Mikhailo Slivka*, Nataliya Korol, Valerij Pantyo, Vjacheslav Baumer and Vasil Lendel

Regio- and stereoselective synthesis of [1,3] thiazolo[3,2-*b*][1,2,4]triazol-7-ium salts via electrophilic heterocyclization of 3-*S*propargylthio-4*H*-1,2,4-triazoles and their antimicrobial activity

DOI 10.1515/hc-2016-0233 Received December 16, 2016; accepted February 27, 2017

Abstract: A procedure for the preparation of the title salts via regioselective halocyclization of 3-*S*-propargylthio-4*H*-1,2,4-triazoles is reported. Stereoselectivity of electrophilic heterocyclization depends on the nature of the electrophilic reagent: bromination is better than iodobromination and iodination. The heterocyclization with tellurium tetrahalogenides leads to the formation of a mixture of geometric isomers of the salts. Their structure was confirmed by ¹H NMR, ¹³C NMR, HMBC and single crystal X-ray diffraction analysis.

Keywords: electrophilic cyclization; halogen; regioselectivity; stereoselectivity; tellurium tetrahalogenides; [1,3] thiazolo[3,2-*b*][1,2,4]triazol-7-ium salts.

Introduction

Küçükgüzel and Çıkla-Süzgün [1] recently reviewed the application of 1,2,4-triazoles in biology and medicine. The electrophilic heterocyclization has become an important tool in the synthesis of bioactive 1,2,4-triazoles, their fused derivatives and analogues [2–28]. This report describes preparative methods for the synthesis of condensed 1,2,4-triazole-3-thione derivatives via electrophilic heterocyclization of 3-*S*-propargylthio-4*H*-1,2,4-triazoles. The regioselectivity and stereoselectivity of this electrophilic heterocyclization is also analyzed.

Results and discussion

In our previous work, we showed the possibility of the synthesis of condensed triazoles by halogenation of 3-alkenvlthio-4,5-diphenvl-3H-1,2,4-triazoles [18, 19]. In order to study the regioselectivity and stereoselectivity of such electrophilic cyclization in this work, we used the propargyl derivatives of 3-mercapto-1,2,4-triazole 2 synthesized by the reaction of propargyl bromide with the corresponding triazoles 1 under basic conditions (Scheme 1). The structure of thioethers 2 was confirmed by ¹H NMR and ¹³C NMR spectroscopy. The cyclization of thioethers 2 in the presence of a halogen in glacial acetic acid at room temperature led to regio-selective formation of condensed [1,3] thiazolo[3,2-b][1,2,4]triazol-7-ium salts 3 and 4. It should be noted that the use of less polar solvents including chloroform, dichloromethane and tetrachloromethane resulted in a non-selective formation of a mixture of halogenated products. The structures of the salts **3** and **4** were confirmed by analysis of ¹H NMR and ¹³C NMR spectra. Thus, the ¹H NMR spectrum of tribromide **3a** lacks the signals of the propargyl fragment. On the other hand, the signal of the proton of bromomethylidene group in the aromatic region and the presence of a proton signal of the endocyclic methylene group at 5.10 ppm confirms the annulation to a thiazoline ring system. In the ¹³C NMR spectrum of tribromide **3a**, all signals correspond to sp³- and sp²-carbons. The lack of signals for *sp*-carbons, which are characteristic for a propargyl fragment, is also consistent with the ring structure for tribromide 3a. The NMR spectra for triiodides 4 are similar to NMR spectra of tribromides **3**. Cyclization of the starting thioether 2 was also carried out by treatment with iodine bromide. Chemical shifts in the NMR spectra of the resultant products 5 are similar to those of triiodides 4.

It should be noted that the halogenation proceeds with different stereoselectivity for different electrophilic reagents. Thus, the ratio of the peaks of methylene protons in ¹H NMR spectra of crude products **3–5** shows that bromination is

^{*}Corresponding author: Mikhailo Slivka, Organic Synthesis Laboratory, Uzhhorod National University, Uzhhorod 88000, Ukraine, e-mail: mikhailslivka@gmail.com

Nataliya Korol, Valerij Pantyo and Vasil Lendel: Organic Synthesis Laboratory, Uzhhorod National University, Uzhhorod 88000, Ukraine Vjacheslav Baumer: SSI "Institute for Single Crystals" NASU, Lenina ave. 60, Kharkiv 61001, Ukraine



Scheme 1 Synthesis of compounds 3-6.

the most stereoselective process resulting in an almost 90% formation of *E*-isomer. By contrast, iodination is practically non-stereoselective, leading to the formation of almost equal amounts of *E*-stereoisomers and *Z*-stereoisomers. Stereoselective formation of the *E*-isomer was confirmed by heteronuclear correlation analysis for tribromide **3a**. It was possible to grow a single crystal of the *E*-isomer of **3a** for X-ray crystallographic diffraction analysis (Figure 1).

