An Efficient and Greener Approach to the Synthesis of 3,5-Dicyanopyridin-2(1*H*)-one Derivatives in Aqueous Media under Microwave Irradiation Conditions

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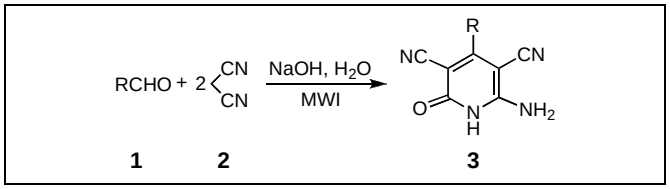

A facile and greener synthesis of a series of 3,5-dicyanopyridin-2(1*H*)-one derivatives was accomplished *via* the one-pot reaction of aldehyde, malononitrile and sodium hydroxide in aqueous media under microwave irradiation. This method had several advantages such as shorter route and time, lower cost, reduced environmental impact.

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INTRODUCTION

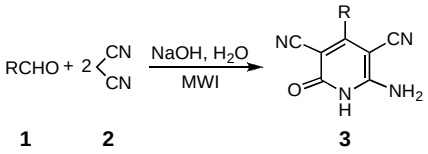
In recent years, amino-substituted 2-pyridones have attracted attention due to their promising features as an important core structure for the development of biologically active molecules [1]. Pharmaceuticals with the 2-pyridone skeleton have emerged as antitumor [2], antifungal [3], antibacterial [4], antiviral [5], antithrombotic [6] agents. Meanwhile it is well-known that the 2-pyridone ring system is a valuable building block in natural product synthesis [7]. On the other hand, pyridine dicarbonitriles have been exhibited as potential novel prion disease therapeutics [8]. Therefore design and synthesis of these compounds has been challenging.

Many synthetic methods for the preparation of 3,5-dicyanopyridin-2(1*H*)-one derivatives have been reported [9], analysis of these literatures reveals that the published approaches involve multi-step procedure, longer reaction time and use of organic solvents. To the best of our knowledge, the synthesis of 3,5-dicyanopyridin-2(1*H*)-one derivatives in aqueous media has seldom been reported [10]. For the stringent and growing environmental regulations, organic chemists are requested to develop environmentally benign synthetic methodologies. The most promising approaches are to perform organic reactions in aqueous media and use the raw material.

The microwave assisted organic synthesis has been a topic of continued studies as it could lead to easier operation and shorter reaction time as compared to the traditional heating methods [11]. Use of microwave irradiation (MWI) for the formation of carbon-heteroatom, especially carbon-nitrogen bonds, has been reported [12].

In continuation of our recent interest in the synthesis of 2-pyridone derivatives [13], we herein developed a greener synthesis of a series of 6-amino-4-aryl-1,2-dihydro-2-oxopyridine-3,5-dicarbonitrile in aqueous media by a one-pot reaction under MWI (Scheme 1).

Scheme 1



The products were synthesized by aldehyde (1 mmol), malononitrile (2 mmol) and sodium hydroxide (10%) in aqueous media under microwave irradiation (Scheme 1). After irradiation for 2-3 min, the 6-amino-4-aryl-1,2-dihydro-2-oxo-pyridine-3,5-dicarbonitrile derivatives were obtained.

RESULTS AND DISCUSSION

In an effort to search the suitable base, six reactions were carried out in parallel, with water as solvent. Several organic bases and inorganic bases have been employed instead of NaOH, it was shown that the reaction using NaOH (entry 6 of Table 1) gave the highest yield and the reaction time was the shortest. Therefore, NaOH was chosen as the optimum base.

To optimize the reaction conditions, the effects of different reaction temperature, concentrations of sodium hydroxide and microwave irradiation power were investigated in the synthesis of **3a**. To optimize the reaction temperature, the reaction of 4-chlorobenzaldehyde **1a** (1 mmol), malononitrile **2** (2 mmol) in the presence of sodium hydroxide (10%) was carried out in water at

temperatures ranging from 70 to 130 °C in an increments of 10 °C each time. The results showed that the yield of product **3a** was improved and the reaction time was shortened as the temperature was increased from 70 to 100 °C. The yield levelled off when the temperature was further increased to 110 and 130 °C. Therefore, 100 °C was chosen for all further reactions. Furthermore, the concentration of NaOH was found to be important as well. The same reaction was tested in different concentrations of NaOH at 100 °C under microwave irradiation conditions. When 10% NaOH was used, the yield was the highest. In addition, the power of MWI was optimized by carrying out the same reaction at 100, 150, 200 and 250 W, respectively, at 100 °C. The results showed that MWI at 150 W gave the highest yield.

