ORGANIC LETTERS

2008
Vol. 10, No. 8
1645−1647

Design, Synthesis, and Self-Assembling Properties of Novel Triazolophanes

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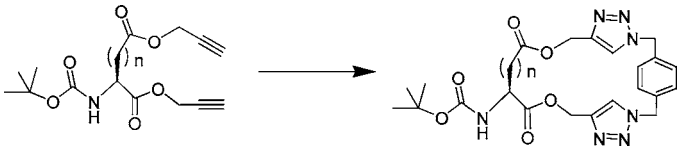
Received February 22, 2008

ABSTRACT



A series of novel triazolophanes containing peptidic and nonpeptidic backbones is reported. The crystal structure of one such macrocycle displays self-assembly through nonconventional hydrogen-bonding interactions.

The synthesis of macrocyclic compounds has attracted the interest of the chemical community because of the diverse utility of these compounds ranging from host−guest chemistry,[1] supramolecular structures,[2] and ionophores[3] to medical applications.[4] The design and synthesis of macrocycles with an appropriate ring size having predictable structure function coupled with elegant synthesis still remains a challenge. Pedersen's classical crown ether synthesis and its ionophoric applications opened new vistas in supramolecular chemistry; however, its biological utility was limited because of the strong binding affinity and slow release rate of crown ethers.[5]

The design and synthesis of macrocyclic structures and their assembly are important research topics in contemporary science.[6] Designed macrocyclic peptides can play a significant role in biology; as a result of the preorganized structure, they can interact with large protein surfaces and thus disrupt protein−protein interactions.[7] Many macrocyclic natural products exhibit biological activities such as immunosuppression,[8] inhibitions of protein biosynthesis,[9] and enzyme inhibition.[10] Macrocyclic heterochiral peptides are known to self-assemble to form supramolecular transmembrane channels and thus transport metal ions.[11] This class of self-assembling compounds provides attractive alternatives to existing antibiotics, as is evident from the action of these compounds against methicillin-resistant *Staphylococcus aureus* infections.[12] Macrocyclic peptides with β-hairpin architecture were shown to mimic the p53 helix region and were used as p53-MDM2 inhibitors.[13] The *Chundle* approach to transmembrane channels is based on grafting several chains onto a polyfunctional macrocycle to improve the ion-transport profile.[14] In this paper, we report the synthesis of a series of macrocyclic compounds, namely triazolophanes, utilizing 1,3-dipolar cycloaddition reactions, and also report

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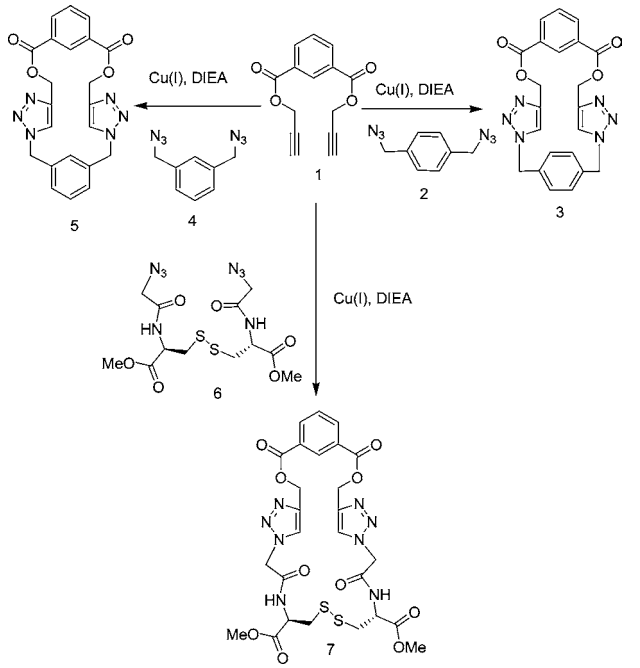
10.1021/ol8003386 CCC: $40.75
Published on Web 03/22/2008

the self-assembly of one such macrocyclic compound devoid of any conventional hydrogen-bond donor sites. This 1,3-dipolar cycloaddition reaction, commonly called a click reaction, involves an azide and an alkyne moiety.[15] This reaction has been successfully employed for the synthesis of designer cyclopeptides with tubular architecture,[16] dendrimer synthesis,[17] and β-turn peptidomimetics.[18] The click reaction has also been employed as a chemical tool to understand biological processes.[19] We envisioned that this reaction would be an effective synthetic methodology to generate macrocyclic compounds with peptidic and nonpeptidic backbones having the propensity for self-assembly.

