Tandem Oxidation Processes: The Direct Conversion of Activated Alcohols into Nitriles

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Abstract: The direct conversion of primary alcohols into nitriles is reported (RCH_2OH into RCN) using manganese dioxide and ammonia in 2-propanol–THF, containing magnesium sulfate at room temperature. This transformation, which proceeds via an in situ oxidation-imination-aldimine oxidation sequence, has been applied to a range of benzylic, heterocyclic, allylic and propargylic alcohols.

Key words: oxidation, imines, nitriles, cyanides, one-pot

As part of a programme to investigate tandem manganese dioxide-mediated alcohol oxidation followed by in situ trapping of the resulting aldehydes, we have studied the use of stabilised phosphoranes,[1] non-stabilised phosphoranes,[2] stabilised phosphonate anions[2] and amines[3] as trapping agents.[4] By including a polymer-supported reducing agent in the amine trapping process, the sequence was extended so that the intermediate imine was reduced in situ: this oxidation-imination-reduction sequence thus provides a one-pot route from alcohols to amines (Equation 1).[3] Inspired by a recent publication by Lai et al.,[5] we decided to investigate the related oxidation-imination-oxidation sequence shown in Equation 2.

$$\mathrm{ArCH_2OH} \xrightarrow[\mathrm{R^1NH_2}\ \ \mathrm{PCSBH}]{\mathrm{MnO_2}} \left[\mathrm{ArCHO} \longrightarrow \mathrm{ArCH{=}NR^1}\right] \xrightarrow{[H]} \mathrm{ArCH_2NHR^1}$$

PCSBH = polymer supported cyanoborohydride

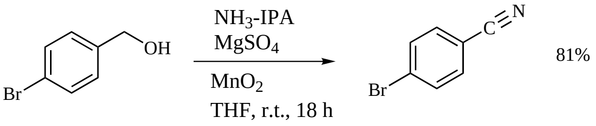
Equation 1

$$\mathrm{RCH_2OH} \xrightarrow[\mathrm{NH_3}]{\mathrm{MnO_2}} \left[\mathrm{RCHO} \longrightarrow \mathrm{RCH{=}NH}\right] \xrightarrow{[O]} \mathrm{RC{\equiv}N}$$

Equation 2

Lai's group showed that aromatic aldehydes could be converted into the corresponding nitriles by treatment with ammonia in 2-propanol (IPA) and THF containing magnesium sulfate and manganese dioxide at room temperature (r.t.) for 16–22 hours.[5] This transformation presumably involves conversion of the aldehyde into the corresponding aldimine followed by in situ oxidation by the manganese dioxide. We hoped to illustrate that this transformation could be carried out directly from primary alcohols (Equation 2).

Initial studies were carried out using 4-bromobenzyl alcohol under Lai's conditions (Equation 3).[5] To our delight the procedure gave the corresponding benzonitrile in 81% isolated yield.[6,7]



Equation 3

We therefore investigated the in situ oxidation-nitrile formation reaction with a range of benzylic alcohols under these conditions (Table 1). They all underwent smooth transformation to give the corresponding nitriles in good yields. The reaction was compatible with electron withdrawing or donating substituents (entries i–iii), and efficiently converted 1,4-benzenedimethanol into terephthalonitrile (entry iv). One naphthalene example was studied and proceeded smoothly (entry v), as did the conversion of indole-3-methanol into 3-cyanoindole (entry vi). In the last example it is noteworthy that *N*-protection was not required.

We next looked at similar reactions with allylic and propargylic alcohols (Table 2). Both *E*- and *Z*-non-2-en-1-ol underwent efficient conversion into the corresponding unsaturated nitriles (entries i and ii), although in the latter example there was a small amount of alkene isomerisation (Z:E = 5:1). Propargyl alcohols were also studied (entries iii and iv): both non-2-yn-1-ol and 3-phenylprop-2-yn-1-ol gave the corresponding nitriles in good yields, the latter reaction taking only 2 hours.

If the reaction with 3-phenylprop-2-yn-1-ol was left for longer than 2 hours, increasing amounts of phenylpropargylamide were observed, presumably by nitrile hydration occurring in situ.[8] A similar result was obtained with pyridine-2-methanol (Equation 4).[8,9] A fair yield (30%) of the nitrile was obtained under the standard (18 h) conditions, but the main product was the corresponding carboxamide.

Attempts to extend this methodology to unactivated alcohols such as decanol[1b] were unsuccessful.

