

Synthesis of γ -amino acid analogues from natural α -amino acids by a radical pathway

M. C. Corvo and M. M. A. Pereira

REQUIMTE/CQFB, Departamento de Quimica, Faculdade de Ciencias e Tecnologia,
Universidade Nova de Lisboa, Caparica, Portugal

Received April 24, 2006

Accepted May 3, 2006

Published online August 2, 2006; © Springer-Verlag 2006

Summary. New γ -amino esters and amides were prepared by a radical 1,4-addition of carbon radicals to acrylic derivatives. α -Amino acids derivatives holding chiral auxiliaries as radical precursors and different chiral olefins were used and chiral induction on the C- γ center was discussed.

Keywords: Amino acids and derivatives – Radicals – Synthesis

Introduction

γ -Amino acids play an important role in biological processes related to Parkinson disease and epilepsy (Burke and Silverman, 1991; Nanavati and Silverman, 1991) and are useful building blocks in the synthesis of new γ -peptides with potential for biomedical application. Recently the folding properties of γ -peptides have been investigated, as they proved to generate stable secondary structures (Trabocchi et al., 2005). In γ -amino acids the introduction of additional substituents and stereocenters expands the number of possible compounds and the corresponding oligomers have additional torsional freedom due to the presence of new sp^3 -hybridized C–C bonds.

There is an increasing demand for the synthesis of γ -amino acid derivatives. Relevant synthetic approaches to new γ -amino acids through the use of sugar chemistry and asymmetric synthesis have been developed. Recently, Skrydstrup and collaborators reported a radical addition of alkyl nitrones to acrylates (Johannesen et al., 2004) and acrylamides (Riber and Skrydstrup, 2003) mediated by samarium diiodide yielding chiral γ -amino acids, using carbohydrate based chiral auxiliaries.

The homologation of α -amino acids is a widespread method to increase the chemical diversity of synthetic γ -amino acids but, to our knowledge, it is the first time that radical species generated from natural α -amino acids are used to synthesise γ -amino acid derivatives **1**.

Materials and methods

Melting points were carried out on a Köfeler Reichert Thermover melting apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer at 400 and 100 MHz, respectively. Infrared spectra were recorded on a Buck Scientific FT-IR 500 spectrometer. High resolution accurate mass determinations were carried out by the Mass Spectrometry Service at The Scripps Research Institute, USA. Optical activities were measured on a Perkin Elmer 241 MC polarimeter. All compounds were fully characterised. Relevant compounds **6** and **1** are presented.

*Synthesis of γ -amino esters and amide derivatives **6** from the corresponding α -amino acids **2** (General procedure)*

To a stirred solution of acid **2** (0.60 mmol) and *N*-hydroxy-2-thiopyridone (0.66 mmol) in dry CH_2Cl_2 (4 ml), under argon atmosphere and light protection at 0 °C, was slowly added a solution of 1,3-dicyclohexylcarbodiimide (0.72 mmol) in CH_2Cl_2 (2 ml). The mixture was allowed to warm up to room temperature. After 4 hours the yellow solution was filtered to remove *N,N*-dicyclohexylurea and concentrated to dryness affording the crude thiohydroxamic ester **3**. The acrylic amide or ester **5** (1.2 mmol) was added to a solution of crude **3** in CH_2Cl_2 (2 ml) at –40 °C. The resulting mixture was irradiated with a Phillips 125 HPR lamp for 40 minutes. After completion of the reaction, the mixture was concentrated to dryness under reduced pressure and the residue was submitted to column chromatography (SiO_2 , hexane/ Et_2O), affording pure **6** as an oil. Pure samples of the isomers were obtained by planar chromatography (SiO_2 , hexane/ethyl acetate/ Et_2O). Compound **6** was characterized as a mixture of diastereoisomers. The minor diastereoisomer presents all the NMR signals superimposed with the major except for the ones mentioned.

Ethyl 5-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylcarbamoyl)-2-(pyridin-2-ylthio)-4-(1*H*-pyrrol-1'-yl)pentanoate (**6g**)

Oil; 41% yield as a diastereoisomeric mixture, d.e. 8% (C- γ).

IR (film) ν_{\max} (cm⁻¹): 3333 (m), 3099 (w), 2954 (s), 1731 (s), 1643 (s), 1578 (m), 1538 (s), 1454 (s).

HRMS – MALDI-FTMS (DHB): 506.2448, [M + Na]⁺ calculated for C₂₇H₃₇N₃NaO₃S requires 506.2448.

