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ORIGINAL ARTICLE

Preparative synthesis of *para*-tert-butylcalix[4]arene monoalkyl ethers

Yuriy I. Matvieiev · Vyacheslav I. Boyko · Anna A. Podoprigorina · V. I. Kalchenko

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Abstract A new simple method of synthesis of monoalkoxy-*p*-tert-butylcalix[4]arenes by the selective dealkylation of 25,26-dialkoxy-*p*-tert-butylcalix[4]arenes with anhydrous aluminum chloride was developed.

Keywords Aluminum chloride · Calix[4]arene · Dealkylation · Monoalkoxy-*p*-tert-butylcalixarenes

Introduction

Design of highly selective receptors on the basis of calixarenes is an intensively developing branch of supramolecular chemistry [1, 2]. The ready availability of calixarenes and versatility of derivatization at the upper and/or lower rim(s) make this family of compounds one of the prime building blocks for supramolecular chemistry [3–9]. Calix[4]arene monoalkyl ethers are interesting as precursors for the construction of heterofunctionalized host molecules. The last decades they are increasingly more used in the synthesis of inherently chiral calixarenes, the chirality of which is determined by asymmetric position of the substituents at the upper or lower macrocycle rim [10–14].

Tert-butyl depleted monoalkoxycalix[4]arenes are obtained in roughly 75% yield by the reaction of tetrahydroxycalix[4]arene with excess amount of alkyl halides in presence of one equivalent of NaOMe [15]. However, direct alkylation of tert-butyl tetrahydroxycalix[4]arene with alkyl halides in the presence of one equivalent of the base (K_2CO_3, CsF [16], NaH [17], $(Bu_3Sn)_2O$ [18]) is less selective and gives the complicated mixture of monoalkoxy-
calixarenes with considerable amounts of deeper alkylation products and unreactive starting tert-butyl tetrahydroxycalixarene. Several indirect methods of synthesis of monoalkoxy-*p*-tert-butylcalixarenes involve preliminary protection of three hydroxyl groups of tetrahydroxycalixarene [19, 20], or selective dealkylation of di- or tetraalkoxycalixarenes with iodotrimethylsilane [21]. However, these methods are preparatively inconvenient.

In the presented paper we propose a convenient method for the synthesis of monoalkoxy-*p*-tert-butylcalix[4]arenes by selective dealkylation of 25,26-dialkoxy-*p*-tert-butylcalix[4]arenes with anhydrous aluminum chloride. 25,26-Dialkoxy-*p*-tert-butylcalix[4]arenes are easily available via the reaction of *p*-tert-butylcalix[4]arenetetrole with alkyl halides in DMSO-NaOH system [22].

Experimental

Melting points were determined on a Boëtius apparatus and are uncorrected. All the reactions were carried out in anhydrous solvents. ^{1}H NMR spectra were recorded on Varian VXR-300 spectrometer with frequency 300 MHz (TMS as internal standard). 25,26-Dialkoxycalixarenes **2a,c** were obtained by the alkylation of *p*-tert-butylcalix[4]arenetetrole **1** in DMSO-NaOH system [22]. Aluminum chloride, anhydrous 99%, from Lancaster was used without further purification.

Y. I. Matvieiev · V. I. Boyko · A. A. Podoprigorina · V. I. Kalchenko (✉)
Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kyiv-94, Murmanska str., 5, 02660 Kyiv, Ukraine
e-mail: vik@bpci.kiev.ua

Synthesis of 25,26-dialkoxycalix[4]arenes **2b,d**

General procedure

The mixture of *p*-tert-butylcalix[4]arenetetrole **1** (1.35 mmol), sodium hydroxide (1 mL 13 M soln NaOH) and DMSO (10 mL) was warmed to 50 °C. Alkyl bromide (5.4 mmol) was added without solvent and the mixture was stirred for 4 h at 75–80 °C. After cooling to 20 °C the reaction mixture was poured into 20 mL 1 M hydrochloric acid. Compound **2b** was filtered off, dried and crystallized from acetonitrile. Compound **2d**—oily residue—was stirred for 40 min with 30 mL water for removal of residual quantity of DMSO, then after water decantation refluxed for 2 h with 20 mL methanol and after cooling to 20 °C stirred still 12 h. The solid product formed was filtered off, washed with methanol (10 mL) and dried.

