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Syntheses and Reactivity of Naphthalenyl-Substituted Arenediynes

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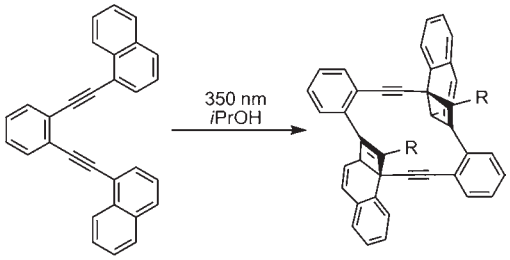
ABSTRACT



A series of naphthalenyl-substituted arenediynes were prepared to examine photochemical reactivity. For naphthalen-1-ylethynyl arenediyne, 350 nm photolysis resulted in a tandem [2 + 2] photocycloaddition to afford cyclobutene adducts. For naphthalen-2-ylethynyl derivatives, electron-donating methoxy substituents were found to facilitate C^1-C^6 Bergman cyclization at 300 nm. Theoretical calculations provided further insight into thermal and photochemical reactivity.

Bergman and related cyclizations of enediynes[1] to produce highly reactive diradical intermediates have drawn considerable interest for applications ranging from DNA cleaving agents[2] to polymer chemistry[3] and syntheses of carbon rich materials.[4] Cyclic enediynes are well documented to undergo C^1-C^6 Bergman cycloaromatization under thermal[5] and photochemical[6] conditions to produce 1,4-dehydrobenzene diradicals. For terminal acyclic enediynes, C^1-C^6 cycloaromatization remains the predominant reaction pathway thermally while no reactivity is observed photochemically. Incorporation of one[7] or two[8] phenyl substituents on the alkyne termini facilitate C^1-C^6 photocyclization of acyclic enediynes; however, increased steric hindrance raises the activation barrier and photochemical yields of phenyl-substituted enediynes are typically lower than those of their cyclic counterparts.[9] In comparison, Pascal demonstrated that the presence of aryl substituents reduces the activation energy of the competing C^1-C^5 cyclization[10] by stabilizing the developing fulvene diradical

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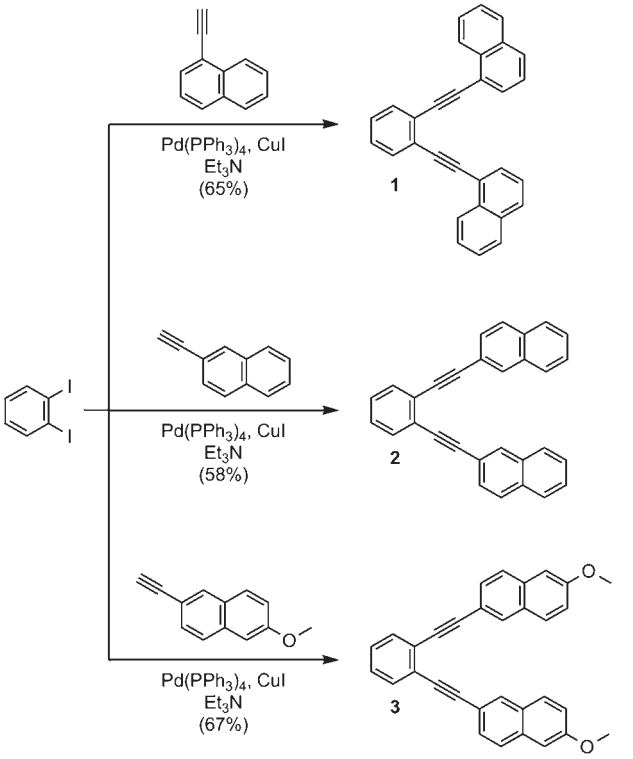
leading to C^1-C^5 thermal cyclization for sterically hindered acyclic enediynes.[11] A direct C^1-C^5 photochemical variant has not been reported to date; however, C^1-C^5 products have been isolated from photoinduced electron transfer pathways[12] as well as by reactions with external radicals[13] and electrophiles.[14] Finally, an alternative photocycloaddition to 1,4-cyclohexadiene has been observed for an acyclic pyrazine enediyne.[15] In the present study we report the syntheses and reactivity of naphthalenylethynyl arenediynes to examine the effect of extended conjugation on the photochemical reactivity of acyclic enediynes.

