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One-pot Two-step Reaction for Synthesis of Poly-substituted Pyrano[3,2-*c*]pyridones and Spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-2,5′(6′*H*)-diones in Water

Zhenhang Xu, Yijun Du, Songxiang Wang, Zeru Wu, Yuhao Lou, and Furen Zhang*

School of Chemistry and Chemical Engineering, Zhejiang Key Laboratory of Alternative Technologies for Fine Chemicals Process, Shaoxing University, Shaoxing, Zhejiang Province 312000, China
*E-mail: frzhang@usx.edu.cn
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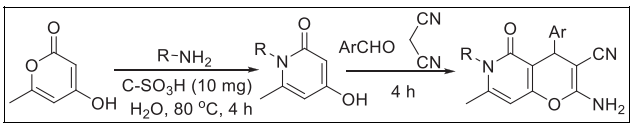

An efficient four-component approach for the synthesis poly-substituted pyrano[3,2-*c*]pyridones and spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-2,5′(6′*H*)-diones in water has been established. During the reaction, the products were readily achieved through one-pot two-step reaction using solid acid as catalyst. The advantages of atom and step economy, the recyclability of heterogeneous solid acid catalyst, easy workup procedure, and the wide scope of substrates make the reaction a powerful tool for assembling pyrano[3,2-*c*]pyridone skeletons of chemical and medical interest.

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INTRODUCTION

Pyran-annulated heterocyclic scaffolds, which process distinct properties of general interest, play an important role in the building of numerous oxygen-containing heterocyclic natural compounds [1–3]. The structurally diverse and intriguing pyranopyridone family has been found to exist in many natural products and exhibit important biological activities, such as antibacterial [4], antifungal and antialgal [5], anti-inflammatory [6], antileishmanial [7], and anticancer [8]. Among these skeletons, the selected pyranopyridone derivatives of 2*H*-pyrano[3,2-*c*]pyridines (I), YCM1008A(1) (II), zanthosimuline (III), and huajiaosimuline (IV) [9], which exhibit a broad range of biological activities, commonly exist in nature (Fig. 1). Because of their unique biological and pharmacological activities, some methodologies for the formation of pyranopyridone derivatives have been developed [10]. However, the scopes of bioactive pyranopyridone molecules are rather limited. Therefore, the development of an efficient synthetic strategy for pyranopyridone derivatives is of chemical and biological importance.

It is an important goal and task of modern organic chemistry to develop new methods aimed at improving the efficiency of synthesis and avoiding the introduction of environmental problems. Because of good stability, highly catalytic efficiency, environmental friendliness, low cost, and recyclability, solid acid as catalyst for organic synthesis has received more and more attention [11]. At present, many organic synthesis reactions catalyzed by solid acid have been reported [12], such as esterification, etherification, dehydration, oxidation, acetylation, and multicomponent reactions. During our continuous efforts on the development of multicomponent domino reaction using solid acid as catalyst [13], herein, we would like to report a new one-pot two-step method for the synthesis of poly-substituted pyrano[3,2-*c*]pyridone and spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-2,5′(6′*H*)-dione derivatives in water. This reaction was performed from readily available materials of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1**, amine **2**, aromatic aldehydes **4**, and malononitrile **5** in water using solid acid as catalyst [14] through one-pot two-step four-component strategy, and the results were shown in Scheme 1. In addition, only three-component reaction product of 2-amino-7-methyl-5-oxo-4-phenyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-3-carbonitrile **7** was obtained when all the substrates submitted the reaction system through one-pot method.

RESULTS AND DISCUSSION

To begin this study, the compounds 4-hydroxy-6-methyl-2*H*-pyran-2-one **1**, *n*-butylamine **2**, benzaldehyde **4**, and malononitrile **5** were chosen as model substrate to screen the reaction conditions for the one-pot two-step reaction. The model reaction was tested under a variety of conditions, and the representative data were shown in Table 1. The reaction did not give desired product without catalyst even at reflux temperature for 24 h (Table 1, entries 1 and 2). The goal product with 10–47% yields was obtained when the model reaction was catalyzed with different heterogeneous catalyst, such as Amberlyst-15, zeolite (HY), and carbon (the carbonaceous material from the single furaldehyde). To

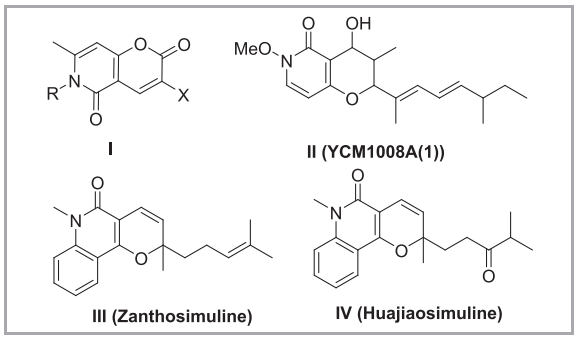


Figure 1. Some of bioactive compounds bearing pyranpyridone-annulated scaffolds.

our delight, up to 91% yield of desired product was obtained when the solid acid (C—SO_3H) was selected to promote the reaction (Table 1, entry 6). Then, different homogeneous acidic catalysts, such as HOAc, TsOH, PhCOOH, CF_3COOH, HCl, and H_2SO_4, were chosen to catalyze the model reaction, and only 16–51% of goal product was obtained (Table 1, entries 9–14). The next loading screening of catalyst indicated that the solid acid (10 mg) was enough to promote the domino reaction forward. Subsequently, the model reaction was carried out with solid acid as catalyst and repeated many times in different solvents, such as MeOH, EtOH, N,N-dimethylformamide, tetrahydrofuran, toluene, and dichloromethane (Table 1, entries 6 and 15–20). The results indicated that none of other media exhibit better suitable for the reaction than water. Thus, water was chosen as the solvent for the following reactions. Finally, the reaction catalyzed by solid acid was performed and repeated many times in different temperature. The yield of product rose when the reaction temperature was increased from room temperature to 80°C (Table 1, entries 6 and 21–23). However, a further increase of reaction temperature failed to improve the yield of the desired product (Table 1, entry 24).

