ORGANIC LETTERS

2001
Vol. 3, No. 18
2855−2858

Synthesis of Novel Derivatives of 1,4,7-Triazacyclononane

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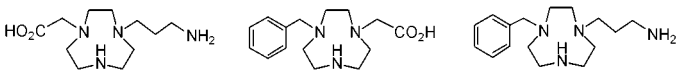
Received June 17, 2001

ABSTRACT



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The coordination environment of 1,4,7-triazacyclononane can be adapted, through sequential functionalization of two secondary amines, to generate ligands applicable in biomimetic studies. Two "amino acids" and an amino derivative have been prepared from 1,4,7-triazatricyclo-[5.2.1.0^{4,10}]decane. This synthon allows efficient attachment of one functional group to the macrocyclic ring, forming a monoamidinium salt. Hydrolysis generates a formyl derivative, which was further functionalized at the secondary amine and hydrolyzed in strong acid to generate ligands 1–3.

Interest in the development of novel acyclic and macrocyclic ligand assemblies continues to be stimulated by the ability of such ligands to form transition metal complexes with tunable physicochemical and functional properties. The resulting complexes find diverse applications as medicinal inorganic compounds,[1] photosensitizers in solar cells,[2] catalysts for organic transformations,[3] molecular devices based on tunable properties,[4] and mimics for enzymes catalyzing redox[5] and hydrolytic[6] processes.

The small tridentate macrocycle 1,4,7-triazacyclononane (tacn) has been at the forefront of developments in several of these areas. Tacn and its derivatives form complexes that, for example, mimic redox metalloenzymes (galactose oxidase, hemocyanin, tyrosinase, and Mn catalases are examples),[7] effectively cleave RNA or DNA,[8,9] and catalyze oxidative organic transformations.[10] Photoelectrochemical devices combining photoactive Ru centers with redox active Mn centers are under development.[11]

Our own research focuses on the application of tacn and derivatives of tacn, including multiple tacn assemblies, in the development of models for multimetal biosites.[12] The recent attachment of tacn to an amino acid through amino

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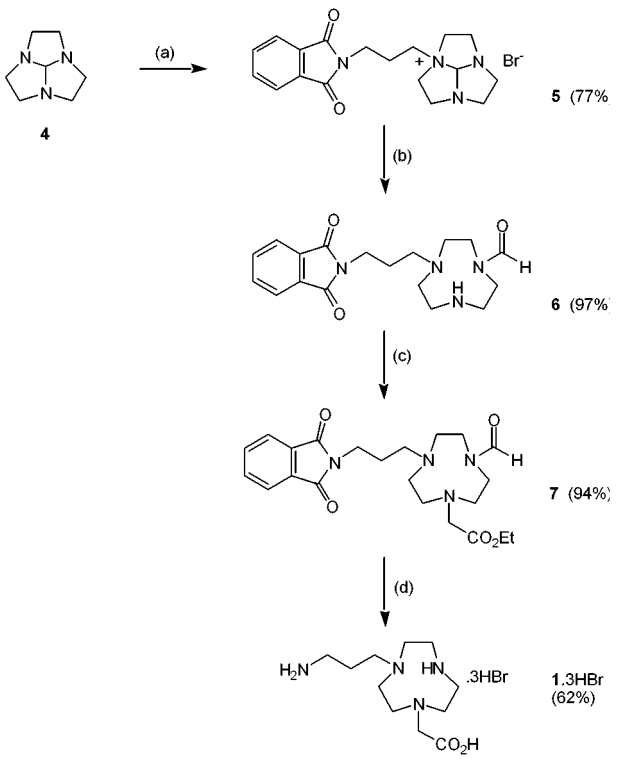
10.1021/ol016291d CCC: $20.00
Published on Web 08/15/2001

acid side chain modification[13] led us to examine synthetic pathways to a wider array of tacn "amino acid" derivatives. We report the synthesis of two "amino acid" derivatives of tacn, 1-aminopropyl-4-acetato-1,4,7-triazacyclononane (**1**) and 1-acetato-4-benzyl-1,4,7-triazacyclononane (**2**), and a new amine derivative, 1-benzyl-4-formyl-7-aminopropyl-1,4,7-triazacyclononane (**3**). The syntheses apply 1,4,7-triazatricyclo[5.2.1.0^{4,10}]decane (tacn orthoamide, **4**),[14] a synthon that has been previously used to prepare functionalized tacn derivatives.[15]