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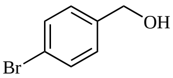
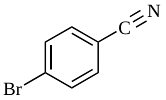
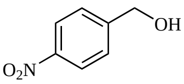
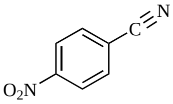
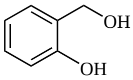
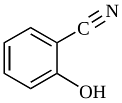
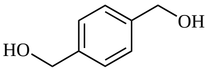
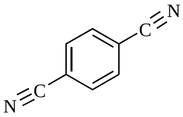
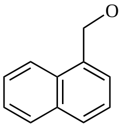
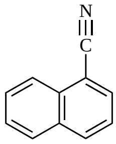
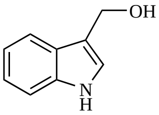
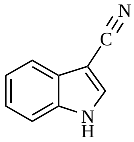
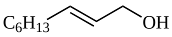
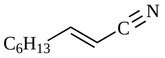
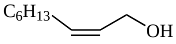
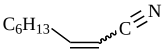
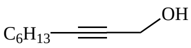
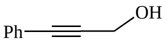
Table 1 In Situ Oxidation-Imination-Oxidation Giving Nitriles:[a] Aromatic Examples

Entry	Alcohol	Product	Product (isolated yield)
(i)			81%
(ii)			81%
(iii)			87%
(iv)			78%
(v)			82%
(vi)			77%

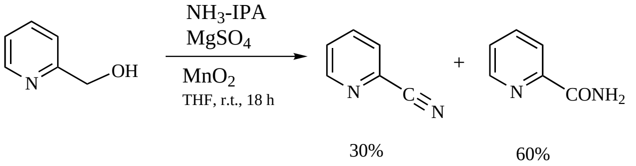
[a] Using ammonia in IPA, $MgSO_4$, manganese dioxide (15 equiv) in THF at r.t. for 18 h;[7] 30 equiv of MnO_2 was used in example (iv).

Table 2 In Situ Oxidation-Imination-Oxidation Giving Nitriles: Allylic and Propargylic Examples[a]

Entry	Alcohol	Product	Product (isolated yield)
(i)			82% (24 h)
(ii)			82% (24 h) Z:E=5:1
(iii)		$C_6H_{13}-C\equiv C-C\equiv N$	87% (18 h)
(iv)		$\mathrm{Ph}-C\equiv C-C\equiv N$	82% (2 h)[b]

[a] Using ammonia in IPA, $MgSO_4$, manganese dioxide (15 equiv.) in THF at r.t. for the time indicated.

[b] When the reaction was left for 3 h, some phenylpropargylamide was observed by TLC. If the reaction was left for 24 h, phenylpropargylamide was the only product (62%).



Equation 4

In conclusion, we have successfully developed a one-pot procedure for the conversion of activated primary alcohols into nitriles which is extremely easy to perform as the oxidant is heterogenous and can be removed by simple filtration, evaporation of the solvent then giving the product. Given the importance of nitriles for the synthesis of fine chemicals, pharmaceuticals and agrochemicals,[10] we feel that this new methodology will be of general interest.

Acknowledgement

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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*, 616. (d) Runcie, K. A.; Taylor, R. J. K. *Chem. Commun.* **2002**, 974.

(2) Blackburn, L.; Pei, C.; 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 preceding and following papers in this series.

(5) (a) Lai, G.; Bhamare, N. K.; Anderson, W. K. *Synlett* **2001**, 230. (b) See also: Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1971**, 733.

(6) The products, which are all known, gave consistent spectroscopic data (and mps if solids).

(7) Representative experimental: A 2 M solution of ammonia in 2-propanol (2.2 mL, 4.28 mmol; Aldrich) and anhydrous magnesium sulfate (1.93 g, 16.0 mmol) were added to a stirred solution of 4-bromobenzyl alcohol (0.200 g, 1.07 mmol) in THF (4.3 mL). Activated manganese dioxide (Aldrich 21764-6; 1.40 g, 16.10 mmol) was added to the solution. The resulting mixture was stirred at room temperature for 18 hours and then diluted with dichloromethane (20 mL). The mixture was filtered through Celite®, the Celite® washed well with dichloromethane and the combined filtrates concentrated under reduced pressure. The solid residue was purified by column chromatography (silica gel, EtOAc–petroleum ether, 1:4) to give 4-bromobenzonitrile (157 mg, 81%) as a white solid, mp 112.8 °C, published mp (Aldrich) 112–114 °C.

(8) Treatment of 2-cyanopyridine with ammonia in 2-propanol and THF containing magnesium sulfate and manganese dioxide at r.t. for 18 hours gave unreacted nitrile (30%) and carboxamide (50%). The fact that the nitrile appears to be formed first and is then converted into the carboxamide, appears to rule out a mechanism involving oxidation of an intermediate $RCH(OH)NH_2$ species.

(9) Carboxamides were also observed with furan- and thiophene-methanols.

(10) (a) For recent references see: Yang, S. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209. (b) Srinivas, K. V. N.; Reddy, E. B.; Das, B. *Synlett* **2002**, 625. (c) Baxendale, I. R.; Ley, S. V.; Sneddon, H. F. *Synlett* **2002**, 775.