Convenient Synthesis of Mesitylene-Bridged Hexaazamacrobicyclic Compounds

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Two mesitylene-bridged hexaazamacrobicyclic ligands **1** and **2** were prepared by a three-step process from available 2,4,6-tris(bromomethyl)mesitylene (**9**) and *N*, *N'*-di-*p*-tosylethylenediamine and *N,N'*-di-*p*-tosyl-1,3-diaminopropane. First, mono-BOC-protected ditosylamines **5** and **6** were prepared by treating the two diamines with BOC-O-BOC. These mono-BOC-protected diamines were treated with the tris(bromomethyl)mesitylene followed by deprotection to give 2,4,6-tris(2,5-ditosyl-2,5-diazapentyl)mesitylene (**3**) and its 2,6-diazahexyl analog **4**. These latter intermediates were treated with tris(bromomethyl)mesitylene to give the mesitylene-bridged hexaazamacrobicycles. This three-step synthesis replaces the reported nine-step process.

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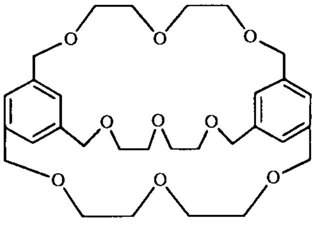
The synthesis of spherical macrocyclic ligating compounds is of interest. These molecules form inclusion complexes with cations, anions and neutral molecules [1-9]. The benzene-bridged macrobicyclic compounds containing both nitrogen and oxygen donor atoms have been prepared in many steps [6,7]. We recently reported the synthesis macrobicyclic polyether A by a five-step process from trimethyl 1,3,5-benzenetricarboxylate [9]. The comparable nitrogen donor atom-containing macrotricycles are more difficult to prepare [6,7].

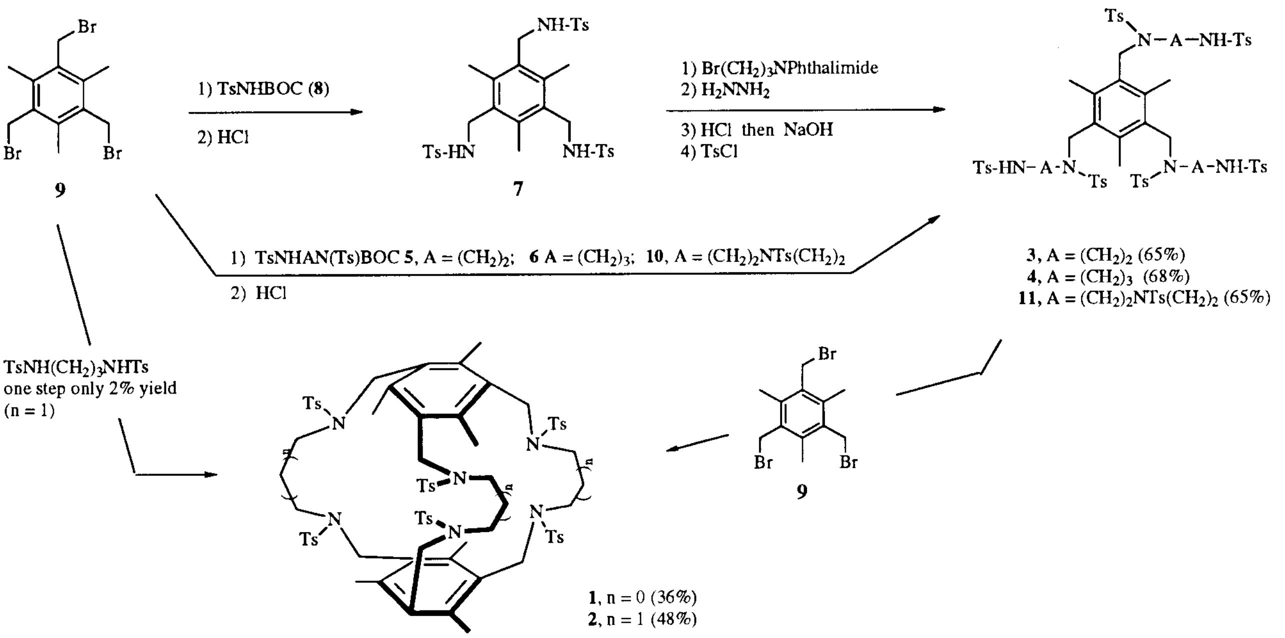


A

We now report a convenient synthesis of hexaazamacrobicyclic ligands **1** and **2** using BOC-protected synthons **5** and **6**. Scheme I shows the synthesis of **1** and **2** by our new method, as well as a low yield one-step process (for **2** only). Scheme I also shows the preparation of intermediate **7** in two steps using BOC-protected tosyl amide **8**. A similar intermediate was prepared in three steps from 1,3,5-tris(aminomethyl)benzene by Heyer and Lehn [6]. Vögtle and coworkers have recently reported the use of *N*-tosylacetamide for similar conversions [10]. Intermediate **4** was prepared from **7** by the four-step process shown in Scheme I.

