

An Efficient and Facile Multicomponent Synthesis of 4,6-Diarylpyridine Derivatives under Solvent-Free Conditions

Hassan A. El-Sayed* and Nabil H. Ouf

Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt
haabel81@yahoo.com

Abstract: An efficient and facile synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles (**4a-j**) via four-component system for aromatic aldehydes **1**, acetophenones (**2**), ethyl cyanoacetate (**3**) and ammonium acetate. The short reaction time coupled with the simplicity of the reaction procedure and clean reaction make this method one of the most efficient methods for the synthesis of this class of compounds.

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Introduction

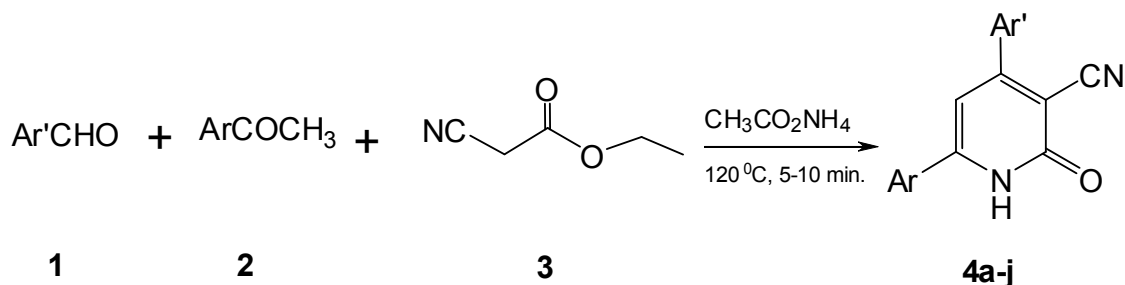
The synthesis of functionalized 3-cyano-2-pyridone derivatives is a continuing area of interest due to the number of biologically active molecules containing this moiety (McKillop and Boulton, 1984). Natural compounds pyridone core has emerged during the last ten years as a potent antitumor (El-Sayed, et al., 2011), antifungal (Cox and O'Hagan, 1991), antiviral (Williams et al., 1997; Moustafa, et al., 2011) and psychotherapeutic (Kozikowski, et al., 1996), anti-HIV drugs (Fraleigh, et al., 2003). Moreover, pyridones are key intermediates in the synthesis of corresponding pyridines (Murrey and Zimmerman, 1995). Numerous methods have been reported for the synthesis of 2-pyridone derivatives (El-Sayed, et al., 2011; Dawoud, 2011; Soliman, et al., 1991; Al-Hajjar and Jarrar, 1980; Donohoe, et al., 2008; Sakurai and Midorikaea, 1967; Desai and Shah, 2003; Cherry, et al., 2003; Jain, et al., 1995; Alberola, et al., 1987; Abadi, et al., 1999; Bekhit and Baraka, 2005), 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 (Tanaka and Toda, 2008) 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 (Kaupp and Naimi-Jamal, 2003; Zolfigol and Safaiee, 2004; Shaabani, et al., 2003).

Multicomponent coupling reactions (MCRs) are of increasing importance in organic and medicinal chemistry (Weber, 2002; Do \ddot{m} ling, 2002,). MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of "drug-like" molecules for biological screening, because the combination of three or more small-molecular-weight building blocks in a single operation leads to high combinatorial efficacy. Development of new solid-phase (solvent-free) MCRs is the subjects of recent interest in organic synthesis (Tanaka and Toda, 2008).

Results and Discussion

In continuation of our work (El-Sayed, et al., 2011; Moustafa, et al., 2011), We herein described a practical, environmentally and simple multicomponent synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridone-3-carbonitriles by heating under fusion of aromatic aldehydes **1**, acetophenones **2**, ethyl cyanoacetate (**3**) and ammonium acetate under solvent-free conditions for 5-10 minutes. Where, the starting materials mixed together and heated with stirring at 120 °C for 5-10 minutes (Scheme 1). A variety of substituted aromatic aldehydes and aromatic ketones underwent competitive formation of 2-pyridones with good yields. This protocol is rapid and efficient to prepare a variety of substituted 2-pyridone from electron donating as well as electron withdrawing aromatic ketones and aldehydes. It follows from Table 1 that variety of functionalities (nitro, halo, alkoxy, alkyl) can be accommodated in 2-pyridone derivatives. 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. The structure of each product **4a-j** was established on the basis of spectroscopic data and elemental analysis.

