Microwave-Assisted, One-Pot Multicomponent Synthesis of Some New Cyanopyridines

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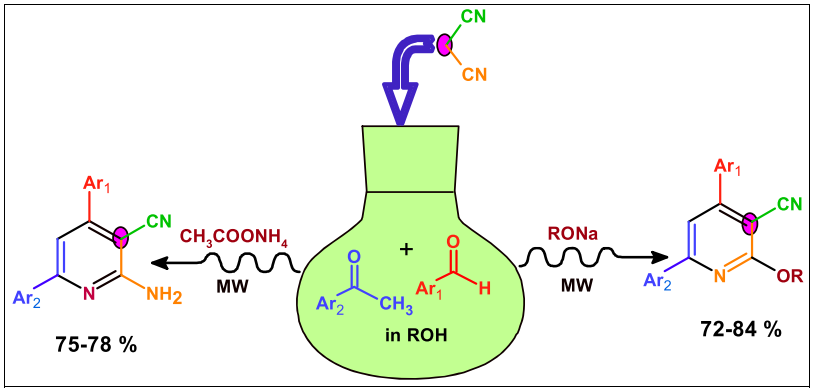

An efficient and facile synthesis of cyanopyridines via a one-pot four-component reaction of aromatic aldehydes, acetophenones, malononitrile, or 2-aminoprop-1-ene-1,1,3-tricarbonitrile in presence of sodium alkoxide or ammonium acetate under both microwave and thermal reaction conditions was introduced.

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INTRODUCTION

The improvement of synthetic methods for functionalized pyridines is a significant research matter in organic chemistry due to their importance in the topics of chemistry and biology. Pyridines are openly dispersed and found in natural products, pharmaceuticals, vitamins, and other functional as well as important materials [1–5]. In fact, the pyridine moiety system emerged integral backbone of more than thousands existing drugs [6–8].

Among a broad range of pyridines, cyanopyridine achieved a special attention due to it great therapeutic importance as antihypertensive [9], anticonvulsant [10], antihypertensive [11], antibacterial [12], anti-inflamatory [13], antifungal [14], cardiovascular [15], anti-Alzheimer's disease [16], antitumor [17], and antiallergic [18] properties. Therefore, the synthesis of cyanopyridinesis of current benefit owes to their massive occurrence in biologically active derivatives.

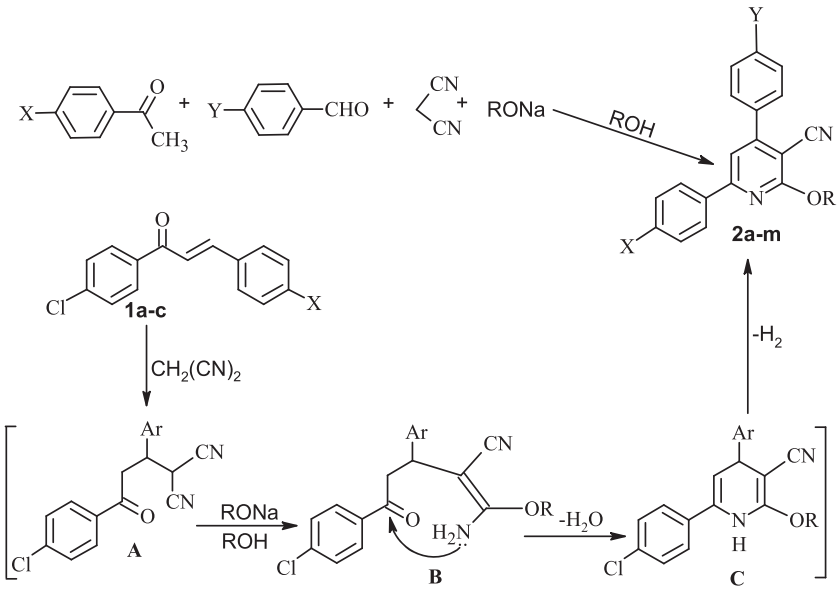
From an environmental and economic perspective, it is becoming obvious that the traditional methods of proceeding chemical synthesis are unsustainable and have to be changed. Multicomponent coupling reactions provide a solution because they are more cost effective, efficient, and less wasteful than traditional methods [19]. Microwave (MW) produces a powerful way to do synthetic chemistry in the light of the current paradigm shift to "green chemistry." Not only can it reduce chemical reaction times from hours to minutes but it can also reduce side reactions, increase yields, and enhance reproducibility compared with conventional heating conditions [20]. According to the current synthetic requirements, environmentally benign multicomponent procedures employing MW methodology are particularly welcome.

