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)
     o 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.
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
  o Number logic: The two nitrogens naturally win over the 3 carbons, so they’ve got to be 1 and 2.
  o Of the 3 carbons, the carbonyl is highest priority.
  o 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/sp³, and the conjugated N2 is sp².
  o N1 is thus more nucleophilic (reactant stability/reactivity principle)
  o N2 is more acidic (product stability/reactivity principle)

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

Pyrazolone vs Pyrazolidinone Rings

Hybridization and Reactivity in Pyrazolidinone Rings

Antipyrine and it's Numbering System
Lead Drug Candidate
What Kind of Activities Do My Students Do?  Generic aspects:

1. We like to build things! 😊😊😊 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! 😊😊😊


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. **C4-Formylation.**

   ![Chemical Structure](image)

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

   **Matt Anderson**

2. **4-Alkylaminomethyl Analogs, from 4-Formyl. Try NaBH₃CN?**

   ![Chemical Structure](image)

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

   **Matt Anderson**

3. **4-Iminomethyl Analogs, from 4-Formyl**

   ![Chemical Structure](image)

   - **Lots of Examples, often with elaborate “R” groups**

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

   **Matt Anderson**

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

   ![Chemical Structure](image)

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

Reductive Amination of Aminoantipyrine: Formation of 4-alkylaminoantipyrine Analogs

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

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. Imine-Formation of 4-AminoAntipyrine
Reductive Alklation at N1. N-Alkylation

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

Does it work for other Pyrazolidinones?

A question is how general the reductive amination can be at N1.
1. Can Mariam's reagent work? (I expect)
2. Can Hawai's reagent work, with N2 blocked?
3. If not, could the N2-methyl reagent work?
4. Any change with Taysir's reagent, a pyrazolone?

1. Carbonyl RCHO or R₂C=O
2. RCOCI
3. Basic Workup

Carbonyl Candies to Try

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

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

Variation at N1 by N-Alkylation. Pyrazolidinone.

Alkylation Agent
- Me₂SO₄
- OTs or Ethyl iodide/Bromide
- NaOtBu
- Dioxane
- Reflux

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

R₁ = Me, Ph, H

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

Untried. Taysir did procedure on oxazolidinone, but not pyrazolidinone. Make Buchwald JACS air-stable catalyst!
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.
1. Table of Contents
2. Intro; Terminology; Numbering; Relative Reactivity; Synthesis of Parent
3. Stock of Home-Made (or Store-Bought) Ready-to-Use Chemicals:

4. **Scheme 1: Variation at C4:**

5. **Scheme 2: Variation at C5:**

6. **Scheme 3: Variation at N1 by N-Alkylation:**

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

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

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

RCOCI
\[
\begin{array}{c}
O \\
Ph \text{ 1. } \text{NEt}_3, \text{ cat. DMAP,} \\
\text{CH}_2\text{Cl}_2, \text{ room temp} \\
2. \text{NH}_4\text{Cl/H}_2\text{O Workup,} \\
\text{Ether/CH}_2\text{Cl}_2 \text{ extract}
\end{array}
\]

Using Acid Chlorides, where available. Easy, fast.

RCO₂H
\[
\begin{array}{c}
O \\
Ph \text{ 1. } \text{NEt}_3, \text{ cat. DMAP,} \\
\text{Mukayama Reagent(water remover)} \\
\text{CH}_2\text{Cl}_2, \text{ room temp} \\
2. \text{NH}_4\text{Cl/H}_2\text{O Workup,} \\
\text{Ether/CH}_2\text{Cl}_2 \text{ extract} \\
3. \text{Silica rinse}
\end{array}
\]

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

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

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

RCOCI
\[
\begin{array}{c}
O \\
Ph \text{ 1. } \text{NEt}_3, \text{ cat. DMAP,} \\
\text{CH}_2\text{Cl}_2, \text{ room temp} \\
2. \text{NH}_4\text{Cl/H}_2\text{O Workup,} \\
\text{Ether/CH}_2\text{Cl}_2 \text{ extract}
\end{array}
\]

Using Acid Chlorides, where available. Easy, fast.

