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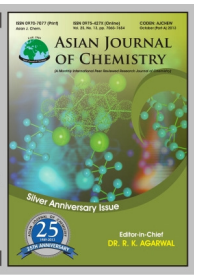

Pyrazolopyridines I: Synthesis of Some Pyrazolo[3,4-*b*]pyridine-4-carboxylates

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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, ^{1}H and ^{13}C 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 significance[1-5]. For example allopurinol a pyrazolopyrimidine, is in use for the treatment of gout[6]. Pyrazolo[3,4-*b*]pyridines have also been evaluated for their diverse biological and pharmacological applications such as antitubercular, antibacterial, antiinflammatory, antipyretic, antileishminial and protein kinase inhibiting agents[7-16].

Recently, some pyrazolo[3,4-*b*]pyridines have been evaluated for antichagasic activity to establish a structure activity relationship[17]. Also another publication deals with their preparation both with classical and microwave methods[18].

In continuation of our work on the chemistry of pyrazolo-[3,4-*b*]pyridines[19], 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 ^{1}H and ^{13}C 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 ºC 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 ºC 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 ºC; lit.[17] m.p. 123 ºC; IR (KBr, ν_{max}, cm^{-1}): 3040-2930 (C-H); 1734 (C=O). ^{1}H NMR ($CDCl_3$) δ: 1.55 (t, 3H, CH_3CH_2, J = 7.15 Hz), 2.80 (s, 3H, CH_3), 4.55 (q, 2H, CH_3CH_2, J = 7.16 Hz), 8.15 (s, 1H, H-5), 7.32-8.39 (m, 10H, ArH), ^{13}C NMR ($CDCl_3$): δ: 4.34 (CH_3CH_2), 16.45 (CCH_3), 62.14 (CH_2), 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 ($C_{22}H_{20}N_3O_2$) $[M + H]^+$: 358.1556; found (%): 358.1553.

Ethyl 6-(2'-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2b): Yield: 33 %, m.p. 125 ºC, IR (KBr, ν_{max}, cm^{-1}): 3020-2960 (C-H); 1730 (C=O); 1572 (C=C) ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, J = 7.15 Hz), 2.75(s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.12 Hz), 7.95 (s, 1H, H-5), 7.21-8.25 (m, 9H, ArH), ^{13}C NMR ($CDCl_3$) δ: 14.29 (CH_3CH_2), 16.42 (CCH_3), 62.15 (CH_2), 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 ($C_{22}H_{19}N_3O_2Cl$) $[M + H]^+$: 392.1166; found (%): 394.1150.

Ethyl 6-(3'-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2c): Yield: 48 %, m.p. 146 ºC, IR (KBr, ν_{max}, cm^{-1}): 3040-2930 (C-H); 1732 (C=O); 1596 (C=C) ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, J = 7.18 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.16 Hz), 8.05 (s, 1H, H-5), 7.20-8.24 (m, 9H, ArH) ^{13}C NMR ($CDCl_3$): δ 14.34 (CH_3CH_2), 16.4 (CCH_3), 62.26 (CH_2), 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 ($C_{22}H_{19}N_3O_2Cl$) $[M + H]^+$: 392.1166; found (%): 394.1152.

Ethyl 6-(4'-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2d): Yield: 45 %, m.p. 127 ºC. lit.[17] m.p. 123 ºC; IR (KBr, ν_{max}, cm^{-1}): 3040-2930 (C-H); 1732 (C=O); 1596 (C=C) ^1H NMR ($CDCl_3$) δ: 1.44 (t, 3H, CH_3CH_2, J = 7.12 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.15 Hz), 7.95 (s, 1H, H-5), 7.20-8.23 (m, 9H, ArH), ^{13}C NMR ($CDCl_3$): δ 14.33 (CH_3CH_2), 16.65 (CCH_3), 62.23 (CH_2), 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 ($C_{22}H_{19}N_3O_2Cl$) $[M + H]^+$: 392.1166; found (%): 394.1212.

