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A new route to highly substituted thieno[2,3-*b*]pyridines *via* cascade heterocyclization of 2-acyl-1,1,3,3-tetracyanopropenide salts

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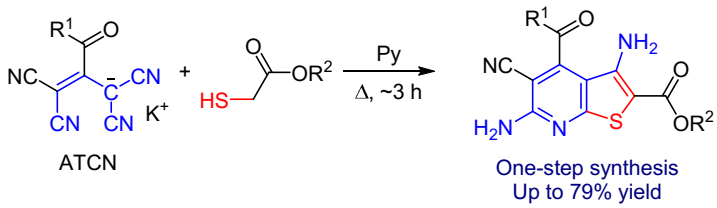


2-Acyl-1,1,3,3-tetracyanopropenides undergo cascade heterocyclization under the action of mercaptoacetic esters, leading to the formation of new 3,6-diamino-4-aroyl-5-cyanothieno[2,3-*b*]pyridine-2-carboxylates. The fast and convenient synthetic way to highly substituted thieno[2,3-*b*]pyridine scaffold is described.

Keywords: organic nitriles, tetracyanopropenides, thieno[2,3-*b*]pyridines, cyano group.

Currently, there is a considerable interest in the thieno-[2,3-*b*]pyridine molecular scaffolds. These compounds exhibit a broad range of biological activities, such as anticancer,[1] anti-inflammatory,[2] antiviral,[3] antimicrobial,[4] antidiabetic,[5] osteogenic,[6] and neuroprotective.[7,8] Additionally, representative compounds have been recognized as death-associated protein kinase inhibitors,[9] multidrug resistance,[10] and mGluR5 receptor[11] modulators.

The most popular routes for the synthesis of thieno[2,3-*b*]-pyridine core are the reaction between 2-aminothiophene-3-carbonitriles and 1,1-dimethoxy-*N*,*N*-dimethylethanamine,[1a] the alkylation of 2-thioxo-1,2-dihydropyridine-3-carbonitriles followed by Thorpe–Ziegler cyclization,[1b–d,2b,3b,5a,b,6b,7b,10,11,12] and the heteroannulation of 2-halonicotinonitriles using methyl/ethyl thioglycolate.[1g,9]

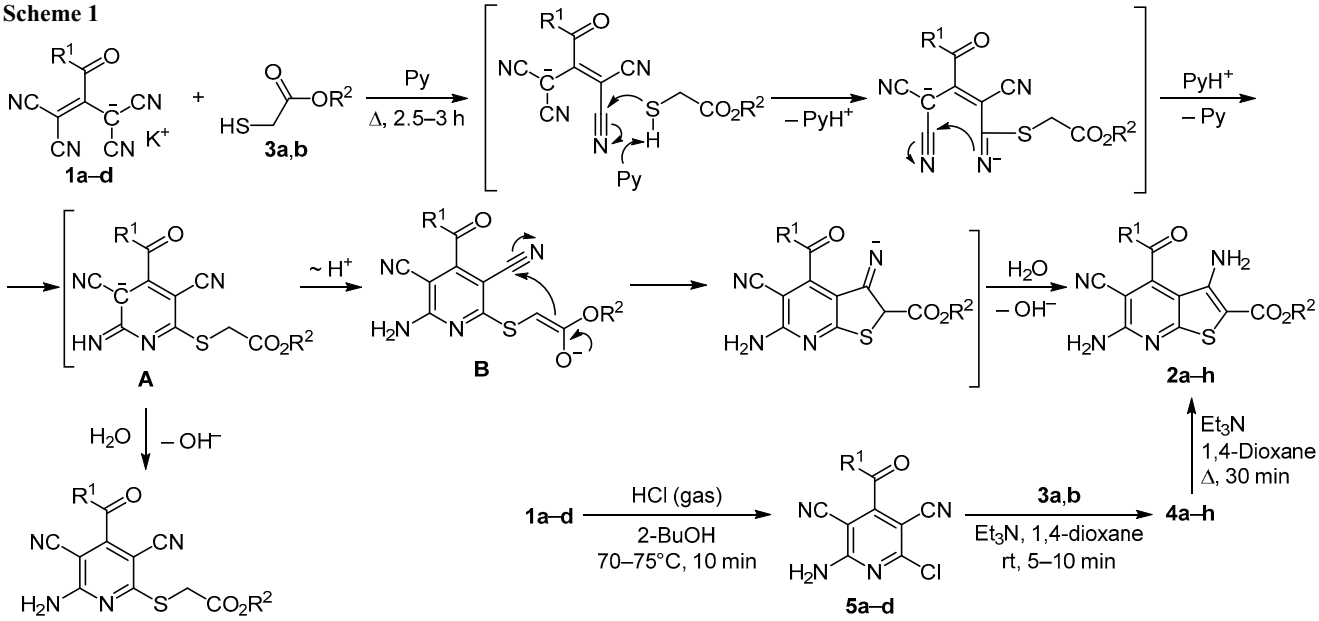
In this work, we described a fast and convenient synthesis of novel methyl/ethyl 3,6-diamino-4-aroyl-5-cyanothieno[2,3-*b*]pyridine-2-carboxylates. These compounds contain a carbonyl substituent in position 4 of the pyridine ring, which reveals broad opportunities for targeted annulation to pyridine [*d*]-bond and other modifications.

