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Synthesis of Isomeric Isothiazolo[4′,3′:4,5]- and Isothiazolo[4′,5′:4,5]thieno[3,2-*b*]pyrano[2,3-*d*]pyridines by Combination of Domino Reactions

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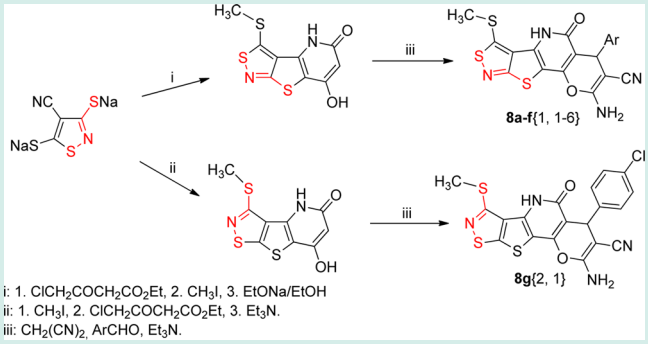
Supporting Information

ABSTRACT: Isothiazolothienopyridines have been prepared by a domino reaction (the S_N2 reaction → the Thorpe−Ziegler reaction → the Thorpe−Guareschi reaction type) from disodium 4-cyanoisothiazole-3,5-dithiolate. By changing the order of addition of the alkylation reagents in the reaction with disodium 4-cyanoisothiazole-3,5-dithiolate both possible isomers of the isothiazolothienopyridines are synthesized. These isomers were further used in three-component domino reaction (the Knoevenagel reaction → the Michael reaction → the hetero-Thorpe−Ziegler reaction type) to obtain wide range of isomeric isothiazolothienopyranopyridines.



KEYWORDS: *disodium 4-cyanoisothiazole-3,5-dithiolate, ethyl 4-chloroacetoacetate, isothiazoles, isothiazolothienopyranopyridines, domino reaction, regioselectivity*

INTRODUCTION

2-Amino-3-cyanopyrans, fused with heterocyclic rings, exhibit a broad range of biological activity, including antibacterial,[1−4] antifungal,[2,4,5] apoptosis induction,[6] and anticancer activity.[6−9] In continuation of our research of the domino reactions,[10,11] for the synthesis of fused heterocycles from vicinal mercaptonitriles and the ethyl 4-chloroacetoacetate, we used the disodium 4-cyanoisothiazole-3,5-dithiolate (**1**). The salt **1**[12,13] is a convenient reagent for synthesis of fused heterocyclic compounds. The significant difference in the values of negative charge of sulfur atoms is the unique property of this compound.[14]

The sulfur atom at position 3 and then at position 5 of isothiazole reacts with alkyl halides to give asymmetrically substituted isothiazoles.[14−16] Further Thorpe−Ziegler cyclization of alkylated isothiazole leads to isomeric thienoisothiazoles.[15,17] We used the properties of the salt **1** for synthesis of number isomeric isothiazolothienopyranopyridines.

RESULTS AND DISCUSSION

Alkylation of dithiolate **1** by ethyl 4-chloroacetoacetate (**2**) and then iodomethane (**3**) results in the compound **4a** in 57% yield, while the reverse order of addition of the alkyl halides **3** and **2** affords isomer **4b** in 52% yield. Treatment of the compound **4a** by the sodium ethylate in boiling ethanol leads to formation of the thienopiridine **5a** in 86% yield and short-time boiling of the compound **4b** in the triethylamine gives isomeric thienopiridine **5b** in 80% yield (Scheme 1, Method A).

The compounds **5a** and **b** were obtained by domino reactions: two S_N2 reactions → the Thorpe−Ziegler reaction → the Thorpe−Guareschi reaction (Scheme 1, Method A). The reaction of salt **1** with the alkyl halide regiospecifically leads to the monothiolates, which without isolation undergo the second S_N2 reaction with another alkyl halide and are converted to the corresponding isomers **4a** and **b**. Further treatment of the compounds **4a** and **b** by the base led to the compounds **5a** and **b** as a result of the Thorpe−Ziegler → Thorpe−Guareschi domino reactions.