Ethyl 6-(2'-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2e): Yield: 44 %, m.p. 126 ºC, IR (KBr, ν_{max}, cm^{-1}): 3040-2920 (C-H); 1731 (C=O); 1592 (C=C). ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, J = 7.18 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.14 Hz), 8.15 (s, 1H, H-5), 6.95-8.25 (m, 9H, ArH), 3.80 (s, 3H, -OCH_3) ^{13}C NMR ($CDCl_3$) δ: 14.30 (CH_3CH_2), 16.41 (CCH_3), 55.71 (OCH_3), 61.93 (CH_2), 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 ($C_{23}H_{22}N_3O_3$) $[M + H]^+$: 388.1661; found (%): 388.1643

Ethyl 6-(3'-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2f): Yield: 48 %, m.p. 96 ºC, IR (KBr, ν_{max}, cm^{-1}): 3030-2940 (C-H); 1715 (C=O); 1594 (C=C). ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, J = 7.13 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.15 Hz), 8.05 (s, 1H, H-5), 6.95-8.27 (m, 9H, ArH), 3.80 (s, 3H, OCH_3), ^{13}C NMR ($CDCl_3$) δ: 14.33 (CH_3CH_2), 16.44 (CCH_3), 62.15(CH_2), 55.40 (OCH_3), 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 ($C_{23}H_{22}N_3O_3$) $[M + H]^+$: 388.1661; found (%): 388.1660.

Ethyl 6-(4'-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2g): Yield: 37 %, m.p. 120 ºC. lit.[17] m.p. 122 ºC; IR (KBr, ν_{max}, cm^{-1}): 3040-2930 (C-H); 1733 (C=O); 1591 (C=C). ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, J = 7.12 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.14 Hz), 7.95 (s, 1H, H-5), 6.94-8.26 (m, 9H, ArH), 3.80 (s, 3H, OCH_3) ^{13}C NMR ($CDCl_3$): δ 14.33 (CH_3CH_2), 16.44 (CCH_3), 55.44 (OCH_3), 62.08 (CH_2), 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 ($C_{23}H_{22}N_3O_3$) $[M + H]^+$: 388.1661; found (%): 388.1667.

Ethyl 3-methyl-6-(2'-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2h): Yield: 49 %, m.p. 134 ºC. IR (KBr, ν_{max}, cm^{-1}): 3040-2930 (C-H); 1709 (C=O); 1596 (C=C); 1528, 1343 (NO_2). ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, J = 7.13 Hz), 2.70 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.16 Hz), 7.85 (s, 1H, H-5), 7.19-8.00 (m, 9H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.30 (CH_3CH_2), 16.44 (CCH_3), 62.32 (CH_2), 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 ($C_{22}H_{19}N_4O_4$) $[M + H]^+$: 403.1406; found (%): 403.1401.

Ethyl 3-methyl-6-(3'-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2i): Yield: 35 %, m.p. 165 ºC. IR (KBr, ν_{max}, cm^{-1}): 3040-2930 (C-H); 1735 (C=O); 1594 (C=C); 1526, 1347 (NO_2). ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, J = 7.16 Hz), 2.75(s,3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.16 Hz), 8.05 (s, 1H, H-5), 7.24-8.90 (m, 9H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.35(CH_3CH_2), 16.42 (CCH_3), 62.43 (CH_2), 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 ($C_{22}H_{19}N_4O_4$) $[M + H]^+$: 403.1406; found (%): 403.1420

Ethyl 3-methyl-6-(4'-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2j): Yield: 52 %, m.p. 144 ºC. lit.[17] m.p. 138; IR (KBr, ν_{max}, cm^{-1}): 3040-2950 (C-H); 1734 (C=O); 1594 (C=C); 1501, 1347 (NO_2). ^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, J = 7.18 Hz), 2.70 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.15 Hz), 8.10(s, 1H, H-5), 7.25-8.30 (m, 9H, ArH) ^{13}C NMR ($CDCl_3$) δ: 14.34 (CH_3CH_2), 16.44 (CCH_3), 62.43 (CH_2), 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 ($C_{22}H_{19}N_4O_4$) $[M + H]^+$: 403.1406; found (%): 403.1392.

