Tetrahedron Letters, Vol. 34, No. 44, pp. 7043-7044, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Facile Synthesis of *N,O-bis*(*tert*-butoxycarbonyl)-Hydroxylamine

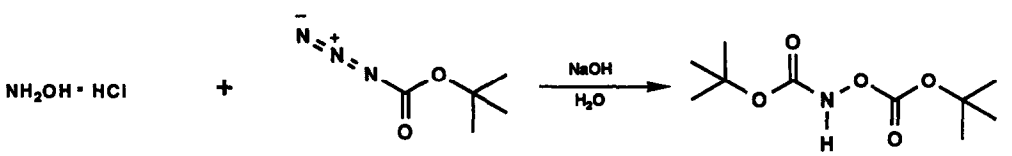
Michael A. Staszak* and Christopher W. Doecke
Process Research & Development
Lilly Research Laboratories
Eli Lilly & Company
Indianapolis, IN 46285-4813

Abstract: *N,O-bis*(*tert*-butoxycarbonyl)hydroxylamine was synthesized in 85% yield from hydroxylamine hydrochloride and di-*tert*-butyl dicarbonate in the presence of triethylamine. The chemistry is facile, utilizes readily available reagents and represents an improvement in safety over the previously published method.

As part of a study to improve the synthesis of a 5-lipoxygenase inhibitor containing an *N*-hydroxyurea subunit, an efficient means of incorporating the hydroxylamine functionality was required. Use of unprotected hydroxylamine was not practical since mixtures of *N*- and *O*-alkylated as well as di- and tri-alkylated products were possible. Recent literature examples have utilized *N,O-bis*(phenoxycarbonyl)hydroxylamine,[1] *N-t*-BOC-*O*-THP or *N-t*-BOC-*O*-TBDMS[2] to prepare similar compounds. However, after examining a number of hydroxylamine derivatives, *N,O-bis*(*tert*-butoxycarbonyl) hydroxylamine became the reagent of choice. Although commercially available,[3] the *bis*-protected hydroxylamine derivative was prohibitively expensive for large scale use, leading us to develop a more cost effective synthesis.

Surprisingly, a search of the literature uncovered only one reference for the synthesis of the title compound, that being the 1959 paper by Carpino, et.al.[4,5] The method described therein (Scheme 1) utilized the highly explosive *tert*-butyl azidoformate[6] to produce *bis-t*-BOC hydroxylamine in 59% yield from hydroxylamine hydrochloride. However, the Carpino synthesis pre-dates the availability of di-*tert*-butyldicarbonate("*t*-BOC anhydride"),[7] a safe and convenient reagent which is key to the improved synthesis described in this paper.

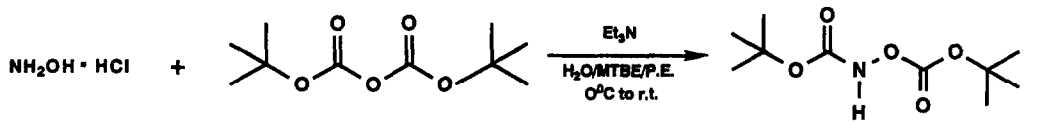
Scheme 1



Thus, *N,O-bis-t*-BOC-hydroxylamine was safely and efficiently prepared by treating hydroxylamine hydrochloride with two equivalents of *t*-BOC anhydride in the presence of slightly more than two equivalents of triethylamine (Scheme 2). Although good results were obtained with a wide range of solvents and conditions, the best results were realized within the following guidelines: (1) Due to the instability of free hydroxylamine at

ambient temperature,[8] maintenance of the initial reaction temperature near 0 °C was critical; (2) Bases stronger than triethylamine were avoided since they led to increased formation of *tris-t*-BOC hydroxylamine; (3) Increasing the polarity of the solvent (e.g. CH_2Cl_2, MeCN) likewise led to increased levels of the *tris-t*-BOC impurity.

Scheme 2



A typical laboratory procedure for the preparation of *N,O -bis-t*-BOC hydroxylamine follows: A pre-cooled mixture(-5 °C) of *t*-BOC anhydride (77.3 g, 354 mmol) and triethylamine (50.6 mL, 363 mmol) in 120 mL of 5:1 petroleum ether/methyl *t*-butyl ether was added dropwise over 45 minutes to a cold (0 °C) aqueous solution of hydroxylamine hydrochloride (12 g, 173 mmol, 120 mL H_2O). The resulting biphasic mixture was stirred vigorously at 0 °C for 6 hours and then allowed to reach ambient temperature while stirring overnight. After layer separation, the organic layer was washed with 2 x 50 mL saturated aqueous NH_4Cl solution, 1 x 50 mL brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was contaminated with residual *t*-BOC anhydride and 2-3% *tris-t*-BOC hydroxylamine.[9] These impurities were easily removed by reslurrying the crude solids in cold petroleum ether. Filtration afforded pure material in 85% yield.[10]

Acknowledgement: The author wishes to thank Dr. Bill G. Jackson and Professor Marvin Miller (University of Notre Dame) for many helpful discussions. Also, the effort of Mr. Joe Turpin to develop the gas chromatography method is greatly appreciated.

References and Notes:

1. Stewart, A.O.; Brooks, D.W. *J.Org.Chem.* **1992**, *57*, 5020-5023.
2. Altenburger, J.M.; Mioskowski, C.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.* **1992**, *35*, 5055-5058.
3. Fluka, 1992 catalog, product number 20426, $92.80/5g.
4. Carpino, L.A.; Giza, C.A.; Carpino, B.A. *J.Am.Chem.Soc.* **1959**, *81*, 955.
5. During the review of this letter for publication, U.S. Patent 5,206,406 was brought to our attention. That document describes the preparation of the title compound using an aqueous sodium carbonate system with good yields.
6. Pope, B.M.; Yamamoto, Y.; Tarbell, D.S. *Organic Syntheses*, **1988**, Coll. Vol. 6, 418.
7. Keller, O.; Keller, W.E.; Van Look, G.; Wersin, G. *Organic Syntheses*, **1989**, Coll. Vol. 7, 70-75.
8. Merck Index, Tenth Edition; Windholz, M. Ed.; Merck & Co., Inc.; Rahway, N.J., **1983**; p.703.
9. Crude purity was determined by gas chromatography. The analytical method employed a 15m x 0.32mm x 0.25μm DB column with flame ionization detector. Flow rate: 1.7 mL/min helium. Oven profile: 40°C (hold 2 min) then ramp to 250°C (@20°C/min) Hold at 250°C for 5 min. Samples were prepared in methylene chloride (5-10 mg/mL).
10. Final purity (>98%) was determined by gas chromatography. The melting point of the reslurried product matched that of a commercially available sample (67-68°C) and the product also gave satisfactory elemental analysis.

(Received in USA 12 July 1993; accepted 31 August 1993)