Table 1

Investigation of bases in the synthesis of **3a** [a]

Entry	Base	Time (min)	Yield (%)
1	DMAP[b]	8	20
2	Pyridine	8	18
3	Et_3N	10	25
4	$NH_3 \cdot H_2O$	12	30
5	K_2CO_3	4	32
6	NaOH	2	48

[a] The product **3a** was synthesized under MWI in 100 °C and the power of MWI was 150W. [b] DMPA = N,N-dimethylamino-pyridine.

Under these optimized reaction conditions, we synthesized a series of products 6-amino-4-aryl-1,2-dihydro-2-oxopyridine-3,5-dicarbonitrile **3** (Table 2).

Table 2

The synthesis of **3** under MWI

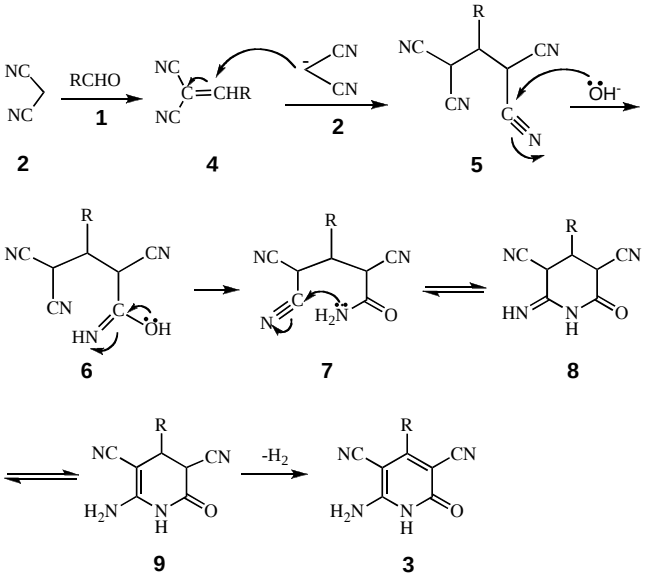
Product	R	Time(min)	Yield (%)	Mp (℃) (lit.)[a]
3a	4-ClC_6H_4	2	48	>300(>320)[b]
3b	4-BrC_6H_4	2	49	>300
3c	4-FC_6H_4	2	49	>300
3d	4-$CH_3C_6H_4$	3	45	>300(>320)[b]
3e	3,4-$(CH_3O)_2C_6H_3$	3	43	>300
3f	3, 4-$OCH_2OC_6H_3$	3	43	>300
3g	4-$CH_3OC_6H_4$	3	44	>300(290)[b]
3h	3,4,5-$(CH_3O)_3C_6H_2$	3	41	>300
3i	3-CH_3O-4-OHC_6H_4	3	41	>300
3j	4-$N(CH_3)_2C_6H_4$	3	47	>300
3k	3-$NO_2C_6H_4$	2	44	>300
3l	C_6H_5	3	42	>300(>320)[b]
3m	2-C_4H_3S	3	46	>300
3n	$CH_3(CH_2)_3$	3	41	>300
3o	$CH_3(CH_2)_2$	3	40	>300

[a] Melting points are uncorrected; [b] Known compounds (**3a**, **3d**, **3g**, **3l**, ref. 12(i).

We found that this protocol can be applied not only for the aromatic aldehydes with either electron-withdrawing groups or electron-donating groups, but also for heterocyclic and aliphatic aldehydes.

This reaction of aldehydes, malonitrile and sodium hydroxide may occur *via* a mechanism of condensation, Michael addition, cyclization and elimination. The condensation between aldehyde **1** and malonitrile **2** gives the intermediate **4** which further undergoes *in situ* Michael addition reaction with another malononitrile **2** to yield intermediate **5**, followed by the nucleophilic attack of OH to CN group to afford compound **6**, which undergoes intramolecular cyclization, isomerisation, dehydrogenization, to finally afford **3** (Scheme 2).

