DOI 10.1007/s10593-020-02852-9
Chemistry of Heterocyclic Compounds **2020**, *56*(12), 1579–1585

Multicomponent synthesis of nicotinic acid derivatives

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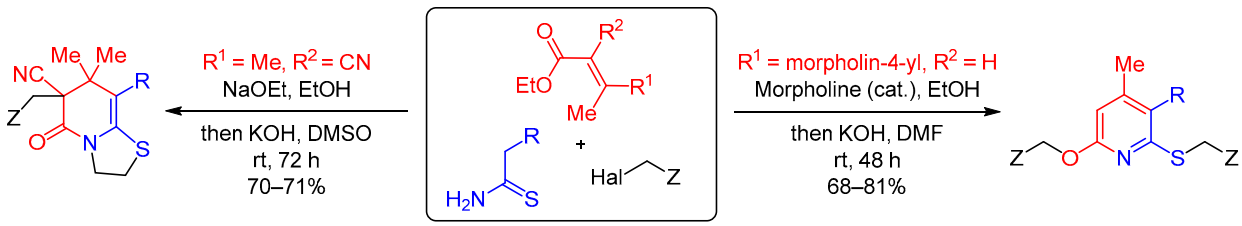
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2020, *56*(12), 1579–1585

Submitted July 8, 2020
Accepted August 26, 2020



The synthesis of previously unknown nitriles, esters, and an amide of 6-alkoxy-2-alkylsulfanyl-4-methyl(4,4-dimethyl)nicotinic acid has been developed. The structure of a number of the obtained derivatives was proved by X-ray structural analysis.

Keywords: 6-alkoxy-2-alkylsulfanyl-4-methyl(4,4-dimethyl)nicotinic acid, CH acids, thiazolo[3,2-*a*]pyridines, alkylation, Michael reaction, multicomponent synthesis, X-ray structural analysis.

Among 2-oxo(thio)nicotinonitrile derivatives, dyes,[1] stimulants of the growth of sunflower seedlings,[2] antidotes to the herbicide 2,4-B,[3] compounds with bactericidal and fungicidal activity,[4] as well as compounds that inhibit acetylcholinesterase and butyrylcholinesterase in the treatment of Alzheimer's disease[5] have been found. The principal methods for the synthesis of 2-oxo(thio)nicotinonitriles involve the condensation of 1,3-dicarbonyl compounds[6] or their enamines[7] with nitrogen-containing CH acids.

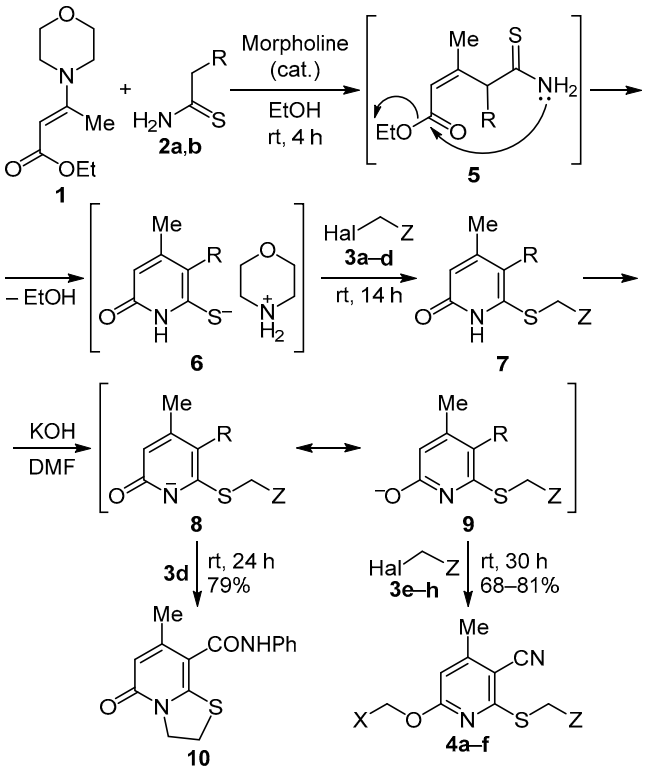
Considering the high practical importance of this class of heterocyclic compounds and in continuation of our research on multicomponent condensations,[8] we studied a new reaction of ethyl β-(morpholin-4-yl)crotonate (**1**) with cyanothioacetamides **2a**,**b**, morpholine, and alkylating agents **3a**–**h**.

The condensation in EtOH at 20°C gives rise to 6-alkoxy-2-alkylsulfanyl-4-methylnicotinonitriles **4a**–**f** (Scheme 1). We believe that the first step of the reaction is the conjugated addition of ethyl β-(morpholin-4-yl)crotonate (**1**) to the activated double bond of substrate **2a**,**b**. In the course of the reaction, a morpholine molecule is eliminated with the formation of the intermediate adduct **5**, which, as a result of intramolecular heterocyclization, forms pyridinethiolate morpholine salt **6**.[9]

Salt **6** is subsequently regioselectively alkylated with alkyl halides **3a**–**d** to form thioesters **7**, the treatment of which with KOH in DMF generates anions **8**, presented in the form of resonance forms **8** and **9**. This fact is confirmed by the formation of compound **10** when using 1,2-dibromoethane (**3d**) as an alkylating agent. As a result of repeated alkylation during this condensation with the use of compounds **3e**–**h**, the expected 4-methylnicotinic acid derivatives **4a**–**f** are formed. Their structure is consistent with the data of spectral studies.

We previously reported that alkylation of morpholinium 3-cyano-4-methyl-6-oxo-1,6-dihydropyridine-2-thiolate with a twofold excess of benzyl chloride[10] or phenacyl bromide[11] in DMF occurs at the S and N atoms.

