Tetrahedron Letters,Vol.28,No.11,pp 1215-1218,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

AN EFFICIENT SYNTHESIS OF N-HYDROXY-α-AMINO ACID DERIVATIVES OF HIGH OPTICAL PURITY

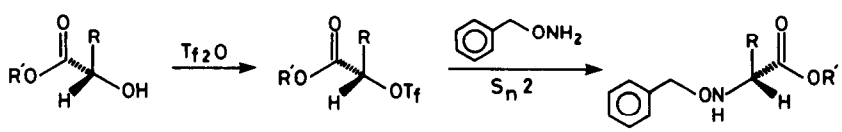
R.W. Feenstra, E.H.M. Stokkingreef, R.J.F. Nivard, H.C.J. Ottenheijm*
Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED Nijmegen, The Netherlands

Abstract: Conversion of α-hydroxy esters *via* triflates into compounds 3 proceeds in chemical yields ranging from 78 to 89% and with optical purities ranging from 76 to 100%.

A substantial number of natural products contains one or more oxidized peptide bonds -C(O)-N(OH)-. It has been suggested that such N-hydroxy peptides play an important role in the biosynthesis of other natural products[1,2]. The preparation of N-hydroxy peptides *in vitro* has to start with N-hydroxy amino acids or derivatives thereof since direct oxidation of peptides appeared not to be possible though oxidation of amides has been described[3]. So, the need for a general and practical synthesis of optically pure N-hydroxy-α-amino acids is obvious.

A large number of syntheses of N-hydroxy-α-amino acids and derivatives thereof has been reported.[1] Most of the methods deal, however, with racemic mixtures, so that an efficient, stereospecific approach remains a challenge. The syntheses of the optically active derivatives of N-hydroxy-α-amino acids reported so far involve either a substitution reaction using α-bromo carboxylic acids[4,5] or α-tosyloxy esters[6] or indirect oxidation of α-amino acids[7,8]. The usefulness of the methods is, however, restricted, because partial racemization occurs during substitution reactions[5,6,9-11], or the procedures are elaborate and inefficient[4,5].

We wish to report now a practical synthesis of O-benzyl derivatives 3 of high optical purity. As precursors we use α-hydroxy esters 1 which are increasingly available in optically pure form.[12-16]



1 2 3

Their triflates 2 are readily prepared *in situ* by reaction with trifluoromethanesulfonic acid anhydride in the presence of lutidine as a base. We observed that the reaction stands or fails with the base used; with other bases than lutidine, *e.g.* pyridine[17], yields are unacceptably low. Reaction of the triflates 2 with O-benzyl-hydroxylamine gave the desired O-benzyl-N-hydroxy-α-amino acid esters 3. The overall yield of the conversion 1 → 3 and the optical purity of 3a-3e are given in the Table.

Preparation of N-benzyloxy-α-amino acid esters

Product	R	Reaction Temp. (°C)	chem. yield (%)	opt.[22] purity (%)	$[\alpha]_D^{20}$ ($CHCl_3$)	eluent (ether/hexane)
(R)-3a	CH_3	0	89	100	+51.7 (c = 1.5)[21]	20/80
(R)-3b	CH_2Ph	-78	84	100	+18.9 (c = 1)[21]	20/80
(R)-3c	$CH_2CH(CH_3)_2$	0	78	100	+50.4 (c = 1.5)[21]	15/85
(R)-3d	CH_2COOCH_3	-78	88	95	+19.5 (c = 1)[24]	30/70
(S)-3e*	Ph	-78	88	76	+55.6 (c = 1)	20/80

3a: R' = Et, 3b–3e: R' = Me

*(R)-1e was used as starting compound.

The reaction sequence 1 → 3 and some data of the Table deserve further comment. Triflates 2 have been employed previously in reactions with amines to yield the corresponding homochiral α-amino acid derivatives[17,18]. It is noteworthy that O-benzylhydroxylamine having a lower nucleophilicity still induces in general a pure S_N2-reaction: only with the triflate of the (R)-mandelic acid ester 2e substitution proceeds with incomplete inversion (50% opt. yield). Addition of an apolar solvent (hexane) to the reaction mixture leads in this case to an increase of the stereoselectivity and raises the optical purity to 76%. Although the triflates 2 are prone to β-elimination yielding α,β-dehydrocarboxylic acid derivatives, we did not observe the formation of elimination products under the reaction conditions employed. The triflate 2a is a stable compound which can be isolated; 2e decomposes at room temperature. Both the lowered stereoselectivity in the substitution of 2e and its reduced stability point to an increased tendency to S_N1-reactivity in comparison with 2a-2d.