Ethyl 6-(2'-bromophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2k): Yield: 35.02 %, m.p. 122 ºC. IR (Kbr, ν_{max}, cm^{-1}): 3040-2920 (C-H); 1731 (C=O); 1572 (C=C). ^1H NMR ($CDCl_3$) δ: 1.45(t, 3H, CH_3CH_2, J = 7.15 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, J = 7.17 Hz), 7.95 (s, 1H, H-5), 7.20-8.25 (m, 9H, ArH), ^{13}C NMR ($CDCl_3$) δ: 14.29 (CH_3CH_2), 16.42 (CCH_3), 62.16 (CH_2), 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 ($C_{22}H_{19}N_3O_2Br$) [M + H]$^+$: 436.0661; found (%): 438.0675.

Ethyl 6-(4'-bromophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2l): Yield: 28 %, m.p. 126 ºC, IR (KBr, ν_{max}, cm^{-1}): 3040-2920 (C-H); 1723 (C=O); 1575 (C=C). ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, *J* = 7.16 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, *J* = 7.12 Hz), 7.25-8.25 (m, 10H, ArH), ^{13}C NMR ($CDCl_3$) δ: 14.33 (CH_3CH_2), 16.42 (CCH_3), 62.24 (CH_2), 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 ($C_{22}H_{19}N_3O_2Br$) [M + H]$^+$: 436.0677; found (%): 438.0729.

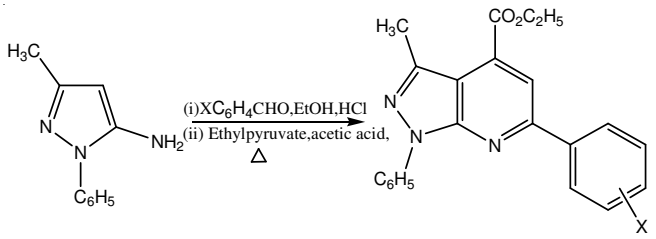
Ethyl 6-(2'-hydroxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2m): Yield: 46 %, m.p. 138 ºC, IR (KBr, ν_{max}, cm^{-1}): 3020-2920 (C-H); 1714 (C=O); 1595 (C=C); 3370(OH). ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, *J* = 7.17 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, *J* = 7.16 Hz), 8.15 (s, 1H, H-5), 6.85-7.90 (m, 9H, ArH), 13.1 (br.s, 1H, OH), ^{13}C NMR ($CDCl_3$): δ 14.32 (CH_3CH_2), 16.29 (CCH_3), 62.42 (CH_2), 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 ($C_{22}H_{20}N_3O_3$) [M + H]$^+$: 374.1505; found (%): 374.1520.

Ethyl 6-(3'-hydroxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (2n): Yield: 42 %, m.p. 142 ºC. IR (KBr, ν_{max}, cm^{-1}): 3020-2920 (C-H); 1733 (C=O); 1596 (C=C); 3380 (OH). ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_3CH_2, *J* = 7.22 Hz), 2.75 (s, 3H, CH_3), 4.45 (q, 2H, CH_3CH_2, *J* = 7.19 Hz), 8.0 (s, 1H, H-5), 7.25-8.25 (m, 9H, ArH), 9.9 (br.s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 14.33 (CH_3CH_2), 16.44 (CCH_3), 62.15 (CH_2), 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 ($C_{22}H_{20}N_3O_3$) [M + H]$^+$: 374.1505; found (%): 374.1499.

RESULTS AND DISCUSSION

Ethyl 3-methyl-1-phenyl-6-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylates (**2a-2n**) were prepared as per **Scheme-I** from 5-amino-3-methyl-1-phenyl-1*H*-pyrazole[20], 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-1*H*-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, ^{1}H, ^{13}C NMR spectra and high resolution mass spectrometry.

Spectral characterization of synthesized compounds: In the IR spectra the characteristic absorption band in the range of 1735-1709 cm^{-1} was due to C=O group of the ester at 4th position. In the ^{1}H 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 ^{13}C 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.



(1) **(2a-2n)**

Scheme-I

TABLE-1
ETHYL 3-METHYL-1-PHENYL-6-ARYL-1*H*-PYRAZOLO[3,4-*b*]PYRIDINE-4-CARBOXYLATES (**2a-2n**)

Compound	X	Yield (%)	m.p. (ºC)
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

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