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Efficient and divergent synthesis of polyfunctionalized 2-pyridones from β -keto amides†

Baochang Gao,^a *^{ab} Yufeng Sun,^b Jun Wang,^a Zhigang Yuan,^b Liwu Zu,^a Xu Zhang^b and Wenbin Liu^{*a}Received 4th July 2018
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Efficient and divergent one-pot synthesis of polyfunctionalized 2-pyridones from β -keto amides based on reaction condition selection was developed. The methodology offers several significant advantages including mild conditions, ease of handling, high yields, and a relatively broad range of substrates. Based on various experiments and observations, a plausible mechanism for the selective synthesis of 2-pyridones was proposed.

Introduction

Molecularly diverse and complex heterocycles make a vital contribution to the organic synthesis and discovery of new pharmaceutical reagents.¹ 2-Pyridone is one of the most significant heteroaromatic rings in natural products, bioactive molecules, and pharmaceutical agents.^{2–5} Such well-known molecules possess a wide spectrum of biological properties such as antimalarial,⁶ anti-hepatitis B,⁷ vasorelaxant,⁸ anti-fungal,⁹ anti-epilepsy,¹⁰ anti-fibrosis,¹¹ anti-HIV,¹² MEK-1 inhibitor,¹³ antitumor,¹⁴ anti-ulcer,¹⁵ antioxidant, and antituberculosis activities.¹⁶ Moreover, molecules bearing 2-pyridone derivatives are also used as important structural units in the synthesis of nitrogen-containing heterocycles, such as pyridines,¹⁷ piperidines,¹⁸ β -lactams,¹⁹ indolizidines, and quinolizidines.²⁰ Thus, the synthesis of 2-pyridone derivatives has attracted considerable attention in recent years. Owing to their biologically and structurally interesting properties, a number of approaches for their construction have been reported. The classical methods for synthesis of 2-pyridones include pyridinium salt chemistry and N-alkylation,^{21,22} Guareschi–Thorpe reaction,²³ Dieckmann-type condensation,²⁴ Diels–Alder reaction,²⁵ and halogenated 2-pyridones under Vilsmeier conditions,²⁶ and other methods from the synthesis of 2-pyridones under metal catalyst.²⁷ Each of these approaches represents an important progress for the synthesis of 2-pyridones, however, the development of an efficient and facile strategies are

desirable for synthesis of the valuable heterocycles. The development of an efficient and facile methodology for the construction of diverse 2-pyridone derivatives still remains a great challenge.

β -Keto amide and their derivatives have been proven to be the important starting materials and reagents in the construction of heterocyclic systems since they possess six reactive sites in the same molecule.^{28–35} They have also been used as building blocks for the construction of biologically interesting heterocycles.³⁶ So far, a number of natural product-like heterocyclic compounds have been successfully synthesized based on β -keto amide and their derivatives. Their synthetic methodology and associated medicinal activity should be engaged in the chemistry community.³⁷ As part of our efforts to discover novel and practical synthesis methods for the construction of heterocyclic compounds, we recently developed an efficient synthesis of substituted thieno[2,3-*b*]pyridines from β -keto amides.³⁸ We are interested in the fields of cleavage or construction of C–C and C–N bonds because of its varied applications.³⁹ The development of a catalytic process for simultaneous cleavage and building of C–N and C–C bonds is a significant challenge in synthetic chemistry.⁴⁰ Liang *et al.* reported a new series of compounds *via* three-component one-pot reactions of 1-acetyl-1-carbamoyl cyclopropanes, malononitrile and cyclic secondary amines.⁴¹ Given that the approach of Liang involved the tandem reaction of β -keto amide reactants to the corresponding fully substituted 2-pyridones, we supposed that the direct reaction of β -keto amides with malononitrile through control reaction conditions would afford 2-pyridones with diverse structures through the control of reaction conditions. When piperidine was replaced with other bases, the poly-substituted 2-pyridones with different substituted patterns could be obtained by using β -keto amides as raw material.

