A general method for the preparation of single pendant arm 2-hydroxyalkyl-1,4,7-triazacyclononane macrocycles

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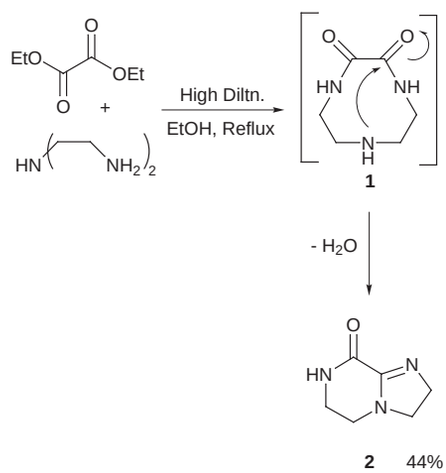
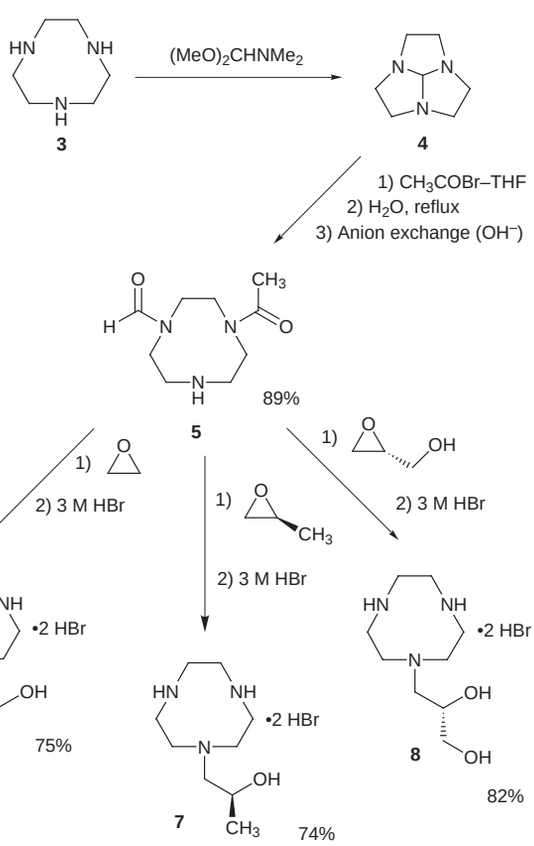
The facile synthesis of a di-protected 1,4,7-triazacyclononane derivative that provides a simple route to single pendant arm 2-hydroxyalkyl triaza-macrocycles through reaction with epoxides is described.

Introduction

The *N*-functionalisation of aza-macrocycles by reaction with substituted epoxides is an area of considerable synthetic activity as such macrocycles yield an impressive array of metal complexes.[1] Although the selective functionalisation of less than the total number of nitrogens of aza-macrocycles is more challenging, it offers the enticing opportunity to produce coordinately unsaturated metal complexes.[2] Recently, a general synthesis of 1,4,7-triazacyclononane, [9]aneN$_3$, substituted by pendant arms at two of the nitrogens was published.[3] We require [9]aneN$_3$ and similar macrocycles substituted with only a single hydroxyalkyl pendant arm for biomimetic studies. Although there are isolated examples of such mono-substituted macrocycles,[4,5] there remains no general synthetic method for attaching a range of single hydroxyalkyl pendant arms to [9]aneN$_3$, the key to which lies in the generation of a suitable di-protected [9]aneN$_3$ intermediate. Existing protection methods involve either selective detosylation[6] or the use of bulky carbamate groups[7] which decrease the reactivity of the third amine donor toward ordinary alkylating agents. Such di-protected species are usually unsuitable for reaction with epoxides and generally require activated alkylating agents such as organo-triflates or acyl-bromide compounds. A more reactive di-protected intermediate, which can react readily with a range of epoxides, is needed.



Scheme 1



Scheme 2

Discussion

In order to maintain an adequate reactivity of the di-protected [9]aneN$_3$ intermediate, we sought to incorporate smaller protecting groups which might impose less steric influence over the third amine donor. We initially attempted to isolate the dioxoamine **1** where two of the amine donors are protected as internal amide groups, however, the high dilution reaction between diethylenetriamine and diethyl oxalate preferentially gave the bicyclic compound **2** (Scheme 1), the structure of which was confirmed by X-ray crystallography.[8]

Our attention then shifted to the introduction of external amide functional groups and we now report the synthesis of a reactive di-protected [9]aneN$_3$ intermediate, **5**, which offers a general route to single pendant arm aza-macrocycles (Scheme 2). The macrocycle [9]aneN$_3$ **3** was first converted to the orthoamide **4** which was then treated with one equivalent of acetyl bromide. Subsequent aqueous hydrolysis followed by anion exchange chromatography gave **5** as a white solid in 89% yield.