The combination of domino reactions have allowed us to synthesize isomeric isothiazolothienopyridines **5a** and **5b** without isolation of intermediate isothiazoles **4a** and **4b** (Scheme1, Method B). Method B, though less labor-consuming than method A, gave significantly lower yields of the compounds **5a** and **5b** up to 21% and 14% accordingly.

The structures of compounds **4** were confirmed by IR spectra and ^{1}H NMR. IR spectra showed similar absorption bands of carbonyl and nitrile groups for both isomers, yet there were significant differences in "fingerprints" region. The ^{1}H

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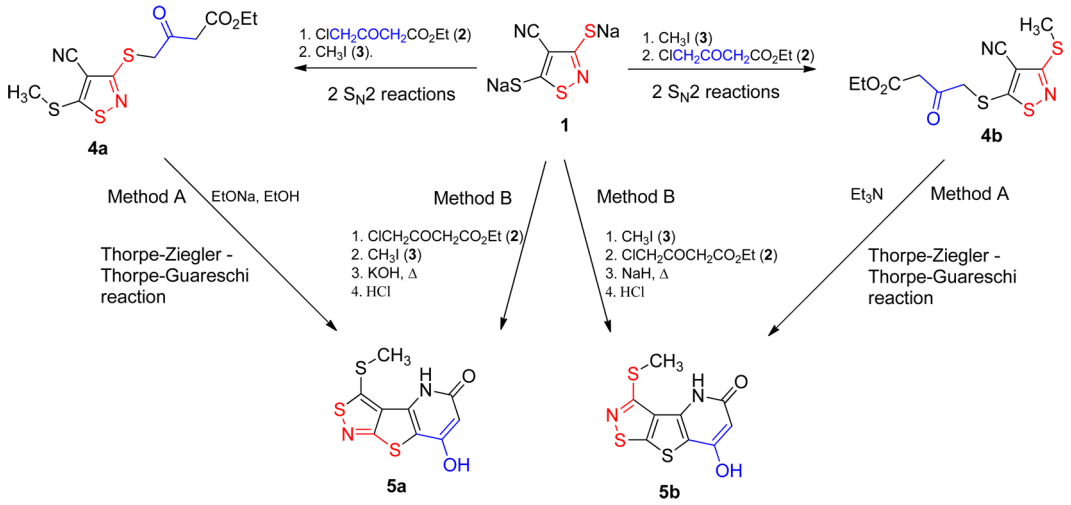
Scheme 1. Synthesis of Isomers of Isothiazolothienopyridines 5a and 5b



NMR spectra of the compounds **4a** and **4b** contained same sets of signals with same multiplicity but the chemical shifts of protons differed markedly. The chemical shifts of SCH_3 group differed by 0.14 ppm and those of $SCH_2C(O)$ group differed by 0.17 ppm. Both signals are singlets without doubling that confirms absence of the second isomer, and it is sufficient proof for regioselectivity of the reaction. The compounds **4a** and **b** are white low-melting powders. The melting point of **4b** is 18 °C less than that of **4a**.

The structures of the compounds **4a** and **4b** were also unambiguously determined by single-crystal XRD studies (Figures 1 and 2).

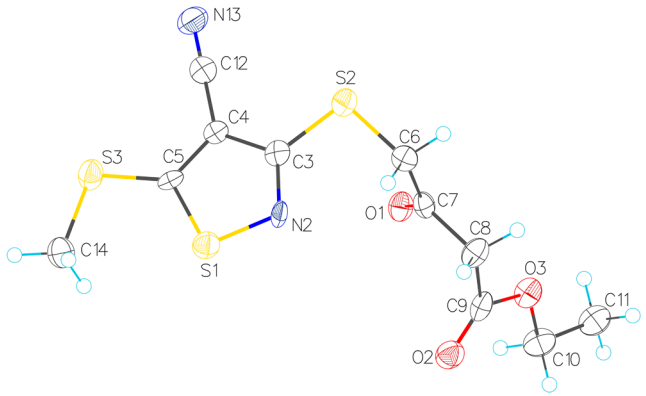


Figure 1. General view of **4a** in crystal. Atoms are represented by thermal displacement ellipsoids (p = 50%).

