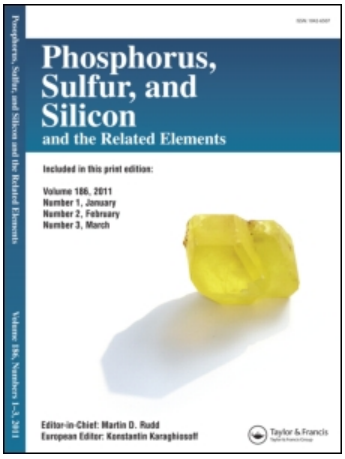

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REACTIONS WITH CYANOTHIOACETAMIDE DERIVATIVES: SYNTHESIS AND REACTIONS OF SOME PYRIDINES AND THIENO[2,3-*b*]PYRIDINE DERIVATIVES

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REACTIONS WITH CYANOTHIOACETAMIDE DERIVATIVES: SYNTHESIS AND REACTIONS OF SOME PYRIDINES AND THIENO[2,3-*b*]PYRIDINE DERIVATIVES

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The styrlpyridinethione **1a–c** reacted with several halogenated compounds; ω-bromoacetophenone, methyl chloroacetate, α-chloroacetylacetone and ethyl-α-chloroacetoacetate to give the corresponding thieno[2,3-*b*]pyridines **3a–c**, **11a–c** and the thiazolo[3,2-*a*]pyridines **14a–c**.

Key words: Styrylpyridine, halogeno-esters, halogeno-ketones, thiazolopyridine and thienopyridine.

INTRODUCTION

During the last few years our research group has been interested in the chemistry of pyridine derivatives.[1–6] Due to the expected biological activities of pyridine and its annelated derivatives as antioipmic,[7] antimycotic,[8] antiarrhythmic,[9] antidepressant[10] and fungicidal agents[11] stimulated our interest in the synthesis of several new derivatives of these ring systems which are required for a medicinal chemistry program. The reaction of styrylpyridines **1a–c** with several halogeno-ketones and halogeno-esters such as chloromethylacetate, ω-bromo-acetophenone, α-chloroacetylacetone and ethyl-α-chloroacetoacetate constituted a direct and easy route for the synthesis of several newly synthesized thienylpyridines and thiazolopyridines **3a–c** **14a–c** of the expected biological activity.

RESULTS AND DISCUSSION

It has been found that the styrylpyridinethione **1a–c** reacted with methyl chloroacetate to give products formed via the loss of hydrogen chloride which could be formulated as the 2-S-methyl methoxycarbonyl pyridine derivatives **2a–c**. The structure of **2a–c** was proved using elemental analyses and spectra data (cf. Tables I and II). A structure proof of **2a–c** was achieved via their cyclization into the corresponding thieno[2,3-*b*]pyridine derivatives **3a–c** respectively, using ethanolic KOH. The structure of **3a–c** was, in turn, established on both elemental and spectral data backgrounds. The IR spectra of **3a–c** did not show any absorption

