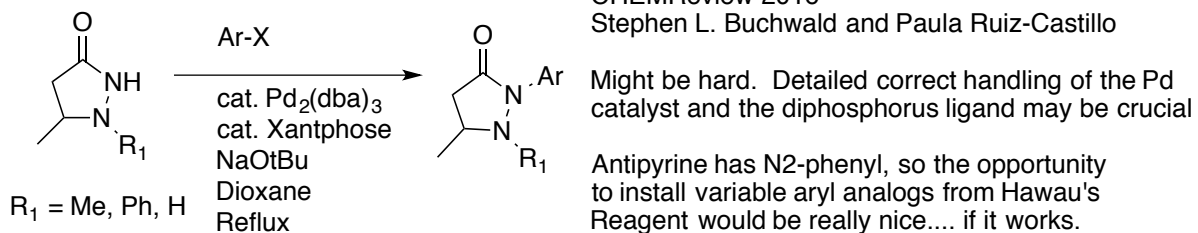
9

Tandem N1-Alkylation-N2-Acylation? Pyrazolidinone.

10

Variation at N1 by N-Alkylation. Pyrazolidinone.**Update: Checked. Works, more easily than Scheme 3. Proof of Principle. (Limited examples, Me, Et.)**

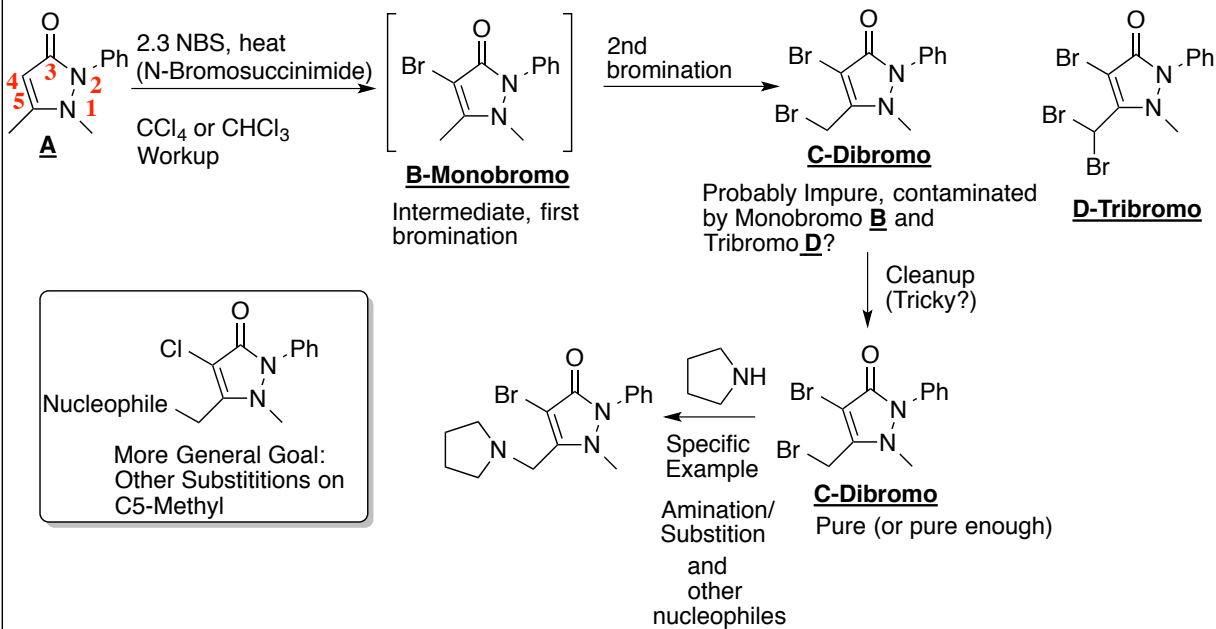
11

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

12

C4,C5-Dibromination



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

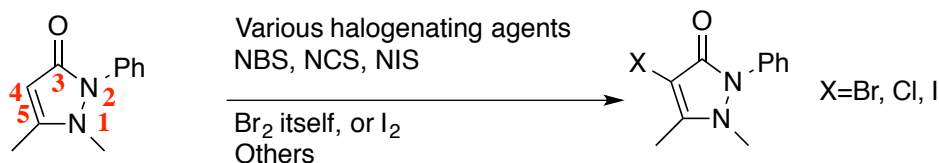
A preliminary proof-of-concept reaction by Kaniel and Bishnu demonstrates that this kind of works.

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



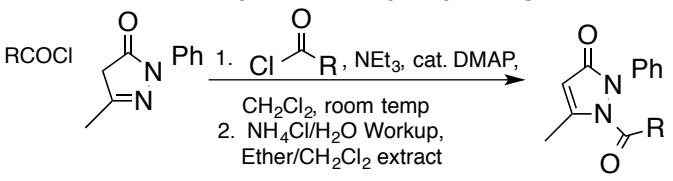
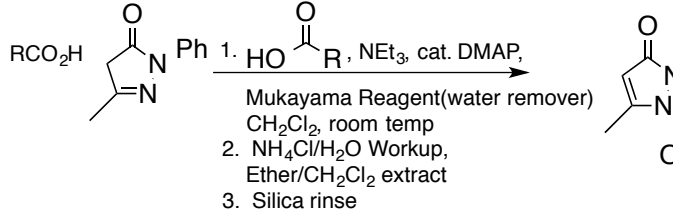
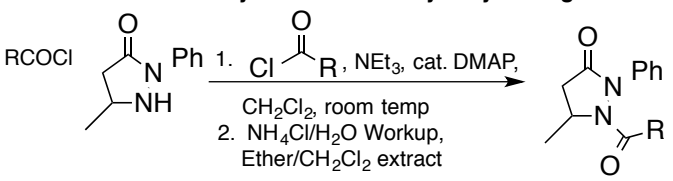
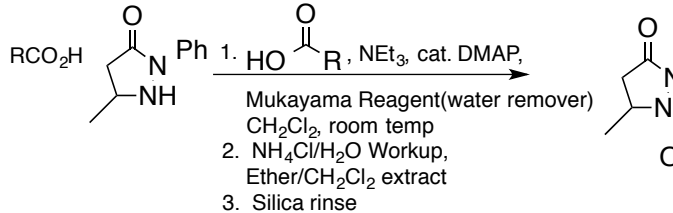
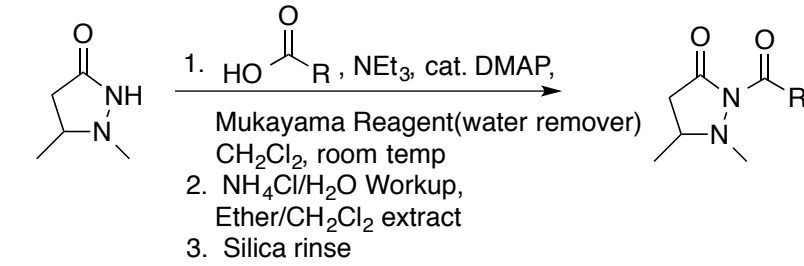
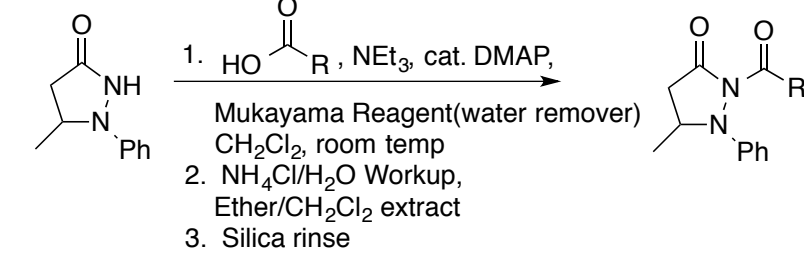
C4-Hetero-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf

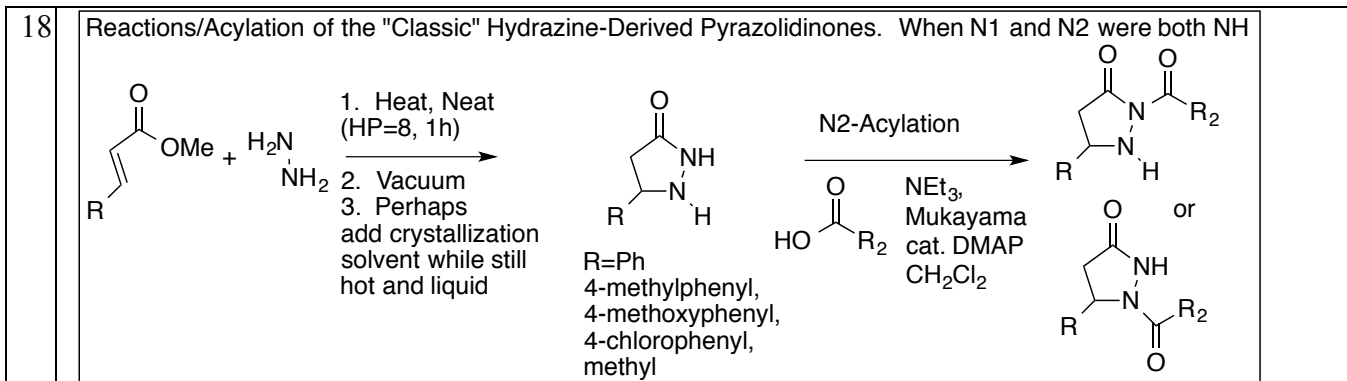
Get and Print documents:

