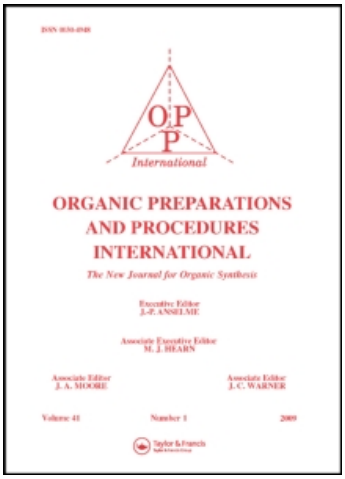

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5-BENZYLOXYRESORCINOL, A MONOPROTECTED PHLOROGLUCINOL

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5-BENZYLOXYRESORCINOL, A MONOPROTECTED PHLOROGLUCINOL

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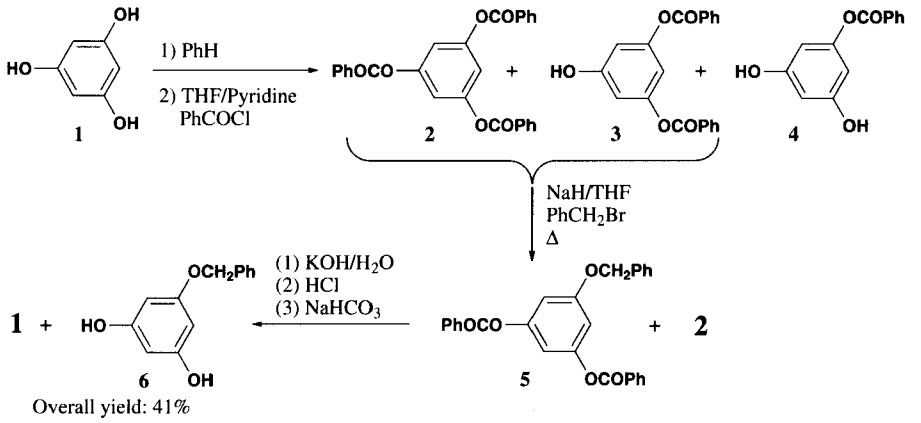
5-Benzyloxyresorcinol (**6**) is a key intermediate in our synthetic schemes directed toward di- and mono-functionalized *bis*(*m*-phenylene) crown ethers[1-7] and related cryptands. The previous one-step synthesis of 5-benzyloxyresorcinol (**6**) from phloroglucinol (**1**) gave only a 9% yield.[8] Although our attempts to improve this method failed, herein we report an alternative synthesis that affords an improved overall yield of the target compound.

Treatment of phloroglucinol (**1**) with two moles of benzoyl chloride produced a mixture of benzoates **2**, **3** and **4**. The monoester **4** was insoluble in $CHCl_3$ and hence could be easily removed from the mixture, since both **2** and **3** were soluble. Analysis of the soluble mixture *via* ^1H NMR spectroscopy revealed a 36:64 ratio of **2: 3**. Pure **3** was prepared as a reference material from pure **2**[9] by hydrolysis with Cs_2CO_3. It was also converted to the desired **6** (34% overall), but this route was less efficient than the one described here. The mixture of **2** and **3**, without further purification, was treated with NaH and one equivalent of benzyl bromide to give a mixture of **2** and **5**, which was hydrolyzed with aqueous methanolic KOH. Neutralization with acid, followed by removal of benzoic acid with saturated aqueous $NaHCO_3$ and removal of phloroglucinol (**1**) derived from **2** by washing with water afforded the desired 5-benzyloxyresorcinol (**6**) in 41% overall yield.

The application of 5-benzyloxyresorcinol (**6**) to the synthesis of monomeric macrocycles, cryptands and polymacrocycles is the subject of current research and will be reported elsewhere. We note that Büchi reported the dibenzyl ether and the monobenzenesulfonate of phloroglucinol.[10]



Overall yield: 41%

EXPERIMENTAL SECTION

Melting points were taken in capillary tubes with a Haake-Buchler apparatus and have been corrected. NMR spectra were obtained at 20° on a Varian Unity 400 MHz instrument using $CDCl_3$ unless otherwise noted and TMS as internal standard. Mass spectroscopy was carried out on VG Quattro instrument. Unless specified otherwise, reagent grade reactants and solvents were used as received from the chemical suppliers. Tetrahydrofuran (THF) was distilled from sodium/benzophenone.

