One-Pot Synthesis of 3-Cyano-2-pyridones

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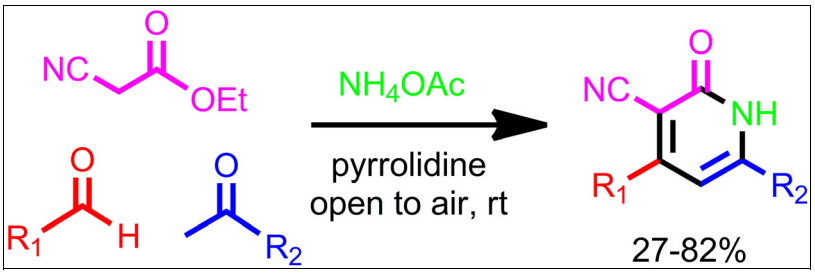

A versatile synthesis of 3-cyano-2-pyridones via a one-pot, four-component condensation of ethyl cyanoacetate, ketones, aldehydes, and ammonium acetate under very mild conditions has been developed. This method provides rapid access to this type of valuable heterocyclic compounds from readily available materials in a single operation.

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INTRODUCTION

The 3-Cyano-2-pyridones are important heterocycles found in many pharmaceuticals (Fig. 1) [1–4]. Milrinone [1] and Olprinone [2] belong to a class of phosphodiesterase III inhibitors and both were approved for heart failure therapy. Other examples in preclinical development include A-769662 (AMPK activator for metabolic disorders) [3] and JNJ-40068782 (metabotropic glutamate receptor mGluR2 modulator for psychiatric disorders) [4]. In addition to the continuous interest of being explored as cardiotonic agents [5–8], 3-cyano-2-pyridones were also explored as antitumor [5,9–14], anticoagulant [15], anti-inflammatory, and analgesic agents [16–18].

Development of methods to prepare substituted 2-pyridones has been a significant area of research in organic synthesis, and a multitude of cyclization strategies based on various bond forming processes have been reported [19–40].

The majority of the recent syntheses of 3-cyano-2-pyridones [5–18] utilized a one-pot four-component condensation (ethyl cyanoacetate, aromatic aldehydes, aromatic ketones, and excess of ammonium acetate) in refluxing ethanol or 2-butanol [41,42]. As a significant improvement from the multiple step reactions, this method offers easy operation and quick assembly from readily available aldehydes and ketones. However, it requires excess of ammonium acetate and refluxing in alcohol solvents, and the yield is quite variable (20–80%) depending on the substrates. Very recently, modification of this method was reported by either changing solvent to polyethylene glycol (yield can be improved from 5% at room temperature (RT) to 80% at 1 10°C) [43], or using microwave to improve the yield [9]. By using malononitrile instead of ethyl cyanoacetate, a solvent-free synthesis of 4,6-diaryl-3-cyano-2-pyridones promoted by sodium hydroxide at 75°C was reported [44].

To expand the substrate scope and to reduce excess reagents, we started to explore this reaction under solvent-free conditions at RT. We now communicate a mild, one-pot synthesis of 3-cyano-2-pyridones with a broad range of substrates including both aliphatic and aromatic aldehydes and ketones.

RESULTS AND DISCUSSION

On the basis of literature precedence in the synthesis of pyridones or dihydropyridines, we screened quite a few catalysts [$Yb(OTf)_3$, $AlCl_3$, $Ln(OTf)_3$, CAN, NaOBz, $NaIO_4$, Li_2CO_3] under solvent-free condition and found none of them gave more than 10% yield. We then looked at secondary amines due to its prevalence in iminium catalysis [45]. At the outset, we sought to prepare 2-pyridone (**5**) from an equimolar mixture of ethyl cyanoacetate (**1**), benzaldehyde (**2**), cyclopropylmethyl ketone (**3**), and ammonium acetate at ambient temperature in open air using various amine catalysts (Table 1). While L-proline was reported to be an efficient catalyst for a facile unsymmetric Hantzsch reaction preparing polyhydroquinoline derivatives [46], it was found to be ineffective for our purpose. To our delight, pyrrolidine (**4c**) gave the desired 2-pyridone (**5**) with 44% yield (entry 3). Aziridine (**4a**) was found to be ineffective (entry 1), while treatment with azetidine (**4b**), piperidine (**4e**) [47], and morpholine (**4f**) [48] led to very low yields (entry 2, 5, and 6).

