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Monosubstituted lower rim thiacalix[4]arene derivatives

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A clean and partially green route to monoalkyld thiacalix[4]arenes has been demonstrated. We have discovered that tetraalkylammonium halide can cleave selectively one of the two aryl alkyl ethers of dialkylated *para-tert*-butylthiacalix[4]arenes. Thus, *p-tert*-butyl thiacalix[4]arenes differently monoalkyld at the lower rim with acetyl, propyl, and benzyl group were synthesized in good yield.

In 1997 Miyano et al. described the first synthesis of *para-tert*-butylthiacalix[4]arene, with sulfur atom bridges between the phenolic units instead of the CH₂ groups.¹ Their ease of preparation and their high potential for numerous applications has increased the popularity of this class of macrocycles.² The first investigations on the chemistry of thiacalix[4]arenes concerned essentially modifications at the lower rim. The Williamson synthesis of ethers, using alkyl halides and a base, is general and the commonly used derivatization for such modifications of thiacalixarenes. Depending on reaction conditions and the ratio of thiacalixarenes to alkylation reagent and base, the reaction provides essentially 1,3-di or tetra-substituted products. Dialkylation of thiacalixarenes leads normally to distally (1,3-)di-substituted products.³ Nevertheless, a few reactions relate to the synthesis of mono or tri substituted macrocycles.⁴ Initially, we carried out a study on the mono-alkylation of thiacalix[4]arenes using alkyl halides. In this Letter, we report a general synthetic method with several alkyl halides to obtain in high yield monoalkyld thiacalix[4]arenes.

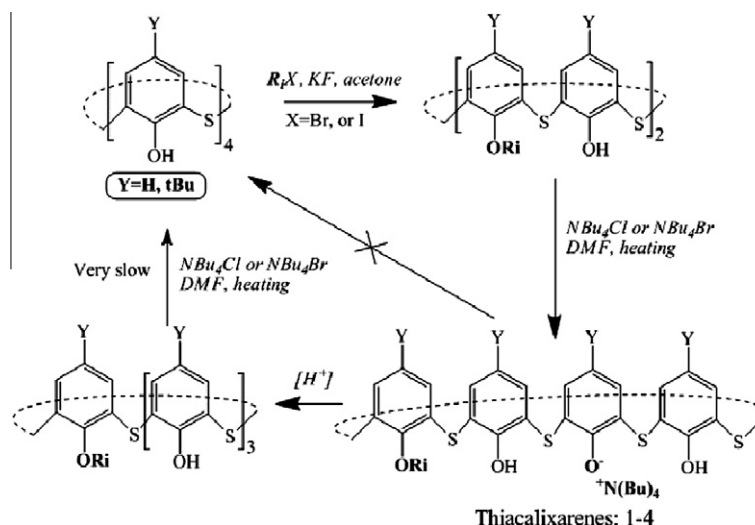
This study initially used ethyl 2-bromoacetate as the alkylation reagent. O-alkylation by ethyl 2-bromoacetate is of particular interest as the ester function introduced is a versatile starting unit for further modifications: hydrolysis, aminolysis, reduction to aldehydes and alcohols, preparation of acylchlorides. The general synthesis uses various ratios of thiacalixarenes/ethyl 2-bromoacetate/alkaline carbonate salts in refluxing acetone. So, in the first place only the nature and proportion

of the base was studied. Several types of bases were studied including carbonate, bicarbonate alkaline salts, fluoride, basic oxides (Al₂O₃).

The proportion of base to macrocycle has been varied from 0.1 to 10. Each reaction was followed by silica gel TLC with tetraalkylated and dialkylated *para-tert*-butylthiacalix[4]arenes as references. Even at low ratios of bases/macrocycle it was difficult to observe other products than the di or tetra-substituted. Indeed all these tests yielded either the di-alkylated compound, or a varied mixture of tetra, dialkylated, and non-substituted *para-tert*-butylthiacalix[4]arene. Of this set of manipulation, one was to be retained. With KF as the base and an excess of alkyl halide, in contrast to the reaction on calix[4]arene which leads to monoalkylated derivatives,⁵ only the 25,27-dialkoxy compound is obtained. This represents a very simple method for a high yield synthesis of the 25,27-dialkoxy thiacalix[4]arenes.

