A convenient synthesis of *N*-(*tert*-butyloxycarbonyl)aminooxy ethers

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Abstract

Alkyl iodides and alkyl bromides can be conveniently converted to *N*-protected *O*-alkyl aminooxy compounds by treatment with *N*-(*tert*-butyloxycarbonyl)hydroxylamine and DBU. The reaction is tolerant of hydroxyl groups and carboxylate esters which can be further derivatized and thus serve as precursors for a number of functionalized *O*-alkyl aminooxy ethers. The reaction can be accomplished neat or with methylene chloride as solvent. © 2000 Elsevier Science Ltd. All rights reserved.

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In the course of developing aminooxy containing bifunctional linkers, a method was needed for converting an alkyl halide to a Boc-protected aminooxy group. In particular, it was desirable to be able to perform the alkylation in the presence of another functionality such as a hydroxyl group. *N*-Boc-*O*-alkyl aminooxy ethers have been prepared by alkylation of *N*-hydroxysuccinimide followed by conversion of the succinimide to a *tert*-butyloxycarbonyl (Boc) protecting group.[1] *N*-Hydroxyphthalimide has been *O*-alkylated using a Mitsunobu process,[2] and by base-catalyzed alkylation of alkyl halides.[3] It appeared that for our purposes a more desirable method of accomplishing the transformation would be *O*-alkylation of *N*-(*tert*-butyloxycarbonyl)hydroxylamine, also known as *tert*-butyl *N*-hydroxycarbamate.

N-(*tert*-Butyloxycarbonyl)hydroxylamine is commercially available. It has been used in the preparation of hydroxamic acids;[4] however, we are not aware of its use in the formation of *O*-alkyl aminooxy ethers. *N*-allyloxycarbonyl hydroxylamine has been *O*-alkylated with an alkyl iodide using sodium hydride in THF;[5] however, when this method was applied to alkylation with iodoalcohol, **1a**, the iodoalcohol was consumed without forming the desired product, **2a**. Presumably, the major reaction was polymerization of the iodoalcohol.

N-Fmoc-hydroxylamine has reportedly been *O*-alkylated with a solid phase trityl chloride derivative, probably by an S_N1 type process, using diisopropylethylamine (DIPEA) as base.[6] When DIPEA was used in an attempt to react *N*-(*tert*-butyloxycarbonyl)hydroxylamine with compound **1e**, no reaction took place at room temperature. Only after heating at 60°C for 24 h was a poor yield of the desired product,

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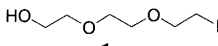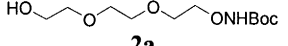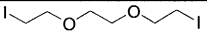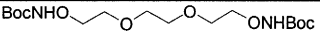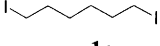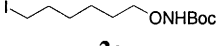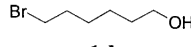
2e, obtained. Several other non-nucleophilic bases were tested, and both DBU and tetramethylguanidine gave higher yields of *O*-alkylated product under milder conditions. DBU became the base of choice because of its ease of use and the fact that it can serve as both base and solvent. The reaction can be run in neat DBU or with a co-solvent such as methylene chloride or DMF.

Table 1 shows the results of a number of experiments with several alkyl halides in reaction with *N*-(*tert*-butyloxycarbonyl)hydroxylamine according to the equation depicted in Scheme 1.[7]
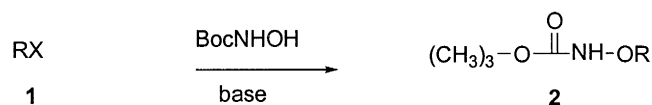
Scheme 1.

Table 1

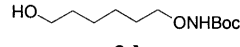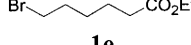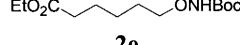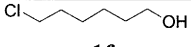| RX	Product	Stoichiometry[a] BocNHOH/DBU	Time/temp (hours/°C)	Solvent	Yield (%)
1a	**2a**	0.83/1.0	18-24/70	DMF	61
		0.83/1.0	48/20	none	68
		0.83/1.0	24/70	none	72
		0.66/1.0	24/55	none	67
		0.66/1.0[b]	60/20	none	60
		0.66/1.0	18-24/120	DMF	29
1b	**2b**	2.5/2.5	1/20	none[c]	66
1c	**2c**	0.26/0.25	18-24/20	none	68
		0.52/0.50	18-24/20	none	31
		0.40/0.48	18-24/20	none	44
1d	**2d**	0.83/1.0	18-24/20	CH_2Cl_2	77
		0.83/1.0	18-24/20	CH_2Cl_2	80
		0.83/1.0	18-24/20	CH_2Cl_2	80
		0.91/1.1	18-24/20	CH_2Cl_2	75
1e	**2e**	1.5/3.0	18-24/20	none	46
		0.83/5.0	18-24/20	none	33
		2.5/5.0	18-24/20	none	69
		2.5/5.0	18-24/20	CH_2Cl_2	59
		2.5/5.0[d]	24/60[e]	none	26
1f	No Reaction	0.80/1.0	18-24/20	CH_2Cl_2	–

[a] Mole equivalents of BocNHOH/mole equivalents of DBU used with one equivalent of RX.

