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Synthesis of New Thieno[2,3-*b*]pyridine Derivatives Based on Fused Thiophenes

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Abstract—Conditions for the Gewald synthesis of 2-amino-5,5-dimethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyrans from 2,2-dimethyltetrahydropyran-4-ones have been optimized, and the yields have been improved. A procedure has been developed for the synthesis of new pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridines by the Thorpe–Ziegler reaction of thieno[2,3-*c*]pyrans. Anticonvulsant activity of the synthesized compounds was studied.

Keywords: thiophene, thieno[2,3-*c*]pyranes, thieno[2,3-*b*]pyridines, pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridines, anticonvulsant activity

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Thieno[2,3-*b*]pyridines and their derivatives display a broad spectrum of biological activity [1–12]. In particular, compounds exhibiting antibacterial [5, 6], antitumor [7, 8], anticonvulsant [9], anti-inflammatory [10], antidepressant [11], and antiviral activities [12] have been found in this series. Therefore, there is an obvious interest in the synthesis and chemical and biological properties of new fused thieno[2,3-*b*]pyridine derivatives. The goal of the present work was to develop preparative procedures for the synthesis of new pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridines, study of their physicochemical properties, and evaluation of the synthesized compounds for anticonvulsant activity.

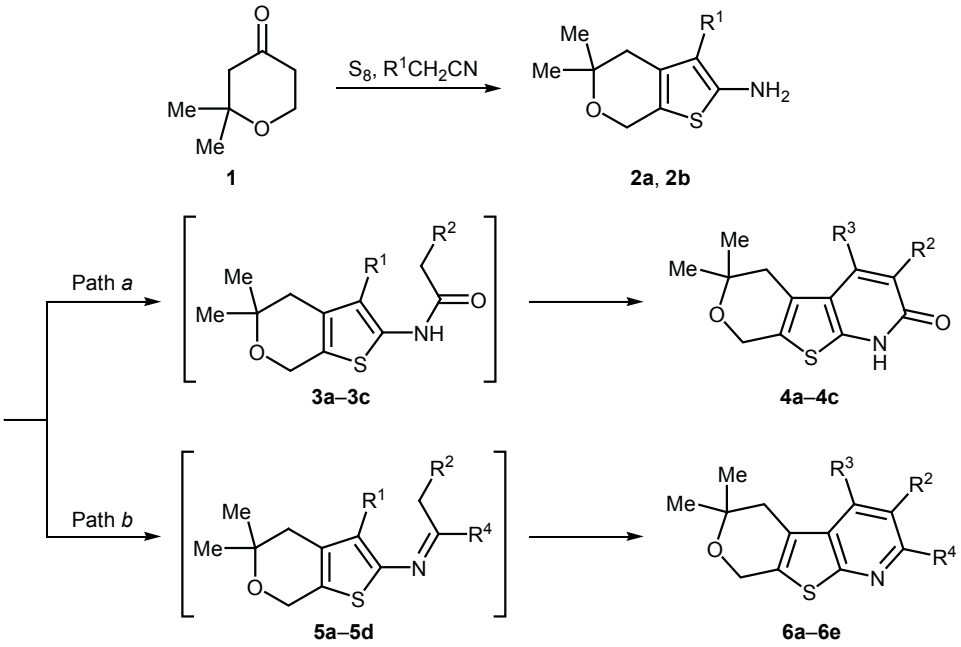
The starting compounds were thieno[2,3-*c*]pyrans **2a** and **2b** which were synthesized by the Gewald reaction of 2,2-dimethyltetrahydropyran-4-one (**1**) with cyanoacetic acid derivatives and sulfur in basic medium [13–15]. It should be noted that the reported synthesis of thieno[2,3-*c*]pyrans **2a** and **2b** was characterized by relatively low yields (40–60%) [14] and that the isolation procedure was quite laborious. We succeeded in finding optimal conditions for the synthesis of these compounds. In particular, a mixture of morpholine and diethylamine was used as catalyst, and the reaction was carried out at a lower temperature (40–41°C), so that the yield was improved to 75–84% and less tar was formed (Scheme 1).

In continuation of our studies, aminothiophenes **2a** and **2b** were involved in the Thorpe–Ziegler reactions with ethyl cyanoacetate, malononitrile, and cyanoacetamide. The reactions led to the formation of pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridines **4** and **6** through intermediates **3** and **5**, respectively, or their tautomers (Scheme 1).

