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Novel construction of diversely functionalized *N*-heteroaryl-2-pyridones *via* copper(II)-catalyzed [3+2+1] annulation†

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A facile and novel one-pot construction of diversely functionalized *N*-heteroaryl-2-pyridones is achieved by $Cu(OTf)_2$-catalyzed [3+2+1] annulation of various 2-aminopyridines and β-enamino esters. The [3+2+1] annulation proceeds *via* domino two Michael additions/elimination/isomerization/intramolecular cyclization.

Introduction

2-Pyridone derivatives are important heterocyclic scaffolds, which constitute the core of a large number of natural alkaloids, pharmaceuticals, and agrochemicals (Fig. 1).[1] 2-Pyridone-based molecules possess a wide spectrum of biological properties like antimalarial,[2] antimicrobial,[3] vasorelaxant,[4] antiasthma,[5] anti-epilepsy,[6] anti-HIV,[7] antitumor,[8] anti-hepatitis B,[9] antioxidant,[10] antiviral,[11] and antituberculosis activities.[12] Some of them are currently used as pharmaceuticals for the treatment of idiopathic pulmonary fibrosis (Pirfenidone, ®Pirfenex, ®Pirespa, ®Esbriet, and Etuary),[13] congestive heart failure (Milrinone, ®Primacor),[14] and epileptic seizures (Perampanel, ®Fycompa).[15] They are also used as building blocks for the synthesis of bioactive and functional materials.[16] Moreover, the versatile nature of 2-pyridones enables their transformation into structurally important heterocyclic scaffolds such as pyridines,[17] piperidines,[18] β-lactams,[19] indolizidines, and quinolizidines.[20]

Owing to the importance and usefulness of 2-pyridones, various approaches for their construction have been reported, including transition-metal-catalyzed [2+2+2] cycloaddition of 1,6-diynes with isocyanates (eqn (1), Scheme 1),[21] oxidative coupling between acrylamides and alkynes (eqn (2), Scheme 1),[22] 1,4-addition of 2-(phenylsulfinyl)acetamide to α,β-unsaturated ketones followed by cyclization and sulfoxide elimination,[23] formation of *N*-alkenyl alkynylamides followed by gold-catalyzed cycloisomerization,[24] nucleophilic addition of malonic esters to alkynyl imines,[25] and Rh(III)-catalyzed C–H activation/annulation of *N*-methoxy methacrylamides with diazo compounds.[26] Despite these reports, more facile and efficient strategies are still highly desirable. This prompted us to develop a new methodology based on the characteristic reactivity of 2-aminopyridines. Recently, *N*-heteroaryl-2-pyridones have received significant attention because of their versatile applications in organic synthesis.[27] Among the applications of *N*-heteroaryl-2-pyridones, the metal-catalyzed direct C–H functionalization reactions of 1-(2-pyridyl)-2-pyridones with 1,3-azoles,[27a] bis(pinacolato)-diboron,[27b] alkyltrifluoroborates,[27c] propargyl alcohols,[27d] anthranil,[27e] and diazo compounds[27f] have been well described. Nevertheless, only a few synthetic routes to *N*-heteroaryl-2-pyridones have been reported, which include the copper-catalyzed coupling reaction of 2-pyridones with heteroaryl halides.[28] To the best of our knowledge, there is no report on the direct synthesis of *N*-heteroaryl-2-pyridones from readily available 2-aminopyridines *via* an annulation

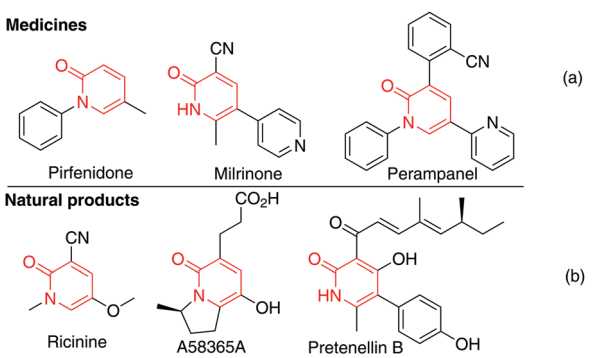

Fig. 1 Selected pharmaceuticals (a) and bioactive natural products (b) containing the 2-pyridone moiety.

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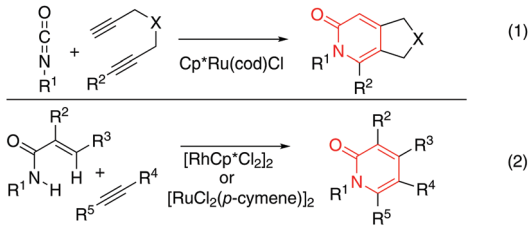
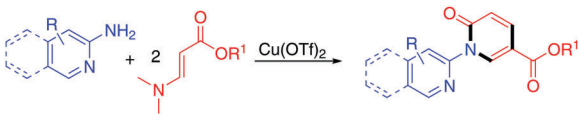


Scheme 1 Representative methods for the synthesis of 2-pyridones.



Scheme 2 Novel *N*-heteroaryl-2-pyridone construction *via* [3+2+1] annulation.

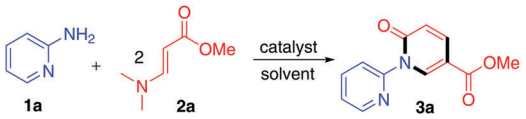
strategy, which have been mainly used as key starting materials for the preparation of bioactive imidazo[1,2-*a*]pyridines.[29]

Recently, we have reported the construction of heterocycles and aromatics such as polyfunctionalized pyridines, chromeno-pyridinones, carbazoles, biaryls, anthraquinones, and 2-hydroxy-benzophenones *via* *N*-annulation and benzannulation reactions.[30] In addition, we have developed an eco-friendly synthesis of 2-pyridones by catalyst- and solvent-free thermal multicomponent domino reaction.[31] As the result of our continued interest in this area, herein we report a simple and efficient methodology for the construction of biologically important *N*-heteroaryl-2-pyridones from readily available 2-aminopyridines (Scheme 2). This is the first example of the direct construction of diversely functionalized *N*-heteroaryl-2-pyridones *via* $Cu(OTf)_2$-catalyzed [3+2+1] annulation of 2-aminopyridines with β-enamino esters.

Results and discussion

To optimize the reaction conditions, the reaction of 2-amino-pyridine (**1a**) with methyl (*E*)-3-(dimethylamino)acrylate (**2a**) was investigated using various metal catalysts and solvents (Table 1). Lewis acids are well-known for the conjugate addition of amines to α,β-unsaturated carbonyl compounds. Hence, several Lewis acids were screened for conjugate addition of aminopyridines to β-enamino esters to form heterocyclics. Toluene is predominantly used as a solvent in cycloaddition. Initially, treatment of **1a** (1.0 mmol) with **2a** (2.0 mmol) in the presence of 10 mol% AgOAc in toluene at room temperature or at reflux for 24 h did not provide the product **3a** (entries 1 and 2); however, using 10 mol% AgOTf in refluxing toluene for 24 h, product **3a** was isolated in 18% yield (entry 3). Encouraged by this result, other catalysts were tested. When the reaction was performed in the presence of the rare-earth metal catalysts $Yb(OTf)_3$, $Sc(OTf)_3$, $InCl_3$, $InBr_3$, and $In(OTf)_3$ in refluxing toluene for 15–24 h, **3a** was formed in 23, 25, 30, 48, and 51% yield, respectively (entries 4–8). The best yield (72%) was achieved with 10 mol% $Cu(OTf)_2$ in refluxing toluene for 10 h (entry 9). Decreasing the $Cu(OTf)_2$ loading to 5 mol% or

Table 1 Optimization of the synthesis of 2-pyridone **3a**[a]



