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Enediynes from Aza-Enediynes: *C,N*-Dialkynyl Imines Undergo Both Aza-Bergman Rearrangement and Conversion to Enediynes and Fumaronitriles

Liping Feng, Aibin Zhang, and Sean M. Kerwin*

Division of Medicinal Chemistry, College of Pharmacy and Institute for Cellular and Molecular Biology, The University of Texas at Austin, Austin, Texas 78712

skerwin@mail.utexas.edu

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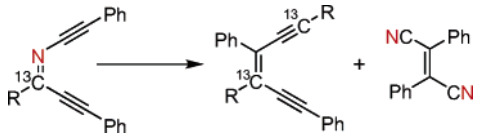
ABSTRACT



Aza-enediynes (*C,N*-dialkynyl imines) undergo thermal aza-Bergman rearrangement to *β*-alkynyl acrylonitriles through 2,5-didehydropyridine (2,5-ddp) intermediates. Certain aza-enediynes also undergo an alternative process affording enediynes and fumaronitriles. Studies employing a specifically ^{13}C-labeled aza-enediyne show that the conversion to enediyne is second order in aza-enediyne, proceeds by a "head-to-tail" coupling, and affords the (*Z*)-enediyne.

Anticancer antibiotics containing the enediyne moiety (**1**, Scheme 1) undergo Bergman cyclization to reactive 1,4-didehydrobenzene (1,4-ddb) diradicals (**2**, Scheme 1).[1] The diradicals derived from these enediynes abstract hydrogen atoms from the sugar phosphate backbone of DNA (**2** → **4**, Scheme 1), leading to oxidative DNA strand scission and ultimately cell death.[1b,c] The isolation of the enediyne antitumor antibiotics has led to a renewed interest in the Bergman cyclization in the design of cancer cell-selective DNA cleavage agents[2] and as an approach to the construction of polycyclic molecules through free-radical cascade cyclizations.[3] More recently, this has led to a search for alternative diradical-generating cyclizations that might be incorporated in the design of improved DNA-cleavage agents[4] or employed in the construction of heterocycles.[5] Aza-enediynes, or *C,N*-dialkynyl imines (**5**, Scheme 1), undergo a Bergman-type rearrangement to the corresponding nitriles (**7**, Scheme 1), presumably through the 2,5-didehydropyridine (2,5-ddp) intermediate (**6**, Scheme 1), which is not trapped by hydrogen atom abstraction.[6]

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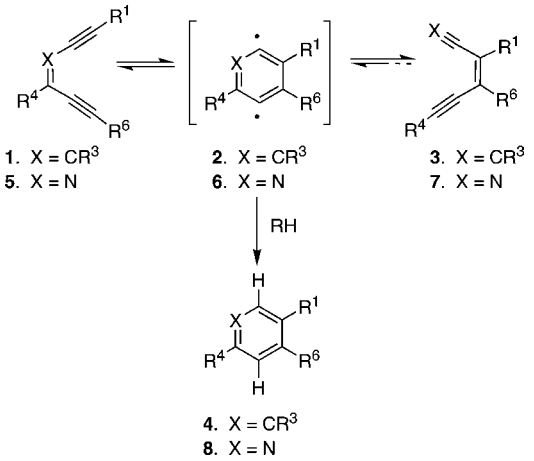
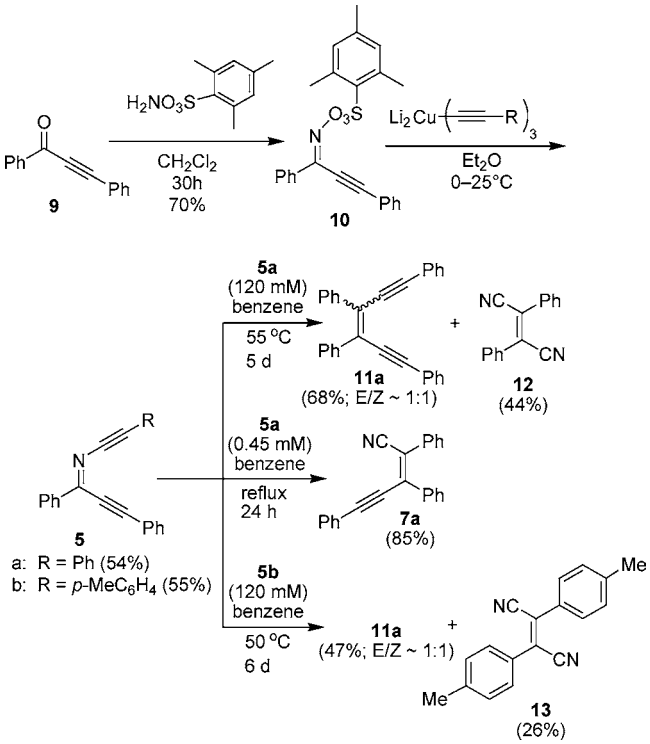
Scheme 1. Thermal Rearrangements of Enediynes and Aza-Enediynes



