CONVERSION OF MONO- AND TETRA-THIACALIX[4]ARENES TO SULFILIMINE DERIVATIVES AND UNEXPECTED FORMATION OF MONOSPIRODIENONE DERIVATIVES

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Abstract: The treatment of mono- and tetra-thiacalix[4]arenes (**2**, **3**) with chloramine T gave unexpected monospirodienone derivatives (**4**, **5**). The reaction of methyl ethers (**6**, **7**) of thiacalix[4]arenes with chloramine T followed by demethylation gave novel derivatives (**10**, **11**) having a sulfilimine group. X-ray analysis revealed that **11** adopts cone conformation in the solid state, in which the sulfilimine group directs toward axial orientation to take part in circular hydrogen bonding with four OH groups.

Introduction

The modification of calix[4]arenes (e.g. **1**) in a stereo- and regio-selective fashion at the upper and lower rims has been commonly understood to develop their new functions.[1] Otherwise, a replacement of the bridging methylene of the calix scaffold with heteroatoms should be highly intriguing but quite challenging field in calixarene chemistry due to synthetic difficulty.

Therefore, our interest was focused on modification of the methylene moiety by changing to another group such as carbonyl, sulfur, or amino acids.[2] For example, we reported the replacement of any of the four bridging methylene groups of calix[4]arene by epithio groups via the stepwise joining of the component phenol units with methylene or epithio bonds followed by ultimate cyclization to produce mono- (**2**) to tetra-thiacalix[4]arene (**3**).[3]

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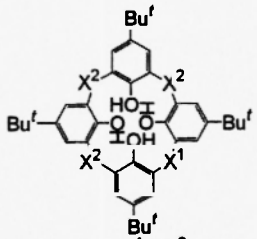


1: $X^1 = X^2 = CH_2$
2: $X^1 = S$, $X^2 = CH_2$
3: $X^1 = X^2 = S$

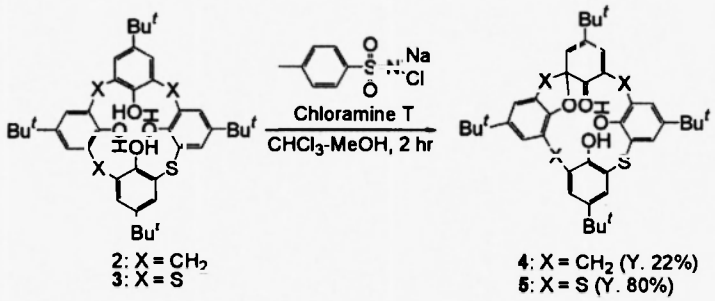
Furthermore, replacement of all of the original methylene bridges between the aromatic units in calixarenes by sulfur atoms has been reported recently, leading to tetrathiacalix[4]arenes **3**.[4] Since then, interest in the development of these thiacalix[4]arenes has been increasing because of their unique properties.[5] The presence of sulfur gives rise to some novel interesting features in thiacalix[4]arene molecules if compared with the chemistry of classical calixarenes. For example, the sulfide moiety could be oxidized to afford either a sulfinyl or sulfonyl analogue by controlling the amount of the oxidizing agent.[6] Furthermore, these sulfur-containig calixarenes showed a preference for particular metal ions, depending upon the oxidation state of the sulfur.[6c] These results indicate that the modification of the sulfide moiety is important strategy for development of the functions of calixarenes. On the other hand, sulfilimine is the nitrogen analogues of sulfoxide. These sulfilimines have been known to be easily prepared by treating the corresponding sulfides with N-sulfonyl-haloamide such as chloramine T.[7] In spite of easy preparation, there is no report about thiacalixarene having sulfilimine group.

Herein, we report the conversion of the sulfide of thiacalixarenes (**2**, **3**) to sulfilimine by reaction with chloramine T. In addition, a facile approach to preparation of calix[4]arene spirodienones was unexpectedly found.

