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Double Anionic Cycloaromatization of 2-(6-Substituted-3-hexene-1,5-diynyl)-benzonitriles Initiated by Methoxide Addition

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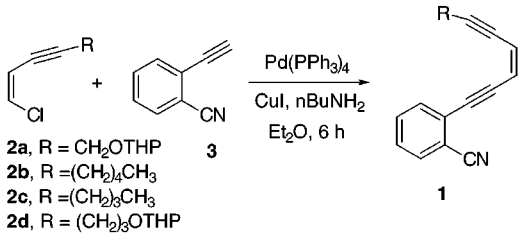
ABSTRACT



Treatment of 2-((3*Z*)-undecene-1,5-diynyl)benzonitrile with 5 equiv of sodium methoxide in refluxing methanol for 16 h gave 1-pentyl-6-methoxyphenanthridine in 12% yield, 1-pentyl-6-phenanthridone in 6% yield, and 2-(2-pentyl-6-methoxyphenyl)benzonitrile in 4% yield. Under the same reaction conditions, methanolysis of several other benzonitriles gave similar results. Phenanthridine and biphenyl derivatives were obtained as the major products. A mechanism for this novel cycloaromatization reaction of enediynes is proposed.

The cycloaromatization of enediynes and structurally related molecules has attracted much attention due to their ability to cleave DNA, their value for theoretical investigation, and their utility in synthetic chemistry.[1] Most of the investigations of the cycloaromatization mechanisms of enediynes and related compounds have concentrated on the formation of diradical intermediates because it has been generally assumed that the formation of a diradical intermediate is a prerequisite for biological activity.[2] Only a few workers have described the nonradical cycloaromatization of enediynes. Recently Magnus[3] reported a nonradical cycloaromatization of the azabicyclo[7.3.1]enediyne core which was initiated by thiolate addition and concluded that diradical formation is not a prerequisite for biological activity in that system. Another nonradical type cycloaromatization of enediynes has been reported by Saito's group[4] which demonstrates that neocarzinostatin cycloaromatizes with incorporation of one deuterium atom (80%) in the aromatic ring under physicological conditions (D_2O/buffered 2-mercaptoethanol). To better understand the duality of the mechanisms of the cycloaromatization of enediynes and the relationship of these mechanisms to their biological activity, we have investigated a direct nonradical cycloaromatization of (3*Z*)-3-hexene-1,5-diyne.

In this paper we report that 2-(6-substituted-3-hexene-1,5-diynyl)benzonitriles (**1**) undergo anionic cycloaromatization upon treatment with sodium methoxide in refluxing methanol to form phenanthridines[5] and biphenyls.[6] Both of these classes of molecules have biological and structural significance.

(1) (a) Nicolaou, K. C.; Dai, W. M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (c) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207.

(2) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497.

(3) Magnus, P.; Eisenbeis, S. A.; Rose, W. C.; Zein, N.; Solomon, W. *J. Am. Chem. Soc.* **1993**, *115*, 12627.

(4) Sugiyama, H.; Yamashita, K.; Nishi, M.; Saito, I. *Tetrahedron Lett.* **1992**, *33*, 515.

(5) Lews, J. R. *Nat. Prod. Rep.* **1997**, *14*, 303.

(6) (a) Mislow, K. *Introduction of Stereochemistry*, Benjamin: Reading, MA, 1965; pp 78−82. (b) Oki, M. *Top. Stereochem.* **1983**, *14*, 1.

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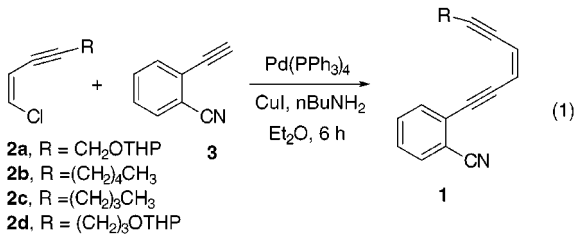
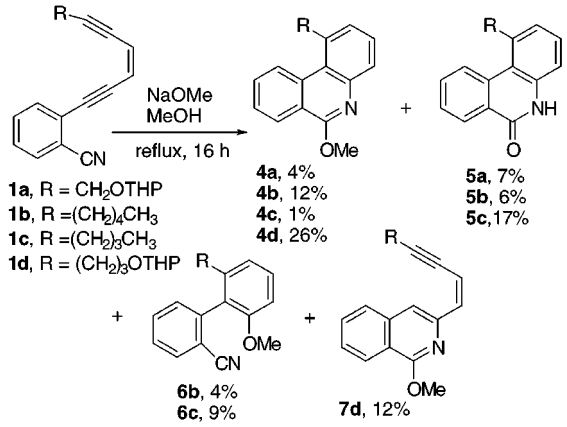
2-(6-Substituted-3-hexene-1,5-diynyl)benzonitriles (**1a**−**d**) were obtained in 17−52% yields by the reaction of vinyl chlorides **2a**−**d** with 2-ethynylbenzonitrile (**3**)[7] in ethyl ether containing 5 mol % tetrakis(triphenylphosphine)palladium (0), 15 mol % cuprous iodide, and 5 equiv of *n*-butylamine (eq 1). The results of the cycloaromatization reactions of



