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In Situ Oxidation–Imine Formation–Reduction Routes from Alcohols to Amines

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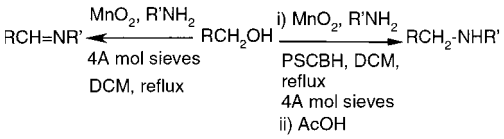
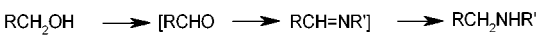
ABSTRACT



Manganese dioxide is employed as an in situ oxidant for the one-pot conversion of alcohols into imines. In combination with polymer-supported cyanoborohydride (PSCBH), a one-pot oxidation–imine formation–reduction sequence is reported. This procedure enables alcohols to be converted directly into both secondary and tertiary amines.

In conventional organic synthesis the combination of a chemical oxidant and reductant is rare, although redox processes are well-known in biological systems. We envisaged a new process for the conversion of alcohols into amines via an in situ oxidation−imine formation−reduction sequence (Scheme 1).[1] Such a process would extend the well-known reductive amination procedure[2] and would have the advantage that the intermediate aldehydes and imines would not require isolation. This should prove particularly useful in cases where these intermediates are unstable or otherwise difficult to handle (e.g. toxic, volatile, or prone to polymerization). In addition, the sequence in Scheme 1 would allow the rapid synthesis of amines for chemical libraries and thus find use in combinatorial chemistry.[3]

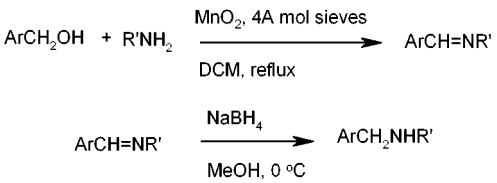
Scheme 1



To test the viability of this proposal, we first investigated the in situ oxidation−imine formation sequence. This is a useful transformation in its own right, given the synthetic utility of the product imines.[4] We have previously described the direct conversion of alcohols into alkenes using an in situ manganese dioxide oxidation-stabilized Wittig procedure.[5] We therefore studied the in situ conversion of benzyl alcohol and substituted benzyl alcohols into imines using manganese dioxide together with a range of amines (Scheme 2 and Table 1).[6] In view of the hydrolytic instability of some of the imine products, all were routinely reduced to the corresponding amine, the amine being fully characterized.

As shown in Table 1, imines were obtained in near quantitative yields in all cases, confirming that under these conditions amines and the product imines are compatible with manganese dioxide. It should be noted that the use of (+)-α-methylbenzylamine gave the expected amine with no loss

Scheme 2



(1) Related one-pot oxidation−reduction routes to amines can be achieved electrolytically or via transition metal mediated processes, although harsh conditions are required and functional group tolerance is limited. For leading references, see: Ohtani, B.; Nakagawa, K.; Nishimoto, S.; Kagiya, T. *Chem. Lett.* **1986**, 1917−1920. Murahashi, S.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229−232.

(2) Tarasevich, V. A.; Kozlov, N. G. *Russ. Chem. Rev.* **1999**, *68*, 55−72, and references therein.

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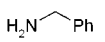
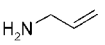
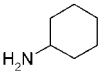
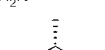
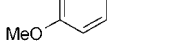
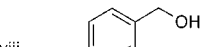
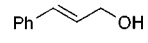
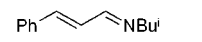
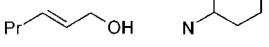
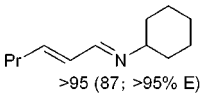
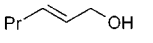
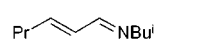
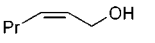
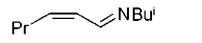
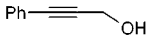
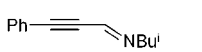
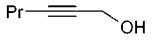
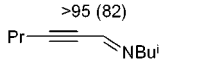
Table 1.[a]

entry	alcohol	amine	yield (%)[b,c] imine (amine)
i[d]			 >95(77)
ii		^{i}BuNH$_2$	 >95 (>95)
iii		BuNH$_2$	 >95 (>95)
iv			 >95 (>95)
v			95 (91)
vi[d]			 89 (78)
vii		^{i}BuNH$_2$	 >95 (>95)
viii		^{i}BuNH$_2$	 >95 (>95)
ix		^{i}BuNH$_2$	 91 (94)

[a] General procedure: manganese dioxide (10 mmol) was added in two portions (2 × 5 mmol) over 1 h to a solution of alcohol (1 mmol), amine (1−3 mmol), and 4A molecular sieves (200 mg) in DCM at reflux and allowed to stir for 24−48 h at reflux. The solution was filtered through Celite and concentrated. [b] Yields of the imine refer to the isolated unpurified product which, unless stated otherwise, was pure by ^{1}H NMR spectroscopy. [c] Yields of the amine refer to isolated unpurified product which, unless stated otherwise, was pure by ^{1}H NMR spectroscopy and was fully characterized if novel (entries vii−ix). [d] In these cases the intermediate imine was contaminated with a minor byproduct (<10%) according to ^{1}H NMR spectroscopy. After reduction, the impurity was removed by acid−base extraction.

