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A Simple and Efficient Procedure for a 2-Pyridones Synthesis under Solvent-Free Conditions

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Abstract

A new series of 3-cyano-2-pyridones derivatives have been prepared by reaction of enamionitriles with primary amine under solvent free condition. This procedure have the advantage of high yields and being environmentally-friendly.

Keywords: 2-Pyridones, Solvent-Free, Enaminonitriles, Green Chemistry

1. Introduction

Nowadays, one powerful solution in the Green & Sustainable Chemistry movement is the replacement of traditional synthetic methods, which use harmful stoichiometric reagents that produce vast amounts of wastes, with clean and simple catalytic alternatives with high atom efficiency [1,2]. Solvent-free and domino reactions represent very powerful green chemical technology procedures from both the economical and synthetic point of view and represent a possible instrument to perform a near-ideal synthesis because they enhance the rate of many organic reactions and afford quantitative yields [3-8]. Heteroaromatic rings containing atoms frequently play an important role as the scaffolds of bioactive substances [9]. It is well-known that the pyridone [9] and its derivatives are among the most popular N-heteroaromatic compounds integrated into the structures of many pharmaceutical compounds and the structural units occur in various molecules exhibiting diverse biological activities [10-12]. This can easily be demonstrated using the following examples (**Figure 1**) [13]. Pyridone L-697,661 [13] has been recognized as a specific non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus-1 (HIV-1) [13], Milrinone WIN 47203 [9,14], Amrinone WIN 40680 [9,14] and their analogues are well time- honored positive inotropic and vasodilatory agents, used in the clinical treatment of heart failure [9,14]. Some others are reported to show antitumor [15], antibacterial activity, evaluated as human rhinovirus (HRV) 3C-protease (3CP) inhibitors [15] and other biological

activities. Others, that share the 2-Pyridone and its derivatives, illustrate a large class as ligands in coordination chemistry [16,17].

The various research teams around the world were and are still interested in the synthesis of 2-Pyridones (Pyridin-2(1H)-ones). The various synthetic approaches to 2-pyridones of this type are described. Many literature sources [18-26] describe more general approaches involving the condensation of unsaturated ketones with methylene active amides, using cyanoacetamide. A number of Milrinone (**Figure 1**) analogues have been obtained [18-26]. Departing from the previous literature, and as part of our continuing interest in the progress of new synthetic methods in heterocyclic chemistry in our laboratory [27-29], we started the development of a new preparative procedure for this class of heterocyclic scaffold compounds.

2. Results and Discussions

In our work, we developed a new method for an easier, simpler and more universal synthesis to prepare this type of heterocycles “2-pyridone”, while trying to respect the criteria of the green chemistry, in which we employed, as a key step, the synthesis of enamionitrile and in the presence of a catalytic amount of NH₄OAc (**Scheme 1**).

From **Scheme 1**, we found that the synthesis under solvent-free of new nitrogen heterocyclic compounds of “2-pyridone derivatives” can be obtained, by a simple, effective, fast and cleaner method, using the three following steps:

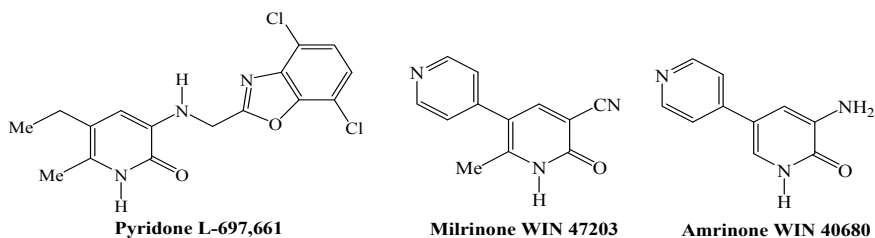
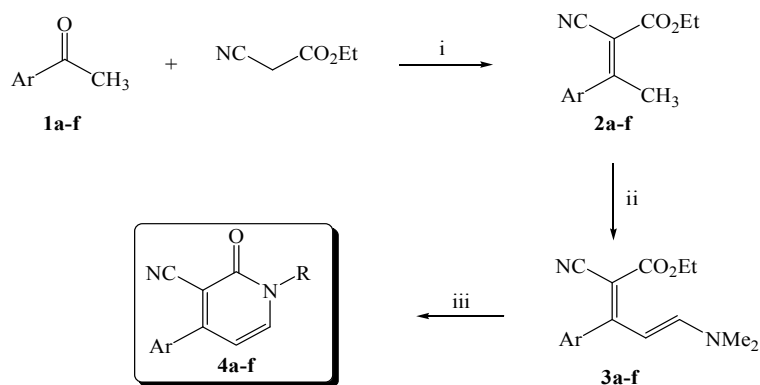