1a 2a 3a

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	AgOAc (10 mol%)	Toluene	r.t.	24	0
2	AgOAc (10 mol%)	Toluene	Reflux	24	0
3	AgOTf (10 mol%)	Toluene	Reflux	24	18
4	$Yb(OTf)_3$ (10 mol%)	Toluene	Reflux	24	23
5	$Sc(OTf)_3$ (10 mol%)	Toluene	Reflux	24	25
6	$InCl_3$ (10 mol%)	Toluene	Reflux	24	30
7	$InBr_3$ (10 mol%)	Toluene	Reflux	15	48
8	$In(OTf)_3$ (10 mol%)	Toluene	Reflux	15	51
9	$Cu(OTf)_2$ (10 mol%)	Toluene	Reflux	10	72
10	$Cu(OTf)_2$ (5 mol%)	Toluene	Reflux	10	63
11	$Cu(OTf)_2$ (20 mol%)	Toluene	Reflux	10	71
12	$Cu(OTf)_2$ (10 mol%)	THF	Reflux	10	15
13	$Cu(OTf)_2$ (10 mol%)	1,4-Dioxane	Reflux	10	23
14	$Cu(OTf)_2$ (10 mol%)	$CHCl_3$	Reflux	10	52
15	$Cu(OTf)_2$ (10 mol%)	CH_3CN	Reflux	10	48
16	$Cu(OTf)_2$ (10 mol%)	EtOH	Reflux	10	0
17	$Cu(OTf)_2$ (10 mol%)	Toluene	r.t.	10	0
18	$Cu(OTf)_2$ (10 mol%)	Toluene	70	24	10
19	TfOH (10 mol%)	Toluene	Reflux	24	26
20[c]	$Cu(OTf)_2$ (10 mol%)	Toluene	Reflux	24	69
21	$CuCl_2$ (10 mol%)	Toluene	Reflux	24	64

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol) and solvent (5.0 mL). [b] Isolated yield after column chromatography. [c] Proton sponge (20 mol%).

increasing it to 20 mol% did not improve the yield (entries 10 and 11). In nonpolar solvents of THF, 1,4-dioxane, and chloroform, **3a** was produced in 15, 23, and 52% yield, respectively (entries 12–14). In polar aprotic acetonitrile, **3a** was isolated in 48% yield, whereas in polar protic ethanol, **3a** was not obtained at all (entries 15 and 16). Effect of temperature showed no improvement in yield of product **3a** when studied at room temperature and 70 °C (entries 17 and 18). In order to investigate the role of *in situ* generated triflic acid, the reaction was carried out with TfOH instead of $Cu(OTf)_2$ as the catalyst. With 10 mol% of triflic acid in refluxing toluene for 24 h, product **3a** was formed but in lower yield of 26% (entry 19). In addition, with 20 mol% of proton sponge and 10 mol% of $Cu(OTf)_2$, **3a** was isolated in 69% yield (entry 20). From this result, TfOH generated *in situ* has no significant role in this transformation. This was further confirmed by using other non-triflate-based copper catalyst $CuCl_2$ which gave the product **3a** in 64% yield (entry 21). The structure of **3a** was established by analysis of its spectral data. The ^1H NMR spectrum exhibited peaks corresponding to the 2-pyridone ring: the singlet at δ 3.85 ppm was attributed to the methoxy protons, two vinyl protons appeared at δ 6.60 and 7.85 ppm as two doublets (J = 9.6 Hz), and one vinyl proton appeared at 8.72 ppm as a singlet. The ^{13}C NMR showed the characteristic methoxy carbon signal at δ 52.0 ppm and carbonyl carbon signals of the ester and amide groups at δ 164.7 and 161.8 ppm, respectively. Based on the X-ray analysis of structurally related compound **3n** (*vide infra*), the structure of **3a** was confirmed in analogy. The ellipsoidal probability for crystal structure **3n** is 50%.

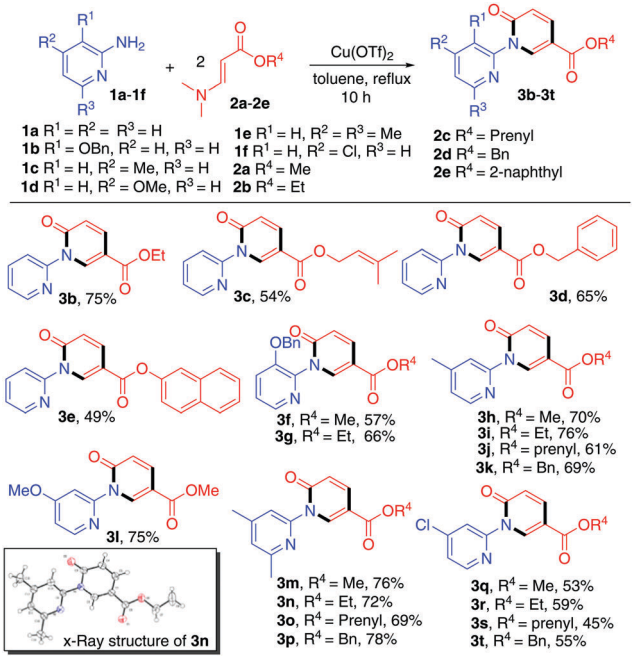
With the optimized conditions in hand, we explored the scope of 2-aminopyridines and β-enamino esters for the synthesis of *N*-heteroaryl-2-pyridones, and the results are depicted in Table 2. Treatment of **1a** with **2b**, **2c**, or **2d** bearing an ethyl, prenyl, or benzyl substituent provided the corresponding products **3b–3d** in 75, 54, and 65% yield, respectively. When β-enamino ester **2e** bearing a 2-naphthyl group was used, compound **3e** was formed in 49% yield. The reactions of **1b–1f** bearing electron-donating or -withdrawing substituents on the pyridine ring were also successful. For example, the combination of 2-aminopyridine **1b**, **1c**, **1d**, or **1e** bearing the electron-donating 3-benzyloxy, 4-methyl, 4-methoxy, or 4,6-dimethyl group, respectively, with β-enamino esters **2a–2d** provided the desired products **3f–3p** in 57–78% yield. Similarly, treatment of **1e** bearing the electron-withdrawing 4-Cl group with β-enamino esters **2a–2d** afforded products **3q–3t** in 53, 59, 45, and 55% yield, respectively. This protocol provides a rapid synthetic route to *N*-(2′-pyridyl)-2-pyridone derivatives bearing a variety of substituents on the 2-pyridone ring in a one-pot fashion.

To demonstrate the versatility of this strategy, we further examined the reactions of 2-aminoquinoline (**1g**) and 3-amino-isoquinoline (**1h**) with β-enamino esters **2a–2d** (Table 3). Compound **1g** reacted with **2a**, **2b**, **2c**, or **2d** in refluxing toluene for 10 h to give products **4a–4d** in 68–83% yield. Similarly, the combination of **1h** with β-enamino esters **2a–2d** successfully afforded the corresponding products **4e–4h** in 67–80% yield.

Next, we explored the annulation reaction of the two-nitrogen-based nucleophiles 3-aminopyridazine (**1i**), 2-aminopyrazine (**1j**), and 2-aminopyrimidine (**1k**) (Table 4). To our delight, the reaction of **1i** with β-enamino ester **2a**, **2b**, **2c**, or **2d** afforded the corresponding products **5a–5d** in 32–54% yield. Similarly, treatment of **1j** with **2a**, **2b**, or **2d** successfully provided products **5e–5g** in 53, 61, and 51% yield, respectively, whereas the reaction of **1k** with **2a** or **2b** afforded product **5h** or **5i** in 58 and 55% yield, respectively.

