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# Convenient Direct Synthesis of Bisformylated Calix[4]arenes via *Ipso* Substitution

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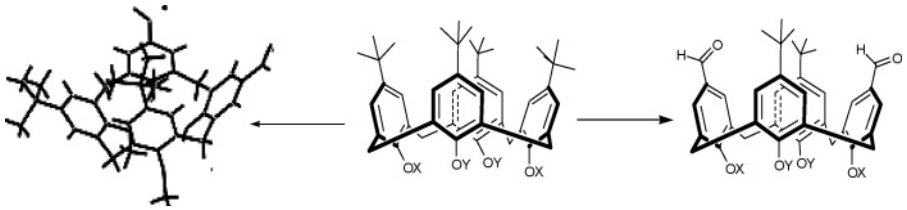
## ABSTRACT




**A facile synthesis of bisformylated calix[4]arenes via *ipso* substitution of *p-tert*-butylcalix[4]arenes through treatment with hexamethylenetetramine/trifluoroacetic acid is described. Under identical conditions, *p-tert*-butylcalix[4]arene tetramethyl ether 4 gives proximally substituted bisformylated derivative 4a in a pinched cone conformation.**

[1*n*] Metacyclophanes represented by calix[*n*]arenes are accessible through acid- or base-catalyzed condensation of *p-tert*-butylphenols with formaldehyde.[1] The spectacular development of calix[4]arenes as molecular receptors is related to many possible structural and functional modifications of their core molecular architecture[2] which constitutes a hollow cavity flanked by a hydrophobic upper rim and a hydrophilic lower rim. Regioselective functionalization of the upper rim can be achieved through partial or total de-*tert*-butylation of *p-tert*-butylcalix[4]arenes followed by the appropriate derivatization.[3] There is a need for direct upper rim functionalization in *p-tert*-butylcalix[4]arenes to introduce suitable signaling functions.[4,5] We report herein a very efficient direct method for the introduction of two formyl groups by *ipso* substitution of *p-tert*-butyl groups in parent *p-tert*-butylcalix[4]arenes in the hope that the method will enrich the chemical repertoire of these calix[4]arenes because the method provides easy access to novel bis- and trisformyl calixarenes to allow synthesis of complex molecular receptors for ionic and molecular recognition.[6]

In our experiments, we have employed hexamethylenetetramine (HMTA) and trifluoroacetic acid (TFA) as reagents for *ipso* formylation. The reaction allowed the isolation of four bisformylated bis(*tert*-butyl)calix[4]arenes[12] which were characterized by IR and $^1$H NMR spectral analyses, as shown in Table 1.

Thus, when *p-tert*-butylcalix[4]arene **1** was reacted with hexamethylenetetramine (HMTA) in trifluoroacetic acid, it

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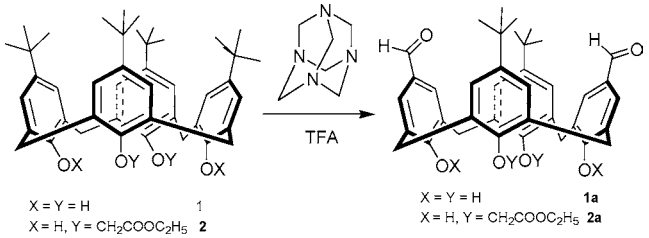
**Table 1.** IR and $^1$H NMR (300 MHz, $CDCl_3$, 25 °C) Assignment of Characteristic Signals of *Ipso*-Formylated Products

| | | | | | $^1$H NMR | |
|---|---|---|---|---|---|---|
| reactant | product | reaction time (h) | % yield | IR $\nu_{C=O}$ | ArC$H_2$Ar | C($CH_3$)$_3$ |
| 1 | **1a** | 18 | 78 | 1683 | 4.26(bs), 3.66(bs) | 1.23(s) |
| 2 | **2a** | 24 | 85 | 1685 | 4.44(d), 3.45(d) | 1.02(s) |
| 3 | **3a** | 24 | 80 | 1686 | 4.19(d), 3.38(d) | 0.95(s) |
| 3 | **3a** | 72 | 66 | 1686 | 4.19(d), 3.38(d) | 0.95(s) |
| 3 | **3b** | 72 | 12 | 1685 | 4.24(d), 4.35(d), 3.57(d), 3.47(d) | 1.04(s) |
| 3 | **3c** | 72 | 18 | 1685 | 4.27(d), 4.33(d), 3.57(d), 3.50(d) | |
| 4 | **4a** | 24 | 62 | 1690 | 4.23−4.46(4d) 3.22−3.48(4d) | 0.75(s), 1.38(s) |

