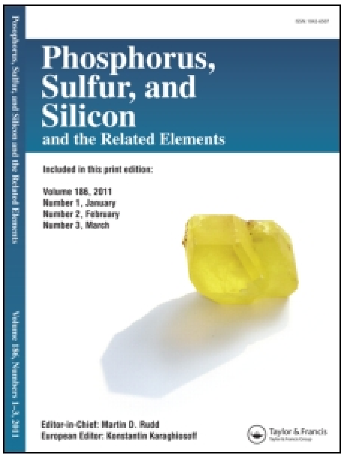

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2-Ethanethioamide in Heterocyclic Synthesis: Synthesis and Characterization of Several New Pyridine and Fused Azolo- and Azinopyridine Derivatives

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2-ETHANETHIOAMIDE IN HETEROCYCLIC SYNTHESIS: SYNTHESIS AND CHARACTERIZATION OF SEVERAL NEW PYRIDINE AND FUSED AZOLO- AND AZINOPYRIDINE DERIVATIVES

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Pyridine-2(1*H*)-thione derivatives 3a,b were synthesized from the reaction of 1-(phenylsulfanyl)acetone (1) and cinnnamonitrile derivatives 2a,b. Compounds 3a,b reacted with different halogenated reagents 7a–f to give 2-*S*-alkylpyridine derivatives 8a–l, which could be, in turn, cyclized into the corresponding thieno[2,3-*b*]pyridine derivatives 9a–l. Compounds 9d,j reacted with acetic anhydride, formic acid, carbon disulfide, phenyl isothiocyanate, and nitrous acid to yield the corresponding pyrido[3′,2′:4,5]thieno[2,3-*d*]pyrimidine 12a,b, 15a,b, 17a,b, 20a,b, and pyrido[3′,2′:4,5]thieno[2,3-*d*][1,2,3]triazinone derivatives 22a,b, respectively.

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Keywords Pyridine-2(1*H*)-thione; pyrido[3′,2′:4,5]thieno[2,3-*d*]pyrimidine; pyrido-[3′,2′:4,5]thieno[2,3-*d*][1,2,3]triazinone

INTRODUCTION

The development of simple synthetic routes for widely used heterocyclic derivatives from readily available reagents and chemicals is one of the major tasks in organic synthesis.[1] For the last three decades, the synthesis and characterization of heterocyclic derivatives of expected biological activities has gained considerable attention by this group of research.[2–12] A vast number of nitrogenous heterocyclic derivatives has been synthesized from which compounds containing the pyridine nucleus and its azolo, azino, and thieno derivatives constituted the main members.

The reason is that these derivatives possess a wide range of biological activities and are commonly used in many pharmaceutical and medicinal preparations. The pyridine nucleus exhibits antitumor[13] and anti-aminesic[14] activities. On the other hand, the *S*-alkylpyridinethione derivatives showed neurotropic[15] activity and are used as adenosine

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receptor ligands.[16,17] They have also cardiovascular activity.[18] In addition, the thieno[2,3-*b*] pyridine derivatives were reported to possess a broad range of biological activities such as antimicrobial,[19–23] anti-inflamatory,[24] neurotropic,[15] and ganadotropin-releasing hormone antagonizing activities.[25]

Furthermore, the pyridothienopyrimidines are reported to possess anti-allergic activity,[26] antiprotozoals active against phelasterides dicentrarchi,[27] anti-anaphylictic,[28,29] and antimicrobial[19,20] activities. In addition, these compounds possess anti-inflamatory,[30–32] antipyretic,[33,34] analgesic,[35] and hypo-holesterolenic[36] activities. The pyridine-2(1*H*)-thiones **3a**,**b** were taken as the starting materials for the present study.

