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An Extremely Facile Aza-Bergman Rearrangement of Sterically Unencumbered Acyclic 3-Aza-3-ene-1,5-diynes

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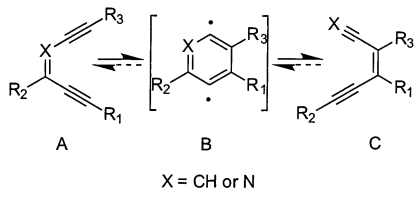
The factors that affect the kinetics of the aza-Bergman cyclization of aza-enediynes (*C*,*N*-dialkynyl imines) have not previously been elucidated. Here we report our kinetic studies of the aza-Bergman reactions of a series of 6-triisopropylsilyl and 6-unsubstituted 1-phenyl-4-aryl-3-aza-3-ene-1,4-diynes in which the aryl group is phenyl, *o*-(methoxy)phenyl, or *p*-(methoxy)phenyl. These aza-enediynes are prepared as single isomers in modest yield from the corresponding 1-aryl-3-(triisopropylsilyl)-propynone oximes. These aza-enediynes undergo aza-Bergman reaction followed by a rapid retro-aza-Bergman cyclization to afford *β*-alkynyl acrylonitrile products. In no case are products corresponding to trapping the intermediate 2,5-didehydropyridine diradical isolated. While the rate of aza-Bergman cyclization is not greatly affected by the nature of the 4-aryl substituent, the rate is very dependent on the nature of the 6-substituent. 1-Phenyl-4-aryl-3-aza-3-ene-1,5-diynes that lack a 6-substituent undergo aza-Bergman cyclization spontaneously at 20 °C with first-order half-lives of 36−78 min. The effect of solvent on the kinetics of aza-Bergman cyclization of 1,4-diphenyl-3-aza-3-ene-1,5-diyne was investigated. The rate of this cyclization is solvent dependent, proceeding more rapidly in less polar solvents.

In 1972 Robert Bergman and co-workers reported the gas-phase thermal rearrangement of substituted 3-hex-ene-1,5-diynes (Scheme 1, **A**, X = CH) and proposed the existence of a 1,4-didehydrobenzene diradical (Scheme 1, **B**, X = CH) in this process (Bergman cyclization).[1] Interest in the Bergman cyclization has increased since the mid-1980s due to the discovery of the naturally occurring enediyne anticancer antibiotics, such as calicheamicin,[2] esperamicin,[3] dynemicin,[4] and kedarcidin.[5] These enediynes are among the most potent antibiotic antitumor agents ever investigated.[6] The phenomenal biological activity of these substances against bacterial and tumor cells results from the fact that enediynes can undergo a Bergman cyclization to benzenoid diradicals, which abstract hydrogen atoms from the sugar phosphate backbone of DNA, leading to oxidative DNA strand scission.[7] The extraordinary reactivity and cytotoxicity

SCHEME 1



of the enediynes has sparked considerable interest, yet the lack of tumor specificity of these compounds has complicated their use in cancer chemotherapy. One approach that has been successfully employed to increase the specificity of these agents is their conjugation to cancer cell targeting antibodies.[8] Alternative approaches involve designing novel triggering mechanisms that may lead to enediynes that only undergo diradical cyclization in cancer cells.[9] A more recent approach involves the redesign of the enediyne core to provide both selective triggering and more discriminating diradical intermediates.[10] However, many factors which affect the Bergman cyclization reaction still remain unresolved.

Although the most studied factors which affect the Bergman cyclization of many natural and synthetic

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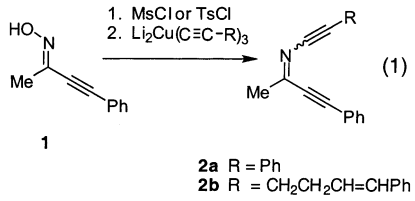
enediynes are molecular strain energy[11] and the distance separating the acetylenic termini,[6] electronic effects also influence this process.[12] Electron-withdrawing substituents either attached to triple-bond termini[12a] or associated with the double bond[12,13] of enediynes can lower the activation enthalpy of the Bergman reaction by decreasing the degree of repulsion of the in-plane π-orbitals in the transition state. We have investigated a new class of compounds, the aza-enediynes, or *C,N*-dialkynyl imines (Scheme 1, **A**, X = N). The replacement of an sp^2 carbon with a nitrogen to afford such aza-enediynes was predicted to facilitate by a similar electronic effect their cyclization by an aza-Bergman process. We reported the first synthesis of the *C,N*-dialkynyl imines (**2a**,**b**, eq 1)



and their aza-Bergman cyclization in 1997.[14] Although these aza-enediynes underwent an aza-Bergman cyclization to generate 2,5-didehydropyridine intermediates (Scheme 1, **B**, X = N), all attempts to trap these intermediates only resulted in the formation of the retro-aza-Bergman products (Scheme 1, **C**, X = N).[14] Numerous computational studies of the aza-Bergman cyclization and the resulting 2,5-didehydropyridine intermediate have been carried out.[15−18] Significantly, the only experimental support for the existence of the elusive 2,5-didehydropyridine intermediate[19] has come from studies of the aza-Bergman cyclization reaction. Chen and co-workers[20] reported the detection of miniscule amounts of pyridine product by GC/MS in the thermolysis of the aza-enediyne **2a** under acidic conditions. These workers propose that the ability to trap the intermediate 2,5-didehydropyridine is critically dependent upon this diradical's singlet−triplet gap, which is predicted to be larger than that of the corresponding *p*-benzyne diradical. Protonation of the 2,5-didehydropyridine intermediate is predicted to lower the singlet−triplet gap, which makes hydrogen atom abstraction more competitive with the retro-aza-Bergman process.[20]

The factors that affect the kinetics of the aza-Bergman cyclization of aza-enediynes have not been elucidated. There are only two reports of kinetic studies of this process, and both of these were carried out on similar aza-enediynes.[14,20] Here we report our kinetic studies of the aza-Bergman reactions of a series of 6-triisopropylsilyl and 6-unsubstituted 4-aryl-3-aza-3-ene-1,4-diynes. These aza-enediynes are prepared as single isomers by an adaptation of our previously reported route to the aza-enediyne system. These aza-enediynes undergo aza-Bergman reaction followed by a rapid retro-aza-Bergman cyclization to afford β-alkynyl acrylonitrile products. In no case are products corresponding to trapping the intermediate 2,5-didehydropyridine diradical isolated. While the rate of aza-Bergman cyclization is not affected by the nature of the aryl substituent, the rate is very dependent on the nature of the 6-substituent. 3-Aza-3-ene-1,5-diynes that lack a 6-substituent undergo an extremely facile aza-Bergman cyclization. The rate of this cyclization is solvent dependent, proceeding more rapidly in less polar solvents. The implications of these findings to drug design efforts are discussed.

