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Enyne [4 + 4] Photocycloaddition: Bridged 1,2,5-Cyclooctatrienes

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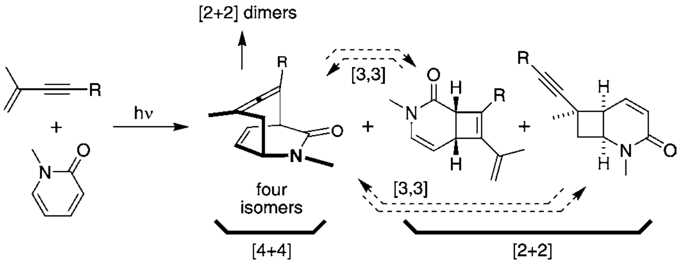
ABSTRACT



Enyne photocycloaddition with a 2-pyridone yields a mixture of products including amide-bridged 1,2,5-cyclooctatrienes, the first examples of enyne [4 + 4] adducts. Four regio- and stereochemical isomers of the [4 + 4] adduct are possible. All appear to be too strained to be isolated, but they have been identified as their [2 + 2] cyclobutane dimers. Cyclobutane and cyclobutene adducts have also been isolated, [2 + 2] addition products possibly related to the unstable [4 + 4] adducts via Cope rearrangement. Calculations suggest that [3,3] rearrangements have high energy barriers, however, making thermal interconversion unlikely.

Photochemistry is a powerful method for construction of complex and strained molecules that are otherwise inaccessible.[1] Particularly important are the synthetically potent cycloaddition reactions that have a rich history of study and implementation.[2] Our investigations of the 2-pyridone [4 + 4] photocycloaddition have been inspired, in part, by its similarities to the thermal [4 + 2] Diels−Alder reaction: both cycloadditions have a strong regioselectivity as well as an intrinsic, but less compelling, stereoselectivity.[3] Although pyridones are reluctant partners in Diels−Alder cycloadditions,[4] they undergo efficient [4 + 4] photocycloaddition reactions with themselves and with other 1,3-dienes, including cyclopentadiene, furan, and naphthalene.[5,6]

One hundred and fifteen years ago, the thermal dimerization of phenylpropiolic acid was described, a “dehydro-Diels−Alder” reaction in which an enyne portion of the phenylacetylene combines in a [4 + 2] cycloaddition to another alkyne, followed by hydrogen migration to yield a new aromatic ring.[7−9] Forty years later, C. S. Marvel found that enynes would undergo a similar reaction with maleic

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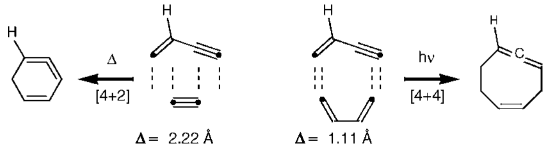
anhydride at 130 °C.[10,11] In recent years new versions of this cycloaddition have been shown to be a powerful method for construction of substituted aromatics from enynes and alkynes.[12,13]

The high temperature required for uncatalyzed enyne Diels−Alder reactions, typically 200 °C and sometimes up to 600 °C,[13,14] reflects both the distance between the reacting ends of the components and the strain of the postulated 1,2,4-cyclohexatriene initial product, Scheme 1. The span of the ground state enyne and alkyne enynophile structures are different by more than 2.2 Å. This gap between the reactive termini is approximately twice that of the facile Diels−Alder reaction between an alkyne and cyclopentadiene (1.1 Å, not shown). In comparison, an enyne/1,3-diene pairing is within 1.1 Å, and an enyne with a 2-pyridone is an even better match at 0.72 Å (not shown). It seemed possible that such a cycloaddition might lead to a bicyclic 1,2,5-cyclooctatriene product. Enyne Diels−Alder reactions have a long history,[12] and [4 + 4] photocycloadditions are even older still.[15] However, there is only one suggestion of an enyne [4 + 4] photocycloaddition, between benzene and butenyne, in which a postulated *para*-benzene adduct led to a polymeric product.[16] Nevertheless, the 1,2,5-cyclooctatriene product would be much more stable than a 1,2,4-cyclohexatriene. We report here the photoreaction of enynes with 2-pyridone and the identification of [4 + 4] cycloaddition-derived products.

Scheme 1. Enyne as a Cycloaddition Partner with an Alkyne and with a 1,3-Diene, Comparing Distances between Reacting Ends



Cycloaddition of enyne **1** with 2-pyridone **2** can proceed through regioisomeric head-to-head and head-to-tail approaches, Scheme 2, and each has two orientations, **13**−**16**. These orientations lead to different allene chiralities, and therefore a [4 + 4] cycloaddition was expected to yield the four diastereomeric products, **7**−**10**.

