Progress towards the Synthesis of a Novel Brønsted Acid

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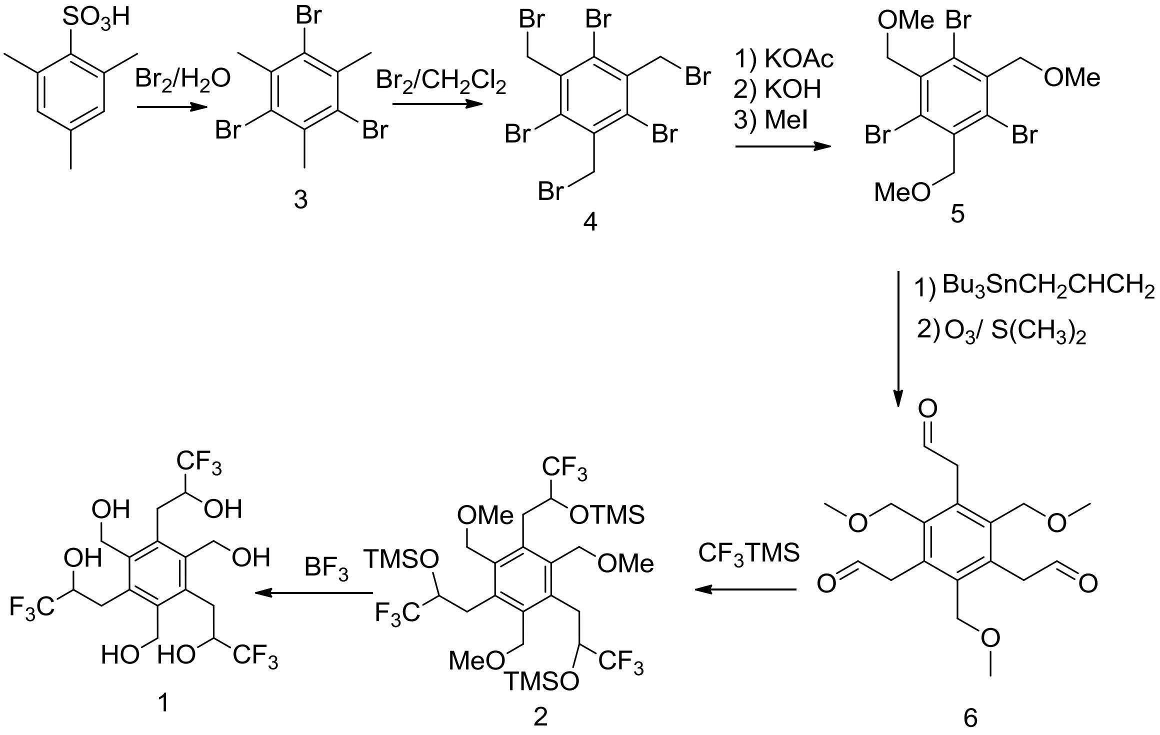
Introduction

Catalysts are an incredibly important and useful tool used in everyday life; they allow plants and animals to metabolize food, allow for cheaper production of numerous products made by industry and aid in the synthesis of pharmaceuticals. As important as catalysts are, there are a number of things that make one desirable for a given synthetic transformation. For example, their cost and availability, toxicity, stability, sensitivity and environmental impact are all huge factors when either using or designing a catalyst. When it comes to organic catalysts, thioureas have been commonly used because of their two relatively acidic nitrogen hydrogen bonds that can be used to form two hydrogen bonds. Certain Bronsted acids also have been shown to have strong catalytic properties thanks to their electrophilic activation of various substrates.[1]

Although thioureas have two acidic hydrogen bonds, the desired hexaol **1** has a total of six hydroxyl groups. This could lead to a hydrogen bond network that increases its catalytic ability and/or molecular recognition properties relative to not only thioureas but also triol **2**. The presence of the three trifluoromethyl groups will enhance the overall acidity of the substrate which should improve its catalytic and binding abilities.[2,3] In particular, the conjugate base may be stabilized by up to five hydrogen bonds and the acid could employ six hydrogen bonds when binding an anion. Thus, it has the potential to be a much more active catalyst and a stronger anion receptor than a thiourea of similar acidity.

