ORIGINAL ARTICLE

HETEROCYCLES 41. SYNTHESIS AND CHARACTERISATION OF NEW THIAZOLE β-AMINO ACIDS AND β-AMINO ESTERS

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Abstract

Being aware of the biological potential, low toxicity as well as biocompatibility of both amino acids and naturally occurring heterocycles, the aim of this study was the synthesis and characterization of new β-amino acids and their ethyl esters bearing the thiazole core. The thiazole β-amino acids were obtained with 52 - 68% yields, by applying a synthetically convenient modification of the Rodionov reaction, consisting in the condensation of 2-arylthiazole-4-carbaldehydes with malonic acid and ammonium acetate. The obtained β-amino acids were converted into ethyl carboxylates by a single-step procedure, involving the activation of the carboxyl group by treatment with thionyl chloride. The synthesized compounds were purified and characterized by melting point, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Rezumat

Având în vedere potențialul biologic, toxicitatea redusă precum și biocompatibilitatea cu sistemele vii atât ale β-aminoacizilor cât și ale sistemelor heterociclice naturale, scopul acestui studiu a fost sinteza și caracterizarea unor noi β-aminoacizi și β-aminoesteri derivați de tiazol. β-Aminoacizii tiazolici s-au obținut cu randamente de 52 - 68%, prin aplicarea reacției Rodionov într-o variantă modificată, constând în condensarea unor 2-arilтiazol-4-carbaldehide cu acid malonic și acetat de amoniu. β-Aminoacizii obținuți au fost transformați în carboxilații de etil corespunzători într-o singură etapă, ce a implicat activarea grupei carboxil prin utilizarea clorurii de tionil. Compușii sintetizați au fost purificați și caracterizați prin punct de topire, ^{1}H RMN, ^{13}C RMN și spectrometrie de masă.

Keywords: thiazole, β-amino acid, β-amino ester

Introduction

Azole heterocycles have a great therapeutic value, being present as pharmacophore groups in the structure of many medicines and new potential drug candidates for the treatment of various diseases [2, 3]. Moreover, their phytobiological potential was also revealed in recent researches [21]. The thiazole ring, originally a naturally occurring heterocycle, is currently present as central core in the structure of many bioactive compounds, some of them being introduced in therapy for the treatment of inflammation, cancer, bacterial and fungal infections [2]. At present, an increasing special attention is attributed to thiazole peptide antibiotics, which are naturally occurring cyclic macromolecules with microbial and marine origins, displaying antimicrobial and anticancer properties [9]. The discovery of thiazole peptides as promising drug candidates encouraged the obtaining of new structurally diverse thiazole based amino acids and peptide sequences for therapeutic purposes [16].

β-Amino acids and their derivatives have been intensively studied due to their utility in drug research, both individually [15], as well as key-intermediates in the synthesis of bioactive compounds [23]. β-Amino acid alkyl esters are currently used in peptide chemistry [10], polymer materials [4] and for the synthesis of other functionalized compounds [5, 6]. Beta-lactams, which are the cyclisation products of β-amino acids, are the central core of many antibiotics [21]. β-Peptides, obtained by the condensation of β-amino acids, have the advantage of a superior metabolic stability than β-peptides, which is due to their resistance to proteolytic degradation [11]. β-Amino acids containing heterocyclic side chains have a promising biological potential, but they are hardly available and, therefore, they have not been studied enough.

One of the synthetic routes to β-amino acids is the Rodionov reaction of aldehydes with malonic acid and ammonia [18, 19]. A.V. Lebedev *et al.* applied a synthetically convenient modification of the Rodionov reaction, in which ammonia was generated from ammonium acetate [12].

The synthesis of amino acid alkyl esters by the esterification of the free amino acids involves several problems, because side-reactions could occur, due to the presence of the unprotected amine group, which can act as a competitive *N*-nucleophile. Therefore, a multi-step sequence is required, consisting in *N*-protection, esterification of the carboxyl group, followed by final *N*-deprotection. Single-step procedures were also proposed, involving the use of gaseous hydrochloric acid or sulfuric acid under reflux [7], or 2,2-di-methoxypropane [17]. An efficient method for the esterification of amino acids uses thionyl chloride for the activation of the carboxyl group [14]. For the preparation of methyl esters, the use of tri-methylsilyl chloride was reported as a convenient method [13].

