Convenient Synthesis of Large Tetraazamacrocycles Bearing Alkylene, Cyclophane and Crown Ether Type Skeletons

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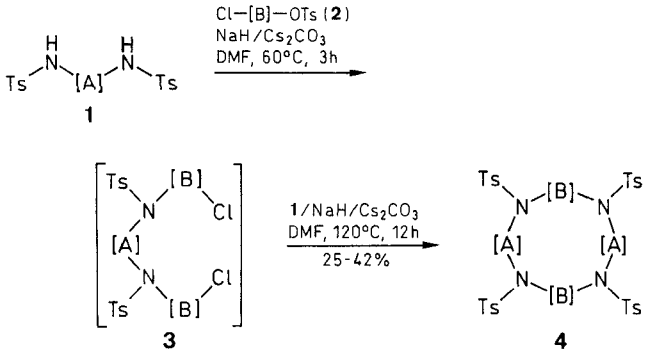
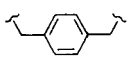
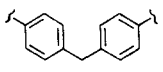
A series of large tetraazamacrocycles with 28- to 44-membered rings consisting of alkylene, phenylene or ether type backbones has been prepared without the use of high-dilution conditions in practically significant yields (25–42%). The reaction can be carried out with a 10 mmol concentration and is applicable to a variety of combinations of different kinds of chains.

Studies on molecular recognition by macrocyclic compounds such as cyclophanes and crown ethers have received much attention in the field of host-guest chemistry.[1] We are currently interested in modeling non-heme iron–sulfur (Fe–S) proteins using macrocyclic tetrathiol ligands,[2] and in applying such Fe–S complexes to carbon dioxide fixation work.[3] However, it is generally not easy to obtain large macrocycles in a practically significant yield, since use of a high-dilution method is often necessary.[4]

We previously reported a synthetic route through 6 reaction steps to tetraazamacrocyclic compounds (28- to 44- membered rings with alkylene skeletons) using ω-bromoalcohols as starting materials with overall yields of 29–51%.[5] We desribe herein a more convenient method for preparing related macrocycles possessing ether, alkylene and phenylene skeletons. Synthesis were successfully carried out employing diamines **1** and ω-chloroalkyl *p*-toluenesulfonate derivatives **2** as starting materials by a one-pot reaction as shown in the Scheme.



1–4	[A]	Type	[B]	Type
a	$(CH_2)_6$	C6	$(CH_2)_6$	C6
b	$(CH_2)_{10}$	C10	$(CH_2)_{10}$	C10
c	$(CH_2)_2O(CH_2)_2O(CH_2)_2$	E	$(CH_2)_2O(CH_2)_2O(CH_2)_2$	E
d	$(CH_2)_6$	C6	$(CH_2)_2O(CH_2)_2O(CH_2)_2$	E
e		xyl	$(CH_2)_6$	C6
f		diph	$(CH_2)_{10}$	C10

Scheme

A characteristic feature of the present method is the employment of ω-chloroalkyl *p*-toluenesulfonates **2** bearing two different leaving groups to control the reaction. Thus, a substitution reaction on the carbon adjacent to the OTs group can take place via the sodium salt of **1** at 60°C, but more drastic reaction conditions (e.g., > 100°C) are necessary for the Cl group. Starting materials **1** and **2** were easily prepared by tosylation of corresponding diamines or ω-chloroalcohols. In addition, there was no requirement for isolating the intermediate **3** or using a high-dilution technique. Actually, the reactions were carried out without difficulty with a 10 mmol concentration of the starting materials to give tetraazamacrocyclic compounds with reasonable yields.

This method is applicable to various combinations of alkylene, ether and phenylene type chains (as in [A] and [B] in the Scheme) as well as to various ring sizes. Therefore, the tetraazamacrocycles with both the same (e.g., **4a–c**) and mixed (e.g., **4d–f**) chains of [A] and [B] could be obtained without difficulty. These results are summarized in Table 1 together with characteristic physical data. FD-mass spectrum of each product gave a corresponding MH^+ peak, and both elemental analysis and NMR data were satisfactory and reasonable.

