

Kurzmitteilung / Short Communication

TiCl₄/NaI – A Novel, Efficient Reagent for Mild Reduction of the N–O Bond in Amine *N*-Oxides and Nitrones

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Heteroaromatic *N*-oxides and nitrones were readily and selectively deoxygenated to the corresponding bases or imines in excellent yields with the TiCl₄/NaI reagent system.

Selective, mild, and rapid deoxygenation of amine *N*-oxides and nitrones is still an area of considerable interest, particularly when a molecule has other reducible or labile moieties. A survey of the literature reveals that many methods have been reported for reduction of amine *N*-oxides and nitrones, including agents such as: metals in acids¹, various selenium and sulfur compounds^{2–4}, trivalent phosphorus compounds^{5,6}, and catalytic hydrogenation⁷. In general, these traditional procedures often require severe reaction conditions and prolonged reaction times, and afford products of insufficient purity in moderate or low yields.

Previously, we reported that heteroaromatic *N*-oxides may be easily and efficiently reduced to the corresponding bases with low-valent titanium, generated through the reaction of TiCl₄ with lithium aluminum hydride⁸ or stannous chloride^{9,10} in tetrahydrofuran.

Excellent results were recently obtained when the deoxygenation of amine *N*-oxides was performed in neutral medium using some hydrogen-transfer agents in the presence of palladium on carbon as catalyst¹¹.

However, our last methods appear to be inappropriate for large-scale preparations due to the necessity of using LiAlH₄ or expensive palladium. In our continuous search for better reducing agents for deoxygenation of the N–O function, we have discovered the mild reductive properties of the TiCl₄/NaI reagent system. Among the alkali iodides tested in this study, NaI gave the best results and can be generally recommended, although KI was also effective to some extent.

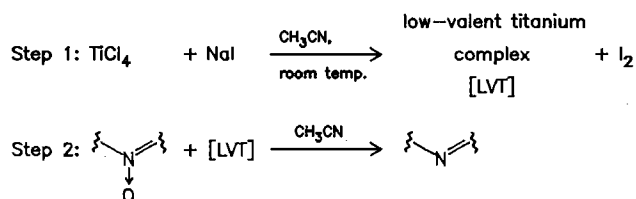
In this communication, we wish to report the application of this reagent for deoxygenation of both amine *N*-oxides and nitrones. The reaction is very simple and proceeds immediately upon addition of NaI to a suspension of TiCl₄, *N*-oxide (nitron) in acetonitrile at room temperature giving the corresponding bases or imines. Similar results were obtained when substrate **1** was added to the combination of TiCl₄/NaI in the same solvent.

The optimum solvent and ratio of reagents were investigated using 4-*tert*-butyl-pyridine *N*-oxide (**1a**) as substrate. Acetonitrile was found to be the solvent of choice. Deoxygenation of **1a** was complete within 2 minutes at room temperature. The optimum ratio of reagents was found to be substrate : TiCl₄ : NaI = 1 : 1 : 3. Although a ratio 1 : 1 : 2 also gave similar results with this particular substrate, it was found that the ratio 1 : 1 : 3 is generally better for a faster

reaction. Acetone is also an acceptable solvent in some cases, but the reaction is slower in this medium and requires a higher temperature.

Although the mechanism of this reaction is still obscure, it can be rationalized as the result of a two-stage process. In the first step, TiCl₄ is probably reduced by the iodide to form a low-valent titanium complex (LVT). This, according to our earlier studies^{8,9}, is able to reductively deoxygenate substrate **1**.

Scheme 1



The advantages of this procedure are the use of inexpensive materials, the mild reaction conditions, the short reaction times, the excellent yields, and the simplicity of workup. The selectivity of our method is demonstrated by several examples. Halogens, alkoxy-carbonyl, nitrile, and amide substituents remain unchanged. It is also noteworthy that the reaction does not require rigorously anhydrous conditions, so that *N*-oxide hydrates (like **1h**) can be used effectively.

In conclusion, we feel that the use of the TiCl₄/NaI reagent offers a useful alternative to existing methods for the reduction of both amine *N*-oxides and nitrones.

Investigations are currently under way in our laboratory in order to establish the actual mechanism of the deoxygenation reaction and to extend the field of application field of the TiCl₄/NaI reagent system.

