Multicomponent Synthesis of Pyridine and Pyrimidine Derivatives Initiated by the Knoevenagel Reaction

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Abstract—Multicomponent condensation of alkylating reagents with carbonyl compounds functionalized by CH-acids is initiated by the Knoevenagel reaction and leads to the formation of substituted pyridines, thienopyridines, pyridothienopyridines, and pyrimidothienopyridopyrimidines. The structure of the key products was studied by the X-ray diffraction method.

Keywords: Knoevenagel reaction, cyanothioacetamide, carbonyl compounds, pyridine, X-ray analysis

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Functionally substituted pyridines are known for their biological activity, and specifically for neurotropic [1], antimicrobial [2], antibacterial [3], anti-HIV [4], and anticancer [5] properties. Pyrimidines condensed with pyridine and thiophene are suitable as antidermatophytic agents [6], antimicrobials grugs [7], and mGluR1 receptor ligands for positron emission tomography [8]. All this point to the high pharmaceutical potential of such heterocycles, and requires further development of methods for their synthesis and use as medical intermediates.

In continuation of research on the chemistry of nitrogen-containing heterocycles [9-15] involving multicomponent reactions [16, 17] based on cyanothioacetamide as the initial reagent [18, 19], we have studied new versions of production of pyridine and pyrimidine derivatives initiated by the Knoevenagel reaction [20]. It was found that multicomponent condensation of acetylacetones **1a**, **1b**, cyanothioacetamide **2**, and alkylating reagents **3a–3c** leads to the formation of substituted thieno[2,3-*b*]-pyridines **4a–4c**. The reaction is carried out in ethanol with short-term boiling in the presence of Et₃N. The

probable reaction scheme includes the formation of the Knoevenagel alkene **A** at the first stage, which is intramolecularly cyclized into 2-thioxopyridine **B**. Then, in an alkaline medium, its regioselective alkylation occurs to thioesters **C,** which intramolecularly close the thiophene cycle to form final **4a–4c** structures (Scheme 1).

The introduction of the fourth component, allyl bromide **5**, into this condensation led to the N-alkylation of the amide fragment of the hypothetical thienopyridine of type **4**. In this way, *N*-allyl-3-amino-4,5,6-trimethyl-*N*-(thiazole-2-yl)thieno[2,3-*b*]pyridine-2-carboxamide **6** was synthesized. The application of α-chloroacetamide **3f** as the fourth component in such condensation led to the formation of acetamide **7**, as a result of the Williamson reaction at the last stage of the process. Benzimidazolylacetonitrile **8** condenses with acetylacetone **1a** in boiling ethanol in the presence of Et₃N to form 1,3-dimethylbenzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitrile **9** (Scheme 1). A possible mechanism of its formation consists in the Knoevenagel condensation and subsequent intramolecular heterocyclization. We note that compound **9** was obtained earlier with a yield

Scheme 1.
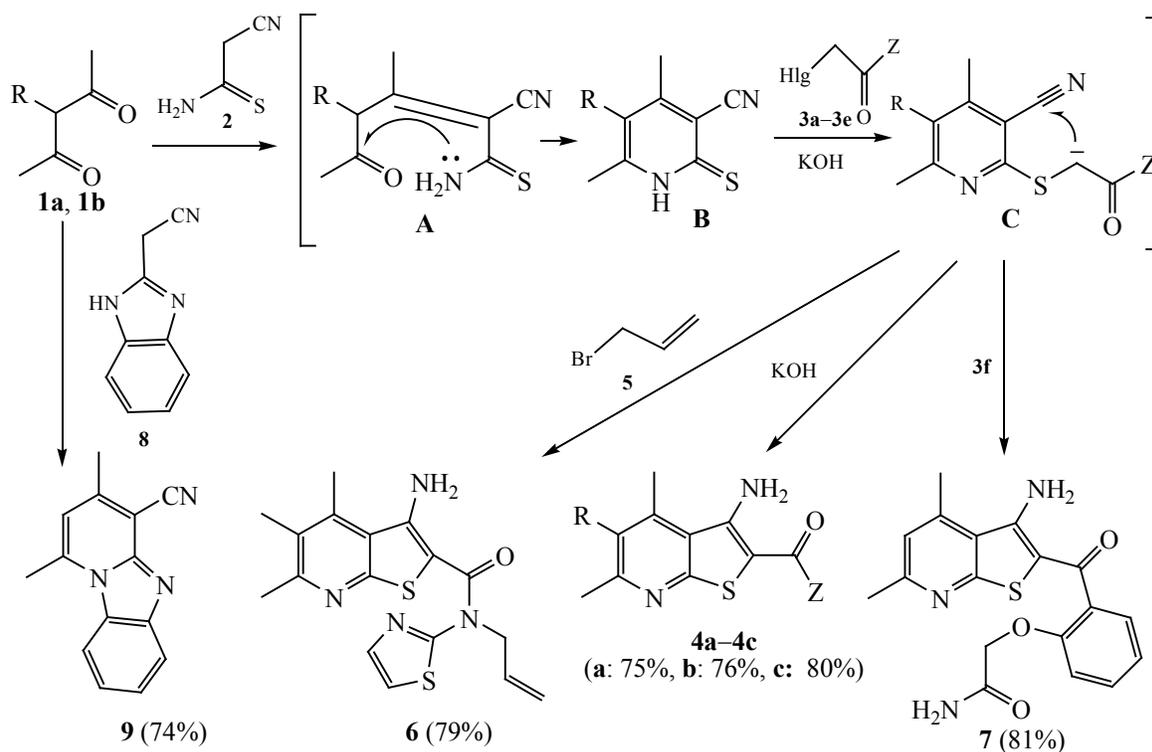
1, R = H (**a**), Me (**b**). **3**, Hlg = Br, Z = 4-BuC$_6$H$_4$ (**a**); Cl, 4-MeOC$_6$H$_4$NH (**b**); Cl, quinoline-8-ilamino (**c**); Cl, thiazole-2-ilamino (**d**); Br, 2-HOC$_6$H$_4$ (**e**); Cl, NH$_2$ (**f**). **4**, R = H, Z = quinoline-8-ilamino (**a**); H, 4-BuC$_6$H$_4$ (**b**); Me, 4-MeOC$_6$H$_4$NH (**c**).

of 59% from reagents **1a** and **8** in boiling ethanol with catalysis by HClO$_4$ [21].

The three-component condensation of croton aldehyde **10a** with CH-acid **2** and α-chloroacetamide **3f** proceeds differently through intermediates **D** and **E**. It is carried out in boiling ethanol in the presence of an equimolar amount of EtONa. The Michael addition, and not the expected Knoevenagel condensation, turned out to be the first stage of the reaction. Resulting 2-[(4-methyl-3-cyanopyridine-2-yl)thio]acetamide **11** in a DMF solution at 20°C under the action of KOH is intramolecularly cyclized into 3-amino-4-methylthieno[2,3-b]pyridine-2-carboxamide **12**, which cyclocondensated with cyclohexanone **13** in boiling glacial acetic acid to form 9′-methyl-1′H-spiro(cyclohexane-1,2′-pyrido[3′,2′:4,5]-thieno[3,2-d]pyrimidine)-4′(3′H)-one **14**, which is a promising intermediate for the creation of anticancer drugs [22] (Scheme 2).

