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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 6329–6331

The formylation of the upper-rims of thiacalixarenes: synthesis of the first tetra-formylated and the first *meta*-substituted thiacalix[4]arenes

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Received 24 February 2004; revised 17 June 2004; accepted 18 June 2004
Available online 10 July 2004

Abstract—The conventional Gross reaction for the formylation of the tetrapropoxythiacalix[4]arene using $TiCl_4$ affords the 18-(chloromethyl)-28-hydroxy-25,26,27-tripropoxythiacalix[4]arene substituted in the *meta*-position of the macrocycle. The *p*-tetra-formyl-tetrapropoxythiacalix[4]arene, which is an interesting intermediate to the upper-rims functionalization of thiacalixarenes, was prepared with a very good yield using BuLi and *N*-formylpiperidine.

The chemistry of thiacalixarenes remains poorly documented compared to their homologous calixarenes. Most of the work reported in the literature concerned until recently the modification of the lower rims.[1–5] The main problem encountered with these macrocycles is their chemical behaviour, which appeared to be often very different from the well known calixarenes. Indeed, some recent works reported interesting functionalizations of the upper-rims using tetraamino- or tetrabromo-derivatives as intermediates to imino- or alkynyl-substituted thiacalixarenes.[6–12] The selective formylation of the macrocycles could be a way to achieve functionalization of the upper-rims using for example Wittig reactions for substitution through ethylenic bonds, imino bonds, or modification with alkoxy groups. Upper-rims formylated thiacalixarenes are thus very interesting intermediates to the formation of molecular receptors, molecular dyes for magnetic or optical properties.

Formylation using the Gross reaction and subsequent modifications were well described for the family of the calixarenes.[13–15] We report in this paper both the first *para*-formylation and the first *meta*-substitution of a thiacalix[4]arene.

We investigated the formylation of thiacalix[4]arenes using the Gross reaction both on tetrahydroxy- and tetrapropoxythiacalix[4]arene. This procedure, which was successfully used for similar calixarenes, consisted in a reaction between the macrocycle and dichloromethyl methyl ether in the presence of a Lewis acid ($TiCl_4$). The Gross formylation on the tetrahydroxythiacalix[4]arene using $TiCl_4$ gave no reaction in our experimental conditions. Miyano and co-workers reported the formation of a complex between $TiCl_4$ and the tetrahydroxythiacalixarene, where the Ti was coordinated with both oxygen and sulfur atoms.[16] In the case of the tetrahydroxythiacalixarene no reaction was observed since this titanium complex probably reduces the reactivity of the benzene rings.

However, the reaction between the tetrapropoxythiacalix[4]arene and Cl_2CHOCH_3 in the presence of titanium tetrachloride lead surprisingly to a monosubstituted thiacalixarene with a chloromethyl group in the *meta*-position (**1**).[17] Such reaction was previously reported on aromatics or *para*-substituted calixarenes using $SnCl_4$ or $ZnCl_2$ as Lewis acid but was never observed, to our knowledge, either on the *meta*-position of calixarenes

Keywords: Calixarene; Formylation; Chloromethylation; *meta*-Substitution.
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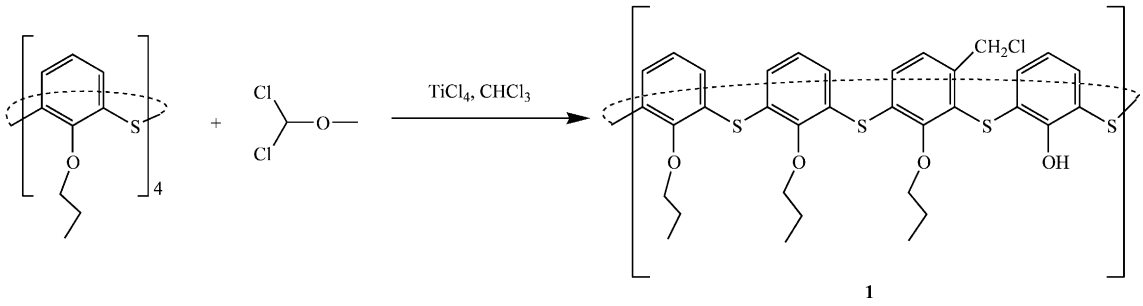
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.06.078



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Scheme 1. Synthesis of the 18-(chloromethyl)-28-hydroxy-25,26,27-tripropoxythiacalix[4]arene (**1**).

or on thiacalixarenes.[18] This compound represents the first *meta*-substitution of a thiacalixarene (Scheme 1) and one of the few asymmetric calixarenes bearing a group, which can be used for further modifications. The structure was determined using single crystal X-ray diffraction (Fig. 1).

