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LETTERS

## A 'building block' approach to functionalized calix[4]pyrroles

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### Abstract

Iodocalix[4]pyrrole **2** and trimethylsilylethynylcalix[4]pyrrole **3** are key intermediates en route to the preparation of the alkynyl-substituted calix[4]pyrrole system **4**. This latter species, in turn, provides a versatile precursor that can be used to prepare a range of arylalkynyl-functionalized calix[4]pyrroles (viz., **5–9**) by reacting with an appropriate aryl iodide under Sonogashira conditions (i.e., in the presence of tetrakis(triphenylphosphine)palladium(0)). Significant red-shifts in the  $\lambda_{\max}$  values and broadenings of the absorption peaks are seen in the UV–vis spectra of systems **6** and **7** upon addition of anions (e.g.,  $F^-$ ,  $Cl^-$ ,  $H_2PO_4^-$ ) in  $CH_2Cl_2$ , a finding that leads to the suggestion that these or other analogous systems could find application as anion sensors. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* calix[4]pyrrole; iodination; Sonogashira coupling; anion sensor.

Calix[4]pyrroles, a class of compounds first synthesized by Baeyer in 1886,<sup>1</sup> have recently been recognized as acting as simple-to-make anion binding agents.<sup>2</sup> In many instances, the utility of this anion recognition capability can be greatly enhanced via the preparation of functionalized systems wherein a calix[4]pyrrole nucleus is linked to some other entity such as a solid support, redox active element, fluorophore, or ancillary recognition unit. To date, we have prepared a range of functionalized calix[4]pyrroles.<sup>3,4</sup> However, in all instances we have relied on one of two basic functionalization strategies, involving either: (1) mixed initial condensations, an approach that leads to the production of *meso*-carbon functionalized materials; or (2) electrophilic attack on a pre-assembled calix[4]pyrrole, a strategy that directly produces systems bearing substituents on one or more of the  $\beta$ -pyrrolic positions.<sup>5–7</sup> Recently, metal-mediated carbon–carbon bond cross coupling reactions, especially the Negishi, Suzuki, Stille and Sonogashira reactions,<sup>8</sup> have begun to play an increasingly important role in the preparation of complex systems, including those associated with supramolecular chemistry (e.g., calixarenes<sup>9</sup> and porphyrins<sup>10</sup>). To the best of our knowledge, however, such attractive synthetic methods have yet to be applied to the problem of calix[4]pyrrole functionalization. Indeed, except in one specific case,<sup>11</sup> relatively little is known about the organometallic carbon–carbon bond forming reactivity of calix[4]pyrroles.

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In this communication, we report on a new synthetic strategy, predicated on the use of a Sonogashira coupling, that allows for the facile introduction of arylalkynyl functionality onto one of the  $\beta$ -pyrrolic positions of the calix[4]pyrrole skeleton. The resulting systems appear particularly attractive for use in applications such as fluorescence-based anion sensing, where direct conjugation between the aryl substituent and the calix[4]pyrrole framework is considered beneficial. Underscoring this latter point is the finding that the mono- and dinitrophenyl-functionalized systems **6** and **7** undergo naked eye-detectable spectral changes upon exposure to the tetrabutylammonium salts of fluoride, chloride, and phosphate anions in a dichloromethane solution.

Monoiodination of a single  $\beta$ -pyrrolic position of calix[4]pyrrole **1**, a species obtained in one step from the acid-catalyzed condensation of pyrrole and acetone, was effected by treatment with iodine-[bis(trifluoroacetoxy)iodo]benzene<sup>12</sup> at room temperature; this gave the monoiodocalix[4]pyrrole **2** in 20% yield. This intermediate, in turn, could be carried on to the key protected alkynyl derivative **3** in 73% yield by exposure to excess TMS acetylene in diisopropylamine–DMF at 80°C in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub>–CuI. Interestingly, efforts to effect this same transformation under standard Sonogashira conditions (i.e., in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>–CuI) gave only deiodinated calixpyrrole **1**, an effect we ascribe to the low reactivity and liability of iodocalixpyrrole **2**.