Heterocyclic system, 6,11-dihydropyrimido[5,4-b]-thieno[3′,2′:2,3]pyrido[2,3-d]pyrimidine **16**, was synthesized by multicomponent condensation of benzaldehyde **10b**, cyanothioacetamide **2**, 4-bromo-phenacyl bromide **15**, and formamide. The Knoevenagel reaction is also initially realized in the course of this process. Resulting benzylidencyanothioacetamide **F** in ethanol in the presence of Et$_3$N attaches CH-acid **2**. Corresponding adduct **G,** that has arisen in this way, is intramolecularly cyclized into triethylammonium pyridine-2-thiolate **H**, alkylated by compound **15** to thioester of type **11**. Subsequently, under the action of alkali, cyclization into thienopyridine **I** occurred, which, when boiled in formamide, formed final tetraheterocyclic system **16** (Scheme 2).

1,3-Diphenylbut-2-en-1-one **17** reacts with a twofold excess of malononitrile **18** in boiling ethanol in the presence of Et$_3$N to form 2-(6-methyl-4,6-diphenyl-3-cyano-5,6-dihydropyridine-2(1H)-ylidene)malononitrile **19** (*method a*). The reaction pathway probably includes

Scheme 2.
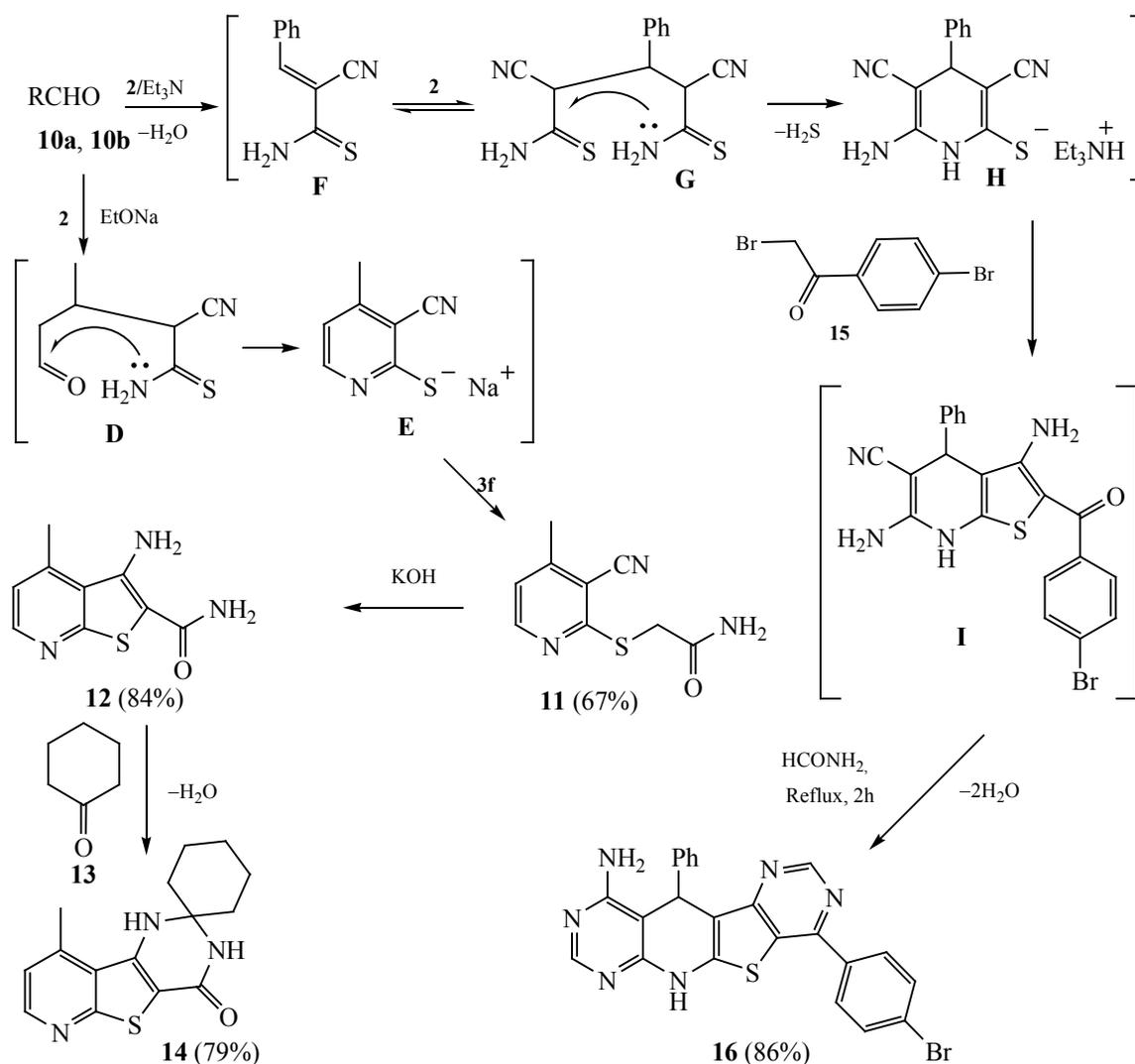
10, R = CH=CHMe (**a**), Ph (**b**).

the formation of Knoevenagel alkene **K**, which was later joined by malonitrile **18** according to Thorpe [20] to form intermediate **L**. The latter is unstable under reaction conditions, which leads to the implementation of the aza-Michael intramolecular reaction and the formation of final structure **19** (Scheme 3).

The same result was obtained by self-condensation of 2-(1-phenylethylidene)malonitrile **20** in ethanol at 20°C, catalyzed by Et₃N (*method b*). The probable reaction scheme involves the formation of Michael adduct **M**, which eliminates malonitrile **18** and forms new alkene **K**. Then released malononitrile **18** attaches to alkene **K**

to form corresponding enaminonitrile **L**. The aza-Michael reaction, which is then realized, stops the formation of final structure **19** (Scheme 3). The process of alkene **20** conversion into intermediate **K** through adduct **M** refers to a variant of the Michael reaction, which proceeds as the exchange by methylene components [23, 24].

The spectral characteristics confirm the structure of the synthesized compounds (see the Experimental). Compounds **4b**, **4c**, **11**, and **19** were studied by the XRD method in order to clarify the mechanism of the above transformations and to determine unambiguously the structure of their products.

