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Efficient Approach to the Synthesis of Ethyl 3-Amino-4,6-diarylfuro [2,3-*b*]pyridine-2-carboxylate

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Abstract: Novel ethyl 3-amino-4,6-diarylfuro[2,3-*b*]pyridine-2-carboxylate were synthesized by Thorpe–Ziegler cyclization using solid–liquid phase-transfer catalysis conditions.

Keywords: Furo[2,3-*b*]pyridine, heterocyclization, solid–liquid PTC, Thorpe–Zeigler reaction

INTRODUCTION

The furopyridine nucleus represents a useful pharmacophore in a variety of therapeutic areas.[1] This structural unit recently has been incorporated into HIV protease inhibitor candidates such as L-754,394.[2] Despite its importance, however, synthetic methodologies for its construction remain limited,[3] and the provision of sufficient amounts of these substances may represent a bottleneck for further studies and development in medicinal chemistry.[4]

In conjunction with a recent drug development program, we became interested in the furopyridine ring system, a key structural subunit

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Dedicated to the memory of Dr. Chaitanya G. Dave.
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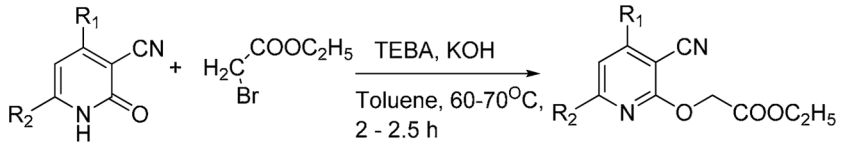
prevalent in numerous natural products and structural analogs associated with interesting biological activities.[5]

The Thorpe–Zeigler[6] reactions are some of the most promising lines in the chemistry of amino heterocycles. They are base catalyzed, and sodium or potassium alkoxide,[7a–f] sodium hydride,[7g,h] potassium hydroxide,[7i] and lithium hydroxide[7j] were employed frequently. Radical alternatives,[8a] solvent-free[8b] strategies as well as iridium hydride complexes,[8c] also have been applied to the Thorpe–Ziegler reaction. Yet, a little to our surprise, no attempt has been made to employ comprehensive strategies for the Thorpe–Zeigler reaction involving phase-transfer conditions.

RESULTS AND DISCUSSION

Traditionally, furo[2,3-*b*]pyridines were prepared in a multistep synthesis using a hard base such as sodium or potassium alkoxide,[7f] sodium hydride, etc., which are relatively difficult to handle, and moreover the yields were low.[7g] Despite the recent emergence of the furo[2,3-*b*]pyridine moiety as a useful pharmacophore, methodology for preparation of this interesting heterocyclic ring system remains severely limited. In lieu of these findings, we decided to set an improved protocol by introducing phase-transfer catalysis conditions for the Thorpe–Ziegler reaction. 2-Oxo-4,6-diaryl-1,2-dihydropyridine-3-carbonitrile **1** was reacted with ethyl bromoacetate in powdered potassium hydroxide (KOH) at 60–70°C using triethylbenzylammonium chloride (TEBA) as phase-transfer catalyst (PTC) and toluene as solvent to furnish ethyl 2-(3-cyano-4,6-diarylpyridin-2-yloxy)acetate **2** (Scheme 1, Table 1). It was envisioned that target compound **1** involves an ambident anion and can be expected to yield a mixture of *N*- and *O*-alkylated products. However, *O*-alkylated product was the main dominant product because of chain length of alkylating reagent and by the steric hindrance offered by the substituted aryl ring present at position 6 of the pyridine ring. The reaction was optimized



1a-m **2a-m**

Scheme 1. Synthesis of ethyl 2-(3-cyano-4,6-diarylpyridin-2-yloxy)acetate **2**.

