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Synthesis and Cyclizations of *N*-(Thieno[2,3-*b*]pyridin-3-yl)cyanoacetamides

E. A. Chigorina[a], A. V. Bespalov[b], and V. V. Dotsenko[b,c]*

[a] *Institute of Chemical Reagents and High Purity Chemical Substances of National Research Centre "Kurchatov Institute," Moscow, Russia*
[b] *Kuban State University, Krasnodar, Russia*
**e-mail: victor_dotsenko_@mail.ru*
[c] *North-Caucasian Federal University, Stavropol, Russia*

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Abstract—3-Aminothieno[2,3-*b*]pyridine-2-carboxylic acid esters readily reacted with 3,5-dimethyl-1-(cyanoacetyl)-1*H*-pyrazole to give previously unknown *N*-(thieno[2,3-*b*]pyridin-3-yl)cyanoacetamides. Reactions of the latter with 2-(arylmethylidene)malononitriles were nonselective, and mixtures of different heterocyclization products were generally formed. The cyclization of ethyl 4,6-dimethyl-3-[(cyanoacetyl)amino]thieno[2,3-*b*]-pyridine-2-carboxylate afforded 2,4-dihydroxy-7,9-dimethylthieno[2,3-*b*:4,5-*b*′]dipyridine-3-carbonitrile whose tautomeric equilibrium was studied by DFT quantum chemical calculations. In silico analysis of biological activity of the synthesized compounds was performed.

Keywords: cyanoacetylation, cyanoacetylpyrazole, thieno[2,3-*b*]pyridines, Dieckmann cyclization, thieno[2,3-*b*:4,5-*b*′]dipyridines

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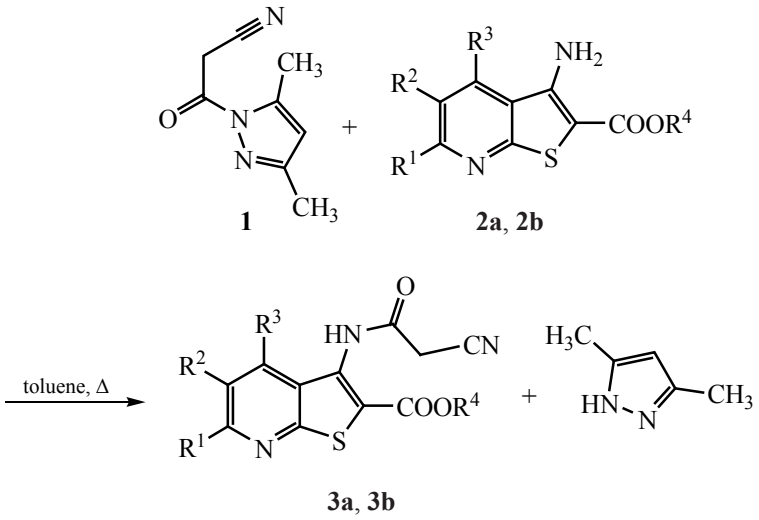
Functional derivatives of cyanoacetic acid are among the most popular building blocks in fine organic synthesis (for reviews, see [1–6]). Numerous examples of introduction of a cyanoacetyl fragment into organic molecules have been reported. The most efficient methods include direct cyanoacetylation of substrates using acylating agents such as cyanoacetyl chloride, cyanoacetic acid/DMAP (dimethylaminopyridine)/DCC (*N*,*N*′-dicyclohexylcarbodimide), cyanoacetic acid/acetic anhydride [4], and 1-(cyanoacetyl)-3,5-dimethylpyrazole (**1**) [7]. The latter reagent is exceptionally convenient in operation and preparatively accessible, and it seems to be preferred alternative to most of the cyanoacetylating agents in reactions with nitrogen nucleophiles and various heterocyclizations [8–12]. Pyrazole **1** reacts with a broad series of amines, including heterocyclic ones [7]; however, its reactions with 3-aminothieno[2,3-*b*]pyridines have not been reported so far.

3-Aminothieno[2,3-*b*]pyridines contain a privileged thienopyridine fragment and constitute a popular class of compounds with a very broad spectrum of biological activity [13–15]. The chemistry of 3-aminothieno[2,3-*b*]-pyridines was the subject of a number of reviews [16–20]. In continuation of the series of our studies in the field of functionalized thienopyridines [21–28], we focused on the possibility of obtaining previously unknown *N*-cyanoacetyl derivatives of 3-aminothieno[2,3-*b*]pyridine using pyrazole **1** as cyanoacetylating agent.

