EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200252

Convenient Direct Syntheses of Selectively *para*-Substituted Di-, Tri- and Tetra-Formylated Thiacalix[4]arenes

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Keywords: Calixarenes / Regioselectivity / Formylation / Substituent effects / Synthetic methods

An efficient direct method for di-, tri- and tetraformylation of thiacalix[4]arenes substituted on the *para* positions is described. Di- and triformylated thiacalix[4]arenes were obtained by formylation of partially propyl- or benzoyl-substituted thiacalix[4]arenes. Complete *para*-formylation was successfully achieved by formylation and dealkylation of tetraisopropoxythiacalix[4]arene conformers in one step. This experimental procedure is a simpler synthesis for completely formylated thiacalix[4]arene than the indirect method reported previously from brominated thiacalix[4]arene.

Introduction

Thiacalix[4]arenes – in which all four methylene bridges from the conventional calix[4]arene are replaced by sulfide bonds – have attracted considerable interest in the broad field of supramolecular chemistry since their first appearance in 1997.[1] The presence of sulfur atoms makes thiacalix[4]arenes very interesting molecules with properties that are not present in the chemistry of classical calixarenes.[2] However, after more than a decade of research, the use of thiacalixarenes in supramolecular chemistry remains restricted because of an absence of suitable methods for regioselective or stereoselective substitution and functionalization of the thiacalix[4]arene skeleton.[2]

Calixarenes formylated on the upper rims obtained through the Gross or Duff reaction are well known and provide useful intermediates for molecular receptors.[3,4] In contrast, formylation of tetraalkoxythiacalix[4]arenes by using conventional methods gives *meta*-substituted products only. The Gross formylation of tetrahydroxythiacalix[4]arene by treatment with $TiCl_4$ gives no reaction.[5] To the best of our knowledge, there is only one example of exclusively *para*-formylated thiacalix[4]arenes, which uses an indirect method from brominated thiacalix[4]arene.[5a,6] The method is a multistep reaction with strict conditions. Therefore, a convenient method to prepare selectively *para*-formylated thiacalix[4]arenes is needed. As reported, partially substituted thiacalix[4]arenes could undergo an electrophilic aromatic substitution reaction to give the corresponding *para*-substituted derivertives (bromination and nitration).[6,7] Therefore, we attempted to synthesize di- and triformylated thiacalix[4]arene derivertives through formylation of partially propyl- or benzoyl-substituted thiacalix[4]arenes. The synthesis of tetraformylated thiacalix[4]arene by using this method is not possible owing to unequal electronic density distributions between the substituted and unsubstituted phenol rings. According to our previous study, isopropyl groups selectively dealkylate during the Duff reaction of calix[4]arenes.[8] Thus, we decided to prepare *para*-tetraformylthiacalix[4]arene derivatives by using a "formylation and deprotection in one step" method.

Results and Discussion

Dipropoxythiacalix[4]arene derivative **1**[9] was prepared according to a known procedure, and its upper rim substitution was carried out by using the Duff reaction. Compound **1** was treated with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) for 72 h to afford a crude mixture that was determined by TLC to be two products. The main products, **1a** and **1b**, were isolated by column chromatography on silica gel in 27 and 50% yields, respectively (Scheme 1). The ^{1}H NMR spectrum of compound **1a** (Figure 1) shows singlets at δ = 9.87 ppm (2 H), corresponding to the formyl groups, and δ = 8.18 ppm (4 H), corresponding to the H atoms of the aromatic rings, indicating that two formyl groups were successfully introduced at the *para* positions of the phenol rings. For compound **1b**, two singlets [δ = 8.21 (4 H) and 8.16 (2 H) ppm] in the aromatic part of the spectrum indicate the presence of two kinds of *para*-substituted aromatic rings. The structure was further confirmed by the presence of two different triplets for the $-OCH_2-$ groups (δ = 4.51 and 4.25 ppm) and two singlets for the formyl groups (δ = 9.92 and 9.23 ppm).