The synthetic route to the trihydrobromide salt of **1** is described in Scheme 1 below. The key synthon, 1,4,7-triazatricyclo[5.2.1.0^{4,10}]decane (tacn orthoamide, **4**), was prepared by refluxing 1,4,7-triazacyclononane with 1 equiv of dimethylformamide dimethylacetal in toluene.[14] Reaction of **4** with *N*-(3-bromopropyl)phthalimide in acetonitrile gave the insoluble monoamidinium bromide salt (**5**) in 71% yield. The ^{1}H NMR spectrum and C=O stretches at 1770 and 1713 cm^{-1} in the IR spectrum confirmed the attachment of the *N*-(3-propyl)phthalimide. Hydrolysis of **5** in water gave the formyl derivative (**6**) in 97% yield, identified by characteristic ^{1}H NMR signals at 8.22 and 8.41 ppm and the expected C=O stretch at 1667 cm^{-1} in the IR spectrum. As is typical for many products containing this group, two conformational isomers are seen in the NMR spectra as a result of slow rotation about the C−N amide bond.[15] Reaction of **6** with ethyl bromoacetate gave **7** as a honey-colored oil in 94% yield, which was hydrolyzed by refluxing in 5 M HCl to remove the phthalimide, formyl, and ester protecting groups from the primary amino, secondary amino, and acetate groups, respectively. Workup of the solution, after filtration to remove the phthalic acid that precipitated on cooling, yielded an oil. As can be the case for molecules exhibiting zwitterionic character or complex acid−base equilibria, because of the presence functional groups with distinctly different acid−base properties, the purification of **1** presented some difficulty. Of the various purification attempts, treatment of the oil with a hydrobromic acid/acetic acid mixture and precipitation with ether was most successful, producing **1** as a white, hygroscopic trihydrobromide salt in 62% yield. The microanalytical data fitted for the dihydrate, the ESI mass spectrum showed a signal due to the parent molecular ion $\{\mathbf{1} + \mathrm{H}\}^+$ at $m/z = 245$, and the spectroscopic data (IR and ^{1}H and ^{13}C NMR) were as expected for **1**.

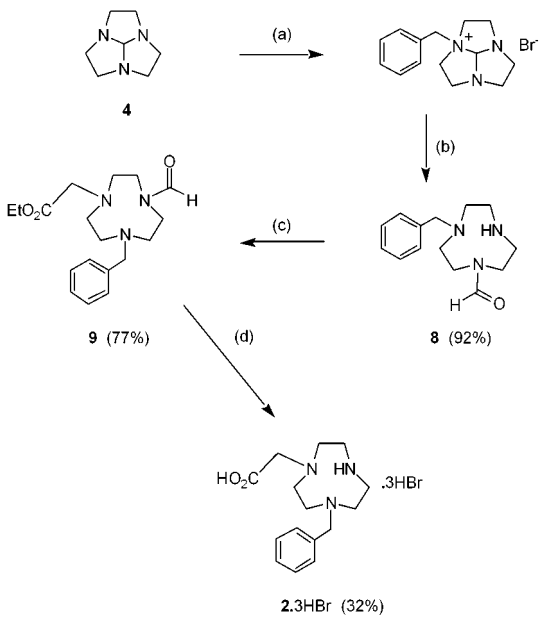
The synthesis of the trihydrobromide salt of **2** is outlined in Scheme 2.

Scheme 1[a]



[a] (a) *N*-(3-Bromopropyl)phthalimide/CH_3CN; (b) H_2O; (c) $BrCH_2CO_2Et/Na_2CO_3/CH_3/CN$; (d) (i) 5 M HCl, (ii) HBr/CH_3COOH.

