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Intramolecular 1,3-dipolar nitrone cycloaddition route to bicyclic fused enediyne

Amit Basak* and Subhash C. Ghosh

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

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Abstract—Bicyclic isooxazolidinyl enediynes **1** and **2** have been prepared by intramolecular nitrone cycloaddition between the two arms of an acyclic enediyne precursor **13**. The reaction is highly regioselective and the two configurational isomers have similar onset temperatures for BC indicating no influence of bridgehead stereochemistry on the kinetics of cyclization.

Enediynes usually undergo Bergman cyclization[1] (cycloaromatization; BC) under ambient conditions when they are cyclic[2] or are capable of forming a pseudo cycle (e.g., a H-bonded or metal ion-chelated network).[3] The inherent strain in a cyclic framework coupled with the close proximity of the acetylenic carbons undergoing covalent connection is responsible for such behavior. Thus, efforts to design enediynes which will undergo BC have mostly focused on the activation of acyclic systems via the formation of a cyclic network[4] or stabilization of reactive cyclic systems by fusion to small strained rings.[5] In our laboratory over the past few years, we have been involved in synthesizing enediynes, both acyclic and cyclic and in tuning their activity through various approaches.[6] Bicyclic enediynes are attractive targets and one can fine tune their activity by controlling the ring size as well as by changing the state of hybridization of the ring atoms.[7] In this connection, we report here a one-step approach to the synthesis of bicyclic isooxazolidine fused enediynes **1** and **2** by a nitrone cycloaddition route. The reactivity of these enediynes and attempts to open the isooxazolidine ring are also described herein.

In order to study the proposed intramolecular cycloaddition, we needed to incorporate the proper functionality in the two arms of the enediyne, namely the 2-electron dienophile and the 4-electron dipolarophile. The dienophile and the dipolarophile in our case are the alkene and a nitrone, respectively. From the stability point of view, we decided to synthesize the enediyne **14** to avoid possible complications arising out of tautomerism or conjugation with the alkyne. One can envisage two possible outcomes of the proposed cycloaddition that will lead to two regioisomeric isooxazolidines (Scheme 1).

Before embarking on the synthesis of the nitrone **14**, we wanted to have some idea as to whether the eneyne system can act as a 2-electron dienophile or whether the conjugation with the alkyne moiety would perturb its electronic nature. In order to clarify this point, the bromoalkene **5**, made by a DBU-mediated elimination from the mesylate **10** (Scheme 1) and was treated with the nitrone **6** in toluene under reflux. The expected [3+2]-cycloaddition indeed took place and we isolated only one regioisomer, which was assigned the structure **3**; its isomer **4** was not observed (Scheme 2).

Thus reassured, we carried out a Sonogashira coupling[8] between the bromoalkene **5** and the 4-pentyn-1-ol. PCC oxidation of the resulting alcohol **12** afforded the unstable aldehyde **13** which was immediately converted to the nitrone **14** by reaction with benzyl hydroxylamine in methanol. The nitrone exists mainly in the *Z*-form as evidenced from ^{1}H NMR analysis and was found to be stable under ambient conditions.

The cycloaddition was then carried out, this time in refluxing benzene, at a sufficiently dilute concentration (0.003 M) to minimize the intermolecular reaction. The reaction was worked up (evaporation of the solvent

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* Corresponding author. Tel.: +91 3222283300; fax: +91 3222282252; e-mail: absk@chem.iitkgp.ernet.in

