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 **70, №1-2, 2017** Chemical Journal of Armenia

ОРГАНИЧЕСКАЯ И БИООРГАНИЧЕСКАЯ ХИМИЯ

UDC 547.294.314.07

FIVE-YEAR ACHIEVEMENTS IN THE FIELD OF THE ASYMMETRIC SYNTHESIS OF UNSATURATED AMINO ACIDS

A. S. SAGHYAN[a,b], Yu. N. BELOKON[d], P. LANGER[c], A. F. MKRTCHYAN[a,b] and Z. Z. MARDIYAN[a]

[a] Scientific and Production Center "Armbiotechnology" NAS RA
14, Gyurjyan Str., Yerevan, 0056, Armenia
Fax: (+37410) 654183, E-mail: saghyan@netsys.am
[b] Yerevan State University, Institute of Pharmacy
1, A. Manoukyan Str., Yerevan, 0025, Armenia
[c] Institute of Chemistry, University of Rostock, 3a, Albert-Einstein-Str.
18059, Rostock, Germany
[d] A.N. Nesmeyanov Institute of Organoelement Compounds RAS (RF)
28, Vavilov Str., 119991, Moscow, RF

α-Amino acids are fundamental life units responsible for the numerous biological functions in the body. They are basic units of peptides and various biomolecules. Tailor-made α-amino acids are unlimitedly used for producing synthetic hormones, enzymes and immunostimulants [1]. Non-protein amino acids occupy a special place since they are widely used in pharmaceutical, chemical, cosmetic, food and agricultural branches [2,3]. Thus, for example, β-amino acids are the main building block in many natural and synthetic drugs, such as taxol and cispentacin, that are used due to their antitumor and antifungal activities, correspondingly [4,5]. Peptides containing synthetic amino acids commonly show higher resistance to peptidazes than their natural analogs [6]. Among non-protein amino acids unsaturated amino acids occupy a special place.

Unsaturated amino acids can serve as building blocks because alkenyl- and alkyl groups due to their unusual structure have a wide spectrum of possible transformations. In particular, unsaturated α-amino acids can participate in cross-coupling and cross-metathesis reactions, as well as in cyclization reactions [7].

The structure of non-protein amino acids includes unsaturated amino acids that are of great interest in the synthetic chemistry as they are a cornerstone for

fundamental modifications of molecules. As examples can serve click reactions, metathesis reactions, Heck, Glaser and Sonogashira reactions. Besides, unsaturated α-amino acids play a significant role in peptide synthesis [8].

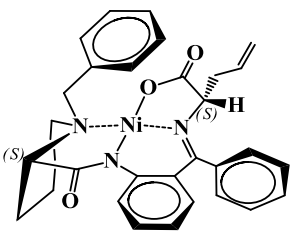
Acetylene-containing amino acids are used as selective inhibitors of Endothelin-converting enzymes and thrombin, inactivators of pyridoxal phosphate-dependent γ-cystathionase, growth inhibitors of B. *Subtilis*B-50 and so on. Thus, for example (*S*)-propargylglycine, isolated from fungi *Streptomyces* and *Amanitapseudoporphyria* inhibits the action of pyridoxal phosphate-dependent γ-cystathionase and L-methionine *S*-adenosyltransferase [9]. Or, for example, non-protein amino acid vinylglycine has a wide range of biological properties. Both (*S*)- and (*R*)-forms of vinylglycine are inhibitors of several transaminases, inactivator of peptide hydroxylating enzyme. It is interesting that vinylglycine served as a model sample in the development of Vigabatrin® drug intended for the treatment of epileptic fits [10]. Or, for example, allylglycin - a synthetic antibiotic, which at the same time inhibits growth of *Escherichiacoli* and *Saccharomyces cereviciae*. The research has shown that allylglycine is inhibitor of glutamatdecarboxylase and an antagonist of α-amino butyric acid. This feature is used in veterinary for provoking convulsions in experimental animals. Allylglycine also inhibits protein synthesis in the brain and nerve endings [9]

Thus, synthetic amino acids are one of the pillars in all spheres of human life. The presence of chiral center in a molecule of non-protein amino acids plays an important role in the compound's display of biological activity (negative or positive). Enantiomers (or diastereomers) of the chiral molecule sometimes show opposite biological activity. So, for example, one enantiomer is physiologically active (inhibitor, activator, etc.), and the other one – is physiologically inactive and shows high toxicity. Therefore, the interest towards the synthesis of optically pure compounds notably grows. Taking into account the significance of chiral unnatural amino acids, the efficient synthesis of these compounds in optically pure forms is one of the most important problems of the past several decades. Nevertheless, as distinct from natural amino acids that are usually obtained by enzymatic and microbial syntheses [11], non-protein amino acids are mainly synthesized by chemical, biocatalytic, catalytic, stoichiometric methods [12,14].

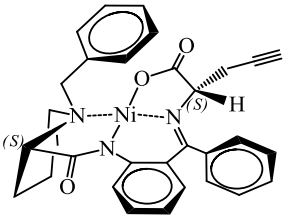
Out of the mentioned methods, one of the prospective and accessible is synthesis of non-protein amino acids with the use of square-planar complexes of nickel ion.

For the past 5 years one of the trends of our research became synthesis of unsaturated enantiomerically enriched amino acids. Ni^{II}-complexes of Schiff base of (*S*)-allylglycine or (propargylglycine) with chiral auxiliary (*S*)-2-N-[N'-(benzylprolyl)amino]benzophenone (BPB) (Fig. 1) [Ni^{II}-(*S*)-BPB-(*S*)-AllylGly (**1**) and Ni^{II}-(*S*)-BPB-(*S*)-PropargylGly] were chosen as starting synthons.

Fig. 1



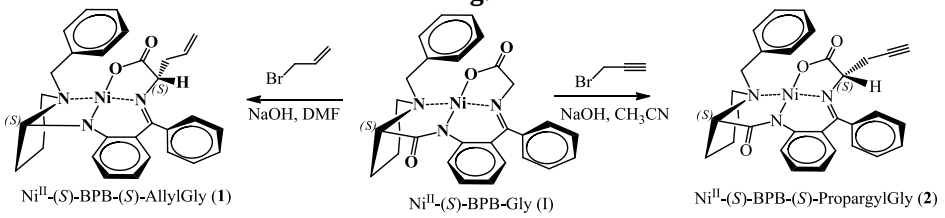
Ni^{II}-(*S*)-BPB-(*S*)-AllylGly (**1**)



Ni^{II}-(*S*)-BPB-(*S*)-PropargylGly (**2**)

These complexes were obtained according to the earlier developed methods [15,16].