In light of the difficulties attendant to its synthesis under normal conditions, a decision was made to characterize compound **3** fully. This intermediate was thus subject to single crystal X-ray diffraction analysis and the resulting structure is shown in Fig. 1. In analogy to what has been observed previously for other calix[4]pyrroles in the absence of an anionic guest,<sup>2</sup> compound **3** adopts a 1,3-alternate conformation in the solid state. Thus, at least in the crystalline lattice, compound **3** appears to behave as a normal calix[4]pyrrole, in spite of the appended TMS acetylene functionality.

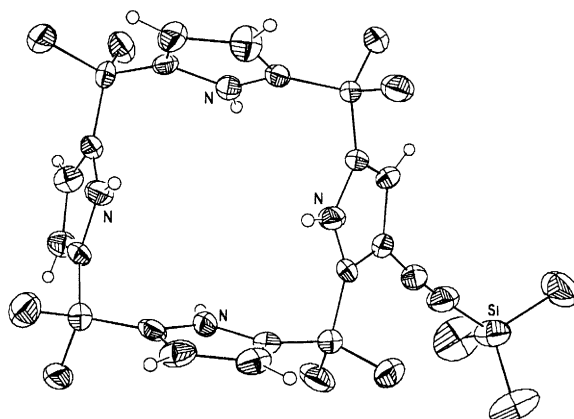
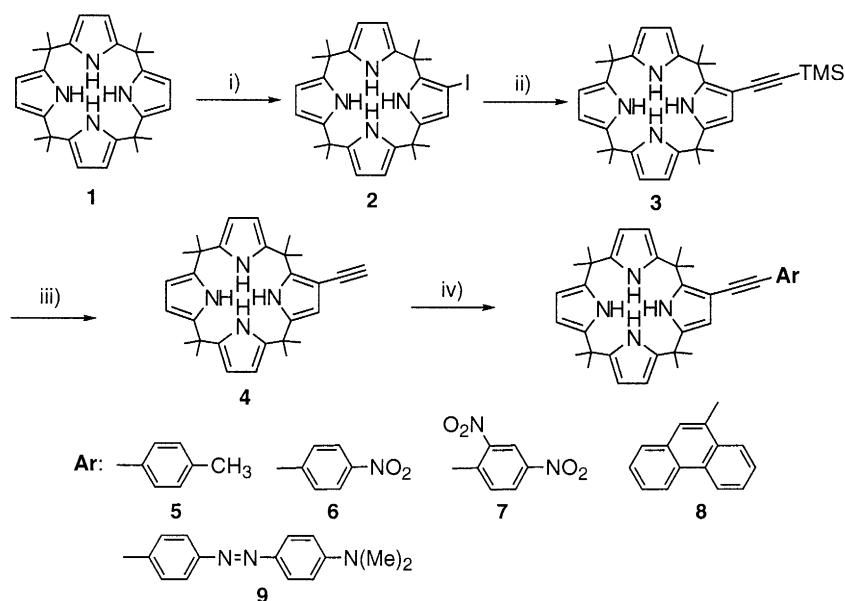


Fig. 1. View of C<sub>33</sub>H<sub>44</sub>N<sub>4</sub>Si (**3**). Displacement ellipsoids are scaled to the 30% probability level. The methyl hydrogen atoms have been omitted for clarity

Compound **3** was deprotected by exposure to tetrabutylammonium fluoride in THF at room temperature; this gave the moderately sensitive desilylated compound **4** in 89% yield after basic work-up. Once in hand, intermediate **4** was reacted with various aromatic iodides in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and CuI to give the arylalkynyl-functionalized products **5–9** in excellent yields as shown in Scheme 1.

Compounds **5–9** were chosen because, taken in concert, they serve to highlight the versatility of the procedure. Compound **5** contains an electron-donating substituent, whereas both calix[4]pyrroles **6** and **7** contain electron-withdrawing aryl subunits. Furthermore, compounds **8** and **9** contain a built-in fluorophore and a built-in chromophore, respectively.



