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Photochemistry of Diethynyl Sulfides: A Cycloaromatization for the Formation of Five-Membered Rings

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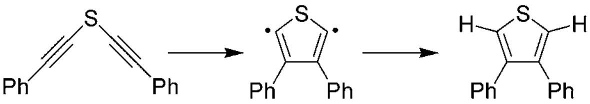
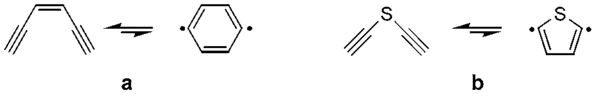
ABSTRACT



The first five-membered ring cycloaromatization reaction has been demonstrated. Photoirradiation of bis(phenylethynyl) sulfide in hexanes/1,4-cyclohexadiene produces 3,4-diphenylthiophene through the presumed intermediacy of 2,5-didehydrothiophene. In addition, phenylacetylene is produced in this reaction consistent with competing direct carbon−sulfur cleavage. For reactions in ethanol or 2-propanol production of the thiophene is accompanied by the formation of phenylacetylene and a thionoester of the corresponding alcohol. Thiophene products also result from the irradiation of other diethynyl sulfides.

The cycloaromatization of enediynes, the Bergman cyclization,[1] has garnered much attention because two highly reactive sp[2] σ-radicals are generated under relatively mild conditions (Scheme 1a). A number of natural products exploit this unique thermal isomerization in their mechanism of action, and this has led to an explosion of research focused on development of related antitumor agents.[2] More recently, this reaction has been recognized by the materials community as a powerful methodology for the synthesis of conjugated organic materials.[3]

Scheme 1



An alternative to thermal cycloaromatizations is the "photo-Bergman" cyclization, which has been reported for a number of enediyne derivatives.[4] We report here an entirely new variant of this cyclization, namely, the reaction of bis(phenylethynyl) sulfide (**3a**) and other diethynyl sulfide derivatives; this constitutes the first five-membered ring cycloaromatization reaction.[5] The reaction course is consistent with the intermediacy of a heretofore inaccessible 2,5-didehydrothiophene,[6] and the product is a 3,4-disubstituted thiophene. As a five-membered ring analogue of the Bergman cyclization (Scheme 1b), this is an important addition to the area of cycloaromatization chemistry both for the potential

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[1] Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25−31.

[2] Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci.* **1993**, *90*, 5881−5888.

[3] (a) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537−553. (b) Shah, H. V.; Babb, D. A.; Smith, D. W. *Polymer* **2000**, *41*, 4415−4422. (c) Chen, X. H.; Tolbert, L. M.; Hess, D. W.; Henderson, C. *Macromolecules* **2001**, *34*, 4104−4108.

[4] (a) Funk, R. L.; Young, E. R. R.; Williams, R. M.; Flanagan, M. F.; Cecil, T. L. *J. Am. Chem. Soc.* **1996**, *118*, 3291−3292. (b) Evenzahav, A.; Turro, N. J. *J. Am. Chem. Soc.* **1998**, *120*, 1835−1841. (c) Clark, A. E.; Davidson, E. R.; Zaleski, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 2650−2657.

[5] (a) Matzger, A. J.; Lewis, K. D.; Rowe, M. P.; Wenzler, D. L. Presented at the 223rd National Meeting of the American Chemical Society, Orlando, FL, April 7−11, 2002. (b) Examples of nonaromatic five-membered ring cyclizations have been reported. For a review concerning the conversion of eneyne-allenes to fulvenes, see: Wang, K. K. *Chem. Rev.* **1996**, *96*, 207−222. (c) For a description of a diyne proceeding via a vinyl diradical, see: Zimmerman, H. E.; Pincock, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 3246−3250.

[6] For isomeric didehydrothiophenes, see: (a) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427−498. (b) Teles, J. H.; Hess, B. A.; Schaad, L. J. *Chem. Ber.* **1992**, *125*, 423−431.

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of creating new therapeutics and as a novel route to polythiophene materials.

Both computation and experiment have demonstrated that the carbon−carbon distance of the enediyne systems substantially affects the barrier of six-membered ring cycloaromatizations.[7] In the simplest enediyne system, hex-3-ene-1,5-diyne (**1**), the a−b distance is 2.93 Å, while the c−d distance is 4.32 Å as determined by microwave spectroscopy.[8] The first microwave and crystal structures of free diethynyl sulfides were recently obtained, revealing the carbon−carbon distances critical for bond formation to obtain the 2,5-didehydrothiophene intermediate (Figure 1).[9] The a−b distances in diethynyl sulfides are shorter than those in enediynes, and the c−d distances are slightly longer. For the parent diethynyl sulfide (**2**), microwave spectroscopy determines these values to be 2.64 and 4.66 Å, respectively. X-ray crystallographic studies on the bis(phenyl) derivative (**3a**) find that the a−b distance is 2.62 Å, while the c−d distance is 4.57 Å. Though the bulk of the substituents in **3a** may hinder bond formation in the transition state,[10] these effects are not evident in the starting diethynyl sulfides.