An initial survey of this reaction with a mixture of *N*-methyl-2-pyridone **2** and a 20-fold excess of isopropenyl acetylene **1a**, irradiated with a water-cooled 450 W medium-pressure mercury lamp, was run to complete conversion of the pyridone (7−40 h depending on reaction solvent and scale). This led to a mixture of at least seven products, in addition to 2-pyridone dimers **11** and **12**, from which **3a** and **5a** were isolated, Table 1. These are [2 + 2] adducts between the pyridone and enyne; however, the regio- and stereochemistry of these adducts, determined by NMR spectroscopy, were also consistent with a [3,3] rearrangement origin from the postulated cycloaddition products **7** and **9**, Scheme 2.[17] Photocycloaddition of enones with enynes normally yields [2 + 2] cyclobutane products from cycloaddition of the alkene component.[18] Examples of alkyne participation to form cyclobutene products have also been observed in some cases.[19]

Other reaction products could not be cleanly separated and identified, so an alcohol was introduced with the hope of facilitating separations. Irradiation of a mixture of 4-methyl-4-penten-2-yn-1-ol **1b** and **2** also gave a complex mixture, from which **3b** and **5b** were isolated. In addition, the new product **4b** was isolated. Once again, the regio- and stereochemistry of these products were consistent with the intermediacy of a cyclooctatriene photoproduct, with **3b** and **4b** potentially formed by rearrangement of **7b** and **5b** from rearrangement of **9b**. Isolation of **3**, **4**, and **5** is consistent with, but not proof of, the intermediacy of cyclooctatrienes

Scheme 2. Four [4 + 4] Cycloaddition Diastereomers **7**−**10** and Potential Cope Rearrangements of **7** and **9**

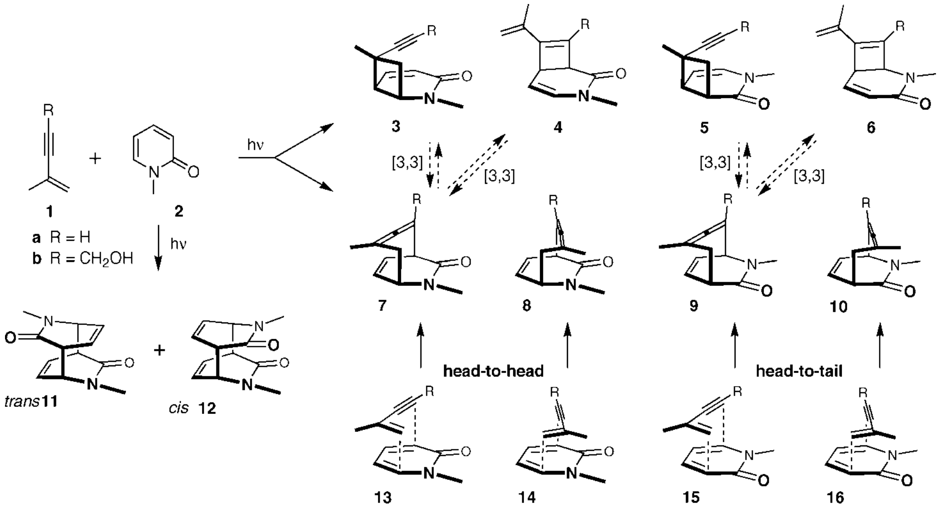


Table 1. Product Ratios[a] (Isolated Yields, %[b]) for Enyne-pyridone Photocycloaddition Products[c]

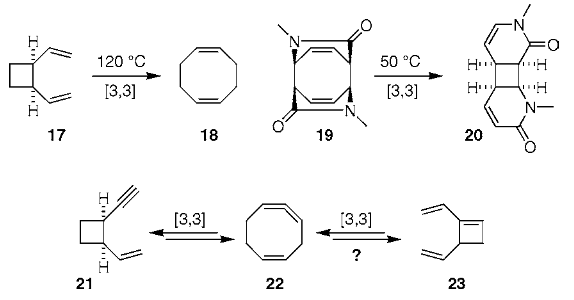
enyne	solvent	**3**	**4**	**5**	**6**	**27**	other allene [2 + 2] products	pyridone dimers **11** and **12**
1a	benzene	0.1 (0.5)		1 (7)			4−5	1−1.4
1b	benzene	3 (3−4)	1 (2.1)	10 (8)		4 (3)	4−6	20
1b	methanol	5 (1.6)	1 (2)	10 (8−9)		2 (1.8)	4−6	30

[a] By NMR. [b] Low isolated yields are largely a conseqence of repetetive chromatotraphies and product instabilities. [c] Reactions were performed in C_6D_6 or methanol-d_4 containing enyne **1** (2 M) and pyridone **2** (0.1 M), at rt or 0 °C, using a pyrex filter with a water cooled 450 W medium-pressure mercury lamp, and run until the 2-pyridone had been consumed (7−40 h).