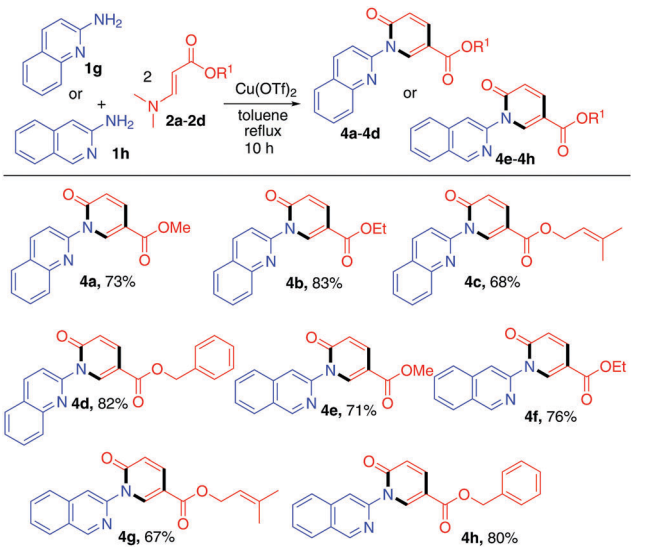
Control experiments were carried out to understand the mechanism for the formation of **3a** (Scheme 3). The reaction

Table 2 Formation of diverse *N*-2′-pyridyl-2-pyridones **3b–3t** by the reaction of **1a–1f** with **2a–2e**[a,b]



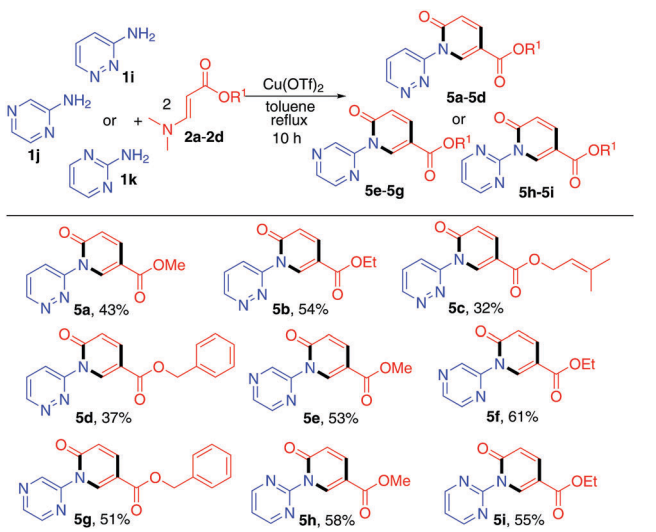
[a] Reaction conditions: 2-amino pyridines (1.0 mmol), β-enamino ester (2.0 mmol), and $Cu(OTf)_2$ (10 mol%) in toluene (5.0 mL). [b] Isolated yield after column chromatography.

Table 3 Formation of diverse 2-pyridones **4a–4h** by the reaction of **1g** or **1h** with **2a–2d**[a,b]

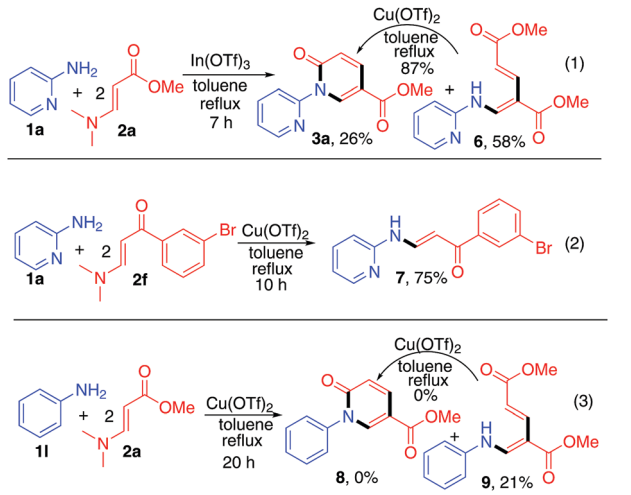


[a] Reaction conditions: aminoquinolines (1.0 mmol), β-enamino esters (2.0 mmol), $Cu(OTf)_2$ (10 mol%) in toluene (5.0 mL). [b] Isolated yield after column chromatography.

Table 4 Formation of diverse 2-pyridones **5a–5i** by the reaction of **1j**, **1k**, or **1l** with **2a–2d**[a,b]



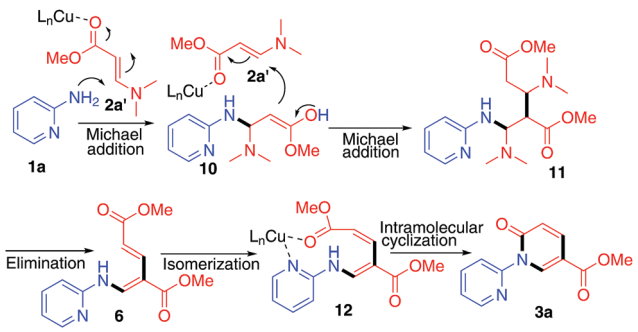
[a] Reaction conditions: 2-amino derivatives (1.0 mmol), β-enamino esters (2.0 mmol), $Cu(OTf)_2$ (10 mol%) in toluene (5.0 mL). [b] Isolated yield after column chromatography.



Scheme 3 Control experiments.

of **1a** with **2a** in the presence of 10 mol% $In(OTf)_3$ in refluxing toluene for 7 h afforded the desired cycloadduct **3a** (26%) and uncyclized product **6** (58%) (eqn (1), Scheme 3). The structure of **6** was elucidated by spectral data analysis. Further reaction of uncyclized **6** under standard conditions using $Cu(OTf)_2$ as the catalyst gave the desired product **3a** in 87% yield. When β-enamino ketone **2f** was used instead of a β-enamino ester, the cycloadduct was not formed, and compound **7** was produced in 75% yield (eqn (2), Scheme 3) In case of β-enamino ketone, the enolate ion formed after Michael addition may be difficult to attack to another β-enamino ketone due to its weaker Michael acceptor ability compared to to β-enamino ester. In addition, the reaction of aniline (**1l**), not containing nitrogen atoms in the benzene ring, with **2a** did not form annulation product **8**, and uncyclized adduct **9** was obtained in 21% yield. Interestingly, further reaction of **9** under standard conditions gave no annulation product **8** (eqn (3), Scheme 3).

Based on the above results, the mechanism for the formation of **3a** is proposed in Scheme 4. In the first step, Michael addition of **1a** to complex **2a′**, generated from **2a** in the presence of a Cu-catalyst, gives intermediate **10**, which subsequently undergoes further Michael addition to another molecule of **2a′** to form intermediate **11**. Elimination of two dimethylamine molecules gives intermediate **6**, which was isolated from the control experiment. Isomerization of **6** in the presence of the Cu



Scheme 4 Proposed reaction mechanism for the formation of **3a**.

catalyst generates copper complex **12**, which is cyclized by intramolecular nucleophilic addition of the amino group to the electrophilic carbonyl carbon to yield final product **3a**. In case of aniline, formation of Cu-complex is not possible due to the absence of coordinating N-atom in the ring. Therefore, only uncyclized product **9** was formed instead of annulated product **8** (eqn (3), Scheme 3).

Conclusions

In conclusion, we have developed a highly efficient $Cu(OTf)_2$-catalyzed one-pot protocol for the synthesis of diversely functionalized *N*-heteroaryl-2-pyridones starting from readily available 2-aminopyridines and β-enamino esters *via* [3+2+1] annulation. This methodology provides a novel synthetic approach for the construction of 2-pyridone derivatives bearing a variety of functional groups on the ring, and has several advantages such as one-pot operation, functional group tolerance, broad substrate scope, and mild reaction conditions.

