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An efficient and eco-friendly protocol to synthesize calix[4]pyrroles

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Abstract—A facile, highly efficient and eco-friendly protocol for the synthesis of calix[4]pyrroles in excellent yields is reported. Instead of tedious column chromatography, simple recrystallization techniques were employed for compound purification yielding better results and leading to multi gram scale synthesis.
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Calix[4]pyrroles, formerly called fully *meso*-substituted porphyrinogens are an important class of macrocycles[1] and have gained significant importance owing to their anion,[2] neutral substrate[3] and metal ion binding ability in deprotonated form.[4] In the host–guest approach, the binding of an anion or cation to a substrate plays a crucial role in biology. In recent years these molecules have been extensively used as fluorescent,[5] colorimetric[6] and electrochemical signalling[7] devices and can also serve as important precursors in novel calixpyridines and calixpyridinopyrrole synthesis.[8] In addition, they can be treated as new solid supports capable of separating anion mixtures.[9] Thin calix[4]pyrrole films are also being used for optical recognition of organic vapors.[10] Thus, selective synthesis of these macromolecules in higher yield via an environmentally clean and cost effective process is of topical interest. The pioneering synthetic work on porphyrinogen was reported by Baeyer[11] in 1886. A number of strategies have been employed over the past two decades to synthesize and characterize various functionalized calix[4]pyrroles.[12–30] A wide variety of catalysts including chlorzink, *p*-toluenesulfonic acid, glacial acetic acid and zeolites were employed and occasionally Schlenk techniques were used to improve the yield for a specific synthesis. Apart from these, the formation of oligomeric and polymeric compounds during condensation led to a mixture of compounds. This required time consuming chromatographic separation which in turn hindered the synthesis on multi gram scale.

To overcome these difficulties we have designed a common strategy with a versatile synthetic protocol adopting a simple recrystallization technique using water as a co-solvent and precipitating solvent to afford good to excellent yields of *meso*-substituted calix[4]pyrroles (Table 1). In a typical synthesis, an aqueous alcoholic mixture (water + ethanol or methanol, 1:1) was used as the reaction medium, HCl as an acid catalyst and all the reactions were carried out in air at room temperature except for the preparation of **5** (Scheme 1). Compound **5** requires refluxing conditions which may be due to the presence of a sterically hindered isobutyl group. On completion of the reaction, the product separated out as a sticky mass which, after decanting off the mother liquor, was thoroughly washed with water. Finally, the product was treated with dilute ammonia (~1 M) solution to neutralize any remaining acid. The pH was maintained between 7 and 8 as the compound precipitated out in neutral to basic (pH, 7–8) medium. The product was washed with methanol to remove any unreacted pyrrole or ketone. Finally, it was recrystallized by dissolving in hot acetone and precipitated by adding methanol. All the compounds were isolated as white microcrystalline solids. A single spot in the TLC for each of these compounds confirmed the presence of one compound in each case. However, for acyclic ketones, some polymeric compounds were also formed and on extracting with hot acetone these were removed. The reaction time, recrystallization protocol and respective yields for **1**–**5** are summarized in Table 1. The experimental details in the synthesis of **1** as a representative case are provided.[31]

For the syntheses of these macrocycles, the relative dependence on the ratio of solvent mixture led to the

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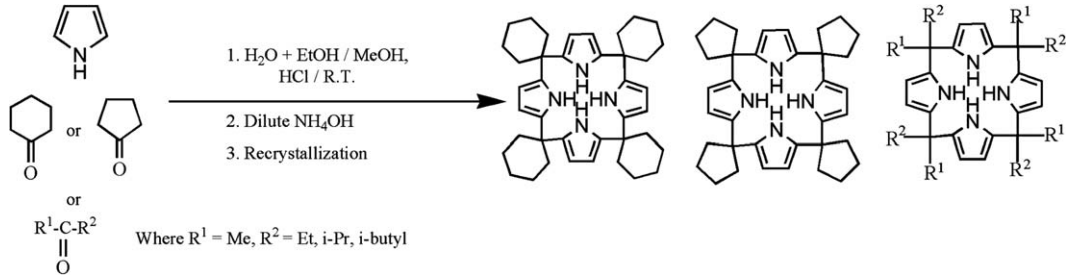
Table 1. Reaction time, recrystallization method and respective yield (%) of *meso*-substituted calix[4]pyrroles **1**–**5**

Entry	Calix[4]pyrrole	Reaction time (h)	Recrystallization protocol	Isolated yield (%)
1	*meso*-Tetrakis-spirocyclohexyl (**1**)	0.5	Acetone/methanol (1:2)	95
2	*meso*-Tetrakis-cyclopentyl (**2**)	1.0	Acetone/methanol/water (1:1:2)	87
3	*meso*-Tetramethyl-tetrakis(ethyl) (**3**)	2.0	Methanol/water (1:2)	82
4	*meso*-Tetramethyl-tetrakis(isopropyl) (**4**)	3.0	Acetone/water (1:2)	62
5	*meso*-Tetramethyl-tetrakis(isobutyl) (**5**)	4.0	Acetone/methanol/water (1:1:2)	58