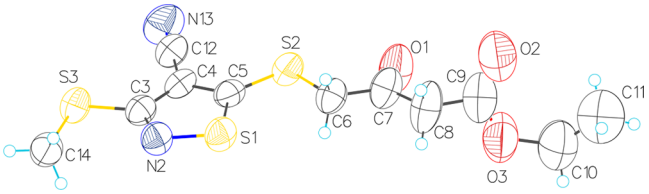


Figure 2. General view of **4b** in crystal. Atoms are represented by thermal displacement ellipsoids (p = 50%). Only one orientation of the disordered C(O)OEt group is shown.

The crystals of **4b** could not be measured at 100 K because of a phase transition, which led to doubling of the c parameter and partial destruction of the crystals, making the R_1-value too high. Thus, the measurements were performed at room temperature. The C(O)OEt group of **4b** was disordered, with relative occupancies of two positions 0.516(7)/0.484(7).

In contrast to the compound **5b**, the compound **5a** has no sharp melting point and decomposes above 300 °C. The ^{1}H NMR data of the compounds **5a** and **5b** showed different chemical shifts for the methylmercapto group (0.16 ppm) and for the protons of pyridine cycle (0.09 ppm). The IR spectrum of the compounds **5a** and **5b** showed essential difference in "fingerprints" region. The compound **5a** has two broad bands at 1645 and 1563 cm^{-1} corresponding to stretching vibrations of CONH (amide I band).[18] These bands of the compound **5b** are shifted to 1601 and 1543 cm^{-1}, respectively.

The synthetic potential for compounds **5a**{*1*} and **5b**{*2*} because the dihydropyridinone fragment[10,16] allowed us to use these compounds in the combinatorial synthesis of the pyranopyridines **8a**−**8g** via a domino reaction sequence of the Knoevenagel → the Michael → the hetero-Thorpe−Ziegler type.

The three-component reaction of the thienopyridine **5a**{*1*} with the malononitrile (**6**) and aromatic aldehydes **7a**−**7f**{*1*−*6*} led to the 2-amino-4-aryl-7-(methylthio)-5-oxo-5,6-dihydro-4*H*-isothiazolo[4′,3′:4,5]thieno[3,2-*b*]pyrano[2,3-*d*]pyridine-3-carbonitriles (**8a**−**8f**){*1,1*−*6*} in high yields (75−88%). Isomer of **8a**{1,1}-2-amino-4-(4-chlorophenyl)-7-(methylthio)-5-oxo-5,6-dihydro-4*H*-isothiazolo[4′,5′:4,5]thieno[3,2-*b*]pyrano[2,3-*d*]pyridine-3-carbonitrile (**8g**){*2,1*} was prepared under similar conditions from the thienopyridine **5b** (Scheme 2).

Fused pyrans **8a**−**8g** are high-melting powders. ^{1}H NMR spectra of the compounds **8a**−**8g** showed signals of methylthio group, aromatic proton, proton of the pyran cycle (C4), protons of the NH_2 group and broad NH signal. It is noteworthy, that values of chemical shifts of methylthio group of isomers **8a**{*1,1*} and **8g**{*2,1*} differ by 0.12 ppm and differences of other protons is negligible. IR spectra of the isomers **8a**{*1,1*} and **8g**{*2,1*} have the significant differences only in "fingerprints" region.

A novel synthetic approach has been developed to the synthesis of substituted isomeric isothiazolothienopyranopyridines **8** from the disodium 4-cyanoisothiazole-3,5-dithiolate (**1**).The method is based on a combination of domino reactions. The first sequence is two "one-pot" S_N2-reactions

