A Novel and Efficient Deoxygenation of Hetero Cyclic N-Oxides Using $ZrCl_4/NaBH_4$

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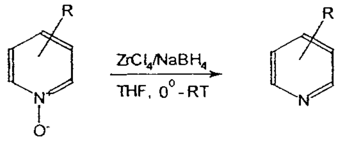
(Received September 16, 1999; CL-990795)

A practical and novel reagent system $ZrCl_4/NaBH_4$ is used for the deoxygenation of N-Oxides to amines is described.

The selective and efficient deoxygenation of the heteroaromatic N-Oxides is an important synthetic transformation that has received considerable attention. Heterocyclic N-Oxides can be deoxygenated by many reagents, including hydrides, trivalent phosphorous compounds, sulfur compounds, dissolved metals, $TiCl_3$, H_2 gas etc.[1-3] Chemoselective deoxygenation of aromatic, heteroaromatic and aliphatic N-Oxides was reported by using borohydride exchange resin (BER)-$CuSO_4$ in methanol at room temperature or under reflux in 3 hours.[4] In general, methods are limited for the specifically reductive cleavage of the N-Oxide bond because of the interference resulting from side reactions,[5] and vigorous conditions.[6]

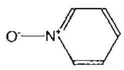
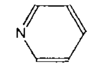
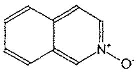
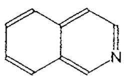
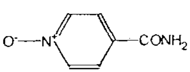
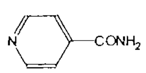
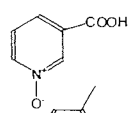
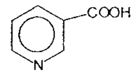
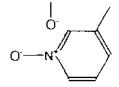
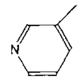
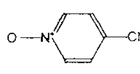
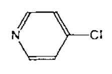
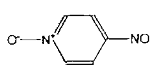
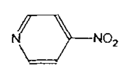
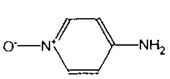
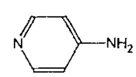
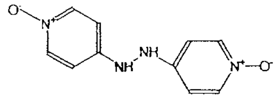
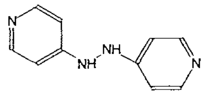
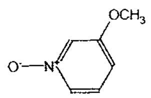
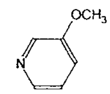
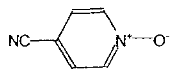
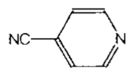
In the course of our program to explore the novel utilities of $ZrCl_4/NaBH_4$ reagent system, we disclosed that this reagent affects the reductive cleavage of acetals and ketals[7] to the corresponding ether alcohols and regioselective conversion of racemic epoxides[8] to furnish optically pure alcohol, also, this reagent system affects the regeneration of alcohols from their O-allyl ethers.[9] In this communication we wish to report the potential utility of $ZrCl_4/NaBH_4$ reagent system for the deoxygenation of heteroaromatic N-Oxides to their respective amines. Treatment of one equivalent of N-Oxide with one equivalent of $ZrCl_4/NaBH_4$ reagent in dry THF solvent under nitrogen atmosphere at 0 °C to room temperature provided quantitative formation of the deoxygenated heterocyclic amines in less than 15 minutes (Scheme 1).

Scheme 1.



This method is applied for selective deoxygenation to substituted heteroaromatic N-Oxides having labile halogen atom to the ring nitrogen (entry 6), which are susceptible to simultaneous dehalogenation reactions.[5] In order to explore the generality and to study the scope of this reagent system we have tested its applicability for selective deoxygenation of N-oxides bearing other potentially sensitive functional groups in the heteroaromatic ring. The generality of the reaction to various hetero aromatic N-Oxides is illustrated in Table 1. The groups like chloro (entry 6), methoxy (entry 10), amino (entry 8) and amide (entry 3) were not effected with this reagent system.[10] In case of amide (entry 3), deoxygenation was found to be time dependent. Deoxygenated amine was obtained in good yields (75%) in shorter duration (15 minutes) in which the amide was unaffected but, prolonged reaction time (> 30 minutes) provided further reduction of amide to deoxygenated primary amine. Deoxygenation of N-Oxides containing electron withdrawing group is difficult.[3] To our surprise aromatic N-Oxides containing electron-withdrawing groups such as cyano (entry 11), nitro (entry 7) and carboxylic acid (entry 4), when treated with this reagent system, gave the corresponding amine in good yields. All the products obtained were fully characterized by H^1 NMR, IR and Mass spectral analysis.

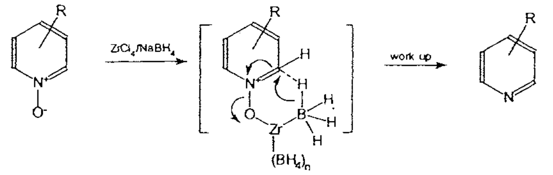
Table 1.

Entry	Substrate	Product [a]	Yield/ %
1			98
2			94
3			75
4			70
5			95
6			95
7			90
8			90
9			80
10			90
11			75

[a] All the reactions were completed in 15 minutes duration.

On the basis of preparation, the reagent $ZrCl_4/NaBH_4$ system is considered to be a mixed borohydride.[11] The deoxygenation of N-Oxides can be imagined by an initial conjugation of Zirconium with the N-Oxide oxygen and subsequent carbocation formation, addition of hydride followed by 1, 2 elimination leading to the formation of deoxygenated amine (Scheme 2).

Scheme 2.



In summary, we have developed an efficient and rapid methodology for the deoxygenation of heteroaromatic N-Oxides in excellent yields under mild reaction conditions using $ZrCl_4/NaBH_4$.

KPC wishes to thank UGC, New Delhi and GHM acknowledges CSIR, New Delhi for the award of research fellowship.

References and Notes

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10 Typical Experimental Procedure: Into a two necked round bottom flask equipped with magnetic bead and nitrogen balloon adapter was placed $ZrCl_4$ (0.213 g, 0.914 mmol, 1 eq), dry THF (15 ml) was syringed into the flask. Immediate formation of red-brown solution was observed. The contents were cooled to 0 °C, $NaBH_4$ (0.138 g, 3.647 mmol, 4 eq) was added in portion to the above solution. Reddish brown solution slowly turned to pale pink. To this reagent system at 0 °C was added N-Oxide (Entry 5) (0.1 g, 0.917 mmol, 1 eq) in dry THF (5 ml). Contents were stirred magnetically. After complete addition of the N-Oxide ice cooling was removed and contents were brought to room temperature (35 °C). The progress of the reaction monitored by TLC clearly indicated the disappearance of the N-Oxide in 15 minutes. Contents were cooled and treated with 5% aq. HCl solution, THF was evaporated under vacuum, then extracted into ethyl acetate (3x20 ml), successively washed with water, saturated $NaHCO_3$ solution, water and dried over anhydrous Na_2SO_4. Filteration followed by evaporation of the organic portion provided pure deoxygenated amine (0.081 g, 95% yield).

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IICT Communication No: 4368