Scheme 3.
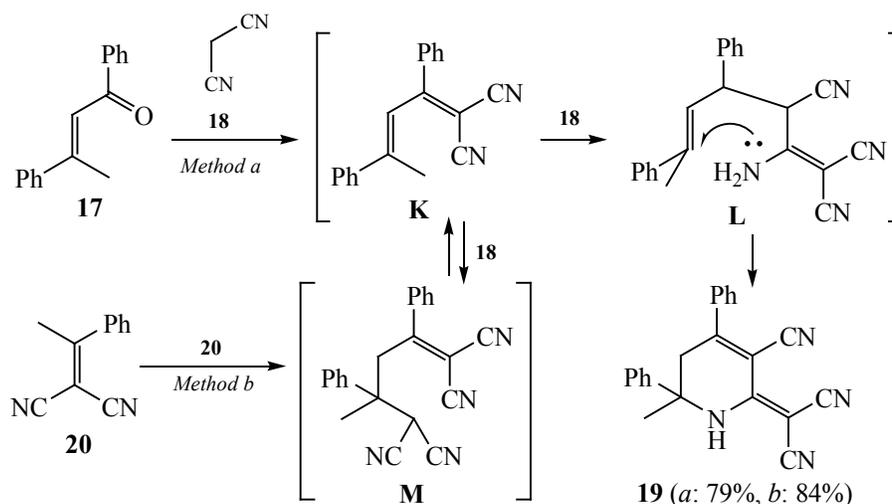
The structure of compound **4b** molecule and the corresponding numbering of atoms are shown in Fig. 1. The amino and carbonyl groups in compound **4b** are practically coplanar to the central bicyclic thieno[2,3-*b*]pyridine fragment (the standard deviation of atoms is 0.029 Å), which is defined by the presence of both a long chain of conjugated bonds and a strong intramolecular hydrogen bond N–H⋯O (Table 1 and Fig. 1). The phenyl cycle is turned relative to the plane of the central bicyclic fragment by 33.9(1)°. The *n-b*utyl substituent takes a typical conformation ("*all-trans*") and is located perpendicular to the phenyl cycle.

In the crystal, the molecules of compound **4b** are located at van der Waals distances (Fig. 2). The structure of the molecule of compound **4c** and the corresponding numbering of atoms are shown in Fig. 3. Unlike compound **4b**, the NH₂ amino group in compound **4c** has a pyramidal configuration (the sum of the valence angles at the nitrogen atom is 350(7)°), and the amide group is slightly twisted with respect to the central bicyclic thieno[2,3-*b*]-pyridine fragment (the corresponding interplane angle is 11.81(17)°). The observed structure of compound **4c** molecule is probably determined by the presence in the crystal structure of a branched system of strong hydrogen bonds of intramolecular N–H⋯O and intermolecular
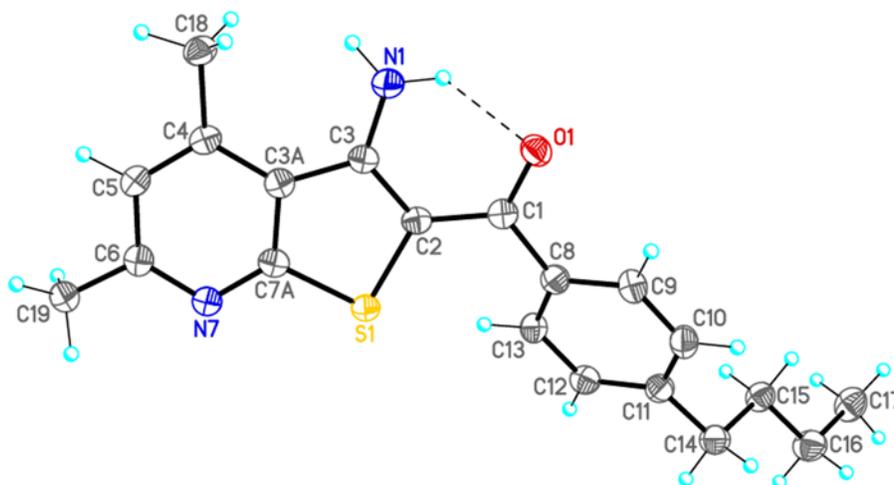
Fig. 1. Molecular structure of compound **4b** in the representation of atoms by ellipsoids of anisotropic displacements with a 50% probability. The dashed line shows the intramolecular hydrogen bond N–H⋯O.

Table 1. Hydrogen bonds in structures **4b**, **4c**, **11**, and **19**

D–H···A	d(D–H), Å	d(H···A), Å	d(D···A), Å	DHA angle, deg
Compound **4b**				
$N^1–H^{1A}···O^1$	0.91(4)	1.96(4)	2.686(4)	136(4)
Compound **4c**				
$N^1–H^1···N^{7\ a}$	0.95(3)	2.17(3)	3.053(3)	154(3)
$N^3–H^{3B}···O^1$	0.93(4)	2.07(4)	2.760(3)	129(3)
$N^3–H^{3B}···O^{1\ b}$	0.93(4)	2.43(4)	3.189(3)	138(3)
Compound **11**				
$N^2–H^{2A}···O^{1\ c}$	0.82(2)	2.06(2)	2.884(2)	179(2)
$N^2–H^{2B}···O^{1\ d}$	0.87(2)	2.25(2)	2.915(2)	133(2)
Compound **19**				
$N^1–H^1···N^{7\ e}$	0.903(16)	2.130(16)	3.0184(15)	167.6(13)

Crystallographic operations for generating symmetrically equivalent atoms: [a] $–x+11/2$, $y–1/2$, $–z+1/2$; [b] $–x+1$, $–y+1$, $–z+1$; [c] $–x+11/2$, $y+1/2$, $–z+11/2$; [d] x, $y+1$, z; [e] $–x+2$, $–y+1$, $–z+1$.

N–H···N types, and also weak intermolecular bonds of N–H···O type (Table 1, Fig. 4, frame structure).

The phenyl substituent is turned by 52.86(6)° relative to the plane of the central bicyclic fragment, and the methoxy group is practically coplanar to the phenyl cycle (the torsion angle $C^{10}–C^{11}–O^{11}–C^{14}$ is –9.7(4)°).
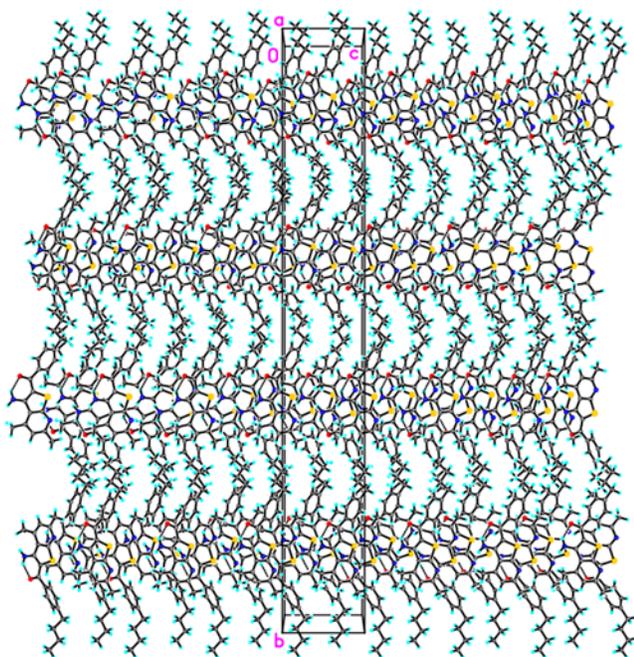
Fig. 2. Crystal structure of compound **4b** along the crystallographic axis *a*. The dashed lines show intramolecular hydrogen bonds.