Scheme 1



2 a R = CN, **b** R = PhNHCO
3 a Hal = I, Z = Me; **b** Hal = Cl, Z = PrOCO; **c** Hal = Cl, Z = Ph
d Hal = Br, Z = $(CH_2)_2Br$; **e** Hal = Br, Z = $CH{=}CH_2$; **f** Hal = Br, Z = 4-ClC_6H_4CO; **g** Hal = I, Z = H; **h** Hal = Br, Z = HC≡C
4 a Z = Me, X = Ph; **b** Z = PrOCO, X = $CH{=}CH_2$; **c** Z = Ph, X = $CH{=}CH_2$; **d** Z = Ph, X = 4-ClC_6H_4CO; **e** Z = Ph, X = H; **f** Z = Me, X = HC≡C

In order to unambiguously establish the direction of alkylation of substituted pyridines containing the O, S, N nucleophilic centers, the structure of compounds **4a**,**b** was proved by X-ray structural analysis (Fig. 1). It is important to note that the 2-alkylsulfanyl and 6-alkoxy substituents in compounds **4a**,**b** are in a tick-shaped mutual conformation, which is apparently determined by steric preferences in the solid phase. In addition, the ester fragment in compound **4b** has the most energetically favorable linear structure.

In the solid state of compound **4a**, the molecules form dimers due to S···S nonvalent interactions with a distance of 3.4705(9) Å (Fig. 2). Dimers are packed in stacks along the crystallographic axis *a* and are located at the distances of the van der Waals radii.

Compound **4b** in the solid state forms zigzag chains along the crystallographic axis *b* *via* intermolecular hydrogen bonds C–H···O (Table 1, Fig. 3).

The introduction of cyanomethylbutene derivative **11**, cyanothioacetamide (**2a**), ethyl monochloroacetate (**12**), and NaOEt at 20°C in EtOH into multicomponent condensation leads to the formation of ethyl 2-[(3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)-sulfanyl]acetate **13**. The conversion probably begins with the Michael addition of the formed CH acid anion **2a** to the activated double bond of cyanomethylbutene **11** with the formation of the corresponding salt **14**. Then, salt **1** is alkylated at the S atom to form sulfide **13**. The use of CH

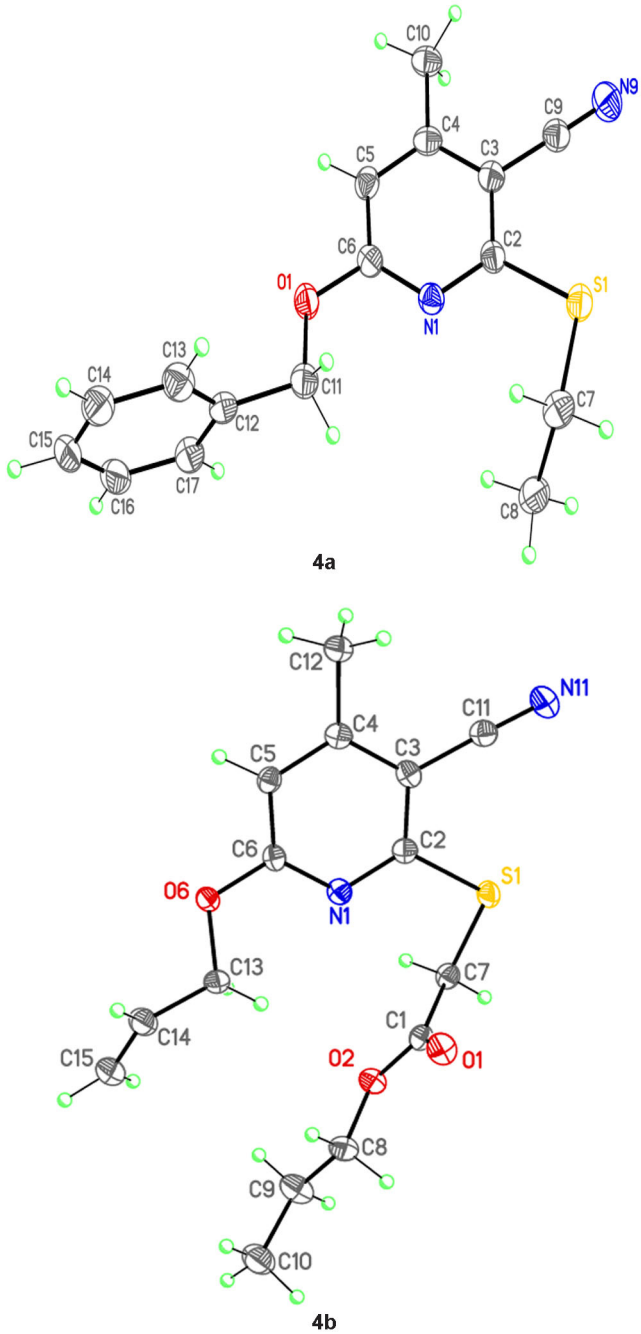


Figure 1. Molecular structure of compounds **4a**,**b** with atoms represented as thermal vibration ellipsoids of 50% probability.

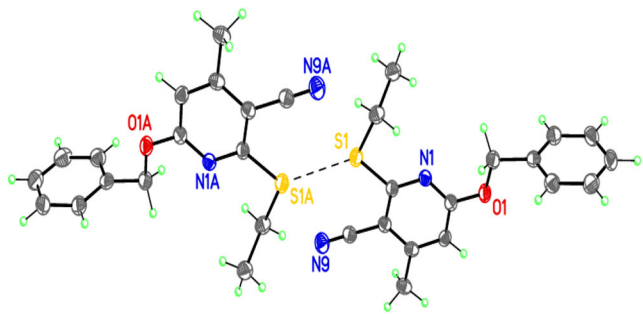


Figure 2. Dimer of compound **4a** in the solid state. The dotted line depicts the intermolecular interaction S···S.

