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Regioselective *ipso* formylation of *p-tert*-butylcalix[4]arene

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Dedicated to Professor Sukhdev on his birthday (17th June)

Abstract—A convenient procedure for direct introduction of one formyl group into *p-tert*-butylcalix[4]arenes through *ipso* substitution is described.

Calixarenes are phenolic metacyclophanes that can be tailored to obtain novel molecular receptors for molecular recognition.[1] Their diverse applications have been primarily due to functionalization at the hydroxyl group (lower rim) and/or at the *p*-position of the phenolic units (upper rim) of the calixarene architecture. Formyl calix[*n*]arenes are one of the most important types of substrates for synthesizing substituted calixarenes. Several studies have been reported in recent years on the introduction of formyl groups into calixarenes[2–4] with or without regioselectivity. Likewise, the synthesis of mono-, di-, tri- and tetraformylated calix[4]arenes in low yields reported by Pochini and co-workers,[3] has been modified by our group.[4a] It has been determined that all the procedures described thus far, for formylated calixarenes (exhaustive or regioselective), involve a three-step sequence which includes (i) de-*tert*-butylation, (ii) treatment with alkyl halide to yield calix[4]arene ethers and (iii) formylation to yield formyl calix[4]arenes.

Though *ipso* substitution involving nitro,[5] sulfonate,[6] acyl[7] and bromo[8] groups at the upper rim of calix[*n*]arenes has been reported by us and others, experimental conditions for the synthesis of formyl calix[4]arenes via *ipso* substitution of a *p-tert*-butyl group have not been described so far.

We report herein, a method to achieve the direct replacement of one *p-tert*-butyl group by a formyl group in *p-tert*-butylcalix[4]arenes, which may initiate new vistas in calixarene chemistry.

The required starting materials were obtained by literature procedures or minor modifications thereof. For example, monoetherification[9] of **1a** was performed with LiOH and an alkyl halide in dry dimethylformamide (DMF) at room temperature for 48 h to give **2a**[10] and **3a** in 85% and 73% yields, respectively. The diether calix[4]arenes (**4a**,[11] **5a**[12] and **6a**[13]) were synthesized by the reported procedures.

ipso Formylation of *p-tert*-butylcalix[4]arene was carried out as shown in Scheme 1. For instance, **5a** was subjected to *ipso*-monoformylation using dichloromethyl methyl ether in the presence of $TiCl_4$ as Lewis acid catalyst at room temperature for 24 h to yield **5b** in 68% yield. The ^{1}H NMR spectrum of **5b**[14] showed a typical AB pattern represented by two pairs of doublets between δ 3.31 and 3.42 and δ 4.27 and 4.31 for the axial and equatorial protons, respectively, indicating that **5b** exists in the cone conformation. The aldehydic proton appeared as a nonexchangeable singlet at δ 9.78, while the OH protons appeared at δ 7.92 and δ 9.27, disappearing on exchange with D_2O. Comparison of the ^{1}H NMR data of **5b** with that of starting compound **5a** indicated that the downfield shift of the characteristic peak of one of the phenolic OH groups from δ 7.8 to δ 9.27 is perhaps due to *ipso* formylation at the *p*-position of the phenolic unit.

Analogously, following the same experimental protocol, **2a**, **3a** and **4a** were converted into **2b**, **3b** and **4b**, respectively. Six examples of monoformylated calix[4]arenes synthesized by the optimized procedure are shown in

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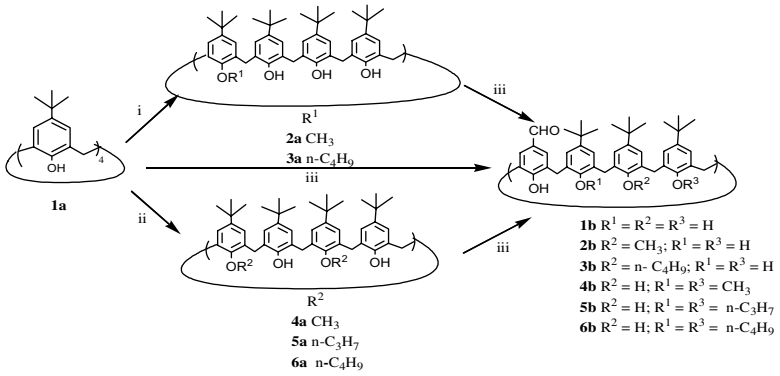

Scheme 1. Reagents and conditions: (i) R^1X, LiOH, DMF, rt; (ii) R^2X, K_2CO_3, CH_3CN, reflux; (iii) Cl_2CHOCH_3, $TiCl_4$, DCM, rt.