Results and Discussion

1. Synthesis of 3-Aza-3-ene-1,5-diynes. Our previous synthesis of *C,N*-dialkynyl imine aza-enediynes proceeded from the (*E*)-oxime **1** (eq 1), which was obtained from the addition of lithium phenylacetylide to the *tert*-butyldimethylsilyl nitronate ester of nitroethane.[14] Activation of the oxime **1** as the sulfonate ester followed by cuprate coupling led to the aza-enediynes **2a**,**b** in modest yields (eq 1). Attempts to employ this same route to access other aza-enediynes were met with difficulty. Additions of lithium phenylacetylide to the silyl nitronate derived from nitromethyl benzene led to intractable mixtures from which the desired oxime could not be isolated. Condensation of 1,3-diphenylpropynone with hydroxylamine only afforded 3,5-diphenylisoxazole. To avoid the problem of isoxazole formation, we chose to prepare propynone oximes bearing a large substituent on the terminal acetylenic carbon. Thus, cuprous iodide-catalyzed addition[21] of triisopropylsilyl acetylene to benzoyl chloride, *p*-anisoyl chloride, or *o*-anisoyl chloride afforded the corresponding propynones **3a**−**c** in good yield (Scheme 2). The conversion of these acetylenic ketones to the corresponding oximes **4a**−**c** proceeded in good yield, although the reactions required 10 days for completion. The oximes **4a**−**c** were isolated as single isomers, as judged from ^{1}H and ^{13}C NMR spectra. The corresponding mesylates **5a**−**c** were also isolated as single isomers of undetermined stereochemistry. Addition of the cuprate reagent[22] derived from phenylacetylene to the mesylates **5a**−**c** affords the *C,N*-dialkynyl imines **6a**−**c** in modest yields along with variable amounts of 1-aryl-3-(triisopropylsilyl)-prop-2-ynylidenamine. The aza-enediynes **6a**−**c** can be purified by chromatography and isolated as relatively stable, yellow oils that can be stored at 0 °C for several months without any signs of decomposition. The aza-enediynes **6a**−**c** are isolated as predominantly one isomer, as judged by ^{1}H and ^{13}C NMR.

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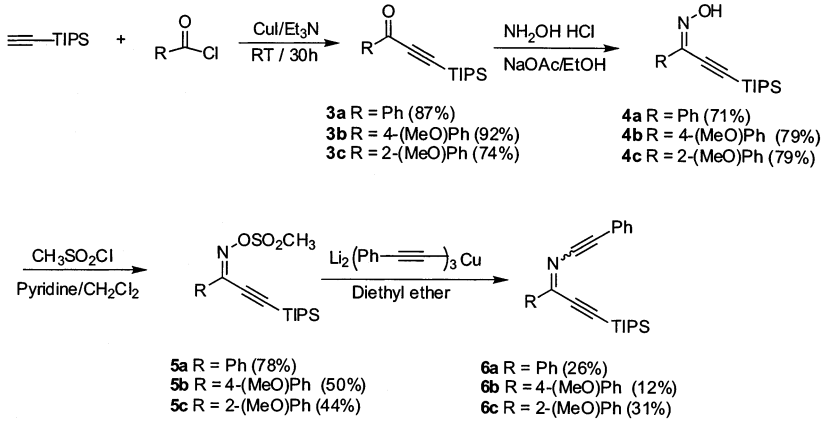
SCHEME 2



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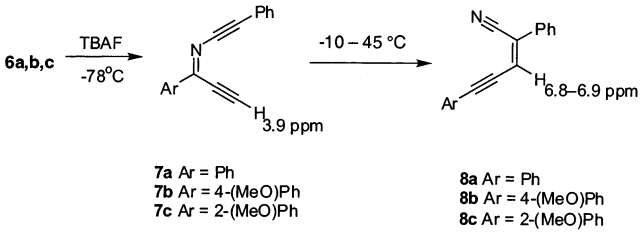
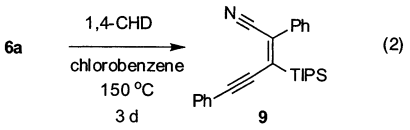


2. Aza-Bergman Kinetics. Thermolysis of **6a** was performed by heating compound **6a** in chlorobezene in the presence of 20 equiv of 1,4-cyclohexadiene (1,4-CHD) as proton donor in a sealed tube at 150 °C. The disappearance of starting material was monitored by TLC, which demonstrated that the reaction required 3 days to reach completion. We were unable to identify the product derived from trapping of the intermediate 2,5-didehydropyridine diradical from the reaction mixture; however, the retro-Bergman cyclization product, 2,5-diphenyl-3-triisopropylsilyl-pent-2-en-4-ynenitrile **9** (eq 2), was isolated in 35% yield.



(2)

Initial attempts to deprotect aza-enediyne **6a** by treatment with TBAF in THF afforded only the rearranged nitrile **8a** as the sole product in 89% yield (Scheme 3). Despite the inability to isolate and purify the intermediate deprotected aza-enediyne **7a**, rapid workup of the deprotection reactions at low temperature followed by ^{1}H NMR of the unpurified reaction product in $CDCl_3$ demonstrated the presence of the deprotected aza-enediyne **7a** (Figure 1). The terminal alkyne resonance for **7a** at 3.9 ppm diminished with time and was replaced by a resonance for the alkene proton at 6.8 ppm as **7a** underwent conversion to the nitrile **8a** over a period of minutes (Figure 1). The conversion of **7a** to **8a** follows first-order kinetics for both the disappearance of **7a** and the appearance of **8a**, and the kinetic yield of **8a** (ratio of the rate of disappearance of **7a** over the rate of appearance of **8a**) is >99%. At 20 °C, the ^{1}H NMR-determined half-life is 79 ± 4 min (average of two runs).

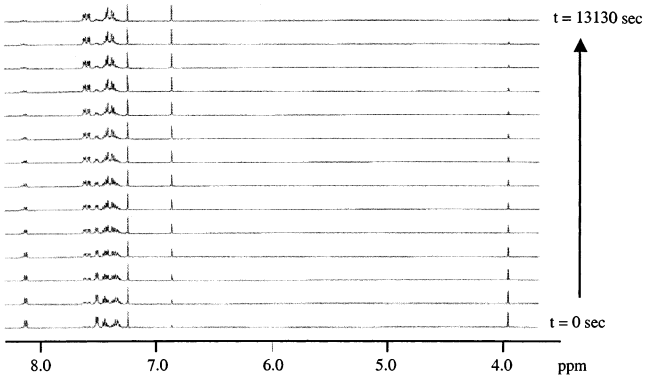


FIGURE 1. The conversion of aza-enediyne **7a** (alkyne resonance at 3.9 pm) to nitrile **8a** (alkene resonance at 6.8 ppm) followed by ^{1}H NMR (500 MHz) in $CDCl_3$ at 20 °C. Spectra were acquired every 1010 s, starting with the bottom spectrum.

