International Journal of Organic Chemistry, 2011, 1, 242-249
doi:10.4236/ijoc.2011.14035 Published Online December 2011 (http://www.SciRP.org/journal/ijoc)

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

Zahira Kibou[1], Nawel Cheikh[1,2], Didier Villemin[2*], Noureddine Choukchou-Braham[1], Bachir Mostefa-Kara[1], Mohamed Benabdallah[1]

[1]*Laboratoire de Catalyse et Synthèse en Chimie Organique, Faculté des Sciences, Université Aboubekr Belkaïd, Tlemcen, Algérie*

[2]*ENSICAEN, LCMT, Caen, France*

*E-mail: *didier.villemin@ensicaen.fr*

Received June 7, 2011; *revised July* 21, 2011; *accepted August* 9, 2011

Abstract

A new series of 3-cyano-2-pyridones derivatives have been prepared by reaction of enaminonitriles 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 dominos 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 vasodilatatory 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 enaminonitrile and in the presence of a catalytic amount of NH_4OAc (**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:

Copyright © 2011 SciRes.

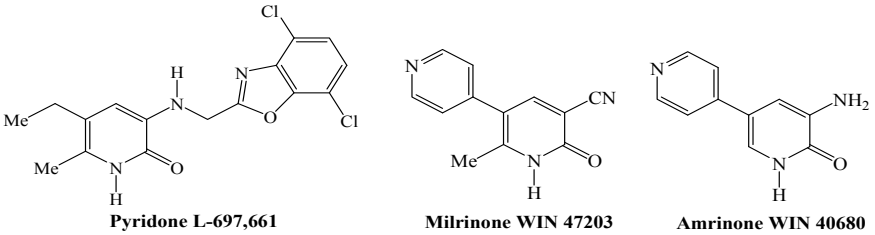
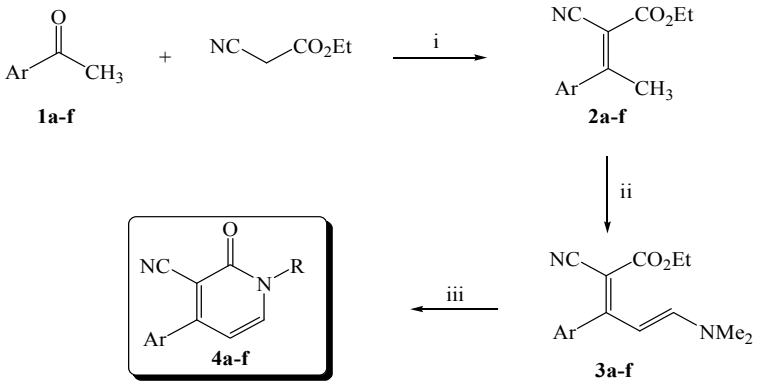


Figure 1. Structures of pyridones L697,661, Milrinone WIN 47203, Amrinone WIN 40680.



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 Kknoevenagel 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 application 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**).

Copyright © 2011 SciRes.

