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An Unusual Pathway to Cyclobutane Formation via Desulfurative Intramolecular Photocycloaddition of an Enone Benzothiazoline Pair

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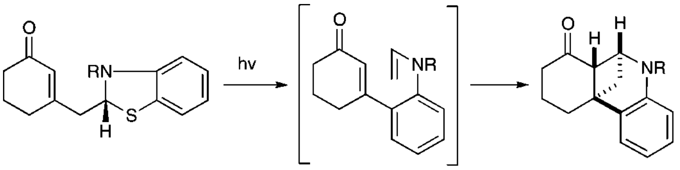
ABSTRACT

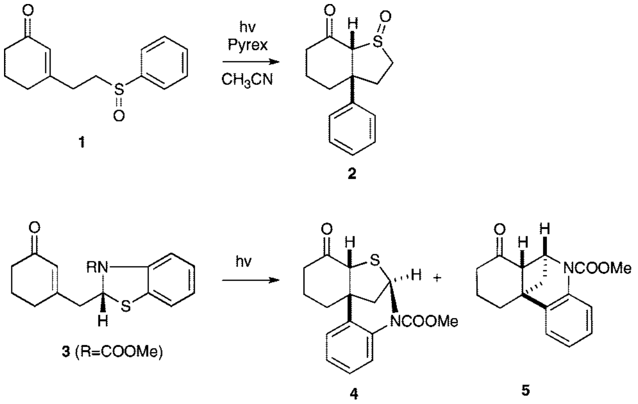


3 (R=COOMe) **14** (R=COOMe) **5** (R=COOMe)

Irradiation of the enone benzothiazoline 3 leads to the formation of cyclobutane 5. Preliminary mechanistic studies establish the intermediacy of an enecarbamate 14 in this photochemical transformation, which could be the result of sulfur extrusion from an episulfide intermediate. Photocycloaddition of the enecarbamate intermediate 14 leads to the formation of "crossed" photoadducts, i.e., 5, in excellent yield, with high levels of regio- and stereochemical control.

The selective synthesis of quaternary carbon centers remains an important challenge in organic synthesis.[1] We have recently reported that intramolecular photocycloaddition of **1** leads to the efficient formation of **2**, which contains an aryl-substituted quaternary center.[2] We describe herein the synthesis and photoreaction of **3**, the predominant product of which is not the analogous thiolane product **4**, but instead cyclobutane **5**, in which the sulfur is extruded in the course of the photoreaction (Scheme 1).

Scheme 1. Desulfurative Photocycloaddition



The synthesis of racemic photosubstrate **3** is outlined in Scheme 2. Addition of *o*-aminothiophenol to the known ethynyl cyclohexenone **6**[3] afforded **7**, which on carbamate formation and reaction with methoxide[4] led to the formation of the photosubstrate **3** (R = COOMe). We found that irradiation of **3** through a uranium filter in benzene gave the

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(1) For a recent review, see: Trost, B. M.; Jiang, C. *Synthesis* **2006**, *36*, 9–396.

(2) Winkler, J. D.; Lee, E. C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 9040–9041.

(3) Larsen, D. S.; O'Shea, M. D. *J. Chem. Soc., Perkin Trans. 1.* **1995**, 1019–1028.

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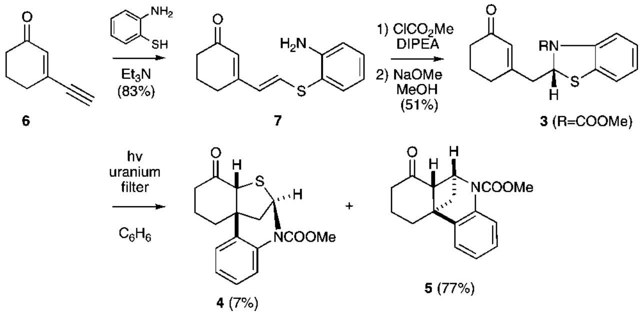
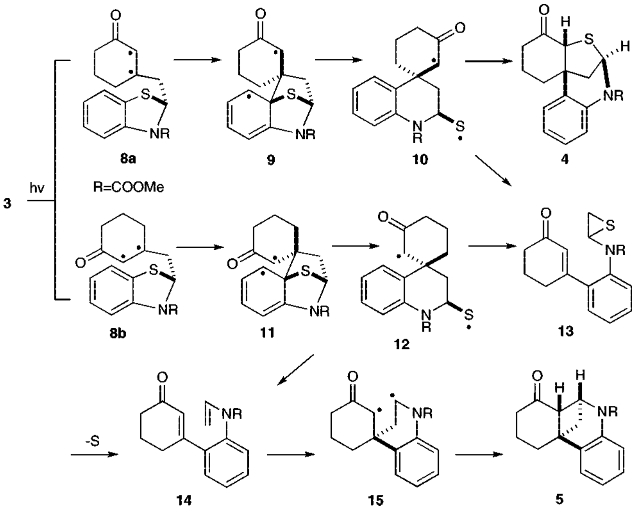
Scheme 2. Formation of Cyclobutane Photoadduct **5**



expected product **4** in only 7% yield, accompanied by the formation of **5** as the major product (77% yield).[5]

Separate irradiation of **4** (uranium filter, benzene, 2 h) does not lead to the formation of **5**, establishing that the expected thiolane product is not an intermediate in the formation of the observed cyclobutane. A mechanistic proposal that is consistent with the formation of both **4** and **5** from **3** is outlined in Scheme 3.

