Tetrahedron Letters 50 (2009) 1041–1044

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Low energy light-triggered oxidative cleavage of olefins

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ARTICLE INFO

Article history:
Received 25 June 2008
Revised 13 December 2008
Accepted 15 December 2008
Available online 24 December 2008

Keywords:
Olefin
Photocleavage
Dioxetane
Singlet oxygen

ABSTRACT

A series of substituted olefins were tested for their reactivity with singlet oxygen as a singlet oxygen-mediated cleavable linker. Low intensity light of 200 mW/cm^2 was irradiated to the solution of an olefin and 5,10,15-triphenyl-20-(4-hydroxyphenyl)-21*H*,23*H*-porphyrin under atmospheric condition. Among the tested olefins, 1,2-*cis*-diphenoxyethylene reacted fast with singlet oxygen, >80% within 15 min yielding a stoichiometric conversion to aldehyde product without any side reactions.

1. Introduction

Singlet oxygen is a toxic species in photodynamic therapy (PDT). PDT involves three main components: low energy (visible/near IR) light, oxygen, and a photosensitizer.[1] The energy of the light is transferred to triplet oxygen through a photosensitizer that generates singlet oxygen. PDT has been clinically practiced in the treatment of various diseases, such as cancers, the wet form of age-related macular degeneration, psoriasis, and acne.[2] Although PDT has been proved effective against such diseases, the mechanistic details of the reactions of singlet oxygen with bio-molecules have not been fully understood at the molecular level.

Applications of the 1,2-cycloaddition reaction of singlet oxygen have been proposed for the photo-triggerable drug delivery systems such as liposomes, cyclodextrin complexes, and prodrugs (Fig. 1).[3–7] Free drugs can be released upon the irradiation of low energy light via the cleavage reaction of singlet oxygen following the 1,2-cycloaddition reaction with olefins (Scheme 1). This strategy provides two critical advantages over other drug delivery or prodrug systems. First, the release of free drugs can be more actively controlled than in the strategies using enzymes or specific pH conditions. Second, low energy light allows practical applications of this strategy at a tissue level. High energy UV has been used for releasing drugs or biologically important molecules by UV irradiation.[8] Although the UV light cannot penetrate deeper than 1 mm into tissues, the low energy light can reach much deeper tissue, ~1 cm.[9]

Ideally, an olefinic linker should be cleaved within a short period of time without any side reactions. Although there are several reports on the kinetic study of the reactions of singlet oxygen with olefins, the irradiation conditions were not described in detail such as intensity and/or wavelength of the light at target samples.[10–16] Since intensity and wavelength of light are important for drug delivery applications, we examined various olefins to find appropriate linkers for this drug delivery strategy and to examine effects of substituents at the olefins on the rate of oxidation. In this Letter, we report the comparative yields of photo-oxidation of a series of substituted olefins after irradiation by visible light (400–800 nm) at 200 mW/cm^2.

2. Results and discussion

To evaluate oxidative cleavage of olefins, we irradiated olefins **1**–**15** in the presence of 5,10,15-triphenyl-20-(4-hydroxyphenyl)-21*H*,23*H*-porphyrin (TPP-OH) as a photosensitizer (Fig. 2). To maintain the significance of this research for biological applications, we used low intensity light (200 mW/cm^2) with a wavelength range of 400–800 nm. At the standard condition, the reaction solution was irradiated for 1 h. Experimental conditions are described in the Supplementary data. The olefins were first irradiated without TPP-OH to observe their stability in the absence of singlet oxygen generation (Table 1). All the substrates showed negligible reactivity (<1%) with atmospheric oxygen and the irradiation without TPP-OH, except for benzophenone oxime **13**, which was oxidized to benzophenone with 7% conversion. It was previously demonstrated that benzophenone oxime was slowly converted to a mixture of benzophenone and nitric acid in the presence of oxygen and moisture.

