A Practical Synthesis of *N*-Hydroxy-α-amino Acid Derivatives

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Natural products containing one or more oxidized peptide bonds —C(O)—N(OH)— are compounds of continuing interest owing to their biological activity[1] as well as to their role in the biosynthesis of microbial metabolites[2,3]. In addition, we have shown that *N*-hydroxy- and *N*-benzyloxyamino acid esters **2** and **4**, respectively, can be converted efficiently into α-methoxy- or dehydroamino acid esters[4,5]. However, the syntheses reported so far for *N*-hydroxy-α-amino acid derivatives are laborious, give poor yields, or have limited application[6,7]. We therefore embarked on a study of a facile synthesis of *N*-hydroxyamino acid derivatives.

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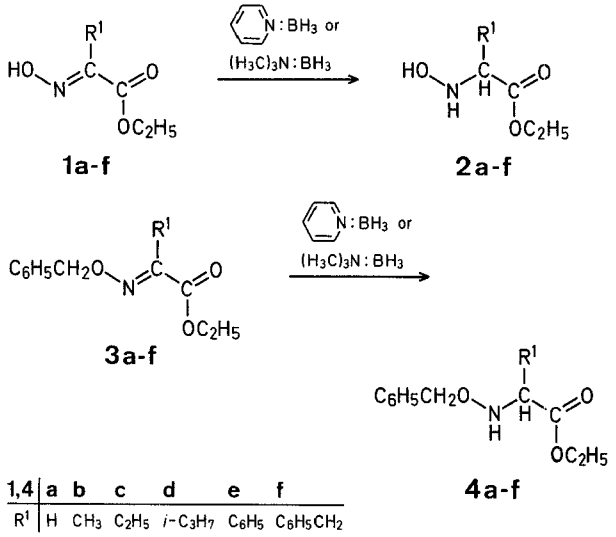
As we have shown earlier[8], α-oximino acid esters **1** and **3** can be reduced to the corresponding *N*-hydroxy-α-amino acid esters **2** and **4**, respectively, with pyridine/borane[9] under strongly acidic conditions. Although most conversions proceeded in fair to good yields (see Table), on reduction of **3f**, 50% starting material was recovered in addition to **4f**, whereas the oxime **3e** could not be reduced at all with pyridine/borane.



The α-oximino amides **5** and **6** could not be reduced completely. This failure is hard to explain, as the mechanism of the reaction is unknown. However, we are inclined to contribute it to steric hindrance in case of the esters **3e, f** and to competitive protonation of the amide function for the compounds **5** and **6**. These two factors might slow down the reaction rate, causing a relatively fast decomposition of the reducing agent under the strongly acidic conditions used[10].

Hence, we studied the reductions that failed with pyridine/borane with an amine/borane complex of higher acid-stability. As can be seen from the Table, all compounds studied could be reduced in fair to good yields when trimethylamine/borane[11] was used.

The synthesis of the α-oximino esters **1** and **3** starts from the corresponding α-keto acids as reported before[8]. Treatment of **1** or **3** with 40% aqueous methylamine in dioxan