5,11,17,23-tetra-tert-butyl-25,26-dibutoxy-27, 28-dihydroxycalix[4]arene **2b**

White solid: yield 77%. Mp 119–122 °C.

^{1}H NMR ($CDCl_3$), δ: 1.05 (t, 6H, $OCH_2CH_2CH_2\mathbf{C}H_3$, $J^3_{H-H} = 7.2$ Hz), 1.11 (s, 18H, t-Bu), 1.20 (s, 18H, t-Bu), 1.53–1.63 (m, 4H, $OCH_2CH_2\mathbf{C}H_2CH_3$), 2.02–2.13 (m, 4H, $OCH_2CH_2CH_2CH_3$), 3.32 (d, 1H, Ar-CH_2-eq, $J^2_{H-H} = 13.4$ Hz), 3.33 (d, 1H, Ar-CH_2-eq, $J^2_{H-H} = 12.5$ Hz), 3.34 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 13.1$ Hz), 3.85–3.95 (m, 2H, $OCH_2CH_2CH_2CH_3$-diastereotopic), 4,03–4.12 (m, 2H, $OCH_2CH_2CH_2CH_3$-diastereotopic), 4.31 (d, 1H, Ar-CH_2-ax, $J^2_{H-H} = 13.4$ Hz), 4.32 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 13.1$ Hz), 4.48 (d, 1H, Ar-CH_2-ax, $J^2_{H-H} = 12.5$ Hz), 6.90 (d, 2H, ArH, $J^4_{H-H} = 2.2$ Hz), 6.96 (d, 2H, ArH, $J^4_{H-H} = 2.5$ Hz), 6.98 (d, 2H, ArH, $J^4_{H-H} = 2.2$ Hz), 7.00 (d, 2H, ArH, $J^4_{H-H} = 2.5$ Hz), 8.92 (s, 2H, OH). Anal. Found: C 81.45; H 9.60. Calc. for $C_{52}H_{72}O_4$: C 82.06, H 9.53.

5,11,17,23-tetra-tert-butyl-25,26-didecyloxy-27, 28-dihydroxycalix[4]arene **2d**

White solid: yield 57%. Mp 77–78 °C.

^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 6H, $OCH_2CH_2(CH_2)_7CH_3$), 1.13 (s, 18H, t-Bu), 1.21 (s, 18H, t-Bu), 1.24–1.53 (m, 28H, $OCH_2CH_2(CH_2)_7CH_3$), 2.03–2.15 (m, 4H, $OCH_2CH_2(CH_2)_7CH_3$), 3.28–3.38 (3d overlapped, 4H, Ar-CH_2-eq, $J^2_{H-H} = 13.4, 12.5, 12.7$ Hz), 3.91–4.06 (2m, 2H each, $OCH_2CH_2(CH_2)_7CH_3$), 4.32, 4.33, 4.48 (3d, 2H, 1H, 1H, Ar-CH_2-ax, $J^2_{H-H} = 12.7, 13.4, 12.5$ Hz), 6.98, 6.94 (2d, 4H, ArH, $J^4_{H-H} = 2.2, 2.5$ Hz), 6.99–7.03 (2d overlapped, 4H, ArH), 8.83 (s, 2H, OH). Anal. Found: C 82.76, H 10.37. Calc. for $C_{64}H_{96}O_4$.: C 82.70, H 10.41.

