



Pyrazolopyridines I: Synthesis of Some Pyrazolo[3,4-*b*]pyridine-4-carboxylates

TAHIR MAQBOOL¹, MISBAHUL AIN KHAN¹, MUHAMMAD NAEEM KHAN^{2,*}, MARK C. ELLIOTT³, MUNAWAR ALI MUNAWAR⁴, MUHAMMAD NASRULLAH¹, ABDUL WAHEED BHATTI¹, AREESHA NAZEER⁴ and WHEI-OH LIN⁵

¹Department of Chemistry, The Islamia University of Bahawalpur, Pakistan

²Applied Chemistry Research Center, PCSIR Laboratories Complex, Lahore, Pakistan

³School of Chemistry, Cardiff University, Cardiff, Wales, CF10 3XQ, United Kingdom

⁴Institute of Chemistry, University of The Punjab, Lahore, Pakistan

⁵Instituto de Quimica, Universidade do Grande Rio, Duque de Caxias, RJ, Brasil

*Corresponding author: E-mail: changwani_1@yahoo.com

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A series of ethyl 3-methyl-1-phenyl-6-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylates were prepared by the reaction of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole with various aromatic aldehydes and ethyl pyruvate. The structure elucidation of the prepared compounds was carried out by spectroscopic techniques (mass, IR, ¹H and ¹³C NMR).

Key Words: Pyrazolopyridines, Doebner reaction, Schiff's bases, Ethyl pyruvate.

INTRODUCTION

Fused heterocyclic ring systems containing a pyrazole nucleus are well known for their wide range of biological and medicinal significance¹⁻⁵. For example allopurinol a pyrazolo-pyrimidine, is in use for the treatment of gout⁶. Pyrazolo[3,4-*b*]pyridines have also been evaluated for their diverse biological and pharmacological applications such as antitubercular, antibacterial, antiinflammatory, antipyretic, antileishmanial and protein kinase inhibiting agents⁷⁻¹⁶.

Recently, some pyrazolo[3,4-*b*]pyridines have been evaluated for antichagasic activity to establish a structure activity relationship¹⁷. Also another publication deals with their preparation both with classical and microwave methods¹⁸.

In continuation of our work on the chemistry of pyrazolo[3,4-*b*]pyridines¹⁹, we would now like to report the preparation of various ethyl 1,6-diaryl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylates.

EXPERIMENTAL

The chemicals used were commercially available from Merck or Fluka and were used as such. However when needed were purified using normal techniques. The solvents used were distilled and dried. FTIR spectra were recorded on Bruker Tensor-27. Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. The ¹H and ¹³C NMR spectra were taken on Bruker DPX instrument at 400

MHz. High resolution mass spectra were recorded on a Micromass Q-TOF Micro spectrometer.

Preparation of ethyl 3-methyl-1-phenyl-6-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylates (2a-2n) (Table-1)

General procedure: A mixture of an equimolar amount of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole (1.73 mmol), appropriate aromatic aldehydes (1.73 mmol) and one drop of HCl in ethanol (5 mL) was heated under reflux for 1 h. Ethanol was evaporated, followed by the successive addition of an equimolar amount of ethyl pyruvate and 3 mL of glacial acetic acid. The mixture was further heated for 1.5 h at 100 °C on an oil bath, allowed to cool to room temperature, filtered and dried. The crude compounds were recrystallized from ethanol.

In case of the liquid aldehydes (products **2a**, **2b**, **2c**, **2f**, **2g**, **2k** and **2m**), the Schiff bases were prepared by heating the mixture at 100 °C without a solvent, followed by the same general procedure as described above.

Ethyl 3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2a): Yield: 51 %, m.p. 134 °C; lit.¹⁷ m.p. 123 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2930 (C-H); 1734 (C=O). ¹H NMR (CDCl₃) δ : 1.55 (t, 3H, CH₃CH₂, *J* = 7.15 Hz), 2.80 (s, 3H, CH₃), 4.55 (q, 2H, CH₃CH₂, *J* = 7.16 Hz), 8.15 (s, 1H, H-5), 7.32-8.39 (m, 10H, ArH), ¹³C NMR (CDCl₃): δ : 4.34 (CH₃CH₂), 16.45 (CCH₃), 62.14 (CH₂), 112.01, 115.21, 121.30, 125.77, 127.55, 128.94, 129.02, 129.90, 134.26,

138.30, 139.35, 142.58, 152.09, 156.62, 165.69 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₂₀N₃O₂) [M + H]⁺: 358.1556; found (%): 358.1553.

