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Rapid Access to Azepine-Fused Oxetanols from Alkoxy-Substituted Maleimides

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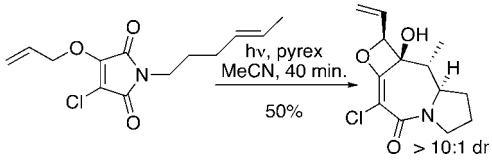
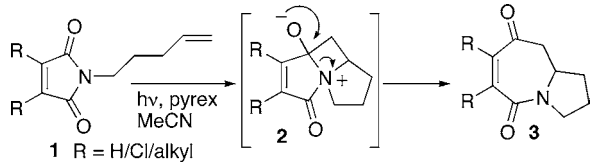
ABSTRACT



UV irradiation of alkoxy-substituted *N*-alkenylmaleimides induces a sequence involving a [5 + 2] cycloaddition followed by a Norrish–Yang cyclization. The resulting highly strained alkylidene oxetanol-fused azepines are formed in good yield and with high diastereoselectivities

Previously, we reported that *N*-pentenyl-substituted maleimide derivatives **1** undergo an efficient formal [5 + 2] cycloaddition reaction on UV irradiation.[1] The reaction has proved to be general for a range of maleimide derivatives and has recently been used by us as a key step in alkaloid synthesis.[2] The reaction is related to similar photochemistry described by Mazzocchi[3] for phthalimide derivatives and is thought to proceed by initial [2 + 2] cycloaddition to form the zwitterion **2**, which then undergoes fragmentation to the azepine **3** (Scheme 1). One limitation is that when the parent

Scheme 1. [5 + 2] Photochemical Cycloaddition of Maleimides



maleimide **1** (R = H) is used, then low yields of cycloadduct **3** (R = H) result due to further [2 + 2] dimerization.[1] In this communication, we describe the novel and unexpected photochemical behavior of methoxy-substituted maleimides and their potential advantages over previously studied maleimides in synthesis.

We sought to explore a range of substituted maleimides that would be amenable to further modification, thus rendering the resulting azepine products more useful in alkaloid synthesis.

It was found that the chloromethoxy maleimide **4** could be synthesized[4] in one pot by addition of sodium methoxide to the previously prepared *N*-pentenyl dichloromaleimide **1** (R = Cl). Irradiation of **4** for 40 min indicated that all the starting material had been consumed, and analysis of the resulting photosylate showed an almost quantitative mass balance of the tricyclic alkylidene oxetanol **5** and the [5 +

† University of Bristol.
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(1) Booker-Milburn, K. I.; Anson, E. A.; Clissold, C.; Costin, N. J.; Dainty, R. F.; Murray, M.; Patel, D.; Sharpe, A. *Eur. J. Org. Chem.* **2001**, 1473.

(2) (a) Booker-Milburn, K. I.; Dudin, L. F.; Anson, C. E.; Guile, S. D. *Org. Lett.* **2001**, *3*, 3005. (b) Booker-Milburn, K. I.; Hirst, P.; Charmant, J. P. H.; Taylor, L. H. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1642.

(3) (a) Mazzocchi, P. H.; Bowen, M.; Narain, N. *J. Am. Chem. Soc.* **1977**, *99*, 7063. (b) Mazzocchi, P. H.; Minamikana, S.; Wilson, P. *J. Org. Chem.* **1979**, *44*, 1186. (c) Mazzocchi, P. H.; Minamikana, S.; Wilson, P.; Bowen, M.; Narain, N. *J. Org. Chem.* **1981**, *46*, 4846. (d) Mazzocchi, P. H.; Khachik, F.; Wilson, P. *J. Am. Chem. Soc.* **1981**, *103*, 6498. (e) Mazzocchi, P. H.; Wilson, P.; Khachik, F.; Klingler, L.; Minamikana, S. *J. Org. Chem.* **1983**, *48*, 2981.

(4) See Supporting Information for preparation of alkoxy maleimides.

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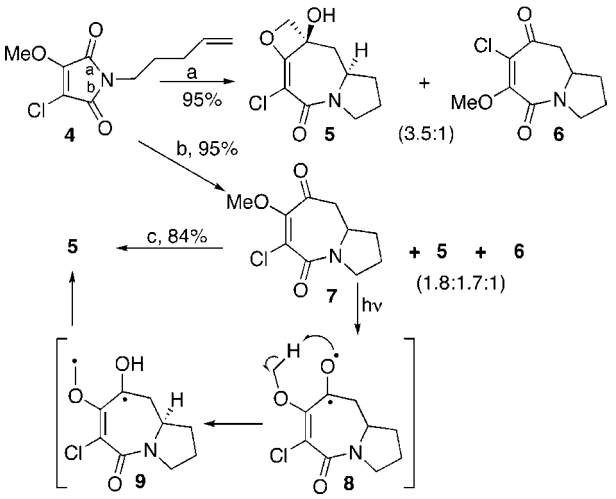
2] cycloaddition regioisomer **6** (3.5:1). It was found that **5** was actually derived from the initially formed [5 + 2] regioisomer **7**, as irradiation of **4** for just 10 min gave a mixture of **5**−**7**. Subsequent irradiation of isolated regioisomer **7** gave **5** in good yield (Scheme 2).

