Synthesis of substituted 4-hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-2-ones

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Substituted 4-hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-2-ones were prepared by the reactions of 3-cyanopyridine-2(1*H*)-thiones with alkyl 4-chloroacetoacetates and by intramolecular cyclization of alkyl 4-(2-pyridylthio)acetoacetates or alkyl 3-(3-aminothieno[2,3-*b*]pyridin-2-yl)-3-oxopropionates under the action of bases.

Key words: 4-hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-2-ones, 3-cyanopyridine-2(1*H*)-thiones, alkyl 4-chloroacetoacetates, alkyl 4-(2-pyridylthio)acetoacetates, alkyl 3-(3-aminothieno[2,3-*b*]pyridin-2-yl)-3-oxopropionates.

Substituted 1*H*-thieno[2,3-*b*;4,5-*b*']dipyridines are difficultly accessible compounds. Only two approaches to the synthesis of these compounds are known.[1—4] The first approach involves the closure of the pyridine ring as a result of the reactions of substituted 3-aminothieno[2,3-*b*]pyridines with malonaldehyde acetal,[1] dimethylformamide diethyl acetal,[2] or malononitrile.[3] The second approach to the synthesis of substituted thieno[2,3-*b*;4,5-*b*']dipyridines involves the coupling of 2-aryl-3-bromo-1,1-dicyanopropene with 3-cyanopyridine-2(1*H*)-thiones occurring as consecutive reactions (nucleophilic substitution, the Thorpe—Ziegler reaction, and the Guareschi—Thorpe reaction).[3,4]

In the present work, we report the synthesis of substituted 4-hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-2-ones. These compounds were prepared in high yields in one stage without isolation of intermediates by the reactions of substituted 3-cyanopyridine-2(1*H*)-thiones (**1a—c'**) with alkyl 4-chloroacetoacetates (**2a,b**) (Scheme 1, method A). High yields of the final reaction products were achieved by introducing the reagents into the reaction mixture in a strictly specified order, the temperature conditions being controlled. Initially, an equimolar amount of KOH or EtONa was added to a suspension of the corresponding pyridine-2(1*H*)-thione **1** in ethanol at 20 °C and then alkyl 4-chloroacetoacetate **2** was added. After 0.5 h, a twofold excess of a base in ethanol was added to the reaction mixture and the mixture was brought to boiling, refluxed, and acidified with hydrochloric acid to produce compounds **3a—c'**. According to the second procedure (method B), compounds **3** were prepared by cyclization of alkyl 4-(3-cyano-2-pyridylthio)acetoacetates (**4** or **5**) under the action of a base (KOH, EtONa, or triethylamine).

We succeeded in preparing difficultly accessible thienopyridines **6f,g,j** under milder conditions, *viz.*, by treating esters **4f,g,j** with triethylamine. These compounds, in turn, underwent cyclization to the corresponding thienodipyridines **3f,g,j** under the action of KOH or EtONa (method C).

Compounds **4** and **5**, which are intermediates in the synthesis of compounds **3**, are readily prepared by the reactions of pyridine-2(1*H*)-thiones **1** with alkyl 4-chloroacetoacetates in DMF in the presence of an equimolar amount of KOH. Since the yields of compounds **3** are virtually independent of the procedure used for their preparation or of the nature of the alkyl chloroacetoacetate (Table 1), it can be noted that method A is the simplest and most convenient procedure.

The procedures developed by us were used for the synthesis of difficultly accessible annelated heterocycles **3** and **6** as well as of their hydrogenated analogs **8** and **9** (Scheme 2).

Pyridothienonaphthyridines **3j,k** were synthesized with the use of 3-cyanonaphthyridine-2(1*H*)-thiones **1j,k**. Compounds **3j,k** were prepared in one stage according to method A in quantitative yields.

The use of 1,4-dihydropyridine-2-thiolate **7** in the synthesis of compounds **8** and **9** is of interest. Assuming that the reaction of salt **7**, which is poorly soluble in ethanol, with compound **2a** can proceed not only at the S atom but also at the N atom, we performed initially the cation exchange reaction by adding a 10% aqueous solution of KOH to a suspension of compound **7** in ethanol, which made it also possible to completely bind HCl that formed. Then, an equimolar amount of ester **2a** was added to the resulting solution at 40 °C. Under these conditions, we succeeded in preparing bicyclic compound **8** in good yield. This compound appeared to be rather stable and underwent cyclization to thienodipyridine **9** upon boiling in ethanol in the presence of an excess of KOH. Analogous stable substituted 3-amino-

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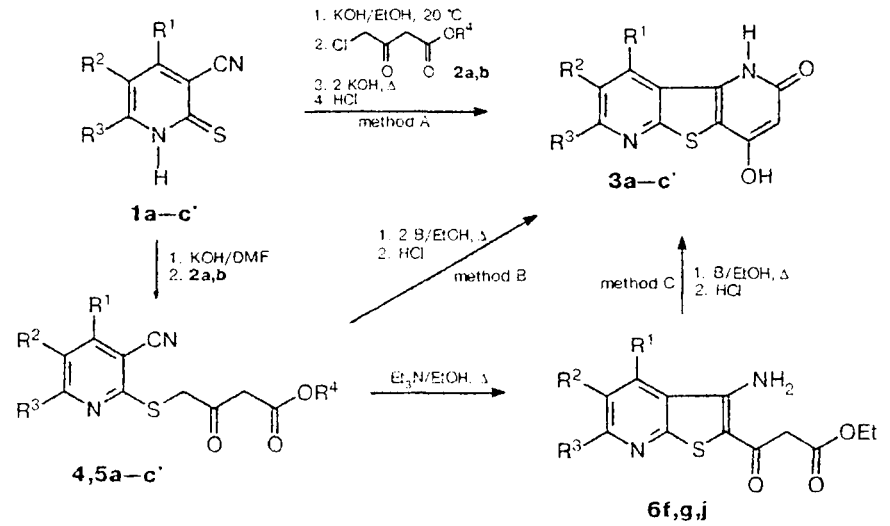
Scheme 1