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

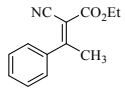
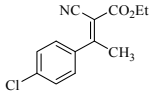
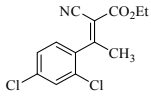
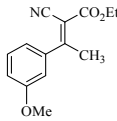
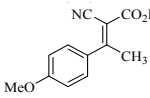
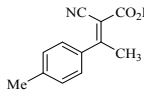
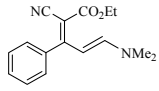
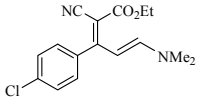
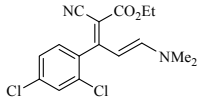
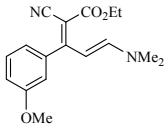
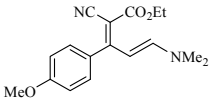
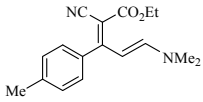
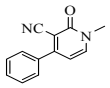
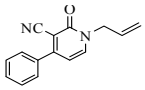
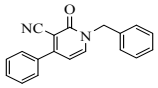
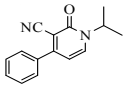
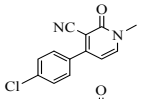
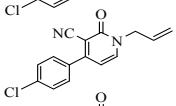
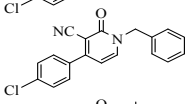
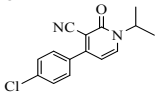
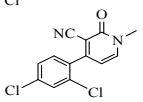
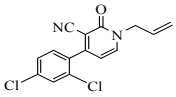
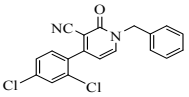
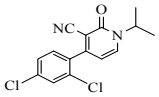
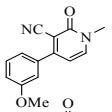
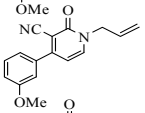
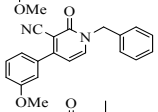
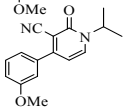
Entry	Ar	Product	Yield (%)
1	C_6H_5-	 **2a**	70
2	*p*-ClC_6H_4-	 **2b**	75
3	2,4-$Cl_2C_6H_3$-	 **2c**	68
4	*m*-$CH_3OC_6H_4$-	 **2d**	73
5	*p*-$CH_3OC_6H_4$-	 **2e**	80
6	*p*-$CH_3C_6H_4$-	 **2f**	65

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

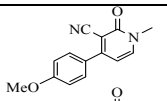
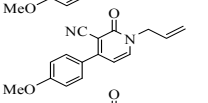
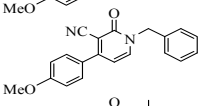
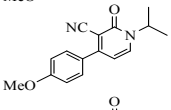
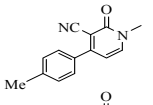
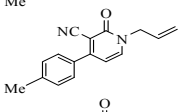
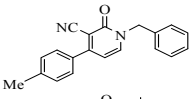
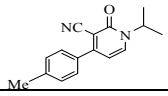
Entry	Ar	Product	Yield (%)
7	C_6H_5-	 **3a**	88
8	*p*-ClC_6H_4-	 **3b**	90
9	2,4-$Cl_2C_6H_3$-	 **3c**	82
10	*m*-$CH_3OC_6H_4$-	 **3d**	75
11	*p*-$CH_3OC_6H_4$-	 **3e**	80
12	*p*-$CH_3C_6H_4$-	 **3f**	77

Copyright © 2011 SciRes.

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

Entry	Enaminonitrile	R	Product		Yield (%)
13		CH_3-		**4a$_1$**	66
14		CH_2=CH-CH_2-		**4a$_2$**	70
	3a				
15		$C_6H_5CH_2$-		**4a$_3$**	73
16		$(CH_3)_2CH$-		**4a$_4$**	48
17		CH_3-		**4b$_1$**	76
18		CH_2=CH-CH_2-		**4b$_2$**	80
	3b				
19		$C_6H_5CH_2$-		**4b$_3$**	85
20		$(CH_3)_2CH$-		**4b$_4$**	50
21		CH_3-		**4c$_1$**	75
22		CH_2=CH-CH_2-		**4c$_2$**	80
	3c				
23		$C_6H_5CH_2$-		**4c$_3$**	84
24		$(CH_3)_2CH$-		**4c$_4$**	52
25		CH_3-		**4d$_1$**	73
26		CH_2=CH-CH_2-		**4d$_2$**	79
	3d				
27		$C_6H_5CH_2$-		**4d$_3$**	80
28		$(CH_3)_2CH$-		**4d$_4$**	53

Copyright © 2011 SciRes.

29		CH_3-		**4e$_1$**	74
30		CH_2=CH-CH_2-		**4e$_2$**	81
	3e				
31		$C_6H_5CH_2$-		**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
	3f				
35		$C_6H_5CH_2$-		**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 NH_4OAc, the enaminonitriles 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 NH_4OAc, 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 ^{1}H NMR spectra were recorded at 400 MHz, on a Brüker AC 400 spectrometers and ^{13}C NMR spectra were recorded in the same spectrometers at 100.6 MHz. Samples were registered in $CDCl_3$ 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 CH_2Cl_2. The organic layer obtained was washed with (3 × 20 ml) of water, (10 ml) of saturated NaCl, dried on $MgSO_4$, 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. ^{1}H NMR (400 MHz, $CDCl_3$): 7.53 - 7.14 (m, 5H), 4.20 (q, 2H, $J_{H\text{-}H}$ = 7.2 Hz), 2.57 (s, 3H), 1.26 (t, 3H, $J_{H\text{-}H}$ = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 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. ^{1}H NMR (400 MHz, $CDCl_3$): 7.51 - 7.18 (m, 4H), 4.20 (q, 2H, $J_{H\text{-}H}$ = 7.2 Hz), 2.62 (s, 3H), 1.29 (t, 3H, $J_{H\text{-}H}$ = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 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.

