Synthesis of Novel Bis[(5-cyanopyridin-6-yl)sulfanyl]butanes, Bis(2-S-alkylpyridines), and Bis(3-aminothieno[2,3-b]pyridines) Incorporating 2,6-Dibromophenoxy Moiety

Sherif M. H. Sanad,a* Mahmoud I. M. Hefny,a Ahmed A. M. Ahmed,a,b and Mohamed A. A. Elneairya

aChemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt
bPreparatory Year Deanship, Jouf University, Sakaka, Kingdom of Saudi Arabia

*E-mail: sherif_hamed1980@yahoo.com

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INTRODUCTION

Dihydropyridines show a wide spectrum of biological activities, such as antiarrhythmic, antihypertensive [1–4], and anticancer agents [5–7]. Moreover, pyridine-2(1H)-thiones show bioactivities such as antifungal and antibacterial [8].

On the other hand, 2-S-alkylpyridines show significant bioactivities as cardiovascular [9,10] and antioxidant [11]. Also, the thieno[2,3-b] pyridine derivatives show broad pharmacological activities such as antiviral [12], anti-inflammatory [13], antidiabetic [14,15], and anticancer [16–19].

This work plan was pointed to design efficient procedures for the synthesis of novel bis(5-cyanopyridin-6-yl)sulfanyl butanes 5a,b, bis(2-S-alkylpyridines) 8a,b, and bis(3-aminothieno[2,3-b]pyridines) 13a–c incorporating 2,6-dibromophenoxy moiety of expected bioactivity using the pyridine-2(1H)-thione derivatives 2a,b and bis(pyridine-2(1H)-thione) derivative 4 as synthetic precursors (Fig. 1).

RESULTS AND DISCUSSION

The first synthetic route which developed to prepare the bis(pyridine-2(1H)-thione) derivative 3, incorporating 2,6-dibromophenoxy moiety, was failed. The failed route came from reacting a ternary mixture of 3,5-dibromobenzaldehyde (1a), 2-cyanoethanethioamide, and ethyl benzoylacetate in pyridine under reflux to prepare the corresponding ethyl 5-cyano-6-thioxo-1,6-dihydropyridine-3-carboxylate derivative 2a whose 1H-NMR spectrum revealed the signals of CH3CH2O (t, 3H, δ = 0.86 ppm), CH3CH2 (q, 2H, δ = 3.98 ppm), aromatic protons in addition to NH (m, 8H, δ = 7.44–7.66 ppm), and OH (s, br, 1H, δ = 10.65 ppm). Compound 2a was reacted with 1,4-dibromobutane in aqueous ethanolic potassium hydroxide solution under reflux to afford such a reaction product whose 1H-NMR spectrum revealed the absence of NH group and the presence of two new signals at δ = 2.01 ppm (t, 4H) and δ = 2.87 ppm (t, 4H) corresponding to the introduction of (CH2)4 junction and the presence of two OH groups (s, 2H, δ = 10.52 ppm). Compound 2a was reacted with 1,4-dibromobutane in aqueous ethanolic potassium hydroxide solution under reflux to afford such a reaction product whose 1H-NMR spectrum revealed the absence of NH group and the presence of two new signals at δ = 2.01 ppm (t, 4H) and δ = 2.87 ppm (t, 4H) corresponding to the introduction of (CH2)4 junction and the presence of two OH groups (s, 2H, δ = 10.52 ppm). Therefore, the product was formulated as the corresponding 1,4-bis[(5-cyano-3-ethoxycarbonylpyridin-6-yl)sulfanyl]butane derivative 5a and not the starting material bis(pyridine-2(1H)-thione) derivative 4 (Scheme 1 and Experimental section). The formation of 5a may be attributed to the higher nucleophilicity of S-atom at 6-position than O-atom at 4-(3,5-dibromo-4-hydroxyphenyl) moiety.
On the other hand, α,β-unsaturated carbonyl derivative 3, prepared via reacting 3,5-dibromo-4-ethoxybenzaldehyde (1b) with acetophenone in ethanolic potassium hydroxide solution with stirring, reacted with 2-cyanoethanethioamide in absolute ethanol containing a catalytic amount of piperidine under reflux to afford the corresponding pyridine-2(1H)-thione derivative 2b whose 1H-NMR spectrum revealed the signals of CH$_3$CH$_2$O (t, 3H, δ = 1.46 ppm), CH$_3$CH$_2$ (q, 2H, δ = 4.15 ppm), and aromatic protons in addition to NH (m, 9H, δ = 7.42–8.14 ppm). Then, 2b reacted with 1,4-dibromobutane to afford the corresponding 1,4-bis[(3-cyano-4-ethoxyphenylpyridin-2-yl)sulfanyl]butane derivative 5b whose 1H-NMR spectrum revealed the absence of NH
group and the presence of two \( \text{SCH}_2\text{CH}_2 \) (t, 4H, \( \delta = 1.95 \text{ ppm} \)) and two \( \text{SCH}_2\text{CH}_3 \) → (t, 4H, \( \delta = 2.87 \text{ ppm} \)) (Scheme 1 and Experimental section).