Figure 1. Structures of pyridones L697,661, Milrinone WIN 47203, Amrinone WIN 40680.



Scheme 1. Synthesis of 3-cyano-2-pyridone derivatives. Reagents and conditions: (i) NH_4OAc , AcOH , 100°C , 3 hours, solvent-free, 65% - 80%; (ii) DMF-DMA (10 mmol), r.t., solvent-free, 24 hours, 75% - 90%; (iii) RNH_2 solvent-free, 1 - 4 hours, 48% - 88%.

2.1. Knoevenagel Condensation of Acetophenone Derivatives

The Knoevenagel condensation is one of the basic necessary reactions in organic chemistry. The research process for this reaction was developed very rapidly. Considering the importance of this condensation, several synthesis methods were carried out. Usually, it is carried out in the presence of harmful organic solvents such as benzene and the DMF [30], and catalysts such as Al_2O_3 [31], silica gel [32], a basic ionic liquid [33], Na_2CO_3 -MS 4 Å [34], Mn (III) salen [35], and NH_4OAc -basic alumina [36].

From our side, as a first step, we have prepared a series of ethyl 2-cyano-3-arylbut-2-enoate (**2a-f**), α , β -unsaturated compounds, according to the Knoevenagel condensation of a sequence of aromatic ketones (**1a-f**), with of the ethyl cyanoacetate catalyzed by ammonium acetate at 100°C , under solvent-free conditions (Scheme 1). The ethyl 2-cyano-3-arylbut-2-enoate **2a-f** was obtained with a moderate to excellent yields. The results are reported in Table 1.

2.2. Synthesis of Enaminonitriles

These olefins, α , β -unsaturated compounds, prepared by Knoevenagel condensations are largely used as key products in organic syntheses. They found a major applica-

tion in medicine, biology, and agriculture; thanks to their Michael acceptor properties [37,38]. Therefore, they are attractive molecules; as they have an exploitable functional richness for organic chemistry, where we were interested in acid methylene, for synthesis of enaminonitriles.

For a long time, many strategies have been considered for the enaminonitriles synthesis [10-12,39]. Promoted by the literature, we prepared the ethyl 2-cyano-5-(dimethylamino)-3-arylpenta-2,4-dienoate **3a-f** (enaminonitriles) using the reaction between **2a-b** and *N,N*-dimethylformamide-dimethylacetal (DMF-DMA) under solvent-free, at room temperature (Scheme 1). The yields obtained are very satisfactory 75% - 90% (Table 2).

2.3. Synthesis of 3-Cyano-2-Pyridones

The enaminonitriles are "push-pull" dienes and a good synthon for the organic synthesis, because they can react with the nucleophilic and electrophilic agents. They are used in the preparation of various heterocycles [39,40].

In this last step, well-known as the cyclization step, and in order to study the reactivity of enaminonitriles, we added various types of primary nucleophilic amines to the ethyl 2-cyano-5-(dimethylamino)-3-arylpenta-2,4-dienoate **3a-f** (enaminonitrile), under solvent-free (Scheme 1). The mixture was heated, for a few hours, to form 3-cyano-2-pyridone derivatives, with moderate to excellent yields (Table 3).

