One-Pot Synthesis of *N*-Substituted Hydroxamic Acids Using *N,N*-Dimethylchloromethaniminium Chloride

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N,N-dimethylchloromethaniminium chloride formed from dimethylformamide and oxalyl dichloride is an efficient reagent for the synthesis of *N*-substituted hydroxamic acids from carboxylic acids and *N*-substituted hydroxylamines in the presence of a base.

We have recently performed syntheses of siderophores and their analogs[1]. The *N*-hydroxycarboxamide group is a key fragment of many siderophores[2,3,4] so we believe that a convenient synthesis of this group is crucial for further progress.

We have employed two methods for the preparation of hydroxamic acids; the unambiguous acylation of *N*-benzyloxyamino acids[5] and the selective acylation with *o*-Nps-*N*-carboxyanhydrides[6].

Unfortunately, these methods are useful for *N*-hydroxypeptides only. We therefore tried to find a more general method for the synthesis of *N*-substituted *N*-hydroxycarboxamides (**5**). Up to now, methods using mixed anhydrides[7,8], *N*-carboxyanhydrides of amino acids[9], active esters[10], or dicyclohexylcarbodiimide (DCC)[11,12] have been tried. However, the problem of simultaneous *N*- and *O*-acylation has not been solved yet. As a result, only two methods are still used for the preparation of *N*-hydroxycarboxamides: a rather drastic method starting with the acid chlorides[13,14,15] and another one which starts from the not very reactive methyl esters[13].

We now report that *N,N*-dimethylchloromethaniminium chloride (**2**) reacts smoothly with various carboxylic acids (**1**) in the presence of a tertiary amine and then with an *N*-alkylhydroxylamine (**4**) under mild conditions to give *N*-substituted hydroxamic acids (**5**) in good yields. The condensation reagent, *N,N*-dimethylchloromethaniminium

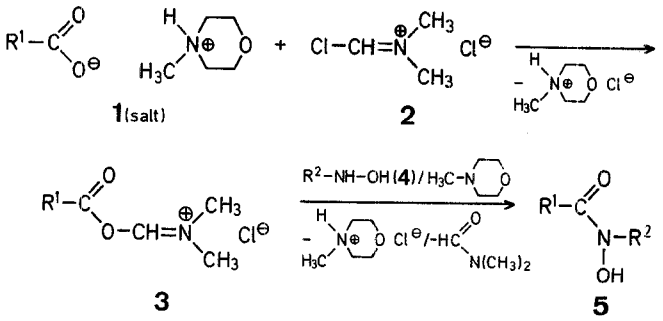
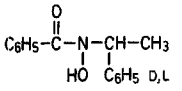
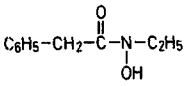
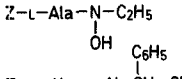
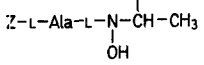
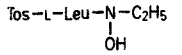
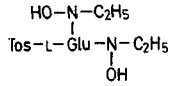
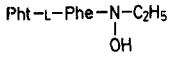
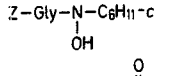
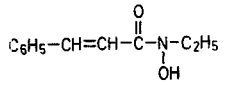
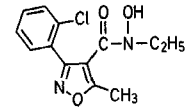