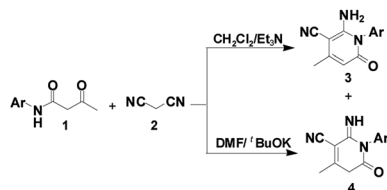
Inspired by these findings, we envisioned the construction of the 2-pyridone core from β -keto amides through intramolecular

^aInstitute of Composite Materials, Key Laboratory of Superlight Material and Surface Technology of Ministry of Education, College of Materials Science and Chemical Engineering, Harbin Engineering University, Harbin 150001, P. R. China. E-mail: chemgbc@hrbeu.edu.cn; liuwenbin@hrbeu.edu.cn

^bDaqing Branch of Heilongjiang Academy of Sciences, Daqing 163319, P. R. China

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Scheme 1 Proposed mechanism for the construction of 2-pyridones 3 and 4.

nucleophilic cyclization. As the result of our continued interest in this area, we have provided an efficient and selective synthesis methodology for the construction of two libraries of 2-pyridones 3 and 4 *via* a tandem annulation of β -keto amides 1 and malononitrile 2 in CH_2Cl_2 and DMF, respectively (Scheme 1). Herein, we wish to report our results and the possible mechanism involved was discussed.

Results and discussion

To reduce this idea to practice, we examined the reactivity of the β -keto amides 1 and 2. We then selected 3-oxo-*N*-phenylbutyramide 1a as the model substrate to screen its reaction conditions. The reaction was executed with EtONa in anhydrous ethanol at room temperature. Unfortunately the reactions was unsuccessful, no reaction occurred even till 2 h as indicated by TLC (Table 1, entry 1). When 1a was heated with 2 (1.1 equiv.) in EtOH at reflux for 6 h, we were delighted to have the desired 2-pyridone 3a, although the yield was very low (38%, Table 1, entry 2). Surprisingly the transformation was observed using EtONa to generate the reaction. The product

was characterized as 2-amino-4-methyl-6-oxo-1-phenyl-1,6-dihydro-pyridine-3-carbonitrile 3a on the basis of its NMR spectra and analytical data (Table 1, entry 2).

To optimize the reaction conditions, the reaction of β -keto amide derivative 1a with 2 was investigated using various bases and solvent (Table 1). Initially, different organic bases, such as DBU and Et_3N , were employed as in EtOH. When EtONa was replaced by DBU or Et_3N , the conversion of (2-amino-4-methyl-6-oxo-1-phenyl-1,6-dihydro-pyridine-3-carbonitrile) 3a was increased, affording compound 3a in yields of 50% and 55%, respectively (Table 1, entries 3–4). The reaction conditions were then optimized by screening several solvents. Hence, treatment of 1a with 2 in the presence of Cs_2CO_3 or DBU in CH_2Cl_2 at reflux, product 3a was formed in 63 and 72% yield, respectively (Table 1, entries 5–6). The best yield was achieved with Et_3N in refluxing CH_2Cl_2 , the yield of desired product 3a reached 88% yield (Table 1, entry 7). When the reaction was performed in the presence of piperidine in DMF at room temperature, a new compound 4a was successfully isolated in 10% yield (Table 1, entry 8). In order to efficiently obtain a single final product 4a, additional attempts were made. The introduction of carbonate such as Cs_2CO_3 or K_2CO_3 did not improve the selectivity and the conversion (Table 1, entries 9–10). However, product 4a was obtained in 85% yield by using $t\text{BuOK}$ in DMF at room temperature (Table 1, entry 11). Thus, dichloromethane was the best medium for selectively obtaining product 3a. Conversely, the best conditions for the preparation of 4a were conducted in DMF at room temperature.

Under the optimal reaction conditions (Table 1, entry 7), the 2-pyridone 3 was tested by using a range of readily available β -keto amides and malononitrile. In the following work, the scope of the substrate was investigated (Table 2). Under the conditions, a series of reactions of β -keto amides with different substitution groups on the phenyl ring were examined, and the results are listed in Table 2. As shown in Table 2, it was observed that the substrate with various electron-donating and -withdrawing groups 1b–1h could easily be converted into the corresponding 2-pyridones 3b–3h in high yields (85–95%) in 6–7.5 hours (Table 2, entries 2–8). Furthermore, the positions of the

