Pergamon

Tetrahedron Letters 43 (2002) 7337–7340

TETRAHEDRON LETTERS

A one-pot oxidation–imine formation–reduction route from alcohols to amines using manganese dioxide–sodium borohydride: the synthesis of naftifine

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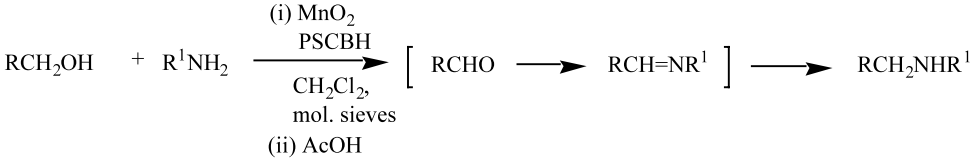
Received 17 July 2002; accepted 16 August 2002

Abstract—A new procedure for the one-pot conversion of alcohols into amines is described which utilises manganese dioxide in the presence of sodium borohydride; the scope of this process is outlined, as is its application to the preparation of the topical antifungal agent, naftifine.

The direct conversion of aldehydes into amines using the reductive amination procedure is an extremely important functional group transformation.[1] We recently reported[2] a related new process which allows the one-pot conversion of alcohols into amines via an in situ oxidation–imine formation–reduction sequence using manganese dioxide and polymer-supported cyanoborohydride (PSCBH; Eq. (1)).[3] This method, which utilises the combination of a heterogeneous oxidant and a heterogeneous reductant, has the advantage that the intermediate aldehydes and imines do not require isolation. The heterogeneity of the reactants also ensures a straightforward work-up procedure.

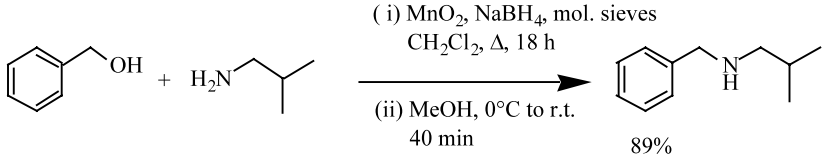
The drawbacks of this procedure include the cost of the resin-bound reductant, and the fact that cyanohydrin-derived by-products arise due to cyanide leaching from the resin.[2,4] To overcome these problems other reductants were explored. Polymer-supported borohydride[5] gave encouraging results but was not investigated in detail in view of the cost factor. Instead, attention was concentrated on the use of non-supported reductants that might be compatible with manganese dioxide. Decaborane, poly(methylhydrosiloxane), sodium acetoxyborohydride and sodium cyanoborohydride were unsuccessful. However, success was achieved with the use of sodium borohydride in dichloromethane (Eq. (2)).

Thus, addition of benzyl alcohol and *iso*-butylamine to a mixture of manganese dioxide and sodium borohydride in dichloromethane at rt followed by heating for 18 h, cooling and then addition of methanol and work-up gave *N*-benzyl(*iso*-propyl)amine in 89% isolated yield. The sodium borohydride is essentially insoluble in dichloromethane, and although some reduction of the intermediate imine to the corresponding amine is observed before the addition of methanol, the addition of the alcoholic solvent speeds up the reduction step.[6]



(1)

PSCBH = polymer-supported cyanoborohydride



(2)

