Synthesis of Pyrazolopyridine 3-Carboxylates by Friedlander Condensation

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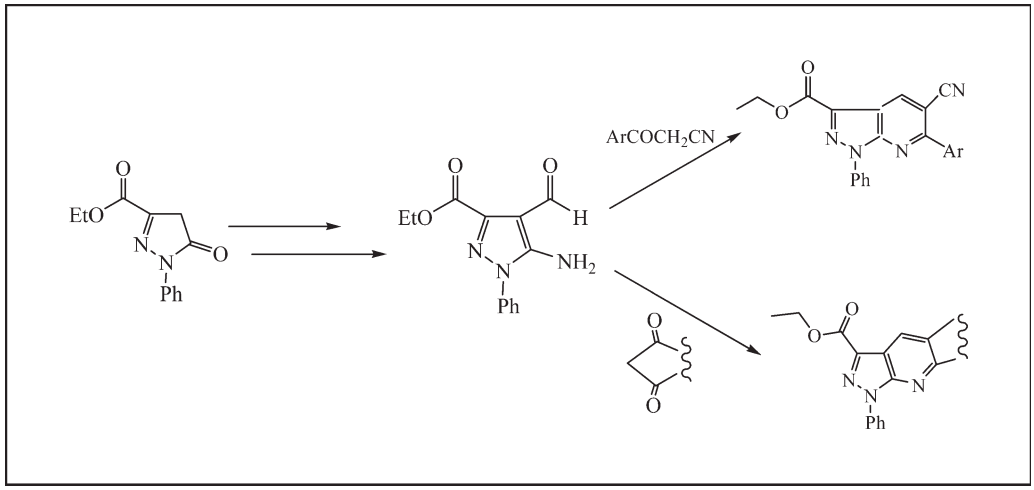

A series of 1,3,6-trisubstituted and 1,3,5,6-tetrasubstituted pyrazolo [3,4-*b*] pyridines **5** have been synthesized by series of reactions on 1-phenyl-3-carboxylate pyrazolone to obtain *o*-aminoaldehyde, which undergo facile condensation with various α-methylene ketones, nitriles, and esters, furnish fused pyridine derivative in good yield.

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INTRODUCTION

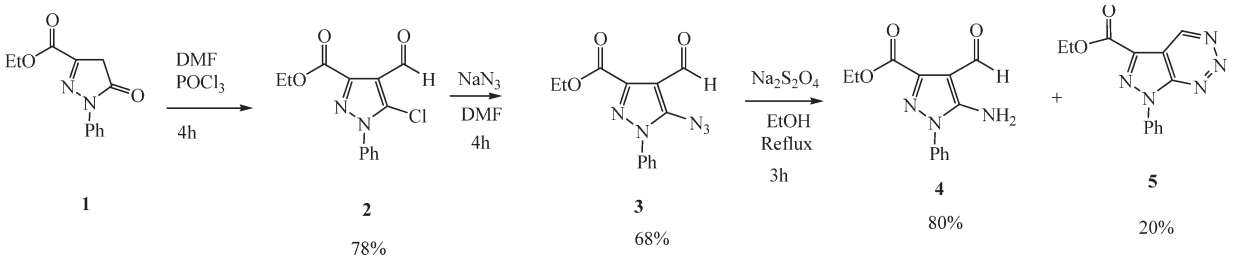
Pyrazolo[3,4-*b*]pyridines as aza-analogues of indazoles are attractive targets in organic synthesis because of their significant biological activities, such as hypoglycemic [1], psychotropic [2], cytotoxic [3], antiviral [4], fungicidal [5], antiasthmatic [6], antiallergic [7], antitumor [8], and antibacterial [9]. These compounds were also used in coronary of neurodegenerative diseases [10,11]. A number of pyrazolo[3,4-*b*]pyridines display interesting anxiolytic activity (*e.g.*, tracazolate), which are potentially biologically active compounds as new inhibitors of xantine oxidases [12]. They have proved to be active against gram-positive and gram-negative bacteria [13] and also as compounds for inhibition of cholesterol formation [14].

o-Aminoaldehydes are the key intermediates for the synthesis of various biologically active heterocycles, *e.g.*, [15,16]. The Friedlander condensation of *o*-aminoaldehyde with ketones furnished required tri/tetra cyclic pyrazolo[3,4-*b*]pyridine. The required starting compound *i.e.*, ethyl 4,5-dihydro-5-oxo-1-phenyl-1*H*-carboxylate **1** is prepared by esterification of ethyl 4,5-dihydro-5-oxo-1-phenyl-1*H*-carboxylicacid [17].