Experimental

All reagents and solvents were purchased at the highest commercial quality and used without further purification. All the reactions were performed in oven-dried glassware with magnetic stirring. Merck, pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC and were visualized with a UV lamp. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR spectra were recorded on Varian VNS or Bruker DPX (600 or 300 MHz, respectively) spectrometers and the chemical shifts were described in parts per million (δ) relative to TMS (0 ppm) as internal standard or relative to the resonance of the residual protonated solvent (^{1}H: $CDCl_3$, δ = 7.24 ppm). ^{13}C NMR spectra were obtained at 150 MHz or 75 MHz spectrometers and referenced to the internal solvent signals (^{13}C: $CDCl_3$, δ = 77.0 ppm). IR spectra were recorded on a PerkinElmer Spectrum Two™ IR spectrometer. Melting points were measured with a Fisher Johns melting point apparatus and uncorrected. The high-resolution mass spectra (HRMS) were measured using a JEOL JMS-600 mass spectrometer (positive ion EI mode) at the Korean Basic Science Institute.

General procedure for synthesis of compounds 3, 4 and 5

To a solution of heterocyclic amino compounds **1** (1.0 mmol) and β-enamino esters **2** (2.0 eq.) in toluene (5.0 mL) was added copper trifluoromethanesulfonate (10 mol%). The mixture was stirred and refluxed for 10 h. After completion of reaction as indicated by TLC, the reaction mixture was evaporated in rotary evaporator and the residue was purified on a silica gel column chromatography using hexane/ethyl acetate as eluent to afford the desired product.

Characterization data of synthesized compounds 3, 4 and 5

Methyl 2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3a). Yield 72% (165 mg) as a white solid: m.p. 161–163 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (1H, d, J = 2.4 Hz), 8.58 (1H, d, J = 4.2 Hz),

7.90–7.87 (2H, m), 7.85–7.83 (1H, m), 7.35 (1H, t, J = 6.0 Hz), 6.60 (1H, d, J = 10.2 Hz), 3.85 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 161.8, 151.0, 149.1, 141.6, 139.0, 137.9, 123.7, 121.2, 121.0, 110.3, 52.1; IR (neat) 3067, 1720, 1667, 1591, 1544, 1434, 1300, 1258, 1235, 1111, 967, 832, 763 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{10}N_2O_3$: 230.0691. Found: 230.0689.

Ethyl 2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3b). Yield 75% (184 mg) as a white solid: m.p. 120–122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (1H, d, J = 2.4 Hz), 8.60 (1H, s), 7.90 (1H, dd, J = 7.2, 2.4 Hz), 7.88–7.83 (2H, m), 7.36 (1H, t, J = 6.6 Hz), 6.60 (1H, d, J = 9.6 Hz), 4.31 (2H, q, J = 7.2 Hz) 1.33 (3H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 161.8, 151.1, 149.0, 141.5, 139.2, 137.9, 123.7, 121.4, 120.9, 110.7, 61.1, 14.3; IR (neat) 3067, 2994, 1679, 1543, 1436, 1303, 1270, 1108, 1017, 838, 765 cm^{-1}; HRMS m/z (M^+) calcd for $C_{13}H_{12}N_2O_3$: 244.0848. Found: 244.0849.

3-Methylbut-2-en-1-yl 2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3c). Yield 54% (154 mg) as a white solid: m.p. 111–113 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (1H, s), 8.58 (1H, d, J = 4.8 Hz), 7.90 (1H, dd, J = 10.2, 1.8 Hz), 7.89–7.82 (2H, m), 7.36–7.34 (1H, m), 6.59 (1H, d, J = 10.2 Hz), 5.40–5.37 (1H, m), 4.75 (2H, d, J = 7.8 Hz), 1.75 (3H, s), 1.72 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 161.8, 151.1, 149.1, 141.5, 139.4, 139.2, 137.8, 123.7, 121.3, 120.8, 118.3, 110.7, 61.9, 25.7, 18.0; IR (neat) 3051, 2978, 1672, 1543, 1434, 1298, 1254, 1103, 959, 835, 754 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{16}N_2O_3$: 284.1161. Found: 284.1158.

Benzyl 2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3d). Yield 65% (199 mg) as a white solid: m.p. 91–93 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (1H, d, J = 2.4 Hz), 8.56 (1H, d, J = 4.8 Hz), 7.91 (1H, dd, J = 9.6, 2.4 Hz), 7.85–7.81 (2H, m), 7.39–7.30 (6H, m), 6.60 (1H, d, J = 9.6 Hz), 5.30 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 161.7, 151.0, 149.1, 141.8, 139.1, 137.8, 135.6, 128.5, 128.38, 128.32, 123.7, 121.2, 120.9, 110.3, 66.7; IR (neat) 3061, 2924, 1677, 1544, 1437, 1298, 1254, 1103, 959, 835, 754 cm^{-1}; HRMS m/z (M^+) calcd for $C_{18}H_{14}N_2O_3$: 306.1004. Found: 306.1003.

Naphthalen-2-yl 2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3e). Yield 49% (167 mg) as a white solid: m.p. 185–187 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98 (1H, d, J = 2.4 Hz), 8.61 (1H, d, J = 4.2 Hz), 8.05 (1H, dd, J = 9.6, 2.4 Hz), 7.93 (1H, d, J = 8.4 Hz), 7.89–7.84 (3H, m), 7.80 (1H, d, J = 7.8 Hz), 7.63 (1H, d, J = 1.8 Hz), 7.50–7.45 (2H, m), 7.39–7.37 (1H, m), 7.30 (1H, dd, J = 9.0, 2.4 Hz), 6.70 (1H, d, J = 9.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0, 161.8, 151.0, 149.2, 148.1, 142.6, 139.1, 138.0, 133.7, 131.5, 129.5, 127.8, 127.6, 126.6, 125.8, 123.9, 121.3, 121.2, 121.0, 118.6, 109.8; IR (neat) 3067, 2922, 2857, 1728, 1693, 1535, 1464, 1430, 1205, 1151, 1071, 750 cm^{-1}; HRMS m/z (M^+) calcd for $C_{21}H_{14}N_2O_3$: 342.1004. Found: 342.1002.

Methyl 4′-(benzyloxy)-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3f). Yield 57% (193 mg) as a white solid: m.p. 127–129 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (1H, d, J = 1.8 Hz), 8.16 (1H, d, J = 4.8 Hz), 7.88 (1H, dd, J = 9.0, 1.8 Hz), 7.38 (1H, d, J = 8.4 Hz), 7.34–7.32 (1H, m), 7.31–7.29 (4H, m), 7.27–7.25 (1H, m), 6.58 (1H, d, J = 9.0 Hz), 5.15 (1H, d, J = 12.0 Hz), 5.11 (1H, d, J = 12.0 Hz), 3.80 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 161.2, 149.8, 142.7, 142.5, 140.8, 139.0, 135.4, 128.6, 128.1, 126.9, 125.7, 122.1, 120.3, 109.7, 70.9, 51.9; IR (neat) 3060, 2950, 1707, 1666, 1438, 1375, 1277, 1239, 1099, 1001, 844, 741 cm^{-1}; HRMS m/z (M^+) calcd for $C_{19}H_{16}N_2O_4$: 336.1110. Found: 336.1109.

Ethyl 4′-(benzyloxy)-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3g). Yield 66% (230 mg) as a white solid: m.p. 129–131 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (1H, d, J = 2.4 Hz), 8.16 (1H, d, J = 3.6 Hz), 7.90 (1H, dd, J = 9.6, 2.4 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.35–7.32 (1H, m), 7.31–7.29 (4H, m), 7.27–7.25 (1H, m), 6.59 (1H, d, J = 9.6 Hz), 5.15 (1H, d, J = 12.0 Hz), 5.11 (1H, d, J = 12.0 Hz) 4.27 (2H, q, J = 7.2 Hz), 1.30 (3H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 161.3, 149.8, 142.5 (*2C), 140.8, 139.1, 135.4, 128.6, 128.1, 126.9, 125.7, 122.1, 120.2, 110.0, 70.9, 60.9, 14.2; IR (neat) 3067, 2825, 1666, 1438, 1375, 1277, 1239, 1099, 1001, 845, 771 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{18}N_2O_4$: 350.1267. Found: 350.1267.

