Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5869–5872

Inter and intramolecular copper(I)-catalyzed 1,3-dipolar cycloaddition of azido-alkynes: synthesis of furanotriazole macrocycles☆

Srivari Chandrasekhar,[a,*] Chennamaneni Lohitha Rao,[a] Chidalla Nagesh,[a] Chada Raji Reddy[a] and Balasubramanian Sridhar[b]

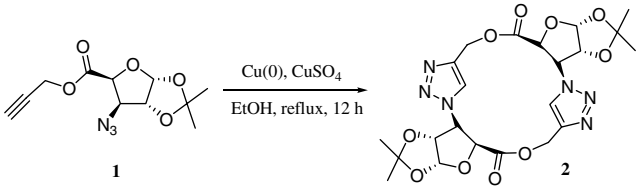
[a]*Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

Received 28 February 2007; revised 5 June 2007; accepted 13 June 2007
Available online 20 June 2007

Abstract—The Cu(I)-catalyzed cycloaddition of azido-alkynes (click reaction) of furanose sugar substrates provides a facile approach for the construction of macrocyclic molecules via an inter and/or intramolecular cycloaddition based on the functionality between alkyne and azide.

'Click' chemistry developed by Meldal[1] and Sharpless[2] has gained strong interest from both synthetic and medicinal chemists, for constructing useful 1,2,3-triazole compounds through Huisgen 1,3-dipolar cycloadditions[3] of alkynes to azides. The reaction proceeds in the presence of copper(I) as a catalyst and has advantages such as quantitative yields, regiospecific conversion and compatibility with a broad range of functional groups and reaction conditions. 'Click' chemistry is so versatile that it has found applications in biology,[4] surface chemistry,[5] polymer chemistry[6] and carbohydrate chemistry.[7] This cycloaddition reaction has also been used for the construction of macrocyclic molecules[8] as well as in peptide chemistry, due to the interesting properties of the 1,2,3-triazole moiety, which include stability towards acidic and basic hydrolysis and active participation in hydrogen bonding and dipole–dipole and π-stacking interactions.[9] In connection with our ongoing programme on the synthesis and oligomerization of β-sugar amino acids[10] and the importance of the 'click' reaction[11] we were interested in exploring this very versatile reaction on some of the key building blocks used in our programme.

Herein, we report our interesting observations on the 'click' chemistry of internal acetylenic azides with special emphasis on furanose sugars. Initially, carbohydrate derived azido-alkyne **1** was synthesized from the known azido acid[10a] by esterification with propargyl alcohol using DCC and a catalytic amount of DMAP in dichloromethane at room temperature. When this azido-alkyne was treated with a copper(I) catalyst in ethanol under refluxing conditions, to our satisfaction, head to tail cyclic dimer **2** was obtained in 70% yield via tandem dimerization–macrocyclization reaction (Scheme 1). This 16-membered macrocycle exhibited C_2-symmetry as evidenced by ^{1}H and ^{13}C NMR spectroscopy[12] and supported by Molecular Dynamics simulation (Fig. 1).[13] To confirm further the structure of the product **2**,[14] partial hydrolysis was carried out on compound **2** to provide the corresponding acyclic compound,[15] which was fully characterized from IR, ^{1}H, ^{13}C NMR and mass spectral



1 2

Scheme 1.

Keywords: 'Click' reaction; Macrocycles; 1,3-Dipolar cycloaddition.
☆ IICT Communication No. 070217.
* Corresponding author. Tel.: +91 40 27193210; fax: +91 40 27160512; e-mail: srivaric@iict.res.in

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.06.062

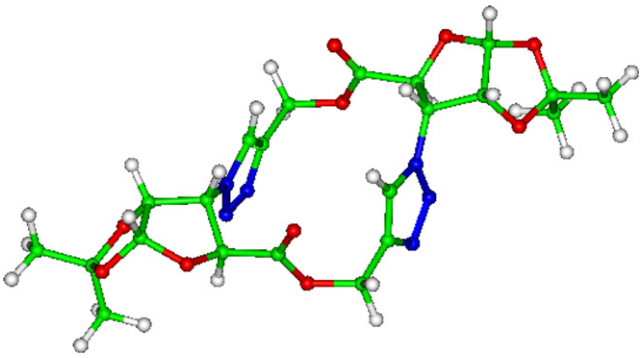


Figure 1. Energy minimized structure of **2**.