o-Aminoaldehyde **4,** the key starting compound, was obtained by series of reactions including Vilsmeir-Haack formylation of **1** to furnish *o*-chloroaldehyde **2**, which on S_N2 displacement of chloride (Cl^-) by azide ($-N_3$) yield **3** in 68% yield. Compound **3** on reductions with sodium dithionate $Na_2S_2O_4$ yields two products *o*-aminoaldehyde **4** in 80% and triazine-5-carboxylate **5** in 20%. The formation of compound **5** can be rationalized by condensation of carbonyl with electronegative nitrogen of azide.

Compounds **4** and **5** were separated on column and were characterized by spectroscopic and analytical methods (Scheme 1), *e.g.*, IR spectra of **4** and **5** both showed ester carbonyl stretching at 1760 cm^{-1}, whereas only **4** showed doublet at 3451 and 3347 cm^{-1} for NH_2 and 2712 and 1716 $cm^{-1}$for CHO groups. The peaks due to NH_2 and CHO are absent in IR spectra of **5**. The ^{1}H-NMR of **4** and **5** also help lot to distinguish between **4** and **5**. The NH_2 and CHO protons were observed at δ 5.91 and 10.26 in compound **4** and both of these signals

Scheme 1

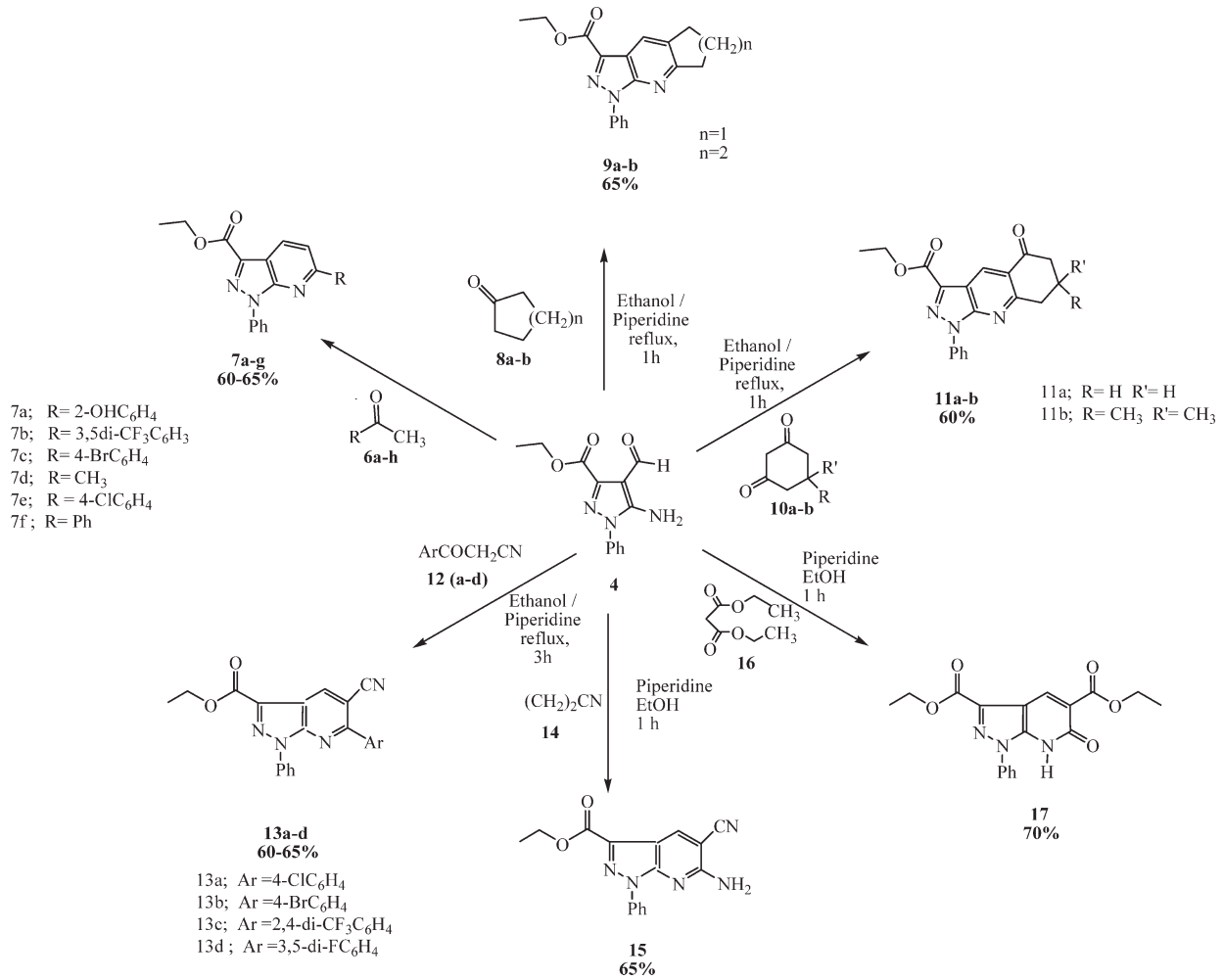


are absent in **5**. While compound **5** showed a sharp singlet at δ 8.31 for C_4H. The elemental analyses were also in agreement with the proposed structures of **4** and **5**.

The novel Friedlander condensation of *o*-aminoaldehyde **4** with α-methylene ketones, nitriles, and esters containing active methylene groups was carried out in the presence of piperidine offered fused pyridines in good yields. Thus, the condensation of aromatic methyl ketones **6** and **4** under ethanol reflux furnishes **7** in 60–65% yields. The cyclic ketones **8** on condensation with **4** yield tricyclic pyridines **9** in 60–65% yield.

Similarly, *o*-aminoaldehyde **4** on condensation with dimedone or cyclohexane 1,2-dione **10** offered **11** in 60% yield. Compound **11** is α-methylene ketones functionality, which has potential to generate new heterocycles (Scheme 2). All the obtained compounds were well characterized by IR, ^{1}H-, ^{13}C-NMR, and mass

Scheme 2



