A convenient method for the synthesis of nitrones by oxidation of *N,N*-disubstituted hydroxylamines with *N*-*t*-butylbenzenesulfinimidoyl chloride

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Dedicated to Professor Kjell Undheim on the occasion of his 70th birthday
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Abstract
Various *N,N*-disubstituted hydroxylamines were smoothly oxidized to the corresponding nitrones under mild conditions (at –78 °C) by using *N*-*t*-butylbenzenesulfinimidoyl chloride and DBU in methylene chloride. Intermolecular 1,3-dipolar cycloaddition of thus formed nitrones with certain kinds of olefines was also performed by one-pot procedure.

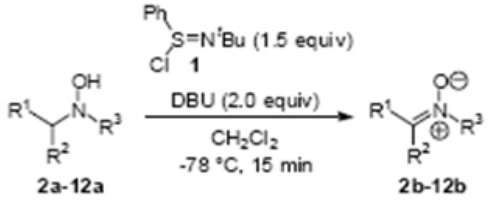
Keywords: Oxidation, *N,N*-disubstituted hydroxylamines, nitrones, 1,3-dipolar cycloaddition

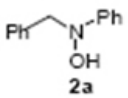
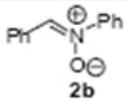
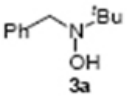
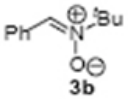
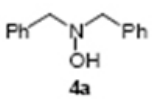
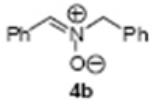
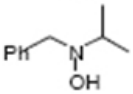
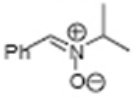
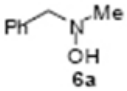
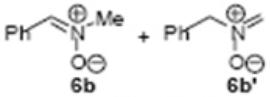
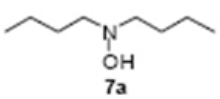
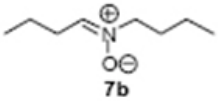
Introduction

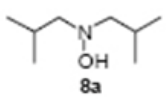
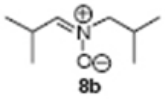
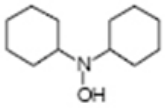
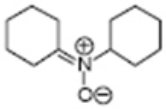
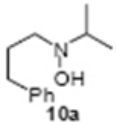
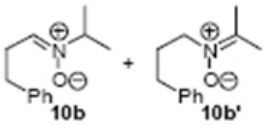
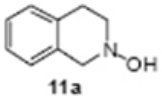
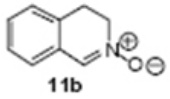
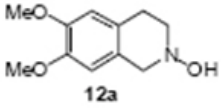
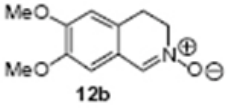
Nitrones[1,2] are quite versatile intermediates in organic synthesis and are employed, for instance, in stereoselective formation of synthetically useful isoxazolidines by their 1,3-dipolar cycloaddition with alkenes.[3-5] For the preparation of nitrones, the most popular method is the condensation of aldehydes or ketones with *N*-monosubstituted hydroxylamines.[6] However, this method is difficult to be applied to the preparation of non-conjugated cyclic nitrones and of ketonitrones having bulky alkyl groups. Direct oxidation of secondary amines to the corresponding nitrones was also studied in these two decades and was found to be a useful method for the preparation of nitrones. Several effective metal catalysts[7-10] and oxidizing agents[11-13] were then developed for this direct oxidation reaction. Another method for the preparation of nitrones is the oxidation of *N,N*-disubstituted hydroxylamines[6,14-16] in which yellow mercuric oxide[17] is most commonly used as an oxidant. Although this method is useful particularly for the preparation of labile nitrones due to its mild reaction conditions, it is yet desired to develop a new and more efficient oxidant other than the toxic mercuric compound in order to establish a useful method for the preparation of nitrones by oxidation of *N,N*-disubstituted hydroxylamines.

It was recently reported from our laboratory that various types of alcohols[18] and amines[19] were successfully oxidized into the corresponding carbonyl compounds and imines, respectively, under mild conditions by using *N*-*t*-butylbenzenesulfinimidoyl chloride **1** in the co-existence of DBU. For example, octanol and cyclohexanol were oxidized within 30 min to octanal (98% yield) and cyclohexanone (91%), respectively, by using **1** (1.5 equiv) and DBU (2.0 equiv) at room temperature.[18] Similarly, the oxidation of *N*-cinnamylaniline completed at –78 °C in 30 min to afford *N*-cinnamylideneaniline in 98% yield.[19] It was then thought that the oxidation of *N*,*N*-disubstituted hydroxylamines would afford the corresponding nitrones under mild conditions by using the above two reagents, **1** and DBU.

