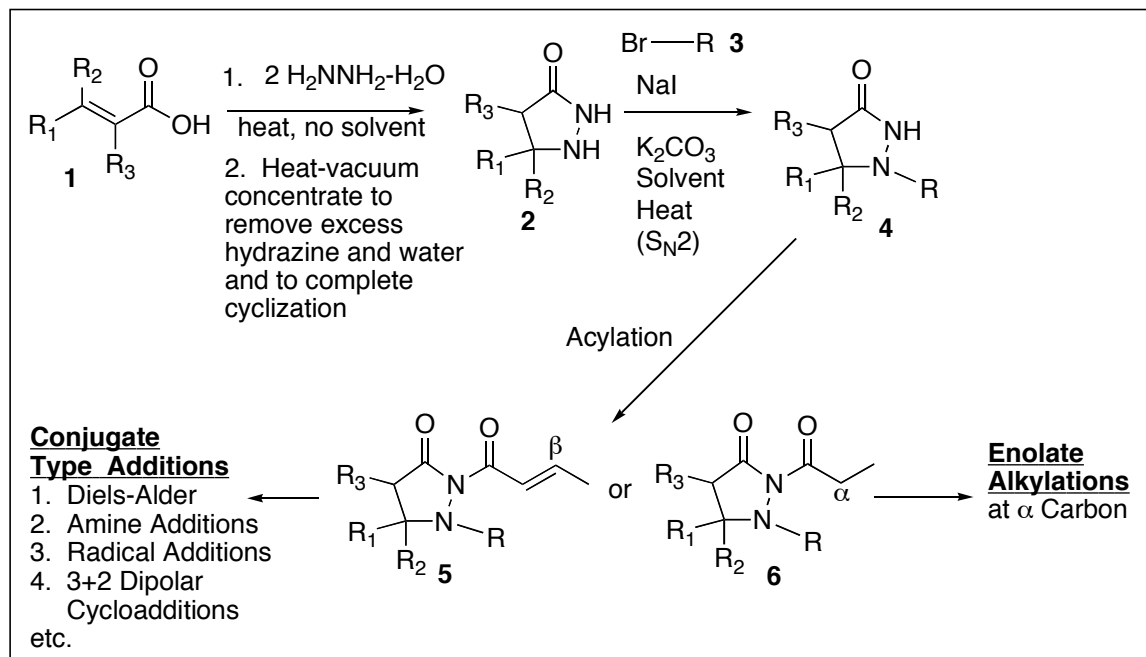


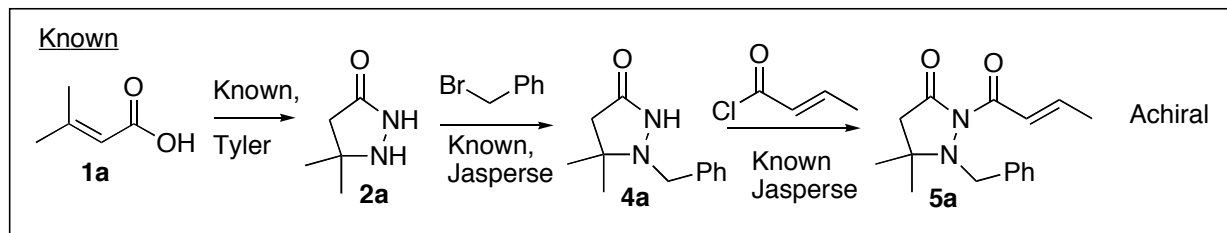
Note: 1/12/2007 Pages 1-7 are the same as what I handed out at start of fall. Pages 8-etc are some new things I've written up more specific for the current status and for Katie and Mike. I'll probably plan to review the total project, and review what has and hasn't been accomplished in the fall, then continue with how we should proceed from here.

