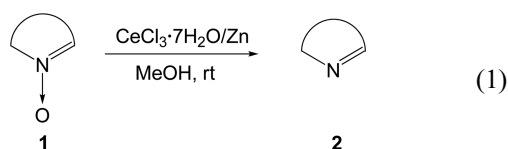


Selective and Efficient Deoxygenation of Amine-*N*-Oxides with CeCl₃·7H₂O/Zinc System

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Received October 26, 2012, Accepted November 22, 2012**Key Words** : Deoxygenation, Amine-*N*-oxides, Cerium(III) chloride, Zinc

The selective and efficient deoxygenation of amine-*N*-oxides in the presence of other functional groups is an important synthetic transformation that has received considerable attention.¹ A number of methods have been developed for the deoxygenation 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 indium/NH₄Cl,⁹ and Mo(CO)₆,¹⁰ Cu(I)-Zn or Cu(I)-Al,¹¹ RuCl₃·xH₂O,¹² Zn/Cu-triflates.¹³ However, many of these methods suffer from one or other disadvantage like low yields, poor chemoselectivity, prolonged reaction times, not readily available reagents, and relatively severe reaction conditions. In certain cases, the reagents employed for this transformation are expensive and hazardous. Consequently, there is still a need to introduce selective and efficient reagents for the deoxygenation of amine-*N*-oxides to amines. Particularly much effort has been devoted to the development of milder conditions where the presence of various sensitive and reducible functional groups can be tolerated. In continuation of our efforts towards metal-metal salt binary systems for organic transformations,¹⁴ we have found that a combination of CeCl₃·7H₂O with zinc brings about the deoxygenation of amine-*N*-oxides under mild conditions. Metal-metal salt binary systems have long been used as reducing agents for many functional groups.¹⁵ To the best of our knowledge, to date there is no report on the use of the CeCl₃·7H₂O/Zn system for the deoxygenation of amine-*N*-oxides in the literature. In recent years cerium(III) chloride (CeCl₃·7H₂O) has gained much popularity, owing to its unique reactivity, ease of handling, low toxicity, and moisture and air tolerance.¹⁶ Cerium(III) is highly oxophilic, and forms strong but labile bonds with oxygen donor ligands. This feature has often allowed the use of cerium(III) chloride as a potential Lewis acid catalyst. In this communication we wish to report a selective and efficient method for the deoxygenation of amine-*N*-oxides using CeCl₃·7H₂O/Zn system at room temperature. The reaction can be generalized as in Eq. (1). The new reducing system was generated by the addition of zinc powder to a stirred solution of CeCl₃·7H₂O in methanol. A variety of amine-*N*-oxides were treated with



CeCl₃·7H₂O/Zn system and the corresponding amines were obtained in high yields. The results are summarized in Table 1. The reactions proceed readily in all cases with substrates reacting completely within 4 h at room temperature. The high yields of the deoxygenation products demonstrate the efficiency of this new method. Some control experiments confirmed that the reaction was not initiated at all using cerium(III) chloride in the absence of zinc metal and was also not very effective with zinc metal without cerium(III) chloride. Thus, a combination of zinc and cerium(III) chloride is essential to carry out the deoxygenation. The optimum molar ratio of substrate to CeCl₃·7H₂O to zinc (1:2:4) is

Table 1. Deoxygenation of amine-*N*-oxides with CeCl₃·7H₂O/Zn system

Entry	Substrate	Product ^a	Time (h)	Yield (%) ^b
1	Pyridine- <i>N</i> -oxide	Pyridine	0.5	96
2	Quinoline- <i>N</i> -oxide	Quinoline	1.5	93
3	Isoquinoline- <i>N</i> -oxide	Isoquinoline	1.0	92
4	4-Picoline- <i>N</i> -oxide	4-Picoline	3.0	88
5			3.5	86
6			1.0	92
7			0.5	95
8			4.0	85
9			1.0	94
10			2.5	87
11			3.0	85

^aAll products were fully characterized by spectral analysis. ^bIsolated yields after chromatographic purification.

found to be ideal for the complete conversion of amine-*N*-oxide **1** into amine **2** in methanol.¹⁷ Methanol has been found to be suitable to favour the reaction at room temperature. 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. A variety of functional groups (methoxy, cyano, chloro, hydroxy, ester, and amide) were tolerated under the reaction conditions. It is worth mentioning that the chloro substituent in 2-chloropyridine-*N*-oxide (entry 7) remains unchanged, even though it is prone to dehalogenation reaction.¹⁸ And the position of the substituent in the heteroaromatic ring does not seem to have any influence in the process. We have been able to demonstrate the utility of the easily accessible CeCl₃·7H₂O/Zn system as a convenient reagent for effecting chemoselective deoxygenation of amine-*N*-oxides. Although the role of cerium(III) chloride is still not clearly understood at this time, it is assumed that cerium(III) chloride is involved in complexation with the substrates. The reduction probably proceeds by a reductive cleavage of polarized N-O bonds through a single electron transfer from zinc metal to the cerium-substrate complex due to the high oxophilic nature of the cerium species. The reducing property exhibited by metal-metal salt combinations proceeds through transfer of one electron from the metal surface to the substrate. We believe that the present procedure using CeCl₃·7H₂O/Zn system proceeds through a SET (single electron transfer) process. The notable advantages of the present method are the mild reaction conditions, the high yields, the experimental simplicity, and the tolerance of other labile functional groups.

In conclusion, we have discovered that CeCl₃·7H₂O/Zn system mediates a selective and efficient deoxygenation of amine-*N*-oxides to the corresponding amines. Although the scope and limitations have not been fully established, the present procedure offers an attractive alternative to the conventional methods with its mildness and chemoselectivity as well as high yields. Further investigations of more useful applications with this system are currently in progress.

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- A general procedure for the deoxygenation of amine-*N*-oxides is as follows: Zinc powder (131 mg, 2.0 mmol), and cerium(III) chloride heptahydrate (373 mg, 1.0 mmol) were mixed in methanol (4 mL). The resulting mixture was sonicated for 0.5 h. 2-Chloropyridine-*N*-oxide (65 mg, 0.5 mmol) was added to this solution and the reaction mixture was stirred for 0.5 h at room temperature. After completion of the reaction, as indicated by TLC, the mixture was diluted with water, extracted with ethyl acetate. The combined organic extract was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to afford 2-chloropyridine (54 mg, 95%). All of the products were characterized by comparison of their spectroscopic and physical data with reported values.¹⁹
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