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TABLE I

Characterization data of the newly synthesized compounds

Comp. & Colour	Solvent of Cryst.	M.P. (C)	Yield %	Mol. Formula	% Analysis Calcd. / Found C	H	N	S	Cl
2a Yellow	Ethanol	150	74	$C_{23}H_{18}N_2O_2S$	71.50 71.3	4.66 4.5	7.25 7.4	8.29 8.1	—— ——
2b Brown	Ethanol	162	79	$C_{25}H_{22}N_2O_6S$	67.26 67.4	4.93 5.1	6.27 6.1	7.17 7.3	—— ——
2c Yellow	Ethanol	160	75	$C_{23}H_{16}N_2O_2SCl_2$	60.65 60.4	3.51 3.4	6.15 6.3	7.03 7.2	15.60 15.4
3a Yellowish brown	Ethanol	180	63	$C_{23}H_{18}N_2O_2S$	71.50 71.3	4.66 4.5	7.25 7.4	8.29 8.1	—— ——
3b Yellowish brown	Ethanol	220	71	$C_{25}H_{22}N_2O_4S$	67.26 67.1	4.93 4.8	6.27 6.3	7.17 7.4	—— ——
3c Brown	Ethanol	210	68	$C_{23}H_{16}N_2O_2SCl_2$	60.65 60.4	3.51 3.4	6.15 6.3	7.03 6.9	15.60 15.8
4a Brown	Ethanol	175	75	$C_{28}H_{20}N_2OS$	77.77 77.6	4.62 4.5	6.48 6.6	7.40 7.5	—— ——
4b Yellow	Ethanol	140	80	$C_{30}H_{24}N_2O_3S$	73.17 73.0	4.87 4.7	5.69 5.8	6.50 6.7	—— ——
4c Yellowish brown	Acetic Acid	185	71	$C_{28}H_{18}N_2OSCl_2$	67.06 66.8	3.59 3.4	5.58 5.7	6.38 6.2	14.17 14.2
5a yellow	Ethanol	180	62	$C_{28}H_{20}N_2OS$	77.77 77.6	4.62 4.8	6.48 6.6	7.40 7.2	—— ——
5b Yellow	Ethanol	170	70	$C_{30}H_{24}N_2O_3S$	73.17 73.4	4.87 4.6	5.69 5.8	6.50 6.4	—— ——
5c Yellow	Acetic Acid	240	73	$C_{28}H_{18}N_2OSCl_2$	67.06 67.2	3.59 3.5	5.58 5.4	6.38 6.5	14.17 14.3
8a Yellow	Ethanol	210 - 2	65	$C_{23}H_{18}N_2OS$	74.59 74.7	4.86 4.7	7.56 7.4	8.64 8.8	—— ——
8b Brown	Ethanol	195 - 7	74	$C_{25}H_{22}N_2O_3S$	69.76 69.9	5.11 5.0	6.51 6.4	7.44 7.3	—— ——
8c Yellowish Brown	Ethanol	170	64	$C_{23}H_{16}N_2OSCl_2$	62.87 62.7	3.64 3.5	6.37 6.5	7.29 7.1	16.17 16.3
9b Yellow	Acetic Acid	160	60	$C_{28}H_{28}N_2O_5S$	66.66 66.8	5.55 5.4	5.55 5.7	6.36 6.2	—— ——
11a Dark Brown	Ethanol	160	58	$C_{24}H_{20}N_2O_2S$	72.00 71.9	5.00 4.9	7.00 7.1	8.00 8.2	—— ——
11b Brown	Ethanol	185	74	$C_{26}H_{24}N_2O_4S$	67.82 67.7	5.21 5.1	6.08 6.2	6.95 6.8	—— ——
11c Brown	Ethanol	170	70	$C_{24}H_{18}N_2O_2SCl_2$	61.40 61.3	3.83 3.7	5.97 6.1	6.82 6.7	15.13 15.3
12a Yellow	Ethanol	195 - 7	70	$C_{22}H_{15}N_3OS$	71.54 71.4	4.06 3.9	11.38 11.5	8.67 8.8	—— ——
12b Brown	Ethanol	200 - 2	65	$C_{24}H_{19}N_3O_3S$	67.13 67.0	4.42 4.6	9.79 9.9	7.45 7.6	—— ——
12c Yellow	Ethanol	210 - 2	62	$C_{22}H_{13}N_3OSCl_2$	60.27 60.1	2.96 2.8	9.58 9.7	7.30 7.2	16.21 16.1
14a Yellow	Ethanol	172	67	$C_{26}H_{22}N_2O_2S$	73.23 73.4	5.16 5.2	6.57 6.4	7.51 7.4	—— ——
14b Yellow	Ethanol	175	72	$C_{28}H_{26}N_2O_4S$	69.13 69.0	5.34 5.5	5.76 5.6	6.58 6.7	—— ——
14c Greenish Yellow	Ethanol	195	82	$C_{26}H_{20}N_2O_5SCl_2$	63.03 62.9	4.04 4.2	5.65 5.7	6.46 6.6	14.34 14.2

