Rapid Bergman Cyclization of 1,2-Diethynylheteroarenes

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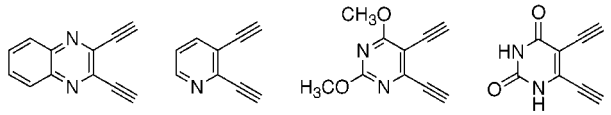
The synthesis and cyclization of acyclic quinoxaline, pyridine, and pyrimidine enediynes (**1**−**3**) are described. These compounds were prepared using palladium(0) coupling of trimethylsilyl acetylene to *o*-dihalo- or *o*-halotriflic heteroarenes. All compounds were prepared in modest to good yields. The enediynes prepared were shown to undergo Bergman cyclization. Kinetics over a minimum of 3 half-lives were used to construct Arrhenius plots. Pyrimidine **3** was found to have an activation energy of 16.1 kcal/mol. Cyclization of the closest known aromatic analogue, *o*-diethynylbenzene (**15**), has E_a = 25.1 kcal/mol (Grissom, J. W.; Calkins, T. L.; McMillen, H. A.; Jiang, Y. *J. Org. Chem.* **1994**, *59*, 5833−5835). Pyridine **2** and quinoxaline **1** gave activation energies of 21.5 and 33.6 kcal/mol, respectively. The results illustrate that heteroarenes can be used to activate Bergman cyclization. We expect these compounds to play an important role in furthering the understanding of Bergman cyclization and in aiding the development of new biologically significant enediynes.

Introduction

Although originally studied in the early 1970s,[1] Bergman cyclization received little attention until nearly a decade and a half later. That changed when a number of natural products incorporating a (*Z*)-3-ene-1,5-diyne and possessing antibiotic anticancer activity were reported.[2] Since that time enormous effort has been poured into elucidating the biological modes of action of these novel natural products.[3] The synthesis of the natural enediynes[4] and the development of simplified synthetic analogues[5] have also been pursued in earnest. However, many factors which govern this enormously important reaction remain unresolved.

Our group has recently begun a program to more closely examine how aromaticity and electronic factors influence the rate of Bergman cyclization. We have started our work with an exciting new class of simple enediynes, in which the double bond is adjacent to one or more heteroatoms (e.g., **1**−**4**). Such targets not only allow investigation of both aromatic character and electronic effects but also provide synthetic entrance to biologically interesting compounds. Herein, we give an account of the synthesis of the first of these compounds, novel arenediynes **1**−**3**. The activation energies of these compounds toward Bergman cyclization, including the remarkable reactivity of **3**, are described.



1 **2** **3** **4**

Bergman cyclization is the orbital-symmetry-allowed rearrangement of a (*Z*)-3-ene-1,5-diyne to a 1,4-didehydrobenzene diradical (**5**, Scheme 1). Depending on its stability, intermediate **6** may undergo dearomatization to form either starting material (**5**) or a rearranged enediyne (**7**). Recently, this has been elegantly demonstrated for the aza-Bergman cyclization of *C,N*-dialkynylimines.[7] Alternatively, in the presence of a suitable radical trapping agent, the intermediate can be irreversibly quenched to maintain the new aromatic moiety (**8**).

Studies have shown that the ring size and strain energy of cyclic enediynes and electronic factors in all enediynes can influence the rate of diradical formation.[8−11] Reports which directly address the electronic nature of simple enediynes include the work of Schmittel and Maier (Table 1). Schmittel demonstrated that electron-withdrawing groups attached to the triple-bond termini (**9**−**11**) lower the activation energy of cycloaromatization. Although not proven, it was suggested that this was the result of decreased steric repulsion between the cyclizing

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(4) For the total synthesis of calicheamicin γ_1^I, see: (a) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1377−1385. (b) Hitchcock, S. A.; Boyer, S. H.; Chu-Moyer, M. Y.; Olson, S. H.; Danishefsky, S. D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 858−862. For the total synthesis of dynemicin A, see: (c) Meyers, A. G.; Fraley, M. E.; Tom, N. J.; Cohen, S. B.; Madar, D. J. *Chem. Biol.* **1995**, *2*, 33−43. (d) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509−9525.

