ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

Divergent Annulation Modes of (*Z*)-4-Aryl-4-oxo-2-(pyridin-2-yl)but-2-enenitrile and Methyl Nitroacetate: Selective Access to 2-Acyl-4*H*-quinolizin-4-one, Isoxazole, and 2-Acylindolizine

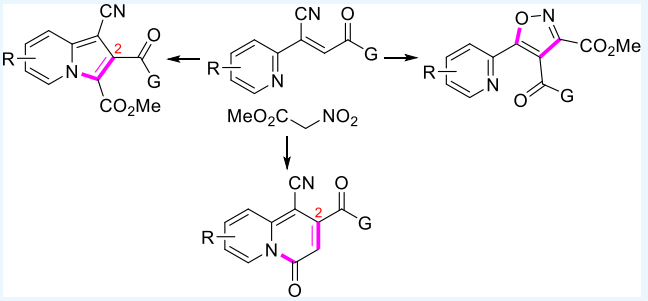
Sunhee Lee, Woojin Kim, and Ikyon Kim*

Cite This: *ACS Omega* 2024, 9, 38126−38141

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

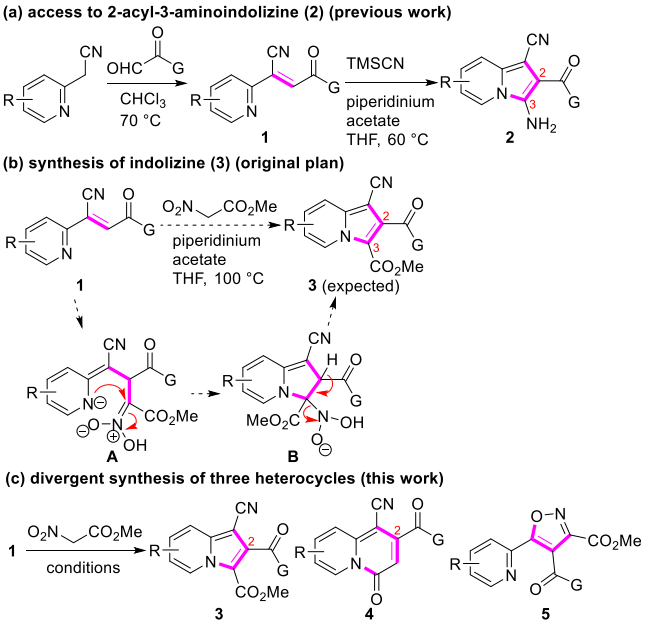
ABSTRACT: Three different annulation modes of (*Z*)-4-aryl-4-oxo-2-(pyridin-2-yl)but-2-enenitrile in the reaction with methyl nitroacetate were discovered, allowing selective access to diverse heterocycles such as quinolizin-4-one, isoxazole, and indolizine with unique substitution patterns in good yields. Ease of operation, good chemical yields, and good functional group tolerance of our protocol enabled us to rapidly construct a number of synthetic analogs based on each scaffold under three reaction conditions.



INTRODUCTION

As part of our ongoing research on annulative functionalization assembly of novel *N*-fused heterocycles,[1] we recently described a modular approach to a wide variety of 2-acyl-3-amino-indolizines **2** by way of **1** utilizing pyridine-2-acetonitrile, (hetero)arylglyoxal, and TMSCN as building blocks (Scheme 1a).[2] In order to install an ester moiety at the C3 site of the resulting indolizine **3**, methyl nitroacetate was employed instead of TMSCN (Scheme 1b). We expected that Michael addition of methyl nitroacetate to the intermediate **1** would provide **A** which would undergo cyclization to give **B**. Final loss of proton and HNO_2 from **B** would occur to afford the indolizine **3**.[3] In the course of our study with this aim, however, we discovered that three different types of compounds were obtained as major products from the reaction of **1** with methyl nitroacetate depending on the reaction conditions (Scheme 1c). Divergent approaches to several heterocycles from common intermediates are efficient ways to maximize structural diversity,[4] which can be achieved by changing either the reacting partners[5] or reaction conditions.[6] As the substitution patterns around the core skeletons synthesized in this study are unknown in the literature even if each basic structure is well-known, we decided to investigate the divergent annulation of the common intermediate **1** and methyl nitroacetate under three different reaction conditions, which we wish to describe here.

Scheme 1. Use of 1 for the Synthesis of *N*-Fused Heterocycles

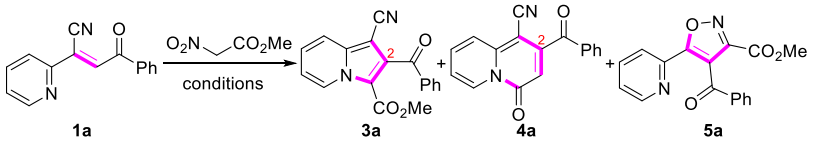


RESULTS AND DISCUSSION

From our previous experience on the synthesis of **2** from **1**, we began our optimization study with **1a**, methyl nitroacetate (1.5 equiv), and piperidinium acetate (1 equiv) in THF at 100 °C (entry 1, Table 1). Surprisingly, the anticipated indolizine **3a**

Received: June 8, 2024
Revised: August 10, 2024
Accepted: August 20, 2024
Published: August 24, 2024

Table 1. Optimization Study for the Synthesis of 4a[a]



1a 3a 4a 5a

					yield (%)[b]		
entry	catalyst (equiv)	solvent	temperature (°C)	time (h)	3a	4a	5a
1	piperidinium acetate (1)	THF	100	1	0	87	11
2	DBU (1)	THF	100	1	0	91	8
3	piperidinium acetate (1)	MeOH	100	1	0	92	7
4	Et_3N (1)	THF	100	4	0	26	60
5	Et_3N (1)	MeOH	80	2	0	16	78
6	Et_3N (1)	toluene	80	2	0	0	63
7	Et_3N (1)	toluene	60	8	0	0	86
8		THF	100	16	0	0	53
9		HFIP	25	52	55	0	4
10		HFIP	60	5	56	0	11
11		HFIP	120[c]	0.5	80	0	8

[a]A solution of **1a** (30 mg, 0.13 mmol), methyl nitroacetate (1.5 equiv), and catalyst in solvent (2 mL) was heated at the indicated temperature for the indicated time. [b]Isolated yield (%). [c]Microwave heating was used.

was not detected from the reaction mixture. Rather, **4a** (87%) and **5a** (11%) were isolated. X-ray crystallographic analysis firmly established the chemical structure of each compound (Figures 1 and 2).[7] When DBU (1 equiv) was used as a base,

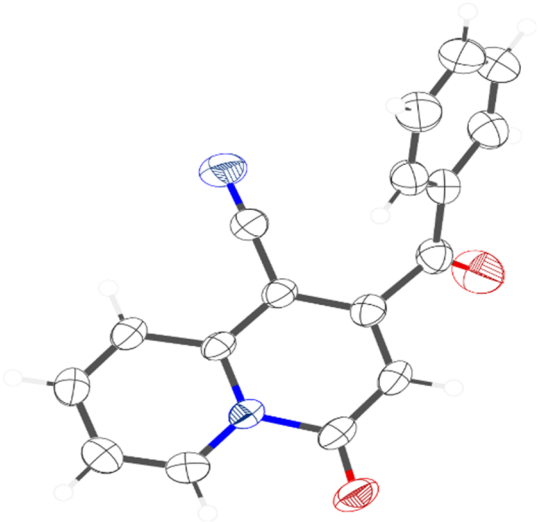


Figure 1. Chemical structure of **4a**.

the same trend was observed (entry 2). Use of MeOH as a solvent with piperidinium acetate (1 equiv) provided **4a** in 92% yield along with **5a** (7%) (entry 3). Interestingly, when the reaction was carried out with Et_3N (1 equiv), isoxazole **5a** was isolated as a major product (entry 4). Brief screening of the solvent and the reaction temperature led us to identify that **5a** was isolated in 86% yield after the reaction in toluene at 60 °C for 8 h (entries 5−7). Neither **3a** nor **4a** was detected under these conditions. Without any catalyst, only **5a** was isolated in 53% yield upon heating a reaction mixture of **1a** and methyl nitroacetate in THF at 100 °C (entry 8). In contrast, the reaction in hexafluoroisopropanol (HFIP)[8] afforded indolizine **3a** as a major product (entries 9 and 10). To our delight, we were able to find that **3a** was produced in 80% yield

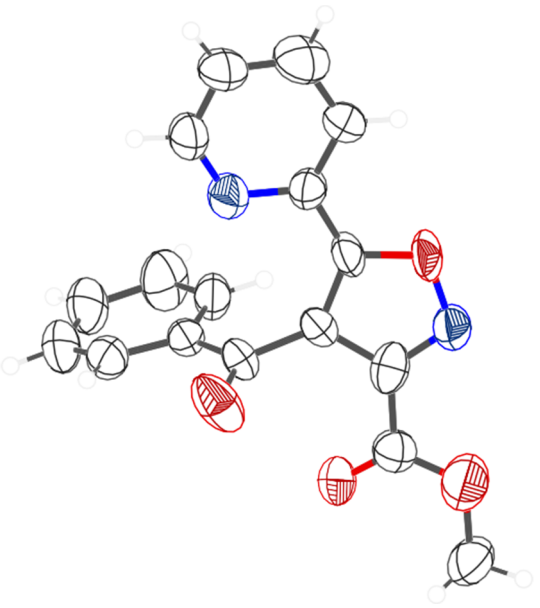


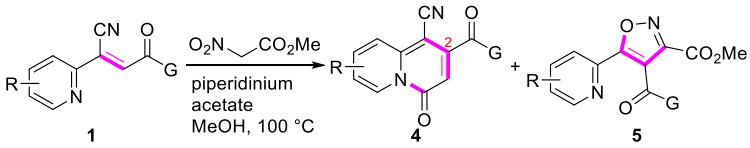
Figure 2. Chemical structure of **5a**.

