One-Pot Four Component Synthesis of 4, 6-Disubstituted 3-Cyano-2-Pyridones in Polyethylene Glycol

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Abstract: The reaction of ketone, aldehyde, ethyl cyanoacetate and ammonium acetate in polyethylene glycol-600 is reported. The reaction proceeds smoothly in the absence of catalyst to yield 2-Pyridones.

Keywords: PEG, 2-pyridone, four components.

INTRODUCTION

The interest of organic chemist increases in developing green protocol for organic synthesis due to environmental demands and sustainability. The development of uncatalysed processes to replace stoichiometric reaction, which produces large amount of waste byproducts, has made a significant contribution to the reduction of environmental pollution. Polyethylene glycol (PEG) hydrophilic, non-ionic polymer is used in many biochemical and industrial applications. Due to its nontoxic character PEG can be found in cosmetics, food and pharmaceutical products. PEG is an environmentally benign, cheap, and easily available, solvent which has been successfully utilized in numerous reactions [1, 2].

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 [3]. Natural compounds pyridone core has emerged during the last ten years as a potent antitumor [4], antifungal [5], antiviral [6] and psychotherapeutic [7], anti-HIV drugs [8]. Moreover, pyridones are key intermediates in the synthesis of corresponding pyridines [9]. Several methods have been reported for the synthesis of substituted 2-pyridones e.g. metathesis-based approach to the synthesis of 2-pyridone [10], cyclisation type reaction [11], one-pot synthesis of pyridones by cross coupling of tributylstanlynallenes with substituted iodopropan-2-enamides [12]. Reaction of α, β-unsaturated carbonyl compounds with cyanoacetamide in the presence of tBuOK [13], in such conventional methods for synthesis of 2-pyridones, the time for completion of reaction is very long ranging from 9-10 hr [14], low yield. Lam *et.al* reported the synthesis of functionalized 2-pyridone with low yield by using solid-phase synthesis method [15]. In this strategy four components were involved to obtain the desired product. Sakurai and co-workers reported the synthesis of 2-pyridone in presence of benzene or without solvent under reflux conditions for 8-12 hrs [11]. Rong *et al.* reported the one-pot synthesis of 4,6-diaryl-2-oxo- 1, 2-dihydropyridine-3-carbonitriles via three-component cyclocondensation in presence of sodium hydroxide [16]. Despite the success of available methods, there is always a need to develop newer and simpler methods for the synthesis of 2-pyridone.

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RESULTS AND DISCUSSION

We report herein the One-pot four component synthesis of 2-pyridone in PEG. A variety of substituted aromatic ketones and aromatic as well as aliphatic aldehydes underwent competitive formation of 2-pyridones. This protocol is rapid and efficient to prepare a variety of substituted 2-pyridone from both electron donating as well as electron withdrawing aromatic ketones and aldehydes. It follows from Table **1** that variety of functionalities (nitro, halo, alkoxy) can be accommodated in 2-pyridone derivatives. The structures of the products were confirmed from melting point and spectroscopic data.

We believe that the condensation between aryl aldehyde, ketones, ethyl cyanoacetate and ammonium acetate leads to substituted 2-pyriodnes via a knoevenagel reaction. The reaction proceeds with the elimination of two moles of water and one mole of alcohol (Scheme **2**). These reactions were completed via dehydrogenation under reflux condition. It is important to mention that dehydrogenation takes place under reflux condition has been described in literature [11]. This mode of dehydrogenation suggests that reflux conditions are essential to favour the formation of the 2-pyridone (Table **3**).

Using PEG-600 as reaction medium, we next examined the scope of the pyridone formation. The cyclic ketones reacted smoothly with aldehydes, ethyl cyanoacetate and ammonium acetate were examined to afford 2-pyridone (**V*o*** and **V*p***).

