An Efficient and Facile Procedure for the Synthesis of 4,6-Diaryl-2(1*H*)-pyridones under Solvent-free Conditions

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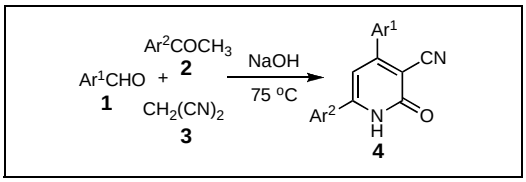

An efficient and convenient method for the preparation of 4,6-diaryl-2(1*H*)-pyridones by the one-pot reaction of aromatic aldehydes, aromatic ketones and malononitrile, in the presence of sodium hydroxide under solvent-free condition is reported. This method has the advantages of good yields, mild reaction conditions, easy work-up, inexpensive reagents and being environmentally friendly over the existing procedures.

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INTRODUCTION

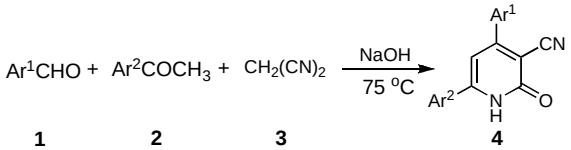
The nucleus of 2-pyridone occurs widely in the structures of biologically natural alkaloids [1]. Many derivatives of 2-pyridone are frequently used as intermediates for the construction of alkaloids [2]. Even some derivatives of 4,6-diaryl-2-pyridone, such as the simple structural related 2-pyridones, are recognized as potent LTB_4 antagonist [3]. Numerous methods [4] have been reported for the synthesis of 2-pyridone derivatives, because of the biological importance associated with these compounds. However, these methods suffer from several drawbacks such as a long reaction time, an excess of volatile organic solvent, lower product yields, and harsh refluxing conditions. Therefore, the development of a simple and efficient method for the preparation of 2-pyridone derivatives is an active area of research and there is scope for further improvement involving milder reaction conditions and higher product yields.

In recent years, solvent-free organic reactions [5] have caused great interests, which have many advantages such as high efficiency and selectivity, easy separation and purification, mild reaction conditions, and benefit to industry as well as environment. Some solvent-free reactions can be carried out with just heating [6]. In continuation to our ongoing endeavour on the application of solvent-free condition for the synthesis of organic compounds [7], we herein describe a practical and simple method to prepare 4,6-diaryl-2-pyridone with heating raw material under dry conditions.

RESULTS AND DISCUSSION

The synthesis of 4,6-diaryl-2-pyridone is illustrated in Scheme 1. In the presence of NaOH, the reactions of various aromatic aldehydes **1** and aromatic ketones **2** with malononitrile **3** were carried out respectively to afford the corresponding products **4** (Table 1). All reactions were completed in about 30 min and the yields of products were high. As shown in Table 1, we can see a series of **1** and **2**, either bearing electron-withdrawing groups (such as halide) or electron-donating groups (such as methyl group and alkoxyl group), reacting with **3** to give the corresponding products **4** under same reaction conditions. Therefore we concluded that the electronic nature of the substituents has no significant effect on this reaction. Because the reaction worked under solvent-free condition, the handling procedure of reaction was very simple.

Scheme I



The structure of each product **4a-r** was established on the basis of spectroscopic data and confirmed by X-ray diffraction studies on single crystals of **4c** [8] (X-ray crystal structure of **4c** shown in Figure 1).

Although the detailed mechanism of the above reaction has not been clarified yet, the formation of compound **4** could be explained by a possible mechanism presented in Scheme 2. At first, the Aldol condensation takes place from aromatic aldehydes **1** and aromatic ketones **2** to give intermediate **5**, or alternatively, the Knoevenagel conden–sation takes place by aldehydes **1** and malono–nitrile **3** to give intermediate **6**. Then, the intermediate **5** and **6** under-goes the Michael reaction with malononitrile **3** and

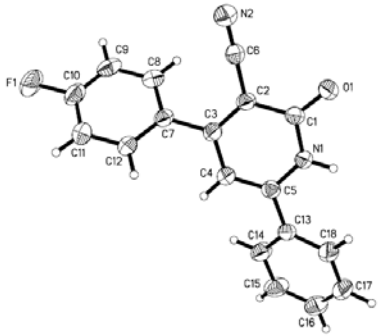


Figure 1. The structure of compound **4c**.

the intramolecule nucleophilic addition and dehydration. The formation product **4** from **10** could be due to dehydrogenation by the atmospheric oxygen.

