N,N',N''-Tris(methoxymethyl)-1,4,7-triazacyclononane: a New Synthetic Tool for the Synthesis of Tris-*N*-substituted 1,4,7-Triazacyclononane Derivatives

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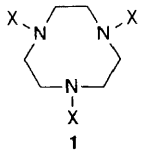
The synthesis of *N,N',N''*-tris(methoxymethyl)-1,4,7-triazacyclononane (NOTMOM, **2**) is described as a useful synthetic intermediate for the preparation of a series of new dialkoxyphosphorylmethyl, ethoxy(ethyl)phosphonyl methyl and 1-imidazolylmethyl group containing *N,N',N''*-trisubstituted triazacyclononanes **3–8**.

Recent interest in derivatives of triaza-macrocycles as efficient chelators,[1,2] magnetic resonance contrast enhancement agents,[3] metal ion selective probes for ^{31}P NMR spectroscopy,[4] or tumour imaging and radiotherapeutic agents[5,6] has led to the synthesis of a variety of new derivatives of 1,4,7-triazacyclononane **1**. Fields[7] has shown that *N*-diethylaminomethyl and *N*-methoxymethyl derivatives of secondary amines react readily with dialkyl phosphites giving virtually quantitative yields, and Bogatsky and coworkers[8] showed that *N*-methoxymethyl derivatives of polyoxaaza and polyoxadiaza macrocycles also react with acidic hydrogen containing compounds, especially with heterocyclic amine or carboxamido N–H groups.

Our first attempts to synthesize the tris-*N,N',N''*-methoxymethyl derivative of **1** using either paraformaldehyde in methanol, or chloromethyl methyl ether† in diethyl ether, chloroform or tetrahydrofuran (THF) in the presence of diisopropylethylamine or dry potassium carbonate all failed. The ^1H NMR spectra of these reaction mixtures indicated that methoxymethyl groups were present, but their integral ratio was very low compared to other unidentified resonances. For those reactions carried out in methanol, there was some evidence for the formation of *N*-methoxymethyl groups followed by their reaction with the remaining amino groups to form cross-linked products. In an attempt to suppress this side reaction, we first used different amounts of sodium methoxide in methanol to react with all available N–H groups. Sodium methoxide did significantly catalyse the reaction between **1**, methanol and paraformaldehyde, but the resulting product was still a crude mixture. We later observed that the amide of **1** could be prepared *in situ* by reaction with sodium metal in THF. After filtering off residual sodium, this was allowed to react with chloromethyl methyl ether in anhydrous THF in the



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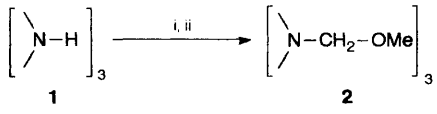
† **Caution:** Chloromethyl methyl ether is an OSHA regulated carcinogen. It is highly toxic and mutagenic. Handle with care.

