New methods for the synthesis of (aza)crowncalix[4]arenes

Elena A. Alyeksyeyeva,* Stepan S. Basok and Andrei I. Gren

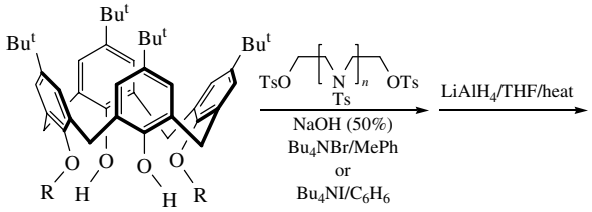
A. V. Bogatsky Physico-Chemical Institute, National Academy of Sciences of Ukraine, 65080 Odessa, Ukraine.
Fax: +38 0482 65 2012; e-mail: elena.cal@paco.net

DOI: 10.1070/MC2005v015n03ABEH002066

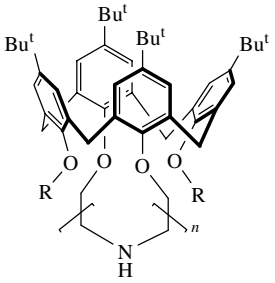
(Aza)crowncalixarenes have been synthesised under conditions of phase-transfer catalysis in the presence of a quaternary ammonium salt or by the cyclization of an isocyanate derivative of *p-tert*-butylcalix[4]arene with a diamine.

The introduction of additional rings with a certain set of donor atoms in calixarene molecules has been considered in the development of highly selective complexones in the calixarene series.[1–5] Derivatives with oxygen atoms at two opposite OH groups in *p-tert*-butylcalix[4]arene bridged by nitrogen-containing chains are especially interesting among a wide range of so-called calix-crown ether compounds.[6–11] An attempt to synthesise calix(aza)-crown by the alkylation of disubstituted *p-tert*-butylcalix[4]arenes with diethanolamine tosylates in the presence of alkali metal carbonates had been reported previously[10–11] but the desired product was not isolated.

To develop efficient methods for obtaining calix[4](aza)crown ethers, we used the alkylation of calix[4]arene hydroxyl groups by the tosylates of diethanolpolyethyleneamine under conditions of phase-transfer catalysis in the presence of a quaternary ammonium salt and a 50% NaOH solution. Alkylation of di(benzyloxy)-*p-tert*-butylcalix[4]arene **1** under these conditions (Scheme 1) by diethanolamine tritosylate led to di(benzyloxy)-*p-tert*-butylcalix[4](aza)crown-3 **3** in 50–55% yield and polyethyleneamine bridge prolongation on one CH_2–NTs–CH_2 group resulting in di(benzyloxy)- and di(2-methyl-2-propenyloxy)-calix[4](diaza)crown-4 **4** and **5**, respectively, in 65% yield. The tosyl group was removed from nitrogen atoms by boiling with a tenfold excess of $LiAlH_4$ in THF.†



1 R = CH_2Ph
2 R = $CH_2C(Me)=CH_2$



3 R = CH_2Ph, n = 1
4 R = CH_2Ph, n = 2
5 R = $CH_2C(Me)=CH_2$, n = 2

Scheme 1

We applied a method based on the interaction of bis(*N*-carbamoyl)methoxy-*p-tert*-butylcalix[4]arene **6**, which was used without isolation (and additional purification), with a diamine for preparing calixarene derivatives that additionally contain carbonyl groups in the azacrown fragment.

Bis[(hydrazydocarbonyl)methoxy]-*p-tert*-butylcalix[4]arene[12] was converted into a bis[(*N*-carbamoyl)methoxy] derivative according to Scheme 2.‡

The reactions of calixarene **6** with *o*- and *m*-phenylenediamine, 1,3-diaminopropane and 1,4-diaminobutane at a reagent ratio of

† *Experimental*: ^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. IR spectra were recorded on a Specord IR-75 instrument in $CHCl_3$. Mass spectra were recorded on MX-1321 and VG 70-70EQ spectrometers; FAB mass spectra were measured on a VG 70-70EQ mass spectrometer using *m*-nitrobenzyl alcohol and poly(propylene glycols) as a matrix.