Major diastereoisomeric pair – major isomer

¹H NMR (CDCl₃) δ (ppm): 0.51 (s, 3H, H_{aliph}), 0.71 (s, 3H, H_{aliph}), 0.75 (s, 3H, H_{aliph}), 1.10 (1H, m, H_{aliph}), 1.14 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 1.17–1.25 (m, 2H, H_{aliph}), 1.47 (m, 1H, H_{aliph}), 1.61–1.83 (m, 3H, H_{aliph}), 2.31 (m, 1H, C(3)H), 2.56 (m, 1H, C(3)H), 2.60 (d, *J* = 7.2 Hz, 2H, C(5)H), 3.73 (dt, *J* = 8.8 and 5.2 Hz, 1H, H_{aliph}), 3.89 (dd, *J* = 10.0 and 4.8 Hz, 1H, C(2)H), 4.01–4.23 (m, 2H, OCH₂CH₃), 4.68 (m, 1H, C(4)H), 5.19 (d, *J* = 8.0 Hz, 1H, NH), 6.09 (t, *J* = 2.0 Hz, 2H, C(3')H, C(4')H), 6.63 (t, *J* = 2.0 Hz, 2H, C(2')H, C(5')H), 6.98 (dd, *J* = 6.6 and 5.4 Hz, 1H, C(5)H_{Spyr}), 7.17 (d, *J* = 8.0 Hz, 1H, C(3)H_{Spyr}), 7.48 (dt, *J* = 7.6 and 1.6 Hz, 1H, C(4)H_{Spyr}), 8.32 (d, *J* = 4.0 Hz, 1H, C(6)H_{Spyr}).

¹³C NMR (CDCl₃) δ (ppm): 11.2, 13.9, 20.1, 26.9, 35.9, 37.7, 38.5, 43.6, 44.3, 44.7, 46.9, 48.2, 54.9, 57.0, 61.4, 108.9, 118.7, 120.0, 122.4, 136.1, 149.2, 156.6, 168.6, 171.7.

Major diastereoisomeric pair – different signals for the minor isomer when mixed with the major

¹H NMR (CDCl₃) δ (ppm): 0.52 (s, 3H, H_{aliph}), 0.82 (3H, s, H_{aliph}), 0.84 (s, 3H, H_{aliph}), 4.01–4.23 (m, 1H, C(2)H), 4.62 (m, 1H, C(4)H), 6.15 (t, *J* = 2.0 Hz, 2H, C(3')H, C(4')H), 6.68 (t, *J* = 2.0 Hz, 2H, C(2')H, C(5')H), 7.11 (d, *J* = 8.0 Hz, 1H, C(3)H_{Spyr}).

¹³C NMR (CDCl₃) δ (ppm): 11.7, 24.9, 33.9, 38.8, 43.2, 44.0, 55.1, 56.7, 108.7, 119.0, 122.2, 149.2.

Synthesis of γ -amino esters and amides **1** from the corresponding γ -amino ester or amide derivatives **6** (General procedure)

To a stirred solution of **6** (0.08 mmol) and nickel chloride hexahydrate (0.8 mmol) in EtOH (5 ml) at 0 °C, was slowly added sodium borohydride (1.6 mmol) in EtOH/H₂O (5 ml/5 ml). The mixture was stirred at room temperature for 3 hours. After completion of the reaction, the suspension was filtered through celite, washed with CH₂Cl₂, and the resulting solution was concentrated under reduced pressure to remove EtOH. The residue was diluted with CH₂Cl₂ and washed with H₂O. It was then dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure. The residue was submitted to planar chromatography (SiO₂, Et₂O), affording pure **1**.

Ethyl 5-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylcarbamoyl)-4-(1*H*-pyrrol-1'-yl)pentanoate (**1g**)

Major diastereoisomer

Oil; 86% yield, $[\alpha]_{\text{D}}^{22} = -33.1^\circ$ (c 1.08, CHCl₃)

IR (film) ν_{\max} (cm⁻¹): 3338 (s), 2954 (s), 1732 (s), 1648 (s), 1541 (s), 1457 (s).

¹H NMR (CDCl₃) δ (ppm): 0.54 (s, 3H, H_{aliph}), 0.73 (s, 3H, H_{aliph}), 0.76 (s, 3H, H_{aliph}), 1.10 (m, 1H, H_{aliph}), 1.22 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 1.17–1.27 (2H, m, H_{aliph}), 1.47 (1H, m, H_{aliph}), 1.62–1.82 (m, 3H, H_{aliph}), 2.03–2.21 (4H, m, C(2)H, C(3)H), 2.58 (d, *J* = 7.2 Hz, 2H, C(5)H), 3.77 (1H, dt, *J* = 8.8 and 4.8 Hz, H_{aliph}), 4.08 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 4.41 (m, 1H, C(4)H), 5.19 (d, *J* = 8.0 Hz, 1H, NH), 6.13 (s, 2H, C(3')H, C(4')H), 6.64 (d, *J* = 1.6 Hz, 2H, C(2')H, C(5')H).

