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Oxidation of natural targets by dioxiranes. Part 4:[†] A novel approach to the synthesis of *N*-hydroxyamino acids using dioxiranes

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Abstract—An efficient approach to the synthesis of *N*-hydroxyamino acids in high enantiomeric excess is described; this involves the high-yielding selective *N*-hydroxylation of *N*-Boc protected primary amino acid esters with methyl(trifluoromethyl)dioxirane under mild conditions. © 2001 Elsevier Science Ltd. All rights reserved.

The development of efficient syntheses of *N*-hydroxy-α-amino acids and derivatives[2] thereof represents a challenging goal in organic synthesis since these compounds are key intermediates in metabolic pathways and can be found in human and animal tumors.[2,3] However, although numerous excellent procedures are available for the asymmetric synthesis of both natural and unnatural α-amino acids, relatively few methods have been described that are satisfactory for the synthesis of the corresponding *N*-hydroxyamino acids.[4,5] The most versatile procedure appears to be the asymmetric oxyamination of enolates prepared from enantiomerically pure

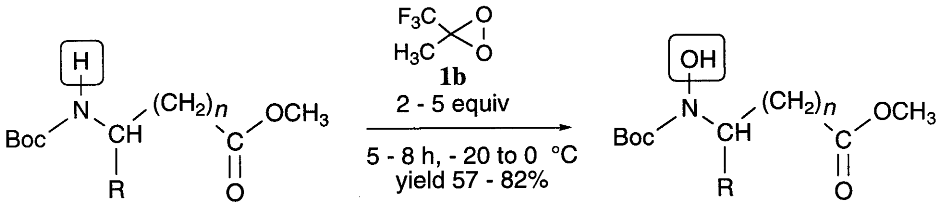
Table 1. Oxidation of some *N*-Boc protected amino acid methyl esters by methyl(trifluoromethyl)dioxirane (**1b**) in CH_2Cl_2[a]

Entry #	Substrate	Dioxirane (equiv.)	Reactn. time (h)	Conversion (%)[b]	Yield (%)[c]
1	**2a**	2.0	5	88	82
2	**2b**	3.1	6	81	75
3	**2c**	5.0	6	91	57
4	**2d**	2.0	8	88	74

[a] All reactions were routinely run at –20 to 0°C.

[b] As determined (±2%) by GC (SPB-1, 0.25 μm film thickness, 30 m×0.25 mm ID, capillary column), octafluoro–naphthalene internal standard.

[c] Yields of corresponding *N*-hydroxyamino acids isolated (cf. Eq. (1)), based on the amount of starting material reacted; products were identified by ^1H NMR, ^{13}C NMR and GC/MS (MDN-1, 0.25 μm film thickness, 30 m×0.25 mm ID, capillary column).



2a-d **3a-d** (1)

$n = 0$: **a**, R = H; **b**, R = $CH(CH_3)_2$; **c**, R = $CH_2CH(CH_3)_2$
$n = 4$: **d**, R = H

Keywords: dioxiranes; *N*-hydroxyamino acids; NH-oxidation; oxidation; chemoselectivity.

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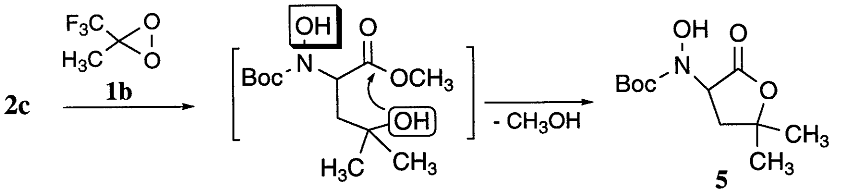


(2)