Although high resolution mass spectrometry of **5** and a single spot observed by TLC infers a single compound, the NMR spectra reveal a mixture of isomeric forms. The ^{13}C NMR spectrum of **5** in $CDCl_3$ shows 21 aliphatic resonances

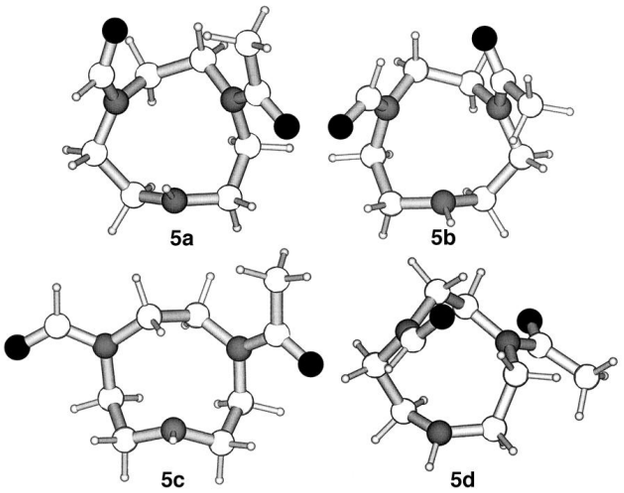


Fig. 1 The four most stable isomers obtained from *ab initio* calculations. The oxygen atoms are represented by black spheres, the nitrogen atoms by grey spheres and the carbon and hydrogen atoms by white spheres.

(three methyl, 18 ring), three formyl C=O resonances and three acetamide C=O resonances as the major spectral components.

Similarly, the ^{1}H NMR spectrum reveals three major methyl singlets and three major formyl singlets. An additional fourth methyl and fourth formyl singlet are also observable but are considerably lower in intensity suggesting a fourth less stable isomer. This number of observed resonances is consistent with **5** existing in three major and one minor isomeric forms which interconvert slowly on the NMR timescale due to restricted rotation about the C–N amide bonds.[9,10] Rotation about each amide group of **5** allows the possibility of four configurational isomers which would each give unique resonances in the ^{13}C NMR spectrum.

Ab initio calculations suggest the lowest energy conformations of each isomer to be those shown in Fig. 1, where the energies of **5a**, **5b**, **5c** and **5d** are −663.783743, −663.783645, −663.779449 and −663.775964 Hartrees respectively in the gas phase (1 Hartree = 2625.5 kJ mol^{-1}). The isomers **5a** and **5b**, where the amide dipoles are directly aligned, represent the most stable configurations. The least stable isomer is **5d** where the oxygen atoms of each amide group are orientated toward each other. While these calculations generate the probable isomeric structures in the gas phase they are not necessarily a guide to the relative stabilities in solution. It is known that tertiary amides form intermolecular dipole–dipole aggregates in solution which may account for the qualitatively similar populations of the three dominant isomers in the NMR spectra.[9]

The reaction of epoxide and orthoamide **4**, as a pathway to mono-alkylated [9]aneN_3, was found to be inappropriate, with the reaction in ethanol giving a mixture of products by TLC and NMR. The reaction of **5** with the epoxides, however, followed by acid hydrolysis of the protecting groups, gave the three single pendant arm macrocycles **6**, **7** and **8** as recrystallisable HBr salts in good yield (Scheme 2). The macrocycles were stored as HBr salts until needed. The free ligands can be obtained by anion exchange chromatography in virtually quantitative yield if required. This represents an improved method for producing mono-functionalised [9]aneN_3 derivatives with small hydroxyalkyl pendant arms.

Experimental

Materials and methods

Melting points were determined on a Kofler hot-stage apparatus equipped with a Reichert microscope and are uncorrected. Infrared spectra were recorded on a Mattson 270-30 FT spectrometer as Nujol mulls or liquid films between sodium chloride plates. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-2000 (300 and 74.47 MHz respectively) spectrometer or a Varian Inova (600 MHz) spectrometer. Spectra were obtained for solutions in $CDCl_3$ [tetramethylsilane (δ_H 0.0) and $CDCl_3$ (δ_C 77.0) as internal standards] at 25 °C, or in D_2O [sodium 3-(trimethylsilyl)propanesulfonate (δ_H 0.0 for $SiMe_3$) and *tert*-butyl alcohol (δ_C 31.6 for CH_3) as external standards] at 25 °C. *J* Values are given in Hz. Electron impact (EI) mass spectra were recorded on a ZAB 2HF mass spectrometer while liquid spray ionisation (LSI) mass spectra were performed by the Central Science Laboratory, Tasmania. Flash chromatography was performed on Silica Gel 60, 230–400 mesh (Merck). Thin layer chromatography (TLC) was performed on either aluminium backed silica gel 60 plates (Merck) or aluminium oxide 150 plates (Merck) and were visualised by UV light (254 nm) or by potassium permanganate dip. All solvents were distilled and dried before use. Dry THF was freshly prepared by distilling over benzophenone and sodium under nitrogen. Ultrapurified deionised water was used for anion exchange chromatography. Elemental analyses were performed by the University of Otago, New Zealand. 1,4,7-Triazacyclononane **3**[11] and its orthoamide derivative, 1,4,7-triazatricyclo-[5.2.1.0^{4,10}]decane **4**,[12] were prepared according to published procedures.