With the earlier results in hand, a series of new pyrano[3,2-*c*]pyridine derivatives were synthesized in order to evaluate the scope of the protocol. Firstly, the effect of various groups bearing aromatic aldehydes was evaluated, after 4 h of the reaction between 4-hydroxy-6-methyl-2*H*-pyran-2-one and *n*-butylamine. To our delight, a variety of functional groups of aromatic aldehydes were found to be well tolerated under selected conditions to give desired products with good to excellent yields (Table 2). The reactions bearing electron-donating groups, such as methyl, isopropyl, and methoxyl-substituted arylaldehyde ring **4**, all worked better to provide the desired products with higher yields than those bearing electron-withdrawing groups, such as fluoromethyl, chloromethyl, bromomethyl, and trifluoromethyl-substituted aromatic aldehydes with **3** and **5**. The results indicated that aromatic aldehydes bearing electron-donating groups were more suitable for the domino reaction. Bulky *o*-substituted aromatic aldehydes were converted into corresponding pyrano[3,2-*c*]pyridine derivatives with slightly lower yields 73–80%. Bulky 1-naphthaldehyde also displays similar activity and gives 2-amino-6-butyl-7-methyl-4-(naphthalen-1-yl)-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile **6o** with 76% yield. Additionally, the heterocyclic 2-thienylaldehyde also exhibits good activity and gives 2-amino-6-butyl-7-methyl-5-oxo-4-(thiophen-2-yl)-5,6-dihydro-4*H*-pyrano [3,2-*c*]pyridine-3-carbonitrile **6p** with 72% yield. Then, different aliphatic and aromatic amines, such as *n*-propylamine, benzylamine, and aniline were tested to expand the scope of the reaction. Pleasantly, we found that the reaction can occur smoothly under the earlier conditions when the aliphatic amines were used. The results are shown in Table 2. The compounds of 2-amino-7-methyl-5-oxo-4-aryl-6-propyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile and 2-amino-6-benzyl-7-methyl-5-oxo-4-aryl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile with 82% and 92% yields, respectively, were obtained. However, the aniline did not exhibit any activity, and no corresponding target product was obtained. The earlier cases exhibit the scope and generality of the four-component one-pot two-step reaction.

Scheme 1. Different one-pot procedure for synthesis of pyrano[4,3-*b*]pyrans and pyrano[3,2-*c*]pyridones.

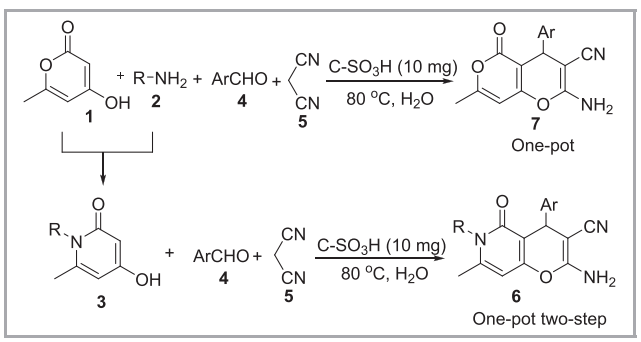
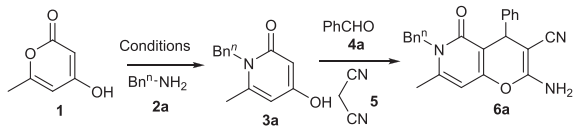


Table 1

Optimization of conditions for one-pot two-step reaction.



Entry	Solvent	Catalyst (mg)	*T* (°C)	Yield[a] (%)
1[b]	—	H_2O	80	—
2	—	H_2O	Reflux	—
3	Amberlyst-15 (10)	H_2O	80	34
4	Zeolite (HY) (10)	H_2O	80	47
5	Carbon (10)[c]	H_2O	80	10
6	C—SO_3H (10)	H_2O	80	91
7	C—SO_3H (20)	H_2O	80	93
8	C—SO_3H (5)	H_2O	80	51
9	HOAc (10)[d]	H_2O	80	38
10	TsOH (10)[d]	H_2O	80	51
11	PhCOOH (10)[d]	H_2O	80	32
12	CF_3COOH (10)[d]	H_2O	80	41
13	HCl (10)[d]	H_2O	80	16
14	H_2SO_4 (10)[d]	H_2O	80	34
15	C—SO_3H (10)	MeOH	Reflux	78
16	C—SO_3H (10)	EtOH	Reflux	76
17	C—SO_3H (10)	DMF	80	42
18	C—SO_3H (10)	THF	Reflux	49
19	C—SO_3H (10)	Toluene	80	41
20	C—SO_3H (10)	DCM	Reflux	14
21	C—SO_3H (10)	H_2O	RT	—
22	C—SO_3H (10)	H_2O	40	39
23	C—SO_3H (10)	H_2O	60	77
24	C—SO_3H (10)	H_2O	Reflux	88

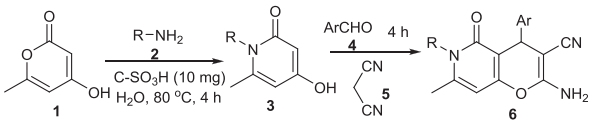
Reaction conditions: **1** (0.5 mmol) and **2a** (0.6 mmol), catalysts (× mg), and solvent (3 mL) were mixed in selected conditions for 4 h, and then **4a** (0.5 mmol) and **5a** (0.6 mmol) submitted the earlier reaction system for another 4 h.
DMF, dimethylformamide; RT, room temperature; THF, tetrahydrofuran.
[a]Isolated yields.
[b]The reaction was carried out for 24 h.
[c]The carbonaceous material from the single furaldehyde.
[d]10 mol%.

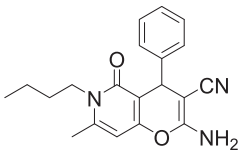
To further expand the scope of the one-pot two-step four-component reaction, different isatins were used to replace the aromatic aldehyde (Table 3). A wide range of substituent isatins including electron-withdrawing groups and electron-donating groups all furnished the expected products **9a**–**9e** with 83–89% yields under the earlier conditions. It is worth mentioning that the protocol provides a straightforward pathway to prepare a variety of poly-substituted spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-2,5′(6′*H*)-diones in one-pot two-step operation. Additionally, the model reaction was performed again using 5,5-dimethylcyclohexane-1,3-dione instead of 4-hydroxy-6-methyl-2*H*-pyran-2-one. The results indicated that the desired product 2-amino-1-butyl-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile was not obtained; instead, the compound 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile was obtained with 63% yield. We attributed to the stronger nucleophilicity of oxygen atom than nitrogen atom to cyano group. The structures of all the products **6** and **9** were unambiguously characterized by ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectrometry (HRMS) spectra (see the Supporting Information).