Table 1. The optimized yield of 5-monoformyl-tris(11,17,23-*tert*-butyl)-25,27-di-propoxycalix[4]arene **5b** could be obtained by using 50 equiv each of $TiCl_4$ and dichloromethyl methyl ether. A larger excess of the formylating reagent did not lead to multiformylation (Table 2). Even when **5b** was subjected to further *ipso* formylation, formation of di-, tri- and tetraformylated compounds could not be detected in the reaction mixture.

The regio and conformational isomerism of the synthesized monoformylated derivatives is being examined, however, preliminary NMR (^1H, ^{13}C and COSY) analysis revealed that the cone conformation of the calixarenes is preserved in the reaction. The formyl group is introduced at the aromatic position, which is not alkoxylated at the *para* position. In the case of monoalkylated monoformylated-tris(*p*-*tert*-butyl)calix[4]arenes, the formyl group in principle can be attached to the distal aromatic ring in front of the alkylated phenol or on the proximal aromatic ring. The appearance of two singlets, each for the *p*-*tert*-butyl group and the methylene bridge, and 12 singlets in the ^{13}C NMR for aromatic carbons revealed that **2b** is the distal isomer which was confirmed by a COSY NMR spectrum. Though the ^1H NMR spectral pattern for **3b** was not unambiguous, COSY and ^{13}C NMR data favour the distal disposition of the formylated and alkylated phenol ring.[15]

The reaction was found to be dependent upon the temperature. The optimum yield of monoformyl derivative **5b** (68%) was obtained when the reaction was performed at 35 °C. Lowering the reaction temperature from 35 to 0 °C was found to decrease the overall yield of the *ipso* formylated product (Table 3). Thus, when the reaction was performed at low temperature (0 °C), it required approximately 48 h for completion. At reflux temperature, the same reaction required 4 h for completion but with a decreased yield of the target compound. These results are contrary to those observed in earlier published methods on formylation of debutylated calixarenes when larger yields of mono- and diformyl derivatives were obtained at lower temperatures.[3a]

Apparently, it appears that further formylation of monoformyl tris(*tert*-butyl)calix[4]arenes does not take place presumably due to steric crowding of the potential intermediate involved and the relative stability of different formyl calixarene derivatives.

We conclude that the selective monoformylated calix[4]-arenes can be obtained through *ipso* formylation of *p*-*tert*-butylcalix[4]arene ethers. The reaction is sensitive to temperature and reagent concentration but seems to be independent of the ether group at the lower rim. This convenient access to monoformyl *p*-*tert*-butyl-calix-[*n*]arenes opens a new perspective on calix[4]arene chemistry.

Table 1. Different products of *ipso* formylation

Entry	Reactant	Reaction time (h)	Product	Yield (%)
1	**1a**	18	**1b**	65
2	**2a**	10	**2b**	72
3	**3a**	53	**3b**	57
4	**4a**	15	**4b**	63
5	**5a**	24	**5b**	68
6	**6a**	65	**6b**	55

Table 2. Effect of reaction conditions on the yields of compound **5b**

$TiCl_4$ (equiv)	Cl_2CHOCH_3 (equiv)	Time (h)	Product	Yield (%)
25	50	12	**5b**	37
30	30	48	**5b**	40
35	35	48	**5b**	55
40	40	48	**5b**	57
50	50	18	**5b**	68
75	75	10	**5b**	68

Table 3. Effect of the temperature and reaction time on the formylation of **5a**

