Synthesis of Pyrazolo-Annelated Heterocyclic Ring Compounds Such As Pyrazolo[3,4-*b*]pyridines and Pyrazolo[4',3':5,6]-pyrido[2,3-*d*]pyrimidines

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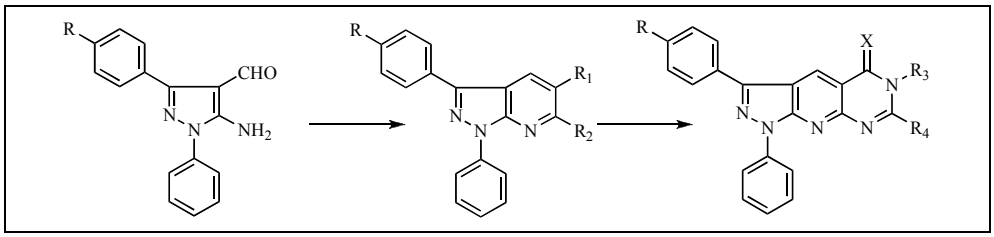

A series of pyrazolo[3,4-*b*]pyridines has been synthesized by *Friedländer* condensation of 5-amino-pyrazole-4-carbaldehyde **1** with active methylene compounds in basic medium. Pyrazolo[4'3':5,6]pyrido-[2,3-*d*]pyrimidines have been synthesized from pyrazolo[3,4-*b*]pyridines using substituted urea and acetic anhydride.

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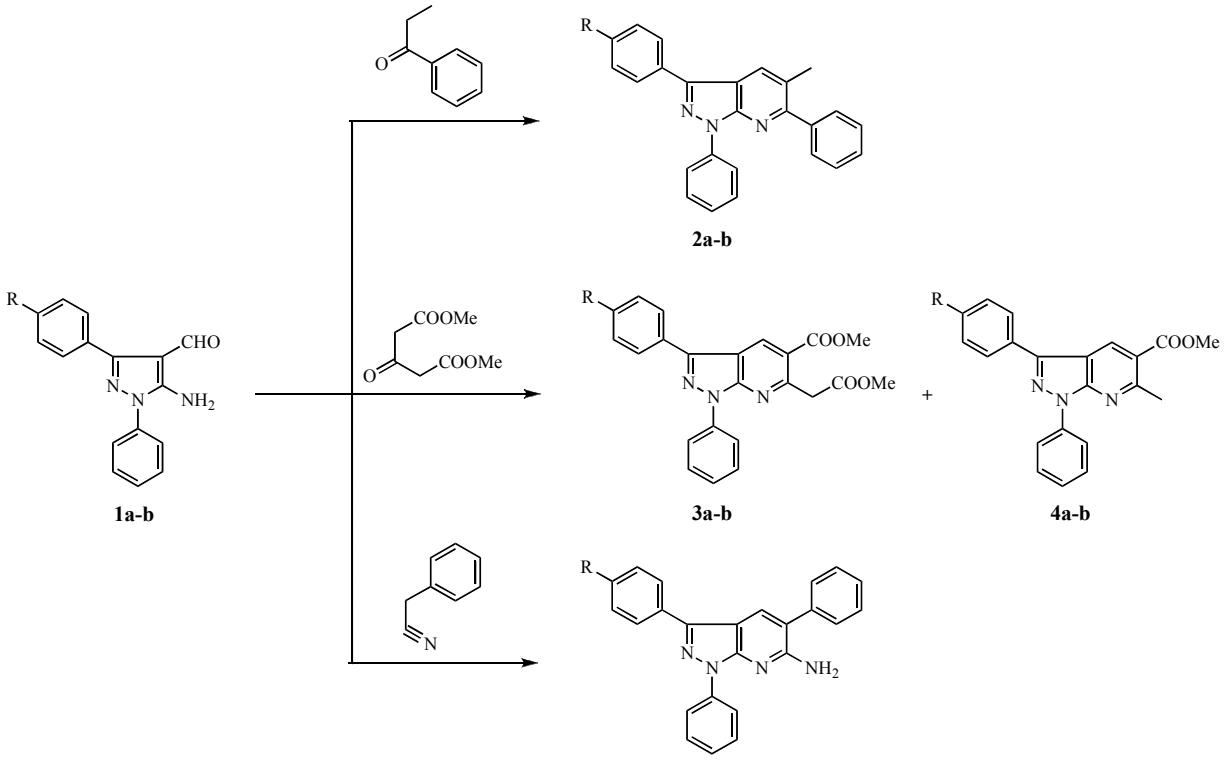
Pyrazolo-annelated heterocycles have demonstrated wide spectrum of agriculture and pharmacological activities [1,2]. We have extensively studied two major classes of pyrazolo-annelated heterocycles which include pyrazolo[3,4-*b*]pyridines and pyrazolo[4',3':5,6]pyrido-[2,3-*d*]pyrimidines. Pyrazolo[3,4-*b*]pyridines are promising candidates in organic synthesis due to their significant medicinal activities, such as diagnosis of brain disorders [3], treatment of coronary heart disease [4], viral diseases [5], central nervous system diseases [6] and show pharmacological efficacy [7]. Pyrazolopyridopyrimidines showed wide spectrum applications such as anticonvulsant agents [8], colorants [9], spectrochemical absorption agents [9], heat/moisture resistant agents [10] thermal transfer printing agent [10], photographic couplers [11]. We have recently reported [12] the use of 5-aminopyrazole-4-carbaldehyde **1** as a key component for the synthesis of fused heterocycles which prompted us to evaluate its potential applications in the preparation of various pyrazolo-annelated heterocycles, namely, pyrazolo[3,4-*b*]pyridine and pyrazolopyridopyrimidine derivatives.