Table 2.[a]

entry	alcohol	amine	yield (%)[b,c] imine (amine)
i		^{i}BuNH$_2$	 >95 (>95; >95%E)
ii			 >95 (87; >95% E)
iii		^{i}BuNH$_2$	 88 (84; >95%E)
iv		^{i}BuNH$_2$	 88 (84; 7:2, E:Z)
v		^{i}BuNH$_2$	 >95 (82)
vi		^{i}BuNH$_2$	 >95 (83)

[a] General procedure: manganese dioxide (10 mmol) was added in two portions (2 × 5 mmol) over 1 h to a solution of alcohol (1 mmol), amine (1.5 mmol), and 4A molecular sieves (200 mg) in DCM at reflux and allowed to stir for 24 h at reflux. The solution was filtered through Celite and concentrated. [b] Yields of the imine refer to the isolated unpurified product which was pure by ^{1}H NMR spectroscopy. [c] Yields of the amine refer to isolated unpurified product which was pure by ^{1}H NMR spectroscopy and was fully characterized if novel (ii, v, vi).

of optical activity {[α]$_D$ 60.1 (*c* 0.5, EtOH); lit.[7] [α]$_D$ 54.4 (*c* 0.5, EtOH)} as shown in entry vi. The results in Table 1 (entries vii and viii) also indicate that the presence of electron-donating and electron-withdrawing substituents have no adverse effect on the in situ oxidation−imine formation reaction. Furthermore, it was established that diols can be converted efficiently into bis-imines (entry ix).

We next investigated the use of allylic and propargylic alcohols (Table 2), the product amines being valuable building blocks in organic synthesis.[8] As can be seen (entries i−iii), the in situ oxidation−imine formation reaction proceeded smoothly with cinnamyl alcohol and (*E*)-hexenol. (*Z*)-Hexenol also underwent efficient oxidation−imine formation, but this was accompanied by a considerable amount of alkene isomerization (entry iv): further studies are underway to overcome this problem.

Propargylic alcohols were also subjected to the in situ oxidation−imine formation conditions (Table 2, entries v and vi). The imines, and the amines produced after subsequent reduction, were obtained in excellent yields. The successful synthesis of propargylic amines affords the possibility of obtaining *Z*-allylic amines by stereoselective reduction.

Having established the viability of the in situ oxidation−imine formation reaction, our attention turned to combining this sequence with an in situ reduction. We required a reductant that would reduce imines selectively in the presence of aldehydes, and felt that a heterogeneous reductant would minimize the likelihood of reaction with manganese dioxide and would also facilitate the workup procedure. With this in mind, the use of polymer-supported cyanoborohydride (PSCBH) was investigated.[9,10] Initial studies were carried out using benzyl alcohol and isobutylamine together with MnO_2 (10 equiv), PSCBH (5 equiv), and acetic acid (2 equiv) as shown in Scheme 3. The reaction mixture was then stirred at room temperature for 48 h, filtered through silica, and concentrated. Much to our delight the ^{1}H NMR spectrum of the unpurified reaction mixture indicated the presence of *N*-benzyl isobutylamine in ca. 30% yield. Although the yield

(3) Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A.-G.; Hall, B. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239−2241. Ley, S. V.; Massi, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3645−3654.

(4) For reviews covering the preparation and utility of imines, see: Adams, J. P. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 125−139. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438.

(5) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815−3818. Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1337−1338. Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616−620.

(6) Isolated reports of this process have been published, see: Iwata, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2835−2836. Medvedeva, A. S.; Safronova, L. P.; Chichkareva, G. G.; Voronkov, M. G. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1976**, *25*, 107−110.

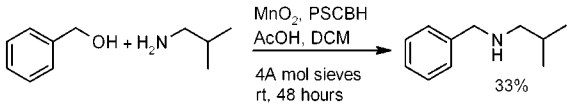
(7) Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243−1246.

(8) Johannsen, M.; Jorgensen, K. A. *Chem Rev.* **1998**, *98*, 1689−1708.

(9) With $NaBH_3CN$ itself, after extensive investigation, optimum conditions afforded the amine in a maximum 40% yield; $NaBH(OAc)_3$ was investigated but none of the amine was produced.