In further investigations to obtain monoalkylated thiacalixarenes, other classes of bases were investigated. Initially our attempts at the preparation of mono-substituted thiacalixarene using various amine bases, mixture of dialkylated products, and starting materials were isolated. However after prolonged stirring of the reaction mixture, the 25,27-dialkoxy product disappeared and mono-substituted thiacalixarene was obtained. After different trials, it was shown that treatment of the mixture of 25,27-dialkoxy thiacalixarene with tetraalkylammonium chloride or bromide salts in a polar solvent such as DMF yields the mono-alkylated thiacalixarene (70–95%). Excess of tetrabutylammonium increased the reaction speed (Scheme 1). Suitable tetraalkylammonium halides can be used as both reagent and solvent (at a temperature

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Scheme 1. Synthesis of di and mono-substituted thiacalixarene.^{11,12}

superior to the melting point of the salt). With per-*O*-tetra-alkylated thiacalixarene the reaction does not occur. A hypothesis about these unexpected reactions can be given. It is well-known that the high nucleophilicity of halide ions can be used for the nucleophilic displacement of an alkyl group to regenerate phenol from the corresponding aryl alkyl ether.⁶ Nucleophilic substitution reactions are solvent dependent, so our reaction media, melting salt, or dimethylformamide, allow obtention of the enhanced halide nucleophilicity necessary for the selective removal of one substitution group from dialkylated thiacalixarene.⁷ Moreover, a driving-force could be the symbiotic phenomena between soft base (thiacalixarene) and soft acid (tetraabutylammonium).⁸

The salt is stable and the addition of acidic reagent is necessary to reprotonate the phenolate group. Different alkylammonium halide salts have been tested with more and less efficiencies. The best salt is tetraalkylammonium (ethyl, propyl or butyl) chloride or bromide. This reaction has been validated with other 25,27-dialkoxy thiacalixarene (Table 1).

The structure of compound **1a** was solved using single crystal X-ray diffraction. Suitable crystals for diffraction were obtained by slow diffusion of methanol into a dichloromethane solution of **1a**.¹⁰ The compound is obtained as the tetraabutylammonium salt. The conformation is a distorted pinched cone. The phenolate anion is stabilized by a strong hydrogen bond (dH91-O4 = 1.70 Å, dH331-O4 = 1.79 Å; (O9-H31-O4) = 170°, (O33-H331-O4) = 164°) (Fig. 1). Another interesting feature of the derivative **1a** complex is represented by its molecular packing. Figure 2a shows that along the *c* axis they pack as anti-parallel columns and along the *b*-axis as head to head to bilayers, with the polar *O* substituents forming the interior of the bilayers. The presence of the *tert*-butyl head groups precludes insertion of the short alkyl chains into the macrocyclic cavity as observed for the *de-tert*-butyl-calix[4]arene analogues.⁹ The integrity of the structure is assured by two CH(ammonium)–O(phenolic) contacts and one bifurcated CH(ammonium)–S.

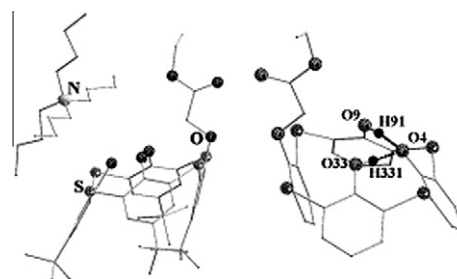


Figure 1. Structure of **1a** complex (left) and a view demonstrating intramolecular hydrogen bonds (right). Hydrogen atoms are omitted for clarity.¹⁰

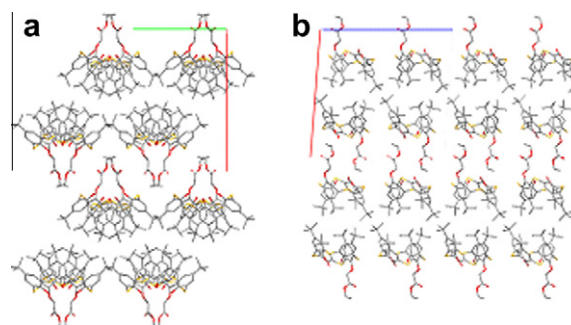


Figure 2. Crystal packing of **1a** complex: (a) view along the *c*-axis, and (b) view along the *b*-axis. Tetraabutylammonium cations are omitted for clarity. Each atom is depicted as follows: S, yellow; O, red; C, gray.

In conclusion, a clean and partially green route to monoalkylated thiacalix[4]arenes has been demonstrated. Work is underway to extend the studies to acylated analogues.

