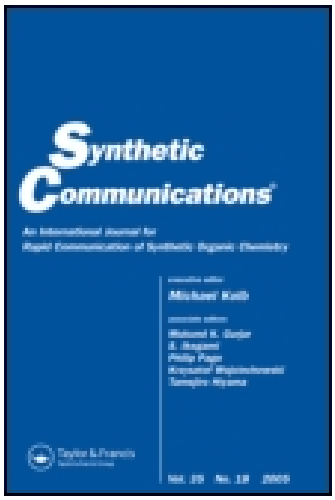

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 21 Aug 2006.

To cite this article: Hyun-soon Chong & Martin W. Brechbiel (2003) A Short and Efficient Synthesis of Mono-substituted 1,4,7-Triazacyclononanes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:7, 1147-1154, DOI: 10.1081/SCC-120017190

To link to this article: http://dx.doi.org/10.1081/SCC-120017190

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 7, pp. 1147–1154, 2003

A Short and Efficient Synthesis of Mono-substituted 1,4,7-Triazacyclononanes

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ABSTRACT

A convenient synthesis of 1,4,7-Triazacyclononane (tacn) derivatives substituted with a single pendant donor group is described. Mono-substituted tacns with a hydroxylalkyl, an aminoalkyl, or a benzyl group are synthesized via efficient cyclization of inexpensive starting materials followed by detosylation.

Key Words: Triazacyclononane; Pendant substituted macrocycle; Mono-substituted tacn.

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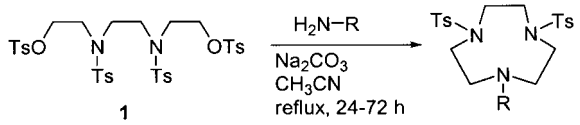
DOI: 10.1081/SCC-120017190 0039-7911 (Print); 1532-2432 (Online)

1,4,7-triazacyclononane (tacn) derivatives substituted with a variety of donor groups are known to form stable complexes with transition and lanthanide metals.[1] The resulting metal complexes have been explored for use in biomimetic studies,[2] biomedical applications,[3] DNA cleavage,[4] and as catalysts for oxidative cleavage.[5] Currently, there is a significant interest in the synthesis of mono-substituted tacn derivatives as either intermediates or as target molecules for diverse areas of research.[6] In our continuing efforts to develop potential novel chelators for radioimmunotherapy applications with Yttrium or lanthanides isotopes,[7] we required an efficient entry to mono-substituted tacn derivatives bearing either an amino or a hydroxyl donor group that was also amenable to being performed on a reasonably large scale.

Although a few synthetic routes to mono-substituted tacns bearing a pendant hydroxyl group are reported,[8,9] there seems to be no straightforward general synthetic route available. Moreover, there also seems to be no example of a simple synthesis of pendant amino-armed tacns. One of the synthetic routes to mono-substituted tacns involves the reaction of di-Boc protected tacn[10] with suitable alkylating agents followed by deprotection of the secondary ring amines.[11] However, unless a very reactive alkylating agent is used, alkylation of di-protected tacn is known to result in low yields due to the presence of the bulky Boc groups in the macrocyclic intermediate.[8,11] The orthoamide derivative 1,4,7-triazatricyclo[5.2.1.0.][4,10] decane derived from tacn also has been employed as a key intermediate for the mono-substituted tacn synthesis. Recently, Pyke and co-workers have published a general method for the preparation of hydroxylalkyl-armed tacn from the orthoamide, which consisted of multiple steps including the use of ethylene oxides as alkylating agents and inconvenient chromatographic purification.[8]

In this paper, we present a convenient synthetic route to mono-substituted tacn derivatives bearing a hydroxylalkyl, an aminoalkyl, or a benzyl group. To the best of our knowledge, this synthetic procedure for mono-substituted tacns is the first example that occurs via direct cyclization of readily available starting materials rather than starting with tacn, which is an expensive reagent, and to date has exclusively been used as a starting point for the preparation of mono-substituted tacns.

This direct cyclization route employs primary amines bearing a variety of substitution that then provide pendant arms as starting materials which are reacted with an *N,N′*-ditosyl protected ditosylate ester to provide the desired 1,4,7-triazacyclononane macrocyclic ring (Sch. 1). Thus, reaction of readily available ditosylate **1**[12] with primary amines in the presence of Na_2CO_3 in acetonitrile afforded the *N,N′*-ditosyl-protected macrocycles **2a–g** in high yield (81–92%). The reactions of **1** with a



