JOC*Note*

pubs.acs.org/joc

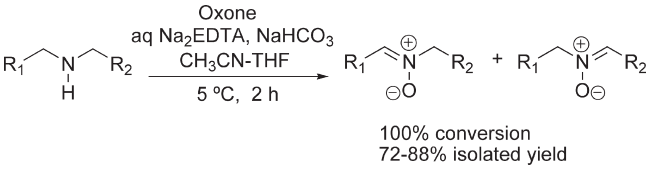
A Metal-Free General Procedure for Oxidation of Secondary Amines to Nitrones

Carolina Gella, Èric Ferrer, Ramon Alibés, Félix Busqué,* Pedro de March, Marta Figueredo,* and Josep Font

Universitat Autònoma de Barcelona, Departament de Química, 08193 Bellaterra, Spain

felix.busque@uab.es; marta.figueredo@uab.es

Received May 26, 2009

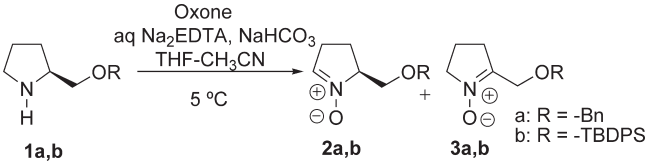


An efficient and metal-free protocol for direct oxidation of secondary amines to nitrones has been developed, using Oxone in a biphasic basic medium as the sole oxidant. The method is general and tolerant with other functional groups or existing stereogenic centers, providing rapid access to enantiomerically pure compounds in good yields.

Nitrones and their derivatives are highly versatile building blocks for the synthesis of a variety of natural products and biologically active compounds.[1] Traditionally, nitrones have been synthesized by condensation of aldehydes with *N*-monosubstituted hydroxylamines,[1,2] or via oxidation of the corresponding hydroxylamines,[3] imines,[4] and amines.[5] These last two options are the most attractive methods because of the greater availability of the required amines or imines compared to the corresponding hydroxylamines. Published methodologies concerning the oxidation of imines to nitrones are scarce and present poor structural diversity application,[4a,4b] with the exception of the work developed by Goti's group.[4c] The direct oxidation of amines to nitrones has been achieved through different procedures, using oxaziridines,[5a] dioxiranes,[5b] or hydroperoxides (including H_2O_2) paired with diverse metal-catalytic systems.[5c−n]

Recently, we have reported a flexible synthetic approach to several *Stemona* alkaloids illustrated with the preparation of the putative structure of stemonidine.[6] In this synthesis, we required an efficient procedure for the preparation of an enantiopure nitrone as **2** (Scheme 1).

SCHEME 1



We had already published the preparation of this type of substituted pyrroline *N*-oxides in enantiopure form by oxidation of the corresponding amine[7] or imine[8] with methyl(trifluoromethyl)dioxirane or dimethyldioxirane, respectively. However, these procedures proved to be difficult to scale up, essentially because of the problematic preparation of the mentioned dioxiranes in multigram quantities. To avoid these difficulties, we envisaged the use of methyl(trifluoromethyl)dioxirane generated in situ from trifluoroacetone using potassium hydrogen persulfate, commercially available as Oxone,[9] following a methodology previously described for the epoxidation of several olefins.[10]

Despite Oxone having been extensively employed as oxidant in organic synthesis,[11] only a few reports have appeared dealing with its use for the oxidation of amines. Thus, the synthesis

(1) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. 2, Chapter 9. (b) Torssell, K. B. G. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH Verlagsgesellschaft: Weinheim, Germany, 1988. (c) Padwa, A.; Pearson, W. H. In *Synthetic Applications of 1,3-Dipolar Cycloadditions. Chemistry Toward Heterocycles and Natural Products*; John Wiley & Sons: Hoboken, NJ, 2003; Chapter 1.

(2) Robl, J. A.; Jih, R. H. *J. Org. Chem.* **1985**, *50*, 5913–5916.