bands of the nitrile function or the saturated CH_2 groups in **2a–c**, which proved that both of the two functions were involved in the cyclization step leading to the formation of **3a–c**. On the other hand, the IR-spectra showed the presence of the band of the newly born NH_2 group at 3440, 3220 cm^{-1} in each case. The ^{1}H-NMR spectra of **2a–c** and **3a–c** were also free from the signals of pyridine H-3 and pyridine H-4 meaning that **2a–c** and **3a–c** were autoxidized under the applied reaction conditions (cf. Experimental and Table II). Furthermore, compounds **1a–c** reacted with ω-bromoacetophenone to yield products formed via dehydrobromonation which could be formulated as the S-phenacylpyridine derivatives **4a–c** which could be cyclized via their reaction with ethanolic KOH into the corresponding thieno[2,3-*b*]pyridine derivatives **5a–c**, respectively. The structures of **4a–c** and **5a–c** were proved using both elemental analyses and spectral data studies. Similar

TABLE II

IR and ^{1}H-NMR spectral data of the newly synthesized compounds

Compd.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
2a	3080 (aromatic and styryl CH); 2980 (sat. CH); 2220 (CN); 1720 (CO-ester); 1625 (C=N) and 1600 (C=C).	2.5 (s, 2H, CH_2); 4.5 (s, 3H, CH_3) and 7.5 - 8.0 (m, 13H, ArH's and styryl CH).
2b	3050 (aromatic and styryl CH); 2960 and 2940 (sat. CH); 2213 (CN); 1745 (CO-ester);1634 (C=N) and 1610 (C=C).	2.8 (s, 2H, CH_2); 3.8 (s, 6H, two OCH_3); 4.5 (s, 3H, CH_3) and 7.6-8.1 (m, 13H, ArH's and styryl CH).
3a	3440, 3220 (NH_2); 3080 (aromatic and styryl CH); 2980 (sat. CH); 1680 (CO-ester); 1630 (C=N) and 1610 (C=C).	4.0 (s, 3H, CH_3); 4.6 (s, 2H, NH_2) and 7.5-8.0 (m, 13H, ArH's and styryl CH).
3c	3480, 3320 (NH_2); 3070 (aromatic and styryl CH); 2950 (sat. CH); 1680 (CO-ester); 1625 (C=N) and 1610 (C=C).	4.1 (s, 3H, CH_3); 4.8 (s, 2H, NH_2) and 7.5 - 8.1 (m, 13H, ArH's and styryl CH).
4a	3080 (aromatic and styryl CH); 2970 (sat. CH); 2220 (CN); 1700 (CO); 1630 (C=N) and 1600 (C=C).	2.8 (s, 2H, CH_2) and 7.5 - 8.2 (m, 18H, ArH's and styryl CH).
5b	3490, 3280 (NH_2); 3080 (aromatic and styryl CH); 2970 (sat. CH); 1635 (CO with H-bonding); 1620 (C=N) and 1600 (C=C).	3.8 (s, 6H, two, OCH_3); 4.6 (s, 2H, NH_2) and 7.6 - 8.1 (m, 16H, ArH's and styryl CH).
5c	3480, 3270 (NH_2); 3070 (aromatic and styryl CH); 1630 (CO with H-bonding); 1620 (C=N) and 1600 (C=C).	4.7 (s, 2H, NH_2) and 7.5-8.0 (m, 16H, ArH's and styryl CH).
8a	3400, 3240 (NH_2); 3060 (aromatic and styryl CH); 2950 (sat. CH); 1640 (CO with H-bonding); 1625 (C=N) and 1610 (C=C).	2.4 (s, 3H, CH_3); 4.6 (s, 2H, NH_2) and 7.5- 8.1 (m, 11H, ArH's and styryl CH).
8b	3480, 3320 (NH_2); 3050 (aromatic and styryl CH); 2930 (sat. CH); 1635 (CO with H-bonding); 1620 (C=N) and 1595 (C=C).	2.6 (s, 3H, CH_3); 3.8 (s, 6H, two OCH_3); 4.5 (s, 2H, NH_2) and 7.0 - 8.0 (m, 11H, ArH's and styryl CH).
9b	3060 (aromatic and styryl CH); 2950 (sat. CH); 2220 (CN); 1730 (CO-ester); 1690 (CO-acetyl); 1635 (C=N) and 1610 (C=C).	1.2 (t,3H, $\underline{CH_3}CH_2$);2.5 (s,3H, CH_3CO); 3.8 (s, 6H, two OCH_3); 4.3 (q, 2H, $\underline{CH_2}CH_3$); 5.0 (s,1H,CH) and 7.0-8.0 (m, 13H, ArH's, pyridine H-3, pyridine H-4, pyridine H-5 and styryl CH).

