Synthesis of a series of triaza-macrocyclicanes

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Condensation of the N,N',N"-tris(p-toluenesulfonyl)diethylenetriamine-N,N"-disodium with bis sulphonate esters of two-, three-, four- and six-carbon diols gives the corresponding 9-, 10-, 11-, 13-membered triamine macrocycles containing N-p-toluene sulfonyl group, respectively. The p-toluene sulfonyl groups are removed with concentrated sulfuric acid, acetic acid-hydrobromic acid or LiAlH4 which give the ammonium salts of 1,4,7-triazacyclononane, 1,4,7-triazacyclodecane, 1,4,7-triazacycloundecane, 1,4,7-triazacycloctadecane, respectively. Comparison and details of the different synthetic procedures of the triamine macrocycles are described as well.

Of late syntheses of cyclic polyamines are usually accomplished by the Richman-Atkins' modification of the method of Koyama and Yoshino2. This synthetic method relies on the condensation of p-toluene sulfonamide sodium salts[-(Ts)N'Na+] with a compound having two p-toluene sulfonate ester groups (-OTs). It facilitates the ring-closure at high reactant concentration and high-dilution operation or eliminating the template metal ions is no longer necessary. Thus, the yields of the reactions enhance greatly and the products are less contaminated with unreacted starting compounds. The relative ease of carrying out the Richman-Atkins cyclization has prompted considerable interest recently in metal complex of these cyclic polyamines3.6.

The entire procedure involves four stages, viz. (i) tosylation of diol, followed by preparation of tosylated diethylenetriamine, (ii) conversion of the tritosylated amine into amine sodium salts, (iii) cyclization in dry DMF, (iv) removal of tosyl group (cf. Scheme I). Thus, synthesis of cyclic polyamine remains tedious, and it is sometimes difficult to obtain the desired amines pure. In this work, four macrocycles (cf. Scheme I, n=2, 3, 4, 6 respectively), all belonging to triamine analog with various cavity, are synthesized systematically. Although these amines have been synthesized previously1,7,9, but most of the cyclic amine hydrochlorides have not been obtained in pure form so far. We found that some improvements, which will be described in detail in the corresponding part, can make the preparation of the intermediates more convenient.

Results and Discussion

Tosylation of diethylenetriamine. The crude tosylated diethylenetriamine (ttdeta) 2 is purified by re-crystallization from acetonitrile, and not from methanol as reported earlier7,8. This trifling modification
makes the operation more convenient because of the much smaller volume of the solvent needed. For example, to recrystallize 100g ttdeta, 800 mL of acetonitrile rather than a larger volume (6L) of methanol is required.

**Cyclization**

Different from that reported previously, after the treatment of ttdeta 2 with sodium hydride to get amino sodium salt 3, on filtration under nitrogen atmosphere, the excess of sodium hydride is left out. The mixture is used directly for cyclization with tosylated diol 1. Namely, the conversion of amine into amino sodium salt and the ring-closure are accomplished in "one pot" reaction. This simplifies the operation and enhances the yield of cyclized product than the corresponding two-step procedure.

The cyclic triamines can also be synthesized by the general p-toluenesulfonate method of Richman-Atkins, but the preparation is proved to be rather difficult. TLC on the mixture indicates the presence of at least six components, which consist of desired product mainly, two starting materials, possible linear polymeric and cyclic polymeric products. When n=2, the ring-closure reaction gives a high yield of cyclized product, and it is proved to be a relatively clean reaction. The desired product is precipitated in 96% yield and with a small amount of impurity. The yields of cyclized products become poorer with longer chain length. These results agree well with those reported earlier for the reaction of the tritosylated diethylentriamine analog. For the reactions between ttdeta and diols (n=2 and n=3), the byproducts could be removed by recrystallizing twice from CHCl₃-CH₂OH to give relatively pure products (yields 87% and 72% respectively). When n=4 and 6, relatively large amount of by-products are produced (TLC IR). ¹H NMR spectra of the reaction mixture, indicates that non-cyclic products are formed. Attempts to separate the desired products by recrystallization with different solvent systems are unsuccessful. In recrystallization, a thick oil is also formed along with the crystallized product. If these impurities persist even after detosylation step, it is impossible to remove the impurities completely by common methods. Fortunately, the impurities, mainly of polymeric materials, are relatively insoluble and remain as an immobile band at the origin of the chromatography column under conditions where the desired rings are quite mobile. Thus the desired rings can be separated by analytical method from the mixture.

