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Synthesis of 24-, 26-, 32- and 36-membered Macrocyclic Polyamines *via* a (2+2) Cyclization Process

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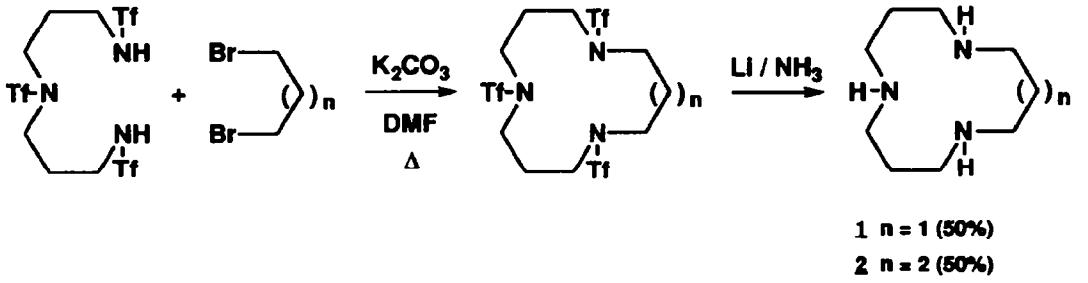
Abstract : At high concentration, N-pertriflated polyamines and ω, ω'-dihalogenoalkanes react to yield large polyazamacrocycles according to a (2+2) cyclization mode.

In a recent paper we described a new and convenient synthesis of tetraazamacrocycles using triflamides as protecting groups[1]. In the cyclization step, a linear N-pertriflated tetraamine was allowed to react with various ω, ω'-dihalogenoalkanes ; ω, ω'-**dibromo**alkanes were found to be the most efficient reagents leading to very clean products, according to a (1+1) cyclization mode.

The deprotection step, previously achieved by sodium in liquid ammonia, is greatly improved when sodium is replaced by lithium, as yields in free tetraazamacrocycles are raised up to 90%.

Now this procedure has been succesfully extended to the synthesis of cyclic triamines 1 and 2 starting from the parent linear N-triflated triamines (Scheme 1).



1 n = 1 (50%)
2 n = 2 (50%)

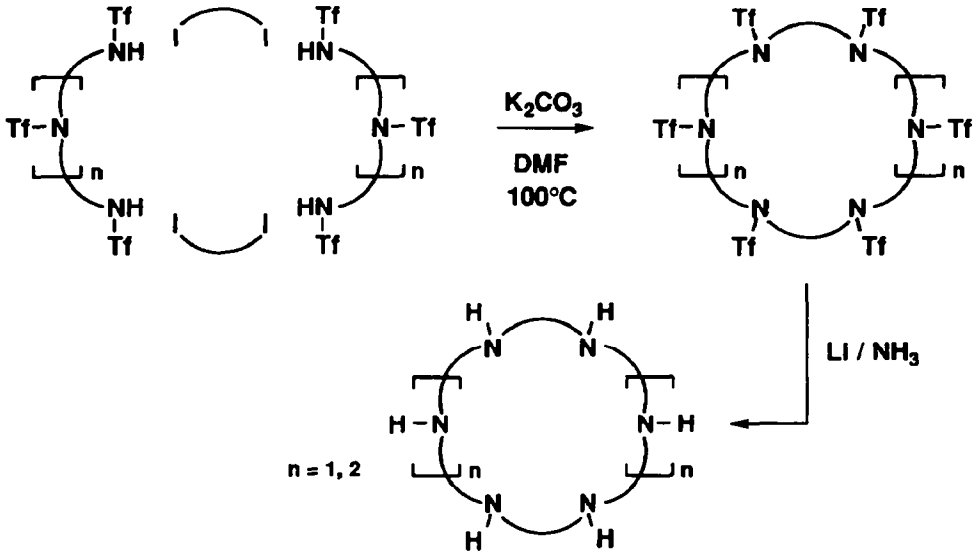
Scheme 1 : (1+1) mode.

Under the same conditions the cyclization of N-triflated triamines or tetraamines with an ω, ω'-**diiodo**alkane leads to a by-product (5-15%) which was identified to be the (2+2) cyclization adduct, that is respectively the cyclic hexaamine or octaamine.

Such dimeric products (≈10%) have already been reported[2, 3] in the Richman and Atkins' procedure for the cyclization of N-tosylamides.

Thus, the different parameters of this reaction have been examined. The reaction was run at different temperatures, in presence of different bases (Na^+, K^+, Cs^+ carbonates) with no noticeable change on the cyclization mode. As well, the addition rate of the reactants did not affect the outcome of reaction. However, we found that the ratio of the (1+1) versus (2+2) cyclization mode is strongly dependent on the reactants' concentration : if at 0,02 M, the (1+1) cyclization process is largely preponderant (95:5), on the other hand at 0,5 M the ratio is reversed as the (2+2) mode is now greatly favoured (10:90) (Scheme 2). This striking effect of the concentration on the fate of the reaction remains whithout satisfying explanation and moreover, at this concentration oligomerization derivatives are not detected. By contrast, all attempts, to prepare tetraazamacrocycles *via* the (2+2) process, have failed ; in all cases the reaction of N-triflated diamines and diiodoalkanes leads to the (1+1) adduct.

Nevertheless, starting from commercially available tri- and tetraamines, this procedure allows the preparation in convenient yield of symmetrical and less symmetrical polyazamacrocycles as shown in table 1.