B = KOH, EtONa
2: R^4 = Et (**a**), Pr^i (**b**); **4**: R^4 = Et, **5**: R^4 = Pr^i

1, 3–6	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
c	H	H	Ad-1
d	H	H	Ph
e	H	Me	Et
m	$(CH_2)_3$		Me

1, 3–6	R^1	R^2—R^3
f	H	$(CH_2)_3$
g	H	$(CH_2)_4$
h	H	$(CH_2)_5$
i	H	$(CH_2)_6$
j	H	$CH_2N(Me)CH_2CH_2$
k	H	$N(CH_2CH_2)_2CH$
l	2-C_4H_3S	$(CH_2)_4$

1, 3–6	R^1	R^2	R^3
n	4-C_5H_4N	H	Me
o	CF_3	H	Me
p	CF_3	H	Ph
q	CF_3	H	2-C_4H_3S
r	Ph	H	Ph
s	4-$MeOC_6H_4$	H	Ph
t	2-C_4H_3S	H	2-C_4H_3S
u	4-FC_6H_4	H	2-C_4H_3S

1, 3–6	R^1	R^2	R^3
v	4-ClC_6H_4	H	2-C_4H_3S
w	4-$MeOC_6H_4$	H	2-C_4H_3S
x	2-$MeOC_6H_4$	H	2-C_4H_3S
y	H	CN	NH_2
z	4-ClC_6H_4	CN	NH_2
a'	2-ClC_6H_4	CN	NH_2
b'	2-C_4H_3S	CN	NH_2
c'	3-C_4H_3S	CN	NH_2

Table 1. 4-Hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-2-ones (**3**)

Compound	Yield (%) (method)	Found (%) / Calculated C	H	N	Molecular formula	IR, ν/cm^{-1} NHCO	OH and others	^{1}H NMR, δ C(3)H	R^1	R^2 (s)	R^3	NH(OH) (br.s)
3a	92 (A)	56.58	3.18	11.81	$C_{11}H_8N_2O_2S$	1624	3405	6.86	8.56 d	7.49	2.61 s	
		56.89	3.47	12.06								
3b	87 (A)	58.34	3.84	11.09	$C_{12}H_{10}N_2O_2S$	1626	3408	6.21	2.67 s	7.13 s	2.90 s	11.30
	99 (B)	58.52	4.09	11.37								
3c	92 (A)	67.75	5.48	7.62	$C_{20}H_{20}N_2O_2S$	1615, 1646	3393 br	5.97	8.69 d	7.54 d	1.75 m, 2.00 m, 2.07 m	
	99 (B)	68.16	5.72	7.95								
3d	95 (A)	65.02	3.24	9.27	$C_{16}H_{10}N_2O_2S$	1628	3410 br	5.99	8.07 d	7.51 m*	8.19 m, 7.51 m*	
	92 (B)	65.29	3.42	9.52								
3e	82 (A)	59.64	4.39	10.58	$C_{13}H_{12}N_2O_2S$	1620	3405 br	5.84	8.42 s	2.40 s	1.26 t, 2.89 q	11.86
	75 (B)	59.98	4.65	10.76								
3f	88 (A)	60.48	3.67	10.63	$C_{13}H_{10}N_2O_2S$	1622 br	3295 br	5.93	8.62 s	2.16 t, 3.46 m		
	86 (B)	60.45	3.90	10.85								
	68 (C)											
3g	90 (A)	61.58	4.14	10.03	$C_{14}H_{12}N_2O_2S$	1634 br	3390 br	5.81	8.42 s	1.86 m, 2.87 t, 2.98 t		11.72
	74 (B)	61.75	4.44	10.29								
	87 (C)											
3h	97 (A)	62.61	4.67	9.52	$C_{15}H_{14}N_2O_2S$	1620 br	3340	5.82	8.40 s	1.66 m, 1.85 m, 2.88 m, 3.06 m		11.60
	99 (B)	62.92	4.93	9.78								
3i	72 (A)	63.71	5.12	9.04	$C_{16}H_{16}N_2O_2S$	1640	3540	5.81	8.42 s	1.34 m, 1.73 m, 2.88 t, 3.04 t		11.80
	99 (B)	63.98	5.37	9.33								
3j	87 (A)	58.23	4.37	14.47	$C_{14}H_{13}N_3O_2S$	1638 br	3410 br	6.07	8.53 s	2.53 s, 2.93 s, 3.18 s, 3.43 m		11.97
	79 (B)	58.52	4.56	14.62								

(*to be continued*)

Table 1. (*continued*)