Thieno[2,3-*b*]pyridines **2** were obtained *via* the reaction of readily available potassium 2-acyl-1,1,3,3-tetracyanopropenides (ATCN)[13] **1** with mercaptoacetic esters **3** in pyridine (Scheme 1, Table 1). Pyridine was used as solvent, as stronger bases give rise to other products.[14] Using of weaker bases leads to low yields.[15] The method is limited to aromatic and heteroaromatic acyl groups, ATCN with aliphatic acyl groups produce dihydrofuran derivatives.[16] A proposed mechanism for this reaction involves nucleophilic addition of thiol to ATCN cyano group and subsequent Thorpe–Ziegler cyclization of the intermediate pyridine **B**.

The formation of intermediate alkyl 2-[(6-amino-4-aroyl-3,5-dicyanopyridin-2-yl)sulfanyl]acetates **A** was confirmed by decreasing refluxing time to 1 h. In this case, the resulting isolated precipitate contains a mixture of compounds **4** and **2** in variable ratio, according to ^{1}H NMR spectroscopy. In our opinion, the Thorpe–Ziegler cyclization proceeds significantly faster than formation of pyridine ring under reaction conditions.

However, compounds **4** can be obtained in 61−72% yields by the reaction between 2-amino-4-acyl-6-chloro-

Scheme 1



1, **5a**, **4a**,**b** R^1 = Ph; **1**, **5b**, **4c**,**d** R^1 = 4-MeC_6H_4; **1**, **5c**, **4e**,**f** R^1 = 4-$MeOC_6H_4$; **1**, **5d**, **4g**,**h** R^1 = 2-Thienyl; **3a**, **4a**,**c**,**e**,**g** R^2 = Me; **3b**, **4b**,**d**,**f**,**h** R^2 = Et

Table 1. Substituents and yields of alkyl 3,6-diamino-4-aroyl-5-cyanothieno[2,3-*b*]pyridine-2-carboxylates **2a**–**h**

Compound	R^1	R^2	Yield, %	
			One-step method*	Two-step method**
2a	Ph	Me	64	44
2b	Ph	Et	67	43
2c	4-MeC_6H_4	Me	76	38
2d	4-MeC_6H_4	Et	73	41
2e	4-$MeOC_6H_4$	Me	79	47
2f	4-$MeOC_6H_4$	Et	77	49
2g	2-Thienyl	Me	68	32
2h	2-Thienyl	Et	65	37

* ATCN **1** (10 mmol), mercaptoacetic ester **3** (15 mmol), pyridine (10 ml), reflux, 2.5–3 h.

** 1) Pyridine **4** (10 mmol), mercaptoacetic ester **3** (10 mmol), Et_3N (10 mmol), 1,4-dioxane (10 ml), rt, 5–10 min; 2) compound **4** (5 mmol), Et_3N (7 mmol), 1,4-dioxane (10 ml), reflux, 30 min. Yields are given for the conversion of compounds **1** to compounds **2**.

pyridine-3,5-dicarbonitriles **5**[17] and thioglycolates **3** in the presence of Et_3N (Scheme 1). This reaction was carried out in order to characterize compounds **4a**–**h**. Compounds **4a**–**h** can be readily transformed to thieno[2,3-*b*]pyridines **2a**–**h** by refluxing in 1,4-dioxane for ~30 min in the presence of Et_3N (Table 1).

The structure of compound **2f** was established by single crystal X-ray diffraction analysis (Fig. 1). The crystal is triclinic with the space group *P*-1. Intramolecular hydrogen bond lengths are 2.943 (N(4)···O(1)) and 2.788 Å (N(4)···O(3)). Each of the two molecules in the unit is connected into a centrosymmetric dimer *via* two intermolecular N(1)···H–N(2^i) hydrogen bonds with lengths 3.061 Å; symmetry codes: (i) 1 – *x*, 2 – *y*, –*z*.