1,3,5-Tribenzoyloxybenzene (2), mp. 175.6-178.0°, lit.[9] mp. 170°, was prepared (98%) from phloroglucinol and benzoyl chloride;[9] ^1H NMR: δ 7.17 (s, 3H), 7.52 (t, J =7.4 Hz, 6H), 7.65 (tt, J = 1.2 and 7.4 Hz, 3H), 8.20 (dd, J = 1.2 and 8.0 Hz, 6H); ^{13}C NMR: δ 113.25, 128.61, 128.96, 130.19, 133.83, 151.52, 164.37.

3,5-Dibenzoyloxyphenol (3).- A selective hydrolysis method developed for another compound[11] was utilized. Cesium carbonate (68.37 g, 210 mmol) was added to a solution of 1,3,5-tribenzoyloxybenzene (**2**, 56.56 g, 129 mmol) in dimethoxyethane (DME) (550 mL). After 30 hrs of reflux, the mixture was filtered and DME was evaporated. The residue was treated with 2N HCl and extracted with Et_2O. The light pink solution was passed through a short silica gel column to yield 32 g (74%) of **3** as a pink oil. ^1H NMR: δ 6.64 (d, J = 2.0 Hz, 2H), 6.72 (t, J = 2.0 Hz, 1H), 7.5 (m, 4H), 7.63 (t, J = 7.4 Hz, 2H), 8.17 (d, J = 8.4 Hz, 4H); ^{13}C NMR: δ 107.38, 107.73, 128.61, 129.08, 130.26, 133.83, 151.88, 157.37, 165.12.

Mixture of 1,3,5-Tribenzoyloxybenzene (2) and 3,5-Dibenzoyloxyphenol (3).- A suspension of phloroglucinol dihydrate (**1**, 53.56 g 330 mmol) in PhH (1 L) was refluxed until no more water was obtained in the Dean-Stark trap (15 h). After removal of PhH, dry THF (1.7 L) and pyridine (54.0 mL, 668 mmol) were added. Benzoyl chloride (38.5 mL, 331 mmol) was added over 1 hr. The cloudy mixture was stirred for 24 hrs before addition of the second portion of benzoyl chloride (38.5 mL, 331 mmol) over 1hr and then under reflux for 48 hrs. The cooled mixture was filtered, concentrated, diluted with Et_2O (1 L) and washed sequentially with 2N HCl (200 mL), water (2 x 200 mL) and sat. aq. NaCl (100 mL). Upon removal of the solvent, the residual oil was triturated with $CHCl_3$ to give a white solid, which was filtered off. The filtrate upon concentration was again triturated with $CHCl_3$ to

give more white solid. The filtrate upon removal of solvent gave a light yellow paste, which was dried at 50° and used for the next reaction. ^{1}H NMR (integration of δ 6.64 vs. δ 7.17 signals) indicated that it was a mixture of **3** (64%) and **2** (36%).

5-Benzyloxyresorcinol (6).- Sodium hydride (7.5 g, 60% in mineral oil, 0.19 mol) was added to a solution of di- and the tri-benzoates (**3** and **2**, 91.85 g, containing about 59.0 grams of **3**, 176 mmol) in anhydrous THF (600 mL). Benzyl bromide (21.0 mL, 177 mmol) was added and the mixture was refluxed for 12 hrs, cooled and filtered. The solid was extracted with EtOAc (100 mL); evaporation of the extract afforded a solid, which was washed with MeOH (100 mL) to give a white solid, which was shown by TLC to be a mixture of **2** and **5**, 102 g (94%), mp. 152.8-178.7°. This mixture was heated with KOH (28.0 g, 500 mmol), 650 mL water and 20 mL MeOH to give a dark brown mixture, which after cooling was filtered. The filtrate was cooled to 0°, neutralized with 2N HCl and filtered; the white product was washed with sat. aq. $NaHCO_3$. After complete removal of benzoic acid, the light brown solid was washed with water and dried at 50° to give 28.8 g (85%) of pure 5-benzyloxyresorcinol (**6**), mp. 80-82°, lit.[8] an oil; ^{1}H NMR (DMSO-d_6): δ 4.06 (s, 2H), 5.84 (t, J = 2.0 Hz, 1H), 5.86 (d, J = 2.0 Hz, 2H), 7.4 (m, 5H), 9.20 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 68.84, 93.47, 95.67, 127.49, 127.66, 128.37, 137.36, 159.00, 160.15. MS (EI) m/z (rel int.): 216 (M^+, 12), 91 [(M- $C_6H_5O_3$)$^+$, 100%].

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