We have found that compounds **2a** and **2b** readily react with 1-(cyanoacetyl)-3,5-dimethylpyrazole (**1**) in boiling toluene to give previously unknown substituted cyanoacetamides **3a** and **3b** in good yields (Scheme 1). Taking into account the synthetic potential of cyanoacetamides [1, 2, 4], it seemed reasonable to study reactions of **3a** and **3b** with 2-(arylmethylidene)malononitriles **4**. It is known that cyanoacetamides generally react with dinitriles **4** to produce pyridines **5** (Scheme 2) [1, 4, 29–31]. However, as shown in [32–34], reactions of **4** with anthranilic acid derivatives **6** can be accompanied by further heterocyclization with the formation of polycyclic structures like **7** (Scheme 2).

We studied cyclizations of **3a** with malononitriles **4**. Regardless of the base catalyst used (morpholine or potassium hydroxide), compound **3a** reacted with **4a** and **4b** in a non-selective manner to give mixtures of compounds **8**–**12** at different ratios, which we failed to sepa-

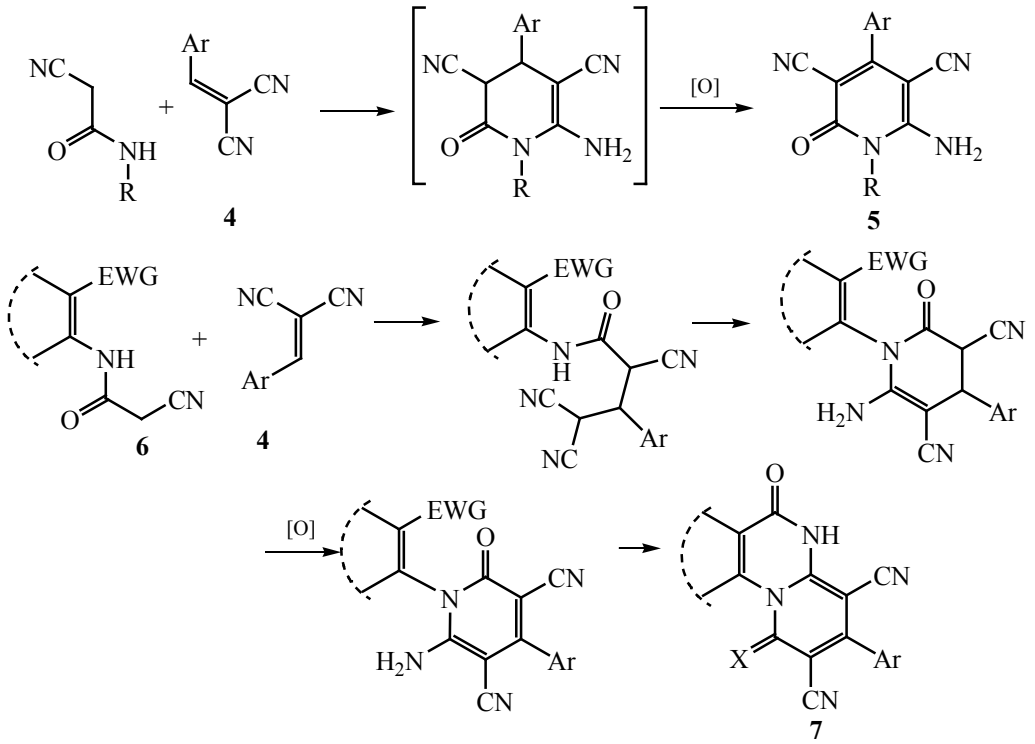
Scheme 1.



$R^1 = R^3 = CH_3$, $R^2 = H$, $R^4 = Et$ (**a**); $R^1 + R^2 = (CH_2)_4$, $R^3 = H$, $R^4 = CH_3$ (**b**).

rate (Scheme 3, Table 1). The products were identified by HPLC/MS and ^1H NMR. Compound **10** was formed via competing intramolecular Dieckmann cyclization of the thienopyridine substrate. Dipyridothiophene **10** was also the only isolated product in the reaction of **3a** with 2-(4-nitrobenzylidene)malononitrile (**4c**). The structure of the isolated compounds was confirmed by NMR, IR, and HPLC/MS data, elemental analyses, and independent synthesis of **10** through sodium isopropoxide-promoted intramolecular cyclization of **3a**.

Scheme 2.



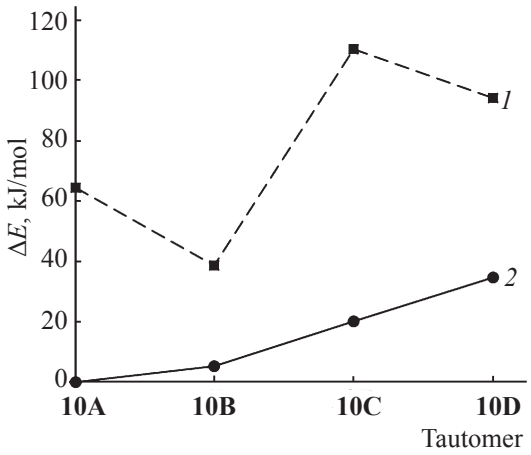
EWG = CN, CO_2Alk; X = O, NH.