Result and discussion

First of all, we examined the reaction of **2**, **3** with chloramine T (Scheme-1). Surprisingly, the reaction of **2** with chloramine T in $CHCl_3$-MeOH (3:1) at 0 °C for 2 hr gave a yellow color compound, which was indicative of the altered calixarene structure.[8] Moreover a signal pattern revealing C_1-symmetry and the absence of tosyl resonances in its ^{1}H NMR spectrum were reminiscent of the monospirodienone derivatives. The FAB(+) MS spectrum confirmed this assumption, showing a molecular peak at 664 m/z besides a peak at 665 m/z due to the parent. Furthermore, two characteristic ^{13}C NMR signals at 83.2 and 195.4 ppm due to the spiro and carbonyl carbons were observed, respectively. Typical ^{1}H NMR signals at 6.03 (H_a) was confidently assigned to vinyl protons of the monospirodienoic moiety (Fig. 1). The regiochemistry was determined by COSY and NOESY experiments. Cross-peaks were observed at H_a/H_b, H_b/H_c, H_d/H_e, and H_f

/H_g in the NOESY spectrum, which are only compatible with **4** among the four possible regio isomers. Similarly, the reaction of **3** with chloramine T gave the corresponding monospirodienone derivative **5** as a red color crystal in high yield.° Calixarene spirodienone derivatives are usually obtained by mild oxidation with trimethylphenylammonium tribromide under basic conditions.[9] We supposed that chloramine T may act as a base and an oxidant in these reactions without oxidation of sulfur. Then, oxidation of **3** by usual system was examined, giving **5** in only 16 % isolated yield (Scheme-2). These results indicate that chloramine T oxidation provides a new efficient route to monospirodienone derivatives.[10]



Scheme-1

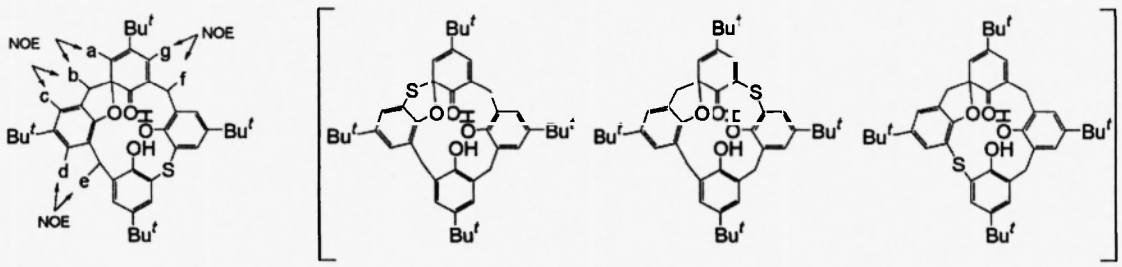
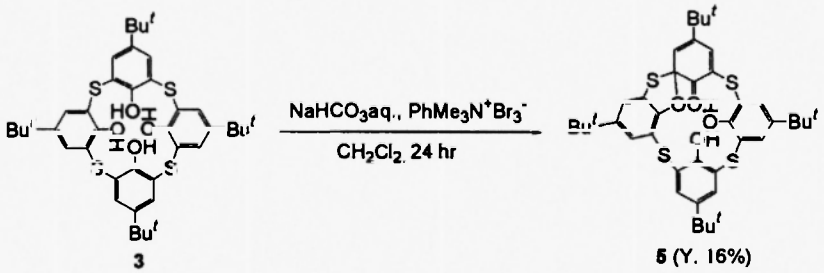


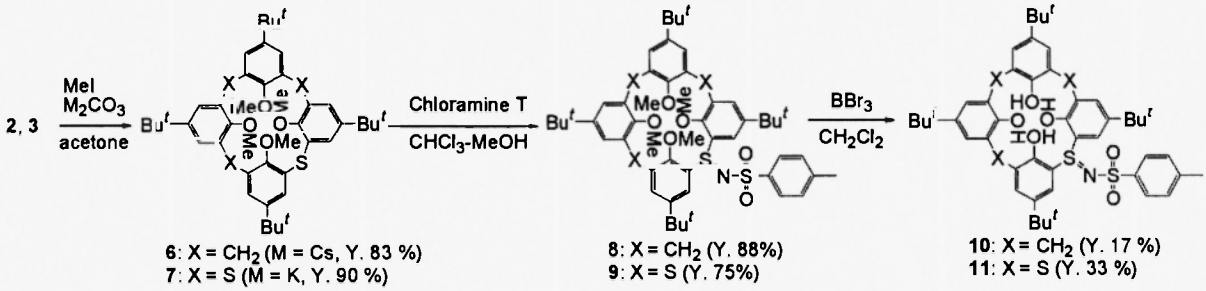
Figure-1 : Noe correlation of 4 and other three possible regio isomers.