1,4,7-Triazabicyclo[4.3.0]non-6-en-5-one 2

Diethylenetriamine (10.0 g, 96.9 mmol) and diethyl oxalate (14.2 g, 97.2 mmol) were each diluted in absolute ethanol to 50 cm^3 and the two solutions added simultaneously to rapidly stirred refluxing ethanol (1.75 dm^3) at a rate of 0.8 cm^3 h^{-1} using a syringe pump. Once addition was complete the stirred reaction mixture was left to reflux for a further 5 days. The solution was then concentrated to *ca*. 200 cm^3 by distillation of the ethanol and the cloudy solution was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* to give a viscous orange oil which was chromatographed on silica gel [(NH_4OH–H_2O)–MeOH–CH_2Cl_2 1 : 59 : 40, R_f = 0.5] to yield **2** as a pale yellow solid (5.90 g, 44%), mp 172–173 °C (Found: C, 51.4; H, 6.29; N, 29.9. $C_6H_9N_3O$ requires C, 51.8; H, 6.52; N, 30.2%); ν_{max}(Nujol mull)/cm^{-1} 3479, 3360, 1680, 1620; δ_H(600 MHz, D_2O) 2.99 (2H, t, *J* 6.6, C=NCH_2), 3.62 (2H, m, NHCH_2), 3.64 (2H, t, *J* 6.6, C=NCH_2CH_2), 3.74 (2H, m, NHCH_2CH_2); δ_C(74.47 MHz) 39.88 (C=NCH_2), 40.05 (NHCH_2), 47.59 (NHCH_2CH_2), 51.88 (C=NCH_2CH_2), 161.56 (C=N), 161.77 (C=O); *m*/*z* (EI) 139 (M$^+$, 100%), 111 (5), 99 (51), 84 (26), 70 (20), 56 (49), 42 (32). This compound has been previously reported in the patent literature.[13]

1-Acetyl-4-formyl-1,4,7-triazacyclononane 5

Acetyl bromide (2.62 g, 21.3 mmol) in dry THF (10 cm^3) was added dropwise to a rapidly stirred solution of orthoamide **4** (2.68 g, 19.3 mmol) in dry THF (200 cm^3) to give an instant white precipitate. After stirring for 3 h the solid was vacuum filtered, dissolved in H_2O (50 cm^3) and then heated at reflux for 24 h. Removal of the solvent *in vacuo* gave an oil which was passed through an anion exchange column of Amberlite IRA-400 generated with 0.1 mol dm^{-3} NaOH. The product was then extracted into C_6H_6 using a Dean–Stark apparatus. Removal of the solvent *in vacuo* gave **5** as a thick colourless oil which crystallised on standing at 0 °C (3.43 g, 89%), mp 79–81 °C (Found: C, 53.3; H, 8.82; N, 20.6. $C_9H_{17}N_3O_2 \cdot \frac{1}{4}H_2O$ requires C, 53.1; H, 8.66; N, 20.6%); R_f = 0.83 (MeOH–CH_2Cl_2 5 : 95 on alumina); ν_{max}(neat)/cm^{-1} 3460, 3357, 1664, 1635; δ_H(300 MHz, D_2O) 2.07, 2.10, 2.13 (minor) and 2.17 [4 × (3H, s, CH_3)], 2.96 (4H, m, CH_2N ring), 3.31 (4H, m, CH_2N ring), 3.72 (4H, m, CH_2N ring), 8.01, 8.11, 8.13 and 8.16 (minor) [4 × (1H, s, HCO)]; δ_C(74.47 MHz) 22.03, 22.11 and 22.23 [3 × (CH_3)], 44.99, 46.19, 46.39 (coincident double), 47.28, 47.51, 48.32, 48.92 49.45, 49.79, 50.30, 50.57, 51.00, 51.81, 52.15, 53.32, 53.91 and 54.37

(ring carbons), 164.05, 164.13 and 164.15 [3 × (HCO)], 171.29, 171.56 and 171.64 [3 × (CH_3CO)]; *m/z* (LSI) 200.1392 $(M + H)^+$, $C_9H_{18}N_3O_2$ requires 200.1399.