Partial racemization took place when triflate 2a was allowed to react with hydroxylamine instead of the O-benzyl derivative. Most likely this is due to the high polarity of the solvent which we had to resort to in order to liberate hydroxylamine from its hydrochloride. When methanol was used as the solvent the optical purity was 50% and the chemical yield 75%.

The presence of the O-protecting group does not imply a limitation of the usefulness of the products 3, but it is even an advantage in their application; the compounds can directly be used for the synthesis of N-hydroxy peptides, whereas unprotected N-hydroxy amino acids require previous O-acylation, which generally leads to N- as well as O-acylated products.[1] When the O-protected derivatives 3 are employed, the O-benzyl groups can be removed selectively by hydrogenolysis subsequent to N-acylation.[20,25]

Our approach is not limited to simple hydroxylamine derivatives. Reaction of 2a with the ethyl ester of racemic N-hydroxy alanine gave (chem. yield 88%) the expected substitution product, which is structurally related to the natural product amavidine[19]. The stereochemical course of this reaction is under investigation.

General procedure for the conversion of 1 into 3

Trifluoromethanesulphonic acid anhydride (3.3 mmol) is added at once to a stirred solution of 1 (3 mmol) in dry CH_2Cl_2 (10 ml) which is kept either at -78°C (acetone/CO_2) or 0°C (ice/water) (see Table) and under an argon atmosphere. For the preparation of 3e CH_2Cl_2/hexane 1/2 was used as the solvent. After five minutes, lutidine (369 mg, 3.45 mmol) is added in one portion. Five minutes later a solution of O-benzylhydroxylamine[26] (738 mg, 6 mmol) in dry

CH_2Cl_2 (5 ml) is added dropwise to the reaction mixture. Subsequently, the cooling bath is removed. When the reaction mixture has reached room temperature, stirring is continued for 25 minutes. The reaction mixture is concentrated *in vacuo* and the residual oil is subjected to flash column chromatography (silica gel, Merck H60, eluent see Table) to yield 3 as an oily product except in the case of 3e, which crystallizes.

Spectroscopic data and elemental analyses

3a: ^{1}H-NMR ($CDCl_3$): δ 1.20 (d, 3H, CH_3CH), 1.27 (t, 3H, OCH_2CH_3), 3.68 (2q, 1H, CH_3CH, superimposed), 4.22 (q, 2H, OCH_2CH_3), 4.71 (s, 2H, OCH_2Ph), 5.94 (d, 1H, NH), 7.34 (s, 5H, Ph); IR (neat, cm^{-1}): 3270 (m), 1730 (s); MS (CI): 224 (M^++1,30), 150 (11), 119 (10), 107 (13), 91 (100), 79 (18), 57 (18); elem. anal. $C_{12}H_{17}NO_3$ (%): calc. C, 64.55; H, 7.67; N, 6.27; found C, 64.10; H, 7.56; N, 6.22.

3b: ^{1}H-NMR ($CDCl_3$): δ 2.91 (d, 2H, $CHCH_2Ph$), 3.70 (s, 3H, $COOCH_3$), 3.73-4.04 (m, 1H, $CHCH_2Ph$), 4.71 (s, 2H, OCH_2Ph), 5.94 (d, 1H, NH), 7.08-7.42 (m, 5H, $CHCH_2Ph$), 7.34 (OCH_2Ph); IR (neat, cm^{-1}): 3270 (m), 1735 (s); MS (CI): 286 (M^++1,33), 226 (12), 194 (13), 119 (12), 91 (100); elem. anal. $C_{17}H_{19}NO_3$ (%): calc. C, 71.56; H, 6.71; N, 4.91; found C, 70.99; H, 6.73; N, 4.61.