The conversion of the aza-enediyne **7a** to nitrile **8a** could also be followed by UV spectroscopy. Nitrile **8a** has a UV absorbance peak at 345 nm and the aza-enediyne **7a** has an absorbance peak at 390 nm. Dilute (μM) solutions of the product mixture from the deprotection of **6a** in $CHCl_3$ were quickly prepared and placed in temperature-controlled cuvettes to monitor the UV absorbance change with time. As shown in Figure 2, the absorbance spectra demonstrate isobestic behavior and the expected first-order kinetics. At 20 °C, the half-life for the conversion of **7a** to **8a** determined spectrophotometrically (71 ± 1 min, average of two runs) is in agreement with that determined by ^{1}H NMR.

3. Substituent Effects. A combination of ^{1}H NMR and spectrophotometric kinetic data were used to follow the conversion of **7b** to **8b** at 20 °C. The time-dependent ^{1}H NMR spectra of crude **7b** in $CDCl_3$ demonstrates the same features noted above for **7a**, namely, the first-order disappearance of a peak at 3.9 ppm corresponding to the terminal alkyne proton in **7b** and the appearance of a new peak at 6.9 ppm, corresponding to the alkene proton in **8b**. In addition, in the case of **7b**, the methoxy protons' resonance for the aza-enediyne (3.86 ppm) is well resolved from the methoxy protons' resonance for the nitrile **8b** (3.82 ppm), and these signals also undergo a first-order decay and increase, respectively, with a kinetic yield of >99% (*data not shown*). The time-dependent UV absorbance spectra of dilute solutions of **7b** in $CHCl_3$ are

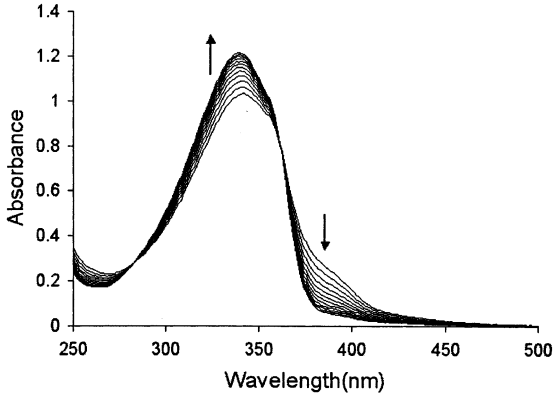


FIGURE 2. The conversion of aza-enediyne **7a** to nitrile **8a** followed by UV-absorption spectroscopy in $CHCl_3$ at 45 °C. The spectra were taken every 1.8 min for 20 min. The arrows indicate the decrease in absorbance due to the aza-enediyne **7a** at 390 nm and the increase in absorbance due to the nitrile **8a** at 345 nm with time.

TABLE 1. Half-Lives ($t_{1/2}$) for the Aza-Bergman Cyclization of Enediynes 2a, 7a, 7b, and 7c

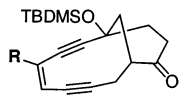
aza-enediyne	temp (°C)	$t_{1/2}$ (min)
7a	0	667[a]
7a	10	276 ± 13[b]
7a	20	75 ± 6[c]
7a	25	40.6 ± 0.1[d]
7a	30	21.5 ± 0.1[d]
7a	37	10.4 ± 0.1[d]
7a	45	4.3 ± 0.1[d]
7b	20	77 ± 3[e]
7c	20	35.6 ± 0.5[e]
2a	110	47[f]

[a] Based on one ^1H NMR run in $CDCl_3$. [b] Average value for two ^1H NMR runs in $CDCl_3$. [c] Based on two ^1H NMR runs in $CDCl_3$ and two spectrophotometric runs in $CHCl_3$. [d] Average of two spectrophotometric runs in $CHCl_3$. [e] Based on one ^1H NMR run in $CDCl_3$ and two spectrophotometric runs in $CHCl_3$. [f] Data from ref 14 in CH_3CN.

characterized by a decrease in a peak at 415 nm, corresponding to the aza-enediyne, and an increase in a peak at 360 nm, corresponding to the nitrile **8b**. The first-order half-life for the conversion of **7b** to **8b** is 77 ± 3 min. Thus, there is no apparent electronic substituent effect on the rate of the aza-Bergman cyclization when comparing **7a** and **7b** (Table 1). This result is in contrast to a number of reports of substituent effects in the Bergman cyclization. Maier and Greiner[23] have reported a pronounced retardation of the Bergman cyclization of the bicyclo[7.3.1]enediyne **10** when the double bond is substituted with an electron-donating group (R = *p*-C_6H_4OMe). Jones and Plourde have reported the retardation of the Bergman cyclization of a series of cyclic enediynes **11** when the double bond is substituted with chlorine.[24] A systematic study of substituent effects in the Bergman cyclization of 1,2-dialkynylbenzene derivatives **12** by Russell and co-workers demonstrated a linear free energy relationship between the cyclization rate and the Hammett σ_m substituent coefficient.[25] In contrast, calculations of a variety of aza-enediynes in which the imine double bond is replaced with an amide, amidine, or amidinium group predict that the barrier to aza-Bergman cyclization is relatively insensitive to these changes.[17] The lack of an observable difference in the rate of aza-Bergman reaction of **7a** and **7b** is not surprising in light of these theoretical studies.

The conversion of the *o*-(methoxy)phenyl-substituted aza-enediyne **7c** to nitrile **8c** can also be followed by ^1H NMR spectroscopy in $CDCl_3$. The overlap of the ^1H NMR signals due to the terminal alkyne proton and methoxy group of **7c** and the methoxy group of **8c** preclude the use of these signals to accurately follow the course of the reaction. Instead, a distinctive aromatic ^1H NMR resonance for **6c** at 7.9 ppm can be used to determine a first-order half-life of 35 min at 20 °C (one run). The UV absorbance changes accompanying the conversion of **7c** to **8c** in $CHCl_3$ are similar to those described above for the para-isomer **7b**, and give a first-order half-life of 36 ± 1 min at 20 °C (for two runs). Thus, the aza-Bergman reaction of **7c** at 20 °C occurs approximately two-times faster than that of either **7a** or **7b** (Table 1). The origin of this modest substituent effect is not known; however, it is likely that the steric interaction between the *o*-methoxy group and the adjacent alkyne moiety in **7c** plays a role.

The relative insensitivity of the rate of aza-Bergman cyclization to the nature of the imine double bond substituent indicates that this region of the aza-enediynes provides a great deal of flexibility in the design of potential warheads for targeting DNA and other receptors. This is significant because the imine double bond of aza-enediynes is a site of hydrolytic instability. Chen and co-workers note that thermolysis reactions of **2a** under acidic conditions afford primarily products of imine hydrolysis.[20] This hydrolytic instability could be remedied by replacing the imine double bond with the amidine group as proposed by Kraka and Cremer,[17] or by incorporating the imine double bond into a heterocyclic ring.[26] The latter approach has the advantage of enforcing the proper orientation of the alkynyl substituents required for aza-Bergman cyclization while providing a diverse set of chemotypes with which to design specific targeting compounds.