spectroscopy given in the Experimental section. In all above reaction, the ester group remains intact in the product. The reactions reported here provide a versatile method for synthesis of various substituted 3-ethycarboxy pyrazolo[3,4-*b*]pyridines. We have extended Friedlander condensation using nitriles and esters having reactive methylene group to generate libraries of new heterocycles having multifunctional groups. Reactions with reactive methylene such as aroylacetonitrile **12** and malanonitrile **14** with **4** furnished 6-aryl 5-cyanopyrazloyridines **13** and 6-amino-5-cyanopyrazloyridines **15** in 60–65% yield. Another multifunctional heterocycle **17** was obtained by condensation of diethylmalonate with *o*-aminopyrazole **4** (Scheme 2). The IR, ^{1}H-NMR, ^{13}C-NMR, Mass, and elemental analysis confirm all structures of these synthesized compounds.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Schimadzu FFTIR-408 spectrophotometer. ^{1}H, ^{13}C-NMR spectra were recorded on a Varian XL-300 (300 MHz, 75 MHz) spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard, and chemical shifts are expressed in δ (ppm) unit. Elemental analyses were carried out on Hosli CH-Analyzer and are within ±0.3 of the theoretical percentages. All reactions were monitored by thin-layer chromatography carried out on 0.2-mm silica gel (sd Fine Chemicals, 60–120 mesh powder). Common reagent grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

Ethyl-5-chloro-4-formyl-4,5-dihydro-1*H*-pyrazole-3-carboxylate (2). To a solution of ethyl-4,5 dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate **1** (0.1 mol, 23.2 g) in dimethyl formamide (0.5 mol, 37 mL) was added phosphorous oxychloride (0.3 mol, 46 mL) in small portions at 10–15°C with stirring. The reaction mixture was stirred at 65–70°C for 4 h and poured into ice-cold water (900 mL). The precipitated product was filtered by suction, washed with water, and recrystallized. Colorless prism (ethanol), mp. 135–136°C, yield 24.5 g (78%), IR: 3417m, 2720, 1739s, 1671m, 1597w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.34 (t, 3H, J = 6.8 Hz, CH_3), 4.41 (q, 2H, J = 6.8 Hz, OCH_2), 7.54–7.61 (m, 5H, Ar-H), 10.31 (S, 1H, CHO). Anal. Calcd. for $C_{13}H_{11}Cl\ N_2O_3$: C, 56.03; H, 3.98; N, 10.05. Found: C, 56.25; H, 3.70; N, 10.23.

