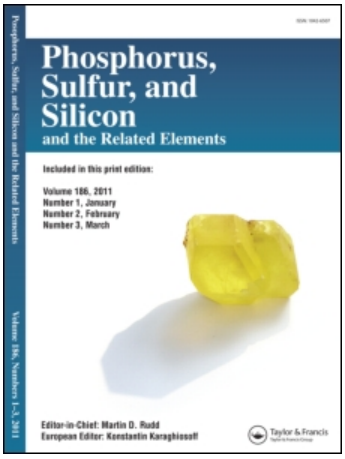

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Reactions with Pyridine-2-Thiones: A New Route for the Synthesis of Several New Pyridines and Fused Azolo- and Azinopyridines

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REACTIONS WITH PYRIDINE-2-THIONES: A NEW ROUTE FOR THE SYNTHESIS OF SEVERAL NEW PYRIDINES AND FUSED AZOLO- AND AZINOPYRIDINES

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*The synthetic potential of our newly synthesized 3-cyano-pyridinethione derivatives (**1a,b**) was further demonstrated via their use to synthesize each of 2-S-ethoxycarbonylmethylpyridines (**3a,b**), thieno[2,3-b] pyridines (**4a,b**); (**7a,b**), pyrido[3',2':4,5]thieno[3,2-c]pyridazines (**8a,b**), 2-methylthiopyridines (**9a,b**), 2-hydrazinopyridines (**10a,b**), 3-aminopyrazolo[3,4-b]pyridines (**11a,b**), pyrazolo[3,4-b]pyridin-3-ylphenylthioureas (**12a,b**), and 3-diazotized aminopyrazolo[3,4-b] pyridine (**13a,b**) derivatives via their reactions with the corresponding reagents. Structures of the newly synthesized heterocyclic derivatives were established on the basis of elemental analyses and spectral data studies.*

Keywords: 2-S-ethoxycarbonylpyridines; Pyrazolopyridines; pyridine-2-thiones; pyridothienopyridazines; thienopyridines

INTRODUCTION

In continuation to our previous work[1–12] directed toward the synthesis of new pyridine and fused azolo and azinopyridine derivatives of anticipated biological activities,[13–18] we report a new and convenient method for the synthesis of such ring systems utilizing new starting materials.

In the last few years several publications[1–12] appeared from this laboratory dealing with the synthesis of pyridine-2-thiones as starting materials for the synthesis of several types of heterocyclics, but none of which utilized 4-naphthyl-3-cyanopyridine-2-thiones as the starting

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materials. The above finding prompted our interest to synthesize new derivatives of such ring systems utilizing the very recently obtained pyridine-2-thiones **1a,b**.[11]

RESULTS AND DISCUSSION

It has been found that each of 3-cyano-4-(α-naphthyl)-5-ethoxycarbonyl-6-methylpyridine-2-thione (**1a**) and 3-cyano-4-(β-naphthyl)-5-ethoxycarbonyl-6-methylpyridine-2-thione (**1b**) reacted with ethyl chloroacetate (**2**) in cold methanolic sodium methoxide to afford the products corresponding to addition and dehydrochlorination reactions in each case. The IR spectra of these products showed bands corresponding to CN and ester-CO groups while their ^{1}H NMR spectra revealed the signals of two CH_3CH_2(q, t), SCH_2(s), CH_3(s) and naphthyl (m) protons in each case (cf. Table I). Based on the above mentioned data these reaction products could be formulated as the 2-S-ethoxycarbonylmethylpyridine derivatives **3a,b**, respectively. Moreover, the mass spectra of compounds **3a,b** gave m/z = 434, which agreed with the molecular weight of the formula $C_{24}H_{22}N_2O_4S$ of the assigned structure (cf. Figure 1). Further confirmation of the structure of **3a,b** arose from their cyclization in boiling ethanolic KOH to give the corresponding thieno[2,3-b]pyridine derivatives **4a,b**. The IR spectrum of each of **4a,b** showed no bands of the CN function while the bands of the new NH_2 group was detected. On the other hand, the ^{1}H NMR spectra of **4a,b** revealed absence of signals of the $-SCH_2-$ group and the presence of the signals of the NH_2 protons. The above findings proved that the CN and the $-SCH_2-$ groups both were involved in the cyclization step leading to **4a,b**. Compounds **4a,b** were also authenticated by heating each of **1a,b** with ethyl chloroacetate (**2**) in boiling 10% ethanolic KOH solution.