N-acylsultams;[4a] Hannessian and Yang have also described the efficient synthesis of *N*-alkoxycarbonyl derivatives of α-hydroxyamino acids by a Mitsunobu displacement reaction of the corresponding α-hydroxy acid esters.[4b] In this context we decided to explore a new approach involving the direct oxyfunctionalization of readily available primary amino acid derivatives to the corresponding *N*-hydroxy derivatives using dioxiranes, a new class of powerful yet selective oxidants.[6,7] In fact, the combination of high reactivity, selectivity, neutral pH, and ease of product isolation presented by dioxiranes[6] has recently spurred their application to the selective oxyfunctionalization of natural products, such as vitamin D_2 and D_3 derivatives.[1,8] Danishefsky et al. have reported on two examples wherein the low-temperature (−45°C) oxidation of unprotected NH_2 groups of amino acid esters to -NH–OH was achieved using dimethyldioxirane (**1a**).[5]

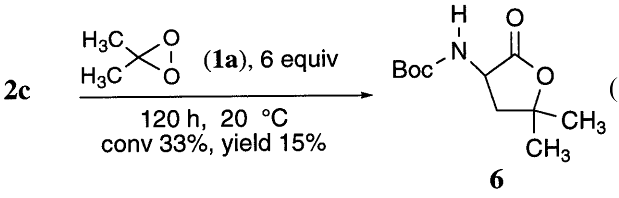
We have now applied dioxiranes **1a** and **1b** to the oxidation of *N*-Boc amino acids and found that their reaction with dioxirane **1b** produces the corresponding *N*-hydroxy derivatives **3a–d** in good yield under mild conditions (Eq. (1)). Representative results are collected in Table 1.

Starting with the corresponding commercially available *N*-Boc amino acids, substrates **2a–d**[9,10] were obtained upon esterification with CH_3I in DMF.[11] Oxidations were carried out by the gradual addition of an aliquot (usually from 0.8 to 1.5 ml) of standardized cold solution of ca. 0.8 M **1b**[7e,12] in 1,1,1-trifluoro-2-propanone (TFP) to a stirred solution of the substrate (100–300 mg) in CH_2Cl_2 (5–30 ml) under the conditions given in Eq. (1). The reactions were monitored by GC and TLC; product isolation simply entailed removal of solvent in vacuo, followed by preparative TLC (silica gel plates, 2.0 mm layer thickness, 60 Å medium pore diameter). The isolated *N*-hydroxyamino acids **3a–d** gave satisfactory ^1H and ^{13}C NMR spectra.[13] Upon reaction with $FeCl_3$ in EtOH, they all yielded the characteristic reddish-brown color of ferric hydroxamate complexes.[14]

Optically active *N*-Boc-L-Val-OMe **2b** and *N*-Boc-L-Leu-OMe **2c** esters (entry 2 and 3) were oxidized to their corresponding *N*-hydroxy derivatives **3b** and **3c** with practically no loss of enantiomeric excess (≥99%), as evidenced by ^1H NMR titration with $Eu(hfc)_3$. Removal of the Boc protecting group using TFA[15] afforded the corresponding pure *N*-hydroxyamino acid methyl esters in high isolated yield; for instance, *N*-OH-L-Val-OMe (**4**)[16] was obtained in 95% yield from product **3b**.

In the oxidation of *N*-Boc-L-Leu-OMe (**2c**) under the conditions given in Table 1, it should be noted that another major product was the *N*-hydroxy 4,4-dimethyl-4-butanolide derivative **5**,[17] which was isolated in 21% yield.

Akin to the high site-selectivity recorded for similar *O*-insertions into tertiary C–H bonds by dioxirane **1b**,[1,6a,8,12a] it is likely that the butanolide **5** derives from concurrent hydroxylation at the tertiary γ–CH bond followed by rapid cyclization, as shown in Eq. (2). This oxidative cyclization is not unprecedented;[18] in fact, it was previously reported that the reaction of substrate **2c** with excess dioxirane **1a** gives 4-butanolide **6** in 93% yield, at 45% substrate conversion after 72 h at room temperature.[19]



(3)

In our hands this transformation turned out to be rather sluggish, requiring longer reaction times to achieve sizable substrate conversions, whereas the butanolide **6** is obtained in considerably lower yields (Eq. (3)).