Table 1. Solvent-free Knoevenagel condensation for the synthesis of 2a-f.

Entry	Ar	Product	Yield (%)
1	C ₆ H ₅ -		70
2	<i>p</i> -ClC ₆ H ₄ -		75
3	2,4-Cl ₂ C ₆ H ₃ -		68
4	<i>m</i> -CH ₃ OC ₆ H ₄ -		73
5	<i>p</i> -CH ₃ OC ₆ H ₄ -		80
6	<i>p</i> -CH ₃ C ₆ H ₄ -		65

Table 2. Synthesis of enaminonitrile (3a-f) without solvent.

Entry	Ar	Product	Yield (%)
7	C ₆ H ₅ -		88
8	<i>p</i> -ClC ₆ H ₄ -		90
9	2,4-Cl ₂ C ₆ H ₃ -		82
10	<i>m</i> -CH ₃ OC ₆ H ₄ -		75
11	<i>p</i> -CH ₃ OC ₆ H ₄ -		80
12	<i>p</i> -CH ₃ C ₆ H ₄ -		77

Table 3. Synthesis of the 3-cyano-2-pyridones.

Entry	Enaminonitrile	R	Product	Yield (%)
13	3a	CH ₃ -		66
14		CH ₂ =CH-CH ₂ -		70
15		C ₆ H ₅ CH ₂ -		73
16		(CH ₃) ₂ CH-		48
17	3b	CH ₃ -		76
18		CH ₂ =CH-CH ₂ -		80
19		C ₆ H ₅ CH ₂ -		85
20		(CH ₃) ₂ CH-		50
21	3c	CH ₃ -		75
22		CH ₂ =CH-CH ₂ -		80
23		C ₆ H ₅ CH ₂ -		84
24		(CH ₃) ₂ CH-		52
25	3d	CH ₃ -		73
26		CH ₂ =CH-CH ₂ -		79
27		C ₆ H ₅ CH ₂ -		80
28		(CH ₃) ₂ CH-		53

29	CH ₃ -		4e ₁	74
30	CH ₂ =CH-CH ₂ -		4e ₂	81
31	C ₆ H ₅ CH ₂ -		4e ₃	88
32	(CH ₃) ₂ CH-		4e ₄	51
33	CH ₃ -		4f ₁	80
34	CH ₂ =CH-CH ₂ -		4f ₂	83
35	C ₆ H ₅ CH ₂ -		4f ₃	88
36	(CH ₃) ₂ CH-		4f ₄	49

3. Conclusions

In summary, we have developed a simple, efficient and rapid method for the synthesis of 3-cyano-2-pyridones, following three steps, *i.e.* the Knoevenagel condensation catalyzed by NH₄OAc, the enamionitriles synthesis, and finally the synthesis of the 3-cyano-2-pyridone under solvent-free conditions. This procedure has the advantages of being a mild conditions reaction, using a catalytic quantity of NH₄OAc, with moderate to excellent yields, and where we operate with simplicity while respecting the criteria of Green Chemistry.

4. Experimental

The melting points were measured using a Bank Kofler HEIZBANK apparatus standard WME 50-260°C and were uncorrected. IR spectra were obtained with solids with a Fourier transform Perkin Elmer Spectrum One with ATR accessory. Only significant absorptions are listed. The ¹H NMR spectra were recorded at 400 MHz, on a Brüker AC 400 spectrometers and ¹³C NMR spectra were recorded in the same spectrometers at 100.6 MHz. Samples were registered in CDCl₃ solutions using TMS as an internal standard. The chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS. The multiplicities are reported as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