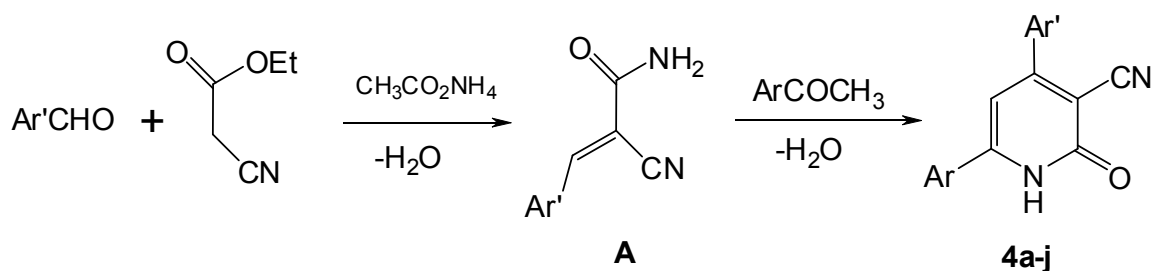


Scheme 1. Multicomponent synthesis of 2-pyridone under free-solvent conditions.

Table 1. Synthesis of 2-pyridone under free-solvent conditions

Cpd. No.	Ar	Ar'	Time/min.	Yield/%
4a	C ₆ H ₅	C ₆ H ₅	8	86
4b	C ₆ H ₅	4.Cl-C ₆ H ₄	5	83
4c	C ₆ H ₅	4.F-C ₆ H ₄	5	88
4d	C ₆ H ₅	4.CH ₃ O-C ₆ H ₄	5	93
4e	C ₆ H ₅	3,4.(CH ₃ O) ₂ -C ₆ H ₃	5	93
4f	C ₆ H ₅	3.NO ₂ -C ₆ H ₄	6	95
4g	C ₆ H ₅	4.NO ₂ -C ₆ H ₄	6	98
4h	C ₆ H ₅	4.(CH ₃) ₂ CH-C ₆ H ₄	10	80
4i	C ₆ H ₅	1-naphthyl	5	83
4j	3.NH ₂ -C ₆ H ₄	C ₆ H ₅	5	92

Although the detailed mechanism of the above reaction has not been clarified yet, while the formation of compound **4** could be explained by a possible aldol condensation take place from aromatic aldehydes **1**, acetophenones **2**, ethyl cyanoacetate (**3**) and ammonium acetate to form the target 2-pyridone take place via the Knoevenagel condensation as described in Scheme 2. Where, one mole of water was eliminated to form the corresponding arylethylene (**A**), followed by reaction with acetophenone derivatives and aromatization via dehydrogenation to give the corresponding 2-pyridone (Scheme 2).



Scheme 2. proposed pathway for 2-pyridone synthesis.

Conclusion

In summary, we have reported a novel, eco-friendly, efficient method for the synthesis of 2-pyridone from various aromatic aldehydes, ketones, in ammonium acetate for providing necessary facilities. The experimental simplicity, excellent product yield, shorter reaction time, and the easy work-up procedure makes this approach more attractive in synthesizing a variety of such derivatives.

Experimental

General

All melting points are uncorrected and were measured using an Electro thermal IA 9100 apparatus. TLC was performed on Merck Silica Gel 60F₂₅₄ with detection by UV light. The IR spectra (KBr disc) were recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The ¹H and ¹³C NMR spectra were determined with JEOL-JNM-LA 300 MHz spectrometer. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. Elemental analysis determined on a Perkin Elmer 240 (microanalysis).

General Procedure for the preparation of substituted 2-pyridones 4a-j. A mixture of aromatic aldehydes **1** (1 mmol), aromatic ketones **2** (1 mmol), ethyl cyanoacetate **3** (1 mmol) and ammonium acetate (1 mmol) was heated under fusion at 120 °C with stirring for 5-10 min. After cooling the crude product was crystallized from absolute ethanol or acetic acid.

