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Bergman cycloaromatization of imidazole-fused enediynes: the remarkable effect of *N*-aryl substitution

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Abstract—A series of *N*-aryl substituted 'imidazole-fused' (*Z*) 3-ene-1,5-diynes was prepared and kinetic parameters for their Bergman cycloaromatization reactivities were determined. N-Arylation enhanced rates relative to *N*-alkyl derivatives by up to sevenfold (ANOVA $p < 0.0001$). The greatest enhancement was exhibited by the *N*-phenyl derivative (sevenfold at 145 °C).

Since its discovery in the early 1970s, the Bergman cycloaromatization reaction[1] (Fig. 1) has been the subject of extensive experimental and theoretical investigation.[2] Interest in this process has been stimulated by the critical role the Bergman cyclization plays in the biological activities of naturally occurring enediyne antitumor antibiotics,[3] and by its potential use in synthetic methods for polycyclic aromatic compounds[4] and polymeric materials.[5] Large numbers of synthetic analogues of DNA-cleaving agents (e.g., calicheamicins, esperamicins, dynemicins, neocarzinostatin, and kedarcidin) have been prepared in efforts to improve upon the properties of the parent compounds,[3] and numerous related (*Z*) 3-ene-1,5-hexadiynes have been studied in order to determine factors that influence the rate of Bergman cycloaromatization. From these latter studies it is clear that several factors contribute to the energy barriers involved in cycloaromatization. Among these are the so-called '*c*,*d*' distance (the distance between the terminal alkynyl carbons),[6] electronic factors,[7] and differences in strain energies for transition state and ground state geometries.[8]

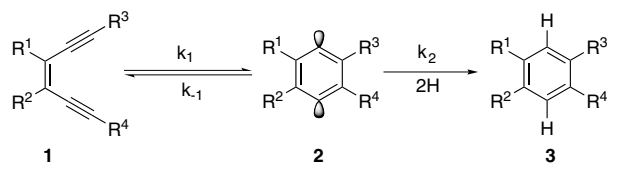

Figure 1. Bergman cycloaromatization.

Attempts to modulate electronic contributions to Bergman cycloaromatization barriers have focused on direct substitution of the ene moiety in monocylic (*Z*) enediynes,[7b,c] or substitution at *ortho*[7a] or *para*[7b] positions in benzannelated enediynes. Of the heterocyclic enediynes reported to date, the 'imidazole-fused' enediynes (4,5-bis-(alkynyl)imidazoles)[9] have received comparatively little attention, and only one report dealing with synthetic methods has appeared in the literature.[9b] The Bergman reactivity of these compounds was apparently never studied. We became interested by the possibility that imidazole-fused enediynes might provide an unusually versatile platform for probing electronic effects due to their possession of three sites for potential functionalization (imidazole positions 1–3). Functionalization at any of these positions might reasonably be expected to influence the electronics of the imidazole ring, providing previously unexplored avenues for modulating rates of Bergman cycloaromatizations.[10] Here we report our findings relative to the effect of N1 substitution.

N-Alkyl and *N*-aryl substituted 4,5-bis-ethynylimidazoles were prepared according to the route depicted in Scheme 1.[11] Sonogashira[12] coupling of **4** with TMS-acetylene gave **5** in 85% yield. N-Alkylation followed by removal of the TMS groups gave **6a**–**e** (45–87%, two steps). N-Arylation was accomplished employing the copper-catalyzed method of Collman and Zhong[13] to provide **7a**–**j** (47–67%, two steps). Conversion of

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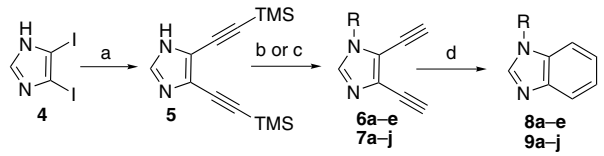


Scheme 1. Reagents and conditions: (a) TMSC≡CH, $(Ph_3P)_4Pd$, CuI. (b) i. Alkylhalide, K_2CO_3, DMF; ii. NH_4F, MeOH. (c) i. $ArylB(OH)_2$, $[Cu(OH)TMEDA]_2Cl_2$, CH_2C1_2; (ii) NH_4F, MeOH. (d) 10 equiv 1,4-cyclohexadiene, benzene-d_6.