Aminothiophenes **2a** and **2b** were also reacted with active methylene compounds such as ethyl 2-phenylacetate, ethyl acetoacetate, and acetylacetone. The reaction of **2a** with ethyl 2-phenylacetate was carried out with a view to obtaining fused thieno[2,3-*b*]pyridine derivative containing a phenyl substituent. However, instead of expected product **4c**, we isolated *N*-phenylacetyl derivative **3c**. The reaction of 3-cyanothieno[2,3-*c*]pyran **2b** with ethyl acetoacetate gave Schiff base **5d** in 40–45% yield. Compound **5d** was synthesized in 89–90% yield by condensation of **2b** with ethyl β-aminocrotonate. Intramolecular cyclization of the latter in the presence of sodium ethoxide afforded 70% of pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine **6d**. By acidification of the mother liquor we isolated amino acid **6e** which was also obtained by heating compound **6d** in 10% aqueous–alcoholic sodium hydroxide under reflux (Scheme 1).

The reaction of amino ester **2a** with ethyl acetoacetate in acetic acid gave compound **6a** in a low yield (path *b* in Scheme 1). When the reaction was carried out in alkaline medium, the product was compound **3d** in a mixture with its keto–enol tautomer **7** at a ratio of 4 : 1 (Scheme 2); attempts to cyclize compound **3d** (**7**)

Scheme 1.



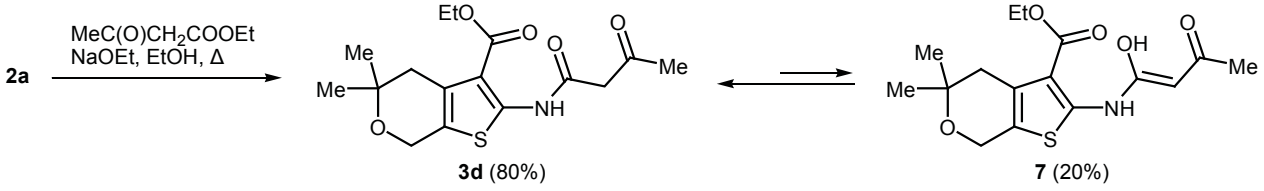
2a, **3a**, **3c**, **5a**, R^1 = COOEt; **2b**, **3b**, **5b**–**5d**, R^1 = CN; **3a**, **3b**, **4a**, **4b**, **5b**, **6b**, R^2 = CN; **5a**, **5d**, **6a**, **6d**, R^2 = COOEt; **3c**, **4c**, R^2 = Ph; **5c**, **6c**, R^2 = $CONH_2$; **6e**, R^2 = COOH; **4a**, **4c**, **6a**, R^3 = OH; **4b**, **6b**–**6e**, R^3 = NH_2; **5a**, **5d**, **6a**, **6d**, **6e**, R^4 = Me; **5b**, **5c**, **6b**, **6c**, R^4 = NH_2.

were unsuccessful. Amino nitrile **2b** reacted with acetylacetone to produce open-chain enamine **5f**. Treatment of the latter with sodium methoxide resulted in the formation of compound **8** containing two thieno[2,3-*c*]pyran fragments (Scheme 3). In the reaction of 2-aminotetrahydro-1-benzothiophene-3-carbonitrile (**9**) [16] with ethyl acetoacetate we isolated and identified 1 : 1 and 2 : 1 condensation products **10** (40%) and **11** (50%) (Scheme 4). Unlike compound **11**, ester **10** underwent cyclization to ethyl 4-amino-2-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine-3-carboxylate [15]. The structures of the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR, IR, and mass spectra.

