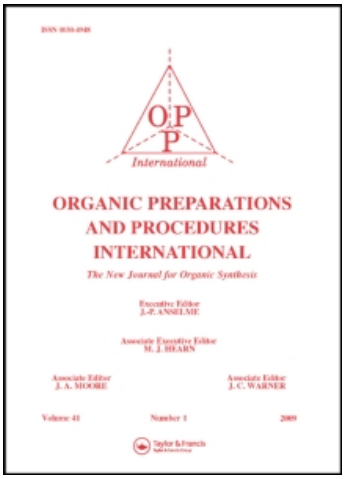

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OPPI BRIEFS

PREPARATION OF *O*-[2-(2-PYRIDYL)ETHYL]- AND *O*-[2-(TRIMETHYLSILYL)ETHYL]HYDROXYLAMINES

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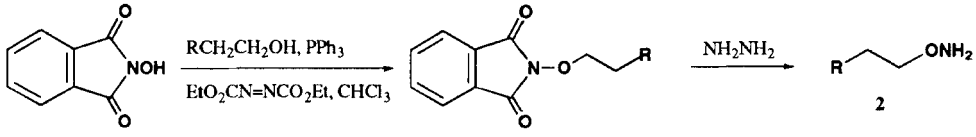
Recently, 2-(2-pyridyl)ethyl and 2-(trimethylsilyl)ethyl groups have been developed as protective groups for carboxylic acids[1] and other functional groups.[1a,2] In our current work, we required the protection of hydroxamic acids with the above mentioned protective groups and explored the practical synthesis of *O*-[2-(2-pyridyl)ethyl]- and *O*-[2-(trimethylsilyl)ethyl]hydroxylamines from readily available starting materials.

Initially, we attempted the synthesis of these compounds following a general literature procedure,[3] for the synthesis of *O*-alkylhydroxylamines *via* *N*-alkoxyphthalimide intermediates by use of the Mitsunobu reaction.[4] Although ordinary *N*-alkoxyphthalimides were synthesized under the reported conditions, we could not obtain **1a** or **1b** in satisfactory yields despite repeated attempts. Finally, we found that yields of **1a** and **1b** were dramatically improved by changing the solvent from tetrahydrofuran to chloroform, and that reaction time was shortened considerably. Although the



1a) R = 2-Pyridyl **b)** R = $SiMe_3$

reason for the effect of solvent on yield is still obscure, we assume that the enhancement of reaction rate by use of chloroform as solvent may help to minimize undesirable side-reactions. The free *O*-substituted hydroxylamines (**2a**, **2b**) were subsequently obtained in high yield by the conventional method.[5]

EXPERIMENTAL SECTION

Melting points are uncorrected and were taken on a Yanagimoto hot-stage melting point apparatus. ^1H NMR spectra were measured on a JEOL JNM-PMX60SI spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. Infrared (IR) spectra were recorded on a JASCO IR810 spectrometer. Mass (MS) spectra were obtained with a JEOL JMS-DX300 spectrometer with a

direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

TABLE. Synthesis of *N*-Substituted Phthalimides **1**

Product	Solvent	Time (hrs)	Yield (%)
1a	THF[a]	1	19
1a	THF	24	32
1a	$CHCl_3$	1	76
1b	THF	18	23
1b	THF	68	43
1b	CH_3CN	20	—[b]
1b	CH_2Cl_2	20	39
1b	$CHCl_3$	1	77
1b	$CHCl_3$	24	85

a) Tetrahydrofuran. b) Complex reactions occurred leading to several unidentified products (TLC).

***N*-[2-(2-Pyridyl)ethoxy]phthalimide(1a).**- Diethyl azodicarboxylate (1.94 g, 11.1 mmol) was added to a solution of 2-(2-pyridyl)ethanol (1.14 g, 9.3 mmol), *N*-hydroxyphthalimide (1.51 g, 9.3 mmol) and triphenylphosphine (2.45 g, 9.3 mmol) in dry $CHCl_3$ (30 mL) with ice cooling, and the mixture then allowed to warm to room temperature. After 1 hr the solvent was removed *in vacuo*. The residue was diluted with AcOEt (30 mL) and the solution was extracted with 10% HCl (10 mL x 2). The aqueous layer was basified with 10% Na_2CO_3 (30 mL) and extracted with AcOEt (80 mL x 2). The combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a column of silica gel with benzene-AcOEt (1:1) as the eluent to give **1a** (1.88 g, 75.5%), mp. 75-76° (benzene-hexane).

