Pergamon

Tetrahedron Letters 40 (1999) 1669–1672

TETRAHEDRON LETTERS

Synthesis of β-Alkoxy α-AminoAcid Esters

Saïd Boukhris, Abdelaziz Souizi *
Laboratoire de Synthèse Organique et d'Agrochimie. Département de Chimie.
Faculté des Sciences. Université Ibn Tofaïl. B.P 133- Kénitra (Maroc)

Received 23 October 1998; accepted 2 January 1999

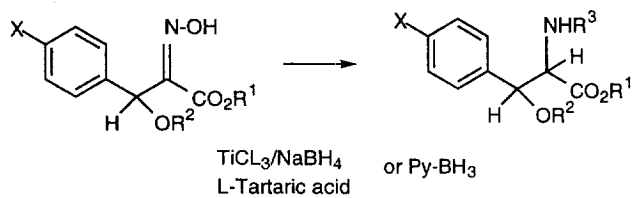
Abstract : β-Alkoxy α-aminoacid esters and N-hydroxy α-amino esters are obtained by the reduction of easily accessible α-oximino esters.

α-Aminoacids play an important role in different areas,[1] e.g. as enzyme inhibitors, antibacterial agents, neuroactive compounds, pharmaceutical starting materials, herbicides and fungicides. However, β-hydroxylated α-aminoacids are biological compounds of major importance. They are components of various peptides possessing a wide range of biological activities such as antibiotic and immunosuppressive properties. In addition, two β-hydroxylated α-aminoacids are present in vancomycine which is a widely used antibiotic in the treatment of methicillin-resistant *Staphylococcus aureus*.[2-3]

These α-amino β-hydroxy acids have been described by Evans[4] and Rao[5] et al.. A variety of approaches have been developped for their synthesis : several methods based on nucleophilic opening of epoxides,[6] on electrophilic amination[7] or asymmetric hydrogenation of N-protected α-amino β-keto esters.[8] However, the synthesis of β-alkoxy α-aminoacid esters has not been well investigated to date. In this paper, we will describe the synthesis of such compounds starting from the α-oximino esters **1**.

α-Oximino acids are particularly useful precursors of α-amino acids. Reduction under a variety of conditions can produce either the corresponding N-hydroxy α-aminoacids derivatives or the parent α-amino acid itself.[9-10]

We report that β-alkoxy α-aminoacid esters can be prepared directly by reduction of easily accessible β-alkoxy α-oximino esters[11] with a buffered combination of titanium (III) chloride and sodium borohydride. Indeed, combination of titanium (III) chloride and sodium borohydride in aqueous solution has been shown to be effective for the reduction of a sugar-derived oxime to the corresponding amino sugar.[12] This prompts us to report on our reductions of α-oximino esters **1a-i** to β-alkoxy α-aminoacid esters **2a-i**.



Scheme 1

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00061-1

As shown by the data in Table 1, the reaction of sodium borohydride and titanium (III) chloride with α-oximino esters **1a-i** (these products are obtained as an oily mixture of two diastereomers E and Z[11]) under appropriately buffered aqueous conditions efficiently produced the desired β-alkoxy α-aminoacid esters **2a-i** (R^3 = H) even when the unhindered methyl and ethyl esters were employed (Scheme 1).

A general procedure for this conversion, which proceeds in fair to good yields (see Table 1), is as follows : to a solution of 61.6 mmol of L-tartaric acid and 148 mmol of sodium hydroxide in 25 mL of water was added 7.0 mL (6.3 mmol) of 0.9 M aqueous titanium trichloride. The pH of the resulting green solution was adjusted to 7.0 (NaOH/HCl). To the mixture was added 5.55 mmol of solid sodium borohydride followed quickly by 2.0 mmol of α-oximino esters **1** in 5.0 mL of methanol.