Total Project Overview



Some Overall General Project Goals:

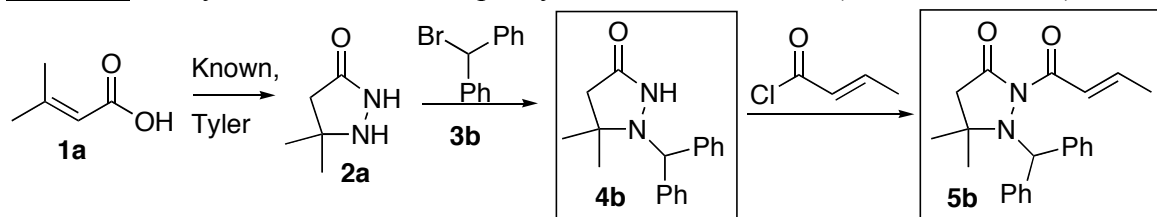
1. Prepare a family of substrates **2**, **4**, **5**, and **6**
2. Optimize methodology for preparing **2** and **4**, and evaluate scope, limitations, and convenience
3. If possible find solvent system that works well for recrystallizing some of these.
4. Use a couple of simple reactions to compare the reactivity and stereoselectivity of substrates **5** and **6** to that of previously known oxazolidinone or pyrazolidinone analogs in the literature.
 - a. Do our compounds perform better?
 - b. Do our compounds perform as well, while being easier to prepare?

A Known Synthesis

1. -substrate **5a** has been reacted with a number of different reactants under Lewis-acid catalysis
2. -Since **5a** is achiral, control over the absolute stereochemistry of a reaction product requires that some other component in the transition state be optically active
 - This has been accomplished using some chiral Lewis acids.
 - That doesn't always work adequately or conveniently
3. The sequence above is potentially good for practice and as a control reaction.

Specific target molecules (and acid precursors)

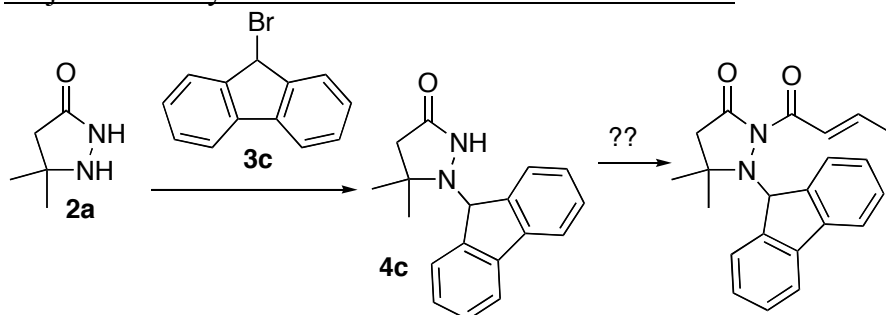
Project 1: Alkylation with Bromodiphenylmethane to make **4b** (Mike and/or Kris)

Notes

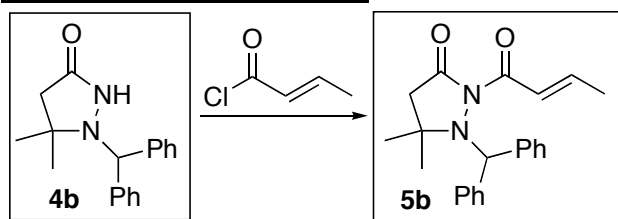
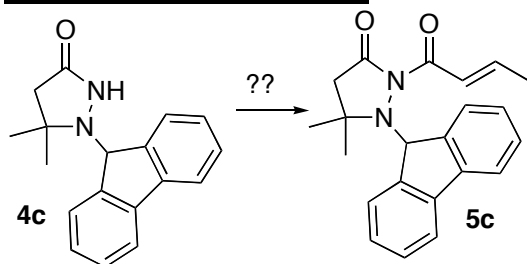
1. I think I successfully conducted **2a** \rightarrow **4b** this summer, based on crude NMR.
 - But I never isolated **4b** or proved it or reproduced it or optimized it, so I'm not sure I really made what I hoped I'd made, and I have no experience in how to isolate, crystallize, or chromatograph it.
2. **2a** \rightarrow **4b** has never been done successfully before. Harder than **4a** for steric reasons.
3. If we can make **4b** and derivative **5b**, and if **5b** reacts comparably to **5a**, the extra steric bulk in **5b** is likely to greatly improve the stereoselectivity for subsequent reactions relative to **5a**
4. **5b** is still achiral. For it to undergo enantioselective reactions, chiral Lewis acid needed.