Compound	Yield (%) method	Found (%) / Calculated C	H	N	Molecular formula	IR, ν/cm^{-1} NHCO	OH and others	^{1}H NMR, δ C(3)H	R^1	R^2 (s)	R^3 NH(OH) (br.s)	
3k	90 (A)	59.34 / 60.19	4.05 / 4.38	13.88 / 14.04	$C_{15}H_{13}N_3O_2S$	1632 br	3392 br	6.03	8.91 s	1.82 m, 2.23 m, 3.12 m, 3.58 m, 3.71 m		12.01
3l	90 (A) 92 (B)	60.72 / 61.00	3.64 / 3.98	7.52 / 7.90	$C_{18}H_{14}N_2O_2S_2$	1628	3412	5.81	7.39 d, 7.48 t, 7.95 d	1.23 m, 1.86 m, 2.60 t, 3.04 t		11.48
3m	79 (A) 91 (B)	61.42 / 61.75	4.18 / 4.44	10.03 / 10.29	$C_{14}H_{12}N_2O_2S$	1632	3418	6.30	2.15 m, 2.52 m, 2.98 m		2.88 s	11.52
3n	96 (A)	61.93 / 62.12	3.34 / 3.58	13.27 / 13.58	$C_{16}H_{11}N_3O_2S$	1627	3392 br	6.26	2.68 s	7.37 s	8.10 d, 8.94 d	11.80
3o	77 (A)[a] 80 (B)	47.72 / 48.00	2.12 / 2.35	9.04 / 9.33	$C_{12}H_7FN_2O_2S$	1642	3444	6.37		7.80 s	3.11 s	10.71
3p	69 (A)	56.14 / 56.35	2.23 / 2.50	7.52 / 7.73	$C_{17}H_9F_3N_2O_2S$	1638	3420	6.39		8.35 s	7.67 m, 8.28 m	11.80
3q	63 (A)[b] 64 (B)	48.62 / 48.91	1.73 / 1.92	7.36 / 7.60	$C_{15}H_7F_3N_2O_2S_2$	1638	3404 br	6.38		8.26 s	7.24 m, 7.79 m, 8.13 d	11.70
3r	61 (A)[c] 72 (B)	71.04 / 71.33	3.63 / 3.81	7.37 / 7.56	$C_{22}H_{14}N_2O_2S$	1622	3395 br	5.87	7.52 m, 7.69 m, 8.21 m*	7.87 s	7.52 m, 7.69 m, 8.21 m*	11.52
3s	70 (A) 59 (B)	68.67 / 68.98	3.84 / 4.03	6.76 / 7.00	$C_{23}H_{16}N_2O_3S$	1628	3407	5.96	3.88 s, 7.17 d, 7.68 d	7.87 s	7.53 m, 8.24 m	11.82
3t	97 (A) 93 (B)	56.28 / 56.53	2.47 / 2.64	7.06 / 7.32	$C_{18}H_{10}N_2O_2S_3$	1626	3418	6.04	7.21 t, 7.76 d, 7.91 d	7.97 s	7.33 t, 7.89 d, 8.02 d	11.79
3u	76 (A) 69 (B)	60.73 / 60.90	2.62 / 2.81	6.86 / 7.10	$C_{20}H_{11}FN_2O_2S_2$	1628	3382	6.04	7.40 t, 7.75 t	7.88 s	7.20 t, 7.71 d, 8.01 d	11.75
3v	64 (A) 93 (B)	58.21 / 58.46	2.59 / 2.70	6.64 / 6.82	$C_{20}H_{11}ClN_2O_2S_2$	1630	3374	6.07	6.61 d, 7.22 d	7.87 s	7.20 t, 7.72 d, 8.00 d	11.67
3w	68 (A)[d] 89 (B)	61.93 / 62.05	3.25 / 3.47	6.72 / 6.89	$C_{21}H_{14}N_2O_3S_2$	1630	3386	5.94	3.94 s, 7.17 d,* 7.64 d	7.85 s	7.21 m,* 7.74 d, 8.02 d	11.78
3x	71 (A)	61.74 / 62.05	3.18 / 3.47	6.54 / 6.89	$C_{21}H_{14}N_2O_3S_2$	1630	3390	5.88	3.70 s, 7.20 m,* 7.29 d, 7.48 d, 7.63 t	7.89 s	7.20 m, 7.75 d, 8.01 d	11.76
3y	75 (A)	51.92 / 51.16	2.13 / 2.34	21.38 / 21.69	$C_{11}H_6N_4O_2S$	1620 (NH), 1634, 2196 (C≡N)	3405	5.73	8.68 s		7.29 br.s	11.74
3z	60 (A)	55.19 / 55.37	2.18 / 2.46	14.95 / 15.19	$C_{17}H_9ClN_4O_2S$	1618 (NH), 1636, 2196 (C≡N)	3986	5.93	7.56 d, 7.67 d		7.34 br.s	11.53
3a′	64 (A)	55.08 / 55.37	2.37 / 2.46	14.87 / 15.19	$C_{17}H_9ClN_4O_2S$	1618 (NH), 1635, 2198 (C≡N)	3400	5.96	7.48–7.70 m		7.38 br.s	11.45
3b′	69 (A)	52.68 / 52.93	2.15 / 2.37	16.22 / 16.46	$C_{15}H_8N_4O_2S_2$	1620 (NH), 1636, 2196 (C≡N)	3403	5.79	7.38 t,* 7.50 d, 8.00 d		7.36 br.s*	11.62

