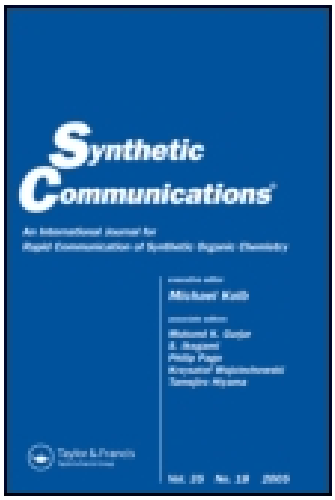

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A FACILE, HIGHLY EFFICIENT SYNTHESIS OF FULLY N-CONFUSED CALIX[5]PYRROLE

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Published online: 21 Aug 2006.

To cite this article: Qingqi Chen , Tianyu Wang , Yi Zhang , Qiuan Wang & Jinshi Ma (2002) A FACILE, HIGHLY EFFICIENT SYNTHESIS OF FULLY N-CONFUSED CALIX[5]PYRROLE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:7, 1041-1049, DOI: 10.1081/SCC-120003152

To link to this article: http://dx.doi.org/10.1081/SCC-120003152

SYNTHETIC COMMUNICATIONS, 32(7), 1041–1049 (2002)

A FACILE, HIGHLY EFFICIENT SYNTHESIS OF FULLY *N*-CONFUSED CALIX[5]PYRROLE

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ABSTRACT

Fully *N*-confused calix[5]pyrroles **3** are prepared in high yield by the oligomerization of 3-hydroxyphenylmethylpyrrole **2** under acid-catalysed conditions at room temperature.

Key Words: Dipyrrinone; Barton-Zard's method; Pyrrole

Although calix[*n*]pyrroles **I** have been known for over a century,[1] their intriguing properties as novel molecule recognition host systems to selectively bind anions,[2,3] neutral small molecules,[4] and transition metal ions,[5] are recently discerned and have attracted a lot of attention.

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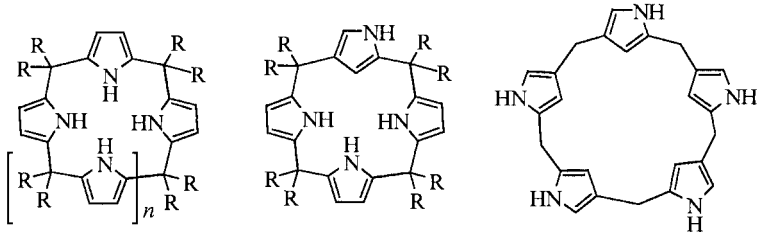
To improve their binding ability so as to develop them as chemsensors to selectively detect anions, small molecules, and metal ions, recent efforts have been focused on preparing structurally modified calix[*n*]pyrroles, such as monosubstituted,[6] functionalized,[7] quinoxaline, anthracene and ferrocene



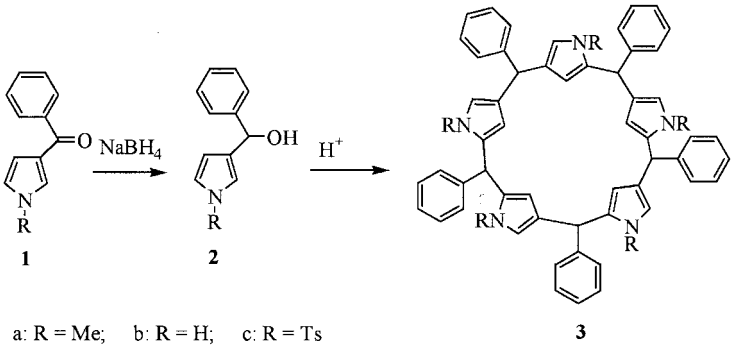
I **II** **III**

conjugates,[8] dimers,[9] extended-cavity,[10] cored modified and expanded cavity calix[*n*]pyrrole.[11]

In this paper we report a new structurally modified calix[5]pyrroles **III**, which may be of importance as novel host systems. They are cyclopentapyrroles, in which the pyrrole rings are linked to each other by $-CH_2-$ bridges at positions 2,4′. In contrast, the pyrrole rings in calix[*n*]pyrroles **I** are linked to each other through positions 2,2′. We thus term **III** as fully *N*-confused calix[5]pyrrole.

N-Confused calix[4]pyrroles **II**, a cyclotetrapyrrole containing one *N*-confused pyrrole rings, was isolated in 6–22% yields as a by-product from the condensation of pyrrole with hexanone under acid-catalysed conditions.[12] A doubly *N*-confused calix[4]pyrroles was also separated in 1–36% yields from the same reaction; however, the author was not able to characterize its structure due to the extremely low solubility in common deuterium solvents.[12] Moreover, fully *N*-substituted *N*-confused calix[5] pyrrole such as **III** was prepared by oligomerization of a *N*-substituted 3-hydroxymethylpyrrole under acid-catalysed condition under low temperature.[13] However, this molecule may not be a receptor with capacity to bind anion or metal ion species since there are no any free NH groups. Thus the *N*-unsubstituted *N*-confused calix[5]pyrroles **III** still remain unknown.