Scheme 1. (i)  $\text{I}_2\text{-(CF}_3\text{CO}_2)_2\text{PhI}$  (20%); (ii) TMS acetylene,  $\text{Pd(PPh}_3)_4$  (73%), CuI; (iii) tetrabutylammonium fluoride, then  $\text{NaHCO}_3$  (89%); (iv) ArI,  $\text{Pd(PPh}_3)_4$ , CuI (**5**, 87%; **6**, 82%; **7**, 67%; **8**, 81%; **9**, 79%)

While systems **8** and **9** are the subject of ongoing studies,<sup>13</sup> the potential utility of compounds **6** and **7** as anion sensors is already apparent. For instance, as shown in Fig. 2, the addition of fluoride anion to dichloromethane solutions of **7** ( $5 \times 10^{-5}$  M) leads to a significant broadening of the UV-vis absorption bands<sup>14</sup> while engendering a noticeable red-shift in the position of the absorption maximum ( $\lambda_{\text{max}}$  shifts from 441 to 498 nm). As a consequence of these anion-induced spectral changes, the solution undergoes a naked-eye detectable color change, namely from yellow to red. Addition of chloride or phosphate anions caused the color to change from yellow to orange (the absorption maximum,  $\lambda_{\text{max}}$ , shifts from 441 to 483 and 478 nm upon the addition of 200 equiv. of tetrabutylammonium chloride and phosphate, respectively). On the other hand, exposure to bromide, iodide and sulfate anions, even in vast excess, did not lead to any noticeable changes in either color or basic spectral properties.

In the case of the mononitrobenzene conjugated calixpyrrole **6**, the absorption peak that is normally seen at 391 nm in dichloromethane was found to be shifted to 433 nm upon treatment with 20 equiv. of tetrabutylammonium fluoride. Under these conditions, the color of the solutions changed from pale yellow to intense yellow.<sup>13</sup> The presence of chloride and phosphate anions could also be detected from the intense final yellow color their exposure to **6** induced. Here again, no discernable change could be noted when dichloromethane solutions of **6** were exposed to 200 equiv. of bromide, iodide or sulfate anions.

In the above experiments, compound **5** served as an important control. This particular calix[4]pyrrole is colorless and displays a maximal absorption peak at 308 nm in its UV-vis spectrum. This latter band was found to be but slightly shifted (to 321 nm) upon the addition of 20 equiv. of tetrabutylammonium fluoride. When viewed in the light of the above results, this latter shift is rather modest. It is thus clear that: (1) 'attachment' of nitro groups produces a bathochromic shift in the absorption peak (an effect that is especially pronounced in the case of dinitrobenzene **7**); and that (2) even greater red-shifts are produced upon exposure to certain anions. We ascribe this latter effect to charge transfer from the calix[4]pyrrole-bound anion(s) and the electron deficient mono- and dinitrobenzene subunits mediated, in all likelihood, by the conjugating alkynyl bond acting as an electron wire (Fig. 3). Independent of its origins, however,

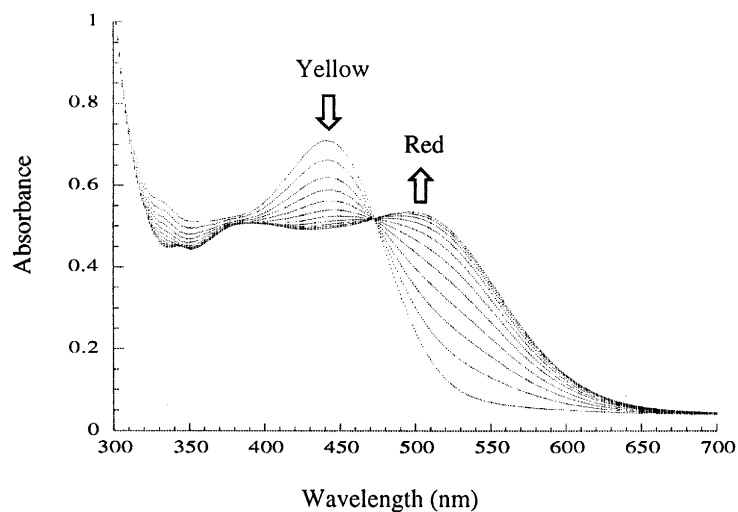


Fig. 2. Absorption spectra of calix[4]pyrrole **7** recorded in  $\text{CH}_2\text{Cl}_2$  ( $5.0 \times 10^{-5}$  M) before and after the addition of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0 equiv. of tetrabutylammonium fluoride

the fact that anion-dependent changes in the spectral features are seen for **6** and **7** leads us to suggest that functionalized calix[4]pyrroles of the type described herein could emerge as useful anion sensors.

