Functionalization of Calix[4]arene with Hydroxyalkyl Groups at Upper Rim

Kyung Lan Hwang, Si-Hyun Ham, and Kwang Hyun No*

Department of Chemistry, Sookmyung Women's University, Seoul 140-742. *Received August 8, 1992*

Synthetic routes are described for the introduction of hydroxyalkyl groups to the upper rim of calix[4]arene. Treatment of *p*-bromocalix[4]arene methyl ether **3** with *n*-BuLi followed by para-formaldehyde produced *p*-hydroxymethylcalix[4]arene methyl ether **4** in 60% yield. *p*-Acetylcalix[4]arene methyl ether **7**, obtained by Friedel-Crafts acetylation of calix[4]arene methyl ether **6**, was reduced with $NaBH_4$ to produce *p*-(1-hydroxy ethyl)calix[4]arene methyl ether **8** in 67% yield.

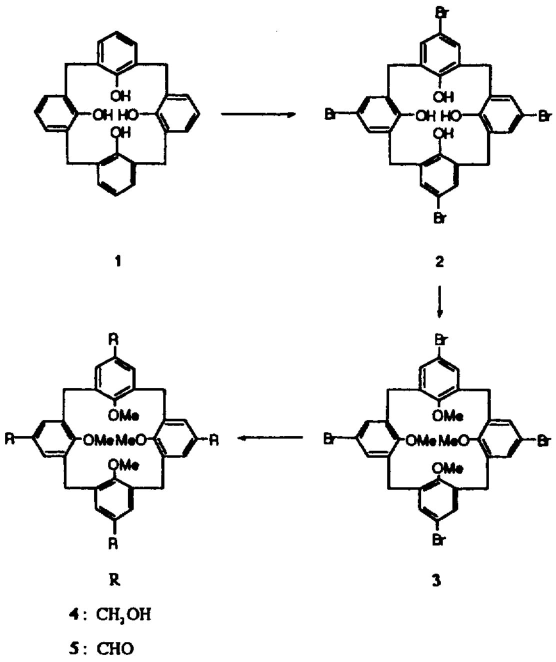
Introduction

Calix[4]arenes are molecules that are receiving increasing attention in the field of supramolecular chemistry, as they are very useful building blocks for host molecules with different properties[1]. The most pronounced features of calix[4]arenes are the relatively simple modification at both the lower rim (by reaction at the OH groups) and at the upper rim (after removal of tert-butyl groups). The cavity of the upper rim can be modified by introducing substituents at the para positions of the phenol rings of calix[4]arene **1**. Gutsche *et al* have described modification by direct substitution[2], via a Claisen rearrangement[3] and via an intermediate *p*-quinone methide[4]. Shinkai *et al* succeeded in sulfonation and nitration[5], Ungaro and coworkers reported the chloromethylation[6] and we have reported the nitration[7] and acylation[8,9]. Due to the fact that the hydroxy group plays an important role at the active site of several enzymes, and can be converted to other functional groups, the introduction of hydroxy groups at the para positions of calixarene has attracted our attention. The preparation of *p*-hydroxymethylcalix[4]arene by direct hydroxymethylation of calix[4]arene or condensation of *p*-hydroxymethylphenol and formaldehyde was not successful. This provides the starting point for the work reported in the present paper where we prepared calix[4]arenes functionalized with hydroxymethyl and 1-hydroxyethyl groups at para positions as shown on Scheme 1 and 2.

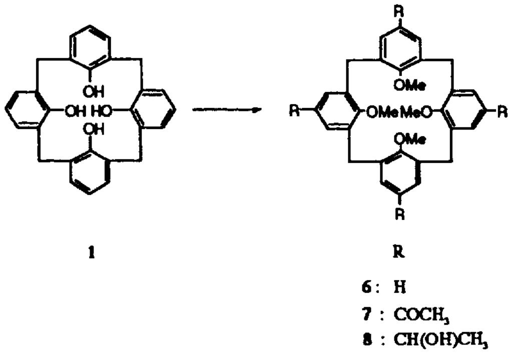
When calix[4]arene **1**[10], obtained by $AlCl_3$-catalyzed removal of the *tert*-butyl groups from *p*-*tert*-butylcalix[4]arene[11], was reacted with Br_2 in methylene chloride, the *p*-bromocalix[4]arene **2** was isolated in 85% yield. To complete introduction of Br, large excess of bromine and longer reaction time were needed. When smaller amount of bromine was used, partially brominate product mixture was resulted and the isolation of pure product was impossible. Compound **2** was also prepared by Gutsche[2] by the BBr_3-catalyzed demethylation of *p*-bromocalix[4]arene methyl ether **3**.