In view of the aforementioned facts, we have developed and designed a strategy to perform and achieve highly substituted pyridines in high yields applying the MW irradiation technique and using multicomponent coupling reaction.

RESULTS AND DISCUSSION

In this work, a simple one-pot and efficient method has been described for the synthesis of substituted cyanopyridines through a four-component reaction of aromatic aldehydes, acetophenones, malononitrile, and sodium alkoxide (molar ratio 1:1:1:1.3) in ethanol or methanol under MW (method A). Products of 4,6-diaryl-2-alkoxypyridine-3-carbonitriles **2a**–**m** were procured (Scheme 1) within a few minutes (1–5 min) of irradiation. The optimized results are summarized in Table 1. Good yields were obtained (72–84%), and problems associated with toxic solvent use were avoided. The same products **2a**–**m** were also produced in good yields under reflux conditions (68–82%) (method B). The reactions proceeded

Scheme 1



to completion almost in 3–9 h. And highly pure components were obtained in good-to-excellent yields, without using any chromatographic techniques, simply by filtration after pouring on ice-cold water and acidification by diluted HCl, washing with water several times, and recrystallization from ethanol. Also, product **2** was obtained by a three-component reaction of malononitrile, sodium alkoxide, and the corresponding chalcone under MW. From Table 1, it is clear that application of the MW technique is an efficient and clean method that is superior to the traditional thermal heating and affords products in excellent yields and high purity after shorter reaction times. On the other hand, we found that the reaction time and the yield vary depending upon the anion catalyst and that methoxypyridines can be produced in less time and more yield than ethoxypyridines.

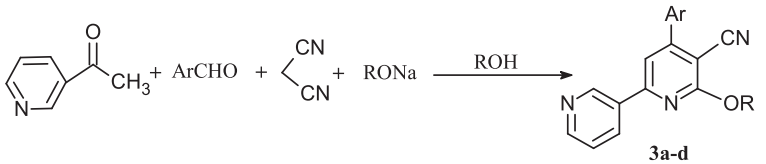
The chemical structure of these components is determined on the basis of IR, NMR spectral data, and elemental analyses. The IR spectra of **2a**–**m** did not contain any absorption band corresponding to a carbonyl group function. On the other hand, bands assignable for the nitrile stretching vibration absorption appeared at 2215–2225 cm^{-1}. In the ^{1}H-NMR spectra of the 2-methoxypyridines **2a**–**f**, a singlet at 4.12 ppm characteristic for the methoxyl group was afforded and the aromatic protons appeared at 7.08–8.03 ppm, while in the 2-ethoxypyridines **2g**–**m**, the ethyl group gave rise to a quartet around 4.59 ppm and a triplet at 1.43 ppm. The

Table 1

Comparison of the yields and reaction times for synthesis of products **2a**–**m** under MW and conventional conditions.

				MW irradiation		Conventional protocol	
				Method A		Method B	
Product	*X*	*Y*	*R*	Yield (%)	Time (min)	Yield (%)	Time (h)
2a	Cl	H	Me	84	2	80	4
2b	Cl	Cl	Me	81	1	79	5
2c	Cl	MeO	Me	83	1	82	3
2d	Cl	$(Me)_2N$	Me	79	2	77	4
2e	MeO	H	Me	80	2	74	4
2f	MeO	MeO	Me	78	3	78	4
2 g	Cl	H	Et	79	2	72	7
2 h	Cl	Cl	Et	80	4	74	6
2i	Cl	MeO	Et	77	2	69	8
2j	Cl	$(Me)_2N$	Et	76	5	70	9
2 k	MeO	H	Et	81	5	79	7
2 l	MeO	Cl	Et	77	3	71	7
2 m	MeO	MeO	Et	72	5	68	8

Scheme 2



3a-d

3a; Ar= 4-$MeOC_6H_4$, R= Me
3b; Ar= 4-$(Me)_2NC_6H_4$, R= Me
3c: Ar= H, R = Et
3d; Ar= 4-$(Me)_2NC_6H_4$, R= Et

aromatic protons show as a multiplet at 7.04–8.21 ppm. ^{13}C-NMR spectra substantiated the results of the IR and ^{1}H-NMR analyses. For example, the ^{13}C-NMR spectrum of **2a** shows that the peak at δ 55.04 could be attributed and characteristic for methoxide carbon in addition to the aromatic carbons at δ 164.83, 157.06, 156.54, 136.25, 136.06, 130.55, 129.72, 129.39, 129.28, 129.05, 115.60, 114.35, and 93.24.

