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The Use of *N,O-bis*(*tert*-Butoxycarbonyl)-hydroxylamine in the Synthesis of *N*-Hydroxylamines and Hydroxamic Acids.

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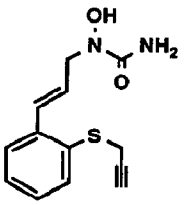
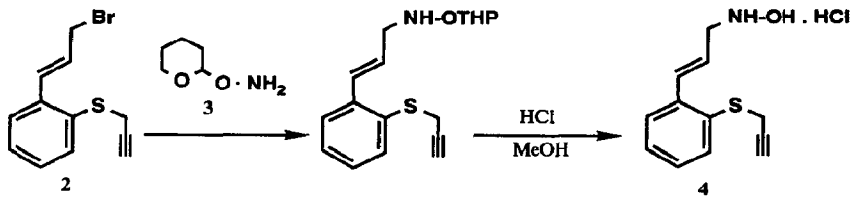
Abstract: *N,O-bis*(*tert*-butoxycarbonyl)-hydroxylamine has been used in the synthesis of 5-lipoxygenase inhibitor LY280810. In addition, this reagent has been utilized to synthesize a number of other hydroxylamine and hydroxamic acid derivatives in high yields.

The enzyme 5-lipoxygenase catalyzes the first step of the arachadonic acid cascade, which leads to the synthesis of peptide and non-peptide leukotrienes, hydroperoxy- and hydroxy-eicosatetraenoic acids and the lipoxins.[1] Since these compounds mediate a number of undesirable inflammatory responses including asthma, inflammatory bowel disease and rheumatoid arthritis,[1] agents which block their production are viewed as potential drugs. LY280810 (**1**, *N*-hydroxy-*N*[3-[2-(2-propynylthio)phenyl]prop-2-enyl]urea), a potent 5-lipoxygenase inhibitor,[2] has been under clinical investigation as a potential therapy for the disease of asthma.



1

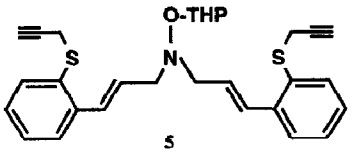
Our goal was to develop a viable synthesis of LY280810 (**1**), and *N*-hydroxylamine **4** was identified as a crucial penultimate intermediate. Initial efforts to synthesize this compound focused upon the alkylation of *O*-THP protected hydroxylamine **3** with allylic bromide **2** followed by deprotection (Scheme 1).



2 **4**

Scheme 1

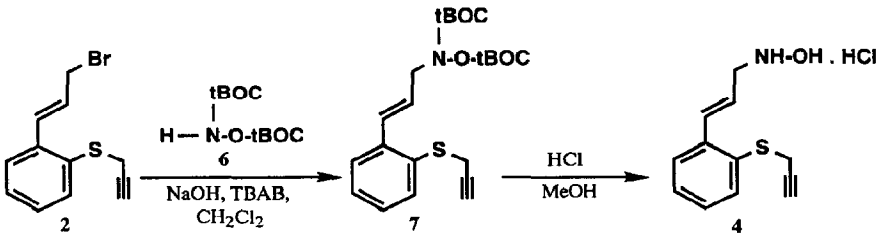
The approach outlined in Scheme 1 has a number of liabilities. First, the synthesis of **3** is an arduous, two step process employing *N*-hydroxyphthalimide and hydrazine,[3] a suspect carcinogen and explosive.[4] Second, the reaction of **2** with **3** suffers from high levels of over-alkylation, forming impurity **5**. Optimum conditions for this alkylation employed an excess (4 equivalents) of **3** in polar aprotic solvents such as DMF or DMSO but still resulted in 20-25% levels of **5**. This impurity was difficult to remove from the desired product. Finally, removal of the THP protecting group led to intractable side products, complicating isolation of **4**.



5

Clearly, an alternative means of supplying the hydroxylamine functionality was required. A strategy employing a bis-protected form of hydroxylamine would eliminate over alkylation by blocking the extra reaction site on nitrogen. Recently, other researchers have utilized *N-t*-BOC-*O*-THP, *N-t*-BOC-*O*-TBDMS, and *N,O-bis*(phenoxycarbonyl) hydroxylamine to prepare hydroxamic acids and N-hydroxy ureas.[5,6] Although the *N-t*-BOC-*O*-THP derivative was found to be useful for the outlined alkylation process, a more desirable goal was to keep both the *N*- and *O*- protecting groups identical, thus simplifying the synthesis of the reagent. Towards that end, *N,O-bis*(*tert*-butoxycarbonyl)-hydroxylamine(**6**) was prepared[7] and tested in the alkylation sequence.

Although alkylation of **6** with **2** (Scheme 2) was successful under a variety of conditions, optimum results were obtained using very mild phase transfer catalysis conditions. Employing tetrabutylammonium bromide (TBAB) and 1N NaOH in CH_2Cl_2 gave essentially quantitative conversion of **2** into **7**. Removal of both *t*BOC groups was then effected with methanolic HCl to afford the desired hydroxylamine as its HCl salt in 87% yield.