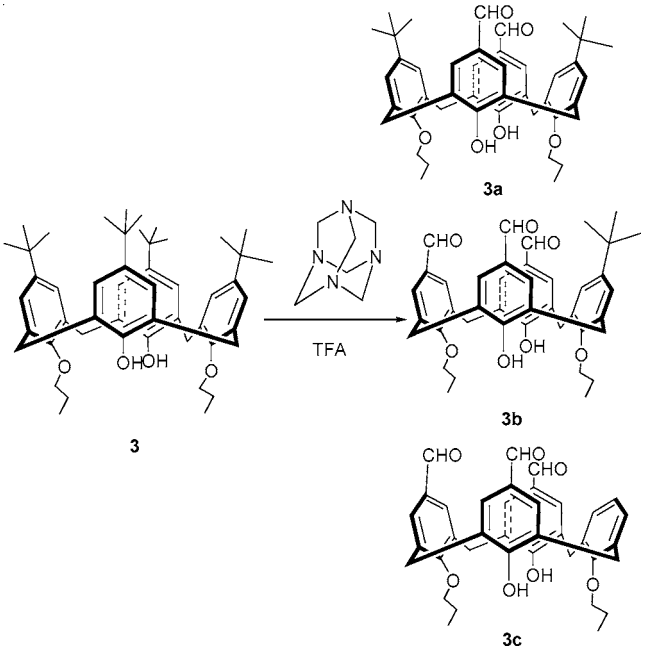
afforded bisformyl bis(*tert*-butyl)calix[4]arene **1a** in 78% yield (Scheme 1). The $^1$H NMR spectrum of **1a** in $CDCl_3$ displayed a very simple profile with resonance signals integrating for 18H for the *tert*-butyl substituent at $\delta$ 1.23 ppm and characteristic broad singlets for methylene bridge protons ($\delta$ = 3.66 and 4.26). The broadness of singlets in this case is probably due to conformational flexibility of the isolated bisformylated calix[4]arene. Detailed NMR investigations revealed that out of two possible bisformylated products, the reaction favors the formation of a distally substituted bisformyl derivative. Though the exact mechanism is uncertain at this stage, the reaction probably takes place through the initially formed iminium ion to yield calixarene imines which get hydrolyzed to provide formylated products.[7]

**Scheme 1.** Regioselective *Ipso* Formylation of Calix[4]arene




The utility of the reaction was indicated by the fact that the reaction is regioselective. The yield of the product was found to be dependent upon the nature of the O substituent. Thus, when **2**[8] was subjected to *ipso* formylation, only one product, 1,3-diformyl derivative **2a**, could be isolated in 85% yield even without column purification to indicate that the formyl group gets introduced at a position para to the free phenolic group. A prolonged reaction time or excess of reagents did not lead to further formylation. On the other hand, when the reaction was tried with dipropyl ether of calix[4]arene **3**[9] under reflux conditions for 72 h, it gave the expected product **3a** in 66% yield as well as additional compounds identified as **3b** and **3c** in 12% and 18% yield. (Scheme 2). Upon restricting the reaction time to 24 h in this case, bisformylated derivative **3a** was obtained in 80% yield. A further decrease in the reaction time resulted in an incomplete reaction.