5,11,17,23-tetra-tert-butyl-25-propoxy-26,27, 28-trihydroxycalix[4]arene **3a**

To a solution of 25,26-dipropoxycalixarene **2a** (1.37 g, 1.87 mmol) in benzene (50 mL), anhydrous $AlCl_3$ (0.5 g, 3.75 mmol) was added. The reaction mixture was stirred at 75–80 °C for 3 h. After cooling to room temperature, 10% HCl (50 mL) was added to the reaction mixture and stirred at room temperature for 1 h. The pink color of the reaction mixture has changed to yellow. The organic layer was separated, washed with water (2 × 20 mL), with brine (20 mL) and dried over $CaCl_2$. The solvent was evaporated, oily residue was treated with hexane (10 mL) and evaporated again. The residue was refluxed for 30 min with methanol (20 mL) and cooled to room temperature. The precipitate was filtered off and dried in the open air to give 0.96 g (75%) of monopropoxycalix[4]arene **3a** as colorless crystalline substance. Mp 236–238 °C (238–239°C [17]).

^{1}H NMR ($CDCl_3$), δ: 1.18–1.29 (m, 39H, t-Bu, $OCH_2CH_2CH_3$), 2.15–2.23 (m, 2H, $OCH_2CH_2CH_3$), 3.43 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 12.9$ Hz), 3.44 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 13.6$ Hz), 4.11 (t, 2H, $OCH_2CH_2CH_3$, $J^3_{H-H} = 6.7$ Hz), 4.28 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 13.6$ Hz), 4.37 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 12.9$ Hz), 6.99, 7.05, 7.07, 7.10 (d, s, d, and s, respectively, 2H each, ArH), 9.61 (s, 2H, OH), 10.20 (s, 1H, OH).

5,11,17,23-tetra-tert-butyl-25-butoxy-26,27, 28-trihydroxycalix[4]arene **3b**

To a solution of 25,26-dibutoxycalixarene **2b** (0.25 g, 0.33 mmol) in benzene (15 mL), anhydrous $AlCl_3$ (0.086 g, 0.65 mmol) was added and stirred at room temperature for 72 h. The solvent was evaporated, chloroform (10 mL) and 10% HCl (10 mL) were added. Organic layer was separated, washed with water (2 × 10 mL) and dried over sodium sulfate. The solvent was evaporated to give colorless crystalline substance **3b**. Yield 0.147 g (63%). Mp 203–206 °C.

^{1}H NMR ($CDCl_3$), δ: 1.09–1.24 (m, 39H, t-Bu, $OCH_2CH_2CH_2CH_3$), 1.24–1.28 (m, 2H, $OCH_2CH_2CH_2CH_3$), 2.07–2.16 (m, 2H, $OCH_2CH_2CH_2CH_3$), 3.41 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 12.8$ Hz), 3.44 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 13.7$ Hz), 4.13 (t, 2H, $OCH_2CH_2CH_2CH_3$, $J^3_{H-H} = 6.8$ Hz), 4.28 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 13.7$ Hz), 4.35 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 12.8$ Hz), 6.98 (d, 2H, ArH, $J^4_{H-H} = 2.2$ Hz), 7.04 (s, 2H, ArH), 7.06 (d, 2H, ArH, $J^4_{H-H} = 2.2$ Hz), 7.09 (s, 2H, ArH), 9.61 (s, 2H, OH), 10.20 (s, 1H, OH).

^{13}C NMR ($CDCl_3$), δ: 13.83, 19.15, 31.15, 31.36, 31.40, 31.42, 31.82, 32.25, 32.95, 33.80, 33.88, 34.10, 125.25, 125.35, 125.40, 126.06, 127.39, 127.80, 128.04, 133.19, 142.72, 143.26, 147.40, 147.64, 148.18, 149.14.

Anal. Found: C 81.60, H 9.24. Calc. for $C_{48}H_{64}O_4$: C 81.77, H 9.15.

5,11,17,23-tetra-tert-butyl-25-octyloxy-26,27,28-trihydroxycalix[4]arene **3c**

To a solution of 25,26-dioctyloxycalixarene **2c** (0.43 g, 0.5 mmol) in benzene (20 mL), anhydrous $AlCl_3$ (0.13 g, 1.0 mmol) was added and stirred at room temperature for 18 h. About 10% Hydrochloric acid (20 mL) was added to the reaction mixture. Organic layer was separated, washed with water (2 × 20 mL), with brine (20 mL) and dried over sodium sulfate. The solvent was evaporated, methanol (15 mL) was added to the oily residue and boiled for 1 h. The mixture was cooled to room temperature and stirred for 12 h. to give white crystalline residue **3c**, which was filtered off and dried. Yield 0.29 g (76%). Mp 164–166 °C.