The *Friedländer* condensation of 5-aminopyrazole-4-carbaldehyde **1** with propiophenone in refluxing ethanolic potassium hydroxide solution afforded 3-(4-aryl)-5-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine derivatives **2**. Analog condensation of **1** with dimethyl 1,3-acetonedicarboxylate yielded mixtures of compounds **3** and **4**. This mixture of compound **3** and **4** was separated by column chromatography using toluene/hexane as the eluent. Structures of **3a** and **4a** were confirmed by ^{1}H nmr which indicated that **3a** showed two methoxy singlets at 3.79 and 3.89 ppm together with singlet of methylene at 4.48 ppm, whereas **4a** showed one methyl singlet at 3.01 ppm due to the decarboxylation of CO_2CH_3 group at position 6. All other signals of aromatic protons are nearly identical. Similarly, the structures of bromo derivatives **3b** and **4b** were confirmed.

Cyclocondensation of compound **1** with methylene active nitriles such as phenylacetonitrile was carried out using strong base such as sodium ethoxide in ethanol to furnish 3-(4-halophenyl)-1,5-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-amine derivatives **5**, (Scheme 1) while piperidine was used as base for the condensation with malononitrile and cyanoacetamide in ethanol which gave 6-amino-3-(4-halophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile derivatives **6**, and 6-amino-3-(4-halophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbox-amide derivatives **7**, respectively (Scheme 2). Various synthetic methodologies using ortho-aminocarbonitriles and ortho-aminocarboxamides as starting materials for the synthesis of pendant and fused heterocycles have been extensively studied [13-22], which prompted us to evaluate the synthetic utility of compounds **6** and compound **7** for the design and synthesis of novel fused heterocycles.

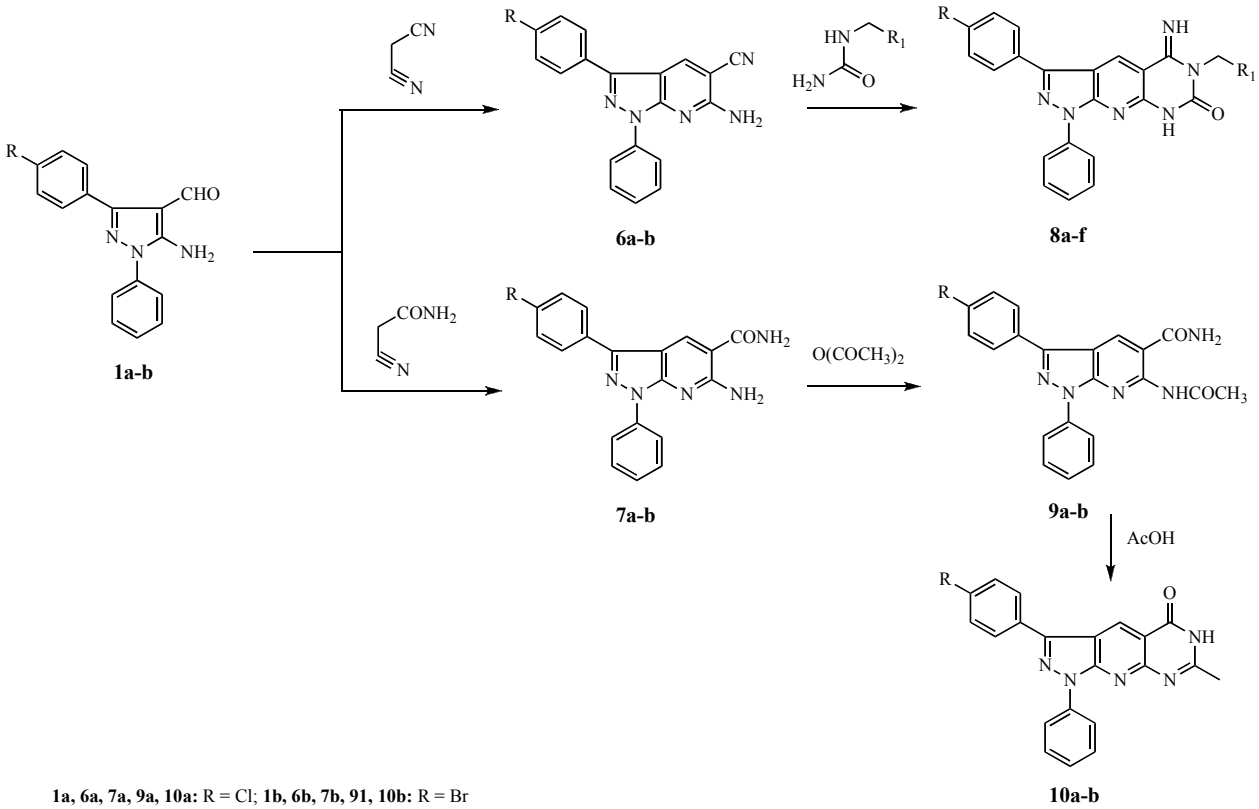
Thus, the reaction of compound **6** with N-substituted ureas at 260-270 °C gave 3-(4-halophenyl)-5-imino-6-alkyl-1-phenyl-1,5,6,8-tetrahydro-7*H*-pyrazolo[4',3':5,6]-pyrido[2,3-*d*]pyrimidin-7-one derivatives **8**. Long range