Table 1. Reaction of compound **3a** with (arylmethylidene)malononitriles **4**

Reactants	Reaction conditions	Yield, %				
		8	**9**	**10**	**11**	**12**
3a + **4a**	Morpholine, EtOH, Δ	~36	~9	~22	0	0
3a + **4a**	KOH, DMF, Δ	~45	Traces	~45	Traces	0
3a + **4b**	KOH, DMF, Δ	Traces	~4	~5	Traces	~19
3a + **4c**	KOH, EtOH, Δ	0	0	81	0	0

Compound **10** can exist as several tautomers **10A**–**10D** (Scheme 4). It was impossible to unambiguously determine the tautomer structure on the basis of NMR and IR data; therefore, the relative stability of different tautomers was estimated by quantum chemical calculations. The calculations were performed in the framework of the density functional theory with the B3LYP hybrid functional (Becke exchange functional [35] and Lee–Yang–Parr correlation functional [36]) and 6-31G(*d*,*p*) split-valence basis set using GAMESS software package. The obtained structures were visualized using Molekel. The ground state energies were calculated with preliminary geometry optimization with a similar basis set. Nonspecific solvation of tautomers in DMSO was taken into account in terms of the conducting polarizable continuum model (CPCM) [37].

The calculated energies of tautomers **10A**–**10D** are given in the figure. The most stable tautomer in the gas phase is **10B**, and the energy of tautomer **10A** is higher by 25.8 kJ/mol. It should be noted that different results were obtained by PCM for DMSO. In this case, the most stable was tautomer **10A**, though the energy difference between **10A** and **10B** was as small as 5.2 kJ/mol. These findings allowed us to presume that compound **10** in the crystalline state has structure **10B** which can be converted to tautomer **10A** upon dissolution in DMSO, since the latter is solvated more effectively. The strongest solvation by DMSO was predicted for tautomer **10C**; however, its energy still remains fairly high (the difference is 20.2 kJ/mol relative to **10A**). Structure **10D** is the least favorable both in the gas phase and in DMSO solution and seems therefore hardly probable. In the future, we plan to perform a more detailed study of tautomeric transformations of similar dipyridothiophenes.