The structure of the compound **11** molecule and the corresponding numbering of atoms are shown in Fig. 5. Excluding the hydrogen atoms of the methyl and methylene groups, the molecule of compound **11** consists of two almost flat fragments, (4-methyl-3-cyanopyridine-2-yl)thiol (the standard deviation of the atoms is 0.064 Å) and acetamide (the standard deviation of the atoms is 0.060 Å), having a common fragment $–S–CH_2–$ and located almost perpendicular to each other (the angle between these planes is equal to 84.16(4)°). In the crystal, the molecules of compound **11** form H-linked tapes along the crystallographic axis *b* (Table 1, Fig. 6). The tapes are located at van der Waals distances (Fig. 7).

The structure of the compound **19** molecule and the corresponding numbering of atoms are shown in Fig. 8. The central tetrahydropyridine cycle in the molecule of compound **19** takes the conformation of an asymmetric bath with the deviation of nitrogen N^1 and carbon C^6 atoms from the middle plane drawn through the remaining atoms of the cycle by 0.421(2) and 0.908(2) Å, respectively. The phenyl substituent at the carbon atom C^4 is turned relative to the basal plane of the tetrahydropyridine cycle by 44.06(7)°. It is important to note that the more voluminous phenyl substituent at the carbon atom C^6 occupies a less sterically preferred axial position, which is determined, apparently, by the direction of the chemical reaction. The molecule of compound **19** contains the asymmetric carbon atom C^6. The crystal of compound **19** represents a racemate.
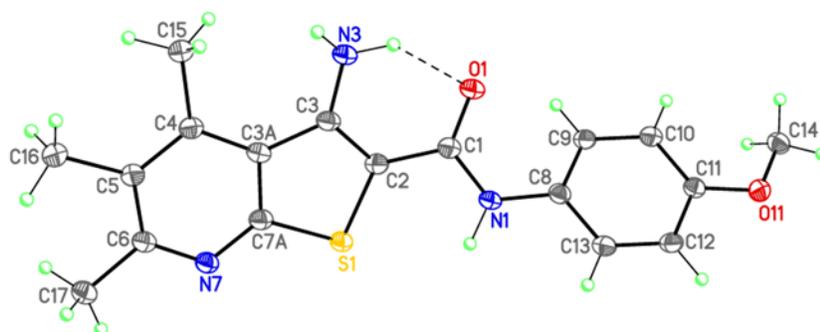
Fig. 3. Molecular structure of compound **4c** in the representation of atoms by ellipsoids of anisotropic displacements with a 50% probability. The dashed line shows the intramolecular hydrogen bond N–H···O.

In the crystal, molecules of compound **19** form centrosymmetric H-linked dimers by means of intermolecular hydrogen bonds N–H···N (Table 1, Fig. 9). Dimers are located at van der Waals distances (Fig. 10).

EXPERIMENTAL

Unit cell parameters and reflection intensities for crystals of compounds **4b, 4c, 11**, and **19** were measured at the "XRD" synchrotron station of the "Kurchatov Institute" National Research Center, using a Rayonix SX-165 two-coordinate detector (φ-scanning in steps of 1.0°). The experimental data were processed using the *iMOSFLM* program, which is part of the CCP4 software package [25]. For the obtained data, the absorption of X-ray radiation was considered according to the Scala program [26]. The main structural data and refinement parameters are presented in Table 2. The structures are determined by direct methods and refined by the full-matrix least squares method by F^2 in the anisotropic approximation for noN–Hydrogen atoms. The hydrogen atoms of amino groups were revealed objectively in difference Fourier syntheses and refined isotropically with fixed displacement parameters ($U_{iso}(H) = 1.2U_{eq}(N)$). The positions of the remaining hydrogen atoms in all compounds were calculated geometrically and included in the refinement with fixed positional parameters (the "rider" model) and isotropic displacement parameters ($U_{iso}(H) = 1.5U_{eq}(C)$ for CH_3 groups and $1.2U_{eq}(C)$ for the remaining groups). All calculations were carried out using the SHELXTL software package [27]. Tables of atomic coordinates, bond lengths, valence and torsion angles, and anisotropic displacement parameters for compounds **4b**,

