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α-HYDROPEROXY SULFIDE IN SULFIDE PHOTOOXIDATION. FORMATION AND ISOLATION IN THE PHOTOOXIDATION OF THIAZOLIDINE DERIVATIVES IN APROTIC MEDIA

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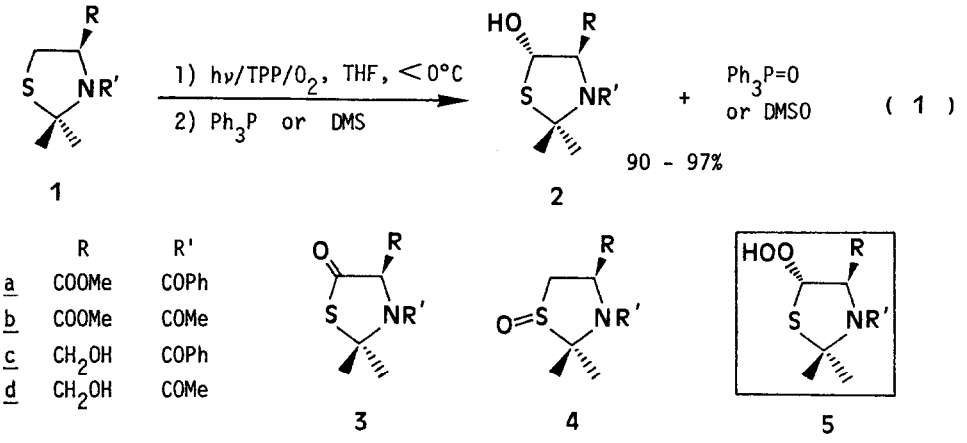
Abstract: In the photooxidation of 3-acyl-2,2-dimethyl-4(R)-substituted thiazolidine derivatives, 5(R)-hydroxy derivative obtained was found to be derived from the 5-hydroperoxy derivative which was isolated and characterized.

Much work has been done in the past decade on the photosensitized oxidation of sulfides.[1-3] Foote et al.[3] have demonstrated that alkyl sulfides undergo oxygenation with singlet oxygen to give sulfoxides and sulfones depending on solvent proticity and temperature via a stepwise mechanism involving a reactive intermediate such as persulfoxide. On the other hand, Corey[4] and Ando[5] showed that photooxidation of benzylic sulfides yielded fragmentation products(aldehyde and sulfenic acid) by C-S bond cleavage, besides sulfoxides and sulfones. For the fragmentation, an α-hydroxy sulfoxide was proposed by Corey[4] as a key intermediate via intramolecular α-proton abstraction in the persulfoxide. Ando, however, pointed out the reasonable intermediacy of α-hydroperoxy sulfide[6] from the characteristic products[5] and the similar reactivity of azodicarbonyl compounds and singlet oxygen toward benzylic sulfides.[5b] In spite of continuous interest in sulfide photooxidations, no proper study on the chemistry of the persulfoxide in such reactions has been done yet.

In this communication, we describe our preliminary results of photooxidation of thiazolidine derivatives in which α-hydroperoxy sulfide formed initially as a result of singlet oxygenation, can be isolated as a sole product which is reduced to α-hydroxy sulfide quantitatively.



In methylene blue(MB)-sensitized photooxidation of 1a[7] at 20°C for 2.5 h, we obtained 5-hydroxy thiazolidine(2a)[8] as major product(62%) in addition to ketone(3a, 9%)[9] and sulfoxide(4a, 14%)[7] in acetonitrile - dimethyl sulfoxide (DMSO)(20:7).[10] Then, a modified procedure involving photoirradiation below 0°C in THF followed by treatment with triphenylphosphine or excess dimethyl sulfide(DMS), led to quantitative yields of both 2 and triphenylphosphine oxide or DMSO(Eq. 1).[11] The reaction did not proceed without sensitizer or in the presence of a quencher(1,4-diazabicyclo[2.2.2]octane), indicating singlet oxygen reaction. Interestingly, both 2 and 3 are the products that have never been found so far in sulfide photooxidations.[1-3] Linear analogue of 1 (S-isopropyl-N-acetylcysteine methyl ester) afforded only sulfoxide(56%) and sulfone(7%) under the same reaction conditions.