Table 1. Oxidation of *N*,*N*-disubstituted hydroxylamines to nitrones by using 1 and DBU



Entry	Hydroxylamine	Nitrone	Yield/%[a]
1	 **2a**	 **2b**	96
2	 **3a**	 **3b**	97
3	 **4a**	 **4b**	85
4	 **5a**	 **5b**	91
5	 **6a**	 **6b** + **6b'** **6b/6b' = 72/28**[b]	85
6	 **7a**	 **7b**	84

7	 **8a**	 **8b**	85
8	 **9a**	 **9b**	86
9	 **10a**	 **10b** + **10b'** **10b/10b' = 98/2**[b]	85
10	 **11a**	 **11b**	89[c]
11	 **12a**	 **12b**	88[d]

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Isoquinoline *N*-oxide (5%) was also isolated. [d]6,7-Dimethoxyisoquinoline *N*-oxide (11%) was also isolated.

Results and Discussion

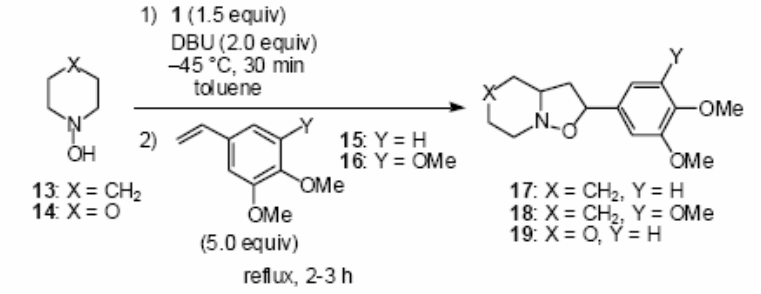
In the first place, *N*-benzyl-*N*-phenylhydroxylamine **2a** was oxidized under the same conditions of oxidation of benzylic alcohols to aldehydes[18] by using **1** (1.5 equiv.) and DBU (2.0 equiv.) in methylene chloride at –78 °C. Expectedly, the oxidation of **2a** proceeded instantaneously and *N*-benzilideneaniline *N*-oxide **2b** was isolated in 96% yield after purification by column chromatography (Table 1, entry 1). Other *N*benzylhydroxylamines were also oxidized smoothly by the present oxidation method to afford the corresponding conjugated nitrones in high yields (entries 2-5). It was noted that the oxidation of benzylic positions was preferred to that of tertially or primary alkyl positions in the case of unsymmetrically substituted *N*,*N*-dialkylhydroxylamines (entry 4 and 5)

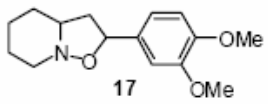
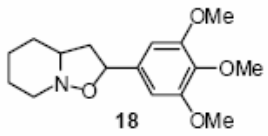
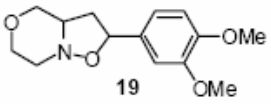
In addition to the above-mentioned conjugated nitrones, non-conjugated aliphatic nitrones were readily formed also by the present oxidation even at –78 °C (entries 6-9). It was interesting to note that the oxidation of *N*,*N*-dicyclohexylhydroxylamine **9a** smoothly proceeded at –78 °C to afford the corresponding ketonitrone, *N*-cyclohexylidene-*N*-cyclohexylamine *N*-oxide **9b**, in 86% yield. This result indicated that *N*,*N*-dialkyl hydroxylamines were oxidized more easily compared to *N*,*N*-dialkyl secondary amines which afforded no corresponding ketimines under the same oxidation conditions.[19] In the case of an unsymmetrical hydroxylamine, *N*-isopropyl-*N*-(3-phenylpropyl)hydroxylamine **10a**, the oxidation took place exclusively at the position of 3-phenylpropyl group, which indicated considerable influence of steric factors on the

regioselectivity of the present nitrone synthesis. Similar regioselectivities were reported also in the oxidation of *N*,*N*-disubstituted hydroxylamines with mercuric(II) oxide.[17] Oxidation of cyclic hydroxylamines, *N*-hydroxy-1,2,3,4-tetrahydroisoquinolines (**11a** and **12a**), also proceeded to give 3,4-dihydroisoquinoline *N*-oxides in high yields together with a small amount of over-oxidized product, isoquinoline *N*-oxides (entry 10 and 11).