On the basis of the earlier results, the possible mechanism for the one-pot two-step reaction is proposed and shown in Scheme 2. The formation of **6a** is expected to proceed *via* initial reaction of the compounds 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** and *n*-butylamine **2** to afford 1-butyl-4-hydroxy-6-methylpyridin-2(1*H*)-one **3a**, which undergoes Michael addition with Knoevenagel condensation indermediate **A**, formed from benzaldehyde **4** and malononitrile **5**, to yield intermediate **B**, Finally, intramolecular nucleophilic addition of **B** afford the

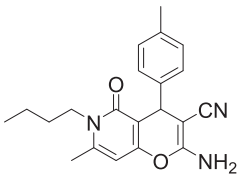
Table 2

Synthesis of substituted 2-amino-7-methyl-5-oxo-4-aryl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile derivatives.

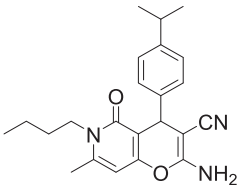




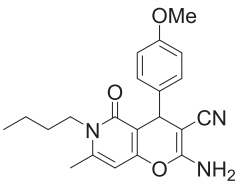
6a, 91%



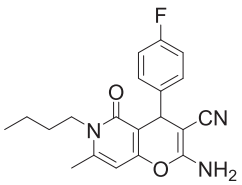
6b, 89%



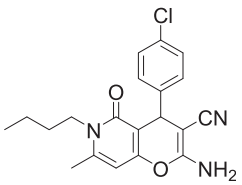
6c, 88%



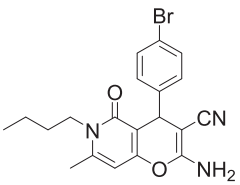
6d, 87%



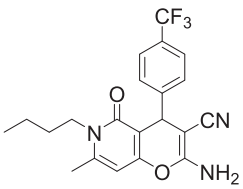
6e, 85%



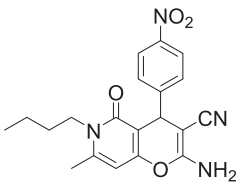
6f, 83%



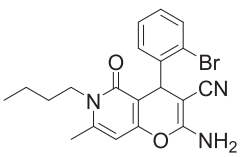
6g, 82%



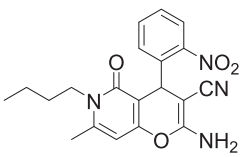
6h, 80%



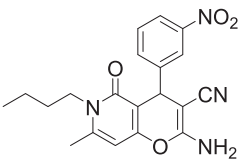
6i, 77%



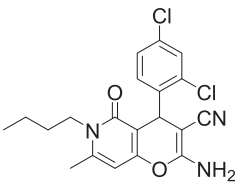
6j, 79%



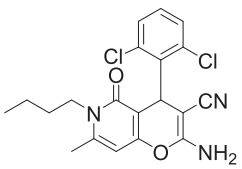
6k, 80%



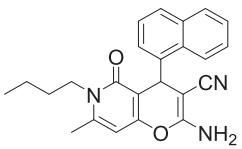
6l, 83%



6m, 77%



6n, 73%



6o, 76%

(*Continues*)

Table 2

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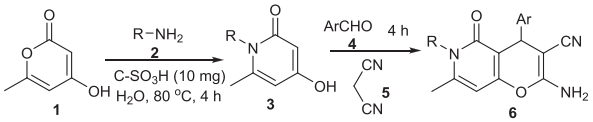
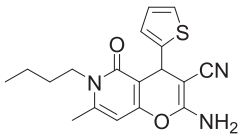
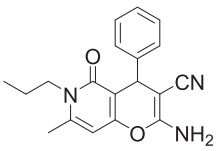
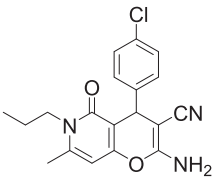




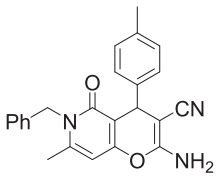
6p, 72%



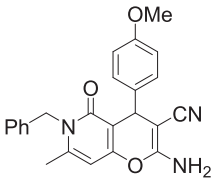
6q, 92%



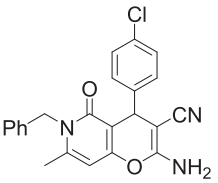
6r, 85%



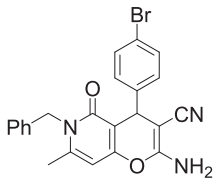
6s, 82%



6t, 85%



6u, 86%



6v, 82%

Reaction conditions: **1** (0.5 mmol) and **2** (0.6 mmol), catalysts (10 mg), and water (3 mL) were mixed in selected conditions for 4 h, and then **4** (0.5 mmol) and **5** (0.6 mmol) submitted the earlier reaction system for another 4 h.

desired product **6a**. The function of the solid acid catalyst is to provide proper acidity for the ammonolysis of lactone, the Michael addition, and the cyclization for the formation of 2-amino-6-butyl-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile **6a**.

The main advantages of solid acid catalysis are the recovery and reusability. The activity of the recovered solid acid catalyst provides useful information about its stability during the catalytic cycle. After completion of one-pot two-step reaction, the solid acid was filtered off and washed with methanol and water, heated at 100°C for 4 h, and used for further runs. The regenerated catalyst was used in the model reaction with a fresh reaction mixture for four times. The results were shown in Figure 2. These results indicated that the decrease of 2-amino-6-butyl-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile **6a** yields is mainly due to the gradual contamination of the active surface of catalyst by the byproduct.

CONCLUSIONS

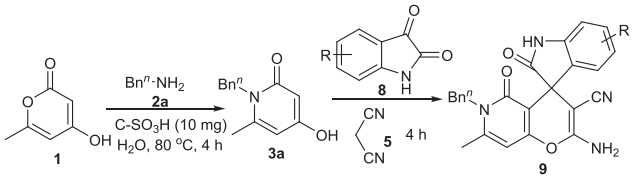
In conclusion, a series of poly-substituted pyrano[3,2-*c*] pyridone and spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-2,5′(6′*H*)-dione derivatives have been obtained with one-pot two-step reaction using solid acid as catalyst in water. The mild and environment-friendly conditions, the efficient and recycle solid acid catalyst, and the operational simplicity are represented in the one-pot two-step transformation, which provides a good methodology for the preparation of pyrano[3,2-*c*] pyridone derivatives.

