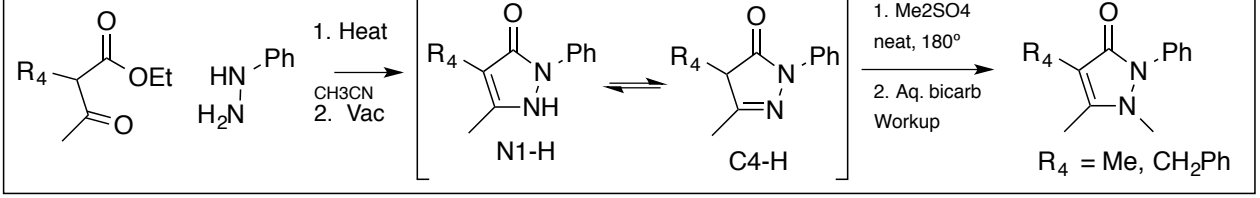
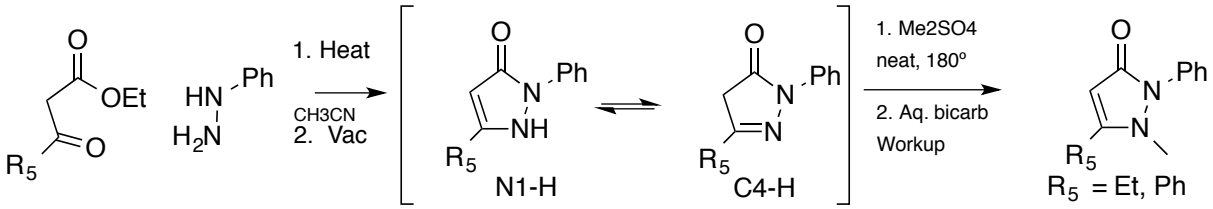
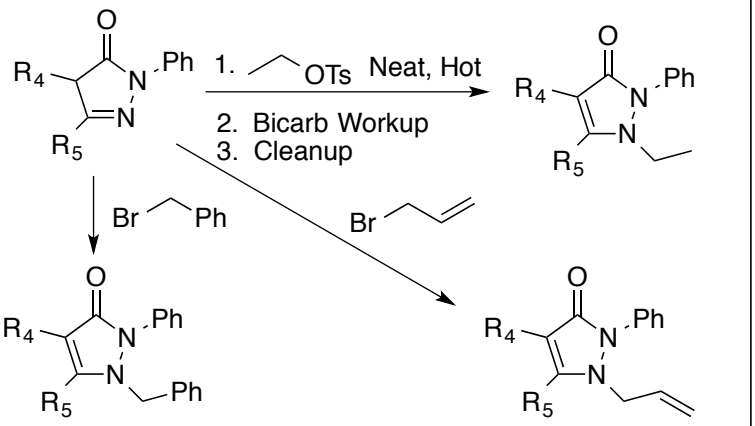
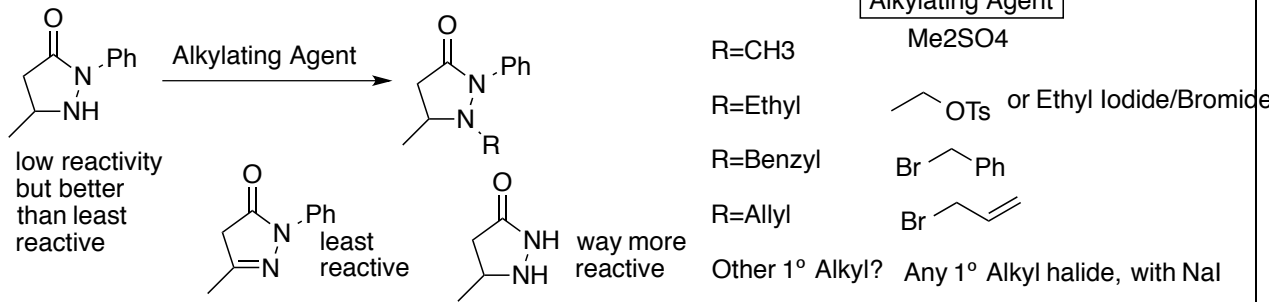
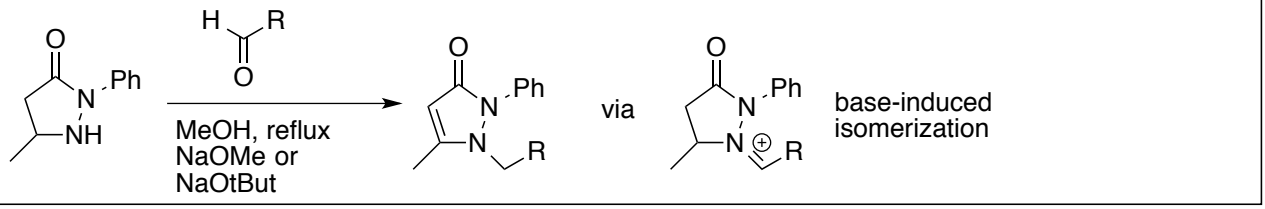
Table of Contents Update1/5/16





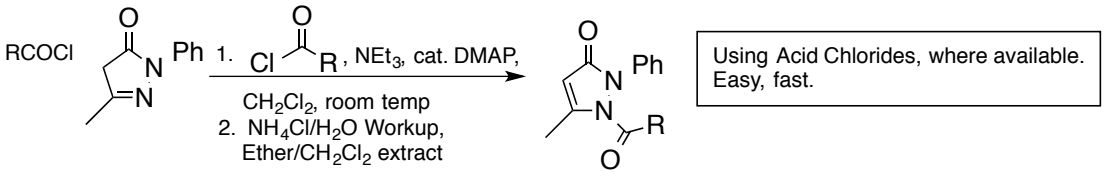




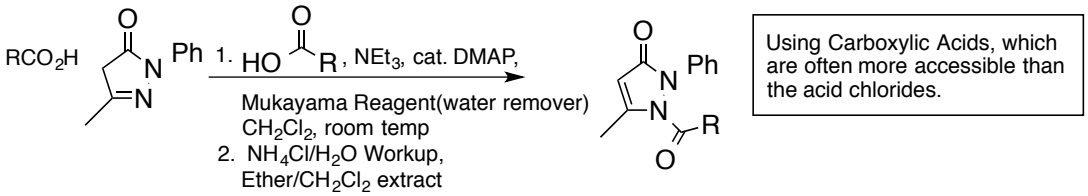


13

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



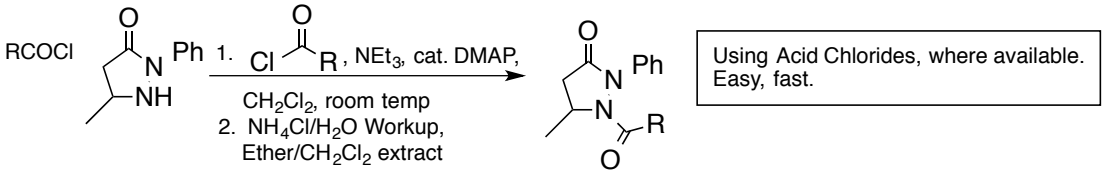
Using Acid Chlorides, where available. Easy, fast.



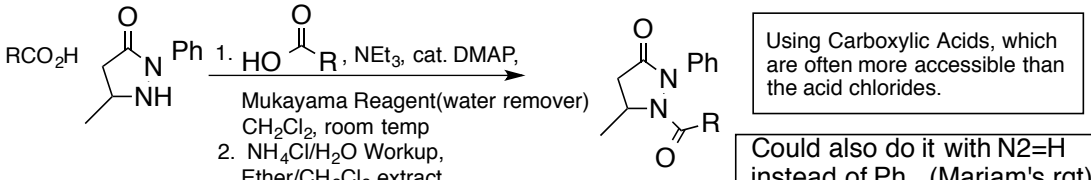
Using Carboxylic Acids, which are often more accessible than the acid chlorides.