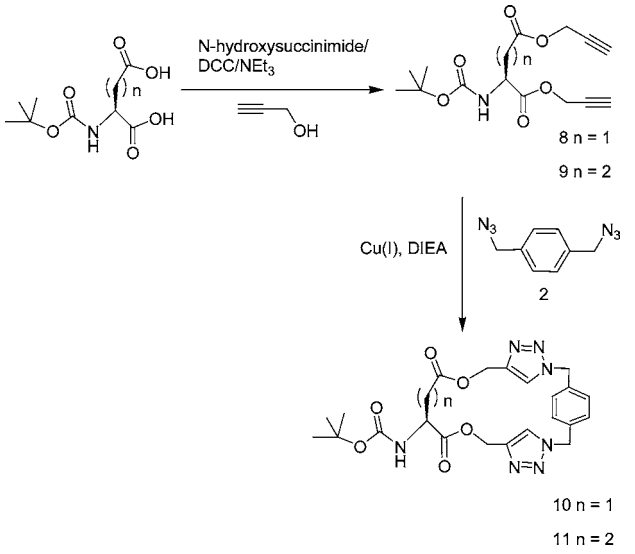
Isophthaloyl chloride on reaction with propargyl alcohol in the presence of 4-dimethylaminopyridine (DMAP) produced dialkyne **1**, which on Cu(I)-mediated reaction with *p*-xylyldiazide **2** in the presence of diisopropylethylamine (DIEA) provided the ester-linked 21-membered triazolophane **3** in ~30% yield (Scheme 1). The versatility of the synthesis

Scheme 1. Synthesis of Triazolophanes **3**, **5**, and **7**



was demonstrated by reacting **1** with various diazides. Dialkyne **1** was reacted with 1,3-xylyldiazide **4** to produce the 20-membered macrocycle **5** in ~71% yield. The cystine-derived diazide **6**, synthesized from cystine methyl ester and azidoacetyl chloride,[20] was reacted with dialkyne **1** to produce the 27-membered macrocycle **7** in ~69% yield. To demonstrate the flexibility of the synthesis, we employed various dialkynes instead of diazides. The chiral amino acids with side-chain carboxylate functionality are ideal candidates for generating dialkynes. Asp and Glu with β- and γ-carboxylates were therefore chosen for this purpose. Boc-aspartic and Boc-glutamic acids on reaction with propargyl alcohol furnished dialkynes **8** and **9** in 80% and 84% yield, respectively (Scheme 2). These on reaction with p-xylyl-

Scheme 2. Synthesis of Triazolophanes **10** and **11**



diazide **2** in the presence of Cu(I) afforded the 20- and 21-membered chiral macrocyclic triazolophanes **10** and **11** in 65 and 68% yields, respectively.

The ester-linked triazolophane **3** is devoid of any conventional H-bonding donor sites and is an ideal candidate for studying nonconventional noncovalent interactions. Therefore, we envisaged that the CH close to the electronegative nitrogen atom can form nonconventional hydrogen-bonding interactions and can organize in the solid state. Our initial efforts to crystallize this compound from various solvents such as chloroform, methanol or ethyl acetate failed to produce good quality crystals. Crystallization of macrocycle **3** from 1:1 (v/v) chloroform and acetonitrile afforded single crystals ideal for X-ray crystallographic analysis.

