Pergamon

Tetrahedron Letters, Vol. 36, No. 31, pp. 5519-5522, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01053-X

Oxidation of Secondary Amines to Nitroxides with Oxone in Aqueous Buffered Solution.

M. E. Brik

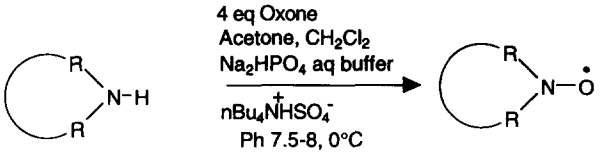
Laboratoire de Chimie Structurale Organique associé au CNRS, ICMO,
Université de Paris-Sud, Bât 410, 91405 Orsay, France

Abstract: Under biphasic conditions (CH_2Cl_2/H_2O) using acetone, oxone, buffer and phase-transfer catalyst $Bu_4NHSO_4^-$, some secondary amines without α hydrogens are oxidized to their corresponding nitroxides in rapid and good yields.

Interest in the chemistry of nitroxides has been stimulated in recent years by their application as probes in materials [1], spin labels in biochemistry [2] and more recently as contrast agents in magnetic resonance imaging [3] or electron spin resonance imaging [4]. However, one of the major trends in modern organic synthesis is the development of very selective reagents. In the field of oxidation of organic compounds, the number of selective oxidizing agents is still fairly small. The preparation of nitroxides by amine oxidation, more recent than the dehydrogenation of hydroxylamine, is currently more widely used and is particularly useful in the preparation of cyclic dialkyl nitroxides.

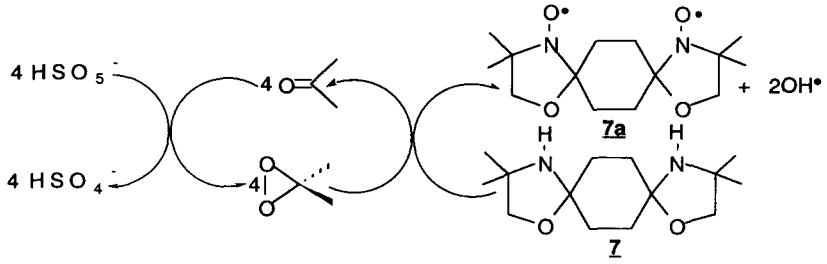
Among the oxidizing agents used to prepare nitroxides are hydroperoxides [5-7] hydrogen peroxide with cerium [8-11], silver oxide [12], alkaline solutions of hydrogen peroxides [13], lead(IV)-oxide [14], various peracids [15], pertungstate ion [16] and benzoyl peroxide [17]. In fact, these reagents, particularly MCPBA, are toxic, commercially expensive, acidic and bulky molecules which could explain why they are not suitable for the oxidation of hindered secondary amines particularly aminoxyls formed in very low chemical yields from the corresponding oxazolidines. Looking for a rapid, facile and large scale oxidation of secondary amines and aminoxyls, we reinvestigated the Murray's procedure [18] to synthesize and isolate dimethyldioxirane. Although oxone [19], the oxidant used by Murray to generate dimethyloxirane is inexpensive, the amount required to produce mole quantities of dioxirane would be enormous. Edwards and Curci [20] as well as Murray [18] and Zabrowski [21] reported a method for forming an excess of the intermediate dimethyloxirane *in-situ* by reaction of potassium peroxomonosulfate with acetone under phase-transfer conditions. This process has initially been used for the stereo and regioselective epoxidation of some allylic alcohols [22], alkenes [23], arenes [24], alkynes [25] and for conversion of isocyanates [26] or amines into nitrocompounds or hydroxylamines [27], as well as for the conversion of sulphides into sulphones and sulphoxides [28]. The phase-transfer reaction reported in this paper (Scheme 1) was carried out at 0°C using only a slight excess of oxone for the oxidative transformation. The acetone-catalyzed oxidation by peroxomonosulfate was readily performed in CH_2Cl_2/buffered water (pH 7.5-8), biphasic system and $Bu_4NHSO_4^-$ as a phase-transfer catalyst. However, in

order to avoid the formation of nitrones, hydroxylamines and nitro compounds, which are not paramagnetic species, the amine functions must be secondary and without α hydrogens (R tertiary carbon).



