Synthesis of Tetra-aza Macrocycles with Remarkably High Efficiency

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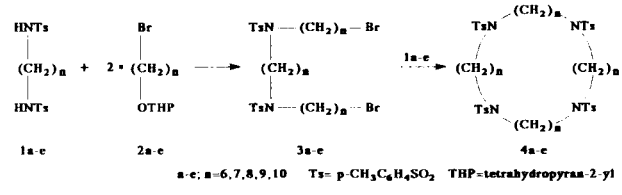
Received March 31, 1988

Tetra-aza macrocycles with 28- to 44-membered rings can be readily synthesized by reaction of dibromide and ditosyldiamide without use of a high dilution method. The reaction proceeded very smoothly with a 10 m*M* concentration in DMF, and gave the macrocycles in excellent yields (60-80%). Favorable effects of cesium ion on the cyclization have been observed.

J. Heterocyclic Chem., **25**, 1463 (1988).

While many studies on crown-ethers have been reported [2], there is little precedent for preparation of cyclic tetraamines and tetralactams with rings larger than 30-membered [3]. Such macrocyclic derivatives are of our current interest for their biological activities (*e.g.*, antitumor [4], antiviral [5] and hypotensive [6] properties) and aza-crown compounds in addition to study on the novel ferredoxin analogues with tetrathiol ligands attached to hydrophobic macrocycles [7-8]. Our previous work showed the synthesis of a symmetric 36-membered tetralactam *via* an active ester [9], and a facile preparation of macrocyclic tetra-amides with 33- to 37-membered rings using diamines and dicarboxylic acid derivatives [10]. In this communication we describe synthesis of tetra-aza macrocycles with practical importance, since formation of tetraamine through simultaneous reduction of the four amide groups was inefficient (*e.g.*, 9% for the 36-membered tetralactam [9]). The present procedure involes a simple double condensation reaction to afford large macrocyclic tetra-aza compounds directly according to Scheme 1.

Scheme 1



This method has turned out to be very efficient, and a series of related large tetra-aza macrocycles has been prepared without difficulty. Sodium hydride is adequate to deprotonate from compound **1** to afford the corresponding disodium salt, and evolution of hydrogen ceases in about 10 minutes after addition of the base. The solution becomes turbid at this point in most cases. Subsequent addition of compound **3** to the suspension brings about rapid consumption of the bromide. Reaction for 2 hours is generally sufficient to complete the double condensation leading to the macrocycles at 60°. The typical results are summarized in Table 1. Even the largest ring prepared, 1,12,23,34-tetraazacyclotetratetracontane (**4e**, as the tosylamide derivative), has been isolated in 59% yield [11]. A smaller ring (*e.g.*, n = 2, 12-membered, 50%) was obtained as well in a reasonable yield [11]. The cyclophane tetraamine was also synthesized similarly, employing *N,N'*-ditosyl-*p,p'*-methylenedianiline instead of **1c**. The corresponding 2 + 2 cyclization [*cf.* 3] gave very poor yield (for example, 4 and 9%, for the above cyclophane and **4c**, respectively, while the corresponding 1 + 1 adducts were obtained in 52 and 72% yields). DMF is the best solvent among them tested.

Table 1

Synthesis of Tetra-aza Macrocycles in DMF [a]

Compound	n	Ring size	Yield % [b]	FD-Mass m/z (MH^+)
4a	6	[28]	70	1013
4b	7	[32]	66	1069
4c	8	[36]	62	1125
4d	9	[40]	63	1181
4e	10	[44]	59	1237

[a] 10 m*M* concentration, sodium hydride, 60°, 2 hours. [b] Isolated yield.

It should be emphasized that these condensations were carried out with a rather high concentration (10^{-2} *M*), and that they are of very practical importance (*cf. ca.* 10^{-4}*M* under high dilution conditions [12]) for synthesizing new tetra-aza macro rings. It is convincing that a higher yield is observed in more dilute solutions, *viz.*, **4c** is obtained in 82% yield in a 10^{-3} *M* solution (compare runs 5 and 6 in Table 2). However, even in the higher concentrations, moderate yields have still resulted; for example, 47 and 31%, respectively, in 20 and 100 m*M* solutions (runs 7 and 8).

