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Stabilization, Isomerization and Rearrangement of Enyne [4 + 4]-Cycloadducts

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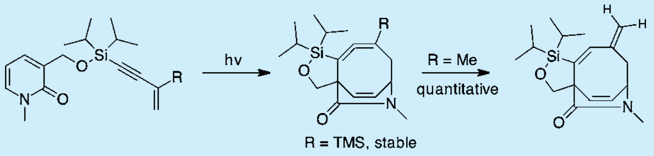
Supporting Information

ABSTRACT: Reactive 1,2,5-cyclooctatrienes, formed by photocycloaddition of 2-pyridones with enynes, are stabilized by steric shielding, slowing or preventing an otherwise facile [2 + 2]-dimerization reaction. Diisopropylsilyl ether-tethered reactants paired with an alkene substituent (R) produce allenes that are stable (R = TMS) or that isomerize to 1,3-dienes by hydrogen migration (R = alkyl). Under acidic conditions, hydrolysis of the photoproduct's silyl ether can lead to a [3,3]-sigmatropic rearrangement.



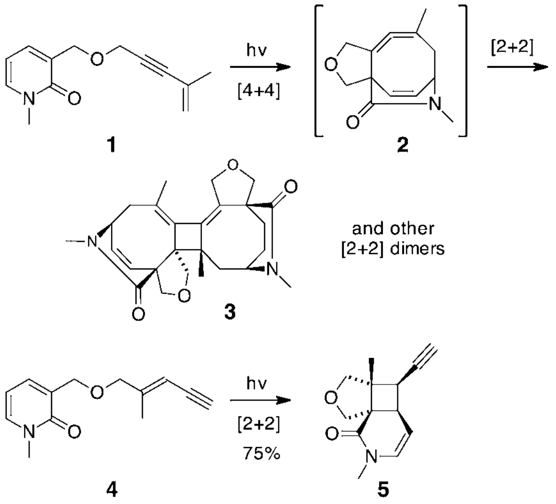
Cycloadditions are among the most efficient and widely studied methods for synthesis[1,2] and a strategic approach for complex molecule synthesis.[3,4] Medium-ring-forming cycloadditions are uncommon, but within this context the [4 + 4]-photocycloaddition of 2-pyridones has proven to be a robust platform for construction of complex polycyclic molecules.[5] Recently we reported a new variation on pyridone photoreactivity, its [4 + 4]-cycloaddition with conjugated enynes.[6−8]

In our initial studies, enynes underwent intermolecular [4 + 4]-photocycloaddition with 2-pyridones, but the reactions proved to be complex for several reasons: both head-to-head and head-to-tail regioisomers were produced, and these strained allene products rapidly underwent a subsequent thermal [2 + 2]-cycloaddition, forming many regioisomeric and diastereomeric dimers.[6] The intramolecular version was simpler and more interesting, Scheme 1: connecting the enyne through the alkyne (e.g., **1**) gave exclusively [4 + 4]-adducts **2** whereas connecting through the alkene (**4**) gave only photo-[2 + 2]-products such as **5**.[7]

Attempts to observe the transient allenes such as **2** by IR did not bear fruit, and we therefore sought substrates that would have more intrinsic stability. Steric shielding has been used to stabilize strained allenes,[9] and so we prepared a series of more substituted photosubstrates for investigation.

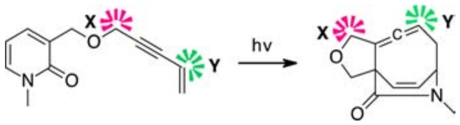
Two sites of the enyne substrate were contenders for steric shielding of the allene product, Scheme 2. The tether atom directly attached to the alkyne could bear bulky substituents (**X**), and the internal position of the alkene could also carry substitution (**Y**). Variations at these sites were probed with both carbon and silicon groups, and the results are summarized in Table 1.

Scheme 1. Enyne−Pyridone Photocycloaddition Mode Is Dependent on the Enyne Attachment[a]



[a]Unhindered allene products undergo dimerization.

