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A facile, solvent free, ecofriendly approach for the synthesis of 2-amino-3(ethylcarboxy)-4,6-disubstituted pyridine **4** and pyrazolo[3,4-*b*]pyridines **6** is herein described employing neat reaction conditions under microwave irradiation. This solventless methodology is environmentally benign as it completely eliminates the use of solvent from the reaction procedure. The observed reaction rate enhancement and high yield of products are due to the neat reaction conditions coupled with microwaves (MWs).

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Industrial chemistry in the new millennium is widely adopted the concept of "Green Chemistry" [1] to meet the fundamental scientific challenges of protecting the human health and environment while maintaining commercial viability. One of the advances in this area where substantial progress has been made is the microwave assisted [2-4] solid supported synthesis [5-7]. But this technique does not meet the ecofriendly goal of clean synthesis as an appreciable amount of solvent, is required for the adsorption of reactants and elution of products. The "neat reaction" technique is an alternative solvent free approach in which the reaction is carried out in the absence of solvent, support and catalyst. Further coupling of this solventless synthesis with MWs has the associated benefits of shorter reaction time, uniform heating and better yield in comparison to conventional heating.

The basic skelton of chalcones which possess α,β-unsaturated carbonyl group is useful as the starting material for the synthesis of various heterocyclic compounds of physiological importance *viz*. pyrazoline [8], pyridines [9], pyrimidine [10] and isooxazoline [11]. The presence of enone functionality in chalcone moiety confers biological activity [12-13]. The importance of pyridines and fused pyridine as calcium antagonists [14] and hypertensives [15] are well known. Also the interest in the synthesis of condensed pyrazoles has recently revived [16-18] because of their wide variety of biological and pharmacological properties [19-20]. Therefore in view of our ongoing program towards green synthesis [21], it was thought worthwhile to synthesize 2-amino-3(ethylcarboxy)-4,6-disubstituted pyridines **4a-f** and pyrazolo[3,4-*b*]pyridines derivatives **6a-f** under neat reaction condition.

Scheme 1

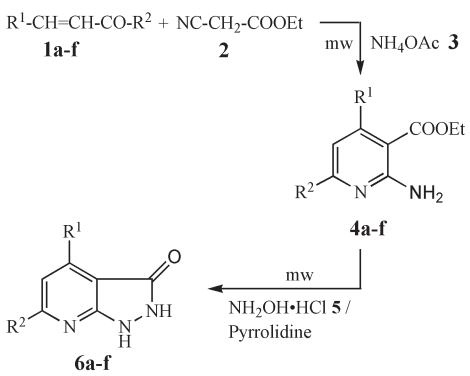

Table 1

Comparison of Reaction Time and Yield for **4a-f** and **6a-f**

Compd. No.	R^1	R^2	Reaction time (min's") / Yield (%) Solid support* MWI	Neat MWI
4a	C_6H_5	C_6H_5	8'50" / 84	3'50" / 92
4b	4-MeO-C_6H_4	C_6H_5	7'40" / 88	2'40" / 94
4c	4-MeO-C_6H_4	3,4-$(CH_3)_2C_6H_3$	9'20" / 82	3'40" / 91
4d	2-Furyl	Methyl	7'20" / 81	2'50" / 93
4e	3-Indolyl	4-Br-C_6H_4	7'10" / 86	3'20" / 89
4f	Benzo[1,3] dioxol-3-yl	4-Br-C_6H_4	7'30" / 80	3'00" / 95
6a	C_6H_5	C_6H_5	6'50" / 81	3'50" / 93
6b	4-MeO-C_6H_4	C_6H_5	7'10" / 83	4'00" / 91
6c	4MeO-C_6H_4	3,4-$(CH_3)_2C_6H_3$	7'00" / 82	4'20" / 92
6d	2-Furyl	Methyl	7'20" / 84	3'40" / 96
6e	3-Indolyl	4-Br-C_6H_4	6'30" / 80	4'40" / 93
6f	Benzo[1,3] dioxol-3-yl	4Br-C_6H_4	6'40" / 86	4'50" / 96

* From **4a-f** – Support used is neutral alumina; From **6a-f** – Support used is basic alumina.

