Efficient One-Pot Four-Component Synthesis and X-ray Crystallographic Structure of 2-Pyridone Derivatives

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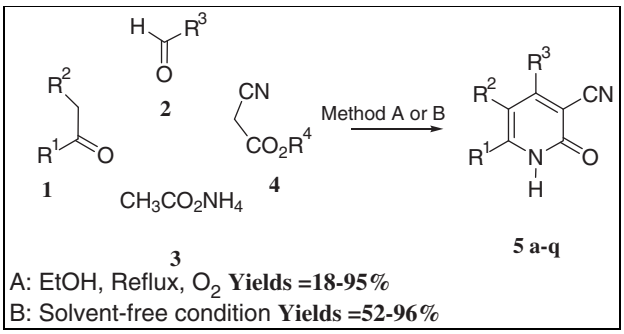
Dedicated to Professor Mohammad Hadi Khorghami on the occasion of his 75th birthday.



A series of 3-cyano-2-pyridone derivatives were synthesized by one-pot four-component condensation reaction involving a benzaldehyde derivative, alkyl cyanoacetate, acyclic or cyclic ketones, and ammonium acetate in reflux condition. The X-ray structure of the products **5a** and **5d** confirm symmetric dimers via hydrogen bonding interactions between individual pyridine molecules showing, in addition, also π–π stacking interactions.

INTRODUCTION

2-Pyridones as heteroaromatic compounds play an important role in bioactive systems and are of significant interest in current medicinal chemistry [1]. These compounds show diverse pharmacological activities such as anti-inflammatory, analgestic, antipyretic, β-adrenolytic, antimicrobial, and antihypertensive activities [2–4]. Some of 2-pyridone derivatives reveal calcium antagonistic activity and are Ikappa B kinase (IKK) inhibitors. Current medical research shows that substituted 2-(1*H*) pyridones act as inhibitor of DNA-dependent protein kinase [5] and also were identified as a primary hit of IKK-β inhibitors [6]. Some of the 2-pyridone derivatives were developed with high affinity for the benzodiazepine binding site of human γ-amino butyric acid receptor ion channels [7]. Meanwhile, 2-pyridones are important and useful intermediates in preparing a variety of heterocyclic compounds, and they are versatile synthetic intermediates for the synthesis of alkaloids, drugs, and herbicides. Many 2-pyridone derivatives have been reported to exhibit antiproliferative activity against intraperitoneally implanted P388 or L1210 lymphocyclic leukemia in mice [8]. 2-Pyridones were proposed as an advantageous alternative to classic digitalis glycosides for the acute treatment of congestive heart failure [9].

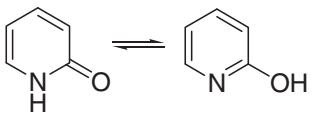
The 2-pyridone skeleton with the *cis*-amide substructure provides an ideal structure for bifunctional catalysis and also supramolecular structures. In addition, the 2-pyridone exists in two tautomeric forms as an amide (**A**) and as 2-hydroxypyridine (**B**). The ratio of these forms depends to the surrounding medium [10] (Scheme 1).

These facts led us to develop a new synthetic method for the synthesis of a new series of highly substituted 3-cyano-2-(1*H*)-pyridone derivatives and to study the crystalline structure of differently substituted compounds.

There are several methods for the synthesis of 2-pyridones [11], and they can be categorized by the following types: (1) condensation of cyanoacetamide with 1,3-diketones [12], (2) condensation of enamines with alkyl acetylenecarboxylates [13], (3) oxidation of pyridine compounds [10], and (4) diazotation of 2-aminopyridine derivatives [14]. However, these methods show limitations, and none o them is suitable for the synthesis of 3-cyano-4-aryl-5,6-dialkyl(aryl)-2-(1*H*)-pyridone derivatives. Some methods involve harsh conditions and can be incompatible with sensitive functional groups.

The synthesis of 3-cyano-2-(1*H*)-pyridone derivatives has been reported in a series of publications [4,15] dealing with Michael condensation of alkyl cyanoacetate or cyanoacetamide [3,16] with α, β-unsaturated ketones. Multistep reactions, complex synthetic materials, using of

Scheme 1



A **B**

harmful organic solvents, harsh reaction conditions, and tedious work-up procedures and also doing of reaction on the surface of Wang's resin were reported in other methods [17,3]. Thus, there is a great need to develop a more effective and milder process with good functional compatibility.

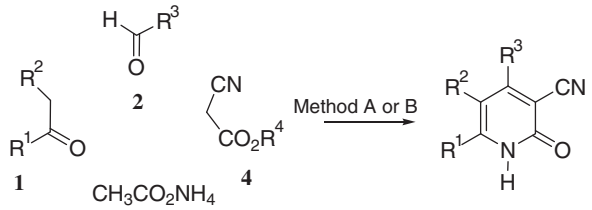
In continuation of our interest on the one-pot multicomponent reactions for the synthesis of various heterocyclic compounds of biological importance [18], 3-cyano-4-aryl-5,6-alkyl- or -aryl 2-(1*H*)-pyridones were simply constructed using a one-pot coupling reaction of four components, alkyl cyanoacetate, aromatic and heteroaromatic aldehyde derivatives, alkyl ketones, and ammonium acetate in ethanol under reflux or solvent-free conditions (Scheme 2). Meanwhile, the X-ray structure of these compounds has been investigated.

RESULTS AND DISCUSSION

Initially, we began our studies with four-component reaction of cyclohexane, ammonium acetate, benzaldehyde, and methyl cyanoacetate as model reaction. The model reaction was carried out in different solvents and also solvent-free conditions. The experimental results are summarized in Table 1.