When a suspension of compound **2** in THF/DMF solvent mixture was treated with MeI in the presence of NaH, O-methylated *p*-bromocalix[4]arene **3** was produced in 60% yield. The same compound was prepared by treating calix[4]arene tetramethyl ether **6** with NBS in MEK[2].

At an early stage of present work, preparation of compound **4** was attempted by Grignard reaction. When the compound **3** was treated with Mg followed by paraformaldehyde, only staring material was recovered. Conversion of the bromocalix[4]arene methyl ether **3** to the corresponding lithio compound was achieved by treatment with *n*-BuLi in THF for 30 min at −78℃. Treatment of the lithio compound with gaseous paraformaldehyde produced the *p*-hydroxymethylcalix[4]arene methyl ether **4** in 60% yield. Treatment of lithio compound with DMF instead of paraformaldehyde produced the *p*-formylcalix[4]arene methyl ether **5** in 68% yield. The IR and NMR spectral characteristics of these products are



Scheme 1.



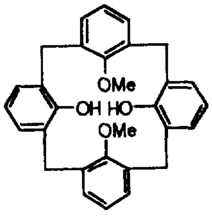
Scheme 2.

commensurated with those expected for compound **4** and **5**, respectively.

In the present work we also investigated another synthetic route to introduce hydroxy function at upper rim of calix[4]arene as shown on Scheme 2.

The methyl ether of calixarene **6** was obtained in 74% yield by treatment of **1** with NaH in THF/DMF followed by methyl iodide[8,12].

It was reported that the treatment of the calix[4]arene **1** with acetyl chloride under Friedel-Crafts condition resulted in O-acetylation, producing the ester, rather than para-acetylation, and the resulting ester failed to undergo further reaction at the para position[8]. Gutsche[12] reported that when calix[4]arene tetramethyl ether **6** was treated under same conditions, C-acetylation at the para positions occurred with concomitant partial demethylation and yield was only 29%. When the compound **9**, which has two phenol rings and two anisol rings, was treated with acetyl chloride under the Friedel-Crafts conditions, two acetyl groups were introduced at anisol rings rather than phenol rings[13]. Treatment of **6** with acetyl chloride in the presence of $AlCl_3$ resulted in complete para acetylation to produce compound **7** in 76% yield. In this preparation the slow addition of a solution of acetyl chloride was important to reduce the concomitant demethylation. The ^{13}C-NMR spectrum of compound **7** showed twelve peaks from phenyl carbons, and three peaks each from the carbonyl, methoxy and methyl adjacent to carbonyl carbons, indicating this compound is in partial cone conformation[14]. Two resonance peaks from the bridge methylene carbons at 35.52 and 30.55 ppm also support the partial cone conformation of compound **7** as reported by Mendoza[15].



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When a THF solution of **7** was treated with $NaBH_4$ at room temperature, the *p*-di(1-hydroxyethyl)calix[4]arene methyl ether **8** was resulted in 67% yield. The reaction was confirmed by spectral characteristics. The OH band was appeared and carbonyl band was disappeared in IR spectrum. ^1H-NMR resonance peaks of methyl protons adjacent to carbonyl in starting material at 2.65-2.28 ppm were shifted to 1.56-1.28 ppm, and those of CH proton were appeared. In ^{13}C-NMR spectrum, peaks of carbonyl were disappeared and resonance peaks of CH were appeared. The partial cone conformation was maintained in compound **8**.

Experimentals

Melting points of all compounds were taken in sealed and evacuated capillary tubes on a Syblon themolyne apparatus with polarizing microscope and were not corrected. IR spectra were determined on a Shimadzu IR-435 spectrometer. ^1H-NMR spectra were recorded on Varian EM-360A (60 MHz) or Varian Gemini 300 (300 MHz) instrument and ^{13}C-NMR spectra on the Varian Gemini 300 (75 MHz) spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS (δ 0.0) as an internal standard. TLC analyses were carried out on silica gel plates (absorbent thickness 250 μm). Flash chromatography[16] was carried out with E. Merck silica gel (230-400 mesh ASTM). Elution rate were 2 in./min.

5, 11, 17, 23-Tetra-*tert*-butyl-25, 26, 27, 28-tetrahydroxycalix[4]arene was prepared in 52% yield from *p*-*tert*-butylphenol and formaldehyde as described elsewhere[11]; mp. 344-346℃ (lit.[11] 344-346℃).

25, 26, 27, 28-Tetrahydroxycalix[4]arene 1 was prepared in 74% yield by $AlCl_3$-catalyzed removal of the *tert*-butyl groups from the *p*-*tert*-butylcalix[4]arene following the published procedure[8], mp. 315-317℃ (lit.[10] 314-318℃).

