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A BIOMIMETIC HETEROATOM OXIDATION

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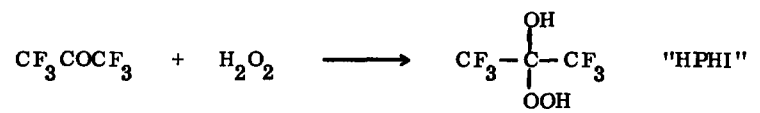
Summary: The oxidation of amines and sulfides to N-oxides, sulfoxides and sulfones is smoothly accomplished using 2-hydroperoxyhexafluoro-2-propanol (HPHI).

We have reported that 2-hydroperoxyhexafluoro-2-propanol (HPHI) constitutes a useful reagent for the oxidation of alkenes to epoxides[2] and aldehydes to carboxylic acids.[3] In this regard, the structure and reactivity of HPHI bear resemblance to the 4a-hydroperoxyflavin coenzymes which have been implicated in some corresponding in vivo processes.[4] Recently Ball and Bruice published preliminary studies of the biomimetic N-oxidation of tertiary amines using oxidized flavins and noted the superior characteristics of the coenzyme reagent as compared with H_2O_2 or t-BuOOH.[5] We also have observed similarly dramatic rate differences in the HPHI-mediated oxidation of trialkylamines and dialkylsulfides and wish to disclose our results in this Letter.



The Table summarizes representative heteroatom oxidations which take place cleanly in CH_2Cl_2 solution. Most are performed conveniently at 0°C although the rate in many instances is appreciable even at sub-zero temperatures. Competitive amine-versus-sulfide experiments (Entry 13) reveal a clear preference for oxidation of the latter, moreover the high yield conversion of diallylsulfide to diallylsulfoxide (Entry 10) illustrates the additional selectivity which can be expected. In the presence of another equiv. of HPHI sulfoxides are further transformed more slowly to sulfones. As in all HPHI oxidations, rates are considerably diminished in hydrogen bonding solvents (compare Entries 1-3).

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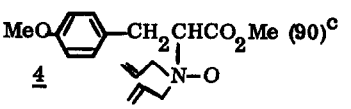
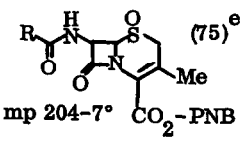
TABLE

Entry	Substrate	Conditions [a]	Products (% Yields) [b]
1	$PhCH_2NMe_2$ 1	CH_2Cl_2, 5 min, 0°	$PhCH_2N(O)Me_2$ (95)
2	1	CH_3OH, 4.5h, rt	2 (>95)
3.	1	EtOAc, 2h, rt	2 (>95)
4	N-methylmorpholine	CH_2Cl_2, 10 min, 0°	N-methylmorpholine-oxide (90)
5	$PhNEt_2$	CH_2Cl_2, 5 min, 0°	$PhN(O)Et_2$ (60)
6	N,N-diallyl-O-methyl-tyrosine methyl ester 3	CH_2Cl_2, 15 min, 0°	 (90)[c]
7	$(nBu)_2S$ 5	CH_2Cl_2, 5 min, 0°	$(nBu)_2SO$ 6 (99)
8	Ph_2S	CH_2Cl_2, 1 min, rt	Ph_2SO (99)
9	Ph_2S	2 equiv HPHI, CH_2Cl_2, 24h, rt	Ph_2SO_2 (98)
10	$(CH_2{=}CHCH_2)_2S$	CH_2Cl_2, 2h, -78° to rt	$(CH_2{=}CHCH_2)_2SO$ (98)
11	Desacetoxycephalosporin[d] V-paranitrobenzyl ester	CH_2Cl_2, 10 min, 0°	 (75)[e] mp 204-7°
12	dl-methionine	CH_3OH, 6.5h, reflux	dl-Methionine sulfoxide (89)
13	1 + 5	CH_2Cl_2, 2h, -78° to rt	6 (98) + 1 (95)

(a) Unless otherwise stated, one equiv of HPHI was added; the products were isolated by washing the organic phase with dilute Na_2CO_3, drying and concentration. (b) Yields reported are for pure compounds which were identified by comparison with authentic samples. (c) We thank Mr. Bennett Laguzza for preparing 3 and performing this experiment. (d) Provided by Dr. Rosanne Bonjouklian of the Lilly Research Laboratories. (e) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, E. M. Van Heyningen, J. Org. Chem., 35, 2430 (1970); sulfoxide stereochemistry undetermined.

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