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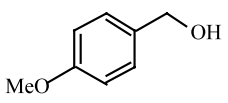
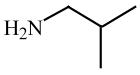
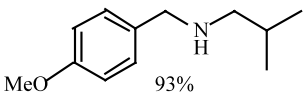
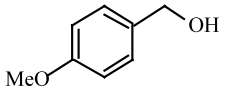
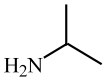
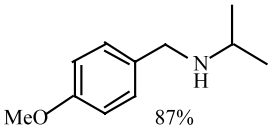
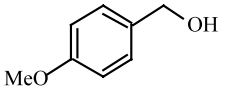
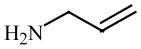
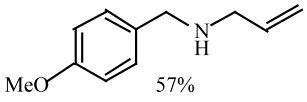
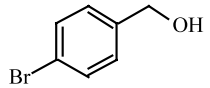
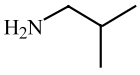
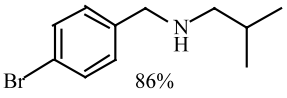
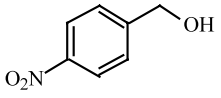
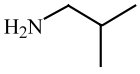
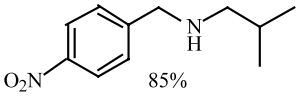
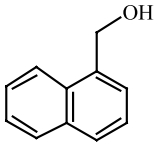
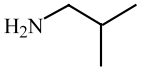
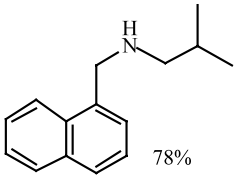
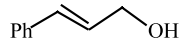
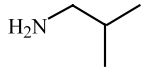
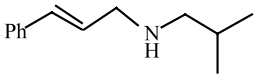
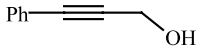
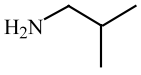
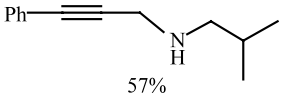
PII: S0040-4039(02)01722-7

In view of this success, we went on to study the in situ oxidation–imination–reduction of a range of substituted benzylic, allylic and propargylic alcohols with primary amines, as shown in Table 1.[7] As can be seen (entries i–v) the oxidation–imination–reduction sequence proceeded efficiently with both electron rich and electron deficient benzyl alcohol derivatives. In addition, success was achieved using 1-naphthalene methanol (entry vi), an allylic alcohol example (entry vii) and a propargylic alcohol example (entry viii). As before,[2] unactivated alcohols could not be successfully employed in this sequence.

Although *iso*-butylamine was used in most examples, we also demonstrated that other primary amines could be employed (entries ii and iii; also see later).[8] Finally, we established that secondary amines do not usually give good yields in the MnO_2–$NaBH_4$ procedure (in

Table 1. One-pot oxidation–imine formation–reduction[a]

Entry	Alcohol	Amine	Product (isolated yield)
(i)			 93%
(ii)			 87%
(iii)			 57%
(iv)			 86%
(v)			 85%
(vi)			 78%
(vii)			 71%
(viii)			 57%

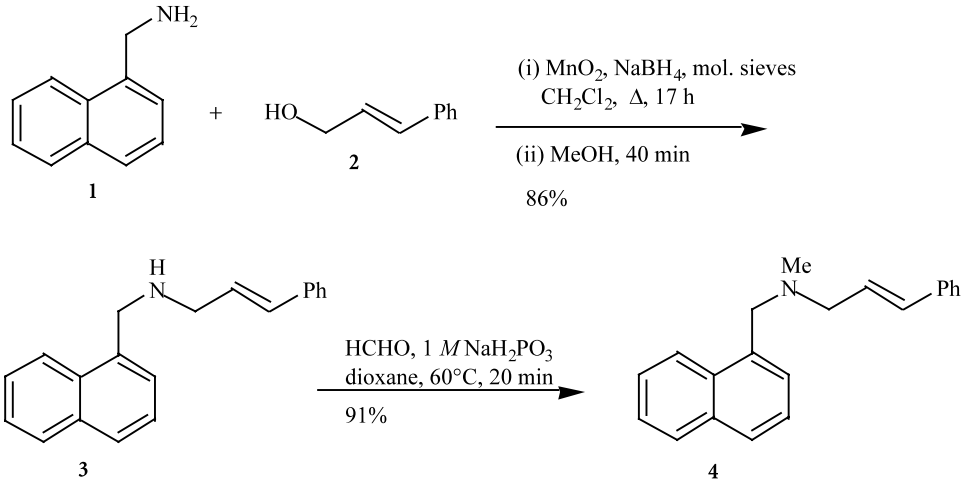
[a]Using manganese dioxide (10 equiv.) and $NaBH_4$ (2 equiv.) in CH_2Cl_2 for 16-21 h and then addition of methanol for 40 min; the product amines were normally pure after an acid-base extractive work-up, although silica chromagraphy was also required for the products in entries (iii), (vii) and (viii).

contrast to the procedure using PSCBH[2]), although yields of around 30% were observed in some cases (see later, Scheme 3).