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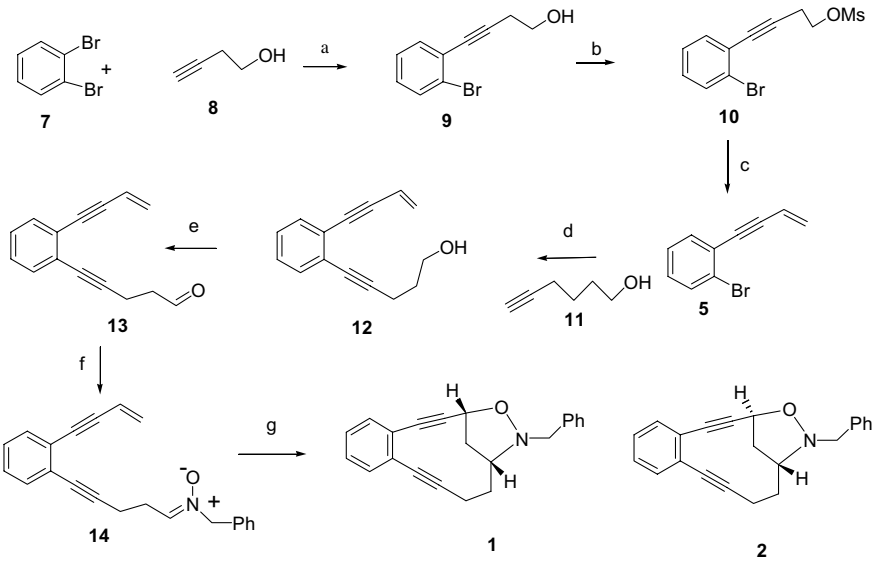
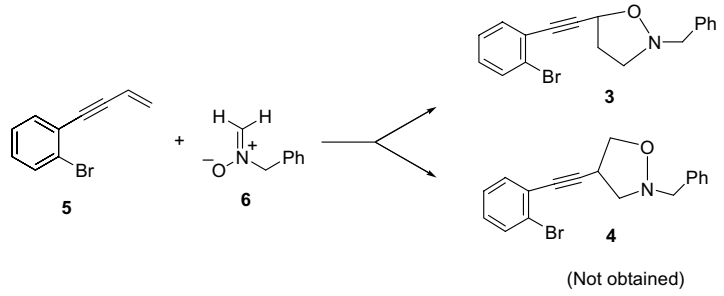


Scheme 1. Possible outcome of intramolecular cycloaddition and synthesis of isooxazolidine-based enediynes **1** and **2**. Reagents: (a) $Pd(PPh_3)_4$, *n*-$BuNH_2$, 80%; (b) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 88%; (c) DBU, CH_2Cl_2, 90%; (d) $Pd(PPh_3)_4$, *n*-$BuNH_2$, 68%; (e) PCC, CH_2Cl_2, 65%; (f) $PhCH_2$-NHOH, MeOH, 85%; (g) benzene, reflux, 75%.



Scheme 2. Outcome of intermolecular cyclization.

under vacuum) after 6 h and the residue was purified by chromatography over silica gel. Two products which were close in their R_f-values in TLC were isolated together as white solid. ^1H NMR analysis confirmed the occurrence of cycloaddition (appearance of several diastereotopic hydrogens indicating generation of stereogenic centers). However, the spectrum was complicated by the presence of two isomers and all attempts to separate these by conventional chromatography failed. The compounds could finally be separated by HPLC using ODS-Diacel column and 90% MeOH/water as the mobile phase. Both the compounds showed molecular ion peak at *m*/*z* 314 (MH^+) showing that they are products from intramolecular cycloaddition. Extensive decoupling experiments proved that the addition was highly regioselective, and that the two compounds differ in the configuration at the bridgehead. The faster running compound, which is incidentally the minor product, was assigned the trans-stereochemistry, **2**. This was based upon a NOESY experiment done on the mixture which showed cross-peaks between the bridge head hydrogen (H_a) and the methylene (H_e or H_f) for the minor isomer (Fig. 1). For the other major isomer, no such cross-peak could be seen in the NOESY spectrum and hence it was assigned the cis-stereochemistry, **1**. The overall yield of the cycloaddition was 75% and the two isomers were produced in a ratio of 1:2.

The thermal stability of **1** and **2** was then studied using differential scanning calorimetry.[9] Both the isomers show very similar onset temperatures for BC (~200 °C) proving that the configuration (cis or trans) does not have any effect on the activation barrier to BC (Fig. 2) in contrast to the cyclic carbonate system of Nicolaou where stereochemistry did play a major role.[5b] Cleavage of the isooxazolidine ring by Zn–HOAc[10] proved to be quite difficult. Although the starting material was consumed, no definite product could be isolated. The reaction (N–O cleavage) was then attempted on the simpler and easily available isooxazolidine **3**. In this case, after the treatment with Zn–HOAc, and work up, the residue was treated with 4-nitrobenzenesulfonyl chloride/Et_3N in order to protect the amine. We were able to isolate the elimination product **16**, the structure of which was confirmed by NMR and mass spectral data. The procedure was then repeated using the bicyclic enediynes, however we could not isolate the desired amine in the hydroxyl or eliminated form. Only the mass spectral data done on a fraction isolated by HPLC showed a molecular ion peak at *m*/*z*

