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Photoinduced Bergman cycloaromatization of imidazole-fused enediynes

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Abstract—A series of 4,5-bis-(alkyn-1-yl)imidazoles—'imidazole-fused' enediynes—were synthesized and their reactivities in photoinduced Bergman cycloaromatization reactions were determined. The more conformationally rigid analogues gave cycloaromatized products in good yields upon irradiation (450 W low-pressure mercury lamp, ambient temperature). A bicyclic analogue (**3**) was shown to cleave supercoiled plasmid DNA.
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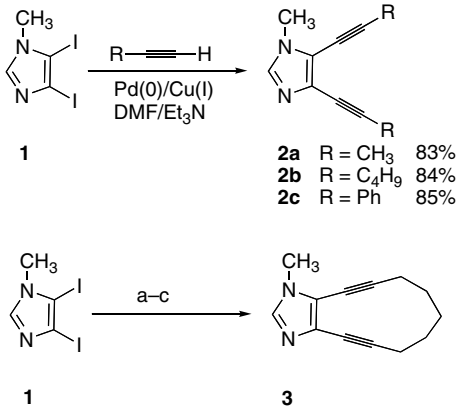
Over the past several decades, the thermal Bergman[1] cycloaromatization reaction has been the subject of extensive theoretical and experimental investigation owing to its relevance to the biological activities of enediyne antitumor antibiotics,[2] and also because of its considerable potential for synthetic methods for polymeric materials[3] and/or polycyclic aromatic compounds.[4] Parameters affecting energy barriers involved in the thermal reaction have been thoroughly studied.[5] However, only a limited number of reports dealing with the photochemical reaction have appeared,[6] and comparatively little is understood about the photoinduced reaction. As part of research directed toward synthesis of photoinducible 'targeted enediynes' (photoreactive enediynes conjugated to biologically important delivery molecules such as enzyme substrates or receptor ligands,[7] etc.), we became interested in 4,5-bis-(alkyn-1-yl)imidazoles, or 'imidazole-fused' enediynes. The imidazole nucleus possesses two sites (N-1 and C-2), which could be exploited for simple, straightforward, conjugation of photoreactive imidazole-fused enediynes to biologically relevant delivery molecules. The availability of these sites makes the imidazole scaffold a more versatile platform than others previously investigated (including benzannelated and/or heteroaromatic enediynes), which cannot be simply or directly conjugated.[7b,8] Of the heteroaromatic enediynes reported to date, imidazole-fused enediynes have received limited attention[9] and the photochemical Bergman reactivities of this class of compounds have apparently not been previously investigated. Here, we report the efficient photochemical Bergman cyclization of imidazole-fused enediynes and their photoinduced reactivities with supercoiled plasmid DNA. The potential for facile conjugation (via coupling chemistries at either N-1 or C-2) to biologically important delivery molecules makes imidazole-fused enediynes exceptionally versatile as new reagents for targeted delivery of photoreactive enediynes.

The synthesis of imidazole-fused enediynes proceeded as depicted (Scheme 1).[9b] Sonogashira[10] coupling of 1-methyl-4,5-diiodoimidazole with the corresponding alkynes gave imidazole-fused enediynes **2a**–**c** in excellent



Scheme 1. Reagents: (a) TMSC≡CH, $(Ph_3P)Pd/CuI$, DMF/Et_3N; (b) $NH_4F/MeOH$; (c) i. BuLi, HMPA, THF, −78 °C; ii. $I(CH_2)_5I$.

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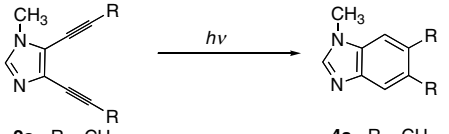
yields.[11] Compound **3** was prepared via a three-step procedure, as described previously.[9a] Irradiation of compounds **2a–c** and **3** (450 W low-pressure Hg)[12] gave benzimidazole derivatives **4a–c** and **5**, respectively (Table 1 and Scheme 2).[11] The cycloaromatized product **4c** was obtained in highest yields (26–64%), with the best yield obtained using THF as solvent. The enhanced yield for compound **5** relative to **4a–b** may be due to the increased conformational rigidity of **3** relative to **2a–b**. Evenzahav and Turro have shown that conformationally more rigid enediynes (such as 1,2-bis-(phenylethyn-1-yl)benzene) are less prone to undergo intersystem crossing from the initial singlet excited state to the triplet state than less rigid analogues (e.g., 1,2-bis-(pentyn-1-yl)benzene), and correspondingly higher cycloaromatization yields are observed for the more rigid system.[6c]

Table 1.

