Pergamon

Tetrahedron Letters 39 (1998) 3029–3030

TETRAHEDRON
LETTERS

Synthesis and Thermal Reactivity of a Novel Macrocyclic Enediyne and its Copper(II) Complex

Amit Basak* and Jagadish Chandra Shain
Department of Chemistry, Indian Institute of Technology,
Kharagpur 721302, India

Received 12 January 1998; accepted 6 February 1998

Abstract: A novel 24-membered tetraazaenediyne and its copper(II) complex have been synthesized via a Pd(0)-catalysed macrocyclization route. DSC measurements revealed a lowering of onset temperature for Bergman Cyclization upon complexation.

The enediyne class of antitumor antibiotics[1] exert their biological action through the formation of diradicals via a process popularly known as Bergman Cyclization (BC)[2]. The rate of BC has been shown to be influenced by ring size[3], state of hybridization[4], incorporation of hetero atom[5] or strained ring system[6] and metal ion complexation[7]. In continuation of our interest on the behaviour of nitrogen-containing enediynes[8] we have synthesized a novel tetraazaenediyne **1** and studied the perturbation of its cyclization behaviour upon complexation.

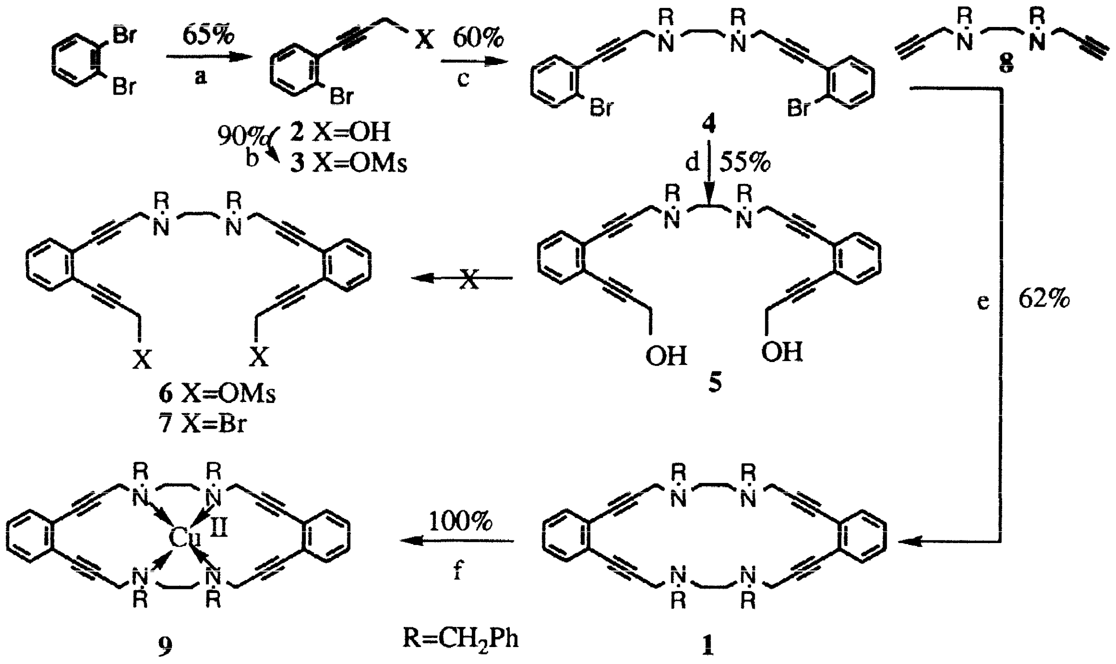
1,2-Dibromobenzene was first converted to the substituted propargyl alcohol **2** by a single Pd(0)-catalysed coupling[9]. Conversion to the mesylate **3** followed by treatment with N,N-dibenzyl ethylenediamine in the presence of K_2CO_3 in DMF produced the dibromo diamine **4**. A second Pd(0)-coupling of **4** with propargyl alcohol furnished the diol **5**. Unfortunately, attempts to prepare the mesylate **6** or the bromide **7** from the diol **5** was unsuccessful ; the reaction led to a considerable amount of decomposition product. Ultimately the target enediyne **1** was synthesized in a single step from **4** via Pd(0)-mediated biscoupling with N,N-dipropargyldibenzyl ethylenediamine **8**. The reaction proceeded very well and serves as a novel example of intramolecular ene-yne coupling leading to a macrocyclic enediyne (**Scheme 1**). The ^{1}H-NMR spectrum of **1** showed three sharp singlets (each 8H) at δ 2.87, 3.65 and 3.74 apart from the aromatic signals at δ 7.21-7.49. Further confirmation about the structure was obtained from the mass spectrum which showed the MH^+ peak at m/z 781. Differential Scanning Calorimetric (DSC)[10] measurements showed the onset temperature for BC to be around 160^0 C. The Cu(II)-complex **9** was prepared by refluxing a methanolic solution of equimolecular amounts of the enediyne **1** and $Cu(OAc)_2$ and then evaporating the solvent. The ^{1}H-NMR spectrum of the complex in $CDCl_3$ showed the aromatic protons appearing in the range of δ 7.0-7.9 whereas all the methylene protons appeared as a very broad signal in the range of δ 3.0-4.2. DSC measurement of the complex **9** showed the exothermic rise starting from 90^0 C thus indicating a lowering of onset temperature for BC by a large margin of about 70^0 C upon complexation.