Scheme 1



1a, 2a, 3a, 4a, 5a: R = Cl; **1b, 2b, 3b, 4b, 5b:** R = Br

Scheme 2



1a, 6a, 7a, 9a, 10a: R = Cl; **1b, 6b, 7b, 91, 10b:** R = Br

8a: R = Cl, R_1 = H; **8b:** R = Cl, R_1 = CH_3; **8c:** R = Cl, R_1 = Ph; **8d:** R = Br, R_1 = H; **8e:** R = Br, R_1 = CH_3; **8f:** R = Br, R_1 = Ph

coupling observed between imino and *N*-methyl or *N*-benzyl substituted compounds . Reaction of compound **7** with acetic anhydride in acetic acid within 15 minute furnished open chain compound 6-(acetylamino)-3-(4-halophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide derivatives **9**, which was cyclized using acetic acid to 3-(4-halophenyl)-7-methyl-1-phenyl-1,6-dihydro-5*H*-pyrazolo[4',3':5,6]-pyrido[2,3-*d*]pyrimidin-5-one derivatives **10** (Scheme 2).

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Schimadzu IR-408 and Shimadzu FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL-300 (300 MHz) spectrometer in DMSO-d_6 and $CDCl_3$ using TMS as an internal standard and chemical shifts are expressed in δ (ppm) values. Elemental analyses were carried out on Hosli CH-Analyser and are within ±0.4 of the theoretical percentages. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Column chromatography was carried out on silica gel (SD Fine Chemicals, 60-80 mesh). Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

General procedure for the synthesis of 3-(halophenyl)-5-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (2). A mixture of (2 mmol) of **(1)** in propiophenone (0.38 ml, 2 mmol) was refluxed under stirring in ethanolic potassium hydroxide solution (10 ml, 2%) for one hour. Completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was then cooled to room temperature, the separated solid product was collected by suction filtration, washed with ethanol, dried and recrystallized.

3-(4-Chlorophenyl)-5-methyl-1,6-diphenyl-1*H*-pyrazolo-[3,4-*b*]pyridine (2a). This compound was obtained as white prisms (ethyl acetate), 0.65 g (82%), mp 201-202°C; ir (potassium bromide): 2341, 1598, 1550 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.53 (s, 3H, CH_3), 7.25-7.67 (m, 10H, Ph-H), 8.00 (d, J = 8.4 Hz, 2H, Ar-H), 8.21 (s, 1H, Ar-H), 8.43 (d, J = 8.4 Hz, 2H, Ar-H). *Anal.* Calcd. for $C_{25}H_{18}ClN_3$: C, 75.84; H, 4.58; N, 10.61. Found: C, 75.92; H, 4.66; N, 10.83.

3-(4-Bromophenyl)-5-methyl-1,6-diphenyl-1*H*-pyrazolo-[3,4-*b*]pyridine (2b). This compound was obtained as colorless prisms (ethyl acetate), 0.71 g (81%), mp 210-211°C; ir (potassium bromide): 2285, 1598, 1550 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.53 (s, 3H, CH_3), 7.46 (m, 5H, Ph-H), 7.65 (m, 5H, Ph-H), 7.94 (d, J = 8.4 Hz, 2H, Ar-H), 8.21 (s, 1H, Ar-H), 8.43 (d, J = 8.4 Hz, 2H, Ar-H). *Anal.* Calcd. for $C_{25}H_{18}BrN_3$: C, 68.19; H, 4.12. Found: C, 68.23; H, 4.27.