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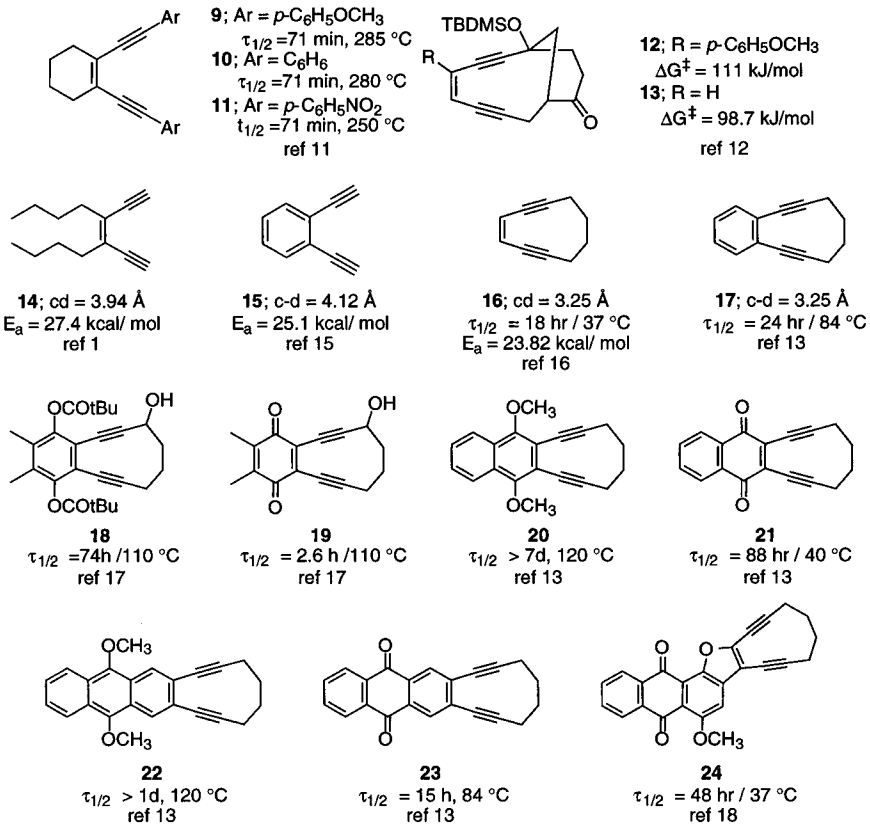
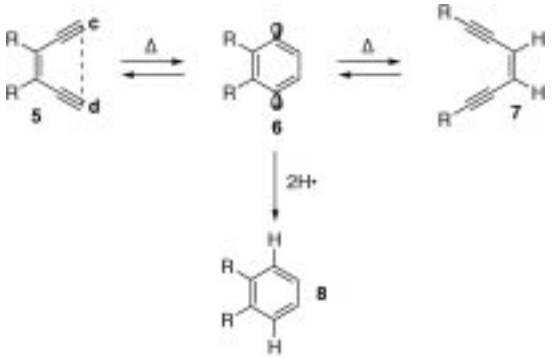
Table 1. c−d Distances and Kinetic Data for Bergman Cyclization of Selected Enediynes



Scheme 1. Bergman Cycloaromatization



in-plane π orbitals.[14] Maier hypothesized that the electron-donating substituent in **12** inhibited cyclization relative to **13** by stabilizing the ground state of the starting material more than destabilizing the transition state.[12]

It has been proposed that the amount of double-bond character in the double bond along with the distance between the diyne termini (**c**−**d**, Scheme 1) determines the activation energy required for cyclization.[13] This was based on the fact that arenediynes generally gave longer half-lives than their nonaromatic counterparts.[14] Although the link between **c**−**d** distance and cyclization has been firmly established, the evidence supporting the double-bond character is less clear.

The activation energies and half-lives for some aromatic and nonaromatic enediynes are given in Table 1. The activation energy determined by Grissom et al. for the cyclization of acyclic aromatic enediyne **15** was found to be lower than that for nonaromatic **14**, suggesting that an aromatic ring in place of the enediyne double bond has no significant influence on the rate of cyclization.[1,15] The situation for cyclic enediynes does not appear to parallel the acyclic case. Ten-membered ring compounds exhibit significantly different rates of cyclization, with the aromatic analogues being slower. For example, nonaromatic **16** cyclizes with a reported half-life of 18 h at 37 °C whereas aromatic **17** cyclizes with a half-life of 24 h at 84 °C.[13,16] The activation energies for **16** and **17** have not been measured.