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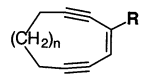

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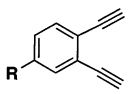

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In contrast to the modest substituent effects observed when comparing the aza-Bergman cyclization rate of **7a**−**c**, the nature of the alkyne substituents appears to play an important role in the rate of aza-Bergman cyclization. The aza-enediyne **6a**, which bears a bulky triiso-

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propylsilyl substituent on the C-alkynyl group, undergoes aza-Bergman cyclization only under rather forcing conditions (eq 2). Removal of the triisopropylsilyl group from **6a** to give **7a** results in facile aza-Bergman cyclization. The phenyl-substituted aza-enediyne **2a** undergoes aza-Bergman cyclization at a rate that is intermediate between that for **6a** and **7a** (Table 1). Schreiner[27] and co-workers have performed calculations on substituent effects on the Bergman cyclization of (*Z*)-1,5-hexadiyne-3-enes. According to these calculations, a diphenyl-substituted enediyne (Figure 1, **A**, X = CH, $R_1 = R_3 =$ Ph, $R_2 =$ H) has a Bergman cyclization transition state that is 10 kcal/mol higher than that for the phenyl-substituted enediyne (Figure 1, **A**, X = CH, $R_1 =$ Ph, $R_2 = R_3 =$ H), an effect that is due to a combination of additional stabilization of the starting enediyne and destabilization of the transition state due to steric repulsion between the phenyl groups in the diphenyl-substituted case. In the parent enediyne case, the effect of changing the size of the terminal substituents on the facility of Bergman cyclization cannot be employed as a triggering mechanism at physiological temperatures due to the large barrier to Bergman cyclization of the unsubstitued enediyne;[28] however, in the case of the aza-enediynes studied here, the terminal alkyne substituent effect can be viewed as a potential triggering device due to the facility with which sterically unencumbered aza-enediynes such as **7a**−**c** undergo aza-Bergman cyclization. Of course, such a triggering device would only lead to hydrogen atom abstraction or cyclization chemistry if the intermediate 2,5-didehydropyridine diradical could enter into free radical reactions prior to retro-aza-Bergman cyclization. This is not the case under the conditions employed in this work. Chen and co-workers have demonstrated that the large singlet−triplet gap for 2,5-didehydropyridine is related to its inability to participate in hydrogen atom abstraction reactions. Protonation of the nitrogen atom of the 2,5-didehydropyridine lowers the singlet−triplet gap and increases the barrier to retro-aza-Bergman rearrangement. Chen and co-workers have reported the trapping of these diradicals when the aza-Bergman cyclization is performed under acidic conditions.[20]

4. Stereochemical Aspects. The aza-Bergman cyclization of *C*,*N*-dialkynyl imine aza-enediynes can only occur through the (*Z*)-imine isomer. Previous studies of the aza-Bergman cyclization have employed aza-enediynes (e.g., **2a,b**, eq 1) that were mixtures of stereochemical isomers about the imine double bond.[14,20] As a result, the observed kinetics for the conversion of these aza-enediynes to products of aza-Bergman cyclization may have been affected by the rate of (*E*)- to (*Z*)-imine isomerization. The deprotected aza-enediynes **7a**−**c** appear to be single isomers (>9:1) by ^{1}H NMR (Figure 1). Density functional theory calculations employing the B3LYP functional[29] predict that the (*Z*)-isomer of **7a** is more stable than the (*E*)-isomer by 4.4 kcal/mol. Assuming that these aza-enediynes undergo thermodynamic equilibration during their preparation and isolation, the predominant isomers observed for **7a**−**c** are the more thermodynamically stable (*Z*)-isomer.

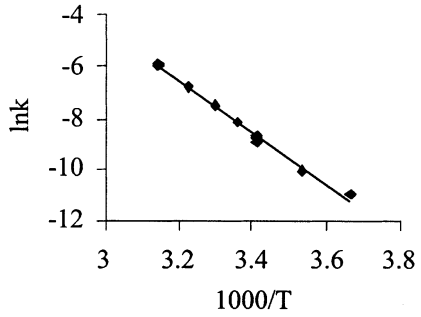

FIGURE 3. Arrhenius plot of the aza-Bergman cyclization of aza-enediyne **7a**. Fifteen points at seven temperatures (0, 10, 20, 25, 30, 37, 45 °C) yield $E_a = 19.9 \pm 0.3$ kcal/mol and log $A = 11.1 \pm 0.2$ ($R^2 = 0.993$).

As expected for an aza-Bergman process, the spontaneous rearrangement of **7a**−**c** to the nitriles **8a**−**c** occurs stereoselectively to afford the nitrile products as single isomers. Assignment of the (*Z*)-stereochemistry of these nitriles is based upon their isomerization to a mixture of (*E*)- and (*Z*)-isomers. The ^{1}H NMR spectum of **8a** in CD_3CN contains a singlet resonance at 7.1 ppm, corresponding to the alkene hydrogen. When this solution is subjected to irradiation at 371 nm, using the excitation beam of a spectroflourimeter,[30] the ^{1}H NMR spectrum shows a new single peak at 6.8 ppm, which is due to the alkene proton of the isomer of **8a**. Because the resonance of the alkene proton of (*E*)-**8a** is predicted to lie 0.34 ppm upfield of that for the (Z)-isomer,[31] we assign the 7.1-ppm peak to the (*Z*)-isomer and the 6.8-ppm peak to the (*E*)-isomer. After 4.5 h of irradiation, 34% (*E*)-**8a** was formed based on the ratio of the peaks at 6.8 and 7.1 ppm. For conversion of imine **7b** to nitrile **8b**, the ^{1}H NMR ($CDCl_3$) of the product mixture prior to purification showed one singlet peak at 6.8 ppm, due to the (Z)-isomer of **8b**. Photochemical isomerization of **8b** results in the formation of an isomer with a new ^{1}H NMR resonance at 6.6 ppm, which is associated with the (*E*)-nitrile (20%).

5. Activation Energy for the Aza-Bergman Cyclization. The kinetics of the conversion of **7a** to **8a** were determined as a function of temperature. At 10 °C, the ^{1}H NMR-determined half-life is 4.6 h, and at 0 °C the half-life is 11 h (Table 1). The half-life for the aza-Bergman reaction of **7a** at 37 °C is only 10.4 min, as determined spectrophotometrically (Table 1). An Arrhenius plot for the aza-Bergman reaction of **7a** to nitrile **8a**, shown in Figure 3, gives $E_a = 19.9 \pm 0.3$ kcal/mol and log $A = 11.1 \pm 0.2$. The activation energy for the aza-Bergman reaction of **7a** is lower than that for 1,6-bis(4-*tert*-butylphenyl)-3-aza-4-methylhex-3-ene-1,5-diyne (Figure 1, **A**, X = N, $R_1 = R_3 =$ 4-(*t*-Bu)Ph, $R_2 =$ Me), which has been studied by Chen and co-workers, who determined $E_a = 23.1 \pm 1.5$ kcal/mol.[20] The lower activation energy for the aza-Bergman reaction of **7a**

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(28) For an example of steric effects in the Bergman cyclization of simple enediyne see: Rawat, D. S.; Zaleski, J. M. *Chem Commun* **2000**, 2493.

