Synthesis of Enantioselective Chiral NMR Shift Reagents

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Abstract

Calix[4]resorcarenes are effective chiral NMR shift reagents for many types of molecules. The synthesis of calix[4]resorcarenes was begun as according to previous literature. Over the course of the experiment, many procedural modifications were made to enhance the yield of the final product. The yield of the product still remains extremely low, and more modifications need to be made to further enhance the yield.

Introduction

Chiral NMR shift reagents allow for the determination of enantiomeric purity for various compounds. They do this by selectively binding to guest molecules, shifting the resulting NMR spectra upfield or downfield for a specific enantiomer. Resorcarenes are especially helpful, since they are water soluble.

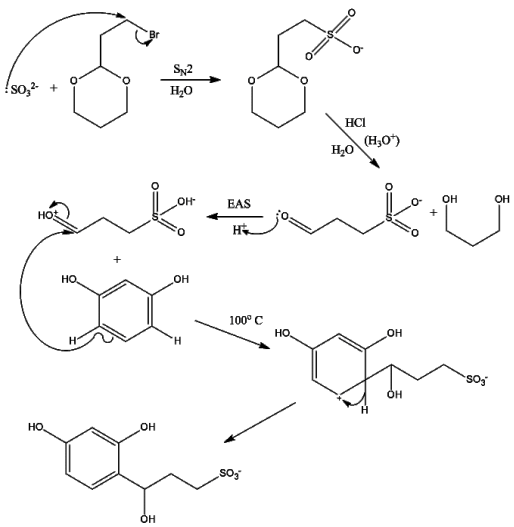

Figure 1: Formation of the monomer

Calix[4]resorcarenes are able to bind various different guest molecules, including amino acids, sugars, and aromatic molecules.[1] In particular, calix[4]resorcarenes with proline groups attached to them are very good chiral NMR shift reagents.[2, 3] This experiment deals specifically with the synthesis of calix[4]resorcarenes, with the hope that in the future, proline groups will be added to the

resorcarene, and it will be interacted with varying guest molecules. The proposed mechanism is as shown in Figures 1 and 2.

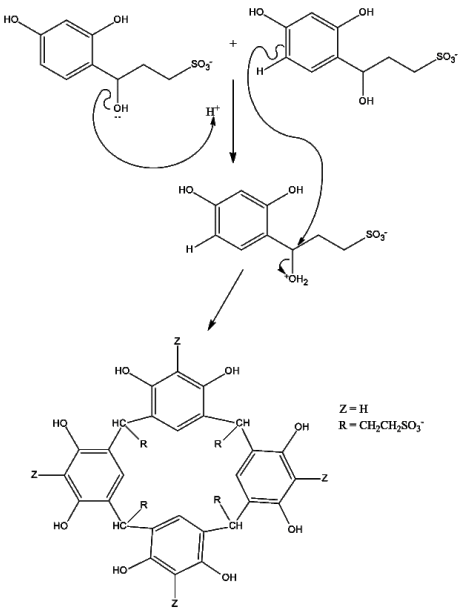

Figure 2: Formation of the tetramer, from the monomer

Experimental

The experiment began by following the procedure in the literature[4]. First, 2.000 g of 2-(2-bromoethyl)-1,3-dioxane was mixed with 10 mL (2.5 g) of Na_2SO_3, then stirred at 100°C for 24 hours. This was then added to 10 mL of water, and washed twice with 20 mL of ether. Next, 20 mL of ethanol, 2.000 g of resorcinol and 3 mL of concentrated HCl were added successively to the solution. This solution was then reacted under nitrogen for 24 hours, at 100°C. The solvents were then evaporated off the solution by placing the solution on the rotary evaporator. Next, 30 mL of water was added to the residue, and then dialyzed three times against 1000 mL of water. The water was then evaporated from solution. Finally, the residue was recrystallized using a water and methanol method.

Results and Discussion

The yield from this synthesis was extremely low. As a result, over the course of the experiment, many portions of the experiment were changed in an effort to increase the yield. However, even after modifications, the highest yield obtained was only 6%. The first attempt to increase yield was to change from ether to methylene chloride in washing the

product. This was done to make the wash layer denser than the product layer, and easier to remove. The next portion that was altered was the recrystallization method. The water and methanol method was unsuccessful at removing the product from solution, and a water and isopropanol method was attempted. The water and isopropanol method was also unsuccessful, and ethanol was then used to recrystallize the product, successfully. Over time, it was established that a methanol and ethanol method of recrystallization was most successful.

Another portion of the experiment that changed with time was the reaction time necessary for each reaction. Thin layer chromatography (TLC) plates were originally used to view progression of the first reaction. However, due to the ionic nature of the sulfonate dioxane, it did not move off of the origin, making it difficult to analyze. Therefore, the reaction was done at 1/20 the literature scale, in an NMR tube, substituting D_2O for water. An NMR was taken on a Brucker spectrospin 300, after the first reaction had run for 6 hours, and then after 24 hours, establishing that the first reaction only needed to run for 6 hours. TLC plates were also used to view the progression of the second reaction, but as with the first reaction, the ionic nature of the tetramer and the sulfonate dioxane resulted in the chemicals not moving from the origin, making it difficult to separate the two from one another. Therefore, the reaction was once again performed at 1/20 scale, with D_2O taking the place of both water and ethanol. Then an NMR was taken of the second reaction at 6 hours, 24 hours, and 48 hours, establishing that the second reaction needed to be run for only 6 hours as well.

In the NMR spectras taken of the product, there seemed to be extra peaks in the aromatic region, possibly from excess resorcinol. One hypothesis for why the resorcinol was not being eliminated during purification was that the resorcinol was interacting with the resorcinarene. Therefore, two experiments were set up to determine the necessary amount of resorcinol in the reaction. A reaction was run with 2.5 mmols of resorcinol, creating a 1:1 ratio of resorcinol to sulfonate dioxane, and another reaction was run with 3.5 mmols of resorcinol. These experiments both resulted in extremely low yields. Based on these experiments, it was determined that the optimal amount of resorcinol was 4.5 mmols, as the literature states.

Based upon another journal article[5], a different method for the second reaction appeared to be more effective for the synthesis. Two reactions were begun, based on that article. One reaction proceeded almost identically to the reaction that was established over the course of the experiment, but with isopropanol instead of ethanol, in the hope that the product would drop out of solution after formation. The other reaction was as written by Höberg, using sulfonate dioxane in place of acetaldehyde.

Conclusion and Future Work

More work remains to be done on this experiment in order to increase the yield. The products of the final two reactions mentioned in the results and discussion section still remains to be worked up, and depending upon the outcome, the experiment will proceed from there. If either reaction gives a better yield than previous methods, that method will be used and enhanced to further the yield.

After a large amount of the product has been produced and stored up, proline groups will be attached to the calix[4]resorcarene. After this addition, the resorcarene will be interacted with various enantiomers. These interactions will be monitored by NMR spectra.

Acknowledgements

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