Table 1 Optimization of the reaction conditions for the model reaction^a

Entry	Solvent	Mediated ^b	Temp. (°C)	Yield ^c (%)	
				3a	4a
1	EtOH	EtONa	rt	n.d.	n.d.
2	EtOH	EtONa	Reflux	38	n.d.
3	EtOH	DBU	Reflux	50	n.d.
4	EtOH	Et_3N	Reflux	55	n.d.
5	CH_2Cl_2	Cs_2CO_3	Reflux	63	n.d.
6	CH_2Cl_2	DBU	Reflux	72	n.d.
7	CH_2Cl_2	Et_3N	Reflux	88	n.d.
8	DMF	Piperidine	rt	32	10
9	DMF	Cs_2CO_3	70	45	n.d.
10	DMF	K_2CO_3	70	41	n.d.
11	DMF	$t\text{BuOK}$	rt	n.d.	85
12	DMF	$t\text{BuOK}$	70	n.d.	87

^a The reaction was performed with 1a (1.0 mmol), 2 (1.1 mmol), and the solvent (10 mL). ^b Mediated (1.0 mmol) was added to the reaction. ^c Isolated yields were based on β -keto amide 1a.

Table 2 Substrate scope of 1 and synthesis of target molecules 3^a

Entry	1	Ar	3	Temp. (°C)	Yield ^b (%)
1	1a	Ph	3a	Reflux	88
2	1b	4-ClC ₆ H ₄	3b	Reflux	95
3	1c	4-MeOC ₆ H ₄	3c	Reflux	85
4	1d	2-ClC ₆ H ₄	3d	Reflux	88
5	1e	2,4-Me ₂ C ₆ H ₃	3e	Reflux	91
6	1f	4-MeC ₆ H ₄	3f	Reflux	85
7	1g	2-MeOC ₆ H ₄	3g	Reflux	87
8	1h	2-MeC ₆ H ₄	4h	Reflux	85

^a All reactions were carried out with 1 (1.0 mmol), 2 (1.1 mmol), Et_3N (1.0 equiv.), in CH_2Cl_2 (5.0 mL) at reflux for 6 hours. ^b Isolated yield.



substituents on the phenyl ring did not show any effects on the reaction. It is noteworthy that all the crude products **3** could be purified simply by recrystallization from ethanol.

Next, with the aim to make product **4** to be the main product (Scheme 1), the selective synthesis of 2-pyridone **4a** under appropriate conditions may be realized. Basic conditions play an important role in the transformation process. The use of Et₃N selectively afforded compound **3** in high conversion. After several trials, we found that when Et₃N was replaced by a stronger base such as ^tBuOK, product **4a** could be obtained in a yield of 85% (Table 1, entry 11). Effect of temperature showed no improvement in the yield of product **4a** at room temperature and 70 °C (Table 1, entry 12). Under the optimal reaction conditions, a series of reactions of β-keto amides with different substitution groups on the phenyl ring were examined, affording 2-pyridones **4b–4h** in good-to-high yields (85–95%). Notably, all the crude products **4** could be purified simply by recrystallization from DMF (Table 3).

On the basis of the obtained results and previously reported work,^{41,42} a plausible mechanism for the syntheses of 2-pyridones **3** and **4** are presented, as depicted in Scheme 2. First, the β-keto amide **1** reacts with malononitrile **2** accompanying the loss of one molecule of H₂O to generate intermediate **5**, and affords intermediate **6**. Then, the isomerization of **6** in the presence of Et₃N forms final product **3** under the control experiments conditions, which is cyclized by intramolecular

nucleophilic process. Likewise, the isomerization of **6** in the presence of the ^tBuOK affords final product **4**.

Conclusions

A simple and efficient one-pot methodology for the divergent synthesis of polysubstituted 2-pyridones **3** and **4** in high yield has been developed. This method illustrates a practical protocol using simple and inexpensive starting materials. Furthermore, the methodology offers several significant advantages, such as economic availability, metal catalyst-free, ease of handling, a relative broad range of substrates, and environmental benignity under mild reaction condition. Further expanding the scope of this reaction and application the products are currently on-going in our laboratory.

Experimental

General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by recrystallization. ¹H and ¹³C NMR spectra were recorded on a Bruker AVANCE-300 spectrometer at 25 °C using TMS as an internal standard and deuterated DMSO (DMSO-*d*₆) as the solvent. Petroleum ether (PE) used was the fraction boiling in the range 30–60 °C. Elemental analyses were obtained on a Vario EL analyzer.

