A Simple and Expedient Method for the Synthesis of Ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate

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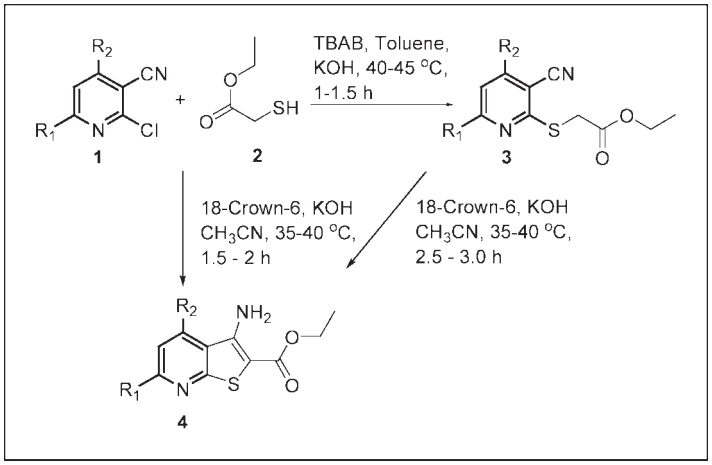
Dedicated to the memory of Dr. Chaitanya G. Dave.



2-Chloro-4,6-diarylnicotinonitrile **1** was reacted with ethyl 2-mercaptoacetate **2** to furnish ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3** as intermediates. These intermediates were cyclized by Thorpe–Zeigler cyclization using solid–liquid phase-transfer catalysis conditions to give ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4**. One-pot heterocyclization without isolating the intermediates was also achieved using solid–liquid phase transfer conditions.

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INTRODUCTION

Many thienopyridines have been evaluated pharmacologically and in particular thieno[2,3-*b*]pyridines are of special importance due to the reported biological activities, including antibacterial [1], anti-inflammatory [2], antiparasitic [3], and antidiabetic [4] agents. Moreover, thieno[2,3-*b*]pyridine-5-carbonitrile were synthesizes as kinase inhibitors [5–7], were as thieno[2,3-*b*]pyridin-4-one derivatives were prepared as orally active, nonpeptide luteinizing hormone-releasing hormone (LHRH) receptor antagonists [8].

Despite the recent emergence of the thieno[2,3-*b*]pyridines moiety as a useful pharmacophore, methodology for preparation of this interesting heterocyclic ring system remains severely limited. Traditionally, the alkylation of substituted 3-cyano-2(1*H*)-pyridinethiones [9a–c] or 2-chloro-4,6-diarylnicotinonitrile [10] and Thorpe–Ziegler cyclization of the latter in alkali medium to give 3-aminothieno[2,3-*b*]pyridines have been extensively studied. Hard base like sodium or potassium alkoxide, which are relatively difficult to handle are used in such multistep synthesis.

The Thorpe–Zeigler cyclizations [11] are one of the most promising lines in the chemistry of amino heterocycles. They are base catalyzed and sodium or potassium alkoxide [12a–f], sodium hydride [12g,h], potassium hydroxide [12i], and lithium hydroxide [12j] were used frequently. Radical alternatives [13a], solvent free [13b] strategies as well as iridium hydride complexes [13c] also have been applied to Thorpe–Ziegler cyclizations. However, a little to our surprise, no attempt has been made to use comprehensive strategies for Thorpe–Zeigler cyclization involving phase-transfer conditions. In light of these considerations, we decided to set an improved protocol by introducing phase-transfer catalysis conditions for the Thorpe–Ziegler cyclization.

RESULTS AND DISCUSSION

2-Chloro-4,6-diarylnicotinonitrile **1** was reacted with ethyl 2-mercaptoacetate **2** in powdered KOH at 40–45°C using triethylbenzylammonium chloride (TEBA) as phase transfer catalyst and toluene as solvent to furnish ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3** as

Table 1

Synthesis of 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3a–k**.