2-Oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile (4a). Yellow crystals, mp 334-336 °C (Lit. (Nalage, et al., 2010) >300 °C) (from acetic acid); (Found: C, 79.38; H, 4.48; N, 10.31. Anal. Calcd. for C₁₈H₁₂N₂O: C, 79.39; H, 4.44; N, 10.29 %.); $\nu_{\max}/\text{cm}^{-1}$ 3380 (NH), 2218 (CN) and 1646 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 6.85 (s, 1H, pyridone C-H), 7.11-7.29 (m, 5H, Ar-H), 7.39 (m, 3H, Ar-H), 7.52 (m, 2H, Ar-H), 12.60 (br, 1H, NH).

4-(4-Chlorophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4b). Yellow crystals, mp 288-289 °C (Lit. (Rong, et al., 2007) 289-291 °C) (from acetic acid); (Found: C, 70.45; H, 3.69; N, 9.10. Anal. Calcd. for C₁₈H₁₁ClN₂O: C, 70.48, H, 3.61, N, 9.13. %.); $\nu_{\max}/\text{cm}^{-1}$ 3152 (NH), 2220 (CN) and 1641 (C=O); ¹H NMR (DMSO-d₆, δ ppm): δ = 6.95 (s, 1H, pyridone C-H), 7.78 (d, 2H, *J* = 8.34 Hz, Ar-H), 7.88 (m, 3H, ArH), 8.04 (m, 2H, Ar-H), 8.18 (2H, d, *J* = 8.34 Hz, ArH), 13.72 (br, 1H, NH)

4-(4-Fluorophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4c). Yellow crystals, mp 272-274 °C (Lit. (Rong, et al., 2007) 271-272 °C) (from ethanol); (Found: C, 74.48; H, 3.89; N, 9.64. Anal. Calcd. for C₁₈H₁₁FN₂O: C, 74.47; H, 3.82; N, 9.65 %.); $\nu_{\max}/\text{cm}^{-1}$ 3184 (NH), 2221 (CN) and 1641 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 6.87 (s, 1H, pyridone C-H), 7.43 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.52-7.61 (m, 3H, ArH), 7.81-7.85 (m, 2H, Ar-H), 7.90 (d, 2H, *J* = 8.4 Hz, ArH), 12.80 (br, 1H, NH)

4-(4-Methoxyphenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4d).

Yellow crystals, mp 318-320°C (from ethanol); (Found: C, 75.47; H, 4.69; N, 9.30. Anal. Calcd. for C₁₉H₁₄N₂O₂: C, 75.48; H, 4.67; N, 9.27 %.); $\nu_{\max}/\text{cm}^{-1}$: 3280 (NH), 2216 (CN) and 1646 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 3.75 (s, 3H, CH₃O), 6.85 (s, 1H, pyridone C-H), 7.75 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.85-8.02 (m, 5H, Ar-H), 8.17 (d, 2H, *J* = 8.4 Hz, Ar-H), 12.85 (br s, 1H, NH); ¹³C NMR (DMSO-d₆, δ ppm): δ = 54.6 (CH₃O), 111.3, 113.0, 115.0, 115.4 (C≡N), 126.1, 126.7, 128.2, 128.9, 129.6, 130.2, 157.0, 158.9, 160.5 and 161.0 (Ar-C and C=O).

4-(3,4-Dimethoxyphenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4e). Yellow crystals, mp 279-280 °C (Lit. (Rong, et al., 2007) 276-277 °C) (from ethanol); (Found: C, 72.25; H, 4.85; N, 8.42. Anal. Calcd. for C₂₀H₁₆N₂O₃: C, 72.28; H, 4.85; N, 8.43. %.); $\nu_{\max}/\text{cm}^{-1}$: 3353 (NH), 2219 (CN) and 1654 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 3.81 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 6.82 (s, 1H, pyridone C-H), 7.12-7.89 (m, 8H, Ar-H), 12.75 (br, 1H, NH).

4-(3-Nitrophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4f).

