DOI 10.1007/s10593-020-02854-7
Chemistry of Heterocyclic Compounds **2020**, *56*(12), 1592–1598

Novel multicomponent synthesis of 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine derivatives

Ivan V. Dyachenko[1], Vladimir D. Dyachenko[1], Pavel V. Dorovatovskii[2], Victor N. Khrustalev[3,4], Valentine G. Nenajdenko[5]*

[1] *Luhansk Taras Shevchenko National University, 2 Oboronna St., Luhansk 91011, Ukraine; e-mail: ivladya87@mail.ru*

[2] *National Research Center "Kurchatov Institute", 1 Akademika Kurchatova Sq., Moscow 123182, Russia; e-mail: paulgemini@mail.ru*

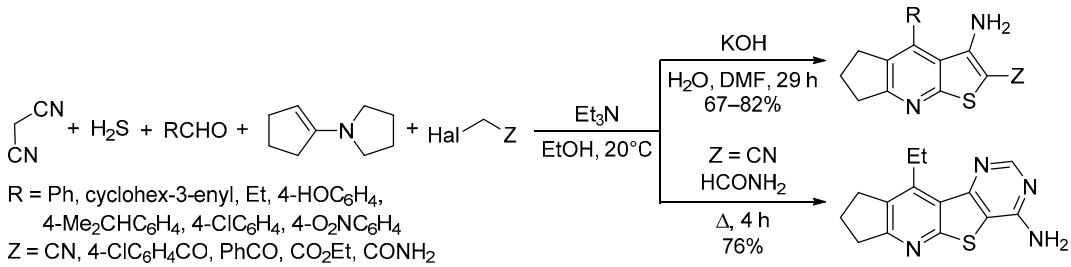
[3] *RUDN University, 6 Miklukho-Maklaya St., Moscow 117198, Russia; e-mail: khrustalev-vn@rudn.ru*

[4] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., Moscow 119991, Russia; e-mail: vnkhrustalev@gmail.com*

[5] *Lomonosov Moscow State University, 1, Build. 3 Leninskie Gory, Moscow 119991, Russia; e-mail: nenajdenko@gmail.com*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2020, *56*(12), 1592–1598

Submitted June 13, 2020
Accepted after revision November 19, 2020



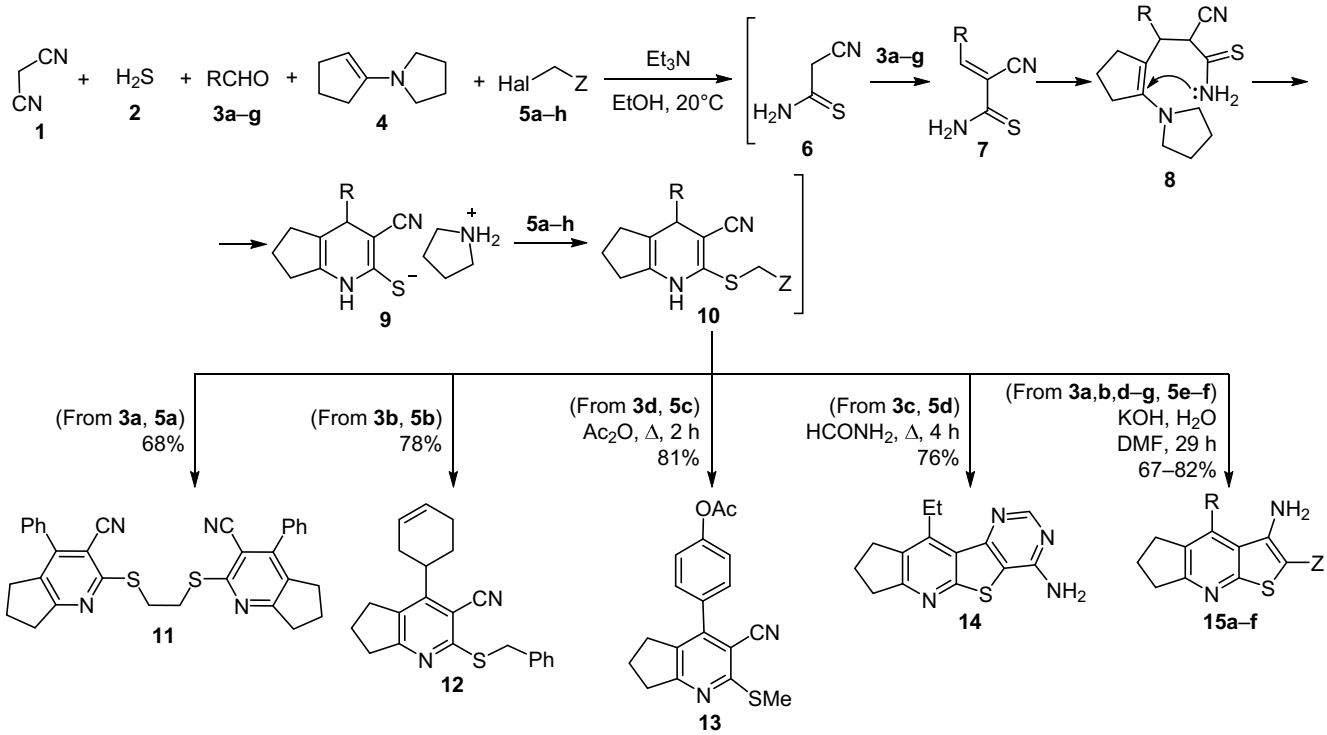
The multicomponent condensation of malononitrile, hydrogen sulfide, aldehydes, 1-(cyclopent-1-en-1-yl)pyrrolidine, and alkylating agents leads to the formation of 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine derivatives. The structure of a number of heterocycles obtained on their basis was studied by X-ray structural analysis.

Keywords: aldehydes, alkylating agents, 1-(cyclopent-1-en-1-yl)pyrrolidine, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridines, hydrogen sulfide, malononitrile, multicomponent synthesis, X-ray structural analysis.

