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Photochemical Analogue of the Bergman Cycloaromatization Reaction

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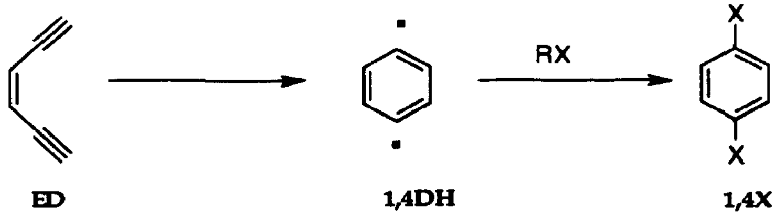
Abstract: Irradiation of an enediyne analog yields a cyclized product expected from a thermal Bergman rearrangement.

Introduction

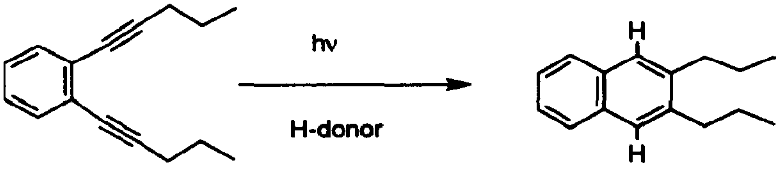
The 3-hexene-1,5-diyne function (**ED**) was initially examined mechanistically by Bergman,[1] who showed that upon heating this functionality produced aromatic structures (**a reaction termed the Bergman cycloaromatization**) as the result of abstraction of two hydrogen (or halogen) atoms (**eq. 1, 1,4X**) by a 1,4-dehydroaromatic intremediate (**eq. 1, 1,4DH**). Although of substantial interest to physical organic chemists, the rearrangement of 3-ene-diynes to aromatics assumed new significance and stimulated considerable synthetic activity [2-4] when it was discovered that certain naturally occurring anticancer antibiotics, such as calicheamycin γ_1, contain a strained enediyne moiety, and under appropriate circumstances undergo nucleophilically induced Bergman cycloaromatization. These 3-ene-diyne species appear to express their biological activity by "nicking or cutting" DNA via hydrogen abstraction from the phosphate backbone by the 1,4-biradical intermediate formed.



(1)

Although the majority of published reports on the 3-ene-diyne conversion to aromatics involve investigation of thermal reactions, it has not escaped the attention of several authors that a photochemical entry into the 1,4-dehydroaromatics could offer a number of interesting features, both of mechanistic and biological significance. Indeed, photolysis of molecules bearing an enediyne functionality has been carried out. For example, cases of cyclization as a result of a chemical transformation within the molecule,[5] and cis-trans isomerization of acyclic enediynes as a result of irradiation[6] have been reported. However, direct irradiation of an enediyne functionality to afford a Bergman-type product has not yet been reported, to the best of our knowledge.

Herein we report the direct photocycloaromatization of a 3-benzo-1,5-diyne (1) to a naphthalene (2) and evidence that the reaction proceeds through a 1,4-dehydroaromatic intermediate.



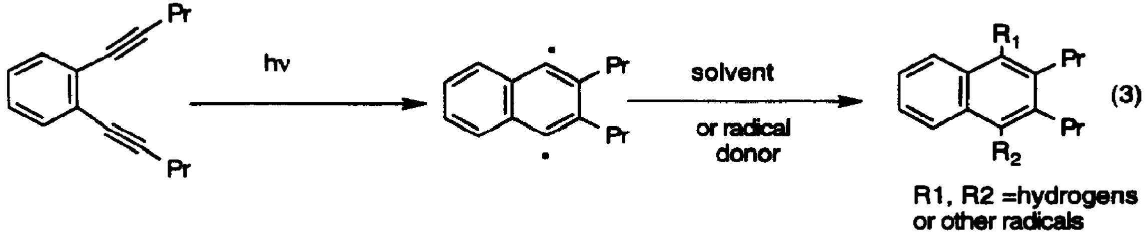
1

2

(2)

Results

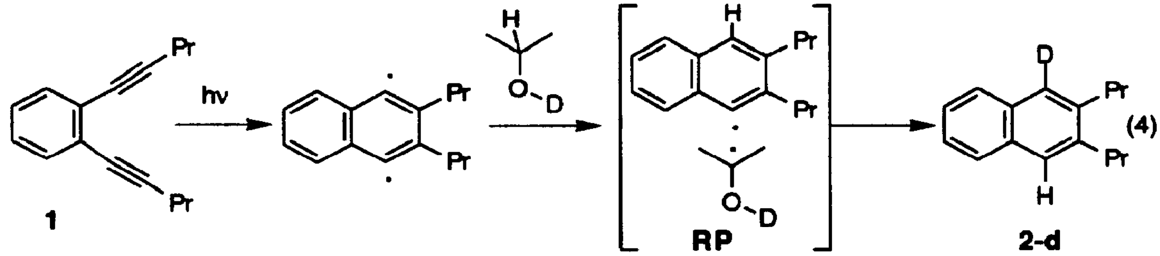
The enediyne 1[7] was irradiated[8] in several solvents (isopropanol, IP, benzene, BZ, and hexane, HX) and the course of reaction was monitored by GC/MS analysis. A finite but variable yield of 2 was observed in each case . In one experiment in BZ as solvent, 1,4-cyclohexadiene (an excellent carbon radical scavenger) was added as a potential scavenger of any biradical intermediates. In this case, in addition to the formation of a product corresponding to 2, a product of molecular weight 290, corresponding to the formation of an adduct of 1 and 1,4-cyclohexadiene was formed. With IP as both solvent and hydrogen donor, no related adduct could be detected by GC and GC/MS analysis. Although conditions were not optimized, the yield of 2 in isopropanol was of the orde of 10-25%. The highest yield of 2 (ca 40%) was obtained in BZ solvent with benzhydrol (0.5 M) as hydrogen donor. These results are consistent with the photoinduced cycloaromatization of **1** to the biradicaloid dehydrocycloaromatic **1c**, which is converted via hydrogen abstraction to the naphthalene **2** (eq. 3).