General procedure for the synthesis of Methyl-3-(4-halophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (3) and (4). A mixture of (2 mmole) of **(1)** in dimethyl 1,3-acetonedicarboxylate (0.30 ml, 2 mmole) was refluxed under stirring in ethanolic potassium hydroxide solution (10 ml, 2%) for one hour. Completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was then cooled to room temperature and the separated colorless solid product was collected by filtration then dried. The product showed two compounds on TLC analysis (R_f values: 0.85 and 0.71 in toluene). The product was dissolved in acetone and separated by column chromatography using toluene/cyclohexane 5:100 as an eluent. The elution volume for **(3)** was 230-250 ml and for **(4)** was 430-450 ml. The TLC analysis showed pure products.

Methyl-3-(4-chlorophenyl)-6-(2-methoxy-2-oxoethyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (3a). This compound was obtained as colorless prisms (ethyl acetate), 0.22 g (26%), mp 146-147°C; ir (potassium bromide): 1738, 1715, 1595, 1556 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.79 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.48 (s, 2H, CH_2), 7.29-7.41 (m, 5H, Ph-H), 8.02 (d, J = 8.4 Hz, 2H, ArH), , 8.38 (d, J = 8.4 Hz, 2H, ArH), 9.08 (s, 1H, Ar-H). *Anal.* Calcd. for $C_{23}H_{18}ClN_3O_4$: C, 63.38; H, 4.16; N, 9.64. Found: C, 63.51; H, 4.34; N, 9.86.

Methyl-3-(4-bromophenyl)-6-(2-methoxy-2-oxoethyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (3b). This compound was obtained as colorless prisms (ethyl acetate), 0.24 g (25%), mp 158-159°C; ir (potassium bromide): 1742, 1720, 1592, 1554 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.78 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.49 (s, 2H, CH_2), 7.30-7.63 (m, 5H, Ph-H), 8.03 (d, J = 8.4 Hz, 2H, ArH), 8.39 (d, J = 8.4 Hz, 2H, ArH), 9.10 (s, 1H, Ar-H). *Anal.* Calcd. for $C_{23}H_{18}BrN_3O_4$: C, 57.51; H, 3.78; N, 8.75. Found: C, 57.63; H, 3.94; N, 8.87.

Methyl-3-(4-chlorophenyl)-6-methyl-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate (4a). This compound was obtained as colorless prisms (ethyl acetate), 0.39 g (52%), mp 162-163 °C; ir (potassium bromide): 1724, 1593, 1552 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.01 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 7.34-7.57 (m, 5H, Ph-H), 7.99 (d, J = 8.4 Hz, 2H, Ar-H), 8.38 (d, J = 8.4 Hz, 2H, Ar-H), 8.93 (s, 1H, Ar-H). *Anal.* Calcd. for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 66.92; H, 4.48; N, 11.27.

Methyl-3-(4-bromophenyl)-6-methyl-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate (4b). This compound was obtained as colorless prisms (ethyl acetate), 0.43 g (51%), mp 174-175 °C; ir (potassium bromide): 1722, 1595, 1556 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.02 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 7.38-7.55 (m, 5H, Ph-H), 7.96 (d, J = 8.4 Hz, 2H, Ar-H), 8.39 (d, J = 8.4 Hz, 2H, Ar-H), 8.95 (s, 1H, Ar-H). *Anal.* Calcd. for $C_{21}H_{16}BrN_3O_2$: C, 59.73; H, 3.82; N, 9.95. Found: C, 59.86; H, 3.97; N, 9.82.

General procedure for the synthesis of 3-(Aryl)-1,5-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-amine (5). A mixture of (2 mmol) of **(1)**, phenylacetonitrile (0.23 ml, 2 mmol) and sodium ethoxide (0.2 g) in ethanol (10 ml) was refluxed under stirring in for one hour. Completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was then cooled to room temperature, the separated solid product was collected by suction filtration, washed with ethanol, dried and recrystallized.

3-(4-Chlorophenyl)-1,5-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-amine (5a). This compound was obtained as colorless prisms (ethyl acetate), 0.58 g (74%), mp 205-206°C; ir (potassium bromide): 3471, 1592, 1552 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 4.98 (bs, 2H, NH_2, exchangeable with D_2O), 7.29-7.57 (m, 10H, Ph-H), 7.96 (d, J = 8.4 Hz, 2H, Ar-H), 7.98 (s, 1H, Ar-H), 8.35 (d, J = 8.4 Hz, 2H, Ar-H). *Anal.* Calcd. for $C_{24}H_{17}ClN_4$: C, 72.63; H, 4.32; N, 14.12. Found: C, 72.76; H, 4.56; N, 14.38.

