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Intramolecular Pyridone/Enyne Photocycloaddition: Partitioning of the [4 + 4] and [2 + 2] Pathways

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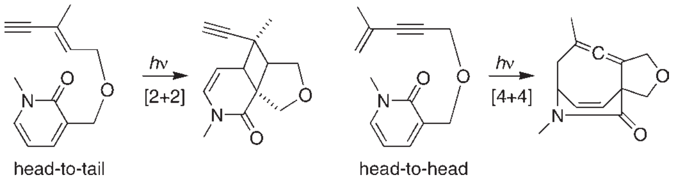
ABSTRACT



Intramolecular photocycloaddition (>290 nm) between a 1,3-enyne and a 2-pyridone is far more selective than the intermolecular version; a three-atom linkage both controls regiochemistry and separates the [2 + 2] and [4 + 4] pathways. All four head-to-head, head-to-tail, tail-to-head, and tail-to-tail tetherings have been investigated. Linkage *via* the ene of the enyne leads to [2 + 2] products regardless of alkene geometry, whereas linkage through the yne results in [4 + 4] cycloadducts. The bridged 1,2,5-cyclooctatriene products of [4 + 4] cycloaddition are unstable and undergo a subsequent [2 + 2] dimerization reaction.

Pyridone photoreactivity is dominated by [4 + 4] dimerization reactions and, at low concentrations, 2-pyridones will undergo isomerization to Dewar-pyridones, processes that occur via a short-lived singlet excited state.[1] When mixed with 1,3-dienes, furan, and napthalene, they can also undergo cross-[4 + 4] cycloadditions.[2]

We recently reported the first [4 + 4] cycloadditions of enynes, performed by irradiation of an enyne/2-pyridone mixture, Scheme 1.[3−5] This reaction of commercially available reagents yields a rich mixture of products, derived from a competition between [2 + 2] and [4 + 4] pathways, both of which produce an array of regio- and stereochemical isomers. Of the six potential constitutional isomers **3**–**8**, examples of all but **8** were isolated. Adding yet another layer of complexity, the 1,2,5-cyclooctatriene products **3** and **4** were apparently unstable, giving [2 + 2] dimers (Scheme 2). The viability of the enyne [4 + 4] cycloaddition however, was demonstrated.[6]

The postphotocycloaddition dimerization of 1,2,5-cyclooctatrienes **3** and **4**, Scheme 2, dramatically enhances

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

(2) Sato, E.; Ikeda, Y.; Kanaoka, Y. *Liebigs Ann. Chem.* **1989**, 781–788. Sato, E.; Ikeda, Y.; Kanaoka, Y. *Heterocycles* **1989**, *28*, 117–120. Sieburth, S. McN.; Zhang, F. *Tetrahedron Lett.* **1999**, *40*, 3527–3530. Sieburth, S. McN.; McGee, K. F. J.; Zhang, F.; Chen, Y. *J. Org. Chem.* **2000**, *65*, 1972–1977.

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

(4) For examples of photosensitized intramolecular cycloaddition of alkenes and alkynes with 2-pyridones, see: Somekawa, K.; Oda, H.; Shimo, T. *Chem. Lett.* **1991**, *12*, 2077–2078. Somekawa, K.; Okuhira, H.; Sendayama, M.; Suishu, T.; Shimo, T. *J. Org. Chem.* **1992**, *57*, 5708–5712.

(5) For triplet-mediated intermolecular photocycloaddition of 1,3-enynes with enones, and related chemistry, see: Witte, B.; Margaretha, P. *Org. Lett.* **1999**, *1*, 173–174. Witte, B.; Meyer, L.; Margaretha, P. *Helv. Chim. Acta* **2000**, *83*, 554–561. Schwebel, D.; Margaretha, P. *Helv. Chim. Acta* **2000**, *83*, 1168–1174. Soltau, M.; Göwert, M.; Margaretha, P. *Org. Lett.* **2005**, *7*, 5159–5161. Inhülsen, I.; Margaretha, P. *Org. Lett.* **2010**, *12*, 728–730. Vallée, M. R.; Inhülsen, I.; Margaretha, P. *Helv. Chim. Acta* **2010**, *93*, 17–24.