As can be seen in Table 1, carrying out the reaction in EtOH had better yield, and because of this result, we used it as reaction media for one-pot four-component reaction of different ketones (**1**), aromatic aldehydes (**2**), ammonium acetate (**3**), and alkyl cyanoacetates (**4**) refluxing. The results are given in Table 2. Because of the potential interest in finding versatile procedures, a solvent-free reaction condition approach was investigated, and the model reaction for the synthesis of **5q** was checked at 80°C in solvent-free conditions. The product was obtained after 2 h with 82%. The results for some 2-pyridones (**5**) are summarized in

Scheme 2



1 **2** **3** **4** **5 a-q**

A: EtOH, Reflux, O_2 **Yields =18-95%**
B: Solvent-free condition **Yields =52-96%**

Table 1

Four-component reaction of cyclohexanone, benzaldehyde, ammonium acetate, and methyl cyanoacetate for the synthesis of 2-pyridone **5q**.

Entry	Solvent	Yield (%)
1	Solvent-free	82
2	EtOH	78
3	MeCN	60
4	Dioxan	67
5	THF	–

Table 2

Synthesis of 2-pyridone derivatives via one-pot four-component condensation refluxing in ethanol.

Entry	R^1	R^2	R^3	R^4	Yield (%)[a]
5a	Me	Me	Ph	Me	57
5b	Me	Me	4-Cl-C_6H_4	Me	38
5c	Me	Me	4-Me-C_6H_4	Me	21
5d	Me	Me	3-NO_2-C_6H_4	Me	35
5e	Me	Me	4-NO_2-C_6H_4	Me	32
5f	Me	Ph	Ph	Me	88
5g	Me	Ph	4-Cl-C_6H_4	Me	74
5h	Me	Ph	2-furyl	Me	54
5i	Me	Ph	2-pyridyl	Me	94
5j	Me	Ph	4-pyridyl	Me	81
5k	Me	Ph	2-thienyl	Me	95
5l	Me	*i*-Bu	Ph	Et	34
5m	Me	*i*-Bu	3-NO_2-C_6H_4	Et	27
5n	Me	Pr	Ph	Et	18
5o	Me	Pr	3-NO_2-C_6H_4	Et	22
5p	$-CH_2CH_2CH_2-$		4-Cl-C_6H_4	Me	89
5q	$-CH_2(CH_2)_2CH_2-$		Ph	Me	78

[a]Yields refer to those of pure isolated products characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data. Reaction time in all reactions was between 2 and 4 h.

Table 3

Synthesis of 2-pyridone derivatives via one-pot four-component condensation in solvent-free conditions.

Entry	R^1	R^2	R^3	R^4	Yield (%)[a]
5a	Me	Me	Ph	Me	74
5c	Me	Me	4-Me-C_6H_4	Me	52
5e	Me	Me	4-NO_2-C_6H_4	Me	59
5f	Me	Ph	Ph	Me	92
5g	Me	Ph	4-Cl-C_6H_4	Me	84
5h	Me	Ph	2-furyl	Me	73
5i	Me	Ph	2-pyridyl	Me	96
5j	Me	Ph	4-pyridyl	Me	87
5p	$-CH_2CH_2CH_2-$		4-Cl-C_6H_4	Me	93
5q	$-CH_2(CH_2)_2CH_2-$		Ph	Me	82

[a]Isolated yields of products.

Table 3. The model reaction in solvent-free conditions was investigated at temperatures 40 and 60°C, but the yields were 50 and 65%, respectively.

One-pot four-component reactions were carried out in refluxing ethanol. The structures of the products were

established by their IR, ^{1}H NMR, ^{13}C NMR, HR mass spectrometry data and by X-ray crystallography. The IR spectra showed characteristic bands at about 3450 cm^{-1} (N-H), 2220 cm^{-1} (CN), 1630–1670 cm^{-1} (CO). The ^{1}H NMR spectra revealed a broad singlet in the region δ12.5–13 ppm because of the N-H proton. ^{13}C NMR spectra exhibit in the region 117–119 ppm signals for the CN group and in the region δ 160–170 ppm for the CO group.

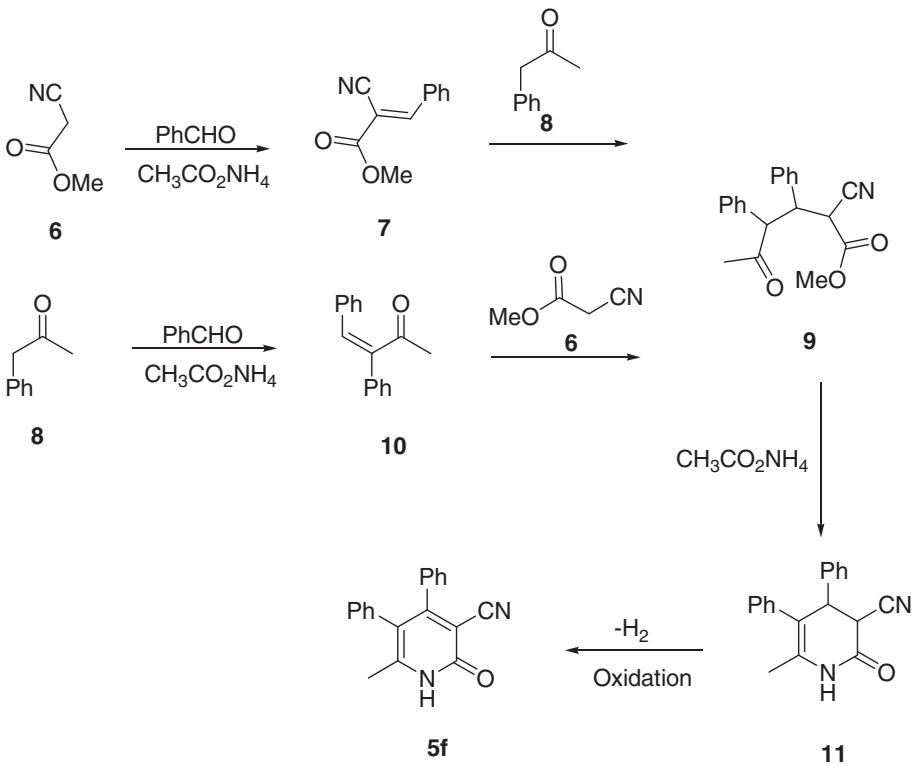
Mechanism. To understand the reaction mechanism, the four-component condensation reaction of benzaldehyde, methyl cyanoacetate, ammonium acetate, and benzyl methyl ketone was chosen as a model. The reaction may be assumed to proceed via (1) initial formation of the benzylidene methyl cyanoacetate (**7**) (Knoevenagel reaction) which then react with the benzyl methyl ketone (**8**) to give the intermediate (**9**) or (2) initial formation of chalcone (**10**) (Aldol condensation reaction, chalcone product) which then reacts with the methyl cyanoacetate (**6**) to give again the intermediate (**9**) which in both reaction pathways cyclized with ammonia (from ammonium acetate) to give the dihydropyridone ring (**11**) (Scheme 3).