Entry	R^1	R^2	Yield[a] (%)	Mp (°C) Found/Lit. [10]
3a	C_6H_5	C_6H_5	90	183–184/181–182
3b	C_6H_5	4-$OCH_3C_6H_4$	93	178–179/177–178
3c	C_6H_5	4-FC_6H_4	89	188–189
3d	C_6H_5	3-Cl-4-FC_6H_3	91	202–203
3e	C_6H_5	4-$CH_3C_6H_4$	80	238–239/238–239
3f	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	90	183–184/182–184
3g	4-$CH_3C_6H_4$	4-ClC_6H_4	89	191–192
3h	4-$CH_3C_6H_4$	4-FC_6H_4	88	195–196
3i	4-$CH_3OC_6H_4$	C_6H_5	94	202–203/202–203
3j	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	91	200–201/198–199
3k	4-FC_6H_4	C_6H_5	93	169–170

[a] Isolated yields.

intermediates (Table 1). The reaction was optimized using different reaction conditions and catalysts, for liquid–liquid phase-transfer conditions CH_2Cl_2/KOH (aq. 40% w/v), the most lipophilic *quats*, the Aliquat, and the tetrabutylammonium cation (TBA) were ineffective phase transfer catalyst were as more hydrophilic cation, TEBA gave poor yields. However in solid–liquid phase-transfer conditions Toluene/powdered KOH TEBA was the preferred choice. These intermediates were cyclized by Thorpe–Zeigler cyclization using 18-crown-6 and potassium hydroxide complex dissolved in acetonitrile, the heterocyclization allowed efficient access to various ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4** in excellent yields. One-pot heterocyclization without isolating the intermediates **3** was also achieved using solid–liquid phase-transfer catalysis (SL-PTC) conditions (Table 2; Scheme 1).

Given the frequent appearance of thieno[2,3-*b*]pyridine fragments in pharmaceutical compounds, we sought to expand the scope of this potentially useful phase-transfer method and optimize its efficiency. To optimize the synthesis of **4**, different catalysts and reaction conditions were examined. For liquid–liquid phase-transfer conditions CH_2Cl_2/KOH (aq. 40% w/v), lack of reactivity was observed in the presence of catalysts such as tetrabutylammonium iodide (TBAI) and tricaprylmethylammonium chloride (Aliquat® 336) even after prolonged heating (24 h, 40°C). Thus, the most lipophilic *quats*, the Aliquat, and the TBA are ineffective as phase-transfer catalysts. Changing the counter ion in the TBA *quat* [iodide (TBAI) or chloride (TBACl)] was also unsuccessful thus discarding the possibility that the lack of reactivity in the presence of the catalyst could be due to the effect of the iodide counter ion (''catalyst poisoning'' by association with the quat in the organic phase [14a–d]) the results also showed that swapping anions such as BF_4^-, ClO_4^-, and HSO_4^- have no catalytic activity. On the other hand, smaller and more

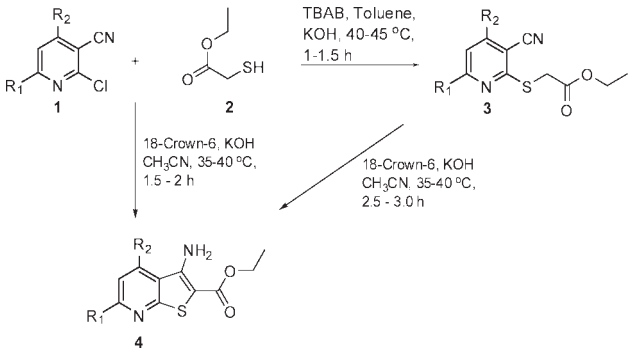
Table 2

Synthesis ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4a–k**.

			Yield (%)		
Entry	R^1	R^2	Method I	Method II[a]	Mp (°C) Found/Lit. [10]
4a	C_6H_5	C_6H_5	90	80	172–173/171–172
4b	C_6H_5	4-$OCH_3C_6H_4$	93	78	184–185/183–184
4c	C_6H_5	4-FC_6H_4	89	75	175–176
4d	C_6H_5	3-Cl-4-FC_6H_3	91	79	183–184
4e	C_6H_5	4-$CH_3C_6H_4$	80	69	175–176/174–175
4f	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	90	78	181–182/181–182
4g	4-$CH_3C_6H_4$	4-ClC_6H_4	89	75	176–177
4h	4-$CH_3C_6H_4$	4-FC_6H_4	88	70	181–182
4i	4-$CH_3OC_6H_4$	C_6H_5	94	84	188–189
4j	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	91	82	175–176/173–174
4k	4-FC_6H_4	C_6H_5	93	80	161–162

[a] Overall yields for method II from compound **1**.

