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SYNTHESIS OF 2-[(ARYLTHIO)METHYL]- AND 2-[(ALKYLTHIO)METHYL]RESORCINOLS

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Abstract: 1,3-Bis(methoxymethoxy)-2-bromomethylbenzene **3**, which was prepared from 2-methylresorcinol by methoxymethylation and bromination, reacted with thiols in the presence of base to give the thioethers **4**, which on treatment with HCl in methanol produced the title compounds **5** in moderate yields.

Recently, the preparation of the calix[4]resorcinarenes possessing arylthiomethyl- or alkylthiomethyl groups at the extraannular positions of the macrocycles has been reported.[1] The thiomethyl groups improve the solubility of calix[4]resorcinarenes in common organic solvents, hence, it is expected that the functionalized macrocycles behave as artificial receptors in these solvents.[2] As a part of our current studies on the development of calix[4]resorcinarene systems with unsubstituted methylene bridges,[3-5] we thought that the resorcinols having an arylthio- or alkylthiomethyl group at the 2-position could be useful as aromatic components for the

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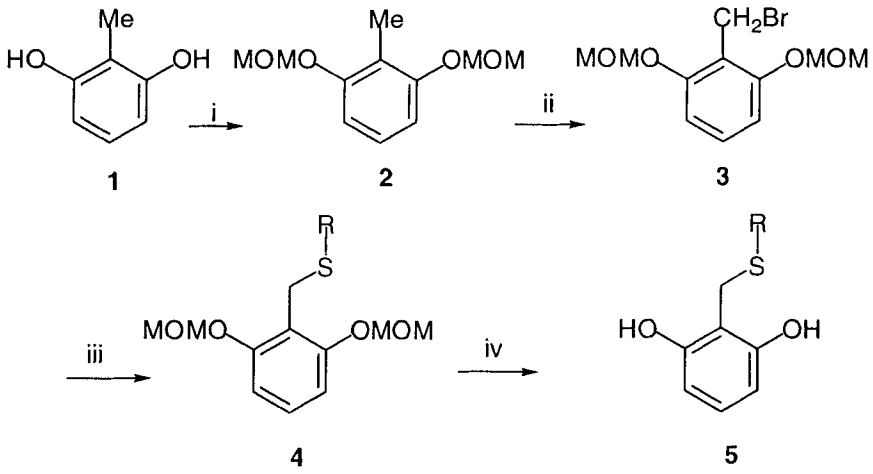
construction of calixresorcinarene frameworks. However, to the best of our knowledge, there is no report on the synthesis of these types of resorcinols.

We, therefore, focused our attention on the preparation of 2-(thiomethyl)resorcinols **5** starting from commercially available 2-methylresorcinol **1**. Its hydroxyl groups were protected by conversion to the methoxymethyl (MOM) ether. Radical bromination of the MOM derivative **2** with NBS in the presence of AIBN in CCl_4 gave the bromide **3** in quantitative yield. The reaction of **3** and the appropriate thiol was carried out in the presence of base in ethanol. Removal of the protecting groups was conducted by treatment with HCl in methanol. Since the C-S bond of the 2,6-dihydroxybenzylthio function is slowly cleaved under acidic conditions, the deprotection resulted in formation of some unidentified by-products. Thus, the crude products were purified by dry column chromatography and recrystallized from appropriate solvents.

The structures of the resorcinols **5** was confirmed by elemental analysis and ^{1}H-NMR, ^{13}C-NMR and mass spectroscopies. In the ^{1}H NMR spectra, the methylene signals of the thiomethyl groups for the arylthiomethyl derivatives **5a-5d** appear at δ 4.2-4.4, and the corresponding signals for the alkylthiomethyl derivatives **5e-5g** appear at δ 3.9-3.95. The hydroxy protons resonate at δ 5.4 for **5a-5d** and at δ 5.8 for **5e-5g**. The downfield shifts of the hydroxy protons as compared with those of 2-alkylresorcinols (ca. δ 4.7) suggest a hydrogen bonding interaction between the OH and S atom.