Scheme 1

The process involves the formation of dimethyloxirane by nucleophilic attack of oxone on the carbonyl carbon with subsequent loss of potassium hydrogen sulfate (HSO_4^-) [22]. The oxygen is transfered to the amine in a biphasic medium affording the oxidized product (nitroxide) and regenerating the initial ketone. Owing to the competitive peroxide decomposition [29, 30], oxone was in large excess over the stoichiometric amount to regenerate more dimethyloxirane required for the oxidation (scheme 2). However, little or no oxidation was observed in the absence of acetone. For example, the diamine 7 oxidized by Rassat [31] using *m*-chloroperbenzoic acid (MCPBA) gives dinitroxide 7a in a 50% yield. Using this method, the biradical 7a is obtained in a 90% yield. The recorded EPR spectrum is characteristic of a biradical with a large exchange interaction **J**, ($\mathbf{J >> a_n}$) [31].



Scheme 2

In addition to the low price of oxone and the rapidity of the reaction, this method for oxidizing secondary amines to nitroxides should be useful when acidic conditions for oxidation cannot be employed, particularly to prepare oxazolidines from aminoxyls. Typical results are shown in table 1.

General procedure. In a typical reaction, a mixture of acetone (80 mL), methylene chloride (60 mL), tetra-n-butylammonium hydrogen sulfate (0.085 g, 0.25 mmol), phosphate buffer (60 mL) and 1,4-bis(4,4-dimethyloxazolidine)cyclohexane 7 [31] (1 g, 4 mmol) was stirred vigorously at 0°C while a solution of oxone (19 g, 31 mmol) in water (90 mL) was added dropwise over a period of 1h. The apparent pH of the mixture was monitored and kept constant at pH 7.5-8 by adding a 2N solution of KOH. The reaction mixture became deep yellow coloured in a few minutes. Upon completion of the addition, the reaction was allowed to proceed at 0-6°C for 3h with stirring during the entire reaction time. The CH_2Cl_2 layer was separated and the aqueous phase extracted with CH_2Cl_2. The combined methylene extracts were dried ($MgSO_4$) and concentrated

in vacuo to give 1g of residue which was recrystallized from ether to afford 1,4-bis(4,4-dimethyloxazolidine-3-oxyl)cyclohexane 7a in 90% yield.

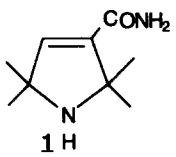
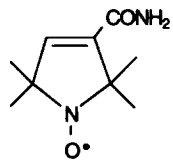
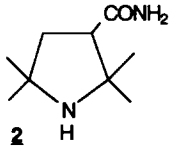
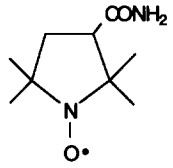
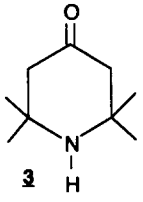
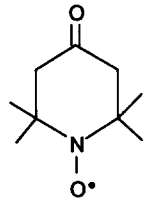
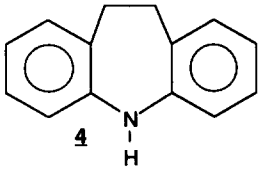
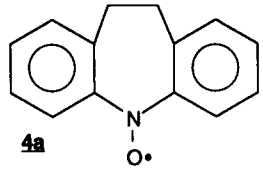
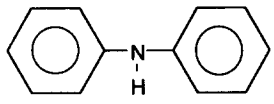
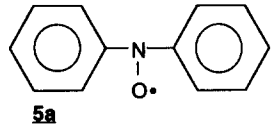
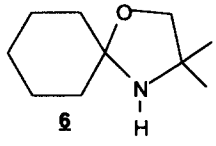
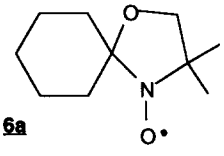
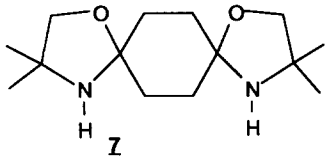
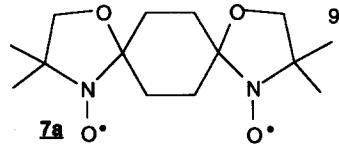
Amines	Nitroxide products *	Isolated yield %	a_N ** (Gauss)	References
 1 H	 1a	85	14.52	32
 2 H	 2a	82	15.54	32
 3 H	 3a	75	14.95	32
 4 H	 4a	89	10.66	
 5	 5a	83	10.69	34
 6 H	 6a	93	16.12	33
 7	 7a	90	$\frac{a_N}{2}$ =7.76	31

Table 1: * All of the nitroxides listed in Table 1 had EPR hyperfine constant (a_N)** and spectral data that were identical with those given in the literature or with those of samples prepared locally by using literature methods.