New synthons **5** and **6** allow the synthesis of intermediates **3** and **4** in only three steps rather than the 6 or 7 steps

Scheme I. Preparation of Hexaazamacrobicycles **1** and **2**



through **7**. Synthons **5** and **6** were prepared in 40-45% yields by treating commercially available *N,N'*-di-*p*-tosylethylenediamine and *N,N'*-di-*p*-tosyl-1,3-diaminopropane with 1 equivalent of di-*tert*-butyl dicarbonate in dimethylformamide (see Scheme I). Mono-BOC-protected **5** and **6** were separated from the di-BOC by-products by column chromatography. Treatment of **9** with **5** and **6** followed by removal of the BOC protecting groups gave **3** and **4** in yields of 65% and 68%, respectively. Cyclic condensation of **3** and **4** with **9** was done in the presence of cesium carbonate in dimethylformamide. Hexaazamacrobicyle **1** was isolated as an ethyl acetate complex.

Synthons **5, 6** and **8** have allowed the preparation of these large bicyclic systems in only a few steps and in reasonable overall yields (15% for **2**). The utility of these mono-BOC-protected synthons to prepare higher order polyamines is shown by the synthesis of 2,4,6-tris(2,5,8-tritosyl-2,5,8-triazaoctyl)mesitylene (**11**) from mono-BOC-protected triamine **10** (Scheme I). These synthons have also been used to prepare linear polyamine compounds [11].

EXPERIMENTAL

Molecular weights were determined by the electron impact method on a Finnegan 8430 high resolution mass spectometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Silica gel 60 (230-400 mesh, EM Science) was used for column chromatography. Thin layer chromatography was performed on silica gel 60 F254 (Merck). All organic starting materials were purchased from Aldrich Chemical Company.

Preparation of 2,4,6-Tris(*N*-tosylaminomethyl)mesitylene (**7**) (Scheme I).

To 11 g (0.041 mole) of BOC-protected tosylamide **8** in 150 ml of dimethylformamide was added 1 g (0.042 mole) of sodium hydride. After 10 minutes of stirring, 4 g of **9** (0.01 mole) was added and stirring was continued for 24 hours at room temperature. The dimethylformamide was evaporated and water and methylene chloride were added. The aqueous layer was extracted 3 times with 30-ml portions of methylene chloride and the combined organic layers were dried over anhydrous magnesium sulfate. After removing the solvent, the residue was chromatographed on silica gel using methylene chloride/ethyl acetate: 100/1 as the eluent to give 7.8 g (80%) of BOC-protected **7**; ^{1}H nmr: δ 1.4 (s, 27 H), 2.2 (s, 9 H), 2.35 (s, 9 H), 5.0 (s, 6 H), 7.1 (d, 6 H), 7.3 (d, 6 H). This product was added to a mixture of 140 ml of methanol, 60 ml of chloroform and 28 ml of hydrochloric acid. The mixture was refluxed for 36 hours, the gaseous products were removed, and the solvents were evaporated to give 5.1 g (95%) of **7** as an oil; ^{1}H nmr: δ 1.95 (s, 9 H), 2.45 (s, 9 H), 3.9 (s, 6 H), 4.5 (b, 3 H), 7.3 (d, 6 H), 7.75 (d, 6 H). A satisfactory elemental analysis was obtained for **2** derived from **7** through **4**.

Preparation of 2,4,6-Tris(2,6-ditosyl-2,6-diazahexyl)mesitylene (**4**) from **7** (Scheme I).