Scheme 2 : (2+2) mode.

In a typical procedure, a mixture of the suited N-pertriflated polyamine (1 mmole), K_2CO_3 (10 mmoles) in freshly distilled DMF (2 ml) is treated at 100°C and under nitrogen with appropried diiodoalkane (1 mmole) for 4 hours. After cooling the solvent is removed under vacuo and 4N NaOH is added to the residue until pH 12. The (2+2) product is selectively extracted with dichloromethane as the (1+1) adduct is not soluble in this solvent[1]. The pertriflated cyclic hexaamines are obtained in 70-80% yield and the cyclic octaamines in 80-85% yield.

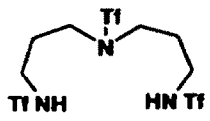
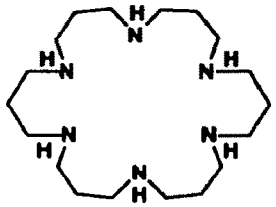
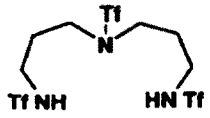
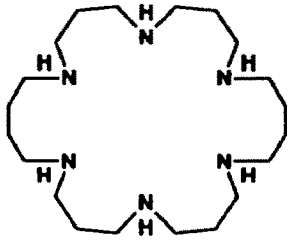
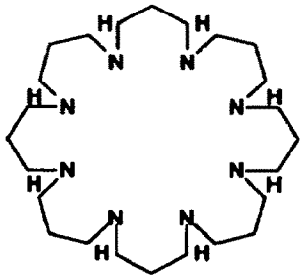
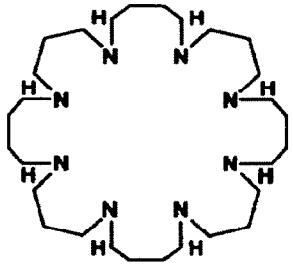
Reagents		Product	* overall yield (%)
		 **3**	70
		 **4**	55
		 **5**	60
		 **6**	55

Table 1 : (2+2) cyclization and deprotection.
* as HCl salts.

The compound resulting from the latter procedure (1 mmole) is taken up in THF (10 ml) ; freshly distilled NH_3 (50 ml) is condensed under nitrogen at -33°C and lithium metal is added until a blue color persisted for 30 minutes (1-2 hrs). The mixture is allowed to warm at room temperature, methanol (1 ml) is added and the solvents are removed under reduced pressure. The residue is acidified with concentrated HBr and the precipitate is washed with acetone (30 ml). After filtration the resulting cristalline solid is dissolved in a minimum amount of water and reprecipitated by addition of ethanol (30 ml). The protonated macrocycle, at this stage a mixed salt of bromide and sulfite, is dissolved in a small amount of water and passed over a column of Amberlyst A-26 resin in the basic form. The aqueous solution of the free base is acidified to pH = 1 with 2N HCl and H_2O removed by evaporation. Cyclic hexaamines hexahydrochlorides are obtained in a 80-90% yield and cyclic octaamines octahydrochlorides in a 70% yield. Compounds 1, 2, 3, 5 have been already described[4, 5] ; spectral data of 4, 6 are given in reference 6.

As 3, 4 chaining can be introduced both in the (1+1) and (2+2) cyclization procedures, therefore, this is a very convenient improvement of the iterative strategy involving the acrylonitrile Michael addition, reduction, N-tosylation, cyclization and detosylation sequence classically used in order to prepare such macrocyclic compounds.

This method has been applied to the synthesis of other macrocycles which will be described in a forecoming full paper.

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1. V. Panetta, J.J. Yaouanc and H. Handel, *Tetrahedron Lett.*, 1992, 33, 5505-5508.
2. J.E. Richman, T.J. Atkins, *J. Am. Chem. Soc.*, 1974, 96, 2268-2270.
3. P.M. Schaber, J.C. Fettinger, M.R. Churchill, D. Nalewajek and K. Fries, *Inorg. Chem.*, 1988, 27, 1641-1646.
4. B. Dietrich, M.W. Hosseini, J.M. Lehn and R.B. Sessions, *Helv. Chim. Acta*, 1983, *66*, 1262-1278.
5. A. Bianchi, M. Micheloni and P. Paoletti, *Coord. Chem. Rev.*, 1991, *110*, 17-113, and references therein.
6. Spectral data of macrocyclic polyamines in protonated forms :

   4 : δppm ^1H (D_2O, 300 MHz) : 3,17 (m, 24 H, N-C<u>H</u>$_2$) ; 2,15 (m, 8 H, N-CH_2-C<u>H</u>$_2$-CH_2-N) ; 1,81 (m, 8 H, N-CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2-N).
   δppm ^{13}C (D_2O, 75 MHz) : 49,7 ; 47,4 ; 47,2 (N-<u>C</u>H_2) ; 25,5 ; 25,5 (N-CH_2-<u>C</u>H_2).

   6 : δppm ^1H (D_2O) : 3,15 (m, 32 H, N-C<u>H</u>$_2$) ; 2,14 (m, 8 H, N-CH_2-C<u>H</u>$_2$-CH_2-N) ; 1,80 (m, 16 H, N-CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2-N).
   δppm ^{13}C (D_2O) : 49,8 ; 47,3 (N-<u>C</u>H_2) ; 25,6 ; 25,5 (N-CH_2-<u>C</u>H_2).

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