The synthesis of 2-amino-3(ethylcarboxy)-4,6-disubstituted pyridine **4a-f** was carried out by subjecting the reactants chalcone **1**, ethylcyanoacetate **2** and ammonium acetate **3** adsorbed over neutral alumina [22a] to MWI for about 8-10 minutes (Table 1). This solid supported synthesis is further modified to a relatively clean, efficient and economical procedure by utilizing the neat reaction technique in which **1**, **2** and **3** were condensed in the absence of support and solvent. To our surprise, excellent yield of products were obtained within just a few minutes (Table 1) of MWI. Further, the use of heterocyclic chalcones led to the synthesis of new pyridine derivatives.

This technique was further extended for the synthesis of 4,6-disubstituted-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one **6a-f**. The reaction of **4a-f** with $NH_2OH.HCl$ **5**, gave the required product **6a-f** in very good yield (Table 1) within 3-5 min of MWI. Few drops of base *i.e*. pyrrolidine was used to trap the HCl released by hydroxylamine hydrochloride. For comparative study **6a-f** was also synthesized from **4a-f** and **5** over basic alumina [22b] (Table 1).

The structural assignment of **4a-f** and **6a-f** was based on spectral and analytical data. The molecular formulae were confirmed by elemental analysis and mass spectroscopy (M^+/m/e). In conclusion, a novel environmentally benign methodology for the synthesis of pyridine and pyrazolo[3,4-*b*]pyridin-3-one has been developed, keeping modernization and simplification of classical procedure, avoiding volatile and toxic organic solvent. This neat reaction under MWs not only gave excellent yield of products with lesser reaction time but is also devoid of hazardous solvents and reagents.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT IR-1710 spectrophotometer. ^1H NMR were recorded on a Bruker Avance Spectrospin 300 (300 MHz) instrument using TMS as an internal standard and $CD_3OD/CDCl_3$/DMSO as a solvent. Elemental analysis was performed on a Heraeus CHN Rapid Analyser. EI mass spectra were recorded on a JEOL-JHS-DX 303 mass spectrometer. Microwave irradiation was carried out in a Kenstar Microwave Oven, Model No. OM 9925E (2450 MHz, 800 W). The temperature of the reaction was measured through an AZ, Mini Gun Type, Non-Contact IR Thermometer, Model No. 8868. The purity of compounds was verified on silica gel coated Al plates (Merck). The synthesis of 2-amino-4,6-diphenyl-3(ethylcarboxy)pyridine **4a** is representative of general procedure employed for **4a-f**.

2-Amino-4,6-diphenyl-3(ethylcarboxy)pyridine (**4a**).

Equimolar amount of benzalacetophenone (chalcone) **1** and ethylcyanoacetate **2** (0.005 mole) were condensed with 0.40 mole of ammonium acetate in a 250 ml Erlenmeyer flask. The reaction mixture was irradiated for the specified time inside the microwave oven (Table 1). Progress of reaction was monitored through TLC at an interval of 30 seconds. On completion of reaction as checked by TLC, the reaction mixture was cooled and the sticky product so obtained was titurated with chilled methanol. The product **4a** was separated, collected by filtration and washed with cold ethanol and recrystalized from ethanol.

The reaction was also persued over neutral alumina in an alumina bath [23] (solid support MWs) wherein the product was obtained on elution with ethanol. This compound **4a** had m.p. – 144-145 °C. IR (KBr) in cm^{-1}, 1656 (C≡N), 3445 (N-H); ^1H NMR (DMSO-d_6): δ 1.12 (t, 3H, CH_3), 4.01 (brs, 2H, NH), 4.31 (q, 2H, OCH_2), 7.21-7.98 (m, 11H, Ar-H).

Anal. Calcd. for $C_{20}H_{18}N_2O_2$ (M^+: m/e 318): C, 75.45; H, 5.66; N, 8.79. Found: C, 75.38; H, 5.42; N, 8.72.

2-Amino-4(4-methoxyphenyl)-6-phenyl-3-(ethylcarboxy)pyridine (**4b**).

This compound has m.p. – 298-299 °C. IR (KBr) in cm^{-1}; 1650 (C=N), 3440 (N-H); ^1H NMR ($CDCl_3$): δ 1.08 (t, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.21 (q, 2H, OCH_2), 4.95 (brs, 2H, NH), 6.83-7.99 (m, 10H, Ar-H).

