New Synthetic Routes to Macrocyclic Triamines

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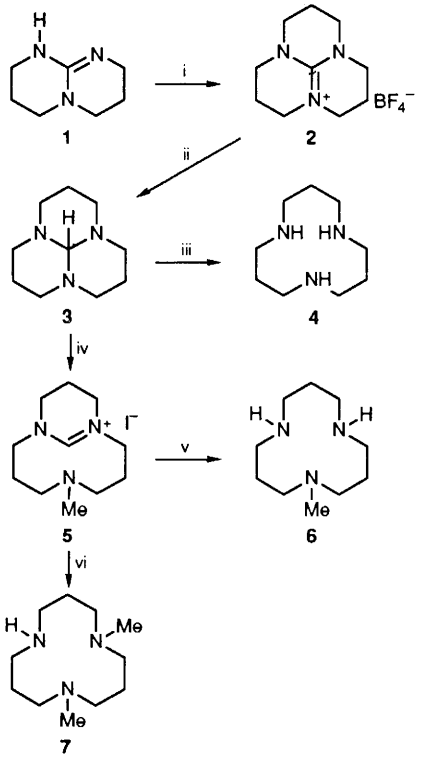
1,5,9-Triazacyclododecane and related macrocyclic triamines can be conveniently constructed around a single carbon atom as template; this route permits the preparation of selectively alkylated derivatives.

Macrocyclic polyamines have found much use as ligands.[1] These compounds are generally prepared by macrocyclisation methods, such as the Richman–Atkins procedure,[2] but there is a continuing demand for improved synthetic methods, especially for the preparation of selectively alkylated compounds.[3–5] In this communication, we describe a new approach in which the macrocycle is built around a single carbon atom as template, thus reducing the cyclisation reactions to those forming 5-, 6- and 7-membered rings. A particular advantage of our route (Scheme 1) is that manipulation of the tricyclic intermediates allows the preparation of selectively alkylated derivatives by the methods already described by Weisman *et al.*[4] or by other transformations as shown for 1,5,9-triazacyclododecane in Scheme 1.

Bicyclic guanidines such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene **1**[6] are commercially available or readily prepared from acyclic triamines and CS_2.[7] Sodium hydride (4.5 g of 60% oil suspension) was added to **1** (13.9 g) in dry tetrahydrofuran (THF) (200 cm^3), cooled to 0 °C under nitrogen, and 1,3-dibromopropane (20.2 g) added. Stirring was continued for 1 h at 0 °C and the reaction mixture was then left to warm to room temperature overnight. Ethanol (5 cm^3) was added to destroy excess NaH, and the hygroscopic 1,5,9-triazatricyclo[7.3.1.$0^{5,13}$]tridecan-13-yl bromide filtered off; addition of diethyl ether (50 cm^3) yielded a little more product. A solution of the bromide and $NaBF_4$ in water (100 cm^3) was extracted with CH_2Cl_2 (3 × 40 cm^3), and after drying, evaporation and recrystallisation from ethanol–ether, 17.5 g (65%) of the tetrafluoroborate **2**[8] was obtained. The procedure above has been carefully optimised; reaction of **1** with 1,3-dibromopropane under these conditions gives **2** and 10–15% of the elimination product 7-(prop-2-enyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene. Use of potassium hydride, higher temperatures, more concentrated solutions, and 1-bromo-3-chloropropane, all led to lower yields of **2**.

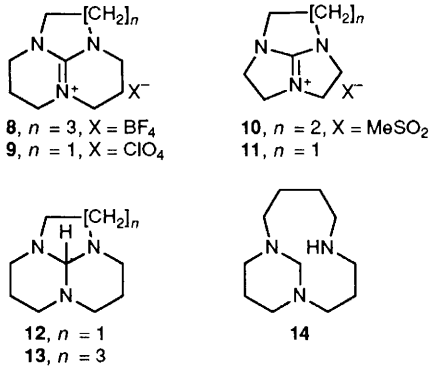


Scheme 1 *Reagents and conditions*: i, NaH, $Br[CH_2]_3Br$ in THF, then $NaBF_4$; ii, $LiAlH_4$ in THF; iii, 3 mol dm^{-3} HCl, then NaOH; iv, MeI; v, OH^-/H_2O; vi, $NaBH_4$ in EtOH

Modifications of the above procedure allow the preparation of other tricyclic guanidinium salts. Thus **8**† could be obtained in 82% yield using 1,4-dibromobutane in the above procedure, but 1,2-dibromoethane only yielded elimination product. However, reaction of **1** with oxirane, followed by treatment of the product with 48% HBr and conversion to the perchlorate gave **9** in 72% yield. Reaction of 1,4,6-triazabicyclo[3.3.0]oct-4-ene[9] with 9-bromopropanol, followed by treatment with methanesulfonyl chloride gave **10** as an oil, which could be converted to a crystalline tetraphenylborate salt, but all attempts to prepare salts of **11** by these methods failed. This guanidinium ion is known to be severely strained.[8]

Tricyclic guanidinium salts **2** and **9** can be reduced in 75% yield to orthoamides **3** and **12**[10] with $LiAlH_4$ in THF; similar reduction of **8** yields a mixture of **13** and **14**. Acid catalysed hydrolyses[4] of **3**, **12** and the mixture of **13** and **14** give the monocyclic triamines in good yields. Thus **3** when refluxed for 22 h with 3 mol dm^{-3} HCl, yielded **4** (89%).

New procedures which result in selective alkylation of these triamines are illustrated for 1,5,9-triazacyclododecane in Scheme 1. Reaction of orthoamide **3** with a variety of alkylating agents gives high yields of bicyclic amidinium salts[4] such as **5**, which can normally be hydrolysed under alkaline conditions to the monoalkylated monocyclic triamine (*e.g.* **6** was obtained in 63% yield). In some instances (with the 4-nitrobenzyl, prop-2-ynyl and phenacyl salts) alkaline hydrolysis resulted in loss of the alkyl group; for the first two cases acid hydrolysis was found to be a satisfactory alternative, but hydrolysis of the phenacyl salt was not successful. Reduction of the amidinium salt **5** with sodium borohydride in refluxing ethanol gave 1,5-dimethyl-1,5,9-triazacyclododecane **7** in 73% yield. This reaction presumably proceeds *via* protonation and ring opening of the first-formed aminal; reduction of **5** with $LiAlH_4$ stopped at the aminal stage. Other



† Satisfactory C, H, N analyses or HRMS were obtained for all new compounds. ^1H and ^{13}C NMR spectra are consistent with the structures assigned.

1-alkyl-5-methyl-1,5,9-triazacyclododecanes should be readily available by this procedure; thus 1-(4-nitrobenzyl)-5-methyl-1,5,9-triazacyclododecane was obtained in 87% yield. Finally, reductive alkylation of **4** with $NaBH_3CN$ and CH_2O or Eschweiler–Clarke reductive alkylation of the orthoamide **3** gave 1,5,9-trimethyl-1,5,9-triazacyclododecane. Eschweiler–Clarke alkylation of **4** itself surprisingly led to partial ring cleavage; this cleavage reaction has been described elsewhere.[11]

We believe that these synthetic routes to macrocyclic triamines offer an attractive alternative to conventional methods, and that the strategy of constructing macrocycles around a (covalently-bound) template atom or group may be applicable to other cases.

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