The credible mechanism for the formation of products **2a**–**m** was presupposed to proceed through production of chalcone **1** by reaction between acetophenones and aromatic aldehydes, then a Michael addition of the malononitrile anion at α, β-unsaturated ketones to generated adduct **A** reacts with alkoxide anion to form intermediate **B**, which undergoes intramolecular cyclization through loss of water to produce **C**, and subsequent dehydrogenation of the cyclized product **C** procures to the 2-alkoxy cyanopyridines **2a**–**m** (Scheme 1).

Under the same reaction conditions, a one-pot reaction of aromatic aldehydes, 3-acetylpyridine, malononitrile, and sodium alkoxide was performing to give a new series of 4-heteroaryl-6-aryl-2-alkoxypyridine-3-carbonitriles **3a**–**d** with high yields (Scheme 2).

The same methodologies were prolonged for the synthesis of {amino[6-(4-chlorophenyl)-2-ethoxy-4-phenylpyridin-3-yl]methylidene}propanedinitrile **4** under the similar reaction conditions, using 4-chlorpacetophenone, benzaldehyde, tricyanoaminopropene, and sodium ethoxide. We have then looked into possible replacing sodium alkoxide by ammonium acetate, hoping to achieve 2-amino-6-(4-chlorophenyl)-4-arylpyridine-3-carbonitrile **5a**,**b** the goal was supposed to implement, and product **5a**,**b** was separated in about 71% yield (Scheme 3). The chemical structure of produces **4** and **5a**, **b** was approved by IR, NMR, and elemental analysis.

CONCLUSION

Microwave irradiation technique can be used as a facile and fast method for synthesis of some new substituted cyanopyridines in high yields compared with the conventional methods. Due to the availability of the starting materials, the simplicity of the procedures, and the high yields of the products, this synthetic approach might be valuable for the synthesis of such heterocyclic systems.

EXPERIMENTAL

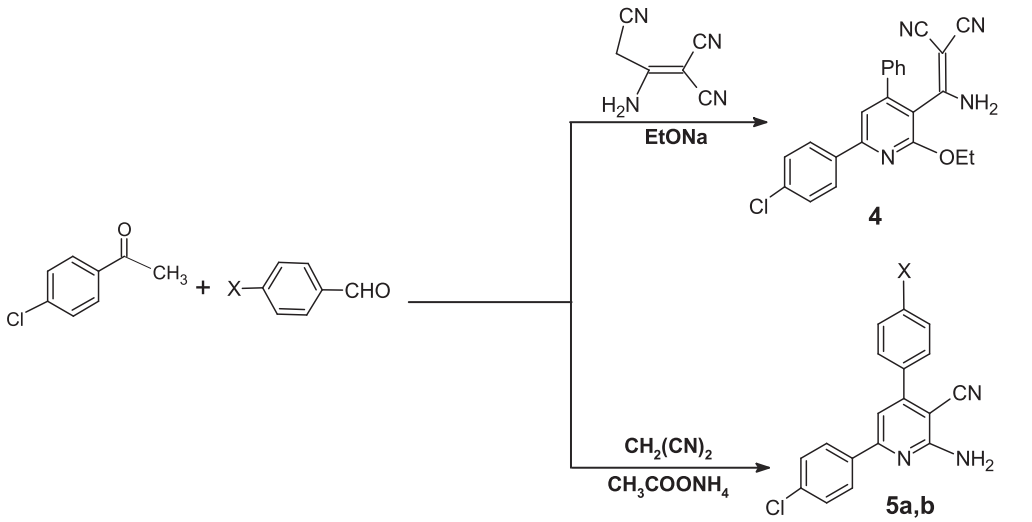
Melting points were measured with a Kofler melting point apparatus and uncorrected. Infrared spectra (IR) were recorded with an FT-IR ALPHBROKER-Platinum-ATR (Bruker, Germany). ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Bruker Bio Spin AG spectrometer (Bruker, Switzerland) at 400 MHz and 100 MHz, respectively. Elemental analyses were obtained on a Perkin-Elmer CHN analyzer (USA) model. MW irradiations were carried out in a Kenstar OM9925E MW oven (2450 MHz, 800 W; India).

General procedure for the synthesis of compounds 2a–m.

Method A: General procedure (MW irradiation). A mixture of 0.02 mol of aromatic aldehydes and 0.02 mol of acetophenone derivatives was added to sodium alkoxide solution (0.022 mol of sodium in 10 mL of each of absolute methanol and ethanol, respectively) and was stirred for 5 min at room temperature, then malononitrile (0.02 mol) was added and the reaction mixture was irradiated in an MW oven for 1–4 min (Table 1). After cooling to room temperature, the precipitated products were filtered and recrystallized from suitable solvent.