3c: ^{1}H-NMR ($CDCl_3$): δ 0.89 (2d, 6H, $CH_2CH(CH_3)_2$), 1.23-1.88 (m, 3H, $CH_2CH(CH_3)_2$), 3.67 (t, 1H, $CHCOOCH_3$), 3.77 (s, 3H, $COOCH_3$), 4.71 (s, 2H, OCH_2Ph), 5.91 (broad, 1H, NH), 7.34 (s, 5H, Ph); IR (neat, cm^{-1}): 3260 (w), 1740 (s); MS (CI): 252 (M^++1,100), 234 (14), 192 (18), 178 (10), 91 (66); elem. anal. $C_{14}H_{21}NO_3$ (%): calc. C, 66.91; H, 8.42; N, 5.57; found C, 66.93; H, 8.52; N, 5.55.

3d: ^{1}H-NMR ($CDCl_3$): δ 2.69 and 2.82 (8 lines, ABX, 2H, J_{ax} = 7.8 Hz, J_{bx} = 5.6 Hz, J_{ab} = 16.2 Hz, CH_2CH), 3.69 and 3.77 (2s, 6H, $COOCH_3$ (2x)), 4.04 (4 lines, ABX, 1H, $J_{ax}+J_{bx}$ = 13.4 Hz, CH_2CH), 4.70 (s, 2H, OCH_2Ph), 6.22 (d, 1H, NH), 7.34 (s, 5H, Ph); IR (neat, cm^{-1}): 3270 (w), 1735 (s); MS (CI): 268 (M^++1,27), 208 (8), 128 (19), 91 (100); elem. anal. $C_{13}H_{17}NO_5$ (%): calc. C, 58.42; H, 6.41; N, 5.24; found C, 58.53; H, 6.40; N, 5.20; see reference 24

3e: ^{1}H-NMR ($CDCl_3$): δ 3.74 (s, 3H, $COOCH_3$), 4.69 (d, 1H, CH), 4.74 (s, 2H, OCH_2), 6.16 (d, 1H, NH), 7.29 (s, 5H, $CHPh$), 7.34 (s, 5H, OCH_2Ph); IR (neat, cm^{-1}): 3270 (s), 1740 (s); MS (CI): 272 (M^++1,22), 212 (38), 164 (32), 149 (18), 104 (27), 91 (100); elem. anal. $C_{16}H_{17}NO_3$ (%): calc. C, 70.83; H, 6.32; N, 5.16; found C, 70.55; H, 6.32; N, 5.13.

References and footnotes

1. For a recent survey about N-hydroxy-α-amino acids, see H.C.J. Ottenheijm and J.D.M. Herscheid, *Chem. Rev.*, 86, 697 (1986).
2. For a recent review on α,β-dehydroamino acids, see U. Schmidt, J. Haŭsler, E. Oehler and H. Poisel, in "Progress in the Chemistry of Natural Products", W. Herz, H. Grisebach, C.W. Kirby, Eds., Springer Verlag, New York, 1979, Vol. 37, p. 251.
3. S.A. Matlin, P.G. Sammes, R.M. Upton, *J. Chem. Soc. Chem. Comm.*, 2481 (1979).
4. T. Kolasa, A. Chimiak, *Tetrahedron*, 30, 3591 (1974).
5. K. Kaminsky, T. Sokolowska, *Roczniki Chemii Ann. Soc. Chim. Polonorum*, 47, 653 (1973).
6. T. Kolasa, *Can. J. Chem.*, 63, 2139 (1985).
7. T. Polonski, A. Chimiak, *Tet. Lett.*, 2453 (1974).

