A Simple Three-Component Condensation: Highly Efficient Microwave-Assisted One-Pot Synthesis of Polyfunctional Pyridine Derivatives

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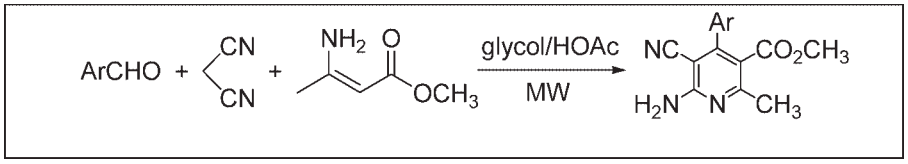

A simple facile one-step microwave-enhanced synthesis of methyl 4-substituted-6-amino-5-cyano-2-methylpyridine-3-carboxylate derivatives *via* a three-component reaction of aromatic aldehydes, malononitrile, and methyl 3-aminobut-2-enoate has been developed. It is an efficient and promising synthetic strategy to build the polyfunctional pyridine skeleton.

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INTRODUCTION

Multicomponent reactions (MCRs), an important class of organic reactions, are one-pot processes with at least three components to form a single product, which incorporates most or even all of the starting materials [1]. The huge interest for such multicomponent reactions during the last years has been oriented toward developing combinatorial chemistry procedures, because of their high efficiency and convenience of these reactions in comparison with multistage procedures. Hence, much scientific effort has been focused on the development of multicomponent procedures to prepare diverse heterocyclic compound libraries [2].

Pyridine and its derivatives have a vast range of biological activities. They have been used as herbicides [3], for enrichment of cereals [4], for regulation of arterial pressure [5], and cholesterol levels in blood [6]. In addition, some pyridines constitute an important class of antitumor compounds, which have been attracting significant attention [7,8]. Some polyfunctional pyridines are used as nonlinear optical materials [9], electrical materials [10], chelating agents in metal-ligand chemistry [11], and as fluorescent liquid crystals [12]. Therefore, development of efficient procedures toward functionalized pyridines is a quite important task in organic synthesis [13].

There is a great variety of methods described in the literature to synthesize similar skeleton [14]. Many precedent methods, however, have inevitable drawbacks: the aromatized polysubstituted pyridines were previously mostly synthesized through two steps: 1,4-DHPs were first prepared, which further proceeded to be oxidized to provide the corresponding aromatized compounds.

As part of an ongoing development of efficient protocols for the preparation of polysubstituted heterocycles from common intermediates [15], we recently discovered a simple and efficient method for the synthesis of polysubstituted pyridines (Scheme 1) *via* aldehydes, malononitrile, and methyl 3-aminobut-2-enoate under microwave (MW) irradiation.

RESULTS AND DISCUSSION

To optimize the reaction conditions, different organic solvents, such as ethanol, glycol, acetic acid, DMF, and mixed glycol-HOAc were tested in the synthesis of **4b** at 100°C. Table 1 show that the reactions in mixed glycol-HOAc (2:1, v/v) gave the best results (entry 6 of Table 1).

Moreover, to further optimize the reaction temperature, reactions using 4-chlorobenzaldehyde (**1b**, 1.0 mmol), malononitrile (**2**, 1.0 mmol), and methyl 3-aminobut-2-enoate (**3**, 1.0 mmol) were carried out in the range of 90–150°C in increments of 10°C each time in mixed glycol-HOAc (2:1, v/v) under microwave irradiation (initial power 100 W, maximum power 200 W). The results are shown in Table 2. When the temperature was increased from 90 to 120°C, the yield of product **4b** was improved. However, no significant increase in the

Scheme 1

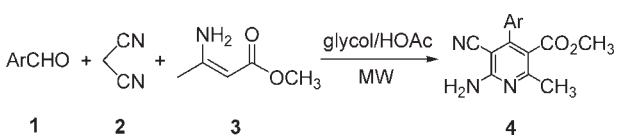

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Table 1

Solvent optimization for the synthesis of **4b** under MW.

Entry	Solvent	Time (min)	Yield (%)
1	EtOH	12	37
2	glycol	10	54
3	HOAc	10	55
4	DMF	10	48
5	glycol-HOAc(1:1)[a]	9	60
6	glycol-HOAc(2:1)[a]	9	76
7	glycol-HOAc(3:1)[a]	9	70
8	glycol-HOAc(4:1)[a]	9	64

[a] Volume ratio.

Table 2

Temperature optimization for the synthesis of **4b** under MW.

Entry	*T* (°C)	Time (min)	Yield (%)
1	90	9	70
2	100	9	76
3	110	9	83
4	120	7	88
5	130	7	85
6	140	7	83
7	150	7	80

yield of product **4b** was observed as the reaction temperature was raised from 130 to 150°C. Therefore, the temperature of 120°C was chosen for all further MW-assisted reactions.