Table 1 Data for the newly synthesized 1,4,7-triazacyclononane derivatives

		Yield (%)	NMR data (δ)
2	$-CH_2-OMe$	44	4.13 (s, 6H, $-OCH_2$) 3.26 (s, 9H,–OMe), 2.91 (s, 12H, $N-CH_2$)
3	$-CH_2P(O)(OMe)_2$	98[a]	3.76 (d, 18H, OMe), 3.03 (d, 6H, $P-CH_2$), 2.95 (s, 12H, $N-CH_2$)
4	$-CH_2P(O)(OEt)_2$	98[a]	4.13 (p, 12H, OCH_2), 3.00 (d, 6H, $N-CH_2-P$, 2.97 (s, 12H, $N-CH_2$), 1.33 (t, 18H,–Me)
5	$-CH_2P(O)(OPr)_2$	97[a]	4.02 (t, 12H, $O-CH_2$), 3.01 (d, 6H, $P-CH_2$), 2.97 (s, 12H, $N-CH_2$), 1.69 (sx, 12H, $C-CH_2-C$), 0.96 (t, 18H,–Me)
6	$-CH_2P(O)(OBu)_2$	99[a]	4.05 (q, 12H, $O-CH_2$), 3.03 (d, 6H, $P-CH_2$), 2.99 (s, 12H, $N-CH_2$), 1.65 (p, 12H, $O-C-CH_2$), 1.40 (sx, 12H, $C-CH_2-C$), 0.94 (t, 18H,–Me)
7	$-CH_2P(O)(Et)OEt$	94[a]	4.07 (p, 6H, $O-CH_2$), 2.97 (s, 12H, $N-CH_2$), 2.89 (d, 6H, $N-CH_2P$), 1.83 (sx, 6H, $P-CH_2$), 1.31 (t, 9H, O–C–Me), 1.16 (m, 9H, P–C–Me)
8	$1\text{-}N_2C_2H_2CH_2$	88[a]	7.52 (s, 3H, C-2 H-), 7.08 (s, 3H, C-4 H-), 6.97 (s, 3H, C-5 H-), 4.76 (s, 6H, $N-CH_2-N$), 2.80 (s, 12H, $N-CH_2$)

[a] Yields for the step represented in Scheme 2.



1 2

Scheme 1. *Reagents and conditions*: i, Na–THF, reflux 1–1.5 h; ii, $ClCH_2OMe$–Pr^i_2EtN–THF, 0 °C

presence of diisopropylethylamine at 0 °C (Scheme 1). After filtration, the supernatant was evaporated and the residue was extracted into dry pentane. Evaporation of the solvent yielded pure NOTMOM **2** as a colourless to pale-yellow liquid. NOTMOM is sensitive to water and other protic materials.

NOTMOM proved to be quite useful for the synthesis of a variety of tris-*N*,*N*′,*N*″-substituted 1,4,7-triazacyclononane derivatives. It reacts readily with dialkyl phosphites, ethyl ethylphosphinate or imidazole in dry refluxing benzene giving pure macrocyclic derivatives in high yields (Scheme 2). Compounds 3–6 were hydrolysed in sodium hydroxide to their respective monoester salts while **7** was hydrolysed in hydrochloric acid yielding the ethylphosphinic acid derivative (NOTEP). Detailed syntheses of **3–8** and the corresponding monoesters will be published elsewhere.[9]

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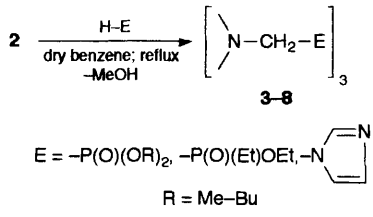

Scheme 2

References

1 A. E. Martell, R. J. Motekaitis and M. J. Welch, *J. Chem. Soc., Chem. Commun.*, 1990, 1748.
2 C. J. Broan, K. J. Jankowski, R. Kataky and D. Parker, *J. Chem. Soc., Chem. Commun.*, 1990, 1738.
3 R. B. Lauffer, *Chem. Rev.*, 1987, **87**, 901, and references cited therein.
4 R. Ramasamy, I. Lazar, E. Brucher, A. D. Sherry and C. R. Malloy, *FEBS Letts.*, 1991, **280**, 121.
5 C. J. Broan, J. P. L. Cox, A. S. Craig, R. Kataky, D. Parker, A. Harrison, A. M. Randall and G. Ferguson, *J. Chem. Soc., Perkin Trans. 2*, 1991, 87.
6 D. Parker, *Chem. Soc. Rev.*, 1990, **19**, 271, and references cited therein.
7 E. K. Fields, *J. Am. Chem. Soc.*, 1952, **74**, 1528.
8 A. V. Bogatsky, N. G. Lukianenkov, V. N. Pastushok and R. G. Kostyanovski, *Synthesis*, 1983, 992.
9 I. Lazar and A. D. Sherry, manuscript in preparation.