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Imidazole-catalyzed Three-component Cascade Reaction for the Facile Synthesis of Highly Substituted 3,4-Dihydropyridin-2-one Derivatives

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A novel one-pot protocol for the synthesis of valuable 3,4-dihydropyridin-2-ones from the condensation of aldehyde with cyanoacetamide and 1,3-dicarbonyl compounds in the presence of imidazole was developed. A series of aldehydes and 1,3-dicarbonyl compounds were employed to examine the scope of substrates for this protocol. This reaction proceeded through the formation of one ring and four new bonds (two C—C, one C—N, one C=C) via the sequence involving Knoevenagel condensation, Michael addition and intramolecular cyclization with moderate to excellent yields. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS.

Keywords multicomponent reactions, 3,4-dihydropyridin-2-one, cyanoacetamide, cyclization, imidazole

Introduction

Multicomponent reactions (MCRs) have become an efficient and powerful tool for the synthesis of biologically relevant or natural-like molecular framework due to their convergence, atom economy and eco-friendliness.[1] These reactions allow three or more reactants in one pot to generate molecular complexity and diversity through the facile formation of several bonds, such as C—C, C—O or C—N. Furthermore, MCRs play the key role in combinatorial synthesis and pharmaceutical and drug discovery research.[2] Especially the construction of six-membered heterocyclic ring of biological activity is facile and interesting.

Dihydropyridine (DHP) heterocyclic ring is well known as a part of the fundamental skeleton of important classes of drugs.[3] For example, 1,4-DHPs systems are of great significance owing to their exceptional properties as calcium antagonists.[4] Moreover, slight structural modification on the DHP ring has been widely studied which may bring about remarkable changes in pharmacological effect.[5] Among them, 3,4-dihydropyridin-2-one is an important moiety because of its extensive occurrence in a large number of natural products which exhibits significant pharmacological activities such as antibacterial,[6] antifungal[7] and antitumor,[8] also served as HIV-1 specific reverse transcriptase inhibitors.[9] Also, 3,4-dihydropyridin-2-ones are the key intermediates in the synthesis of the corresponding pyridines.[10]

Due to the important building blocks of many natural products, lots of methods in exploring polysubstituted 3,4-dihydropyridin-2-ones have been developed. Many involve 1-azadienes,[11] aza-annulation of enamines,[12] carboxylic acid derivatives[13] or α-metallated acetate derivatives.[14] Also the 3,4-dihydro-pyridin-2-one could be gotten as the byproduct through the reaction of hydrazone with methyl 3-aminocrotonate in hot acetic acid.[15] However, developing a novel reaction, a non-toxic and efficient catalyst for the construction of this ring system from readily available components is still highly desirable. Imidazole has emerged as a generalist which can act not only as reactant[16] but also as catalyst[17] or additive.[18] Nevertheless, MCRs catalyzed by imidazole were really rare,[19] Liu[20] reported the imidazole-mediated cascade annulation reaction from two units of (arylmethylidene) malononitriles and one unit of nitroalkenes.

Here we will present a new one-pot method for the synthesis of a set of 3,4-dihydropyridin-2-ones via the condensation of aldehyde, cyanoacetamide and 1,3-dicarbonyl compounds catalyzed by trace imidazole, in which cyanoacetamide acted as ammonia source.

Results and Discussion

We started our research by carrying out the three-component reaction of *p*-nitrobenzaldehyde (**1**), cyanoacetamide (**2**) and acetyl acetone (**3**), in equimolecular amounts of 0.5 mmol, using 5 mg imidazole as the base and 1 mL ethylene glycol (EG) as the solvent. After 24 h at 50 ℃, the cascade reaction provided a considerable

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64% yield of 5-acetyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (**4**) (Table 1, Eentry 7). Encouraged by this, the organic base screening was developed. As shown in Table 1, the nature of base had big influence on the yield. Morpholine and 4-methylimidazole could also catalyze the reaction to get the desired product though with the decrease in the yield (Table 1, Entries 1 and 3). However, the reaction became sluggish with yields below 20% when 2-methylimidazole, 4-dimethylamiopyridine (DMAP), triethylamine and piperidine were used (Table 1, Entries 2, 4, 5, and 6). Maybe the moderate basicity of imidazole is just right for the reaction. While basicity of general organic bases is strong, resulting in too many by-products that cannot be confirmed. Considering the importance of the reaction medium, a series of solvents were used to examine the effect on the yield. Polar, aprotic solvents like dioxane, *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and toluene were used as solvents, the yields were low although the substrates dissolved completely (Table 1, Entries 9, 10, 11 and 12). The three-component reaction could not proceed in other protic solvents involving glycerol and 1,4-butylene glycol (Table 1, Entries 13 and 14). Interestingly, EG emerged as the best solvent and di-EG took the second place (Table 1, Entries 7 and 8). It seemed that EG played the vital role due to its good solubility and double hydroxyl group. We also performed the reaction in hexane and chloroform, but the cyanoacetamide failed to dissolve in them.

