Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5397-5400, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01087-8

Pyridoxal-Mediated Cycloaromatization of an Enediyne Model System

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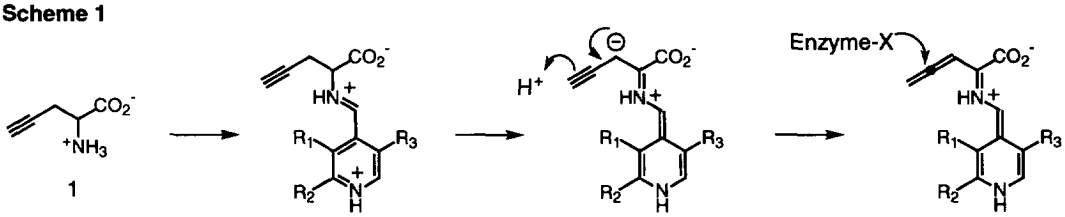
Abstract: The acyclic enediyne possessing an aminomethyl group was designed and synthesized as a potential substrate for pyridoxal-dependent enzymes. Compound **2** was shown to give cycloaromatized products by the reaction with pyridoxal or isonicotinaldehyde *via* the toluene biradical intermediate.

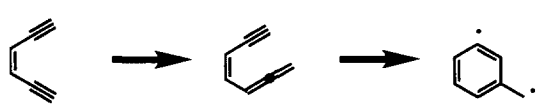
Much of the interest in the biological formation and reactions of allenes is related to the development of enzyme-generated irreversible inhibitors.[1] Such inactivators are termed suicide substrates and contain potential reactive systems, which are unmasked by various catalytic actions of the target enzymes.[2] For instance, propargyl glycine **1** inactivates a number of pyridoxal-dependent enzymes such as γ-cystathionase,[2] cystathionine γ-synthetase,[4] glutamic-pyruvic transaminase,[4] and *L*-aspartate aminotransferase.[5] The proposed mechanism involves enzymatic formation of a propargylic anion, its rearrangement to an electrophilic conjugated allenic system, and nucleophilic addition of an amino acid residue at the active site of enzyme (Scheme 1).[6] As part of our program in DNA cleaving substances, we have been developing enediyne models

Scheme 1

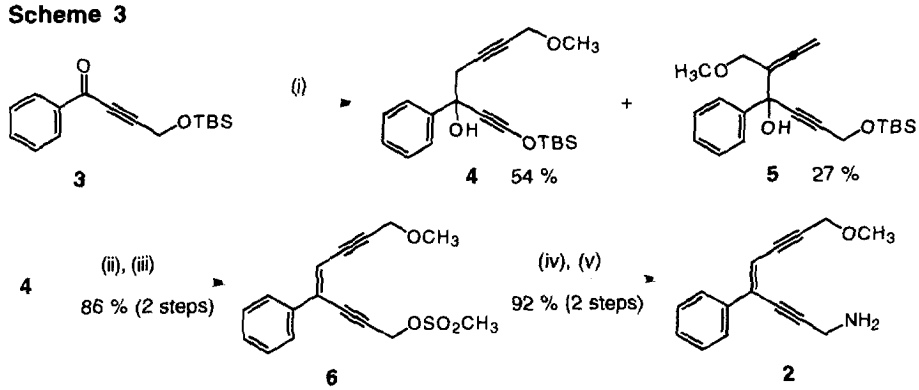


which produce the reactive enyne-allenes and ultimately generate toluene biradicals *via* a reaction cascade triggered by various chemical reactions (Scheme 2).[7] Recently, Zein *et al.* reported that a synthetic enediyne caused extensive protein damage *in vitro* at concentrations which would seem to be relevant to the mechanism of the drug.[8] From these points of view, a biradical generating enediyne which is activated by pyridoxal would be a potential inactivator of pyridoxal-dependent enzymes. In the present paper, we wish to describe that the synthetic enediyne **2** is activated by pyridoxal to produce biradicals.

Scheme 2



Scheme 3

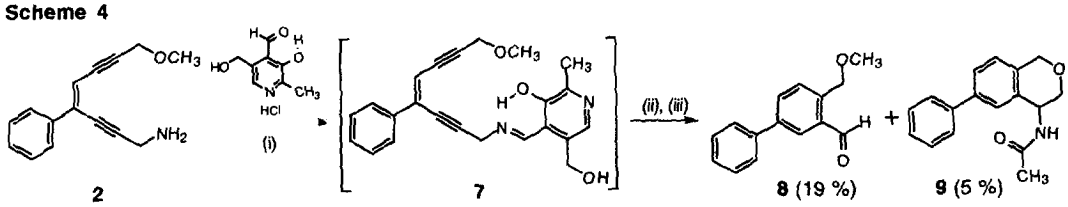


(i) $BrCH_2C{\equiv}CCH_2OMe$, Zn, THF, rt, 2.5 h; (ii) $(C_4H_9)_4NF$, THF, 0 °C, 15 min.; (iii) MsCl. NEt_3, Et_2O, rt, 1 h; (iv) NaN_3, DMF, rt, 20 min.; (v) PPh_3, Et_2O, rt, 5 h

