Synthesis of Isoxazoline-Fused Bicyclic Enediynes via Intramolecular Nitrile Oxide–Alkene Cycloaddition

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Dedicated to Professor Sir Jack Baldwin FRS on the occasion of his 70th birthday

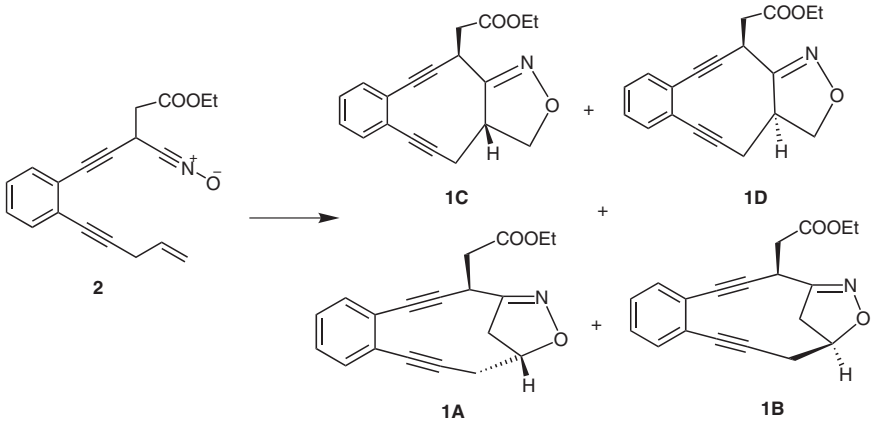
Abstract: The intramolecular nitrile oxide–alkene cycloaddition has been studied in an enediyne system. It has been shown to be an efficient method for one-step synthesis of isoxazoline-fused bicyclic enediynes. The thermal reactivity of these enediynes is similar to the isoxazolidine-fused counterparts, thus ruling out any significant effect by the bridgehead double bond.

Key word: enediyne, cycloaddition, Bergman cyclization, intramolecular, activation

Bicyclic enediynes are attractive targets as the non-enediyne cyclic moiety can be used to modulate their thermal reactivity.[1] Recently,[2,3] we have synthesized β-lactam and isoxazolidine-fused enediynes via nitrone–alkyne and nitrone–olefin cycloaddition routes, respectively. We were curious to know the effect of a bridgehead double bond[4] on the thermal behavior of isoxazoline-fused enediyne system as represented by structures **1A** and **1B**. These molecules were synthesized via an intramolecular nitrile oxide–olefin cycloaddition.[5] The synthesis, structure elucidation and reactivity of these molecules are described herein.

Towards studying the proposed intramolecular cycloaddition, we needed to incorporate the proper functionality in the two arms of the enediyne; namely the 2-electron dipolarophile and the 4-electron dipole. The dienophile and the dipole in our case were an alkene and a nitrile oxide, respectively, between which an intramolecular [3+2]-cycloaddition reaction may take place to produce products **1A**–**1D** (Scheme 1). We started the synthesis of the cycloaddition precursor by carrying out sequential Sonogashira coupling[6] of 1,2-diiodobenzene with THP-protected propargyl alcohol and TMS-acetylene to produce **5**. After desilylation, the terminal alkyne carbon was allylated[7] with allyl bromide in the presence of K_2CO_3 and copper iodide using acetone as solvent to produce the alkene **7**. The alcohol **8** obtained upon deprotection of the THP ether was converted to the corresponding aldehyde **9** with Dess–Martin reagent.[8] The aldehyde was subjected to Wittig reaction using ethyl (triphenylphosphoranylidene)acetate in benzene which resulted in the formation of α,β-unsaturated ester **10**. Base-catalyzed Michael addition of nitromethane (also acting as solvent) was performed to obtain the corresponding nitro compound **11**.