RCO₂H
\[
\begin{array}{c}
O \\
Ph \text{ 1. } \text{NEt}_3, \text{ cat. DMAP,} \\
\text{Mukayama Reagent(water remover)} \\
\text{CH}_2\text{Cl}_2, \text{ room temp} \\
2. \text{NH}_4\text{Cl/H}_2\text{O Workup,} \\
\text{Ether/CH}_2\text{Cl}_2 \text{ extract} \\
3. \text{Silica rinse}
\end{array}
\]

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

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


\[
\begin{array}{c}
O \\
\text{1. } \text{HO} \text{, } \text{NEt}_3, \text{ cat. DMAP,} \\
\text{Mukayama Reagent(water remover)} \\
\text{CH}_2\text{Cl}_2, \text{ room temp} \\
2. \text{NH}_4\text{Cl/H}_2\text{O Workup,} \\
\text{Ether/CH}_2\text{Cl}_2 \text{ extract} \\
3. \text{Silica rinse}
\end{array}
\]

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

Untried on dimethyl. Should work.

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

\[
\begin{array}{c}
O \\
\text{1. } \text{HO} \text{, } \text{NEt}_3, \text{ cat. DMAP,} \\
\text{Mukayama Reagent(water remover)} \\
\text{CH}_2\text{Cl}_2, \text{ room temp} \\
2. \text{NH}_4\text{Cl/H}_2\text{O Workup,} \\
\text{Ether/CH}_2\text{Cl}_2 \text{ extract} \\
3. \text{Silica rinse}
\end{array}
\]

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

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

\[
\text{H}_2\text{N} \quad \text{Me}_2\text{SO}_4 \quad \text{neat}, 180^\circ
\]

Potential Alkylation Agents:
- Me$_2$SO$_4$,
- Ethyl tosylate or iodide,
- Benzyl or Allyl bromide, etc.

Potential Solvents: MeOH, CH$_3$CN, DMF...

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

CHEMReview 2016
Stephen L. Buchwald and Paula Ruiz-Castillo

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

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

Untried. Taysir did procedure on oxazolidinone, but not pyrazolidinone. Make Buchwald JACS air-stable catalyst!
Scheme 4: Variation at N2 By Use of MethylHydrazine:

![Chemical Structure](image)

Untried. Would enable N2-methyl analogs.

C4-Aminomethylation, Using Paraformaldehyde. Pyrazolone

![Chemical Structure](image)


Untried/slightly tried. Craig got one to work; Amanda tried 1º that didn’t? 2º should work, literature.

Oxidation of Pyrazolidinones to Pyrazolones

![Chemical Structure](image)

Oxidizing agent candidates:
1. \( H_2O_2, CH_3CO_2H \)
2. \( O_2, \text{cat. FeCl}_3 \)
3. \( K_2S_2O_8 \)
4. NBS etc.

Somewhat tried. mCPBA looked good for one or two, failed other (Hawaii); 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.

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

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

Untried. Tandem alkylation/acylation would be cool, if it worked.
Untried. Have chems. Might be good to try the Buchwald catalyst, once made?

Kaniel is trying.

C4-Nitrogen Varients. Pyrazolone. "Analgin" Derivatives

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


C4-Aldehyde Reaction

Untried. One literature example, iffy. Combo with 35.
35. **C4-Aldehyde Reaction**

\[
\begin{align*}
\text{R}_4\text{CHO,} & \quad 0.3 \text{ AcOH} \\
1.5 \text{ pyrididine} & \quad \text{CH}_2\text{CN solvent} \\
& \quad 65^\circ, \ 1 \text{ hour}
\end{align*}
\]

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

36. **C4-Alkylation or Acylation Reaction?**

- 1. NaOttBu, iPrOH
- 2. R-X (SN2 Electrophile)
- or \( R^\prime \text{Cl} \)

via:

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

37. **Acylation of Aminoantipyrine Using Acid Chlorides**

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{Cl}\text{O}, \ \text{NEt}_3, \ \text{cat. DMAP}, \\
& \quad \text{CH}_2\text{Cl}_2, \ \text{room temp} \\
& \quad 2. \ \text{NH}_2\text{Cl}/\text{H}_2\text{O Workup}, \\
& \quad \text{Ether/CH}_2\text{Cl}_2 \text{ extract}
\end{align*}
\]

4-aminoantipyrine

"Analgin"

Commercially Available, Alfa-Aeser

Literature extensive for acylation. They worked very well. Easy to Crystallize and purify.