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doi:10.1016/j.tetlet.2008.12.069

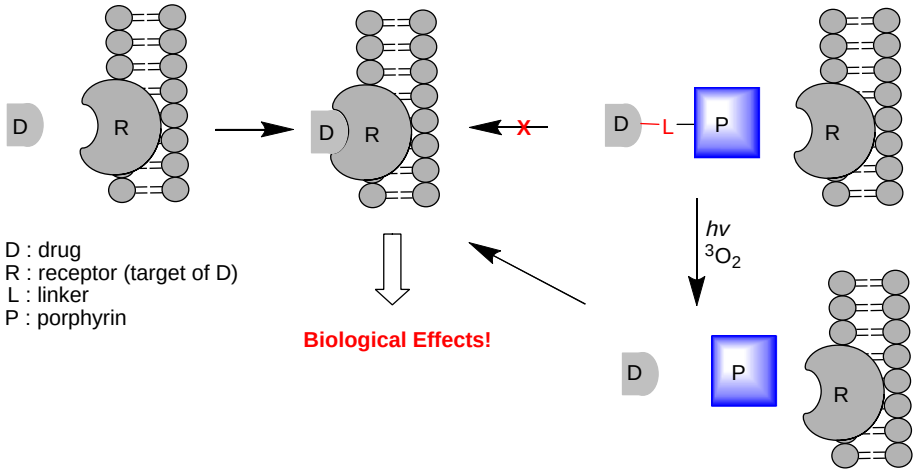
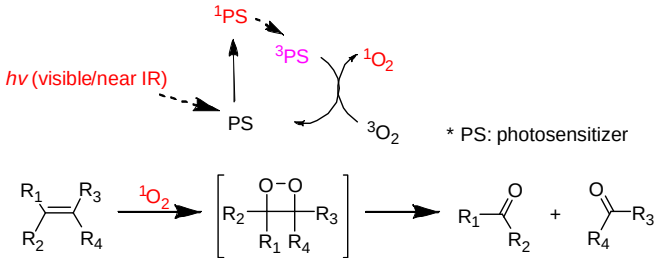


Figure 1. Singlet oxygen cleavable prodrug.

The photo-oxidation of 2,3-dimethyl-2-butene **1** resulted in the formation of 3-hydroperoxy-2,3-dimethyl-1-butene **1a** in 99% by ene reaction.[17,18] The higher reactivity of **1** with singlet oxygen, as compared to other substrates, can be attributed to its electron-rich double bond.[19] Substrate **2** was studied to observe 1,2-cycloaddition reaction with singlet oxygen yielding the dicarbonyl compounds as oxidative cleavage products. It also seemed interesting to study the effect of aryl groups as substituents on the olefin. As previously reported, singlet oxygen reaction with aryl-substituted olefins does not tend to be an accelerated process.[20] Benzaldehyde **2a** was formed as the only product in a low conversion.

Substrates **3** to **6** are vinyl ethers and diethers. Substrate **3** afforded the ene reaction product **3a** due to the presence of three hydrogens at the allylic position. The hydroperoxide **3a** was formed in competition with carbonyl compounds as oxidative cleavage products via the 1,2-cycloaddition reaction. For the carbonyl compounds, we detected only ethyl formate **3b** in the reaction mixture by ^{1}H NMR. The other product, acetaldehyde, seemed to evaporate due to its low boiling point, 21 °C. Dihydropyran **4** also exhibited a similar reactivity to the substrate **3**. The 1,2-cycloaddition reaction product **4b** was formed twice more than the ene reaction product **4a** which was consistent with previous reports.[21] However, for substrate **3**, the ene reaction product **3a** was formed slightly more than the 1,2-cycloaddition reaction product **3b**. Both substrates **5** and **6** on photo-oxidation gave high yields of the product esters **5a** and **6a**, respectively. The strong electron-donating effects of disubstituted hetero atoms O and S enhanced the reactivity with singlet oxygen.