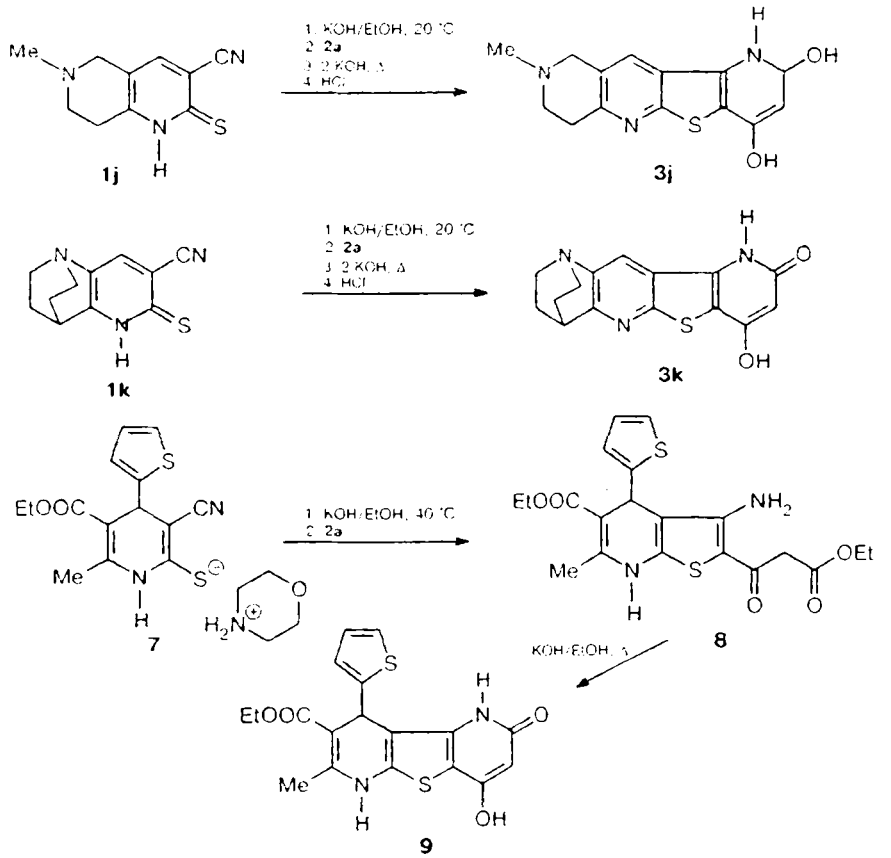
(*to be continued*)

Table 1. *(continued)*

Compound	Yield (%) method	Found / Calculated (%) C	H	N	Molecular formula	IR, ν/cm^{-1} NHCO	OH and others	^{1}H NMR, δ C(3)H	R^1	R^2 (s)	R^3	NH(OH) (br.s)
3c[a]	64 (A)	52.71 52.93	2.12 2.37	16.18 16.46	$C_{15}H_8N_4O_2S_2$	1618 (NH), 1635, 2198 (C≡N)	3406	5.73	7.42 d.[*] 7.91 d. 8.03 s		7.35 br.s[*]	11.56

[*] The signal is overlapped with the signal for the protons of another fragment. [a] M.p. 333–335 °C. [b] M.p. 352–353 °C. [c] M.p. 356–357 °C. [d] M.p. 319–321 °C.

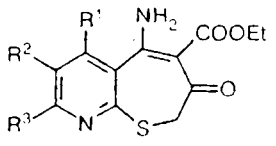
Scheme 2



4,7-dihydrothieno[2,3-*b*]pyridines were isolated in other cascade reactions of salts of substituted 3-cyano-1,4-dihydropyridine-2-thiolates with *N*-cyanochloroacetamide[5] or 2-aryl-3-bromo-1,1-dicyanopropene.[4]

The suggested procedure was used for the synthesis of pyridothienopyrimidine **12**. This compound was prepared according to two procedures (Scheme 3) from the corresponding pyrimidine-6(1*H*)-thione **10** and compound **2a** either directly or in a stepwise manner with isolation of ethyl 4-(pyrimidin-4-ylthio)acetoacetate (**11**) followed by its cyclization.

In the conversions under study, analogous sequences of the reactions were observed, *viz.*, the nucleophilic substitution, the closure of the five-membered ring, and then the closure of the six-membered ring. Although molecules of compounds **4**, **5**, and **11** contain two nucleophilic carbon atoms of the $CH_2(S)$ and $CH_2(COOR)$ groups, we did not observe cyclization to the seven-membered ring yielding compounds **13**.