Scheme 1. Modified protocol for the synthesis of different calix[4]pyrroles having cyclic and acyclic *meso*-substitution.

conclusion that water was the best solvent where the activity of the catalyst was increased followed by the phasing out of the desired product. The use of an aqueous alcoholic mixture as solvent served to maintain the reactants in a homogeneous solution phase. This green approach was found to be very convenient even for large scale preparation up to 100 g where the % yield of the product was maintained except for **5** where the yield decreased on scaling up the reaction. Advantageously, the alcohol used in the synthesis can be recovered and reused. The products were characterized by elemental analysis for C, H and N and by IR, NMR and FAB-mass spectroscopy.[32] The X-ray crystal structure analyses for **1** and **5** were identical to those reported earlier.[2,30] For **2**, the X-ray crystal structure is presented in this study.[33] Single crystals of **2** were grown from acetone/methanol/water solution, the structure is shown in Figure 1 showing the hydrogen bonding interaction of **2** with two methanol molecules present in the lattice.

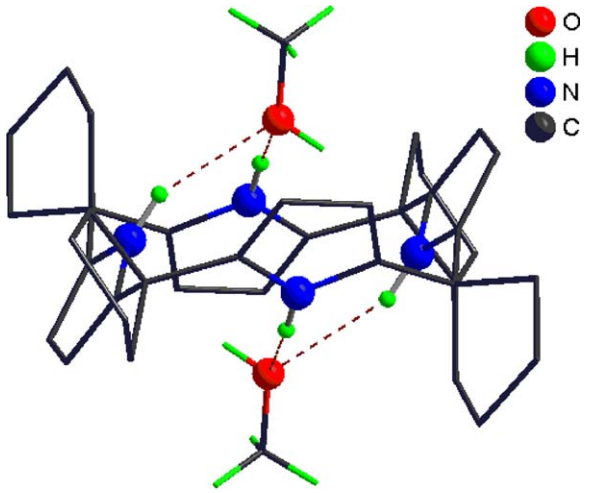


Figure 1. Diamond view of the crystal structure of **2**. Hydrogen atoms are omitted except for solvent molecules and pyrrole N–H's for clarity.

In conclusion, we have developed a convenient and cost effective synthetic procedure for the preparation of various calix[4]pyrroles with retention of percentage yield even on large scale. This modified protocol offers improved performance over many conventional procedures. It also permits recycling of the solvent. Anion binding studies, including removal of some deleterious pollutant anions such as arsenate and selenates is in progress. In addition, the structural flexibility of calix[4]pyrroles due to the variation in hydrogen bonding with different solvated adducts is under investigation and will be communicated later.