Dihydropyridone (**11**) must be oxidized to give pyridone (**5f**) as final product. Two possible mechanisms for this oxidation are discussed in the literature [16,17]. First, as shown in Scheme 4, dihydropyridone (**11**) is converted in alkali media to dianion (**12**). Single electron transfer from the dianion (**12**) to O_2 yields the radical anion (**13**), aromatization of which involves either H atom transfer to O_2 or further single electron transfer chemistry or even combination with an oxygen species, followed by elimination [16]. A second possible mechanism is shown in Scheme 4 and involves oxidation of dihydropyridone (**11**) with reduction of benzylidene methylcyanoacetate (**7**) to 2-cyano-3-phenyl-propionic acid methyl ester (**14**) [17].

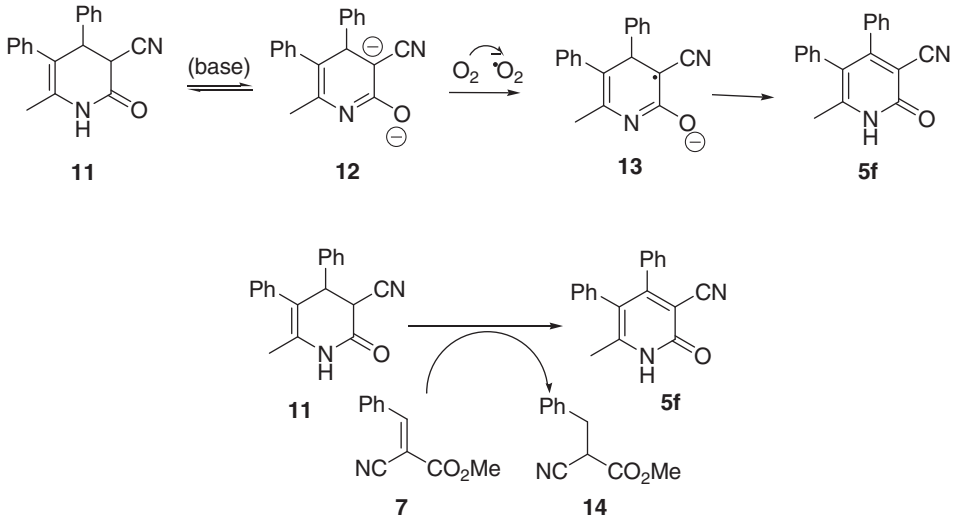
X-ray crystallography. Investigation of the X-ray structure of pyridine derivatives has been studied, and there are some reports about it [19]. We were able to crystallize the compounds from chloroform/methanol (1/1) to obtain crystals of suitable quality for X-ray structural analysis. The structures of the compounds **5a** and **5d** were confirmed by X-ray crystal structure determination. As shown in Figures 1 and 2, hydrogen atoms in the structures can be located bonded to the nitrogen atoms, and this indicates clearly that we have -NH-(C=O), units (**1**), rather than -N-(C-OH), units (**2**). The results show that in both molecules, the amide structure is prevailing (Scheme 5).

This observation is supported by the bond lengths and angles found in the hetero ring of structure **5a**. The comparison of the C_3-N_4-C_5 angle (125.3°) with this angle for pyridinium (mean 122.5°) and pyridine (mean 117.3°) skeletons shows that the nitrogen atom in the C-N-C unit is carrying a hydrogen atom, and the comparison of the C_2-C_3(O)-N_4 angle (114.1°) with this for phenolate or ketone (mean 116.0°) and phenol (mean 120.4°) skeletons [19] shows unequivocally that we do not have a phenol group here.

Scheme 3



Scheme 4



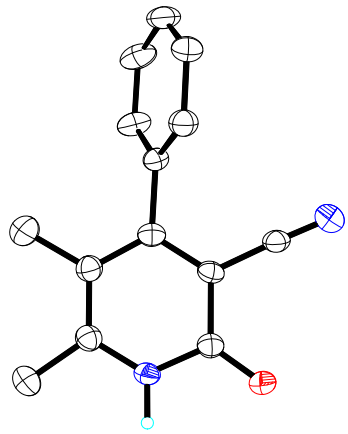


Figure 1. ORTEP structure of compound **5a**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

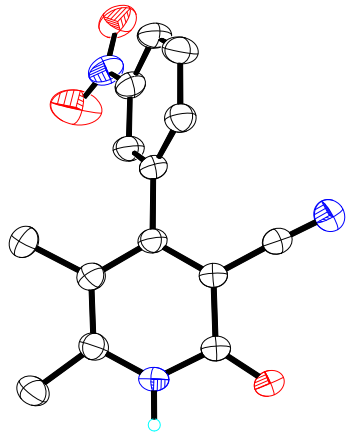
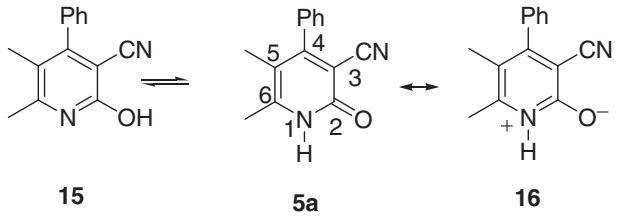


