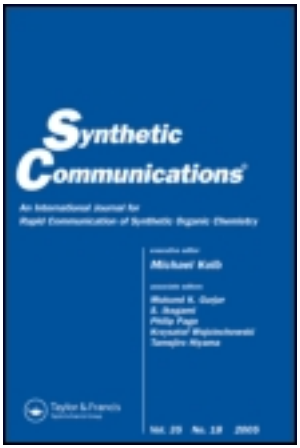

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One-Pot Synthesis and Hydroxylaminolysis of Asymmetrical Acyclic Nitrones

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Abstract: Aromatic aldehydes **1** were reductively aminated to the corresponding secondary amines **2** using $NaBH_4$ in methanol in good yields. Amines **2** were oxidized with H_2O_2-WO_4^{2-} regioselectively to nitrones **3**, the structures of which were easily determined by reacting them with hydroxylamine hydrochloride as well as by spectral means. The products of hydroxylaminolysis in ether proved to be the corresponding benzaldehyde oximes **4** and benzyl or methyl hydroxylamine hydrochlorides **5**.

Keywords: Acyclic nitrone, alkyl hydroxylamine hydrochloride, oxidation

INTRODUCTION

Nitrones are well known 1,3-dipoles in thermal cycloaddition reactions with a wide variety of carbon–carbon, carbon–nitrogen, carbon–sulphur, and nitrogen–phosphorus multiple-bond systems that provide various heterocyclic five-membered ring systems.[1] The cycloadducts of di- and triarylimidazoline 3-oxides[2] with variety of dipolarophiles[3] give bicyclic compounds with potentially interesting biological activity. (A series of tetrahydroimidazo compounds including tetrahydroimidazooxadiazolones were tested for their anticancer activity and found to be quite active at 10^{-5} molar concentrations.) Conversely, they are a source of new heterocyclic compounds via interesting ring-opening reactions.[4] As a continuation of our interest in the synthesis of five-membered heterocycles and their ring-opening reactions, we needed to prepare acyclic nitrones. Condensation of an N-alkylhydroxylamine with

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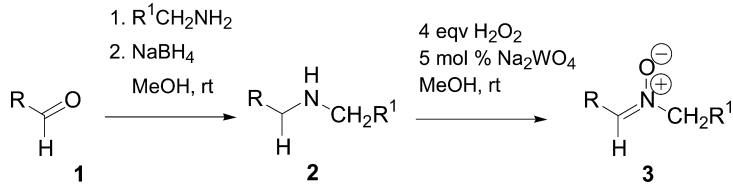
a carbonyl compound and oxidation of N,N-dialkylhydroxylamine and dialkylamines are the most common methods for the synthesis of nitrones.[5] N-Alkyl hydroxylamines are accessible via reduction of aldoximes and ketoximes with $NaBH_3CN$ at pH 3–4.[6] Recently primary amines were converted to the corresponding N-monoalkylhydroxylamines by a three-step protocol involving the selective mono-cyanomethylation of primary amines, regioselective formation of nitrones by m-CPBA oxidation, and hydroxylaminolysis of the nitrones with hydroxylamine hydrochloride.[7]

RESULTS AND DISCUSSION

We report herein the synthesis of asymmetrical acyclic nitrones **3** via oxidation of secondary amines **2** with H_2O_2-WO_4^{2-} in methanol at room temperature. The hydroxylaminolysis of compounds **3** serve as a useful tool for the determination of the regiochemistry of the oxidation. The hydroxylamine hydrochlorides were reacted with the corresponding aldehydes to give the corresponding nitrones.

Aldehydes **1** were reductively aminated[8] to the corresponding secondary amines **2** using $NaBH_4$ in methanol in good yields. These compounds were oxidized with H_2O_2-WO_4^{2-} in methanol at room temperature to the corresponding nitrones **3** (Scheme 1, Table 1) in moderate yields, which were isolated and purified by recrystallization. The structures of the nitrones prepared were easily determined by reacting them with hydroxylamine hydrochloride in ether. The products of the reaction proved to be the corresponding benzaldehyde oximes **4** and benzyl or methyl hydroxylamine hydrochlorides **5** (Scheme 2, Table 1). This reaction, beside its usefulness in the structure determination of nitrones, is also a good alternative to the limited methods for the synthesis of synthetically important N-alkyl(benzyl)-substituted hydroxylamines.

In addition to the chemical method of structure determination, all new compounds were fully characterized by analytical and spectral means. The elemental analyses and IR, ^1H, and ^{13}C NMR spectral data are in agreement with the proposed nitrone structures. The structures of the newly prepared N-substituted hydroxylamines were proven spectrally as well as by converting them to the corresponding nitrones in THF at room temperature.

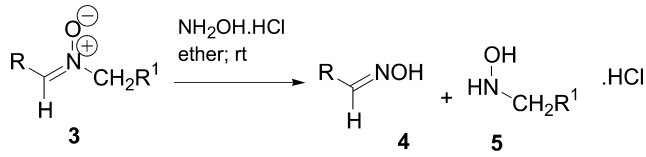


Scheme 1.