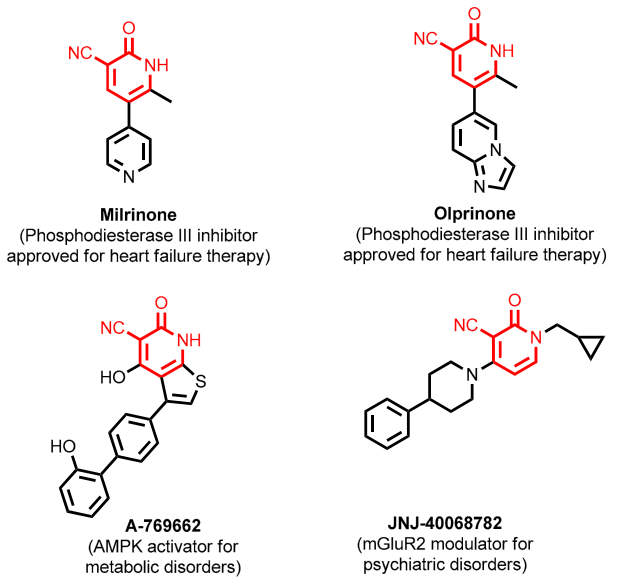


Figure 1. Representative drugs containing 3-cyano-2-pyridones. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

This exciting result prompted us to explore the substrate cope of the method. Indeed, the reaction tolerates a wide range of structural changes of both aldehydes and ketones. Both aromatic and aliphatic aldehydes (6) can participate in the reaction to give desired products with moderate yields (Table 2). Although this reaction can proceed under a solvent-free condition (Table 1), it was found that addition of a minimal amount of dimethyl sulfoxide (DMSO) can increase the solubility of the starting materials and intermediates to improve the yield. Both electron-donating and electron-withdrawing groups are tolerated on aromatic aldehydes (**8a**, **8b**, **8c**). Alkyl aldehydes (second row) delivered similar yields at a par with aromatic aldehydes (first row). In some cases, increasing the reaction temperature improves yield by promoting a more facile oxidation step (e.g., **8d**).

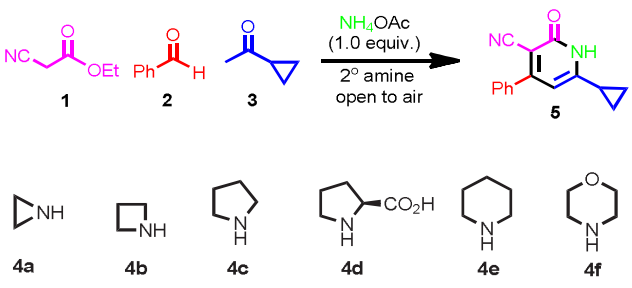
Variation of the ketones revealed that aromatic ketones with various substituents tended to give modest yields (Table 3, **11a–11c**), while modest to good yields (59–82%) were obtained when a series of aliphatic ketones (**11d–11l**) were employed. Both electron-donating and electron-withdrawing groups are tolerated on aromatic ketones (**8a**, **11a–11c**). Using a methyl benzyl ketone, the method was regioselective for the less sterically hindered methyl instead of the activated benzylic position (**11d**).

Entry to bicyclic 2-pyridones and 5-substituted pyridones was realized through the use of cyclic and symmetric ketones, respectively (Table 4). This method tolerates different ring sizes giving 5, 6, and 7-membered ring-fused 2-pyridones (**13a–13c**).

Mechanistically, this process (Scheme 1) could occur via a Knoevenagel condensation between ethyl cyanoacetate **1** and the aldehyde **6** followed by a Michael addition of **15** (derived from **10** and **4**) to deliver the δ-keto α-cyano esters **16**, which we recently prepared under similar condition without NH_4OAc [49]. Other supporting evidence for this mechanism includes liquid chromatography–mass spectrometry (MS) detection of MS corresponding to **14** being converted to **16** over time (when $R_1 = R_2 = Ph$), and clean reaction of **1** and **6** to give **14** promoted by pyrrolidine (when $R_1 = Ph$).