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Table 1
De-alkylation of dialkylated thiacalix[4]arenes using the tetraBuCl/DMF system

Compounds	Y	Ri	Yield (%)
1a	tBu	–CH ₂ COOEt	95
1b	H	–CH ₂ COOEt	71
2	tBu	–CH ₂ –C ₆ H ₅ –	78
3	tBu	–CH ₂ CH ₂ CH ₃	75

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- Crystallographic data: $C_{60}H_{89}N_1O_6S_4$, fw = 1048.63, monoclinic, P 1 21/c 1 (14), $a = 20.307(2)$ Å, $b = 13.913(9)$ Å, $c = 21.853(1)$ Å, $\beta = 94.574(6)^\circ$, 6154.49 (400) Å³, $Z = 4$, 14992 independent reflections, 10903 reflections were observed ($I > 2.0\sigma(I)$), $R1 = 0.055$, $wR2 = 0.166$ (observed). Crystallographic data reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 847210.
- Dialkylation of thiacalixarene **10**—To a suspension of thiacalix[4]arenes or para-tert-butylthiacalix[4]arenes (5.55 mmol) and KF (34 mmol) in dry acetone (100 mL) was added propyl iodide or benzyl bromide or ethyl 2-bromoacetate (70 mmol). The reaction mixture was refluxed for 72 h and then allowed to cool to room temperature. After evaporation of the solvent with a rotary evaporator, the mixture was taken up in $CHCl_3$ (50 mL) and washed with 1 M HCl solution (50 mL) and with brine (50 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. Recrystallization from acetone gave pure 25,27-dialkylated thiacalix[4]arene (60–80%) as white crystals.
- De-alkylation of 25,27-dialkoxy thiacalix[4]arenes, *Method A*: A mixture of 25,27-dialkoxy thiacalix[4]arenes (4.82 mmol) and tetrabutylammonium chloride or bromide (14 mmol) was dissolved in 6 mL of dimethylformamide. The yellow solution was stirred for 6 h at 120 °C and hydrolyzed with 1 M HCl solution (50 mL). The resulting precipitate was filtered and was taken up in $CHCl_3$ (50 mL). The organic phase was extracted and washed with water (50 mL) and with brine (50 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. The product was obtained by precipitation from methanol. Recrystallization from acetone gave pure 25-monoalkylated thiacalix[4]arene (70–95%) as white powder.
Method B: A mixture of dialkylated thiacalix[4]arenes TTBi or TDBi (4.82 mmol) and tetrabutylammonium chloride or bromide (14 mmol) was dissolved in minimum of CH_2Cl_2 to give solution. CH_2Cl_2 was removed and the solid was heated at 120 °C during 6 h. The mixture was taken up in $CHCl_3$ (50 mL). The organic phase was extracted and washed with water (50 mL) and with brine (50 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. The product was obtained by precipitation from methanol. Recrystallization from acetone gave pure 25-monoalkylated thiacalix[4]arene (70–95%) as white powder.
