



Pergamon

Tetrahedron Letters 41 (2000) 7231–7234

TETRAHEDRON
LETTERS

Synthesis and thermal reactivity of a novel bis-salicylaldimino enediyne and its Cu(II) and Ni(II) complexes

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Received 17 July 2000; accepted 21 July 2000

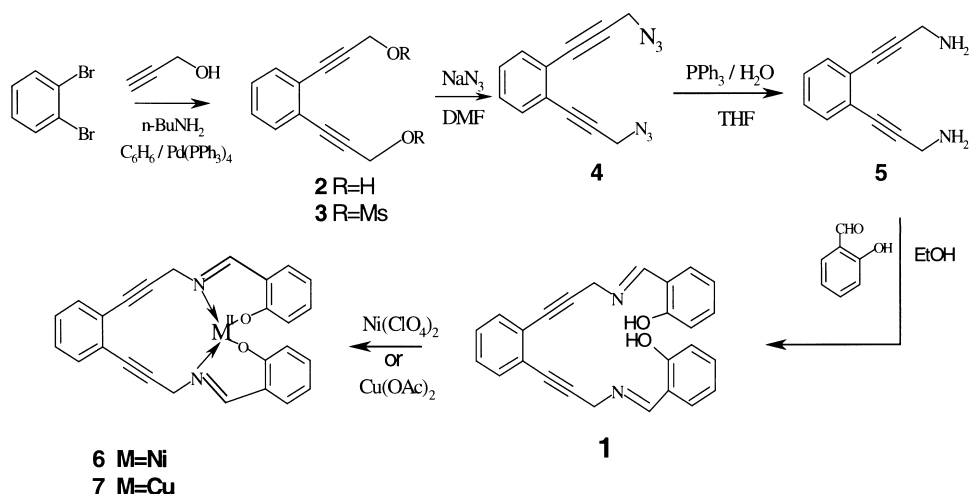
Abstract

A novel bis-salicylaldimino enediyne **1**, along with its Ni(II) and Cu(II) complexes **6** and **7**, respectively, were prepared. Differential Scanning Calorimetric studies revealed an elevation of the onset temperature for Bergman cyclization upon complexation. © 2000 Published by Elsevier Science Ltd.

Harnessing the DNA-damaging activity of enediynes through rational design has been an active area of research in recent years.¹ An important criteria for a successful design is the incorporation of attachments (functionalities) to the enediyne framework which may act as devices to modulate the kinetics of the Bergman cyclization (BC).² One approach towards that end is to synthesize enediynes with side-chains capable of ligating to metal ions. Complexation, in most cases,³ leads to a lowering of the activation barrier for BC. Only in cases of crown ether containing enediynes, did complexation⁴ to alkali metal ions such as Na⁺ or K⁺ cause an elevation of onset temperature for BC, compared to that for the free ligands. In this communication, we provide an interesting example of a bis-salicylaldimino enediyne **1** which upon complexation to transition metal ions like nickel(II) or copper(II) undergoes BC at a temperature much higher than the parent ligand.

The synthesis of **1** is shown in Scheme 1. First of all, the enediyne diol **2** was prepared from 1,2-dibromobenzene and propargyl alcohol (2 equiv.) via a double Pd(0)-mediated Sonogashira coupling.⁵ Conversion to the dimesylate **3** followed by displacement with sodium azide furnished the diazide **4**. Reduction of both azide groups with PPh₃ and water gave the diamine **5** which was isolated pure by column chromatography (Si-gel, 50% MeOH–CH₂Cl₂). The bis-salicylaldehyde imine **1** was obtained as an orange-yellow viscous oil by refluxing a solution of the diamine **5** and salicylaldehyde (1:2 molar ratio) in ethanol, followed by chromatography of the residual oil obtained after evaporation (Si-gel, hexane:EtOAc 7:1). The combined yield over the final two steps was 60%. The Ni²⁺ and Cu²⁺ complexes (**6** and **7**) were prepared as brown and green solids,

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Scheme 1. Spectral data for **1**: δ_{H} (CDCl₃, 300 MHz) 8.74 (2H, s, NCH=), 7.50 (2H, m, Ar-H), 7.30–7.23 (6H, m, Ar-H), 6.93 (2H, *d*, $J=8.3$ Hz, H-3'), 6.83 (2H, *t*, $J=7.6$ Hz, H-5'), 4.71 (4H, s, NCH₂); Mass (FAB) m/z 393 (MH⁺), 289, 273, 244

respectively, by refluxing the solution of **1** and nickel(II) perchlorate or copper(II) acetate in methanol. The formation of the complex was also shown by the appearance of a strong emission band at 318 nm for the Ni complex in methanol (Fig. 1) when the excitation was carried out at 268 nm. The free ligand at a similar concentration failed to show any strong emission band.