Table 1. Synthesis of ethyl 2-(3-cyano-4,6-diarylpyridin-2-yloxy)acetate **2a–m**

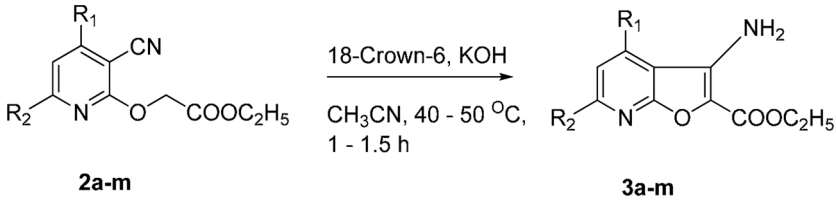
Entry	R^1	R^2	Yield[a] (%)	Mp (°C)
2a	C_6H_5	C_6H_5	80	136–137
2b	C_6H_5	4-$CH_3C_6H_4$	78	184–185
2c	C_6H_5	4-$CH_3OC_6H_4$	76	173–175
2d	C_6H_5	4-ClC_6H_4	72	158–160
2e	4-$CH_3C_6H_4$	C_6H_5	75	140–141
2f	4-$CH_3C_6H_4$	4-ClC_6H_4	81	167–168
2g	4-$CH_3OC_6H_4$	C_6H_5	78	145–146
2h	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	84	150–151
2i	4-ClC_6H_4	C_6H_5	79	147–149
2j	4-ClC_6H_4	4-$CH_3C_6H_4$	72	189–190
2k	2-Furyl	C_6H_5	80	129–130
2l	2-Furyl	4-$CH_3C_6H_4$	88	130–131
2m	2-Thienyl	C_6H_5	79	135–137

[a]Isolated yields.

using various PTCs, and TEBA was the preferred choice. As this occurs between phases, interphase, stirring was important and was optimized at 150 rpm.

Intermediates **2** were cyclized by the Thorpe–Zeigler cyclization using 18-crown-6 and KOH complex dissolved in acetonitrile; the heterocyclization allowed efficient access to various furo[2,3-*b*]pyridine nucleus in excellent yields (Scheme 2, Table 2). The structure of compound ethyl 3-amino-6-phenyl-4-tolylfuro[2,3-*b*]pyridine-2-carboxylate[9] was confirmed using x-ray crystallography (Fig. 1).

Given the frequent appearance of furo[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 **3a–m**, 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



2a-m **3a-m**

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

Table 2. Ethyl 3-amino-4,6-diarylfuro[2,3-*b*]pyridine-2-carboxylate **3a–m**

Entry	R^1	R^2	Yield[a] (%)	Mp (°C)
3a	C_6H_5	C_6H_5	82	185–187
3b	C_6H_5	$4\text{-}CH_3C_6H_4$	65	148–149
3c	C_6H_5	$4\text{-}CH_3OC_6H_4$	75	155–156
3d	C_6H_5	$4\text{-}ClC_6H_4$	78	161–162
3e	$4\text{-}CH_3C_6H_4$	C_6H_5	60	165–166
3f	$4\text{-}CH_3C_6H_4$	$4\text{-}ClC_6H_4$	70	185–186
3g	$4\text{-}CH_3OC_6H_4$	C_6H_5	77	169–170
3h	$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	81	152–154
3i	$4\text{-}ClC_6H_4$	C_6H_5	72	167–168
3j	$4\text{-}ClC_6H_4$	$4\text{-}CH_3C_6H_4$	65	192–193
3k	2-Furyl	C_6H_5	80	205–207
3l	2-Furyl	$4\text{-}CH_3C_6H_4$	70	180–182
3m	2-Thienyl	C_6H_5	72	177–178

[a]Isolated yields.

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 tetrabutylammonium cation (TBA) are ineffective as PTCs. Changing

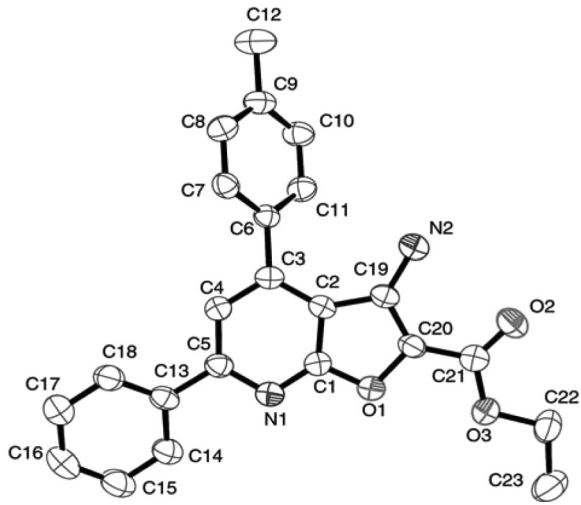


Figure 1. X-ray structure of ethyl 3-amino-6-phenyl-4-tolylfuro[2,3-*b*]pyridine-2-carboxylate.[9]

