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# A chemoselective deoxygenation of *N*-oxides by sodium borohydride–Raney nickel in water

Narendra B. Gowda [a], Gopal Krishna Rao [b], Ramesha A. Ramakrishna [c,*]

[a] Department of Pharmaceutical Chemistry, Visveswarapura Institute of Pharmaceutical Sciences, Bangalore 560070, India
[b] Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Bangalore 560027, India
[c] R L Fine Chem. No. 15, KHB Industrial Area, Yelahanka Newtown, Bangalore 560106, India

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ABSTRACT

A simple and convenient protocol for deoxygenation of aliphatic and aromatic *N*-oxides to the corresponding amines in good to excellent yield using sodium borohydride–Raney nickel in water is reported. Other functional moieties such as alkenes, halides, ethers, and amides are unaffected under the present reaction condition.



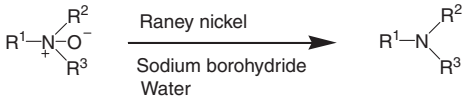
The chemoselective and efficient deoxygenation of *N*-oxides to corresponding amines is an important synthetic transformation in organic synthesis.[1] *N*-Oxides are an important intermediate in regioselective transformations of pyridine heterocyclic compounds.[2] Moreover, *N*-oxides have been identified as one of the major pathways of drug metabolism of many nitrogen-containing pharmaceutically active molecules.[3]

Over the years, numerous methods have been developed for the reduction of *N*-oxides to the corresponding amine, which include reduction with Pd–C/$H_2$,[4] $H_2SO_3$,[5] Ni–Al alloy,[6] alkali metal hydrides,[7] $TiCl_3$,[8] Zn–$NH_4Cl$,[9] Zn–$HCO_2NH_4$,[10] $TiCl_4$–$SnCl_2$,[11a] $TiCl_4$–Zn,[11b] $TiCl_4$–Mg,[11c] $TiCl_4$–NaI,[11d] $TiCl_4$–$NaBH_4$,[11e] $SmI_2$,[12] tertathiomoplybdate[13] $ZrCl_4$–$NaBH_4$,[14a] LiCl–$NaBH_4$,[14b] $InCl_3$,[15a] In–$NH_4Cl$,[15b] $RuCl_3{\cdot}H_2O$[16] and $CoCl_2{\cdot}6H_2O$–In,[17] $MoCl_2$–NaI,[18] $NbCl_5$-Zn,[19] Pd–C/ammonium formate,[20] $NaBH_4$–$CuSO_4$,[21] phosphorous compounds,[22] Iron[23] and Zn in acetic acid,[24] Zn–NaOH,[25] $R_3N$–$SO_2$ complex,[26] $AlI_3$,[27] acetic formic anhydride,[28] NaHTe, and [29] Cr(II)$Cl_2$.[30a] Triphenyl phosphine-mediated deoxygenation catalyzed by Rhenium porphyrin complex and [30b] deoxygenation by silanes catalyzed by $MoO_2Cl_2$[30c] were also reported. Also, there is a recent report on deoxygenation of aromatic *N*-oxide by Raney nickel in ethanol.[31] However, the generality of this method has not been established. The deoxygenation of *N*-oxides is also catalyzed by microbes,[32] heme moiety of cytochrome P-450,[33] and rat liver preparation[34] at ambient temperature.

In these reported methods, either organic solvents or combination of organic solvents with water are used as the reaction medium. Although sodium borohydride has been used in combination with metal salts for the reduction of *N*-oxides, in most cases large excess of sodium borohydride (4–10 mol equiv) is required. In general, the methods have been extensively applied for the reduction of aromatic *N*-oxides and the application of these methods for the reduction of aliphatic *N*-oxides containing beta hydrogen has not been established due to possible Cope elimination reaction. Therefore, real assessment of method robustness must be made for the deoxygenation of *N*-oxide.

