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Ultrasound mediated selective monoalkylation of 4-*tert*-butylcalix[6]arene at the lower rim

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Abstract—Regioselective synthesis of monoalkyl ethers of 4-*tert*-butylcalix[6]arene in good yield was achieved with a variety of electrophiles using 2.2 equiv. of potassium carbonate as base in acetonitrile under ultrasonic irradiation at ambient temperature. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Calix[*n*]arenes (*n*=4,6,8), which belong to the class of [1_n]-metacyclophanes, are a class of cyclic oligomers prepared from base induced phenol-formaldehyde condensation.[1] These molecules have a cavity shaped architecture having a polar lower rim (phenolic OH groups) and non-polar upper rim (*tert* butyl groups). The increasing interest in these macromolecules for use as hosts is not only due to their easy synthesis,[2] but also due to the possibility of their functionalization at both lower and upper rims. This has been one of the most active areas in supramolecular chemistry. Selective alkylation of the phenolic OH groups of calixarenes is very important for the construction of bigger molecules with preorganized structures having specific molecular recognition abilities. Several reports are available on the high affinity of the derivatives of calix[4] and calix[6]arenes for alkali metal cations.[3] Herein we report the results of our study on the selective monoalkylation of 4-*tert*-butylcalix[6]arene (Chart 1) at the lower rim under ultrasonic irradiation.

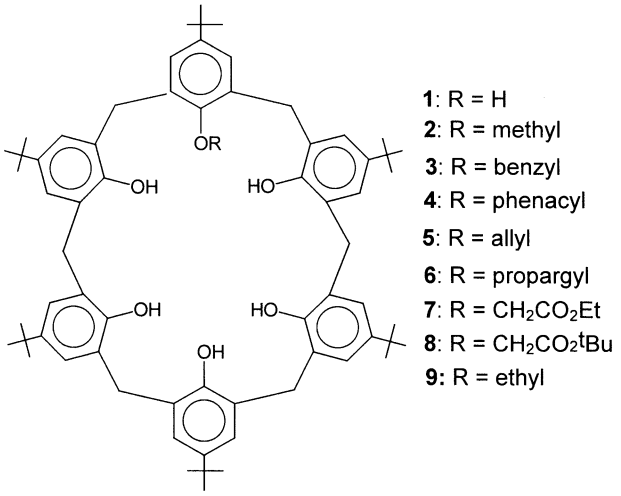

Chart 1.

In recent years, considerable attention has been devoted to the development of efficient and general methodology for access to selective derivatization of calixarene phenols. This is important mainly for the construction of bigger molecules using calixarenes as building units.[4] Thus, selective alkylation of calix[4]arenes was successful and established procedures are available for their functionalization at both upper and lower rims. Pioneering work from Reinhoudt's group have revealed the selective mono- and 1,3-dialkylation of calix[4]arene using a weak base such as K_2CO_3 in acetonitrile.[5] The selectivity observed has been explained on the basis of the difference in the pK_a values for the first and second deprotonation step and the stability of the respective phenoxide ions.

Despite their greater potential as hosts, the bigger calix[6]-arenes have received little attention. Compared with calix[4]arenes, the regiochemical control of calix[6]arene derivatization is difficult due to the presence of a large number of reactive centers and a higher conformational mobility. This makes the isolation and characterization of the reaction products more difficult. Consequently, little is known about the chemistry of calix[6]arene.[6] Although the selective synthesis of monobenzyl and monomethyl ethers of 4-*tert*-butylcalix[6]arene using K_2CO_3 is known in the literature,[7] it took a longer time for completion of the reaction. Similarly, monoalkylation with allyl bromide,[8]

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Table 1. Monomethylation of **1** under ultrasonic irradiation: influence of base, solvent and stoichiometry

Entry	Solvent	Base (equiv.)	Electrophile (equiv.)	Product/s (% yield)[a]
1	Acetonitrile	K_2CO_3 (1.2)	CH_3OTs (1.1)	**2** (39)[b]+**1** (30)
2	Acetonitrile	K_2CO_3 (2.2)	CH_3OTs (2.2)	**2** (68)[b]+**1** (5)
3	Acetonitrile	K_2CO_3 (2.2)	CH_3OTs (1.2)	**2** (32)[b]+**1** (75)
4	Acetone	K_2CO_3 (2.2)	CH_3OTs (2.2)	**2** (25)[b]+**1** (45)
5	THF/DMF (5:1)	K_2CO_3 (2.2)	CH_3OTs (2.2)	Complex mixture
6	Acetonitrile	Cs_2CO_3 (2.2)	CH_3OTs (2.2)	Complex mixture
7	Acetonitrile	$KHCO_3$ (2.2)	CH_3OTs (2.2)	No reaction

All the reactions were carried out for 5.5 h at 20°C.
[a] Isolated yield after preparative thin layer chromatography or crystallization.
[b] Yields were calculated on the basis of the reacted **1**.

propargyl bromide[8] and ethyl bromoacetate[8] took a very long time (4 d) to afford the desired products in moderate yields (47–52%). Keeping this in view, it was of interest to develop more efficient protocols for the selective derivatization of calix[6]arene at the lower rim.