General procedure for the synthesis of compounds **3a–h**

To a solution of β-keto amides **1** (1.0 mmol) and malononitrile (1.1 mmol) in CH₂Cl₂ (10 mL) was added Et₃N (1.0 mmol) in one portion. The mixture was well stirred for 6 h at reflux. When consumption of **1** was complete (TLC), the mixture was washed with saturated sodium chloride solution (10 mL × 3) and dried over anhydrous MgSO₄. The organic solvent CH₂Cl₂ was then removed under reduced pressure and the residue was purified by recrystallization from ethanol to give product **3a–h**.

2-Amino-4-methyl-6-oxo-1-phenyl-1,6-dihydro-pyridine-3-carbonitrile (3a). White solid; mp 281–282 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.57–7.47 (m, 3H), 7.24 (t, *J* = 7.0 Hz, 2H), 6.68 (s, 2H), 5.67 (s, 1H), 2.17 (s, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 161.1, 156.3, 152.1, 135.2, 130.6, 129.9, 129.3, 129.1, 118.0, 117.7, 105.5, 71.8, 20.9; anal. calcd for C₁₃H₁₁N₃O: C, 76.98; H, 7.00; N, 7.48; found: C, 76.96; H, 7.01; N, 7.49.

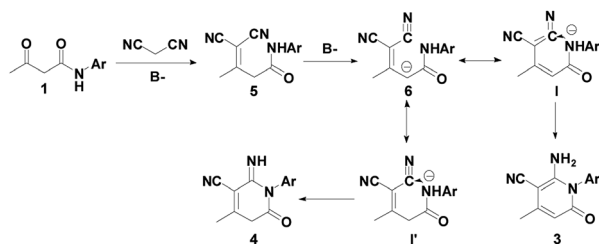
2-Amino-4-methyl-6-oxo-1-phenyl-1,6-dihydro-pyridine-3-carbonitrile (3b). White solid; mp 328–329 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.62–7.57 (m, 2H), 7.31–7.26 (m, 2H), 6.91 (s, 2H), 5.66 (d, *J* = 1.1 Hz, 1H), 2.18 (s, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 161.0, 156.4, 152.4, 134.5, 134.3, 131.4, 130.6, 117.6, 105.2, 71.8, 20.9; anal. calcd for C₁₃H₁₀ClN₃O: C, 60.12; H, 3.88; N, 16.18; found: C, 60.11; H, 3.90; N, 16.17; MS: *m/z* calcd for C₁₃H₁₀ClN₃O, 259.05; found, 260.1 [*M* + 1].

2-Amino-1-(4-methoxy-phenyl)-4-methyl-6-oxo-1,6-dihydro-pyridine-3-carbonitrile (3c). White solid; mp 273–274 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.16–7.12 (m, 2H), 7.09–7.05 (m, 2H), 6.68 (s, 2H), 5.65–5.64 (d, *J* = 3 Hz, 1H), 3.81 (s, 3H), 2.16 (s,

Table 3 Substrate scope of **1** and synthesis of target molecules **4a**

Entry	1	Ar	4	Temp. (°C)	Yield ^b (%)
1	1a	Ph	4a	rt	88
2	1b	4-ClC ₆ H ₄	4b	rt	95
3	1c	4-MeOC ₆ H ₄	4c	rt	85
4	1d	2-ClC ₆ H ₄	4d	rt	88
5	1e	2,4-Me ₂ C ₆ H ₃	4e	rt	91
6	1f	4-MeC ₆ H ₄	4f	rt	85
7	1g	2-MeOC ₆ H ₄	4g	rt	87
8	1h	2-MeC ₆ H ₄	4h	rt	85

^a All reactions were carried out with **1** (1.0 mmol), **2** (1.1 mmol), ^tBuOK (1.0 equiv.), in CH₂Cl₂ (5.0 mL) at room temperature. ^b Isolated yield.



Scheme 2 Plausible mechanism for the construction of 2-pyridones **3** and **4**.



3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 161.3, 160.1, 156.7, 152.0, 130.4, 127.5, 117.7, 115.8, 105.4, 71.6, 55.8, 20.9; anal. calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$: C, 65.87; H, 5.13; N, 16.46; found: C, 65.88; H, 5.11; N, 16.47.

