Photochemical Activation

DOI: 10.1002/anie.200703034

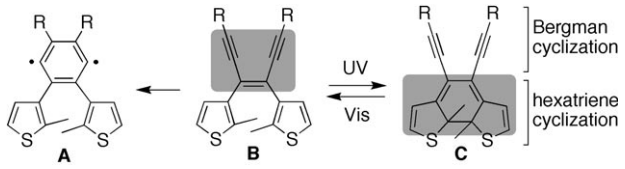
Creating a Reactive Enediyne by Using Visible Light: Photocontrol of the Bergman Cyclization**

*David Sud, Tony J. Wigglesworth, and Neil R. Branda**

The use of light to interconvert chemical structures between two isomeric forms has matured into an exciting field. It has the potential to impact a wide range of applications from optoelectronics to photorelease because it offers a convenient means to modulate the way materials absorb, emit, and rotate light, or the way they accept and transport charge.[1] Only recently have some research groups refocused their efforts to apply the concepts of molecular photoswitching to control chemical reactivity, despite the fact the concept was introduced over 20 years ago.[2]

The potential role of light integrated with chemical reactivity is especially significant in modern therapeutic technologies. It can be used to trigger the rearrangement of a molecular structure to activate "masked" chemotherapeutic agents that are broadly toxic, have severe side effects and cannot be administered in their "unmasked" forms. One notable example that would benefit from such photocontrol is the Bergman cyclization of the enediyne architecture, a reaction that is important in antitumor activity and one where the presence of a precise arrangement of π bonds is essential.[3,4] The attempts made to regulate the activity of enediynes have all met with different levels of success,[5] and suitable photoactivation of enediynes for clinical settings has remained an elusive goal. Here we describe our approach to activate enediynes by taking advantage of the fact that the hexatriene structures found in the dithienylethene (DTE) backbones (compounds **B**, **1o**, and **6**, for example) undergo reversible ring-closing reactions when irradiated with UV and visible light.[6]

This concept is illustrated in Scheme 1. By integrating the hexatriene and enediyne structures into a single molecule (compound **B**), we have developed a system that uses visible light to control the Bergman cyclization. Only ring-open isomer **B** contains the enediyne architecture (highlighted in **B** by the shaded box) that undergoes spontaneous cyclization and yields the active diradical (**A**), which is the chemical species responsible for the high antitumor activity. UV light triggers the photocyclization of the hexatriene in **B** and converts it to its ring-closed counterpart **C**. This photochemical reaction also rearranges the π system and localizes it along the rigid backbone formed during the ring-closing reaction (highlighted in **C** by the shaded box). The consequence is the removal of the enediyne architecture necessary for spontaneous conversion to the diradical, making ring-closed isomer **C** inactive. Visible light activates the system by triggering the ring-opening reaction, regenerating enediyne **B**. The fact that this system is activated with visible light, which penetrates tissue deeper and with less damage than the more commonly used UV-light, is particularly important and adds to the appeal of the system. This offers a significant advantage over previously reported examples that require extended irradiation periods with high-energy UV light to alter ring strain,[7] cleave a protecting group[8] or create the enediyne structure.[9]



Scheme 1. Photochemical rearrangement used to create the enediyne structure. Only isomer **B** has the conjugated π system that undergoes the Bergman cyclization and produces the diradical **A**. Isomer **C** is inactive.

