Tetrahedron Letters 54 (2013) 6133–6136

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of cryptands with di-yne units via acetylenic homocoupling reactions of C_3 tripodands

Vlad Paşcanu [a,†], Monica Cîrcu [a,†], Crina Socaci [a,b,*], Anamaria Terec [a], Albert Soran [a], Ion Grosu [a,*]

[a] Babeş-Bolyai University, Center of Supramolecular Organic and Organometallic Chemistry (CSOOMC), 11 Arany Janos Str., 400028 Cluj-Napoca, Romania
[b] National Institute of Research and Development for Isotopic and Molecular Technologies–INCDTIM, 65-103 Donath, 400293 Cluj-Napoca, Romania

ARTICLE INFO

Article history:
Received 9 July 2013
Revised 14 August 2013
Accepted 4 September 2013
Available online 11 September 2013

Keywords:
Cryptands
Bismacrocycles
Hay homocoupling reaction
Di-ynes
Tripodands

ABSTRACT

Cryptands with di-yne units were obtained in good yields by the acetylenic homocoupling reaction of tripodands possesing terminal ethynyl units on the pendant arms. The coupling reactions also led to isomeric bismacrocylic compounds, and the shifting of the process toward the products of intramolecular or intermolecular coupling reactions was influenced by the structure of tripodands and by the coupling reaction conditions.

© 2013 Elsevier Ltd. All rights reserved.

The synthesis of three-dimensional, cage-like molecules is of interest in the field of supramolecular chemistry.[1] A large amount of work has been dedicated toward the investigation of molecules with a well-defined cavity, especially for their potential binding properties.[1] Due to their relative rigidity, buta-1,3-diyne-diyl spacers represent a secure building block for the construction of such three-dimensional molecular frameworks. Cryptands bearing this structural unit have already proved to be useful in the study of host–guest complexes.[2,3] Despite their obvious potential, access to these cage architectures is somewhat limited due to the lack of consistent information on oxidative homoacetylenic coupling as a synthetic pathway for the one-pot macrocyclization reaction.

As part of our work in this direction, we decided to investigate the macrocyclization reaction of tripodands with different C_3 central units and similar pendant arms exhibiting terminal triple bonds (**I**) and to monitor the formation of the corresponding cryptand-like compounds (**II**, Fig. 1). Symmetric tris-heteroaromatics are interesting skeletons[4] for capping cage molecules. Trithienylmethanophanes were reported by Oda,[5] the thiophene rings being bridged by alkene groups. The triphenylamine capping unit is known for its fluorescence properties and its tri-amino derivative has been reported by Vögtle as a precursor for the synthesis of a bismacrocycle.[6] The third target external unit (Fig. 1) bears three 1,3-dioxane groups (the linkage points are situated in the ketal part of the heterocycles), and was reported by our group[7] as a possible pre-organized synthon due to the conformational equilibrium being shifted toward the conformer with the phenyl ring in an axial position for all three 1,3-dioxane units.

The proposed podands (**I**) exhibit favorable structures for the building of cryptand-like architectures (**II**) due to the C_3 symmetry of the aromatic platforms, the presence of three terminal attachment points with high reactivity (triple bonds), and the flexibility of the pendant arms. In addition, they possess other advantages such as being readily available and the reduced costs of starting materials.

The synthesis of podands **4**–**6** started from the corresponding alcohols **1**–**3**[8] via nucleophilic substitution reactions with propargyl bromide in a heterogeneous mixture of dichloromethane and sodium hydroxide solution with tetrabutylammonium bromide as a phase-transfer catalyst (Scheme 1). Podands **4**–**6** were isolated in fair to good yields, either as oils in the case of triaromatic external units (**4** and **5**; 90% and 87%, respectively), or as a solid in the case of podand **6** (52%). The compounds were characterized in solution by ^{1}H and ^{13}C NMR spectroscopy and by MS. The procedure and the physico-chemical description of compounds **4** and **5** are provided in the Supplementary data section, while the synthesis of **6** has already been reported.[9]

For podand **6**, the solid state molecular structure was obtained by single crystal X-ray diffraction measurements and the results are reported in the Supplementary data section.[10]

The three podands with terminal triple bonds were submitted to Cu(I)-catalyzed acetylenic homocoupling reactions (Scheme 2).