References and notes

1. Miller, W. G. *Spin Labelling II, Theory and application*; Berliner, L. J, Ed.; Acad. Press: New York, **1976**; pp. 173.
2. (a) Berliner. L. J. *Spin Labelling Theory and applications*; vols. *1* and *2* Acad. Press: New York, **1976** and **1979**. (b) McConnell, H. M.; McFarland, G. B. *Quart. Rev. Biophys.* **1970**, *3*, 91-136. (c) Likhenstein, G. T. *Spin labelling methods in molecular biology*; Wiley-Interscience: New York, **1976**.
3. (a) Brasch, R. C. *Radiology*. **1983**, *147*, 781-788. (b) Brik, M. E.; Courtieu. J.; Lecayon, M.; Pechiné, J. M.*J. Radiol.* **1989**, *70*, 11, 653-658. (c) Brik, M. E.; Courtieu, J.; Lecayon, M.; Pechiné, J. M. *J. Radiol.* **1990**, *71*, 2, 125-131, and references therein
4. Kuppusamy, P.; Chzhan, M.; Zweir, J. L. *J. Magn. Reson. (b)*. **1995**, *106*, 26, 122-130.
5. Coppinger, G. M.; Swalen, J. D. *J. Am. Chem. Soc*. **1961**, *83*, 4900-4902.
6. Buchachenko, A. L. *Optika i Spectroskopiya*. **1962**, *13*, 795-798.
7. Pannel, J. *Mol. Phys*. **1962**, *5*, 291-300.
8. Florin, R. E. *J. Chem. Phys*. **1967**, *47*, 345-346.
9. Thomas, J. R. *J. Am. Chem. Soc*. **1960**, *82*, 5955-5956.
10. Baird, J. C.; Thomas, J. R. *J. Chem. Phys*. **1961**, *35*, 1507-1509.
11. Adams, J. A.; Nicksic, S. W.; Thomas, J. R. *J. Chem. Phys*. **1966**, *45*, 654-661.
12. Frangopol, R. T.; Frangopol, M.; Negoita, N.; Balaban, A. T. *Rev. Roumain*. **1969**, *14*, 385-387.
13. Hudson, A.; Hussain, H. A. *J. Chem. Soc. (b)*. **1967**, 1299-1300.
14. Neugebauer, F. A.; Fischer, P. H. *Z. Naturforsch. (b)*. **1966**, *21*, 1036-1038.
15. (a) Chapelet-Letourneux, G.; Lemaire, H.; Rassat, A. *Bull. Soc. Chim. Fr*. **1965**, 3283-3298. (b) Gilbert, B. C.; Stell, J. K.; Whitwood, A. C.; Haliwell, C.; Sanderson, W. R. *J. Chem. Soc.* Perkin. Trans. **1991**, *2*, 629-634, (c) Sufiallin, R. L.; Enikeeva, L. R.; Bukin, I. I.; Makhametova, G. A.; Shishlov, N. M.; Komissarov, V. D. *Izv. Akad. Nauk. SSSR.*,Ser. Khim. **1990**, *5*, 1162-1163. (d) Rozantsev, E. G.; Neiman, N. B. *Tetrahedron*. **1964**, *20*, 131-137. (e) Rozantsev, E. G.; Burmistrova, R. S. *Izv. Akad. Nauk. SSSR. Ser. Khim*. **1966**, *8*, 1477-1479. (f) Rozantsev, E. G.; Kokhanov. Yu. V. *Bull. Acad. Sci. USSR*. **1966**, 1422-1430.
16. Lebedev, O. L.; Khiedekel, M. L.; Razuvaev, G. A. *Dok. Akad. Nauk .SSSR*. **1961**, *140*, 1327-1329.
17. Someno, K.; Kekuchi, O. *Kogyo Kogaku Zasshi*. **1965**, *68*, 1527-1530.
18. Murray, R. W.; Jeyarannan. R. *J. Org. Chem*. **1985**, *50*, 2847-2853.
19. The commercially oxone known as peroxomonosulfate or Caro's salt is represented by the formula ($2KHSO_5.KHSO_4.H_2SO_4$)
