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Microwave assisted synthesis and reactions of novel pyrazolo [3,4-b]pyridine derivatives

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ABSTRACT

*5-Amino pyrazole **1**, the key intermediate was converted to pyrazolopyridine derivatives **3** by reaction of diethylethoxymethylene malonate **2** in ethanol. Compound **3** was on heating in bromobenzene converted to pyrazolopyridine **4** which was on refluxing in $POCl_3$ yielded chloro compound **5**. Compound **4** further was used for the synthesis of 4-chloro-5-carboxypyrazolopyridine derivatives **6** and urea derivatives **7** which was also synthesized by microwave irradiation techniques. It was observed that the compounds obtained by both the methods are one and the same, it was confirmed by taking TLC, M.P., mix M.P., IR, ^1H NMR and elemental analysis. All synthesized compounds were characterized by spectral and analytical methods.*

Keywords: Microwave technique, 5-Amino pyrazole, Pyrazolo [3, 4-b] pyridine, Urea derivatives

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INTRODUCTION

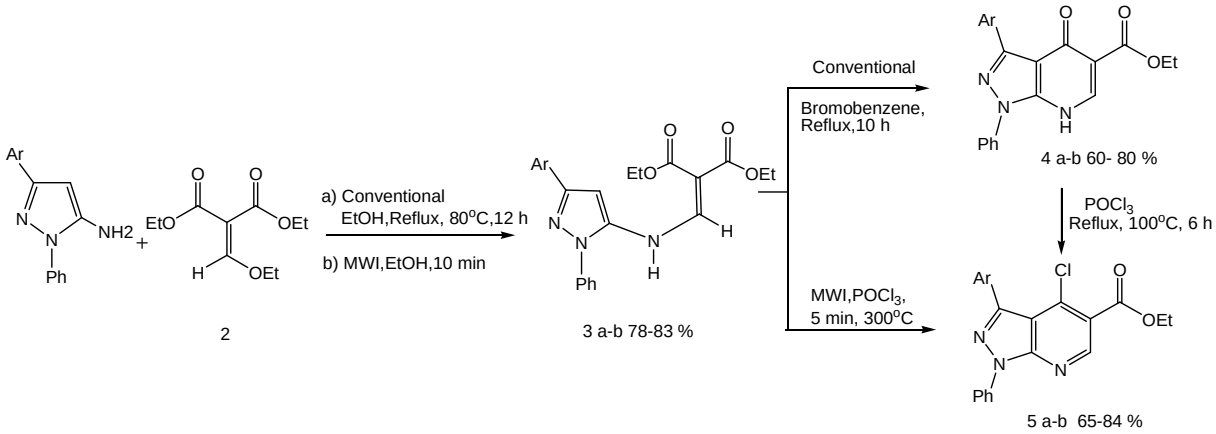
Fused heterocyclic systems containing pyrazole ring are ranked among the most versatile bioactive compounds and number of procedures have been described their synthesis [1-4]. The pyrazolo [3,4-*b*]pyridines as aza analogues of indazoles [5] are attractive target in organic synthesis. Pyrazolo [3, 4-*b*] pyridine derivatives were first synthesized by Ortoleva in 1906 [6]. They showed number of interesting pharmacological activities such as hypotensive [7], hypoglycemic [8-9], cyatostatic [10], psychotropic [11] and used as coronary vasodilators agent [12-13] or neurodegenerative diseases [14]. The latter heterocyclic system represents the core of several biologically active compounds, acting, for instance, as cytotoxic [15] or antiviral [16] activity. These compounds are also act as potential purine antagonists [17], anti-asthmatic [18], anti-allergic [19], anti tumor [20] and anti-bacterial [21]. The pyrazolopyridine derivatives also known to have activity of recombinant reverse transcriptase (RT) of HIV-1 and on Human DNA polymerase [22].

Recently X. Zou *et. al.* [23] reported the synthesis of pyrazolo[3,4-*b*]pyridine derivatives **4** by reaction of 5-aminopyrazole **2** with chalcone **3** in presence of $ZnCl_2$, under MW irradiation.