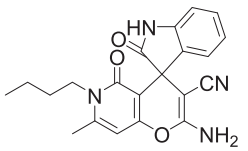
EXPERIMENTAL

General. All reagents were commercial products without further purification, unless otherwise stated. Analytical thin-layer chromatography (TLC) was

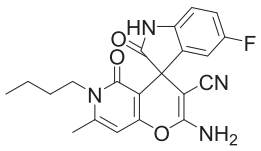
Table 3

Synthesis of 2′-amino-6′-butyl-7′-methyl-2,5′-dioxo-5′,6′-dihydrospiro [indoline-3,4′-pyrano[3,2-*c*]pyridine]-3′-carbonitriles.

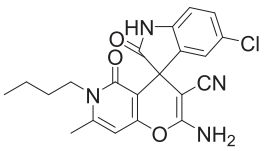




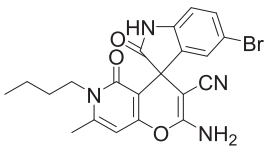
9a, 89%



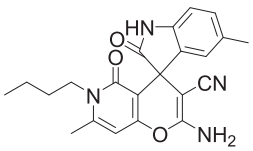
9b, 83%



9c, 86%



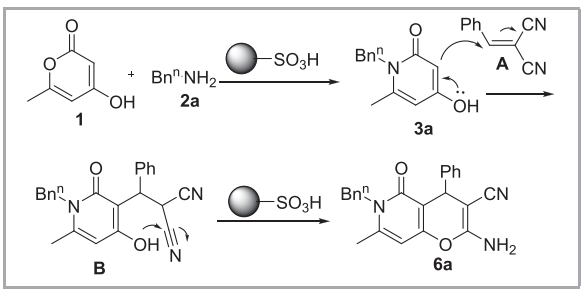
9d, 84%



9e, 88%

Reaction conditions: **1** (0.5 mmol) and **2a** (0.6 mmol), catalysts (10 mg), and water (3 mL) were mixed in selected conditions for 4 h, and then **8** (0.5 mmol) and **5** (0.6 mmol) submitted the earlier reaction system for another 4 h.

Scheme 2. Probable mechanism for the formation of compound **6a**.



performed using Merck silica gel GF254 plates (Merck, Kenilworth, NJ). Melting points were measured on an X-4 melting point apparatus. ^{1}H-NMR spectra were recorded on a 400-MHz instrument (Bruker Avance 400 Spectrometer; Bruker Corp., Billerica, MA). Chemical shifts (δ) were given in parts per million relative to tetramethylsilane (TMS) as the internal reference, with coupling constants (*J*) in Hertz. ^{13}C-NMR spectra were recorded at 100 MHz. Chemical shifts were reported in parts per million with the internal DMSO-d_6 signal at 39.0 ppm as a standard. HRMS (ESI) was measured with Bruker Daltonics APEXII instrument (Bruker Corp.).

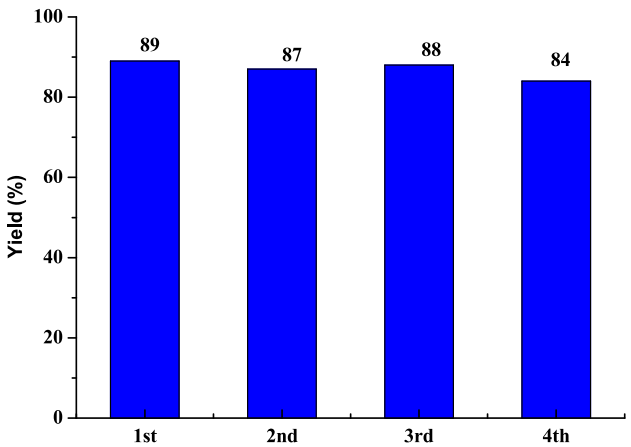


Figure 2. Studies in recycling of solid acid in the synthesis of **6a**. [Color figure can be viewed at wileyonlinelibrary.com]

The preparation of substituted 2-amino-7-methyl-5-oxo-4-aryl-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile derivatives 6a–6w. In a 10-mL reaction vial, **1** (0.5 mmol) and **2** (0.6 mmol), solid acid (10 mg), and water (3 mL) were mixed and then capped at 80°C for 4 h, and then **4** (0.5 mmol) and **5** (0.6 mmol) submitted the earlier reaction system for another 4 h, which were monitored

by TLC until conversion of the substrates was complete. The mixture was cooled to room temperature. The resulted precipitate was filtered and dried along with the catalyst. The crude product was further purified by recrystallization from hot ethanol/*N*,*N*-dimethylformamide to give the pure desired product.

The preparation of 2′-amino-6′-butyl-7′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-3′-carbonitrile 9. In a 10-mL reaction vial, **1** (0.5 mmol) and **2** (0.6 mmol), solid acid (10 mg), and water (3 mL) were mixed and then capped at 80°C for 4 h, and then **7** (0.5 mmol) and **5** (0.6 mmol) submitted the earlier reaction system for another 4 h, which were monitored by TLC until conversion of the substrates was complete. The mixture was cooled to room temperature. The resulted precipitate was filtered and dried along with the catalyst. The crude product was further purified by recrystallization from hot ethanol/*N*,*N*-dimethylformamide to give the pure desired product.

2-Amino-6-butyl-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6a). Pale yellow powder; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.26 (t, *J* = 7.2 Hz, 2H, ArH), 7.13–7.18 (m, 3H, ArH), 7.03 (br, s, 2H, NH_2), 6.05 (s, 1H, CH), 4.34 (s, 1H, CH), 3.80–3.86 (m, 1H, CH_2), 3.69–3.76 (m, 1H, CH_2), 2.36 (s, 3H, CH_3), 1.41–1.44 (m, 2H, CH_2), 1.22–1.27 (m, 2H, CH_2), 0.85 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.3, 159.5, 155.3, 147.3, 145.3, 128.7, 127.8, 126.9, 120.5, 106.4, 97.7, 58.1, 44.0, 30.3, 20.1, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}N_3O_2$ [M + H]$^+$: 336.1707, found: 336.1711.

2-Amino-6-butyl-7-methyl-5-oxo-4-(p-tolyl)-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6b). White powder; mp: 280–282°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 6.99–7.07 (m, 6H, ArH + NH_2), 6.03 (s, 1H, CH), 4.28 (s, 1H, CH), 3.80–3.87 (m, 1H, CH_2), 3.68–3.76 (m, 1H, CH_2), 2.36 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.39–1.46 (m, 2H, CH_2), 1.22–1.28 (m, 2H, CH_2), 0.85 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.2, 159.4, 155.2, 147.2, 142.3, 136.0, 129.2, 127.7, 120.5, 106.6, 97.7, 58.3, 44.0, 36.9, 30.3, 21.1, 20.1, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{24}N_3O_2$ [M + H]$^+$: 350.1863, found: 350.1861.