So imidazole and EG acted as the choice of base-solvent combination for the cascade reaction. Then the amount of imidazole was established. From the data listed in Figure 1, it could be seen that the reaction hardly happened without imidazole. When just 0.1 mg imidazole was applied, the yield of target molecular could reach 30%. With further increase to 0.6 mg, we obtained the product in 61% yield shown as the inflection point in Figure 1. However, the yield showed platform trend when the mount exceeded 0.6 mg. That meant trace imidazole had good catalytic activity to the three-component cascade reaction.

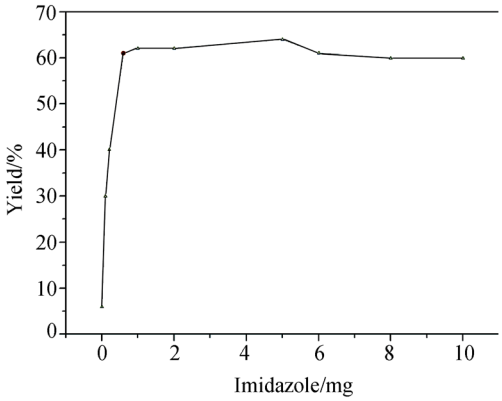
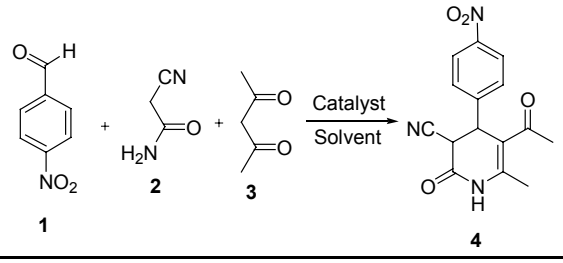


Figure 1 The influence of imidazole loading on the yield.

Table 1 Catalyst and solvent screen[a]



Entry	Catalyst	Solvent	Yield[b]/%
1	Morpholine	EG	42
2	2-Methylimidazole	EG	11
3	4-Methylimidazole	EG	52
4	DMAP	EG	10
5	Triethylamine	EG	12
6	Piperidine	EG	9
7	Imidazole	EG	64
8	Imidazole	Di-EG	46
9	Imidazole	Dioxane	10
10	Imidazole	DMF	2
11	Imidazole	DMSO	22
12	Imidazole	Toluene	15
13	Imidazole	Glycerol	＜1
14	Imidazole	1,4-Butylene glycol	4

[a] The reaction was carried out with **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol) and catalyst (5 mg) in 1 mL solvent at 50 ℃ for 24 h. [b] determined by HPLC.

In order to get better reaction conditions, we studied the ratio of substrates and reaction temperature. The best result of further screening on the ratio of three substrates was aldehyde 0.5 mmol, cyanoacetamide 1 mmol and 1,3-dicarbonyl compound 0.75 mmol, the yield of the model reaction was 75% after 24 h at 50 ℃. Next, as the increase of temperature from 50 to 70 ℃, the yield increased by 22%.

With optimal reaction conditions in hand, the generality and limitation of the reaction were investigated by changing aldehydes, cyanoacetamide and 1,3-dicarbonyl compounds. The results were summarized in Table 2. The reactions proceeded in good to excellent yields though involving a number of individual steps. It seemed that electronic nature had a little effect on the yield. Strong electron-donating group (such as methoxy) on the *para* of benzaldehyde diminished much compared to electron-withdrawing group (Table 2, Entry 8 and Entries 4, 6). While *meta*-hydroxyl benzaldehyde achieved high yield (Table 2, Entry 9). Aliphatic and heterocyclic aldehyde could also build the corresponding product successfully (Table 2, Entry 10 and Entries 11, 12). Nevertheless, the yield decreased as the carbon chain lengthening (Entries 11 and 12). To our delight, methyl acetoacetate and acetoacetanilide could substitute acetyl acetone as 1,3-dicarbonyl compound, which demonstrated the broad application of the reaction.