Table 1. *N*-Alkyl-*N*-hydroxycarboxamides (Hydroxamic Acids, **5**) prepared

Product	Yield [%]	m.p. [°C] (solvent)	$[\alpha]_D^{20}$ (solvent)	Molecular Formula[a]	M.S. *m/e* (M^+)
5a 	54 (37)[b]	116° (ethanol/water)	–	$C_{15}H_{15}NO_2$ (241.3)	–
5b 	66	66° (ether/hexane)	–	$C_{10}H_{13}NO_2$ (179.2)	–
5c 	64	90–92° ($CHCl_3$/hexane)	very low	$C_{13}H_{18}N_2O_4$ (266.3)	–
5d 	60 (26)[b]	126–128° (ethyl acetate/hexane)	+44° (*c* 1, $CHCl_3$)	$C_{19}H_{22}N_2O_4$ (342.3)	–
5e 	68	162–164° (ethyl acetate/hexane)	+29° (*c* 3, $CHCl_3$)	$C_{15}H_{24}N_2O_4S$ (328.4)	–
5f 	56[c]	150–152° (ethyl acetate/hexane)	+67° (*c* 2, ethanol)	$C_{16}H_{25}N_3O_6S$ (387.4)	–
5g 	34 (26)[b]	146–147° ($CHCl_3$/hexane)	−118° (*c* 2, $CHCl_3$)	$C_{19}H_{18}N_2O_4$ (338.35)	–
5h 	48 (36)[b]	132–133° ($CHCl_3$/hexane)	–	$C_{16}H_{22}N_2O_4$ (306.4)	–
5i 	70	95–97° ($CHCl_3$/hexane)	–	$C_{11}H_{13}NO_2$ (191.2)	191
5j 	70	146–148° (ethyl acetate/hexane)	–	$C_{13}H_{13}ClN_2O_3$ (280.7)	280, 281

[a] The microanalyses were in satisfactory agreement with the calculated values: C ± 0.36, H ± 0.15, N ± 0.30.

[b] Yield [%] of *O*-acyl derivative, as analyzed by ^{1}H-N.M.R. spectrometry.

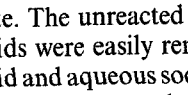
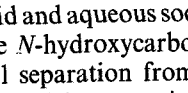
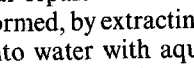
[c] (α + γ)-Tos-L-Glu-N(OH)-C_2H_5 was formed in 20% yield (as indicated by T.L.C.); the isomers were not separated.

chloride (**2**), is easily available from the reaction of dimethylformamide with oxalyl dichloride in a suitable solvent such as di- or trichloromethane[16,17,18]. First, nucleophilic attack of the carboxylate anion on reagent **2** gives the acyloxymethaniminium chloride **3**, which then reacts with the added *N*-alkylhydroxylamine **4** to give the *N*-alkyl-*N*-hydroxycarboxamide **5**.

The syntheses of **2** and **3** were performed at − 20 °C; then, the *N*-alkylhydroxylamine and *N*-methylmorpholine were added and the mixture was allowed to warm up to room temperature. After a few hours, the *N*-substituted hydroxamic acids could be isolated by extraction with ethyl acetate. The unreacted *N*-alkylhydroxylamines and carboxylic acids were easily removed during subsequent washing with acid and aqueous sodium hydrogen carbonate. The acidity of the *N*-hydroxycarboxamides **5** was utilized for the additional separation from the *O*-acyl derivative, which may be formed, by extracting the hydroxamic acid from ethyl acetate into water with aqueous 1 normal sodium hydroxide and, after acidification, reextracting it into ethyl acetate. In this manner, we obtained chromatographically pure, $FeCl_3$-positive, *N*-hydroxycarboxamides (**5**) in good yields. In several cases, when the carboxylic acid **1** or the *N*-substituted hydroxylamine **4** contained bulky groups we observed formation of *O*-acylhydroxylamines as side products (cf **5a, d, g, h** in Table 1).

The present method was also applied to the synthesis of *N*-ethyl-*N*-hydroxycarboxamides of several benzyloxycarbonyl-ω-amino acids such as β-alanine, γ-aminobutyric acid, and ε-aminocaproic acid (Table 2). These compounds were used in syntheses of amino acids analogues of citric acid siderophores[1].