Aza-enediynes have been the subject of a number of theoretical[7−11] and experimental studies.[6,11−14] The 2,5-ddp diradical is predicted to be a very short-lived, unreactive species, and with one exception,[11] efforts to trap this intermediate have not been successful.[6,12−14] As part of our ongoing investigation into the unique chemistry of aza-enediynes,[12,14,15] we have uncovered a remarkable transformation of aza-enediynes to enediynes that can occur in parallel with aza-Bergman rearrangement. Here we describe this transformation and insights gained from the study of a specifically ^{13}C-labeled aza-enediyne.

The aza-enediynes **5a**,**b** were prepared from 1,3-diphenylpropynone (**9**) via the corresponding oxime mesitylate (**10**), which undergoes cuprate coupling with higher order alkynyl cuprates as shown in Scheme 2. These aza-enediynes are isolated as predominantly a single imine double bond isomer, presumably the more thermodynamically stable (*Z*)-configuration.[13] Aza-enediyne **5a** is unstable when stored neat for extended periods at −10 °C. In benzene (120 mM) at 55 °C over a course of days, **5a** is converted to the enediyne **11a**, isolated as a 1:1 *E*/*Z* mixture after chromatography, and the diphenylfumaronitrile **12**.[16] However, under more dilute conditions (0.45 mM) and higher temperature, **5a** undergoes aza-Bergman rearrangement to **7a** (Scheme 2). In the case

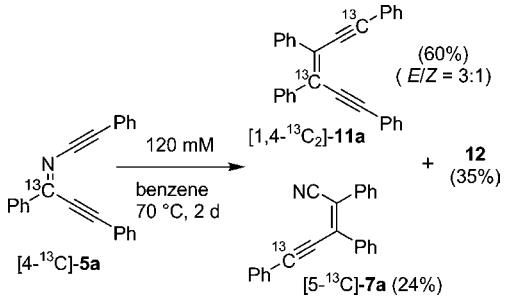
Scheme 2. Synthesis of Aza-Enediynes and Their Conversion to Enediynes[17]



of the *p*-toluyl-substituted aza-enediyne **5b**, mild thermolysis in benzene affords the enediyne **11a** and the toluylbisnitrile **13**[18] (Scheme 2).