Method B: General procedure (conventional heating). A mixture of 0.02 mol of aromatic aldehydes and 0.02 mol of acetophenone derivatives was added to sodium alkoxide solution (0.022 mol of sodium in 60 mL of each of absolute methanol and ethanol, respectively) and was stirred for 5 min at room temperature, then malononitrile (0.02 mol) was added and the reaction mixture was refluxed for 3–9 h (Table 1). On completion of the reaction (TLC monitoring), the reaction mixture was allowed to cool to room temperature. The solid precipitates were collected by filtration, dried, and recrystallized from suitable solvent.

Scheme 3



5a: X= H; **5b**: X= OMe

6-(4-Chlorophenyl)-2-methoxy-4-phenylpyridine-3-carbonitrile (2a). mp 180°C; IR: 2987, 2946 (CH-aliph), 2225 (CN); ^{1}H-NMR: δ 8.30 (t, J = 4, 8 Hz, 2H, arom), 7.86 (s,1H, pyridine nucleus), 7.76 (s, 2H, arom), 7.60 (s, 5H, arom), 4.15 (s, 3H, OCH_3); ^{13}C-NMR: δ 164.83, 157.06, 156.54, 136.25, 136.06, 130.55, 129.72, 129.39, 129.28, 129.05, 115.60, 114.35, 93.24, 55.04. *Anal*. Calcd. for $C_{19}H_{13}ClN_2O$: C, 71.14; H, 4.08; N, 8.73. Found: C, 71.08; H, 4.20; N, 8.69.

4,6-Bis(4-chlorophenyl)-2-methoxypyridine-3-carbonitrile (2b). mp >300°C; IR: 2990, 2942 (CH-aliph), 2224 (CN); ^{1}H-NMR: δ 8.27 (d, J = 8 Hz, 2H, arom), 7.95 (d, J = 8 Hz, 2H, arom), 7.87 (s,1H, pyridine nucleus), 7.58 (t, J = 4, 12 Hz, 3H, arom), 7.12 (s, 1H, arom), 4.01 (s, 3H, OCH_3). *Anal*. Calcd. for $C_{19}H_{12}Cl_2N_2O$: C, 64.24; H, 3.40; N, 7.89. Found: C, 64.25; H, 3.43; N, 7.75.

6-(4-Chlorophenyl)-2-methoxy-4-(4-methoxyphenyl)pyridine-3-carbonitrile (2c). mp 236°C; IR: 2981, 2945 (CH-aliph), 2221 (CN); ^{1}H-NMR: δ 8. 30 (d, J = 8 Hz, 2H, arom), 7.82 (s, 1H, pyridine nucleus), 7. 75 (d, J = 8 Hz, 2H, arom), 7.60 (d, J = 4 Hz, 2H, arom), 7.15 (d, J = 8 Hz, 2H, arom), 4.14 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); ^{13}C-NMR: δ 161.44, 156.62, 156.31, 136.15, 135.96, 130.69, 129.69, 129.36, 114.84, 114.09, 92.73, 55.95, 54.97. *Anal*. Calcd. for $C_{20}H_{15}ClN_2O_2$: C, 68.48; H, 4.31; N, 7.99. Found: C, 68.50; H, 4.20; N, 8.01.

6-(4-Chlorophenyl)-4-[4-(dimethylamino)phenyl]-2-methoxypyridine-3-carbonitrile (2d). mp 287°C; IR: 2994, 2946 (CH-aliph), 2215 (CN); ^{1}H-NMR: δ 8.28 (s, 2H, arom), 7.77 (s, 1H, pyridine nucleus), 7.68 (s, 2H, arom), 7.60 (s, 2H, arom), 6.86 (s, 2H, arom), 4.12 (s, 3H, OCH_3), 3.02 (s, 6H, $N(CH_3)_2$). *Anal*. Calcd. for $C_{21}H_{18}ClN_3O$ (363): C, 69.32; H, 4.99; N, 11.55. Found: C, 69.42; H, 4.80; N, 11.45.

2-Methoxy-6-(4-methoxyphenyl)-4-phenylpyridine-3-carbonitrile (2e). mp 180°C; IR: 2950, 2844 (CH-aliph), 2217 (CN); ^{1}H-NMR: δ 8.24 (s, 2H, arom), 7.73 (s, 3H, 2H, arom + 1H, pyridine nucleus), 7.59 (s, 3H, arom), 7.08 (s, 2H, arom), 4.13 (s, 1H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C-NMR: δ 164.79, 162.01, 157.68, 156.66, 136.53, 130.37, 129.62, 129.24, 128.98, 114.82, 113.24, 91.73, 55.89, 54.82. *Anal*. Calcd. for $C_{20}H_{16}N_2O_2$ (316): C, 75.93; H, 5.10; N, 8.86. Found: C, 76.02; H, 5.19; N, 8.85.