The final cycloaddition was then carried out via the in situ generated nitrile oxide **2** in refluxing benzene at sufficient dilution (0.003 M) to minimize intermolecular reactions. The experimental procedure involved refluxing the reaction mixture comprising of the nitroenediyne **11**, *p*-chlorophenyl isocyanate and triethylamine[9] in benzene for 30 hours. Workup and purification yielded two products **1A** and **1B** (Scheme 2) which could not be separated by conventional chromatography and were isolated together as a white solid. The compounds could only be separated by



Scheme 1 Four possible isoxazoline-fused bicyclic enediynes

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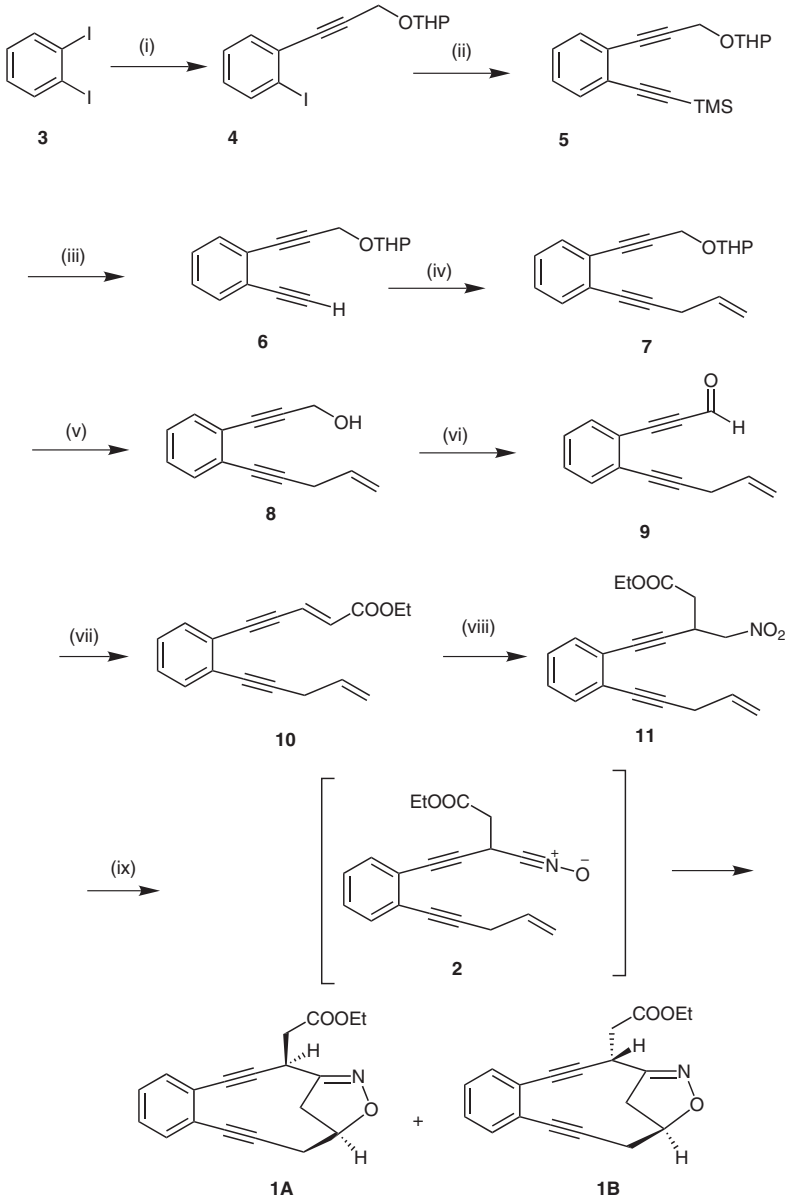

Scheme 2 Synthesis of bicyclic isoxazoline-fused enediynes. *Reagents and conditions*: (i) THP-protected propargyl alcohol, $Pd(PPh_3)_4$, CuI, Et_3N, r.t.; (ii) TMS-acetylene, $Pd(PPh_3)_4$, CuI, Et_3N, r.t.; (iii) KF, methanol; (iv) allyl bromide, K_2CO_3, CuI, anhyd acetone, reflux; (v) PPTS, EtOH; (vi) Dess–Martin oxidation; (vii) ethyl (triphenylphosphoranylidene)acetate, anhyd benzene, reflux; (viii) $MeNO_2$, DBU, 0 °C, 2 h; (ix) *p*-chlorophenyl isocyanate, Et_3N, benzene, 30 h, reflux.

