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New method of *in situ* generation of nitrile oxides by MnO_2 oxidation of aldoximes

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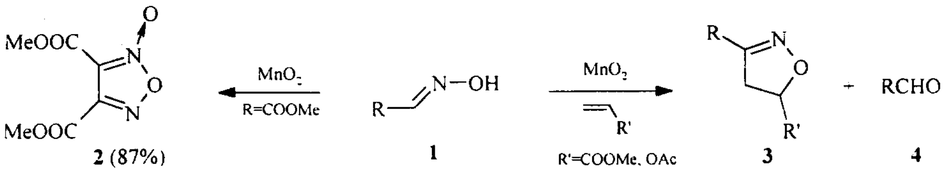
Abstract: Manganese(IV) oxide (MnO_2) was found to oxidize aldoximes to nitrile oxides. Nitrile oxides were trapped *in situ* with dipolarophiles to furnish 2-oxazolines. The best results were obtained with hydroximinoacetates as nitrile oxide precursors. © 1999 Elsevier Science Ltd. All rights reserved.

Nitrile oxides are versatile intermediates for the preparation of heterocyclic compounds *via* 1,3-dipolar cycloaddition.[1] However, nitrile oxides are unstable and dimerize readily, hence they are usually generated *in situ*. There are two frequently utilized methods of generation of nitrile oxides. The Mukaiyama method is based on reaction of primary nitroalkanes with phenyl isocyanate and a catalytic amount of triethylamine.[2] The use of benzenesulfonyl chloride or ethyl chloroformate[3] in the presence of triethylamine or *p*-toluenesulfonic acid[4] as dehydrating agents are modifications of this procedure. The other most frequently used method is base-mediated dehydrohalogenation of hydroximoyl halides obtained by reaction of aldoximes with N-chlorosuccinimide[5] or N-bromosuccinimide,[6] halogens,[7] 1-chlorobenzotriazol,[8] sodium hypochlorite[9] and chloramine-T.[10]

There are few direct methods for the oxidation of aldoximes to nitrile oxides. The use of lead tetraacetate requires cooling (-78°C) and only (*Z*)-aldoximes react this way.[11] Use of hypervalent iodine compounds as oxidizing agents requires alkaline workup that limits the range of substrates to alkaline-resistant compounds.[12] Potassium ferricyanide oxidation proceeds only in aqueous media.[13] Ceric ammonium nitrate (CAN) has been used on only aromatic aldoximes and also produces a number of undesired byproducts.[14] All three cited methods have their disadvantages and finding a new oxidizing agent may contribute to the chemistry of nitrile oxides.

Active MnO_2[15] has recently been shown to convert aldoximes and ketoximes to aldehydes and ketones, respectively.[16] However, when we carried out this reaction with methyl hydroximinoacetate the only compound isolated was furoxane **2**, the product of nitrile oxide dimerization (Scheme 1). The same reaction with the addition of threefold molar excess of dipolarophiles such as methyl acrylate or vinyl acetate gave 2-oxazolines **3**



Scheme 1

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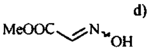
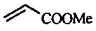
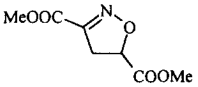
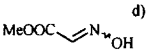
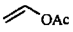
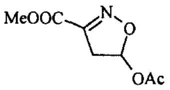
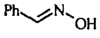
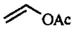
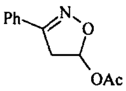
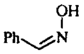
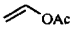
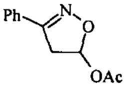
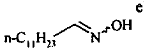
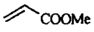
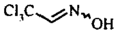
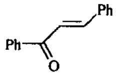
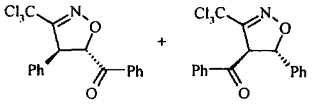
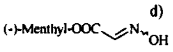
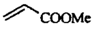
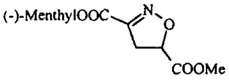
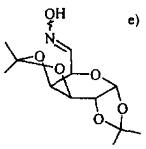
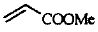
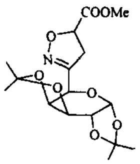
in high yields (Table 1, Entries 1 and 2). 5-Substituted-2-oxazolines **3** are typical products of the 1,3-dipolar cycloaddition of nitrile oxides to mono-substituted olefins. Encouraged by these results we attempted to find the preliminary scope and limitations of this new method of nitrile oxide generation. Our findings are presented in Table 1.

Both (*E*)- and (*Z*)-benzaldoximes gave identical results in the presence of a dipolarophile - almost equal amounts of [2+3] cycloadduct and aldehyde were isolated (Entries 3 and 4). Similar reaction with dodecanal oxime gave dodecanal as a sole product (Entry 5). On the contrary, chloral oxime and chalcone in the presence of MnO$_2$ (Entry 6) gave regioisomeric [2+3] cycloadducts[17a] in 64% overall yield.

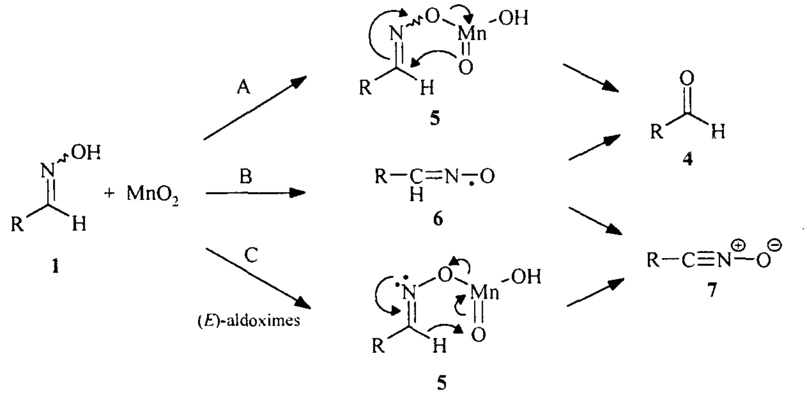
Table 1. Results of the oxidation of aldoximes with MnO$_2$ in the presence of dipolarophiles.