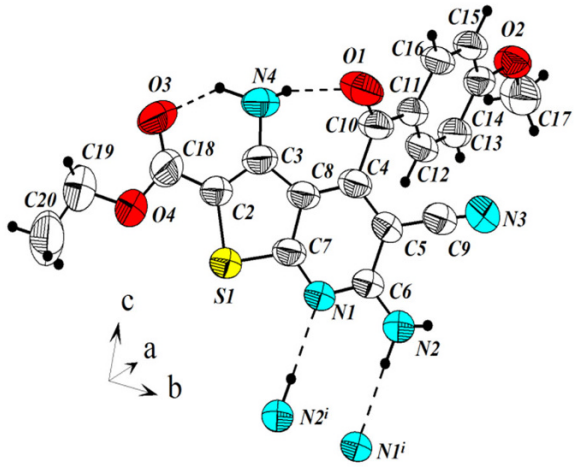


Figure 1. Molecular structure of compound **2f** with atoms represented by thermal vibration ellipsoids of 50% probability.

In conclusion, the novel methyl/ethyl 3,6-diamino-4-aroyl-5-cyanothieno[2,3-*b*]pyridine-2-carboxylates were obtained *via* two routes. The one-step synthesis *via* refluxing a mixture of 2-acyl-1,1,3,3-tetracyanopropenides with thioglycolates is a more convenient procedure due to the exclusion of isolation of intermediates, which positively affects the yield. Due to their structure, the obtained thieno[2,3-*b*]pyridines may be interesting in the targeted synthesis of biologically active compounds.

Experimental

IR spectra were recorded in samples dispersed in mineral oil on a OKB Spectr FTIR spectrophotometer FSM-1202. ^1H and ^{13}C NMR spectra were registered on a Bruker Avance III HD spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, internal standard was TMS.

Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (electron impact energy 70 eV). Elemental analysis was performed on a varioMICROcube CHN-analyzer. Melting points were determined using an Electrothermal IA 9000 series II apparatus. The reaction progress and purity of the obtained compounds were controlled by TLC on Sorbfil PTSH-AF-A-UF plates (eluent EtOAc), visualization under UV light, with iodine vapor, or thermal decomposition.

Synthesis of alkyl 3,6-diamino-4-aroyl-5-cyanothieno-[2,3-*b*]pyridine-2-carboxylates 2a–h (General methods). Method I: one-step. Potassium ATCN **1a**–**d** (10 mmol) and mercaptoacetic ester **3a**,**b** (15 mmol) were dissolved in pyridine (10 ml). The reaction mixture was refluxed for 2.5–3 h (TLC control), then cooled and poured into saturated aqueous KCl (50 ml). The dark-orange precipitate was filtered off, recrystallized from AcOH, and dried *in vacuo*.

Method II: two-step. 4-Acyl-2-amino-6-chloropyridine-3,5-dicarbonitrile **5a**–**d** (10 mmol), prepared by a published method,[17] mercaptoacetic ester **3a**,**b** (10 mmol), and Et_3N (1.0 g, 10 mmol) were dissolved in 1,4-dioxane (10 ml). The reaction mixture was stirred at room temperature for 5–10 min (TLC control), then poured into water (30 ml). The white alkyl 2-[(6-amino-4-aroyl-3,5-dicyanopyridin-2-yl)sulfanyl]acetate **4a**–**h** was filtered off, recrystallized from AcOH–H_2O, 1:1, and dried *in vacuo*. Compound **4a**–**h** (5 mmol) and Et_3N (0.7 g, 7.0 mmol) were dissolved in 1,4-dioxane (10 ml). The reaction mixture was refluxed for 30 min (TLC control), then cooled and poured into water (30 ml). The dark-orange precipitate **2a**–**h** was filtered off, recrystallized from AcOH, and dried *in vacuo*.

Methyl 3,6-diamino-4-benzoyl-5-cyanothieno[2,3-*b*]-pyridine-2-carboxylate (2a). Yield 64% (method I), 44% (method II), orange powder, mp 258–259°C (decomp.). IR spectrum, ν, cm^{-1}: 3343 (NH_2), 3279 (NH_2), 2221 (CN), 1752 (CO_2Me), 1672 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.71 (3H, s, OCH_3); 5.83 (2H, s, NH_2); 7.61 (2H, t, *J* = 7.2, H Ph); 7.73 (2H, br. s, NH_2); 7.81 (1H, t, *J* = 6.7, H Ph); 7.91 (2H, d, *J* = 7.3, H Ph). ^{13}C NMR spectrum, δ, ppm: 51.9; 86.6; 92.3; 112.3; 115.0; 130.0; 130.6; 134.6; 136.5; 147.4; 149.8; 158.9; 164.8; 165.8; 193.7. Mass spectrum, *m*/*z* (I_{rel}, %): 352 $[M]^+$ (24), 337 $[M–CH_3]^+$ (7), 321 $[M–CH_3O]^+$ (6), 277 (23), 105 $[C_6H_5CO]^+$ (42), 77 $[C_6H_5]^+$ (100). Found, %: C 57.99; H 3.45; N 15.86. $C_{17}H_{12}N_4O_3S$. Calculated, %: C 57.95; H 3.43; N 15.90.