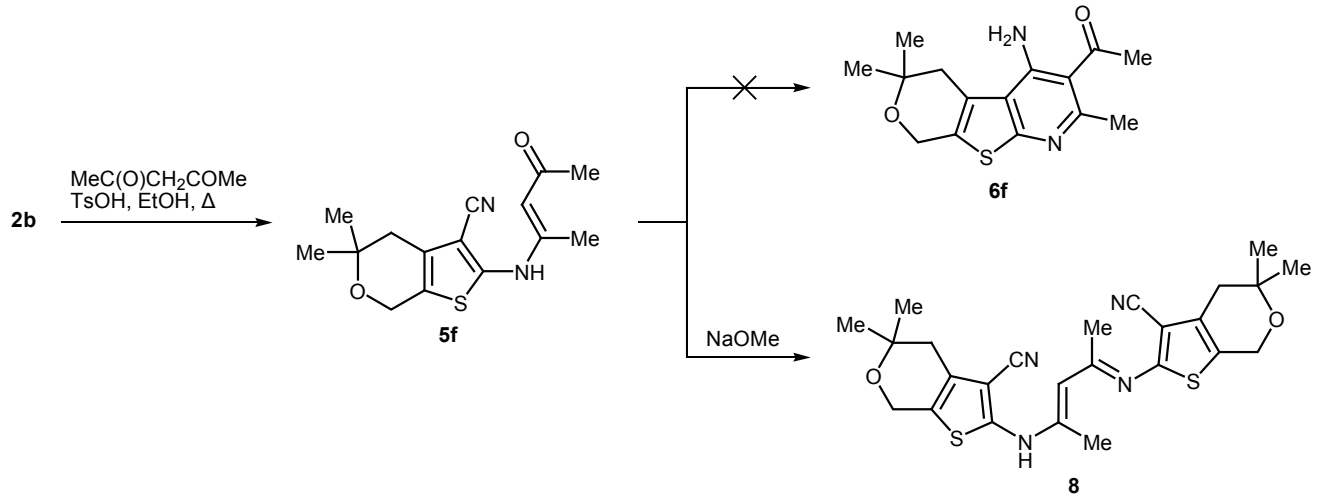
The anticonvulsant activity of the synthesized compounds was assessed by their effect on pentylenetetrazol-induced seizures [17] in male and female white mice with a weight of 18–24 g. Pentylenetetrazol (Acros organics, NJ, USA) was administered subcutaneously at a dose of 90 mg/kg as a suspension with carboxymethylcellulose (*Viadi-Ingredienty*, St. Petersburg, Russia) and Tween 80 (Ferak Berlin, Germany). The anticonvulsant activity was evaluated by the prevention of clonic twitches and clonic seizure component. Thieno[2,3-*c*]pyran derivative **5f** at a dose of 50 mg/kg prevented pentylenetetrazol-induced clonic seizures in 60% of animals. Among thieno[2,3-*b*]pyridine derivatives, the most active were compounds **4a**, **4b**, and **6a**–**6e**, while the other compounds showed no anticonvulsant activity. In the series of hydroxy nitriles, a more pronounced effect (40–60%) was observed for compounds **4a**, **4b**, and **6a**. Ester **6d** at a dose of 50 mg/kg showed 60% anticonvulsant activity; compound **5f** exerted a similar effect. The activity of carboxylic acid **6e** was lower. Amines **6b** and **6c** exhibited a weak anticonvulsant activity. Compounds **4a**, **5f**, and **6d** also displayed sedative activity.

In summary, we have optimized conditions for the synthesis of 2-amino-5,5-dimethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyrans and obtained new pyrano-

Scheme 2.



Scheme 3.



[4′,3′:4,5]thieno[2,3-*b*]pyridines based thereon. The reaction of 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile with ethyl acetoacetate has been found to afford a mixture of 1 : 1 and 2 : 1 condensation products. Analogous 2 : 1 adduct was formed on attempted cyclization of 5,5-dimethyl-2-{[(1*E*)-1-methyl-3-oxobut-1-en-1-yl]amino}-4,7-dihydro-5*H*-thieno-[2,3-*c*]pyran-3-carbonitrile. Some of the synthesized compounds (**4a**, **5f**, and **6d**) showed a pronounced anticonvulsant activity in combination with low toxicity and insignificant side effects.