¹³C NMR (CDCl₃) δ (ppm): 11.2, 14.1, 20.1, 26.9, 30.7, 31.4, 35.9, 39.0, 44.4, 44.8, 47.0, 48.3, 56.5, 56.9, 60.5, 108.7, 118.6, 168.7, 172.7.

Minor diastereoisomer

Oil; 61% yield, $[\alpha]_{\text{D}}^{22} = -13.1^\circ$ (c 0.55, CHCl₃)

IR (film) ν_{\max} (cm⁻¹): 3337 (s), 2927 (s), 1732 (s), 1652 (s), 1538 (s), 1456 (s).

¹H NMR (CDCl₃) δ (ppm): 0.66 (s, 3H, H_{aliph}), 0.74 (s, 3H, H_{aliph}), 0.77 (s, 3H, H_{aliph}), 1.08 (m, 1H, H_{aliph}), 1.21 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 1.17–1.33 (m, 2H, H_{aliph}), 1.50 (m, 1H, H_{aliph}), 1.61–1.68 (m, 3H, H_{aliph}), 2.04–2.20 (m, 4H, C(2)H, C(3)H), 2.52–2.60 (m, 2H, C(5)H), 3.75 (dt, *J* = 9.0 and 5.2 Hz, 1H, H_{aliph}), 4.08 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 4.34 (m, 1H, C(4)H), 5.01 (d, *J* = 8.4 Hz, 1H, NH), 6.14 (t, *J* = 2.0 Hz, 2H, C(3')H, C(4')H), 6.64 (t, *J* = 2.0 Hz, 2H, C(2')H, C(5')H).

¹³C NMR (CDCl₃) δ (ppm): 11.7, 14.1, 20.1, 20.2, 26.9, 30.7, 31.3, 35.9, 38.6, 44.7, 45.0, 47.0, 48.2, 56.7, 56.9, 60.5, 108.9, 118.6, 168.7, 172.6.

HRMS – MALDI-FTMS (DHB): 375.2643, [M + H]⁺ calculated for C₂₂H₃₅N₂O₃ requires 375.2642.

