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Diazo coupling: an alternative method for the upper rim amination of thiacalix[4]arenes

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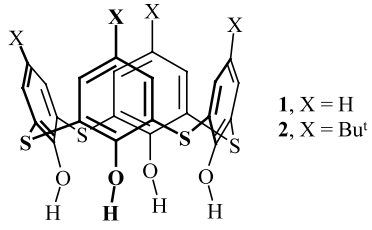
Abstract—A common method for the introduction of amino groups into the upper rim of calix[*n*]arene—nitration and subsequent reduction of nitro derivatives—is not possible in the thiacalixarene series due to the easy oxidation of the sulphur bridges during the nitration step. Alternatively, thiacalix[4]arene reacts smoothly with diazonium salts to form the corresponding tetrasubstituted azo derivatives in high yields. These compounds can then be reduced to give upper rim amino substituted thiacalixarene derivatives. © 2002 Elsevier Science Ltd. All rights reserved.

Recently, it was demonstrated that the novel members of the well-known calix[*n*]arene family,[1,2] so-called thiacalix[4]arenes[3] **1** and **2**, possess many uncommon properties when compared with the chemistry of 'classical' calixarenes. Thus, the presence of sulphur atoms instead of the typical bridging CH_2 groups enables, for instance, the regio- and stereoselective oxidation of sulphur to the sulphoxide[4] or sulphone[5] derivatives having many possible applications. Some reactions essentially unknown in the chemistry of 'classical' calixarenes, such as the intramolecular formation of lactone derivatives[6] or the introduction of amino groups into the lower rim[7] of thiacalixarenes have also been described. These novel features make thiacalixarenes very promising molecules in the design of more complicated molecular systems where they could serve as building blocks or molecular scaffolds.

Unfortunately, the full employment of thiacalixarenes in supramolecular chemistry is still limited by the lack of knowledge regarding the chemistry of these compounds and the lack of general derivatisation methods. During our studies on the electrophilic substitution of thiacalix[4]arene, we have found that this new system behaves very differently from calix[4]arene. All our attempts at the halogenation, nitration, acylation or formylation of the upper rim of tetraalkoxythiacalix[4]arenes using procedures known in classical calixarene chemistry have failed. Very recently, we have succeeded with the bromination of the 25,27-dialkoxy-derivative of thiacalix[4]arene **1** to form the corresponding dibromo or tetrabromo derivatives.[8] Another example of upper rim chemistry is the *ipso*-sulphonation of **2** with concentrated sulphuric acid to give the corresponding tetrasulphonated derivative in good yield.[9] In this paper we report a novel method for the derivatisation of the thiacalix[4]arene upper rim by reaction with diazonium salts leading to the corresponding tetraazo compounds in high yields. This reaction allowed us to introduce amino groups onto the upper rim of the thiacalixarene without the undesirable oxidation of sulphur atoms.



1, X = H
2, X = Bu^t

Tetraamino substituted calix[4]arenes represent very useful intermediates suitable for the preparation of many other derivatives or calixarene-based receptors. Their common synthesis consists of two steps: (i) nitration/*ipso*-nitration of the upper rim and (ii) reduction of corresponding nitro compounds. During our attempts at nitration of thiacalixarenes we found that all the reaction conditions normally used in 'classical' calixarene chemistry lead only to the oxidation of the bridging sulphur atoms.[10] Starting from **1**, **2** or their

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tetraalkylated derivatives, the formation of nitro compounds was never observed under the conditions tested (conc. HNO_3 or 100% HNO_3/CH_2Cl_2 or acetic acid, 100% HNO_3/CF_3COOH, $NaNO_3/CF_3COOH$). On the other hand, the aforementioned nitration agents were proven to be excellent oxidation agents for the preparation of sulphones or sulphoxides.[10]

To achieve the introduction of amino groups onto the upper rim of thiacalixarenes we have focused our interest on the reaction well known in classical calix[*n*]arene chemistry—diazo coupling.[11] To our surprise, the reaction between thiacalixarene **1** and diazonium salts proceeded smoothly to yield the corresponding tetraazo compounds **3** (Scheme 1). The reaction was carried out in THF solution using stable diazonium salts[12] (separately prepared tetrafluoroborates) under the catalysis of pyridine. The addition of the diazonium salt to a solution of **1** led immediately to a change of colour (orange to dark red) indicating the formation of an azo compound. Stirring the reaction mixture at room temperature gave a coloured precipitate that was purified by dissolving in pyridine and subsequent reprecipitation with conc. hydrochloric acid. In the case of carboxy derivative **3a** an alternative synthetic route was used, where an in situ prepared solution of the corresponding diazonium chloride (*p*-aminobenzoic acid/$NaNO_2$/HCl) was added dropwise[13] to the solution of **1** and sodium acetate in DMF at 0–5°C. The yields of **3a–d** are given in Table 1.