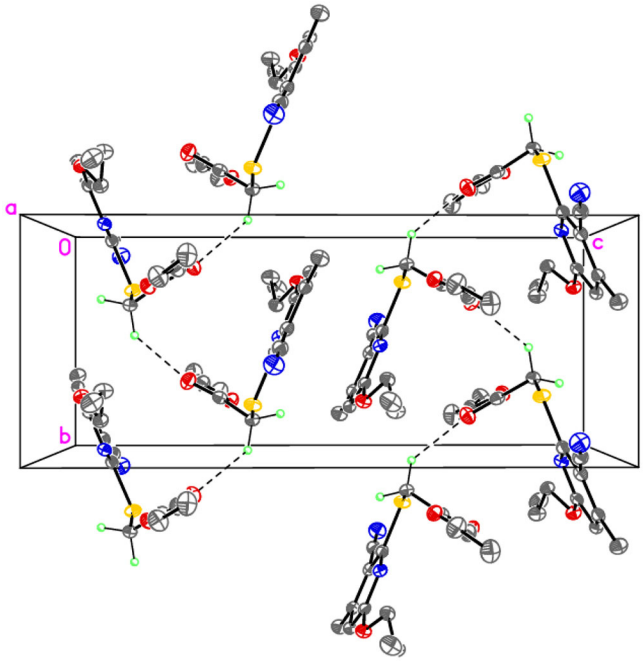


Figure 3. Zigzag chains of compound **4b** in the solid state. The dotted lines depict intermolecular hydrogen bonds.

Table 1. Hydrogen bonds and their characteristics (bond lengths and angles) in compounds **4b**, **13**, and **17**

D–H···A	*d*(D–H), Å	*d*(H···A), Å	*d*(D···A), Å	DHA angle, °
	Compound **4b**			
C(7)–H(7B)···O(1)*	0.99	2.38	3.174(2)	137
	Compound **13**			
N(1)–H(1)···O(6)**	0.94(3)	1.91(3)	2.840(3)	177(2)
C(7)–H(7A)···O(1)***	0.99	2.38	3.361(2)	169
C7─H(7B)···O(6)**	0.99	2.37	3.324(3)	161
	Compound **17**			
C(3)–H(3A)···O(5)*[4]	0.99	2.44	3.356(2)	153

* Symmetry operations: $-x + 1, y + 1/2, -z + 1/2$.
** Symmetry operations: $-x, -y + 1, -z + 2$.
*** Symmetry operations: $-x + 1, -y, -z + 2$.
*[4] Symmetry operations: $-x + 2, -y + 2, -z + 1$.

acids **2a**,**c** and 1,2-dibromoethane (**3d**), and benzyl chloride (**3c**) or 2-bromoacetophenone (**15**) as alkylating agents in this condensation leads to the formation of condensation products **16** and **17**. We assume that the thioether of tetrahydropyridine **18** is formed as an intermediate in the course of the reaction (Scheme 2).

Note that the second alkylation happens at the C-6 atom of the thiazolopyridine ring, not at the O atom of the carbonyl fragment of the molecule. Obviously, this is due to the absence of the possibility of enolization and aromatization of the pyridine ring.

Spectral data confirm the structure of the synthesized compounds **4a**–**f**, **10**, **13**, **16**, **17**. A characteristic feature of the ^{1}H NMR spectra of compounds **13** and **16** is the splitting of the proton signals of the methylene fragments SCH_2 and $PhCH_2$ into two doublets, which indicates the

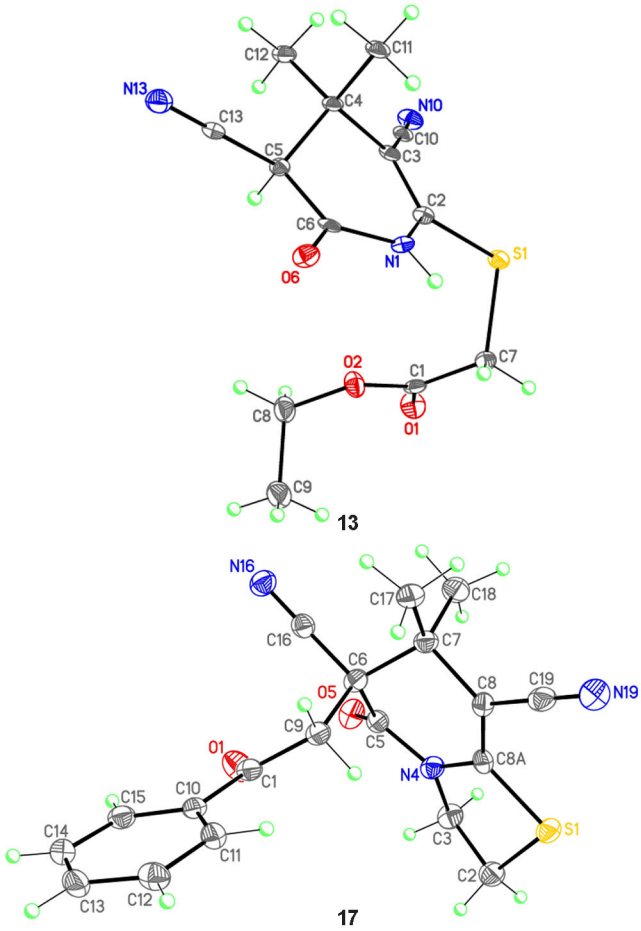
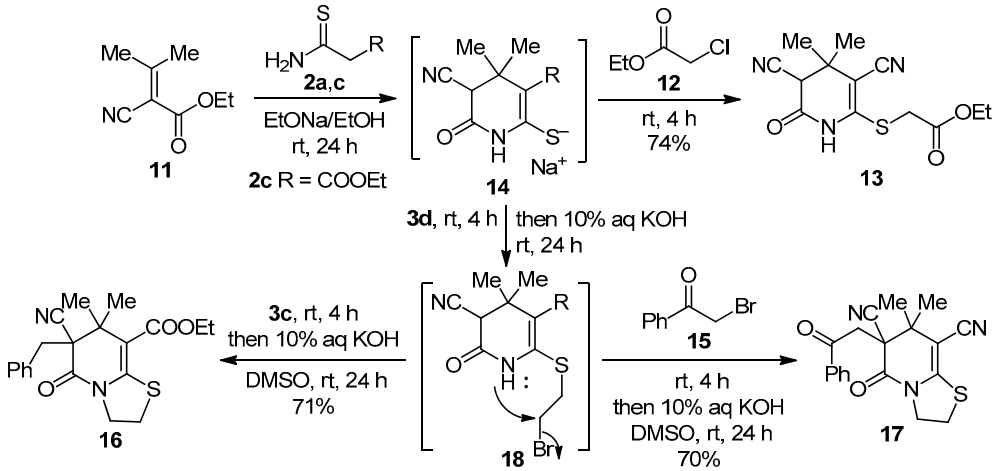