The failure of the first synthetic route to prepare bis(pyridine-2(1H)-thione) derivative 4 stimulate our interest to design another route via reacting \( \text{Ia} \) with 1,4-dibromobutane in dry acetone containing anhydrous potassium carbonate and potassium hydroxide under reflux to afford the novel 1,4-bis(4-formylyphenoxo) butane derivative 6 \( ^1\text{H}-\text{NMR} \) spectrum revealed the absence of OH signal and the presence of signals of O\( \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O} \) (m, 4H, \( \delta = 2.10 \text{ ppm} \)), O\( \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O} \) (t, 4H, \( \delta = 4.16 \text{ ppm} \)), and two \( \text{CH}_2\text{O} \) (s, 2H, \( \delta = 9.90 \text{ ppm} \)) (Scheme 2 and Experimental section). Then the bis(aldehyde) 6 reacted with 2-cyanoethanethioamide and ethyl benzoylacetate in pyridine under reflux to give the corresponding bis(pyridine-2(1H)-thione) derivative 4 whose \( \text{IR} \) spectrum (cm\(^{-1}\)) showed the absorption bands of NH and the presence of two \( \text{SCH}_3 \) (s, 6H, \( \delta = 2.76 \text{ ppm} \)), and two \( \text{SCH}_2 \) (s, 3H, \( \delta = 2.71 \text{ ppm} \)) and aromatic protons in addition to two NH groups (m, 16H, \( \delta = 7.51 \text{ ppm} \)) (Scheme 2 and Experimental section). Moreover, pyridine-2(1H)-thione derivative 2b reacted with each of \( \text{7a,b} \) to afford the corresponding 2-methylsulfanylpyridine derivative 9c and 2-benzylsulfanylpyridine derivative 9d respectively in excellent yields (Scheme 3 and Experimental section).

Unfortunately, our trails to prepare bis(thieno[2,3-b] pyridine) derivatives 13a–c by the direct reaction of bis(pyridine-2(1H)-thione) derivative 4 with \( \text{10a–c} \) under various reaction conditions were failed. Therefore, another synthetic route was developed to achieve the synthesis of bis(thieno[2,3-b]pyridine) derivatives 13a–c by performing the reaction of halo-containing compounds \( \text{10a–c} \) with pyridine-2(1H)-thione derivative 2a to afford the corresponding thieno[2,3-b] pyridine derivatives 12a–e incorporating hydroxy group which then used as synthetic precursors to synthesize bis(thieno[2,3-b]pyridine) 13a–c (Scheme 4).

Thus, compound 2a reacted with ethyl chloroacetate (10a) in ethanolic sodium acetate solution under reflux to give the corresponding ethyl 5-cyano-6-(ethoxycarbonylmethylsulfanyl) nicotinate derivative 11a whose \( \text{IR} \) (\( \nu \text{ cm}^{-1} \)) showed the absorption bands corresponding to OH group at 3380, CN group at 2224 in addition to CO groups at 1726 and 1704 and whose \( ^1\text{H}-\text{NMR} \) spectrum revealed the signals due to two \( \text{OCH}_2\text{CH}_2 \) groups (t, 6H, \( \delta = 0.85 \text{ ppm} \)), two \( \text{OCH}_2\text{CH}_3 \) groups (q, 4H, \( \delta = 3.93 \text{ and } 4.04 \text{ ppm} \)), and \( \text{CH}_2\text{O} \) (s, 2H, \( \delta = 2.71 \text{ ppm} \)) (Experimental section). Compound 11a

Scheme 2. Synthesis of bis(pyridine-6(1H)-thione) derivative 4.