Scheme 2. Methoxymaleimide [5 + 2]/Norrish II Cascade[a]



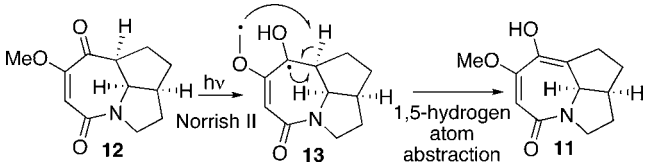
[a] Conditions: (a) *hν*, Pyrex, MeCN, 40 min; (b) *hν*, Pyrex, MeCN, 10 min; (c) *hν*, Pyrex, MeCN, 2 h.

It is most likely that **5** is formed from **7** by the Norrish−Yang sequence described in Scheme 2. Further excitation of **7** results in the formation of **8**, which undergoes 1,5-hydrogen atom abstraction (Norrish II) from the methoxy group to give the diradical **9**, which then undergoes recombination to **5**. A related reaction was observed by Feigenbaum[5] for methoxy-substituted cholestenones. Intermolecular [2 + 2] photocycloaddition onto methoxy-substituted chromones, followed by oxetane formation, has also been reported by Mal and Venkateswaran.[6] There are several noteworthy features concerning this overall sequence. First, recombination of **9** is highly stereoselective (>99% de), presumably a result of the methylene radical approaching the α-hydroxy radical from the least hindered, convex face of the azulene ring system. The methoxy group in **4** is clearly exerting a powerful directing effect on the initial [5 + 2] cycloaddition, resulting in the predominance of regioisomer **7** and ultimately **5**. In the case of **4**, cycloaddition could proceed via the two possible amide bonds "a" and "b". Cycloaddition via bond a leads to the major regioisomer **7**, whereas reaction through bond b leads to the minor isomer **6**. As carbonyl b can be considered a vinylogous carbamate, then the cycloaddition selectivity is likely to be a result of absorption differences between these two carbonyls, although detailed modeling is likely to be required to explain these differences. Mazzocchi also observed regioselective alkene insertion reactions with methoxy phthalimide, although it is interesting to note that in a vinylogous sense, the regioselectivity obtained was opposite that of the methoxy maleimides in this study.[1d,e] The initial [5 + 2] reaction of **4** is much faster than previous maleimides studied. For example, **4** undergoes complete [5 + 2] cycloaddition in under 10 min, whereas **1** (R = Me) requires 2.5 h of irradiation for complete conversion. This may be explained by the fact that the key absorption for **1** (R = Me) is in general a weak band observed in the UV spectra at around 300 nm, which is probably excited by the relatively weak 302 and 313 nm emissions from the medium-pressure mercury source used in this study. The same absorption in **4** is shifted to a maximum at around 330 nm with a continuum >370 nm. As this lies close to the most powerful Hg lamp emission at 365 nm, it is therefore likely that the excited state of **4** is populated much more efficiently than **1**. It is also likely that the weak emission at 334 nm contributes.

We then set out to explore the scope of this reaction by synthesizing a range of alkoxy maleimide derivatives and investigating their photocycloaddition reactions (Table 1). The photosubstrates were prepared by either Mitsunobu alkylation of monomethoxy maleimide[7] or by alkoxylation of the N-alkylated dichloromaleimides.[8] Generally, the various maleimides displayed the same trend with oxetane formation predominating. Excellent stereocontrol was observed in the formation of the cycloadducts where up to four contiguous centers could be formed in a single irradiation (e.g., entry 3).

The five-membered alkene substrate **10** (entry 7) proved to be very interesting, as no oxetane product was isolated. With care, the [5 + 2] enol **11** could be isolated in up to 60% yield. It is likely that the ketone carbonyl in the initially formed [5 + 2] cycloadduct **12** undergoes photoenolization faster than Norrish−Yang oxetane formation.[9] This in essence protects the ketone carbonyl from undergoing further photoreactions. This photoenolization may occur through a diradical intermediate such as **13**, where 1,5-hydrogen atom abstraction leads to enol formation instead of the oxetane (Scheme 3).