Caesium ion showed a positive effect on this cyclization reaction.[6–8] The effect was particularly large using caesium carbonate in the case of **4c** (twice), significantly high for **4f** (xl. 4) and **4b** (xl. 3), and slightly effective (10–20% up) for the others. Lithium carbonate was less reactive toward this substitution reaction even at 120°C (Table 2). The favorable effect of the caesium ion observed on the cyclization is believed due to the increased solubility and reactivity of the anionic reactant,[6] or to the formation of a "triple-ion".[6] The yields seemed to largely depend on the solubility and concentration of the disodium salts used in the first step. The diaza derivatives were also isolated as byproducts and their structures were determined by ^1H NMR and mass spectra.

Detosylation of **4c** (ether type skeleton) into the free tetraamine compound was achieved quantitatively using lithium aluminum hydride in tetrahydrofuran under reflux overnight. Conversion of **4a,b** (alkyl chains) and the phenylene type compounds into the corresponding cyclic tetraamines was achieved earlier.[5] We have also found that this method was applicable to the preparation of the hexaaza derivatives and tetrathioxa macrocycles (e.g., xylene–methylene type) whose structures were confirmed by NMR and mass spectra. Moreover, functional groups can be introduced into the skeletons choosing appropriate protecting groups towards the cyclization and detosylation conditions.

Conclusively, the present reaction can be performed without use of a high-dilution technique in one-pot with comparatively good yields, and can be applied to a variety

Table 1. Synthesis of Tetraaza Rings **4**

Product	Chain Type[a]	Yield (%)	mp (°C)	Molecular Formula[b]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	FAB MS m/z (MH^+)
4a	C6C6	39	168–170	$C_{52}H_{76}N_4O_8S_4$ (1013.5)	1.36 (brs, 16H), 1.40–1.80 (m, 16H), 2.41 (s, 12H), 3.05 (t, 16H, J = 6.8), 7.29 (d, 8H, J = 7.6), 7.67 (d, 8H, J = 7.6)	1013
4b	C10C10	32	67–68.5	$C_{68}H_{108}N_4O_8S_4$ (1237.9)	1.25 (brs, 48H), 1.40–1.80 (m, 16H), 2.40 (s, 12H), 3.07 (t, 16H, J = 7.3), 7.29 (d, 8H, J = 8.4), 7.68 (d, 8H, J = 8.4)	1237
4c	EE	42	oil	$C_{52}H_{76}N_4O_{16}S_4$ (1141.5)	2.41 (s, 12H), 3.35 (t, 16H, J = 5.9), 3.49 (s, 16H), 3.60 (t, 16H, J = 5.9), 7.29 (d, 8H, J = 8.2), 7.69 (d, 8H, J = 8.2)	1141
4d	EC6	30	124–125.5	$C_{52}H_{76}N_4O_{12}S_4$ (1077.5)	1.10–1.40 (br, 8H), 1.40–1.70 (br, 8H), 2.41 (s, 12H), 3.13 (t, 8H, J = 7.3), 3.25 (t, 8H, J = 5.9), 3.52 (s, 8H), 3.59 (t, 8H, J = 5.9), 7.29 (d, 8H, J = 8.2), 7.68 (d, 8H, J = 8.2)	1077
4e	xylC6	32	277–279	$C_{56}H_{68}N_4O_8S_4$ (1053.4)	0.70–0.90 (br, 8H), 0.90–1.20 (br, 8H), 2.46 (s, 12H), 2.91 (t, 8H, J = 7.6), 4.19 (s, 8H), 7.23 (s, 8H), 7.41 (d, 8H, J = 8.2), 7.68 (d, 8H, J = 8.2)	1053
4f	diPhC10	25	217–220	$C_{74}H_{88}N_4O_8S_4$ (1289.8)	1.10–1.50 (br, 32H), 2.42 (s, 12H), 3.46 (t, 8H, J = 6.4), 3.94 (s, 4H), 6.94 (d, 8H, J = 8.4), 7.08 (d, 8H, J = 8.4), 7.24 (d, 8H, J = 8.5), 7.46 (d, 8H, J = 8.5)	1289

[a] See Scheme 1 for the abbreviations.

