ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

Հայաստանի քիմիական հանդես
Химический журнал Армении **71, №4, 2018** Chemical Journal of Armenia

UDC 547.294.314.07

SYNTHESIS OF NEW ACHIRAL *BIS*-ALKYLATED GLYCINE ANALOGS

Z. Z. MARDIYAN[a,b], A. F. MKRTCHYAN[a,b] and A. S. SAGHYAN[a,b]

[a]Scientific and Production Center "Armbiotechnology" NAS RA
14, Gyurjyan Str., Yerevan, 0056, Armenia
Fax: (+37410) 654180, E-mail: zmardiyan89@gmail.com
[b]Yerevan State University
Institute of Pharmacy
1, A. Manoukyan Str., Yerevan, 0025, Armenia

A method for the synthesis of α-bis-alkyl substituted derivatives of glycine by means of C-alkylation of the amino acid moiety of Ni^{II}-complex of Schiff base of glycine with a chiral auxiliary reagent (S)-2-N-[N'-(benzylprolyl)amino]benzophenone (BPB) by propargyl-, allyl-, 2-bromobenzyl- and 4-fluorobenzyl bromides under conditions of base catalysis has been developed.

Tables 2, references 15.

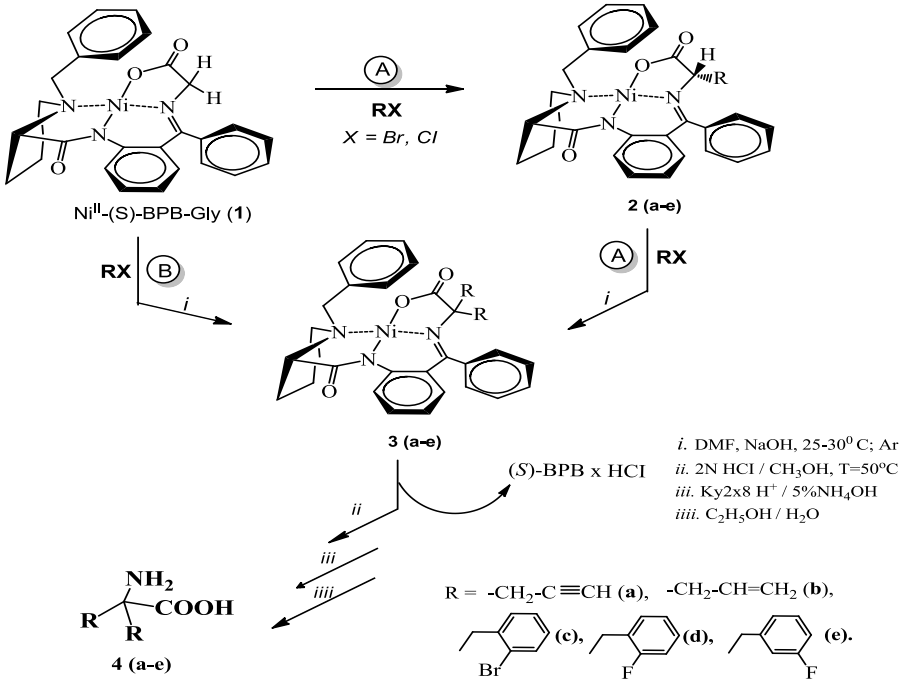
α-Amino acids of non-protein origin, as irreversible inhibitors of enzymes with high specificity and duration of action, are widely used in medicine, pharmaceutical chemistry, microbiology and other fields of science and technology [1-4]. In a series of non-proteinogenic amino acids, α-alkyl substituted α-amino acids that have strong antihypertensive, antiseptic and antitumor activities [5-8] are of certain interest. Among them halogen-containing aromatic ring derivatives of phenylalanine and its α-alkylated analogs occupy a special place [9, 10]. Amino acids containing unsaturated groups (acetylene, allyl, etc.) in the side radical [11, 12] can have important pharmacological properties. There is a limited number of acetylenic amino acids, mainly isolated from fungal cells, which have an inhibitory effect on many enzymes [7]. For example, (*S*)-2-aminobut-3-ynic acid (propargylglycine) isolated from the fungi *Steroptpmyces catenula*, inhibits the action of *Saccharomyces cerevisiae* and *Esherichia coli* cells; it is an inhibitor of amylase synthesis, an activator of pyridoxalphosphate-dependent enzymes [8] and is a component of antibiotic FR 900130 [9].

Earlier, to obtain α-substituted α-amino acids, the unique properties of square-planar Ni^{II} complexes of Schiff base of amino acids and chiral auxiliary (*S*)-2-N-[N'-(benzylprolyl)amino] benzophenone (BPB) were used. Due to high CH-acidity of

the α-carbon atom of the amino acid moiety of these complexes, its C-alkylation by alkyl halides resulted in the asymmetric syntheses of a wide range of α-monosubstituted α-amino acids (glycine, alanine, etc.) containing different alkyl substituents in the side radical [13].