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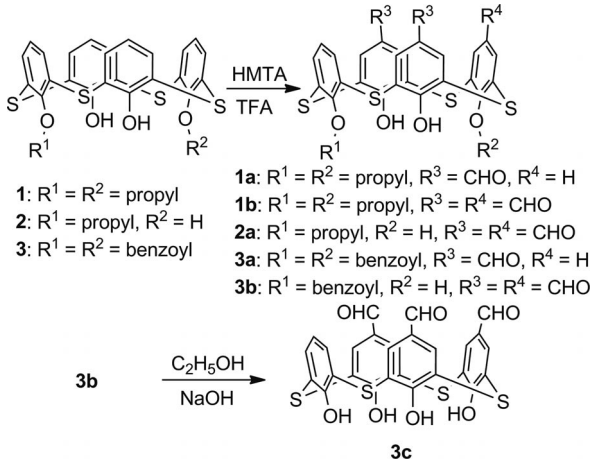
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200252.



Scheme 1. Preparation of di- and triformylated thiacalix[4]arenes.

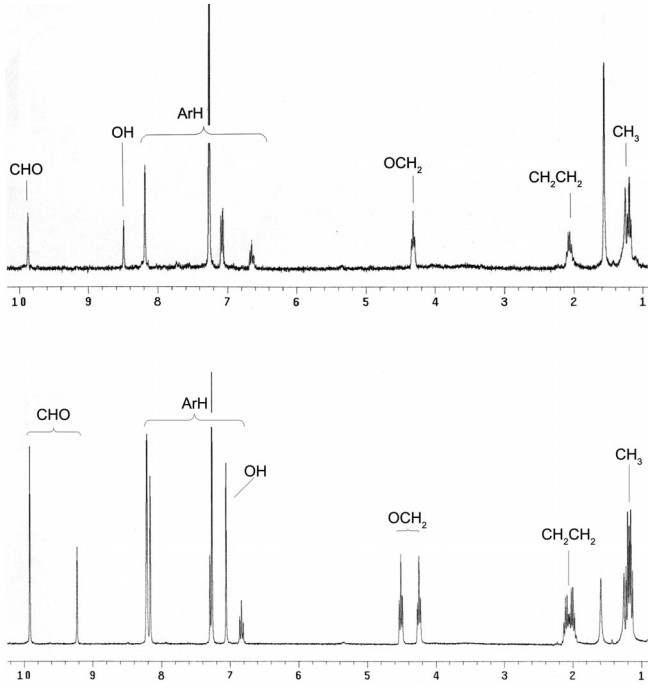


Figure 1. ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of compounds **1a** (top) and **1b** (bottom).

In order to prepare di- and triformylated thiacalix[4]-arenes more selectively, two partially substituted derivatives **2**[7c] and **3**[7a] were prepared (Scheme 1). When **2** was subjected to formylation for 72 h only one product, triformyl derivative **2a**, was isolated in 71% yield. The spectrum of **2a** displayed two characteristic broad singlets for the Ar–OH protons in the ratio of 2:1. No distinct downfield shift for the resonance signals of Ar–OCH_2– ($\Delta\delta$ = 0.02 ppm) was observed. Thus, **2a** was a triformylated derivative in which the alkylated phenol ring was not substituted. The structure of **2a** was unequivocally confirmed by single-crystal X-ray diffraction analysis. Suitable crystals of **2a** were obtained by slow crystallization from $CHCl_3$/hexane. Compound **2a** adopts a partial cone conformation in which one of phenol rings linking with the alkylated ring is inverted from top to bottom (Figure 2).

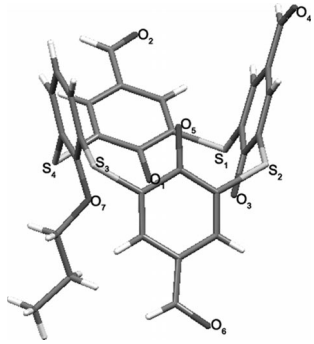


Figure 2. Crystallographic structure of compound **2a**.