2. Results and discussion

The selective alkylation of phenolic OH groups of calixarenes with weak bases (K_2CO_3, Cs_2CO_3 etc.) is usually carried out in acetone or acetonitrile as solvents. However, these reactions are heterogeneous in nature and often take a long time to reach completion. For example, methylation of 4-*tert*-butylcalix[6]arene (**1**) with K_2CO_3 (1.03 equiv.) and methyl iodide (6.2 equiv.) in acetone yielded a difficult to separate mixture of monomethyl ether (**2**) and 1,3-dimethylether in 35 and 10% yield, respectively after 20 h of refluxing.[6a] Since ultrasound is known to have a beneficial effect in accelerating the kinetics of heterogeneous reactions,[9] it was of interest to see its effect on the alkylation of calix[6]arene. In a model reaction, a mixture of **1**, anhydrous K_2CO_3 (1.2 equiv.) and methyl tosylate (1.1 equiv.) in dry acetonitrile was exposed to ultrasonic irradiation at 20°C. The progress of the reaction was monitored by tlc. After 5.5 h of sonication, tlc showed the formation of a product along with some unreacted starting material **1** (Table 1, entry 1). After purification by column chromatography, the minor product was characterized as the monomethyl ether of 4-*tert*-butylcalix[6]arene (**2**).[7]

Encouraged by this result, the above reaction was carried out under identical conditions using a higher amount of both K_2CO_3 (2.2 equiv.) and methyl tosylate (2.2 equiv.) when a considerable amount of starting material was consumed and **2** was obtained as the sole product in good yield (68%). No higher alkylated product was detected from the reaction mixture (Table 1, entry 2). When the reaction was carried out under identical conditions but under reflux (5.5 h), formation of **2** was not observed and a complex mixture of methylated products was formed (checked by tlc and ^{1}H NMR spectra). This clearly indicated the beneficial effect of ultrasound in the alkylation of calixarenes.

Since 1 equiv. of the electrophile is actually consumed during monoalkylation of **1**, the reaction was also carried out with a mixture of **1**/K_2CO_3/CH_3OTs in the ratio of 1:2.2:1.2 under ultrasonic irradiation when **2** was obtained along with the starting material **1** in 32 and 75% yield, respectively (Table 1, entry 3).

The effect of solvents and different bases on the above reaction was also investigated (Table 1). It is clear from the table that although acetone afforded **2** in moderate yield (Table 1, entry 4), use of a mixture of THF/DMF (5:1) as the solvent yielded a complex mixture of products (Table 1, entry 5). Interestingly, use of Cs_2CO_3 in place of K_2CO_3 also led to a complicated mixture of products (Table 1, entry 6). However, no reaction was observed using a combination of $KHCO_3$ (2.2 equiv.)/CH_3OTs (2.2 equiv.) in CH_3CN, and **1** was recovered quantitatively (Table 1, entry 7). In view of the best result of monomethylation of **1** using K_2CO_3 (2.2 equiv.) and CH_3OTs (2.2 equiv.) in acetonitrile, the same conditions were adopted for all subsequent reactions.

To see the scope of the above ultrasound mediated protocol for the monoalkylation of calix[6]arenes, the alkylation of **1** was carried out with different electrophiles such as benzyl bromide, phenacyl bromide, allyl bromide, propargyl bromide, ethyl bromoacetate, *tert*-butyl bromoacetate and ethyl bromide. In all cases, the corresponding monoalkylated derivatives **3**–**9** were obtained as the sole products respectively in 30–74% yields (Table 2, entries 1–7). All the compounds synthesized were characterized by their respective IR, ^{1}H NMR and ^{13}C NMR data which were in accordance with the literature values.