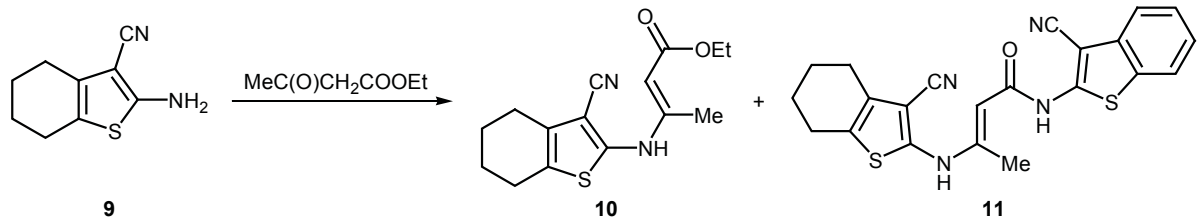
EXPERIMENTAL

The IR spectra were recorded on a Nicolet Avatar 330 FT-IR spectrometer (USA) from samples dispersed in mineral oil. The mass spectra (electron impact, 50 eV) were obtained on an MKh-1321A spectrometer (USSR) with direct sample admission into the ion source; the batch inlet probe temperature was set 15–20°C lower than the melting point of a sample. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 VX spectrometer (USA) at 300.08 and 75.462 MHz, respectively, using DMSO-d_6, DMSO-d_6–CCl_4 (1 : 3), DMSO-d_6–CF_3COOD, or $CDCl_3$ as solvent and tetramethylsilane as internal standard. The elemental compositions were determined with a Euro EA 3000 elemental analyzer (Germany), as well as by the Korshun−Klimova (C, H) and Dumas–Pregl methods (N). The melting points were measured on a Boetius micro hot stage. Analytical thin-layer chromatography was performed on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor. Commercially available reagents were purchased from Fluka (Germany), Aldrich, and Sigma (USA). The solvents used were purified according to standard procedures.

Compounds 2a and 2b (*general procedure***).** A suspension of 12.8 g (10 mmol) of 2,2-dimethyltetrahydropyran-4-one (**1**), 10 mmol of ethyl cyanoacetate or malononitrile, and 3.2 g (10 mmol) of sulfur powder in 50 mL of 96% ethanol was heated to 30–40°C, and a mixture of 3 mL of diethylamine and 5 mL of morpholine in 10 mL of ethanol was added dropwise with stirring over a period of 30 min. The mixture was stirred at 40–41°C for 3 h, cooled with ice water, and left overnight in a refrigerator. The crystalline solid was filtered off, washed with water, dried, and recrystallized from ethanol.

Ethyl 2-amino-5,5-dimethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate (2a). Yield 21.5 g (84%) [14].

Scheme 4.



2-Amino-5,5-dimethyl-4,7-dihydro-5*H*-thieno-[2,3-*c*]pyran-3-carbonitrile (2b). Yield 15.7 g (76%) [14].

Ethyl 5,5-dimethyl-2-[(phenylacetyl)amino]-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate (3c). Compound **2a**, 2.6 g (10 mmol), and ethyl 2-phenylacetate, 5.0 g (30 mmol), were added to a solution of sodium ethoxide prepared from 0.46 g (20 mmol) of sodium and 10 mL of anhydrous ethanol. The mixture was refluxed for 2 h and allowed to cool down, and the precipitate was filtered off, washed with diethyl ether and water, dried, and recrystallized from ethanol. Yield 3.2 g (86%), mp 105–107°C, R_f 0.56 (acetone–pentane, 1:2). IR spectrum, ν, cm^{-1}: 3285, 3200 br (NH, OH), 1680, 1653 s (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.22 s (6H, CH_3), 1.32 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.62 t (2H, CH_2, J = 1.6 Hz), 3.81 s (2H, PhC$\mathbf{H}_2$), 4.23 q (2H, OC$\mathbf{H}_2$CH$_3$, J = 7.1 Hz), 4.58 t (2H, OCH_2, J = 1.6 Hz), 7.41–7.21 m (5H, Ph), 11.00 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 373 (97) $[M]^+$, 374 (23), 315 (29), 254 (56), 197 (47), 125 (31). Found, %: C 64.24; H 6.12; N 3.87; S 8.65. $C_{20}H_{23}NO_4S$. Calculated, %: C 64.32; H 6.21; N 3.75; S 8.59.