Scheme 1. Synthesis of ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4**.



hydrophilic cations such as tributylmethylammonium and TEBA were unsuccessful to facilitate the reaction. These results indicate that the structure of the quaternary ammonium cation (*quat*) does not seem to be crucial for the success of the reaction. Catalyst loading, changing the solvent, or change in temperature resulted the same. The heterocyclization in SL-PTC conditions using 18-crown-6, KOH along with acetonitrile as solvent furnished products **4** in excellent yields. One-pot synthesis of thieno[2,3-*b*]pyridine-2-carboxylate **4** without isolation of intermediates **3** from 2-chloro-4,6-diarylnicotinonitrile **1** using same conditions was successful. Solvents like toluene, benzene, chlorobenzene, diethyl ether, methanol, and hexane were used, however, acetonitrile was the best choice for such heterocyclization.

The structure of compound ethyl 3-amino-4-tolyl-6-phenylthieno[2,3-*b*]pyridine-2-carboxylate **4e** was confirmed using X-ray crystallography [15] (Fig. 1).

A plausible mechanism for the Thorpe–Zeigler cyclization is proposed in Figure 2. The initial complex formation between crown ether and potassium hydroxide extracts proton from ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3**, resulting into the intermediate, followed by intramolecular nucleophilic addition of —CH— onto an imine that could yield an enamine and also aromatic system for the formation of ethyl 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylate **4**.

CONCLUSIONS

In conclusion, we have described a simple, cleaner, and convenient synthesis of ethyl 3-amino-4,6-diarylthieno[2,3-b]pyridine-2-carboxylate **3**, which are important building blocks for the construction of various fused heterocycles. SL-PTC conditions using 18-crown-6 is the method of choice with excellent yields even for one-pot heterocyclization. The ease with which phase-transfer catalyst reacts, presents new opportunities for expanding Thorpe–Zeigler cyclization for the synthesis of numerous heterocycles.

EXPERIMENTAL

Melting points were determined by electro thermal method in open capillary tube and are uncorrected. The IR spectra were recorded in cm^{-1} for KBr pellets on a Buck-500 spectrophotometer. The ^1H NMR spectra were recorded on a Varian 300 MHz spectrophotometer in DMSO-d_6 using TMS as internal standard and the chemical shifts are expressed in δ ppm. MS spectra were recorded on a JEOL/ SX-102 mass spectrophotometer under electron-impact (EI) ionization. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. The completion of the reaction was checked by TLC using silica gel G and spots were exposed to iodine vapor. 2-Chloro-4,6-diarylnicotinonitrile **1** were synthesized by refluxing 2-oxo-4,6-diaryl-1,2-dihydropyridine-3-carbonitrile [16] in phosphoryl trichloride.

General procedure for the synthesis of ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate (3a-k). To a well stirred mixture of powdered potassium hydroxide (0.7 g, 12.5 mmol), triethylbenzylammoniumchloride (0.113 g, 0.5 mmol) and 2-chloro-4,6-diarylnicotinonitrile **1** (5 mmol) in toluene (25 mL), was added drop wise ethyl 2-mercaptoacetate **2** (6 mmol). The reaction mixture was heated up to 40–45°C. After the completion of reaction 1–1.5 h (TLC), water (25 mL) was added to the reaction mixture and stirring was continued for 5 min. Organic layer was separated and aqueous layer was washed with toluene (15 mL). The combined organic layer was dried over anhydrous magnesium sulfate, the solvent was removed *in vacuo*, and the solid **3a–k** thus obtained was crystallized from EtOH-DMF mixture.

Ethyl 2-(3-cyano-4,6-diphenylpyridin-2-ylthio)acetate (3a). IR (KBr): ν = 3020, 2940, 2228, 1748, 1584 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.47 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.35 (s, 2H, —CH_2—), 4.56 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.60–8.30 (m, 11H, Ar—H); MS: m/z = 374 (M^+). *Anal*. Calcd for $C_{22}H_{18}N_2O_2S$ (374.46): C, 70.57; H, 4.85; N, 7.48; Found: C, 70.63; H, 4.90; N, 7.61%.

