

Communications

A Facile Deoxygenation of Amine-*N*-oxides with NiCl₂·6H₂O/Indium System

Jung Hwa Han, Jin Woo Choi, Kyung Il Choi,[†] Joong Hyup Kim,[†] Cheol Min Yoon, and Byung Woo Yoo*

Department of Advanced Materials Chemistry, Korea University, Jochiwon, Chungnam 339-700, Korea

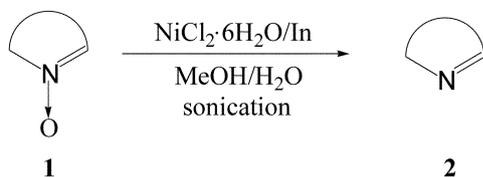
*E-mail: bwyoo@korea.ac.kr

[†]Biochemicals Research Center, Korea Institute of Science and Technology, Cheongryang, Seoul 130-650, Korea

Received September 16, 2005

Key Words : Deoxygenation, Amine-*N*-oxides, Nickel chloride, Indium

The deoxygenation of amine-*N*-oxides to amines is an important transformation in the synthesis of nitrogenous aromatic heterocycles and an area of considerable interest, particularly when a molecule has other reducible or labile moieties.¹ A number of methods have been described for the reduction of amine-*N*-oxides, including agents such as low-valent titanium,² Zn/HCOONH₄,³ InCl₃,⁴ tributyltin hydride,⁵ Pd/C,⁶ tetrathiomolybdate,⁷ SmI₂,⁸ and indium/NH₄Cl.⁹ However, some of these reagents are associated with limitations with regard to compatibility with other functional groups, ready availability, and harsh reaction conditions. Consequently, there is still a need for introducing mild and efficient reagents for the deoxygenation of amine-*N*-oxides to amines. The reduction of NiCl₂ to low-valent nickel species and the synthetic utility of such species are well documented in the literatures.¹⁰ In continuation of our efforts towards the development of the low-valent metal reagents for organic transformations,¹¹ we observed that a combination of NiCl₂ with indium could bring about the deoxygenation of amine-*N*-oxides under mild condition. The new reducing system was generated by the addition of indium powder to a stirred solution of nickel(II) chloride hexahydrate under sonication. We herein wish to report a mild



and efficient method for the deoxygenation of amine-*N*-oxides using the NiCl₂·6H₂O/In system in aqueous methanol.¹² The high yields of the deoxygenation products demonstrate the efficiency of this new method. Table 1 summarizes our results on the reduction of various amine-*N*-oxides. Some control experiments revealed that amine-*N*-oxides could not be deoxygenated by indium alone under the present reaction condition and the starting materials were recovered unchanged. The optimum ratio of reagents was found to be

Table 1. Deoxygenation of amine-*N*-oxides with NiCl₂·6H₂O/In system

Entry	Substrate	Product	Time (hr)	Yield (%) ^a
1	Quinoline- <i>N</i> -oxide	Quinoline	4.0	95
2	Isoquinoline- <i>N</i> -oxide	Isoquinoline	6.0	91
3	4-Picoline- <i>N</i> -oxide	4-Picoline	6.0	91
4	4- <i>t</i> -Butylpyridine- <i>N</i> -oxide	4- <i>t</i> -Butylpyridine	6.0	88
5	Morpholine- <i>N</i> -oxide	Morpholine	8.0	83
6			7.0	86
7			5.0	89
8			4.0	92
9			6.0	90
10			6.0	86
11			4.0	91
12			3.0	87
13			4.0	88
14			6.0	85

^aIsolated yields

substrate : NiCl₂ : indium = 1 : 2 : 4. In order to explore the scope and limitation of this reagent system we have tested its applicability to the selective deoxygenation of the amine-*N*-oxides bearing other potentially sensitive functional groups in the heteroaromatic ring. The functional group tolerance of this deoxygenation system is evident from the table which shows that cyano, bromo, chloro, ester, methoxy, and amide groups remain unchanged under the reaction conditions. No isolable product was formed when the reaction was carried out in water or methanol alone. After screening the reaction conditions, the optimum solvent for the reaction was a 1 : 1 mixture of MeOH-H₂O. The reaction with no ultrasound gave no products. Thus ultrasonic irradiation is necessary to activate the reaction. We have been able to demonstrate the utility of the easily accessible NiCl₂·6H₂O/In system as a convenient reagent for effecting chemoselective deoxygenation of amine-*N*-oxides. All the compounds obtained showed IR, NMR and mass spectral data consistent with the structure. Although the reaction mechanism is still unclear, it can be rationalized as a two-stage process. In the first step, nickel(II) chloride is probably reduced by indium to form the low-valent nickel species, which, in the subsequent step, would reductively deoxygenate amine-*N*-oxides **1** to give the corresponding amines **2**. The notable advantages of the present methodology are the mild reaction condition, the excellent yields, and the tolerance of other labile functional groups.