Ethyl 3,6-diamino-4-benzoyl-5-cyanothieno[2,3-*b*]-pyridine-2-carboxylate (2b). Yield 67% (method I), 43% (method II), orange powder, mp 234–236°C (decomp.). IR spectrum, ν, cm^{-1}: 3339 (NH_2), 3286 (NH_2), 2227 (CN), 1758 (CO_2Et), 1664 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.1, CH_3); 4.19 (2H, q, *J* = 7.1, OCH_2); 5.82 (2H, s, NH_2); 7.61 (2H, t, *J* = 7.8, H Ph); 7.72 (2H, br. s, NH_2); 7.80 (1H, t, *J* = 7.4, H Ph); 7.90 (2H, d, *J* = 7.4, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.8; 60.6; 86.9; 92.6; 112.4; 115.0; 130.0; 130.6; 134.6; 136.4; 147.3; 149.7; 158.8; 164.5; 165.7; 193.7. Mass spectrum, *m*/*z* (I_{rel}, %): 366 $[M]^+$ (26), 338 $[M–C_2H_4]^+$ (8), 321 $[M–C_2H_5O]^+$ (5), 291 (21), 105 $[C_6H_5CO]^+$ (46), 77 $[C_6H_5]^+$ (100). Found, %: C 58.85; H 3.87; N 15.18. $C_{18}H_{14}N_4O_3S$. Calculated, %: C 59.01; H 3.85; N 15.29.

Methyl 3,6-diamino-5-cyano-4-(4-methylbenzoyl)thieno-[2,3-*b*]pyridine-2-carboxylate (2c). Yield 76% (method I), 38% (method II), yellow powder, mp 271–272°C (decomp.). IR spectrum, ν, cm^{-1}: 3336 (NH_2), 3269 (NH_2), 2218 (CN), 1746 (CO_2Me), 1670 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.41 (3H, s, CH_3); 3.71 (3H, s, OCH_3); 5.82 (2H, s, NH_2); 7.41 (2H, d, *J* = 8.0, H Ar); 7.71 (2H, br. s, NH_2); 7.80 (2H, d, *J* = 8.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.0; 51.9; 86.6; 92.1; 112.3; 115.1; 130.6; 130.8; 132.2; 147.4; 147.7; 150.0; 158.9; 164.8; 165.7; 193.0. Mass spectrum, *m*/*z* (I_{rel}, %): 366 $[M]^+$ (21), 351 $[M–CH_3]^+$ (6), 335 $[M–CH_3O]^+$ (5), 291 (19), 119 $[CH_3C_6H_4CO]^+$ (43), 91 $[CH_3C_6H_4]^+$ (100). Found, %: C 58.89; H 3.88; N 15.20. $C_{18}H_{14}N_4O_3S$. Calculated, %: C 59.01; H 3.85; N 15.29.

Ethyl 3,6-diamino-5-cyano-4-(4-methylbenzoyl)thieno-[2,3-*b*]pyridine-2-carboxylate (2d). Yield 73% (method I), 41% (method II), yellow powder, mp 252–253°C (decomp.). IR spectrum, ν, cm^{-1}: 3328 (NH_2), 3289 (NH_2), 2213 (CN), 1739 (CO_2Et), 1666 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.1, CH_3); 2.40 (3H, s, CH_3); 4.18 (2H, q, *J* = 7.0, OCH_2); 5.81 (2H, s, NH_2); 7.41 (2H, d, *J* = 8.0, H Ar); 7.71 (2H, br. s, NH_2); 7.80 (2H, d, *J* = 8.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 14.8; 21.9; 60.6; 86.6; 92.5; 112.4; 115.1; 130.6; 130.8; 132.2; 147.3; 147.7; 149.9; 158.9; 164.5; 165.7; 193.1. Mass spectrum, *m*/*z* (I_{rel}, %): 380 $[M]^+$ (65), 352 $[M–C_2H_4]^+$ (12), 335 $[M–C_2H_5O]^+$ (5), 305 (37), 119 $[CH_3C_6H_4CO]^+$ (54), 91 $[CH_3C_6H_4]^+$ (100). Found, %: C 59.86; H 4.26; N 14.63. $C_{19}H_{16}N_4O_3S$. Calculated, %: C 59.99; H 4.24; N 14.73.