Ethyl 6-(2'-chlorophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2b): Yield: 33 %, m.p. 125 °C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3020-2960 (C-H); 1730 (C=O); 1572 (C=C) ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.15 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.12 Hz), 7.95 (s, 1H, H-5), 7.21-8.25 (m, 9H, ArH), ¹³C NMR (CDCl₃) δ : 14.29 (CH₃CH₂), 16.42 (CCH₃), 62.15 (CH₂), 112.00, 119.29, 121.36, 125.92, 127.11, 129.06, 130.19, 130.42, 131.97, 132.62, 133.54, 138.43, 139.17, 142.63, 151.63, 156.34, 165.48 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₁₉N₃O₂Cl) [M + H]⁺: 392.1166; found (%): 394.1150.

Ethyl 6-(3'-chlorophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2c): Yield: 48 %, m.p. 146 °C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2930 (C-H); 1732 (C=O); 1596 (C=C) ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.18 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.16 Hz), 8.05 (s, 1H, H-5), 7.20-8.24 (m, 9H, ArH) ¹³C NMR (CDCl₃) δ : 14.34 (CH₃CH₂), 16.4 (CCH₃), 62.26 (CH₂), 112.37, 115.05, 121.36, 125.63, 125.95, 127.57, 129.07, 129.81, 130.16, 134.47, 134.97, 139.16, 140.06, 142.6, 151.8, 155.00, 165.46 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₁₉N₃O₂Cl) [M + H]⁺: 392.1166; found (%): 394.1152.

Ethyl 6-(4'-chlorophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2d): Yield: 45 %, m.p. 127 °C. lit.¹⁷ m.p. 123 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2930 (C-H); 1732 (C=O); 1596 (C=C) ¹H NMR (CDCl₃) δ : 1.44 (t, 3H, CH₃CH₂, J = 7.12 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.15 Hz), 7.95 (s, 1H, H-5), 7.20-8.23 (m, 9H, ArH), ¹³C NMR (CDCl₃) δ : 14.33 (CH₃CH₂), 16.65 (CCH₃), 62.23 (CH₂), 112.13, 114.86, 121.36, 125.91, 128.76, 129.13, 129.04, 129.13, 134.43, 136.08, 136.69, 139.20, 142.64, 151.95, 155.31, 165.55 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₁₉N₃O₂Cl) [M + H]⁺: 392.1166; found (%): 394.1212.

Ethyl 6-(2'-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2e): Yield: 44 %, m.p. 126 °C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2920 (C-H); 1731 (C=O); 1592 (C=C) ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.18 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.14 Hz), 8.15 (s, 1H, H-5), 6.95-8.25 (m, 9H, ArH), 3.80 (s, 3H, -OCH₃) ¹³C NMR (CDCl₃) δ : 14.30 (CH₃CH₂), 16.41 (CCH₃), 55.71 (OCH₃), 61.93 (CH₂), 111.44, 111.59, 120.01, 121.18, 121.24, 125.62, 128.29, 128.99, 130.84, 131.63, 132.99, 139.47, 142.46, 151.93, 155.89, 157.51, 165.99 (C=O). HRMS (ESI): calcd. (%) for (C₂₃H₂₂N₃O₃) [M + H]⁺: 388.1661; found (%): 388.1643

Ethyl 6-(3'-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2f): Yield: 48 %, m.p. 96 °C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3030-2940 (C-H); 1715 (C=O); 1594 (C=C) ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.13 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.15 Hz), 8.05 (s, 1H, H-5), 6.95-8.27 (m, 9H, ArH), 3.80 (s, 3H, OCH₃), ¹³C NMR (CDCl₃) δ : 14.33 (CH₃CH₂), 16.44 (CCH₃), 62.15 (CH₂), 55.40 (OCH₃), 112.11, 112.98, 115.30, 115.47, 119.99, 121.29, 125.77, 128.98, 129.93, 134.24, 139.33,

139.74, 142.59, 151.98, 156.32, 160.08, 165.67 (C=O). HRMS (ESI): calcd. (%) for (C₂₃H₂₂N₃O₃) [M + H]⁺: 388.1661; found (%): 388.1660.

Ethyl 6-(4'-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2g): Yield: 37 %, m.p. 120 °C. lit.¹⁷ m.p. 122 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2930 (C-H); 1733 (C=O); 1591 (C=C) ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.12 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.14 Hz), 7.95 (s, 1H, H-5), 6.94-8.26 (m, 9H, ArH), 3.80 (s, 3H, OCH₃) ¹³C NMR (CDCl₃) δ : 14.33 (CH₃CH₂), 16.44 (CCH₃), 55.44 (OCH₃), 62.08 (CH₂), 111.46, 114.27, 114.64, 121.27, 125.66, 128.92, 128.98, 130.83, 134.10, 139.41, 142.5, 152.11, 156.29, 161.19, 165.79 (C=O). HRMS (ESI): calcd. (%) for (C₂₃H₂₂N₃O₃) [M + H]⁺: 388.1661; found (%): 388.1667.