Cyclopenta[*b*]pyridine derivatives are structural fragments of alkaloids[1] and exhibit a wide spectrum of biological activity. Thus, derivatives with hypoglycemic activity,[2] antagonists of calcium channels,[3] fluorescent probes,[4] and inhibitors of protein kinase FGFR1[5] were found among these compounds. The main methods of the synthesis of cyclopenta[*b*]pyridines principally involve annulation of the pyridine ring to substituted cyclopentanone[6] or to its enamine.[7] Synthesis of these compounds from linear molecules[8] and by intramolecular recyclization of substituted pyrimidine[9] is possible.

Considering the high practical importance of cyclopenta[*b*]pyridine derivatives, the promise of domino reactions for organic synthesis,[10] in continuation of our studies of multicomponent condensations,[11] we studied a novel version of this type of synthesis based on the reaction of malononitrile (**1**), hydrogen sulfide (**2**), aldehydes **3a**–**g**, 1-(cyclopent-1-en-1-yl)pyrrolidine (**4**), alkylating agents **5a**–**h**, and Et_3N. This reaction represents a profound structural transformation. According to chromatography data, cyanothioacetamide (**6**) is initially formed which then undergoes the Knoevenagel condensation with aldehydes **3a**–**g**. The resulting alkenes **7** are involved in the Stork alkylation with enamine **4**. The obtained adducts **8** undergo intramolecular cyclotransamination with the formation of salts **9** containing the target bicyclic cyclopenta[*b*]pyridine structure. The addition of alkylating agents **5a**–**h** to the reaction mixture leads to the production of thioesters **10**

Scheme 1



3 a R = Ph, **b** R = cyclohex-3-enyl, **c** R = Et, **d** R = 4-HOC_6H_4, **e** R = 4-$Me_2CHC_6H_4$, **f** R = 4-ClC_6H_4, **g** R = 4-$O_2NC_6H_4$
5 a Hal = Br, Z = CH_2Br; **b** Hal = Cl, Z = Ph; **c** Hal = I, Z = H; **d** Hal = Cl, Z = CN; **e** Hal = Br, Z = 4-ClC_6H_4CO; **f** Hal = Br, Z = PhCO;
g Hal = Cl, Z = CO_2Et; **h** Hal =Cl, Z = $CONH_2$
15 a R = 4-$Me_2CHC_6H_4$, Z = 4-ClC_6H_4CO; **b** R = 4-ClC_6H_4, Z = PhCO; **c** R = 4-HOC_6H_4, Z = 4-ClC_6H_4CO;
d R = cyclohex-3-enyl, Z = CO_2Et; **e** R = Ph, Z = $CONH_2$; **f** R = 4-$O_2NC_6H_4$, Z = $CONH_2$

(Scheme 1), which, by aromatization of the dihydropyridine ring, apparently with atmospheric oxygen, are converted into various end products, as shown below.

The use of 1,2-dibromoethane (**5a**) as an alkylating agent makes it possible to synthesize 2,2'-[ethane-1,2-diylbis(sulfanediyl)]bis(4-phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carbonitrile) (**11**), whereas the use of benzyl chloride (**5b**) leads to the formation of 2-benzylsulfanyl-4-(cyclohex-3-en-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carbonitrile (**12**).

When *p*-hydroxybenzaldehyde (**3d**) and MeI (**5c**) are introduced into this multicomponent reaction and its product is heated under reflux in Ac_2O, esterification of the hydroxy group of the phenol substituent occurs with the formation of 4-(3-cyano-2-methylsulfanyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-4-yl)phenyl acetate (**13**).

The use of chloroacetonitrile (**5d**) as an alkylating agent and heating of the reaction product under reflux in formamide results in the formation of the tetracyclic system 10-ethyl-8,9-dihydro-7*H*-cyclopenta[5',6']pyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidin-4-amine (**14**).

Substituted 3-amino-6,7-dihydro-5*H*-cyclopenta[*b*]thieno-[3,2-*e*]pyridines **15a**–**f** are easily formed when active methylene halogen derivatives **5e**–**f** are used as alkylating agents. The closure of the thiophene ring is catalyzed by an aqueous KOH in DMF.

The spectral data confirm the structure of the synthesized compounds **11**–**14**, **15a**–**f**. IR spectra contain characteristic absorption bands of the stretching vibrations of the conjugated cyano group, amino and carbonyl moieties.

The ^{1}H NMR spectra exhibit signals of the protons of the trimethylene moiety, aromatic substituents, amino group, and alkylsulfanyl group with the characteristic splitting patterns and chemical shifts. ^{13}C NMR spectra contain signals of all carbon atoms with the typical chemical shift values.

Of note is the doubling of some signals in the ^{1}H and ^{13}C NMR spectra of compound **14** which can apparently be explained by tautomerism of the aminopyrimidine fragment.

To elucidate the mechanism of the considered multicomponent reaction and unambiguously establish the structure of its products, compounds **11**, **12**, and **15a**,**b** were studied by X-ray structural analysis (Figs. 1–4)

Compound **11** exists as a dimer in which two 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine fragments are joined *via* an ethylene disulfide bridge and which has its own inversion center. A solvate 1,4-dioxane molecule was revealed in the solid state occupying a particular position in the inversion center. The central 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine fragments in compounds **11** and **12** have a characteristic structure with a cyclopentene ring in the envelope conformation.[4] The phenyl substituent in compound **11** is rotated relative to the basal plane of the central bicyclic fragment (standard deviation is 0.018 Å) by 52.58(6)°. The ethylene disulfide bridge conformation is

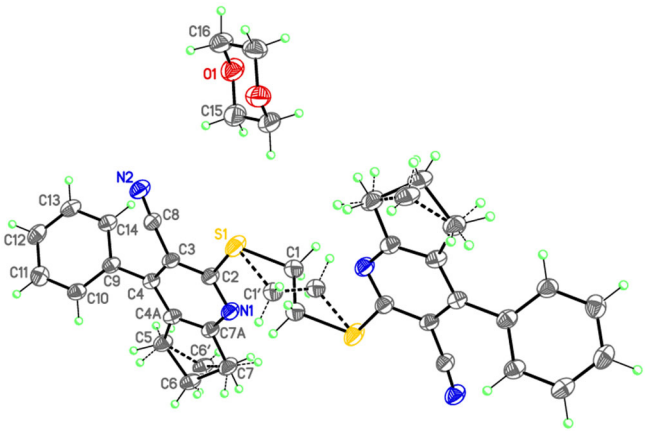


Figure 1. Molecular structure of compound **11**·$C_4H_8O_2$ with atoms represented as thermal vibration ellipsoids of 50% probability. Dashed lines show alternative positions of disordered fragments.