Fig. 2



Ni^{II}-(*S*)-BPB-(*S*)-AllylGly (**1**)

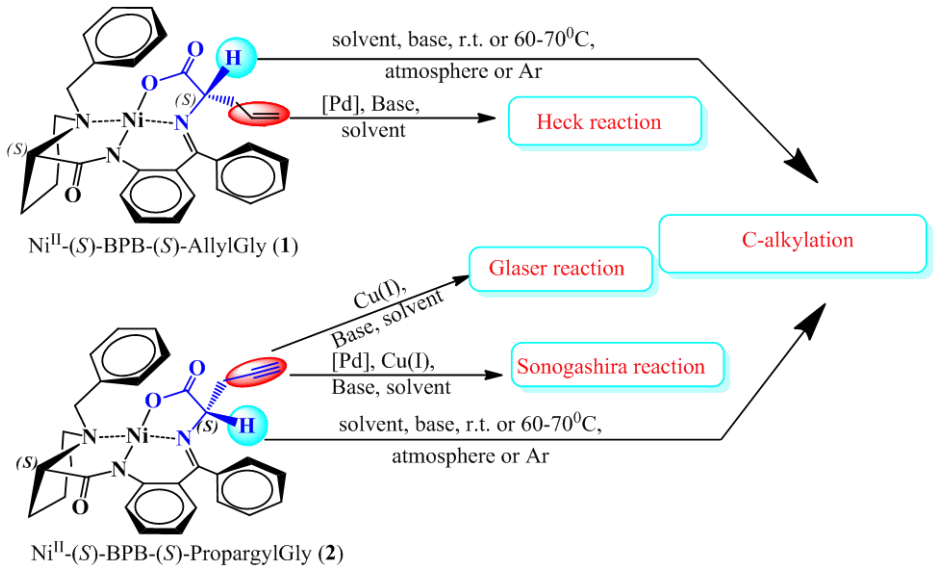
Ni^{II}-(*S*)-BPB-Gly (I)

Ni^{II}-(*S*)-BPB-(*S*)-PropargylGly (**2**)

The research with the use of complexes **1** and **2** were carried out in four directions (Scheme 1):

- use of CH-acidity of allylglycine and propargylglycine moieties of these complexes to study the reaction of C-alkylation,
- use of the acetylene bond for the Sonogashira reaction,
- use of the acetylene bond for the Glaser reaction,
- use of the ethylene bond for the Heck reaction.

Scheme 1

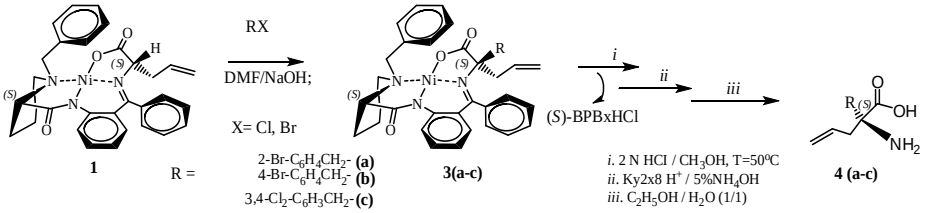


Ni^{II}-(*S*)-BPB-(*S*)-AllylGly (**1**)

Ni^{II}-(*S*)-BPB-(*S*)-PropargylGly (**2**)

Reaction of C-alkylation of allylglycine and propargylglycine moieties of complexes 1 and 2

a) The reaction of C-alkylation of allylglycine moiety of complex 1 (Scheme 2).



To determine optimal reaction conditions for C-alkylation of complex **1** on the example of adding the alkylating agent 4-bromobenzylbromide, various conditions (solvent and base) CH_3CN/KOH, CH_3CN/K_2CO_3, $CH_3CN/NaOH$, DMF/K_2CO_3, DMF/KOH, DMF/NaOH were studied. The reaction was carried out at both room temperature and upon heating up to 60°C. The alkylation reaction was monitored by TLC [SiO2, $CH_3COOC_2H_5/CH_3COCH_3$=5/1] following the disappearance of traces of the initial complex **1** and formation of the diastereomeric mixture of complexes **3 (a-c)**. The results are given in Table 1.

Table 1

Alkylation of complex 1 by 4-bromobenzylbromide (4-BrBnBr)

No.	4-**BrBnBr , (equiv.)**	**Solvent**	**Base (equiv.)**	**Reaction time, *min***	**T°,C**	**Chemical yield %***
1	1	CH_3CN	K_2CO_3(3)	120	60	<20
2	1.1	CH_3CN	K_2CO_3(5)	120	20	<20
3	1	CH_3CN	KOH(3)	60	60	30
4	1.2	CH_3CN	KOH(5)	120	20	35
5	1.2	CH_3CN	NaOH(5)	45	20	25
6	1.2	CH_3CN	NaOH(3)	45	65	25
7	1.5	DMF	KOH(3)	45	20	40
8	1.2	DMF	NaOH(3)	45	20	50
9	1.2	DMF	NaOH(5)	60	20	75
10	1.2	DMF	NaOH(5)	60	60	63
11	1.2	DMF	NaOH(5)	45	60	40
12	1.2	DMF	NaOH(10)	30	20	35
13	1.2	DMF	K_2CO_3	100	65	<20

As follows from the data of Table 1, the best results by the degree of conversion of the starting complex **1** were fixed in the DMF medium at room temperature and at 5-fold excess of base NaOH. Adding of other alkylating agents to complex **1** was carried out under the same conditions.

Alkylation of complex **1** is a kinetically monitored process and its stereoselectivity is determined by relative rates of ***si-*** and ***re***-attack of the alkylating agent on the intermediate prochiral sp^2-carbanion. The ratio of (*S,S*)- and (*S,R*)-

diastereomers of alkylated complexes **3(a-c)** was determined by the ^{1}H NMR analysis of a mixture of diastereomers (before chromatography) by the ratio of the signal integrals of methylene protons of N-benzyl group in the range of 3.60-3.75 and 4.20-4.45 ppm (Table 2).

