# Oxidation of Primary Amines to *N*-Monoalkylhydroxylamines using Sodium Tungstate and Hydrogen Peroxide-Urea Complex

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Dedicated to the memory of Ali Karimian.

**Abstract:** The sodium tungstate-catalyzed (10 mol %) oxidation of primary amines with a urea-hydrogen peroxide complex (UHP) gives the corresponding *N*-monoalkylhydroxylamines, which are important biologically active compounds, in good to excellent yields. The method is applicable for a wide range of primary amines, including chiral benzylic amines, α-1,2-hydroxylamine and α-amino esters.

**Keywords:** homogeneous catalysis; hydroxylamines; tungsten; urea-hydrogen peroxide complex

α-Hydroxylamino acids and hydroxamic acids have important biological activities. The synthesis of their precursors, *N*-monoalkylhydroxylamines, has been a topic of considerable research interest.[1] Our investigations have revealed only few examples of the synthesis of *N*-monoalkylhydroxylamines from primary amines. These involve the oxidation of the amine with an appropriate oxidation reagent such as benzoyl peroxide (this method requires treatment of an intermediate *O*-benzylated hydroxylamine with base in order to obtain the free hydroxylamine),[2] hydrogen peroxide or *m*-chloroperbenzoic acid (this often leads to overoxidation products such as nitroso and nitro compounds and is generally ineffective),[3] or the reduction of the corresponding nitroso and/or nitro compound, or oxime (this method is not applicable to the synthesis of optically active *N*-alkylhydroxylamines).[4] Other reported methods include the oxidation of a primary amine with dimethyldioxirane (this protocol is applicable to only a limited range of substrates),[5] and the indirect oxidation of primary amines, involving imine formation, oxidation, and oxaziridine hydrolysis[6] (this method is amenable to the synthesis of optically active hydroxylamines, although the acid-labile Schiff base is one of its disadvantages). The direct microwave-induced oxidation of primary amines with oxone over silica gel or alumina,[7] the three-step procedure involving cyanomethylation of primary amines, nitrone formation, and hydroxylaminolysis of the nitrones,[8] the asymmetric hydrogenation of nitrones with an iridium catalyst system,[9] the oxidation of primary amines to nitrones followed by hydrolysis under acidic conditions, or treatment with hydroxylamine to afford the desired *N*-alkylhydroxylamine (this protocol is applicable only to a limited substrates),[10] and finally the alkylation of amines with α-haloacetonitrile followed oxidation to give the convertible nitrone[11] should also be mentioned.

In connection with our interest in one-pot, three-component coupling reactions involving 1,3-asymmetric induction of aldehydes, hydroxylamines and nucleophiles in a 5.0 M solution of lithium perchlorate in diethyl ether,[12] we required access to various optically active *N*-alkylhydroxylamines. In the course of these studies we encountered difficulties in the oxidation of primary amines to the corresponding hydroxylamines. We investigated a series of reagents for this transformation and discovered that using sodium tungstate ($Na_2WO_4$) in the presence of the hydrogen peroxide/urea complex[13] (UHP) is the superior procedure for direct and selective oxidation of primary amines to the corresponding hydroxylamines.

First, we explored the optimum conditions for the selective oxidation of sterically hindered amine such as *tert*-butylamine. In order to find the best conditions, we first investigated the reaction of UHP with *tert*-butylamine in diethyl ether with different loading of $Na_2WO_4$. Thus, after stirring the reaction mixture for 6 h at room temperature the corresponding *N*-alkylhydroxylamine was formed. The oxidation of **1a** tolerated the use of $Na_2WO_4$ in catalytic amounts; however, the best conversion was achived by using 10 mol % of catalyst. The absence of $Na_2WO_4$ resulted in no oxidation, with starting materials being recoverd intact even after long reaction times (72 h). To this end, we developed the direct synthesis of *N*-substituted hydroxylamines from primary amines. To investigate the scope and limitations of this method, we have prepared hydroxylamines from a range of structurally different primary amines. As shown in Scheme 1, a variety of *N*-monoalkylhydroxylamines could be synthesized by this protocol in high yields.