Semmelhack and Nicolaou have prepared a series of quinone/dihydroquinone enediyne pairs (**18**−**23**).[13,17] In each case, the quinone was found to react significantly faster than the dihydroquinone analogue. Even when the quinone is removed from the enediyne by an aromatic ring (**23**), the cyclization rate was faster. This substantiates the position that electron-withdrawing groups associated with the double bond can facilitate Bergman cyclization. Anthraquinone **24** suggests that the situation is actually more complicated.[18] The enediyne is attached to an electron-rich furan, which itself is attached to the electron-deficient anthraquinone. This molecule shows unexpected reactivity, cyclizing nearly twice as fast

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Table 2. Synthesis of Protected and Deprotected Heteroarenediynes

entry	reactant	catalyst[a]	solvent	temp, °C	time, h	coupling prod (% yield)	deprotection prod (% yield)
1	**25a**	A	Et_3N	100	10	not isolated	**1** (71)
2	**26a**	A	Et_3N	170	48	**26d** (trace)	
3	**26a**	A	Et_3N	197	27	**26d** (20)	
4	**26a**	B	*i*-Pr_2NH	140	1.5	**26d** (67)	**26f** (40)
5	**26a**	B	*i*-Pr_2NH	170	15	**26e** (34)	**2** (48)
6	**26b**	A	*i*-Pr_2NH	100	16	**26e** (19)	
7	**26b**	B	*i*-Pr_2NH	100	16	**26e** (47)	**2** (50)
8	**27c**	A	*i*-Pr_2NH	117	4.3	**27d** (32)	**27f** (78)[c]
9	**27c**	A	*i*-Pr_2NH	130	4.3	**27d** (9)	**27f** (78)[c]
10	**27c**	A	*i*-Pr_2NH	152	4.3	**27d** (6.7)	**27f** (78)[c]
11	**27c**	B	*i*-Pr_2NH	130	4.2	**27e** (49)	**3** (77)[d]
12	**27c**	B	*i*-Pr_2NH	120	5.3	**27d** (7.9)[b] **27e** (61)[b]	**3** (77)[d]
13	**27c**	B	*i*-Pr_2NH	152	4.3	**27d** (2.4)[b] **27e** (35)[b]	**3** (77)[d]

[a] A: 10% w/w $Pd(PPh_3)_2Cl_2$, 10% w/w CuI. B: 10% w/w $Pd(PPh_3)_4$. [b] Separated prior to deprotection. [c] Entries 8−10 were combined for deprotection. [d] Entries 11−13 were combined for deprotection.

as quinone **21**, which contains no intervening aromatic moiety. Certainly, more studies are needed to ferret out the causes of the apparent anomalous behavior of these compounds.

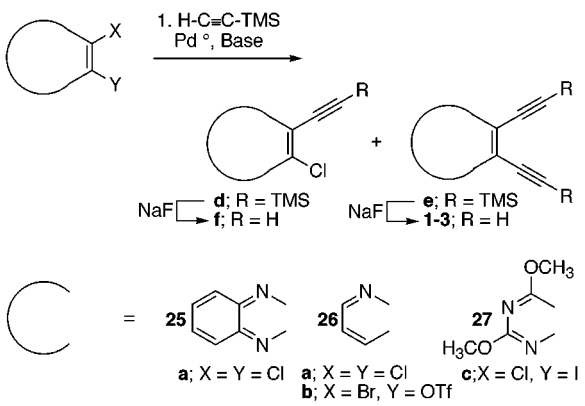
To explore how both electronics and aromaticity can influence Bergman cyclization, we have turned our attention to the heteroarenediynes in this study. The fusion of heteroaromatics with enediynes also has the advantage of providing a convenient handle for further modification through the use of the heteroatom lone pairs. Furthermore, these compounds give easy access to biological enediyne chimeras, which may find utility as biological probes or pharmaceuticals. Although reports of heteroarenediynes have begun to surface,[18,19] no accounts of the activation energies of these compounds have been described.

Results and Discussion

Synthesis. Targets **1**−**3** were selected so that they could be directly synthesized from commercially available starting materials via palladium-mediated coupling strategies. Although the reactivity of halogens toward Stille or Suzuki couplings is known to be I > Br ≫ Cl,[20] we were somewhat limited by the lack of commercially available *o*-dihaloheteroarenes, with the exception of some dichloro compounds. As an alternative, we turned to triflates, which have also enjoyed success in palladium-catalyzed acetylene couplings,[21] and these allowed access to our enediynes via the heteroaryl alcohols. The results of our coupling reactions are summarized in Scheme 2 and Table 2.