Ethyl-5-azido-4-formyl-4,5-dihydro-1-phenyl-1*H*-pyrazole-3-carboxylate (3). To the solution of ethyl-5-chloro-4-formyl-4,5-dihydro-1*H*-pyrazole-3-carboxylate **2** (27.869 g, 0.1 mol) in dimethylformamide (150 mL), sodium azide (7.15 g, 0.109 mol) was slowly added for 30 min. The reaction mixture was stirred for 4 h (TLC check, toluene/acetone 8:2) and poured in ice-cold water (1000 mL). The precipitated solid was filtered on suction pump and dried to give colorless prism (ethanol), mp. 75–76°C. Yield 19.38 g (68%), IR: 3419m, 3390m, 2164m, 1720s, 1668m, 1597w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.33 (t, J = 6.8 Hz, 3H, CH_3); 4.46 (q, J = 6.8 Hz, 2H, —OCH_2); 7.50–7.60 (m, 5H, Ar-H), 10.26 (s, 1H CHO). Anal. Cacld. for $C_{13}H_{11}N_5O_3$: C, 54.74; H, 3.89; N, 24.55. Found: C, 54.67; H, 3.78; N, 24.38. *m*/*z* (70 eV): 285.

General procedure for the synthesis of ethyl-5-amino-4-formyl-4,5-dihydro-1-phenyl-1*H*-pyrazole-3-carboxylate (4) and ethyl-7-phenyl-7*H*-pyrazolo[3,4-d][1,2,3]triazene-5-carboxylate (5). A mixture of ethyl-5-azido-4-formyl-4,5-dihydro-1-phenyl-1*H*-pyrazole-3-carboxylate (25 g, 0.089 mol) and sodium dithionate (0.1 mol, 17.4 g) in ethanol (275 mL) was refluxed for 3 h (TLC check, toluene/acetone, 8:2). The mixture was then poured into ice-cold water (800 mL). The precipitated solid was filtered by suction, washed with water, and dried. The obtained solid was separated by column chromatography using silica 60–120 mesh powder and eluting with toluene/acetone as 9:1. mp. 183–184°C, yield 18.44 g (80%), pale-yellow-color needles (ethanol) IR: 3451m, 3347m, 2712s, 1716m, 1677s, 1597w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.41 (t, J = 7.2 Hz, 3H, CH_3), 4.49 (q, J = 7.2 Hz, 2H, OCH_2), 5.91 (bs, 2H, exchange with D_2O, NH_2), 7.47–7.48 (m, 5H, Ar-H), 10.26 (s, 1H, CHO). ^{13}C-NMR (75 MHz DMSO-d_6) 15.0, 61.9, 105.6, 125.5, 129.7 (2C'S), 130.6 (2C'S), 137.4, 143.0, 151.4, 162.2, 186.3. Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N,16.21. Found: C, 60.34; H, 5.23; N, 16.46.

Ethyl-7-phenyl-7*H*-pyrazolo[3,4-d][1,2,3]triazene-5-carboxylate (5). Yellow needle (ethanol) mp. 216–217°C, yield 4.61 g (20%), IR: 2980m, 1760s, 1710s, 1610m, 1510s cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.44 (t, J = 6.2 Hz, 3H, CH_3), 4.45 (q, J = 6.2 Hz, 2H, —OCH_2), 7.43–7.48 (m, 5H, Ar-H), 8.31 (s, 1H, CH). Anal. Calcd. for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 57.82; H, 4.20; N, 26.18.

General procedure for the synthesis of 1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxylate (7a–g). A mixture of 4 (0.2 g, 7.0 mmol) and substituted acetophenone 6 (0.12 g, 8.0 mmol) in ethanol (15–20 mL) with catalytic amount of piperedine (0.5 mL) was refluxed for 3 h (TLC check. toluene/acetone, 8:2). The reaction mixture was then cooled to room temperature, and the obtained solid was collected by suction filtration, washed with ethanol, and recrystallized.