Methyl 3,6-diamino-5-cyano-4-(4-methoxybenzoyl)-thieno[2,3-*b*]pyridine-2-carboxylate (2e). Yield 79% (method I), 47% (method II), orange powder, mp 275–276°C (decomp.). IR spectrum, ν, cm^{-1}: 3331 (NH_2), 3292 (NH_2), 2224 (CN), 1751 (CO_2Me), 1682 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.71 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 5.84 (2H, s, NH_2); 7.12 (2H, d, *J* = 8.9, H Ar); 7.68 (2H, br. s, NH_2); 7.87 (2H, d, *J* = 8.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 51.9; 56.4; 86.7; 91.9; 112.2; 115.1; 115.4; 127.6; 133.4; 147.4; 150.1; 158.9; 164.8; 165.7; 165.8; 191.5. Mass spectrum, *m*/*z* (I_{rel}, %): 382 $[M]^+$ (20), 367 $[M–CH_3]^+$ (9), 351 $[M–CH_3O]^+$ (7), 307 (28), 135 $[CH_3OC_6H_4CO]^+$ (37), 107 $[CH_3OC_6H_4]^+$ (100). Found, %: C 56.39; H 3.72; N 14.52. $C_{18}H_{14}N_4O_4S$. Calculated, %: C 56.54; H 3.69; N 14.65.

Ethyl 3,6-diamino-5-cyano-4-(4-methoxybenzoyl)-thieno[2,3-*b*]pyridine-2-carboxylate (2f). Yield 77% (method I), 49% (method II), yellow powder, mp 238–239°C (decomp.). IR spectrum, ν, cm^{-1}: 3334 (NH_2), 3286 (NH_2), 2230 (CN), 1748 (CO_2Et), 1681 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.1, CH_3); 3.87 (3H, s, OCH_3); 4.18 (2H, q, *J* = 7.1, OCH_2); 5.82 (2H, s, NH_2); 7.11 (2H, d, *J* = 8.9, H Ar); 7.68 (2H, br. s, NH_2); 7.87 (2H, d, *J* = 8.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 14.8; 56.4; 60.5; 86.7; 92.3; 112.3; 115.1; 115.4; 127.6; 133.4; 147.3; 150.1; 158.9; 164.5; 165.7; 165.8; 191.5. Mass spectrum, *m*/*z* (I_{rel}, %): 396 $[M]^+$ (54), 368 $[M–C_2H_4]^+$ (6), 351 $[M–C_2H_5O]^+$ (4), 321 (15), 135 $[CH_3OC_6H_4CO]^+$

(51), 107 $[CH_3OC_6H_4]^+$ (100). Found, %: C 57.46; H 4.08; N 14.04. $C_{19}H_{16}N_4O_4S$. Calculated, %: C 57.57; H 4.07; N 14.13.

Methyl 3,6-diamino-5-cyano-4-(thiophene-2-carbonyl)-thieno[2,3-*b*]pyridine-2-carboxylate (2g). Yield 68% (method I), 32% (method II), orange powder, mp 243–244°C (decomp.). IR spectrum, ν, cm^{-1}: 3343 (NH_2), 3266 (NH_2), 2225 (CN), 1741 (CO_2Me), 1662 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.72 (3H, s, OCH_3); 5.93 (2H, s, NH_2); 7.30 (1H, t, *J* = 4.4, H thienyl); 7.72 (2H, s, NH_2); 7.82 (1H, d, *J* = 3.9, H thienyl); 8.37 (1H, d, *J* = 4.8, H thienyl). ^{13}C NMR spectrum, δ, ppm: 51.9; 87.0; 92.2; 112.0; 115.1; 130.4; 140.2; 140.9; 141.3; 147.3; 148.8; 158.9; 164.8; 165.8; 185.1. Mass spectrum, *m*/*z* (I_{rel}, %): 358 $[M]^+$ (29), 343 $[M–CH_3]^+$ (10), 327 $[M–CH_3O]^+$ (8), 283 (19), 111 $[C_5H_3SCO]^+$ (51), 83 $[C_5H_3S]^+$ (100). Found, %: C 50.17; H 2.83; N 15.49. $C_{15}H_{10}N_4O_3S_2$. Calculated, %: C 50.27; H 2.81; N 15.63.