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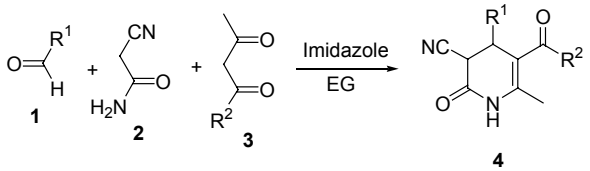
Table 2 Substrate scope of the imidazole catalyzed cascade reaction[a]



Entry	R^1	R^2	Product	Yield[b]/%
1	Ph	Me	**4a**	87
2	2-$NO_2C_6H_4$	Me	**4b**	82
3	3-$NO_2C_6H_4$	Me	**4c**	88
4	4-$NO_2C_6H_4$	Me	**4d**	92
5	2-ClC_6H_4	Me	**4e**	86
6	4-ClC_6H_4	Me	**4f**	89
7	4-MeC_6H_4	Me	**4g**	84
8	4-$OMeC_6H_4$	Me	**4h**	67
9	3-OHC_6H_4	Me	**4i**	95
10	2-Furyl	Me	**4j**	78
11	CH_3CH_2	Me	**4k**	98
12	$CH_3CH_2CH_2$	Me	**4l**	78
13	3-$NO_2C_6H_4$	OMe	**4m**	87
14	4-ClC_6H_4	OMe	**4n**	94
15	4-MeC_6H_4	OMe	**4o**	70
16	CH_3CH_2	OMe	**4p**	87
17	4-ClC_6H_4	4-NHC_6H_5	**4q**	73
18	4-MeC_6H_4	4-NHC_6H_5	**4r**	84
19	2-Furyl	4-NHC_6H_5	**4s**	93

[a] The reaction was carried out with **1** (0.5 mmol), **2** (1.0 mmol), **3** (0.75 mmol) and catalyst (0.6 mg) in 1 mL EG at 70 ℃ for 24 h. [b] Determined by HPLC.

A plausible mechanism to rationalize the formation of 3,4-dihydropyridin-2-one derivatives is outlined in Scheme 1. Firstly, the Knoevenagel condensation product **1** was initially formed via the reaction of benzaldehyde and cyanoacetamide. Then intermediate **1** was trapped by dicarbonyl compound to produce the Michael product **2**, which was deprived one proton of amino by imidazole. Finally, intermediate **2** underwent intramolecular nucleophilic attack to generate compound **3** which subsequently lost one molecular water and regenerated imidazole at the same time.

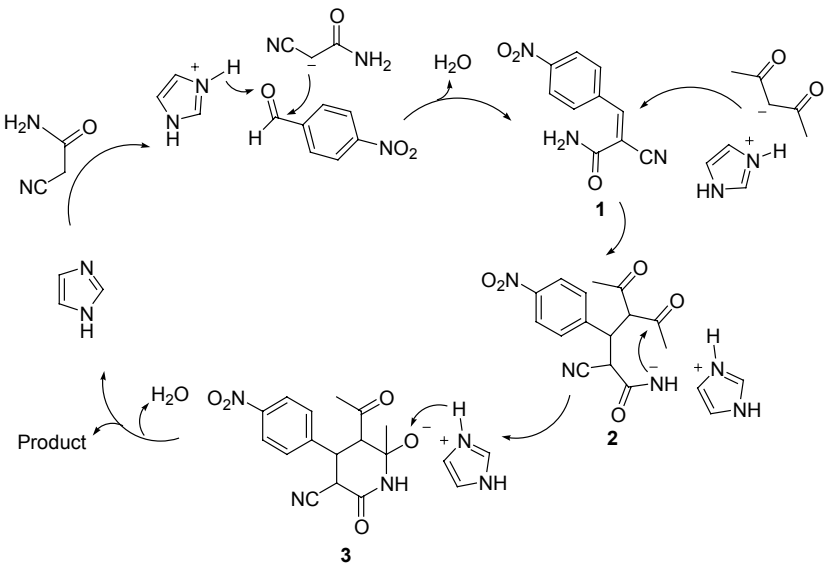
Conclusions

In summary, we have developed a novel three-component cascade reaction to construct multisubstituted 3,4-dihydropyridin-2-ones in good to excellent yield from the reaction of aldehyde, cyanoacetamide and 1,3-dicarbonyl compound in the presence of trace imidazole in ethylene glycol. This reaction had prominent advantages of easy operation, convergence and broad scope of applicability.