Figure 4. Molecular structure of compounds **13** and **17** with atoms represented as thermal vibration ellipsoids of 50% probability.

Scheme 2



absence of free rotation of these groups and, as a consequence, nonequivalence of the indicated protons.

The X-ray structural analysis data for single crystals **13** and **17** conclusively confirm the structures of the compounds obtained in the course of multicomponent condensation (Fig. 4).

It should be noted that molecule **13** assumes a spatial arrangement in which the thioacetate fragment is located practically above the tetrahydropyridine ring. The tetrahydropyridine ring has a distorted half-chair conformation with the carbon atom C(4) exiting from the plane drawn through the rest of the ring atoms (the standard deviation of 0.082 Å).

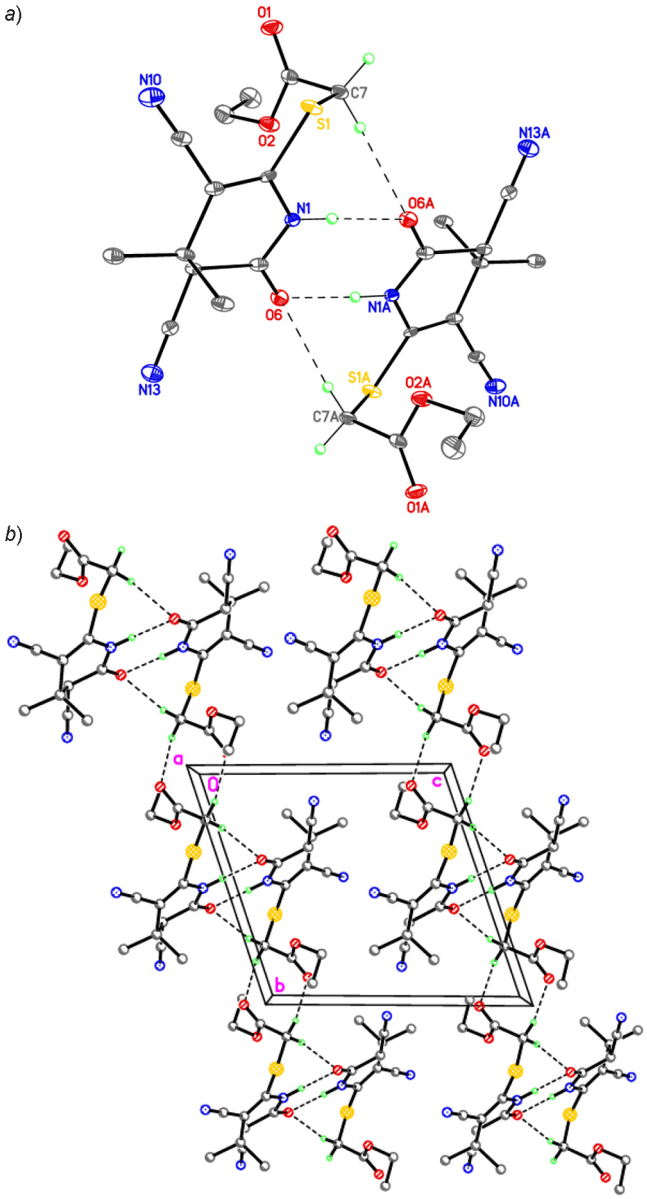


Figure 5. *a*) Centrosymmetric hydrogen-bonded dimers of compound **13** in the solid state. The dotted lines depicts intermolecular hydrogen bonds N–H···O and C–H···O. *b*) Hydrogen-bonded ribbons of compound **13** in the solid state. The dotted lines depict intermolecular hydrogen bonds N–H···O and C–H···O.

In the bicyclic structure **17**, the thiazole ring has the envelope conformation with the carbon atom C(2) exiting from the plane drawn through the rest of the ring atoms (the standard deviation of 0.044 Å), and the six-membered tetrahydropyridine ring has the half-chair conformation with the carbon atom C(6) exiting from the plane drawn through the remaining atoms of the ring (the standard deviation of 0.032 Å). It should be noted that the bulky 2-oxo-2-phenylethyl substituent occupies a sterically less preferred axial position.