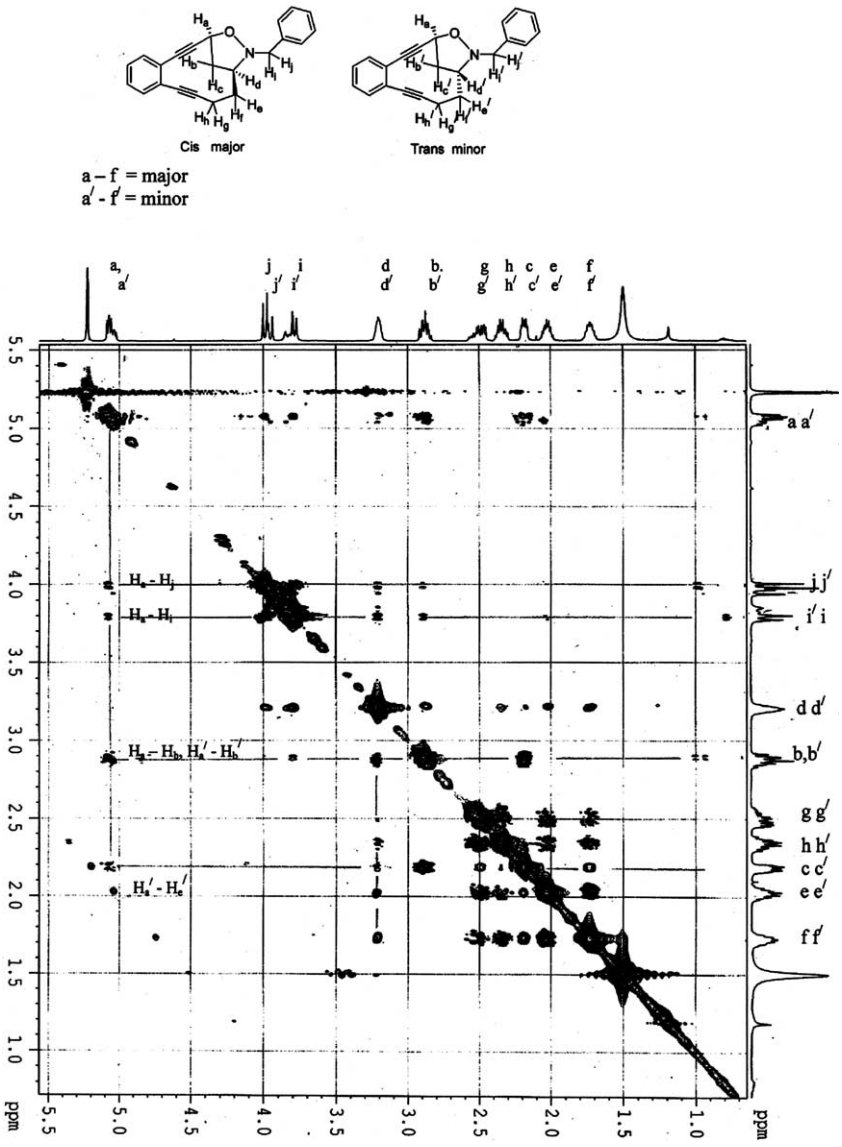


Figure 1. NOESY spectrum of mixture of **1** and **2** (assignments for hydrogens b,c/b′,c′ or e,f/e′,f′ or g,h/g′,h′ can be interchanged).

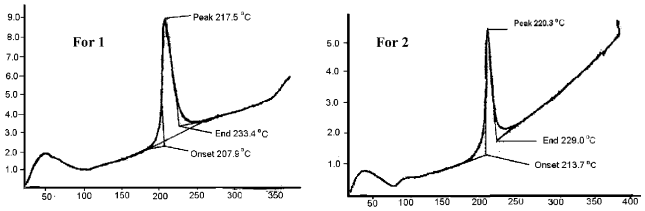
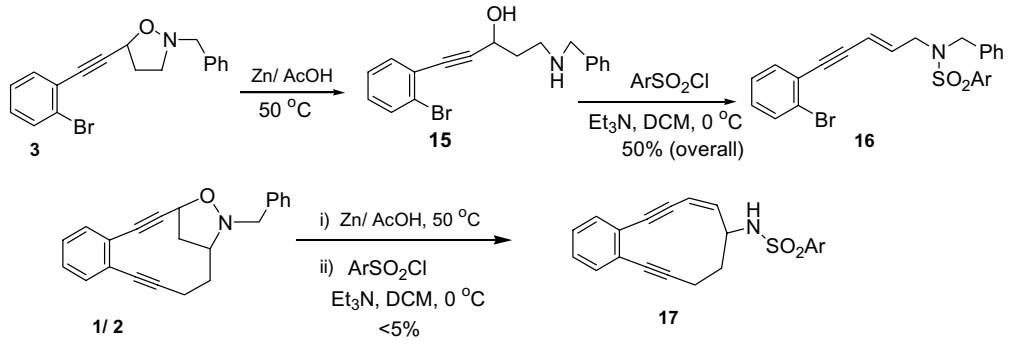


