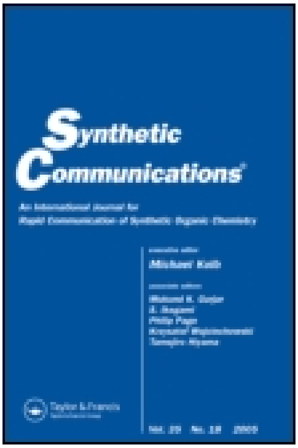

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Facile and Efficient Deoxygenation of Amine-*N*-oxides with Gallium in Water

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ABSTRACT

A facile and efficient procedure for the deoxygenation of amine-*N*-oxides with gallium metal in water is described. The experimental procedure is quite simple and the products are obtained in high yields without any activating agent.

Key Words: Deoxygenation; Amine-*N*-oxides; Amine; Gallium.

The deoxygenation of amine-*N*-oxides to amines in the presence of other functional groups is an important transformation in the synthesis of nitrogenous

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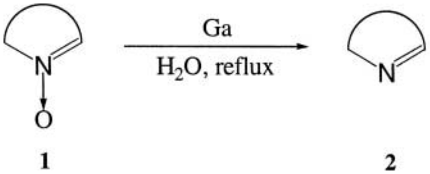
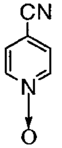
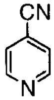
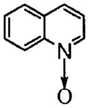
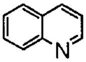
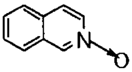
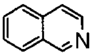
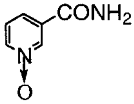
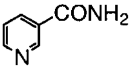
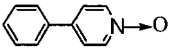
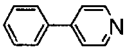
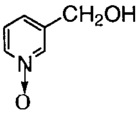
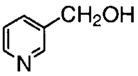
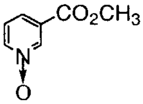
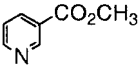
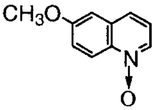
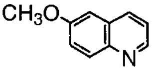
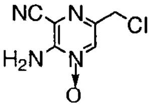
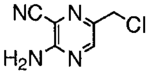
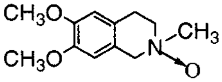
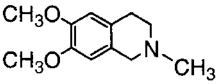
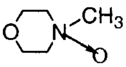
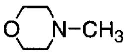
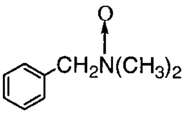
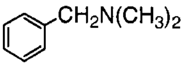
aromatic heterocycles.[1] A number of reagents have been reported to be effective in mediating the deoxygenation of amine-*N*-oxides. Examples include low-valent titanium,[2] phosphorous[3] and sulfur[4] compounds, tributyltinhydride,[5] Pd/C,[6] tetrathiomolybdate,[7] SmI_2,[8] etc. However, many of these reagents require relatively long reaction times, drastic reaction conditions, and are sensitive to both air and moisture. Consequently, there is still a need for introducing mild and efficient reagents for the deoxygenation of amine-*N*-oxides to amines. Recently, it was reported that indium metal could be used for the deoxygenation of various amine-*N*-oxides.[9] Because of the close resemblance of gallium to indium in several respects, including first ionization potential and reduction potential (Ga: FIP, 5.99 eV, E°, $Ga^{3+}/Ga = -0.56\,V$; In: FIP, 5.79 eV, E°, $In^{3+}/In = -0.345\,V$), we envisaged that gallium metal could also be a potential reducing agent. In this communication we report a novel method for the deoxygenation of amine-*N*-oxides using gallium metal in water at reflux, which occurs to afford the corresponding amines. Although gallium has been used in carbonyl addition reactions,[10,12] its use in other domains has not been investigated. This prompted us to initiate an investigation into the reduction of amine-*N*-oxides by gallium metal and we have found that various amine-*N*-oxides **1** on treatment with gallium metal in water are smoothly converted into the corresponding amines **2** in high yields without activating agents such as ammonium chloride or hydrochloric acid (Eq. (1)). The results of reduction of amine-*N*-oxides using gallium metal are summarized in Table 1. Recently, growing interest has been focused on synthetic organic reactions in aqueous media from both economical and ecological points of view. The use of water as a solvent to carry out organic reactions offers practical convenience as it alleviates the need to handle flammable and anhydrous organic solvents. Particularly metal-mediated organic reactions in aqueous media (such as In, Zn, Bi, Sn, Sm, etc.) have received considerable attention in organic synthesis over the last decade.[11] However, the reactions promoted by gallium in aqueous media have not been widely studied.[12] To determine the optimum conditions, the reaction was performed under several reaction conditions. The best result was obtained when the reaction was carried out using gallium (3 equiv) in water at reflux in terms of yields and reaction times. The reaction was not significantly improved by increasing the quantity of metallic gallium and the reaction time. It was also found that at room tempera-