compounds **6a**–**e** and **7a**–**j** to the corresponding cycloaromatized products **8a**–**e** and **9a**–**j**[11] was followed by ^1H NMR,[14] and kinetic parameters for these studies are presented in Table 1. *N*-Aryl substitution enhanced the rates relative to the *N*-alkyl derivatives in all cases (ANOVA $p < 0.0001$). The greatest enhancement was observed for the *N*-phenyl derivative **7a** (Table 1, entry 6). At 145 °C, the rate for **7a** was from four to seven times greater than rates for *N*-alkyl derivatives (entries 1–5). Substituents on the phenyl ring did not seem to have a pronounced effect, and Hammet plots for compounds **7a**–**j** did not show linear free-energy relationships. This is in contrast to benzannelated enediynes where substitution on the phenyl ring significantly impacts rates, and linear free-energy relationships have been reported.[7d] The relative insensitivity of imidazole-fused enediynes to phenyl substitution may be explained by significant population of nonplanar conformations of *N*-aryl derivatives **7a**–**j**. The π–system of the phenyl ring of nonplanar conformers would not be conjugated with the imidazole π–system. Conjugative and field effects may not be transmitted to the enediyne moiety when the phenyl ring and imidazole moieties are not in the same plane. Monte Carlo calculations[15] indicate that the phenyl ring and imidazole moieties are approximately 20° out of planarity for minimum energy conformations of compounds **7a**–**j**.[16]

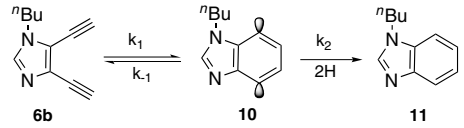
To investigate possible similarities between imidazole-fused enediynes and the analogous benzannelated congeners, **6b** was treated with varying concentrations of 1,4-cyclohexadiene (1,4-CHD) and the reaction kinetics were determined (Table 2).[14] The concentration of 1,4-CHD did not significantly affect the rate of disappearance of **6b**, in sharp contrast to the concentration dependence observed for the reaction of 1,2-diethynylbenzene.[17] The kinetic behavior exhibited by **6b** paralleled behavior exhibited by (*Z*) 3-ene-1,5-hexadiyne and cyclodec-3-ene-1,5-diyne (**1**, $R_1{=}R_2{=}H$, $R_3{=}R_4{=}CH_2{-}CH_2{-}$) where Bergman cycloaromatization has been shown to be independent of the concentration of 1,4-CHD.[1,17a,b] This observation indicates that k_1 is rate determining for imidazole-fused enediynes, and suggests by analogy that $k_2 > k_{-1}$ as has been calculated for cyclodec-3-ene-1,5-diyne.

Table 1. Kinetic parameters for Bergman cycloaromatization of imidazole-fused enediynes **6a**–**e** and **7a**–**j**

Entry	Compound	R	*T* (°C)	k (10^{-5} s^{-1})[a]	$t_{1/2}$ (h)
1	**6a**	Methyl	125	0.42 ± 0.05	46
			145	2.5 ± 0.3	7.7
2	**6b**	*n*-Butyl	125	0.51 ± 0.06	38
			145	2.2 ± 0.2	8.8
3	**6c**	Benzyl	125	0.41 ± 0.02	47
			145	2.0 ± 0.07	9.7
4	**6d**	*p*-Methoxybenzyl	125	0.35 ± 0.02	55
			145	1.3 ± 0.2	15
5	**6e**	*p*-Nitrobenzyl	125	0.36 ± 0.02	54
			145	1.6 ± 0.2	12
6	**7a**	**Phenyl**	125	**2.2 ± 0.04**	**10**
			145	**9.7 ± 0.4**	**2.0**
7	**7b**	*p*-Fluorophenyl	125	1.3 ± 0.07	15
			145	4.8 ± 0.18	4.0
8	**7c**	*p*-Chlorophenyl	125	1.5 ± 0.09	13
			145	4.2 ± 0.4	4.1
9	**7d**	*p*-Bromophenyl	125	1.7 ± 0.2	11
			145	4.6 ± 0.03	4.2
10	**7e**	*p*-Iodophenyl	125	1.9 ± 0.06	10
			145	4.8 ± 0.06	4.0
11	**7f**	*p*-Methoxyphenyl	125	1.0 ± 0.04	19
			145	4.7 ± 0.2	4.1
12	**7g**	*p*-Methoxycarbonylphenyl	125	1.6 ± 0.06	12
			145	5.2 ± 0.2	3.7
13	**7h**	*m*-Nitrophenyl	125	1.3 ± 0.1	15
			145	4.7 ± 0.1	4.1
14	**7i**	*p*-Ethylphenyl	125	1.4 ± 0.2	14
			145	3.9 ± 0.2	4.9
15	**7j**	*p*-*tert*-Butylphenyl	125	0.89 ± 0.1	22
			145	3.0 ± 0.1	7.4