2-Methoxy-4,6-bis(4-methoxyphenyl)pyridine-3-carbonitrile (2f). mp 196°C; IR: 2951, 2931, 2838 (CH-aliph), 2215 (CN); ^{1}H-NMR: δ 8.24 (s, 2H, arom), 7.72 (s, 3H, 2H, arom + 1H, pyridine nucleus), 7.14 (s, 2H, arom), 7.08 (s, 2H, arom), 4.13 (s, 3H, OCH_3), 3.85 (s, 6H, $2OCH_3$). *Anal*. Calcd. for $C_{21}H_{18}N_2O_3$ (346): C, 72.82; H, 5.24; N, 8.09. Found: C, 72.79; H, 5.32; N, 8.17.

6-(4-Chlorophenyl)-2-ethoxy-4-phenylpyridine-3-carbonitrile (2g). mp 148°C; IR: 2984, 2973 (CH-aliph), 2220 (CN); ^{1}H-NMR: δ 8.26 (t, J = 4 Hz, 2H, arom), 7.79 (s, 1H, pyridine nucleus), 7.74 (s, 2H, arom), 7.9 (m, 5H, arom), 4.64 (q, J = 4, 2H, CH_2), 1.46 (t, J = 4 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.47, 157.04, 156.52, 136.31, 136.03, 130.49, 129.65, 129.37, 129.25, 129.03, 115.59, 114.15, 93.28, 63.67, 15.00. *Anal*. Calcd. for $C_{20}H_{15}ClN_2O$ (334.5): C, 71.75; H, 4.52; N, 8.37. Found: C, 71.43; H, 4.28; N, 8.18.

4,6-Bis(4-chlorophenyl)-2-ethoxypyridine-3-carbonitrile (2h). mp 240°C; IR: 2995, 2961 (CH-aliph), 2218 (CN); ^{1}H-NMR: δ 8.30 (d, J = 8 Hz, 2H, arom), 7.87 (s, 1H, pyridine nucleus), 7.80 (d, J = 8 Hz, 2H, arom), 7.68 (d, J = 8 Hz, 2H, arom), 7.62 (d, J = 8 Hz, 2H, arom), 4.65 (q, J = 7 Hz, 2H, CH_2), 1.45 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{14}Cl_2N_2O$ (369): C, 65.06; H, 3.82; N, 7.59. Found: C, 65.21; H, 3.68; N, 7.58.

6-(4-Chlorophenyl)-2-ethoxy-4-(4-methoxyphenyl)pyridine-3-carbonitrile (2i). mp 162°C; IR: 2993, 2955, 2848 (CH-aliph), 2217 (CN); ^{1}H-NMR: δ 8.29 (d, J = 9 Hz, 2H, arom), 7.82 (s, 1H, pyridine nucleus), 7.76 (d, 2H, J = 9 Hz, arom), 7.72 (d, 2H, J = 9 Hz, arom), 7.16 (d, J = 9 Hz, 2H, arom), 4.63 (q, J = 7 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 1.44 (t, J = 7 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.61, 161.40, 156.62, 156.31, 136.20, 135.92, 130.66, 129.62, 129.35, 128.41, 115.89, 114.82, 113.90, 92.79, 63.57, 55.93, 14.78. *Anal*. Calcd. for $C_{21}H_{17}ClN_2O_2$ (364.5): C, 69.14; H, 4.70; N, 7.68. Found: C, 69.19; H, 4.99; N, 7.61.

6-(4-Chlorophenyl)-4-[4-(dimethylamino)phenyl]-2-ethoxypyridine-3-carbonitrile (2j). mp 209°C; IR: 2971, 2917, 2848 (CH-aliph), 2216 (CN); ^{1}H-NMR: δ 8.24 (s, 2H, arom), 7.72 (m, 3H, 2H, arom + 1H, pyridine nucleus), 7.66–758 (m, 2H, arom), 6.85 (s, 2H, arom), 4.59 (q, J = 5 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.01 (s, 6H, $N(CH_3)_2$), 1.42 (t, J = 5 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.84, 156.87, 155.88, 152.07, 136.40, 135.71, 130.11, 129.51, 129.29, 122.76, 116.39, 113.24, 112.25, 91.68, 63.38, 40.14, 14.80. *Anal*. Calcd. for $C_{22}H_{20}ClN_3O$ (377.5): C, 69.93; H, 5.33; N, 11.12. Found: C, 69.87; H, 5.22; N, 11.10.