Table 1. *N*-Hydroxy-α-amino Acid Derivatives **2, 4, 7,** and **8**

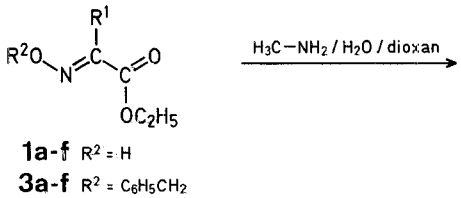
Product	Yield [%][a] by Method A	Method B	m.p. [°C][c] (CH_2Cl_2/*n*-C_6H_{14}) or n_D^{25}	Molecular formula[b]	M.S. *m/e* for M[+] found[d]	calculated
2a	47	60	50–52°	$C_4H_9NO_3$	119.0580	119.0582
2b	75	58	1.4399	$C_5H_{11}NO_3$	133.0724	133.0739
2c	100[e]	92[f]	1.4557	$C_6H_{13}NO_3$	147.0887	147.0895
2d	100[e]	94[f]	1.4429	$C_7H_{15}NO_3$	161.1062	161.1057
2e	—[j]	—	—	—	—	—
2f	82	95[f]	43–45°	$C_{11}H_{15}NO_3$	209.1070	209.1052
4a	95	100[e]	1.5010	$C_{11}H_{15}NO_3$	209.1072	209.1052
4b	94	100[e]	1.4928	$C_{12}H_{17}NO_3$	223.1228	223.1208
4c	80	100[e]	1.4904	$C_{13}H_{19}NO_3$	237.1345	237.1365
4d[i]	—	82[f]	1.4906	$C_{13}H_{19}NO_3$	237.1366	237.1365
4e	0	65[g]	1.5410	$C_{17}H_{19}NO_3$	285.1354	285.1365
4f	50	80[f]	1.5365	$C_{18}H_{21}NO_3$	299.1509	299.1521
7a	80[e]	40	100–102°	$C_3H_8N_2O_2$	104.0562	104.0586
7b	85[e]	40	70–72°	$C_4H_{10}N_2O_2$	118.0753	118.0742
7c	—	61[f]	78–80°	$C_5H_{12}N_2O_2$	132.0884	132.0899
7d	—	70[f]	110–112°	$C_6H_{14}N_2O_2$	146.1061	146.1058
7e	—[j]	—	—	—	—	—
7f	40[e]	70[g]	128–130°	$C_{10}H_{14}N_2O_2$	194.1043	194.1055
8a	90[e]	78	63–65°	$C_{10}H_{14}N_2O_2$	194.1080	194.1055
8b	65[e]	89[f]	32–33°	$C_{11}H_{16}N_2O_2$	208.1205	208.1212
8c	70[e]	90[f]	68–70°	$C_{12}H_{18}N_2O_2$	222.1364	222.1368
8d	—	73[g]	41–43°	$C_{13}H_{20}N_2O_2$	236.1526	236.1525
8e	—	95[h]	53–55°	$C_{16}H_{18}N_2O_2$	270.1391	270.1386
8f	0	94[h]	1.5538	$C_{17}H_{20}N_2O_2$	284.1511	284.1525

[a] Yield of product isolated by preparative HPLC, unless otherwise stated.
[b] Reproducible microanalyses could not be obtained because of the instability of the products in air.
[c] Measured on a Kofler hot-stage (Leitz-Wetzlar); not corrected.
[d] Recorded with a Varian SMIB spectrometer.
[e] Yield estimated from the ^{1}H-N.M.R. spectrum.
[f] 2 equivalents of trimethylamine/borane used.
[g] 4 equivalents of trimethylamine/borane used.
[h] 8 equivalents of trimethylamine/borane used.
[i] Methyl ester.
[j] Decomposition of starting material under the reaction conditions.

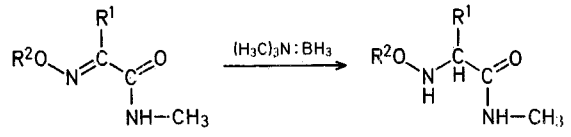
Table 2. ^{1}H-N.M.R. Spectra[a] of Compounds **2, 4, 7,** and **8**