Scheme 3. Mechanistic Proposal for the Formation of **4** and **5**

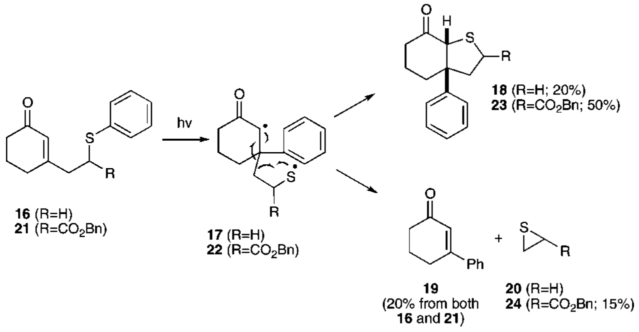


We propose that the triplet of enone **3**, shown in conformations **8a** and **8b**, can react at the ipso position of the benzothiazoline to give **9** and **11**, respectively. Rearomatization with concomitant ejection of the thiyl radical would give **10** and **12**, respectively. Diradical **10**, in which the sulfur radical and the α-keto radical are *cis* on the reduced quinoline ring, can undergo recombination to afford the expected photoproduct **4**, along with episulfide **13**, which would result from homolytic fragmentation of the indicated σ-bond in **10** (red). However, the *trans* stereochemical relationship between the radical centers in **12** precludes carbon−sulfur bond formation but could still lead to the formation of episulfide **13**. Extrusion of sulfur from **13** can then lead to the formation of enecarbamate **14** (R = COOMe).[6] Alternatively, Grob-like fragmentation of **10/12** could lead to the direct formation of **14** with loss of elemental sulfur.

Triplet-mediated cycloaddition of **14** could then lead to the formation of the crossed[7] photoproduct **5** via **15**. Careful ^{1}H NMR analysis of the reaction mixture in the course of the irradiation of **3** revealed the presence of **14**. Isolation of **14** and its conversion to **5** in quantitative yield (uranium filter, benzene, 0 °C, 1 h) established its competence as an intermediate in the formation of **5** from **3**. Failure to observe the formation of **5** from **14** under nonphotochemical condition (benzene, 25 °C, 72 h; or benzene reflux, 1 h) suggested that the formation of **5** was exclusively due to excited-state reaction of **14**.

While the intermediacy of enecarbamate **14** could be directly observed on irradiation of **3**, the presence of the episulfide **13**, which we propose as a possible precursor to **14**, could not. In an effort to obtain evidence for the intermediacy of the episulfide, we re-examined the photoreaction of **16**, the sulfide corresponding to **1** (Scheme 4).

Scheme 4. Episulfide Formation in the Photoreaction



Irradiation of **16** led to the formation of nearly equimolar quantities of thiolane **18** and 3-phenyl-cyclohexenone **19**. The formation of the latter product is consistent with the intermediacy of episulfide **20** in the reaction, although the volatility of **20** would presumably preclude its isolation.

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[4] Heindel, N. D.; Ko, C. C. H. *J. Heterocycl. Chem.* **1970**, *7*, 1007–1011.

[5] The structure and stereochemistry of **4** were confirmed by X-ray crystallographic analysis of the corresponding sulfoxide **26**, which on chemical reduction (PBr$_3$, CH$_2$Cl$_2$, 25 °C, 100% yield) gave **4**.The structure and stereochemistry of **5** were confirmed by X-ray crystallographic analysis of the corresponding N-acetylated product, which was obtained on irradiation of **3** (R = Ac).The N-acetylated photosubstrate **3** was prepared from amine **7** by acetylation and subsequent NaOMe-mediated cyclization.Experimental details and spectral data are included in the Supporting Information.

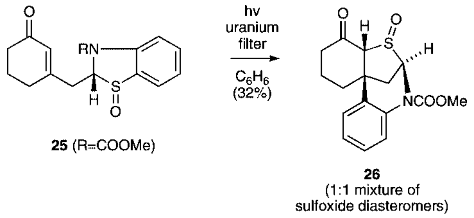
[6] For an example of photochemically mediated extrusion of sulfur from an episulfide, see: Puiatti, M.; Arguello, J.; Penonory, A. *Eur. J. Org. Chem.* **2006**, 4528–4536.