Copyright © 2011 SciRes.

***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. ^{1}H NMR (400 MHz, $CDCl_3$): 7.32 - 7.25 (m, 5H), 6.57 (d, 1H, $J_{H\text{-}H}$ = 12.8 Hz), 5.98 (d, 1H, $J_{H\text{-}H}$ = 12.8 Hz), 4.32 (q, 2H, $J_{H\text{-}H}$ = 7.2 Hz), 3.07 (s, 3H), 3.04 (s, 3H), 1,39 (t, 3H, $J_{H\text{-}H}$ = 7.2 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): 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-(dimethy-lamino) 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. ^{1}H NMR (400 MHz, $CDCl_3$): 7.35 - 7.20 (m, 4H), 6.48 (d, 1H, $J_{H\text{-}H}$ = 12.8 Hz), 5,90 (d, 1H, $J_{H\text{-}H}$ = 12.8 Hz), 4.26 (q, 2H, $J_{H\text{-}H}$ = 7.2 Hz,), 3.01 (s, 3H), 2.99 (s, 3H), 1.33 (t, 3H, $J_{H\text{-}H}$ = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 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 4a$_1$. The general procedure 3, using (0.43 g, 2 mmol) of **3a** and (0.06 g, 2 mmol) of methylamine, gave 66% of compound **4a$_1$** as white solid, mp 174˚C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.55 (d, 1H, $J_{H\text{-}H}$ = 6.7 Hz), 7.51 - 7.50 (m, 5H), 6.62 (d, 1H, $J_{H\text{-}H}$ = 6.4 Hz), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 4a$_2$. The general procedure 3, using (0.43 g, 2 mmol) **3a** and (0.11g, 2 mmol) of allylamine, gave 76% of compound **4a$_2$** as white solid, mp 99˚C - 100˚C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (d, 1H), 7.53 - 7.49 (m, 5H), 6.36 (d, 1H, $J_{H\text{-}H}$ = 6.7 Hz), 6.02 - 5.92 (m, 1H), 5.37 - 5.30 (m, 2H), 4.64-4.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 4a$_3$. The general procedure 3, using (0.43 g, 2 mmol) of **3a** and (0.21 g, 2 mmol) of benzylamine, gave 73% of compound **4a$_3$** as white solid, mp 134˚C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.60 (d, 1H, $J_{H\text{-}H}$ = 7.2 Hz), 7.58 - 7.38 (m, 2×5H), 6.31 (d, 1H, $J_{H\text{-}H}$ = 7.2 Hz), 5.19 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 4a$_4$. The general procedure 3, using (0.43 g, 2 mmol) of **3a** and of (0.11 g, 2 mmol) isopropylamine gave 48% of compound **4a$_4$** as withe solid, mp 144˚C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.57 (d, 1H, $J_{H\text{-}H}$ = 6.8 Hz), 7.49 - 7.50 (m, 5H), 6.38 (d,1H, $J_{H\text{-}H}$ = 6.8 Hz), 5.24 - 5.31 (m, 1H), 1.42 (d, 6H, $J_{H\text{-}H}$ = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 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 4b$_1$. The general procedure 3, using (0.60 g , 2 mmol) of **3b** and (0.06 g, 2 mmol) of methylamine, gave 76% of compound **4b$_1$** as white solid, mp 184˚C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.55 (d, 1H, $J_{H\text{-}H}$ = 6.7 Hz), 7.54 - 7.47 (m, 4H), 6.30 (d,1H, $J_{H\text{-}H}$ = 6.4 Hz), 3.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 4b$_2$. The general procedure 3, using (0.60 g, 2 mmol) of **3b** and (0.11 g, 2 mmol) of allylamine, gave 80% of compound **4b$_2$** as white solid, mp 172˚C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.62 (d, 1H), 7.56 - 7.41 (m, 4H), 6.44 (d, 1H, $J_{H\text{-}H}$ = 6.7 Hz), 5.93 - 5.58 (m, 1H), 5.34 - 5.28 (m, 2H), 4.76 - 4.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 4b$_3$. The general procedure 3, using (0.60 g, 2 mmol) of **3b** and (0.21 g, 2 mmol) of benzylamine gave 85% of compound **4b$_3$** as white solid, mp 214˚C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.62 (d, 1H), 7.49-7.30 (m, 4H), 7.29 - 7.19 (m, 5H), 6.20 (d, 1H), 5.12 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 4b$_4$. The general procedure 3,

