Chemistry of enediynyl azides: activation through a novel pathway†

Amit Basak,*[a] Sandip K. Roy,[a] Sanket Das,[a] Amrita B. Hazra,[a] Subhash C. Ghosh[a] and Shailendra Jha[b]

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The spontaneous activation of a nonaromatic enediynyl azide under ambient conditions has been demonstrated. The aromatic enediyne followed the expected cycloaddition with the alkene in the neighbouring arm to form a stable bridged bicyclic enediyne.

Enediynes usually undergo Bergman cyclization (BC)[1] under ambient conditions when they are cyclic[2] or are capable of forming a pseudo cyclic network mediated by ligand–metal[3] or H-bond[4] or charge transfer[5] interactions. The inherent strain[6] in a cyclic framework coupled with the close proximity[7] of the acetylenic carbons undergoing covalent connection is responsible for such behaviour. Since the spontaneity of BC of monocyclic enediynes can be controlled by fusion of an extra ring on to the parent molecule, bicyclic enediynes continue to be attractive targets. One can fine tune their reactivity by perturbing the size of the ring[8] or by changing the hybridization of the ring atom.[9] Recently, we have reported an intramolecular cycloaddition route to isooxazoline[10] and β-lactam fused enediynes[11] in a single step starting from an acyclic enediyne precursor. In this communication, we describe a similar approach, this time involving an alkene and an azide. During the course of our work, we observed many interesting results which are presented here. One particularly important observation is the activation of an enediyne through a novel pathway.

1,3-Dipolar cycloaddition of an azide with alkene/alkyne is well-known to lead to the formation of fused ring heterocycles.[12] A variety of heterocycles like imines, aziridines, pyrrolidines formed using an alkene as the dipolarophile by the loss of molecular nitrogen from the initial adduct which is usually a mixture of regioisomeric 1,2,3-triazolines. For inducing an intramolecular cycloaddition, the azide and the dienophile should be placed in the two arms of an acyclic enediyne. Accordingly, we have designed the enediyne scaffolds **1–4** containing the required functionalities (Fig. 1). These are classified into two groups, one having the alkene functionality conjugated to the enediyne (**1** and **2**) while the other having an isolated alkene (**3** and **4**).

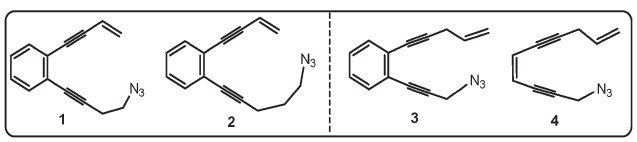
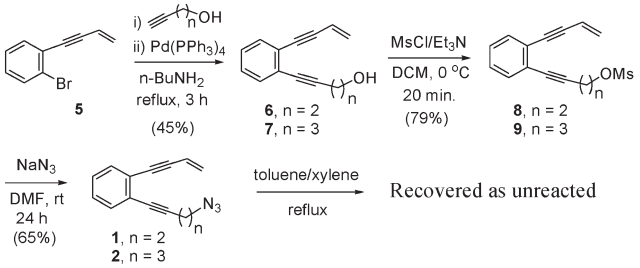


Fig. 1 Structure of **1–4**.

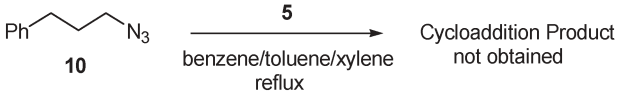
As an initial study, compound **1** was taken up for synthesis. Thus the bromoalkene **5**, made by our published procedure,[10] was coupled to 3-butyn-1-ol under Sonogashira conditions.[13] The resulting alcohol **6** was mesylated and then converted to the azide (Scheme 1). The azide **1**[14] was, however, found to be stable and reluctant to undergo cycloaddition even when refluxed in toluene or xylene for 35–40 h. Initially, we thought that the acetylene arm containing the azide was too short to come within reacting distance with the alkene. However, the homologous azide **2**,[14] prepared in a similar manner, also failed to react thus ruling out the above logic. It appears that the alkene being conjugated to the benzene ring is deactivated and the HOMO–LUMO energy difference is perhaps too large for the reaction between the partners to occur. This argument was supported by the fact that an attempted intermolecular reaction between the alkene **5** and the 3-phenyl propyl azide **10** also did not go through (Scheme 2).