When the reaction was carried out with dibenzoxythiacalix[4]arene **3** under reflux conditions for 24 h, **3a** was isolated in 69% yield as well as a small amount (19%) of monobenzoyl compound **3b** (Scheme 1). The solubilities of compounds **3a** and **3b** differ greatly. Compound **3a** dissolves easily in $CHCl_3$, whereas **3b** only dissolves in strong polar solvents (e.g., methanol, acetone, DMF, and DMSO). The structure of **3a** was confirmed by ^{1}H NMR spectroscopy. In addition, X-ray diffraction analysis confirmed that **3a** was *para*-formylated and adopts a pinched-cone conformation (Figure 3). The two opposite phenol units bearing formyl groups are pointing outward with an interplanar angle of approximately 131°. The remaining aromatic units are tilted toward each other inside the cavity with an interplanar angle of 39.6°.

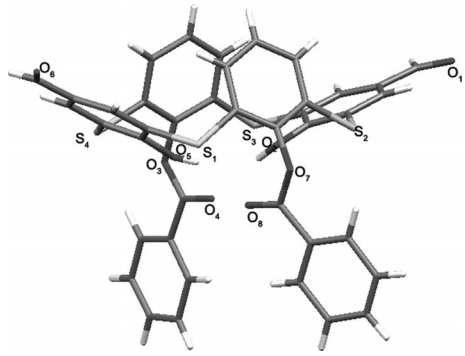


Figure 3. Crystallographic structure of **3a**. Disordered water molecules are omitted for clarity.

The ^{1}H NMR and ^{13}C NMR spectra of **3b** showed very complicated splitting patterns in the aromatic regions owing to the presence of five phenol rings in different chemical or magnetic environments. According to the ESI-MS data, which showed a peak at *m*/*z* = 683 in negative-ion mode, compound **3b** was determined to be a triformylated monobenzoxythiacalix[4]arene. Because we were not able to obtain suitable crystals for X-ray diffraction analysis to confirm the structure of **3b**, we decided to hydrolyze the benzoxy group. When heated to reflux with NaOH in eth-

anol for 12 h compound **3b** afforded **3c** in almost quantitative yield (Scheme 1). The ^{1}H NMR spectral data of **3c** (showing two singlets for the formyl groups at δ = 9.67 and 9.63 ppm in a ratio of 1:2) and ESI-MS data (m/z = 579.3 in negative-ion mode) proved that **3c** was a triformylated thiacalix[4]arene (Figure 4) and also confirmed the structure of **3b**. Interestingly, when the reaction time for the formylation of **3** was extended to 72 h, the yields of compounds **3a** and **3b** changed to 31 and 48%, respectively. However, completely debenzoylated products were not isolated even when the reaction time was further prolonged. It is possible that the esterification reaction is reversible under acidic conditions.

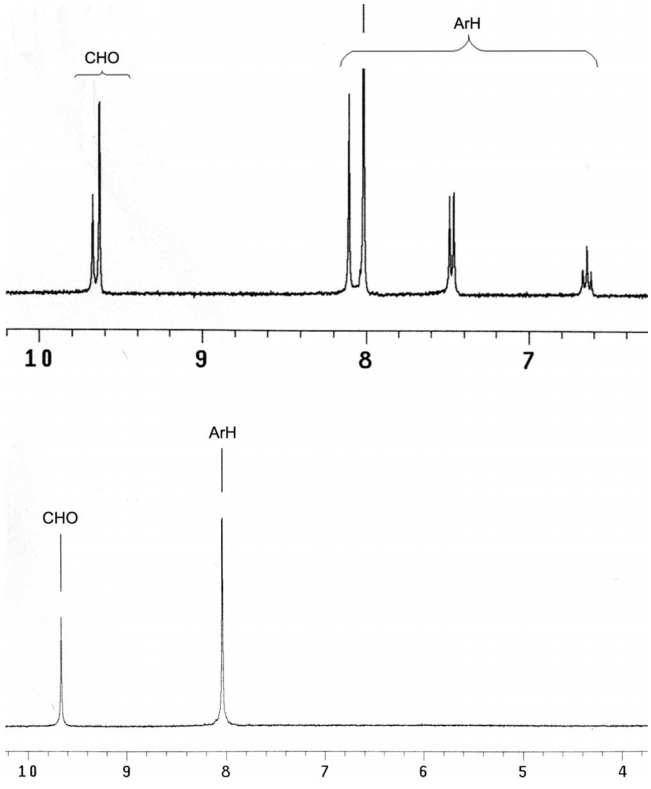
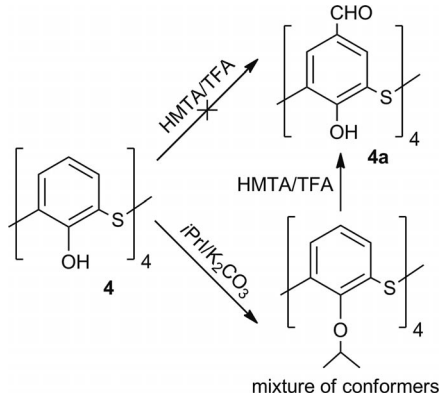