(6) The initially formed bridged 1,2,5-cyclooctatrienes **3** and **4** are highly strained and most likely have allenes that are substantially bent, possibly as much as 20°; see: Price, J. D.; Johnson, R. P. *Tetrahedron Lett.* **1986**, *27*, 4679–4682. Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111–1124. Daoust, K. J.; Hernandez, S. M.; Konrad, K. M.; Mackie, I. D.; Winstanley, J.; Johnson, R. P. *J. Org. Chem.* **2006**, *71*, 5708–5714.

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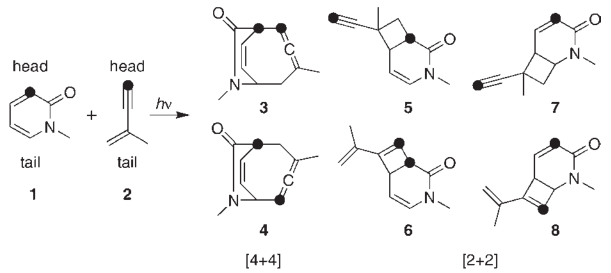
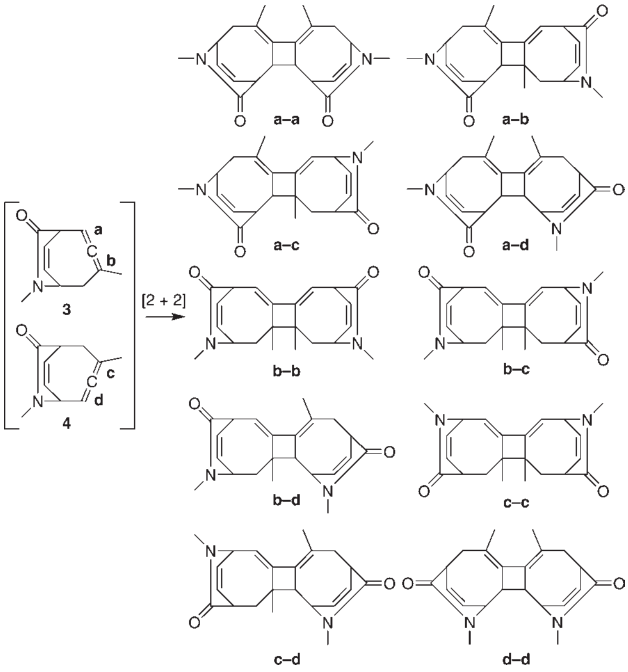
Scheme 1. Intermolecular Pyridone–Enyne Photocycloadditions[1]



the reaction complexity. With two diastereomers for both **3** and **4**, each with two different alkenes (**a**–**d**), their [2 + 2] dimerization can lead to a set of ten [2 + 2] combinations, each with six stereogenic centers, and up to eight possible diastereomers. More than 70 racemic [2 + 2] adducts from the dimerization of **3** and **4** are possible. From this complex mixture, examples of **5**, **6**, **7**, and several dimers were isolated. A crystal structure of an **a**–**d** dimer was obtained.[3]

Scheme 2. Dimerization of **3** and **4**



Control of regiochemistry was expected to substantially reduce the product diversity. Selection for only head-to-head regioisomers, for example, would eliminate **4**, **5**, **7**, and **8** (Scheme 1). With only one allene **3** formed, [2 + 2] dimerization would lead not to ten possible cyclobutanes (Scheme 2), but "only" three, **a**–**a**, **a**–**b**, and **b**–**b**. We report here that tethering the reacting components leads to much more than regiocontrol; it also separates the [2 + 2] and [4 + 4] pathways.

To explore the viability of intramolecularity for control of enyne cycloaddition, we have investigated seven tethered enyne–pyridone substrates, Figure 1, representing all four possible linkages between these two unsymmetrical reaction partners, as well as (*E*) and (*Z*) isomers of the alkene-linked **11** and **12**. In our description of the photosubstrates **9**–**12**, the first head/tail refers to the pyridone substitution, and the second head/tail refers to the enyne attachment. The presence or absence of nitrogen substitution on these substrates was not expected to affect the photochemistry[1] and was dictated by the ease of photoproduct separation. In all cases, the substrates were prepared by Williamson ether synthesis (see Supporting Information).