The low toxicity and biocompatibility with living organisms of both amino acids and naturally occurring heterocycles led us to orient our research to the synthesis of new amino acids containing bioactive heterocyclic moieties, for medicinal applications. We have recently reported the synthesis of new neurotensin peptide analogues incorporating 2-aryl-thiazole alanines, with improved plasma stability and selectivity towards NTS1 receptors, while also preserving the native receptor binding affinity and biological activity of neurotensin [8]. Several reported studies revealed also the vast biological potential of the 2-phenylthiazole scaffold [1].

In the continuation of our researches regarding thiazole derived amino acids with biological potential, the aim of this study is the synthesis and characterization of new β-amino acids and β-amino esters bearing 2-arylthiazole moieties. For this purpose, we made an attempt of the Rodionov reaction, using as substrates different 2-aryl-thiazole-4-carbaldehydes, malonic acid and ammonium acetate. For the synthesis of β-amino esters, we opted for a single-step procedure involving the use of thionyl chloride for the activation of the carboxyl group.

Materials and Methods

The reagents and solvents necessary for the synthesis of the target compounds and intermediates were purchased from Sigma Aldrich, Germany. MS spectra were recorded on Agilent 6410 Triple Quadrupole LC/MS mass spectrometry system. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker Avance DPX-300 spectrometer operating at 600 and 150 MHz, respectively. Chemical shifts on the δ scale are expressed in ppm values from TMS as internal standard.

Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60F254 sheets, and different eluents as mobile phase: a mixture of petroleum ether: ethyl acetate 4:1 *v/v* for the thiazolic aldehydes, and respectively a mixture of *n*-butanol:acetic acid: water 3:1:1 *v/v/v* for the thiazolic β-amino acids and their ethyl esters. In all cases, the spots were visualized in UV light at 254 nm. Preparative chromatographic purifications were performed for the thiazolic aldehydes, using column chromatography on Merck Kieselgel 60Å (63 - 200 μm) and a mixture of petroleum ether: ethyl acetate 4:1 *v/v* as eluent.

Melting points were determined on open glass capillaries using an Electrothermal IA 9000 digital apparatus.

The thiazole aldehydes **3a-e**, necessary as precursors in the Rodionov reaction, were synthesized according to the previously reported procedure [20], by the Hantzsch condensation of thiobenzamides **1a-e** with 1,3-dichloroacetone, followed by Sommelet reaction (Figure 1).

The synthesis of thiazole β-amino acids was performed by a one-step procedure, which consists in the condensation of 2-arylthiazole-4-carbaldehydes, ammonium acetate and malonic acid (Figure 1).

The obtained β-amino acids were esterified by treatment with anhydrous ethanol, in the presence of thionyl chloride (Figure 2).

*Synthesis of 3-amino-3-(2-arylthiazol-4-yl)propanoic acids (**5a-e**)*

To a solution of 2-arylthiazol-4-carbaldehyde **3a-e** (3 mmol) in glacial acetic acid (6 mL), anhydrous ammonium acetate (12 mmol, 924 mg) and one drop of water were added. The solution was stirred at 40°C for 10 minutes. Then, malonic acid (3.3 mmol, 343.2 mg) was added and the reaction mixture was stirred at 85°C for 3 hours. After the completion of the reaction, the mixture was poured into ice and the formed precipitate was removed by filtration under reduced pressure. The filtrate was concentrated under rotatory evaporation at reduced pressure, at 40°C, and the concentrated solution was neutralized with a 30% NaOH solution. After cooling the mixture, the formed crystals of β-amino acid were separated by filtration and washed with acetone.