Table 2

No.	**RX**	***Alkylated complex***			***Target amino acid***		
		Major Diastereomer (*S,S*)	*de*, %[b]	Chem. yield, %[c]	Amino acids *(S)*	*ee*,%[d]	Chem. yield, %[e]
1	2-Br-$C_6H_4CH_2Br$	3a	94.5/5.5	78	4a	94.86	69
2	4-Br-$C_6H_4CH_2Br$	3b	94.2/5.8	74	4b	96.24	71
3	3.4- Cl_2-$C_6H_3CH_2Cl$	3c	95.6/4.4	68	4c	95.46	80

A small portion (1g) of the reaction mixture was chromatographed [20x30*cm*, SiO_2, $CHCI_3/CH_3COCH_3$=3/1], major (*S,S*)-diastereomers of complexes **3(a-c)** were isolated and characterized by modern methods of physicochemical analyses.

Isolation and purification of the target amino acids **4(a-c)** from the reaction mixture of alkylated complexes **3(a-c)** were carried out by the standard procedure [17,18]. Enantiomeric excess (*ee*) of the isolated amino acids according to the chiral HPLC exceeded 95%.

As a result of the performed investigations the efficient method for the asymmetric synthesis of new enantiomerically enriched analogs of (*S*)-α-allyl-β-phenylalanine containing halogen atoms in different positions of the phenyl group has been elaborated.

Thus, using this approach we managed to obtain 4 novel, earlier not described in the literature, non-protein unsaturated α-amino acids of (*S*)-configuration and in 95% asymmetric yield, as well as their intermediate complexes, correspondingly.

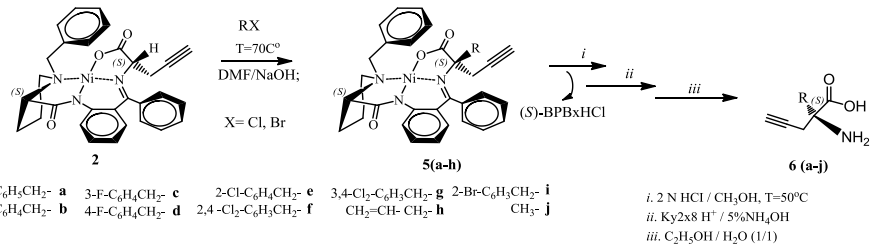
b) The reaction of C-alkylation of amino acid moiety of complex 2 was conducted in DMF/NaOH.

When the reaction of alkylation was carried out in DMF in the presence of NaOH, substitution of α-H-amino acid moiety with the formation of complexes of α-alkyl substituted (*S*)-propargyl glycines (**5a-j**) was observed for all halogenides.

The major fractions of synthesized complexes (**5a-j**) were chromatographed.

Isolation of the target enantiomerically enriched amino acids (**6(a-j)**) from the major diastereomeric complexes (**5a-j**) was conducted according to a general procedure [17,18].

Scheme 3



The ratio of (*S*,*S*)- and (*S*,*R*)-diastereomers of alkylation products was evaluated by ^{1}H NMR analysis of the mixture of diastereomeric complexes (before chromatography) by the ratio of the signal integrals of methylene protons of N-benzylproline moiety in the range of 2.55–4.40 ppm. Besides, the ratio of diastereomeric complexes was additionally verified by chiral HPLC analysis of the mixture of amino acids isomers obtained after acidic decomposition of the mixture of diastereomeric complexes (before chromatography) and ion-exchange demineralization.

The results are given in Table 3.

Table 3

The results of asymmetric C-alkylation of Ni^{II}-(*S*)-BPB-(*S*)-PGly[a]

No.	**RX**	***Alkylated complex***			***Target amino acid***		
		Major diastereomer	*de*, %[b]	Chem. yield, %[c]	Amino acids	*ee*,%[d]	Chem. yield, %[e]
1	$C_6H_5CH_2Br$	5a	72	55	6a	97.5	60
2	2-F-$C_6H_4CH_2$ Br	5b	70	52	6b	95.5	64
3	3-F-$C_6H_4CH_2$ Br	5c	68	62	6c	96.5	71
4	4-F-$C_6H_4CH_2$ Br	5d	76	67	6d	95.0	64
5	2-Cl-$C_6H_4CH_2$ Br	5e	73	58	6e	96.4	64
6	2.4-Cl_2-$C_6H_3CH_2Cl$	5f	69	68	6f	97.8	64
7	3.4-Cl_2-$C_6H_3CH_2Cl$	5g	71	60	6g	95.3	64
8	CH_2=CH-CH_2-Br	5h	75	55	6h	96.4	59
9	2-Br-$C_6H_4CH_2$ Br	5i	90	60	6i	96.4	57
10	CH_3I	5j	84	45	6j	95	62

[a] – *reaction conditions*: DMF/NaOH, 70°C.

[b] – *de-determined by NMR*

[c] – *chemical yield of diastereomeric complexes at the stage of alkylation*

[d] – *determined by the method of chiral HPLC of the amino acid obtained after decomposition of the mixture of diastereomeric complexes and ion-exchange demineralization*

[e] – *chemical yield of the isolated amino acid (calculated based on complex* ***5(a-j)****).*

The target α-alkyl substituted propargylglycines **6(a-j)** were isolated from the diastereomeric mixtures of alkylated complexes according to the standard procedure and crystallized from aqueous alcoholic solutions. The structures and absolute configuration of synthesized amino acids were established by physicochemical methods.

The absolute configuration of α-carbon atom of the amino acid moiety of the afore-mentioned complexes was determined by the method of polarimetric measuring as it was done earlier for the similarly constructed complexes of other amino acids [17,18]. The positive sign of the optical rotation of major diastereomers of complexes ***3(a-c)*** *and* ***5(a-j)*** *with larger values of* ***Rf*** *on silica gel at the wave length of 589 nm prove (S)-absolute configuration of α-carbon atom of their amino acid moieties ((S,S)-diastereomers).*

The structure and absolute configuration of the synthesized new amino acids were identified by modern methods of physicochemical analysis [19,20].