In conclusion, we have demonstrated a convenient route to

Table 2. Monoalkylation of **1** with various electrophiles under ultrasonic irradiation

Entry	Electrophile	Product/s (% yield)[a]
1	$C_6H_5CH_2Br$	**3** (74)
2	$C_6H_5COCH_2Br$	**4** (38)[b]
3	$CH_2{=}CH{-}CH_2Br$	**5** (64)
4	$CH{\equiv}C{-}CH_2Br$	**6** (53)[c]+**1** (49)
5	EtO_2CCH_2Br	**7** (65)
6	$^tBuO_2CCH_2Br$	**8** (65)[c]+**1** (4)
7	CH_3CH_2Br	**9** (30)[c]+**1** (78)

All the reactions were carried out using 2.2 equiv. each of the electrophiles and K_2CO_3 as base in acetonitrile for 5.5 h at 20°C.
[a] Isolated yield after crystallization or column chromatography.
[b] Complex mixture of higher alkylated products was also obtained.
[c] Yields were calculated on the basis of the reacted **1**.

the selective monoalkylation of 4-*tert*-butylcalix[6]arene in moderate to good yields with a variety of electrophiles at a faster rate using K_2CO_3 as the base under ultrasonic irradiation at ambient temperature. The use of these monoalkylated derivatives for the recognition of specific metal ions or molecules[6,11] and for the synthesis of bigger host molecules[8,10] is currently under investigation.

3. Experimental

The FT-IR spectra were scanned with a Nicolet FT-IR spectrophotometer (model 410). The ^{1}H NMR spectra were recorded with a Bruker AC 200 (200 MHz) spectrometer. All reactions were carried out under an argon atmosphere. Acetonitrile and acetone were distilled over P_2O_5. THF was distilled from sodium-benzophenone ketyl prior to use. DMF was dried over CaH_2. *p-tert*-Butylcalix[6]arene and methyl tosylate, purchased from Fluka and Aldrich Chemical Co., respectively were used as such. Benzyl bromide, phenacyl bromide, allyl bromide, propargyl bromide, ethyl bromoacetate, *tert*-butylbromoacteate and ethyl bromide were purchased from Aldrich Chemical Co.

3.1. General procedure for the monoalkylation of 4-*tert*-butylcalix[6]arene (1)

A slurry of **1** (0.5 mmol), K_2CO_3 (1.1 mmol) and the alkylating agent (1.1 mmol) in acetonitrile (20 mL) was sonicated in an ultrasonic cleaning bath (40 kHz) at 20°C. After 5.5 h (cf. tlc), the solvent was removed and water was added to the residue when a white solid precipitated. The mixture was acidified with 1N HCl and the compound was filtered. The solid was washed with water and dried in air. Purification by column chromatography (CH_2Cl_2/hexane) or crystallization from $CHCl_3$/MeOH yielded the monoalkylated product.

3.1.1. 5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-methoxycalix[6]arene (2). Yield: 68%; colorless solid; mp >300°C (lit.[7] mp >320°C). ^{1}H and ^{13}C NMR spectra of **2** are identical to those reported in the literature.[7]

3.1.2. 37-Benzyloxy-5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-calix[6]arene (3). Yield: 74%; colorless solid; mp 224–225°C (lit.[7] mp 225–227°C). ^{1}H and ^{13}C NMR spectra of **3** are identical to those reported in the literature.[7]

3.1.3. 37-Benzoylmethyloxy-5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-calix[6]arene (4). Yield: 38%; colorless solid; mp 190°C; [Found: C, 81.04; H, 8.57%. $C_{74}H_{90}O_7$ requires C, 81.43; H, 8.31%]; R_f (10% EtOAc/hexane) 0.4; ν_{max} ($CHCl_3$): 3292, 2969, 1702, 1484, 1361, 1300 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 9.90 (s, 2H, ArOH), 9.68 (b s, 1H, ArOH), 9.09 (s, 2H, ArOH), 7.92 (d, 2H, J=7.0 Hz, ArH), 7.63–7.39 (m, 3H, ArH), 7.26–7.13 (b m, 12H, ArH), 5.31 (s, 2H, OCH_2), 4.34 (d, 2H, J=13.9 Hz, $ArCH_2Ar$), 4.14 (d, 2H, J=13.7 Hz, $ArCH_2Ar$), 4.01 (d, 2H, J=13.9 Hz, $ArCH_2Ar$), 3.78–3.65 (m, 6H, $ArCH_2Ar$), 1.34–1.31 [b s, 45H, $C(CH_3)_3$], 1.28 [s, 9H, $C(CH_3)_3$]; δ_C (50 MHz, $CDCl_3$): 193.8, 150.7, 149.2, 148.3, 147.9, 147.3, 143.8, 143.2, 142.7, 133.8, 132.5, 128.6, 127.7, 126.9, 126.7, 126.1, 126.0, 125.7, 125.4, 77.1, 34.2, 33.8, 33.0, 32.6, 32.5, 31.5, 31.2.

