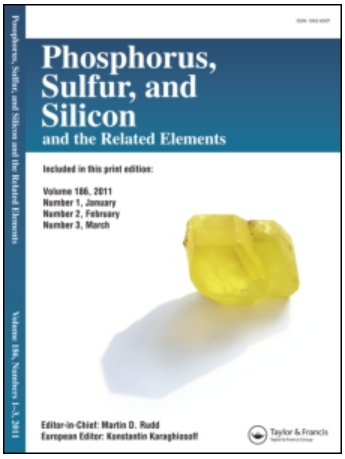

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Reactions of Cyanothioacetamide: Synthesis of Several New Thioxohydro-pyridine-3-carbonitrile and Thieno[2,3-b]pyridine Derivatives

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REACTIONS OF CYANOTHIOACETAMIDE: SYNTHESIS OF SEVERAL NEW THIOXOHYDRO-PYRIDINE-3-CARBONITRILE AND THIENO[2,3-b]PYRIDINE DERIVATIVES

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*Cyanothioacetamide (**1**) reacted with α,β-unsaturated carbonyl compounds **2a–d** to afford thioxohydropyridine-3-carbonitriles **5a–d**, which were used as the starting materials for the preparation of several thienopyridines via their reactions with active halogen-containing compounds, e.g., 2-bromo-1-phenylethanone (**7a**), 2-bromo-1-p-tolylethanone (**7b**), chloroacetone (**10a**), α-chloroacetylacetone (**10b**), and chloroacetic acid ethyl ester (**13**). The structure of the newly synthesized heterocyclic compounds were established based on the data of elemental analyses, IR, ^1H NMR, and mass spectra.*

Keywords: 2-Methylthio-pyridines; 2-oxopropylthiopyridines; 3-aminothieno[2,3-b]pyridines; cyanothioacetamide; thioxohydropyridines

INTRODUCTION

In the last few years our group has been interested in the synthesis of heterocyclic derivatives with potential biological activity, and we have published several articles on this subject.[1–17] On the other hand, the reported biological activities of thioxohydropyridines[18,19] and thienopyridines[20–22] stimulated our interest for the synthesis of several derivatives of these ring systems that are required for the medicinal chemistry program.

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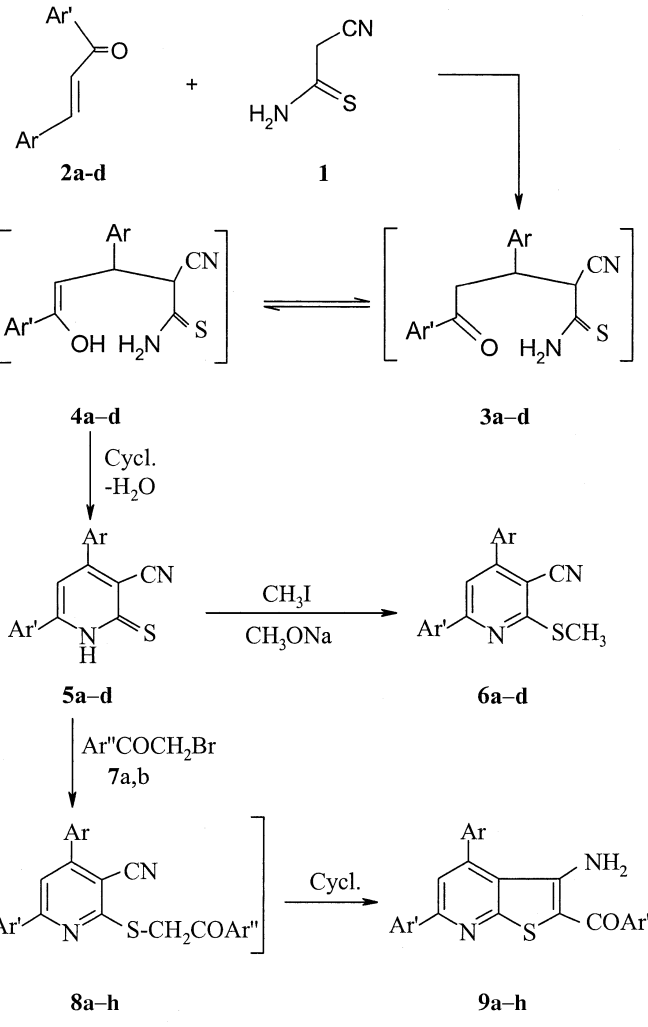
RESULTS AND DISCUSSION

It has been found that the α,β-unsaturated ketones **2a–d** reacted with cyanothioacetamide (**1**) in ethanol in the presence of catalytic amounts of piperidine to afford the corresponding 2-thioxohydropyridine-3-carbonitrile derivatives **5a–d**, respectively, via the nonisolable intermediates **3a–d** and **4a–d**. The structure of **5a–d** was established based on elemental analyses, IR, and ^{1}H NMR spectral data. The mass spectrum of **5d**, as a typical example, gave m/z = 352, which is the molecular weight of the molecular formula $C_{23}H_{16}N_2S$ of the assigned structure (cf. Chart 1). Compounds **5a–d** were taken as the starting materials for the present study owing to the presence of more than one active center in their structure.

Compound **5a** reacted with methyl iodide in methanolic sodium methoxide to give the corresponding 4-(1-naphthyl)-2-methylthio-6-phenylpyridine-3-carbonitrile **6a**, whose structure was elucidated based on elemental analysis, IR, and ^{1}H NMR spectral data. Other analogues **5b–d** were reacted similarly with methyl iodide to afford the corresponding 2-methylthiopyridine-3-carbonitrile derivatives **6b–d**, respectively (Chart 1).

Similarly, **5a–d** reacted with the ω-bromoacetophenone derivatives **7a**, **b** in methanolic sodium methoxide solution to give the corresponding 2-aroyl-3-aminothieno[2,3-b]pyridine derivatives **9a–h**. Compounds **9a–h** were most probably formed via the nonisolable intermediates **8a–h** through dehydrobromination. Both the CH_2 and the CN groups were involved in the cyclization step to give the nonisolable intermediates, which rearranged to give **9a–h** (Chart 1).