5, 11, 17, 23-Tetrabromo-25, 26, 27, 28-tetrahydroxycalix[4]arene 2. To a solution of calix[4]arene **1** (0.70 g 1.65 mmol) in 40 *ml* chloroform, Br_2 (0.9 *ml*) in 40 *ml* chloroform was added dropwise during 1.5 h at room temperature, and stirring was extended for overnight. The reaction mixture was stirred with 10% aqueous solution of $NaHSO_3$, the resulting white solid was collected by filtration, washed with water, dried and boiled with chloroform. The chloroform insoluble solid was collected and recrystallized from pyridine to yield 1.04 g (85%) of the desired product as white powder, mp. >400℃; IR (KBr) 3140 cm^{-1} (OH stretching); ^1H-NMR (DMSO d_6) 8.62 (s, 4, OH), 7.31 (s, 8, ArH), 3.95 (s, 8, CH_2).

5, 11, 17, 23-Tetrabromo-25, 26, 27, 28-tetramethoxycalix[4]arene 3. A suspension of compound **2** (1.50 g, 2.03 mmol) in 100 *ml* THF containing 10 *ml* DMF was treated with 1.0 g NaH, after stirred for 20 min, 5 *ml* MeI was added dropwise. The resulting mixture was refluxed 2 h, the THF was evaporated, and the resulting residue was treated with 150 *ml* ice-water, extracted with chloroform (100 *ml*×2 times). Organic layer was washed with water, dried and evaporated, the residue was treated with hexane to give white solid, which was recrystallized from chloroform/methanol to yield 0.97 g (60.0%) of the desired product as slightly yellow colored crystal, mp. 270-271℃ (lit.[2] 269-270℃); ^1H-NMR ($CDCl_3$) 7.55-6.70 (m, 8, ArH), 4.18-3.10 (m, 20, $ArCh_2Ar$, OCH_3). The same compound was also prepared from compound **6** via treatment with N-bromosuccinimide following the published procedure[2]. A 2.0 g (4.17 mmol) sample of compound **6** in 100 *ml* MEK was treated with 5.01 g (28.2 mmol) NBS, and the resulting solution was heated at 60℃ for 24 h. The mixture was then stirred with 10% $NaHSO_3$ and worked up to yield a light yellow colored solid. Recrystallization from chloroform/methanol yielded 2.50 g (75%) of white crystalline solid.

5, 11, 17, 23-Tetrahydroxymethyl-25, 26, 27, 28-tetramethoxycalix[4]arene 4. Under nitrogen atmosphere, compound **3** (1.00 g, 1.25 mmol) was dissolved in 20 *ml* THF, chilled in dry-ice/acetone bath and then 3.5 *ml* of *n*-BuLi (1.6 M in hexane) was added dropwise during 30 min with stirring. Gaseous paraformaldehyde was introduced via steady stream of nitrogen until the orange color of solution was disappeared using a small amount of 2,2′-bipyridyl as an indicator and then warmed to room temperature (approximately 50 min). The reaction was quenched by the addition of 10 *ml* of NH_4Cl saturated solution and the resultant mixture poured into 50 *ml* of NaCl saturated solution, extracted three times with 40 m*l* portions of chloroform. The organic layer was washed with water, dried and then evaporated to afforded crude product as a slightly waxy solid. A flash chromatography on silica gel yielded 0.45 g (60%) of the desired product as white solid; mp. 154-155℃; IR (KBr) 3340 cm^{-1} (OH stretching); ^{1}H-NMR ($CDCl_3$) δ 6.90 (br.s, 8, ArH), 4.35-3.70 (m, 28, $ArCH_2Ar$, OCH_3, OCH_2), 2.80 (br.s, 4, OH).

5, 11, 17, 23-Tetraformyl-25, 26, 27, 28-tetramethoxycalix[4]arene 5. A solution of compound **3** (1.00 g, 1.25 mmol) in 20 m*l* THF was chilled in an acetone/dry-ice bath under nitrogen atmosphere, 3.5 m*l* of *n*-BuLi (1.6 M in hexane) was added dropwise during 30 min, stirred for 1 h and then 2 m*l* of DMF was added. After removal of cooling bath, the reaction mixture was warmed to room temperature (approximately 50 min) and then quenched by addition of 10 m*l* of NH_4Cl saturated solution. The resulting mixture was poured into 50 m*l* of NaCl saturated solution, extracted twice with 40 m*l* portion of chloroform. The organic layer was washed with water, dried and evaporated to give a light brown colored residue, which was recrystallized from chloroform/hexane to yield (68%) crystalline solid; mp. 147-148℃; IR (KBr) 2830, 2730 (CHO stretching), 1685 cm^{-1} (C=O stretching); ^{1}H-NMR ($CDCl_3$) δ 10.17-9.66 (br.m, 4, CHO), 8.01-6.95 (br.m, 8, ArH), 4.58-3.02 (br.m, 20, $ArCH_2Ar$, OCH_3).