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 counterion (“catalyst poisoning” by association with the quat in the organic phase[10]). On the other hand, smaller and more hydrophilic cations such as tributylmethylammonium and TEBA did not 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 changing the temperature resulted in the same. The heterocyclization in solid–liquid phase-transfer catalysis conditions using 18-crown-6 KOH along with acetonitrile as solvent furnished products **3a**–**m** in excellent yields. Solvents such as toluene, benzene, chlorobenzene, diethyl ether, methanol, and hexane were employed; however, acetonitrile was the best choice for such heterocyclization. Synthesis of furo[2,3-*b*]pyridine-2-carboxylate **3** without isolation of intermediates **2** from 2-oxo-4,6-diaryl-1, 2-dihydropyridine-3-carbonitrile **1** using solid–liquid phase-transfer conditions was unsuccessful.

A plausible mechanism for the Thorpe–Zeigler reaction is proposed in Fig. 2. The initial complex formation between crown ether and KOH extracts the proton from ethyl 2-(3-cyano-4,6-diarylpyridin-2-yloxy) acetate **2**, resulting in the intermediate, which was followed by intramolecular nucleophilic addition of -CH- onto an imines that could yield

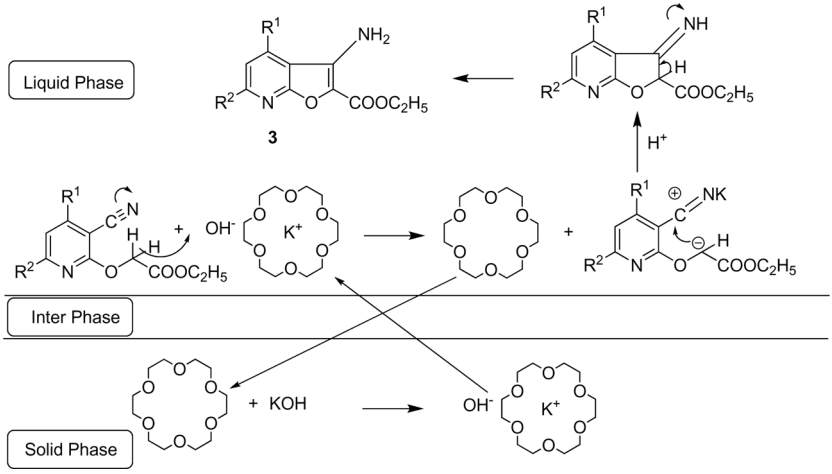


Figure 2. A plausible mechanism for the Thorpe–Zeigler cyclization in solid–liquid phase-transfer catalysis conditions.

an enamine and also an aromatic system for the formation of ethyl 3-amino-4,6-diarylfuro[2,3-*b*]pyridine-2-carboxylate **3**.

CONCLUSIONS

In conclusion, we have described a simple, clean, and convenient synthesis of ethyl 3-amino-4,6-diarylfuro[2,3-b]pyridine-2-carboxylate **3**, which is an important building block for the construction of various fused heterocycles. A comparison of the conventional method and solid–liquid PTC suggests that the solid–liquid PTC conditions using 18-crown-6 is the method of choice with excellent yields. The ease with which the PTC reacts presents new opportunities for expanding the Thorpe–Zeigler reaction for the synthesis of numerous heterocycles.

EXPERIMENTAL

Melting points were determined by the electrothermal method in an open capillary tube and are uncorrected. The infrared (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 $CDCl_3$ using tetramethylsilane (TMS) as internal standard, and the chemical shifts are expressed in δ ppm. Mass spectra (MS) 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 purity of the compounds was routinely checked by thin-layer chromatography (TLC) using silica gel G, and spots were exposed to iodine vapor.

Synthesis of Ethyl 2-(3-cyano-4,6-p-tolylpyridin-2-yloxy)acetate 2a–m: General Procedure

Ethyl bromoacetate (6 mmol) was added dropwise to a well-stirred mixture of powdered KOH (0.7 g, 12.5 mmol), triethylbenzylammoniumchloride (0.113 g, 0.5 mmol), and 2-oxo-4,6-diaryl-1,2-dihydropyridine-3-carbonitrile **1** (5 mmol) in toluene (25 mL). The reaction mixture was heated up to 60–70°C. After the completion of the reaction ca. 1 h (TLC), water (25 mL) was added to the reaction mixture and stirring was continued for 5 min. The organic layer was separated, and the 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 solids (**2a–w**) thus obtained were crystallized from methanol.