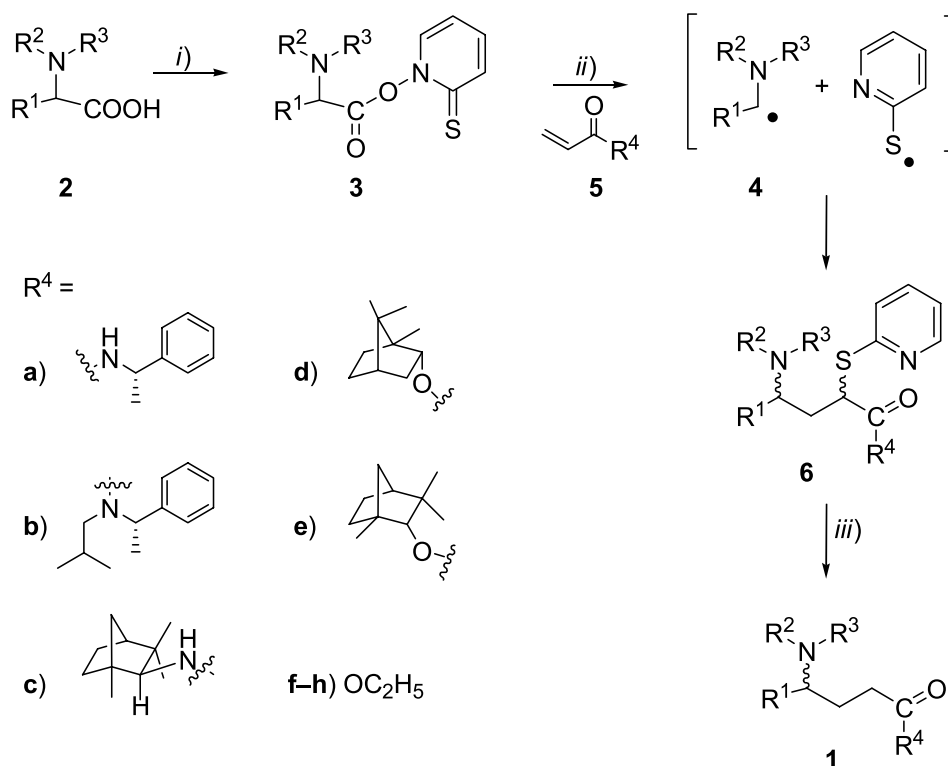
Results and discussion

Herein we report a general method for obtaining γ -amino acid derivatives **1** from α -amino acid **2** in three steps involving a nucleophilic carbon radical intermediate **4** able to add to the electron withdrawing olefins **5**. In this transformation the initial addition reaction generated two new α and γ stereogenic carbon centers in compounds **6**. To improve the asymmetric addition several chiral auxiliaries located on the olefin or amino acid moieties were tested. The chiral induction achieved in the radical addition step and the generation of diastereoisomers could allow the purification of the pure isomers of the addition compounds **6a–h**. γ -Amino amides **1a–c** or esters **1d–h** were subsequently obtained by nickel boride treatment (Barton and Liu, 1997) of the corresponding α -substituted γ -amino compounds **6** carrying a thiopyridyl group (Scheme 1).

The N-protected α -amino acids **2** were prepared from the available free or equivalent α -amino acids, DL-norvaline, L-aspartic acid and *N*-carbobenzyloxy-L-threonine, by standard transformations. Conversion into the corresponding Barton esters **3** was achieved by treatment with DCC and *N*-hydroxy-2-thiopyridone, and low temperature irradiation[†] yielded the radicals **4**. The racemic radical **4a** was obtained from **3a** while the optically pure carbon radicals **4b–d** holding chiral auxiliaries were synthesised from **3b–d**. Addition to the chiral acryl amides **5a–c** and esters **5d–e** were performed by the radical **4a** yielding 11–58% of **6a–e** (Table 1).

In the radical addition study several chiral auxiliaries located on the olefin moieties were tested. The addition of the radical **4a** to the *N*-(1-phenylethyl)acryl amide (**5a**) and to the (*S*)-*N*-isopropyl-*N*-(1-phenylethyl)acryl amide

[†] Phillips high pressure mercury vapour lamp with internal reflector, 125 HPR.



Scheme 1. Synthesis of γ -amino acid analogues **1**. **1a–e**, **2–4a** and **6a–e**: $R^1 = n\text{-C}_3\text{H}_7$, $\text{--}R^2\text{--}R^3\text{--} = \text{--C}_4\text{H}_4\text{--}$; **1f**, **2–4b** and **6f**: $R^1 = \text{CH}_2\text{CON}(\text{H})[(S)\text{-1-phenylethyl}]$, $\text{--}R^2\text{--}R^3\text{--} = \text{--C}_4\text{H}_4\text{--}$; **1g**, **2–4c** and **6g**: $R^1 = \text{CH}_2\text{CON}(\text{H})\text{exo-bornyl}$, $\text{--}R^2\text{--}R^3\text{--} = \text{--C}_4\text{H}_4\text{--}$; **1h**, **2–4d** and **6h**: $R^1 = (S)\text{-CH}(\text{CH}_3)\text{OTBDMS}$, $R^2 = \text{BOC}$, $R^3 = \text{H}$. i) DCC, *N*-hydroxy-2-thiopyridone, CH_2Cl_2 , 0°C ; ii) $h\nu$, CH_2Cl_2 , -40°C ; iii) NiCl_2 , NaBH_4 , $\text{EtOH}/\text{H}_2\text{O}$, 0°C to r.t.

Table 1. Chemical yields and diastereoisomeric excesses of γ -amino acid derivatives **6** and **1**

6 precursors			η (%)	d.e. C- α (%)	d.e. C- γ (%)	η (%)	
4a	5a	6a	43	32	6	1a	82
4a	5b	6b	11	^a	12	1b	71
4a	5c	6c	18	54	14	1c	71
4a	5d	6d	58	24	0	1d	42
4a	5e	6e	38	30	0	1e	30
4b	5f	6f	35	^a	4	1f	91
4c	5f	6g	41	^a	8	1g	86
4d	5f	6h	45	22	28	1h	100

^a Undetermined

(**5b**) led to low yields but some chiral induction on the α and γ carbon centers of the addition product is observed. The amide **6a** was achieved in 43% yield with a chiral induction of 6% in the C- γ center and 32% in the C- α , while the amide **6b** was obtained in 11% yield, with an excess of 12% on the γ carbon center and the amide **6c** in 18% yield, presenting a chiral excess of 54% on the C- α and 14% on the C- γ . The higher rotamer energy and the bulky substituents of the acryl amides led to low yields

confirmed by the lack of reactivity observed in the addition of **4a** to the bulky (*S*)-*N*-neopentyl-*N*-(1-phenylethyl)acryl amide. Further, the addition products **6d–f** derived from (1*S*)-*endo*-(-)-bornyl acrylate (**5d**) and (1*R*)-*endo*-(+)-fenchyl acrylate (**5e**) presented higher yields, but chiral induction only on the C- α stereogenic carbon center providing, respectively, 24 and 30% of diastereoisomeric excess.