The work was extended to shed more light on the reactivity of **5a–d** towards the active halogen-containing reagents. Thus, **5a**, **b**, **d** reacted with chloroacetone (**10a**) and with α-chloroacetylacetone (**10b**) in methanolic sodium methoxide to afford directly the corresponding 3-amino-2-acetylthieno[2,3-b]pyridine derivatives **12a**, **b**, **d** respectively, via the nonisolable intermediates **11a**, **b**, **d**, **e**, **f**, **h**. The structures of **12a**, **b**, **d** were established based on elemental analyses and IR spectra. The mass spectrum of **12b** as a typical example gave m/z = 408 which agreed with the molecular weight of a molecular formula $C_{26}H_{20}N_2OS$ of the assigned structure (Chart 2). It is notable to report here that all trials to isolate the intermediates **11a**, **b**, **d**, **e**, **f**, **h** were unsucessful under a variety of reaction conditions. Moreover, an additional confirmation of the structures of **12a**, **b**, **d** was achieved via their alternative synthesis by the reaction of **5a**, **b**, **d** with **10a**, **b** in boiling ethanol containing a catalytic amount of triethylamine (Scheme 1).



5,6	Ar	Ar'
a	α-naphthyl	C_6H_5
b	α-naphthyl	C_6H_4-CH_3-4
c	β-naphthyl	C_6H_5
d	β-naphthyl	C_6H_4-CH_3-4

9	Ar	Ar'	Ar"
a	α-naphthyl	C_6H_5	C_6H_5
b	α-naphthyl	C_6H_4-CH_3-4	C_6H_5
c	β-naphthyl	C_6H_5	C_6H_5
d	β-naphthyl	C_6H_4-CH_3-4	C_6H_5
e	α-naphthyl	C_6H_5	C_6H_4-Cl-4
f	α-naphthyl	C_6H_4-CH_3-4	C_6H_4-Cl-4
g	β-naphthyl	C_6H_5	C_6H_4-Cl-4
h	β-naphthyl	C_6H_4-CH_3-4	C_6H_4-Cl-4

CHART 1

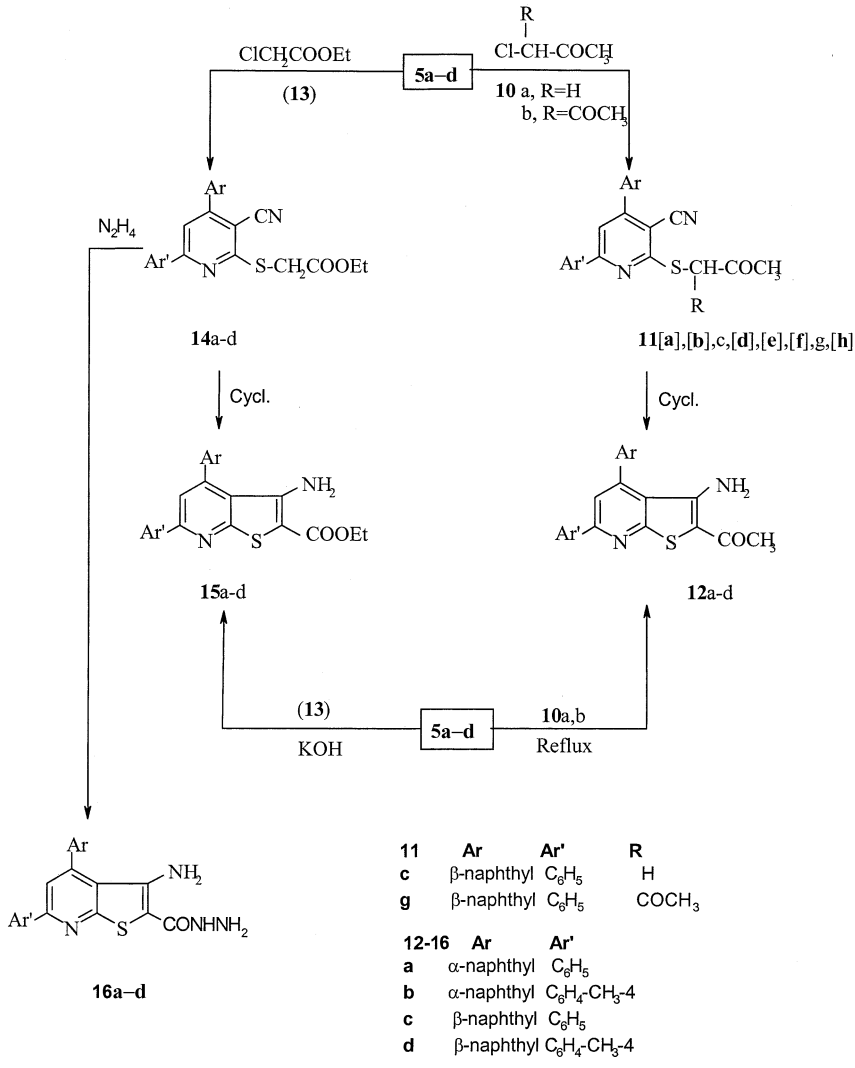
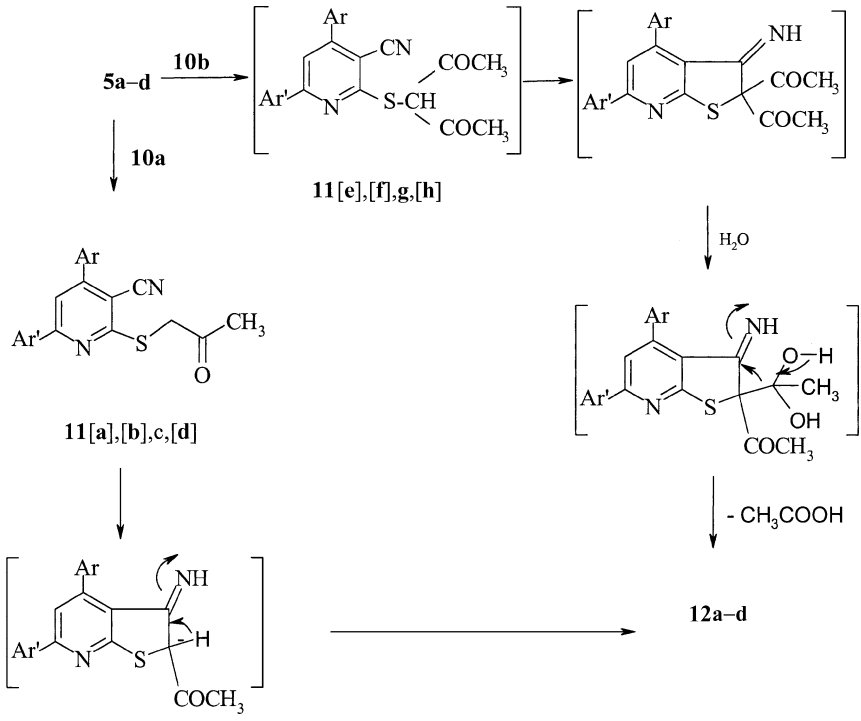