Data

Ethyl 2-(3-Cyano-4,6-diphenylpyridin-2-yloxy)acetate (**2a**)

IR (KBr): $\nu = 3020$, 2940, 2228, 1748, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 4.32 (q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.72 (s, 2H, -CH_2), 7.51–8.65 (m, 11H, Ar-H); MS: $m/z = 358$ ($\overline{M^+}$). Anal. calcd. for $C_{22}H_{18}N_2O_3$ (358.39): C, 73.73; H, 5.06; N, 7.82. Found: C, 73.83; H, 5.26; N, 7.76%.

Ethyl 2-(3-Cyano-4-phenyl-6-p-tolylpyridin-2-yloxy)acetate (**2b**)

IR (KBr): $\nu = 3004$, 2980, 2222, 1752, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.51 (s, 3H, CH_3), 4.36 (q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.72 (s, 2H, -CH_2), 7.55–8.60 (m, 10H, Ar-H); MS: $m/z = 372$ (M^+). Anal. calcd. for $C_{23}H_{20}N_2O_3$ (372.42): C, 74.18; H, 5.41; N, 7.52. Found: C, 74.23; H, 5.26; N, 7.76%.

Ethyl 2-(3-Cyano-6-(4-methoxyphenyl)-4-phenylpyridin-2-yloxy)acetate (**2c**)

IR (KBr): $\nu = 3030$, 2994, 2232, 1756, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 3.89 (s, 3H, OCH_3), 4.36 (q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.79 (s, 2H, -CH_2), 7.56–8.35 (m, 10H, Ar-H); MS: $m/z = 388$ (M^+). Anal. calcd. for $C_{23}H_{20}N_2O_4$ (388.42): C, 71.12; H, 5.19; N, 7.21. Found: C, 71.18; H, 5.31; N, 7.32%.

Ethyl 2-(6-(4-Chlorophenyl)-3-cyano-4-phenylpyridin-2-yloxy)acetate (**2d**)

IR (KBr): $\nu = 3004$, 2980, 2216, 1758, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (t, 3H, $J = 7.2$ Hz, -$CH_2\underline{CH_3}$), 4.34 (q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.87 (s, 2H, -CH_2), 7.50–8.31 (m, 10H, Ar-H); MS: $m/z = 392$ ($\overline{M^+}$). Anal. calcd. for $C_{22}H_{17}ClN_2O_3$ (392.83): C, 67.26; H, 4.36; N, 7.13. Found: C, 67.12; H, 4.29; N, 7.21.

Ethyl 2-(3-Cyano-6-phenyl-4-p-tolylpyridin-2-yloxy)acetate (**2e**)

IR (KBr): $\nu = 3010$, 2940, 2236, 1748, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.53 (s, 3H, CH_3), 4.39 (q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.75 (s, 2H, -CH_2), 7.58–8.56 (m, 10H,

Ar-H); MS: m/z = 372 (M^+). Anal. calcd. for $C_{23}H_{20}N_2O_3$ (372.42): C, 74.18; H, 5.41; N, 7.52. Found: C, 74.12; H, 5.39; N, 7.41.

Ethyl 2-(6-(4-Chlorophenyl)-3-cyano-4-p-tolylpyridin-2-yloxy)acetate (**2f**)

IR (KBr): $\nu = 3010$, 2992, 2232, 1744, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (t, $J = 7.2$ Hz, 3H, $-CH_2\underline{CH_3}$), 2.52 (s, 3H, CH_3), 4.37 (q, $J = 7.0$ Hz, 2H, $-\underline{CH_2}CH_3$), 4.77 (s, 2H, $-CH_2$), 7.58–8.51 (m, 9H, Ar-H); MS: m/z = 406 (M^+). Anal. calcd. for $C_{23}H_{19}ClN_2O_3$ (406.86): C, 67.90; H, 4.71; N, 6.89. Found: C, 67.87; H, 4.65; N, 6.81.