**Detosylation**

It is well-known that the tosylated amines are extremely stable in alkaline solution and are difficult to be hydrolysed with acid, thus, the removal of toluenesulfonate groups is difficult and requires vigorous conditions. As reported earlier, both concentrated sulfuric acid and hydrobromic acid-acetic acid methods for detosylation have been used for the preparation of macro-azacycles, successfully. In detosylation with H₂SO₄, the protective groups (Ts-) are removed by acid hydrolysis. However, the detosylation with HBr·CH₃COOH is not just a simple procedure of acid hydrolysis, but a procedure of reduction and decomposition of the Ts-groups. The yields of the HBr·CH₃COOH detosylation products could be enhanced by the addition of phenol which increases the solubility of the tosylated amine and provides a scavenger for the bromine from the reduction. LiAlH₄ method was also tried to reduce Ts-groups for detosylation in the presence of THF. The results show that higher yields were obtained with the LiAlH₄ method as compared to H₂SO₄ and HBr·CH₃COOH methods. Only disadvantage of LiAlH₄ method is that the crude products are obtained as viscous pastes, which are difficult to be purified by recrystallization. Therefore, the crude products are purified by column chromatography on a fluorescent silica gel, and eluted with HCl of proper concentration. Thus, the LiAlH₄ method is not of great practical value. However, the LiAlH₄ method would be useful in the syntheses of macrocycles consisting of acid-sensitive groups, such as azaoxocrown ether.

Further the detosylation step in LiAIH₄ method is time-consuming (about 72hr) as compared to detosylation with H₂SO₄ or HBr·CH₃COOH (at least 24hr). However, if the reaction is stopped in less than the required time, mono-, or bis-detosylated amine can be isolated and characterized.

**Experimental Section**

Pyridine (A. R.) and DMF (A. R.) were dried with calcium hydride and distilled under reduced pressure before use. p-Toluenesulfonyl chloride (TsCl) was recrystallized from chloroform. Diethylentriamine (Deta) and diols were of analytical grade and used without further purification. All solvents used were of analytical grade regents.

Elemental analysis was measured with a Carlo-Erba 1106 spectrophotometer. A Yamamoto apparatus (corrected) was used to detect the melting point. IR spectra were recorded in KBr pellets, using an Al-
pha Centaur FT-IR spectrophotometer; \(^{1}H\) NMR spec-
tra on a Bruker AC-80 spectrometer with TMS (in
DCl) or sodium trimethylsilyl propane sulfonate
(in \(D_{2}O\)) as internal references.

The reactions were monitored on TLC. The reac-
tions were carried out on precoated TLC plate of
fluoro-silica gel 60 F-254 under radiation at 254nm
with chloroform-methanol (1:5) mixture as an eluent.

**General procedure of tosylation**

To a solution of p-toluenesulfonyl chloride (39g,
0.3mole) in dry pyridine (90 mL) kept 0°C, a solu-
tion of diol (0.15 mole) in pyridine (90 mL) was
added dropwise and the mixture stirred for 2hr, the
mixture's temperature was raised to room tempera-
ture. The mixture was poured into ice-water (2L),
con. HCl (50 mL) was then added to give a white
precipitate. It was dried and recrystallized from the
required solvent to get the bisulfonate ester in
60-80% yield. The yields, solvents of recrystallization
and characterization data are listed in Table I.