These literature reports prompted us to develop a new method for the synthesis of pyrazolo pyridine. A convenient route for the synthesis of new pyrazolo[3,4-b]pyridines was successfully developed using microwave technique

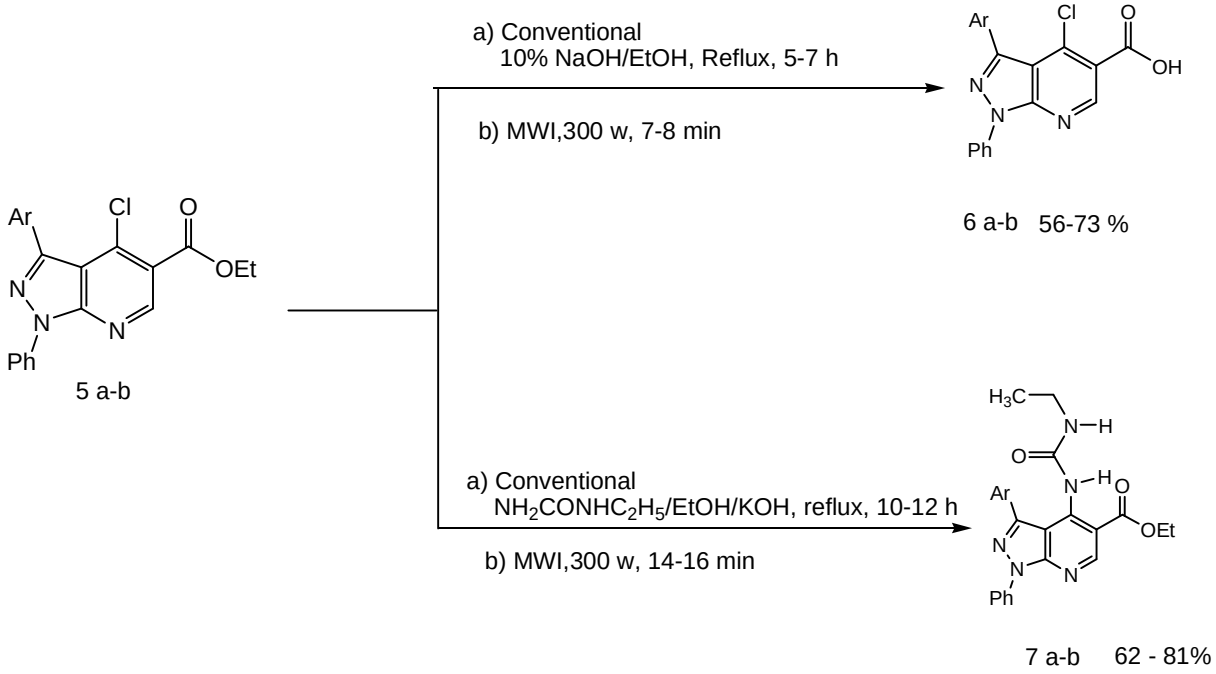
RESULTS AND DISCUSSION

Pyrazolo[3,4-*b*]pyridine nucleus were synthesized by Quiroga and co-workers [24-25] using 5-aminopyrazoles and chalcones derived from benzoylacetonitrile/ malononitrile with aromatic aldehydes by *Michael* addition. We have adopted different strategy for synthesis of these compounds. In our method we have condensed 5-aminopyrazole **1** and diethylethoxymethylene-alonate **2** in ethanol to furnish pyrazolopyridine **3**.



Ar, a=4-ClPh; b=4BrPh

Scheme 1 Synthesis of Ethyl 3-(4-substituted phenyl)-4-oxo1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (4a-b) and Ethyl 4-chloro-3-(4-substituted phenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (5a-b)



Ar, a=4-ClPh; b=4BrPh

Scheme 2 Synthesis of 4-chloro-3-(4-substituted phenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (6a-b) and ethyl 3-(4-substituted phenyl)-4-(3-ethylureido)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (7a-b)

5-Amino pyrazole **1** [22] and diethylethoxymethylene malonate **2** was refluxed in ethanol for 12 h furnished intermediate compound **3** which was cyclized to pyrazol0[3,4-b]pyridine **4** by refluxing in bromobenzene. The compound **4** was also converted to compound **5** by microwave irradiation using $POCl_3$. The validity of both methods

was by confirmed by TLC, M.P., mix M.P., IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. Compound **5** which is already in our hands was utilized for the synthesis of 4-chloro-5-carboxypyrazolopyridine derivatives and urea derivatives (Scheme 1).

The hydrolysis of compounds **5** was carried out by using 10% aqueous NaOH at refluxing temperature for 7-8 h to yield acid **6** in good yield. The C4-Cl of compound 5 was replaced N-ethyl urea in ethanol in presence catalytic amount of potassium hydroxide yielded urea derivative **7** in 60-70% yield.

