A New Synthesis of *N*-Hydroxyamides Using Trimethylsilyl Protection

Łucja Nakonieczna,* Andrzej Chimiak

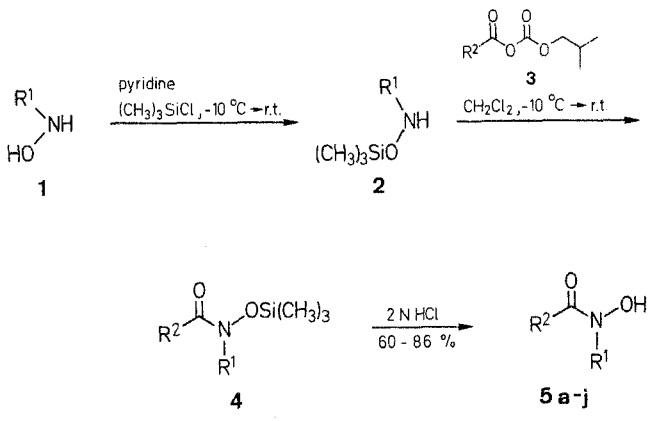
Department of Organic Chemistry, Technical University of Gdańsk, PL-80-952 Gdańsk, Poland

The concept of transient hydroxylamine oxygen protection for the unambiguous synthesis of *N*-hydroxyamides has been applied in the amino acid field. First, hydroxylamines **1** were silylated in pyridine with chlorotrimethylsilane; then **2** was immediately *N*-acylated with mixed anhydride **3** of a protected amino acid or peptide; and finally, the *O*-trimethylsilyl protection was removed during the isolation procedure giving pure *N*-hydroxyamides **5**.

Hydroxylamines are ambident reagents. In spite of this well known fact, simple condensing agents have been applied in the synthesis of *N*-hydroxycarboxamides (hydroxamic acids) and it is not surprising that the yields of hydroxamic acids were low.[1,2] Even with procedures with conditions specially chosen to favor the *N*-acylation process, as, for example, our method using *N,N*-dimethylchloromethaniminium chloride,[3] some undesirable *O*-acyl derivatives of hydroxylamine are formed in a few cases. We therefore concluded that a transient oxygen protection of the hydroxylamine function would be advantageous for an unambiguous, effective synthesis of *N*-hydroxycarboxamides. We chose the trimethylsilyl group since it is easily introduced and removed, and is stable under acylation conditions.

The idea of protection of the hydroxyl group by silylation is well documented; examples include that of serine for peptide synthesis,[7] as well as sugar hydroxyl protection in nucleoside synthesis.[8,9] Mono *N*-, *O*- and *N,O*-di trimethylsilyl derivatives of hydroxylamines have been described in the literature.[4,5,6] We have found by ^{1}H-NMR analysis that chlorotrimethylsilane in pyridine introduces only one silyl group on the hydroxylamine molecule.

In our one-pot procedure for the synthesis of *N*-substituted *N*-hydroxycarboxamides, *N*-substituted hydroxylamine **1** dissolved in dry pyridine is treated with a six-fold excess of chlorotrimethylsilane. *N*-Substituted *O*-trimethylsilylhydroxylamine **2** is directly acylated without isolation with mixed anhydride **3** (formed from an *N*-proteced amino acid or peptide and isobutylcarbonochloridate in the presence of *N*-methylmorpholine). Compounds **4**, which are thus formed, are not isolated; the trimethylsilyl protecting group was immediately removed in the work-up procedure. The total yield of pure *N*-substituted *N*-hydroxycarboxamide **5**, after all steps, was satisfactory to good (60–86%).



Yield, physical, and spectral data for the *N*-alkyl-*N*-hydroxycarboxamides **5** obtained by this method, are reported in Tables 1 and 2.

Our experiments have shown, that the structure of the *N*-substituted-*O*-trimethylsilylhydroxylamine **2** does not have a significant effect on the yield of the synthesized *N*-hydroxycarboxamides **5** (cf. **5a, b, c** in Table 1). However, the synthesis of *N*-hydroxycarboxamides **5** with another tertiary amine (triethylamine) present during the generation of the mixed anhydride **3** results in smaller yields of products **5** (cf. **5a, b, c** in Table 1 – yields in brackets), because *N*-hydroxyurea derivatives were formed, a result that has been confirmed by other research groups.[10,11]

Silylated *N*-hydroxyamides have been obtained earlier by the reaction of *N*-hydroxyamides with silylating reagents[12,13,14] or in the reaction of acyl chlorides with *N,O*-bis(silyl-) or *N,N,O*-tris(silyl)hydroxylamine.[12,15,16] However, employment of silylated *N*-hydroxyamides for the synthesis of *N*-hydroxyamides, has until now been limited to the use of isolated *N,N,O*-tris(trimethylsilyl)hydroxylamine.[15]