Methyl 4′-methyl-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3h). Yield 70% (172 mg) as a white solid: m.p. 156–158 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (1H, s), 8.40 (1H, t, J = 4.8 Hz), 7.88–7.85 (1H, m), 7.64 (1H, s), 7.15 (1H, s), 6.58 (1H, dd, J = 9.0, 3.6 Hz) 3.83 (3H, s), 2.41 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 161.8, 151.2, 149.6, 148.7, 141.8, 138.9, 124.8, 121.8, 120.9, 110.2, 52.0, 21.1; IR (neat) 2961, 1722, 1677, 1545, 1436, 1265, 1100, 960, 836, 763 cm^{-1}; HRMS m/z (M^+) calcd for $C_{13}H_{12}N_2O_3$: 244.0848. Found: 244.0845.

Ethyl 4′-methyl-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3i). Yield 76% (196 mg) as a white solid: m.p. 110–112 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (1H, d, J = 3.0 Hz), 8.39 (1H, d, J = 4.8 Hz), 7.86 (1H, dd, J = 10.2, 2.4 Hz), 7.61 (1H, s), 7.13 (1H, d, J = 4.8 Hz), 6.56 (1H, d, J = 10.2 Hz), 4.27 (2H, q, J = 7.2 Hz), 2.39 (3H, s), 1.29 (3H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 161.8, 151.2, 149.5, 148.6, 141.6, 138.9, 124.8, 121.8, 120.7, 110.4, 60.9, 21.0, 14.2; IR (neat) 3108, 2996, 1725, 1675, 1542, 1295, 1253, 1167, 1105, 1028, 827, 761 cm^{-1}; HRMS m/z (M^+) calcd for $C_{14}H_{14}N_2O_3$: 258.1004. Found: 258.1006.

3-Methylbut-2-en-1-yl 4′-methyl-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3j). Yield 61% (182 mg) as a white solid: m.p. 81–83 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (1H, d, J = 3.0 Hz), 8.39 (1H, d, J = 5.4 Hz), 7.89 (1H, dd, J = 9.6, 2.4 Hz), 7.63 (1H, s), 7.16 (1H, d, J = 5.4 Hz), 6.59 (1H, d, J = 9.6 Hz), 5.39–5.36 (1H, m), 4.74 (2H, d, J = 7.2 Hz), 2.42 (3H, s), 1.74 (3H, s), 1.72 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 161.9, 151.3, 149.7, 148.7, 141.7, 139.4, 139.1, 124.9, 121.9, 120.8, 118.4, 110.6, 61.9, 25.7, 21.1, 18.0; IR (neat) 2971, 1676, 1606, 1439, 1374, 1300, 1260, 1093, 839, 766 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{18}N_2O_3$: 298.1317. Found: 298.1319.

Benzyl 4′-methyl-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3k). Yield 69% (221 mg) as a white solid: m.p. 119–121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (1H, d, J = 2.4 Hz), 8.40 (1H, d, J = 5.4 Hz), 7.90 (1H, dd, J = 9.6, 1.8 Hz), 7.62 (1H, s), 7.38–7.31 (5H, m), 7.15 (1H, d, J = 4.8 Hz), 6.59 (1H, d, J = 9.6 Hz), 5.29(2H, s), 2.41 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 161.8, 151.2, 149.6, 148.7, 142.0, 139.0, 135.6, 128.5, 128.3, 128.3, 124.9, 121.8, 120.8, 110.1, 66.7, 21.1; IR (neat) 3025, 2969, 1723, 1680, 1544, 1437, 1370, 1258, 1091, 835, 759 cm^{-1}; HRMS m/z (M^+) calcd for $C_{19}H_{16}N_2O_3$: 320.1161. Found: 320.1164.

Methyl 4′-methoxy-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3l). Yield 75% (194 mg) as a white solid: m.p. 150–152 °C;

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (1H, d, J = 2.4 Hz), 8.37 (1H, d, J = 5.7 Hz), 7.89 (1H, dd, J = 9.6, 2.7 Hz), 7.39 (1H, d, J = 2.1 Hz), 6.88 (1H, dd, J = 5.7, 2.1 Hz), 6.60 (1H, d, J = 9.6 Hz), 3.89 (3H, s), 3.85 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 164.6, 161.8, 152.5, 149.7, 141.7, 139.0, 121.0, 110.9, 110.2, 106.8, 55.7, 52.1; IR (neat) 3088, 2956, 1724, 1677, 1547, 1436, 1312, 1267, 1098, 1026, 833, 763 cm^{-1}; HRMS m/z (M^+) calcd for $C_{13}H_{12}N_2O_4$: 260.0797. Found: 260.0796.

Methyl 4′,6′-dimethyl-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3m). Yield 76% (196 mg) as a white solid: m.p. 175–177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (1H, d, J = 2.4 Hz), 7.85 (1H, dd, J = 9.6, 2.4 Hz), 7.38 (1H, s), 7.01 (1H, s), 6.56 (1H, d, J = 9.6 Hz), 3.83 (3H, s), 2.51 (3H, s), 2.36 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 161.9, 158.3, 150.5, 149.7, 142.0, 138.8, 124.4, 120.8, 118.8, 110.0, 52.0, 23.9, 20.9; IR (neat) 2924, 1694, 1546, 1439, 1365, 1276, 1217, 1103, 843, 765 cm^{-1}; HRMS m/z (M^+) calcd for $C_{14}H_{14}N_2O_3$: 258.1004. Found: 258.1003.

Ethyl 4′,6′-dimethyl-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3n). Yield 72% (195 mg) as a white solid: m.p. 105–107 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (1H, d, J = 1.8 Hz), 7.87 (1H, dd, J = 10.2, 2.4 Hz), 7.37 (1H, s), 7.02 (1H, s), 6.57 (1H, d, J = 9.6 Hz), 4.30 (2H, q, J = 7.2 Hz), 2.52 (3H, s), 2.36 (3H, s), 1.32 (3H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 161.9, 158.3, 150.6, 149.7, 141.9, 138.9, 124.4, 120.7, 118.9, 110.3, 61.0, 23.9, 20.9, 14.3; IR (neat) 2973, 1718, 1659, 1609, 1440, 1370, 1252, 1111, 857, 769 cm^{-1}; HRMS m/z (M^+) calcd for $C_{15}H_{16}N_2O_3$: 272.1161. Found: 272.1162.

3-Methylbut-2-en-1-yl 4′,6′-dimethyl-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3o). Yield 69% (215 mg) as a white solid: m.p. 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (1H, d, J = 2.4 Hz), 7.86 (1H, dd, J = 9.6, 2.7 Hz), 7.34 (1H, s), 7.01 (1H, s), 6.55 (1H, d, J = 9.6 Hz), 5.36 (1H, t, J = 7.2 Hz), 4.72 (2H, d, J = 7.2 Hz), 2.50 (3H, s), 2.34 (3H, s), 1.72 (3H, s), 1.70 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 161.9, 158.2, 150.5, 149.7, 141.9, 139.3, 139.0, 124.4, 120.6, 118.9, 118.3, 110.3, 61.8, 25.7, 23.9, 20.9, 18.0; IR (neat) 2971, 1740, 1538, 1438, 1369, 1268, 1097, 941, 844, 767 cm^{-1}; HRMS m/z (M^+) calcd for $C_{18}H_{20}N_2O_3$: 312.1474. Found: 312.1473.