This paper reports on the synthesis of achiral α,α-disubsituted glycine analogs with the propargyl, allyl, 2-bromobenzyl, 2-fluorobenzyl and 3-fluorobenzyl groups in the α-position, by *bis*-alkylation of the glycine moiety of the Ni^{II} complex of its Schiff base with chiral auxiliary (*S*)-BPB (Scheme). To obtain achiral *bis*-alkylated glycine derivatives, the reactions of both stepwise monoalkylation of the amino acid moiety of complexes **1** and **2** (**a-e**) (**path A**), and direct *bis*-alkylation of the glycine moiety of complex **1** (**path B**) were studied.

Scheme



Complexes **2(a-e)** were obtained from complex **1** according to the previously developed procedure [12,14]. Propargyl bromide (***a***), allyl bromide (***b***), 2-bromobenzyl bromide (***c***), 2-fluorobenzyl chloride (***d***) and 3-fluorobenzyl bromide (***e***) were used as alkylating agents.

The alkylation reactions were tested in DMF/KOH, DMF/NaOH, CH_2Cl_2/NaOH, THF/NaOH and CH_3CN/NaOH at both room temperature and under heating to 55°C. To define the optimal conditions for alkylation on the example of propargyl bromide condensation (***a***) to complex **1**, different stoichiometric ratios of the substrate, alkylated reagent and base were studied. Investigations have shown that the optimal conditions for the alkylation reaction of complex **1** are: DMF as a

medium, NaOH – as a base, room temperature, the ratio of complex **1**/base/alkylating agent = 1/3/1.5 (see Table 1, exp. 9).

Table 1

Results of alkylating complex 1 by propargyl bromide (a) under different conditions*

No.	Quantity $Br\text{-}CH_2\text{-}C\equiv CH$(equiv.)	Medium	Base (equiv.)	Reaction time (min.)	T ^oC	Chemical yield (%) **
1	1.2	CH_3CN	NaOH (3)	120	60	<20
2	3	CH_3CN	NaOH (5)	120	20	<20
3	1.2	CH_3CN	KOH (3)	60	60	<20
4	1.2	CH_3CN	KOH (5)	60	20	<20
5	1.2	CH_2Cl_2	NaOH (5)	120	20	25
6	1.2	CH_2Cl_2	NaOH (3)	45	40	25
7	1.5	DMF	KOH (3)	70	20	42
8	1.2	DMF	NaOH (3)	30	60	55
9	**1.2**	**DMF**	**NaOH (3)**	**60**	**20**	**92**
10	1.2	DMF	NaOH (5)	60	20	62
11	**1.2**	**DMF**	**KOH (3)**	**60**	**20**	**74**
12	1.2	THF	NaOH (3)	100	20	<20
13	1.2	THF	NaOH (5)	60	60	<20
14	1.2	THF	KOH (5)	70	60	<20

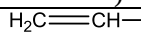
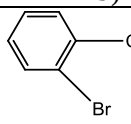
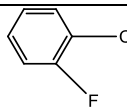
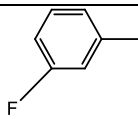
**The reactions were carried out in the argon atmosphere, **chemical yield is based on the TLC data and the isolated quantity of the alkylated complex (after crystallization from methanol)*

The course of the alkylation reaction was monitored by TLC [SiO_2, $C_2H_5COOCH_3/CH_3COCH_3$(3/1)]. For quantitative assessment of the alkylation reaction, the TLC data were used, and for more successful TLC-based reactions, chemical yields were determined on the basis of the amount of isolated alkylated complexes after crystallization from methanol (Table 1, exp. 7-11).

A quantitative characteristic of the C-alkylation reaction of the amino acid moiety of complexes **1** and **2 (*a*-*e*)** is shown in Table 2.

Table 2

The results of alkylation of complexes by different alkyl halides in DMF in the presence of NaOH at room temperature*

No.	Alkyl halide	Chem. yield of *bis*-alkylated complexes (%)		
		Bis-alkylated complexes	Path A **	Path B
1	 (***a***)	**3*a***	83 (92)	45
2	 (***b***)	**3*b***	80 (89)	48
3	 (***c***)	**3*c***	73 (82)	44
4	 (***d***)	**3*d***	68 (76)	46
5	 (***e***)	**3*e***	72 (84)	48

Chemical yield of bis-alkylated complexes based on the initial amount of the glycine complex (1**), ** in parenthesis is the chemical yield of bis-alkylated complexes **3(a-e)** after crystallization based on the amount of complexes **2(a-e)** (path A, stage 2).*

Both the stepwise alkylation of the amino acid moiety of complexes **1** and **2 (*a-e*)** (**path A**) and the direct *bis*-alkylation of complex **1** (**path B**) were conducted under specially selected optimal conditions for the alkylation reaction (See Table 1, exp. 9). However, in the case of direct *bis*-alkylation of the glycine complex, the alkylating agent and the base were taken in about double excess.

As follows from the data of Table 2, for almost all alkylating agents, *bis*-alkylation of glycine complex **1** proceeds most quantitatively with the method of two-step alkylation (**path A**) than in the case of the direct *bis*-alkylation of the glycine complex (**path B**). In the case of using the method of direct *bis*-alkylation of the glycine moiety of complex **1**, up to 30% of a side fraction, less mobile on the SiO_2, is formed with an unusual for these complexes dark color (oxidation products). Similar was also observed earlier in the study of the reaction of *bis*-alkylation of complex **1** by methyl iodide [14].