Compounds **1a,b** reacted also with chloroacetone (**5a**) in cold methanolic sodium methoxide to afford the corresponding thieno[2,3-b] pyridine derivatives **7a,b** via the nonisolable intermediates **6a,b**. The reaction seemed to proceed through dehydrochlorination to give the nonisolable intermediates **6a,b** which underwent cyclization via addition of the $-SCH_2-$ hydrogens to the nitrile function. IR, ^{1}H NMR, and elemental analyses were the basis on which the structures of **7a,b** were established (cf. Tables I and II). Furthermore, compounds **7a,b** were authenticated via the reaction of each of **1a,b** with each of α-chloroacetylacetone (**5b**) and ethyl α-chloroacetoacetate (**5c**) via the intermediacy of each of the nonisolable **6c–f**. The nonisolable intermediates **6c–f** are assumed to be cyclized to give the corresponding nonisolable 3-imino

TABLE I IR and ^{1}H NMR Data

Comp.	IR [KBr, cm^{-1}]	^{1}H NMR [δ ppm]
3a	3056 (aromatic-CH); 2943 (sat. CH); 2189 (CN) and 1722 (ester-CO)	0.5 (t, 3H, pyridine $CH_2\mathbf{CH_3}$); 1.1 (t, 3H, $-CH_2COOCH_2\mathbf{CH_3}$); 2.8 (s, 3H, CH_3); 3.1 (s, 2H, CH_2); 3.8 (q, 2H, pyridine $\mathbf{CH_2}CH_3$); 4.1 (q, 2H, $-CH_2COO\mathbf{CH_2}CH_3$) and 7.3–8.0 (m, 7H, ArH's)
3b	3050 (aromatic-CH); 2933 (sat. CH); 2199 (CN) and 1728 (ester-CO)	
4a	3489, 3357 (NH_2); 3047 (aromatic-CH); 2981 (sat. CH): 1726 (pyridine ester-CO) and 162 (thiophene ester-CO)	0.4 (t, 6H, two $CH_2\mathbf{CH_3}$); 2.7 (s, 3H, CH_3); 3.7 (q, 4H, two $\mathbf{CH_2}CH_3$); 5.2 (s, br., 2H, NH_2) and 7.2–8.1 (m, 7H, ArH's)
4b	3472, 3343 (NH_2); 3036 (aromatic-CH): 2967 (sat. CH): 1722 (pyridine ester-CO) and 1683 (thiophene ester-CO)	
7a	3467, 3293 (NH_2); 3047 (aromatic-CH): 2976 (sat. CH) and 1714 (ester-CO)	0.5 (t, 3H, $CH_2\mathbf{CH_3}$); 2.8 (s, 3H, CH_3); 3.7 (q, 2H, $\mathbf{CH_2}CH_3$); 3.8 (s, 3H, $CO\mathbf{CH_3}$); 5.2 (s, br., 2H, NH_2) and 7.3–8.1 (m, 7H, ArH's)
7b	3445, 3312 (NH_2); 3039 (aromatic CH): 2976 (sat. CH) and 1718 (ester-CO)	0.45 (t, 3H, $CH_2\mathbf{CH_3}$); 2.75 (s, 3H, CH_3); 3.75 (q, 2H, $\mathbf{CH_2}CH_3$); 3.8 (s, 3H, $CO\mathbf{CH_3}$); 5.9 (s, br., 2H, NH_2) and 7.3–8.1 (m, 7H, ArH's)
8a	3032 (aromatic-CH); 2978 (sat. CH); 1725 (ester-CO) and 1702 (ketonic-CO)	0.8 (t, 3H, $CH_2\mathbf{CH_3}$); 2.4 (s, 3H, CH_3); 2.8 (s, 2H, CH_2); 3.9 (q, 2H, $\mathbf{CH_2}CH_3$) and 7.2–8.1 (m, 7H, ArH's)
8b	3041 (aromatic-CH); 2981 (sat. CH): 1722 (ester-CO) and 1700 (ketonic-CO)	
9a	3054 (aromatic-CH); 2978 (sat. CH); 2221 (CN) and 1725 (ester-CO)	0.4 (t, 3H, $CH_2\mathbf{CH_3}$); 2.8 (s, 6H, CH_3 and S-CH_3); 3.7 (q, 2H, $\mathbf{CH_2}CH_3$) and 7.3–8.0 (m, 7H, ArH's)
9b	3032 (aromatic-CH): 2980 (sat. CH); 2224 (CN) and 1722 (ester-CO)	
10a	3456, 3282, 3189 (NH_2, NH); 3071 (aromatic-CH): 2945 (sat. CH); 2216 (CN) and 1717 (ester-CO)	0.45 (t, 3H, $CH_2\mathbf{CH_3}$); 2.3 (s, br., 3H, NH, NH_2); 2.85 (s, 3H, CH_3); 3.75 (q, 2H, $\mathbf{CH_2}CH_3$) and 7.4–8.0 (m, 7H, ArH's)
10b	3451, 3287, 3195 (NH_2, NH); 3048 (aromatic-CH); 2965 (sat. CH); 2219 (CN) and 1721 (ester-CO)	

