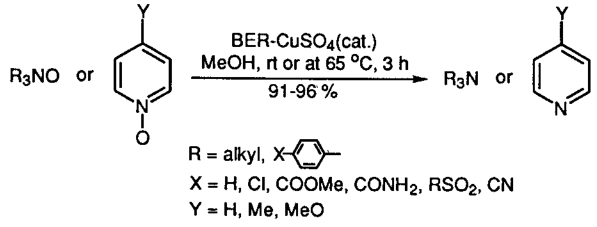
Selective Deoxygenation of Amine *N*-Oxides Using Borohydride Exchange Resin–Copper Sulfate in Methanol

Tae Bo Sim, Jin Hee Ahn, Nung Min Yoon*
Department of Chemistry, Sogang University, Seoul 121-742, South Korea
Fax +82(2)7010967

Received 18 July 1995

Borohydride exchange resin–copper sulfate in methanol readily deoxygenates quantitatively both tertiary amine *N*-oxides and heteroaromatic *N*-oxides at room temperature or under reflux. It tolerates many functional groups such as carbon–carbon double bond, chloride, epoxide, ester, amide, nitrile, sulfoxide, sulfone, and aliphatic disulfide moieties.

The deoxygenation of heteroaromatic *N*-oxides is important in the synthesis of nitrogenous heterocyclic compounds.[1] Although catalytic hydrogenation[1,2] and phosphorus compounds[1,2] have traditionally been utilized for deoxygenation, more selective deoxygenating reagents such as trialkylamine–sulfur dioxide complexes,[3] aluminum iodide,[4] acetic formic anhydride,[5] ammonium formate–Pd/C,[6] sodium hydrogen telluride,[7] tin reagents,[8] and low-valent titanium reagents[9] have often been reported. However, some of these reagent systems suffer from their own limitations: trialkylamine–sulfur dioxide complexes give somewhat low yields,[3] and acetic formic anhydride[5] and sodium hydrogen telluride[7] cannot deoxygenate heteroaromatic *N*-oxides. Recently, we have studied the reducing characteristics of the borohydride exchange resin (BER)–cat. $CuSO_4$ system in methanol and reported the selective reduction of α,β-unsaturated acid derivatives to the corresponding saturated acid derivatives.[10] We report herein another application of this reagent system to the selective deoxygenation of amine *N*-oxides, both tertiary amine *N*-oxides and heteroaromatic *N*-oxides, in the presence of many other functional groups.



The results are summarized in Table 1. As shown there, tertiary amine *N*-oxides were readily deoxygenated quantitatively in 3 hours at room temperature, using 3.0 equivalents of BER and 0.1 equivalent of $CuSO_4$. *N,N*-Dimethylaniline *N*-oxide was quantitatively deoxygenated in 3 hours (entry 2); but the deoxygenation of this *N*-oxide by sodium hydrogen telluride[7] required 18 hours at 78 °C. BER–cat. $CuSO_4$ system in methanol selectively deoxygenated an *N*-oxide function in the presence of chloro, ester, amide, nitrile, and sulfone groups in the same molecule (entries 4–10). Tin reagents[8] and low-valent titanium reagents[9] are also reported to tolerate halides and carboxylic acid derivatives, but ammonium formate[6] as a catalytic hydrogen transfer agent affected halides. The deoxygenation of pyridine *N*-oxides was slow compared with tertiary amine *N*-oxides, but could be carried out smoothly using 5.0 equivalents of BER at 65 °C (entries 11–13). In contrast, quinoline *N*-oxides were more reactive and readily deoxygenated at room temperature (entries 14–16). Unfortunately, a concomitant reduction of the heteroaromatic ring occurred in the cases of quinoline and quinaldine *N*-oxides (entries 14–15). Pyridine *N*-oxide can be selectively deoxygenated in the presence of sulfoxides, terminal olefins, and epoxides (entries 17–19). Acetic formic anhydride[5] and sodium hydrogen telluride[7] were also reported to deoxygenate tertiary amine *N*-oxides in the presence of sulfoxide; but many reagents, such as trialkylamine–sulfur dioxide complexes,[11] aluminum iodide,[12] and low-valent titanium reagents[13] deoxygenate sulfoxides as well as pyridine *N*-oxides. Therefore, BER–cat. $CuSO_4$ should be a valuable reagent for such selective reductions.[14] Finally, the BER–cat. $CuSO_4$ system in methanol has the significant advantage of simple workup. In most cases, simple filtration of BER–Cu and the evaporation of methanol give an almost pure product.