Figure 2. ORTEP structure of compound **7d**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 5



Focusing on the bond length pattern of the hetero ring can reveal more about the mesomeric structure. The carbonyl bond length (1.25 Å) is longer than in a normal carbonyl group (≈1.20 Å) [19]. The recorded bond lengths in the heterocycle correspond to a resonance between **5a** (pyridone) and **16** (aromatic zwitterion mesomer) given in Scheme 5. They show a substantial differentiation, even though they do, of course, not respond to isolated single and double bonds. Short C-C bonds are the bonds C_3-C_4 (1.39 Å) and C_5-C_6 (1.38 Å) at the positions of the double bonds in the mesomer **5a**; long C-C bonds are the bonds C_2-C_3 (1.44 Å) and C_4-C_5 (1.42 Å) at the positions of the single bonds in mesomer **5a**. The nitrogen–carbon bonds N_1-C_2 and N_1-C_6 are with 1.37 Å and 1.36 Å nearly equal and fit much better to a C(sp2)-NH-C(sp2) single bond (mean 1.37 Å) than to an aromatic pyridinium bond (mean 1.34 Å) [18]. Thus, we can state that the mesomeric structure **5a** is the best one to describe the found structure, although there are, of course, contributions of the aromatic mesomer **16**.

Structure **5d** (Fig. 2) has a C-N-C angle (125.5°), C-C-N angle (114.5°), a C=O carbonyl bond length (1.25 Å), single C_8-C_9 bond length (1.43 Å), single C_7-C_{12} bond (1.41 Å), single N_{10}-C_{11} and C_9-N_{10} bonds (1.36 Å and 1.37 Å), double C_7=C_8 bond (1.39 Å), and double C_{11}=C_{12} bond (1.38 Å), which show clearly that structure **5d** is similar to structure **5a**.

We can see a deviation from 180° for the nitrile group, 177.4° for compound **5a**, and 177.3° for compound **5d**. The torsion angle between the aromatic and the pyridone rings for compound **5a** is 122° and for compound **5d** is 118°, and in compound **5d**, the torsion between the aromatic ring and the nitro group is 14°.

Hydrogen bonding interactions in 2-pyridones are very crucial not only because of their strength but also because of their importance in bifunctional catalysis. Two of the more important hydrogen bonding parameters are depicted for all systems: the distance r(NH. . .O) and its correlation with angle α(C═O..H). Because of difficulties in localizing the position of the hydrogen atoms accurately, the N. . .O distance has most often been used in the past in analyzing hydrogen bonding interactions. However, with larger deviations of the N-H-O fragment from linearity, the direct N. . .O distance becomes less and less descriptive.

As shown in Figures 3 and 4, the N-H and C-O moieties form pairs of N-H. . .O hydrogen bridge to connect the molecules to coplanar (with respect to the hetero rings) molecule pairs. The N. . .O distances amount to 2.772 Å and 2.763 Å for compounds **5a** and **5d**, respectively. In these compounds, the hetero rings stack parallel to pairs with a symmetry equivalent ring with close distances of 3.58 Å for compound **5a** and even 3.35 Å for compound **5d** indicating π–π interactions.[20] There is also a hydrogen bonding interaction between two molecules of **5a** forming symmetrical dimmers with r(NH + OH) = 2.772 Å and α(C═O..H) = 121.87°. Again, two molecules of **5d** form a symmetrical dimmer with r(NH + OH) = 2.771 Å and α(C═O···H) = 123.23°. The hydrogen bond is almost linear with the NH. . .O angle178.59 in **5d** (Figs 5, and 6).

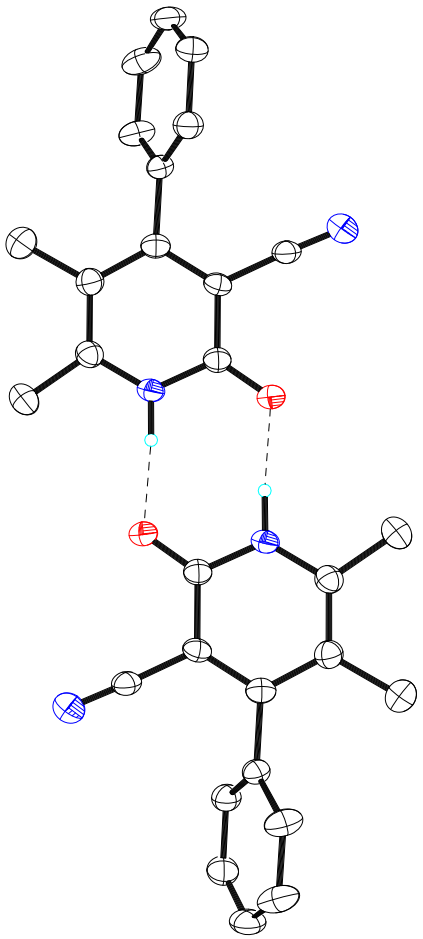


Figure 3. Intermolecular hydrogen bonding for compound **5a**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

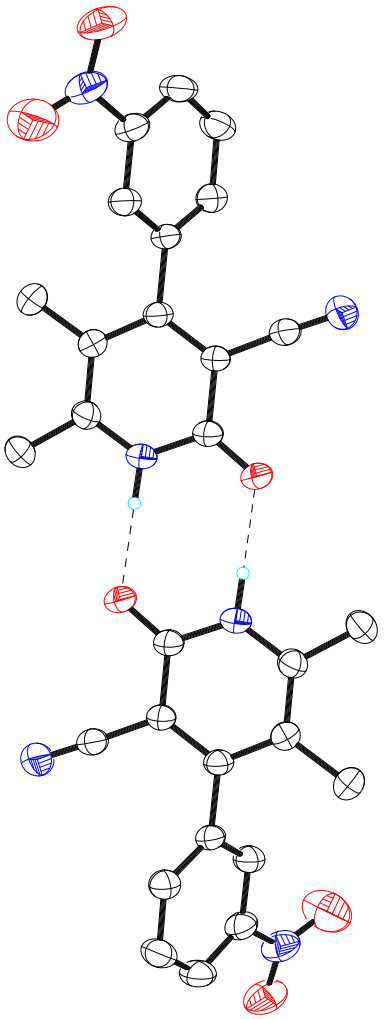


Figure 4. ORTEP structure of compound **5d**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 4 shows selected structural parameters for the crystals **5a** and **5d**.