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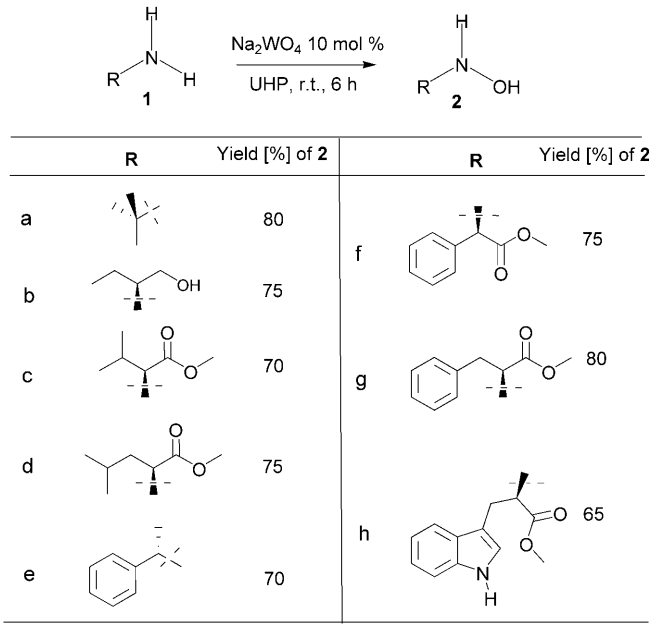


**Scheme 1.** Oxidation of primary amines using $Na_2WO_4$ and UHP.

In summary, we have developed a novel methodology for the direct conversion of primary amines to the corresponding *N*-monoalkylhydroxylamines by way of oxidation. The present protocol seems to be applicable to a wide range of primary amines.

## Experimental Section

### Typical Procedure: Preparation of *N*-Monoalkylhydroxylamine 2f

To a mixture of $Na_2WO_4$ (0.032 g, 0.01 mmol, 10 mol %) and 1.2 mmol UHP (the exact concentration of $H_2O_2$ in UHP was determined by the addition of KI in 15 mL of acidic $Et_2O$ to the solution of 0.1 g of UHP in water and then titration with $Na_2S_2O_3$) in 15 mL of ether was added 0.165 g (1 mmol) of phenylglycine methyl ester. After stirring for 6 h at room temperature, the resulting suspension was filtered through a pad of Celite, and the filtrate concentrated on a rotary evaporator. Purification of the residue by flash column chromatography on silica gel (50% ethyl acetate in hexanes) gave the desired *N*-monoalkylhydroxylamine **2f**;[14] yield: 75%.

### Product Characterization

**2a·HCl:** White crystals, mp 176–180 °C; IR (KBr): ν = 3000–3500 (br), 1430, 1200, 1000 $cm^{-1}$; $^1H$ NMR (90 MHz, DMSO/$CDCl_3$): δ = 1.4 (s, 9H, $CH_3$), 7.8–8.5 (br, 2H, NHOH); $^{13}C$ NMR (22.4 MHz, DMSO, $CDCl_3$): δ = 26 ($CH_3$), 50 (C). The spectral data of the product were identical with those of authentic samples.[15]

**2b:** Oil; IR (KBr): ν = 3315 (br), 2905, 1452, 1057 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): δ = 0.9 (d, *J* = 8 Hz, 3H, $CH_3$), 1.35 (m, 2H, $CH_2$), 2.4–2.7 (br, 3H, NHOH, OH), 3.3 (m, 1H, CHN), 3.6 (dd, *J* = 4 Hz, *J* = 10 Hz, 2H, $CH_2OH$); $^{13}C$ NMR (22.4 MHz, $CDCl_3$): δ = 9.8 ($CH_3$), 26 ($CH_2$), 53.9 ($CH_2OH$), 65.6 (CHN).