The main α,α-dialkyl-substituted **3(*a-e*)** complexes with a relatively large R_f value on the SiO_2 were isolated from the reaction mixture by crystallization from methanol and characterized by physicochemical analysis methods (see Experimental Part).

To isolate the target α,α–*bis*-alkylated glycine analogs, preparative experiments using the two-step stepwise alkylation method (**path A**) were carried out and the samples of **3**(***a-e***) complexes were obtained. Decomposition of **3**(***a-e***) complexes and isolation of the target α,α–dialkyl-substituted glycine derivatives **4*(a-e)*** were carried out according to a standard procedure [15]. The structures of the synthesized new achiral analogs of glycine were investigated and established by spectral analysis methods (see Experimental Part).

Thus, an efficient method for obtaining achiral α,α-*bis*-alkylated analogs of glycine by C-alkylation of glycine in the chiral Ni^{II} complex of its Schiff base with (*S*)-BPB by alkyl halides has been developed. For the first time the following complexes were synthesized - α,α-dipropargyl glycine (**4*a***), α,α-diallylglycine (**4*b***), α,α-di-(2-bromobenzyl)glycine (**4*c***),α,α-di-(2-fluorobenzyl)glycine (**4*d***) and α,α-di-(3-fluorobenzyl)glycine (**4*e***). The presence of acetylene, allyl and aromatic groups in the side radical of the synthesized amino acids allows makes it possible to use them as initial synthons in the reactions of Suzuki, Heck, Sonogashira to obtain more complex unsaturated amino acids.

The preliminary medicobiological screening of the obtained samples proves that the synthesized amino acids can serve as potential enzyme inhibitors of the amylase class.

Experimental Part

^{1}H NMR and ^{13}C NMR spectra were recorded on a "Mercury-300 Varian" (300 *MHz*), the melting point was measured on a "StuartSMP3" device. Amino acids and other chemical reagents produced by "Aldrich" and "Reachim" were used in the work.

Complex Ni^{II}-(S)-BPB-Gly (**1**) was obtained according to [15], and monoalkylated complexes **2(a-e)** were synthesized according to [13].

General procedure of monoalkylation of complexes 2(*a-e*) (Path A). To 10 *g* (0.018 *mol*) of complex **2*a*** in 50 *ml* of DMF were added at room temperature 2.2 *g* (0.055 *mol*) of NaOH and 1.9 *ml* (0.22 *mol*) of propargyl bromide (***a***). The reaction mixture was stirred for 1-1.5 *h* at room under argon atmosphere. The course of the reaction was monitored by TCL [SiO_2, CH_3COOEt/CH_3COCH_3(3/1)] following the disappearance of the traces of initial complex **2**. Upon completion of the reaction, the mixture was neutralized with CH_3COOH, 100 *ml* of water was added and the alkylated product was precipitated from water. The obtained complex **3*a*** was crystallized from methanol.

***Bis-alkylation of complex* 1 (*Path B*).** The direct *bis*-alkylation of the glycine moiety of complex **1** was carried out according to the afore-mentioned procedure for monoalkylation of complexes **2(*a-e*)** with the difference that the base and alkylating agents were taken in a 5-6-fold excess with respect to complex **1**, and the reaction mixture was stirred for 2-3 *h*. The results are given in Table 2.

Complex 3*a*. Yield 90%, mp 217-218 °C. ^{1}H NMR (300 *MHz*, $CDCl_3$): δ = 1.99-2.11 (m, 2 H, γ-Hα Pro); 2.12 (dd, 1 H, *J*=17.2, *J*=2.7, CH_2 C≡); 2.20 (dd, 1 H, *J*=17.2, *J*=2.5, CH_2 C≡); 2.38 (t,1 H, *J*=2.5, ≡CH); 2.46-2.65 (m, 2 H, β-CH_2Pro); 2.61 (t, 1 H, *J*=2.7, ≡CH); 2.67 (dd, 1 H, *J*=17.0, *J*=2.7 CH_2 C≡); 2.73 (dd, 1 H, *J*=17.2, *J*=2.5 CH_2 C≡); 3.40 (dd, 1 H, *J*=10.7, *J*=5.9 α-HPro); 3.50 (d, 1 H, *J*= 12.5, $\underline{CH_2}$Ph); 3.46-3.59 (m, 1 H, δ-H_bPro); 3.71-3.78 (m, δ-CH_2Pro); 4.47 (d, 1 H, *J*=12.5, $\underline{CH_2}$Ph); 6.57-6.65 (m, 2 H, H-3,4, C_6H_4), 7.09 (ddd, 1 H, *J*=8.6, *J*=4.8, *J*=3.7, H-5 C_6H_4); 7.17-7.26 (m, 2 H, H-Ar); 7.33-7.45 (m, 3 H, H-Ar); 7.48-7.55 (m, 2 H, H-Ar); 7.67-7.73 (m, 1 H, H-Ar); 7.90 (d, 1 H, *J*=8.6, H-Ar); 8.37-8.41 (m, 2 H, H-Ar); ^{13}C NMR (75 *MHz*, $CDCl_3$): δ = 23.2 (γ- CH_2Pro); 29.2 (CH_2); 30.9 (β-CH_2Pro); 31.9 (CH_2); 58.3 (δ-CH_2, Pro); 64.5 ($\underline{CH_2}$Ph); 70.8 (α-C$\underline{H}$Pro); 77.1 (Cq); 79.1 (≡CH), 79.7 (CH_2 $\underline{C}$≡); 120.7 (C-4 C_6H_4); 124.3 (CH-6 C_6H_4); 127.5, 127.7, 128.1, 128.3, 128.8 (CH-Ar); 128.9 (3,3'-CHPh); 129.0, 130.0, 131.7 (CH-Ar); 131.8 (2,2'-CHPh); 133.4, 134.4, 136.3, 142.1 (C); 172.8 (C=N-), 180.6, 180.8 (C=O).

