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BOC-protected *m*-xylylenediamine was treated with tetraethyleneglycol ditosylate to form BOC-protected diazabenzo-18-crown-5 (**5**) in a good yield. BOC-protected diazabenzo-21-crown-6 (**6**) was prepared in the same manner from BOC-protected *m*-xylylenediamine and pentaethylene glycol ditosylate. Bis-BOC-protected diaza-17-crown-5 (**12**) was prepared by treating BOC-protected 1,4-diaminobutane with 1,11-diiodo-3,6,9-trioxaundecane. The BOC-protecting groups were removed in methanolic 2 *N* hydrogen chloride to form the corresponding diaza-crown ethers **7**, **8** and **13**.

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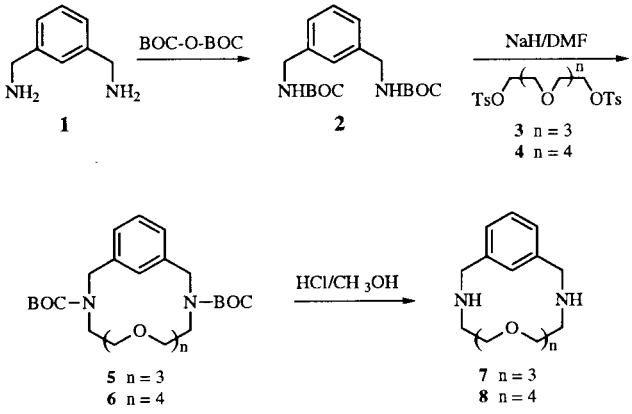
There are many methods to prepare the diaza-crown ethers [1]. Direct methods were used to prepare the diaza-crown ethers from bisprimary amines and diiodides [2] or from bissecondary amines and bis(α-chloroamides) followed by reduction (the "crab-like"method) [3]. However, the main preparative methods for the diaza-crowns and cyclams have been from the per-*N*-tosylated di- and polyamines [1,4-7]. The *N*-tosylamides prepared from primary amines are very reactive nucleophiles in base media. In addition, the *N*-tosyl groups protect the internal amines from undergoing nucleophilic reactions. The *N*-tosyl species are very stable so that removal of the tosyl groups after ring formation is often difficult [1,5-8]. The use of concentrated sulfuric acid or reductive conditions to remove the tosyl groups can often cause unwanted reactions or decomposition in other parts of the macrocycle. Other *N*-sulfonyl groups, such as benzenesulfonyl or methanesulfonyl, suffer from the same removal problems. The bis(α-chloroamides) can be used to prepare diaza- or polyaza-crown ethers to avoid the use of *N*-protecting groups [3,9]. Other *N*-protecting groups that are easy to remove, such as phosphoryl and trifluoroacetyl, have been used but with low overall macrocycle yields [10-12]. We report here the use of BOC (*t*-butoxycarbonyl) as a protecting group in the synthesis of the diaza-crown ethers. The BOC group is the most common protecting group in peptide chemistry. It is easy to introduce in the amine using available BOC-O-BOC or other BOC carriers and it is readily removed after the peptide is formed [13]. In only a few cases has a BOC-protected primary amine been used for further reactions on the protected amine nitrogen [14-16]. BOC-protected diamines have not previously been used in ring closure reactions.

Two types of diaza-crown ethers have been prepared using this new ring-closure procedure from *m*-xylylenediamine (see Scheme 1) and 1,4-diaminobutane (see Scheme 2). BOC-protected diazabenzo-18-crown-5 (**5**) and 21-crown 6 (**6**) were prepared in 30-40% yields by treating 1,3-bis(*tert*-butoxycarbonylaminomethyl)benzene (**2**) with triethylene glycol ditosylate (**3**) or tetraethylene glycol ditosylate (**4**) in dimethylformamide in the presence of sodium hydride (Scheme 1). The BOC-protecting

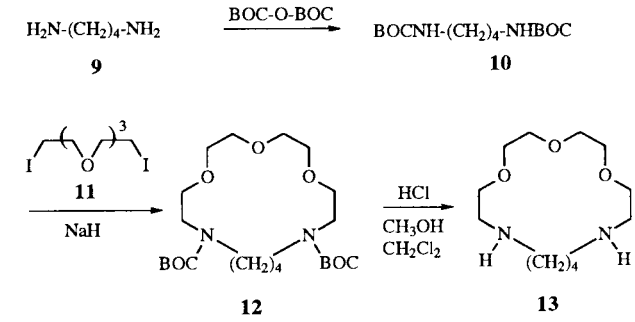
Scheme 1. Preparation of Diazabenzo-crown Ethers Using BOC Protecting Groups



groups were removed in 80-85% yields using hydrochloric acid in methanol. Diaza-17-crown-5 (**13**) was prepared in an overall yield of 24% in a similar fashion from 1,4-bis(*tert*-butoxycarbonylamino)butane (**10**) and 1,11-diiodo-3,6,9-trioxaundecane (**11**) (Scheme 2).