Table 1. Synthesis of nitrones **3** and hydroxylamines **5**

			Yields of **3** (%)				
3–5	R	R^1	Method A	Method B	Mp of **3** (°C)	Yield of **5** (%)	Mp of **5** (°C)
a	3,4-$(MeO)_2C_6H_3$	H	61	93	126–127	93	80–81
b	2-$NO_2C_6H_4$	H	55	99	94–95	98	78–80
c	Ph	Ph	68	92	82–83	96	101–103
d	2-$NO_2C_6H_4$	2,3-$(MeO)_2C_6H_3$	50[a]	96	95	93	120–121
e	2-$NO_2C_6H_4$	Ph	52[a]	91	120–121	91	101–103
f	2,3-$(MeO)_2C_6H_3$	Ph	47	92	123–124	83	103

[a]The inspection of the ^1H NMR spectra of the crude reaction mixtures shows the presence of second regioisomers in ca. 20% for **3d** and 28% for **3e**.



3 4 5

Scheme 2.

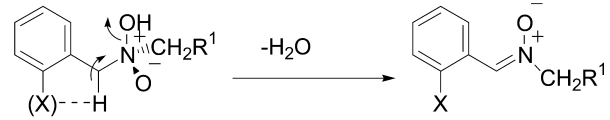
In the cases of **2a, c** the oxidation occurs at the benzylic carbon, leading to the more stable C-aryl nitrones **3a, c**. It is surprising that the main products in the case of **3d, e** are formed at the more electron-deficient benzylic carbon whereas the opposite is true for **3f**. The oxidation of secondary amines to nitrones is expected to proceed through corresponding hydroxylamine as an intermediate. In our recent report we were able to isolate intermediate hydroxylamines from the oxidation of tetrahydroquinazolines.[9] The probable next step in the oxidation of the hydroxylamine is the formation of corresponding N-oxide **A** (see Scheme 3), which could lose water to give the corresponding nitrone. The regioselectivity of the oxidation in the cases of **2c, d, f**, is probably determined by the ortho substituents, which probably favor the water elimination of the N-oxide (see Scheme 3).

EXPERIMENTAL

Melting points were taken on an Electrothermal Digital melting-point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. Proton magnetic-resonance spectra were recorded on a Bruker Dpx 400-MHz spectrometer. Visualization was effected with UV light. Freshly prepared nitrones were used after recrystallization from ether–petroleum ether. The elemental analyses were performed on a EuroEA 3000 CHNS analyzer.

Synthesis of Nitrones 3, Method A, General Procedure

To a solution of aldehyde **1** (10 mmol) in methanol (15 mL), benzyl or methylamine (10 mmol) dissolved in methanol (2 mL) was added dropwise. The mixture was stirred at room temperature for 10 min in the cases of methylamine



X = MeO; or NO_2

A **3d-f**

Scheme 3.

and 1 h for benzylamines. An equimolar amount of $NaBH_4$ was added portionwise and the reduction was completed within 1 h. The solvent was evaporated, and the residue dissolved in hydrochloric acid and extracted with ether (3 × 15 mL). The water phase was basified with ammonia and extracted with ether (4 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent evaporated. The residue was dissolved in MeOH (15 mL), and 35% H_2O_2 (40 mmol) and 5 mol % Na_2WO_4 were added to the solution. The mixture was stirred at room temperature for 1 h and poured into water (25 mL), and then extracted with chloroform (4 × 15 mL). The combined extracts were dried (anhydrous Na_2SO_4) and filtered, and the solvent evaporated. The residue was treated with ether to give the crystalline nitrone after cooling in a refrigerator.

C-(3,4-Dimethoxyphenyl)-N-methyl-nitrone 3a. IR (KBr) $\nu_{C=N}$ 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 6.84 (1H, d, $J = 8.3$), 7.26 (1H, s), 7.40 (1H, d, $J = 8.3$), 8.26 (1H, s). ^{13}C NMR δ 54.41; 56.31; 56.40; 109.39; 110.80; 111.27; 123.35; 127.21; 148.89; 151.21. Anal. calcd. for $C_{10}H_{13}NO_3$ (195.22): C, 61.53; H, 6.71; N, 7.18. Found: C, 60.83; H, 6.74; N, 6.84.

C-(2-Nitrophenyl)-N-methyl-nitrone 3b. IR (KBr) $\nu_{C=N}$ 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (3H, s), 7.45 (1H, t, $J = 7.6$), 7.62 (1H, t, $J = 7.6$), 7.93 (2H, m), 9.05 (1H, d, $J = 7.9$). Anal. calcd. for $C_8H_8N_2O_3$ (180.16): C, 53.33; H, 4.48; N, 15.55. Found: C, 53.46; H, 4.66; N, 15.02.