CHART 2

In contrast to the behavior of **5a**, **b**, **d** towards the reaction of **10a**, **b**, it has been found that compound **5c** reacted with **10a**, **b** to afford the corresponding 4-(2-naphthyl)-2-(oxopropylthio)-6-phenylpyridine-3-carbonitrile (**11c**) and 2-(1-acetyl-2-oxopropyl-thio)-4-(2-naphtyl)-6-phenylpyridine-3-carbonitrile (**11g**), respectively. The IR spectra of **11c**, **g** showed the presence of absorption bands of the nitrile function and the acetyl CO group in their proper positions, while the ^{1}H NMR



SCHEME 1

spectrum of **11c** revealed the signals of CH_3, CH_2, and aromatic protons; the ^{1}H NMR spectrum of **11g** revealed the signals of two CH_3, CH, and aromatic protons. More evidence for the structure of **11c**, **g** was obtained through their cyclization using ethanolic potassium hydroxide solution to afford the 2-acetyl-3-aminothieno[2,3-b] pyridine derivatives **12c**, **d**. The IR spectra of **12c**, **d** showed no bands of the CN group, while the bands of the newly born NH_2 were detected and the ^{1}H NMR spectra revealed the signals of CH_3, NH_2, and the aromatic protons (Scheme 1).

Compounds **5a–d** underwent a nucleophilic substitution reaction with ethyl chloroacetate **(13)** in methanolic sodium methoxide to afford the products corresponding to the dehydrochlorination reactions. The IR spectra of such products showed the bands corresponding to CN and ester-CO groups. By considering the above-mentioned data in addition to the ^{1}H NMR spectra and the chemical analyses data, such reaction products could be formulated as the ethyl 2-[6-aryl-4-aryl-3-cyano-2-pyridylthio]acetate derivatives **14a–d**, respectively. Further confirmation of the structure of each of **14a–d** arose from their cyclization in ethanolic potassium hydroxide (10% KOH) to give the corresponding

ethyl 3-aminothieno[2,3-b]pyridine-2-carboxylate derivatives **15a–d**. The IR spectrum of each of **15a–d** showed no bands of the CN function, while the bands of the newly formed NH_2 group were detected. By considering the above-mentioned data in addition to ^{1}H NMR spectra it can be proposed that both the CN and SCH_2 groups were involved in the cyclization step. Compounds **15a–d** were also synthesized authentically by heating **5a–d** with ethyl chloroacetate **(13)** in ethanolic potassium hydroxide (10% KOH). It is remarkable to report here that the compounds **15a–d** obtained by the two pathways are identical in all physical and chemical properties (m.p., mixed m.p., and IR).

The position and chemical reactivity of the ethoxycarbonyl group in **15a–d** were confirmed by their reaction with hydrazine hydrate. Thus, **15a** reacted with hydrazine hydrate in boiling ethanol to give a product of a molecular formula corresponding to simple addition of one molecule of **15a** to one molecule of hydrazine hydrate, followed by loss of ethanol. An elemental analysis of the reaction product gave the data corresponding to a molecular formula $C_{24}H_{18}N_4OS$, and its IR spectrum showed no bands of the ester-CO, group, while the bands related to the NH, two NH_2 and hydrazidic-CO groups were detected. By considering the above-mentioned data in addition to ^{1}H NMR spectrum, this reaction product could be formulated as N-amino[3-amino-4-(1-naphthyl)-6-phenylthieno[2,3-b]pyridin-2-yl]carboxamide (**16a**) (Chart 2).

Similarly, **15b–d** reacted with hydrazine hydrate to furnish the corresponding N-amino(3-amino-4,6-diarylthieno[2,3-b]pyridin-2-yl]carboxamides **16b–d**, whose structures were also confirmed by elemental analysis and spectral data studies. The mass spectrum of **16c**, as a typical example, gave $m/z = 410$, which agreed with the molecular weight of the molecular formula $C_{24}H_{18}N_4OS$ of the assigned structure (Chart 2).

EXPERIMENTAL

All melting points are uncorrected. IR (KBr discs) were recorded on Shimadzu FTIR-8201PC Spectrophotometer. ^{1}H NMR spectra were recorded on Varian Mercury 300 MHz. and Varian Gemini 200 MHz. Spectrometers using TMS as an internal standard and $CDCl_3$, DMSO-d_6 and $(CD_3)_2CO$ as solvents and chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Shimadzu GCMS-QP1000EX using inlet type at 70 eV. Microanalyses were performed by the Microanalytical Center of Cairo University.

Synthesis of 5a–d: General Method

A solution of each of **1** (1 g) and **2a–d** (2.58 g, 2.72 g, 2.58 g, and 2.72 g, respectively) in absolute ethanol (30 ml) containing a catalytic amount of piperidine (0.4 ml) was heated under reflux for 5 h. The reaction mixture was then evaporated till dryness and cooled and titurated with ethanol. The product formed was collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent to give the corresponding **5a–d**, respectively.