Key issues:

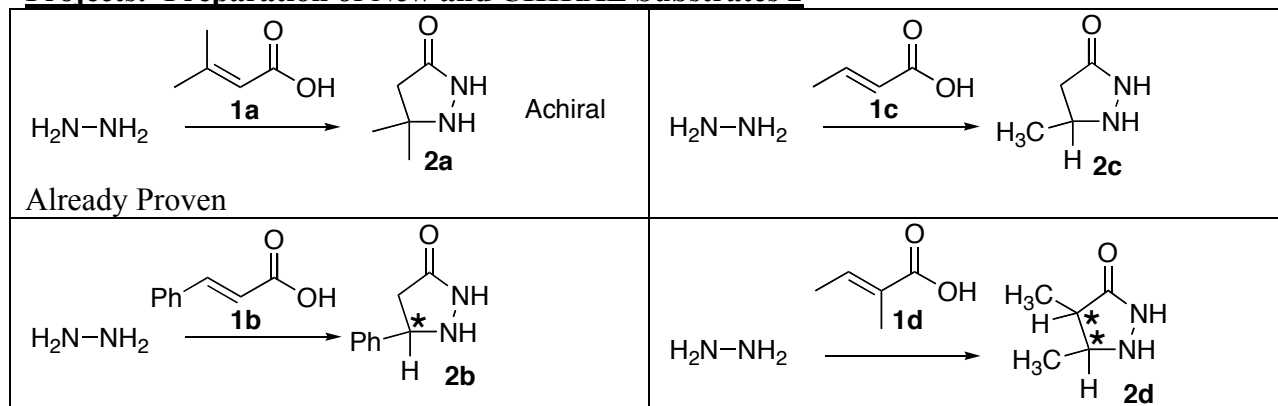
1. Can we really make **4b** and do so reproducibly? (It seemed easy when I did it, but did I really make what I hope I made?)
2. If so, can we isolate it and handle it without decomposition?
3. If so, what kind of yield can we make it in?
4. Yield and method optimization issues?
 - a. Solvent screen?
 - b. Time and temperature screen?
 - c. Stability screen?
 - d. Learn how to isolate?
5. Can we crystallize **4b**?
6. If we can make **4b** effectively, can we convert it to **5b**? Or does the extra steric bulk interfere?
7. **4b** and **5b** might be somewhat sensitive; assign to advanced student

Project 1b: Alkylation with 9-bromofluorene to make 4c

1. This is similar to project 1a above.
2. If we can make **4b**, we should definitely try to make **4c**.
3. If we can't make **4b**, we might still want to try for **4c**, but there is much in common so they might succeed or fail together.
4. The ring tie-back helps to constrain the conformation. This could make it more likely to crystallize, and might perhaps make it a better blocking group. Not sure whether it would be easier or harder to build. It may be so big that it might be difficult to work with.

Project: Preparation of 5bProject: Preparation of 5c

1. These are obviously contingent on success in making **4b** and/or **4c**
2. They could work similarly to formation of **5a**, but the greater steric congestion might make them more challenging
3. Might either **5b** or **5c** be easily crystalline?
4. Does the acylation depend on air-sensitive butyl lithium? Or might it work using NEt₃/DMAP?