![Scheme 2](image-url)
underwent a Thrope-Ziegler reaction via its boiling in methanolic sodium methoxide solution to give the corresponding diethyl 3-aminothieno[2,3-b]pyridine-2,5-dicarboxylate derivative 12a whose IR (υ cm⁻¹) showed the absorption bands corresponding to OH group at 3477, NH₂ group at 3347 and 3189 in addition to CO group at 1723 and 1680 and whose ¹H-NMR revealed the absence of SCH₂ signal and the presence of signals due to two OCH₂CH₃ groups (t, 6H, δ = 0.71 and 0.83 ppm) and two OCH₁CH₂CH₂O (m, 4H, δ = 2.14 ppm) (Scheme 4 and Experimental section). The structure of 12a was more confirmed by its independent synthesis via another route by reacting 2a with 10a in boiling methanolic sodium methoxide solution under reflux to give such a reaction product which was found completely identical in all aspects with 12a prepared via the first route (Scheme 4 and Experimental section). In a similar manner, thieno[2,3-b] pyridine derivatives 12b–e were prepared either by the direct reaction of 2a,b with each of chloroacetone (10b) and 2-bromo-1-phenylethanone (10c) respectively in boiling methanolic sodium methoxide solution under reflux or by the two steps synthesis via reacting 2a,b with each of 10b and 10c respectively in ethanolic sodium acetate solution under reflux to afford the corresponding 2-S-alkylpyridine derivative 11c–e respectively followed by their Thrope-Ziegler cyclization, via boiling in methanolic sodium methoxide solution, to afford identical reaction products. Ethyl 2-acetyl-3-aminothieno[2,3-b]pyridine-5-carboxylate derivative 12b was prepared directly by the reaction of 2a with chloroacetone (10b) in ethanolic sodium acetate solution under reflux without the isolation of 2-(2-oxopropylsulfanyl) nicotinonitrile [11b] (Scheme 4 and Experimental section).

The isolation of ethyl 3-aminothieno[2,3-b]pyridine-5-carboxylate derivatives 12a–c with 3,5-dibromo-4-hydroxyphenyl moiety at 4-position facilitates the reaction of their potassium salts with 1,4-dibromobutane in dry acetone to afford the corresponding bis(thieno[2,3-b] pyridine) derivatives 13a–c (Scheme 4). Thus, diethyl 3-aminothieno[2,3-b]pyridine-2,5-dicarboxylate derivative 12a reacted with 1,4-dibromobutane in dry acetone containing a catalytic amount of anhydrous potassium carbonate and potassium hydroxide under reflux to afford the corresponding 1,4-bis(4-[3-amino-2,5-diethoxy carbonylthieno[2,3-b]pyridin-4-yl]phenoxy) butane derivative 13a whose ¹H-NMR revealed the absence of the signal corresponding to OH group and the presence of the signals due to OCH₂CH₂CH₂O (m, 4H, δ = 2.14 ppm) and OCH₂CH₂CH₂O (m, 4H, δ = 4.19 ppm) (Scheme 4 and Experimental section). In a similar manner, the potassium salts of thieno[2,3-b] pyridine derivatives 12b,c were reacted with 1,4-dibromobutane to afford the corresponding bis(thieno[2,3-b]pyridine) derivatives 13b,c, respectively (Scheme 4 and Experimental section).
EXPERIMENTAL

Introduction. All organic solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck, Aldrich, or Acros and used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile Attenuated Total Reflectance sampling accessory on the Nicolet iS10 FT-IR spectrometer. 1H-NMR spectra were recorded on Varian Mercury at 300 MHz spectrophotometer using TMS as an internal standard and DMSO-d$_6$ as solvent and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series.

