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### THERMAL REMOVAL OF BOC-PROTECTING GROUPS DURING PREPARATION OF OPEN-CHAIN POLYAMINES

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Abstract: Per-N-tosylated 3,8-diaza-1,10-decanediamine (9), 4,9-diaza-1,12dodecanediamine (spermine) (10) and 3,6,9,14,17,20-hexaaza-1,22-docosanediamine (11) were prepared by treating mono-BOC-protected, per-N-tosylated 1,2ethanediamine (5), 1,3-propanediamine (6) and triethylenetetraamine (7), respectively, with 1,4-dibromobutane and removing the BOC-protecting groups at 100-120 °C.

In view of their considerable medicinal interest, a great deal of effort has been devoted to the design of new convenient routes to produce the polyamines.<sup>14</sup> Recent interest stems from the fact that polyamines are potential vehicles for delivering cytoxic agents into cells in cancer therapy. Also, they possess antineoplastic properties and are antiviral, antipsorias and radioprotective agents.<sup>5-8</sup> Other medicinal applications of the polyamines have been discussed in books and reviews.<sup>9-11</sup>

Methods for preparing polyamines containing alkyl substituents on the terminal

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nitrogen atoms have recently been exploited. These particular N,N'-dialkylsubstituted polyamines are among the most important of the polyamine family.<sup>1,2,4,7,12,13</sup> In general, these N-alkyl-substituted polyamines are prepared by alkylating the per-Ntosylated derivatives of the polyamines followed by detosylation. This method is used when the polyamines are available. When they are not available, their preparation is not always straightforward and usually requires more steps. The preparation is more complicated when long polyamines are required.

No general methods for preparing the unsubstituted polyamines are available. Instead, specific synthetic methods have been introduced for the different families of polyamines.<sup>1,2,14,15</sup> These methods mainly include preparation of polyamines by extension of the polyamine chain by 2-aminoethyl, 3-aminopropyl or 4-aminobutyl units.<sup>1,2</sup>

The method presented here uses BOC- and tosyl-protecting groups which can be removed from the polyamine product. The starting pertosylated diamine, triamine or polyamine is first protected on one end by a BOC group and then treated with a dibromide in DMF at rt and heating the mixture to 70 °C. The two BOC-protecting groups on the resulting pertosylated, di-BOC-protected product were cleanly removed when the reaction mixture was heated to 100-120 °C. Thus, per-N-tosylated 1,2-diaminoethane (1), 1,3-diaminopropane (2) and triethylenetetraamine (3) were treated with one equivalent of di-*tert*-butyl dicarbonate (BOC-O-BOC) in the presense of a small amount of 4-(dimethylamino)pyridine (DMAP) in DMF at rt. Resulting mono-BOC-protected compounds 5-7 were treated with 1,4-dibromobutane (8) in DMF at rt in the presence of Cs<sub>2</sub>CO<sub>3</sub>. The temperature was slowly increased

#### **OPEN-CHAIN POLYAMINES**



to 70-80 °C over a 3-h period. The BOC-protecting groups were removed by heating to 100-120 °C to give pertosylated products 9-11. Spermine can be produced by treating 10 with HBr and phenol in acetic acid to remove the tosyl groups as others have reported for similar polymines.<sup>7</sup> The tosyl groups could not be removed using sodium amalgam. In this case, one or two tosyl groups always remained on the spermine. Pertosylated compounds 9-11 can be used to prepare the unsubstituted polyamines or can be alkylated and then detosylated to form the polyamines containing alkyl groups on the terminal nitrogen atoms.<sup>5,7,8</sup> 9-11 can also be used to prepare various perazamacrocycles.<sup>2</sup> BOC-protecting groups have been removed thermally from other amine compounds at 180-220 °C.<sup>16</sup>

Preparation of BOC-Protected, Per-N-tosylated Compounds 5-7. To 0.1 mole of compound 1, 2, or 3<sup>17</sup> dissolved in 400-600 mL of DMF was added 10 mL of triethylamine, 2 g of DMAP and 24 g (0.11 mole) of BOC-O-BOC. The mixture was stirred for 24 h at rt and carefully evaporated under reduced pressure at a temperature not higher than 50 °C. The crude solid gave three TLC spots (silica gel): di-BOC compound, mono-BOC-compound, and unreacted starting material. In order to remove undesired di-BOC and starting compounds, the residue was added to  $CH_2Cl_2$ or toluene, stirred and filtered. The solution was evaporated and chromatographed on silica gel using  $CH_2Cl_2$  then  $CH_2Cl_2$ /ethyl acetate: 100/1, 50/1 and 30/1 as eluants, to give 5-7 as oils in yields of 40-45%; <sup>1</sup>H NMR of 5: ( $\delta$ ) 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); <sup>1</sup>H NMR of 6: ( $\delta$ ) 1.3 (s, 9 H), 1.8 (t, 2 H), 2.4 (s, 3 H), 2.42 (s, 3 H), 3.05 (m, 2 H), 3.85 (t, 2 H), 5.3 (t, 1 H), 7.3 (m, 4 H), 7.75 (m, 4 H); <sup>1</sup>H NMR of 7: ( $\delta$ ) 1.35 (s, 9 H), 2.4 (s, 3 H), 2.42 (s, 3 H), 2.44 (s, 3 H), 2.47 (s, 3 H), 3.2 (s, 4 H), 3.3 (m, 6 H), 3.9 (m, 2 H), 5.25 (b, 1 H), 7.3 (m, 8 H), 7.75 (m, 8 H).

**Preparation of Per-N-tosylated Compounds 9-11** (Scheme 1). To 0.011 mole of compounds 5-7 in 150 mL of DMF containing 30 g of  $Cs_2CO_3$  was added 0.005 mole of 1,4-dibromobutane (8). The mixture was stirred first at rt for 4 h and then slowly increasing the temperature to 70 °C during 3 h. The mixture was stirred at 70 °C for 24 h and finally at 100°-120°C for 24 h. After cooling, the solvent was evaporated under reduced pressure and 200-500 mL of  $CH_2Cl_2$  was added and the mixture was stirred and filtered. The solvent was evaporated and the residue was chromatographed on silica gel using  $CH_2Cl_2$  and ethyl acetate as eluants to give 9 (75%), 10 (69%), and 11 (72%) as glassy solids. Properties of 9 include <sup>1</sup>H NMR ( $\delta$ ): 1.6 (m, 4 H), 2.4 (s, 6 H), 2.41 (s, 6 H), 3.1 (m, 12 H), 5.45 (b, 2 H), 7.3 (d, 8 H),

7.7 (m, 8 H); *Anal.* Calcd for  $C_{36}H_{46}O_8S_4$ : C, 54.65; H, 5,86. Found: C, 54.77; H, 6.00. Properties of 11 include <sup>1</sup>H NMR (ð): 1.6 (s, 4 H), 2.4 (m, 24 H), 3.2 (m, 14 H), 3.3 (s, 14 H), 5.4 (b, 2 H), 7.3 (m, 16 H), 7.7 (m, 16 H); mp 204-206 °C; *Anal.* Calcd for  $C_{72}H_{90}N_8O_{16}S_8$ : C, 54.73; H, 5.74. Found: C, 54.77; H, 5.63. The physical and spectral properties for **10** were the same as those reported.<sup>5,8</sup>

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