Ethyl 2-(3-cyano-4-(4-methoxyphenyl)-6-phenylpyridin-2-ylthio)acetate (3b). IR (KBr): ν = 3030, 2994, 2232, 1756, 1590 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, J =

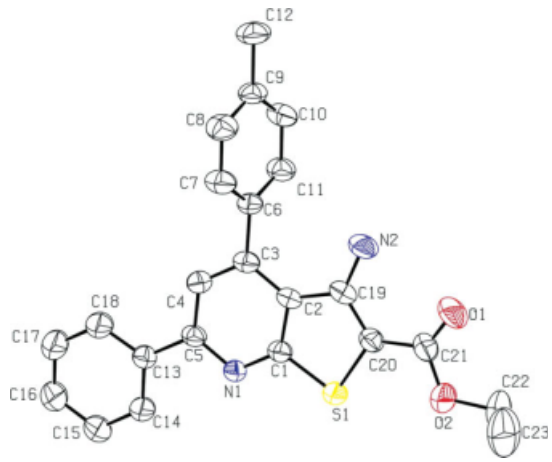


Figure 1. Ethyl 2-amino-6-phenyl-4-p-tolylthieno[2,3-*b*]pyridine-3-carboxylate [15] (**4e**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

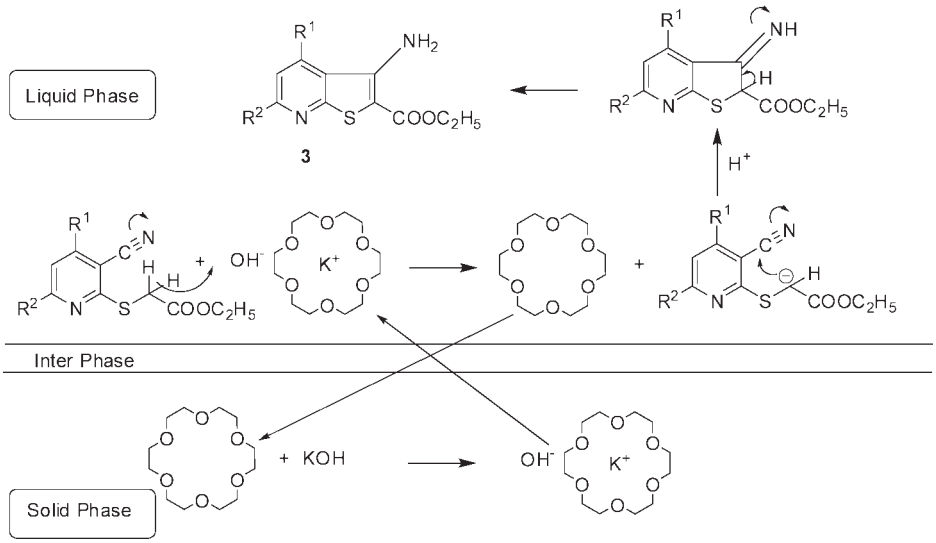


Figure 2. A plausible mechanism for the Thorpe–Zeigler cyclization in solid–liquid phase-transfer catalysis conditions.

7.2 Hz, 3H, —CH_2CH_3), 3.98 (s, 3H, OCH_3), 4.25 (s, 2H, —CH_2) 4.52 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.12–8.15 (m, 10H, Ar—H); MS: m/z = 404 (M^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3S$ (404.48): C, 68.30; H, 4.98; N, 6.93; Found: C, 68.35; H, 5.12; N, 7.06%.

Ethyl 2-(3-cyano-4-(4-fluorophenyl)-6-phenylpyridin-2-ylthio)acetate (3c). IR (KBr): ν = 3004, 2980, 2216, 1758, 1600 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.32 (t, 3H, J = 7.2 Hz, —CH_2CH_3), 4.35 (s, 2H, —CH_2), 4.60 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.50–8.31 (m, 10H, Ar—H); MS: m/z = 392 (M^+). *Anal*. Calcd for $C_{22}H_{17}FN_2O_2S$ (392.45): C, 67.33; H, 4.37; N, 7.14; Found: C, 67.44; H, 4.26; N, 7.26%.