Scheme-2

Above mentioned results indicate the necessity of protection of phenolic oxygens for conversion of sulfide to sulfilimine by the reaction with chloramine T. Thus, **2**, **3** were treated with methyl iodide in acetone using alkali carbonate as a base catalyst to give the corresponding tetra methyl ether **6**, **7** in a satisfactory yield, respectively (Scheme-3).[11,12] The reaction of **6** with chloramine T in $CHCl_3$-MeOH (1:1) gave smoothly **8**

with the sulfilimine moiety, which is confirmed by ^{1}H NMR, FAB MS.[13] Thus, compound **8** possesses two doublets due to the tosyl group (δ 6.82 and 8.11 ppm (each 2H)) with typical coupling constants (J = 7.8 Hz) together with the singlet of the methyl group at 1.93 ppm (3H). Similarly, the reaction of **7** with chrolamine T gave **9**.[14] This was confirmed by FAB MS (893 m/z) and ^{1}H NMR, which showed only one singlet of methyl protons at δ 2.30 (3H) and two doublets of aryl protons of tosyl group (δ 7.09 and 7.70 ppm (each 2H)). The examination of this reaction at several temperature with changing equiv. of chloramines T resulted in isolation of only **9**. Thus, the other three sulfides of **7** could not be converted to sulfilimine under these reaction conditions.



Scheme -3

Treatment of **8**, **9** with BBr_3 eliminated the methyl groups to give novel monosulfilimine calix[4]arenes **10**, **11**, respectively.[15] The OH resonance of ^{1}H NMR of **10**, **11** was observed at 10.20 and 9.83 ppm, respectively, suggesting that hydrogen bondings comprising a cyclic array of the phenolic OH groups exist in these compounds. The final evidence for the structure of **11** was demonstrated using single crystal X-ray diffraction analysis (single crystals were obtained by slow diffusion of CH_3CN to CH_2ClCH_2Cl solution).[16] It has been revealed that sulfilimine group directs toward axial orientation in the crystal state (Fig. 2). Therefore, the molecule adopts a cone conformation, which is stabilized by intramolecular hydrogen bonds between four OH groups and nitrogen of the sulfilimine group.

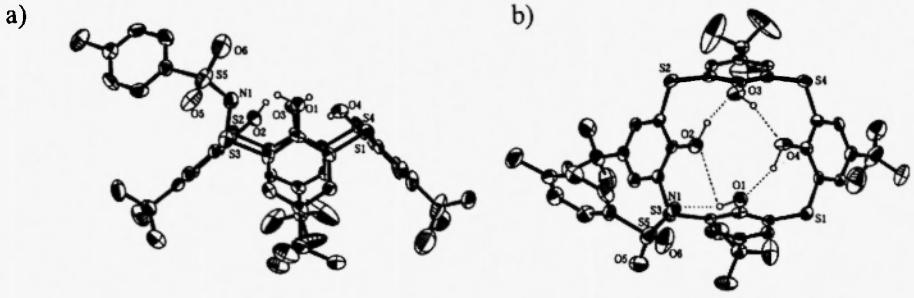


Figure-2 ORTEP drawing with thermal ellipsoids at 30 % probability of **11**. a) Side view and b) top view. Hydrogen atoms except of OH are omitted for clarity.

In conclusion, we described the first example of conversion of thiacalix[4]arenes to sulfilimine derivatives

by reaction with chloramine T. It was necessary to protect the OH groups for this conversion. The function of these new derivatives is currently under investigation. Also, we found, rather serendipitously, a new efficient method for preparation of novel thiacalixarene monospirodienones based on chloramine T oxidizing system. The presence of diene, hydroxyl and carbonyl groups may make the monospirodienone a very attractive intermediate to prepare newly modified thiacalix[4]arene derivatives with novel chemical properties.