This new diaza-crown ether synthesis method is based on the easy application of the BOC-protecting group to the bisprimary amine, the reactivity of the resulting bis(BOC-protected)diamine in base towards the relevant ditosylate or dihalide to effect ring closure, and the easy removal of the BOC groups to form the diaza-crown ethers [17]. This new method will be particularly useful when removal of

Scheme 2. Preparation of Diaza-17-crown-5 Using BOC Protecting Groups



N-tosyl protecting groups is difficult. The method should find good use in the synthesis of the diaza-crown ethers.

EXPERIMENTAL

Di-*tert*-butyl dicarbonate (BOC-O-BOC), *m*-xylylenediamine (**1**) and 1, 4-diaminobutane (**9**) were used as purchased from Aldrich Chemical Company. 1,11-Diiodo-3,6,9-trioxaundecane (**11**) was purchased from Parish Chemical Company. Ditosylates **3** and **4** were prepared as reported [18]. Proton nmr spectra were recorded in deuteriochloroform on a Varian Gemni 200 MHz spectrometer. Tlc spots were visualized for **10** and **12** by exposure to chlorine (bleach) followed by dicarboxidine spray (violet-blue color).

1,3-Bis(*tert*-butoxycarbonylaminomethyl)benzene (**2**).

A mixture of 5.4 g (0.04 mole) of *m*-xylylenediamine, 21.8 g (0.1 mole) of BOC-O-BOC and 400 ml of methylene chloride was stirred for 12 hours. The mixture was evaporated under reduced pressure. The resulting solid was recrystallized from ethyl acetate/hexane to give 11 g (82%) of bis(BOC-protected) diamine **2**, mp 91°. The physical properties of this material agreed with those reported for **2** [19].

6,9,12-Trioxa-3,15-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**7**) (Scheme 1).

Tetraethyleneglycol ditosylate (**3**) (2.6 g, 5.1 mmoles) was slowly added to a stirred mixture of 1.7 g (5 mmoles) of **2**, 0.3 g (12.5 mmoles) of sodium hydride in 100 ml of dimethylformamide. The mixture was stirred at room temperature for 10 hours and at 60° for 36 hours. The solvent was removed under reduced pressure. The residue was purified in silica gel using toluene/tetrahydrofuran: 10/1 as eluant to give 1 g (41%) of bis(BOC-protected) macrocycle **5**. The BOC groups were removed by stirring 1 g (2 mmoles) of **5** in a mixture of 20 ml of 6 *N* hydrochloric acid and 40 ml of methanol for 36 hours. The solution was made basic by adding aqueous cesium carbonate. The solvents were removed under reduced pressure. Toluene (100 ml) was added and removed under reduced pressure three times to remove all water. Diaza-crown **7** was purified on silica gel using chloroform/methanol: 10/1 as eluant to give 0.5 g (85%) as an oil; ^{1}H nmr: δ 2.3 (s, 2 H, disappeared in deuterium oxide), 2.8 (t, 4 H), 3.55 (m, 12 H), 3.8 (s, 4 H), 7.2 (m, 3 H), 7.45 (s, 1 H).

Anal. Calcd. for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90. Found: C, 65.12; H, 8.71.

6,9,12,15-Tetraoxa-3,18-diazabicyclo[18.3.1]tetracosa-1(24),20,22-triene (**8**) (Scheme 1).

Macrocycle **8** was prepared as **7** above from pentaethyleneglycol ditosylate (**4**) to give an overall yield of 38%; ^{1}H nmr: δ 2.0 (s, 2 H), 2.8 (m, 4 H), 3.6 (m, 16 H), 3.8 (s, 4 H), 7.2 (m, 3 H), 7.4 (s, 1 H).

Anal. Calcd. for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.95. Mol. wt., 338.45. Found: C, 63.63; H, 8.77. Mol. wt., 339.

4,9-Diaza-1,12,15-trioxacycloheptadecane (**13**) (Scheme 2).

1,4-Bis(*tert*-butoxycarbonylamino)butane (**10**) [20] was prepared in a manner similar to that above for **2**. Diiodide **11** (2.2 g, 5.2 mmoles) was slowly added to a stirred mixture of 1.44 g (5.1 mmoles) of **10**, 0.3 g (12.5 mmoles) of sodium hydride and 100 ml of dimethylformamide. The mixture was stirred at room temperature for 2 hours and at 80° for 16 hours. The solvent was removed under reduced pressure and 20 ml of 10% aqueous hydrochloric acid was added. The mixture was stirred at 80° for 16 hours. The resulting mixture was cooled and made basic by adding solid sodium hydroxide. The mixture was extracted three times with 30-ml portions of methylene chloride. The organic layers were combined, dried over anhydrous magnesium sulfate and evaporated. The residue was purified on silica gel using methanol/ammonia: 20/1 and 10/1 as eluants to give 0.3 g (24%) of **13** as an oil; ^{1}H nmr: δ 1.4 (m, 4 H), 2.3 (b, 2 H, disappeared in deuterium oxide), 2.45 (t, 4 H), 2.6 (t, 4 H), 3.45 (m, 12 H).

Anal. Calcd. for $C_{12}H_{26}N_2O_3$: C, 62.57; H, 11.37. Found: C, 62.75; H, 11.50.

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