Benzyl 4′,6′-dimethyl-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3p). Yield 78% (261 mg) as a white solid: m.p. 136–138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (1H, d, J = 1.8 Hz), 7.89 (1H, dd, J = 9.6, 2.4 Hz), 7.38–7.30 (6H, m), 7.01 (1H, s), 6.57 (1H, d, J = 9.6 Hz), 5.28 (2H, s), 2.50 (3H, s), 2.35 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 161.8, 158.2, 150.4, 149.6, 142.1, 138.8, 135.5, 128.4, 128.2, 128.1, 124.4, 120.6, 118.8, 109.9, 66.6, 23.8, 20.9; IR (neat) 3029, 1739, 1612, 1547, 1439, 1368, 1273, 1217, 1108, 846, 767 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{18}N_2O_3$: 334.1317. Found: 334.1315.

Methyl 4′-chloro-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3q). Yield 53% (141 mg) as a white solid: m.p. 184–186 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (1H, d, J = 2.4 Hz), 8.47 (1H, d, J = 5.4 Hz), 7.99 (1H, s), 7.89 (1H, dd, J = 9.6, 2.4 Hz), 7.35 (1H, d, J = 5.4 Hz), 6.60 (1H, d, J = 9.6 Hz), 3.85 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 161.5 151.7, 149.4, 145.5, 141.1, 139.1, 124.1, 121.6, 121.1, 110.6, 52.2; IR (neat) 3065, 2966, 1723, 1678, 1579, 1433, 1404, 1304, 1257, 1110, 835, 761 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_9ClN_2O_3$: 264.0302. Found: 264.0303.

Ethyl 4′-chloro-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3r). Yield 59% (165 mg) as a white solid: m.p. 164–166 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (1H, d, J = 2.4 Hz), 8.47 (1H, d, J = 5.4 Hz), 7.97 (1H, s), 7.89 (1H, dd, J = 9.6, 2.4 Hz), 7.35 (1H, d, J = 4.8 Hz), 6.59 (1H, d, J = 9.6 Hz), 4.31 (2H, q, J = 7.2 Hz), 1.33 (3H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 161.6, 151.8, 149.4, 145.5, 141.0, 139.2, 124.1, 121.7, 121.0, 110.9, 61.2, 14.2; IR (neat) 3094, 2989, 1720, 1677, 1545, 1393, 1307, 1267, 1107, 1018, 830, 766 cm^{-1}; HRMS m/z (M^+) calcd for $C_{13}H_{11}ClN_2O_3$: 278.0458. Found: 278.0459.

3-Methylbut-2-en-1-yl 4′-chloro-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3s). Yield 45% (145 mg) as a white solid: m.p. 124–126 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (1H, d, J = 2.4 Hz), 8.48 (1H, d, J = 4.8 Hz), 7.96 (1H, d, J = 1.2 Hz), 7.90 (1H, dd, J = 10.2, 2.4 Hz), 7.36 (1H, dd, J = 5.4, 1.8 Hz), 6.60 (1H, d, J = 10.2 Hz), 5.39 (1H, t, J = 7.2 Hz), 4.76 (2H, d, J = 7.8 Hz), 1.75 (3H, s), 1.73 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 161.6, 151.8, 149.5, 145.5, 141.0, 139.6, 139.3, 124.2, 121.7, 121.0, 118.2, 111.0, 62.1, 25.7, 18.1; IR (neat) 3072, 2979, 1690, 1580, 1402, 1299, 1263, 1101, 956, 827, 766 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{15}ClN_2O_3$: 318.0771. Found: 318.0774.

Benzyl 4′-chloro-2-oxo-2*H*-[1,2′-bipyridine]-5-carboxylate (3t). Yield 55% (188 mg) as a white solid: m.p. 105–107 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (1H, s), 8.46 (1H, d, J = 5.4 Hz), 7.96 (1H, s), 7.91 (1H, dd, J = 9.6, 2.4 Hz), 7.39–7.31 (6H, m), 6.60 (1H, d, J = 9.6 Hz), 5.30 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 161.5, 151.7, 149.5, 145.5, 141.3, 139.2, 135.5, 128.6, 128.4, 128.3, 124.2, 121.7, 121.1, 110.6, 66.9; IR (neat) 3072, 2930, 1681, 1578, 1402, 1303, 1263, 1102, 831 cm^{-1}; HRMS m/z (M^+) calcd for $C_{18}H_{13}ClN_2O_3$: 340.0615. Found: 340.0611.

Methyl 6-oxo-1-(quinolin-2-yl)-1,6-dihydropyridine-3-carboxylate (4a). Yield 73% (204 mg) as a white solid: m.p. 203–205 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.83 (1H, s), 8.27 (1H, d, J = 9.0 Hz), 8.08 (1H, d, J = 9.0 Hz), 7.93 (1H, dd, J = 9.0, 1.2 Hz), 7.90–7.87 (2H, m), 7.75 (1H, t, J = 7.2 Hz), 7.60 (1H, d, J = 7.2 Hz), 6.64 (1H, d, J = 9.6 Hz), 3.87 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 162.1, 150.9, 147.0 141.9, 139.3, 137.9, 130.3, 129.0, 127.7, 127.58, 127.54, 121.0, 118.9, 110.5, 52.1; IR (neat) 2986, 2897, 1725, 1672, 1587, 1502, 1435, 1264, 1107, 1008, 832, 753 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{12}N_2O_3$: 280.0848. Found: 280.0847.

Ethyl 6-oxo-1-(quinolin-2-yl)-1,6-dihydropyridine-3-carboxylate (4b). Yield 83% (244 mg) as a white solid: m.p. 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, d, J = 2.4 Hz), 8.25 (1H, d, J = 8.7 Hz), 8.08 (1H, d, J = 8.4 Hz), 7.95–7.85 (3H, m), 7.74 (1H, t, J = 7.2 Hz), 7.60 (1H, t, J = 7.2 Hz), 6.62 (1H, d, J = 9.6 Hz), 4.33 (2H, q, J = 7.2 Hz), 1.34 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 162.1, 151.0, 147.1, 141.7, 139.3, 137.9, 130.2, 129.1, 127.8, 127.5 (*2C), 121.0, 119.0, 110.9, 61.1, 14.3; IR (neat) 2986, 2900, 1726, 1670, 1587, 1500, 1433, 1260, 1102, 1028, 827, 756 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{14}N_2O_3$: 294.1004. Found: 294.1006.

3-Methylbut-2-en-1-yl 6-oxo-1-(quinolin-2-yl)-1,6-dihydropyridine-3-carboxylate (4c). Yield 68% (228 mg) as a white solid: m.p. 139–141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (1H, s), 8.27 (1H, d, J = 9.0 Hz), 8.08 (1H, d, J = 9.0 Hz), 7.96–7.94 (1H, m), 7.89–7.86 (2H, m), 7.76 (1H, t, J = 7.2 Hz), 7.61 (1H, t, J = 7.2 Hz),

6.63 (1H, d, J = 9.0 Hz), 5.41–5.38 (1H, m), 4.77 (2H, d, J = 6.6 Hz), 1.74 (3H, s), 1.73 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 162.2, 150.9, 147.0, 141.8, 139.55, 139.52, 137.9, 130.3, 129.0, 127.7, 127.58, 127.55, 120.9, 119.0, 118.3, 110.9, 62.0, 25.7, 18.0; IR (neat) 2969, 1722, 1672, 1591, 1500, 1385, 1261, 1113, 942, 830, 755 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{18}N_2O_3$: 334.1317. Found: 334.1315.

Benzyl 6-oxo-1-(quinolin-2-yl)-1,6-dihydropyridine-3-carboxylate (4d). Yield 82% (293 mg) as a white solid: m.p. 169–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 (1H, d, J = 2.4 Hz), 8.25 (1H, d, J = 8.4 Hz), 8.06 (1H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 10.2, 2.4 Hz), 7.88–7.86 (2H, m), 7.74 (1H, t, J = 7.8 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.40 (2H, d, J = 6.6 Hz), 7.35 (2H, t, J = 7.2 Hz), 7.32 (1H, d, J = 7.2 Hz), 6.63 (1H, d, J = 10.2 Hz), 5.32 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 162.0, 150.8, 147.0, 142.0, 139.3, 137.9, 135.6, 130.2, 129.0, 128.5, 128.3, 128.2, 127.7, 127.5, 127.4, 121.0, 118.9, 110.5, 66.7; IR (neat) 2926, 1721, 1676, 1547, 1435, 1366, 1272, 1103, 832, 759 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{16}N_2O_3$: 356.1161. Found: 356.1160.