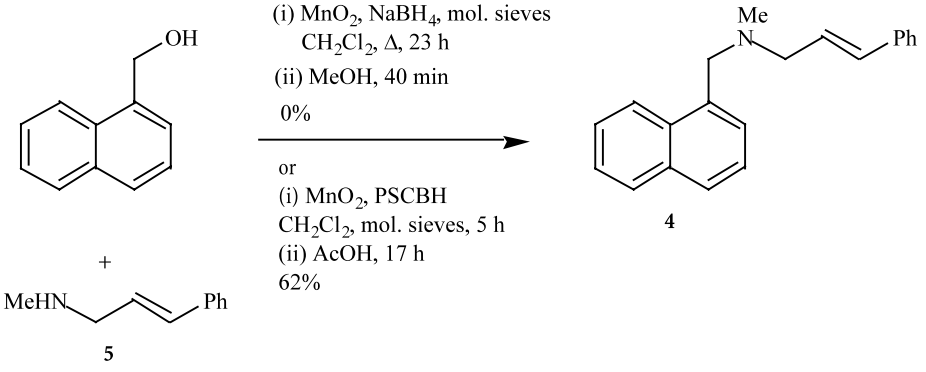
We next went on to utilise this methodology to prepare the topical antifungal agent naftifine **4**,[9,10] as shown in Scheme 1. Thus, 1-(aminomethyl)naphthalene **1** and cinnamyl alcohol **2** produced the secondary amine **3** in 86% yield.[11] This was then methylated using a published[10] procedure to give naftifine **4** in 91% yield with fully consistent spectroscopic data [e.g. δ_H ($CDCl_3$) 2.29 (3H, s), 3.30 (2H, d, J 6.5 Hz); lit.[9b] δ_H ($CDCl_3$) 2.32 (3H, s), 3.32 (2H, d, J 6.5 Hz)].

Further approaches were explored to avoid the methylation step and generate naftifine directly. Thus, in an analogous manner to the earlier study, 1-naphthalenemethanol and amine **5**[12] were subjected to the standard oxidation–imination–reduction sequence (Scheme 2). Unfortunately, as was anticipated from the preliminary studies, no naftifine **4** was produced. Use of our polymer-supported cyanoborohydride (PSCBH) method,[2] however, produced naftifine **4** in an acceptable 62% yield.

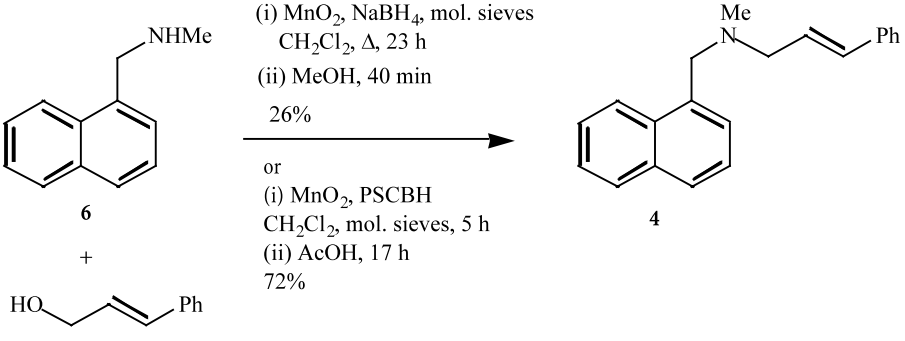
The alternative coupling mode was also studied (Scheme 3). The use of the sodium borohydride method



Scheme 1.