Yellow crystals, mp 358-360°C (from ethanol); (Found: C, 68.13; H, 3.49; N, 13.29. Anal. Calcd. for C₁₈H₁₁N₃O₃: C, 68.14; H, 3.49; N, 13.24 %.); $\nu_{\max}/\text{cm}^{-1}$: 3360 (NH), 2225 (CN) and 1651 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 6.89 (s, 1H, pyridone C-H), 7.32-8.11 (m, 9H, Ar-H), 12.72 (br s, 1H, NH); ¹³C NMR (DMSO-d₆, δ ppm): δ = 112.0, 114.3, 115.6 (C≡N), 121.0, 124.1, 128.1, 128.7, 129.0, 130.5, 132.1, 135.3, 135.5, 147.5, 158.1, 160.0 and 162.2 (Ar-C and C=O).

4-(4-Nitrophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4g).

Brownish crystals, mp 308-310°C (Lit. (Nalage, et al., 2010) >300 °C) (from ethanol); (Found: C, 68.12; H, 3.53; N, 13.20. Anal. Calcd. for C₁₈H₁₁N₃O₃: C, 68.14; H, 3.49; N, 13.24 %.); $\nu_{\max}/\text{cm}^{-1}$ 3320 (NH), 2226 (CN) and 1654 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 6.88 (s, 1H, pyridone C-H), 7.42 (d, 2H, *J* = 8.23 Hz, Ar-H), 7.54-7.60 (m, 5H, ArH), 7.98 (d, 2H, *J* = 8.23 Hz, Ar-H), 13.10 (br s, 1H, NH).

4-(4-Isopropylphenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4h). Yellow crystals, mp 258-360°C (from acetic acid); (Found: C, 80.20; H, 5.76; N, 8.88. Anal. Calcd. for C₂₁H₁₈N₂O: C, 80.23; H, 5.77; N, 8.91 %.); $\nu_{\max}/\text{cm}^{-1}$: 3230 (NH), 2215 (CN) and 1642 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 1.67 (d, 6H, J = 6.5 Hz, 2CH₃), 2.71 (m, 1H, CH(CH₃)₂) 6.70 (s, 1H, pyridone C-H), 7.13 (d, 2H, J = 8.10 Hz, Ar-H), 7.32-7.35 (m, 5H, Ar-H), 7.45 (d, 2H, J = 8.10 Hz, Ar-H), 12.84 (br, 1H, NH); ¹³C NMR (DMSO-d₆, δ ppm): δ = 24.3 (2CH₃), 35.5 (CH(CH₃)₂), 112.0, 113.1, 115.4 (C≡N), 126.1, 128.0, 128.7, 129.1, 131.5, 135.6, 135.8, 145.0, 156.1, 157.8 and 160.3 (Ar-C and C=O).

4-(Naphthalen-1-yl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4i). Yellow crystals, mp 264-366°C (from acetic acid); (Found: C, 82.01; H, 4.39; N, 8.70. Anal. Calcd. for C₂₂H₁₄N₂O: C, 81.97; H, 4.38; N, 8.69%.); $\nu_{\max}/\text{cm}^{-1}$ 3201 (NH), 2220 (CN) and 1648 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 6.86 (s, 1H, pyridone C-H), 7.15-8.10 (m, 12H, Ar-H), 12.93 (br, 1H, NH); ¹³C NMR (DMSO-d₆, δ ppm): δ = 112.0, 114.8, 115.6 (C≡N), 125.9, 126.8, 126.9, 128.5, 128.7, 129.1, 130.3, 130.5, 131.2, 131.6, 133.0, 135.6, 141.0, 151.1, 156.8, 162.2 and 166.7 (Ar-C and C=O).

6-(3-Aminophenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (4j).

Yellow crystals, mp 358-360°C (from acetic acid); (Found: C, 75.24; H, 4.56; N, 14.61. Anal. Calcd. for C₁₈H₁₃N₃O: C, 75.25; H, 4.56; N, 14.63 %.); $\nu_{\max}/\text{cm}^{-1}$: 3321 (NH₂), 3181 (NH), 2217 (CN) and 1645 (C=O, amide); ¹H NMR (DMSO-d₆, δ ppm): δ = 6.75 (s, 1H, pyridone C-H), 7.12-7.95 (m, 9H, Ar-H), 6.23 (br, 2H, NH₂), 12.68 (br, 1H, NH)

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