**Tosylation of diethylenetriamine**

A solution of TsCl (125.8g, 0.66 mole) in acetone
(250 mL) and potassium carbonate (91.2g, 0.66
mole) in 100 mL water were added dropwise simulta-
neously to a solution of Deta (20.6g, 0.2
mole) in 100 mL acetone maintained at 0°C in ice-bath
while stirring for 2hr. The mixture was stirred at
room temperature for another 3hr, and then poured into
3L of ice-water. The precipitate thus formed was filtered
and dried at 100°C. The product was crystallized from
acetone/nitrite (800 mL), yield 100.2g (92%), m.p.
174-75°C, IR 0.21. (Found: C, 53.3; H, 5.7; N, 7.4. Calcd::
C, 53.1; H, 5.5; N, 7.4%); \(^{1}H\) NMR (9H, \(CH_{3}Ar\), 2.80
(4H, \(CH_{2}NTs\)), 2.99 (4H, \(CH_{3}NHTs\)).

**Cyclization of 2 and 3. General procedure**

Sodium hydride (6.1g of 80% Paraffin powder, excess
about 20%) was added to a solution of Deta (42.5g,
0.075 mole) in dry DMF (350 mL) at 70°C. After vig-
orous effervescence, the mixture was stirred for about
1hr at 105°C, and a solution of tosylated diol (the
diols were equal to each other as 0.075 mole) in
DMF (100 mL) was added during 2 hr. The mixture was
then stirred at 105°C for additional 6hr. After reduction
of the volume to crystallization, it was gradually added
into ice-water (1L) to give a precipitate. It was washed
with water, ethanol and ether, and dried at 100°C. This
crude product was a complicated mixt ure of different
compounds according to TLC. The derivative was
taken up in methanol and dichloromethane, filtered hot
from insoluble by-products and chromatographed on a
silica gel G60 and the column eluted with the same
solvent used for TLC monitored by a UV
lamp (\(\lambda=254nm\)). The purified tritosylated derivative
was crystallized from \(CH_{2}Cl_{2}-MeOH\). Their characteriza-
tion data are given in Table II.

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**Table I — Diols toluenesulphonate**

<table>
<thead>
<tr>
<th>Starting compound</th>
<th>Recrystallization Solvent</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>(^{1}H) NMR (in (\delta), ppm, CDCl(_3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-Ethanediol</td>
<td>Acetone</td>
<td>125-26</td>
<td>79</td>
<td>7.58(dd,8H), 4.29(s,4H), 2.46(s,6H)</td>
</tr>
<tr>
<td>1,3-Propanediol</td>
<td>Ethanol</td>
<td>96-98</td>
<td>84</td>
<td>7.64(dd,8H), 4.17(t,4H), 2.40(s,6H), 1.64(m,2H)</td>
</tr>
<tr>
<td>1,4-Butanediol</td>
<td>Ethanol</td>
<td>81-82</td>
<td>72</td>
<td>7.70(dd,8H), 4.06(m,4H), 2.44(s,6H), 1.72(m,4H)</td>
</tr>
<tr>
<td>1,6-Hexanediol</td>
<td>Methanol</td>
<td>71-72</td>
<td>64</td>
<td>7.54(dd,8H), 3.97(t,4H), 2.42(s,6H), 1.46(m,8H)</td>
</tr>
</tbody>
</table>

All the compounds gave satisfactory C and H analysis

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**Table II — Tosylated cyclization products**