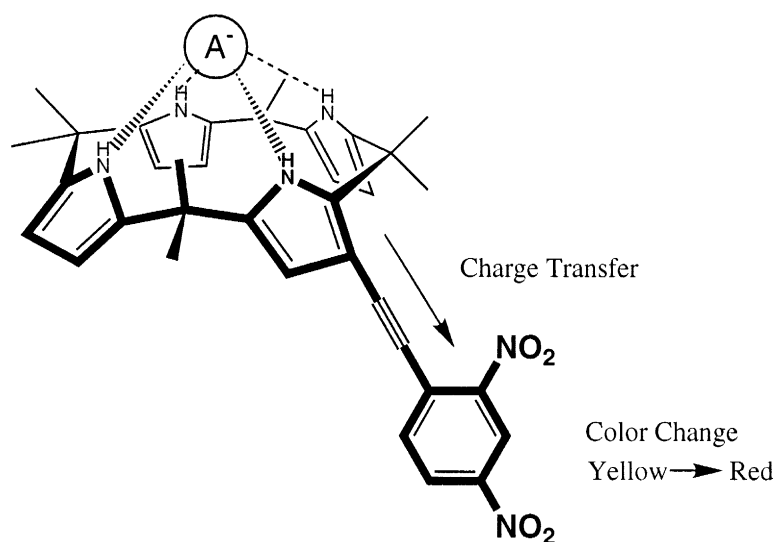


Fig. 3. Schematic representation showing the mechanism proposed to account for the changes in color observed when calix[4]pyrrole **7** is exposed to certain anions

