55137-UR4:
The Strength of Intramolecular Hydrogen Bonds in Fluoro-organic Molecules.
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Introduction

The goal of this project is to determine the strengths of intramolecular hydrogen bonds, IMHBs. Included in this task is a) computational study of the compounds of interest, b) development of an experimental method to measure IMHB energies, and c) synthesis of compounds capable of forming IMHBs, and d) study of compounds in c) using the method in b).

Computational results.

In a recent paper, (Rosenberg, R. E. The Strength of Hydrogen Bonds between Fluoro-Organics and Alcohols, a Theoretical Study J. Phys. Chem. A 2018, 122, 4521-4529.) I published energies of intermolecular HBs and IMHBs. While the former did not vary much with structure, the latter was most sensitive to molecular flexibility. My reviewers were both surprised that 2-fluorocycloalkanols would show an IMHB, as typically 3-fluorocycloalkanols have been examined.

Synthesis

In previous summers, the synthesis of new (and unknown) compounds moved slowly. Moreover, it was difficult to transfer knowledge among students as the syntheses were very different. This summer, I decided to re-orient and focus on the synthesis of a series of similar molecules, many of which had been made before. The new targets, shown in Figure 1, are all cis 2-fluorocycloalkanols, from the same class of compounds that intrigued my reviewers.

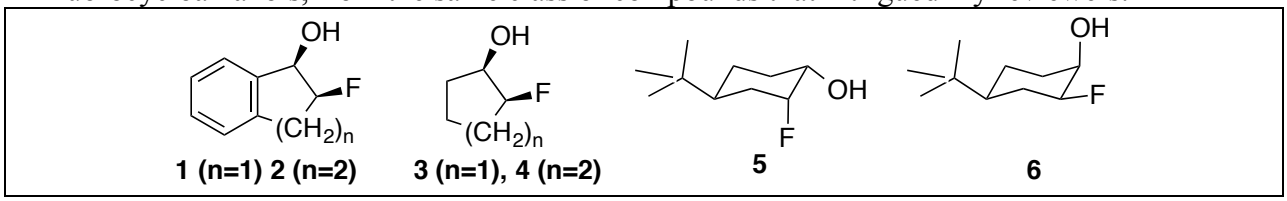
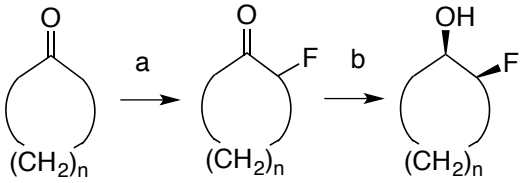


Figure 1. Synthetic targets. All compounds are cis 1,2-fluorhydrins.

With the newer targets, we were able to make good progress. This progress may be because all of these compounds have been previously synthesized (though none have been analyzed). Secondly, the synthetic routes involve the same chemicals, allowing the students to be able to discuss their work with their peers. This improved cooperation among the students.



. a. Selectfluor. b. L-selectride

Scheme 1. Synthetic plan for making cis 2-fluorocycloalkanols

The syntheses for all compounds followed the general plan of scheme 1, above. In the first step, the ketone could be directly fluorinated with Selectfluor. Depending on the ketone, the solvent used might be methanol, dichloromethane, or DMF. Instead of the ketone, an activated

enol form could also be used. Thus, 1-(trimethylsilyloxy)cyclohexene gave higher fluorination yields than cyclohexanone did. For 4-tert-butylcyclohexanone, the acetoxy enol ether gave a higher ratio of the precursors **5** vs **6** compared to direct fluorination. We were able to make the fluoroketone precursors for **1**, **2**, **4**, **5**, and **6**. I did not have the personnel to make the precursor to **3**, though it should certainly be possible. Reduction of the ketones by $NaBH_4$ led to mixtures of cis and trans alcohols that were characterized by 1H, 13C, and 19F NMR. Reduction by L-Selectride led exclusively to the cis isomers. For compounds **1** and **2**, the published spectral data for the cis and trans compound were reversed. A second source validated our assignment for **1**. The alternative is that L-Selectride gave reduction exclusively from the more hindered side, which is chemically unreasonable.

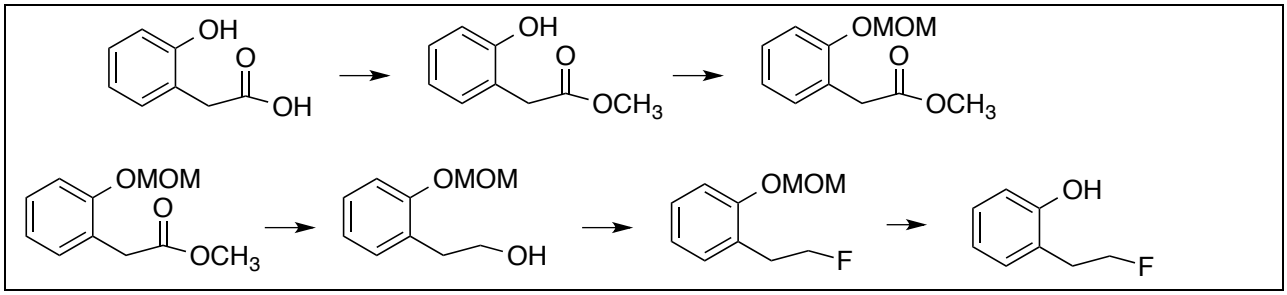
The syntheses are not complete. For **1**, **2**, and **4** the remaining problem is separation of the desired compound from the corresponding alcohols. There are two possible solutions to this problem: 1) separation of the fluoroketone from the ketone in the first step or 2) separation of the fluoroalcohol from the corresponding alcohol in the second step.

For **5** and **6**, there is an additional problem. Here the two fluoroketone precursors need to be separated from each other before reduction. While this separation has been accomplished in the literature, it has resisted our efforts on the two occasions that it was tried.

2. Synthesis of 2-(2-fluoroethyl)phenol

The title compound is predicted to show a very weak IMHB because the F-C-C-C-C-O-H chain is very flexible. The results would be compared with cis 3-fluorocyclohexanol derivatives, which should show a stronger IMHB. We hoped that its synthesis would be straightforward.

Our plan is shown in Scheme 2 below. While this scheme is long, the steps should be straightforward. However, we had unexpected trouble in attaching the MOM protecting group in the second step. It is not clear if we will continue to work on this compound in the future.



Scheme 2. Synthesis of 2-(2-fluoroethyl)phenol

Training of undergraduates

This is the third year of the grant. I hired six students. Of these, I have three biochemistry majors, one neuroscience major and two biology majors. One of the biology majors intends to seek a Ph. D. The other students are all directed towards medical school..