Intermediate **7** (3 g, 4.5 mmoles), 3.6 g (13.5 mmoles) of *N*-(3-bromopropyl)phthalimide and 15 g of cesium carbonate in 100 ml of dimethylformamide were stirred at room temperature for 48 hours. After the solvent was evaporated, water and methylene chloride were added to the residue. The aqueous layer was extracted 3 times with 30-ml portions of methylene chloride and the organic layers were dried using anhydrous magnesium sulfate. After evaporation of the solvent, the residue was purified using silica gel chromatography with methylene chloride/ethyl acetate: 50/1, 30/1 and 20/1 as eluants. The above trisphthalimide product was added to a mixture of 50 ml of tetrahydrofuran, 200 ml of ethanol and 3 g of hydrazine hydrate and the mixture was refluxed for 8 hours. After cooling, 2 *N* hydrochloric acid was added to *p*H 1. The acidified mixture was refluxed for 2 hours. After cooling, the hydrazide was filtered and nearly all of the solvent was distilled from the filtrate. To this concentrated solution, 30% sodium hydroxide was added and the triamine product was extracted 3 times using methylene chloride. The organic layers were combined and evaporated. The residue was purified on silica gel using methanol/ammonium hydroxide: 40/1, 20/1, 10/1 and 5/1 as eluants to give 2 g (77%); ^{1}H nmr: δ 1.2 (s, 6 H), 2.3 (s, 9 H), 2.35 (m, 6 H), 2.45 (s, 9 H), 2.85 (t, 6 H), 4.3 (s, 6 H), 7.35 (d, 6 H), 7.7 (d, 6 H).

The above crude triamine product was dissolved in 100 ml of pyridine. Into this solution was dropped 3 g of tosyl chloride in 20 ml of pyridine at room temperature. The resulting mixture was heated at 70° for 16 hours. Then 6 *N* hydrochloric acid was added to a pH = 2 and the mixture was extracted 2 times with 30-ml portions of methylene chloride. The organic layers were dried using anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified on silica gel using toluene/tetrahydrofuran/methylene chloride: 10/1/1 as eluant to give 3.1 g (69%) of **4**; ^{1}H nmr: δ 1.2 (m, 6 H), 2.3 (s, 9 H), 2.48 (s, 9 H), 2.50 (s, 9 H), 2.8 (m, 6 H), 2.9 (m, 6 H), 4.3 (s, 6 H), 5.1 (t, 3 H), 7.35 (m, 12 H), 7.75 (m, 12 H). A satisfactory elemental analysis was obtained for **2**, a derived from of **4**.

Preparation of Mono-BOC-protected Starting Materials **5**, **6** and **10**.

To 0.1 mole of *N,N'*-di-*p*-tosylethylenediamine, *N,N'*-di-*p*-tosyl-1,3-diaminopropane or *N,N'N''*-tri-*p*-tosyldiethylenetriamine dissolved in 400-600 ml of dimethylformamide was added, 10 ml of triethylamine, 2 g of 4-(*N,N*-dimethylamino)pyridine and 24 g (0.11 mole) of di-*tert*-butyl dicarbonate. The mixture was stirred for 24 hours at room temperature and carefully evaporated under vacuum using an aspirator and then a vacuum pump at a temperature not higher that 50°. The crude solid gave three tlc spots: the di-BOC-protected compound, mono-BOC-protected compound (**5** or **6**) and unreacted starting pertosylated compound (R_f value from the highest to the lowest). The residue was added to methylene chloride or toluene and stirred and filtered to remove the two undesired products. The solution was evaporated and the residue chromatographed on silica gel using methylene chloride, then methylene chloride/ethyl acetate:100/1, 50/1 and 30/1 as eluants to give **5**, **6** and **10** in 40-45% yields. The ^{1}H nmr: spectrum of **5** exhibited the following peaks: δ 1.3 (s, 9 H), 2.4 (s, 6 H), 3.3 (m, 2 H), 3.9 (t, 2 H), 5.1 (b, 1 H), 7.3 (m, 4 H), 7.8 (m, 4 H). The ^{1}H nmr: spectrum of **6** exhibited the following peaks δ 1.3 (s, 9 H), 1.8 (t, 2 H), 2.4 (s, 3 H), 2.42 (s, 3 H), 3.01 (m, 2 H), 3.85 (t, 2 H), 5.3 (t, 1 H), 7.3 (m, 4 H), 7.75 (m, 4 H). The ^{1}H nmr spectrum of **10** exhibited the following peaks: δ 1.35 (s, 9 H), 2.35 (s, 3H), 2.40 (s, 3 H), 2.42 (s, 3 H), 2.44 (s, 3 H), 3.2 (s, 4 H), 3.35 (m, 6 H), 3.95 (t, 2 H), 5.2 (b, 1 H), 7.3 (m, 8 H), 7.8 (m, 8 H).

