J. Org. Chem. **1995,** *60,* 7070−7071

A Simple Synthesis of Supercryptands

Krzysztof E. Krakowiak*,[†] and Jerald S. Bradshaw[‡]

IBC Advanced Technologies, Inc., P.O. Box 98,
American Fork, Utah 84003 and Department of Chemistry,
Brigham Young University, Provo, Utah 84602

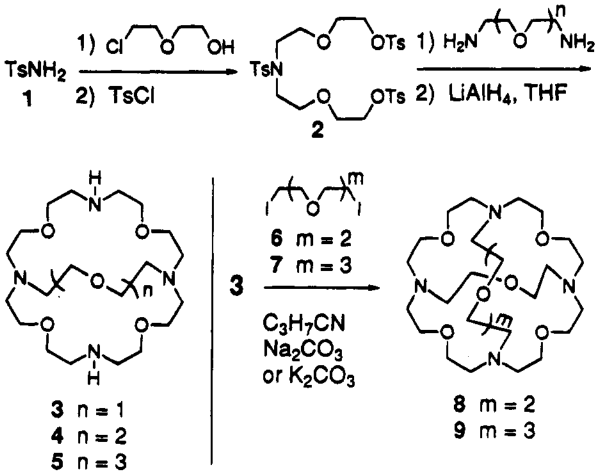
Received July 20, 1995

Supercryptands, the spherical macrotricyclic ligands with at least ten ligating atoms and prepared from diazacryptands, are among the best complexing agents known.[1−3] The highest reported stability constants in water for rubidium and cesium are attributed to a supercryptand.[1,4] Supercryptands can also complex ammonium cations and organic molecules.[5−11] The protonated forms of the supercryptands have high selectivities for fluoride and other halide anions.[12−14]

The first synthesis of a supercryptand was long and tedious.[5] Only three research groups have synthesized supercryptands using the long procedures.[4,12,15] We present here an efficient six-step synthesis of the supercryptands starting from *p*-toluenesulfonamide (see Scheme 1). Compound **2** (2.1 mol) was treated with 1 mol of the appropriate diamino ether (n = 1, 2, or 3) in CH_3CN in the presence of Na_2CO_3 or K_2CO_3 to give the corresponding ditosyl-substituted cryptands **3−5**. Higher cyclization yields were obtained when the reactions were carried out under high dilution conditions. The tosyl protecting groups were removed using a standard procedure ($LiAlH_4$ in THF). Cryptands **3−5** were purified by silica gel chromatography. In the next step, cryptand **3** was treated with an excess of the appropriate diiodo compounds in C_3H_7CN in the presence of Na_2CO_3 to form supercryptands **8** or **9** with yields of 30−40%. It should be possible to prepare other supercryptands by this method or by treating diazacryptands **4** and **5** with various diacid chlorides followed by reduction as reported for similar spherical macrotricyclic ligands.[4,12]

This new six-step synthesis of these interesting spherical macrotricycles takes advantage of the synthesis of the bis(N-tosylated)cryptands by a one-step, 2:1 cycloaddition of per-N-tosylated azatetraethylene glycol (**2**) and a diamine in a manner similiar to that reported by us for the aliphatic cryptands.[16] The *N*-tosyl groups were readily removed followed by another cyclization reaction of the diazacryptand with a diiodide. This new synthetic route will provide these interesting macrotricyclic ligands for a more serious study of their complexing properties.

Scheme 1. Preparation of New Diazacryptands 3−5 and Supercryptands 8 and 9



Experimental Section

All proton NMR spectra were recorded at 200 MHz. Compound **2** was prepared as reported.[17] The α,ω-diaminooligoazaalkanes were purchased from Fluka. Other starting compounds were purchased from Aldrich.

General Procedure for the Preparation of Diazacryptands 3−5. A mixture of 0.01 mol of the appropriate α,ω-diaminooligooxaalkane, 0.02 mol of tritosyl **2**, and 0.1 mol of Na_2CO_3 or K_2CO_3 was refluxed in 400 mL of CH_3CN for 6 days. After cooling, the solvent was removed under reduced pressure and water and CH_2Cl_2 were added. The mixture was thoroughly mixed, and the organic layer was separated and dried ($MgSO_4$). The solvent was removed, and the residue was passed through a short alumina column using THF/$C_6H_5CH_3$:5/1 as eluant. The solvent was removed, and the residue was purified on a silica gel column using CH_3OH/NH_4OH: 30/1, 20/1, and 10/1 as eluants. The fractions corresponding to the third spot from the solvent front on silica gel TLC using CH_3OH/NH_4OH:10/1 as eluant were collected and evaporated. CH_2Cl_2 was added, and the solution was filtered and evaporated. The bis(N-tosylated) cryptands were not further purified but were dissolved in 50 mL of THF and slowly added to 0.15 mol of $LiAlH_4$ in 200 mL of THF. This mixture was refluxed for 72 h under N_2. After cooling, 40 mL of water was carefully added, and the resulting mixture was filtered and evaporated under reduced pressure. CH_2Cl_2 (100 mL) was added to the residue. The mixture was filtered and evaporated. The residue was purified in a short silica gel column using CH_3OH/NH_4OH: 20/1, 10/1 and 5/1 as eluants. The appropriate fractions were evaporated, 50 mL of CH_2Cl_2 was added, and the mixture was filtered. Cryptands **3−5** were obtained from the final solutions in yields of 38, 24, and 18%, respectively. The products had the following properties:

3: ^1H NMR was the same as that reported.[4]

4: ^1H NMR δ 2.1−2.3 (br, 2 H), 2.7−3.0 (m, 20 H), 3.5−3.7 (m, 24 H); MS m/z 462; MS (CI) m/z 463; ^{13}C NMR δ 48.95, 53.70, 54.75, 69.30, 70.00, 70.30, 70.76; mp 80−84 °C. Anal. Calcd for $C_{22}H_{46}N_4O_6$: C, 57.11; H, 10.02. Found: C, 56.94; H, 9.98.