The synthesis of **1** proceeded smoothly from commercially available 2,3-dichloroquinoxaline (**25a**) through couplings at moderate temperatures (entry 1). No monoacetylene products were observed under these conditions. The final enediyne was obtained without isolation of the TMS intermediate in 71% yield. Because the yield of **1** was acceptable, no further efforts were made to improve the synthesis either by changing the reaction conditions or by using other halogens or triflate couplings. Recently, an alternate synthesis of **1** was reported using a condensation strategy.[19]

Scheme 2



Pyridine **2** was prepared by two separate routes (entries 2−7). Coupling dichloride **26a** with $Pd(PPh_3)_2Cl_2$/CuI catalyst in Et_3N at 170 °C gave only a trace of monoacetylene **26d** after 2 days of reaction (entry 2). Elevating the temperature to 197 °C resulted in a 20% yield of **26d** in 27 h (entry 3). Changing to the $Pd(PPh_3)_4$ catalyst and *i*-Pr_2NH solvent resulted in a good yield of **26d**, with no detectable diacetylene adduct (entry 4). Notably, the $Pd(PPh_3)_4$ catalyst required both lower temperatures (140 °C) and shorter reaction times (1.5 h) than did the $Pd(PPh_3)_2Cl_2$ catalyst. Increasing the temperature to 170 °C with the $Pd(PPh_3)_4$ catalyst furnished **2** in a disappointing 16% overall yield after cleavage of the TMS groups (entry 5). The lack of reactivity of **26a** relative to **25a** is not unexpected. It has been established that positions ortho or para to the ring nitrogen of pyridine are usually reactive enough with chlorine to give acceptable yields of coupled products whereas meta positions require bromine, iodine, or triflates for sufficient reactivity.[22] Although some arenediynes have been reported to decompose before they cyclize,[13,14,19] one cause for the low yields may be the reactivity of **26e** and **2** toward Bergman cyclization at the coupling temperature. Although no efforts were made to identify cyclization products from the coupling reactions, the presence of substantial amounts of insoluble black material is in agreement with the polymers formed from cyclization.[23]

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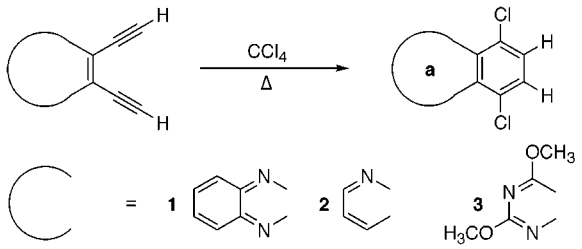
Scheme 3



Reaction of isolated monoacetylene **26d** with excess TMS−acetylene under the same conditions as in entry 5 also resulted in a poor yield of **26e** (not shown) with no recovered starting material. An attempt was also made to couple a second acetylene to **26d** after protection of the triple bond as its cobalt carbonyl complex. Unfortunately, coupling at 140 °C for 10 h with $Pd(PPh_3)_4$ catalyst and *i*-Pr_2NH only resulted in recovery of uncomplexed starting material.

Alternatively, 2-bromo-3-pyridinol was converted to triflate **26b** and coupled to an excess of TMS−acetylene (entries 6 and 7). As with **26a**, the coupling was catalyst dependent, with $Pd(PPh_3)_2Cl_2$−CuI being inferior to $Pd(PPh_3)_4$, the yield of diacetylene **26e** at 100 °C over 10 h was 19% and 47%, respectively, for the two catalysts. After TMS deprotection with NaF−HF buffer, pure **3** was obtained in 50% yield (24% for the two steps).

The synthesis of pyrimidine analogue **3** was accomplished by iodination of 6-chloro-2,4-dimethoxypyrimidine with *N*-iodosuccinimide in trifluoroacetic acid[24] to yield the dihalopyrimidine (**27c**) in 98% yield. Coupling reactions were carried out using the conditions shown in entries 8−13. The use of the $Pd(PPh_3)_2Cl_2$−CuI catalyst gave selective monosubstitution for the iodine (**27d**), and no desired diacetylene adducts were detected (entries 8−10). Elevation of the temperature did not improve the situation: only lower yields of **27d** were obtained. The observed selectivity is likely based on the reactivity of iodine vs chlorine in these reactions. Literature precedent has shown there to be little difference in reactivity among 2, 4, and 5 positions of substituted pyrimidines toward palladium-catalyzed couplings.[25] This is contrary to those observations relating activating and deactivating positions in pyridines. The most efficient coupling conditions used the $Pd(PPh_3)_4$ catalyst and *i*-Pr_2NH as the solvent. At 120 °C, **27e** was generated in 61% yield along with 8% **27d** (entry 12). At 130 °C, the yield of **27e** was lower, with a smaller amount of monosubstituted material present (entry 11). At 152 °C, the yields of **27d** and **27e** were even lower (entry 13). This may be indicative of a competition between coupling and cyclization or of decomposition reactions. Again, no starting material was left at the end of the coupling reactions. Pure **27g** was isolated after separation of the TMS products and deprotection.