In conclusion, we have developed a simple and novel method for the synthesis of 4,6-diaryl-2-pyridone under solvent-free condition by one-pot reactions of aromatic aldehydes, aromatic ketones, and malononitrile. Because of avoiding the use of toxic organic solvent, this protocol has advantages of cheap starting materials, excellent yield, mild reaction conditions, simple experimental procedure and friendly environment. We believe that the present methodology addresses the current devise toward green chemistry.

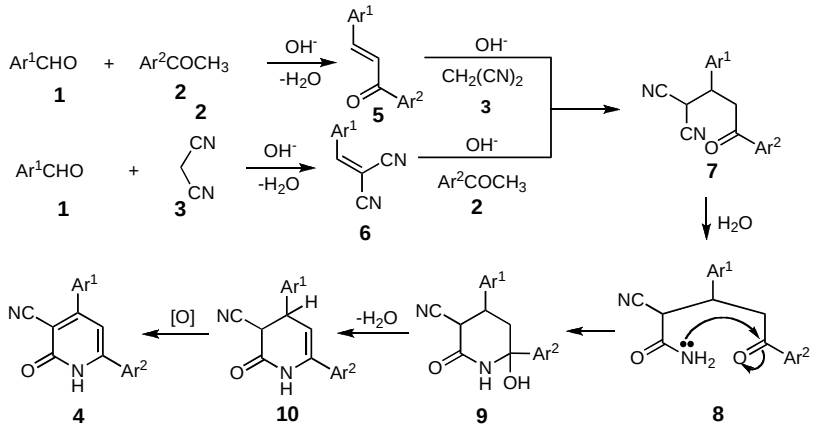
Table

Synthesis of product **4** under solvent-free conditions

Entry	Ar^1	Ar^2	Product	Yeilds
1	C_6H_5	4-$CH_3OC_6H_4$	**4a**	80
2	C_6H_5	4-ClC_6H_4	**4b**	78
3	4-FC_6H_4	C_6H_5	**4c**	83
4	4-ClC_6H_4	C_6H_5	**4d**	81
5	2-ClC_6H_4	C_6H_5	**4e**	81
6	2,4-$Cl_2C_6H_3$	C_6H_5	**4f**	83
7	3,4-$Cl_2C_6H_3$	C_6H_5	**4g**	85
8	4-BrC_6H_4	C_6H_5	**4h**	79
9	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	**4i**	80
10	3,4-$OCH_2OC_6H_3$	C_6H_5	**4j**	78
11	4-$CH_3C_6H_4$	4-BrC_6H_4	**4k**	87
12	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	**4l**	84
13	4-BrC_6H_4	4-ClC_6H_4	**4m**	80
14	3,4-$(CH_3)_2C_6H_3$	4-$CH_3C_6H_4$	**4n**	72
15	3,4-$Cl_2C_6H_3$	4-$CH_3C_6H_4$	**4o**	78
16	4-ClC_6H_4	4-$CH_3OC_6H_4$	**4p**	77
17	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**4q**	76
18	2,4-$Cl_2C_6H_3$	4-$CH_3OC_6H_4$	**4r**	80

aromatic ketones **2** respectively and the same 2-(3-oxo-1,3-diarylpropyl)malononitrile **7** is obtained. Subsequently, **7** is hydrolyzed to form the amide **8**. The **10** was gained from

Scheme II



EXPERIMENTAL

Melting points were determined on XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a FT Bruker Tensor 27 spectrometer. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. Microanalyses were carried out using a Perkin-Elmer 2400 II analyzer. X-ray diffraction was measured on a Siemens P4 diffractometer.

General Procedure. A mixture of aromatic aldehydes **1** (2 mmol), aromatic ketones **2** (2 mmol), malononitrile **3** (3 mmol) and NaOH (3 mmol) was put in a reaction flask and heated to a temperature of 75 °C for about 30 min. After completing the reaction, the reaction mixture was poured into water, and then washed with water thoroughly. The product was collected bt filtration, dried, and recrystallized from 95% ethanol.

1,2-Dihydro-6-(4-methoxyphenyl)-2-oxo-4-phenylpyridine-3-carbonitrile (4a). This compound was obtained as yellow crystals, mp 255–257 °C; ir (KBr, ν, cm^{-1}): 3180 (NH), 2220 (CN), 1625 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.71 (1H, s, NH), 7.91 (2H, d, J = 8.4 Hz, ArH), 7.72–7.74 (2H, dd, J = 3.2 Hz, J = 3.2 Hz, ArH), 7.57 (3H, t, J = 3.2 Hz, J = 3.2 Hz, ArH), 7.08 (2H, d, J = 8.4 Hz, ArH), 6.78 (1H, s, C^5–H), 3.84 (3H, s, OCH_3). *Anal.* Calcd. For $C_{19}H_{14}N_2O_2$: C 75.48, H 4.67, N 9.27. Found: C 75.65, H 4.41, N 9.20.