Experimental

Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with iodine as an indicator and compounds were visualized by irradiation with UV light. Flash column chromatography was carried out using silica gel (400 mesh). The ^{1}H NMR and ^{13}C NMR spectra were recorded with TMS as internal standard using a Bruker AMX-400 MHz spectrometer. Analytical HPLC was performed using an Agilent 1100 series with a reversed-phase Shim-Pack VP-ODS column (150 ×4.6 mm) and a UV detector (290 nm). IR spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. Melting points were determined using XT-4 apparatus and were not corrected. All the known products were characterized by comparing the ^{1}H NMR data

Scheme 1 A proposed mechanism of the imidazole-mediated reaction



with those reported in the literature. The structures of new compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS.

General experimental procedure

A mixture of aldehyde (0.5 mmol), cyanoacetamide (84 mg, 1 mmol), 1,3-dicarbonyl compound (0.75 mmol), and a catalytic amount of imidazole (0.6 mg) in 1 mL EG was stirred at 70 ℃ for 24 h. After completion of the reaction detected by TLC, the solution was directly separated by column chromatography using about 50 mL petroleum ether firstly, then the eluent was changed into petroleum ether/ethyl acetate mixture (1∶1, *V*∶*V*). Finally the product was obtained after rotation under reduced pressure.

5-Acetyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridine-3-carbonitrile (4a)[21]

Light yellow solid; m.p. 152—153 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (d, J=11.6 Hz, 3H, CH_3C=O), 2.39 (d, J=10.4 Hz, 3H, CH_3C=C), 3.95 (q, J=6.4 Hz, 1H, CHC=C), 4.40 (q, J=6.4 Hz, 1H, CHCN), 7.17—7.40 (m, 4H, ArH), 8.51—8.59 (m, 1H, NH); IR (neat) ν: 3224, 3139, 2257, 1713, 1668 cm^{-1}.

5-Acetyl-6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4b)

Light yellow solid; m.p. 106—107 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.65 (d, J=12.8 Hz, 3H, CH_3C=O), 1.87 (d, J=16.8 Hz, 3H, CH_3C=C), 4.13 (q, J=7.6 Hz, 1H, CHC=C), 4.71 (q, J=7.2 Hz, 1H, CHCN), 6.82—7.61 (m, 4H, ArH), 10.20 (d, J=69.6 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.4, 30.8, 35.4, 115.1, 115.6, 125.8, 128.9, 130.0, 133.0, 134.8, 148.2, 149.1, 162.8, 196.6; IR (neat) ν: 3237, 3139, 2254, 1712, 1686 cm^{-1}. HRMS calcd for $C_{15}H_{13}N_3O_4$ 299.0906, found 299.0910.

5-Acetyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4c)[22]

Light yellow solid; m.p. 183—184 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.04 (d, J=6.0 Hz, 3H, CH_3C=O), 2.29 (d, J=4.4 Hz, 3H, CH_3C=C), 4.43 (q, J=6.4 Hz, 1H, CHC=C), 4.89 (q, J=6.8 Hz, 1H, CHCN), 7.60—8.15 (m, 4H, ArH), 10.60 (d, J=30.0 Hz, 1H, NH); IR (neat) ν: 3261, 3167, 2257, 1717, 1679 cm^{-1}.

5-Acetyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4d)

Light yellow solid; m.p. 105—106 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.00 (d, J=10.0 Hz, 3H, CH_3C=O), 2.25 (d, J=6.0 Hz, 3H, CH_3C=C), 4.56 (d, J=6.4 Hz, 1H, CHC=C), 4.75 (q, J=6.8 Hz, 1H, CHCN), 7.42—8.13 (m, 4H, ArH), 10.52 (d, J=44.4 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.1, 30.3, 40.0, 41.0, 114.4, 115.7, 124.3, 124.4, 129.3, 129.9, 145.1, 147.7, 148.0, 162.8, 196.8; IR (neat) ν: 3266, 3165, 2257, 1719, 1677 cm^{-1}. HRMS calcd for $C_{15}H_{13}N_3O_4$ 299.0906, found 299.0909.