The multistep synthesis of hexaol **1** was designed in an attempt to create a new molecule that would excel as an anion acceptor and/or a hydrogen bond catalyst. The preparation of the desired compound starts with commercially available 2-mesitylene sulfonic acid, and hopefully will be produced nine steps later as shown in scheme 1. The first four steps were previously reported in the literature,[4] and were followed as described except for the second step in which bromine was diluted with CH_2Cl_2 before its addition. Compounds **5**, **6**, **1** and **2**, on the other hand, have not been made before. In addition the target hexaol and its immediate precursor **2** have three chiral centers and thus two diastereomers of each should be formed. These species will be separated, and if warranted, so will the individual enantiomers of both diastereomers since this would allow us to explore enantioselective transformations.

Scheme 1. Synthetic scheme for the synthesis of hexaol **1**.



Experimental

General. All anhydrous CH_2Cl_2 (DCM) and $(CH_3)_2NCHO$ (DMF) were used as supplied and were not dried further.

1,3,5-Tribromo-2,4,6-tris(methyl)benzene (3). 2-Mesitylene sulfonic acid (22.3 g, 111 mmol) was dissolved in water (150 ml) by swirling in a 500 ml round bottomed flask and heat was evolved. Bromine (30.0 ml, 93.1 g, 590 mmol) was added in 10 ml portions to the flask in succession. The reaction was then swirled by hand for 10-30 seconds every 3-5 minutes over the course of 1h 30 min during which time it cooled down to room temperature. The resulting orange solid was filtered and washed with 250 ml of water before being recrystallized from acetic acid to afford 20.8 g (55%) of **3** as a white solid. (m.p. 224-226 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 125.0, 26.3. IR (neat) 2921, 1540 cm^{-1}.

1,3,5-Tribromo-2,4,6-tris(bromomethyl)benzene (4). In a 1 L three necked round bottomed flask equipped with a condenser and an additional funnel, **3** (24.8 g, 69.7 mmol) and 600 ml of anhydrous CH_2Cl_2 were added and allowed to stir under a stream of nitrogen. Bromine (13.5 ml, 41.9 g, 262 mmol) was diluted with 40 ml of CH_2Cl_2 and then added dropwise over the course of two hours while the reaction mixture was irradiated with an ordinary desk lamp equipped with a 60 W light bulb. The solution was then gently refluxed at 40 °C for 24 hours while still being irradiated. Hexanes were then added to the solution causing a white precipitate to form which was collected via filtration to afford 37.1 g (90%) of **4** as a white solid. (m.p. 223-226 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 128.5, 35.6; IR (neat) 3042, 2989, 1531, 1523 cm^{-1}.

1,3,5-Tribromo-2,4,6-tris(methoxymethyl)benzene (5). To a 500 ml round bottomed flask under nitrogen, 30.01g (50.02 mmol) of **4**, 30.01 g (305.8 mmol) of potassium acetate and 150 ml of anhydrous $(CH_3)_2NCHO$ were added. The temperature was raised to 70-80°C and the reaction stirred for 24 hours. After the solution cooled down to room temperature, it was filtered and the filtrate diluted with 1.1 L of CH_2Cl_2. This solution was divided into four equal fractions and each one was extracted with water (5 x 175 ml) and brine (2 x 175 ml). The organic phases were combined, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure to afford 26.0 g (97%) of 1,3,5-tribromo-2,4,6-tris(acetoxymethyl)benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (s, 2H), 2.14 δ (s, 3H); IR (neat) 2968, 1725, 1540 cm^{-1}.