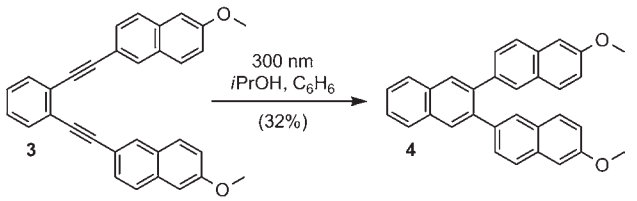
Scheme 1. Syntheses of Naphthalenyl-Substituted Arenediynes



Naphthalenyl-substituted arenediynes were prepared via Sonogashira[16] coupling of 1,2-diiodobenzene as illustrated in Scheme 1. Coupling 1-ethynylnaphthalene, 2-ethynylnaphthalene,[17] and 2-ethynyl-6-methoxynaphthalene with 1,2-diiodobenzene in the presence of $Pd(PPh_3)_4$ and CuI in Et_3N readily afforded naphthalenyl-substituted arenediynes **1**–**3**, respectively, in 58–67% yields. Each naphthalenyl-substituted arenediyne was purified by column chromatography and recrystallization prior to photochemical studies. The absorbance spectra of compounds **1**–**3** all display prominent absorption peaks near 300 nm with weaker absorptions or shoulders from 330 to 360 nm (spectral data provided in the Supporting Information).

Photochemical reactions were conducted in a Rayonet RPR 100 reactor equipped with sixteen 3000 or 3500 Å lamps. Dilute solutions of naphthalen-1-yl arenediyne **1** were prepared in isopropanol, the optimal solvent reported for phenyl-substituted arenediynes, while naphthalen-2-yl arenediynes **2** and **3** required 3:1 isopropanol/benzene as these derivatives have limited solubility in isopropanol. We initially examined irradiation of naphthalenyl arenediynes with 300 nm light, conditions under which 1,2-bis(phenylethynyl)benzene affords C^1-C^6 cyclization products in isolated yields of 5–10% in our hands. Under these conditions, irradiation of **1** at 300 nm for 12–24 h gave no isolable amounts of C^1-C^6 or C^1-C^5 derived products. Analysis of the crude ^1H NMR spectrum showed unreacted starting material present with significant broadening throughout the aromatic region indicative of polymerization. Similar results are obtained in the photolysis of **2** with 300 nm lamps. Reaction of 6-methoxynaphthalen-2-yl arenediyne **3**, on the other hand, gives the C^1-C^6 cyclization product **4** upon photolysis at 300 nm in an isolated yield of 32% (Scheme 2). As observed for 1,2-bis(phenylethynyl)benzene, however, no evidence of competing C^1-C^5 cyclization products was observed in the photolysis of **3** at 300 nm.

Scheme 2. Photo-Bergman Cyclization of **3**



Turning to photolysis at 350 nm, irradiation of naphthalen-1-yl arenediyne **1** gave slow conversion to afford a 4:1 mixture of photoadducts. Upon purification, high resolution mass spectrometry indicated that the products resulted from photodimerization of starting arenediyne **1** (Scheme 3). The structure of the major product **5a**, elucidated by X-ray crystallographic analysis (Figure 1), resulted from tandem [2 + 2] photocycloaddition between the alkyne and the C^1-C^2 bond of the naphthalene substituent. The presence of the cyclobutene ring in **5a** was characterized by an upfield doublet of doublets (J = 4.4, 1.1 Hz) at ~5.25 ppm assigned to the aliphatic CH of the newly formed cyclobutene ring. In the ^{13}C spectra, the newly created aliphatic methine signal was observed at 51 ppm while the quaternary carbon was observed at

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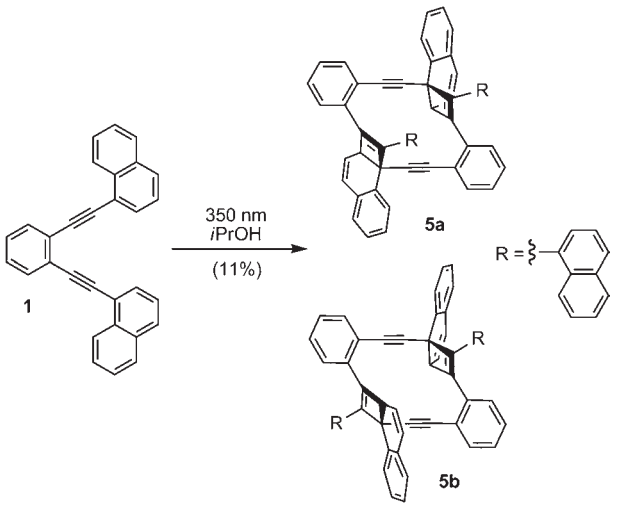
47 ppm. In addition to isopropanol, dimers **5a** and **5b** are produced upon photolysis of **1** in benzene and acetonitrile, with isolated yields of **5a** ranging from 11 to 15%. The structure of the minor product **5b** has been assigned as a diastereomer of **5a** as this structure gives nearly identical spectral data with 18 proton and 30 carbon resonances with the characteristic signals for the cyclobutene ring.[18] While trace amounts of other products are formed from photolysis of **1** at 350 nm, neither the mono [2 + 2] photoadduct nor any products derived from C^1-C^6 or C^1-C^5 cyclization of the enediyne were isolated. No reaction is observed in the photolysis of **2** and **3** with 350 nm lamps.