(Continued on next page)

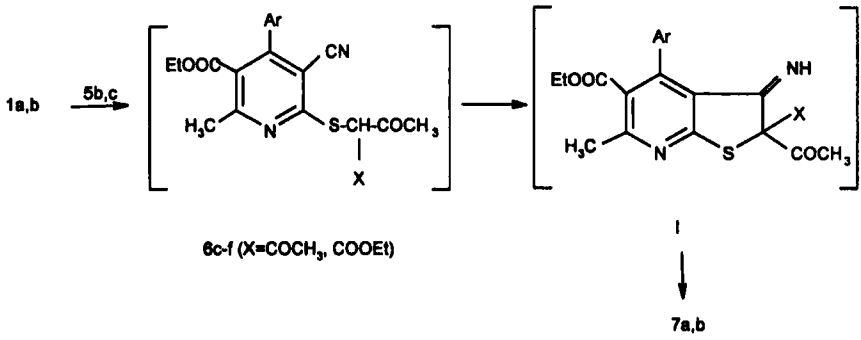
TABLE I IR and ^{1}H NMR Data *(Continued)*

Comp.	IR [KBr, cm^{-1}]	^{1}H NMR [δ ppm]
11a	3456, 3277, 3183 (NH_2, NH); 3037 (aromatic-CH); 2980 (sat. CH) and 1710 (ester-CO)	
11b	3455, 3280, 3196 (NH_2, NH); 3030 (aromatic-CH); 2976 (sat. CH) and 1715 (ester-CO)	0.8 (t, 3H, $CH_2\mathbf{CH_3}$); 2.6 (s, 3H, CH_3); 3.6 (s, br., 3H, NH, NH_2); 4.0 (q, 2H, $\mathbf{CH_2}CH_3$); and 7.4–8.0 (m, 7H, ArH's).
12a	3228, 3201, 3186 (three NH); 3047 (aromatic-CH); 2968 (sat. CH) and 1723 (ester-CO)	0.5 (t, 3H, $CH_2\mathbf{CH_3}$); 1.9 (s, br., 3H, NH, NH_2); 2.9 (s, 3H, CH_3); 3.8 (q, 2H, $\mathbf{CH_2}CH_3$); and 7.2–8.2 (m, 12H, ArH's)
12b	3221, 3197, 3173 (three NH); 3027 (aromatic-CH); 2973 (sat. CH) and 1718 (ester-CO).	
13a	3428 (NH); 3054 (aromatic-CH); 2979 (sat. CH) and 1715 (ester)	
13b	3398 (NH); 3038 (aromatic-CH); 2963 (sat. CH) and 1710 (ester-CO)	0.65 (t, 3H, $CH_2\mathbf{CH_3}$); 1.9 (s, br., 1H, NH); 2.85 (s, 3H, CH_3); 3.9 (q, 2H, $\mathbf{CH_2}CH_3$); and 7.3–8.1 (m, 7H, ArH's)
14a	3471 (OH); 3227 (NH); 3057 (aromatic-CH); 2973 (sat. CH) and 1717 (ester-CO)	
14b	3486 (OH); 3209 (NH); 3036 (aromatic-CH); 2971 (sat. CH) and 1723 (ester-CO)	0.8 (t, 3H, $CH_2\mathbf{CH_3}$); 2.35 (s, br., 1H, NH); 2.8 (s, 3H, CH_3); 4.0 (q, 2H, $\mathbf{CH_2}CH_3$); 6.4 (s, br., 1H, phenolic OH) and 7.2–8.2 (m, 13H, ArH's)
15a	3498 (OH); 3178 (NH); 3039 (aromatic-CH); 2968 (sat. CH) and 1728 (ester-CO)	
15b	3501 (OH); 3179 (NH); 3042 (aromatic-CH); 2975 (sat. CH) and 1725 (ester-CO)	

derivatives that hydrolyzed readily with liberation of acetic acid and ethyl formate under the applied reaction conditions to afford the final isolable **7a,b** (cf. Scheme 1).

Compounds **7a,b** reacted with nitrous acid in ethanol to afford the pyrido[2,3:2′,3′]thieno[2,3-c]pyridazines **8a,b** whose structures were established based on the data of IR, ^{1}H NMR and elemental analysis (cf. Tables I and II). Moreover, the mass spectra of **7a,b** and **8a,b** gave m/z = 404 and 415 respectively, which corresponded to the molecular weights of the formulas $C_{23}H_{20}N_2O_3S$ and $C_{23}H_{17}N_3O_3S$ of the assigned structures (cf. Figure 1).

Work was also extended to shed more light on the chemical reactivity of **1a,b**. Thus, it has been found that each **1a,b** reacted with methyl