Cyclization. Enediynes **1**−**3** were examined for their propensity to undergo Bergman cyclization (Scheme 3). Cyclizations were conducted by heating pure samples of the enediynes in CCl_4 at 120 °C for 20 h. The products were isolated by column chromatography or HPLC. Cyclization of quinoxaline **1** yielded 81% of 2,5-dichlorophenazine (**1a**). No other characterizable products were isolated. However, the presence of 2-chlorophenazine was detected by GC−MS. The cyclization product of pyridine **2** was troublesome to isolate. The reaction led to large amounts of dark, insoluble materials. These may be polyquinoline-type compounds, as previously discussed. The identity of **2a** was only confirmed by GC−MS and was the only identifiable product. The major cyclization product of pyrimidine **3** was substituted quinazoline **3a**, isolated in 15% yield.

Table 3. Cyclization Rates (k_{obs}) and Half-Lives ($\tau_{1/2}$) for Heteroarenediynes 1−3 in CCl_4

compd	temp, °C	k_{obs}, s^{-1}	$\tau_{1/2}$, min	R
1[a]	140	1.7×10^{-5}	680	0.994
	152	7.8×10^{-5}	148	0.994
	162	1.6×10^{-4}	72	0.992
	175	4.5×10^{-4}	26	0.994
2[b]	135	2.5×10^{-4}	46	0.991
	145	3.8×10^{-4}	30	0.993
	155	8.9×10^{-4}	13	0.996
	175	2.0×10^{-3}	6	0.997
3[c]	139	9.2×10^{-4}	13	0.993
	154	1.6×10^{-3}	7	0.981
	173	4.1×10^{-3}	3	0.992

[a] E_a = 33.6 kcal/mol (R = 0.994). [b] E_a = 21.5 kcal/mol (R = 0.994). [c] E_a = 16.1 kcal/mol (R = 0.993).

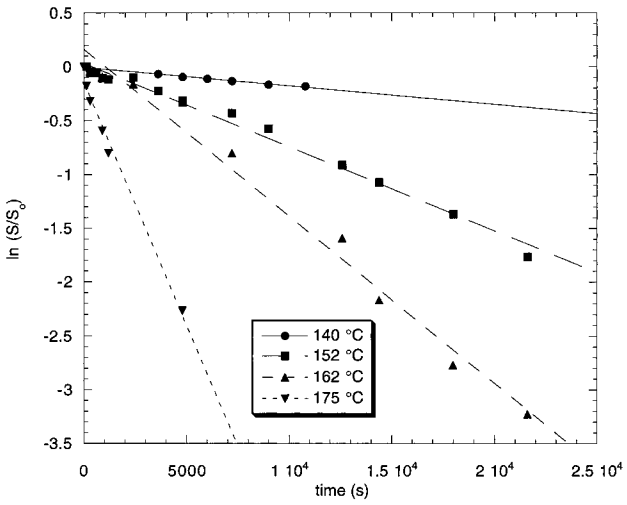


Figure 1. Plot of the rate of disappearance of **1** vs time in CCl_4 at various temperatures.

Kinetics. The kinetics of **1**−**3** were measured, and their activation energies were calculated from the Arrhenius relationship as has been done for other arenediynes.[15] All cyclization reactions showed first-order kinetics over a minimum of 3 half-lives and a temperature range of 35−40 °C. The data are summarized in Table 3. Figure 1 shows the rates of cyclization of quinoxaline **1**, which was the slowest of the three compounds examined. The activation energy calculated from the Arrhenius plot gave a value of 33.6 kcal/mol. That is less reactive than *o*-diethynylbenzene (**15**, E_a = 25.1 kcal/mol) and more comparable to the energies reported for terminally substituted acyclic enediynes.[1] In this case, it appears that the acceleration from the heteroatoms is more than compensated for by the presence of a second aromatic ring. Pyridine **2** showed enhanced reactivity (E_a = 21.5 kcal/mol) which was somewhat faster than **15**. Introduction of a second nitrogen into the arene, **3**, further accelerated cyclization,

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even with the presence of two donating oxygen atoms (E_a = 16.1 kcal/mol). This compound is the most reactive acyclic arenediyne reported to date. The lowest activation energy reported for a Bergman cyclization is 12.3 kcal/mol.[26] This was for an enediyne activated by metal coordination and resulted in severe **c**−**d** contraction.

Conclusion

We have reported the synthesis of novel heteroarenediynes **1**−**3** in reasonable yields. All of these molecules were shown to undergo thermal Bergman cyclization. The rate of cyclization was shown to be accelerated relative to the rates of simple arenediynes by the incorporation of heteroatoms into the aromatic ring. Pyrimidine **3**, in particular, showed remarkable reactivity. This compound has the greatest intrinsic reactivity of any reported acyclic arenediyne. This raises the possibility for the preparation of acyclic enediynes with reactivity comparable to those which use **c**−**d** contraction to lower the activation energy of cyclization. These investigations open the door to rate modulation of enediynes by pH dependence or Lewis acid complexation. Conversion of these enediynes into the more reactive 10-membered ring analogues should give these compounds reasonable reaction rates under physiological conditions. Furthermore, even greater reactivity should be possible by the hydrolysis of **3** to afford uracil **4**, which may have a number of important biological applications. The synthesis and kinetics of **4**, as well as the ability of **1**−**3** to cleave DNA, will be reported elsewhere.