Ansu had one success with CH3PhCOCl. Not so good with crotonyl, benzoyl.

Check RCOCl, NMR’s, etc; maybe do control? Find some others that are good/clean?

Ansu has established strong proof of principle and has made several of these.
Home-made synthesis:

- Have worked out procedure for this home-made synthesis of antipyrine parent
- Antipyrine itself is commercial and inexpensive, so no actual need for us to make it.
### Stock of Home-Made (or Store-Bought) Ready-to-Use Chemicals:

<table>
<thead>
<tr>
<th>Formula</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Antipyrine. $$</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>4-aminoantipyrine = “Analgin”. $$</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Taysir’s Reagent.</td>
</tr>
<tr>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Hawau’s N1-Methyl Reagent</td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Hawau’s N2-Phenyl Reagent</td>
</tr>
<tr>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Sunny’s Reagent</td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>Jasperse Diphenyl Reagent</td>
</tr>
<tr>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>Mariam’s Reagent</td>
</tr>
<tr>
<td><img src="image9" alt="Chemical Structure" /></td>
<td>Trinh’s Reagents</td>
</tr>
</tbody>
</table>

$$ $$
C4-Variation (Alkyl/Benzyl)

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

![Scheme 1: Variation at C4](image)

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/ToDo:
   a. Scaleup/ Reproduce
   b. Cleanup
   c. Test
   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?

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Commercial?</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ethyl 2-methylacetoacetate</td>
<td>Bought it</td>
<td></td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl 2-ethylacetoacetate</td>
<td>Could buy</td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td>Ethyl 2-acetylpentanoate</td>
<td>Super expensive, NO</td>
<td></td>
</tr>
<tr>
<td>iPr</td>
<td>Ethyl 2-isopropylacetoacetate</td>
<td>Could buy</td>
<td></td>
</tr>
<tr>
<td>Bn</td>
<td>Ethyl 2-benzylacetoacetate</td>
<td>Bought it</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>R₅</th>
<th>CAS</th>
<th>One Name variant</th>
<th>Commercial?</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>4949-44-4</td>
<td>Ethyl 3-oxopentanoate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>94-02-0</td>
<td>Benzenepropanoic acid, β-oxo-, ethyl ester</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
N1-Variation: Alkylation of Double-Bonded Rings (Pyrazoles)

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

N-Ethylation Reagents and Catalysts

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-40-0</td>
<td>Ethyl Tosylate</td>
<td>Sigma/Aldrich: $26/50g</td>
</tr>
<tr>
<td></td>
<td>No other tosylates commercial.</td>
<td>Sigma/Aldrich: $26/50g</td>
</tr>
</tbody>
</table>
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 $\Rightarrow$ Pyrazolone

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

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-Benzyllox-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-Benzyllox-5-chloro-benzyl)-5-methylH-pyrazo3-
3. N1-Aldehyde use, followed by NaOMe/MeOH isomerization: N1 plus Aldehyde to make imminium, with some base-isomerization, then base isomerization.
4. No preliminary data.
5. Some potential advantages:
   a. Aldehydes are more reactive than alkyl halides, etc., so this could be much easier than SN2 alkylation
   b. There are a lot of aldehydes available.
   c. This gets directly to the double-bond pyrazole rather than the di-hydro pyrazolidinone
N1-Acylation of Pyrazolones: Using Acid Chlorides or Acids (with Mukayama’s Reagent).

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

Use General Thing for pyrazolone or pyrazolidinone
N1-ACYLation of Pyrazolidinones.