g-t-g (t – *trans*, 180°; g – *gauche*, ± 60°), which is described by the three torsion angles C(2)–S(1)–C(1)–C(1A), S(1)–C(1)–C(1A)–S(1A), and C(1)–C(1A)–S(1A)–C(2A), respectively.[4] The cyclohexene ring in compound **12** has the half-chair conformation with a carbon atom C(15) out of the plane drawn through the rest of the ring atoms (the standard deviation is 0.016 Å) by 0.432(8)Å. The angle between the basal planes of the cyclohexene ring and the central bicyclic fragment in compound **12** is 87.15(16)°.[2] The benzylsulfide substituent is *trans*-arranged with respect to the central bicyclic fragment, and the angle between the plane of the benzyl substituent and the basal plane of the central bicyclic structure is 60.96(8)°. In the solid state, the molecules of compounds **11** and **12** are stacked along the crystallographic *a* axis and are located at the distances of the van der Waals radii.

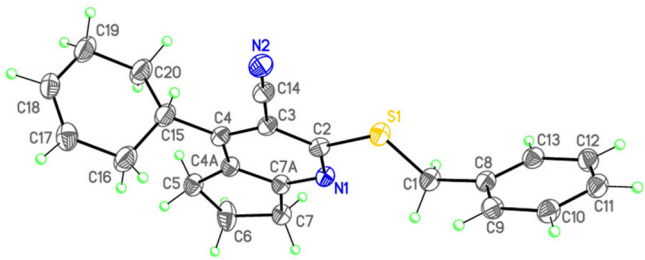


Figure. 2. Molecular structure of compound **12** with atoms represented as thermal vibration ellipsoids with 40% probability.

Compound **15a** crystallizes with six crystallographically independent molecules in the unit cell, differing mainly in the orientation of the chlorophenyl substituent relative to the central tricyclic 6,7-dihydro-5*H*-cyclopenta[*b*]thieno-[3,2-*e*]pyridine fragment: in three molecules, the corresponding interplanar angle is 50.39(7), 50.55(7), and 50.58(7)°, while in the other three it is respectively 134.81(7), 134.78(7), and 134.71(7)°. It is important to note that the conformation of molecule **15b** corresponds to an orientation with the interplanar angle of 53.98(5)°.

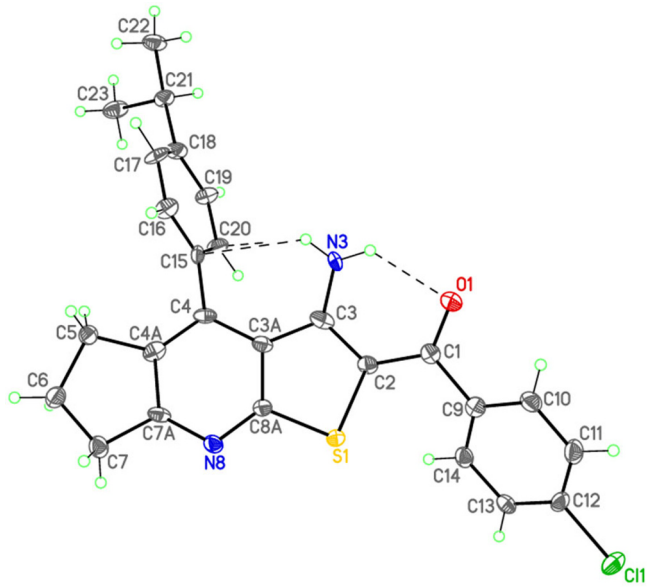


Figure 3. Molecular structure of compound **15a** with atoms represented as thermal vibration ellipsoids of 50% probability (one of six crystallographically independent molecules is presented). Dotted lines depict intramolecular hydrogen bonds N–H···O and N–H···π.

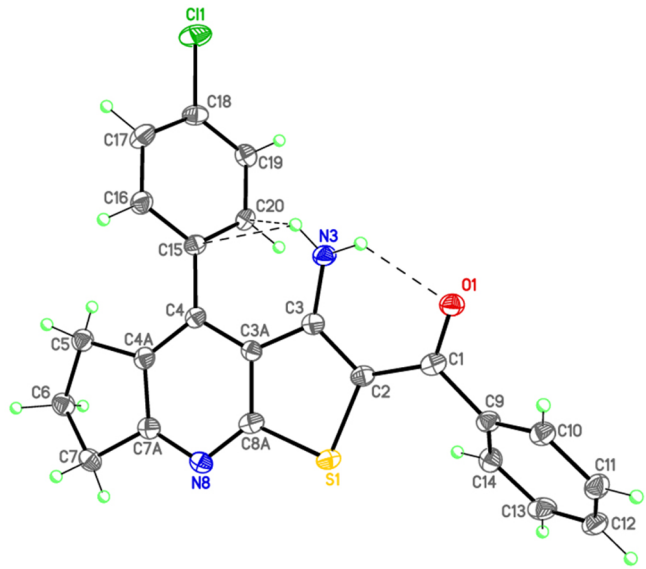


Figure 4. Molecular structure of compound **15b** with atoms represented as thermal vibration ellipsoids of 50% probability (one of six crystallographically independent molecules is presented). Dotted lines depict intramolecular hydrogen bonds N–H···O and N–H···π(C=C).

The structure of molecules **15a**,**b** is largely determined by the presence of quite strong intramolecular hydrogen bonds N–H···O and N–H···π(C=C) (Table 1). As a result, the amino and carbonyl groups in both compounds are practically coplanar to the thieno[3,2-*e*]pyridine fragment.