Cyclization of thioethers **2** by treatment with tellurium tetrachloride or tellurium tetrabromide was also studied. The analysis of the ¹H NMR and ¹³C NMR spectra of crude cyclization products shows that the heterocyclization leads regioselectively to a single *E*-diastereomer of [1,3]thiazolo[3,2-*b*][1,2,4]triazol-7-ium salt **6** in each case. By contrast, a similar treatment of **2** with a selenium tetrahalide yielded amorphous selenium and several oily products that defied purification. This result can be explained in terms of low stability of the selenium-containing products, which agrees with the literature data [26].

Antimicrobial activity

Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ampicillin

(10 μ g/mL) and fluconazole (5 μ g/mL) were used as standard drugs. The antimicrobial activity (at 10 µg/mL) results are summarized in Figure 2. As can be seen, compound **2b** exhibits moderate activity against *Staphy*lococcus aureus ATCC 25923. Compounds 5a and 5b demonstrate slight activity against Escherichia coli ATCC 25922 and Candida albicans ATCC60193. Compound 6a shows considerable activity against Gram-negative bacteria Escherichia coli ATCC 25922 and Salmonella enter*itidis*. Importantly, compound **6c** shows high inhibitory activities towards Escherichia coli ATCC 25922 and Salmonella enteritidis that are superior to the activities of the reference antibiotic ampicillin. This compound also has moderate activity against Staphylococcus aureus ATCC 25923 and Klebsiella pneumoniae. Only compounds 2b, 5a and 6a show moderate antifungal activity against Candida albicans ATCC60193.

Conclusions

Treatment of 3-propargylthio-1,2,4-triazoles with bromine, iodine, iodine bromide, and tellurium tetrahalides leads to the formation of [1,3]thiazolo[3,2-*b*][1,2,4]triazol-7-ium salts. The stereoselectivity of the cyclization process was studied. Several products are antimicrobial and antifungal agents.



Figure 2 Antimicrobial activity of compounds 2b, 5a,b, 6a. Relative zones of inhibition are shown.

Experimental

¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded in DMSO- d_{c} on a Varian VXR 400 instrument. Melting points were determined on a Stuart SMP30 instrument. Elemental analyses were performed on an Elementar Vario analyzer.

General procedure for synthesis of 3-*S*-prop-2-yn-1ylsulfanyl-4*H*-1,2,4-triazoles 2a-c

A substituted triazole **1** (10.0 mmol) was dissolved in ethanol (20 mL) with the addition of potassium hydroxide (10.0 mmol) under heating. Propargyl bromide (12.0 mmol) in ethanol (5 mL) was added to this solution and the mixture was heated under reflux for 1 h. After cooling, the precipitated product **2** was filtered, washed with water, dried and crystallized from ethanol.

3,4-Diphenyl-5-(prop-2-yn-1-ylsulfanyl)-4H-1,2,4-triazole (2a) This compound was obtained from **1a**; yield 93% (colorless crystals); mp 133–135°C; ¹H NMR: δ 7.50–7.57 (m, 3H); 7.29–7.45 (m, 7H), 3.97 (s, 2H), 3.23 (s, 1H); ¹³C NMR: δ 155.3, 151.0, 134.4, 130.7, 130.6, 130.4, 129.2, 128.6, 128.3, 127.2, 80.0, 75.3, 21.6. Anal. Calcd for C₁₇H₁₃N₃S: C, 70.08; H, 4.50; N, 14.42; S, 11.00. Found: C, 70.36; H, 4.46; N, 14.35; S, 10.97.