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14. Log $K_a$  values (from UV-vis titration experiments for the association of **5**, **6** and **7** with fluoride, chloride, phosphate in  $\text{CH}_2\text{Cl}_2$ ) were 4.04 (**5** with  $\text{F}^-$ )  $\text{M}^{-1}$ , 3.36 (**5** with  $\text{Cl}^-$ )  $\text{M}^{-1}$ , 2.68 (**5** with  $\text{H}_2\text{PO}_4^-$ )  $\text{M}^{-1}$ , 4.23 (**6** with  $\text{F}^-$ )  $\text{M}^{-1}$ , 3.67 (**6** with  $\text{Cl}^-$ )  $\text{M}^{-1}$ , 3.03 (**6** with  $\text{H}_2\text{PO}_4^-$ )  $\text{M}^{-1}$ , 4.51 (**7** with  $\text{F}^-$ )  $\text{M}^{-1}$ , 3.84 (**7** with  $\text{Cl}^-$ )  $\text{M}^{-1}$ , and 3.28 (**7** with  $\text{H}_2\text{PO}_4^-$ )  $\text{M}^{-1}$ . Errors <15%. Compound **5**:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 7.32 (d, 2H,  $J=8.1$  Hz), 7.23 (s, 1H), 7.14 (s, 1H), 7.13 (d, 2H,  $J=8.1$  Hz), 6.94 (s, 1H), 6.89 (s, 1H), 6.06 (d, 1H,  $J=3.0$  Hz), 5.94–5.83 (m, 6H), 2.34 (s, 3H) 1.72 (s, 6H), 1.51 (s, 12H), 1.48 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 141.02, 139.55, 139.76, 138.21, 137.97, 137.92, 137.74, 137.45, 130.92, 129.46, 121.93, 108.58, 104.07, 104.04, 103.87, 103.22, 103.14, 102.44, 99.33, 90.55, 86.08, 37.35, 35.51, 35.43, 30.11, 29.35, 28.89, 28.56, 21.54. HRMS ( $\text{Cl}^+$ ) calcd for  $\text{C}_{37}\text{H}_{43}\text{N}_4$ : 543.3488; found: 543.3481. Compound **6**:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 8.17 (d, 2H,  $J=8.8$  Hz), 7.55 (d, 2H,  $J=8.8$  Hz), 7.30 (s, 1H), 7.25 (s, 1H), 6.99 (s, 1H), 6.93 (s, 1H), 6.11 (d, 1H,  $J=3.0$  Hz), 5.96–5.82 (m, 6H), 1.74 (s, 6H), 1.51 (s, 12H), 1.49 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 146.60, 142.83, 139.74, 139.32, 138.88, 138.20, 138.11, 137.65, 137.27, 132.22, 131.38, 124.05, 108.73, 104.32, 104.30, 103.99, 103.32, 103.14, 102.33, 98.41, 93.57, 89.78, 37.49, 35.54, 35.51, 35.45, 30.11, 29.30, 28.85, 28.76, 28.66. HRMS ( $\text{Cl}^+$ ) calcd for  $\text{C}_{36}\text{H}_{40}\text{N}_5\text{O}_2$ : 574.3182; found: 574.3179. Compound **7**:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 8.91 (d, 1H,  $J=2.4$  Hz), 8.36 (dd, 1H,  $J=8.7, 2.4$  Hz), 7.76 (d, 1H,  $J=8.7$  Hz) 7.30 (s, 1H), 7.27 (s, 1H), 7.09 (s, 1H), 6.92 (s, 1H), 6.19 (d, 1H,  $J=3.0$  Hz), 5.97–5.81 (m, 6H), 1.75 (s, 6H), 1.51 (s, 12H), 1.50 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 148.04, 145.50, 145.09, 139.91, 139.35, 138.93, 138.63, 138.08, 137.41, 136.78, 135.02, 127.26, 126.95, 121.04, 109.53, 104.60, 104.46, 104.09, 103.95, 103.39, 103.17, 102.24, 98.12, 87.76, 46.69, 37.58, 37.58, 35.58, 35.51, 35.45, 29.32, 28.84, 28.73, 28.66. HRMS ( $\text{Cl}^+$ ) calcd for  $\text{C}_{36}\text{H}_{39}\text{N}_6\text{O}_4$ : 619.3033; found: 619.3037. Compound **8**:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 8.73–8.71 (m, 1H), 8.67 (d, 1H,  $J=8.2$  Hz), 8.52–8.51 (m, 1H), 7.97 (s, 1H), 7.87 (d, 1H,  $J=8.2$  Hz), 7.73–7.59 (m, 4H), 7.35 (s, 1H), 7.27 (s, 1H), 6.97 (s, 2H), 6.24 (d, 1H,  $J=3.0$  Hz), 5.97–5.85 (m, 6H), 1.83 (s, 6H), 1.52 (s, 18H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 141.37, 139.63, 139.28, 138.82, 138.20, 137.90, 137.72, 137.61, 131.95, 131.71, 130.60, 130.54, 130.20, 128.67, 127.39, 123.20, 122.99, 121.41, 109.02, 104.17, 104.16, 103.92, 103.24, 102.44, 99.26, 91.60, 88.90, 37.44, 35.57, 35.52, 35.45, 30.10, 29.37, 28.90, 28.80. HRMS ( $\text{Cl}^+$ ) calcd for  $\text{C}_{44}\text{H}_{45}\text{N}_4$ : 629.3644; found: 629.3648. Compound **9**:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 7.85 (d, 2H,  $J=9.2$  Hz), 7.79 (d, 2H,  $J=8.7$  Hz), 7.52 (d, 2H,  $J=8.7$  Hz), 7.31 (s, 1H), 7.25 (s, 1H), 6.95 (s, 2H), 6.78 (d, 2H,  $J=9.2$  Hz), 6.10 (d, 1H,  $J=3.0$  Hz), 5.95–5.83 (m, 6H), 3.09 (s, 6H), 1.75 (s, 6H), 1.51 (s, 12H), 1.49 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 153.11, 152.25, 143.99, 141.63, 139.64, 139.29, 138.80, 138.20, 137.92, 137.65, 137.63, 131.64, 126.02, 125.34, 122.60, 111.87, 108.69, 104.17, 104.12, 103.91, 103.23, 103.17, 102.42, 99.18, 90.88, 89.11, 40.50, 37.43, 35.54, 35.51, 35.44, 29.36, 28.90, 28.79, 28.63. HRMS ( $\text{Cl}^+$ ) calcd for  $\text{C}_{44}\text{H}_{50}\text{N}_7$ : 676.4128; found: 676.4137.