Typical procedure for the synthesis of (aza)crowncalixarenes **3–5**: a mixture of disubstitiuted calix[4]arene (**1**, **2**) (1 mmol), an aqueous NaOH solution (50%, 3.4 ml), Bu_4NBr or Bu_4NI (1.1 mmol) and diethanolpolyethyleneamine tosylate (1.1 mmol) in 50 ml of benzene or toluene was stirred at 60 °C for 6–10 h. Then, water (20 ml) was added, and the organic phase was separated; washed with water, HCl, $NaHCO_3$ and water; and dried over anhydrous $MgSO_4$. The solvent was removed under a reduced pressure. The crude product was crystallised from ethanol and additionally purified by column chromatography on SiO_2 (hexane–chloroform 3:1).

3: yield 55%, mp 220–223 °C (EtOH). ^{1}H NMR, δ: 1.22 (s, 18H, Bu^t), 1.25 (s, 18H, Bu^t), 2.43 (s, 1H, NH), 2.92 (d, 1H, CH_2N), 3.10 (d, 1H, CH_2N), 3.14 (d, 2H, CH_2N), 3.97 (d, 4H, $ArCH_2Ar$, J 13.07 Hz), 4.3 (d, 4H, $ArCH_2Ar$), 4.54 (t, 2H, OCH_2), 4.8 (t, 2H, OCH_2), 5.1 (s, 4H, CH_2O), 6.9 (s, 4H, Ar), 7.11 (s, 4H, Ar), 7.23–7.38 (m, 10H, Bzl). Found (%): C, 80.95; H, 8.40; N, 1.39. Calc. for $C_{62}H_{75}O_4N$ (%): C, 82.90; H, 8.42; N, 1.56. MS, *m/z*: 897 (M^+, 95%).

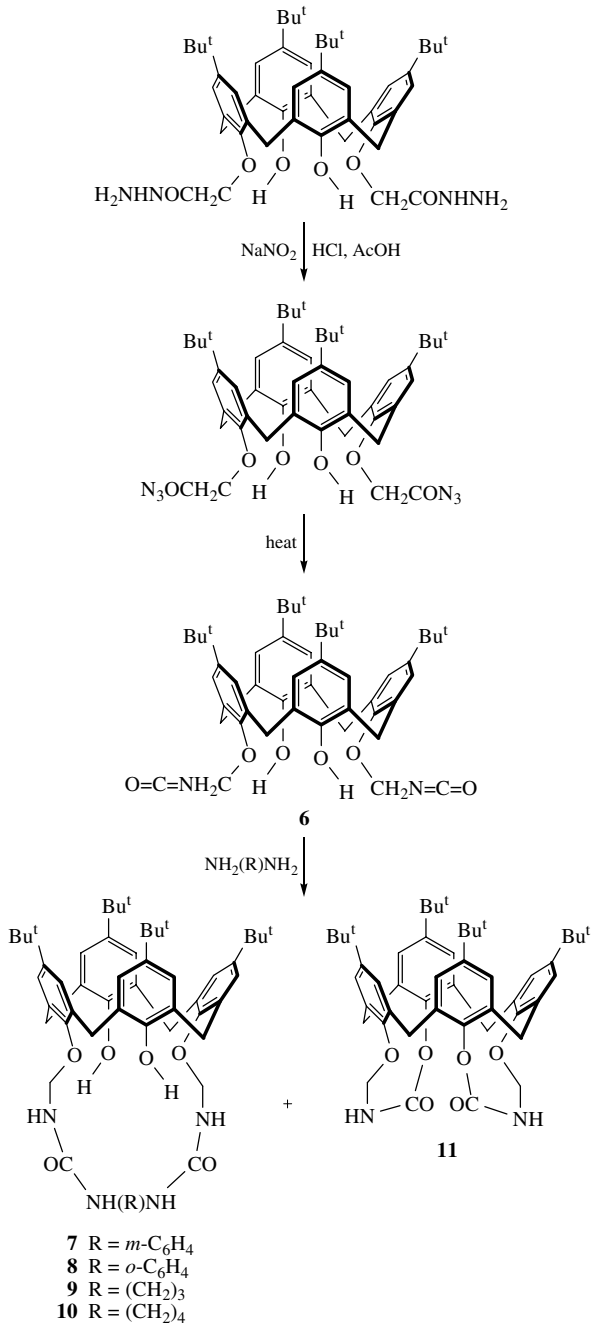
4: yield 65%, mp 217–218 °C (EtOH). ^{1}H NMR, δ: 1.21 (s, 18H, Bu^t), 1.22 (s, 18H, Bu^t), 2.85 (s, 2H, NH), 3.39 (s, 4H, CH_2N), 3.42 (m, 4H, CH_2N), 4.1 (d, 4H, $ArCH_2Ar$, J 13.8 Hz), 4.13 (m, 2H, OCH_2), 4.33 (m, (2H, OCH_2), 4.38 (d, 4H, $ArCH_2Ar$), 5.23 (s, 4H, CH_2O), 6.99 (s, 4H, Ar), 7.05 (s, 4H, Ar), 7.24–7.4 (m, 10H, Bzl). Found (%): C, 79.97; H, 8.69; N, 2.79. Calc. for $C_{64}H_{80}O_4N_2$ (%): C, 81.66; H, 8.57; N, 2.98. MS, *m/z*: 940 (M^+, 80%).