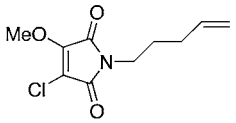
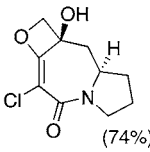
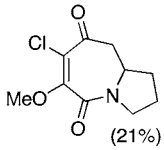
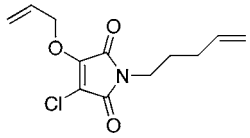
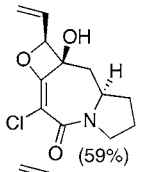
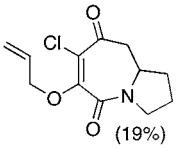
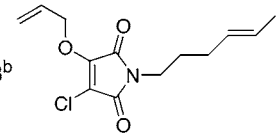
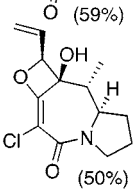
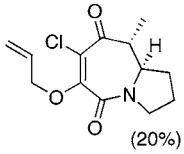
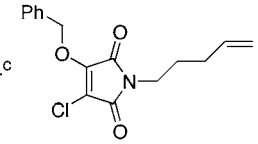
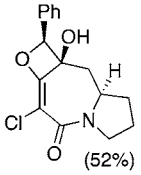
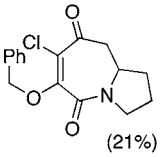
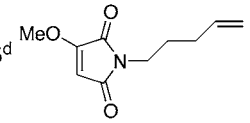
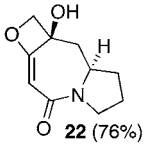
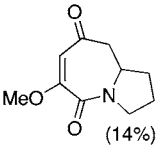
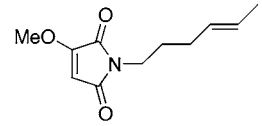
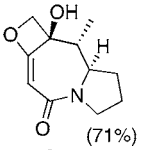
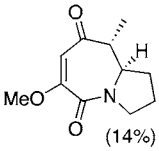
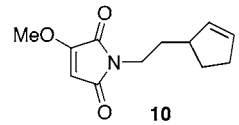
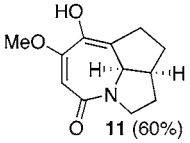
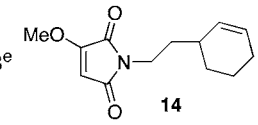
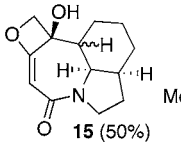
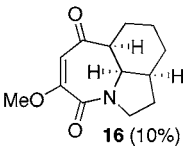
Scheme 3. Proposed Mechanism for Photoenolization



When the six-membered alkene substrate **14** was irradiated, only the oxetane **15** and the regioisomer **16** were obtained, and no sign of the enol was observed. However,

(5) Feigenbaum, A.; Pete, J. P. *Tetrahedron Lett.* **1972**, *13*, 2767.
(6) (a) Mal, J.; Venkateswaran, R. V. *J. Org. Chem.* **1998**, *63*, 3855. (b) See also: Wender, P. A.; Rawlins, D. B. *Tetrahedron* **1992**, *48*, 7033.
(7) (a) Nicolaus, R. A.; Nicoletti, R. *Rend. Accad. Sci. Fis. Mat., Naples* **1959**, *26*, 148. (b) Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352.
(8) Lynch, D. M.; Crovetti, A. J. *J. Heterocycl. Chem.* **1972**, *9*, 1027.
(9) For reference to photoenolization during Norrish−Yang cyclization, see: Wagner, P. J. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; CRC Press: Boca Raton, FL, 2004, Chapter 58, pp 1−70.

Table 1. Photochemical Cascade Reactions of Methoxymaleimides[a]

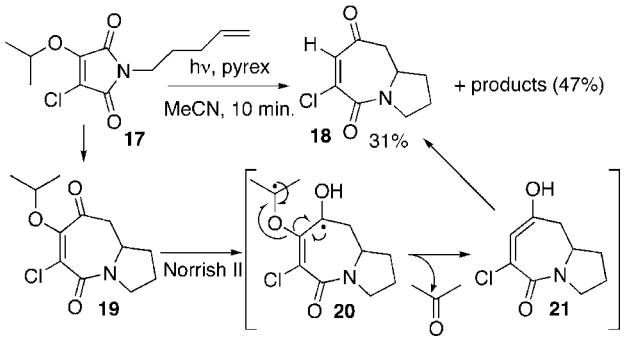
entry	maleimide	products (isolated yields)
1		 (74%)  (21%)
2		 (59%)  (19%)
3[b]		 (50%)  (20%)
4[c]		 (52%)  (21%)
5[d]		 **22** (76%)  (14%)
6		 (71%)  (14%)
7	 **10**	 **11** (60%)
8[e]	 **14**	 **15** (50%)  **16** (10%)