3-(4-Bromophenyl)-4-phenyl-5-(prop-2-yn-1-ylsulfanyl)-4H-1,2,4-triazole (2b) This compound was obtained from **1b**; yield 92% (colorless crystals); mp 127–129°C; ¹H NMR: δ 7.56–7.63 (m, 5H); 7.41–7.47 (m, 2H), 7.31 (d, J=6.8 Hz, 2H), 3.99 (s, 2H), 3.26 (s, 1H). Anal. Calcd for C₁₇H₁₂BrN₃S: C, 55.14; H, 3.27; N, 11.35; S, 8.66. Found: C, 55.21; H, 3.24; N, 11.28; S, 8.74.

3-Benzyl-4-phenyl-5-(prop-2-yn-1-ylsulfanyl)-4H-1,2,4-triazole (2c) This compound was obtained from 1c; yield 88% (colorless crystals); mp 139–141°C; ¹H NMR: δ 6.90–7.51 (m, 10H), 3.99 (s, 2H), 3.88 (s, 2H), 2.49 (s, 1H). Anal. Calcd for $C_{18}H_{15}N_3$ S: C, 70.79; H, 4.95; N, 13.76; S, 10.50. Found: C, 70.91; H, 4.76; N, 13.82; S, 10.54.

General procedure for the electrophilic heterocyclization of 3-*S*-prop-2-yn-1-ylsulfanyl-4*H*-1,2,4-triazoles 2a–c

A solution of iodine (20.0 mmol), bromine (10.0 mmol), iodine bromide (10 mmol), tellurium tetrabromide (10.0 mmol) or tellurium tetraiodide (10 mmol) in glacial acetic acid was added dropwise to the solution of triazole **2** (10.0 mmol) in glacial acetic acid with constant stirring at room temperature for 24 h. The resultant solid product was filtered, washed with hot acetic acid (3×5 mL), cooled and then washed again with diethyl ether (2 mL).

(5*E*)-6-(bromomethylidene)-2,3-diphenyl-5,6-dihydro-3*H*-[1,3] thiazolo[3,2-*b*][1,2,4]triazol-7-ium tribromide (3a) This compound was obtained from **2a** via bromination; yield 88%; yellow crystals; mp 167–168°C; ¹H NMR: δ 7.47–7.88 (m, 11H), 5.10 (s, 2H); ¹³C NMR: δ 162.2, 157.7, 133.6, 133.1, 132.5, 132.0, 131.4, 129.9, 129.6, 126.6, 123.3, 97.5, 42.3. Anal. Calcd for $C_{17}H_{13}Br_4N_3S$: C, 33.42; H, 2.14; 6.88; S, 5.25. Found: C, 33.12; H, 2.05; N, 6.82; S, 5.03.

(5*E*)-2-benzyl-6-(bromomethylidene)-3-phenyl-5,6-dihydro-3*H*-[1,3]thiazolo[3,2-*b*][1,2,4]-triazol-7-ium tribromide (3c) This compound was obtained from 2c via bromination; yield 59%; mp 178–179°C; ¹H NMR: δ 7.57–7.66 (m, 4H) 7.41 (s, 1H), 7.10–7.33 (m, 6H), 5.00 (s, 2H), 4.25 (s, 2H). Anal. Calcd for C₁₈H₁₅Br₄N₃S: C, 34.59; H, 2.42; N, 6.72; S, 5.13. Found: C, 34.33; H, 2.36; N, 6.63; S, 5.04.

(5*E*)-6-(iodomethylidene)-2,3-diphenyl-5,6-dihydro-3*H*-[1,3] thiazolo[3,2-*b*][1,2,4]triazol-7-ium triiodide (4a) This compound was obtained from **2a** via iodination; yield 82% (brown crystals); ¹H NMR: δ 8.34 (s, 1H), 7.45–7.68 (m, 10H), 5.00 (s, 2H); ¹³C NMR: δ 161.9, 157.4, 133.0, 132.8, 132.4, 131.8, 131.4, 129.7, 129.4, 126.5, 123.1, 80.4, 35.6. A triiodide **4a**: mp 147–149°C. Anal. Calcd for $C_{17}H_{13}I_4N_3$ S: C, 25.56; H, 1.64; N, 5.26; S, 4.01. Found: C, 25.27; H, 1.59; N, 5.11; S, 3.91.