Table 1

Screening of secondary amines[a]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Entry	Secondary amine	Yield[b] (%)
1	Aziridine **4a**	0
2	Azetidine **4b**	13
3	Pyrrolydine **4e**	44
4	L-proline	0
5	Piperidine	8
6	Morpholine **4f**	8

[a]Reaction condition: a mixture of 1/2/3 = 1:1:1 (1 mmol scale) was treated with a secondary amine (**4a–f**, 1.5 equiv.), followed by ammonium acetate (1.0 equiv.), solvent free.
[b]Isolated yields.

CONCLUSION

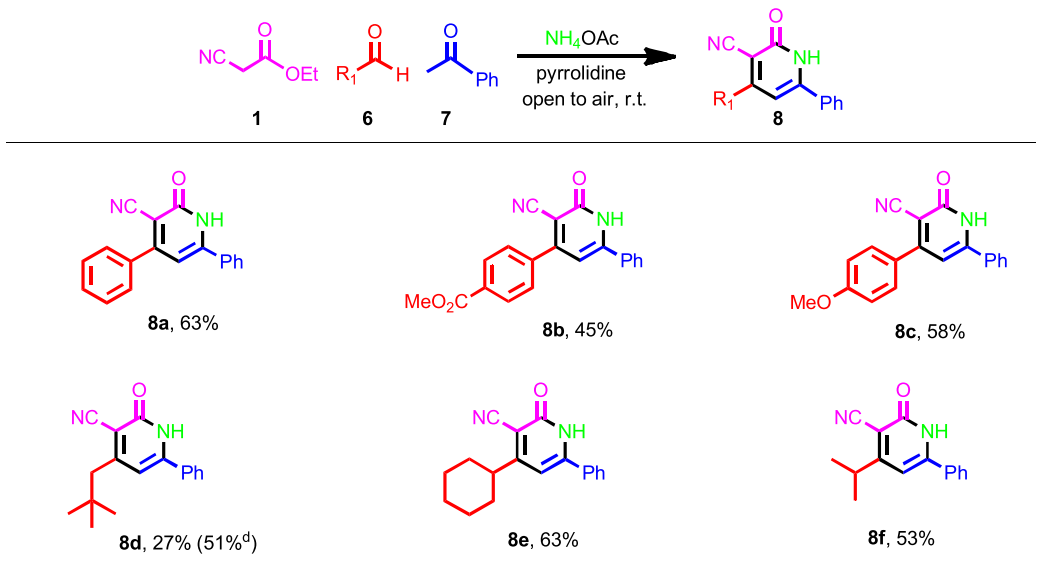
In summary, we have developed an efficient one-pot synthesis of substituted 3-cyano-2-pyridones promoted by pyrrolidine. The mild reaction conditions and rapid assembly from simple, readily available materials make it a very practical protocol for the synthesis of these important heterocycles.

EXPERIMENTAL

General information. All reactions were carried out open to air. DMSO was purchased from EMD; ethyl cyanoacetate, ammonium acetate, and pyrrolidine were purchased from Aldrich. Aldehydes and ketones were purchased from common suppliers such as Aldrich, Acros, TCI, etc. Reactions were monitored by Agilent 1200 series LC connected to an Agilent 6140 quadrupole MS analyzer. Product purification by flash chromatography was performed using Teledyne-ISCO Redisep

Table 2

Screening of aldehydes[a,b,c]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



[a]Reaction condition: a mixture of 1/6/7 = 1:1:1 (1 mmol scale) was treated with pyrrolidine (1.3 equiv.), followed by ammonium acetate (1.5–1.8 equiv.).
[b]DMSO (0.2 mL) as solvent.
[c]Isolated yields.
[d]Heated at 80°C.

normal phase silica gel columns (24 g size) on a Teledyne-ISCO Companion. ^{1}H and ^{13}C spectra were recorded on a Bruker 500 spectrometer in DMSO-d6. Chemical shifts are reported in δ ppm relative to the DMSO-d6 peak at 2.50 ppm (^{1}H) or 39.51 ppm (^{13}C). High resolution mass spectra (HRMS) were determined on Agilent 1200 series LC connected to an Agilent 6510 Q-TOF MS analyzer.