Ethyl 3,6-diamino-5-cyano-4-(thiophene-2-carbonyl)-thieno[2,3-*b*]pyridine-2-carboxylate (2h). Yield 65% (method I), 37% (method II), yellow powder, mp 234–235°C (decomp.). IR spectrum, ν, cm^{-1}: 3334 (NH_2), 3270 (NH_2), 2228 (CN), 1749 (CO_2Et), 1671 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.1, CH_3); 4.19 (2H, q, *J* = 7.1, OCH_2); 5.91 (2H, s, NH_2); 7.23–7.35 (1H, m, H thienyl); 7.72 (2H, br. s, NH_2); 7.81 (1H, d, *J* = 3.1, H thienyl); 8.37 (1H, d, *J* = 4.8, H thienyl). ^{13}C NMR spectrum, δ, ppm: 14.8; 60.6; 87.0; 92.6; 112.1; 115.1; 130.4; 140.1; 140.9; 141.3; 147.2; 148.8; 158.9; 164.5; 165.8; 185.1. Mass spectrum, *m*/*z* (I_{rel}, %): 372 $[M]^+$ (51), 344 $[M–C_2H_4]^+$ (9), 327 $[M–C_2H_5O]^+$ (6), 297 (19), 110 $[C_5H_3SCO]^+$ (56), 83 $[C_5H_3S]^+$ (100). Found, %: C 51.50; H 3.27; N 14.94. $C_{19}H_{12}N_4O_3S_2$. Calculated, %: C 51.60; H 3.25; N 15.04.

Methyl 2-[(6-amino-4-benzoyl-3,5-dicyanopyridin-2-yl)-sulfanyl]acetate (4a). Yield 69%, white powder, mp 209–210°C. IR spectrum, ν, cm^{-1}: 3330 (NH_2), 3226 (NH_2), 2223 (CN), 1751 (CO_2Me), 1632 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.69 (3H, s, OCH_3); 4.22 (2H, s, SCH_2); 7.63 (2H, t, *J* = 7.8, H Ph); 7.82 (1H, t, *J* = 7.4, H Ph); 7.95 (2H, d, *J* = 7.4, H Ph); 8.33 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 32.2; 53.1; 83.5; 89.9; 114.1; 114.3; 130.1; 130.5; 133.5; 136.5; 156.8; 159.5; 166.4; 168.8; 191.4. Mass spectrum, *m*/*z* (I_{rel}, %): 352 $[M]^+$ (52), 337 $[M–CH_3]^+$ (13), 279 $[M–CH_2CO_2CH_3]^+$ (17), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (19). Found, %: C 57.99; H 3.46; N 15.87. $C_{17}H_{12}N_4O_3S$. Calculated, %: C 57.95; H 3.43; N 15.90.

Ethyl 2-[(6-amino-4-benzoyl-3,5-dicyanopyridin-2-yl)-sulfanyl]acetate (4b). Yield 64%, white powder, mp 161–162°C. IR spectrum, ν, cm^{-1}: 3329 (NH_2), 3233 (NH_2), 2219 (CN), 1760 (CO_2Et), 1634 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.1, CH_3); 4.13 (2H, q, *J* = 7.0, OCH_2); 4.21 (2H, s, SCH_2); 7.63 (2H, t, *J* = 7.7, H Ph); 7.82 (1H, t, *J* = 7.4, H Ph); 7.94 (2H, d, *J*=7.7, H Ph); 8.32 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 14.5; 32.4; 61.9; 83.5; 90.0; 114.1; 114.3; 130.1; 130.5; 133.5; 136.5; 156.9; 159.5; 166.5; 168.2; 191.4. Mass spectrum, *m*/*z* (I_{rel}, %): 366 $[M]^+$ (48), 337 $[M–C_2H_4]^+$ (10), 279 $[M–CH_2CO_2C_2H_5]^+$ (23), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (21). Found, %: C 58.85; H 3.87; N 15.17. $C_{18}H_{14}N_4O_3S$. Calculated, %: C 59.01; H 3.85; N 15.29.

Methyl 2-{[6-amino-3,5-dicyano-4-(4-methylbenzoyl)-pyridin-2-yl]sulfanyl}acetate (4c). Yield 61%, white powder, mp 183–184°C. IR spectrum, ν, cm^{-1}: 3322 (NH_2), 3231 (NH_2), 2218 (CN), 1761 (CO_2Me), 1632 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.42 (3H, s, CH_3); 3.69 (3H, s, OCH_3); 4.21 (2H, s, SCH_2); 7.43 (2H, d, *J* = 8.1, H Ar); 7.85 (2H, d, *J* = 8.2, H Ar); 8.32 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.9; 32.2; 53.1; 83.5; 90.0; 114.2; 114.3; 130.6; 130.7; 131.1; 147.7; 157.1; 159.5; 166.4; 168.8; 190.8. Mass spectrum, *m*/*z* (I_{rel}, %): 366 $[M]^+$ (49), 351 $[M–CH_3]^+$ (10), 293 $[M–CH_2CO_2CH_3]^+$ (14), 119 $[CH_3C_6H_4]^+$ (100), 91 $[CH_3C_6H_4]^+$ (22). Found, %: C 59.06; H 3.88; N 15.20. $C_{18}H_{14}N_4O_3S$. Calculated, %: C 59.01; H 3.85; N 15.29.

