Tetrahedron Letters,Vol.22,No.46,pp 4591-4594,1981 0040-4039/81/464591-04$02.00/0
Printed in Great Britain

OXIDATION OF AMINES AND SULFIDES BY 3-BROMO-4,5-DIHYDRO-5-HYDROPEROXY-4,4-DIMETHYL-3,5-DIPHENYL-3H-PYRAZOLE

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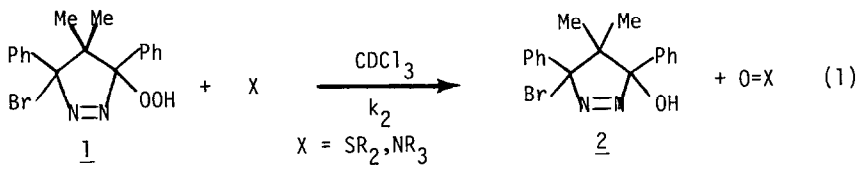
Summary: The reaction of 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3H-pyrazole with tertiary amines and sulfides produced amine oxides and sulfoxides in high yield with k_2's for amines similar to those reported for reaction of amines with a 4a-hydroperoxyflavin.

Recently, we have shown[1] that 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3H-pyrazole[2] (1), without added catalysts, is sufficiently reactive to effect the epoxidation of 2,3-dimethyl-2-butene under mild conditions. There are structural similarities[1] between 1 and flavin 4a-hydroperoxides, important intermediates in external flavoprotein monoxygenase activity[3]. It is of interest to investigate the oxygen-atom transfer capabilities of 1 as a possible model for the chemistry of 4a-hydroperoxyflavins. We wish to report the rapid oxidation of tertiary amines and sulfides by 1, under mild conditions, to the corresponding amine oxides and sulfoxides and 3-bromo-4,5-dihydro-5-hydroxy-4,4-dimethyl-3,5-diphenyl-3H-pyrazole (2) in high yield (reaction 1).



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One equivalent of amine or sulfide was added, via syringe, to a solution of 1 (0.033 mmole) in 0.40 ml of $CDCl_3$ (Merck, No TMS) in a new 5-mm NMR tube.[4] Anisole or CH_2Cl_2 had been previously added as an internal standard. Reaction progress at 34° was monitored by integration of the upfield[1,2] methyl signals of 1 and 2 and the signals for amine or sulfide and amine oxide or sulfoxide. The rate of appearance of product(s) was equal to the rate of disappearance of starting materials. The reaction of 1 with amines or sulfides was found to be of the first order with respect to each reagent. The final product yield of 2 was found

to be in the range of 93-100% vs internal standard for all cases. Careful crystallization afforded 2 in 50% isolated yield from both amine and sulfide oxidation reactions. The structure of 2 was proven by comparison with an authentic sample.[1] The sulfoxides were isolated by preparative G.C. and identified by comparison with authentic samples prepared by oxidation of the sulfides with m-chloroperbenzoic acid or hydrogen peroxide. The amine oxides were isolated as hydrates from the reaction mixtures and identified by comparison with authentic samples prepared by the oxidation of the amines with m-chloroperbenzoic acid. The product yields for the reaction of 1 with amines and sulfides as well as the corresponding second-order rate constants are listed in Table I.

Table I. Second-Order Rate Constants and Product Yields for the Reaction of Sulfides and Amines with 1[a] in $CDCl_3$ at 34°.

Substrate[b]	k_2 M^{-1} sec^{-1}	oxide	% yield[c]
BzSMe	fast[d]	BzS(O)Me	93
PhSMe	0.95	PhS(O)Me	94
BzSPh	0.80	BzS(O)Ph	90
Ph_2S[e]	0.012±0.005	Ph_2SO	92
Et_3N	0.48	$Et_3N{\rightarrow}O$	100
$BzNMe_2$	0.15	$BzN(O)Me_2$	97
N-Methyl-morpholine	0.10±0.04	N-Methyl-morpholine oxide	95
$PhNMe_2$[e,f]	0.0011	$PhN(O)Me_2$	90[f]

a) $[1]_0$ = 0.08 M. b) $[Substrate]_0$ = 0.08 M except as noted. c) Relative to internal standard. d) This reaction was too rapid to allow determination of k_2 by the NMR method. e) One-to five-fold excess employed. f) Under equal-molar conditions, the thermal decompostion[2] of 1 was competitive with oxidation by $PhNMe_2$ and the yield of oxide was reduced to ~50%.