SCHEME 1

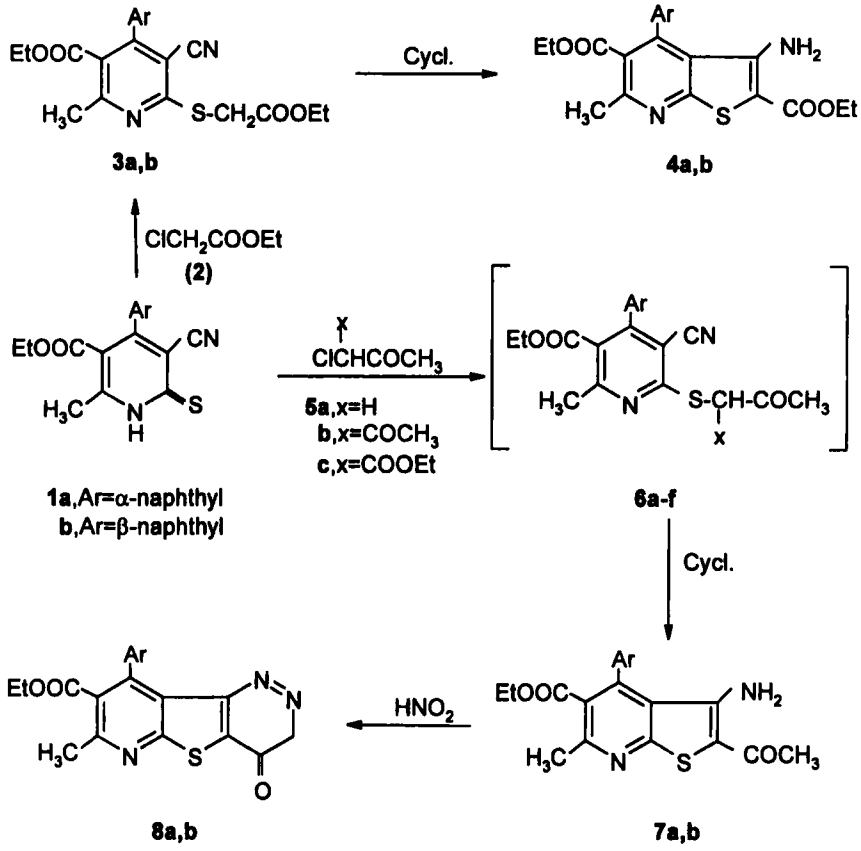


FIGURE 1

TABLE II Characterization Data of the Newly Synthesized Compounds

Comp.	M.P. (°C) (Color)	Yield (%)	Molecular formula	% Analysis calcd./found C	H	N	S	Cl
3a	162	81	$C_{24}H_{22}N_2O_4S$	66.35	5.06	6.45	7.37	—
	Yellow			66.5	5.2	6.3	7.5	—
3b	212	87	$C_{24}H_{22}N_2O_4S$	66.35	5.06	6.45	7.37	—
	Yellow			66.6	5.3	6.6	7.1	—
4a	214	85	$C_{24}H_{22}N_2O_4S$	66.35	5.06	6.45	7.37	—
	Yellow			66.6	5.3	6.7	7.2	—
4b	244-5	80	$C_{24}H_{22}N_2O_4S$	66.35	5.06	6.45	7.37	—
	Yellow			66.5	5.2	6.5	7.5	—
7a	170	92	$C_{23}H_{20}N_2O_3S$	68.31	4.95	6.93	7.92	—
	Yellow			68.6	4.7	6.8	8.2	—
7b	218	88	$C_{23}H_{20}N_2O_3S$	68.31	4.95	6.93	7.92	—
	Yellow			68.1	4.8	6.7	7.8	—
8a	204	86	$C_{23}H_{17}N_3O_3S$	66.50	4.09	10.12	7.71	—
	Yellow			66.8	4.2	10.3	7.9	—
8b	232-4	76	$C_{23}H_{17}N_3O_3S$	66.50	4.09	10.12	7.71	—
	Yellow			66.7	4.2	10.3	7.5	—
9a	132	91	$C_{21}H_{18}N_2O_2S$	69.61	4.97	7.73	8.83	—
	White			69.8	4.8	7.9	8.6	—
9b	126	93	$C_{21}H_{18}N_2O_2S$	69.61	4.97	7.73	8.83	—