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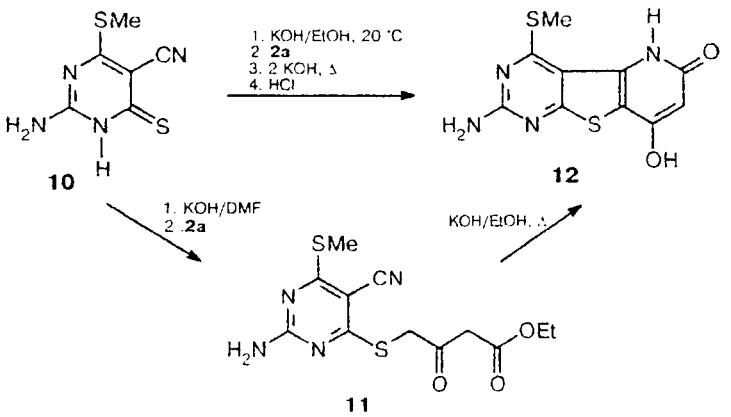
Probably, the regioselectivity observed is associated with different nucleophilicities of the CH_2 groups in compounds **4**, **5**, and **11**. Apparently, the $CH_2(S)$ group is more nucleophilic than the $CH_2(COOR)$ group. The ^{1}H NMR spectra of these compounds have two signals

Scheme 3



for the protons of the $CH_2(S)$ and $CH_2(COOR)$ groups as singlets at δ 4.18—4.48 and 3.28—3.86, respectively, along with signals for the protons of the substituted heterocyclic fragment and the ester group (Table 2). The ^1H NMR spectra of compounds **6** and **8** have signals for the protons of the NH_2 and CH_2COOEt groups.

Based on comparison of the ^1H NMR spectra of compounds **3**, **9**, and **12** with the spectra of substituted pyridin-2(1*H*)-ones,[3,6] it can be suggested that thieno[2,3-*b*;4,5-*b*']dipyridines exist as pyridin-2(1*H*)-ones. The signal for the proton of the C(3)H group is shielded by the C(2)=O and C(4)—OH groups and is shifted upfield to δ 5.81—6.86. In the NMR spectrum of sodium 2-oxo-7,8,9,10,11,12-hexahydrocycloocta[*e*']-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-4-olate **3i**, this signal is even more shielded and is shifted to δ 4.89. The signal for the proton of the NH group is broadened and is observed at δ 10.71—12.01, which is characteristic of pyridin-2(1*H*)-ones.[3] It was difficult to assign the signal for the proton of the OH group due to deuterium exchange, association with water, and poor solubility of compounds **3** in other solvents used in NMR spectroscopy.

The structures of compounds **3**, **4**—**6**, **8**, **9**, **11**, and **12** are also confirmed by their IR spectra. The IR spectra of compounds **4** and **5** have absorption bands of the CN, C=O, and COOR groups (see Table 2). On going from compounds **4** and **5** to compounds **6** and **8**, absorption bands of the NH_2 group appear in the IR spectra. The absorption band of the C=O group is decreased due to conjugation of the latter with the C(2)=C(3) group of the thiophene fragment (see Table 1). The IR spectra of compounds **3**, **9**, and **12** have absorption bands of the NH(CO) and OH groups.

To summarize, we developed regioselective procedures for the synthesis of functionally substituted 4-hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-2-ones, including those fused with tetrahydropyridine and quinuclidine.

Experimental

The ^1H NMR spectra were recorded on a Bruker AM-300 instrument (300 MHz) in DMSO-d_6. The IR spectra were obtained on a Perkin—Elmer 577 instrument in KBr pellets. The characteristics of compounds **3a**—**c**' are given in Table 1. The characteristics of esters **4** and **5a**—**w** are listed in Table 2.

Alkyl 4-(3-cyano-2-pyridylthio)acetoacetate (4 and 5a—w). A 10% aqueous solution of KOH (5.6 mL) was added with stirring to a suspension of 3-cyanopyridine-2(1*H*)-thione (**1a**—**w**) (0.01 mol) in DMF. Then the corresponding ester **2a** or **2b** (0.01 mol) was added and the reaction mixture was stirred at room temperature. After 20—30 min, the mixture was diluted with water. The precipitate that formed was separated and washed successively with water, ethanol, and hexane (see Table 2).

4-Hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-2-ones (3a—c').

Method *A*. The corresponding pyridine-2(1*H*)-thione (**1a**—**c**') (0.01 mol) was added to a solution of KOH or EtONa (0.01 mol) in EtOH (30 mL) and then ester **2** (0.01 mol) was added. After 0.5 h, a solution of KOH or EtONa (0.02 mol) in EtOH (20 mL) was added to the resulting suspension. The reaction mixture was refluxed for 3—5 min, cooled, and acidified with concentrated HCl (3 mL). The precipitate that formed was separated and washed successively with water, ethanol, and hexane and compounds **3a**—**c**' were obtained (see Table 1).

Sodium 2-oxo-7,8,9,10,11,12-hexahydrocycloocta-1*H*-thieno[2,3-*b*;4,5-*b*']dipyridin-4-olate **3i** was prepared analogously without acidification of the reaction mixture. The yield was 62%, m.p. >360 °C. ^1H NMR, δ: 1.32 (m, 4 H, CH_2, CH_2); 1.70 (m, 4 H, CH_2, CH_2); 2.83 (t, 2 H, CH_2); 3.00 (t, 2 H, CH_2); 4.89 (s, 1 H, C(3)H); 8.32 (s, 1 H, C(13)H). IR, ν/cm^{-1}: 1615 br (NHCO), 3100—3580 w (OH).

Method *B*. The corresponding ester **4** or **5a**—**w** (0.01 mol) was added to a solution of KOH or EtONa (0.02 mol) in EtOH (40—50 mL) and the reaction mixture was refluxed for 3—5 min. Then the reaction mixture was worked up analogously to method A.