Methyl 1-(isoquinolin-3-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (4e). Yield 71% (198 mg) as a white solid: m.p. 183–185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.18 (1H, s), 8.78 (1H, s), 8.22 (1H, s), 7.98 (1H, d, J = 8.4 Hz), 7.87–7.85 (2H, m), 7.70 (1H, t, J = 7.2 Hz), 7.61 (1H, t, J = 7.2 Hz), 6.61 (1H, d, J = 9.6 Hz), 3.81 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 162.0, 152.1, 145.3, 142.2, 138.7, 136.7, 131.2, 128.27, 128.22, 127.4, 127.3, 120.9, 117.5, 110.2, 52.0; IR (neat) 3052, 2966, 1716, 1680, 1613, 1544, 1447, 1302, 1267, 1101, 948, 837, 746 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{12}N_2O_3$: 280.0848. Found: 280.0845.

Ethyl 1-(isoquinolin-3-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (4f). Yield 76% (225 mg) as a white solid: m.p. 126–128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.20 (1H, s), 8.77 (1H, d, J = 2.4 Hz), 8.22 (1H, s), 7.99 (1H, d, J = 7.8 Hz), 7.90 (1H, dd, J = 9.0, 2.4 Hz), 7.87 (1H, d, J = 8.4 Hz), 7.71 (1H, t, J = 7.8 Hz), 7.62 (1H, t, J = 7.8 Hz), 6.63 (1H, d, J = 9.6 Hz), 4.30 (2H, q, J = 7.2 Hz), 1.31 (3H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 161.9, 152.1, 145.3, 142.0, 138.7, 136.6, 131.1, 128.19, 128.13, 127.3, 127.2, 120.7, 117.5, 110.4, 60.9, 14.2; IR (neat) 3062, 2989, 1713, 1668, 1543, 1443, 1389, 1292, 1243, 1167, 1100, 1014, 846, 750 419 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{14}N_2O_3$: 294.1004. Found: 294.1005.

3-Methylbut-2-en-1-yl 1-(isoquinolin-3-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (4g). Yield 67% (224 mg) as a white solid: m.p. 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (1H, s), 8.77 (1H, d, J = 2.4 Hz), 8.22 (1H, s), 7.99 (1H, d, J = 8.1 Hz), 7.92–7.86 (2H, m), 7.72 (1H, td, J = 6.9, 1.2 Hz), 7.62 (1H, td, J = 6.9, 1.2 Hz), 6.63 (1H, d, J = 9.6 Hz), 5.40–5.35 (1H, m), 4.75 (2H, d, J = 7.2 Hz), 1.73 (3H, s), 1.71 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 162.0, 152.1, 145.4, 142.1, 139.3, 138.8, 136.6, 131.1, 128.2, 128.1, 127.3, 127.2, 120.7, 118.3, 117.5, 110.5, 61.8, 25.6, 18.0; IR (neat) 2938, 1676, 1542, 1441, 1372, 1250, 1168, 1094, 937, 837, 753 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{18}N_2O_3$: 334.1317. Found: 334.1317.

Benzyl 1-(isoquinolin-3-yl)-6-oxo-1,6-dihydropyridine-3-carboxylate (4h). Yield 80% (284 mg) as a white solid: m.p. 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (1H, s), 8.80 (1H, s), 8.20 (1H, s), 7.99–7.85 (3H, m), 7.71 (1H, t, J = 6.9 Hz), 7.62 (1H, t, J = 6.9 Hz), 7.37–7.29 (5H, m), 6.64 (1H, d, J = 9.6 Hz), 5.29 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 161.8, 152.1, 145.1, 142.3, 138.7, 136.4, 135.5, 131.1, 128.4, 128.29, 128.24, 128.1, 128.0, 127.3, 127.2, 120.7, 117.5, 110.0, 66.6; IR (neat) 3032, 1718, 1677, 1544, 1442, 1301, 1259, 1105, 950, 834, 742 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{16}N_2O_3$: 356.1161. Found: 356.1163.

Methyl 6-oxo-1-(pyridazin-3-yl)-1,6-dihydropyridine-3-carboxylate (5a). Yield 43% (99 mg) as a white solid: m.p. 192–194 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (1H, d, J = 4.8 Hz), 8.89 (1H, d, J = 2.4 Hz), 8.18 (1H, d, J = 9.0 Hz), 7.96 (1H, dd, J = 10.2, 2.4 Hz), 7.64 (1H, dd, J = 9.0, 4.8 Hz), 6.63 (1H, d, J = 9.0 Hz), 3.86 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 161.5, 155.5, 151.4, 141.0, 140.0, 127.4, 125.5, 120.9, 111.1, 52.2; IR (neat) 3072, 2963, 1676, 1435, 1273, 1101, 831, 761 cm^{-1}; HRMS m/z (M^+) calcd for $C_{11}H_9N_3O_3$: 231.0644. Found: 231.0646.

Ethyl 6-oxo-1-(pyridazin-3-yl)-1,6-dihydropyridine-3-carboxylate (5b). Yield 54% (133 mg) as a white solid: m.p. 175–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (1H, d, J = 4.2 Hz), 8.87 (1H, d, J = 2.4 Hz), 8.17 (1H, d, J = 8.7 Hz), 7.98 (1H, dd, J = 9.6, 2.4 Hz), 7.65 (1H, dd, J = 8.7, 4.8 Hz), 6.64 (1H, d, J = 9.6 Hz), 4.33 (2H, q, J = 7.2 Hz), 1.34 (3H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.8, 161.5, 155.5, 151.4, 140.8, 140.1, 127.4, 125.6, 120.8, 111.4, 61.3, 14.2; IR (neat) 3095, 2993, 1723, 1678, 1433, 1362, 1277, 1103, 831, 764 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{11}N_3O_3$: 245.0800. Found: 245.0803.

3-Methylbut-2-en-1-yl 6-oxo-1-(pyridazin-3-yl)-1,6-dihydropyridine-3-carboxylate (5c). Yield 32% (92 mg) as a brown solid: m.p. 80–82 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (1H, d, J = 4.8 Hz), 8.86 (1H, d, J = 2.4 Hz), 8.16 (1H, d, J = 7.8 Hz), 7.97 (1H, dd, J = 9.6, 2.4 Hz), 7.64 (1H, dd, J = 9.0, 4.8 Hz), 6.63 (1H, d, J = 9.6 Hz), 5.38 (1H, t, J = 7.2 Hz), 4.76 (2H, d, J = 7.2 Hz), 1.75 (3H, s), 1.73 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 161.5, 155.5, 151.5, 140.9, 140.2, 139.8, 127.4, 125.5, 120.8, 118.1, 111.5, 62.1, 25.7, 18.0; IR (neat) 3085, 2927, 1705, 1674, 1436, 1277, 1109, 931, 766 cm^{-1}; HRMS m/z (M^+) calcd for $C_{15}H_{15}N_3O_3$: 285.1113. Found: 285.1112.

Benzyl 6-oxo-1-(pyridazin-3-yl)-1,6-dihydropyridine-3-carboxylate (5d). Yield 37% (115 mg) as a brown semi solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.21 (1H, dd, J = 4.8, 1.5 Hz), 8.87 (1H, d, J = 2.4 Hz), 8.14 (1H, dd, J = 8.7, 1.5 Hz), 7.99 (1H, dd, J = 9.6, 2.4 Hz), 7.63 (1H, dd, J = 8.7, 4.8 Hz), 7.37–7.36 (5H, m), 6.63 (1H, d, J = 9.6 Hz), 5.30 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 161.5, 151.5, 141.1, 140.1, 135.4, 128.66, 128.61, 128.5, 128.4, 127.4, 125.5, 120.9, 111.1, 67.0; IR (neat) 3062, 2929, 1720, 1674, 1432, 1275, 1099, 829, 746 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{13}N_3O_3$: 307.0957. Found: 307.0956.