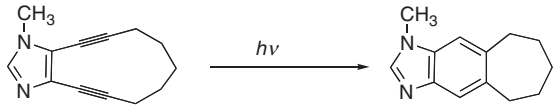


2a R = CH_3
2b R = C_4H_9
2c R = Ph

4a R = CH_3
4b R = C_4H_9
4c R = Ph

Solvent	4a	4b	4c
THF	6%	31%	64%
i-PrOH	Trace	24%	58%
Hexane	7%	22%	47%
Cyclohexane	6%	16%	51%
CH_3CN	6%	Trace	46%
n-Hexane/1,4-cyclohexadiene	6%	15%	44%
CH_2Cl_2	Trace	Trace	40%
tert-Butanol	Trace	Trace	26%

Yield given as percent conversion.



3 **5** 45%

Scheme 2.

Imidazole-fused enediyne **3** was also examined for its ability to promote photochemical cleavage of DNA. Accordingly, compound **3** was irradiated (450 W low-pressure Hg, Pyrex filter, ambient temperature) with supercoiled plasmid DNA (Fig. 1).[13] Significant non-background cleavage was observed within 60 min at concentrations as low as 15 μM.[14]

In summary, imidazole-fused enediynes **2a–c** and **3** underwent efficient photoinduced Bergman cycloaromatization. The conformationally more rigid enediynes **2c** and **3** gave higher yields than the less rigid congeners **2a–b**, in harmony with observed reactivities for the related benzannelated enediynes studied by Evenzahav and Turro.[6c] Imidazole-fused enediyne **3** cleaved supercoiled plasmid DNA when irradiated (450 W low-pressure Hg). The imidazole scaffold provides two sites for potential conjugation to biologically important delivery molecules, and thus represents an improvement over known photoreactive benzannelated or heteroaromatic enediynes, which cannot be simply or directly conjugated. An additional benefit provided by the imidazole scaffold is its potential to undergo hydrogen bonding with the heterocyclic bases of DNA.[15] This could be exploited to develop sequence-selective DNA cleaving agents, and this is an application we are currently exploring.

Acknowledgements

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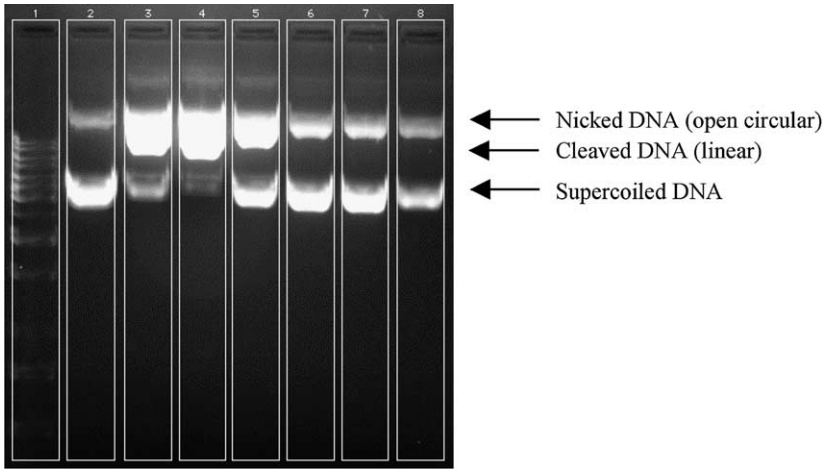

Figure 1. Cleavage of supercoiled plasmid DNA:[13] (1) DNA basepair ladder; (2) dark DNA control; (3) 1500 μM of **3**, 30 min; (4) 1500 μM of **3**, 60 min; (5) 150 μM of **3**, 60 min; (6) 15 μM of **3**, 60 min; (7) 1.5 μM of **3**, 60 min; (8) light DNA control.[14]