3-(4-Bromophenyl)-1,5-diphenyl-1*H*-pyrazolo[3,4-b]pyridin-6-amine (5b). This compound was obtained as colorless prisms (ethyl acetate), 0.63 g (72%), mp 216-217°C; ir (potassium bromide): 3470, 1595, 1551 cm^{-1}; ^{1}H nmr ($CDCl_3$):

δ 4.96 (bs, 2H, NH_2, exchangeable with D_2O), 7.29-7.62 (m, 10H, Ph-H), 7.87 (d, J = 8.4 Hz, 2H, Ar-H), 7.94 (s, 1H, Ar-H), 8.31 (d, J = 8.4 Hz, 2H, Ar-H). *Anal.* Calcd. for $C_{24}H_{17}BrN_4$: C, 65.32; H, 3.88; N, 12.69. Found: C, 65.58; H, 3.97; N, 12.84.

General procedure for the synthesis of 6-Amino-3-(halophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (6). A mixture of (2 mmol) of **(1)** in malononitrile (0.13 g, 2 mmol) was refluxed under stirring in ethanol (10 ml) and piperidine (0.5 ml) for one hour. Completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was then cooled to room temperature, the separated solid product was collected by suction filtration, washed with ethanol, dried and recrystallized.

6-Amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (6a). This compound was obtained as colorless prisms (ethanol:DMF), 0.47 g (68%), mp 201-202 °C; ir (potassium bromide): 3476, 1592, 1554 cm^{-1}; ^1H nmr ($CDCl_3$): δ 5.42 (bs, 2H, NH_2, exchangeable with D_2O), 7.33-7.54 (m, 5H, Ph-H), 7.85 (d, J = 8.4 Hz, 2H, Ar-H), 8.16 (d, J = 8.4 Hz, 2H, Ar-H), 8.38 (s, 1H, Ar-H). *Anal.* Calcd. for $C_{19}H_{12}ClN_5$: C, 66.00; H, 3.50; N, 20.25. Found: C, 66.14; H, 3.78; N, 20.56.

6-Amino-3-(4-bromophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (6b). This compound was obtained as colorless prisms (ethanol:DMF), 0.51 g (66%) mp 258-259°C; ir (potassium bromide): 3473, 1593, 1552 cm^{-1}; ^1H nmr ($CDCl_3$): δ 5.42 (bs, 2H, NH_2, exchangeable with D_2O), 7.33-7.67 (m, 5H, Ph-H), 7.79 (d, J = 8.4 Hz, 2H, Ar-H), 8.16 (d, J = 8.4 Hz, 2H, Ar-H), 8.38 (s, 1H, Ar-H). *Anal.* Calcd. for $C_{19}H_{12}BrN_5$: C, 58.48; H, 3.10; N, 17.95. Found: C, 58.24; H, 3.34; N, 18.12.

General procedure for the synthesis of 6-Amino-3-(halophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (7). A mixture of (2 mmol) of **(1)** in cyanoacetamide (0.1 g, 2 mmol) was refluxed under stirring in ethanol (10 ml) and piperidine (0.5 ml) for one hour. Completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was then cooled to room temperature, the separated solid product was collected by suction filtration, washed with ethanol, dried and recrystallized.

6-Amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxamide (7a). This compound was obtained as colorless prisms (ethanol:DMF), 0.50 g (69%), mp 250-251°C; ir (potassium bromide): 3473, 3417, 3354, 3305, 1592, 1556 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.76 (bs, 1H, NH), 7.17 (t, J = 7.8 Hz, 1H, Ph-H), 7.28 (bs, 1H, NH), 7.36 (m, 4H, Ar-H), 7.72 (bs, 1H, NH), 8.02 (d, J = 8.4 Hz, 2H, Ar-H), 8.12 (bs, 1H, NH), 8.22 (d, J = 8.4 Hz, 1H, Ar-H), 8.63 (s, 1H, Ar-H). *Anal.* Calcd. for $C_{19}H_{14}ClN_5O$: C, 62.73; H, 3.88; N, 19.25. Found: C, 62.95; H, 4.17; N, 19.56.

6-Amino-3-(4-bromophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxamide (7b). This compound was obtained as colorless prisms (ethanol:DMF), 0.55 g (67%) mp 270-271 °C; ir (potassium bromide): 3417, 3419, 3315, 3363, 1594, 1554 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.76 (bs, 1H, NH), 7.17 (t, J = 7.8 Hz, 1H, Ph-H), 7.28 (bs, 1H, NH), 7.36 (m, 4H, Ar-H), 7.72 (bs, 1H, NH), 8.02 (d, J = 8.4 Hz, 2H, Ar-H), 8.12 (bs, 1H, NH), 8.22 (d, J = 8.4 Hz, 2H, Ar-H), 8.63 (s, 1H, Ar-H). *Anal.* Calcd. for $C_{19}H_{14}BrN_5O$: C, 55.90; H, 3.46; N, 17.15. Found: C, 56.08; H, 3.64; N, 17.34.