In conclusion, we believe that the mild and efficient method described here offers an attractive alternative to the existing methods available for the reduction of amine-*N*-oxides to the corresponding amines. Further investigations of NiCl₂·6H₂O/In system as a reducing agent in organic synthesis are currently in progress.

Acknowledgements. This work was financially supported by Korea Institute of Science and Technology (2E16800) and partially by Korea University.

References

- Ochiai, E. In *Aromatic Amine Oxides*; Elsevier: Amsterdam, 1967; pp 184-209.
- (a) Malinoswaki, M. *Synthesis* **1987**, 732; (b) Balicki, R. *Chem. Ber.* **1990**, 647; (c) Balicki, R.; Kaczmarek, L.; Malinowski, M. *Synth. Commun.* **1989**, 19, 897; (d) Yoo, B. W.; Choi, J. W.; Kim, D. Y.; Hwang, S. K.; Choi, K. I.; Kim, J. H. *Bull. Korean Chem. Soc.* **2002**, 23, 797.
- Balick, R.; Cybulski, M.; Maciejewski, G. *Synth. Commun.* **1989**, 19, 897
- Ilias, M.; Barman, D. C.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Letters* **2002**, 43, 1877.
- (a) Kozuka, S.; Akasaka, K.; Furumai, T.; Dae, S. *Chem. Ind. (London)* **1974**, 452; (b) Jousseume, B.; Chanson, E. *Synthesis* **1987**, 55.
- Balicki, R. *Synthesis* **1989**, 645.
- Ilan Kumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1995**, 36, 4881.
- Handa, Y.; Tanaka, W.; Ohta, A. *J. Chem. Soc. Chem. Commun.* **1994**, 10, 1225.
- Yadav, J. S.; Reddy, B. V. S.; Reddy, M. M. *Tetrahedron Lett.* **2000**, 41, 2663.
- (a) Wu, H.; Chen, R.; Zhang, Y. *Synth. Commun.* **2002**, 32, 189; (b) Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J. S.; Ghosh, A. C. *Tetrahedron Lett.* **1996**, 37, 4559. (c) Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. *Synlett.* **1997**, 1253. (d) Bezbarua, M. S.; Bez, G.; Barua, N. *Chem. Lett.* **1999**, 325.
- (a) Yoo, B. W.; Choi, K. H.; Ko, J. J.; Nam, G. S.; Chang, K. Y.; Choi, K. I.; Kim, J. H. *Bull. Korean Chem. Soc.* **2001**, 22, 541; (b) Yoo, B. W.; Choi, K. H.; Lee, S. J.; Yoon, C. M.; Kim, S. H.; Kim, J. H. *Synth. Commun.* **2002**, 32, 63; (c) Yoo, B. W.; Lee, S. J.; Yoo, B. S.; Choi, K. I.; Kim, J. H. *Synth. Commun.* **2002**, 32, 2489; (d) Yoo, B. W.; Choi, K. H.; Kim, D. Y.; Choi, K. I.; Kim, J. H. *Synth. Commun.* **2003**, 33, 53; (e) Yoo, B. W.; Kim, D. Y.; Choi, J. W.; Hwang, S. K.; Choi, K. I.; Kim, J. H. *Bull. Korean Chem. Soc.* **2003**, 24, 263.
- A typical procedure for the deoxygenation of amine-*N*-oxides is as follows: Indium powder (230 mg, 2.0 mmol), and nickel(II) chloride hexahydrate (238 mg, 1.0 mmol) were mixed in aqueous methanol (MeOH : H₂O = 1 : 1, 3 mL) under sonication. The resulting mixture was stirred at room temperature for 1 hr to get a solution of the low-valent nickel-indium complex. 4-*tert*-Butylpyridine-*N*-oxide (75 mg, 0.5 mmol) was added to this solution and the reaction mixture was stirred for 6 hr at room temperature under sonication. The solvent was removed under reduced pressure and the residue was extracted with ether, washed with water, dried over anhydrous MgSO₄. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to afford 4-*tert*-butylpyridine (60 mg, 88%).