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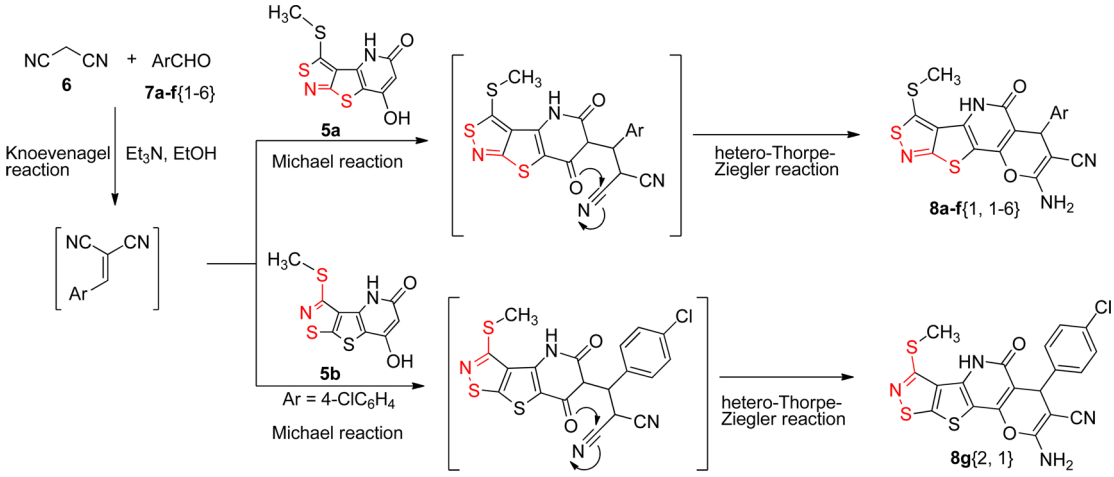
Scheme 2. Synthesis of Isomeric Isothiazolothieno-4*H*-pyranopyridines 8a−8g



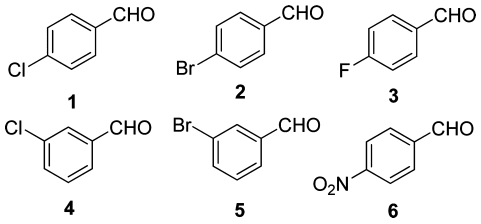


Figure 3. Diversity of the aromatic aldehydes **7a**−**7f**{*1*−*6*}.

Table 1. Isothiazolothieno-4*H*-pyranopyridines 8a−g

entry	product	Ar	yield (%)
1	**8a**{*1,1*}	4-Cl-C_6H_6	82
2	**8b**{*1,2*}	4-Br-C_6H_6	88
3	**8c**{*1,3*}	4-F-C_6H_6	75
4	**8d**{*1,4*}	3-Cl-C_6H_6	77
5	**8e**{*1,5*}	3-Br-C_6H_6	83
6	**8f**{*1,6*}	4-NO_2-C_6H_6	86
7	**8g**{*2,1*}	4-Cl-C_6H_6	30

followed by a "one-pot" Thorpe−Ziegler → the Thorpe−Guareschi reaction. The second sequence is a three-component domino reaction of the Knoevenagel → the Michael → the hetero-Thorpe−Ziegler type. This method allows one to obtain a large library of new substituted fused heterocyclic compounds easily by using simple starting compounds.

EXPERIMENTAL PROCEDURES

The ^{1}H NMR spectra were recorded on a "Bruker AM300" (300.13 MHz) using internal standard with DMSO-d_6 as the solvent, a chemical shifts were reported in ppm (δ) and coupling constants (J) values were given in Hertz (Hz). IR spectra were recorded on a "Bruker Alpha" in KBr pellets, the frequencies were expressed in cm^{-1}. Mass spectra were collected on a Kratos MS-30 spectrometer with direct sample injection at an ionization voltage of 70 eV. The high-resolution mass spectra (HRMS) measured on a Bruker micrOTOF using electrospray ionization (ESI). Milting points measured on a Kofler bench. Single crystals of **4a** and **4b** were crystallized from ethanol. Suitable crystals were selected and mounted on a glass needle on Bruker SMART APEX II and APEX DUO diffractometers respectively. The crystal of **4a** was kept at 120 K during data collection, **4b** was measured at 300 K.