General procedure for the synthesis of 3-(4-halophenyl)-5-imino-6-(alkyl/aryl)-1-phenyl-1,5,6,8-tetrahydro-7*H*-pyrazolo[4',3':5,6]-pyrido[2,3-*d*]pyrimidin-7-one (8). A mixture of (1 mmol) of **(6)** in substituted urea (2 mmol) was heated at 250-260°C for 30 minutes. Completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was then cooled to room temperature, the separated solid product was suction filtered, washed with ethanol, dried and recrystallized.

3-(4-Chlorophenyl)-5-imino-6-methyl-1-phenyl-1,5,6,8-tetrahydro-7*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-7-one (8a). This compound was obtained as yellow prisms (DMF), 0.514 g (64%), mp < 300 °C dec.; ir (potassium bromide): 3338, 3219, 1631, 1502 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.15 (d, J = 20.4 Hz, 3H, CH_3), 7.35-7.66 (m, 5H, Ph-H), 8.11 (d, J = 8.4 Hz, 2H, Ar-H), 8.31 (d, J = 8.4 Hz, 2H, Ar-H), 8.75 (d, J = 3.6 Hz, 1H, NH), 9.23 (s, 1H, Ar-H), 11.28 (bs, 1H, NH). *Anal.* Calcd. for $C_{21}H_{15}ClN_6O$: C, 62.61; H, 3.75; N, 20.86. Found: C, 62.81; H, 3.89; N, 20.98.

3-(4-Chlorophenyl)-6-ethyl-5-imino-1-phenyl-1,5,6,8-tetrahydro-7*H*-pyrazolo[4',3':5,6]-pyrido[2,3-*d*]pyrimidin-7-one (8b). This compound was obtained as yellow prisms (DMF), 0.27 g (65%) mp < 300 °C dec.; ir (potassium bromide): 3338, 3220, 1602, 1550 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.06 (t, J = 7.2 Hz, 3H, CH_3), 3.92 (q, J = 7.2 Hz, 2H, CH_2), 7.18-7.45 (m, 5H, Ph-H), 7.92 (d, J = 8.4 Hz, 2H, Ar-H), 8.13 (d, J = 8.4 Hz, 2H, Ar-H), 8.55 (s, 1H, NH), 9.06 (s, 1H, Ar-H), 11.10 (bs, 1H, NH). *Anal.* Calcd. for $C_{22}H_{17}ClN_6O$: C, 63.38; H, 4.11; N, 20.16. Found: C, 63.54; H, 4.32; N, 20.38.

6-Benzyl-3-(4-chlorophenyl)-5-imino-1-phenyl-1,5,6,8-tetrahydro-7*H*-pyrazolo[4',3':5,6]pyrido [2,3-*d*]pyrimidin-7-one (8c). This compound was obtained as yellow prisms (DMF), 0.31 g (65%) mp < 300 °C dec.; ir (potassium bromide): 3352, 3227, 1614, 1556 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.83 (d, J = 4.8 Hz, 2H, CH_2), 7.20-7.36 (m, 5H, Ph-H), 7.47-7.52 (m, 5H, Ph-H), 8.08 (d, J = 8.4 Hz, 2H, Ar-H), 8.31 (d, J = 8.4 Hz, 2H, Ar-H), 9.11 (d, J = 0.6 Hz, 1H, NH), 9.35 (s, 1H, Ar-H), 11.16 (bs, 1H, NH). *Anal.* Calcd. for $C_{27}H_{19}ClN_6O$: C, 67.71; H, 4.00; N, 17.54. Found: C, 67.86; H, 4.29; N, 17.82.

3-(4-Bromophenyl)-5-imino-6-methyl-1-phenyl-1,5,6,8-tetrahydro-7*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-7-one (8d). This compound was obtained as yellow prisms (DMF), 0.28 g (62%) mp < 300 °C dec.; ir (potassium bromide): 3338, 3219, 1631, 1502 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.17 (d, J = 20.4 Hz, 3H, CH_3), 7.34-7.83 (m, 5H, Ph-H), 8.11 (d, J = 8.4 Hz, 2H, Ar-H), 8.25 (d, J = 8.4 Hz, 2H, Ar-H), 8.78 (d, J = 3.6 Hz, 1H, NH), 9.28 (s, 1H, Ar-H), 11.31 (bs, 1H, NH). *Anal.* Calcd. for $C_{21}H_{15}BrN_6O$: C, 56.39; H, 3.38; N, 18.79. Found: C, 56.61; H, 3.58; N, 18.93.