(5*E***)-2-(4-bromophenyl)-6-(iodomethylidene)-3-phenyl-5,6-dihydro-3***H***-[1,3]thiazolo[3,2-***b***][1,2,4]triazol-7-ium triiodide (4b)** This compound was obtained from **2b** via iodination; yield 77% (brown crystals); mp 182–184°C; ¹H NMR: δ 8.32 (s, 1H), 7.32–7.76 (m, 9H), 5.01 (s, 2H). ¹³C NMR : δ 162.0, 156.7, 136.0, 132.9, 132.7, 131.6, 131.2, 127.4, 127.1, 126.8, 121.7, 80.7, 35.6. Anal. Calcd for $C_{17}H_{12}BrI_4N_3S$: C, 23.26; H, 1.38; N, 4.79; S, 3.65. Found: C, 23.09; H, 1.32; N, 4.72; S, 3.58.

(5*E*)-2-benzyl-6-(iodomethylidene)-3-phenyl-5,6-dihydro-3*H*-[1,3]thiazolo[3,2-*b*][1,2,4]-triazol-7-ium triiodide (4c) This compound was obtained from 2c via iodination; yield 62% (brown crystals); mp 197–199°C; ¹H NMR: δ 8.34 (s, 1H), 770–7.68 (m, 10H), 4.94 (s, 2H), 4.22 (s, 2H). Anal. Calcd for $C_{18}H_{15}I_4N_3$ S: C, 26.59; H, 1.86; N, 5.17; S, 3.94. Found: C, 26.43; H, 1.78; N, 5.08; S, 3.83.

(5*E***)-6-(iodomethylidene)-2,3-diphenyl-5,6-dihydro-3***H***-[1,3] thiazolo[3,2-***b***][1,2,4]triazol-7-ium bromide (5a)** This compound was obtained from **2a** via iodo-bromination; yield 84% (pale-yellow crystals); mp 152–153°C; ¹H NMR: δ 8.33 (s, 1H), 7.41–7.67 (m, 10H), 5.01 (s, 2H). ¹³C NMR: δ 161.7, 157.3, 133.0, 132.9, 132.3, 131.8, 131.3, 129.7, 129.3, 126.2, 123.2, 80.4, 35.6. Anal. Calcd for C₁₇H₁₃BrIN₃S: C, 40.99; H, 2.63; N, 8.43; S, 6.44. Found: C, 41.12; H, 2.58; N, 8.35; S, 6.61.

(5*E*)-2-(4-bromophenyl)-6-(iodomethylidene)-3-phenyl-5,6dihydro-3*H*-[1,3]thiazolo[3,2-*b*][1,2,4]triazol-7-ium bromide (5b) This compound was obtained from 2b via iodo-bromination; yield 63% (pale-yellow crystals); mp 185–187°C; ¹H NMR: δ 8.33 (s, 1H), 7.32–7.76 (m, 9H), 5.00 (s, 2H). Anal. Calcd for $C_{_{17}}H_{12}Br_2IN_3S$: C, 35.38; H, 2.10; N, 7.28; S, 5.56. Found: C, 35.43; H, 2.12; N, 7.15; S, 5.60.

(5*E*)-2-(4-bromophenyl)-3-phenyl-6-[(trichloro-λ⁴-telluranyl) methyl]-5,6-dihydro-3*H*-[1,3]thiazolo[3,2-*b*][1,2,4]triazol-7-ium chloride (6a) This compound was obtained from 2b and tellurium tetrachloride; yield 61% (white powder); mp 188–189°C; ¹H NMR: δ 8.32 (s, 1H), 7.59 (m, 5H), 7.44 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.91 (s, 2H) ¹³C NMR: 154.1, 151.6, 133.6, 132.2, 130.9, 130.6, 128.2, 128.1, 128.0, 125.5, 124.4, 79.7, 21.4. Anal. Calcd for C₁₇H₁₂Br-Cl₄N₃STe: C, 31.92; H, 1.89; N, 6.57; S, 5.01. Found: C, 32.03; H, 1.83; N, 5.64; S, 5.12.

(5*E*)-2-benzyl-3-phenyl-6-[(trichloro- λ^4 -telluranyl)methyl]-5,6-dihydro-3*H*-[1,3]thiazolo-[3,2-*b*][1,2,4]triazol-7-ium chloride (6b) This compound was obtained from 2c and tellurium tetrachloride; yield 58% (white powder); mp 182–183°C; ¹H NMR: δ 8.30 (bs, 1H+H₂O), 6.98–7.60 (m, 10H), 4.88 (s, 2H), 4.12 (s, 2H). Anal. Calcd for C₁₈H₁₅Cl₄N₃STe: C, 37.61; H, 2.63; N, 7.31; S, 5.58. Found: C, 37.54; H, 2.68; N, 7.25; S, 5.63.