Scheme 2



Moreover, we performed the synthesis of **3** under both MWI and classical heating conditions at 100 °C. The reactions were efficiently promoted by MWI and the reaction time was strikingly shortened to 2–3 min from 2–3 h required under traditional heating conditions and the yields were increased to 40–49% from 25–37%. Therefore, microwave irradiation exhibited several advantages over the conventional heating by significantly reducing the reaction time and dramatically improving the reaction yield owing to a specific nonthermal microwave effect.

All the products were characterized by IR, ^{1}H NMR and elemental analysis. Furthermore, the structure of **3a** was established by an X-ray crystallographic analysis [14] (Figure 1).

In conclusion, we developed a greener synthesis of amino-substituted 3,5-dicyanopyridone using raw material. This method not only afforded a new method for the synthesis of 3,5-dicyanopyridone derivatives but also avoided using the organic solvent reducing environmental impact.

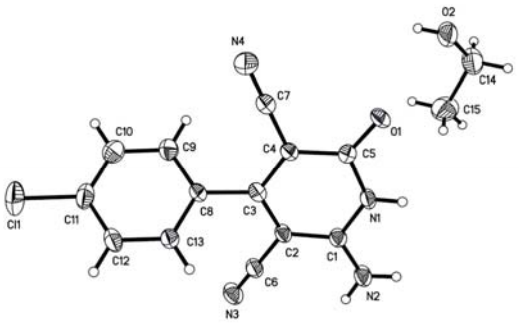


Figure 1

EXPERIMENTAL

All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT-IR-tensor 27 spectrometer. ^{1}H NMR spectra were measured on a 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.

General Procedure for preparation of 6-amino-4-substituted-1,2-dihydro-2-oxopyridine-3,5-dicarbonitrile (3). A solution of the appropriate aldehyde (1 mmol), malononitrile (2 mmol), sodium hydroxide (10%) and water (2 mL) was irradiated for 2-3 min (TLC) at 100°C with power 150 W. The reaction mixture was cooled to room temperature, neutralized with HOAc and then washed out with water until neutral pH was obtained, filtered to give the crude product, which was further purified by recrystallization from EtOH-DMF (**3a**-**3o**). All the products were characterized by IR, ^{1}H NMR and elemental analysis.

6-Amino-4-(4-chlorophenyl)-1,2-dihydro-2-oxopyridine-3,5-dicarbonitrile (3a). This compound was obtained according to above general procedure; ir (potassium bromide): 3450, 3317, 3205, 2216, 1669, 1590, 1484, 1378, 1267, 1094, 1015, 831, 679 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.53 (d, 2H, ArH, J = 8.4 Hz), 7.64 (d, 2H, ArH, J = 8.4 Hz), 7.72 (brs, 2H, NH_2), 11.94 (s, 1H, NH). *Anal*. Calcd. for $C_{13}H_7ClN_4O$: C, 57.69; H, 2.61; N, 20.70. Found: C, 57.75; H, 2.54; N, 20.63.

6-Amino-4-(4-bromophenyl)-1,2-dihydro-2-oxopyridine-3,5-dicarbonitrile (3b). This compound was obtained according to above general procedure; ir (potassium bromide): 3450, 3320, 3206, 2216, 1668, 1590, 1484, 1392, 1265, 1042, 1011, 823, 671 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.46 (d, 2H, ArH, J = 8.8 Hz), 7.77 (d, 2H, ArH, J = 8.4 Hz), 7.95 (brs, 2H, NH_2), 11.98 (s, 1H, NH). *Anal*. Calcd. for $C_{13}H_7BrN_4O$: C, 49.55; H, 2.24; N, 17.78. Found: C, 49.63; H, 2.17; N, 17.82.

6-Amino-4-(4-fluorophenyl)-1,2-dihydro-2-oxopyridine-3,5-dicarbonitrile (3c). This compound was obtained according to above general procedure; ir (potassium bromide): 3445, 3326, 3208, 2218, 1681, 1588, 1483, 1376, 1267, 1165, 840, 685 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.40 (t, 2H, ArH, J = 8.8 Hz), 7.57 (t, 2H, ArH, J = 8.8 Hz), 8.00 (brs, 2H, NH_2), 11.88 (s, 1H, NH). *Anal*. Calcd. for $C_{13}H_7FN_4O$: C, 61.42; H, 2.78; N, 22.04. Found: C, 61.55; H, 2.59; N, 22.12.