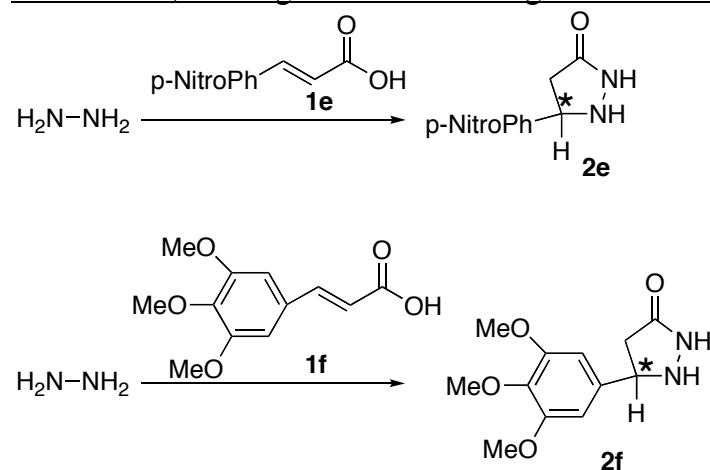
Projects: Preparation of New and CHIRAL Substrates 2

- Each of products **2b-2d** would represent novel compounds
- I assume their synthesis should work
- Their purification might be new, not sure how easy or hard it would be
- Target **2b**: rapid priority, experienced student, Mike and/or Kris?
- Target **2c**:
- Target **2d**:
- The above 2b and 2c would check aryl and alkyl substituted systems.
- 2d would check for a two-stereocenter system.
 - Will the product 2d be a cis/trans mixture, or will it be diastereoselective?
 - If so, cis or trans?

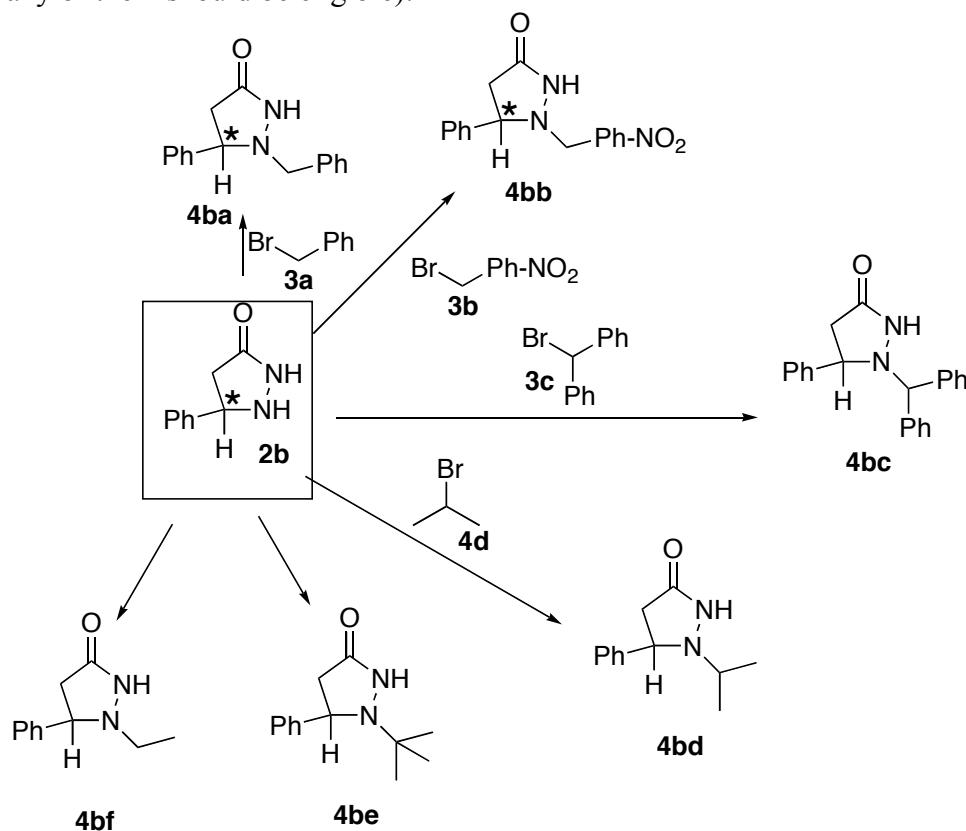
Technical Questions

- How long/how much heat does it take for hydrazine to add to the original alkenes?
- How much heat is required to complete cyclizations and to vacuum pump off the excess hydrazine and water?
- Technically what is the best way to remove the water? How hot do we need to go? How dry do we need to get?

