The first direct synthesis of β-unsubstituted meso-decamethylcalix[5]pyrrole

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Abstract
The first direct synthesis of β-unsubstituted meso-decamethylcalix[5]pyrrole from pyrrole and acetone, with moderate yield, is described. The results showed that a bismuth salt was necessary to obtain calix[5]pyrrole, with the best results obtained using Bi(NO₃)₃.

Results and Discussion
Calix[n]pyrroles have attracted attention because of their ability to recognize anions [1,2]. To date, the calix[4]pyrroles have been studied the most, in part due to the ease with which the macrocycle can be obtained by the condensation of pyrrole with a ketone catalyzed by a Brønsted-Lowry acid such as HCl or methanesulfonic acid, or a Lewis acid such as zeolites with aluminium or cobalt, BF₃ or a bismuth salt [2-5]. The synthesis of calix[n]pyrroles where \( n > 4 \) has been reported for \( n = 5 \) or 6. The latter compounds have been synthesized via two routes: a) from the sterically hindered diaryldi(pyrrrol-2-yl)methane with 25% yield; and b) through the conversion of a calix[6]furan into the corresponding calix[6]pyrrole by an opening process of the six heterocycles, a selective reduction of the double bond and then a Paal-Knorr condensation with ammonium acetate with 40% yield [6,7]. On the other hand, β-unsubstituted calix[5]pyrroles have been obtained by two routes: a) from the corresponding meso-decamethylcalix[5]furan, via a method analogous to that reported for calix[6]pyrroles, with 1% yield; and b) directly when the macrocycle is covalently bound to a calix[5]arene, with 10% yield [8,9]. However, these approaches afford calix[5]pyrroles in low yield, which has limited the study of these compounds as anion receptors.

One explanation for why it is difficult to obtain calix[5]pyrroles via direct condensation of a pyrrole and the corresponding ketone is that the five heterocycle system is unstable: it opens and loses a pyrrole-isopropyl fragment to give the calix[4]pyrrole [8,10].
In a recent report we described the synthesis of calix[4]pyrroles via the direct condensation of pyrrole with a series of ketones in the presence of a bismuth salt such as Bi(NO\(_3\))\(_3\), BiCl\(_3\), BiI\(_3\), and Bi(CF\(_3\)SO\(_3\))\(_3\), in a 1 : 1 : 0.25 (pyrrole : ketone : BiX\(_3\)) ratio or with the ketone as a solvent at room temperature [5]. Here we describe the first direct synthesis of β-unsubstituted meso-decamethylcalix[5]pyrrole (2) with Bi(NO\(_3\))\(_3\) in moderate yield (Scheme 1).

While studying the role of bismuth as a Lewis acid in the synthesis of calix[4]pyrroles, we found that at low catalyst concentrations some additional products were formed, as observed by \(^1\)H NMR spectroscopy. These byproducts exhibited \(^1\)H NMR, \(^{13}\)C NMR and MS data consistent with those reported for calix[n]pyrroles with \(n = 4, 5\) and 6 (compounds \(1\)–3, respectively) and 5,5-dimethylpyrromethane (4); see Experimental section [5,6,8]. The relative proportions of these four products obtained using different catalyst equivalents are listed in Table 1. Compounds 1 and 2 were almost indistinguishable on TLC because of their similar \(R_f\) values, and recrystallization from ethanol, as reported in other works, was not satisfactory to give the pure compounds. However, it was possible to separate 1 and 2 by HPLC, to obtain 2 in 25% yield (using the conditions specified in Table 1, entry 12). Compound 2 was found to be unstable, which probably decreased the yield.

To determine whether the reaction proceeds with other Lewis acids, we explored the use of MgCl\(_2\), CuCl\(_2\), ZnCl\(_2\), AlCl\(_3\), BiCl\(_3\), BiI\(_3\), BiPO\(_4\), Bi(OTf)\(_3\) and Bi(NO\(_3\))\(_3\) under the conditions described above. Except for MgCl\(_2\), which gave none of the byproducts, all of these Lewis acids catalyzed the reaction to give 1 and/or 4 in amounts ranging from traces to moderate yields. Bismuth salts also produced 3. The results showed that a bismuth salt was necessary to obtain calix[5]pyrrole 2, with the best results being obtained with Bi(NO\(_3\))\(_3\). The advantages of the method described here—namely that bismuth is relatively non-toxic, the macrocycle is obtained in moderate yield, and the synthesis proceeds without any intermediates—make it the best route to β-unsubstituted meso-decamethylcalix[5]pyrrole reported to date.