In the solid state, the molecules of compound **13** form centrosymmetric dimers due to the intermolecular hydrogen bonds N–H···O and C–H···O (Table 1, Fig. 5*a*), which form hydrogen-bonded ribbons along the crystallographic axis *b* located at the distance of the van der Waals radii (Fig. 5*b*).

Molecules **17** in the solid state form centrosymmetric dimers due to intermolecular hydrogen bonds C–H···O (Table 1, Fig. 6). The dimers are packed in stacks along the crystallographic axis *a* and are located at the distance of the van der Waals radii.

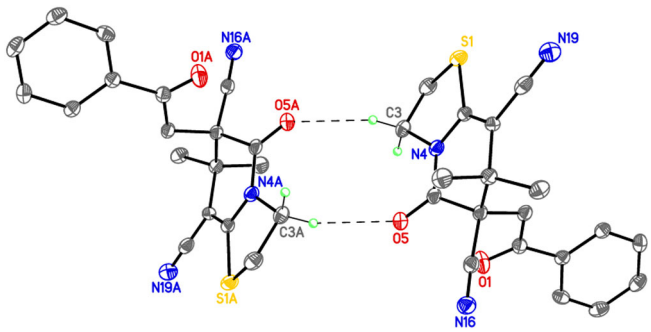


Figure 6. Centrosymmetric hydrogen-bonded dimers of compound **17** in the solid state. The dotted lines depict intermolecular hydrogen bonds C–H···O.

To conclude, new derivatives of 6-alkoxy-2-alkylsulfanyl-4-methyl(4,4-dimethyl)nicotinonitriles, as well as esters and an amide of nicotinic acid were synthesized as a result of multicomponent condensation of ethyl β-(morpholin-4-yl)crotonate or ethyl isopropylidenecyanoacetate, CH acids with the thioamide group, alkylating derivatives, and morpholine or sodium ethylate.

Experimental

IR spectra were registered on a IKS-40 spectrometer in thin film (suspension in petroleum jelly). ^{1}H and ^{13}C NMR spectra were acquired on a Varian VXR-400 spectrometer (400 MHz) in DMSO-d_6, using residual solvent signals as internal standard (2.50 ppm for ^{1}H nuclei, 39.5 for ^{13}C nuclei). High-resolution mass spectra were recorded on an Orbitrap Elite mass spectrometer, DMSO solvent, atmospheric pressure electrospray ionization, voltage 3.5 kV, capillary temperature 275°C. Mass spectra were recorded in the positive and negative ion modes in an orbital trap with a resolution of 480,000. Mass spectra of compounds **4c–f** were 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).

Elemental analysis was performed on a PerkinElmer CHN-analyzer. 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, eluent Me_2CO–hexane, 5:3, visualization by iodine vapor and UV light.

Synthesis of 6-alkoxy-2-alkylsulfanyl-4-methylnicotinonitriles 4a–f (General method). Morpholine (3 drops) was added to a mixture of ethyl β-(morpholin-4-yl)crotonate (**1**) (2.0 g, 10 mmol), cyanothioacetamide **2a** (1.0 g, 10 mmol), and anhydrous EtOH (30 ml) at 20°C; and the resulting mixture was stirred for 4 h. Then, alkylating agent **3a**–**d** (10 mmol) was added, and the mixture was stirred for 14 h. DMF (30 ml), 10% aqueous KOH (5.6 ml, 10 mmol), and alkyl halide **3e**–**h** (10 mmol) were then successively added. The reaction mixture was stirred for 30 h and diluted with an equal volume of H_2O. The formed precipitate was filtered off, washed with H_2O (20 ml), EtOH, and hexane.

6-Benzyloxy-2-ethylsulfanyl-4-methylnicotinonitrile (4a). Yield 2.2 g (77%), colorless crystals, mp 78–80°C (AcOH). IR spectrum, ν, cm^{-1}: 2218 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.3, C<u>H</u>$_3$CH$_2$); 2.33 (3H, s, CH_3); 3.14 (2H, q, *J* = 7.3, CH_3C<u>H</u>$_2$); 5.43 (2H, s, CH_2O); 6.66 (1H, s, H-5 Py); 7.21–7.48 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 15.1; 20.1; 24.6; 68.3; 100.1; 107.4; 115.8; 128.0 (2C); 128.4; 128.9 (2C); 137.0; 155.0; 162.4; 164.2. Found, *m*/*z*: 285.1056 $[M+H]^+$. $C_{16}H_{17}N_2OS$. Calculated, *m*/*z*: 285.0983. Found, %: C 67.46; H 5.55; N 9.73. $C_{16}H_{16}N_2OS$. Calculated, %: C 67.58; H 5.67; N 9.85.

Propyl 2-[(6-allyloxy-3-cyanopyridin-2-yl-4-methyl)-sulfanyl]acetate (4b). Yield 2.1 g (68%), colorless plates, mp 68–70°C (AcOH). IR spectrum, ν, cm^{-1}: 2215 (C≡N), 1707 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.78 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$CH$_2$); 1.42–1.61 (2H, m, CH$_3$C<u>H</u>$_2$CH$_2$); 2.34 (3H, s, CH_3); 3.98 (2H, t, *J* = 6.6, CH$_3$CH$_2$C<u>H</u>$_2$); 4.10 (2H, s, SCH_2); 4.79 (2H, d, *J* = 11.7, OC<u>H</u>$_2$CH); 5.24 (1H, d, J_{cis} = 11.7, CH_2=); 5.33 (1H, d, J_{trans} = 17.2, CH_2=); 5.89–6.14 (1H, m, =CH); 6.64 (1H, s, H-5 Py). ^{13}C NMR spectrum, δ, ppm: 10.5; 20.0; 21.8; 32.6; 67.1; 67.5; 99.5; 107.7; 115.6; 118.7; 133.3; 155.1; 161.2; 164.1; 169.0. Found, *m*/*z*: 307.1111 $[M+H]^+$. $C_{15}H_{19}N_2O_3S$. Calculated, *m*/*z*: 307.1038. Found, %: C 58.74; H 5.84; N 9.03. $C_{15}H_{18}N_2O_3S$. Calculated, %: C 58.80; H 5.92; N 9.14.