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31. The experimental operations were performed under ambient conditions. Pyrrole and ketones were distilled immediately before use. All the solvents were used as received and distilled water was used for both synthesis, washing and crystallizations of **1**–**5**. Representative experimental procedure for the synthesis of *meso-tetrakisspirocyclohexylcalix-[4]pyrrole* ($C_{40}H_{52}N_4$) (**1**): 20 ml (0.29 mol) of pyrrole and 30.7 ml (0.29 mol) of cyclohexanone were taken in a 500 ml round bottom flask. Ethanol (75 ml) and water (75 ml) were added followed by concentrated hydrochloric acid (8 ml) in a dropwise manner. Since the reaction is highly exothermic, care was taken not to add the acid all at once. At first, a white milky suspension appeared which turned pale violet with time. Finally, the formation of a sticky mass stopped the stirring after 30 min. The reaction mass was washed thoroughly with water (50 ml × 3), then with 10 ml of 1 M ammonia solution followed by ethanol (25 ml × 2) to remove trace acid and any remaining reagents. The crude was recrystallized by dissolving in hot acetone followed by the slow addition of methanol and then cooling to room temperature. Finally, the crystals were washed with methanol and vacuum dried. Yield: 40 g (95%). Mp 276 °C; FT-IR (KBr pellet, cm^{-1}): 3402 (s, pyrrole N-H), 3100 (β-pyrrole C–H), 2927, 2855, 1415, 1180, 1045, 764. ^1H NMR: ($CDCl_3$, 400 MHz, 298 K, ppm): δ 7.03 (br s, 4H, N–H); 5.83 (s, 4H, C_4H_2N); 5.82 (s, 4H, C_4H_2N); 1.83 (m, 16H, C_6H_{10}); 1.40 (m, 16H, C_6H_{10}), 1.33 (m, 8H, C_6H_{10}). CHN: calcd for $C_{40}H_{52}N_4$: C, 81.59; H, 8.90; N, 9.51%; found: C, 82.01, H, 8.82; N, 9.37%. FAB-MASS: *m*/*z* 588.
32. Compounds **2**–**4** were also synthesized using a similar procedure. For **5**, water/alcohol (1:2) as solvent and refluxing for 4 h was required. Several recrystallizations were needed to obtain pure compounds. Spectral data for **2**–**5**: for compound **2**: mp 236 °C, FTIR: (KBr pellet, cm^{-1}): 3495 (s, pyrrole N–H), 3105 (β-pyrrole C–H), 2970, 2931, 2869, 1232, 1044, 759, 519. ^1H NMR: ($CDCl_3$, 400 MHz, ppm): 7.02 (br s, 4H, N–H, C_4H_2N), 5.79 (s, 4H, C_4H_2N), 5.78 (s, 4H, C_4H_2N), 1.93 (s, 16H, CH_2, cyclopentane), 1.61 (s, 16H, CH_2, cyclopentane). CHN: calcd for $C_{38}H_{52}N_4$ (**2**·2MeOH) C 81.27, H 8.27, N 10.52%; found, C 81.16, H 8.22, N 10.59%; FAB-MS: *m*/*z* 532. For compound **3**: mp 146 °C; FTIR: (KBr pellet, cm^{-1}): 3436 (s, pyrrole N–H), 3111 (β-pyrrole C–H), 2968, 2930, 2874, 1210, 1041, 763. ^1H NMR: ($CDCl_3$, 400 MHz, ppm): 6.97 (br s, 4H, N–H, C_4H_2N); 5.81 (s, 4H, C_4H_2N), 5.80 (s, 4H, C_4H_2N), 1.78 (m, 8H, CH_2, Et), 1.35 (s, 12H, CH_3, Me), 0.62 (m, 12H, CH_3, Et); CHN: calcd for $C_{34}H_{52}N_4$ (**3**·2MeOH): C, 74.41; H, 9.55; N, 10.21%; found: C, 74.37, H, 9.52; N, 10.17%. FAB-MS: *m*/*z* 484. For compound **4**: mp 168 °C, FTIR: (KBr pellet, cm^{-1}): 3422 (s, pyrrole N–H), 3099 (β-pyrrole C–H), 2934, 2830, 1203, 771. NMR: ($CDCl_3$, 400 MHz, ppm): 7.00 (br s, 4H, N–H, C_4H_2N), 5.79 (s, 4H, C_4H_2N), 5.78 (s, 4H, C_4H_2N), 1.81 (m, 4H, CH, *i*-Pr) 1.34 (s, 12H, CH_3, Me), 0.64 (d, 24H, $J = 6.78$, CH_3, *i*-Pr); CHN: calcd for $C_{38}H_{60}N_4$ (**4**·2MeOH): C, 75.45, H, 10.00, N, 9.26%; found: C, 75.39, H, 9.72; N, 9.11%. FAB-MS: *m*/*z* 540 for compound **5**: mp 184 °C, FTIR: (KBr pellet, cm^{-1}): 3420 (s, pyrrole N–H), 3099 (β-pyrrole C–H), 2965, ^1H NMR: ($CDCl_3$, 400 MHz, ppm): 7.02 (br s, 4H, N–H, C_4H_2N), 5.80 (s, 4H, C_4H_2N), 5.79 (s, 4H, C_4H_2N), 1.67 (m, 8H, CH_2, isobutyl), 1.44 (m, 4H, *i*-Bu), 1.35 (s, 12H, CH_3, Me), 0.63 (d, $J = 6.84$, 24H, CH_3, *i*-Bu). CHN: calcd for $C_{42}H_{68}N_4$ (**5**·2MeOH): C,76.31, H, 10.37, N, 8.48%; found: C, 76.25, H, 10.41, N, 8.36%. FAB-MS: *m*/*z* 596.
33. Single crystals of compound **2** were grown by slow diffusion of water into a 2:1 acetone/methanol mixed solution at 4 °C. The crystal structure shows the presence of two molecules of methanol symmetrically placed above and below the molecule forming hydrogen bonds with two adjacent pyrroles of **2** (Fig. 1). The molecule adopts a 1, 2 alternate conformation. Crystal data for **2**·2MeOH: $C_{38}H_{52}N_4O_2$, $M = 596.84$, colorless blocks, $0.20 \times 0.10 \times 0.08$ mm^3, monoclinic, space group $C2/c$, $a = 15.447$ (5) Å, $b = 12.448$ (5) Å, $c = 16.397$ (5) Å; $\alpha = 90.000$ (5)°, $\beta = 91.251$ (5)°, $\gamma = 90.000$ (5)°, volume 3152.1 (19) $Å^3$, $Z = 4$, $D_c = 1.258$ gm/cm^3, $F(000) = 1296$, Bruker SMART APEX, Mo-Kα radiation ($\lambda = 0.71069$ Å), $T = 100$ (2) K, ($2.10 \leqslant \theta \leqslant 28.34$), 10429 reflections collected, 3900 unique, $R(\text{int}) = 0.0546$, final GooF 1.110,

$R1 = 0.0636$, $wR2 = 0.1382$, R indices based on 3900 reflections with $I > 2\sigma(I)$, (refinement on F^2), 201 parameters, 0 restraints, absorption corrections empirical, $\mu = 0.071\ \text{mm}^{-1}$. Crystallographic data for **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 605563. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].