	White			69.8	5.2	7.6	9.0	—
10a	248-9	79	$C_{20}H_{18}N_4O_2$	69.36	5.20	16.18	—	—
	Yellow			69.4	5.4	16.3	—	—
10b	234-5	81	$C_{20}H_{18}N_4O_2$	69.36	5.20	16.18	—	—
	Yellow			69.2	5.4	16.0	—	—
11a	280-2	87	$C_{20}H_{18}N_4O_2$	69.36	5.20	16.18	—	—
	Yellow			69.5	5.0	16.4	—	—
11b	288-9	89	$C_{20}H_{18}N_4O_2$	69.36	5.20	16.18	—	—
	Yellow			69.1	5.0	16.0	—	—
12a	206	78	$C_{27}H_{23}N_5O_2S$	67.36	4.78	14.55	6.65	—
	Yellow			67.6	5.0	14.7	6.5	—
12b	224-5	72	$C_{27}H_{23}N_5O_2S$	67.36	4.78	14.55	6.65	—
	Yellow			67.5	4.6	14.4	6.8	—
13a	154 (dec.)	92	$C_{20}H_{16}N_5O_2Cl$	60.99	4.06	17.79	—	9.02
	White			61.3	4.3	17.6	—	9.2
13b	160 (dec.)	94	$C_{20}H_{16}N_5O_2Cl$	60.99	4.06	17.79	—	9.02
	White			60.8	4.3	17.5	—	9.2
14a	296-8	79	$C_{30}H_{23}N_5O_3$	71.85	4.59	13.97	—	—
	Brown			71.9	4.7	13.7	—	—
14b	348-9	80	$C_{30}H_{23}N_5O_3$	71.85	4.59	13.97	—	—
	Orange			71.6	4.7	13.8	—	—
15a	280-1	79	$C_{20}H_{17}N_3O_3$	69.16	4.89	12.10	—	—
	Brown			69.4	4.7	12.3	—	—
15b	325-7	84	$C_{20}H_{17}N_3O_3$	69.16	4.89	12.10	—	—
	Brown			69.3	4.6	12.0	—	—