1 2

(1)

Table 1. Deoxygenation of amine-*N*-oxides with gallium metal.

Entry	Substrate	Product	Reaction time (hr)	Yield (%)[a]
1			0.5	90
2			4	83
3			4	88
4			3	85
5			0.5	96
6			7	84
7			8	81
8			7	95
9			3	92
10			24	0
11			24	0
12			24	0

[a] Isolated yields.

ture no significant formation of the desired product was observed even after prolonged stirring. In order to explore the scope and limitations of this reagent we have tested its applicability for selective deoxygenation of amine-*N*-oxides bearing other potentially sensitive functional groups in the aromatic ring. Unfortunately the application of this approach to aliphatic-*N*-oxide proved unsuccessful and only recovered starting material was isolated (entries 10, 11, and 12). The high yields of the reduction products demonstrate the efficiency of this new method. The functional group tolerance of this deoxygenation system is evident from the table, which shows that halogen, hydroxy, ester, cyano, methoxy, and amino remain unchanged under the present reaction conditions. All the compounds obtained showed IR, NMR, and mass spectral data compatible with the structure. Thus, we have been able to demonstrate the utility of easily accessible gallium metal as a reducing agent for effecting chemoselective deoxygenation of amine-*N*-oxides. The notable advantages of the present methodology are high isolated yields of products, operational simplicity, tolerance of other labile functional groups, and environmentally friendly reaction conditions. Although the mechanism of the reaction is not yet clear, it may be assumed that these reductions are also going through a single electron transfer (SET) process like other metal-mediated reactions in aqueous media.

In conclusion, we have demonstrated that gallium is an effective metal for the reduction of aromatic amine-*N*-oxides in water. Further studies to develop other new reactions using gallium metal in aqueous media are currently in progress.

GENERAL PROCEDURE FOR THE REACTION

A typical procedure for the deoxygenation of amine-*N*-oxide is as follows: Gallium metal (104 mg, 1.5 mmol) in water (1 mL) was stirred for 1 hr under sonication and then to this solution 4-cyanopyridine-*N*-oxide (60 mg, 0.5 mmol) in water (2 mL) was added slowly. The resulting mixture was heated under reflux for 30 min. After completion of the reaction, as indicated by TLC, the resultant mixture was filtered through Celite and extracted with ether (4 × 10 mL). The organic layer was washed with saturated brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent in vacuo, the crude product was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 1) to afford 4-cyanopyridine (47 mg, 90%).

Spectroscopic data of 2-amino-3-cyano-5-chloromethylpyrazine (entry 9): pale yellow solid, mp 152°C–154°C. ^1H NMR (DMSO-d_6): δ 4.54 (s, 2H, CH_2Cl), 7.36 (br s, 2H, NH_2), 8.21 (s, 1H, H_{arom}). IR (KBr) 3410–3210 (NH_2), 2230 (CN) cm^{-1}.

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