Scheme 3. Photodimerization of **1**



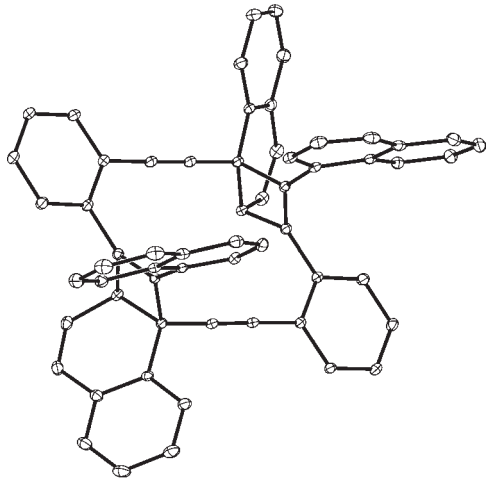


Figure 1. View of the X-ray crystal structure of **5a**. Thermal ellipsoids are drawn at the 30% probability level (hydrogen atoms omitted for clarity).

To examine the ability of naphthalenyl-substituted arenediynes to undergo thermal C^1-C^6 and C^1-C^5 enediyne cyclizations, activation energies ($\Delta G^{\ddagger}$) and free energies of reaction (ΔG) have been calculated at the mPW1PW91/cc-pvtz//mPW1PW91/6-31G(d,p) level of theory and the results are shown in Tables 1 and 2.[19] For phenyl- and naphthalenyl-substituted arenediynes **1**–**3**, activation energies favor C^1-C^5 cyclization over C^1-C^6 cyclization by 3.0–4.9 kcal/mol (Table 1). There is thus an evident kinetic preference for the C^1-C^5 cyclization pathway, which can be attributed to less steric hindrance between the naphthalenyl substituents in the transition state geometries as well as greater stabilization (due to spin delocalization) of the evolving vinyl radical in the C^1-C^5 transition states compared to that of the developing radicals in the C^1-C^6 transition states. The energetic results are consistent with those of Pascal who found activation energies favored C^1-C^5 cyclization of 1,2-bis(phenylethynyl)benzene by 2.2 kcal/mol over C^1-C^6 cyclization at the BLYP/6-31G-(d)//BLYP/6-31G(d) level of theory.[11] Addition of the larger naphthalenyl substituents at the naphthalen-2-yl position leads to only minimal change in the relative difference in activation energies ($\Delta\Delta G^{\ddagger}$) compared to the diphenyl analog. However, when naphthalenyl substituents are attached at the naphthalen-1-yl position, the kinetic preference for C^1-C^5 cyclization increases by 1.7 kcal/mol versus the diphenyl analog. Although thermal C^1-C^5 cyclization is favored over the C^1-C^6 pathway, elevated reaction temperatures would be required for cyclization to occur due to high activation barriers for each reaction pathway. The free energies of reaction (Table 2), however, indicate a thermodynamic preference for C^1-C^6 cyclization by 4.3–7.1 kcal/mol with the naphthalenyl substituents and by 6.8 kcal/mol with the diphenyl analog. In either diradical cyclization product, C^1-C^5 or C^1-C^6, steric effects cease to be an issue and the dominant factor is the gain of aromaticity in the C^1-C^6 product.[20]

Table 1. Activation Energies ($\Delta G^{\ddagger}$, gas phase, 25 °C) for Cyclization of 1,2-Bis(arylethynyl)benzenes (kcal/mol)

aryl substituent	$\Delta G^{\ddagger}$ C^1-C^5	$\Delta G^{\ddagger}$ C^1-C^6	$\Delta\Delta G^{\ddagger}$
phenyl	42.45	45.70	−3.25
naphthalen-1-yl	41.11	46.04	−4.93
naphthalen-2-yl	42.16	45.54	−3.38
6-methoxynaphthalen-2-yl	41.83	44.80	−2.97

Experimentally, thermal cyclization of 1,2-bis(phenylethynyl)benzene leads to C^1-C^5 and C^1-C^6 derived

(18) Computations indicate that **5b** is 2.86 kcal/mol higher in energy than **5a**, which is approximately consistent with the experimentally observed 4:1 ratio at 35 °C, which according to Boltzmann statistics corresponds to an energy difference between the isomers of 0.85 kcal/mol.