Method *C*. The corresponding thienopyridine **6f,g,j** (0.01 mol) was added to a solution of KOH or EtONa (0.01 mol) in EtOH (40—50 mL) and the reaction mixture was refluxed for 3—5 min. Then the reaction mixture was worked up analogously to method *A*.

Thienopyridines (6f,g,j). Triethylamine (0.2 mL) was added to a suspension of the corresponding alkyl 4-(2-pyridyl-

Table 2. Alkyl 4-(2-pyridylthio)acetoacetates (**4** and **5**)

Compound	Y[a] (%)	M.p./°C	Found (%) / Calculated C	H	N	Molecular formula	IR, ν/cm⁻¹ C=O	COOR	C≡N	^{1}H NMR, δ R¹	R²	R³	R⁴	S-CH₂ (s)	H₂ (s)
4a	73	97–99	49.86 / 50.10	4.82 / 5.07	9.68 / 10.06	$C_{13}H_{14}N_2O_3S$	1722	1745	2218	8.15 d	7.34 d	2.51 s	1.17 t, 4.12 q	4.22	3.72
4b	93	103–104	57.24 / 57.52	5.19 / 5.52	9.31 / 9.58	$C_{14}H_{16}N_2O_3S$	1720	1746	2217	2.43 s	4.05 s	2.49 s	1.26 t, 4.12 q	4.18	3.74
4c	84	91–92	66.08 / 66.31	6.25 / 6.58	6.73 / 7.03	$C_{22}H_{26}N_2O_3S$	1727	1745	2216	8.13 d	7.24 d	1.73 m, 1.88 m, 2.07 m	1.18 t, 4.09 q	4.33	3.28
4d	82	93–95	63.09 / 63.51	4.48 / 4.74	7.96 / 8.23	$C_{18}H_{16}N_2O_3S$	1724	1744	2215	8.27 d	7.88 d	7.54 m, 8.10 m	1.12 t, 4.07 q	4.45	3.82
4e	90	83–84	58.45 / 58.80	5.64 / 5.92	8.85 / 9.14	$C_{15}H_{18}N_2O_3S$	1725	1740	2216	7.96 s	2.26 s	1.21 t,[b] 2.87 q	1.21 t,[b] 4.10 q	4.30	3.77
4f	84	90–92	58.84 / 59.19	5.11 / 5.30	8.93 / 9.20	$C_{15}H_{16}N_2O_3S$	1726	1742	2218	8.00 s	2.08 q, 2.96 t	2.88 t,	1.20 t, 4.10 q	4.23	3.80
4g	82	94–95	60.08 / 60.36	5.53 / 5.70	8.61 / 8.80	$C_{16}H_{18}N_2O_3S$	1723	1743	2218	7.90 s	1.78 m, 2.82 t	2.69 t,	1.20 t, 4.12 q	4.21	3.80
4h	80	96–98	61.19 / 61.42	5.85 / 6.06	8.22 / 8.43	$C_{17}H_{20}N_2O_3S$	1720	1738	2219	7.95 s	1.57 m, 2.74 t,	1.80 m, 2.96 t	1.19 t, 4.10 q	4.25	3.79
4i	81	105–107	62.09 / 62.40	6.24 / 6.40	7.83 / 8.09	$C_{18}H_{22}N_2O_3S$	1722	1748	2216	7.97 s	1.30 br.s, 2.74 t,	1.65 m, 2.91 t	1.19 t, 4.10 q	4.25	3.79
4l	70	71–72	59.64 / 59.98	4.82 / 5.03	6.72 / 6.99	$C_{20}H_{20}N_2O_3S_2$	1724	1746	2218	7.25 t, 7.30 d, 7.86 d	1.69 q, 2.54 t,	1.82 q, 2.92 t	1.21 t, 4.13 q	4.25	3.84
4m	68	84–87	60.14 / 60.36	5.53 / 5.70	8.61 / 8.80	$C_{16}H_{18}N_2O_3S$	1720	1743	2218	2.08 m, 2.97 q	2.85 q,	2.40 s, 4.10 q	1.19 t,	4.22	3.79
4o	87	98–100	48.19 / 48.55	3.49 / 3.78	7.74 / 8.09	$C_{14}H_{13}F_3N_2O_3S$	1728	1752	2220		7.62 s	2.63 s	1.22 t, 4.12 q	4.37	3.81
4q	84	114–116	49.39 / 49.27	3.22 / 3.16	6.84 / 6.76	$C_{17}H_{13}F_3N_2O_3S_2$	1722	1744	2220		8.13 s	7.29 t, 7.96 d, 8.23 d	1.17 t, 4.10 q	4.48	4.32
4t	85	131–132	55.83 / 56.05	3.52 / 3.76	6.35 / 6.54	$C_{20}H_{16}N_2O_3S_3$	1722	1742	2218	7.25 t, 7.84 d, 7.95 d,[b]	7.89 s	7.33 t, 7.95 d,[b] 8.10 d	1.18 t, 4.10 q	4.43	3.74
4u	82	173–174	59.63 / 59.99	3.68 / 3.89	6.07 / 6.36	$C_{22}H_{17}FN_2O_3S_2$	1722	1740	2216	7.42 t, 7.78 m	7.82 s	7.25 t, 7.85 d, 8.09 d	1.18 t, 4.11 q	4.44	3.86
4v	87	138–139	57.74 / 57.83	3.67 / 3.75	6.02 / 6.13	$C_{22}H_{17}ClN_2O_3S_2$	1720	1734	2215	7.65 d, 7.75 d	7.81 s[b]	7.24 t, 7.85 d,[b] 8.09 d	1.19 t, 4.11 q	4.45	3.84
4w	86	143–144	61.18 / 61.04	4.57 / 4.45	6.08 / 6.19	$C_{23}H_{20}N_2O_4S_2$	1722	1738	2216	3.37 s,[b] 7.16 d, 7.72 d	7.83 s	7.15 t, 7.88 d, 8.10 d	1.17 t, 4.10 q	4.45	3.37[b]
5b	81	92–93	58.67 / 58.80	5.71 / 5.92	8.93 / 9.14	$C_{15}H_{18}N_2O_3S$	1727	1746	2216	2.47 s	7.10 s	2.42 s	1.20 s, 1.24 s, 4.94 m	4.24	3.77
5l	77	68–70	60.63 / 60.85	5.18 / 5.35	6.64 / 6.76	$C_{21}H_{22}N_2O_3S$	1725	1740	2217	7.25 t, 7.70 d, 7.85 d	1.69 m, 2.54 t,	1.82 m, 2.93 t	1.20 s, 1.23 s, 4.96 m	4.24	3.80
5r	85	84–86	69.48 / 69.75	4.93 / 5.15	6.34 / 6.51	$C_{25}H_{22}N_2O_3S$	1724	1742	2215	7.60 m, 8.20 m	7.91 s	7.54 m, 7.77 m	1.13 s, 1.17 s, 4.91 m	4.49	3.83
5s	90	93–95	67.64 / 67.81	5.05 / 5.25	5.86 / 6.08	$C_{26}H_{24}N_2O_4S$	1725	1745	2216	3.87 s, 7.15 d, 7.75 d	7.86 s	7.54 m, 8.18 m	1.12 s, 1.18 s, 4.90 m	4.45	3.80
5u	71	173–174	60.53 / 60.78	4.06 / 4.21	5.92 / 6.16	$C_{23}H_{19}FN_2O_3S_2$	1726	1744	2215	7.45 t, 7.80 d	7.89 s	7.25 t, 7.86 d, 8.10 d	1.15 s, 1.19 s, 4.92 m	4.45	3.84
5v	83	159–162	58.42 / 58.65	3.88 / 4.07	5.72 / 5.95	$C_{23}H_{19}ClN_2O_3S_2$	1725	1743	2216	7.68 d, 7.75 d	7.88 s	7.25 t, 7.86 d, 8.10 d	1.15 s, 1.19 s, 4.92 m	4.44	3.84

