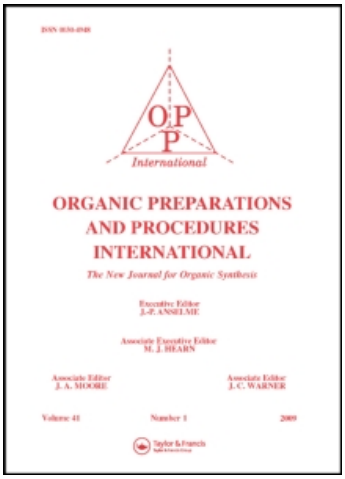

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A FACILE SYNTHESIS OF 3-BENZYLOXY-5-METHOXYPHENOL

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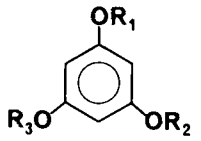
During an approach directed to the synthesis of aflatoxins,[1,2] we needed to prepare phloroglucinol benzyl methyl ether 1 (3-benzyloxy-5-methoxyphenol) as an A-ring intermediate.[2] A survey of the literature revealed that 1 has been obtained from methyl 2,6-dihydroxy-4-methoxybenzoate[3] by benzylation followed by basic hydrolysis and decarboxylation, although it had been prepared either by selective methylation of phloroglucinolcarboxylic acid with diazomethane (no yield quoted)[4] or by a multi-stage synthesis from 4-hydroxy-6-methyl-2-pyrone.[5] More recently, Büchi et al.[6] mentioned the use of 1 in their synthesis of aflatoxin M_1 with no experimental details for its preparation. We have therefore developed the following route based in the well-known formation and selective basic hydrolysis of arylsulfonates,[7] such as 3[7b] combined with standard methods for O-alkylation.

Sulfonylation of phloroglucinol dihydrate (2) with 3.1 eq. of benzenesulfonyl chloride and $Ca(OH)_2$ in water at 25° gave 3 (94%). Treatment of 3 with 2.5 eq. of 20% aqueous methanolic (1:1) potassium hydroxide solution at 7° produced phenol 4 (95%). If the temperature is increased to 20°, the yield decreased owing to formation of small amounts of 5 and phloroglucinol dimethyl ether monobenzenesulfonate. Methylation of 4 with diazomethane gave 5 (91%). Hydrolysis of the second sulfonate ester

was accomplished by further treatment of 5 with 2.8 eq. of 20% methanolic potassium hydroxide solution at 25° affording 93% of 6. At 58° with 6 eq. of base, phloroglucinol dimethyl ether monobenzenesulfonate was the major product (70%). Phenol 6 was then alkylated with benzyl bromide and K_2CO_3 in refluxing acetone to produce 7 (92%). Finally, 7 was hydrolyzed by heating with 2.8 eq. of 20% methanolic potassium hydroxide giving 94% of phenol 1 (65% overall yield from 2).



	R_1	R_2	R_3
1,	H	$PhCH_2$	Me
2,	H	H	H
3,	$PhSO_2$	$PhSO_2$	$PhSO_2$
4,	$PhSO_2$	$PhSO_2$	H

	R_1	R_2	R_3
5,	$PhSO_2$	$PhSO_2$	Me
6,	$PhSO_2$	H	Me
7,	$PhSO_2$	$PhCH_2$	Me

This sequence shows the advantages of the combination of partial hydrolysis of polyarylsulfonate esters of polyhydric phenols[7] with standard methods for ether formation, which allows the preparation of a large variety of O-alkyl phenol derivatives.

EXPERIMENTAL SECTION

Melting points were taken on a Culatti capillary melting point apparatus and are corrected. Column chromatography was carried out by using Merck silica gel 60 (0.063-0.2 mm). The preparative TLC plates were of Merck silica gel 60 F-254 (20 x 20 x 0.2 cm). In order to follow the progress of the reactions or the purity of the compounds, Merck F-254 thin-layer plates 250 (μm) cut into small slides (5 x 2.5 cm) were used. The products were visualized by UV absorption or I_2 vapor. IR spectra were taken on a Perkin-Elmer 552 instrument in $CHCl_3$. ^1H NMR spectra were obtained in $CDCl_3$ on Varian HA-100 and FT-80A spectrometers with Me_4Si, as an internal reference, and are expressed as δ values. Mass spectra were recorded on a Hewlett Packard 5985-B spectrometer at 70 eV.