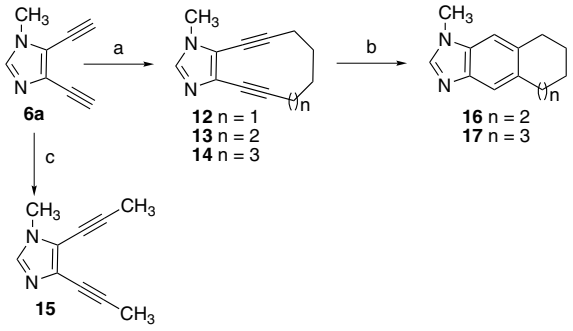
[a] Kinetic data were measured in triplicate and all first order plots gave excellent linear correlations ($R > 0.990$).

Table 2. Effect of concentration of 1,4-cyclohexadiene on Bergman cycloaromatization of **6b** at 145 °C[a]



[1,4-CHD] (M)	k (10^{-5} s^{-1})	$t_{1/2}$ (h)
0.3	2.2	8.8
0.7	2.0	9.4
1.3	2.1	9.2
2.3	2.3	8.3

[a] Kinetic data were measured in triplicate and all first order plots gave excellent linear correlations ($R > 0.990$).



Scheme 2. Reagents and conditions: (a) i. *n*-BuLi (2.0 equiv), HMPA, THF; ii. $I(CH_2)_nI$ ($n = 4$–6). (b) 10 equiv 1,4-cyclohexadiene, benzene-d_6. (c) i. *n*-BuLi (2.0 equiv), HMPA, THF; ii. CH_3I (excess).

To probe additional factors that might influence the rate of Bergman cyclization of imidazole-fused enediynes, we attempted to prepare bicyclic analogues **12**–**14** (Scheme 2). The calculated[15] *c*,*d*-distance for imidazole-fused cyclodec-3-ene-1,5-diyne **12** is 3.41 Å. This is near the critical range suggested to be required for Bergman cycloaromatization of simple monocyclic enediynes at 37 °C.[6]

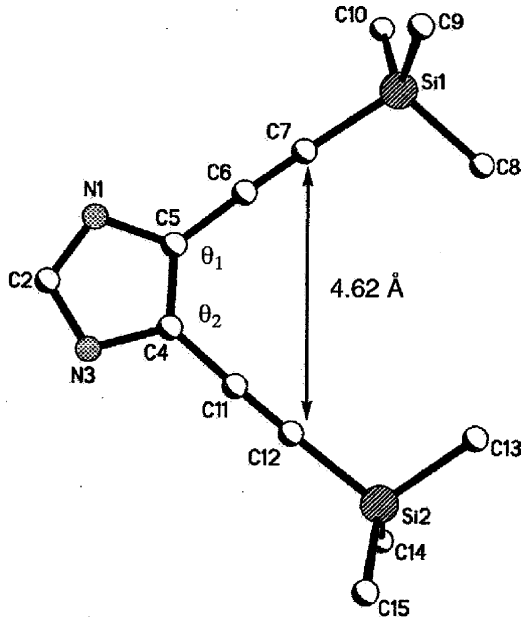


Figure 2. Crystal structure for compound **5** (hydrogens omitted for clarity).[18]