Copyright © 2011 SciRes.

using (0.60g , 2 mmol) of **3b** and (0.11 g, 2 mmol) of isopropylamine, gave 50% of compound **4b$_4$** as white solid, mp 142˚C. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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.

5. References

[1] D. Blasco-Jiménez, A. J. Lopez-Peinado, R. M. Martin-Aranda, M. Ziolek and I. Sobczak, "Sonocatalysis in Solvent-Free Conditions: An Efficient Eco-Friendly Methodology to Prepare N-Alkyl Imidazoles Using Amino-Grafted NbMCM-41," *Catalysis Today*, Vol. 142, No. 3-4, 2009, pp. 283-287. doi:10.1016/j.cattod.2008.11.028

[2] D. Kumar, V. B. Reddy, B. G. Mishra, R. K. Ranna, M. N. Nadagouda and R. S. Varma, "Nanosized Magnesium Oxide as Catalyst for the Rapid and Green Synthesis of Substituted 2-Amino-2-Chromenes," *Tetrahedron*, Vol. 63, No. 15, 2007, pp. 3093-3097. doi:10.1016/j.tet.2007.02.019

[3] L. F. Teitze, "Domino Reactions in Organic Synthesis," *Chemical Reviews*, Vol. 96, No. 1, 1996, pp. 115-136. doi:10.1021/cr950027e

[4] R. Maggi, R. Ballini and G. Sartori, "Basic Alumina Catalysed Synthesis of Substituted 2-Amino-2-chromenes via Three-Component Reaction," *Tetrahedron Letters*, Vol. 45, No. 11, 2004, pp.2297-2299. doi:10.1016/j.tetlet.2004.01.115

[5] J. A. Wang, X. Bokhimi, O. Novaro, T. Lopez, F. Tzompantzi, R. Gomez, J. Navarrete, M. E. Llanos and M. Lopez-Salinas, "Effects of Structural Defects and Acid-Basic Properties on the Activity and Selectivity of Isopropanol Decomposition on Nanocrystallite Sol-Gel Alumina Catalyst," *Journal of Molecular Catalysis A*: *Chemical*, Vol. 137, No. 1-3, 1999, pp. 239-256. doi:10.1016/S1381-1169(98)00077-6

[6] S. Paul, P. Nanda, R. Gupta and A. Loupy, "Ac_2O-Py/Basic Alumina as a Versatile Reagent for Acetylations in Solvent-Free Conditions under Microwave Irradiation," *Tetrahedron Letters*, Vol. 43, No. 23, 2002, pp. 4261-4265. doi:10.1016/S0040-4039(02)00732-3

[7] C. M. Figueiredo, "Preparation of Aluminas from a Basic Aluminium Carbonate," *Catalysis Today*, Vol. 5, 1989, pp. 433-442. doi:10.1016/0920-5861(89)80007-0

[8] S. Carre, B. Tapin, N. S. Gnep, R. Revel and P. Magnoux, "Model Reactions as Probe of the Acid-Base Properties of Aluminas: Nature and Strength of Active sites. Correlation with Physicochemical Characterization," *Applied Catalysis A*: *General*, Vol. 372, No. 1, 2010, pp. 26-33. doi:10.1016/j.apcata.2009.10.005