^{1}H NMR ($CDCl_3$), δ: 0.91 (t, 3H, $OCH_2CH_2(CH_2)_5CH_3$, $J^3_{H-H} = 7.2$ Hz), 1.20 (s, 9H, t-Bu), 1.21 (s, 18H, t-Bu), 1.23 (s, 9H, t-Bu), 1.27–1.51 (m, 10H, $OCH_2CH_2(CH_2)_5CH_3$), 2.11–2.19 (m, 2H, $OCH_2CH_2(CH_2)_5CH_3$), 3.41 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 13.1$ Hz), 3.44 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 13.4$ Hz), 4.13 (t, 2H, $OCH_2CH_2(CH_2)_5CH_3$, $J^3_{H-H} = 7.2$ Hz), 4.28 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 13.4$ Hz), 4.36 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 13.1$ Hz), 6.99 (d, 2H, ArH, $J^4_{H-H} = 2.5$ Hz), 7.05 (s, 2H, ArH), 7.06 (d, 2H, ArH, $J^4_{H-H} = 2.5$ Hz), 7.09 (s, 2H, ArH), 9.61 (s, 2H, OH), 10.20 (s, 1H, OH).

^{13}C NMR ($CDCl_3$), δ: 13.97, 22.56, 25.87, 29.11, 29.32, 29.77, 31.15, 31.36, 31.40, 31.70, 32.26, 32.95, 33.79, 33.87, 34.10, 125.25, 125.34, 125.40, 126.06, 127.40, 127.81, 128.04, 133.20, 142.70, 143.25, 147.42, 147.63, 148.20, 149.16.

Anal. Found: C 82.20, H 9.59. Calc. for $C_{52}H_{72}O_4$: C 82.06, H 9.53.

5,11,17,23-tetra-tert-butyl-25-decyloxy-26,27,28-trihydrocalix[4]arene **3d**

This compound was obtained similarly to compound **3c** from 25,26-didecyloxycalixarene **2d** (0.46 g, 0.5 mmol) in benzene (20 mL) and anhydrous $AlCl_3$ (0.13 g, 1.0 mmol). Yield 0.254 g (65%).

Mp 159–160 °C.

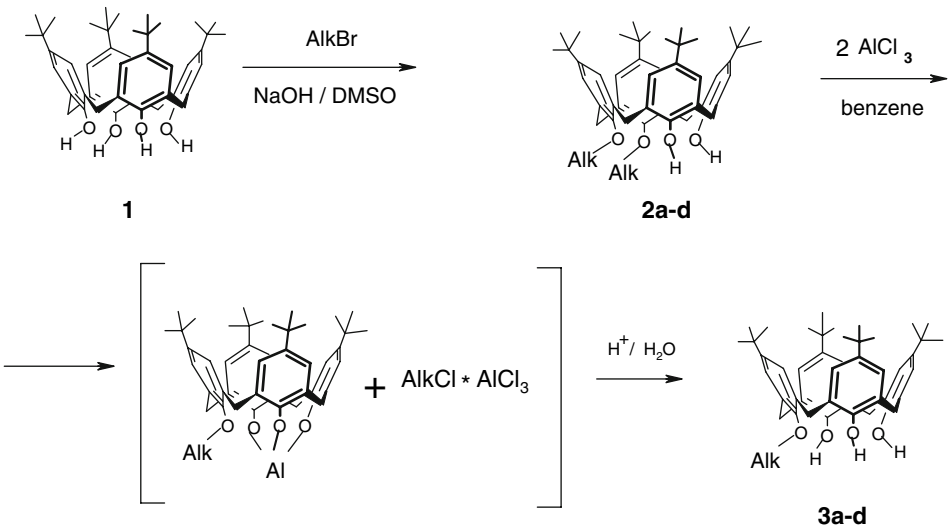
^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3H, $OCH_2CH_2(CH_2)_7CH_3$, $J^3_{H-H} = 7.2$ Hz), 1.20 (s, 9H, t-Bu), 1.22 (s, 18H, t-Bu), 1.23 (s, 9H, t-Bu), 1.25–1.49 (m, 14H, $OCH_2CH_2(CH_2)_7CH_3$), 2.11–2.21 (m, 2H, $OCH_2CH_2(CH_2)_7CH_3$), 3.42 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 12.8$ Hz), 3.44 (d, 2H, Ar-CH_2-eq, $J^2_{H-H} = 13.7$ Hz), 4.13 (t, 2H, $OCH_2CH_2(CH_2)_7CH_3$, $J^3_{H-H} = 7.2$ Hz), 4.28 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 13.7$ Hz), 4.36 (d, 2H, Ar-CH_2-ax, $J^2_{H-H} = 12.8$ Hz), 6.99 (d, 2H, ArH, $J^4_{H-H} = 2.5$ Hz), 7.05 (s, 2H, ArH), 7.06 (d, 2H, ArH, $J^4_{H-H} = 2.5$ Hz), 7.09 (s, 2H, ArH), 9.61 (s, 2H, OH), 10.20 (s, 1H, OH).

