Tandem Oxidation Processes: The Direct Conversion of Activated Alcohols into Oximes; Synthesis of Citaldoxime

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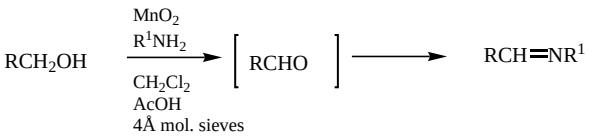
Abstract: The direct conversion of primary alcohols into oximes is reported using manganese dioxide and alkoxylamines/hydroxylamine as their hydrochloride salts or supported on Amberlyst 15. This transformation has been applied to a range of benzylic, allylic and propargylic alcohols and utilised to prepare the natural product citaldoxime.

Key words: oxidation, *O*-alkyl oximes, oximes, citaldoxime, one-pot

We have recently designed a range of transformations based on the manganese dioxide-mediated oxidation of primary alcohols followed by in situ trapping of the resulting aldehydes.[1–4] This one-pot, tandem methodology avoids the need to isolate the intermediate aldehydes, which is particularly useful in the case of volatile, toxic or highly reactive examples. We first employed stabilised phosphoranes,[1] non-stabilised phosphoranes[2] and stabilised phosphonate anions as trapping agents.[2] We then went on to extend this concept by incorporating amines as the nucleophilic trapping agent (Equation 1).[3] In this way alcohols can be converted into imines in a one-pot process.[3,4] In this paper we report that *O*-alkoxylamines (and in certain cases, hydroxylamine itself) can also be employed as trapping agents in a similar sequence (Equation 2). We also describe the use of this methodology for the preparation of the antifungal natural product citaldoxime.

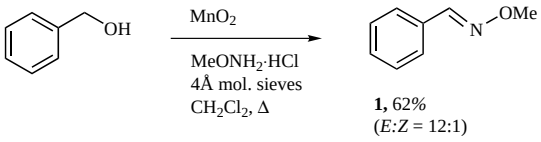


R = aryl, alkenyl, alkynyl; R^1 = alkyl

Equation 1

Equation 2

Initial studies were carried out using benzyl alcohol, manganese dioxide, molecular sieves and methoxylamine hydrochloride in dichloromethane as shown in Equation 3. To our delight the procedure gave the corresponding *O*-methyl oxime **1** in 62% isolated yield with NMR data in accord with the literature.[5] It should be noted that when amine bases were added to this mixture in an attempt to increase the rate of reaction by releasing free methoxylamine, the yield of adduct **1** decreased dramatically. We assume that the hydrochloride salt is stable to the oxidative conditions, whereas free methoxylamine is probably oxidised by manganese dioxide.[6]



Equation 3

We went on to investigate the in situ oxidation-oxime formation reaction with a range of benzylic alcohols under these conditions (Table 1).[7,8] They all underwent smooth transformation to give the corresponding *O*-methyl oximes in good yields. The reaction was compatible with electron withdrawing or donating substituents (entries ii and iii), and 1,4-benzenedimethanol was efficiently converted into the corresponding di-oxime (entry iv). Other alkoxylamines were tried with less success (entries v–vii). Thus, treatment of benzyl alcohol under the standard conditions with *O*-*tert*-butoxylamine hydrochloride or *O*-alloxylamine hydrochloride gave only trace amounts of the desired oximes (entry v). With benzoxylamine hydrochloride and 4-methoxybenzyl alcohol a reasonable yield of the corresponding *O*-benzyl oxime was obtained (entry vi, 68%), but all attempts to utilise hydroxylamine hydrochloride in this sequence to produce the parent oximes were disappointing, the best result being shown in entry vii (ca. 16% with benzyl alcohol).

We next looked at similar reactions with allylic, propargylic and related alcohols (Table 2). Cinnamyl alcohol, *E*-non-2-en-1-ol and non-2-yn-1-ol reacted smoothly under the standard conditions to give the corresponding *O*-methyl oximes (Table 2 entries i, ii and iv). With *Z*-non-2-en-1-ol, however, there was a significant amount of alkene isomerisation (entry iii, *Z:E* = 2.4:1). This procedure was also successful with an α-hydroxy ketone,[9] hydroxyacetophenone giving the corresponding *O*-methyl oxime