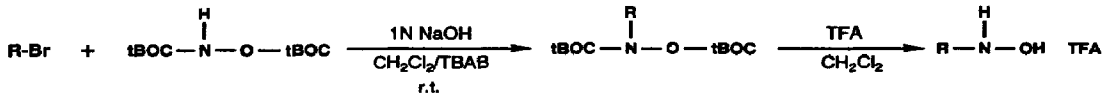


2 7 4

Scheme 2

To further demonstrate the utility of *bis-t*-BOC hydroxylamine and to show the efficacy of the developed alkylation method, we prepared a number of other derivatives. Tables 1 and 2 list the hydroxylamines and hydroxamic acids which were synthesized using this methodology. The reported yields

Table 1. Hydroxylamine Derivatives



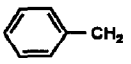
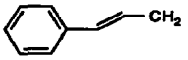
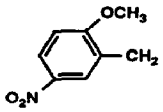
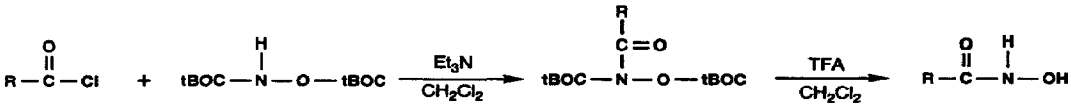
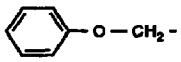
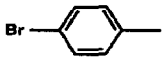
"R"	% Yield of alkylated *bis*-*t*-BOC hydroxylamine	% Yield of deprotected hydroxylamine
	96.5	80.3
	96.6	89.5
	96.3	80.8
	98.0	82.8
	85.3	79.0

Table 2. Hydroxamic Acid Derivatives



"R"	% Yield of *bis*-*t*-BOC hydroxamic acid	% Yield of deprotected hydroxamic acid
	93.9	80.6
	94.0	81.4
	95.2	94.1
	93.2	80.1

represent purified products, for which correct spectroscopic and elemental analysis data were secured. Typical laboratory procedures are outlined in note 8.

In conclusion, we have presented a facile method for the preparation of hydroxylamine and hydroxamic acid derivatives using *N,O-bis*(*tert*-butoxycarbonyl)-hydroxylamine. The procedure is simple and efficient, affording high yields of potentially useful intermediates for the production of 5-lipoxygenase inhibitors.

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References and notes:

1. Musser, J. H.; Kreft, A. F. *J. Med. Chem.* **1992**, *35*, 2501-2524.
2. Unpublished results from the Lilly Research Laboratories.
3. Warrener, R. N.; Cain, E. N. *Angew. Chem. Internat. Edit.* **1966**, *5*, 511.
4. Merck Index, Tenth Edition; Windholz, M. ed.; Merck & Co., Inc.; Rahway, N.J., **1983**; 690-691.
5. Mioskowski, C.; Altenburger, J. M.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.*, **1992**, *33*, 5055-5508.
6. Stewart, A.O.; Brooks, D. W. *J. Org. Chem.* **1992**, *57*, 5020-5023.
7. Staszak, M. A.; Doecke, C. W. *Tetrahedron Lett.* **1993**, *34*, 7043-7044.
8. A typical laboratory procedure for the preparation of *N*-alkylated hydroxylamine derivatives follows: p-Nitrobenzyl bromide (2.5 g, 11.6 mmol) and *bis-t*-BOC hydroxylamine (2.75 g, 11.8 mmol) were dissolved in CH_2Cl_2 (25 mL). The mixture was treated with 1N NaOH (12.7 mL, 12.7 mmol) and TBAB (186 mg, 0.58 mmol) and stirred vigorously overnight at room temperature. Thin layer chromatography (silica, 1:1 ethyl acetate/hexanes) indicated the reaction was complete. The reaction mixture was transferred to a separatory funnel and washed with 2x50 mL water, 1x50 mL brine and dried over $MgSO_4$. Concentration *in vacuo* afforded 4.39 g of thick oil, which crystallized upon standing in the freezer. The crude product was washed with cold petroleum ether to afford 4.12 g of white crystals (96.6% yield).
   Deprotection of the *bis-t*-BOC intermediates was effected as follows: The p-nitrobenzyl derivative from above (2.0 g, 5.4 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to 0°C. Trifluoroacetic acid (4.2 mL, 54.0 mmol) was added and the mixture stirred for 18 hours. The reaction mixture was concentrated *in vacuo* to afford 1.63 g of solids. The crude TFA salt was slurried in 12 mL of 10:1 pet-ether/CH_2Cl_2, cooled, filtered and rinsed with cold pet-ether to afford 1.37g of white solids (89.5%).
   The protected hydroxamic acids were prepared as follows: *N,O-bis-t*-BOC hydroxylamine (3.2 g, 13.7 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0°C. To this was added triethylamine (2.1 mL, 15 mmol) and the mixture recooled to 0°C. p-Bromo-benzoyl chloride was dissolved in 30 mL CH_2Cl_2 and added dropwise to the above mixture. After 18 hours, TLC indicated the reaction was complete. The mixture was transferred to a separatory funnel, diluted with 50 mL water and the layers were separated. The organics were washed with 1x25 mL saturated NH_4Cl, 2x25 mL water and 1x25 mL brine. After drying over $MgSO_4$, concentration *in vacuo* afforded 5.75 g of tan solids. The crude material was slurried in 50 mL of 10:1 pet-ether/CH_2Cl_2. After cooling, filtration and rinsing with cold pet-ether, 5.42 g of white solids were recovered (95.2%). Deprotection was carried out using TFA as described above for the hydroxylamine derivatives.

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