14

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



Using Acid Chlorides, where available. Easy, fast.

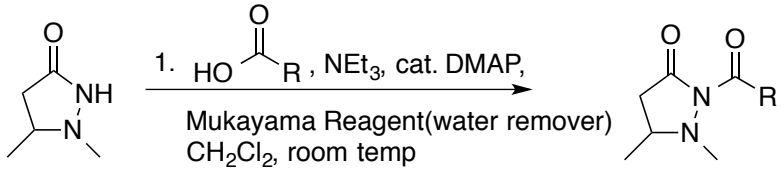


Using Carboxylic Acids, which are often more accessible than the acid chlorides.

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

15

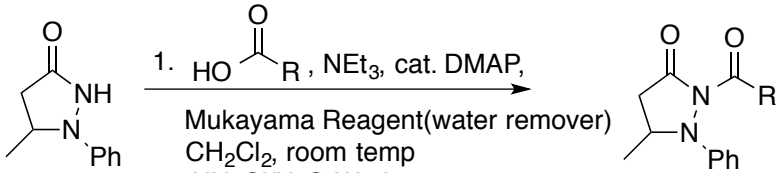
N2-Acylation of N1-Methyl Pyrazolidinones: Using RCO2H and Mukayama's Reagent.



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

16

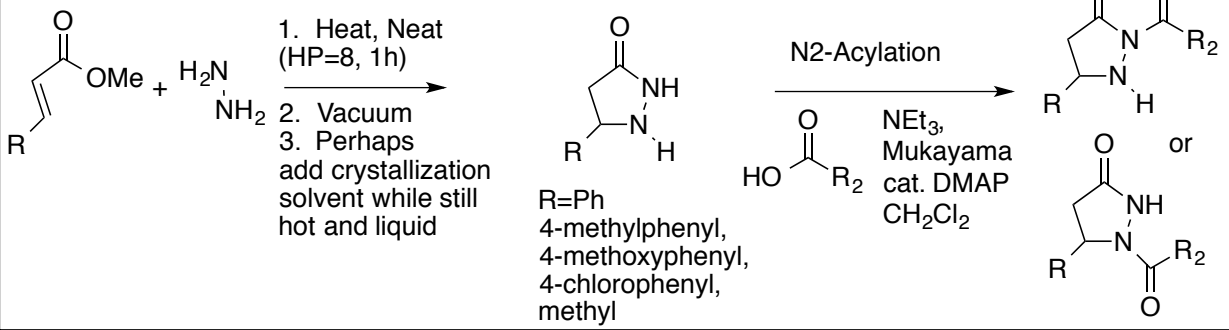
N2-Acylation of N1-Phenyl Pyrazolidinone (Sunny's Reagent) Pyrazolidinones.



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

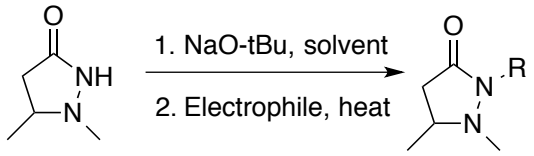
17

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



18

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

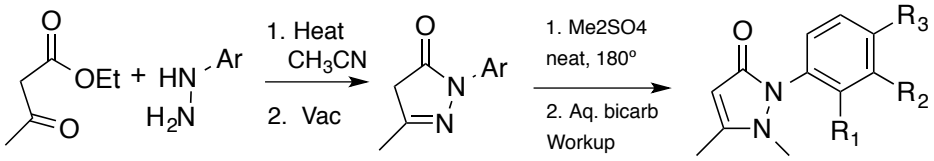


Potential Alkylation Agents:
Me_2SO_4, Ethyl tosylate or iodide,
Benzyl or Allyl bromide, etc.

Potential Solvents: MeOH, CH_3CN, DMF...

19

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

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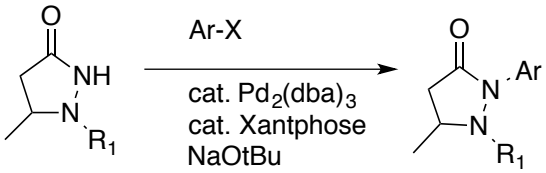
N2-Arylation of Pyrazolidinone, Pd-catalyzed. Might be Harder Project, But High-Impact if we could Figure it Out.



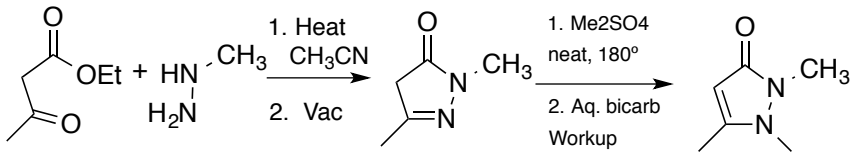
CHEMReview 2016
Stephen L. Buchwald and Paula Ruiz-Castillo

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.

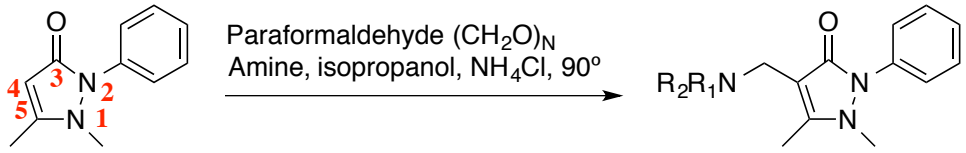
21

Scheme 4: Variataion at N2 By Use of MethylHydrazine:



22

C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone



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

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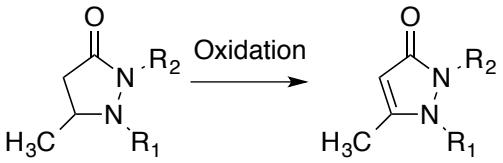
Oxidation of Pyrazolidinones to Pyrazolones



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

24 Continuation of Page 21, Oxidation

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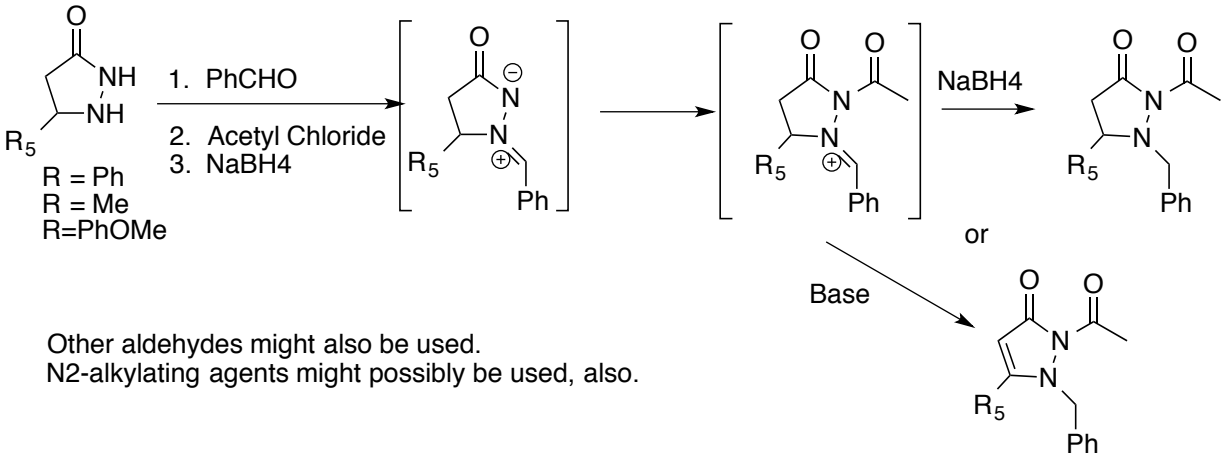
Sequential Concept: Sequential alkylation-acylation-reduction for N1-alkylation and N2-acylation. Alternative to the NaBH4 might perhaps be the use of base, to produce pyrazolone.