[b] Satisfactory microanalyses obtained: C ± 0.49, H ± 0.31, N ± 0.17.

Table 2. Synthesis of **4c** Under Various Reaction Conditions

Run	Base	Yield (%) tetraaza	diaza
1	NaH	20	24
2	NaH/Cs_2CO_3	42	28
3	Cs_2CO_3	26	17
4	K_2CO_3	10	33
5	Li_2CO_3	trace	trace

of combinations of skeleton units (backbone chains) such as alkylene, ether and phenylene types. This method is of practical importance for the preparation of large tetraazamacrocycles.

Melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. Flash chromatographic separations were carried out on Merck 230–400 mesh Kieselgel 60 or Wakogel C-300. DMF, CH_2Cl_2, $CHCl_3$, benzene and hexane were distilled from calcium hydride. EtOAc was purified by distillation. Dimethylaminopyridine (DMAP) was recrystallized from benzene/hexane. Other materials were purchased from appropriate sources and used as received. The NMR spectra were determined on a Bruker AC-200 or a Hitachi R-40 spectrometer with TMS as an internal reference. Mass spectra were measured on a JEOL JMS-D300 spectrometer.

Bis-(*p*-toluenesulfonamido) Derivatives (1a–f); General Procedure:
To a solution of the diamine (20 mmol), Et_3N (84 mmol) and DMAP (42 mmol) in dry CH_2Cl_2 (80 mL) was added a solution of TsCl (42 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, and the mixture was stirred for 3 h at r.t. After washing with 3 N HCl, sat. aq $NaHCO_3$ and brine, the mixture was dried ($MgSO_4$) and evaporated to dryness in vacuo. Separation of products was carried out by column chromatography on silica gel eluted with CH_2Cl_2/EtOAc (20:1–50:1), followed by further purification by recrystallization.

ω-Chloroalkyl Tosylate Derivatives (2a–c); General Procedure:
TsCl (55 mmol) in dry CH_2Cl_2 (50 mL) was added to a solution of ω-chloroalcohol (50 mmol), Et_3N (54 mmol) and DMAP (100 mmol) in dry CH_2Cl_2 (250 mL) at 0 °C, and the mixture was stirred for 3 h at r.t. After washing with 1 N HCl, sat. aq $NaHCO_3$ and brine, the organic layer was dried ($MgSO_4$) and evaporated to dryness in vacuo. The residue was purified by column chromatography on silica gel.

1,10,19,28-Tetratosyl-4,7,13,16,22,25,31,34-octaoxa-1,10,19,28-tetraazacyclohexatriacontane (4c); Typical Procedure:
A DMF solution (5 mL) of **1c** (228 mg, 0.5 mmol), **2c** (323 mg, 1.0 mmol), NaH (25 mg, 1.05 mmol) and Cs_2CO_3 (172 mg, 0.55 mmol) was stirred at 60 °C for 3 h under N_2. The resultant suspension was then added to a DMF solution (50 mL) of an additional amount of dianion of **1c** and Cs_2CO_3 (1 equiv), and the mixture was further heated at 120 °C overnight (12 h) with vigorous stirring under N_2. After evaporation of the solvent in vacuo, brine (100 mL) was added to the residue, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). Evaporation of the organic layer gave a colorless viscous oil which was chromatographed on silica gel eluted with benzene/EtOAc (1:2) to afford 0.24 g (42%) of **4c**.

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