The cyclopentene rings in compounds **15a**,**b** assume the typical envelope conformations, and 4-phenyl substituents are rotated relative to the basal plane of the central tricyclic fragment (the standard deviations are 0.025, 0.024, 0.045, 0.025, 0.045, and 0.044 Å for six crystallographically

Table 1. Hydrogen bonds and their characteristics (bond lengths and angles) in structures **15a**,**b**

D–H···A	*d*(D–H), Å	*d*(H···A), Å	*d*(D···A), Å	DHA angle, °
Compound **15a**				
N(3)–H(3B) ··O(1)	0.82(3)	2.15(3)	2.744(3)	129(2)
N(3)–H(3B) ··O(1)*	0.82(3)	2.28(3)	2.951(3)	140(2)
N(26)–H(26B)···O(2)	0.87(3)	2.13(3)	2.746(3)	127(2)
N(26)–H(26B) ··O(4)**	0.87(3)	2.23(3)	2.948(3)	140(2)
N(49)–H(49B) ··O(3)	0.93(3)	2.09(2)	2.718(3)	124(2)
N(49)–H(49B) ··O(3)***	0.93(3)	2.21(3)	3.063(3)	152(2)
N(72)–H(72B) ··O(2)*[4]	0.78(3)	2.30(3)	2.963(3)	143(3)
N(72)–H(72B) ··O(4)	0.78(3)	2.25(3)	2.760(3)	124(3)
N(95)–H(95B) ··O(5)	0.86(3)	2.09(3)	2.723(3)	130(2)
N(95)–H(95B) ··O(6)	0.86(3)	2.30(3)	3.060(3)	147(2)
N(118)–H(11H) ··O(5)	0.85(3)	2.26(3)	3.055(3)	154(2)
N(118)–H(11H) ··O(6)	0.85(3)	2.15(3)	2.721(3)	124(2)
Compound **15b**				
N(3)–H(3B) ··O(1)	0.87(2)	2.12(2)	2.753(2)	130(2)
N(3)–H(3B) ··O(1)*[5]	0.87(2)	2.36(2)	2.897(2)	121(2)

* Symmetry operations: $-x + 1, -y + 1, -z$.
** Symmetry operations: $x + 1, y + 1, z$.
*** Symmetry operations: $-x, -y, -z$.
*[4] Symmetry operations: $x - 1, y - 1, z$.
*[5] Symmetry operations: $-x + 1, -y + 1, -z + 1$.

independent **15a** molecules, respectively) at angles of 66.47(7), 66.55(7), 66.89(6), 66.54(7), 67.11(7), and 67.30(7)° (for six crystallographically independent molecules **15a**, respectively), and 56.30(6)° (for molecule **15b**).

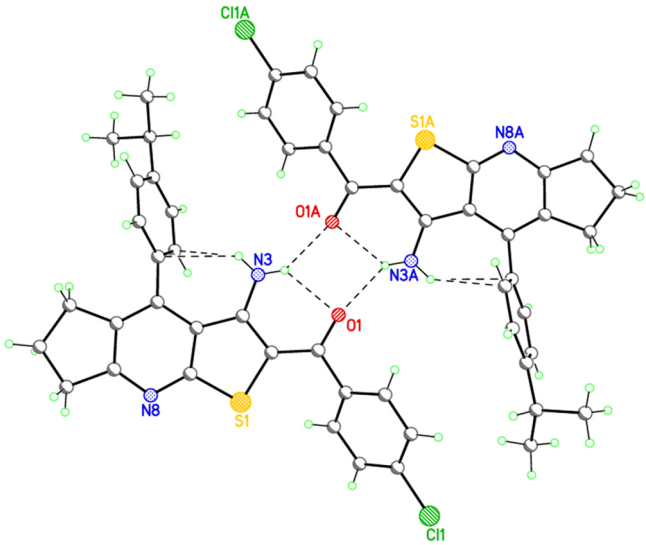


Figure 5. Centrosymmetric dimers of compound **15a** (one of six crystallographically independent dimers is presented). Dotted lines depict intra- and intermolecular hydrogen bonds.

In the solid state, the molecules of compounds **15a**,**b** form centrosymmetric dimers due to intermolecular hydrogen bonds N–H···O (Table 1, Figs. 5 and 6). Dimers are packed in stacks along the crystallographic axis *a* (in the case of compound **15a**) and *b* (in the case of compound **15b**) and are located at the distances of the van der Waals radii.

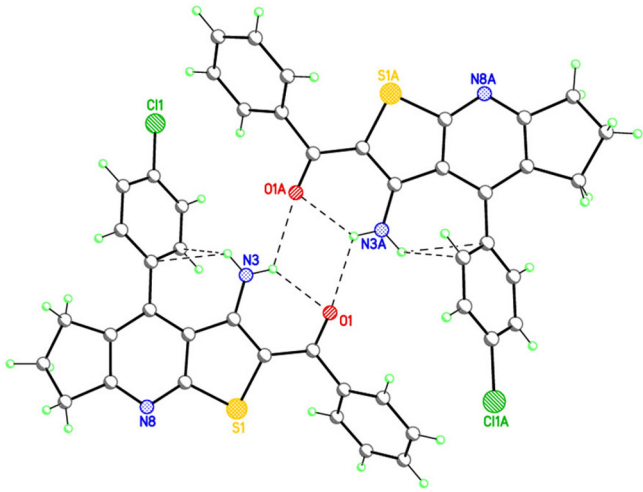


Figure 6. Centrosymmetric dimers of compound **15b**. Dotted lines depict intra- and intermolecular hydrogen bonds.

To conclude, the multicomponent reaction of malononitrile, hydrogen sulfide, aldehydes, 1-(cyclopent-1-en-1-yl)pyrrolidine, alkylating agents, and triethylamine leads to the formation of new derivatives of 2-alkylsulfanyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carbonitriles, 3-amino-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridines and the heterocyclic system 10-ethyl-8,9-dihydro-7*H*-cyclopenta[5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4-amine.