The compounds **6** and **7** were also synthesis by using same reagents under microwave irradiation in 77-81% yields with reduced reaction time (scheme 2). The compounds obtained by both the methods are validated by TLC, m.p., mix m.p., IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

MATERIALS AND METHODS

Melting points were determined on a Gallenkamp melting point apparatus, Mod.MFB-595 in open capillary tube and are uncorrected. FT-IR spectra were recorded on Schimadzu FTIR-408 instrument in KBr pellets. ^{1}H and ^{13}C spectra were recorded on Varian XL -300 spectrometer (300MHz) in $CDCl_3$ and DMSO. Chemical shifts are reported in ppm with respect to tetra methyl silane as an internal standard. Elemental analyses were carried out on Hosli CH analyzer and are within ± 0.4 of theoretical percentages. The progress of the reaction was monitored by thin layer chromatography (TLC, 0.2 mm silica gel 60 F_{254}, Merck plates) and visualized using UV light (254 and 366 nm) for detection. Microwave assisted synthesis was carried out in an Emery synthesizer single wave microwave cavity producing controlled irradiation at 2450 MHz, the temp was measured with IR sensor on the outside of reaction vessels. All commercial grade chemicals were purchased from S.D. Fine chemicals India and used without further purification while solvents were purified by standard literature procedures.

Synthesis of *Diethyl–(3(4-substituted phenyl)-1-phenyl-1H-pyrazol-5-yl-amino-methylene)malonate* (3a-b)

A. Conventional Method

A mixture of 5-aminopyrazole **1** (0.01 mole and diethylethoxymethylenemalonate **2** in absolute ethanol (20 ml) and refluxed for 12 h at 80^{o}C. Reaction was monitored by TLC (toluene: acetone, 8:2). The reaction mixture after cooling was stirred in ice cold water to remove excess of impurities formed during the reaction. The solid obtained was collected by filtration and washed with water, dried and recrystallized from ethanol-DMF (7:3). The solid obtained to yield compound **3.**

B. Microwave Method

A mixture of 5-aminopyrazole **1** (0.01 mol) and diethylethoxymethylenemalonate **2** irradiated in microwave for 10 minute at 200^{o}C. Reaction was monitored by TLC (TLC check toluene: acetone, 8:2).The reaction mixture was cooled at room temp and pour in ice cold water. The solid obtained was collected by filtration and washed with water, dried and recrystalized from ethanol-DMF (7:3). The solid obtained to yield compound **3.**

Diethyl –(3(4-chlorophenyl)-1-phenyl-1H-pyrazol-5-yl-amino-methylene)malonate (3a)

M. P.: 120-122^{o}C; Yield: Conventional; 2.91g, 65% and Microwave; 3.42g, 78%; IR KBr: 2983, 1691, 1643, 1604, 1552, 1444, 1384, 1336, 1271, 954, 839 Cm^{-1}, ^{1}H NMR ($CDCl_3$): δ : 1.28 (m,6H, $2CH_3$), 4.21 (m, 4H, $2CH_3$),6.49 (s,1H, C_4H), 7.37 (m,9H, Ar-H), 8.22 (d,1H, Ar-H), 11.03 (d,1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ: 17.6, 18.3, 60.8, 61.4, 98.6, 116.5, 121.3(2C'S), 126.5, 128.5(2C'S), 129.8(2C'S), 130.5(2C'S), 131.8, 134.7, 140.6, 149.5, 152.3, 163.4, 165,3, 188.8 ppm; MS (m/z %): 440[M^{+}] and 442[M^{+2}], Analysis Calculated for $C_{23}H_{22}ClN_3O_4$: Calcd: C (62.80); H (5.03); N (9.54); Found: C (62.84); H (5.02); N (9.57)

Diethyl –(3(4-Bromophenyl)-1-phenyl-1H-pyrazol-5-yl-amino-methylene)malonate (3b)