In a 1 L round bottomed flask, a potassium hydroxide solution was made by dissolving 35.01 g of KOH (624.0 mmol) in 500 ml of water. To this solution, 26.0 g (49.0 mmol) of 1,3,5-tribromo-2,4,6-tris(acetoxymethyl)benzene was added in one portion and the reaction mixture was gently refluxed for 24 hours. It was then allowed to cool to room temperature and the off white solid was isolated by filtration. The resulting material was washed with 95 ml of water, 70 ml of acetone and 70 ml of diethyl ether. The resulting solid was air dried to afford 18.9 g (93%) of 1,3,5-tribromo-2,4,6-tris(hydroxymethyl)benzene. ^{1}H NMR (500MHz, DMSO) δ 5.24 (s, 1H), δ 4.89 (d, 2H); ^{13}C NMR (125 Hz, DMSO) δ 140.1, 129.0, 65.9.

To a 1 L round bottomed flask under nitrogen, 9.33 g NaH (233 mmol) as a 60% oil dispersion was combined with 350 ml of anhydrous $(CH_3)_2NCHO$. The flask was cooled to ~0 °C in an ice bath before 18.9 g (46.6 mmol) of 1,3,5-tribromo-2,4,6-tris(hydroxymethyl)benzene was added in one portion with stirring. After 50 minutes, 10.0 ml (161 mmol, 22.9 g, 3.4 eq.) of iodomethane was added to the solution and the reaction mixture quickly became too thick to stir properly. Consequently it was quenched by slowly adding water and TLC analysis using a (1:3) ethyl acetate/hexanes solvent system confirmed the completion of the reaction and the disappearance of the starting material. Filtration and recrystallization of the resulting solid from ethanol afforded white crystals which were washed with water (4 x 25 ml) to afford 15.0 g of **5**. When additional water was added to the filtrate more product precipitated resulting in an additional 3.0 g of **5**. The combined material was washed with 125 ml of a (1:4) water, ethyl acetate mixture and allowed to air dry to afford a total of 18.0 g (86%) of **5**. ^{1}H NMR (500MHz, CD_3CN) δ 4.88 (s, 2H), δ 3.43 (s, 3H); ^{13}C NMR (125 Hz, CD_3CN) δ 137.3, 130.6, 75.4, 58.6; IR (neat) 2982, 2920, 2890, 2804, 1538 cm^{-1}.

1,3,5-Tripropylaldehyde -2,4,6-tris(methoxymethyl)benzene (6). To a 50 ml round bottomed flask, **5** (2.23 g, 4.99 mmol), 5.0 ml of $(CH_3)_2NCHO$ and allytributylstannane (5.2 ml, 5.56 g, 16.8 mmol) were added. Tetrakis(triphenylphosphine)palladium(0) (0.43 g, 0.37 mmol) was then added to catalyze the reaction and the resulting solution heated to 120 °C under reflux for 24 hours under a nitrogen atmosphere. The resulting reaction mixture was filtered using a silica plug, washed with diethyl ether and the solvent removed resulting in a yellowish/orange compound. This material gave two spots by TLC (R_f = 0.35 and 0.46 using 1:3 ethyl acetate/hexanes) and was purified by medium pressure liquid chromatography (MPLC) to afford 1.96 g of the slower moving material. It still was impure by TLC so MPLC was performed again using a (2:1) ethanol/hexanes solvent system (R_f = 0.20 and 0.37) to afford 1.36 g (82%) of 1,3,5-triallyl-2,4,6-tris(methoxymethyl)benzene (i.e. the faster moving material). ^{1}H NMR (500MHz, $CDCl_3$) δ 6.05 (m, 3H), δ 4.38 (s, 6H), δ 3.61 (d, 6H), δ 3.39 (s, 9H);