Substrate **7** is sulfur-activated olefin and exhibited a comparatively lower reactivity than vinyl ethers **3** and **4**. Substrates **8** and **9** were chosen to compare the reactivities of dioxygen versus disulfur-substituted olefins. Substrate **8** was synthesized by the previous method.[22] Initially, **8** and **9** disappeared completely after the 1 h irradiation with TPP-OH. Hence, a time-dependent study was conducted to determine the reaction kinetics of **8** and **9**. They were irradiated for every 5 min with TPP-OH and monitored by ^{1}H NMR each time. The formation of product **8a** was directly proportional to the decrease of substrate **8** (Fig. 3). However, the conversion of substrate **9** did not show a corresponding increase of product **9a**. Product **9a** was formed in much lower yield although the starting material was consumed to a much greater extent, 88% after 15 min. There might be other oxidation products as side products which cannot be detected by ^{1}H NMR. Substrate **8** seemed to be a better linker for the singlet oxygen-cleavable drug delivery systems with respect to its reaction kinetics and side reactions. However, if the formyl group of the cleaved product (i.e., a formylated drug) is stable, it might attenuate the activity of a drug. To address this concern, the kinetics of regeneration of a phenol from the formate (**8a**) by biological nucleophiles such as amines and thiols is under investigation.



Scheme 1. Singlet oxygen generation and 1,2-cycloaddition reaction of olefin followed by cleavage of dioxetane.

N-Methyl-*N*-vinyl acetamide **10** showed a reasonable reactivity with singlet oxygen as compared to vinyl ethers (Table 1). This is probably due to the keto-amine resonance which can decrease the electron density of the π bond, thereby retarding the 1,2-cycloaddition reaction. Substrate **11** showed a higher reactivity with singlet oxygen possibly due to the availability of the lone pair electrons of nitrogen for enriching the double bond. Substrate **12** on irradiation showed complete disappearance of the starting material without any formation of the aldehyde product. However, some unrecognizable products in ^{1}H NMR were obtained in the reaction mixture.

Substrates **13**–**15** are examples of the reactivity of a π bond between carbon and nitrogen other than olefins. Substrate **13** was more reactive than **14**. On the contrary, **13** showed lower reactivity with singlet oxygen than **14** under a saturated oxygen condition and in methanol.[23] Oxidation of imine **15** gave benzaldehyde in a 16% conversion. Interestingly, **15** showed a similar reactivity to **13**.

3. Conclusion

In summary, heteroatom-activated olefins, **5**, **6**, **8**, and **9**, showed a promising reactivity with singlet oxygen, >75% conversion within 1 h. Olefins **8** and **9** were cleaved more than 80% by the irradiation of light of 400–800 nm at 200 mW/cm^2 within 15 min without oxygen saturation. 1,2-Dioxy olefin **8** seems more advantageous because the cleavage reaction does not generate any