We then synthesized the nonconjugated enediynes **3** and **4**[14] to find out whether deconjugation facilitates the reaction or not. The synthesis of **3** and **4** was achieved by two Sonogashira coupling steps followed by a Cu(I)-mediated alkylation of the terminal alkyne[15] and subsequent conversion of the alcohol to azide. The entire synthesis is shown in Schemes 3 and 4.

Both the aromatic and nonaromatic enediynes were found to be unstable even under ambient conditions. Upon refluxing in benzene in the presence of 1,4-CHD for 5 h, the aromatic enediyne **3** underwent intramolecular cycloaddition to give mainly one triazoline fused enediyne **22** (yield ~42%) (Scheme 5). The occurrence of cycloaddition was indicated by the disappearance of the characteristic absorption band for the azide at 2120 cm^{-1} and

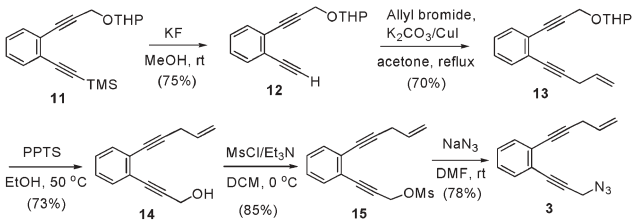


Scheme 1 Synthesis of **1** and **2**.

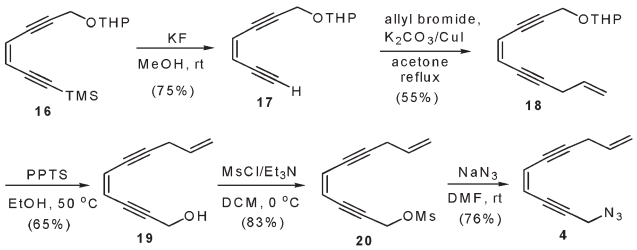


Scheme 2 Attempted intermolecular 1,3-dipolar cycloaddition.

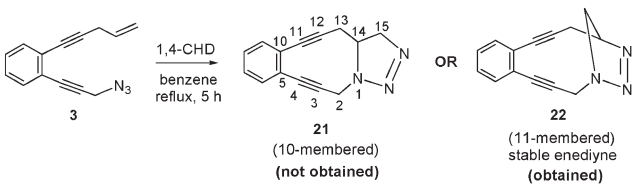
[a]*Bioorganic Laboratory, Department of Chemistry, Indian Institute of Technology, Kharagpur, India. E-mail: absk@chem.iitkgp.ernet.in; Fax: 91 3222 282252; Tel: 91 3222 283300*
[b]*Department of Chemistry, Jadavpur University, Kolkata, 700 032, India*
† The HTML version of this article has been enhanced with colour images.



Scheme 3 Synthesis of **3**.



Scheme 4 Synthesis of **4**.



Scheme 5 Reactivity of **3**.

also by the absence of the signals for the vinyl group in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum showed the characteristic signals for the four acetylenic carbons between δ 80–100 thus ruling out any cycloaromatization during the azide–alkene cycloaddition. Between the two possible regioisomeric triazolines, the one with a bridgehead was favoured due to the following reasons: (i) the non-occurrence of BC which was expected for the other isomer **21** containing a 10-membered ring; and (ii) the absence of any 1,4-cross peak in the NOESY spectrum. A cross peak between H-2 and H-13 was expected for structure **21**.

The nonaromatic enediyne **4**, upon similar refluxing in benzene in presence of 1,4-CHD for 5 h also produced only one major product, characterized as the benzotriazine derivative **27** (yield ~35%). The structure elucidation was based upon the following: (i) disappearance of the peak for the azide at 2107 cm^{-1} in the FT-IR spectrum; (ii) presence of allyl group as revealed in the ^{1}H-NMR; (iii) appearance of three aromatic protons characteristic of a 1,2,3-trisubstituted benzene; (iv) a D_2O-exchangeable peak at δ 8.06 due to NH and appearance of a peak at *m*/*z* 146 (MH^+–N_2) in the ESI mass spectrum. Structure **27** was favoured over structure **26** because of the low chemical shift of NH proton.[16] Interestingly, the same product could also be obtained (in lower yield ~15%) if the solution was kept at room temperature for 7 d. The mesylate **20** could be converted into the azide (~30% yield) if it was stirred in water under similar concentrations at room temperature and the resulting azide **4** has also been shown to undergo slow decomposition in aqueous medium thus opening the possibility of DNA-cleavage under aqueous conditions. The low yield was due to the competing hydrolysis back to the starting alcohol **19**.