Ethyl 5,5-dimethyl-2-(3-oxobutanamido)-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylate (3d). A solution of 0.7 g (5.5 mmol) of ethyl acetoacetate and 0.05 g of triethanolamine in 5 mL of xylene was heated to the boiling point, and a solution of 1.3 g (5 mmol) of compound **2a** in 5 mL of xylene was added dropwise. The mixture was refluxed for 1 h and was then cooled with stirring. The crystalline solid was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 1.1 g (65%, a mixture of tautomers **3d** and **7** at a ratio of 4:1), mp 119–121°C, R_f 0.60 (acetone–pentane, 1:3). IR spectrum, ν, cm^{-1}: 3240, 3190 br (NH, OH), 1730, 1680, 1650 s (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.25 s (6H, CH_3), 1.39 t (0.6H, $CH_2C\mathbf{H}_3$, J = 7.0 Hz, **7**), 1.40 t (2.4H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz, **3d**), 2.00 s (0.6H, CH_3, **7**), 2.26 s (2.4H, CH_3, **3d**), 2.66 t (0.4H, CH_2, J = 1.6 Hz, **7**), 2.68 t (1.6H, CH_2, J = 1.7 Hz, **3d**), 3.77 s (1.6H, C$\mathbf{H}_2$Ac, **3d**), 4.31 q (0.4H, C$\mathbf{H}_2$CH$_3$, J = 7.0 Hz, **7**), 4.36 q (1.6H, C$\mathbf{H}_2$CH$_3$, J = 7.1 Hz, **3d**), 4.65 t (0.4H, OCH_2, J = 1.6 Hz, **7**), 4.65 t (1.6H, OCH_2, J = 1.7 Hz, **3d**), 5.23 s (0.2H, CH, **7**), 11.04 br.s (0.2H, NH, **7**), 11.51 br.s (0.8H, NH, **3d**), 11.04 br.s (0.2H, OH, **7**). Found, %: C 56.75; H 6.35; N 4.06; S 9.34. $C_{20}H_{23}NO_4S$. Calculated, %: C 56.62; H 6.24; N 4.13; S 9.45.

4-Hydroxy-6,6-dimethyl-2-oxo-1,5,6,8-tetrahydro-2*H*-pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine-3-carbonitrile (4a). Ethyl cyanoacetate, 3.4 g (30 mmol), and compound **2a**, 2.55 g (10 mmol), were added to a solution of sodium ethoxide prepared from 1 g (43 mmol) of sodium and 40 mL of anhydrous ethanol (99.95%). The mixture was refluxed for 1 h, cooled, poured into 150 mL of cold water, and acidified with aqueous HCl. The crystalline solid was filtered off, washed with water, and recrystallized from DMF. Yield 2.5 g (89%), mp 341–344°C, R_f 0.64 (chloroform–ethanol–hexane, 1:1:3). IR spectrum, ν, cm^{-1}: 3390 br (NH), 3480 br (OH), 2230 v.s (C≡N), 1640 s (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 s (6H, CH_3), 2.80 t (2H, CH_2, J = 1.9 Hz), 4.60 t (2H, OCH_2, J = 1.9 Hz), 12.40 br.s (2H, NH, OH). Found, %: C 56.07; H 4.49; N 10.22; S 12.06. $C_{13}H_{12}N_2O_3S$. Calculated, %: C 56.51; H 4.38; N 10.14; S 11.6.

4-Amino-6,6-dimethyl-2-oxo-1,5,6,8-tetrahydro-2*H*-pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine-3-carbonitrile (4b). Ethyl cyanoacetate, 1.13 g (10 mmol), and compound **2b**, 2.08 g (10 mmol), were added to a solution of sodium ethoxide prepared from 0.8 g (35 mmol) of sodium and 25 mL of anhydrous ethanol. The mixture was refluxed for 2.5 h, cooled, diluted with 200 mL of water, and filtered, and the filtrate was acidified with glacial acetic acid. The crystalline solid was filtered off, washed with water, dried, and recrystallized from DMF. Yield 2.2 g (82%), mp 346–350°C, R_f 0.63 (DMF–ethanol, 3:2). IR spectrum, ν, cm^{-1}: 3500 br (NH), 3330, 3240 br (NH_2), 2206 v.s (C≡N), 1640 s (C=O). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.28 s (6H, CH_3), 2.82 s (2H, CH_2), 4.60 s (2H, OCH_2), 6.48 s (2H, NH_2), 11.95 br.s (1H, NH). Found, %: C 56.61; H 4.59; N 15.37; S 11.71. $C_{13}H_{13}N_3O_2S$. Calculated, %: C 56.72; H 4.76; N 15.26; S 11.65.

