A VERSATILE ONE-POT SYNTHESIS OF SYMMETRICAL N-TOSYLAZAMACROCYCLES

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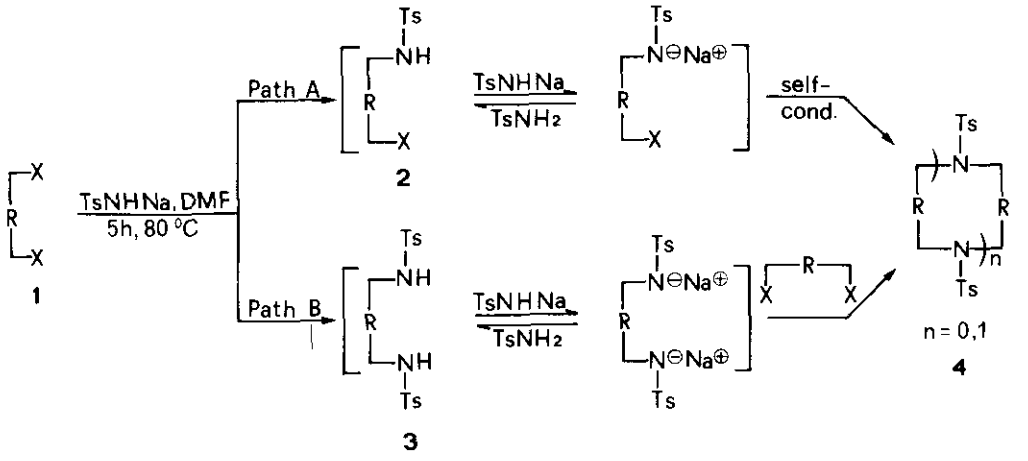
Abstract — A variety of title compounds (azacrown ethers, pyridino-azacrown analogues and azacyclophanes) have been synthesized in moderate to good yield by coupling appropriate bis(halomethyl) or bis(tosylate ester) precursors with tosylamide monosodium salt. A revised mechanism is proposed.

Synthetic azamacrocycles have attracted considerable attention in recent years because of their ability to selectively bind both metal[1] and organic ammonium cations[2], and also because of their possible use as model carriers for selective transport of cations across liquid membranes[3]. Conventional strategies for the preparation of these compounds rely upon the availability of appropriate acyclic mono- or polyamino precursors, which are relatively inaccessible at best and, when commercially available, are often remarkably expensive[4]. Vögtle and co-workers, however, have shown that the base-catalysed reaction of suitable oxaoligomethylene ditosylates or dihalides with mono- and bifunctional tosylamides often leads to the formation of cyclic azacrown ethers[5].

In order to search for a simple, cheap and general route to azamacrocycles, we have re-examined and extended Vögtle s procedure to the synthesis of a variety of N-tosyl-azamacrocycles including azacrown ethers, azacyclophanes and azaheterophanes, and gained further insight into the reaction mechanism. The method, shown in Scheme 1, is based on the one-pot nucleophilic condensation of appropriate bis (halomethyl) or bis(tosylate ester) compounds (1) with two equivalents of tosylamide monosodium salt (TsNHNa) in dimethylformamide (DMF) under moderate dilution. The choice of DMF over other polar solvents is crucial to avoid or minimize side reactions and oligomerization; moreover, the reaction is fast and clean, the isolation of the product(s) being achieved by simply evaporating the solvent followed by crystallization or chromatography. The N-tosyl-azamacrocycles synthesized by this procedure and their physical and spectral properties are listed in Table 1.

The reaction is best envisioned as proceeding through the monoalkylated key-intermediate (2), which quickly undergoes self-condensation (path A) in the presence of excess TsNHNa (as the base) to give the desired 1:1 (n=0) and/or 2:2 (n=1) macrocycles (Scheme 1). Alternatively, 2:2 macrocycles can arise from the N,N'-ditosyl intermediate (3) through path B. Both proposed pathways gain support by



Scheme 1

the isolation of intermediates (2b) and (3b), along with macrocycles (4b) and (4b'), from initial experiments on diiodide (1b) carried out in absolute ethanol, in which the reaction is found to be slower than in DMF[13].

In view of the isolation of the 9-membered macrocycle (4b) (undetected by Vögtle) as the major cyclic product both in DMF and ethanol, the reported[5] inability of the monoalkylated intermediate to cyclizate must be therefore revised. Since Vögtle used 1,2-bis-(2-chloroethoxy)ethane instead of (1b), just to rule out reactivity factors between the reagents used, we repeated the reaction of the dichloride with TsNHNa following strictly the experimental conditions described by Vögtle. In our hands, macrocycle (4b) was obtained in a 32% yield, along with the reported 18-membered macrocycle (4b')(15%).

The following experimental procedure is typical for the one-pot synthesis of symmetrical N-tosyl-azamacrocycles. To a stirred solution of TsNHNa (0.965 g, 5 mmole) in anhydrous DMF (100 ml) at 80 °C was added dropwise under nitrogen a solution of dihalide or ditosylate (1) (5 mmole) in DMF (10 ml). After 1h, one more equivalent of TsNHNa was added in a single portion, and the mixture was kept at 80 °C for an additional 4h. On cooling, N-tosyl-azacyclophanes and azaheterophanes precipitated from the reaction mixture, or crystallized out on distilling off most of the solvent under reduced pressure, and were purified by recrystallization from the stipulated solvents (Table 1). In the case of the more soluble azacrown compounds, concentration of the reaction mixture to dryness gave an oily residue, which was dissolved in chloroform, throughly washed with 1N NaOH, dried (Na_2SO_4) and chromatographed on silica gel (eluent cyclohexane-ethyl acetate 2:1) to afford the desired compound(s).

