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TITANIUM(III) INDUCED TRANSFORMATIONS OF N,N-DISUBSTITUTED HYDROXYLAMINES TO IMINES AND SECONDARY AMINES

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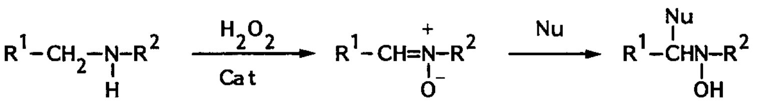
Summary: The reaction of N,N-disubstituted hydroxylamines with anhydrous $TiCl_3$ gives the corresponding imines, while that with aqueous $TiCl_3$ gives secondary amines.

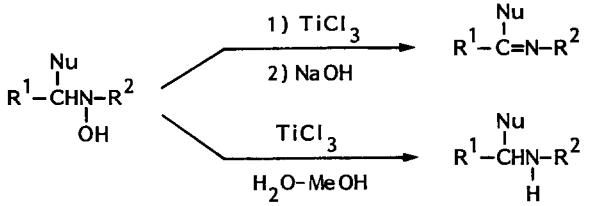
Tungstate catalyzed oxidation of secondary amines with hydrogen peroxide gives the corresponding nitrones efficiently.[1] Nitrones thus obtained react with various nucleophiles to give α-substituted hydroxylamines[2] (eq 1). We have found that the reaction of N,N-disubstituted hydroxylamines with anhydrous $TiCl_3$ in dry THF at room temperature gives the corresponding imines (eq 2),



$$R^1-CH_2-\underset{H}{N}-R^2 \xrightarrow[Cat]{H_2O_2} R^1-CH=\overset{+}{\underset{O^-}{N}}-R^2 \xrightarrow{Nu} R^1-\overset{Nu}{C}H\underset{OH}{N}-R^2$$

(1)

while that with aqueous $TiCl_3$ gives the corresponding secondary amines (eq 3). Therefore, combining the reactions illustrated by eq 1, secondary amines can be readily converted into either α-substituted imines or amines upon treatment with $TiCl_3$ depending on the reaction medium utilized.



$$R^1-\overset{Nu}{C}H\underset{OH}{N}-R^2 \xrightarrow[2)\ NaOH]{1)\ TiCl_3} R^1-\overset{Nu}{C}=N-R^2 \qquad (2)$$

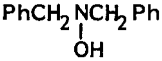
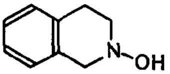
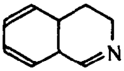
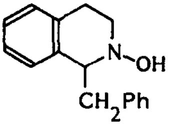
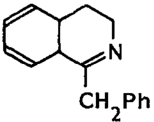
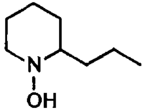
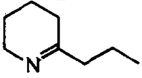
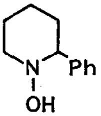
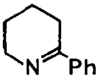
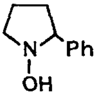
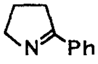
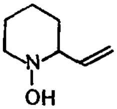
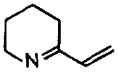
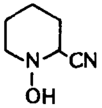
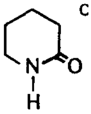
$$R^1-\overset{Nu}{C}H\underset{OH}{N}-R^2 \xrightarrow[H_2O-MeOH]{TiCl_3} R^1-\overset{Nu}{C}H\underset{H}{N}-R^2 \qquad (3)$$

Although the synthetic methods of imines are well documented,[3] the methods for the preparation of cyclic imines, which are key intermediates of nitrogen containing naturally occurring compounds, are limited.[4] The reported methods for the transformation of N,N-disubstituted hydroxylamines to the imines require severe reaction conditions and give quite low yields (< 30 %) of the imines.[5] The present method provides an efficient method for the preparation of imines, which are particularly useful synthetic intermediates such as cyclic imines and azadienes.[6] The representative results of the dehydration are shown in Table 1. This is the first example of the dehydration induced by Ti(III) compounds.

The starting hydroxylamines were readily prepared by the reaction of various nucleophiles with the corresponding nitrones, which were given by the single step oxidation of secondary amines with hydrogen peroxide.[1] The present reaction proceeds efficiently in THF but does not in the other solvents such as benzene, ether, and dichloromethane. Lewis acids such as $TiCl_4$, $AlCl_3$, VCl_3, and $MoCl_5$ are not effective for the present reaction.

The preparation of 2-phenyl-3,4,5,6-tetrahydropyridine (Entry 5) is a typical example of the present reaction. To a suspension of anhydrous $TiCl_3$ (0.215 g, 1.15 mmol)[7] in dry THF (1.3 mL) was added dropwise a solution of 1-hydroxy-2-phenylpiperidine (0.204 g, 1.15 mmol) in dry THF (2.5 mL) at -78°C, then the temperature was raised to room temperature with stirring. After stirring for 15 min, the solvent was removed under reduced pressure. Addition

Table 1 Transformation of Hydroxylamines to Imines with Anhydrous $TiCl_3$[a)]

Entry	Hydroxylamine	Product[b)]	Isolated yield (%)
1	 $PhCH_2\underset{OH}{N}CH_2Ph$	$PhCH_2N{=}CHPh$	78
2			89
3			99
4			83
5			89
6			53
7			73
8		 c)	90