[a] The yield of the product. [b] The signal is overlapped with the signal for the protons of another fragment.

thio)acetoacetate (**4f,g,j**) (0.01 mol) in EtOH (30—40 mL) and the reaction mixture was refluxed for 10—20 min. After cooling, the precipitate that formed was separated and washed with ethanol and hexane.

Ethyl 3-(3-amino-6,7-dihydro-5*H*-cyclopenta[*e*]thieno[2,3-*b*]pyridin-2-yl)-3-oxopropionate (6f). The yield was 2.6 g (87%), m.p. 193—195 °C. Found (%): C, 58.72; H, 5.21; N, 9.03. $C_{15}H_{16}N_2O_3S$. Calculated (%): C, 59.19; H, 5.30; N, 9.20. ^{1}H NMR, δ: 1.23 (t, 3 H, CH_3); 2.17 (m, 2 H, C(6)H_2); 3.00 (m, 4 H, C(5)H_2, C(7)H_2); 3.71 (s, $COCH_2$); 4.13 (q, 2 H, CH_2); 8.00 (br.s, 2 H, NH_2); 8.36 (s, 1 H, C(4)H). IR, ν/cm^{-1}: 1615 (NH_2), 1727 (C=O), 3179, 3273, 3380 (NH_2).

Ethyl 3-(3-amino-5,6,7,8-tetrahydrocyclohexa[*e*]thieno-[2,3-*b*]pyridin-2-yl)-3-oxopropionate (6g). The yield was 2.7 g (84%), m.p. 199—200 °C. Found (%): C, 60.08; H, 5.56; N, 8.63. $C_{16}H_{18}N_2O_3S$. Calculated (%): C, 60.36; H, 5.70; N, 8.80. ^{1}H NMR, δ: 1.38 (t, 3 H, CH_3); 1.89 (m, 4 H, C(6)H_2, C(7)H_2); 2.93 (m, 4 H, C(5)H_2, C(8)H_2); 3.67 (s, 2 H, $COCH_2$); 4.18 (q, 2 H, CH_2); 7.96 (br.s, 2 H, NH_2); 8.25 (s, 1 H, C(4)H). IR, ν/cm^{-1}: 1620 (NH_2), 1728 (C=O), 3180, 3270 sh, 3384 (NH_2).