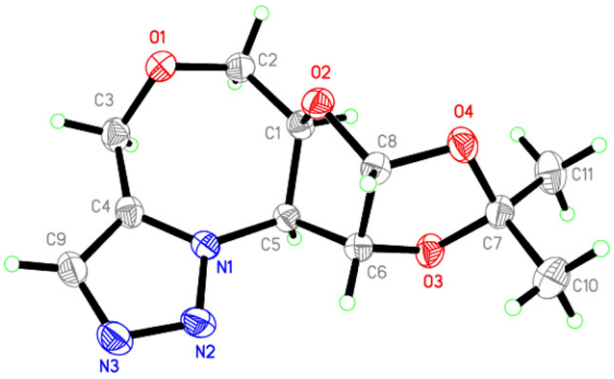


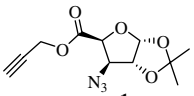
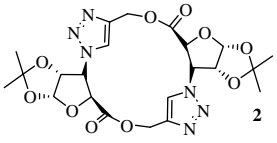
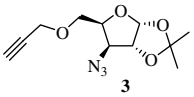
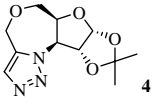
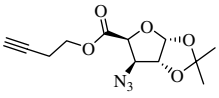
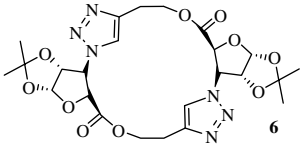
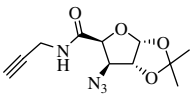
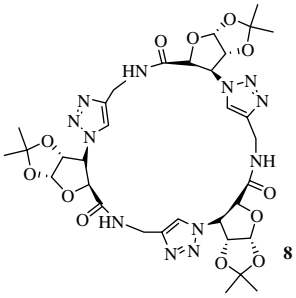
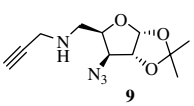
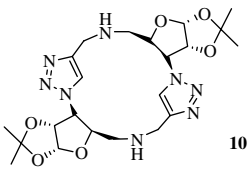
Figure 2. ORTEP diagram of compound **4**.

data after esterification.[16] This data clearly supported the formation of cyclic dimer **2**.

We next synthesized azido-alkyne **3** and subjected it to similar reaction conditions to give the triazole-fused tetracyclic compound **4** in 85% yield. The structure of compound (**4**) was determined by X-ray crystallographic studies[16] (Fig. 2) and fully characterized by spectral analysis.[17] The bond lengths C4–C9 and N2–N3 are 1.368(3) Å and 1.307(2) Å, respectively, confirming the presence of double bonds in the fused 1,2,3-triazole moiety.

In the case of substrate **5** (prepared from the corresponding azido carboxylic acid) cyclic dimer **6** (18-membered macrocycle) was obtained in 61% yield. These

Table 1. 'Click' reaction of furanose derived azido-alkynes

Entry	Azido-alkyne	Time (h)	Product	Yield[a] (%)
1	 **1**	12	 **2**	70
2	 **3**	6	 **4**	85
3	 **5**	12	 **6**	61
4	 **7**	14	 **8**	48[b]
5	 **9**	6	 **10**	64

[a] Isolated yields after column chromatography.
[b] The formation of 5% of the dimer product was observed.

interesting results from azido-alkynes having an ester linkage **1** and **5** and ether linkage **3**, prompted us to study substrates possessing amide and amine linkages between the alkyne and azido groups. Accordingly, the azido-alkyne **7** containing an amide linkage was obtained from the corresponding acid under standard EDCI–HOB*t* reaction conditions. Surprisingly, the 1,3-dipolar cycloaddition of azido-alkyne **7** afforded the 24-membered macrocycle **8** (trimer) in 48% yield along with the cyclic dimer (5%). In another variation of the reaction, the cycloaddition was tested on substrate **9** bearing an amine linkage between the azide and alkyne functionality. Azido-alkyne **9**, in the presence of catalytic amounts of copper, underwent cycloaddition to afford the triazole **10** as a cyclic dimer in 64% yield. All the products were characterized from ^{1}H, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of macrocyclic products **2**, **6** and **10** supported the C_2-symmetric nature and that of **8** supported the C_3-symmetry. These observations open up new avenues in the synthesis of functionalized macrocycles with potential applications in supramolecular chemistry (see Table 1).

In summary, we have successfully demonstrated the applications of 1,3-dipolar cycloaddition reactions on azido-alkynes of furanose sugars, which provided several interesting macrocyclic products based on the linkage between the alkyne and azido functionalities.