Ethyl 2-{[6-amino-3,5-dicyano-4-(4-methylbenzoyl)-pyridin-2-yl]sulfanyl}acetate (4d). Yield 63%, white powder, mp 165–166°C. IR spectrum, ν, cm^{-1}: 3335 (NH_2), 3236 (NH_2), 2224 (CN), 1758 (CO_2Et), 1639 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.1, CH_3); 2.42 (3H, s, CH_3); 4.14 (2H, q, *J* = 7.1, OCH_2); 4.20 (2H, s, SCH_2); 7.43 (2H, d, *J* = 8.0, H Ar); 7.83 (2H, d, *J* = 8.1, H Ar); 8.29 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 14.5; 21.9; 32.4; 61.9; 83.5; 90.0; 114.2; 114.3; 130.6; 130.7; 131.2; 147.7; 157.1; 159.5; 166.5; 168.3; 190.8. Mass spectrum, *m*/*z* (I_{rel}, %): 380 $[M]^+$ (52), 351 $[M–C_2H_4]^+$ (12), 293 $[M–CH_2CO_2C_2H_5]^+$ (21), 119 $[CH_3C_6H_4]^+$ (100), 91 $[CH_3C_6H_4]^+$ (26). Found, %: C 59.79; H 4.27; N 14.62. $C_{19}H_{16}N_4O_3S$. Calculated, %: C 59.99; H 4.24; N 14.73.

Methyl 2-{[6-amino-3,5-dicyano-4-(4-methoxybenzoyl)-pyridin-2-yl]sulfanyl}acetate (4e). Yield 71%, white powder, mp 139–140°C. IR spectrum, ν, cm^{-1}: 3334 (NH_2), 3238 (NH_2), 2226 (CN), 1752 (CO_2Me), 1629 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 4.21 (2H, s, SCH_2); 7.13 (2H, d, *J* = 8.8, H Ar); 7.90 (2H, d, *J* = 8.7, H Ar); 8.28 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 32.2; 53.1; 56.4; 83.5; 90.0; 114.2; 114.4; 115.5; 126.5; 133.2; 157.4; 159.5; 165.8; 166.3; 168.9; 189.3. Mass spectrum, *m*/*z* (I_{rel}, %): 382 $[M]^+$ (56), 367 $[M–CH_3]^+$ (16), 309 $[M–CH_2CO_2CH_3]^+$ (19), 135 $[CH_3OC_6H_4CO]^+$ (100), 107 $[CH_3OC_6H_4]^+$ (12). Found, %: C 56.38; H 3.72; N 14.51. $C_{18}H_{14}N_4O_4S$. Calculated, %: C 56.54; H 3.69; N 14.65.

Ethyl 2-{[6-amino-3,5-dicyano-4-(4-methoxybenzoyl)-pyridin-2-yl]sulfanyl}acetate (4f). Yield 72%, white powder, mp 122–123°C. IR spectrum, ν, cm^{-1}: 3331 (NH_2), 3239 (NH_2), 2220 (CN), 1757 (CO_2Et), 1630 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.1, CH_3); 3.89 (3H, s, OCH_3); 4.14 (2H, q, *J* = 7.1, OCH_2); 4.20 (2H, s, SCH_2); 7.13 (2H, d, *J* = 8.9, H Ar); 7.90 (2H, d, *J* = 8.8, H Ar); 8.28 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 14.5; 32.4; 56.4; 61.9; 83.5; 90.1; 114.2; 114.4; 115.5; 126.5; 133.2; 157.4; 159.5; 165.8; 166.4; 168.3; 189.3. Mass spectrum, *m*/*z* (I_{rel}, %): 396 $[M]^+$ (51), 367 $[M–C_2H_4]^+$ (9), 309 $[M–CH_2CO_2C_2H_5]^+$ (17), 135 $[CH_3OC_6H_4CO]^+$ (100), 107 $[CH_3OC_6H_4]^+$ (25). Found, %: C 57.40; H 4.09;

N 14.04. $C_{19}H_{16}N_4O_4S$. Calculated, %: C 57.57; H 4.07; N 14.13.