Oxidation of six-membered aliphatic hydroxylamines such as *N*-hydroxypiperidine **13** and *N*-hydroxymorpholine **14** was carried out at –45 °C in toluene since the reaction in toluene took place very slowly at –78 °C. The formation of these labile nitrones was confirmed by one-pot 1,3-dipolar cycloaddition reaction with electron-rich styrenes.[20] (Table 2).

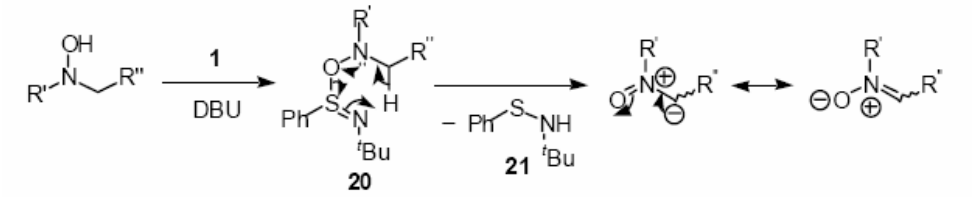
Table 2. One-pot synthesis of isoxazolidines from cyclic aliphatic hydroxylamines



Entry	Hydroxylamine	Styrene	Isoxazolidine	Isolated yield/%
1	**13**	**15**	 **17**	90
2	**13**	**16**	 **18**	84
3	**14**	**15**	 **19**	39

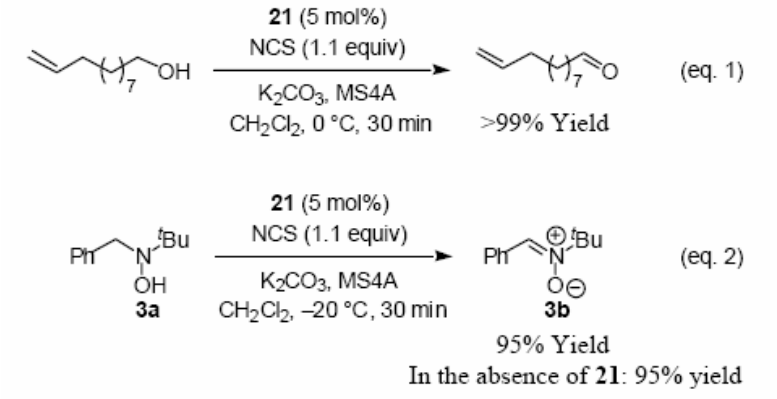
The cyloaddition reactions of the nitrone generated from **13** proceeded effectively in the presence of five equivalents of electron-rich alkenes **15** and **16** in refluxing toluene to afford cycloadducts (**17** and **18**) in high yields. When the amount of the alkenes decreased, the yield of cycloadducts turned lower. On the other hand, oxidation of *N*hydroxymorpholine **14** and successive cycloaddition reaction with **15** gave the cyclized product **19** in a low yield (38%) probably due to the unstability of the formed nitrone.

It was assumed that the present oxidation of hydroxylamines to nitrones would proceed via an intermediate **20**, which was formed, from a hydroxylamine and **1** in the presence of DBU. The intermediate **20** was in turn converted into a nitrone and *N*-*t*-butylbenzenesulfenamide **21** by the intramolecular proton-transfer via six-membered cyclic transition state (Scheme 1).



Scheme 1

Very recently, the stoichiometric oxidation of alcohols by using **1** and DBU was further modified to the catalytic process by using *N*-chlorosuccinimide (NCS) in the presence of a catalytic amount of *N*-*t*-butylbenzenesulfenamide (**21**) (Scheme 2, eq. 1).[21] When catalytic oxidation of hydroxylamines to the corresponding nitrones was examined by the similar procedure, nitrone **3b** was obtained in 95% yield. However, **3a** was found to be readily oxidized to **3b** in the absence of the catalyst **21** (Scheme 2, eq. 2); that is, **3a** was oxidized with NCS in the co-existence of K_2CO_3.



Scheme 2

In conclusion, oxidation of hydroxylamines to the corresponding nitrones was performed under mild conditions by using **1** and DBU, and 1,3-dipolar cycloaddition reaction took place in a one-pot manner. Therefore, the present method would provide a new and mild procedure for the preparation of various nitrones.