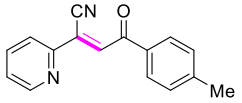
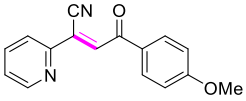
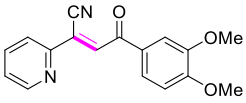
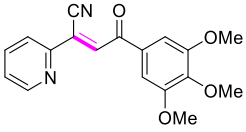
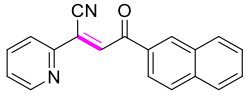
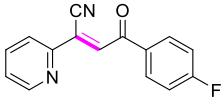
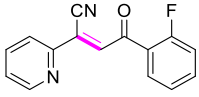
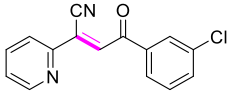
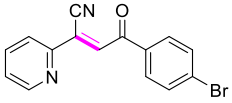
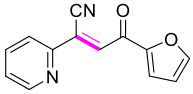
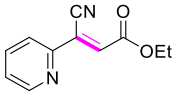
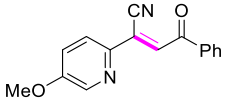
upon exposure of the reaction mixture in HFIP to microwave heating conditions (120 °C, 30 min) (entry 11).

Having found the optimal conditions for selective synthesis of **3**−**5**, the reaction scope was examined with various substrates **1** and methyl nitroacetate (Tables 2−4). In the presence of piperidinium acetate (1 equiv) as a mild catalyst, a wide variety of 2-acyl-4*H*-quinolizin-4-ones **4** were readily accessed in good yields indicating that functional groups such as alkyl, alkoxy, and halogen are well tolerated under these conditions (Table 2). The isoxazoles **5** were obtained as minor products under these conditions. Although several synthetic approaches to 4*H*-quinolizin-4-ones have been known in the literature,[9] the one with a cyano group at the C1 site and an acyl motif at the C2 site has not been disclosed yet, to the best of our knowledge. Moreover, most known methods require multistep sequence, harsh conditions, and/or expensive metal catalysts.

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

Table 2. Synthesis of 4[a,b]

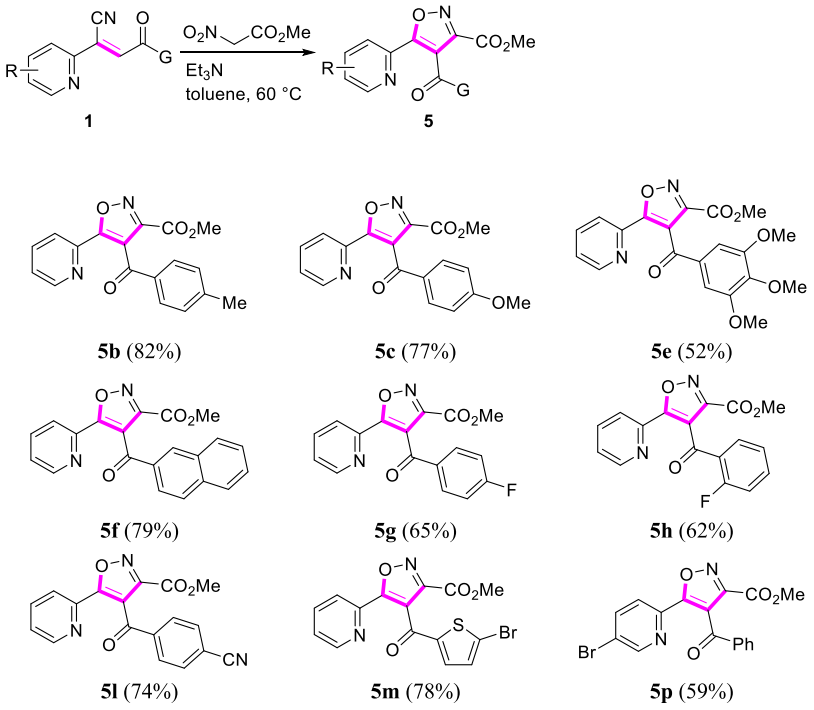


entry	1	yield (%)[b] 4	5
1		**4b** (82)	**5b** (9)
2		**4c** (88)	**5c** (10)
3		**4d** (80)	**5d** (14)
4		**4e** (73)	**5e** (12)
5		**4f** (89)	**5f** (10)
6		**4g** (66)	**5g** (19)
7		**4h** (62)	**5h** (16)
8		**4i** (77)	**5j** (13)
9		**4j** (74)	**5k** (15)
10		**4k** (60)	-
11		**4l** (92)	**5n** (1)
12		**4m** (49)	**5o** (16)

[a]A mixture of **1** (0.13 mmol, 1 equiv), methyl nitroacetate (1.5 equiv), and piperidinium acetate (1 equiv) in MeOH (2 mL) was heated at 100 °C. [b]Isolated yield (%).

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

Table 3. Synthesis of 5[a,b]

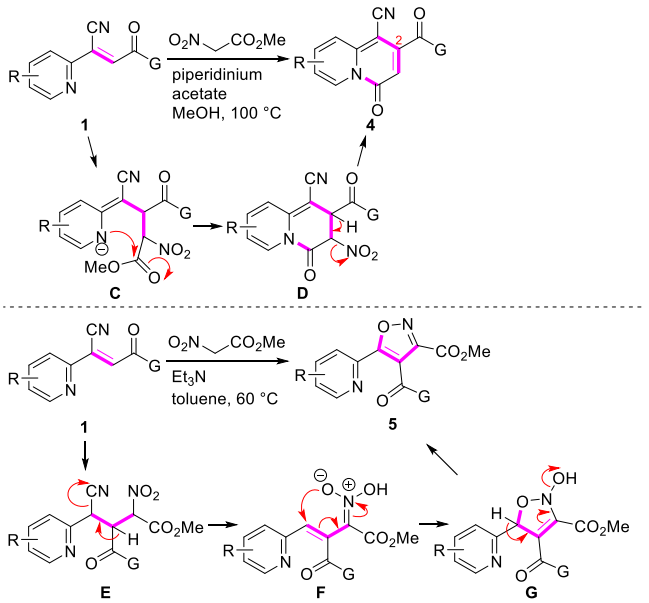


[a]A mixture of **1** (0.13 mmol, 1 equiv), methyl nitroacetate (1.5 equiv), and Et_3N (1 equiv) in toluene (2 mL) was heated at 60 °C. [b]Isolated yield (%).

As synthesis of the isoxazole **5a** was favored in the presence of Et_3N in toluene at 60 °C, several substrates **1** and methyl nitroacetate were exposed to the same conditions to give the corresponding isoxazoles **5** in good yields and the results are outlined in Table 3.

As illustrated in Scheme 2, formation of 2-acyl-4*H*-quinolizin-4-one **4** would be explained by nucleophilic acyl substitution at the ester in **C** by the pyridinyl nitrogen to give the amide **D**. Subsequent loss of HNO_2 would give rise to **4**.

Scheme 2. Proposed Mechanisms for the Synthesis of 4 and 5



For the synthesis of isoxazole **5**,[10] elimination of HCN and tautomerization in Michael adduct **E** is proposed to occur to afford **F** which would undergo cyclization to furnish **G**. Final loss of H_2O in **G** would lead to **5**.

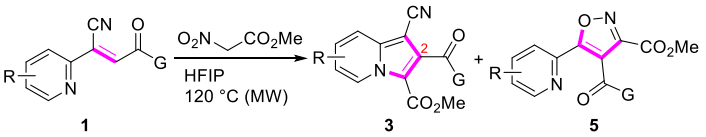
Finally, the synthesis of indolizines **3** from the reactions of **1** with methyl nitroacetate in HFIP at 120 °C was investigated as shown in Table 4. Under microwave heating conditions, the expected indolizines **3** were isolated as major products along with the isoxazoles **5** as minor ones. The structure of compound **3b** was determined through X-ray crystallographic analysis (Figure 3).[11] Notably, indolizines bearing one cyano group and two different acyl motifs at the C1−C3 positions have not been reported yet.

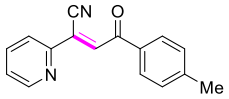
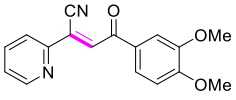
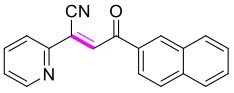
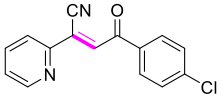
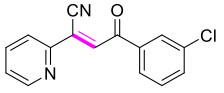
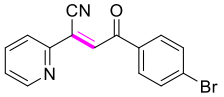
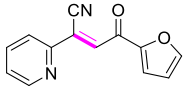
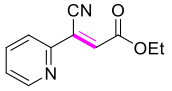
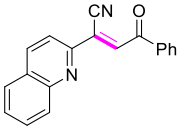
Scale-up experiments with **1a** (300 mg) proceeded well under three different conditions to give **3a**, **4a**, and **5a** in good yields (Scheme 3). When ethyl nitroacetate was used instead of methyl nitroacetate, the same results were observed; the reaction in the presence of Et_3N in toluene gave the isoxazole **6** in 72% yield whereas the one in HFIP furnished the indolizine **7** as a major product. When benzoylnitromethane was allowed to react with **1a** in HFIP, the corresponding isoxazole **8** was isolated as a major product along with a small amount of the indolizine **9**. Use of malononitrile in the reaction with **1a** in the presence of piperidinium acetate in MeOH at 100 °C provided **10** having a cyano and an amino group at the C4 and C5 site, respectively.[12]