25, 26, 27, 28-Tetramethoxycalix[4]arene 6. Following the published procedure[12] a 3.14 g (7.64 mmol) sample of compound **1** was dissolved in 150 m*l* THF containing 15 m*l* DMF and treated with 3.0 g NaH followed by 30.0 g MeI. The mixture was refluxed 1 h, the THF was removed by evaporation, the residue was treated with 100 m*l* ice-water and extracted with 150 m*l* chloroform. The organic layer was washed with water several times, dried, evaporated, and the yellow colored residue was recrystallized from *n*-BuOH to give 2.59 g (74%) of the desired product as white crystalline solid; mp. 234-236℃ (lit.[12] 234-235℃); ^{1}H-NMR ($CDCl_3$) 6.65 (br.s, 12, ArH), 3.8 (br.s, 20, $ArCH_2Ar$, OCH_3).

5, 11, 17, 23-Tetraacetyl-25, 26, 27, 28-tetramethoxycalix[4]arene 7. To a solution of compound **6** (0.55 g, 1.15 mmole) in 40 m*l* of CH_2Cl_2, cooled in the ice-bath, a solution of 1.22 g $AlCl_3$ and 1.8 m*l* acetyl chloride in 20 m*l* CH_2Cl_2 was added dropwise with stirring. After stirring was continued for 2.5 h at room temperature, the reaction mixture was poured into 100 m*l* of 6 N HCl. The organic layer was separated, washed with water several times, dried, evaporated and the residue was triturated with hexane to give a white powder. flash chromatography (eluent was 2 : 1 mixture of hexane and acetone) on silica gel yielded 0.56 g (76%) of the desired product as a white powder; mp. 242-244℃ (lit.[2] 244-246℃); IR (KBr) 1680 cm^{-1} (C=O stretching); ^{1}H-NMR ($CDCl_3$) δ 7.94, 7.80, 7.58, 6.89 (s, 8, ArH), 4.43-2.90 (m, 20, $ArCH_2Ar$, OCH_3), 2.65-2.28 (m, 12, $COCH_3$); ^{13}C-NMR ($CDCl_3$) 198.51, 198.11, 179.95 (C=O), 162.76, 162.00, 137.13, 135.47, 134.23, 132.62, 132.0, 131.56, 130.40, 130.29, 129.38, 129.12 (Ar), 62.07, 61,54, 59.96 (OCH_3), 35.52, 30.55 (CH_2), 26.72, 26.44, 26.27 ($COCH_3$).

5, 11, 17, 23-Tetra(1-hydroxyethyl)-25, 26, 27, 28-tetramethoxycalix[4]arene 8. A mixture of compound **7** (0.73 g, 1.10 mmol) and $NaBH_4$ (1.0 g) in 30 m*l* of dry THF was stirred for 1.5 h after adding 2 m*l* of methanol. The reaction was quenched with adding 40 m*l* of 1.5% KOH solution, extracted twice with 30 m*l* portion of chloroform. The organic layer was separated, washed with water, dried, evaporated and the resulting residue was triturated with hexane to give a slightly brown colored powder. Flash chromatography (eluent was 1 : 1 mixture of hexane and acetone) on silica gel yielded 0.50 g (67%) of the desired product as a white powder, mp. 148-150℃; IR (KBr) 3375 cm^{-1} (OH stretching); ^{1}H-NMR ($CDCl_3$) δ 7.27-6.26 (m, 8, ArH), 4.89, 4.68, 4.38 (br.s, 4, OH), 4.00-2.99 (m, 24, $ArCH_2Ar$, OCH_3 and CH), 1.56-1.28 (m, 12, CH_3); ^{13}C-NMR ($CDCl_3$) 157.43, 155.72, 141.74, 134.99, 134.39, 134.02, 129.74, 128.37, 127.81, 127.08, 126.13, 126.03 (Ar), 77.20, 70.27, 69.67 (CH), 60.73, 58.23 (OCH_3), 37.17, 30.86 (CH_2), 24.72, 24.27, 23.13 (CH_3).

Acknowledgment. The authors are grateful for the support of this work from the Organic Chemistry Research Center and also thanks to the Korean Science and Engineering Foundation for the financial support (KOSEF 901-0302-031-2). The use of a Varian Gemini 300 NMR spectrometer is financially supported by the OCRC.

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