Figure 4. ^{1}H NMR spectra (300 MHz, [D$_6$]DMSO, 298 K) of **3c** (top) and **4a** (bottom).

Complete formylation of partially substituted thiacalix[4]arenes is difficult to achieve directly, because the electronic density distributions are not equal between the substituted and unsubstituted phenol rings. Considering the preference for *meta* substitution of tetraalkoxy thiacalix[4]arenes,[5] we attempted to prepare *para*-tetraformylated thiacalix[4]arene by using **4** as the starting compound. However, the Duff reaction did not work in our hands.

Inspired by the formylation of compound **3**, we decided to prepare a *para*-tetraformylthiacalix[4]arene derivative by a "formylation and deprotection in one step" method. As mentioned above, because of the reversible nature of the ester bond, a benzoyl group was not suitable. Monodemethylation and monodepropylation have been observed by treating tetramethylated *p-tert*-butylcalix[4]arene under Duff reaction conditions[10] and tetrapropylated thiacalix[4]arene under Gross reaction conditions,[5a] respectively. However, in reactions with compounds **1** and **2**, even with prolonged reaction times, no dealkylation and further formylation took place. According to our previous study, isopropyl groups on calix[4]arenes would dealkylate selectively under Duff reaction conditions.[8] In addition, the preparation of tetraalkylated thiacalix[4]arene was easier to achieve than that of partially substituted derivatives. Therefore, tetraisopropoxythiacalix[4]arene was prepared as the starting compound.

Compound **4** was treated with isopropyl iodide in acetone with K_2CO_3 as a base according to a literature procedure (Scheme 2).[11] The crude products[12] were treated with HMTA in TFA for 120 h without purification to give tetraformylated tetrahydroxythiacalix[4]arene **4a** successfully in 70% yield. The structure of **4a** was confirmed by the simple ^{1}H NMR (Figure 4) and ^{13}C NMR spectra and the ESI-MS data (m/z = 607.1).



Scheme 2. Preparation of completely formylated thiacalix[4]arene **4a**.

The formation of *meta*- or *para*-substituted products is probably related to the activating abilities of the substituents on the benzene rings. The activating ability of the sulfide bonds is stronger than that of methylene bridges of conventional calix[4]arenes. Therefore, in the reactions of tetrapropoxythiacalix[4]arenes, the sulfide bonds play a major role, and the formyl groups are introduced in the *meta* positions (*ortho*/*para* positions of the sulfide bonds). Whereas for the unsubstituted phenol rings, the activating ability of the –OH groups is stronger than both of the –OR groups and the sulfide bonds, resulting in formyl groups being introduced at the *para* positions of the –OH groups.

Conclusion

Di- and triformylated thiacalix[4]arenes substituted on the *para* positions were obtained by formylation of partially propyl- or benzoyl-substituted thiacalix[4]arenes. The number of introduced formyl groups at the upper rims was influenced by the nature and number of the substituents on the lower rims. Prolonged reaction times resulted in the hydrolysis of one of the benzoyl groups of dibenzoxythiacalix[4]arene to give a triformylated product. Inspired by this, complete *para*-formylation was successfully achieved by for-

mylation and dealkylation of tetraisopropoxythiacalix[4]-arene conformers in one step. This new direct formylation method provides a new route to functionalized thiacalixarenes and may extend their use in synthetic procedures.