Fig. 4. Crystal structure of compound **4c** along the crystallographic axis *c*. Dashed lines show intra- and intermolecular hydrogen bonds.
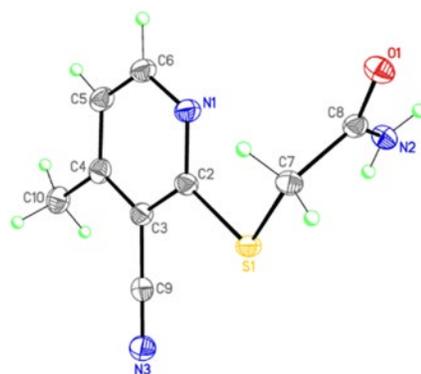
Fig. 5. Molecular structure of compound **11** in the representation of atoms by ellipsoids of anisotropic displacements with a 50% probability.
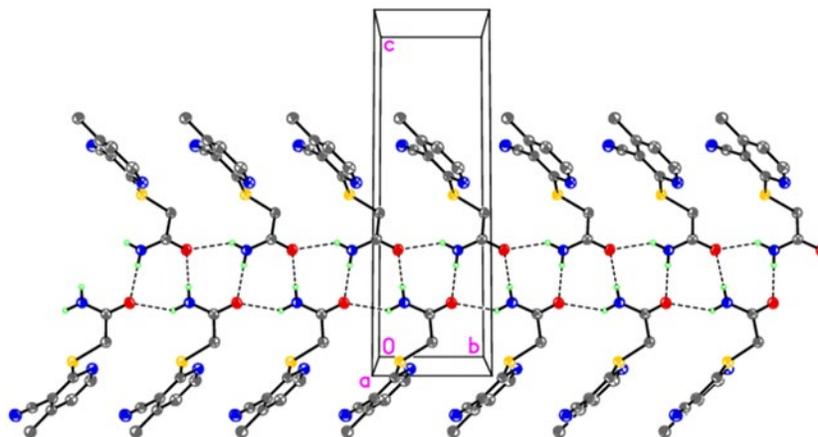
Fig. 6. H-linked bands of compound **11** molecules along the crystallographic axis *b*. The dashed lines show intermolecular hydrogen bonds N–H⋯O.
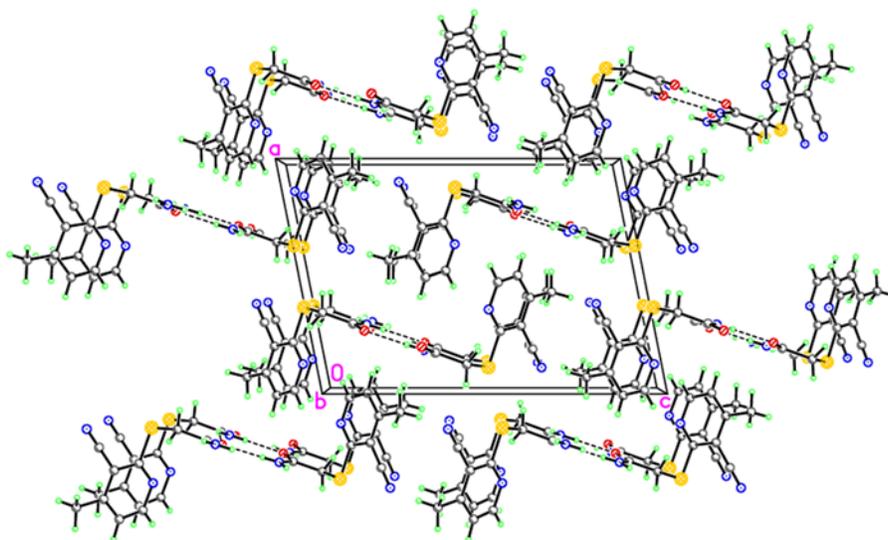
Fig. 7. Crystal structure of compound **11** along the crystallographic axis *b*. Dashed lines show intermolecular hydrogen bonds.
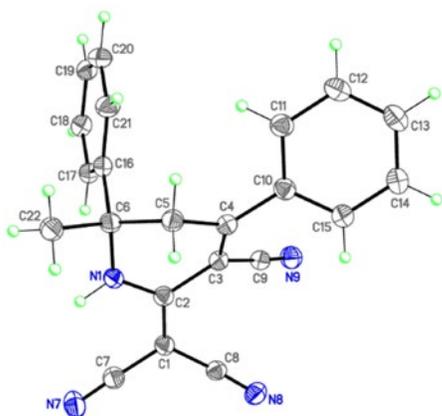
Fig. 8. Molecular structure of compound **19** in the representation of atoms by ellipsoids of anisotropic displacements with a 50% probability.
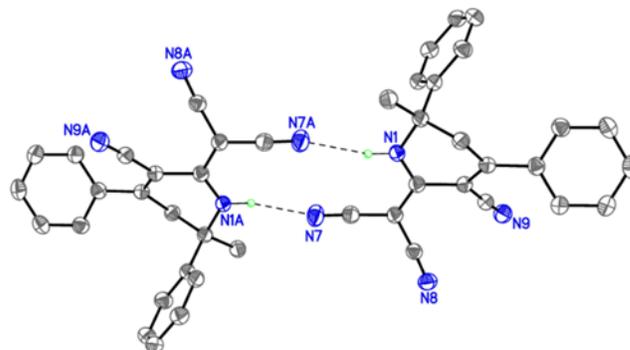
Fig. 9. Centrosymmetric H-linked dimers of compound **19** molecules. Dashed lines show intermolecular hydrogen bonds N–H⋯N.
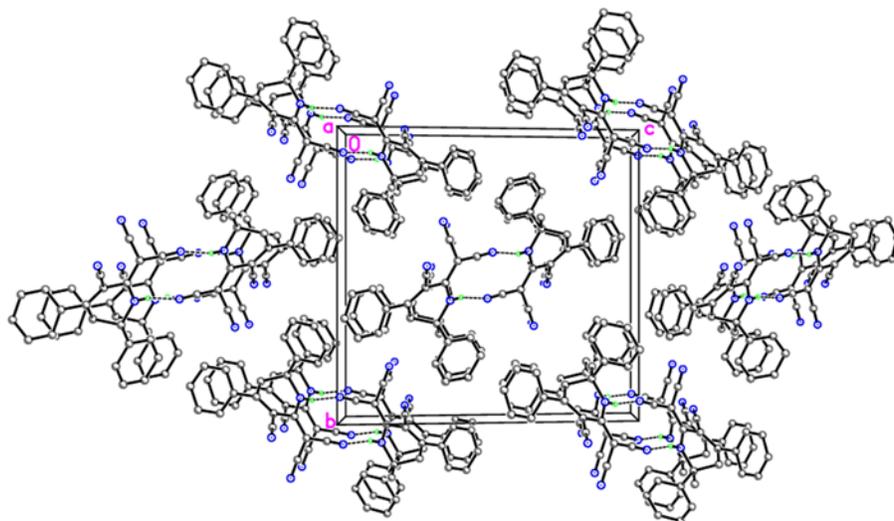
Fig. 10. Crystal structure of compound **19** along the crystallographic axis *a*. Dashed lines show intermolecular hydrogen bonds N–H···N.

Table 2. Crystal structure data for compounds **4b**, **4c**, **11**, and **19**

Compound	**4b**	**4c**	**11**	**19**
Elemental composition	$C_{20}H_{22}N_2OS$	$C_{18}H_{19}N_3O_2S$	$C_9H_9N_3OS$	$C_{22}H_{16}N_4$
Molecular weight	338.46	341.42	207.25	336.39
λ, Å	0.79313	0.79475	0.79373	0.79373
T, K	100(2)	100(2)	100(2)	100(2)
Single crystal size, mm	0.12×0.15×0.15	0.03×0.15×0.15	0.19×0.23×0.26	0.12×0.18×0.25
Syngony	Rhombic	Monoclinic	Monoclinic	Monoclinic
Space group	*F*dd2	*P*2₁/n	*P*2₁/n	*P*2₁/n
a, Å	10.9809(12)	13.783(3)	11.4899(16)	6.4330(7)
b, Å	67.403(7)	7.3400(9)	5.1570(7)	16.6089(17)
c, Å	9.1603(9)	16.159(3)	16.476(2)	17.229(2)
α, deg	90	90	90	90
β, deg	90	101.364(13)	101.239(13)	99.745(6)
γ, deg	90	90	90	90
V, Å³	6780.0(12)	1602.7(5)	957.5(2)	1814.3(3)
Z	16	4	4	4
d_{calc}, g/cm³	1.326	1.415	1.438	1.232
F(000)	2880	720	432	704
μ, mm⁻¹	0.263	0.289	0.408	0.094
$θ_{max}$, deg	2.02–31.03	1.99–30.97	2.22–30.98	1.92–30.98
Measured reflections	14445	13374	11570	14003
Independent reflections, R_{int}	3834, 0.071	3480, 0.032	2182, 0.063	4075, 0.044
Observed reflections (with $I > 2σ(I)$)	3638	3017	1865	3357
Refinement parameters	228	231	135	240
R_1 ($I > 2σ(I)$)	0.041	0.056	0.038	0.040
wR_2 (all data)	0.095	0.153	0.102	0.108
GOF by F^2	1.042	1.050	1.039	1.046
T_{min}; T_{max}	0.954; 0.963	0.945; 0.985	0.891; 0.916	0.963; 0.975
Extinction coefficient	0.0028(3)	0.052(5)	0.019(2)	0.034(3)
$Δρ_{max}$; $Δρ_{min}$, e/Å³	0.433; –0.385	0.454; –0.447	0.301; –0.326	0.204; –0.161

4c, **11**, and **19** are deposited in the Cambridge Structural Data Bank, the deposit numbers CCDC 2269289 (**4b**), CCDC 2269290 (**4c**), CCDC 2269291 (**11**) and CCDC 2269292 (**19**).