From the aforementioned discussion of structural data, it is clear that three types of intramolecular interactions appear to exist in the crystals: (1) hydrogen bonding interactions between the pyridone carbonyl oxygen and the pyridone N-H group forming either cyclic dimer and (2) interactions between the cyano nitrogen atom and also

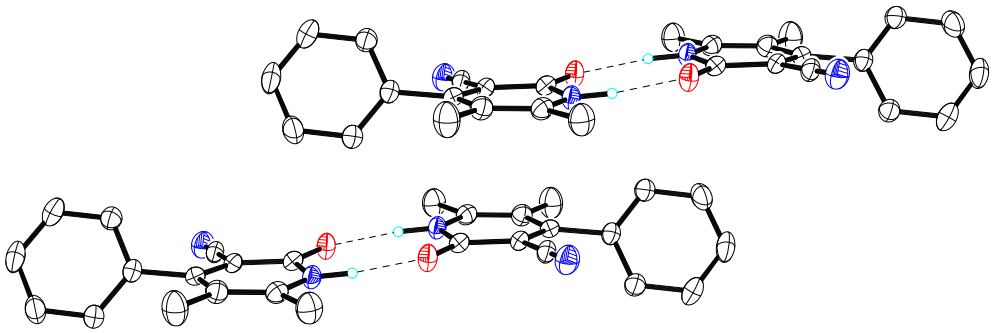


Figure 5. Intermolecular hydrogen boding and π–π interaction for compound **5a**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

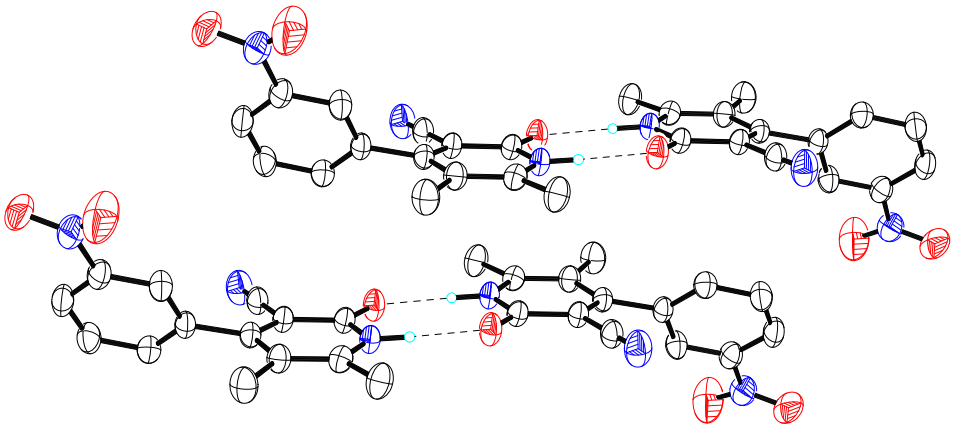


Figure 6. Intermolecular hydrogen boding and π–π interaction for compound **5d**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 4

Structural parameters for the crystals **5a** and **5d**.

	5a	**5d**
r(N. . .O)	2.765	2.771
r_A(N. . .H)	0.952	0.925
r_B(H. . .O)	1.820	1.846
r(NH + HO)	2.772	2.763
α(N-H. . .O)	172.01	178.59
α(C═O. . .H)	121.87	123.23

hydrogen atoms located either in aryl skeleton in C-4 of the pyridine ring. Strength of hydrogen bonding can affect on the bifunctional catalysis activity of 2-pyridones.

CONCLUSION

Some novel 3-cyano-2-pyridone derivatives were efficiently synthesized via a one-pot four component reaction. Carrying out the reaction under (multicomponent reactions) condition, using of simple starting materials, good yields, and high diversity of pyridine derivatives are advantages of this method compared with reported methods. The *cis*-amide motifs present in the 3-cyano-4,6-dialkyl-2-pyridones were studied and provided the basis for the formation of two different supramolecular structures in the solid state. According to the X-ray crystallographic data, intermolecular hydrogen bonding and π–π stacking interaction were observed.

EXPERIMENTAL

Melting points were obtained on Electrothermal 9100 apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were measured in DMSO-d_6 with Bruker AS 300 spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz) and with Bruker DRX-500 AVANCE spectrometer (^{1}H at 500 MHz and ^{13}C at 125 MHz). The chemical shifts are quoted in ppm on the δ scale, with the residual protonated solvent as internal standard. IR spectra were recorded on a Unicam/Mattson 8700 FTIR spectrometer in KBr disks. High resolution mass spectra (HRMS) were obtained with a ZAB high resolution mass spectrometer (Vacuum Generators). X-ray diffraction analyses: The reflections were collected on a Bruker Smart CCD diffractometer using Mo-K_α radiation and a graphite monochromator. Intensities were corrected for Lorentz and polarization effects; an empirical absorption correction was applied based on the Laue symmetry of the reciprocal space [21]. Full matrix least squares refinement was carried out against F^2. The nonhydrogen atoms were refined anisotropically as well as the hydrogen atoms at the nitrogen atoms. The other hydrogen atoms were treated using appropriate ring models. Structure

solution and refinement were carried out with the SHELXTL (5.0) software package [22].