Otherwise the chiral auxiliary located on the α -amino acid moieties **2b–d** led to chiral induction at the γ -carbon center on the resulting γ -amino analogues **6f–h** in moderate diastereomeric excess. When optically pure L-aspartic acid derivatives holding the (*S*)-phenylethylamine (**2b**) and the *exo*-bornylamine (**2c**) moieties as chiral auxiliaries were transformed into the corresponding carbon radicals **4b–c** and added to ethyl acrylate, the corresponding chiral γ -amino esters **6f** and **6g** were achieved. Likewise the chiral L-threonine silyl radical **4d** in the presence of ethyl acrylate led to the corresponding addition product **6h**.

Treatment of **6a–h** with nickel boride led to the desulfurized **1a–h** with concomitant loss of the chirality on the α carbon center. While compounds **1d–e** were

obtained as racemic mixtures all the others were generated as mixtures enriched in one single diastereoisomer. Although the chiral inductions presented in the new γ -amino esters **1f–g** were low, their diastereoisomeric relationship allowed their purification as optically active pure isomers.

The selectivity displayed in conjugated radical additions of α -amino acids derivatives holding chiral auxiliary **2b–d** may be attributed to the energetic control of several rotamers. In our case the higher stereoselectivity observed in the γ center of the γ -amino ester **1h** can be explained by an intramolecular hydrogen bond in the radical intermediate **4d** that promoted the generation of one of the epimers. The absence of a rigid conformation by the other radicals **4b–c** resulted in a decrease of the energy barrier between the conformers and lead to a poor asymmetric induction in the γ carbon center of the γ -amino esters **1f** and **g**.

In summary, we have developed a method for preparing optically pure γ -amino esters and amides from natural occurring α -amino acids by a radical pathway generated from a Barton ester derivative. Desulfurization of the amides and esters derivatives led to the corresponding γ -amino compounds of which subsequent hydrolysis can generate the desired γ -amino acids. Using chiral auxiliaries in the amino acid moieties led to some chiral induction on the C- γ center of the γ -amino acids derivatives allowing the synthesis of optically pure γ -amino acids. Otherwise, this method presents a promising alternative for the synthesis of C- α and/or C- γ substituted γ -amino

acids through the exploitation of the radical addition product. Further application of this method to the synthesis of other γ -amino acids with biological interest is being pursued.

Acknowledgements

We thank Fundação para a Ciência e Tecnologia, POCTI and FEDER for financial support.

References

- Barton DH, Liu W (1997) The invention of radical reactions. Part XXXVIII. Homologation of carboxylic acids with acrylamide and synthetic studies of 3-deoxy-D-arabino-2-heptulosonic acid (DAH) and its 4-epimer. *Tetrahedron* 53: 12037–12088
- Burke JR, Silverman RB (1991) Mechanism of inactivation of γ -aminobutyric acid aminotransferase by 4-amino-5-hexynoic acid (γ -ethynyl GABA). *J Am Chem Soc* 113: 9329–9340
- Johannessen SA, Albu S, Hazell RG, Skrydstrup T (2004) Radical addition of nitrones to acrylates mediated by SmI_2 : asymmetric synthesis of γ -amino acids employing carbohydrate-based chiral auxiliaries. *Chem Commun* 17: 1962–1963
- Nanavati SM, Silverman RB (1991) Mechanisms of inactivation of γ -aminobutyric acid aminotransferase by the antiepilepsy drug γ -vinyl GABA (vigabatrin). *J Am Chem Soc* 113: 9341–9349
- Riber D, Skrydstrup T (2003) SmI_2 -Promoted radical addition of nitrones to α,β -unsaturated amides and esters: synthesis of α -amino acids via a nitrogen equivalent to the ketyl radical. *Org Lett* 5: 229–231
- Trabocchi A, Guarna F, Guarna A (2005) γ - and δ -amino acids: synthetic strategies and relevant applications. *Curr Organ Chem* 9: 1129–1153

Authors' address: M. Manuela A. Pereira, Departamento de Química, FCT/UNL, Campus da Caparica, 2829-516 Caparica, Portugal, Fax: +35-1212948550, E-mail: mmm@dq.fct.unl.pt