5-Acetyl-4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4e)

White solid; m.p. 220—221 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.02 (d, J=6.8 Hz, 3H, CH_3C=O), 2.30 (d, J=49.6 Hz, 3H, CH_3C=C), 4.83 (d, J=6.8 Hz, 1H, CHC=C), 4.99 (d, J=6.8 Hz, 1H, CHCN), 7.11—7.52 (m, 4H, ArH), 10.58 (d, J=58.0 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.1, 30.0, 37.4, 40.3, 114.8, 115.5, 128.5, 128.6, 130.4, 130.4, 133.8, 135.5, 147.8, 162.7, 196.9; IR (neat) ν: 3221, 3134, 2251, 1716, 1675 cm^{-1}. HRMS calcd for $C_{15}H_{13}N_2O_2Cl$ 288.0666, found 288.0664.

5-Acetyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4f)

Light yellow solid; m.p. 173—174 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.12 (d, J=10.0 Hz, 3H, CH_3C=O), 2.38 (d, J=10.4 Hz, 3H, CH_3C=C), 3.94 (q, J=6.8 Hz, 1H, CHC=C), 4.42 (q, J=6.8 Hz, 1H, CHCN), 7.12—7.36 (m, 4H, ArH), 8.76 (d, J=11.2 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.0, 30.1, 40.7, 41.4, 114.7, 116.0, 129.2, 130.2, 133.3, 136.2, 147.3, 162.9, 197.1; IR (neat) ν: 3255, 3167, 2257, 1712, 1675 cm^{-1}. HRMS calcd for $C_{15}H_{13}N_2O_2Cl$ 288.0661, found 288.0660.

5-Acetyl-6-methyl-2-oxo-4-*p*-tolyl-1,2,3,4-tetrahydropyridine-3-carbonitrile (4g)[21]

Light yellow solid; m.p. 212—213 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.00 (s, 3H, $ArCH_3$), 2.22 (d, J=6.8 Hz, 3H, CH_3C=O), 2.27 (s, 3H, CH_3C=C), 4.21 (q, J=4.0 Hz, 1H, CHC=C), 4.62 (q, J=4.0 Hz, 1H, CHCN), 7.07—7.15 (m, 4H, ArH), 10.45 (d, J=48.8 Hz, 1H, NH); IR (neat) ν: 3234, 3139, 2260, 1702, 1678 cm^{-1}.

5-Acetyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4h)[21]

Light yellow solid; m.p. 157—158 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.00 (s, 3H, CH_3C=), 2.27 (d, J=5.2 Hz, 3H, CH_3C=C), 3.68 (d, J=5.2 Hz, 3H, OCH_3), 4.37 (d, J=6.4 Hz, 1H, CHC=), 4.60 (q, J=6.8 Hz, 1H, CHCN), 6.87—7.14 (m, 4H, ArH), 10.46 (d, J=1.2 Hz, 1H, NH); IR (neat) ν: 3257, 3172, 2210, 1713, 1608 cm^{-1}.

5-Acetyl-4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4i)

Yellow solid; m.p. 249—250 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.99 (s, 3H, CH_3C=O), 2.23 (d, J=5.6 Hz, 3H, CH_3C=C), 4.30 (d, J=6.4 Hz, 1H, CHC=C), 4.58 (q, J=6.8 Hz, 1H, CHCN), 6.57—7.13 (m, 4H, ArH), 9.68 (d, J=10.8 Hz, 1H, OH), 10.41 (d, J=52.8 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.9, 30.1, 41.5, 115.0, 115.1, 115.5, 116.2, 119.1, 130.4, 138.8, 146.9, 157.8, 163.2, 197.4; IR (neat) ν: 3355, 3262, 2255, 1712, 1664 cm^{-1}. HRMS calcd for

$C_{15}H_{14}N_2O_3$ 270.1011, found 270.1004.