General procedure for the synthesis of 2-pyridones 5a–q. Alkylcyanoacetate (10 mmol), aromatic and heteroaromatic aldehyde (10 mmol), ketone (5 mmol), and ammonium acetate (1.5 g) in ethanol 95% (20 mL) were stirred at reflux for 2–4 h. The progress of reaction was monitored by TLC. Work-up process was performed in two different ways: (1) for compounds **5a–5i**, after cooling to room temperature, the solvent was evaporated under reduced pressure. Ethyl acetate was added to the residue, the organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from acetonitrile or THF. (2) For compounds **5j–5s**, two-thirds of the solvent was evaporated under reduced pressure. The solid formed was collected by filtration, washed with ethanol (minimum amount), dried at room temperature, and recrystallized from acetonitrile or THF. In the case of solvent-free reaction condition, after completion of reaction, 10 mL water was added to the mixture and after decantation, the mixture was crystalized by EtOH.

Selected data for compounds 5a–5q. ***3-Cyano-4-phenyl-5,6-dimethyl-2(1H)-pyridone (5a)***. Yield: 57%; mp (Dec) 260–261°C; IR (KBr): 3453, 2923, 2223, 1653 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.68 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.26–7.29 (m, 2H, H_{Ar}), 7.46–7.53 (m, 3H, H_{Ar}), 12.6 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 18.0, 99.6, 111.4, 116.3, 127.6, 128.7, 129.0, 136.4, 150.5, 160.1, 161.9; HRMS (EI^+): $C_{14}H_{12}N_2O$, found 224.0958, Calcd 224.0949.

X-ray: $C_{14}H_{12}N_2O$, $M = 224.269$ g mol^{-1}, triclinic, $a = 7.3862$ (3), $b = 9.4458(1)$, $c = 9.6700(3)$ Å, $\alpha = 62.669(2)$, $\beta = 82.671(2)$, $\gamma = 89.980(2)°$, $V = 593.15(3)$ $Å^3$, Space group Pī, Z = 2, density (calculated) = 1.26 g cm^{-3}. Crystal size $0.50 \times 0.24 \times 0.03$ mm^3, $T = 200(2)$ K, μ [mm^{-1}] = 0.08, $t_{min} = 0.96$, $t_{max} = 0.99$, $h_{min}/h_{max} = -9/9$, $k_{min}/k_{max} = -11/11$, $l_{min}/l_{max} = -12/11$, Refl. Collected = 4760, Refl. unique = 2360, Refl. observed = 1457, Parameter = 160, S (Gof) on $F^2 = 0.97$, $R(F) = 0.045$, $R_w(F^2) = 0.104$, $(\Delta\rho)_{max} = 0.2$ e.$Å^{-3}$, $(\Delta\rho)_{min} = 593.15(3)$ e.$Å^{-3}$. CCDC 635909 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

***3-Cyano-4-(4-chlorophenyl)-5,6-dimethyl-2(1H)-pyridone* (5b)**. Yield: 38%; mp (Dec) 258–260°C; IR (KBr): 3561, 2754, 2223, 1654 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.69 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 7.34 (d, 2H, $J = 8.4$ Hz, H_{Ar}), 7.58 (d, 2H, $J = 8.4$ Hz, H_{Ar}), 12.55 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 18.0, 100.0, 111.3, 116.2, 125.8, 128.8, 128.7, 129.6, 129.9, 133.9, 135.1, 150.7, 159.9, 160.6; HRMS (EI^+): $C_{14}H_{11}ClN_2O^{37}Cl$ found 260.0526, Calcd 260.0530, mmu −0.4, $C_{14}H_{11}ClN_2O$ ^{35}Cl found 258.0558, Calcd 258.0560.

3-Cyano-4-(4-methylphenyl)-5,6-dimethyl-2(1H)-pyridone (5c). Yield: 21%; mp (Dec) 253–255°C; IR (KBr): 3446, 2753, 2223, 1654 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.71 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.18 (d, 2H, $J = 7.9$ Hz, H_{Ar}), 7.33 (d, 2H, $J = 7.9$ Hz, H_{Ar}),, 12.63 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.0, 18.0, 20.9, 99.4, 111.8, 116.4, 127.5, 129.2, 133.4, 138.5, 150.6, 160.1, 162.3; HRMS(EI^+): $C_{15}H_{14}N_2O$, found 238.1089, Calcd 238.1106.

3-Cyano-4-(3-nitrophenyl)-5,6-dimethyl-2(1H)-pyridone (5d). Yield: 35%; mp (Dec) 243–244°C; IR (KBr): 3469, 2900, 2223, 1646, 1538, 1361 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.71 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.80 (m, 2H, H_{Ar}), 8.21 (brs, 1H, H_{Ar}), 8.36 (d, 1H, $J = 9.0$ Hz, H_{Ar}), 12.69 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 18.1, 101.0, 111.8, 116.1, 122.7, 124.0, 130.7, 134.5, 137.8, 147.9, 151.3, 158.6, 159.8; HRMS(EI^+): $C_{14}H_{11}N_3O_3$, found 269.0810, Calcd 269.0800.