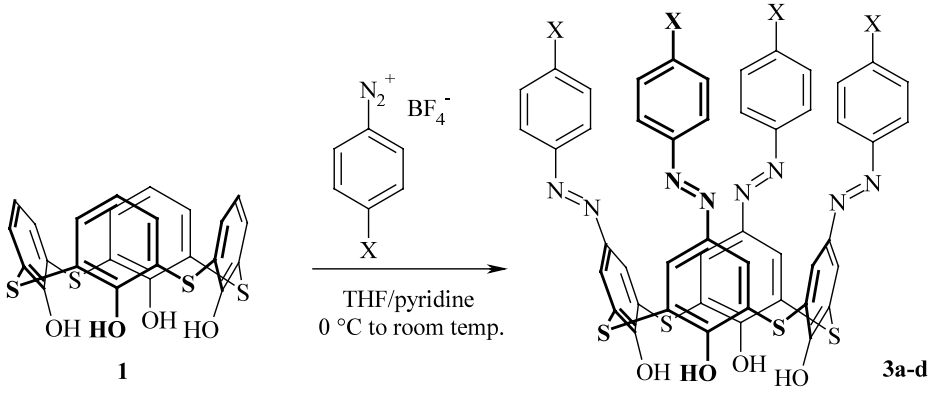
The structures of the novel azo compounds were confirmed by ^{1}H NMR analysis. Thus, compound **3b** possesses two doublets due to the *p*-substituted phenyl rings (δ 7.31 and 8.24 ppm) with typical coupling constants ($J=8.2$ Hz) together with the singlets at δ 2.36 ppm (methyl groups) and δ 8.09 ppm (calix). In all cases, the signals of the OH groups were not observed under the conditions used (DMSO-d_6, 300 MHz). The NMR spectrum reflects the high symmetry of the compound, which could correspond either to the *cone* or the *1,3-alternate* conformations. We were not able to prepare suitable crystals for X-ray analysis of **3**, nevertheless, based on analogy with other lower rim unsubstituted thiacalixarenes we assume that they adopt the *cone* conformation.

To achieve the reduction of the azo groups to the amino groups we tried several different methods described in the literature.[14,15] The most efficient reduction of the azo compounds was achieved using $Na_2S_2O_4$ and NaOH in an aqueous solution[15] (Scheme 2). The carboxy substituted derivative **3a** was used to enhance the solubility in the reaction medium. Stirring the reaction mixture at elevated temperature gave the expected product as a white powder in 90% yield.[16] Unfortunately, compound **4** was unstable in air and the original white colour quickly changed to black. Due to the problems with the solubility of **4** in common organic solvents, we decided to transform this compound into a more stable and more soluble derivative before analysis. Reaction of **4** with *p*-methylbenzaldehyde in toluene gave Schiff's base[17] **5** which was analysed using common techniques. The ^{1}H NMR spectrum again corresponds to the assumed *cone* conformation.

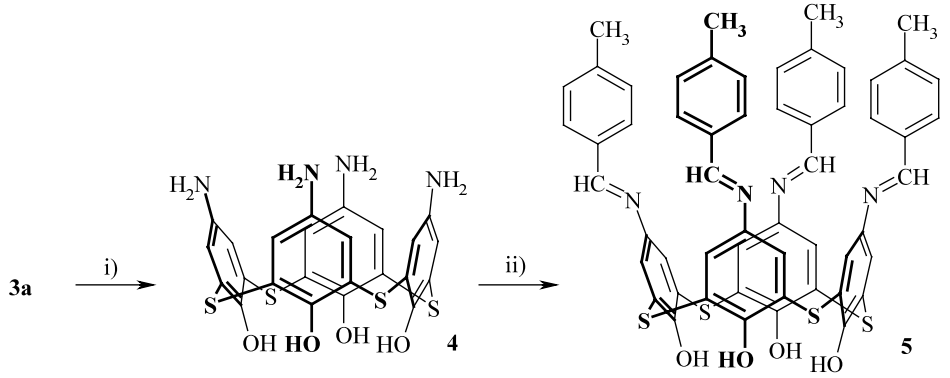
In conclusion, direct nitration of the thiacalixarene upper rim was not possible due to oxidation of the sulphur bridges. We have demonstrated that thiacalix[4]arene reacts smoothly with diazonium salts to form azo compounds which can be reduced to give amino substituted thiacalixarenes. Further utilisation of this novel method is under study in our laboratory.

Table 1. Preparation of azo compounds **3a–d**

Derivative	X	Yield (%)
3a	COOH	77
3b	CH_3	72
3c	OCH_3	32
3d	Br	52



Scheme 1. Preparation of azo compounds **3**.



Scheme 2. *Reagents and conditions*: (i) $NaOH/Na_2S_2O_4$, water, 90°C (90%); (ii) p-CH_3-C_6H_4-CH=O, toluene, rt (56%).

