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Regiochemistry of Intramolecular Photocycloaddition of 1,3-Dioxin-4-ones Tethered through the Ketal Carbon.

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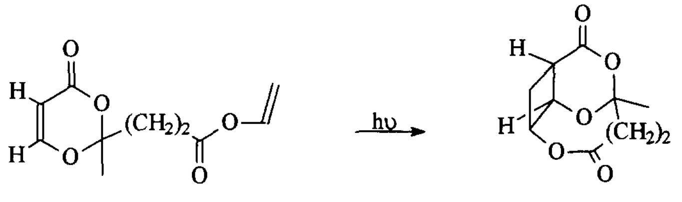
Abstract: 1,3-Dioxin-4-one photosubstrates were prepared by condensation of alkenones with ketoesters or formyl Meldrum's Acid. The resulting dioxinones contained enone and alkene chromophores, linked through the ketal carbon of the dioxinone ring. The dioxinones were irradiated and the regiochemistry of the photoproducts was established. Substrates with a two carbon tether gave head to head products, while substrates with a three or four carbon tether gave predominantly head to tail products. © 1997 Elsevier Science Ltd.

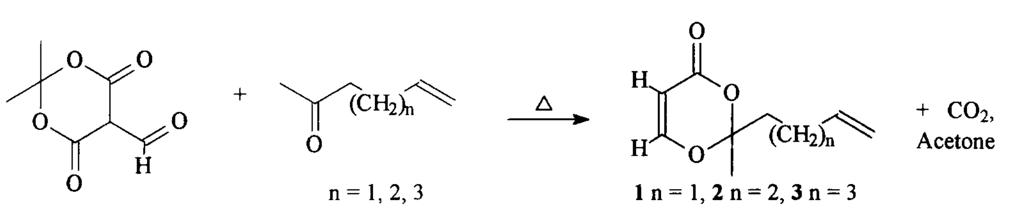
Intramolecular [2+2] photocycloaddition is a valuable reaction for the preparation of complex carbocyclic and heterocylic compounds.[1] 1,3-Dioxin-4-ones with tethered alkenes have been used in several routes to natural products. Rings are formed efficiently, and fragmentation of the dioxanone in the photoproduct can unveil functionality for further synthetic transformations.[2] The vast majority of previously reported intramolecular dioxinone photoadducts have the alkene tethered through the *alpha* or *beta* carbon of the chromophore. These photosubstrates all give fused ring products; alkenes tethered to the *alpha* carbon give head to head adducts, and alkenes tethered to the *beta* carbon give head to tail adducts, independently of the length of the tether. We were intrigued by a novel type of dioxinone substrate in which the alkene is tethered through the ketal carbon of the dioxinone. In these compounds, fused rings cannot be formed due to the point of attachment of the tethered alkene. Instead bridged structures, head to head or head to tail isomers, are possible. Our study sought to explore the regioselectivity of photocycloaddition in these compounds as a function of the length of the alkene tether.

Simple examples of this type of dioxinone have been prepared by Sato, *et al.*[3] from alkenyl esters of 4-oxopentanoic acid (Scheme 1) or pyruvic acid. In general, the substrates gave photocycloadducts with predominantly head to tail regioselectivity.