4-(1-Naphthyl)-6-phenyl-2-thioxohydropyridine-3-carbonitrile (5a)

Crystallized from ethanol as orange crystals (70%), m.p. 264–266°C. IR (ν cm^{-1}): 3346 (NH), 3051 (aromatic-CH) and 2217 (CN). ^1H NMR (δ ppm): 5.25 (s, br., 1H, NH) and 7.25–7.99 (m, 13H, ArH's). Anal. for $C_{22}H_{14}N_2S$ (338.43) Calcd. (%): C, 78.08; H, 4.17; N, 8.28; S, 9.47; Found: C, 78.3; H, 4.0; N, 8.5; S, 9.3.

6-(4-Methylphenyl)-4-(1-naphthyl)-2-thioxohydropyridine-3-carbonitrile (5b)

Crystallized from ethanol as yellow crystals (72%), m.p. 258–259°C. IR (ν cm^{-1}): 3217 (NH), 3049 (aromatic-CH), 2931 (sat. CH) and 2209(CN). ^1H NMR (δppm): 2.83 (s. 3H, CH_3), 5.28 (s, br., 1H, NH) and 7.25–7.97 (m, 12H, ArH's). Anal. for $C_{23}H_{16}N_2S$ (352.46): Calcd. (%): C, 78.38; H, 4.58; N, 7.95; S, 9.10. Found: C, 78.1; H, 4.8; N, 7.7; S, 9.4.

4-(2-Naphthyl)-6-phenyl-2-thioxohydropyridine-3-carbonitrile (5c)

Crystallized from ethanol as yellow crystals (85%), m.p. 252–254°C. IR (ν cm^{-1}): 3339 (NH), 3051 (aromatic-CH) and 2219 (CN). ^1H NMR (δ ppm): 5.67 (s, br., 1H, NH) and 7.18–8.08 (m, 13H, ArH's). Anal. for $C_{22}H_{14}N_2S$ (338.43): Calcd. (%): C, 78.08; H, 4.17; N, 8.28; S, 9.47. Found: C, 78.4; H, 4.4; N, 8.0; S, 9.1.

6-(4-Methylphenyl)-4-(2-naphthyl)-2-thioxohydropyridine-3-carbonitrile (5d)

Crystallized from ethanol as orange crystals (87%), m.p. 250–252°C; IR (ν cm^{-1}): 3317 (NH), 3056 (aromatic-CH), 2937 (sat. CH) and 2218 (CN). ^1H NMR (δ ppm): 2.91 (s. 3H, CH_3), 5.56 (s, br., 1H, NH) and 7.23–7.87 (m, 12H, ArH's). Anal. for $C_{23}H_{16}N_2S$ (352.46): Calcd. (%): C, 78.38; H, 4.58; N, 7.95; S, 9.10. Found: C, 78.5; H, 4.3; N, 7.7; S, 9.3.

Synthesis of 9a–h, 12a–d, and 15a–d: General Method

A solution of each of **5a–d** (1.69 g, 1.76 g, 1.69 g, and 1.76 g, respectively) in ethanol and potassium hydroxide solution (10 ml of 10% KOH) was

heated with each of **7a** (0.99 g), **7b** (1.16 g), **10a** (0.46 g), **10b** (0.67 g), and **13** (0.61 g) under reflux for 2–3 h. The reaction mixture was cooled, poured into 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 the proper solvent to give **9a–h**, **12a–d**, and **15a–d**, respectively.

3-Amino-2-benzoyl-4-(1-naphthyl)-6-phenylthieno-[2,3-b]pyridine (9a)

Crystallized from ethanol as yellow crystals (78%); m.p. 174°C; IR (ν cm^{-1}): 3446, 3316 (NH_2) and 3021 (aromatic-CH); ^1H NMR (δ ppm): 6.14 (s, br., 2H, NH_2) and 7.29–8.11 (m, ArH's). Anal. for $C_{30}H_{20}N_2OS$ (456.57): Calcd. (%) C, 78.92; H, 4.42; N, 6.14; S, 7.02. Found: C, 78.7; H, 4.6; N, 6.5; S, 7.4.

3-Amino-2-benzoyl-6-(4-methylphenyl)-4-(1-naphthyl)-thieno[2,3-b]pyridine (9b)

Crystallized from ethanol as yellow crystals (79%), m.p. 182°C; IR (ν cm^{-1}): 3437, 3306 (NH_2), 3042 (aromatic-CH) and 2931 (sat. CH). ^1H NMR (δ ppm): 2.75 (s, 3H, CH_3), 6.11 (s, br., 2H, NH_2) and 7.26–8.07 (m, 17H, ArH's). Anal. for $C_{31}H_{22}N_2OS$ (470.60): Calcd. (%): C, 79.12; H, 4.71; N, 5.95; S, 6.81. Found: C, 79.4; H, 4.5; N, 5.8; S, 6.6.

3-Amino-2-benzoyl-4-(2-naphthyl)-6-phenylthieno[2,3-b]pyridine (9c)

Crystallized from ethanol as yellow crystals (73%), m.p. 198°C; IR (ν cm^{-1}) 3443, 3322 (NH_2) and 3021 (aromatic-CH). ^1H NMR (δ ppm): 6.41 (s, br., 2H, NH_2) and 7.23–7.95 (m, 18H, ArH's). Anal. for $C_{30}H_{20}N_2OS$ (456.57): Calcd. (%): C, 78.92; H, 4.42; N, 6.14; S, 7.02. Found: C, 79.1; H, 4.2; N, 6.3; S, 7.2.

3-Amino-2-benzoyl-6-(4-methylphenyl)-4-(2-naphthyl)-thieno[2,3-b]pyridine (9d)

Crystallized from ethanol as yellow crystals (78%), m.p. 182°C; IR (ν cm^{-1}): 3431, 3315 (NH_2), 3027 (aromatic-CH) and 2924 (sat. CH). ^1H NMR (δ ppm): 3.03 (s, 3H, CH_3), 5.88 (s, br., 2H, NH_2) and 7.27–7.84 (m, 17H, ArH's). Anal. for $C_{31}H_{22}N_2OS$ (470.60): Calcd. (%): C, 79.12; H, 4.71; N, 5.95; S, 6.81. Found: C, 79.4; H, 4.9; N, 5.7; S, 7.1.