General procedures and spectral data.

General procedure for compounds 2a and 4. A ternary mixture of each of 1a (10 mmol) or 6 (5 mmol), 2-cyanoethanethioamide (10 mmol) and ethyl benzoylacetae (10 mmol) in pyridine (20 mL) was heated under reflux for 5 h. The reaction mixture was heated to evaporate half its volume, cooled, poured onto ice-cold water, and then neutralized (pH = 7) with drops of glacial acetic acid. The products so formed were collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield 2a and 4, respectively.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-2-phenyl-6-thioxo-1,6-dihydro-pyridine-3-carboxylate (2a). Yellow crystals recrystallized from dioxane/ethanol mixture (62%); m.p. 216–218°C; IR (υ cm$^{-1}$): 3427 (OH), 3218 (NH), 2230 (CN), 1697 (CO), and 1572 (CS); 1H-NMR (DMSO-d$_6$): δ 0.86 (t, 3H, CH$_3$CH$_2$), 3.98 (q, 2H, CH$_3$CH$_2$), 7.44–7.66 (m, 8H, 7 ArH’s and NH) and 10.65 (s, br, 1H, OH); Anal. Calcd for C$_{21}$H$_{14}$Br$_2$N$_2$O$_3$S (534.22): C, 47.21; H, 2.64; N, 5.24; S, 6.00; found: C, 47.35; H, 2.58; N, 5.05; S, 6.11%.

1,4-Bis(2,6-dibromo-4-[5-cyano-3-ethoxycarbonyl-2-phenyl-6-thioxo-1,6-dihydropyridin-4-ylphenoxo) butane (4). Yellow crystals recrystallized from dioxane/ethanol mixture (41%); m.p. 158–160°C; IR (υ cm$^{-1}$): 3417 (NH), 2213 (CN), 1708 (CO), and 1557 (CS); 1H-NMR (DMSO-d$_6$): δ 0.80 (t, 6H, 2 CH$_3$CH$_2$O), 2.09 (m, 4H, Scheme 4. Synthesis of bis(thieno[2,3-b]pyridine) derivatives 13a–c.

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OCH2CH2O), 4.14 (m, 8H, OCH2CH2CH2CHO and 2 CH2CH2), and 7.51–7.94 (m, 16H, 14 ArH’s and 2 NH); Anal. Calcd for C46H34Br4N4O6S2 (1122.53): C, 49.92; H, 3.05; N, 4.99; S, 5.71; found: C, 49.40; H, 3.23; N, 4.74; S, 5.99%.

Procedure for 4-(3,5-dibromo-4-ethoxyphenyl)-6-phenyl-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile (2b) . A mixture of 3 (10 mmol) and 2-cyanoethanethioamide (10 mmol) in 30 mL of ethanol containing three drops of piperidine was heated under reflux for 5 h. The solid product so formed was collected by filtration, washed with cold ethanol, and then recrystallized from ethanol/dioxane mixture as yellow crystals (70%); m.p. 226–228°C; IR (ν cm–1): 3159 (NH), 2219 (CN), and 1560 (CS); 1H-NMR (DMSO-d6): δ 1.46 (t, 3H, CH3CH2), 4.15 (q, 2H, CH2S), and 7.42–8.14 (m, 9H, 8 ArH’s and NH); Anal. Calcd for C20H14Br2N2OS (490.21): C, 49.79; H, 3.44; found: C, 49.62; H, 3.55%.

Procedure for 3-(3,5-dibromo-4-ethoxyphenyl)-1-phenylprop-2-en-1-one (3). A solution of potassium hydroxide (prepared from 10 mmol of KOH in 2 mL of water) was added to a solution of acetophenone (10 mmol) in 10 mL acetone, and the mixture was cooled to room temperature and then poured onto a beaker containing 100-g ice. The products were collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield 6a, b, and 13a–c, respectively.