The effect of temperature was also studied at different temperature. The reaction did proceed but the yield obtained

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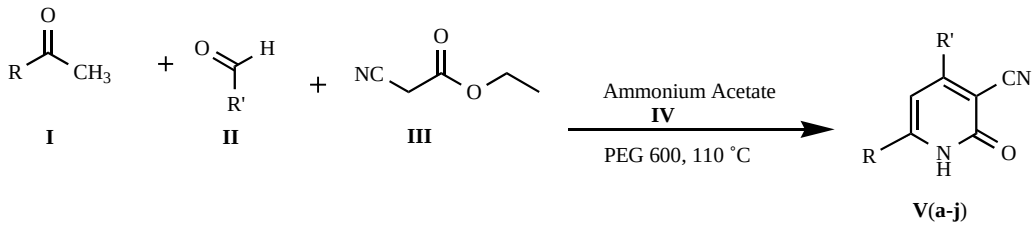
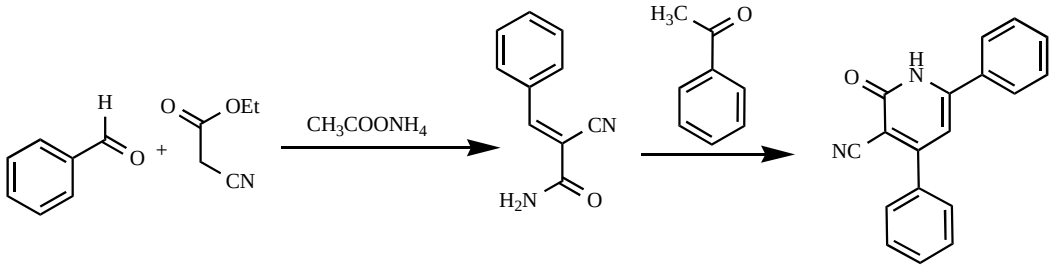


Scheme 1.

Table 1. Synthesis of 2-Pyridones in Polyethylene Glycol-600[a]

Entry	R	R'	Time (h)	Product	Yield (%)[b]	Mp ^{0}C
1	C_6H_5	C_6H_5	3.0	**V*a***	80	> 300
2	C_6H_5	3,4-$(OCH_3)C_6H_3$	3.5	**V*b***	71	276-277
3	4-ClC_6H_4	3,4-$(OCH_3)C_6H_3$	4.0	**V*c***	68	> 300
4	4-BrC_6H_4	3,4-$(OCH_3)C_6H_3$	4.0	**V*d***	67	300
5	4-$CH_3C_6H_4$	3,4-$(OCH_3)C_6H_3$	5.0	**V*e***	60	268
6	4-$OMeC_6H_4$	3,4-$(OCH_3)C_6H_3$	4.0	**V*f***	70	266
7	4-BrC_6H_4	C_6H_5	4.0	**V*g***	68	290
8	4-$NO_2C_6H_4$	3,4-$(OCH_3)C_6H_3$	4.5	**V*h***	65	250
9	C_6H_5	4-$NO_2C_6H_4$	4.0	**V*i***	68	> 300
10	$C_{12}H_{10}O$	C_6H_5	4.0	**V*j***	65	> 300
11	C_6H_5	n-Heptanal	3.0	**V*k***	68	156-158
12	C_6H_5	Isovaleraldehyde	3.5	**V*l***	60	188-190
13	C_6H_5	Valeraldehyde	3.0	**V*m***	72	142-144
14	C_6H_5	Propanal	3.0	**V*n***	75	208

[a]All the reactions were performed with ethyl cyanoacetate and ammonium acetate.
[b]Isolated yield.



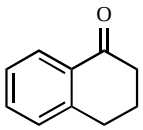
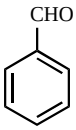
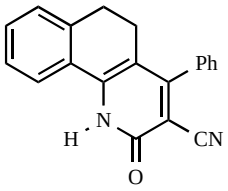
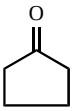
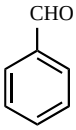
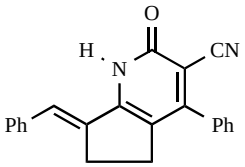
Scheme 2. Proposed pathway for the reaction in Scheme **1**.

remained low even after longer reaction time. Several solvents like ethanol, H_2O, PEG-H_2O, were tested but very low yield were obtained. However, an elevated temperature (110^0C) using PEG-600 gave better results in terms of yield (summarized in Table **3**).