2-Ethoxy-6-(4-methoxyphenyl)-4-phenylpyridine-3-carbonitrile (2k). mp 181°C; IR: 2984, 2947, 2898 (CH-aliph), 2216 (CN); ^{1}H-NMR: δ 8.21 (s, 2H, arom), 7.72 (m, 3H, 2H, arom + 1H, pyridine nucleus), 7.58 (m, 3H, arom), 7.07 (s, 2H, arom), 4.61 (q, J = 7 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 1.44 (t, J = 7 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.45, 161.98, 157.67, 156.68, 136.60, 130.33, 129.69, 129.55, 129.22, 128.96, 115.86, 114.82, 113.08, 91.79, 63.42, 55.89, 14.80. *Anal*. Calcd. for $C_{21}H_{11}N_2O_2$ (330): C, 76.34; H, 5.49; N, 8.48. Found: C, 76.57; H, 5.35; N, 8.31.

4-(4-Chlorophenyl)-2-ethoxy-6-(4-methoxyphenyl)pyridine-3-carbonitrile (2l). mp 231°C; IR: 2973, 2939, 2840 (CH-aliph), 2217 (CN); ^{1}H-NMR: δ 8.16 (s, 2H, arom), 7.71 (m, 2H, arom), 7.64 (m, 3H, 2H, arom + 1H, pyridine nucleus), 7.04 (s, 2H, arom) 4.56 (q, J = 4 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 1.42 (t, J = 4 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.38, 162.01, 157.77, 155.24, 135.41, 135.31, 130.84, 129.54, 129.24, 115.70, 114.77, 112.91, 91.65, 63.45, 55.85, 14.76. *Anal*. Calcd. for $C_{21}H_{17}ClN_2O_2$ (364.5): C, 69.14; H, 4.70; N, 7.68. Found: C, 79.31; H, 4.71; N, 7.70.

2-Ethoxy-4,6-bis(4-methoxyphenyl)pyridine-3-carbonitrile (2m). mp 184°C; IR: 2984, 2950, 2835 (CH-aliph), 2218 (CN); ^{1}H-NMR: δ 8.20 (s, 2H, arom), 7.71–7.66 (m, 3H, 2H, arom + 1H, pyridine nucleus), 7.13–7.07 (m, 2H, arom) 4.59 (q, J = 4 Hz, 2H, CH_2), 3.85 (s, 6H, $2OCH_3$), 1.43 (t, J = 4 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.57, 161.90, 161.26, 157.45, 156.23, 130.4, 129.80, 129.49, 128.70, 116.15, 114.78, 112.80, 91.36, 63.32, 55.89, 14.81. *Anal*. Calcd. for $C_{22}H_{20}N_2O_3$ (360): C, 73.32; H, 5.59; N, 7.77. Found: C, 73.31; H, 5.42; N, 7.64.

General procedure for the synthesis of compounds 3a–d.

Method A: General procedure (MW irradiation). A mixture of 0.02 mol of aromatic aldehydes and 0.02 mol of 3-acetylpyridine was added to sodium alkoxide solution (0.022 mol of sodium in 10 mL of each of absolute methanol and ethanol, respectively) and was stirred for 5 min at room temperature, then malononitrile (0.02 mol) was added and the reaction mixture was irradiated in a MW oven for 1–4 min. (Table 1). After cooling to room temperature, the precipitated products were filtered and recrystallized from suitable solvent.

Method B: General procedure (conventional heating). A mixture of 0.02 mol of aromatic aldehydes and 0.02 mol of 3-acetylpyridine was added to sodium alkoxide solution (0.022 mol of sodium in 60 mL of each of absolute methanol and ethanol, respectively) and was stirred for 5 min at room temperature, then malononitrile (0.02 mol) was added and the reaction mixture was refluxed for the time indicated in Table 1. On completion of the reaction (TLC monitoring), the reaction mixture was allowed to cool to room temperature. The solid precipitate was collected by filtration, dried, and recrystallized from suitable solvent.

6-Methoxy-4-(4-methoxyphenyl)-2,3′-bipyridine-5-carbonitrile (3a). Yield (method A 83%, method B 80); mp 241°C; IR: 2953, 2845 (CH-aliph), 2219 (CN); ^{1}H-NMR: δ 9.43 (s, 1H, pyridine nucleus), 8.71 (s, 1H, pyridine nucleus), 8.60 (d, J = 7 Hz, 1H, pyridine nucleus), 7.66 (s, 1H, pyridine nucleus), 7.77 (d, J = 9 Hz, 2H, arom), 7.57 (s, 1H, pyridine nucleus), 7.16 (d, J = 8 Hz, 2H, arom), 4.18 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3); ^{13}C-NMR: δ 165.09, 161.49, 156.69, 155.44., 151.55, 149.10, 135.26, 132.91, 130.75, 128.24, 124.24, 115.82, 114.87, 114.47, 93.15, 55.96, 55.10. *Anal*. Calcd. for $C_{19}H_{15}N_3O_2$ (317): C, 71.91; H, 4.76; N, 13.24, Found: C, 72.00; H, 4.62; N, 13.19.