3-(4-Bromophenyl)-6-ethyl-5-imino-1-phenyl-1,5,6,8-tetrahydro-7*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-7-one (8e). This compound was obtained as yellow prisms (DMF), 0.29 g (63%) mp < 300 °C dec.; ir (potassium bromide): 3338, 3220, 1602, 1550 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.14 (t, J = 7.2 Hz, 3H, CH_3), 3.96 (q, J = 7.2 Hz, 2H, CH_2), 7.33-7.73 (m, 5H, Ph-H), 8.01 (d, J = 8.4 Hz, 2H, Ar-H), 8.23 (d, J = 8.4 Hz, 2H, Ar-H), 8.76 (s, 1H, NH), 9.33 (s, 1H, Ar-H), 11.29 (bs, 1H, NH). *Anal.* Calcd. for $C_{22}H_{17}BrN_6O$: C, 57.28; H, 3.71; N, 18.22. Found: C, 57.52; H, 3.94; N, 18.37.

6-Benzyl-3-(4-bromophenyl)-5-imino-1-phenyl-1,5,6,8-tetrahydro-7*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-7-one (8f). This compound was obtained as yellow prisms (DMF), 0.34 g (65%) mp < 300 °C dec.; ir (potassium bromide): 3352, 3227, 1614, 1556 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.80 (d, J = 4.8

Hz, 2H, CH_2), 7.28-7.41 (m, 5H, Ph-H), 7.56-7.81 (m, P5H, h-H), 8.08 (d, J = 8.4 Hz, 2H, Ar-H), 8.34 (d, J = 8.4 Hz, 2H, Ar-H), 9.29 (d, J = 0.6 Hz, 1H, NH), 9.39 (s, 1H, Ar-H), 11.39 (bs, 1H, NH). *Anal.* Calcd. for $C_{27}H_{19}BrN_6O$: C, 61.96; H, 3.66; N, 16.06. Found: C, 62.14; H, 3.87; N, 16.28.

General procedure for the synthesis of 6-Acetylamino-3-(halophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (9). A mixture of (1 mmol) of **(7)** in acetic anhydride (1.5 ml) and acetic acid (1.5 ml) was refluxed under stirring for 15 minutes. Completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was then cooled to room temperature, the separated solid product was collected by suction filtration, washed with ethanol, dried and recrystallized.

6-Acetylamino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxamide (9a). This compound was obtained as colorless prisms (ethanol:DMF), 0.35 g (86%) mp 228-229 °C; ir (potassium bromide): 3361, 3253, 3203, 1645, 1606 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.28-7.52 (m, 5H, Ph-H), 7.93 (bs, 1H, NH), 8.16 (d, J = 8.4 Hz, 2H, Ar-H), 8.36 (d, J = 7.8 Hz, 2H, Ar-H), 8.62 (bs, 1H, NH), 8.98 (s, 1H, Ar-H), 12.14 (bs, 1H, NH). *Anal.* Calcd. for $C_{21}H_{16}ClN_5O_2$: C, 62.15; H, 3.97; N, 17.26. Found: C, 62.33; H, 4.21; N, 17.54.

6-(Acetylamino)-3-(4-bromophenyl)-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxamide (9b). This compound was obtained as white prisms (ethanol:DMF), 0.37 g (84%) mp 237-238 °C; ir (potassium bromide): 3327, 3166, 1674, 1593 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.34-7.60 (m, 5H, Ph-H), 7.92 (bs, 1H, NH), 8.11 (d, J = 8.4 Hz, 2H, Ar-H), 8.28 (d, J = 7.8 Hz, 2H, Ar-H), 8.61 (bs, 1H, NH), 8.97 (s, 1H, Ar-H), 11.91 (bs, 1H, NH). *Anal.* Calcd. for $C_{21}H_{16}BrN_5O_2$: C, 56.01; H, 3.58; N, 15.55. Found: C, 56.28; H, 3.76; N, 15.76.

General procedure for the synthesis of 3-(4-halophenyl)-7-methyl-1-phenyl-1,6-dihydro-5*H*-pyrazolo[4',3':5,6]pyrido-[2,3-*d*]pyrimidin-5-one (10). A mixture of (1 mmol) of **(9)** in acetic acid (5 ml) was refluxed under stirring for 7 hours. Completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was then cooled to room temperature, the separated solid product was collected by suction filtration, washed with ethanol, dried and recrystallized.

3-(4-Chlorophenyl)-7-methyl-1-phenyl-1,6-dihydro-5*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-5-one (10a). This compound was obtained as colorless prisms (DMF), 0.28 g (74%), mp < 300 °C dec.; ir (potassium bromide): 3325, 3170, 1674, 1593 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.46 (s, 3H, CH_3), 7.36-7.62 (m, 5H, Ph-H), 8.12 (d, J = 8.4 Hz, 2H, Ar-H), 8.36 (d, J = 7.8 Hz, 2H, Ar-H), 9.19 (s, 1H, Ar-H), 12.57 (bs, 1H, NH). *Anal.* Calcd. for $C_{21}H_{14}ClN_5O$: C, 65.04; H, 3.64; N, 18.06. Found: C, 65.26; H, 3.81; N, 18.34.