Some others, that might be worth making in search of an easily-crystalline product:

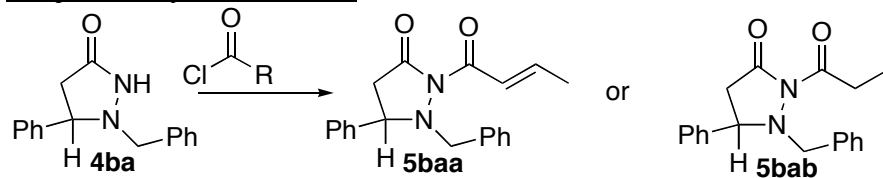


N-Substitution on one (or more) of the chiral pyrazolidinones 2b or 2c: (I'll just use **2b**, but any of them should be eligible):



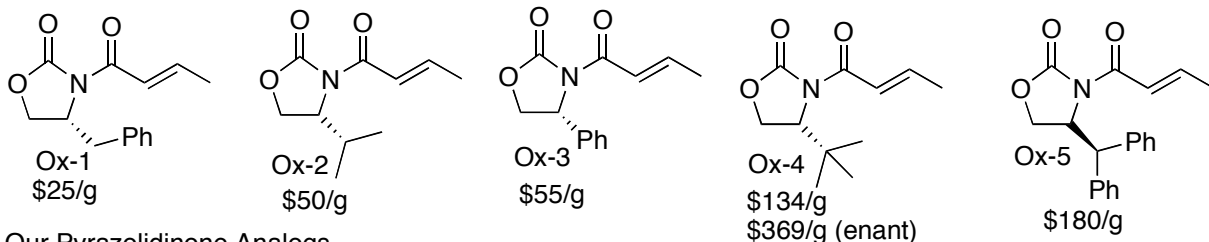
1. Formation of **4ba** would be a rush priority
2. Issues:
 - a. How long and how hot?
 - b. What solvent to use? (2-butanone is starting default)
 - c. Some are S_N2 , others some S_N1 . Reactivity could vary widely
 - d. How easy to isolate?
 - e. How stable are the products?

Project: Acylation of 4ba

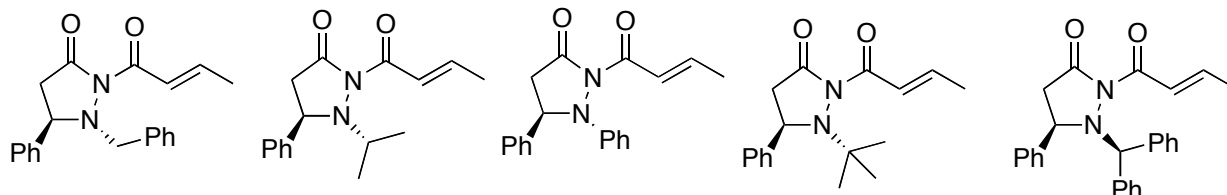


Project: Comparison of Chiral 5baa or 5bab of Others with Chiral Oxazolidinone Analogs in Some Common Reactions (Mike?)