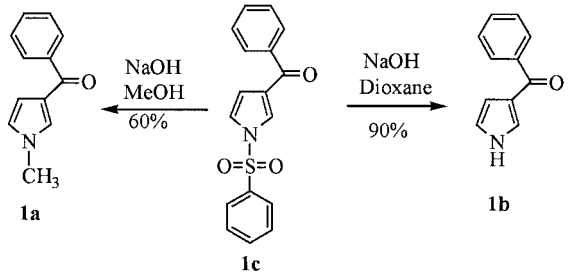
Our synthetic route, as outlined in Scheme 1, involves cyclization of the 5-unsubstituted 3-hydroxyphenylmethylpyrrole **2** in the presence of *p*-toluenesulfonic acid monohydrate with yields 60–75%. Compounds **2**, prepared in high yields by treating 3-benzoylpyrrole **1** sodium borohydride in tetra-



Scheme 1.

hydrofurane, are not stable, and are used immediately without further purification. It is worth pointing out that attempts to convert **3c** to the corresponding fully *N*-confused calix[5]pyrrole **3b** under standard deprotection procedure[14] disappointedly failed.

The important starting material **1b** was prepared by deprotection of 3-benzoyl-*N*-tosyl-pyrrole (**1c**). It is interesting to note that when treating **1c** with potassium hydroxide in dioxane, the expected product **1b** was obtained in 90%. However, when the same reaction was carried out in methanol, a *N*-methyl-3-benzoyl-pyrrole (**1a**) was obtained in 60% (Scheme 2).



Scheme 2.

The structure of *N*-confused calix[5]pyrroles **3** followed the structures of their starting materials, **2**, and was confirmed by ^{1}H NMR, MS spectra, and combustion analysis. Due to the possibility of *cis*- and *trans*-arrangement of the five phenyl groups at *meso*-positions, the cyclization of **2** might produce a number of steroisomers of **3**, which could be observed in their ^{13}C NMR spectra. Although the X-ray structure of **3** are currently not

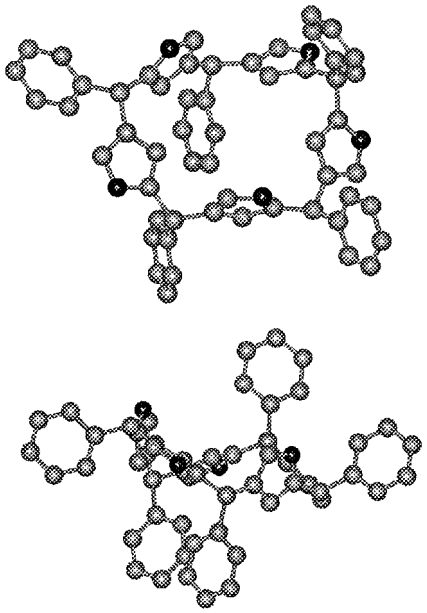


Figure 1. View of lowest-energy dominant conformation of **3b**, generated by HyperChem™, Releases 6.0 for Windows. Upper: top view. Lower: side view. For clarity, all hydrogen atoms are omitted.

available, the lowest-energy dominant conformation (Figure 1), generated by HyperChem,[15] showed that **3b** adopts a 1,3-alternate conformation wherein adjacent pyrrole rings are oriented in opposite directions just as is true in the case of the reported calyx[4]pyrrole.[2e] This suggests that **3b** may be a novel host system for binding anions, neutral small molecules, or metal ion.

In summary, a convenient and efficient route for the preparation of fully *N*-confused calix[5]pyrroles **3** through the cyclization of 3-hydroxyphenylmethylpyrrole **2** is reported. Their binding properties are currently under study.

EXPERIMENTAL SECTION

Melting points were determined on a Yanaco MP-500 micro-melting point apparatus and uncorrected. IR spectra were recorded on BIO-RAD FT-165 IR spectrometer. NMR spectra were recorded on a Varian Gemini-200 MHz instrument using tetramethylsilane as internal standard. UV-VIS

spectra were obtained on a Hitachi U-2001 spectrophotometer. Mass spectra were obtained on a VG TR10-200 spectrometer. Elemental analyses were performed on a Carlo Erba-120 elemental analyzer.