Complex 3*b* Yield 87%, mp 203-204 °C. ^{1}H NMR (300 *MHz*, $CDCl_3$): δ = 1.96-2.12 (m, 2 H, γ-Hα Pro); 2.19 (ddt, 1 H, *J*=14.5, *J*=6.6, *J*=1.2, CH_2 CH=CH_2); 2.33-2.54 (m, 4 H, CH_2 CH=CH_2 и β-H_aPro); 2.62-2.73 (m, 1 H, β-H_bPro); 3.25-3.42 (m, 1 H, γ-H_bPro); 3.40 (dd, 1 H, *J*=10.7, *J*=5.9 α-HPro); 3.58 (d, 1 H, *J*= 12.5, $\underline{CH_2}$Ph); 3.65-3.72 (m, 1 H, δ-H_bPro); 4.38 (d, 1 H, *J*=12.5, $\underline{CH_2}$Ph); 5.24(ddt, 1 H, *J*=17.2, *J*=1.6, *J*=1.3, =CH_2); 5.31 (ddt, 1 H, *J*=10.5, *J*=1.6, *J*=1.3, =CH_2); 5.38 (ddt, 1 H, *J*=17.1, *J*=1.6, *J*=1.3, =CH_2); 5.49 (ddt, 1 H, *J*=10.3, *J*=1.6, *J*=1.2, =CH_2); 5.80 (ddt, 1 H, *J*=17.1, *J*=10.5, *J*=6.6, =CH); 6.62 (ddt, 1 H, *J*=17.2, *J*=10.3, *J*=6.6, =CH); 6.57-6.63 (m, 2 H, H-3.4, C_6H_4), 7.05-7.09 (m, 1 H, H-Ar); 7.11 (ddd, 1 H, *J*=8.7, *J*=5.5, *J*=3.0, C_6H_4); 7.22-7.28 (m, 1 H, H-Ar); 7.37-7.54 (m, 6 H, H-Ar); 7.95 (d, 1 H, *J*=8.7, H-Ar); 8.16-8.21 (m, 2 H, H-Ar); ^{13}C NMR (75 *MHz*, $CDCl_3$): δ = 23.3 (γ- CH_2Pro); 30.9 (β- CH_2Pro); 42.5, 44.2 (CH_2 CH=CH_2); 57.8 (δ-CH_2, Pro); 64.2 ($\underline{CH_2}$Ph); 70.9 (α-C$\underline{H}$Pro); 81.7 ($\underline{C}$-Alyl$_2$), 119.0, 119.7 (=CH_2); 120.7 (C-4 C_6H_4); 124.3 (CH-6 C_6H_4); 127.2, 127.9 128.0, 128.6, 128.7 (CH-Ar); 129.0 (3,3'-CHPh); 129.1, 129.8, 131.6(CH-Ar); 131.7 (2,2'-CHPh); 132.4, 132.7, 133.2 (CH-Ar); 134.3, 136.8, 141.9, (C); 172.8 (C=N-), 180.6, 180.8 (C=O).

Complex 3*c*. Yield 78%, mp 231-232 °C. ^{1}H NMR (300 *MHz*, $CDCl_3$): δ = 1.68-1.79 (m, 1 H, γ-Hα Pro); 2.01-2.13 (m, 1 H, δ-HPro); 2.25-2.46 (m, 3 H, γ-Hв и β-Hα, Pro); 2.44 (d, 1 H, *J*=18.0, CH_2 C_6H_4Br); 3.20 (d, 1 H, *J*=18.0, CH_2 C_6H_4Br); 3.22-3.28 (m, 1 H, δ-HPro); 3.39 (d, 1 H, *J*=14.4, CH_2 C_6H_4Br);3.41 (dd, 1 H, *J*=9.0, *J*=7.2, α-CHPro); 3.49 (d, 1 H, *J*=12.6, $\underline{CH_2}$Ph); 3.72 (d, 1 H, *J*=14.4, CH_2 C_6H_4Br); 4.39 (d, 1 H, *J*=12.6,$\underline{CH_2}$Ph); 6.33 (d, 1H, *J*=7.8, C_6H_5); 6.43-6.55 (m, 2 H, H-3.4, C_6H_4), 7.04-7.18 (m, 3H, H-Ar); 7.20-7.29 (m, 3H, H-Ar); 7.33-7.51 (m, 6 H, H-Ar); 7.56-7.64 (m, 2 H, H-Ar); 7.70-7.76 (m, 2 H, H-Ar); 8.04-8.16 (m, 3 H, H-Ar). ^{13}C NMR (75 *MHz*, $CDCl_3$): δ = 23.4 (γ- CH_2Pro); 30.9 (β- CH_2Pro); 46.5 (CH_2 C_6H_4Br); 47.2 (CH_2 C_6H_4Br); 58.1 (δ-CH_2, Pro); 64.1 ($\underline{CH_2}$Ph); 70.5 (α-CPro); 80.9 ($\underline{C}$-CH_2 C_6H_4Br), 120.5 (C-4 C_6H_4); 123.9 (CH-6 C_6H_4); 125.8, 126.5126.7, 127.3, 127.6 (CH-Ar); 127.8 (3,3'-CHPh); 127.9, 128.0, 128.2, 129.0, 129.6 (CH-

