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SENSITIZED PHOTOOXYGENATION OF β,β-DIMETHYLSTYRENES; SYNTHESIS OF (±)-CROTEPOXIDE

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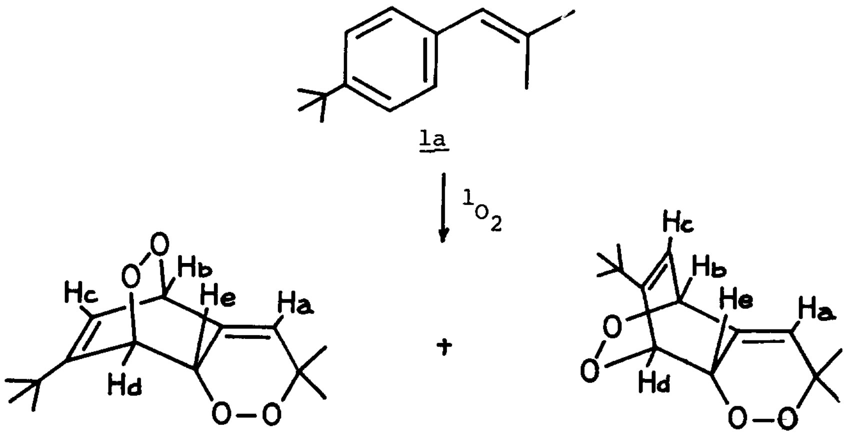
Some styrenes have recently been found to undergo 1,4-cycloaddition of singlet oxygen ($^1O_2$) to give 1:2 styrene - O_2 adducts.[1] This reaction may provide a new method of direct oxygenation of benzene ring, though the selectivity seemed to be not necessarily satisfactory in view of our aim to applying the method to the synthesis of natural products such as crotepoxide. We wish to report here that, (1) the sensitized photooxygenation of β,β-dimethylstyrenes gives the 1:2 styrene - O_2 adducts in favorable yields and (2) it can be easily applied to the synthesis of (±)-crotepoxide, which is known to possess significant inhibitory activity against Lewis lung carcinoma and Walker intramuscular carcinoma.[2,3]

A 70 ml solution of 1-tert-butyl-4-(2-methyl-1-propenyl)benzene (p-tert-butyl-β,β-dimethylstyrene, 1a, 1.62 g) and tetraphenylporphine (5 mg) in CCl_4 was irradiated externally with 60-W low-pressure sodium vapor lamps (National SOI-60) under an oxygen atmosphere at 5°C for 1.5 hr. The photolysate was condensed under reduced pressure and chromatographed on silica gel. Elution with benzene gave two isomeric peroxides 2a (colorless granules, mp 112°C, 41% yield)[4,5] and 3a (colorless needles, mp 83°C, 41% yield).[6] The NMR spectrum (in CCl_4)[7] of 2a showed three singlets at δ1.07 (9H, t-butyl), 1.16 and 1.21 (6H, two methyl), and five multiplets centered at 4.82 (H_b), 4.84 (H_d), 5.08 (H_e), 5.37 (H_a), and 6.29 (H_c)ppm; J_{bc} = 7.3, J_{de} = 3.5, J_{cd} = 2.0, J_{ae} = 1.5, and J_{ab} = 0.5 Hz. The NMR spectrum (in CCl_4) of 3a displayed three singlets at δ1.15 (9H, t-butyl), 1.20 and 1.44 (6H, two, methyl), and five multiplets centered at 4.33 (H_e), 4.74 (H_b), 4.87 (H_d), 5.89 (H_a), and 6.20 (H_c)ppm; J_{bc} = 4.5, J_{ac}= J_{de} = 2.0, J_{ae} = J_{bd} = 1.0, J_{ad} = 0.6, and J_{ab} = J_{cd} = 0.5 Hz. The structures of the peroxide 2a and 3a were further confirmed by the NOE technique.[8]

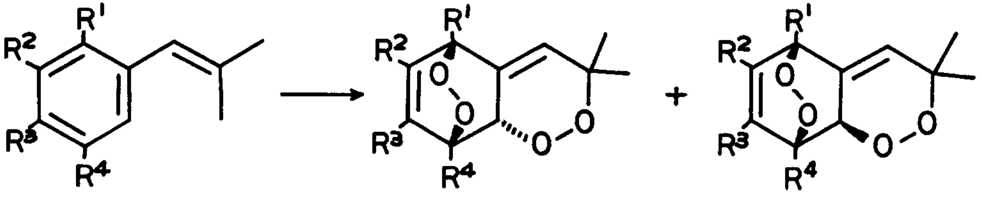


1a

2a

3a

Similar irradiation of unsubstituted (1b), p-methyl- (1c), o-methyl- (1d), and 3,5-dimethyl-β,β-dimethylstyrene (1e) gave a mixture of corresponding 2 and 3. These results were summarized in Table I. Thus, β,β-dimethylstyrenes were shown to undergo mainly the 1,4-cycloaddition of $^1O_2$.