In a typical experiment aromatic aldehydes (1mmol), aromatic ketones (1mmol), ethyl cyano acetate (1mmol), and ammonium acetate (8mmol) in PEG-600 were stirred at 110^0C for appropriate time (mentioned in Tables **1**, **2**). After the completion of reaction (monitored by TLC) the reaction mass was poured in to cold water. The solid 2-pyridone product, which separated out, was filtered washed with water and dried. The crude product was recrystallised from ethanol/DMF mixture provided substituted 2-pyridone with 60-80% yield.

The generality of PEG was examined using PEG-400 and PEG-600 as shown in Table **4**. In presence of PEG-400 the yield of product was slightly changed. All reactions proceeded very smoothly and clearly were stirred at 110^0C condition in this method. This protocol is advantageous since reaction was carried out in absence of catalyst, operational

Table 2. Synthesis of 2-Pyridones by Using Cyclic Ketones in Polyethylene Glycol-600[a]

Entry	Cyclic Ketone	Aldehyde	Product	Time (h)	Yield (%)[b]	Mp ˚C
1			 **V*o***	3.0	74	>300
2			 **V*p***	4.0	60	>300

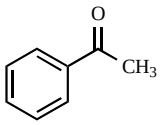
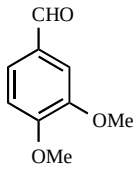
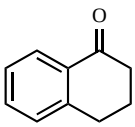
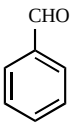
[a]All the reactions were performed with ethyl cyanoacetate and ammonium acetate.
[b]Isolated yield.

Table 3. Synthesis of 2-Pyridone[a] (V*a*) at Different Temperatures

Entry	Solvent	Temperature/^{0}C	Time(h)	Yield (%)[b]
1	PEG-600	25^{0}C	24	05
2	PEG-600	50^{0}C	12	24
3	PEG-600	75^{0}C	12	45
4	PEG-600	110^{0}C	3	80
5	PEG+H_2O(1:1)	100^{0}C	8	20
6	H_2O	100^{0}C	8	04
7	Ethanol	70^{0}C	12	18

[a]Reaction was carried out with Benzaldehyde (1mmol), Acetophenone (1mmol), Ethyl cyanoacetate (1mmol), and ammonium acetate (8mmol).
[b]Isolated yield.

Table 4. Synthesis of 2-Pyridones[a] in Polyethylene Glycol-600 and 400

Entry	Starting Material I	Starting Material II	Product	Solvent	Time (h)	Yield (%)[b]
1a			V*b*	PEG-600 PEG-400	4.0 4.0	71 67
2b			V*o*	PEG-600 PEG-400	4.0 4.0	73 74

[a]All the reactions were performed with ethyl cyanoacetate and ammonium acetate.
[b]Isolated yield.

simplicity, good yields and purification simply by crystallization.

CONCLUSION

In summary, we have reported a novel, eco-friendly, efficient method for the synthesis of 2-pyridones from various aromatic aldehydes, ketones, in polyethylene glycol in absence of catalyst. The simple and mild reaction conditions are an alternative to existing methods.

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EXPERIMENTAL SECTION

Melting points were uncorrected and IR Spectra were recorded using Nujol for solids on a Perkin-Elmer-1710 spectrophotometer. ^{1}H NMR spectra were recorded at 200 MHz and 300 MHz in $CDCl_3$ and DMSO-*d6* using TMS as an internal standard. Mass spectra were recorded under ESI mode, on Thermo Finnigan (Model-LCQ Advantage MAX) mass spectrometer.

General Procedure for the Preparation of Substituted 2-Pyridones

A mixture of aromatic ketone **I** (1mmol), aldehydes **II** (1mmol), ethyl cyanoacetate **III** (1mmol), and ammonium acetate **IV** (8mmol), in PEG-600(5-6ml) was stirred at 110^{0}C for appropriate time (mentioned in Tables **1**, **2**). After completion of the reaction (monitored by TLC), the reaction mass poured in to cold water. The solid 2-pyridone product, which separated out, was filtered washed with water and dried. The crude products were recrystallized from ethanol/DMF mixture provided substituted 2-pyridone (Scheme **1**) with 60-80% yield.