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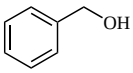
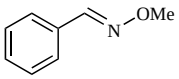
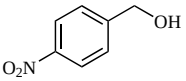
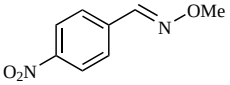
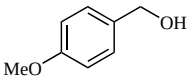
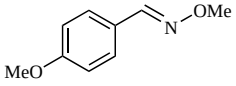
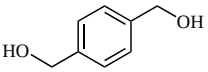
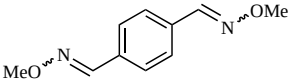
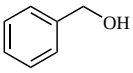
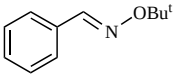
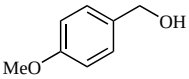
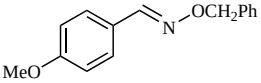
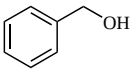
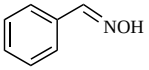
Table 1 In Situ Oxidation-Oxime Formation:[a] Benzylic Examples

Entry	Alcohol	Alkoxylamine	Product (isolated yield)
(i)		$MeONH_2 \cdot HCl$	 62% (*E*:*Z*=12:1)
(ii)		$MeONH_2 \cdot HCl$	 85% (*E*:*Z*=13:1)
(iii)		$MeONH_2 \cdot HCl$	 88% (*E*:*Z*=8:1)
(iv)		$MeONH_2 \cdot HCl$	 84%[b]
(v)		$^tBuONH_2 \cdot HCl$	 trace[c]
(vi)		$PhCH_2ONH_2 \cdot HCl$	 68% (*E*:*Z*=7:1)
(vii)		$HONH_2 \cdot HCl$	 ca. 16%[d]

[a] Using manganese dioxide (5–20 equiv.) and 4Å molecular sieves in CH_2Cl_2 at reflux for overnight.[8]
[b] 30 equiv of manganese dioxide were used in this example; the product was obtained as a separable mixture of isomers (*E*,*Z*:*E*,*E*:*Z*,*Z* = 2.7:1.7:1).
[c] $AllylONH_2 \cdot HCl$ also gave only trace amounts of the expected product.
[d] Crude yield based on NMR integration.

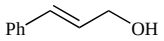
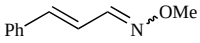
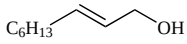
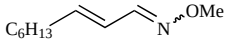
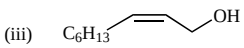
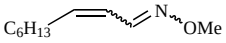
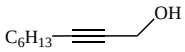
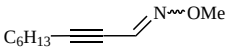
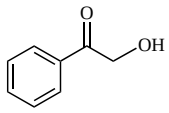
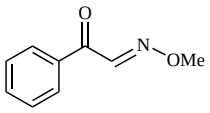
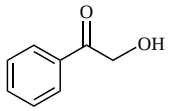
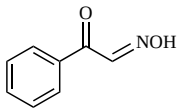
and parent oxime in just over 40% yield for each (entries v and vi).

The disappointing yields with oximes other than methoxylamine encouraged us to look at alternative systems. The earlier discovery that hydrochloride salts were preferable to the free amines, and the presumption that this was due to their low solubility preventing oxidative degradation, prompted us to look at other heterogeneous systems. Success was achieved when the oximes were supported on Amberlyst 15 resin (Table 3).[10] Thus, benzyl alcohol reacted with supported methoxylamine in 59% yield (entry i), which was about the same as using $MeONH_2 \cdot HCl$. However, with benzyl alcohol and supported alloxylamine and *tert*-butoxylamine, fair yields of the corresponding *O*-alkyl oxime adducts were obtained (entries ii and iii); this contrasts to the reactions using the hydrochloride salts which failed. We have also shown that supported benzoxylamine is compatible with this procedure (entry iv), that 4-nitrobenzyl alcohol gives a good yield with supported allyloxylamine (entry v), and that hydroxyacetophenone can be employed with supported hydroxylamine (entry vi).