In our hands, compound **12** proved to be impossible to prepare via the route depicted in Scheme 2. A number of different conditions were examined, and each failed to give the desired product. Yields for the imidazole-fused cycloundec- and cyclododec-3-ene-1,5-diynes **13** and **14** were also disappointingly low (16% and 27%, respectively). To determine if these yields were at least partly due to quenching of the butyllithium via deprotonation of imidazole C-2, we prepared compound **15** as a model system. Compound **15** was obtained in 67% yield and products arising from C-2 alkylation were not detected. An X-ray crystal structure for **5** (Fig. 2)[18] reveals that the *c*,*d* distance (4.62 Å) and bond angles ($\theta_1 = \theta_2 = 129.4°$) are greater than in 1,2-diethynylbenzene (calculated values for 1,2-diethynylbenzene are: *c*,*d* distance=4.13 Å, and $\theta_1 = \theta_2 = 121.3°$).[15] These features may contribute to less favorable energy barriers for ring closure in imidazole-fused enediynes owing to increased ring strain.

The Bergman reactivities of compounds **13** and **14** were also determined. Compound **14** did not react at $T \leqslant 180$ °C. Compound **13** had half-lives of 114 and 35 h at 145 and 165 °C, respectively. In comparison, compound **6a** had half-lives of 7.7 and 3.7 h at the same temperatures, respectively. This behavior parallels behavior exhibited by benzannelated enediynes (e.g., 3,4-benzo-cycloundec-3-ene-1,5-diyne reacts less rapidly than its monocyclic congener 1,2-diethynylbenzene).[17c] However, it is interesting to note the significant retardation in cyclization rate for compound **13** relative to 3-chloro-cycloundec-3-ene-1,5-diyne at similar temperature ($t_{1/2} = 2$ h at 170 °C, vs 35 h at 165 °C for **13**).

In summary, *N*-aryl and *N*-alkyl substituted imidazole-fused enediynes undergo thermally promoted Bergman cycloaromatization. All compounds examined underwent smooth conversion to their corresponding benzimidazole products,[11] and *N*-aryl substitution enhanced rates by up to sevenfold at 145 °C. Although the cause for this rate enhancement is uncertain, the absence of any clear linear free-energy relationship for the *N*-aryl derivatives suggests that steric effects may be an important factor.[7a] The rate of reaction did not depend on the concentration of trapping agent (in contrast to benzannelated enediynes), and the presumably more reactive imidazole-fused cyclodec-3-ene-1,5-diyne **12** was apparently too strained to allow preparation via the route investigated. Imidazole-fused enediynes hold considerable potential as synthetic reagents for novel polymeric materials and/or pharmaceuticals (e.g., ribosylated derivatives may mimic purine nucleosides) and this work provides a foundation for exploring these potential applications.