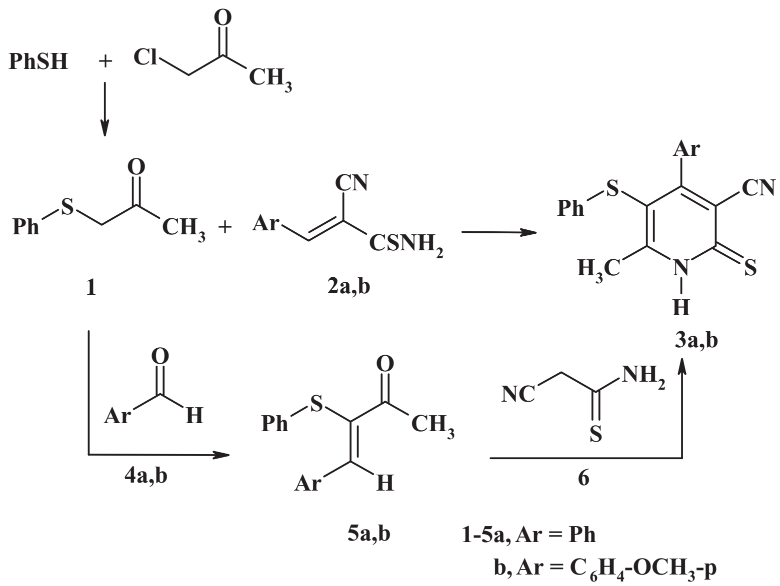
RESULTS AND DISCUSSION

The starting materials 6-methyl-3-cyano-4-aryl-5-phenylsulfanylpyridine-2(1*H*)-thiones **3a**,**b** were prepared in good yields via the reaction of 1-(phenylsulfanyl)acetone, (compound **1**, prepared by the reaction of benzene thiol and chloroacetone in cold methanol according to the method of Karthikeyan et al.[37]) with the thiocarboxamidocinnamonitrile derivatives **2a**,**b** in absolute ethanol in the presence of catalytic amounts of triethylamine. To our knowledge, compounds **3a**,**b** have been prepared for the first time and are not previously reported in the literature. Thus, the IR spectrum of **3a** showed the presence of the bands of the NH group (3310 cm^{-1}) and the nitrile function at 2221 cm^{-1}. The ^1H NMR spectrum of **3a** revealed signals of ring NH at $\delta = 6.58$ ppm, ring-CH_3 at $\delta = 2.46$ ppm in addition to the aromatic protons (m, 10H, at $\delta = 7.12$–7.43 ppm). On the other hand, the ^1H NMR spectrum of **3b** revealed signals of ring NH, ring-CH_3, phenyl-OCH_3 in addition to the aromatic protons (m, 9H, at $\delta = 7.20$–7.51 ppm).

The structure of both **3a**,**b** was further established by their alternative synthesis via another route by the reaction of **1** with the appropriate aromatic aldehydes **4a**,**b** to give the corresponding ylidene derivatives **5a**,**b**, respectively.[37] Compounds **5a**,**b** then reacted with cyanothioacetamide (**6**) in absolute ethanol in the presence of triethylamine to yield the corresponding **3a**,**b** in good yields. Compounds **3a**,**b** prepared via this route were found to be identical in all aspects to **3a**,**b** previously prepared (see Scheme 1 and the Experimental section).

The synthetic potential of **3a**,**b** was demonstrated via their reactions with a variety of halogenated reagents **7a**–**f**. Thus, it has been found that **3a** reacted with chloroacetone (**7a**) in hot ethanol in the presence of sodium acetate to give a reaction product resulting from equimolecular addition of **7a** to **3a** and loss of one molecule of hydrogen chloride. The IR spectrum of this reaction product showed among its absorption bands those corresponding to the presence of CN group (2221 cm^{-1}) and chain C=O (1715 cm^{-1}). Its ^1H NMR spectrum revealed signals of two CH_3 at $\delta = 2.55$ and 3.58 ppm and CH_2 at $\delta = 4.00$ ppm. Based on the above data, in addition to the correct elemental analysis, this compound was formulated as the 2-*S*-acetonylpyridine derivative **8a**.

In a similar manner, **3a** reacted with each of chloroacetonitrile (**7b**), ethyl chloroacetate (**7c**), chloroacetamide (**7d**), 1-(4-chlorophenyl)-2-bromoethanone (**7e**), and 1-(4-bromophenyl)-2-bromoethanone (**7f**) to give the corresponding 2-*S*-alkylpyridine derivatives **8b**–**f**, respectively. Structures of **8b**–**f** were established based on the correct data of elemental analyses, IR and ^1H NMR spectral data, which were found also to be in a good agreement with the assigned structures (see the Experimental section).



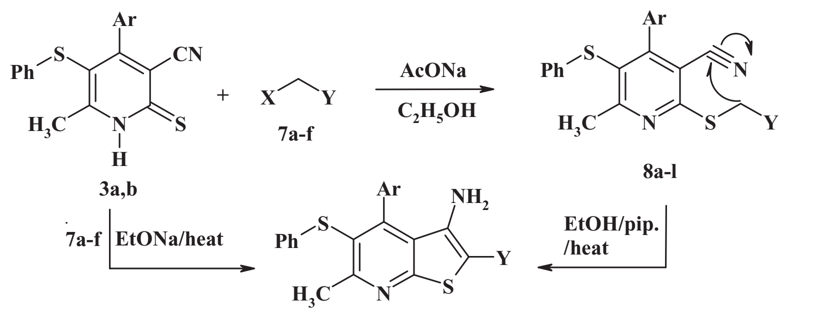
Scheme 1

A further proof for the structure of **8a–f** came from their cyclization by boiling their ethanolic solutions in the presence of catalytic amounts of piperidine to give the corresponding thieno[2,3-*b*]pyridine derivatives **9a-f**, respectively. The IR spectra of **9a–f** were found to be free from the absorption bands of the nitrile function, and instead new bands of the NH_2 function were detected. Analytical data of **9a–f** were found to be almost identical to that of **8a–f**, respectively, proving that the nitrile function is involved in the cyclization step via addition of the active methylene to the nitrile function in compounds **8a–f**. The ^{1}H NMR spectra of **9a–f** were also found to be free from the signals of the active methylene group proving also its involvement in the cyclization step leading to the formation of **9a–f.**