1 **1c** **2**

Preparative photolysis of **1** in isopropanol allowed for characterization of **2** by NMR and GC/MS spectroscopy. Both yielded results consistent with the structure proposed for **2**. Moreover, these spectra were identical to those of 2,3-di-(1-propyl)naphthalene (**2**), synthesized via a rational route.[9]

When the photolysis of **1** was conducted in IP-Od, at the GC retention time corresponding to **2**, a product of mass 213, corresponding to **2** (X = H, X = D) was eluted. No significant production of products of mass 212 or 214 was observed by GC/MS analysis. This result is consistent with the formation of a radical pair (eq.4, **RP**) formed through hydrogen abstraction from IP-Od by the dehydrocycloaromatic intermediate **1c**, followed by disproportionation of RP .



In an attempt to explain the effectiveness of benzhydrol in formation of **2**, the possibility of sensitization by benzophenone, an expected product of the reaction, was investigated. However, irradiation of benzophenone in the presence of **1** yielded no cyclized **2**. The same results were obtained with irradiation of the triplet sensitizers acetophenone, acetonaphthone and xanthone in the presence of **1**.

As a control experiment, photolysis of **2** was conducted in IP and IP-Od solvents. Neither reaction of **2** nor deuterium incorporation was observed after 3.5 hours of irradiation, a time period during which a significant amount of conversion had been achieved from photolysis of **1**.

Conclusion

A photochemical analog of the thermal Bergman cycloaromatization (**1** → 2) is reported for the first time. The experiments are consistent with, but do not require the intermediacy of a dehydroaromatic species possessing biradical character.[1, 10, 11] This result is of potential relevance to the design of a photochemical analog of the thermally active antibiotic antitumor natural products which would possess an advantage of being stable over a large temperature range, which could be structurally tailored to specific site delivery and specific spatial excitation by optical fiber techniques.

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References

(1) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25; (b) For recent theoretical analysis see Krada, E.: Cremer, D. *J. Am. Chem. Soc.*, **1994**, *116*, 4929.

(2) Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1377-1500.

(3) Nicolaou, K. C. ;. Liu, A.; Zeng, Z.; McComb, S. *JACS* **1992**, *114*, 9279-9282.

(4) Zein, N. ;. Sinha, A.M.; McGahren, W.J.; Ellestad, G.A. *Science* **1988**, *240*, 1198-1201.

(5) Wender, P. A.; Zercher, C. K.; Beckham, S.; Haubold, E.-M. *J. Org. Chem.* **1993**, *58*, 5867-5869; Shiraki, T.; Sugiura, Y. *Biochemistry* **1990**, *29*, 9795-9798.

(6) Kagan, J.; Wang, X.; Chen, X.; Lau, K. Y.; Batac, I. V.; Tuveson, R. W.; Hudson, J. B. *J. Photochem. Photobiol. B: Biol.* **1993**, *21*, 135-142.

(7) **1** was synthesized by reaction of 1,2 -diiodobenzene with 1-pentynein the presence of CuI, $Pd(PPh_3)_4$ and isopropylamine, and purified by flash chromatography (silica gel, hexane eluent). For a description of the reaction conditions, see reference 3.

(8) A medium-pressure Hg lamp was used for all irradiation experiments with a cutoff filter at 313 nm.

(9) Reaction of 2,3-naphthalenedicarboxaldehyde with $Ph_3PEt^{+-}Br$ in the presence of $(Me_3Si)_2N^{-}$ ^{+}Na afforded 2,3-di-(1-propenyl)naphthalene, which was further catalytically hydrogenated to yield **2**, purified by column chromatography (silica gel, hexane eluent).

(10) The yield of **2** appears not to be a simple function of conversion, raising the possibility that the pathway tc **2** may be more complex than the elementary steps shown in **eq. 3** ($R_1 = R_2 = H$).

(11) Recent theoretical studies of the thermal Bergman rearrangement have indicated that the 1,4-phenyl biradical species may not be an intermediate. The relevance of these findings, however, to the results reported herein is presently not apparent. (a) Lindh, R.; Persson, B. J. *J. Am. Chem. Soc.*, **1994**, *116*, 4963.

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