(5*E*)-2-(4-bromophenyl)-3-phenyl-6-[(tribromo- λ^4 -telluranyl) methyl]-5,6-dihydro-3*H*-[1,3]thiazolo[3,2-*b*][1,2,4]triazol-7-ium bromide (6c) This compound was obtained from 2b and tellurium tetrabromide; yield 48% (yellow powder); mp 179–181°C; ¹H NMR: δ 8.32 (s, 1H), 7.58 (m, 5H), 7.44 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.03 (s, 2H); ¹³C NMR: 154.1, 151.6, 133.7, 132.2, 130.9, 130.6, 130.5, 128.1, 125.6, 124.4, 79.7, 21.4. Anal. Calcd for C₁₇H₁₂Br₅N₃STe: C, 24.98; H, 1.48; N, 5.14; S, 3.92. Found: C, 25.11; H, 1.51; N, 5.05; S, 4.01.

(5*E*)-2-benzyl-3-phenyl-6-[(tribromo-λ⁴-telluranyl)methyl]-5,6-dihydro-3*H*-[1,3]thiazolo-[3,2-*b*][1,2,4]triazol-7-ium bromide (6d) This compound was obtained from 2c and tellurium tetrabromide; yield 46% (yellow powder); mp 186–188°C; ¹H NMR: δ 8.31 (s, 1H), 6.97–7.67 (m, 10H), 5.02 (s, 2H), 4.08 (s, 2H). Anal. Calcd for $C_{18}H_{15}Br_4N_3STe: C, 28.73; H, 2.01; N, 5.58; S, 4.26.$ Found: C, 28.82; H, 2.04; N, 5.49; S, 4.31.

X-ray diffraction analysis of 3a

Single crystals of $C_{17}H_{13}N_3SBr_4$ **3a** were crystallized from ethanol. The single crystal was placed in an inert oil and then transferred to the diffractometer under a cold stream of an inert gas. The structure of salt **3a** was performed on an automatic diffractometer Oxford Diffraction Xcalibur at room temperature [293(2) K], interpreted by a direct method and refined by the full-matrix least-squares technique in an anisotropic approximation for non-hydrogen atoms using the SHELX-97 program package [29]. The program WinGX [30] was used to analyze the structure and production of the illustrations. All C-H hydrogen atoms were placed in calculated positions and refined as a riding model. For all distance bonds and valence angles of expected values in cation of tribromide **3a** were found.

Crystal structure determination of **3a**: $C_{12}H_{13}N_3SBr_4$, M=611.00, monoclinic, a=12.1614(12) Å, b=7.2386(4) Å, c=24.0202(17) Å, β =102.896(8)°, U=2061.2(3) Å³, T=293.0, space group $P2\overline{1}n$ (no. 14), Z=4, μ (Mo K α)=7.917, 7981 reflections measured, 4369 unique (Rint=0.0621) which were used in all calculations. The final wR(F2) was 0.2376 (all data).

Acknowledgments: The authors thank the International Centre for Diffraction Data for financial support (Grant #03-02).