Using Olex2,[19] the structures were solved with the XS[20] structure solution program using direct methods and refined with the ShelXLMP-2012[21] refinement package using least squares minimization. The disodium 4-cyanoisothiazole-3,5-dithiolate (**1**) was synthesized by known method.[12]

Synthesis of Isothiazoles 4a and 4b. *General Experimental Procedure.* To the solution of disodium 4-cyanoisothiazole-3,5-dithiolate tetrahydrate (**1**) (5.8 g, 20 mmol) in 50% aqueous ethanol (75 mL) appropriate alkylating agent (**2** or **3**) (20 mmol) was added dropwise for 15 s during intensive stirring. The mixture stirred for 10 min then diluted with water up to 150 mL and filtered through a fluted filter. To obtained filtrate the second alkylating agent (**3** or **2**, respectively) (20 mmol) was added at once at stirring. The reaction mixture stirred for 10 min then diluted with water up to 250 mL volume, cooled to 8 °C. The precipitate filtered off and recrystallized from 50% aqueous ethanol.

*Ethyl 4-((4-Cyano-5-(methylthio)isothiazol-3-yl)thio)-3-oxobutanoate (**4a**).* Yield: 3.60 g (57%); mp =77−78 °C. ^{1}H NMR: 1.19 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 2.79 (s, 3H, SCH_3), 3.77 (s, 2H, CH_2CO), 4.10 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.40 (s, 2H, SCH_2). ESI-HRMS: m/z calcd for $C_{11}H_{12}N_2OS_3$ [M + H]$^+$ 317.0083; found 317.0088. EIMS (70 eV) m/z: 316 [M$^+$], 271, 270, 228, 202, 201, 126, 115 (100), 109, 87, 69, 47. IR (KBr): 2220, 1739, 1718, 1289, 1203, 1122, 1025, 950, 818 cm^{-1}. Crystal data for **4a**: $C_{11}H_{12}N_2O_3S_3$ (M = 316.41) orthorhombic, space group $P2_12_12_1$ (no. 19), a = 4.650(4) Å, b = 13.822(11) Å, c = 21.585(17) Å, V = 1387.3(19) Å^3, Z = 4, T = 120 K, μ(MoKα) = 0.538 mm^{-1}, D_{calcd} = 1.515 g/mm^3, 12649 reflections measured (3.774 ≤ 2Θ ≤ 52.74), 2833 unique (R_{int} = 0.2069) which were used in all calculations. The final R_1 was 0.0590 ($I > 2\sigma(I)$) and R_2 was 0.1193 (all data).

*Ethyl 4-((4-cyano-3-(methylthio)isothiazol-5-yl)thio)-3-oxobutanoate (**4b**).* Yield: 3.27 g (52%); mp = 59 − 60 °C. ^{1}H NMR: 1.19 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 2.65 (s, 3H, SCH_3), 3.79 (s, 2H, CH_2CO), 4.10 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.57 (s, 2H, SCH_2). ESI-HRMS: m/z calcd for $C_{11}H_{12}N_2OS_3$ [M + H]$^+$ 317.0083; found 317.0089. EIMS (70 eV) m/z: 316 [M$^+$], 270, 228, 202, 169, 115 (100), 86, 69. IR (KBr): 2220, 1744, 1720, 1468, 1308, 1288, 1196, 1108, 1028, 820 cm^{-1}. Crystal data for **4b**: $C_{11}H_{12}N_2O_3S_3$ (M = 316.41) monoclinic, space group $P2_1/c$ (no. 14), a = 23.160(5) Å, b = 4.6826(11) Å, c = 13.811(3) Å, β = 99.849(16)°, V = 1475.7(6) Å^3, Z = 4, T = 300 K, μ(CuKα) = 4.653 mm^{-1}, D_{calcd} = 1.424 g/mm^3, 10726

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reflections measured ($7.748 \leq 2\Theta \leq 134.06$), 2581 unique ($R_{int} = 0.0556$), which were used in all calculations. The final R_1 was 0.0593 ($I > 2\sigma(I)$) and R_2 was 0.1710 (all data).