In addition, postmodification experiments of the resulting products (**3**, **4**, and **5**) demonstrated the feasibility of expanding the heterocyclic chemical space associated with these scaffolds (Scheme 4). Exposure of **3a** to hydrazine in EtOH allowed construction of the pyridazine ring to give **11**.[13] While partial reduction of **4a** with H_2 and Pd/C provided **12** and **13**,[14] treatment of **4a** with NBS installed Br at the C3 site, delivering **14** in 96% yield.[15] Suzuki-Miyaura coupling of **14**

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

Table 4. Synthesis of 3[a,b]



entry		yield (%)[b] 3	5
1		**3b** (82)	**5b** (9)
2		**3c** (84)	**5d** (8)
3		**3d** (70)	**5f** (11)
4		**3e** (62)	**5i** (10)
5		**3f** (56)	**5j** (11)
6		**3g** (70)	**5k** (15)
7		**3h** (68)	-
8		**3i** (85)	**5n** (3)
9		**3j** (59)[c]	**5q** (24)[c]

[a]A mixture of **1** (0.13 mmol, 1 equiv) and methyl nitroacetate (1.5 equiv) in HFIP (2 mL) was heated at 120 °C (microwave heating for 0.5 h). [b]Isolated yield (%). [c]Reaction at 100 °C.

with 4-methoxyphenylboronic acid afforded a highly functionalized 2-acyl-4*H*-quinolizin-4-one **15**. Hydrolysis of **4b** under basic conditions produced the amide **16** in an excellent yield.[16] Reduction of **5a** with $NaBH_4$ gave the diol **17** in 94% yield.

In summary, three divergent pathways in the annulation process of (*Z*)-4-aryl-4-oxo-2-(pyridin-2-yl)but-2-enenitrile with methyl nitroacetate were discovered to provide ready access to three distinctive skeletons in good to excellent yields. Simple synthetic elaboration of these scaffolds was further demonstrated enabling facile expansion of these heterocyclic chemical space. We believe that three heterocyclic scaffolds with unique substitution patterns described here should be helpful in finding new biologically active compounds in medicinal chemistry. Along this line, biological evaluation of these compounds is underway and the results will be communicated soon.

EXPERIMENTAL SECTION

General Methods. Reagents and starting materials were obtained from commercial suppliers and used directly without further purification. "Concentrated" refers to the removal of volatile solvents through rotary evaporation. "Dried" refers to treating the material with anhydrous magnesium sulfate, followed by filtration. Flash chromatography was conducted using silica gel (230−400 mesh) with hexanes, ethyl acetate, and dichloromethane as the eluents. The progression of all the

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

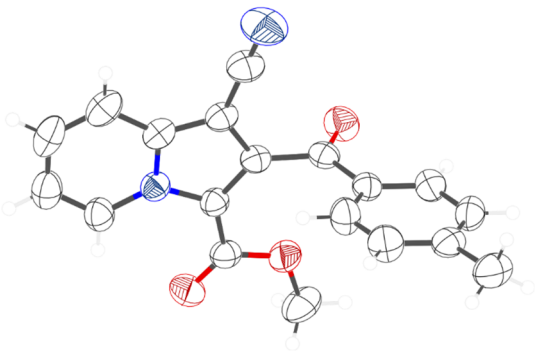
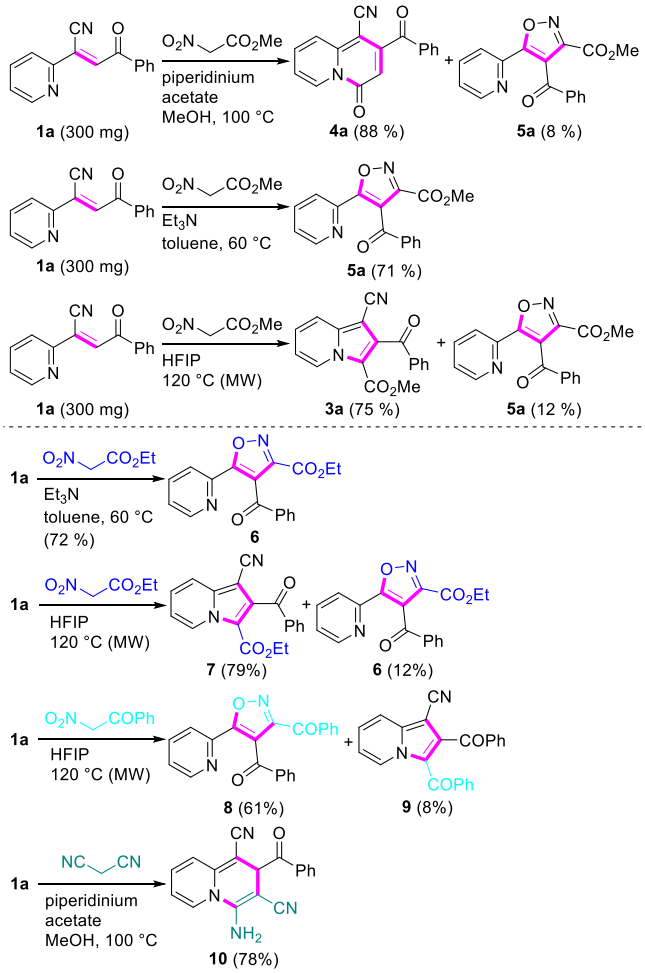


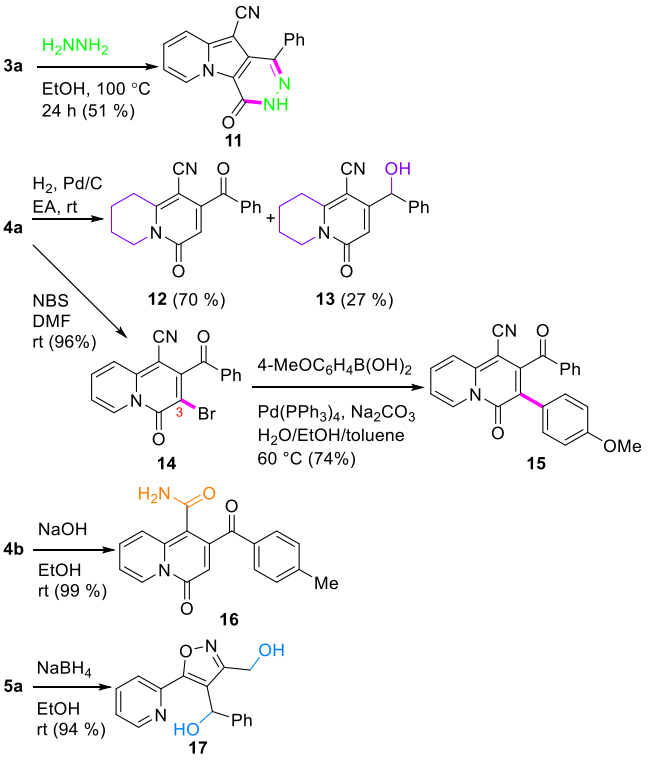
Figure 3. Chemical structure of **3b**.

Scheme 3. Scale-Up and Applications



reactions was monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) and visualized under UV light. Melting points were determined with a capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer and the data were reported as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet), coupling constants in hertz (Hz), and number of protons. High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) and a Q-TOF mass analyzer. X-ray crystallographic analyses of compounds **3b**, **4a**, and **5a** were carried out with a SuperNova, Dual, Cu at home/near, AtlasS2 diffractometer.

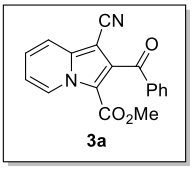
Scheme 4. Derivatization



General Procedure for the Synthesis of 3. A solution of **1a** (30 mg. 0.13 mmol) and methyl nitroacetate (18.0 μL, 1.5 equiv) in HFIP (2 mL) was heated at 120 °C (microwave heating was used) for 0.5 h. After concentration *in vacuo*, the crude residue was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 30:1:2) to afford **3a** (31.6 mg, 80%) as a white solid and **5a** (3.2 mg, 8%) as a white solid.

Scale-Up Experiment. Reaction with **1a** (300 mg, 1.3 mmol) under the same conditions gave **3a** (296.7 mg, 75%) and **5a** (48.1 mg, 12%).

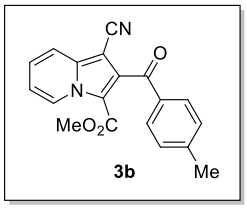
*Methyl 2-Benzoyl-1-cyanoindolizine-3-carboxylate (**3a**).*



White solid, mp: 147.8−148.2 °C (31.6 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, J = 6.8 Hz, 1H), 7.84 (t, J = 7.2 Hz, 3H), 7.61 (t, J = 7.2 Hz, 1H), 7.51−7.44 (m, 3H), 7.16 (t, J = 6.8 Hz, 1H), 3.56 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.5, 160.0, 139.8, 137.4, 136.9, 136.6, 134.0, 129.5, 128.7, 128.3, 127.1, 117.9, 116.1, 113.5, 84.5, 51.7; **HRMS** (ESI-QTOF) m/z [M + H]$^{+}$ calcd for $C_{18}H_{13}N_2O_3$ 305.0921, found 305.0920.