C-Phenyl-N-benzyl-nitrone 3c. IR (KBr) $\nu_{C=N}$ 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.95 (2H, s), 7.30 (7H, m), 7.35 (2H, m), 8.12 (2H, m). ^{13}C NMR δ 71.67; 128.86; 129.01; 129.37; 129.62; 130.01; 130.84; 130.88; 133.71; 134.62. Anal. calcd. for $C_{14}H_{13}NO$ (211.26): C, 79.59; H, 6.20; N, 6.63. Found: C, 79.50; H, 6.36; N, 6.58.

C-(2-Nitrophenyl)-N-(2,3-dimethoxybenzyl)-nitrone 3d. IR (KBr) $\nu_{C=N}$ 1576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (3H, s), 3.84 (3H, s), 5.08 (2H, s), 6.90 (1H, m), 7.00 (2H, s), 7.40 (1H, t, $J = 7.5$), 7.52 (1H, t, $J = 7.5$), 7.91 (1H, t, $J = 8.0$), 8.05 (1H, s), 9.08 (1H, d, $J = 8.0$). ^{13}C NMR δ 56.26; 61.35; 67.26; 114.29; 123.42; 124.67; 125.27; 125.69; 126.66; 128.59; 129.75; 130.32; 133.68; 147.60; 148.27; 153.12. Anal. calcd. for $C_{16}H_{16}N_2O_5$ (316.31): C, 60.75; H, 5.10; N, 8.86. Found: C, 60.68; H, 5.26; N, 8.62.

C-(2-Nitrophenyl)-N-benzyl-nitrone 3e. IR (KBr) $\nu_{C=N}$ 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.02 (2H, s), 7.34–7.43 (6H, m), 7.60 (1H, t, $J = 7.6$), 7.94 (1H, d, $J = 7.9$), 8.00 (1H, s), 9.05 (1H, d, $J = 7.9$). ^{13}C NMR δ 72.81; 124.78; 125.22; 128.61; 129.46; 129.63; 129.79; 130.50; 132.66; 133.01; 133.79; 147.55. Anal. calcd. for $C_{14}H_{12}N_2O_3$ (256.26): C, 65.62; H, 4.72; N, 10.93. Found: C, 65.49; H, 4.86; N, 10.45.

C-(2,3-Dimethoxyphenyl)-N-benzyl-nitrone 3f. IR (KBr) $\nu_{C=N}$ 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (3H, s), 3.80 (3H, s), 5.04 (2H, s), 6.95 (1H, m), 7.05 (1H, m), 7.31 (3H, m), 7.43 (2H, m), 7.76 (1H, s), 8.72 (1H, d, $J = 7.5$). Anal. calcd. for $C_{16}H_{17}NO_3$ (271.31): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.39; H, 6.52; N, 5.16.

Synthesis of N-Methyl and N-Benzyl Hydroxylamine Hydrochlorides, General Procedure

To a solution of nitrone **3** (1 mmol) in ether (20 mL) was added equimolar amount of hydroxylamine hydrochloride dissolved in methanol (4 mL). The reaction mixture was stirred for 4 h. The solvent was evaporated and the product hydroxylamine solidifies after addition of ether. The product was filtered and dried under vacuum. The filtrate contains the corresponding benzaldoxime, which was isolated and compared with authentic samples.

N-Methyl hydroxylamine hydrochloride obtained from the reactions of nitrones **3a, b** and N-Benzyl hydroxylamine hydrochloride obtained from the reactions of nitrones of **3c, e, f** were identical with the commercially available products. These compounds were used in the synthesis of nitrones **3** by method B.

N-(2,3-Dimethoxybenzyl) hydroxylamine hydrochloride. From the reaction of (2-nitrobenzylidene)-(2,3-dimethoxybenzyl)-amine oxide **3d**. IR (KBr) ν_{OH} 3424 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.79 (3H, s), 3.81 (3H, s), 4.29 (2H, s), 7.05–7.10 (3H, m), 10.98 (1H, s), 11.58 (2H, brs). ^{13}C NMR δ 49.25; 56.55; 61.25; 114.81; 123.64; 123.99: 124.61; 148.30; 152.96. Anal. calcd. for $C_9H_{14}ClNO_3$ (219.67): C, 49.21; H, 6.42; N, 6.38. Found: C, 49.60; H, 6.06; N, 6.05.

Synthesis of Nitrones 3, Method B, General Procedure

To a solution of N-methyl or N-benzylhydroxylamine hydrochlorides **5** (1 mmol) in THF (20 mL), aldehyde (1 mmol) was added, and the mixture stirred at room temperature for 4 h. The solvent was evaporated and water was added (10 mL) to the residue and extracted with $CHCl_3$ (2 × 15 mL). The combined extracts were dried and filtered, and the solvent evaporated under vacuum. The residue was treated with ether to give crystalline nitrones **3**, which were collected by filtration. The melting points and the IR spectra of the prepared nitrones were identical with those prepared by Method A.

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