Regioselective Monoalkylation of Calixarenes. Synthesis of Homodimer Calixarenes

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Received March 13, 2000

The selective monoalkylation at the smaller (lower) rim of the p-tert-butylcalix[4]- and -[6]arenes using bis(butyltin)oxide and different alkylation agents is described. The procedure is remarkable for the mild conditions used allowing an efficient access to monoalkylated calixarene derivatives in moderate to good yields. Monoalkynylcalix[4]arene and monoalkynylcalix[6]arenes have been synthetically exploited for the synthesis of bis-calix[n]arenes (n = 4, 6) with a diyne bridge by oxidative coupling of alkenes. In addition, intermolecular methathesis of the obtained monoalkynyl-calix[4]arene allowed the preparation of bis-calix[4]arene that are single bridged at the smaller (lower) rim with a 2-butenyl moiety.

Introduction

The development of supramolecular chemistry has led to a growing interest in the design and synthesis of macrocyclic molecules containing intramolecular cavities.1 In this regard, calixarenes2 have been used as building blocks for the synthesis of a large host molecules with different supramolecular functions because they are readily accessible for chemical modification on both smaller (lower) and larger (upper) rims by attachment of a wide range of potential ligating groups.

General and efficient procedures for the selective alkylation of calix[4]arenes at the smaller (lower) rim have been reported allowing the synthesis of monoalkoxy-calixarenes and 1, 2- and 1, 3-dialkoxy-calixarenes. The reason of the observed selectivity is mainly due to the different acidities of the phenolic OH groups which can be selectively ionized by using an appropriate base. The regioselective reaction of a single hydroxy group in calixarenes is in particular important for the construction of larger molecules using calixarenes as building units.3

One of the first examples described of selective functionalization from unsubstituted calix[4]arene was the synthesis of a tribenzoate derivative from which monoethers were prepared after hydrolysis of the ester groups.4 Another indirect procedure for the preparation of monoalkoxy-calix[4]arenes has been devised that uses the controlled cleavage of 1,3-dialkoxy- or tetraalkoxy-calix[4]arenes with either 1 or 3 equiv of trimethylsilyl iodide.5 Complementary to those indirect monoalkylation procedures, regioselective monoalkylation has been carried out using an excess of the alkylation agent and K2CO3 or CsF as a weak base.6 NaH7 or Ba(OH)2.8 Compared with calix[4]arenes, the regiochemical control of calix[6]arene functionalization is more difficult because of the presence of a larger number of reactive centers and a higher conformational mobility. However, high selectivity has been obtained in the synthesis of monobenzyl ethers of calix[6]arene and p-tetral-calix[6]arene, using a weak base (K2CO3) and stoichiometric amount of benzyl bromide in dry acetonitrile.9

The versatility of calix[4]arenes as host molecules has suggested that they can serve as potential building blocks for designing more elaborate structures consisting of double calix[4]arenes. Three possibilities have been envisaged: connection via both larger (upper) rings, head-to-head, via both smaller (lower) rings, tail-to-tail, or via the larger rim of one with the smaller rim of another, head-to-tail. Shinkai et al.10 have reported the synthesis of a series of bis-calix[4]arenes possessing two metal binding sites, each of which contains four ester or four dibromoalkanes, respectively.20 Double and triple calix[4]arenes connected via the oxygen atoms have been described11 by reactions of bis(alkoxystanny1)calix[4]arenes with NaH,16 by condensation of hydroxycalix[4]arenes with dialkenylcalix[4]arene derivatives.20 calix[4]arenes have been obtained by intermolecular condensation of carbohydrate derivatives.21 The transformation of bis-calix[4]arenes possessing two metal binding sites, each of which contains four ester or four dibromoalkanes, respectively.

Recently, Rebek et al. have described14 the synthesis and the encapsulation behavior of bis-calix[4]arenes linked via one bridge at the larger (upper) rim and bearing urea groups on the larger (upper) rims.17,18 Furthermore, Rebek et al. have described14 the synthesis and the encapsulation behavior of bis-calix[4]arenes linked via one bridge at the larger (upper) rim, via both larger (upper) rings, head-to-tail, via both smaller (lower) rings, tail-to-tail, or via the larger rim of one with the smaller rim of another, head-to-tail. Shinkai et al.10 have reported the synthesis of a series of bis-calix[4]arenes possessing two metal binding sites, each of which contains four ester or four dibromoalkanes, respectively.20

We report in this paper the results of a systematic study on the selective monoalkylation of the smaller (lower) rim of the p-tert-butylcalix[4]- and -[6]arenes using bis(butyltin)oxide and the synthetic applications of the obtained monoalkynyl- and mononallycalix[4]arene (n = 4, 6) derivatives for the synthesis of bis-calix[4]-arenes by oxidative coupling of alkylnes and intermolecular methathesis, respectively.