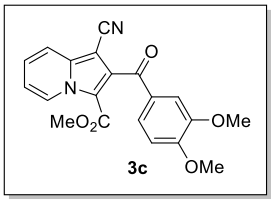
https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

*Methyl 1-Cyano-2-(4-methylbenzoyl)indolizine-3-carboxylate (**3b**).*



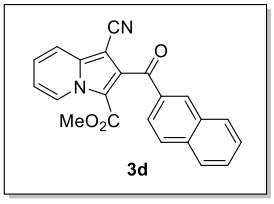
White solid, mp: 199.2−199.9 °C (33.9 mg, 82%); **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 9.57 (dt, J = 7.2, 0.8 Hz, 1H), 7.92 (dt, J = 8.8, 1.2 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.69−7.64 (m, 1H), 7.40−7.34 (m, 3H), 3.55 (s, 3H), 2.42 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.1, 160.1, 145.1, 139.7, 137.2, 134.1, 129.7, 129.4, 128.3, 127.0, 117.8, 116.0, 113.6, 112.7, 84.4, 51.7, 21.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{19}H_{15}N_2O_3$ 319.1077, found 319.1075. Dissolution of the compound in a mixed solvent (ethyl acetate:EtOH, 1:1) and slow evaporation of the solvent at room temperature afforded the crystal **3b** for X-ray crystallographic analysis.

*Methyl 1-Cyano-2-(3,4-dimethoxybenzoyl)indolizine-3-carboxylate (**3c**).*



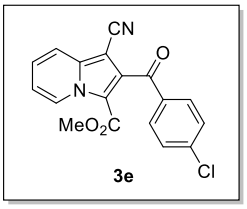
White solid, mp: 147.8−148.2 °C (39.8 mg, 84%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.57 (d, J = 7.2 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 1.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.22 (dd, J = 8.4, 1.6 Hz, 1H), 7.15 (t, J = 6.8 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.64 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.0, 160.2, 154.2, 149.3, 139.7, 137.3, 123.0, 128.4, 127.0, 126.1, 117.8, 116.0, 113.6, 112.8, 110.1, 109.9, 84.5, 56.14, 56.10, 51.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{20}H_{17}N_2O_5$ 365.1132, found 365.1134.

*Methyl 2-(2-Naphthoyl)-1-cyanoindolizine-3-carboxylate (**3d**).*



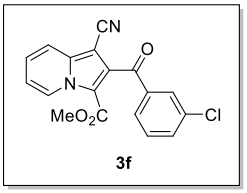
White solid, mp: 169.8−170.2 °C (32.2 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.61 (d, J = 7.2 Hz, 1H), 8.20 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.96−7.84 (m, 4H), 7.63 (t, J = 7.2 Hz, 1H), 7.57−7.47 (m, 2H), 7.19 (t, J = 6.8 Hz, 1H), 3.53 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.5, 160.1, 139.8, 137.1, 136.0, 134.1, 132.41, 132.36, 129.8, 129.1, 128.8, 128.4, 127.9, 127.1, 126.9, 124.0, 117.9, 116.1, 113.5, 112.9, 84.6, 51.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{22}H_{15}N_2O_3$ 355.1077, found 355.1087.

*Methyl 2-(4-Chlorobenzoyl)-1-cyanoindolizine-3-carboxylate (**3e**).*



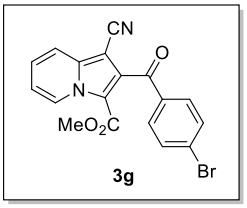
White solid, mp: 159.2−159.9 °C (27.3 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 3.59 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.2, 159.9, 140.6, 139.8, 136.3, 135.0, 130.8, 129.1, 128.3, 127.2, 117.9, 116.2, 113.4, 112.7, 84.4, 51.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{12}ClN_2O_3$ 339.0531, found 339.0532.

*Methyl 2-(3-Chlorobenzoyl)-1-cyanoindolizine-3-carboxylate (**3f**).*



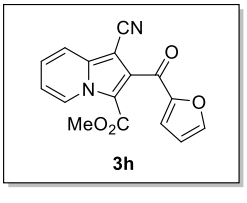
White solid, mp: 166.2−166.9 °C (24.7 mg, 56%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 7.6 Hz, 1H), 7.61−7.57 (m, 1H), 7.49 (dd, J = 8.0, 7.2 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 3.60 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.2, 159.8, 139.8, 138.2, 136.1, 135.1, 133.9, 130.1, 129.2, 128.3, 127.6, 127.3, 118.0, 116.3, 113.3, 112.8, 84.4, 51.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{12}ClN_2O_3$ 339.0531, found 339.0532.

*Methyl 2-(4-Bromobenzoyl)-1-cyanoindolizine-3-carboxylate (**3g**).*



White solid, mp: 182.3−182.9 °C (34.9 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.55 (d, J = 7.2 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.47 (t, J = 8.8 Hz, 1H), 7.16 (t, J = 6.8 Hz, 1H), 3.59 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.5, 159.8, 139.8, 136.3, 135.4, 132.1, 130.9, 129.4, 128.3, 127.2, 117.9, 116.2, 113.4, 112.7, 84.4, 51.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{12}BrN_2O_3$ 383.0026, found 383.0039.

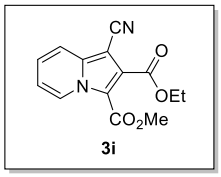
*Methyl 1-Cyano-2-(furan-2-carbonyl)indolizine-3-carboxylate (**3h**).*



https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

Orange solid, mp: 160.5−160.8 °C (26.0 mg, 68%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (d, J = 4.8 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.55 (s, 1H), 7.31 (dd, J = 7.6, 4.8 Hz, 1H), 7.15 (d, J = 2.8 Hz, 1H), 6.54−6.52 (m, 1H), 3.91 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.0, 168.4, 159.2, 154.9, 153.0, 150.2, 147.2, 144.9, 137.0, 125.2, 121.8, 119.1, 116.2, 112.7, 87.7, 53.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{16}H_{11}N_2O_4$ 295.0713, found 295.0702.

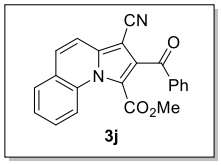
*2-Ethyl 3-Methyl 1-Cyanoindolizine-2,3-dicarboxylate (**3i**).*



3i

White solid, mp: 157.8−158.2 °C (30.1 mg, 85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.45 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.40 (t, J = 9.2 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.8, 160.2, 139.2, 129.9, 128.2, 126.8, 118.0, 116.1, 113.6, 113.2, 84.5, 62.4, 52.2, 14.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{14}H_{13}N_2O_4$ 273.0870, found 273.0858.

*Methyl 2-Benzoyl-3-cyanopyrrolo[1,2-a]quinoline-1-carboxylate (**3j**).*



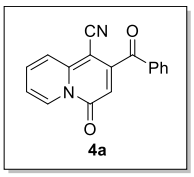
3j

White solid, mp: 156.2−156.9 °C (27.2 mg, 59%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 7.6 Hz, 3H), 7.70−7.63 (m, 4H), 7.58 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 3.57 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.0, 161.7, 139.5, 136.9, 134.4, 133.9, 132.8, 129.52, 129.49, 129.4, 128.8, 128.7, 126.5, 125.4, 120.4, 118.7, 115.6, 113.5, 87.2, 52.6; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{22}H_{15}N_2O_3$ 355.1077, found 355.1078.

General Procedure for the Synthesis of 4. A solution of **1a** (30 mg. 0.13 mmol), methyl nitroacetate (18.0 μL, 1.5 equiv), and piperidinium acetate (18.9 mg, 1.0 equiv) in methanol (2 mL) was heated at 100 °C for 1 h. After concentration *in vacuo*, the crude residue was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 5:1:2) to give **4a** (32.8 mg, 92%) as a yellow solid and **5a** (2.8 mg, 7%) as a white solid.

Scale-Up Experiment. Reaction with **1a** (300 mg, 1.3 mmol) under the same conditions furnished **4a** (313.8 mg, 88%) and **5a** (32.1 mg, 8%).

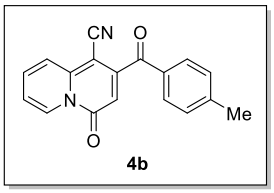
*2-Benzoyl-4-oxo-4H-quinolizine-1-carbonitrile (**4a**).*



4a

Yellow solid, mp: 195.8−196.5 °C (32.8 mg, 92%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.27 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 9.2 Hz, 1H), 7.91−7.88 (m, 2H), 7.84 (t, J = 7.2 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.59 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.3, 156.7, 149.7, 146.4, 135.6, 134.7, 134.4, 130.4, 129.0, 128.9, 124.0, 117.5, 115.2, 107.6, 83.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{11}N_2O_2$ 275.0815, found 275.0807. Dissolution of the compound in a mixed solvent (dichloromethane:ethyl acetate:EtOH, 1:1:1) and slow evaporation of the solvent at room temperature gave the crystal **4a** for X-ray crystallographic analysis.

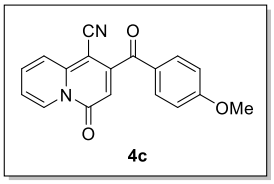
*2-(4-Methylbenzoyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4b**).*



4b

Yellow solid, mp: 147.8−148.2 °C (30.7 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.26 (d, J = 6.8 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 6.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 6.56 (s, 1H), 2.43 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 191.9, 156.7, 150.1, 146.3, 146.1, 135.6, 131.9, 130.6, 129.6, 128.9, 123.9, 117.6, 115.3, 107.4, 83.2, 21.9; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}N_2O_2$ 289.0972, found 289.0967.

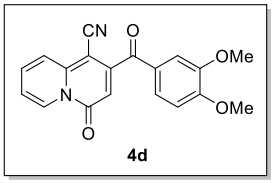
*2-(4-Methoxybenzoyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4c**).*



4c

Yellow solid, mp: 218.9−219.5 °C (34.8 mg, 88%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.28 (d, J = 6.8 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.84 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 6.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.58 (s, 1H), 3.89 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.7, 164.9, 156.7, 150.5, 146.3, 135.4, 133.0, 128.9, 127.4, 123.9, 117.4, 115.3, 114.2, 107.3, 83.4, 55.7; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}N_2O_3$ 305.0921, found 305.0920.

