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An organic template approach for the synthesis of selectively functionalised tetraazacycloalkanes

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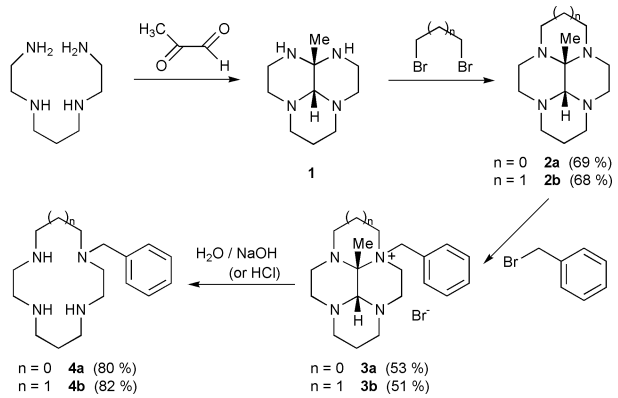
Selectively functionalised tetraazacycloalkanes are obtained from the open-chain tetraamine by using a bisaminal moiety acting both as a template agent and as a N-protecting group.

Cyclic tetraamines have received considerable attention owing to their coordination properties towards various metal cations.[1] The increasing need of finely tuned macrocycles requires the development of new synthetic tools for the preparation of such ligands. The research in this field has been focused on the synthesis of bifunctional chelating agents (BFCs or BCAs) based on a cyclic amine containing two kinds of functional groups, one for the coordination of the guest, another one for the anchoring of the macrocycle onto a solid support or an antibody.[2] In a recent review, we have described the different strategies for the regioselective functionalisation of tetraazacycloalkanes.[3] Besides some typical procedures developed for the synthesis of some target molecules, mono-N-functionalisation of cyclic tetraamines usually involves the use of a large excess of macrocycle relative to the electrophile agent, typically five equivalents in the cyclam series. Although the excess of the ligand might be recovered and re-used in most cases, such an approach is macrocycle consuming and the formation of small amounts of polysubstituted macrocycles may not be completely avoided. Another method consists of protecting three nitrogen atoms with Boc groups prior to the functionalisation of the remaining secondary amine.[4] This procedure has been successfully used for the synthesis of many different ligands but its main drawback is the chromatographic work-up necessary to separate the triprotected macrocycle from the reaction mixture. Finally, the above methods involve the use of a high cost macrocycle, *i.e.* cyclam or cyclen, as starting material and they cannot be utilized in the case of unsymmetrical macrocycles such as 1,4,7,10-tetraazacyclotridecane for which two different mono- or tri-N-functionalised compounds may be formed.

Substituting the hydrogen atom of one secondary amine of a cyclic tetraamine by a benzyl group is also a convenient method for synthesis of trifunctionalised cyclams, since the benzylic C–N bond is easily hydrogenolysed. The mild conditions used to remove the protecting group allow the survival of many different functionalities. Conveniently substituted benzene rings, such as nitrobenzene, may allow a further functionalisation of the arm to graft, for example, the macrocycle on an antibody. Moreover, such benzylated tetraazacycloalkanes, and especially bismacrocycles containing two cyclam units linked together through a xylyl spacer, are highly potent anti-HIV compounds.[5]

In this paper, we wish to report a convenient and general synthesis of mono-N-benzylated tetraazacycloalkanes starting from the suitable open-chain tetraamine. The reaction proceeds as depicted in Scheme 1. The first step involves the reaction of the linear tetraamine with pyruvic aldehyde to form the bisaminal derivative **1**. Cyclisation occurs in a second step, by condensation of the bisaminal compound with the convenient biselectrophile, leading to **2a** and **2b** in good yields. The addition of benzyl bromide to **2a** and **2b** gives the monobenzylated bisaminal protected tetraazamacrocycles as quaternary salts **3a** and **3b**. These compounds are easily deprotected in very mild conditions to yield the desired monobenzylated 1,4,7,10-tetraazacyclotridecane **4a** and cyclam **4b**. These deprotection conditions might slightly differ depending on the nature of the macrocycle. Thus, while refluxing NaOH solution is necessary to remove the bisaminal bridge from **3a**, the benzylcyclam **4b** is already released at rt, proving that the quaternary ammonium salt **3a** is more stable than **3b**. The yields for each step are nearly identical in both series and the monobenzylated macrocycles, **4a** and **4b**, can be readily obtained from the linear tetraamine in overall yields close to 30%. The structures of compounds **1** and **3b** have been confirmed by single crystal X-ray analyses (Fig. 1). The compound **1** is obtained as the sole product and no trace of the other seven possible isomers has been detected in the NMR spectra. An interesting characteristic of compound **3b** is the exceptional length of the bond between the ammonium nitrogen atom and the aminal-type carbon atom (N1–C41 = 1.582 (4) Å) when compared to similar ammonium salts (1.547 (6) Å in the glyoxal adduct).[6]