Thus metal hydrides are strong enough to deprotonate the tosylates, and no remarkable difference in the yield have been observed between three metal hydrides examined here; Li, Na and K (runs 4, 6 and 9). A facile and efficient method for detosylation at four sites simultaneously is a prerequisite for the usefulness of the present method. The procedure which utilizes HBr-phenol [12] was very ef-

Table 2

Synthesis of the 36-Membered Tetra-aza Ring (**4c**) under Various Reaction Conditions [a]

Run	Base [b]	Temperature °C	Concentration of **1c**, m*M*	Yield of **4c**, % [c]
1	Li_2CO_3	120	10	trace
2	K_2CO_3	"	"	21
3	Cs_2CO_3	"	"	46
4	LiH	60	"	59
5	NaH	"	1	82
6	"	"	10	62
7	"	"	20	47
8	"	"	100	31
9	KH	"	10	57
10	NaH + K_2CO_3 [d]	"	"	57
11	NaH + Cs_2CO_3 [d]	"	"	77

[a] Two hours in DMF. [b] 1.1-1.2 Equivalent amounts were used. [c] Isolated yield. [d] One equivalent each was employed.

fective in the present case. For example, by application of this, the corresponding free tetra-amine from compound **4c** has been obtained pure in 91% yield [7,13]. An examination of alkali metal carbonates (M_2CO_3; M = Li, K and Cs) [14] showed that the strength of their basicities reflected directly on the product yields. Namely, while **4c** was isolated in poor yields with lithium carbonate and potassium carbonate (1.8 and 21%, respectively) even at 120°, cesium carbonate gave the product in 46% yield (runs 1, 2 and 3). These observations are consistent with the earlier work that lithium carbonate and potassium carbonate are incapable of deprotonating the tosylamide, but cesium carbonate can do this quantitatively in the formation of diaza compounds [15]. If the deprotonation was performed with sodium hydride first, and then potassium or cesium ion added, significant differences in the yields were observed between the two reactions (57% with K^+ and 77% with Cs^+ as given in runs 10 and 11). An increased yield (59%) of **4c** resulted as well with 2 equivalents of cesium carbonate (*cf.* 46% with 1 equivalent of cesium carbonate; run 3). The favorable effects of Cs^+ ion on cyclization may be regarded as due to the increased solubility and reactivity of the anionic reactant, or to the formation of a "triple-ion" [15,16]. Detailed studies are in progress and will be given in a full paper in due course.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Shimadzu IR-440 spectrometer in chloroform solution. The pmr spectra were recorded on a JEOL FX-90A spectrometer in deuteriochloroform solution. Chemical shifts are experssed as ppm downfield from tetramethylsilane as an internal standard. Dibromides **3** are derived from ditosylamides **1** and monobromoalcohol derivatives **2** [7,17].

Experimental Procedure.

1,10,19,28-Tetra-*p*-toluenesulfonyltetraazacyclohexatriacontane (**4c**).

To a DMF solution (20 ml) of ditosylamide **1c** (108 mg, 0.239 mmoles), sodium hydride (23 mg in oil, 0.575 mmole) in DMF (4 ml) was added, and stirred at 60° for 30 minutes under reduced pressure. Dibromide **3c** (200 mg, 0.24 mmole) in DMF (9.5 ml) was then added to the above mixture, and stirred at 60° for 2 hours under nitrogen. The solvent was removed at 40° *in vacuo*, then to the residue was added *N* hydrochloric acid (20 ml), and extracted with dichloromethane washed with water, and dried over magnesium sulfate. Purification by a silica gel column eluted with dichloromethane-ethyl acetate (20:1) gave a colorless solid which was further purified by recrystallization from chloroform-*n*-hexane to afford 166 mg (62%) of **4c** as colorless leaflets, mp 140.5-142°; ir: 1145, 1325 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.24 (br s, 32H, CH_2 [skeleton]), 1.3-1.7 (m, 16H, N_β-CH_2), 2.42 (s, 12H, CH_3-Ph), 3.05 (t, 16H, J = 6.8 Hz, N_α-CH_2), 7.29 (d, 8H, J = 8.4 Hz, arom), 7.69 (d, 8H, J = 8.4 Hz, arom).