Experimental

IR spectra were registered on a IKS-40 spectrometer in petroleum jelly. ^{1}H and ^{13}C NMR spectra were acquired on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 ($CDCl_3$ for ^{1}H NMR spectrum of compound **15f**), with TMS as internal standard. High-resolution mass spectra were recorded on an Orbitrap Elite mass spectrometer. Samples for mass spectrometry were dissolved in DMSO (1 ml), diluted 100 times with 1% HCOOH in MeCN, injected with a syringe pump at a rate of 40 μl/min into the electrospray ionization source. The source gas flows were turned off, the voltage across the needle was 3.5 kV, and the capillary temperature was 275°C. Mass spectra were recorded in the positive and negative ion modes in an orbital trap with a resolution of 480,000. Internal calibrant was 2DMSO+H$^+$ ion (*m*/*z* 157.03515). The mass spectrum of compound **15e** was registered on an Agilent 1100 mass spectrometer with an Agilent LS/MSDLS selective detector (the sample was injected in an AcOH matrix, EI ionization, 70 eV). Melting points were determined on a Kofler bench. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silufol UV-254 plates, eluent hexane–Me_2CO, 5:3, visualization by iodine vapor and UV light.

2,2'-[Ethane-1,2-diylbis(sulfanediyl)]bis(4-phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carbonitrile (11). A moderate stream of H_2S (**2**) was bubbled through a solution of malononitrile (**1**) (0.7 g, 10 mmol) and Et_3N (3 drops) in EtOH (50 ml) at 20°C for 1 h until crystallization of cyanothioacetamide **6** started. At this point, bubbling was stopped, and benzaldehyde (**3a**) (1 ml,

10 mmol) was added to the mixture. The mixture was stirred for 30 min until crystallization of benzylidenecyanothioacetamide **7**, and enamine **4** (1.4 g, 10 mmol) was added. The mixture was stirred for 20 min and kept for 24 h. 1,2-Dibromoethane (**5a**) (0.45 ml, 5 mmol) was added to the mixture with stirring. After stirring for 2 h, the mixture was kept for 24 h. The mixture was then diluted with H_2O (50 ml), the formed precipitate was filtered off and washed with H_2O (20 ml), EtOH (10 ml), and hexane (10 ml). Yield 1.8 g (68%), colorless crystals (fluoresce under UV light), mp 223–225°C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 2218 (C≡N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.86–2.15 (4H, m, $2CH_2$); 2.75 (4H, t, *J* = 7.5, $2CH_2$); 3.00 (4H, t, *J* = 7.7, $2CH_2$); 3.67 (4H, s, $2SCH_2$); 7.38–7.54 (10H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 22.6 (2C); 29.8 (2C); 30.3 (2C); 35.3 (2C); 103.7 (2C); 116.1 (2C); 128.7 (2C); 129.1 (4C); 129.9 (4C); 132.2 (2C); 135.1 (2C); 149.7 (2C); 160.8 (2C); 170.1 (2C). Found, *m*/*z*: 531.1674 $[M+H]^+$. $C_{32}H_{27}N_4S_2$. Calculated, *m*/*z*: 531.1672.

2-Benzylsulfanyl-4-(cyclohex-3-en-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carbonitrile (12) was prepared similarly from cyclohex-3-ene-1-carbaldehyde (**3b**) (1.2 ml, 10 mmol) and benzyl chloride (**5b**) (1.2 ml, 10 mmol). Yield 2.7 g (78%), yellow crystals, mp 107–109°C (MeOH) (mp 111–113°C[7b]). ^1H NMR spectrum matches the published spectrum.[7b] ^{13}C NMR spectrum, δ, ppm: 22.4; 25.6; 25.8; 29.2; 29.7; 33.9; 34.8; 39.3; 102.8; 116.3; 126.1; 127.4; 127.6; 128.8 (2C); 129.6 (2C); 131.8; 138.0; 154.9; 161.1; 170.2. Found, *m*/*z*: 347.1579 $[M+H]^+$. $C_{22}H_{23}N_2S$. Calculated, *m*/*z*: 347.1577.

4-(3-Cyano-2-methylsulfanyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-4-yl)phenyl acetate (13) was prepared similarly from *p*-hydroxybenzaldehyde (**3d**) (1.2 g, 10 mmol) and MeI (**5c**) (0.62 ml, 10 mmol). Then, the precipitate was filtered off and heated under reflux in Ac_2O (20 ml) for 2 h. After cooling, the cotton-like colorless precipitate was washed with Et_2O (10 ml) to obtain chromatographically pure product. Yield 2.6 g (81%), mp 177–179°C. IR spectrum, ν, cm^{-1}: 2219 (C≡N), 1712 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.82–2.17 (2H, m, CH_2); 2.28 (3H, s, SCH_3); 2.58 (3H, s, CH_3); 2.75 (2H, t, *J* = 7.6, CH_2); 3.02 (2H, t, *J* = 7.6, CH_2); 7.29 (2H, d, *J* = 7.4, H Ar); 7.54 (2H, d, *J* = 7.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.5; 21.3; 22.7; 29.8; 35.3; 103.1; 116.4; 122.6 (2C); 130.3 (2C); 131.7; 132.4; 148.6; 151.7; 162.1; 169.4; 170.2. Found, *m*/*z*: 325.1012 $[M+H]^+$. $C_{18}H_{17}N_2O_2S$. Calculated, *m*/*z*: 325.1005.

10-Ethyl-8,9-dihydro-7*H*-cyclopenta[5',6']pyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidin-4-amine (14) was prepared similarly from propionaldehyde (**3c**) (0.73 ml, 10 mmol) and chloroacetonitrile (**5d**) (0.73 ml, 10 mmol). The resulting precipitate was filtered off and heated under reflux in formamide (20 ml) for 4 h. After cooling, the yellow powder was filtered off, washed with Et_2O (10 ml) to obtain chromatographically pure product. Yield 2.1 g (76%), mp 305–307°C. IR spectrum, ν, cm^{-1}: 3195, 3311, 3338 (NH_2), 1645 (δ NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, t, *J* = 7.3, CH_3); 2.05 (2H, t, *J* = 7.3, $C\underline{H}_2CH_3$); 2.94 (2H, t, *J* = 7.8, CH_2); 2.99 (2H, t, *J* = 7.8, CH_2); 3.26–3.37 (2H, m, CH_2); 7.42 (2H, br. s, NH_2); 8.30* and 8.47 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 18.9, 19.1*; 27.3; 27.6; 32.7; 39.1; 116.6; 126.3*; 128.0, 128.5*; 138.5, 138.8*; 152.0; 152.5*, 152.6; 157.1*; 159.8*, 160.1; 162.6; 163.5; 165.6*; 165.9*; 172.7; 172.9*. Found, *m*/*z*: 271.1021 $[M+H]^+$. $C_{14}H_{15}N_4S$. Calculated, *m*/*z*: 271.1012.