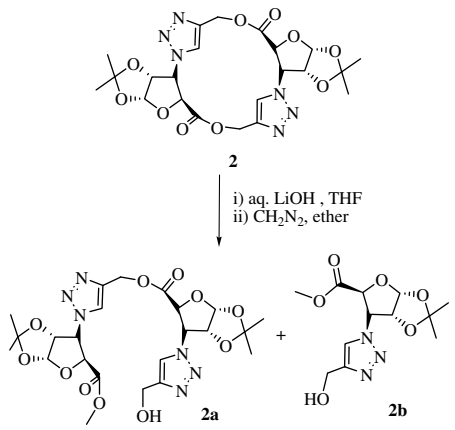
Representative experimental procedure: To a solution of azido-alkyne **1** (0.1 g, 0.37 mmol) in 10 mL of ethanol was added copper turnings (10 mg) and saturated copper sulfate solution (0.2 mL, 1 M) and the reaction mixture was refluxed for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite. The Celite pad was washed with $CHCl_3$ and volatiles were removed on a rotary evaporator. The residue was purified by column chromatography over silica gel, to afford triazole **2** in 70% yield.

Acknowledgements

C.L.R. and C.N. thank CSIR, New Delhi, for fellowships. S.C. thanks DST for funding the project. We are very much thankful to the referees for valuable suggestions.

References and notes

1. Tornoe, C. M.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
2. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596; (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2702; (c) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.
3. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.
4. (a) Buckle, D. R.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1986**, *29*, 2269; (b) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, J. M. *J. Med. Chem.* **1994**, *37*, 4185; (c) Genin, M. J.; Alwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.
5. (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928; (b) Daz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4392; (c) Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. D. *Langmuir* **2004**, *20*, 1051; (d) Lee, J. K.; Chi, Y. S.; Choi, I. S. *Langmuir* **2004**, *20*, 3844.
6. Laurent, B. A.; Grayson, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 4238, and references cited therein.
7. (a) Al-Maoudi, N. A.; Al-Soud, A. Y. *Tetrahedron Lett.* **2002**, *43*, 4021; (b) Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. B. R.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123; (c) Srinivas, Ch.; Fang, X.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331; (d) Hotha, S.; Anegundi, R. I.; Natu, A. A. *Tetrahedron Lett.* **2005**, *46*, 4585; (e) Hotha, S.; Kashyap, S. *J. Org. Chem.* **2006**, *71*, 364.
8. (a) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638; (b) Dorner, S.; Westermann, B. *Chem. Commun.* **2005**, 2852; (c) Punna, S.; Kuzelka, J.; Wang, Q.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2215; (d) Billing, J. F.; Nilsson, U. J. *J. Org. Chem.* **2005**, *70*, 4847.
9. (a) van Maarseveen, J. H.; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7*, 4503; (b) Oh, K.; Guan, Z. *Chem. Commun.* **2006**, 3069; (c) Whiting, M.; Muldoon, J.; Lin, Y. C.; Silverman, S. M.; Lindstrom, W.; Olson, A. J.; Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 1435.
10. (a) Chandrasekhar, S.; Reddy, M. S.; Jagadeesh, B.; Prabhakar, A.; Ramana Rao, M. H. V.; Jagannadh, B. *J. Am. Chem. Soc.* **2004**, *126*, 13586; (b) Jagannadh, B.; Reddy, M. S.; Rao, C. L.; Prabhakar, A.; Jagadeesh, B.; Chandrasekhar, S. *Chem. Commun.* **2006**, 4847.
11. Chandrasekhar, S.; Basu, D.; Rambabu, Ch. *Tetrahedron Lett.* **2006**, *47*, 3059.
12. Characterization data of compound **2**: White solid, mp >270 °C; IR (KBr): ν 3436, 1765, 1629, 1205, 1088, 1032, 862 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (s, 2H), 6.16 (d, $J = 3.85$ Hz, 2H), 5.50 (d, $J = 3.84$ Hz, 2H), 5.33 (d, $J = 12.50$ Hz, 2H), 5.19 (d, $J = 3.84$ Hz, 2H), 4.99 (d, $J = 12.50$ Hz, 2H), 4.66 (d, $J = 3.84$ Hz, 2H), 1.33 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.2 (2C), 141.3 (2C), 125.3 (2C), 112.8 (2C), 105.3 (2C), 83.7 (2C), 79.5 (2C), 77.8 (2C), 65.5 (2C), 26.8 (2C), 26.4 (2C); ESI (MS): 535 (M^++H), 557 (M^++Na); HRMS (ESI) Calcd for $C_{22}H_{26}N_6O_{10}Na$: 557.1608 $[M+Na]^+$. Found: 557.1611 $[M+Na]^+$.
13. Molecular dynamics for the energy minimized conformation of **2** were carried out using Insight II program on a Silicon Graphics work station.
14. We have tried to prepare the cyclic monomer from compound **1** under high dilution conditions to compare the spectral data with cyclic dimer **2**, however, formation of the cyclic monomer was not observed.
15. Compound **2** was hydrolyzed using aqueous LiOH in THF followed by esterification to furnish the acyclic products **2a** and **2b** in 42% and 18% yields, respectively.[18]