5: ^1H NMR δ 2.1−2.3 (br, 2 H), 2.7−2.9 (m, 20 H), 3.4−3.7 (m, 28 H); MS m/z 507. Anal. Calcd for $C_{24}H_{50}N_4O_7$: C, 56.89; H, 9.94. Found: C, 56.96; H, 9.94.

The yields of **3−5** increased by 10−20% when the diamine and tritosylate solutions were added slowly and equally by means of syringe pumps to the base in refluxing CH_3CN in the first step. Cryptands **3−5** could also be isolated after the $LiAlH_4$ reduction step by adding HCl to pH = 1 followed by extraction with $CHCl_3$. A solution of LiOH was added to the aqueous phase to a pH value of 1. This basic mixture was extracted three times with 50 mL portions of $CHCl_3$. The organic layers were combined, dried ($MgSO_4$), and evaporated to give crude **3−5**.

[†] IBC Advanced Technologies.

[‡] Brigham Young University.

(1) Lehn, J. M. *Acc. Chem. Res.* **1978,** *11,* 49.

(2) Dietrich, B. *Pure Appl. Chem.* **1993,** *65,* 1457.

(3) Schmidtchen, F. P; Gleich, A; Schummer, A. *Pure Appl. Chem.* **1989,** *61,* 1535.

(4) Graf, E.; Lehn, J. M. *Helv. Chim. Acta* **1981,** *64,* 1040.

(5) Graf, E.; Lehn, J. M. *J. Am. Chem. Soc.* **1975,** *97,* 5022.

(6) Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1977,** *16,* 720.

(7) Schmidtchen, F. P. *J. Org. Chem.* **1986,** *51,* 5161.

(8) Schmidtchen, F. P. *J. Am. Chem. Soc.* **1986,** *108,* 8249.

(9) Graf, E.; Lehn, J. M. *J. Am. Chem. Soc.* **1976,** *98,* 6403.

(10) Schmidtchen, F. P. *Chem. Ber.* **1981,** *114,* 597.

(11) Schmidtchen, F. P. *Chem. Ber.* **1984,** *117,* 725.

(12) Hossain, M. A.; Ichikawa, K. *Tetrahedron Lett.* **1994,** *35,* 8393.

(13) Worm, K.; Schmidtchen, F. P.; Schier, A.; Schafer, A.; Hesse, M. *Angew. Chem., Int. Ed. Engl.* **1994,** *33,* 327.

(14) Worm, K.; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1995,** *34,* 65.

(15) Schmidtchen, F. P. *Chem. Ber.* **1980,** *113,* 864.

(16) Krakowiak, K. E.; Krakowiak, P. A.; Bradshaw, J. S. *Tetrahedron Lett.* **1994,** *34,* 777.

(17) Anneli, P. L.; Mantanari, F.: Quici, S. *J. Org. Chem.* **1988,** *53,* 5292.

0022-3263/95/1960-7070$09.00/0

General Procedure for the Preparation of Supercryptands 8 and 9. A mixture of 15 g of Na_2CO_3 and 200 mL of C_3H_7CN was refluxed for a short time. **3** (0.6 g, 1.5 mmol) in 60 mL of C_3H_7CN and 1.6 mmol of **6** or **7** in 60 mL of C_3H_7CN were each slowly added at the same rate to the above mixture by means of syringe pumps. The mixture was stirred under reflux for 48 h and another 1.6 mmol of **6** or **7** was added in the same manner. The mixture was refluxed another 48 h, cooled and filtered, and the solvent was removed under reduced pressure. The residue was passed through a short alumina column using THF/C_2H_5OH: 100/1 as eluant. The crude product was purified on silica gel using CH_3OH/NH_4OH: 40/1, 20/1, and 10/1 as eluants. The solvent was removed from the appropriate fractions, and 20 mL of CH_2Cl_2 was added. The mixture was filtered and evaporated to give supercryptands **8** (37%) and **9** (33%). The properties of **8** and **9** are as follows:

8: ^1H NMR δ 2.7–2.95 (m, 24 H), 3.55–3.70 (m, 28 H); ^{13}C NMR δ 55.17, 55.52, 56.24, 56.40, 70.00, 70.18, 71.15; MS *m/z* 533; MS (CI) m/z 534. Anal. Calcd for $C_{26}H_{52}N_4O_7$: C, 58.62; H, 9.83. Found: C, 58.56; H, 9.77.

9: ^1H δ 2.7–2.95 (m, 24 H), 3.5–3.7 (m, 32 H); MS *m/z* 577; MS (CI) *m/z* 578. Anal. Calcd for $C_{28}H_{56}N_4O_8$: C, 58.30; H, 9.78. Found: C, 58.09; H, 9.61.

Acknowledgment. This work was supported by the Department of Energy, Office of Basic Energy Sciences, Contract No. DE-FG02-86ER 13463.

JO9513119