Anal. Calcd. for $C_{60}H_{92}N_4O_8S_4$: C, 64.02; H, 8.24; N, 4.98. Found: C, 64.22; H, 8.25; N, 4.79.

The following compounds were similarly prepared.

1,8,15,22-Tetra-*p*-toluenesulfonyltetraazacyclooctacontane (**4a**).

This compound had mp 168-170°; ir: 1140, 1320 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.36 (br s, 16H, CH_2 [skeleton]), 1.4-1.8 (m, 16H, N_β-CH_2), 2.41 (s, 12H, CH_3-Ph), 3.05 (t, 16H, J = 6.8 Hz, N_α-CH_2), 7.29 (d, 8H, J = 7.6 Hz, arom), 7.67 (d, 8H, J = 7.6 Hz, arom).

Anal. Calcd. for $C_{82}H_{76}N_4O_8S_4$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.22; H, 7.55; N, 5.43.

1,9,17,25-Tetra-*p*-toluenesulfonyltetraazacyclodotriacontane (**4b**).

This compound had mp 138-139.5°; ir: 1150, 1330 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.29 (br s, 24H, CH_2 [skeleton]), 1.4-1.7 (m, 16H, N_β-CH_2), 2.41 (s, 12H, CH_3-Ph), 3.05 (t, 16H, J = 7.0 Hz, N_α-CH_2), 7.30 (d, 8H, J = 8.5 Hz, arom), 7.68 (d, 8H, J = 8.5 Hz, arom).

Anal. Calcd. for $C_{56}H_{84}N_4O_8S_4$: C, 62.88; H, 7.91; N, 5.23. Found: C, 62.68; H, 8.18; N, 5.26.

1,11,21,31-Tetra-*p*-toluenesulfonyltetraazacyclotetracontane (**4d**).

This compound had mp 119-120°; ir: 1150, 1330 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.26 (br s, 40H, CH_2 [skeleton]), 1.4-1.8 (m, 16H, N_β-CH_2), 2.41 (s, 12H, CH_3-Ph), 3.07 (t, 16H, J = 6.9 Hz, N_α-CH_2), 7.29 (d, 8H, J = 7.8 Hz, arom), 7.69 (d, 8H, J = 7.8 Hz, arom).

Anal. Calcd. for $C_{64}H_{100}N_4O_8S_4$: C, 65.05; H, 8.53; N, 4.74. Found: C, 64.74; H, 8.69; N, 4.79.

1,12,23,34-Tetra-*p*-toluenesulfonyltetraazacyclotetratetracontane (**4e**).

This compound had mp 67-68.5°; ir: 1150, 1330 cm^{-1}; ^{1}H-nmr (deuteriochloroform): ppm 1.25 (br s, 48H, CH_2 [skeleton]), 1.4-1.8 (m, 16H, N_β-CH_2), 2.40 (s, 12H, CH_3-Ph), 3.07 (t, 16H, J = 7.3 Hz, N_α-CH_2), 7.29 (d, 8H, J = 8.4 Hz, arom), 7.68 (d, 8H, J = 8.4 Hz, arom).

Anal. Calcd. for $C_{68}H_{108}N_4O_8S_4$: C, 65.98; H, 8.79; N, 4.52. Found: C, 66.49; H, 9.10; N, 4.36.

Acknowledgement.

We are very grateful to Ms. Touko Fujita and Mr. Kenji Watanabe of Hokkaido University for their help in measuring FD-mass spectra. Microanalyses were carried out at the Analytical Laboratory of Tsukuba University, for which the authors express their deep thanks.

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