*2-(3,4-Dimethoxybenzoyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4d**).*

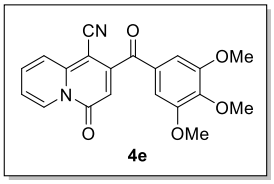


4d

Yellow solid, mp: 247.2−247.6 °C (34.7 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.30 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 9.2 Hz, 1H), 7.84 (dd, J = 8.8, 7.2 Hz, 1H), 7.63 (s, 1H), 7.40−7.32 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 3.97 (s, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.7, 156.7, 154.9, 150.5, 149.6, 146.3, 135.4, 129.0, 127.5, 126.9, 123.9, 117.4, 115.3, 110.9, 109.9, 107.4, 83.5, 56.3, 56.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{19}H_{15}N_2O_4$ 335.1026, found 335.1046.

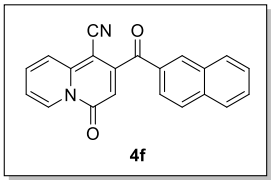
https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

*4-Oxo-2-(3,4,5-trimethoxybenzoyl)-4H-quinolizine-1-carbonitrile (**4e**).*



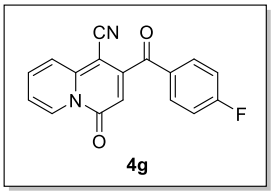
Yellow solid, mp: 208.2−208.6 °C (34.6 mg, 73%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.31 (d, J = 7.2 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.89−7.83 (m, 1H), 7.39−7.34 (m, 1H), 7.17 (s, 2H), 6.62 (s, 1H), 3.97 (s, 3H), 3.88 (s, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 191.0, 156.6, 153.2, 150.0, 146.4, 144.2, 135.5, 129.3, 129.0, 124.0, 117.5, 115.1, 108.1, 107.3, 83.4, 61.1, 56.5; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{17}N_2O_5$ 365.1132, found 365.1136.

*2-(2-Naphthoyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4f**).*



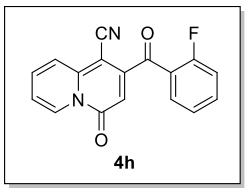
Yellow solid, mp: 214.1−214.6 °C (37.5 mg, 89%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.34 (d, J = 7.2 Hz, 1H), 8.33 (s, 1H), 8.19 (d, J = 9.2 Hz, 1H), 8.08 (dd, J = 8.8, 1.6 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.92 (t, J = 7.2 Hz, 2H), 7.89−7.85 (m, 1H), 7.69−7.64 (m, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.38 (td, J = 7.2, 1.2 Hz, 1H), 6.70 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.2, 156.7, 150.1, 146.4, 136.3, 135.5, 133.7, 132.2, 131.8, 129.8, 129.6, 129.2, 129.0, 128.0, 127.2, 124.5, 124.1, 117.5, 115.2, 107.7, 83.5; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{21}H_{13}N_2O_2$ 325.0972, found 325.0960.

*2-(4-Fluorobenzoyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4g**).*



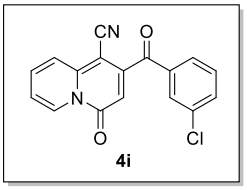
Yellow solid, mp: 236.0−236.8 °C (25.1 mg, 66%); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 9.23 (d, J = 6.8 Hz, 1H), 8.11−8.02 (m, 4H), 7.58 (t, J = 6.4 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 6.59 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $(CD_3)_2SO$) δ 191.9, 166.4 (J = 253.0 Hz), 156.8, 149.8, 146.7, 137.7, 133.9 (J = 10.0 Hz), 131.7 (J = 3.0 Hz), 129.5, 123.7, 118.9, 116.8 (J = 22.0 Hz), 116.2, 106.2, 81.4; **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ −102.8; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{10}FN_2O_2$ 293.0721, found 293.0717.

*2-(2-Fluorobenzoyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4h**).*



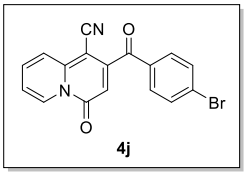
Yellow solid, mp: 216.5−217.4 °C (23.6 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.26 (d, J = 6.8 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.84 (t, J = 7.6 Hz, 2H), 7.68−7.62 (m, 1H), 7.36−7.31 (m, 2H), 7.16 (t, J = 10.0 Hz, 1H), 6.61 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.8, 161.6 (J = 256.0 Hz), 157.1, 149.9, 146.4, 136.2 (J = 9.0 Hz), 135.4, 131.6, 128.9, 124.9 (J = 4.0 Hz), 124.2, 124.1, 117.5, 116.8 (J = 21.0 Hz), 115.2, 107.6 (J = 2.0 Hz), 82.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ −111.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{10}FN_2O_2$ 293.0721, found 293.0724.

*2-(3-Chlorobenzoyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4i**).*



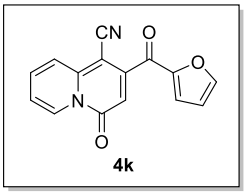
Yellow solid, mp: 194.2−194.9 °C (30.9 mg, 77%); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 9.23 (d, J = 7.2 Hz, 1H), 8.13−8.05 (m, 2H), 7.96 (s, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.60−7.55 (m, 1H), 6.61 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $(CD_3)_2SO$) δ 192.3, 156.8, 149.1, 146.8, 137.7, 136.8, 135.1, 134.5, 131.6, 130.1, 129.5, 129.3, 123.8, 118.9, 116.2, 106.5, 81.4; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{10}ClN_2O_2$ 309.0425, found 309.0435.

*2-(4-Bromobenzoyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4j**).*



Yellow solid, mp: 254.2−254.8 °C (34.0 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.30 (d, J = 7.2 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.87 (t, J = 7.2 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 6.59 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 191.3, 156.6, 149.2, 146.4, 135.7, 133.2, 132.4, 131.7, 130.4, 129.1, 124.1, 117.6, 115.1, 107.4, 83.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{10}BrN_2O_2$ 352.9920, found 352.9919.

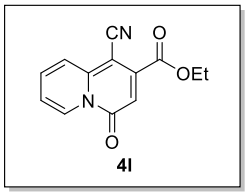
*2-(Furan-2-carbonyl)-4-oxo-4H-quinolizine-1-carbonitrile (**4k**).*



Yellow solid, mp: 175.5−176.0 °C (20.6 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.28 (d, J = 7.2 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.78−7.76 (m, 1H), 7.38−7.33 (m, 2H) 6.80 (s, 1H), 6.68−6.56 (m, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.6, 156.8, 150.7, 149.1, 148.1, 146.4, 135.5, 128.9, 124.2, 122.8, 117.6, 115.1, 113.2, 107.9, 83.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{15}H_9N_2O_3$ 265.0608, found 265.0594.

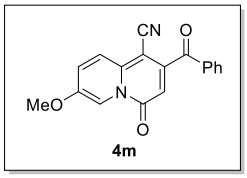
https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

*Ethyl 1-Cyano-4-oxo-4H-quinolizine-2-carboxylate (**4l**).*



Yellow solid, mp: 205.2−205.9 °C (32.3 mg, 92%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.24 (d, J = 5.6 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.83 (t, J = 6.8 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.09 (s, 1H), 4.47 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.6 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 163.3, 157.0, 146.4, 140.5, 135.3, 128.9, 124.4, 117.7, 115.6, 109.6, 83.9, 63.0, 14.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{13}H_{11}N_2O_3$ 243.0764, found 243.0763.

*2-Benzoyl-7-methoxy-4-oxo-4H-quinolizine-1-carbonitrile (**4m**).*

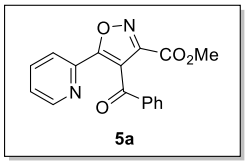


Yellow solid, mp: 256.6−257.2 °C (19.4 mg, 49%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.11 (d, J = 9.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.62 (dd, J = 9.6, 2.0 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 6.61 (s, 1H), 4.01 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.4, 156.3, 152.6, 148.1, 142.5, 134.63, 134.60, 130.6, 130.4, 128.9, 124.8, 115.4, 109.2, 107.0, 83.8, 56.6; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{13}N_2O_3$ 305.0921, found 305.0922.

General Procedure for the Synthesis of 5. A solution of **1a** (30 mg. 0.13 mmol), methyl nitroacetate (18.0 μL, 1.5 equiv), and Et_3N (18.1 μL, 1 equiv) in toluene (2 mL) was heated at 60 °C for 8 h. After the solvent was evaporated under reduced pressure, the crude residue was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 10:1:2) to afford **5a** (34.5 mg, 86%) as a white solid.

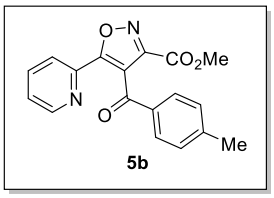
Scale-Up Experiment. Reaction with **1a** (300 mg, 1.3 mmol) under the same conditions gave **5a** (288.6 mg, 71%).

*Methyl 4-Benzoyl-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5a**).*



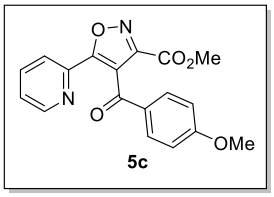
White solid, mp: 140.1−140.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (d, J = 4.8 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.90−7.86 (m, 2H), 7.81 (td, J = 8.0, 1.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.29−7.25 (m, 1H), 3.85 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.4, 167.7, 159.2, 155.0, 150.1, 144.9, 137.1, 137.0, 133.6, 129.2, 128.6, 125.0, 121.5, 117.2, 53.1; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_4$ 309.0870, found 309.0866. Dissolution of the compound in a mixed solvent (ethyl acetate:EtOH, 1:1) and slow evaporation of the solvent at room temperature afforded the crystal **5a** for X-ray crystallographic analysis.

