Tetrahedron Letters 49 (2008) 6778–6780

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of a β-cyclodextrin derivative bearing an azobenzene group on the secondary face

Juan M. Casas-Solvas, Antonio Vargas-Berenguel *

Área de Química Orgánica, Univesidad de Almería, 04120 Almería, Spain

ARTICLE INFO

Article history:
Received 26 June 2008
Revised 5 September 2008
Accepted 8 September 2008
Available online 11 September 2008

Keywords:
β-Cyclodextrin
Azobenzene
Oxidative coupling
Sonogashira reaction

ABSTRACT

An oxidative coupling Sonogashira-type reaction has been used to synthesize a β-cyclodextrin derivative bearing an azobenzene group on the secondary face for the first time starting from a β-cyclodextrin propargylated at one of its C-2 positions. The de-*O*-propargylation reaction and the formation of an oxidative homocoupling dimer were found to compete with the desired product under several Sonogashira-type reaction conditions. However, the use of a diluted reductive atmosphere of H_2 avoided the former and diminished the latter.

β-Cyclodextrin (β-CD) is a naturally occurring cyclic oligosaccharide comprising seven D-glucopyranose units linked by α-(1→4) bonds. It possesses a relatively rigid thorus-shaped structure, which defines an inner hydrophobic cavity rimmed by two hydrophilic openings. These openings are different in diameter, the narrower containing the primary hydroxy groups located on the C-6 of the glucopyranose units and the wider containing the secondary ones on C-2 and C-3 positions (Chart 1). As a consequence, β-CD is well-known to form inclusion complexes in aqueous solution with a large variety of organic molecules of hydrophobic nature and suitable size and geometry.[1] In addition to other applications, this feature has been explored for the design and construction of molecular machines in which the inclusion of the guest molecule can be controlled through external stimuli.[2] One of the strategies followed to reach this goal has been the attachment of a chemical group sensitive to pH variations,[3] metallic cations,[4] electrochemical signals,[5] or irradiation with light[6] onto the β-CD. Among the photosensitive groups, azobenzene has received much attention in recent years due to its easy and reversible cis–trans isomerization.[7] Azobenzene derivatives undergo trans to cis isomerization upon irradiation with UV light and isomerize back to trans with visible light exposure or simply in the dark. Such remarkable behavior makes azobenzene a good building block for the preparation of photoswitchable molecular receptors by conjugation with molecules involved in molecular recognition processes.

As a part of a project that involved β-CD-based photocontrollable receptors, we turned our attention to the synthesis of azobenzene-containing β-CD derivatives.[8] Recently, we have prepared some azobenzene derivatives carrying one or two β-CD residues linked through their primary faces.[9] In this Letter, we wish to report the synthesis of a β-CD derivative bearing an azobenzene group on the secondary face. Location of the photosensitive residue in such face could enhance the effect of the light over the supramolecular chemistry of the conjugate given that guest molecules preferably penetrate the cavity through such opening.[1] To the best of our knowledge, this is the first time that an azobenzene structure is grafted onto the secondary face of the β-CD.

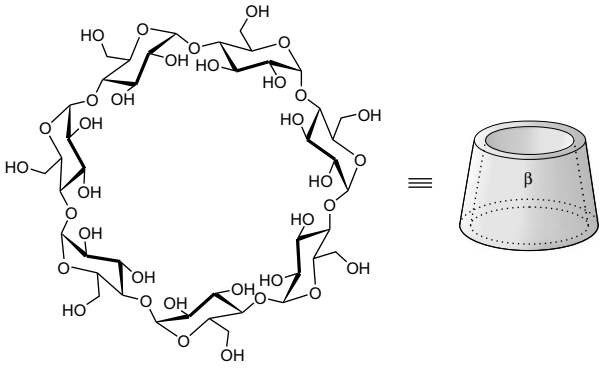
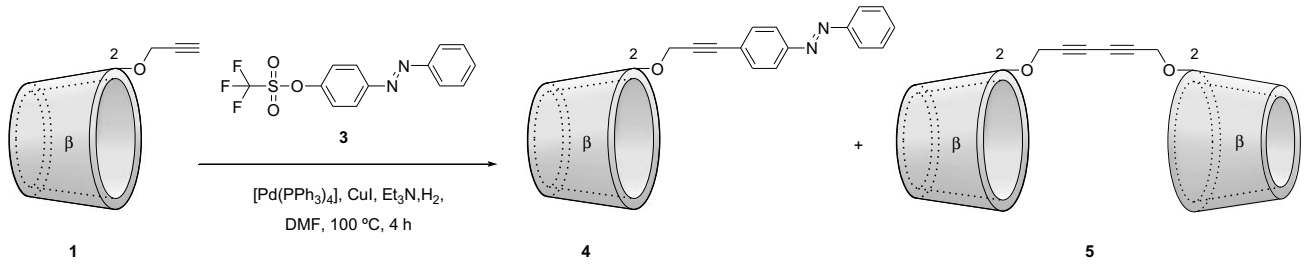