HPLC using ODS-Daicel column and 15% water–MeOH as the mobile phase. The overall yield was 75% and the two isomers **1A** and **1B** were produced in a ratio of 1:1.

The fact that intramolecular cycloaddition had taken place was confirmed by the ESI spectrum which showed a peak at m/z = 330 [M + Na^+] for both the enediynes, commensurate with the molecular formula of the proposed structure. Between the two possible modes of cyclization, ^1H NMR spectroscopic analysis clearly showed that the cycloaddition had taken place via reaction of the nitrile oxide oxygen with the internal carbon of the alkene. This was proved by the downfield shift of the H_a proton at δ = 4.98 adjacent to the oxygen atom. For the alternative mode of cycloaddition which can lead to the structures **1C** and **1D**, an upfield shift of the H_a proton would be expected. Moreover, H_a showed four cross-peaks in the NOESY spectrum corresponding to interactions with H_b, H_c,H_d and H_e. This allowed us to assign the chemical shifts of the different protons but not the stereochemistry. Further confirmation of the structures came from the HMBC spectrum which showed cross-peaks corresponding to H_b and H_c with C-10 as well as H_d and H_e with C-1 (Figure 1).

The distinguishing feature between the structures is the difference in chemical shifts for the H_f proton. Energy-minimized structures using PM3[10] (Figure 2) showed the dihedral angle in H_f–C–C=N to be 168° in structure **1A**. For structure **1B**, the dihedral angle came out to be 18°. Thus, C–H_f can interact with the σ-antibonding orbital of the C–N bond which induces its downfield shift in structure **1A**.

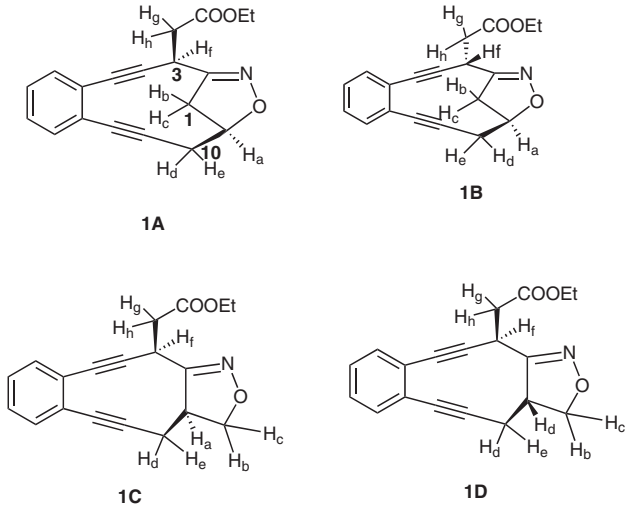

Figure 1

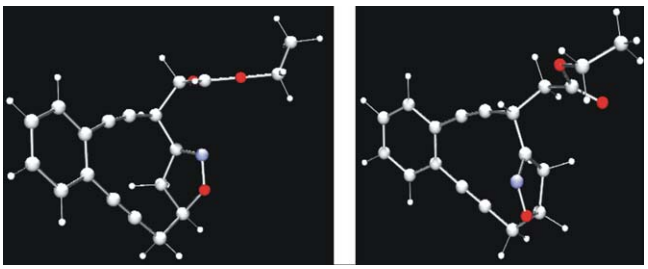

Figure 2 MM2 structures of **1A** and **1B**

The onset temperatures for Bergman cyclization (BC) for these bicyclic isoxazoline-fused enediynes **1A** and **1B** were determined using differential scanning calorimetric (DSC)[11] measurements which were recorded without solvent. Both the isomers **1A** and **1B** showed very close onset temperatures for BC at 210 °C and 212 °C, respectively proving that the bridgehead configuration does not have any effect on the activation barrier to BC. The result was compared with the onset temperatures of isoxazolidine-fused enediynes **12A** and **12B** (Figure 3).[3] While the *cis* form showed an onset temperature of ca 207 °C, for the *trans* isomer the onset temperature was found to be ca 213 °C. These values are very similar to those of isoxazoline-fused enediynes, thus ruling out the significant effect on the activation barrier of BC on fusing of the isoxazoline ring (an anti-Bredt system) to the enediyne system as compared to the isoxazolidine ring.