6-(4-Chlorophenyl)-1,2-dihydro-2-oxo-4-phenylpyridine-3-carbonitrile (4b). This compound was obtained as yellow crystals, mp 284–286 °C; ir (KBr, ν, cm^{-1}): 3142 (NH), 2220 (CN), 1636 (CO); ^{1}H nmr (400MHz, DMSO-d6) (δ, ppm): 12.89 (1H, s, NH), 7.96 (2H, d, J = 8.4 Hz, ArH), 7.73–7.96 (2H, m, ArH), 7.58–7.63 (5H, m, ArH), 6.87 (1H, s, C^5–H). *Anal.* Calcd. For $C_{18}H_{11}ClN_2O$: C 70.48, H 3.61, N 9.13. Found: C 70.62, H 3.55, N 9.01.

4-(4-Fluorophenyl)-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile (4c). This compound was obtained as yellow crystals, mp 271–272 °C; ir (KBr, ν, cm^{-1}): 3144 (NH), 2218 (CN), 1641 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.81 (1H, s, NH), 7.91 (2H, d, J = 8.4 Hz, ArH), 7.81–7.85 (2H, m, ArH), 7.52–7.60 (3H, m, ArH), 7.43 (2H, t, J = 8.0 Hz, ArH), 6.87 (1H, s, C^5–H). *Anal.* Calcd. For $C_{18}H_{11}FN_2O$: C 74.47, H 3.82, N 9.65. Found: C 74.60, H 3.78, N 9.62.

4-(4-Chlorophenyl)-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile (4d). This compound was obtained as yellow crystals, mp 289–291 °C; ir (KBr, ν, cm^{-1}): 3150 (NH), 2220 (CN), 1645 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 13.71 (1H, s, NH), 8.18 (2H, m, ArH), 8.03–8.05 (3H, m, ArH), 7.88 (2H, m, ArH), 7.74–7.80 (2H, m, ArH), 7.48 (1H, s, C^5–H). *Anal.* Calcd. For $C_{18}H_{11}ClN_2O$: C 70.48, H 3.61, N, 9.13. Found: C 70.58, H 3.50, N 9.04.

4-(2-Chlorophenyl)-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile (4e). This compound was obtained as yellow crystals, mp 290–291 °C; ir (KBr, ν, cm^{-1}): 3140 (NH), 2221 (CN), 1643 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.88 (1H, s, NH), 7.91 (2H, d, J = 8.0 Hz, ArH), 7.60–7.64 (4H, m, ArH), 7.43–7.50 (3H, m, ArH), 6.72 (1H, s, C^5–H). *Anal.* Calcd. For $C_{18}H_{11}ClN_2O$: C 70.48, H 3.61, N 9.13. Found: C 70.53, H 3.48, N 9.03.

4-(2,4-Dichlorophenyl)-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile (4f). This compound was obtained as yellow crystals, mp 279–280 °C; ir (KBr, ν, cm^{-1}): 3138 (NH), 2220 (CN), 1648 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 13.03 (1H, s, NH), 7.91 (2H, d, J = 8.0 Hz, ArH), 7.62–7.67 (2H, m, ArH), 7.52–7.58 (4H, m, ArH), 6.82 (1H, s, C^5–H). *Anal.* Calcd. For $C_{18}H_{10}Cl_2N_2O$: C 63.36, H 2.95, N 8.21. Found: C 63.43, H 2.94, N 8.26.

4-(3,4-Dichlorophenyl)-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile (4g). This compound was obtained as yellow crystals, m.p. >300 °C; ir (KBr, ν, cm^{-1}): 3130 (NH), 2220 (CN), 1651 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.86 (1H, s, NH), 7.50–7.92 (8H, m, ArH), 6.93 (1H, s, C^5–H). Anal. Calcd. For $C_{18}H_{10}Cl_2N_2O$: C 63.36, H 2.95, N 8.21. Found: C 63.50, H 2.71, N 8.37.