References

- Küçükgüzel, Ş. G.; Çıkla-Süzgün, P. Recent advances bioactive 1,2,4-triazole-3-thiones. *Eur. J. Med. Chem.* 2015, *97*, 830–870.
- [2] Godoi, B.; Schumacher, R. F.; Zeni, G. Synthesis of heterocycles via electrophilic cyclization of alkynes containing heteroatom. *Chem. Rev.* 2011, 111, 2937–2980.
- [3] Rodriguez, F.; Fananas, F. J. In *Handbook of Cyclization Reactions*. Ma, S., Ed. Wiley-VCH: New York, 2010; Vol. 4, pp. 951–990.
- [4] Nesterenko, A. M.; Vas'kevich, R. I.; Zborovskii, Yu. L.; Staninets,
 V. I. Reactions of 3-allyl-4-oxothieno[2,3-d]pyrimidin-2-yl
 disulfides with iodine. *Russ. Chem. Bull.* 2005, *54*, 2582–2585.
- [5] Vas'kevich, R. I.; Khripak, S. M.; Staninets, V. I.; Zborovskii, Yu. L.; Chernega, A. N. Synthesis of fused thiazolothienopyrimidine derivatives. *Russ. J. Org. Chem.* 2000, *36*, 1091–1096.
- [6] Vas'kevich, R. I.; Khripak, S. M.; Zborovskii, Yu. L.; Staninets, V. I.; Nesterenko, A. M.; Pyrozhenko V. V. Synthesis of thiazinothienopyrimidine derivatives and their rearrangement into thiazolothienopyrimidines. *Ukr. Khim. Zh.* 2000, *66*, 47–52.
- [7] Khripak, S. M.; Plesha, M. V.; Slivka, M. V.; Yakubets, V. I.;
 Krivovyaz, A. A. Syntesis and reactivity of 1-bromomethyl-5-oxo-4-phenyl-1,2,4,5,6,7,8,9-octahydrobenzo[4,5]thieno[3,2-e][1,3] oxazolo[3,2-a]-pyrimidin-11-ium bromides. *Russ. J. Org. Chem.* 2004, 40, 1705–1706.
- [8] Wippich, P.; Gutschow, M.; Leistner, S. Regioselective preparation of 1-(bromomethyl)-5H-thiazolo[3,2-a]quinazolin-5-ones and analogous 5H-thieno[3,2-e]thiazolo[3,2-a]-pyrimidin-5-ones from fused 2-(alkenylthio)pyrimidin-4-ones. *Synthesis*. 2000, *5*, 714–720.
- [9] Svaljavyn, O. V.; Onysko, M. Yu.; Turov, A. V.; Vlasenko, Yu. G.; Lendel V. G. Peculiar electrophilic heterocyclization of 5-allyl-6-thioxopyrazolo[3,4-d]pyrimidin-4-one. *Chem. Heterocycl. Compd.* 2013, 49, 491–495.

- [10] Slivka, M. V.; Krivovjaz, A. A.; Slivka, M. V.; Lendel, V. G. Stereoselective synthesis of (E)-halogenmethylidene[1,3] thiazolo[3,2-a]-thieno[3,2-e]-pyrimidinium and analogous [1,3] oxazolo[3,2-a]thieno[3,2-e]pyrimidinium halogenides from 3-N-substituted 2-propargylthio(oxy)thieno-[2,3-d]pyrimidin-4-ones. *Heterocycl. Commun.* 2013, 19, 189–193.
- Kut, M. M.; Onysko, M. Yu.; Lendel, V. G. Heterocyclization of 5,6-disubstituted 3-alkenyl-2-thioxothieno[2,3-d]pyrimidin-4-one with *p*-alkoxyphenyltellurium trichloride. *Heterocycl. Commun.* 2016, *22*, 347–350.
- [12] Onysko, M. Yu.; Lendel, V. G. Haloheterocyclization of 2-methallyl(propargyl)-thioquinoline-3-carbaldehydes. *Chem. Heterocycl. Compd.* 2009, 45, 853–855.
- [13] Onysko, M. Yu.; Filak, I. O.; Lendel, V. G. Halogenoheterocyclization of 2-(allylthio)-quinolin-3-carbaldehyde and 2-(propargylthio)-quinolin-3-carbaldehyde. *Heterocycl. Commun.* 2016, *22*, 295–299.
- [14] Ernst, S.; Jelonek, S.; Sieler, J.; Schulze, K. 4-Methallyl substituted 1,2,4-triazoline-3-thiones as a source of N-bridgehead heterocycles. *Tetrahedron* 1996, *52*, 791–798.
- [15] Fizer, M. M.; Slivka, M. V.; Rusanov, E.; Turov, A.; Lendel, V. G.
 [1,3]Thiazolo[2',3':3,4][1,2,4]triazolo[1,5-*a*]pyrimidines a new heterocyclic system accessed via bromocyclization. *J. Heterocyc. Chem.* 2015, *52*, 949–952.
- [16] Khripak, S.; Slivka, M.; Vilkov, R.; Usenko, R.; Lendel, V. Regioselectivity of the monohalogenation of 4-allyl-3-allylamino-1,2,4triazole-5-thione. *Chem. Heterocycl. Comp.* 2007, 43, 781–785.
- [17] Slivka, M.; Khripak, S.; Britsun, V.; Staninets, V. Stereose-lective synthesis of (*E*)-halomethylidene[1,3]thiazolo[3,2-*a*] thieno[3,2-*e*]pyrimidinium and analogous [1,3]oxazolo[3,2-*a*] thieno[3,2-*e*]pyrimidinium halides starting from 3-*N*-substituted 2-propargylthio(oxy)thieno[2,3-*d*]pyrimidin-4-ones. *Russ. J. Org. Chem.* 2000, *36*, 1033–1038.
- [18] Usenko, R. M.; Slivka, M. V.; Lendel, V. G. Electrophilic heterocyclization of 4,5-disubstituted 3-allylthio-4H-1,2,4-triazoles by the action of halogens. *Chem. Heterocycl. Comp.* 2011, 47, 1029–1036.
- [19] Slivka, M. V.; Korol, N. I.; Rusin I. F.; Lendel, V. G. Synthesis of
 [1,3]thiazolo[3,2-b][1,2,4]triazol-7-ium and [1,2,4]triazolo[5,1-b]
 [1,3]thiazin-4-ium salts via regioselective electrophilic cyclization of 3-[(2-alken-1-yl)sulfanyl]-4H-1,2,4-triazoles. *Heterocycl. Commun.* 2016, *21*, 397–401.