Synthesis of the enediyne **2** (Scheme 3) started with the known benzoyl alkyne **3**[9] which was condensed with 1-bromo-4-methoxy-2-butyne to give a readily separable mixture of the diyne **4** and the allene **5**. Desilylation of **4** and the resulting diol was then reacted with 2.2 mol. equiv of methanesulfonyl chloride in the presence of triethylamine. Under these conditions, the *tert*-hydroxy group was eliminated simultaneously to yield the enediyne **6** in good yield.[10] The terminal amino group was introduced by the reaction of **6** with sodium azide and subsequent reduction with triphenyl phosphine to afford the desired aminomethyl enediyne **2**.

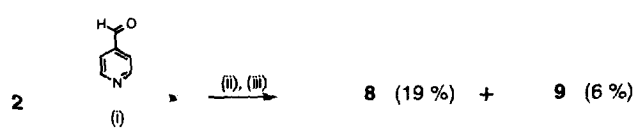
Equimolar quantities of the amine **2** and pyridoxal hydrochloride were reacted to produce the Schiff base **7** easily, but this product was found to be unstable and it gradually hydrolyzed under purification by silica gel chromatography, although the pure Schiff base **7** was isolated (39 % yield). Therefore, a model study of pyridoxal-mediated cycloaromatization reaction of **2** was conducted as shown in Scheme 4. The condensation of **2** with pyridoxal hydrochloride was achieved in the presence of 2 equiv of triethylamine at 37 °C. The Schiff base formation was observed on TLC almost instantly, and then it disappeared gradually within 40 minutes. In order to facilitate the isolation of the products from the crude reaction mixture, subsequent acetylation and acid hydrolysis were carried out after the solvent was removed. Thus, two products were isolated and characterized

Scheme 4



(i) PL-HCl (1 equiv), NEt_3 (2 equiv), dioxane, 37 °C, 40 min.; (ii) Ac_2O, Pyr., rt, 12 h; (iii) HCl, H_2O, acetone, rt, 1.5 h

Scheme 5



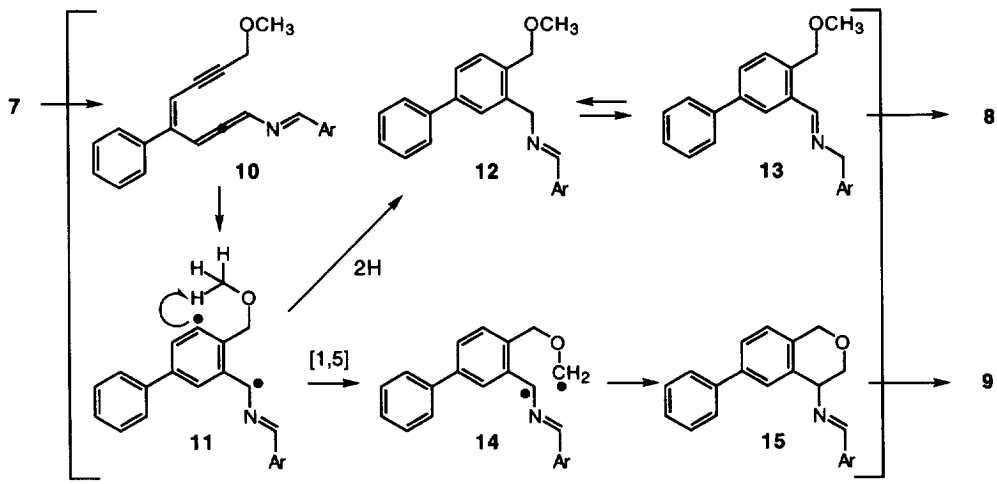
(i) isonicotinaldehyde (1 equiv), NEt_3 (1 equiv), dioxane, 37 °C, 180 min.; (ii) Ac_2O, Pyr., rt, 12 h; (iii) HCl, H_2O, acetone, rt, 1.5 h

as the aldehyde **8** and the amide **9** by means of the spectroscopic analysis. A similar reaction of **2** using isonicotinaldehyde instead of pyridoxal gave almost similar results, except that the reaction was much slower (Scheme 5). These results suggest that the phenolic hydroxy group in pyridoxal plays an important role in this reaction such as has been suggested in various vitamin B_6 catalyzed reactions of α-amino and α-keto acids.[11]