IR spectra were obtained on an IKS-40 device in vaseline oil. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR–400 spectrophotometer (399.97 and 100 MHz, respectively) in DMSO-d_6 solutions with TMS as the internal standard. Mass spectra were taken on an Agilent 1100 Series spectrometers with a selective detector: Agilent LS/MSDLS (samples of compounds **4b**, **7**, **11**, **12**, **14**, **16**, and **19** were injected in a CH$_3$COOH matrix, EI ionization, 70 eV), KRATOS MS-890 (70 eV) with direct injection of compounds **4c** and **6** into an ion source, and a high-resolution Orbitrap Elite mass spectrometer (**4a** and **9**). The HRMS sample was dissolved in 1 mL of DMSO, diluted 100 times with 1% HCOOH in CH$_3$CN, and injected into an ionization source by electrospraying with a syringe pump at a rate 40 µL/min. The gas flows of the source were switched off, the voltage on the needle was 3.5 kV, and the capillary temperature was 275°C. The mass spectra were recorded in the modes of positive and negative ions in an orbital trap with a resolution of 480000. Internal calibrants were 2DMSO + H$^+$ ion (*m/z* 157.03515) for positive ions and dodecyl sulfate anion (*m/z* 265.14789) for negative ions. Melting points were determined on a Kofler block. The course of the reaction and the purity of the obtained compounds were controlled by TLC on Silufol UV-254 plates in the acetone-hexane system (3 : 5), with development by iodine vapor and UV irradiation.

3-Amino-4,6-dimethyl-5-*R*-2-*Z*-carbonylthieno-[2,3-*b*]pyridines (4a–4c). General procedure. To a mixture of 10 mmol of the corresponding 1,3-diketone **1a**, **1b** and 1.0 g (10 mmol) of cyanothioacetamide **2** in 20 mL of absolute ethanol, three drops of Et$_3$N were added and refluxed for 15 min. After cooling, 5.6 mL (10 mmol) of 10% KOH aqueous solution and 10 mmol of alkylating reagent **3a-3c** were successively added to the stirred mixture, stirred for 2 h, the same amount of alkali was added again, stirred for 1 h, and diluted with an equal volume of water. The resulting precipitate was filtered off and washed with water, ethanol, and hexane.

3-Amino-4,6-dimethyl-*N*-(quinoline-8-yl)-thieno[2,3-*b*]pyridine-2-carboxamide (4a). Yield 2.6 g (75%), colorless powder, mp 275–277°C (BuOH), fluoresces under UV irradiation. IR spectrum, ν, cm^{-1}: 3411, 3332, 3300, 3288 (NH, NH$_2$), 1686 (CONH), 1645

(δ(NH$_2$)). ^{1}H NMR spectrum, δ, ppm: 2.49 s (3H, Me), 2.74 s (3H, Me), 7.07 br. s (3H, NH$_2$+H$_{arom}$), 7.59–7.70 m (3H$_{arom.}$), 8.42 d (1H$_{arom.}$, *J* 8.0 Hz), 8.67 d (1H$_{arom.}$, *J* 7.4 Hz), 8.96 s (1H$^5_{Py}$), 9.98 br. s (1H, NH). ^{13}C NMR spectrum, δ$_C$, ppm: 19.9, 23.9, 96.7, 99.5, 105.0, 109.8, 121.8, 122.3, 124.1 (2C), 125.2, 127.4 (2C), 128.5, 133.2, 136.7, 137.5, 146.4, 164.9. HRMS (ESI), *m/z*: found 349.1126 [*M* + H]$^+$. C$_{19}$H$_{16}$N$_4$OS. Calculated 349.1045.

(3-Amino-4,6-dimethylthieno[2,3-*b*]pyridine-2-yl)(4-butylphenyl)methanon (4b). Yield 2.4 g (76%), colorless crystals, mp 113–114°C (MeOH). IR spectrum, ν, cm^{-1}: 3316, 3284, 3202 (NH$_2$), 1699 (C=O), 1645 (δ(NH$_2$)). ^{1}H NMR spectrum, δ, ppm: 0.91 t (3H, Me, *J* 6.4 Hz), 1.12–1.81 m (4H, 2CH$_2$), 2.52 s (3H, Me), 2.76 s (3H, Me), 7.09 s (1H$^5_{Py}$), 7.34 d (2H$_{arom.}$, *J* 8.3 Hz), 7.69 d (2H$_{arom.}$, *J* 8.3 Hz), 8.00 br. s (2H, NH$_2$). Mass spectrum, *m/z* (I_{rel}, %): 339.1 (100) [*M* + 1]$^+$. C$_{20}$H$_{22}$N$_2$OS. *M* 338.5.

3-Amino-*N*-(4-methoxyphenyl)-4,5,6-tri-methylthieno[2,3-*b*]pyridine-2-carboxamide (4c). Yield 2.7 g (80%), colorless powder, mp 271–273°C (BuOH). IR spectrum, ν, cm^{-1}: 3330, 3300, 3244 (NH$_2$), 1670 (CONH), 1638 (δ(NH$_2$)). ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, Me), 2.56 s (3H, Me), 2.70 s (3H, Me), 3.75 s (3H, Me), 6.79 br. s (2H, NH$_2$), 6.85 d (2H$_{arom}$, *J* 7.9 Hz), 7.57 d (2H$_{arom.}$, *J* 7.9 Hz), 9.10 br. s (2H, NH). Mass spectrum , *m/z* (I_{rel}, %): 343 (2) [*M* + 2]$^+$, 342 (6) [*M* + 1]$^+$, 341 (39) [*M*]$^+$, 219 (52) [*M* − MeOC$_6$H$_4$NH]$^+$, 191 (10), 123 (100) [MeOC$_6$H$_4$NH$_2$]$^+$, 108 (17), 44 (7) [C=S]$^+$, 41 (4). C$_{18}$H$_{19}$N$_3$O$_2$S. *M* 341.4.