The mixture became lighter in color and was stirred for 25 mn under nitrogen and then for 20 h in air. The pH of the final colorless mixture was exactly 7.0 and was adjusted to 8.5 with saturated aqueous dipotassium hydrogen phosphate. The mixture was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered and evaporated to afford the residual α-amino esters. Purification was done by column chromatography (silica gel hexane / ethyl acetate 7 : 3 as eluent) to give the β-alkoxy α-aminoacid esters **2a-i**,[13] as oily products.

The reaction always gives a mixture of two diastereomers A and B (unknown configuration), with one as the major product, which we did not manage to isolate by column chromatography.

We wish also to report our initial synthesis of new N-hydroxy α-amino esters by reduction of the α-oximino esters.

Indeed, a substantial number of natural products containing one or more oxidized peptide bonds -C(O)-N(OH)- have been found in nature. These compounds act variously as potent growth factors, antibiotics, antibiotic antagonists or tumor inhibitors.[14] In addition, it has been suggested that N-hydroxy peptides play an important role in the biosynthesis of β-lactam antibiotics.[15]

Table 1: Synthesis of β-alkoxy α-aminoacid esters **2a-i** and N-hydroxy α-amino esters **2j-k**

Substrate	R^1	R^2	X	R^3	Products	Yields %	(B/A) ratio[a]
1a	Et	Et	CH_3	H	**2a**	82	80/20
1b	Et	Et	Cl	H	**2b**	78	84/16
1c	Et	Et	H	H	**2c**	66	76/24
1d	Me	Et	CH_3	H	**2d**	83	82/18
1e	Me	Et	Cl	H	**2e**	80	80/20
1f	Me	Et	H	H	**2f**	75	75/25
1g	Et	Me	CH_3	H	**2g**	84	84/16
1h	Et	Me	Cl	H	**2h**	78	76/24
1i	Me	Me	H	H	**2i**	76	74/26
1j	Et	Et	CH_3	OH	**2j**	72	76/24
1k	Et	Me	CH_3	OH	**2k**	74	78/22

a. The determination of the ratio is based on ^{1}H NMR analysis of the crude reaction mixture.

The reduction of α-oximino acids to the corresponding N-hydroxy α-aminoacids is known.[16] We tried to apply the reduction with pyridine-borane, with a slight modification, for the selective reduction of β-alkoxy α-oximino esters **1j-k** to the corresponding N-alkoxy α-amino esters **2j-k** (R^3 = OH) (Scheme 1). **2j-k** are obtained as an oily mixture of two diastereomers A and B (see Table 1 : entries j-k), which we did not manage to separate by column chromatography.

The reported yields represent purified products, for which correct spectroscopic datas were secured.

A typical laboratory procedure is outlined in note 17.

In summary, the widespread availability of the starting materials and the simplicity of the experimental procedure enable a wide variety of inaccessible unnatural β-alkoxy α-aminoacid esters and unnatural β-alkoxy N-hydroxy α-amino esters. Further studies of the stereochemical aspects (dieastereo/enantioselection), of the potential biological properties and of the synthetic utility of the products are under investigation.