(3) (a) Murahashi, S.-I.; Mitsui, H.; Watanabe, T.; Zenki, S. I. *Tetrahedron Lett.* **1983**, *24*, 1049–1052. (b) Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571–6574. (c) Ali, Sk. A.; Hashmi, S. M. A.; Siddiqui, M. N.; Wazeer, M. I. M. *Tetrahedron* **1996**, *52*, 14917–14928. (d) Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, *64*, 7243–7245. (e) Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett.* **1999**, *40*, 1989–1992. (f) Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503–6505. (g) Saladino, R.; Neri, V.; Cardona, F.; Goti, A. *Adv. Synth. Catal.* **2004**, *346*, 639–647.

(4) (a) Christensen, D.; Jørgensen, K. *J. Org. Chem.* **1989**, *54*, 126–131. (b) Hanquet, G.; Lusinchi, X. *Tetrahedron* **1994**, *50*, 12185–12200. (c) Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2007**, *9*, 473–476. (d) Cardona, F.; Bonanni, M.; Soldaini, G.; Goti, A. *ChemSusChem.* **2008**, *1*, 327–332.

(5) (a) Zajac, W. W.; Walters, T. R.; Darcy, M. G. *J. Org. Chem.* **1988**, *53*, 5856–5860. (b) Murray, R. W.; Singh, M. *J. Org. Chem.* **1990**, *55*, 2954–2957. (c) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383–2386. (d) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736–1744. (e) Ballistreri, F. P.; Chiacchio, U.; Rescifina, A.; Tomaselli, G. A.; Toscano, R. M. *Tetrahedron* **1992**, *48*, 8677–8684. (f) Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170–6172. (g) Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett.* **1995**, *36*, 3561–3562. (h) Murray, R. W.; Iyanar, K.; Chen, J.; Wearing, J. T. *J. Org. Chem.* **1996**, *61*, 8099–8102. (i) Goti, A.; Nannelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025–6028. (j) Murahashi, S.-I.; Ohtake, H.; Imada, Y. *Tetrahedron Lett.* **1998**, *39*, 2765–2766. (k) Forcato, M.; Nugent, W. A.; Licini, G. *Tetrahedron Lett.* **2003**, *44*, 49–52. (l) Choudary, B. M.; Reddy, Ch. V.; Prakash, B. V.; Bharathi, B.; Kantam, M. L. *J. Mol. Catal. A: Chem.* **2004**, *217*, 81–85. (m) Colladon, M.; Scarso, A.; Strukul, G. *Green Chem.* **2008**, *10*, 793–798. (n) Zonta, C.; Cazzola, E.; Mba, M.; Licini, G. *Adv. Synth. Catal.* **2008**, *350*, 2503–2506.

(6) Sánchez-Izquierdo, F.; Blanco, P.; Busqué, F.; Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Parella, T. *Org. Lett.* **2007**, *9*, 1769–1772.

(7) Closa, M.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1031–1037.

(8) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437–445.

(9) Oxone is a product consisting of a 2:1:1 mixture of the active ingredient $KOSO_2OOH$, along with $KHSO_4$ and K_2SO_4, respectively.

(10) (a) Evarts, J. B. Jr.; Fuchs, P. L. *Tetrahedron Lett.* **2001**, *42*, 3673–3675. (b) Wei, L.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2853–2856.

(11) Burke, S. D.; Danheiser, R. L. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents*; John Wiley & Sons: Chichester, UK, 1999.

(12) (a) Kennedy, R.-J.; Stock, A.-M. *J. Org. Chem.* **1960**, *25*, 1901–1906. (b) Priewisch, B.; Rück-Braun, K. *J. Org. Chem.* **2005**, *70*, 2350–2352. (c) Crandall, J. K.; Reix, T. *J. Org. Chem.* **1992**, *57*, 6759–6764. (d) Kettani, A. E.-C.; Bernadou, J.; Meunier, B. *J. Org. Chem.* **1989**, *54*, 3213–3215. (e) Fields, J. D.; Kropp, P. J. *J. Org. Chem.* **2000**, *65*, 5937–5941. (f) Aggarwal, V. K.; Lopin, Ch.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596–7601.

