Tetrahedron Letters No. 35, pp 3227 - 3230.
© Pergamon Press Ltd. 1978. Printed in Great Britain.

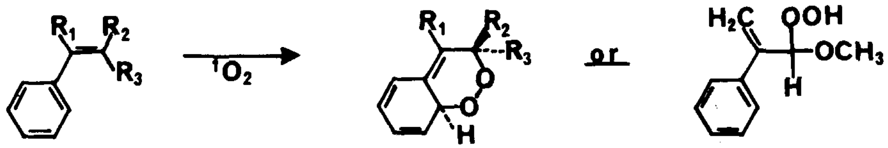
0040-4039/78/0822-3227$02.00/0

CHEMISTRY OF SINGLET OXYGEN. XXVII. DIRECTING EFFECT OF METHOXY GROUP IN ADDITIONS TO METHOXYSTYRENES

Duane Lerdal and Christopher S. Foote*
Department of Chemistry, University of California
Los Angeles, California 90024[1]

Summary: A methoxy group on a styrene double bond directs $^1O_2$ attack *cis*, giving 1,4 addition if the phenyl is *cis*, or ene reaction if a CH_3 is *cis*. If no substituent is *cis*, 1,4 attack on the *trans* phenyl occurs at a slower rate.

Recent reports on the reaction of singlet oxygen with substituted styrenes and stilbenes[2], and of a remarkable *cis* directing effect of a methoxy group[3] as well as theoretical studies[4,5] prompt us to report novel findings with six methoxystyrenes. As with similar systems[6], most of these compounds give 1,4 addition of singlet oxygen to the side chain β position and the ortho position of the ring. However, the methoxy group has a strong influence on both the rate and the product of the reaction. Compounds with a methoxy group *cis* to the benzene ring (1a, c and e) reacted rapidly (20 to 25 min) with singlet oxygen to give 1,4 cycloadduct, 2. Under the same conditions, the *trans* isomers (1b and d) gave 1,4 addition but required over 3 hours to react completely. Compound 1f, with a methyl group *cis* to the methoxy group, reacted completely within 20 min. to form the allylic hydroperoxide 3 in an "ene" reaction; no 1,4-product was observed.



2

3

(If CH_3 and CH_3O are *cis*)

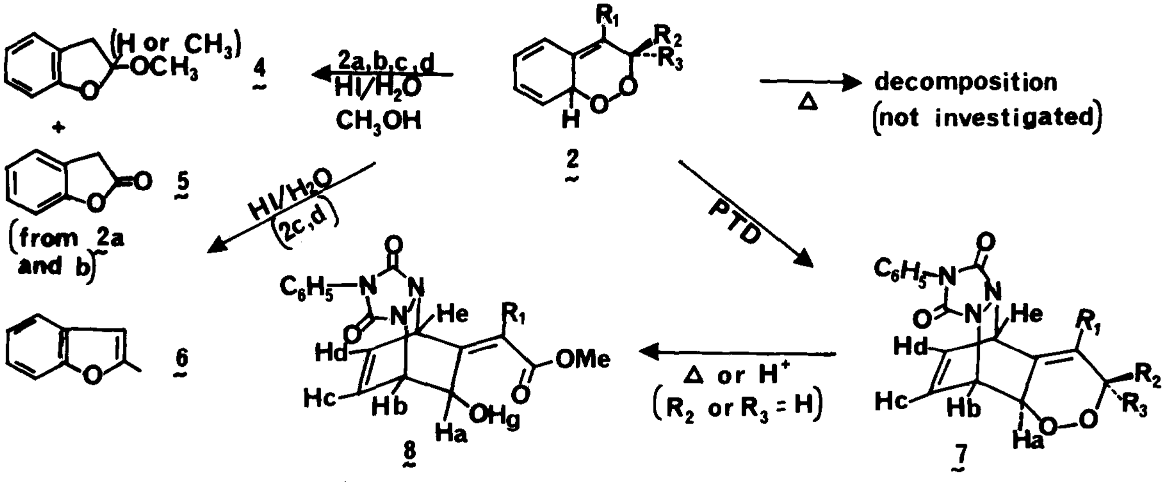
1	R_1	R_2	R_3
a	H	H	OCH_3
b	H	OCH_3	H
c	H	CH_3	OCH_3
d	H	OCH_3	CH_3
e	CH_3	H	OCH_3
f	CH_3	OCH_3	H

A solution of 1.0 mmole cis-β-methoxystyrene in 10 ml of Freon 11 containing 0.5 mg of dinaphthylenethiophene as sensitizer was photolyzed at -78° with a 650W DWY Tungsten-Halogen lamp. After 30 min, oxygen uptake stopped and 1 mmole of oxygen had reacted. Solvent was removed at low temperature; the product had UV absorption ($CHCl_3$), λ_{max} = 304 nm, ε > 8000. Woodward's rules[7] predict λ_{max} 303 nm for 2. The product decomposed at ambient temperature. Similar conditions were used for photooxidations of 1b-e. As compounds 1c and d were sensitive to hydrolysis and autoxidation, freshly prepared samples were always used.