M. P.: 128-129^{o}C; Yield: Conventional; 3.52g, 73% and Microwave; 4.05, 84%; IR KBr: 2970, 1680, 1633, 1601, 1545, 1441, 1384, 1324, 1241, 954, 825 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ : 1.29 (m,6H, $2CH_3$), 4.25 (m, 4H, $2CH_3$),6.51 (s,1H, C_4H), 7.30 (m,9H, Ar-H), 8.20 (d,1H, Ar-H), 11.01 (d,1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ: 17.6, 18.2, 60.8, 61.4, 98.6, 116.4, 121.2(2C'S), 126.5, 127.6(2C'S), 128.7(2C'S), 129.9(2C'S), 131.6, 133.6, 140.6, 149.6, 152.1, 163.3, 165,7, 187.3 ppm; MS (m/z %): 484[M^{+}] and 486[M^{+2}], Analysis Calculated for $C_{23}H_{22}BrN_3O_4$: Calcd: C (57.04); H (4.57); N (8.67); Found: C (57.01); H (4.50); N (8.63)

Synthesis of *Ethyl 3-(4-substituted phenyl)-4-oxo1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxylate* (4a-b) and *Ethyl 4-chloro-3-(4-substituted phenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate* (5a-b)

A. Conventional Method

A mixture of compound **3** (0.01 mol**)** was refluxed in bromobenzene (20 ml) for 10 h. The completion of reaction was checked by TLC (toluene: acetone, 8:2). The solid formed on cooling was washed with water, dried and recrystallized in ethanol to yield compound **4.** Compound **4** (0.01 mol) was further reflux in $POCl_3$ (5 ml) for 8-10 hrs. The residue obtained was then cooled to room temp and pour into crushed ice. The solid formed was filtered, dried and recrystallized from ethanol to yield compound **5.**

B. Microwave Method

A mixture of compound **3** (0.01 mol**)** and $POCl_3$ (0.03 mol**)** was irradiated in microwave at 300^oC for 7-8 min. The completion of reaction was checked by TLC. The solid formed on cooling was stirred in ice. Wash with water, dried and recrystallized in ethanol to yield compound **5** in single step.

Ethyl 3-(4-chlorophenyl)-4-oxo1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (4a)

M. P.: 136-137 ^oC; Yield: Conventional; 2.52g, 60% and Microwave; 3.14g, 75%; IR KBr: 2916, 2848, 1687, 1598, 1552, 1446, 1334, 1284, 1163, 935, 761 cm^{-1}, ^1H NMR ($CDCl_3$): δ : 1.45 (t,3H, CH_3), 4.46 (q, 2H, CH_2),7.25 (m,9H, Ar-H), 8.20 (d,1H, C_6H), 8.97(bs,1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ: 14.5, 62.3, 96.4, 112.8, 121.3(2C'S), 126.5, 128.5(2C'S), 129.8(2C'S), 130.6(2C'S),131.4, 134.9, 138.7, 144.5, 150.3, 158.2, 165.9, 178.3ppm; MS (m/z %): 393[M^+] and 395[M^{+2}], Analysis Calculated for $C_{21}H_{16}ClN_3O_3$: Calcd: C (64.20); H (4.03); N (10.54); Found: C (62.24); H (4.02); N (10.57)

Ethyl 3-(4-Bromophenyl)-4-oxo1-phenyl-4,7-dihydro-1H-pyrazol0[3,4-b]pyridine-5-carboxylate (4b)

M. P.: 140-141^oC Yield: Conventional; 2.78g, 62 % and Microwave; 3.70g, 80 %; IR KBr: 2926, 2858, 1677, 1578, 1552, 1447, 1355, 1281, 1161, 945, 753 cm^{-1}, ^1H NMR ($CDCl_3$): δ : 1.47 (t,3H, CH_3), 4.44 (q, 2H, CH_2), 7.24 (m,9H, Ar-H), 8.18 (d,1H, C_6H), 8.94 (bs,1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ: 14.3, 62.4, 96.6, 112.6, 121.2(2C'S), 126.6, 128.7, (2C'S), 129.7(2C'S), 130.6(2C'S), 132.8, 134.8, 138.6, 144.7, 150.6, 158.6, 166.3, 178.4 ppm; MS (m/z %): 437[M^+] and 439[M^{+2}], Analysis Calculated for $C_{21}H_{16}BrN_3O_3$: Calcd: C (57.62 H (3.68); N (9.54) Found: C (57.64); H (4.72); N (9.57)

Ethyl 4-chloro-3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (5a)