5: yield 60%, mp 234–236 °C (EtOH). ^{1}H NMR, δ: 1.21 (s, 18H, Bu^t), 1.26 (s, 18H, Bu^t), 2.1 (s, 6H, Me), 3.0 (s, 2H, NH), 3.30 (d, 4H, $ArCH_2Ar$, J 12.77 Hz), 3.39 (s, 4H, CH_2N), 3.4 (m, 4H, CH_2N), 3.78 (m, 2H, CH_2O), 4.13 (m, 2H, OCH_2), 4.3 (d, 4H, $ArCH_2Ar$), 4.4 (s, 4H, CH_2O), 5.1 (s, 2H, CH_2=), 5.72 (s, 2H, CH_2=), 6.95 (s, 4H, Ar), 7.04 (s, 4H, Ar). Found (%): C, 79.79; H, 9.48; N, 3.65. Calc. for $C_{58}H_{80}O_4N_2$ (%): C, 80.24; H, 9.28; N, 3.22. MS, *m/z*: 868 (M^+, 93%).

‡ *Synthesis of calixarenes* **7–11**: to a suspension of bis[(hydrazydocarbonyl)methoxy]-*p-tert*-butylcalix[4]arene (1 mmol) in 6 ml AcOH and 1 ml HCl at –5 °C, a cold aqueous solution of $NaNO_2$ (2 mmol) was added. After stirring (for 10–15 min), the product was extracted with $CHCl_3$, the organic layer was washed with water, a 3% $NaHCO_3$ solution and water and dried over anhydrous Na_2SO_4. After removing the solvent under a reduced pressure, 10–15 ml of benzene was added to the residue, and the mixture was refluxed for 30–45 min; a corresponding diamine (1 mmol) was added to calixarene isocyanate **6**. After cooling, the solvent was removed, and the crude product was purified by recrystallization.

7: yield 65%, mp 267–269 °C (MeOH–H_2O). ^{1}H NMR, δ: 1.23 (s, 18H, Bu^t), 1.27 (s, 18H, Bu^t), 3.85 (d, 4H, $ArCH_2Ar$, J 13.8 Hz), 4.1 (t, 4H, O–CH_2), 4.42 (d, 4H, $ArCH_2Ar$), 6.9 (s, 4H, ArH), 7.1 (s, 4H, ArH), 7.2–7.45 (m, 4H, NH, ArH), 7.6–7.8 (m, 2H, ArH), 9.4 (s, 2H, OH), 10.1 (s, 2H, NH). IR ($CHCl_3$, ν/cm^{-1}): 3300 (NH), 1680 (C=O). Found (%): C, 75.12; H, 8.10; N, 6.82. Calc. for $C_{54}H_{66}O_6N_4$ (%): C, 74.80; H, 7.67; N, 6.46. FAB-MS, *m/z*: 889 (M + Na)$^+$.

