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Synthesis and Characterization of Mono- and Di-O-Alkylated Derivatives of Methyl 3,5-Dihydroxy Benzoate

Michele Paccagnini FCRH '12
Fordham University, furj17@fordham.edu

Matthew Tracey FCRH '11
Fordham University, furj17a@fordham.edu

J. Ryan Combs FCRH '10
Fordham University, furj17b@fordham.edu

Amy M. Balija
Fordham University, furj17c@fordham.edu

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Michele Paccagnini, FCRH '12

Matthew Tracey, FCRH '11

J. Ryan Combs, FCRH '10

Dr. Amy M. Balija, Chemistry

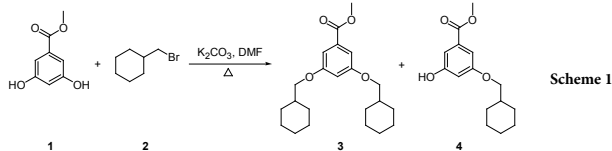
Synthesis and Characterization of Mono- and Di-O-Alkylated Derivatives of Methyl 3,5-Dihydroxy Benzoate

Introduction

In the course of searching for monomers for larger macromolecular structures, we attempted the bis-O-alkylation of methyl 3,5-dihydroxy benzoate (**1**) with (bromomethyl)cyclohexane (**2**). To our knowledge, no literature procedures have been published on the preparation of ethers by alkylation of a phenol substrate with (bromomethyl)cyclohexane. We were surprised to find that the mono-O-alkylated product was predominantly obtained in this reaction. This finding is in contrast with those reported for alkylations, utilizing benzyl bromide where bis-O-alkylation is the predominant reaction (Yan et al. 2011). Herein we report a convenient synthesis of the bis-alkylated product **3** in good yield.

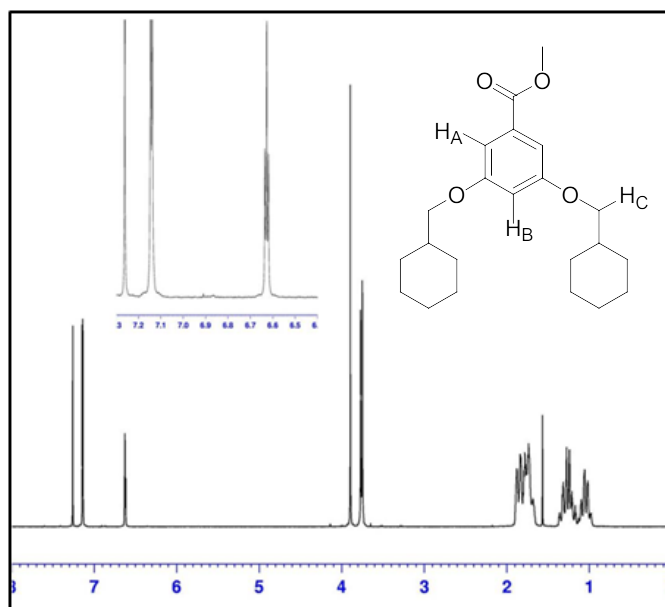
Results and Discussion

Initial attempts to prepare di-O-alkylated ether **3** involved reacting **1** with **2** in the presence of K_2CO_3 with 18-[C]-6 in acetone at 60 °C. This di-alkylation did not proceed presumably due to the decreased reactivity of (bromomethyl)cyclohexane relative to other alkyl halides such as benzyl bromide. To identify conditions that favor the formation of **3**, we modified the reaction solvent and temperature. Upon exposure of the (bromomethyl)cyclohexane and **2** with K_2CO_3 in DMF at 60 °C (Scheme 1), two new products were observed by thin layer chromatography (TLC). After workup and separation by silica gel column chromatography, we identified the products as the mono-O-alkylated **4** and di-O-alkylated **3** derivatives of methyl 3,5-dihydroxybenzoate. Subjecting **4** to further alkylation with **2** increased the overall yield of **3** from 10% to 49%.