1

2

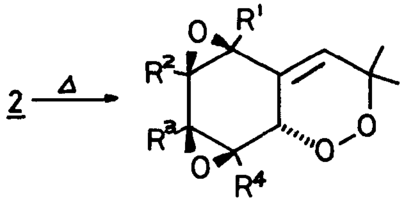
3

Table I.[a)]

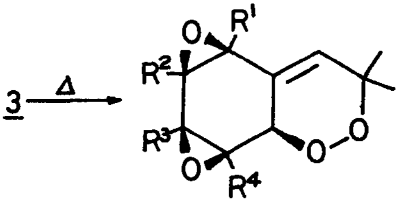
	R^1	R^2	R^3	R^4	Yield ($\underline{2}+\underline{3}$, %)	2	: 3	Mp (°C) 2	3
b	H	H	H	H	51	32	68	75	125
c	H	H	CH_3	H	60	42	58	66	124
d	CH_3	H	H	H	58	30	70	89	114
e	H	Ch_3	H	CH_3	33	60	40	127	112
f	R^1=CH_2OCOPh, R^2,R^3,R^4=H				40	33	67	128	132

a) All the peroxides were isolated by chromatography on silica gel.

The peroxides 2 and 3 were easily isomerized on heating into the corresponding diepoxyperoxides 4 and 5 respectively, though they were stable in crystalline form at room temperature; when the peroxide 2a was stirred in hot 1,2-dichloropropane for 1 hr, the corresponding diepoxyperoxide 4a was obtained as colorless granules (mp 121 - 123°C, from hexane)[9] in 41% yield. These thermal isomerization proceeded with retention of stereochemistry.[10]

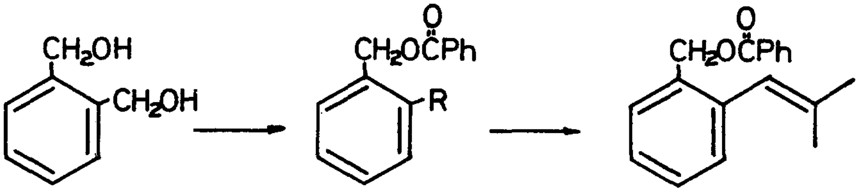


4



5

The reaction sequence (1→2→4) described above was now applied to the synthesis of (±)-crotepoxide (10). The starting styrene 1f[11] was easily obtained from benzaldehyde 8 by a Wittig reaction with isopropyltriphenylphosphonium bromide in 80% yield. The aldehyde 8 was prepared by MnO$_2$ oxidation of the corresponding alcohol 7 in hot benzene (82%). The alcohol 7 was obtained from phthalyl alcohol (6) by the esterification with benzoyl chloride and triethylamine in ether (63%). Similar photooxygenation of the styrene 1f gave the desired peroxide 2f together with its isomer 3f (see Table I). Then the peroxide 2f was isomerized into the epoxide 4f (56%, colorless needles, mp 150 - 151°C, from hexane - CH$_2$Cl$_2$) as in the cases described above.