Methyl 2-{[6-amino-3,5-dicyano-4-(thiophene-2-carbonyl)-pyridin-2-yl]sulfanyl}acetate (4g). Yield 64%, white powder, mp 119–120°C. IR spectrum, ν, cm^{-1}: 3336 (NH_2), 3229 (NH_2), 2217 (CN), 1760 (CO_2Me), 1636 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (3H, s, OCH_3); 4.21 (2H, s, SCH_2); 7.34 (1H, t, *J* = 4.4, H thienyl); 7.97 (1H, d, *J* = 3.7, H thienyl); 8.30 (2H, br. s, NH_2); 8.36 (1H, d, *J* = 4.8, H thienyl). ^{13}C NMR spectrum, δ, ppm: 32.2; 53.1; 83.6; 90.0; 114.1; 114.3; 130.4; 140.0; 140.2; 140.7; 156.1; 159.5; 166.4; 168.8; 183.0. Mass spectrum, *m*/*z* (I_{rel}, %): 358 $[M]^+$ (51), 343 $[M–CH_3]^+$ (15), 284 $[M–CH_2CO_2CH_3]^+$ (21), 111 $[C_5H_3SCO]^+$ (100), 83 $[C_5H_3S]^+$ (9). Found, %: C 50.16; H 2.83; N 15.52. $C_{15}H_{10}N_4O_3S_2$. Calculated, %: C 50.27; H 2.81; N 15.63.

Ethyl 2-{[6-amino-3,5-dicyano-4-(thiophene-2-carbonyl)-pyridin-2-yl]sulfanyl}acetate (4h). Yield 71%, white powder, mp 107–108°C. IR spectrum, ν, cm^{-1}: 3331 (NH_2), 3230 (NH_2), 2219 (CN), 1758 (CO_2Me), 1634 (COAr). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.2, CH_3); 4.16 (2H, q, *J* = 7.2, OCH_2); 4.22 (2H, s, SCH_2); 7.36 (1H, t, *J* = 4.3, H thienyl); 7.97 (1H, d, *J* = 3.9, H thienyl); 8.33 (2H, br. s, NH_2); 8.37 (1H, d, *J* = 4.7, H thienyl). ^{13}C NMR spectrum, δ, ppm: 14.5; 32.4; 61.9; 83.6; 90.1; 114.1; 114.3; 130.4; 139.9; 140.2; 140.6; 156.1; 159.5; 166.5; 168.2; 183.0. Mass spectrum, *m*/*z* (I_{rel}, %): 372 $[M]^+$ (48), 344 $[M–C_2H_4]^+$ (12), 285 $[M–CH_2CO_2C_2H_5]^+$ (19), 111 $[C_5H_3SCO]^+$ (100), 83 $[C_5H_3S]^+$ (8). Found, %: C 51.52; H 3.26; N 15.06. $C_{16}H_{12}N_4O_3S_2$. Calculated, %: C 51.60; H 3.25; N 15.04.

2-Amino-6-chloro-4-(thiophene-2-carbonyl)pyridine-3,5-dicarbonitrile (5d). Yield 76%, white powder, mp 255–257 °C (decomp.). IR spectrum, ν, cm^{-1}: 3211 (NH_2); 2217 (C≡N); 1662 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.38 (1H, dd, *J* = 4.2, *J* = 4.8, H Ar); 8.05 (1H, d, *J* = 3.8, H Ar); 8.40 (1H, d, *J* = 4.8, H Ar); 8.45 (1H, br. s) and 8.97 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 87.1; 96.2; 113.6; 115.3; 130.4; 138.0; 140.6; 141.0; 148.3; 157.2; 160.2; 182.3. Mass spectrum, *m*/*z* (I_{rel}, %): 290 $[M(^{37}Cl)]^+$ (5), 288 $[M(^{35}Cl)]^+$ (14), 111 $[C_4H_3SCO]^+$ (100), 116 (12), 83 $[C_4H_3S]^+$ (11). Found,%: C 49.98; H 1.79; N 19.51. $C_{12}H_5ClN_4OS$. Calculated, %: C 49.92; H 1.75; N 19.41.

X-ray structural investigation of compound 2f. A syngle crystal of compound **2f** for X-ray diffraction purposes was obtained by slow evaporation of acetic acid solution in air at room temperature. The X-ray data of compound **2f** collected by using a STOE diffractometer Pilatus100K detector, focusing mirror collimation, CuKα (1.54086 Å) radiation, rotation method mode. The STOE X-AREA 1.67 software was used for unit refinement and data reduction, as well as for the data collection and image processing. Intensity data were scaled with the LANA program (part of X-Area package) in order to minimize differences of intensities of symmetry-equivalent reflections (multiscan method). The structures were solved and refined with the SHELX[18] program. The non-hydrogen atoms were refined by using the anisotropic full-matrix least-square procedure. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared by using the DIAMOND[19] software. The complete X-ray structural data set for compound **2f** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1502502).

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