Kaniel NCS General Procedure Suggestion.docx

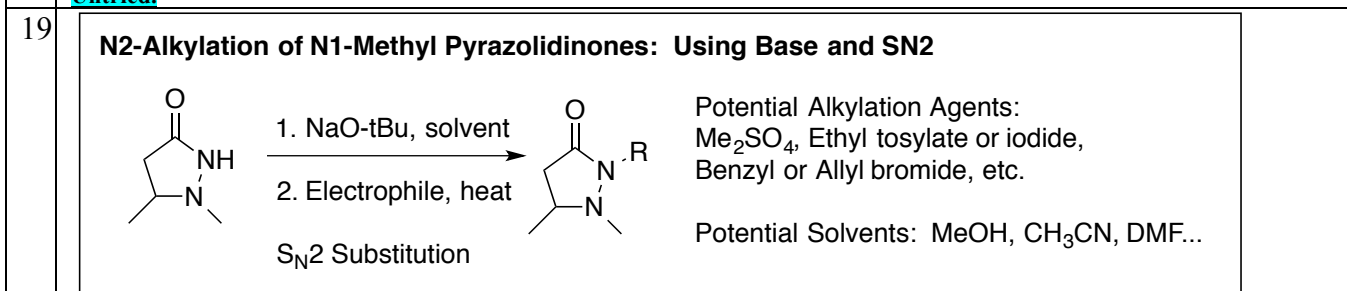
NCS Procedure and Reference.pdf

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	<p>Scheme 1: Variataion at C4:</p> <p>1. Heat CH₃CN 2. Vac</p> <p>1. Me₂SO₄ neat, 180° 2. Aq. bicarb Workup</p> <p>R₄ = Me, CH₂Ph</p> <p>Update: Checked. Works. Taysir. Proof of Principle. (limited examples)</p>												
10	<p>Scheme 2: Variataion at C5:</p> <p>1. Heat CH₃CN 2. Vac</p> <p>1. Me₂SO₄ neat, 180° 2. Aq. bicarb Workup</p> <p>R₅ = Et, Ph</p> <p>Update: Checked. Works. Taysir. Proof of Principle. (limited examples)</p>												
11	<p>Scheme 3: Variataion at N1 by N-Alkylation:</p> <p>1. OTs Neat, Hot 2. Bicarb Workup 3. Cleanup</p> <p>Br-CH₂-Ph</p> <p>Br-CH₂-CH=CH₂</p> <p>Update: Checked. Works, somewhat. Craig, Erhiga. Proof of Principle. (limited examples, Me, Et.)</p>												
12	<p>Variation at N1 by N-Alkylation. Pyrazolidinone.</p> <p>low reactivity but better than least reactive</p> <p>least reactive</p> <p>way more reactive</p> <table border="1"> <thead> <tr> <th colspan="2">Alkylating Agent</th> </tr> </thead> <tbody> <tr> <td>R=CH₃</td> <td>Me₂SO₄</td> </tr> <tr> <td>R=Ethyl</td> <td>CH₃CH₂OTs or Ethyl Iodide/Bromide</td> </tr> <tr> <td>R=Benzyl</td> <td>Br-CH₂-Ph</td> </tr> <tr> <td>R=Allyl</td> <td>Br-CH₂-CH=CH₂</td> </tr> <tr> <td>Other 1° Alkyl?</td> <td>Any 1° Alkyl halide, with NaI</td> </tr> </tbody> </table> <p>Update: Checked. Works, more easily than Scheme 3. Proof of Principle. (Limited examples, Me, Et.)</p>	Alkylating Agent		R=CH ₃	Me ₂ SO ₄	R=Ethyl	CH ₃ CH ₂ OTs or Ethyl Iodide/Bromide	R=Benzyl	Br-CH ₂ -Ph	R=Allyl	Br-CH ₂ -CH=CH ₂	Other 1° Alkyl?	Any 1° Alkyl halide, with NaI
Alkylating Agent													
R=CH ₃	Me ₂ SO ₄												
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Other 1° Alkyl?	Any 1° Alkyl halide, with NaI												
13	<p>Variation at N1 by N-Aldehyde Reaction, then Alkoxide Isomerization. Pyrazolidinone to Pyrazolone</p> <p>H-C(=O)-R</p> <p>MeOH, reflux NaOMe or NaOtBut</p> <p>base-induced isomerization</p> <p>Update: Checked. Works with Aldehydes. Proof of Principle. Fails if N2 is substituted. Ketones Unchecked. (Taysir)</p>												

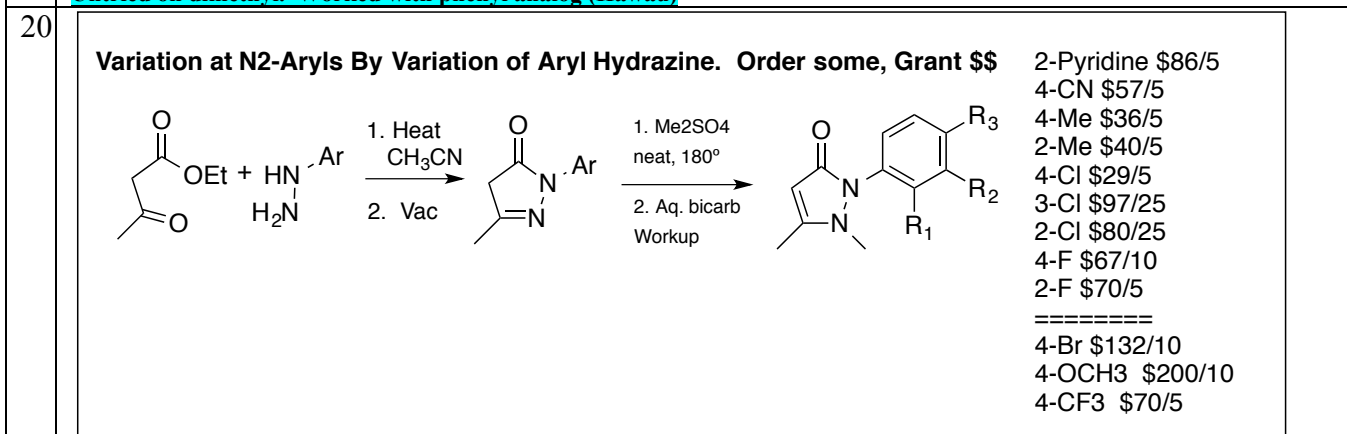
14	<p>N1-ACYLATION of Pyrazolone Very Easy! Using RCOCl or RCO₂H Pyrazolones.</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>RCOCl </p> <p>RCO₂H </p> </div> <div style="width: 45%; border: 1px solid black; padding: 5px;"> <p>Using Acid Chlorides, where available. Easy, fast.</p> <p>Using Carboxylic Acids, which are often more accessible than the acid chlorides.</p> </div> </div> <p>Update: Works with Acid Chloride. (Andrea). Easy. Didn't Try with Acid/Mukayama.</p>
15	<p>N1-ACYLATION of Pyrazolidinone Very Easy! Using RCOCl or RCO₂H Pyrazolidinones.</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>RCOCl </p> <p>RCO₂H </p> </div> <div style="width: 45%; border: 1px solid black; padding: 5px;"> <p>Using Acid Chlorides, where available. Easy, fast.</p> <p>Using Carboxylic Acids, which are often more accessible than the acid chlorides.</p> <p>Could also do it with N₂=H instead of Ph. (Mariam's rgt)</p> </div> </div> <p>Update: Works with Acid Chloride, although not Super Clean. (Val). Easy. Didn't Try with Acid/Mukayama..</p>
16	<p>N2-Acylation of N1-Methyl Pyrazolidinones: Using RCO₂H and Mukayama's Reagent.</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p></p> </div> <div style="width: 45%; border: 1px solid black; padding: 5px;"> <p>Using Carboxylic Acids, which are proven. Doubtful if RCOCl work</p> </div> </div> <p>Untried on dimethyl. Should work.</p>
17	<p>N2-Acylation of N1-Phenyl Pyrazolidinone (Sunny's Reagent) Pyrazolidinones.</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p></p> </div> <div style="width: 45%; border: 1px solid black; padding: 5px;"> <p>Using Carboxylic Acids, which are proven. Doubtful if RCOCl work</p> </div> </div> <p>Untried. Should work.</p>



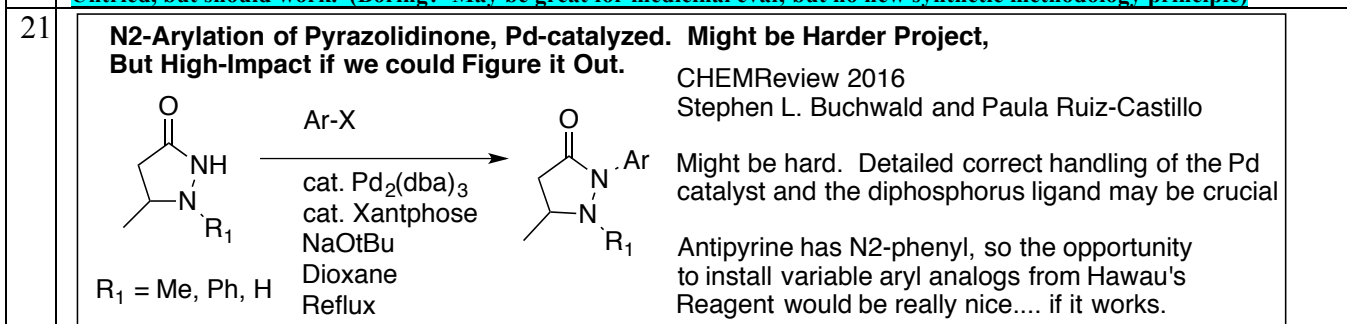
Untried.



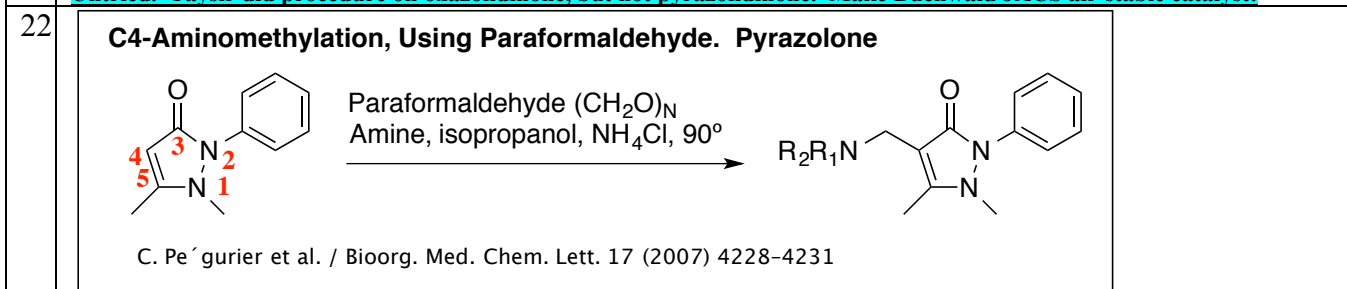
Untried on dimethyl. Worked with phenyl analog (Hawau)



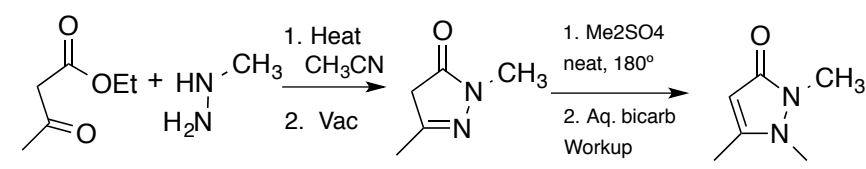
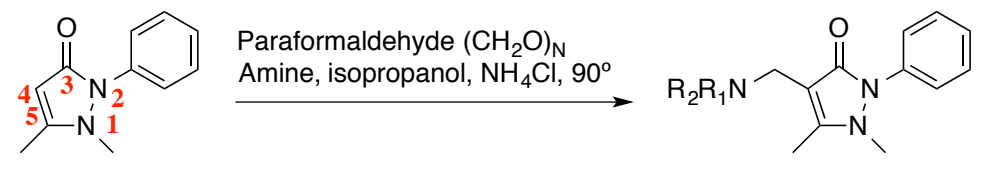
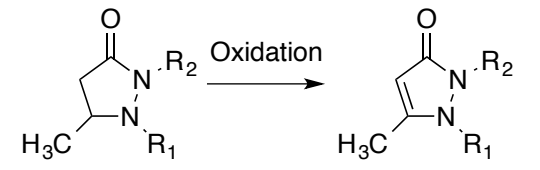
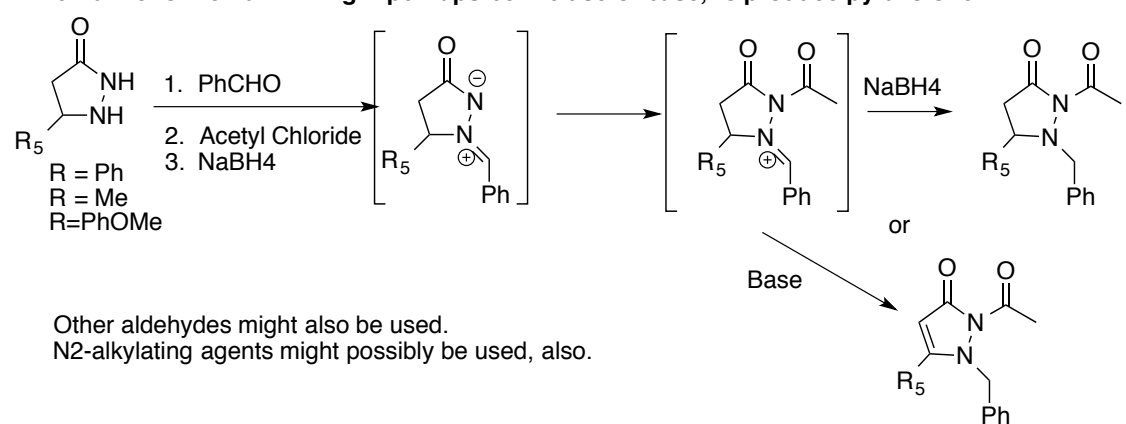
Untried, but should work. (Boring? May be great for medicinal eval; but no new synthetic methodology principle)