---

* Corresponding authors. Tel.: +40 264593833; fax: +40 264590818.
E-mail address: igrosu@chem.ubbcluj.ro (I. Grosu).
† These authors contributed equally to this work.

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.007

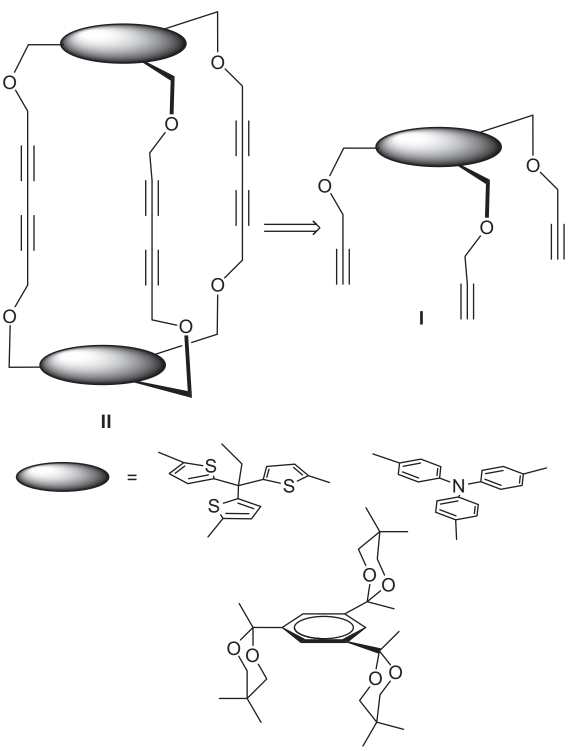
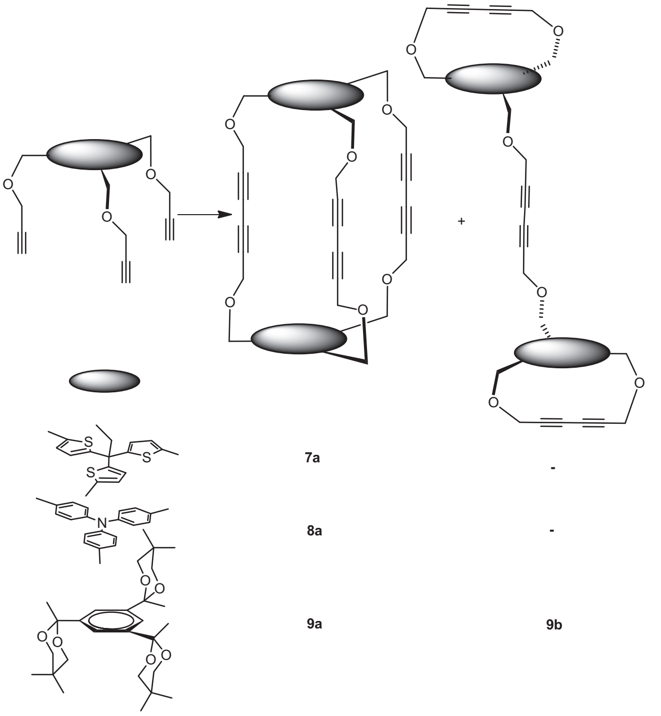


Figure 1. Target tripodands (**I**) and cryptands (**II**).