Anal. Calcd. for $C_{21}H_{20}N_2O_3$ (M^+ : m/e 348): C, 72.41; H, 5.74; N, 8.04. Found: C, 72.39; H, 5.79; N, 8.10.

2-Amino-4(4-methoxyphenyl)-6-(3,4-dimethylphenyl)-3(ethylcarboxy)pyridine (**4c**).

This compound has m.p. – 158-159 °C. IR (KBr) in cm^{-1}; 1660 (C=N), 3449 (N-H); ^1H NMR (DMSO-d_6): δ 1.02 (t, 3H, CH_3), 2.35 (s, 6H, 3,4-CH_3-Ar), 3.74 (s, 3H, OCH_3), 4.20 (q, 2H, OCH_2), 4.98 (brs, 2H, NH), 6.82-7.68 (m, 8H, Ar-H).

Anal. Calcd. for $C_{23}H_{24}N_2O_3$ (M^+ : m/e 376) C, 73.40; H, 6.38; N, 7.44. Found: C, 73.88; H, 6.29; N, 7.48.

2-Amino-4(2-furyl)-6-methyl-3(ethylcarboxy)pyridine (**4d**).

This compound has m.p. – 192-193 °C. IR (KBr) in cm^{-1}; 1658 (C=N), 3440 (N-H); ^1H NMR ($CDCl_3$ + CD_3OD): δ 1.12 (t, 3H, CH_3), 3.10 (s, 3H, CH_3), 4.12 (q, 2H, OCH_2), 4.76 (brs, 2H, NH), 6.60 (s, 1H, Ar-H), 7.71 (d, 1H, furan C_5H), 6.31 (m, 2H, furan C_3-C_4-H).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$ (M^+: m/e 234): C, 63.41; H, 5.69; N, 11.38. Found: C, 63.36; H, 5.58; N, 11.30.

2-Amino-4(3-indolyl)-6-(4-bromophenyl)3-(ethylcarboxy)pyridine (**4e**).

This compound has m.p. – 185-186 °C. IR (KBr) in cm^{-1}; 1662 (C=N), 3441 (N-H); ^1H NMR ($CDCl_3$ + CD_3OD): δ 1.23 (t, 3H, CH_3), 4.05 (q, 2H, OCH_2), 4.25 (brs, 2H, N-H), 7.02-7.83 (m, 9H, Ar-H), 10.1 (brs, 1H, N-H indole).

Anal. Calcd. for $C_{22}H_{18}BrN_3O_2$ (M^+: m/e 435.9): C, 60.56; H, 4.12; N, 9.63. Found: C, 60.49; H, 4.23; N, 9.71.

2-Amino-4(benzo[1,3]dioxol-3-yl)-6-(4-bromophenyl)-3(ethylcarboxy)pyridine (**4f**).

This compound has m.p. – 252-253°C. IR (KBr) in cm^{-1}; 1665 (C=N), 3450 (N-H); ^1H NMR (DMSO-d_6): δ 1.18 (t, 3H, CH_3), 4.08 (q, 2H, OCH_2), 4.35 (brs, 2H, N-H), 5.82 (s, 2H, CH_2-piperonal), 7.21-7.45 (m, 8H, Ar-H).

Anal. Calcd. for $C_{21}H_{17}BrN_2O_4$ (M^+: m/e 440.9); C, 57.15; H, 3.85; N, 6.35. Found: C, 57.12; H, 3.79; N, 6.40.

4,6-Diphenyl-1,2-dihydropyrazolo[3,4-*b*]pyridine-3-one (**6a**).

Equimolar amount of **4a** (prepared above) and hydroxylamine hydrochloride was mixed in 100 ml Erlenmeyer flask. To the above reaction mixture few drops of pyrrolidine was added in

order to remove the excess of HCl. The reaction mixture was irradiated for 2-4 min inside the microwave oven. Progress of reaction was monitored through TLC. On completion of reaction, the flask was cooled the product was extracted from methanol and recrystallized from methanol. The reaction was also persued over basic alumina (solid support MW) in place of pyrrolidine where product was obtained on elution with ethanol. This compound **6a** had m.p. – 142-143 °C. IR (KBr) in cm^{-1}; 1631 (C=O), 3373 (NH); ^1H NMR ($CDCl_3$): δ 4.10 (brs, 1H, N-H), 7.21-7.98 (m, 11H, Ar-H), 8.01 (d, 1H, N-H).