References and Notes

1. Kleeman, A.; Lenchtenberger, N.; Hoppe, B.; Tanner, H. *Amino acids* in : *Ullman's Encyclopedia of industrial Chemistry*, **1985**, A2, VCH Verlagsgesellschaft, Weinheim p. 57.
2. Mc Cornick, M. H.; Stark, W. M.; Pittenger, G. F.; Pittenger, R. C.; Mc Gvire, G. M. *Antibiot. Annual* **1955-1956** Medicinal Encyclopedia, Int. : New York, **1956**, pp 606-611.
   Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135-2167 and references cited therein
3. Nicolaou, K. C.; Chu, X. J.; Ramanjulu, J. M.; Natarajan, S.; Brase, S.; Rubsam, F.; Boddy, C. N. C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36* 1539-1540.
   Nicolaou, K. C.; Natarajan, S.; Hui Li; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N. C.; Takayanagi, M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37* , 2708-2714.
   Nicolaou, K. C.; Jain, N. F.; Natarajan, S.; Hughes, R.; Solomon, M. E.; Hui Li; Ramanjulu, J. M.; Takayanagi, M.; Koumbis, A. E.; Bando, T. *Angew. Chem. Int. Ed. Engl.* **1998**, *37* , 2714-2716.
   Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37* , 2717-2719.
4. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761.
   Evans, D. A.; Weber, A. E. *Ibid* **1987**, *109*, 7151-7157.
   Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39-42.
5. Rao, A. V. R.; Chakraborty, T. K.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1994**, *35*, 5043-5046.
6. Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560-1563.
   Pons, D.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett.* **1990**, *31*, 5023-5026.
   Genêt, J. P.; Durant, J. O.; Savignac, M.; Pons, D. *Ibid* **1992**, *33*, 2497-2500.
7. Genêt, J. P.; Jugé, S.; Mallart, S. *Tetrahedron Lett.* **1988**, *29*, 6765-6768.
   Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553-5562.
   Gautshi, M.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1083-1085.
8. Genêt, J. P.; Mallart, S.; Jugé, S.; Laffite, J. A. *French Patent* n° 8911159, Aug **1989**.
   Genêt, J. P.; Pinel, C.; Mallart, S.; Jugé, S.; Thorimbert, S.; Laffite, J. A. *Tetrahedron* : Asymmetry **1991**, *2*, 555-567.
   Girard, A.; Greck, C.; Ferroud, D.; Genêt, J. P. *Tetrahedron Lett.* **1996**, *37*, 7967-7970.
9. Ottenheijm, H. C. J.; Herscheid, J. D. M. *J. Org. Chem.* **1986**, *51*, 697-698.
10. Hoffman, C.; Tanke, R. S.; Miller, M. J. *Tetrahedron Lett.* **1989**, *30*, 3750-3751.
11. A mixture of epoxide cyano ester[18] (10 mmol) in alcohol (50 ml) and hydroxylamine hydrochloride (10 mmol) was refluxed for 5h. After evaporation of the solvent, the crude product was dissolved in Et_2O and extracted with aqueous 1N NaOH (2 x 50 ml). The aqueous solution was neutralized with 2N HCl and extracted with Et_2O (2 x 50 ml). The combined organic layers were dried (Na_2SO_4) and after removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with hexane / ethyl acetate (6:4) to afford β-alkoxy α-oximino ester **1**. The reaction always gives a mixture of two diastereoisomers E and Z, with the latter as the major product which we did not manage to isolate by column chromatography.
    For example Ethyl 3-ethoxy-3-(4-methylphenyl)-2-hydroxyiminopropanoate **1a**:
    Oil; two diastereomers (E and Z: 25/75) : IR (CCl_4): ν : 3300 (OH), 1600 (C=N) and 1720 (CO) cm^{-1}.
    ^1H NMR ($CDCl_3$/ 250 MHz) δ ppm: 7.12-7.43 (m, 4H, Ar); 3.58 (q, 2H, $O\underline{CH_2}CH_3$); 1.24 (t, 3H, $OCH_2\underline{CH_3}$); 4.22 (q, 2H, $CO_2\underline{CH_2}CH_3$); 1.24 (t, 3H, $CO_2CH_2\underline{CH_3}$); 5.96 (s, 1H, CH, isomer Z); 5.15 (s, 1H, CH, isomer E); 2.32 (s, 3H, CH_3); 9.9 (s, 1H, OH).
    See Boukhris, S.; Souizi, A.; Robert, A. *Tetrahedron Lett.* **1996**, *37* (27), 4693-4696.
12. Leeds, J. P.; Kirst, H. A. *Synth. Commun.* **1988**, *18*, 777-782.
13. All isolated compounds gave satisfactory mass spectra. Spectral data are in full agreement with the proposed structures.