Ethyl-6-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazolo-[3,4-b]pyridine-3-carboxylate (7a). Colorless prism (methanol) mp. 140–141°C, yield 1.5 g (60%), IR: 3450m, 1835s, 1730s, 1668m cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.43 (t, J = 6.8 Hz, 3H, CH_3), 4.45 (q, J = 6.8 Hz, 2H, OCH_2), 7.0 (t, J = 7.1 Hz, 2H Ar-H), 7.2 (t, J = 7.1 Hz, 2H, Ar-H), 7.6 (d, 1H, J = 6.8 Hz, Ar-H), 8.0–8.1 (m, 5H, Ar-H), 8.3 (d, J = 6.8 Hz,1H, Ar-H), 11.90 (bs, 1H —OH). ^{13}C-NMR (75 MHz, DMSO-d_6) 15.1, 62.0, 115.2, 118.4, 119.6, 120.4, 122.2, 123.6 (2C), 128.9, 130.3, 130.5 (2C), 132.8, 133.1, 136.3, 138.7, 149.4, 157.9, 158.6, 162.0. Anal. Calcd. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N,11.69. Found: C, 70.24; H, 4.58; N,11.87. *m*/*z* (70 eV): 359 [M + 1].

Ethyl-6-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (7b). Colorless needle (ethanol/water, 8:2), mp. 168–170°C, yield 1.94 g (58%), IR: 3280m, 1710s, 1640w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.42 (t, J = 6.8 Hz, 3H, CH_3), 4.46 (q, 2H, J = 6.8 Hz, —OCH_2), 7.45 (d, J = 8.1 Hz, 2H, Ar-H), 7.56 (d, J = 8.1 Hz, 2H, Ar-H), 8.14 (s, 1H, Ar-H), 8.25 (d, J = 7.6 Hz, 2H, Ar-H), 8.48 (d, J = 7.6 Hz, 2H, Ar-H), 8.70 (s, 1H, Ar-H). Anal. Calcd. for $C_{23}H_{15}F_6N_3O_2$: C, 57.63; H, 3.15; N, 8.77. Found: C, 57.48; H, 3.29; N, 8.84; *m*/*z* (70 eV) = 482 [M + 1, 90%], 481 [M + 1, 60%], 480, 439, 338, 254.

Ethyl-6-(4-bromophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (7c). Colourless needles (ethanol/water, 8:2), mp. 170–172°C, yield 1.76 g (60%), IR: 1760w, 1620m, 1091w cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.50 (t, J = 6.8 Hz, 3H, CH_3), 4.60 (q, J = 6.8 Hz, 2H, OCH_2), 8.31 (dd, J = 8.2 and 2.3 Hz 2H, Ar-H), 7.92 (dd, J = 8.2 and 2.3 Hz, 2H, Ar-H), 7.23–7.7 (m, 5H, Ar-H), 9.01 (d, 1H, J = 8.60 Hz, Ar-H); 9.21 (d, 1H, J = 8.60 Hz Ar-H). Anal. Calcd. for $C_{21}H_{16}BrN_3O_2$: C, 59.73; H, 3.82; N, 9.95. Found C, 59.68; H, 3.79; N, 9.90.

Ethyl-6-methyl-1-phenyl-1*H*-pyrazolo [3,4-*b*]pyridine-3-carboxylate (7d). Colorless needles (ethanol/water, 8:2) mp. 136–137°C, yield 1.21 g (62%), IR: 2350s, 1668m, 1610s, 1540w, 1410w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.41 (t, J = 6.8 Hz, 3H, CH_3), 4.40 (q, J = 6.8 Hz, 2H, CH_2), 2.67 (s, J = 6.6 Hz, 3H, CH_3), 7.22 (t, J = 6.3 Hz, 2H, Ar-H), 7.61 (t, J = 6.3 Hz, 1H, Ar-H), 8.0–8.1 (m, 2H, Ar-H), 8.32 (d, J = 7.3 Hz, 1H, Ar-H), 8.60 (d, J = 7.2 Hz, 1H, Ar-H). Anal. Calcd. for: $C_{16}H_{15}N_3O_2$ Calcd: C, 68.34, H, 5.37, N,14.94. Found: C, 68.33, H, 5.36, N, 14.90.

Ethyl-6-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-b]pyridine-3-carboxylate (7e). Colorless needles (ethanol: water, 8:2) mp. 186–187°C, yield 1.45 g (55%). IR: 2339m, 1668s, 1630w, 1576s cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.70 (t, J = 6.4 Hz, 3H, CH_3), 4.41 (q, J = 6.4 Hz, 2H, OCH_2), 7.23–7.70 (m, 5H, Ar-H), 7.75 (d, J = 8.2 Hz, 2H, Ar-H), 7.99 (d, J = 8.2 Hz, 2H Ar-H), 8.11 (d, J = 8.2 Hz, 1H, Ar-H), 8.32 (d, J = 8.3 Hz, 1H, Ar-H). Anal. Calcd. for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 59.54; H, 3.98; N, 11.32.