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(31) Predictions of ^{1}H NMR resonances based on the ChemDraw Ultra program.

TABLE 2. First-Order Half-Lives ($t_{1/2}$) for the Aza-Bergman Cyclization of Aza-Enediyne 7a in Various Solvents at 45 °C

solvent[a]	half-life[b] ($t_{1/2}$, min)	dielectric constant (D)
hexanes	3.61 ± 0.03	1.89
chlorobenzene	4.2 ± 0.1	2.71
chloroform	4.3 ± 0.1	4.81
THF	6.4 ± 0.2	7.60
isopropyl alcohol	7.91 ± 0.04	18.30
acetonitrile	8.14 ± 0.03	37.50

[a] All solvents were HPLC or ACS grade and used directly without further purification. [b] Average value ± standard deviation for two spectrophotometric runs.

relative to the 1,6-diaryl aza-enediyne studied by Chen and co-workers is most likely due to the substituent effects discussed above in the comparison of the facility of cyclization of **7a** versus **2a**. The activation energy for the aza-Bergman cyclization of **7a** is lower than the barrier for aza-Bergman cyclization of the parent aza-enediyne system (Figure 1, **A**, X = N, $R_1 = R_2 = R_3 = H$) calculated at the CASMP2 level of theory (27.7 kcal/mol),[20] but close to the value determined by B3LYP calculations (21.8 kcal/mol),[17] and that calculated by Cramer using a composite energy term (19.1 kcal/mol).[16] It is probable that the true energy barrier for cyclization in the parent aza-enediyne system is even lower than that determined for **7a**, in which case the later calculations may also overestimate this barrier.

6. Solvent Effects. We have performed kinetic studies of **7a** in various solvents to determine solvent effects on the aza-Bergman cyclization. The conversion of **7a** to **8a** at 45 °C in various solvents was followed by UV−vis spectroscopy. Kinetic data in all solvents were first-order and analysis of the reaction mixtures by TLC and mass spectroscopy confirmed the presence of **8a** as the sole reaction product. The aza-Bergman cyclization rates were found to be solvent dependent, with slightly faster rates in nonpolar solvents (Table 2). The effect is not large; the half-lives varied from 3.6 min in hexanes to 8.2 min in acetonitrile. There are examples of enediynes that undergo solvent-dependent Bergman cycloaromatization rates,[32,33] but these cases are complicated by the solvent effects on the rate of hydrogen atom abstraction by the diradical intermediate, which impacts the observed rate of disappearance of enediyne. In the case of the conversion of **7a** to **8a**, it is clear that the rate determining step is the initial aza-Bergman cyclization. We believe that the solvent-dependent rate of aza-Bergman reaction of **7a** shown in Table 3 is due to preferential solvation of **7a** by more polar solvents, resulting in ground-state stabilization and concomitant decreased rate.

In our previous studies of the aza-Bergman reaction of aza-enediyne **2a**, we noted that the reaction rates were nearly identical in acetonitrile and heptane, the only two solvents investigated.[14] The lack of an apparent solvent dependence on the aza-Bergman reaction of **2a** may be due to its decreased interaction with polar solvents when compared to **7a**. In addition, as noted above, the aza-enediyne **2a** was isolated as a mixture of (*E*)- and (*Z*)-isomers. While the aza-Bergman reaction of **2a** would be expected to show a similar solvent dependence as **7a**, the (*E*)- to (*Z*)-isomerization rate may have a more complicated solvent dependence,[34] resulting in a fortuitous canceling of solvent polarity effects for the two solvents investigated.

Although the solvent dependence of the rate of aza-Bergman cyclization of **7a** is small, the increased facility of aza-Bergman cyclization in nonpolar solvents implies that aza-enediynes such as **7a** would be somewhat more stable to aza-Bergman cyclization in aqueous solution as compared to when bound to a target receptor, where the microenvironment is less polar.

Conclusion

Since the initial report[14] of the aza-Bergman reaction of aza-enediynes, these compounds have been the subject of a number of theoretical studies.[16−18,20] These studies have focused on two issues associated with these aza-enediynes and their aza-Bergman cyclization: the facility of the cyclization and the potential reactivity of the resulting 2,5-didehydropyridine intermediate. For these aza-enediynes to serve as potential warheads for targeting cancer cells, the aza-Bergman cyclization rate must be sufficiently fast at physiological temperature, and the resulting diradical must be capable of entering into free radical chemistry in competition with its collapse via a retro-aza-Bergman cyclization to the thermodynamically stable β-alkynyl acrylonitrile product. There have only been two experimental reports on aza-enediynes that addressed either of these issues, and both of these were carried out with similar aza-enediynes.[14,20] Thus, the effects of substituents on the rate of aza-Bergman cyclization had not previously been explored. Here we report the synthesis and kinetic studies of the aza-Bergman reactions of a series of 6-triisopropylsilyl and 6-unsubstituted 4-aryl-3-aza-3-ene-1,4-diynes. There are two types of substituent effects in this system: The aza-Bergman reaction rate is not greatly affected by changing the 4-aryl substituent on the aza-enediyne imine double bond, but is very sensitive to the nature of the 6-substitutent at the alkyne terminus. The aza-Bergman cyclization of sterically unencumbered, 6-unsubstituted aza-enediynes occurs readily at temperatures as low as 0 °C. These observations provide the basis for the design of a novel aza-Bergman triggering device involving the conversion of a sterically blocked aza-enediyne to a sterically unencumbered one mediated by a cancer cell-specific enzymatic activity.

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One issue that remains to be addressed is the reactivity of the 2,5-didehydropyridine intermediates involved in the aza-Bergman cyclization of these aza-enediynes. In this study, there is no evidence of any products corresponding to trapping of these 2,5-didehydropyridine intermediates. These results are in accord with many theoretical predictions of an extremely low barrier to retro-aza-Bergman cyclization of these intermediates to afford the observed β-alkynyl acrylonitrile products.[15,16,20,27] The lack of diradical reactivity associated with the 2,5-didehydropyridine intermediate has been rationalized based upon its large singlet−triplet gap.[20] Substituting the aza-enediyne imine double bond[17,20] or incorporating it within a heterocyclic ring[26] has the potential to both increase the barrier to retro-aza-Bergman reaction and increase the diradical character of the aza-Bergman-derived 2,5-didehydropyridine intermediates. The results presented here indicate that such substitutions may be compatible with physiologically relevant aza-Bergman cyclization rates.