Table 2. *N*-Ethyl-*N*-hydroxyamides of Benzyloxycarbonyl-ω-amino Acids (**5**) prepared

Product	Yield [%]	m.p. [°C] (solvent)	Molecular[a] Formula	M.S. *m/e* (M^+)
5k 	73	64–66° ($CHCl_3$/hexane)	$C_{13}H_{18}N_2O_4$ (266.3)	266, 267
5l 	57	75–78° ($CHCl_3$/hexane)	$C_{14}H_{20}N_2O_4$ (280.3)	280
5m 	80	83–85° ($CHCl_3$/hexane)	$C_{16}H_{24}N_2O_4$ (308.4)	308

[a] The microanalyses were in good agreement with the calculated values: C ± 0.14, H ± 0.28, N ± 0.10.

[b] γ-Aminobutyric acid.

[c] ε-Aminocaproic acid.

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

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

To a stirred mixture of dimethylformamide (1 ml) and di- or trichloromethane (4 ml) at −20 °C, a solution of oxalyl dichloride (0.38 ml, 4.4 mmol) in di- or trichloromethane is added dropwise. After 20 min, the carboxylic acid **1** (4 mmol) and *N*-methylmorpholine (0.44 ml, 4 mmol) are added at −20 °C and after a further 20 min, the *N*-alkylhydroxylamine (**4**; 8 mmol) and *N*-methylmorpholine (0.88 ml, 8 mmol) are added. The mixture is stirred for 4 h at room temperature, then diluted with ethyl acetate (10 ml). The resultant mixture is washed with 0.5 normal hydrochloric acid (20 ml), with water (30 ml), and with 3% sodium hydrogen carbonate solution (20 ml). The *N*-alkylhydroxamic acid **5** is extracted with aqueous 1 normal sodium hydroxide. The aqueous layer is acidified with conc. sulfuric acid to pH 2–4 and the product is reextracted with ethyl acetate (2 × 20 ml). The combined extracts are washed with water (30 ml), dried with magnesium sulfate, filtered, and evaporated. The crude hydroxamic acids **5** are purified by recrystallization. [The purity of the hydroxamic acids thus prepared was checked by I.R. and ^{1}H-N.M.R. spectroscopy and by T.L.C. (silica gel, isopropanol/hexane 1/9)].

