A Large-Scale Low-Cost Preparation of *N*-Benzylhydroxylamine Hydrochloride

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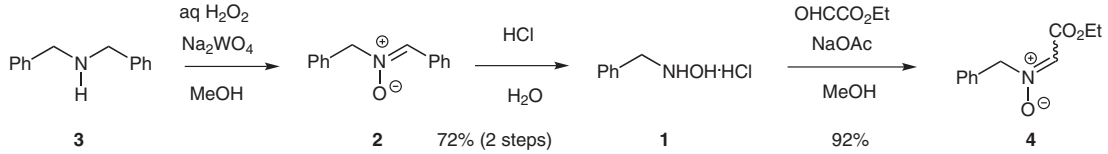
Abstract: A high-yielding, practical two-step procedure for the preparation of *N*-benzylhydroxylamine starting from dibenzylamine is described. As specified in the detailed protocol, the reaction can be conveniently carried out on a > 0.5 mol laboratory scale.

Key words: *N*-benzylhydroxylamine, *N*-benzylnitrones, 1,3-dipolar cycloaddition, secondary amine oxidation, nitrone hydrolysis



Scheme 1

N-Benzylhydroxylamine has become one of the most popular reagents in nitrone chemistry. Its condensation with an aldehyde or a ketone[1] and its addition to an activated triple bond[2] are among the most common methods to *N*-benzylnitrones. 1,3-Dipolar cycloaddition of these nitrones with alkenes provides *N*-benzylisoxazolidines in which the benzyl group can be easily removed from nitrogen in order to perform further manipulations at that atom. The retail price of *N*-benzylhydroxylamine hydrochloride (**1**) (approx. 5000 €/mol) is notably high for such a simple molecule. During the course of our research on new methodological developments concerning the 1,3-dipolar cycloaddition of nitrones,[1b,3] a large quantity of *N*-benzylhydroxylamine was used as the starting material. We considered the benefit of being able to prepare *N*-benzylhydroxylamine on a large-scale by a cheap and reliable procedure.

In the literature, some methods for the preparation of this compound have been reported. Direct benzylation of the hydroxylamine results in a complex mixture of polybenzylated products, in which *N*,*N*-dibenzylhydroxylamine is the major product.[4] Reduction of benzaldoxime by $NaBH_3CN$ in buffered diethyl ether solution affords the desired *N*-benzylhydroxylamine in moderate and hardly reproducible yields possibly due to a pH change during the course of the process.[5] Moreover, use of $NaBH_3CN$ is highly toxic and can generate deleterious side products after workup.

The preparation of *N*-benzylhydroxylamine[6] by acid hydrolysis of nitrone **2** and subsequent neutralization attracted our attention. Based on this result, we thought that nitrone **2** could be an interesting precursor for **1**, provided that **2** could be obtained in a high-yielding and simple way. Our attention was directed to the preparation of nitrone **2** by oxidation of dibenzylamine **3**, given that **3** is quite inexpensive (approx. 13 €/mol) as it can be easily made by the reaction between NH_3 and benzyl chloride in industrial scale.

This transformation was previously carried out by using H_2O_2 in the presence of a catalyst such as Na_2WO_4,[7] SeO_2,[8] or $MeReO_3$,[9] or by using dimethyldioxirane,[10] and *N*-phenylsulfonyl-*C*-phenyloxaziridine.[11] Among the methods reported on a large-scale,[7,9] Murahashi's procedure[7] using Na_2WO_4 (2 mol%) seems to be the most economic and practical as low-cost reagents (H_2O_2, Na_2WO_4)[12] and solvent (MeOH) were used, and the desired nitrone could be obtained in excellent yield (85–96% after recrystallization).

However, in the original Murahashi's procedure,[7] the crude reaction mixture was subjected to methanol evaporation without prior removal or treatment of the residual oxidative agent H_2O_2. Despite the high yield, this method seemed to be unsafe, especially for a larger scale synthesis. Following our modified procedure, simple addition of ice was found to precipitate the nitrone **2** from the crude reaction mixture. By simple filtration, we could recover the nitrone in high yield (~80%) and avoid hazardous manipulations.[13] Moreover, this modification of the procedure prevents the use of a large amount of CH_2Cl_2,

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previously used for extraction of nitrone **2**. Given that water is not detrimental for the next reaction, we used the wet nitrone directly in the subsequent acidic hydrolysis step. Treatment of this crude mixture with an aqueous hydrochloric acid solution (20%) followed by steam distillation under reduced pressure in order to eliminate PhCHO afforded pure BnNHOH·HCl **1** as colorless crystals after only one recrystallization from hot methanol with good overall yield (72%) (Scheme 1). This access to the hydrochloric salt **1** from nitrone **2** compares well with the previous synthesis of free *N*-benzylhydroxylamine by a similar procedure[6] or with the formation of relevant oxalates via hydroxylaminolysis of nitrones.[14] The purity of **1** obtained by this procedure on a 0.5 mole scale was attested by elemental analysis.