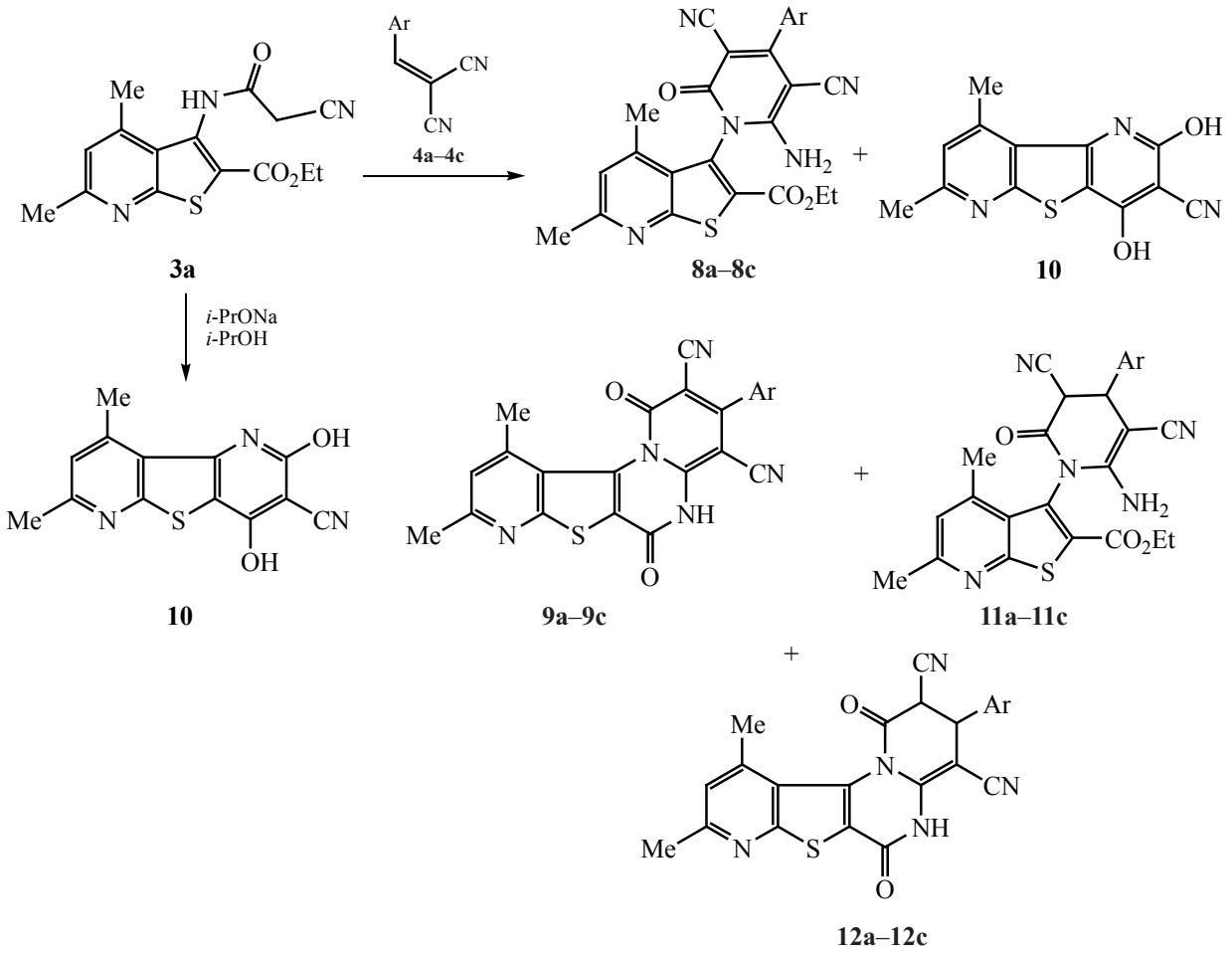


Relative energies of tautomers **10A**–**10D** calculated (*1*) with account taken of non-specific solvation in DMSO and (*2*) for the gas phase; the energy of the most stable tautomer (**10A**) in DMSO was assumed to be zero.

Compounds **3a**, **3b**, and **10** were evaluated *in silico* for drug likeness, and their ADMET (absorption, distribution, metabolism, excretion, toxicity) parameters and probable biological activity were predicted using OSIRIS Property Explorer [38], SwissADME [39], SwissTargetPrediction [40], PASS Online [41], and Molinspiration Property Calculation Service [42]. OSIRIS Property Explorer was used to estimate the lipophilicity (*c* Log *P*), solubility (log *S*), topological polar surface area (TPSA), and toxicological parameters (risks of side mutagenic, oncogenic, and reproductive effects), drug likeness, and drug score [38]. This online service makes it possible to perform primary analysis of a structure for its correspondence to Lipinski's rule of five [*c* Log $P \le 5.0$, molecular weight (MW) ≤ 500, TPSA ≤ 140, number of hydrogen bond acceptors ≤ 10, number of hydrogen donors ≤ 5] [43–45]. The results of calculations by OSIRIS Property Explorer are collected in Table 2.

It is seen that *c*Log *P* values for **3a**, **3b**, and **10** do not exceed 3.0 (Table 2), indicating their probable good absorption and permeability [43–45]. The molecular weight of all compounds is lower than 350, which is also consistent with Lipinski's rule of five. However, none of these compounds showed positive drug likeness or high

Scheme 3.



Ar = 4-$MeOC_6H_4$ (**a**), Ph (**b**), 4-$NO_2C_6H_4$ (**c**).

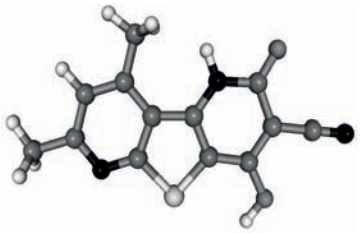
drug score (>0.5). On the other hand, low probability of toxicity was predicted for **3a**, **3b**, and **10**.

The log *S* parameter indicated relatively low predicted solubility of these compounds. It should be noted that the log *S* value of 80% of commercially available drugs is no less than –4 [38]. According to the PASS Online data, compound **10** should inhibit insulinase with a probability of 0.711. Molinspiration Property Calculation Service predicted possible kinase inhibitory activity of **3a**, **3b**, and **10** (Molinspiration bioactivity score –0.34, –0.29, and 0.14, respectively; the higher the score, the higher the probability of biological activity).

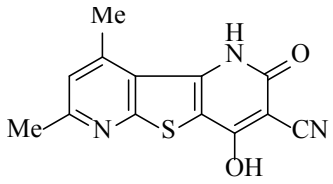
High gastrointestinal absorption, no BBB (blood–brain barrier) permeability, and inhibition of a series of proteins of the cytochrome P450 family (CYP) were predicted for all compounds (Table 3). According to the data of SwissTargetPrediction analysis, the most probable targets of **3a** are microtubule-associated protein tau (MAPT) and TDP1 (tyrosyl-DNA phosphodiesterase 1), of **3b**, MAPT and MBNL (muscleblind-like splicing regulator) protein family, and of **10**, MBNL proteins. The bioavailability index of all compounds was equal to 0.55, in keeping with the Lipinski rule of five [46].