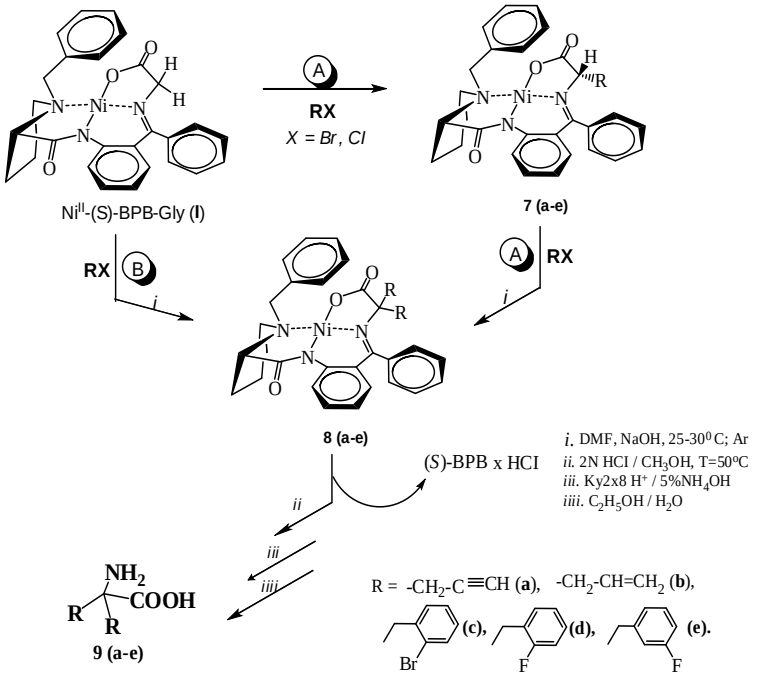
Thus, using this approach we managed to obtain 10 novel, earlier not described in the literature, non-protein unsaturated α-amino acids of (*S*)-configuration and in 96% asymmetric yield, as well as their intermediate complexes, correspondingly.

c) Synthesis of achiral α,α-disubstituted glycine analogs

This direction was of interest to us because the presence of acetylene, allyl and aromatic groups in the side-chain radical of the synthesized compounds allows to use them as the starting synthons in the Suzuki, Heck, Sonogashira reactions for producing more complex unsaturated amino acids.

This section is devoted to the synthesis of complexes containing in α-position propargyl, allyl, 2-bromobenzyl, 2-fluorobenzyl and 3-fluorobenzyl groups via *bis*-alkylation of the glycine moiety in the Ni^{II} complex of its Schiff base with chiral auxiliary (*S*)-BPB (Scheme 4). To obtain achiral *bis*-alkylated glycine derivatives, the reactions of both stepwise monoalkylation of amino acid moiety of complexes **1** and **7**(***a-e***) (path **A**), and direct *bis*-alkylation of glycine moiety of complex **I** (path **B**) were studied.

Scheme 4



Complexes **8(a-e)** were obtained from complex **I** according to the previously developed method [14]. As alkylating agents propargylbromide (***a***), allybromide (**b**), 2-bromobenzyl- bromide (***c***), 2-fluorobenzylchloride (***d***) and 3-fluorobenzylbromide (***e***) were used.

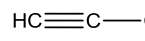
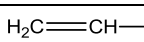
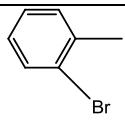
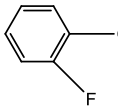
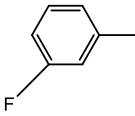
Alkylation reactions were tested in DMF/KOH, DMF/NaOH, CH_2Cl_2/NaOH, THF/NaOH and CH_3CN/NaOH media at both room temperature and upon heating up to 55^{o}C. To determine optimal conditions for alkylation, on the example of the condensation reaction of propargylbromide (***a***) to complex **I,** various stoichiometric ratios of substrate, alkylating reagent and base were investigated. Studies have shown that the optimum conditions for the alkylation reaction of complex **I** are the following: DMF as a medium, NaOH as a base, room temperature, the ratio of complex **I**/base/ alkylating agent =1/3/1.5.

The alkylation reaction was monitored by TLC [SiO_2, $CH_3COOC_2H_5$/CH_3COCH_3=3/1]. For quantitative evaluation of the alkylation reaction TLC data were used. The highest chemical yields, shown by some of compounds, were determined by the number of alkylated complexes isolated after crystallization from methanol.

Quantitative characteristics of C-alkylation reaction of the amino acid moiety of complexes **I** and **7**(***a-e***) are presented in Table 4.

Table 4

Results of complexes alkylation by various alkylhalogenides in DMF in the presence of NaOH at room temperature*

No.	Alkylhalogenide	Chem. yield of *bis*-alkylated complexes (%)		
		Bis-alkylated complexes	Path A **	Path B
1	 (***a***)	**8*a***	83 (92)	45
2	 (***b***)	**8*b***	80 (89)	48
3	 (***c***)	**8*c***	73 (82)	44
4	 (***d***)	**8*d***	68 (76)	46
5	 (***e***)	**8*e***	72 (84)	48

chemical yield of bis-alkylated complexes based on the starting number of glycine complex (I**);*

***in brackets – chemical yield of bis-alkylated complexes **8(a-e)** after crystallization based on the number of complexes **7(a-e)** (path A, stage 2).*

Both stepwise alkylation of the amino acid moiety of complexes **I** and **7**(***a-e***) (path **A**), and direct *bis*-alkylation of complex **I** (path **B**) were carried out under specially selected optimal conditions for alkylation reactions, however, in case of direct *bis*-alkylation of glycine complex the alkylating agent and base were taken in relatively double excess.

Practically for all alkylating agents *bis*-alkylation of glycine complex **I** proceeds more quantitatively with the use of a method of two-stage stepwise alkylation (path A) than with immediate *bis*-alkylation of glycine complex (path B). In case of using a method of direct *bis*-alkylation of the glycine moiety of complex **I**, about 30% of less mobile on the SiO_2 sideline fraction is formed with not typical for these complexes dark color (oxidation products). The similar was also observed earlier while studying the reaction of *bis*- alkylation of complex **I** by methyl iodide [22]. The main α,α-dialkyl substituted complexes **8**(**a-e**) were isolated from the reaction mixture by crystallization from methanol. With the purpose to isolate target α,α-*bis*-alkylated glycine analogs, preparative experiments using the method of two-stage stepwise alkylation (path A) were carried out and samples of complexes **8(a-e)** were obtained. Decomposition of complexes **8(a-e)** and isolation of target α,α-dialkyl substituted glycine derivatives **9(a-e)** were conducted by the standard procedure [17,18].