2,4-Substituted 3-amino-6,7-dihydro-5*H*-cyclopenta-[*b*]thieno[3,2-*e*]pyridines 15a–f were prepared similarly from the corresponding aldehyde **3a**,**b**,**d**–**f** (10 mmol) and the alkylating agent **5e**–**f** (10 mmol). The resulting precipitate was filtered off and dissolved in DMF (25 ml). 10% Aqueous KOH (5.6 ml, 10 mmol) was added with stirring, the stirring was continued for 5 h, and the mixture was kept for 24 h, then diluted with an equal volume of H_2O. The formed precipitate was filtered off, washed with H_2O (20 ml), followed by EtOH (20 ml), and hexane (10 ml).

[3-Amino-4-(4-isopropylphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridin-2-yl](4-chlorophenyl)methanone (15a). Yield 3.1 g (70%), yellow crystals (fluoresce under UV light), mp 147–149°C (BuOH). IR spectrum, ν, cm^{-1}: 3288–3415 (NH_2), 1705 (C=O), 1633 (δ NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (6H, d, *J* = 6.9, $2CH_3$); 1.99–2.14 (2H, m, CH_2); 2.47 (2H, t, *J* = 5.5, CH_2); 2.84–2.96 (1H, m, $C\underline{H}(CH_3)_2$); 3.04 (2H, t, *J* = 7.6, CH_2); 6.76 (2H, br. s, NH_2); 7.36 (2H, d, *J* = 8.0, H Ar); 7.45 (2H, d, *J* = 8.0, H Ar); 7.57 (2H, d, *J* = 8.7, H Ar); 7.72 (2H, d, *J* = 8.7, H Ar). Found, *m*/*z*: 447.1297 $[M+H]^+$. $C_{26}H_{24}ClN_2OS$. Calculated, *m*/*z*: 447.1292.

[3-Amino-4-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridin-2-yl](phenyl)methanone (15b). Yield 3.3 g (82%), yellow crystals (fluoresce under UV light), mp 187–189°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3290–3412 (NH_2), 1707 (C=O), 1630 (δ NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.02–2.18 (2H, m, CH_2); 2.64 (2H, t, *J* = 7.4, CH_2); 3.05 (2H, t, *J* = 7.7, CH_2); 6.70 (2H, br. s, NH_2); 7.43–7.58 (5H, m, H Ph); 7.63 (2H, d, *J* = 8.5, H Ar); 7.70 (2H, d, *J* = 6.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.0; 29.1; 34.6; 103.7; 119.5; 127.6 (2C); 128.8 (2C); 129.7 (2C); 130.5 (2C); 131.4; 133.8; 133.9; 134.5; 141.3; 142.2; 150.7; 161.4; 169.5; 189.5. Found, *m*/*z*: 405.0827 $[M+H]^+$. $C_{23}H_{18}ClN_2OS$. Calculated, *m*/*z*: 405.0823.

[3-Amino-4-(4-hydroxyphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridin-2-yl](4-chlorophenyl)methanone (15c). Yield 2.8 g (67%), yellow powder, mp 282–284°C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 3415 (OH), 3150–3395 (NH_2), 1704 (C=O), 1648 (δ NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.05 (2H, t, *J* = 7.4, CH_2); 2.68 (2H, t, *J* = 7.4, CH_2); 3.04 (2H, t, *J* = 7.6, CH_2); 6.77 (2H, br. s, NH_2); 6.95 (2H, d, *J* = 8.0, H Ar); 7.25 (2H, d, *J* = 8.0, H Ar); 7.58 (2H, d, *J* = 8.4, H Ar); 7.74 (2H, d, *J* = 8.4, H Ar); 9.95 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 23.4; 28.2; 34.9; 102.9; 117.2 (2C); 119.9; 124.6; 128.6 (2C); 129.3 (2C); 129.4 (2C); 133.8; 136.7; 139.8; 143.9; 152.1; 158.0; 161.7; 169.6; 187.2. Found, *m*/*z*: 421.0779 $[M+H]^+$. $C_{23}H_{18}ClN_2O_2S$. Calculated, *m*/*z*: 421.0772.

* The signals of the minor tautomer are marked with an asterisk.

Ethyl 3-amino-4-(cyclohex-3-en-1-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridine-2-carboxylate (15d). Yield 2.3 g (68%), yellow powder (fluoresce under UV light), mp 218–220°C (EtOH). IR spectrum, ν, cm^{-1}: 3172–3411 (NH_2), 1712 (C=O), 1649 (δ NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.1, CH_3); 1.72–1.81 (1H, m), 1.91–2.12 (4H, m), 2.19–2.23 (2H, m), 2.29–2.42 (1H, m) and 2.82–2.94 (2H, m, $5CH_2$); 3.04 (2H, t, *J* = 6.9, CH_2); 3.75–3.86 (1H, m, CH); 4.23 (2H, q, *J* = 7.1, CH_2O); 5.65–5.79 (2H, m, CH=CHCH$_2$); 6.57 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 14.8; 23.8; 25.6; 26.6; 29.7; 31.5; 33.7; 35.4; 60.6; 116.6; 121.9; 126.5; 127.5; 132.4; 149.5; 151.2; 160.2; 165.4; 169.2. Found, *m*/*z*: 343.1476 $[M+H]^+$. $C_{19}H_{23}N_2O_2S$. Calculated, *m*/*z*: 343.1475.