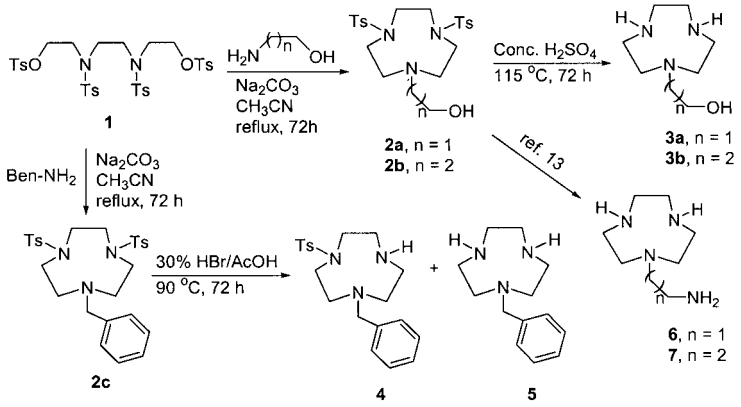
Scheme 1. **2a.** R = CH_2CH_2OH; **2b.** R = $CH_2CH_2CH_2OH$; **2c.** R = Ben; **2d.** R = $CH_2CH_2CO_2t$Bu **2e.** R = $CH_2CHOHCH_2OH$; **2f.** R = $CH_2CHOHCH_3$ **2g.** R = $CH(CH_2OH)_2$

Table 1. Reactions of **1** with R-NH_2.

Entry	R	Product	Yield (%)
1	CH_2CH_2OH	**2a**	86
2	$CH_2CH_2CH_2OH$	**2b**	92
3	Ben	**2c**	82
4	$CH_3CH_2CO_2t$-Bu	**2d**	84
5	$CH_2CHOHCH_2OH$	**2e**	86
6	$CH_2CHOHCH_3$	**2f**	91
7	$CH(CH_2OH)_2$	**2g**	81

variety of primary amines are summarized in Table 1. This cyclization method is convenient, clean, and a high yield route using highly cost effective starting materials. This strategy can be applied to the construction of a wide range of macrocyclic rings by using modified primary amines.

The desired mono-substituted tacns having a hydroxylalkyl pendant arm (**3a** and **3b**) were obtained from deprotection of the tosyl groups in compound **2a**[13] and **2b**[13] (Sch. 2). Thus, deprotection was effected with concentrated sulfuric acid at 115°C for 72 h. Tacn derivatives **3a** and **3b** were obtained in high yield (>90%) without any further purification procedures. The overall yields for synthesis of **3a** and **3b** were 89% and 94%, respectively. Tacn derivatives bearing an aminoalkyl group (**6** and **7**) were prepared in high yield after conversion of the hydroxyl group in **2a** and **2b** to an amino group and subsequent detosylation.[13] Deprotection of the tosyl groups in **2c** was attempted under the same conditions used for the preparation of **3a** and **3b** to generate the mono-benzyl tacn. However, treatment of **2c** with sulfuric acid failed to afford **5**. Acid hydrolysis of tosyl groups in **2c** with a hydrobromic acid/acetic acid mixture in the presence of phenol was attempted at lower temperature (90°C). This reaction provided a mixture of



Scheme 2.

compounds **4** and **5** as a 3:1 ratio, which were separated by column chromatography (see Experimental section). While not entirely as successful in providing a single chromatography free route to the desired **5**, the ability to access **4** as a potential intermediate for further dervatization of tacn seems an attractive side benefit.

In summary, mono-substituted tacn derivatives with an amino, a hydroxyl, or a benzyl pendant group were prepared via an efficient direct cyclization procedure using inexpensive starting materials followed by detosylation. This synthetic procedure allows for a cost-efficient and high yield production of mono-substituted tacns in a large scale that may be employed for a variety of applications via further modification.

EXPERIMENTAL

Melting points were recorded on a Thomas Hoover capillary melting point apparatus and were uncorrected. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Fast atom bombardment (FAB-MS) mass spectra were obtained on an Extrel 4000 in the positive ion detection mode.

General Procedure For Reaction of 1 With Amines (2c–2g)

To a mixture of primary amines (10 mmol) and Na_2CO_3 (10.6 g, 100 mmol) in CH_3CN (300 mL) was added 1[12] (7.65 g, 10 mmol) and

the resulting mixture was refluxed for 72 h. The reaction mixture was allowed to cool to ambient temperature and filtered, and washed with CH_2Cl_2 (100 mL) and the filtrate was concentrated in vacuo.

1-benzyl-4,7-*bis*-(toluene-4-sulfonyl)-[1,4,7]triazonane (2c). The crude product was purified via column chromatography on silica gel by eluting with 25% EtOAc-hexane. Pure **2c** (4.31 g, 82%) was thereby obtained as a colorless micro-crystalline solid: M.p. 144°C; ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 6 H), 3.11 (t, 4 H), 3.24 (t, 4 H), 3.85 (s, 4 H), 7.23 – 7.49 (m, 9 H), 7.76 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 51.3 (t), 52.2 (t), 54.5 (t), 61.1 (t), 126.8 (d), 126.9 (d), 128.1 (d), 128.9 (d), 129.6 (d), 135.2 (s), 139.2 (s), 143.2 (s); Anal. Calcd. for $C_{27}H_{33}N_3S_2O_4$: C, 61.46; H, 6.30; Found: C, 61.13; H, 6.56.