Anal. Calcd. for $C_{18}H_{13}N_3O_1$ (M^+: m/e 287): C, 75.26; H, 4.52; N, 14.63. Found: C, 75.22; H, 4.49; N, 14.58.

4-(4-methoxyphenyl)-6-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridine-3-one (**6b**).

This compound was prepared according the method described above for compound **6a** and has m.p. – 197-198 °C. IR (KBr) in cm^{-1}; 1634 (C=O), 3373 (N-H); ^1H NMR ($CDCl_3$): δ 3.73 (s, 3H, OCH_3), 4.02 (brs, 1H, N-H), 6.83-7.9 (m, 10H, Ar-H), 8.10 (d, 1H, N-H).

Anal. Calcd. for $C_{19}H_{15}N_3O_2$ (M^+: m/e 317): C, 71.92; H, 4.73; N, 13.24. Found: C, 71.98; H, 4.79; N, 13.18.

4-(4-Methoxyphenyl)-6-(3,4-dimethylphenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (**6c**).

This compound was prepared according the method described above for compound **6a** and has m.p. – 207-208 °C. IR (KBr) in cm^{-1}; 1632 (C=O), 3375 (N-H); ^1H NMR (CD_3OD + $CDCl_3$): δ 2.35 (s, 6H, CH_3), 3.74 (s, 3H, OCH_3), 4.21 (brs, 1H, N-H), 6.82-7.68 (m, 8H, Ar-H), 8.06 (d, 1H, N-H).

Anal. Calcd. for $C_{21}H_{19}N_3O_2$ (M^+: m/e 345); C, 73.04; H, 5.50; N, 12.17. Found: C, 73.10; H, 5.55, N, 12.20.

4-(2-Furyl)-6-methyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (**6d**).

This compound was prepared according the method described above for compound **6a** and has m.p. – 210-211 °C. IR (KBr) in cm^{-1}; 1630 (C=O), 3370 (N-H), ^1H NMR (CD_3OD + $CDCl_3$): δ 3.10 (s, 3H, CH_3), 4.10 (brs, 1H, N-H), 6.60 (s, 1H, Ar-H), 7.71 (d, 1H, furan C_5-H), 6.31 (m, 2H, furan C_3-C_4-H), 8.05 (d, 1H, N-H).

Anal. Calcd. for $C_{11}H_9N_3O_2$ (M^+: m/e 215); C, 61.39; H, 41.8; N, 19.53. Found: C, 61.30; H, 4.21; N, 19.49.

4-(3-Indolyl)-6-(4-bromophenyl)-1,2-dihydropyrazolo[3,4-*b*]pyridine-3-one (**6e**).

This compound was prepared according the method described above for compound **6a** and has m.p. – 182-183 °C. IR (KBr) in cm^{-1}; 1630 (C=O), 3372 (N-H); ^1H NMR ($CDCl_3$ + CD_3OD): δ 4.03 (brs, 1H, N-H), 7.02-7.83 (m, 9H, Ar-H), 8.12 (d, 1H, N-H), 10.10 (brs, 1H, N-H indole).

Anal. Calcd. for $C_{20}H_{13}BrN_4O$ (M^+: m/e 404.9); C, 59.27; H, 3.21; N, 13.83. Found: C, 59.30; H, 3.25; N, 13.90.

4-(Benzo[1,3]dioxol-3-yl)-6(4-bromophenyl)-1,2-dihydropyrazolo[3,4-*b*]pyridine-3-one (**6f**).

This compound was prepared according the method described above for compound **6a** and has m.p. – 126-127 °C. IR (KBr) in cm^{-1}; 1632 (C=O), 3374 (N-H); ^1H NMR (DMSO-d_6): δ 4.20 (brs, 1H, N-H), 5.82 (s, 2H, CH_2-piperonal), 7.21-7.45 (m, 8H, Ar-H), 8.06 (d, 1H, N-H).

Anal. Calcd. for $C_{19}H_{12}BrN_3O_3$ (M^+: m/e 409.9). C, 55.62; H, 2.92; N, 10.24. Found: C, 55.70; H, 2.98; N, 10.29.