6-Allyloxy-2-benzylsulfanyl-4-methylnicotinonitrile (4c). Yield 2.3 g (79%), colorless crystals, mp 66–68°C (AcOH). IR spectrum, ν, cm^{-1}: 2220 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, CH_3); 4.50 (2H, s, SCH_2); 4.87 (2H, d, *J* = 5.0, OCH_2); 5.22 (1H, d, J_{cis} = 10.5, CH_2=); 5.34 (1H, d, J_{trans} = 17.5, CH_2=); 5.81–6.15 (1H, m, =CH); 6.60 (1H, s, H-5 Py); 7.23 (1H, t, *J* = 7.5, H Ph); 7.30 (2H, t, *J* = 7.5, H Ph); 7.39 (2H, t, *J* = 7.5, H Ph). ^{13}C NMR spectrum, δ, ppm: 21.3; 33.9; 66.8; 99.3; 106.4; 115.1; 117.6; 126.8; 127.3 (2C); 127.9 (2C); 132.5; 137.1; 154.0; 158.2; 163.3. Mass spectrum, *m*/*z* (I_{rel}, %): 297 $[M+H]^+$ (100). Found, %: C 68.75; H 5.39; N 9.33. $C_{17}H_{16}N_2OS$. Calculated, %: C 68.85; H 5.49; N 9.45.

2-Benzylsulfanyl-6-[2-(4-chlorophenyl)-2-oxoethyl]-4-methylnicotinonitrile (4d). Yield 3.3 g (81%), colorless needles, mp 101–103°C (AcOH). IR spectrum, ν, cm^{-1}: 2217 (C≡N), 1702 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3); 4.14 (2H, s, SCH_2); 5.83 (2H, s, OCH_2); 6.82 (1H, s, H-5 Py); 7.11–7.23 (5H, m, H Ph); 7.57 (2H, d, *J* = 8.4, H Ar); 7.97 (2H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.2; 33.9; 69.0; 100.3; 107.8; 115.5; 127.5; 128.7 (2C); 128.8 (2C); 129.5 (2C); 130.2 (2C); 133.1; 137.0; 139.3; 155.5; 161.5; 163.7; 193.2. Mass spectrum, *m*/*z* (I_{rel}, %): 409 $[M+H]^+$ (100). Found, %: C 64.24; H 4.08; N 6.79. $C_{22}H_{17}ClN_2O_2S$. Calculated, %: C 64.62; H 4.19; N 6.85.

2-Benzylsulfanyl-6-methoxy-4-methylnicotinonitrile (4e). Yield 2.0 g (75%), colorless crystals, mp 114–116°C (AcOH). IR spectrum, ν, cm^{-1}: 2219 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, CH_3); 3.94 (3H, s, CH_3O); 4.54 (2H, s, CH_2); 6.61 (1H, s, H-5 Py); 7.25 (1H, t, *J* = 7.5, H Ph); 7.31 (2H, t, *J* = 7.5, H Ph); 7.41 (2H, d, *J* = 7.0, H Ph). ^{13}C NMR spectrum, δ, ppm: 20.1; 34.0; 54.8; 99.7; 107.5; 115.8; 127.8; 129.0 (2C); 129.2 (2C); 137.9; 154.9; 161.9; 164.9. Mass spectrum, *m*/*z* (I_{rel}, %): 271 $[M+H]^+$ (100). Found, %: C 66.55; H 5.14; N 10.27. $C_{15}H_{14}N_2OS$. Calculated, %: C 66.64; H 5.22; N 10.36.

2-Ethylsulfanyl-4-methyl-6-(prop-2-yn-1-yloxy)nicotinonitrile (4f). Yield 1.8 g (76%), colorless powder, mp 75–77°C (EtOH). IR spectrum, ν, cm^{-1}: 3300 (≡C–H), 2256 (C≡C), 2218 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.3, C<u>H</u>$_3$CH$_2$); 2.34 (3H, s, CH_3); 3.21 (2H, q, *J* = 7.3, CH_3C<u>H</u>$_2$); 3.52 (1H, s, HC≡C); 5.02 (2H, s, CH_2); 6.62 (1H, s, H-5 Py). ^{13}C NMR spectrum, δ, ppm: 15.3; 20.1; 24.8; 54.5; 78.2; 79.3; 100.5; 107.2; 115.6; 155.2; 162.4; 163.2. Mass spectrum, *m*/*z* ($I_{rel.}$, %): 233 $[M+H]^+$ (100). Found, %: C 61.96; H 5.14; N 11.92. $C_{12}H_{12}N_2OS$. Calculated, %:C 62.04; H 5.21; N 12.06.