8: yield 63%, mp 258–259 °C (MeOH–H_2O). ^{1}H NMR, δ: 1.20 (s, 18H, Bu^t), 1.23 (s, 18H, Bu^t), 4.0 (d, 4H, $ArCH_2Ar$, J 13.2 Hz), 4.2 (t, 4H, O–CH_2), 4.5 (d, 4H, $ArCH_2Ar$), 6.8 (s, 4H, ArH), 7.13 (s, 4H, ArH), 7.2–7.4 (m, 3H, NH, ArH), 7.7–8.0 (m, 3H, ArH), 9.4 (s, 2H, OH), 10.3 (s, 2H, NH). IR ($CHCl_3$, ν/cm^{-1}): 3300 (NH), 1680 (C=O). Found (%): C, 75.12; H, 8.01; N, 6.78. Calc. for $C_{54}H_{66}O_6N_4$: C, 74.80; H, 7.67; N, 6.46. FAB-MS, *m/z*: 889 (M + Na)$^+$.



7 R = *m*-C_6H_4
8 R = *o*-C_6H_4
9 R = $(CH_2)_3$
10 R = $(CH_2)_4$

Scheme 2

9: yield 67%, mp 260 °C (PrOH–H_2O). ^{1}H NMR, δ: 0.95 (s, 18H, Bu^t), 1.21 (s, 18H, Bu^t), 2.20–2.28 (m, 2H, CH_2), 3.13–3.20 (m, 4H, CH_2), 3.45 (d, 4H, $ArCH_2Ar$, *J* 13.2 Hz), 4.4 (d, 4H, $ArCH_2Ar$), 4.6 (t, 4H, O–CH_2), 6.85 (s, 4H, ArH), 7.1 (s, 4H, ArH), 7.25 (s, 2H, NH), 8.7 (s, 2H, NH), 9.3 (s, 2H, OH). IR ($CHCl_3$, ν/cm^{-1}): 3300 (NH), 1680 (C=O). Found (%): C, 72.81; H, 8.03; N, 7.00. Calc. for $C_{51}H_{68}O_6N_4$ (%): C, 73.53; H, 8.23; N, 6.73. FAB-MS, *m*/*z*: 855 (M + Na)$^+$.

10: yield 67%, mp 265–267 °C (PrOH–H_2O). ^{1}H NMR, δ: 1.0 (s, 18H, Bu^t), 1.23 (s, 18H, Bu^t), 2.15–2.24 (m, 4H, CH_2), 3.22–3.30 (m, 4H, CH_2), 3.5 (d, 4H, $ArCH_2Ar$, *J* 12.8 Hz), 4.42 (d, 4H, $ArCH_2Ar$), 4.7 (t, 4H, O–CH_2), 6.9 (s, 4H, ArH), 7.13 (s, 4H, ArH), 7.2 (s, 2H, NH), 8.65 (s, 2H, NH), 9.4 (s, 2H, OH). IR ($CHCl_3$, ν/cm^{-1}): 3300 (NH), 1680 (C=O). Found (%): C, 73.02; H, 7.98; N, 6.97. Calc. for $C_{52}H_{70}O_6N_4$ (%): C, 73.73; H, 8.33; N, 6.61. FAB-MS, *m*/*z*: 869 (M + Na)$^+$.

11: mp 285 °C (decomp.) (MeOH). ^{1}H NMR, δ: 1.25 (s, 18H, Bu^t), 1.27 (s, 18H, Bu^t), 3.5 (d, 2H, $ArCH_2Ar$, *J* 13 Hz), 4.0 (d, 2H, $ArCH_2Ar$), 4.2 (d, 2H, $ArCH_2Ar$, *J* 14.1 Hz), 4.56 (d, 2H, $ArCH_2Ar$), 4.84 (d, 4H, O–CH_2), 7.15 (s, 4H, ArH), 7.2 (s, 4H, ArH), 8.4 (br. s, 2H, NH). Found (%): C, 76.02; H, 7.61; N, 3.60. Calc. for $C_{48}H_{58}O_6N_2$ (%): C, 75.96; H, 7.70; N, 3.69. FAB-MS, *m*/*z*: 781 (M + Na)$^+$.