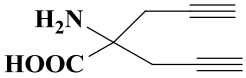
Ar);131.6 (2,2'-CHPh); 131.9, 133.2, 133.6, 133.7, 133.8 (CH-Ar); 133.9, 136.3, 136.4, 137.4, 142.5 (C); 172.6 (C=N-); 178.0, 180.3 (C=O).

Complex 3*d*. Yield 72%, mp 227-228 °C. ^{1}H NMR (300 *MHz*, $CDCl_3$): δ = 1.57-1.72 (m, 1 H, γ-Hα Pro); 2.01-2.32 (m, 4 H, δ-H, γ-Hв и β-Hα, Pro); 2.53 (d, 1 H, *J*=17.7, CH_2 C_6H_4F); 3.02 (d, 1 H, *J*=14.6, CH_2 C_6H_4F); 3.18 (d, 1 H, *J*=17.7, CH_2 C_6H_4F); 3.19-3.28 (m, 1 H, δ-HPro); 3.33 (dd, 1 H, *J*=9.3, *J*=7.4, α-CHPro); 3.40 (d, 1 H, *J*=14.6, CH_2 C_6H_4F); 3.43 (d, 1 H, *J*=12.6, $\underline{CH_2}$Ph);4.36 (d, 1 H, *J*=12.6,$\underline{CH_2}$Ph); 6.50 (dd, 1 H, *J*=8.5,*J*=2.1 C_6H_4); 6.53 (ddd, 1 H, *J*=8.5,*J*=6.4,*J*=1.1 C_6H_4); 6.64 (dt, 1 H, *J*=7.8,*J*=1.4 C_6H_4); 7.03-7.11 (m, 2 H, H-3.4, H-Ar); 7.16-7.25 (m, 4 H, H-Ar); 7.28-7.53 (m, 8 H, H-Ar); 7.72-7.79 (m, 1 H, H-Ar); 7.83 (td, 1 H, *J*=7.6, *J*=1.6 H-Ar); 7.99-8.06 (m, 3 H, H-Ar). ^{13}C NMR (75 *MHz*, $CDCl_3$): δ = 23.1 (γ- CH_2Pro); 30.8 (β- CH_2Pro); 39.5 (CH_2 C_6H_4F); 40.6 (CH_2 C_6H_4F); 58.0 (δ-CH_2, Pro); 63.9 ($\underline{CH_2}$Ph); 700 (α-CHPro); 79.8 (C-CH_2 C_6H_4F), 115.2 (d, *J*=22.1C_6H_4F); 115.9 (d, *J*=23.0C_6H_4F); 120.4 (CHC_6H_4); 123.6 (CHC_6H_4); 124.0 (d, ^{3}*J*=15.8C_6H_4F); 124.1 (d, *J*=3.8C_6H_4F); 124.8 (d, *J*=3.2C_6H_4F); 125.1 (d, ^{2}*J*=14.7C_6H_4F); 127.1 (d, *J*=6.3C_6H_4F); 127.4, 127.9 128.0, 128.2, 128.3 (CH-Ar); 129.0 (3,3'-CHPh); 129.3 (d, *J*=8.2C_6H_4F); 129.6 (CH-Ar); 129.9 (d, *J*=4.0C_6H_4F); 131.6 (2,2'-CHPh); 131.8, 133.2 (d, ^{4}*J*=4.5C_6H_4F); 133.6, 133.9 (CH-Ar); 136.7, 142.4 (C); 161.0 (d, ^{1}*J*=246.0C_6H_4F); 162.3 (d, *J*=246.4CF); 173.6 (C=N-), 179.3, 180.3 (C=O).