^{13}C NMR ($CDCl_3$), δ: 13.97, 22.58, 25.86, 29.21, 29.35, 29.45, 29.47, 29.77, 31.15, 31.37, 31.40, 31.81, 32.27, 32.95, 33.80, 33.87, 34.10, 125.25, 125.34, 125.40, 126.06, 127.40, 127.81, 128.04, 133.21, 142.70, 143.25, 147.42, 147.63, 148.20, 149.12.

Anal. Found: C 82.20, H 9.84. Calc. for $C_{54}H_{76}O_4$: C 82.18, H 9.71.

Results and discussion

As is well known, aluminum chloride is used for the exhaustive de-tert-butylation of tetrahydroxy-*p*-tert-butylcalix[4]arene [20] and for selective removal of two tert-butyl groups of 25,27-dimethoxy(ethoxy)-*p*-tert-butylcalixarenes



[23]. Surprisingly, tert-butyl groups of 25,26-dialkoxy-*p*-tert-butylcalix[4]arenes **2a–d** are not touched in the reaction with two moles of aluminum chloride. The removal of only one alkyl group from the lower rim of the compounds **2a–d** takes place. The reaction results in 63–76% yields of *p*-tert-butylcalix[4]arene monoalkyl ethers **3a–d**.

The selectivity of the reaction seems to be stipulated by formation of aluminate **A** which is hydrolized to the target monoalkyl ethers **3a–d** with the hydrochloric acid. The eliminated alkyl chloride is bound by aluminum chloride. The ease of dealkylation increases with increasing length of the alkyl substituent. Thus, the dealkylation of 25,26-dipropoxycalix[4]arene **2a** proceeds in benzene at 75–80 °C for 3 h. Dealkylation of 25,26-dialkoxycalix[4]arenes **2b–d** proceeds in benzene at room temperature for 72 h (**2b**) and for 18–20 h (**2c,d**).

In contrast to 25,26-dipropoxy-*p*-tert-butylcalix[4]arene **2a** depropylation of 25,27-dipropoxy-*p*-tert-butylcalix[4]arene [16] with aluminum chloride proceeds less selectively**.** Under analogous conditions of the synthesis, the yield of monopropoxycalix[4]arene **3a** constitutes 40%.

Monoalkyl ethers **3a–d** are colorless crystalline substances, their structure is confirmed by ^{1}H NMR method and elemental analysis.

Conclusion

In summary, we have developed the facile and preparatively convenient synthesis of *p*-tert-butylcalix[4]arene monoalkyl ethers by the reaction of easily available 25,26-dialkoxy-*p*-tert-butylcalix[4]arenes with aluminum chloride.

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