Tetrahedron Letters, Vol. 33, No. 38, pp. 5505-5508, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

# Triflamides for Protection and Cyclization of Tetraamines to Tetraazamacrocycles

**V. Panetta, J.J. Yaouanc and H. Handel**

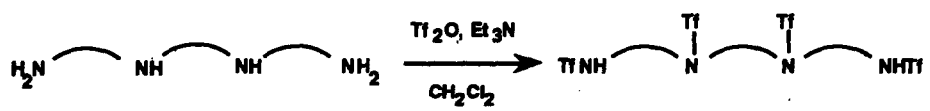
Laboratoire de Chimie, Electrochimie Moléculaire et Chimie Analytique, associé CNRS 322,
Faculté des Sciences et Techniques,
6, avenue le Gorgeu - 29287 BREST, FRANCE.

***Abstract*** : A facile two-step synthesis of tetraazamacrocycles is reported starting from trifluoromethanesulfonyl derivatives of linear tetraamines. After cyclization, the macrocycle was deprotected using sodium in liquid ammonia.

Different types of procedures are used to prepare tetraazamacrocyclic ligands[1], the most used one being the Richman and Atkins' synthesis[2,3] which is one extension of the Stetter and Roos' pionnering work on macrocyclization[4] (Schemes 2, 3, R = Ts).
In this procedure, one precursor is a *preformed* salt of a ditosylamide and the other precursor contains sulfonate esters as leaving groups.

The cyclization step of this method works well[1,2], provided that great care is dedicated to the use of very pure and dry materials. After cyclization, drastic conditions are required to remove the tosyl groups. The most used detosylation process is sulfuric acid hydrolysis. However, acid hydrolysis of tosylates does not always give good yields. Alternatively, the procedure of Snyder and Heckert[5] using 33% HBr, AcOH, phenol could be preferred. Anyway, the Richman and Atkins' method is often tedious and time-consuming.

The purpose of this paper is to report a new and convenient synthesis of tetraazamacrocycloalkanes using triflamides as protecting groups. The linear precursors 1 are easily prepared according to the following general procedure (Scheme 1).



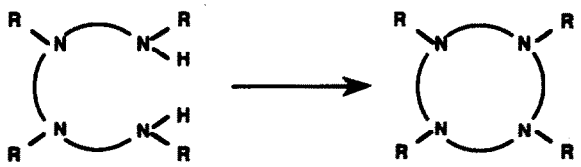

1

Tf = $SO_2CF_3$

Scheme 1

To a well stirred solution of tetraamine (1 mmole) and triethylamine (4 mmoles) in $CH_2Cl_2$ (30 ml) is added trifluoromethanesulfonic anhydride (4 mmoles) at -30°C. The mixture is allowed to warm at room temperature and stirred for an additionnal hour, upon which 4N NaOH (3 ml) is added. The basic aqueous phase is extracted with $CH_2Cl_2$ (2x30 ml), and the combined organic phases are discarded. After acidification to pH 1 with conc. HCl, the aqueous phase is extracted with $CH_2Cl_2$ (3x20 ml) or ethylacetate (30 ml). The combined organic phases are dried ($MgSO_4$) and concentrated to dryness to yield the crude tetratriflamide 1 pure enough for next purpose (yield 70-90 %).

Like the tosylamides, these triflamides can be cyclized (Scheme 2, R=Tf) : the disalt of 1 is generated *in situ* by action of $K_2CO_3$ and reacted with a dibromoalkane, leading cleanly to the cyclic adduct 2 in high yield [6].



1 2

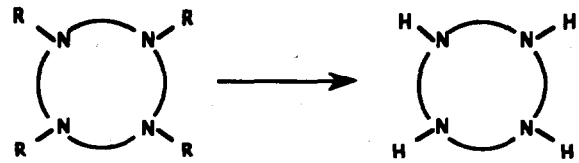
R = Ts: 1) EtONa, EtOH 2) $TsO(CH_2)_nOTs$, DMF, 100°C

R = Tf: $K_2CO_3$, $Br(CH_2)_nBr$, DMF, 110°C

Scheme 2

In a typical procedure, a mixture of 1 (1 mmole), $K_2CO_3$ (10 mmoles) in freshly distilled DMF (50 ml) is treated at 110°C and under nitrogen with the suitable dibromoalkane (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 aqueous phase is extracted with ethylacetate (30 ml). The organic phase is washed twice with water (2 x 3 ml), dried over $MgSO_4$ and concentrated to dryness to give the expected cyclic tetratriflamide 2 (yield 90-95 %)[7]. If necessary, 2 can be easily purified by precipitation in dichloromethane[6].

Finally, the deprotection step can be performed under very mild conditions using sodium in liquid ammonia (Scheme 3)[8].



2 3

R = Ts: 98% $H_2SO_4$, 100°C, 48 hrs

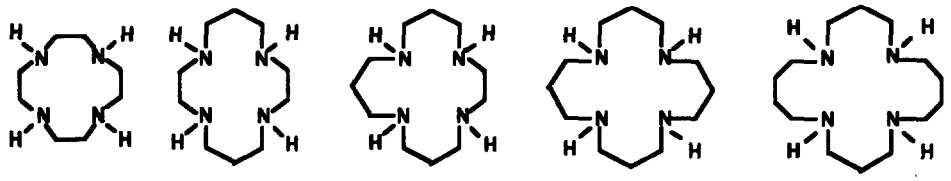
R = Tf: Na, $NH_3$, -33°C, 2 hrs

Scheme 3

Compound 2 (1 mmole) resulting from the latter procedure is taken up in THF (10 ml) ; freshly distilled $NH_3$ (50 ml) is condensed under nitrogen at -33°C and sodium 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 taken up in water (3 ml) and extracted with dichloromethane (2x30 ml). The combined organic phases are dried over $MgSO_4$ and concentrated to dryness yielding the free tetraazamacrocycle 3 (yield 60-70 %) as the only detected product.