Endoperoxides (2a-e) were not purified because of their instability, but crude yields appeared to be > 90% by nmr; the Freon could be removed at low temperature and replaced by various solvents (violent decomposition of residue on warming!). The crude peroxides were characterized by their spectra and reactions. The nmr spectra were not terribly informative; they had unanalyzable complex multiplets in the olefinic region, but no aromatic protons, and were consistent with expectation for structures 2a-e based on spectra of analogous compounds.[2,6] The methyl resonances of 2c and d appeared at 1.52 and 1.28 ppm respectively. Kondo[2] has reported the methyl resonances of the analogous products from trans and cis 1-propenylnaphthalene to appear at 1.51 and 1.21 ppm, respectively. Thus the stereochemistry of the addition of $^1O_2$ appears to give H and R_3 cis in 2, as in the case reported by Kondo[2] and similar compounds.[6]

Reduction of 2a or b with 47% HI/H_2O in CH_3OH gave 80% of the theoretical amount of I_2; ketal 4 was the major product (40% yield), along with lactone 5 (9% by nmr), formed by acid catalyzed rearrangement of peroxide 2a. Compounds 2c and d gave I_2 in 80 and 95 % yields with HI in CH_3OH, producing 4; with HI/H_2O, the main product was 2-methylbenzofuran (6) (and some phenylacetone from hydrolysis of 2). Compound 2e gave a 75% yield of I_2 and a complex reaction mixture with HI/CH_3OH, from which only 2-phenyl-2-hydroxypropionaldehyde (10%), a rearrangement product, could be isolated. These reactions establish the peroxidic nature of 2 and support the assigned structure.

In order to stabilize and identify the initial product, 2a-e, a methylene chloride solution of 1-phenyl-1,3,4-triazoline-2,5-dione (PTD) was slowly added to the cold reaction solutions until the red color of the dione persisted. The precipitates were filtered and recrystallized to give white crystals of 7a-e, whose structures were assigned on the basis of their spectral and chemical properties. Yields were ~50% in each case.



The nmr spectra (Table) show resonances with the expected positions and areas. Spin-spin decoupling (HA-100) did not permit complete simplification of the complex spectrum of 7a, but allowed determination of the coupling patterns. The following couplings were determined: J_{ab}, J_{af}, J_{ag} and J_{bg}, ~2 Hz; and $J_{bf} < 1$ Hz. Protons b, c, d, and e form a virtually coupled system in which c and d behave as a single unit with apparent couplings to b and e of 3 Hz. Compounds 7a and e were purified, m.p. 118 - 122°d and 123 - 126°d, respectively; satisfactory elemental analyses were obtained; both compounds had m/e 341 as the molecular ion.

Table. Resonance positions (δ, ppm, $CDCl_3$) of various protons in compounds 7a-e and 8

	H_a	H_b	$H_{c,d}$	H_e	R_1	R_2	R_3
					H_f	H_g	OMe
7a	4.86	5.19	6.67	5.40	6.09	5.76	3.54
					H_f	OMe	H_g
7b	4.57	5.20	6.60	5.36	6.10	3.48	5.06
					H_f	Me	OMe
7c	4.78	5.2	6.67	5.37	5.96	1.50	3.29
					H_f	OMe	Me
7d	4.58	5.2	6.67	5.37	6.13	3.31	1.38
					Me	H_g	OMe
7e	4.77	5.20	6.58	5.6	1.90	5.6	3.50
					H_f	OH(Hg)	OMe
8a	4.68	5.2	6.60	5.2	6.03	4.87*	3.76

*Sharp doublet which exchanges in D_2O and is coupled with H_a.

Attempted chromatography of 7a on silica gel resulted in a clean rearrangement to 8a, mp = 172-3°, IR ($CHCl_3$) 3500 cm^{-1}, molecular ion at m/e = 341, NMR see Table. In compound 8a, overlap of resonances H_b and H_e prevented complete (HA 100) decoupling analysis, but partial assignments could be made. The OH proton (g) is coupled to H_a (3 Hz). H_a is also coupled to H_f (2 Hz) and to either H_b or H_e (2 Hz), but not both; H_b is the more likely. H_b or H_e, or both, are also coupled to the H_{cd} system. Other couplings could not be determined. The correspondence of couplings in 8a and 7a lends strength to the assignments in both systems. The rearrangement of 7b to 8b occurred spontaneously as well, and rapidly enough to prevent purification of 7b.