iodide in boiling methanolic sodium methoxide to give the corresponding 2-methylthiopyridines **9a,b**. Compounds **9a,b** reacted with hydrazine hydrate in ethanol to afford the sulfur-free reaction products which were formulated as the 2-hydrazinopyridines **10a,b**. Compounds **10a,b** were cyclized in boiling hydrazine hydrate to give the corresponding 3-aminopyrazolo[3,4-b]pyridine derivatives **11a,b**. Compounds **11a,b** were in turn authenticated via the reaction of either **9a,b** or **1a,b** with hydrazine hydrate. Structures of **9–11** were established on the basis of the data of IR, ^{1}H NMR and elemental analysis (cf. Tables I and II). Moreover, the mass spectra of **9a** and **10b** gave m/z = 362 and 346 respectively, which agreed with the molecular weights of the formulas $C_{21}H_{18}N_2O_2S$ and $C_{20}H_{18}N_4O_2$ of the assigned structures (cf. Figure 2).

The activity of the NH_2 group in **11a,b** was demonstrated by the reactions with phenylisothiocyanate and nitrous acid. Thus, each of **11a,b** reacted with phenylisothiocyanate in boiling pyridine to give the corresponding pyrazolo[3,4-b]pyridin-3-yl-phenylthiourea derivatives **12a,b** respectively. Also, **11a,b** reacted with nitrous acid to give the corresponding 3-diazotized aminopyrazolo[3,4-b]pyridine derivatives **13a,b**. Furthermore, the structure of **13a,b** was confirmed via their coupling with β-naphthol in sodium hydroxide to give the corresponding 3-(1′-azo-2′-hydroxynaphthyl)pyrazolo[3,4-b]pyridine derivatives **14a,b** respectively. Compounds **13a,b** were also hydrolyzed using dilute sulfuric acid to give the corresponding 3-hydroxypyrazolo[3,4-b]pyridine derivatives **15a,b**. Structures of compounds **12–15** were elucidated on the basis of correct elemental analyses and spectral data studies (cf. Tables I and II).

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr discs) were recorded on Bruker Vector 22 and Perkin-Elmer FT-IR type 4 spectrophotometers. ^{1}H NMR spectra were recorded on Varian Gemini-200 MHz and Brucker WP-80 spectrometers using TMS as an internal standard and $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are expressed as ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 using inlet type at 70eV. Microanalyses were performed by the Microanalytical Center of Cairo University.