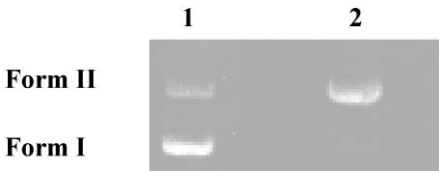
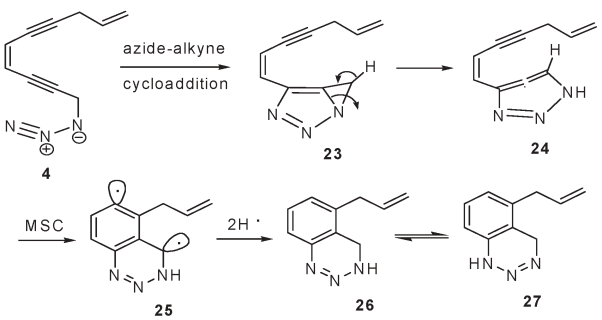


Fig. 2 Picture of DNA cleavage. **Lanes**: 1. DNA in TAE buffer (pH 8) (5 μL) + acetonitrile (15 μL) at 37 °C; 2. DNA in TAE buffer (pH 8) (5 μL) + azide **4** (40 μM, 48 h) in acetonitrile (15 μL) at 37 °C.



Scheme 6 Reactivity of **4**.

The probable mechanism of formation of the product is shown in Scheme 6. It is based on the initial dipolar cycloaddition with the alkyne[12a,17] followed by rearrangement to form the eneyne-allene **24**. Myers–Saito cyclization[18] and subsequent abstraction of hydrogen atoms lead to the final product **27**. Similar cascade of reactions is not possible in the aromatic system because of deactivation of the alkynes which is conjugated to the benzene ring. Since the mechanism involves the formation of diradicals under ambient conditions, radical-mediated cleavage of ds-DNA can be expected. In fact, azide showed DNA-cleavage under ambient conditions. Thus, supercoiled plasmid DNA (pBR 322) underwent single strand cuts when incubated with the enediyne **4** at 37 °C for 48 h (Fig. 2).

In conclusion, we have demonstrated the spontaneous activation of a nonaromatic enediynyl azide under ambient conditions. The aromatic enediyne followed the expected cycloaddition with the alkene in the neighbouring arm to form a bridged bicyclic enediyne. Current studies are aimed towards exploring the novel rearrangement in other nonaromatic analogues.

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Notes and references

1 (*a*) R. G. Bergman, *Acc. Chem. Res.*, 1973, **6**, 25; (*b*) T. P. Lockhart and a. R. G. Bergman, *J. Am. Chem. Soc.*, 1981, **103**, 4091.
2 K. C. Nicolaou, G. Zuccarello, Y. Ogawa, E. J. Schweiger and T. Kumazawa, *J. Am. Chem. Soc.*, 1988, **110**, 4866.
3 B. P. Warner, S. P. Miller, R. D. Broee and S. L. Buchwald, *Science*, 1995, **269**, 814.
4 A. Basak, S. S. Bag and H. M. M. Bdour, *Chem. Commun.*, 2003, 2614.
5 A. Basak, S. S. Bag and A. K. Das, *Eur. J. Org. Chem.*, 2005, 1239.
6 (*a*) K. C. Nicolaou, G. Zuccarello, Y. Oogawa, E. J. Schweiger and T. Kumazawa, *J. Am. Chem. Soc.*, 1988, **10**, 4866; (*b*) P. R. Schreiner, *J. Am. Chem. Soc.*, 1998, **120**, 4184.

7 (*a*) P. Magnus, D. Parry, T. Iliadis, S. A. Eisenbeis and R. A. Fairhurst, *J. Chem. Soc., Chem. Commun.*, 1994, 1543; (*b*) P. Magnus, S. Fortt, T. Pitterna and J. P. Snyder, *J. Am. Chem. Soc.*, 1990, **112**, 4986.

8 (*a*) L. Banfi and G. Guanti, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2393; (*b*) K. C. Nicolaou, E. J. Sorensen, R. Discordia, C.-K. Hwang, R. E. Minto, K. N. Bharucha and R. G. Bergman, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1044; (*c*) A. Basak, U. K. Khamrai and U. K. Mallick, *Chem. Commun.*, 1996, 749.