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8 To a solution of **2** (0.3 g, 0.45 mmol) in $CHCl_3$-MeOH (3:1) was added chloramine T (0.19g, 0.68 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h and evaporated to dryness. The powder was dissolved in $CHCl_3$, and the insoluble part was filtered. After the filtrate was evaporated, the residue was purified by column chromatography on silica gel to give 4 (0.07 g, 22 %) as yellow powder. In a similar manner, treatment of **3** with chloramine T gave **5** (80 %) as red powder. Compound **4**: Mp >350 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 9H, ^{t}Bu), 1.23 (s, 9H, ^{t}Bu), 1.25 (s, 9H, ^{t}Bu), 1.28 (s, 9H, ^{t}Bu), 3.05 (d, 1H, J = 15.8 Hz, CH_2), 3.46 (d, 1H, J = 14.3 Hz, CH_2), 3.61(d, 1H, J = 15.8 Hz, CH_2), 3.64 (d, 1H, J = 15.5 Hz, CH_2), 3.70 (d, 1H, J = 15.5 Hz, CH_2), 4.02 (d, 1H, J = 14.3 Hz, CH_2), 6.03 (d, 1H, J = 2.5 Hz, Ar*H*), 7.06 (d, 1H, J = 2.0 Hz, Ar*H*), 7.12-7.19 (m. 3H, Ar*H*), 7.31 (d, 1H, J = 2.5 Hz, Ar*H*), 7.44 (s, 1H, O*H*), 7.53 (d, 1H, J = 2.5 Hz, Ar*H*), 8.01 (s, 1H, O*H*); ^{13}C NMR δ 28.5, 31.4, 31.4, 31.7, 32.7, 34.0, 34.1, 34.3, 34.5, 36.5, 38.8, 83.2 (C(sp^3)O), 120.1, 120.8, 121.6, 124.9, 125.1, 125.5, 126.4, 126.6, 127.0, 128.4, 130.5, 131.3,

131.7, 134.4, 139.0, 142.7, 144.5, 145.4, 145.4, 150.7, 152.0, 153.3, 195.4 (C=O); FAB MS 665 ([M+1]$^+$). Compound **5**: Mp 327.4-330.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 9H, ^{t}Bu), 1.24 (s, 9H, ^{t}Bu), 1.24 (s, 9H, ^{t}Bu), 1.25 (s, 9H, ^{t}Bu), 6.44 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.03 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.27 (d, 1H, *J* = 2.5 Hz, Ar*H*), 7.33 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.44 (d, 1H, *J* = 2.5 Hz, Ar*H*), 7.53 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.54 (d, 1H, *J* = 2.3 Hz, Ar*H*), 7.63 (d, 1H, *J* = 2.3 Hz, Ar*H*), 7.79 (s, 1H, O*H*), 8.25 (s, 1H, O*H*); ^{13}C NMR δ 28.5, 31.2, 31.3, 31.3, 34.2, 34.2, 34.6, 34.8, 91.6 (C(sp^3)O), 114.3, 119.4, 119.8, 120.9, 121.2, 121.4, 124.6, 127.0, 128.8, 130.2, 131.1, 132.1, 134.8, 136.5, 139.7, 143.1, 144.4, 145.3, 146.8, 153.0, 154.3, 155.7, 187.2 (C=O); FAB MS 719 ([M+1]$^+$).

9 For example: S. E. Biali, *Synlett.*, 1 (2003).

10 Actually, treatment of **1** with chloramine T gave the corresponding monospirodienone in 64 % isolated yield.

11 Spectral data of compound 6: Mp 224.9-225.7 °C; ^{1}H NMR (500 MHz, C_6D_6, 343 K) δ 1.26 (s, 18H, ^{t}Bu), 1.28 (s, 18H, ^{t}Bu), 3.40 (s, 6H, OCH_3), 3.58 (s, 6H, OCH_3), 3.20-4.10 (br, 6H, CH_2), 7.00-7.61 (m, 8H, Ar*H*); FAB MS 723 ([M+1]$^+$).

12 Spectral data of compound **7**, see: N. Morohashi, N. Iki, T. Onodera, C. Kabuto, and S. Miyano, *Tetrahedron Lett.*, **41**, 5093 (2000).

13 To a solution of 6 (0.6 g, 0.82 mmol) in $CHCl_3$-MeOH (1:1) was added chloramine T (0.68 g, 2.4 mmol). The mixture was refluxed for 12 h and evaporated to dryness. The powder was dissolved in $CHCl_3$, and the insoluble part (excess chloramine T) was filtered. After the filtrate was evaporated, the residue was purified by column chromatography on silica gel to give **8** (0.65 g, 88%) as colorless powder. Compound **8**: Mp 300.3-301.7 °C; ^{1}H NMR (500MHz, C_6D_6, 343 K) δ 1.12 (s, 18H, ^{t}Bu), 1.21 (s, 18H, ^{t}Bu), 1.93 (s, 3H, CH_3), 2.67-4.40 (br, 9H, CH_2), 6.82 (d, 2H, *J* = 7.8 Hz, Ar*H*), 6.82-8.00 (m, 8H, Ar*H*), 8.11 (d, 2H, *J* = 7.8 Hz, Ar*H*); FAB MS 893 ([M+1]$^+$).