Ethyl (2*E*)-3-[(3-cyano-5,5-dimethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-2-yl)amino]but-2-enoate (5d). *a*. A mixture of 2.1 g (10 mmol) of 2-amino-5,5-dimethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile (**2b**), 1.3 g (10 mmol) of ethyl β-aminocrotonate, and 0.1 g of *p*-toluenesulfonic acid in 20 mL of toluene was refluxed for 16 h. The mixture was cooled and filtered, excess solvent was distilled off, 10 mL of ethanol was added to the residue, and the mixture was left overnight in a refrigerator. The crystalline solid was filtered off, washed with cold ethanol and water, dried, and recrystallized from ethanol–water (3:1). Yield 2.23 g (89%).

b. A mixture of 2.1 g (10 mmol) of compound **2b**, 1.3 g (10 mmol) of ethyl acetoacetate, and 0.1 g of *p*-toluenesulfonic acid in 20 mL of anhydrous benzene was refluxed in a flask equipped with a Dean–Stark trap until water no longer separated. The solvent was distilled off, and the residue was treated with 10 mL of ethanol and left overnight in a refrigerator. The crystalline solid was filtered off, washed with cold ethanol and water, dried, and recrystallized from ethanol–water (3:1). Yield 1.1 g (45%). mp 125–127°C, R_f 0.57 (chloroform–ethanol, 1:2). IR spectrum, ν, cm^{-1}: 3510, 3350 br (NH_2), 2200 v.s (C≡N), 1670 s (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 m (9H, CH_3, $CH_2C\mathbf{H}_3$), 2.07 s (3H, CH_3), 2.60 s (2H, CH_2), 4.20 q (2H, $C\mathbf{H}_2CH_3$, J = 7.0 Hz), 4.65 s (2H, OCH_2), 4.90 s (1H, CH), 11.03 s (1H, NH). Found, %: C 60.08; H 6.17; N 8.68; S 10.13. $C_{16}H_{20}N_2O_3S$. Calculated, %: C 59.98; H 6.29; N 8.74; S 10.01.

5,5-Dimethyl-2-{[(2*E*)-4-oxopent-2-en-2-yl]-amino}-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile (5f). A mixture of 2.1 g (10 mmol) of compound **2b**, 1.5 g (15 mmol) of acetylacetone, and 0.05 g of *p*-toluenesulfonic acid in 10 mL of anhydrous toluene was refluxed in a flask equipped with a Dean–Stark trap until water no longer separated (2 h). The mixture was cooled and left overnight in a refrigerator, and the precipitate was filtered off, washed with ethanol and water, dried, and recrystallized from ethanol. Yield 2.9 g (82%), mp 157–158°C, R_f 0.59 (ethyl acetate–methanol, 1:1). IR spectrum, ν, cm^{-1}: 3407, 3186 br (NH), 2202 v.s (C≡N), 1615 s (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 m (6H, CH_3), 2.10 s (3H, CH_3), 2.15 d (3H, CH_3, J = 0.6 Hz), 2.55 t (2H, CH_2, J = 1.7 Hz), 4.59 t (2H, OCH_2, J = 1.9 Hz), 5.39 d (1H, CH, J = 0.6 Hz), 13.15 br.s (1H, NH). Found, %: C 61.98; H 6.17; N 9.78; S 11.13. $C_{15}H_{18}N_2O_2S$. Calculated, %: C 62.04; H 6.25; N 9.65; S 11.04.

Ethyl 4-hydroxy-2,6,6-trimethyl-5,8-dihydro-6*H*-pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine-3-carboxylate (6a). A mixture of 2.6 g (10 mmol) of compound **2a** and 1.43 g (11 mmol) of ethyl acetoacetate in 30 mL of acetic acid was refluxed for 2 h. The solvent was distilled off, the residue was treated with 10 mL of ethanol, and the mixture was left overnight in a refrigerator. The precipitate was filtered off and washed with cold ethanol and water. Yield 1.8 g (57%), mp 293–295°C, R_f 0.58 (acetone–pentane, 1:3). IR spectrum, ν, cm^{-1}: 3970 br (OH), 1680 s (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.20 s (6H, CH_3), 1.37 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.09 s (3H, CH_3), 2.65 s (2H, CH_2), 4.32 q (2H, $OC\mathbf{H}_2CH_3$, J = 7.0 Hz), 4.53 s (2H, OCH_2), 14.04 br.s (1H, NH). Found, %: C 59.6; H 6.03; N 4.25; S 10.07. $C_{16}H_{19}NO_4S$. Calculated, %: C 59.79; H 5.96; N 4.36; S 9.98.