*Methyl 4-(4-Methylbenzoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5b**).*



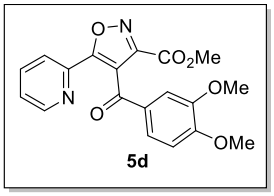
White solid, mp: 152.8−153.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (d, J = 4.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.81 (dd, J = 8.0, 1.2 Hz, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.30−7.27 (m, 1H), 7.23 (d, J = 8.0 Hz, 2H), 3.85 (s, 3H), 2.40 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.0, 167.6, 159.2, 155.0, 150.2, 144.9, 144.6, 137.0, 134.7, 129.4, 129.3, 125.0, 121.5, 117.4, 53.1, 21.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_4$ 323.1026, found 323.1028.

*Methyl 4-(4-Methoxybenzoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5c**).*



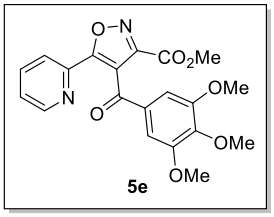
White solid, mp: 147.8−148.3 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, J = 4.8 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 9.2 Hz, 2H), 7.79 (td, J = 8.0, 1.6 Hz, 1H), 7.27 (t, J = 4.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.9, 167.4, 164.0, 159.3, 155.0, 150.2, 145.0, 136.9, 131.6, 130.3, 125.0, 121.5, 117.4, 113.9, 55.5, 53.1; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_5$ 339.0975, found 339.0985.

*Methyl 4-(3,4-Dimethoxybenzoyl)-5-(pyridin-2-yl)-isoxazole-3-carboxylate (**5d**).*



White solid, mp: 158.9−159.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.80 (td, J = 7.6, 1.6 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.30−7.27 (m, 1H), 7.26−7.22 (m, 1H), 6.77 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.9, 167.5, 159.3, 155.0, 153.9, 150.3, 149.2, 145.0, 137.0, 130.5, 125.1, 125.0, 121.6, 117.2, 110.0, 109.9, 56.1, 56.0, 53.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_6$ 369.1081, found 369.1091.

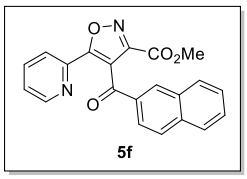
*Methyl 5-(Pyridin-2-yl)-4-(3,4,5-trimethoxybenzoyl)-isoxazole-3-carboxylate (**5e**).*



https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

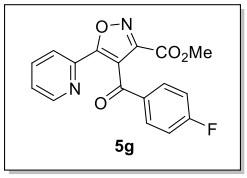
White solid, mp: 162.2−162.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, J = 4.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.82 (td, J = 7.6, 1.6 Hz, 1H), 7.32−7.27 (m, 1H), 7.12 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.80 (s, 6H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.1, 167.7, 159.3, 155.1, 153.1, 150.3, 144.9, 143.1, 137.0, 132.2, 125.1, 121.7, 117.0, 106.6, 60.9, 56.2, 53.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{19}N_2O_7$ 399.1187, found 399.1209.

*Methyl 4-(2-Naphthoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5f**).*



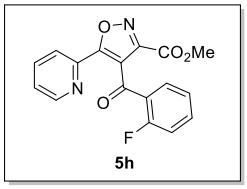
White solid, mp: 155.5−155.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (d, J = 4.0 Hz, 1H), 8.25 (s, 1H), 8.09 (dd, J = 8.4, 1.6 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.79 (td, J = 7.6, 1.6 Hz, 1H), 7.62−7.56 (m, 1H), 7.53−7.48 (m, 1H), 7.25−7.21 (m, 1H), 3.83 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.4, 167.8, 159.2, 155.1, 150.2, 144.9, 137.0, 135.9, 134.7, 132.4, 131.7, 129.7, 128.7, 128.6, 127.8, 126.7, 125.0, 124.2, 121.5, 117.3, 53.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{21}H_{15}N_2O_4$ 359.1026, found 359.1040.

*Methyl 4-(4-Fluorobenzoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5g**).*



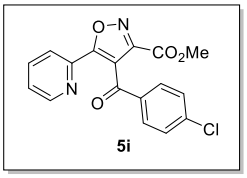
White solid, mp: 148.9−149.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (d, J = 4.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.92−7.86 (m, 2H), 7.80 (t, J = 8.0 Hz, 1H), 7.29−7.23 (m, 1H), 7.12−7.05 (m, 2H), 3.86 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.9, 167.7, 166.0 (J = 254.0 Hz), 159.2, 154.9, 150.1, 144.8, 137.1, 133.7 (J = 3.0 Hz), 131.8 (J = 10.0 Hz), 125.1, 121.5, 116.9, 115.8 (J = 22.0 Hz), 53.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ −104.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}FN_2O_4$ 327.0776, found 327.0785.

*Methyl 4-(2-Fluorobenzoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5h**).*



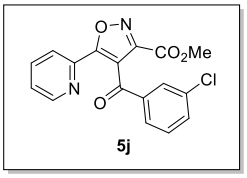
White solid, mp: 99.5−100.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (d, J = 4.0 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.55−7.47 (m, 1H), 7.27 (t, J = 6.8 Hz, 2H), 7.01 (t, J = 8.8 Hz, 1H), 3.88 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 184.5, 167.2, 161.9 (J = 257.0 Hz), 159.4, 154.5, 150.0, 145.0, 137.0, 135.2 (J = 9.0 Hz), 131.2, 125.8 (J = 9.0 Hz), 125.0, 124.3 (J = 4.0 Hz), 121.3, 119.5, 116.6 (J = 22.0 Hz), 53.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ −111.4; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}FN_2O_4$ 327.0776, found 327.0777.

*Methyl 4-(4-Chlorobenzoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5i**).*



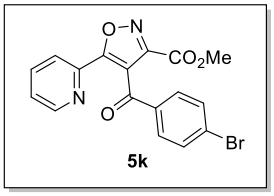
White solid, mp: 190.1−190.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, J = 4.8 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.85−7.79 (m, 3H), 7.41 (d, J = 8.8 Hz, 2H), 7.31−7.27 (m, 1H), 3.88 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.2, 167.8, 159.2, 154.9, 150.1, 144.7, 140.0, 137.1, 135.6 130.5, 129.0, 125.2, 121.4, 116.8, 53.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}ClN_2O_4$ 343.0480, found 343.0492.

*Methyl 4-(3-Chlorobenzoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5j**).*



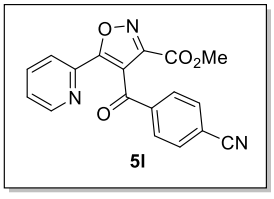
White solid, mp: 188.6−189.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.30−7.27 (m, 1H), 3.88 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.1, 167.9, 159.1, 154.9, 150.1, 144.6, 138.7, 137.1, 134.9, 133.5, 129.9, 128.9, 127.4, 125.2, 121.4, 116.7, 53.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}ClN_2O_4$ 343.0480, found 343.0477.

*Methyl 4-(4-Bromobenzoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5k**).*



White solid, mp: 201.3−201.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, J = 3.6 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.31−7.27 (m, 1H), 3.88 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 187.4, 167.8, 159.2, 154.9, 150.1, 144.7, 137.1, 136.0, 132.0, 130.6, 128.9, 125.2, 121.4, 116.8, 53.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}BrN_2O_4$ 386.9975, found 386.9973.

*Methyl 4-(4-Cyanobenzoyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5l**).*

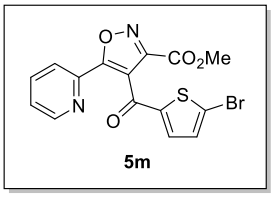


White solid, mp: 178.2−178.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (d, J = 4.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.84 (t, J = 7.2 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 5.2 Hz, 1H), 3.89 (s, 3H); **^{13}C{^{1}H}**

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

NMR (100 MHz, $CDCl_3$) δ 187.0, 168.1, 159.1, 154.9, 150.0, 144.4, 140.2, 137.2, 132.5, 129.4, 125.4, 121.4, 118.0, 116.5, 116.3, 53.3; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{12}N_3O_4$ 334.0822, found 334.0819.

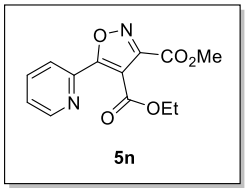
*Methyl 4-(5-Bromothiophene-2-carbonyl)-5-(pyridin-2-yl)isoxazole-3-carboxylate (**5m**).*



5m

White solid, mp: 126.2−126.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53−8.51 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.84 (td, J = 7.6, 1.6 Hz, 1H), 7.34−7.30 (m, 1H), 7.16 (d, J = 4.0 Hz, 1H), 7.03 (d, J = 4.0 Hz, 1H), 3.93 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.0, 168.0, 159.0, 154.7, 150.3, 145.7, 144.6, 137.1, 134.1, 131.4, 125.3, 123.9, 121.6, 116.1, 53.3; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{15}H_{10}BrN_2O_4S$ 392.9539, found 392.9535.

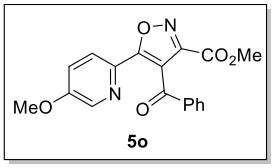
*4-Ethyl 3-Methyl 5-(Pyridin-2-yl)isoxazole-3,4-dicarboxylate (**5n**).*



5n

White solid, mp: 147.8−148.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, J = 4.8 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.87 (td, J = 7.6, 1.2 Hz, 1H), 7.41 (dd, J = 7.6, 4.8 Hz, 1H), 4.46 (q, J = 7.2 Hz, 2H), 4.01 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.4, 161.5, 159.3, 154.5, 150.2, 144.9, 137.0, 125.4, 122.4, 111.8, 62.2, 53.3, 14.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{13}H_{13}N_2O_5$ 277.0819, found 277.0822.