Chart 1. Schematic representation of β-CD.

To achieve this aim, we decided to start from mono-2-*O*-propargyl-β-CD **1** (Scheme 1). This compound is a very convenient building block for the construction of β-CD functionalized on the secondary face. The terminal alkyne group linked to C-2 of the

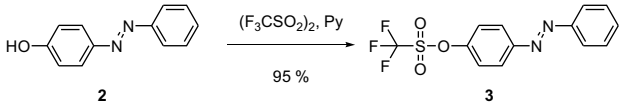
* Corresponding author. Tel.: +34 950 015315; fax: +34 950 015481.
E-mail address: avargas@ual.es (A. Vargas-Berenguel).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.032



1 3 4 5

Scheme 1.



2 3

Scheme 2.

macrocycle offers the possibility of the attachment of the azobenzene structure by oxidative coupling Sonogashira reaction. The necessary electrophile for the oxidative coupling reaction was provided by triflation of 4-hydroxyazobenzene **2** to give the triflated azobenzene **3** (Scheme 2). This reaction was performed in the presence of triflic anhydride in pyridine and gave desired compound in 95% yield. Triflation was easily confirmed by ^{13}C NMR as it showed the appearance of a quartet at 118.8 ppm with a coupling constant of 320.9 Hz, which is typical of the CF_3 group. In addition, the signal of C-4 carbon of the phenol ring suffered a significant displacement of ca. 10 ppm to lower frequency.

Targeting β-CD bearing azobenzene on secondary face **4** (Scheme 1), we performed the reaction of **1** and **3** under several Sonogashira-type reaction conditions.[10,11] Presence of CuI and Et_3N as a nitrogenated base showed to be essential for the synthesis of **4**. We found that the formation of oxidative homocoupling product **5** and the de-*O*-propargylation reaction competed with the formation of **4** in all cases. In fact, compound bis(β-CD) **5** was obtained in 98% yield, after column chromatography purification, when the oxidative coupling reaction was performed in the absence of compound **3**. Our attempts to reduce the homocoupling reaction included the use of $[Pd(PPh_3)_4]$ instead of $[PdCl_2(PPh_3)_2]$, exhaustive degassing of the reaction mixture before adding the propargyl derivate **1**, and pre-heating of the oil bath. These conditions led to a slight decrease in the extension of the homocoupling though dimer **5** remained the major product. However, a much better result for the heterocoupling reaction was obtained when the reaction was performed in DMF at 100 °C with Et_3N as a base using $[Pd(PPh_3)_4]$ and CuI as catalysts and an atmosphere of hydrogen gas diluted with nitrogen (see Supplementary data). The reductive atmosphere was key for diminishing homocoupling, since it seems to reduce the concentration of oxygen in the reaction which may be the major responsible for the homocoupling reaction.[11c] Under these reaction conditions, compounds **1** and **3** gave rise to the desired 2-*O*-azobenzene-β-CD **4** in 62% yield along with homocoupling product **5** in 37% yield, after silica gel column chromatography. Furthermore, no traces of the de-*O*-propargylation product were found in this case.