8. H.T. Nagasawa, J.G. Kohlhoff, P.S. Fraser, A.A. Mikhail, *J. Med. Chem.*, 15, 483 (1972).
9. M. Gacek, K. Undheim, *Tetrahedron*, 29, 863 (1973).
10. K. Undheim, T. Gronneberg, *Act. Chem. Scand.*, 25, 18 (1971).
11. B. Liberek, Z. Palacz, *Roczniki Chemii Ann. Soc. Chim. Polonorum*, 45, 1173 (1971).
12. D.A. Evans, M.M. Morrissey, R.L. Dorow, *J. Am. Chem. Soc.*, 107, 4346 (1985).
13. F.A. Davis, L.C. Vishwakarma, *Tet. Lett.*, 26, 3539 (1985).
14. H.C. Brown, G.G. Pai, P.K. Jadhav, *J. Am. Chem. Soc.*, 106, 1531 (1984).
15. J.K. Whitesell, A. Bhattacharya, K. Henke, *J. Chem. Soc. Chem. Comm.*, 988 (1982); J.K. Whitesell, D. Deyo, A. Bhattacharya, *ibid*, 802 (1983).
16. W.H. Kruizinga, B. Strijtveen, R.M. Kellogg, *J. Org. Chem.*, 46, 4321 (1981).
17. F. Effenberger, U. Burkard, J. Willfahrt, *Angew. Chem.*, 95, 50 (1983).
18. F. Effenberger, U. Burkard, *Liebigs Ann. Chem.*, 334 (1986).
19. H. Kneifel, E. Bayer, *Angew. Chem.*, 85, 542 (1973).
20. T. Kolasa, A. Chimiak, *Tetrahedron*, 33, 3285 (1977).
21. These compounds have been prepared previously, see T. Kolasa, A. Chimiak, A. Kitowska, *J. Prakt. Chem.*, 317, 252 (1975). We concluded that the optical purity of compounds 3a and 3c reported by these authors must have been 61% and 60%, respectively.
22. The optical purity was determined by reduction of compounds 3 (Pd/C, MeOH, H_2, 1 atm.) to the corresponding α-amino acid esters 4 which were purified by column chromatography (Merck silica gel H60, eluent 2% MeOH in CH_2Cl_2). Treatment with an ethereal HCl solution afforded the corresponding hydrochlorides 5, which were not recrystallized to prevent enrichment of one enantiomer. The optical purities were calculated by comparing their specific rotations with those of the pure hydrochlorides 6 derived from the corresponding L-(S)-amino acids, see reference 23.
23. Specific rotations of hydrochlorides 5 and 6:

(R)-5a	$[\alpha]_D^{20}$ -2.58 (c = 2, EtOH),	(S)-6a	$[\alpha]_D^{20}$ +2.55 (c = 3, EtOH)
(R)-5b	$[\alpha]_D^{20}$ -37.8 (c = 2, EtOH),	(S)-6b	$[\alpha]_D^{20}$ +37.9 (c = 2, EtOH)
(R)-5c	$[\alpha]_D^{20}$ -24.5 (c = 0.5, EtOH),	(S)-6c	$[\alpha]_D^{20}$ +24.3 (c = 0.5, EtOH)
(R)-5d	$[\alpha]_D^{20}$ -14.7 (c = 2, MeOH),	(S)-6d	$[\alpha]_D^{20}$ +15.5 (c = 2, MeOH)
(S)-5e	$[\alpha]_D^{20}$ +101.2 (c = 1, MeOH),	(S)-6e	$[\alpha]_D^{20}$ +135.2 (c = 1, MeOH)

24. According to our method, the (+)-R-enantiomer of 3d was prepared in an optical yield of 95%, having $[\alpha]_D^{20}$ +21.7 (c = 7.8, MeOH). For the (-)-S-enantiomer of 3d (see reference 6) was reported $[\alpha]_D^{25}$ -2.7 (c = 7, MeOH); from this data we conclude that the optical purity of this (-)-S-3d must have been 12%.
25. It should be pointed out here that whereas hydrogenolysis of O-benzyl-N-hydroxy amides leads to the corresponding N-hydroxy amides, the same reaction conditions will convert N-benzyloxy-amino acid esters into the corresponding amines. Neglect of this finding has led to erroneous conclusions (see reference 6).
26. O-benzyl-hydroxylamine was liberated from its hydrochloride salt by addition of one equivalent of triethylamine to a solution of one equivalent of the hydrochloride salt in MeOH. Then the solvent was removed *in vacuo*. The residue was extracted twice with ether. The combined ethereal fractions were concentrated *in vacuo*, after which the residue was subjected to vacuum destillation (0.5 mm Hg, 50°C) to yield O-benzylhydroxylamine which was homogeneous by ^{1}H-NMR and TLC.

(Received in UK 19 December 1986)