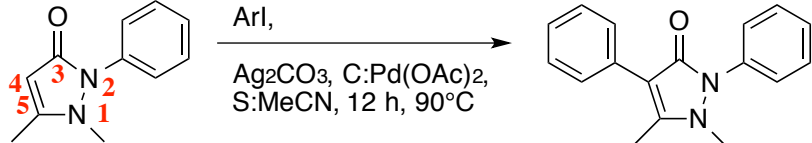
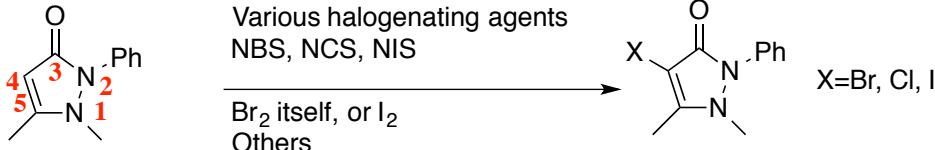
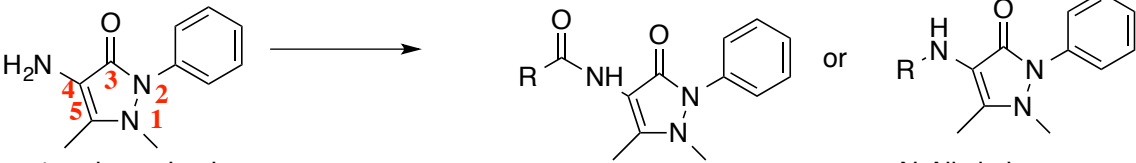
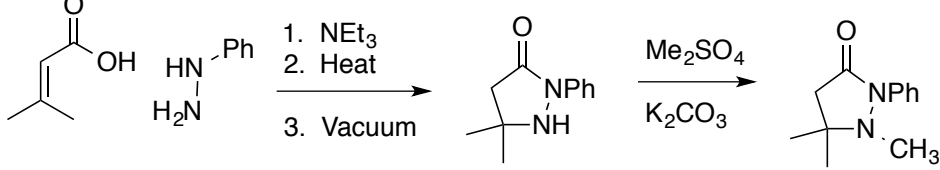
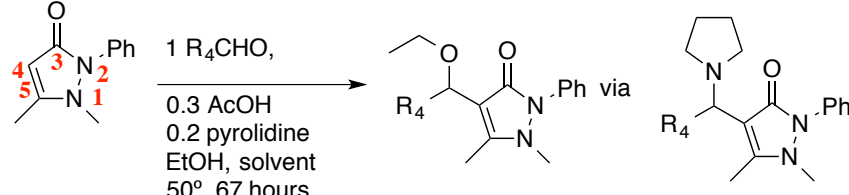


Untried. Taysir did procedure on oxazolidinone, but not pyrazolidinone. Make Buchwald JACS air-stable catalyst!

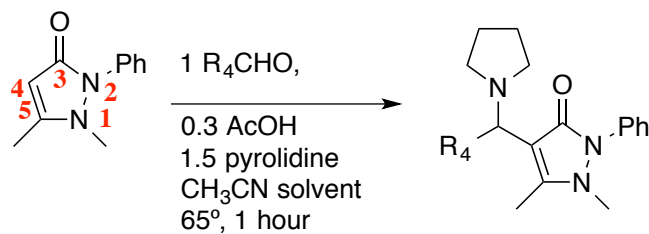


Untried/slightly tried. Craig got one to work; Amanda tried 1° that didn't? 2° Should work, literature.

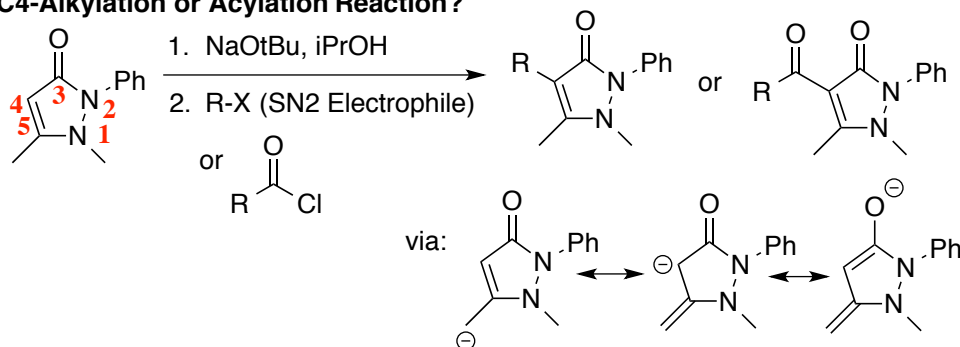
23	<p>Scheme 4: Variataion at N2 By Use of MethylHydrazine:</p>  <p>1. Heat CH₃CN 2. Vac</p> <p>1. Me₂SO₄ neat, 180° 2. Aq. bicarb Workup</p>	
	<p>Untried. Would enable N2-methyl analogs.</p>	
24	<p>C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone</p>  <p>Paraformaldehyde (CH₂O)_N Amine, isopropanol, NH₄Cl, 90°</p> <p>C. Pe'gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228-4231</p>	
	<p>Untried/slightly tried. Craig got one to work; Amanda tried 1° that didn't? 2° Should work, literature.</p>	
25	<p>Oxidation of Pyrazolidinones to Pyrazolones</p>  <p>Oxidation</p> <p>Oxidizing agent candidates: 1. H₂O₂, CH₃CO₂H 2. O₂, cat. FeCl₃ 3. K₂S₂O₈ 4. NBS etc.</p>	
	<p>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.</p>	
26	Continuation of Page 21, Oxidation	
27	Continuation of Page 21, Oxidation	
28	Continuation of Page 21, Oxidation	
29	<p>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.</p>  <p>1. PhCHO 2. Acetyl Chloride 3. NaBH₄</p> <p>R = Ph R = Me R = PhOMe</p> <p>Other aldehydes might also be used. N2-alkylating agents might possibly be used, also.</p>	
	<p>Untried. Tandem alkylation/acylation would be cool, if it worked.</p>	

30	<p>C4-Arylation. Pyrazolone</p>  <p>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</p>
<p>Untried. Have chems. Might be good to try the Buchwald catalyst, once made?.</p>	
31	<p>C4-Bromination/Chlorination/Iodination</p>  <p>C4-Hetero-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf</p>
<p>Kaniel is trying.</p>	
32	<p>C4-Nitrogen Varients. Pyrazolone. "Analgin" Derivatives</p>  <p>4-aminoantipyrine "Analgin" Commercially Available, Alfa-Aeser</p> <p>N-Acylation or N-Alkylation</p>
<p>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.</p>	
33	<p>5,5-Dimethyl Pyrazolidinone Analog</p>  <p>Other N1-alkylations Should be Possible</p>
<p>Update. Slow; Joshua got small scale and crystalline. Methylation small scale worked, kind of. Proof of principle. Scaleup.</p>	
34	<p>C4-Aldehyde Reaction</p> 
<p>Untried. One literature example, iffy. Combo with 35.</p>	

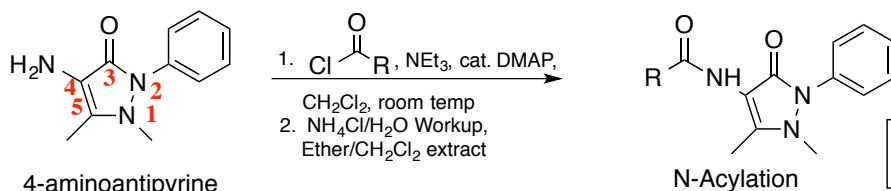
35

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.**

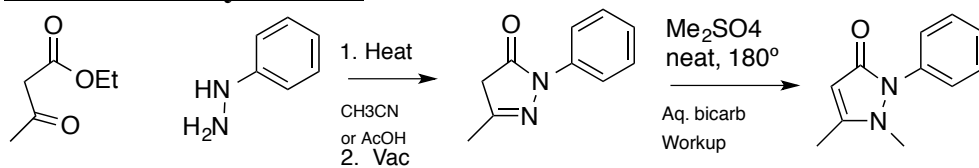
37

Acylation of Aminoantipyrine Using Acid Chlorides

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

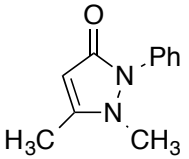
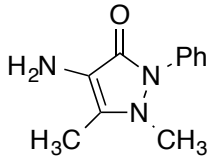
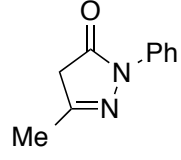
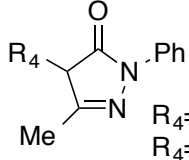
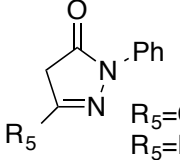
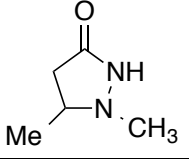
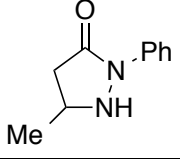
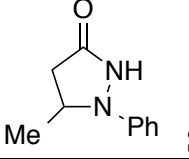
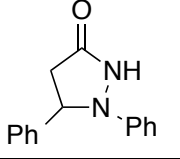
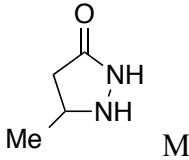
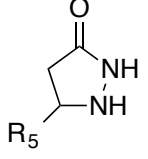
Using Acid Chlorides, where available.
Easy, fast.

Literature extensive for acylation.**Ansu worked several of these. They worked very well. Easy to Crystallize and purify..**Ansu had one success with CH_3PhCOCl . 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:

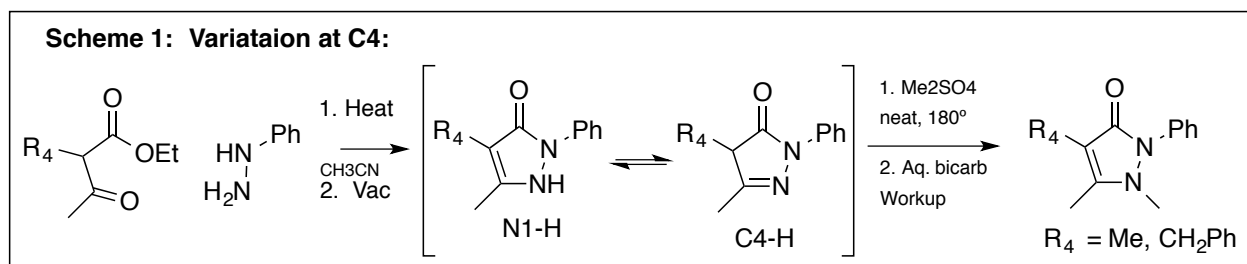
- Have worked out procedure for this home-made synthesis of antipyrine parent
- Antipyrine itself is commercial and inexpensive, so no actual need for us to make it.