An earlier work[11] on crown ethers containing enediyne moiety showed a rise of onset temperature of BC upon complexation with alkali metal ions. The repulsion between the the like charges or the accommodation of a large K^+ ion was predicted to be the cause behind such a rise. In the tetraaza system **1**, the inner cavity size seems sufficient to accommodate Cu(II) ion and thus form an 11-membered ring. As a result the distance between the acetylenic carbons undergoing covalent connection is lowered and hence BC is facilitated at a lower temperature.

*Current Address: Visiting Associate Professor, Department of Chemistry, Johns Hopkins University, 3400 Charles Street, Baltimore MD 21218, USA.

0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00325-6

Acknowledgement: Auther (AB) thanks CSIR, Government of India for financial assitance. We thank Dr. A.Basak, IRCM, Montreal,Canada for the Mass Spectral data.



a:Pd$(PPh_3)_4$,$CHCCH_2OH$,n-$BuNH_2$ b:$MeSO_2Cl$,NEt_3 c:$RNHCH_2CH_2NHR$,K_2CO_3

d:Pd$(PPh_3)_4$,$CHCCH_2OH$,n-$BuNH_2$ e:Pd$(PPh_3)_4$,n-$BuNH_2$,reflux f:Cu$(OAc)_2$,MeOH

Scheme 1

Selected Spectral Data: For **1** δ_H 2.87 (8H, *s*), 3.65 (8H, *s*), 3.74 (8H, *s*), 7.21-7.49,(28H, *m*); δ_C 42.53, 51.27, 58.25, 84.85, 88.29, 25.70, 127.10, 127.63, 128.23, 129.18, 132.34, 138.69; γ_{max}(KBr) 613, 694, 747, 812, 942, 983, 1033, 1075, 1112, 1318, 1350, 1442, 1480, 1545, 1603, 1723, 2362, 2921, 3069 cm .; Mass(FAB) 781 (MH$^+$); λ_{max} (MeOH) 259.8, 232.4 nm; For **9** δ_H 3.0-4.2 (24H, *bm*), 7.0-7.9 (28H, *bm*); γ_{max} (KBr) 648, 693, 749, 1026, 1119, 1234, 1428, 1569, 1724, 2355, 2933 cm ; λ_{max} (MeOH) 247, 232, 215 nm.

References :

1. Jones, B.R.; Bergman, R.G. *J. Am. Chem. Soc.* **1972**, *94*, 660; Bergman, R. G. *Acc. Chem.Res.* **1973**, *6*, 25; Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J . Am. Chem. Soc.* **1981**, *103*, 4091.
2. Nicolaou, K. C.; Dai, W.M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387; Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron*, **1996**, *52*, 6453.
3. Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.
4 De Voss, J. J.; Hangeland, J. J.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *12*, 4554.
5. Sakai, Y.; Nishiwaki, E.; Shishido, K.; Shibuya, M. *Tetrahedron Lett.* **1991**, *32*, 4363.
6. Nicolaou, K. C.; Sorensen, E. J.; Discordia, R.; Hwang, C. K.; Minto, R. E.; Bharucha, K. N.; Bergman, R. G. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1044; Basak, A.; Khamrai, U. K. *J. Chem. Soc. Chem. Commun.* **1996**, 749; Banfi, L.; Guanti, G *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2393.
7. Konig, B.; Hollnagel, H.; Ahrens, B.; Jones, P. G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2538.
8. Shain, J. C.; Khamrai, U. K.; Basak, A. *Tetrahedron Lett.* **1987**, *38*, 6067; Basak, A.; Shain, J. S. *Tetrahedron Lett.* **1998**, *39*, 1623.
9. Just, G.; Singh, R. *Tetrahedron Lett.* **1987**, *28*, 5981.
10. Burkhead, K.; Rutters, H. *Tetrahedron Lett.* **1994**, *35*, 3501.
11. Sigman, D. S. *Acc. Chem. Res.* **1986**, *19*, 180.; Ranganathan, D.; Misra, R. K.; Patel, B. K.; Vaish, N. K. *Proc. Ind. Acad. Sci.* **1994**, *106*, 1071.