Experimental

General Procedure: To a magnetically stirred solution of *N*-oxide or nitron **1** (0.003 mol) in acetonitrile (6 ml), TiCl₄ (0.25 ml, 0.003 mol) and NaI (1.35 g, 0.009 mol) were added at room temp. The reaction mixture turned dark brown almost immediately, and TLC

after 2–10 min confirmed complete reaction. Mild heating in some cases is recommended. The whole was decomposed with dil. aqueous KOH (5 ml) and extracted with chloroform or ether (3 × 20 ml). The combined organic layers were successively washed with an aqueous sodium thiosulfate solution and water. The solvent was then removed, and the residue was passed through a column of silica gel using hexane/ethyl acetate (9:1) as eluent to give the pure bases. The results are summarized in Table 1.

Table 1. Deoxygenation of heteroaromatic *N*-oxides and nitrones 1 with the TiCl₄/NaI reagent system to the corresponding bases

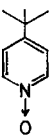
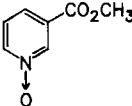
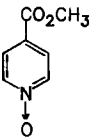
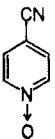
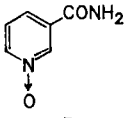
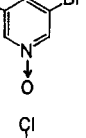
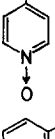
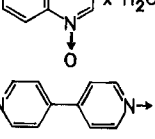
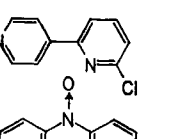
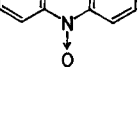

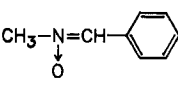
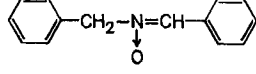

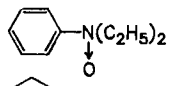
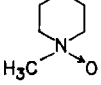
Substrate ^{a)}	Reaction time [min]	Temp. [°C]	Yield ^{b)} (%)
1a ¹²⁾ 	2	20	92
1b ¹³⁾ 	2	20	95
1c ¹⁴⁾ 	2	20	95
1d ¹⁵⁾ 	5	20	83
1e ¹⁶⁾ 	10	40	80
1f ¹⁷⁾ 	5	30	91
1g 	10	20	82
1h 	5	30	90
1i ¹⁸⁾ 	2	20	95
1j ¹⁹⁾ 	5	20	95
1k ²⁰⁾ 	10	30	90

Table 1 (Continued)

Substrate ^{a)}	Reaction time [min]	Temp. [°C]	Yield ^{b)} (%)
1l ²¹⁾ 	5	20	90 ²²⁾
1m ²³⁾ 	5	20	92 ²⁴⁾
1n ²⁵⁾ (C ₂ H ₅) ₂ N x H ₂ O 	5	20	55 ^{c)}
1o ²⁶⁾ 	2	30	85
1p ²⁷⁾ 	5	20	81

^{a)} Commercial materials unless otherwise specified. — ^{b)} Most of the products are commercially available and were characterized by comparison with authentic samples (TLC, IR, MS); yields of isolated products (corresponding bases) are based on a single experiment. — ^{c)} Characterized as hydrochloride, mp 253–254°C; the lower yield is due to the low bp of the amine.

CAS Registry Numbers

1a: 23569-17-7 / **1b:** 15905-18-7 / **1c:** 3783-38-8 / **1d:** 14906-59-3 / **1e:** 1986-81-8 / **1f:** 2402-99-5 / **1g:** 1121-76-2 / **1h:** 1613-37-2 / **1i:** 24573-15-7 / **1j:** 119492-89-6 / **1k:** 303-83-3 / **1l:** 3376-23-6 / **1m:** 3376-26-9 / **1n:** 2687-45-8 / **1o:** 826-42-6 / **1p:** 17206-00-7 / Bases from: **1a:** 3978-81-2 / **1b:** 93-60-7 / **1c:** 2459-09-8 / **1d:** 100-48-1 / **1e:** 98-92-0 / **1f:** 625-92-3 / **1g:** 626-61-9 / **1h:** 91-22-5 / **1i:** 553-26-4 / **1j:** 39883-34-6 / **1k:** 92-82-0 / **1l:** 622-29-7 / **1m:** 780-25-6 / **1n:** 121-44-8 / **1o:** 91-66-7 / **1p:** 626-67-5 / NaI: 7681-82-5 / TiCl₄: 7550-45-0

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