X-ray: $C_{14}H_{11}N_3O_3$, $M = 269.265$ g mol^{-1}, monoclinic, $a = 5.7992$ (5), $b = 17.2087(14)$, $c = 12.8130(11)$ Å, $\alpha = 90$, $\beta = 90.877(2)$, $\gamma = 90°$, $V = 1278.55(19)$ $Å^3$, Space group$P2_1/c$, Z = 4, density (calculated) = 1.40 g cm^{-3}. Crystal size $0.40 \times 0.20 \times 0.15$ mm^3, $T = 296(2)$ K, μ [mm^{-1}] = 0.10, $t_{min} = 0.96$, $t_{max} = 0.98$, $h_{min}/h_{max} = -7/7$, $k_{min}/k_{max} = -22/22$, $l_{min}/l_{max} = -16/17$, Refl. Collected = 13112, Refl. unique = 3182, Refl. observed = 2539, Parameter = 187, S (Gof) on $F^2 = 1.04$, $R(F) = 0.051$, $R_w(F^2) = 0.138$, $(\Delta\rho)_{max} = 0.32$ e.$Å^{-3}$, $(\Delta\rho)_{min} = -0.21$ e.$Å^{-3}$. CCDC 635910 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3-Cyano-4-(4-nitrophenyl)-5,6-dimethyl-2(1H)-pyridone (5e). Yield: 32%; mp (Dec) 262–264°C; IR(KBr): 3461, 2846, 2223, 1646, 1530, 1338 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.69 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.65 (d, 2H, $J = 8.7$ Hz, H_{Ar}), 8.38 (d, 2H, $J = 8.7$ Hz, H_{Ar}), 12.71 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.9, 18.1, 99.4, 111.0, 116.0, 124.0, 129.4, 142.8, 147.8, 151.4, 159.7, 159.8; HRMS(EI^+): $C_{14}H_{11}N_3O_3$, found 269.0808, Calcd 269.0801.

***3-Cyano-4,5-diphenyl-6-methyl-2(1H)*-pyridone (5f)**. Yield: 88%; mp (Dec) 318–320°C; IR (KBr): 3461, 2831, 2223, 1646 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 2.04 (s, 3H, CH_3), 6.91–7.22 (m, 10H, H_{Ar}), 12.78 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.7, 103.4, 112.3, 122.2, 133.4, 133.6, 134.4, 135.9, 136.1, 141.7, 142.0, 160.6, 165.6, 167.3.; HRMS (EI^+): $C_{19}H_{14}N_2O$, found 286.1099, Calcd 286.1106.

3-Cyano-4-(4-chlorophenyl)-5-phenyl-6-methyl-2(1H)-pyridone (5g). Yield: 74%; mp (Dec) 310–312°C; IR (KBR): 3546, 2910, 2223, 1654 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.10 (s, 3H, CH_3), 7.03 (d, 2H, $J = 7.7$ Hz, H_{Ar}), 7.15–7.24 (m, 5H, H_{Ar}), 7.88 (d, 2H, $J = 7.7$ Hz, H_{Ar}), 12.89 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.0, 105.7, 121.7, 124.5, 133.0, 133.6, 133.8, 134.6, 135.9, 136.5, 139.0, 140.5, 156.3, 165.5, 165.8.; HRMS(EI^+): $C_{19}H_{13}N_2O^{35}Cl$, found 320.0723, Calcd 322.0716. $C_{19}H_{13}N_2O^{37}Cl$, found 322.0706, calc 322.0687.

3-Cyano-4-(2-furyl)-5-phenyl-6-methyl-2(1H)-pyridone (5h). Yield: 54%; mp (Dec) 263–264°C; IR(KBr): 3431, 2784, 2215, 1646 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.04 (s, 3H, CH_3), 6.02 (d, 1H, $J = 1.6$ Hz, H_{furyl}), 6.47 (d, 1H, $J = 3.6$, Hf_{uryl}), 7.14 (m, 2H, H_{Ar}), 7.35 (m, 3H, H_{Ar}), 7.69 (d, 1H, $J = 3.6$ Hz, H_{furyl}), 12.72 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.4, 107.5, 117.6, 121.7, 133.4, 133.5, 134.6, 136.0, 141.4, 150.8, 152.3, 155.8, 158.3, 163.3, 166.6. HRMS (EI^+): $C_{17}H_{12}N_2O_2$, found 276.0899, Calcd 276.0900.

3-Cyano-4-(2-pyridyl)-5-phenyl-6-methyl-2(1H)-pyridone (5i). Yield: 94%; mp (Dec) 312–313°C; IR (KBr): 3469, 1638 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.13 (s, 3H, CH_3), 7.01 (d, 1H, $J = 6.3$ Hz, $H_{pyridyl}$), 7.16 (m, 5H, H_{Ar}), 7.25 (m, 1H, $H_{pyridyl}$), 7.64 (m, 1H, $H_{pyridyl}$), 8.50 (d, 1H, $J = 4.7$ Hz, $H_{pyridyl}$),12.94 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.2, 105.4, 121.3, 124.1, 129.1, 129.5, 132.9, 133.6, 136.4, 140.3, 141.8, 154.6, 156.8, 159.7, 165.0, 165.8.; HRMS(EI^+) $C_{18}H_{13}N_3O$, found 287.1026, Calcd 287.1058.

3-Cyano-4-(4-pyridyl)-5-phenyl-6-methyl-2(1H)-pyridone (5j). Yield: 81%; mp (Dec) 290–293°C; IR (KBr): 3454, 2950, 2215, 1677 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H, CH_3), 7.06 (d, 2H, $J = 5.7$ Hz, $H_{pyridyl}$), 7.20 (m, 5H, H_{Ar}), 8.47

(d, 2H, $J = 5.7$ Hz, $H_{pyridyl}$) 12.98 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.0, 103.3, 114.8, 120.1, 123.0, 128.5, 133.1, 133.8, 136.4, 140.1, 147.6, 154.9, 164.1, 165.0.; HRMS (EI^+) $C_{18}H_{14}N_3O$, found 288.1113, Calcd 288.1137.