Ethyl 2-(4-(3-chloro-4-fluorophenyl)-3-cyano-6-phenylpyridin-2-ylthio)acetate (3d). IR (KBr): ν = 3020, 2940, 2224, 17408, 1580 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.38 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.32 (s, 2H, —CH_2), 4.59 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.45–8.60 (m, 9H, Ar—H); MS: m/z = 426 (M^+). *Anal*. Calcd for $C_{22}H_{16}ClFN_2O_2S$ (426.89): C, 61.90; H, 3.78; N, 6.56; Found: C, 61.83; H, 3.66; N, 6.60%.

Ethyl 2-(3-cyano-6-phenyl-4-p-tolylpyridin-2-ylthio)acetate (3e). IR (KBr): ν = 3020, 2980, 2208, 1736, 1600 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.43 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.40 (s, 3H, CH_3), 4.44 (s, 2H, —CH_2), 4.70 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.12–8.55 (m, 10H, Ar—H); MS: m/z = 388 (M^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_2S$ (388.48): C, 71.11; H, 5.19; N, 7.21; Found: C, 71.14; H, 5.02; N, 7.14%.

Ethyl 2-(3-cyano-4,6-dip-tolylpyridin-2-ylthio)acetate (3f). IR (KBr): ν = 3010, 2940, 2236, 1748, 1612 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, J =7.2 Hz, 3H, —CH_2CH_3), 2.53 (s, 6H, CH_3), 4.33 (s, 2H, —CH_2), 4.62 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.58–8.56 (m, 9H, Ar—H); MS: m/z = 402 (M^+). *Anal*. Calcd for $C_{24}H_{22}N_2O_2S$ (402.51): C, 71.62; H, 5.51; N, 6.96; Found: C, 71.70; H, 5.46; N, 6.86%.

Ethyl 2-(4-(4-chlorophenyl)-3-cyano-6-p-tolylpyridin-2-ylthio)acetate (3g). IR (KBr): ν = 3020, 2970, 2228, 1742, 1584 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.34 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.49 (s, 3H, CH_3), 4.38 (s, 2H, —CH_2), 4.66 (q, J =7.0 Hz, 2H, —CH_2CH_3), 7.30–8.25 (m, 9H, Ar—H); MS: m/z = 422 (M^+). *Anal*. Calcd for $C_{23}H_{19}ClN_2O_2S$ (422.93): C, 65.32; H, 4.53; N, 6.62; Found: C, 65.43; H, 4.56; N, 6.76%.

Ethyl 2-(3-cyano-4-(4-fluorophenyl)-6-p-tolylpyridin-2-ylthio)acetate (3h). IR (KBr): ν = 3010, 2992, 2232, 1744, 1596 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.39 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 2.47 (s, 3H, CH_3), 4.37 (s, 2H, —CH_2), 4.67 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.23–8.55 (m, 9H, Ar—H); MS: m/z = 406 (M^+). *Anal*. Calcd for $C_{23}H_{19}FN_2O_2S$ (406.47): C, 67.96; H, 4.71 N, 6.89; Found: C, 67.83; H, 4.86; N, 6.96%.

Ethyl 2-(3-cyano-6-(4-methoxyphenyl)-4-phenylpyridin-2-ylthio)acetate (3i). IR (KBr): ν = 3000, 2988, 2212, 1756, 1584 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.43 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.05 (s, 3H, OCH_3), 4.30 (s, 2H, —CH_2), 4.66 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.20–8.37 (m, 10H, Ar—H); MS: m/z = 404 (M^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3S$ (404.48): C, 68.30; H, 4.98; N, 6.93; Found: C, 68.33; H, 5.06; N, 7.12%.

Ethyl 2-(3-cyano-4,6-bis(4-methoxyphenyl)pyridin-2-ylthio)acetate (3j). IR (KBr): ν = 3010, 2960, 2236, 1756, 1600 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.33 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 3.64 (s, 2H, —CH_2), 4.12 (s, 6H, OCH_3), 4.50 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 6.99–8.19 (m, 9H, Ar—H); MS: m/z = 434 (M^+). *Anal*. Calcd for $C_{24}H_{22}N_2O_4S$ (434.51): C, 66.34; H, 5.10; N, 6.45; Found: C, 66.37; H, 5.16; N, 6.55%.