Development of new methodology in organic synthesis based on Green Chemistry principle is an important goal toward sustainable future. Our aim was to develop a practical method for the deoxygenation in water. This seems to be a possibility as *N*-oxides are ionic in nature and are partly or completely soluble in water.

Herein, we report an environmentally friendly and highly efficient and chemoselective method for deoxygenation of *N*-oxides




**Scheme 1.** Deoxygenation of tertiary amine *N*-oxide.

* Corresponding author. Fax: +91 08 28566904.
*E-mail address:* ramesha63@hotmail.com (R.A. Ramakrishna).

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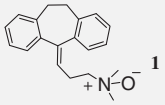
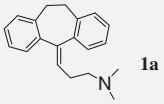
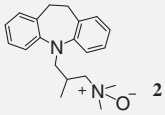
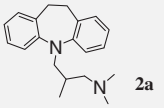
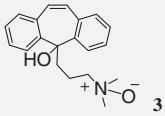
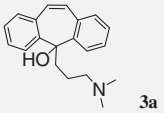
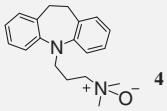
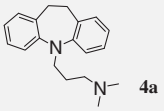
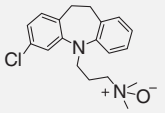
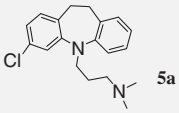
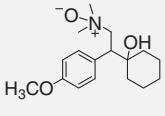
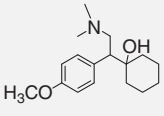
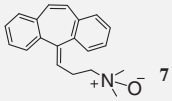
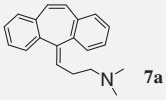
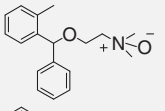
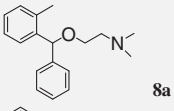
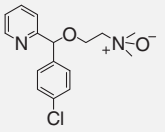
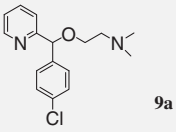
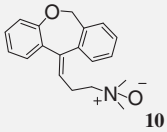
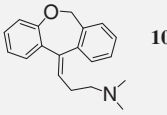
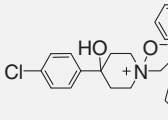
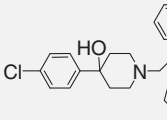
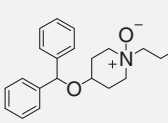
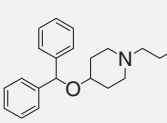
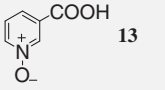
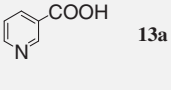
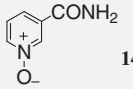
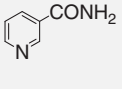
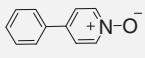
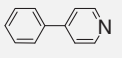
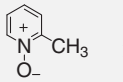
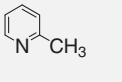
with sodium borohydride–Raney nickel system in water. In a typical experiment, the *N*-oxide is dissolved in water at 60 °C, then Raney nickel (W6) about 30–40% was added. The reaction mixture was stirred for 10 min and sodium borohydride was added slowly, the mixture was allowed to warm and maintained at 50–60 °C, while reaction progress was monitored by TLC. Upon completion of reaction, the product was extracted with chloroform or dichloromethane and filtered to remove Raney nickel and worked up in the standard procedure. Various aliphatic and aromatic *N*-oxides (Scheme 1) were readily reduced in good to excellent yields. The selectivity of this method is demonstrated by several examples and the results are summarised in Table 1.