3-Cyano-4-(2-thienyl)-5-phenyl-6-methyl-2(1H)-pyridone (5k). Yield: 95%; mp (Dec) 242–243°C; IR (KBr): 3446, 2215, 1646 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.07 (s, 3H, CH_3), 6.97 (d, 1H, $J = 4.8$ Hz, $H_{thienyl}$), 7.08 (m, 2H, H_{Ar}), 7.15 (quint, 1H, $H_{thienyl}$), 7.26 (m, 3H, H_{Ar}), 7.59 (d, 1H, $J = 4.2$ Hz, $H_{thienyl}$), 12.87 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.5, 105.7, 122.0, 124.6, 132.4, 133.4, 133.9, 134.5, 135.7, 136.0, 136.5, 137.5, 140.7, 142.3, 159.2, 165.9.; HRMS(EI^+) $C_{17}H_{12}N_2OS$, found 292.0646, Calcd 292.0671.

***3-Cyano-4-phenyl-6-iso*-butyl-2-(1*H*)-pyridone (5l).** Yield: 34%; mp (Dec) 238–239°C; IR (KBr): 3623, 2954, 2215, 1654 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (d, 6H, $J = 5.8$ Hz, $2CH_3$), 2.01 (m, 1H, CH), 2.45 (d, 2 H, $J = 5.9$ Hz, CH_2), 6.33 (s, 1H, CH),7.55 (m, 3H, H_{Ar}), 7.61 (m, 2H, H_{Ar}), 12.61 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.5, 33.7, 47.1, 103.3, 112.2, 122.2, 133.6, 134.4, 135.9, 141.7, 160.6, 165.6, 167.2. HRMS(EI^+): $C_{16}H_{16}N_2O$, found 252.3152, Calcd 252.3164.

***3-Cyano-4-(3-nitrophenyl)-6-iso*-butyl-2(1*H*)-pyridone (5m).** Yield: 27%; mp (Dec) 205–206°C; IR(KBr): 3415, 2961, 2223, 1654, 1538, 1353 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (brs, 6H, $2CH_3$), 2.01 (m, 1H, CH), 2.46 (brs, 2H, CH_2), 6.45 (s, 1H, CH),7.85 (m, 1H, H_{Ar}), 8.08 (m, 1H, H_{Ar}), 8.40 (m, 2H, H_{Ar}), 12.76 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.5, 33.8, 47.1, 103.8, 112.1, 121.8, 128.5, 130.5, 136.1, 140.3, 143.1, 153.4, 161.5, 163.2, 166.9. HRMS(EI^+) $C_{16}H_{15}N_3O_3$, found 297.1113, Calcd 297.1116.

3-Cyano-4-phenyl-6-propyl-2(1H)-pyridone (5n). Yield: 18%; mp (Dec) 238–239°C; IR (KBr): 3623, 2954, 2215, 1654 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (d, 6H, $J = 5.8$ Hz, $2CH_3$), 2.01 (m, 1H, CH), 2.45 (d, 2H, $J = 5.9$ Hz, CH_2), 6.33 (s, 1H, CH),7.55 (m, 3H, H_{Ar}), 7.61 (m, 2H, H_{Ar}), 12.61 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.5, 33.7, 47.1, 103.3, 112.2, 122.2, 133.6, 134.4, 135.9, 141.7, 160.6, 165.6, 167.2. HRMS(EI^+): $C_{15}H_{14}N_2O$, found 238.2884, Calcd 238.2876.

3-Cyano-4-(3-nitrophenyl)-6-propyl-2(1H)-pyridone (5o). Yield: 22%; mp (Dec) 213–215°C; IR (KBr): 2980, 2223, 1654, 1530, 1353 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.91 (t, 3H, $J = 7.3$ Hz, CH_3), 1.66 (m, 2H, CH_2), 2.57 (t, 2H, $J = 7.6$ Hz, CH_2), 6.46 (s, 1H, CH), 7.85 (t, 1H, $J = 7.9$ Hz, H_{Ar}), 8.10 (d, 1H, $J = 7.7$ Hz, H_{Ar}), 8.41 (m, 2H, H_{Ar}), 12.77 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.0, 27.2, 40.2, 103.8, 111.4, 121.8, 128.5, 130.6, 136.1, 140.3, 143.1, 153.4, 162.2, 163.4, 166.9.; HRMS(EI^+): $C_{15}H_{13}N_3O_3$, found 283.0936, Calcd 269.0957.

3-Cyano-4-(4-chlorophenyl)-5,6-(1,3-propanediyl)-2(1H)-pyridone (5p). Yield: 89%; mp (Dec) 256–266°C; IR (KBr): 3453, 2938, 2223, 1646 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.00 (m, 2H, CH_2), 2.52 (t, 2H, $J = 7.1$ Hz, CH_2), 2.88 (t, 2H, $J = 7.6$ Hz, CH_2),7.53 (d, 2H, $J = 8.0$ Hz, H_{Ar}), 7.61 (d, 2H, $J = 8.0$ Hz, H_{Ar}), 12.87 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.7, 34.3, 37.3, 103.6, 122.4, 123.3, 134.3, 134.5, 135.6, 139.7, 140.2, 162.0, 163.1, 167.2.; HRMS(EI^+): $C_{15}H_{11}N_2O^{35}Cl$, found 270.0561, Calcd 270.0562, mmu = +0.1., $C_{15}H_{11}N_2O^{37}Cl$, found 272.0519, Calcd 270.0507.

3-Cyano-4-phenyl-5,6-(1,4-butanediyl)-2(1H)-pyridone (5q). Yield: 78%; mp 256–259°C; IR(KBr): 3415, 2938, 2215, 1623 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.55 (m, 2H, CH_2), 1.67 (m, 2H, CH_2), 2.03 (t, 2H, $J = 5.9$ Hz, CH_2), 2.64 (t, 2H, $J = 6.1$ Hz, CH_2),7.31 (m, 2H, H_{Ar}), 7.50 (m, 3H, H_{Ar}), 12.44 (brs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.2, 27.4, 30.5, 32.9, 106.0, 117.9, 121.7, 133.1, 134.3, 134.7, 141.2, 155.9, 165.5, 167.5.; HRMS(EI^+): $C_{16}H_{14}N_2O$, found 250.1085, Calcd 250.1106.

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