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11. All compounds gave clean ^{1}H and ^{13}C NMR spectra that were consistent with the assigned structures. Molecular formulas were confirmed by high resolution mass spectrometry (M^+ within ±10 ppm of theory). Characterization data were as follows: (**2a**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 (s, 1H), 3.61 (s, 3H), 2.16 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.0, 128.2, 96.3, 88.9, 79.8, 72.7, 32.6, 5.13, 4.90; MS (EI) *m/z* 158.0830 (M^+ [$C_{10}H_{10}N_2$] = 158.0844); UV (MeOH) max: 217, 261 nm, min: 213, 228 nm; (**2b**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 (s, 1H), 3.54 (s, 3H), 2.45 (t, J = 7.2 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 1.61–1.38 (m, 8H), 0.91 (t, J = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.8, 128.6, 119.7, 100.4, 92.8, 73.8, 68.2, 32.3, 30.7, 22.0, 19.5, 19.3, 13.7, 13.6; MS (EI) *m/z* 242.1783 (M^+ [$C_{16}H_{22}N_2$] = 242.1783); UV (MeOH) max: 219, 264 nm, min: 212, 230 nm; (**2c**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.55 (m, 5H), 7.46 (br s, 1H), 7.40–7.33 (m, 5H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.3, 131.8, 131.6, 129.2, 129.1, 128.7, 128.4, 123.3, 122.4, 99.9, 92.6, 82.8, 76.7, 32.8; MS (EI) *m/z* 282.1147 (M^+ [$C_{20}H_{14}N_2$] = 282.1157); UV (MeOH) max: 224, 252, 266, 322 nm, min: 241, 260, 279 nm; (**4a**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.25 (s, 1H), 7.78 (s, 1H), 7.35 (s, 1H), 4.16 (s, 3H), 2.45 (s, 3H), 2.42 (s, 3H); MS (EI) *m/z* 160.1013 (M^+ [$C_{10}H_{12}N_2$] = 160.1001); UV (MeOH) max: 250, 278, 285 nm, min: 263, 282 nm; (**4b**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (br s, 1H), 7.61 (s, 1H), 7.19 (s, 1H), 3.87 (s, 3H), 2.79–2.71 (m, 4H), 1.66–1.40 (m, 8H), 0.97 (q, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.5, 139.9, 137.4, 136.5, 132.5, 119.3, 109.4, 34.1, 34.0, 33.2, 32.8, 31.6, 23.1, 22.9, 14.3; MS (EI) *m/z* 244.1949 (M^+ [$C_{16}H_{24}N_2$] = 244.1939); UV (MeOH) max: 251, 281, 291 nm, min: 269, 288 nm; (**4c**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96 (br s, 1H), 7.87 (br s, 1H), 7.44 (br s, 1H), 7.27–7.19 (m, 10H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.3, 142.2, 136.9, 136.1, 132.4, 132.2, 130.5, 130.4, 128.8, 128.6, 128.03, 127.97, 126.6, 126.3, 122.0, 111.3, 31.4; MS (EI) *m/z* 284.1307 (M^+ [$C_{20}H_{16}N_2$] = 284.1314); UV (MeOH) max: 241 nm, min: 227 nm.
12. The general procedure for the photoreaction is illustrated for the conversion of **3** to **5**. A degassed solution of **3** (20 mg, 0.10 mmol) in solvents (20 mL) (i. hexanes; ii. *i*-PrOH) was irradiated in a quartz flask under N_2 at room temperature with a low-pressure mercury lamp (450 W) for 16 h. Volatiles were evaporated in vacuo, and the residue was purified by preparative TLC ($MeOH/CH_2Cl_2$, 5:95) to give **5** (9 mg, 45% in hexane; 9 mg, 45% in *i*-PrOH) with ^{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 (d_6–benzene, 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, 132.9, 119.5, 109.4, 37.3, 37.0, 32.7, 31.4, 29.3, 29.2; MS (EI) *m/z* 200.1302 (M^+ [$C_{13}H_{16}N_2$] = 200.1314); UV (MeOH) max: 251, 258, 280, 290 nm, min: 234, 255, 267, 287 nm.
13. Reaction mixtures were prepared by addition of super-coiled plasmid pGL3con DNA (2 μL of 1 μg/μL solution; 2 μg DNA), and TBE buffer (2.5 μL of 0.5× buffer), to appropriate stock solutions of compound **3** (20.5 μL of 1830, 183, 18.3, and 1.83 μM) to give a total volume of 25 μL. Samples were irradiated at room temperature with a 450 W mercury light source equipped with a Pyrex filter. The mixtures were analyzed on a 1.0% agarose gel at 80 V for 2 h.
14. Densitometer readings showed non-background cleavage in lanes 2–6: lane 2 (upper/lower) = 0.3005; lane 3 (upper/lower) = 4.588; lane 4 (upper/lower) = 13.64; lane 5 (upper/lower) = 1.707; lane 6 (upper/lower) = 0.74011; lane 7 (upper/lower) = 0.5983; lane 8 (upper/lower) = 0.5729.
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