Ethyl 2-(3-cyano-6-(4-fluorophenyl)-4-phenylpyridin-2-ylthio)acetate (3k). IR (KBr): ν = 3000, 2980, 2224, 1752, 1604 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.38 (t, J = 7.2 Hz, 3H, —CH_2CH_3), 4.35 (s, 2H, —CH_2), 4.62 (q, J = 7.0 Hz, 2H, —CH_2CH_3), 7.55–8.48 (m, 10H, Ar—H); MS: m/z = 392 (M^+). *Anal*. Calcd for $C_{22}H_{17}FN_2O_2S$ (392.45): C, 67.33; H, 4.37; N, 7.14; Found: C, 67.46; H, 4.26; N, 7.20%.

General procedure for the synthesis of ethyl 3-amino-4,6-diarylthieno[2,3-b]pyridine-2-carboxylate 4a–k. ***Method I.*** To the well stirred solution of MeCN (20 mL), powdered KOH (0.700 g, 12.5 mmol), and 18-crown-6 (0.132 g, 0.5 mmol) was added ethyl 2-(3-cyano-4,6-diarylpyridin-2-ylthio)acetate **3** (5 mmol). The reaction mixture was further stirred

at 35–40°C for 1.5–2 h (TLC). The solvent was distilled under reduced pressure and the reaction mixture was poured onto crushed ice (20 g) and neutralized with acetic acid (50% v/v). The products thus obtained were filtered, washed with water, dried, and crystallized from glacial acetic acid.

Method II. Ethyl 2-mercaptoacetate **2** (6 mmol) was added drop wise to a stirred mixture of powdered potassium hydroxide (15 mmol, 0.84 g) and 18-crown-6 (1 mmol, 0.264 g) in acetonitrile (20 mL). 2-Chloro-4,6-diarylnicotinonitrile **1** (5 mmol) was added portion wise to the reaction mixture with stirring. The reaction was further stirred at 35–40°C for 2.5–3.0 h (TLC). The solvent was distilled under reduced pressure and the reaction mixture was poured onto crushed ice (20 g) and neutralized with acetic acid (50% v/v). The products thus obtained were filtered, washed with water, dried, and crystallized from glacial acetic acid.

Ethyl 3-amino-4,6-diphenylthieno[2,3-b]pyridine-2-carboxylate (4a). IR (KBr): ν = 3510, 3380, 3020, 2900, 1686, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.42 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 4.42 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.70 (s, 2H, —NH_2), 7.23–8.16 (m, 11H, Ar—H); MS: m/z = 374 (M^+). *Anal*. Calcd for $C_{22}H_{18}N_2O_2S$ (374.46): C, 70.57; H, 4.85; N, 7.48; Found: C, 70.51; H, 4.89; N, 7.42%.

Ethyl 3-amino-4-(4-methoxyphenyl)-6-phenylthieno[2,3-b]pyridine-2-carboxylate (4b). IR (KBr): ν = 3480, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.41 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 3.95 (s, 3H, —OCH_3), 4.49 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.85 (s, 2H, —NH_2), 7.18–8.10 (m, 10H, Ar—H); MS: m/z = 404 (M^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3S$ (404.48): C, 68.30; H, 4.98; N, 6.93; Found: C, 68.35; H, 4.88; N, 6.88%.

Ethyl 3-amino-4-(4-fluorophenyl)-6-phenylthieno[2,3-b]pyridine-2-carboxylate (4c). IR (KBr): ν = 3480, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.43 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 4.40 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.65 (s, 2H, —NH_2), 7.45–8.15 (m, 10H, Ar—H); MS: m/z = 392 (M^+). *Anal*. Calcd for $C_{22}H_{17}FN_2O_2S$ (392.45): C, 67.33; H, 4.37; N, 7.14; Found: C, 67.41; H, 4.45; N, 7.10%.

Ethyl 3-amino-4-(3-chloro-4-fluorophenyl)-6-phenylthieno-[2,3-b]pyridine-2-carboxylate (4d). IR (KBr): ν = 3455, 3300, 3010, 2980, 2204, 1624, 1596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 4.24 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), δ = 5.34 (s, 2H, NH_2), 7.67–8.14 (m, 9H, Ar—H); MS: m/z = 426 (M^+). *Anal*. Calcd for $C_{22}H_{16}ClFN_2O_2S$ (426.89): C, 61.90; H, 3.78; N, 6.56; Found: C, 61.81; H, 3.88; N, 6.60%.