Ethyl 3-(3-amino-6-methyl-5,6,7,8-tetrahydrothieno[2,3-*b*]-1,6-naphthyridin-2-yl)-3-oxopropionate (6j). The yield was 2.6 g (78%), m.p. 136—137 °C. Found (%): C, 57.32; H, 5.60; N, 12.41. $C_{16}H_{19}N_3O_3S$. Calculated (%): C, 57.64; H, 5.74; N, 12.60. ^{1}H NMR, δ: 1.27 (t, 3 H, CH_3); 2.43 (s, 3 H, N—CH_3); 2.68 (t, 2 H, C(7)H_2); 3.09 (m, 4 H, C(5)H_2, C(8)H_2); 4.15 (q, 2 H, CH_2); 7.94 (br.s, 2 H, NH_2); 8.20 (s, 1 H, C(4)H). IR, ν/cm^{-1}: 1618 (NH_2), 1727 (C=O), 3180, 3262 sh, 3382 (NH_2).

Ethyl 3-amino-2-ethoxycarbonylacetyl-6-methyl-4-(2-thienyl)-4,7-dihydrothieno[2,3-*b*]pyridin-5-carboxylate (8). Ester **2a** (1.65 g, 0.01 mol) and KOH (0.56 g, 0.01 mol) were added to a suspension of salt **7** (3.9 g, 0.01 mol) in ethanol (30—40 mL). The reaction mixture was heated to 40 °C. The precipitate that formed was separated and washed with ethanol and hexane. The yield of ester **8** was 3.6 g (86%), m.p. 115—117 °C. Found (%): C, 54.34; H, 5.34; N, 6.61. $C_{20}H_{22}N_2O_5S_2$. Calculated (%): C, 55.28; H, 5.10; N, 6.45. ^{1}H NMR, δ: 1.16 (t, 3 H, CH_3); 1.20 (t, 3 H, CH_3); 2.31 (s, 3 H, CH_3); 3.48 (s, 2 H, $COCH_2$); 3.59 (t, 2 H, CH_2O); 4.12 (t, 2 H, CH_2O); 5.47 (s, 1 H, C(4)H); 6.85 (s, 2 H, NH_2); 6.93 (t, 1 H, CH of thiophene); 7.23 (d, 1 H, CH of thiophene); 7.33 (m, 2 H, NH, CH of thiophene). IR, ν/cm^{-1}: 1627, 1638 (NH, NH_2); 1687, 1703, 1712 (C=O); 3128, 3245, 3326 (NH, NH_2).

Ethyl 4-hydroxy-7-methyl-2-oxo-9-(2-thienyl)-1,2,6,9-tetrahydrothieno[2,3-*b*;4,5-*b*′]dipyridine-8-carboxylate (9). Compound **8** (4.2 g, 0.01 mol) was added to a solution of KOH (0.56 g, 0.01 mol) in ethanol (40 mL) and the reaction mixture was refluxed for 5 min, cooled, and acidified with a 10% HCl solution (10 mL). The precipitate that formed was separated and washed successively with water, ethanol, and hexane. The yield of compound **9** was 2.8 g (72%), m.p. >300 °C. Found (%): C, 56.02; H, 3.97; N, 7.02. $C_{18}H_{16}N_2O_4S_2$. Calculated (%): C, 55.65; H, 4.15; N, 7.21. ^{1}H NMR, δ: 1.18 (t, 3 H, CH_3); 2.35 (s, 3 H, CH_3); 4.20 (q, 2 H, CH_2); 5.48 (s, 1 H, C(9)H); 5.97 (s, 1 H, C(3)H); 6.92 (t, 1 H, CH of thiophene); 7.24 (d, 1 H, CH of thiophene); 7.31 (d, 1 H, CH of thiophene); 7.44 (s, 1 H, N(6)H); 11.98 (br.s, 1 H, N(6)H). IR, ν/cm^{-1}: 1632, 1638 (NHCO); 1643 (NH); 1682, 1708 (C=O); 3190, 3226 (NH); 3470 (OH).

Ethyl 4-(2-amino-5-cyano-6-methylthiopyrimidin-4-ylthio)-acetoacetate (11) was prepared analogously to compounds **4**. The yield was 2.9 g (94%), m.p. 245—248 °C. Found (%): C, 46.95; H, 4.43; N, 18.51. $C_{12}H_{14}N_4O_2S_2$. Calculated (%): C, 46.44; H, 4.55; N, 18.05. ^{1}H NMR, δ: 1.21 (t, 3 H, CH_3); 2.52 (s, 3 H, CH_3); 3.80 (d, 2 H, CH_2S); 4.07—4.25 (m, 4 H, CH_2CH_3, CH_2O); 7.67 (br.s, 2 H, NH_2). IR, ν/cm^{-1}: 1628, 1639 (NH_2); 1684, 1712 (C=O); 2223 (C≡N); 3142, 3278 (NH_2).

2-Amino-8-hydroxy-4-methylthiopyrido[3′,2′:4,5]thieno-[2,3-*d*]pyrimidin-6(5*H*)-one (12) was prepared analogously to compounds **3** according to methods A and B in 64% and 71% yields, respectively. M.p. >300 °C. Found (%): C, 43.72; H, 3.13; N, 19.63. $C_{10}H_8N_4O_2S_2$. Calculated (%): C, 42.85; H, 2.88; N, 19.99. ^{1}H NMR, δ: 2.47 (s, 3 H, CH_3); 6.75 (s, 1 H, C(7)H); 7.72 (s, 2 H, NH_2); 11.20 (s, 1 H, NH); 11.68 (s, 1 H, OH). IR, ν/cm^{-1}: 1627, 1645 (NH, NH_2); 3185, 3245, 3468 (NH, NH_2, OH).

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