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> SHORT COMMUNICATIONS

Enantioselectivity of the Reaction of α-Amino Acids with Sodium Azide and Triethyl Orthoformate in the Synthesis of Tetrazoles

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Tetrazolyl derivatives or analogs of amino acids are important pharmacophoric fragments in the design of new drugs [1, 2]. 1-Substituted 1*H*-tetrazoles can be synthesized by heterocyclization of primary amines with sodium azide and ortho esters [1, 3–6]. We previously reported the synthesis of natural amino acid analogs containing a 1*H*-tetrazol-1-yl fragment in the side chain at a considerable distance from the asymmetric carbon atom, so that their optical purity was retained [7, 8]. Such compounds were used, e.g., in the synthesis of peptidomimetics [8].

Voitekhovich et al. [9] described a procedure for the synthesis of tetrazol-1-ylacetic acid derivatives via reaction of α -amino acids with sodium azide and triethyl orthoformate. However, the optical purity of the products was not discussed. Taking into account that the amino group in α -amino acids is directly linked to the asymmetric carbon atom, the problem of enantioselectivity of such reactions remains unresolved.

In this work we used enantiomerically pure L- and D-amino acids and their benzyl esters 1a-1g to synthesize the corresponding 2-(1H-tetrazol-1-yl)acetic acids 2a-2g. The substrates were amino acids of different natures, including aliphatic and aromatic amino acids, amino dicarboxylic acid benzyl esters, and those containing an ester group in the side chain. The reactions were carried out by heating a mixture of amino acid derivative 1a-1g with sodium azide and triethyl orthoformate in glacial acetic acid at 55°C. All compounds 2, except for tryptophan analog 2g, were

isolated in good yields. The product structure was confirmed by ¹H and ¹³C NMR and mass spectra, and their enantiomeric purity was determined by HPLC.

In the ¹H NMR spectra of **2a–2g**, the 5-H proton of the tetrazole ring resonated as a downfield singlet at δ 9.1–9.4 ppm, and the corresponding carbon signal was observed in the ¹³C NMR spectra at δ_C 144–



Stereoisomeric purity of tetrazolyl amino acid analogs 2a-2g according to the HPLC data (λ 254 nm)^a

Comp. no.	R	Major stereoisomer	ee, %
2a	PhCH ₂ OC(O)CH ₂	S	20
2b	PhCH ₂ OC(O)CH ₂ CH ₂	S	100
2c	MeCH ₂ CH(Me)	S,S	94 ^b
2d	PhCH ₂	S	84
2e	4-HOC ₆ H ₄ CH ₂	S	58
2f	$4-HOC_6H_4CH_2$	R	40
2g	1H-Indol-3-ylmethyl	R	96

^a All initial amino acids and amino acid esters **1a–1g** were 100% enantiomerically pure.

^b Detection wavelength λ 220 nm; *de* value is given.

146 ppm. The positions of these signals, as well as of the other signals in the NMR spectra of 2a-2g, unambiguously confirmed their structure as 1H-tetrazol-1-yl derivatives.

The stereoisomeric excess (*ee* and *de*) values of 2a-2g determined by chiral HPLC are given in table. Only tetrazolyl analog of glutamic acid ester (2b) was characterized by 100% *ee*. The other products had *ee* values ranging from 20 to 96%. We have found no relation between the enantiomeric purity and amino acid nature or reaction conditions. Obviously, the described reaction is inappropriate for the preparation of optically pure compounds since the primary amino group involved in heterocyclization is directly attached to the asymmetric carbon atom. Factors responsible for the observed partial racemization cannot be elucidated on the basis of the heterocyclization mechanism proposed in [10] and therefore further studies are necessary.

Compounds 2a–2g (general procedure). A solution of 22.4 mmol of amino acid in 40 mL of glacial acetic acid was added to a suspension of 44.8 mmol of sodium azide in 67.2 mmol of triethyl orthoformate. The mixture was carefully heated to 55° C and was stirred for 4 h at that temperature. It was then cooled, and concentrated aqueous HCl was added until a solid no longer separated. The precipitate was filtered off, chloroform was added to the filtrate, and the mixture was evaporated under reduced pressure. The product was purified by column chromatography using chloroform–methanol (50:50) as eluent.