Scheme 2. Steric Shielding Options for the Strained Allene Adduct



In his studies of 1,2-cyclooctadiene chemistries, Johnson demonstrated that a single *tert*-butyl group is sufficient to stabilize and prevent its dimerization at ambient temperature.[9,10] Nevertheless, irradiation of **6a** gave trimethylsilyl-substituted product **7a** (site **Y**) that was only marginally stable, dimerizing with a half-life of 1.3 h (0.03 M).[11−13] Incorporating a diisopropylsilyl group into the tether (**6b**, site **X**) gave an allene **7b** that dimerized more rapidly, with a half-life of 0.3 h. Combining these **X** and **Y** substitutions gave substrate **6c** that produced a single, rather stable allene photoproduct **7c**, with an ambient temperature half-life of 133 h. This product did not

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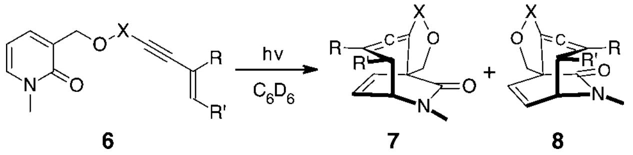
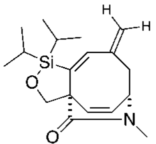
Table 1. Photoproduct Diastereomers, Properties, and Fate



substrate	X	R	R′	adduct	$t_{1/2}$ (h, rt)[a]	IR (cm^{-1})[b]	fate[c]
6a	CH_2	$SiMe_3$	H	**7a**	1.3	–	D
6b	i-Pr_2Si	H	H	**7b**/**8b**	0.3	–	D 27%
6c	i-Pr_2Si	Me_3Si	H	**7c**	133	1874	C
6d	i-Pr_2Si	CH_3	H	(**7d**/**8d**)	nd[d]	–	I 65% (**9**)
6e	i-Pr_2Si	CH_2OH	H	**7e**/**8e**	41	1898	D
6f	i-Pr_2Si	cyclopropyl	H	**7f**	4.5	1806	I 58% (**10**), D
6g	i-Pr_2Si	CH_3	CH_2OH	**7g**/**8g**	83[e]	1903	D
6h	i-Pr_2Si	$-(CH_2)_4-$		**7h**/**8h**	78[f]	1893	I 6% (**11**), D

[a] Initial concentration of **6** of 0.03 M.[13] [b] Allene IR absorbance; see Supporting Information. [c] C = Cope rearrangement, D = [2 + 2]-dimerization, I = isomerization of 1,2-diene to 1,3-diene. Total yields for isolated products are indicated. [d] nd = no data as primary [4 + 4]-adduct was not observed. [e] Products are unstable to air. [f] Continuous irradiation leads to apparent photodegradation.



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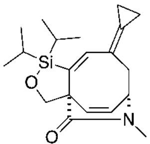

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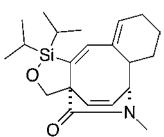

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dimerize but instead underwent a rearrangement reaction, *vide infra*.

A series of additional diisopropylsilane substrates were tested (**d**–**h**). When the enyne was substituted with diisopropylsilyl on one end and methyl on the other, **6d**, isomerization of the presumed 1,2-diene intermediate to a 1,3-diene was observed, yielding compound **9**. This isomerization was fast, clean, and quantitative; inspection of the crude reaction mixture by ^{1}H NMR spectroscopy at any point during the irradiation (2–5 h) revealed only the presence of starting **6d** and **9**. Without shielding from the diisopropylsilyl group, dimerization of the similar intermediate **2** was sufficiently fast that isomerization to the corresponding 1,3-diene was not observed. Isolation by silica gel chromatography gave **9** in 65% yield. Surprisingly, when the methyl group was replaced with hydroxymethyl **6e**, isomerization to a 1,3-diene was not observed, only dimerization of the allene product mixture **7e**/**8e**.