Synthesis of 5,11,17,23-tetra-tert-butyl-25-(ethoxycarbonyl)methoxy-2,8,14,20-tetrathiacalix[4]arene (1a): mp: 320 °C. ¹H NMR (300 MHz, $CDCl_3$): δ H (ppm): 9.53 (s, 2H, -OH), 9.23 (s, 1H, -OH), 7.58 (2s, 2H, Ar), 7.62 (m, 6H, Ar), 5.21 (s, 2H, -O-CH₂), 4.45 (q, 2H, $J = 7.05$ Hz, -O-CH₂-CH₃), 1.42 (t, 3H, $J = 7.3$ Hz, -CH₂-CH₃), 1.22 (s, 9H, C-CH₃), 1.21 (s, 18H, C-CH₃), 1.18 (s, 9H, C-CH₃). ¹³C NMR (75 MHz, $CDCl_3$): δ C (ppm) 169.6 (O=C-O), 158.06 (Ar C-O-Acetate), 157.7, 156.73 (Ar C-OH), 137.12, 136.5, 136.27 (Ar CH), 128.47 (Ar C-S), 121.65, 121.07, 121.02 (Ar C-tertbutyl), 72.47 (Ar-O-CH₂), 62.02 (O-CH₂-C), 34.75, 34.45, 34.4 (tert-butyl C), 31.6, 31.57, 31.33 (tert-butyl CH₃), 14.66 (-CH₃). IR ν_{max} (cm⁻¹) 3332, 2958, 1751, 1447, 1211, 1095, 893, 743, 553 (s). MS-ESI: calcd for $C_{44}H_{54}O_6S_4$: 806, found ESI (+) $m/z = 807$ [M+H]⁺, 1635.5 [2M+Na]⁺; ESI(-) 805 [M-H]⁻.
Synthesis of 25-(ethoxycarbonyl)methoxy-2,8,14,20-tetrathiacalix[4]arene (1b): mp: 219 °C ¹H NMR (300 MHz, $CDCl_3$): δ H (ppm) 9.04 (m, 3H, -OH), 7.6 (m, 6H, Ar), 7.51 (m, 2H, Ar), 6.92 (t, 1H, Ar), 6.7 (m, 3H, Ar), 5.21 (s, 2H, -O-CH₂), 4.46 (q, 2H, $J = 7.2$ Hz -O-CH₂-CH₃), 1.445 (t, 3H, $J = 7.3$ Hz, -CH₂-CH₃). ¹³C NMR (75 MHz, $CDCl_3$): δ C (ppm) 169.09 (O=C-O), 159.89 (Ar C-O-Acetate), 158.77, 158.08 (Ar C-OH), 139.22, 138.55, 138.39 (Ar CH), 128.83 (Ar C-S), 126.57, 121.52, 121.11 (Ar C-H), 72.24 (Ar-O-CH₂-), 61.73 (O-CH₂-C), 14.16 (-CH₃). IR ν_{max} (cm⁻¹) 3280, 1745, 1414, 1190, 825, 730. MS-ESI: calcd for $C_{28}H_{22}O_6S_4$: 582; found: ESI(+) $m/z = 583$ [M+H]⁺, 605 [M+Na]⁺, 621 [M+K]⁺.
Synthesis of 5,11,17,23-tetra-tert-butyl-25-(benzoyl)methoxy-2,8,14,20-tetrathiacalix[4]arene (2): mp: 247.8 °C ¹H NMR (300 MHz, $CDCl_3$): δ H (ppm) 8.89 (s, 1H, -OH), 7.7 (m, 2H, Ar), 7.55 (m, 4H, Ar), 7.49 (m, 4H, Ar), 7.4 (m, 3H, Ar), 5.34 (s, 2H, -O-CH₂), 1.12 (m, 36H, C-CH₃). ¹³C NMR (75 MHz, $CDCl_3$): δ C (ppm) 157.49 (C-O-Benzyl), 156.64, 156.04, (Ar C-OH), 136.54, 135.82, 135.66 (Ar C-H), 129.4 (Ar C-S), 128.72, 128.63, 128.58 (Benz C-H), 122.19 (Ar C-CH₂), 120.24, 120.64, 120.83 (Ar C-tertbutyl), 79.67 (O-CH₂), 34.42, 34.10, 34.05 (tert-butyl C-), 31.74, 31.69, 31.51 (tert-butyl CH₃). IR ν_{max} (cm⁻¹) 3332, 2961, 1457, 1236, 887, 746, 550. MS-ESI calcd for $C_{47}H_{54}S_4O_4$: 810; found ESI(+) $m/z = 811$ [M+H]⁺, 833 [M+Na]⁺.
Synthesis of 5,11,17,23-tetra-tert-butyl-25-propoxy-2,8,14,20-tetrathiacalix[4]arene (3): mp: 247.8 °C ¹H NMR (300 MHz, $CDCl_3$): δ H (ppm) 9.27 (s, 1H, -OH), δ H 9.14 (s, 1H, -OH), 7.56 (m, 4H, Ar), 7.51 (m, 4H, Ar), 4.28 (t, 2H, $J = 6.6$ Hz, -O-CH₂), 2.139 (m, 2H CH₂-CH₃), 1.59 (m, 39H, -CH₃). ¹³C NMR (75 MHz, $CDCl_3$): δ C (ppm) 157.12 (Ar C-O-propyl), 149.38, 143.98 (Ar C-OH), 136.49, 136.24, 136.14 (Ar CH), 128.86 (Ar C-S), 121.28, 121.17, 120.84 (Ar C-tertbutyl) 80.49 (O-CH₂), 34.84, 34.56, 34.5 (tert-butyl C-), 31.73, 31.67, 31.48 (tert-butyl CH₃), 23.53 (CH₂), 10.9 (propyl CH₃). IR ν_{max} (cm⁻¹) 3286, 2952, 1457, 1248, 988, 890, 743. MS-ESI calcd for $C_{43}H_{54}S_4O_4$: 762; found ESI (+) $m/z = 763.3$ [M+H]⁺, 785.3 [M+Na]⁺, ESI(-) 761.3 [M-H]⁻.