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

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

Methyl Hydrazine Process:

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me 60-34-4</td>
<td>Methyl hydrazine</td>
<td>Sigma/Aldrich: $308/25</td>
</tr>
</tbody>
</table>

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:

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

1. NaOtBu
2-propanol (Very Dry)
Heat (High)
2. Vacuum
3. NH₄Cl Workup

General N2-Acylation

1. Using Carboxylic Acids, and Mukayama
2. Using Hawau and Sunny Reagents
3. Try pre-oxidizing both?
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 SN2 Reaction:

<table>
<thead>
<tr>
<th>N2-Alkylation of N1-Methyl Pyrazolidinones: Using Base and SN2</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Potential Alkylation Agents: Me₂SO₄, Ethyl tosylate or iodide, Benzylic or Allyl bromide, etc.</td>
</tr>
<tr>
<td>Potential Solvents: MeOH, CH₃CN, DMF...</td>
</tr>
</tbody>
</table>

1. This could also be attempted using Sunny’s N1-Phenyl or Mariam’s N1-H pyrazolidinones.
2. No preliminary results done on this.
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 $$

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>4930-98-7</td>
<td>2-Hydrazinopyridine</td>
<td>Sigma/Aldrich: $86/5, $292/25</td>
</tr>
<tr>
<td>2863-98-1</td>
<td>4-Cyanophenylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $57/5</td>
</tr>
<tr>
<td>637-60-5</td>
<td>4-Methylphenyl hydrazine</td>
<td>VWR-AA, $35.59/5g</td>
</tr>
<tr>
<td>635-26-7</td>
<td>o-Tolylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $39/5</td>
</tr>
<tr>
<td>1073-70-7</td>
<td>4-Chlorophenylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $29/5, $97/25</td>
</tr>
<tr>
<td>2312-23-4</td>
<td>3-Chlorophenylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $97/25</td>
</tr>
<tr>
<td>41052-75-9</td>
<td>2-Chlorophenylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $80/25</td>
</tr>
<tr>
<td>823-85-8</td>
<td>4-Fluorophenylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $67/10,</td>
</tr>
<tr>
<td>2924-15-4</td>
<td>2-Fluorophenylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $70/5</td>
</tr>
</tbody>
</table>

**TOO EXPENSIVE**

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>622-88-8</td>
<td>4-Bromophenylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $132/10 (expensive)</td>
</tr>
<tr>
<td>19501-58-7</td>
<td>4-Methoxyphenylhydrazine hydrochloride</td>
<td>Sigma/Aldrich: $200/10 (expensive)</td>
</tr>
<tr>
<td>368-90-1</td>
<td>4-(Trifluoromethyl)phenylhydrazine</td>
<td>Sigma/Aldrich: $125/5 (Too expensive)</td>
</tr>
</tbody>
</table>

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 actually 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
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.  

\[
\begin{align*}
\text{O} & \quad \text{Ar-X} \\
\text{N} & \quad \text{cat. Pd}_2(\text{dba})_3 \\
\text{N} & \quad \text{cat. Xantphose} \\
\text{R}_1 & \quad \text{NaOttBu} \\
\text{R}_1 & \quad \text{Dioxane} \\
\text{Refux} & \quad \text{Ar} \\
\end{align*}
\]

\[
R_1 = \text{Me, Ph, H}
\]

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.

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.
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) SnCl₂, conc. HCl, EtOH; (b) NaNO₂, conc. HCl; (e) SnCl₂, conc. HCl; (d) methyl acetoacetate, CH₃CN, reflux; (e) Me₂SO₄, CaO, MeOH; (f) TFA, DCM; (g) R²CCl₃, NEt₃, DCM; (h) R²NH, NaBH₄(AlCl₃), DCE, AcOH, molecular sieves; (i) paraformaldehyde, iPrOH, NH₄Cl, 90 °C; (j) methanolic HCl, ether.
Oxidation protocol to convert Dihydro (Pyrazolidinone) rings to Pyrazolone rings

**Oxidation of Pyrazolidinones Using Hydrogen Peroxide**

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

   • 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

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Oxidation of Pyrazolidinones to Pyrazolones

<table>
<thead>
<tr>
<th>Oxidizing agent candidates:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. H₂O₂, CH₃CO₂H</td>
</tr>
<tr>
<td>2. O₂, cat. FeCl₃</td>
</tr>
<tr>
<td>3. K₂S₂O₈</td>
</tr>
<tr>
<td>4. NBS etc.</td>
</tr>
</tbody>
</table>

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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
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, 87 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-methyropyrazolidin-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-Benzylxylo-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-Benzylxylo-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 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, alkylation, benzylaion, 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.
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
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\textsubscript{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.