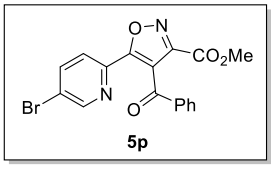
*Methyl 4-Benzoyl-5-(5-methoxypyridin-2-yl)isoxazole-3-carboxylate (**5o**).*



5o

White solid, mp: 185.2−185.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, J = 2.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.88−7.85 (m, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.24 (dd, J = 8.8, 3.2 Hz, 1H), 3.838 (s, 3H), 3.836 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.7, 167.8, 159.3, 156.6, 154.9, 138.4, 137.4, 137.3, 133.5, 129.2, 128.6, 122.4, 120.3, 115.7, 55.7, 53.1; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_5$ 339.0975, found 339.0979.

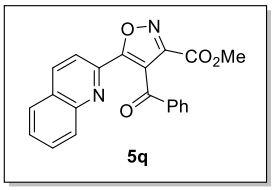
*Methyl 4-Benzoyl-5-(5-bromopyridin-2-yl)isoxazole-3-carboxylate (**5p**).*



5p

White solid, mp: 132.2−132.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.4, 2.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 3H), 7.59 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.2 Hz, 2H), 3.86 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.1, 166.7, 160.2, 159.0, 155.1, 151.4, 143.2, 139.7, 136.9, 133.8, 129.1, 128.7, 122.6, 122.4, 53.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}BrN_2O_4$ 386.9975, found 386.9976.

*Methyl 4-Benzoyl-5-(quinolin-2-yl)isoxazole-3-carboxylate (**5q**).*

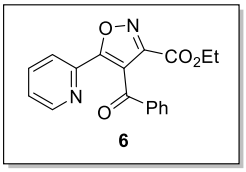


5q

White solid, mp: 144.2−144.7 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.62−7.57 (m, 1H), 7.54 (d, J = 6.4 Hz, 3H), 7.45 (t, J = 7.6 Hz, 2H), 3.90 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.6, 167.8, 159.3, 155.2, 147.6, 144.3, 137.44, 137.39, 133.5, 130.3, 129.7, 129.1, 128.6, 128.1, 128.0, 127.5, 117.9, 53.2; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{21}H_{15}N_2O_4$ 359.1026, found 359.1027.

Synthesis of 6. A solution of **1a** (30 mg. 0.13 mmol), ethyl nitroacetate (17.2 μL, 1.5 equiv), and Et_3N (18.1 μL, 1.0 equiv) in toluene (2 mL) was heated at 60 °C for 8 h. After concentration *in vacuo*, the crude residue was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 10:1:2) to give **6** (30.2 mg, 72%) as a white solid.

*Ethyl 4-Benzoyl-5-(pyridin-2-yl)isoxazole-3-carboxylate (**6**).*

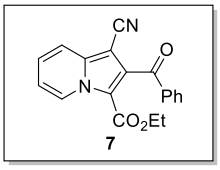


6

White solid, mp: 90.1−90.6 °C (30.2 mg, 72%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43−8.39 (m, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.90−7.86 (m, 2H), 7.80 (td, J = 8.0, 2.0 Hz, 1H), 7.60−7.54 (m, 1H), 7.43 (t, J = 8.0 Hz, 2H), 7.27 (td, J = 4.8, 1.2 Hz, 1H), 4.29 (q, J = 6.8 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.5, 167.7, 158.6, 155.2, 150.2, 144.9, 137.2, 137.0, 133.6, 129.2, 128.6, 125.0, 121.5, 117.1, 62.6, 13.7; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_4$ 323.1026, found 323.1026.

Synthesis of 7. A solution of **1a** (30 mg. 0.13 mmol) and ethyl nitroacetate (17.2 μL, 1.5 equiv) in HFIP (2 mL) was heated at 120 °C (microwave heating was used) for 0.5 h. After concentration under reduced pressure, the crude residue was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 30:1:2) to afford **7** (32.7 mg, 79%) as a white solid and **6** (5.0 mg, 12%) as a white solid.

*Ethyl 2-Benzoyl-1-cyanoindolizine-3-carboxylate (**7**).*



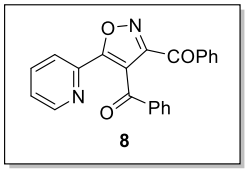
7

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

White solid, mp: 177.1−177.7 °C (32.7 mg, 79%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.58 (d, J = 6.8 Hz, 1H), 7.88−7.84 (m, 2H), 7.82 (d, J = 8.8 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.49−7.43 (m, 3H), 7.15 (td, J = 6.8, 0.8 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 0.83 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.5, 159.6, 139.8, 136.8, 136.7, 133.9, 129.6, 128.6, 128.3, 127.0, 117.8, 116.0, 113.6, 112.8, 84.3, 61.1, 13.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{19}H_{15}N_2O_3$ 319.1077, found 319.1092.

Synthesis of 8 and 9. A solution of **1a** (30 mg. 0.13 mmol) and benzoylnitromethane (32.7 mg, 1.5 equiv) in HFIP (2 mL) was heated at 120 °C (microwave heating was used) for 0.5 h. After concentration under reduced pressure, the crude residue was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 30:1:2) to give **8** (28.0 mg, 61%) as a white solid and **9** (3.6 mg, 8%) as a brown gum.

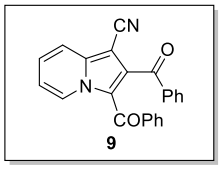
*(5-(Pyridin-2-yl)isoxazole-3,4-diyl)bis(phenylmethanone) (**8**).*



8

White solid, mp: 139.6−140.4 °C (28.0 mg, 61%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44−8.41 (m, 1H), 8.29−8.26 (m, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.93−7.88 (m, 2H), 7.81 (td, J = 8.0, 1.6 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.56−7.49 (m, 3H), 7.41 (t, J = 8.0 Hz, 2H), 7.27 (td, J = 4.8, 0.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 188.9, 184.4, 166.8, 161.1, 150.2, 145.0, 137.3, 136.9, 135.1, 134.4, 133.4, 130.7, 129.2, 128.6, 128.5, 125.0, 121.6, 118.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{22}H_{15}N_2O_3$ 355.1077, found 355.1087.

*2,3-Dibenzoylindolizine-1-carbonitrile (**9**).*

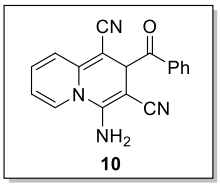


9

Brown gum (3.6 mg, 8%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.59 (d, J = 7.2 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.37−7.32 (m, 3H), 7.29 (d, J = 7.6 Hz, 2H), 7.21 (t, J = 7.6 Hz, 3H), 7.11 (t, J = 7.6 Hz, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 189.8, 186.6, 139.8, 137.7, 137.0, 133.3, 132.4, 129.4, 128.9, 128.8, 128.5, 128.3, 128.2, 128.0, 121.9, 118.1, 116.8, 113.7, 86.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{23}H_{15}N_2O_2$ 351.1128, found 351.1125.

Synthesis of 10. A solution of **1a** (10 mg. 0.04 mmol), malononitrile (4.2 mg, 1.5 equiv), and piperidinium acetate (6.2 mg, 1.0 equiv) in methanol (1 mL) was heated at 100 °C for 1 h. After concentration under the reduced pressure, the crude residue was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 2:1:2) to afford **10** (10.0 mg, 78%) as a yellow gum.

*4-Amino-2-benzoyl-2H-quinolizine-1,3-dicarbonitrile (**10**).*

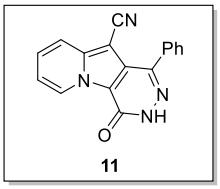


10

Yellow gum (10.0 mg, 78%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.8 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.62−7.53 (m, 5H), 7.18 (t, J = 8.4 Hz, 1H), 6.78 (t, J = 6.8 Hz, 1H), 6.50 (s, 1H), 5.96 (s, 1H), 4.80 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 164.2, 138.0, 130.2, 129.8, 126.8, 126.3, 124.2, 124.1, 118.0, 117.8, 115.4, 115.0, 113.9, 93.0, 81.4, 35.5; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}N_4O$ 301.1084, found 301.1153.

Synthesis of 11. A solution of **3a** (30 mg. 0.1 mmol) in ethanol (2 mL) was added hydrazine hydrate (3.1 μL, 2.0 equiv) at 0 °C. After being heated at 100 °C for 19 h, the reaction mixture was cooled to room temperature. The precipitated solid was filtered and washed with hexane to afford **11** (14.2 mg, 51%) as a yellow solid.

*4-Oxo-1-phenyl-3,4-dihydropyridazino[4,5-b]indolizine-10-carbonitrile (**11**).*

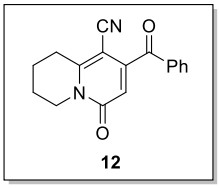


11

Yellow solid, mp: 365.1−365.9 °C (14.2 mg, 51%); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 13.28 (s, 1H), 9.62 (d, J = 6.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.79−7.68 (m, 3H), 7.55 (t, J = 3.2 Hz, 3H), 7.38 (t, J = 7.2 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $(CD_3)_2SO$) δ 154.5, 142.6, 142.4, 134.6, 130.4, 129.9, 129.4, 128.9, 128.7, 125.5, 118.4, 117.6, 116.1, 114.6, 75.8; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{17}H_{11}N_4O$ 287.0927, found 287.0929.