In conclusion, the present system is an alternative reagent of choice for the selective deoxygenation of amine *N*-oxides, both tertiary amine *N*-oxides and heteroaromatic *N*-oxides, because of its excellent yield, selectivity, and simple workup procedure.

Preparation of BER:
An aqueous solution of sodium borohydride (1 M, 500 mL) was stirred with wet chloride-form anion exchange resin (Amberlite IRA-400 [20–50 mesh], 200 g) for 15 min. The resulting resin was washed thoroughly with distilled water until free from excess $NaBH_4$. The borohydride-form anion exchange resin was then dried under vacuum at 60 °C for 5 h to give 102 g of dried borohydride exchange resin (BER). The dried resin was analyzed for borohydride content by hydrogen evolution upon acidification with 2 N HCl, and the average hydride content of BER was found to be 3.0 mmol of BH_4^- per gram. The dried resin was stored under nitrogen in a refrigerator (~ 4 °C). The hydride content was constant over 6 weeks.

Deoxygenation of Methyl *p*-Dimethylaminobenzoate *N*-Oxide; Typical Procedure:
When BER (9.68 g, 30.0 mmol) was added to the solution of copper sulfate (0.249 g, 1.0 mmol) in MeOH (100 mL), an immediate black coating of resin was observed. Methyl *p*-dimethylaminobenzoate *N*-oxide (1.95 g, 10 mmol) in methanol (20 mL) was added, and the reaction mixture was stirred for 3 h at r.t. The resin was removed by filtration, and methanol was evaporated under reduced pressure to give methyl *p*-dimethylaminobenzoate; yield: 1.68 g (94%).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 9.0$ Hz, 2 H), 6.65 (d, $J = 8.8$ Hz, 2 H), 3.86 (s, 3 H), 3.04 (s, 6 H).

IR (NaCl, CH_2Cl_2): $\nu = 2989, 2949, 2903, 1705, 1606, 1529, 1435$ cm^{-1}.

MS (EI): *m/e* (relative intensity) = 77 (28), 104 (20), 148 (100), 178 (49), 179 (84).

Table 1. Selective Deoxygenation of Amine *N*-Oxides Using Borohydride Exchange Resin–Copper Sulfate in Methanol[a]

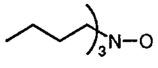
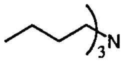
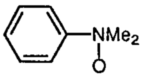
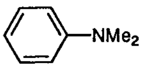
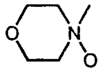
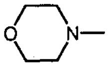
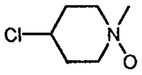
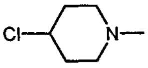
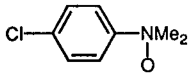
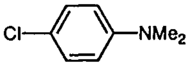
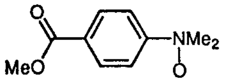
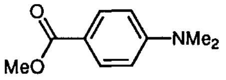
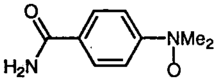
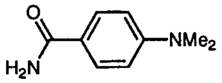
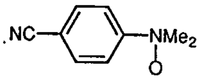
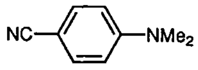
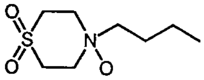
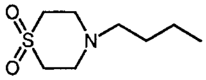
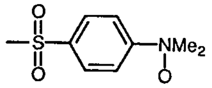
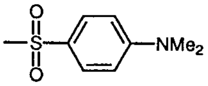
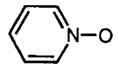
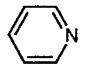
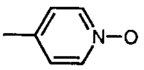
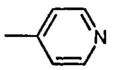
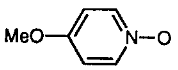
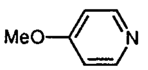
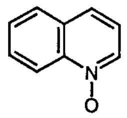
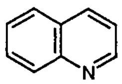
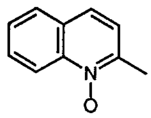
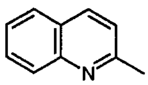
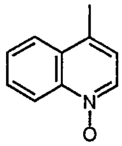
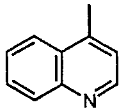
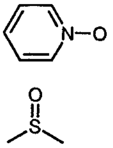
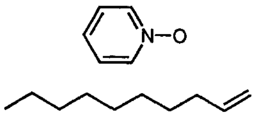
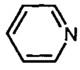
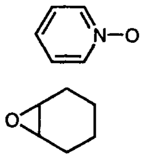
Entry	*N*-oxide	BER (eq)	Temperature	Time (h)	Amine	Isolated yields (%)[b]
1		3	r.t.	3		93
2		3	r.t.	3		94
3		3	r.t.	3		96[c]
4		3	r.t.	3		93[c]
5		3	r.t.	3		95
6		3	r.t.	3		94[d]
7		3	r.t.	3		95
8		3	r.t.	3		91[d]
9		3	r.t.	3		94[d]
10		3	r.t.	3		96
11		5	65°C	3		94[c]
12		5	65°C	3		93[c]
13		5	65°C	3		93[c]
14		5	r.t.	1		61
15		5	r.t.	2		73[d]