4-[4-(Dimethylamino)phenyl]-6-methoxy-2,3′-bipyridine-5-carbonitrile (3b). Yield (method A 85%, method B 83); mp 264°C; IR: 2995, 2946, 2856 (CH-aliph), 2215 (CN); ^{1}H-NMR: δ 9.40 (s, 1H, pyridine nucleus), 8.69 (s, 1H, pyridine nucleus), 8.56 (d, J = 7 Hz, 1H, pyridine nucleus), 7.81 (s, 1H, pyridine nucleus) 7.69 (d, J = 8 Hz, 2H, arom), 7.55 (s, 1H, pyridine nucleus), 6.86 (d, J = 8 Hz, 2H,arom), 4.14 (s, 3H, OCH_3), 3.02 (s, 6H, $N(CH_3)_2$). *Anal*. Calcd. for $C_{20}H_{18}N_4O$ (330): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.83; H, 5.50; N, 17.00.

6-Ethoxy-4-phenyl-2,3′-bipyridine-5-carbonitrile (3c). Yield (method A 79%, method B 78); mp 232°C; IR: 2974, 2918, 2848 (CH-aliph), 2223 (CN); ^{1}H-NMR: δ 9.37 (s, 1H, pyridine nucleus), 8.64 (s, 1H, pyridine nucleus), 8.30 (m, 1H, pyridine nucleus), 7.93 (t, 3H, J = 8 Hz, 2H, arom + 1H, pyridine nucleus), 7.57–7.09 (m, 2H, arom), 7.09 (s, 1H, pyridine nucleus), 4.50 (q, J = 8 Hz, 2H, CH_2), 1.41 (t, J = 8 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.52, 155.78, 152.79, 150.70, 150.33, 148.50, 136.51, 134.75, 134.45,

134.27, 129.41, 124.04, 107.62, 93.67, 61.96, 14.97. *Anal*. Calcd. for $C_{19}H_{15}N_3O$ (301): C, 75.73; H, 5.02; N, 13.94. Found: C, 75.80; H, 5.00; N, 13.69.

4-[4-(Dimethylamino)phenyl]-6-ethoxy-2,3′-bipyridine-5-carbonitrile (3d). Yield (method A 82%, method B 80); mp 261°C; IR: 2984, 2900, 2812 (CH-aliph), 2216 (CN); ^{1}H-NMR: δ 9.37 (s, 1H, pyridine nucleus), 8.68 (d, J = 4 Hz, 1H, pyridine nucleus), 8.54 (d, J = 8 Hz, 1H, pyridine nucleus), 7.78 (s, 1H, pyridine nucleus), 7.78 (d, J = 9 Hz, 2H, arom), 7.54 (t, J = 8 Hz, 1H, pyridine nucleus), 6.85 (d, J = 8 Hz, 2H, arom), 4.62 (q, J = 7 Hz, 2H, CH_2), 3.02 (s, 6H, $N(CH_3)_2$), 1.44 (t, J = 7 Hz, 3H, CH_3); ^{13}C-NMR: δ 169.26, 167.42, 166.90, 151.31, 148.94, 135.07, 139.13, 130.17, 129.76, 129.46, 124.17, 113.60, 112.23, 107.62, 92.17, 63.50, 40.17, 14.79. *Anal*. Calcd. for $C_{21}H_{20}N_4O$ (344): C, 73.23; H, 5.85; N, 16.27. Found: C, 73.30; H, 5.78; N, 16.20.

Synthesis of {[6-(4-chlorophenyl)-2-ethoxy-4-phenylpyridin-3-yl] methylidene}-propanedinitrile 4. ***Method A: General procedure (MW irradiation).*** A mixture of benzaldehyde (0.02 mol), 4-chloroacetophenone (0.02 mol), and sodium ethoxide solution (0.022 mol of sodium in 15 mL of each of absolute methanol and ethanol, respectively) was stirred for 10 min at room temperature, then 2-aminoprop-1-ene-1,1,3-tricarbonitrile (0.02 mol) was added and the reaction mixture was irradiated in an MW oven for 3 min. On cooling at room temperature, the precipitated products were filtered and recrystallized from ethanol.