1:1 gave corresponding (aza)crown derivatives: 25,27-[*N*,*N*′-phenyl-1,3-di(aminocarbonyl)-, 25,27-[*N*,*N*′-phenyl-1,2-di(aminocarbonyl)-, 25,27-[*N*,*N*′-propyl-1,3-di(aminocarbonyl)- and 25,27-[*N*,*N*′-butyl-1,4-di(aminocarbonyl)aminomethoxy]-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arenes **7**–**10** in 65–68% yields.

Note that an (aza)crowncalixarene with an urethane fragment bridging the phenol rings of calixarene **11** was isolated as a by-product in the formation of isocyanate (N-carbamoyl)group and at the interaction of compound **7** with a diamine.

The structures of compounds were proved by ^{1}H NMR spectroscopy. In the spectra of compounds **3**–**10**, there are two singlets from *tert*-butyl groups at δ 0.95–1.27 ppm, and a pair of doublets from bridging methylene protons at δ 3.5–4.2 ppm and *J* 12.2–14.1 Hz. These spectra indicate the presence of the considered calix(aza)crown ether molecules in a cone conformation. It follows from the splitting and chemical shifts of protons of the major fragments of a calixarene ring, this conformation is partially distorted. According to published data, this results from a change in the inclination angles of aromatic rings to the plane formed by methylene groups. The IR spectra of compounds **7**–**11** contain the absorption bands of the amide C=O group at 1675–1690 cm^{-1} and an absorption band of the NH group at 3300 cm^{-1}.

In the ^{1}H NMR spectra of compounds **3**–**5**, which were recrystallised from ethanol, there are signals corresponding to the protons of an alcohol guest. An absorption band at 3200 cm^{-1} in the IR spectra suggests the presence of a strong complex with alcohol molecules.

Thus, the proposed methods for the synthesis of calix[4]arene (aza)crown ethers allowed us to prepare new ionophores based on calixarenes with different fragments.

References

1 J. Vicens and V. Böhmer, *Calixarenes: a Versatile Class of Macrocyclic Compounds*, Kluwer Academic Publishers, Dordrecht, 1991, p. 263.
2 E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A. Abu El-Fadl and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1990, **112**, 6979.
3 Z. Asfari, S. Wenger and J. Vicens, *J. Incl. Phenom.*, 1994, **19**, 137.
4 V. S. Talanov, G. G. Talanova and R. A. Bartsch, *Tetrahedron Lett.*, 2000, **41**, 8221.
5 Y. Kubo, S. Obera and S. Tokita, *Chem. Commun.*, 1999, 2399.
6 R. Seangparsertkij, Z. Asfari and J. Vicens, *J. Incl. Phenom.*, 1994, **17**, 111.
7 Y. He, Y. Xiao, L. Meng, Z. Zeng, X. Wu and Ch.-T. Wu, *Tetrahedron Lett.*, 2002, **43**, 6249.
8 B. Pipoosananakaton, M. Sukwattanasinitt, N. Jaiboon, N. Chaichit and T. Tuntulani, *Tetrahedron Lett.*, 2000, **41**, 9095.
9 J. S. Kim, O. J. Shon, J. K. Lee, S. H. Lee, J. Y. Kim, K.-M. Park and Sh. S. Lee, *J. Org. Chem.*, 2002, **67**, 1372.
10 J. S. Kim, W. K. Lee, K. No, Z. Asfari and J. Vicens, *Tetrahedron Lett.*, 2000, **41**, 3345.
11 J. S. Kim, O. J. Shon, J. W. Ko, M. H. Cho, I. Y. Yu and J. Vicens, *J. Org. Chem.*, 2000, **65**, 2386.
12 E. A. Alekseeva, V. A. Bacherikov, A. I. Gren, A. V. Mazepa, V. Ya. Gorbatiuk and S. P. Krasnoschekaya, *Zh. Org. Khim.*, 2000, **36**, 1361 (*Russ. J. Org. Chem.*, 2000, **36**, 1321).

Received: 26th October 2004; Com. 04/2391