**Table 1**
Deoxygenation of *N*-oxides using Raney nickel in aqueous sodium borohydride

| Entry | Substrate | Time (h) | Yield[a] (%) | Product[b] |
|---|---|---|---|---|
| 1 |  **1** | 2 | 98 |  **1a** |
| 2 |  **2** | 2 | 95 |  **2a** |
| 3 |  **3** | 2 | 95 |  **3a** |
| 4 |  **4** | 2 | 96 |  **4a** |
| 5 |  **5** | 2 | 82 |  **5a** |
| 6 |  **6** | 1.5 | 92 |  **6a** |
| 7 |  **7** | 2.5 | 92 |  **7a** |
| 8 |  **8** | 2 | 90 |  **8a** |
| 9 |  **9** | 2 | 96 |  **9a** |
| 10 |  **10** | 2 | 93 |  **10a** |
| 11 |  **11** | 3.5 | 95[c] |  **11a** |
| 12 |  **12** | 3.5 | 89[d] |  **12a** |
| 13 |  **13** | 4.5 | 65 |  **13a** |

(*continued on next page*)

**Table 1** (*continued*)

| Entry | Substrate | Time (h) | Yield[a] (%) | Product[b] |
|---|---|---|---|---|
| 14 |  **14** | 4.5 | 62 |  **14a** |
| 15 |  **15** | 4.5 | 79 |  **15a** |
| 16 |  **16** | 4.5 | 74 |  **16a** |

[a] Yields of isolated products.
[b] Most of the products are commercially available and were identified by comparison of their NMR and mass spectra with those of authentic samples.
[c] *N*-Oxides dissolved in water and ethanol (2:1).
[d] *N*-Oxides dissolved in water and methanol (2:1).

When amitriptyline *N*-oxide[35,45] (entry 1) and cyclobenzaprine *N*-oxide (entry 7) were subjected to deoxygenation, complete chemoselective deoxygenation occurred to give good yield of **1a** and **7a**. In both the cases, double bond was not affected. The utility of the method has been extended to the deoxygenation of many pharmacologically active *N*-oxides. Similarly in entry 3, *tert*-hydroxyl and olefin groups remained intact, and the reaction gave 92% of the deoxygenated product, **3a**. This product is an intermediate in the synthesis of cyclobenzaprine.[37] Trimipramine *N*-oxide and imipramine *N*-oxide (entries 2 and 4) were deoxygenated to the corresponding amines **2a** and **4a**[38] in good yields. Clomipramine *N*-oxide (entry 5) was completely reduced to Clomipramine and the halogen group remained intact. Venlafaxine *N*-oxide (entry 6) was deoxygenated to venlafaxine[39] with 92% yield. Similarly ether groups and pyridine groups were unaffected during the reduction of Orphenadrine *N*-oxide (entry 8), carbinoxamine *N*-oxide, and doxepin *N*-oxide[41] (entries 9 and 10) to afford the corresponding amines **9a**[40] and **10a** in good yields. Loperamide *N*-oxide and ebastine *N*-oxide (entries 11 and 12) also reacted well to give corresponding reduced product of **11a**[42] and **12a**. In the case of ebastine (entry 12), keto group was also reduced. Other aromatic *N*-oxides[36,43,44] (entries 13–16) were completely reduced to their corresponding amines. The moderate yields in these examples are due to the partial solubility of these products in water. This method however failed to work for triphenyl phosphine oxide and chlorpromazine sulfoxide.

In conclusion, this new deoxygenative method using sodium borohydride–Raney nickel in water offers a useful alternative to other methods available for reduction of *N*-oxides. Unlike many of the reported procedures, this works very well for aliphatic and aromatic *N*-oxides. We have also been able to reduce the use of sodiumborohydride by 50–75% compared to earlier methods. More over commercially available Raney nickel is used as a catalyst, which can be reused many times. Excellent chemo selectivity and use of water as a medium would be an added advantage of this new methodology.

## Acknowledgments

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## Supplementary data

Supplementary data (spectral data and $^{1}H$ and $^{13}C$ NMR of *N*-oxides and corresponding products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.045.