In summary, we have achieved a four-step synthesis of a range of resorcinols possessing thiomethyl groups at their 2-positions in 28 - 47% overall yields based

on commercially available material **1**. This procedure will be useful for the preparation of some 2-substituted resorcinols.



a: Phenyl
b: 4-Tol
c: 4-ClC_6H_4
d: 2-Naphthyl
e: *n*-Hex
f: *n*-Oct
g: *tert*-Bu

Reaction conditions (i) CH_3OCH_2Cl / K_2CO_3 / 18-crown-6 /MeCN / rt / 75 h / 77% (ii) NBS / AIBN / CCl_4 / reflux / 7 h / 100% (iii) RSH / KOH / EtOH / reflux / 9 h (iv) HCl / MeOH / 25 °C / 8 h / 31 – 61% from **3**.

EXPERIMENTAL

Melting points were taken on a MEL-Temp apparatus (Laboratory Devices) and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a JEOL GX-270 spectrometer, and the chemical shifts are reported as δ values. The ^1H NMR spectra are referenced to tetramethylsilane, and the ^{13}C NMR spectra are referenced to $CDCl_3$ (77.00). Infrared spectra were taken with a Perkin Elmer 1610

spectrophotometer. All solvents were deaerated by purging with argon. Other chemicals were reagent grade, and were used without further purification. Dry column chromatography was done on silica gel (Merck Art 10757, Silica gel 60F 254). Preparative thin layer chromatography was done on silica gel (Merck Art 7747, Silica gel 60 PF254). Microanalytical samples were dried for at least 8 h at 80 °C at reduced pressure. Analyses were performed at the Microanalysis Center of Kyoto University. Mass spectra were recorded on a JEOL Automass 20 spectrometer at the Center for Joint Research and Development of Tottori University.

1,3-Bis(methoxymethoxy)-2-methylbenzene (2). A mixture of 2-methylresorcinol **1** (496 mg, 4.0 mmol), 18-crown-6 (530 mg, 2.0 mmol), and K_2CO_3 (2.76 g, 20 mmol) in CH_3CN (15 mL) was stirred at 25 °C under Ar for 0.5 h. To this mixture was added a solution of chloromethyl methyl ether (1.60 g, 20 mmol) in CH_3CN (5 mL). After further stirring for 75 h, the insoluble material was removed by suction, and the filtrate was concentrated to dryness. The resulting residue was dissolved in diethyl ether, washed with 10% NaOH, and dried (Na_2SO_4). The solvent was removed under reduced pressure on a rotary evaporator to give a semisolid material, which was purified by Kugelrohr distillation (40 Pa, 110 °C); yield 654 mg (77%), mp 42-45 °C. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.02; H, 7.61. Found: C, 62.25; H, 7.60. IR (KBr) ν = 2953, 2845, 1596, 1472, 1440, 1108 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 2.16 (s, 3H, Ar-$\underline{CH_3}$), 3.49 (s, 6H, OCH_3), 5.18 (s, 4H, OCH_2O), 6.73-7.09 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$) δ = 8.6, 56.0, 94.8, 108.2, 116.9, 126.3, 156.2.

2-(Bromomethyl)-1,3-bis(methoxymethoxy)benzene (3). A mixture of the MOM ether **2** (106 mg, 0.50 mmol), NBS (100 mg, 0.55 mmol) and AIBN (8

mg, 0.05 mmol) in CCl_4 was heated at reflux for 7 h. To the reaction mixture were added H_2O (20 mL) and $CHCl_3$ (25 mL). The organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent in vacuo yielded the bromomethyl derivative **3** as a light yellow oil, which was used for the next reaction without further purification; yield 140 mg (100%). MS m/z 290. IR (KBr) ν = 2900, 2848, 1596, 1470, 1401, 1108 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 3.52 (s, 6H, OCH_3), 4.72 (s, 2H, Ar-$\underline{CH_2}$Br), 5.26 (s, 4H, OCH_2O), 6.74-7.22 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$) δ = 23.2, 56.3, 94.3, 107.7, 116.3, 130.0, 156.0.