Scheme 1

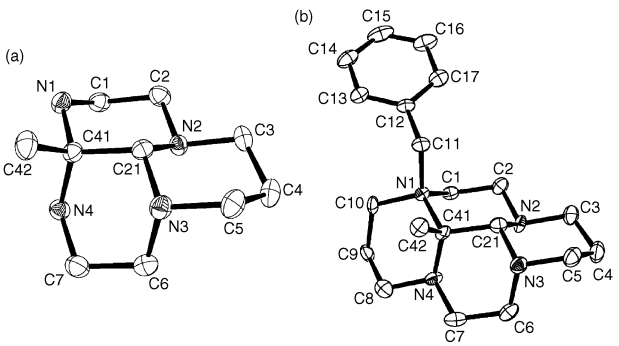


Fig. 1 ORTEP[13] views of (a) *cis*-9a-methyloctahydro-1*H*,4*H*,7*H*-1,3a,6a,9-tetraazaphenalene (**1**) and (b) the *cis*-3a-benzyl-10b-methyldecahydro-1*H*,6*H*-5a,8a,10a-triaza-3a-azoniapyrene cation of (**3b**), showing thermal ellipsoids at the 50% probability level. Selected bond distances: N1–C41 = 1.455 (2) and 1.582 (4) Å, N2–C21 = 1.478 (2) and 1.480 (4) Å, N3–C21 = 1.463 (2) and 1.460 (4) Å, N4–C41 = 1.491 (2) and 1.482 (5) Å, C21–C41 = 1.544 (2) and 1.561 (5) Å, for (a) and (b), respectively. H-atoms omitted for clarity.†

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The interest of the method lies in the use of a bisaminal moiety both as an organic template and as a protecting group for selective functionalisation. Indeed, the rigidity of the bisaminal type tricyclic adduct **1** enables the cyclisation key step to occur in very good yields without any high dilution conditions. The formation of **1** as the unique product of the condensation of the tetraamine with pyruvic aldehyde is consistent with the results reported with glyoxal or butanedione which have already been used as dicarbonyl compounds for the synthesis of cyclen, cyclam and 1,4,7,10-tetraazacyclotridecane after removal of the bisaminal group.[7] Indeed, the formation of three six-membered fused rings is favoured, as well as the *cis* configuration of the bisaminal bridge. Yet, there are still two possible isomers in the case of pyruvic aldehyde, depending on the relative position of the hydrogen atom and the methyl group on the bisaminal moiety. As evidenced by the crystallographic structure, only the isomer in which the methyl group is connected to the aminal-type carbon atom between the two secondary amines is obtained. The X-ray structure of **3b** shows that the quaternization of the bisaminal protected macrocycle occurs selectively on the nitrogen atom linked to the aminal carbon bearing the methyl group. In fact, the steric repulsions between the methyl and the benzyl groups are minimized in this case as shown by a simple model examination. This feature is responsible for the exceptional selectivity of our method since *trans* di-N-quaternization of **2b** does not occur, unlike the results reported with other aminal type macrocyclic compounds.[6,8,9] For similar reasons, attempts to quaternize the butanedione protected cyclam failed, due to the presence of two methyl groups on the bisaminal bridge which hinder the two nitrogen atoms available for quaternization. When using glyoxal instead of butanedione, it is known that two isomers are obtained, depending on whether the glyoxal is condensed with cyclam or with the linear tetraamine prior to the cyclisation.[9,10] In the latter case, although quaternization of the glyoxal protected cyclam occurs in good yield, the bisaminal bridge cannot easily be removed in the ultimate step. Conversely, the bisaminal bridge in **3a** and **3b** can be readily removed in mild conditions to release the monobenzylated macrocycles, owing mainly to the large distance between the ammonium nitrogen atom and the aminal-type carbon atom.