- [20] Kochikyan, T. V.; Samvelyan, M. A.; Petrosyan, A. M.; Langer P. D. Synthesis and properties of thiazolo[2,3-*c*][1,2,4]triazoles. *Russ. J. Org. Chem.* 2015, *51*, 1469–1473.
- [21] Fizer, M. M.; Slivka, M. V.; Lendel V. G. New method of synthesis of 3,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-2(1*H*)-thione. *Chem. Heterocycl. Comp.* **2013**, *49*, 1243–1245.
- [22] Fizer, M. M.; Slivka, M. V. Synthesis of [1,2,4]triazolo[1,5-a] pyrimidine (microreview). *Chem. Heterocycl. Comp.* 2016, *52*, 155–157.
- [23] Fizer, M. M.; Sukharev, S. M.; Slivka, M. V.; Mariychuk, R. I.; Lendel, V. G. Preparation of bisthiourea and 5-amino-4-benzoyl-1,2,4-triazol-3-thione complexes of copper (II), nickel and zinc and its biological evolution. *J. Organomet. Chem.* 2016, 804, 6–12.
- [24] Orysyk, V. V.; Zborovskii, Yu. L.; Staninets, V. I.; Dobosh, A.
 A.; Khripak, S. M. Synthesis of thiazino- and thiazoloquinazolinones by cyclization of *S*-(2-propenyl) derivatives of 2-thioxo-2,3-dihydro-4(1*H*)-quinazolinone. *Chem. Heterocycl. Comp.* 2003, *39*, 740–744.
- [25] Zborovskii, Yu. L.; Orysyk, V. V.; Dobosh, A. A.; Pirozhenko, V. V.; Chernega, A. N. Heterocyclization reactions of 2-(2-propynylthio)-4(1*H*)-quinazolinone derivatives when treated with electrophilic and nucleophilic reagents. *Chem. Heterocycl. Comp.* 2003, *39*, 1099–1106.
- [26] Lendel, V. G.; Krivovjaz, A. A.; Zborovskii, Yu. L.; Staninets, V. I.; Turov, O. V. Interaction of 2-allyl-(2-propargyl)-mercapto-5R-1,3,4-oxadiazoles with phenylselenium trihalogenides. Ukr. Khim. Zh. 2002, 68, 47–52.
- [27] Vas'kevich, R. I.; Dyachenko, I. V.; Vas'kevich, A. I.; Rusanov, E. B.; Vovk, M. V. Fused pyrimidine systems: XV. Intramolecular electrophilic cyclization of 2-allyl(propargyl, cinnamyl)aminopyrido[2,3-*d*]pyrimidin-4(3*H*)-ones. *Russ. J. Org. Chem.* 2015, *51*, 556–565.
- [28] Vas'kevich, R. I.; Bentya, A. V.; Turov, A. V.; Rusanov, E. B.; Staninets, V. I.; Vovk, M. V. Iodocyclization of 6-allylamino-4,5-dihydropyrazolo[3,4-d]pyrimidines. *Russ. J. Org. Chem.* 2012, 48, 713–720.
- [29] Sheldrick, G. M. A short history of SHELX. Acta Crystallogr. 2008, 64A, 112–122.
- [30] Farrugia, L. J. WinGX suite for small molecule single-crystal crystallography. J. Appl. Crystallogr. 1999, 32, 837–838.