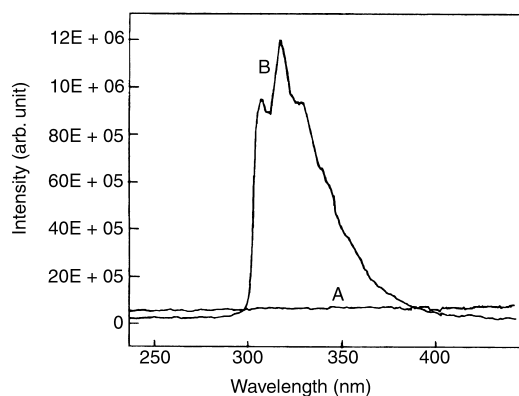


Figure 1. Fluorescence spectra at 319 nm with excitation at 268 nm; A for free ligand and B for Ni complex

The onset temperatures for BC of **1** and its complexes **6/7** were recorded by Differential Scanning Calorimetry (DSC).⁴ For the starting enediyne **1**, cyclization started at $\sim 137^{\circ}\text{C}$ (Fig. 2). This high onset temperature was expected because of its acyclic nature. Interestingly, both the Ni²⁺ and the Cu²⁺ complexes **6** and **7** showed an elevation of the onset temperature of BC. For the Ni²⁺ complex **6**, the cyclization started at $\sim 225^{\circ}\text{C}$, (Fig. 3) whereas for the Cu²⁺ complex **7**, the onset temperature was found to be $\sim 215^{\circ}\text{C}$ (Fig. 4). The incorporation of metal ions to form the complex is probably forcing the acetylenic carbons to move away from each other,⁶ thus

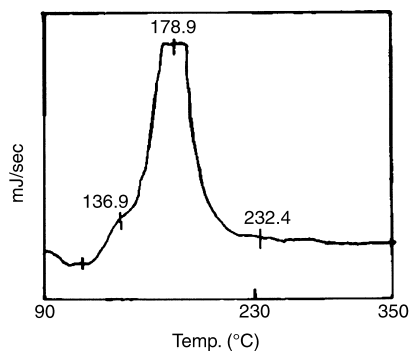
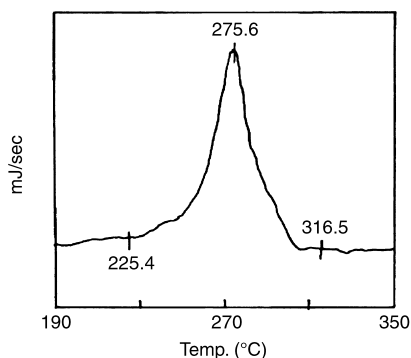
Figure 2. DSC of enediyne **1**

Figure 3. DSC of Ni complex

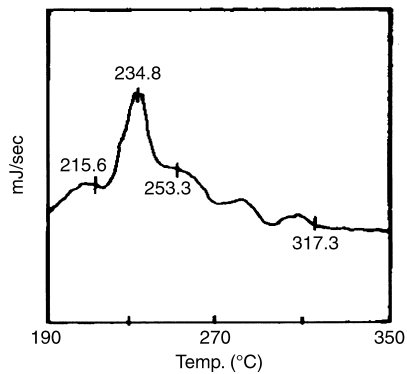


Figure 4. DSC of Cu complex

raising the activation barrier for BC. However, until we get a crystal structure for the complex, the exact reason for the elevation of cyclization temperature cannot be definitely established.

In conclusion we have provided the first example of a novel bis-salen type enediyne. The substantial elevation of the onset temperature for BC upon metal ion complexation is an interesting feature of the enediyne. Efforts are currently underway to study the DNA cleavage activity of various metal complexes of **1** under oxidative conditions.⁶

Acknowledgements

The author (A.B.) thanks CSIR, New Delhi for financial assistance.

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