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

 <p>Antipyrine. \$\$.</p>		 <p>4-aminoantipyrine = "Analgin". \$\$</p>	
 <p>Taysir's Reagent.</p>	 <p>$R_4 = \text{CH}_3$ $R_4 = \text{CH}_2\text{Ph}$</p>	 <p>$R_5 = \text{CH}_2\text{CH}_3$ $R_5 = \text{Ph}$</p>	
 <p>Hawau's N1-Methyl Reagent</p>		 <p>Hawau's N2-Phenyl Reagent</p>	
 <p>Sunny's Reagent</p>		 <p>Jasperse Diphenyl Reagent</p>	
 <p>Mariam's Reagent</p>		 <p>$R_5 = \text{phenyl}$ $R_5 = 4\text{-methylphenyl}$ $R_5 = 4\text{-chlorophenyl}$ $R_5 = 4\text{-methoxyphenyl}$</p> <p>Trinh's Reagents</p>	

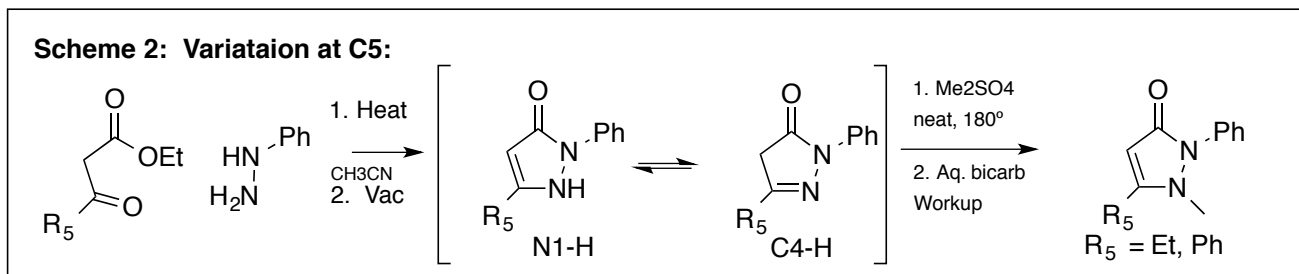
C4-Variation (Alkyl/Benzyl)

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



- 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,
- Notes: Not sure how easy step one is. E/Z issues with the hydrazine? NOT A PROBLEM
- Preliminary data: Small-scale prep of both R₄=Me, CH₂Ph.
- Seems very accessible process.
- Targets/To-Do:
 - Scaleup/ Reproduce
 - Cleanup
 - Test
- Puzzle with form of intermediate. Mixture of structural isomers.
 - Acid-base sensitive. Upon treatment with acid, it presents in the N-H form.
 - Under bicarb conditions, appears to be substantially in the C4-H form.
 - Which at biological pH?
 - Once formed, is either stable enough to survive, or will they simply bio-equilibrate?
 - Do they differ meaningfully in their reactivity?
 - Do they interchange and equilibrate under the high-temp methylation?
- Note: should be able to submit the N1-Me, N1-H, and C4-H analogs for testing.
- 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

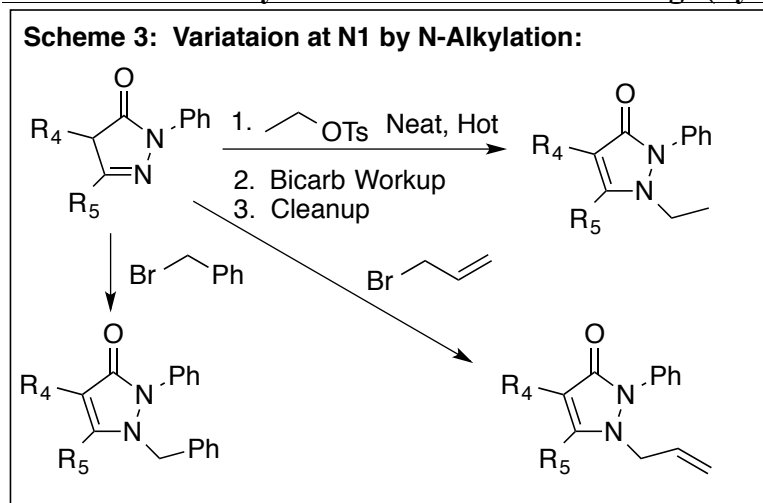


CAS ID:

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 Me₂SO₄/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)

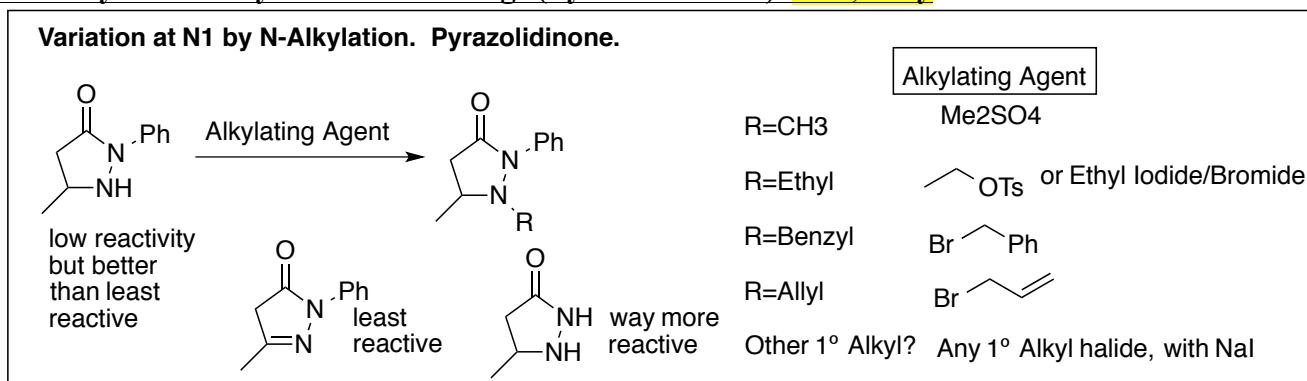


- Alkylation is pretty slow
- Preliminary results: Works well with dimethylsulfate hot/neat (see scheme 1)
- Tried ethyl iodide, and that works, slowly, but partially/incomplete. Seemed very clean, just didn't go to completion in preliminary attempt.
 - Problem is getting hot enough without having the ethyl bromide or iodide boil away, I think? Perhaps with scaleup and reflux condenser that would be better and easily resolved?
- 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.
- Ethyl will provide a check on modest extension of N1-chain (Methyl to Ethyl)
- 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?)
- Neat, with stoichiometry control, and with limited time, it appears to work mostly well.
- But may not be super clean, so may require a recrystallization or chromatography to clean it up.
- No preliminary chromatography results thus far.
- Don't remember whether having base present (K₂CO₃) was helpful or not.
- Allyl bromide should be plenty reactive
- Ethyl tosylate seems to be about the only commercial tosylate (other than methyl).
- Update: Try the ethyl tosylate under the dimethyl-sulfate conditins. Does it work?
-
- 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.
- In fact, getting comfortable with combiflash might be a great way to clean many of these types of products up.

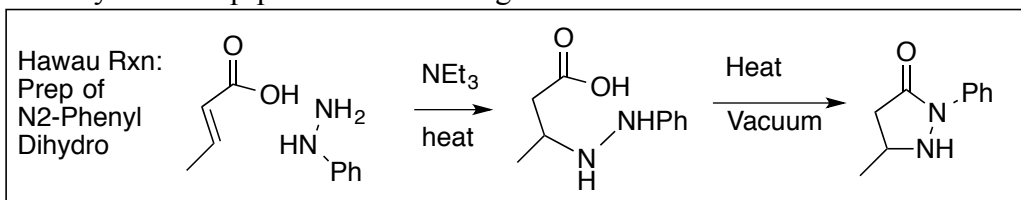
N-Ethylation Reagents and Catalysts

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

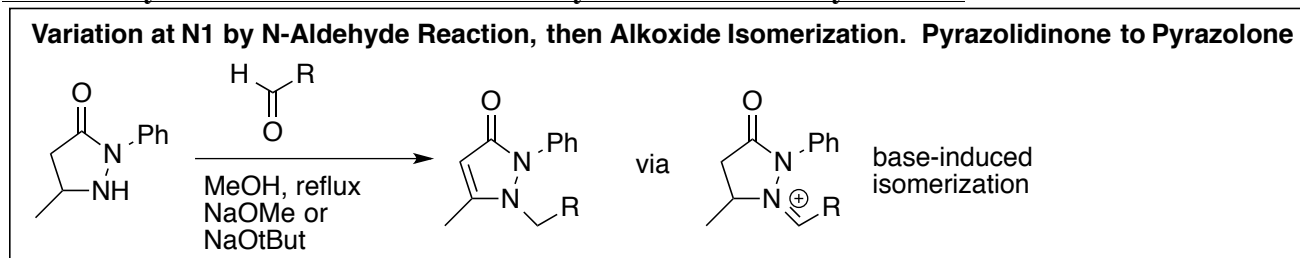
N1-Alkylation of Pyrazolidinone Rings (Pyrazolidinones) **Safe, Easy**



- 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.
- Preliminary data: This worked well for ethyl iodide, but was slow.
- 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.
- 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.
- In preliminary ethyl experiment, there was no problem using solvent (refluxing acetonitrile, but neater and hotter naturally went faster).
- Hawau's starting material is really clean, so not complications from that.
- Hawau's preparation is shown below, it is very clean and she has a nice process for producing nice, clean, crystalline material.
- Easy to scaleup-produce the starting material if stock runs low.

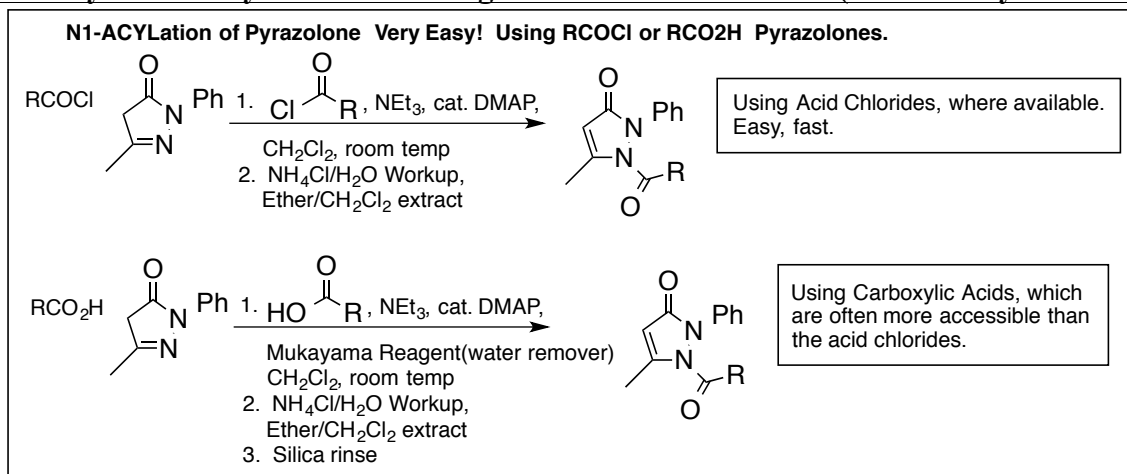


Variation at N1 Pyrazolones. By Reaction of Hawau Phenyl-Pyrazolidinone with Aldehyde, followed by NaOR/ROH isomerization. Pyrazolidinone => Pyrazolone

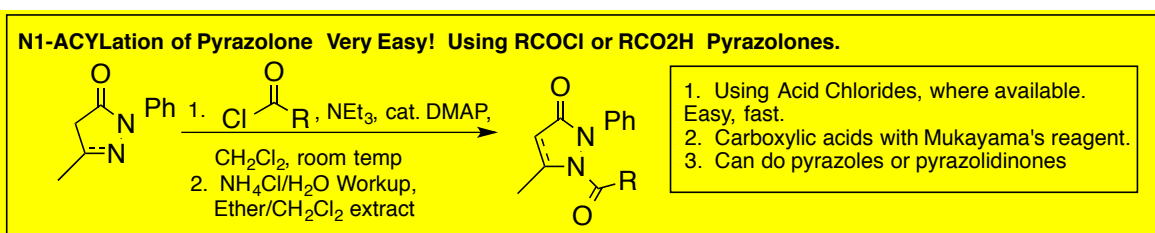


1. Kangasmetsa, Jussi J. et al From PCT Int. Appl., 2013096501, 27 Jun
2. N1-Aldehyde use, followed by NaOMe/MeOH isomerization: N1 plus Aldehyde, then NaOMe/MeOH reflux to isomerize
 - ... 35 mmol... 5-methylpyrazolidin-3-one. This oil was dissolved in MeOH (20 mL), cooled to 0°C under N₂ atmosphere 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 iminium, 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 S_N2 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).