1-(3-*tert*-butoxycarboethyl)-(4,7-*bis*-(toluene-4-sulfonyl)-[1,4,7]triazonane (2d). The crude product was purified via column chromatography on silica gel by eluting with 25% EtOAc-hexane. Pure **2d** (4.70 g, 84%) was thereby obtained as a colorless micro-crystalline solid: M.p. 147–148°C; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.47 (s, 6 H), 2.88–2.95 (m, 4 H), 3.23 (t, 4 H), 3.54 (s, 4 H), 7.36 (d, $J_{AB} = 8.0$ Hz, 4 H), 7.72 (d, $J_{AB} = 8.0$ Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.2 (q), 27.8 (q), 34.0 (t), 50.8 (t), 52.1 (t), 52.5 (t), 55.7 (t), 80.1 (s), 127.0 (d), 129.5 (d), 135.0 (s), 143.2 (s), 171.8 (s); Anal. Calcd. for $C_{27}H_{39}N_3S_2O_6$: C, 57.32; H, 6.95; N, 7.43; Found: C, 57.19; H, 6.98; N, 7.20; MS (positive ion FAB) m/z 566 $[M_r + H]^+$.

1-[(2R)-2,3-Dihydroxypropyl]-4,7-*bis*-(toluene-4-sulfonyl)-[1,4,7]triazonane (2e). The crude product was purified via column chromatography on silica gel by eluting with EtOAc. Pure **2e** (4.4 g, 86%) was thereby obtained as a colorless micro-crystalline solid: M.p. 116°C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 6 H), 2.64–2.90 (m, 4 H), 3.10–3.57 (m, 8 H), 3.78–3.85(m, 4 H), 7.39 (d, $J_{AB} = 7.7$ Hz, 4 H), 7.73 (d, $J_{AB} = 7.7$ Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.4 (q), 52.6 (t), 53.0 (t), 55.3 (t), 60.7 (t), 64.2 (t), 68.6 (d), 127.0 (d), 129.7 (d), 135.0 (s), 143.6 (s); Anal. Calcd. for $C_{27}H_{33}N_3S_2O_4$: C, 53.99; H, 6.50; Found: C, 52.06; H, 6.19.

1-[(2s)-2-Hydroxypropyl)]-4,7-*bis*-(toluene-4-sulfonyl)-[1,4,7]triazonane (2f). The crude product was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Pure **2f** (4.65 g, 91%) was thereby obtained as a colorless micro-crystalline solid: M.p. 102–103°C; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 6 H), 3.05 (d, 2 H), 3.13 (t, 4 H), 3.10–3.89 (m, 4 H), 7.42 (d, $J_{AB} = 8.4$ Hz, 4 H), 7.76 (d, $J_{AB} = 8.4$ Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.8 (q), 21.4 (q), 52.8 (t), 53.0 (t), 55.3 (t), 63.8 (d), 66.9 (t), 127.1 (d), 129.8 (d), 135.0 (s), 143.6 (s); Anal. Calcd. for $C_{23}H_{33}N_3S_2O_5(H_2O)_{0.5}$: C, 54.74; H, 6.84; N, 8.33; Found: C, 55.07; H, 6.79; N, 7.76; MS (positive ion FAB) m/z 496 $[M_r + H]^+$.

1-[(2R)-1,3-Dihydroxy-*iso*-propyl]-4,7-*bis*-(toluene-4-sulfonyl)-[1,4,7] triazonane (2g). The crude product was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Pure **2g** (4.14 g, 81%) was thereby obtained as a colorless micro-crystalline solid: M.p. 133°C; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 1H), 2.51 (s, 6 H), 2.89–3.89 (m, 8 H), 7.42 (d, $J_{AB} = 8.0$ Hz, 4 H), 7.76 (d, $J_{AB} = 8.0$ Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.4 (q), 51.8 (t), 53.0 (t), 53.3 (t), 60.4 (t), 66.2 (d), 127.1 (d), 129.8 (d), 134.7 (s), 143.6 (s); Anal. Calcd. for $C_{27}H_{33}N_3S_2O_4$: C, 54.84; H, 6.71; Found: C, 54.01; H, 6.92.