MALDI-TOF mass spectrometry verified the molecular weight of compounds **4** and **5**. In addition, we used NMR spectroscopic techniques with COSY, HMQC, and HMBC experiments for their characterization. Cursory inspection of ^1H NMR spectra showed the absence of a signal at 3.52 ppm, corresponding to alkyne proton of compound **1** and the appearance, in the case of **4**, of signals at 7.95–7.60 ppm, corresponding to the aromatic azobenzene protons. In the ^{13}C NMR spectrum of **4** appeared a series of peaks between 151.9 and 122.7 ppm indicating the presence of the azobenzene rings. Likewise, alkyne carbons signals observed at 79.9 and 77.8 ppm on the spectrum of **1** did not appear on the spectra of **4** and **5**. Instead, the spectrum of **4** showed peaks at 88.5 and 85.6 ppm corresponding to aryl alkyne carbons, while that of **5** showed signals at 76.4 and 69.8 assigned to the 1,3-diyne carbons.

In conclusion, an oxidative coupling Sonogashira-type reaction has been used to synthesize a β-cyclodextrin derivative bearing an azobenzene group on the secondary face for the first time. We started from a β-cyclodextrin propargylated at C-2 position of only one of its D-glucose units. The de-*O*-propargylation reaction and the formation of an oxidative homocoupling dimer were found to compete with the desired product under several Sonogashira-type reaction conditions. However, the exhaustive degassing of the reaction mixture and the use of $[Pd(PPh_3)_4]$ instead of $[PdCl_2(PPh_3)_2]$, a pre-heated oil bath, and a diluted reductive atmosphere of H_2 avoided the former and diminished the latter.

Acknowledgments

The authors acknowledge the Spanish Ministry of Education and Science for the financial support (Grant CTQ2007-61207) and for a Ph.D. scholarship (J.M.C.-S.).

Supplementary data

Supplementary data (general methods, ^1H NMR, ^{13}C NMR and MALDI-TOF-MS spectra for compounds **1** and **3**–**5**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.032.

References and notes

1. (a) Szejtli, J., Osa, T., Eds. *Comprehensive Supramolecular Chemistry: Cyclo dextrins*; Pergamon: Berlin, 1996; Vol. 3; (b) Thematic issue: D'Souza, V. T.; Lipkowitz, K. B., Guest Eds. *Chem. Rev.* **1998**, *98*, 1741–2076.; (c) *Cyclodextrins and Their Complexes*; Dodziuk, E., Ed.; Wiley-VCH: Weinheim, 2006; (d) Hapiot, F.; Tilloy, S.; Monflier, E. *Chem. Rev.* **2006**, *106*, 767–781.
2. (a) Feringa, B. L. *Molecular Switches*; Wiley-VCH: Weinheim, 2001; (b) Harada, A. *Acc. Chem. Res.* **2001**, *34*, 456–464; (c) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines. A Journey into the Nanoworld*; Wiley-VCH: Weinheim, 2003.
3. (a) Nelissen, H. F. M.; Venema, F.; Uittenbogaard, R. M.; Feiters, M. C.; Nolte, R. J. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2045–2053; (b) Liu, Y.; Chen, G.-S.; Chen, Y.; Ding, F.; Liu, T.; Zhao, Y.-L. *Bioconjugate Chem.* **2004**, *15*, 300–306; (c) Alvarez Alcalde, M.; Gancedo, C.; Jover, A.; Carrazana, J.; Soto, V. H.; Meijide, F.; Vazquez Tato, J. *J. Phys. Chem. B* **2006**, *110*, 13399–13404; (d) Becuwe, M.; Cazier, F.; Bria, M.; Woisel, P.; Delattre, F. *Tetrahedron Lett.* **2007**, *48*, 6186–6188.
4. (a) Corradini, R.; Dossena, A.; Impellizzeri, G.; Maccarrone, G.; Marchelli, R.; Rizzarelli, E.; Sartor, G.; Vecchio, G. *J. Am. Chem. Soc.* **1994**, *116*, 10267–10274; (b) Haskard, C. A.; Easton, C. J.; May, B. L.; Lincoln, S. F. *Inorg. Chem.* **1996**, *35*, 1059–1064; (c) West, L. C.; Wyness, O.; May, B. L.; Clements, P.; Lincoln, S. F.; Easton, C. J. *Org. Biomol. Chem.* **2003**, *1*, 887–894; (d) Potter, C. F.; Russell, N. R.; McNamara, M. *J. Inclusion Phenom. Macrocyclic Chem.* **2006**, *56*, 395–403; (e) Pham, D.-T.; Clements, P.; Easton, C. J.; Lincoln, S. F. *Tetrahedron: Asymmetry* **2008**, *19*, 167–175.