3-Amino-2-(4-chlorobenzoyl)-4-(1-naphthyl)-6-phenyl-thieno[2,3-b]pyridine (9e)

Crystallized from ethanol as yellow crystals (75%), m.p. 194°C; IR (ν cm^{-1}): 3437, 3332 (NH_2), and 3026 (aromatic-CH). ^1H NMR (δ ppm): 6.27 (s, br., 2H, NH_2) and 7.27–7.93 (m, 17H, ArH's). Anal. for $C_{30}H_{19}N_2OSCl$ (491.02): Calcd. (%): C, 73.39; H, 3.90; N, 5.71; S, 6.53; Cl, 7.22. Found: C, 73.5; H, 3.7; N, 5.9; S, 6.2; Cl, 7.5.

3-Amino-2-(4-chlorobenzoyl)-4-(1-naphthyl)-6-(4-methylphenyl)thieno-[2,3-b]-pyridine (9f)

Crystallized from ethanol as yellow crystals (77%), m.p. 186°C; IR (ν cm^{-1}): 3446, 3317 (NH_2), 3019 (aromatic-CH) and 2927 (sat. CH). ^1H NMR (δ ppm): 2.92 (s, 3H, CH_3), 5.78 (s, br., 2H, NH_2) and 7.29–7.91 (m, 16H, ArH's). Anal. for $C_{31}H_{21}N_2OSCl$ (505.04): Calcd. (%): C, 73.73; H, 4.19; N, 5.55; S, 6.35; Cl, 7.02. Found: C, 73.6; H, 4.2; N, 5.7; S, 6.1; Cl, 7.2.

3-Amino-2-(4-chlorobenzoyl)-4-(2-naphthyl)-6-phenyl-thieno[2,3-b]pyridine (9g)

Crystallized from ethanol as yellow crystals (76%), m.p. 184°C; IR (ν cm^{-1}): 3443, 3322 (NH_2) and 3021 (aromatic-CH). ^1H NMR (δ ppm): 6.09 (s, br., H, NH_2) and 7.23–7.85 (m, 17H, ArH's). Anal. for $C_{30}H_{19}N_2OSCl$ (491.02): Calcd. (%): C, 73.39; H, 3.90; N, 5.71; S, 6.53; Cl, 7.22. Found: C, 73.2; H, 3.6; N, 5.5; S, 6.7; Cl, 7.5.

3-Amino-2-(4-chlorobenzoyl-4-(2-naphthyl)-6-(4-methylphenyl)thieno[2,3-b]-pyridine (9h)

Crystallized from ethanol as yellow crystals (79%), m.p. 206–208°C. IR (ν cm^{-1}): 3431, 3315 (NH_2), 3027 (aromatic-CH) and 2924 (sat. CH). ^1H NMR (δ ppm): 2.55 (s, 3H, CH_3), 6.31 (s, br., 2H, NH_2) and 7.23–8.03 (m, 16H, ArH's). Anal. for $C_{31}H_{21}N_2OSCl$ (505.04): Calcd. (%): C, 73.73; H, 4.19; N, 5.55; S, 6.35; Cl, 7.02. Found: C, 73.9; H, 4.0; N, 5.8; S, 6.0; Cl, 7.4.

Ethyl 3-Amino-4-(1-naphthyl)-6-phenylthieno[2,3-b]-pyridine-2-carboxylate (15a)

Crystallized from ethanol as yellow crystals (76%), m.p. 208–210°C; IR (ν cm^{-1}): 3446, 3287 (NH_2), 3057 (aromatic-CH) and 2931 (sat. CH). ^1H NMR (δ ppm): 0.71 (t, 3H, $J = 7.2$ Hz, $CH_2\mathbf{CH}_3$), 3.93 (d, 2H, $J =$ 7.2 Hz, $\mathbf{CH}_2CH_3$) 5.96 (s, br., 2H, NH_2) and 7.24–8.04 (m, 12H, ArH's). Anal. for $C_{26}H_{20}N_2O_2S$ (424.53): Calcd. (%): C, 73.56; H, 4.75; N, 6.60; S, 7.55. Found: C, 73.4; H, 4.9; N, 6.4; S, 7.4.

Ethyl 3-Amino-6-(4-methylphenyl)-4-(1-naphthyl) thieno[2,3-b]pyridine-2-carboxylate (15b)

Crystallized from ethanol as orange crystals (81%), m.p. 236–238°C; IR (ν cm^{-1}): 3446, 3287 (NH_2), 3057 (aromatic-CH) and 2931 (sat. CH). ^1H NMR (δ ppm): 0.58 (t, 3H, $J = 7.1$ Hz, $CH_2\mathbf{CH}_3$), 3.02 (s, 3H, CH_3), 3.92 (q, 2H, $J = 7.1$ Hz, $\mathbf{CH}_2CH_3$) 5.74 (s, br., 2H, NH_2) and 7.22–8.06

(m, 12H, ArH's). Anal. for $C_{27}H_{22}N_2O_2S$ (438.55): Calcd. (%): C, 73.95; H, 5.06; N, 6.39; S, 7.31. Found: C, 73.8; H, 5.2; N, 6.7; S, 7.6.

Ethyl 3-Amino-4-(2-naphthyl)-6-phenylthieno[2,3-b]-pyridine-2-carboxylate (15c)

Crystallized from ethanol as yellow crystals (86%), m.p. 228–230°C; IR (ν cm^{-1}): 3419, 3287 (NH_2), 3052 (aromatic-CH) and 2953 (sat. CH). ^1H NMR (δ ppm): 0.61 (t, 3H, $J = 7.0$ Hz, $CH_2\mathbf{CH}_3$), 3.84 (q, 2H, $J = 7.0$ Hz, $\mathbf{CH}_2CH_3$), 6.17 (s, br., 2H, NH_2) and 7.24–7.83 (m, 12H, ArH's). Anal. for $C_{26}H_{20}N_2O_2S$ (424.53): Calcd. (%): C, 73.56; H, 4.75; N, 6.60; S, 7.55. Found: C, 73.7; H, 4.6; N, 6.9; S, 7.2.