Experimental Section

All commercial chemicals were used without further purification unless otherwise noted. Tetrahydrofuran (THF) was re-distilled from Na/benzophenone, methylene chloride and pyridine were re-distilled from calcium hydride, and diethyl ether was re-distilled from lithium aluminum hydride (LAH) prior to use. All reactions were performed under argon. Unless otherwise noted, organic extracts were dried with Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20−30 mmHg). R_f values are reported for thin-layer chromatography (TLC) performed on silica gel TLC plates, using the indicated mobile phase. Flash chromatography was preformed with EM silica gel. ^{1}H NMR spectra were recorded at 500, 300, and 250 MHz and ^{13}C NMR spectra were recorded at 75 and 62 MHz. Spectroscopic studies were performed on a spectrophotometer with a Peltier thermostated cuvette holder. All mass spectra were obtained by chemical ionization with methane as the ionizing gas. Melting points are uncorrected. Density functional theory computations were carried out with Guassian 98.[35]

1-Phenyl-3-(triisopropylsilyl)-propynone (3a). To a mixture of triisopropylsilyl acetylene (0.5 g, 2.74 mmol) and cuprous iodide (26.6 mg, 0.14 mmol) in triethylamine (9 mL) was added benzoyl chloride (0.5 g, 3.56 mmol). The reaction mixture was stirred at room temperature under argon for 30 h. After the removal of the solvent, methanol (3 mL) was added and the mixture was stirred for an additional 5 min, during which time the mixture became clear. The methanol was distilled off under vacuum, and the residue was poured into water and extracted with dichloromethane (2 × 20 mL) and dried over Na_2SO_4. The solvent was distilled off and the product was purified by Kugelrohr distillation (110 °C, 1 mmHg) to afford 0.693 g (87%) of propynone **3a** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.01−1.22 (m, 21H), 7.46−7.55 (m, 3H), 8.16−8.23 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.07, 18.53, 97.91, 103.01, 128.53, 129.49, 134.00, 136.70, 177.43; HRMS *m*/*z* 287.1826 (calcd 287.1831, $C_{18}H_{26}OSi$).

1-(4-Methoxyphenyl)-3-(triisopropylsilyl)-propynone (3b). Propynone **3b** was prepared from *p*-anisoyl chloride by a procedure analogous to that described for the preparation of **3a**. The product was purified by flash chromatography (0−30% CH_2Cl_2 in hexanes) to afford 4.8 g (92%) of **3b** as a transparent oil: R_f 0.85 (CH_2Cl_2); ^{1}H NMR (CD_2Cl_2) δ 1.11−1.30 (m, 21H), 3.86 (s, 3H), 6.95 (d, J = 8.0 Hz, 2H), 8.13 (d, J = 8.0 Hz, 2H); ^{13}C NMR (CD_2Cl_2) δ 11.54, 18.74, 55.99, 97.21, 103.87, 114.24, 130.80, 132.12, 165.04, 176.23; HRMS *m*/*z* 317.1930 (calcd 317.1936, $C_{19}H_{28}O_2Si$).

1-(2-Methoxyphenyl)-3-(triisopropylsilyl)-propynone (3c). Propynone **3c** was prepared from *o*-anisoyl chloride by a procedure analogous to that described for the preparation of **3a**. The product was purified by flash chromatography (10% EtOAc in hexanes) to afford 4.62 g (74%) of **3c** as a transparent oil: R_f 0.85 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.95−1.20 (m, 21H), 3.85 (s, 3H), 6.90−7.01 (m, 2H), 7.45 (ddd, J = 8.2, 6.0, 2.0 Hz, 1H), 7.99 (dd, J = 8.2, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.94, 18.34, 55.51, 95.50, 105.11, 111.84, 119.96, 126.25, 132.56, 134.72, 159.96, 176.11; HRMS *m*/*z* 317.1944 (calcd 317.1936, $C_{19}H_{28}O_2Si$).

1-Phenyl-3-(triisopropylsilyl)-propynone Oxime (4a). To a solution of **3a** (0.64 g, 2.23 mmol) in 8 mL of EtOH was added hydroxylamine hydrochloride (186 mg, 2.68 mmol) and sodium acetate (220 mg, 2.68 mmol). The mixture was stirred at room temperature under argon for 10 days. The reaction mixture was poured into water (20 mL), and the water layer was extracted by CH_2Cl_2 (3 × 15 mL). The residue upon drying and concentration of the organic layer was purified by flash chromatography (0−20% CH_2Cl_2 in hexanes) to afford 0.51 g (77%) of oxime **4a** as a transparent oil: R_f 0.54 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.04−1.30 (m, 21H), 7.38−7.42 (m, 3H), 7.80−7.89 (m, 2H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.13, 18.61, 94.61, 107.42, 126.46, 128.46, 129.82, 133.12, 141.97; HRMS *m*/*z* 302.1946 (calcd 302.1940, $C_{18}H_{27}NOSi$).

1-(4-Methoxyphenyl)-3-(triisopropylsilyl)propynone Oxime (4b). Oxime **4b** was prepared from propynone **3b** by a procedure analogous to that described for the preparation of **4a**. The product was purified by flash chromatography on silica gel (0−20% CH_2Cl_2 in hexanes) to afford 2.01 g (79%) of oxime **4b** as a light yellow oil: R_f 0.50 (CH_2Cl_2); ^{1}H NMR (CD_2Cl_2) δ 0.96−1.35 (m, 21H), 3.85 (s, 3H), 6.93 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H), 8.80 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 11.58, 18.80, 55.74, 97.90, 107.23, 114.26, 126.14, 128.26, 142.00, 161.52; HRMS *m*/*z* 332.2036 (calcd 332.2045, $C_{19}H_{29}NO_2Si$).

1-(2-Methoxyphenyl)-3-(triisopropylsilyl)propynone Oxime (4c). Oxime **4c** was prepared from propynone **3c** by a procedure analogous to that described for the preparation of **4a**. The product was purified by flash chromatography (0−20% CH_2Cl_2 in hexanes) to afford 1.24 g (79%) of oxime **4c** as a white solid: R_f 0.40 (CH_2Cl_2); mp 120.2−121.0 °C; ^{1}H NMR (CD_2Cl_2) δ 1.10−1.22 (m, 21H), 3.89 (s, 3H), 6.97−7.08 (m, 2H), 7.39 (ddd, J = 8.0, 7.0, 2.0 Hz, 1H), 7.80 (dd, J = 8.0, 2.0 Hz, 1H); ^{13}C NMR (CD_2Cl_2) δ 11.57, 18.78, 55.71, 96.46, 105.56, 111.84, 120.77, 122.20, 131.01, 131.39, 140.42, 157.68; HRMS *m*/*z* 332.2058 (calcd 332.2045, $C_{19}H_{29}NO_2Si$).