3-Amino-4-phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridine-2-carboxamide (15e). Yield 2.2 g (70%), yellow powder (fluoresce under UV light), mp 238–240°C (BuOH). IR spectrum, ν, cm^{-1}: 3288–3415 (NH_2), 1660 (CONH), 1628 (δ NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.95–2.16 (2H, m, CH_2); 2.63 (2H, t, *J* = 5.6, CH_2); 3.05 (2H, t, *J* = 7.1, CH_2); 5.67 (2H, br. s, NH_2); 7.02 (2H, br. s, NH_2); 7.28–7.53 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 23.1; 29.2; 34.4; 97.7; 120.7; 128.6 (2C); 129.3 (3C); 133.1; 135.6; 142.2; 146.1; 158.5; 167.0; 167.5. Mass spectrum *m*/*z* (I_{rel}, %): 310 $[M+H]^+$ (100). Found, %: C 65.92; H 4.77; N 13.49. $C_{17}H_{16}N_3OS$. Calculated, %: C 66.00; H 4.89; N 13.58.

3-Amino-4-(4-nitrophenyl)-6,7-dihydro-5*H*-cyclopenta-[*b*]thieno[3,2-*e*]pyridine-2-carboxamide (15f). Yield 2.7 g (77%), yellow powder, mp 315–317°C (AcOH). IR spectrum, ν, cm^{-1}: 3296–3433 (NH_2), 1668 (CONH), 1632 (δ NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.00–2.18 (2H, m, CH_2); 2.63 (2H, t, *J* = 5.5, CH_2); 3.05 (2H, t, *J* = 7.7, CH_2); 5.70 (2H, br. s, NH_2); 7.17 (2H, br. s, NH_2); 7.70 (2H, d, *J* = 8.6, H Ar); 8.36 (2H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.2; 29.2; 34.3; 120.3; 124.3 (2C); 132.9 (2C); 134.3; 140.1; 142.3; 146.7; 148.4; 158.5; 164.6; 166.8; 167.5. Found, *m*/*z*: 355.0860 $[M+H]^+$. $C_{17}H_{15}N_4O_3S$. Calculated, *m*/*z*: 355.0859.

X-ray structural analysis of compounds 11, 12, and 15a,**b** was performed on the BELOK synchrotron station of National Research Center "Kurchatov Institute" using a Rayonix SX165 CCD two-dimensional detector (100.0(2) K, λ 0.96990 Å, φ-scanning with a 1.0° step). Experimental data were processed using the iMOSFLM program included in the CCP4 software package.[12] The correction for X-ray absorption for the obtained data was done using the SCALA software.[13] All calculations were performed using the SHELXTL software package.[14]

Compound 11. Colorless prisms ($C_{32}H_{26}N_4S_2 \cdot C_4H_8O_2$, *M* 618.79), monoclinic, space group *C*2/c; *a* 21.983(4), *b* 13.640(3), *c* 10.860(2) Å; β 93.220(12)°; *V* 3251.2(11) $Å^3$; *Z* 4; d_{calc} 1.264 g/cm^3; *F*(000) 1304; μ 0.464 mm^{-1}. A total of 20510 reflections were collected (3365 independent reflections, R_{int} 0.059, 2θ 76.90°). The structure was solved by direct methods and refined by the least squares technique against F^2 in the full-matrix anisotropic approximation for non-hydrogen atoms. The SCH_2CH_2S fragment and cyclopentene rings are disordered over two positions with populations 0.70:0.30 and 0.75:0.25, respectively. The positions of hydrogen atoms were calculated geometrically and included in the refinement with fixed positional parameters (the rider model) and isotropic displacement parameters (U_{iso}(H) = 1.2U_{eq}(C)). The final probability factors R_1 0.054 for 2799 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.141 for all independent reflections, *S* 1.079. Maximum and minimum values of the peaks of residual electron density were 0.46 and –0.62 e/$Å^3$, respectively. The full set of X-ray structural data for compound **11**·$C_4H_8O_2$ was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2008389).

Compound 12. Yellow needles ($C_{22}H_{22}N_2S$, *M* 346.47), monoclinic, space group $P2_1/c$; *a* 10.484(2), *b* 19.995(4), *c* 9.5601(19) Å; β 112.311(15)°; *V* 1854.0(7) $Å^3$; *Z* 4; d_{calc} 1.241 g/cm^3; *F*(000) 736; μ 0.412 mm^{-1}. A total of 23906 reflections were collected (3975 independent reflections, R_{int} 0.082, 2θ 76.96°). The structure was solved by direct methods and refined by the least squares technique against F^2 in the full-matrix anisotropic approximation for non-hydrogen atoms. The positions of hydrogen atoms were calculated geometrically and included in the refinement with fixed positional parameters (the rider model) and isotropic displacement parameters (U_{iso}(H) = 1.2U_{eq}(C)). The final probability factors R_1 0.085 for 2687 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.233 for all independent reflections, *S* 1.058. Maximum and minimum values of the peaks of residual electron density were 0.66 and –0.53 e/$Å^3$, respectively. The full set of X-ray structural data for compound **12** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2008390).

Compound 15a. Yellow prisms ($C_{26}H_{23}ClN_2OS$, *M* 446.97), triclinic, space group *P*-1; *a* 16.730(3), *b* 17.270(4), *c* 24.100(5) Å; α 102.55(3), β 102.60(3), γ 90.86(3)°; *V* 6619(3) $Å^3$; *Z* 12; d_{calc} 1.346 g/cm^3; *F*(000) 2808; μ 0.675 mm^{-1}. A total of 58383 reflections were collected (22544 independent reflections, R_{int} 0.070, 2θ 76.84°). The structure was solved by direct methods and refined by the least squares technique against F^2 in the full-matrix anisotropic approximation for non-hydrogen atoms. Hydrogen atoms of amino groups are localized objectively in difference Fourier syntheses and included in the refinement with fixed positional parameters (the rider model) and isotropic displacement parameters (U_{iso}(H) = = 1.2U_{eq}(N)). The remaining hydrogen atoms, the positions of which were calculated geometrically, were included in the refinement with fixed positional parameters (the rider model) and isotropic displacement parameters (U_{iso}(H) = 1.5U_{eq}(C) for CH_3 group and U_{iso}(H) = 1.2U_{eq}(C) for the remaining groups). The final probability factors R_1 0.052 for 6381 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.152 for all independent reflections, *S* 0.890. Maximum and minimum values of the peaks of residual electron density were 0.542 and −0.54 e/$Å^3$, respectively. The full set of X-ray structural data for compound **15a** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2008391).