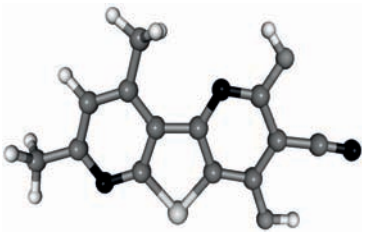
In summary, *N*-(thieno[2,3-*b*]pyridin-3-yl)cyanoacetamides can be synthesized by direct cyanoacetylation of 3-aminothieno[2,3-*b*]pyridine-2-carboxylates with 1-(cyanoacetyl)-3,5-dimethylpyrazole. However, in contrast to published data for structurally related compounds, the obtained cyanoacetamides react with 2-(arylmethylidene)malononitriles in a non-selective manner, obviously depending on the reaction conditions and unsaturated nitrile structure. Studies aimed at optimizing the reaction conditions and developing selective procedures for the synthesis of polycyclic structures based on *N*-(thieno[2,3-

Scheme 4.

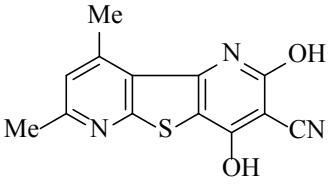


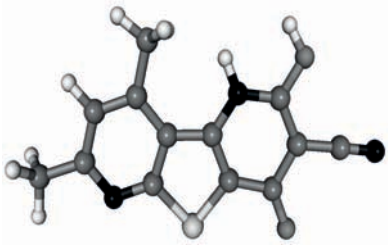
10A



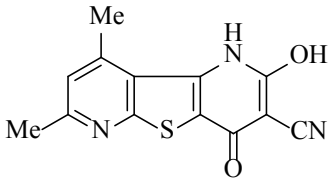


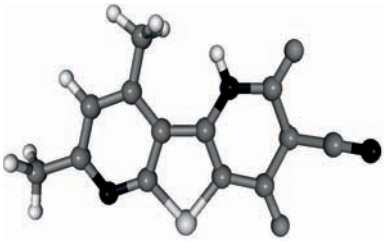
10B



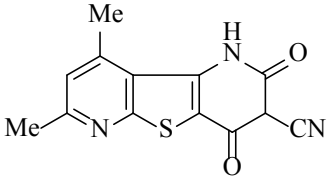


10C





10D



b]pyridin-3-yl)cyanoacetamides are now in progress. *In silico* analysis of possible biological activity of the synthesized compounds indicated correspondence to bioavailability criteria for oral administration and probable broad spectrum of action.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.4 MHz using DMSO-d_6 as solvent; the chemical shifts were measured relative to the residual proton signal of the solvent or tetramethylsilane. The IR spectra were recorded on Thermo Nicolet Magna 750 IR and LOMO IKS-29 (**3**, **10**) instruments from samples prepared as KBr pellets. The HPLC/MS analysis was performed with a Shimadzu LC-10AD liquid chromatograph equipped with Shimadzu SP D-10A UV–Vis (λ 254 nm) and Sedex 75 ELSD detectors and coupled with a PE SCIEX API 150EX mass spectrometer (ES-API, positive ion detection). The elemental compositions were determined using a Carlo Erba 1106 elemental analyzer. The purity of the synthesized compounds was checked by TLC on Silufol UV254 plates using acetone–hexane (1 : 1) as eluent; spots were visualized by treatment with iodine vapor or under UV light.

Initial 1-(cyanoacetyl)-3,5-dimethylpyrazole (**1**) was synthesized from cyanoacetohydrazide and acetylacetone according to the procedure described in [47].

3-[(Cyanoacetyl)amino]thieno[2,3-*b*]pyridine-2-carboxylates 3a and 3b (*general procedure*). A hot solution of 15 mmol of thienopyridine **2a** or **2b** in 25–30 mL of anhydrous toluene was added dropwise to a solution of 3.00 g (18.4 mmol) of 1-(cyanoacetyl)-3,5-

Table 2. Toxicity risks and physicochemical characteristics of compounds **3a**, **3b**, and **10**, predicted by OSIRIS Property Explorer

Comp. no.	Toxicity risks[a]				Physicochemical parameters					
	mutagenicity	oncogenicity	rritant	reproductive effects	cLog*P*	log*S*	MW	TPSA	drug likeness	drug Score
3a	–	–	–	–	2.24	–4.81	317.0	120.3	–7.53	0.36
3b	–	–	–	–	2.71	–5.21	343.0	120.3	–12.79	0.322
10	–	–	–	–	2.11	–4.64	271.0	118.2	–5.36	0.376

[a] "–" No toxicity prediction.