Ethyl 2-amino-6-phenyl-4-p-tolylthieno[2,3-b]pyridine-2-carboxylate (4e). IR (KBr): ν = 3520, 3400, 3000, 2980, 1674, 1608 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 2.45 (s, 3H, CH_3), 4.42 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.75 (s, 2H, —NH_2), 7.04–8.25 (m, 10H, Ar—H); MS: m/z = 388 (M^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_2S$ (388.48): C, 71.11; H, 5.19; N, 7.21; Found: C, 71.22; H, 5.05; N, 7.15%.

Ethyl 3-amino-4,6-dip-tolylthieno[2,3-b]pyridine-2-carboxylate (4f). IR (KBr): ν = 3480, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.39 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 2.47 (s, 6H, CH_3), 4.43 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.63 (s, 2H, —NH_2), 7.38–8.11 (m, 9H, Ar—H); MS: m/z = 402 (M^+). *Anal*. Calcd for $C_{24}H_{22}N_2O_2S$ (402.51): C, 71.62; H, 5.51; N, 6.96; Found: C, 71.68; H, 5.45; N, 6.89%.

Ethyl 3-amino-4-(4-chlorophenyl)-6-p-tolylthieno[2,3-b]pyridine-2-carboxylate (4g). IR (KBr): ν = 3510, 3380, 3000, 2940, 1676, 1616 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.35 (t, *J* =7.2 Hz, 3H, —CH_2CH_3), 2.40 (s, 3H, CH_3), 4.36 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.60 (s, 2H, —NH_2), 7.18–8.21 (m, 9H, Ar—H); MS: m/z = 422 (M^+). *Anal*. Calcd for $C_{23}H_{19}ClN_2O_2S$ (422.93): C, 65.32; H, 4.53; N, 6.62; Found: C, 65.23; H, 4.44; N, 6.55%.

Ethyl 3-amino-4-(4-fluorophenyl)-6-p-tolylthieno[2,3-b]pyridine-2-carboxylate (4h). IR (KBr): ν = 3500, 3390, 3010, 2940, 1682, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.33 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 2.39 (s, 3H, CH_3), 4.35 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.62 (s, 2H, —NH_2), 7.13–8.19 (m, 9H, Ar—H); MS: m/z = 406 (M^+). *Anal*. Calcd for $C_{23}H_{19}FN_2O_2S$ (406.47): C, 67.96; H, 4.71; N, 6.89; Found: C, 67.99; H, 4.80; N, 6.86%.

Ethyl 3-amino-6-(4-methoxyphenyl)-4-phenylthieno[2,3-b]-pyridine-2-carboxylate (4i). IR (KBr): ν = 3520, 3400, 3000, 2980, 1676, 1608 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.39 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 3.98 (s, 3H, OCH_3), 4.36 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.96 (s, 2H, —NH_2), 7.27–8.24 (m, 10H, Ar—H); MS: m/z = 404 (M^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3S$ (404.48): C, 68.30; H, 4.98; N, 6.93; Found: C, 68.38; H, 4.88; N, 6.87%.

Ethyl 3-amino-4,6-bis(4-methoxyphenyl)thieno[2,3-b]pyridine-2-carboxylate (4j). IR (KBr): ν = 3510, 3300, 3020, 2970, 1672, 1596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.42 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 4.02 (s, 6H, OCH_3), 4.39 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.99 (s, 2H, —NH_2), 7.26–8.20 (m, 9H, Ar—H); MS: m/z = 434 (M^+). *Anal*. Calcd for $C_{24}H_{22}N_2O_4S$ (434.51): C, 66.34; H, 5.10; N, 6.45; Found: C, 66.30; H, 5.12; N, 6.39.

Ethyl 3-amino-6-(4-fluorophenyl)-4-phenylthieno[2,3-b]pyridine-2-carboxylate (4k). IR (KBr): ν = 3500, 3390, 3010, 2980, 1668, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.45 (t, *J* = 7.2 Hz, 3H, —CH_2CH_3), 4.46 (q, *J* = 6.9 Hz, 2H, —CH_2CH_3), 5.55 (s, 2H, —NH_2), 7.21–8.24 (m, 10H, Ar—H); MS: m/z = 392 (M^+). *Anal*. Calcd for $C_{22}H_{17}FN_2O_2S$ (392.45): C, 67.33; H, 4.37; N, 7.14; Found: C, 67.22; H, 4.25; N, 7.26.

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