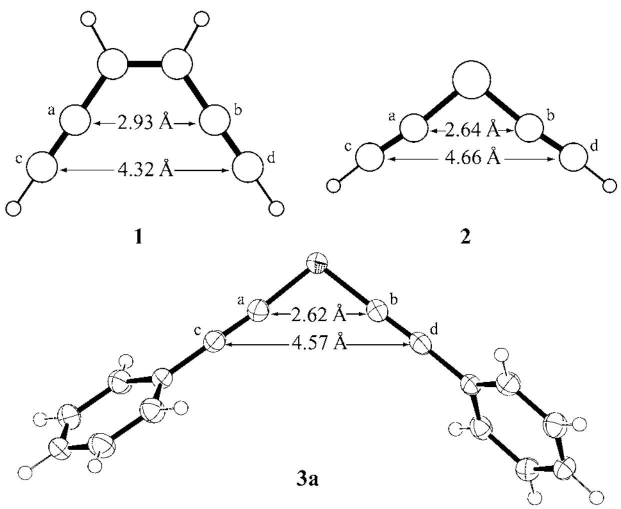


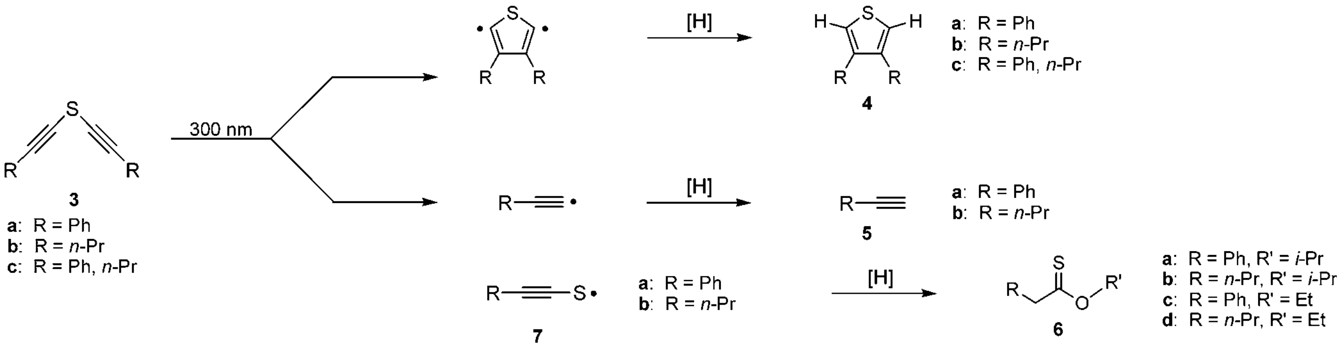
Figure 1. Key structural parameters for the precursors to six- and five-membered ring cycloaromatization reactions determined by microwave spectroscopy (**1**, **2**) and X-ray diffraction (**3a**).

Although thermal reaction below 240 °C led exclusively to recovered starting material,[11] irradiation of **3a** at 300 nm in hexanes in the presence of 1,4-cyclohexadiene (CHD, 2 mM) as the trapping agent consistently results in the production of two species: 3,4-diphenylthiophene (**4a**) and phenylacetylene (**5a**) in yields of 16 and 33%, respectively. A substantial increase in the concentration of CHD leads to lower yields of **4a** while leaving that of **5a** relatively unchanged. Substituting γ-terpinene as the trapping agent results in similar yields of both **4a** and **5a** compared to CHD. In addition, irradiation of **3a** at 350 nm leads to similar yields and ratios of products, but with a slower rate of reaction (see Supporting Information). A precipitate that forms during the reaction displays broad peaks in the proton NMR spectrum (7.0−8.0 ppm in $CDCl_3$), and LDI-TOF MS analysis is consistent with oligomerization occurring as a major side reaction.

Utilization of an alcohol to function as both solvent and trapping agent in the irradiation of **3a** results in the formation of three products: **4a**, **5a**, and the appropriately substituted thionoester **6a** or **6c** (Scheme 2). The yield of **4a** in ethanol and 2-propanol was 11 and 8%, respectively. The yield of **5a** in both solvents was approximately 30%, and the thionoesters were produced in 20% yield. Triplet sensitization (acetophenone or xanthone) in these solvents leads to modestly decreased yields of **4a**. The use of alcohols that are poorer hydrogen atom donors, methanol and *t*-butanol, results in drastically reduced yields of all products consistent with competing polymerization processes.