Table 3. ADMET parameters and biological activity of compounds **3a**, **3b**, and **10**, predicted by SwissADME and SwissTargetPrediction[a]

Comp. no.	Gastrointestinal absorption	BBB permeability	Cytochrome P450 inhibition					Probable targets	Bioavailability inde
			CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4		
3a	High	–	+	+	+	–	–	MAPT, TDP2	0.55
3b	High	–	+	+	+	–	+	MAPT, MBNL1, MBNL2, MBNL3	0.55
10	High	–	+	–	+	–	+	MBNL1, MBNL2, MBNL3	0.55

[a] The signs "+" or "–" denote the presence or absence of effect.

dimethylpyrazole **1** in 10 mL of anhydrous toluene. The resulting solution was refluxed for 5 h (TLC); after ~20 min, the product began to precipitate. The mixture was cooled, and the white solid was filtered off, washed with toluene and ethanol, and dried.

Ethyl 3-[(cyanoacetyl)amino]-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxylate (3a). Yield 71%, colorless crystals pourly soluble in acetone and insoluble in boiling ethanol. An analytical sample was obtained by recrystallization from ethanol–acetic acid (1 : 3). IR spectrum, ν, cm^{-1}: 3240 br (N–H), 2250 w (C≡N), 1715 s and 1670 s (C=O). ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, ^3J = 6.9 Hz), 2.55 s (3H, CH_3), 2.58 s (3H, CH_3), 3.96 s (2H, CH_2CN), 4.31 q (2H, OCH_2, ^3J = 6.9 Hz), 7.19 s (1H, 5-H), 10.35 s (1H, NH). Found, %: C 56.73; H 4.85; N 13.21. $C_{15}H_{15}N_3O_3S$. Calculated, %: C 56.77; H 4.76; N 13.24.

Methyl 3-[(cyanoacetyl)amino]-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxylate (3b). Yield 70%, colorless crystals. IR spectrum, ν, cm^{-1}: 3250 br (N–H), 2250 w (C≡N), 1710 s and 1665 s (C=O). ^{1}H NMR spectrum, δ, ppm: 1.70–1.82 m (2H, CH_2), 1.85–1.90 m (2H, CH_2), 2.85–2.87 m (2H, CH_2), 2.94–2.97 m (2H, CH_2), 3.76 s (3H, OCH_3), 4.01 s (2H, CH_2CN), 8.26 s (1H, 4-H), 10.40 s (1H, NH). Found, %: C 58.30; H 4.65; N 12.71. $C_{16}H_{15}N_3O_3S$. Calculated, %: C 58.34; H 4.59; N 12.76.

Reaction of compound 3a with 2-(4-methoxybenzylidene)malononitrile (4a) in the presence of morpholine. Morpholine, 1.0 mL (0.011 mol), was added to

a mixture of 427 mg (1.345 mmol) of cyanoacetamide **3a** and 287 mg (1.56 mmol) of dinitrile **4a** in 15 mL of ethanol. The mixture was refluxed with stirring for 2 h; amide **3a** gradually dissolved, and the product began to precipitate after ~30 min. The mixture was cooled, and the precipitate was filtered off, washed with ethanol, and dried. The product was 370 mg of green–brown finely crystalline solid poorly soluble in ethanol and acetone. According to the ^{1}H NMR and HPLC/MS data, it was a mixture of ethyl 3-[6-amino-3,5-dicyano-4-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-4,6-dimethylthieno[2,3-*b*]-pyridine-2-carboxylate (**8a**), 3-(4-methoxyphenyl)-9,11-dimethyl-1,6-dioxo-5,6-dihydro-1*H*-pyrido[1,2-*a*]pyrido[3′,2′ : 4,5]thieno[2,3-*e*]pyrimidine-2,4-dicarbonitrile (**9a**), and 2,4-dihydroxy-7,9-dimethylthieno[2,3-*b* : 4,5-*b*′]dipyridine-3-carbonitrile (**10**) at a molar ratio of ~100 : 24 : 61. Yield ~36% (**8a**), ~9% (**9a**), ~22% (**10**). ^{1}H NMR spectrum (identified signals), δ, ppm: **8a**: 1.28 t (3H, $CH_2C\mathbf{H}_3$, ^3J = 7.0 Hz), 2.32 s (3H, CH_3), 2.62 s (3H, CH_3), 3.88 s (3H, MeO), 4.31 q (2H, OCH_2, ^3J = 7.0 Hz), 7.12 d (2H, *m*-H, ^3J = 8.3 Hz), 7.24 s (1H, 5-H), 7.54 d (2H, *o*-H, ^3J = 8.3 Hz), 8.36 br.s (2H, NH_2); **9a**: 2.61 s (3H, CH_3), 2.97 s (3H, CH_3), 3.87 s (3H, MeO), 7.26 s (1H, 5-H), 8.02 d (2H, *o*-H, ^3J = 8.8 Hz); **10**: 2.59 s (3H, CH_3), 2.91 s (3H, CH_3), 6.28*[1] br.s (1H, OH), 7.19 s (1H, 5-H), 11.44* br.s (OH, NH). Mass spectrum, *m*/*z*: 272.5 $[M + H]^+$ (**10**), 389.3 $[M - MeOC_6H_4 + MeCN + H]^+$ (**9a**), 472.0 $[M + NH_4]^+$ (**9a**), 500.5 $[M + H]^+$ (**8a**), 543.3 $[2M + H]^+$ (**10**), 999.3 $[2M + H]^+$ (**8a**).