General procedure 1: Synthesis of ethyl 2-cyano-3-(aryl) but-2-enoate 2a-b

A mixture of acetophenone or substituted acetophenone (10 mmol), ethyl cyanoacetate (10 mmol), ammonium acetate (10 mmol) and some drops of icy acetic acid were stirred and heated at 100°C during 3 hours. The reaction mixture was cooled down to room temperature, diluted with 30 ml of CH₂Cl₂. The organic layer obtained was washed with (3 × 20 ml) of water, (10 ml) of saturated NaCl, dried on MgSO₄, filtered then evaporated under vacuum. The compounds **2a-f** were obtained as colourless oil.

none (10 mmol), ethyl cyanoacetate (10 mmol), ammonium acetate (10 mmol) and some drops of icy acetic acid were stirred and heated at 100°C during 3 hours. The reaction mixture was cooled down to room temperature, diluted with 30 ml of CH₂Cl₂. The organic layer obtained was washed with (3 × 20 ml) of water, (10 ml) of saturated NaCl, dried on MgSO₄, filtered then evaporated under vacuum. The compounds **2a-f** were obtained as colourless oil.

Ethyl 2-cyano-3-phenylbut-2-enoate 2a. The general procedure 1, using (1.20 g, 10 mmol) of acetophenone, (1.13 g, 10 mmol) of ethyl cyanoacetate, (0.77 g, 10 mmol) of ammonium acetate and some drops of icy acetic acid, gave 70% of **2a** as burn oil. ¹H NMR (400 MHz, CDCl₃): 7.53 - 7.14 (m, 5H), 4.20 (q, 2H, *J*_{H-H} = 7.2 Hz), 2.57 (s, 3H), 1.26 (t, 3H, *J*_{H-H} = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): 172.21, 162.12, 136.91 - 128.10, 116.01, 104.95, 61.83, 24.50, 13.75. IR (neat, cm⁻¹): 2225, 1747, 1682.

Ethyl 3-(4-chlorophenyl)-2-cyanobut-2-enoate 2b. The general procedure 1, using (1.54 g, 10 mmol) of 4-chloroacetophenone, (1.13 g, 10 mmol) of ethyl cyanoacetate and (0.77 g, 10 mmol) of ammonium acetate and some drops of icy acetic acid, gave 75% of **2b** as burn oil. ¹H NMR (400 MHz, CDCl₃): 7.51 - 7.18 (m, 4H), 4.20 (q, 2H, *J*_{H-H} = 7.2 Hz), 2.62 (s, 3H), 1.29 (t, 3H, *J*_{H-H} = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): 174.81, 164.23, 136.75 - 128.60, 115.38, 102.00, 62.10, 24.50, 24.75. IR (neat, cm⁻¹): 2222, 1747, 1682.

General procedure 2: Synthesis of ethyl 2-cyano-5-(dimethylamino)-3-arylpenta-2, 4-dienoate 3a-b

A mixture of ethyl 2-cyano-3-arylbut-2-enoate (10 mmol) **2a-b**, *N,N*-dimethylformamide dimethyl acetal (10 mmol) were stirred at room temperature without solvent during 24 hours. The solution takes a colouring increasingly dark burn. The purple solid obtained was washed several times with diethyl ether and crystallised in absolute ethanol to provide products **3a-b**.

Ethyl 2-cyano-5-(dimethylamino)-3-phenylpenta-2, 4-dienoate 3a. The general procedure 2, using (2.15 g, 10 mmol) of **2a** and (1.19 g, 10 mmol) of *N,N*-dimethylformamide dimethyl acetal, gave 85% of compound **3a** as yellow solid, mp 142°C. ¹H NMR (400 MHz, CDCl₃): 7.32 - 7.25 (m, 5H), 6.57 (d, 1H, *J*_{H-H} = 12.8 Hz), 5.98 (d, 1H, *J*_{H-H} = 12.8 Hz), 4.32 (q, 2H, *J*_{H-H} = 7.2 Hz), 3.07 (s, 3H), 3.04 (s, 3H), 1.39 (t, 3H, *J*_{H-H} = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): 169.41, 165.56, 156.71, 137.80 - 127.70, 119.88, 99.75, 86.04, 60.07, 45.43, 37.48, 14.37. IR (neat, cm⁻¹): 2191, 1674, 1609, 1508.