Replacing the methyl group of **6d** with a cyclopropane (**6f**), with the potential for strain relief of the cyclopropane and the allene through ring expansion, gave a slightly stable allene that slowly dimerized with a half-life of 4.5 h. When the irradiation was continued beyond the cycloaddition, isomerization of the allene to a 1,3-diene was observed, yielding methylene cyclopropane product **10**, isolated in 58% yield.

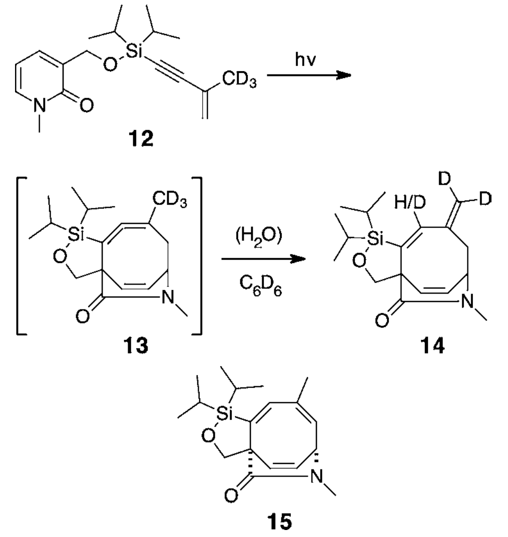
Substitution on both alkene carbons, as with photosubstrates **6g** and **6h**, gave allene products of intermediate stability, with half-lives for both of ca. 80 h. For substrate **6g**, with methyl and hydroxymethyl on the starting alkene, only apparent thermal-[2 + 2]-dimerization of the allene photoproducts was observed. With cyclohexenyl alkyne substrate **6h**, this thermal [2 + 2]-dimerization appeared to be the major reaction pathway, accompanied by isomerization to give **11** after extended irradiation, isolated in 8% yield.

With allenes that were sufficiently long-lived, **7c** and **7**/**8e**–**h**, the IR spectrum contained an absorbance in the region 1806–1902 cm^{-1}, consistent with a twisted allene structure. In addition, **7c** and **7e**/**8e** were found to have ^{13}C NMR absorbances of 210 and 206 ppm, respectively, consistent with the central allene carbon. We have not been able to purify these two compounds by standard methods, but solutions can be stored at −25 °C for weeks without change.

Isomerization of the 1,2-diene intermediates **7**/**8d** and **f** to the corresponding 1,3-dienes could proceed by several different processes. In principle an antarafacial 1,3-hydrogen shift is possible, but the thermal version of this reaction has a very high energy barrier.[14−17] Johnson has reported examples of photochemical isomerization of allenes, possibly accessing a suprafacial pathway.[10,18] This isomerization route is consistent with our observation that cyclopropyl-substituted **7**/**8d** undergoes a 1,3-hydrogen shift to give **10** only when irradiated. Without irradiation, products **7**/**8d** undergo dimerization only.

An ionic mechanism, of either the ground or the excited state allene, could result in exogenous hydrogen addition to the allene rather than hydrogen migration from the methyl group. Johnson found that addition of a Brønsted acid to 1-*tert*-butyl-1,2-cyclooctadiene produced isomerization to the corresponding 2-*tert*-butyl-1,3-cyclooctadiene.[9] To evaluate the origin of the hydrogen in **9**, we prepared trideuteromethyl substituted enyne **12** and subjected it to our standard photocycloaddition method in C_6D_6 (Scheme 3). Under anhydrous conditions the resulting isomerized product **14** was found to be 86% trideuterated and 14% dideuterated. When the C_6D_6 solvent was saturated with H_2O, **14** was found to be only 10% trideuterated. These results are consistent with a largely ionic mechanism for the isomerization of the allene adduct **13**. In no case did we obtain the isomeric hydrogen migration product **15**, which is more thermodynamically favorable.[19] It is likely that the absence of isomer **15** is due to an unfavorable overlap of the methylene proton bonds with the allene orbitals whereas the methyl and cyclopropyl groups leading to **9** and **10** can readily align their C−H bonds with the allene orbitals. An ionic component to this rearrangement is also suggested by the fact that hydrogen migration to give a 1,3-diene is *not* observed for

Scheme 3. Testing the 1,3-Proton Shift Mechanism



substrates with a more electronegative hydroxymethyl group instead of only a methyl group (**6e** and **6g**).