Compound 15b. Yellow prisms ($C_{23}H_{17}ClN_2OS$, *M* 404.90), monoclinic, space group *C*2/c; *a* 19.080(4), *b* 12.780(3), *c* 17.200(3) Å; β 112.95(3)°; *V* 3862.1(16)Å^3; *Z* 8; d_{calc} 1.393 g/cm^3; *F*(000) 1680; μ 0.755 mm^{-1}. A total of 16750 reflections were collected (3633 independent reflections, R_{int} 0.069, 2θ 76.76°). The structure was solved by direct methods and refined by the least squares technique against F^2 in the full-matrix anisotropic approximation for non-hydrogen atoms. Hydrogen atoms of the amino group are localized objectively in difference Fourier syntheses and included in the refinement with fixed positional parameters (the rider model) and isotropic displacement parameters (U_{iso}(H) = 1.2U_{eq}(N)). The remaining hydrogen atoms, the positions of which were calculated geometrically, were included in the refinement with fixed positional parameters (the rider model) and isotropic displacement parameters (U_{iso}(H) = = 1.2U_{eq}(C)). The final probability factors R_1 0.046 for 3144 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.104 for all independent reflections, *S* 1.064. Maximum and minimum values of the peaks of residual electron density were 0.30 and −0.41 e/Å^3, respectively. The full set of X-ray structural data for compound **15b** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2008392).

This study was carried out with the financial support of the Ministry of Science and Higher Education of the Russian Federation (project FSSF-2020-0017).

References

1. Ohno, S.; Katsuyama, Y.; Toyima, Y.; Izumikama, M.; Takagh, M.; Fujie, M.; Satoh, N.; Shin-Ya, K.; Ohnishi, Y. *Chem. Biochem.* **2015**, *16*, 2385.
2. Nawaz, M.; Arayne, M. S.; Sultana, N. *Med. Chem. Res.* **2013**, *22*, 3581.
3. Litden, A.; Şafak, C.; Şimşek, R.; Gündüz, M. G. *Acta Crystallogr*., *Sect. C*: *Cryst. Struct. Commun.* **2011**, *C67*, o80.
4. Chunikhin, S. S.; Ershov, O. V.; Ievlev, M. Yu.; Belikov, M. Yu.; Tafeenko, V. A. *Dyes Pygm.* **2018**, *156*, 357.
5. Starosila, S. A.; Protopopov, M. V.; Dyachenko, I. V.; Balanda, A. O.; Dyachenko, V. D.; Yarmolyuk, S. M. *Ukr. Bioorg. Acta* **2013**, *11*(2), 32.
6. (a) Ershov, O. V.; Maksimova, V. N.; Lipin, K. V.; Belikov, M. Yu.; Ievlev, M. Yu.; Tafeenko, V. A.; Nasakin, O. E. *Tetrahedron* **2015**, *71*, 7445. (b) Abdel-Rahman, A. E.; Bakhite, E. A.; Mohamed, O. S.; Thabet, E. A. *Phosphorus*, *Sulfur Silicon Relat. Elem.* **2000**, *166*, 149. (c) Gürdere, M. B.; Yilmaz, B.; Budak, Y. *Synth. Commun.* **2014**, *44*, 981.
7. (a) Dyachenko, V. D.; Dyachenko, A. D. *Russ. J. Org. Chem*. **2007**, *43*, 280. [*Zh. Org. Khim.* **2007**, *43*, 286.] (b) Dyachenko, V. D. *Russ. J. Gen. Chem*. **2005**, *75*, 1537. [*Zh. Obshch. Khim.* **2005**, *75*, 1612.] (c) Dyachenko, V. D. *Ukr. Khim. Zh.* **2006**, *72*(2), 116. (d) Dyachenko, V. D.; Karpov, E. N.; Dyakonenko, V. V.; Shishkin, O. V. *Russ. J. Gen. Chem*. **2010**, *80*, 2032. [*Zh. Obsh. Khim.* **2010**, *80*, 1723.] (e) Dyachenko, A. D.; Desenko, S. M.; Dyachenko, V. D. *Chem. Heterocycl. Compd.* **2002**, *38*, 747. [*Khim. Geterotsikl. Soedin.* **2002**, 845.]
8. Xie, L.-G.; Shaaban, S. S.; Chen, X.; Maulide, N. *Angew. Chem.*, *Int. Ed.* **2016**, *55*, 12864.
9. Martin, R. E.; Morawitz, F.; Kuratli, C.; Alker, A. M.; Alanine, A. I. *Eur. J. Org. Chem.* **2012**, 47.
10. Tittse, L.; Brashe, G.; Gerike, K. *Domino-reaktsii v organicheskom sinteze* (*Domino Reactions in Organic Synthesis* [in Russian]); Moscow: BINOM. Laboratoriya znanii, 2010.
11. (a) Dyachenko, I. V.; Dyachenko, V. D.; Dorovatovskii, P. V.; Khrustalev, V. N.; Nenajdenko, V. G. *Chem. Heterocycl. Compd*. **2019**, *55*, 442. [*Khim. Geterotsikl. Soedin.* **2019**, *55*, 442.] (b) Dyachenko, I. V.; Kalashnik, I. N.; Dyachenko, V. D.; Dorovatovskii, P. V.; Khrustalev, V. N.; Nenajdenko, V. G. *Russ. J. Org. Chem*. **2019**, *55*, 1019. [*Zh. Org. Khim.* **2019**, *55*, 1127.] (c) Dyachenko, I. V.; Dyachenko, V. D.; Dorovatovskii, P. V.; Khrustalev, V. N.; Nenajdenko, V. G. *Russ. J. Org. Chem*. **2019**, *55*, 215. [*Zh. Org. Khim.* **2019**, *55*, 266.]
12. Battye, T. G.; Kontogiannis, L.; Johnson, O.; Powell, H. R.; Leslie, A. G. W. *Acta Crystallogr*., *Sect. D*: *Biol. Crystallogr.* **2011**, *D67*, 271.
13. Evans, P. *Acta Crystallogr*., *Sect. D*: *Biol. Crystallogr.* **2006**, *D62*, 72.
14. Sheldrick G. M. *Acta Crystallogr*., *Sect. C*: *Struct. Chem.* **2015**, *C71*, 3.