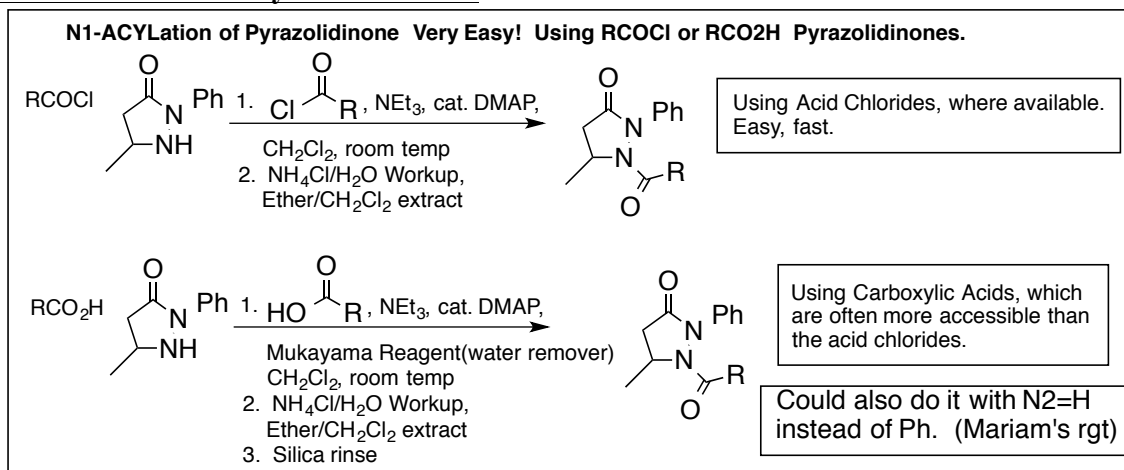


1. Super Easy and flexible
2. Preliminary result using 4-toluyyl chloride appears to complete within minutes at room temp, and was easy to work up.
3. Preliminary experiment using crotonic acid also appeared to proceed very quickly and easily.
4. Antipyrene of course does not have the carbonyl attachment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

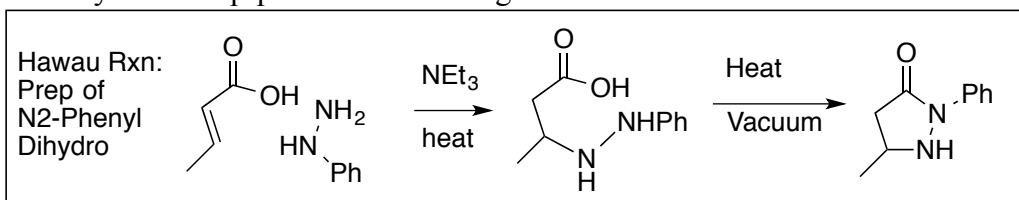


Use General Thing for pyrazolone or pyrazolidinone

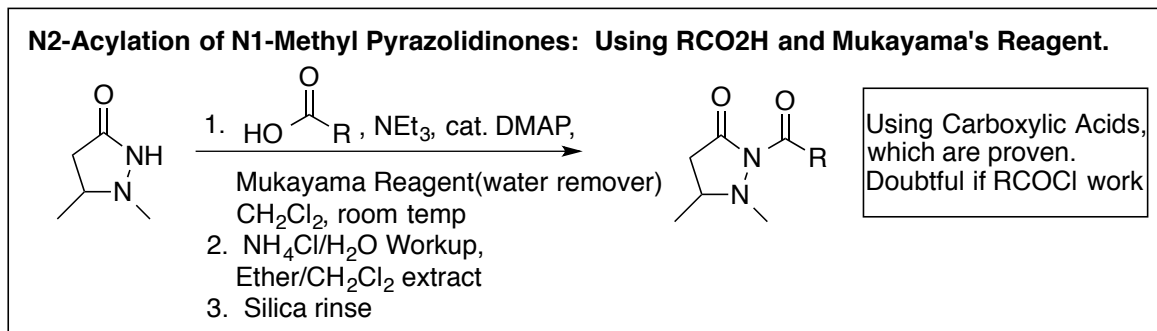
N1-ACYLation of Pyrazolidinones.



- 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.
- Preliminary data: This worked well for ethyl iodide, but was slow.
- 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.
- 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.
- In preliminary ethyl experiment, there was no problem using solvent (refluxing acetonitrile, but neater and hotter naturally went faster.
- Hawau's starting material is really clean, so not complications from that.
- Hawau's preparation is shown below, it is very clean and she has a nice process for producing nice, clean, crystalline material.
- 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



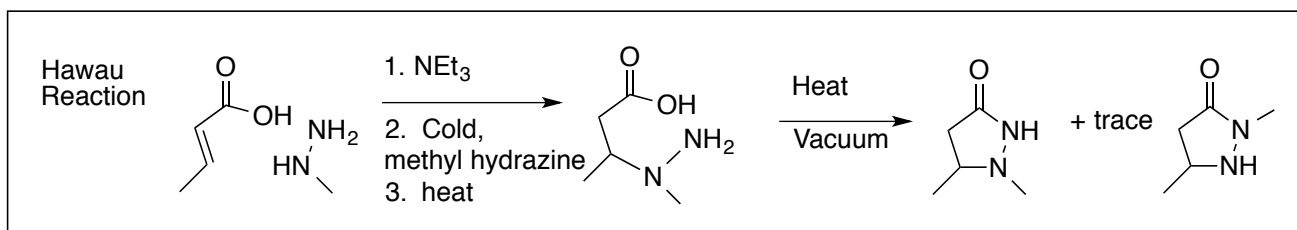
1. Starting chemical synthesis nicely developed by Hawau
2. Starting material isn't completely clean; contaminated by modest amount of N2-methyl isomer
3. The simplest to make here would be R=Ph
4. Antipyrene of course does not have the carbonyl attachment on at N2. So who knows what assay-impact this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

Methyl Hydrazine Process:

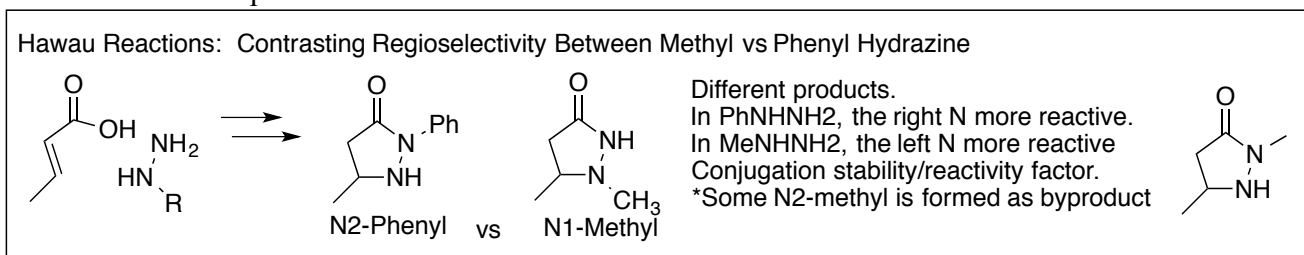
	CAS	One Name variant	Supplier, Price
Me	60-34-4	Methyl hydrazine	Sigma/Aldrich: \$308/25

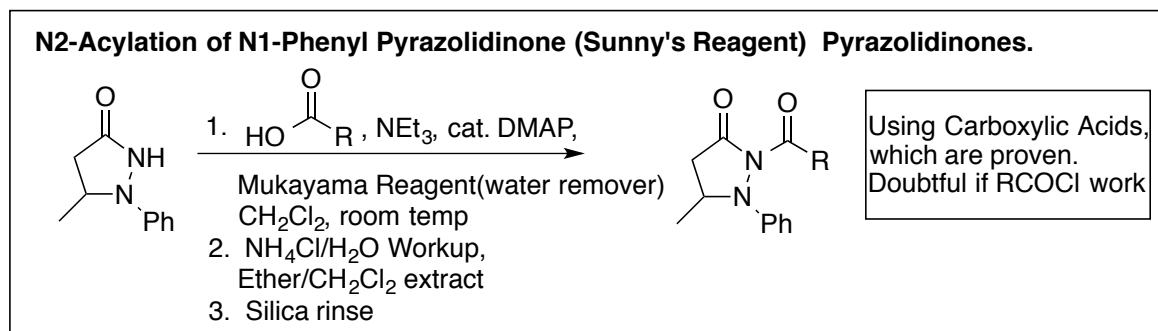
Note: Aldrich is cheapest here, and good.

- 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!



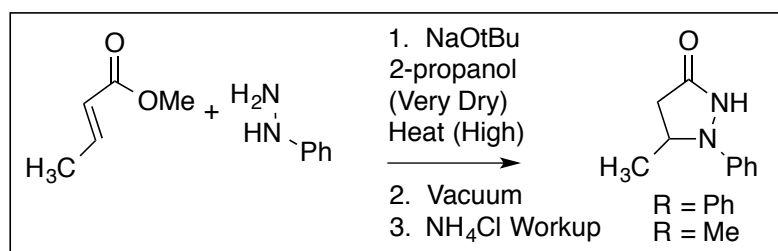
Note the interesting contrast between Hawau reactions, depending on whether or not the hydrazine is or is not conjugated. In methyl hydrazine, the methyl-substituted nitrogen is more electron rich and more reactive nucleophile. In phenyl hydrazine, the phenyl-substituted nitrogen is conjugated and is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



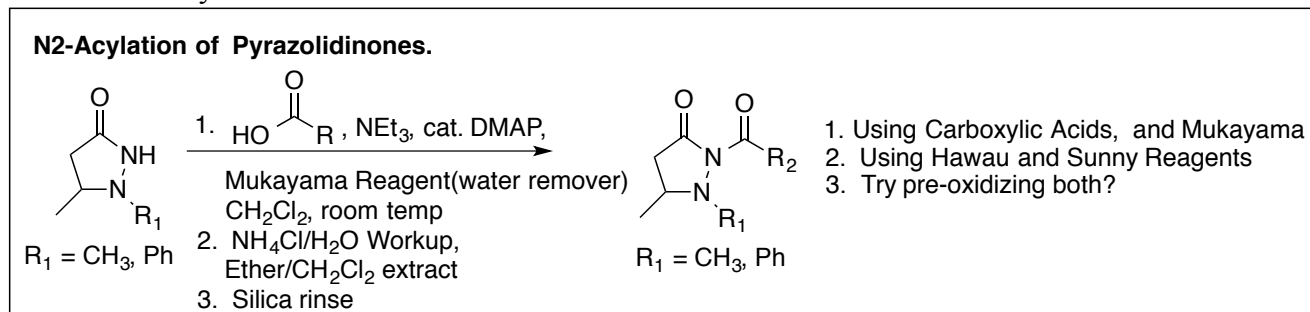
N2-Acylation of N1-Phenyl Pyrazolidinone, Using Sunny's Phenyl Reagent:

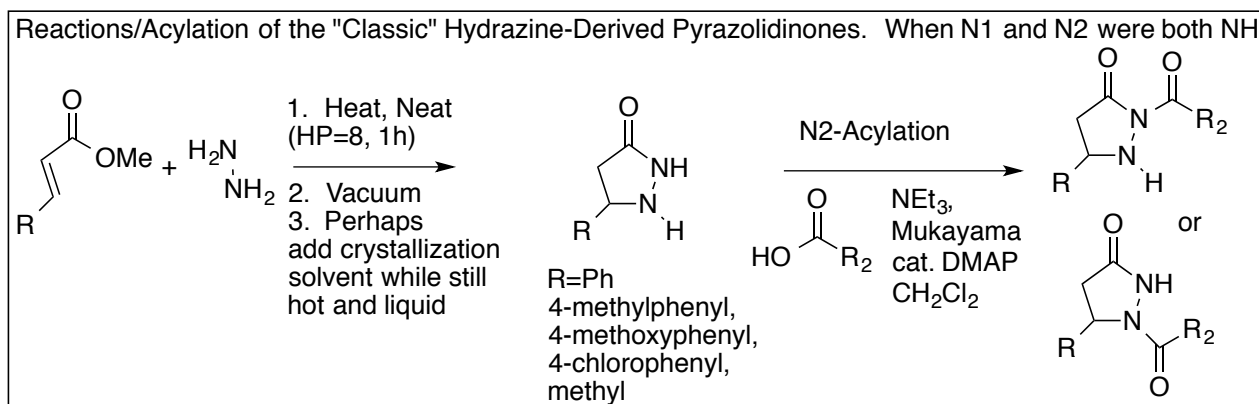
1. The N2-acylation using carboxylic acid and Mukayama reagent works to make derivative
2. This will function as an "Antipyrine-Twist" analog. If three core components of antipyrine are the aromatic ring, the 5-ring, and the carbonyl, this will effectively push the carbonyl over relative to the arene.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