2,4-Diamino-6,6-dimethyl-5,8-dihydro-6*H*-pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine-3-carbonitriles 6b and 6c (*general procedure*). Compound **2b**, 2.1 g (10 mmol), and malononitrile or cyanoacetamide (10 mmol) were added to a solution of sodium ethoxide prepared from 0.25 g (11 mmol) of sodium and 12 mL of anhydrous ethanol (99.9%). The mixture was refluxed for 3–4.5 h and allowed to cool down, and the crystalline solid was filtered off, washed with water, dried, and recrystallized from ethanol.

2,4-Diamino-6,6-dimethyl-5,8-dihydro-6*H*-pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine-3-carbonitrile (6b). Yield 1.7 g (63%), mp 276–278°C, R_f 0.62 (chloroform–ethanol, 2:3). IR spectrum, ν, cm^{-1}: 3454–3125 br (NH_2), 2260 v.s (C≡N), 1641 s (C=O). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.30 s (6H, CH_3), 2.89 s (2H, CH_2), 3.94 s (2H, NH_2), 4.72 t (2H, OCH_2, J = 1.9 Hz), 6.90 br.s (1H, NH_2). Found, %: C 56.76; H 4.99; N 20.57; S 11.78. $C_{13}H_{14}N_4OS$. Calculated, %: C 56.92; H 5.14; N 20.42; S 11.69.

2,4-Diamino-6,6-dimethyl-5,8-dihydro-6*H*-pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine-3-carboxamide (6c). Yield 1.4 g (48%), mp 234–235°C, R_f 0.66 (chloroform–ethanol, 2:3). IR spectrum, ν, cm^{-1}: 3450–3125 br (NH_2), 2215 v.s (C≡N), 1650 s (C=O). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.26 s (6H, CH_3), 2.89 t (2H, CH_2, J = 1.9 Hz), 3.48 s (2H, NH_2), 4.73 t (2H, OCH_2, J = 1.9 Hz), 6.83 br.s (1H, NH_2), 6.93 br.s and 7.43 br.s (1H each, $CONH_2$). Mass spectrum, m/z (I_{rel}, %): 292 (36) $[M]^+$, 249 (43), 234 (16), 192 (16), 191 (100), 151 (15), 150 (24). Found, %: C 53.61; H 5.39; N 19.27; S 11.85. $C_{13}H_{16}N_4O_2S$. Calculated, %: C 53.41; H 5.52; N 19.16; S 10.97.

Ethyl 4-amino-2,6,6-trimethyl-5,8-dihydro-6*H*-pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine-3-carboxylate (6d). Compound **5d**, 3.2 g (10 mmol), was added to a solution of sodium ethoxide prepared from 0.35 g (15 mmol) of sodium and 50 mL of anhydrous ethanol. The mixture was left to stand for 12 h at room temperature and was then refluxed for 3 h. After cooling, the mixture was kept for 2 days in a refrigerator, and the precipitate was filtered off, washed with ethanol and water, dried, and recrystallized from ethanol. Yield 2.2 g (70%), mp 160–161°C, R_f 0.61 (ethyl acetate–chloroform–pentane, 1:1:1). IR spectrum, ν, cm^{-1}:

3510, 3350 br (NH_2), 1670 s (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.33 s (6H, CH_3), 1.35 m (3H, $CH_2C\mathbf{H}_3$), 2.63 s (3H, CH_3), 2.80 s (2H, CH_2), 4.35 q (2H, $C\mathbf{H}_2CH_3$, J = 6.1 Hz), 4.70 s (2H, OCH_2), 6.77 s (2H, NH_2). Found, %: C 59.89; H 6.39; N 8.85; S 9.92. $C_{16}H_{20}N_2O_3S$. Calculated, %: C 59.98; H 6.29; N 8.74; S 10.01.