General procedure for the synthesis of 2-pyridones. To a solution of ethyl cyanoacetate (1.0 mmol), aldehyde (1.0 mmol) and ketone (1.0 mmol) in 0.2 mL DMSO was added pyrrolidine (0.1 equiv) stirred for 1 h. Ammonium acetate (1.5 to 1.8 equiv) was then added, and the mixture was stirred vigorously for 30 min. Pyrrolidine (1.2 equiv) was then added and stirred for 12–18 h. The reaction vessel was left uncapped and open to atmospheric air throughout the reaction sequence. The crude mixture, without any work-up, was purified directly by medium pressure flash chromatography using 0–5% MeOH in DCM. All yields refer to isolated yields unless otherwise stated.

Characterization data. ***6-Cyclopropyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (5).*** (53% yield). ^{1}H-NMR (500 MHz; DMSO-d$_6$): δ = 12.66 (br s, 1H), 7.57–7.62 (m, 2 H), 7.49–7.54 (m, 3 H), 6.04 (br s, 1H), 1.92–2.01 (m, 1H), 1.09–1.16 (m, 2H), 1.03–1.09 ppm (m, 2H); ^{13}C-NMR (125 MHz; DMSO-d$_6$): δ = 161.5, 159.8, 158.8, 136.3, 130.2, 128.7, 128.0, 116.8, 101.2, 96.3, 13.7, 10.7 ppm; HRMS (TOF) Calculated for $C_{15}H_{13}N_2O$ [M+H]$^+$ 237.1023, Found: 237.1028.

2-Oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile (8a). (63% yield). ^{1}H-NMR (500 MHz; DMSO-d$_6$): δ = 12.81 (br s, 1H), 7.90 (d, *J* = 7.1 Hz, 2H), 7.70–7.77 (m, 2H), 7.49–7.61 (m, 6H), 6.83 ppm (br s, 1H); ^{13}C-NMR (125 MHz; DMSO-d$_6$): δ = 162.0, 159.8, 151.5, 136.0, 132.3, 131.2, 130.4, 128.9, 128.8, 128.2, 127.8, 116.5, 106.2, 98.5 ppm; HRMS (TOF) Calculated for $C_{18}H_{13}N_2O$ [M+H]$^+$ 273.1023, Found: 273.1028.

Methyl 4-(3-cyano-2-oxo-6-phenyl-1,2-dihydropyridin-4-yl) benzoate (8b). (45% yield). ^{1}H-NMR (500 MHz; DMSO-d$_6$): δ = 12.86 (br s, 1H), 8.12 (d, *J* = 8.3 Hz, 2H), 7.90–7.94 (m, 2H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.47–7.62 (m, 3H), 6.85 ppm (br s, 1H), 3.90 ppm (s, 3H); ^{13}C-NMR (125 MHz; DMSO-d$_6$): δ = 165.5, 161.8, 140.4, 131.1, 131.0, 129.6, 129.3, 128.8, 128.6, 127.6, 127.2, 126.9, 116.0, 109.4, 106.0, 52.2 ppm; HRMS (TOF) Calculated for $C_{20}H_{15}N_2O_3$ [M+H]$^+$ 331.1077, Found: 331.1085.

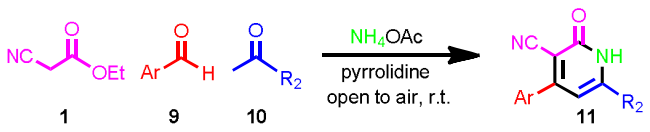
4-(4-Methoxyphenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (8c). (58% yield). ^{1}H-NMR (500 MHz; DMSO-d$_6$): δ = 12.71 (br s, 1H), 7.88 (d, *J* = 6.6 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.49–7.58 (m, 3H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.78 ppm (br s, 1H), 3.84 (s, 3H); ^{13}C-NMR (125 MHz; DMSO-d$_6$): δ = 162.2, 161.1, 159.2, 150.9, 132.3, 131.1, 130.0, 128.9, 128.0, 127.7, 116.9, 114.2, 105.9, 97.7, 55.4 ppm; HRMS (TOF) Calculated for $C_{19}H_{15}N_2O_2$ [M+H]$^+$ 303.1128, Found: 303.1131.