To exemplify the quality and utility of BnNHOH·HCl (**1**) obtained by this simplified and safe procedure, we prepared the activated nitrone **4**, which is a pivotal synthon in amino acid synthesis. By a highly simple procedure starting from this salt and ethyl glyoxylate in an acetate-buffered methanol solution, nitrone **4** was prepared in excellent yield (92%) (Scheme 1). This procedure compares well with those previously described by condensing free BnNHOH and ethyl glyoxylate in the presence of $CaCl_2$ as catalyst.[15]

To conclude, we have described here a large-scale, simple, economic, and safe procedure for the preparation of *N*-benzylhydroxylamine hydrochloride (**1**). This two-step method requires only low-cost starting materials (Bn_2NH, H_2O_2, Na_2WO_4, HCl) and solvents (H_2O, MeOH) with highly simple purification (recrystallization, evaporation, and steam distillation) in good overall yield.

All reagents and solvents were used as received without any further purification. ^{1}H NMR spectra were recorded on a Bruker DPX-200 spectrometer in D_2O for **1** and $CDCl_3$ for **4** using TMS as a reference.

BnNHOH·HCl (1)

In a 2-L, three-necked, round-bottomed flask equipped with a 500-mL pressure-equalizing dropping funnel, a thermometer, and a magnetic stirring bar were placed $Na_2WO_4{\cdot}2H_2O$ (2.94 g, 10 mmol), Bn_2NH (98.5 g, 0.5 mol) and MeOH (0.5 L). The flask was cooled with an ice bath to 0–5 °C (internal temperature) and 30% aq H_2O_2 (170 mL, 1.5 mol) was added dropwise over a period of ca. 2 h. During the period of addition, the reaction mixture should be carefully kept at a temperature below 5 °C. The cooling bath was removed 2 h after the end of the addition of H_2O_2, and the mixture was stirred for 18 h at r.t. The contents of the flask were first transferred to a 5 L beaker and then crushed ice (3 kg) was next added to the mixture with vigorous stirring. The white precipitate of nitrone **2** was filtered, washed with ice water until the filtrate gave a negative result with peroxide test (ca. 0.5 L of H_2O was needed). The wet crude nitrone **2** was then placed in a 2-L round-bottomed flask containing aq 20% HCl (1 L). The flask was fitted to a rotary evaporator keeping the water bath temperature at 70 °C with slow rotation under atmospheric pressure. After 30 min, the pressure was carefully reduced to 100 mmHg while benzaldehyde was distilled off with H_2O. When the total volume remained 130 mL, the flask was removed from the rotary evaporator. The semi-solid mixture was washed with toluene (3 × 100 mL) and then concentrated in vacuo (the last trace of H_2O could be removed by adding toluene and distilling). The residue was dried overnight in a vacuum desiccator to afford pale yellow solid of crude BnNHOH·HCl (62 g) which was purified by recrystallization from hot MeOH (120 mL) and then Et_2O (350 mL) to yield the pure desired product as white crystals (57.4 g, 72%).

^{1}H NMR (200 MHz, D_2O): δ = 11.9 (br, 2 H), 11.0 (br, 1 H), 7.57–7.37 (m, 5 H), 4.31 (s, 2 H).

^{13}C NMR (100 MHz, D_2O): δ = 131.6, 130.3, 129.1, 128.0, 62.2.

Anal. Calcd for $C_7H_{10}ClNO$ (159.61): C, 52.67; H, 6.31; N, 8.78. Found: C, 52.59; H, 6.40; N, 8.77.

Nitrone 4

A slurry of BnNHOH·HCl (3.20 g, 20 mmol) and anhydrous NaOAc (2.18 g, 26 mmol) in MeOH (20 mL) was stirred for 10 min at r.t. A solution of 50% ethyl glyoxylate in toluene (4.08 g, 20 mmol) was then added. After stirring for 3 h at r.t., the reaction mixture was concentrated under vacuum. The white residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (30 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and filtered through a short pad of silica gel. The filtrate was concentrated under vacuum to yield pure nitrone **4** as white crystals (4.10 g, 92%).

^{1}H NMR (200 MHz, $CDCl_3$): δ (*E*/*Z* = 3:1) = 7.58–7.33 (m, 5 H_{arom}), 7.20 [s, 1 H, N=C*H* (*E*)], 7.05 [s, 1 H, N=CH (*Z*)], 5.70 [s, 2 H, CH_2Ph (*E*)], 4.99 [s, 2 H, CH_2Ph (*Z*)], 4.26 and 4.24 (q, $^3J_{3,4}$ = 7.1 Hz, CH_2CH$_3$) 1.32 and 1.28 (t, $^3J_{3,4}$ = 7.1 Hz, CH$_2$CH_3).

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