Product	Chemical Shift ($CDCl_3$/TMS) δ [ppm]						
	NH—OH	OCH_2CH_3	OCH_2CH_3	$OCH_2C_6H_5$	$OCH_2C_6H_5$	α-CH	R^1 Signals
2a	5.11	4.25	1.30	—	—	3.68 (2H)	—
2b	5.75	4.22	1.30	—	—	3.71	1.26 (d, 3H)
2c	5.61	4.22	1.30	—	—	3.58	1.6 (m, 2H); 0.97 (t, 3H)
2d	5.30	4.25	1.31	—	—	3.44	1.6–2.2 (m, 1H); 0.98, 0.97 (2 d, 6H)
2f	5.42	4.25	1.20	—	—	3.85	7.3 (m, 5H); 2.93 (d, 2H)[b]
	NH	OCH_2CH_3	OCH_2CH_3	$OCH_2C_6H_5$	$OCH_2C_6H_5$	α-CH	R^1 Signals
4a	6.04	4.22	1.29	4.73	7.34	3.59 (2H)	—
4b	5.90	4.22	1.29	4.71	7.33	3.71	1.19 (d, 3H)
4c	5.95	4.20	1.28	4.67	7.31	3.51	1.6 (m, 2H); 0.92 (t, 3H)
4d	5.96	3.75 (OCH_3)		4.67	7.32	3.45	1.7–2.0 (m, 1H); 0.91, 0.89 (2 d, 6H)
4e	6.16	4.23	1.24	4.76	7.33	4.67	7.31 (s, 5H)
4f	5.90	4.13	1.16	4.68	7.30	3.85	7.2 (m, 5H); 2.87 (d, 2H)
	NH—OH	NH—CH_3	NH—CH_3	$OCH_2C_6H_5$	$OCH_2C_6H_5$	α-CH	R^1 Signals
7a[c]	—	—	2.87	—	—	3.57 (2H)	—
7b	5.26	7.26	2.83	—	—	3.60	1.21 (d, 3H)
7c	5.70	7.20	2.83	—	—	3.45	1.6 (m, 2H); 0.95 (t, 3H)
7d	5.30	6.67	2.86	—	—	3.28	1.7–2.0 (m, 1H); 0.98, 0.96 (2d, 6H)
7f	3.99	6.60	2.81	—	—	3.63	7.3 (m, 5H); 3.10, 2.76 (2H)[b]
	NH	NH—CH_3	NH—CH_3	$OCH_2C_6H_5$	$OCH_2C_6H_5$	α-CH	R^1 Signals
8a	5.90	6.43	2.69	4.69	7.36	3.51 (2H)	—
8b	5.90	6.90	2.70	4.68	7.35	3.60	1.21 (d, 3H)
8c	5.94	6.83	2.73	4.68	7.35	3.55	1.6 (m, 2H); 0.92 (t, 3H)
8d	5.78	6.25	2.74	4.66	7.34	3.24	1.8–2.1 (m, 1H); 0.94, 0.88 (2 d, 6H)
8e	5.91	6.35	2.73	4.69	7.34	4.54	7.31 (s, 5H)
8f	5.77	6.70	2.66	4.61	7.30	3.63	7.3 (m, 5H); 3.10, 2.70 (2H)[b]

[a] Recorded with a Bruker WH-90 spectrometer.
[b] Diastereotopic protons.
[c] Recorded in CD_3OD.



1a-f R^2 = H
3a-f R^2 = $C_6H_5CH_2$



5a-f
6a-f

7a-f
8a-f

gave quantitatively the amides **5** and **6**, respectively. Thus, α-keto acids can now be converted into *N*-hydroxy-α-amino esters and amides via the corresponding oximes. This sequence of reactions is of importance for the synthesis of *N*-hydroxy peptides. These compounds are now accessible either by acylation of the *N*-hydroxy-α-amino acid derivatives[4,12], or by conversion of peptides having an *N*-terminal α-keto acyl function[13,14]. Work is in progress towards this directive. From studies to be published we have evidence that the peptides having an *O*-protected α-oximino function can be reduced selectively with trimethylamine/borane to the corresponding *N*-hydroxy compounds.

***N*-Hydroxy-α-amino Acid Esters (2, 4) and Amides (7, 8):**

Method A: Reduction with pyridine/borane complex: A stirred solution of the oxime (2 mmol) and pyridine/borane complex (10 mmol) in dry ethanol (4 ml) is treated at room temperature with ~7 normal ethanolic hydrochloric acid (3 ml) at such a rate that the temperature of the mixture remains below 40 °C. Stirring is continued at room temperature for 16 h after which the solvent is evaporated. Then dichloromethane (25 ml) is added, together with solid sodium carbonate (1 g). After stirring for several hours, the suspension is filtered, and the solvent evaporated. The residue is chromatographed by preparative H.P.L.C.[15] on Merck silica gel H (type 60) with a dichloromethane/methanol mixture as eluent to give the *N*-hydroxy-α-amino acid esters and amides which are homogeneous on T.L.C. (silica gel plates, dichloromethane/methanol mixtures)[16].

Method B: Reduction with trimethylamine/borane complex: 7 Normal ethanolic hydrochloric acid (15 ml) is added in one portion to a stirred mixture of the oxime (2 mmol) and trimethylamine/borane complex (2 mmol) at room temperature. The temperature of the reaction mixture increases only slightly. Stirring is continued at room temperature for 16 h after which the solvent is evaporated. After this the residue is handled further as described for Method A. ^{1}H-N.M.R. spectra indicate that all of the reductions proceeded to completeness. After preparative H.P.L.C.[15], the compounds were homogeneous on T.L.C. (silicagel plates, dichloromethane/methanol mixtures)[16].

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