## References and notes

1. *Aromatic Amine Oxides*; Ochiai, E., Ed.; Elsevier: Amsterdam, 1967; pp 184–209.
2. Lukevits, E. *Chem. Heterocycl. Compd.* **1995**, *31*, 639.
3. Bickel, M. H. *Pharmacol. Rev.* **1969**, *29*, 325.
4. (a) Katritzky, A. R.; Monro, A. M. *J. Chem. Soc.* **1958**, 1263; (b) Zacharie, B.; Moreau, N.; Doekendorff, C. *J. Org. Chem.* **2001**, *66*, 5264.
5. Hayashi, E.; Iijima, C. *Yakugaku Zasshi* **1962**, *82*, 1093.
6. Lunn, G.; Sansone, B. *Synthesis* **1985**, 1104.
7. Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.
8. McCall, J. M.; Tenbrink, R. E. *Synthesis* **1975**, 335.
9. Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997**, 891.
10. Balicki, R.; Cybulski, M.; Maeiejewski, G. *Synth. Commun.* **2003**, *23*, 4137.
11. (a) Balicki, R.; Kaczmarck, L.; Malinnowski, M. *Synth. Commun.* **1989**, *19*, 897; (b) Homaidan, F. R.; Issidorides, C. H. *Heterocycles* **1981**, *16*, 411; (c) George, J.; Chandrasekaran, S. *Synth. Commun.* **1983**, *13*, 495; (d) Balicki, R. *Chem. Ber.* **1990**, 647; (e) Kano, S.; Tanaka, Y.; Sugino, E.; Hibino, S. *Synthesis* **1980**, 695.
12. Handa, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1989**, 298.
13. Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1995**, *36*, 4881.
14. (a) Chary, K. P.; Mohan, G. H.; Iyengar, D. S. *Chem. Lett.* **1999**, *12*, 1339; (b) Ram, S. M.; Chary, K. P.; Iyengar, D. S. *Synth. Commun.* **2000**, *30*, 3511.
15. (a) Ilias, M.; Barmen, D. C.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **2002**, *43*, 1877; (b) Yadav, J. S.; Subbareddy, B. V.; Reddy, M. M. *Tetrahedron Lett.* **2000**, *41*, 2663.
16. Kumar, S.; Saini, A.; Sandhu, J. S. *Tetrahedron Lett.* **2005**, *46*, 8737.
17. Han, J. H.; Choi, K. I. I.; Kim, J. H.; Yoon, C. M.; Yoo, B. W. *Synth. Commun.* **2006**, *36*, 415.
18. Yoo, B. W.; Park, M. C. *Synth. Commun.* **2008**, *38*, 1646.
19. Oh, K.; Knabe, W. E. *Tetrahedron* **2009**, *65*, 2966.
20. Balicki, R. *Synthesis* **1989**, 645.
21. Sim, T. B.; Yoon, N. M. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1101.
22. Hamana, M. *Yakugaku Zasshi* **1951**, *71*, 263.
23. D-Hertog, H. J.; Hoogzand, C. *Recl. Trav. Chem.* **1957**, *76*, 261.
24. Fujimoto, M. *Chem. Pharm. Bull.* **1956**, *4*, 1.
25. Krohnke, F.; Schafer, H. *Ber. Dtsch. Ger.* **1962**, *95*, 1098.
26. Geroge, A.; Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *Synthesis* **1980**, 660.
27. Konwar, D.; Boruah, R. C.; Sandhu, J. S. *Synthesis* **1990**, 337.
28. Tokitoh, N.; Okazaki, R. *Chem. Lett.* **1985**, 1517.
29. Barton, D. H. R.; Fekih, A.; Lusinchi, X. *Tetrahedron Lett.* **1985**, *38*, 4603.
30. (a) Akita, Y.; Miru, K.; Watanabe, T.; Ohta, A. *Chem. Pharm. Bull.* **1976**, *24*, 1839; (b) Motoki, T.; Keitaro, F.; Shinya, I.; Hiroyuki, F. *Tetrahedron Lett.* **2008**, *49*, 1488; (c) Ana, C. F.; Carlos, C. R. *Tetrahedron* **2006**, *62*, 9650.
31. Mucha, P.; Mloston, G.; Jasinski, M.; Linden, A.; Heimgartner, H. *Tetrahedron: Asymmetry* **1600**, *2008*, 19.
32. Johnson, R. A.; Marshall, V. P.; Li, G. P.; Sih, J. C.; Cialdella, J. I.; Liggett, W. F.; Nidy, E. G. *J. Antibiot.* **1996**, *49*, 788.
33. Takekawa, K.; Kitamura, S.; Sugihara, K.; Ohta, S. *Xenobiotica* **2001**, *31*, 11.
34. Kitamura, S.; Tatsumi, K. *Biochem. Mol. Biol. Int.* **1997**, *42*, 271.
35. Pederson, J. B.; Hvidovre, C. U.S. Patent 3299139, 1967.
36. Taylor, E. C.; Crovetti, A. J. *J. Org. Chem.* **1954**, *19*, 1633.
37. Wintrop, S. O.; Davis, A.; Myers, G. S.; Gavin, J. G.; Thomas, R.; Barber, R. *J. Org. Chem.* **1962**, *27*, 230.
38. Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett.* **1985**, *26*, 5367.

