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Intramolecular Photocycloaddition of Dioxenones with Alkynes: Formation of Secondary Photoproducts from Cyclobutene Photoadducts

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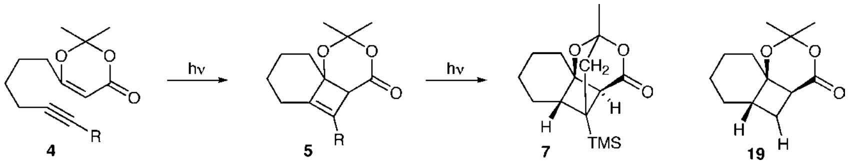
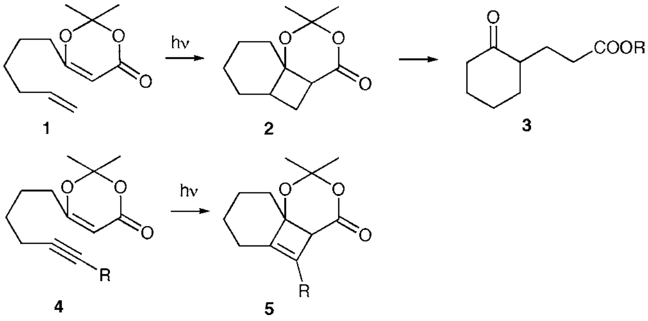
ABSTRACT



Intramolecular photocycloaddition of 4 leads to the formation of cyclobutene photoadduct 5. Secondary photoreaction of 5 then affords either cyclobutane 19 or the bridged product 7, as a function of R (H or TMS).

The intramolecular photocycloaddition−fragmentation reaction of dioxenones with alkenes affords a general approach for the synthesis of cycloalkanone propionates, as outlined in Scheme 1.[1] Irradiation of **1** leads to the formation of photoadduct **2**,[2] which on fragmentation under either acidic or basic reaction conditions generates the ketopropionate **3**.[3] The application of this methodology to the syntheses of perhydrohistronicotoxin,[2] saudin,[3] and ingenol[4] attests to the utility of this approach to the stereochemically controlled synthesis of diverse structures.

Scheme 1



We report herein that the analogous reaction of dioxenones with alkynes leads to the formation of cyclobutene photoadducts **5**, which are unstable under the photochemical reaction conditions and afford secondary photoproducts whose structures differ markedly as a function of the R substituent on the alkyne photosubstrate.

The trimethysilyl acetylenic dioxenone photosubstrate **6** (Scheme 2) was readily prepared by alkylation of the conjugate base of the commercially available 2,2,6-trimethyldioxenone with 5-trimethylsilyl-4-pentynyl iodide (LDA/THF, −78 to 25 °C, 39% yield).[5] Irradiation of **6** for 90 min [2.0 mM, 450 W Hanovia mercury lamp, 0 °C, MeCN/Me$_2$CO (9:1)] led to the formation of the bridged tetracyclic product **7** in 50% yield, the structure of which was

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(1) Winkler, J.; Mazur, C.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.
(2) Winkler, J.; Hershberger, P. *J. Am. Chem. Soc.* **1989**, *111*, 4852.
(3) Winkler, J.; Doherty, E. *J. Am. Chem. Soc.* **1999**, *121*, 7425.
(4) Winkler, J.; Rouse, M.; Greaney, M.; Harrison, S.; Jeon, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9726.
(5) Baldwin, J.; Adlington, R.; Singh, R. *Tetrahedron* **1992**, *48*, 3385.

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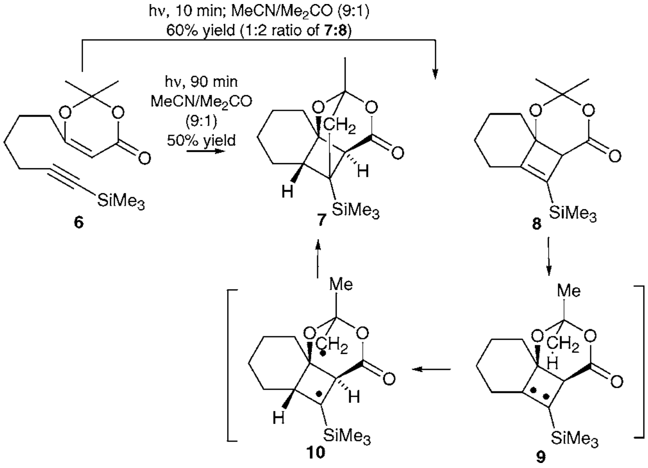
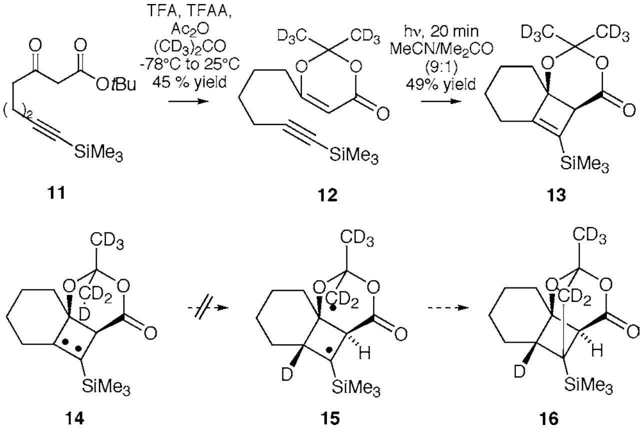
Scheme 2



unambiguously established by single-crystal X-ray analysis.[6] In an effort to determine whether **7** represented a primary photoproduct, the irradiation of **6** was examined for shorter reaction times. We were delighted to find that irradiation of **6** for only 10 min (2 mM, 0 °C) led to complete disappearance of the starting material and formation of a 1:2 mixture of **7** and **8** in 60% yield. The intermediacy of cyclobutene **8** in the formation of **7** could be unambiguously established by irradiation of **8** for 15 min to give a quantitative yield of a 1.3:1 ratio of **7**:**8**. The formation of **7** from **8** is consistent with 1,5 hydrogen atom abstraction from the excited cyclobutene **9** to give diyl **10**, which can then lead to the formation of the observed product **7**.[7]