Figure 2. DSC curves of enediynes **1** and **2**.

392 (M^+), consistent with the structure **17** (Scheme 3). However, the yield of **17** was so poor (<5%) that we could not proceed further to check its thermal reactivity. Thus the effect of fusion of the isooxazolidine ring on the enediyne core could not be established. A related 10-membered N-containing benzene-fused enediyne showed an onset temperature of ~110 °C.[6j] Assuming that an 11-membered enediyne will have higher onset temperature, a difference of 90 °C does indicate locking ability of the isooxazolidine ring in lowering the reactivity of the enediyne core to some extent. Current efforts are aimed toward finding suitable reaction conditions for N–O bond cleavage in the enediynes **1** and **2** to firmly establish this aspect.

In conclusion, we have successfully synthesized two stereoisomeric isooxazolidine fused enediynes by a highly regioselective 1,3-cycloaddition approach. We are now trying to explore the possibility of using other dipolarophiles to induce the formation of more reactive bicyclic enediyne systems.

Selected spectral data: All new compounds were characterized by spectroscopic data. Some of these are mentioned below (the ^1H and ^{13}C NMR were recorded in $CDCl_3$ at 200 and 50 MHz, respectively): For compound **1** δ_H (200 MHz): 1.85–1.78 (1H, m, H_f), 2.13–2.04 (1H, m, H_e), 2.30–2.19 (1H, m, H_c), 2.55–2.40 (2H, m, H_g, H_h), 2.99–2.92 (1H, m, H_b), 3.29–3.25



Scheme 3. Results of isooxazolidine ring openings.

(1H, m, H_d), 3.86 (1H, d, $J = 13.1$ Hz, H_i), 4.07 (1H, d, $J = 13.1$ Hz, H_j), 5.14 (1H, dd, $J = 6.0$, 8.6 Hz, H_a), 7.42–7.13 (9H, m, Ar–H); Mass (EI) *m/z*: 314 (MH^+); For compound **2** δ_H (200 MHz): 1.85–1.74 (1H, m, H_f), 2.21–2.05 (1H, m, H_e), 2.36–2.24 (1H, m, H_c), 2.60–2.41 (2H, m, H_g and H_h), 2.98–2.90 (1H, m, H_b), 3.30–3.26 (1H, m, H_d), 3.90 (1H, d, $J = 13.0$ Hz, H_i), 4.03 (1H, d, $J = 13.2$ Hz, H_j), 5.11 (1H, dd, $J = 6.0$, 8.2 Hz, H_a), 7.40–7.15 (9H, m, Ar–H); Mass (EI) *m/z*: 314 (MH^+); for **12** δ_H (200 MHz): 1.94–1.81 (2H, m, CH_2CH_2OH), 2.60 (2H, t, $J = 6.8$ Hz, CH_2CH_2-CH_2OH), 3.87 (2H, t, $J = 6.1$ Hz, CH_2OH), 5.57 (1H, dd, $J = 2.3$, 11.0 Hz, CH=CH_2), 5.76 (1H, dd, $J = 2.3$, 17.5 Hz, CH=CH_2), 6.08 (1H, dd, $J = 11.0$, 17.5 Hz, CH=CH_2), 7.25–7.20 (2H, m, Ar–H), 7.44–7.36 (2H, m, Ar–H); δ_C (50 MHz): 16.11, 31.14, 61.50, 79.82, 88.88, 91.43, 93.72, 117.17, 125.35, 126.02, 127.18, 127.33, 127.94, 131.70, 131.76; Mass (EI) *m/z*: 210 (M^+); for **13** δ_H (200 MHz): 2.79 (4H, s, CH_2CH_2CHO), 5.58 (1H, dd, $J = 2.3$, 11.0 Hz, CH=CH_2), 5.75 (1H, dd, $J = 2.3$, 17.5 Hz, CH=CH_2), 6.08 (1H, dd, $J = 11.0$, 17.5 Hz, CH=CH_2), 7.26–7.20 (2H, m, Ar–H), 7.44–7.34 (2H, m, Ar–H), 9.88 (1H, s, *CH*O); δ_C (50 MHz): 12.88, 42.54, 80.10, 88.66, 91.52, 92.03, 117.13, 125.46, 125.62, 127.20, 127.54, 127.90, 131.40, 200.44; Mass (EI) *m/z*: 208 (M^+); for **14** δ_H (200 MHz): 2.79–2.67 (4H, m, CH_2CH_2CH=N), 4.88 (2H, s, CH_2Ph), 5.54 (1H, dd, $J = 2.0$, 10.8 Hz, CH=CH_2), 5.71 (1H, dd, $J = 2.0$, 17.5 Hz, CH=CH_2), 6.02 (1H, dd, $J = 11.0$, 17.5 Hz, CH=CH_2), 6.94 (1H, t, $J = 5.3$ Hz), 7.46–7.16 (9H, m, Ar–H).

