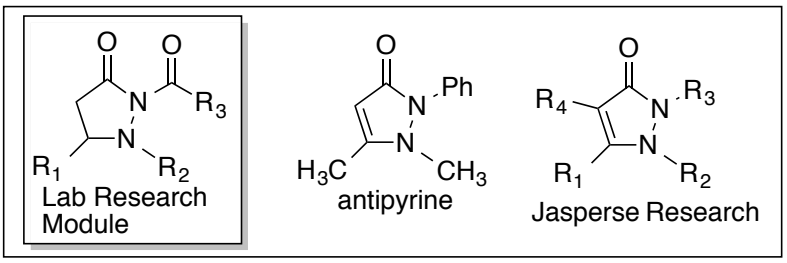
Chem 365 Lab Manual Part II

Multistep synthesis of an Acyl Pyrazolidinone

Introduction

We will begin a multi-step semi-research sequence in which we make a library of different "acyl pyrazolidinones" (see left-most "Lab Research Module" structure). The project will illustrate a variety of fundamental organic reactions and fundamental procedures. The acyl pyrazolidinones are of interest as medicinal candidates, as well as for use in further synthetic reactions. (The Jasperse research group is involved in making and bio-screening a large, diverse library of analogs for "antipyrine", a lead/best but very imperfect drug candidate for pulmonary fibrosis.)

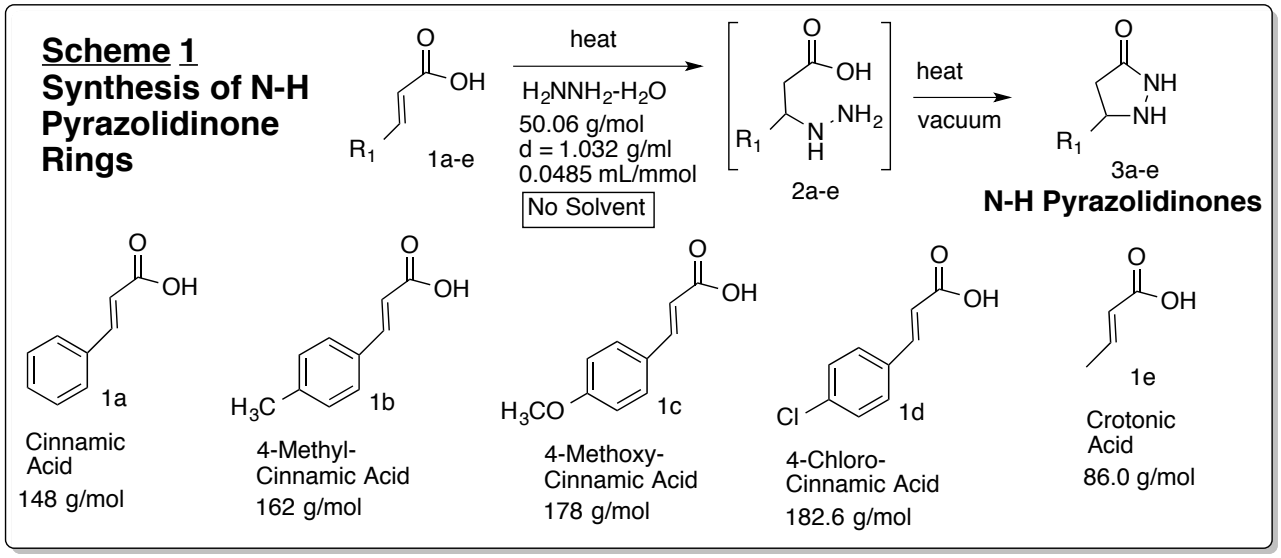


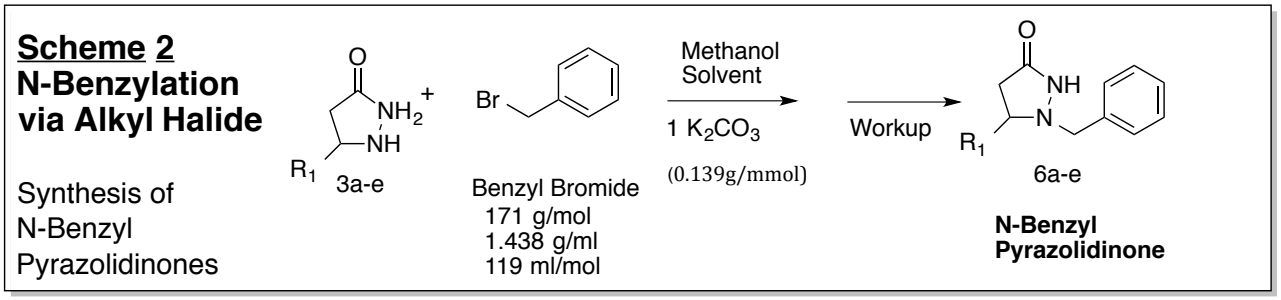
As shown in the "Lab Research Module" picture, there are three different variable R groups in the acyl pyrazolidinones. We will use five different R_1 groups; one, two, or three different R_2 groups; and for this year we'll use a single R_3 group. But imagine if we used five of each group; we could then produce a library of up to 5 x 5 x 5 = 125 different products! This kind of modular preparation of chemical libraries is routine in industry and medicinal chemistry. Subsequent biological testing can provide insights into the relationships between structure and activity. (Which parts of the molecule matter? Where does getting bigger or smaller help? Etc.)