Known Chiral Oxazolidinones

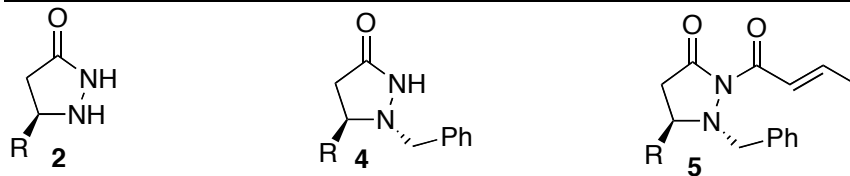


Our Pyrazolidinone Analogs



- Chiral oxazolidinones are derived from amino acids via a multi-step method.
 - The identity of the substituent group is limited to cheap amino acids
 - The best ones are the hardest to make, and very expensive!
- Our pyrazolidinone analogs might be much easier to make
 - We might be able to easily install whichever substituent group we want to afford optimal performance
- One problem: our is racemic (unless we resolve), chiral oxazolidinones are optically active!
- What reaction(s) might we wish to try? There are hundreds of papers involving chiral oxazolidinones in the literature. I haven't decided yet, but I'd like to use a technically easy reaction for comparison purposes.
- We would be looking for diastereoselectivity in reactions. This can be assessed via NMR integration, which we have. No need to take optical rotations or have chiral HPLC.

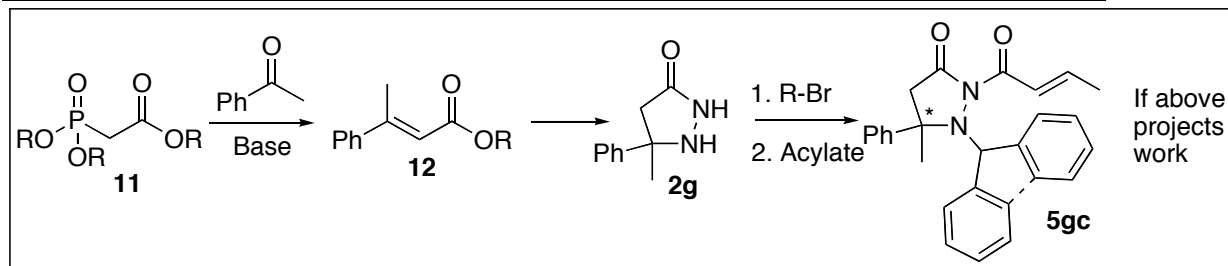
Hope-You-Get-Lucky Project: Resolution of Racemic Chiral Pyrazolidinones



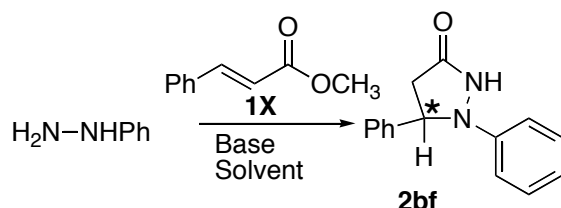
- Each of our chiral compounds 2, 4, and 5 would be formed racemic.
- Upon treatment with an optically active acid, two diastereomeric salts would form.
- If one crystallizes selectively, you could separate enantiomers and get both (R) and (S) enantiomers pure.
- These protocols are case-by-case sensitive, could be tough.

Later Project:

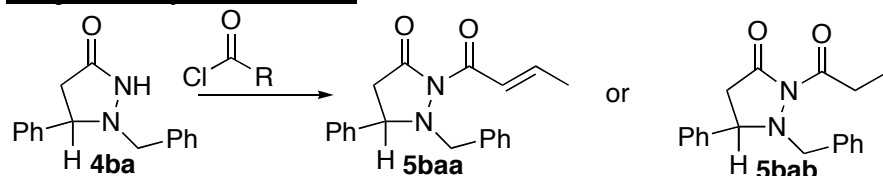
Look up Sibi and Sateo(?) article on formation of chiral pyrazolidinones. Any chance we could do it with anhydrous hydrazine and a crotonate or cinnamate, using chiral Lewis acid?