Experimental Section

General: All organic reagents were obtained from commercial suppliers and used without further purification. Organic solvents and inorganic reagents were purified according to standard drying methods before use. TLC analysis was performed on precoated glass plates. Column chromatography was performed on silica gel (200–300 mesh). All NMR spectroscopic data was recorded with an NMR spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei with TMS as an internal standard. Mass spectra were recorded by using ESI technique. Samples for elemental analysis were dried in a desiccator with P_2O_5 under vacuum at 80 °C overnight.

Compound 2: Propyl iodide (1.08 g, 6.37 mmol, 0.62 mL) was added to a suspension of **4** (0.8 g, 1.61 mmol) and K_2CO_3 (0.25 g, 1.81 mmol) in dry acetone (50 mL). The reaction mixture was heated to reflux for 100 h. An HCl solution (ca. 15 mL, 1 M) was added to the mixture (pH < 7). The aqueous layer was washed with $CHCl_3$ (3× 20 mL). The combined organic fractions were washed with water and dried with $MgSO_4$. The solution was filtered and the solvent removed under reduced pressure. After recrystallization from acetone, **2** was obtained as white solid (0.51 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (s, 3 H, ArOH), 7.62 (d, J = 7.8 Hz, 4 H, ArH), 7.53 (d, J = 7.5 Hz, 2 H, ArH), 7.44 (d, J = 7.5 Hz, 2 H, ArH), 6.90 (t, J = 7.5 Hz, 1 H, ArH), 6.74 (t, J = 7.5 Hz, 2 H, ArH), 6.64 (t, J = 7.5 Hz, 1 H, ArH), 4.31 (t, J = 6.6 Hz, 2 H, OCH_2), 2.13–2.25 (m, 2 H, CH_2CH_2), 1.25 (t, J = 7.2 Hz, 3 H, CH_3) ppm. $C_{27}H_{22}O_4S_4$ (538.71): calcd. C 60.20, H 4.12, S 23.81; found C 60.01, H 3.91, S 23.52. ESI-MS: m/z = 537 [M – H]$^-$.

General Procedure for the Synthesis of 1–3a, 1b and 3b: Substituted thiacalix[4]arene (0.6 mmol) and hexamethylenetetramine (18 mmol) were added to trifluoroacetic acid (50 mL), and the mixture was heated to reflux. When the reaction was complete, it was quenched with ice-cold water and the mixture extracted with $CHCl_3$. The organic layer was washed with water and dried with $MgSO_4$. The solution was filtered and the solvent removed under reduced pressure. The residue was purified by using column chromatography.

Compound 1a: According to the General Procedure, **1** was allowed to react for 72 h to give **1a** (0.10 g, 27%) after purification ($CHCl_3$/ethyl acetate, 60:1, v/v). M.p. > 250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.87 (s, 2 H, CHO), 8.49 (s, 2 H, ArOH), 8.18 (s, 4 H, ArH), 7.08 (d, J = 7.5 Hz, 4 H, ArH), 6.65 (t, J = 7.5 Hz, 2 H, ArH), 4.32 (t, J = 6.9 Hz, 4 H, OCH_2), 2.01–2.13 (m, 4 H, CH_2CH_2), 1.20 (t, J = 7.5 Hz, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.7, 163.6, 159.3, 138.6, 136.7, 129.1, 128.7, 125.8, 123.9, 79.5, 29.9, 23.5, 10.7, 1.3 ppm. $C_{32}H_{28}O_6S_4$ (636.81): calcd. C 60.35, H 4.43, S 20.14; found C 60.02, H 4.63, S 19.87. ESI-MS: m/z = 635 [M – H]$^-$.