16. Compound **4** was crystallized by slow evaporation from hexanes: chloroform (1:1); Crystal data: $C_{11}H_{15}N_3O_4$, $M = 253.26$, orthorhombic, space group $P2_12_12_1$, $a = 9.0565(4)$ Å, $b = 9.9048(4)$ Å, $c = 13.0341(6)$ Å, $V = 1169.20(9)$ Å^3, $Z = 4$, $D_{calcd} = 1.439$ mg m^{-3}, $T = 294(2)$ K, $\mu = 0.111$ mm^{-1}, $F(000) = 536$, $\lambda = 0.71073$ Å. Data collection yielded 11224 reflections resulting in 1206 unique, averaged reflections, 1196 with $I > 2\sigma(I)$. Full-matrix least-squares refinement led to a final $R = 0.0261$, $wR = 0.0712$ and GOF = 1.128. Intensity data were measured on a Bruker Smart Apex with CCD area detector. Crystallographic data has been deposited for compound **4** with the Cambridge Crystallographic Data Centre, [CCDC No. 649353]. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

17. Characterization data of compound **4**: White solid, mp 149–152 °C; IR (KBr): ν 3438, 1377, 1017, 831 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56 (s, 1H), 6.03 (d, $J = 3.5$ Hz, 1H), 5.91 (d, $J = 3.5$ Hz, 1H), 5.03 (s, 2H), 4.72–4.55 (m, 2H), 4.30–4.01 (m, 2H), 1.59 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.6, 132.4, 112.3, 104.0, 82.3, 76.5, 69.9, 66.0, 62.8, 26.3, 26.0; ESI (MS): 254 (M^++H); HRMS (ESI) Calcd for $C_{11}H_{15}N_3O_4Na$: 276.0960 [M+Na]$^+$. Found: 276.0966 [M+Na]$^+$.

18. (a) Characterization data of compound **2a**: White solid, mp 205–207 °C; IR (KBr): ν 3433, 1745, 1634, 1378, 1215, 1031 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.93 (s, 1H), 7.81 (s, 1H), 6.25 (t, $J = 4.2$ Hz, 2H), 5.60–5.56 (m, 2H), 5.30 (t, $J = 5.7$Hz, 1H), 5.17 (t, $J = 4.8$ Hz, 2H), 5.12 (d, $J = 3.6$ Hz, 1H), 5.02 (d, $J = 3.6$ Hz, 1H), 4.95 (s, 2H), 4.50 (d, $J = 5.7$ Hz, 2H), 3.57 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.7, 166.0, 147.9, 140.9, 125.5, 123.3, 112.3 (2C), 105.4 (2C), 83.0, 82.9, 78.1, 78.0, 65.2, 65.1, 57.6, 54.8, 51.9, 26.5 (2C), 26.19, 26.14; ESI (MS): 567 (M^++H), 589 (M^++Na); HRMS (ESI) Calcd for $C_{23}H_{30}N_6O_{11}Na$: 589.1870 [M+Na]$^+$. Found: 589.1887 [M+Na]$^+$. (b) Characterization data of compound **2b**: White solid, mp 114–115 °C; IR (KBr): ν 3316, 1757, 1374, 1218, 1032, 860 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (s, 1H), 6.33 (d, $J = 3.6$ Hz, 1H), 5.39 (d, $J = 4.2$ Hz, 1H), 5.14 (d, $J = 4.2$ Hz, 1H), 5.00 (d, $J = 3.6$ Hz, 1H), 4.75 (d, $J = 5.7$ Hz, 2H), 3.58 (s, 3H), 1.59 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 148.3, 122.1, 113.4, 106.1, 83.5, 78.5, 66.5, 56.4, 52.9, 26.9, 26.4; ESI (MS): 300 (M^++H), 322 (M^++Na); HRMS (ESI) Calcd for $C_{12}H_{17}N_3O_6Na$: 322.1015 [M+Na]$^+$. Found: 322.1011 [M+Na]$^+$.