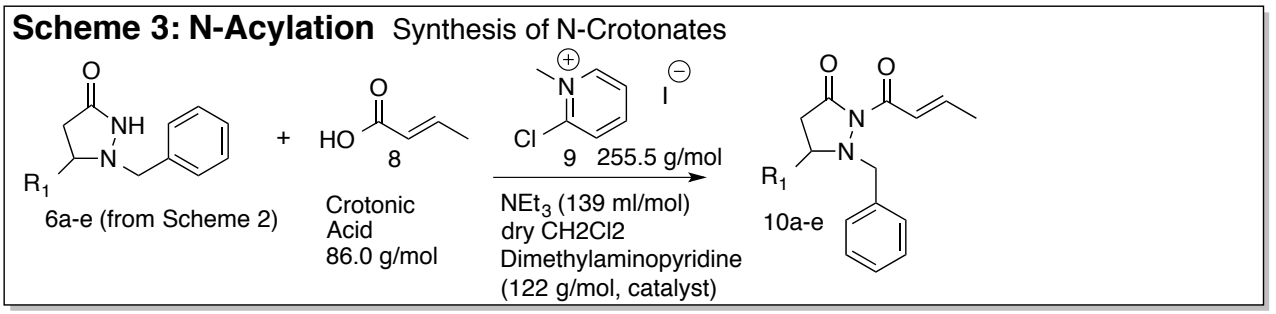
In the first stage, pyrazolidinone rings will be assembled with just one of the substituents attached, R_1, which is bound to the C5-carbon. (See Scheme 1, next page). In the pyrazolidinone ring numbering, the two nitrogens are #1 and #2, the carbonyl carbon is #3, etc.). An unsaturated acid will be treated with excess hydrazine hydrate. The nitrogen will initially add nucleophilically to the alkene, in a mechanism that can be viewed as involving either an enol or an enolate intermediate. This reaction is done in the absence of any solvent other than the hydrazine hydrate itself. Following addition, the product **2** undergoes loss of water and cyclic amide formation under high-temperature and vacuum, again with no solvent. The vacuum is important because it helps to distill off the water, whose hydrogen-bonding otherwise inhibits the ring closure. The pyrazolidinone rings **3** are often thick and gummy. The product (**3**) following the vacuum heating will need to be evaluated by NMR and GC-MS. Unfortunately getting rid of the excess hydrazine is hard, and it doesn't display under either our NMR or GC conditions.

A second substituent (R_2) will be attached to N1, using Scheme 2. The bottom N1-nitrogen will effectively exchange a hydrogen for a new carbon substituent, CH_2Ph (which is called a "benzyl" group). This alkylation involves an S_N2 reaction, with the N1-nitrogen acting as nucleophile despite being neutral. The potassium carbonate serves to remove the proton after the nitrogen has become four-bonded with a formal plus charge. The risk in the S_N2 mechanism is that the nitrogen can perhaps alkylate twice, leading to a quaternary ammonium salt. Because of the S_N2 mechanism, the alkyl halide electrophile must be an S_N2-eligible alkyl halide.

It is noteworthy that the two nitrogens in pyrazolidinones **3** behave very differently. The bottom nitrogen is sp^3-hybridized and is basic/nucleophilic, essentially like an "amine" nitrogen. The top nitrogen is sp^2-hybridized and is non-basic/non-nucleophilic because it is essentially an "amide" nitrogen, and is stabilized by conjugation to the carbonyl. Thus, as is typical when there are two functional groups of unequal reactivity, reaction proceeds selectively on the more reactive one.







The last stage (Scheme 3) will involve acylation of the top amide nitrogen. The procedure has been invented and developed by MSUM students (most notably Amie Nowacki and Kris Brandvold). A water molecule effectively needs to be eliminated (H from the amide nitrogen in structure **6**, OH from the carboxylic acid **8**). The water oxygen gets absorbed by "Mukayama's Reagent" **9**, and the two H's end up getting absorbed by basic triethylamine. Dimethylaminopyridine functions as an essential catalyst. Since the function of **9** is to absorb water, the solvent needs to be dry, so that Mukayama's agent acts on reactants **6** and **10** rather than getting destroyed by water in the solvent. This reaction take several hours at least. So it will be desirable to start it at the end of the second lab period, and worked up during the third week. The risks in this reaction are various. First, if things are wet, it's a problem. Second, if there are other NH or OH bonds present in residual contaminants, they will also be able to react to give new contaminants. The reaction should really work with any carboxylic acid, so if a student wanted to try something other than crotonic acid **8**, it should be possible.