1-Phenyl-3-(triisopropylsilyl)-propynone Mesylate (5a). To a solution of oxime **4a** (2.7 g, 8.96 mmol) in 60 mL of dry CH_2Cl_2 was added dry pyridine (3.6 mL, 44.8 mmol). The reaction mixture was cooled to 0 °C, followed by dropwise addition of a solution of methanesulfonyl chloride (1.28 g, 11.2 mmol) in 5 mL of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 3 days. The solvent volume was reduced by rotary evaporation, and the residue was poured into ice−water. The aqueous layer was extracted by CH_2Cl_2 three times. The residue upon drying and concentration of the organic layer was purified by flash chromatography (0−20% CH_2Cl_2 in hexanes) to afford 2.6 g (78%) of mesylate **5a** as a yellow oil: R_f 0.76 in CH_2Cl_2; ^{1}H NMR ($CDCl_3$) δ 1.04−1.28 (m, 21H), 3.25 (s, 3H), 7.39−7.52 (m, 3H), 7.94 (dd, J = 8.0, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.01, 18.50, 36.71, 93.37, 111.53, 127.52, 128.68, 130.89, 131.79, 148.58; HRMS *m*/*z* 380.1718 (calcd 380.1715, $C_{19}H_{29}NOSSi$).

1-(4-Methoxyphenyl)-3-(triisopropylsilyl)-propynone Mesylate (5b). Mesylate **5b** was prepared from oxime **4b** by a procedure analogous to that described for the preparation of **5a**. The product was purified by flash chromatography on silica gel (0−30% CH_2Cl_2 in hexanes) to afford 450 mg (50%) of mesylate **5b** as a yellow solid: mp 85.8−86.9 °C; R_f 0.73 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.05−1.20 (m, 21H), 3.20 (s, 3H), 3.81 (s, 3H), 6.91 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H);

^{13}C NMR ($CDCl_3$) δ 10.98, 18.46, 36.59, 55.35, 93.53, 110.61, 114.05, 123.27, 129.19, 148.20, 162.53; HRMS *m/z* 410.1828 (calcd 410.1821, $C_{20}H_{31}NO_4SSi$).

1-(2-Methoxyphenyl)-3-(triisopropylsilyl)-propynone Mesylate (5c). Mesylate **5c** was prepared from oxime **4c** by a procedure analogous to that described for the preparation of **5a**. The product was purified by flash chromatography (0−15% CH_2Cl_2 in hexanes) to afford 90 mg of a yellow oil consisting of an inseparable mixture of mesylate **5c** along with Beckman rearrangement product 3-(triisopropylsilyl)-propynoic acid (2-methoxyphenyl)amide in 6 to 1 ratio, as judged by ^{1}H NMR. A pure sample of 3-(triisopropylsilyl)-propynoic acid (2-methoxyphenyl)amide was obtained as a yellow solid in 72% yield after chromatography from a reaction allowed to proceed for 6 days. Mesylate **5c**: R_f 0.65 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.01−1.19 (m, 21H), 3.18 (s, 3H), 3.83 (s, 3H), 6.93−7.05 (m, 2H), 7.43 (ddd, J = 9.3, 7.5, 1.8 Hz, 1H), 7.55 (dd, J = 7.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.93, 18.38, 36.57, 55.55, 94.39, 110.12, 111.55, 120.45, 120.59, 130.64, 132.43, 147.87, 157.91; HRMS *m/z* 410.1825 (calcd 410.1821, $C_{20}H_{31}NO_4SSi$). 3-(Triisopropylsilyl)-propynoic acid (2-methoxyphenyl)amide: R_f 0.67 (CH_2Cl_2); mp 32.0−32.9°C; ^{1}H NMR δ ($CDCl_3$) 1.00−1.19 (m, 21H), 3.88 (s, 3H), 6.82−6.98 (m, 2H), 7.00−7.08 (m, 1H), 8.05 (s, 1H), 8.29 (dd, J = 8.7, 2.0, 1H); ^{13}C NMR ($CDCl_3$) δ 10.98, 18.45, 55.76, 89.10, 100.31, 109.86, 120.21, 121.08, 124.32, 127.15, 147.43, 149.81; HRMS *m/z* 332.2042 (calcd 332.2045, $C_{19}H_{29}NO_2Si$).

1,4-Diphenyl-6-(triisopropylsilyl)-3-aza-3-ene-1,5-diyne (6a). To a solution of phenylacetylene (410 mg, 4.02 mmol) in 5 mL of dry ether at −78 °C was added dropwise a solution of *n*-butyllithium (2.89 mL, 1.6 M in hexanes, 4.02 mmol) such that the temperature was maintained at −78 °C. The reaction mixture was stirred for 20 min at the same temperature. In a separate flask, a suspension of cuperous iodide (251 mg, 1.32 mmol) in 5 mL of dry ether was cooled to −40 °C. The phenylacetylide solution was added slowly via cannula to this suspension. After the addition was complete, the mixture was stirred at room temperature for 40 min. The resulting light yellow suspension was added to a solution of mesylate **5a** (500 mg, 1.32 mmol) in 5 mL of dry ether at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 2 h. The solvent was evaporated, and the product was purified by flash chromatography on silica gel (hexanes) to afford 110 mg (26%) of aza-enediyne **6a** as a yellow oil: R_f 0.56 (40% CH_2Cl_2 in hexanes); ^{1}H NMR ($CDCl_3$) δ 1.10−1.25 (m, 21H), 7.28−7.39 (m, 3H), 7.39−7.55 (m, 5H), 8.14 (dd, J = 7.6, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.55, 18.79, 93.75, 100.27, 100.60, 106.79, 124.90, 128.26, 128.52, 128.66, 128.92, 131.77, 132.49, 136.22, 158.96; HRMS *m/z* 386.2310 (calcd 386.2304, $C_{26}H_{31}NSi$).

1-Phenyl-4-(4-methoxyphenyl)-6-(triisopropylsilyl)-3-aza-3-ene-1,5-diyne (6b). Aza-enediyne **6b** was prepared from mesylate **5b** by a procedure analogous to that described for the preparation of **6a**. The product was purified by preparative TLC on silica gel (hexanes) to afford 12 mg (15%) of aza-enediyne **6b** as a yellow oil: R_f 0.35 (30% CH_2Cl_2 in hexanes); ^{1}H NMR ($CDCl_3$) δ 1.08−1.25 (m, 21H), 3.85 (s, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.25−7.34 (m, 3H), 7.44 (dd, J = 8.4, 1.5 Hz, 2H), 8.08 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.16, 18.65, 55.47, 93.60, 97.86, 100.00, 105.35, 113.94, 124.90, 127.82, 128.14, 128.99, 129.86, 131.38, 131.92, 163.00; HRMS *m/z* 416.2407 (calcd 416.2409, $C_{27}H_{33}NOSi$).

1-Phenyl-4-(2-methoxyphenyl)-6-(triisopropylsilyl)-3-aza-3-ene-1,5-diyne (6c). Aza-enediyne **6c** was prepared from mesylate **5c** by a procedure analogous to that described for the preparation of **6a**. The product was purified by flash chromatography (0−20% CH_2Cl_2 in hexanes) to afford 22 mg (31%) of aza-enediyne **6c** as a yellow oil: R_f 0.45 (40% CH_2Cl_2 in hexanes); ^{1}H NMR ($CDCl_3$) δ 1.05−1.19 (m, 21H), 3.88 (s, 3H), 6.95−7.02 (m, 2H), 7.26−7.34 (m, 3H), 7.36−7.48 (m, 3H), 7.86 (d, J = 7.6, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.19, 18.60, 55.70, 93.21, 100.66, 101.82, 105.05, 111.77, 120.44, 124.86, 125.99, 127.77, 128.11, 130.81, 131.27, 132.64, 157.66, 158.60; HRMS *m/z* 416.2404 (calcd 416.2409, $C_{27}H_{33}NOSi$).