4-(4-Bromophenyl)-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile (4h). This compound was obtained as yellow crystals, mp 293–295 °C; ir (KBr, ν, cm^{-1}): 3139 (NH), 2219 (CN), 1648 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.90 (1H, s, NH), 7.88 (2H, m, ArH), 7.80 (2H, d, J = 8.4 Hz, ArH), 7.71 (2H, d, J = 8.4 Hz, ArH), 7.53–7.58 (3H, dd, J = 8.4 Hz, J = 8.4 Hz, ArH), 6.80 (1H, s, C^5–H). *Anal.* Calcd. For $C_{18}H_{11}BrN_2O$: C 61.56, H 3.16, N 7.98. Found: C 61.45, H 3.28, N 7.80.

1,2-Dihydro-4-(3,4-dimethoxyphenyl)-2-oxo-6-phenylpyridine-3-carbonitrile (4i). This compound was obtained as yellow crystals, mp 276–277 °C; ir (KBr, ν, cm^{-1}): 3136 (NH), 2219 (CN), 1649 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.76 (1H, s, NH), 7.88 (2H, d, J = 6.0 Hz, ArH), 7.55 (2H, d, J = 6.0 Hz, ArH), 7.36 (2H, d, J = 8.0 Hz, ArH), 7.14 (2H, d, J = 8.0 Hz, ArH), 6.84 (1H, s, C^5–H), 3.85 (3H, s, OCH_3), 3.38 (3H, s, OCH_3). *Anal.* Calcd. For $C_{20}H_{16}N_2O_3$: C 72.28, H 4.85, N 8.43. Found: C 72.45, H 4.73, N 8.30.

4-(3,4-Methylenedioxylphenyl)-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile (4j). This compound was obtained as yellow crystals, mp 290–291 °C; ir (KBr, ν, cm^{-1}): 3160 (NH), 2220 (CN), 1653 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.78 (1H, s, NH), 7.88–7.91 (1H, m, ArH), 7.53–7.55 (3H, m, ArH), 7.29 (2H, d, J = 8.0 Hz, ArH), 7.11 (2H, d, J = 8.0 Hz, ArH), 6.76 (1H, s, C^5–H), 6.15 (2H, s, OCH_2O). *Anal.* Calcd. For $C_{19}H_{12}N_2O_3$: C 72.15, H 3.82, N 8.86. Found: C 72.02, H 3.79, N 8.80.

6-(4-Bromophenyl)-1,2-dihydro-2-oxo-4-p-tolylpyridine-3-carbonitrile (4k). This compound was obtained as yellow crystals, mp 294–296 °C; ir (KBr, ν, cm^{-1}): 3160 (NH), 2222 (CN), 1660 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.84 (1H, s, NH), 7.85 (2H, m, ArH), 7.75 (2H, d, J = 8.4 Hz, ArH), 7.66 (2H, d, J = 8.4 Hz, ArH), 7.39 (2H, d, J = 8.4 Hz, ArH), 6.86 (1H, s, C^5–H), 3.34 (3H, s, CH_3). *Anal.* Calcd. For $C_{19}H_{13}BrN_2O$: C 62.48, H 3.59, N 7.67. Found: C 62.37, H 3.63, N 7.61.

1,2-Dihydro-2-oxo-4,6-di-p-tolylpyridine-3-carbonitrile (4l). This compound was obtained as yellow crystals, mp 295–297 °C; ir (KBr, ν, cm^{-1}): 3142 (NH), 2220 (CN), 1627 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.74 (1H, s, NH), 7.80 (2H, d, J = 8.4 Hz, ArH), 7.65 (2H, d, J = 8.4 Hz, ArH), 7.33–7.40 (4H, m, ArH), 6.75 (1H, s, C^5–H), 2.40 (3H, s, CH_3), 2.38 (3H, s, CH_3). *Anal.* Calcd. For $C_{20}H_{16}N_2O$: C 79.98, H 5.37, N 9.33. Found: C 79.85, H 5.48, N 9.39.

4-(4-Bromophenyl)-6-(4-chlorophenyl)-1,2-dihydro-2-oxo-pyrid-ine-3-carbonitrile (4m). This compound was obtained as yellow crystals, mp 282–284 °C; ir (KBr, ν, cm^{-1}): 3160 (NH), 2222 (CN), 1665 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.74 (1H, s, NH), 7.80 (2H, d, J = 8.4 Hz, ArH), 7.65 (2H, d, J = 8.4 Hz, ArH), 7.34–7.40 (4H, m, ArH), 6.76 (1H, s, C^5–H). *Anal.* Calcd. For $C_{18}H_{10}BrClN_2O$: C 56.06, H 2.61, N 7.26. Found: C 56.16, H 2.64, N 7.30.