The spectra and coupling patterns described above support the assigned structures of the PTD adducts, and thus the structures of peroxides 2. The only evidence that R_3 and H are *cis* comes from the methyl shifts in 2c and d and analogy to similar systems.[2,6] No definite assignment of the stereochemistry of the PTD addition can be made, but it is likely that it is *endo* as shown in 7.

Compound 1f reacted rapidly with singlet oxygen to form 3. NMR of the crude reaction mixture showed 3 to be the sole product. The compound is a colorless liquid; IR: 3400 cm^{-1} (OH) and no carbonyl; NMR (CCl_4) δ 8.6 (s,1H, OOH), 7.13-7.52 (m,5H, arom), 5.51 (s,2H,$=CH_2$), 5.46 (s,1H,C-H) and 3.42 (s,3H,OCH_3). Reduction of 3 with HI/H_2O gave 95% I_2 and a compound which was identified from its spectra (IR and NMR) as atropaldehyde (2-phenylacrolein).

These results allow the following interesting conclusions to be drawn. 1) The 2 + 4 reaction in these systems is general. 2) It is a stereospecific and regiospecific reaction; the products from 1a and b and from 1c and d are clearly different (probably the *cis* adducts). No dioxetanes or diadducts[8] with $^1O_2$ are formed under these conditions. 3) The CH_3O group exerts a profound influence on the reaction rate and product; as in Conia's[3] systems, the oxygen attacks the group on the end of the double bond β to the CH_3O (i.e., R_1 or C_6H_5, since no ene products are found with 1c or 1d); it also attacks the group *cis* to CH_3O with high preference, leading to ene or 2 + 4 product, respectively. If there is no *cis* group, 2 + 4 attack on the phenyl can still occur, but more slowly.

This specificity has been subjected to theoretical interpretation. Goddard and Harding have suggested the anomeric effect on an intermediate diradical is involved[5], whereas Fukui believes stabilization of a perepoxide-like intermediate by the oxygen lone-pair electrons is the cause of the specificity.[4] It seems to us that the anomeric effect may well be involved, but that the results are equally compatible with concerted, perepoxide, or diradical mechanisms, in which the CH_3O lone pair electrons interact with the incoming singlet oxygen to direct its regioselectivity, for example as suggested by Fukui *et al*..[4] The reason for the absence of any dioxetane is the subject of current investigation.

REFERENCES

1. Paper XXVI: M. J. Thomas and C. S. Foote, *Photochem. Photobiol.*, in press. Supported by National Science Foundation grants No. GP 25790 and GP 37165X and by United States Public Health Service grant No. GM 20080. Contribution No. 4018.
2. M. Matsumoto, S. Dobashi, and K. Kondo, *Tetrahedron Lett.*, 2329, 3361, 4471 (1977); M. Matsumoto and K. Kondo, *ibid*, 3935 (1975); J. Rigaudy, M. Maumy, P. Capdevielle, and L. Breton, *Tetrahedron*, **33**, 53 (1977).
3. G. Rousseau, P. Le Perchec and J. M. Conia, *Tetrahedron Lett.*, 2517 (1977); *Synthesis*, 67 (1978).
4. S. Inagaki, H. Fujimoto and K. Fukui, *Chem. Lett.*, 749 (1976).
5. L. B. Harding and W. A. Goddard, III, *Tetrahedron Lett.*, 747 (1978).
6. C. S. Foote, S. Mazur, P. A. Burns, and D. Lerdal, *J. Amer. Chem. Soc.*, **95**, 586 (1973); G. Rio, D. Bricout, and L. Lacomb, *Tetrahedron*, **29**, 3553 (1973); P. A. Burns, C. S. Foote, and S. Mazur, *J. Org. Chem.*, **41**, 899 (1976); P. A. Burns and C. S. Foote, *ibid.*, **41**, 908 (1976).
7. L. F. Fieser and M. Fieser, *Steroids*, Reinhold, N.Y., 1959, pp. 15-21.
8. Such as that reported from benzhydrylidene-cyclobutane: G. Rio, D. Bricout and L. Lacombe, *Tetrahedron*, **29**, 3553 (1973).

(Received in USA 11 May 1978; received in UK for publication 4 July 1978)