2-Amino-6-butyl-4-(4-isopropylphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6c). White solid; mp: 245–246°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.13 (d, *J* = 8.0 Hz, 2H, ArH), 7.04 (d, *J* = 8.4 Hz, 2H, ArH), 7.01 (s, 2H, NH_2), 6.04 (s, 1H, CH), 4.30 (s, 1H, CH), 3.83–3.90 (m, 1H, CH_2), 3.67–3.74 (m, 1H, CH_2), 2.78–2.85 (m, 1H, CH), 2.36 (s, 3H, CH_3), 1.39–1.47 (m, 2H, CH_2), 1.22–1.28 (m, 2H, CH_2), 1.16 (d, *J* = 7.2 Hz, 6H, CH_3), 0.86 (d, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.3, 159.5, 155.3, 147.2, 146.9, 142.7.0, 127.6, 126.6, 106.6, 97.8, 58.2, 42.5, 36.9, 33.5, 30.4, 24.3, 20.1, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{28}N_3O_2$ [M + H]$^+$: 378.2176, found: 378.2181.

2-Amino-6-butyl-4-(4-methoxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6d). Pale yellow powder; mp: 239–240°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.02 (d, *J* = 8.4 Hz, 2H, ArH), 6.99 (s, 2H, NH_2), 6.83 (d, *J* = 8.0 Hz, 2H, ArH), 6.03 (s, 1H, CH), 4.28 (s, 1H, CH), 3.80–3.85 (m, 1H, CH_2), 3.70 (s, 4H, OMe + CH_2), 2.35 (s, 3H, CH_3), 1.38–1.46 (m, 2H, CH_2), 1.21–1.26 (m, 2H, CH_2), 0.85 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.3, 159.4, 158.3, 155.0, 147.1, 137.3, 128.8, 114.0, 106.7, 97.7, 58.4, 55.4, 44.0, 36.5, 30.3, 20.1, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{24}N_3O_3$ [M + H]$^+$: 366.1812, found: 366.1809.

2-Amino-6-butyl-4-(4-fluorophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6e). Pale yellow powder; mp: 233–234°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.15–7.19 (m, 2H, ArH), 7.08 (d, *J* = 8.8 Hz, 2H, ArH), 7.05 (s, 2H, NH_2), 6.04 (s, 1H, CH), 4.35 (s, 1H, CH), 3.80–3.88 (m, 1H, CH_2), 3.69–3.76 (m, 1H, CH_2), 2.36 (s, 3H, CH_3), 1.36–1.48 (m, 2H, CH_2), 1.21–1.29 (m, 2H, CH_2), 0.84 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 162.5, 161.2, 159.7 ($^1J_{CF}$ = 66.0 Hz), 155.2, 147.5, 141.4, 129.6 ($^3J_{CF}$ = 8.0 Hz), 129.6, 120.4, 115.3 ($^2J_{CF}$ = 21.0 Hz), 106.2, 97.8, 57.9, 44.0, 36.7, 30.3, 20.1, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{21}FN_3O_2$ [M + H]$^+$: 354.1612, found: 354.1609.

2-Amino-6-butyl-4-(4-chlorophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6f). White solid; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.32 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 (d, *J* = 8.4 Hz, 2H, ArH), 7.06 (s, 2H, NH_2), 6.04 (s, 1H, CH), 4.35 (s, 1H, CH), 3.10–3.84 (m, 1H, CH_2), 3.72–3.77 (m, 1H, CH_2), 2.36 (s, 3H, CH_3), 1.38–1.43 (m, 2H, CH_2), 1.21–1.26 (m, 2H, CH_2), 0.84 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.2, 159.4, 155.3, 147.6, 144.2, 131.5, 129.7, 128.6, 120.3, 105.9, 97.8, 57.6, 44.0, 36.9, 30.3, 20.1, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{21}ClN_3O_2$ [M + H]$^+$: 370.1317, found: 370.1321.

2-Amino-6-butyl-4-(4-bromophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6g). White powder; mp: 254–256°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 8.01 (d, *J* = 8.4 Hz, 2H, ArH), 7.66 (d, *J* = 8.4 Hz, 4H, ArH), 6.61 (s, 1H, CH), 4.90 (s, 1H, CH), 4.35–4.42 (m, 1H, CH_2), 4.25–4.32 (m, 1H, CH_2), 2.91 (s, 3H, CH_3), 1.92–2.01 (m, 2H, CH_2), 1.77–1.82 (m, 2H, CH_2), 1.40 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.2, 159.4, 155.3, 147.6, 144.6, 131.5, 130.1, 120.4, 120.0, 105.8, 97.8, 57.5, 44.0, 36.9, 30.3, 20.1, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{21}BrN_3O_2$ [M + H]$^+$: 414.0812, found: 414.0817.

2-Amino-6-butyl-7-methyl-5-oxo-4-(4-(trifluoromethyl) phenyl)-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6h). White solid; mp: 265–266°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.63 (d, J = 8.0 Hz, 2H, ArH), 7.37 (d, J = 8.0 Hz, 2H, ArH), 7.14 (s, 2H, NH_2), 6.07 (s, 1H, CH), 4.46 (s, 1H, CH), 3.80–3.86 (m, 1H, CH_2), 3.72–3.76 (m, 1H, CH_2), 2.37 (s, 3H, CH_3), 1.36–1.43 (m, 2H, CH_2), 1.20–1.25 (m, 2H, CH_2), 0.82 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.3, 159.5, 155.4, 149.8, 147.8, 128.7, 127.8, 126.1, 125.6 ($^1J_{CF}$ = 3.3 Hz), 120.3, 105.5, 97.8, 57.3, 44.0, 37.4, 30.3, 20.0, 14.0; HRMS (ESI) m/z calcd for $C_{21}H_{21}F_3N_3O_2$ [M + H]$^+$: 404.1580, found: 404.1577.