Scheme 2.



Scheme 3.

with the naphthyl amine **6** and cinnamyl alcohol produced naftifine **4** in 26% yield. This yield was improved to 72% with the polymer-supported cyanoborohydride method. These results confirm the supremacy of the PSCBH method[2] when using secondary amines as reactants.

In summary, we have shown that activated alcohols (benzylic, allylic and propargylic) will undergo the manganese dioxide/sodium borohydride-mediated oxidation–imination reduction sequence with primary amines to afford secondary amines in good to excellent yields. This methodology has been applied to a short synthesis of the topical antifungal agent naftifine **4**. We have established that secondary amines are not normally good substrates for this one-pot procedure, but that in certain circumstances tertiary amines can be prepared in this way. We are currently optimising and expanding the scope of this sequence and investigating its applications to other antifungal allyl amines[9] and for the synthesis of more complex target molecules.

Acknowledgements

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

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4. Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synlett* **2002**, 1293–1295.
5. For the preparation of borohydride exchange resin (BER), see: Gibson, H. W.; Bailey, F. C. *J. Chem. Soc., Chem. Commun*. **1977**, 815; using BER and MnO_2 with $^{i}BuNH_2$ and 4-methoxybenzyl alcohol in CH_2Cl_2 followed by the addition of methanol gave the expected amine product in 82% yield.
6. If methanol is present from the start of the reaction no conversion is observed.
7. All products gave consistent spectroscopic data which were comparable to published data where available; compounds **3** and **4** were fully characterised (including high field NMR spectroscopy and HRMS).
8. *tert*-Butylamine was also employed in the reaction with benzyl alcohol giving *N*-benzyl(*tert*-butyl)amine in 42% yield, although the reaction was slower then normal and unreacted starting material was recovered.
9. (a) Review: Monk, J. P.; Brogden, R. N. *Drugs* **1991**, *42*, 659; (b) for a recent publication, see: Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett*. **1993**, *34*, 583–586 and references cited therein.
10. Loibner, H.; Pruckner, A.; Stütz, A. *Tetrahedron Lett*. **1984**, *25*, 2535–2536.
11. Preparation of *N*-(1-naphthylmethyl)-(*E*)-cinnamylamine **3**: Activated manganese dioxide (Aldrich 21,764–6, 0.870 g, 10 mmol) was added to a stirred solution of (*E*)-cinnamyl alcohol (0.134 g, 1 mmol), 1-(aminomethyl)naphthalene (0.314 g, 2 mmol) and sodium borohydride (0.113 g, 3 mmol) in dichloromethane (20 mL) containing 4 Å molecular sieves (ca. 0.2 g). The mixture was stirred at reflux for 17 h and then cooled in an ice bath. Methanol (5 mL) was added to the reaction mixture which was stirred for 10 min in an ice-bath and then 30 min at room temperature. The reaction mixture was filtered through Celite® washing well with EtOAc. The combined filtrates were concentrated and then ether (30 mL) and a saturated aq. $NaHCO_3$ solution (30 mL) were added to the residue. A standard ether work-up followed by silica chromatography (EtOAc–petroleum ether, 2:1 to EtOAc–MeOH, 10:1) gave the desired compound **3** (0.234 g, 86%) as a yellow solid, mp 39.5–40.5°C, R_f 0.38 (EtOAc–MeOH, 10:1); [HRMS (CI), MH^+: 274.159970. $C_{20}H_{19}N$ requires MH^+, 274.159575 (1.4 ppm error)] which gave consistent spectroscopic data (for hydrochloride salt, see: Stütz, A.; Goergopoulos, A.; Granitzer, W.; Petranyi, G.; Berney, D. *J. Med. Chem*. **1986**, *29*, 112–125).
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