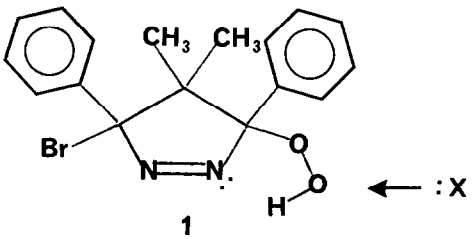
The greater reactivity of 1 with sulfides than with amines is in accord with the findings for similar oxidations with 2-hydroperoxyhexafluoro-2-propanol.[5] The relative reactivity series: Ph_2S(1) < PhSBz (67) < PhSMe (90) < BzSMe is consistent with that observed[6a,b] for the reaction of the same sulfides with hydrogen peroxide in protic solvent at 25°. The reaction of Ph_2S with 1 (in $CDCl_3$) is approximately 35 times faster than the reaction of Ph_2S with H_2O_2. The reaction of sulfides with 1 is approximately 10 times more sensitive to

substituent effects on the sulfide than observed[6] in the H_2O_2-sulfide reaction as judged by comparison of the calculated[6c] relative reactivity series.

Bruice has shown[7] that the reaction of the 4a-hydroperoxide of N^5-ethyl-3-methyllumiflavin (FlEtOOH) with amines provides a model for the enzymatic oxidation of amines by hepatic flavoprotein microsomal oxidase[8]. The relative reactivity series of tertiary amines with 1: $PhNMe_2$ (1) < N-methylmorpholine (91) < $BzNMe_2$ (134) < Et_3N (436) closely matches that calculated from the data[9] of Bruice and Ball in the reaction of FlEtOOH and tertiary amines in aprotic medium at 30°. The reactivity of 1 toward tertiary amines is essentially identical to that of FlEtOOH. As observed in the case of FlEtOOH, the second-order rate constant for reaction of 1 with $BzNMe_2$ is approximately 10^{+4}-10^{+5} times faster than those of the corresponding reactions[10] of $BzNMe_2$ with H_2O_2 or t-butyl hydroperoxide.

In aprotic solvent, the reaction of sulfides with hydroperoxides has been found[11] to be strongly acid catalyzed as evidenced by the observation that the reaction is of the second order with respect to hydroperoxides. In the present case and as noted[7] in the S-oxidation reactions of FlEtOOH[7], the reactions are of the first order with respect to hydroperoxide. General acid catalysis appears not to be required for highly reactive hydroperoxides. The oxidation of amines by hydroperoxide has been found[11b] not to require acid catalysis. No acid catalysis is observed in the present case and none was observed[7] for the reaction of FlEtOOH and amines.

The relative reactivity order for the reaction of amines and sulfides corresponds to the increase in nucleophilicity of the amines and the sulfides. The observation that a phenyl substituent on the amine or sulfide greatly slows the oxidation appears to rule out an electron transfer mechanism. A free radical and a caged radical mechanism were previously ruled out[7] for the reaction of FlEtOOH with amines based on similar arguments. The N-oxidation and S-oxidation reactions with 1 are consistent with a nucleophilic displacement by the hetroatom on the terminal oxygen atom of the hydroperoxide. Intramolecular hydrogen



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bonding to the nearest nitrogen atom of the azo function may assist the displacement process. Thus the reaction of 1 with amines and sulfides closely parallel the analagous reactions of 4a-hydroperoxyflavins. It appears that the reactivity of 4a-hydroperoxyflavins can be explained by normal peroxide chemistry.

Work is in progress to further investigate the oxygen-transfer reactions of 1 to evaluate 1 as a model for oxidation in flavin systems.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to NIH (RR 09201).

References and Notes

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4. As previously noted[1], 2 is not stable to the reaction conditions unless in the presence of an alkene. Inclusion of small amounts (up to ~10 mol%) of cis-3-hexene in the reaction mixture resulted in the stabilization of 2 to the reaction conditions and allowed isolation of 2 by selective crystallization. cis-3-Hexene is inert[1] to reaction with 1 under these reaction conditions.

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9. Calculated relative reactivity series: $PhNMe_2$(1) < N-methylmorpholine (59) < $BzNMe_2$ (125) < Et_3N (427)[7a].

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(Received in USA 25 June 1981)