The structures of the products(2 - 4) were determined by spectroscopic data[7-9] and further, as for 2a, in comparison with an authentic sample prepared by the use of Woodward's method.[12] The structure of 2 bearing 4,5-trans configuration was confirmed by zero coupling between the 4- and 5-methine protons,[13] suggesting that both protons have ca 90° dihedral angle each other(Fig. 1, B).

Careful TLC observation of the photooxidation of 1a[11] revealed the formation of a relatively stable intermediate(R_f 0.40, benzene - ethyl acetate (10:1) on silica gel), which was quantitatively reduced to 2a(R_f 0.32) by the addition of DMS. Then, the reaction mixture before adding DMS was carefully chromatographed and the product[14] was quickly subjected to the measurement of NMR and IR spectra. IR spectrum involving OH absorption around 3225 cm^{-1} and two singlet methine proton signals at 5.46 and 5.63 ppm in ^1H NMR(Fig. 1, A) unambiguously suggest the structure of 5-hydroperoxy thiazolidine 5a. In ^1H NMR study, addition of excess DMS to the product caused clear spectral change from A to B(Fig. 1). The formation of equimolar amount of 2a and DMSO (spectrum B) is also consistent with the structure of the hydroperoxide which should have the same configuration as the alcohol(2a).

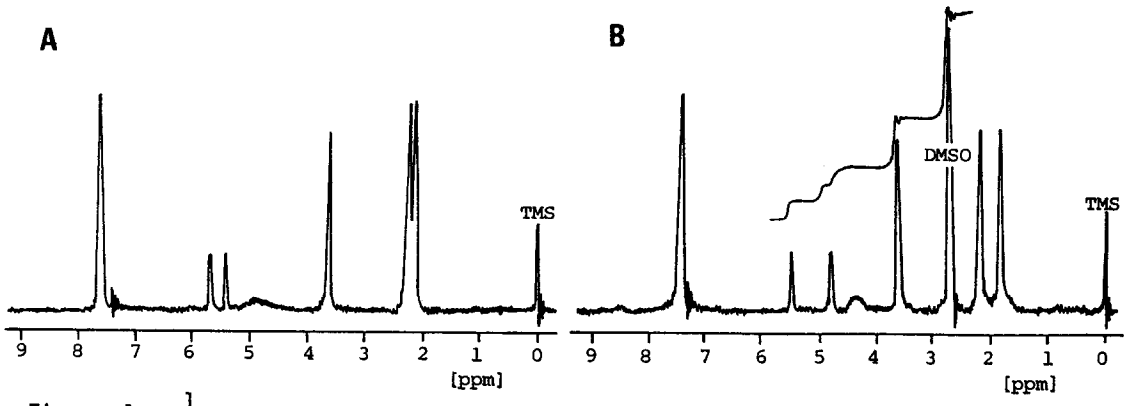
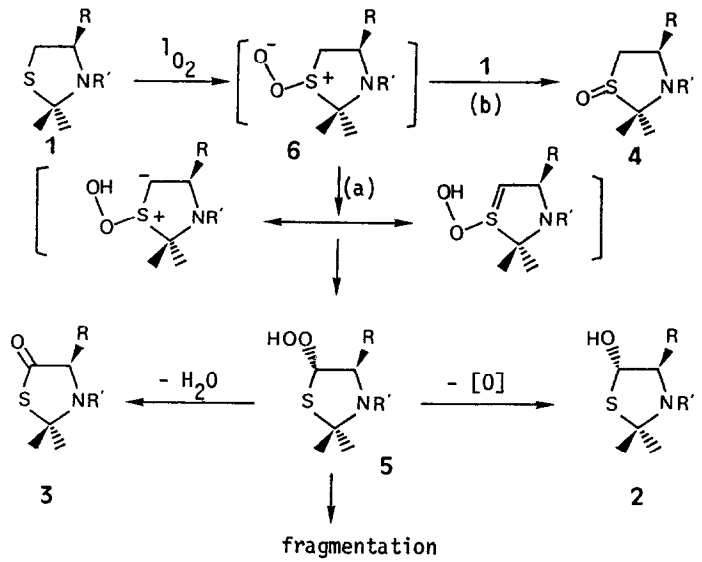


Figure 1. ^{1}H NMR Spectra. A: Hydroperoxide(**5a**) in $CDCl_3$. B: Alcohol(**2a**) + DMSO in $CDCl_3$, obtained by treatment of sample of A with DMS and subsequent removal of excess DMS.