DOI: 10.1021/jo901108u Published on Web 07/16/2009

TABLE 1. Optimization of Oxone Oxidation of Secondary Amines 1 to Nitrones 2 and 3

entry[a]	amine	oxidant	mixture of solvents	other changes	yield,[b] %	ratio **2**:**3**
1	**1a**	Oxone−ketone **4**[c]	aq 0.01 M Na_2EDTA−CH_3CN−THF	[**1a**] = 0.03 M	49	1:2.8
2	**1a**	Oxone−ketone **4**	aq 0.01 M Na_2EDTA−CH_3CN−THF		69	1:2.2
3	**1a**	Oxone−ketone **4**	aq 0.01 M Na_2EDTA−CH_3CN−THF	rt	30[d]	1: 2.1
4	**1a**	Oxone−ketone **5**[e]	aq 0.01 M Na_2EDTA−CH_3CN−THF		58	1: 1.7
5	**1a**	$PhSO_2NOCHPh$	$CHCl_3$		62	1: 1.8
6	**1b**	Oxone−ketone **5**	aq 0.01 M Na_2EDTA−CH_3CN−THF		79	1.3: 1
7	**1b**	Oxone	aq 0.01 M Na_2EDTA−CH_3CN−THF		88	1.3: 1
8	**1b**	Oxone	aq 0.01 M Na_2EDTA−MeOH		76	1.3: 1
9	**1b**	Oxone	aq 0.1 M Na_2EDTA−CH_3CN−THF		82	1.3: 1
10	**1b**	Oxone	H_2O−CH_3CN−THF		78	1: 1.3
11	**1b**	Oxone	aq 0.1 M Na_2EDTA−CH_3CN−THF	without $NaHCO_3$		

[a]All reactions were performed at 5 °C with amine **1** (2 mmol), Oxone (2.1 mmol), and $NaHCO_3$ (10 mmol) in 6.5 mL of a mixture of (aq 0.01 M Na_2EDTA)−CH_3CN−THF (1:1:0.25) ([**1a**] = 0.3 M) and reached complete conversion unless otherwise indicated. [b]Yields of isolated pure nitrones. [c]Ketone **4**: *p*-F-C_6H_4-$COCF_3$. [d]40% conversion. [e]Ketone **5**: CH_3COCF_3.

of nitroso compounds[12a,12b] or oximes[12c] from primary amines, amine oxides from tertiary amines,[12d,12e] and hydroxylamines from the corresponding amines has been described.[12e] Secondary amines are reported to remain intact with use of Oxone in acid media.[12a] The unique example describing the oxidation of a secondary amine to a mixture of nitrones (31% yield) was reported in a work dealing with the asymmetric epoxidation of alkenes by Oxone under basic conditions,[12f] when studying the fate of an enantiopure pyrrolidine derivative used as catalyst.

Herein, we report that Oxone can be used effectively, in a biphasic basic medium as the sole oxidant, for the direct conversion of secondary amines to nitrones through a straightforward and simple procedure.

Initially, oxidation of amine (*S*)-**1a** (Scheme 1) was performed in similar experimental conditions to those previously described for the epoxidation of olefins[10] (Table 1, entry 1), leading to a chromatographically inseparable 1:2.8 mixture of the desired aldonitrone **2a** and ketonitrone **3a** in 49% overall yield.

Increasing the amine concentration in the biphasic system showed little influence on the regioselectivity of the reaction. Thus, when the amine concentration was changed from 0.03 to 0.3 M, a 1:2.2 mixture of nitrones **2a** and **3a** was obtained in 69% yield (entry 2). This higher concentration was adopted for the general procedure because it was advantageous in order to scale up the process.

Changing the temperature from 5 °C to room temperature decreased the conversion of the transformation, due to Oxone decomposition[13] at the basic pH of reaction conditions (entry 3). A modification of the fluorinated ketone did not show any significant influence in the outcome of the reaction (entry 4). When Davis oxaziridine[5a] was used as the oxidant, no substantial change was observed on the regioselectivity of the reaction either (entry 5). In all these cases, the ratio between nitrones **2a** and **3a** could not be determined by NMR analysis of the mixtures, and it was estimated from the ratio between their 1,3-dipolar cycloaddition products with dimethyl acetylenedicarboxylate. Similar yields of cycloadducts were obtained by performing the cycloaddition in situ in the oxidation media, after amine consumption, or with the crude material after workup of the oxidation reaction.