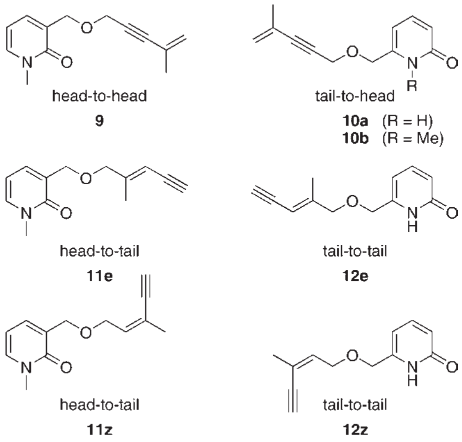
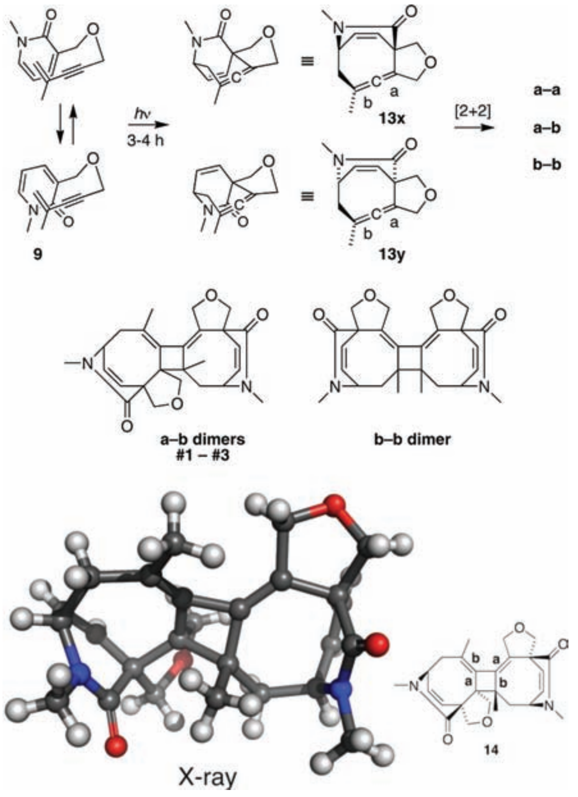


Figure 1. Four three-atom tethered enyne–pyridone substrates.

Irradiation of head-to-head **9** as a 0.03 M solution in C_6D_6 using a Pyrex-filtered 400 W medium-pressure mercury lamp gave a mixture of four major products, all presumably derived from allenes formed by [4 + 4] cycloaddition, Scheme 3. These compounds were present in a ratio of 10:8:4:5 (NMR). Chromatographic separation gave these in yields of 28%, 10%, 10%, and 4%, respectively (52% total isolated yield). The first three products were identified as **a**–**b** dimers along with one **b**–**b** dimer. The dominant product structure was determined by X-ray crystallography as **14**, an unsymmetric dimer between identical allenes but combining two different allene double bonds. The methyl group on the enyne of **9** becomes an allene substituent in **13**. Dimerization of the allene places the methyl group on an alkene and/or a saturated cyclobutane carbon. This allows one to distinguish between the possible [2 + 2] products by NMR. The proton NMR spectrum of **14** and two other dimers have one methyl singlet at 1.55 (±0.02) ppm, consistent with attachment to an alkene, and one methyl singlet between 1.34 and 1.22 ppm, consistent with attachment to an sp^3 carbon. These can therefore only be **a**–**b** dimers. The fourth product is a symmetric dimer, with only eleven signals in the ^{13}C NMR spectrum. The proton NMR chemical shift of the methyl signal at 1.29 ppm is consistent with a **b**–**b** dimer.

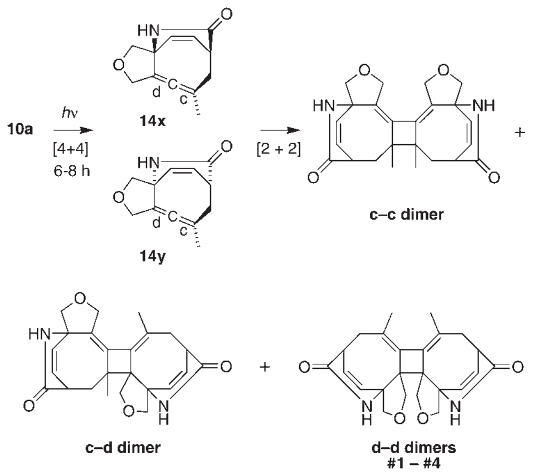
Similarly, irradiation of the tail-to-head substrate **10b** gave a mixture of dimeric products, but these proved to be