Thermolysis of aza-enediyne [4-^{13}C]-**5a** (120 mM) at 70 °C in benzene afforded [1,4-$^{13}C_2$]-enediynes (*Z*)-**11a** and (*E*)-**11a** (1:3 ratio after chromatography, 60%), [5-^{13}C]-**7a** (24%), and unlabeled bisnitrile **12** (35%) (Scheme 3). The presence

Scheme 3



of two ^{13}C-labeled positions in both (*Z*)- and (*E*)-**11a** is apparent from the ^{13}C NMR spectra, in which the pair of labeled carbons in each compound are coupled (4.1 and 4.6 Hz, respectively).[19]

The rate of disappearance of **5a** monitored by ^{1}H NMR (120 mM **5a** in benzene-d_6, 70 ± 1 °C) does not follow either

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(15) Nadipuram, A.; Kerwin, S. M. *Tetrahedron* **2006**, *62*, 3798−3808.
(16) Refat, H. M.; Waggenspack, J.; Dutt, M.; Zhang, H.; Fadda, A. A.; Biehl, E. *J. Org. Chem.* **1995**, *60*, 1985−1989

(17) The reported yields of **11** and **12** assume a 2:1:1 stoichiometry of starting aza-enediyne to enediyne to bisnitrile.
(18) Pochat, F. *Tetrahedron Lett.* **1978**, 1055−1058.

first-order or second-order (with respect to **5a**) kinetics, but can be fit to a rate equation for parallel first- and second-order reactions (Table 1).[20] Data obtained from ^{13}C NMR

Table 1. Rate Constants for the First-Order Aza-Bergman Rearrangement of **5a** and the Second-Order Transformation of **5a** to **11a** at 70 °C

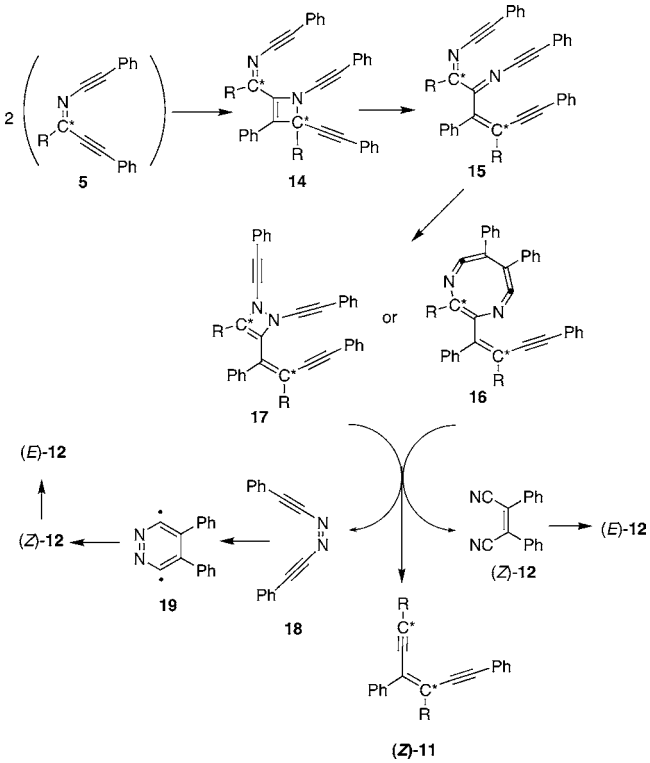
solvent[a]	first-order rate constant[b] (s^{-1})	second-order rate constant[b] ($L\ mol^{-1}\ s^{-1}$)
benzene-d_6[c]	$(4.4 \pm 0.3) \times 10^{-5}$	$(4.1 \pm 0.2) \times 10^{-4}$
THF-d_8[d]	$(1.8 \pm 1.3) \times 10^{-5}$	$(2.1 \pm 0.8) \times 10^{-4}$

[a] Initial **5a** or [1-^{13}C]-**5a** concentration of 120 mM. [b] The rate of disappearance of **5a** determined from NMR integrals versus an internal standard (2,5-dimethylfuran for ^{1}H NMR and solvent for ^{13}C NMR) was fit to simultaneous, parallel first- and second-order processes. For details see the Supporting Information. [c] Average values from both ^{1}H and ^{13}C NMR data. [d] Values from ^{13}C NMR data.