Compound 1b: According to the General Procedure, **1** was allowed to react for 72 h to give **1b** (0.20 g, 50%) after purification ($CHCl_3$/ethyl acetate, 15:1, v/v). M.p. > 250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.92 (s, 2 H, CHO), 9.23 (s, 1 H, CHO), 8.21 (s, 4 H, ArH), 8.16 (s, 2 H, ArH), 7.28 (d, J = 7.5 Hz, 2 H, ArH), 7.06 (s, 2 H, ArOH), 6.83 (t, J = 7.5 Hz, 1 H, ArH), 4.51 (t, J = 6.6 Hz, 2 H, OCH_2), 4.25 (t, J = 6.3 Hz, 2 H, OCH_2), 1.95–2.15 (m, 4 H, CH_2CH_2), 1.20 (t, J = 7.5 Hz, 3 H, CH_3), 1.16 (t, J = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.4, 189.1, 163.5, 162.4, 158.7, 139.1, 138.3, 137.3, 133.61, 133.55, 132.5, 131.8, 129.2, 127.3, 124.3, 122.9, 81.6, 76.6, 23.5, 23.0, 10.4, 1.0 ppm. $C_{33}H_{28}O_7S_4$ (664.82): calcd. C 59.62, H 4.25, S 19.29; found C 59.59, H 4.56, S 19.21. ESI-MS: m/z = 663 [M – H]$^-$, 685 [M + Na^+ – 2 H]$^-$.

Compound 2a: According to the General Procedure, **2** was allowed to react for 72 h to give **2a** (0.27 g, 71%) after purification ($CHCl_3$/acetone, 3:1, v/v). M.p. 211 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.84 (s, 2 H, CHO), 9.65 (s, 1 H, CHO), 9.09 (s, 2 H, ArOH), 9.78 (s, 1 H, ArOH), 8.21 (s, 4 H, ArH), 7.94 (s, 2 H, ArH), 7.62 (d, J = 7.5 Hz, 2 H, ArH), 7.01 (t, J = 7.5 Hz, 1 H, ArH), 4.33 (t, J = 6.3 Hz, 2 H, OCH_2), 2.11–2.29 (m, 2 H, CH_2CH_2), 1.25 (t, J = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.3, 163.7, 162.9, 159.8, 140.3, 139.1, 130.6, 130.0, 127.7, 127.3, 122.2, 121.2, 81.5, 23.3, 10.7 ppm. $C_{30}H_{22}O_7S_4$ (622.74): calcd. C 57.86, H 3.56, S 20.60; found C 57.55, H 3.60, S 20.29. ESI-MS: m/z = 621 [M – H]$^-$.

Compound 3a: According to the General Procedure, **3** was allowed to react for 24 h to give **3a** (0.31 g, 69%) after purification ($CHCl_3$). M.p. > 250 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.85 (s, 2 H, ArOH), 9.07 (s, 2 H, CHO), 7.92 (t, J = 7.2 Hz, 2 H, ArH), 7.84 (d, J = 7.2 Hz, 4 H, ArH), 7.71 (d, J = 7.2 Hz, 4 H, ArH), 7.56 (t, J = 7.2 Hz, 4 H, ArH), 7.43 (s, 4 H, ArH), 7.26 (t, J = 7.2 Hz, 2 H, ArH) ppm. $C_{40}H_{24}O_8S_4$ (760.86): calcd. C 63.14, H 3.18, S 16.86; found C 62.96, H 3.35, S 16.57. ESI-MS: m/z = 759 [M – H]$^-$.

Compound 3b: According to the General Procedure, **3** was allowed to react for 72 h to give **3b** (0.20 g, 48%) after purification ($CHCl_3$/acetone, 3:1, v/v). M.p. > 250 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 9.54–9.62 (m, 3 H, CHO), 6.90–8.20 (m, 14 H, ArH) ppm. $C_{34}H_{20}O_8S_4$ (684.77): calcd. C 59.63, H 2.94, S 18.73; found C 59.49, H 2.75, S 18.52. ESI-MS: m/z = 683 [M – H]$^-$.