Entry	Oxime a)	Dipolarophile	[2+3] Cycloadduct (3) b)	3 (% yield) c)	4 (% yield) c)
1	 d)			79	0
2	 d)			84	0
3				42	40
4				42	44
5	 e)		-	0	85
6	 d)			64 f)	0
7	 d)			92 g)	0
8	 e)			41 g)	52

a) Oximes were synthesized using literature procedures. b) Cycloadducts **3** (entries 1-5) have their spectroscopic data consistent with literature. For those not described before (entries 6-8) see ref. 17. c) Isolated yield. d) Single geometric isomer was used. e) A ~1:1 mixture of *E* and *Z* isomers was used. f) A 1:1 mixture of regioisomers was obtained. g) A ~1:1 mixture of diastereoisomers was obtained.

Finally, we oxidized two chiral compounds. (1*R*)-Menthyl hydroximinoacetate with methyl acrylate gave the [2+3] cycloadduct[17b] in very high yield (Entry 7). 6-Deoxy-6-(*N*-hydroxyimino)-1,2:3,4-di-*O*-isopropylidene--*α*-*D*-galactopyranose under the same conditions yielded cycloadduct[17c] and aldehyde in ~4:5 ratio (Entry 8). In both cases the cycloadduct was obtained as a 1:1 mixture of diastereoisomers at the C-5 position of 2-oxazoline ring.

Shinada and Yoshihara[16] proposed a mechanism for MnO_2 conversion of oximes to aldehydes and ketones which included [2,3]-sigmatropic rearrangement of an initially formed manganese(IV) intermediate **5** (Scheme 2, path A). A mechanism for the oxidation of (*E*)-aldoximes to nitrile oxides with lead tetraacetate involving six-membered ring transition state has been presented before[11a]and a similar transition state could be proposed for the oxidation of (*E*)-aldoximes with MnO_2 (path C). Paths A and C could not be exclusive for the MnO_2 oxidation of benzaldoxime, since both (*E*) and (*Z*) isomers produce a considerable amount of cycloadduct. These results suggest formation of an iminoxy radical **6** and/or other common intermediates for aldehyde **4** and nitrile oxide **7** (path B). Other aldoximes investigated may follow alternative or even more complex reaction pathways.



Scheme 2

The product distribution of MnO_2 oxidation of aldoximes seems to depend on the electronic properties of the substrate. In consequence, 1,3-cycloaddition proceeds very effectively for oximes bearing electron-withdrawing groups. On the other hand, dodecanal oxime yields exclusively an aldehyde. This limitation in mind, the application of MnO_2 may become a method of choice where simplicity of procedure and mild reaction conditions are required.

In a typical procedure 10 mmol of aldoxime with 30 mmol of dipolarophile were stirred in 10 ml of methylene dichloride at room temperature. MnO_2[18] (180 mmol) was added in six equal portions and the mixture was stirred for 3 hrs after each addition. The reaction was monitored by TLC. After completion, MnO_2 was filtered through the Celite, the filtrate was concentrated under reduced pressure and products were isolated by means of column chromatography on silica gel.

Acknowledgements

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[17] Selected spectroscopic data for newly synthesized compounds **3**:

a) 3/entry 6 (mixture of regioisomers): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.36 (d, 1H, J_{AB} = 6 Hz), 5.39 (d, 1H, J_{AB} = 4.4 Hz), 5.94 (d, 1H, J_{AB} = 4.4 Hz), 5.99 (d, 1H, J_{AB} = 6 Hz), 7.26 - 7.75 (m, 16H), 7.94 - 8.15 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.08, 61.05, 88.16, 88.40, 92.27, 93.24, 125.58, 128.24, 128.86, 128.97, 129.17, 129.28, 129.33, 129.38, 129.53, 133.61, 134.31, 134.48, 135.36, 137.02, 138.34.

b) 3/entry 7: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (d, 6H, J = 6.5 Hz), 0.86-0.94 (m, 2H), 0.90 (d, 6H, J = 7 Hz), 0.92 (d, 6H, J = 7 Hz), 1.03-1.17 (m, 4H), 1.47-1.56 (m, 4H), 1.67-1.74 (m, 4H), 1.86-1.95 (m, 2H), 2.02-2.08 (m, 2H), 3.45-3.57 (m, 4H), 3.826 (s, 3H), 3.833 (s, 3H), 4.85- 4.91 (m, 2H), 5.20 (d, 1H, J = 8.5 Hz), 5.22 (d, 1H, J = 7 Hz). LSIMS (m/z): 334 ($[M+Na]^+$, 100).

c) 3/entry 8: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.33 (s, 3H), 1.35 (s, 6H), 1.46 (s, 3H), 1.47 (s, 3H), 1.55 (s, 6H), 3.36--3.57 (m, 4H), 3.80 (s, 3H), 3.81 (s, 3H), 4.33-4.37 (m, 4H), 4.64-4.67 (m, 2H), 4.82 (s, 2H), 4.96-5.00 (m, 1H), 5.02-5.06 (m, 1H), 5.52 (t, 2H, J=4.5 Hz). LSIMS (m/z) 380 ($[M+Na]^+$, 15).

[18]. Commercial MnO_2 (Merck) was used. However, MnO_2 aged for more than 5 years as well as MnO_2 freshly prepared by the method of Attenburrow (*J. Chem. Soc.* **1952**, 1094) gave the same product distribution.