<table>
<thead>
<tr>
<th>Products</th>
<th>Appearance</th>
<th>m.p. °C</th>
<th>(^{1}H) NMR (CDCl(_3), (\delta), ppm)</th>
<th>Yield (%)</th>
<th>Found (%) (Calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9]JaneN(_3)3Ts</td>
<td>white needle</td>
<td>220-21</td>
<td>2.43(s,9H),3.44(s,12H), 7.60(m, 12H)</td>
<td>87</td>
<td>55.0 5.4 7.2</td>
</tr>
<tr>
<td>[10]JaneN(_3)3Ts</td>
<td>white granule</td>
<td>231-33</td>
<td>2.02(m,2H),2.48s,9H),3.23-3.41(m,12H),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.21-7.90(m,12H),</td>
<td>72</td>
<td>55.3 5.7 6.9</td>
</tr>
<tr>
<td>[11]JaneN(_3)3Ts</td>
<td>white thin piece</td>
<td>182-83</td>
<td>1.92(t,4H), 2.34(s,9H),3.10-3.38(m,12H),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.30-7.64(m,12H),</td>
<td>53</td>
<td>56.1 6.1 6.4</td>
</tr>
<tr>
<td>[12]JaneN(_3)3Ts</td>
<td>white granule</td>
<td>209-10</td>
<td>1.85-2.02(m,6H),2.36(s,9H), 3.04-3.40(m,12H),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.41-7.82(m,12H),</td>
<td>67</td>
<td>57.4 6.5 6.2</td>
</tr>
</tbody>
</table>

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Note: The prefixes "[9]", "[10]", "[11]", and "[12]" in Table II correspond to the entries in Table I.
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Table III — Characterization data of the products

<table>
<thead>
<tr>
<th>Products</th>
<th>m.p.,°C</th>
<th>1H NMR (D$_2$O, in 8, ppm)</th>
<th>Found (%)(Calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9]aneN$_3$·3HCl</td>
<td>264-66</td>
<td>2.19(q,2H),3.35-3.50(m,12H), 3.64(s,12H)</td>
<td>30.5 6.5 17.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(30.7 6.5 17.9)</td>
<td></td>
</tr>
<tr>
<td>[10]aneN$_3$·3HCl</td>
<td>243-46</td>
<td>2.18(m,2H),3.40-3.72(m,12H),</td>
<td>33.9 6.6 16.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(33.9 6.9 16.9)</td>
<td></td>
</tr>
<tr>
<td>[11]aneN$_3$·3HCl</td>
<td>257-59</td>
<td>1.95(m,4H),3.20(t,4H), 3.50(s,8H)</td>
<td>36.7 7.2 15.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(36.6 7.3 16.0)</td>
<td></td>
</tr>
<tr>
<td>[13]aneN$_3$·3HCl</td>
<td>263-64</td>
<td>1.60-1.80(m,4H), 3.25(t,4H), 59(s,8H)</td>
<td>41.2 8.0 14.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(41.4 8.0 14.5)</td>
<td></td>
</tr>
</tbody>
</table>

Table IV — Yields (%) from the different methods (A, B and C)

<table>
<thead>
<tr>
<th>Products</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9]aneN$_3$·3Cl</td>
<td>83</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>[10]aneN$_3$·3Cl</td>
<td>86</td>
<td>84</td>
<td>92</td>
</tr>
<tr>
<td>[11]aneN$_3$·3Cl</td>
<td>79</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>[13]aneN$_3$·3Cl</td>
<td>71</td>
<td>80</td>
<td>88</td>
</tr>
</tbody>
</table>

General procedure for detosylation

A mixture of triazacycle (0.02 mole) and phenol (10g) in HBr-CH$_2$COOH (50 mL, w/w; 1:1) was heated for about 24hr. The dark solution thus obtained was reduced to one-fifth in volume and was then extracted continuously with CHCl$_3$ until the washings were slightly coloured. It was then cooled in an ice-bath, and its pH was adjusted to 12 with 10 mol/L NaOH. It was extracted continuously with CHCl$_3$ for 3 days. The chloroform was then separated with a separatory funnel and evaporated to dryness. The residue obtained was neutralized with hydrochloric acid and reduced to a small volume. It was then crystallized from ethanol, filtered and washed with HOAc and ethanol respectively. Recrystallization from dilute hydrochloric acid (0.5 mL/L) followed by ethanol gave pure product. Its characterization data are given in Table III.

The yields of the products obtained by different methods are shown in Table IV.

Acknowledgement

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References

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