Experimental Section

General Procedures. All melting points were determined on a Yanagimoto micro melting point apparatus (Yanaco MP-S3) and are uncorrected. Infrared (IR) spectra were recorded on a Horiba FT300 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a JEOL EX270 (270 MHz) spectrometer using $CDCl_3$ as a solvent; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Spilitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; hept, heptet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on a JEOL EX270 (68 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in

parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ77.0 ppm). High-resolution mass spectra (HRMS) were recorded on a HiTACHI M-80B mass spectrometer or a JEOL JMS-AX505HA mass spectrometer. Analytical TLC was performed on Merk precorted TLC plates (silica gel 60 GF254, 0.25 mm). Silica-gel column chromatography was carried out on Merk silica gel 60 (0.063-0.200 mm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. Unless otherwise noted, commercially available reagents were used without purification. Dry CH_2Cl_2 and toluene were prepared by distillation under appropriate drying agents. The oxidizing agent **1**[18] and hydroxylamines **2a**,[22] **3a**,[23] **5a**,[22] **6a**,[24] **7a**,[25] **8a**,[25] **9a**,[25] **11a**,[25] and **14**[26] were prepared according to the reported procedure. Nitrones **2b**,[27] **3b**,[8] **4b**,[8] **5b**,[17] **6b**,[17] **7b**,[8] **8b**,[10] **11b**,[8] and **12b**[28] were known compounds.

Typical experimental procedure for the oxidation of hydroxylamines to nitrones by using 1 and DBU (Oxidation of 3a to 3b). To a stirred solution of *N*-benzyl-*N*-*tert*-butylhydroxylamine **3a**[23] (76 mg, 0.42 mmol) and DBU (129 mg, 0.85 mmol) in CH_2Cl_2 (1.7 mL) was added a solution of **1** (136 mg, 0.63 mmol) in CH_2Cl_2 (1.7 mL) at –78 °C. After stirring the reaction mixture for 15 min at the same temperature, brine was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by thin layer chromatography (silica gel) to give *N*-benzylidene-*N*-*tert*-butylamine *N*-oxide **3b**[8] (73 mg, 0.41 mmol, 97%) as a colorless oil.

***N*-Cyclohexylidenecyclohexylamine *N*-oxide (9b).** Isolated as a colorless solid: mp 53-55 °C. IR (KBr, νcm^{-1}) 3818, 3340, 2931, 1651, 1149. ^{1}H NMR δ1.20-2.14 (16H, m), 2.53 (2H, t, J = 6.4 Hz), 4.07-4.17 (1H, m). ^{13}C NMR δ24.4, 24.6, 24.8, 24.9, 25.7, 26.9, 28.9, 29.8, 64.8, 147.6. HRMS (ESI positive) *m/z*: found: 196.1698; calcd for $C_{12}H_{22}NO[M+H]^+$: 196.1701.

***N*-Isopropyl-*N*-(3-phenylpropyl)hydroxylamine (10a).** To a stirred solution of *N*-(3-phenylpropyl)isopropylamine (2.67 g, 15.1 mmol) in methanol (35 mL) was added Na_2WO_4•$2H_2O$ (0.15 g, 0.45 mmol) at room temperature. Then, 10% H_2O_2 solution (4.27 g, 37.7 mmol) was added to the reaction mixture at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. After evaporation of solvents, brine was added to the residue, and the mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*.The crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH as an eluent) to give *N*-(3-phenylpropylidene)isopropylamine *N*-oxide (2.00 g, 10.46 mmol, 70%) as a colorless oil.

To the solution of *N*-(3-phenylpropylidene)isopropylamine *N*-oxide (1.87 g, 9.78 mmol) in ethanol (20 mL) was added $NaBH_4$ (925 mg, 24.5 mmol) at room temperature, and the reaction mixture was kept at the same temperature over night. The solvent was evaporated and H_2O was added to the resulting residue. The mixture was extracted with CH_2Cl_2, and combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane-ethyl acetate 3:1) to give *N*-

Isopropyl-*N*-(3-phenylpropyl)hydroxylamine 10a (1.11 g, 5.74 mmol, 59%) as a colorless oil. IR (neat, νcm^{-1}) 3432, 2892, 1597, 1450, 1173, 741. ^{1}H NMR δ1.60 (6H, d, *J* = 6.4 Hz), 1.86-1.97 (2H, m), 2.59-2.70 (4H, m), 2.94 (1H, hept, *J* = 6.4 Hz), 7.13-7.28 (5H, m). ^{13}C NMR δ18.1, 28.7, 33.5, 54.7, 57.1, 125.7, 128.2, 128.3, 142.0. HRMS: found: *m/z* 193.1471; calcd for $C_{12}H_{19}NO$: 193.1467.