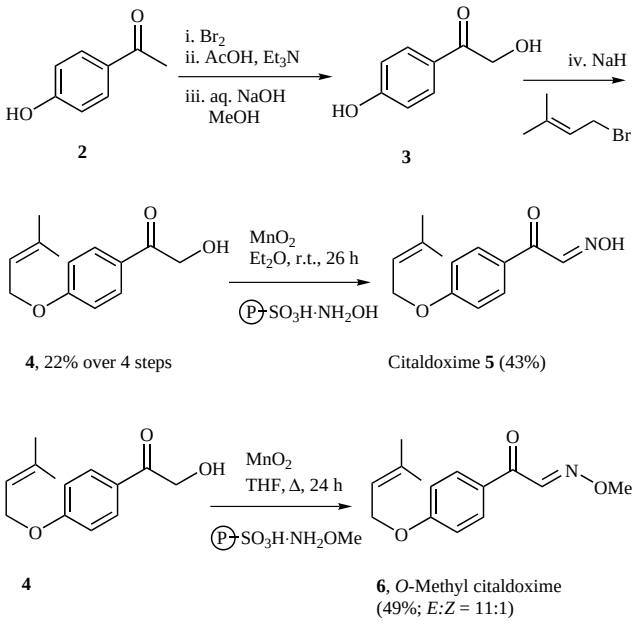
We next went on to apply this new methodology. Citaldoxime **5** is an antifungal natural product first obtained as a radiation-induced stress metabolite of *Citrus sinensis*,[11] and later isolated from the roots of several different *citrus* plants.[12] Citaldoxime was conveniently prepared using the in situ oxidation-oxime formation procedure as shown in Scheme 1. Bromination-acetoxylation-hydrolysis of methyl ketone **2** gave alcohol **3**[13] which on alkylation with prenyl bromide produced the key α-hydroxy ketone precursor **4**. Oxidation-oxime formation using Amberlyst-supported hydroxylamine proceeded in 43% yield in diethyl ether[14] producing citaldoxime **5** in a one step process (mp 104–105 °C; lit.[11] mp 104–105 °C).

We also prepared the novel citaldoxime analogue **6** as shown in Scheme 1. Thus, oxidation-oxime formation of α-hydroxy ketone **4** using Amberlyst-supported methoxylamine gave a 49% yield of *O*-methyl citaldoxime **6** which was fully characterised.

Table 2 In Situ Oxidation-Oxime Formation:[a] Allylic, Propargylic and Related Examples

Entry	Alcohol	Alkoxylamine	Product (isolated yield)
(i)		$MeONH_2$·HCl	 91% (*E*,*E*:*E*,*Z*=5:4)
(ii)		$MeONH_2$·HCl	 61% (*E*,*E*:*E*,*Z*=1:1.4)
(iii)		$MeONH_2$·HCl	 87% (Z,*E*:*Z*,*Z*:*E*,*E*:*E*,*Z*=2.9:2.4:1:1.2)
(iv)		$MeONH_2$·HCl	 71% (*E*:*Z*=3:10)
(v)		$MeONH_2$·HCl	 45% (*E*:*Z*=2:1)
(vi)		$HONH_2$·HCl	 44%[c]

[a] Using manganese dioxide (5–20 equiv.) and 4Å molecular sieves in CH_2Cl_2 at reflux for overnight.
[b] *E*,*E* and *E*,*Z* indicates the configuration of the alkene followed by the configuration of the oxime.
[c] This reaction was only successful when THF was used as solvent (no product observed in dichloromethane).



Scheme 1

In conclusion, we have successfully developed a simple one-pot procedure using MnO_2–NH_2OMe·HCl for the conversion of activated primary alcohols into *O*-methyl oximes. We have also developed a variant using Amberlyst 15-supported alkoxylamines, which can be employed to prepare other types of *O*-alkyl oximes as well as the parent hydroxylamines. This latter procedure has been used as the cornerstone of an efficient synthesis of the antifungal natural product citaldoxime.

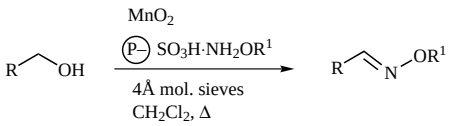
Acknowledgement

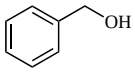
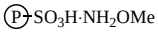
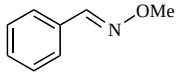
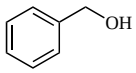
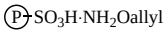
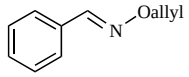
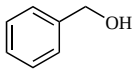
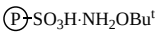
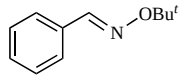
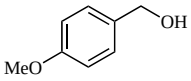
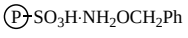
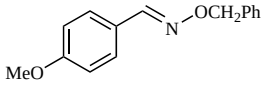
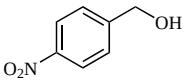
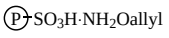
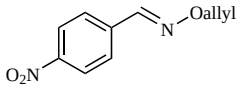
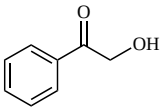
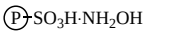
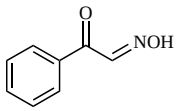
We are grateful to the Kureha Chemical Industry for studentship support (H. K.).