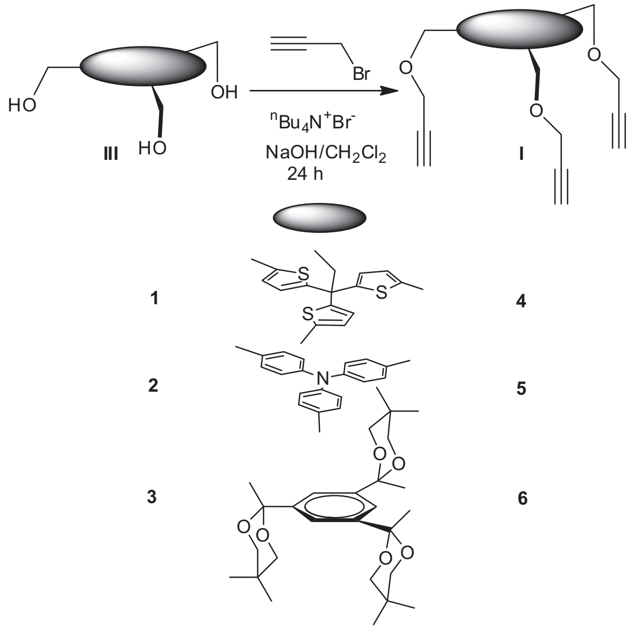


Scheme 2.

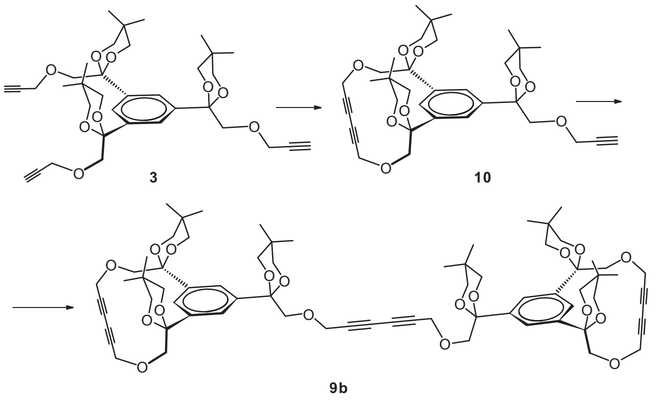
From the two variations of the Glaser coupling: Eglinton [Cu(I), Cu(II)] and Hay [Cu(I), TMEDA, O_2],[3a] the preliminary studies and our previous experiments[11] proved that only the second procedure was efficient in our hands and was the method of choice for accessing the target di-yne cryptands.

We considered it useful to investigate the conditions for the acetylenic coupling reaction with podand **6,** in order to determine the optimum procedure for the synthesis of the cryptand-like compounds. The identification of the possible products in the coupling reaction of **6** was accomplished by NMR spectroscopy. The reaction led to mixtures of cryptand **9a** and bismacrocycle **9b**. These compounds had close R_f values in the majority of the investigated elution systems and hence monitoring of the reaction by TLC was difficult. During the coupling reaction, the formation of a third product with a significantly different R_f value than those of **9a** and **9b** was observed. The intensity of the spot corresponding to this compound increased at the beginning and diminished considerably at the end of the reaction. This compound was successfully separated and its structure determined using NMR data and single crystal X-ray diffraction.[10] The isolated compound was a macrocycle (**10**, Scheme 3, Fig. 2) obtained via intramolecular acetylenic coupling involving two of the pendant arms of the tripodand **6**. Macrocycle **10** is an intermediate in the formation of bismacrocycle **9b**.

In order to determine the optimum conditions for obtaining these cryptands, the reaction was carried out using different copper salts (CuCl or CuI), concentrations of the podand, and copper salt/TMEDA ratios. The reactions were monitored by TLC and par-



Scheme 1.



Scheme 3.