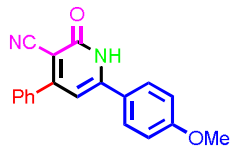
4-Neopentyl-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (8d). (27% yield at RT; 51% yield at 80°C). ^{1}H-NMR (500 MHz; DMSO-d$_6$): δ = 12.62 (br s, 1H), 7.76–7.81 (m, 2H), 7.50–7.59 (m, 3H), 6.62 (br s, 1H), 2.66 (s, 2H), 1.02 ppm (s, 9H); ^{13}C-NMR (125 MHz; DMSO-d$_6$): δ = 161.6, 161.0, 149.7, 132.3, 131.0, 128.9, 127.5, 116.6, 108.0, 102.0, 47.5, 33.3, 29.5 ppm; HRMS (TOF) Calculated for $C_{17}H_{19}N_2O$ [M+H]$^+$ 267.1492, Found: 267.1500.

4-Cyclohexyl-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (8e). (63% yield). ^{1}H-NMR (500 MHz; DMSO-d$_6$): δ = 12.58 (br s, 1H), 7.83 (d, *J* = 6.8 Hz, 2H), 7.47–7.58 (m, 3H), 6.74

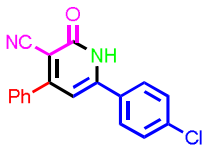
Table 3

Screening of ketones. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

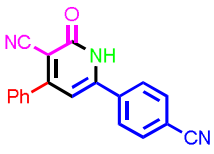




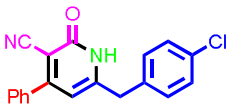
11a, 42%



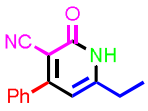
11b, 67%



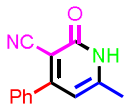
11c, 51%



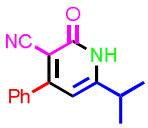
11d, 36%



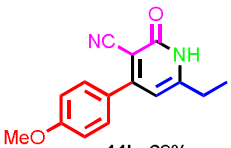
11e, 82%



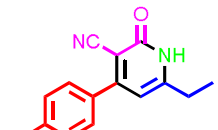
11f, 54%



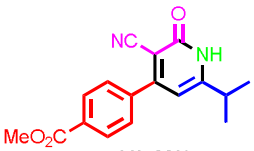
11g, 76%



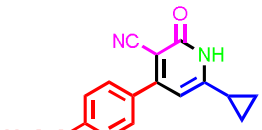
11h, 69%



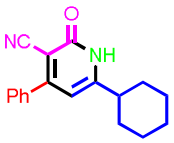
11i, 72%



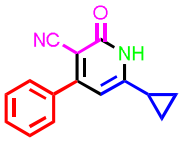
11j, 69%



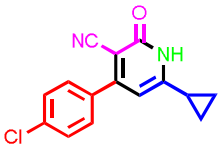
11k, 78%



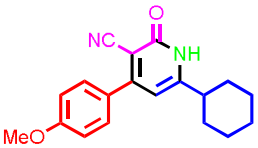
11l, 73%



5, 53%



11m, 64%



11n, 59%

(brs, 1H), 2.76 (tt, J = 11.9, 2.9 Hz, 1H), 1.82 (d, J = 12.7 Hz, 2H), 1.67–1.77 (m, 3H), 1.52–1.64 (m, 2H), 1.21–1.43 ppm (m, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 168.1, 161.6, 151.4, 132.3, 132.1, 132.3, 131.0, 128.8, 127.6, 115.7, 103.3, 99.1, 43.5, 31.1, 25.8, 25.1 ppm; HRMS (TOF) Calculated for $C_{18}H_{19}N_2O$ [M+H]$^+$ 279.1492, Found: 279.1489.