4-Amino-2,6,6-trimethyl-5,8-dihydro-6*H*-pyrano[4′,3′:4,5]thieno[2,3-*b*]pyridine-3-carboxylic acid (6e). *a*. Compound **2b**, 3.2 g (10 mmol), was added to a freshly prepared solution of 0.68 g (10 mmol) of sodium ethoxide in 20 mL of anhydrous ethanol. The mixture was refluxed for 8 h, cooled, poured into 50 mL of cold water, acidified with concentrated aqueous HCl, and left overnight in a refrigerator. The precipitate was filtered off, washed with ethanol and water, dried, and recrystallized from ethanol. Yield 1.65 g (57%).

b. Compound **6d**, 3.2 g (10 mmol), was added to a solution of sodium ethoxide prepared from 0.23 g (10 mmol) of sodium and 20 mL of ethanol. The mixture was refluxed for 3 h and was then treated as described above in *a*. Yield 2.25 g (78%), mp 226–228°C, R_f 0.68 (ethyl acetate–chloroform–pentane, 1:1:2). IR spectrum, ν, cm^{-1}: 3500, 3350 br (NH_2), 3310 br (OH), 1660 s (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.33 s (6H, CH_3), 2.62 s (3H, CH_3), 2.95 t (2H, CH_2, J = 1.9 Hz), 3.03 br.s (1H, OH), 4.71 t (2H, OCH_2, J = 1.9 Hz), 6.80 br.s (2H, NH_2). Mass spectrum, m/z (I_{rel}, %): 292 (15) $[M]^+$, 247 (13), 235 (15), 234 (76), 219 (32), 217 (21), 193 (31). Found, %: C 57.45; H 5.60; N 9.47; S 17.06. $C_{14}H_{16}N_2O_3S$. Calculated, %: C 57.52; H 5.52; N 9.58; S 10.97.

2-({(2*E*,3*E*)-4-[(3-Cyano-5,5-dimethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-2-yl)amino]methylpent-3-en-2-ylidene}amino)-5,5-dimethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carbonitrile (8). Compound **2b**, 2.9 g (10 mmol), was added to a solution of sodium methoxide prepared from 0.25 g (11 mmol) of sodium and 25 mL of anhydrous methanol. The mixture was refluxed for 15 min and was left to stand for 12 h. The crystalline solid was filtered off, washed with cold methanol and water, dried, and recrystallized from methanol. Yield 1.0 g (21%), mp 259–260°C, R_f 0.63 (ethyl acetate–methanol, 3:1). IR spectrum, ν, cm^{-1}: 3190 br (NH), 2219, 2205 v.s (C=N). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.30 s (12H, CH_3), 2.24 s (6H, CH_3), 2.45–2.62 m (4H, CH_2), 4.63 s (4H, OCH_2), 5.27 s (1H, CH), 13.20 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 20.74, 25.68, 35.03, 58.83, 70.13, 101.35, 102.13, 113.25, 126.65, 130.04, 153.31, 159.64. Found, %: C 62.34; H 5.76; N 11.75; S 13.22. $C_{25}H_{28}N_4O_2S_2$. Calculated, %: C 62.47; H 5.87; N 11.66; S 13.34.

Compounds 10 and 11. A mixture of 1.8 g (10 mmol) of compound **9**, 1.3 g (10 mmol) of ethyl acetoacetate, and 0.1 g of *p*-toluenesulfonic acid in 20 mL of anhydrous benzene was refluxed in a flask equipped with a Dean–Stark trap until water no longer separated. After cooling, the crystals of **11** were filtered off, washed with ethanol and water, dried, and recrystallized from ethanol. The solvent was distilled off from the filtrate, the residue was treated with 10 mL of ethanol, and the mixture was left overnight in a refrigerator. The crystals of **10** were filtered off, washed with cold ethanol and water, dried, and recrystallized from ethanol.

Ethyl 4-amino-2-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine-3-carboxylate (10). Yield 2.23 g (40%) [15].

(2*E*)-*N*-(3-Cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-3-[(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)amino]but-2-enamide (11). Yield 2.13 g (50%), mp 266–267°C, R_f 0.68 (acetone–pentane, 1:2). IR spectrum, ν, cm^{-1}: 3240, 3170 br (NH), 2206 v.s (C≡N), 1680 s (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.78–1.91 m (8H, CH_2), 2.16 d (3H, CH_3, J = 0.8 Hz), 2.53–5.67 m (8H, CH_2), 5.46 q (1H, CH, J = 0.8 Hz), 10.96 br.s (1H, NH), 11.57 br.s (1H, NH). Found, %: C 62.68; H 5.17; N 13.17; S 15.23. $C_{22}H_{22}N_4OS_2$. Calculated, %: C 62.53; H 5.25; N 13.26; S 15.18.

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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