Another piece of solid evidence for the structure of **9a–f** came from their independent synthesis by performing the reaction between **3a** and **7a-f**, respectively, in boiling ethanolic sodium ethoxide. Compounds **9a–f** prepared via this route were found to be completely identical in all aspects (analyses, IR, and ^{1}H- MR spectra) with **9a–f** prepared via the first route (see Scheme 2 and the Experimental section).

The other starting compound **3b** was also involved in the same series of reactions as for **3a** described before. Thus, **3b** reacted with the halogenated reagents **7a–f** in hot ethanolic sodium acetate to give the corresponding 2-*S*-alkyl substituted pyridine derivatives **8g–l**, respectively, in good yields. Again the structures **8g–l** were established based on correct elemental analyses and spectral data studies. These data were found to be consistent with the assigned structure in each case (see Scheme 2 and the Experimental section). Cyclization of each of **8g–l** by boiling their ethanolic solutions in the presence of piperidine afforded the corresponding thieno[2,3-*b*]pyridine derivatives **9g–l**, respectively.

Again the IR spectra of **9g–l** did not show the bands of the nitrile function and showed the bands of the newly born NH_2 group in each case. In addition, no signals of CH_2 groups were detected in the ^{1}H NMR spectra of **9g–l**.



9a-l

7a, X = Cl; Y = $COCH_3$
b, X = Cl; Y = CN
c, X = Cl; Y = CO_2Et
d, X = Cl; Y = $CONH_2$
e, X = Br; Y = COC_6H_4-Cl-p
f, X = Br; Y = COC_6H_4-Br-p

8-9a, Ar = Ph; Y = $COCH_3$
b, Ar = Ph; Y = CN
c, Ar = Ph; Y = CO_2Et
d, Ar = Ph; Y = $CONH_2$
e, Ar = Ph; Y = COC_6H_4-Cl-p
f, Ar = Ph; Y = COC_6H_4-Br-p
g, Ar = C_6H_4-OCH_3-p; Y = $COCH_3$
h, Ar = C_6H_4-OCH_3-p; Y = CN
i, Ar = C_6H_4-OCH_3-p; Y = CO_2Et
j, Ar = C_6H_4-OCH_3-p; Y = $CONH_2$
k, Ar = C_6H_4-OCH_3-p; Y = COC_6H_4-Cl-p
l, Ar = C_6H_4-OCH_3-p; Y = COC_6H_4-Br-p