General Procedure for Detosylation

Compound **2a** or **2b** (1 mmol) was dissolved in concentrated H_2SO_4 (5 mL) and heated to 115°C for 72 h under argon. The resulting solution was cooled to ambient temperature and added in portions to Et_2O (150 mL) at −60°C. The resulting precipitate was collected, washed with Et_2O (20 mL), and immediately dissolved in H_2O (25 mL). The aqueous solution was extracted with Et_2O (10 mL), concentrated to 5 mL, and neutralized with 50% NaOH. The resulting mixture was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo to afford **3a** or **3b**.

2-[1,4,7]Triazonan-1-yl-ethanol (3a). Pure **3a** (158 mg, 91%) was thereby obtained as a colorless viscous oil. Melting point of **3a** as an HCl salt was obtained: M.p. 209–211°C; ^{1}H NMR ($CDCl_3$) δ 2.79–2.83 (m, 4 H), 2.92–3.03 (m, 10 H), 4.06 (t, 2 H), 4.88 (s, 1 H); ^{13}C NMR ($CDOD_3$) δ 44.74 (t), 45.92 (t), 51.86 (t), 56.74 (t), 67.65 (t); HRMS (positive ion FAB) Calcd. for $C_9H_{19}N_3O$: $[M+H]^+$ m/z 174.1606; Found: $[M+H]^+$ m/z 174.1604. The ^{1}H NMR, ^{13}C NMR, Mass spectra of the material thereby obtained is essentially identical with the corresponding spectral data that has been reported previously for authentic **3a**.[9]

(3-[1,4,7]Triazonan-1-yl-propan-1-ol (3b). Pure **3b** (179 mg, 96%) was thereby obtained as a colorless viscous oil. Melting point of **3b** as an HCl salt was obtained: M.p. 245–248°C; ^{1}H NMR ($CDCl_3$) δ 1.50–1.56 (m, 2 H), 2.32–2.64 (m, 14 H), 3.84 (t, 2 H), 4.35 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.40 (t), 43.99 (t), 45.02 (t), 50.53 (t), 53.43 (t), 66.43 (t); HRMS (positive ion FAB) Calcd. for $C_{10}H_{21}N_3O$: $[M+H]^+$ m/z 189.1140; Found: $[M+H]^+$ m/z 189.1134.

Deprotection of tosyl groups in 2c. 1-benzyl-4-(toluene-4-sulfonyl)-[1,4,7]triazonane (4) and 1-benzyl-[1,4,7]triazonane (5). A mixture of **2c** (1.85 g, 3.52 mmol) and phenol (2.47 g) was dissolved into 30% HBr in

AcOH (30 mL) and was heated to 90°C for 72 h under argon. The resulting solution was cooled to ambient temperature and added in portions to Et_2O (150 mL) at −60°C. The resulting precipitate was collected, washed with Et_2O (20 mL), and immediately dissolved in H_2O (25 mL). The aqueous solution was extracted with Et_2O (10 mL), concentrated to 5 mL, and neutralized with 50% NaOH. The resulting mixture was extracted with $CHCl_3$ (3×50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The crude product was purified via column chromatography on neutral alumina by eluting with 10% MeOH–CH_2Cl_2. Pure **4** (830 mg, 63%) was thereby obtained as a colorless oil. Melting point of **4** as an HCl salt was obtained: M.p. 186–188°C; ^{1}H NMR ($CDCl_3$) δ 2.84–3.04 (m, 6 H), 3.17–3.35 (m, 6 H), 3.79 (s, 2 H), 7.22–7.44 (m, 5 H), 7.76 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 47.5 (t), 49.0 (t), 51.6 (t), 51.8 (t), 54.0 (t), 55.5 (t), 61.6 (t), 126.9 (d), 127.0 (d), 128.2 (d), 128.9 (d), 129.5 (d), 135.4 (s), 139.3 (s), 143.1 (s); HRMS (positive ion FAB) Calcd. for $C_{10}H_{21}N_3O$: $[M+H]^+$ m/z 374.1902; Found: $[M+H]^+$ m/z 374.1885.

Further elution with 20% NH_4OH-MeOH afforded **5** (250 mg, 33%) as a colorless oil. Melting point of **5** as an HCl salt was obtained: M.p. 134–137°C; ^{1}H NMR ($CDCl_3$) δ 2.46–2.59 (m, 12 H), 3.53 (s, 2 H), 7.32–7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 46.06 (2t), 52.3 (t), 61.5 (t), 127.1 (d), 128.3 (d), 128.9 (d), 139.3 (s); MS (positive ion FAB) m/z 220 $[M_r+H]^+$. The ^{1}H NMR, ^{13}C NMR, and mass spectra of the obtained oil are essentially identical with the corresponding spectral data that has been reported previously for authentic **5**.

ACKNOWLEDGMENT

We thank the structural Mass Spectra Group (Dr. L. Pannell, NIDDK, Bethesda, MD) for obtaining the mass spectra of compounds.

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Received in the USA May 15, 2002