Synthesis of Isothiazolothienopyridinones 5a and b. *7-Hydroxy-3-(methylthio)isothiazolo[4′,3′:4,5]thieno[3,2-b]-pyridin-5(4H)-one (**5a**). Method A.* To the solution of sodium ethylate in absolute ethanol (75 mL) (prepared by dissolving of 280 mg, 12 mmol of sodium in 75 mL of absolute ethanol) the ethyl 4-((4-cyano-5-(methylthio)isothiazol-3-yl)thio)-3-oxobutanoate (**4a**) (3.16 g, 10 mmol) was added. The reaction mixture was refluxed and stirred for 3 h. Cold water (75 mL) was added to the reaction mixture and then filtered through a fluted filter. The mixture was acidified by 10% hydrochloric acid to pH = 4 and the precipitate was filtered off, washed with water, ethanol, and hexane, and dried on air. Yield: 2.32 g (86%); mp = 315 °C (decomp.). ^{1}H NMR: 2.80 (s, 3H, SCH_3), 6.17 (s, 1H, CH), 11.54 (s, 1H, NH). The proton of −OH group is at deuterium exchange and was not observed in the spectrum. ESI-HRMS: m/z calcd for $C_9H_6N_2O_2S_3$ $[M + H]^+$ 270.9664; found 270.9662. EIMS (70 eV) m/z: 271, 270 $[M^+]$, 237(100), 94. 84, 79, 69, 48, 43. IR (KBr): 1645, 1563, 1286, 1234, 1122, 948, 815 cm^{-1}.

Method B. To the solution of (**1**) (5.8 g, 20 mmol, calculated for complex with 4 H_2O) in 75 mL of 50% aqueous ethanol the ethyl 4-chloroacetoacetate 3.28 g (20 mmol) at intensive stirring was added for 15 s then stirred for 10 min then mixture was filtered. To the solution the iodomethane (**3**) 2.84 g (20 mmol) was added at once and mixture stirred for 10 min. To the mixture the solution 11.2 mL of 10% KOH (20 mmol) was added then mixture was reflux at stirring for 1 h. Cooled solution was filtered and acidified with 10% HCl up to pH = 4. The precipitate was filtered off, washed with water, ethanol, and hexane, and dried on air. Yield: 1.14 g (21%).

*7-Hydroxy-3-(methylthio)isothiazolo[4′,5′:4,5]thieno[3,2-b]pyridin-5(4H)-one (**5b**). Method A.* The compound (**4b**) (3.16 g, 10 mmol) in triethylamine (75 mL) was refluxed at stirring for 3 h. The reaction mixture treated as it was described above for **5a** (Method A). Yield: 2.18 g (80%); mp >300 °C (decomp.). ^{1}H NMR: 2.64 (s, 3H, SCH_3), 6.26 (s, 1H, CH), 11.55 (s, 1H, NH). The proton of −OH group is at deuterium exchange and was not observed in the spectrum. ESI-HRMS: m/z calcd for $C_9H_6N_2O_2S_3$ $[M + H]^+$ 270.9664; found 270.9659. IR (KBr): 1601, 1543, 1225, 1068, 962, 828, 736 cm^{-1}.

Method B. To the solution of **1** (2.9 g, 10 mmol, calculated for complex with 4 H_2O) in 20 mL of DMF the iodomethane, **3** (1.42 g, 10 mmol) at intensive stirring was added for 15 s and was stirred for 10 min. To the reaction mixture, the ethyl 4-chloroacetoacetate (1.64 g, 10 mmol) was added and stirred for 10 min, and then, the NaH (0.36 g, 15 mmol) added and stirred for 30 min at 70 °C. The solution was cooled and diluted with water (50 mL), Then, it was filtered and acidified by 10% HCl up to pH = 4. The precipitate (**5b**) filtered off washed with water, ethanol, and hexane and then dried on air. Yield: 0.38 g (14%).

Synthesis of Isothiazolothieno[3,2-*b*]pyrano[2,3-*d*]-pyridine-3-carbonitriles 8a−8g{*1−2,1−6*}. *General Procedure.* To the solution of the compound **5a**,**5b**{*1−2*} (270 mg, 1 mmol) in 7 mL of DMF, the malononitrile **6** (70 mg, 1.05 mmol), corresponding aromatic aldehyde **7a−7f**{*1−6*} (1.05 mmol) and 2 drops of *N*-methyl morpholine in 7 mL of the ethanol were added. The reaction mixture was stirring for 30 min at 90 °C then the solution cooled and diluted with water up to 25 mL. The precipitate filtered off then washed with water, ethanol, and hexane and dried on air.