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

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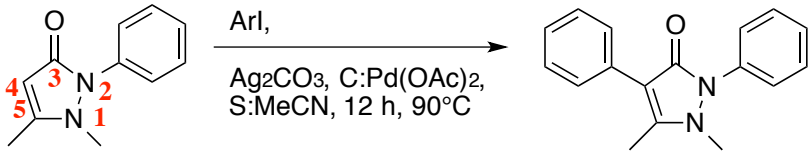
C4-Arylation. Pyrazolone



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

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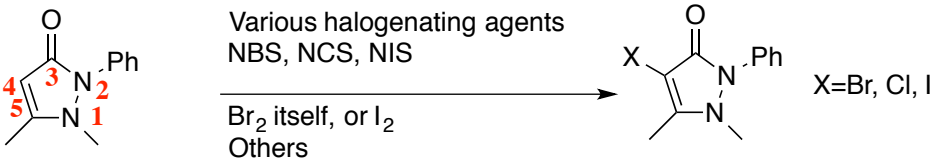
C4-Bromination/Chlorination/Iodination



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

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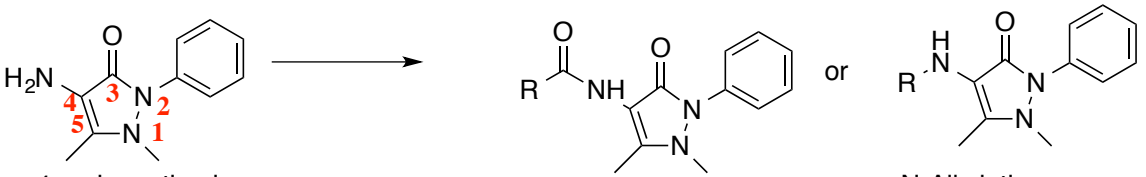
C4-Nitrogen Varients. Pyrazolone. "Analgin" Derivatives



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

N-Acylation

N-Alkylation

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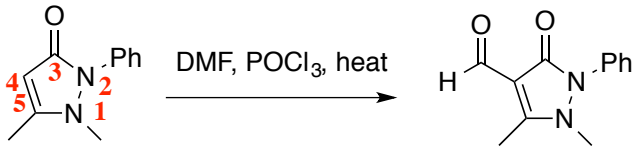
C4-Formylation.



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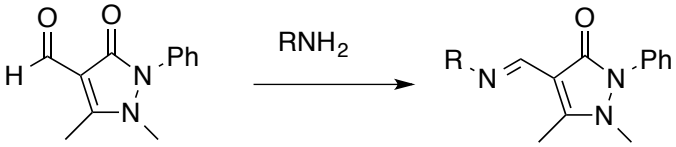
4-Iminomethyl Analogs, from 4-Formyl



Lots of Examples, often with elaborate "R" groups

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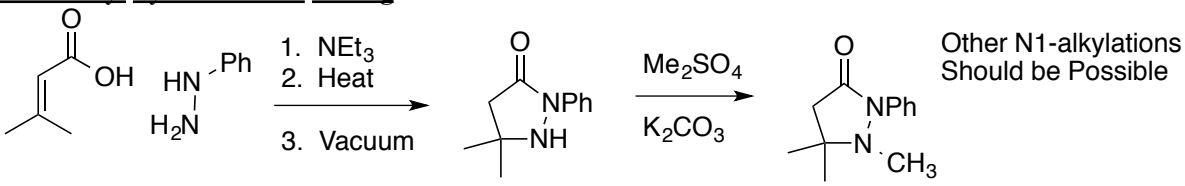
5,5-Dimethyl Pyrazolidinone Analog



Other N1-alkylations Should be Possible

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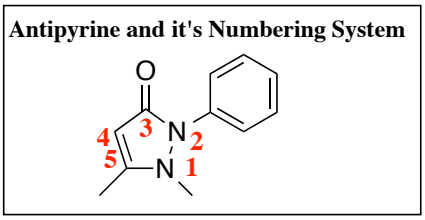
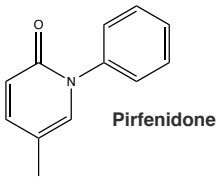




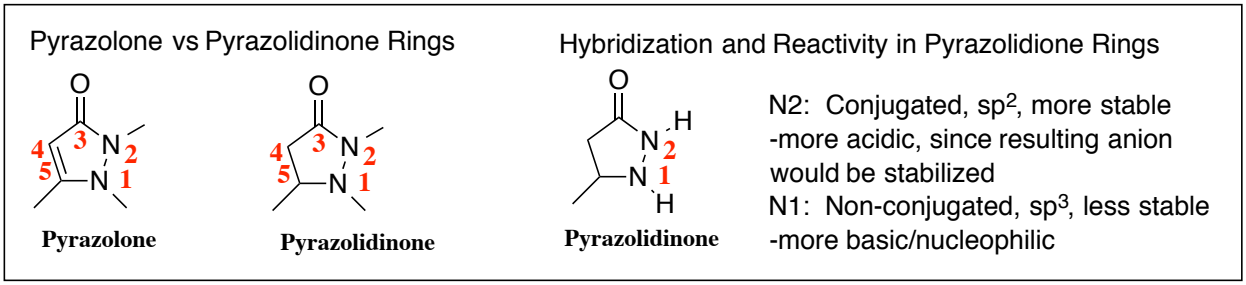
antipyrine Synthesis.pdf

Big Picture Concept:

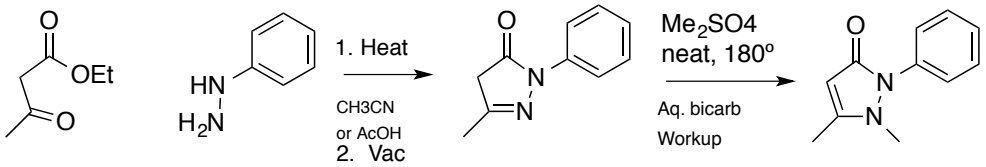
1. Perfenidone is a medicines used to treat pulmonary fibrosis
   - It is not a life-saver, and isn't very good in terms of potency, efficacy, toxicity, or expense
2. An extensive "chemical library" study has found antipyrine as a "lead chemical"
3. Group goal: Make as many analogs of antipyrine as we can, in hopes that we can make something better yet
   - Potency
   - Efficacy
   - Toxicity

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)



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:

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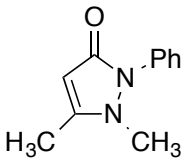
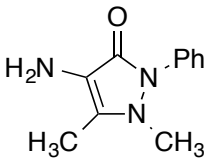
<td>  Antipyrine. $$.</td>
<td>  4-aminoantipyrine = “Analgin”. $$</td>
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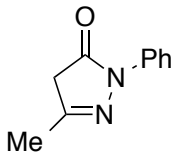
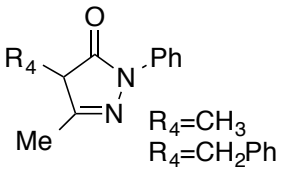
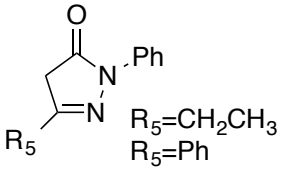
<td>  Taysir’s Reagent.</td>
<td>  </td>
<td>  </td>
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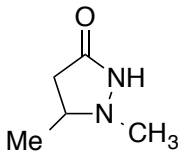
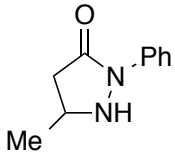
<td>  Hawau’s N1-Methyl Reagent</td>
<td>  Hawau’s N2-Phenyl Reagent</td>
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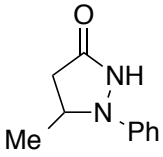
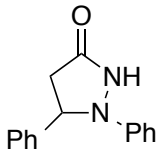
<td>  Sunny’s Reagent</td>
<td>  </td>
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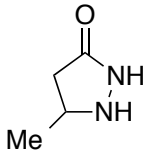
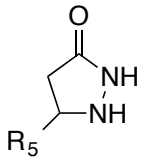
<td>  Mariam’s Reagent</td>
<td>  Trinh’s Reagents</td>
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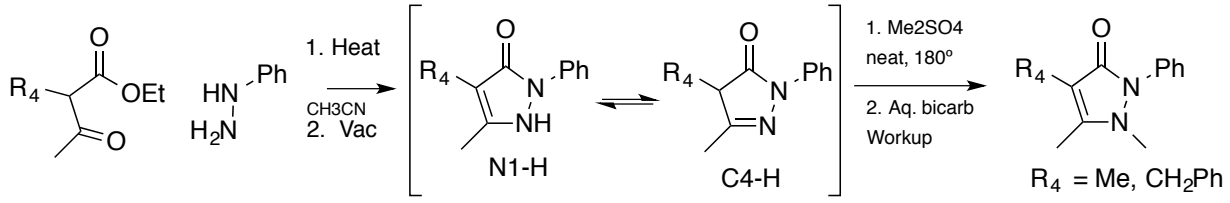
C4-Variation (Alkyl/Benzyl)

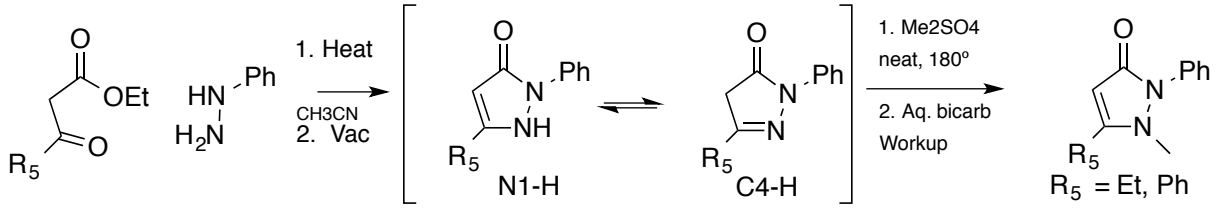
Scheme 1: Variataion at C4:



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:



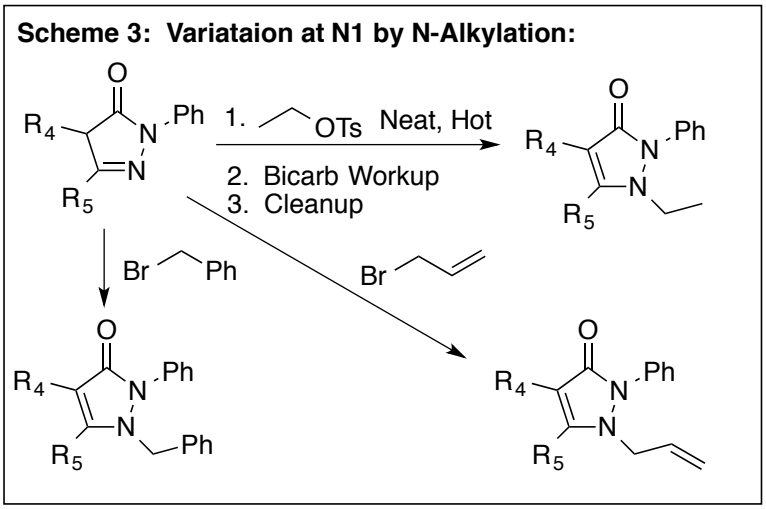
CAS ID:

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:

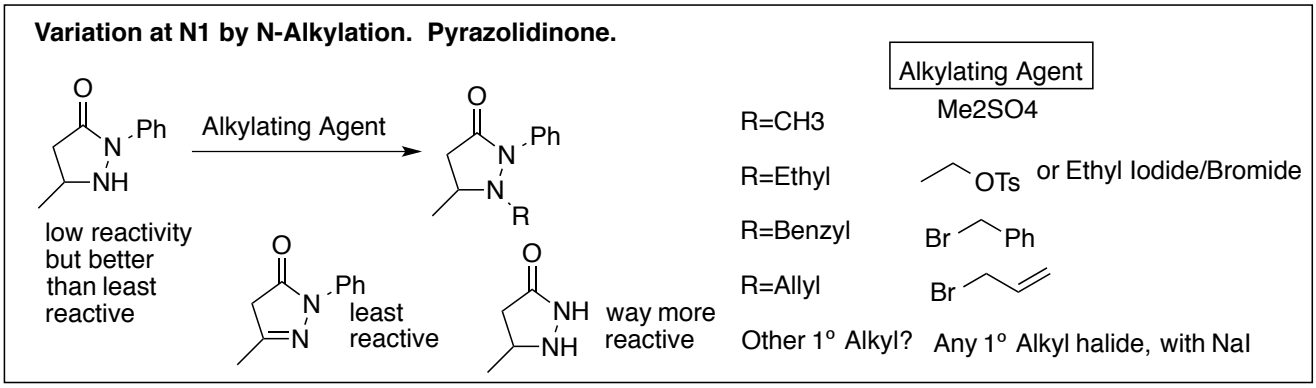


1. Alkylation is pretty slow
2. Preliminary results: Works well with dimethylsulfate hot/neat (see scheme 1)
3. Tried ethyl iodide, and that works, slowly, but partially/incomplete. Seemed very clean, just didn't go to completion in preliminary attempt.
   - Problem is getting hot enough without having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

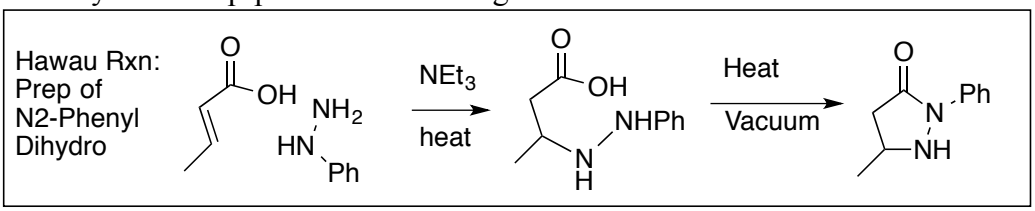
N-Ethylation Reagents and Catalysts

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

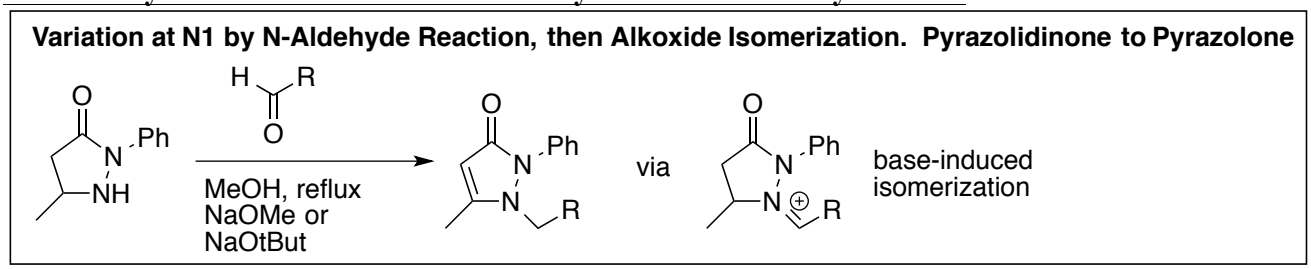
N1-Alkylation of Pyrazolidinone Rings (Pyrazolidinones)



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.