C4-Nitrogen Varients. Pyrazolone. "Analgin" Derivatives

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.
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).
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C4-Aldehyde Reaction

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
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 antipyrine. Nice in that the starting material is cheap and clean and commercially available.
**Stock of Home-Made (or Store-Bought) Ready-to-Use Chemicals:**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipyrine</td>
<td><img src="image" alt="Antipyrine" /></td>
</tr>
<tr>
<td>4-aminoantipyrine = “Analgin”</td>
<td><img src="image" alt="4-aminoantipyrine" /></td>
</tr>
<tr>
<td>Taysir’s Reagent</td>
<td><img src="image" alt="Taysir’s Reagent" /></td>
</tr>
<tr>
<td>Hawau’s N1-Methyl Reagent</td>
<td><img src="image" alt="Hawau’s N1-Methyl Reagent" /></td>
</tr>
<tr>
<td>Hawau’s N2-Phenyl Reagent</td>
<td><img src="image" alt="Hawau’s N2-Phenyl Reagent" /></td>
</tr>
<tr>
<td>Sunny’s Reagent</td>
<td><img src="image" alt="Sunny’s Reagent" /></td>
</tr>
<tr>
<td>Mariam’s Reagent</td>
<td><img src="image" alt="Mariam’s Reagent" /></td>
</tr>
<tr>
<td>Trinh’s Reagents</td>
<td><img src="image" alt="Trinh’s Reagents" /></td>
</tr>
</tbody>
</table>
### Some Chemical Ordering info:

#### Palladium coupling:

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Commercial?</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>161265-03-8</td>
<td>Xantphos</td>
<td>Not that bad</td>
<td>Strem, I think? ~$38/g</td>
</tr>
<tr>
<td>51364-51-3</td>
<td>Pd2(dba)_3 Tris(dibenzylideneacetone)dipalladium(0)</td>
<td>Not that bad</td>
<td>0.5g scales are best, Acros ~$40/0.5g</td>
</tr>
<tr>
<td>534-17-8</td>
<td>Cesium Carbonate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Scheme 1: C4-Varients, Ethylacetoacetates.

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

#### Scheme 2: C5-Varients, Ethylacetoacetates.

<table>
<thead>
<tr>
<th>R5</th>
<th>CAS</th>
<th>One Name variant</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>4949-44-4</td>
<td>Ethyl 3-oxopentanoate</td>
<td>VWR-AA, $73.40/5g</td>
</tr>
<tr>
<td>Ph</td>
<td>94-02-0</td>
<td>Benzenepropanoic acid, β-oxo-, ethyl ester</td>
<td>I probably still have some? VWR-AA, $27.46/50g</td>
</tr>
</tbody>
</table>
Scheme 3, Scheme 4, Scheme 6: Different Hydrazines, N1 Varients and N2 Varients, whether with ethylacetoacetates, or with unsaturated acids.

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

N-Arylation Reagents and Catalysts
Palladium coupling:

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Commercial?</th>
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<tbody>
<tr>
<td>161265-03-8</td>
<td>Xantphos</td>
<td>Not that bad</td>
<td>Strem, I think? ~$38/g</td>
</tr>
<tr>
<td>51364-51-3</td>
<td>Pd2(dbac3) Tris(dibenzylideneacetone)dipalladium(0)</td>
<td>Not that bad</td>
<td>0.5g scales are best, Acros ~$40/0.5g</td>
</tr>
<tr>
<td>534-17-8</td>
<td>Cesium Carbonate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>128-08-5</td>
<td>N-Bromosuccinimide</td>
<td>VWR-AA, $36.39/250g</td>
</tr>
<tr>
<td>591-50-4</td>
<td>Iodobenzene</td>
<td>Stockroom probably has? Jasperse research area or stockroom shelf 8B</td>
</tr>
<tr>
<td>534-17-8</td>
<td>Cesium Carbonate</td>
<td>Stockroom probably has? Stockroom shelf 16C</td>
</tr>
</tbody>
</table>
### Antipyrine projects