TABLE II (*Continued*)

Compd.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
11a	3500, 3350 (NH_2); 3080 (aromatic and styryl CH); 2950 (sat. CH); 1680 (CO-ester with H-bonding); 1640 (C=N) and 1610 (C=C).	1.2 (t, 3H, CH_3 CH_2); 4.5 (q, 2H, CH_2 CH_3); 5.9 (s, 2H, NH_2) and 7.0-8.0 (m, 13H, ArH's and styryl CH).
11c	3480, 3330 (NH_2); 3070 (aromatic and styryl CH); 2960 (sat. CH); 1675 (CO-ester with H-bonding); 1630 (C=N) and 1610 (C=C).	1.2 (t,3H, CH_3CH_2);4.1(q,2H, CH_2 CH_3); 5.4 (s, 2H, NH_2) and 7.0-8.0 (m, 11H, ArH's and styryl CH).
12a	3440 (OH); 3260 (NH); 3070 (aromatic and styryl CH); 1620 (C=N) and 1600 (C=C).	7.1-8.0 (m,13H,ArH's and styryl CH); 12.4 (s, 1H, NH) and 15.0 (s, 1H, enolic OH).
12b	3440 (OH); 3280 (NH); 3060 (aromatic and styryl CH); 2960 (sat. CH); 1625 (C=N) and 1610 (C=C).	3.8 (s, 6H, OCH_3); 7.2 - 8.1 (m, 11H, ArH's and styryl CH); 12.2 (s, 1H, NH) and 15.2 (s, 1H, enolic OH).
14a	3080 (aromatic and styryl CH); 2960 (sat. CH); 2220 (CN); 1710 (CO-ester) and 1620 (C=C).	1.1 (s, 3H,CH_3);1.3 (t, 3H, CH_3 CH_2);4.5 (q, 2H, CH_2 CH_3); 7.0 (d, 1H, pyridine H-4); 7.4 (d,1H, pyridine H-5) and 7.6- 8.2 (m, 12H, ArH's and styryl CH).
14c	3040 (aromatic and styryl CH); 2910 (sat. CH); 2200 (CN); 1700 (CO-ester); and 1620 (C=C).	1.1 (s, 3H, CH_3); 1.3 (t, 3H, CH_3 CH_2); 4.4 (q, 2H, CH_2 CH_3); 6.8 (d, 1H, pyridine H-4); 7.2 (d, 1H, pyridine H-5) and 7.4-8.2 (m, 10H, ArH's and styryl CH).