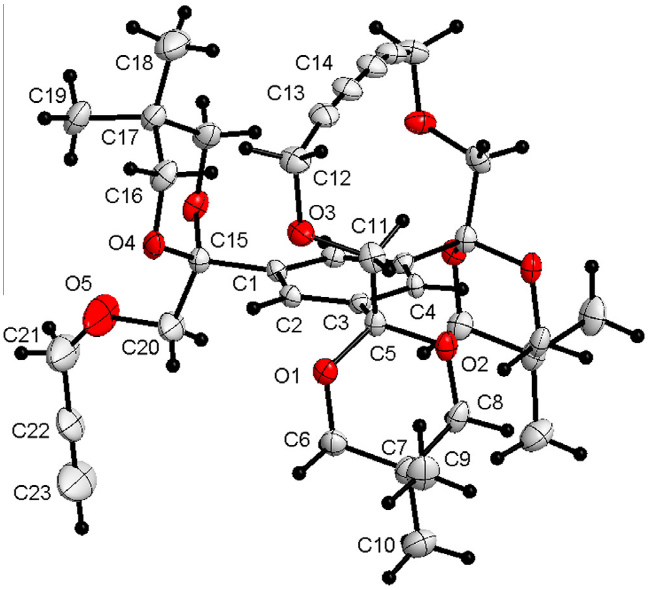


Figure 2. Solid state molecular structure of **10** (view of the asymmetric unit with 40% probability ellipsoids).

ticular attention was devoted to monitoring the intensity of the spot belonging to macrocycle **10**.

The best results for the synthesis of **9a** were obtained with CuI using a 1 mM solution of podand **6** and podand/CuI = 1/5 and CuI/TMEDA = 1/17 ratios.[12] After separation of the products the yields were: 52% for cryptand **9a**; 30% for bismacrocycle **9b**, and 5% for macrocycle **10**. The structures of these compounds were confirmed by NMR and MS analysis.

The coupling reactions carried out with podands **4** and **5** under similar conditions[12] resulted in the isolation of the corresponding cryptands **7a** and **8a** in good to very good yields (42 and 61%, respectively). No intramolecular coupling products (macrocycles or bismacrocycles) were observed during the NMR and MS investigations of the crude products of these reactions. Cryptands **7a** and **8a** exhibit symmetric structures, as evidenced by the number of signals in their NMR spectra (see Supplementary data section). Cryptands **8a** and **7a** could exhibit *in* and *out* isomers with respect to the orientation of the pair of electrons on the N atoms (for **8a**) or of the ethyl group located on the corresponding C atoms (for **7a**) being *inside* or *outside* the cage of the cryptand. For **8a** only the *out*–*out* isomer is possible, while for **7a** the NOESY spectrum, showing no relevant correlations, also suggested formation of an *out*–*out* isomer.

The solid state molecular structure of **10** (Fig. 2)[10] revealed a peculiar arrangement in which the 1,3-dioxane rings attached to the macrocycle were located on the same side of the central aromatic unit, while the third heterocycle is in the opposite orientation. The 1,3-dioxane ring of the free pendant arm is oriented toward the diyne group and this position is consolidated due to C–H···π contacts (the distance between the H atom of the equatorial methyl group and the centroid of the diyne moiety is $d = 2.872$ Å). The asymmetric unit consists of half of the formula unit, the molecule being on a crystallographic mirror plane containing the free propargyl pendant arm and bisecting the diyne bridge and the central aromatic ring.

In the crystal state (Fig. 3), the molecules are associated through C–H···π interactions involving the diyne bridge of each molecule and one of the equatorial hydrogen atoms on each of the heterocycles placed on the same side of the central aromatic ring of neighboring molecules [$d(C^{13,14})$centroid···H^{8A} = 2.92 Å].