Results and Discussion

In a project directed to the synthesis of modified calixarenes, an efficient and general methodology was needed for access to monoalkylated calixarenes. Considering the demonstrated utility of stannylene acetals for the regioselective alkylation and acylation in the sugar chemistry, it was thought that formation of these intermediates in the case of calixarenes could be a useful feature for the synthesis of the desired target. To find the optimal conditions for these transformations, p-tert-butylcalix[4]arene (1) was chosen as the starting material and propargyl bromide as the electrophile reagent. The reaction was initially performed using Bu4SnO (0.5 equiv) in refluxing toluene with azeotropic removal of water for 8 h. After this time, Bu4NBr and propargyl bromide were added keeping the reflux for additional 2 h. Compound 3 was thus isolated in 33% yield (see Scheme 1). It was found that the use of Bu4NBr instead of Bu4NBF and propargyl bromide were added keeping the reflux for additional 2 h. After several experiments, it was finally found that the use of (Bu4Sn)2O (0.5 equiv) allowed better results by extending the treatment of 1 with this reagent for 4 days and subsequent treatment with the alkylation reagent in the presence of Bu4NBF. Thus, the monoalkylated derivative 3 was obtained in 76% yield (see Scheme 1), and these conditions were adopted for the present study. Also, it should be mentioned that compound 3 was prepared following the conditions described by Reinhoudt et al. for the synthesis of several monoalkylated calix[4]arenes by using C5F. However, in our hands this procedure led to compound 3 in low yield (31%). Compound 1 was then subsequently treated with (Bu4Sn)2O (0.5 equiv) and bromoacetonitrile, allyl bromide, ethyl bromoacetate, 4-i-dodebenzyl iodide, benzyl bromide, and 5-i-iodo-1-pentene, respectively. In all of those reactions the corresponding monoalkylated derivatives 4–9 were easily obtained in 34–84% yield (see Scheme 1). The study was then extended to p-tert-butylcalix[6]arene 2 using the same alkylation reagents. In this case, the reaction with propargyl bromide led to a complex mixture from which compound 10 could not be isolated. In the rest of the cases, the corresponding monoalkylated derivatives 11–16 were obtained but with yields (23–}

52%) lower than those obtained when 1 was the starting material (see Scheme 1).

Once the monoalkylated calixarenes were synthesized, we thought that the alkynyl 3, 9, 16 and allyl 5, 12 derivatives could be adequate precursors for the synthesis of homodimer calixarenes using carbon–carbon bond-forming reactions such as oxidative dimerization under Glasser’s conditions or olefin methathesis. Both types of reactions were successfully carried out. Thus, treatment of 3, 9, and 16 with cuprous iodide and a catalytic amount of bis(triphenylphosphine) palladium dichloride in DMF/Et3N23 gave the corresponding diynes 17–19 in moderate to high yields (37–95%) (see Scheme 2). On the other hand, homodimerization of compound 5 in refluxing dichloromethane in the presence of the Grubb’s catalyst24 [bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] allowed the preparation of a Z/E mixture of dimers 20 + 21 in a 3:1 proportion. Pure Z-isomer 20 could be obtained when calix[4]arene 1 was reacted with (Z)-1,4-dichlorobutene following the procedure described by Gutsche et al.15 in good yield (69%). Olefin hydrogenation of the Z/E mixture of isomers 20 + 21 or pure Z-isomer 20 was effected using Pd/C, and compound 22 was obtained (40%) (see Scheme 3).

In conclusion, use of bis(butyltin) oxide is first described in the calixarene chemistry allowing the regioselective synthesis of monoalkylated calix[4]arenes and calix[6]arenes. The procedure is remarkable for its efficiency and mild conditions. This last characteristic allowed the use of alkylating agents having different functionalities (nitrile, esters, alkynes). Finally, we used the monoalkynyl and monoalkenyl calixarenes for the synthesis of homodimer calixarenes connected by the smaller (lower) rims.

Experimental Section

General Experimental Details. TLC was performed on Merck silica gel 60F245 aluminum sheets with detection using the Mostain reagent [ceric sulfate (1%w/v) and ammonium