1,3,5-Triallyl-2,4,6-tris(methoxymethyl)benzene (1.20 g, 3.63 mmol) was added to a 100 ml round bottomed flask and dissolved in 20 ml of anhydrous dichloromethane. The flask was cooled to -78 °C using dry ice and acetone and ozone was flowed into the solution. When the reaction was complete (~15 minutes) the solution turned blue indicating the presence of excess ozone. The reaction mixture was then flushed with oxygen until the color disappeared and ice was observed indicating that the starting material had been wet. Dimethyl sulfide (3.50 ml, 3.85 g, 49.3 mmol) was added while still maintaining the temperature of -78 °C. The resulting solution was stirred for approximately 24 hours and during this time it was allowed to warm to room temperature. TLC analysis of the resulting material revealed two spots (R_f = 0.20 and 0.37 using 2:1 ethanol/hexanes and a $KMNO_4$ stain) suggesting the presence of two different aldehydes. Purification by MPLC using the same solvent system afforded two components and the slower moving one was collected for NMR analysis. This material was found to give two spots by TLC using 1:19 methanol/CH_2Cl_2 (R_f = 0.37 and 0.50) and after removal of the solvent under reduced pressure 1.18 g of crude material was obtained. Purification via MPLC was performed with acetonitrile and TLC with a 1:9 acetone/CH_2Cl_2 solvent system showed the presence of only one spot. Removal of solvent afforded 230 mg (19%) of product that was confirmed by NMR to be the trialdehyde. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (s, 3H), δ 4.38 (s, 6H), δ 3.90 (s, 6H), δ 3.28 (s, 9H). IR (neat) 2923, 1715, 1578 cm^{-1}

Results and Discussion

The synthesis of **3** from 2-mesitylene sulfonic acid was confirmed by melting point and both ^{1}H and ^{13}C NMR indicating a pure product was created. One hydrogen peak representative of the nine equivalent protons and three carbon peaks were seen in the NMR spectra as expected. Just as reported from literature sources, a modest yield (55%) near 50% was obtained. However, in an attempt to increase the yield, a larger excess of bromine was used than called for in the literature procedure, but this did not significantly increase the efficiency of the reaction.[4] The preparation of **4** was verified via its melting point, ^{1}H and ^{13}C NMR spectra; all of the hydrogens are equivalent leading to a singlet in the ^{1}H NMR spectrum and three singlets in the ^{13}C NMR spectrum for the three different carbons. Compound **4** is a useful substrate for synthesizing a variety of molecules with a central benzene core since the benzylic and aryl bromides can be readily manipulated.

The synthesis of **5** is a somewhat tedious three-step process in which all of the bromomethyl groups are first converted to acetoxymethyl groups (i.e. CH_2OAc) and then are hydrolyzed with base to hydroxymethyl substituents (i.e. CH_2OH). In the last step of this sequence the alcohols are protected as methyl ethers by alkylating them with methyl iodide. This three step route is efficient and can be accomplished in an overall yield of 78%. This is the case because all of the steps have yields of greater or equal to 86%. Nevertheless, a small improvement may be possible by using a larger amount of solvent in the alkylation so as to facilitate stirring of the reaction mixture.

To synthesize **6**, a coupling reaction was performed in which the three aryl bromine atoms were replaced with allyl groups. Ozonolysis of this intermediate afforded the desired tris(aldehyde) but these steps still need to be improved. We discovered early on that the addition of the allyl groups does not take place when the reaction is run in toluene but works well in dimethylformamide. Isolation of the tris(aldehyde) from the ozonolysis reaction has proven to be tricky. The TLC of the crude product shows two streaks with R_f values of 0.20 and 0.37 using a 2:1 ethanol/hexanes solvent system. These spots presumably correspond to the desired aldehyde and one or more byproducts. After several attempts to purify **6**, it was obtained by MPLC using pure acetonitrile as the solvent system. TLC analysis using a 1:9 acetone/CH_2Cl_2 mixture revealed only one spot with an R_f value of about 0.40. Its ^1H and ^{13}C NMR spectrum are consistent with what is expected for **6**, but a small impurity was also apparent and so the sample was purified further by MPLC.

