An Improved Synthesis of 1,4,7-Triazacyclononanes (tacns) and 1,4,7,10-Tetraazacyclododecanes (cyclens)

Jianying Huang, Zhongyuan Zhou, Tak Hang Chan*

Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, P. R. of China
Fax +852 23649932; E-mail: bcchanth@polyu.edu.hk

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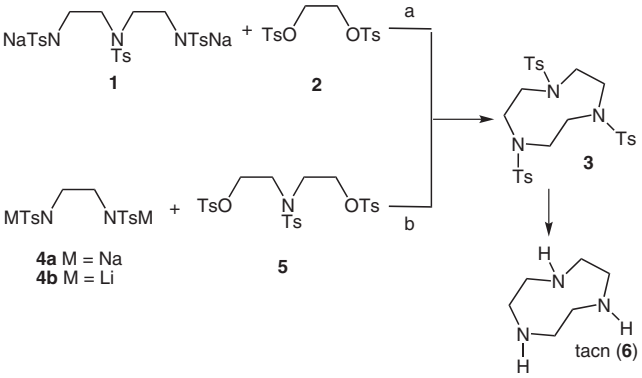
Abstract: Reaction of tosylbis[2-(tosyloxy)ethyl]amine with ethylenediamine gives 1-tosyl-1,4,7-triazacyclononane in good yield. A similar reaction of tosylbis[2-(tosyloxy)ethyl]amine with diethylenetriamine gives 1-tosyl-1,4,7,10-tetraazacyclododecane. These tosylated compounds can be further transformed to give 1,4,7-triazacyclononane (tacn) or 1,4,7,10-tetraazacyclododecane (cyclen) or their derivatives.

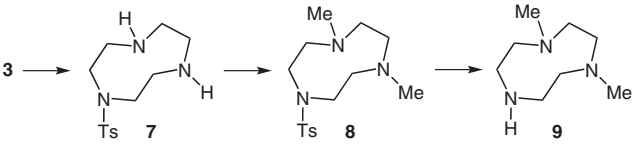
Key words: cyclic amines, cyclizations, detosylation, macrocycles, methylations

1,4,7-Triazacyclononane (tacn, **6**) and 1,4,7,10-tetraazacyclododecane (cyclen, **18**) and their derivatives have been used extensively as ligands in many areas. They chelate with a wide variety of metal cations to form complexes which find applications in catalysis,[1] medical imaging and radiotherapy,[2] metal extraction,[3] and protein purification.[4] Traditionally, tacn (**6**) is synthesized according to the method of Richman and Atkins[5] (Scheme 1, route a). According to this method, the disodium salt of *N*,*N*′,*N*″-tritosyldiethylenetriamine (**1**) is alkylated with ethylene glycol ditosylate (**2**) to give 1,4,7-tritosyl-1,4,7-triazacyclononane (**3**) in 71% yield.[5] Hydrolysis of **3** with concentrated sulfuric acid gives 1,4,7-triazacyclononane (tacn, **6**). An alternative approach, the reaction of the disodium salt of *N*,*N*′-ditosylethylenediamine (**4a**) with tosylbis[2-(tosyloxy)ethyl]amine (**5**) gives only a moderate yield of **3** (Scheme 1, route b).[6] It was postulated that the low yield may be due to steric and/or electronic effects in the first substitution step between **4a** and **5**.[6] More recently, it was found that if the dilithium salt **4b** is used for the reaction with **5**, a high yield of **3** is obtained.[7] This approach has been used to make a number of chiral triazacyclononanes.[7] While these two routes are quite successful in making tacn (**6**), derivatives of tacn bearing different substituents on the three nitrogen atoms require selective removal of the tosyl groups from **3**, followed by N-derivatization.

In connection with another project, we required 1,4-dimethyl-1,4,7-triazacyclononane (**9**), a known compound, which was synthesized from **3** via **8** according to Scheme 2.[8] In our hands, while the route did give **9**, the selective detosylation of **3** to give 1-tosyl-1,4,7-triazacyclonone (**7**) under acidic conditions was difficult to control,[9] giving a mixture of mono- and di-tosyltriazacyclononanes.