Synthesis of the 2-S-ethoxycarbonylmethylpyridines 3a,b

A solution of each of **1a,b** (0.01 mol) and ethyl chloroacetate (**2**, 0.01 mol) in methanolic sodium methoxide (prepared from 0.01 atom of Na metal

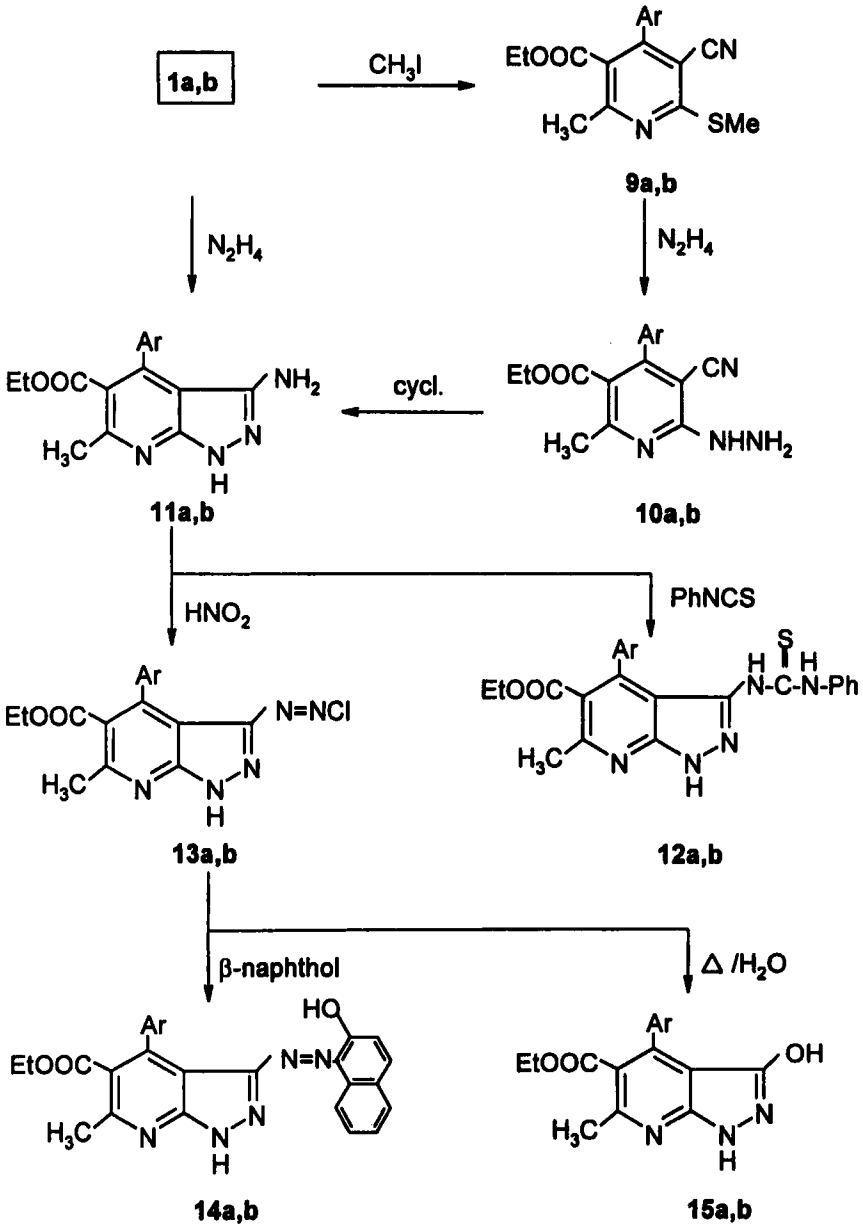


FIGURE 2

in 15 mL of methanol) was stirred for 1 h. The product so formed was collected by filtration, washed with cold ethanol, and then crystallized from ethanol to give **3a,b** respectively.

Synthesis of the Thieno[2,3-b]pyridines 4a,b

Method A

A solution of each of **1a,b** (0.01 mol) and ethyl chloroacetate (**2**, 0.01 mol) in 10% ethanolic KOH (10 mL) was heated under reflux for 3 h. The reaction mixture was cooled, poured onto ice-cold water, and acidified with hydrochloric acid. The product formed was collected by filtration, washed with water followed by cold ethanol, and crystallized from ethanol to give **4a,b** respectively.