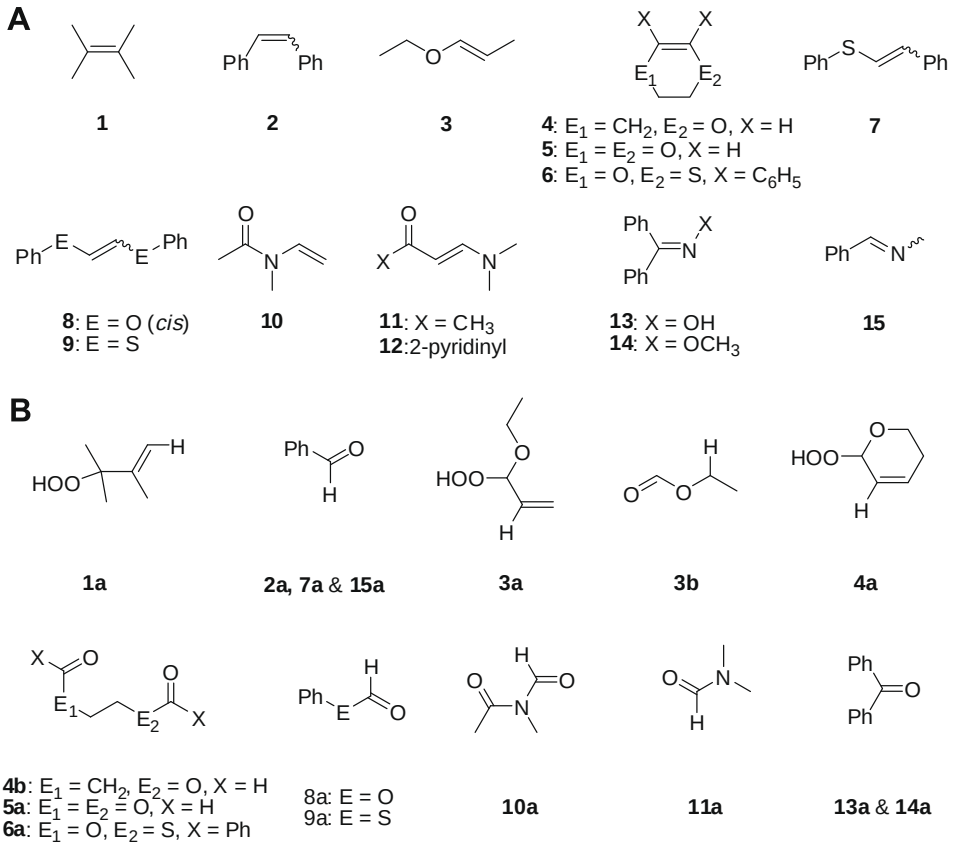


Figure 2. (A) Olefins studies for photo-oxidation, (B) photo-oxidation products of olefins **1**–**15** with hydrogen used for the quantification by ^{1}H NMR.

Table 1
Conversion of the photo-oxidation products

Olefin	Products
1	**1a** (99%)[a]
2	**2a** (11%)
3	**3a** (23%) and 3b (18%)
4	**4a** (34%) and 4b (65%)
5	**5a** (77%)
6	**6a** (99%)
7	**7a** (22%)
8[b]	**8a** (80%)
9[b]	**9a** (14%)
10	**10a** (30%)
11	**11a** (64%)
12[c]	—
13	**13a** (18%)
14	**14a** (1%)
15	**15a** (16%)

[a] Conversion determined by NMR integration from photo mixture, except substrates **6**, **13**, and **14** determined by HPLC.
[b] Substrates irradiated only for 15 min.
[c] Olefin peaks completely consumed but no aldehyde peak was observed on ^{1}H NMR.

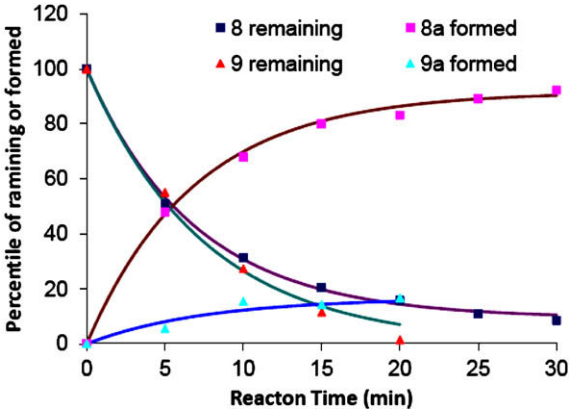


Figure 3. Comparison of reaction kinetics of **8** and **9**.

side products. Recently, Dr. Dolphin's group showed the potential of dioxy olefin as a linker for the site-specific prodrug release.[7] The low energy light-induced C=C bond cleavage reaction is practical, fast, and clean providing a new tool for drug delivery strategies.

Acknowledgment

Financial support from the South Dakota Board of Regents is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.069.

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