An alternative synthetic strategy different from that outlined in Scheme 1 was attempted. That is, **5** was reacted with cuprous cyanide in $(CH_3)_2NCHO$. This coupling reaction was carried out over two days at room temperature, but no product was observed by TLC (1:2 ethyl acetate/ hexanes) and this approach was abandoned given the success of the tris(allylation).

Conclusion

Although the synthesis of hexaol **1** has not yet been completed, seven of the nine steps were accomplished. To finish the preparation of **1**, three trifluoromethyl groups need to be added to **6** and such an addition has been carried out successfully as shown in the literature.[5] Deprotection of the methyl ethers is also expected to be straight forward and is well precedented.[6,7] Thus far the seven completed steps have had very high yields ranging from 55% to 97% with an overall yield of 22%, which gives a lot of hope for the efficient creation of the desired molecule. The addition of the trifluoromethyl groups is now the critical step in the synthesis of **1** and **2**. Current attempts to synthesize **2** using (trifluoromethyl)trimethylsilane have given very low yields of less than 4% regardless of solvent conditions. Acetonitrile, tetrahydrofuran and 1,2-dimethoxyethane so far have been used, in that order, with the yield increasing each time, showing that the use of a less polar solvent could be beneficial to the reaction. Although no large yields have yet been obtained encouragement can be found in the fact that a product with the expected hydrogen, carbon and fluorine NMRs of **2** has been isolated. Once a larger quantity of **2** is created the methyl ethers can be deprotected and the trimethylsilyl groups removed, potentially using boron tribromide, to produce hexaol **1**. The binding affinities of **1** and **2** can then be measured to specific anions such as chloride to see whether or not the addition of three hydroxyl groups is beneficial to the molecules binding and catalytic abilities.

References

1. Uraguchi, D., and M. Terada. "Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation." Journ. Amer. Chem. Society 126 (2004): 5356-357.

2. Smart, B. E. "Fluorine Substituent Effects (on Bioactivity)." J. Fluor. Chem. 109 2001: 3-11. Benkovic, S. J., and S. Hammes-Schiffer. "A Perspective on Enzyme Catalysts."Science 301 2003: 1196-1202

3. Betageri, R., Y. Zhang, R. M. Zindell, D. Kuzmich, R. M. Kirrance, J. Bentzien, M. Cardozo, A. J. Capolino, R. N. Fadra, R. M. Nelson, Z. Paw, D. Shih, C. Shih, L. Zuvela-Jelaska, G. Nabozny, and D. S. Thompson. "Trifluoromethyl Group as a Pharmacophore: Effect of Replacing a CF3 Group on Binding and Agonist Activity of a Glucocorticoid Receptor Ligand." Bio. Med. Chem. Letters 15 2005: 4761-769.

4. Bruns, Dirk; Miura, Hirokazu; Vollhardt, K. Peter C.; Stanger, Amnon Organic Letters, 2003: 5, 549-552

5. Singh, R. P., G. Cao, R. L. Kirchmeier, and J. M. Schreeve. "Cesium Fluoride Catalyzed Trifluoromethylation of Esters, Aldehydes, and Ketones with Trifluoromethyl)trimethylsilane." *J. Org. Chem.* 64 **1999**; 2873-876.

6. Ryu, I., H. Matsubara, S. Yasuda, H. Nakamura, and D. Curran. "Phase-Vanishing Reactions That Use Fluorous Media as a Phase Screen. Facile, Controlled Bromination of Alkenes by Dibromine and Dealkylation of Aromatic Ethers by Boron Tribromide." *J. Am. Chem. Soc.*124 **2002**: 12946-2947.

7. Kosikowski, A. P., and J. Wu. "Protection of Alchols as Their (p-Methyoxybenzyloxy)methyl Ethers." *Tetrahedron Letters* 28 **1987**: 5125-5128.