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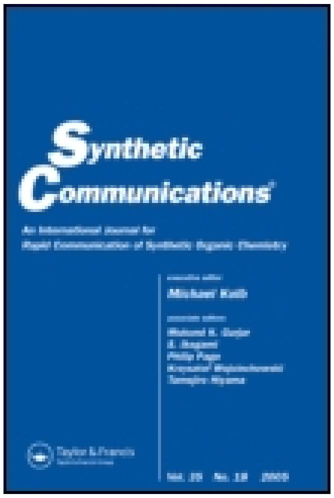

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

DOUBLY N-CONFUSED CALIX[4]PYRROLE PREPARED BY RATIONAL SYNTHESIS

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Published online: 21 Aug 2006.

To cite this article: Qingqi Chen, Tianyu Wang, Yi Zhang, Qiuan Wang & Jinshi Ma (2002) DOUBLY N-CONFUSED CALIX[4]PYRROLE PREPARED BY RATIONAL SYNTHESIS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:7, 1051-1058, DOI: 10.1081/SCC-120003153

To link to this article: http://dx.doi.org/10.1081/SCC-120003153

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SYNTHETIC COMMUNICATIONS, 32(7), 1051–1058 (2002)

DOUBLY *N*-CONFUSED CALIX[4]PYRROLE PREPARED BY RATIONAL SYNTHESIS

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ABSTRACT

Doubly *N*-confused calix[4]pyrrole **4** is prepared in high yield by the $[3+1]$ condensation of tripyrrane **3** with 2,4-dihdoxymethylpyrrole **2** under acid-catalysed conditions.

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

Although known for over a century,[1] calix [*n*]pyrroles **I**, the unconjugated cyclopolypyrroles prepared from the oligomerization of pyrrole with ketone, have recently become the subject of intensive research targeted at the development of novel receptors for anionic,[2,3] neutral small molecules,[4] and transition metal ions.[5] To improve their binding ability, a

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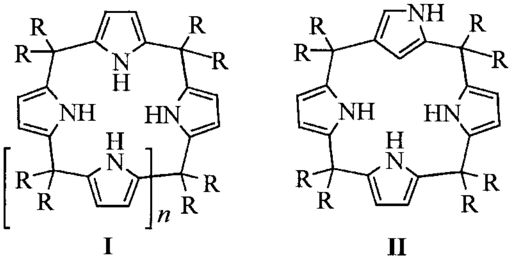
number of structurally modified calix[4]pyrroles such as monosubsitituted,[6] functionalized,[7] core modified,[3a] quinoxaline, anthracene, and ferrocene conjugates,[8] dimers,[9] extended-cavity,[10] have recently been prepared.

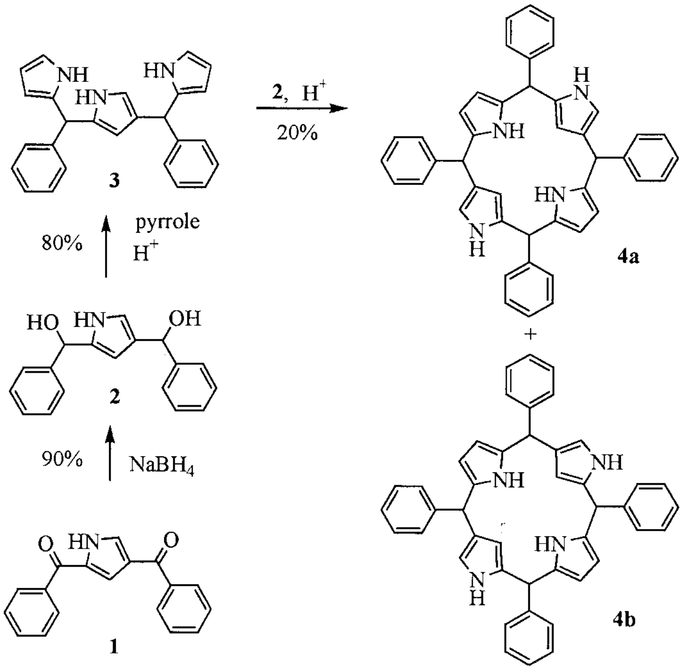


In spite of these successes, however, the need to prepare other new systems for the study of molecule recognition, anion, neutral small molecule and metal ion binding remains. We therefore wish to report here the rational synthesis of a new class of calix[4]pyrrole: the doubly *N*-confused system **4**, which may be of importance as novel host systems.