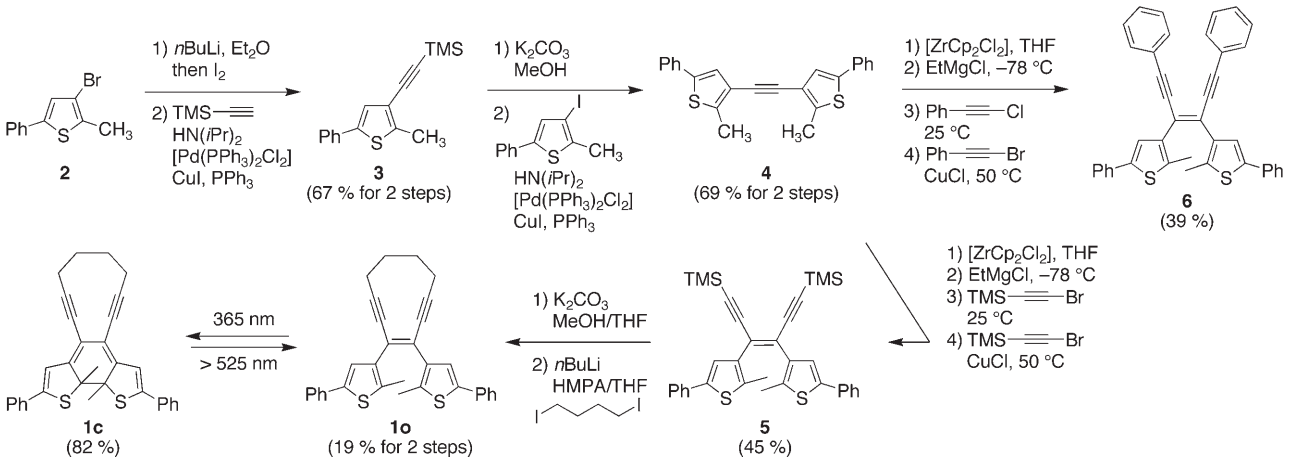
Two enediyne derivatives are described herein. Both compounds, **1o** and **6**, can be prepared from the same alkyne-linked bis(thiophene) **4** as shown in Scheme 2. Compound **4** is prepared in four steps from 3-bromo-2-methyl-5-phenylthiophene (**2**)[10] by first converting the bromide into the iodide in order for it to undergo a more facile palladium-catalyzed Sonogashira coupling reaction with trimethylsilylacetylene. After removing the silyl protecting group, alkynylthiophene **3** can be subjected to another Sonogashira coupling with the same iodothiophene as was used to prepare it in the first place. The enediyne portions of compounds **1o** and **6** are installed by one-pot alkylzirconations with halogenated phenylacetylene (for **6**) or trimethylsilylacetylene (for **1o**).[11] This multistep method ensures that the two alkyne groups are appropriately positioned *cis* to each other so that the enediynes can eventually undergo the Bergman cyclization. This step completes the synthesis of compound **6**. In the case of compound **1o**, the ten-membered ring is best formed by deprotecting the trimethylsilylacetylene moieties using strong base and quenching the generated anion with 1,4-diiodobutane.

Because the distance between the two alkyne groups in enediyne **6** is large enough to prevent spontaneous cyclization

[*] D. Sud, T. J. Wigglesworth, Prof. N. R. Branda
4D LABS, Department of Chemistry
Simon Fraser University
8888 University Drive, Burnaby, BC V5A 1S6 (Canada)
Fax: (+1) 604-291-3765
E-mail: nbranda@sfu.ca

[**] This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Canada Research Chair Program and the Simon Fraser University.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Synthesis of DTE derivatives **1o** and **6** with enediyne substructures. Cp = cyclopentadienyl, HMPA = hexamethylphosphoric triamide, TMS = trimethylsilyl.

to the diradical at room temperature,[4,12] compound **6** represents a useful model to characterize the photochemical properties of the generalized hexatriene backbone. This thermal stability is supported by lack of degradation at ambient temperature when compound **6** is kept in the dark. Only when the compound is heated to ca. 175 °C is degradation apparent. The hexatriene in **6** is very sensitive to UV light, and irradiation of solutions of **6** with $\lambda = 365$ nm immediately leads to significant optical changes. The photoinduced cyclization is best monitored using UV/Vis absorption spectroscopy (Figure 1 a), where there is an obvious

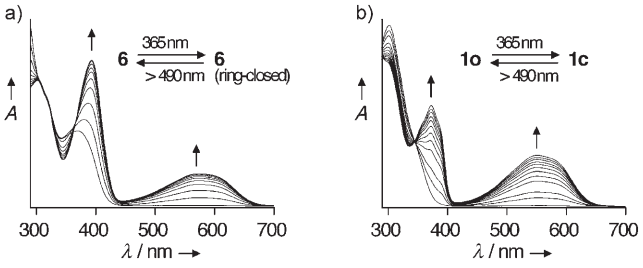


Figure 1. Changes in the UV/Vis absorption spectra of compound **6** (a) and **1o** (b) upon irradiation with $\lambda = 365$ nm (benzene solutions, 2.65×10^{-5} M and 8.22×10^{-5} M for **6** and **1o**, respectively). Spectra were recorded every 10 seconds until a 90-second period (for **6**) and a 120-second period (for **1o**) were completed.

decrease in the high-energy absorptions of the ring-open isomer and an accompanying emergence of absorption bands in the lower-energy regions of the spectrum ($\lambda_{max} = 575$ and 393 nm).[13] These trends are typical for the cyclizations of DTE derivatives and account for the change of the solutions from colorless to purple due to the creation of the linearly conjugated pathway in the ring-closed form. The spectral changes stop after 90 seconds (at a concentration of 2.65×10^{-5} M), and a photostationary state containing 92 % of the ring-closed isomer is formed according to ^{1}H NMR spectroscopy. The ring-closed isomer is stable at ambient temperature as long as it is kept in the dark. Irradiation of the colored solution with visible light ($\lambda > 490$ nm)[14] converts the ring-closed isomer back to **6** and regenerates the original absorption spectrum.