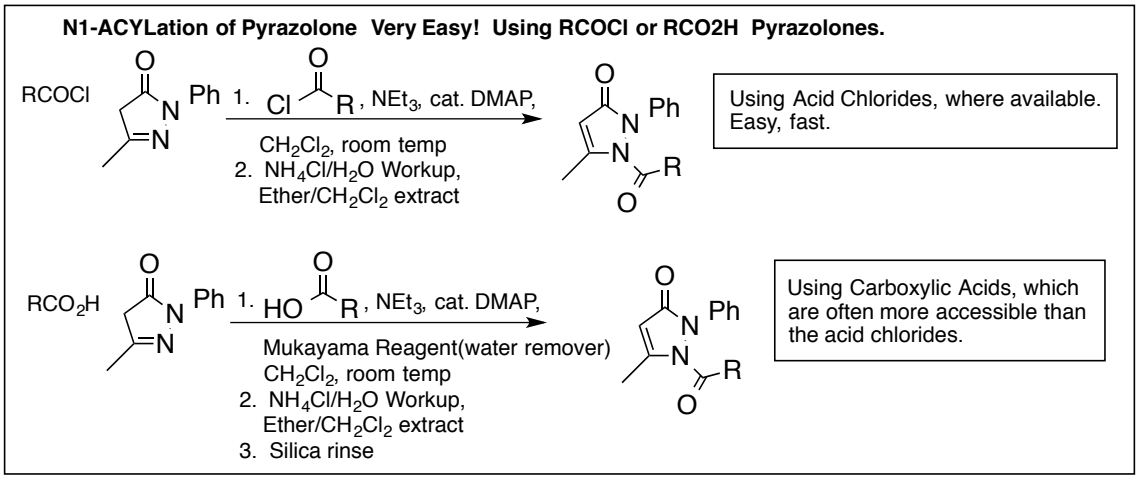


Variation at N1 Pyrazolones. By Reaction of Hawau Phenyl-Pyrazolidinone with Aldehyde, followed by NaOR/ROH isomerization. Pyrazolidinone => Pyrazolone



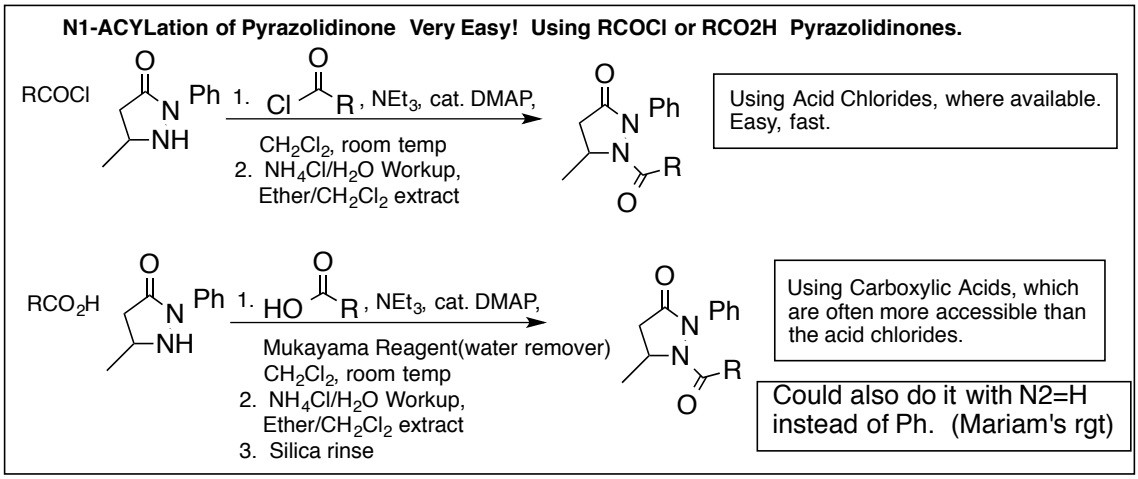
1. Kangasmetsa, Jussi J. et al From PCT Int. Appl., 2013096501, 27 Jun
2. N1-Aldehyde use, followed by NaOMe/MeOH isomerization: N1 plus Aldehyde, then NaOMe/MeOH reflux to isomerize
   - … 35 mmol… 5-methypyrazolidin-3-one. This oil was dissolved in MeOH (20 mL), cooled to 0°C under N2 atmosphere and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

N1-ACYLation of Pyrazolidinones.



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   - See discussion and observations from the Page 3/Scheme 3 alkylations
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6. Hawau's starting material is really clean, so not complications from that.
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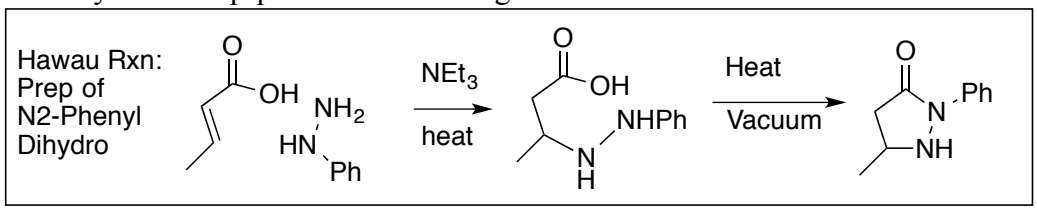
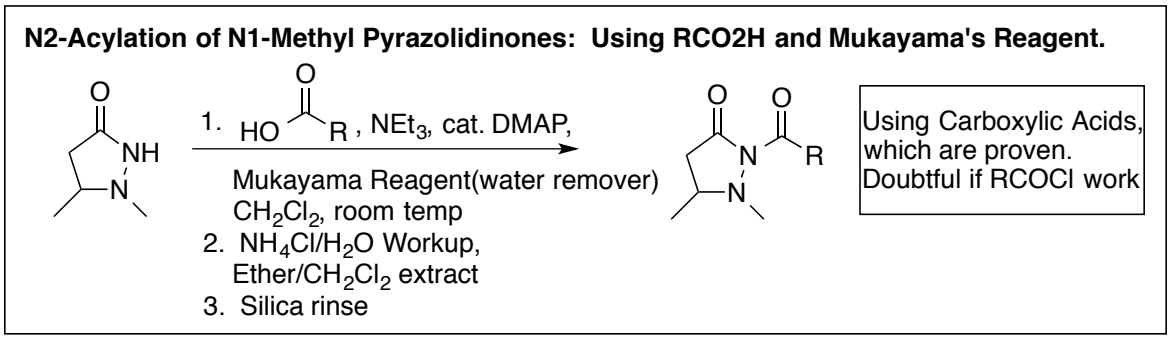


N2-Acylation of N1-Methyl Pyrazolidinone, Using Hawau's Methyl Reagent:
Acylation Using Acids and Mukayama's Reagent: Pyrazolidinone



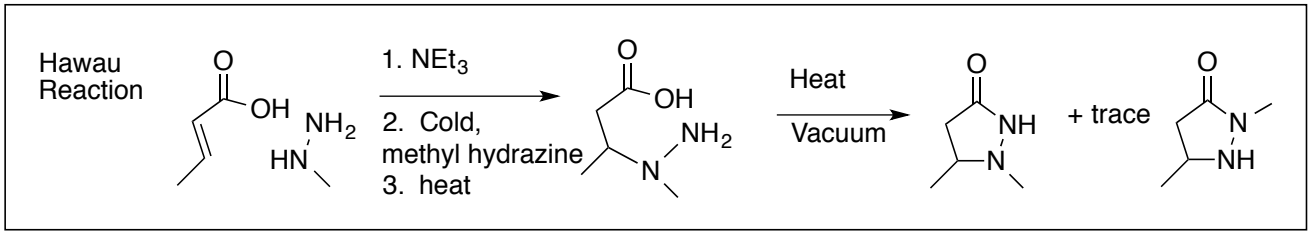
1. Starting chemical synthesis nicely developed by Hawau
2. Starting material isn't completely clean; contaminated by modest amount of N2-methyl isomer
3. The simplest to make here would be R=Ph
4. Antipyrine of course does not have the carbonyl attachment on at N2. So who knows what assay-impact this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