Ethyl 3-(4-chlorophenyl)-2-cyano-5-(dimethylamino) penta-2,4-dienoate 3b. The general procedure 2, using (2.49 g, 10 mmol) of **2b**, and (1.19 g, 10 mmol) of *N,N*-dimethylformamide dimethyl acetal, gave 90% of compound **3b** as yellow solid, mp 208°C. ¹H NMR (400 MHz, CDCl₃): 7.35 - 7.20 (m, 4H), 6.48 (d, 1H, *J*_{H-H} = 12.8 Hz), 5.90 (d, 1H, *J*_{H-H} = 12.8 Hz), 4.26 (q, 2H, *J*_{H-H} = 7.2 Hz), 3.01 (s, 3H), 2.99 (s, 3H), 1.33 (t, 3H, *J*_{H-H} = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): 169.88, 158.38, 140.75, 137.20 - 128.75, 115.41, 107, 89.08, 60.01, 47.80, 38.77, 14.28. IR (neat, cm⁻¹): 2199, 1680, 1604, 1507.

General procedure 3: Synthesis of 2-Pyridones 4a_i-b_i

A mixture of ethyl 2-cyano-5-(dimethylamino)-3-arylpenta-2,4-dienoate **3a-b** (2 mmol) and primary amine (2 mmol) were heated for a few hours. After cooling, the solid obtained was washed several times with diethyl ether to give 2-pyridone derivatives **4a_i-b_i**.

1,2-dihydro-1-methyl-2-oxo-4-phenylpyridine-3-carbonitrile 4a₁. The general procedure 3, using (0.43 g, 2 mmol) of **3a** and (0.06 g, 2 mmol) of methylamine, gave 66% of compound **4a₁** as white solid, mp 174°C. ¹H NMR (400 MHz, CDCl₃): 7.55 (d, 1H, *J*_{H-H} = 6.7 Hz), 7.51 - 7.50 (m, 5H), 6.62 (d, 1H, *J*_{H-H} = 6.4 Hz), 3.62 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 159.82, 158.87, 134.46, 129.69 - 127.00, 114.57, 106.04, 101.42, 37.12. IR (neat, cm⁻¹): 2220, 1645, 1597.

1-allyl-1,2-dihydro-2-oxo-4-phenylpyridine-3-carbonitrile 4a₂. The general procedure 3, using (0.43 g, 2 mmol) **3a** and (0.11 g, 2 mmol) of allylamine, gave 76% of compound **4a₂** as white solid, mp 99°C - 100°C. ¹H NMR (400 MHz, CDCl₃): 7.61 (d, 1H), 7.53 - 7.49 (m, 5H), 6.36 (d, 1H, *J*_{H-H} = 6.7 Hz), 6.02 - 5.92 (m, 1H),

5.37 - 5.30 (m, 2H), 4.64-4.62 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): 160.2, 159.78, 140.41, 135.46, 131.29-128.03, 120.29, 115.55, 107.26, 102.76, 51.26. IR (neat, cm⁻¹): 2216, 1634, 1591.

1-benzyl-1,2-dihydro-2-oxo-4-phénylpyridine-3-carbonitrile 4a₃. The general procedure 3, using (0.43 g, 2 mmol) of **3a** and (0.21 g, 2 mmol) of benzylamine, gave 73% of compound **4a₃** as white solid, mp 134°C. ¹H NMR (400 MHz, CDCl₃): 7.60 (d, 1H, *J*_{H-H} = 7.2 Hz), 7.58 - 7.38 (m, 2×5H), 6.31 (d, 1H, *J*_{H-H} = 7.2 Hz), 5.19 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): 160.55, 159.66, 140.44, 135.43, 134.96 - 128.71, 128.03, 115.98, 107.36, 52.69. IR (neat, cm⁻¹): 2220, 1645, 1597.