Calix[4]pyrroles **II**, a cyclotetrapyrrole containing one *N*-confused pyrrole ring, was isolated in 6–22% yields as a by-product from the condensation of pyrrole with hexanone under acid-catalysed conditions.[11] A doubly *N*-confused calix[4]pyrrole was also isolated in 1–36% yields from the same reaction; however, the author was not able to characterize its structure due to its extremely low solubility in common deuterium solvents.[11]

To synthesize doubly *N*-confused calix[4]pyrrole, we are attracted to the [3 + 1] condensation of a tripyrrane with a pyrrolic precusor since this method has been extensively used to prepare prophyrins and their analogues,[12] core modified prophyrins,[13] *N*-confused prophyrins,[14] carabachlorins,[15] and calix[*n*]pyrroles.[3a] Our synthetic route, outlined as Scheme 1, involves the synthesis of 2,4-*bis*[1-phenyl-1-(pyrrole-2-yl)methyl]pyrrole (**3**) via acid-catalysed condensation of 2,4-*bis*[(1-hydroxy-1-phenyl)methyl]-pyrrole (**2**) in the presence of excess of pyrrole. The 3 + 1 condensation of these two affords a new class of novel calix[4]pyrrole system, in which two pyrrole rings are *N*-confused. The important starting material **2** is prepared in two steps: first acylation[16] of pyrrole with excess of benzoyl chloride to give 2,4-dibenzoylpyrrole (**1**) in 62% in the presence of anhydrous aluminum chloride. Followed to convert **1** to the corresponding dihydroxy **2** in methanol in the presence of sodium boronhydride.

The [3 + 1] condensation of **3** with **2** affords in 20% yield a mixture of regioisomers **4a** and **4b**. Due to their very close R_f values in different solvent systems, it is not possible to isolate one of the isomers by common



Scheme 1.

chromatographic purification procedures. Their MS, *m/e* 620, and combustion analysis suggest a molecular formula of $C_{44}H_{36}N_4$, which is consistent with the [3 + 1] condensation product of **3** with **2**. The constitutional structures are confirmed by the ^{1}H NMR in DMSO-d_6, which exhibits 8 : 1 ratio of the signals of *meso*-CH groups between 5.00–6.00 ppm and the signals of pyrrolyl-CH, pyrrolyl-NH, and phenyl-CH groups between 6.60–7.50 ppm.

In summary, doubly *N*-confused calix[4]pyrroles are synthesized by [3 + 1] condensation of tripyrrane **3** with 2,4-dihydroxymethylpyrrole **2** under acid-catalysed conditions. Their binding abilities 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 a 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 VG TR10-200 spectrometer. Elemental analyses were performed on Carlo Erba-120 elemental analyzer.

2,4-Dibenzoylpyrrole [1, $C_{18}H_{13}NO_2$, FW = 275]

A 2-l three-necked round-bottomed flask equipped with a reflux condenser and mechanic stirrer was charged with anhydrous aluminum chloride (163 g, 1.20 mol, 2.40 equiv.) and dichloromethane (400 ml). The stirrer was started, and a solution of pyrrole (35 ml, 0.5 mol) in dichloromethane (50 ml) was added at 0°C over a period of 10 min, followed by a solution of benzoyl chloride (164 ml, 1.12 mol, 2.24 equiv.) in dichloromethane (100 ml) which was added dropwise over a period of 60 min. The mixture was stirred at the same temperature for another two days before pouring into a mixture of ice–conc. hydrochloric acid (100 g ice plus 100 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 (2 × 200 ml), and brine (200 ml). After removal of the solvent under vacuum, the residue was crystallized from methanol. The desired compound was obtained (85.82 g, 62.4%). M.p. 136–138°C (lit.[16] 140°C), ^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.24–8.00 (m, 12H), 11.00 (brs, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$), δ: 102.87, 120.27, 126.25, 128.48, 128.61, 128.94, 129.13, 130.70, 131.78, 132.67, 137.37, 139.08, 185.74 (C=O), 190.49 (C=O) ppm.