*Synthesis of ethyl 3-amino-3-(2-arylthiazol-4-yl)-propanoates (**6a-e**)*

Freshly distilled thionyl chloride (3 mmol, 218 μL) was added dropwise in a round bottom flask containing anhydrous ethanol (12 mL) cooled at 0°C, under continuous stirring. Then, 3-amino-3-(2-arylthiazol-4-yl)propanoic acid **5a-e** (1 mmol) was added and the reaction mixture was stirred over-night, at room temperature. After the completion of the reaction (checked by TLC, eluent: *n*-butanol:acetic acid:water 3:1:1 *v/v/v*), the solvent was evaporated to dryness at 40°C, under rotatory evaporation at reduced pressure. The crude product was triturated in diethyl ether and the insoluble crystals were separated by filtration and washed with diethyl ether, to give the products β-amino ester hydro-chlorides. The products were dissolved in a small

amount of water and the solution was treated with a saturated solution of Na_2CO_3 until neutral pH. The formed precipitate was extracted with ethyl acetate and the organic layer was dried with anhydrous Na_2SO_4. Then, the organic solvent was evaporated to dryness under rotatory evaporation at reduced pressure, at 40°C, to give the thiazole β-amino esters as pale-yellow oily liquids.

Results and Discussion

The aim of this study was to exploit the Rodionov reaction for the synthesis of new unnatural β-amino acids and esters containing the 2-arylthiazole moiety in the side chain.

The first goal was to find the optimal reaction conditions for the synthesis of thiazole β-amino acids by the Rodionov reaction, starting from the corresponding 2-arylthiazole-4-carbaldehydes, malonic acid and ammonium acetate. As shown in Figure 1, ammonia is produced *in situ* by the hydrolysis of ammonium acetate, and forms an imine by the condensation with the aldehyde. By further attack of the malonic acid to the electrophile centre of the imine group, followed by a decarboxylation, the corresponding β-amino acid is formed. According to the studies of A. V. Lebedev [12], propenoic acid derivatives and ylidenemalonic acids can be formed as by-products during the Rodionov reaction, because the Knoevenagel condensation of aldehyde with malonic acid can occur as side-reaction.

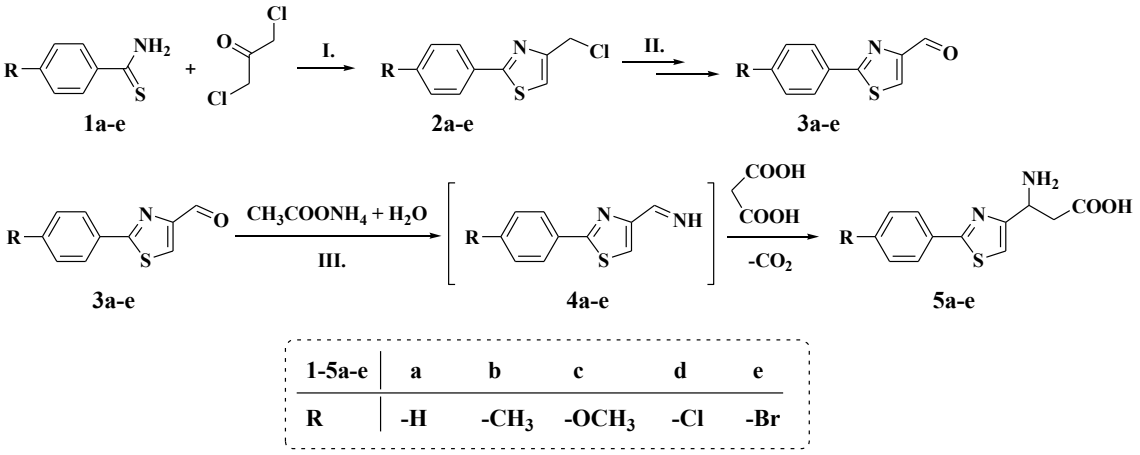


Figure 1.
Synthesis of β-amino acids with 2-arylthiazole side chain
Reaction conditions: **I.** anhydrous acetone, r.t. 24 h; **II.** 1). urotropine, $CHCl_3$, reflux 1.5 h, 2). urotropine, acetic acid 50%, reflux 1 h; **III.** glacial acetic acid, 85°C, 3 h