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REFERENCES AND NOTES

[1] F. Bigi, L. Chesini, R. Maggi and G. Sartori, *J. Org. Chem.*, **64**, 1033 (1999).

[2] R. S. Varma, *Green Chemistry*, **1**, 43045 (1999).

[3] P. Hermkens, H. Ottenheijm and D. Rees, *Tetrahedron*, **53**, 5643 (1997).

[4] J. Rebek, D. Brown and S.J. Zimmerman, *J. Am. Chem. Soc.*, **97**, 454 (1995).

[5] M. Kidwai, R. Venkataramanan, R.G. Garg and K.R. Bhushan, *J. Chem. Research(S)*, 586 (2000).

[6] M. Kidwai, P. Sapra, K.R. Bhushan and P. Misra, *Synthesis*, **10**, 1509 (2001).

[7] M. Kidwai, R. Venkataramanan and B. Dave, *J. Heterocyclic. Chem.*, **39**, 1045 (2002).

[8] M. Ankhiwaler and M.V. Hathi, *J. Indian Chem. Soc.*, **71**, 587 (1994).

[9] A. M. Van Leusen and J.W. Terpstra, *Tetrahedron Lett.*, **22**, 5097 (1981).

[10] D. J. Brown, *Comprehensive Heterocyclic Chemistry*, Boulton McKillop, **3**, 150 (1984).

[11] S. A. Lang, Y. I. Lin, *Comprehensive Heterocyclic Chemistry*, Boulton McKillop, **6**, 27 (1984).

[12] R. Li, G. L. Kenyon, F. E. Cohen, X. Chen B. Gong, J. N. Dominguez, E. Davidson, G. Miller, R. E. Miller, E. O. Nuzum, P. J. Rosenthal and J. H. McKerrow, *J. Med. Chem.*, **38**, 5031 (1995).

[13] J. C. Onyilagha, B. Malhotra, M. Elder, J. Christopher and G. H. N. Towers, *J. Plant Pathol.*, **19**, 133 (1997); *Chem. Abstr.*, **127**, 157896 (1997).

[14] G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. Dimarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, R. Zhang and S. Moreland, *J. Med. Chem.*, **38**, 119 (1995).

[15] J. L. Archibald, G. Bradley, A. Opaklo, T. J. Ward, J. C. White, C. Ennis, N. B. Shapperson, *J. Med. Chem.*, **33**, 646 (1990).

[16] M. H. Elnagdi, M. R. H. El Moghayar and G. E. H. Elgemie, *Adv. Heterocyclic. Chem.*, **41**, 319 (1987).

[17] M. H. Elnagoli, M. R. H. Elmoghayar and K. U. Sadek, *Adv. Heterocyclic. Chem.*, **48**, 223 (1990).

[18] M. N. Elnagdi, N. H. Taha, F. M. Abd El Ali, R. M. Abdel-Motaleb and F. F. Mahmoud, *Collect. Czech. Commun.*, **53**, 1089 (1988).

[19] C. R. Hardy, *Adv. Heterocyclic. Chem.*, **36**, 343 (1984).

[20] R. E. Orth, *J. Pharm. Sci.*, **57**, 537 (1968) and references cited therein.

[21a] M. Kidwai, S. Saxena, R. Mohan and R. Venkataramanan, *J. Chem. Soc. Perkin Trans. 1*, **16**, 1845 (2002); [b] M. Kidwai, R. Mohan, *Canadian J. Chem.*, **82**, 427 (2004); [c] M. Kidwai, Ruby, S. Rastogi, *Indian J. Chem.*, **43B**, 423 (2004); [d] M. Kidwai, S. Rastogi, Ruby, S. Saxena, *Zeitschrift fur Naturforscung*, **59B**, 606 (2004).

[22a] Aluminium oxide neutral, Brockmann I (Adrich Chem. Co., Cat No. 19, 997.4, ~ 150 mesh, 58 Å surface area 155 m^2/g) was used; [b] Aluminium oxide basic, Brockmann I (Aldrich Chem. Cat. No. 19, 944-3, ~ 150 mesh, 58 Å, surface area 155 m^2/g) was used.

[23] G. Bram, A. Loupy and M. Majdoub, *Tetrahedron*, **46**, 5167 (1990).