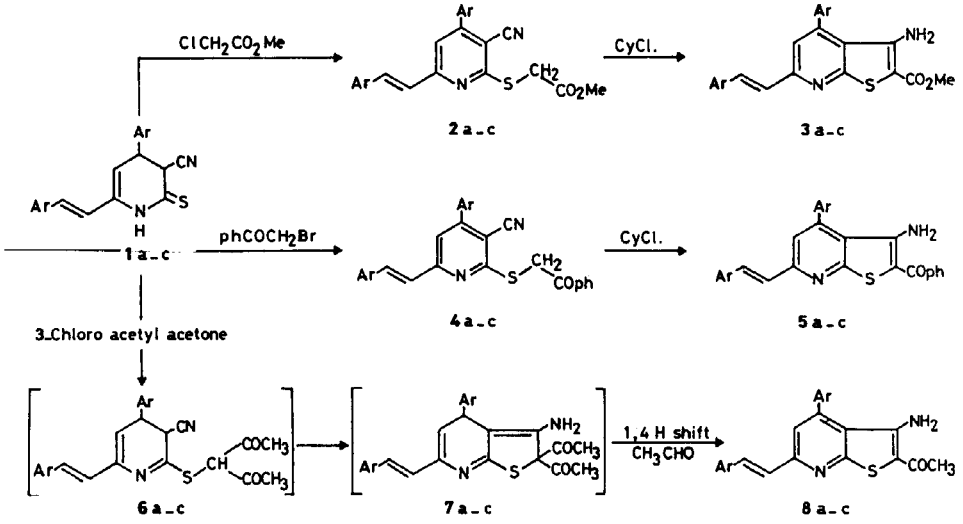

CHART 1

to the behaviour of **2a–c**, compounds **4a–c** underwent autoxidation under the applied reaction conditions and this was deduced from the absence of signals of pyridine H-3 and pyridine H-4 in their ^{1}H-NMR spectra, (cf. Table II). The reaction of **1a–c** with a variety of halogenated carbonyl compounds was also investigated. Thus, it has been found that **1a–c** reacted with α-chloroacetylacetone to give

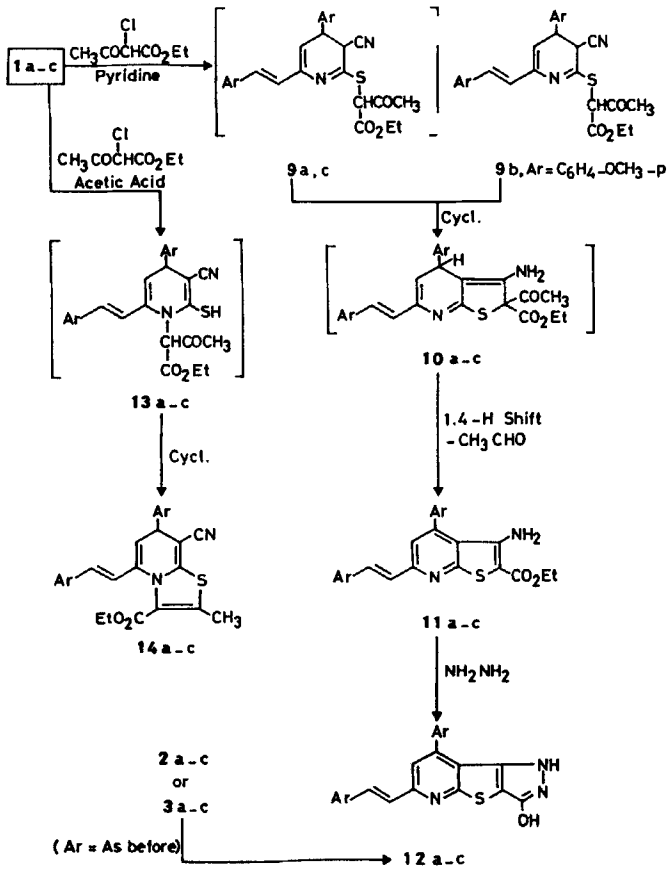

CHART 2

products which were formulated as the thieno[2,3-*b*]pyridine derivatives **8a–c**. These products were most likely formed via initial formation of the non-isolable intermediates **6a–c** via dehydrochlorination. In support to this idea no signals for pyridine protons were detected in ^{1}H-NMR spectra of **8a–c** (cf. Table II). Moreover, the reaction of **1a–c** with ethyl-α-chloroacetoacetate was also investigated. The reaction product was found to be highly dependent on the solvent used for performing the reaction. Thus, it has been found that **1a–c** reacted with ethyl-α-chloroacetoacetate in glacial acetic acid under reflux to give products which could be formulated as the thiazolo[3,2-*a*]pyridine derivatives **14a–c** via initial dehydrochlorination to yield the condensation product **13a–c** which then could be cyclized via enolization and loss of water molecule under the applied reaction condition to yield the final isolable **14a–c**.