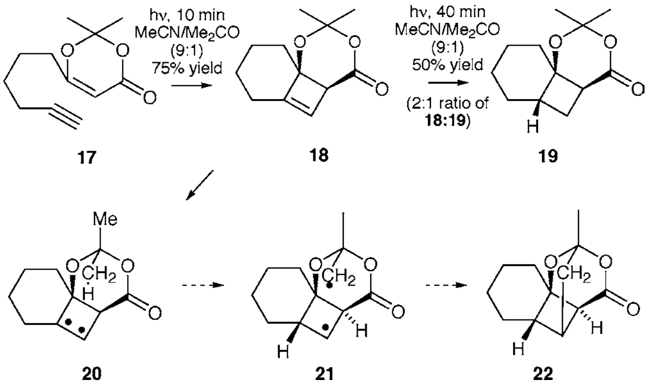
The results that we have obtained on irradiation of the deuterated photosubstrate **12** (Scheme 3) are consistent with our proposed mechanism for the formation of **7** (Scheme 2). The deuterated trimethylsilyl acetylenic dioxenone **12** was prepared via standard dioxenone formation conditions[2] from trimethylsilyl acetylenic β-ketoester **11**. Upon irradiaton of dioxenone **12**, only the primary cyclobutene product **13** was observed with none of the bridged product **16** corresponding to **7**. The absence of **16** can be attributed to the decreased homolytic lability of the carbon−deuterium bond in **14** relative to the corresponding C−H bond in **9** (Scheme 2).

Scheme 3



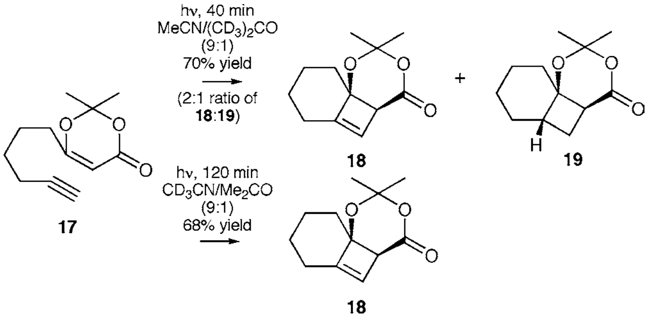
To determine the role of the silyl substituent in **6** (Scheme 2) in the formation of **7**, we examined the photocycloaddition of the desilylated alkyne **17** (Scheme 4), which was available by exposure of **6** to TBAF under carefully controlled reaction conditions (1.1 equiv of TBAF, 0 °C, 2 min). Irradiation of **17** for 10 min afforded a 75% yield of the cyclobutene **18**, which on irradiation for an additional 40 min under the same reaction conditions gave a 2:1 mixture of cyclobutene **18** and the reduced product **19** with none of the tetracyclic product **22** corresponding to **7** (Scheme 2). Having established that the trimethylsilyl group is necessary for the formation of the bridged product, we next sought to determine the source of the hydrogen atom in the photoreduced product **19**.

Scheme 4



We have examined the irradiation of **17** in both deuterated acetone and in deuterated acetonitrile, as outlined in Scheme 5. Irradiation of dioxenone **17** in deuterated acetone leads to the same mixture of products observed on irradiation of **17** in nondeuterated acetone. However, irradiation of **17** in deuterated acetonitrile leads to the formation of photoadduct

Scheme 5



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(6) All new compounds were characterized by full spectroscopic (^{1}H and ^{13}C NMR, IR, HRMS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

18 with none of the photoreduction product **19**, a result that is consistent with acetonitrile as the hydrogen-atom source in the formation of **19**. Extensive literature precedent exists for the photoreduction of $\beta-\gamma$-unsaturated ketone in which the solvent provides the source of the requisite hydrogen atoms.[8] Further studies to elucidate the mechanism of these remarkable transformations are currently in progress in our laboratory, and our results will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental procedures for the preparation of **6−8**, **11−13**, **17**, and **18** and X-ray data for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For examples of intramolecular hydrogen atom abstraction and recombination in the excited state, see: (a) Herz, W.; Nair, M. G. *J. Am. Chem. Soc*. **1967** *89*, 5474. (b) Wolff, S.; Schriber, W. L.; Smith, A. B., III; Agosta, W. C. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1550. (c) Paquette, L. A.; Pansegrau, P.; Wiedeman, P.; Springer, J. *J. Org. Chem.* **1988**, *53*, 1461. (d) Winkler, J.; Gretler, E.; Williard, P. *J. Org. Chem.* **1993**, *58*, 1973.

(8) Mancini, I.; Cavazza, M.; Guella, G.; Pietra, F. *Perkin Trans. 1* **1994**, 2181.