For example : **2a** : IR (CCl_4) : ν : 3300-3450, 1725 cm^{-1}.
^1H NMR ($CDCl_3$/ 250 MHz) δ ppm: 7.15-7.40 (m, 4H, Ar); 3.52 (q, 2H, $O\underline{CH_2}CH_3$); 1.23 (t, 3H, $OCH_2\underline{CH_3}$); 4.25 (q, 2H, $CO_2\underline{CH_2}CH_3$); 1.25 (t, 3H, $CO_2CH_2\underline{CH_3}$); 2.30 (s, 3H, CH_3); major diastereoisomer : 4.31 (d, 1H, ^2J = 4.0 Hz, CH); 4.45 (dt, 1H, ^2J = 9.8 and 4.0 Hz, $CHNH_2$); 3.52 (d, 2H, ^2J = 9.8 Hz, NH_2); minor diastereoisomer : 4.40 (d, 1H, ^2J = 3.9 Hz, CH); 4.60 (dt, 1H, ^2J = 9.7 and 3.9 Hz, $CHNH_2$); 3.52 (d, 2H, ^2J = 9.6 Hz, NH_2).
^{13}C NMR : major diastereomer : 125.7, 129.3, 136.5, 137.6 (Ar-ring C); 70.5 (dd, ^1J = 146.6 and ^2J = 5.0 Hz, CH); 65.5 (dd, ^1J = 145.5 and ^2J = 5.0 Hz, $CHNH_2$); 64.9 (tq, ^1J = 142.6 and ^2J = 4.6 Hz, $O\underline{CH_2}CH_3$); 15.2 (qt, ^1J = 126.4 and ^2J = 4.6 Hz, $OCH_2\underline{CH_3}$); 61.6 (tq, ^1J = 145.6 and ^2J = 4.7 Hz, $CO_2\underline{CH_2}CH_3$); 14.1 (qt, ^1J = 127.3 and ^2J = 4.7 Hz, $CO_2CH_2\underline{CH_3}$); 167.7 (s, CO); 21.2 (q, ^1J = 127.0 Hz, CH_3). Minor diastereomer : 127.2, 130.1, 136.1, 138.0 (Ar- ring C); 71.4 (dd, ^1J = 146.3 and ^2J = 5.0 Hz, CH); 64.2 (dd, ^1J = 145.2 and ^2J = 5.0 Hz, $CHNH_2$); 64.4 (tq, ^1J = 142.2 and ^2J = 4.7 Hz, $O\underline{CH_2}CH_3$); 14.7 (qt, ^1J = 126.4 and ^2J = 4.7 Hz, $OCH_2\underline{CH_3}$); 61.2 (tq, ^1J = 145.6 and ^2J = 4.8 Hz, $CO_2\underline{CH_2}CH_3$); 14.5 (qt, ^1J = 127.3 and ^2J = 4.8 Hz, $CO_2CH_2\underline{CH_3}$); 167.2 (s, CO); 21.2 (q, ^1J = 127.0 Hz, CH_3).
HMRS Calc. for $C_{14}H_{21}NO_3$ 251.3251 found 251.323.

14. Weisburger, J. H.; Weisburger, E. K. *Pharmacol. Rev.* **1973**, *1*, 25-32.
Maehr, H. *Pure App. Chem.* **1971**, *28*, 603-636.
15. Scott, A. I.; Yoo, S. E.; Chung, S. K.; Lacadie, J. A. *Tetrahedron Lett.* **1976**, 1137-1140.
16. Ahmad, A. *Bull. Chem. Soc. Japan* **1974**, *47*, 1819-1820.
Moller, B. L.; Mc Farlane, I. J.; Conn, E. E. *Acta Chem. Scand.* **1977**, *31*, 343-344.
Herscheid, J. D. M.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1978**, *51*, 5143-5144.