7-Methyl-5-oxo-*N*-phenyl-3,5-dihydro-2*H*-thiazolo-[3,2-*a*]pyridine-8-carboxamide (10). Morpholine (3 drops) was added to a mixture of ethyl β-(morpholin-4-yl)-crotonate (**1**) (2.0 g, 10 mmol), cyanothioacetamide **2b** (1.94 g, 10 mmol), 1,2-dibromoethane (**3d**) 0.9 ml, 10 mmol), and anhydrous EtOH (30 ml) at 20°C; and the resulting mixture was stirred for 30 h. Then, DMF (30 ml) and 10% aqueous KOH (5.6 ml, 10 mmol) were added to the reaction mixture. After 24 h, the reaction mixture was diluted with an equal volume of H_2O. The formed precipitate was filtered off, washed with H_2O (20 ml), EtOH, and hexane. Yield 2.3 g (79%), yellow needles, mp 268–270 °C (AcOH), sublimate into rhombic crystals. IR spectrum, ν, cm^{-1}: 1664 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, CH_3); 3.43 (2H, t, *J* = 6.4, SCH_2); 4.31 (2H, t, *J* = 6.4, NCH_2); 6.02 (1H, c, H-5 Py); 7.11 (1H, t, *J* = 7.6, H Ph); 7.30 (2H, t, *J* = 7.6, H Ph); 7.60 (2H, d, *J* = 7.6, H Ph); 10.18 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 20.0; 28.6; 51.1; 112.6; 114.4; 120.0 (2C); 124.2; 129.2 (2C); 139.2; 149.4; 150.4; 160.4; 164.6. Found, *m*/*z*: 287.0851 $[M+H]^+$. Calculated, *m*/*z*: 287.0849. Found, %: C 62.86; H 4.88; N 9.69. $C_{15}H_{14}N_2O_2S$. Calculated, %: C 62.92; H 4.93; N 9.78.

Ethyl 2-[(3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)sulfanyl]acetate (13). Na (0.23 g, 10 mmol) in anhydrous EtOH (10 ml) was added with stirring to a solution of cyanomethylbutene **11** (1.53 g, 10 mmol) and cyanothioacetamide **2a** (1.0 g (10 mmol) in anhydrous EtOH (15 ml). The resulting mixture was stirred for 15 min and kept for 24 h. Then, ethyl chloroacetate (**12**)

(1.1 ml, 10 mmol) was added to the mixture, stirring was continued for 4 h, and the mixture was diluted with an equal volume of H_2O. The formed precipitate was filtered off, washed with H_2O (20 ml), EtOH, and hexane. Yield 2.2 g (74%), colorless plates, mp 133–135°C (AcOH). IR spectrum, ν, cm^{-1}: 3300 (NH), 2202 (C≡N), 1708 (C=O), 1666 (CONH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.11 (3H, s, CH_3); 1.17 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 1.30 (3H, s, CH_3); 3.90 (1H, d, ^2J = 15.7, SCH_2); 3.95 (1H, d, ^2J = 15.7, SCH_2); 4.09 (2H, q, *J* = 7.1, OCH_2); 4.53 (1H, s, H-5 Py); 11.22 (1H, br. s, NH). 13C NMR spectrum, δ, ppm: 14.4; 22.3; 29.7; 32.8; 36.6; 46.5; 61.9; 100.0; 115.1; 116.2; 145.2; 162.9; 168.3. Found, *m*/*z*: 292.0761 $[M–1]^-$. $C_{13}H_{14}N_3O_3S$. Calculated, *m*/*z*: 292.0834. Found, %: C 53.16; H 5.06; N 14.22. $C_{13}H_{15}N_3O_3S$. Calculated, %: C 53.23; H 5.15; N 14.32.

Synthesis of tetrahydro-2*H*-thiazolo[3,2-*a*]pyridines 16 and 17 (General method). Na (0.23 g, 10 mmol) in anhydrous EtOH (10 ml) was added with stirring to a solution of cyanomethylbutene **11** (1.53 g, 10 mmol), and cyanothioacetamide **2a** (1.00 g, 10 mmol) or ethyl 3-amino-3-thioxopropanoate (**2c**) (1.5 g, 10 mmol) in anhydrous EtOH (15 ml). The resulting mixture was stirred for 15 min and kept for 24 h. Then, 1,2-dibromoethane (**3d**) (0.9 ml, 10 mmol) was added to the mixture, stirring was continued for 4 h. 10% Aqueous KOH (5.6 ml, 10 mmol) was then added, the mixture was stirred for 15 min and kept for 24 h. The reaction mixture was diluted with an equal volume of H_2O. The formed precipitate was filtered off and dissolved in DMSO (20 ml). 10% Aqueous KOH (5.6 ml, 10 mmol) and benzyl chloride (**3c**) (1.15 ml, 10 mmol) or 2-bromoacetophenone (**15**) (1.99 g, 10 mmol) were then successively added. Stirring was continued for 2 h, and the mixture was kept for 24 h. It was then diluted with an equal volume of H_2O. The formed precipitate was filtered off, washed with H_2O (20 ml), EtOH, and hexane.

Ethyl 6-benzyl-6-cyano-7,7-dimethyl-5-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*a*]pyridine-8-carboxylate (16). Yield 2.5 g (71%), colorless powder, mp 150–152°C (EtOH). IR spectrum, ν, cm^{-1}: 2244 (C≡N), 1707 (C=O), 1666 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, s, CH_3); 1.25 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 1.54 (3H, s, CH_3); 2.94 (1H, d, ^2J = 13.8, C<u>H</u>$_2$Ph); 3.15 (1H, d, ^2J = 13.8, C<u>H</u>$_2$Ph); 3.17–3.28 (2H, m, SCH_2); 3.73–3.86 (1H, m, NCH_2); 3.98–4.13 (1H, m, NCH_2); 4.16 (2H, q, *J* = 7.1, OCH_2); 7.06 (2H, d, *J* = 6.9, H Ph); 7.19–7.32 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 17.4; 22.6; 25.1; 27.9; 36.9; 42.1; 49.0; 60.5; 60.8; 105.1; 117.9; 128.0; 128.8 (2C); 130.2 (2C); 134.8; 151.4; 162.1; 166.2. Found, *m*/*z*: 371.1432 $[M+H]^+$. Calculated, *m*/*z*: 371.1424. Found, %: C 64.76; H 5.86; N 7.49. $C_{20}H_{22}N_2O_3S$. Calculated, %: C 64.85; H 5.99; N 7.56.