1,4-Bis(3-cyano-4-(3,5-dibromo-4-ethoxyphenyl)-6-phenylpyridin-2-yl)sulfanyl-butane (5b). Colorless crystals recrystallized from ethanol (61%); m.p. 108–110°C; IR (ν cm–1): 2222 (CN); 1H-NMR (DMsO-d6): δ 1.08 (t, 6H, 2 CH3CH2O), 1.95 (t, 4H, SCH2CH2CH2CH2S), 2.87 (t, 4H, SCH2CH2CH2CH2S), 3.95 (m, 4H, 2 CH3CH2), and 7.01–8.20 (m, 16H, ArH’s); Anal. Calcd for C46H34Br4N4O6S2 (1034.51): C, 51.08; H, 3.31; N, 5.42; S, 6.20; found: C, 51.23; H, 3.47; N, 5.35; S, 6.932%.

General procedure for compounds 6a, b, and 13a–c. A mixture of 1,4-dibromobutane (5 mmol) and each of the appropriate aromatic hydroxy compounds 1a, 9a,b, and 12a–c (10 mmol), potassium hydroxide (2 mmol), and anhydrous potassium carbonate (20 mmol) in dry acetone (50 mL) was heated under reflux for 12 h. The reaction mixture was cooled to room temperature and filtered off, and the filtered cake was washed with 10 mL of dry acetone, and the filtrate was added to the above mother liquor, and then the resulting solution was concentrated to its half volume, cooled, and poured into a beaker containing 100-g ice. The products were collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent to yield 6a, 8a, b, and 13a–c, respectively.

1,4-Bis(2,6-dibromo-4-formylphenoxy) butane (6). Colorless crystals recrystallized from dioxane/ethanol mixture (85%); m.p. 188–190°C; IR (ν cm–1): 2848, 2750 (ald. H stretch), and 1689 (CO); 1H-NMR (DMSO-d6): δ 2.10 (m, 4H, OCH2CH2CH2CH2O), 4.16 (t, 4H, OCH2CH2CH2CH2O), 8.18 (s, 4H, ArH’s), and 9.90 (s, 2H, CHO); Anal. Calcd for C18H14Br4O4 (613.92): C, 35.22; H, 2.30; found: C, 35.10; H, 2.39%.

1,4-Bis(2,6-dibromo-4-(6-methylsulfanyl-5-cyano-3-ethoxycarbonyl-2-phenyl-pyridin-4-ylphenoxy) butane (8a). Colorless crystals recrystallized from ethanol (44% from 4 or 76% from 9a); m.p. 116–118°C; IR (ν cm–1): 2214 (CN) and 1705 (CO); 1H-NMR (DMSO-d6): δ 0.82 (t, 6H, 2 CH3CH2O), 2.12 (m, 4H, OCH2CH2CH2CH2O), 2.71 (s, 6H, 2 SCh3), 3.91 (m, 4H, 2 CH3CH2O), 4.12 (m, 4H, OCH2CH2CH2CH2O), and 7.54–8.24 (m, 14H, ArH’s); Anal. Calcd for C18H14Br4N4S4O4 (615.98): C, 50.11; H, 3.33; N, 4.87; S, 5.57; found: C, 50.19; H, 3.49; N, 4.69; S, 5.61%.

1,4-Bis(2,6-dibromo-4-(6-benzylsulfanyl-5-cyano-3-ethoxycarbonyl-2-phenyl-pyridin-4-ylphenoxy) butane (8b). Colorless crystals recrystallized from ethanol (40% from 4 or 72% from 9b); m.p. 138–140°C; IR (ν cm–1): 2214 (CN) and 1705 (CO); 1H-NMR (DMSO-d6): δ 0.82 (t, 6H, 2 CH3CH2O), 2.12 (m, 4H, OCH2CH2CH2CH2O), 3.91 (m, 4H, 2 CH3CH2O), 4.12 (m, 8H, 2 SCh3 and OCH2CH2CH2CH2O), and 7.48–7.85 (m, 24H, ArH’s); Anal. Calcd for C46H34Br4N4O6S2 (1302.78): C, 55.32; H, 3.56; N, 4.30; S, 4.92; found: C, 55.48; H, 3.41; N, 4.60; S, 4.61%.
1,4-Bis(2,6-dibromo-4-[3-amino-2,5-diethoxycarbonyl-6-phenylthiolo[2,3-b]-pyridin-4-yl]phenoxy) butane (13a). Yellow crystals recrystallized from ethanol (58%); m.p. 110–112°C; IR (υ cm⁻¹): 3347, 3189 (NH₃), 1723, and 1680 (CO); ¹H-NMR (DMSO-d₆); δ 0.81 (m, 12H, 4 OCH₂CH₂), 2.14 (m, 4H, OCH₂CH₂CH₂CH₂O), 3.88 (m, 8H, 4 OCH₂CH₂), 4.19 (m, 4H, OCH₂CH₂CH₂CH₂O), 5.80 (s, br, 4H, 2 NH₂), and 7.50–7.82 (m, 14H, ArH’s); Analog. Calculated for C₅₂H₄₂Br₄N₆O₈S₂ (1254.36): C, 50.35; H, 3.25; N, 4.72; S, 5.43%.