(19) $\Delta G^{\ddagger}$ and ΔG have also been calculated in various solvents (benzene, isopropanol, and acetonitrile) for both cyclization pathways. The results show that the effect of solvent is essentially nominal. The values of $\Delta G^{\ddagger}$ and ΔG in the three solvents are provided in the Supporting Information (Tables S4 and S5).

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Table 2. Free Energies of Reaction (ΔG, gas phase, 25 °C) for Cyclization of 1,2-Bis(arylethynyl)benzenes (kcal/mol)

aryl substituent	ΔG C^1-C^5	ΔG C^1-C^6	$\Delta\Delta G$
phenyl	35.49	28.68	6.81
naphthalen-1-yl	34.60	30.32	4.28
naphthalen-2-yl	35.23	28.13	7.10
6-methoxynaphthalen-2-yl	33.83	27.80	6.03

products[21] while under photochemical conditions only low yields of C^1-C^6 Bergman cyclization are observed at 300 nm.[8] The lack of C^1-C^5 product in the photocyclization of 1,2-bis(arylethynyl)benzene derivatives may be explained by a reversible C^1-C^5 cyclization in the excited state. As benzannelated enediynes are well documented to undergo reversible thermal cyclizations in the presence of 1,4-cyclohexadiene,[22] reopening of C^1-C^5 diradicals in the excited state to give starting arenediyne is likely in the presence of the weaker H-atom donor isopropanol, leading to the thermodynamic C^1-C^6 products.[23] Based on the data in Tables 1 and 2, naphthalenyl-substituted arenediynes **1**–**3** would be expected to give thermal cyclization outcomes similar to the diphenyl analog. Reaction energetics, however, are not the only factor governing the photochemical reactivity of arenediynes, as the photophysical properties of each respective arenediyne must be taken into consideration.[8] Experimentally at 300 nm, neither C^1-C^5 nor C^1-C^6 cyclization products are isolated in the photolysis of **1** due to increased sterics. However, despite similar thermal activation barriers compared to 1,2-bis(phenylethynyl)benzene, photolysis of **2** at 300 nm does not afford any cyclization products while photolysis of **3** affords the C^1-C^6 product exclusively. The role of the methoxy substituent on the cyclization of naphthalen-2-yl-substituted arenediyne **3** at 300 nm, affording improved isolated yields of C^1-C^6 products compared to **2** and 1,2-bis(phenylethynyl)benzene, is under further investigation and will be reported elsewhere.

For the reactions with 350 nm irradiation, only naphthalenyl-substituted arenediyne **1** displays reactivity leading to cyclobutene adducts. Time-dependent DFT (TD-DFT) calculations were conducted to determine the wavelength of maximum absorption (λ_{max}) and to examine the molecular orbitals involved in the associated electronic excitation (Table S6). Excitation of arenediyne **1** with 350 nm lamps occurs from the naphthyl substituent and into the arenediyne unit (Figure S1). As a result, irradiation of the naphthyl substituent in **1** at 350 nm leads to the observed photochemically allowed [2 + 2] cycloaddition to generate dimers **5a** and **5b** as opposed to C^1-C^5 or C^1-C^6 enediyne cyclization products which would arise from excitation of the acetylenic units.[24]

In summary, we describe the syntheses and photochemical reactivity of a series of naphthalenyl-substituted arenediynes. While computational studies suggest similar thermal reactivity compared to 1,2-bis(phenylethynyl)-benzene, interesting substituent effects are observed upon photolysis. Methoxy substituents were found to dramatically improve isolated yields of C^1-C^6 products for naphthalen-2-yl derivatives upon irradiation at 300 nm while naphthalen-1-yl substituted arenediynes undergo [2 + 2] photocycloaddition with longer wavelength irradiation.

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Supporting Information Available. Full experimental procedures and spectroscopic data for compounds **1**–**5**, computational details, Cartesian coordinates for geometry optimized structures, and CIF files for **1** and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) From the data in Tables 1 and 2, reopening of the C^1-C^5 diradical has an average barrier of 7.1 kcal/mol, versus an average barrier of 16.8 kcal/mol for opening of the C^1-C^6 diradical.

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