Prep of Sunny's Reagent:



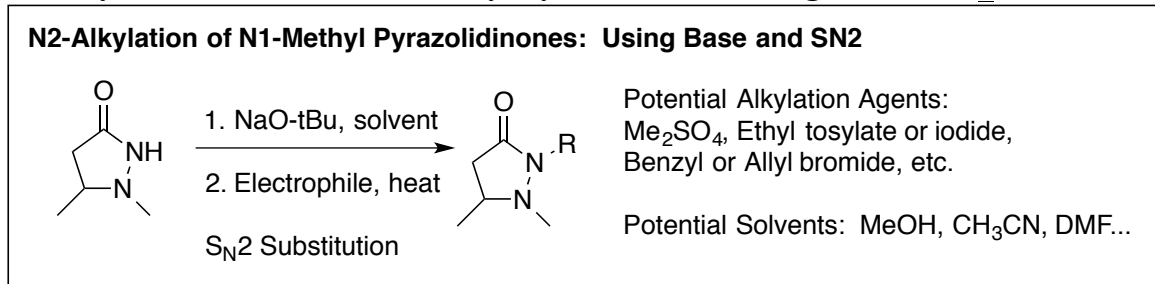
General N2-Acylation



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.)**

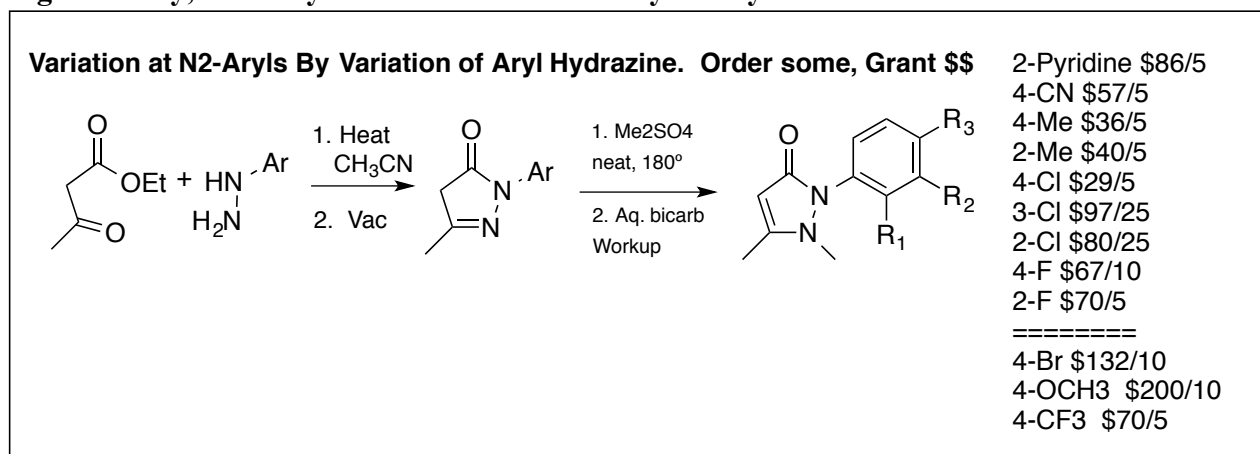
1. The initial products are well available
2. The extra time and crystallization procedure is good, other than for the 5-methyl case.
3. The N2-acylation using carboxylic acid and Mukayama reagent works to make derivative
4. The benzoyl case (R₂=Ph) would be the natural target, to be closest to antipyrine
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:



- 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?



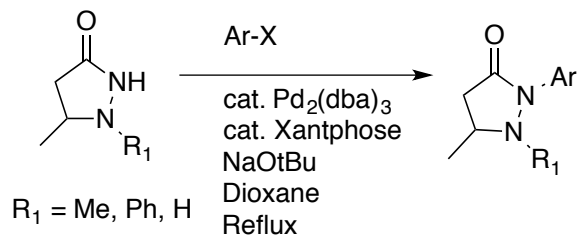
Notes:

- 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 figure 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.



CHEMReview 2016

Stephen L. Buchwald and Paula Ruiz-Castillo

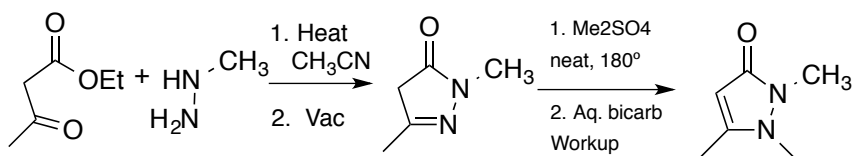
Might be hard. Detailed correct handling of the Pd catalyst and the diphosphorus ligand may be crucial

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:

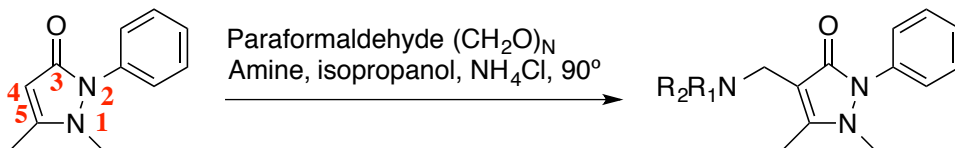


Notes:

- 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.

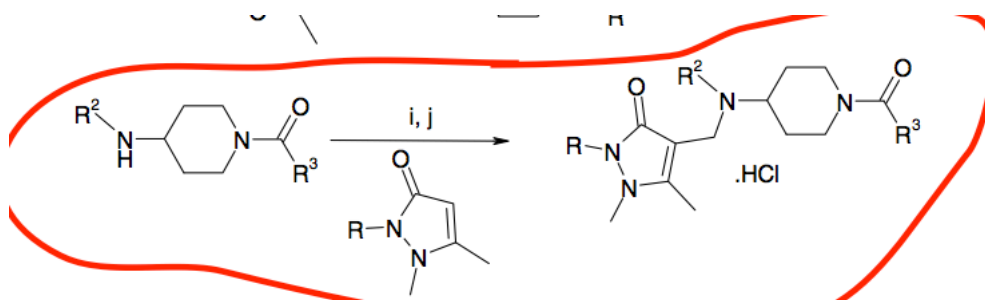
C4-Aminomethyl Analogs

C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone



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

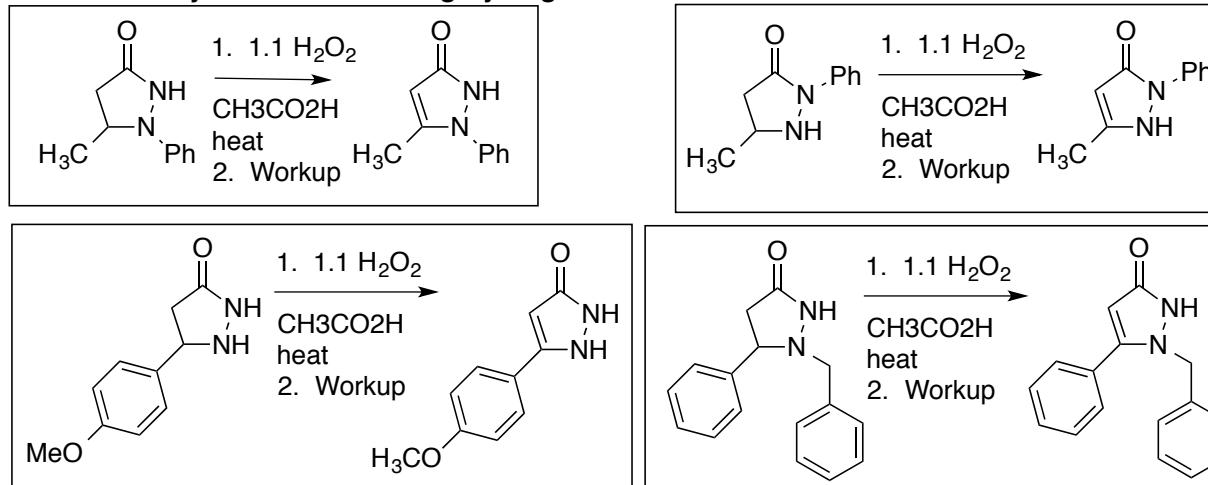
1. C. Pe'gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231
2. Reference shows reaction, but provides zero experimental details
3. We haven't done any preliminary work on this, so not sure on stoichiometry, length, yields, etc..
4. Order: Paraformaldehyde (or borrow from Sibi)
5. We have lots 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_3 , DCM ; (h) R^2NH_2 , $\text{NaBH}(\text{OAc})_3$, 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

Oxidation of Pyrazolidinones Using Hydrogen Peroxide

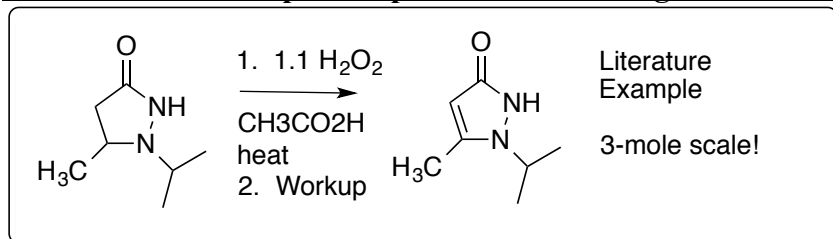


Suggest First Experiment to Try

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 ether 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.

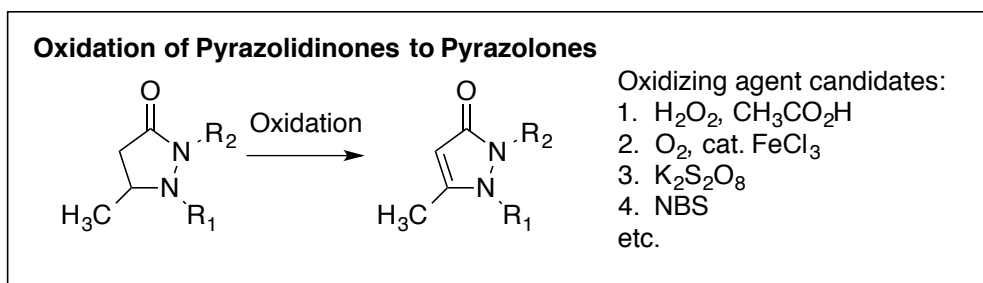
22. If Jasperse is around, come over and tell him mass, % yield, and show NMR. Is he's not around, email mass, % yield, and what spot your NMR was in. (Like spot 32 or spot 12 or whatever, so I can view your NMR myself, even if from home or wherever.)
23. To evaluate the NMR, compare your product to 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:

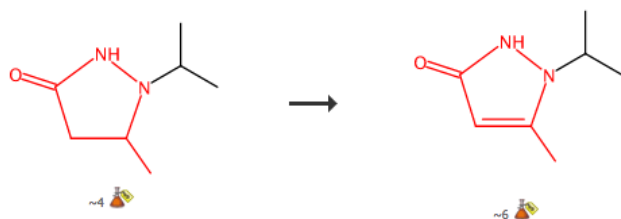


- Example: (N1-isopropyl, C5-methyl example) Preparation of 1,2-dihydro-1-(1-methylethyl)-5-methyl-3H-pyrazol-3-one (VI.1) 1-(1-methylethyl)-5-methyl-3-pyrazolidinone (390 g; 2.74 mol) is dissolved in acetic acid (170 ml) with warming. 35% aqueous hydrogen peroxide (260 ml; 3.0 mol) is added within 3 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 Pyrazole rings



1. No preliminary results on these yet.
2. A couple of SciFinder references.
 - d. One used FeCl_3 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.