*2-Amino-4-(4-chlorophenyl)-7-(methylthio)-5-oxo-5,6-dihydro-4H-isothiazolo[4′,3′:4,5]thieno[3,2-b]pyrano[2,3-d]-pyridine-3-carbonitrile **8a**{1,1}.* Yield: 82%; mp = 312 °C. ^{1}H NMR: 2.79 (s, 3H, SCH_3), 4.61 (s, 1H, CH), 7.20 (d, J = 7.8 Hz, 2H, Ar), 7.30 (s, 2H, NH_2), 7.35 (d, J = 7.8 Hz, 2H, Ar),11.57 (br s, 1H, NH). ESI-HRMS: m/z calcd for $C_{19}H_{11}ClN_4O_2S_3$ $[M + H]^+$ 458.9805; found 458.9804. EIMS (70 eV) m/z: 458 $[M^+]$, 347, 188, 152, 83, 73, 66 (100), 57, 55,43. IR (KBr) ν cM^{-1}: 3348, 3308, 3188, 2196, 1660, 1626, 1296, 1172, 1088, 848, 784.

*2-Amino-4-(4-bromophenyl)-7-(methylthio)-5-oxo-5,6-dihydro-4H-isothiazolo[4′,3′:4,5]thieno[3,2-b]pyrano[2,3-d]-pyridine-3-carbonitrile (**8b**){1,2}.* Yield: 88%; mp = 315 °C. ^{1}H NMR: 2.78 (s, 3H, SCH_3), 4.59 (s, 1H, CH), 7.14 (d, J = 8.3 Hz, 2H, Ar), 7.27 (s, 2H, NH_2), 7.48 (d, J = 8.3 Hz, 2H, Ar),11.55 (br s, 1H, NH). ESI-HRMS: m/z calcd for $C_{19}H_{11}BrN_4O_2S_3$ $[M + H]^+$ 503.9123; found 503.9114. EIMS (70 eV) m/z: 504 $[M^+ + 2]$, 502 $[M^+]$, 437, 436, 357, 270, 237, 207, 189, 73 (100). IR (KBr) ν cM^{-1}: 3400, 3312, 3188, 2200, 1668, 1628, 1172, 1072, 968, 832, 780.

*2-Amino-4-(4-fluorophenyl)-7-(methylthio)-5-oxo-5,6-dihydro-4H-isothiazolo[4′,3′:4,5]thieno[3,2-b]pyrano[2,3-d]-pyridine-3-carbonitrile (**8c**){1,3}.* Yield: 75%; mp = 305 °C. ^{1}H NMR: 2.77 (s, 3H, SCH_3), 4.60 (s, 1H, CH), 7.10 (m, 2H, Ar), 7.24 (m, 4H, Ar, NH_2), 11.45 (br s, 1H, NH). ESI-HRMS: m/z calcd for $C_{19}H_{11}FN_4O_2S_3$ $[M + H]^+$ 443.0101; found 443.0097. EIMS (70 eV) m/z: 442 $[M^+]$, 378, 377, 376 (100), 375, 347, 270. IR (KBr): ν cM^{-1} 3380, 3252, 3184, 2192, 1664, 1626, 1296, 1172, 1032, 912, 848, 744.