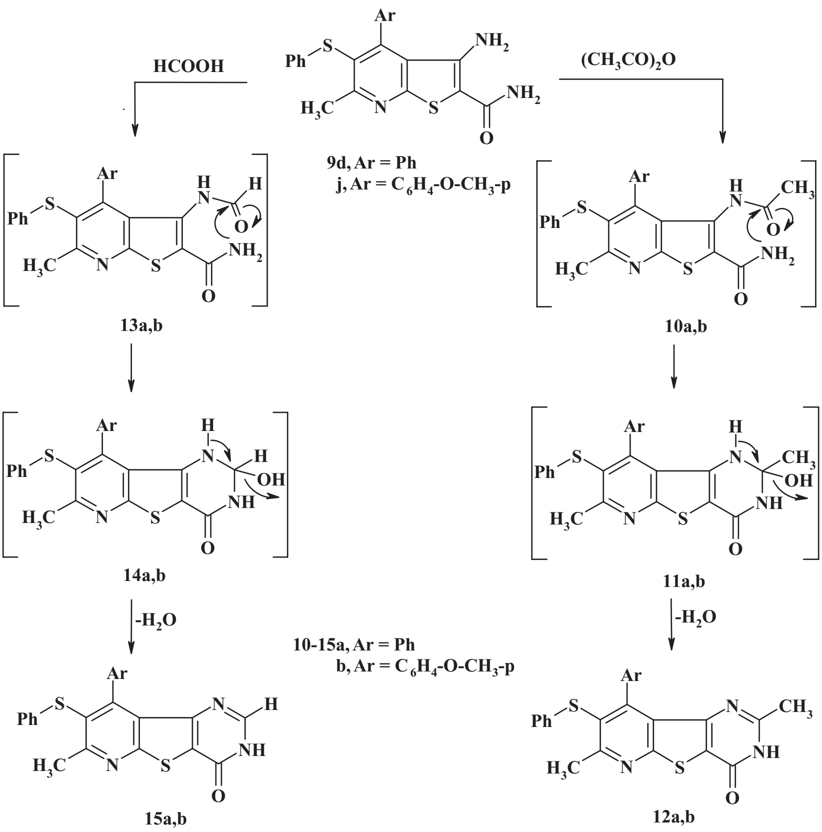
Scheme 2

Another piece of solid evidence for the structure of **9g–l** came from their independent synthesis by performing the reaction between **3b** and **7a–f**, respectively, in boiling ethanolic sodium ethoxide. Compounds **9g–l** prepared via this route were found to be completely identical in all aspects (analyses, IR, and ^{1}H NMR spectra) with **9g–l** prepared via the first route (see Scheme 2 and the Experimental section).

The isolation of a large number of compounds of **9a–l** with their active polyfunctional groups stimulated the interest to utilize them as excellent candidates for the synthesis of other new heterocyclic derivatives via their reactions with a variety of different reagents.

Thus, **9d**, as an example of the series, reacted with acetic anhydride to give a reaction product corresponding to the addition of one molecule of **9d** to another molecule of the anhydride followed by the loss of one molecule of acetic acid and one molecule of water to afford the corresponding 2,7-dimethyl-9-phenyl-8-phenyl-thiopyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidin-4(3*H*)-one (**12a**) through the intermediates **10a** and **11a**, whose structure was established based on correct elemental analysis and spectral data studies (see Scheme 3 and the Experimental section).

In a similar manner, **9j** reacted with acetic anhydride also to afford the corresponding 9-(4-methoxyphenyl)-2,7-dimethyl-8-phenylthiopyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**12b**). The IR spectrum of this reaction product showed the presence of an absorption band of NH group (3413 cm^{-1}) in addition to the band of ring C=O (1675 cm^{-1}) only. Its ^{1}H NMR spectrum revealed signals of two CH_3 groups at $\delta = 2.10$ and 2.66 ppm, one methoxy group (OCH_3) at $\delta = 3.82$ ppm, a signal for NH group (s, 1H, NH, at $\delta = 12.80$ ppm) in addition to the multiplet of the aromatic protons (m, 9H, at $\delta = 6.90$–7.29 ppm). Based on the above findings, in addition to correct elemental analysis and spectral



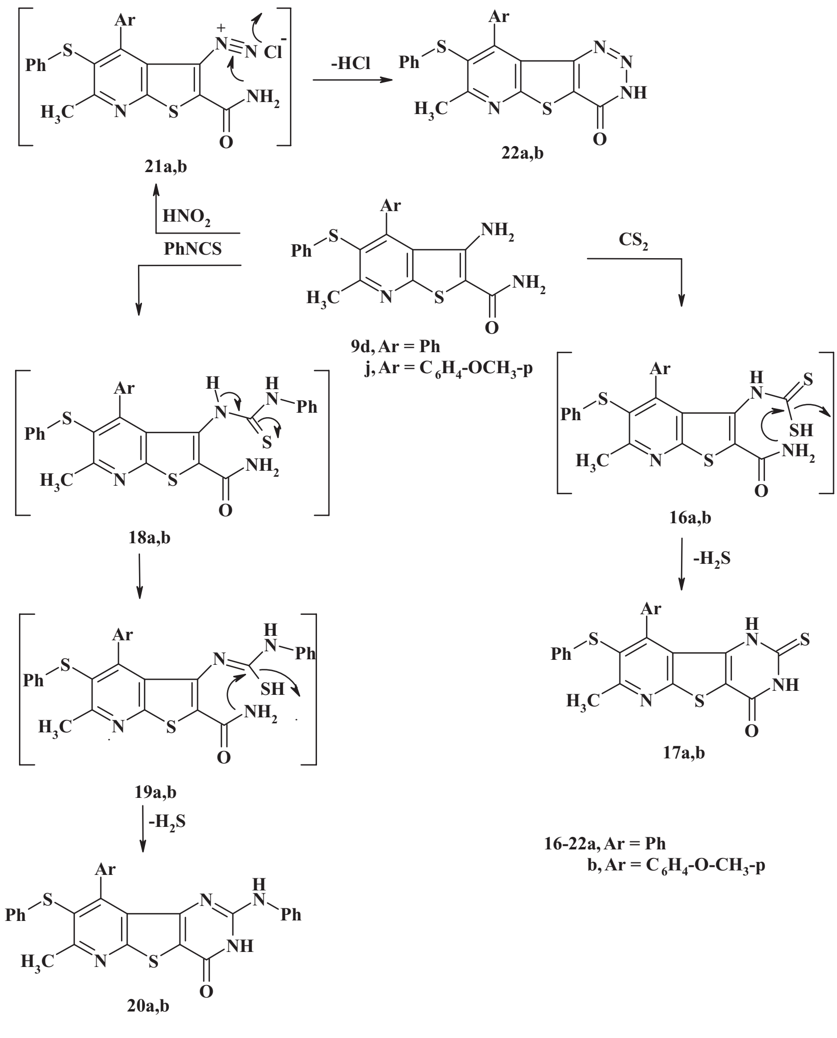
Scheme 3

data studies which were found to be in a good agreement with the assigned structure, the reaction product was formulated as **12b** (see Scheme 3 and the Experimental section).