Ethyl 2-(3-Cyano-4-(4-methoxyphenyl)-6-phenylpyridin-2-yloxy)acetate (**2g**)

IR (KBr): $\nu = 3000$, 2988, 2212, 1756, 1584 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H, $-CH_2\underline{CH_3}$), 3.98 (s, 3H, OCH_3), 4.40 (q, $J = 7.0$ Hz, 2H, $-\underline{CH_2}CH_3$), 4.86 (s, 2H, $-CH_2$), 7.50–8.41 (m, 10H, Ar-H); MS: m/z = 388 (M^+). Anal. calcd. for $C_{23}H_{20}N_2O_4$ (388.42): C, 71.12; H, 5.19; N, 7.21. Found: C, 71.14; H, 5.34; N, 7.31.

Ethyl 2-(3-Cyano-4,6-bis(4-methoxyphenyl)pyridin-2-yloxy)acetate (**2h**)

IR (KBr): $\nu = 3010$, 2960, 2236, 1756, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (t, $J = 7.2$ Hz, 3H, $-CH_2\underline{CH_3}$), 3.92 (s, 6H, OCH_3), 4.38 (q, $J = 7.0$ Hz, 2H, $-\underline{CH_2}CH_3$), 4.84 (s, 2H, $-CH_2$), 7.58–8.49 (m, 9H, Ar-H); MS: m/z = 418 (M^+). Anal. calcd. for $C_{24}H_{22}N_2O_5$ (418.44): C, 68.89; H, 5.30; N, 6.69. Found: C, 68.99; H, 5.34; N, 6.51.

Ethyl 2-(4-(4-Chlorophenyl)-3-cyano-6-phenylpyridin-2-yloxy)acetate (**2i**)

IR (KBr): $\nu = 3000$, 2980, 2224, 1752, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$ (t, $J = 7.2$ Hz, 3H, $-CH_2\underline{CH_3}$), 4.35 (q, $J = 7.0$ Hz, 2H, $-\underline{CH_2}CH_3$), 4.79 (s, 2H, $-CH_2$), 7.55–8.48 (m, 10H, Ar-H); MS: m/z = 392 (M^+). Anal. calcd. for $C_{22}H_{17}ClN_2O_3$ (392.83): C, 67.26; H, 4.36; N, 7.13. Found: C, 67.44; H, 4.30; N, 7.31.

Ethyl 2-(4-(4-Chlorophenyl)-3-cyano-6-p-tolylpyridin-2-yloxy)acetate (**2j**)

IR (KBr): $\nu = 3020$, 2970, 2228, 1742, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J = 7.2$ Hz, 3H, $-CH_2\underline{CH_3}$), 2.49 (s, 3H, CH_3), 4.38

(q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.80 (s, 2H, -CH_2), 7.50–8.42 (m, 9H, Ar-H); MS: $m/z = 406$ (M^+). Anal. calcd. for $C_{23}H_{19}ClN_2O_3$ (406.86): C, 67.90; H, 4.71; N, 6.89. Found: C, 67.74; H, 4.60; N, 6.74.

Ethyl 2-(3-Cyano-4-(furan-2-yl)-6-phenylpyridin-2-yloxy)acetate (**2k**)

IR (KBr): $\nu = 3010$, 2990, 2216, 1744, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 4.30 (q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.76 (s, 2H, -CH_2), 6.79–7.48 (m, 9H, Ar-H); MS: $m/z = 348$ (M^+). Anal. calcd. for $C_{20}H_{16}N_2O_4$ (348.35): C, 68.96; H, 4.63; N, 8.04. Found: C, 68.74; H, 4.60; N, 8.19.

Ethyl 2-(3-Cyano-4-(furan-2-yl)-6-p-tolylpyridin-2-yloxy)acetate (**2l**)

IR (KBr): $\nu = 3000$, 2980, 2220, 1740, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.59 (s, 2H, CH_3), 4.35 (q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.78 (s, 2H, -CH_2), 6.75–7.46 (m, 9H, Ar-H); MS: $m/z = 362$ (M^+). Anal. calcd. for $C_{21}H_{18}N_2O_4$ (362.38): C, 69.60; H, 5.01; N, 7.73. Found: C, 69.74; H, 4.89; N, 7.56.

Ethyl 2-(3-Cyano-6-phenyl-4-(thiophen-2-yl)pyridin-2-yloxy)acetate (**2m**)

IR (KBr): $\nu = 3020$, 2960, 2228, 1756, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 4.37 (q, $J = 7.0$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.70 (s, 2H, -CH_2), 6.65–7.43 (m, 9H, Ar-H); MS: $m/z = 364$ (M^+). Anal. calcd. for $C_{20}H_{16}N_2O_3S$ (364.42): C, 65.92; H, 4.43; N, 7.69. Found: C, 65.74; H, 4.59; N, 7.56.