1,4-Bis(2,6-dibromo-4-[2-acetyl-3-amino-5-ethoxy-carbonyl-6-phenylthiolo[2,3-b]-pyridin-4-yl]phenoxy) butane (13b). Yellow crystals recrystallized from dioxane/ethanol mixture (63%); m.p. 240–242°C; IR (υ cm⁻¹): 3365, 3272 (NH₃), 1724 (CO); ¹H-NMR (DMSO-d₆); δ 0.83 (t, J = 7.2 Hz, 6H, 2 CH₃CH₂), 2.15 (m, 4H, OCH₂CH₂CH₂CH₂O), 2.40 (s, 6H, 2 COCH₃), 3.89 (q, J = 7.2 Hz, 4H, 2 CH₂O), 4.19 (m, 4H, OCH₂CH₂CH₂CH₂O), 6.51 (s, br, 4H, 2 NH₂), and 7.49–7.80 (m, 14H, ArH’s); Analog. Calculated for C₅₆H₄₆Br₄N₄O₈S₂ (1294.71): C, 50.09; H, 3.58; N, 4.33; S, 4.95; found: C, 50.20; H, 3.38; N, 4.40; S, 4.80%.

1,4-Bis(2,6-dibromo-4-[3-amino-5-ethoxycarbonyl-6-phenylthiolo[2,3-b]-pyridin-4-yl]phenoxy) butane (13c). Yellow crystals recrystallized from dioxane/ethanol mixture (59%); m.p. 108–110°C; IR (υ cm⁻¹): 3355, 3274 (NH₃), and 1720 (CO); ¹H-NMR (DMSO-d₆); δ 0.83 (t, J = 7.2 Hz, 6H, 2 CH₃CH₂), 2.15 (m, 4H, OCH₂CH₂CH₂CH₂O), 3.89 (q, J = 7.2 Hz, 4H, 2 CH₂O), 4.19 (m, 4H, OCH₂CH₂CH₂CH₂O), 6.92 (s, br, 4H, 2 NH₂), and 7.52–7.78 (m, 24H, ArH’s); Analog. Calculated for C₅₆H₄₆Br₄N₄O₈S₂ (1359.90): C, 54.80; H, 3.41; N, 4.12; S, 4.72; found: C, 54.96; H, 3.52; N, 3.94; S, 4.60%.

General procedure for compounds 8a, 9a, and 9c. A mixture of each of 4 or 2a,b (10 mmol) and iodomethane (7a, 20 mmol for 4 or 10 mmol for 2a,b) in methanolic sodium methoxide solution (20 mmol of sodium metal for 2a and 4 or 10 mmol of sodium metal for 2b in 20 mL of methanol) was heated under reflux for 2 h. The products so formed were collected by filtration, washed with cold ethanol, and then recrystallized from the proper solvent to yield 8a, 9a, and 9c, respectively.

Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-methylsulfanyl-2-phenyl-nicotinate (9a). Colorless crystals recrystallized from ethanol (88%); m.p. 242–244°C; IR (υ cm⁻¹): 3427 (OH), 2222 (CN), and 1693 (CO); ¹H-NMR (DMSO-d₆); δ 0.85 (t, J = 7.2 Hz, 3H, CH₃CH₂O), 2.76 (s, 3H, S(CH₃)), 3.95 (q, J = 7.2 Hz, 2H, CH₂CH₃O), 7.53–7.70 (m, 7H, ArH’s), and 10.53 (s, br, 1H, OH); Anal. Calculated for C₂₂H₂₀Br₃N₂O₅S (548.25): C, 48.20; H, 2.94; N, 5.11; S, 5.85; found: C, 48.35; H, 2.78; N, 5.00; S, 5.70%.

4-(3,5-Dibromo-4-ethoxyphenyl)-2-methylsulfanyl-6-phenyl nicotinonitride (9c). Colorless crystals recrystallized from dioxane/ethanol (90%); m.p. 164–166°C; IR (υ cm⁻¹): 2219 (CN); ¹H-NMR (DMSO-d₆); δ 1.45 (t, J = 6.9 Hz, 3H, CH₃CH₂), 2.76 (s, 3H, S(CH₃)), 4.11 (q, J = 6.9 Hz, 2H, CH₂CH₃O), and 7.55–8.32 (m, 8H, ArH’s); Anal. Calculated for C₂₁H₁₆Br₃N₂O₅S (504.24): C, 50.02; H, 3.20; N, 5.56; S, 6.36; found: C, 50.24; H, 3.04; N, 5.70; S, 6.45%.
Ethyl 5-cyano-4-(3,5-dibromo-4-hydroxyphenyl)-6-(2-oxo-2-phe nylthiylsulfanyl)-2-phenylnicotinate (11e). Pale yellow crystals recrystallized from ethanol (81%); m.p. 188–190°C; IR (ν cm⁻¹): 3462 (OH), 2220 (CN), and 1718 (CO); ¹H-NMR (DMSO-d₆): δ 0.82 (t, J = 6.3 Hz, 3H, OCH₂CH₃), 3.90 (q, J = 6.3 Hz, 2H, CH₂CH₃), 5.02 (s, 2H, S(CH₂)), 7.19–8.09 (m, 12H, ArH’s), and 10.53 (s, br, 1H, OH); Anal. Calcd for C₂₃H₁₈Br₂N₂O₂S (546.27): C, 50.57; H, 3.32; N, 5.13; S, 5.87; found: C, 53.19; H, 3.09; N, 4.29; S, 4.92; found: C, 53.20; H, 3.00; N, 4.40; S, 5.06%.

4-(3,5-Dibromo-4-ethoxyphenyl)-2-(2-oxo-2-phe nylthiylsulfanyl)-6-phenylnicotinonitrile (11d). Yellow crystals recrystallized from ethanol (81%); m.p. 170–172°C; IR (ν cm⁻¹): 2207 (CN) and 1711 (CO); ¹H-NMR (DMSO-d₆): δ 1.44 (t, J = 6.9 Hz, 3H, CH₂CH₃O), 2.30 (s, 3H, COCH₃), 4.10 (q, J = 6.9 Hz, 2H, CH₂CH₂O), 4.37 (s, 2H, S(CH₂)), and 7.53–8.21 (m, 8H, ArH’s); Anal. Calcd for C₂₈H₂₀Br₂N₂O₄S (608.34): C, 55.28; H, 3.31; N, 4.60; S, 5.09; found: C, 55.01; H, 3.20; N, 4.95; S, 6.05%.

4-(3,5-Dibromo-4-ethoxyphenyl)-6-phenylnicotinonitrile (11e). Colorless crystals recrystallized from ethanol/dioxane (90%); m.p. 196–198°C; IR (ν cm⁻¹): 2212 (CN) and 1680 (CO); ¹H-NMR (DMSO-d₆): δ 1.45 (t, J = 7.2 Hz, 3H, CH₂CH₃O), 4.12 (q, J = 7.2 Hz, 2H, CH₂CH₂O), 5.06 (s, 2H, S(CH₂)), 7.17–8.15 (m, 13H, ArH’s); Anal. Calcd for C₂₉H₂₁Br₂N₂O₆S (652.35): C, 53.39; H, 3.22; N, 4.13; S, 5.07; found: C, 53.20; H, 3.00; N, 4.40; S, 5.06%.

