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Manganese dioxide oxidation of hydroxylamines to nitrones

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Abstract—Several structurally differentiated N,N-dialkylhydroxylamines were oxidised to the corresponding nitrones using MnO₂. Manganese dioxide revealed an efficient and mild reagent for oxidation of hydroxylamines, showing a level of regioselectivity comparable to HgO. Its non-toxicity makes MnO₂ the reagent of choice for replacing HgO in this oxidation. © 2001 Elsevier Science Ltd. All rights reserved.

Nitrones are useful synthetic tools displaying a high reactivity, mainly as 1,3-dipoles in cycloaddition reactions¹ or as imines in nucleophilic additions,² that allows the straightforward synthesis of structurally complex molecules with a high degree of selectivity. Condensation of a *N*-alkylhydroxylamine with a carbonyl compound and oxidation of a *N*,*N*-dialkylhydroxylamine are the two commonest methods for the synthesis of nitrones (Scheme 1).³ Recently, the second strategy was used to obtain a variety of enantiopure five membered cyclic nitrones.⁴

Many methods have been employed for the oxidation of N,N-dialkylhydroxylamines into the corresponding nitrones. However, many of them lack generality and the most widely used oxidant for this transformation is yellow HgO.³ Mercury oxide has proven a mild and selective oxidant for this class of compounds, but its high toxicity together with the large excess that is



Scheme 1.

needed to ensure complete oxidation, raises severe concerns regarding its use and disposal. This issue prompted the development of alternative methods. Various metal (copper, silver, lead and ruthenium) salts as well as organic oxidants and (salen)Mn(III) complexes proved useful for this oxidation.^{3,5} Recently, we have reported an environmentally friendly oxidation method with bleach;⁶ this method resulted valuable and general although it suffered from low yields for water soluble nitrones and low regioselectivity with non-symmetrically substituted dialkylhydroxylamines. In this communication we propose MnO₂ as a valid non-toxic substitute of HgO for the oxidation of N,N-dialkylhydroxylamines. Manganese(IV) oxide is a well known oxidant for the dehydrogenation of activated alcohols and amines, as well as for the oxidative cleavage of 1,2-diols and has found broad application due to the mildness of the reagent.⁷ A perusal of the literature showed that MnO₂ was used only occasionally for the oxidation of hydroxylamines with peculiar structures to the corresponding nitrones,8 and has never reached the reputation of a first choice reagent for this reaction.

The oxidation of several structurally differentiated hydroxylamines with commercial MnO_2 ('activated', 90% purity, Fluka catalogue no. 63548) gave nitrones in good to excellent yield (Table 1).

Open-chain hydroxylamines 6-9 afforded the more stable Z stereoisomers in over 90% yield, with 8 and 9 the oxidation took place only on the more reactive benzylic position. Substituted N-hydroxypyrrolidines, either at C-2 and C-3, allowed the evaluation of the regioselectivity of the reaction. Hydroxylamine 10 afforded a

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Table 1. Oxidations of hydroxylamines with MnO₂

Entry	Hydroxylamines ¹⁰	Reaction time (h)	Nitrones	Yield (%)
1	N OH 6	2	N+ 0 ⁻ 14	90
2	Ph N Ph OH 7 Ph	2	Ph N Ph O 15 Ph	93
3		12		96
4	8 >0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	12	$\begin{array}{c} 16 \\ \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	96
5	∧ ∧ ⊖H 10	2	N+ 0-18 5:1 0-19	92
6	N N OH	2	Ot-Bu $Ot-Bu$ $Ot-Bu$ $Ot-Bu$ $Ot-Du = 0$	Bu 1 ⁸⁵
7	BnO, OBn N 12 OH	2	BnO, OBn 22	95
8	о 13 о́н	2	0 0 0 23 0 ⁻ 23	91

mixture of the two regioisomeric nitrones 18 and 19 in 5:1 ratio showing a higher selectivity with respect to HgO (3:1)⁹ and bleach (2:1).⁶ Conversely the selectivity is slightly lower, compared to HgO, in the oxidation of hydroxylamine 11 (7:1 versus 9:1),^{4d} but still much higher than with bleach. This selectivity suggests a common mechanism for MnO₂ and HgO in the oxidation of hydroxylamines.^{4b,d} Other commercially available types of MnO₂ were tested in the oxidation. Pure MnO₂ (99%, Riedel de Haen) was found to be a poor oxidant for hydroxylamines, as already reported for other substrates,^{7a} while 75% MnO₂ (Aldrich) gave in the oxidation of 10 a similar yield but a lower selectivity (3.5:1).

General procedure: All reactions were performed using a small excess (1.5 equiv.) of commercially available 'activated' MnO_2 (90% purity) added to an ice-cooled solu-

tion of the hydroxylamine¹⁰ (1–5 mmol) in CH_2Cl_2 (0.5 M). The resulting dispersion was stirred at rt for the appropriate time (Table 1) then filtered (gravity) through a short pad of Celite and Na₂SO₄. The resulting solution was concentrated to afford spectroscopically pure compounds.

These results show that MnO_2 is a suitable and general oxidant for hydroxylamines, able to give the corresponding nitrones in good to excellent yields. This reagent allows therefore the replacement of HgO, thus providing a less hazardous method.¹¹

Acknowledgements

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- Hydroxylamines 6 and 7 were purchased from Aldrich and used without further purification. Hydroxylamine 10 was synthesised according to Ref. 4e, 11 according to Ref. 4b, 12 to Ref. 4e, 13 to Ref. 5c. Hydroxylamines 8 and 9 are new compound fully characterised, manuscript in preparation. For nitrone 17 see also Merino, P.; Franco, S.; Merchan, F.L., Tejero, T. Synth. Commun. 1997, 27, 3529–3537.
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