Methyl 6-oxo-1-(pyrazin-2-yl)-1,6-dihydropyridine-3-carboxylate (5e). Yield 53% (123 mg) as white solid: m.p. 142–144 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.29 (1H, s), 8.70 (1H, d, J = 2.4 Hz), 8.62 (1H, d, J = 1.8 Hz), 8.56 (1H, t, J = 1.8 Hz), 7.92 (1H, dd, J = 9.6, 2.4 Hz), 6.63 (1H, d, J = 9.6 Hz), 3.86 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 161.4, 147.6, 143.8, 143.1, 143.0, 140.6, 139.5, 121.1, 111.2, 52.2; IR (neat) 3072, 2956, 1727, 1678, 1413, 1309, 1258, 1106, 1014, 841, 763 cm^{-1}; HRMS m/z (M^+) calcd for $C_{11}H_9N_3O_3$: 231.0644. Found: 231.0641.

Ethyl 6-oxo-1-(pyrazin-2-yl)-1,6-dihydropyridine-3-carboxylate (5f). Yield 61% (149 mg) as white solid: m.p. 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (1H, s), 8.68 (1H, d, J = 2.1 Hz), 8.62 (1H, s), 8.57 (1H, s), 7.92 (1H, dd, J = 9.6, 2.4 Hz), 6.63 (1H, d, J = 9.6 Hz), 4.32 (2H, q, J = 7.2 Hz), 1.33 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 161.5, 143.7, 143.1, 143.0, 140.5, 139.6, 137.6, 121.0, 111.5, 61.3, 14.2; IR (neat) 3095, 2995, 1715, 1657, 1472, 1398, 1250, 1131, 1012, 836, 760 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{11}N_3O_3$: 245.0800. Found: 245.0797.

Benzyl 6-oxo-1-(pyrazin-2-yl)-1,6-dihydropyridine-3-carboxylate (5g). Yield 51% (158 mg) as a brown semi solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (1H, d, J = 1.2 Hz), 8.71 (1H, d, J = 2.4 Hz), 8.61 (1H, d, J = 2.4 Hz), 8.56–8.54 (1H, m), 7.94 (1H, dd, J = 9.6, 2.4 Hz), 7.40–7.30 (5H, m), 6.63 (1H, d, J = 9.9 Hz), 5.31 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 161.4, 147.5, 143.8, 143.1, 142.9, 140.8, 139.5, 135.3, 128.5, 128.4, 128.3, 121.0, 111.1, 66.9; IR (neat) 3064, 1714, 1672, 1407, 1299, 1237, 1099, 839, 746 cm^{-1}; HRMS m/z (M^+) calcd for $C_{17}H_{13}N_3O_3$: 307.0957. Found: 307.0955.

Methyl 6-oxo-1-(pyrimidin-2-yl)-1,6-dihydropyridine-3-carboxylate (5h). Yield 58% (134 mg) as a white solid: m.p. 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (2H, d, J = 5.1 Hz), 8.49 (1H, d, J = 2.4 Hz), 7.89 (1H, dd, J = 9.6, 2.4 Hz), 7.42 (1H, t, J = 4.8 Hz), 6.64 (1H, d, J = 9.6 Hz), 3.85 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 161.4, 159.2 (*2C), 158.7, 141.4, 139.0, 121.5, 120.9, 110.0, 52.1; IR (neat) 2923, 1685, 1571, 1405, 1254, 1108, 832, 763 cm^{-1}; HRMS m/z (M^+) calcd for $C_{11}H_9N_3O_3$: 231.0644. Found: 231.0647.

Ethyl 6-oxo-1-(pyrimidin-2-yl)-1,6-dihydropyridine-3-carboxylate (5i). Yield 55% (135 mg) as a white solid: m.p. 146–148 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89 (2H, d, J = 4.8 Hz), 8.46 (1H, d, J = 2.4 Hz), 7.89 (1H, dd, J = 9.0, 2.4 Hz), 7.22 (1H, t, J = 4.8 Hz), 6.62 (1H, d, J = 9.0 Hz), 4.30 (2H, q, J = 7.2 Hz), 1.32 (3H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 161.4, 159.2, 158.7, 141.2, 139.1, 121.4, 120.9, 110.3, 61.1, 14.2; IR (neat) 3049, 2988, 1698, 1573, 1405, 1262, 1109, 846, 764 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{11}N_3O_3$: 245.0800. Found: 245.0799.

Dimethyl (2*E*,4*E*)-4-((pyridin-2-ylamino)methylene)pent-2-enedioate (6). Yield 58% (151 mg) as a white solid: m.p. 128–130 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.83 (1H, d, J = 12.0 Hz), 8.53 (1H, d, J = 12.0 Hz), 8.27 (1H, d, J = 4.8 Hz), 7.59 (1H, t, J = 8.4 Hz), 7.50 (1H, d, J = 15.6 Hz), 6.95 (1H, t, J = 5.4 Hz), 6.77 (1H, d, J = 8.4 Hz), 6.21 (1H, d, J = 15.6 Hz), 3.81 (3H, s), 3.72 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 168.5, 150.5, 148.5, 145.6, 142.1, 138.4, 119.1, 111.9, 111.7, 99.8, 51.4, 51.2; IR (neat) 3281, 2952, 1709, 1664, 1606, 1558, 1430, 1285, 1189, 1151, 983 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{11}N_3O_3$: 262.0954. Found: 262.0951.

(*E*)-1-(3-Bromophenyl)-3-(pyridin-2-ylamino)prop-2-en-1-one (7). Yield 75% (228 mg) as a white solid: m.p. 118–120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.1 (1H, d, J = 10.8 Hz), 8.28 (1H, d, J = 4.8 Hz), 8.27–8.23 (1H, m), 8.05 (1H, t, J = 1.8 Hz), 7.83 (1H, d, J = 8.4 Hz), 7.61–7.58 (2H, m), 7.30 (1H, d, J = 7.8 Hz), 6.94 (1H, dd, J = 7.8, 4.2 Hz), 6.81 (1H, d, J = 8.4 Hz), 6.04 (1H, d, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.9, 151.4, 148.4, 143.5, 140.8, 138.4, 134.5, 130.5, 129.9, 125.9, 122.7, 118.7, 111.7, 94.8; IR (neat) 3070, 1627, 1542, 1474, 1429, 1270, 1222, 1146, 988, 742 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{11}N_3O_3$: 302.0055. Found: 302.0056.

Dimethyl (2*E*,4*E*)-4-((phenylamino)methylene)pent-2-enedioate (9). Yield 21% (55 mg) as a yellow solid: m.p. 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.73 (1H, d, J = 12.9 Hz), 7.73 (1H, d, J = 13.2 Hz), 7.45 (1H, d, J = 15.6 Hz), 7.34 (2H, t, J = 7.5 Hz), 7.05 (1H, d, J = 7.5 Hz), 7.05 (2H, d, J = 8.1 Hz), 6.16 (1H, d, J = 15.9 Hz), 3.83 (3H, s), 3.73 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 168.8, 148.0, 142.4, 139.2, 129.8, 124.5, 116.6, 110.6, 98.3, 51.3, 51.3; IR (neat) 3331, 2957, 1735, 1594, 1497, 1442, 1245, 1101, 756 cm^{-1}; HRMS m/z (M^+) calcd for $C_{12}H_{11}N_3O_3$: 261.1001. Found: 261.1004.

Conflicts of interest

There are no conflicts to declare.

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