**Scheme 2.** Different Products Obtained on *Ipso* Formylation of Calix[4]arene Dipropyl Ether **3**




The products obtained from **3** were separated by silica gel chromatography and were identified as cone conformers by $^1$H NMR analysis. **3a** was identified as a bisformylated derivative, and **3b** and **3c** were found to be trisformyl derivatives of calix[4]arene dipropyl ether **3**. One of these trisformyl calix[4]arenes contained the *p-tert*-butyl group (**3b**) at the fourth aromatic ring, whereas the other trisformyl derivative did not have the *p-tert*-butyl group (**3c**). These trisformyl calix[4]arene derivatives exhibit characteristic pairs of doublets for methylene bridge protons and two overlapping signals for OPr group protons. The distinguishing feature in the spectra of these two derivatives is the appearance of a doublet at $\delta$ 6.91 and a triplet at $\delta$ 6.77 indicating the

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presence of a debutylated phenyl ether ring in **3c**. On the other hand, the $^1$H NMR spectrum of **3b** displayed three singlets at $\delta$ 7.68 (2H), 7.49(1H), and 6.91 (1H) for aromatic protons and a singlet at $\delta$ 1.04 (9H) for *p-tert*-butyl group protons (Figure 1).

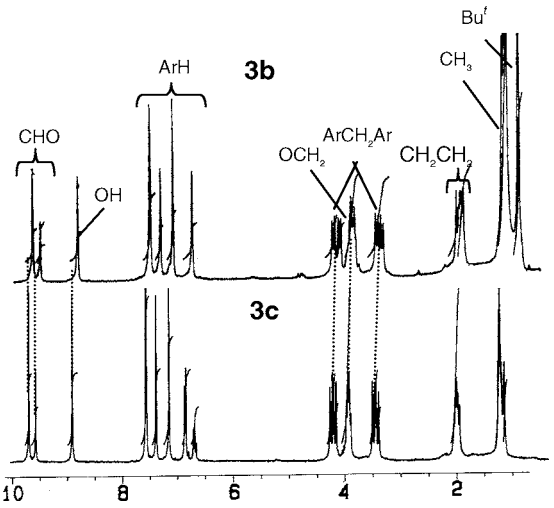
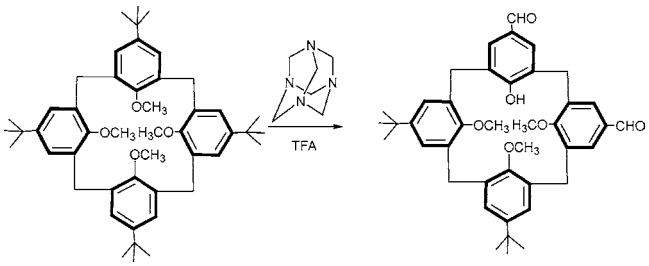



**Figure 1.** $^1$H NMR spectrum (300 MHz, $CDCl_3$, 25 °C) of **3b** and **3c**.

It was interesting to observe that when completely alkylated calix[4]arenes such as **4**[10] were treated with HMTA in TFA, they also underwent partial demethylation to give bisformyl bis(*p-tert*-butyl)calix[4]arene trimethyl ether, **4a** (Scheme 3), which exhibited four pairs of doublets for the

**Scheme 3.** *Ipso* Formylation of Calix[4]arene Tetramethyl Ether




methylene protons in the range of $\delta$ 3.23−3.48 and 4.23−4.46 (Figure 2) in its NMR spectrum. Two singlets for the

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(12) **General procedure for the synthesis of bisformyl calix[4]arenes (1−4)a**: *p-tert*-Butylcalix[4]arene (0.15 mol) and hexamethylenetetramine (6.17 mmol) were taken in trifluoroacetic acid (50 mL). The reaction mixture was refluxed until the starting materials had disappeared (TLC). On completion, the mixture was quenched with ice cold water and extracted with chloroform. The organic layer was washed with water and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure, and the residue was purified as mentioned to yield the desired bisformyl calix[4]-arene product.

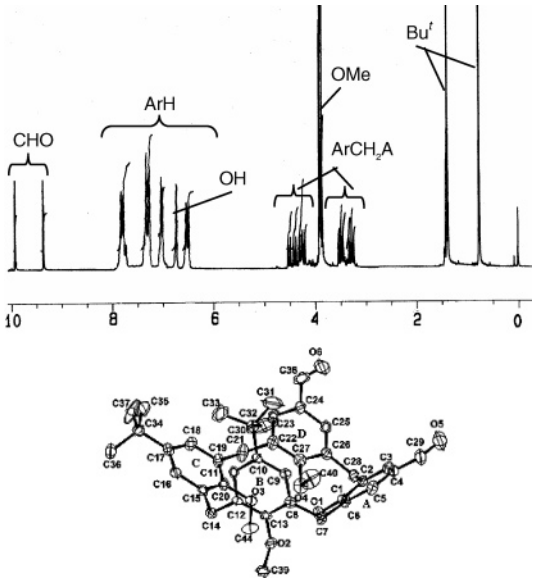


**Figure 2.** $^1$H NMR spectrum (300 MHz, $CDCl_3$, 25 °C) and ORTEP diagram (hydrogens and the disordered oxygen of the formyl group are omitted for clarity) of **4a**.

