Conversion of N-Substituted *N*-Sulfonylhydrazines into Hydroperoxides—A New Synthetic Route to Hydroperoxides via Hydroperoxydeamination[1]

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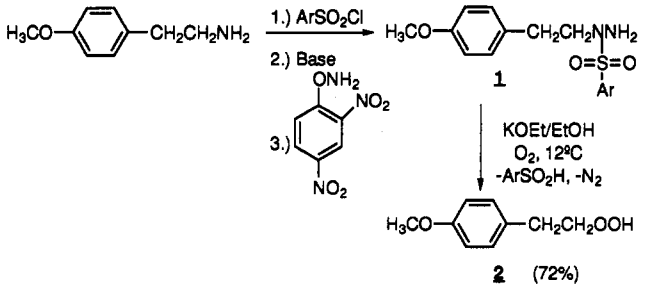
Summary: N-Substituted *N*-sulfonylhydrazines, obtained by amination of primary amine sulfonamides, can be readily oxygenated by atmospheric oxygen under basic conditions below room temperature to cleanly afford alkyl hydroperoxides in good yield.

Standard approaches to the synthesis of organic hydroperoxides are often severely limited in scope.[2] These limitations can involve the inherent selectivity associated with direct radical oxygenations, the high reactivity of intermediate organometallic reagents, or the steric and electronic requirements in a displacement using hydrogen peroxide or a peroxide derivative.[3] Alternate routes to hydroperoxides involving readily available starting materials and mild reaction conditions could prove to be very useful in the preparation of complex hydroperoxides.

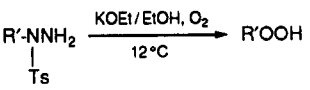
Recently, we published methods for the convenient conversion of primary amines into the corresponding reduced products (hydrodeamination),[4] halides (halodeamination),[4] or alcohols (hydroxydeamination).[5] In this last transformation an intermediate hydroperoxide could be observed and isolated under carefully controlled conditions. We would now like to report methods that allow for the ready preparation and isolation of these hydroperoxides starting from primary amines—hydroperoxydeamination.

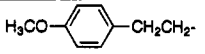
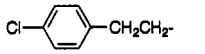
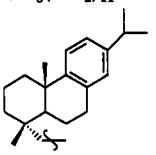
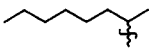
The preparation of the hydroperoxide involves conversion of the primary amine into the corresponding *p*-toluenesulfonamide[6] followed by amination to the N-substituted *N*-tosylhydrazine 1.[7] Treatment of the tosylhydrazine with base in ethanol at 12 °C for 17 h affords the corresponding hydroperoxide **2** in good yield (Table I).[8] After workup the crude hydroperoxide is obtained in



reasonable purity, generally only contaminated by small amounts of starting tosylhydrazine. Pure hydroperoxide can be obtained by flash chromatography on silica.

Table I. Preparation of Hydroperoxides via Hydroperoxydeamination



R'	% yield[a]
	72[b]
	77
$CH_3(CH_2)_{15}$–	77[c]
$CH_3(CH_2)_{11}$–	67[d]
	78
	71[d]

[a] Isolated unoptimized yields of pure products. [b] See ref 5. [c] See refs 3 and 9. [d] See ref 3.

While the mechanistic details of this reaction are as yet unclear, some insights into the mechanism have been obtained by examining the limiting reaction conditions necessary for hydroperoxydeamination. The source of the hydroperoxide oxygens in these transformations is atmospheric oxygen. It should be noted that it is not necessary to bubble oxygen or air through the reaction mixtures to obtain high yields of peroxide. Simple diffusion of air into the reaction mixtures is adequate for the transformation. Careful degassing of the reaction mixture with argon lowers significantly, but does not completely eliminate, the observed oxygenation product.

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(1) Presented at the 205th American Chemical Society National Meeting, Denver, CO, 1993, ORG 135.