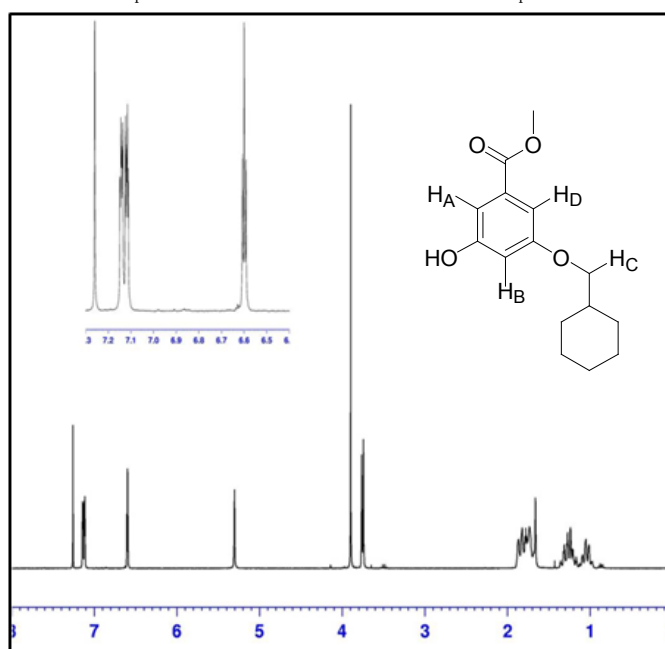


Optimized conditions were obtained when **1** was reacted with 2.1 equivalents of **2** and 2.0 equivalents of K_2CO_3 in anhydrous DMF under an inert atmosphere at 80 °C for 3 hours. The resulting mixture of mono- and di-alkylated product was washed with copious amounts of water to remove excess DMF. After purification by silica gel column chromatography, **3** and **4** were isolated as yellow solids. The mono-alkylated phenol **4** was then resubjected to the optimized alkylation conditions described above to obtain exclusively **3**. Upon purification by silica gel column chromatography, the di-alkylated product obtained in the first alkylation

Figure 1
Color changed observed before (left vial) and after (right vial) upon trituration of **3**.



(above) Figure 2
 1H NMR spectrum of **3**.



(below) Figure 3
 1H NMR spectrum of **4**.

and the di-alkylated product isolated from the second was triturated with ice-cold petroleum ether to provide a white powder (Figure 1). The additional purification step improved the overall yields of the subsequent steps utilizing **3** as the starting material. Overall, the yield of the di-O-alkylated product rose to 87%.

The mono- and di-O-alkylated structures were further characterized using ^1H and ^{13}C NMR spectroscopy. We expect that **3** would have a simplified NMR spectrum compared to **4** due to its inherent symmetry. As seen in Figure 2, **3** exhibited a triplet at 6.63 ppm and a doublet at 7.15 ppm which corresponded to the nonequivalent protons H_{BA} and $\text{H}_{\text{AB'}}$, respectively. Furthermore, the doublet at 3.77 ppm integrated to four, corresponding to the correct number of methylene protons labeled H_{C} . However, the aromatic region is more complex for mono-alkylated **4** (Figure 3), with a triplet at 6.60 ppm two overlapping doublet of doublets at 7.13 ppm, corresponding to H_{BA} and $(\text{H}_{\text{BA}} + \text{H}_{\text{D}})$ respectively. The doublet at 3.76 ppm, corresponding to the methylene protons (H_{C}) integrated to two and a broad singlet was observed at 5.41 ppm for the free phenol proton.

The ^{13}C NMR spectra for **3** and **4** also displayed distinguishing differences. Because of the inherent symmetry, four aromatic carbon peaks were observed for **3** (160.3, 131.8, 107.6, and 106.5 ppm) while six aromatic carbon peaks were observed for **4** (160.6, 156.6, 132.0, 108.9, 107.9, 107.0 ppm). In both cases, the ^1H and ^{13}C NMR spectra of **3** and **4** were different from the corresponding spectra for commercially available methyl 3,5-dihydroxy benzoate.

One potential use for di-alkylated **3** is as a monomer for larger molecular structures such as polymers² and dendrimers (Fréchet and Tomalia 2002). Because of its unique molecular structure containing polar and nonpolar moieties, compound **3** is an interesting monomer for incorporation into macromolecules that might be able to remove hydrophobic, nonpolar organic pollutants from aqueous environments. Previous work in our group has demonstrated that the incorporation of different functional groups influences the pollutant entrapment (Triano et al. 2011). We anticipate that cyclohexane groupings will influence the encapsulation properties of dendrimers. Compounds **3** and **4** are also novel synthons for organic synthesis: the ester group serves as a handle for further functionalization through the formation of new carbon-carbon bonds or hydrolysis to the carboxylic acid.