\[\text{Scheme 1. Synthesis of Monoalkylated Calix[n]arenes (n = 4, 6)a,b} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Calixarene</th>
<th>R-X</th>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (n = 4)</td>
<td>BrCH2CH=CH2</td>
<td>3 (n = 4)</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>1 (n = 4)</td>
<td>BrCH2CN</td>
<td>4 (n = 4)</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>1 (n = 4)</td>
<td>BrCH2=CH2</td>
<td>5 (n = 4)</td>
<td>80</td>
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<tr>
<td>4</td>
<td>1 (n = 4)</td>
<td>BrCH2COOEt</td>
<td>6 (n = 4)</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>1 (n = 4)</td>
<td>4-IGHCH=CH2</td>
<td>7 (n = 4)</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>1 (n = 4)</td>
<td>CdH3CH=Br</td>
<td>8 (n = 4)</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>1 (n = 4)</td>
<td>(CH2)3C=CH</td>
<td>9 (n = 4)</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>2 (n = 6)</td>
<td>BrCH2CH=CH2</td>
<td>10 (n = 6)</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>2 (n = 6)</td>
<td>BrCH2CN</td>
<td>11 (n = 6)</td>
<td>23</td>
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<td>10</td>
<td>2 (n = 6)</td>
<td>BrCH2=CH2</td>
<td>12 (n = 6)</td>
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<tr>
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<td>BrCH2COOEt</td>
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<td>12</td>
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<tr>
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<td>CdH3CH=Br</td>
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</tr>
<tr>
<td>14</td>
<td>2 (n = 6)</td>
<td>(CH2)3C=CH</td>
<td>16 (n = 6)</td>
<td>27</td>
</tr>
</tbody>
</table>

a A complex mixture was obtained from which compound 10 could not be isolated. b Reagents and conditions: (i) (Bu3Sn)2O, toluene, reflux; (ii) RX, Bu4NI, toluene, reflux.

molybdate (2.5% w/v) in 10% (v/v) aqueous sulfuric acid) and by UV light when applicable. Flash column chromatography on silica gel Merck or Scharlau (230–400 mesh ASTM). All the concentrations were carried out under diminished pressure at 40 °C. Melting points were determined with a Gallenkamp apparatus and are uncorrected. NMR spectra were recorded at room temperature on a Bruker AM-300 spectrometer. 1H NMR chemical shifts are given in ppm and referenced to internal CDCl 3 (δ = 7.26) for CDCl 3 solutions. 13C NMR chemical shifts are given in ppm and referenced to CDCl 3 (δ = 77.0). FAB mass spectra were obtained on a Fisons VG Autospec-Q spectrometer using m-nitrobenzyl alcohol or thiglicerol as matrix. Anhydrous solvents were prepared according to standard procedures and were freshly distilled immediately before use.

5-Iodo-1-pentyne was obtained from 4-penty-1-ol in two steps.25 4-Iodo-benzyl iodide was obtained from 4-nitrobenzyl alcohol or 6.7 Hz, 2.6 Hz), 1.99 (q, 2 H, J = 6.7, 2.6 Hz), 1.98 (m, 1 H); 13C NMR (75 MHz, CDCl 3 ) 82.3, 68.5, 57.2, 35.9, 33.5. 1.20 (s, 18 H), 1.20 (s, 9 H); 13C NMR (75 MHz, CDCl 3 ) δ 149.2, 148.6, 148.0, 147.8, 147.3, 143.3, 133.8, 128.2, 121.7, 128.8, 125.8, 125.6, 78.0, 77.4, 63.5, 63.4, 34.0, 33.0, 30.3, 32.5; HRMS (FAB) m/z 877.3511 for [M + Na]+, calscd for CaH 38O 4Na M 737.4553.

25-Benzoxyl-5,11,17,23-tetatra-t-butyl-26,27,28-triarylhycalix[4]arene (6). Column chromatography of the crude (dichloromethane/hexane 1:3) gave 6 (47%) as a solid: mp 198–200 °C (lit. mp 202–203 °C); 1H and 13C NMR identical to those described in ref 5.

5,11,17,23-Tetra-t-butyl-26,27,28-triarylhycalix[4]arene (6). Column chromatography of the crude (dichloromethane/hexane 1:3) gave 6 (56%) as a solid: mp 122–124 °C; IR (KBr) ν 3318, 1485, 1364, 1203 cm⁻¹; 1H NMR (300 MHz, CDCl 3 ) δ 10.15 (s, 1 H); 7.52 (s, 4 H), 7.09 (s, 2 H), 7.05 (d, 2 H, J = 2.4 Hz), 7.02 (d, 2 H, J = 13.7 Hz), 4.28 (d, 2 H, J = 6.4 Hz), 4.05 (d, 2 H, J = 3.4 Hz), 3.43 (m, 1 H), 2.75 (s, 2 H); 3.25 (m, 2 H). 13C NMR (75 MHz, CDCl 3 ) 149.2, 129.7, 127.9, 127.6, 127.6, 125.8, 125.7, 95.0, 78.4, 34.4, 34.1, 33.0, 32.5; HRMS (FAB) m/z 877.3511 for [M + Na]+, calscd for CaH 38O 4Na M 737.4553.

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solution of $\text{Na}$ was added $\text{Pd(PPh}_3\text{)}_2\text{Cl}_2$ (0.026 g) and $\text{CuI}$ (0.075 g). The resulting solution was allowed to reflux under a nitrogen atmosphere.