Moreover, compounds **9d,j** also reacted with formic acid to afford reaction products resulting from equimolecular addition of each of **9d,j** to the acid followed by the loss of two molecules of water in each case to yield **15a**,**b**.

The IR spectra of the reaction products showed the disappearance of the absorption bands of the two NH_2 groups and instead showed the presence of only one NH in each case, a fact which was confirmed by the ^1H NMR data. Based on the above findings, the reaction products could be formulated as the pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one derivatives **15a**,**b**, respectively, which could be formed through the intermediates **13a**,**b** and **14a**,**b** (see Scheme 3 and the Experimental section).

An interesting reaction with carbon disulfide took place with each of **9d,j** to give reaction products formed via the addition of each of **9d,j** to carbon disulfide followed by elimination of one molecule of hydrogen sulfide to give **17a**,**b**. The IR spectra of these reaction products showed the presence of a NH group, a ring-CO group, and a ring C=S group in each case. The ^1H NMR spectrum of compound **17b** revealed signals of one CH_3 and one OCH_3 groups at $\delta = 2.58$ and 3.79 ppm, respectively, and two NH groups at $\delta = 5.60$ and 12.38 ppm, in addition to the multiplet of the aromatic protons



Scheme 4

at δ = 6.86–7.37 ppm. The reaction products could be formulated as the 2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(1*H*)-one derivatives **17a**,**b**, respectively, (see Scheme 4 and the Experimental section).

The synthetic potential of each of **9d**,**j** was further explored via their reactions with phenyl isothiocyanate. Thus, **9d**,**j** reacted with phenyl isothiocyanate in pyridine to yield products corresponding to equimolecular addition of the reactants and then cyclization via loss of hydrogen sulfide in each case. The IR spectra of the reaction products showed the presence of NH and one ring-CO in each case. The singlet signals of two NH and that of the ring CH_3 in addition to the aromatic protons were revealed in the ^{1}H NMR spectra of the reaction products. Collecting the above data together with the correct analytical data led to formulation of the reaction products as the 2-anilinopyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidin-4(3*H*)-one derivatives **20a**,**b**, respectively (see Scheme 4 and the Experimental section).

Work was also extended to shed more light on the synthetic potential of compounds **9**. Thus, each of **9d**,**j** reacted with nitrous acid to give the corresponding pyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-one derivatives **22a**,**b**, respectively, whose structures were confirmed based on both elemental analysis and spectral data. In this respect, the IR spectrum of **22a** showed the absorption bands of one NH (3397 cm^{-1}) and the ring-CO group (1665 cm^{-1}) only. The IR spectrum of **22b** showed the absorption bands of the NH and ring-CO groups in their proper positions, while its ^1H NMR spectrum revealed the signal of the OCH_3 group at $\delta = 3.73$ ppm in addition to those of the NH (s, 1H, 8.00 δppm), pyridine-CH_3 at $\delta = 2.55$ ppm, and the aromatic protons (m, 9H, at $\delta = 6.83–7.37$ ppm) (see Scheme 4 and the Experimental section).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded as KBr discs on a Shimadzu FTIR-8201PC Spectrophotometer. ^1H NMR spectra were recorded on a Varian Mercury 300 MHz and Varian Gemini 200 MHz spectrometers using TMS as an internal standard and $CDCl_3$ and DMSO-d_6 as solvents; chemical shifts are expressed as δ ppm units. Mass spectra were recorded on a Shimadzu GCMS-QP1000EX using inlet type at 70 eV. The Microanalytical Center of Cairo University performed microanalyses. Compounds **2a**,**b** were prepared according to the procedures in the literature.[38]

Synthesis of 6-Methyl-4-phenyl-5-phenylthio-2-thioxo-1,2-dihydropyridine-3-carbonitrile (3a)

A mixture of **1** (0.01 mol, 1.66 g) and **2a** (0.01 mol, 1.88 g) in absolute ethanol (30 mL) containing a catalytic amount of triethylamine (0.4 mL) was heated under reflux for 5 h. The product formed was collected by filtration, washed with cold ethanol, and then crystallized from ethanol to give **3a** as yellow crystals (63%); mp 220–222°C; IR (υ cm^{-1}): NH (3310), CN (2221), C=S (1541); ^1H NMR (δ ppm): 2.46 (s, 3H, CH_3 at pyridine), 6.58 (br, 1H, NH), 7.12–7.43 (m, 10H, ArH's); Anal. for $C_{19}H_{14}N_2S_2$ (334.5): calcd./found(%): C (68.23/68.20), H (4.22/4.25), N (8.38/8.37), S (19.17/19.13).