**2c:** White crystals, mp 158–159 °C; IR (KBr): ν = 3370, 1727, 1432, 1189, 1010 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 9 Hz, 3H, $CH_3$), 0.97 (d, *J* = 9 Hz, 3H, $CH_3$), 2 (m, 1H, CH), 3.35 (d, *J* = 7 Hz, 1H, CHN), 3.75 (s, 3H, $OCH_3$); $^{13}C$ NMR (22.4 MHz, $CDCl_3$): δ = 18.2 ($CH_3$), 25.3 ($CH_3$), 31.5 (CH), 52 ($OCH_3$), 61 (CHN), 164 (C=O). The spectra datal of the product were identical with those of authentic samples.[5]

**2d:** White crystals, mp 65–67 °C; IR (KBr): ν = 3355, 2925, 1727, 1431, 1193 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): δ = 0.9 (d, *J* = 2 Hz, 3H, $CH_3$), 0.95 (d, *J* = 2 Hz, 3H, $CH_3$), 1.2–1.6 (m, 3H, CH, $CH_2$), 3.4 (dd, *J* = 5 Hz, *J* = 13.5 Hz, 1H, CHN), 3.75 (s, 3H, $OCH_3$); $^{13}C$ NMR (22.4 MHz, $CDCl_3$): δ = 21.4 ($CH_3$), 22.6 ($CH_3$), 24.3 (CH), 43.8 ($CH_2$), 51.5 ($OCH_3$), 52.5 (CHN), 177.4 (C=O).

**2e:** White crystals, mp 69–71 °C; IR (KBr): ν = 3000–3500 (bs), 3064, 1487, 1439, 1369, 1298, 1154, 1074 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): δ = 1.4 (d, *J* = 7 Hz, 3H, $CH_3$), 4.1(q, *J* = 7 Hz, 1H, CH), 5.5–6.0 (br, 2H, NHOH), 7.2–7.5 (s, 5H, Ph). The spectroscopic data are comparable with those reported in the literature.[16]

**2f:** Pale yellow crystals, mp 140–142 °C; IR (KBr): ν = 3210 (bs), 1726, 1431, 1196, 1008 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): δ = 3.7 (s, 3H, $OCH_3$), 4.75 (s, 1H, CHN), 6.2–6.6 (br, 2H, NHOH), 7.2–7.7 (s, 5H, Ph); $^{13}C$ NMR (22.4 MHz, $CDCl_3$): δ = 52.9 ($OCH_3$), 58.4 (CHN), 127 (CH), 128.4 (CH), 129.6 (CH), 141 (C), 174.5 (C=O). The spectral data of the product were identical with those of authentic samples.[4c]

**2g:** White crystals, mp 69–71 °C; IR (KBr): ν = 3000–3500 (br), 3064, 1487, 1439, 1369, 1298, 1154, 1074 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): δ = 2.2–2.4 (bs, 2H, NHOH), 2.9 (dd, *J* = 14 Hz, 8 Hz, 1H), 3.04 (dd, *J* = 13.5 Hz, 5.2 Hz, 1H), 3.68 (s, 3H, $OCH_3$), 3.7 (m, 1H, CH), 7.4 (s, 5H, Ar); $^{13}C$ NMR (22.4 MHz, $CDCl_3$): δ = 40 ($CH_2$), 51.7 ($OCH_3$), 55.5 (CH), 126.6 (CH), 128 (CH), 129 (CH), 136.9 (C), 175(CO). The spectral data of the product were identical with those of authentic samples.[5,16a]

**2h:** Pale yellow crystals, mp 82 °C; IR (KBr): ν = 3340 (br), 1719, 1430, 1200 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$): δ = 1.7–2.0 (bs, 2H, NHOH), 3.2 (q, *J* = 5.5 Hz, *J* = 7.2 Hz, 2H, $CH_2$), 3.5–4.0 (m, 4H, CH, $OCH_3$), 7.0–7.7 (m, 5H, aryl), 8.5 (br, 1H, NH); $^{13}C$ NMR (22.4 MHz, $CDCl_3$): δ = 30.4 ($CH_2$), 51.8 ($OCH_3$), 54.7 (CHN), 110.9 (CH), 111.4 (CH), 118.9 (CH), 119.6 (CH), 122.3 (CH), 123 (C), 127.6 (C), 136.5 (C), 178 (C=O); The spectral data of the product were identical with those of authentic samples.[17]

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