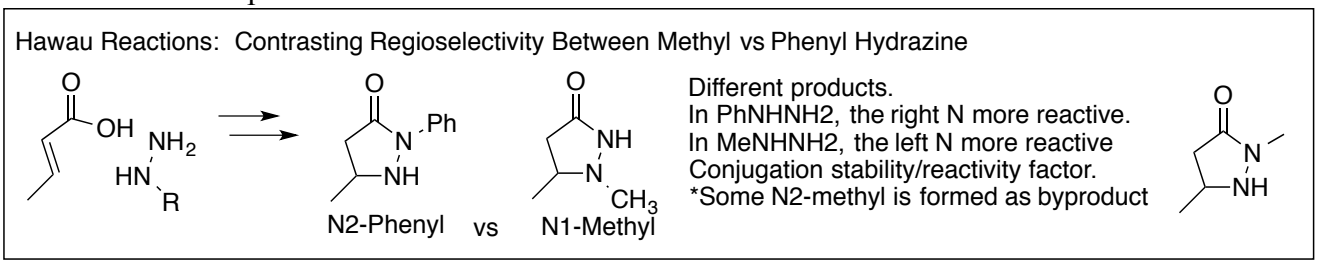
	CAS	One Name variant	Supplier, Price
Me	60-34-4	Methyl hydrazine	Sigma/Aldrich: $308/25

Note: Aldrich is cheapest here, and good.

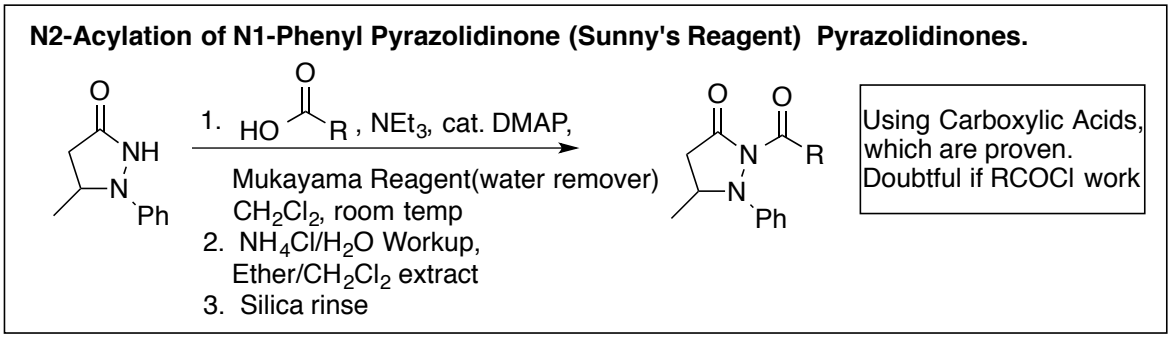
- Price looks worse than it is, because it's so small. So you get a lot of moles per gram.
- INCLUDE IN GRANT TO BUY A BUNCH
- Note: In the Hawau reaction, starting ice-cold and doing a lot of low-temp improves the selectivity for the N1-Me product. So, if you need more, don't just mix and heat!



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.

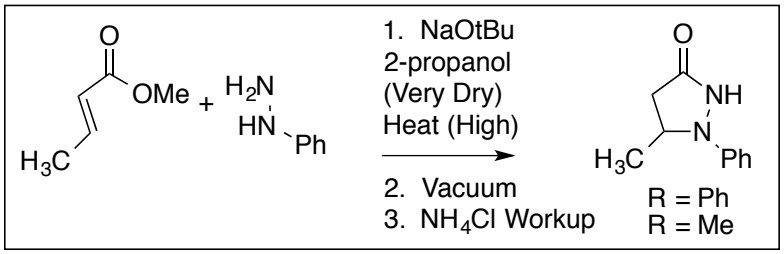


N2-Acylation of N1-Phenyl Pyrazolidinone, Using Sunny's Phenyl Reagent:

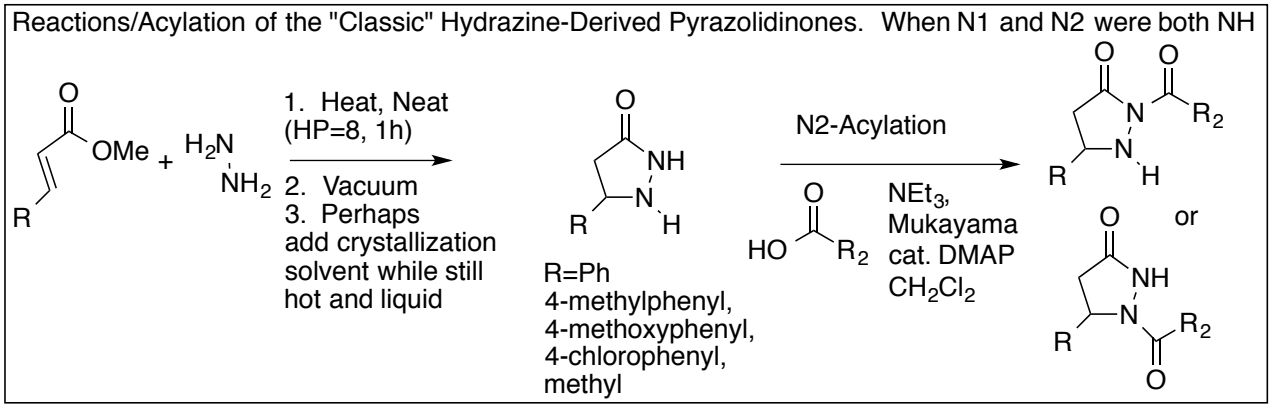


1. The N2-acylation using carboxylic acid and Mukayama reagent works to make derivative
2. This will function as an "Antipyrine-Twist" analog. If three core components of antipyrine are the aromatic ring, the 5-ring, and the carbonyl, this will effectively push the carbonyl over relative to the arene.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

Prep of Sunny's Reagent:



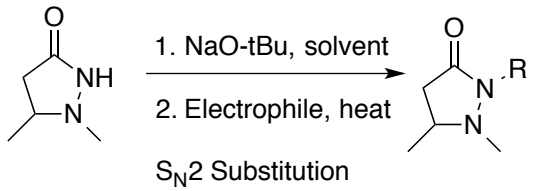
N2-Acylation of N1-H Rings, Using Trinh's Reagents:
Acylation Using Acids and Mukayama's Reagent: Di-Hydro Rings
(Actually, I'm not sure what will happen here. Maybe just some exploring to check.)



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



S_N2 Substitution

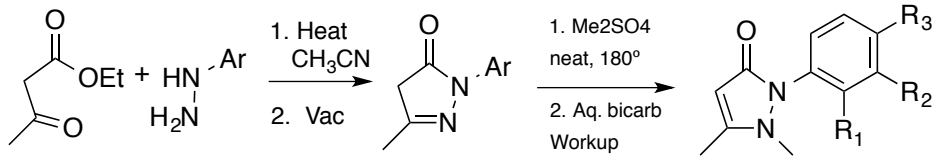
Potential Alkylation Agents:
Me_2SO_4, Ethyl tosylate or iodide,
Benzyl or Allyl bromide, etc.