Overview

Steps/Stages

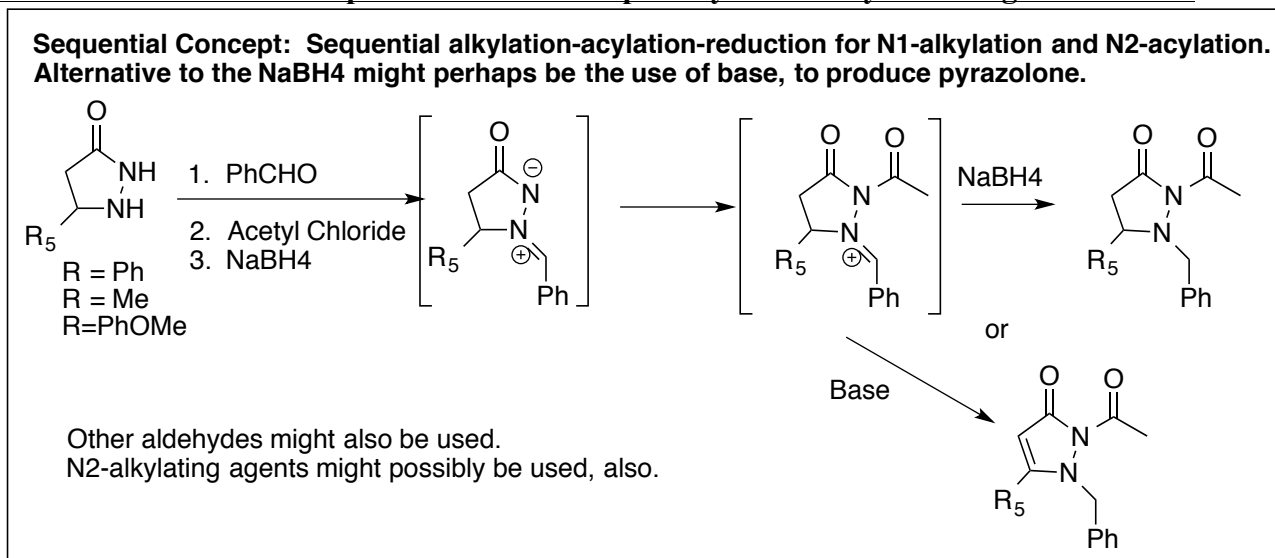
- 1.1 R:AcOH, R:H₂O₂, S:H₂O, 3 h, 65°C; 15 h, 20-25°C
- 1.2 R:NaOH, S:H₂O, 20-25°C, pH 7; 25°C → 5°C

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

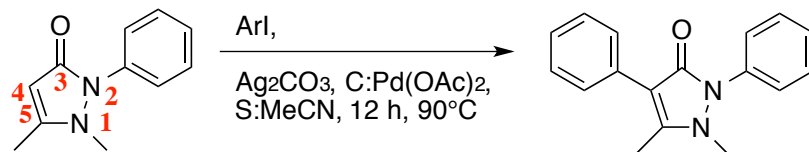
addition of approx. 1 L 50%-weight aqueous sodium hydroxide solution. Upon cooling to 5°C the reaction mixture is filtered.

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 **K₂S₂O₈** (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-methylpyrazolidin-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.



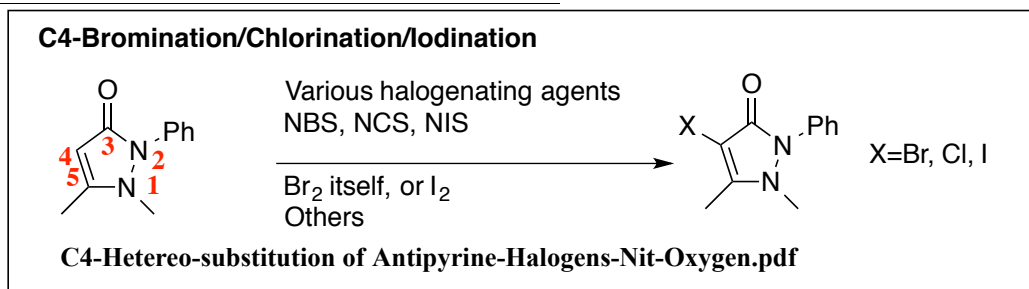
1. Lot of steps involved: Might be really efficient!
2. Might the iminium rearrange, perhaps with base, into the pyrazolone?
3. That would be super cool
4. Would direct acyl chloride work?
5. Would Mukayama and acid work?
6. Would N2-alkylation (methylation, allylation, benzylation, for example)
7. Would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

C4-Arylation. C4-Aryl Analogs**C4-Arylation. Pyrazolone**

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

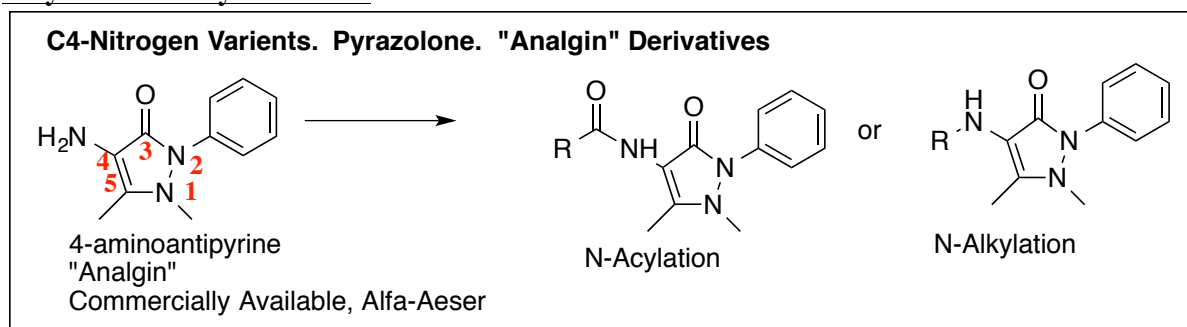
11. Gong, Hao et al From Beilstein Journal of Organic Chemistry, 9, 2033-2039, 7 pp.; 2013
12. We haven't done any preliminary work on this, so not sure on stoichiometry, length, yields, etc..
13. 4-Arylation of Antipyrine-Good using PdOAc₂ + AgOAc.pdf
14. Looks very straightforward. Not sure how new/good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

C4-Bromination/Chlorination/Iodination



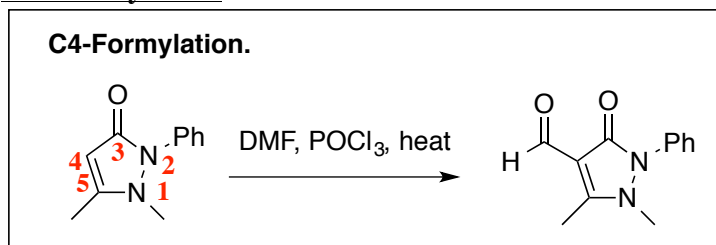
1. C4-Hetero-substitution of Antipyrine-Halogens-Nit-Oxygen.pdf
2. These have all been reported in high yields
3. Seems like simple NBS/NCS works well
4. I have good NBS. Have some NIS? Don't think we have any NCS. Sibi might?
5. Br₂ seems to work fine, too.
6. Some fancier halogenation agents have also 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.



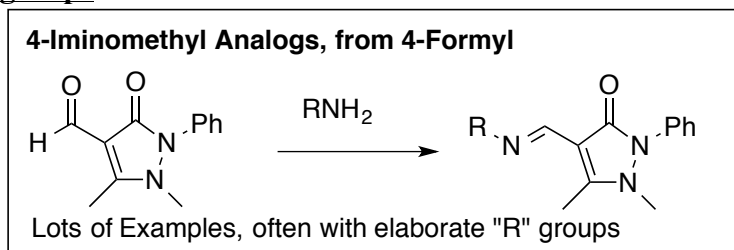
1. 4-Aminoantipyrine is called "Analgin", it's a commercial drug (that was banned for a while)
2. It is cheap and commercially available from Alfa-Aeser.
3. Should be able to do amine reactions to make analogs.
4. It's a conjugated nitrogen, so it's not super reactive, maybe.
5. But should be easy to 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

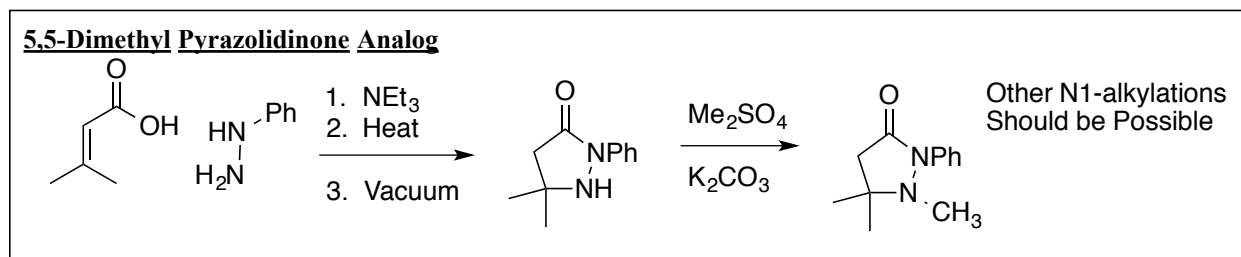


- C4-Formylation of Antipyrine.pdf
- The aldehyde provides a functional group that can then be converted into lots of other stuff

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

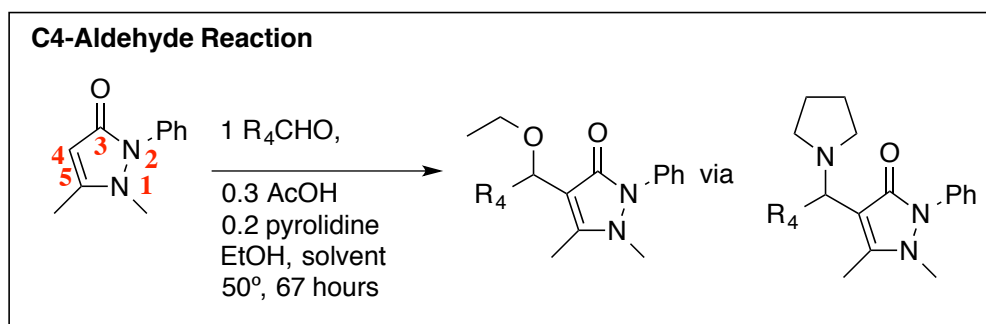


- Easy Sci-Finder Search

5,5-Dimethyl Pyrazolidinone

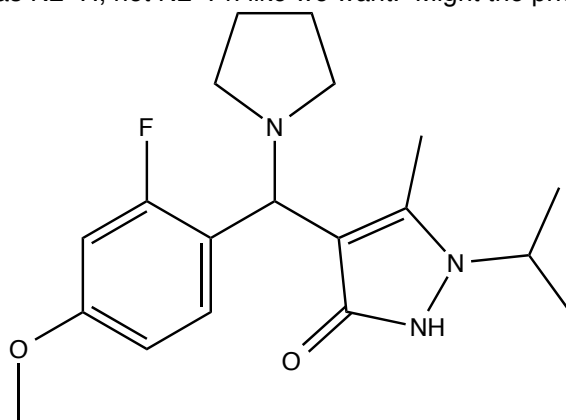
1. This one is interesting in that with the 5,5-dimethyl, there is no way the ring can be oxidized to the pyrazolone form. It's pyrazolidinone, and no redox is going to change that, whether in lab or in the cell
2. The first reaction hasn't been tried yet.
3. Based on earlier Hawau reactions, it would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

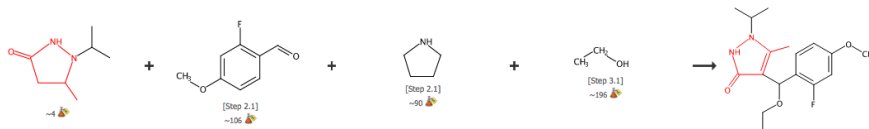
Note: The literature example has N2=H, not N2=Ph like we want. Might the phenyl deactivate somewhat?