Acknowledgements

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10. Theoretical calculations indicate that the energy barrier for imidazolium-fused enediynes is 2.8 kcal/mol greater than for the corresponding imidazole-fused enediyne (see Ref. 7b).
11. All compounds gave clean ^{1}H and ^{13}C NMR spectra consistent with the assigned structures, and molecular formulas were confirmed by high resolution mass spectrometry (M^+ within ±10 ppm of theory). Characterization data for representative compounds follow: (**5**) UV (MeOH) max 223, 275, 291 nm, min 239, 287 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.95 (br s, 1H), 7.62 (s, 1H), 0.22 (s, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.6, 123.4, 101.0, 94.9, 0.001, −0.373; MS (FAB) m/z 283.1056 (MNa^+ $[C_{13}H_{20}N_2NaSi_2]$=283.1063); (**7a**) UV (MeOH) max 220, 264 nm, min 244 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (s, 1H), 7.54–7.49 (m, 5H), 3.59 (s, 1H), 3.37 (s, 1H); ^{1}H NMR (benzene-d_6, 300 MHz) 7.00 (s, 1H), 6.90–6.87 (m, 3H), 6.79–6.77 (m, 2H), 2.95 (s, 1H), 2.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 135.5, 132.1, 129.8, 128.5, 127.9, 124.8, 88.4, 81.6, 76.0, 71.2; MS (EI) m/z 192.0680 (M^+ $[C_{13}H_8N_2]$=192.0688); (**9a**) UV (MeOH) max 241 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (br s, 1H), 7.94–7.90 (m, 1H), 7.60–7.54 (m, 6H), 7.37–7.35 (m, 2H); ^{1}H NMR (benzene-d_6, 300 MHz) 8.10 (m, 1H), 7.70 (br s, 1H), 7.19–7.11 (m, 4H), 6.98–6.94 (m, 2H), 6.85–6.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 130.3, 128.3, 124.3, 123.1, 120.7, 110.8; MS (EI) m/z 194.0837 (M^+ $[C_{13}H_{10}N_2]$=194.0844); (**13**) UV (MeOH) max 219, 270, 286 nm, min 231, 284 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (s, 1H), 3.60 (s, 3H), 2.54 (t, J = 6.3 Hz, 2H), 2.48 (t, J = 6.3 Hz, 2H), 2.02 (pent, J = 7.2 Hz, 2H), 1.72–1.64 (m, 4H); ^{1}H NMR (benzene-d_6, 300 MHz) δ 6.63 (s, 1H), 2.59 (s, 3H), 2.25–2.18 (m, 4H), 2.01–1.90 (m, 2H), 1.40–1.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 133.1, 115.7, 105.2, 97.2, 79.8, 71.7, 32.8, 25.9, 24.4, 19.4, 19.3, 19.2; MS (FAB) m/z 199.1233 ($[M+1]^+$ $[C_{13}H_{15}N_2]$=199.1235); (**14**) UV (MeOH) max 219, 268, 283 nm, min 211, 231, 281 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (br s, 1H), 3.60 (s, 3H), 2.54 (t, J = 6.0 Hz, 2H), 2.48 (t, J = 6.0 Hz, 2H), 1.83–1.80 (m, 4H), 1.70–1.63 (m, 4H); ^{1}H NMR (benzene-d_6, 300 MHz) δ 6.61 (s, 1H), 2.57 (s, 3H), 2.26 (t, J = 6.3 Hz, 2H), 2.24 (t, J = 6.3 Hz, 2H), 1.73–1.67 (m, 4H), 1.43–1.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.3, 131.3, 122.2, 102.7, 94.8, 75.5, 70.0, 32.5, 27.4, 26.4, 26.3, 19.8, 19.5; MS (FAB) m/z 213.1374 ($[MH]^+$ $[C_{14}H_{17}N_2]$=213.1392); (**16**) UV (MeOH) max 251, 258, 280, 290 nm, min 234, 255, 267, 287 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.0 (s, 1H), 7.55 (s, 1H), 7.15 (s, 1H), 3.84 (s, 3H), 2.96–2.91 (m, 4H), 1.90–1.78 (m, 2H), 1.75–1.65 (m, 4H); ^{1}H NMR (benzene-d_6, 300 MHz) δ 7.84 (s, 1H), 7.26 (s, 1H), 6.79 (s, 1H), 2.84–2.76 (m, 4H), 2.68 (s, 3H), 1.70–1.62 (m, 4H), 1.59–1.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.7, 141.0, 140.0, 139.0, 119.5, 109.4, 37.3, 37.0, 32.7, 29.3, 29.2; MS (EI) m/z 200.1302 ($M^+[C_{13}H_{16}N_2]$=200.1314).
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14. Kinetics were followed by ^{1}H NMR. Integrations for resonances specific to the starting material were compared to resonances specific to the products or anthracene as an internal standard.
15. Molecular modeling calculations were performed using MacSpartan Pro, Wave Function, Inc. Monte Carlo conformational searches employed MMFF94 parameters, and geometry optimizations were performed at the semi-empirical level (PM3).
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18. X-ray data for **5**: The unit cell is trigonal, space group $P3_221$, with $a = b = 10.986(2)$ Å, and $c = 13.724(10)$ Å, $V = 1435.5(11)$ Å^3, $Z = 3$. There were 889 independent reflections ($R_{int} = 0.0599$) with $R_1 = 0.0515$ for [$I > 2s(I)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2317SH. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].