6-Amino-1,2-dihydro-2-oxo-4-p-tolylpyridine-3,5-dicarbonitrile (3d). This compound was obtained according to above general procedure; ir (potassium bromide): 3445, 3326, 3208, 2218, 1681, 1588, 1483, 1376, 1267, 1165, 840, 685 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 7.40 (t, 2H, ArH, J = 8.8 Hz), 7.57 (t, 2H, ArH, J = 8.8 Hz), 8.00 (brs, 2H, NH_2), 11.88 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39. Found: C, 67.23; H, 4.14; N, 22.51.

6-Amino-1,2-dihydro-4-(3,4-dimethoxyphenyl)-2-oxopyridine-3,5-dicarbonitrile (3e). This compound was obtained according to above general procedure; ir (potassium bromide): 3530, 3321, 3211, 2217, 1672, 1552, 1482, 1332, 1270, 1148, 1023, 870, 682 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 7.06–7.13 (m, 3H, ArH), 7.61 (brs, 2H, NH_2), 11.90 (s, 1H, NH). *Anal*. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.93; H, 4.04; N, 18.98.

6-Amino-1,2-dihydro-4-(3,4-methylenedioxylphenyl)-2-oxopyridine-3,5-dicarbonitrile (3f). This compound was obtained according to above general procedure; ir (potassium bromide): 3450, 3324, 3114, 2217, 1678, 1570, 1484, 1343, 1260, 1161, 1041, 927, 810, 686 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 6.15 (s, 2H, OCH_2O), 6.98 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz, ArH), 7.07-7.09 (m, 2H, ArH), 7.78 (brs, 2H, NH_2), 11.92 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_8N_4O_3$: C, 60.00; H, 2.88; N, 19.99. Found: C, 60.08; H, 2.79; N, 19.89.

6-Amino-1,2-dihydro-4-(4-methoxyphenyl)-2-oxopyridine-3,5-dicarbonitrile (3g). This compound was obtained according to above general procedure; ir (potassium bromide): 3566, 3329, 3189, 2232, 2217, 1678, 1590, 1484, 1304, 1266, 1190, 1029, 833, 687 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 7.09 (d, 2H, J = 8.8 Hz, ArH), 7.45 (d, 2H, J = 8.8 Hz, ArH), 7.78 (brs, 2H, NH_2), 11.87 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.22; H, 3.83; N, 21.12.

6-Amino-1,2-dihydro-4-(3,4,5-trimethoxyphenyl)-2-oxopyridine-3,5-dicarbonitrile (3h). This compound was obtained according to above general procedure; ir (potassium bromide): 3418, 3330, 3189, 2213, 1680, 1594, 1513, 1414, 1323, 1253, 1131, 995, 850, 671 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.74 (s, 3H, OCH_3), 3.82 (s, 6H, $2OCH_3$), 6.83 (s, 2H, ArH), 7.94 (brs, 2H, NH_2), 11.88 (s, 1H, NH). *Anal*. Calcd. for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.95; H, 4.26; N, 17.26.

6-Amino-1,2-dihydro-4-(4-hydroxy-3-methoxyphenyl)-2-oxopyridine-3,5-dicarbonitrile (3i). This compound was obtained according to above general procedure; ir (potassium bromide): 3450, 3329, 3173, 2214, 1687, 1604, 1549, 1444, 1281, 1215, 1137, 878, 818, 667 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 6.87-6.93 (m, 2H, ArH), 7.06 (s, 1H, ArH), 7.70 (brs, 2H, NH_2), 9.53 (s, 1H, OH), 11.87 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.67; H, 3.45; N, 19.99.

6-Amino-4-(4-(dimethylamino)phenyl)-1,2-dihydro-2-oxopyridine-3,5-dicarbonitrile (3j). This compound was obtained according to above general procedure; ir (potassium bromide): 3440, 3330, 3201, 2214, 1685, 1587, 1531, 1478, 1371, 1205, 1168, 946, 819, 684 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.00 (s, 6H, $2CH_3$), 6.80 (d, 2H, J = 8.8 Hz, ArH), 7.37 (d, 2H, J = 8.8 Hz, ArH), 7.62 (brs, 2H, NH_2), 11.66 (s, 1H, NH). *Anal*. Calcd. for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.69; N, 25.07. Found: C, 64.66; H, 4.61; N, 25.16.