^{1}H NMR: δ 3.30 (2H, t, J = 7.0), 4.67 (2H, t, J = 7.0), 6.97 (3H, m), 7.80 (4H, s), 8.53 (1H, d, J = 6.0). IR(KBr): 1780, 1720 (C=O) cm^{-1}. MS: m/z (relative intensity) 163 (M^+-C_7H_8N, 4), 147 (6), 122 (89), 106 (100), 93 (22), 78 (21), 65 (8), 51 (8).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.07; H, 4.63; N, 10.41

***O*-[2-(2-Pyridyl)ethyl]hydroxylamine(2a).**- A solution of anhydrous NH_2NH_2 (50 mg, 2.89 mmol) and **1a** (388 mg, 1.45 mmol) in EtOH (10 mL) was stirred for 45 min at room temperature. Insoluble products were filtered off and the filtrate was concentrated. The residue was diluted with ether (10 mL), insoluble materials were filtered, and the filtrate was concentrated. The crude product was chromatographed on a column of silica gel with AcOEt as the eluent to give **2a** (181 mg, 90.6%).

^{1}H NMR: δ 3.07 (2H, t, J = 6.0), 4.03 (2H, t, J = 6.0), 4.87 (2H, s), 6.93-7.73 (3H, m), 8.43-8.67 (1H, m). IR (neat): 3400-3200, 3000-2800, 1590, 1475, 1430, 1050, 1020 cm^{-1}.

2a was converted to the di-HCl salt, mp. 170-172° (MeOH).

Anal. Calcd for $C_7H_{12}Cl_2N_2O$: C, 39.83; H, 5.73; N, 13.27. Found: C, 39.77; H, 5.68; N, 13.35

***N*-(2-Trimethylsilylethoxy)phthalimide(1b).**- This compound was prepared from 2-trimethylsilylethanol by the procedure described above for **1a**. Slow addition of diethyl azodicarboxylate to the reaction mixture is important to obtain a high yield of **1b**, mp. 57-58° (hexane).

^{1}H NMR: δ 0.07 (9H, s), 1.20 (2H, t, *J* = 9.0), 4.23 (2H, t, *J* = 9.0), 7.50-7.90 (4H, m). IR(KBr): 1790, 1730 (C=O) cm^{-1}. MS: m/z (relative intensity) 248 (M^+-CH_3, 0.4), 220 (100), 163 (3), 146 (30), 130 (7), 90 (5).

Anal. Calcd for $C_{13}H_{17}NO_3Si$: C, 59.29; H, 6.51; N, 5.32. Found: C, 59.28; H, 6.50; N, 5.03

***O*-(2-Trimethylsilylethyl)hydroxylamine(2b).**- A mixture of **1b** (4.12g, 15.7 mmol), 80% $NH_2NH_2 \cdot H_2O$ (1.0 mL, 16.4 mmol), and EtOH (45 mL) was stirred overnight at room temperature. Concentrated HCl (3.9 mL) was added to the mixture with cooling. After filtration of insoluble materials the filtrate was concentrated to dryness. The residual solid was recrystallized from *iso*-Pr_2O to give pure **2b**•HCl (2.15g, 81.0%), mp. 138-140°.

^{1}H NMR: δ 0.03 (9H, s), 1.09 (2H, t, *J* = 8.5), 4.34 (2H, t, *J* = 8.5), 10.1 (3H, brs). IR(KBr): 3450, 2950, 2680, 1570, 1250, 860, 830 cm^{-1}.

Anal. Calcd for $C_5H_{16}ClNOSi$: C, 35.38; H, 9.50; N, 8.25. Found: C, 35.17; H, 9.26; N, 8.22

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