3.1.4. 5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-(2-propen-1-yloxy)calix[6]arene (5). Yield: 64%; colorless solid; mp 150°C (lit.[8] mp 150–152°C). ^{1}H and ^{13}C NMR spectra of **5** are identical to those reported in the literature.[8]

3.1.5. 5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-propargyloxycalix[6]arene (6). Yield: 53%; colorless solid; mp 194°C (lit.[10] mp 194–195°C).; R_f (10% EtOAc/hexane) 0.53; ν_{max} ($CHCl_3$): 3300, 2964, 2864, 1597, 1484, 1361 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 9.77 (s, 2H, ArOH), 9.60 (b s, 1H, ArOH), 8.50 (s, 2H, ArOH), 7.12–6.99 (b m, 12H, ArH), 4.83 (d, 2H, J=2.1 Hz, OCH_2), 4.08–3.60 (b m, 12H, $ArCH_2Ar$), 2.70 (t, 1H, J=2.4 Hz, ≡CH), 1.28, 1.26, 1.21, 1.13 [s, 54H, $C(CH_3)_3$]; δ_C (50 MHz, $CDCl_3$): 149.4, 149.2, 148.2, 148.2, 146.7, 144.4, 143.6, 143.1, 132.6, 127.5, 127.3, 126.9, 126.8, 126.2, 126.0, 125.9, 125.5, 78.3, 77.2, 63.1, 34.3, 34.0, 33.1, 32.8, 32.6, 31.6, 31.4, 31.2.

3.1.6. 5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-ethoxycarbonylmethyloxycalix[6]arene (7). Yield: 65%; colorless solid; mp 274°C (lit.[8] mp: 273–275°C). ^{1}H and ^{13}C NMR spectra of **7** are identical to those reported in the literature.[8]

3.1.7. 5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-*tert*-butoxycarbonylmethyloxycalix[6]-arene (8). Yield: 65%; colorless solid; mp >300°C; [Found: C, 79.14; H, 8.87%. $C_{72}H_{94}O_8$ requires C, 79.52; H, 8.71%]; R_f (10% EtOAc/hexane) 0.6; ν_{max} ($CHCl_3$): 3304, 2965, 1747, 1485, 1363, 1293, 1155 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 9.90 (s, 2H, ArOH), 9.52 (b s, 1H, ArOH), 8.99 (s, 2H, ArOH), 7.23–7.10 (b m, 12H, ArH), 4.74 (s, 2H, OCH_2), 4.49 (d, 2H, J=13.9 Hz, $ArCH_2Ar$), 4.25 (d, 2H, J=14.1 Hz, $ArCH_2Ar$), 4.07 (d, 2H, J=13.9 Hz, $ArCH_2Ar$), 3.75–3.58 (m, 6H, $ArCH_2Ar$), 1.69 [s, 9H, $C(CH_3)_3$], 1.38, 1.35, 1.33, 1.24 [s, 54H, $C(CH_3)_3$]; δ_C (50 MHz, $CDCl_3$): 167.8, 149.7, 149.2, 148.3, 147.9, 147.1, 144.0, 143.3, 142.7, 132.1, 127.0, 126.9, 126.7, 126.7, 126.0, 125.7, 125.2, 82.9, 72.0, 34.1, 33.8, 33.1, 32.5, 31.5, 31.4, 31.1, 28.1.

3.1.8. 37-Ethoxy-5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-calix[6]arene (9). Yield: 30%; colorless solid; mp 225°C; [Found: C, 81.23; H, 9.08%. $C_{68}H_{88}O_6$ requires C, 81.56; H, 8.86%]; R_f (10% EtOAc/hexane) 0.52; ν_{max} ($CHCl_3$): 3275, 2964, 1485, 1309 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 9.70 (s, 2H, ArOH), 9.19 (b s, 1H, ArOH), 9.02 (s, 2H, ArOH), 7.14–7.01 (b m, 12H, ArH), 4.23 (q, 2H, J=7.0 Hz, OCH_2), 3.90–3.76 (b m,12H, $ArCH_2Ar$), 1.71 (t, 3H, J=7.0 Hz, CH_3), 1.29, 1.26, 1.23, 1.16 [s, 54H, $C(CH_3)_3$]; δ_C (50 MHz, $CDCl_3$): 149.6, 149.3, 148.2, 147.7, 146.9, 144.3, 143.5, 142.9, 132.4, 127.1, 126.8, 126.1, 126.0, 125.7, 125.3, 71.5, 34.2, 33.9, 33.1, 32.7, 32.6, 31.5, 31.4, 31.2, 29.7.

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