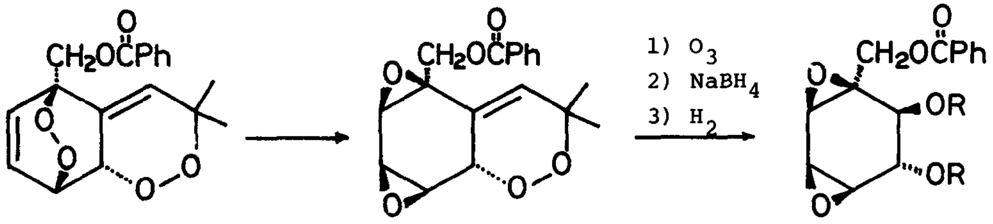
6

7: R=CH$_2$OH

8: R=CHO

1f

In order to obtain crotepoxide from the 1,2-dioxin 4f, the oxidative cleavage of the remaining double bond and reductive cleavage of the peroxy bond are required. Thus, the peroxide 4f was oxidized with ozone in dichloromethane at -78°c for 6 hr. The resulting ozonide was reduced without isolation with $NaBH_4$ in methanol and successively hydrogenated with $Pd\text{-}CaCO_3$ to afford the diol 9 (colorless needles, mp 145 - 146.5°C, from CH_2Cl_2)[12] in 39% yield. Finally, the diol 9 was treated with acetyl chloride and pyridine to give (±)-crotepoxide 10 (colorless needles, mp 110 - 111°C, from methanol) in quantitative yield. The TLC and NMR, IR, and MS spectra were identical with those of natural crotepoxide.



2f 4f 9 : R=H

10: $R=CH_3CO$

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References and Notes

(1) (a) C. S. Foote, S. Mazur, P. A. Burns, and D. Lerdal, J. Am. Chem. Soc., 95, 586 (1973); (b) G. Rio, D. Bricout, and L. Lacomb, Tetrahedron, 29, 3553 (1973); (c) P. A. Burns, C. S. Foote, and S. Mazur, J. Org. Chem., 41, 899 (1976); (d) P. A. Burns and C. S. Foote, ibid., 41, 908 (1976); (e) M. Matsumoto, S. Dobashi, and K. Kondo, Tetrahedron Lett., in press.

(2) (a) S. M. Kupchan, R. J. Hemingway, P. Coggon, A. T. McPhail, and G. A. Sin, J. Am. Chem. Soc., 90, 2982 (1968); (b) S. M. Kupchan, R. J. Hemingway, and R. M. Smith, J. Org. Chem., 34, 3898 (1969); (c) S. Takahashi, Phytochemistry, 8, 321 (1969).

(3) Syntheses of (±)-crotepoxide by different routes have been recently reported; K. Oda, A. Ichihara, and S. Sakamura, Tetrahedron Lett., 3187 (1975); M. R. Demuth, P. E. Garrett, and J. D. White, J. Am. Chem. Soc., 98, 634 (1976).

(4) All the peroxides 2 and 3 were recrystallized from ether - hexane.

(5) IR (KBr); 1045 cm^{-1} ; MS (m/e): 191 (20), 163 (23), 121 (26), 57 (62), and 43 (100). Anal ($C_{14}H_{20}O_4$) C 66.78, H 8.09.

(6) IR (KBr): 1060 cm^{-1}; MS (m/e): 163 (25), 147 (18), 121 (42), 57 (50), 55 (18), and 43 (100). Anal ($C_{14}H_{20}O_4$) C 66.92, H 7.98.

(7) Tetramethylsilane was used as internal standard.

(8) For 3a, on irradiation of the tert-butyl signal, a 6% signal increase is observed for the He proton signal, while for 2a, an NOE is scarcely observed between the tert-butyl group and the proton He.

(9) NMR (in $CDCl_3$) δ1.00 (s, 9H), 1.28, 1.31 (two s, 6H), 3.02 (s, 1H), 3.53 (m, 2H), 4.58 (m, 1H), 6.00 (d, J=2.0 Hz, 1H)ppm. IR (KBr) 1045 cm^{-1}. MS (m/e) 191 (9), 111 (11), 57 (78), 43 (100). Anal ($C_{14}H_{18}O_4$) C 66.66, H 7.83.

(10) It has been well known that 1,4-endoperoxides are thermally isomerized into diepoxides stereospecifically; for example, see K. Gollnick and G. O. Schenck,"1,4-cycloaddition Reactions", Ed. J. Hamer, Academic Press, New York, N. Y., p255 (1967).

(11) A colorless liquid, bp 161 - 164°C/1.5 mmHg. NMR (in CCl_4) δ1.64, 1.84 (two s, 6H), 5.21 (s, 2H), 6.26 (broad s, 1H), 6.98 - 8.05 (m, 9H), IR (liquid film) 1725 cm^{-1}.

(12) NMR (in d_8-dioxane) δ2.92, 3.25 (two m, 2H), 3.7 - 4.2 (m, 3H), 4.49 (q_{AB}, J=12 Hz, 2H), 7.3 - 8.1 (m, 5H)ppm. IR (KBr) 3470, 1710 cm^{-1}. MS (m/e) 279 (M^{+}+1). Aanl ($C_{14}H_{14}O_6$) C 60.32, H 5.00.