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

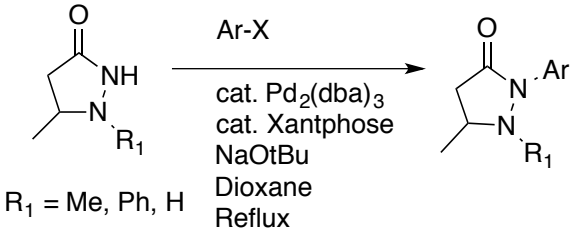
Notes:

- 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

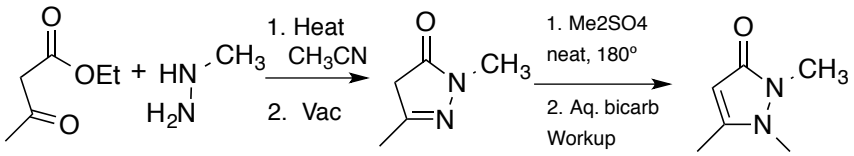
Might be hard. Detailed correct handling of the Pd catalyst and the diphosphorus ligand may be crucial

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:

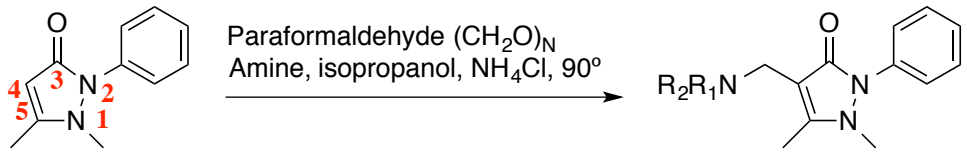


Notes:

- 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.

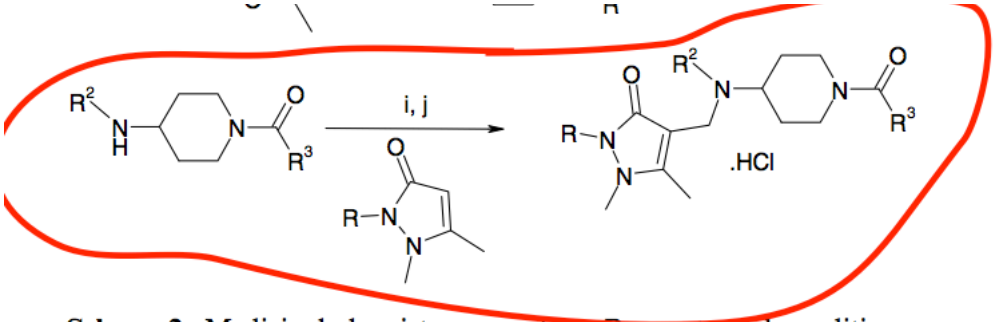
C4-Aminomethyl Analogs

C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone



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

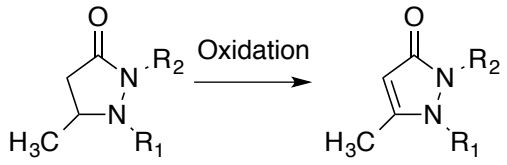
1. C. Pe´gurier et al. / Bioorg. Med. Chem. Lett. 17 (2007) 4228–4231
2. Reference shows reaction, but provides zero experimental details
3. We haven't done any preliminary work on this, so not sure on stoichiometry, length, yields, etc..
4. Order: Paraformaldehyde (or borrow from Sibi)
5. We have lots 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 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.

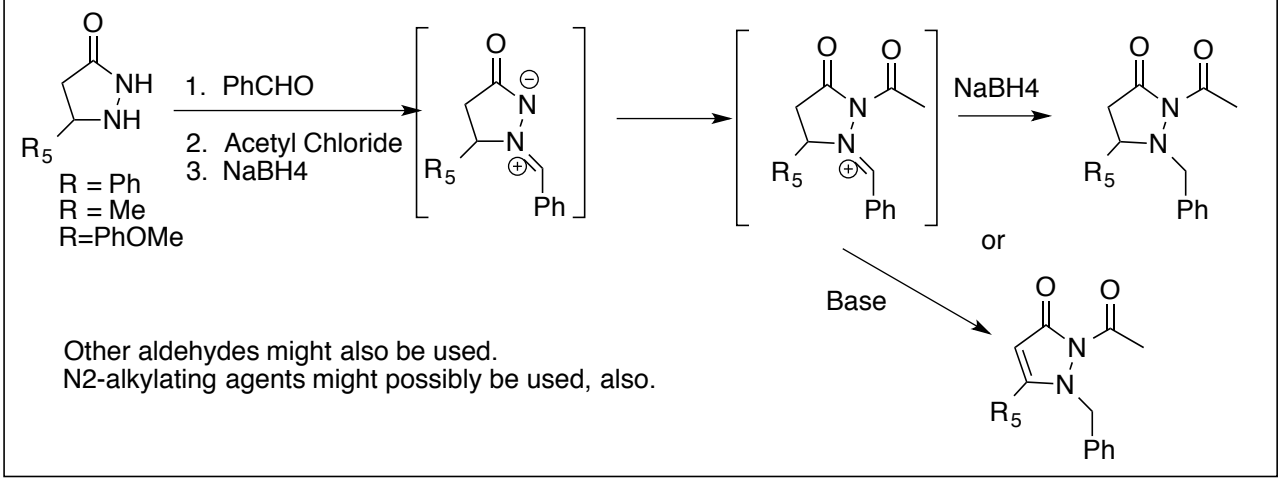
1. No preliminary results on these yet.
2. A couple of SciFinder references.
    d. One used FeCl3 and oxygen
    e. The other uses a sulfur reagent.
    f. Third used hydrogen peroxide
    g. Some experimental, although a bit vague.
    h. See PDF file called: Pyrazolidinone Oxidation to Pyrazolinone 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
    - 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

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

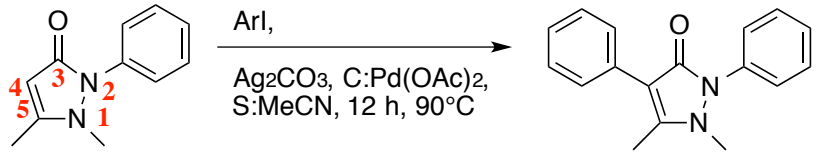
Sequential Concept: Sequential alkylation-acylation-reduction for N1-alkylation and N2-acylation. Alternative to the NaBH4 might perhaps be the use of base, to produce pyrazolone.



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

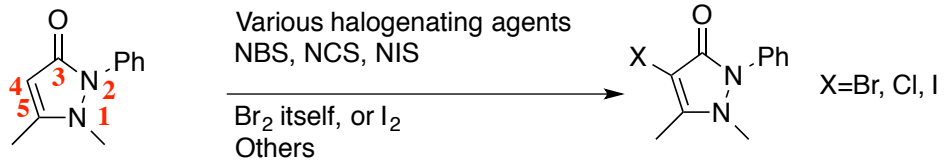


4-Arylation of Antipyrine-Good using PdOAc2 + AgOAc.pdf
Gong, Hao et al From Beilstein Journal of Organic Chemistry, 9, 2033-2039, 7 pp.; 2013

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

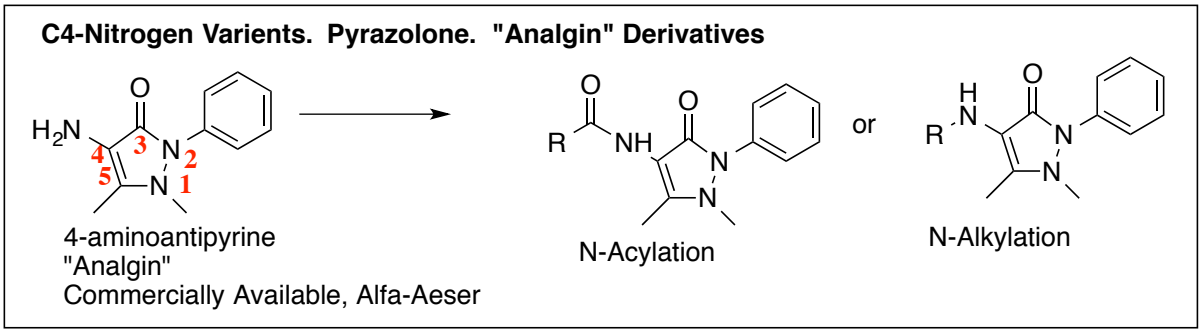
C4-Bromination/Chlorination/Iodination



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.