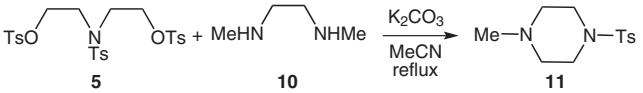


Scheme 1 Synthesis of tacn reported in the literature



Scheme 2 Synthesis of 1,4-dimethyl-1,4,7-triazacyclononane reported in the literature

We therefore looked for a simpler method to synthesize 1,4-dimethyl-1,4,7-triazacyclononane (**9**). First, we examined the reaction of *N*,*N*′-dimethylethylenediamine (**10**) with **5** in refluxing acetonitrile with potassium carbonate as the base (Scheme 3). Compound **11** was obtained in 82% yield, but the desired compound **8** was not obtained. When bis(2-bromoethyl)(tosyl)amine[10] was used instead of **5** in the reaction with **10**, the same product **11** was obtained. Compound **11** was identified as 1-methyl-4-tosylpiperazine[11] on the basis of its spectroscopic properties, and its structure was further confirmed by single-crystal X-ray crystallography (Figure 1).



Scheme 3 Formation of compound **11**

We were therefore pleasantly surprised when the reaction of **5** with ethylenediamine (**12**) under identical conditions gave 1-tosyl-1,4,7-triazacyclononane (**7**) in 78% isolated yield (Scheme 4). There was little evidence of formation

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of a six-membered-ring compound corresponding to **11**. Compound **7** can be readily methylated with formaldehyde/formic acid to give 1,4-dimethyl-7-tosyl-1,4,7-triazacyclononane (**8**) in 82% yield. Hydrolysis of **8** with concentrated sulfuric acid gave 1,4-dimethyl-1,4,7-triazacyclononane (**9**) in 68% yield (Scheme 4).

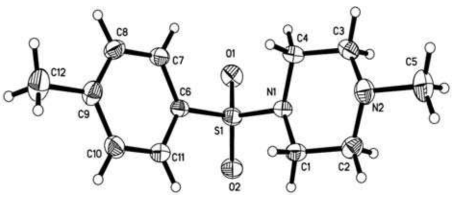
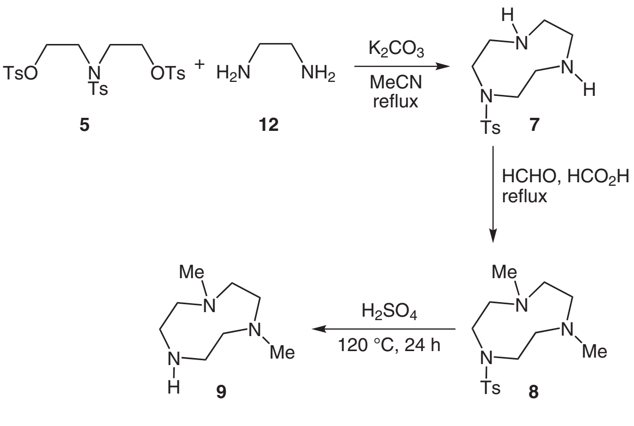
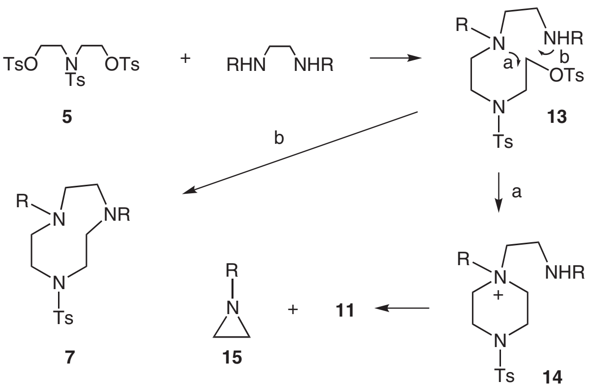


Figure 1 Molecular stereo structure of compound **11**



Scheme 4 A simplified synthesis of 1,4-dimethyl-1,4,7-triazacyclononane (**9**)