[a] Reactions carried out in 100 mL of MeCN at a 0.01 M concentration using a 150 mL standard immersion well (Pyrex) apparatus with a 125 W medium-pressure Hg lamp. [b] Contains minor oxetane diastereomer (>10:1). [c] Contains minor oxetane diastereomer (4:1). [d] Contains minor oxetane diastereomer (6.5:1). [e] **15** was obtained as a 1:1 mixture of diastereomers.

the 1:1 mixture of oxetane epimers obtained may indicate that the enol may also be formed photochemically but equilibrates to the more stable keto form in this case. It is interesting to note that this phenomenon would appear to be limited to methoxy maleimides, as the dimethyl analogue of **12** showed no evidence of epimerization or enolization.[1]

The isopropoxy derivative **17** proved to be very interesting, as it led to significant amounts of the dealkoxylated [5 + 2] product **18** on irradiation. Other products included the isopropoxy adduct **19**, the corresponding oxetane, and the other [5 + 2] regioisomer (47% yield as a mixture). A plausible mechanism is shown in Scheme 4 and would involve

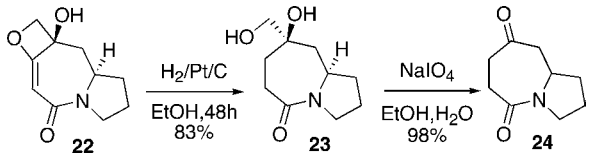
Scheme 4. Photodealkoxylation of Isopropoxy [5 + 2] Adduct



initial formation of **19** followed by Norrish II to the diradical **20**. Presumably due to increased steric demands, ring closure to the oxetane is slower than normal and a significant proportion of this diradical undergoes β-scission to the seven-membered hydroxy-allene **21**. This then would undergo tautomerization to **18**. Highly strained seven-membered allenes are not without precedent; for example, 1,2-cycloheptadiene has been prepared and trapped out in situ as a Diels−Alder adduct.[10] Although this type of fragmentation is a well-known process in Norrish II reactions of saturated alkoxy-ketones,[11] we believe that this is the first report of such a Norrish II cleavage on a vinyl group.

Finally, we investigated reduction[12] of the alkylidene oxetanol ring system in **22**, which initially proved to be resistant to cleavage by hydrogenation over Pd.[13] Hydrogenation under Pt catalysis using conditions described by Laffan for the cleavage of 3-methoxy enones[14] eventually yielded the diol **23** in high yield. Oxidative cleavage of the diol with periodate gave the keto-amide **24** in excellent overall yield (Scheme 5).

Scheme 5. Oxetane Cleavage



The reduced azepine product **24** has previously been sourced from Zn/AcOH reduction of the dichloromaleimide

(10) Bottini, A. T.; Hilton, L. L. *Tetrahedron* **1975**, *31*, 2003.
(11) Sonawane, R. H.; Bellur, N. S.; Nazeruddin, G. M. *Tetrahedron* **1995**, *51*, 11281.
(12) Reductive cleavage of saturated hydroxyoxetanes has been reported previously using metal hydride reagents; see: Bach, T.; Kather, K. *J. Org. Chem.* **1996**, *61*, 3900.

adduct **3** (R = Cl).[1] Recently, however, we have found that dichloromaleimides bearing more complex alkene substituents have proved to be troublesome [5 + 2] substrates, with much photodegradation of the products observed. It is possible, therefore, that more complicated analogues of **24** will be accessible via methoxy maleimide adducts using this oxetane cleavage sequence.

In summary, a new maleimide [5 + 2]/Norrish−Yang cascade has been reported that results in the stereoselective formation of highly functionalized azepine-fused oxetanes from simple alkoxymaleimide building blocks. One of the most important aspects of this cascade is that, unlike unsubstituted maleimides, it yields cycloadducts that do not undergo further synthetically unproductive dimerizations. These findings are likely to have a significant impact in the application of the [5 + 2] cycloaddition in alkaloid synthesis.

Acknowledgment. We thank the EPSRC (GR/R02382/01) and Novartis for a CASE award to J.R.B. We also thank Merck Sharp and Dohme and Pfizer, Ltd., for additional funding.

Supporting Information Available: Experimental procedures and characterization for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049645K

(13) Feigenbaum et al. report small amounts of reductively cleaved products on Pd-catalyzed hydrogenation of an alkylideneoxetane. The major product was the saturated hydroxyoxetane; see: Arnould, J. C.; Enger, A.; Feigenbaum, A.; Pete, J. P. *Tetrahedron* **1979**, *35*, 2501.

(14) Laffan, D. D. P.; Banziger, M.; Duc, L.; Evans, A. R.; McGarrity, J. F.; Meul, T. *Helv. Chim. Acta* **1992**, *75*, 892.