Later project, only if the formation of things like 4b and 4c and 4bc are working:

1. We'd need to learn how to make substrate **12**
2. Product **2g** and **5gc** are of interest to me because **2g** is chiral, like **2b-f**. But the quaternary carbon versus tertiary carbon appears likely to significantly alter the conformation of N-substituted derivatives such as **5gc** in a favorable way.
3. If we could make **5gc** in a reasonably efficient way, and it had reactivity not unlike **5a**, calculations suggest that this could be a ****really**** good substrate for stereoselective reactions.

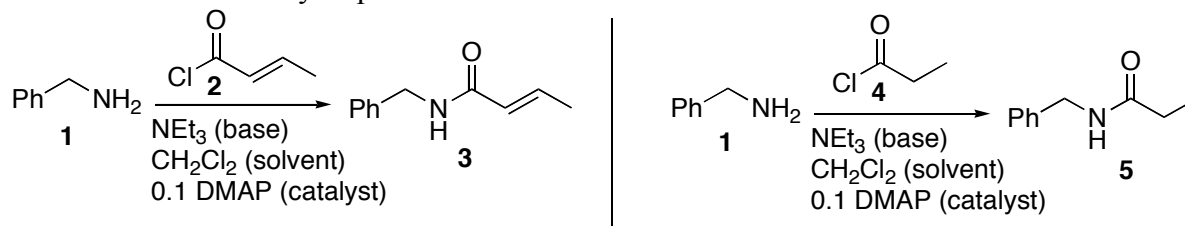
Later project, for comparison purposes: N-Phenyl compounds: 1 step from phenylhydrazine

1. This will be with the ester, not the free acid
2. What combination of base and solvent is required?
3. Could be a high-speed sequence with good crystallinity
 - The oxazolidinone phenyl analog Ox-3 is often quite effective, but expensive.
4. This is procedure used with methyl acrylate to make the dihydro analog
5. Many SciFinder hits for analog reaction on methyl acrylate

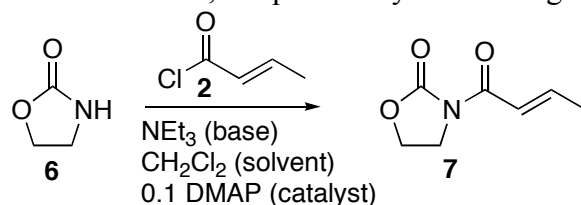
Acylation Development. New Work for Katie and Mike**Project: Acylation of 4ba**

Known:

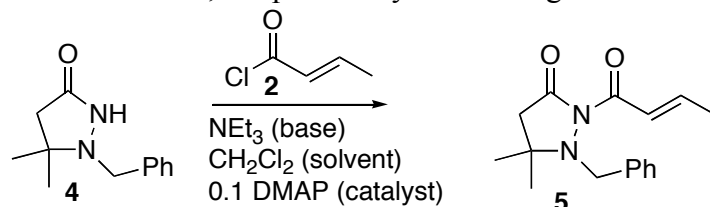
Control Reactions to try as practice.



Known Product, but previously made using a much more complicated and expensive procedure.



Known Product, but previously made using a much more complicated and expensive procedure.

**Practical questions:**

- Do they work?
- How much extra acid chloride or triethylamine is required?
- How crucial is it for the solvent to be scrupulously dry?
- Time and temperature requirements?
- Does success depend on a particular solvent?
- What kind of workup is best for preserving product but ousting side products?
- What is the reaction generality?
 - do different types of nitrogen compounds work, including oxazolidinones (6 \rightarrow 7) and pyrazolidinones (4 \rightarrow 5)?
 - Do different types of acid chlorides work, including unsaturated and saturated and benzoyl?

Purpose: Acyl oxazolidinones and acyl pyrazolidinones are abundantly used in organic synthesis. But the usual procedure is time consuming; technically demanding; requires strong,

unstable reactants; and requires lots of scrupulously anhydrous tetrahydrofuran as solvent. The proposed procedure, if it worked reliably, could be much more convenient, require not too much scientist time, and use smaller volumes of cheaper, more accessible solvents.