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[17] Spectral data for selected compound:
1,2-dihydro-2-oxo-4,6-diphenylpyridine-3-carbonitrile [V*a*]: Yield - 80%, M.p.: >300^{0}C. IR(Nujol): (NH) 3382, (CN) 2218, (C=O) 1647 *cm*$^{-1}$. ^{1}H NMR (200 MHz,$CDCl_3$+ DMSO-*d6*) δ=12.60 (br, s, 1H, N-H), 7.53(m, 2H), 7.40 (m, 3H), 7.10-7.29 (m, 5H),6.80 (s, 1H, pyridone C-H), MS (*m/z*): 273 (M+H)$^+$, 272(M$^+$).
1,2-dihydro-4-(3,4-dimethoxyphenyl)-2-oxo-6-phenylpyridine-3-carbonitrile [V*b*]: Yield- 71%, M.p.: 276-277^0 C, IR(Nujol): (NH) 3355, (CN) 2219, (C=O) 1651 *cm*$^{-1}$, ^{1}H NMR (300 MHz, DMSO-*d6*): δ = 12.75 (br, s, 1H, NH), 7.88 (d, 2H), 7.53-7.55 (m, 3H), 7.34-7.36 (m, 2H), 7.12 (d, 1H), 6.83 (s, 1H, pyridone H), 3.83 (s, 6H, -OCH3), MS (*m/z*): 332 (M$^+$).
6-(4-chlorophenyl)-1,2-dihydro-4-(3,4-dimethoxyphenyl)-2-oxo-pyridine-3-Carbonitrile [V*c*]: Yield - 68%, M.p.: >300^{0}C, IR(Nujol): (N-H) 3305, (CN) 2221, (C=O) 1633 *cm*$^{-1}$. ^{1}H NMR (300 MHz, DMSO-*d6*) δ = 12.51 (br, s, 1H, NH), 7.92 (d, 2H), 7.60 (d, 2H), 7.33-7.36 (m, 2H), 7.12 (d, 1H), 6.89 (s, 1H), 3.83 (s, 6H, -OCH3), MS (*m/z*): 366 (M$^+$).
6-(4-bromophenyl)-1,2-dihydro-4-(3,4-dimethoxyphenyl)-2-oxo-pyridine-3-carbonitrile [V*d*]**:** Yield- 67%, M.p.: 300 ^{0}C, IR(Nujol): (N-H) 3431, (CN) 2222, (C=O) 1635 *cm*$^{-1}$. ^{1}H NMR (300 MHz, DMSO-*d6*): δ= 12.74 (br, s, 1H, NH), 7.84 (d, 2H), 7.73-7.76 (m, 2H), 7.34-7.37 (m, 2H), 7.13 (d, 1H), 6.90 (s, 1H, pyridone H), 3.84 (s, 6H, -OCH3), MS (*m/z*): 411 (M$^+$).
1,2-dihydro-4-(3,4-dimethoxyphenyl)-6-(4-methoxyphenyl)-2-oxopyridine-3-carbonitrile [V*f*]: Yield-65%, M.p.: 266^{0}C, IR(Nujol): (N-H) 3350, (CN) 2222, (C=O) 1652 *cm*$^{-1}$. ^{1}H NMR (300 MHz , $CDCl_3$+ DMSO-*d6*): δ= 12.58 (br, s, 1H, NH), 7.88 (d, 2H), 7.32-7.34 (m, 2H), 7.12 (d, 1H), 7.07 (d, 2H), 6.78 (s, 1H, pyridone H), 3.83 (s, 9H, -OCH3), MS (*m/z*): 363 (M$^+$+H), 362(M$^+$).
6-(4-bromophenyl)-1,2-dihydro-2-oxo-4-phenylpyridine-3-carbonitrile6 [V*g*]: Yield-68%, M.p**:** 290^{0}C, IR(Nujol): (N-H) 3300, (CN) 2223, (C=O) 1652 *cm*$^{-1}$, ^{1}H NMR (200 MHz, $CDCl_3$+ DMSO-*d6*): δ= 12.75 (br, s, 1H, NH), 8.00-8.14 (m, 2H), 7.82 (m, 2H), 7.61-7.63 (m, 2H), 7.30-7.47 (m, 3H), 6.54 (s, 1H, pyridone H), MS (*m/z*): 351 (M$^+$).
1, 2-dihydro-6-(naphthalen-3-yl)-2-oxo-4-phenylpyridine-3-carbonitrile [V*j*]: Yield-70%, M.p.: >300^{0}C**,** IR (Nujol): (N-H) 3320, (CN) 2226, (C=O) 1639 *cm*$^{-1}$, ^{1}H NMR (300 MHz, DMSO-*d6*): δ= 12.83 (br, s, 1H, NH), 8.55 (s, 1H), 7.98-8.06 (m, 4H), 7.75-7.78 (m, 2H), 7.58-7.63 (m, 5H), 7.01 (s, 1H), MS (*m/z*): 322 (M$^+$).
4-hexyl-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile [V*k*]: Yield- 68%, M.p.: 156-158^{0}C, IR (Nujol): (N-H) 3400, (CN) 2217, (C=O) 1653 *cm*$^{-1}$, ^{1}H NMR **(**300 MHz DMSO-*d6*): δ=12.52 (br, s, 1H, N-H), 7.79 (d, 2H), 7.52-7.54 (m, 3H), 6.75 (s, 1H), 2.67 (t, 2H), 1.63 (t, 2H), 1.30 (m, 6H), 0.85 (t, 3H) MS (*m/z*): 281 (M$^+$).
1,2-dihydro-4-isobutyl-2-oxo-6-phenylpyridine-3-carbonitrile [V*l*]: Yield-60%, M.p.: 188-190^{0}C, IR (Nujol): (N-H) 3390, (CN) 2216, (C=O)1646 *cm*$^{-1}$, ^{1}H NMR **(**300 MHz DMSO-*d6*): δ= 12.5 (br, s, 1H, N-H), 7.80 (d, 2H), 7.52-7.54 (m, 3H), 6.72 (s, 1H), 2.57 (d, 2H), 2.02-2.07 (m, 1H), 0.94 (d, 6H), MS (*m/z*): 253 (M$^+$).
4-butyl-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile [V*m*]: Yield-72%, M.p.: 142-144^{0}C, IR (Nujol): (N-H) 3400, (CN) 2219, (C=O)1629 *cm*$^{-1}$, ^{1}H NMR **(**300 MHz DMSO-*d6*): δ= 12.52 (br, s,