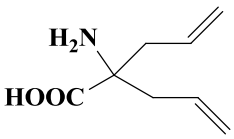
Complex 3*e*. Yield 81%, mp 205-206 °C. ^{1}H NMR (300 *MHz*, $CDCl_3$): δ = 1.62-1.74 (m, 1H, γ-HaPro); 1.96-2.36 (m, 4H, β-Ha,b, γ-Hb, δ–HaPro); 2.74 (d, 1H, *J*=16.9, CH_2-Ar); 3.01 (d, 1H, *J*=14.4, CH_2-Ar); 3.12 (d, 1H, *J*=14.4, CH_2-Ar); 3.21 (dd, 1H, *J*=10.5,*J*=5.8,α-HPro); 3.25-3.33 (m, 1H, δ–HbPro); 3.29 (d, 1H, *J*=16.9, CH_2-Ar); 3.29 (d, 1H, *J*=12.5, CH_2-Ph); 4.34 (d, 1H, *J*=12.5, CH_2-Ph); 6.51 (dd, 1H, *J*=8.4, 1.7, H-C_6H_4); 6.56 (dd, 1H, *J*=8.4, *J*=6.8, *J*=1.1, H-C_6H_4); 6.96-7.21 (m, 8H, Ar.); 7.29-7.55 (m, 9H, Ar.); 7.84 (dd, 1H, *J*=8.7, *J*=1.1, H-C_6H_4); 8.04-8.08 (m, 2H, H-Ph). ^{13}C NMR (75 *MHz*, $CDCl_3$): δ = 23.0 (γ-$\underline{C}H_2$Pro); 30.7 (β-$\underline{C}H_2$Pro); 45.1 ($\underline{C}H_2$-Ar); 46.0 ($\underline{C}H_2$-Ar); 58.5 (δ-$\underline{C}H_2$Pro); 64.3 ($\underline{C}H_2$-Ph); 70.1 (α-$\underline{C}$HPro); 80.5 ($\underline{C}$-CH_2-Ar.); 113.6 (d, $J_{C,F}$=21.0, C_6H_4F); 114.5 (d, $J_{C,F}$=20.9, C_6H_4F); 116.2 (d, $J_{C,F}$=21.6, C_6H_4F); 118.2 (d, $J_{C,F}$=21.1, C_6H_4F); 120.6 (CH-C_6H_4); 124.2 (CH-C_6H_4); 125.2 (d, $J_{C,F}$=2.6, C_6H_4F); 126.7 (d, $J_{C,F}$=2.8, C_6H_4F); 127.4 (CH); 127.6 (CH); 127.9; 128.2 (CH); 128.9 (CH); 129.0 (3,3'-CHPh); 130.0 (d, $J_{C,F}$=8.4, C_6H_4F); 130.3 (d, $J_{C,F}$=8.4, C_6H_4F); 131.6 (2,2'-CHPh); h); 131.7 (CH); 131.9 (CH-C_6H_4); 133.5 (CH-C_6H_4); 133.7; 136.8; 139.1 (d, $J_{C,F}$=7.3, C_6H_4F); 139.5 (d, $J_{C,F}$=7.3, C_6H_4F); 142.5; 163.1 (d, $J_{C,F}$=246.4, C_6H_4F); 163.3 (d, $J_{C,F}$=246.4, C_6H_4F); 172.7 (C=N-); 179.3; 180.5(C=O).

Isolation of the target amino acids 4(*a-e*). Decomposition of complexes **3(*a-e*)** and isolation of α,α-dialkylated analogs of glycine **4**(***a-e***) were carried out according to the standard procedure [15]. For this, the dry moiety of the complexes was dissolved in 50 *ml* of CH_3OH and the solution was slowly added to 50 *ml* of 2N HCl solution heated to 60°C. After the disappearance of red color, typical for these complexes, the solution was concentrated under vacuum, 50 *ml* of water was added

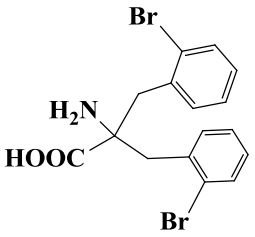
and the initial chiral auxiliary reagent (*S*)-BPB was filtered off as hydrochloride. From the aqueous filtrate, the amino acid was isolated by passing the solution through an ion exchange column with 100 *ml* of Ku-2x8 resin in H^+-form, and the resin was washed with 5% NH_4OH solution. The ammonia eluate was concentrated in vacuum and the amino acid was crystallized from a water-alcohol (1/1) solution. The structure of the obtained α,α-dialkyl-substituted glycine derivatives **4(*a-e*)** was studied by spectral analysis methods.



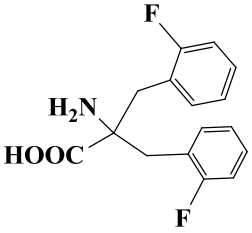
2-Amino-2-(prop-2-yn-1-yl)pent-4-ynoic acid. 4*a*. Yield 81%, mp 227-228 °C. ^{1}H NMR (300 *MHz*, DOD): δ = 2.53 (t, 2 H, *J*=2.44, CH_2-C≡CH); 2.82 (dd, 4H, *J*=17.7, *J*=2.5 CH_2-C≡CH): ^{13}C NMR (75 *MHz*, DOD): δ = 25.5 (CH_2-C≡CH); 62.2 (C-CH_2-C≡CH); 74.3 (CH_2-C≡CH); 76.8 (CH_2-C≡CH); 173.0 (C=O).