(2) Hiatt, R. In *Organic Peroxides;* Swern, D., Ed.; Wiley-Interscience: New York, 1971; Vol. II, pp 1–151.

(3) Dussault, P.; Sahli, A. *J. Org. Chem.* **1992,** *57,* 1009–1012.

(4) Guziec, F. S., Jr.; Wei, D. *J. Org. Chem.* **1992,** *57,* 3772–3776.

(5) Guziec, F. S., Jr.; Wei, D. *Tetrahedron Lett.* **1992,** *49,* 7465–7468.

(6) The reaction also proceeds with methanesulfonamide derivatives; however, the required intermediate mesylhydrazines were more difficult to purify.

(7) Aminations using *O*-(2,4-dinitrophenyl)hydroxylamine proved to be more convenient than reactions using *O*-mesitylenesulfonylhydroxylamine.[4,5] See: (a) Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* **1972,** *28,* 3833–3843. (b) Sheradsky, T. *Tetrahedron Lett.* **1968,** 1909–1910. (c) Sheradsky, T. *J. Heterocycl. Chem.* **1967,** *4,* 413–414. (d) Ilvespõõ, A. O.; Marxer, A. *Helv. Chim. Acta* **1963,** *46,* 2009–2020.

(8) The preparation of 2-(4-methoxyphenyl)ethyl hydroperoxide is outlined below. A 0.25 M ethanolic solution of KOEt, prepared from potassium metal and EtOH (48 mL), was added to a cooled (12 °C) solution of 1-tosyl-1-[2-(4-methoxyphenyl)ethyl]hydrazine[4] (0.50 g, 1.56 mmol) in EtOH (50 mL). H_2O (1 mL) was added, and the mixture was stirred for 17 h at 12 °C. Progress of the reaction was monitored by TLC using *N,N*-dimethyl-*p*-phenylenediamine as a visualizing agent (See: Smith, L. L.; Hill, F. L. *J. Chromatogr.* **1972,** *66,* 101–109). The crude mixture was poured into an equal volume of ice–water, neutralized with 1 M HCl, and then extracted with $CHCl_3$ (3 × 100 mL). The extracts were washed with brine (120 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude hydroperoxide containing a small amount of unreacted tosylhydrazine. Flash chromatography on silica (hexanes/ether) afforded the pure hydroperoxide as an oil, 189 mg (72% yield): FTIR (neat) 3392, 2936, 2836, 1612, 1514, 1246, 1034, 830 (–OO–) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (s, 1H, D_2O exchangeable), 7.14 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.20 (t, J = 7.2 Hz, 2H, $-CH_2OOH$), 3.79 (s, 3H), 2.92 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 158.1 (s), 130.2 (s), 129.9 (d), 114.1 (d), 77.8 (t, $-CH_2OOH$), 55.4 (q), 33.4 (t). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.01. **(Caution:** While no particular problems have been noted during these preparations, adequate safety precautions should be taken when working with potentially explosive hydroperoxides.)

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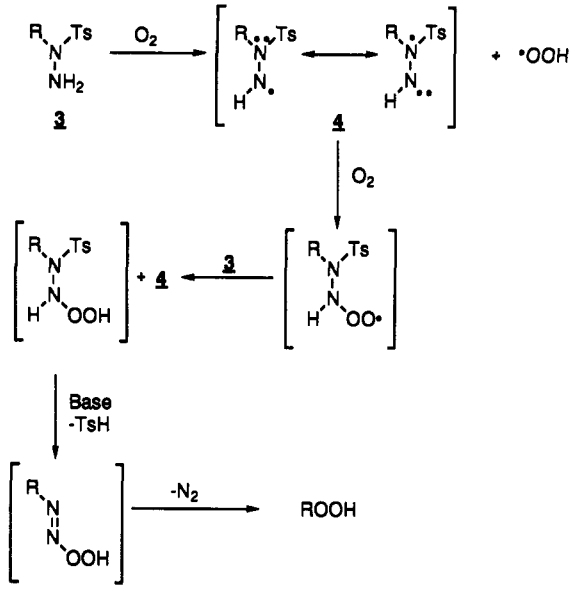
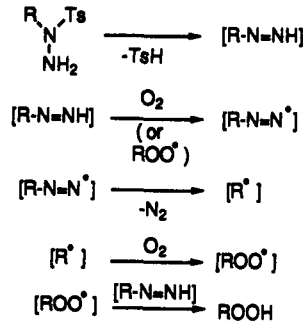
Scheme I