14 To a solution of 7 (3.8 g, 4.9 mmol) in $CHCl_3$-MeOH (4:1) was added chloramine T (11.1 g, 39.2 mmol). The mixture was stirred at room temperature for 12 h and evaporated to dryness. The powder was dissolved in $CHCl_3$, and the insoluble part was filtered. After the filtrate was evaporated, the residue was purified by column chromatography on silica gel to give 9 (3.4 g, 75%) as colorless powder. Compound 9: Mp 251.9-252.7 °C; ^{1}H NMR (500 MHz) δ 1.18 (brs, 36H, ^{t}Bu), 2.30 (s, 3H, CH_3), 3.57 (s, 6H, OCH_3), 3.76 (s, 6H, OCH_3), 7.09 (d, 2H, *J* = 8.3 Hz, Ar*H*), 7.40-7.56 (m, 8H, Ar*H*), 7.70 (d, 2H, *J* = 8.3 Hz, Ar*H*); FAB MS 946 ([M+1]$^+$).

15 Spectral data of Compound **10**: Mp 178.1-182.3 °C; ^{1}H NMR (500 MHz, C_6D_6, 343 K) δ 0.90 (s, 18H, ^{t}Bu), 1.04 (s, 18H, ^{t}Bu). 1.90 (s, 3H, CH_3), 3.06-4.20 (m, 9H, CH_2), 6.76 (d, 2H, *J* = 8.3 Hz, Ar*H*), 6.82 (2H, *J* = 2.5 Hz, Ar*H*), 6.96 (d, 2H, *J* = 2.5 Hz, Ar*H*), 7.03 (d, 2H, *J* = 2.0 Hz, Ar*H*), 7.16 (d, 2H, *J* = 2.0 Hz, Ar*H*), 8.03 (d, 2H, *J* = 2.0 Hz, Ar*H*), 10.20 (brs, 4H, -OH); FAB MS 836 ([M+1]$^+$). Spectral data of Compound **11**: Mp 170.1-172.3 °C; ^{1}H NMR (500 MHz, C_6D_6, 273 K) δ 0.82 (s, 18H, ^{t}Bu), 0.89 (s, 18H, ^{t}Bu), 1.86 (s, 3H, CH_3), 6.71 (d, 2H, *J* = 8.3 Hz, Ar*H*), 7.16 (d, 2H, *J* = 2.5 Hz, Ar*H*), 7.47 (d, 2H, *J* = 1.5 Hz, Ar*H*), 7.54 (d, 2H, *J* = 1.5 Hz, Ar*H*), 7.56 (d, 2H, *J* = 2.5 Hz, Ar*H*), 8.03 (d, 2H, *J* = 8.3 Hz, Ar*H*), 9.83 (brs, 4H, O*H*); FAB MS 890 ([M+1]$^+$).

16 Crystal data: $C_{48}H_{55}N_2O_6S_5 \cdot H_2O$, *M* = 934.29, colorless, crystal dimensions 0.80×0.60×0.40mm, orthorhombic, space group *Pbca*(No. 61), *a* = 15.823(5), *b* = 23.754(7), *c* = 25.542(7) Å, α = β = γ = 90°, *V* = 9600 (5) Å^3, *Z* = 8, Cu Kα radiation (λ = 1.5419 Å), D_{calcd} = 1.293 g cm^3, *T* = 230 K, μ(Cu Kα) = 2.639 cm^{-1}, Rigaku RAXIS RAPID imaging plate diffractometer, 101966 measured reflections, 8767 unique reflections (R_{int} = 0.052), 2939 observed reflections ($I > 3.00\sigma(I)$), 540 parameters, *R* = 0.070, *wR* = 0.073, refined against |*F*|, GOF = 0.987. Crystallographic data for this crystal has been deposited with the Cambridge Crystallographic Date Centre as supplementary publication no. CCDC 258069. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK.

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