Acknowledgements

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12. **Typical procedure for the diazo coupling of 1**: The mixture of thiacalix[4]arene **1** (1.00 g, 2.0 mmol) and 1.7 g of p-methylbenzenediazonium tetrafluoroborate (8 mmol) was dissolved in 40 ml THF and 2 ml of pyridine was added. The solution was stirred at room temperature for 3 days. A coloured precipitate (yellow to red) was collected by filtration and redissolved in 100 ml of pyridine. The solution was treated with charcoal for 15 min at room temperature, then filtered and evaporated to dryness. The residue was stirred with 20 ml of conc. HCl and 10 ml of water. The resulting precipitate was filtered, washed with water and methanol and dried overnight at 80°C to yield 1.30 g of **3b** (72%) as orange crystals. Mp >350°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.36 (s, 12H, -$\underline{CH_3}$), 7.31 (d, 8H, J=8.2 Hz, H-arom.), 7.70 (d, 8H, J=8.2 Hz, H-arom), 8.09 (s, 8H, H-calix). EA calcd for $C_{52}H_{40}N_8O_4S_4$: C, 64.44; H, 4.16; N, 11.56; S, 13.23; Found: C, 64.03; H, 4.06; N, 11.81; S, 12.96. FAB MS m/z (rel. int.) 967.8 $[M]^+$ (100). Similarly, **3c** (32%), dark red crystals with mp >350°C. **3d** (52%) orange crystals with mp >350°C.
13. **Preparation of 3a**: p-Aminobenzoic acid (1.37 g, 0.01 mol) and 2 ml of conc. HCl (0.02 mol) were added to 15 ml of water and the resulting solution was cooled to 2°C. Then, a solution of $NaNO_2$ (0.8 g, 0.01 mol) in 10 ml of water was added dropwise at such a rate to maintain the temperature below 5°C. The resulting mixture was slowly added to a solution of thiacalixarene **1** (0.51 g, 1 mmol) and sodium acetate (2.08 g, 0.02 mol) in 20 ml of dimethylformamide at 5°C. The reaction mixture was stirred for 15 min at the same temperature, allowed to stay at room temperature for 2 h and then heated to 60°C for 30 min. The mixture was acidified with 2 M HCl to pH 5 and the resulting precipitate was filtered off and washed with water and methanol. The resulting red solid was dissolved in a hot solution of sodium hydrogencarbonate (8.4 g) and reprecipitated by addition of conc. HCl. The mixture was stirred overnight at room temperature, the red precipitate filtered off, washed with water and methanol and dried overnight at 80°C to yield 0.85 g of **3a** (77%) as a red solid with mp >350°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.87 (d, 8H, J=8.2 Hz, H-arom), 8.06 (d, 8H, J=8.3 Hz, H-arom), 8.18 (s, 8H, H-calix). IR (KBr) ν_{max} (cm^{-1}): 1694 (C=O), 3386 (OH). EA calcd for $C_{52}H_{32}N_8O_{12}S_4$: C, 57.35; H, 2.96; N, 10.29; Found: C, 56.93; H, 3.06; N, 11.01.

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16. **5,11,17,23-Tetraaminothiacalix[4]arene 4**: Azo compound **3a** (500 mg, 0.5 mmol) was dissolved in a mixture of NaOH (0.5 g) and 25 ml of water. The resulting dark red solution was reduced by stirring with $Na_2S_2O_4$ (2.5 g, 14.4 mmol) for 1 h at 90°C. The reaction mixture was cooled to room temperature, the resulting white precipitate was filtered and washed with water and methanol. The product was dried at reduced pressure to give 240 mg of **4** (90%) as a white solid. The solid was unstable in air and quickly turned black.
17. **Characterisation of 4**: A mixture of **4** (340 mg, 0.6 mmol) and *p*-methylbenzaldehyde (360 mg, 3 mmol) in 5 ml of toluene was stirred for 7 days at room temperature. The precipitate was filtered, dissolved in dichloromethane and reprecipitated from methanol under external cooling. The resulting solid was dried under vacuum to yield 214 mg of **5** (36%) in the form of grey crystals, mp: 265–268°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.39 (s, 12H, $\underline{CH_3}$), 7.24 (d, 8H, $J=8.1$ Hz, H-arom), 7.58 (s, 8H, H-calix), 7.73 (d, 8H, $J=8.2$ Hz, H-arom), 8.36 (s, 4H, -$\underline{CH}$=N), 9.33 (s, 4H, -OH). EA calcd for $C_{56}H_{44}N_4O_4S_4$: C, 69.68; H, 4.59; N, 5.80; Found: C, 69.43; H, 4.46; N, 5.71. FAB MS m/z (rel. int.) 963.8 $[M]^+$ (100).