The structures of synthesized new achiral complexes as well as of achiral glycine analogs were determined by modern methods of physicochemical analysis [23].

Sonogashira reaction

In case of the Sonogashira, Heck and Glaser reactions, the objective of the research was use of the unsaturated bond with its directed modification to obtain non-protein amino acids of a new generation, containing substituents added immediately to the unsaturated bond.

We have also studied arylation of acetylene group of propargylglycine moiety of complex **2** using the Sonogashira reaction (Scheme 5). Bromobenzene was used as an arylating agent, and various phosphorus Pd-complexes were tested as catalysts. The arylation reaction was studied in different media. The results are given in Table 5.

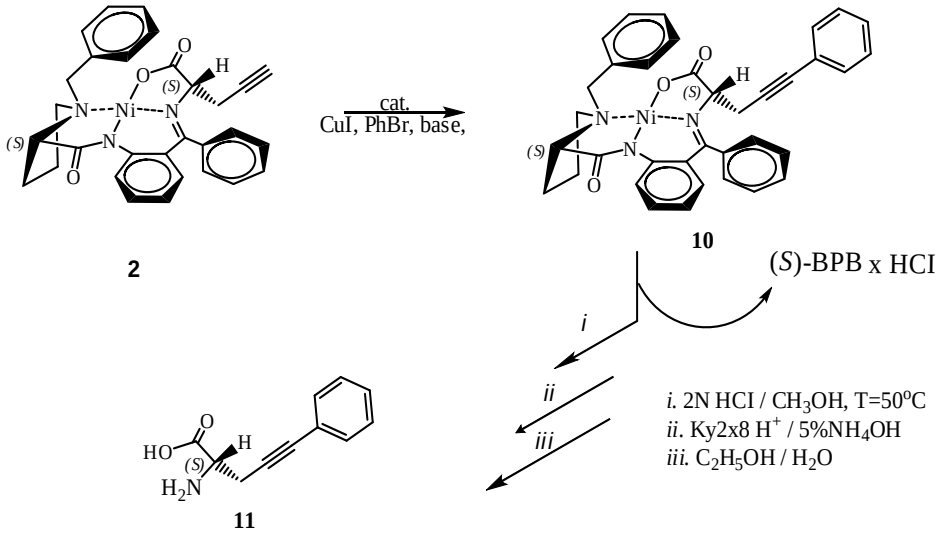
Table 5

Optimization of conditions of the Sonogashira reaction

No.	Catalyst	Co-catalyst	Solvent	Base	T°,C	Chem. yield, %[e a]
1	$PdCl_2(PPh_3)_2$ 5 *mol*%	CuI 10 *mol*%	1.4-Dioxane	DIPA	90	46
2	$Pd(PPh_3)_4$ 5 *mol*%	CuI 10 *mol*%	DMF	DIPA	90	64
3	$Pd(PPh_3)_4$ 5 *mol*%	CuI 10 *mol*%	THF	DIPA	60	58
4	**$Pd(PPh_3)_4$ 5 mol%**	**CuI 10 mol%**	**1.4-Dioxane**	**DIPA**	**90**	**70**
5	$Pd(PPh_3)_4$ 5 *mol*%	CuI 10 *mol*%	CH_3CN	DIPA	90	59
6	$Pd(PPh_3)_4$ 5 *mol*%	CuI 10 *mol*%	1.4-Dioxane	Et_3N	90	45
7	$Pd(PPh_3)_4$ 2.5 *mol*%	CuI 5 *mol*%	1.4-Dioxane	DIPA	90	40
8	$Pd(PPh_3)_4$ 5 *mol*%	CuI 5 *mol*%	1.4-Dioxane	DIPA	90	57

*Conditions: i: **1** (0.25 mmol), $Pd(PPh_3)_4$(5 mol%), CuI(10 mol%), PhBr (0.21 mmol), DIPA (0.5 mL), 1,4-Dioxane (1 mL), 90°C, 6 h.*

Scheme 5



As follows from the Table, maximum 70% chemical yield was registered in the case of catalysts 5 mol% $Pd(PPh_3)_4$ and 10 mol% CuI, base DIPA (diisopropylamide) in 1.4-dioxan (exp. 4). The reaction was carried out in the argon stream at 90^0C.

The target arylated (*S*)-2-amino-5-phenylpent-4-ynoic amino acid **13** was isolated from the reaction mixture by the general procedure. It was obtained in 85% chemical and 97% enantiomeric yields and its physicochemical parameters were in full agreement with the literature data.

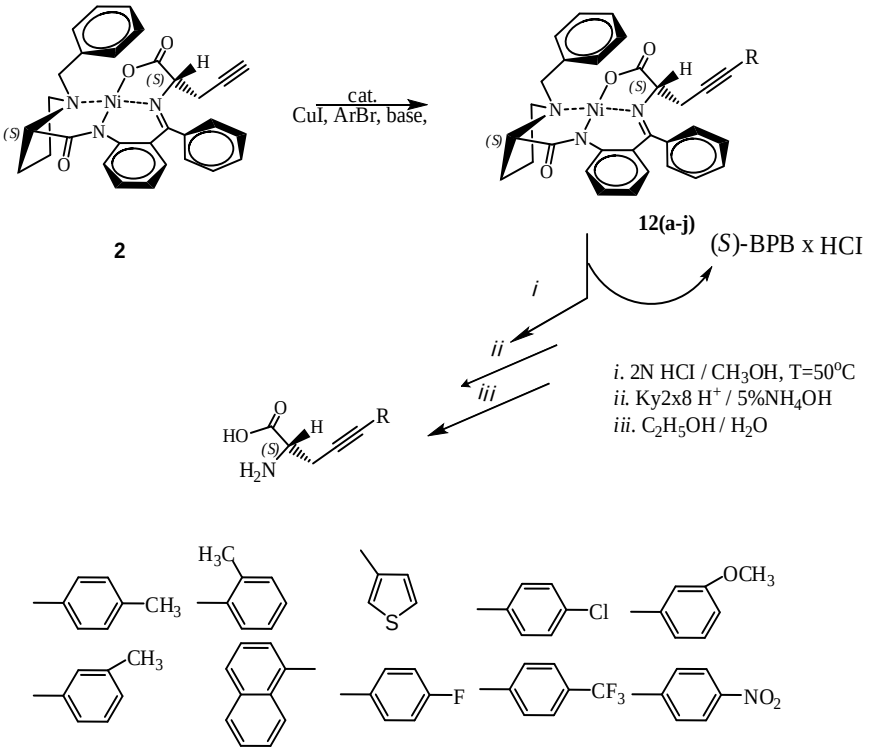
Based on the obtained data, a number of aryl bromides were tested in the Sonogashira reaction (Scheme 6, Table 6):