General Procedure/Stoichiometry:

Amine/oxazolidinone/Pyrazolidinone: 1 equivalent (limiting reagent)

Solvent: 2-5 mL per mmol (this doesn't necessarily need to be measured)

DMAP: 0.1 equivalent (means 0.1 mmol per 1 mmol of Amine/oxazolidinone/Pyrazolidinone)

Triethylamine: 1.2 equivalents (in other words, use as excess to both amine and acid chloride)

Acid chloride: 1.1 equivalent (excess to amine, but less of this than the triethylamine)

General Unoptimized Procedure: Use dry glassware, either from oven or after flame-drying, with a stir bar and a septum attached to exclude air. Add the Amine/oxazolidinone/Pyrazolidinone first. If it's a liquid, you can add via syringe, right through the septum. If it's a solid, weigh it on the balance, then remove the septum, pour the solid in, and put the septum back in place. Then weigh and add the solid DMAP. Add the solvent, either via syringe or by temporarily pulling the septum off. First try for solvent: dry dichloromethane. Stir at room temperature to try to ensure that the solution is homogeneous. Cool the solution in an icewater bath. Prepare two syringes, one with the triethylamine and the other with the acid chloride. Get a third syringe needle, and stick it through the septum to provide a pressure escape channel. Add the acid chloride via syringe. Then add the triethylamine via syringe, perhaps dropwise at first. Add as fast as is convenient, but not so fast that perhaps the reaction goes crazy or boils over. (This could perhaps happen with a simple amine, perhaps less likely with oxazolidinone or pyrazolidinone.) Once everything is added and settled down, remove the ice bath and let stir at room temperature. For the simple amine, let stir for one hour, then pour into a separatory funnel. (For the oxazolidinone and pyrazolidinones, this may take more time, and will require monitoring.) Rinse with dichloromethane and NaOH/water (maybe 1 molar?). Use a volume of NaOH/water comparable to your original volume of solvent. The dichloromethane layer should sink to the bottom layer. Drain the dichloromethane layer through a filter pad of MgSO₄ (special fritted filter unit) into a pre-weighed roundbottomed flask. Extract the residual aqueous phase with two additional dichloromethane extractions. Concentrate by rotary evaporation, perhaps with additional strong vacuum to remove all solvents and triethylamine. Measure the mass of the crude product, then take an H-NMR.

Suggested first experiments:

3 mmol of benzyl amine, using 10 mL of dichloromethane as solvent. Crotonyl chloride as acid chloride. One hour.

Second experiment: 3 mmol of oxazolidinone. Take a pipet pull out after one hour and rotovap, then take NMR to check for progress. If done, then done! If incomplete, then repeat at a later time, etc., until progress has stalled. Once complete, do workup as above.

Third: 3 mmol of pyrazolidinone. Monitor progress as above.

Mechanism:

Update on progress:

We can successfully make any of the pyrazolidinones.

Only ones that weren't too hot were with tiglic acid and perhaps nitrocinnamic acid

General procedure involves:

Solubility of the pyrazolidinones: Somewhat problematic.

Good in methanol, DMF (polar solvents)

Fringy in CH_2Cl_2 and CH_3CN .

Benzylation:

Problems:

Solutions:

1. Hot DMF, K_2CO_3
 - a. Good for the methyl subbed compound (both Tyler and Kris)
 - i. Still a hassle to pump off the high-boiling DMF
 - ii. Yield?
 - b. Not so good for the phenyl subbed compound? (Mike)
 - i. Why? Are you sure?
2. Use of soluble triethylamine as base
 - a. Pretty good, although perhaps not quite as clean
 - b. Mike did in methanol
 - c. Didn't even need heat
 - d. Benzyl bromide, no catalyst needed

Discussion, mechanism, explanation:

Game Plan: Who's going to do what and how do we advance things fastest?