Table 3. Spectral Data of Compounds **5**

5	I.R. (KBr) ν [cm^{-1}] of —CO—N(OH)—	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	1610	1.7 (d, 3H, J = 7 Hz, CH—CH$_3$); 5.25 (q, 1H, J = 7 Hz, CH—CH$_3$); 7.2 (s, 5H, CH—C$_6$H$_5$); 7.3 (s, 5H, C$_6$H$_5$—CO); 8.3 (br.s, 1H, OH)
b	1640	1.1 (t, 3H, J = 7 Hz, CH$_2$—CH$_3$); 3.6 (q, 2H, J = 7 Hz, CH$_2$—CH$_3$); 3.7 (s, 2H, CH$_2$—C$_6$H$_5$); 7.2 (s, 5H, C$_6$H$_5$); 8.5 (br.s, 1H, OH)
c	1645	1–1.6 (m, 6H, 2CH$_3$); 3.7 (q, 2H, CH$_2$—N); 4.8 (m, 1H, CH); 5.0 (s, 2H, CH$_2$—C$_6$H$_5$); 5.9 (m, 1H, NH); 7.3 (s, 5H, C$_6$H$_5$); 8.9 (br.s, 1H, OH)
d	1610	1.35 (d, 3H, J = 7 Hz, C$_6$H$_5$—CH—CH$_3$); 1.65 (d, 3H, J = 7 Hz, H$_3$C—CH—NH); 5.0 (m, 1H, H$_3$C—CH—NH); 5.25 (s, 2H, CH$_2$—C$_6$H$_5$); 5.8–6.2 (m, 2H, C$_6$H$_5$—CH—CH$_3$ + NH); 7.5 (s, 10H, 2C$_6$H$_5$); 9.0 (br.s, 1H, OH)
e	1610	0.8–1.5 [m, 11H, (H$_3$C)$_2$CH + CH$_2$—CH$_3$ + CH—CH$_2$—CH]; 2.4 (s, 3H, H$_3$C—C$_6$H$_4$); 3.5 (q, 2H, J = 7 Hz, CH$_2$—N); 4.5 [m, 1H, (H$_3$C)$_2$CH]; 5.5 (m, 1H, CH—CO); 7.2–7.8 (m, 4H, H$_3$C—C$_6$H$_4$—SO$_2$)
f	1610	0.5–1 (m, 6H, 2CH$_3$); 1.5 (m, 2H, CH$_2$—CH); 2.2 (s, 3H, H$_3$C—C$_6$H$_4$); 2.2 (m, 2H, CH$_2$—CO); 3.3 (m, 4H, 2CH$_2$—CH$_3$); 4.3 (m, 1H, CH—CO); 7.2–7.7 (m, 4H, C$_6$H$_4$)[a]
g	1640	1.15 (t, 3H, J = 7 Hz, CH$_2$—CH$_3$); 3.4–3.85 (m, 4H, CH$_2$—CH$_3$ + CH$_2$—CH); 5.5 (m, 1H, CH—CH$_2$); 7.1–7.8 (m, 9H, C$_6$H$_5$ + C$_6$H$_4$); 9.4–9.8 (m, 2H, 2OH)
h	1640	1.1–1.8 (m, 11H, C$_6$H$_{11}$); 4.15 (d, 2H, J = 7 Hz, CH$_2$—CO); 5.15 (s, 2H, CH$_2$—C$_6$H$_5$); 6.0 (m, 1H, NH); 7.4 (s, 5H, C$_6$H$_5$)
i	1645	1.3 (t, 3H, J = 7 Hz, CH$_2$—CH$_3$); 3.85 (q, 2H, J = 7 Hz, CH$_2$—CH$_3$); 7.17 (d, 1H, J = 16 Hz, CH=CH—CO); 7.37 (m, 5H, C$_6$H$_5$); 7.7 (d, 1H, J = 16 Hz, CH=CH—CO); 8.85 (s, 1H, OH)
j	1645	0.8 (t, 3H, J = 7 Hz, CH$_2$—CH$_3$); 2.2 (s, 3H, CH$_3$); 3.3 (q, 2H, J = 7 Hz, CH$_2$—CH$_3$); 7.23 (s, 4H, C$_6$H$_4$); 9.43 (s, 1H, OH)[a]
k	1640	1.1 (t, 3H, J = 7 Hz, CH$_2$—CH$_3$); 2.45 (t, 2H, J = 7 Hz, CO—CH$_2$); 3.4 (q, 4H, J = 7 Hz, CH$_2$—N); 5.0 (s, 2H, CH$_2$—C$_6$H$_5$); 5.73 (t, 1H, J = 7 Hz, NH); 7.26 (s, 5H, C$_6$H$_5$); 7.56 (s, 1H, OH)
l	1640	1.15 (t, 3H, J = 7 Hz, CH$_2$—CH$_3$); 1.83 (m, 2H, C—CH$_2$—C); 2.46 (t, 2H, J = 7 Hz, CH$_2$—CO); 3.2 (q, 2H, J = 7 Hz, CH$_2$—NH); 3.63 [q, 2H, J = 7 Hz, CH$_2$—N(OH)]; 5.06 [s, 2H, CH$_2$—C$_6$H$_5$]; 5.5 (m, 1H, NH); 7.33 (s, 5H, C$_6$H$_5$)
m	1645	1.23 (t, 3H, J = 7 Hz, CH$_2$—CH$_3$); 1.45 [m, 6H, —(CH$_2$)$_3$—]; 2.35 (t, 2H, J = 7 Hz, CH$_2$—CO); 3.1 (q, 2H, J = 7 Hz, CH$_2$—NH); 3.65 [q, 2H, J = 7 Hz, CH$_2$—N(OH)]; 5.07 [s, 2H, CH$_2$—C$_6$H$_5$]; 5.7 (m, 1H, NH); 7.3 (s, 5H, C$_6$H$_5$)

[a] ^{1}H-N.M.R. (DMSO-d_6/TMS_{int}).

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