Synthesis of 4-(4-Methoxyphenyl)-6-methyl-5-phenylthio-2-thioxo-1,2-dihydropyridine-3-carbonitrile (3b)

A mixture of **1** (0.01 mol, 1.66 g) in sodium methoxide (prepared from 0.01 mol of sodium metal in methanol 10 mL) and **2b** (0.01 mol, 2.18 g) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto ice-cold water, and then acidified with HCl. The product formed was collected by filtration, washed with cold ethanol, and crystallized from ethanol to give **3b** as yellow crystals (65%); mp 220–222°C; IR (υ cm^{-1}): NH (3311), CN (2220), C=S (1540); ^1H NMR (δ ppm): 2.56 (s, 3H, CH_3 at pyridine), 3.73 (s, 3H, OCH_3), 6.62 (br., 1H, NH), 7.20–7.51 (m, 9H, ArH's); Anal. for $C_{20}H_{16}N_2OS_2$ (364.4): calcd./found(%): C (65.90/65.93), H (4.42/4.40), N (7.69/7.68), S (17.60/17.64).

Synthesis of 3a,b

A mixture of **5a**,**b** (0.01 mol) and cyanothioacetamide (**6**, 0.01 mole, 1.0 g) in sodium methoxide (prepared from 0.01 mol of sodium metal in methanol 10 mL) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto ice-cold water, and then acidified with HCl. The product formed was collected by filtration, washed with cold ethanol, and crystallized from ethanol to give **3a**,**b**, respectively.

Synthesis of 8a–l

A mixture of each of the reactants **A** (0.01 mol) in ethanol (30 mL), sodium acetate (0.015 mole, 2.04 g), and reactants **B** (0.01 mol, of each) was heated under reflux for 2 h. The products so formed were collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent. As an example of the characterization provided, ***8a*** is shown below. Complete data for ***8b–8l*** are found in the Supplemental Materials (available online).

6-Methyl-2-[(2-oxopropyl)thio]-4-phenyl-5-phenylthionicotinonitrile (8a). Crystallized from ethanol as yellow crystals (75%); mp 112–4°C; IR (υ cm^{-1}): CN (2221), C=O (1715); ^{1}H NMR (δ ppm): 2.55 (s, 3H, CH_3 at pyridine), 3.58 (s, 3H, CO$\underline{CH_3}$), 4.00 (s, 2H, -S$\underline{CH_2}$), 6.89–7.42 (m, 10H, ArH's); Anal. for $C_{22}H_{18}N_2OS_2$ (390.5): calcd./found(%): C (67.66/67.69), H (4.65/4.66), N (7.17/7.14), S (16.42/16.44).

Synthesis of the Thienopyridine Derivatives 9a–l

Method A. A mixture of each of the reactants **A** (0.01 mol of each) in ethanolic sodium ethoxide and reactants **B** (0.01 mol) was heated under reflux for 2 h. The products so formed were collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent to give **9a–l**, respectively. As an example of the characterization provided, ***9a*** is shown below. Complete data for ***9b–9l*** are found in the Supplemental Materials.

Method B. A mixture of each of the reactants **C** (0.01 mole of each) in ethanolic sodium ethoxide was heated under reflux for 2 h. The products so formed were collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent.

2-Acetyl-3-amino-6-methyl-4-phenyl-5-phenylthiothieno [2,3-*b*]pyridine (9a). Orange crystals (72%); mp 248–250°C; crystallized from ethanol/dioxane; IR (υ cm^{-1}): NH_2 (3436, 3484), C=O (1680); ^{1}H NMR (δ ppm): 1.61 (s, 2H, NH_2), 2.44 (s, 3H, CH_3 at pyridine), 2.76 (s, 3H, CO$\underline{CH_3}$), 7.07–7.50 (m, 10H, ArH's); Anal. for $C_{22}H_{18}N_2OS_2$ (390.5): calcd./found(%): C (67.66/67.62), H (4.65/4.62), N (7.17/7.14), S (16.42/16.44).

Synthesis of the Pyridothienopyrimidinone Derivatives 12a,b

A mixture of **9d**,**j** (0.01 mol of each) and acetic anhydride (20 mL) was heated under reflux for 3 h. The reaction mixture was then evaporated to half of its volume and allowed to cool. The solid products formed were collected by filtration and crystallized from the proper solvent to give **12a**,**b**, respectively.