Based on the reported studies by A. V. Lebedev *et al.* [12], we chose to perform first the Rodionov reaction in different aliphatic alcohols as solvents: methanol, ethanol, *n*-propanol and *n*-butanol, using as model substrate 2-phenylthiazole-4-carbaldehyde. The molar *ratio* between reagents was initially chosen according to the reported studies of A. V. Lebedev [12], respectively aldehyde: malonic acid: ammonium acetate of 1:1.1:2.3. These first attempts were not satisfactory, because significant amount of propenoic acid derivative was formed as by-product, together with the desired β-amino acid. Due to the obtained low conversions in β-amino acid, we decided to investigate the Rodionov reaction in other solvents. We opted for the use of acetic acid, considering that acidic catalysis could favour the formation of the imine intermediate.

A considerable increase of the reaction yield was achieved when concentrated acetic acid was used as solvent in the Rodionov reaction, at reflux (85°C), with the addition of a drop of water necessary for the hydrolysis of ammonium acetate. By increasing the amount of ammonium acetate from 2.3 to 4 equiv., the β-amino acids were formed in higher yields, between 52 and 68% (Table I). The undesired by-products were easy removed during the isolation process, by pouring into ice the reaction mixture followed by filtration. The β-amino acids were isolated from the filtrate solution, by precipitation at their isoelectric point, and then washed with acetone.

The obtained β-amino acids were transformed into their corresponding ethyl esters in a single step procedure, by treatment with anhydrous ethanol in excess and thionyl chloride (3 equiv.), at 0°C (Figure 2). In this reaction, thionyl chloride has a double role: it activates the carboxyl group by transforming it into acyl chloride, and secondly, the formed hydrochloric acid protonates the nitrogen atom, this way preventing the free amine group to act as a nucleophile.

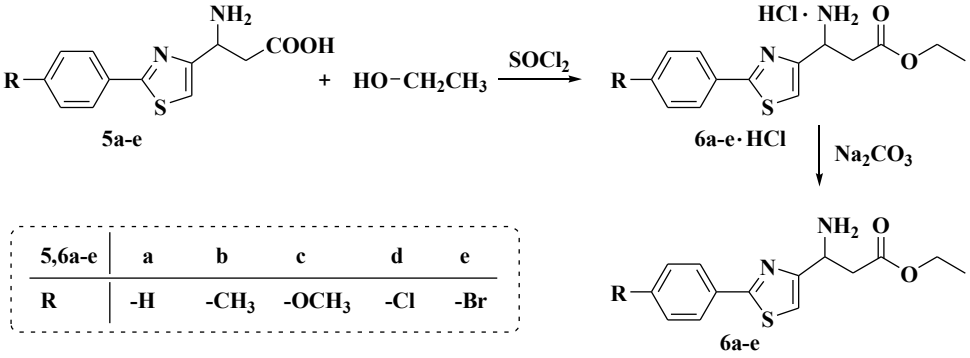


Figure 2.
Synthesis of thiazole β-amino esters
Reaction conditions: anhydrous ethanol, thionyl chloride (3 eq.), 0°C (30 min), r.t. (24 h)

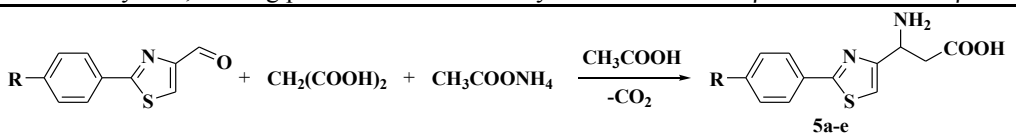
The thiazole β-amino esters were obtained by this procedure with 88 - 92% yields.