4-(Benzyloxy)-4-oxo-2-(1*H***-tetrazol-1-yl)butanoic acid (2a).** Yield 4.02 g (65%), mp 188– 190°C, $[\alpha]_D^{23.5} = +35^{\circ}$ ($c = 1.0, H_2O$). ¹H NMR spectrum (D₂O), δ , ppm: 3.38–3.41 m (2H, β -H), 5.05–5.06 t (2H, PhCH₂), 5.65 d.d (1H, α -H, ³J = 11.2, 4.8 Hz), 7.21–7.36 m (5H, H_{arom}), 9.11 s (1H, 5-H). ¹³C NMR spectrum (D₂O), δ_C , ppm: 36.53, 59.85, 66.13, 67.45, 128.29, 128.78, 135.15, 144.49 (C⁵), 171.50, 171.81.

(2*S*)-5-(Benzyloxy)-5-oxo-2-(1*H*-tetrazol-1-yl)pentanoic acid (2b). Yield 3.92 g (64%), white crystals, mp 195–198°C, $[\alpha]_D^{23.5} = +40°$ (*c* = 1.0, H₂O). ¹H NMR spectrum (D₂O), δ , ppm: 2.22–2.25 m (2H, γ -H), 3.21–3.24 m (2H, β -H), 5.11–5.13 t (2H, PhCH₂), 5.53 d.d (1H, α -H, ³*J* = 11.4, 3.8 Hz), 7.17–7.34 m (5H, H_{arom}), 9.13 s (1H, 5-H). ¹³C NMR spectrum (D₂O), δ_C , ppm: 28.80, 31.15, 53.95, 66.13, 67.45, 126.14, 126.64, 132.45, 144.85 (C⁵), 170.41, 171.22.

3-Methyl-2-(1*H***-tetrazol-1-yl)pentanoic acid (2c).** Yield 3.42 g (83%), yellow oily liquid. ¹H NMR

spectrum (D₂O), δ, ppm: 0.78–0.82 t (3H, CH₃), 1.02– 1.06 t (3H, CH₃), 1.28–1.34 m (2H, γ-H), 2.32–2.38 m (1H, β-H), 5.44 d.d (1H, α-H, ${}^{3}J$ = 11.2, 3.2 Hz), 9.32 s (1H, 5-H). 13 C NMR spectrum (D₂O), δ_C, ppm: 10.38, 14.35, 24.76, 37.21, 66.86, 144.42 (C⁵), 170.89.

2-(1*H***-Tetrazol-1-yl)-3-phenylpropanoic acid (2d).** Yield 3.08 g (63%), white crystals, $[\alpha]_D^{21.5} = -5.3^{\circ}$ (*c* = 0.75, MeOH). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 3.32–3.40 m (1H, β -H), 3.60 d.d (1H, β -H, ²*J* = 14.5, ³*J* = 4.0 Hz), 5.26 d.d (1H, α -H, ³*J* = 11.4, 4.1 Hz), 7.05–7.20 m (5H, H_{arom}), 9.29 s (1H, 5-H). ¹³C NMR spectrum (DMSO-*d*₆), δ_C , ppm: 38.57, 66.02, 126.78, 128.68, 129.09, 138.40, 144.12 (C⁵), 169.50. Mass spectrum (ESI): *m/z* 218.0811 [*M* + Na]⁺. C₁₀H₁₀N₄O₂. Calculated: *M* + Na 218.0803.

3-(4-Hydroxyphenyl)-2-(1*H***-tetrazol-1-yl)propanoic acids 2e and 2f.** Acid 2e: yield 4.1 g (79%), light yellow crystals, $[\alpha]_D^{22.0} = +14.3^{\circ}$ (c = 1.0, MeOH); **2f**: yield 3.93 g (76%), light yellow crystals, $[\alpha]_D^{22.0} = -13.1$ (c = 1.0, MeOH). ¹H NMR spectrum (DMSO- d_6), δ , ppm: 3.17–3.29 m (1H, β -H), 3.45 d.d (1H, β -CH, ²J = 14.6, ³J = 3.6 Hz), 5.17 d.d (1H, α -H, ³J = 11.2, 4.1 Hz), 6.57 d (2H, H_{arom}, ³J = 8.3 Hz), 6.83 d (2H, H_{arom}, ³J = 8.3 Hz), 9.25 s (1H, 5-H). ¹³C NMR spectrum (DMSO- d_6), δ_C , ppm: 37.87, 66.54, 115.58, 128.05, 129.95, 144.09 (C⁵), 156.53, 169.93. Mass spectrum (ESI): m/z 257.0651 [M + Na]⁺. C₁₀H₁₀N₄O₃. Calculated: M + Na 257.0645.