[9] M. T. Cocco, C. Congiu and V. Onnis, "Synthesis and Antitumor Activity of 2-Hydroxy-2-pyridones Derivatives," *European Journal of Medicinal Chemistry*, Vol. 35, No. 5, 2000, pp. 545-552. doi:10.1016/S0223-5234(00)00149-5

[10] F. Manna, F. Chimenti, A. Bolasco, A. Filippelli and E. Lampa, "Antiinflammatory, Analgesic and Antipyfuztic 4,6-Disubstituted 3-Cyanopyridine-2-ones and 3-Cyano-2-aminopyridines," *Pharmacological Research*, Vol. 26, Suppl. 1, 1992, pp. 267-277. doi:10.1016/1043-6618(92)91243-A

[11] R. L. Parreira, O. Abrahão and S. E. Galembeck, "Conformational Preferences of Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors," *Tetrahedron*, Vol. 57, No. 16, 2001, pp. 3243-3253. doi:10.1016/S0040-4020(01)00193-4

[12] X. Fan, D. Feng, Y. Qu, X. Zhang, J. Wang, P. M. Loiseau, G. Andrei, R. Snoeck, E. De Clercq, "Practical and Efficient Synthesis of Pyrano[3,2-c]pyridone, Pyrano [4,3-b]pyran and Their Hybrids with Nucleoside as Potential Antiviraland Antileishmanial Agents," *Bioorganic & Medicinal Chemistry Letters*, Vol. 20, No. 3, 2010, pp. 809-813. doi:10.1016/j.bmcl.2009.12.102

[13] E. L. Presti, R. Boggia, A. Feltrin, G. Menozzi, P. Dorigo and L. Mosti, "3-Acetyl-5-acylpyridin-2(1*H*)-ones and 3-Acetyl-7,8-dihydro-2,5(1*H*,6*H*)-quinolinediones: Synthesis, Cardiotonic Activity and Computational Studies," *II Farmaco*, Vol. 54, No. 7, 1999, pp. 465-447. doi:10.1016/S0014-827X(99)00053-1

[14] W. K. Anderson, D. C. Dean and T. Endo, "Synthesis, Chemistry, and Antineoplastic Activity of α-Halopyridinium Salts: Potential Pyridone Prodrugs of Acylated Vinylogous Carbinolamine Tumor Inhibitors," *Journal of Medicinal Chemistry*, Vol. 33, No. 6, 1990, pp. 1667-1675. doi:10.1021/jm00168a021

[15] P. S. Dragovich, T. J Prins, Z. Ru, E. L. Brown, F. C. Maldonado, S. A. Fuhrman, L. S. Zalman, L. Iuniland, C. A. Lee and S. T. Worland, "Structure-Based design, Synthesis, and Biological Evaluation of Irreversible Human Rhinovirus 3C Protease Inhibitors. 6. Struc-ture-Activity Studies of Orally Bioavailable, 2-Pyridone- Containing Peptidomimetics," *Journal of Medicinal Chemistry*, Vol. 45, No. 8, 2002, pp. 1607-1623. doi:10.1021/jm010469k

[16] B. Kozlevcar, M. Radisek, Z. Jaglicic, F. Merzel, L. Glazar, A. Golobic and P. Segedin, "Strong Antiferromagnetism in the Dinuclear 2-Pyridone Complex with N-C-O Bridges: A Paddle-Wheel Analogue of the Dinuclear Tetracarboxylates," *Polyhedron*, Vol. 26, 2007, pp. 5414-5419. doi:10.1016/j.poly.2007.08.019

[17] T. Mochida, M. Ueda, C. Aoki and H. Mori, "Structures and Properties of *Trans*-Dichloro{Tetrakis (5-Chloro-2 (1H)-pyridone-*O*)}M(II) [M=Mn, Fe, Co, Ni, Cu]; Formation of Quasi-Macrocyclic Metal Complexes through Hydrogen Bonding," *Inorganica Chimica Acta*, Vol. 335, No. 27, 2002, pp. 151-155. doi:10.1016/S0020-1693(02)00817-4

[18] K. R. Gibson, L. Hitzel, R. J. Mortishire-Smith, U. Gerhard, R.A. Jelley, A. J. Reeve, M. Rowley, A. Nadin and A. P. Owens, "Synthesis and Conformational Dynamics of Tricyclic Pyridones Containing a Fused Seven-

Copyright © 2011 SciRes.