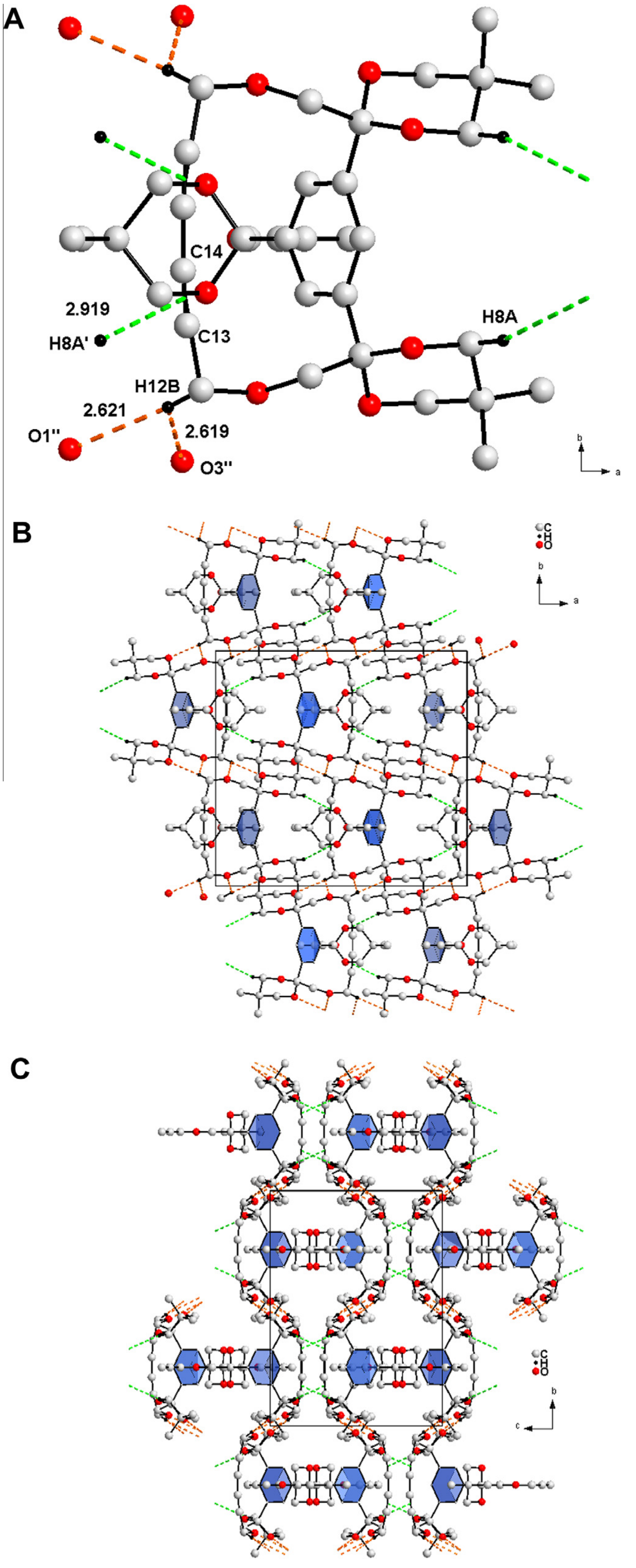


Figure 3. Arrangement of the molecules in the lattice of **10** [close-up view of the C–H···π and C–H···O interactions (A) and views along the c (B) and a (C) crystallographic axes].

Further bridging C–H···O interactions between one methylenic hydrogen atom of the diyne bridge and one oxygen atom of each of the heterocycles placed on the same side of the central aromatic ring resulted in a three dimensional supramolecular arrangement $d(O^{1''}\cdots H^{12B}) = 2.62$ Å, $C^{12}–H^{12B}\cdots O^{1''} = 173.6(2)°$, and $d(O^{3''}\cdots H^{12B}) = 2.62$ Å; $C^{12}–H^{12B}\cdots O^{3''} = 124.7(2)$ (Fig. 3).