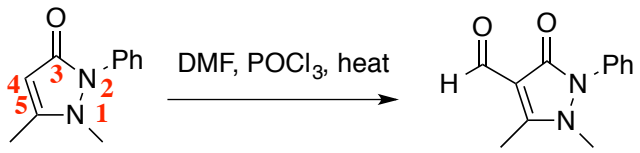
4-Acylamino and Alkylamino Analogs. Analgin Reactions. C4-Aminoantipyrine to Amides or alkyl amines. Pyrazolones.



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

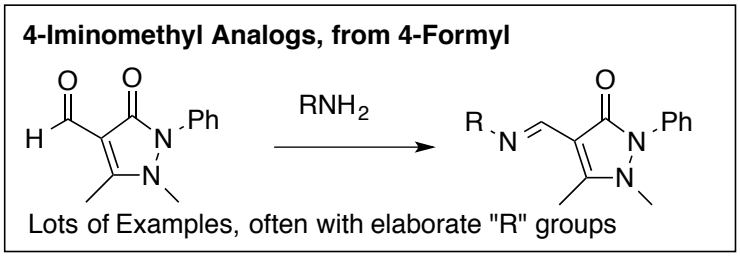
C4-Formylation

C4-Formylation.



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

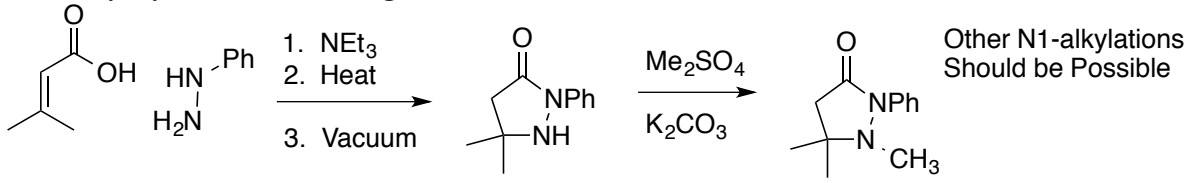
C4-Iminomethyl Analogs. From the Formyl Derivative. Lots of examples with elaborate "R" groups



- Easy Sci-Finder Search

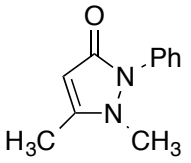
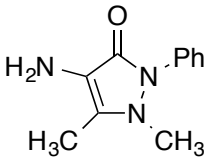
5,5-Dimethyl Pyrazolidinone

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).

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

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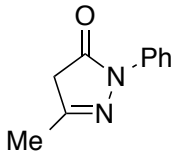
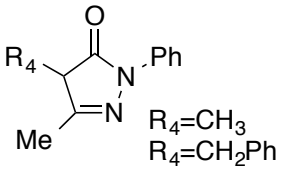
<tr>
<td>  Taysir’s Reagent.</td>
<td>  </td>
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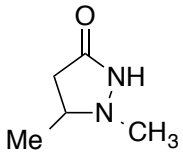
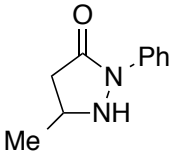
<td>  Hawau’s N1-Methyl Reagent</td>
<td>  Hawau’s N2-Phenyl Reagent</td>
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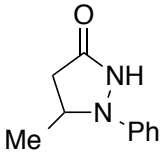
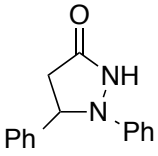
<td>  Sunny’s Reagent</td>
<td>  </td>
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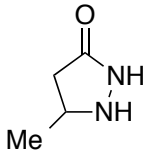
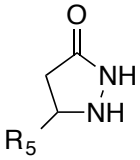
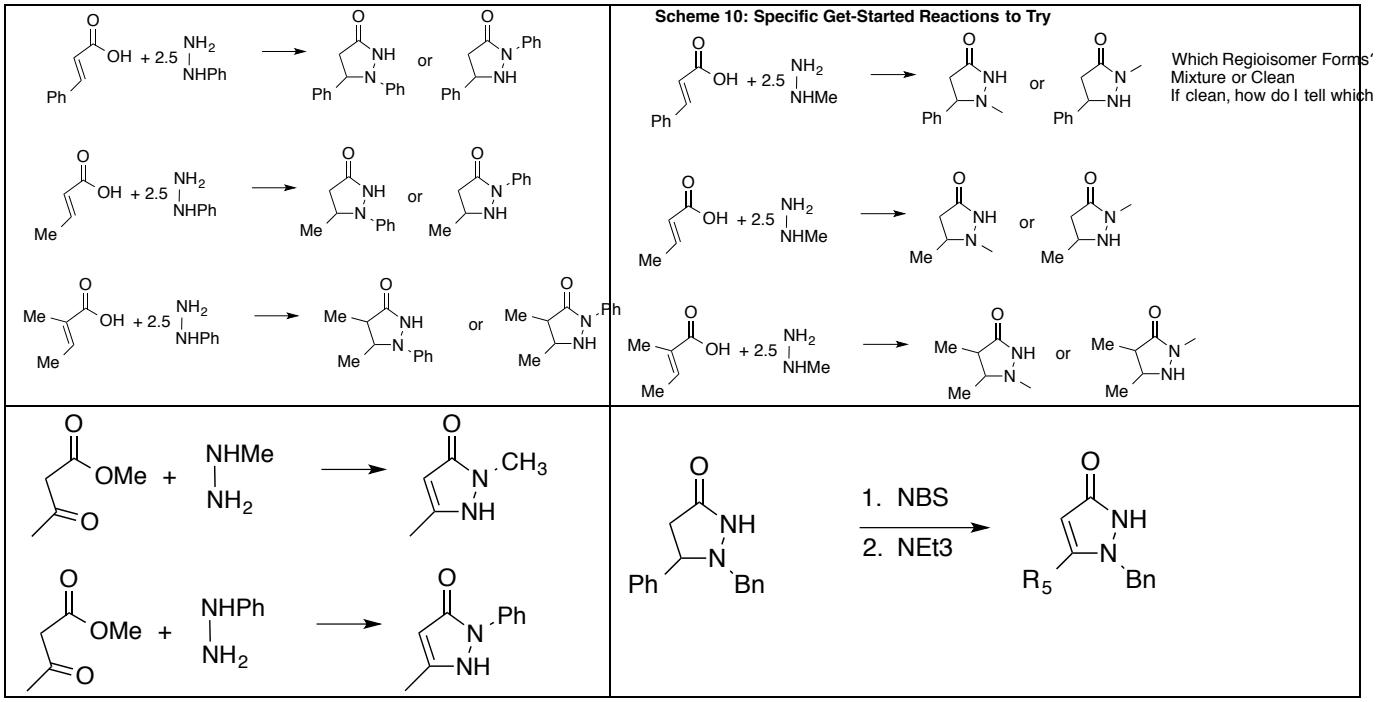
<td>  Mariam’s Reagent</td>
<td>  Trinh’s Reagents</td>
</tr>
</table>

This might be hard, since we're not Pd experts and have limited stock.
Review might really inform.

CAS ID:

	CAS	One Name variant	Commercial?	Supplier, Price
	161265-03-8	Xantphos		Catalyst, 1-2 grams is plenty
	591-50-4	Iodobenzene		
	51364-51-3	Pd2(dba)3 Tris(dibenzylideneacetone)dipalladium(0)		Catalyst, 1-2 grams is plenty
	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

	CAS	One Name variant	Supplier, Price
	161265-03-8	Xantphos	Catalyst, 1-2 grams is plenty VWR-AA, $237.03/5g
	51364-51-3	Pd2(dba)3 Tris(dibenzylideneacetone)dipalladium(0)	Catalyst, 1-2 grams is plenty VWR-Acros, $34.88/500mg

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