2-Amino-6-butyl-7-methyl-4-(4-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6i). Yellow solid; mp: 261–262°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 8.14 (d, J = 8.4 Hz, 2H, ArH), 7.42 (d, J = 8.8 Hz, 2H, ArH), 7.20 (s, 2H, NH_2), 6.08 (s, 1H, CH), 4.52 (s, 1H, CH), 3.78–3.85 (m, 1H, CH_2), 3.72–3.76 (m, 1H, CH_2), 2.37 (s, 3H, CH_3), 1.36–1.43 (m, 2H, CH_2), 1.17–1.26 (m, 2H, CH_2), 0.82 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.2, 159.5, 155.5, 152.9, 148.1, 146.6, 129.2, 124.0, 120.1, 105.1, 97.8, 56.8, 44.1, 37.4, 30.3, 20.1, 13.9; HRMS (ESI) m/z calcd for $C_{20}H_{21}N_4O_4$ [M + H]$^+$: 381.1557, found: 381.1560.

2-Amino-4-(2-bromophenyl)-6-butyl-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6j). White powder; mp: 275–276°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.52 (d, J = 7.2 Hz, 1H, ArH), 7.25 (t, J = 6.8 Hz, 1H, ArH), 7.10 (t, J = 6.0 Hz, 1H, ArH), 7.03 (s, 3H, ArH + NH_2), 6.05 (s, 1H, CH), 4.87 (s, 1H, CH), 3.77–3.83 (m, 1H, CH_2), 3.67–3.72 (m, 1H, CH_2), 2.37 (s, 3H, CH_3), 1.35–1.43 (m, 2H, CH_2), 1.20–1.25 (m, 2H, CH_2), 0.84 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.1, 159.4, 155.7, 147.7, 132.9, 130.4, 128.8, 128.5, 123.5, 119.0, 105.6, 97.6, 57.1, 44.0, 36.7, 30.3, 20.1, 14.0; HRMS (ESI) m/z calcd for $C_{20}H_{21}BrN_3O_2$ [M + H]$^+$: 414.0812, found: 414.0811.

2-Amino-6-butyl-7-methyl-4-(2-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6k). Brown solid; mp: 245–246°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.81 (d, J = 8.0 Hz, 1H, ArH), 7.60 (t, J = 7.6 Hz, 1H, ArH), 7.40 (t, J = 7.6 Hz, 1H, ArH), 7.28 (d, J = 7.2 Hz, 1H, ArH), 7.20 (s, 2H, NH_2), 6.06 (s, 1H, CH), 5.11 (s, 1H, CH), 3.73–3.80 (m, 1H, CH_2), 3.62–3.69 (m, 1H, CH_2), 2.35 (s, 3H, CH_3), 1.28–1.42 (m, 2H, CH_2), 1.14–1.23 (m, 2H, CH_2), 0.83 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.2, 160.0, 155.0, 149.8, 148.0, 139.6, 133.8, 131.0, 128.1, 124.0, 119.9, 105.8, 97.7, 56.3, 43.9, 31.7, 30.2, 20.0, 14.0; HRMS (ESI) m/z calcd for $C_{20}H_{21}N_4O_4$ [M + H]$^+$: 381.1557, found: 381.1558.

2-Amino-6-butyl-7-methyl-4-(3-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6l). White powder; mp: 289–290°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 8.63 (d, J = 8.0 Hz, 1H, ArH), 8.55 (s, 1H, ArH), 8.23 (d, J = 7.6 Hz, 1H, ArH), 8.15 (t, J = 8.0 Hz, 1H, ArH), 7.77 (s, 2H, NH_2), 6.65 (s, 1H, CH), 5.13 (s, 1H, CH), 4.36–4.43 (m, 1H, CH_2), 4.25–4.36 (m, 1H, CH_2), 2.93 (s, 3H, CH_3), 1.93–1.99 (m, 2H, CH_2), 1.75–1.80 (m, 2H, CH_2), 1.38 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.2, 159.6, 155.4, 148.1, 148.0, 147.5, 134.9, 130.3, 122.3, 122.2, 120.2, 105.2, 97.8, 57.0, 44.0, 37.2, 30.3, 20.1, 20.0, 13.9; HRMS (ESI) m/z calcd for $C_{20}H_{21}N_4O_4$ [M + H]$^+$: 381.1557, found: 381.1556.

2-Amino-6-butyl-4-(2,4-dichlorophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6m). Yellow solid; mp: 239–240°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.50 (d, J = 2.0 Hz, 1H, ArH), 7.31 (dd, J = 8.4, 2.0 Hz, 1H, ArH), 7.10 (s, 3H, ArH + NH_2), 6.06 (s, 1H, ArH), 4.82 (s, 1H, CH), 3.77–3.84 (m, 1H, CH_2), 3.67–3.74 (m, 1H, CH_2), 2.38 (s, 3H, CH_3), 1.34–1.46 (m, 2H, CH_2), 1.20–1.27 (m, 2H, CH_2), 0.84 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.1, 159.4, 155.8, 147.9, 141.5, 133.7, 133.0, 132.0, 129.1,128.0, 119.9, 104.8, 97.6, 56.2, 44.0, 30.3, 20.1, 20.1, 14.0; HRMS (ESI) m/z calcd for $C_{20}H_{20}Cl_2N_3O_2$ [M + H]$^+$: 404.0927, found: 404.0930.

2-Amino-6-butyl-4-(2,6-dichlorophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6n). White solid; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.45 (d, J = 7.2 Hz, 1H, ArH), 7.22–7.27 (m, 2H, ArH), 7.10 (s, 2H, NH_2), 5.99 (s, 1H, CH), 5.37 (s, 1H, CH), 3.74–3.81 (s, 1H, CH_2), 3.63–3.71 (s, 1H, CH_2), 2.36 (s, 3H, CH_3), 1.35–1.40 (m, 2H, CH_2), 1.22–1.30 (m, 2H, CH_2), 0.83 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.0, 160.2, 156.3, 147.8, 137.1, 136.6, 134.4, 130.5, 129.3, 128.8, 119.8, 103.5, 97.5, 53.5, 43.9, 33.8, 30.3, 20.0, 14.0; HRMS (ESI) m/z calcd for $C_{20}H_{20}Cl_2N_3O_2$ [M + H]$^+$: 404.0927, found: 404.0928.

2-Amino-6-butyl-7-methyl-4-(naphthalen-1-yl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6o). White powder; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 8.45 (d, J = 6.8 Hz, 1H, ArH), 7.93 (d, J = 8.0 Hz, 1H, ArH), 7.77 (d, J = 8.0 Hz, 1H, ArH), 7.51–7.59 (m, 2H, ArH), 7.41 (t, J = 7.6 Hz, 1H, ArH), 7.12 (d, J = 6.8 Hz, 1H, ArH), 7.00 (s, 2H, NH_2), 6.13 (s, 1H, CH), 5.33 (s, 1H, CH), 3.67–3.76 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.34–1.42 (m, 2H, CH_2), 1.17–1.22 (m, 2H, CH_2), 0.81 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.3, 159.3, 155.8, 147.3, 133.7, 131.6, 128.8, 127.3, 126.2, 126.0, 124.2, 120.4, 107.2, 97.4, 58.9, 44.0,

30.3, 20.1, 14.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}N_3O_2$ [M + H]$^+$: 386.1863, found: 386.1863.