Ethyl 3-Amino-6-(4-methylphenyl)-4-(2-naphthyl)-thieno[2,3-b]pyridine-2-carboxylate (15d)

Crystallized from ethanol as orange crystals (78%), m.p. 224–226°C; IR (ν cm^{-1}): 3417, 3287 (NH_2), 3041 (aromatic-CH) and 2943 (sat. CH). ^1H NMR (δ ppm): 0.48 (t, 3H, $J = 7.1$ Hz, $CH_2\mathbf{CH}_3$), 2.98 (s, 3H, CH_3), 3.71 (q, 2H, $J = 7.1$ Hz, $\mathbf{CH}_2CH_3$) 5.42 (s, br., 2H, NH_2) and 7.27–7.98 (m, 12H, ArH's). Anal. for $C_{27}H_{22}N_2O_2S$ (438.55): Calcd. (%): C, 73.95; H, 5.06; N, 6.39; S, 7.31. Found: C, 73.7; H, 5.2; N, 6.6; S, 7.1.

Synthesis of 6a–d, 11c, g, 12a, b, d, e, f, h, 14a–d: General Method

A mixture of each of **5a–d** (1.69 g, 1.76 g, 1.69 g, and 1.76 g) in methanolic sodium methoxide (prepared from 0.12 g of sodium metal in 10 ml methanol) and each of methyl iodide (1.4 g), **10a** (0.46 g), **10b** (0.67 g), and **13** (0.61 g) was heated under reflux for 2–3 h. The reaction mixture was evaporated to dryness and then cooled and titurated with ethanol was collected by filtration. Crystallization from the proper solvent gave the corresponding products **6a–d**, **11c**, **g**, **12a**, **b**, **d**, **e**, **f**, **h**, and **14a–d**, respectively.

Another Method for Synthesis of 12a, b, d, e, f, h

A mixture of each of **5a** (1.69 g), **5b** (1.76 g), **5d** (1.76 g) and each of **10a** (0.46 g), **10b** (0.67 g) in methanolic sodium methoxide (prepared as above) was stirred for 3–4 h. The product formed was collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent to give **12a**, **b**, **d**, **e**, **f**, **h**, respectively.

2-Methylthio-4-(1-naphthyl)-6-phenylpyridine-3-carbonitrile (6a)

Crystallized from ethanol as white crystals (91%), m.p. 174°C; IR (ν cm^{-1}): 3056 (aromatic-CH), 2963 (sat. CH) and 2212 (CN). ^1H NMR (δ ppm): 2.69 (s, 3H, -S-CH_3) and 7.23–7.97 (m, 13H, ArH's). Anal. for $C_{23}H_{16}N_2S$ (352.45): Calcd. (%): C, 78.38; H, 4.58; N, 7.95; S, 9.10. Found: C, 78.5; H, 4.4; N, 7.6; S, 9.3.

6-(4-Methylphenyl)-2-methylthio-4-(1-naphthyl)pyridine-3-carbonitrile (6b)

Crystallized from ethanol as white crystals (87%), m.p. 154°C. IR (ν cm^{-1}): 3058 (aromatic-CH); 2964 (sat. CH) and 2212 (CN). ^1H NMR (δ ppm): 2.63 (s, 3H, CH_3), 2.85 (s, 3H, —S—CH_3) and 7.31–7.89 (m, 12H, ArH's). Anal. for $C_{24}H_{18}N_2S$ (366.49): Calcd.: C, 78.66; H, 4.95; N, 7.64; S, 8.75. Found: C, 78.9; H, 4.7; N, 7.9; S, 8.9.

2-Methylthio-4-(2-naphthyl)-6-phenylpyridine-3-carbonitrile (6c)

Crystallized from ethanol as white crystals (88%), m.p. 186°C; IR (ν cm^{-1}): 3051 (aromatic-CH) and 2219 (CN). ^1H NMR (δ ppm): 2.70 (s, 3H, —S—CH_3) and 7.24–7.83 (m, 13H, ArH's). Anal. for $C_{23}H_{16}N_2S$ (352.46): Calcd. (%): C, 78.38; H, 4.58; N, 7.95; S, 9.10. Found: C, 78.6; H, 4.4; N, 7.7; S, 8.8.

6-(4-Methylphenyl)-2-methylthio-4-(2-naphthyl)pyridine-3-carbonitrile (6d)

Crystallized from ethanol as white crystals (82%), m.p. 164°C; IR (ν cm^{-1}): 3058 (aromatic-CH), 2964 (sat. CH) and 2212 (CN). ^1H NMR (δ ppm): 2.6 (s, 3H, CH_3), 2.7 (s, 3H, —S—CH_3) and 7.2–7.9 (m, 12H, ArH's). Anal. for $C_{24}H_{18}N_2S$ (366.49): Calcd. (%): C, 78.66; H, 4.95; N, 7.64; S, 8.75. Found: C, 78.5; H, 4.7; N, 7.7; S, 9.0.

2-Acetyl-3-amino-4-(1-naphthyl)-6-phenylthieno[2,3-b]pyridine (12a)

Crystallized from ethanol as yellow crystals (77%), m.p. 210–212°C. IR (ν cm^{-1}): 3447, 3312 (NH_2), 3021 (aromatic-CH) and 2923 (sat. CH). ^1H NMR (δ ppm): 3.44 (s, 3H, $COCH_3$), 6.42 (s, br., 2H, NH_2), and 7.28–7.97 (m, 13H, ArH's). Anal. for $C_{25}H_{18}N_2OS$ (394.50): Calcd. (%): C, 76.12; H, 4.60; N, 7.10; S, 8.13. Found: C, 76.3; H, 4.9; N, 6.8; S, 8.3.