Membered Ring," *Journal of Organic Chemistry*, Vol. 67, No. 26, 2002, pp. 9354-9360. doi:10.1021/jo026411a

[19] I. Collins, C. Moyes, *et al.*, "3-Heteroaryl-2-pyridones: Benzodiazepine Site Ligands with Functional Delectivity for Alpha 2/Alpha 3-Subtypes of Human GABA (A) Receptor-Ion Channels," *Journal of Medicinal Chemistry*, Vol. 45, No. 9, 2002, pp. 1887-1990. doi:10.1021/jm0110789

[20] F. A. Abu-Shanab, A. D. Redhouse, J. R. Thompson and B. J. Wakefield, "Synthesis of 2,3,5,6-Tetrasubtituted Pyridines from Enamines Derived from N, N-Dimethylformamide Dimethyl Acetal," *Synthesis*, Vol. 5, 1995, pp. 557-560. doi:10.1055/s-1995-3954

[21] W. D. Jones, R. A. Schnettler and E. W. Huber, "A Convenient Synthesis of 5-Acyl-6-substituted 3-cyano-2 (1*H*)-pyridinones," *Journal of Heterocyclic Chemistry*, Vol. 27, No. 3, 1990, pp. 511-518. doi:10.1002/jhet.5570270307

[22] H. Fukatsu, Y. Kato, S. Murase and S. Nakagawa, "Synthesis and Cardiotonic Activity of 5-(2-Substituted thiazol-4-yl)-2-pyridones and Thiazolo[4,5-f] quinolinones," *Heterocycles*, Vol. 29, No. 8, 1989, pp. 1517-1528. doi:10.3987/COM-89-4984

[23] I. Sircar, B. L. Duell, J. A. Bristol, R. E. Weishaar and D. B. Evans, "Cardiotonic Agents. 5. 1,2-Dihydro-5-[4-(1Himidazol-1-yl)phenyl]-6-methyl-2-oxo-3-pyridinecarbonitriles and Related Compounds. Synthesis and Inotropic Activity," *Journal of Medicinal Chemistry*, Vol. 30. No. 6, 1987, pp. 1023-1029. doi:10.1021/jm00389a011

[24] D. W. Robertson, E. E. Beedle, J. K. Swartzendruber, N. D. Jones, T. K. Elzey, R. F. Kauffman, H. Wilson and J. S. Hayes, "Bipyridine Cardiotonics: The Three-Dimensional Structures of Amrinone and Milrinone," *Journal of Medicinal Chemistry*, Vol. 29, No. 5, 1986, pp. 635-640. doi:10.1021/jm00155a009

[25] J. J. Chen and I. J. Wang, "Synthesis and Colour Assessment of Some 3-Cyano-4-pyrenyl-6-substituted-2-pyridone Derivatives," *Dyes and Pigments*, Vol. 29, No. 4, 1995, pp. 305-313. doi:10.1016/0143-7208(95)00055-0

[26] A. H. Abadi, T. M. Ibrahim, K. M. Abouzid, J. Lehmann, H. N. Tinsley, B. D. Gary and G. A. Piazza, "Design, Synthesis and Biological Evaluation of Novel Pyridine Derivatives as Anticancer Agents and Phosphodiesterase 3 Inhibitors," *Bioorganic & Medicinal Chemistry*, Vol. 17, No. 16, 2009, pp. 5974-5982. doi:10.1016/j.bmc.2009.06.063

[27] D. Villemin, B. Mostefa-Kara, N. Bar, N. Choukchou-Braham, N. Cheikh, A. Benmeddah, H. Hazimeh and C. Ziani-Cherif, "Base Promoted Reaction in Ionic Liquid Solvent: Synthesis of Butenolides," *Letters in Organic Chemitry*, Vol. 3, 2006, pp. 558-559. doi:10.2174/157017806778341807