General procedure for alkylation and hydrolysis

Epoxide (3 mol equiv.) was added to a solution of **5** in ethanol at 0 °C and then stirred at 25 °C for 3–4 days. The solvent was removed *in vacuo* and the product was refluxed in 3 mol dm^{-3} HBr at 110 °C for 2.5 h. Removal of the solvent *in vacuo* gave each product as a brittle yellow–white solid. Products **6** and **8** were recrystallised from H_2O–EtOH while product **7** was precipitated from MeOH–CH_2Cl_2. If required, the free ligands may be obtained by passage through an anion exchange column of Amberlite IRA-400 generated with 0.1 mol dm^{-3} NaOH followed by *in vacuo* removal of H_2O.

1-(2-Hydroxyethyl)-1,4,7-triazacyclononane dihydrobromide 6

White crystals (75%), mp 203–206 °C (Found: C, 28.7; H, 6.59; N, 12.3. $C_8H_{21}Br_2N_3O$ requires C, 28.7; H, 6.32; N, 12.5%); δ_H(300 MHz, D_2O) 2.88 (2H, m, NCH_2 arm), 3.05 (4H, m, NCH_2 ring), 3.33 (4H, m, NCH_2 ring), 3.61 (4H, br s, NCH_2 ring), 3.77 (2H, m, CH_2OH); δ_C(74.47 MHz) 44.93, 46.46, 50.85 (ring carbons), 58.68 (NCH_2 arm), 60.58 (CH_2OH arm); *m/z* (LSI) 174.1614 $(M + H)^+$, $C_8H_{20}N_3O$ requires 174.1606. Spectral data is consistent with the literature values for the free ligand.[4]

1-[(2*S*)-2-Hydroxypropyl]-1,4,7-triazacyclononane dihydrobromide 7

White solid (74%); δ_H(300 MHz, D_2O) 1.14 (3H, d, *J* 6.0, CH_3), 2.59 (1H, dd, *J* 10.5, 13.8, NCH_2 arm), 2.80 (1H, dd, *J* 2.7, 13.8, NCH_2 arm), 3.06 (4H, m, NCH_2 ring), 3.32 (4H, m, NCH_2 ring), 3.60 (4H, m, NCH_2 ring), 4.07 (1H, ddq, *J* 2.7, 6.0, 10.5, 13.8, CHOH arm); δ_C(74.47 MHz) 22.46 (CH_3), 44.30, 45.92, 50.38 (ring carbons), 63.62 (NCH_2 arm), 66.92 (CHOH arm); *m/z* (LSI) 188.1767 $(M + H)^+$, $C_9H_{22}N_3O$ requires 188.1762.

1-[(2*R*)-2,3-Dihydroxypropyl]-1,4,7-triazacyclononane dihydrobromide 8

White crystals (82%), mp 186–188 °C (Found: C, 29.4; H, 6.34; N, 11.3. $C_9H_{23}Br_2N_3O_2$ requires C, 29.6; H, 6.35; N, 11.5%); δ_H(600 MHz, D_2O) 2.76 (1H, dd, *J* 9.4, 13.9, NCH_2 arm), 2.86 (1H, dd, *J* 3.3, 13.9, NCH_2 arm), 3.04 (2H, m, NCH_2 ring), 3.11 (2H, m, NCH_2 ring), 3.34 (4H, m, NCH_2 ring), 3.53 (1H, dd, *J* 5.3, 11.9, CH_2OH arm), 3.63 (1H, dd, *J* 4.4, 11.9, CH_2OH arm), 3.64 (4H, m, NCH_2 ring), 3.97 (1H, dddd, *J* 3.3, 4.4, 5.3, 9.4, CHOH arm); δ_C(74.47 MHz) 44.26, 45.97, 50.56 (ring carbons), 59.26 (NCH_2 arm), 66.18 (CH_2OH arm), 70.93 (CHOH arm); *m/z* (LSI) 204.1701 $(M + H)^+$, $C_9H_{22}N_3O_2$ requires 204.1711.

Molecular modelling

Geometries for each isomer of **5** were fully optimised at the Hartree–Fock (HF) level of theory using the 6-31G* basis set. All calculations were carried out using the Gaussian 94 program suite.[14] In addition to configurational isomerism, the conformation of the nine membered ring may also vary by rotation of individual ring atoms. The combination of these effects produced a range of isomers corresponding to 18 local energy minima. The four lowest energy isomers are shown in Fig. 1.

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