Scheme 2[a]



[a] (a) $BrCH_2Ph$/THF; (b) H_2O; (c) $BrCH_2CO_2Et/Na_2CO_3/CH_3CN$; (d) (i) 5 M HCl, (ii) CH_3COOH/HBr(g).

The monobenzyl, formyl derivative, **8**, was produced in 92% yield by the reaction of **4** with 1 molar equiv of benzyl bromide in THF and hydrolysis in water. The ^{1}H and ^{13}C NMR spectra of **8** exhibited characteristic signals due to the benzyl group and the tacn ring, confirming the formation of

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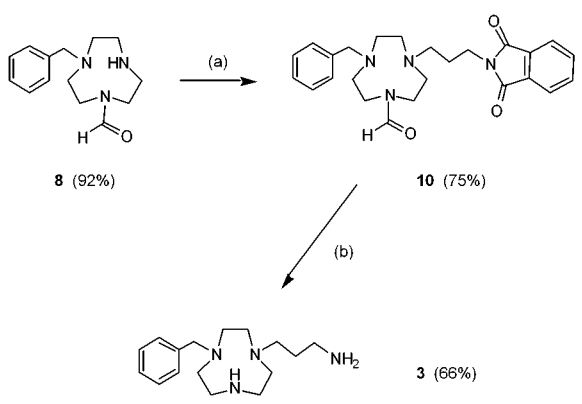
the product. As for **6**, two signals due to the formyl proton were observed in the ^{1}H NMR spectrum (at 7.97 and 8.12 ppm). In the IR spectrum, a C═O stretch associated with formyl groups was observed at 1662 cm^{-1}, and bands at 700 and 731 cm^{-1} confirmed the presence of the aromatic ring. Attachment of the carboxylate ester was achieved in 77% yield by refluxing **8** in CH_3CN with 1 equiv of ethyl bromoacetate in the presence of a base. The NMR spectra of **9** also exhibited the duplicity imparted by the resonance forms of the amide group. The presence of the ester group was confirmed by characteristic NMR signals and a ν_{CO} stretch at 1739 cm^{-1}. Hydrolysis of **10** by refluxing in 5 M HCl, followed by a workup similar to that used for **1**, gave an oil, which was dissolved in glacial acetic acid and treated with HBr(g) to yield the trihydrobomide dihydrate salt of **2**. The microanalytical data fitted for this composition, and the ESI mass spectrum showed a signal due to the parent molecular ion $\{\mathbf{2} + \mathrm{H}\}^+$ at $m/z = 278$. The ^{1}H and ^{13}C NMR spectra provided further confirmation of the constitution of the product.

Scheme 3 outlines the synthesis of **3**. Treatment of **8** with *N*-(3-bromopropyl)phthalimide (1 equiv) in CH_3CN attached

Scheme 3[a]



[a] (a) *N*-(3-Bromoprophyl)phthalimide/Na_2CO_3/CH_3CN; (d) (i) 5 M HCl, (ii) $CHCl_3$.

the *N*-(3-propyl)phthalimide pendant arm to the tacn ring. The product, **10**, was isolated as an orange oil and showed C═O stretches due to the phthalimide (1770 and 1711 cm^{-1}) and the formyl (1667 cm^{-1}) groups in the IR spectrum. It was anticipated that base hydrolysis of **10** would remove the formyl group, thereby generating a secondary amine, which could be derivatized through the attachment of a carboxylate ester group and, finally, hydrolyzed to produce a tacn "amino acid" derivative. However, a time-dependent IR study of the hydrolysis of **10** in a KOH/ethanol solution established that the C═O stretches at 1713 and 1770 cm^{-1} gradually diminished, indicating the loss of the phthalimide group. Over the same period of time, there was little change in the intensity of the formyl C═O stretch located at 1668 cm^{-1}. Full hydrolysis of **10** to generate **3** was achieved at elevated temperatures under both acidic (as used for **1** and **2**) and basic conditions. Since **3** is neutral in basic conditions, it was extracted into an organic solvent and isolated as the oil. The analytical data confirmed the formation of the ligand.