***N*-Allyl-3-amino-4,5,6-trimethyl-*N*-(thiazole-2-yl)thieno[2,3-*b*]pyridine-2-carboxamide (6)** was obtained similarly to compounds **4**, starting from 1.16 mL (10 mmol) of 1,3-diketone **1b**, 1.0 g (10 mmol) of CH-acid **2**, and 1.44 g (10 mmol) of α-chloro-*N*-(thiazol-2-yl) acetamide **3d**. The resulting precipitate was dissolved in 15 mL of DMF, and 5.6 mL (10 mmol) of a 10% aqueous solution of KOH and 0.85 mL (10 mmol) of allyl bromide **5** were successively added, stirred for 1 h, and left. After 24 h, the mixture was diluted with an equal volume of water, the resulting precipitate was filtered off, and washed with water, ethanol, and hexane. Yield 2.8 g (79%), yellow powder, mp 213–215°C (BuOH), fluoresces under UV irradiation. IR spectrum, ν, cm^{-1}: 3402, 3311, 3205 (NH$_2$), 1666 (CONH), 1642 (δ(NH$_2$)). ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, Me), 2.49 s (3H, Me), 2.64 s (3H, Me), 4.80 d (2H, NCH$_2$, *J* 4.0 Hz), 5.21 d (1H, CH$_2$=, $^2J_{trans}$ 17.0 Hz), 5.25 d (1H, CH$_2$=, $^2J_{cis}$ 10.3 Hz), 5.92–6.08 m (1H, =CH), 6.88 br. s (2H,

NH$_2$), 6.99 d (1H$^5_{thiazole}$, J 3.8 Hz), 7.48 d (1H$^4_{thiazole}$, J 3.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.4, 15.6, 24.0, 50.3, 105.9, 108.9, 118.6, 124.0, 125.9, 127.3, 132.0, 142.3, 147.1, 157.2, 157.3, 164.8, 172.0. HRMS (ESI), m/z: found 359.0998 [M + H]$^+$. C$_{17}$H$_{18}$N$_4$OS$_2$. Calculated 359.0922.

2-[2-(3-Amino-4,6-dimethylthieno[2,3-b]pyridine-2-carboxy)phenoxy]acetamide (7) was obtained similarly to compounds **4**, starting from 1.0 mL (10 mmol) of acetylacetone **1a**, 1.0 g (10 mmol) of CH-acid **2**, and 2.15 g (10 mmol) of *o*-hydroxyphenacyl bromide **3e**. The resulting precipitate was dissolved in 15 mL of DMF and 5.6 mL (10 mmol) of a 10% aqueous solution of KOH, and 0.94 g (10 mmol) of α-chloroacetamide **3f** were successively added, stirred for 1 h, and left. After 24 h, the mixture was diluted with an equal volume of water, the resulting precipitate was filtered off, and washed with water, ethanol, and hexane. Yield 2.9 g (81%), bright yellow powder, mp 205–207°C (BuOH). IR spectrum, ν, cm^{-1}: 3410, 3335, 3300, 3245 (NH$_2$), 1676 (CONH), 1644 (δ(NH$_2$)). ^{1}H NMR spectrum, δ, ppm: 2.47 s (3H, Me), 2.72 s (3H, Me), 4.50 s (2H, CH$_2$), 7.05 t (1H$_{arom}$, J 8.1 Hz), 7.11 d (1H$_{arom}$, J 8.4 Hz), 7.13 br. s (2H, NH$_2$), 7.36 d (1H$_{arom}$, J 7.5 Hz), 7.42 t (1H$_{arom}$, J 6.2 Hz), 7.46 s (1H$^5_{arom}$), 7.94 br. s (2H, CONH$_2$). ^{13}C NMR spectrum, δ_C, ppm: 20.5, 24.4, 67.7, 105.2, 114.0, 121.6, 122.1, 122.4, 128.4, 131.0, 131.9, 146.6, 152.5, 154.7, 161.3, 162.2, 170.4, 188.9. HRMS (ESI), m/z: found 356.1066 [M + H]$^+$. C$_{18}$H$_{17}$N$_3$O$_3$S. Calculated 356.0991.

1,3-Dimethylbenzene[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (9). To a solution of 1.0 mL (10 mmol) of acetylacetone **1a** in 25 mL of ethanol, 1.6 g (10 mmol) of benzimidazolylacetonitrile **8** and 1.4 mL (10 mmol) of triethylamine was added and refluxed for 2 h. After cooling the reaction mixture to room temperature, the resulting precipitate was filtered off and washed with ethanol and hexane. Yield 1.64 g (74%), light yellow cotton wool-like product, mp 235–237°C (AcOH), fluoresces under UV irradiation. IR spectrum, ν, cm^{-1}: 2214 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.58 s (3H, Me), 3.04 s (3H, Me), 6.83 s (1H$^2_{Py}$), 7.37 t (1H$_{arom}$, J 7.2 Hz), 7.56 t (1H$_{arom}$, J 7.5 Hz), 7.87 d (1H$_{arom}$, J 8.0 Hz), 8.22 d (1H$_{arom}$, J 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.6, 21.1, 113.4, 115.5, 115.9, 119.5, 121.7, 126.1 (2C), 130.1, 144.6, 145.0, 147.2, 149.7. Mass spectrum, m/z (I_{rel}, %): 222.2 (100) [M + 1]$^+$. Found, %: C 75.92; H .13; N 8.95. C$_{14}$H$_{11}$N$_3$. Calculated, %: C 76.00; H 5.01; N 18.99. M 221.3.

2-[(4-Methyl-3-cyanopyridine-2-yl)thio]acetamide (11). To a stirred solution of 0.83 mL (10 mmol) of crotonal **10a** in 10 mL of absolute ethanol, 1.0 g (10 mmol) of CH acid **2** and a solution prepared from 0.23 g of Na and 15 mL of absolute ethanol was added. After stirring for 10 min, the mixture was refluxed for 2 h and left. After 2 h, 0.94 g (10 mmol) of α-chloroacetamide **3f** was added to the stirred mixture, stirred for 3 h, and diluted with an equal volume of water. The resulting precipitate was filtered off and washed successively with water, ethanol, and hexane. Yield 1.4 g (67%), yellow crystals, mp 208–210°C (AcOH), sublimates into needle-shaped crystals at 175°C. IR spectrum, ν, cm^{-1}: 3398, 3325, 2990 (NH$_2$), 1666 (CONH), 2218 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, Me), 3.89 s (2H, CH$_2$), 6.99 br. s (1H, NH$_2$), 7.13 d (1H$^5_{Py}$, J 5.1 Hz), 7.37 br. s (1H, NH$_2$), 8.45 d (1H$^6_{Py}$, J 5.1 Hz). Mass spectrum, m/z (I_{rel}, %): 208.1 (100) [M + 1]$^+$. Found, %: C 52.02; H 4.32; N 20.20. C$_9$H$_9$N$_3$OS. Calculated, %: C 52.16; H 4.38; N 20.28. M 207.3.