Ethyl-1,6 diphenyl-1*H*-pyrazolo [3,4-*b*] pyridine-3-carboxylate (7f). Colorless needles (ethylacetate), mp.176–177°C, yield 1.44 g (60%). IR: 2339m, 1587w cm^{-1} ^{1}H-NMR ($CDCl_3$): δ 1.70 (t, J = 6.4 Hz, 3H, CH_3), 4.45 (q, J = 6.4 Hz, 2H, OCH_2), 7.23–7.70 (m, 10H, Ar-H), 7.75 (d, J = 8.1 Hz, 1H, Ar-H), 8.11 (d, J = 8.1 Hz, 1H, Ar-H). Anal. Calcd. for: $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.26; H, 4.75; N, 12.42.

General procedure for the synthesis of pyrazolo-[4,3-*e*]pyridine-3-carboxylate (9a, b). The mixture of 4 (0.2 g, 7.0 mmol) and aromatic ketones 8 (7.0 mmol) with catalytic amount of piperedine (0.2 mL) was dissolved in ethanol (15 mL). The reaction mixture was then refluxed for 4 h (TLC check, toluene/acetone, 8:2). The reaction mixture was then cooled to room temperature, and the obtained solid was collected by suction filtration, washed with ethanol, and recrystallized to furnish compound 9.

Ethyl-1-phenyl-1,5,6,7-tetrahydrocyclopenta[*b*]pyrazolo [4,3-*e*]pyridine-3-carboxylate (9a). Colorless needles (ethanol/DMF, 5:1), mp.160–161°C, yield 1.39 g (65%). IR: 1740m, 1605s, 1510 w cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.43 (t, 3H, J = 6.8 Hz, CH_3), 2.21 (t, 2H, J = 6.4 Hz, CH_2), 3.21 (t, J = 6.4 Hz, CH_2), 3.45 (t, 2H, J = 6.4 Hz, CH_2), 4.51 (q, 2H, J = 6.8 Hz, OCH_2), 7.17–8.32 (m, 5H, Ar-H), 8.44 (s, 1H, C_4H). m/z (70 eV): 307 (M + 1, 90%). ^{13}C-NMR (75 MHz, DMSO-d_6). 144.2, 160.4, 60.9, 14.1, 110.3,147.8, 134.0, 33.1, 135.5, 165.1, 34.9, 25.3, 139.7, 120.2, 129.4, 126.3, 129.4, 120.2. Anal. Cacld. for $C_{18}H_{16}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.30; H, 5.62; N, 13.60.

Ethyl-1-phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo-[3,4-b] quinoline-3-carboxylate (9b). Colorless needles (ethanol/DMF, 5:1), mp. 163–164°C, yield 1.33 g (62%), IR: 1742w, 1605s, 1510 w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.52 (t, J = 6.4 Hz, 3H, CH_3), 2.10 (t, J = 6.4 Hz, 4H, 2 (CH_2), 2.90 (t, J = 6.4 Hz, 2H, CH_2), 3.01 (t, 2H, J = 6.4 Hz, CH_2), 4.60 (q, J = 7.1 Hz, 2H, OCH_3), 7.5–8.10 (m, 5H, Ar-H), 8.20 (s, 1H. C_4—H). Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.11; H, 5.98; N, 13.11.

General procedure for the synthesis of pyrazolo [3,4-b]quinoline-3-carboxylate (11a, b). The mixture of 4 (0.2 g, 7.0 mmol) and dimedone 10 (7.0 mmol) with catalytic amount of piperedine (0.2 mL) was refluxed in ethanol (15 mL) for 4 h (TLC check). The reaction mixture was then cooled to room temperature, and the obtained solid was collected by suction filtration, washed with ethanol, and recrystallized to afford compound 11.

Ethyl-5,6,7,8-tetrahydro-5-oxo-1-phenyl-1*H*-pyrazolo [3,4-*b*]quinoline-3-carboxylate (11a). Colorless needles (ethanol/DMF, 8:2), mp. 201–202°C, yield 1.31 g (56%). IR: 2990w, 1740s, 1640s, 1620s, 1590w, 1410w cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.40 (t, J = 6.8 Hz, 3H, CH_3), 2.10 (t, 4H, J = 6.3 Hz, $2CH_2$), 2.72 (t, 2H, J = 6.8 Hz, CH_2), 3.24 (t, J = 6.3 Hz, 2H, CH_2), 4.51 (q, 2H, J = 6.8 Hz, CH_2), 7.5–8.20 (m, 5H, Ar-H), 8.90 (s, 1H, Ar-H). m/z (70 eV): 335 (M + 1, 80%). Anal. Calcd. for: $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.11; H, 5.06; N, 12.48.