3-(1*H***-Indol-3-yl)-2-(1***H***-tetrazol-1-yl)propanoic acid (2g). Yield 1.32 g (23%), yellow–orange crystals, [\alpha]_D^{21.6} = +55^\circ (c = 0.75, MeOH). ¹H NMR spectrum (DMSO-d_6), \delta, ppm: 3.58 d.d (1H, \beta-H, ²J = 15.2, ³J = 11.2 Hz), 3.75 d.d (1H, \beta-H, ²J = 15.2, 3.8 Hz), 5.54 d.d (1H, \alpha-H, ³J = 11.2, 3.9 Hz), 6.91 d (1H, H_{arom}, ³J = 2.2 Hz), 6.93–7.00 m (1H, H_{arom}), 7.01– 7.08 m (1H, H_{arom}), 7.29 d (1H, H_{arom}, ³J = 8.1 Hz), 7.51 d (1H, H_{arom}, ³J = 7.9 Hz), 9.39 s (1H, 5-H). ¹³C NMR spectrum (DMSO-d_6), \delta_C, ppm: 28.52, 64.58, 109.93, 111.90, 118.49, 118.90, 121.46, 123.96, 127.26, 136.49, 144.16 (C⁵), 170.38. Mass spectrum (ESI), m/z: 257.0923 [M + Na]⁺. C₁₂H₁₁N₅O₂. Calculated: M + Na 257.0912.**

The ¹H and ¹³C NMR spectra were recorded on Varian DPX-300 (300 and 75.5 MHz, respectively) and Bruker Avance-III-400 (400 and 100 MHz) spectrometers at 25°C; the chemical shifts were measured relative to the residual proton and carbon signals of the deuterated solvent. The high-resolution mass spectra were obtained on Bruker MicroTOF and Bruker Daltonik MaXis instruments. The melting points were ENANTIOSELECTIVITY OF THE REACTION OF α-AMINO ACIDS

melting point. The optical rotations were measured on an AA-55 Series automatic polarimeter. The progress of reactions was monitored by TLC on Silufol UV-254 and Merck Kieselgel 60F₂₅₄ plates; solvent systems for elution was selected individually for each substrate. The ee values were determined by chral HPLC using a Dionex ICS-500 liquid chromatograph equipped with a Chirobiotic T (Astec) column, 250×4.6 mm [eluent 1% aqueous solution of triethylammonium acetate (pH 4)-ethanol, 90:10; flow rate 1 mL/min; detection at λ 254 (2a, 2b, 2d–2g) and 220 nm (2c)].

determined with a PTP melting point apparatus at

a heating rate of 1 deg/min in the vicinity of the

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REFERENCES

1. Ostrovskii, V.A., Koldobskii, G.I., and Trifonov, R.E., Comprehensive Heterocyclic Chemistry III, Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., and Taylor, R.J.K., Eds., Amsterdam: Elsevier, 2008, vol. 6, p. 257.

- 2. Popova, E.A. and Trifonov, R.E., Russ. Chem. Rev., 2015, vol. 84, p. 891.
- 3. Voitekhovich, S.V., Gaponik, P.N., Grigor'ev, Yu.V., and Ivashkevich, O.A., Khim. Probl. Sozdaniya Nov. Mater. Tekhnol., 2008, p. 117.
- 4. Gaponik, P.N., Khim. Probl. Sozdaniya Nov. Mater. Tekhnol., 1998, p. 185.
- 5. Gaponik, P.N., Karavai, V.P., and Grigor'ev, Yu.V., Chem. Heterocycl. Compd., 1985, vol. 21, no. 11, 1255.
- 6. Gaponik, P.N., Karavai, V.P., Davshko, I.E., Degtyarik, M.M., and Bogatikov, A.N., Chem. Heterocycl. Compd., 1990, vol. 26, no. 11, p. 1274.
- 7. Chuprun, S.S., Popova, E.A., Mukhametshina, A.V., and Trifonov, R.E., Russ. J. Org. Chem., 2015, vol. 51, p. 1671.
- 8. Popova, E.A., Nikolskaya, S.K., Gluzdikov, I.A., and Trifonov, R.E., Tetrahedron Lett., 2014, vol. 55, p. 5041.
- 9. Voitekhovich, S.V., Grigor'ev, Yu.V., Gaponik, P.N., and Ivashkevich, O.A., Vestn. Beloruss. Gos. Univ., Ser. 2, 2010, no. 3, p. 11.
- 10. Gaponik, P.N., Doctoral (Chem.) Dissertation, Minsk, 2000.