Table 6

No.	Product-complex	Ar	The reaction duration, h	Chem. yield, %
1	12a	4-$C_6H_4CH_3$	3.0	67
2	12b	3-$C_6H_4CH_3$	3.0	71
3	12c	2-$C_6H_4CH_3$	3.0	46
4	12d	napht-1-yl	4.5	68
5	12e	thiophen-2-yl	3.5	78
6	12f	4- C_6H_4F	3.0	71
7	12g	4- C_6H_4Cl	3.0	72
8	12h	4- $C_6H_4CF_3$	3.0	76
9	12i	3- $C_6H_4OCH_3$	3.5	67
10	12j	4- $C_6H_4NO_2$	3.0	7

*Conditions: **2** (1.0 eq.), ArBr (1.2 eq.), $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), $HNiPr_2$ (1 ml/0.25 mmol), 1,4-dioxane (1 ml/0.25 mmol).*

Scheme 6



Thus, using this approach we succeeded to produce 10 novel, earlier not described in the literature non-protein unsaturated α-amino acids of (*S*)-configuration, as well as their intermediate complexes in quantitative chemical yields [24].

Heck reaction

This section is devoted to the synthesis of unsaturated amino acids based on the Heck reaction (Scheme 7).

Scheme 7

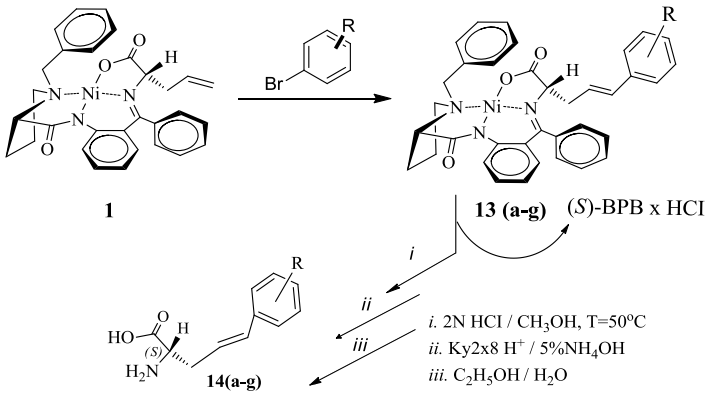
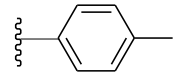
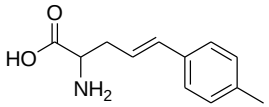
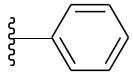
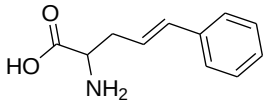
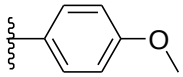
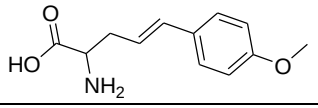
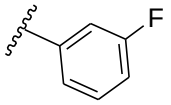
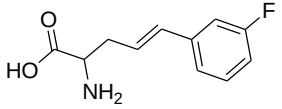
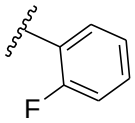
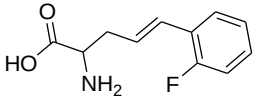
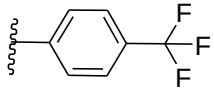
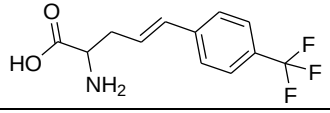
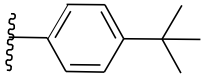
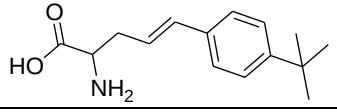


Table 7

No.	Complex-product		Chemical Yield, %	Amino Acid		Chemical yield, %
1	**13a**		82		**14a**	65
2	**13b**		27		**14b**	92
3	**13c**		29		**14c**	83
4	**13d**		85		**14d**	97
5	**13e**		45		**14e**	98
6	**13f**		69		**14f**	88
7	**13g**		75		**14g**	91
*Condition: **1** (1.0 eq.), ArBr (1.2 eq.), $Pd(PPh_3)_4$ (5 mol%), $HNiPr_2$ (1 ml/0.25 mmol **1**), 1,4-dioxane (1 ml/0.25 mmol **1**), reaction duration 48 h*						

The reaction was carried out in the argon stream at 90^0 C with 5 *mol*% of $Pd(PPh_3)_4$ in 1,4-dioxane. The duration of reaction was 48 h.

Thus, using this approach we succeeded to produce 7 novel, earlier not described in the literature non-protein unsaturated α-amino acids of (*S*)-configuration, as well as their intermediate complexes in quantitative chemical yields.

Glaser reaction

In this section we outline study of the Glaser reaction. Initially, the reaction of hetero-coupling of complex 2 with allylbromide was investigated. The reaction was tested at room temperature in DMF/NaOH, CH_3CN/NaOH and CH_3CN/K_2CO_3 media. The best results were obtained with CH_3CN/K_2CO_3 (Table 8, Scheme 8).