39. Yardley, J. P.; Morris Husbands, J. G. E.; Stack, G.; Butch, J.; Bicksler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, H.; James, M. N. G.; Sielecki, A. R. *J. Med. Chem.* **1990**, *33*, 2899.
40. Swain, A. P.; Township, S.; County, M. U.S. Patent 2800485, 1957.
41. Moody, J. D.; Freeman, J. P.; Cernigla, C. A. *Drug Metab. Dispos.* **1990**, *27*, 1157.
42. Chen, Z.; Davies, E.; Miller, W. S.; Shan, S.; Valenzano, K. J.; Kyle, D. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5275.
43. Toganoh, M.; Fujino, K.; Ikeda, S.; Furuta, H. *Tetrahedron Lett.* **2008**, *49*, 1488.
44. Demoura, M. F. V.; Matso, J. R.; Defaris, R. F. *J. Coord. Chem.* **2004**, *57*, 747.
45. *General procedure for deoxygenation of N-oxides*: 0.293 g (1 mmol) of *N*-oxides was dissolved in 2.5 mL of water at 60 °C, then Raney nickel (0.10 g, W6 grade) was added .The reaction mixture was stirred for 10 min and 0.076 g (2 mmol) of sodium borohydride was added slowly in portions over 15–20 min. The reaction mixture was allowed to stir at the same temprature till the completion of the reaction as monitored by TLC. Once the reaction was completed, chloroform or dichloromethane (50 mL) was added and then the resulted mixture was filtered to remove Raney nickel. Chloroform or dichloromethane layer was dried over anhydrous magnesium sulfate, filtered, and evaporated under vacuum. The residue thus obtained was purified through short path flash chromatography with silica gel and chloroform to get the product. Amitriptyline 0.271 g (98%) **1a**: $^{1}$H NMR (200 MHz, $CDCl_3$) $\delta$: 2.15 (s, 6H, N–$CH_3$), 2.21–2.41(m, 4H, $CH_2$), 2.78–3.41 (m, 4H, $CH_2$), 5.85 (t, $J$ = 6.0 Hz, 1H, CH), 6.98–7.29 (m, 8H, ArH). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 28.48, 32.61, 34.38, 45.88, 59.99, 126.32, 126.55, 127.59, 127.97, 128.79, 129.22, 129.85, 130.55, 137.61, 139.89, 140.66, 141.82, 144.09. ESI-MS ($m/z$): calcd for $C_{20}H_{23}N$: 278.19, found: 278.53.