2-Acetyl-3-amino-6-(4-methylphenyl)-4-(1-naphthyl)-thieno[2,3-b]pyridine (12b)

Crystallized from ethanol as yellow crystals (86%), m.p. 176°C; IR (ν cm^{-1}): 3441, 3315 (NH_2), 3019 (aromatic-CH) and 2916 (sat. CH). ^1H NMR (δ ppm): 2.81 (s, 3H, CH_3), 3.22 (s, 3H $COCH_3$), 5.63 (s, br., 2H, NH_2) and 7.31–8.06 (m, 12H, ArH's). Anal. for $C_{26}H_{20}N_2OS$ (408.53): Calcd. (%): C, 76.44; H, 4.93; N, 6.86; S, 7.85. Found: C, 76.1; H, 5.2; N, 6.6; S, 7.5.

2-Acetyl-3-amino-4-(2-naphthyl)-6-phenylthieno[2,3-b]-pyridine (12c)

Crystallized from ethanol as yellow crystals (89%); m.p. 244–246°C; IR (ν cm^{-1}): 3427, 3297 (NH_2), 3024 (aromatic-CH) and 2921 (sat. CH); ^1H NMR (δ ppm): 3.37 (s, 3H, $COCH_3$), 6.10 (s, br., 2H, NH_2), and 7.36–8.17 (m, 13H, ArH's); Anal. for $C_{25}H_{18}N_2OS$ (394.50): Calcd. (%): C, 76.12; H, 4.60; N, 7.10; S, 8.13. Found: C, 76.4; H, 4.4; N, 7.4; S, 8.13.

2-Acetyl-3-amino-6-(4-methylphenyl)-4-(2-naphthyl)-thieno[2,3-b]pyridine (12d)

Crystallized from ethanol as yellow crystals (78%), m.p. 220–222°C; IR (ν cm^{-1}): 3446, 3313 (NH_2), 3052 (aromatic-CH) and 2926 (sat. CH). ^1H NMR (δ ppm): 2.72 (s, 3H, CH_3), 3.46 (s, 3H $COCH_3$), 5.91 (s, br., 2H, NH_2) and 7.33–7.90 (m, 12H, ArH's). Anal. for $C_{26}H_{20}N_2OS$ (408.53): Calcd. (%): C,76.44; H, 4.93; N, 6.86; S, 7.85. Found: C, 76.7; H, 4.6; N, 6.4; S, 7.5.

Synthesis of 11c, g and 14a–d: General Method

A solution of each of **5c** (1.69 g) and **5a–d** (1.69 g, 1.76 g, 1.69 g, and 1.76 g, respectively) in sodium methoxide (prepared as above) and **10a** (0.46 g), **10b** (0.67 g), and **13** (0.61 g) was stirred for 2–3 h. The product formed was collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent to give the products **11c**, **g** and **14a–d**, respectively.

4-(2-Naphthyl)-2-(2-oxopropylthio)-6-phenylpyridine-3-carbonitrile (11c)

Crystallized from ethanol as yellow crystals (77%), m.p. 160°C; IR (ν cm^{-1}): 3021 (aromatic-CH), 2212 (CN) and 1722 (ketonic-CO). ^1H NMR (δ ppm): 3.02 (s, 2H, CH_2), 3.33 (s, 3H, CH_3) and 7.32–8.18 (m, 13H, ArH's). Anal. for $C_{25}H_{18}N_2OS$ (394.50): Calcd. (%): C, 76.12; H, 4.60; N, 7.10; S, 8.13. Found: C, 76.3; H, 4.8; N, 6.9; S, 8.3.

2-[1-Acetyl-2-(oxopropylthio)]-4-(2-naphthyl)-6-phenylpyridine-3-carbonitrile (11g)

Crystallized from ethanol as brown crystals (81%), m.p. 202–204°C; IR (ν cm^{-1}): 3049 (aromatic-CH), 2974 (sat. CH), 2218 (CN) and 1702 (ketonic-CO). ^{1}H NMR (δ ppm): 3.23 (s, 1H, CH), 3.46 (s, 6H, two CH_3) and 7.34–8.11 (m, 13H, ArH's). Anal. for $C_{27}H_{20}N_2O_2S$ (436.54): Calcd. (%): C, 74.29; H, 4.62; N, 6.42; S, 7.35. Found: C, 74.5; H, 4.7; N, 6.1; S, 7.6.

Ethyl 2-[3-Cyano-4-(1-naphthyl)-6-phenylpyrid-2-ylthio]-acetate (14a)

Crystallized from ethanol as white crystals (91%), m.p. 162°C; IR (ν cm^{-1}): 3033 (aromatic-CH), 2929 (sat. CH), 2217 (CN) and 1738 (ester-CO). ^{1}H NMR (δ ppm): 0.91 (t, 3H, $J = 7.1$ Hz, $CH_2\mathbf{CH}_3$), 3.42 (s, 2H, CH_2), 4.15 (q, 2H, $J = 7.1$ Hz, $\mathbf{CH}_2CH_3$) and 7.26–7.99 (m, 13H, ArH's). Anal. for $C_{26}H_{20}N_2O_2S$ (424.53): Calcd. (%): C, 73.56; H, 4.75; N, 6.60; S, 7.55. Found: C, 73.7; H, 4.4; N, 6.7; S, 7.9.

Ethyl 2-[3-Cyano-6-(4-methylphenyl)-4-(1-naphthyl)pyrid-2-ylthio]acetate (14b)

Crystallized from ethanol as orange crystals (79%), m.p. 188°C. IR (ν cm^{-1}): 3037 (aromatic-CH), 2931 (sat. CH), 2215 (CN) and 1728 (ester-CO). ^{1}H NMR (δ ppm): 1.03 (t, 3H, $J = 7.2$ Hz, $CH_2\mathbf{CH}_3$), 2.84 (s, 3H, CH_3), 3.22 (s, 2H, CH_2), 4.02 (q, 2H, $J = 7.2$ Hz, $\mathbf{CH}_2CH_3$) and 7.23–7.95 (m, 12H, ArH's). Anal. for $C_{27}H_{22}N_2O_2S$ (438.55): Calcd. (%): C, 73.95; H, 5.06; N, 6.39; S, 7.31. Found: C, 74.1; H, 4.8; N, 6.6; S, 7.1.