1,2-Dihydro-4-(3,4-dimethylphenyl)-2-oxo-6-p-tolylpyrid-ine-3-carbonitrile (4n). This compound was obtained as yellow crystals, mp 260–262 °C; ir (KBr, ν, cm^{-1}): 3150 (NH), 2217

(CN), 1645 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.77 (1H, s, NH), 7.80 (2H, d, J = 8.0 Hz, ArH), 7.47 (2H, d, J = 8.0 Hz, ArH), 7.32–7.40 (3H, m, ArH), 6.76 (1H, s, C^5–H), 2.38 (3H, s, CH_3), 2.30 (6H, s, 2 × CH_3). *Anal*. Calcd. For $C_{21}H_{18}N_2O$: C 80.23, H 5.77, N 8.91. Found: C 80.38, H 5.74, N 8.87.

4-(3,4-Dichlorophenyl)-1,2-dihydro-2-oxo-6-p-tolylpyridine-3-carbonitrile (4o). This compound was obtained as yellow crystals, mp 197–198 °C; ir (KBr, ν, cm^{-1}): 3180 (NH), 2222 (CN), 1650 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.88 (1H, s, NH), 8.00 (1H, m, ArH), 7.84 (2H, d, J = 8.4 Hz, ArH), 7.70 (1H, d, J = 8.4 Hz, ArH), 7.32 (1H, d, J = 8.0 Hz, ArH), 7.14 (2H, d, J = 8.0 Hz, ArH), 6.48 (1H, s, C^5–H), 2.32 (3H, s, CH_3). *Anal*. Calcd. For $C_{19}H_{12}Cl_2N_2O$: C 64.24, H 3.41, N 7.89. Found: C 64.16, H 3.44, N 7.86.

4-(4-Chlorophenyl)-1,2-dihydro-6-(4-methoxyphenyl)-2-oxopyridine-3-carbonitrile (4p). This compound was obtained as yellow crystals, mp 275–276 °C; ir (KBr, ν, cm^{-1}): 3190 (NH), 2218 (CN), 1652 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.68 (1H, s, NH), 7.08–7.92 (9H, m, ArH, C^5–H), 3.85 (3H, s, OCH_3). Anal. Calcd. For $C_{19}H_{13}ClN_2O$: C 67.76, H 3.89, N 8.32. Found: C 67.65, H 3.78, N 8.39.

1,2-Dihydro-4,6-bis(4-methoxyphenyl)-2-oxopyridine-3-carbonitrile (4q). This compound was obtained as yellow crystals, mp 232–234 °C; ir (KBr, ν, cm^{-1}): 3140 (NH), 2220 (CN), 1655 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.59 (1H, s, NH), 7.07–7.91 (9H, m, ArH, C^5–H), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3). *Anal*. Calcd. For $C_{20}H_{16}N_2O_3$: C 72.28, H 4.85, N 8.43. Found: C 72.40, H 4.75, N 8.30.

4-(3,4-Dichlorophenyl)-1,2-dihydro-6-(4-methoxyphenyl)-2-oxopyridine-3-carbonitrile (4r). This compound was obtained as yellow crystals, mp > 300 °C; ir (KBr, ν, cm^{-1}): 3170 (NH), 2221 (CN), 1642 (CO); ^{1}H nmr (400MHz, DMSO-d_6) (δ, ppm): 12.83 (1H, s, NH), 7.11–7.85 (8H, m, ArH, C^5–H), 3.85 (3H, s, OCH_3). *Anal*. Calcd. For $C_{19}H_{12}C_{l2}N_2O$: C 61.47, H 3.26, N 7.55. Found: C 61.35, H 3.38, N 7.15.

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[8] X-ray crystallography for **4c**: Empirical formula $C_{18}H_{11}FN_2O$, Fw = 290.29, T = 173(2) K, monoclinic, space group p 21/c, a = 8.705 (2) Å, b = 7.9408(18) Å, c = 20462(5) Å, α = 90°, β = 97.309(5)°, γ = 90°, V = 14029(6) Å^3, Z = 4, Dcalcd. = 1.374 Mg/m^3, λ (MoKα) = 0.71070 Å, μ = 0.096 mm^{-1}, F(000) = 600. 3.26°< θ <25.34°, R = 0.0624, wR = 0.1373. s = 1.173. largest diff. peak and hole: 0.207 and -0.218 e. Å^{-3}.