We noticed that treatment of **2c** with dioxirane **1a** does not result in the formation of *N*-hydroxylation products in any appreciable amount, a feature which is in common with all of the substrates examined herein. Hence, at variance with that observed for unprotected -NH_2 functionalities,[5] the less powerful dioxirane **1a** is not as effective as **1b** in bringing about *O*-insertion into a -N(Boc)–H bond; most likely because of the diminished electron density at the N–H due to the electron-withdrawing effect of the Boc substituent, as well as to steric shielding. It should be recalled that the dioxirane oxidation of unprotected -NH_2 groups in simple and complex primary amines appears to be an ubiquitous process.[6] In fact, oximes, nitroso dimers, nitrones, nitroalkanes, and oxaziridines can all be produced via oxidation,[6] along with or instead of the corresponding hydroxylamines.[5,6] The mechanism of this oxidation has not been established in detail; it seems that, as an alternative to straightforward 'oxenoid' *O*-insertion into the N–H bond, *O*-transfer to the nitrogen lone-pair or even one-electron transfer processes[6,20] also represent viable pathways.

Whatever the mechanistic details, the procedure reported herein shows promise as a useful addition to the general methods for the synthesis of enantiomerically pure or enriched *N*-hydroxyamino acids. It offers a valid alternative to the low-temperature direct oxidation of unprotected -NH_2 amino acid esters using dimethyldioxirane

(**1a**) reported by Danishefsky et al.[5] Indeed, dioxirane **1b** is quite efficient in performing selective hydroxylation at the -N(Boc)–H bond, without overoxidation at the nitrogen functionality. Then, the -N(Boc)–OH functionality can be easily unmasked by the facile removal of the Boc protecting group, as mentioned above. The overall process is simple, applicable to readily available starting materials, and occurs with no loss in enantiomeric purity.