Table. (continued)

Entry	*N*-oxide	BER (eq)	Temperature	Time (h)	Amine	Isolated yields (%)[b]
16		5	r.t.	2		92
17		5	65°C	3		99
18		5	65°C	3		97
19		5	65°C	3		98

[a] Reductions were carried out using BER (3.0 or 5.0 eq) and $CuSO_4$ (0.1 eq) in methanol.

[b] Yields in parenthesis were estimated by GC.

[c] Isolated as hydrochloride salt.

[d] Satisfactory C,H,N analyses were obtained (± 0.29%).

p-Dimethylaminobenzonitrile:

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.46$ (d, $J = 9.1$ Hz, 2H), 6.64 (d, $J = 9.0$ Hz, 2H), 3.03 (s, 6H).

IR (NaCl, CH_2Cl_2): $\nu = 2987$, 2912, 2870, 2214, 1608, 1527, 1445 cm^{-1}.

MS (EI): *m/e* (relative intensity) = 102 (22), 129 (15), 145 (100), 146 (60).

4-Butyl-1,4-thiazinane 1,1-Dioxide:

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.03$–2.98 (m, 8H), 2.50 (t, $J = 6.9$ Hz, 2H), 1.50–1.27 (m, 4H), 0.92 (t, $J = 6.7$ Hz, 3H).

IR (NaCl, neat): $\nu = 2957$, 2933, 2823, 1467, 1302, 1190, 1122 cm^{-1}.

MS (EI): *m/e* (relative intensity) = 56 (17), 82 (7), 148 (100), 191 (5).

Lepidine:

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.77$ (d, $J = 3.1$ Hz, 1H), 8.12–8.09 (m, 1H), 8.00–7.97 (m, 1H), 7.72–7.68 (m, 1H), 7.58–7.53 (m, 1H), 7.28–7.22 (m, 1H), 2.69 (s, 3H).

IR (NaCl, neat): $\nu = 3396$, 3063, 3036, 1595, 1572, 1510, 1454, 1392 cm^{-1}.

MS (EI): *m/e* (relative intensity) = 89 (22), 104 (11), 115 (67), 128 (4), 143 (100).

This work was supported by the Organic Chemistry Research Center sponsored by the Korea Science and Engineering Foundation.

(1) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534.
(2) Tjomas, K.; Jerchel, D. *Angew. Chem.* **1958**, *70*, 731.
(3) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *Synthesis* **1980**, 660.
(4) Konwar, D.; Boruah, R. C.; Sandhu, J. S. *Synthesis* **1990**, 337.
(5) Tokitoh, N.; Okazaki, R. *Chem. Lett.* **1985**, 1517.
(6) Balicki, R. *Synthesis* **1989**, 645.
(7) Barton, D. H. R.; Fekih, A.; Lusinchi, X. *Tetrahedron Lett.* **1985**, *26*, 4603.
(8) Jousseaume, B.; Chanson, E. *Synthesis* **1987**, 55.
(9) Balicki, R.; Kaczmarek, L.; Malinowski, M. *Synth. Commun.* **1989**, *19*, 897.
(10) Sim, T. B.; Yoon, N. M. *Synlett* **1995**, 1073.
(11) Olah, G. A.; Vankar, Y. D.; Arvanaghi, M. *Synthesis* **1979**, 984.
(12) Babu, J. R.; Bhatt, M. V. *Tetrahedron Lett.* **1986**, *27*, 1073.
(13) Drabowicz, J.; Mikolajczyk, M. *Synthesis* **1978**, 138.
(14) Hydrogenation over Pd/C might also accomplish the selective reduction. Deoxygenation of sulfoxide required 4 days at 86–90°C under 78 atm, whereas picoline *N*-oxides could be deoxygenated easily at 50°C under 50 atm in 4 h.
Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Synthesis* **1975**, 385.
Taylor, E. C.; Crovetti, A. J.; Boyer, N. E. *J. Am. Chem. Soc.* **1957**, *79*, 3549.