[b] Tetramethylguanidine was used as base.

[c] The reaction went for 1h without solvent then for 2.0 h with CH_2Cl_2.

[d] DIPEA was used as base.

[e] No reaction was observed after five days at 20°C.

A simple procedure has been developed which can be performed without rigorous exclusion of oxygen or water. The reaction is compatible with hydroxyl groups and carboxylate esters. A typical reaction procedure is as follows for the preparation of compound **2e**: To a magnetically-stirred mixture of 500 mg (3.76 mmol) of N-(*tert*-butyloxycarbonyl)hydroxylamine (Aldrich Chemical Co.) and 267 μL (335 mg, 1.50 mmol) of ethyl 6-bromohexanoate was added 1.12 mL (1.14 g, 7.51 mmol) of DBU over a period of approximately 1 min. The mixture was allowed to stir for 24 h, at which time it had partially solidified. The mixture was dissolved in 100 mL of CH_2Cl_2, and the resulting solution was shaken in a separatory funnel with four 25 mL portions of 1N HCl and 25 mL of brine. The aqueous layers were discarded, and the CH_2Cl_2 layer was dried ($MgSO_4$), filtered, and concentrated. The resulting yellow oil was purified by silica gel chromatography (3:7, EtOAc:hexane) to provide 285 mg of compound **2e**.

References

1. Lemieux, G. A.; Yarema, K. J.; Jacobs, C. L.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1999**, *121*, 4278–4279.

2. Barlaam, B.; Hamon, A.; Maudet, M. *Tetrahedron Lett.* **1998**, *39*, 7865–7868.

3. Mikola, H.; Hanninen, E. *Bioconjugate Chem.* **1992**, *3*, 182–186.

4. Altenburger, J. M.; Mioskowski, C.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.* **1992**, *33*, 5055–5058.

5. Lang, I.; Donze, N.; Garrouste, P.; Dumy, P.; Mutter, M. *Journal of Peptide Science* **1998**, *4*, 72–80.

6. Mellor, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311–3314.

7. Analytical data for compounds **2a–e** are as follows: Compound **2a**: ^{1}H NMR CDCl$_3$ (δ) 1.50 (s, 9H), 3.61 (m, 2H), 3.69 (s, 4H), 3.74 (m, 4H), 4.03 (m, 2H), 7.83 (brd s, 1H); ^{13}C NMR CDCl$_3$ (δ) 28.3, 61.6, 69.1, 70.2, 70.5, 72.8, 75.3, 81.6, 157.1; HRMS (FAB) calculated for (M+Na) $C_{11}H_{23}NaNO_6$: 288.1423. Found: 288.1426. Compound **2b**: ^{1}H NMR CDCl$_3$ (δ) 1.48 (s, 18H), 3.68 (s, 4H), 3.72 (m, 4H), 4.03 (m, 4H), 7.80 (brd s, 2H); ^{13}C NMR CDCl$_3$ (δ) 28.2, 69.0, 70.3, 75.2, 81.3, 156.6; HRMS (MALDI–FTMS) calculated for (M+Na) $C_{16}H_{32}NaN_2O_8$: 403.2056. Found: 403.2040. Compound **2c**: ^{1}H NMR CDCl$_3$ (δ) 1.40 (m, 2H), 1.48 (s, 9H), 1.61 (t, 2H), 1.83 (t, 2H), 3.19 (t, 2H), 3.84 (t, 2H), 7. 08 (brd s, 1H); ^{13}C NMR CDCl$_3$ (δ) 7.1, 25.1, 28.0, 28.4, 30.4, 33.5, 76.8, 81.8, 157.1; HRMS (ES) calculated for (M+Na) $C_{11}H_{22}INaNO_3$: 366.0542. Found: 366.0547. Compound **2d**: ^{1}H NMR CDCl$_3$ (δ) 1.40 (m, 4H), 1.48 (s, 9H), 1.58–1.69 (brd m, 4H), 3.64 (t, 2H), 3.85 (t, 2H), 7. 40 (brd s, 1H); ^{13}C NMR CDCl$_3$ (δ) 25.6, 25.8, 28.1, 28.4, 32.6, 62.8, 76.8, 81.7, 157.2; HRMS (ES) calculated for (M+Na) $C_{11}H_{23}NaNO_4$: 256.1525. Found: 256.1530. Compound **2e**: ^{1}H NMR CDCl$_3$ (δ) 1.25 (t, 3H), 1.42 (m, 2H), 1.50 (s, 9H), 1.65 (m, 4H), 2.30 (t, 2H), 3.83 (t, 2H), 4.12 (q, 2H), 7.28 (s, 1H); ^{13}C NMR CDCl$_3$ (δ) 14.4, 24.9, 25.6, 27.8, 28.4, 34.3, 60.4, 76.6, 81.7, 157.1, 173.8; HRMS (MALDI–FTMS) calculated for (M+Na) $C_{13}H_{25}NaNO_5$: 298.1630. Found: 298.1631.