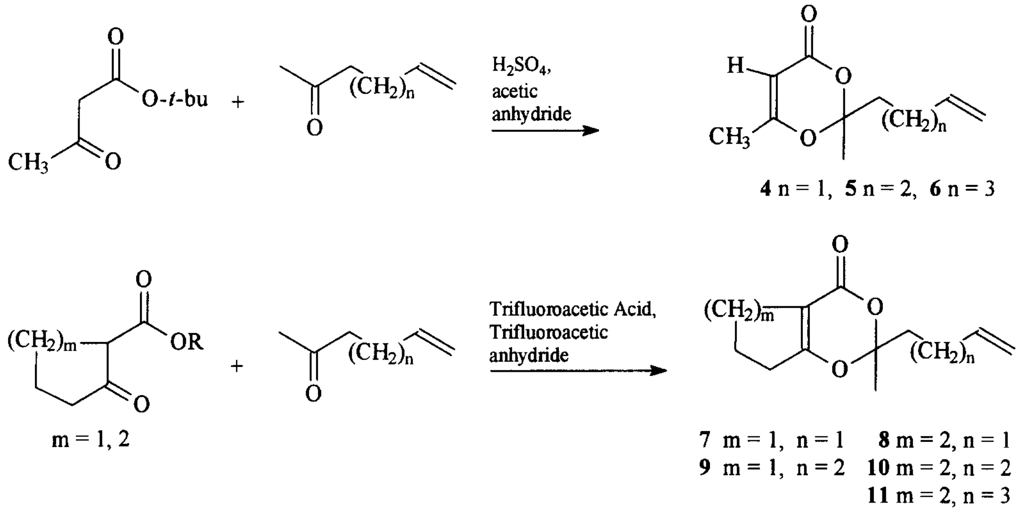


Scheme 1

We prepared several different types of dioxinone photosubstrates, using alkenones in place of the unsaturated ketoesters used by Sato. Unsubstituted dioxinone photosubstrates were prepared by the thermal reaction of formyl Meldrum's Acid[4] with alkenones (Scheme 2).[5] Other substituted photosubstrates were prepared by condensing acid-labile *t*-butyl or *p*-methoxybenzyl β-ketoesters with alkenones (Scheme 3).[6,7]



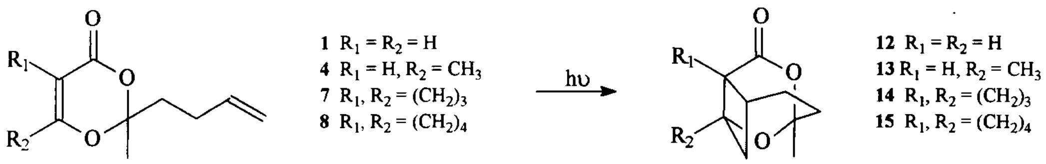
Scheme 2



Scheme 3

The substrates were irradiated,[8] and the regiochemistry of the products established by NMR spectroscopy and X-ray crystallography.

For substrates **1**, **4**, **7**, and **8** prepared from 5-hexen-2-one, the products resulting from head to head addition of the alkene to the enone were formed (Scheme 4). For **14** and **15**, X-ray crystal structures were obtained (Figure 1),[9] while for other products, the regiochemistry was established by NMR.



Scheme 4

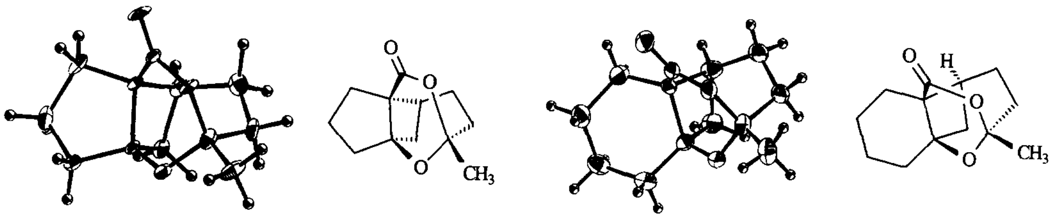
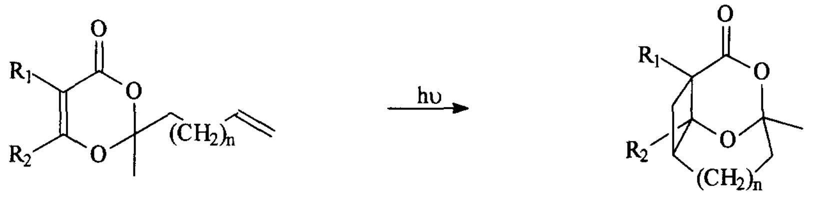


Figure 1. ORTEP[9c] Diagrams of **14** and **15**.

For substrates **2**, **5**, **9**, and **10** prepared from 6-hepten-2-one, as well as for substrates **3** and **6** prepared from 7-octen-2-one, the head to tail adduct was produced (Scheme 5).[10] For dioxinone **8**, no intramolecular photoproduct was isolated; instead a small amount of dimer from intermolecular cycloaddition was formed.