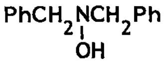
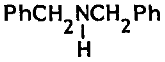
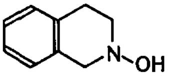
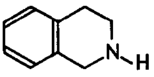
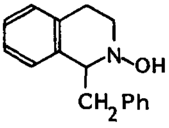
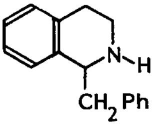
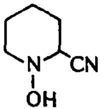
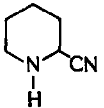
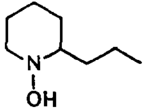
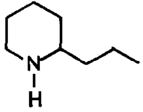
a)The procedure is described in the text. b)The products gave satisfactory IR, NMR, and mass spectral data. c) Under the reaction condition 2-cyano-3,4,5,6-tetrahydropyridine was easily hydrolyzed.

of an 1N NaOH solution (4 mL), extraction with CH_2Cl_2, filtration, evaporation of the solvent, and Kugelrohr distillation (bp. 105-115°C/3 mm Hg) gave 2-phenyl-3,4,5,6-tetrahydropyridine (0.163 g, 89 %).

In contrast to the dehydration with anhydrous $TiCl_3$, the reaction of N,N-disubstituted hydroxylamines with aqueous $TiCl_3$ results in the reduction of the hydroxylamines.[8] Thus, the reaction of N,N-disubstituted hydroxylamines with an aqueous $TiCl_3$ solution[9] in methanol at room temperature gives the corresponding secondary amines efficiently. The representative results are summarized in Table 2. In a typical case, a solution of N,N-dibenzylhydroxylamine (0.106 g, 0.5 mmol) in methanol (5 mL) was added to a 20 % aqueous $TiCl_3$ solution (0.670 g, 0.87 mmol)[10] at room temperature. After stirring for 15 min, the solvent was removed under reduced pressure. The residue was treated with a 20 % NaOH solution (2 mL). Extraction with CH_2Cl_2, followed by Kugelrohr distillation gave dibenzylamine (0.089 g, 91 %).

Although we have no evidence for the mechanism, the reaction of the dehydration can be rationalized by assuming the reaction of hydroxylamine with $TiCl_3$ to form Ti(III) complex, which undergoes β-elimination to give imine·HCl. The mechanism for the reduction seems to be different from that for the above dehydration. Noteworthy is that the product amines are not simply derived from the reduction of the imines. The electron transfer mechanism seems to be operative likewise the reductive coupling of carbonyl compounds.[11]

Table 2 Reduction of N,N-Disubstituted Hydroxylamines with Aqueous $TiCl_3$ [a)]

Entry	Hydroxylamine	Product[b)]	Isolated yield (%)
1	 $PhCH_2N(OH)CH_2Ph$	 $PhCH_2N(H)CH_2Ph$	93
2			91
3			75
4			75
5			86

a) The procedure is described in the text. b) The products gave satisfactory IR, NMR, and mass spectral data.

It is noteworthy that the reaction of nitrones with $TiCl_3/LiAlH_4$[12] gave the corresponding secondary amines quantitatively. Thus, the treatment of 3,4-dihydroisoquinoline N-oxide with $TiCl_3/LiAlH_4$ (1:2.5) in THF at room temperature gave the tetrahydroisoquinoline quantitatively. As expected, the treatment of the same nitrone with $LiAlH_4$ alone gave the corresponding N-hydroxylamine in 98 % yield. However, no reaction takes place, when the nitrone was treated with $TiCl_3$ alone or $TiCl_3$/Mg.

The mechanistic study concerning to the descrepancy between the $TiCl_3$ induced dehydration and the reduction of hydroxylamines, and the application of the present imine synthesis are currently under active investigation.

References and Notes

1) H. Mitsui, S. Zenki, T. Shiota, and S.-I. Murahashi, J. Chem. Soc., Chem. Commun., 874 (1984).
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4) (a) L. E. Overman and R. M. Burk, Tetrahedron Lett., 5739 (1984). (b) J. P. Marino and R. D. Larsen, Jr., J. Am. Chem. Soc., 103, 4642 (1981). (c) P. H. Lambert, M. Vaultier, and R. Carrié, J. Chem. Soc., Chem. Commun., 1224 (1982).
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6) a) Y.-S. Cheng, A. T. Lupo, Jr., and F. W. Fowler, J. Am. Chem. Soc., 105, 7696 (1983). b) M. Komatsu, S. Takamatsu, M. Uesaka, S. Yamamoto, Y. Ohshiro, and T. Agawa, J. Org. Chem., 49, 2691 (1984).
7) Commercial anhydrous $TiCl_3$ contains 82 % of $TiCl_3$ (Wako Pure Chemical Industries, titrated with Fe^{3+}).
8) The relative preparation of amine derivatives from the reaction of N-hydroxyimidazoles with $TiCl_3$ has been described. See, B. H. Lipshutz and M. C. Morey, Tetrahedron Lett., 1319 (1984).
9) A. Clerici and O. Porta, J. Org. Chem., 47, 2852 (1982).
10) For the complete reduction, 1.5 equivalents of a 20 % aqueous $TiCl_3$ are required.
11) No reaction takes place, when imines was treated with an aqueous $TiCl_3$ solution. However, imines can be readily converted into the corresponding amines and alcohols upon treatment of imines with three equivalents of an aqueous $TiCl_3$ solution in the presence of an NaOH solution (in basic media). See, A. Clerici and O. Porta, J. Org. Chem., 50, 76 (1985).
12) H. M. Walborsky and H. H. Wüst, J. Am. Chem. Soc., 104, 5807 (1982), and references cited therein.

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