Therefore, the mechanism of the photooxidation may be explained by assuming the Pummerer type rearrangement[15] of the persulfoxide(6) via abstraction of an α-proton(path a) with competition with sulfoxidation(path b) (Scheme 1). In accordance with the mechanism, protic solvent such as methanol altered the reaction course by suppressing the proton abstraction of the persulfoxide(6), giving mainly 4. Thus, the results demonstrate that the persulfoxide undergoes competitively either S-oxidation or Pummerer type rearrangement depending on solvent proticity.

Further investigation on the detail mechanism is in active progress,[16] and will also explain the photooxidation of benzylic sulfide clearly.

Scheme 1



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6. In the photooxidation of sulfides, possible formation of α-carbon oxidation products[6a,b] or α-hydroperoxide[6c,d] has been suggested without any evidence.
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   c) Sinnereich, D.; Lind, H.; Baster, H. Tetrahedron Lett. 1976, 3541.
   d) However, it[6c] was ruled out by Tezuka et al.: Tezuka, T.; Miyazaki, H.; Suzuki, H. Tetrahedron Lett. 1978, 1959.
7. Optically pure 1a and authentic sample of 4a were prepared by Iwakawa's method with some modifications: Iwakawa, M.; Pinto, B. M.; Szarek, W. A. Can. J. Chem. 1978, 56, 326.
8. 2a: mp. 170 -171°C; IR(KBr, cm^{-1}) 3360(-OH), 1740(C=O), 1630(C=O); ^1H NMR (see Fig. 1); ^{13}C NMR δ($CDCl_3$) 170.7(s), 168.7(s), 138.1(s), 129.4(d), 128.9 (d), 128.6(d), 127.3(d), 77.6(d), 75.7(d), 74.2(s), 52.8(q), 32.4(q), 28.7 (q); MS m/e 295(M^+); Anal.($C_{14}H_{17}O_4NS$) C, H, N, S. No other isomer was detected by the experiment using chiral NMR shift reagent.
   Specific rotation of 2a: $[\alpha]_D^{26}$ - 75.3°(c 1.26, $CHCl_3$).
9. 3a: oil; IR($CHCl_3$, cm^{-1}) 1745(C=O), 1700(C=O), 1655(C=O); ^1H NMR δ($CDCl_3$) 7.43(s,5H), 5.21(s,1H), 3.60(s,3H), 2.22(s,6H); ^{13}C NMR δ($CDCl_3$) 191.2(s), 169.7(s), 165.7(s), 136.4(s), 130.3(d), 128.6(d), 126.2(d), 76.1(s), 73.8(d), 53.5(q), 30.4(q), 29.8(q); MS m/e 295(M^+).
10. Hoshino, K. Ms. Thesis, The University of Tsukuba, 1982.
11. A mixture of 1a(1.0 mmol) and TPP(tetraphenylporphyrin, 15 mg) dissolved in dry THF(5.4 mL) in Pyrex tube was irradiated below 0°C for 1.5 h with 300W halogen lamp under bubbling oxygen.
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13. Baldwin, J. E.; Au, A.; Christie, M.; Haber, S. B.; Hesson, D. J. Am. Chem. Soc. 1975, 97, 5957.
14. The product hydroperoxide was stable in dilute solution for a few hours but easily decomposed to several components involving 2a by concentration.
15. For example, Oae, S.; Numata, T.," Isotopes in Organic Chemistry ", Ed. by Buncel, E.; Lee, C. C., Elsevier, New York, Chapt. 2, 1980.
16. Synthetic application of the alcohol formation is submitted for publication.

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