The ten-membered carbocycle in enediyne **1o** is installed to facilitate the Bergman cyclization at lower temperatures.[4] The photochemical reaction of compound **1o** is shown in Figure 1 b. Ring-closing to isomer **1c** is also accomplished using $\lambda = 365$ nm, while the reverse reaction is triggered with visible light ($\lambda > 490$ nm). In this case, the photostationary state contains 82 % of **1c**, as determined by ^{1}H NMR spectroscopy. Similar trends are observed in the UV/Vis absorption spectrum as were already described for compound **6**, including the unchanged spectrum corresponding to the photostationary state when the sample is stored in the dark at ambient temperature.

A first indication of the difference in thermal reactivity between isomers **1o** and **1c** is that when a mixture is heated to 75 °C, isomer **1o** completely degrades while **1c** can still be detected by ^{1}H NMR spectroscopy long after all of **1o** is consumed. In fact, we took advantage of this selective reactivity to isolate pure samples of compound **1c** from the photostationary state for further studies.[15]

The formation of the reactive diradical, Bergman cyclization product of the ring-open isomer, **1o**, can be probed by using ^{1}H NMR spectroscopy and 1,4-cyclohexadiene as a radical-trapping agent. When a mixture of **1o** and a large excess of 1,4-cyclohexadiene were heated at 75 °C the peaks corresponding to **1o** decreased while peaks assigned to compound **7** appeared. The reaction follows pseudo-first-order kinetics (Figure 2) with apparent rate constants being $k = 7.0 \times 10^{-5}$ s^{-1} for the disappearance of **1o** (corresponding to a half-life of 165 min) and $k = 6.8 \times 10^{-5}$ s^{-1} for the formation of **7**.[15,16]

On the other hand, the ring-closed isomer (**1c**) shows significant thermal stability. When a solution of **1c** was heated (in the presence or absence of 1,4-cyclohexadiene) under identical conditions used to convert isomer **1o** to **7**, only minimal decay was observed (Figure 2) and no characterizable compounds were produced, demonstrating how the Bergman cyclization can be photoregulated by rearranging

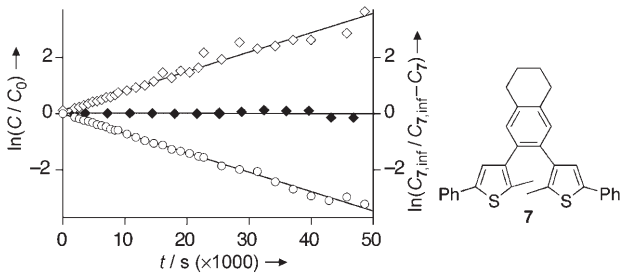


Figure 2. Changes in the concentrations of compounds **1o** (○; initial concentration 4.22×10^{-3} M), **1c** (◆; initial concentration 2.42×10^{-3} M), and **7** (◇) as monitored by ^{1}H NMR spectroscopy. The concentrations are measured by comparing the integrated areas under the peaks for each compound against *p*-nitroanisole as an internal standard and are normalized for easier comparison. The left vertical axis corresponds to the disappearance of compounds **1o** and **1c**, where C is the concentration of **1o** or **1c** at a given period of time and C_0 is initial concentration of each compound. The right vertical axis corresponds to the appearance of compound **7**, where C_7 is concentration at a monitored period of time and $C_{7,inf}$ is the final concentration of **7**.

the π bonds in the dithienylethene structure. Future generations of the photoswitches will contain modifications to induce the Bergman cyclization at biological temperatures and present appropriate functionality for biocompatibility.

Received: July 7, 2007
Published online: September 13, 2007

Keywords: cyclization · dithienylethenes · enediynes · molecular switches · photochromism

[1] *Molecular Switches* (Ed.: B. L. Feringa), Wiley-VCH, Weinheim, **2001**; *Organic Photochromic and Thermochromic Compounds*, *Vol. 1* (Eds.: J. C. Crano, R. J. Guglielmetti), Plenum, New York, **1999**.