2 $n = 2, R_1 = R_2 = H$, **3** $n = 3, R_1 = R_2 = H$

5 $n = 2, R_1 = H, R_2 = CH_3$ **6** $n = 3, R_1 = H, R_2 = CH_3$

9 $n = 2, R_1, R_2 = (CH_2)_3$ **10** $n = 2, R_1, R_2 = (CH_2)_4$

16 $n = 2, R_1 = R_2 = H$, **17** $n = 3, R_1 = R_2 = H$,

18 $n = 2, R_1 = H, R_2 = CH_3$ **19** $n = 3, R_1 = H, R_2 = CH_3$

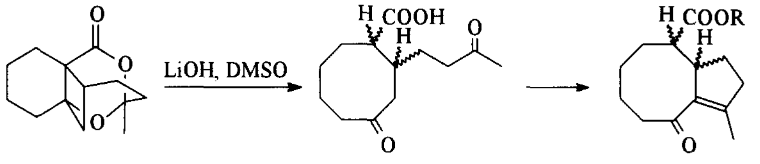
20 $n = 2, R_1, R_2 = (CH_2)_3$ **21** $n = 2, R_1, R_2 = (CH_2)_4$

Scheme 5

At first glance, comparison of the photoadduct regiochemistry found here with Sato's results shows largely similar results. For our dioxinones with longer tethers prepared from the 6-hepten-2-one and 7-octen-2-one, the regiochemistry of photocycloaddition was also head to tail. This might be expected, since these substrates and most of Sato's dioxinones have three, four, or five atoms in the tether between the ketal center and the alkene.

Two results stand out however. First, for dioxinones prepared from 5-hexen-2-one, the regioselectivity is reversed, and head to head products are formed. Secondly, one of Sato's substrates, prepared from allyl pyruvate, yields no cycloaddition product, even though this substrate has the same number of atoms (three) in the tether as our substrates based on 6-hepten-2-one. It is likely that these results are caused by different conformations of the tether and alkene, which depend upon the number of atoms in the tether, as well as the type of atom: carbons of differing hybridization, or oxygen.

We are studying the fragmentation of the dioxanone photoadducts and the subsequent conversion of these to polycylic compounds for use in the syntheses of natural products in the ophibolin and taxane families. Preliminary studies on photoadduct **15** show that it can be fragmented and cyclized to epimeric enone-acids **23**, presumably via the formation of intermediate dione acid **22** (Scheme 6). Treatment with diazomethane yielded diastereomeric enone esters **24**.[11] Further results will be reported in due course.



15 **22** **23** R = H, **24** R = CH_3

Scheme 6

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⌘ Author to whom correspondence regarding the X-ray crystal structure should be addressed.

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8. The dioxinones were irradiated in a Rayonet reactor, 300 nm mercury lamps, Pyrex filter, at 3 to 15 mmolar concentration, in 1:9 acetone/acetonitrile.
9. X-ray structure analysis. **14**: Formula $C_{12}H_{16}O_3$, MW= 208.26, monoclinic, a =7.429(3) Å, b=15.509(3) Å, c=9.181(2) Å, β=98.79°(2), space group $P2_1/n$ (#14), z=4, F(000)=448, V=1045.4(9) $Å^3$, d_c= 1.323g cm^{-3}, λ(Mo K_α)=0.71069, μ= 0.88 cm^{-1}. R=0.046, and R_w=0.052 for 840 reflections measured on the Rigaku AFC6S diffractometer, 742 unique, and 552 with Fo>3σ(Fo) considered observed. **15**: Formula $C_{13}H_{18}O_3$, MW= 222.28, orthorhombic, a =14.791(5) Å, b=13.878(4) Å, c=11.081(3) Å, space group Pbca (#61), z=8, F(000)=960, V= 2275(2) $Å^3$, d_c= 1.298g cm^{-3}, λ(Mo K_α)=0.71069, μ=0.85 cm^{-1}. R = 0.049 and R_w = 0.047 for 2603 reflections measured on the Rigaku AFC6S diffractometer of which 544 with Fo>3σ(Fo) considered observed. The structures were solved by direct methods[a] and refined by full matrix least squares. Non-hydrogen atoms were refined anisotropically. All hydrogens were located from calculated positions and refined isotropically. All calculations were performed using the TEXSAN crystallographic software package.[b] Lists of fractional atomic coordinates, displacement parameters, bond lengths and angles, and structure factor tables have been deposited at the Cambridge Crystallographic Data Center, U. K. as supplementary material. (a) Gilmore, C. J.; MITHRIL-An Integrated Direct Methods Computer Program. *J. Appl. Cryst.* **17**, 42-46, Univ. of Glasgow, Scotland (1984) (b) TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985). (c) ORTEP. Johnson, C. K.; ORTEPII. Report ORNL-5138. Oak Ridge national Laboratory, Oak Ridge, TN (1976).
10. The crude samples contained traces of materials which may be the head to head isomers.
11. The esters **24** are separable on silica gel flash chromatography.

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