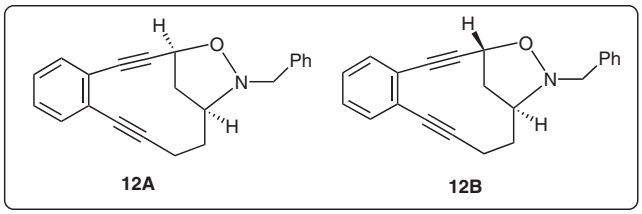

Figure 3 Isoxazolidine-fused enediynes

In conclusion, we have successfully synthesized two stereoisomeric isoxazoline-fused enediynes[12] by a highly regioselective one-step nitrile oxide–alkene [2+3]-cycloaddition approach. The structures of the two stereoisomeric bicyclic isoxazoline-fused enediynes were fully characterized by ^{1}H NMR, mass spectroscopy, and NOESY experiment. The thermal reactivity was studied for the isoxazoline-fused enediynes and was found to be similar to that of the isoxazolidine-fused systems.

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References and Notes

(1) (a) Basak, A.; Shain, J. C.; Khamrai, U. K.; Rudra, K. R.; Basak, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1955. (b) Kar, M.; Basak, A. *Chem. Rev.* **2007**, *107*, 2861. (c) Basak, A.; Bdour, H. M.; Shain, J. C.; Mandal, S.; Rudra, K. R.; Nag, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1321.
(2) Pal, R.; Basak, A. *Chem. Commun.* **2006**, 2992.
(3) Basak, A.; Ghosh, S. C. *Tetrahedron Lett.* **2005**, *46*, 7385.
(4) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellested, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6888. (c) Lee, M. D.; Manning, J. K.; Williams, D. R.; Kuck, N. A.; Testa, R. T.; Borders, D. B. *J. Antibiot.* **1989**, *42*, 1070. (d) De Voss, J. J.; Hangeland, J. J.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 4554. (e) De Voss, J. J.; Townsend, C. A.; Ding, W.-D.; Morton, G. O.; Ellested, G. A.; Zein, N.; Tabor, A. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9669. (f) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Siegel, M. M.; Morton, G. M.; Ellested, G. A.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 985.
(5) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, **1990**, 269. (b) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*, Vol. 2; Padwa, A., Ed.; Wiley: New York, **1984**, 83. (c) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; Wiley: U.S.A., **1988**.
(6) (a) Sonogashira, K.; Tohoda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.
(7) For synthesis of allylacetylenes from terminal acetylenes and allyl halides, see: Bumagin, N. A.; Ponomarev, A. B.; Beletskaya, I. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, *7*, 1565.
(8) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(9) (a) Mukhopadhyay, R.; Datta, S.; Chattopadhyay, P. C.; Bhattacharjya, A.; Patra, A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1996**, *35*, 1190. (b) Shing, T. K. M.; Fung, W. C.; Wong, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 449.
(10) ArgusLab version 4.0.1, Thomson and Planaria Software LLC.
(11) (a) Elias, H.-G. *Macromolekule*, Vol. 1; Huthig & Wepf Verlag: Basel, **1990**, 817. (b) Grubbs, R. H.; Kratz, D. *Chem. Ber.* **1993**, *126*, 149.