The reaction mixture was washed with 1 N HCl (25 mL) and water (25 mL) and then dried (Na$_2$SO$_4$) to yield after concentration a crude product that was purified by column chromatography (dichloromethane/hexane 1:1) giving 20 (0.714 g, 69%) as a yellow oil.

To a solution of 1 (1.54 mmol) in dry dichloromethane (50 mL) was added NaH (0.07 g, 3.06 mmol). The mixture was stirred for 30 min under an inert atmosphere. The resulting mixture was treated with 5% H$_2$O$_2$ (0.57 g, 5.14 mmol) and tert-butyllammonium iodide (0.57 g), and stirred at room temperature for 24 h. The reaction mixture was washed with 1 N HCl (25 mL) and water (25 mL) and then dried (Na$_2$SO$_4$) to yield after concentration a crude product that was purified by column chromatography (dichloromethane/hexane 6:4) giving 21 (0.174 g, 69%) as a yellow oil.

To a solution of 2 (1.54 mmol) in dry dichloromethane (50 mL) was added Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] (0.023 g, 0.03 mol). The resulting solution was allowed to reflux under a nitrogen atmosphere for 7 h. Concentration yielded a crude product that was purified by column chromatography (dichloromethane/hexane 1:1) giving 20 (0.68 g, 72%) as a yellow oil.

To a solution of 5 (0.200 g, 0.029 mmol) in dry dichloromethane (2 mL) was added Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] (0.012 g, 0.003 mmol). The resulting solution was allowed to reflux under a nitrogen atmosphere for 7 h. Concentration yielded a crude product that was purified by column chromatography (dichloromethane/hexane 1:1) giving 20 (0.140 g, 72%) as a yellow oil.

To a solution of 6 (1.54 mmol) in dry dichloromethane (50 mL) was added NaH (0.07 g, 3.06 mmol). The mixture was stirred for 30 min under an inert atmosphere. The resulting mixture was treated with 5% H$_2$O$_2$ (0.57 g, 5.14 mmol) and tert-butyllammonium iodide (0.57 g), and stirred at room temperature for 24 h. The reaction mixture was washed with 1 N HCl (25 mL) and water (25 mL) and then dried (Na$_2$SO$_4$) to yield after concentration a crude product that was purified by column chromatography (dichloromethane/hexane 6:4) giving 21 (0.174 g, 69%) as a yellow oil.

To a solution of 2 (1.54 mmol) in dry dichloromethane (50 mL) was added Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] (0.023 g, 0.03 mol). The resulting solution was allowed to reflux under a nitrogen atmosphere for 7 h. Concentration yielded a crude product that was purified by column chromatography (dichloromethane/hexane 1:1) giving 20 (0.68 g, 72%) as a yellow oil.

To a solution of 5 (0.200 g, 0.029 mmol) in dry dichloromethane (2 mL) was added Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] (0.012 g, 0.003 mmol). The resulting solution was allowed to reflux under a nitrogen atmosphere for 7 h. Concentration yielded a crude product that was purified by column chromatography (dichloromethane/hexane 1:1) giving 20 (0.140 g, 72%) as a yellow oil.
hydrogenated (3 atm) in the presence of Pd–C (50 mg). The reaction was monitored by TLC (dichloromethane/hexane 1:2). Filtration over Celite was followed by concentration and purification of the resulting crude product by column chromatography (dichloromethane/hexane 1:2) giving 22 (0.090 g, 40%) as a solid: mp 258–259 °C; IR (KBr) ν 3358, 3230, 1492, 1205, 1064 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.18 (s, 2 H), 9.61 (s, 4 H), 7.10 (s, 4 H), 7.06 (d, 4 H, J = 2.4 Hz), 7.03 (s, 4 H), 6.96 (d, 4 H, J = 2.4 Hz), 4.43 (d, 4 H, J = 12.9 Hz), 4.38 (br s, 4 H), 4.21 (d, 4 H, J = 13.6 Hz), 3.46 (d, 4 H, J = 13.0 Hz), 3.38 (d, 4 H, J = 13.8 Hz), 2.62 (br s, 4 H), 1.21 (s, 18 H), 1.20 (s, 36 H), 1.19 (s, 18 H); ¹³C NMR (75 MHz, CDCl₃) δ 149.4, 148.6, 143.6, 148.3, 147.8, 143.1, 133.6, 128.4, 128.2, 127.6, 126.6, 125.8, 125.9, 76.5, 34.3, 34.1, 34.0, 33.0, 32.4, 29.8, 26.6; HRMS (FAB) m/z 1373.8712 for [M + Na]⁺, calcd for C₉₂H₁₁₈O₈Na M 1373.8724.

Acknowledgment. We thank Dirección General de Investigación Científica y Técnica for financial support (PB95-1207).