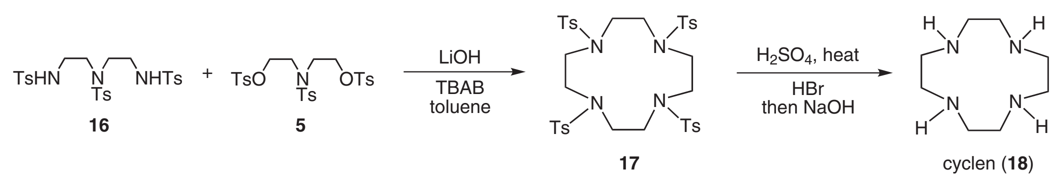


Scheme 5 Explanation of different products

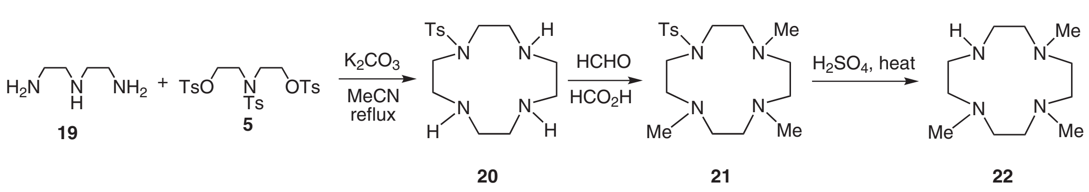
To account for the formation of the different products in the two reactions, we postulate that after the first substitution reaction between **5** and diamine **10** or **12**, intermediate **13** is formed (Scheme 5). In the case of **13** with R = Me, the substitution via path a is favored, giving rise to the piperazine intermediate **14**. The alternative path b will require a *cis*-hydrindane-like transition state with the *N*-methyl and the tosyloxy groups *syn* to each other, thus exerting an unfavorable steric interaction. Fragmentation of **14** gives compound **11** and *N*-methylaziridine (**15**, R = Me), which is volatile and presumably lost from the reaction mixture (Scheme 5). On the other hand, in the case of **13** with R = H, the substitution via path b, with less steric interaction between the N–H and the tosyloxy groups, is now competitive with path a, thus leading to compound **7**. The facile preparation of **7** from **5** and **12** allows for an improved synthesis of tacn (**6**) (from the hydrolysis of **7**), as fewer tosyl groups are required for the protection and deprotection steps. It is also convenient for the synthesis of various N-substituted derivatives, as exemplified by the preparation of 1,4-dimethyl-1,4,7-triazacyclononane (**9**) in Scheme 4.

1,4,7,10-Tetraazacyclododecane (cyclen, **18**) is now commercially available. Its synthesis was first reported by Stetter and Mayer in 1961.[12] The most efficient synthesis of cyclen (**18**) reported so far is a modified Richman–Atkins process,[5a] as shown in Scheme 6.[13] *N*,*N*′,*N*″-Tritosyldiethylenetriamine (**16**) is coupled with **5** in the presence of lithium hydroxide and a phase-transfer catalyst, leading to tetratosylcyclen **17**.[13a] Hydrolysis of **17** with concentrated sulfuric acid at 165 °C in a two-step procedure gives cyclen (**18**).[13b] The starting material *N*,*N*′,*N*″-tritosyldiethylenetriamine (**16**) is prepared by the tosylation of diethylenetriamine (**19**).[13b]

In view of the successful cyclization of ethylenediamine (**12**) with **5** (Scheme 4), we also examined the reaction of diethylenetriamine (**19**). To our delight, the same coupling of **5** with diethylenetriamine (**19**) in the presence of potassium carbonate under reflux in acetonitrile took



Scheme 6 Synthesis of cyclen reported in the literature



Scheme 7 An improved synthesis of 1,4,7-trimethylcyclen (**22**)

place to give 1-tosyl-1,4,7,10-tetraazacyclododecane (**20**) in 83% yield (Scheme 7).[14] Methylation of **20** with formaldehyde/formic acid gave 1,4,7-trimethyl-10-tosyl-1,4,7,10-tetraazacyclododecane (**21**) in 68% yield. Hydrolysis of **21** with concentrated sulfuric acid at 120 °C gave 1,4,7-trimethyl-1,4,7,10-tetraazacyclododecane (**22**) in 60% yield.[14] The use of **19** instead of **16** as the precursor for the construction of the cyclen macrocycle represents an improvement over the existing approach by reducing the need for tosylation and subsequent detosylation.

In conclusion, we have found that ethylenediamine (**12**) and diethylenetriamine (**19**) can react with **5**, without the need for high dilution conditions, to give the corresponding polyazamonocycles. This provides an improved synthesis of tacn and cyclen and their derivatives.

Chemicals were purchased from commercial suppliers and were used without further purification unless noted otherwise. Solvents were distilled under an anhyd N_2 atmosphere with appropriate drying agents (solvent/drying agent): MeCN/CaH_2, CH_2Cl_2/CaH_2. TLC was performed on silica gel plates. Silica gel (Merck, 230–400 mesh) was used for flash column chromatography unless noted otherwise. NMR spectra were obtained on a Bruker DPX 400 spectrometer. Chemical shifts are reported relative to residual protons of the deuterated solvents. MS and HRMS were carried out on a VG MICROMASS, Fison VG platform, Finnigan Model Mat 95 ST instrument. Melting points were measured on a BUCHI Melting Point B-545 machine. Crystals were obtained from EtOAc–hexane (1:5). The X-ray crystal structure of **11** was determined on a Bruker CCD area detector diffractometer.