Ethyl 2-[3-Cyano-4-(2-naphthyl)-6-phenylpyrid-2-ylthio]-acetate (14c)

Crystallized from ethanol as white crystals (90%), m.p. 176°C; IR (ν cm^{-1}): 3041 (aromatic-CH), 2935 (sat. CH), 2220 (CN) and 1729 (ester-CO). ^{1}H NMR (δ ppm): 0.87 (t, 3H, $J = 6.9$, Hz, $CH_2\mathbf{CH}_3$), 3.11 (s, 2H, CH_2), 4.20 (q, 2H, $J = 6.9$ Hz, $\mathbf{CH}_2CH_3$) and 7.23–7.83 (m, 13H, ArH's). Anal. for $C_{26}H_{20}N_2O_2S$ (424.53): Calcd. (%): C, 73.56; H, 4.75; N, 6.60; S, 7.55. Found: C, 73.4; H, 4.6; N, 6.5; S, 7.8.

Ethyl 2-[3-Cyano-6-(4-methylphenyl)-4-(2-naphthyl)pyrid-2-ylthio]acetate (14d)

Crystallized from ethanol as white crystals (87%), m.p. 196°C; IR (ν cm^{-1}): 3037 (aromatic-CH), 2946 (sat. CH), 2223 (CN) and 1733 (ester-CO). ^{1}H NMR (δ ppm): 0.91 (t, 3H, $J = 7.0$ Hz, $CH_2\mathbf{CH}_3$), 2.79 (s, 3H, CH_3), 3.37 (s, 2H, CH_2), 4.02 (q, 2H, $J = 7.0$ Hz, $\mathbf{CH}_2CH_3$) and

7.23–8.09 (m, 12H, ArH's). Anal. for $C_{27}H_{22}N_2O_2S$ (438.55): Calcd. (%): C, 73.95; H, 5.06; N, 6.39; S, 7.31. Found: C, 74.7; H, 5.1; N, 6.4; S, 7.1.

Synthesis of 16a–d: General Method

A mixture of each of **14a–d** (0.01 mole of each) and hydrazine hydrate (20–25 ml) was heated under reflux for 6–8 h. The product formed after cooling was filtrated off, washed with cold ethanol and crystallized from the proper solvent to give the products **16a–d**, respectively.

N-Amino-[3-amino-4-(1-naphthyl)-6-phenylthieno[2,3-b]-pyridin-2-yl]carboxamide (16a)

Crystallized from ethanol as yellow crystals (70%), m.p. 248–250°C. IR (ν cm^{-1}): 3451, 3325, 3217, 3161 (two NH_2, NH), 3029 (aromatic-CH) and 1687 (amidic-CO). ^{1}H NMR (δ ppm): 3.82 (s, br., 2H, thiophene-NH_2), 5.84 (s, br., 2H, CONH**N**$\mathbf{H}_2$), 6.27 (s, br., 1H, CO**NH**NH_2) and 7.23–7.97 (m, 13H, ArH's). Anal. for $C_{24}H_{18}N_4OS$ (410.50): Calcd. (%): C, 70.22; H, 4.42; N, 13.65; S, 7.81. Found: C, 70.4; H, 4.2; N, 13.8; S, 7.7.

N-Amino-[3-amino-6-(4-methylphenyl)-4-(1-naphthyl)-thieno[2,3-b]pyri-din-2-yl]carboxamide (16b)

Crystallized from ethanol as yellow crystals (79%), m.p. 240–242°C; IR (ν cm^{-1}): 3447, 3307, 3231, 3172 (two NH_2, NH), 3039 (aromatic-CH), 2943 (sat. CH) and 1677 (amidic-CO). ^{1}H NMR (δ ppm): 2.76 (s, 3H, CH_3), 3.85 (s, br., 2H, thiophene-NH_2), 5.84 (s, br., 2H, CONH**N**$\mathbf{H}_2$), 6.21 (s, br., 1H, CO**NH**NH_2) and 7.21–7.99 (m, 12H, ArH's). Anal. for $C_{25}H_{20}N_4OS$ (424.53): Calcd. (%): C, 70.73; H, 4.75; N, 13.20; S, 7.55. Found: C, 70.9; H, 4.9; N, 13.5; S, 7.3.

N-Amino-[3-amino-4-(2-naphthyl)-6-phenylthieno[2,3-b]-pyridin-2-yl]carboxamide (16c)

Crystallized from ethanol as yellow crystals (69%), m.p. 244–246°C; IR (ν cm^{-1}): 3445, 3323, 3251, 3168 (two NH_2, NH), 3037 (aromatic-CH) and 1683 (amidic-CO). ^{1}H NMR (δ ppm): 3.62 (s, br., 2H, thiophene-NH_2), 5.75 (s, br., 2H, CONH**N**$\mathbf{H}_2$), 6.18 (s, br., 1H, CO**NH**NH_2) and 7.33–8.12 (m, 13H, ArH's). Anal. for $C_{24}H_{18}N_4OS$ (410.50): Calcd. (%): C, 70.22; H, 4.42; N, 13.65; S, 7.81. Found: C, 70.0; H, 4.7; N, 13.4; S, 8.0.

N-Amino-[3-amino-6-(4-methylphenyl)-4-(2-naphthyl)-thieno[2,3-b]pyridin-2-yl]carboxamide (16d)

Crystallized from ethanol as yellow crystals (66%), m.p. 236–823°C; IR (ν cm^{-1}): 3443, 3315, 3247, 3168 (two NH_2, NH), 3024 (aromatic-CH), 2950 (sat. CH) and 1686 (amidic-CO). ^1H NMR (δ ppm): 2.93 (s, 3H, CH_3), 3.71 (s, br., 2H, thiophene-NH_2), 5.43 (s, br., 2H, CONH**NH**$_2$), 7.27–8.03 (m, 12H, ArH's), and 8.77 (s, br., 1H, CO**NH**NH_2); Anal. for $C_{25}H_{20}N_4OS$ (424.53): Calcd. (%): C, 70.73; H, 4.75; N, 13.20; S, 7.55. Found: C, 70.5; H, 4.4; N, 13.5; S, 7.6.

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