***N*-(3-Phenylpropylidene)isopropylamine *N*-oxide (10b).** Isolated as a colorless oil. IR (neat, νcm^{-1}) 3432, 2892, 1597, 1450, 1173, 741. ^{1}H NMR δ1.73 (6H, d, *J* = 6.6 Hz), 2.76-2.91 (2H, m), 3.98 (1H, hept, *J* = 6.6 Hz), 6.70 (1H, t, *J* = 5.4 Hz), 7.17-7.32 (5H, m). ^{13}C NMR δ20.5, 27.5, 31.0, 65.9, 126.1, 128.1, 128.3, 135.5, 140.3. HRMS: found: *m/z* 191.1317; calcd for $C_{12}H_{17}NO$: 193.1310.

6,7-Dimethoxy-2-hydroxy-1,2,3,4-tetrahydroisoquinoline (12a). This compound was prepared according to the method described in the synthesis of **10a**, and isolated as a colorless solid: mp 125-126 °C. IR (neat, νcm^{-1}) 3210, 2915, 2839, 1612, 1519, 1241, 1119. ^{1}H NMR δ2.95 (2H, brs), 3.41 (2H, brs), 3.84 (6H, s), 4.18 (2H, brs), 6.51 (1H, s), 6.56 (1H, s). ^{13}C NMR δ27.7, 55.4, 55.8, 59.6, 109.5, 110.9, 124.7, 124.8, 147.5, 147.8. HRMS (ESI positive, *m/z*): found: 210.1127; calcd for $C_{11}H_{16}NO_3$ $[M+H]^+$: 210.1130.

Typical experimental procedure for the one-pot synthesis of 2-(3,4-dimethoxyphenyl)-3,3a,4,5,6,7-hexahydro-2*H*-isoxazolo[2,3-*b*]pyridine (17). To a stirred solution of *N*-hydroxypiperidine 13 (24 mg, 0.24 mmol) and DBU (73 mg, 0.48 mmol) in toluene (2.0 mL) was added a solution of 1 (78 mg, 0.36 mmol) in toluene (1.5 mL) at – 45 °C. After stirring the reaction mixture for 30 min at the same temperature, MeOH (0.5 mL) and 3,4-dimethoxystyrene (98 mg, 1.21 mmol) were added successively. The mixture was refluxed for 3 h, cooled to room temperature, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by thin layer chromatography to afford the isoxazoline 17[20] (57 mg, 0.22 mmol, 90%) as a colorless oil.

2-(3,4,5-Trimethoxyphenyl)-3,3a,4,5,6,7-hexahydro-2*H*-isoxazolo[2,3-*b*]pyridine (18). Isolated as colorless oil. IR (neat, ν cm^{-1}) 3695, 3371, 2915, 2831, 2314, 1589, 1458, 1126. ^{1}H NMR δ1.28-2.67 (10 H, m), 3.53-3.60 (1H, m), 3.83 (3H, s), 3.87 (6H, s), 4.97 (1H, m), 6.61 (2H, brs). ^{13}C NMR δ23.7, 24.7, 29.3, 42.9, 55.2, 56.0, 59.8, 66.7, 77.6, 102.8, 103.5, 137.4, 153.1. HRMS: found: *m/z* 293.1617; calcd for $C_{16}H_{23}NO_4$: 293.1627.

2-(3,4-Dimethoxyphenyl)-hexahydro-isoxazolo[3,2-*c*][1,4]oxazine (19). Isolated as colorless oil. IR (neat, ν cm^{-1}) 3849, 3564, 2962, 2870, 1597, 1512, 1250, 741. ^{1}H NMR δ2.08-2.17 (1H, m), 2.81-2.93 (1H, m), 3.09-3.14 (2H, m), 3.55-3.65 (2H, m), 3.87-3.92 (7H, m), 3.94-3.95 (2H, m), 5.37 (1H, dd, *J* = 4.1, 9.7 Hz), 6.82-6.92 (3H, m). ^{13}C NMR δ37.5, 49.8, 55.8, 55.8, 60.0, 65.1, 65.3, 78.5, 109.2, 110.9, 118.5, 134.7, 148.4, 148.9. HRMS: found: *m/z* 265.1314; calcd for $C_{14}H_{19}NO_4$: 265.1314.

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