Tosylbis[2-(tosyloxy)ethyl]amine (5)[13b]

Diethanolamine (27.5 g, 0.262 mol) was dissolved in distilled CH_2Cl_2 (500 mL) in a three-necked flask. The soln was cooled to 0 °C under a stream of anhyd N_2, and Et_3N (122 mL, 88.6 g, 0.880 mol) was added. With the temperature maintained at 0 °C, solid TsCl (157 g, 0.823 mol) was added in portions to the vigorously stirred reaction mixture over 5 h. The reaction mixture was then stirred at r.t. overnight. The $Et_3N{\cdot}HCl$ that had formed was removed by filtration, and the resulting pale yellow filtrate was washed with 1 M aq HCl (3 × 100 mL), followed by H_2O (5 × 200 mL) and sat. aq $NaHCO_3$ (5 × 200 mL). The organic layer was dried ($MgSO_4$). The solvent was removed by rotary evaporation and the residue was recrystallized (EtOH); this gave a white product.

Yield: 120 g (80%); mp 98–99 °C (Lit.[13b] 97–99 °C).

1-Methyl-4-tosylpiperazine (11)[11]

Compound **5** (5.83 g, 10 mmol), K_2CO_3 (8.00 g, 58.0 mmol), diamine **10** (0.088 g, 10.0 mmol), and anhyd MeCN (50 mL) were added to a round-bottom flask. The mixture was heated to reflux under a N_2 atmosphere for 12 h, after which it was cooled to r.t. and filtered. The filtrate was evaporated and the residue was purified by flash column chromatography (silica gel, hexane–EtOAc, 2:1); this gave a white solid.

Yield: 2.0 g (82%); mp 102–103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 2.99 (s, 4 H), 2.44 (t, *J* = 4.6 Hz, 4 H), 2.39 (s, 3 H), 2.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 132.2, 129.5, 127.8, 54.0, 45.89, 45.64, 21.4.

X-ray crystal data: CCDC 722652 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1-Tosyl-1,4,7-triazacyclononane (7)[8]

Compound **5** (5.83 g, 10.0 mmol), K_2CO_3 (8.00 g, 58.0 mmol), ethylenediamine (**12**; 0.060 g, 10.0 mmol), and anhyd MeCN (50 mL) were added to a round-bottom flask. The mixture was heated to reflux under a N_2 atmosphere for 12 h, and then cooled to r.t. and filtered. The filtrate was concentrated and the residue was purified by flash column chromatography (silica gel, CH_2Cl_2–MeOH–Et_3N, 2:1:0.05); this gave **7** as pale yellow oil.

Yield: 2.0 g (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.4 Hz, 2 H), 7.24 (d, *J* = 7.4 Hz, 2 H), 3.12–3.00 (m, 4 H), 2.97–2.96 (m, 4 H), 2.80 (s, 4 H), 2.46 (s, 2 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 135.3, 129.6, 127.1, 53.7, 49.32, 49.23, 21.4.

1,4-Dimethyl-7-tosyl-1,4,7-triazacyclononane (8)[8a]

Compound **7** (1.30 g, 4.70 mmol) was mixed with H_2O (1.0 g) and 37% formaldehyde (3.0 mL). The mixture was cooled with an ice bath, and 98% formic acid (3.0 mL) was carefully added. After stirring for 1 h, the red-brown soln was refluxed for a further 20 h. After the mixture had cooled to r.t., 30% aq HCl (2 mL) was added, and the volatiles were evaporated. The resulting brown oil was dissolved in H_2O (3 mL), and 2 M aq NaOH (5 mL) was added, upon which a white solid precipitated. (The pH of the mother liquor was 10.) The mother liquor was filtered and the solid was washed with 2 M aq NaOH (2 × 2 mL) and H_2O (3 × 3 mL). The solid was then dried overnight.

Yield: 1.2 g (82%); mp 113–114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.7 Hz, 2 H), 7.24 (d, *J* = 7.7 Hz, 2 H), 3.39–3.12 (m, 4 H), 2.86–2.84 (m, 4 H), 2.64 (s, 4 H), 2.36 (s, 3 H), 2.34 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 135.8, 129.6, 127.0, 57.3, 56.9, 51.2, 46.1, 21.4.