**Experimental**

*meso*-Decamethylcalix[5]pyrrole (2). In a typical reaction, 6 mg of Bi(NO\(_3\))\(_3\), 2 mL of acetone and 0.09 mL of pyrrole were mixed with stirring at room temperature for 6 h. The reaction mixture was filtered and the solvent evaporated without heat. Reactants were not distilled prior to use and heat was avoided throughout the process. *meso*-Decamethylcalix[5]pyrrole was purified from the crude reaction mixture using an Agilent Tech-

![Scheme 1: Products obtained by the reaction of pyrrole and acetone with bismuth(III).](image)

**Table 1: Catalyst conditions and relative proportions of compounds 1, 2, 3 and 4 detected in the crude reaction mixture by \(^1\)H NMR spectroscopy.**

| Entry | Catalyst          | % mol | 1     | 2     | 3     | 4     |
|-------|-------------------|-------|-------|-------|-------|-------|
| 1     | MgCl\(_2\) · 6H\(_2\)O | 9.5   | –     | –     | –     | –     |
| 2     | CuCl\(_2\) · 2H\(_2\)O | 9.5   | 100   | –     | –     | –     |
| 3     | ZnCl\(_2\)       | 9.5   | 80    | –     | –     | 20    |
| 4     | AlCl\(_3\)       | 5     | –     | –     | –     | 100   |
| 5     | BiCl\(_3\)       | 9.5   | 50    | 40    | 10    | –     |
| 6     | BiI\(_3\)        | 9.5   | 44    | 42    | 12    | 2     |
| 7     | BiPO\(_4\)       | 9.5   | 53    | 45    | –     | 2     |
| 8     | Bi(OTf)\(_3\)    | 9.5   | 80    | 20    | –     | –     |
| 9     | Bi(NO\(_3\))\(_3\) | 0.095 | –     | –     | –     | 100   |
| 10    | Bi(NO\(_3\))\(_3\) | 0.18  | 40    | –     | –     | 60    |
| 11    | Bi(NO\(_3\))\(_3\) | 0.32  | 50    | 50    | –     | –     |
| 12    | Bi(NO\(_3\))\(_3\) | 0.65  | 33    | 67    | –     | –     |
| 13    | Bi(NO\(_3\))\(_3\) | 0.95  | 90    | 10    | –     | –     |
| 14    | Bi(NO\(_3\))\(_3\) | 9.5   | 95    | <5    | –     | –     |
| 15\(^a\) | Bi(NO\(_3\))\(_3\) | 25    | 100   | –     | –     | –     |

\(^a\)As reported in [5].
nologies HPLC 1200 system equipped with a multiple wavelength detector (G1365D) operating at 350 nm. Purification was performed on an analytical Zorbax Eclipse XDB-C18 column (150 × 4.6 mm, Agilent Tech. Santa Clara, CA, USA). The column temperature was maintained at room temperature and the mobile phases consisted of solvent A (80% MeOH/20% H₂O) and solvent B (100% EtOAc). Separations were performed by the following solvent gradient: 0 min 20% B, 2.5 min 22.5% B, 20–22.5 min 50% B, 24–26 min 80% B, 31–34 min 100% B, 42–47 min 20% B. All increases of solvent B were linearly programmed. The flow rate was 1 mL/min and the injection volume 20 µL. Yield ca. 25%; mp 208–210 °C; 1H NMR (400 MHz, CDCl₃): 1.51 (s, 30H, CH₃), 5.77 (d, J = 2.8 Hz, 10H, CH), 7.54 (bs, 5H, NH); 13C NMR: 29.3 (CH₃), 35.3 (C(CH₃)₂), 102.8 (CH), 138.5 (β-C pyrrole); EIMS m/z: 535 (M⁺).

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