According to it, the compound conserves a thiacalixarene identity, that is, the core of four benzene rings bound by sulfur bridges in *ortho*-positions. Two of the initially identical four fragments remain almost unchanged in both chemical composition and conformation, while the third and the fourth are modified, one—by introduction of a chloromethyl group in *meta*-position and the other—by hydrolytic elimination of the initially present *n*-propoxy group leaving a hydroxyl group in its place. The structure can be considered as a pseudo partial cone since the sulfur plane and the phenolic unit bearing the hydroxy group are almost coplanar with an angle of 26.1(3)°. The strong distortion of the conformation is stabilized by hydrogen bonds between the hydroxy group and the oxygen of the nearest propoxy groups with distances between the oxygens of 2.823 and 2.981 Å.

The ^{1}H NMR spectroscopy shows several signals for the propoxy groups. This is probably due to the presence of different conformers of the macrocycle in solution. This monochloromethylated macrocycle can be an interesting intermediate to the monosubstitution of thiacalixarenes and moreover to the preparation of asymmetric thiacalixarenes. The same reaction on tetrapropoxythiacalix[4]arene using a stronger Lewis acid such as $AlCl_3$ led to the complete removal of the propoxy groups and no formation of formyl or other substituted species.

We investigated some other reactions such as the Vilsmeier–Haack[19–22] or the Reimer–Tiemann[20,23,24] formylations but no formylated thiacalixarene could be isolated.

The 5,11,17,23-tetraformyl-25,26,27,28-tetrapropoxythiacalix[4]arene (**2**) could be isolated from the reaction between the tetrabromo-tetrapropoxythiacalix[4]arene, butyllithium and *N*-formylpiperidine (Scheme 2).[25,26] This was confirmed by the ^{1}H NMR spectrum, which showed one singlet at 9.84 ppm for the formyl group, one singlet at 7.96 ppm for the aromatic protons, a triplet at 4.03 ppm, a multiplet at 1.33 ppm and a triplet at 0.69 ppm for, respectively, the OCH_2, CH_2 and CH_3 of the propyl groups. The integrations are in perfect agreement with a tetrafunctionalization of the macrocycle. The conformation of the thiacalixarene (**2**) can be assumed to be 1,3-alternate since the starting tetrabromo-tetrapropoxythiacalix[4]arene was shown to adopt the same conformation, which is blocked by the steric hindrance of the propyl groups.[8,10]

In conclusion we were able to isolate and characterize a *meta*-substituted thiacalix[4]arene with a chloromethyl group and the tetraformylthiacalix[4]arene for the first time. Both species can be used as intermediates to the selective upper-rim functionalization of the thiacalixarenes.

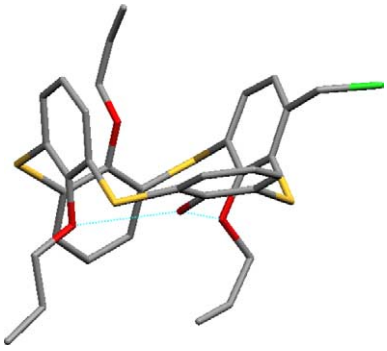
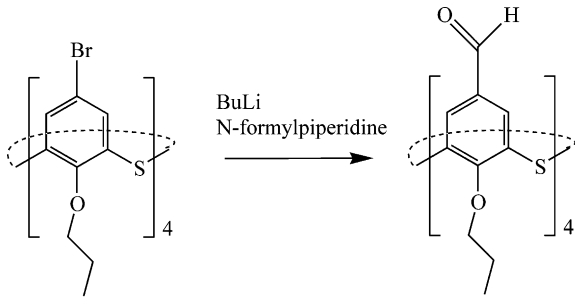


Figure 1. Molecular structure of the 18-(chloromethyl)-28-hydroxy-25,26,27-tripropoxythiacalix[4]arene (**1**).



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Scheme 2. Synthesis of the 5,11,17,23-tetraformyl-25,26,27,28-tetrapropoxythiacalix[4]arene (**2**).

Acknowledgements

C.D. thanks the Foreign Affairs Ministry for a visiting Lavoisier scholarship at the Department of Inorganic Chemistry, Chalmers University of Technology, Göteborg, Sweden.