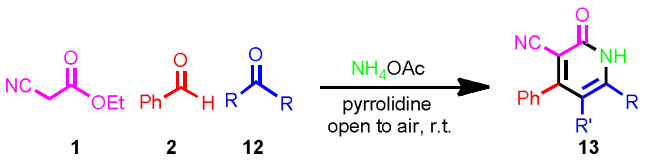
4-Isopropyl-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (8f). (53% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.52 (br s, 1H), 7.78–7.87 (m, 2H), 7.47–7.58 (m, 3H), 6.75 (br s, 1H), 3.12 (spt, J = 6.8 Hz, 1H), 1.27 ppm (d, J = 7.1 Hz, 6H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 169.2, 161.5, 151.4, 132.2, 131.0, 128.8, 127.6, 115.6, 102.8, 99.1, 33.2, 21.3 ppm; HRMS (TOF) Calculated for $C_{15}H_{15}N_2O$ [M+H]$^+$ 239.1179, Found: 239.1183.

6-(4-Methoxyphenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (11a). (42% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 7.84 (d, J = 8.8 Hz, 2H), 7.66–7.70 (m, 2H), 7.52–7.56 (m, 3H), 7.04 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 3.80 ppm (s, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 162.4, 161.9, 160.0, 151.3, 136.4, 130.6, 129.7, 129.0, 128.2, 124.3, 116.9, 114.6, 105.4, 97.5, 55.7 ppm; HRMS (TOF) Calculated for $C_{19}H_{15}N_2O_2$ [M+H]$^+$ 303.1128, Found: 303.1137.

6-(4-Chlorophenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (11b). (67% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.85 (br s., 1H), 7.93 (d, J = 8.6 Hz, 2H), 7.68–7.77 (m, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.56–7.58 (m, 3H), 6.89 ppm (br s, 1H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 162.2, 159.6, 150.5, 136.0, 135.9, 131.3, 130.4, 129.6, 128.9, 128.8, 128.3, 116.4, 106.7,

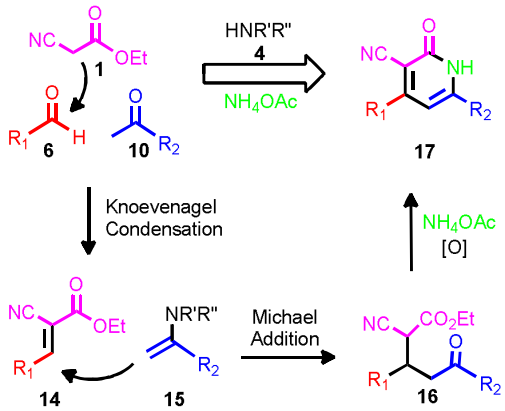
Table 4

4-Aryl-5,6-dialkyl 3-cyano-2-pyridones.[a] [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



[a]Heated at 80°C.

Scheme 1. Possible mechanism. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



98.4 ppm; HRMS (TOF) Calculated for $C_{18}H_{12}ClN_2O$ $[M+H]^+$ 307.0633, Found: 307.0642.

6-(4-Cyanophenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (11c). (51% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 8.12 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.6 Hz, 2H), 7.75 (td, *J* = 3.8, 2.0 Hz, 2H), 7.56–7.60 (m, 3H), 7.05 ppm (br s, 1H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 162.4, 159.4, 150.3, 137.1, 135.8, 132.7, 130.5, 128.8, 128.7, 128.4, 118.3, 116.2, 113.2, 108.2, 98.8 ppm; HRMS (TOF) Calculated for $C_{19}H_{12}N_3O$ $[M+H]^+$ 298.0975, Found: 298.0980.

6-(4-Chlorobenzyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (11d). (36% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.80 (br s, 1H), 7.56–7.60 (m, 2H), 7.52–7.55 (m, 3H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 6.37 (s, 1H), 3.93 ppm (s, 2H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.5, 160.3, 153.8, 136.0, 135.7, 131.8, 130.9, 130.4, 128.8, 128.6, 127.9, 116.4, 106.3, 98.2, 37.6 ppm; HRMS (TOF) Calculated for $C_{19}H_{14}ClN_2O$ $[M+H]^+$ 321.0789, Found: 321.0791.

6-Ethyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (11e). (82% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.50 (br s, 1H), 7.60–7.64 (m, 2H), 7.53–7.56 (m, 3H), 6.34 (s, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.20 ppm (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.5, 160.3, 157.2, 135.9, 130.3, 128.8, 128.0, 116.8, 105.1, 97.5, 26.1, 12.7 ppm; HRMS (TOF) Calculated for $C_{14}H_{13}N_2O$ $[M+H]^+$ 225.1023, Found: 225.1027.