Ethyl 3-methyl-6-(2'-nitrophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2h): Yield: 49 %, m.p. 134 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2930 (C-H); 1709 (C=O); 1596 (C=C); 1528, 1343 (NO₂). ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.13 Hz), 2.70 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.16 Hz), 7.85 (s, 1H, H-5), 7.19-8.00 (m, 9H, ArH). ¹³C NMR (CDCl₃) δ : 14.30 (CH₃CH₂), 16.44 (CCH₃), 62.32 (CH₂), 112.53, 116.91, 121.65, 124.64, 126.31, 129.09, 129.83, 131.49, 132.32, 134.19, 134.79, 139.66, 142.67, 149.78, 151.26, 154.17, 165.16 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₁₉N₄O₄) [M + H]⁺: 403.1406; found (%): 403.1401.

Ethyl 3-methyl-6-(3'-nitrophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2i): Yield: 35 %, m.p. 165 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2930 (C-H); 1735 (C=O); 1594 (C=C); 1526, 1347 (NO₂). ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.16 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.16 Hz), 8.05 (s, 1H, H-5), 7.24-8.90 (m, 9H, ArH). ¹³C NMR (CDCl₃) δ : 14.35 (CH₃CH₂), 16.42 (CCH₃), 62.43 (CH₂), 112.81, 114.82, 121.38, 122.29, 124.34, 126.16, 129.13, 129.97, 133.26, 134.89, 139.01, 139.95, 142.76, 148.82, 151.52, 153.70, 165.25 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₁₉N₄O₄) [M + H]⁺: 403.1406; found (%): 403.1420

Ethyl 3-methyl-6-(4'-nitrophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2j): Yield: 52 %, m.p. 144 °C. lit.¹⁷ m.p. 138; IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2950 (C-H); 1734 (C=O); 1594 (C=C); 1501, 1347 (NO₂). ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.18 Hz), 2.70 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.15 Hz), 8.10 (s, 1H, H-5), 7.25-8.30 (m, 9H, ArH) ¹³C NMR (CDCl₃) δ : 14.34 (CH₃CH₂), 16.44 (CCH₃), 62.43 (CH₂), 112.87, 115.35, 121.38, 124.12, 126.18, 128.27, 129.12, 134.76, 139.01, 142.76, 144.07, 148.51, 151.85, 153.69, 165.22 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₁₉N₄O₄) [M + H]⁺: 403.1406; found (%): 403.1392.

Ethyl 6-(2'-bromophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (2k): Yield: 35.02 %, m.p. 122 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2920 (C-H); 1731 (C=O); 1572 (C=C) ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, J = 7.15 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, J = 7.17 Hz), 7.95 (s, 1H, H-5), 7.20-8.25 (m, 9H, ArH), ¹³C NMR (CDCl₃) δ : 14.29 (CH₃CH₂), 16.42 (CCH₃), 62.16 (CH₂), 112.01, 119.22, 121.42, 122.05, 122.52, 125.95, 127.64,

127.85, 129.06, 129.80, 130.53, 132.88, 133.50, 133.53, 139.72, 140.38, 142.64, 151.49, 157.67, 165.45 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₁₉N₃O₂Br) [M + H]⁺: 436.0661; found (%): 438.0675.

Ethyl 6-(4'-bromophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2l): Yield: 28 %, m.p. 126 °C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3040-2920 (C-H); 1723 (C=O); 1575 (C=C). ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, *J* = 7.16 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, *J* = 7.12 Hz), 7.25-8.25 (m, 10H, ArH), ¹³C NMR (CDCl₃) δ : 14.33 (CH₃CH₂), 16.42 (CCH₃), 62.24 (CH₂), 112.20, 114.83, 121.37, 124.50, 125.92, 129.05, 132.11, 134.48, 137.19, 139.20, 142.65, 151.98, 155.39, 165.54 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₁₉N₃O₂Br) [M + H]⁺: 436.0677; found (%): 438.0729.

Ethyl 6-(2'-hydroxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2m): Yield: 46 %, m.p. 138 °C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3020-2920 (C-H); 1714 (C=O); 1595 (C=C); 3370(OH). ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, *J* = 7.17 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, *J* = 7.16 Hz), 8.15 (s, 1H, H-5), 6.85-7.90 (m, 9H, ArH), 13.1 (br.s, 1H, OH), ¹³C NMR (CDCl₃): δ 14.32 (CH₃CH₂), 16.29 (CCH₃), 62.42 (CH₂), 111.67, 114.25, 118.66, 118.68, 119.43, 122.71, 127.33, 127.59, 129.56, 129.54, 132.51, 135.31, 138.16, 143.28, 148.84, 157.01, 159.51, 165.14 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₂₀N₃O₃) [M + H]⁺: 374.1505; found (%): 374.1520.