Experimental Section

General. All commercial chemicals were purchased from Aldrich, were ACS-certified grade, and were used without further purification unless otherwise noted. Triethylamine and *N*,*N*-diisopropylamine were distilled from phosphorus pentoxide prior to use. Carbon tetrachloride was purified by filtration through basic alumina. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are recorded in parts per million on the δ scale referenced to the solvent peak as an internal standard. Thin-layer chromatography was conducted on Merck F254 silica gel TLC plates with fluorescent indicator. Normal-phase HPLC was performed with a spheri-5 silica column (5 μ, 250 × 46 mm) for purification and kinetic studies. Flash chromatography was performed with Baker silica gel (40 μm). Melting points are uncorrected. *All palladium coupling reactions were performed in Ace pressure tubes with the added protection of a blast shield.*

General Experimental Procedure for Palladium Coupling Reactions. Triethylamine or *N*,*N*′-diisopropylamine (13 mL) was placed in a 15-mL Ace pressure tube and degassed by bubbling with an Ar stream for 10 min. The corresponding dihalide or halotriflate (3.0 mmol), bis(triphenylphosphine)-palladium chloride (10% w/w) and copper(I) iodide (10% w/w), or tetrakis(triphenylphosphine)palladium(0) (10% w/w) were added to the solvent, and the slurry was stirred and bubbled with Ar for an additional 1 or 2 min. Trimethylsilylacetylene (7.5 mmol, 2.5 equiv) was added to the solution. The pressure tube was sealed and placed in a preheated oil bath behind a blast shield. The reaction mixture was stirred at the temperatures and for the times listed in Table 2. After being cooled to room temperature, the product was isolated for characterization by flash chromatography or filtered through a plug of silica gel using EtOAc/Hex (1:9, v/v) prior to deprotection.

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General Method for TMS Deprotection. The product from the coupling reaction was dissolved in ethanol, and excess hydrogen fluoride−sodium fluoride buffer solution (pH 5.5) was added. The solution was stirred at room temperature overnight. The product was extracted with ethyl acetate, and the organic extracts were dried over anhydrous magnesium sulfate. The drying agent was filtered, and the volatiles were removed by rotary evaporation under reduced pressure. The products were isolated by flash chromatography as described in the individual experiments.

2,3-Diethynylquinoxaline (1). The title compound was prepared as described in the general procedure on the following scale. Dichloroquinoxaline (**25a**; 1.3 g, 6.6 mmol), dichlorobis-(triphenylphosphine)palladium (130 mg), copper(I) iodide (130 mg), and trimethylsilylacetylene (2.3 mL, 17 mmol, 2.5 equiv) were reacted for 13 h at 80 °C. The crude product was filtered through a plug of silica gel using EtOAc/Hex (1:9, v/v) and directly deprotected. The product was isolated by flash chromatography using the same solvent as above. The title compound was isolated as a tan solid (830 mg, 71% yield) after two columns: mp 140 °C (dec); ^{1}H NMR ($CDCl_3$) δ 8.05 (dd, 2H, J = 3.6, 6.4 Hz), 7.79 (dd, 2H, J = 3.6, 6.4 Hz), 3.56 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 140.6, 139.6, 131.4, 129.0, 83.4, 80.0; FTIR (KBr) ν_{max} 3266, 2104 cm^{-1}. EIMS calcd: 178.05. Found: 178. Anal. Calcd for $C_{12}H_6N_2$: C, 80.89; H, 3.39; N, 15.72. Found: C, 80.74; H, 3.41; N, 15.61.

2-Bromo-3-triflic Pyridinate (26b). 2-Bromo-3-pyridinol (2.00 g, 11.6 mmol) was dissolved in dry dichloromethane (30 mL) in a two-neck round-bottom flask fitted with a rubber septum and a gas inlet. The solution was cooled to 0 °C under an atmosphere of Ar, and triethylamine (1.8 mL) was added, followed by the slow addition of triflic anhydride (2.3 mL) via syringe. The mixture was allowed to warm to room temperature and to stir overnight. The volatiles were removed by rotary evaporation under reduced pressure, and the black, oily solution was subjected to flash chromatography (EtOAc/Hex/1:10, v/v), to give a clear, yellowish oil (3.3 g, 93%): ^{1}H NMR ($CDCl_3$) δ 8.36 (d, 1H, J = 4.4 Hz), 7.64 (d, 1H, J = 8.4 Hz), 7.36 (dd, 1H, J = 8.4, 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 149.0, 144.6, 135.6, 130.2, 124.0, 118.4 (q, C−F coupling; J = 320 Hz); FTIR (KBr) ν_{max} 3072, 1575, 1411 cm^{-1}. GC−MS calcd: 304.9. Found: 305.