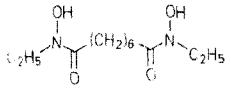
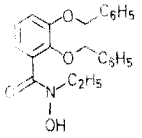
We intend to extend our method to other acylations of *N*-substituted-*O*-trimethylsilylhydroxylamines **2**. It will be applied to the synthesis of siderophores and their analogues, as well as to other ligands, forming complexes with other metals.[17]

All melting points are uncorrected. The IR and ^{1}H-NMR spectra were recorded on Jena-Zeiss UR-10 and Varian EM-360A instruments, respectively.

N-Alkyl-N-hydroxycarboxamides (N-Alkyl-hydroxamic Acids) 5; General Procedure:

Chlorotrimethylsilane (3 ml, 0.024 mol) is added dropwise to a stirred solution of *N*-alkylhydroxylamine (**1**; 0.004 mol) in dry pyridine (12 ml)

Table 1. *N*-Alkyl-*N*-hydroxycarboxamides (Hydroxamic Acids) **5** Prepared

Product		Yield[a] (%)	m.p. (°C) (solvent)	Molecular Formula[b] or Lit. m.p. (°C)
5a	Z-L-Ala-N(OH)C_2H_5	85 (84)[d]	92 ($CHCl_3$/hexane)	90–92[3]
5b	Z-L-Ala-N(OH)$CH(CH_3)C_6H_5$	85[c](67)[d]	126–128 (ethyl acetate/hexane)	126–128[3]
5c	Z-L-Ala-N(OH)C_6H_{11}-*c*	86[c](62)[d]	104–105 (ethyl acetate/hexane)	$C_{17}H_{24}N_2O_4$ (320.3)
5d	BOC-Gly-N(OH)C_6H_{11}-*c*	86	85–86 ($CHCl_3$/hexane)	$C_{13}H_{24}N_2O_4$ (272.3)
5e	Z-Gly-L-Ala-N(OH)C_2H_5	60	150–151 (ethyl acetate/hexane)	$C_{15}H_{21}N_3O_5$ (323.3)
5f	α-Z-ε-BOC-L-Lys-N(OH)$(C_2H_5$	60	90–92 (ethyl acetate/hexane)	$C_{21}H_{33}N_3O_6$ (423.6)
5g	Z-DL-Phe-N(OH)C_2H_5	74	117–118 (ethyl acetate/hexane)	$C_{19}H_{22}N_2O_4$ (342.4)
5h	Z-L-Pro-N(OH)C_2H_5	66	87–89 ($CHCl_3$/hexane)	$C_{15}H_{20}N_2O_4$ (292.3)
5i		65	92–93 (ethyl acetate/hexane)	$C_{12}H_{24}N_2O_4$ (260.3)
5j		80	76–78 ($CHCl_3$/hexane)	$C_{23}H_{23}NO_4$ (377.4)

[a] Yield of crystallized product **5** based on **3**.

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.32, N ±0.31.

[c] After crystallization of compound **5**, *i*-$C_4H_9OCON(OH)CH(CH_3)C_6H_5$ and *i*-$C_4H_9OCON(OH)C_6H_{11}$-*c* were found (TLC) in the mother liquor.

[d] The yields of compound **5**, obtained in the presence of triethylamine are given in parentheses. *i*-$C_4H_9OCON(OH)C_2H_5$ (traces). *i*-$C_4H_9OCON(OH)CH(CH_3)C_6H_5$ and *i*-$C_4H_9OCON(OH)C_6H_{11}$-*c* were found (TLC) in the mother liquor.