Reaction of compound 3a with 2-(4-methoxybenzylidene)malononitrile (4a) in the presence of potassium hydroxide. Powdered potassium hydroxide, 110 mg (1.96 mmol), was added to a suspension of 291 mg (0.92 mmol) of cyanoacetamide **3a** and 169 mg (0.92 mmol) of dinitrile **4a** in 2.5 mL of DMF. The mixture was heated to the boiling point, and the resulting red–orange solution was heated for 3–4 min with stirring. The product precipitated during this period. The mixture was cooled and treated in succession with 1 mL of acetic acid and 1 mL of 10% aqueous HCl. The precipitate was filtered off, washed with ethanol, and dried. The product was 320 mg of yellow–orange powder poorly soluble in EtOH, DMSO, and acetone. According to the ^{1}H NMR and HPLC/MS data, it was a mixture of **8a** and **10** at a ratio of ~1 : 1. Yield ~45% (**8a**), ~45% (**10**). Traces (<5%) of **9a** and ethyl 3-[6-amino-3,5-dicyano-4-(4-methoxyphenyl)-2-oxo-3,4-dihydropyridin-1(2*H*)-yl]-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxylate (**11a**) were also detected by HPLC/MS. IR spectrum, ν, cm^{-1}: 3509 br, 3273 br, 3150 br (N–H, O–H); 2227 s, 2212 s (C≡N); 1723 s, 1672 s (C=O). ^{1}H NMR spectrum (identified signals), δ, ppm: **8a**: 1.23 t (3H, $CH_2C\mathbf{H}_3$, ^3J = 7.0 Hz), 2.30 s (3H, CH_3), 2.61 s (3H, CH_3), 3.86 s (3H, MeO), 4.30 q (2H, OCH_2, ^3J = 7.0 Hz), 7.14 d (2H, *m*-H, ^3J = 8.3 Hz), 7.30 s (1H, 5-H), 7.57 d (2H, *o*-H, ^3J = 8.3 Hz), 8.47 br. s (2H, NH_2); **10**: 2.56 s (3H, CH_3), 2.88 s (3H, CH_3), 7.22 s (1H, 5-H). Mass spectrum, *m*/*z*: 273.1 $[M + H]^+$ (**10**), 453.8 $[M + H]^+$ (**9a**), 472.0 $[M + NH_4]^+$ (**9a**), 500.3 $[M + H]^+$ (**8a**), 502.0 $[M + H]^+$ (**11a**), 543.0 $[2M + H]^+$ (**10**), 813.8 $[3M + H]^+$ (**10**), 999.0 $[2M + H]^+$ (**8a**), 1001.0 $[2M + H]^+$ (**11a**), 1084.9 $[4M + H]^+$ (**10**).