For photosubstrates **6a**, **c**, and **6f**, only one of the two possible stereoisomeric products were formed, Figure 1. In these cases the stereochemistry was enumerated by nOe, Figure 1. Illustrated for **7c**, a significant nOe is observed between the TMS group and one of the vinyl protons. This stereoselectivity can be rationalized as resulting from a steric clash between the TMS group and the *N*-methyl group of the amide. A related steric interaction has been invoked for intramolecular photocycloadditions of 2-pyridones and substituted furans.[20] It should be noted that this interaction may be more pronounced in the approach of the reacting chromophores than after the cycloaddition, before rehybridization of the insipient bridgehead carbons.

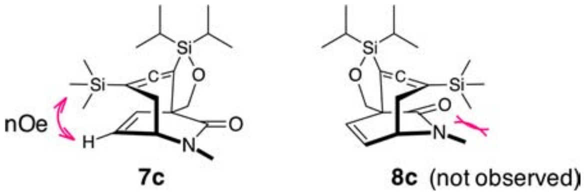
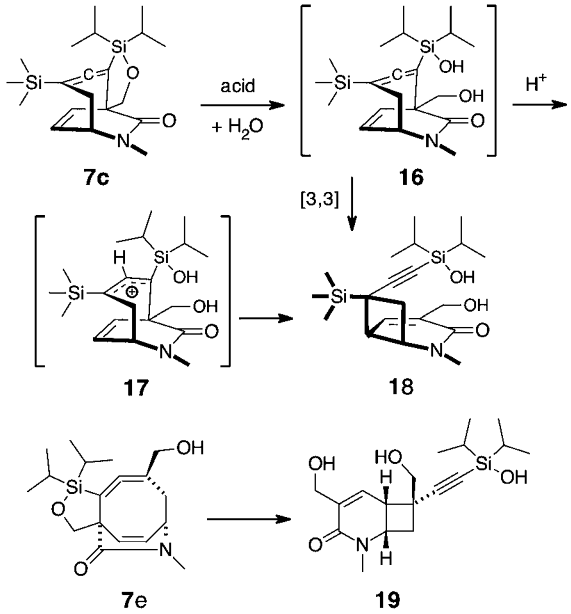


Figure 1. Photoproduct **7c** (observed) and **8c** (not observed) and the identifying nOe signal.

Attempts to isolate disilane **7c** by silica gel chromatography gave a new product, identified as cyclobutane **17**, Scheme 4. This transformation appears to involve initial hydrolysis of the silyl ether followed by a Cope rearrangement.[21,22] Hydrolysis is presumably a required first step, as heating a solution of **7c** to 65 °C overnight did not result in rearrangement. This transformation can be catalyzed by a range of Brønsted and Lewis acids, but silica gel gives the cleanest transformation, with few side products. Compound **18** was isolated in 33% yield (overall from **6c**). Similar treatment of the mixture of **7e**/**8e** gave **19** (41% yield from **6e**). It is possible that the [3,3]-rearrangement is a purely strain-promoted sigmatropic event; it is also possible that it is an acid catalyzed reaction, proceeding via the allylic cation **17**.

Scheme 4. Acid Catalyzed Hydrolysis and Cope Rearrangement



Our initial efforts to probe the potential for conjugated enynes to participate in [4 + 4]-photocycloaddition with 2-pyridones was plagued with the instability of the allene product and a facile dimerization reaction that led to complex mixtures. The examples here demonstrate that steric hindrance can stabilize these highly strained allenes. By slowing the dimerization reaction, this shielding can allow for the emergence of strain-relief pathways other than dimerization, such as isomerization of the allene to a 1,3-diene. In addition, an unusual, apparent [3,3]-sigmatropic rearrangement can occur, leading to highly substituted and stereochemically rich cyclobutane products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Wender, P. A.; Love, J. A. *Advances in Cycloaddition.* **1999**, *5*, 1−45.