Satisfactory elemental analyses were obtained for **1**, **2** and **11** derived from **5**, **6** and **10**, respectively.

Preparation of Intermediates 2,4,6-Tris-(2,5-ditosyl-2,5-diazapentyl)mesitylene (**3**), **4** and **11** from **9** (Scheme I).

To 0.011 mole of **5**, **6** or **10** in 150 ml of dimethylformamide containing 20 g of potassium carbonate was added 3.2 mmoles of **9**. The mixture was stirred at room temperature for 48 hours. The solvent was evaporated and 400 ml of methylene chloride was added, the mixture was filtered. The filtrate was evaporated and the residue was chromatographed on silica gel using toluene/THF: 20/1, 10/1, and 5/1 or methylene chloride/ethyl acetate: 20/1 as eluants. It was also possible to use the above crude product without purification for the next step. The purified or crude products were added to 100 ml of methylene chloride and 150 ml of methanol containing 40 ml of hydrochloric acid and the resulting mixture was refluxed for 24-48 hours. After cooling, the solvents were evaporated to dryness. The residue was purified on silica gel using toluene/tetrahydrofuran/methylene chloride: 10/1/1 and 5/1/1 or 10/1/2 as eluants. The yields of **3**, **4** and **11** were 65%, 68% and 65% , respectively. The ^{1}H nmr: spectrum for **3** exhibited the following peaks: δ 2.2 (s, 9 H), 2.45 (s, 9 H), 2.5 (s, 9 H), 2.8 (s, 12 H), 4.3 (s, 6 H), 5.1 (s, 3 H), 7.3 (m, 12 H), 7.7 (m, 12 H). The ^{1}H nmr: spectrum of **4** was the same as reported above. A satisfactory elemental analysis was obtained for **1** derived from **3**. The ^{1}H nmr spectrum for **11** (mp 98-101°) exhibited the following peaks: δ 2.2 (s, 9 H), 2.35 (s, 9 H), 2.4 (s, 9 H), 2.45 (s, 9 H), 2.8 (s, 24 H), 4.3 (s, 6 H), 5.1 (b, 3 H), 7.3 (m, 12 H), 7.5 (m, 12 H), 7.7 (m, 12 H).

Anal. Calcd. For $C_{87}H_{105}N_9O_{18}S_9$: C, 56.37; H,5.71. Found: C, 56.25; H, 5.83.

Preparation of Mesitylene-Bridged Hexaazamacrobicycles **1** and **2**.

Intermediate **3** (6.2g, 4.9 mmoles) or 5.8 g (4.5 mmoles) of **4** was dissolved in 60 ml of dimethylformamide and placed in a syringe. To a second syringe was added 1.97 g (4.9 mmoles) or 1.78 g (4.46 mmoles) of **9** in 60 ml of dimethylformamide. The compounds from the two syringes were simultaneously added to 600 ml of dimethylformamide containing 50 g of cesium carbonate at 70° over a 24-hour period. The resulting solution was stirred at 70° for 72 hours. The dimethylformamide was evaporated and water and methylene chloride were added. The mixture was separated and the organic phase was extracted three times and the organic layers were dried using anhydrous magnesium sulfate. After removing the solvent, the residue was chromatographed on silica gel using methylene chloride/ethyl acetate: 100/1 and then 50/1 as eluants to give 2.7 g (36%) of **1** as a solid, mp 220 dec; ^{1}H nmr: δ 1.25 (t, 3 H), 2.05 (s, 3 H), 2.1 (s, 18 H), 2.48 (s, 18 H), 3.0 (s, 12 H), 3.8 (s, 12 H), 4.15 (q, 2 H), 7.4 (d, 12 H), 7.95 (d, 12 H).

Anal. Calcd. For $C_{72}H_{84}N_6O_{12}S_6$ $CH_3COOC_2H_5$: C, 60.61; H, 6.15. Found: C, 60.70; H, 6.21.

Compound **2** was isolated as a solid, mp >300 ; 3.1 g (48%); ^{1}H nmr: δ 1.4 (m, 6 H), 2.35 (s, 18 H), 2.42 (s, 18 H), 3.1 (b, 12 H); 4.2 (b, 12 H), 7.4 (d, 12 H), 7.8 (d, 12 H).

Anal. Calcd. For $C_{75}H_{90}N_6O_{12}S_6$: C, 61.70; H, 6.21. Found: C, 61.63; H, 6.31.

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