The method reported here represents a very powerful route from a linear tetraamine towards monobenzylated cyclam and 1,4,7,10-tetraazacyclotridecane, and indirectly to BFCs based on these macrocycles. In contrast to glyoxal or butanedione, pyruvic aldehyde allows the selective mono-N-functionalisation of the protected macrocycle before removal of the bisaminal bridge. In order to obtain various mono-N-functionalised tetraazacycloalkanes, we are currently extending the scope of this method to the cyclen series and to different quaternizing agents. For example, methyl iodide or ethyl iodoacetate have been successfully employed. Biselectrophilic reagents such as α,α'-dibromo-*p*-xylene can also be used, thus providing a much better alternative synthesis of highly potent antiviral bisazamacrocycles when compared to the existing ones.

Notes and references

† *Typical experimental procedure*: synthesis of 4-benzyl-1,4,7,10-tetraazacyclotridecane **4a**. To a solution of *N*,*N*′-bis(2-aminoethyl)-1,3-propanediamine (1.22 g; 7.65 mmol) in 50 ml of acetonitrile cooled to 4 °C was added dropwise a solution of pyruvic aldehyde (40 wt% solution in water; 1.38 g; 7.65 mmol). After completion of the reaction (4 h) the solution was heated under reflux, potassium carbonate (5.28 g; 38.25 mmol) and 1,2-dibromoethane (1.43 g; 7.65 mmol) were added. After 48 h, the mixture was filtered, the filtrate was evaporated and the residue was chromatographed over an alumina plug using dichloromethane as eluent to give **2a** as a colorless oil (1.17 g; 5.27 mmol; yield 69%). A mixture of **2a** and benzyl bromide (0.90 g; 5.27 mmol) in 10 ml of acetonitrile was stirred at rt for 24 h, the white precipitate formed was filtered off and washed with diethyl ether and salt **3a** was obtained as a white powder (1.10 g; 2.80 mmol; yield 53%). The solid was dissolved in 10 ml of water, 100 ml of 3M aqueous NaOH solution was added and the mixture was refluxed for 12 h. The solution was extracted with chloroform, the organic phase was dried over $MgSO_4$ and evaporated to give the compound **4a** as a colorless oil. δ_H 1.56 (m, 2H), 2.20 (bs, 3H), 2.46–2.69 (m, 16H), 3.50 (s, 2H), 7.16 (m, 5H), δ_C 28.9; 47.2; 47.9; 48.4 (2C); 49.4; 50.7; 54.3; 54.4; 60.4; 127.3; 128.5; 129.4; 139.7. [M+] 276.7.

X-Ray suitable crystals of **1** and **3b** were grown from chloroform. In both cases the structure was solved using direct methods[11] and refined by full matrix least-squares on F^2.[12] H-Atoms were observed in the Fourier synthesis and refined with a global isotropic thermal factor in each structure.

Crystal data for $C_{10}H_{20}N_4$ (**1**): M = 196.30, monoclinic, a = 9.3721(4), b = 7.8942(4), c = 14.4579(7) Å, β = 91.1640(2) Å, U = 1069.23(9) Å^3, T = 110(2) K, space group $P2_1/n$, Z = 4, μ(Mo-K$_\alpha$) = 0.077 mm^{-1}, 4135 reflections measured, 2448 unique (R_{int} = 0.0303) which were used in all calculations. The final $wR(F^2)$ was 0.1043 (all data). CCDC 172982.

Crystal data for $C_{23}H_{34}BrCl_9N_4$ for (**3b**): M = 765.50, monoclinic, a = 10.4280(2), b = 28.2670(7), c = 11.6960(4) Å, β = 110.544(1) Å, U = 3228.35(15) Å^3, T = 110(2) K, space group $P2_1/n$, Z = 4, μ(Mo-Kα) = 2.040 mm^{-1}, 12777 reflections measured, 7271 unique (R_{int} = 0.0999) which were used in all calculations. The final $wR(F^2)$ was 0.0958 (all data). CCDC 172981. See http://www.rsc.org/suppdata/cc/b1/b108244b/ for crystallographic files in .cif or other format.

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