Mechanistically, the formation of **8** and **9** can be rationalized in terms of the following pathway (Scheme 6). In the first step, enyne-allene **10** is generated from the Schiff base **7** (or the Schiff base generated from **2** and isonicotinaldehyde), which produces the toluene biradicals **11** according to the Myers-Saito reaction.[12] The biradicals **11** abstract hydrogens from the solvent to give the equilibrium mixture of the imines **12** and **13**, which produces the aldehyde **8** by the two-step work-up process. For the mechanism of this process (**11** → **8**), the ionization of **11** generating the zwitterionic intermediates which we have reported previously[7d] can not be ruled out.[13] On the other hand, methoxy hydrogens of **10** are favorably located in a position which permits the abstraction by the predicted benzene σ-radical[7d, 14] generating another biradical **14**. The recombination of **14** affords the isochroman **15** which ultimately produces the amide **9**. The formation of the amide **9** strongly suggests the generation of toluene biradicals during the reaction cascade.

In summary, this study demonstrates that the aminomethyl derivatives of acyclic Z-hex-3-ene-1,5-diyne can be used to generate biradicals *via* the reaction cascade mediated by pyridoxal. Studies on the analogues of this class of compounds involving an *in vitro* and an *in vivo* inactivation of pyridoxal-dependent enzymes are continuing.[15]

Scheme 6



Acknowledgment: This work was supported by Grant-in-Aid for Scientific Research on Priority Areas No. 07229238 and 07457521 from the Ministry of Education, Science and Culture, Japan.

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13. For an alternative experiment for Scheme 4, the reaction was carried out in the presence of 40 equiv of cyclohexadiene to give **8** in a higher yield (26 %), while product **9** was not detected from the products, indicating the radical mechanism is preferable for these reactions.
14. Several examples of homolytic intramolecular 1,5-hydrogen atom shift have been reported in the field of enediyne chemistry. See, Chin, D.-H.; Goldberg, I. H. *J. Am. Chem. Soc.* **1992**, 114, 1914-1915; Wender, P. A.; Tebbe, M. J. *Tetrahedron*, **1994**, 50, 1419-1934; Audrain, H.; Skrydstrup, T.; Ulibarri, G.; Riche, C.; Chiaroni, A.; Grierson, D. S. *Tetrahedron* **1994**, 50, 1469-1502; Kawata, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1994**, 35, 4595-4598; Wang, Z.; Wang, K. K. *J. Org. Chem.* **1994**, 59, 4738-4742.
15. Selected data, **2**: colorless oil; IR (neat) 3376, 3302, and 2215 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$): 7.59-7.64 (2H, m), 7.33-7.41 (3H, m), 6.31 (1H, t, J = 2.0), 4.36 (2H, d, J = 2.0), 3.73 (2H, s), 3.47 (3H, s), and 1.79 (2H,s); MS: m/z Calcd. for $C_{15}H_{15}NO$: 225.1154. Found: 225.1157. **7**: pale yellow amorphous; IR ($CHCl_3$) 3605, 3339, 2219, and 1635 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$): 13.56 (1H, br), 9.35 (1H, t, J = 1.2), 7.90 (1H, s), 7.62-7.66 (2H, m), 7.36-7.39 (3H, m), 6.39 (1H, t, J = 2.0), 4.92 (2H, d, J = 1.2), 4.78 (2H, s), 4.28 (2H, t, J = 2.0), 3.35 (3H, s), and 2.51 (3H, s); MS: m/z Calcd. for $C_{23}H_{22}N_2O_3$: 374.1630. Found: 374.1628. **8**: mp 37-39 °C; IR (neat) 1698 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$): 10.27 (1H, s), 8.08 (1H, d, J = 1.7), 7.82 (1H, dd, J = 1.7, 7.9), 7.60-7.70 (3H, m), 7.34-7.51 (3H, m), 4.90 (2H, s), and 3.50 (3H, s); MS: m/z Calcd. for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0990. **9**: mp 192-194°C; IR (KBr) 1638 and 1534 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$): 7.35-7.61 (7H, m), 7.11 (1H, d, J = 8.1), 6.08 (1H, d, J = 8.7), 5.15 (1H, d, J = 8.7), 4.88 (1H, d, J = 15.3), 4.76 (1H, d, J = 15.3), 4.12 (1H, d, J = 11.9), 3.90 (1H, d, J = 11.9), and 2.01 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$): 169.22 (C), 140.47 (C), 140.22 (C), 133.80 (C), 133.68 (C), 128.87 (2 x CH), 128.14 (CH), 127.55 (CH), 127.02 (2 x CH), 126.78 (CH), 124.82 (CH), 70.08 (CH_2), 67.90 (CH_2), 45.46 (CH), and 23.45 (CH_3); MS: m/z Calcd. for $C_{17}H_{17}NO_2$: 267.1259. Found: 267.1277.

(*Received in Japan* 17 *May* 1996; *accepted* 3 *June* 1996)