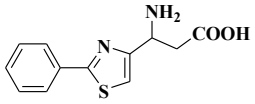
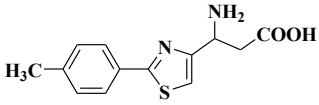
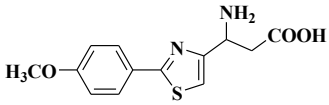
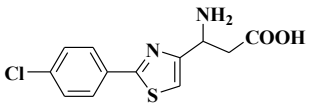
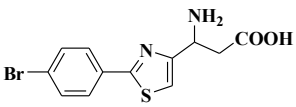
All synthesized compounds were characterized by melting point, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The reaction yields, melting points and molecular peaks for the synthesized β-amino acids and their ethyl esters are given in Table I.

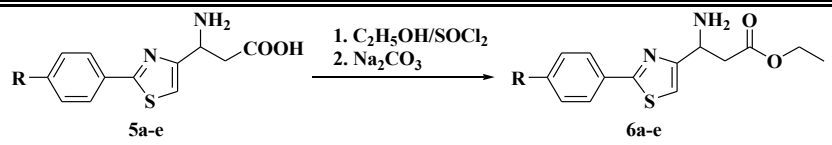
In the ^{1}H NMR spectra of the thiazole β-amino acids are present the characteristic signals corresponding to the protons from the β position (-C*H*$_2$-COOH), as a doublet (d) or multiplet (m), in the aliphatic area, at 3.01 - 2.36 ppm. The C*H* proton located in the β position of the propanoic acid chain appears as a triplet (t) or double doublet (dd) at chemical shifts between 4.72 ppm and 4.17 ppm. All signals corresponding to the protons located on the benzene ring and thiazole ring are present in the aromatic region. The proton located in the 5th position of the thiazole ring appears as a singlet at 7.58 - 6.98 ppm.

In the ^{1}H NMR spectra of the corresponding amino acid ethyl esters **6a-e**, two characteristic signals are present in the aliphatic area, indicating the presence of the ethyl group: the -O-C*H*$_2$- protons give a signal (quartet (q), doublet of triplets of triplets (dtt), quartet of doublets (qd), double doublet (dd)) at 4.14 - 4.05 ppm and the -C*H*$_3$ protons give a triplet at 1.16 - 1.09 ppm. The signals of the β C*H*$_2$ protons from the propanoate chain are present at 3.22 - 3.12 ppm (d, qd), while the signals of the β C*H* proton are present as a triplet at chemical shifts of 5.01 - 4.91 ppm.

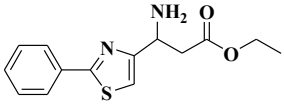
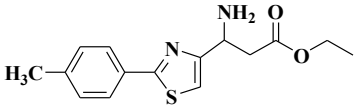
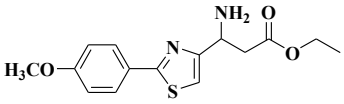
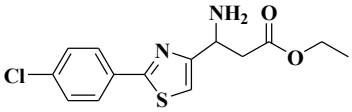
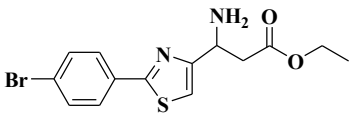
Table I
Reaction yields, melting points and LC-MS analysis for the thiazole β-amino acids and β-amino esters



	Product	Yield (%)	Physical properties	LC-MS analysis $[M+H]^+$ (m/z)
5a		56	white solid, m.p. 207 - 211°C	249.10
5b		52	white solid, m.p. 220 - 225°C	263.10
5c		53	white solid, m.p. 213 - 217°C	279.10
5d		68	white solid, m.p. 206 - 210°C	283.00 (^{35}Cl) 285.00 (^{37}Cl)
5e		61	white solid, m.p. 218 - 222°C	326.90 (^{79}Br) 328.90 (^{81}Br)



5a-e 6a-e

	Product	Yield (%)	Physical properties 6a-e	Physical properties 6a-e HCl	LC-MS analysis $[M+H]^+$ (m/z)
6a		90	pale-yellow oily liquid	white solid, m.p. 144 - 151°C	277.10
6b		92	pale-yellow oily liquid	white solid, m.p. 149 - 158°C	291.10
6c		91	pale-yellow oily liquid	white solid, m.p. 155 - 163°C	307.10
6d		91	pale-yellow oily liquid	white solid, m.p. 195 - 199°C	311.00 (^{35}Cl) 313.10 (^{37}Cl)
6e		88	pale-yellow oily liquid	white solid, m.p. 186 - 190°C	355.00 (^{79}Br) 356.90 (^{81}Br)