As shown on table 1, the pure and free tetraazamacrocycle is easily obtained, except in one case where the cyclization step fails : cyclen can not be prepared according to this procedure which leads essentially to oligomerization products.

| Reagents | | Product | overall |
|---|---|---|---|
| Triflamide | X(R)X | | yield (%) |
| $TfHN(CH_2)_2NTf(CH_2)_2NTf(CH_2)_2NHTf$ | $Br(CH_2)_2Br$ | 2222 | <5 |
| $TfHN(CH_2)_3NTf(CH_2)_2NTf(CH_2)_3NHTf$ | $Br(CH_2)_2Br$ | 2323 | 57 |
| $TfHN(CH_2)_3NTf(CH_2)_2NTf(CH_2)_3NHTf$ | $Br(CH_2)_3Br$ | 2333 | 60 |
| $TfHN(CH_2)_3NTf(CH_2)_3NTf(CH_2)_3NHTf$ | $Br(CH_2)_3Br$ | 3333 | 57 |
| $TfHN(CH_2)_3NTf(CH_2)_4NTf(CH_2)_3NHTf$ | $Br(CH_2)_4Br$ | 3434 | 59 |



2222 (cyclen) 2323 (cyclam) 2333 3333 3434

Table 1 : Cyclization and Deprotection of Linear Tetratriflamides

Other leaving groups (tosylates, chlorides and iodides) have been checked, but we found that bromides are the most efficient as very clean products are obtained. So it is a straighforward and easy to run procedure.

We are now investigating extension of this procedure to larger polyazamacrocycles.

## References


1. A. Bianchi, M. Micheloni and P. Paoletti, *Coord. Chem. Rev.*, **1991**, *110* , 17.
2. J.E. Richman, T.J. Atkins, *J. Am. Chem. Soc.*, **1974**, *96*, 2268.
3. T.J. Atkins, J.E. Richman and W.F. Oettle, *Org. Synth.*, **1988**, VI (collective volume), 652.
4. H. Stetter, E.E. Roos, *Chem. Ber.*, **1954**, *87*, 566.
5. H.R. Snyder, R.E. Heckert, *J. Am. Chem. Soc.*, **1952**, *74*, 2006.
6. The cyclic tetratriflamides 2 have been compared with authentic samples obtained after the reaction of the corresponding tetraazamacrocycles with trifluoromethanesulfonic anhydride under the conditions described above (these compounds are poorly soluble in $CH_2Cl_2$ and precipitate during the reaction).
7. 2323$(Tf)_4$, δ ppm $^1H$ ($d_6$-acetone, 300 MHz) : 3.91 (s, 8H, $NCH_2CH_2N$); 3.74 (t, $J_{H-H}$ = 7.8 Hz, 8H, $NCH_2CH_2CH_2N$); 2.33 (m, 4H, $NCH_2CH_2CH_2N$) - $^{13}C$ (75 MHz) : 121.2 (q, $J_{C-F}$ = 323.2 Hz, $CF_3$); 48.8; 48.5 ($NCH_2$); 28.4 ($NCH_2CH_2CH_2N$) - $^{19}F$ (94 MHz) : -75.1 - m.p. : 225°C.

   2333$(Tf)_4$, δ ppm ($d_6$-acetone) $^1H$ : 3.91 (s, 4H, $NCH_2CH_2N$); 3.70 (m, 12H, $NCH_2CH_2CH_2N$); 2.33 (m, 6H, $NCH_2CH_2CH_2N$) - $^{13}C$ : 121.3 (q, $J_{C-F}$ = 324.9 Hz, $CF_3$); 120.8 (q, $J_{C-F}$ = 323.1 Hz, $CF_3$); 49.2; 49.1; 48.5; 48.0 ($NCH_2$); 32.5; 30.0 ($NCH_2CH_2CH_2N$) - $^{19}F$ : -75.5, -74.9 - m.p. : 110°C.

   3333$(Tf)_4$, δ ppm ($d_6$-acetone) $^1H$ : 3.63 (m, 16H, $N\text{-}CH_2$); 2.33 (m, 8H, $NCH_2CH_2CH_2N$) - $^{13}C$ : 121.2 (q, $J_{C-F}$ = 324.0 Hz, $CF_3$); 48.8 ($NCH_2$); 31.5 ($NCH_2CH_2CH_2N$) - $^{19}F$ : -75.0 - m.p. : 264°C.

   3434$(Tf)_4$, δ ppm ($d_6$-acetone) $^1H$ : 3.59 (m, 16H, $NCH_2$ ); 2.22 (m, 4H, $NCH_2CH_2CH_2N$ ) ; 1 .88 (m, 8H, $NCH_2CH_2CH_2CH_2N$) - $^{13}C$ : 121.1 (q, $J_{C-F}$ = 323.8 Hz, $CF_3$); 50.5; 48.1 ($NCH_2$ ); 30.4 ($NCH_2CH_2CH_2N$); 27.1 ($NCH_2CH_2CH_2CH_2N$)- $^{19}F$ : -75.1 - m.p. : 219°C.
8. M.L. Edwards, D.M. Stemerick and J.R. McCarthy, *Tetrahedron Lett.*, **1990**, *31*, 3417.


(Received in France 12 June 1992)