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Rapid Synthesis of Alkoxyamine Hydrochloride Derivatives from Alkyl Bromide and N,N'-Di-tert-butoxycarbonylhydroxylamine [(Boc)₂NOH]

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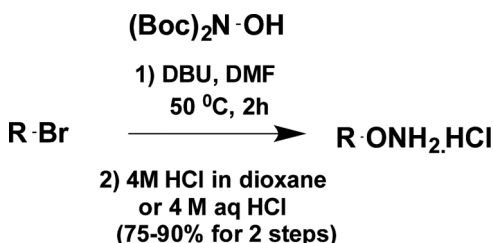
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RAPID SYNTHESIS OF ALKOXYAMINE HYDROCHLORIDE DERIVATIVES FROM ALKYL BROMIDE AND *N,N'*-DI-*TERT*-BUTOXYCARBONYLHYDROXYLAMINE [(Boc)₂NOH]

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GRAPHICAL ABSTRACT



Abstract The conventional route to alkoxyamine hydrochloride derivatives is by reaction of alkyl bromides with *N*-hydroxyphthalimide or *N*-hydroxysuccinimide followed by addition of hydrazine and HCl. Transformation of an alkyl bromide to the corresponding alkoxyamine hydrochloride can be accomplished more rapidly in good yields without using hazardous hydrazine by reaction of (Boc)₂NOH (*N,N'*-di-*tert*-butoxycarbonylhydroxylamine) and alkyl bromide followed by addition of HCl. Alkoxyamine hydrochlorides are powerful reagents in organic synthesis that can be used to synthesize alkoxyimino derivatives after condensation with a ketone or aldehyde.

Keywords Alkoxyamine; alkyl bromide; *O*-alkylation

INTRODUCTION

Synthesis of alkoxyimino derivatives through condensation of an alkoxyamine hydrochloride with a ketone or aldehyde with is a very powerful tool to introduce a heteroatom (i.e., nitrogen) in organic synthesis.^[1] There are two current approaches to the synthesis of R-OH₂ (alkoxyamino derivatives). One approach involves conversion of an alcohol to R-OH₂ using (a) displacement of an alcohol using

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N-hydroxyphthalimide under Mitsunobu conditions and subsequent treatment with hydrazine^[2] or (b) by direct amination through reaction of an alcohol and a substituted oxaziridine.^[3] Another approach consists of substitution of R-Br/I with *N*-hydroxyphthalimide (Gabriel synthesis), *N*-hydroxysuccinimide, or another *N*-protected hydroxylamine.^[4] It appears that new methods for this conversion are needed, and here we have developed a method through which R-ONH₂ can be synthesized rapidly and in good yield from R-Br by reaction with (Boc)₂NOH.

RESULTS

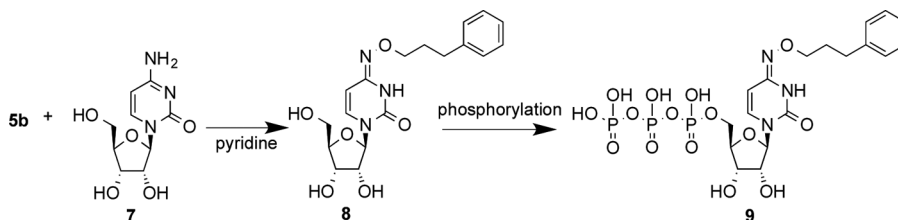
N,N'-Di-*tert*-butoxycarbonylhydroxylamine [(Boc)₂NOH] **1** was synthesized from BzONH₂·HCl as a white solid in good yield.^[5] Reaction of (Boc)₂NOH and R-Br with Hünig's base (DIPEA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethylformamide (DMF) at room temperature is slow and normally requires 12–24 h for reaction completion. The reaction rate can be accelerated by heating at 50 °C in DMF to achieve completion, typically in 1 to 2 h. Unlike the synthesis of R-ONH₂ using R-Br and *N*-hydroxyphthalimide or *N*-hydroxysuccinimide, by this method hydrazine is not needed to convert the acylated *N*-hydroxy adduct to R-ONH₂, and the Boc protecting groups can be removed easily in acidic conditions. Normally, the intermediate R-ON(Boc)₂ is dissolved in CH₂Cl₂ and treated with 4 M HCl (16 eq) in dioxane at room temperature, and the mixture is stirred for 6–12 h. The resulting R-ONH₂·HCl can be isolated as a precipitate by filtration.

Thus, we have demonstrated a practical and efficient synthetic route to R-ONH₂·HCl from R-Br in two steps. The product R-NH₂·HCl can be easily isolated in good yield mainly by precipitation. The starting (Boc)₂NOH is very stable for several months at room temperature and for more than 1 year at 4 °C. Although

Table 1. Results of reaction of R-Br and (Boc)₂NOH, varying group R

R-Br	Product	Yield (%) (2 steps)
2a	2b	85
3a	3b	76 ^a
4a	4b	79 ^a
5a	5b	75
6a	6b	87

^aProduct was isolated from 4 M aqueous HCl.



Scheme 1. Intended biological application of alkoxyamine hydrochloride **5b** and related derivatives for the study of P2Y nucleotide receptor agonists, such as **9** (MRS4062).