In the ^{13}C NMR spectra of the thiazole β-amino acids **5a-e**, a characteristic signal at 181.5 ppm indicates the presence of the carboxyl group. The carbon from the β position appears at 44.9 - 44.8 ppm, while the carbon from the β position appears at 49.4 - 49.3 ppm. In the case of the ethyl esters **6a-e**, are present, in addition, two other aliphatic signals, at 62.4 and 13.2 ppm, indicating the presence of the ethyl group. All aromatic signals are also present, thus confirming the chemical structures of the products.

The ESI MS spectra are revealing the presence of the molecular ions $[M+H]^+$ in the positive ionization mode for the analysis of compounds **5a-e, 6a-e**, and respectively $[M-H]^-$, in the case of negative ionization mode for the free amino acids **5a-e**.

*3-Amino-3-(2-phenylthiazol-4-yl)propanoic acid (**5a**)*: white solid, R_f = 0.74 (eluent: *n*-butanol:acetic acid:water 3:1:1 *v/v/v*), ^{1}H NMR (600 MHz, MeOD) δ 8.06 - 7.92 (m, 2H), 7.57 (s, 1H), 7.52 - 7.41 (m, 3H), 4.72 (dd, *J* = 8.5, 5.4 Hz, 1H), 2.88 - 2.78 (m, 2H). ^{13}C NMR (151 MHz, D_2O) δ 181.5, 179.6, 169.2, 159.9, 130.4, 129.1, 126.4, 114.2, 49.3, 44.9. LC-MS: positive ionization mode: *m/z* 249.10 (calculated: 249.07 for $C_{12}H_{12}N_2O_2S$ $[M+H]^+$), negative ionization mode: *m/z* 247.00 (calculated: 247.05 for $C_{12}H_{12}N_2O_2S$ $[M-H]^-$).

*3-Amino-3-(2-p-tolylthiazol-4-yl)propanoic acid (**5b**)*: white solid, R_f = 0.75 (eluent: *n*-butanol:acetic acid:water 3:1:1 *v/v/v*), ^{1}H NMR (600 MHz, MeOD) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.70 (dd, *J* = 8.4, 5.5 Hz, 1H), 3.01 - 2.60 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (151 MHz, D_2O) δ 181.5, 179.6, 169.5, 159.7, 140.9, 129.6, 126.2, 113.6, 49.3, 44.9, 20.5. LC-MS: positive ionization mode: *m/z* 263.10 (calculated: 263.09 for $C_{13}H_{14}N_2O_2S$ $[M+H]^+$), negative ionization mode: *m/z* 261.10 (calculated: 261.07 for $C_{13}H_{14}N_2O_2S$ $[M-H]^-$).

*3-Amino-3-(2-p-methoxyphenylthiazol-4-yl)propanoic acid (**5c**)*: white solid, R_f = 0.73 (eluent: *n*-butanol: acetic acid:water 3:1:1 *v/v/v*), ^{1}H NMR (600 MHz, MeOD) δ 7.92 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.43 (s, 1H), 7.00 (dd, *J* = 6.8, 2.0 Hz, 2H), 4.66 (t, *J* = 6.9 Hz, 1H), 3.84 (s, 3H), 2.80 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (151 MHz, D_2O) δ 181.5, 179.6, 169.0, 160.4, 127.8, 125.6, 114.2, 113.1, 55.3, 49.3, 44.9. LC-MS: positive ionization mode: *m/z* 279.10 (calculated: 279.08 for $C_{13}H_{14}N_2O_3S$ $[M+H]^+$), negative ionization mode: *m/z* 277.00 (calculated: 277.06 for $C_{13}H_{14}N_2O_3S$ $[M-H]^-$).

