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

Thanh Binh Nguyen, Arnaud Martel, Robert Dhal, Gilles Dujardin*
Laboratoire de Synthèse Organique, UCO2M, UMR 6011 CNRS, Université du Maine, 72085 Le Mans, France
E-mail: gilles.dujardin@univ-lemans.fr
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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-benzynitrones, 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 and its addition to an activated triple bond are among the most common methods to N-benzynitrones. 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, 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. Reduction of benzaldoxime by NaBH₃CN 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. Moreover, use of NaBH₃CN is highly toxic and can generate deleterious side products after workup.

The preparation of N-benzylhydroxylamine 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 NH₃ and benzyl chloride in industrial scale.

This transformation was previously carried out by using H₂O₂ in the presence of a catalyst such as Na₂WO₄, SeO₂, or MeReO₃, or by using dimethyldioxirane and N-phenylsulfonyl-C-phenyloxaziridine. Among the methods reported on a large-scale, Murahashi’s procedure using Na₂WO₄ (2 mol%) seems to be the most economic and practical as low-cost reagents (H₂O₂, Na₂WO₄) 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, the crude reaction mixture was subjected to methanol evaporation without prior removal or treatment of the residual oxidative agent H₂O₂. 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. Moreover, this modification of the procedure prevents the use of a large amount of CH₂Cl₂.
previously used for extraction of nitrones. Given that water is not detrimental for the next reaction, we used the wet nitrite 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 BnNH-Cl I 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 nitrones 2 compares well with the previous synthesis of free N-benzylhydroxylamine by a similar procedure6 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 BnNH-Cl (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 methanol solution, nitrone directly in the subsequent acidic hydrolysis step. By a highly simple purification (recrystallization, evaporation, and steam distillation) in good overall yield.

All reagents and solvents were used as received without any further purification.11 NMR spectra were recorded on a Bruker DPX-200 spectrometer in D2O for 1 and CDCl3 for 4 using TMS as a reference.

**BnNH-Cl (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 Na2WO4·2H2O (2.94 g, 10 mmol) pressure-equalizing dropping funnel, a thermometer, and a magnetic stirring bar were placed Na2WO4·2H2O (2.94 g, 10 mmol), Bn2NH, H2O2, Na2WO4, HCl) and solvents (H2O, MeOH) with initial methanol solution. 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 H2O2, and the mixture was stirred for 2 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 nitrene 2 was filtered, washed with ice water until the filtrate gave a negative reaction with 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 H2O. 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.


(12) The cost of the tungstate catalyst, used at a 2 mol%, is approximately 60 €/mol.

(13) Evaporation of the solvent (MeOH) at reduced pressure in the presence of large quantities of aqueous H$_2$O$_2$, as described in reference 7.
