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Selective *ipso*-Nitration of tert-Butylcalix[4]arene Tripropylether

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Abstract: An improved selective *ipso*-nitration of the tripropoxy derivative of tert-butylcalix[4]arene at the upper rim is described. The synthesized products are key intermediates for construction of molecular receptors based on calixarenes.

Keywords: Ipso-nitration, calixarenes.

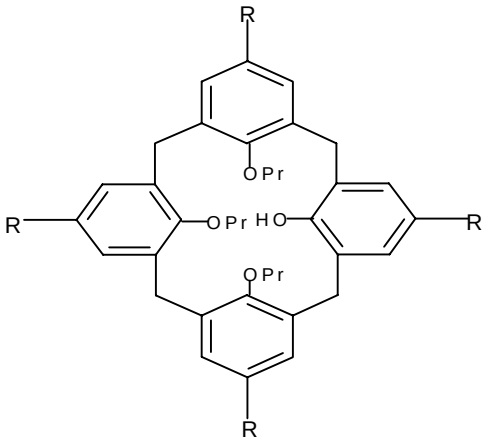
Introduction

Calix[4]arenes have attracted considerable interest as building blocks for constructing selective host molecules [1]. Upper rim functionalised compounds can be obtained in a multi-step procedure from suitably substituted precursors [2]. Mono and dinitrated calix[4]arene are especially useful for this purpose. Several methods have been reported for selective substitution of nitro groups at the upper rim [3-5]. Selective *ipso*-nitration of partial ethers has only been described for a few ethers of tert-butylcalix[4]arene [6-9]. In this paper we report the selective substitution of one or two nitro group(s) by direct replacement of tert-butyl group(s) via an *ipso*-aromatic nitration. These compounds afford important starting materials for the construction of molecular receptors based on calixarenes.

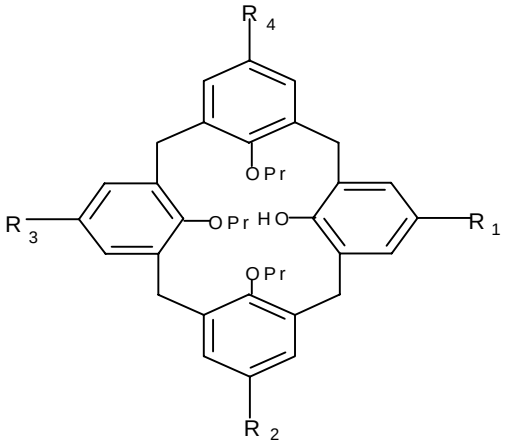
Results and Discussion

The cone conformation of 5,11,17,23-tetra-tert-butyl-25-hydroxy-26,27,28-tripropoxycalix[4]arene (**1**) reacts with 10 eq. of 63% HNO_3 in a mixture of dichloromethane and glacial acetic acid in less than 5 min. to afford the 23-mononitro calix(4)arene **2** in 85% yield. Compared to the published procedure [7], the present method offers both milder reaction conditions and an improved yield. In the ^{1}H-NMR spectrum of **2**, the aromatic meta protons in the nitrated phenolic ring shift downfield from δ 5.41 (in **1**) to δ 7.22 (in **2**), and the protons ortho to the nitro group appears at δ 8.06. The ^{1}H-NMR spectrum of

2 exhibits two doubles of doublets signals for the bridge methylene protons, indicating the symmetrical structure of **2**.



1: R = tert-butyl



2: $R_1 = NO_2$, $R_2 = R_3 = R_4 =$ *tert*-butyl
3: $R_1 = NO_2$, $R_3 = NO_2$, $R_2 = R_4 =$ *tetr*-butyl
4: $R_1 = NO_2$, $R_2 = NO_2$, $R_3 = R_4 =$ *tert*-butyl

Figure 1.

Treatment of **1** with 10 equivalents of 63% HNO_3 for 5 min. in dichloromethane and in presence of Ac_2O, afforded the dinitro compounds **3** and **4** in a ratio of 3:1, judged from the ^{1}H-NMR of the crude reaction mixture. The spectrum of **3** exhibits two doublets of doublets for the bridge methylene protons, indicating a central plane of symmetry. The spectrum of **4** exhibits four doublets of doublets signals for the bridge methylene protons indicating an asymmetric molecule. Symmetrical dinitro derivatives of calix[4]arene have been synthesized from the diether precursors [3], however by the present procedure the chiral dinitro derivative **4** is obtained. This compound could be used as a starting material to build up chiral hosts based on calix[4]arene to mimic the enzyme functions [1].

Experimental

General

Melting points are taken on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-400 MHz in $CDCl_3$ with Me_4Si as an internal standard. Elemental analysis were carried out on Carlo-Erba-Analyser Model 1104. IR spectra were recorded on a Bruker IFS-25 spectrophotometer. The calix(4)arene **1** was prepared according to the published procedure [10].

Procedure for the preparation of **2**

To a solution of 10g (12.9 mmol) **1** in dichloromethane (50mL) and glacial acetic acid (30 mL), 63% HNO_3 (5 mL) was added dropwise at -15°C in 2 min and the reaction mixture was then stirred at room temperature for 4 min and poured into water (250 mL). The organic layer was extracted with dichloromethane (2x100mL), the solvent was removed and solid residue was dissolved in methanol (100

mL), concentration of solution to a volume of ca. 50 mL led to the appearance of a pale yellow precipitate (yield 85%).The product thus obtained was pure enough for subsequent reactions but could be further purified by recrystallization from a mixture of dichloromethane and methanol; mp 182-184°C.