(12) **Selected Spectroscopic Data: Compound 11**: ^{1}H NMR (400 MHz): δ = 1.22 (t, *J* = 7.0 Hz, 3 H, $COOCH_2CH_3$), 2.64–2.76 (m, 1 H, $CHCH_2COOEt$), 3.20–3.22 (m, 2 H, $CCCH_2CH$), 3.82–3.89 (m, 2 H, $CCCHCH_2NO_2$), 4.26 (q, *J* = 7.2 Hz, 2 H, $COOCH_2CH_3$), 4.55–4.66 (m, 2 H, $CHCH_2NO_2$), 5.13 (dd, *J* = 1.6, 10.0 Hz, 1 H, CH_2CHCH_2), 5.40 (dd, *J* = 2.0, 17.2 Hz, 1 H, CH_2CHCH_2), 5.84–5. 90 (m, 1 H, $CH_2CH{=}CH_2$), 7.12–7.19 (m, 2 H, ArH), 7.28–7.38 (m, 2 H, ArH). ^{13}C NMR (100 MHz): δ = 0.96**,** 14.1, 30.1, 31.7, 36.4, 61.2, 81.2, 83.3, 88.6, 90.9, 115.7, 125.1, 126.2, 126.5, 128.2, 128.7, 130.8, 140.7, 170.0. MS (ESI): *m*/*z* = 325 [M^+]. **Compound 1A**: ^{1}H NMR (400 MHz): δ = 1.29 (t, *J* = 6.0 Hz, 3 H, $COOCH_2CH_3$), 2.68 (dd, *J* = 7.2, 12.8 Hz, 1 H, H_g), 2.74 (dd, *J* = 3.2, 14.8 Hz, 1 H, H_d), 2.83 (dd, *J* = 5.6, 12.8 Hz, 1 H, H_h), 2.91 (dd, *J* = 1.6, 14.8 Hz, 1 H, H_e), 3.20 (dd, *J* = 8.4, 13.2 Hz, 1 H, H_c), 3.60 (dd, *J* = 2.8, 13.2 Hz, 1 H, H_b), 4.20 (q, *J* = 5.6 Hz, 2 H, $COOCH_2CH_3$), 4.45 (dd, *J* = 1.6, 5.6 Hz, 1 H, H_f), 4.93–4.97 (m, 1 H, H_a), 7.21–7.29 (m, 2 H, ArH), 7.34–7.36 (m, 2 H, ArH). ^{13}C NMR (100 MHz): δ = 14.1, 27.3, 28.7, 29.6, 35.7, 36.3, 61.2, 81.6, 85.0, 88.4, 92.0, 124.9, 127.6, 128.1, 128.2, 129.1, 130.8, 155.5, 169.7. MS (ESI): *m*/*z* = 330 [M + Na^+]. HRMS: *m*/*z* calcd for $C_{19}H_{18}NO_3$ [M + H^+]: 308.3512; found: 308.3510. **Compound 1B**: ^{1}H NMR (400 MHz): δ = 1.28 (t, *J* = 5.6 Hz, 3 H, $COOCH_2CH_3$), 2.72 (dd, *J* = 3.4, 14.6 Hz, 1 H, H_e), 2.91 (dd, *J* = 3.2, 14.6 Hz, 1 H, H_d), 2.95 (dd, *J* = 1.6, 14.4 Hz, 1 H, H_g), 3.23 (dd, *J* = 4.8, 14.4 Hz, 1 H, H_h), 3.30 (dd, *J* = 7.2, 14.0 Hz, 1 H, H_b), 3.63 (dd, *J* = 2.8, 14.0 Hz, 1 H, H_c), 3.96 (dd, *J* = 4.8, 7.2 Hz, 1 H, H_f), 4.20 (q, *J* = 2.4 Hz, 2 H, $COOCH_2CH_3$), 4.92–4.96 (m, 1 H, H_a), 7.20–7.29 (m, 2 H, ArH), 7.34–7.36 (m, 2 H, ArH). ^{13}C NMR (100 MHz): δ = 14.1, 27.2, 28.5, 29.6, 35.6, 39.9, 60.9, 81.5, 84.9, 88.6, 92.3, 125.0, 127.6, 128.0, 128.3, 129.1, 130.8, 156.3, 171.0. MS (ESI): *m*/*z* 330 [M + Na^+]. HRMS: *m*/*z* calcd for $C_{19}H_{18}NO_3$ [M + H^+]: 308.3512; found: 308.3509.