1,2-dihydro-1-isopropyl-2-oxo-4-phenylpyridine-3-carbonitrile 4a₄. The general procedure 3, using (0.43 g, 2 mmol) of **3a** and of (0.11 g, 2 mmol) isopropylamine gave 48% of compound **4a₄** as white solid, mp 144°C. ¹H NMR (400 MHz, CDCl₃): 7.57 (d, 1H, *J*_{H-H} = 6.8 Hz), 7.49 - 7.50 (m, 5H), 6.38 (d, 1H, *J*_{H-H} = 6.8 Hz), 5.24 - 5.31 (m, 1H), 1.42 (d, 6H, *J*_{H-H} = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): 160.274, 158.80, 136.85, 135.56 - 127.57, 115.86, 107.01, 102.34, 47.68, 21.78. IR (neat, cm⁻¹): 2219, 1640, 1592, 1517.

4-(4-chlorophenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 4b₁. The general procedure 3, using (0.60 g, 2 mmol) of **3b** and (0.06 g, 2 mmol) of methylamine, gave 76% of compound **4b₁** as white solid, mp 184°C. ¹H NMR (400 MHz, CDCl₃): 7.55 (d, 1H, *J*_{H-H} = 6.7 Hz), 7.54 - 7.47 (m, 4H), 6.30 (d, 1H, *J*_{H-H} = 6.4 Hz), 3.64 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 162.12, 157.66, 135.56, 127.33 - 129.88, 115.08, 107.80, 103.34, 34.20. IR (neat, cm⁻¹): 2221, 1644, 1599.

1-allyl-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile 4b₂. The general procedure 3, using (0.60 g, 2 mmol) of **3b** and (0.11 g, 2 mmol) of allylamine, gave 80% of compound **4b₂** as white solid, mp 172°C. ¹H NMR (400 MHz, CDCl₃): 7.62 (d, 1H), 7.56 - 7.41 (m, 4H), 6.44 (d, 1H, *J*_{H-H} = 6.7 Hz), 5.93 - 5.58 (m, 1H), 5.34 - 5.28 (m, 2H), 4.76 - 4.68 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): 162.11, 160.22, 143.11, 136.80, 134.2 - 126.50, 122.18, 115.9, 107.80, 103.11, 48.02. IR (neat, cm⁻¹): 2216, 1637, 1595.

4-(4-chlorophenyl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 4b₃. The general procedure 3, using (0.60 g, 2 mmol) of **3b** and (0.21 g, 2 mmol) of benzylamine gave 85% of compound **4b₃** as white solid, mp 214°C. ¹H NMR (400 MHz, CDCl₃): 7.62 (d, 1H), 7.49-7.30 (m, 4H), 7.29 - 7.19 (m, 5H), 6.20 (d, 1H), 5.12 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): 167.98, 156.50, 136.67, 135.10, 130.29 - 128.27, 119.84, 100.70, 45.63. IR (neat, cm⁻¹): 2219, 1656, 1597.

4-(4-chlorophenyl)-1-isopropyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 4b₄. The general procedure 3,

using (0.60 g, 2 mmol) of **3b** and (0.11 g, 2 mmol) of isopropylamine, gave 50% of compound **4b₄** as white solid, mp 142°C. ¹H NMR (400 MHz, CDCl₃): 7.52 (d, 1H, *J*_{H-H} = 6.8 Hz), 7.50 - 7.40 (m, 4H), 6.27 (d, 1H, *J*_{H-H} = 6.8 Hz), 5.24 - 5.17 (m, 1H), 1.29 (d, 6H, *J*_{H-H} = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): 163.32, 159.18, 134.88, 136.42 - 127.80, 115.9, 106.08, 101.54, 48.78, 21.26. IR (neat, cm⁻¹): 2221, 1648, 1599, 1512.

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