Table 8

Testing of the Glaser hetero-coupling reaction of complex 2 and allylbromide at room temperature

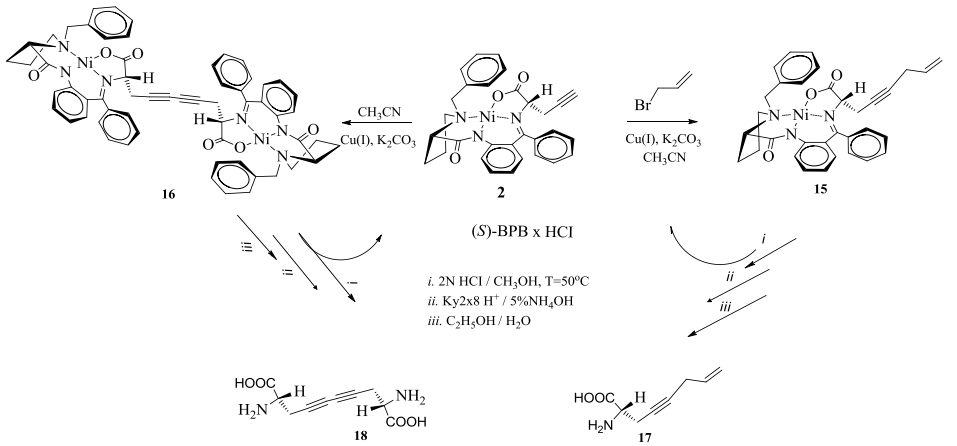
№	Solvent/ base	Time, *min*	*de*, % [a]	Chem. yield, % [б]
1	DMF/NaOH	300	–	20
2	CH_3CN/NaOH	140	62.32	55
3	CH_3CN/K2CO3	45	74.30	74

a – determined by the method of HPLC analysis of the amino acid produced after decomposition of a mixture of diastereomeric complexes and ion-exchange demineralization;

b–the total chemical yield of diastereomeric complexes at the stage of hetero-coupling.

After decomposition of a diastereomeric mixture of product **15** by 2N HCl solution, the target amino acid was isolated from hydrolisate by the standard procedure [17-18] using ion-exchange resin Ku-2x8 and crystallization from water-alcoholic solutions. A new enantiomerically enriched non-protein amino acid - (*S*)-2-aminoocta-7-en-4-yneic acid (**17**) was obtained in >71% chemical yield (calculated based on the mixture of addition products) and optical purity 98.5% (according to HPLC analysis data).

Scheme 8



Oxidative demineralization of Ni^{II}-(*S*)-BPB-(*S*)-PGly **2** complex was carried out in CH_3CN/K_2CO_3 medium in the presence of CuCl catalyst (Scheme 8). The diastereomeric excess (*de*) of the obtained complex **16** determined by NMR was 98% [25].

Thus, our team has succeeded in synthesis of more than 30 novel, previously not described in the literature, unsaturated non-protein amino acids and their intermediate complexes, correspondingly. Among the new synthetic amino acids inhibitors of some enzymes including inhibitors of serine proteases and metalloproteases were also revealed.

Thus, using this approach we managed to produce 4 novel earlier not described in the literature non-protein unsaturated α-amino acids of (S)-configuration in 95% asymmetric yield as well as their intermediate complexes, correspondingly. The significance of this approach is enhanced by the fact that the replacement of the initial synthon of (*S*)-configuration by the (*R*)-configuration makes it possible to produce the same unsaturated α-amino acids but already of (*R*)-configuration.

This work was supported in part by the RA MES State Committee of Science and Russian Foundation for Basic Research *(RF)* in the frames of the joint research projects SCS 15RF-035 as well as by the RA MES State Committee of Science, in the frames of the research project №15T-1D260.

This work was awarded the State Award 2015 of the Republic of Armenia in the sphere of exact and natural sciences.

ՉՀԱԳԵՑԱԾ ԱՄԻՆԱԹԹՈՒՆԵՐԻ ԱՍԻՄԵՏՐԻԿ ՍԻՆԹԵԶԻ ԲՆԱԳԱՎԱՌՈՒՄ ՀԻՆԳ ՏԱՐԻՆԵՐԻ ՁԵՌՔԲԵՐՈՒՄՆԵՐԸ

Ա. Ս.ՍԱՂՅԱՆ, Յու. Ն. ԲԵԼՈԿՈՆ, Պ. ԼԱՆԳԵՐ,
Ա. Ֆ. ՄԿՐՏՉՅԱՆ և Ջ. Ջ. ՄԱՐԴԻՅԱՆ

Վերջին 5 տարիներին մեր հետազոտությունների ուղղություններից մեկն է դարձել չհագեցած կապեր պարունակող էնանթիոմերապես հարստացված ամինաթթուների սինթեզը: Ներկայացված հոդվածը նվիրված է այդ ամինաթթուների ասիմետրիկ սինթեզին

Որպես ելային սինտոններ ընտրվել են (S)-ալիլգլիցինի կամ (S)-պրոպարգիլգլիցինի և քիրալային օժանդակ ռեագենտ (S)-2-N-(N′-բենզիլպրոլիլ)ամինաբենզոֆենոնի(BPB) Շիֆի հիմքի առաջացրած NiII կոմպլեքսները [NiII-(S)-BPB-(S)-AllylGly և NiII-(S)-BPB-(S)-PropargylGly]:

NiII-(S)-BPB-(S)-AllylGly և NiII-(S)-BPB-(S)-PropargylGly կոմպլեքսների կիրառմամբ հետազոտությունները տարվել են չորս ուղղություններով՝

- *կոմպլեքսների ալիլգլիցինային և պրոպարգիլգլիցինային ֆրագմենտների CH-թթվայնության կիրառումը C-ալկիլման ռեակցիաների հետազոտման համար,*
- *ացետիլենային կապի կիրառումը Սոնոգաշիրայի ռեակցիայում,*
- *ացետիլենային կապի կիրառումը Գլայզերի ռեակցիայում,*
- *էթիլենային կապի կիրառումը Հեկի ռեակցիայում:*

Այսպիսով, օգտագործելով այս մոտեցումը, մեզ հաջողվել է ստանալ ավելի քան 20 նոր, նախկինում գրականության մեջ չնկարագրված, չհագեցած կապեր պարունակող (S)-կոնֆիգուրացիայի α-ամինաթթուներ բարձր ասիմետրիկ ելքերով, ինչպես նաև դրանց համապատասխան միջանկյալ կոմպլեքսները:

ДОСТИЖЕНИЯ ПЯТИ ЛЕТ В ОБЛАСТИ АСИММЕТРИЧЕСКОГО СИНТЕЗА НЕНАСЫЩЕННЫХ АМИНОКСИЛОТ

А. С. САГИЯН[а,б], Ю. Н. БЕЛОКОНЬ[в], П. ЛАНГЕР[г], А. Ф. МКРТЧЯН[а,б] и З. З. МАРДИЯН[а]