5. (a) Kaifer, A. E. *Acc. Chem. Res.* **1999**, *32*, 62–71; (b) Liu, J.; Li, Y.; Fang, Y. *Prog. Nat. Sci.* **2005**, *15*, 1057–1065; (c) Bilewicz, R.; Chmurski, K. In *Cyclodextrins and Their Complexes*; Dodziuk, H., Ed.; Wiley-VCH: Weinheim, 2006; pp 298–318.
6. (a) Mulder, A.; Jukovic, A.; Lucas, L. N.; van Esch, J.; Feringa, B. L.; Huskens, J.; Reinhoudt, D. N. *Chem. Commun.* **2002**, 2734–2735; (b) Mulder, A.; Jukovic, A.; Huskens, J.; Reinhoudt, D. N. *Org. Biomol. Chem.* **2004**, *2*, 1748–1755; (c) Mulder, A.; Jukovic, A.; van Leeuwen, F. W. B.; Kooijman, H.; Spek, A. L.; Huskens, J.; Reinhoudt, D. N. *Chem. Eur. J.* **2004**, *10*, 1114–1123; (d) Kuad, P.; Miyawaki, A.; Takashima, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* **2007**, *129*, 12630–12631.
7. (a) Beveridge, D. L.; Jaffé, H. H. *J. Am. Chem. Soc.* **1966**, *88*, 1948–1953; (b) Griffiths, J. *Chem. Soc. Rev.* **1972**, 481–493; (c) Tamai, N.; Miyasaka, H. *Chem. Rev.* **2000**, *100*, 1875–1890.
8. (a) Ueno, A.; Yoshimura, H.; Saka, R.; Osa, T. *J. Am. Chem. Soc.* **1979**, *101*, 2779–2780; (b) Ueno, A.; Takahashi, K.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1981**, 94–96; (c) Ueno, A.; Fukushima, M.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1067–1072; (d) Fukushima, M.; Osa, T.; Ueno, A. *J. Chem. Soc., Chem. Commun.* **1991**, 15–17; (e) Aoyagi, T.; Ueno, A.; Fukushima, M.; Osa, T. *Macromol. Rapid Commun.* **1998**, *19*, 103–105; (f) Kuwabara, T.; Nakajima, H.; Nanasawa, M.; Ueno, A. *Anal. Chem.* **1999**, *71*, 2844–2849; (g) Lee, W.-S.; Ueno, A. *Macromol. Rapid Commun.* **2001**, *22*, 448–450; (h) Kikuchi, T.; Narita, M.; Hamada, F. *J. Inclusion Phenom. Macrocyclic Chem.* **2002**, *44*, 329–334; (i) Liu, Y.; Zhao, Y.-L.; Zhang, H.-Y.; Fan, Z.; Wen, G.-D.; Ding, F. *J. Phys. Chem. B* **2004**, *108*, 8836–8843; (j) Liu, Y.; Kang, S.; Chen, Y.; Yang, Y.-W.; Huskens, J. *J. Inclusion Phenom. Macrocyclic Chem.* **2006**, *56*, 197–201; (k) Ma, X.; Wang, Q.; Tian, H. *Tetrahedron Lett.* **2007**, *48*, 7112–7116; (l) Liu, Y.; Yang, Z.-X.; Chen, Y. *J. Org. Chem.* **2008**, *73*, 5298–5304.
9. Casas-Solvas, J. M.; Martos-Maldonado, M. C.; Vargas-Berenguel, A. *Tetrahedron* **2008**, doi:10.1016/j.tet.2008.08.098.
10. For a recent review of the Sonogashira reaction conditions, see: Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.
11. (a) Ortega-Caballero, F.; Giménez-Martínez, J. J.; Vargas-Berenguel, A. *Org. Lett.* **2003**, *5*, 2389–2392; (b) Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653–8656; (c) Elangovan, A.; Wang, Y.-H.; Ho, T.-I. *Org. Lett.* **2003**, *5*, 1841–1844; (d) Ahmed, M. S. M.; Mori, A. *Tetrahedron* **2004**, *60*, 9977–9982.