2,4-*Bis*(1-Phenyl-1-hydroxymethyl)pyrrole [2, $C_{18}H_{17}NO_2$, FW = 279]

A 100-ml three-necked round-bottomed flask equipped with a magnetic stirrer bar and reflux condenser was charged with 1,3-dibenzoylpyrrole (4.0 g, 14.5 mmol) and ethanol (50 ml). The mixture was stirred and sodium boronhydride (1.38 g, 36.4 mmol, 2.5 equiv.) was added over a period of 20 min. The mixture was then stirred at 50°C until TLC indicated that the reduction was complete (about 4 h). The solvent was removed under vacuum, and the oily residue was dissolved in 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 (2 × 200 ml), and brine (100 ml). After drying over anhydrous sodium sulfate, and removing the solvent under vacuum, a colorless oil product was obtained (3.65 g, 90%). NMR experiments showed the product was a mixture of RR, SS, RS, SR isomers. ^{1}H NMR (200 MHz, $CDCl_3$), δ: 5.20 (brs, 1H, OH), 5.85 (s, 2H, 2CH), 6.40 (s, 1H, OH), 7.00–7.60 (m, 10H), 7.60–7.80 (m, 2H), 9.20 (brs, 1H, NH) ppm. ^{13}C NMR (50 HMz, $CDCl_3$), δ: 69.95 (CHOH), 83.45 (CHOH), 102.47, 102,89, 108.32, 113.86, 126.43, 128.18, 128.64, 128.88, 131.48, 135.70, 139.71, 141.54 ppm.

2,4-*Bis*[Phenyl-(Pyrrole-2-yl)methyl]pyrrole

[3, $C_{26}H_{23}N_3$, FW = 377]

A 500 ml three-necked round-bottomed flask equipped a magnetic stirrer, a reflux condenser, and a nitrogen inlet was charged with 2,4-*bis*(1-phenyl-1-hydroxymethyl)pyrrole **2** (0.3 g, 10.9 mmol) and dichloromethane (200 ml). The mixture was stirred and nitrogen was bubbled through the solution. After 20 min, a solution of pyrrole (1.5 ml, 21.8 mmol, 2.0 equiv.) in dichloromethane (10 ml) was added followed trifluoroacetic acid (2 ml). The mixture was stirred at room temperature for 3 days 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 × 100 ml), aqueous saturated sodium bicarbonate (2 × 200 ml), and brine (100 ml). After drying over anhydrous sodium sulfate, and passing through a flash silica gel chromatographic column, the solvent was removed under vacuum and the oily product was obtained (3.3 g, 80%). ^{1}H NMR ($CDCl_3$, 200 MHz), δ = 5.20–5.30 (m, 2H), 5.80–6.30 (m, 8H, 8 pyrrole-H), 7.20–7.60 (m, 10H, 10 phenyl-H), 7.80–8.10 (very broad, 3H, 3 NH) ppm. MS (EI) *m*/*e* (%) = 377 (M^+, 5), 310 (M^+-pyrrole, 16), 233 (12), 221 (15), 222 (100), 204 (5), 194 (6), 156 (40), 145 (900), 128 (5), 105 (6).

Tetraphenyl-Doubly *N*-Confused Calix[4]pyrrole

[4, $C_{44}H_{36}N_4$, FW = 620]

A 250-ml three-necked round-bottomed flask equipped with a magnetic stirrer, a reflux condenser, and a nitrogen inlet, was charged with 2,4-*bis*[phenyl-(pyrrole-2-yl)methyl]pyrrole (**3**, 2.73 g, 7.25 mmol), 2,4-*bis* (1-phenyl-1-hydroxymethyl)pyrrole (**2**, 2.02 g, 7.25 mmol), and dichloromethane (150 ml). The mixture was stirred and nitrogen was bubbled through the solution. After 30 min, trifluoroacetic acid (3 ml) was added at once. The mixture was stirred at room temperature for three days under nitrogen before pouring into water (100 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 (2 × 200 ml), and brine (100 ml). After drying over anhydrous sodium sulfate, and passing through a flash silica gel chromatographic column, the solvent was removed under vacuum, and the residue was crystallized from dichloromethane-hexane to yield the expected compound (0.9 g, 20%) as colorless powder. ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 5.00–6.00 (m, 4H, 4CH), 6.60–7.50 (m, 32H, 4NH, 8 pyrrole-H, 20 phenyl-H) ppm. MS DCI *m/e* (%) = 620 (M^+, 1), 553(2), 463 (70), 398 (60), 308 (70), 247 (30), 221 (20), 156 (100). Calcd. for $C_{44}H_{36}N_4$, required, C, 85.13; H, 5.84; N, 9.04. Found: C, 84.85; H, 5.44; N, 8.78.

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