Synthesis of Ethyl 3-Amino-4,6-diarylfuro[2,3-*b*]pyridine-2-carboxylate 3a–m: General Procedure

Ethyl 2-(3-cyano-4,6-diarylpyridin-2-yloxy)acetate (5 mmol) was added 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). The reaction mixture was further stirred at 40–50°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 absolute ethyl alcohol.

Data

Ethyl 3-Amino-4,6-diphenylfuro[2,3-*b*]pyridine-2-carboxylate (**3a**)

IR (KBr): $\nu = 3510$, 3380, 3020, 2900, 1686, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 4.42 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.25 (s, 2H, -NH_2), 7.23–8.16 (m, 11H, Ar-H); MS: m/z = 358 (M^+). Anal. calcd. for $C_{22}H_{18}N_2O_3$ (358.39): C, 73.73; H, 5.06; N, 7.82. Found: C, 73.64; H, 5.19; N, 7.76.

Ethyl 3-Amino-4-phenyl-6-p-tolylfuro[2,3-*b*]pyridine-2-carboxylate (**3b**)

IR (KBr): $\nu = 3490$, 3390, 3030, 2950, 1674, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.44$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.48 (s, 3H, CH_3), 4.35 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.09 (s, 2H, -NH_2), 7.18–8.10 (m, 10H, Ar-H); MS: m/z = 372 (M^+). Anal. calcd. for $C_{23}H_{20}N_2O_3$ (372.42): C, 74.18; H, 5.41; N, 7.52. Found: C, 74.21; H, 5.55; N, 7.76.

Ethyl 3-Amino-6-(4-methoxyphenyl)-4-phenylfuro[2,3-*b*] pyridine-2-carboxylate (**3c**)

IR (KBr): $\nu = 3480$, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.48 (s, 3H, CH_3), 4.41 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.09 (s, 2H, -NH_2), 7.18–8.10 (m, 10H, Ar-H); MS: m/z = 388 (M^+). Anal. calcd. for $C_{23}H_{20}N_2O_4$ (388.42): C, 71.12; H, 5.19; N, 7.21. Found: C, 71.22; H, 5.25; N, 7.36.

Ethyl 3-Amino-6-(4-chlorophenyl)-4-phenylfuro[2,3-*b*] pyridine-2-carboxylate (**3d**)

IR (KBr): $\nu = 3480$, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 4.40 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.18 (s, 2H, -NH_2), 7.45–8.15 (m, 10H, Ar-H); MS: m/z = 392 (M^+). Anal. calcd. for $C_{22}H_{17}ClN_2O_3$ (392.83): C, 67.26; H, 4.36; N, 7.13. Found: C, 67.22; H, 4.25; N, 7.36.

Ethyl 3-Amino-6-phenyl-4-p-tolylfuro[2,3-*b*]pyridine-2-carboxylate (**3e**)

IR (KBr): $\nu = 3480$, 3380, 3030, 2990, 1664, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.42 (s, 3H, CH_3), 4.43 (q,

$J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.21 (s, 2H, -NH_2), 7.38–8.11 (m, 10H, Ar-H); MS: m/z = 372 ($\overline{M^+}$). Anal. calcd. for $C_{23}H_{20}N_2O_3$ (372.42): C, 74.18; H, 5.41; N, 7.52. Found: C, 74.22; H, 5.25; N, 7.36.

Ethyl 3-Amino-6-(4-chlorophenyl)-4-p-tolylfuro[2,3-*b*] pyridine-2-carboxylate (**3f**)

IR (KBr): $\nu = 3500$, 3390, 3010, 2940, 1682, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.39 (s, 3H, CH_3), 4.35 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.25 (s, 2H, -NH_2), 7.13–8.19 (m, 9H, Ar-H); MS: m/z = 406 (M^+). Anal. calcd. for $C_{23}H_{19}ClN_2O_3$ (406.86): C, 67.90; H, 4.71; N, 6.89. Found: C, 67.98; H, 4.89; N, 6.76.