It is noteworthy that the nature of the protecting group showed an influence not only on the regiochemistry of the reaction, but also on the properties of nitrones **2** and **3**. Thus, oxidation of amine (*S*)-**1b** gave a 1.3:1 mixture of nitrones (*S*)-**2b** and **3b** in 79% yield (entry 6). These compounds proved to be separable by means of standard flash column chromatography through silica gel in multigram quantities. In this case, the ratio between nitrones **2b** and **3b** can be easily established by integration of the H-1′ proton signals in the ^1H NMR spectrum of the mixtures.

Remarkably, the reaction worked equally well with Oxone as oxidant without the addition of any trifluoroketone (entry 7). This last reaction was repeated starting from the enantiomer of amine (*S*)-**1b**, affording the corresponding nitrones (*R*)-**2b** and **3b**. The optical rotation values of nitrones (*S*)-**2b** {$[\alpha]_D$ −13.0 (*c* 1.56, CH_2Cl_2)} and (*R*)-**2b** {$[\alpha]_D$ +13.3 (*c* 1.58, CH_2Cl_2)} proved to be consistent. The enantiomeric purity of nitrones (*S*)-**2b** and (*R*)-**2b** was confirmed by chiral HPLC of a derivative.[14]

Replacement of the solvent mixture of CH_3CN−THF by MeOH (entry 8) or the use of more concentrated solutions of aqueous Na_2EDTA (entry 9) did not alter the course of the reaction. On the contrary, when the aqueous Na_2EDTA solution was substituted by water, an undesired change in the regioselectivity of the reaction was observed (entry 10). As expected,[12a] when the amine **1b** was submitted to the action of Oxone in acid medium without addition of $NaHCO_3$, only starting amine unaltered with several degradation products was obtained (entry 11).

In summary, after much experimentation, we have developed a new procedure for the preparation of enantiopure nitrone **2b** from the corresponding amine in 50% yield (Table 1, entry 7). It was possible to scale up the reaction to obtain 10 g of nitrone without detriment of yield or optical purity. This nitrone was used by our research group for the synthesis of the putative structure of stemonidine,[6] and this methodology has recently been applied by another research group in the synthesis of an enantiopure nitrone from the corresponding pyrrolidine.[15]

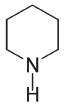
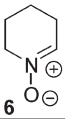
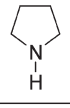
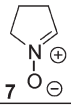
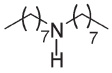
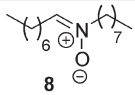
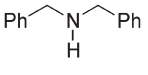
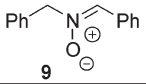
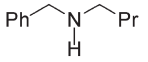
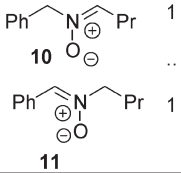
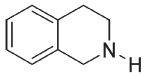
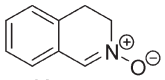
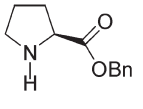
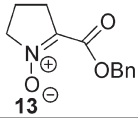
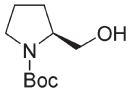
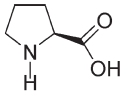
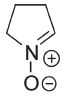
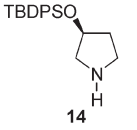
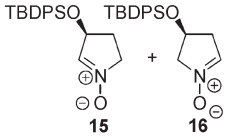
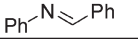
The experimental procedure herein described was judged specially interesting owing to its low cost, simplicity, and environmentally friendly character, considering the absence

(13) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391–1407.

(14) The enantiomeric purity of nitrones **2b** and *ent*-**2b** can be easily confirmed by chiral HPLC of the corresponding *endo* cycloadducts derived from the 1,3-dipolar cycloaddition with (*E*)-2-hexenedioic acid dimethyl ester. See the Supporting Information1 for more details.

(15) Cordero, F. M.; Bonanno, P.; Neudeck, S.; Vurchio, C.; Brandi, A. *Adv. Synth. Catal.* **2009**, *351*, 1155–1161.