General procedure “A” for compounds 12a-c-e. A mixture of each of 11a,c-e (10 mmol) in methanolic sodium methoxide solution (prepared from 20 mmol of sodium metal in 20 mL of methanol) was heated under reflux for 2 h. The products so formed (by cooling, pouring onto 100 g of crushed ice, and adding dil. HCl for 12a,c or by cooling only for 12d,e) were collected by filtration, washed with cold ethanol, dried, and then recrystallized from the proper solvent to give the 12a-c-e, respectively.

General procedure “B” for compounds 12a-c-e. A mixture of 2a,b (10 mmol) and each of 10a-c (10 mmol) in methanolic sodium methoxide solution (prepared from 30 mmol of sodium metal in 20 mL of methanol) was heated under reflux for 4 h. The products so formed (by cooling, pouring onto 100 g of crushed ice, and adding dil. HCl for 12a,c or by cooling only for 12d,e) were collected by filtration, washed with cold ethanol, dried, and then recrystallized from the proper solvent to give the 12a-e, respectively.

Diethyl 3-amino-4-(3,5-dibromo-4-hydroxyphenyl)-6- phenylthiopheno[2,3-b]pyridine-2,5-dicarboxylate (12a). Yellow crystals recrystallized from ethanol/dioxane mixture (77% from 2a or 84% from 11a); m.p. 228–230°C; IR (ν cm⁻¹): 3477 (OH), 3347, 3189 (NH₂), 1723, and 1680 (CO); ¹H-NMR (DMSO-d₆): δ 0.71 (t, J = 6.9 Hz, 3H, OCH₂CH₃), 0.83 (t, 3H, OCH₂CH₃), 3.78 (q, 2H, OCH₂CH₃), 3.90 (q, 2H, OCH₂CH₃), 7.46–7.69 (m, 9H, 7 ArH’s and NH₂), and 10.57 (s, br, 1H, OH); Anal. Calcd for C₉₂H₅₂Br₂N₂O₄S (620.31): C, 48.41; H, 3.25; N, 4.52; S, 5.17; found: C, 48.54; H, 3.40; N, 4.68; S, 5.01%.

Ethyl 2-acetyl-3-amino-4-(3,5-dibromo-4-hydroxyphenyl)-6- phenylthiopheno[2,3-b]pyridine-5-carboxylate (12b). Yellow crystals recrystallized from ethanol/dioxane mixture (82%); m.p. 270–272°C; IR (ν cm⁻¹): 3448 (OH), 3365, 3272 (NH₂), and 1724 (CO); ¹H-NMR (DMSO-d₆): δ 0.83 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 2.40 (s, 3H, CH₃), 3.88 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 6.50 (s, br, 2H, NH₂), 7.50–7.67 (m, 7H, ArH’s), and 10.46 (s, 1H, OH); Anal. Calcd for C₂₉H₁₈Br₂N₂O₇S (590.28): C, 48.83; H, 3.07; N, 4.75; S, 5.43; found: C, 48.95; H, 3.16; N, 4.52; S, 5.35%.

Ethyl 3-amino-2-benzyl-4-(3,5-dibromo-4-hydroxyphenyl)-6- phenylthiopheno[2,3-b]pyridine-5-carboxylate (12c). Yellow crystals recrystallized from ethanol/dioxane mixture (80% from 2a or 90% from 11e); m.p. 258–260°C; IR (ν cm⁻¹): 3458 (OH), 3355, 3274 (NH₂), and 1720 (CO); ¹H-NMR (DMSO-d₆): δ 0.85 (t, J = 6.9 Hz, 3H, OCH₂CH₃), 3.92 (q, J = 6.9 Hz, 2H, CH₂CH₂O), 6.92 (s, br, 2H, NH₂), 7.50–7.79 (m, 12H, ArH’s), and 10.48 (s, br, 1H, OH); Anal. Calcd for C₃₀H₂₂Br₂N₂O₇S (652.35): C, 53.39; H, 3.09; N, 4.29; S, 4.92; found: C, 53.20; H, 3.00; N, 4.40; S, 5.06%.

REFERENCE AND NOTES