studies of the disappearance of [4-^{13}C]-**5a** were also fit to parallel first- and second-order processes, which match the appearance of ^{13}C NMR signals for **12** and (*Z*)-**11a**, respectively. These ^{13}C NMR kinetic studies show that enediyne **11a** is formed predominantly as the (*Z*)-isomer, which undergoes isomerization during extended heating[21] to afford mixtures of (*E*)- and (*Z*)-**11a**. NMR kinetic studies of [4-^{13}C]-**5a** were also carried out in THF-d_8 (Table 1). Previous studies have shown that the rate of aza-Bergman rearrangement of 6-unsubstituted-3-aza-hex-3-ene-1,5-diynes shows a slight solvent dependence; proceeding more slowly in more polar solvents.[13] Both the first- and second-order components of the rate of disappearance of aza-enediyne **5a** show a similar decrease in the more polar solvent (Table 1).

Thermolysis of aza-enediyne **5a** carried out in neat 1,4-cyclohexadiene in attempts to trap the 2,5-ddp **6a** or other intermediates, such as 1,3-diphenylpropargyl carbene,[21] that might be involved in a dissociative process leading to **11a** failed to afford either the pyridine **8a** or any other trapping products; only **7a**, **11a**, and **12** were obtained. This, together with the labeling studies and the observation that the rate of conversion of **5a** to **11a** is second order in **5a** leads to the proposal that the conversion of aza-enediynes to enediynes proceeds through an initial head-to-tail coupling. One possibility involves a concerted [2+2] dimerization to an azacyclobutene[22] (e.g., **14**, Scheme 4), ring opening of which produces an intermediate (**15**) similar to that involved in the oxidative formation of alkynes from 1,2-hydrazones.[23] In the

Scheme 4



present case, the formation of the alkyne moiety is accompanied by elimination of the bisnitrile **12** (or in the case of **15b** the bisnitrile **13**), which provides a strong thermodynamic driving force for the conversion. This may involve initial cyclization (to **16** or **17**[24]) and elimination to produce the enediyne **11** and **12** directly (from **16**), or after diaza-Bergman rearrangement of the azoacetylene **18**[25] derived from **17** (Scheme 4). While **12** is predicted to be formed initially as the (*Z*)-isomer, isomerization may occur during thermolysis or chromatographic isolation,[26] the later being complicated by trace amounts of an unidentified product of similar mobility, which may explain the nonequivalence of the isolated yields of **12** and **11**. There is some evidence for these proposed intermediates. ESI-MS analysis of samples of **5a** stored at −10 °C in benzene demonstrate initial formation of dimer, followed by formation of enediyne over the course of days. Careful chromatography of these samples affords trace amounts of colored compounds that upon mass spectrometric analysis produce ions corresponding to dimers of **5a**; however, the small amount obtained and conversion of these compounds to **11a** and **12** has prevented their complete characterization. Further evidence for the azacyclobutene **14** comes from the ^{13}C NMR kinetic studies of [4-^{13}C]-**5a**, which demonstrate a low-intensity peak whose chemical shift (54.6 ppm) and appearance and disappearance over time is commensurate with such an intermediate.

(19) (a) Krivdin, L. B.; Della, E. W. *Prog. NMR Spectrosc.* **1991**, *23*, 301−610. (b) Porwoll, J. P.; Leete, E. *J. Labelled Compd. Radiopharm.* **1985**, *22*, 257−271. (c) Lambert, J.; Klessinger, M. *Magn. Reson. Chem.* **1987**, *25*, 456−461.

(20) The kinetic model is for two parallel, irreversible reactions of **5a**, one first-order in **5a** and the other second-order in **5a**: **5a** → **7a** (k_1); 2(**5a**) → **11a** + **12** (k_2).

(21) Shimizu, T.; Miyasaka, D.; Kamigata, N. *Org. Lett.* **2000**, *2*, 1923−1925.

(22) For an apparent [2+2] cycloaddition of a propyne iminium salt to afford an azacyclobutene see: Nikolai, J.; Schlegel, J.; Regitz, M.; Maas, G. *Synthesis* **2002**, 497−504.