7 and **9**; however, other cyclobutane or cyclobutene isomers have not been found in this reaction product mixture.

The unstable 1,2,5-cyclooctatrienes **7** and **9** have the potential for two Cope rearrangement paths, Scheme 2. As a reference point, the well-known 1,5-cyclooctadiene **18**/divinylcyclobutane **17** equilibrium favors the eight-membered ring **18**, but bridging the cyclooctadiene with amide groups (**19**) reverses the thermodynamics, favoring cyclobutane **20**, Scheme 3.[20,21] Although 1,2-cyclooctadiene has some stability,[22] it seems likely that the amide bridge in **7** and **9** would generate additional strain and destabilize these trienes.

Scheme 3. Thermal Rearrangements of 1,5-Cyclooctadienes



Allene-containing cyclooctatriene **22** has two possible Cope rearrangement isomers, cyclobutane **21** and cyclobutene **23**. Rearrangements of enyne **21** to **22** have been studied both experimentally and theoretically.[17,23] An interconversion between **22** and divinylcyclobutene **23**, however, appears to be new.[24] The corresponding transformation of **7b** to **4b** may therefore represent a new transformation.

To evaluate these possible rearrangements, we have calculated the energies of **24**−**26**, Figure 1, arbitrarily choosing these analogues of **3**, **4** and **7**. Alkyne **24** is calculated to be only slightly lower in energy than the allene **25**, and cyclobutene **26** is significantly lower in energy. Moreover, initial calculations of the transition state energies for these two transformations indicate the transitions are too high to be observable at ca. 25 °C, the temperature during the irradiation.[25]

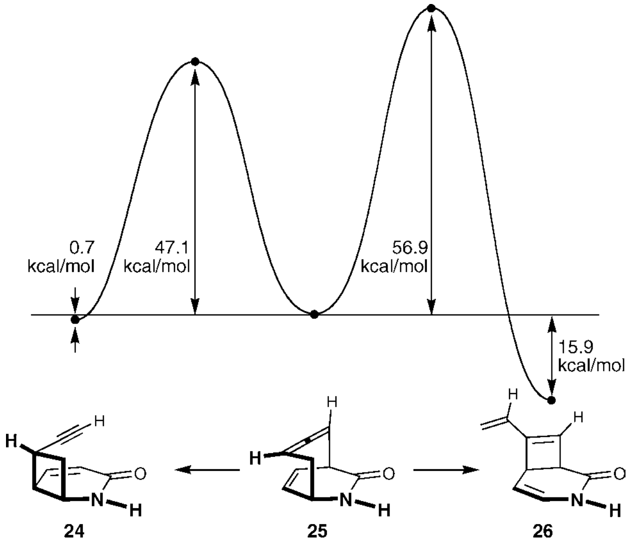


Figure 1. Calculated relative energies and transition energies for Cope rearrangement of [4 + 4] adduct **25**.[22]

Despite the high calculated activation energies for Cope rearrangement of allenes **25** (and therefore **7** and **9**), allenes were not found in the product mixture. One of the isolated products from photoreaction of **1b** and **2** was clearly dimeric, with twice the molecular weight and a doubling of each

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signal in the NMR spectra. Fortuitously, suitable crystals were obtained and X-ray crystallography found it to be cyclobutane **27**, Figure 2.[26] Structure **27** appears to be a [2 + 2] cycloaddition product of allenes **8b** and **10b**, one head-to-head [4 + 4] adduct and one head-to-tail [4 + 4] adduct. This product is a significant component of the crude photoproduct mixture (Table 1).

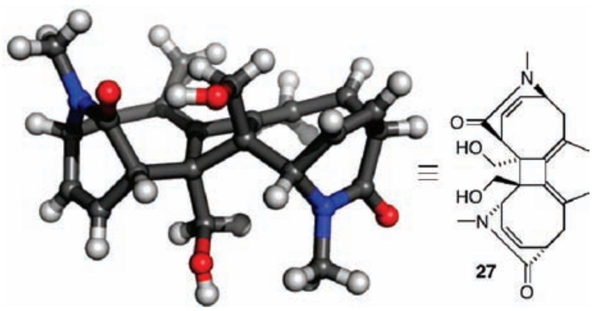

Figure 2. Allene adduct **27**, formed from **8b** and **10b**.