Acknowledgements

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13. *N*-Hydroxy-*N*-(*t*-butoxycarbonyl)-glycine methyl ester (*N*-OH-*N*-Boc-Gly-OMe) (**3a**): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 9 H), 3.72 (s, 3 H), 4.21 (s, 2 H), 7.24 (s, 1 H). {^{1}H} ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.03, 52.23, 52.51, 82.54, 157.20, 169.57; FT-IR (neat) 3345, 1746, 1702 cm^{-1}, etc.; MS (EI, 70 eV), *m*/*z* 146 (1), 105 (8), 104 (4), 59 (7), 58 (5), 57 (100). *N*-Hydroxy-*N*-(*t*-butoxycarbonyl)-L-valine methyl ester (*N*-OH-*N*-Boc-L-Val-OMe) (**3b**): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (d, $J=6.8$ Hz, 6 H), 1.43 (s, 9 H), 2.34 (m, 1 H), 3.70 (s, 3 H), 4.32 (d, $J=8.2$ Hz, 1 H), 6.74 (broad s, 1 H). {^{1}H} ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.55, 19.60, 28.12, 28.43, 51.97, 66.71, 82.13, 156.89, 171.89; FT-IR (neat) 3369, 1747, 1698 cm^{-1}, etc.; MS (EI, 70 eV), *m*/*z* 173 (2), 172 (15), 130 (10), 116 (45), 88 (10), 72 (56), 59 (27), 57 (100); $[\alpha]_D$ −5.64 (*c* 1.28, $CHCl_3$). *N*-Hydroxy-*N*-(*t*-butoxycarbonyl)-L-leucine methyl ester (*N*-OH-*N*-Boc-L-Leu-OMe) (**3c**): white solid, mp 42–45°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (d, $J=6.5$ Hz, 3 H), 0.92 (d, $J=6.7$ Hz, 3 H), 1.44 (s, 9 H), 1.56 (m, 1 H), 1.76–1.68 (m, 1 H), 1.94 (m, 1 H), 3.70 (s, 3 H), 4.65 (m, 1 H), 6.65 (broad s, 1 H). {^{1}H} ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.89, 23.16, 24.16, 28.10, 36.79, 52.29, 59.91, 82.21, 157.25, 172.45; FT-IR (neat) 3371, 1745, 1666 cm^{-1}, etc.; MS (EI, 70 eV), *m*/*z* 190 (1), 189 (1), 187 (3), 186 (22), 144 (15), 130 (84), 100 (6), 88 (20), 87 (10), 86 (91), 74 (10), 59 (57), 58 (21), 57 (100); $[\alpha]_D$ −5.69 (*c* 1.14, $CHCl_3$). 6-*N*-Hydroxy-*N*-(*t*-butoxycarbony)aminocaproic acid methyl ester (**3d**): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (m, 2 H), 1.42 (s, 9 H), 1.57-1.64 (m, 4 H), 2.27 (t, $J=7.6$ Hz, 2 H), 3.43 (t, $J=7.0$ Hz, 2 H), 3.62 (s, 3 H), 7.58 (broad s, 1 H). {^{1}H} ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.47, 25.97, 26.53, 28.26, 33.88, 49.83, 51.45, 81.53, 156.97, 174.10; FT-IR (neat) 3363, 1739, 1697 cm^{-1}, etc.; MS (EI, 70 eV), *m*/*z* 161 (9), 130 (10), 129 (24), 84 (31), 59 (14), 57 (100).
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16. *N*-Hydroxy-L-valine methyl ester (*N*-OH-L-Val-OMe) (**4**): white solid mp 161–163°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (d, $J=11.6$ Hz, 3 H), 0.93 (d, $J=11.7$ Hz, 3 H), 1.87 (m, 1 H), 3.43 (d, $J=6.7$ Hz, 3 H), 3.74 (s, 3 H), 5.70–6.55 (broad s, 2 H). {^{1}H} ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.21, 19.24, 29.01, 51.77, 71.23, 173.95; FT-IR (neat) 3262, 3197, 1745 cm^{-1}, etc.; MS (EI, 70 eV), *m*/*z* 147 (1), 104 (22), 88 (100), 72 (36), 56 (4), 55 (11); $[\alpha]_D$ −8.19° (*c* 0.65, $CHCl_3$).
17. *N*-Hydroxy-2-(*t*-butoxycarbonylamino)-4,4-dimethyl-4-butanolide (**5**): white solid, mp 131–135°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 3 H), 1.41 (s, 9 H), 1.49 (s, 3 H), 2.41–2.31 (m, 2 H), 5.07 (t, $J=10.0$ Hz, 1 H), 6.92 (broad s, 1 H); {^{1}H} ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.62, 28.12, 28.85, 36.56, 80.06, 82.26, 83.27, 156.76, 172.76; FT-IR (KBr) 3354, 1772, 1736 cm^{-1}, etc.; MS (EI, 70 eV) *m*/*z* 189 (1), 174 (1), 145 (8), 100 (32), 59 (9), 57 (100); $[\alpha]_D$ −3.94° (*c* 0.51, $CHCl_3$).
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mp 140–143°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 3 H), 1.42 (s, 9 H), 1.47 (s, 3 H), 1.92 (m, 1 H), 2.63 (m, 1 H), 4.53 (m, 1 H), 5.06 (m, 1 H); {^{1}H} ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.85, 28.24, 28.95, 42.60, 51.26, 80.48, 82.45, 155.47, 174.58; FT-IR (KBr) 3319, 1757, 1708 cm^{-1}, etc.; MS (EI, 70 eV) *m*/*z* 174 (1), 158 (3), 156 (8), 129 (22), 114 (9), 70 (20), 59 (11), 57 (100); $[\alpha]_D$ −16.5 (*c* 0.52, $CHCl_3$).

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