2-Thiomethylated Resorcinols 5; General procedure. To a mixture of thiol (4.0 mmol) and KOH (168 mg, 4.0 mmol) in EtOH (5 mL) was added a solution of the bromide **3** (1.17 g, 4.0 mmol) in EtOH (13 mL). The mixture was heated at reflux for 9 h. After removal of the insoluble material by suction, the filtrate was evaporated in vacuo. The resulting residue was dissolved in EtOAc, and washed with water. Removal of the solvent in vacuo yielded a light yellow oil, which was dissolved in MeOH (8 mL). To this was dropwise added concd. HCl (0.8 mL), and the solution was stirred for 8 h at 25 °C. The mixture was then diluted with water, and extracted with EtOAc. The organic layer was dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. The residual material was purified by dry column chromatography or preparative thin layer chromatography.

2-[(Phenylthio)methyl]-1,3-dihydroxybenzene (5a). Purification by dry column chromatography (EtOAc/hexane 1/2) gave **5a** as a light yellow oil, which was recrystallized from chloroform/toluene to produce a crystalline material in 50 % yield; mp 105-107 °C. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; S, 13.80. Found: C, 66.60; H, 5.21; S, 13.89. MS m/z 232. IR (KBr) ν = 3316, 1610,

1467, 1001 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.28 (s, 2H, CH_2), 5.45 (s, 2H, OH), 6.39 (d, 2H, ArH, *J* = 8.1Hz), 6.97 (t, 1H, ArH, *J* = 8.1Hz), 7.16-7.29 (m, 3H, ArH), 7.38-7.42 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 28.0, 108.8, 110.0, 127.0, 128.9, 130.6, 131.0, 134.6, 155.4.

2-[(4-Methylphenylthio)methyl]-1,3-dihydroxybenzene (5b). Purification by preparative TLC (EtOAc/hexane 1/2) and recrystallization from chloroform gave **5b** as a light vague crystalline material in 45% yield; mp 132-134 °C. Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.27; H, 5.73; S, 13.02. Found: C, 67.97; H, 5.77; S, 12.92. MS m/z 246. IR (KBr) ν = 3341, 1611, 1466, 1001 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 2.30 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 5.47 (s, 2H, OH), 6.39 (d, 2H, *J* = 8.1 Hz, ArH), 6.97 (t, 1H, *J* = 8.1 Hz, ArH), 7.05-7.31 (AA'BB', 4H, ArH). ^{13}C NMR ($CDCl_3$) δ = 21.0, 28.6, 108.8, 110.3, 128.7, 129.7, 130.7, 131.3, 137.3, 155.4.

2-[(4-Chlorophenylthio)methyl]-1,3-dihydroxybenzene (5c). Purification by dry column chromatography (EtOAc/hexane 1/2) and recrystallization from chloroform afforded **5c** as a light yellow solid in 45% yield; mp 125-130 °C. Anal. Calcd for $C_{13}H_{11}O_2SCl$: C, 58.54; H, 4.16; S, 12.02. Found: C, 58.54; H, 4.16; S, 11.92. MS m/z 266. IR (KBr) ν = 3345, 1614, 1466, 999 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.25 (s, 2H, CH_2), 5.38 (s, 2H, OH), 6.38 (d, 2H, *J* = 8.1 Hz, ArH), 6.98 (t, 1H, *J* = 8.1 Hz, ArH), 7.17-7.34 (AA'BB', 4H, ArH). ^{13}C NMR ($CDCl_3$) δ = 28.0, 108.7, 109.9, 128.9, 129.7, 132.0, 133.0, 133.2, 155.3.