2,7-Dimethyl-9-phenyl-8-phenylthiopyrido[3′,2′:4,5]thieno[3,2-d]pyrimi din-4(3*H*)-one (12a). Crystallized from ethanol/dioxane as white crystals (69%); mp 350–352°C; IR(υ cm^{-1}): NH (3410), C=O (1673), ^{1}H NMR (δ ppm): 2.01 (s, 3H, CH_3 at pyridine), 2.68 (s, 3H, CH_3 at pyrimidine), 6.91–7.39 (m, 10H, ArH's), 12.66 (1H, NH at pyrimidine); Anal. for $C_{23}H_{17}N_3OS_2$ (415.5): calcd./found(%): C (66.48/66.51), H (4.12/4.15), N (10.11/10.08), S (15.43/15.47).

9-(4-Methoxyphenyl)-2,7-dimethyl-8-phenylthiopyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidin-4(3*H*)-one (12b). Greenish-white crystals (70%); mp 318–320°C; crystallized from ethanol-dioxane mixture; IR (υ cm^{-1}): NH (3413), C=O (1675); ^{1}H-NMR (δ ppm): 2.10 (s, 3H, CH_3 at pyrimidinone), 2.66 (s, 3H, CH_3 at pyridine), 3.82 (s, 3H, O$\underline{CH_3}$), 6.90–7.29 (m, 9H, ArH's), 12.80 (s, 1H, NH); Anal. for $C_{24}H_{19}N_3O_2S_2$ (445.5): calcd./found(%): C (64.70/64.74), H (4.30/4.33), N (9.43/9.42), S (14.39/14.36).

Synthesis of 15a,b

Compounds **9d**,**j** (0.01 mol of each) and formic acid (15 mL) were heated under reflux for 3 h. The reaction mixture was evaporated to two-thirds of its volume and then allowed to cool. The solid products formed were collected by filtration and crystallized from the proper solvent to give **15a**,**b**, respectively.

7-Methyl-9-phenyl-8-phenylthiopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (15a). Crystallized from ethanol/dioxane as pale yellow crystals (68%); mp 340–341°C; IR (υ cm^{-1}): NH (3416), C=O (1677); ^{1}H NMR (δ ppm): 2.71 (s, 3H, CH_3 at pyridine), 6.95–7.41 (m, 10H, ArH's), 8.04 (s, 1H, pyrimidine-H5), 12.92 (s, 1H, NH at pyrimidine); Anal. for $C_{22}H_{15}N_3OS_2$ (401.5): calcd./found(%): C (65.81/65.83), H (3.77/3.79), N (10.47/10.50), S (15.97/15.93).

9-(4-Methoxyphenyl)-7-methyl-8-phenylthiopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (15b). Crystallized from ethanol/dioxane as pale yellow crystals (70%); mp 182–184°C; IR (υ cm^{-1}): NH (3414), C=O (1677); ^{1}H NMR (δ ppm): 2.63 (s, 3H, CH_3 at pyridine), 3.77 (s, 3H, O$\underline{CH_3}$), 7.95 (s, 1H, CH), 12.79 (s, 1H, NH), 6.86–7.22 (m, 9H, ArH's); Anal. for $C_{23}H_{17}N_3O_2S_2$ (431.5): calcd. /found(%): C (64.02/64.05), H (3.97/3.94), N (9.74/9.77), S (14.86/14.83).

Synthesis of 17a,b

A mixture of **9d**,**j** (0.01 mol of each) and carbon disulfide (4 mL) in pyridine (20 mL) was heated under reflux for 48 h. The reaction mixture was cooled, poured onto ice-cold water, and then neutralized (pH = 7) with hydrochloric acid. The product formed was collected by filtration, washed with cold ethanol, and crystallized from the proper solvent to give **17a**,**b**, respectively.

7-Methyl-9-phenyl-8-phenylthio-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-4(1*H*)-one (17a). Crystallized from ethanol/dioxane mixture as brown crystals (70%); mp 266–268°C; IR (υ cm^{-1}): NH (3400), C=S (1540), C=O (1668), ^{1}H NMR (δ ppm): 2.68 (s, 3H, CH_3 at pyridine), 6.89–7.83 (m, 11H, ArH's and NH pyrimidine-H1), 13.05 (s, 1H, NH pyrimidine-H3); Mass: M^{+} (100%), 432 (14.9%), 373 (17.8%), 356 (42.5%), 343 (26.8%), 267 (10.2%), 78 (12.1%), 77 (25.5%); Anal. for $C_{22}H_{15}N_3OS_3$ (433.5): calcd./found(%): C (60.94/60.91), H (3.49/3.52), N (9.69/9.66), S (22.19/22.15).