5-Acetyl-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4j)[23]

Yellow solid; m.p. 152—153 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.72 (d, J=8.8 Hz, 3H, CH_3C=O), 1.77 (d, J=11.6 Hz, 3H, CH_3C=C), 3.94 (q, J=6.0 Hz, 1H, CHC=C), 4.23 (d, J=6.4 Hz, 1H, CHCN), 5.90 (q, J=1.2 Hz, 1H, C=CH), 5.93 (q, J=2.0 Hz, 1H, OC=HC=CH), 7.07 (d, J=1.2, 1H, OCH=), 10.04 (d, J=32.8 Hz, 1H, NH); IR (neat) ν: 3286, 3179, 2260, 1707, 1663 cm^{-1}.

5-Acetyl-4-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (4k)

Yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.96 (t, J=7.6 Hz, 3H, CH_2CH_3), 1.39—1.87 (m, 2H, CH_2CH_3), 2.32 (d, J=5.6 Hz, 3H, CH_3C=O), 2.39 (d, J=6.0 Hz, 3H, CH_3C=C), 3.18—3.21, 3.32—3.37 (m, 1H, CHC=C), 3.73 (q, J=5.6 Hz, 1H, CHCN), 8.69 (d, J=60.4 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.0, 11.1, 19.5, 19.6, 23.5, 24.6, 30.4, 30.5, 35.9, 36.7, 39.5, 39.6, 114.8, 115.4, 116.5, 117.0, 143.0, 143.7, 162.3, 163.9, 196.7, 196.8; IR (neat) ν: 3258, 3152, 2253, 1717, 1617 cm^{-1}. HRMS calcd for $C_{11}H_{14}N_2O_2$ 206.1055, found 206.1053.

5-Acetyl-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyridine-3-carbonitrile (4l)

Yellow solid; m.p. 138—139 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, J=6.8 Hz, 3H, CH_2CH_3), 1.26—1.77 (m, 4H, CH_2CH_2), 2.29—2.33 (m, 3H, CH_3C=O), 2.36—2.39 (m, 3H, CH_3C=C), 3.26—3.29, 3.37—3.41 (m, 1H, CHC=C), 3.70 (q, J=5.2 Hz, 1H, CHCN), 8.68 (d, J=1.2 Hz, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 14.2, 19.5, 19.6, 19.8, 20.0, 30.4, 30.6, 32.7, 33.6, 35.5, 36.2, 37.7, 39.8, 114.8, 115.3, 116.8, 117.7, 142.8, 143.3, 162.4, 163.9, 196.6, 196.7; IR (neat) ν: 3221, 3134, 2251, 1716, 1675 cm^{-1}. HRMS calcd for $C_{12}H_{16}N_2O_2$ 220.1212, found 220.1213.

Methyl-5-cyano-2-methyl-4-(3-nitrophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (4m)[24]

White solid; m.p. 207—208 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.35 (d, J=13.6 Hz, 3H, CH_3C=C), 3.50 (d, J=5.6 Hz, 3H, OCH_3), 4.39 (q, J=6.8 Hz, 1H, CHC=C), 4.79 (q, J=7.6 Hz, 1H, CHCN), 7.60—8.16 (m, 4H, ArH), 10.70 (d, J=46 Hz, 1H, NH); IR (neat) ν: 3272, 3182, 2268, 1709, 1639 cm^{-1}.

Methyl-4-(4-chlorophenyl)-5-cyano-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (4n)[25]

White solid; m.p. 189—190 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.33 (d, J=18.8 Hz, 3H, CH_3C=C), 3.51 (s, 3H, OCH_3), 4.35 (d, J=6.8 Hz, 1H, CHC=C), 4.65 (q, J=7.2 Hz, 1H, CHCN), 7.17—7.37 (m, 4H, ArH), 10.58 (d, J=66.8 Hz, 1H, NH); IR (neat) ν: 3275, 3170, 2254, 1711, 1637 cm^{-1}.

Methyl-5-cyano-2-methyl-6-oxo-4-*p*-tolyl-1,4,5,6-tetrahydropyridine-3-carboxylate (4o)[21]

White solid; m.p. 206—207 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.26 (d, J=6.4 Hz, 3H, CH_3Ph), 2.35 (d, J=22.2 Hz, 3H, CH_3C=C), 3.54 (d, J=3.6 Hz, 3H, OCH_3), 4.29 (q, J=6.8 Hz, 1H, CHC=C), 4.66 (q, J=6.8 Hz, 1H, CHCN), 7.05—7.15 (m, 4H, ArH), 10.56 (d, J=48.4 Hz, 1H, NH); IR (neat) ν: 3283, 3181, 2265, 1713, 1639 cm^{-1}.