Phloroglucinol Tribenzenesulfonate (3) and Phloroglucinol Dibenzenesulfonate (4).- These compounds were prepared by the procedure of Kampouris.[7b] 3, mp. 123-125°, lit.[7b] mp. 122°; ^1H NMR: δ 6.67 (s, 3H), 7.40-7.85 (m, 15H); MS, m/e (rel.int.): 546 (M^+, 3), 341 (21), 141 (74), 77 (100). 4,

mp. 125-126°, lit.[7b] mp. 120-121°; ^{1}H NMR: δ 2.4 (br, 1H, exchangeable with D_2O), 6.17 (t, J = 1.5 Hz, 1H), 6.42 (d, J = 1.5 Hz, 2H), 7.35-7.82 (m, 10H); MS, m/e (rel.int.): 406 (M^+, 3), 141 (32), 131 (10), 51 (20), 77 (100).

Phloroglucinol Monomethyl Ether Dibenzenesulfonate (5).- The phenol 4 (4.06 g, 0.01 mol) in 100 mL of Et_2O was treated with an excess of an ethereal solution of CH_2N_2 at 0°. The mixture was kept at 0° for 1 hr and then allowed to stand at 25° for 12 hrs. The volatiles were evaporated and the resulting solid was recrystallized from MeOH to give 3.8 g (91%) of 5, mp. 92-93°, lit.[7b] mp. 92°; ^{1}H NMR: δ 3.58 (s, 3H), 6.25 (t, J = 2 Hz, 1H), 6.40 (d, J = 2 Hz, 2H), 7.35-7.80 (m, 10H); MS, m/e (rel.int.): 420 (M^+, 15), 215 (79), 187 (21), 141 (47), 77 (100).

Phloroglucinol Monomethyl Ether Monobenzenesulfonate (6).- A 20% MeOH solution of KOH (2.4 mL, 8.4 mmol) was added dropwise to a stirred solution of 5 (1.26 g, 3 mmol) in 5 mL of MeOH at 25°. After addition, the solution was stirred 5 hrs at 25°, diluted with water (70 mL), acidified to pH 5 with 5% HCl and decolorized with a few grains of $Na_2S_2O_3$. The mixture was extracted with EtOAc (3 x 25 mL). The extracts were washed with water, dried and evaporated affording a pale brown solid, which was recrystallized from $CHCl_3$-C_6H_{14} to give 0.42 g of 6. The mother liquors were chromatographed on three preparative plates with C_6H_{14}-EtOAc (55:45), as the developing solvent. The elution produced another 0.36 g (93%) of product, mp. 115-116°, lit.[7b] mp. 111-112°; ^{1}H NMR: δ 3.62 (s, 3H), ∿4.30 (br, 1H, exchangeable with D_2O), 6.07 (t, J = 2 Hz, 1H), 6.12 (t, J = 2 Hz, 1H), 6.25 (t, J = 2 Hz, 1H), 7.35-7.90 (m, 5H); MS, m/e (rel.int.): 280 (M^+, 21), 141 (32), 77 (100), 69 (20).

Benzyl Methyl Phloroglucinol Monobenzenesulfonate (7).- A mixture of 6 2.8 g, 10 mmol), benzyl bromide (1.7 g, 10 mmol), and anh. K_2CO_3 (2.8 g,

20 mmol) in 15 mL of acetone was refluxed for 4 hrs. After removal of the unreacted benzyl bromide by steam distillation, the remainder was extracted with EtOAc (3 x 30 mL). The combined extract was washed, dried and concentrated. The resultant solid was recrystallized from $CHCl_3$-C_6H_{14} to produce 3.4 g (92%) of 7, mp. 89-91°; ^1H NMR: δ 3.62 (s, 3H), 4.87 (s, 2H), 6.12 (t, J = 2 Hz, 1H), 6.22 (t, J = 2 Hz, 1H), 6.37 (t, J = 2 Hz, 1H), 7.32 (m, 5H), 7.35-7.90 (m, 5H); MS, m/e (rel.int.): 370 (M^+, 4), 229 (11), 91 (100), 77 (11), 65 (7).

Benzyl Methyl Phloroglucinol (1).- To a stirred mixture of 7 (7 g, 19 mmol) in 40 mL of MeOH, a 20% MeOH solution of KOH (14 mL) was added. The solution was refluxed for 4 hrs. After cooling, the solution was diluted with 300 mL of water, acidified to pH 6 with 5% HCl and decolorized with 1 g of $Na_2S_2O_3$. The mixture was stirred for 1 hr at 25° and extracted with EtOAc (3 x 75 mL). The combined extract was washed, dried and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using C_6H_{14}-EtOAc (65:35), as the eluent. Concentration of the eluates gave an oil, which after vacuum distillation produced 4.1 g (94%) of 1, bp. 185°/ 0.02 mm; ^1H NMR: δ 3.70 (s, 3H), 4.95 (s, 2H), 5.40 (br, 1H, exchangeable with D_2O), 5.90-6.25 (m, 3H), 7.35 (s, 5H); MS, m/e (rel.int.): 230 (M^+, 28), 92 (7), 91 (100), 65 (13).

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