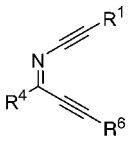
(23) Tsuji, J.; Kezuka, H.; Toshida, Y.; Takayanagi, H.; Yamamoto, K. *Tetrahedron* **1983**, *39*, 3279−3282.

(24) We thank one of the reviewers for suggesting this possibility.

(25) For a discussion of the difficulties in preparing azoacetylenes, see: Denonne, F.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2003**, *86*, 3096−3117.

(26) Yeh, H.-C.; Wu, W.-C.; Wen, Y.-S.; Dai, D.-C.; Wang, J.-K.; Chen, C.-T. *J. Org. Chem.* **2004**, *69*, 6455−6462 and references therein.

Examination of other aza-enediynes demonstrates that there are certain structural requirements in order for the conversion of aza-enediynes to enediynes to compete with aza-Bergman rearrangement. Aza-enediyne **5c**[6] (Figure 1)



5c: $R^1 = R^6 = Ph$, $R^4 = Me$
5d: $R^1 = R^4 = Ph$, $R^6 = H$
5e: $R^1 = Ph$, $R^4 = p\text{-}MeC_6H_4$, $R^6 = H$
5f: $R^1 = R^4 = Ph$, $R^6 = TIPS$
5g: $R^1 = TIPS$, $R^4 = R^6 = Ph$

Figure 1. Aza-enediyne structural effects on the conversion to enediynes.

also apparently undergoes this transformation; chromatography of a sample of **5c** stored neat at −10 °C for 2 years afforded the corresponding enediyne[27] (14% yield, ∼1:1 mixture of *E*/*Z* isomers) and the bisnitrile **12** (35% yield). For sterically unencumbered aza-enediynes **5d**,**e** (Figure 1), which undergo rapid aza-Bergman rearrangement at subambient temperatures,[3,10] no enediyne formation is observed. Similarly, aza-enediynes that have terminal triisopropylsilyl substituents (**5f**,**g**) which undergo aza-Bergman rearrangement more slowly,[10] also do not undergo conversion to enediynes, presumably due to steric effects on the initial dimerization to **14.** However, for aza-enediynes bearing terminal aryl substituents (e.g., **5a**,**b**), the conversion to enediynes can predominate over aza-Bergman rearrangement, particularly at high concentrations of aza-enediyne or lower temperatures.

The remarkable conversion of aza-enediynes to enediynes adds another facet to the distinct chemistry[12,14,15] of this class of compounds, whose design was inspired by analogy to the enediyne Bergman cyclization. Aza-enediynes have now come full circle, serving as synthetic precursors to the source of inspiration for their conception. Benzenoid diradicals derived from Bergman cyclization of enediynes can be efficiently trapped through hydrogen atom abstraction reactions.[1] There have been a number of attempts to detect similar chemistry from aza-enediyne-derived 2,5-didehydropyridines.[6,11−13] The conversion of aza-enediynes to enediynes reported here, which can occur in parallel with the thermal aza-Bergman rearrangement of these compounds, should inform future studies of the thermal chemistry of aza-enediynes. For example, reactive diradicals from aza-enediynes may arise from Bergman cyclization of the enediynes derived from them rather than aza-Bergman-derived 2,5-didehydropyridines.

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Supporting Information Available: Experimental details and kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0600638

(27) The structure of the enediyne was assigned based on UV, IR, HRMS, and comparison of the ^{1}H NMR spectrum to that of 1,6-dimethyl-3,4-diphenyl-3-hexene-1,5-diyne (Hayashi, M.; Saigo, K. *Tetrahedron Lett.* **1997**, *38*, 6241−6244) and 3,4-dimethyl-1,6-diphenyl-3-hexene-1,5-diyne (Blackwell, J. M.; Figueroa, J. S.; Stephens, F. H.; Cummins, C. C. *Organometallics* **2003**, *22*, 3351−3353).