The X-ray crystal structure of **3** is consistent with the NMR and mass spectral analysis. The X-ray crystal structure of **3** demonstrates a unique type of organization as a result of nonclassical hydrogen-bonding interactions.[21] The only hy-

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drogen bond donor available is the CH of the triazole ring. Interestingly, the crystal structure displayed a unique type of organization mediated by solvent molecules with CH···π and CH···N interactions. The two phenyl groups in **3** are orthogonal to each other, providing a rigid cavity. The six nitrogens, three from each triazole unit, point away from the cavity. The cavity size is 6.792(3) Å from triazole C19 to triazole C17 and 7.105(4) Å from phenyl C12 to the center of the phenyl unit (cent(C1−C6)). The macrocycle **3** acts as a receptor for an acetonitrile molecule (Figure 1), where the

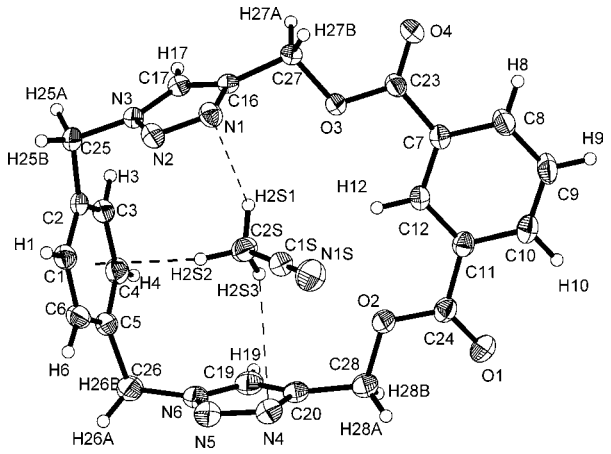

Figure 1. X-ray structure of macrocycle (**3**) with bound acetonitrile molecule.

acetonitrile is bound to the macrocycle by two CH···N hydrogen-bonding and one CH···π interactions. The nitrogen atom of the acetonitrile is further linked to the second macrocyclic molecule (triazole CH) to generate a ribbon assembly of cyclic triazolophanes. The CH of the second triazole ring is hydrogen bonded to a second acetonitrile molecule via a CH···N interaction (Figure 2). The macrocycles are slightly out of alignment. The molecules of **3** are arranged in an interdigitated fashion with the methyl group of the second acetonitrile occupying the hydrophobic region. This array of molecules is further connected to another array by a CH···π interaction involving the CH_2 of the xylyl unit and the aromatic ring of the xylyl unit.

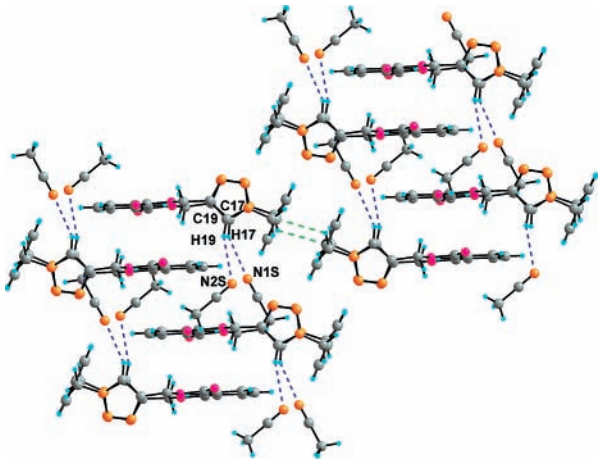

Figure 2. Self-assembly of macrocycle **3** mediated by solvent molecules.

In conclusion, we have shown that the click reaction can be employed to synthesize simple triazolophanes having peptidic and nonpeptidic backbone with propensity for self-assembly by nonclassical noncovalent interactions. The X-ray crystal structure of **3** provided evidence for assembly through complete nonconventional noncovalent interactions. These self-assembling macrocycles may find use as ionophores or as receptors for neutral organic molecules. The three nitrogen atoms on each triazole ring can be exploited for metal-ion binding and we are presently investigating the ionophoric applications and the metal-directed self-assembly of these macrocyclic compounds.

Acknowledgment. Support for this work by the Department of Science and Technology (DST, New Delhi) is gratefully acknowledged. Support from DST for the single-crystal X-ray facility at IITD is acknowledged.

Supporting Information Available: Experimental procedures, characterization of new compounds (**1**−**5** and **7**−**11**), and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8003386