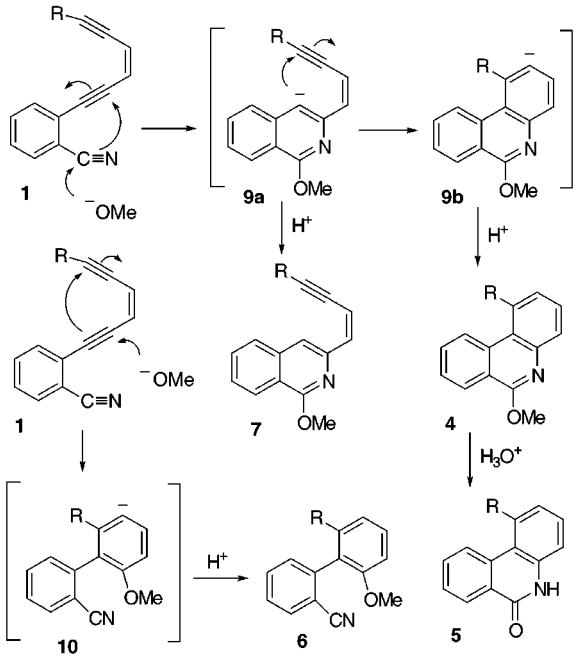
1a−**d** are summarized in Scheme 1. Treatment of **1a** with 5 equiv of sodium methoxide in refluxing methanol for 16 h gave, after the isolation of the products and column chromatography, phenanthridine **4a** in 4% yield along with phenanthridinone **5a** in 7% yield. Methanolysis of **1b** under the same reaction conditions gave **4b** in 12% yield, **5b** in 6% yield, and **6b** in 4% yield. Similarly, cycloaromatization of **1c** gave biphenyl **6c** in 9% yield along with **4c** (1%) and **5c** (17%). Under the same reaction conditions, compound **1d** cyclized in the same manner as **1a**−**c** to give **4d** in 26% yield and isoquinoline **7d** in 12% yield (Scheme 1).

Scheme 1



A plausible mechanistic explanation for the formation of **4**, **5**, and **7** involves methoxide addition to the cyano group of **1**. The initially formed iminium anion undergoes an anionic cycloaromatization to form anion **9a**. Anion **9a** then undergoes a second anionic cycloaromatization to give anion **9b**. Protonation of **9b** affords phenanthridine **4** which is hydrolyzed during acid workup to give phenanthridinone **5**. If protonation of **9a** takes place faster than the second anionic cycloaromatization, isoquinoline **7** is obtained. The formation of **6** involves the addition of methoxide to C2 of the enediyne unit and anionic cycloaromatization by the initially formed vinyl anion to give **10**. Finally, protonation of **10** leads to biphenyl **6** (Scheme 2).

Scheme 2



In conclusion, we have demonstrated that treatment of (3*Z*)-2-(6-substituted-3-hexene-1,5-diynyl)benzonitriles with sodium methoxide in refluxing methanol gave phenanthridines and biphenyls. A reaction mechanism is proposed which is the anionic cycloaromatization of the enediyne, and product formation is dependent upon the regiochemistry of the nucleophilic addition. This novel cascade cyclization provides another aspect of enediyne chemistry which is not only of pharmaceutical and theoretical value but also has potential synthetic applications.

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Supporting Information Available: Listing of selected spectroscopic data for compounds **1a**−**d**, **4a**−**d**, **5a**−**c**, **6b**−**c**, and **7d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) 2-Ethynylbenzonitrile (**3**) was prepared from 1,2-diiodobenzene in three steps: palladium-catalyzed coupling reaction of trimethylsilylacetylene with 1,2- diiodobenzene to give 2-(2-trimethylsilylethynyl)iodobenzene (**11**) in 58% yield; iodobenzene **11** was then coupled with $Zn(CN)_2$ using palladium(0) as a catalyst to give 2-(2-trimethylsilylethynyl)benzonitrile (**12**) in 45% yield; and finally the trimethylsilyl group of **12** was removed by treatment of **12** with tetrabutylammonium fluoride to give **3** in 97% yield.