3-Amino-1-(2-chloro-phenyl)-4-methyl-6-oxo-1,6-dihydro-pyridine-3-carbonitrile (3d). White solid; mp 265–266 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 7.65 (dd, J_1 = 7.3 Hz, J_2 = 1.9 Hz, 1H), 7.54–7.48 (m, 2H), 7.40 (dd, J_1 = 7.2 Hz, J_2 = 2.2 Hz, 1H), 7.00 (s, 2H), 5.66 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 160.3, 156.1, 152.8, 132.9, 132.5, 131.8, 131.6, 131.1, 129.5, 117.6, 105.1, 71.6, 21.0; anal. calcd for $\text{C}_{13}\text{H}_{10}\text{ClN}_3\text{O}$: C, 60.12; H, 3.88; N, 16.18; found: C, 60.11; H, 3.90; N, 16.17.

2-Amino-1-(2,4-dimethyl-phenyl)-4-methyl-6-oxo-1,6-dihydro-pyridine-3-carbonitrile (3e). White solid; mp 296–297 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 7.21 (s, 1H), 7.14 (d, J = 7.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.67 (s, 2H), 5.65 (s, 1H), 2.16 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ = 160.6, 156.1, 152.2, 139.4, 135.8, 132.5, 131.6, 128.9, 128.8, 117.7, 105.4, 71.6, 21.2, 20.9, 17.1; anal. calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$: C, 71.13; H, 5.97; N, 16.59; found: C, 71.15; H, 5.96; N, 16.60.

2-Amino-4-methyl-6-oxo-1-*p*-tolyl-1,6-dihydro-pyridine-3-carbonitrile (3f). White solid; mp 264–265 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 7.35 (d, J = 8.0 Hz, 2H), 7.13–7.09 (m, 2H), 6.66 (s, 2H), 5.66 (d, J = 1.1 Hz, 1H), 2.38 (s, 3H), 2.16 (d, J = 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 161.1, 156.4, 152.0, 139.2, 132.5, 131.1, 128.9, 117.7, 105.5, 71.7, 21.3, 20.9. anal. calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}$: C, 70.28; H, 5.48; N, 17.56; found: C, 70.26; H, 5.49; N, 17.57.

2-Amino-1-(2-methoxy-phenyl)-4-methyl-6-oxo-1,6-dihydro-pyridine-3-carbonitrile (3g). White solid; mp 281–282 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 7.52–7.47 (m, 1H), 7.24–7.19 (m, 1H), 7.18–7.16 (m, 1H), 7.12–7.06 (m, 1H), 6.72 (s, 2H), 5.64 (s, 1H), 3.75 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 160.7, 156.4, 155.4, 152.1, 131.5, 130.5, 123.2, 121.8, 117.8, 113.6, 105.4, 71.5, 56.2, 20.9; anal. calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$: C, 65.87; H, 5.13; N, 16.46; found: C, 65.88; H, 5.11; N, 16.47.

2-Amino-4-methyl-6-oxo-1-*o*-tolyl-1,6-dihydro-pyridine-3-carbonitrile (3h). White solid; mp 284–285 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 7.43 (d, J = 4.6 Hz, 2H), 7.40–7.38 (m, 1H), 7.16 (d, J = 7.4 Hz, 1H), 6.72 (s, 2H), 5.71 (s, 1H), 2.21 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 160.5, 156.0, 152.4, 136.2, 134.2, 131.9, 130.1, 129.2, 128.2, 117.6, 105.5, 71.7, 20.9, 17.2; anal. calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}$: C, 70.28; H, 5.48; N, 17.56; found: C, 70.26; H, 5.49; N, 17.57.

General procedure for the synthesis of compounds 4a–h

To a solution of β -keto amides **1** (1.0 mmol) and malononitrile (1.1 mmol) in DMF (10 mL) was added $^t\text{BuOK}$ (1.0 mmol) in one portion. The mixture was well stirred for 4 hours at room temperature. When consumption of **1** was complete (TLC), the mixture was poured into sat. aq. NaCl (50 mL) under stirring. The precipitated solid was collected by filtration, washed with water (3 \times 20 mL) and dried *in vacuo* to afford the product **4a–h**.

2-Imino-4-methyl-6-oxo-1-phenyl-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (4a). White solid; mp 130–131 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 10.36 (s, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.33

(t, J = 7.8 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 3.77 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 178.3, 164.7, 138.9, 129.3, 124.3, 119.8, 112.6, 112.6, 87.2, 45.1, 24.1; anal. calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}$: C, 69.32; H, 4.92; N, 18.66; found: C, 69.31; H, 4.94; N, 18.65; MS: m/z calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}$, 225.09; found, 226.0 [$M + 1$].