The structure of **14a–c** was proved based on both elemental analyses and spectral data studies (cf. Tables I, II and Chart 2). The IR spectra of **14a–c** showed the absorption bands corresponding to ester carbonyl (1710 cm^{-1}). The ^{1}H-NMR spectra of **14a–c** revealed signals for CH_3CH_2; CH_3; pyridine H-4; styryl and aromatic protons (cf. Table II).

Compounds **1a–c** reacted also with the same reagent in pyridine under reflux instead of glacial acetic acid to give products with no nitrile functions in their IR spectra and no signals corresponding to CH_3 protons in their ^{1}H-NMR spectra. The reaction products could, however, be formulated as the thieno[2,3-*b*]pyridine derivatives **11a–c**, respectively. The reaction product **11a–c** were formed via the initial dehydrochlorination products **9a–c**. It is remarkable to report here that the intermediate **8a–c** could not be isolated while **9b** was isolated in a pure state (cf. Tables I, II and Chart 2). Compounds **9a–c** could then be cyclized to give the non-isolable **10a–c** via the addition to the cyano function which underwent 1,4-H shift with loss of acetaldhyde to give the aromatized reaction products **11a–c**, respectively. In addition, the isolable **9b** could be converted into the corresponding **11b** via boiling in glacial acetic acid solution for 4 hours (cf. Chart 2). Compounds **11a–c** reacted with hydrazine hydrate to give thieno[3,2-*c*]pyrazolo[2,3-*b*]pyridine derivatives **12a–c**, respectively which also can be obtained via another route by the reaction of each of **2a–c** or **3a–c** with hydrazine hydrate.

The structure of compounds **12a–c** could however, be proved based on both elemental analyses and spectra data studies (cf. Chart 2, Experimental, Tables I and II).

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on Pye Unicam SP-1100 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM 390/90 MHz spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard and chemical shifts are expressed as δ ppm units. Microanalyses were performed at the Microanalytical center of Cairo University using Perkin Elmer 2400 CHN Elemental Analyzer.

Synthesis of **2a**

A solution of **1a** (0.01 mole) in sodium methoxide (prepared from 0.01 atom of sodium metal in 30 ml of methanol) was treated with 0.01 mole of methylchloroacetate. The reaction mixture was heated under reflux for 6 hours, then cooled and poured onto ice-cold water. The solid product obtained after acidification with concentrated HCl was filtered off, washed with water and crystallized from ethanol to afford the 2-S-methyl methoxycarbonylpyridine derivative **2a** as a yellow product with m.p. 150C° (cf. Tables I and II).

Synthesis of **2b, c**

A solution of each of **1b, c** (0.01 mole) in pyridine (15 ml) was treated with 0.01 mole of methyl chloroacetate. The reaction mixture was heated under reflux for 5 hours. The reaction mixture was cooled, poured onto ice-cold water and then acidified with concentrated HCl. The solid products obtained were filtered off, washed with water and crystallized from ethanol to afford the corresponding compounds **2b, c**, respectively (cf. Tables I and II).

Synthesis of **3a–c**

A solution of each of **2a–c** (0.01 mole) in a mixture of 20% ethanolic KOH solution (20 ml) was heated under reflux for 5 hours. The reaction mixture was cooled, poured onto ice-cold water and then acidified with concentrated HCl. The solid products obtained were filtered off, washed with water and crystallized from the proper solvents to afford the corresponding thieno[2,3-*b*]pyridine derivatives **3a–c**, respectively (cf. Tables I and II).