M. P.: 186-187 ^oC; Yield: Conventional; 2.81g, 68 % and Microwave; 3.46g, 84 %; IR KBr: 1733, 1581, 1552, 1458, 1363, 1288, 1255, 1176, 937, 844, 721 cm^{-1}, ^1H NMR ($CDCl_3$): δ : 1.43 (t,3H, CH_3), 4.43 (q, 2H, CH_2),7.38 (m,9H, Ar-H), 9.05(s,1H, Ar-H) ppm; ^{13}C NMR($CDCl_3$) δ: 14.5, 60.8, 106.9, 120.3 (2C'S), 125.5. 126.6, 128.5(2C'S), 129.3(2C'S), 129.8(2C'S), 131.5, 134.6, 140.2, 140.8 146.3, 150.8, 151.6, 166.3 ppm; MS (m/z %): 411[M^+] and 413[M^{+2}], Analysis Calculated for $C_{21}H_{15}Cl_2N_3O_2$: Calcd: C (58.20), H (3.50), N (9.81); Found: C (58.80), H (3.35), N(9.75)

Ethyl 4-chloro-3-(4-Bromophenyl)-1-phenyl-1H-pyrazolo [3,4-b]pyridine-5-carboxylate (5b)

M. P.: 182-183^oC; Yield: Conventional; 2.97g, 65 % and Microwave; 3.94g, 86%; IR KBr: 1725, 1563, 1552, 1435, 1343, 1285, 1235, 1164, 935, 834, 722 cm^{-1}, ^1H NMR ($CDCl_3$): δ : 1.44 (t,3H, CH_3), 4.46 (q, 2H, CH_2), 7.33 (m,9H, Ar-H), 9.01(s,1H, Ar-H) ppm; ^{13}C NMR($CDCl_3$) δ: 14.2, 60.6, 107.8, 120.4(2C'S), 125.6, 126.8, 128.6(2C'S), 129.5(2C'S), 129.9(2C'S), 131.6, 135.3, 140.6, 140.9, 146.5, 150.7, 151.4, 166.8 ppm; MS (m/z %): 455[M^+] and 457[M^{+2}], Analysis Calculated for $C_{21}H_{15}BrClN_3O_2$: Calcd: C (55.24), H (3.28), N(9.19); Found: C (55.15), H (3.15), N (9.05)

***Synthesis of 4-chloro-3-(4-substituted phenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid* (6a-b)**

A. Conventional Method

A solution of compound **5** (0.01 mol) and 10% aqueous NaOH in ethanol was refluxed for 6-7 h (Completion of reaction was checked by TLC). Then the solution was allowed to cool and poured in ice cold water and acidified with conc. HCL. The solid separated was filtered, washed with water, dried and recrystalized from ethanol to furnished compound **6** in good yield.

B. Microwave Method

A solution of compound **5** (0.01 mol**)** and 10% aqueous NaOH was irradiated in microwave at 200^{o}C for 7-8 min. The completion of reaction was checked by TLC .The solid formed on cooling was stirred in ice. Wash with water, dried and recrystallized in ethanol to yield compound **6** in single step.

Synthesis of 4-chloro-3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (6a)

M. P.: 97-98 ^{o}C; Yield: Conventional; 2.15g, 56 % and Microwave; 2.81g, 73 %; IR KBr: 1733, 1581, 1552, 1458, 1363, 1288, 1255, cm^{-1}, ^{1}H NMR ($CDCl_3$): δ : 7.38 (m,9H, Ar-H), 9.05(s,1H, Ar-H) ,11.6(s,1H,-OH) ppm; ^{13}C NMR($CDCl_3$) δ: 107.8, 120.6(2C'S), 125.6, 126.8, 128.3(2C'S), 129.5(2C'S), 129.7(2C'S), 131.5, 134.6, 140.3, 140.7, 146.5, 150.8, 151.8, 167.2 ppm; MS (m/z %): 383[M^{+}] and 385[M^{+2}], Analysis Calculated for $C_{19}H_{11}Cl_2N_3O_2$: Calcd: C (59.39), H (2.89), N (10.94); Found: C (59.12), H (3.14), N(11.17)

Synthesis of 3-(4-bromophenyl)-4-chloro-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (6b)

M. P.: 91-92 ^{o}C; Yield: Conventional; 2.36g, 61 % and Microwave; 2.94g, 76 %; IR KBr: 1725, 1563, 1552, 1435, 1343, 1285, 1235, cm^{-1}, ^{1}H NMR ($CDCl_3$): δ : 7.33 (m,9H, Ar-H), 9.01(s,1H, Ar-H),11.4 (s,1H,-OH) ppm; ^{13}C NMR($CDCl_3$) δ: 106.9, 120.6(2C'S), 125.6, 126.9, 128.7(2C'S), 129.5(2C'S), 129.9(2C'S), 131.6, 135.6, 140.8, 140.9, 146.6, 150.8, 151.6, 168.6 ppm; MS (m/z %): 426[M^{+}] and 428[M^{+2}], Analysis Calculated for $C_{19}H_{11}BrClN_3O_2$: Calcd: C (53.24), H (2.59), N(9.80); Found: C (53.01), H (2.88), N (10.7)