In summary, the acetylenic homocoupling reaction was successfully used for the synthesis of cryptands with triphenylamine, trithienylmethane, and 1,3,5-trisubstituted-benzene units. The competition between the intermolecular and intramolecular coupling reactions, resulting in the formation of the cryptand and an isomeric bismacrocyclic derivative (via the macrocyclic intermediate **10**) was monitored by TLC for tripodand **6**, and the homocoupling reaction conditions were optimized in order to improve the yields for the synthesis of cryptand **9a**.

Acknowledgment

We are grateful for the financial support of this work by CNCS-UEFISCDI (Project PN-II-ID-PCCE-2011-2-0050).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.007.

References and Notes

1. Atwood, J. L.; Steed, J. W. *Encyclopedia of Supramolecular Chemistry*; Marcel Dekker, Inc., 2004.
2. a) Han, T.; Chen, C.-F. J. *Org. Chem.* **2007**, *72*, 7287–7293; b) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2002**, *4*, 11–14.
3. a) Piron, F.; Cismas, C.; Terec, A.; Roncali, J.; Grosu, I. *Mini-Rev. Org. Chem.* **2009**, *6*, 78–85; b) Tominaga, M.; Masu, H.; Azuyama, I. J. *Org. Chem.* **2009**, *74*, 8754–8760.
4. Nair, V.; Thomas, S.; Mathew, S. C.; Vidyaa, N.; Rath, N. P. *Tetrahedron* **2005**, *61*, 9533–9540.
5. a) Kurata, H.; Nakaminami, H.; Matsumoto, K.; Kawase, T.; Oda, M. *Chem. Commun.* **2001**, 529–530; (b) Kurata, H.; Haruki, K.; Nakaminami, H.; Kawase, T.; Oda, M. *Chem. Lett.* **2003**, *32*, 422–423.
6. a) Schrage, H.; Franke, J.; Vögtle, F.; Steckhan, E. *Angew. Chem.* **1986**, *98*, 335–337; b) Ghosh, S.; Gole, B.; Bar, A. K.; Mukherjee, P. S. *Organometallics* **2009**, *28*, 4288–4296; c) Conerey, B.; Jensen, P.; Kruger, P. E. MacGloinn *Chem. Commun.* **2003**, 1274–1275.
7. Florian, M. C.; Cîrcu, M.; Toupet, L.; Terec, A.; Grosu, I.; Ramondenc, Y.; Dinca, N.; Ple, G. *Cent. Eur. J. Chem.* **2006**, *4*, 808–821.
8. Cîrcu, M.; Pascanu, V.; Soran, A.; Braun, B.; Terec, A.; Socaci, C.; Grosu, I. *CrystEngComm* **2012**, *14*, 632–639.
9. Cîrcu, M.; Soran, A.; Hădade, N. D.; Rednic, M.; Terec, A.; Grosu, I. *J. Org. Chem.* **2013**. http://dx.doi.org/10.1021/jo401432y.
10. Crystallographic data for the structures reported in this Letter have been deposited at the Cambridge Crystallographic Data Centre as supplementary publications (CCDC-948558 for **6** and CCDC-948559 for **10**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. See also the Supplementary data to this Letter.
11. Pop, F.; Socaci, C.; Terec, A.; Condamine, E.; Varga, R. A.; Rat, C. I.; Roncali, J.; Grosu, I. *Tetrahedron* **2012**, *68*, 8581–8588.
12. *General procedure for compounds* ***7–9***. To a 1 mM solution of podand (0.1 mmol) in CH_2Cl_2 (100 mL, dried over anhydrous $MgSO_4$ and molecular sieves 3 Å), CuI (0.5 mmol) and TMEDA (1.7 mmol, 154 mg) were added under anhydrous conditions. The mixture was stirred vigorously at room temperature for 12 h, while bubbling dry air (O_2) through a $CaCl_2$ tube. The resulting mixture was filtered over silica gel and washed with $CHCl_3$ (3 × 20 ml) and Et_2O (3 × 20 ml). The organic phases were combined and the solvent removed under vacuum. The residue was subjected to column cromatography for purification.