Molecular mechanics calculations[16] were carried out on the neutral forms of **1** and **2** in order to establish the preferred conformations of these ligands. Both ligands were anticipated to exist as zwitterions with one protonated amine group and deprotonated carboxylate group. Because several zwitterionic forms are possible for **1** and **2** (as a result of the presence of primary (**1**), secondary (**1** and **2**), and tertiary (**1** and **2**) amine groups), it was important to establish the preferred site of protonation and conformation of these ligands. It was also of interest to examine whether interactions such as hydrogen-bond stabilization could be important in determining the structures of **1** and **2**.

For **1**, the compound with one pendant carboxylate and one pendant propylamino group, four zwitterionic forms are possible because four different amino groups are present. The most stable conformation is the zwitterion in which the pendant primary propylamine is protonated (see Figure 1)

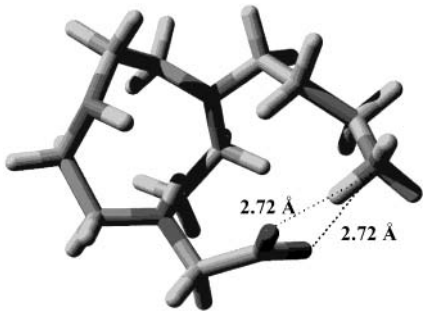


Figure 1. Energy-minimized structure of **1**.

rather than the secondary or tertiary amines of the tacn ring. This zwitterion is stabilized by a moderately strong hydrogen-bonding interaction between the protonated pendant propylamino group and the carboxylate group, N···O distance 2.72 Å. The formation of such a H-bond is facilitated by the flexibility of the pendant propylamino group. Zwitterionic forms with the site of protonation at either the secondary or tertiary ring nitrogens give rise to minimized structures with much higher strain energies (typically 70−100 kcal mol^{-1} higher), as does the nonzwitterionic neutral form in which the carboxylate group is protonated. Thus, for **1** energetically favorable intramolecular H-bonding interactions between the positively charged primary amine and the negatively charged carboxylate force the two pendant groups on the same side on the macrocyclic ring, thereby significantly influencing the preferred conformation of the ligand.

For **2**, the compound with one pendant carboxylate and one pendant benzyl group, three zwitterions are possible, and our calculations indicate that these are energetically favored over the nonzwitterionic form with the protonated carbox-

(16) Molecular mechanics calculations applied the cvff force field in the Biosym/MSI Discover II molecular simulation package.

ylate. The lowest energy conformation is one in which the proton is located on the secondary amine rather than the two tertiary amines bearing either the benzyl or the carboxylate pendant groups. In contrast to **1**, the lowest energy conformation has the carboxylate and the protonated amine hydrogens on the opposite side of the tacn ring (Figure 2) and not involved in H-bonding to each other. Weak H-bonding interactions between the protonated secondary amine and the two tertiary amines (N···N = 2.92 and 3.00 Å) stabilize this conformation. The most notable feature that distinguishes the predicted structure of **2** from that of **1** is that the two pendant groups (i.e., the aromatic ring and the carboxylate group) lie on the opposite sides of the plane formed by the nitrogens of the macrocyclic ring, an orientation likely to be preferred on steric grounds.

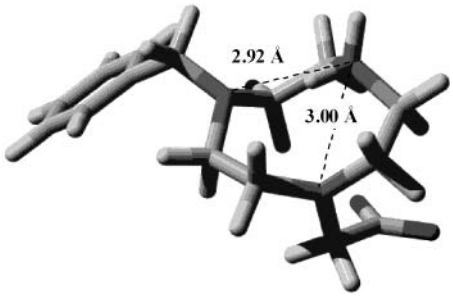


Figure 2. Energy-minimized structure of **2**.

In summary, convenient synthetic procedures are reported for three derivatives of tacn. Notably, molecular mechanics calculations carried out on **1** and **2** indicate that, as a result of difference in the strength of intramolecular H-bonding interactions, these derivatives are likely to adopt quite different conformations. The application of these ligands in biomimetic studies focusing on various metalloproteins is currently under examination.

Acknowledgment. This work was supported by the Australian Research Council. B.G. was the recipient of an Australian Postgraduate Award.

Supporting Information Available: Detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016291D