*3-Amino-3-(2-p-chlorophenylthiazol-4-yl)propanoic acid (**5d**)*: white solid, R_f = 0.75 (eluent: *n*-butanol: acetic acid:water 3:1:1 *v/v/v*), ^{1}H NMR (600 MHz, MeOD) δ 7.99 (dd, *J* = 6.7, 2.0 Hz, 2H), 7.58 (s, 1H), 7.48 (dd, *J* = 6.7, 2.0 Hz, 2H), 4.71 (t, *J* = 7.0 Hz, 1H), 2.81 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (151 MHz, D_2O) δ 181.5, 179.5, 167.3, 135.6, 131.1, 128.9, 127.42, 114.2, 49.4, 44.8. LC-MS: positive ionization mode: *m/z* 283.00 ($[M+H]^+$, ^{35}Cl), 285.00 ($[M+H]^+$, ^{37}Cl) (calculated for $C_{12}H_{11}ClN_2O_2S$: 283.03 $[M+H]^+$, ^{35}Cl, 285.06 $[M+H]^+$, ^{37}Cl), negative ionization mode: *m/z* 281.00 ($[M-H]^-$, ^{35}Cl), 283.00 ($[M-H]^-$, ^{37}Cl)

(calculated for $C_{12}H_{11}ClN_2O_2S$: 281.04 $[M-H]^-$, ^{35}Cl, 283.04 $[M-H]^-$, ^{37}Cl).

*3-Amino-3-(2-p-bromophenylthiazol-4-yl)propanoic acid (**5e**)*: white solid, R_f = 0.70 (eluent: *n*-butanol: acetic acid:water 3:1:1 *v/v/v*), ^1H NMR (600 MHz, D_2O) δ 7.18 - 7.05 (m, 4H), 6.98 (s, 1H), 4.17 (dd, *J* = 9.9, 3.9 Hz, 1H), 2.36 (ddd, *J* = 25.4, 15.4, 7.0 Hz, 2H). ^{13}C NMR (151 MHz, D_2O) δ 181.5, 179.4, 167.2, 160.7, 131.9, 127.6, 124.2, 114.1, 49.4, 44.8. LC-MS: positive ionization mode: *m/z* 326.90 ($[M+H]^+$, ^{79}Br), 328.90 ($[M+H]^+$, ^{81}Br) (calculated for $C_{12}H_{11}BrN_2O_2S$: 326.98 ($[M+H]^+$, ^{79}Br), 328.98 ($[M+H]^+$, ^{81}Br)), negative ionization mode: *m/z* 324.90 ($[M-H]^-$, ^{79}Br), 326.90 ($[M-H]^-$, ^{81}Br) (calculated for $C_{12}H_{11}BrN_2O_2S$: 324.97 ($[M-H]^-$, ^{79}Br), 326.96 ($[M-H]^-$, ^{81}Br).

*Ethyl 3-amino-3-(2-phenylthiazol-4-yl)propanoate (**6a**)*: R_f = 0.83 (eluent: *n*-butanol:acetic acid:water 3:1:1 *v/v/v*), ^1H NMR (400 MHz, D_2O) δ 7.86 - 7.77 (m, 2H), 7.58 (s, 1H), 7.48 - 7.39 (m, 3H), 4.93 (t, *J* = 7.2 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.15 (d, *J* = 7.1 Hz, 2H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, D_2O) δ 171.3, 170.5, 149.8, 132.0, 131.0, 129.3, 126.6, 119.1, 62.4, 47.4, 37.0, 13.2. LC-MS: positive ionization mode: *m/z* 277.10 (calculated: 277.10 for $C_{14}H_{16}N_2O_2S$ $[M+H]^+$).

*Ethyl 3-amino-3-(2-p-tolylthiazol-4-yl)propanoate (**6b**)*: R_f = 0.82 (eluent: *n*-butanol:acetic acid:water 3:1:1 *v/v/v*), ^1H NMR (600 MHz, D_2O) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.53 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.91 (t, *J* = 6.9 Hz, 1H), 4.05 (dtt, *J* = 10.7, 7.0, 3.6 Hz, 2H), 3.12 (qd, *J* = 16.8, 6.9 Hz, 2H), 2.16 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, D_2O) δ 171.2, 170.4, 149.8, 141.7, 129.7, 129.4, 126.4, 118.5, 62.4, 47.4, 37.0, 20.5, 13.2. LC-MS: positive ionization mode: *m/z* 291.10 (calculated: 291.12 for $C_{15}H_{18}N_2O_2S$ $[M+H]^+$).