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17. Synthesis of 18-(chloromethyl)-28-hydroxy-25,26,27-tripropoxythiacalix[4]arene (**1**): Tetrapropoxythiacalix[4]arene (0.4 g, 0.6 mmol) was dissolved in chloroform (15 mL). A 1 M solution of titanium tetrachloride in dichloromethane (15 mL) was added to the thiacalixarene. The dark red solution was stirred for 35 min at 40 °C and hydrolyzed with H_2O (120 mL). The organic phase was separated and washed with H_2O (80 mL) and dried over Na_2SO_4. The organic phase was evaporated and the product was precipitated using the mixture hexane/ethyl acetate (9/1). The powder was crystallized from diethyl ether and obtained with a 68% yield. Purification using column chromatography is also possible with the mixture hexane/ethyl acetate (9/1) for eluant. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.8–6.6 (m, 11H, Ar), 5.08, 4.56 (d, 2H, CH_2Cl), 4.45, 4.25, 4.03, 3.85 (m, 6H, O–CH_2–CH_2–CH_3), 1.85 (m, 6H, O–CH_2–CH_2–CH_3), 0.95, 0.85 (m, 9H, O–CH_2–CH_2–CH_3); ^{13}C NMR ($CDCl_3$): 161.5, 160.9, 159.8 (*Ar*–OR), 143.8 (*Ar*–OH), 137.2, 136.9, 136.4, 135.9, 135.7, 135 (*Ar*–H), 130.1, 129.5, 128.8, 128.5 (*Ar*–S), 127 (CH_2Cl), 126, 123.6, 119.6, 119.4 (*Ar*–H), 77.8, 77.6, 77.4, 77, 76.7, 73.2 (O–CH_2), 44.6, 23.6, 23.5, 23.3 (CH_2), 10.8, 10.7, 10.6 (CH_3). Anal. Calcd for $C_{34}H_{35}ClO_4S_4$: (671.3 g mol^{-1}): C 60.83%, H 5.25%, S 19.11%. Found: C 60.80%, H 5.29%, S 19.30%. Crystal data for **1**: $C_{34}H_{35}ClO_4S_4$, M = 671.31, monoclinic, space group *P2(1)/c*, a = 18.108(4), b = 10.640(2), c = 17.645(3), α = 90.00, β = 99.214(6), γ = 90.00, V = 3355.6(11)^3, Z = 4, T = 295(2) K, μ = 0.399 mm^{-1}, F(000) = 1408, 2584 unique reflections [R_{int} = 0.0300] were collected for $2\theta \leqslant 40.00°$. The structure was solved by direct methods, the majority of the nonhydrogen atoms were obtained from the initial solution, the others being obtained from the difference Fourier syntheses. All nonhydrogen atoms were refined first in isotropic and then in anisotropic approximations. The positions of all the hydrogen atoms were calculated geometrically and included in the final cycles of refinement in isotropic approximation. Final discrepancy factors were R_1 = 0.0588, WR_2 = 0.1576 (for 1632 reflections with $I > 2\sigma(I)$). All the calculations were performed on an IBM PC using SHELXTL-NT program package.[27] Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 227818. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-0-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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26. Synthesis of 5,11,17,23-tetraformyl-25,26,27,28-tetrapropoxythiacalix[4]arene (**2**): the tetrabromotetrapropoxythiacalix[4]arene was prepared according a previously reported procedure.[8] Tetrabromo-tetrapropoxythiacalix[4]arene (0.2 g, 0.2 mmol) was dissolved in toluene (15 mL) and butyllithium (1.6 M in hexane) was added (5 mL). The mixture was stirred for 2 h and a rose suspension was formed. *N*-Formylpiperidine (1.5 mL) was added to the suspension at 0 °C. The orange solution was slowly warmed up to room temperature and 3 M HCl (10 mL was added. The solution was stirred for 20 h and diethyl ether (20 mL) was added. The organic phase was washed with diethyl ether (40 mL), dried over $MgSO_4$ and evaporated to dryness. The yellow powder was precipitated using the mixture hexane/ethyl acetate (9/1) in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.8 (s, 1H, C*H*O), 7.9–6.7 (m, 9H, Ar), 5.08 (d, 1H, CHO–Ar–H_α), 4.58 (d, 1H, CHO–Ar–H_β), 4.5–3.7 (t, 6H, O–CH_2–CH_2–CH_3), 2–1.5 (m, 6H, O–CH_2–CH_2–CH_3), 1–0.8 (t, 9H, O–CH_2–CH_2–CH_3); ^{13}C NMR ($CDCl_3$): 189.5 (*C*HO), 165.2 (*Ar*–CHO), 134.7 (*Ar*–H), 131.6, 129.7 (*Ar*–O, *Ar*–S), 77.2 (CH_2), 30.9 (CH_3), 22.8 (CH_2), 9.8 (CH_3). Anal. Calcd for $C_{40}H_{40}O_8S_4$: (776.26 g mol^{-1}): C 61.89%, H 5.19%, S 16.51%. Found: C 61.81%, H 5.22%, S 16.23%.
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