To explore the generality of this five-membered ring cycloaromatization, a diethynyl sulfide with two propyl substituents (**3b**) and one with both a propyl and a phenyl substituent (**3c**) were examined. Irradiation of **3b** at 300 nm in hexanes with CHD results in the formation of 3,4-dipropylthiophene (**4b**) in 2% yield, reflecting a reduced efficiency of the cyclization with alkyl substituents on the diethynyl sulfide. These effects are still evident in **3c**, which produces 3-phenyl-4-propylthiophene (**4c**) in 3% yield. The rate of consumption of **3b** during irradiation is approximately five times slower when compared to the other substrates and is likely due to the lack of an efficient chromophore.

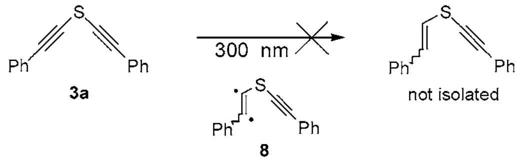
Scheme 2



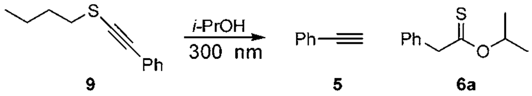
Reactions of **3c** in alcohols led to the competitive production of both the alkyl- (R = *n*-propyl) and aryl- (R = phenyl) substituted thionoesters (**6b** or **6d**) of the corresponding alcohols (see Supporting Information).

A mechanism consistent with the above results is outlined in Scheme 2. Irradiation of the diethynyl sulfide results in competing cycloaromatization to the 2,5-didehydrothiophene or cleavage of a σ-bond between an sp-carbon and sulfur. The five-membered ring diradical intermediate is trapped by a hydrogen donor to form the thiophene product (**4**).[12] The substituted ethynyl radical that results from the carbon−sulfur bond cleavage is trapped to provide a terminal alkyne (**5**). The thiyl radical (**7**) abstracts hydrogen from the solvent and is trapped as the thionoester (**6**), likely via the corresponding alkyl- or phenylthioketene. Photoreduction of the triple bond, as observed in much alkyne photochemistry,[4b,5c] does not take place for **3a** (Scheme 3).[13] Furthermore, because independently synthesized *trans*,*trans*-bis(2-phenylvinyl) sulfide and *trans*-(2-phenylvinyl)-2-phenylethynyl sulfide are not rapidly consumed under these reaction conditions, either alone or in the presence of **3a**, the absence of the vinyl species indicates that photoreduction is not an important pathway in this system. Support for competing cycloaromatization and direct σ-cleavage is provided by irradiation of butyl phenylethynyl sulfide (**9**) at 300 nm in 2-propanol (Scheme 4)[14] to yield **5a** (2%) and **6a** (17%). The increased yield of the thionoester relative to phenylacetylene is consistent with preferential cleavage of the weaker sulfur-butyl bond under these conditions to form **7a** and its subsequent conversion to **6a**.

Scheme 3



Scheme 4



In summary, the first five-membered ring cycloaromatization has been demonstrated for the formation of thiophenes and has considerable potential in organic and materials synthesis. This is the first in a potentially general series of reactions that can include cycloaromatizations leading to furans, pyrroles, and phospholes. Studies along these lines are currently underway.

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Supporting Information Available: Synthetic procedures, spectral and analytical data, and tables containing photochemical yields. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Higher temperatures led to a mixture of products consistent with a radical chain process where **4a** was only a minor product. (b) Recently published computational results for enthalpies of the thermal cyclization depicted in Scheme 1b indicate a barrier of 55.8 kcal/mol and endothermicity of 19.3 kcal/mol: Kawatkar, S. P.; Schreiner, P. R. *Org. Lett.* **2002**, *4*, 3643−3646.

(12) Photoirradiation of 2,5-diiodo-3,4-diphenylthiophene in hexanes in the absence of trapping agent exclusively yields **4a**, indicating that formation of **5** or **7** from a thiophene monoradical is not facile.

(13) Vinyl diradical (**8**) is not trapped in the experiment, suggesting that either it does not form or that reactions competing with its trapping are more rapid than in the analogous hydrocarbon in ref 5c.

(14) Acetylenic ether photochemistry has also been proposed to involve cleavage of the weaker heteroatom−carbon bond; see: Smith, B. A.; Callinan, A. J.; Swenton, J. S. *Tetrahedron Lett.* **1994**, *35*, 2283−2286.