In conclusion, it has been demonstrated the utility of this method for the synthesis of a wide variety of N-tosyl-azamacrocycles. Noteworthy, the present procedure overcomes the cumbersome preparation and hazardous handling of suitable aryl and heteroaryl diamino precursors, providing an easy approach to azacyclophanes and azaheterophanes. Furthermore, these compounds can be converted, by removal of the tosyl function[11,14], to the corresponding (poly)amino macrocycles, which might provide the matrix for more sophisticated macrocyclic[15] and macropolycyclic[16] host molecules, and for macromolecular systems[17]. Further work on the synthesis and binding properties of polymer-bound pyridino-azacrown compounds is in progress.

Table 1. Physical and critical ^{1}H nmr data of the N-tosyl-azamacrocycles synthesized.

Reagent	n	Compound (4)[a]	Mp, °C (Recr. Solv.)	Yield[b] (%)	Methylene Chem Shift(s)[c]
(1a) 2-Iodoethyl ether	0	(4a) Morpholine	147-148[d] (MeOH)	99	2.99 (t, J=4.8 Hz) 3.74 (t, J=4.8 Hz)
(1b) 1,2-Bis-(2-iodoethoxy) ethane	0	(4b) Aza-9-crown-3[7,8]	98-100 (Et_2O)	25	3.33 (t, J=4.2 Hz) 3.75 (s) 3.91 (t, J=4.2 Hz)
	1	(4b') 1,10-Diaza-18-crown-6[8]	164-166[e] (EtOH)	5	3.41 (d, J=5.5 Hz) 3.55 (s) 3.62 (d, J=5.5 Hz)
(1c) *Tetraethylene glycol* ditosylate	0	(4c) Aza-12-crown-4[7,8]	63-65 (Et_2O)	31	3.33 (t, J=4.9 Hz) 3.64 (t, J=4.8 Hz) 3.82 (t, J=5.3 Hz)
(1d) 2,6-Bis(chloromethyl) pyridine	1	(4d) 2,11-Diaza[3.3](2,6)PP[7,8,10]	247(dec) (Dioxane)	66	4.48 (s)
(1e) 6,6'-Bis(chloromethyl) 2,2'-dipyridine	1	(4e) 2,17-Diaza[3.3](6,6')BPP	>280[f] (DMF)	43	[g]
(1f) α,α'-Dibromo-o-xylene	0	(4f) Dihydroisoindole	178-179[h] (MeOH)	99	4.62 (s)
(1g) α,α'-Dibromo-m-xylene	1	(4g) 2,11-Diaza[3.3]MCP[7,10]	266-268 (Dioxane)	53	4.32 (s)
(1h) α,α'-Dibromo-p-xylene	1	(4h) 2,11-Diaza[3.3]PCP[7]	>280 (Dioxane)	28	4.16 (s)[i]

[a] For brevity, the tosyl protecting groups are omitted in the nomenclature, and the following abbreviations are used: pyridinophane = PP; bipyridinophane = BPP; metacyclophane = MCP; paracyclophane = PCP. [b] Yields are not optimized. [c] Unless otherwise stated, chemical shifts (δ) refer to $CDCl_3$ solutions from internal TMS. [d] Lit.[6] *mp* 147 °C. [e] Lit.[9] *mp* 163.5-164.5 °C. [f] Lit.[11] mp>260 °C. [g] Not recorded due to solubility problems. [h] Lit.[12] mp 176 °C. [i] In Me_2SO-d_6.

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13. In a typical procedure, diiodide (1b) and TsNHNa were refluxed in absolute ethanol for 24 h. Usual work-up, followed by chromatography afforded unreacted (1b) (5%), sizeable amounts of intermediates (2b) [mp 57-59 °C (Et_2O-hexane); ^{1}H nmr ($CDCl_3$) 2.43 (s, $TsCH_3$, 3H), 3.18 (t, αCH_2, J=6.5 Hz, 2H), 3.26 (t, $\alpha'CH_2$, J=6.5 Hz, 2H), 3.47-3.83 (m, $(\beta+\beta'+\gamma+\gamma')CH_2$, 8H), 5.24 (t, NH, J=5 Hz, 1H), 7.31 (d, TsH, J=8.4 Hz, 2H), and 7.77 (d, TsH, J=8.4 Hz, 2H)] and (3b) [mp 56-58 °C (Et_2O); ^{1}H nmr ($CDCl_3$) 2.41 (s, $TsCH_3$, 6H), 3.08-3.24 (m, αCH_2, 4H), 3.51 (m, $(\beta+\gamma)CH_2$, 8H), 5.42 (t,NH, J=6 Hz, 2H), 7.29 (d, TsH, J=8.4 Hz, 4H), and 7.76 (d, TsH, J=8.4 Hz, 4H)], along with macrocycles (4b) (14%) and (4b') (7%).
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