1H, N-H), 7.86 (d, 2H), 7.58-7.60 (m, 3H), 6.81 (s, 1H), 2.75 (t, 2H), 1.64-1.74 (m, 2H), 1.35-1.48 (m, 2H), 0.94 (t, 3H), MS (*m/z*): 253 (M^+).

4-ethyl-1,2-dihydro-2-oxo-6-phenylpyridine-3-carbonitrile [V*n*]: Yield-75%, M.p.: 208^{0}C, IR (Nujol): (N-H) 3380, (CN) 2222, (C=O) 1625 *cm*$^{-1}$, ^{1}H NMR **(**300 MHz DMSO-*d6*): δ= 12.6 (br, s, 1H, N-H), 7.80 (d, 2H), 7.53 (m, 3H), 6.75 (s, 1H), 2.65-2.70 (m, 2H), 1.23 (t, 3H), MS (*m/z*): 225 (M^+).

1,2,5,6-tetrahydro-2-oxo-4-phenylbenzo[h]quinoline-3-carbonitrile [V*o*]: Yield-74%, M.p: >300^{0}C, IR (Nujol): (N-H) 3356, (CN) 2221, (C=O) 1635 *cm*$^{-1}$, ^{1}H NMR **(**200 MHz DMSO-*d6*): δ= 12.30 (br, s, 1H, N-H), 7.98-8.10 (m, 5H), 7.33-7.45 (m, 4H), 2.76 (t, 2H, CH_2), 2.38 (t, 2H, CH_2), MS (*m/z*): 299 (M^++H), 298 (M^+).