2-Amino-6-butyl-7-methyl-5-oxo-4-(thiophen-2-yl)-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6p). Yellow powder; mp: 222–224°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.27 (t, *J* = 3.6 Hz, 1H, ArH), 7.16 (s, 2H, NH_2), 6.89 (t, *J* = 5.2 Hz, 2H, ArH), 6.03 (s, 1H, CH), 4.68 (s, 1H, CH), 3.80–3.87 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.42–1.48 (m, 2H, CH_2), 1.24–1.30 (m, 2H, CH_2), 0.86 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.3, 160.0, 155.0, 149.7, 147.7, 127.2, 124.7, 124.5, 106.4, 97.9, 57.7, 44.1, 32.2, 30.3, 20.1, 14.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_3O_2S$ [M + H]$^+$: 342.1271, found: 342.1270.

2-Amino-7-methyl-5-oxo-4-phenyl-6-propyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6q). White powder; mp: 261–262°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.26 (t, *J* = 7.2 Hz, 2H, ArH), 7.13–7.18 (m, 3H, ArH), 7.04 (s, 2H, NH_2), 6.05 (s, 1H, CH), 4.34 (s, 1H, CH), 3.76–4.34 (m, 1H, CH_2), 3.66–3.73 (m, 1H, CH_2), 2.36 (s, 3H, CH_3), 1.43–1.49 (m, 2H, CH_2), 0.81 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.3, 159.5, 155.3, 147.4, 145.2, 128.7, 127.0, 120.5, 106.4, 97.7, 58.1, 45.7, 37.3, 21.6, 20.1, 11.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_3O_2$ [M + H]$^+$: 322.1550, found: 322.1555.

2-Amino-4-(4-chlorophenyl)-7-methyl-5-oxo-6-propyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6r). White powder; mp: 252–254°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.31 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 (d, *J* = 8.0 Hz, 2H, ArH), 7.06 (s, 2H, NH_2), 6.04 (s, 1H, CH), 4.35 (s, 1H, CH), 3.70–3.78 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.43–1.48 (m, 2H, CH_2), 0.80 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.3, 159.5, 155.3, 147.6, 144.2, 131.5, 129.7, 128.6, 120.3, 105.9, 97.8, 57.6, 45.7, 36.9, 21.6, 20.1, 11.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}ClN_3O_2$ [M + H]$^+$: 356.1160, found: 356.1164.

2-Amino-6-benzyl-7-methyl-5-oxo-4-(p-tolyl)-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6s). White powder; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.24–7.29 (m, 3H, ArH), 7.07 (s, 8H, ArH + NH_2), 6.11 (s, 1H, CH), 5.23–5.29 (m, 1H, CH_2), 5.03–5.11 (m, 1H, CH_2), 4.38 (s, 1H, CH), 2.24 (s, 6H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 159.4, 155.6, 147.7, 142.3, 136.1, 129.2, 129.1, 127.7, 126.5, 98.2, 58.4, 46.7, 37.1, 21.1, 20.2; HRMS (ESI) *m/z* calcd for $C_{24}H_{22}N_3O_2$ [M + H]$^+$: 384.1707, found: 384.1711.

2-Amino-6-benzyl-4-(4-methoxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6t). White powder; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.22–7.28 (m, 3H, ArH), 7.11 (d, *J* = 8.0 Hz, 2H, ArH), 7.02 (d, *J* = 8.4 Hz, 4H, ArH + NH_2), 6.86 (d, *J* = 8.0 Hz, 2H, ArH), 6.10 (s, 1H, CH), 5.28 (d, *J* = 16.0 Hz, 1H, CH_2), 5.07 (d, *J* = 16.0 Hz, 1H, CH_2), 4.37 (s, 1H, CH), 3.71 (s, 3H, CH_3), 2.23 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.8, 159.3, 158.4, 155.4, 147.6, 137.3, 129.1, 128.8, 127.5, 126.5, 120.5, 114.0, 106.9, 98.2, 58.5, 55.5, 46.7, 36.6, 20.2; HRMS (ESI) *m/z* calcd for $C_{24}H_{22}N_3O_3$ [M + H]$^+$: 400.1656, found: 400.1660.

2-Amino-6-benzyl-4-(4-chlorophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6u). White powder; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.19–7.35 (m, 7H, ArH), 7.09 (s, 2H, NH_2), 7.01 (d, *J* = 6.8 Hz, ArH), 6.12 (s, 1H, CH), 5.25 (d, *J* = 16.0 Hz, 1H, CH_2), 5.07 (d, *J* = 16.0 Hz, 1H, CH_2), 4.42 (s, 1H, CH), 2.24 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.7, 159.4, 148.1, 144.2, 137.2, 131.6, 129.7, 129.1, 128.6, 127.6, 126.5, 106.1, 98.2, 57.8, 46.7, 36.9, 20.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}ClN_3O_2$ [M + H]$^+$: 404.1160, found: 404.1161.

2-Amino-6-benzyl-4-(4-bromophenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (6v). White powder; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.47 (s, 2H, ArH), 7.21–7.27 (m, 4H, ArH), 7.11–7.16 (m, 4H, ArH + NH_2), 7.00 (s, 2H, ArH), 6.12 (s, 1H, CH), 5.25 (d, *J* = 15.2 Hz, 1H, CH_2), 5.07 (d, *J* = 14.4 Hz, 1H, CH_2), 4.42 (s, 1H, CH), 2.23 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 161.7, 159.4, 155.7, 148.1, 144.6, 137.2, 131.6, 130.1, 129.1, 127.6, 126.5, 120.2, 120.1, 106.0, 98.3, 57.7, 46.7, 37.0, 20.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}BrN_3O_2$ [M + H]$^+$: 448.0655, found: 448.0652.

2-Amino-7-methyl-5-oxo-4-phenyl-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (7a). White powder; mp: 235–236°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.31 (t, *J* = 7.2 Hz, 2H, ArH), 7.17–7.24 (m, 5H, ArH + NH_2), 6.28 (s, 1H,CH), 4.28 (s, 1H, CH), 2.21 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 163.4, 161.8, 158.6, 158.5, 144.1, 128.9, 127.9, 127.4, 119.8, 101.2, 98.4, 58.3, 36.7, 19.7.