7,7-Dimethyl-5-oxo-6-(2-oxo-2-phenylethyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*a*]pyridine-6,8-dicarbonitrile (17). Yield 2.5 g (70%), colorless prisms, mp 166–168°C (AcOH). IR spectrum, ν, cm^{-1}: 2248 (C≡N), 1707, 1668 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, s, CH_3); 1.34 (3H, s, CH_3); 3.25–3.48 (2H, m, CH_2S); 3.59 (2H, s, CH_2); 3.82–3.94 (1H, m, CH_2N); 4.11–4.23 (1H, m, CH_2N); 7.52 (2H, t, *J* = 7.0, H Ph); 7.67 (1H, t, *J* = 7.0, H Ph); 7.98 (2H, d, *J* = 7.0, H Ph). ^{13}C NMR spectrum, δ, ppm: 22.3; 24.0; 29.1; 32.5; 42.0; 50.8; 51.7; 86.5; 117.0; 117.3; 128.8 (2C); 129.1 (2C); 134.1; 136.6; 154.2; 161.3; 195.5. Found, *m*/*z*: 352.1115 $[M+H]^+$. $C_{19}H_{17}N_3O_2S$. Calculated, *m*/*z*: 352.1114.

X-ray structural analysis of compounds 4a,b, 13, and 17 was performed on the BELOK synchrotron station of the 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 4a. Colorless plates ($C_{16}H_{16}N_2OS$, *M* 284.37), triclinic, space group $P\bar{1}$; *a* 7.1700(11), *b* 8.3464(12), *c* 12.2736(19) Å; α 88.844(10), β 84.381(11), γ 84.474(12)°; *V* 727.53(19) Å^3; *Z* 2; d_{calc} 1.298 g/cm^3; *F*(000) 300; μ 0.506 mm^{-1}. A total of 9830 reflections were collected (2876 independent reflections, R_{int} 0.079, 2θ 76.80°). 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) = 1.5U_{eq}(C) for CH_3 group and U_{iso}(H) = 1.2U_{eq}(C) for the remaining groups). The final probability factors R_1 0.062 for 2409 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.125 for all independent reflections, *S* 1.068. Maximum and minimum values of the peaks of residual electron density were 0.35 and –0.47 e/Å^3, respectively. The full set of X-ray structural data for compound **4a** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2013812).

Compound 4b. Colorless plates ($C_{15}H_{18}N_2O_3S$, *M* 306.37), monoclinic, space group $P2_1/c$; *a* 12.1141(14), *b* 7.3360(9), *c* 17.9322(19) Å; β 91.166(14)°; *V* 1593.3(3) Å^3; *Z* 4; d_{calc} 1.277 g/cm^3; *F*(000) 648; μ 0.494 mm^{-1}. A total of 20726 reflections were collected (2977 independent reflections, R_{int} 0.054, 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 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) = 1.5U_{eq}(C) for CH_3 group and U_{iso}(H) = 1.2U_{eq}(C) for the remaining groups). The final probability factors R_1 0.045 for 2511 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.119 for all independent reflections, *S* 1.098. Maximum and minimum values of the peaks of residual electron density were 0.33 and –0.44 e/Å^3, respectively. The full set of X-ray structural data for compound **4b** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2013813).

Compound 13. Colorless plates ($C_{13}H_{15}N_3O_3S$, *M* 293.34), triclinic, space group $P\bar{1}$; *a* 6.9299(11), *b* 10.1301(15), *c* 10.6602(16) Å; α 71.220(11), β 84.130(12), γ 86.331(12)°; *V* 704.41(19) Å^3; *Z* 2; d_{calc} 1.383 g/cm^3; *F*(000) 308; μ 0.557 mm^{-1}. A total of 5935 reflections were collected

(2346 independent reflections, R_{int} 0.065, 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. The hydrogen atom of the amino group is 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 rest of the hydrogen atoms, the positions of which were calculated geometrically, and 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 0.053 for 1873 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.157 for all independent reflections, S 1.099. Maximum and minimum values of the peaks of residual electron density were 0.44 and −0.54 e/Å^3, respectively. The full set of X-ray structural data for compound **13** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2013814).

Compound 17. Colorless prisms ($C_{19}H_{17}N_3O_2S$, M 351.42), triclinic, space group $P\bar{1}$; a 8.2999(12), b 10.3501(15), c 10.9502(16) Å; α 107.470(11), β 95.711(11), γ 98.639(12)°; V 876.6(2) Å^3; Z 2; d_{calc} 1.331 g/cm^3; F(000) 368; μ 0.463 mm^{-1}. A total of 12885 reflections were collected (3011 independent reflections, R_{int} 0.048, 2θ 76.80°). 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) = 1.5U_{eq}(C) for CH_3 and U_{iso}(H) = 1.2U_{eq}(C) for the remaining groups). The final probability factors R_1 0.041 for 2672 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.111 for all independent reflections, S 1.018. Maximum and minimum values of the peaks of residual electron density were 0.30 and −0.33 e/Å^3, respectively. The full set of X-ray structural data for compound **17** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2013815).

This work was supported by the Ministry of Science and Higher Education of the Russian Federation (project No. 075-03-2020-223 (FSSF-2020-0017)).

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