6-Amino-1,2-dihydro-4-(3-nitrophenyl)-2-oxopyridine-3,5-dicarbonitrile (3k). This compound was obtained according to above general procedure; ir (potassium bromide): 3546, 3338,

3189, 2214, 1670, 1646, 1529, 1479, 1353, 1269, 1092, 840, 785, 669 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.88-8.01 (m, 4H, ArH), 7.87 (brs, 2H, NH_2), 11.85 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_7N_5O_3$: C, 55.52; H, 2.51; N, 24.90. Found: C, 55.66; H, 2.43; N, 24.84.

6-Amino-1,2-dihydro-2-oxo-4-phenylpyridine-3,5-dicarbonitrile (**3l**). This compound was obtained according to above general procedure; ir (potassium bromide): 3460, 3311, 3110, 2218, 1675, 1635, 1540, 1486, 1440, 1266, 1043, 874, 718, 649 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.47-7.50 (m, 2H, ArH), 7.52-7.56 (m, 3H, ArH), 7.81 (brs, 2H, NH_2), 11.90 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_8N_4O$: C, 66.10; H, 3.41; N, 23.72. Found: C, 66.03; H, 3.38; N, 23.66.

6-Amino-1,2-dihydro-2-oxo-4-(thiophen-2-yl)pyridine-3,5-dicarbonitrile (**3m**). This compound was obtained according to above general procedure; ir (potassium bromide): 3443, 3309, 3228, 2213, 1680, 1634, 1540, 1477, 1427, 1240, 1042, 862, 719, 683 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.25-7.28 (m, 1H, thiophenyl-H), 7.53-7.53 (m, 1H, thiophenyl-H), 7.81 (brs, 2H, NH_2), 7.92-7.94 (m, 1H, thiophenyl-H), 11.90 (s, 1H, NH). *Anal.* Calcd. for $C_{11}H_6N_4OS$: C, 54.54; H, 2.50; N, 23.13; S, 13.24. Found: C, 54.46; H, 2.63; N, 23.26; S, 13.31.

6-Amino-4-butyl-1,2-dihydro-2-oxopyridine-3,5-dicarbonitrile (**3n**). This compound was obtained according to above general procedure; ir (potassium bromide): 3440, 3326, 3203, 2216, 1672, 1634, 1589, 1494, 1374, 1270, 1166, 853, 720, 667 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.92 (t, 3H, J = 7.2 Hz, CH_3), 1.35-1.40 (m, 2H, CH_2), 1.55-1.59 (m, 2H, CH_2), 2.61 (t, 2H, J = 7.6 Hz, CH_2), 7.71 (brs, 2H, NH_2), 11.68 (s, 1H, NH). *Anal.* Calcd. for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.22; H, 5.61; N, 25.99.

6-Amino-1,2-dihydro-2-oxo-4-propylpyridine-3,5-dicarbonitrile (**3o**). This compound was obtained according to above general procedure; ir (potassium bromide): 3445, 3325, 3201, 2217, 1672, 1635, 1589, 1494, 1374, 1272, 1167, 835, 704, 669 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.97 (t, 3H, J = 7.6 Hz, CH_3), 1.61-1.67 (m, 2H, CH_2), 2.60 (t, 2H, J = 7.2 Hz, CH_2), 7.70 (brs, 2H, NH_2), 11.69 (s, 1H, NH). *Anal.* Calcd. for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.55; H, 4.87; N, 27.88.

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[14] 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 Siemens P4 diffractometer. Crystal data for **3a**: $C_{13}H_7ClN_4O{\cdot}C_2H_5OH$, yellow, crystal dimension 0.14 x 0.09 x 0.03mm, Triclinic, space group P-1, a = 6.779 (15) Å, b = 10.43 (2) Å, c = 11.29 (2) Å, α = 88.63 (4) °, β = 84.64 (5) °, γ = 81.70 (5) °, V = 786 (3) $Å^3$, Mr = 316.74, Z = 2, Dc = 1.338 g/cm^3, λ = 0.71073 Å, μ ($Mo K\alpha$) = 0.255 mm^{-1}, $F(000)$ = 328, S = 1.001, R_1 = 0.0580, wR_2 = 0.1258.