Temperature (°C)	Time (h)	Yield (%)
0	48	68
25	24	68
35	18	55
Reflux	4	45

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9. The physical constants and spectroscopic data for starting materials (**2a**,[10] **4a**,[11] **5a**[12] and **6a**[13] were identical with those published earlier in Refs. 10–13). General experimental procedure for the synthesis of 25-mono-alkoxy-5,11,17,23-tetrakis(*tert*-butyl)calix[4]arene **2a**, **3a**: A suspension of 5,11,17,23-tetra-(*tert*-butyl)calix[4]arene (1.5 mmol), LiOH (30 mmol) and alkyl halide (10 mmol) in DMF (10 mL) was stirred at room temperature for 48 h. The reaction mixture was quenched with 10% HCl (100 mL) and extracted with chloroform. The organic phase was separated and washed with water. The $CHCl_3$ layer was dried over Na_2SO_4 and the solvent distilled to afford a crude product which could be purified by column chromatography (hexane–chloroform 1:1). Compound **3a**: Found: C, 81.51; H, 9.11. $C_{48}H_{64}O_4$ requires C, 81.77; H, 9.15; FAB-MS *m*/*z* Calcd: 704.48. Found 705. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18, 1.21 and 1.26 (3s, 36H, –C(CH_3)$_3$), 1.09 (t, 3H, $J = 7.3$ Hz, CH_3), 1.67 (quintet, 2H, $J = 7.4$ Hz, –$OCH_2CH_2CH_2CH_3$), 2.13 (quintet, 2H, $J = 7.35$ Hz, –$OCH_2CH_2CH_2CH_3$), 3.37 and 3.42 (2d, 4H, $J = 14.1$ Hz, ArCH_2Ar), 4.13 (t, 2H, $J = 6.9$ Hz, OCH_2), 4.25 and 4.34 (2d, 4H, $J = 13.7$ Hz, ArCH_2Ar), 6.98, 7.01, 7.03, 7.07 (4s, 8H, Ar*H*), 9.41 and 9.96 (2s, 3H, D_2O exch. O*H*).
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14. General procedure for the synthesis of monoformyl calix[4]arenes (**1**–**6**)**b**: To a solution of calix[4]arene (0.07 mmol) in dichloromethane (35 mL) were added a solution of 1,1-dichloromethyl methyl ether (3.5 mmol) in dichloromethane (5 mL) and a solution of titanium tetrachloride (3.5 mmol) in dichloromethane (5 mL) simultaneously and as quickly as possible. The reaction mixture was stirred at room temperature until the starting material had been consumed (TLC) and was quenched with ice cold water (50 mL). The organic layer was separated, washed twice with water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to yield the desired monoformyl calix[4]arene product. The synthesis and characterization of new monoformyltris(*p*-*tert*-butyl)calix[4]arenes are discussed below: Compound **1b**: Starting compound **1a**, reaction time 18 h, eluent chloroform. Compound **1b**; 65% yield; mp > 250 °C. Found: C, 79.50; H, 7.75. $C_{41}H_{48}O_5$ requires C, 79.32; H, 7.79; FAB-MS *m*/*z* Calcd: 620.82. Found 620. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18, 1.21 (2s, 27H, –C(CH_3)$_3$), 3.53 (br s, 4H, ArCH_2Ar), 4.26 (br s, 4H, ArCH_2Ar), 7.03, 7.08, 7.10 and 7.61 (4s, 8H, Ar*H*), 9.7 (s, 1H, C*H*O), 10.33 (s, 4H, D_2O exch. O*H*). Compound **2b**: Starting compound **2a**, reaction time 10 h, recrystallization: chloroform/methanol. Compound **2b**: 72% yield; mp 112 °C. Found: C, 79.50; H, 7.92. $C_{42}H_{50}O_5$ requires C, 79.46; H, 7.94; FAB-MS *m*/*z* Calcd: 634.84. Found: 635. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88, and 1.22 (2s, 27H, –C(CH_3)$_3$), 3.34 and 3.44 (2d, 4H, $J = 13$ Hz, ArCH_2Ar), 3.89 (s, 3H, –OCH_3), 4.18 (d, 4H, $J = 13.2$ Hz, ArCH_2Ar), 6.68, 6.78, 7.00 and 7.18 (4s, 8H, Ar*H*), 9.76 (s, 1H, C*H*O), 8.44 and 7.58 (2s, 3H, D_2O exch. O*H*); ^{13}C NMR ($CDCl_3$): δ 31.0, 31.2, 31.3, 31.6, 63.5, 125.0, 125.3, 126.2, 127.7, 128.4, 129.0, 130.8, 132.5, 147.4, 150.1, 151.0, 159.5, 191.1. Compound **3b**: Starting compound **3a**, reaction time 53 h, eluent for chromatography (hexane–chloroform 1:1). Compound **3b**: 57% yield; mp 125 °C. Found: C, 79.73; H, 8.37. $C_{45}H_{56}O_5$ requires C, 79.84; H, 8.34; FAB-MS *m*/*z* Calcd: 676.92. Found: 677. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, $J = 7.2$ Hz, CH_3), 1.07, 1.09 and 1.36 (3s, 27H, –C(CH_3)$_3$), 1.26 (sextet, 2H, $J = 4.5$ Hz, $OCH_2CH_2CH_2CH_3$), 1.79 (quintet, 2H, $J = 7.1$ Hz, –$OCH_2CH_2CH_2CH_3$), 3.21 and 3.26 (2d, 4H, $J = 13.7$ Hz, ArCH_2 Ar), 3.52 (t, 2H, $J = 7.2$ Hz, –OCH_2), 3.84 and 3.90 (2d, 4H, ArCH_2Ar), 6.74, 6.81, 6.85, 6.89, 6.94, 7.15, 7.24 and 7.19 (8s, 8H, Ar*H*), 8.17 (s, 1H, C*H*O), 8.76 and 7.57 (2s, 3H, D_2O exch. O*H*). ^{13}C NMR ($CDCl_3$): δ 14.0, 22.6, 25.9, 29.7, 29.9, 31.2, 31.9, 78.0, 125.0, 125.4, 128.5, 129.3, 130.8, 132.3, 141.2, 146.6, 149.8, 150.8, 151.7, 159.6, 190.8. Compound **4b**: Starting compound **4a**, reaction time 15 h, eluent hexane–EtOAc 95:5. Compound **4b**: 63% yield; mp 114 °C. Found: C, 79.50; H, 8.01. $C_{43}H_{52}O_5$ requires C, 79.59; H, 8.08; FAB-MS *m*/*z* Calcd: 648.87. Found: 649. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 and 1.24 (2s, 27H, –C(CH_3)$_3$), 3.24 and 3.27 (2d, 4H, $J = 13.3$ Hz, ArCH_2Ar), 3.83 (s, 6H, –OCH_3), 4.11 (d, 4H, $J = 13.1$ Hz, ArCH_2Ar), 6.71, 6.77, 7.01 and 7.04 (4s, 8H, Ar*H*), 9.85 (s, 1H, C*H*O), 7.36 and 8.32 (2s, 2H, D_2O exch. O*H*). Compound **5b**: Starting compound **5a**, reaction time 24 h, solvent for recrystallization: chloroform/methanol. Compound **5b**: 68% yield; mp 109–110 °C. Found: C, 80.10; H, 8.65. $C_{47}H_{60}O_5$ requires C, 80.07; H, 8.58; FAB-MS *m*/*z* Calcd: 704.98. Found: 705. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 and 1.25 (2s, 27H, –C(CH_3)$_3$), 1.3 (t, 6H, $J = 6.4$ Hz, –$OCH_2CH_2CH_3$), 2.05 (sextet, 4H, $J = 6.69$ Hz, –$OCH_2CH_2CH_3$), 3.31 and 3.42 (2d, 4H, $J = 13.1$ Hz, ArCH_2Ar), 3.95 (t, 4H, $J = 8.9$ Hz, –OCH_2-CH_2CH_3), 4.27 (d, 4H, $J = 12.7$ Hz, ArCH_2Ar), 6.85, 6.94, 7.03 and 7.62 (4s, 8H, Ar*H*), 9.78 (s, 1H, C*H*O), 7.92 and 9.27 (2s, 2H, D_2O exch. O*H*); ^{13}C NMR ($CDCl_3$): δ 10.8,