[28] D. Villemin, N. Cheikh, B.Mostefa-Kara, N. Bar, N. Choukchou-Braham and M. A. Didi, "Solvent-Free Reaction on KF-Alumina under Microwave: Serendipitous One-Pot Domino Synthesis of New Isobenzofuran-1(3*H*) -ones from Alpha-Hydroxyketones," *Tetrahedron Letters*, Vol. 47, No. 31, 2006, pp. 5519-5521. doi:10.1016/j.tetlet.2006.05.137

[29] N. Cheikh, N. Bar, *et al.*, "Efficient Synthesis of New Butenolides by Subsequent Reactions: Application for the Synthesis of Original Iminolactones, Bis-Iminolactones and Bis-Lactones," *Tetrahedron*, Vol. 67, No. 8, 2011, pp. 1540-1557. doi:10.1016/j.tet.2010.12.062

[30] Q. Shi, J. Chen, Q. Zhunag and X. Wang, "The Condensation of Aromatic Aldehydes with Acidic Methylene Compounds in Water," *Chinese Chemical Letters*, Vol. 14, 2003, pp. 1242-1245.

[31] T. B. FranColse and F. Andre, "Knoevenagel Condensation Catalysed by Aluminium Oxide," *Tetrahedron Letters*, Vol. 23, No. 47, 1982, pp. 4927-4928. doi:10.1016/S0040-4039(00)85749-4

[32] P. de la Cruz, E. Diez-Barra, A. Loupy and F. Langa, "Silica Gel Catalysed Knoevenagel Condensation in Dry Media under Microwave Irradiation," *Tetrahedron Letters*, Vol. 37, 1996, pp. 1113-1116. doi:10.1016/0040-4039(95)02318-6

[33] G.-H. Gao, L. Lu, *et al.*, "Basic Ionic Liquid: A Reusable Catalyst for Knoevenagel Condensation in Aqueous Media," *Chemical Research in Chinese Universities*, Vol. 23, No. 2, 2007, pp. 169-172. doi:10.1016/S1005-9040(07)60035-X

[34] B. Siebenhaar, B. Casagrande, M. Studer and H. U. Blaser, "An Easy-to-Use Heterogeneous Catalyst for the Knoevenagel Condensation," *Canadian Journal of Chemistry*, Vol. 79, No. 5-6, 2001, pp. 566-569. doi:10.1139/v01-072

[35] M. L. Kantam and B. Bharathi, "Mn(III) Salen Catalyst for Knoevenagel Condensation a Novel Heterogeneous System," *Catalysis Letters*, Vol. 55, No. 3-4, 1998, pp. 235-237. doi:10.1023/A:1019051416463

[36] S. Balalaie and N. Nemati, "Ammonium Acetate-Basic Alumina Catalyzed Knoevenagel Condensation under Microwave Irradiation under Solvent-Free Conditions," *Synthetic Communications*, Vol. 30, No. 5, 2000, pp. 869-875. doi:10.1080/00397910008087099

[37] A. McCluskey, P. J. Robinson and T. Hill, "Green Chemistry Approaches to the Knoevenagel Condensation: Comparison of Ethanol, Water and Solvent Free (Dry Grind) Approaches," *Tetrahedron Letters*, Vol. 43, No. 17, 2002, pp. 3117-3120. doi:10.1016/S0040-4039(02)00480-X

[38] F. Freeman, "Properties and Reactions of Ylidenemalononitriles," *Chemical Reviews*, Vol. 80, No. 4, 1980, pp. 329-350. doi:10.1021/cr60326a004

[39] A. W. Erian, S. M. Sherif, A. Alassar and Y. M. Elkholy, "*β*-Enaminonitriles in Heterocyclic Synthesis: A Novel Synthesis and Transformations of α-Substituted-β-enaminonitriles," *Tetrahedron*, Vol. 50, No. 6, 1994, pp. 1877-1884. doi:10.1016/S0040-4020(01)80859-0

[40] A. W. Erian, "The Chemistry of *β*-Enamino Nitriles as Versatile Reagents in Heterocyclic Synthesis," *Chemical Reviews*, Vol. 93, No. 6, 1993, pp. 1991-2005. doi:10.1021/cr00022a002

Copyright © 2011 SciRes.