Method B

A solution of each of **3a,b** (0.01 mol) in 10% ethanolic KOH (10 mL) was heated under reflux for 3 h. The reaction mixture was cooled, poured onto ice-cold water, and acidified with hydrochloric acid. The product so formed was collected by filtration, washed with water followed by cold ethanol, and crystallized from ethanol to give **4a,b** respectively.

Synthesis of the Thieno[2,3-b]pyridines 7a,b

General Procedure

A solution of each of **1a,b** (0.01 mol) and each of **5a–c** (0.01 mol) in methanolic sodium methoxide was stirred for 1–2 h or heated under reflux for 30 min. The product so formed was filtrated off, washed with cold ethanol, and crystallized from ethanol to give **7a,b** respectively.

Synthesis of the Pyridothienopyridazines 8a,b

General Procedure

A cold solution of each of **7a,b** (0.01 mol) in a mixture of ethanol (10 mL) and hydrochloric acid (1 mL) at 0°C was treated dropwise with a cold aqueous solution of sodium nitrite (0.01 mol) with stirring for 2–3 h. The product so formed was collected by filtration, washed with cold water, and then ethanol and crystallized from ethanol to give **8a,b** respectively.

Synthesis of the 2-Methylthiopyridines 9a,b

A solution of each of **1a,b** (0.01 mol) and methyl iodide (0.01 mol) in methanolic sodium methoxide (prepared from the equivalent amount

of sodium metal and 20 mL of methanol) was heated under reflux for 2 h. The product formed after cooling was filtrated off, washed with cold ethanol, and crystallized from ethanol to give **9a,b** respectively.

Synthesis of the 2-Hydrazinopyridines 10a,b

A solution of each of **9a,b** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (20 mL) was heated under reflux for 6 h. The product formed after cooling was filtrated off, washed with cold ethanol, and crystallized from ethanol to give **10a,b** respectively.

Synthesis of the Pyrazolo[3,4-b]pyridines 11a,b

General Procedure

A mixture of each of **1a,b**, **9a,b**, or **10a,b** (0.01 mol) and hydrazine hydrate (0.01 mol) was heated under reflux for 6 h. The product formed after cooling was filtrated off, washed with cold ethanol, and crystallized from ethanol to give **11a,b** respectively in each case.

Synthesis of the Pyrazolo[3,4-b]pyridin-3-ylphenylthioureas 12a,b

A solution of each of **11a,b** (0.01 mol) and phenylisothiocyanate (0.01 mol) in pyridine (15 mL) was heated under reflux for 5 h. The reaction mixture was poured onto ice-cold water and acidified with acetic acid. The product so formed was filtrated off, washed with cold ethanol, and crystallized from ethanol to give **12a,b** respectively.

Synthesis of the 3-Diazotized Aminopyrazolo[3,4-b]pyridines 13a,b

A cold solution of each of **11a,b** (0.01 mol) in a mixture of ethanol (10 mL) and hydrochloric acid (1 mL) at 0°C was treated dropwise with a cold aqueous solution of sodium nitrite (0.01 mol) with stirring for 2–3 h. The product so formed was collected by filtration, washed with cold water and then cold ethanol, and crystallized from ethanol to give **13a,b** respectively.

Synthesis of the Azo Dyes 14a,b

To a cold solution of each of **13a,b** (0.01 mol) in water (15 mL) was added a solution of β-naphthol (0.01 mol) in sodium hydroxide dropwise at 0°C with stirring. After complete addition, stirring was continued for 1 h. The reaction mixture was acidified with hydrochloric acid and the

product so formed was filtered off, washed with water, then crystallized from ethanol to give **14a,b** respectively.

Synthesis of the 3-Hydroxypyrazolo[3,4-b]pyridines 15a,b

A solution of each of **13a,b** (0.01 mol) in water (10 mL) was treated with concentrated sulfuric acid (5 mL) and heated on the water bath at 60°C for 15–20 min. The reaction mixture was cooled and the product so formed was collected by filtration, washed with water, and crystallized from ethanol to give **15a,b** respectively.

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