*tert*-butyl groups and three signals for the methoxy group indicated that **4a** is a highly unsymmetrical compound with proximal substitution of the formyl group. Notably, a signal for one of the methoxy protons resonated at a relatively higher field ($\delta$ 3.84) as compared to the other two methoxy groups ($\delta$ 3.88 and 3.90). This is probably because the methoxy group is located within the shielding region of the neighboring aryl groups. The presence of a molecular ion peak at *m*/*z* 634 in its FAB-MS spectrum is in accordance with the bisformyl derivative **4** in which one methoxy group was demethylated. The presence of one OH group was also supported by a broad band in its IR spectrum at 3505 cm$^{-1}$.

To rule out the possibilities of other possible products, the structure of **4a** was unequivocally confirmed by its single-

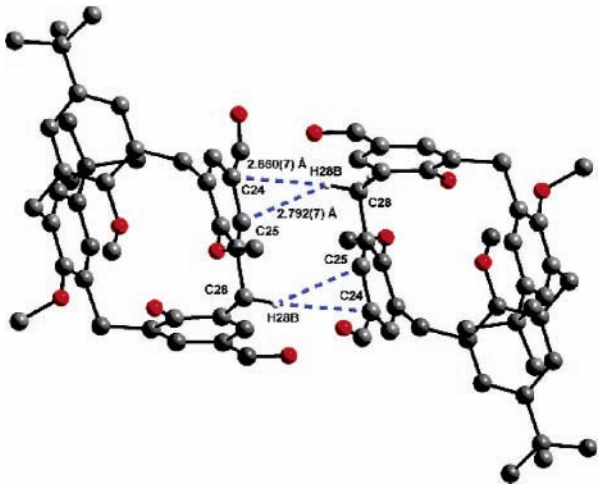


**Figure 3.** CH−$\pi$ interactions in **4a**. Distances are given in Å.

crystal X-ray analysis.[13] Diffraction-grade crystals of **4a** were obtained by slow crystallization from chloroform−methanol. It was determined that **4a** adopts a pinched cone conformation. The dihedral angles between the mean plane defined by the four methylene bridges and aromatic rings B and D are 87.96° and 82.62°, respectively, and the planes of the other two rings A and C are pinched to form an angle of 33.62° and 33.70°, respectively. The oxygen (O6) of the formyl group at the anisole ring is disordered at two crystallographically independent positions with 50% occupancy. **4a** is characterized by four intermolecular CH/$\pi$ interactions between one of the methylene bridge hydrogens and the aromatic ring (Figure 3). The presence of one intramolecular (OH···O) and two intermolecular (CHO···H) hydrogen bond interactions could be easily discerned (Figure 4).

The formation of a proximally substituted product with partial dealkylation instead of a distally substituted formyl derivative is under investigation in our lab.

We conclude that two formyl groups in one pot can be introduced via *ipso* formylation of *p-tert*-butylcalix[4]arene with HMTA/TFA. Such a selectivity is unprecedented and is influenced by the nature of the substituent R (alkyl/ester) on the phenolic units of the calix[4]arene. The gathered results suggest that the reaction is sequential, and a prolonged treatment may promote exhaustive formylation in the absence of steric hindrance as observed in the case of debutylated calix[4]arenes with HMTA.[11]

(13) Crystal data of **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 294073.


**Figure 4.** H-bonded network found in the X-ray crystal structure of **4a** among the CHO···OMe group. CH−$\pi$ interactions in **4a**. Distances are given in Å.

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**Supporting Information Available:** Characterization details of compounds **(1−4)a**, **3b**, and **3c** as well as details of crystal structure and refinement in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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