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References and notes

1. (a) Jones, R. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660–661; (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25–31; (c) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082–4090; (d) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091–4096.
2. Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866–4868.
3. (a) Basak, A.; Mandal, S.; Bag, S. S. *Chem. Rev.* **2003**, *103*, 4077–4094; (b) Basak, A.; Bag, S. S.; Bdour, H. M. M. *J. Chem. Soc., Chem. Commun.* **2003**, 2614–2615.
4. Nicolaou, K. C.; Dai, W. M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387–1416.
5. (a) Banfi, L.; Guanti, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2393–2395; (b) 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*, 1044–1046; (c) Banfi, L.; Guanti, G. *Eur. J. Org. Chem.* **1998**, 1543–1548; (d) Basak, A.; Khamrai, U. K.; Mallick, U. K. *Chem. Commun.* **1996**, 749–750.
6. (a) Basak, A.; Bag, S. S.; Basak, A. *Bioorg. Med. Chem.* **2005**, *13*, 4096–4102; (b) Basak, A.; Bag, S. S.; Das, A. K. *Euro. J. Org. Chem.* **2005**, 1239–1245; (c) Basak, A.; Kar, M.; Mandal, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2061–2064; (d) Basak, A.; Roy, S. K.; Mandal, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 132–135; (e) Basak, A.; Bag, S. S.; Majumder, P. A.; Das, A. K.; Bertolasi, V. *J. Org. Chem.* **2004**, *69*, 6927–6930; (f) Basak, A.; Rudra, K. R.; Bag, S. S.; Basak, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1805–1809; (g) Basak, A.; Mandal, S. *Tetrahedron Lett.* **2002**, *43*, 4241–4243; (h) Basak, A.; Mandal, S.; Das, A. K.; Bertolasi, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 873–877; (i) Basak, A.; Bdour, H. M.; Shain, J. C.; Mandal, S.; Rudra, K. R.; Nag, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1321–1325; (j) Basak, A.; Shain, J. C.; Khamrai, U. K.; Rudra, K. R.; Basak, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1955–1964; (k) Basak, A.; Bdour, H. M.; Shain, J. C. *J. Ind. Chem. Soc.* **1999**, *76*, 679–688; (l) Basak, A.; Bdour, H. M. *Tetrahedron Lett.* **1999**, *40*, 995–996; (m) Basak, A.; Shain, J. C. *Tetrahedron Lett.* **1998**, *39*, 3029–3030; (n) Basak, A.; Khamrai, U. K. *Tetrahedron Lett.* **1996**, *37*, 2475–2478.
7. (a) Magnus, P.; Lewis, R. T. *Tetrahedron Lett.* **1989**, *30*, 1905–1906; (b) Basak, A.; Bag, S. S.; Das, A. K. *Eur. J. Org. Chem.* **2005**, 1239–1245.
8. Sonogashira, K.; Tohoda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
9. Koenig, B.; Ruetters, H. *Tetrahedron Lett.* **1994**, *35*, 3501–3504.
10. (a) Whisler, M. C.; Beak, P. *J. Org. Chem.* **2003**, *68*, 1207–1215; (b) Roger, C.; Grierson, D. S. *Tetrahedron Lett.* **1998**, *39*, 27–30.