Compound 3c: A mixture of **3b** (0.20 g, 0.29 mmol) and NaOH (0.46 g, 11.5 mmol) in a mixture of EtOH (15 mL) and H_2O (5 mL) was heated to reflux for 12 h. After cooling, the solution was acidified to pH = 5–6 with HCl (1 M) to give a white precipitate. Pure **3c** (0.16 g, 0.28 mmol, 97% yield) was collected by filtration and washed with water. M.p. > 250 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 9.67 (s, 1 H, CHO), 9.63 (s, 2 H, CHO), 8.11 (s, 2 H, ArH), 8.02 (s, 4 H, ArH), 7.47 (d, J = 7.8 Hz, 2 H, ArH), 6.65 (t, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 190.2, 169.9, 168.2, 160.2, 139.8, 139.2, 137.5, 127.5, 126.7, 124.0, 123.3, 122.7, 122.0, 120.2 ppm. $C_{27}H_{16}O_7S_4$ (580.66): calcd. C 55.85, H 2.78, S 22.09; found C 55.94, H 2.81, S 22.14. ESI-MS: m/z = 579.3 [M – H]$^-$.

Compound 4a: A mixture of **4** (0.67 g, 1.35 mmol), potassium carbonate (3.56 g, 26.18 mmol) and 2-iodopropane (2.7 mL, 27 mmol) was stirred in acetone (35 mL) and heated to reflux for 48 h. The reaction mixture was then poured into diluted HCl and extracted with $CHCl_3$. The organic layer was washed with water, dried with $MgSO_4$ and concentrated to yield the crude product. Without further purification the crude product was allowed to react with HMTA (5.68 g, 40.50 mmol) in TFA (50 mL) for 120 h. The reaction was quenched with ice-cold water and the mixture filtered. The crude mixture was added to $CHCl_3$ (50 mL) and heated to reflux for 2 h. The suspension was filtered to give pure **4a** (0.58 g, 70% yield). M.p. > 250 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.66 (s, 4 H, CHO), 8.04 (s, 8 H, ArH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 190.5, 167.9, 139.3, 127.8, 123.2 ppm. $C_{28}H_{16}O_8S_4$

(608.67): calcd. C 55.25, H 2.65, S 21.07; found C 55.31, H 2.75, S 21.15. ESI-MS: m/z = 607 $[M - H]^-$.

X-ray Structure Determinations: For the structures of compounds **2a** and **3a** intensity data were collected with a Bruker APEX-II CCD diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). All the calculations involving structure solution, refinement and graphics were performed by using SHELXTL-PC. CCDC-867096 (for **2a**) and -867095 (for **3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Characterization details of compound **2**, **(1–4)a**, **1b**, **3b**, and **3c** as well as X-ray crystal data.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (20772092) and the Hubei Province Natural Science Fund for Distinguished Young Scholars (2007ABB021) for financial support.

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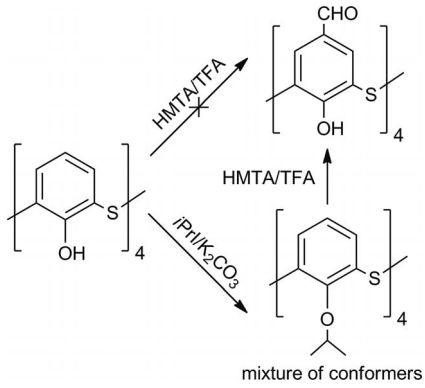
[12] The crude product was determined by ^{1}H NMR spectroscopy to be a mixture of conformers containing 1,2-alternate, partial-cone, and 1,3-alternate compounds in a ratio of approximately 2:3:5.

Received: March 2, 2012
Published Online: ■

Formylated Thiacalix[4]arenes

Di- and triformylated thiacalix[4]arenes substituted on the *para* positions have been synthesized by formylation of partially propyl- or benzoyl-substituted thiacalix[4]arenes. The formylation of tetraisopropoxythiacalix[4]arene conformers gave the completely dealkylated tetraformylthiacalix[4]arene derivative. This result differs from the formylation of propoxythiacalix[4]arene.



Keywords: Calixarenes / Regioselectivity / Formylation / Substituent effects / Synthetic methods