(2) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25−31.

(3) Bertz, S. H. *New J. Chem.* **2003**, *27*, 870−879.

(4) Bertz, S. H.; Sommer, T. J. *Chem. Commun.* **1997**, 2409–2410.

(5) Sieburth, S. McN. Photochemical reactivity of pyridones. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; pp 103/1–103/18.

(6) Kulyk, S.; Dougherty, W. G., Jr.; Kassel, W. S.; Fleming, S. A.; Sieburth, S. McN. *Org. Lett.* **2010**, *12*, 3296–3299.

(7) Kulyk, S.; Dougherty, W. G.; Kassel, W. S.; Zdilla, M. J.; Sieburth, S. McN. *Org. Lett.* **2011**, *13*, 2180–2183.

(8) For a conceptually related strategy utilizing enyne cycloadditions, see: Robinson, J. M.; Tlais, S. F.; Fong, J.; Danheiser, R. L. *Tetrahedron* **2011**, *67*, 9890–9898.

(9) Price, J. D.; Johnson, R. P. *Tetrahedron Lett.* **1986**, *27*, 4679–4682.

(10) Price, J. D.; Johnson, R. P. *J. Org. Chem.* **1991**, *56*, 6372–6376.

(11) Irradiations were performed using a 450 W medium-pressure mercury lamp with a Pyrex filter. Additional details can be found in the Supporting Information.

(12) A trimethylsilyl group has a 20% larger volume than a *tert*-butyl group; however, the longer C–Si bond length can mitigate the steric interaction of the former. This is reflected in the *A*-values for the two substituents. See: Kitching, W.; Olszowy, H. A.; Drew, G. M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153. White, D. P.; Anthony, J. C.; Oyefeso, A. O. *J. Org. Chem.* **1999**, *64*, 7707.

(13) These estimated half-lives were determined by measuring the disappearance of the allene signals in the ^{1}H NMR spectra over time with residual solvent signal as the internal standard (C_6D_6).

(14) Pasto, D. J.; Brophy, J. E. *J. Org. Chem.* **1991**, *56*, 4554–4556.

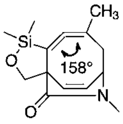
(15) Hayashi, R.; Feltenberger, J. B.; Lohse, A. G.; Walton, M. C.; Hsung, R. P. *Beilstein. J. Org. Chem.* **2011**, *7*, 410–420.

(16) Jensen, F. *J. Am. Chem. Soc.* **1995**, *117*, 7487–7492.

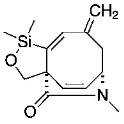
(17) Basak, A.; Gupta, S. N.; Chakrabarty, K.; Das, G. K. *Comput. Theor. Chem.* **2013**, *1007*, 15–30.

(18) Stierman, T. J.; Shakespeare, W. C.; Johnson, R. P. *J. Org. Chem.* **1990**, *55*, 1043–1047.

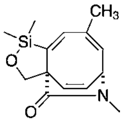
(19) The following structures, analogous to **13**, **14**, and **15** (with dimethylsilyl in place of diisopropylsilyl), have been calculated to have the following energies by AM1, Spartan 10.1. The allene is calculated to be bent by 22°. See Supporting Information.



-179 kJ/mol



-263 kJ/mol



-273 kJ/mol

(20) Chen, P.; Carroll, P. J.; Sieburth, S. McN. *Org. Lett.* **2010**, *12*, 4510–4512.

(21) Black, K. A.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 5622–5627.

(22) Duncan, J. A.; Spongy, M. C. *J. Phys. Org. Chem.* **2005**, *18*, 462–467.