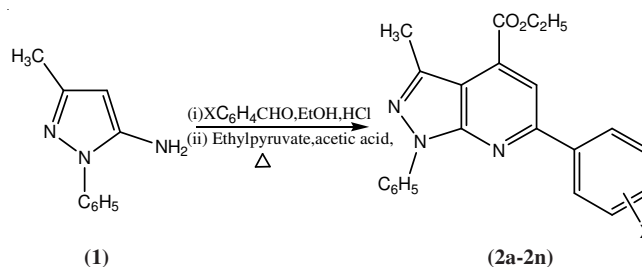
Ethyl 6-(3'-hydroxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2n): Yield: 42 %, m.p. 142 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): 3020-2920 (C-H); 1733 (C=O); 1596 (C=C); 3380 (OH). ¹H NMR (CDCl₃) δ : 1.45 (t, 3H, CH₃CH₂, *J* = 7.22 Hz), 2.75 (s, 3H, CH₃), 4.45 (q, 2H, CH₃CH₂, *J* = 7.19 Hz), 8.0 (s, 1H, H-5), 7.25-8.25 (m, 9H, ArH), 9.9 (br.s, 1H, OH). ¹³C NMR (CDCl₃) δ : 14.33 (CH₃CH₂), 16.44 (CCH₃), 62.15 (CH₂), 112.11, 112.98, 115.30, 115.47, 119.99, 121.29, 125.77, 128.98, 129.93, 134.24, 139.33, 139.74, 142.59, 151.98, 156.32, 160.08, 165.67 (C=O). HRMS (ESI): calcd. (%) for (C₂₂H₂₀N₃O₃) [M + H]⁺: 374.1505; found (%): 374.1499.

RESULTS AND DISCUSSION

Ethyl 3-methyl-1-phenyl-6-aryl-1H-pyrazolo[3,4-*b*]pyridine-4-carboxylates (**2a-2n**) were prepared as per **Scheme-I** from 5-amino-3-methyl-1-phenyl-1H-pyrazole²⁰, aromatic aldehydes and ethyl pyruvate. 5-Aminopyrazole was made to react with various aromatic aldehydes to obtain respective Schiff's bases which were, without isolation, subjected to condensation with ethyl pyruvate to give ethyl 3-methyl-1-phenyl-6-aryl-1H-pyrazolo[3,4-*b*]pyridine-4-carboxylates (**2a-2n**). The yields of the recrystallized products are in the range of 28-51 %; the crude yields are although much higher. No attempts, at this stage, were made to optimize them. Products (**2a-2n**) (Table-1) obtained as fine crystals, all are stable compounds at room temperature and were characterized by IR, ¹H, ¹³C NMR spectra and high resolution mass spectrometry.

Spectral characterization of synthesized compounds:

In the IR spectra the characteristic absorption band in the range



Scheme-I

Compound	X	Yield (%)	m.p. (°C)
2a	H	51	134*
2b	2-Cl	33	125
2c	3-Cl	48	146
2d	4-Cl	45	127**
2e	2-OCH ₃	44	126
2f	3-OCH ₃	48	96
2g	4-OCH ₃	37	120 ⁺
2h	2-NO ₂	49	134
2i	3-NO ₂	35	165
2j	4-NO ₂	52	144 ⁺⁺
2k	2-Br	35	122
2l	4-Br	28	126
2m	2-OH	46	138
2n	3-OH	42	142

*lit.¹⁷ m.p. 123; **lit.¹⁷ m.p. 123; ⁺lit.¹⁷ m.p. 122; ⁺⁺lit.¹⁷ m.p. 138

of 1735-1709 cm⁻¹ was due to C=O group of the ester at 4th position. In the ¹H NMR spectra, the ester group signals appeared as typical triplets and quartets at 1.45 and 4.45 ppm, respectively with *J* value of around 7.14 Hz. The H-5 of the pyridine ring showed a neat singlet in the range of 6.85-8.15 ppm. The singlet at 2.70-2.75 ppm was due to methyl group on the pyrazole ring while the rest of the aromatic protons signals appeared between δ 6.85-8.90 ppm. In all the ¹³C NMR spectra the carbonyl carbon of the ester at 4 position gave a discrete signal in the range of 165.14-165.79 ppm. High resolution mass spectrometry results also confirmed the structures of the prepared compounds.

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