Mild and Efficient Deoxygenation of Amine-*N*-Oxides with $FeCl_3 \cdot 6H_2O$-Indium System under Ultrasonication[†]

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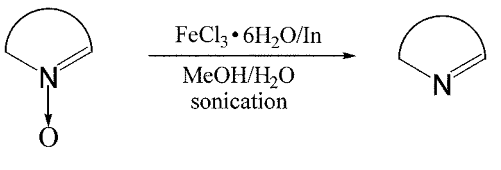
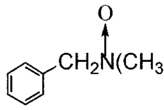
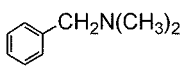
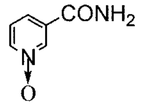
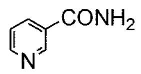
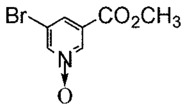
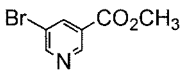
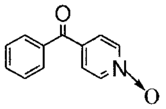
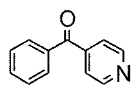
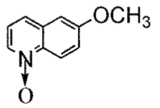
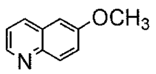
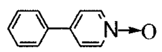
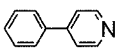
The deoxygenation of amine-*N*-oxides to amines in the presence of other functional groups is an important transformation in the synthesis of nitrogenous aromatic heterocycles.[1] Many reagents have been employed for the deoxygenation of amine-*N*-oxides, including agents such as: low-valent titanium,[2] phosphorous[3] and sulphur[4] compounds, tributyltin hydride,[5] Pd/C,[6] tetrathiomolybdate,[7] SmI_2,[8] indium/NH_4Cl.[9] Recently we reported that Cp_2TiCl_2/In system could be used for the deoxygenation of various amine-*N*-oxides.[10] It is expected that $FeCl_3 \cdot 6H_2O$/In system can also be an efficient reagent for the deoxygenation of amine-*N*-oxides to amines. We have found that various amine-*N*-oxides **1** on treatment with $FeCl_3 \cdot 6H_2O$/In system are smoothly converted into the corresponding amines **2** in high yields. The new reducing system was generated by the addition of indium powder to a stirred solution of ferric chloride hexahydrate in aqueous methanol under sonication.[11] We herein wish to report a mild and efficient method for the deoxygenation of amine-*N*-oxides using $FeCl_3 \cdot 6H_2O$/In system. The reactions can be generalized as in eq. 1. Some control experiments revealed that amine-*N*-oxides could not be deoxygenated either by $FeCl_3 \cdot 6H_2O$ or indium alone under the reaction condition and were recovered unchanged. It was observed that 2 : 1 ratio of indium and $FeCl_3$ was found to be the best ratio in terms of yield and reaction time.[12] In order to explore the scope and limitations of this reagent system we have tested its applicability for selective deoxygenation of amine-*N*-oxides bearing other potentially sensitive functional groups in the heteroaromatic ring. The results are outlined in Table 1. It is interesting to note that the nature of the solvent controlled the formation of desired products. No isolable products 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 1 : 1 mixture of



(1)

1 **2**

Table 1. Deoxygenation of amine-*N*-oxides with $FeCl_3 \cdot 6H_2O$/In system under sonication

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1	3-Picoline-*N*-oxide	3-Picoline	6	88
2	Quinoline-*N*-oxide	Quinoline	5	91
3	Isoquinoline-*N*-oxide	Isoquinoline	6	93
4	4-*t*-Butylpyridine-*N*-oxide	4-*t*-Butylpyridine	5	92
5	2-Chloropyridine-*N*-oxide	2-Chloropyridine	5	91
6	4-Cyanopyridine-*N*-oxide	4-Cyanopyridine	3	90
7	3-Hydroxypyridine-*N*-oxide	3-Hydroxypyridine	7	86
8	Morpholine-*N*-oxide	Morpholine	4	89
9			4	90
10			8	87
11			4	92
12			3	80
13			4	91
14			4	92

[a]Isolated yields.

[†] Dedicated to Professor Yong Hae Kim for his distinguished achievements in organic chemistry.
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MeOH-H_2O. No isolable products was formed when the reaction was carried out in either water or methanol alone. The reaction with no ultrasound gave no products. Thus, ultrasonic irradiation is necessary to accelerate the reaction. The functional group tolerance of this deoxygenation system is evident from the table which show that bromo, ester, cyano, methoxy, and amide remain unchanged under the reaction conditions. Aliphatic amine-*N*-oxides were also deoxygenated smoothly under the current conditions (entries 8 and 9). All the compounds obtained showed IR, NMR and mass spectral data compatible with the structure. We have been able to demonstrate the utility of easily accessible $FeCl_3 \cdot 6H_2O$/In system as a convenient reagent for effecting chemoselective deoxygenation of amine-*N*-oxides. Although the reaction mechanism is still unclear, the reaction can be envisaged to proceed in two stages. In the first, iron(III) chloride is probably reduced by indium to form low-valent iron species, which in the subsequent step would deoxygenate amine-*N*-oxides **1** to give the corresponding amines **2**. The notable advantages of the present methodology are the mild reaction conditions, the high yields, environment-friendly reaction conditions, and the tolerance of some functional groups.

In conclusion, we believe that the mild and efficient method described here will present an attractive alternative to the existing methods available for the reduction of amine-*N*-oxides to the corresponding amines. Further investigations of $FeCl_3 \cdot 6H_2O$/In system as reducing agent in organic synthesis are currently in progress.

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11. Sonications were carried out in a BRANSONIC ultrasonic cleaner bath, which delivered a 47 kHz wave, with a fixed elecrrical power of 125 Watts.
12. A typical procedure for the deoxygenation of amine-*N*-oxide is as follows: Indium powder (232 mg, 2.0 mmol) and ferric chloride hexahydrate (270 mg, 1.0 mmol) in aqueous methanol (MeOH : H_2O = 1 : 1, 3 mL) were mixed under sonication and the resulting mixture was stirred at room temperature for 1 hr to get a gray solution of the low-valent iron-indium complex. 4-Cyanopyridine-*N*-oxide (60 mg, 0.5 mmol) was added to this solution and the mixture was stirred for 3 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 $MgSO_4$. The crude product was purified by silica gel column chromatography (ethyl acetate:hexane = 1 : 1) to afford 4-cyanopyridine (42 mg, 90%).