2-[(2-Naphthylthio)methyl]-1,3-dihydroxybenzene (5d). Purification by dry column chromatography (EtOAc/hexane 1/2) and recrystallization from

chloroform gave **5d** as a pink solid in 42% yield; mp 142-146 °C. Anal. Calcd for $C_{17}H_{14}O_2S$: S, 11.35. Found: S, 11.14. MS m/z 282. IR (KBr) ν = 3396, 3053, 1613, 1500, 1467, 1002 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.38 (s, 2H, CH_2), 5.46 (s, 2H, OH), 6.38 (d, 2H, *J* = 8.1 Hz, ArH), 6.97 (t, 1H, *J* = 8.1 Hz, ArH), 7.40-7.85 (m, 7H, ArH). ^{13}C NMR ($CDCl_3$) δ = 28.1, 108.9, 110.3, 126.0, 126.5, 127.3, 127.7, 128.3, 128.4, 128.8, 129.2, 132.25, 132.28, 133.8, 155.5.

2-[(Hexylthio)methyl]-1,3-dihydroxybenzene (5e). Purification by preparative TLC (EtOAc/hexane 1/2) and recrystallization from chloroform/hexane gave **5e** as a white solid in 31% yield; mp 52-54 °C. Anal. Calcd for $C_{13}H_{20}O_2S$: S, 13.34. Found: S, 13.25. MS m/z 240. IR (KBr) ν = 3321, 2920, 1616, 1463, 1001 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 0.84-1.63 (m, 11H, $(CH_2)_4CH_3$), 2.44 (t, 2H, *J* = 8.1 Hz, SCH_2), 3.91 (s, 2H, $ArCH_2$), 5.84 (s, 2H, OH), 6.43 (d, 2H, *J* = 8.1 Hz, ArH), 7.00 (t, 1H, *J* = 8.1 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.0, 22.5, 24.5, 28.4, 29.1, 30.9, 31.3, 108.7, 110.1, 128.5, 155.8.

2-[(Octylthio)methyl]-1,3-dihydroxybenzene (5f). Purification by preparative TLC (silica gel EtOAc/hexane 1/3) and recrystallization from chloroform/hexane afforded **5f** as a white solid in 43% yield; mp 54-55 °C. Anal. Calcd for $C_{15}H_{24}O_2S$: C, 67.12; H, 9.01; S, 11.94. Found: C, 66.84; H, 9.08; S, 12.10. MS m/z 268. IR (KBr) ν = 3335, 2921, 1615, 1463, 1009 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 0.84-1.63 (m, 15H, $(CH_2)_6CH_3$), 2.43 (t, 2H, *J* = 7.3 Hz, SCH_2), 3.90 (s, 2H, $ArCH_2$), 5.82 (s, 2H, OH), 6.43 (d, 2H,*J* = 8.1 Hz, ArH), 7.00 (t, 1H,*J* = 8.1 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.0, 22.6, 24.5, 28.8, 29.06, 29.09, 29.12, 31.0, 31.8, 108.7, 110.1, 128.5, 155.8.

2-[(1,1-Dimethylethylthio)methyl]-1,3-dihydroxybenzene (5g).

Purification by preparative TLC (silica gel EtOAc/hexane 1/2) and recrystallization from chloroform gave **5g** as a white solid in 61% yield; mp 54-55 °C. Anal. Calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60; S, 15.10. Found: C, 62.01; H, 7.69; S, 15.21. MS m/z 212. IR (KBr) ν = 3432, 3264, 2965, 1613, 1467, 1001 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 1.38 (s, 9H, CH_3), 3.95 (s, 2H, $ArCH_2$), 5.83 (s, 2H, OH), 6.42 (d, 2H, *J* = 8.1 Hz, ArH), 6.99 (t, 1H, *J* = 8.1 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ = 22.3, 30.6, 43.7, 108.9, 110.7, 128.4, 155.4.

REFERENCES

(1) Konishi, H.; Yamaguchi, H.; Miyashiro, M.; Kobayashi, K. and Morikawa, O. *Tetrahedron Lett.*, **1996**, *37*, 8547.

(2) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.

(3) Konishi, H. and Morikawa, O. *J. Chem. Soc., Chem. Commun.*, **1993**, 34.

(4) Konishi, H.; Ohata, K.; Morikawa, O. and Kobayashi, K. *J. Chem. Soc., Chem. Commun.*, **1995**, 309.

(5) Konishi, H. and Iwasaki, Y. *Synlett*, **1995**, 612.

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