3-Benzoyl-*N*-tosylpyrrole [1c, $C_{18}H_{15}NO_3S$, FW = 325]

A 1-l three-necked round-bottomed flask equipped with a reflux condenser and magnetic stirrer was charged with anhydrous aluminum chloride (16 g, 0.12 mol, 1.20 mol equiv.), dichloromethane (250 ml) and *N*-tosylpyrrole[14] (22.1 g, 0.1 mol). The mixture was stirred, and a solution of benzoyl chloride (14 ml, 0.12 mol, 1.20 mol equiv.) in dichloromethane (50 ml) was added dropwise over a period of 5 min. The mixture was allowed to stir another 10 min before pouring into an ice-concentration hydrochloric acid mixture (100 g ice mixed with 50 ml 35% hydrochloric acid). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3×100 ml). The combined organic extracts were successively washed with water (2×200 ml), aqueous saturated sodium bicarbonate (200 ml $\times$ 2), and brine (200 ml). After removing the solvent under vacuum, the crude product was crystallized from methanol. The desired product was obtained (29 g, 89%) as gray needle crystal. M.p. 75–77°C [lit.[14b] 77°C], ^{1}H NMR (200 MHz $CDCl_3$), δ: 2.20 (s, 3H, CH_3), 6.80 (d, $J = 2.56$Hz, 1H, pyrr-H), 7.20–7.80 (m, 11H, 2 pyrr-H, 9 phenyl-H) ppm.

3-Benzoylpyrrole [1c]

N-Tosyl-3-benzoylpyrrole (42 g, 0.13 mol) was suspended in a solution of dioxane (150 ml). The mixture was stirred at room temperature, then a solution of aqueous potassium hydroxide (5 N, 150 ml) was added at once. The mixture was stirred at reflux over a period of 12 h. After removing all solvent under vacuum, the residue was taken up by dichloromethane (200 ml), and partitioned by water (200 ml). The organic phase was separated, and the aqueous phase was extracted by dichloromethane (3×100 ml). The combined organic extracts were successively washed with water (2×200 ml), aqueous saturated sodium bicarbonate (200 ml $\times$ 2), and brine (200 ml). After removing the solvent under vacuum, the title compound was obtained as white crystals after crystallization for methanol (20.8 g, 94%). M.p. 98–100°C [lit.[14b] 99°C], ^{1}H NMR (200 MHz, $CDCl_3$), δ: 6.80 (mm, 2H, 2 pyrrole-H), 7.20–7.80 (m, 5H, phenyl-H), 9.20 (brs, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$), δ: 102.86, 110.56, 119.83, 128.91, 124.44, 126.34, 128.91, 131.53, 139.97, 191.90 (C=O) ppm.

N-Methyl-3-benzoylpyrrole [1b]

A 250-ml three-necked round-bottomed flask equipped with a magnetic stirrer bar and reflux condenser was charged with *N*-tosyl-3-benzoylpyrrole (13 g, 40 mmol) and methanol (50 ml). The mixture was stirred and a solution of potassium hydroxide (20 g, 0.36 mol, 8.9 mol equiv.) in water (50 ml) was added at once. The mixture was stirred at reflux, and was monitored by TLC (dichloromethane/methanol, 97/3, v/v). After 10 h, the reaction was completed. The solvent was removed under vacuum, and the residue was taken up by dichloromethane (150 ml) and partitioned by water (80 ml). The organic phase was separated and the aqueous was extracted with dichloromethane (2×50 ml). The combined organic extracts were successively washed with water (2×100 ml), aqueous saturated sodium bicarbonate (200 ml $\times$ 2), and brine (100 ml). After removing the solvent under vacuum, the reside was crystallized from aqueous methanol (95%) to offer the expected product as colorless crystalline (4.4 g, 60%). M.p. 127–129°C. ^{1}H NMR (200 MHz, $CDCl_3$), δ: 3.65 (s, 3H, CH_3), 6.33 (m, 2H, 2 pyrrole-H), 7.20 (s, 1H, pyrrole-H), 7.40 (m, 3H, 3 phenyl-H), 7.80 (m, 2H, 2 phenyl-H) ppm. ^{1}H NMR (200 MHz, dimethyl sulfoxide -d_6) δ: 3.65 (s, 3H, CH_3), 6.52 (m, 1H, pyrrole-H), 6.91 (s, 1H, pyrrole-H), 7.41 (s, 1H, pyrrole-H), 7.65 (m, 3H, 3 phenyl-H), 7.80 (m, 2H, 2 phenyl-H) ppm. ^{13}C NMR ($CDCl_3$), δ: 36.63 (CH_3), 111.08, 123.11, 124.60, 128.12, 128.55, 131.23, 140.13, 190.54 (C=O) ppm. MS (EI), $m/e = 185$ (M^+, 52%), 170 (M^+-CH_3, 5), 108 (M^+-Ph, 100), 80 (M^+-PhCO, 6), 77 (8), 53 (4). For $C_{12}H_{11}NO$, calcd C, 77.81; H, 5.99; N, 7.56%. Found: C, 77.45; H, 6.12; N, 7.43.