3-Amino-4-methylthieno[2,3-b]pyridine-2-carboxamide (12). To a stirred solution of 2.1 g (10 mmol) of compound **11** in 15 mL of DMF, 5.6 mL (10 mmol) of a 10% aqueous solution of KOH was added at 20°C, stirred for 2 h, and diluted with an equal volume of water. The resulting precipitate was filtered off and washed successively with water, ethanol, and hexane. Yield 1.74 g (84%), light yellow crystals, mp 225–227°C (BuOH), sublimates into needle-shaped crystals at 200°C. IR spectrum, ν, cm^{-1}: 3402, 3385, 3330, 2296 (NH$_2$), 1672 (CONH), 1641 (δ(NH$_2$)). ^{1}H NMR spectrum, δ, ppm: 2.80 s (3H, Me), 6.69 br. s (2H, NH$_2$), 6.85 br. s (2H, NH$_2$), 6.99 d (1H$^5_{Py}$, J 4.3 Hz), 8.33 d (1H$^6_{Py}$, J 4.3 Hz). Mass spectrum, m/z (I_{rel}, %): 209 (5) [M + 2]$^+$, 208 (13) [M + 1]$^+$, 207 (100) [M]$^+$, 190 [M – NH$_3$]$^+$, 162 (33), 135 (42), 118 (40), 91 (17), 65 (18), 45 (19), 39 (15). C$_9$H$_9$N$_3$OS. M 207.3.

9′-Methyl-1′H-spiro(cyclohexane-1,2′-pyrido-[3′,2′:4,5]thieno[2,3-d]pyrimidine)-4′(3′H)-one (14). A mixture of 2.07 g (10 mmol) of compound **12** and 1.03 mL (10 mmol) of cyclohexanone **13** was refluxed for 2 h in 20 mL of glacial acetic acid. After the reaction mixture cooled, the resulting crystals were filtered off and washed with diethyl ether. Yield 2.3 g (79%), colorless fine-crystalline powder, mp 235–237°C (AcOH), fluoresces under UV irradiation. IR spectrum, ν, cm^{-1}: 3335 (NH), 1668 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.02–2.14 m (1H$_{cyclohexane}$), 1.43–1.59 m (7H$_{cyclohexane}$), 1.83–2.15 m

($2H_{cyclohexane}$), 2.78 s (3H, Me), 5.94 br. s (H^1, NH), 7.19 d (H^8, J 4.5 Hz), 7.93 br. s (1H, CONH), 8.43 d (H^7, J 4.5 Hz). Mass spectrum, m/z (I_{rel}, %): 288.1 (100) $[M + 1]^+$. Found, %: C 62.51; H 5.88; N 14.50. $C_{15}H_{17}N_3OS$. Calculated, %: C 62.69; H 5.96; N 14.62. M 287.1.

10-Amino-4-(4-bromophenyl)-11-phenyl-6,11-dihydropyrimido[5,4-*b*]thieno[3′,2′:2,3]pyrido[2,3-*d*]-pyrimidine (16). To a stirred solution of 1.0 mL (10 mmol) of benzaldehyde **10b** in 20 mL of ethanol at 20°C, 1.0 g (10 mmol) of CH acid **2** and 1 drop of Et_3N, stirred for 15 min until the crystallization of benzylidenecyanothioacetamide **F** began, was added. Then the same amount of cyanothioacetamide **2** and 1.4 mL (10 mmol) of Et_3N was added again, stirred for 1 h, and left. After 24 h, 2.8 g (10 mmol) of *p*-bromophenacyl bromide **15** was added, stirred for 4 h, 10 mL of DMF and 5.6 mL (10 mmol) of a 10% aqueous solution of KOH were added, stirred for 1 h, and diluted with an equal volume of water. The resulting precipitate was filtered off and refluxed in 20 mL of formamide for 2 h. After the reaction mixture cooled, the resulting precipitate was filtered off and washed with diethyl ether. Yield 4.2 g (86%), yellow powder, mp 338–340°C (dioxane), fluoresces under UV irradiation. IR spectrum, ν, cm^{-1}: 3404, 3381, 3300 (NH_2), 1644 ($\delta(NH_2)$). ^1H NMR spectrum, δ, ppm: 5.70 s (H^{11}), 6.66 br. s (2H, NH_2), 7.10 t ($1H_{arom}$, J 5.8 Hz), 7.20 t ($2H_{arom}$, J 6.0 Hz), 7.45 d ($2H_{arom}$, J 6.0 Hz), 7.82 d ($2H_{arom}$, J 6.6 Hz), 7.95 d ($2H_{arom}$, J 6.6 Hz), 9.02 s ($1H_{arom}$), 11.02 br. s (1H, NH^6). ^{13}C NMR spectrum, δ, ppm: 36.3, 66.8, 95.2, 111.4, 122.1, 124.8, 127.0, 128.2 (2C), 128.6 (2C), 130.3 (2C), 132.6 (2C), 136.6, 144.7, 149.5, 155.3, 155.5, 156.9, 160.0, 162.2. Mass spectrum, m/z (I_{rel}, %): 486 (100) $[M − 1]^+$. $C_{23}H_{15}BrN_6S$. M 487.4.

2-(6-Methyl-4,6-diphenyl-3-cyano-5,6-dihydropyridine-2(1*H*)-ylidenmalononitrile (19). *Method a.* A mixture of 2.2 g (10 mmol) of compound **17**, 1.32 g (20 mmol) of malononitrile **18**, and 3 drops of Et_3N in 20 mL of ethanol was refluxed for 1 h. After cooling the reaction mixture, the resulting precipitate was filtered off and washed with ethanol and hexane. Yield 2.7 g (79%).

Method b. A solution of 1.7 g (10 mmol) of substituted crotononitrile **20** and 3 drops of Et_3N in 20 mL of ethanol at 20°C was stirred for 2 h and left. After 24 h, the resulting precipitate was filtered off and washed with ethanol and hexane. Yield 2.8 g (84%), yellow crystals, mp 110–112°C (EtOH). IR spectrum, ν, cm^{-1}: 3538, 3474 (NH), 2219 sh. (C≡N). ^1H NMR spectrum, δ, ppm: 1.73 s (3H, Me), 3.32 d ($1H^5_{Py}$, ^2J 8.5 Hz), 3.77 d ($1H^5_{Py}$, ^2J 18.5 Hz), 7.11–7.32 m ($10H_{arom}$), 9.75 br. s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 28.5, 44.2, 49.6, 57.1, 101.2, 113.8, 115.0, 115.6, 125.0 (2C), 127.6, 127.8 (2C), 128.3, 128.8, 129.0, 132.2, 135.6, 142.9, 157.9, 169.0, 186.5. Mass spectrum, m/z (I_{rel}, %): 335 (100) $[M − 1]^+$. $C_{22}H_{16}N_4$. M 336.4.

CONCLUSION

Multicomponent condensation of carbonyl compounds, CH-acids, and alkylating reagents is initiated by the Knoevenagel reaction under mild conditions, and results in pyridines, tetrahydropyridines, thienopyridines, pyridothienopyrimidines, and pyrimido-thienopyridopyrimidines.

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