9 (*a*) P. Magnus, R. T. Lewis and J. C. Huffman, *J. Am. Chem. Soc.*, 1988, **110**, 6921; (*b*) P. Magnus, S. Fortt, T. Pitterna and J. P. Snyder, *J. Am. Chem. Soc.*, 1990, **112**, 4986; (*c*) P. Magnus and R. A. Fairhurst, *J. Chem. Soc., Chem. Commun.*, 1994, 1541; (*d*) D. K. Moss, J. D. Spence and M. H. Nantz, *J. Org. Chem.*, 1999, **64**, 4339; (*e*) M. H. Nantz, D. K. Moss, J. D. Spence and M. M. Olmstead, *Angew. Chem., Int. Ed.*, 1998, **37**, 47.

10 A. Basak and S. C. Ghosh, *Tetrahedron Lett.*, 2005, **46**, 7385.

11 R. Pal and A. Basak, *Chem. Commun.*, 2006, 2992.

12 (*a*) J. J. Young and C. K. Sha, *Heterocycles*, 1984, **22**, 2571; (*b*) R. Fusco, L. Garanti and G. Zecchi, *J. Org. Chem.*, 1975, **40**, 1906; (*c*) Z.-Y. Chen and M.-J. Wu, *Org. Lett.*, 2005, **7**, 475; (*d*) K. B. Sharpless, V. V. Fokin, L. G. Green and V. V. Rostovtsev, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; (*e*) J. K. Cha, R. B. Bannett, III, J.-R. Choi and W. D. Montgomery, *J. Am. Chem. Soc.*, 1989, **111**, 2580; (*f*) J. G. Buchanan, A. R. Edgar and B. D. Hewitt, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2371; (*g*) S. M. Weinreb, G. T. Anderson and J. R. Henry, *J. Org. Chem.*, 1991, **56**, 6946.

13 (*a*) K. Sonogashira, Y. Tohoda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467; (*b*) S. Takahashi, Y. Kuroyama, K. Sonogashira and N. Hagihara, *Synthesis*, 1980, 627.