(*Z*)-2,5-Diphenyl-pent-2-en-4-ynenitrile (8a). A solution of **6a** (68 mg, 0.176 mmol) in dry THF (6 mL) was cooled to −78 °C and then a 1 M solution of TBAF (0.194 mmol) was added slowly. After being stirred at −78 °C for 5−10 min the mixture was poured into ice−water (10 mL) and extracted by CH_2Cl_2 (2 × 15 mL). The dry organic solution was plugged through a small column before evaporation. The conversion of aza-enediyne **7a** to (*Z*)-nitrile **8a** was followed by ^{1}H NMR and/or UV−vis spectroscopy. After the conversion was complete, the (*Z*)-nitrile **8a** was purified by flash chromatography on silica gel (0−10% CH_2Cl_2 in hexanes) to afford 36 mg (89%) of nitrile **8a** as a yellow solid: R_f 0.41 (50% CH_2Cl_2 in hexanes); mp 79.3−80.7 °C; ^{1}H NMR (CD_2Cl_2) δ 6.92 (s, 1H), 7.38−7.50 (m, 6H), 7.55−7.67 (m, 4H); ^{1}H NMR (CD_3CN) δ 7.1 (s, 1H), 7.41−7.50 (m, 6H), 7.54−7.61 (m, 2H), 7.65−7.71 (m, 2H); ^{13}C NMR (CD_2Cl_2) δ 86.45, 102.23, 116.90, 121.87, 122.43, 124.09, 126.03, 128.99, 129.54, 130.15, 130.52, 132.48, 133.04; HRMS *m/z* 230.0972 (calcd 230.0969, $C_{17}H_{11}N$).

(*Z*)-5-(4-Methoxyphenyl)-2-phenyl-pent-2-en-4-ynenitrile (8b). (*Z*)-Nitrile **8b** was prepared from aza-enediyne **6b** by a procedure analogous to that described for the preparation of **8a**. The conversion of imine **6b** to nitrile **8b** was followed by ^{1}H NMR and/or UV−vis. The nitrile **8b** was purified by flash chromatography on silica gel (0−5% CH_2Cl_2 in hexanes) to afford 4 mg (72%) of (*Z*)-nitrile **8b** as a light yellow solid: R_f 0.35 (40% CH_2Cl_2 in hexanes); mp 85.5−86.6 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 6.84 (s, 1H), 6.88 (d, J = 8.9 Hz, 2H), 7.36−7.44 (m, 3H), 7.52 (d, J = 8.9 Hz, 2H), 7.57−7.62 (dd, J = 7.7, 1.5 Hz, 2H); HRMS *m/z* 260.1070 (calcd 260.1075, $C_{18}H_{13}NO$).

(*Z*)-5-(2-Methoxyphenyl)-2-phenyl-pent-2-en-4-ynenitrile (8c). (*Z*)-Nitirle **8c** was prepared from aza-enediyne **6c** by a procedure analogous to that described for the preparation of **8a**. The conversion of imine **7c** to nitrile **8c** was followed by ^{1}H NMR and/or UV−vis. The nitrile **8c** was purified by flash chromatography (0−10% CH_2Cl_2 in hexanes) to afford 10 mg (91%) of (*Z*)-nitrile **8c** as a light yellow solid: R_f 0.30 (40% CH_2Cl_2 in hexanes); mp 57.7−58.6 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.88−6.98 (m, 3H), 7.33−7.48 (m, 4H), 7.50−7.57 (dd, J = 7.8, 1.8 Hz, 1H), 7.58−7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.87, 90.44, 99.41, 110.74, 111.21, 120.65, 120.82, 121.56, 122.95, 125.61, 129.14, 129.94, 131.41, 132.50, 134.27, 160.54; HRMS *m/z* 260.1077 (calcd 260.1075, $C_{18}H_{13}NO$).

(*E*)-2,5-Diphenyl-3-(triisopropylsilyl)-pent-2-ene-4-ynenitrile (9). To a solution of the aza-enediyne 6a (20 mg, 0.0518 mmol) in chlorobenzene (1.5 mL) was added 1,4-cyclohexadiene (83.19 mg, 1.036 mmol, 20 equiv). The mixture was heated at 150 °C for 3 days. The solvent was evaporated and the residue purified by chromatography to afford nitrile **9** (7 mg, 35%) as a yellow oil: R_f 0.51 (40% CH_2Cl_2 in hexanes); ^{1}H NMR ($CDCl_3$) δ 1.10−1.22 (d, J = 7.5 Hz, 18H), 1.68−1.85 (p, J = 7.5 Hz, 3H), 7.24−7.34 (m, 5H), 7.37−7.48 (m, 3H), 7.84 (dd, J = 7.7, 1.9, 2H); ^{13}C NMR ($CDCl_3$) δ 12.27, 18.78, 91.31, 108.25, 120.38, 122.98, 128.12, 128.51, 128.70, 129.23, 129.42, 131.44, 134.10, 136.07, 139.69; HRMS *m/z* 386.2317 (calcd 386.2304, $C_{26}H_{31}NSi$).

Spectroscopic Kinetics. To a solution of aza-enediyne **6a** or **6b** (0.0052 mmol) in dry THF (2 mL) cooled to −78 °C was added slowly a 1 M solution of tetrabutylammonium floride in dry THF (0.0059 mmol). The reaction mixture was allowed to stir at −78 °C for 5−10 min, and the mixture was poured into ice−water (10 mL) and extracted by CH_2Cl_2 (2 × 15 mL). The dry organic solution was chromatographed through a small plug of silica gel to remove tetrabutylammonium species before evaporation. The residue was storred at −80 °C and quickly redissolved in $CHCl_3$ or other solvents (THF, *i*PrOH, chlorobenzene, hexanes, CH_3CN) and the resulting solution transferred to a thermostated cuvette at 20, 25, 30, 37, or 45 °C. The conversion of aza-enediyne **7a**/**7b** to (*Z*)-nitrile **8a**/**8b**

was followed spectrophotometrically by periodically acquiring UV absorbance spectra (250−500 nm) over a period of at least 2 half-lives. The first-order rate constants were obtained by fitting plots of the normalized absorbance at 390 nm (**7a**) or 415 nm (**7b**) versus time to an exponential decay.

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Supporting Information Available: Spectroscopic data for compounds **3a**,**b**,**c**−**9**; ^{1}H NMR and spectroscopic kinetic data for the aza-Bergman reaction of **7a**, **7b**, and **7c**; and Cartesian coordinates and energies for (*Z*)-**7a** and (*E*)-**7a** (B3LYP/6-31G(d,p) level). This material is available free of charge via the Internet at http://pubs.acs.org.

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