17. A 7N ethanolic HCl solution (7 mL) was added dropwise to a stirred solution of **1j-k** (5 mmol) and pyridine-borane complex (25 mmol) in ethanol (10 mL) at such a rate that the temperature did not exceed 40°C. Stirring was continued for one hour after which the solvent was evaporated. The residue was taken up in CH_2Cl_2, Washed with 1N NaOH, the organic layer was dried (Na_2SO_4) and evaporated. Purification was done by column chromatography (Merck silica gel 60, hexane/ ethyl acetate 3 : 2 as eluent) to give the pure N-hydroxy α-amino acid esters **2j-k**.
For example : **2j** : IR (CCl_4) : ν : 3350-3450, 1720 cm^{-1}.
^1H NMR ($CDCl_3$/ 250 MHz) δ ppm : 7.20-7.40 (m, 4H, Ar); 3.52 (q, 2H, $O\underline{CH_2}CH_3$); 1.23 (t, 3H, $OCH_2\underline{CH_3}$); 4.25 (q, 2H, $CO_2\underline{CH_2}CH_3$); 1.25 (t, 3H, $CO_2CH_2\underline{CH_3}$); 2.30 (s, 3H, CH_3); 4.35 (s, 1H, OH); major diastereoisomer : 4.45 (d, 1H, ^2J = 3.8 Hz, CH); 4.62 (dd, 1H, ^2J = 9.9 and 3.8 Hz, CHNH); 3.52 (d, 1H, ^2J = 9.9 Hz, NH);.minor diastereoisomer : 4.35 (d, 1H, ^2J = 3.6 Hz, CH); 4.62 (dd, 1H, ^2J = 9.6 and 3.8 Hz, CHNH); 3.52 (d, 1H, ^2J = 9.6 Hz, NH).
^{13}C NMR δ : major diastereomer : 124.7, 129.3, 135.5, 137.6 (Ar-ring C); 72.5 (dd, ^1J = 145.6 and ^2J = 5.0 Hz, CH); 65.7 (dd, ^1J = 143.5 and ^2J = 5.0 Hz, CHNH); 64.9 (tq, ^1J = 142.6 and ^2J = 4.6 Hz, $O\underline{CH_2}CH_3$); 15.2 (qt, ^1J = 126.4 and ^2J = 4.6 Hz, $OCH_2\underline{CH_3}$); 61.6 (tq, ^1J = 145.6 and ^2J = 4.7 Hz, $CO_2\underline{CH_2}CH_3$); 14.1 (qt, ^1J = 127.3 and ^2J = 4.7 Hz, $CO_2CH_2\underline{CH_3}$); 167.7 (s, CO); 21.2 (q, ^1J = 127.0 Hz, CH_3). Minor diastereoisomer : 125.3, 130.1, 136.7, 138.8 (Ar-ring C); 71.7 (dd, ^1J = 145.3 and ^2J = 4.8 Hz, CH); 64.8 (dd, ^1J = 143.3 and ^2J = 5.0 Hz, CHNH); 64.3 (tq, ^1J = 142.4 and ^2J = 4.5 Hz, $O\underline{CH_2}CH_3$); 14.9 (qt, ^1J = 126.2 and ^2J = 4.5 Hz, $OCH_2\underline{CH_3}$); 61.2 (tq, ^1J = 145.1 and ^2J = 4.5 Hz, $CO_2\underline{CH_2}CH_3$); 14.5 (qt, ^1J = 127.3 and ^2J = 4.5 Hz, $CO_2CH_2\underline{CH_3}$); 167.5 (s, CO); 21.2 (q, ^1J = 127.0 Hz, CH_3).
HMRS Calc. for $C_{14}H_{21}NO_4$ 267.4215 found 267.425.

18. Epoxides cyano esters were prepared in a two-step procedure : for the first one, a Knoevenagel-cope condensation, see Gardner, P. D.; Brandon, R. L. *J. Org. Chem.* **1957**, *22*, 1704-1707.
Texier-Boullet, F.; Foucaud, A. *Tetrahedron Lett.* **1982**, *23*, 4927-4930.
For the second step, an epoxidation of the olefin by sodium hypochlorite, see Baudy, M.; Robert, A; Foucaud, A. *J. Org. Chem.* **1978**, *43*, 3732-3735.