23.4, 31.1, 31.6, 34.0, 78.2, 124.9, 125.2, 126.1, 127.6, 128.3, 128.9, 130.9, 131.3, 133.3, 141.6, 147.3, 149.8, 150.4, 160.0, 191.1. Compound **6b**: Starting compound **6a**, reaction time 65 h, solvent for recrystallization: chloroform/methanol. Compound **6b**: 55% yield; mp 143 °C. Found: C, 80.32; H, 8.75. $C_{49}H_{64}O_5$ requires C, 80.29; H, 8.75; FAB-MS *m/z* Calcd: 733.03. Found: 733. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 and 1.18 (2s, 27H, –C(CH_3)$_3$), 1.0 (t, 6H, $J = 7.1$ Hz, CH_3), 1.68 (sextet, 4H, $J = 7.14$ Hz, –$OCH_2CH_2CH_2CH_3$), 1.95 (quintet, 4H, $J = 6.5$ Hz, –$OCH_2CH_2CH_2CH_3$), 3.24 and 3.35 (2d, 4H, $J = 13.1$ Hz, ArCH_2Ar), 3.91 (t, 4H, $J = 7.0$ Hz, –OCH_2), 4.20 (d, 4H, $J = 12.6$ Hz, ArCH_2Ar), 6.77, 6.89, 6.96 and 7.55 (4s, 8H, Ar*H*), 9.71 (s, 1H, C*H*O), 9.17 and 7.81 (2s, 2H, D_2O exch. O*H*).

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