IR ν_{max} (KBr)/cm^{-1} 3456, 1592, 1472, 1334, 1201, 1006; δH(400 MHz; $CDCl_3$) 0.83[18H, s, $C(CH_3)_3$)], 0.95[3H, t, CH_3], 1.10 [6H, t, CH_3], 1.35[9H, s, $C(CH_3)_3$], 1.93[4H, m, CH_2], 2.2[2H, m, CH_2], 3.19 and 4.34[4H, d of d, J=12.6 Hz, $ArCH_2$ Ar], 3.75[2H, t, OCH_2], 3.81[4H, t, O CH_2], 3.39 and 4.31[4H, d of d, J=13.9 Hz, $ArCH_2$ Ar], 6.45[2H, d, J=2.3 Hz, ArH], 6.60[2H, d, J=2.3Hz, ArH], 7.16[2H, s, ArH], 7.22[1H, s, OH], 8.06[2H, s, ArH]; δC(100 MHz) 9.56, 10.70, 22.55, 23.37, 31.10, 31.36, 31.47, 31.68, 33.74, 34.15, 58.46, 76.15, 78.01, 124.31, 125.68, 125.70,129.80, 132.65, 135.76, 139.34, 145.82, 151.75, 153.78, 159.98; M/Z (FD) 764(m^+ , 100%). Anal. Calcd for $C_{49}H_{65}NO_6$: C, 77.06%; H, 8.52%; N, 1.84%. Found C, 76.8%, H, 8.7%; N, 2.2%.

Procedure for the preparation of **3** and **4**

To a solution of 2g (2.58 mmol) **1** in dichloromethane (25mL) and acetic anhydride (4mL) at -10°C, 63% HNO_3 (1 mL) was added in 2 min and the reaction mixture was then stirred at room temperature for 5 min and poured into water (250mL). The organic layer was extracted by dichloromethane (2x100mL), the solvent was removed and the solid residue was dissolved in methanol (100mL), concentration of solution to ca. 50 mL led to a white precipitate. **3** is obtained as a white crystals in 63% separated yield (crystallized from a mixture of CH_2Cl_2 and CH_3OH). mp, 214-217°C; **4** was purified by column chromatography of the mother liquors (silicagel, CH_2Cl_2 , n-hexane, 1:4); yield 22% mp, 225-228°C.

Spectral data for **3**

IR ν_{max} (KBr)/cm^{-1} 3510, 1598, 1513, 1343 and 1014. δH(400 MHz; $CDCl_3$) 0.86[18H, s, $C(CH_3)_3$], 0.97[3H, t, CH_3], 1.11 [6H, t, CH_3],1.94 [4H, m, CH_2], 2.22[2H, m, CH_2], 3.35 and 4.42[4H, d of d, J=12.9 Hz, $ArCH_2Ar$], 3.78[4H, t, OCH_2], 3.96[2H, t, OCH_2], 3.43, 4.29[4H, d of d, J=13.8 Hz, $ArCH_2Ar$], 6.56[4H, s, ArH], 7.37[1H, s, OH], 8.07[2H, s, ArH], 8.10[2H, s, ArH]; δC(100 MHz) 9.48, 10.66, 22.44, 23.40, 33.01, 31.13, 31.43, 33.87, 76.67, 78.15, 124.12, 124.46, 125.28, 125.46, 129.43, 130.30, 130.98, 138.06, 140.10, 143.05, 146.64; 151.83, 159.70, 164.05; M/Z (FD) 753(m^+, 100%). Anal. Calcd for $C_{45}H_{56}N_2O_8$: C, 71.79%; H, 7.50%; N, 3.72%. Found C, 71.5%, H, 7.5%; N, 3.1%.

Spectral data for **4**

IR ν_{max} (KBr)/cm^{-1} 3508, 1592, 1521, 1341 and 1005. δH(400 MHz; $CDCl_3$) 0.74[9H, s, $C(CH_3)_3$], 0.92[3H, t, CH_3], 1.12 [3H, t, CH_3], 1.13[3H, t, CH_3], 1.40[9H, s, $C(CH_3)_3$], 1.90 [2H, m, CH_2], 2.08[2H, m, CH_2], 2.23[2H, m,CH_2], 3.21 and 4.40[2H, d of d, J=13.1 Hz, $ArCH_2Ar$], 3.25 and 4.30[2H, d of d, J=13.0 Hz, $ArCH_2Ar$], 3.42 and 4.46[2H, d of d, J=13.7 Hz, $ArCH_2Ar$], 3.51 and 4.20[2H, d of d, J=14.5 Hz, $ArCH_2Ar$], 3.77[6H, m, OCH_2], 6.17[1H, s, OH], 6.45[1H, d, J=2.1 Hz, ArH], 6.51[1H, d, J=2.1 Hz, ArH], 7.21[1H, d, J=2.3 Hz, ArH], 7.22[1H, d, J=2.6 Hz, ArH], 7.24[1H, d, J=2.2 Hz, ArH], 7.27[1H, d, J=2.6 Hz, ArH], 8.11[1H, d, J=2.5 Hz, ArH], 8.14[1H, d, J=2.5 Hz,

ArH]; δC(100 MHz) 9.43, 10.69, 10.71, 22.52, 23.34, 23.46, 30.63, 30.80, 31.05, 31.08, 31.63, 34.01, 34.30, 76.45, 77.63, 78.24, 122.31, 123.51, 124.30, 124.66, 124.77, 125.88, 126.72, 126.77,128.64, 128.77, 129.94, 133.56, 133.78, 134.80, 135.08, 136.00, 139.93, 142.81, 146.78, 147.54, 150.68, 153.79, 159.31, 161.73; M/Z (FD) 753(m^+, 100%). Anal. Calcd for $C_{45}H_{56}N_2O_8$: C, 71.79%; H, 7.50%; N, 3.72%. Found C, 71.6%, H, 7.5%; N, 3.1%.

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Sample Availability: Available from the authors.