2,3-Diethynylpyridine (2). Method A. 2,3-Dichloropyridine (**26a**; 500 mg, 3.4 mmol), trimethylsilylacetylene (1.2 mL, 8.5 mmol), and tetrakis(triphenylphosphine)palladium (50 mg) were prepared in diisopropylamine (13 mL) as described in the general procedure. The reaction mixture was stirred at 170 °C for 13 h. The TMS derivative (**26d**; 313 mg, 1.2 mmol, 34%) was isolated by flash chromatography using EtOAc/Hex (1:9, v/v) as the eluent. The product was subjected to deprotection as described above and purified by flash chromatography using EtOAc/Hex (1:9, v/v) as the eluent to give the title compound as a white solid (70 mg, 48% for deprotection, 16% overall).

Method B. 2-Bromo-3-triflic pyridinate (**26b**; 100 mg, 0.3 mmol), trimethylsilylacetylene (0.24 mL, 1.7 mmol), and Pd-(PPh_3)$_4$ (10 mg) in diisopropylamine (4 mL) were stirred at 100 °C for 13 h to give **26e** (42 mg, 0.16 mmol, 47%) as a brown oil. After deprotection and isolation as described in method A, **2** was isolated as a white solid (10 mg, 50% yield): mp 128−130 °C (dec); ^{1}H NMR (CD_2Cl_2-d_2) δ 8.53 (dd, 1H, J = 8.1, 1.6 Hz), 7.81 (dd, 1H, J = 4.8, 1.6 Hz), 7.27 (dd, 1H, J = 8.0, 4.8 Hz), 3.51 (s, 1H), 3.42 (s, 1H); ^{13}C NMR (acetone-d_6) δ 150.3, 145.2, 140.6, 123.9, 123.0, 85.9, 82.5, 82.3, 80.4; FTIR (CCl_4) ν_{max} 3310, 2125 cm^{-1}. GC−MS calcd: 127.04. Found: 127. Anal. Calcd for C_9H_5N: C, 85.02; H, 3.96; N, 11.02. Found: C, 84.76; H, 4.02; N, 10.84.

6-Chloro-2,4-dimethoxy-5-iodopyrimidine (27c). A mixture of 6-chloro-2,4-dimethoxypyrimidine (100 mg, 0.57 mmol), trifluoroacetic acid (5.0 mL), and trifluoroacetic anhydride (1.0 mL) was refluxed for 30 min. *N*-Iodosuccinimide (128 mg, 0.572 mmol) was added, and the reaction mixture was refluxed overnight. The solution was cooled to room temperature, and the solvent was evaporated under reduced pressure. Ethanol (20 mL) was added and evaporated under reduced pressure.

The residue was dissolved in chloroform (20 mL) and washed with a saturated sodium bicarbonate solution (100 mL). The organic phase was dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated under reduced pressure. The title compound, a white solid, was collected and dried under high vacuum (167.5 mg, 98%): mp 126 °C; ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 3H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.6, 170.7, 164.6, 164.5, 55.9, 55.5; IR (CCl_4) ν_{max} 1554, 1538, 1267, 1037 cm^{-1}. FABMS calcd: 299.91. Found: 301($M^+ + 1$). Anal. Calcd for $C_6H_6N_2ClI$: C, 23.98; H, 2.01; N, 9.32. Found: C, 24.13; H, 1.97; N, 9.19.

5,6-Diethynyl-2,4-dimethoxypyrimidine (3). The title compound was prepared as described in the general procedure on the following scale. **27c** (1.0 g, 3.3 mmol), trimethylsilylacetylene (1.4 mL, 10 mmol), and tetrakis(triphenylphosphine)palladium(0) (100 mg) in diisopropylamine (13 mL) were reacted for 5 h at 135 °C to give **27e** (651 mg, 61%). After deprotection of the product (620 mg, 1.9 mmol), **3** was obtained as a white solid (274 mg, 77%): mp 135−136 °C (dec); ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 3H), 4.01 (s, 3H), 3.57 (s, 1H), 3.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.6, 163.6, 153.1, 102.1, 87.1, 84.1, 79.7, 74.7, 55.4, 55.1; FTIR (CCl_4) ν_{max} 3272, 3233, 2116 cm^{-1}. FABMS calcd: 189.06. Found: 189 (M^+).