Ethyl-5,6,7,8-tetrahydro-7,7-dimemehtyl-5-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline-3-carboxylate (11b). Colorless needles (ethanol/DMF, 8:2), mp. 204–206°C, yield 1.40 g (60%), IR: 2980m, 1750m, 1700, 1640, 1410 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.42 (t, J = 6.8 Hz, 3H, CH_3), 2.47 (s, 2H, CH_2), 2.62 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 3.28 (s, 2H, OCH_2), 7.45 (t, 1H, Ar-H), 7.62 (t, J = 7.1 Hz, 2H, Ar-H), 8.21 (d, J= 7.1 Hz 1H, Ar-H), 8.90 (s,1H, C_4—H). m/z (70 eV): 363[M + 1]. ^{13}C-NMR(75 MHz, DMSO-d_6), 144.2, 160.4, 60.9, 14.2, 110.3, 147.8, 135.9, 133.1, 168.1, 52.3, 33.2, 53.2, 196.9,26.7, 26.7, 139.7, 120.2, 129.4, 126.3, 129.3, 120.2. Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.43; H, 5.78; N, 11.52.

General procedure for the synthesis of pyrazolo-[3,4-b]pyridine-3-carboxylate (13a–d). The mixture of **4** (0.2 g, 7.0 mmol), benzoylacetonitrile **12** (7.0 mmol), and catalytic amount of piperedine (0.5 mL) were dissolved in ethanol (15 mL). The reaction mixture was then refluxed for 4 h (TLC check, toluene/acetone, 8:2). The mixture was then cooled to room temperature, and the obtained solid was collected by suction filtration, washed with ethanol, and recrystallized to afford compound **13**.

Ethyl-6-(4-chlorophenyl)-5-cyano-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxylate (13a). Colorless solid (ethanol/DMF, 8:2), mp. 246–247°C, yield 1.74 g (62%), IR: 3000w, 2240w, 1740m, 1680m, 1620s, 1510, 1420w cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.62 (t, 3H, J = 6.8 Hz, CH_3), 4.70 (q, J = 6.8 Hz, 2H, —OCH_2), 7.1–7.82 (m, 5H, ArH), 7.92 (d, J = 6.8 Hz, 2H, CH_2), 8.15 (d, J = 8 Hz, 2H, CH_2), 9.01 (s, 1H, C_4H). ^{13}C-NMR (75 MHz, DMSO-d_6), 110.3, 147.8, 163.9, 108.7, 141.3, 134.4, 144.2, 160.4, 60.9, 14.1, 129.0, 129.4, 132.9, 129.4, 129.0, 139.7, 120.2, 129.4, 126.3, 129.4, 120.2, 117.0. Anal. Calcd. for $C_{22}H_{15}ClN_4O_2$: C, 65.59; H, 3.75; N, 13.91. Found: C, 65.59; H, 3.75; N, 13.91.

Ethyl-6-(4-bromophenyl)-5-cyano-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (13b). Pale-yellow-color solid (ethanol/DMF, 8:2), mp. 261–262°C, yield 1.87 g (55–58%), IR: 2240s, 1780s, 1680w, 1620s, 1510w, 1420w cm^{-1}. ^{1}H-

NMR ($CDCl_3$): δ 1.60 (t, J = 6.74 Hz, 3H, CH_3), 4.70 (q, J = 6.74 Hz, 2H, OCH_2), 7.20–7.80 (m, 5H, Ar-H), 7.92 (d, J= 8.2 Hz, 2H, CH_2), 8.18 (d, J = 8.2 Hz, 2H, CH_2), 9.03 (s, 1H, Ar-H). Anal. Calcd. for $C_{22}H_{15}BrN_4O_2$: C, 59.08; H, 3.38; N,12.53. Found: C, 59.13; H, 3.35; N, 12.48.