3-(4-Bromophenyl)-7-methyl-1-phenyl-1,6-dihydro-5*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-5-one (10b). This compound was obtained as colorless prisms (DMF) 0.31 g (72%) mp < 300 °C dec.; ir (potassium bromide): 3326, 3173, 1672, 1596 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.47 (s, 3H, CH_3), 7.36-7.59 (m, 5H, Ph-H), 8.07 (d, J = 8.4 Hz, 2H, Ar-H), 8.37 (d, J = 7.8 Hz, 2H, Ar-H), 9.21 (s, 1H, Ar-H), 12.58 (bs, 1H, NH). *Anal.* Calcd. for $C_{21}H_{14}BrN_5O$: C, 58.35; H, 3.26; N, 16.20. Found: C, 58.61; H, 3.49; N, 16.42.

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REFERENCES AND NOTES

[1] H Y. Sato, Y. Shimoji, S. Kumakura and H. Takagi, *Japan Kokai Tokkyo Koho JP* 75151896 (1976); *Chem. Abstr.* **84**, 164771 (1976).

[2] S. Kuo, L. Huang and H. Nakamura, *J. Med. Chem.*, **27**, 539 (1984).

[3] I. Ait, A. Resink and F. Schweighoffer, *U.S. Patent Appl. Publ.* 2004219552 (2004); *Chem. Abstr.*, **141**, 388737 (2004).

[4] H. Bischoff and J. Stasch, *PCT Intl. Appl. WO* 2003015770 (2003); *Chem. Abstr.*, **138**, 180718 (2003).

[5] S. Ludwig, O. Planz, H. Sedlacek and S. Pleschka, *German Offen DE* 10138912 (2003); *Chem. Abstr.*, **138**, 198569 (2003).

[6] A. Feurer, J. Luithle, S. Wirtz, G. Koenig, J. Stasch, E. Stahl, R. Schreiber, F. Wunder and D. Lang, *PCT Intl. Appl. WO* 2004009589 (2004); *Chem. Abstr.*, **140**, 146157 (2004).

[7] F. J. Ehlert, P. Ragan, A. Chen, W. R. Roeske and H. I. Yamamura, *Eur. J. Pharmacol.*, **78**, 249 (1982).

[8] S. Selleri, F. Burni, A. Castanzo, G. Guerrini, P. Malmberg-Aiello, G. Iavarone and C. Martini, *J. Med. Chem.*, **27**, 985 (1992).

[9] K. Yutaka, *Japan Kokai Tokkyo Koho JP* 03221948 (1992); *Chem. Abstr.*, **116**, 95912 (1992).

[10] K. Yutaka, *Japan Kokai Tokkyo Koho JP* 02277050 (1991); *Chem., Abstr.*, **115**, 18527 (1991).

[11] K. Yutaka, *Japan Kokai Tokkyo Koho JP* 02,220,050 (1991); *Chem. Abstr.*, **114**, 111844 (1991).

[12] M. Jachak, A. Avhale, C. Tantak, R. Toche, C. Reidlinger and W. Stadlbauer, *J. Heterocyclic Chem.*, **42**, 1311 (2005).

[13] G. Coppola and M. Shapiro, *J. Heterocyclic Chem.*, **17**, 1163 (1980).

[14] Y. Imai, S. Sato, R. Takasawa and M. Ueda, *Synthesis*, 35 (1981).

[15] J. Clark and G. Hitiris G, *J. Chem. Soc. Parkin. Trans. 1*, 2005 (1984).

[16] T. Stevenson, F. Kazmierczak and N. Leonard, *J. Org. Chem.*, **51**, 616 (1986).

[17] H. R. Sharma, R. Goyal and L. Prakash, *Indian J. Chemistry*, **31B**, 719 (1992).

[18] H. Emam, S. Hassan and Al-Najjar, *J. Chem. Res. Synopsis*, **11**, 474 (1995).

[19] Y. Mohamed, M. Zahran, M. Ali, A. El-Agrody and U. El-Said, *J. Chem. Res. Synopsis*, **8**, 322 (1995).

[20] G. Singh, A. Yadav and A. Mishra A, *Indian J. Chem.*, **41B**, 430 (2002).

21] V. Ahluwalia, A. Dahiya, V. Gard, *Indian J. Chem.*, **35B**, 1208 (1996); V. Ahluwalia and his coworkers have done similar type of reactions on different Pyrazoles.

[22] V. Ahluwalia, B. Goyal, *Synth. Comm.*, **26,** 1341 (1996); V. Ahluwalia and his coworkers have done similar type of reactions on different Pyrazoles.