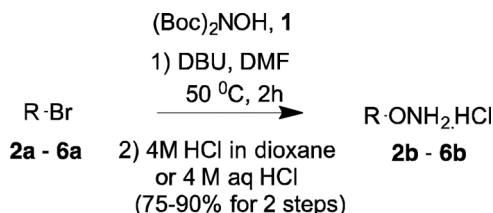
several methods for the synthesis of $R-NH_2 \cdot HCl$ from $R-Br$ are available, improved methods to obtain $R-ONH_2$ are needed to overcome some of the existing drawbacks, most notably use of toxic and hard-to-remove hydrazine in the Gabriel synthesis. One important biological application of $R-ONH_2 \cdot HCl$ (e.g., **5b**) is in the synthesis of N^4 -alkoxy modified cytidine derivatives (Scheme 1), which after phosphorylation have proven to be potent and selective ligands of P2Y nucleotide receptors.^[1d,1e] The target *O*-substituted hydroxylamine compounds are also useful for the orthogonal labeling of proteins and surfaces of cells and biomaterials.^[1a,1b,5]

Chemical Synthesis

***N,N'*-Di-*tert*-butoxycarbonylhydroxylamine (1).** Compound **1** was obtained by a modification of two literature procedures (see the supporting information).^[6,7] The product **1** was isolated as a homogeneous, white crystalline solid. 1H NMR (400 MHz, $CDCl_3$): 1.50. ^{13}C NMR (100 MHz, $CDCl_3$): 150.9, 84.5, 28.0. Melting point ($^{\circ}C$): 87.4 ± 0.5 . HRMS EI m/z ($M-H$); found: 232.1186; calc. for $C_{10}H_{18}O_5N$: 232.1190.

The alkoxyamine hydrochloride derivatives (**2b–6b**) were prepared using the synthetic routes shown in Scheme 2. A typical reaction procedure to obtain $R-ONH_2$ is as follows:

DBU (0.42 mmol, 60 μ L, 1.2 eq) was added to a magnetically stirred mixture of **6a** (0.36 mmol, 83 mg, 1 eq) and **1** (0.34 mmol, 79 mg, 0.95 eq) in 0.5 mL of DMF at room temperature under N_2 . Then, the mixture was heated to $50^{\circ}C$ and stirred for 2 h. The reaction was monitored using thin-layer chromatography (TLC). After completion, the solvent was removed and the mixture was dissolved in EtOAc (50 mL) and washed with water and brine. The organic phase was dried (Na_2SO_4),



Scheme 2. General reaction conditions for *O*-alkylation of hydroxylamine in two steps.

redissolved in CH_2Cl_2 (1 mL) in a round-bottom flask, treated with 4 M HCl in dioxane (5.7 mmol, 1.4 mL, 16 eq), and stirred overnight. The resulting white precipitate was filtered, washed with 1 mL of CH_2Cl_2 , and dried to obtain **6b** (0.30 mmol, 65 mg, 87%).

O-(3-(4-Methoxyphenyl)propyl)hydroxylamine Hydrochloride (6b). ^1H NMR (400 MHz, MeOD): 7.06 (d, $J_1 = 8.52$ Hz, 2H), 6.80 (d, $J_1 = 8.50$ Hz, 2H), 3.97 (t, $J_1 = 6.44$ Hz, 2H), 3.72 (s, 3H), 2.62 (t, $J_1 = 7.44$ Hz, 2H), 1.94 (m, 2H). ^{13}C NMR (100 MHz, MeOD): 158.2, 132.5, 128.9, 113.5, 74.1, 54.2, 30.2, 29.2. HRMS ESI m/z (M + H) found: 182.1183; calc. for $\text{C}_{10}\text{H}_{16}\text{NO}_2$: 182.1181.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. (a) Lemieux, G. A.; Yarema, K. J.; Jacobs, C. L.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1999**, *121*, 4278–4279; (b) Perouzel, E.; Jorgensen, M. R.; Keller, M.; Miller, A. D. *Bioconjug. Chem.* **2003**, *14*, 884–898; (c) Sadamoto, R.; Niikura, K.; Ueda, T.; Monde, K.; Fukuhara, N.; Nishimura, S. I. *J. Am. Chem. Soc.* **2004**, *126*, 3755–3761; (d) Maruoka, H.; Jayasekara, M. P. S.; Barrett, M. O.; Franklin, D. A.; de Castro, S.; Kim, N.; Costanzi, S.; Harden, T. K.; Jacobson, K. A. *J. Med. Chem.* **2011**, *23*(12), 4018–4033; (e) Jayasekara, P. S.; Barrett, M. O.; Ball, C. B.; Brown, K. A.; Kozma, E.; Costanzi, S.; Squarzialupi, L.; Balasubramanian, R.; Maruoka, H.; Jacobson, K. A. *Med. Chem. Commun.* **2013**, *4*(8), 1156–1165.
2. Palandoken, H.; Bocian, C. M.; McCombs, M. R.; Nantz, M. H. *Tetrahedron Lett.* **2005**, *46*(39), 6667–6669.
3. Choong, I. C.; Ellman, J. C. *J. Org. Chem.* **1999**, *64*, 6528–6529.
4. Rougny, A.; Daudon, M. *Bulletin de la Societe Chimique de France* **1976**, 5–6(Pt. 2), 833–838.
5. Fleissner, M. R.; Brustad, E. M.; Kálai, T.; Altenbach, C.; Cascio, D.; Peters, F. B.; Hideg, K.; Peuker, S.; Schultz, P. G.; Hubbell, W. L. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 21637–21642.
6. Gouliaev, A. H.; Brown, W. D.; Wätjen, F. PCT Int. Appl., 2004018466, Mar. 4, 2004.
7. Chilkoti, A.; Gao, W. PCT Int. Appl., 2010096422, Aug. 26, 2010.