[7] Exclusive formation of the bridged cyclobutane is an exception to the empirical "rule of five" as described by: Srinivasan, R.; Carlough, K. H. *J. Am. Chem. Soc.* **1967**, *89*, 4932–4936. For an example of the observation of the crossed product as a minor component in a photochemical reaction, see: Basler, B.; Schuster, O.; Bach, T. *J. Org. Chem.* **2005**, *70*, 9798–9808. Le Blanc, S.; Pete, J.-P.; Piva, O. *Tetrahedron Lett.* **1993**, *34*, 635–638. For a clever example of a conformationally constrained system that leads to the selective formation of the crossed photoproduct, see: Crimmins, M.; Hauser, E. *Org. Lett.* **2000**, *2*, 281–284.

However, irradiation of **21**[8] led to the formation of **24**, albeit in modest yield. Furthermore, the presence of benzyl acrylate was observed by ^{1}H NMR spectroscopy during the course of the irradiation of **21**, a result that is consistent with the extrusion of sulfur from the episulfide intermediate to generate alkene. We note, however, that this result does not preclude the direct fragmentation pathway for the formation of **14** from **10** and/or **12** (Scheme 3).

Based on the results that were obtained with **16** and with **1**,[2,9] we anticipated that irradiation of **25**, the sulfoxide corresponding to **3**, would lead to the selective formation of the thiolane S-oxide corresponding to **4**, at the expense of the episulfide/enecarbamate pathway. In the event, irradiation of **25** (R = COOMe), available by *m*-CPBA oxidation of **3** (generating a single diasteromer which is assumed to be the anti compound), afforded **26** as a 1:1 mixture of diastereomeric sulfoxides in modest yield, although none of the cyclobutane product **5** could be detected in the reaction mixture (Scheme 5). Thus, the stability of the sulfur-centered radical,[10] corresponding to **10/12** in Scheme 3, appears to be a crucial factor in the formation of the cyclobutane product **4**.

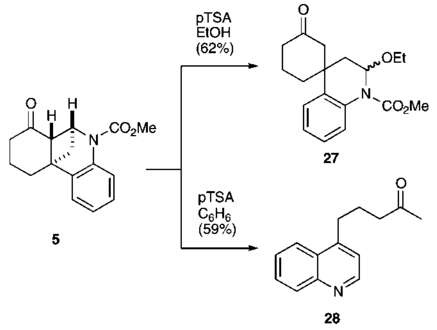
Scheme 5. Photoreaction of *S*-Oxide **20**



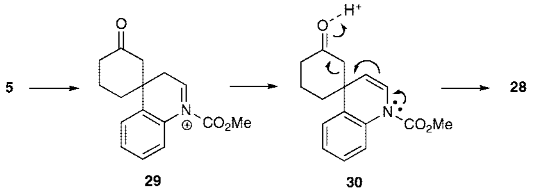
The unexpected formation of cyclobutane **5** prompted us to examine its retro-Mannich fragmentation, which could lead to the formation of spirocyclic products. In the event, exposure of **5** to pTSA in ethanol led to the formation of **27** in 62% yield, based on recovered starting material (Scheme 6). We observed a pronounced solvent effect in this reaction, as reaction of **5** with pTSA in benzene led to the formation of quinoline **28**.

The formation of **28** could result from retro-Mannich fragmentation of **5** to give **29** (Scheme 7), which on tautomerization and protonation could generate **30**, which on retro-vinylogous Mannich fragmentation and loss of the methyl carbamate would give **28**.

Scheme 6. Retro-Mannich Reaction of the Photoproduct **5**



Scheme 7. Proposed Mechanism for the Formation of **28**



In conclusion, we have discovered a novel desulfurative photocycloaddition and results that are consistent with in situ generation of an episulfide that affords an enecarbamate intermediate, which subsequently undergoes a highly regioselective "crossed" intramolecular [2 + 2] photoreaction. Further studies on the photochemistry of these enone−enecarbamate systems are underway in our laboratory, and our results will be reported in due course.

Acknowledgment. We dedicate this paper to our friend and mentor Professor Deukjoon Kim in celebration of his 60th birthday. H.J. thanks the Department of Defense for a Prostate Cancer Research Program Predoctoral Traineeship Award (W81XWH-06-1-0092).

Supporting Information Available: Experimental procedures and NMR spectra for **3**, **4**, **5**, **7**, **14**, **21**, and **24**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] The preparation of **21** is based on the related work of: Fu, X.; Zhang, S.; Yin, J.; McAllister, T. L.; Jiang, S. A.; Tann, C.-H.; Thiruvengadam, T. K.; Zhang, F. *Tetrahedron Lett.* **2002**, *43*, 573–576.

[9] Lee, E. C.-Y. Ph. D. Dissertation, University of Pennsylvania, Philadelphia, PA, 2007.

[10] Vos, B. W.; Jenks, W. S. *J. Am. Chem. Soc.* **2002**, *124*, 2544–2547.