14 Selected spectral data: **For 1**: δ_H (200 MHz, $CDCl_3$) 8.25 (dd, ^3J (H,H) = 1.6, 7.8 Hz, 1H; Ar–*H*), 7.60 (dd, ^3J (H,H) = 1.4, 7.8 Hz, 1H; Ar–*H*), 7.43-7.12 (m, 2H; Ar–*H*), 6.62–6.48 (m, 1H; C*H*CH_2), 5.87–5.54 (m, 1H; CHCH_2), 5.34 (dd, ^3J (H,H) = 2.2, 10.4 Hz, 1H; CHCH_2), 3.54–3.44 (m, 2H; CH_2N), 2.80–2.63 (m, 2H; C$H_2$$CH_2$N); HRMS (ES+) calcd for $C_{14}H_{11}N_3$ (MH^+) 222.1029, found 222.1046; **For 2**: δ_H (200 MHz, $CDCl_3$) 7.45–7.35 (m, 2H; Ar–*H*), 7.29–7.20 (m, 2H; Ar–*H*), 6.07 (dd, ^3J (H,H) = 11.0, 17.5 Hz, 1H; C*H*CH_2), 5.75 (dd, ^3J (H,H) = 2.2, 17.5 Hz, 1H; CHCH_2), 5.58 (dd, ^3J (H,H) = 2.2, 11.0 Hz, 1H; CHCH_2), 3.54 (t, ^3J (H,H) = 6.7 Hz, 2H; CH_2N), 2.59 (t, ^3J (H,H) = 6.8 Hz, 2H; CC$H_2$$CH_2$), 1.95–1.82 (m, 2H; C$H_2$$CH_2$N); HRMS (ES+) calcd for $C_{15}H_{13}N_3$ (MH^+) 236.1185, found 236.1201; **For 3**: δ_H (200 MHz, $CDCl_3$) 7.47–7.38 (m, 2H; Ar–*H*), 7.31–7.20 (m, 2H; Ar–*H*), 5.96–5.85 (m, 1H; CH_2C*H*), 5.48 (dd, ^3J (H,H) = 1.8, 16.9 Hz, 1H; CH_2CHCH_2), 5.18 (dd, ^3J (H,H) = 1.8, 10.0 Hz, 1H; CH_2CHCH_2), 4.17 (s, 2H; CH_2N), 3.25 (t, ^3J (H,H) = 2.4 Hz, 2H; CCH_2CH); HRMS (ES+) calcd for $C_{14}H_{11}N_3$ (MH^+) 222.1029, found 222.1011; **For 4**: δ_H (200 MHz, $CDCl_3$) 5.94–5.74 (m, 1H; C*H*CH_2), 5.38 (qd, ^3J (H,H) = 1.8, 18.6 Hz, 1H; CH_2CHCH_2), 5.13 (qd, ^3J (H,H) = 1.8, 10.0 Hz, 1H; CH_2CHCH_2), 4.09 (d, ^3J (H,H) = 1.4 Hz, 2H; CH_2N), 3.19–3.15 (m, 2H; CCH_2CH); HRMS (ES+) calcd for $C_{10}H_9N_3$ (MH^+) 172.0873, found 172.0880; **For 22**: δ_H (500 MHz, $CDCl_3$) 7.46 (d, ^3J (H,H) = 8.5 Hz, 1H; Ar–*H*), 7.28–7.06 (m, 2H; Ar–*H*), 7.05 (d, ^3J (H,H) = 6.4 Hz, 1H; Ar–*H*), 5.05 (d, ^3J (H,H) = 18.3 Hz, 1H; CCH_2N), 4.72–4.66 (m, 1H; NCH_2C*H*), 4.06 (d, ^3J (H,H) = 18.3 Hz, 1H; CCH_2N), 3.61 (t, ^3J (H,H) = 9.2 Hz, 1H; NCH_2CH), 3.36 (dd, ^3J (H,H) = 2.4, 18.0 Hz, 1H; CCH_2CH), 3.27 (t, ^3J (H,H) = 9.2 Hz, 1H; NCH_2CH), 2.79 (dd, ^3J (H,H) = 4.4, 18.0 Hz, 1H; CCH_2CH); HRMS (ES+) calcd for $C_{14}H_{11}N$ (MH^+) 194.0967, found 194.1044; **For 27**: δ_H (200 MHz, $CDCl_3$) 8.06 (s, 1H; N*H*), 7.34 (d, ^3J (H,H) = 8.0 Hz, 1H; Ar–*H*), 7.07 (d, ^3J (H,H) = 8.0 Hz, 1H; Ar–*H*), 7.01 (d, ^3J (H,H) = 8.0 Hz, 1H; Ar–*H*), 6.03–5.86 (m, 1H; C*H*CH_2), 5.10 (s, 2H; CH_2N), 5.05–5.00 (m, 1H; CHCH_2), 4.92 (d, ^3J (H,H) = 1.6 Hz, 1H; CHCH_2), 3.52 (d, ^3J (H,H) = 6.2 Hz, 2H; CCH_2CH); HRMS (ES+) calcd for $C_{10}H_{11}N$ (MH^+) 146.0967, found 146.1026.

15 Synthesis of allylacetylenes from terminal acetylenes and allyl halides. N. A. Bumagin, A. B. Ponomarev and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, **7**, 1565 (in Russian).

16 The chemical shift of NH proton for naphtho[1,8-*de*][1,2,3]triazine has been reported to be δ 13.29 in d_6-DMSO see H. Al-Awadi, M. R. Ibrahim, H. H. Dib, N. A. Al-Awadi and Y. A. Ibrahim, *Tetrahedron*, 2005, **61**, 10507.

17 (*a*) S. Roper, M. H. Franz, R. Wartchow and H. M. R. Hoffman, *Org. Lett.*, 2003, **5**, 2773; (*b*) C. von Riesen and H. M. R. Hoffman, *Chem.–Eur. J.*, 1996, **2**, 680.

18 (*a*) R. Nagata, H. Yamanaka, E. Okazaki and I. Saito, *Tetrahedron Lett.*, 1989, **30**, 4995; (*b*) A. G. Myers, E. Y. Kuo and N. S. Finnney, *J. Am. Chem. Soc.*, 1989, **111**, 8057; (*c*) A. G. Myers and P. S. Dragovich, *J. Am. Chem. Soc.*, 1989, **111**, 9130; (*d*) R. Nagata, H. Yamanaka, E. Murahashi and I. Saito, *Tetrahedron Lett.*, 1990, **31**, 2907.