Scheme 3. Head-to-Head Photochemistry of **9** Gave a Mixture Derived from [4 + 4] Products, including **a**–**b** Dimer **14**



very difficult to separate. Irradiation of **10a**, without a nitrogen substituent, gave a separable mixture, Scheme 4. During irradiation an insoluble isomer precipitated from solution and was isolated by filtration in 36% yield. This proved to be an unsymmetric **c**–**c** dimer. Five additional (soluble) dimeric products were found, in a ratio of 12:10:3:10:3 (NMR), and these were isolated in yields of 7%, 6%, 3%, 7%, and 4%, respectively (63% total isolated yield). Once again, the identity of the cyclobutane isomers was discernible from the chemical shift of the methyl singlets (see above): one **c**–**c** dimer, one **c**–**d** dimer, and four **d**–**d** dimers.

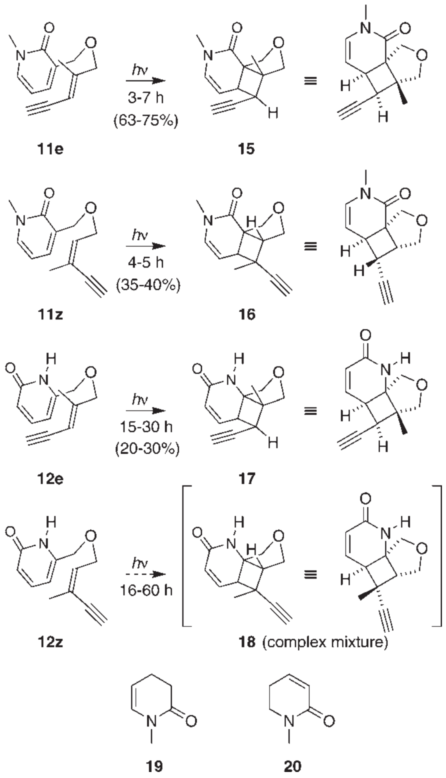
Scheme 4. Dimerization of **3** and **4**



It is notable that in the photochemistry of head-to-head **9**, Scheme 3, dimerization of the photoadduct gave only four major products and did not lead to significant quantities of **a**–**a** products. In contrast, tail-to-head **10a** (Scheme 4) gave isolable yields of all possible alkene combinations, one **c**–**c**, one **c**–**d**, and four **d**–**d** dimers, but only six major products. In each case, far fewer than the 20 possible allene dimers were formed.

For the photosubstrates tethered from the alkyne end of the enyne, little or no [2 + 2] product was discernible. In contrast, when the enyne was tethered through the alkene, [2 + 2] adducts were formed, to the near exclusion of [4 + 4] products, Scheme 5.

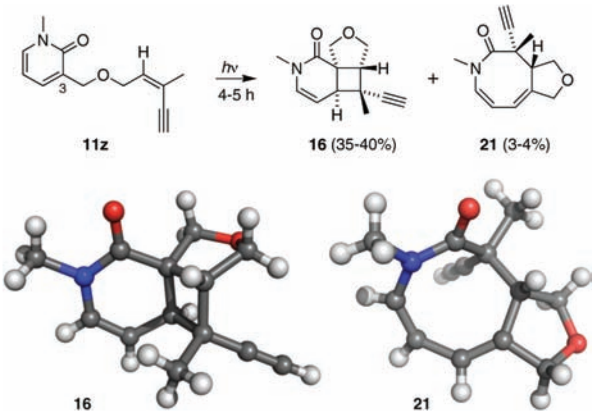
Scheme 5. Alkene-Tethered Substrates Yield [2 + 2] Products



For (*E*) and (*Z*) isomers of the head-to-tail substrates **11e** and **11z**, irradiation for 3–7 h gave one major product each, **15** and **16**, respectively. Product **15** was isolated in 63–75% yield, and **16** was isolated in 35–40% yield. In each case the alkene geometry was retained in the product. The stereochemistry of **16** was verified by both NOE studies and an X-ray crystal structure (see Scheme 6).

Tail-to-tail substrates **12e** and **12z** were significantly lower yielding substrates. Compound **12e** required irradiation for at least 15 h and gave the [2 + 2] adduct **17** in 20–30% yield, while **12z** required up to twice as long an irradiation time and gave only a complex mixture from which no pure product could be isolated.

