Beilstein Journal of Organic Chemistry

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

Luis Chacón-García*, Lizbeth Chávez, Denisse R. Cacho and Josue Altamirano-Hernández

Preliminary Communication

Open Access

Address:
Laboratorio de Diseño Molecular, Instituto de Investigaciones Químico Biológicas, Edificio B-1 Ciudad Universitaria CP 58030, Morelia, Mich., México, Fax: +52 443 3265788, Tel: +52 443 3265790

Email:
Luis Chacón-García* - lchacon@umich.mx

* Corresponding author

Keywords:
bismuth; calix[5]pyrrole; calix[*n*]pyrrole

Beilstein Journal of Organic Chemistry **2009,** *5,* No. 2.
doi:10.3762/bjoc.5.2

Received: 06 November 2008
Accepted: 13 January 2009
Published: 28 January 2009

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 $Bi(NO_3)_3$.

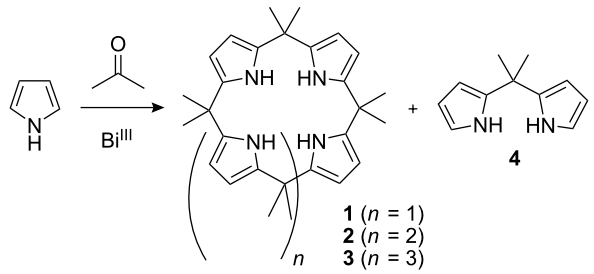
Results and Discussion

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, BF_3 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(pyrrol-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 $Bi(CF_3SO_3)_3$, 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-dimethyldipyrromethane (**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.



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

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-

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	$MgCl_2 \cdot 6H_2O$	9.5	–	–	–	–
2	$CuCl_2 \cdot 2H_2O$	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% H_2O) 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; ^{1}H NMR (400 MHz, $CDCl_3$): 1.51 (s, 30H, CH_3), 5.77 (d, J = 2.8 Hz, 10H, CH), 7.54 (bs, 5H, NH); ^{13}C NMR: 29.3 (CH_3), 35.3 ($C(CH_3)_2$), 102.8 (CH), 138.5 (β-C pyrrole); EIMS *m*/*z*: 535 ($M^{\bullet+}$).

Acknowledgments

We thank for financial support from CONACYT (47907) and CIC- UMSNH (2.19).

References

1. Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998,** 1–8. doi:10.1039/a706280j
2. Gale, P. A.; Anzenbacher, P., Jr.; Sessler, J. L. *Coord. Chem. Rev.* **2001,** *222,* 57–102. doi:10.1016/S0010-8545(01)00346-0
3. Radha Kishan, M.; Radha Rani, V.; Kulkarni, S. J.; Raghavan, K. V. *J. Mol. Catal. A: Chem.* **2005,** *237,* 155–160. doi:10.1016/j.molcata.2005.03.006
4. Dey, S.; Pal, K.; Sarkar, S. *Tetrahedron Lett.* **2006,** *47,* 5851–5854. doi:10.1016/j.tetlet.2006.06.085
5. Mejía-Farfán, I.; Contreras-Celedon, C.; Avina-Verduzco, J.; Chacón-García, L. *Lett. Org. Chem.* **2008,** *5,* 237–239. doi:10.2174/157017808783955808
6. Turner, B.; Botoshansky, M.; Eichen, Y. *Angew. Chem.* **1998,** *110,* 2633–2637. doi:10.1002/(SICI)1521-3757(19980918)110:18<2633::AID-ANGE2633>3.0.CO;2-7
   Angew. Chem., Int. Ed. **1998,** *37,* 2475–2478. doi:10.1002/(SICI)1521-3773(19981002)37:18<2475::AID-ANIE2475>3.0.CO;2-7.
7. Cafeo, G.; Kohnke, F. H.; La Torre, G. L.; White, A. J. P.; Williams, D. J. *Angew. Chem.* **2000,** *112,* 1556–1558. doi:10.1002/(SICI)1521-3757(20000417)112:8<1556::AID-ANGE1556>3.0.CO;2-B
   Angew. Chem., Int. Ed. **2000,** *39,* 1496–1498. doi:10.1002/(SICI)1521-3773(20000417)39:8<1496::AID-ANIE1496>3.0.CO;2-I.
8. Cafeo, G.; Kohnke, F. H.; Parisi, M. F.; Pistone Nascone, R.; La Torre, G. L.; Williams, D. J. *Org. Lett.* **2002,** *4,* 2695–2697. doi:10.1021/ol0262082
9. Gale, P. A.; Genge, J. W.; Král, V.; McKervey, M. A.; Sessler, J. L.; Walker, A. *Tetrahedron Lett.* **1997,** *38,* 8443–8444. doi:10.1016/S0040-4039(97)10275-1
10. Sessler, J. L.; Anzenbacher, P., Jr.; Shriver, J. A.; Jursíková, K.; Lynch, V. M.; Marquez, M. *J. Am. Chem. Soc.* **2000,** *122,* 12061–12062. doi:10.1021/ja005650h

License and Terms