The use of these optimal microwave experimental conditions [120°C, glycol-HOAc (2:1)] for the reactions of different aromatic aldehydes afforded good yields of polysubstituted pyridine derivatives. The results (Table 3, entries 1–10) indicated that aromatic aldehydes bearing either electron-donating (such as alkoxyl groups) or electron-withdrawing (such as nitro or halide groups) functional groups were all suitable for the reaction. Moreover, a heterocyclic aldehyde, thiophene-2-carbaldehyde (Table 3, entry 11), still showed high reactivity under these standard conditions.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of **4** could be explained by a possible reaction sequence presented in Scheme 2. Compound **4** is expected to proceed *via* initial condensation of aromatic aldehydes with malononitrile to afford alkylidenemalononitrile **5**, which further undergoes *in situ* Michael addition with methyl 3-aminobut-2-enoate **3**, to yield intermediate **7**, which is then cyclized and subsequently dehydrogenated to afford the aromatized product **4**. This type of hydrogen loss was well precedented [16].

To test the mechanism described earlier, the reaction of intermediate product **5c** and methyl 3-aminobut-2-enoate **3** was carried out under microwave irradiation conditions. The target compound **4c** was obtained, in similar yields by the one-pot reaction. The results supported the proposed mechanism (Scheme 3).

In this study, all the products were characterized by IR and ^{1}H NMR spectral data as well as elemental analyses. Furthermore, the structure of **4a** [17] was established by X-ray crystallographic analysis. The molecular structure of **4a** was shown in Figure 1.

In conclusion, the microwave-assisted synthesis of polysubstituted pyridines in this paper is an efficient methodology allowing the facile preparation of these important polycyclic compounds. This procedure offers several advantages including operational simplicity, increased safety for small-scale high-speed synthesis that makes it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

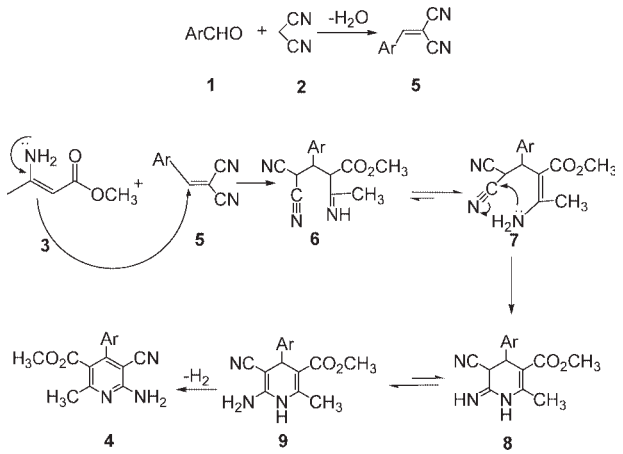
Microwave irradiation was carried out with a microwave oven Emrys™ Creator from Personal Chemistry, Uppsala,

Table 3

Synthesis of products **4** under MW.

Entry	Product	Ar	Time (min)	Yield (%)	Mp (°C)
1	**4a**	4-FC_6H_4	6	89	279–281
2	**4b**	4-ClC_6H_4	7	88	254–256
3	**4c**	4-BrC_6H_4	6	89	248–250
4	**4d**	4-$NO_2C_6H_4$	6	87	280–282
5	**4e**	4-$CH_3C_6H_4$	9	88	295–297
6	**4f**	2-ClC_6H_4	7	85	268–270
7	**4g**	C_6H_5	6	86	256–258
8	**4h**	3,4-$Cl_2C_6H_3$	8	88	252–254
9	**4i**	2,3-$(CH_3O)_2C_6H_3$	10	84	230–232
10	**4j**	3,4-$(OCH_2O)C_6H_3$	9	83	263–265
11	**4k**	thiophen-2-yl	8	82	274–276

Scheme 2



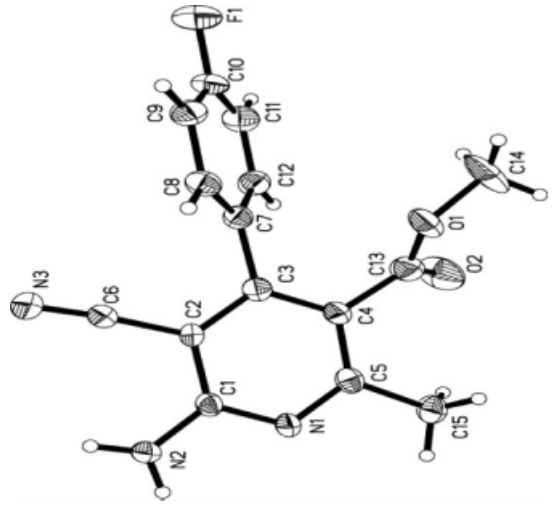


Figure 1. ORTEP diagram of **4a**.