Ethyl-6-(2,4-bis(trifluoromethyl)phenyl)-5-cyano-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (13c). Pale-yellow-color solid (ethanol/DMF, 8:2), mp. 190–192°C, yield 2.10 g (60%), IR: 3100s, 2250s, 1710m, 1610m, 1540w, 1410w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.51 (t, 3H, J = 6.8 Hz, CH_3), 4.60 (q, 2H, J = 6.8 Hz, CH_2), 7.58–7.61 (m, 5H, Ar-H), 8.08 (s, 1H, Ar-H), 8.82 (s, 1H, Ar-H), 8.46 (s, 1H, Ar-H), 9.11 (s, 1H, C_4H). Anal. Calcd. for $C_{24}H_{14}F_6N_4O_2$: C, 57.15; H, 2.80; N, 11.11. Found: C, 57.10; H, 2.83; N, 11.08.

Ethyl-5-cyano-6-(3,5-difluorophenyl)-1-phenyl-1*H*-pyrazolo [3,4-*b*] pyridine-3-carboxylate (13d). Colorless needles (ethanol/DMF, 8:2), mp. 204–206°C. Yield 1.64 g (58–60%), IR: 3080w, 2240s, 1745m, 1620s, 1540m, 1420w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.55 (t, J = 6.8 Hz, 3H, CH_3), 4.60 (q, J = 6.8 Hz, 2H, —OCH_2), 7.10 (dd, J = 8.3 and 2.3 Hz, 1H, Ar-H), 7.40 (d, J = 8 Hz, 1H, Ar-H), 7.50 (d, J = 2.3 Hz, 1H, Ar-H), 7.55–7.85 (m, 5H, Ar-H), 9.10 (s, 1H, Ar-H). Anal. Calcd. for $C_{22}H_{14}F_2N_4O_2$: C, 65.35; H, 3.49; N, 13.86. Found: C, 65.31; H, 3.46; N, 13.84.

Ethyl-6-amino-5-cyano-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (15). To the reaction mixture of **4** (0.2 g, 7.0 mmol) and malononitrile **14** (0.05 g, 8.0 mmol) in ethanol (15 mL), catalytic amount of piperedine (0.5 mL) was added. The reaction mixture was refluxed for 4 h (TLC check, toluene/acetone, 8:2) and then cooled to room temperature. The separated solid was filtered by suction to afford colorless needles (ethanol/DMF, 8:2), mp. 206–207°C, yield 1.40 g (65%), IR: 3476w, 2240s, 1610s, 1590w, 1554w cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.55 (t, J = 6.8 Hz, 3H, CH_3), 4.60 (q, J = 6.8 Hz, 2H, OCH_2), 5.40 (bs, 2H, NH_2, D_2O exchange), 7.20–8.10 (m, 5H, Ar-H), 8.6 (s, 1H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 15.0 (2C), 62.1 (2C), 91.9, 108.6, 117.5, 122.8, 128.2, 130.1, 139.1, 140.0, 152.4, 159.8,161.7. Anal. Calcd. for $C_{16}H_{13}N_5O_2$: C, 62.51; H, 4.26; N, 22.79. Found: C, 62.53; H, 4.23; N, 22.75.

Diethyl 6,7-dihydro-6-oxo-1-phenyl-1*H*-pyrazolo [3,4-*b*]pyridine-3,5-dicarboxylate (17). A mixture of **4** (0.2 g, 7.0 mmol) and diethylmalonate **16** (0.14 g, 9.0 mmol) in ethanol (15 mL) with catalytic amount of piperedine (0.5 mL) was refluxed for 4 h (TLC check, toluene/acetone, 8:2). The reaction mixture was cooled at room temperature. The separated solid was filtered by suction to afford pale-yellow solid (ethanol/DMF, 8:2), mp. 142–143°C, yield 1.73 g (70%), IR: 3450w, 1710s, 1674s, 1610s, 1595w cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.20 (t, J = 6.4 Hz, 3H, CH_3), 1.42 (t, J = 6.8 Hz, 3H, CH_3), 4.11 (q, J = 6.3 Hz, 2H, OCH_2), 4.39 (q, J = 6.3 Hz, 2H, —OCH_2); 7.25–8.30 (m, 5H, Ar-H), 8.40 (s, 1H, C_4H); 12.60 (bs, 1H, NH). m/z (70 eV): 354 [M − 1]. ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.1 (2C), 61.0 (2C), 139.7, 120.2, 129.4, 126.3, 129.4, 120.2, 143.4, 97.0, 136.6, 161.2, 120.9, 135.8, 165.0, 160.4. Anal. Calcd. for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.83; H, 4.85; N, 11.80.

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