Strained cyclic allenes are known to undergo thermal [2 + 2] dimerization.[27] The unsubstituted 1,2,5-cyclooctatriene parent **22**, prepared by gas phase thermolysis of *cis*-1-ethynyl-2-vinyl cyclobutane **21**, undergoes [2 + 2] dimerization at ambient temperature.[17]

Dimerization of allenes similar to **8b** and **10b**, carrying four carbon substituents, has only been described for cyclopropanated and ester-substituted allenes at elevated temperatures.[28,29] That the very hindered allenes described here will undergo [2 + 2] cycloadditions under such mild conditions is consistent with a high degree of strain in these amide-bridged intermediates. This cycloaddition path also indicates that these allene isomers have some level of stability. We have not, however, been able to spectroscopically identify an allene intermediate in the reaction mixture.

Compound **27** is one of several related adducts isolated from this reaction mixture. Three others have been isolated that are apparently cyclobutane dimers related to **27** but with structures that have not been fully characterized, Figure 3. Ten [2 + 2] adducts can be anticipated between **7b**/**8b** and **9b**/**10b** (ignoring stereochemistry!), as a result of the coupling of the four different alkenes in the two head-to-head and head-to-tail [4 + 4] adducts, Figure 3. In addition to **27**, which is a **wz** example, three more purified cyclobutane isomers have been tentatively identified. One appears to be another **wz** product, but a diastereomer different from **27**. A product of the **xy** variety and a very unsymmetric **wx** dimer have also been identified (see Supporting Information).

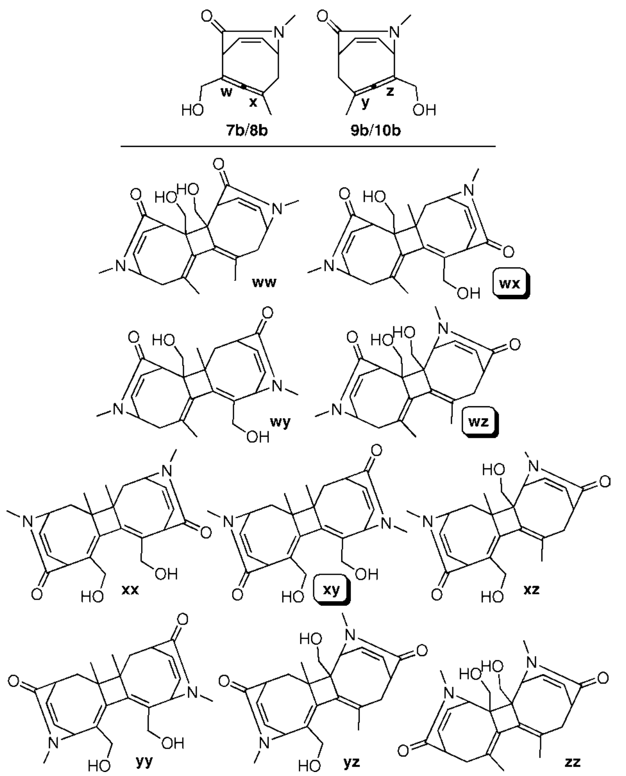

Figure 3. Possible 2 + 2 adducts from combination of two allene double bonds, ignoring stereochemistry. Two examples of the **wz** dimer have been purified, including **27**. Examples of **wx** and **xy** have also been isolated (see Supporting Information).

In the present work we have found a new higher order cycloaddition reaction that leads to strained allene products. It is possible that the excited states arrive at a conical intersection that partitions to the [4 + 4] and [2 + 2] products. Challenges for application of this new reaction include control of the product mixture and methods for productive trapping of the allene intermediates, results that will be reported in due course.

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Supporting Information Available: Experimental details, characterization data and proton NMR spectra for new compounds, and crystallographic data for **27** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[26] Compound **27** crystallized in the centrosymmetric, monoclinic space group, $P2(1)/n$, with $a = 13.688(1)$, $b = 9.8076(7)$, $c = 15.774(1)$ Å, $\beta = 90.763(3)°$, $V = 2117.4(3)$ Å^3. Data collection gave 8075 unique reflections and the goodness of fit on $F2$ was 1.016 with $R1(wR2)$ 0.0647(0.1582) for $[I\theta > 2(I)]$ and with largest difference peak and hole of 0.835 and −0.694 e/Å^3. Additional details can be found in the Cambridge Crystallographic Data Centre deposition no. 7670069. (http://www.ccdc.cam.ac.uk/).

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