*2-Amino-4-(3-chlorophenyl)-7-(methylthio)-5-oxo-5,6-dihydro-4H-isothiazolo[4′,3′:4,5]thieno[3,2-b]pyrano[2,3-d]-pyridine-3-carbonitrile **8d**{1,4}.* Yield: 77%; mp = 303 °C. ^{1}H NMR: 2.78 (s, 3H, SCH_3), 4.63 (s, 1H, CH), 7.13 (d, J = 7.3 Hz, 1H, Ar), 7.23 (s, 1H, Ar), 7.29 (m, 4H, Ar, NH_2),11.53 (br s, 1H, NH). ESI-HRMS: m/z calcd for $C_{19}H_{11}ClN_4O_2S_3$ $[M + H]^+$ 458.9805; found: 458.9815. EIMS (70 eV) m/z: 460 $[M^+ + 2]$, 458 $[M^+]$, 392, 357, 349, 347, 270, 188, 152, 73 (100). IR (KBr): ν cM^{-1} 3388, 3316, 3172, 2200, 1662, 1626, 1296, 1172, 1032, 916, 860, 748.

*2-Amino-4-(3-bromophenyl)-7-(methylthio)-5-oxo-5,6-dihydro-4H-isothiazolo[4′,3′:4,5]thieno[3,2-b]pyrano[2,3-d]-pyridine-3-carbonitrile **8e**{1,5}.* Yield: 83%; mp = 308 °C. ^{1}H NMR: 2.78 (s, 3H, SCH_3), 4.62 (s, 1H, CH), 7.18 (d, J = 7.3 Hz, 2H, Ar), 7.29 (m, 3H, Ar, NH_2), 7.38 (m, 2H, Ar),11.54 (br s, 1H, NH). ESI-HRMS: m/z calcd for $C_{19}H_{11}BrN_4O_2S_3$ $[M + H]^+$ 503.9123; found 503.9109. EIMS (70 eV) m/z: 504 $[M^+ + 2]$, 502 $[M^+]$, 438, 435, 357, 348, 347 (100), 332, 234, 232, 152. IR (KBr): ν cM^{-1} 3380, 3176, 2200, 1668,1648, 1296, 1172, 1032, 996, 916, 748.

*2-Amino-4-(4-nitrophenyl)-7-(methylthio)-5-oxo-5,6-dihydro-4H-isothiazolo[4′,3′:4,5]thieno[3,2-b]pyrano[2,3-d]-pyridine-3-carbonitrile **8f**{1,6}.* Yield: 86%; mp = 316 °C. ^{1}H NMR: 2.78 (s, 3H, SCH_3), 4.78 (s, 1H, CH), 7.37 (s, 2H, NH_2), 7.47 (d, J = 7.3 Hz, 2H, Ar), 8.16 (d, J = 7.3 Hz, 2H, Ar),11.58 (br s, 1H, NH). ESI-HRMS: m/z calcd for $C_{19}H_{11}N_5O_4S_3$ $[M + H]^+$: 470.0046; found: 470.0030. EIMS (70 eV) m/z: 469 $[M^+]$, 403, 356, 348, 347, 270, 207, 199, 169, 152, 73 (100). IR (KBr): ν cM^{-1} 3340, 3316, 3180, 2200, 1664, 1636, 1516, 1348, 1296, 1232, 1112, 1032, 824, 744.

2-Amino-4-(4-chlorophenyl)-7-(methylthio)-5-oxo-5,6-dihydro-4H-isothiazolo[4′,5′:4,5]thieno[3,2-b]pyrano[2,3-d]-

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pyridine-3-carbonitrile ***8g****{2,1}*. Yield: 30%; mp = 307 °C, ^{1}H NMR: 2.64 (s, 3H, SCH_3), 4.60 (s, 1H, CH), 7.20 (m, 2H, Ar), 7.32 (m, 4H, Ar, NH_2), 11.39 (br s, 1H, NH). ESI-HRMS: *m/z* calcd for $C_{19}H_{11}ClN_5O_4S_3$ $[M + H]^+$: 458.9804; found 458.9805. EIMS (70 eV) *m/z*: 458 [M^+], 347, 274, 161, 153, 125, 95, 91 (100), 66, 43. IR (KBr): ν cM^{-1} 3346, 3308, 3270, 3184, 2188, 1663, 1618, 1556, 1386, 1291, 1237, 1172, 1088, 1014, 836, 773.

■ ASSOCIATED CONTENT

Supporting Information

Detailed crystallographic data for the compounds **4a** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ DEDICATION

This paper is dedicated to the memory of our colleague and friend Ph.D. Kyrill Nikishin (1967−2010).

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