[а]Научно-производственный центр "Армбиотехнология" НАН РА
Армения, Ереван, 0056, ул. Гюрджяна, 14
Факс: (+37410) 654180, E-mail: saghyan@netsys.am
[б]Ереванский государственный университет, Институт фармации
Армения, Ереван, 0025, ул. А. Манукяна, 1
[в] Институт элементоорганических соединений им. А.Н. Несмеянова РАН
Российская Федерация, 119991, Москва, ул. Вавилова, 28
[г] Университет Ростока, Институт химии
Германия, 18059, Росток, ул. А.Эйнштейна, 3а

В последние пять лет одним из направлений наших исследований стал синтез ненасыщенных энантиомерно обогащенных аминокислот. Данная статья посвящена синтезу выше отмеченных α-аминокислот, основанному на использовании Ni^{II}-комплексов основания Шиффа аминокислот с хиральным вспомогательным реагентом (S)-2-N-(N`-бензилпролил)аминобензофеноном (BPB) в различных именных реакциях. В качестве исходного синтона были выбраны Ni^{II}-комплексы основания Шиффа (*S*)-аллилглицина или (пропаргилглицина) и хирального вспомогательного реагента (*S*)-2-N-[N'-(бензилпролил)амино]бензофенона (BPB) [Ni^{II}-(*S*)-BPB-(*S*)-AllylGly и Ni^{II}-(*S*)-BPB-(*S*)-PropargylGly].

Исследования с использованием комплексов Ni^{II}-(*S*)-BPB-(*S*)-AllylGly и Ni^{II}-(*S*)-BPB-(*S*)-PropargylGly проводились по четырем направлениям□

- использования CH-кислотности аллилглицинового и пропаргилглицинового фрагментов этих комплексов для исследования реакции С-алкилирования,
- использование ацетиленовой связи для реакции Соногаширы,
- использование ацетиленовой связи для реакции Глазера,

- использование этиленовой связи для реакции Heck-a.

Таким образом, используя данный подход, нам удалось получить более 20 новых, ранее не описанных в литературе ненасыщенных α-аминокислот (*S*)-конфигурации с высоким асимметрическим выходом.

REFERENCES

[1] *Singh P., Kumar S. L., Samanta K., Panda G.* // Tetrahedron, 2017 (accepted).
[2] *Friedman M.* // Chemistry & Biodiversity, 2010, v. 7, p. 1491.
[3] *Friedman M., Levin C.E.* // Amino Acids, 2012, v. 42, p. 1553.
[4] *Ma J.S.* // Chim. Oggi, 2003, v. 21, p. 65.
[5] *Ojima I., Lin S., Wang T.* // Curr. Med. Chem., 1999, v. 6, p. 927.
[6] *Jianga1 J., Chena X., Feng J., Wu Q., Zhua D.* // Journal of Molecular Catalysis B: Enzymatic, 2014, v. 100, p. 32.
[7] *Fanelli R., Julien L.J., René A., Martinez J., Cavelier F.* // Amino Acids, 2015, v. 47, p. 1107.
[8] *Kaiser J., Kinderman S.S., Esseveldt B.C.J., Delft F.L., Schoemaker H.E., Blaauw R.H., Rutjes F.T.* // Org. Biomol. Chem., 2006, v. 3, p. 3435.
[9] *Мкртчян А.Ф., Мардиян З.З., Карапетян А.Ж., Погосян А.С., Петросян С.Г., Симонян А.М., Цатурян А.О., Сагиян А.С.* // Хим. ж. Армении, 2015, т. 68, №3, с. 403.
[10] *Berkheij M.* // Dissertation, 2008, chapter 1.
[11] *Leuchtenberger W., Huthmacher K., Drauz K.* // Appl. Microbiol. Biotechnol., 2005, v. 69, p. 1.
[12] *Höhne M., Bornscheuer U.T.* // ChemCatChem, 2009, v. 1, p. 42.
[13] *Weiner B., Szymanski W., Janssen D.B., Minnaard A.J., Feringa B.L.* // Chem. Soc.Rev., 2010, v. 39, p. 1656.
[14] *Saghyan A.S., Langer P.* // Wiley-VCH, 2016.
[15] *Сагиян А.С., Петросян С.Г., Мкртчян А.Ф., Мкртчян Г.М., Лангер П.* // Хим. ж. Армении, 2013, т. 66, №4, с. 588.
[16] *Мардиян З.З.* // Хим. ж. Армении, 2016, т. 69, №4, с. 486.
[17] *Belokon' Yu.N., Saghiyan A.S., Djamgaryan S.M., Bakhmutov B.I., Belikov V.M.* // Tetrahedron, 1988, v. 44, №17, p.5507.
[18] *Belokon Yu.N., Saghyan A.S., Djamgaryan S.M., Bakhmutov V.I., Vitt S.V., Batsanov A.S., Struchkov Yu.T., Belikov V.M.* // J. Chem. Soc., Perkin Trans. 1, 1990, v. 1990, issue 8, p. 2301.
[19] *Сагиян А.С., Едоян Д.А., Мкртчян А.Ф., Овсепян Г.Ц., Цатурян Г.Ц., Цатурян А.О., Лангер П.* // Хим. ж. Армении, 2014, т. 67, №1, с. 67.
[20] *Saghyan A.S., Mkrtchyan A.F., Karapetyan A.J., Mardiyan Z.Z., Hayriyan L.A., Simonyan H.M.* // International Journal of Chemical Engineering and Applications, 2016, v. 7, p. 413.
[21] *Saghyan A.S., Langer P.* / Asymmetric synthesis of non-proteinogenic amino acids, ISBN: 978-3-527-34041-5; 2016, 376 page, Wiley-VCH.
[22] *Mkrtchyan A.F., Mardiyan Z.Z., Karapetyan A.Zh., Poghosyan A.S., Petrosyan S.G., Tsaturyan A.O., Saghyan A.S.* // Chemical Journal of Armenia, 2015, v. 68, p. 403.
[23] *Мардиян З.З.* // Хим. ж. Армении, 2016, т. 69, №4, с. 486.
[24] *Parpart S., Petrosyan A., Shah A., Adewale A., Peter Ehlers, Grigoryan T., Mkrtchyan A.F., Mardiyan Z.Z., Karapetyan A.J., Tsaturyan A.H., Saghyan A.S., Iqbal J., Langer P.* RSC Adv., 2015, v. 5, p. 107400.
[25] *Сагиян А.С., Петросян С.Г., Мкртчян А.Ф., Мкртчян Г.М., Лангер П.* Хим. ж. Армении, 2013, т. 66, №4, с. 588.