<table>
<thead>
<tr>
<th>CAS</th>
<th>One Name variant</th>
<th>Supplier, Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-40-0</td>
<td>Ethyl Tosylate</td>
<td>Sigma/Aldrich: $26/50g</td>
</tr>
<tr>
<td>74-88-4</td>
<td>Iodomethane, 99%, stab. with copper</td>
<td>Alfa Aesar: $20/50g</td>
</tr>
<tr>
<td>30525-89-4</td>
<td>Paraformaldehyde</td>
<td>Sigma/Aldrich: $45/100g 158127-100G</td>
</tr>
<tr>
<td>83-07-8</td>
<td>4-Aminoantipyrine, 97%</td>
<td>Alfa Aesar: $43/100g</td>
</tr>
</tbody>
</table>
Ignore these, these are for Research Grant.

<table>
<thead>
<tr>
<th>R4</th>
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</tr>
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<tbody>
<tr>
<td>Et</td>
<td>607-97-6</td>
<td>Ethyl 2-ethylacetoacetate</td>
<td>Sigma Aldrich, $108/25g</td>
</tr>
<tr>
<td>iPr</td>
<td>1522-46-9</td>
<td>Ethyl 2-isopropylacetoacetate</td>
<td>Sigma Aldrich, $130/25g</td>
</tr>
<tr>
<td></td>
<td>128-09-6</td>
<td>N-Chlorosuccinimide, 98%</td>
<td>Alfa Aesar $15/50g</td>
</tr>
<tr>
<td>Me</td>
<td>60-34-4</td>
<td>Methyl hydrazine</td>
<td>Aldrich: $51/25g or $137/100g</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sigma/Aldrich: $71/50</td>
</tr>
<tr>
<td></td>
<td>10025-87-3</td>
<td>Phosphorus(V) oxychloride</td>
<td>Aldrich, 79582-25ML, 47.90</td>
</tr>
</tbody>
</table>

### Aryl Hydrazines

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<thead>
<tr>
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<tbody>
<tr>
<td>Pyridine</td>
<td>4930-98-7</td>
<td>2-Hydrazinopyridine</td>
</tr>
<tr>
<td>p-CN</td>
<td>2863-98-1</td>
<td>4-Cyanophenylhydrazine hydrochloride</td>
</tr>
<tr>
<td>p-Tol</td>
<td>637-60-5</td>
<td>4-Methylphenyl hydrazine</td>
</tr>
<tr>
<td>o-Tol</td>
<td>635-26-7</td>
<td>o-Tolylhydrazine hydrochloride</td>
</tr>
<tr>
<td>p-Cl</td>
<td>1073-70-7</td>
<td>4-Chlorophenylhydrazine hydrochloride</td>
</tr>
<tr>
<td>m-Cl</td>
<td>2312-23-4</td>
<td>3-Chlorophenylhydrazine hydrochloride</td>
</tr>
<tr>
<td>o-Cl</td>
<td>41052-75-9</td>
<td>2-Chlorophenylhydrazine hydrochloride</td>
</tr>
<tr>
<td>p-F</td>
<td>823-85-8</td>
<td>4-Fluorophenylhydrazine hydrochloride</td>
</tr>
<tr>
<td>2-F</td>
<td>2924-15-4</td>
<td>2-Fluorophenylhydrazine hydrochloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>TOO EXPENSIVE</strong></td>
</tr>
<tr>
<td>p-Br</td>
<td>622-88-8</td>
<td>4-Bromophenylhydrazine hydrochloride</td>
</tr>
<tr>
<td>p-OCH3</td>
<td>19501-58-7</td>
<td>4-Methoxyphenylhydrazine hydrochloride</td>
</tr>
<tr>
<td>p-CF3</td>
<td>368-90-1</td>
<td>4-(Trifluoromethyl)phenylhydrazine</td>
</tr>
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*Note: Some prices are very expensive.*
Ignore these, these were already bought October 2016

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