Sweden. Melting points were determined in the open capillaries and were uncorrected. IR spectra were taken on a FTIR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin–Elmer 240c elemental analysis instrument. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the one-pot synthesis of compounds 4 under microwave irradiation conditions. Typically, in a 10-mL Emrys™ reaction vial, aldehyde **1** (1 mmol), malononitrile **2** (1 mmol, 0.066 g), methyl 3-aminobut-2-enoate **3** (1 mmol, 0.115 g), glycol (1.0 mL), and HOAc (0.5 mL) were mixed and then capped. The mixture was irradiated for a given time at 120°C under microwave irradiation (initial power 100 W and maximum power 200 W). Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was collected by Büchner filtration and was further purified by recrystallization from EtOH (95%) to give the pure product.

Methyl 6-amino-5-cyano-4-(4-fluorophenyl)-2-methyl-pyridine-3-carboxylate (4a). This compound was obtained according to the above general procedure; ir (potassium bromide): 3390, 3321, 3172, 3076, 2220, 1715, 1652, 1565, 1434, 1376, 1229, 1166, 1077, 958, 882, 665 cm^{-1}; ^1H NMR: 7.39–7.37 (m, 2H, 3′,5′-ArH), 7.36 (s, 2H, NH_2), 7.34–7.31 (m, 2H, 2′,4′-ArH), 3.43 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}FN_3O_2$: C, 63.15; H, 4.24; N, 14.73. Found: C, 63.12; H, 4.28; N, 14.75.

Methyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-pyridine-3-carboxylate (4b). This compound was obtained according to the above general procedure, this compound is known (RN: 176689-71-7) [14d]; ir (potassium bromide): 3383, 3324, 3178, 3086, 2221, 1721, 1653, 1576, 1496, 1378, 1284, 1197, 1094, 960, 863, 661 cm^{-1}; ^1H NMR: 7.57 (d, 2H, J = 8.4 Hz, 2′,4′-ArH), 7.40 (s, 2H, NH_2), 7.34 (d, 2H, J = 8.4 Hz, 3′,5′-ArH), 3.44 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.76; H, 4.05; N, 13.90.

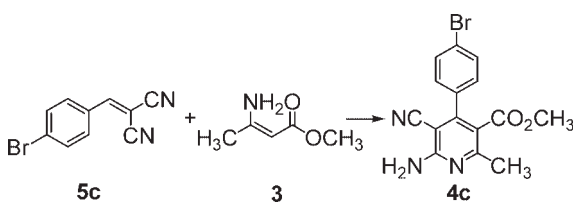
Methyl 6-amino-4-(4-bromophenyl)-5-cyano-2-methyl-pyridine-3-carboxylate (4c). This compound was obtained according to the above general procedure; ir (potassium bromide): 3405, 3313, 3161, 3069, 2217, 1718, 1651, 1557, 1437, 1376, 1283, 1104, 1012, 957, 882, 665 cm^{-1}; ^1H NMR: 7.71 (d, 2H, J = 8.4 Hz, 3′,5′-ArH), 7.40 (s, 2H, NH2), 7.27 (d, 2H, J = 8.4 Hz, 2′,4′-ArH), 3.45 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}BrN_3O_2$: C, 52.04; H, 3.49; N, 12.14. Found: C, 52.00; H, 3.45; N, 12.15.

Methyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-pyridine-3-carboxylate (4d). This compound was obtained according to the above general procedure; ir (potassium bromide): 3383, 3331, 3151, 3061, 2222, 1720, 1661, 1562, 1433, 1382, 1282, 1107, 1017, 955, 888, 665 cm^{-1}; ^1H NMR: 8.35 (d, 2H, J = 8.8 Hz, 3′,5′-ArH), 7.62 (d, 2H, J = 8.4 Hz, 2′,4′-ArH), 7.53 (s, 2H, NH_2), 3.40 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.70; H, 3.85; N, 17.95.

Methyl 6-amino-5-cyano-2-methyl-4-p-tolylpyridine-3-carboxylate (4e). This compound was obtained according to the above general procedure; ir (potassium bromide): 3338, 3321, 3173, 3048, 2219, 1712, 1652, 1560, 1434, 1376, 1286, 1110, 1077, 961, 882, 664 cm^{-1}; ^1H NMR: 7.30 (d, 2H, J = 7.6 Hz, 2′,4′-ArH), 7.19 (d, 2H, J = 8.0 Hz, 3′,5′-ArH), 7.11 (s, 2H, NH_2), 3.43 (s, 3H, OCH_3), 2.37 (s, 6H, CH_3). Anal. calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.35; H, 5.39; N, 14.95.

Methyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-methyl-pyridine-3-carboxylate (4f). This compound was obtained according to the above general procedure; ir (potassium bromide): 3385, 3325, 3177, 3052, 2222, 1717, 1654, 1594, 1431, 1378,

Scheme 3



1283, 1168, 1035, 958, 802, 663 cm^{-1}; ^1H NMR: 7.61–7.59 (m, 1H, ArH), 7.49 (s, 2H, NH2), 7.47–7.42 (m, 2H, ArH), 7.29–7.27 (m, 1H, ArH), 3.37 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.75; H, 4.04; N, 13.95.

Methyl 6-amino-5-cyano-2-methyl-4-phenylpyridine-3-carboxylate (4g). This compound was obtained according to the above general procedure, this compound is known (RN: 176689-69-3) [14d]; ir (potassium bromide): 3395, 3320, 3169, 3057, 2219, 1714, 1652, 1558, 1436, 1377, 1284, 1168, 1077, 960, 803, 662 cm^{-1}; ^1H NMR: 7.50–7.48 (m, 3H, ArH), 7.35 (s, 2H, NH_2), 7.31–7.29 (m, 2H, ArH), 3.39 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72; Found: C, 67.44; H, 4.95; N, 15.70.

Methyl 6-amino-4-(3,4-dichlorophenyl)-5-cyano-2-methylpyridine-3-carboxylate (4h). This compound was obtained according to the above general procedure; ir (potassium bromide): 3395, 3315, 3168, 3066, 2216, 1712, 1650, 1505, 1449, 1377, 1287, 1167, 1038, 926, 820, 775 cm^{-1}; ^1H NMR: 7.78 (d, 1H, J = 8.4 Hz, ArH), 7.68–7.67 (m, 1H, ArH), 7.47 (s, 2H, NH_2), 7.32 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.4 Hz, ArH), 3.47 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3). Anal. calcd for $C_{15}H_{11}Cl_2N_3O_2$: C, 53.59; H, 3.30; N, 12.50. Found: C, 53.60; H, 3.33; N, 12.55.

Methyl 6-amino-5-cyano-4-(2,3-dimethoxyphenyl)-2-methylpyridine-3-carboxylate (4i). This compound was obtained according to the above general procedure; ir (potassium bromide): 3384, 3331, 3177, 3050, 2224, 1713, 1657, 1567, 1433, 1335, 1265, 1193, 1091, 818, 743 cm^{-1}; ^1H NMR: 7.31 (s, 2H, NH_2), 7.15–7.09 (m, 2H, ArH), 6.64 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.4 Hz, ArH), 3.86 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3). Anal. calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.36; H, 5.25; N, 12.80.

Methyl 6-amino-4-(benzo[d][1,3]dioxol-6-yl)-5-cyano-2-methylpyridine-3-carboxylate (4j). This compound was obtained according to the above general procedure; ir (potassium bromide): 3380, 3325, 3171, 3052, 2225, 1712, 1658, 1567, 1430, 1338, 1264, 1183, 1090, 810, 750 cm^{-1}; ^1H NMR: 7.27 (s, 2H, NH_2), 7.02 (d, 1H, J = 8.0 Hz, ArH), 6.92–6.91 (m, 1H, ArH), 6.75 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz, ArH), 6.12 (s, 2H, CH_2), 3.48 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3). Anal. calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.76; H, 4.25; N, 13.54.

Methyl 6-amino-5-cyano-2-methyl-4-(thiophen-2-yl)pyridine-3-carboxylate (4k). This compound was obtained according to the above general procedure; ir (potassium bromide): 3390, 3320, 3163, 3060, 2219, 1713, 1654, 1560, 1434, 1330, 1261, 1168, 1041, 839, 736 cm^{-1}; ^1H NMR: 7.81 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.2 Hz, ArH), 7.35 (s, 2H, NH_2), 7.29–7.28 (m, 1H, ArH), 7.21–7.19 (m, 1H, ArH), 3.55 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3). Anal. calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73. Found: C, 57.16; H, 4.05; N, 15.34; S, 11.75.

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[17] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, MoKa radiation λ = 0.71073 Å). Crystal data for **4a**: Empirical formula $C_{15}H_{12}FN_3O_2$, colorless, crystal dimensions 0.38 × 0.10 × 0.07 mm, triclinic, space group p-1, a = 6.549(5) Å, b = 7.658(5) Å, c = 14.093(10) Å, α = 81.691(11)°, β = 86.585(11)°, γ = 84.035(10)°, V = 694.8(8) $Å^3$, M_r = 285.28, Z = 2, D_c = 1.364 Mg/m^3 , λ = 0.71073 Å, μ (MoKα) = 0.102 mm^{-1}, $F(000)$ = 296, S = 0.937, R_1 = 0.0655, wR_2 = 0.1296.