Table 2. Spectral Data for *N*-Alkyl-*N*-hydroxycarboxamides **5**

Compound	IR (KBr) ν (cm^{-1}) –CO–N(OH)–	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
5a	1645	1.0–1.6 (m, 6H, $2CH_3$); 3.7 (q, 2H, J = 7 Hz, CH_2N); 4.8 (m, 1H, CH); 5.0 (s, 2H, $C\underline{H}_2C_6H_5$); 5.9 (m, 1H, NH); 7.3 (s, 5H, C_6H_5); 8.9 (br s, 1H, OH)
5b	1610	1.35 (d, 3H, J = 7 Hz, $C_6H_5CHC\underline{H}_3$); 1.65 (d, 3H, J = 7 Hz, $\underline{H}_3CCHNH$); 5.0 (m, 1H, $CH_3C\underline{H}NH$); 5.25 (s, 2H, $C\underline{H}_2C_6H_5$); 5.8–6.2 (m, 2H, $C_6H_5C\underline{H}CH_3$ and NH); 7.5 (s, 10H, $2C_6H_5$); 9.0 (br s, 1H, OH)
5c	1600	1.3 (d, 3H, J = 8 Hz, CH_3); 1.6 (br s, 10H, C_6H_{10+1}); 4.2 (m, 1H, C_6H_{10+1}); 4.7 (m, 1H, $C\underline{H}CH_3$); 5.0 (s, 2H, $C\underline{H}_2C_6H_5$); 5.8 (m, 1H, NH); 7.2 (s, 5H, C_6H_5); 8.5 (s, 1H, OH)
5d	1640	1.37 [s, 9H, $(CH_3)_3$]; 1.6 (br s, 10H, C_6H_{10+1}); 3.9–4.33 (m, 3H, CH_2 and C_6H_{10+1}); 5.6 (m, 1H, NH); 8.77 (m, 1H, OH)
5e	1620	1.2 (2t, 6H, J = 6 Hz, $2CH_3$); 3.6 (q, 2H, J = 7 Hz, CH_2N); 3.8 (d, 2H, J = 6 Hz, CH_2CO); 4.8 (m, 1H, $C\underline{H}CH_3$); 5.03 (s, 2H, $C\underline{H}_2C_6H_5$); 5.9 (br s, 1H, NH); 7.23 (s, 5H, C_6H_5); 8.5 (m, 1H, OH)
5f	1590	1.1 (t, 3H, J = 7 Hz, CH_3); 1.37 [s, 15H, $(CH_3)_3$ and $(CH_2)_3$]; 3.0 (m, 2H, $C\underline{H}_2NH$); 3.6 [q, 2H, J = 7 Hz, $C\underline{H}_2N(OH)$]; 4.73 (m, 1H, $C\underline{H}NH$); 4.95 (s, 2H, $C\underline{H}_2C_6H_5$); 5.77 (m, 2H, 2NH); 7.2 (s, 5H, C_6H_5); 8.93 (br s, 1H, OH)
5g	1620	1.0 (t, 3H, J = 7 Hz, CH_3); 3.0 (d, 2H, J = 7 Hz, $C\underline{H}_2CH$); 3.5 (q, 2H, J = 7 Hz, CH_2N); 4.9 (s, 2H, $C\underline{H}_2C_6H_5$); 5.1 (m, 1H, CHCO); 5.8 (m, 1H, NH); 7.1, 7.2 (2s, 10H, $2C_6H_5$); 8.4 (br s, 1H, OH)
5h	1635	1.1 (t, 3H, J = 7 Hz, CH_3); 2.0 [m, 4H, $(CH_2)_2$]; 3.53 (m, 4H, $2CH_2N$); 4.87 (m, 1H, CH); 5.07 (s, 2H, CH_2O); 7.3 (s, 5H, C_6H_5); 9.5 (m, 1H, OH)
5i	1610, 1640	1.0–1.7 [m, 14H, $2CH_3$ and $(CH_2)_4$]; 2.3 (m, 4H, $2CH_2CO$); 3.55 (q, 4H, J = 7 Hz, $2CH_2N$); 8.7 (m, 2H, 2OH)
5j	1600	1.1 (t, 3H, J = 7 Hz, CH_3); 3.5 (m, 2H, CH_2N); 5.05, 5.15 (2s, 4H, $2CH_2O$); 7.1 (m, 3H, C_6H_3); 7.3, 7.4 (2s, 10H, $2C_6H_5$); 8.5 (m, 1H, OH)

cooled to −10 °C. After 15 minutes at room temperature the reaction mixture is again cooled to −10 °C. Then the mixed anhydride [**3**, 0.002 mol; also cooled to −10 °C; synthesized from *N*-protected amino acid or peptide (0.0021 mol) dissolved in dry dichloromethane (6 ml), *N*-methylmorpholine (0.22 ml, 0.002 mol) and isobutyl chloroformate (0.27 ml, 0.002 mol)] is added. The solution is stirred for several hours at room temperature. Then pyridine and dichloromethane are evaporated at reduced pressure. The residue is acidified with 2 normal hydrochloric acid (to pH 2) and extracted with ethyl acetate (2 × 10 ml). The ethyl acetate layer is washed with 0.5 normal hydrochloric acid (10 ml), water (20 ml), 3% sodium hydrogen carbonate solution (10 ml) and dried with magnesium sulfate. After filtration and evaporation one obtains hydroxamic acids **5**, which are purified by recrystallization (Tables 1 and 2). The purity of the prepared hydroxamic acids is checked by IR and ^{1}H-NMR spectroscopy and by TLC (silica gel, 2-propanol/hexane, 1:9, and hexane/ethyl acetate/ethanol, 6:2:1).

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