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

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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.

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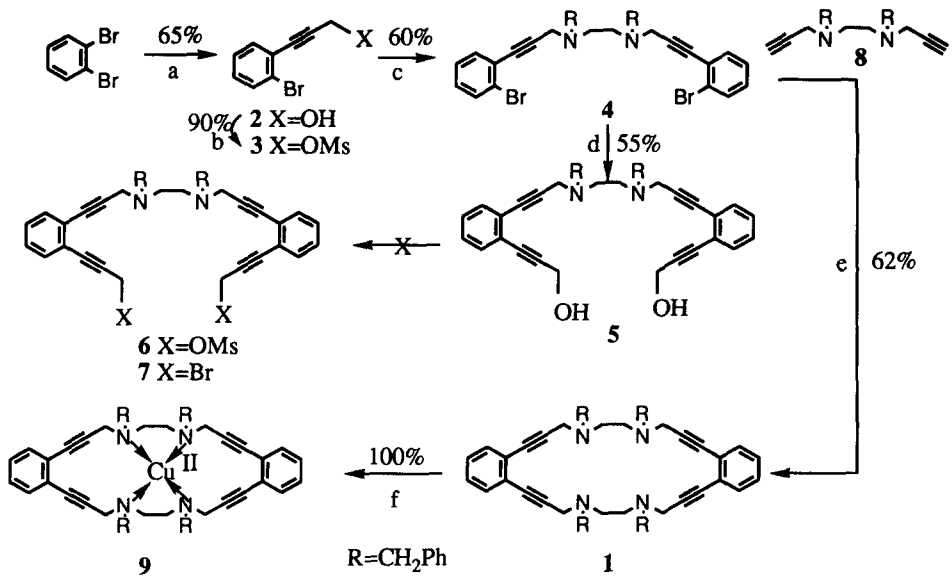

a:$Pd(PPh_3)_4$,$CHCCH_2OH$,n-$BuNH_2$ b:$MeSO_2Cl$,NEt_3 c:$RNHCH_2CH_2NHR$,K_2CO_3

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.

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