1-(4-Chloro-phenyl)-2-imino-4-methyl-6-oxo-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (4b). White solid; mp 125–126 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 10.50 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 3.78 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 178.1, 164.9, 137.9, 129.2, 127.9, 121.4, 112.6, 112.5, 87.3, 45.0, 24.1; anal. calcd for $\text{C}_{13}\text{H}_{10}\text{ClN}_3\text{O}$: C, 60.12; H, 3.88; N, 16.18; found: C, 60.13; H, 3.88; N, 16.17.

2-Imino-1-(4-methoxy-phenyl)-4-methyl-6-oxo-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (4c). White solid; mp 138–139 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 10.21 (s, 1H), 7.48 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 3.73 (s, 2H), 3.72 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 178.4, 164.2, 156.0, 132.0, 121.4, 114.4, 112.6, 112.6, 87.0, 55.6, 45.0, 24.1; anal. calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$: C, 65.87; H, 5.13; N, 16.46; found: C, 65.86; H, 5.15; N, 16.45.

1-(2-Chloro-phenyl)-2-imino-4-methyl-6-oxo-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (4d). White solid; mp 145–146 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 10.04 (s, 1H), 7.65 (dd, J_1 = 8.0, J_2 = 1.7 Hz, 1H), 7.51 (dd, J_1 = 7.9, J_2 = 1.5 Hz, 1H), 7.36–7.28 (m, 1H), 7.27–7.19 (m, 1H), 3.83 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 178.0, 165.3, 134.7, 130.0, 128.0, 127.6, 127.5, 127.2, 112.6, 112.5, 87.2, 44.6, 24.0; anal. calcd for $\text{C}_{13}\text{H}_{10}\text{ClN}_3\text{O}$: C, 60.12; H, 3.88; N, 16.18; found: C, 60.13; H, 3.88; N, 16.17.

1-(2,4-Dimethyl-phenyl)-2-imino-4-methyl-6-oxo-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (4e). White solid; mp 137–138 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 9.67 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.04 (s, 1H), 6.97 (d, J = 8.1 Hz, 1H), 3.77 (s, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 178.6, 164.8, 135.4, 133.5, 132.5, 131.4, 127.0, 125.8, 112.7, 112.6, 87.0, 44.6, 24.1, 21.0, 18.2; anal. calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$: C, 71.13; H, 5.97; N, 16.59; found: C, 71.12; H, 5.99; N, 16.58.

2-Imino-4-methyl-6-oxo-1-*p*-tolyl-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (4f). White solid; mp 100–101 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 10.25 (s, 1H), 7.45–7.41 (m, 2H), 7.13–7.10 (m, 2H), 3.73 (s, 2H), 2.34 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 178.4, 164.5, 136.4, 133.3, 129.7, 119.8, 112.6, 112.6, 87.1, 45.1, 24.1, 20.9; anal. calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}$: C, 70.28; H, 5.48; N, 17.56; found: C, 70.30; H, 5.47; N, 17.55.

2-Imino-1-(2-methoxy-phenyl)-4-methyl-6-oxo-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (4g). White solid; mp 101–102 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 9.70 (s, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.16–7.06 (m, 2H), 6.96–6.91 (m, 1H), 3.88 (s, 2H), 3.86 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 178.5, 165.1, 150.5, 127.0, 125.7, 123.0, 120.7, 112.7, 112.6, 111.8, 87.1, 56.2, 45.0, 23.9; anal. calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$: C, 65.87; H, 5.13; N, 16.46; found: C, 65.86; H, 5.15; N, 16.45.

2-Imino-4-methyl-6-oxo-1-*o*-tolyl-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (4h). White solid; mp 154–155 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 9.75 (s, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.23 (d,



$J = 7.2$ Hz, 1H), 7.13 (dd, $J_1 = 12$ Hz, $J_2 = 6$ Hz, 2H), 3.80 (s, 2H), 2.37 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 178.5, 164.9, 136.1, 132.5, 130.9, 126.5, 126.2, 125.7, 112.7, 112.6, 87.0, 44.6, 24.1, 18.3$; anal. calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}$: C, 70.28; H, 5.48; N, 17.56; found: C, 70.30; H, 5.47; N, 17.55.

Conflicts of interest

There are no conflicts to declare.

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