Ethyl 3-Amino-4-(4-methoxyphenyl)-6-phenylfuro[2,3-*b*] pyridine-2-carboxylate (**3g**)

IR (KBr): $\nu = 3520$, 3400, 3000, 2980, 1676, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 3.98 (s, 3H, OCH_3), 4.36 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.20 (s, 2H, -NH_2), 7.27–8.24 (m, 10H, Ar-H); MS: m/z = 388 (M^+). Anal. calcd. for $C_{23}H_{20}N_2O_4$ (388.42): C, 71.12; H, 5.19; N, 7.21. Found: C, 71.12; H, 4.99; N, 7.16.

Ethyl 3-Amino-4,6-bis(4-methoxyphenyl)furo[2,3-*b*] pyridine-2-carboxylate (**3h**)

IR (KBr): $\nu = 3510$, 3300, 3020, 2970, 1672, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 3.88 (s, 6H, OCH_3), 4.39 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.19 (s, 2H, -NH_2), 7.26–8.20 (m, 9H, Ar-H); MS: m/z = 418 (M^+). Anal. calcd. for $C_{24}H_{22}N_2O_5$ (418.44): C, 68.89; H, 5.30; N, 6.69. Found: C, 68.99; H, 5.12; N, 6.89.

Ethyl 3-Amino-4-(4-chlorophenyl)-6-phenylfuro[2,3-*b*] pyridine-2-carboxylate (**3i**)

IR (KBr): $\nu = 3500$, 3390, 3010, 2980, 1668, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 4.46 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.25 (s, 2H, -NH_2), 7.21–8.24 (m, 10H,

Ar-H); MS: m/z = 392 (M^+). Anal. calcd. for $C_{22}H_{17}ClN_2O_3$ (392.83): C, 67.26; H, 4.36; N, 7.13. Found: C, 67.22; H, 4.25; N, 7.36.

Ethyl 3-Amino-4-(4-chlorophenyl)-6-p-tolylfuro[2,3-*b*] pyridine-2-carboxylate (**3j**)

IR (KBr): $\nu = 3510$, 3380, 3000, 2940, 1676, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.40 (s, 3H, CH_3), 4.36 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.22 (s, 2H, -NH_2), 7.18–8.21 (m, 9H, Ar-H); MS: m/z = 406 (M^+). Anal. calcd. for $C_{23}H_{19}ClN_2O_3$ (406.86): C, 67.90; H, 4.71; N, 6.89. Found: C, 67.78; H, 4.68; N, 6.95.

Ethyl 3-Amino-4-(furan-2-yl)-6-phenylfuro[2,3-*b*] pyridine-2-carboxylate (**3k**)

IR (KBr): $\nu = 3490$, 3390, 3000, 2950, 1672, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 4.37 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 4.98 (s, 2H, -NH_2), 7.08–8.25 (m, 9H, Ar-H); MS: m/z = 348 (M^+). Anal. calcd. for $C_{20}H_{16}N_2O_4$ (348.35): C, 68.96; H, 4.63; N, 8.04. Found: C, 68.74; H, 4.80; N, 8.12.

Ethyl 3-Amino-4-(furan-2-yl)-6-p-tolylfuro[2,3-*b*] pyridine-2-carboxylate (**3l**)

IR (KBr): $\nu = 3490$, 3370, 3020, 2980, 1668, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 2.44 (s, 3H, CH_3), 4.45 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.15 (s, 2H, -NH_2), 7.05–8.14 (m, 8H, Ar-H); MS: m/z = 362 (M^+). Anal. calcd. for $C_{21}H_{18}N_2O_4$ (362.38): C, 69.60; H, 5.01; N, 7.73. Found: C, 69.42; H, 5.25; N, 7.66.

Ethyl 3-Amino-6-phenyl-4-(thiophen-2-yl) furo[2,3-*b*]pyridine-2-carboxylate (**3m**)

IR (KBr): $\nu = 3490$, 3370, 3020, 2980, 1668, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (t, $J = 7.2$ Hz, 3H, -$CH_2\underline{CH_3}$), 4.41 (q, $J = 6.9$ Hz, 2H, -$\underline{CH_2}CH_3$), 5.07 (s, 2H, -NH_2), 7.10–8.21 (m, 9H, Ar-H); MS: m/z = 362 (M^+). Anal. calcd. for $C_{20}H_{16}N_2O_3S$ (362.42): C, 65.92; H, 4.43; N, 7.69. Found: C, 65.99; H, 4.25; N, 7.66.

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