References

(1) (a) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815. (b) Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1337. (c) Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 617.
(2) Blackburn, L.; Pei, X.; Taylor, R. J. K. *Synlett* **2002**, 215.
(3) Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 1637.
(4) For other tandem oxidation processes see the following two papers.
(5) (a) Gordon, M. S.; Sojka, S. A.; Krause, J. G. *J. Org. Chem.* **1984**, *49*, 97. (b) Tanimoto, S.; Yamadera, T.; Sugimoto, T.; Okano, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 4897. (c) Mauleon, D.; Granados, R.; Minguilon, C. *J. Org. Chem.* **1983**, *48*, 3105.
(6) Carey, F. A.; Hayes, L. J. *J. Org. Chem.* **1973**, *38*, 3107.
(7) Known products gave consistent spectroscopic data (and mps if solids); novel products were fully characterised.
(8) Representative Procedure: Activated manganese dioxide (Aldrich, 21764-6; 0.87 g, 10 mmol) was added to a stirred solution of 4-nitrobenzyl alcohol (0.153 g, 1 mmol), methoxylamine hydrochloride (0.251 g, 3 mmol) and 4 Å molecular sieves (ca. 0.2 g) in dichloromethane (15 mL) and the mixture was heated to reflux for 22 h. After cooling, the

Table 3 In Situ Oxidation-Oxime Formation Using Amberlyst 15-Supported Alkoxylamines[a]



Entry	Alcohol	Alkoxylamine	Product (isolated yield)
(i)			 59% (*E*:*Z*=11:1)
(ii)			 69% (*E*:*Z*=13:1)
(iii)			 44% (*E*:*Z*=17:1)
(iv)			 83% (*E*:*Z*=9:1)
(v)			 87% (>97% *E*)
(vi)			 60%[b]

[a] Using manganese dioxide (5–10 equiv), supported oxime (2–5 equiv.), and 4Å molecular sieves in CH_2Cl_2 at reflux overnight.
[b] Using THF as solvent (32% in dichloromethane).

reaction mixture was filtered through Celite®, washing well with dichloromethane. The combined organic fractions were concentrated in vacuo and the resulting product purified by column chromatography on silica. Elution with petroleum ether–ethyl acetate (4:1) gave 4-nitrobenzaldehyde *O*-methyl oxime (0.154 g, 85%; *E*:*Z* = 13.1) as a yellow solid, mp 97.6–98.0 °C (lit.[15] mp for *E*-isomer, 102–104 °C) which displayed spectroscopic data consistent with those published.[5]

(9) Runcie, K. A.; Taylor, R. J. K. *Chem. Commun.* **2002**, 974.
(10) Representative procedure for the preparation of Amberlyst-supported alkoxylamine: A solution of sodium methoxide in methanol (4.37 M, 0.75 mL, 3.3 mmol) was added to a stirred solution of methoxylamine hydrochloride (0.251 g, 3 mmol) in methanol (10 mL) and the mixture was stirred at r.t. for 0.5 h. Amberlyst 15 (1.06 g, 5 mmol) was added and the resulting mixture was stirred for 1 h. The resin was removed by filtration, washed with methanol (50 mL) and dichloromethane (3 × 20 mL), and then used in the manganese dioxide reaction without further purification.
(11) (a) Dubery, I. A.; Holzhapfel, C. W.; Kruger, G. J.; Schabort, J. C.; Van Dyk, M. *Phytochemistry* **1988**, *27*, 2769. (b) Dubery, I. A.; Louw, A. E.; van Heerden, F. R. *Phytochemistry* **1999**, *50*, 983.
(12) Ito, C.; Tanahashi, S.; Tani, Y.; Ju-ichi, M.; Omura, M.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 2586.
(13) Zhang, K.; Corrie, J. E. T.; Munasinghe, V. R. N.; Wan, P. *J. Am. Chem. Soc.* **1999**, *121*, 5625; and references therein.
(14) The yield was only 9% in dichloromethane at r.t. and 30% in refluxing THF.
(15) Hegarty, A. F.; Tuohey, P. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1313.