9-(4-Methoxyphenyl)-7-methyl-8-phenylthio-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(1*H*)-one (17b). Crystallized from ethanol/ dioxane as brown crystals (69%); mp 148–150°C; IR(υ cm^{-1}): NH (3402), C=S (1543), C=O (1666); ^{1}H NMR (δ ppm): 2.58 (s, 3H, CH_3 at pyridine), 3.79 (s, 3H, O$\underline{CH_3}$), 5.60 (s, 1H, NH), 6.86–7.37 (m, 9H, ArH's), 12.38 (s, 1H, CO-$\underline{NH}$-CS); Mass: M^{+} (33%), 423 (16.9%), 422 (36%), 421 (100%), 405 (13.9%), 403 (86.8%), 375 (28%), 284 (11.4%), 163

(15.9%), 149 (15.9%), 77 (15.3%); Anal. for $C_{23}H_{17}N_3O_2S_3$ (463.5): calcd./found(%): C (59.59/59.57), H (3.70/3.74), N (9.06/9.05), S (20.75/20.77).

Synthesis of 20a,b

A mixture of **9d**,**j** (0.01 mol of each) and phenyl isothiocynate (0.01 mol) in pyridine (20 mL) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto ice-cold water, and then acidified with a few drops of hydrochloric acid. The product formed was collected by filtration, washed with cold ethanol, and crystallized from the proper solvent to give **20a**,**b**, respectively.

7-Methyl-9-phenyl-8-phenylthio-2-anilinopyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidin-4(3*H*)-one (20a). Crystallized from dioxane as pale yellow crystals (66%); mp 180–182°C; IR(υ cm^{-1}): NH (3410), C=O (1669); ^{1}H NMR (δ ppm): 2.59 (s, 3H, CH_3 at pyridine), 5.56 (s, 1H, NH-Ph), 6.90–7.48 (m, 15H, ArH's), 9.80 (s, 1H, NH in pyrimidinone); Anal. for $C_{28}H_{20}N_4OS_2$ (492.5): calcd./found(%): C (68.27/68.29), H (4.09/4.11), N (11.37/11.40), S (13.02/13.00).

9-(4-Methoxyphenyl)-7-methyl-8-phenylthio-2-anilinopyrido[3′,2′:4,5] thieno[3,2-*d*]pyrimidin-4(3*H*)-one (20b). Crystallized from dioxane as pale yellow crystals (65%); mp 270–272°C; IR (υ cm^{-1}): NH (3411), C=O (1670); ^{1}H NMR (δ ppm): 2.67 (s, 3H, CH_3 at pyridine), 3.84 (s, 3H, OCH_3), 6.46–7.37 (m, 14H, ArH's), 7.64 (s, 1H, -NH-Ph), 9.95 (s, 1H, NH in pyrimidinone); Anal. for $C_{29}H_{22}N_4O_2S_2$ (522.5): calcd./found(%): C (66.64/66.65), H (4.24/4.26), N (10.72/10.74), S (12.27/12.31).

Synthesis of 22a,b

A stirred cold solution (0–5°C) of each of **9d**,**j** (0.01 mol) in acetic acid (10 mL) and concentrated hydrochloric acid (2 mL) was treated with a cold solution of sodium nitrite (0.01 mole, 0.23 g in 5 mL) dropwise with stirring. Stirring was continued for 1 h. The reaction mixture was then allowed to stand at room temperature for 15 min. The solid obtained was collected by filtration and crystallized from the proper solvent to give **22a**,**b**, respectively.

7-Methyl-9-phenyl-8-phenylthiopyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]-triazin-4(3*H*)-one (22a). Crystallized from ethanol/dioxane as pale yellow crystals (68%); mp > 360°C; IR (υ cm^{-1}): NH (3397), C=O (1665); ^{1}H NMR (δ ppm): 2.85 (s, 3H, CH_3 at pyridine), 6.89–7.45 (m, 10H, ArH's), 12.94 (s, 1H, NH); Anal. for $C_{21}H_{14}N_4OS_2$ (402.5): calcd./found(%): C (62.67/62.64), H (3.51/3.55), N (13.92/13.96), S (15.93/15.94).

9-(4-Methoxyphenyl)-7-methyl-8-phenylthiopyrido[3′,2′:4,5]thieno[3,2-*d*] [1,2,3]-triazin-4(3*H*)-one (22b). Crystallized from ethanol as pale yellow crystals (69%); decompose at 160–162°C; IR (υ cm^{-1}): NH (3400), C=O (1667); ^{1}H NMR (δ ppm): 2.55 (s, 3H, CH_3 at pyridine), 3.73 (s, 3H, OCH_3), 6.83–7.37 (m, 9H, ArH's), 8.00 (s, 1H, NH); Anal. for $C_{22}H_{16}N_4O_2S_2$ (432.5): calcd./found(%): C (61.09/61.06), H (3.73/3.77), N (12.95/12.99), S (14.83/14.81).

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