6-Methyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (11f). (54% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.60 (br s, 1H), 7.57–7.62 (m, 2H), 7.51–7.57 (m, 3H), 6.34 (s, 1H), 2.31 ppm (s, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.5, 160.1, 152.2, 136.1, 130.3, 128.8, 127.9, 116.6, 106.5, 97.3, 19.1 ppm; HRMS (TOF) Calculated for $C_{13}H_{11}N_2O$ $[M+H]^+$ 211.0866, Found: 211.0869.

6-Isopropyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (11g). (76% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.55 (br s, 1H), 7.63 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.52–7.57 (m, 3H), 6.31 (s, 1H), 2.88 (spt, *J* = 6.9 Hz, 1H), 1.23 ppm (d, *J* = 7.1 Hz, 6H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.1, 161.3, 160.5, 136.2, 130.3, 128.8, 128.0, 116.5, 103.2, 97.9, 32.0, 20.9 ppm; HRMS (TOF) Calculated for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1179, Found: 239.1188.

6-Ethyl-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (11h). (69% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.47 (br s, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.31 (s, 1H), 3.83 (s, 3H), 2.57 (q, *J* = 7.3 Hz, 2H), 1.19 ppm (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.8, 161.0, 159.7, 156.8, 129.8, 128.1, 116.9, 114.2, 104.8, 96.7, 55.4, 26.1, 12.7 ppm; HRMS (TOF) Calculated for $C_{15}H_{15}N_2O_2$ $[M+H]^+$ 255.1128, Found: 255.1135.

4-(4-Chlorophenyl)-6-ethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (11i). (72% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.64 (br s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 6.33 (s, 1H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.19 ppm (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.4, 159.1, 157.5, 135.2, 134.9, 129.9, 128.9, 116.4, 104.9, 97.7, 26.1, 12.6 ppm; HRMS (TOF) Calculated for $C_{14}H_{12}ClN_2O$ $[M+H]^+$ 259.0633, Found: 259.0636.

Methyl 4-(3-cyano-6-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)benzoate (11j). (69% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.66 (br s, 1H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 6.34 (s, 1H), 3.88 (s, 3H), 2.89 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.23 ppm (d, *J* = 7.1 Hz, 6H); ^{13}C-NMR (125 MHz; DMSO-d_6):

δ = 165.6, 161.6, 161.4, 159.4, 140.6, 131.0, 129.4, 128.6, 116.2, 103.0, 98.2, 52.4, 32.0, 20.9 ppm; HRMS (TOF) Calculated for $C_{17}H_{17}N_2O_3$ $[M+H]^+$ 297.1234, Found: 297.1237.

Methyl 4-(3-cyano-6-cyclopropyl-2-oxo-1,2-dihydropyridin-4-yl)benzoate (11k). (78% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.74 (br s, 1H), 8.06 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 6.07 (br s, 1H), 3.89 (s, 3H), 1.94–2.01 (m, *J* = 3.2 Hz, 1H), 1.14 (dt, *J* = 8.3, 3.1 Hz, 2H), 1.03–1.10 ppm (m, 2H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 165.7, 161.3, 159.6, 158.9, 140.7, 130.9, 129.3, 128.6, 116.4, 101.0, 96.3, 52.4, 13.8, 10.9 ppm; HRMS (TOF) Calculated for $C_{17}H_{15}N_2O_3$ $[M+H]^+$ 295.1077, Found: 295.1079.

6-Cyclohexyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (11l). (73% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.52 (br s, 1H), 7.57–7.64 (m, 2H), 7.47–7.56 (m, 3H), 6.26 (s, 1H), 2.55 (dt, *J* = 12.0, 2.9 Hz, 1H), 1.82 (d, *J* = 11.7 Hz, 2H), 1.75 (d, *J* = 13.0 Hz, 2H), 1.64 (d, *J* = 12.0 Hz, 1H), 1.47 (qd, *J* = 12.3, 2.4 Hz, 2H), 1.09–1.33 ppm (m, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.6, 160.4, 160.0, 136.2, 130.3, 128.8, 128.0, 116.5, 103.5, 97.8, 41.7, 30.8, 25.7, 25.0 ppm; HRMS (TOF) Calculated for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1492, Found: 279.1491.