2-Amino-4-(4-bromophenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (7b). White powder; mp: 217–218°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 7.49 (d, *J* = 8.0 Hz, 2H, ArH), 7.26 (s, 2H, NH_2), 7.15 (d, *J* = 8.0 Hz, 2H, ArH), 6.26 (s, 1H,CH), 4.29 (s, 1H, CH), 2.20 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 163.6, 161.9, 158.8, 158.5, 131.7, 130.3, 120.5, 119.7, 100.5, 98.4, 57.7, 36.2, 19.8.

2′-Amino-6′-butyl-7′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]pyridine]-3′-carbonitrile (9a). White solid; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 10.23 (s, 1H, NH), 7.01 (s, 1H, NH_2), 6.92 (t, *J* = 7.6 Hz, 1H, ArH), 6.69 (d, *J* = 6.8 Hz, 1H, ArH), 6.64 (t, *J* = 7.2 Hz, 1H, ArH), 6.57 (d, *J* = 7.6 Hz, 1H, ArH), 5.88 (s, 1H, CH), 3.40–3.54 (m,

2H, CH_2), 2.16 (s, 3H, CH_3), 1.10–1.15 (m, 2H, CH_2), 0.96–1.02 (m, 2H, CH_2), 0.60 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 178.6, 160.2, 159.6, 156.2, 148.2, 142.9, 134.8, 128.5, 123.6, 122.0, 118.2, 109.5, 103.9, 97.6, 57.4, 48.1, 44.1, 30.3, 20.1, 19.9, 14.0; HRMS (ESI) m/z calcd for $C_{21}H_{21}N_4O_3$ $[M + H]^+$: 377.1608, found: 377.1605.

2′-Amino-6′-butyl-5-fluoro-7′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]pyridine]-3′-carbonitrile (9b). Gray solid; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 10.47 (s, 1H, NH), 7.29 (s, 2H, NH_2), 6.94–6.99 (m, 1H, ArH), 6.88–6.90 (m, 1H, ArH), 6.76–6.79 (m, 1H, ArH), 6.10 (s, 1H, CH), 3.64–3.79 (m, 2H, CH_2), 2.38 (s, 1H, CH_3), 1.34–1.39 (m, 2H, CH_2), 1.16–1.25 (m, 2H, CH_2), 0.82 (t, J = 6.4 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 178.6, 160.3 ($^1J_{CF}$ = 54.0 Hz), 159.8, 157.5, 156.3, 148.4, 139.1, 136.6 ($^3J_{CF}$ = 8.0 Hz), 118.1, 114.7 ($^2J_{CF}$ = 23.0 Hz), 111.5 ($^{2'}J_{CF}$ = 24.0 Hz), 110.1 ($^{3'}J_{CF}$ = 8.0 Hz), 103.5, 97.7, 56.8, 48.6, 44.1, 30.3, 20.0, 19.9, 14.0; HRMS (ESI) m/z calcd for $C_{21}H_{20}FN_4O_3$ $[M + H]^+$: 395.1514, found: 395.1516.

2′-Amino-6′-butyl-5-chloro-7′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]pyridine]-3′-carbonitrile (9c). Gray solid; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 10.59 (s, 1H, NH), 7.31 (s, 2H, NH_2), 7.19 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 7.04 (d, J = 1.2 Hz, 1H, ArH), 6.81 (d, J = 8.0 Hz, 1H, ArH), 6.10 (s, 1H, CH), 3.73–3.80 (m, 1H, CH_2), 3.63–3.70 (m, 1H, CH_2), 2.37 (s, 1H, CH_3), 1.34–1.41 (m, 2H, CH_2), 1.18–1.23 (m, 2H, CH_2), 0.82 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 178.4, 160.3, 159.8, 156.4, 148.5, 141.9, 136.9, 128.4, 126.0, 123.8, 118.1, 110.9, 103.3, 97.8, 56.6, 48.4, 44.1, 30.3, 20.0, 19.9, 14.0; HRMS (ESI) m/z calcd for $C_{21}H_{20}ClN_4O_3$ $[M + H]^+$: 411.1218, found: 411.1221.

2′-Amino-5-bromo-6′-butyl-7′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]pyridine]-3′-carbonitrile (9d). Gray solid; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 10.48 (s, 1H, NH), 7.20 (s, 3H, ArH + NH_2), 7.04 (s, 1H, ArH), 6.65 (d, J = 7.6 Hz, 1H, ArH), 6.00 (s, 1H, CH), 3.60–3.67 (m, 1H, CH_2), 3.53–3.59 (m, 1H, CH_2), 2.27 (s, 3H, CH_3), 1.23–1.29 (m, 2H, CH_2), 1.07–1.12 (m, 2H, CH_2), 0.72 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 178.3, 160.3, 159.8, 156.4, 148.5, 142.3, 137.3, 131.3, 126.5, 118.1, 113.7, 111.5, 103.3, 97.8, 56.6, 48.4, 44.1, 30.3, 20.0, 20.0, 14.0; HRMS (ESI) m/z calcd for $C_{21}H_{20}BrN_4O_3$ $[M + H]^+$: 455.0713, found: 455.0711.

2′-Amino-6′-butyl-5,7′-dimethyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]pyridine]-3′-carbonitrile (9e). Gray solid; mp: >300°C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 10.31 (s, 1H, NH), 7.19 (s, 2H, NH_2), 6.93 (d, J = 8.0 Hz, 1H, ArH), 6.72 (s, 1H, ArH), 6.67 (d, J = 7.6 Hz, 1H, ArH), 6.09 (s, 1H, CH), 3.73–3.80 (m, 1H, CH_2), 3.62–3.69 (m, 1H, CH_2), 2.38 (s, 3H, CH_3), 2.17 (s, 1H, CH_3), 1.34–1.41 (m, 2H, CH_2), 1.19–1.24 (m, 2H, CH_2), 0.83 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, TMS): δ 178.5, 160.2, 159.6, 156.2, 148.2, 140.5, 134.9, 130.8, 128.8, 124.2, 118.3, 109.3, 104.1, 97.6, 57.6, 48.1, 44.0, 30.3, 21.0, 20.1, 19.9, 14.0; HRMS (ESI) m/z calcd for $C_{22}H_{23}N_4O_3$ $[M + H]^+$: 391.1765, found: 391.1769.

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