Methyl-5-cyano-4-ethyl-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (4p)

White solid; m.p. 133—134 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.81 (t, J = 8.0 Hz, 3H, CH_2CH_3), 1.29—1.68 (m, 2H, CH_2CH_3), 2.23 (d, J=19.6 Hz, 3H, CH_3C=C), 3.06—3.09, 3.15—3.19 (m, 1H, CHC=C), 3.67 (d, J=12.8 Hz, 3H, OCH_3), 4.24 (q, J=6.0 Hz, 1H, CHCN), 10.40 (d, J=78.8 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 10.6, 18.4, 23.7, 35.7, 36.0, 51.6, 105.3, 116.7, 147.4, 164.2, 166.8; IR (neat) ν: 3229, 3137, 2248, 1701, 1648 cm^{-1}. HRMS calcd for $C_{11}H_{14}N_2O_3$ 222.1004, found 222.1001.

4-(4-Chlorophenyl)-5-cyano-2-methyl-6-oxo-*N*-phenyl-1,4,5,6-tetrahydropyridine-3-carboxamide (4q)

Yellow solid; m.p. 157—158 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.03 (d, J=37.2 Hz, 3H, CH_3C=C), 4.34 (d, J=7.2 Hz, 1H, CHC=C), 4.78 (d, J=6.8 Hz, 1H, CHCN), 6.99—7.49 (m, 9H, ArH), 9.89 (d, J=31.2 Hz, 1H, NH), 10.15 (s, 1H, NHPh); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 17.7, 41.1, 41.3, 111.6, 116.2, 120.2, 124.4, 128.9, 129.1, 129.2, 130.2, 130.3, 133.3, 136.2, 136.9, 138.5, 138.5, 138.8, 162.5, 165.8; IR (neat) ν: 3281, 3161, 2257, 1712, 1652 cm^{-1}. HRMS calcd for $C_{20}H_{16}N_3O_2Cl$ 365.0935, found 365.0931.

5-Cyano-2-methyl-6-oxo-*N*-phenyl-4-*p*-tolyl-1,4,5,6-tetrahydropyridine-3-carboxamide (4r)

White solid; m.p. 108—109 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.09 (d, J=22.4 Hz, 3H, CH_3Ph), 2.25 (d, J=17.2 Hz, 3H, CH_3C=C), 4.61 (q, J=7.2 Hz, 1H, CHC=C), 4.32 (d, J=7.2 Hz, 1H, CHCN), 6.97—7.58 (m, 9H, ArH), 9.70 (d, J=12.0 Hz, 1H, NH), 10.21 (d, J=7.2 Hz, 1H, NHPh); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 17.8, 21.0, 41.1, 41.4, 112.2, 116.5, 120.0, 120.0, 123.9, 128.2, 128.9, 129.0, 129.5, 129.7, 134.4, 137.7, 138.4, 139.3, 162.7, 165.5; IR (neat) ν: 3278, 3140, 2257, 1709, 1654 cm^{-1}. HRMS calcd for $C_{21}H_{19}N_3O_2$ 345.1477, found 345.1476.

5-Cyano-4-(furan-2-yl)-2-methyl-6-oxo-*N*-phenyl-1,4,5,6-tetrahydropyridine-3-carboxamide (4s)

Yellow solid. m.p. 98—99 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.07 (s, 3H, CH_3C=C), 4.63 (q, J=6.4 Hz, 1H, CHC=C), 4.62 (d, J=6.8 Hz, 1H, CHCN), 6.30 (d, J=2.8 Hz, 1H, CH=C), 6.40 (s, 1H, OCH), 7.05 (t, J=7.2 Hz, 1H, OCH=CH), 7.27—7.62 (m, 5H, ArH), 9.77 (d, J=22.4 Hz, 1H, NH), 10.25 (d, J=31.6 Hz, 1H, NHPh); ^{13}C NMR (100 MHz, DMSO-d_6) δ:

17.9, 30.0, 36.1, 108.1, 109.5, 110.9, 116.3, 120.1, 123.9, 129.0, 129.0, 129.2, 139.4, 139.6, 143.7, 151.2, 162.7, 165.1; IR (neat) *v*: 3284, 3134, 2259, 1712, 1654 cm^{-1}. HRMS calcd for $C_{18}H_{15}N_3O_3$ 321.1113, found 321.1112.

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