20. Cicula, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem*. **1982**, *47*, 2670-2673
21. Zabrowski, D. L.; Moormann, A. E.; Beck, K. R. *Tetrahedron Lett*. **1988**, *29*, 36, 4501-4504.
22. Denmark, S. E.; Forbes, D. C.; Hays, D. S.; De Pue, J. S.; Wilde, R. G. *J. Org. Chem*. **1995**, *60*, 1391-1407.
23. (a) Curci, R.; Fiorentino, M.; Troisi. L.; Edwards, J. O.; Pater, R. H.*J. Org. Chem*. **1980**, *45*, 4758-4760. (b) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc. Chem. Comm*. **1984**, 155-156.
24. Jayaraman, R.; Murray, R. W. *J. Am. Chem. Soc*. **1984**, *106*, 2462-2463.
25. (a) Murray, R. W. *Chem. Rev*. **1989**, *89*, 1187-1801. (b) Curci, R. *Advances in oxygenated Processes* ; Baumstark, A. L. Ed.; JAI: Greenwich, CT, USA, 1988, Vol. *2*, pp. 1-83. (c) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res*. **1989**, *22*, 205-211.
26. Eaton, P. E.; Wicks, G. E. *J. Org. Chem*. **1988**, *53*, 5353-5355.
27. (a) Crandall.; J. K.; Thierry. R. *J. Org. Chem*. **1992**, *57*, 6759-6764. (b) Murray, R. W.; Singh, M. *Terahedron Lett*. **1988**, *29*, 37, 4677-4680. (c) Webb, K. S.; Seneviratne, V. *Tetrahedron Lett*. **1995**, *36*, 14, 2377-2378. (d) Murray, R. W.; Rajadhyaksha, S. N.; Mohan, L. *J. Org. Chem*. **1989**, *54*, 5783-5788. (e) Murray, R. W.; Singh, M. *J. Org. Chem*. **1990**, *55*, 2954-2957. (f) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem*. **1990**, *55*, 1981-1983.
28. (a) Colonna, S.; Gaggero, N. *Tetrahedron Lett*. **1989**, *30*, 45, 6233-6236. (b) Colonna, S.; Gaggero, N.; Leone, M. *Tetrahedron Lett*. **1991**, *47*, 39, 8385-8398. (c) Grenhalgh, R. P. *Synlett*. **1992**, 235-236. (d) Evans, T. L.; and Grade, M. M. *Synth. Comm*. **1986**, *16*, 10, 1207-1216. (e) Volkmann, R. A.; Kolbaugh, P. R.; Nason, D. M.; Jasys, V. J. *J. Org. Chem*. **1992**, *57*, 4352-4361. (f) Quallich, G. J.; Lackey, J. W. *Tetrahedron Lett*. **1990**, *31*, 26, 3685-3686. (g) Trost, B. M.; Curran, D. P. *Tetrahedron Lett*. **1981**, *22*, 14, 1287-1290. (h) K. S. Webb, K. S. *Tetrahedron Lett*. **1994**, *55*, 21, 3457-3460.
29. Edwards, J. O.; Pater, R. H.; Curci, R.; Difuria, F. *Photochem. Photobiol*. **1979**, *30*, 63-70.
30. Gallopo, A. R.; Edwards, J. O. *J. Org. Chem*. **1981**, *46*, 1684-1688.
31. Michon, P.; Rassat, A. *J. Am. Chem. Soc*. **1975**, *97*, 4, 696-200.
32. (a) Rozantsev, E. G.; Sholle, V. D. *Synthesis*. **1971**, 190-202. (b) Rozantsev, E. G.; Krinitzkaya, L. *Tetrahedron*. **1965**, *21*, 491-499.
33. Keana, J. F. W. *Chem. Rev*. **1978**, *78*, 1, 37-64.
34. Rassat, A.; Lemaire, H. *J. Chim. Phys*. **1964**, 1576-1579.

(*Received in France* 9 *May* 1995; *accepted* 12 *June* 1995)