General Procedure for Synthesis of 3

A 100 ml round-bottomed flask equipped with a magnetic stirrer bar and a reflux condenser was charged with 3-benzoylpyrrole (**3**, 3.08 mmol), dichloromethane (5 ml) and ethanol (50 ml). To this mixture, sodium boronhydride (0.175 g, 4.6 mmol, 1.5 equiv.) was added. The mixture was stirred at 50°C until TLC (dichloromethane/methanol, 99/1, v/v) indicated that the reaction was completed (about 3 h). The solvent was removed under vacuum, and the residue was dissolved in dichloromethane (80 ml) and partitioned by water (50 ml). The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×50 ml). The combined organic extracts were successively washed with water (2×50 ml), aqueous saturated sodium bicarbonate (50 ml $\times$ 2), and brine (50 ml). After drying over anhydrous sodium sulfate, the resulting solution was transferred into a 100 ml round bottom flask, equipped with a magnetic stirrer, a reflux con-

denser, and a nitrogen inlet. The stirrer was started and nitrogen was bubbled through the solution. After 20 min, trifluoroacetic acid (1 ml) was added. The mixture was allowed to stir 2 h under nitrogen protecting before pouring into water (100 ml). The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×50 ml). The combined organic extracts were successively washed with water (2×50 ml), aqueous saturated sodium bicarbonate ($50 \text{ ml} \times 2$), and brine (50 ml). After drying over anhydrous sodium sulfate, the solvent was removed under vacuum, and the residue was dissolved in a minimum amount of dichloromethane, and purified by flash chromatographic column (dichloromethane/methanol, v/v, 97/3), and crystallized from methanol to yield the expected compound.

N-Tosyl *N*-Confused Calix[5]pyrrole [3c]

Yield: 60%, m.p. 205°C (dec.). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 2.20 (m, 15H, 5 CH_3), 5.20–6.00 (m, 5H, 5CH), 6.90–8.00 (m, 55H, 10 pyrrolyl-H, 45 phenyl-H) ppm. ^{1}H NMR (DMSO-d_6, 200 MHz), δ: 1.80–2.00 (m, 15H, 5 CH_3), 5.00–5.20 (m, 5H, 5CH), 6.20–7.20 (m, 55H, 10 pyrrolyl-H, 45 phenyl-H) ppm. MS(EI), *m*/*e* (%) = 1546 (M^+, 2), 1391 (M^+-tosyl, 5), 1237 (32), 1083 (41), 927 (38), 773 (23), 619 (25), 551 (10), 465 (15), 310 (61), 244 (100). For $C_{90}H_{75}N_5O_{10}S_5$, calcd C, 69.88; H, 4.89; N, 4.53%. Found: C, 70.12; H, 4.67; N, 4.33%.

N-Methyl *N*-Confused Calix[5]pyrrole [3a]

Yield: 70%, m.p. 189°C (dec.). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 3.20 (m, 15H, 5 CH_3), 5.20, 5.80 (mm, 5H, 5CH), 7.00–8.00 (m, 35H, 10 pyrrolyl-H, 25 phenyl-H) ppm. MS(EI), *m*/*e* (%) = 846 (M^+, 2), 765 (5), 675 (23), 600 (5), 599 (15), 507 (49), 430 (15), 349 (10), 338 (100), 261 (74), 170 (25). For $C_{60}H_{55}N_5$, calcd C, 85.17; H, 6.55; N, 8.28. Found: C, 84.89; H, 6.23; N, 8.01.

N-Confused Calix[5]pyrrole [3b, $(C_{11}H_9N)_n$, $n \times 155$]

Yield: 75%, m.p. 195°C (dec.). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 5.00–5.30, 5.70 (mm, 5H, 5CH), 5.80–6.90, 7.00–7.80 (mm, 35H, 10 pyrrolyl-H, 25 phenyl-H), 7.90–8.00, 8.60–8.80 (brs, 5H, 5 NH) ppm. MS (EI) at 200°C, *m*/*e* (%) = 775 (M^+, 2), 708 (3), 620 (31), 553 (10), 532 (5), 479 (13), 465 (52), 402 (8), 398 (23), 309 (93), 244 (23), 233 (35), 156 (100).

For $C_{55}H_{45}N_5$, calcd C, 85.13; H, 5.84; N, 9.03%. Found: C, 84.85; H, 5.64; N, 8.88%.

ACKNOWLEDGMENTS

Q.C. thanks professor David Dolphin (University of British Columbia), in whose laboratory part of this work was initialized. J.M. thanks the 973 Project (G2000078100) and NSFC (20172055) and the National Key Laboratory for Structural Chemistry of Unstable and Stable Species who supported this work.

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Received in the USA March 29, 2001