(10) Hutchins, R. O.; Natale, N. R.; Taffer, I. M. *Chem. Commun.* **1978**, 1088−1089. Commercially available from Novabiochem, catalog no. 01-64-0337, although the reagent prepared according to the literature procedure gave more consistent results.

Scheme 3



was moderate, it clearly indicated that the oxidation−imine formation−reduction sequence is viable.

Optimization studies were then carried out and resulted in an improvement of the isolated yield of *N*-benzyl isobutylamine to 74% by increasing the reaction temperature and delaying the addition of acetic acid until the oxidation of the alcohol was essentially complete as shown by TLC analysis. The addition of acetic acid was essential for the reduction of the imine to the corresponding amine. The generality of this procedure was then explored (Table 3).

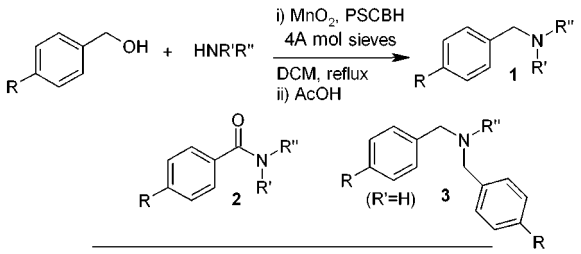
As shown in Table 3, entries i−v, the in situ oxidation−imine formation−reduction sequence proceeded efficiently with benzyl alcohol and with an electron-rich and an electron-deficient example. In these systems the only significant contaminant was the amide **2** (ca. 20%) which could be removed by acid−base extraction. However, with 4-nitrobenzyl alcohol (entry vi) this material was the major product (60%). It seems likely that the intermediate aldehyde is being converted into the corresponding cyanohydrin, which in turn is oxidized to the acyl cyanide, which is then trapped by the amine to give the amide via a precedented process.[11] The use of an alternative reductant should remove this problem, and current efforts are being focused in this direction. In addition, a second minor byproduct, dialkylated analogue **3**, was present in only small quantities (detected by mass spectrometry and TLC).

Finally, we established that secondary amines are also compatible with the in situ oxidation−imine formation−reduction sequence (Table 3, entries vii−ix). In these examples, intermediate iminium species are formed which undergo in situ reduction to give tertiary amines.

In summary, we have shown that activated alcohols (benzylic, allylic, and propargylic) will undergo the manganese dioxide-mediated in situ oxidation−imine formation reaction to afford imines in excellent yields. Preliminary studies on benzyl alcohols have also indicated the viability of an in situ oxidation−imine formation−reduction sequence leading to secondary and tertiary amines, demonstrating that a chemical oxidant and reductant can coexist in the appropriate circumstances.[12] This sequence should be applicable to a range of activated alcohols and may be even more general.

(11) Gilman, N. W. *Chem. Commun*. **1971**, 733−734.

Table 3. In Situ Oxidation−Imine Formation−Reduction[a]



	R	R'	R"	isolated yield(%) of **1**
i	H	H	^{i}Bu	74
ii[b]	H	H	$^{n}C_5H_{11}$	58
iii[b]	H	H	Bu	57
iv	OMe	H	^{i}Bu	76
v	Br	H	^{i}Bu	60
vi	NO_2	H	^{i}Bu	39
vii	H	^{i}Pr	^{i}Pr	63
viii[c]	H	^{i}Bu	^{i}Bu	80
ix[d]	H	Et	Et	41

[a] General procedure: manganese dioxide (10 mmol) was added in two portions (2 × 5 mmol) over 1 h to a solution of alcohol (1 mmol), amine (2−4 mmol), 4A molecular sieves (200 mg), and PSCBH (5 mmol) in DCM (25 mL) at reflux. AcOH (2 mmol) was added when TLC showed all the alcohol had essentially been oxidized (ca. 3−4 h) and the reaction mixture was then allowed to stir for 24−64 h at reflux. The solution was filtered through silica and concentrated. Impurities were removed by acid−base extraction unless stated. [b] Purified by the formation of the *N*-Boc derivative and subsequent column chromatography. [c] Purified by column chromatography. [d] Purified by disillation.

It should be noted that the process is practically straightforward in that the oxidant and reductant are removed by filtration and the product is isolated simply by evaporation of the solvent. We are currently optimizing and expanding the scope of this novel sequence and investigating its applications in target molecule synthesis.

Acknowledgment. We thank EPSRC for funding (L.B.) and Pfizer for additional financial support.

Supporting Information Available: Detailed experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.ac.org.

OL015819B

(12) For other ways of utilizing potentially incompatible reagents, see: Gelman, F.; Blum, J.; Avnir, P. *J. Am. Chem. Soc.* **2000**, *122*, 11999−12000. Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1977**, *99*, 4165−4167 and references therein.