[2] A. Ueno, K. Takahashi, T. Osa, *J. Chem. Soc. Chem. Commun.* **1981**, 94–96; F. Würthner, J. Rebek, Jr., *Angew. Chem.* **1995**, *107*, 503–505; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 446–448; S. H. Kawai, S. L. Gilat, J.-M. Lehn, *Eur. J. Org. Chem.* **1999**, 2359–2366; R. Cacciapaglia, S. Di Stefano, L. Mandolini, *J. Am. Chem. Soc.* **2003**, *125*, 2224–2227; D. Sud, T. B. Norsten, N. R. Branda, *Angew. Chem.* **2005**, *117*, 2055–2057; *Angew. Chem. Int. Ed.* **2005**, *44*, 2019–2021; V. Lemieux, N. R. Branda, *Org. Lett.* **2005**, *7*, 2969–2972; H. D. Samachetty, N. R. Branda, *Chem. Commun.* **2005**, 2840–2842; V. Lemieux, S. Gauthier, N. R. Branda, *Angew. Chem.* **2006**, *118*, 6974–6978; *Angew. Chem. Int. Ed.* **2006**, *45*, 6820–6824; H. D. Samachetty, N. R. Branda, *Pure Appl. Chem.* **2006**, *78*, 2351–2359; Y. Odo, K. Matsuda, M. Irie, *Chem. Eur. J.* **2006**, *12*, 4283–4288.

[3] R. G. Bergman, *Acc. Chem. Res.* **1973**, *6*, 25–31; R. R. Jones, R. G. Bergman, *J. Am. Chem. Soc.* **1972**, *94*, 660–661; A. L. Smith, K. C. Nicolaou, *J. Med. Chem.* **1996**, *39*, 2103–2117.

[4] K. C. Nicolaou, W. M. Dai, *Angew. Chem.* **1991**, *103*, 1453–1481; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387–1416.

[5] J. S. Thorson, E. L. Sievers, J. Ahlert, E. Shepard, R. E. Whitwam, K. C. Onwueme, M. Ruppen, *Curr. Pharm. Des.* **2000**, *6*, 1841–1879; S. Bhattacharyya, J. M. Zaleski, *Curr. Top. Med. Chem.* **2004**, *4*, 1637–1654; D. S. Rawat, J. M. Zaleski, *Synlett* **2004**, 393–421; A. Basak, S. Mandal, S. S. Bag, *Chem. Rev.* **2003**, *103*, 4077–4094.

[6] M. Irie in *Organic Photochromic and Thermochromic Compounds*, *Vol. 1* (Eds.: J. C. Crano, R. J. Guglielmetti), Plenum, New York, **1999**, p. 207; M. Irie, *Chem. Rev.* **2000**, *100*, 1685; M. Irie in *Molecular Switches* (Ed.: B. L. Feringa), Wiley-VCH, Weinheim, **2001**, p. 37; H. Tian, S. Yang, *Chem. Soc. Rev.* **2004**, *33*, 85.

[7] G. V. Karpov, V. V. Popik, *J. Am. Chem. Soc.* **2007**, *129*, 3792–3793; M. Kar, A. Basak, M. Bhattacharjee, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5392–5396; A. Basak, H. M. Bdour, J. C. Shain, S. Mandal, K. R. Rudra, S. Nag, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1321–1325.

[8] P. A. Wender, C. K. Zercher, S. Beckham, E. M. Haubold, *J. Org. Chem.* **1993**, *58*, 5867–5869; K. C. Nicolaou, G. Zuccarello, C. Riemer, V. A. Estevez, W. M. Dai, *J. Am. Chem. Soc.* **1992**, *114*, 7360–7371.

[9] Y. Tachi, W. M. Dai, K. Tanabe, S. I. Nishimoto, *Bioorg. Med. Chem.* **2006**, *14*, 3199–3209; A. Poloukhtine, V. V. Popik, *J. Org. Chem.* **2006**, *71*, 7417–7421; A. Poloukhtine, V. V. Popik, *Chem. Commun.* **2005**, 617–619; J. M. Nuss, M. M. Murphy, *Tetrahedron Lett.* **1994**, *35*, 37–40.

[10] M. Irie, T. Lifka, S. Kobatake, N. Kato, *J. Am. Chem. Soc.* **2000**, *122*, 4871–4876.

[11] Y. Liu, Z. Zhong, K. Nakajima, T. Takahashi, *J. Org. Chem.* **2002**, *67*, 7451–7456.

[12] M. Prall, A. Wittkopp, A. A. Fokin, P. R. Schreiner, *J. Comput. Chem.* **2001**, *22*, 1605–1614; P. R. Schreiner, *J. Am. Chem. Soc.* **1998**, *120*, 4184–4190.

[13] Standard hand-held lamps used for visualizing TLC plates (Spectroline E-series, 470 mW cm^{-2}) were used to carry out the ring-closing reactions at 365 nm.

[14] The ring-opening reactions were carried out using the light of a 150-W tungsten source that was passed through a 490-nm cutoff filter to eliminate higher-energy light.

[15] See the Supporting Information for details.

[16] T. A. Zeidan, S. V. Kovalenko, M. Manoharan, I. V. Alabugin, *J. Org. Chem.* **2006**, *71*, 962–975.