Synthesis of **4a–c**

A solution of each of **1a–c** (0.01 mole) and 0.01 mole of ω-bromoacetophenone in pyridine (20 ml) was heated under reflux for 4 hours. The reaction mixture was cooled, poured onto ice-cold water and then acidified with concentrated HCl. The solid products obtained were filtered off, washed with water and crystallized from ethanol to afford the corresponding S-phenacyl derivatives **4a–c**, respectively (cf. Tables I and II).

Synthesis of **5a–c**

A solution of each of **4a–c** (0.01 mole) in a mixture of 20% ethanolic KOH solution (20 ml) was heated under reflux for 5 hours. The reaction mixture was cooled, and poured onto ice-cold water. The solid products obtained after acidification with concentrated HCl were filtered off, washed with water and crystallized from the proper solvents to afford the corresponding thieno[2,3-*b*]pyridine derivatives **5a–c**, respectively (cf. Tables I and II).

Synthesis of **8a, c**

A solution of each of **1a, c** (0.01 mole) in glacial acetic acid (15 ml) was treated with 0.01 mole of α-chloroacetylacetone. The reaction mixture was heated under reflux for 6 hours. The solid products obtained after cooling were filtered off and crystallized from the ethanol to afford the corresponding thieno[2,3-*b*]pyridine derivatives **8a, c**, respectively (cf. Tables I and II).

Synthesis of **8b**

A solution of **1b** (0.01 mole) and 0.01 mole of α-chloroacetylacetone in pyridine (15 ml) was heated under reflux for 5 hours. The reaction mixture was cooled, and poured onto ice-cold water. The solid products obtained after acidification with concentrated HCl, was filtered off, washed with water and crystallized from ethanol to afford the corresponding thieno[2,3-*b*]pyridine derivatives **8b**, respectively (cf. Tables I and II).

Synthesis of the thiazolo[2,3-a]pyridine derivatives **14a–c**

A solution of each of **1a–c** (0.01 mole) and 0.01 mole of ethyl-α-chloroacetoacetate in glacial acetic acid (20 ml) was heated under reflux for 5 hours. The solid products obtained after cooling were filtered off and crystallized from ethanol to afford the corresponding compounds **14a–c** (cf. Tables I and II).

Synthesis of **9b**

A solution of **1b** (0.01 mole) and 0.01 mole of ethyl-α-chloroacetoacetate in pyridine (20 ml) was heated under reflux for 5 hours. The reaction mixture was cooled and poured onto ice-cold water. The solid products obtained after acidification with concentrated HCl were filtered off, washed with water and crystallized acetic acid to afford **9b** as a yellow product with m.p. 160C° (cf. Tables I and II).

Synthesis of **11b**

A solution of each **9b** (0.01 mole) in glacial acetic acid (10 ml) was heated under reflux for 4 hours. The solid products obtained after cooling were filtered off and crystallized from ethanol to afford the corresponding thieno[2,3-*b*]pyridine derivatives **11b** as a brown product with m.p. 185C° (cf. Tables I and II).

Synthesis of **11a, c**

A solution of **1a, c** (0.01 mole) and 0.01 mole of ethyl-α-chloroacetoacetate in pyridine (15 ml) was heated under reflux for 6 hours. The reaction mixture was cooled and poured onto ice-cold water and acidified with concentrated HCl. The solid products obtained were filtered off, washed with water and crystallized from ethanol to afford the corresponding thieno[2,3-*b*]pyridine derivatives **11a, c**, respectively, (cf. Tables I and II).

Synthesis of **12a–c**

A solution of each of **11a–c, 2a–c** or **3a–c** (0.01 mole) and hydrazine hydrate (20 ml) was heated under reflux for 6 hours. The reaction mixture was cooled and poured onto ice-cold water. The solid products obtained were filtered off, washed with water and crystallized from the proper solvents to afford the corresponding thieno[3,2-*c*]pyrazolo[2,3,*b*]pyridine derivatives **12a–c**, respectively (cf. Tables I and II).

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