5-Chloro-6-ethynyl-2,4-dimethoxypyrimidine (27f): mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H), 3.99 (s, 3H), 3.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 132.2, 131.5, 128.5, 128.4, 87.5, 73.5, 55.6, 55.4; FTIR (CCl_4) ν_{max} 2219, 1581 cm^{-1}. FABMS calcd: 198.02. Found: 198 (M^+). Anal. Calcd for $C_8H_7N_2O_2Cl$: C, 48.38; H, 3.55; N, 14.10. Found: C, 48.48; H, 3.62; N, 14.07.

General Procedure for Bulk Thermocyclization. Enediynes **1**−**3** (0.1 mmol) were dissolved in carbon tetrachloride (20 mL), and the solution was heated in a pressure tube at 165 °C until TLC indicated that no more starting material remained. The solvent was then removed by rotary evaporation, and the products were isolated by flash column chromatography, HPLC, or both.

Thermocyclization of Quinoxaline 1. 2,5-Dichlorophenazine (**1a**) was isolated as an off-white solid in 81% yield by column chromatography using EtOAc/Hex (1:9, v/v) as the eluent: ^{1}H NMR ($CDCl_3$) δ 8.39 (dd, J = 3.6, 3.2 Hz), 7.93 (dd, J = 3.6, 3.2 Hz), 7.88 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 143.6, 140.5, 132.3, 132.0, 130.0, 129.1; FTIR (CCl_4) ν_{max} 2926, 2854, 1559, 1554 cm^{-1}. GC−MS calcd: 249.0. Found: 249.

Thermocyclization of Pyridine 2. 5,8-Dichloroquinoline (**2a**) was only identified by GC−MS (calcd, 196.98; found, 197).

Thermocyclization of Pyrimidine 3. 5,8-Dichloro-2,4-dimethoxyquinazoline (**3a**) was isolated as a white solid by normal-phase HPLC using EtOAc/Hex (2:8, v/v) as the eluent (15% yield): ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 4.0 Hz), 7.28 (d, J = 4.0 Hz), 4.13 (s, 1H), 4.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 169.1, 161.9, 150.4, 133.0, 129.7, 126.4, 55.12, 55.09.[27] GC−MS calcd: 258.0. Found: 258.

Procedure for the Rate Determination for Enediynes 1−3. Method A: HPLC . Stock solutions of 6.0 mM **1** (10.6 mg, 0.06 mmol) and 6.0 mM **2** (7.6 mg, 0.060 mmol) in $CDCl_3$ containing naphthalene (22.9 mg, 0.18 mmol for **1**; 7.7 mg, 0.06 mmol for **2**) as an internal standard were prepared in 10.00-mL volumetric flasks. Aliquots of the solutions (50 μL each) were transferred into melting-point tubes and sealed under vacuum. Twenty sample tubes were prepared for each of four temperatures (140 ± 1, 152 ± 1, 162 ± 1, and 175 ± 1 °C for **1**; **2**: 140 ± 1, 145 ± 1, 155 ± 1, and 175 ± 1 °C for **2**). Tubes were removed from the oil baths at regular intervals and quickly cooled in water to room temperature. The reaction course was followed by HPLC using EtOAc/Hex (25:75, v/v) and a flow rate of 1.5 mL/min on a spheri-5 silica gel column. The disappearance of starting material versus the internal standard was measured at wavelengths of 254 and 261 nm for **1** and **2**, respectively.

Method B: NMR. A 6.0 mM stock solution of **3** (11.2 mg, 0.06 mmol) was prepared in $CDCl_3$ with 0.05 M CH_3CN in a 10.00-mL volumetric flask. Aliquots of the stock solution (1.0 mL) were transferred to NMR tubes, and the tubes were flame-sealed under vacuum. Three samples were heated in oil baths at each of three temperatures (139 ± 1, 154 ± 1, and 173 ± 1 °C). At regular intervals the samples were removed from the oil baths and quickly cooled in water to room temperature. The reaction course was followed by ^{1}H NMR spectroscopy, comparing the integration of terminal acetylene protons relative to that of the acetonitrile standard.

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Supporting Information Available: ^{1}H NMR spectra, graphs of kinetics data, and Arrhenius plots for **1**−**3** at various temperatures (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(27) Two of the quaternary carbons in the ^{13}C NMR spectrum were not visible. The eight visible signals in the ^{13}C NMR spectrum and all other spectral data are consistent with the assigned structure.