Reaction of compound 3a with 2-benzylidenemalononitrile (4b) in the presence of potassium hydroxide. Powdered potassium hydroxide, 110 mg (1.96 mmol), was added to a suspension of 251 mg (0.79 mmol) of cyanoacetamide **3a** and 197 mg (1.28 mmol) of dinitrile **4b** in 10 mL of ethanol. The mixture was heated to the boiling point, and the resulting yellow solution was refluxed for 25 min with stirring. The product precipitated from the solution during the process. The mixture was cooled and treated in succession with 1 mL of acetic acid and 1 mL of 10% aqueous HCl, and the precipitate was filtered off, washed with ethanol, and dried. The product was 89 mg of yellow–orange powder poorly soluble in ethanol and acetone. According to the ^{1}H NMR and HPLC/MS data, it was a mixture of compound **10**, 9,11-dimethyl-1,6-dioxo-3-phenyl-5,6-dihydro-1*H*-pyrido[1,2-*a*]pyrido[3′,2′ : 4,5]thieno[2,3-*e*]pyrimidine-2,4-dicarbonitrile (**9b**), and 9,11-dimethyl-1,6-dioxo-3-phenyl-2,3,5,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrido[3′,2′ : 4,5]thieno[2,3-*e*]pyrimidine-2,4-dicarbonitrile (**12b**) at a molar ratio of ~2.5 : 2 : 9. Yield ~5% (**10**), ~4% (**9b**), ~19% (**12b**). The product also contained ~3–4 mol % of **8b** and/or **11b** (^{1}H NMR: δ 1.22 ppm, t, ^3J = 7.0 Hz). ^{1}H NMR spectrum (identified signals), δ, ppm: **9b**: 2.61 s (3H, CH_3), 2.96 s (3H, CH_3), 7.24 s (1H, 5-H), 7.65–7.66 m (3H, Ph), 7.99–8.01 m (2H, Ph); **10**: 2.58 s (3H, CH_3), 2.92 s (3H, CH_3), 6.20* br.s (1H, OH), 7.19 s (1H, 5-H); **12b**: 2.58 s (3H, CH_3), 2.90 s (3H, CH_3), 3.96 d (CHCN, 1H, ^3J = 12.4 Hz), 7.15 s (1H, 5-H), 7.53–7.59 m (5H, Ph), 10.07* br.s (1H, NH). Mass spectrum, *m*/*z*: 261.6 $[M - 164]^+$ (**12b**), 272.5 $[M + H]^+$ (**10**), 359.8 $[M - NCCH{=}C{=}O + H]^+$ (**12b**), 398.5 $[M - CO + H]^+$ (**9b**), 413.8 $[M - 2HCN + MeCN + H]^+$ (**12b**), 424.5 $[M + H]^+$ (**9b**), 426.5 $[M + H]^+$ (**12b**),

[1] (*) The signal intensity is underestimated, presumably because of H–D exchange.

543.7 [2*M* + H]$^+$ (**10**), 717.5 [2*M* – 2 NCCH=C=O + H]$^+$ (**12b**), 795.5 [2*M* – 2CO + H]$^+$ (**12b**), 814.8 [3*M* + H]$^+$ (**10**), 825.8 [2 *M* – 4 HCN + 2 MeCN + H]$^+$ (**12b**), 847.3 [2*M* + H]$^+$ (**9b**).

2,4-Dihydroxy-7,9-dimethylthieno[2,3-*b*:4,5-*b′*]-dipyridine-3-carbonitrile (10). *a. Reaction of **3a** with 2-(4-nitrobenzylidene)malononitrile* (***4c***) *in the presence of KOH*. Powdered potassium hydroxide, 110 mg (1.96 mmol), was added to a suspension of 173 mg (0.55 mmol) of cyanoacetamide **3a** and 160 mg (0.80 mmol) of dinitrile **4c** in 10 mL of DMF. The mixture was refluxed for 1 h with stirring, and a solid precipitated. The mixture was cooled, treated in succession with 1 mL of acetic acid and 1 mL of 10% aqueous HCl, and the precipitate was filtered off, washed with ethanol, and dried. Yield 120 mg (81%), yellow powder poorly soluble in ethanol and acetone. IR spectrum, ν, cm^{-1}: 3500–3150 br (N–H, O–H), 2220 s (C≡N), 1650 s (C=O). ^{1}H NMR spectrum, δ, ppm: 2.59 s (3H, CH_3), 2.91 s (3H, CH_3), 6.12* br.s (1H, OH), 7.16 s (1H, 5-H), 11.58* br.s (OH or NH). Mass spectrum, *m*/*z*: 272.5 [*M* + H]$^+$, 543.5 [2*M* + H]$^+$, 815.0 [3*M* + H]$^+$. Found, %: C 57.64; H 3.48; N 15.33. $C_{13}H_9N_3O_2S$. Calculated, %: C 57.55; H 3.34; N 15.49.

b. *Intramolecular cyclization of **3a***. A hot solution of sodium isopropoxide, prepared from 100 mg (4.35 mmol) of sodium and 10 mL of anhydrous propan-2-ol, was added to a suspension of 330 mg (1.04 mmol) of cyanoacetamide **3a** in 8 mL of anhydrous propan-2-ol. The mixture was refluxed for 3 h with stirring, and it thickened due to formation of a gel-like sodium salt. The mixture was cooled and treated in succession with 1 mL of acetic acid and 1 mL of 10% aqueous HCl, and the light yellow solid was filtered off, washed with ethanol, and dried. Yield 233 mg (83%). The spectral characteristics of the product were identical to those of a sample prepared as described above in *a*.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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