Conclusion

In summary, we have disclosed a previously unknown alkylation reaction between methyl 3,5-dihydroxymethyl benzoate **1** and (bromomethyl)cyclohexane **2**. The reaction proceeds by initial mono-O-alkylation to furnish an intermediate that was isolated and subjected to the same alkylation conditions to obtain the desired product in good yield. Purification by silica gel column chromatography followed by trituration resulted in an analytically pure product. Because of its unique physical properties, di-O-alkylated product **3** has been incorporated into dendrimers for encapsulating organic pollutants from aqueous environments. Future studies of the effectiveness of this monomer in the encapsulation of pollutants will be disclosed in due time. Furthermore, our di-O-alkylation protocol may find broader use in other synthetic targets.

Experimental Procedure

All reactions are performed under an argon gas atmosphere using oven-dried glassware. Solvents and reagents are used without further purification. Reactions are monitored by TLC using silica gel 60 F_{254} glass plates. TLC bands are visualized by UV. Eluent solvent ratios are reported in v/v. ^1H spectra are recorded at 300 MHz

and ^{13}C NMR spectra are recorded at 75 MHz on a Bruker Avance DPX300 spectrometer. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported in Hertz (Hz). ^1H NMR spectra obtained in CDCl_3 are referenced to 7.26 ppm. ^{13}C NMR spectra obtained in CDCl_3 are referenced to 77.16 ppm.

Synthesis of bis-O-dialkylated compound **3**.

A mixture of methyl 3,5-dihydroxy benzoate (5.00 g, 29.7 mmol) and K_2CO_3 (8.50 g, 61.5 mmol) in DMF (37.5 mL) is stirred at room temperature. After 2 h, (bromomethyl)cyclohexane (8.80 mL, 63.1 mmol) is added to the reaction mixture in 1 mL portions over 10 min. The mixture is then heated at 80 °C for 3 h. After the reaction cooled to room temperature, ethyl acetate (100 mL) is added and the organic layer is washed with water (5X, 70 mL each) and brine (1X, 70 mL). The organic layer is then dried over anhydrous sodium sulfate before the solvent is removed by rotary evaporation. Purification of the product by column chromatography (silica gel, petroleum ether:diethyl ether, 1:1) results in the isolation of **3** and **4** as yellow solids. A mixture of **4** (2.08 g, 12.4 mmol) and K_2CO_3 (3.54g, 25.6 mmol) in DMF (15.6 mL) is stirred at room temperature. After 2 h, (bromomethyl)cyclohexane (3.67 mL, 26.5 mmol) is added to the reaction mixture dropwise and the mixture is then heated at 80 °C for 3 h. After the reaction cooled to room temperature, ethyl acetate (20 mL) is added and the organic layer is washed with water (6X, 15 mL each) and brine (1X, 15 mL). The organic layer is then dried over anhydrous sodium sulfate before the solvent is removed by rotary evaporation. Purification of the product by column chromatography (silica gel, petroleum ether:diethyl ether, 1:1) resulted in the isolation of **3** as a yellow solid. Trituration with ice-cold petroleum ether afforded **3** in 4.36 g (87%) as a white powder. R_f : petroleum ether:ethyl acetate 1:1, **3**: 0.72, **4**: 0.88.

3: ^1H NMR(300 MHz): δ = 7.15 (d, 2H, $J=2.3$), 6.63 (t, 1H, $J=2.3$), 3.91 (s, 3H), 3.77 (d, 4H, $J=6.2$), 1.03-1.88 (m, 22H). ^{13}C NMR(75 MHz): δ = 167.0, 160.3, 131.8, 107.6, 106.5, 73.8, 52.2, 37.7, 29.9, 26.5, 25.8.

4: ^1H NMR(300 MHz): δ = 7.13 (m, 2H), 6.60 (t, 1H, $J=2.3$), 5.41 (s, 1H), 3.90 (s, 3H), 3.76 (d, 2H, $J=6.2$), 1.01-1.87 (m, 11H). ^{13}C NMR(75 MHz): δ = 167.00, 160.6, 156.6, 132.0, 108.9, 107.9, 107.0, 73.8, 52.3, 37.6, 29.8, 26.5, 25.8.

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