TABLE 2. Scope of Oxone Oxidation of Secondary Amines to Nitrones

entry	amine	products	yield[a]
1		 **6**	85%
2		 **7**	77%
3		 **8**	72%
4		 **9**	86%
5		 **10** : **11** 1 : 1	84%
6		 **12**	79%
7		 **13**	82%
8		Starting material	
9			56%
10	 **14**	 **15** : **16** 2.5 : 1	83%
11		Degradation products	

[a]Yields of isolated pure nitrones All reactions reached complete conversion unless otherwise indicated.

of unstable reagents as dioxiranes,[5b,7] metals, and halogenated compounds or solvents, usually present in other methodologies previously described.[5a,5c−l] Therefore, we decided to study the scope of this protocol extending it to other amines (Table 2). In most of the cases, the oxidation proceeds efficiently with yields over 70%.

Symmetrically substituted secondary amines (Table 2, entries 1−4) were cleanly converted to the corresponding nitrones with yields between 72% and 86% without any further purification needed. Asymmetrically substituted amines (entries 5−7) were oxidized in similar yields to the corresponding conjugated nitrones (entries 6 and 7), or to a 1:1 mixture of regioisomeric conjugated and nonconjugated nitrones (entry 5). The experiment performed in entry 7 showed too that the ester moiety is stable under the reaction conditions of the present oxidation protocol. Similarly, hydroxyl and carbamate moieties proved to be stable, according to the experiment of entry 8, where the starting material was recovered unaltered. As previously described with use of other methodologies,[5f] when L-proline was submitted to this oxidation protocol, the decarboxylated nitrone was obtained as the main product (entry 9).

Remarkably, oxidation of amine **14** (entry 10) afforded a 2.5:1 mixture of regioisomeric nitrones **15** and **16** in 83% total yield. These compounds proved to be easily separable by means of standard chromatography through silica gel, furnishing synthetically valuable[16] nitrone **15** in multigram quantities. Again, the ratio between nitrones **15** and **16** was established from ^{1}H NMR analysis of the mixture.

It has to be pointed out that when an imine was exposed to the oxidation conditions (entry 11), only degradation products were obtained. This result discards the hypothesis of an imine as intermediate in the reaction mechanism.

In conclusion, an efficient and metal-free general protocol for direct oxidation of secondary amines to nitrones has been developed, using Oxone in a biphasic basic medium as the sole oxidant. The method is general and tolerant with other functional groups or existing stereogenic centers, providing rapid access to enantiomerically pure compounds in good yields.

Experimental Section

General Procedure for the Oxidation. To a stirred solution of amine (2.0 mmol) in a mixture of acetonitrile−THF 4:1 (3.5 mL) and 0.01 M aqueous EDTA solution (2.8 mL) at 5 °C was added $NaHCO_3$ (0.84 g, 10.0 mmol). While cooling to maintain the temperature at 5 °C, Oxone (1.29 g, 2.1 mmol) was added over 2 h under vigorous stirring. The mixture was stirred for 20 min at 5 °C and then ethyl acetate (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 ×10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. In most cases, the remaining crude material does not need further purification. If necessary, regioisomeric nitrones were separated and purified by flash column chromatography over silica gel.

Acknowledgment. We acknowledge financial support from DGES (projects CTQ2004-2539 and CTQ2007-60613/BQU) and a grant from *Generalitat de Catalunya* (E.F.) and acknowledge MCYT-ERDF for a Ramón y Cajal contract (F.B.). We also want to acknowledge graduate student Nuria Bardají for some work related to the development of the general oxidation procedure.

Supporting Information Available: General experimental procedures, experimental details, and characterization data of new compounds (**3b**, **13**, **14**, **15**, **16**), ^{1}H and ^{13}C NMR spectra of all new compounds and ^{1}H NMR of the known nitrones, and CHPLC chromatograms of derivatives of nitrones **2b** and *ent*-**2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) (a) Goti, A.; Cacciarini, M.; Cardona, F.; Brandi, A. *Tetrahedron Lett.* **1999**, *40*, 2853–2856. (b) Cordero, F. M.; Gensini, M.; Goti, A.; Brandi, A. *Org. Lett.* **2000**, *2*, 2475–2477. (c) Alibés, R.; Blanco, P.; Casas, E.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Alvarez-Larena, A. *J. Org. Chem.* **2005**, *70*, 3157–3167.