*Ethyl 3-amino-3-(2-p-methoxyphenylthiazol-4-yl-)propanoate (**6c**)*: R_f = 0.84 (eluent: *n*-butanol: acetic acid:water 3:1:1 *v/v/v*), ^1H NMR (400 MHz, D_2O) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.51 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.92 (t, *J* = 6.4 Hz, 1H), 4.09 (dd, *J* = 13.0, 6.8 Hz, 2H), 3.72 (s, 3H), 3.15 (d, *J* = 6.8 Hz, 2H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, D_2O) δ 171.2, 170.2, 161.0, 149.5, 128.1, 125.1, 118.0, 114.5, 62.4, 55.4, 47.4, 36.9, 13.2. LC-MS: positive ionization mode: *m/z* 307.10 (calculated: 307.11 for $C_{15}H_{18}N_2O_3S$ $[M+H]^+$).

*Ethyl 3-amino-3-(2-p-chlorophenylthiazol-4-yl)-propanoate (**6d**)*: R_f = 0.82 (eluent: *n*-butanol:acetic acid:water 3:1:1 *v/v/v*), ^1H NMR (600 MHz, D_2O) δ 7.64 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.98 (t, *J* = 6.7 Hz, 1H), 4.06 (qd, *J* = 6.8, 2.9 Hz, 2H), 3.18 (d, *J* = 6.2 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, D_2O) δ 171.4, 169.2, 150.2, 136.2, 130.9, 129.3, 127.9, 119.3, 62.5, 47.5, 37.1, 13.2. LC-MS: positive ionization mode: *m/z* 311.00 ($[M+H]^+$, ^{35}Cl), 313.10 ($[M+H]^+$, ^{37}Cl) (calculated for $C_{14}H_{15}ClN_2O_2S$: 311.06 ($[M+H]^+$, ^{35}Cl), 313.09 ($[M+H]^+$, ^{37}Cl).

*Ethyl 3-amino-3-(2-p-bromophenylthiazol-4-yl)-propanoate (**6e**)*: R_f = 0.82 (eluent: *n*-butanol:acetic acid:water 3:1:1 *v/v/v*), ^1H NMR (600 MHz, D_2O) δ 7.69 (d, *J* = 6.4 Hz, 2H), 7.65 (s, 1H), 7.54 (d, *J* = 6.6 Hz, 2H), 5.01 (t, *J* = 6.8 Hz, 1H), 4.14 (dd, *J* = 13.3, 6.3 Hz, 2H), 3.22 (d, *J* = 6.8 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, D_2O) δ 171.3, 169.0, 150.3, 132.2, 131.3, 128.0, 124.5, 119.2, 62.4, 47.5, 37.1, 13.2. LC-MS: positive ionization mode: *m/z* 355.00 ($[M+H]^+$, ^{79}Br), 356.90 ($[M+H]^+$, ^{81}Br) (calculated for $C_{14}H_{15}BrN_2O_2S$: 355.01 ($[M+H]^+$, ^{79}Br), 357.01 ($[M+H]^+$, ^{81}Br)).

Conclusions

We have successfully optimized and implemented the Rodionov reaction for the synthesis of new thiazole β-amino acids, with 52 - 68% yields. In terms of reaction conditions, it was found that the use of glacial acetic acid as solvent increased the conversion in β-amino acids, when compared to the use of aliphatic alcohols. The obtained thiazole β-amino acids were converted into the corresponding ethyl esters in a single-step procedure, using thionyl chloride, with 88 - 92% yields. The structures of all synthesized compounds were confirmed by spectral analysis ^1H NMR, ^{13}C NMR and mass spectrometry.

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