***Synthesis of ethyl 3-(4-substituted phenyl)-4-(3-ethylureido)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate* (7a-b)**

A. Conventional Method

A solution of compound **5** (0.01 mol) and ethyl urea (0.02 mol) in ethanol containing catalytical amount of potassium hydroxide was refluxed for 10-12 h. (Completion of reaction was checked by TLC). Then the solution was allowed to cool and poured in ice cold water. The solid separated was filtered, washed with water, dried and recrystallized from ethanol to furnished compound **7** in good yield.

B. Microwave Method

A solution of compound **5** (0.01 mol**)** and ethyl urea (0.02 mol) was irradiated in microwave at 500 ^{o}C for 14-16 min. The completion of reaction was checked by TLC. The solid formed on cooling was stirred in ice. Wash with water, dried and recrystallized in ethanol to yield compound **7** with excellent yield.

Synthesis of ethyl 3-(4-chlorophenyl)-4-(3-ethylureido)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (7a)

M. P.: 135-137 ^{o}C; Yield: Conventional; 2.88g, 62 % and Microwave; 3.58g, 77 %; IR KBr: 1735, 1588, 1552, 1478, 1369, 1285, 1250, 1178, 935, 847, 723 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ : 0.99 (t,3H, CH_3), 4.39(t,3H, CH_3), 2.83 (q, 2H, CH_2), 4.33(q, 3H, CH_3),7.24 (m,9H, Ar-H), 8.72(bs, 1H, -NH), 8.95(bs, 1H, -NH) ppm; ^{13}C NMR($CDCl_3$) δ: 14.4, 14.8, 36.9, 60.6, 104.7, 120.2(2C'S), 125.3, 126.5, 128.6(2C'S), 129.5(2C'S), 129.8(2C'S), 131.5, 135.7, 140.6, 145.9, 149.8, 151.8, 156.5, 158.5, 168.5 ppm; MS (m/z %): 463[M^{+}] and 465[M^{+2}], Analysis Calculated for $C_{24}H_{22}ClN_5O_3$: Calcd: C (62.14), H (4.78), N (15.10); Found: C (61.88), H (5.03), N(15.36)

Synthesis of ethyl 3-(4-bromophenyl)-4-(3-ethylureido)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (7b)

M. P.: 156-157 ^{o}C; Yield: Conventional; 3.72g, 66% and Microwave; 3.72g, 81 %; IR KBr: 1740, 1592, 1556, 1483, 1375, 1280, 1265, 1186, 938, 844, 722 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ : 0.98 (t,3H, CH_3), 4.40(t,3H, CH_3), 2.87 (q, 2H, CH_2), 4.31(q, 3H, CH_3),7.28 (m,9H, Ar-H), 8.77(bs, 1H, -NH), 8.91(bs, 1H, -NH) ppm; ^{13}C NMR($CDCl_3$) δ: 14.3, 14.7, 36.8, 60.5, 104.8, 120.5(2C'S), 125.7, 126.6, 128.6(2C'S), 129.7(2C'S), 129.9(2C'S), 131.6, 135.8, 140.3, 145.7, 149.6, 151.5, 156.6, 158.4, 168.7 ppm; MS (m/z %): 507[M^{+}] and 509[M^{+2}], Analysis Calculated for $C_{24}H_{22}BrN_5O_3$: Calcd: C (56.70), H (4.36), N (13.78); Found: C (56.44), H (4.66), N(14.04)

CONCLUSION

We have explored a facile and efficient protocol for the synthesis of pyrazolo[3,4-b]pyridine derivatives **3a-b** to **7a-b** with good yields. Particularly valuable features of present method include broad substrate scope, short reaction time, straight forward procedure and easy aqueous work up that facilitated 80-85% recovery of pure product and use of inexpensive chemicals and reagents. Microwave irradiation has recently been used as an efficient technique to

increase reaction rates. Thus, we attempted to take advantage of this technique to decrease the reaction time and to increase yield of the product.

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