While basic conditions are used in these transformations, the initial oxygenation reaction proceeds equally well under neutral conditions. In this case a 1:1 mixture of hydroperoxide and alcohol is obtained without added base under essentially the same reaction conditions. The well-documented stabilizing effect of base on peroxides may lead to a purer peroxide product being obtained under basic conditions.[10] The sulfur-containing byproduct under the basic reaction conditions is potassium *p*-toluenesulfinate.

These data suggest that the oxygenation reaction may involve a radical chain mechanism. One possible mechanism consistent with the above information is indicated in Scheme I. The ready formation of the hydrazyl radical from the tosylhydrazine **3** may be due to the resonance stabilization of **4** through a "three-electron bond"[11] as well as "captodative" stabilization.[12] Oxygenation of **4** followed by base-promoted elimination of *p*-toluenesulfinate and extrusion of nitrogen would afford the hydroperoxide.[13] Consistent with this mechanism is the fact that the oxygenation is almost completely suppressed in the presence of 0.2 molar equiv of 2,6-di-*tert*-butylphenol. An alternative radical oxygenation mechanism is depicted in

Scheme II



Scheme II. Elimination of *p*-toluenesulfinate from the tosylhydrazine would afford a diazene intermediate which could react with oxygen to afford a diazene radical. The diazene (or its anion) could further react in a radical chain process to afford the hydroperoxide. It is, however, unlikely that diazenes are intermediates in these reactions. The oxygenation reaction proceeds well under neutral conditions making an initial elimination step unlikely. In addition, molecular oxygen is known to promote reductive loss of nitrogen from diazenes.[14] It should also be noted that no significant amounts of reductive hydrodeamination products are obtained under the basic hydroperoxydeamination conditions, suggesting that the oxygenation is much faster than diazene formation. Another possible alternative mechanism involving initial rearrangement of the N-substituted *N*-tosylhydrazines to the isomeric N-substituted *N'*-tosylhydrazines[9] prior to oxygenation can also be eliminated. These latter compounds do not undergo facile air oxygenation, indicating that they are not intermediates in the hydroperoxydeamination.

For the moment, our investigations into the scope of the hydroperoxydeamination reaction have been limited by difficulties in isolating hindered N-substituted *N*-sulfonylhydrazines. Very hindered *in situ* generated hydrazines were, however, used as intermediates in the hydrodeamination and halodeamination reactions.[4] The successful hydroperoxydeamination at both a secondary carbon in the case of 2-aminooctane and at a neopentyl center in the case of dehydroabietylamine suggests that problems with the amination reaction will not ultimately limit the method. Further studies in these areas are currently underway.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra and spectroscopic characterization of hydroperoxides (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) Caglioti, L.; Gasparrini, F.; Misiti, D.; Palmieri, B. *Tetrahedron* **1978**, *34*, 135–139.
(10) Reference 2, p 9.
(11) Nelson, S. F. In *Organic Free Radicals*; Pryor, W. A., Ed.; ACS Symposium Series 69; American Chemical Society: Washington, 1978; pp 309–320.
(12) Viehe, H. G.; Janousek, Z; Merenyi, R., Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148–154.
(13) A reviewer has pointed out that there is no precedent for oxygenation of nitrogen radicals, aside from NO, and has suggested the diazene intermediate mechanism presented in Scheme II. We had previously rejected this mechanism for the reasons indicated below.
(14) Kosower, E. M. *Acc. Chem. Res.* **1971**, *4*, 193–198.