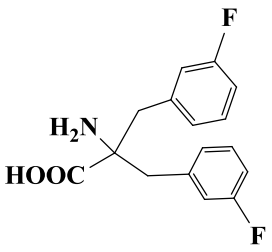
2-Allyl-2-aminopent-4-enoic acid. 4*b*.Yield 75%, mp 234-235°C. ^{1}H NMR (300 *MHz*, DOD): δ = 2.46 (dd, 2 H, *J*=14.5, *J*=8.5 CH_2-CH=CH_2); 2.67 (dd, 2 H, *J*=14.5, *J*=6.4 CH_2-CH=CH_2); 5.26 (d, 4 H, *J*=14.5, CH_2-CH=CH_2); 5.66-5.78 (m, 2 H, CH_2-CH=CH_2). ^{13}C NMR (75 *MHz*, DOD): δ = 40.1 (CH_2-CH=CH_2); 63.9 (C-CH_2-CH=CH_2); 121.5 (CH_2-CH=CH_2); 130.3 (CH_2-CH=CH_2); 174.8 (C=O).



2-Amino-2-(2-bromobenzyl)-3-(2-bromophenyl) propanoic acid. 4*c*. Yield 78%, mp 181-182°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4): δ = 3.50 (d, 2 H, *J*=14.6, CH_2 C_6H_4Br); 3.68 (d, 2 H, *J*=14.6, CH_2 C_6H_4Br); 7.16 (ddd, 2 H, *J*=8.0, *J*=7.4, *J*=1.6, C_6H_4); 7.30 (ddd, 2 H, *J*=7.7, *J*=7.4, *J*=1.3, C_6H_4); 7.54 (dd, 2 H, *J*=8.0, *J*=1.3, C_6H_4); 7.65 (dd, 2 H, *J*=7.7, *J*=1.6, C_6H_4); 8.92 (m, 3H, NH_2 and COOH). ^{13}C NMR (75 *MHz*, DMSO/CCl_4): δ = 39.47 (CH_2 C_6H_4Br); 62.6(C- CH_2 C_6H_4Br), 125.7 (C-Ar); 127.2, 128.5, 132.4, 132.5 (CH-Ar); 133.5 (C-Ar); 170.2 (C=O).



2-Amino-2-(2-fluorobenzyl)-3-(2-fluorophenyl) propanoic acid. 4*d*. Yield 70%, mp 228-229°C. ^{1}H NMR (300 MHz, DOD): δ = 3.31 (d, 2 H, *J*=14.7, CH_2 C_6H_4F); 3.39 (d, 2 H, *J*=14.7, CH_2 C_6H_4F); 7.04-7.14 (m, 4 H, C_6H_4F); 7.22-7.35 (m, 4 H, C_6H_4F).



2-Amino-2-(3-fluorobenzyl)-3-(3-fluorophenyl) propanoic acid. 4*e*. Yield 62%, mp 231-232 °C. ^{1}H NMR (300 *MHz*, DOD): δ = 3.18 (d, 2 H, *J*=14.6, CH_2 C_6H_4F); 3.29 (d, 2 H, *J*=14.6, CH_2 C_6H_4F); 7.01-7.09 (m, 4 H, C_6H_4F); 7.12-7.24 (m, 4 H, C_6H_4F).

ԳԼԻՑԻՆԻ α,α-ԲԻՍ-ՏԵՂԱԿԱԼՎԱԾ ԱՔԻՐԱԼ ՆՄԱՆԱԿՆԵՐԻ ՍԻՆԹԵԶ

Զ. Զ. ՄԱՐԴԻՅԱՆ, Ա. Ս. ՍԱՂՅԱՆ և Ա. Ֆ. ՄԿՐՏՉՅԱՆ

Աշխատանքում հետազոտվել է գլիցինի α,α-երկտեղակալված աքիրալ նմանակների սինթեզի հնարավորությունը միևնույն ալկիլող ագենտով՝ գլիցինի էլեկտրոֆիլ բիս-տեղակալման ճանապարհով: Դրա համար որպես ելային ամինոթթվային սինտոն օգտագործվել է գլիցինի NiII-(S)-BPB-Gly (1) կոմպլեքսը: Ուսումնասիրվել է այդ կոմպլեքսի ամինոթթվային մնացորդի էլեկտրոֆիլ տեղակալումը պրոպարգիլբրոմիդով (a), ալիլբրոմիդով (b), 2-բրոմբենզիլբրոմիդով (c), 2-ֆտորբենզիլբրոմիդով (R) և 3-ֆտորբենզիլբրոմիդով (e), ինչպես հաջորդաբար մոնոտեղակալմամբ արդեն իսկ հայտնի մեթոդներով (A), այնպես էլ անմիջական (միանգամից) երկտեղակալման ճանապարհով (B):

Էլեկտրոֆիլ տեղակալման ռեակցիաներն իրականացվել են DMF/NaOH համակարգում, արգոնի մթնոլորտում, սենյակային ջերմաստիճանի պայմաններում: Տեղակալման ռեակցիաների ընթացքին հարմար է հետևել ՆՇՔ մեթոդով՝ սիլիկագելի թիթեղների վրա, $CH_3COOC_2H_5/(CH_3)_2CO$ (3/1) լուծիչների համակարգում:

Ինչպես երևում է արձանագրված արդյունքներից, նպատակահարմար է սինթեզն իրականացնել երկփուլանի (A) ալկիլման եղանակով, քանզի միաժամանակյա (B) երկտեղակալման ժամանակ ելքը չի գերազանցում 50%-ը: Իսկ հաջորդաբար՝ մոնոտեղակալմամբ երկտեղակալման դեպքում արգասիք կոմպլեքսների ելքը գերազանցում է 70%-ը հաշվարկված (1) կոմպլեքսի ելային քանակությամբ:

Նպատակային ոչ սպիտակուցային աքիրալ α,α-երկտեղակալված ամինոթթուների (4a-e) անջատումը արգասիք կոմպլեքսներից (3a-e) իրականացվել է նախկինում մշակված ստանդարտ մեթոդով:

Այսպիսով, սինթեզվել են գրականությյան մեջ չնկարագրված գլիցինի α,α-բիս-տեղակալված աքիրալ նմանակներ 2,2-դի(պրոպարգիլ)գլիցին, 2,2-դի(ալիլ)գլիցին, 2-ամինո-2-(պրոպ-2-ին-1-իլ)պենտ-4-յինաթթու (4a), 2-ալիլ-2-ամինոպենտ-4-էնաթթու (4b), 2-ամինո-2-(2-բրոմբենզիլ)-3-(2-բրոմֆենիլ)պրոպա-նաթթու (4c), 2-ամինո-2-(2-ֆտորբենզիլ)-3-(2-ֆտորֆենիլ)պրոպանաթթու (4d) 2-ամինո-2-(3-ֆտորբենզիլ)-3-(3-ֆտորֆենիլ)պրոպանաթթու (4e).

СИНТЕЗ НОВЫХ АХИРАЛЬНЫХ *БИС*-АЛКИЛИРОВАННЫХ АНАЛОГОВ ГЛИЦИНА

З. З. МАРДИЯН [а,б], А. Ф. МКРТЧЯН [а,б] и А. С. САГИЯН

[а]Научно-производственный центр “Армбиотехнология” НАН РА
Ереван 0056, ул. Гюрджяна, 14
Факс: (+37410) 654180, E-mail: zmardiyan89@gmail.com
[б]Ереванский государственный университет, институт Фармации
Ереван 0025, ул. А. Манукяна, 1

Разработан метод синтеза α-*бис*-алкилзамещенных производных глицина путем С-алкилирования аминокислотного остатка Ni^{II}-комплекса основания Шиффа глицина и хирального вспомогательного реагента (S)-2-N-[N’-(бензилпролил)амино]бензофенона (BPB) пропаргил-, аллил-, 2-бромбензил- и 4-фторбензилбромидами в условиях основного катализа.

REFERENCES

[1] *Yoshioka H., Aoki T., Goko H., Nakatsu K., Noda T.,Sakakibara H., Take T., Nagata A., Abe J.,Wakamiya T., Shiba T., Kaneko T.* // Tetrahedron Letters, 1971, p. 2043.

[2] *Takita T., Muraoka Y., Yoshioka T., Fuji A., Naeda K., Umezawa H.* // J. Antibiot., 1972, v. 25, p. 755.

[3] *Jakubke H6D., Jeschkeit H.* Aminosauren, Peptide, Proteine, Akademie6Veriag, Berlin, 1982.

[4] *Radahhisman A.N.* // J. Biochem., 1970, p.117.

[5] *Lambertine J.B., Coulier A.W., Talalay P.* // Mol. Pharmacol., 1970, v. 6, p. 481.

[6] *Mori Y., Truboi M., Fukushima K., Aroi T.* // Jour. Soc. Chem. Comm., 1982, p. 94.

[7] *Barret G.C.* Chemistry and Biochemistry of Amino acids, Chapman and Hall, Oxford, 1984, p.132.

[8] *Burnett G., Marcotte P., Walsh C.* // J. Biol. Chem., 1980, v.255, p. 3487

[9] *Kuroda Y., Okuhara M., Goto T., Iguchi R., Kohsaka M., Aoki H., Imanaka H.* // Antibiot. (Tokyo), 1980, v. 33, p. 125.

[10] *Janecka A., Janecki T., Bowers C., Janecka K. Reduced-Aize* // A. J. Med Chem., 1995, v. 38, p. 2922.

[11] *Dong L., Markovits J., Hou X., Guo Ch., Gteasley S.* // Biootg . Med. Chem., 2010 Lett. 20, p. 2210.

[12] *Collet S., Bauchat P., Danion-Bougot R., Danion D.* // Tetrahedron: Asymmetry, 1998, v. 9, p. 2121.

[13] *Belokon' Yu.N., Chernoglazava N.I., Kachetkov K.A.* // J.Chem. Soc. Commun., 1985. p. 171.

[14] *Сагиян А.С.* Энантиомерно чистые небелковые аминокислоты. Способы получения. М., Наука, 2010, с. 88.

[15] *Belokon' Yu.N., Tararov V.I., Maleev V.I.* // Tetrahedron: Asymmetry, 1998 v. 9, p. 4249.