Method B: General procedure (conventional heating). A mixture of benzaldehyde (0.02 mol), 4-chloroacetophenone (0.02 mol), and sodium ethoxide solution (0.022 mol of sodium in 60 mL of each of absolute methanol and ethanol, respectively) was stirred for 10 min at room temperature, then 2-aminoprop-1-ene-1,1,3-tricarbonitrile (0.015 mol) was added and the reaction mixture was refluxed for the time indicated in Table 1. On completion of the reaction (TLC monitoring), the reaction mixture was allowed to cool to room temperature. The solid precipitate was collected by filtration, dried, and recrystallized from ethanol.

Yield (method A 89%, method B 87); mp > 300°C; IR: 3455, 3363 (NH_2), 2954, 2928, 2833 (CH-aliph), 2190, 2139 (2CN); ^{1}H-NMR: δ 8.09 (d, J = 8 Hz, 2H, arom), 7.71 (d, J = 8 Hz, 2H, arom), 7.53–7.46 (m, 5H, 3H, arom + 2H, NH_2), 7.27 (s, 1H, pyridine nucleus), 6.81 (s, 12H, arom); ^{13}C-NMR: δ 162.10, 154.35, 146.56, 138.77, 138.17, 133.82, 133.66, 128.91, 128.75, 128.68, 125.20, 109.68, 107.06, 56.50, 19.00. *Anal*. Calcd. for $C_{23}H_{17}ClN_4O$ (400.5): C, 68.91; H, 4.27; N, 13.98. Found: C, 68.89; H, 4.21; N, 13.41.

General procedure for the synthesis of compounds 5a,b. ***Method A: General procedure (MW irradiation).*** A mixture of aromatic aldehydes (0.02 mol), 4-chloroacetophenone (0.02 mol), and ammonium acetate (0.03 mol) was stirred for 15 min at room temperature, then malononitrile (0.02 mol) in 10 mL of ethanol was added and the reaction mixture was irradiated in an MW oven for 6 min. On cooling at room temperature, the precipitated products were filtered and recrystallized from ethanol.

Method B: General procedure (conventional heating). A mixture of aromatic aldehydes (0.02 mol), 4-chloroacetophenone (0.02 mol), and ammonium acetate (0.03 mol) was stirred for 15 min at room temperature, then malononitrile (0.02 mol) in 60 mL of ethanol was added and the reaction mixture was allowed to reflux for 9 h. On completion of the reaction (TLC monitoring), the reaction mixture was allowed to cool to room temperature. The solid precipitate was collected by filtration, dried, and recrystallized from ethanol.

2-Amino-6-(4-chlorophenyl)-4-phenylpyridine-3-carbonitrile (5a). Yield (method A 78%, method B 76); mp 228°C; IR: 3500, 3395 (NH_2), 2209 (CN); ^{1}H-NMR: δ 8.18 (d, J = 8 Hz, 2H, arom), 7.68 (d, 2H, J = 8 Hz, 2H, arom), 7.55 (d, J = 4 Hz, 5H, arom), 7.32 (s, 1H, pyridine nucleus), 7.06 (br, s, 2H, NH_2); ^{13}C-NMR: δ 161.27, 157.80, 155.57, 137.40, 136.91, 135.44, 130.06, 129.49, 129.15, 128.77, 117.28, 114.37, 109.81, 87.69. *Anal*. Calcd. for $C_{18}H_{12}ClN_3$ (305.5): C, 70.71; H, 3.96; N, 13.74. Found: C, 70.70; H, 4.00; N, 13.69.

2-Amino-6-(4-chlorophenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile (5b). Yield (method A 75%, method B 76); mp 243°C; IR: 3455, 3363 (NH_2), 2205(CN); ^{1}H-NMR: δ 8.16 (d, J = 12 Hz, 2H, arom), 7.67 (d, 2H, J = 8 Hz, 2H,arom), 7.56 (d, J = 8 Hz, 2H, arom), 7.28 (s, 1H, pyridine nucleus), 7.12 (d, J = 12 Hz, 2H, arom), 7.00 (br, s, 2H, NH_2), 3.85(s, 3H, OCH_3); ^{13}C-NMR: δ 161.36, 161.09, 157.68, 155.12, 137.06, 135.37, 130.26, 129.54, 129.44, 129.07, 117.51, 114.75, 109.69, 87.54, 55.90. *Anal*. Calcd. for $C_{19}H_{14}ClN_3O$ (335.5): C, 67.96; H, 4.20; N, 12.51. Found: C, 67.64; H, 4.13; N, 12.20.

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