4-(4-Chlorophenyl)-6-cyclopropyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (11m). (64% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.70 (br s, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 6.03 (br s, 1H), 1.92–2.00 (m, 1H), 1.10–1.17 (m, 2H), 1.02–1.09 ppm (m, 2H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.4, 159.3, 158.8, 135.1, 135.0, 130.0, 128.7, 116.6, 101.0, 96.2, 13.7, 10.8 ppm; HRMS (TOF) Calculated for $C_{15}H_{12}ClN_2O$ $[M+H]^+$ 271.0633, Found: 271.0640.

6-Cyclohexyl-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (11n). (59% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.33 (br s, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.27 (s, 1H), 3.83 (s, 3H), 2.55 (dt, *J* = 12.0, 2.9 Hz, 1H), 1.72–1.87 (m, 4H), 1.66 (d, *J* = 12.2 Hz, 1H), 1.49 (qd, *J* = 12.3, 2.3 Hz, 2H), 1.28 ppm (d, *J* = 13.0 Hz, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.8, 161.0, 159.8, 159.6, 129.8, 128.2, 116.9, 114.2, 103.4, 96.9, 55.4, 41.7, 30.8, 25.7, 25.0 ppm; HRMS (TOF) Calculated for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1598, Found: 309.1603.

2-Oxo-4-phenyl-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carbonitrile (13a). (86% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.84 (br s, 1H), 7.50–7.56 (m, 3H), 7.45–7.50 (m, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.52 (t, *J* = 6.8 Hz, 2H), 1.97 ppm (quin, *J* = 6.8 Hz, 2H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.7, 157.6, 157.1, 135.3, 129.7, 128.6, 127.8, 117.7, 116.9, 98.0, 31.6, 28.9, 22.0 ppm; HRMS (TOF) Calculated for $C_{15}H_{13}N_2O$ $[M+H]^+$ 237.1023, Found: 237.1031.

2-Oxo-4-phenyl-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (13b). (49% yield at RT; 89% yield at 80°C). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.40 (br s, 1H), 7.45–7.55 (m, 3H), 7.28–7.33 (m, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.03 (t, *J* = 6.2 Hz, 2H), 1.62–1.71 (m, 2H), 1.50–1.59 ppm (m, 2v); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.9, 159.8, 150.2, 135.5, 129.0, 128.7, 127.4, 116.1, 112.3, 100.4, 27.2, 24.9, 21.8, 20.6 ppm; HRMS (TOF) Calculated for $C_{16}H_{15}N_2O$ $[M+H]^+$ 251.1179, Found: 251.1182.

2-Oxo-4-phenyl-2,5,6,7,8,9-hexahydro-1H-cyclohepta[b] pyridine-3-carbonitrile (13c). (74% yield at 80 °C). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.60 (br s, 1H), 7.43–7.57 (m, 3H), 7.20–7.32 (m, 2H), 2.78–2.87 (m, 2H), 2.19–2.28 (m, 2H), 1.71 (d, *J* = 4.9 Hz, 2H), 1.63 (d, *J* = 4.6 Hz, 2H), 1.35–1.43 ppm (m, 2H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 161.1, 160.0, 157.3, 136.4, 128.9, 128.7, 127.5, 118.3, 116.4, 99.2, 32.9, 31.0, 27.6, 26.6, 25.1 ppm; HRMS (TOF) Calculated for $C_{17}H_{17}N_2O$ $[M+H]^+$ 265.1336, Found: 265.1339.

6-Ethyl-5-methyl-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (13d). (69% yield). ^{1}H-NMR (500 MHz; DMSO-d_6): δ = 12.53 (br s, 1H), 7.45–7.56 (m, 3H), 7.27–7.33 (m, 2H), 2.62 (q, *J* = 7.4 Hz, 2H), 1.73 (s, 3H), 1.15 ppm (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (125 MHz; DMSO-d_6): δ = 162.5, 160.1, 154.8, 136.4, 129.0, 128.7, 127.5, 115.7, 110.4, 100.4, 24.6, 13.4, 12.7 ppm; HRMS (TOF) Calculated for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1179, Found: 239.1186.

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