Scheme 6. Crystal Structures of **16** and **21**



One additional product was isolated from photocycloaddition of **11z**, albeit in low yield. X-ray crystallography of both products from **11z** allowed determination of their structures, Scheme 6. These confirmed that the major product was a [2 + 2] adduct retaining the alkene stereochemistry of **11z**. It also revealed that the minor product was an eight-membered ring in which the alkene had inserted between the pyridone carbonyl and C3 of the pyridone, structure **21**. This interesting product, intriguingly, also retains the alkene stereochemistry of the starting enyne. The mechanism for formation of **21**, however, is not obvious.

The difference in isolated yields between substrates **11** (35–75%) and substrates **12** (0–30%) may be a function of the 3,4- and 5,6-dihydropyridone product structures, e. g., **19** and **20**. Structure **20**, the parent of **17** and **18**, retains an α,β-unsaturated carbonyl, whereas **19**, the parent of **15** and **16**, has an *N*-alkenyl amide functionality. In each case, a cyclobutane bond overlaps with the unsaturated system, and excitation of the unsaturated system would be expected to result in cleavage of that cyclobutane. Pyridone-derived cyclobutanes have been shown to undergo photocleavage reactions.[7] The literature, however, does not support this analysis. For 3,4-dihydropyridone structures such as **19**, the UV absorption is found at $\lambda_{\max} = 260$ nm ($\varepsilon \approx 5000$),[8] and a 5,6-dihydropyridone structure as in **20** has a $\lambda_{\max} = 250$ nm ($\varepsilon \approx 1500$).[9] These data suggest that the differences in the yield for photocycloaddition of **11** relative to **12** may lie in the 2-pyridone excited state and not the photoinstability of the [2 + 2] products. Kaneko observed that for some pyridones, electron-deficient alkenes would undergo [2 + 2] photocycloaddition at the 5,6-position, whereas electron-rich alkenes preferentially added to the pyridone 2,3-bond.[10] Somekawa has calculated the electronic structure of excited states of 2-pyridones and related these to site and regioselectivity.[11]

Conservation of alkene geometry in the [2 + 2] photocycloaddition of **11** and **12** contrasts with enone [2 + 2] photocycloadditions where alkene geometry is usually scrambled, a consequence of the triplet enone excited state.[12] The stereochemical integrity of the alkene in the pyridone [2 + 2] photocycloadditions discussed here is more consistent with a singlet manifold. While we have not verified the mechanism, Hammond's detailed investigation into 2-pyridone photoisomerization found that it derived from a short-lived (ca. 200 ps) singlet excited state.[13]

Three-atom tethering of an enyne to a pyridone through the alkene yields [2 + 2] products, whereas [4 + 4] products result when the alkyne is the attachment point. For the latter, a single [4 + 4]-derived allene regioisomer is produced, and dimerization of this product gave only 4–6 cyclobutanes out of a possible 20. This contrasts with the intermolecular case where 72 allene dimers are possible, and many are formed. With alkene linked substrates, photocycloaddition yields a single [2 + 2] adduct but does so in good yield only when attached at C3 of the pyridone. Investigations into this photochemistry, and applications of these photoproducts, are continuing.

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Supporting Information Available. Experimental details, characterization data, and proton NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Sieburth, S. McN.; Lin, C.-H. *J. Org. Chem.* **1994**, *59*, 3597–3599.

(8) Chiba, T.; Kato, T.; Yoshida, A.; Moroi, R.; Shimomura, N.; Momose, Y.; Naito, T.; Kaneko, C. *Chem. Pharm. Bull.* **1984**, *32*, 4707–4720.

(9) Shamma, M.; Rosenstock, P. D. *J. Org. Chem.* **1961**, *26*, 718–725.

(10) Fujii, H.; Shiba, K.; Kaneko, C. *Chem. Commun.* **1980**, 537–538.

(11) For a recent review and discussion, see: Somekawa, K.; Odo, Y.; Shimo, T. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1447–1469.

(12) Schuster, D. I. In *Organic Photochemistry and Photobiology*; Horspool, W., Lenci, F., Eds.; CRC: New York, 2004; pp 72-1–72-24. Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297–588. Weedon, A. C. In *Synthetic Organic Photochemistry*; Horspool, W. M., Eds.; Plenum: New York, 1984; pp 61–143.

(13) Sharp, L. J.; Hammond, G. S. *Mol. Photochem.* **1970**, *2*, 225–250.