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

103. [View Reaction Detail](#) [Link](#)

3 Steps Hover over any structure for more options.



Overview

Steps/Stages

- 1.1 R_4CHO , $S: H_2O$, $S: AcOH$, 3 h, 65°C; 15 h, 20-25°C
- 1.2 R_4CHO , $S: H_2O$, pH 7
- 2.1 R_4CHO , $S: MeCN$, 20°C; 1 h, 20°C → 75°C; 75°C → 3°C; 30 min, 3°C
- 3.1 R_4CHO , $S: H_2O$, $S: EtOH$, 2-3 h, rt → 50°C

Notes

Reactants: 4, Reagents: 4, Solvents: 4, Steps: 4, Stages: 4, Most stages in any one step: 2

References

Commercial scale process for the preparing pyrazole-o-glycoside derivatives with low tech. expenditure in a high space/time yield
[Quick View](#) [PatentPlex™](#)
 By Pirella, Göttsche, Loewig
 From PCT Int. Appl., 2007/010015, 25 Jan 2007

Experimental Procedure

Step 1

Example 1.4: Preparation of 1,2-dihydro-1-(1-methylethyl)-5-methyl-3H-pyrazol-3-one (VI.1) Variant 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.

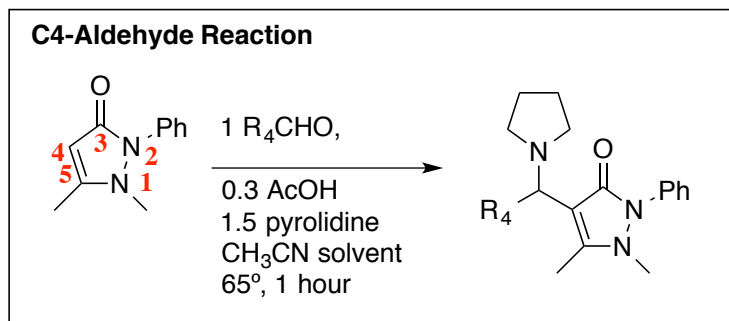
Step 2

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-methoxybenzaldehyde 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.

Step 3

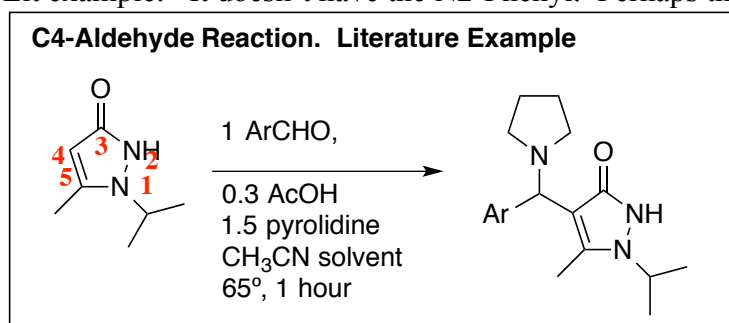
Variant 3: To a mixture of 50 g (0.144 mol) 1,2-dihydro-1-(1-methylethyl)-4-[(2-fluor-4-methoxyphenyl)-(1-pyrrolidino)methyl]-5-methyl-3H-pyrazol-3-one and 500 mL ethanol is added aq. 30% hydrochloric acid. The reaction mixture is heated to 50°C for 2-3 h. 175 mL of water is then added and the mixture is cooled. The product is isolated by filtration and washed with ethanol. It is dried under inert gas atmosphere at 45°C. Mass and ¹H-NMR-spectra are in accordance with the assigned structure. Mass spectrum (ESI⁺): m/z = 323 [M+H]⁺

C4-Aldehyde + Amine then Alcohol.pdf



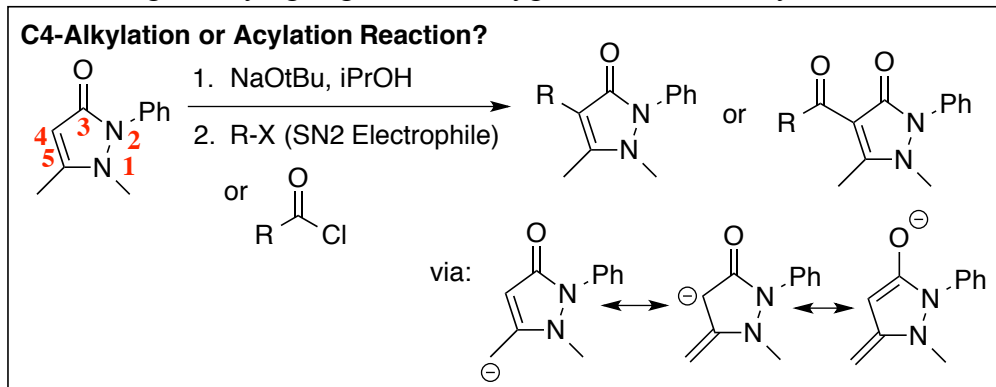
Example 3a: Synthesis of 1,2-Dihydro-1-(1-methylethyl)-4-[(2-fluor-4-methoxyphenyl)-(1-pyrrolidino)methyl]-5-methyl-3H-pyrazol-3-one (IV.1a) To a mixture of 70 g (0.50 mol) 1,2-dihydro-1-(1-methylethyl)-5-methyl-3H-pyrazol-3-one and 350 mL acetonitrile is added a solution of 77 g (0.50 mol) 2-fluor-4-methoxybenzaldehyde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



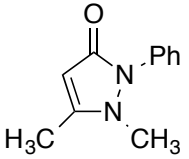
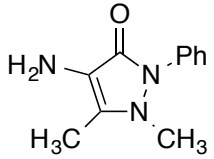
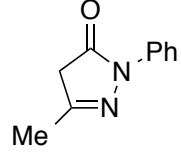
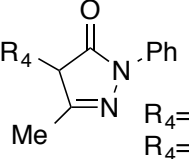
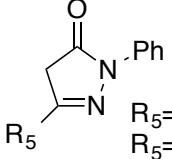
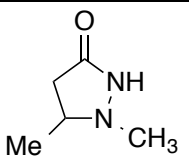
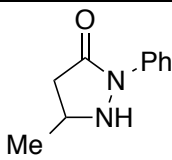
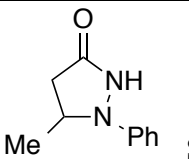
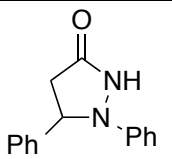
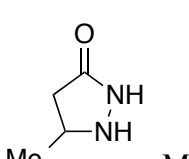
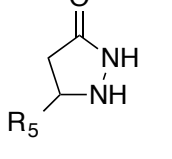
C4-Alkylation or Acylation via Anion/Enolate?

- 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.



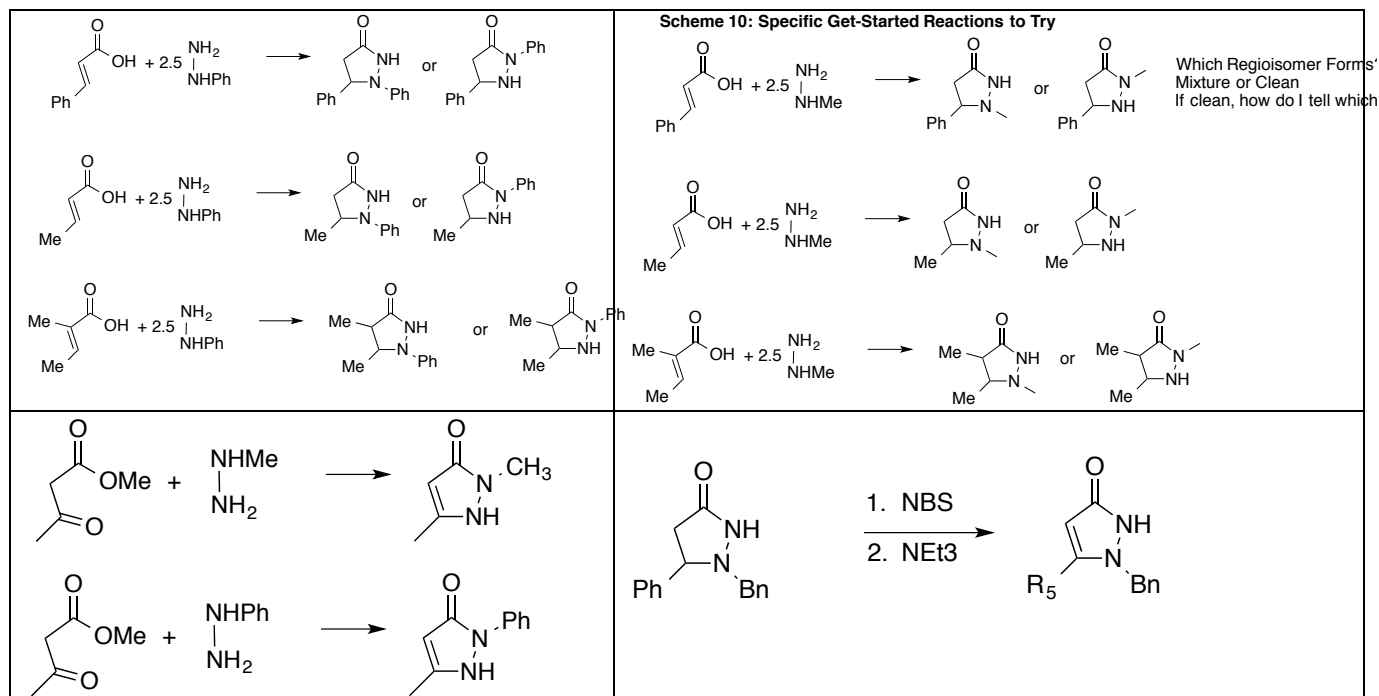
Zero literature precedence. Which is why it would be cool and more publishable if it worked! 😊
If so, could be a really convenient way to install new chunks onto antipyrene. Nice in that the starting material is cheap and clean and commercially available.

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

 <p>Antipyrine. \$\$.</p>		 <p>4-aminoantipyrine = "Analgin". \$\$</p>	
 <p>Taysir's Reagent.</p>	 <p>$R_4 = \text{CH}_3$ $R_4 = \text{CH}_2\text{Ph}$</p>	 <p>$R_5 = \text{CH}_2\text{CH}_3$ $R_5 = \text{Ph}$</p>	
 <p>Hawau's N1-Methyl Reagent</p>		 <p>Hawau's N2-Phenyl Reagent</p>	
 <p>Sunny's Reagent</p>			
 <p>Mariam's Reagent</p>		 <p>$R_5 = \text{phenyl}$ $R_5 = 4\text{-methylphenyl}$ $R_5 = 4\text{-chlorophenyl}$ $R_5 = 4\text{-methoxyphenyl}$</p> <p>Trinh's Reagents</p>	

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-Variants, 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-Variants, 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 Variants and N2 Variants, whether with ethylacetates, 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	Stockroom probably has? Jasperse research area or stockroom shelf 8B
	534-17-8	Cesium Carbonate	Stockroom probably has? Stockroom shelf 16C

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

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

Ignore these, these are for Research Grant.

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

Aryl Hydrazines

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

Ignore these, these were already bought October 2016

Scheme 1: C4-Varients, Ethylacetoacetates.

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

R5	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