ESI-MS: *m*/*z* = 334 $[M + Na]^+$.

1,4-Dimethyl-1,4,7-triazacyclononane (9)[8a]

Compound **8** (1.19 g, 3.82 mmol) was carefully added to concd aq H_2SO_4 (5 mL); this yielded a dark brown soln which was stirred for 24 h at 120 °C under a N_2 atmosphere. After cooling, the mixture was poured onto crushed ice (5 g), and aq NaOH was added until the pH of the mixture exceeded 10. The brown aqueous layer was extracted with $CHCl_3$ (4 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (alumina; MeOH–CH_2Cl_2, 1:50); this gave a brown oil.

Yield: 0.41 g (68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.45 (s, 1 H), 3.10–3.04 (m, 4 H), 2.72–2.60 (m, 4 H), 2.51 (s, 4 H), 2.20 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.1, 48.6, 43.8, 43.4.

ESI-MS: *m*/*z* = 158 $[M + H]^+$.

HRMS (**??**): *m*/*z* calcd for $C_8H_{20}N_3$: 158.1657; found: 158.1683.

1-Tosyl-1,4,7,10-tetraazacyclododecane (20)

Diethylenetriamine (**19**, 0.400 g, 4.00 mmol), compound **5** (2.30 g, 4.00 mmol), K_2CO_3 (6.00 g, 40.0 mmol), and anhyd MeCN (20 mL) were added to a round-bottom flask. The mixture was heated to reflux under a N_2 atmosphere for 18 h, after which the mixture was cooled to r.t. and filtered. The filtrate was concentrated and the res-

idue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 2:1); this gave a pale yellow oil.

Yield: 1.2 g (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 8.1 Hz, 2 H), 2.91 (m, 4 H), 2.64 (m, 2 H), 2.54 (m, 4 H), 2.41 (m, 6 H), 2.33 (s, 3 H), 2.30 (s, 3 H).

ESI-MS: *m*/*z* = 327 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{27}N_4O_2S$: 327.1855; found: 327.1870.

1,4,7-Trimethyl-10-tosyl-1,4,7,10-tetraazacyclododecane (21)

Compound **20** (5.70 g, 18.0 mmol) followed by a 37% aq formaldehyde soln (25.0 mL) were added to a 50-mL round-bottom flask. The mixture was cooled with an ice bath and formic acid (25.0 mL) was carefully added dropwise. After stirring for 0.5 h, the red-brown soln was refluxed for 20 h. After the mixture had cooled to r.t., 37% aq HCl (3 mL) was added and the volatiles were removed by evaporation. The resulting brown oil was dissolved in H_2O (5 mL), and aq NaOH (2 M; 35 mL) was added, whereupon a white solid precipitated. (The pH of the mother liquor was 10.) The soln was extracted with $CHCl_3$ (4 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, hexane–EtOAc, 1:1); this gave a pale yellow syrupy compound.

Yield: 4.50 g (68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.1 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 2.92 (s, 4 H), 2.51–2.26 (m, 15 H), 2.13–2.11 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5, 132.1, 129.5, 127.8, 57.1, 55.8, 55.7, 55.2, 52.5, 45.9, 45.7, 42.8, 21.4.

ESI-MS: *m*/*z* = 369 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{33}N_4O_2S$: 369.2324; found: 369.2330.

1,4,7-Trimethyl-1,4,7,10-tetraazacyclododecane (22)

Concd aq H_2SO_4 (4 mL) was carefully added to compound **21** (1.0 g, 2.7 mmol) to yield a dark brown soln which was stirred for 24 h at 120 °C under a N_2 atmosphere. After cooling, the mixture was poured onto crushed ice (5 g) and aq NaOH was added until the pH of the mixture exceeded 10. The brown aqueous layer was extracted with $CHCl_3$ (4 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated; this gave a yellow oil.

Yield: 0.35 g (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (t, *J* = 4.8 Hz, 4 H), 2.10–1.92 (m, 12 H), 1.82 (s, 3 H), 1.79 (s, 6 H), 1.60 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.0, 56.7, 55.6, 54.8, 54.6, 45.6, 45.5, 42.6.

ESI-MS: *m*/*z* = 215 [M + H].

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{27}N_4$: 215.2236; found: 215.2230.

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