Synthesis of 12 and 13. A solution of **4a** (30 mg. 0.1 mmol) and 10% Pd/C (5 mg) in ethyl acetate (2 mL) was stirred under H_2 balloon atmosphere at rt for 24 h. The catalyst was removed by filtration and washed with ethyl acetate (4 mL). After concentration of the filtrate under reduced pressure, the crude residue was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 5:1:2) to give **12** (21.3 mg, 70%) as a yellow oil and **13** (8.3 mg, 27%) as a white solid.

*8-Benzoyl-6-oxo-1,3,4,6-tetrahydro-2H-quinolizine-9-carbonitrile (**12**).*



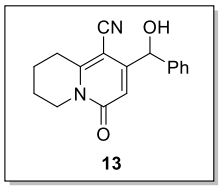
12

Yellow oil (21.3 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 6.50 (s, 1H), 4.02 (t, J = 6.0 Hz, 2H), 3.16 (d, J = 6.8 Hz, 2H), 2.03 (p, J = 6.4 Hz, 2H), 1.93 (p, J = 6.8 Hz, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 191.9, 161.1, 157.8,

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

147.6, 134.7, 134.4, 130.3, 128.9, 116.8, 114.8, 88.9, 43.5, 28.5, 21.5, 17.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_2$ 279.1128, found 279.1123.

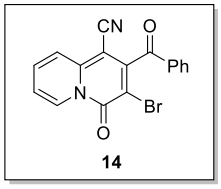
*8-(Hydroxy(phenyl)methyl)-6-oxo-1,3,4,6-tetrahydro-2H-quinolizine-9-carbonitrile (**13**).*



White solid, mp: 90.2−90.9 °C (8.3 mg, 27%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.2 Hz, 2H), 7.40−7.31 (m, 3H), 6.83 (s, 1H), 5.80 (s, 1H), 4.00−3.85 (m, 2H), 3.07−2.90 (m, 3H), 1.98−1.89 (m, 2H), 1.88−1.80 (m, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.3, 156.3, 154.1, 139.9, 128.8, 127.5, 115.6, 113.0, 89.7, 73.3, 43.0, 28.2, 21.6, 18.0; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1285, found 281.1282.

Synthesis of 14. A solution of **4a** (30 mg. 0.1 mmol) and *N*-bromosuccinimide (38.9 mg, 2.0 equiv) in DMF (0.5 mL) was stirred at rt for 1 h. The reaction mixture was diluted with dichloromethane (3 mL) and washed with water (10 mL). The water layer was extracted with dichloromethane (3 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford **14** (37.1 mg, 96%) as a yellow solid.

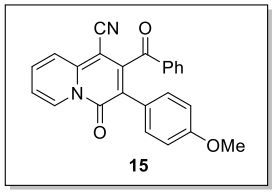
*2-Benzoyl-3-bromo-4-oxo-4H-quinolizine-1-carbonitrile (**14**).*



Yellow solid, mp: 122.8−123.2 °C (37.1 mg, 96%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.35 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.94−7.90 (m, 2H), 7.90−7.85 (m, 1H), 7.69 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.41 (td, J = 7.2, 1.2 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.7, 154.2, 151.2, 144.8, 135.5, 135.2, 133.3, 130.0, 129.4, 129.3, 123.7, 118.2, 114.2, 99.9, 83.5; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{17}H_{10}BrN_2O_2$ 352.9920, found 352.9903.

Synthesis of 15. To a solution of **14** (10 mg, 0.03 mmol), 4-methoxyphenylboronic acid (4.7 mg, 1.1 equiv), and Na_2CO_3 (9.0 mg, 3.0 equiv) in a mixed solvent (water:-ethanol:toluene = 1:2:2, 1 mL) was added tetrakis-(triphenylphosphine)palladium (2.0 mg, 0.06 equiv) under N_2 balloon atmosphere. The reaction mixture was purged by nitrogen for 5 min and then heated at 60 °C for 2 h. The reaction mixture was concentrated under reduced pressure, diluted with dichloromethane (2 mL), and washed with water (1 mL). The water layer was extracted with dichloromethane (2 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 3:1:2) to give **15** (8.4 mg, 74%) as a yellow solid.

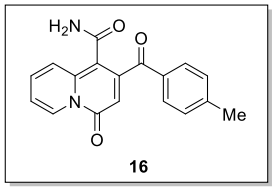
*2-Benzoyl-3-(4-methoxyphenyl)-4-oxo-4H-quinolizine-1-carbonitrile (**15**).*



Yellow solid, mp: 182.2−182.8 °C (8.4 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.34 (d, J = 7.2 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.82−7.76 (m, 1H), 7.74−7.69 (m, 2H), 7.50 (d, J = 7.2 Hz, 1H), 7.37−7.29 (m, 3H), 7.24 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 3.71 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 193.4, 159.4, 157.2, 148.8, 145.0, 134.73, 134.66, 134.3, 131.7, 129.6, 129.2, 128.7, 125.4, 123.6, 118.8, 117.2, 115.4, 113.7, 83.1, 55.1; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{24}H_{17}N_2O_3$ 381.1234, found 381.1231.

Synthesis of 16. A solution of **4b** (20 mg. 0.07 mmol) and 40% aqueous NaOH solution (0.2 mL) in ethanol (0.8 mL) was stirred at rt for 10 min. The reaction mixture was concentrated under reduced pressure to give the crude residue, which was acidified with aq. 15 % HCl solution (3 mL). Filtration and drying gave **16** as a yellow solid (21.0 mg, 99%).

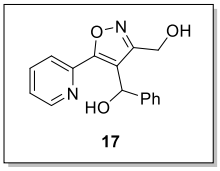
*2-(4-Methylbenzoyl)-4-oxo-4H-quinolizine-1-carboxamide (**16**).*



Yellow solid, mp: 254.3−254.9 °C (21.0 mg, 99%); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 9.07 (s, 1H), 9.04 (d, J = 7.2 Hz, 1H), 8.80 (d, J = 8.8 Hz, 1H), 7.94−7.88 (m, 1H), 7.42−7.37 (m, 3H), 7.17 (d, J = 8.0 Hz, 2H), 7.05 (s, 1H), 6.12 (s, 1H), 2.28 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $(CD_3)_2SO$) δ 167.8, 161.4, 158.5, 140.8, 138.9, 137.8, 135.2, 129.3, 128.6, 126.0, 121.6, 117.6, 101.0, 99.5, 86.5, 21.1; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_3$ 307.1077, found 307.1074.

Synthesis of 17. A solution of **5a** (30 mg. 0.1 mmol) and $NaBH_4$ (3.7 mg, 2.0 equiv) in ethanol (1 mL) was stirred at rt. After 24 h, the mixture was quenched with saturated NH_4Cl (2 mL) and the organic solvent was evaporated *in vacuo*. After concentration under reduced pressure, the crude residue was diluted with dichloromethane (2 mL) and washed with water (1 mL). The water layer was extracted with dichloromethane (2 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford **17** (25.8 mg, 94%) as a white solid.

*(3-(Hydroxymethyl)-5-(pyridin-2-yl)isoxazol-4-yl)(phenyl)-methanol (**17**).*



White solid, mp: 115.1−115.9 °C (25.8 mg, 94%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.87 (td, J = 8.0, 1.6 Hz, 1H), 7.56 (s, 1H), 7.38 (d, J = 7.2 Hz, 2H), 7.34 (dd, J = 7.6, 6.0 Hz, 1H), 7.25−7.16 (m,

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141

3H), 6.29 (s, 1H), 4.69−4.59 (m, 2H), 3.23 (s, 1H); $^{13}C\{^{1}H\}$ **NMR** (100 MHz, $CDCl_3$) δ 163.8, 162.6, 148.6, 146.4, 142.7, 138.0, 128.4, 127.5, 126.1, 124.4, 122.3, 120.8, 66.5, 56.1; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_3$ 283.1077, found 283.1079.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c05375.

^{1}H and ^{13}C NMR spectra of synthesized compounds and CIF files for **3b**, **4a**, and **5a** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Ikyon Kim − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea;* orcid.org/0000-0002-0849-5517; Phone: +82 32 749 4515; Email: ikyonkim@yonsei.ac.kr; Fax: +82 32 749 4105

Authors

Sunhee Lee − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

Woojin Kim − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c05375

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Research Foundation of Korea (NRF-2018R1A6A1A03023718 and NRF-2020R1A2C2005961) is acknowledged. We also thank Professors Kyungsoo Oh and Hun Young Kim (Chung-Ang University) for helpful discussions.

■ REFERENCES

(1) Joshi, D. R.; Kim, I. Recent advances in the synthesis of *N*-fused heterocycles from *N*-aroylmethylpyrrole-2-carboxaldehyde derivatives via annulative functionalization strategies. *Tetrahedron* **2024**, *151*, 133787.

(2) Nam, S.; Lee, S.; Kim, W.; Kim, I. Divergent synthesis of two types of indolizines from pyridine-2-acetonitrile, (hetero)arylglyoxal, and TMSCN. *Org. Biomol. Chem.* **2023**, *21*, 3881−3895.

(3) (a) Gao, M.; Tian, J.; Lei, A. A Reagent-Free Oxidative Cyclization Approach to Indolizine Derivatives from α-Picoline Derivatives and Nitroolefins. *Chem.—Asian J.* **2014**, *9*, 2068−2071. (b) Chen, Y.; Liu, Y.; Yang, H.; Li, Z.; Xu, X. Catalyst-free oxidative [3 + 2]-annulation of (2-nitroethene-1,1-diyl)bis(methylsulfane) and pyridinium ylides: Efficient synthesis of (methylsulfanyl)indolizines heterocycles. *J. Heterocycl. Chem.* **2023**, *60*, 1894−1902.

(4) (a) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules. *Nat. Commun.* **2010**, *1*, 80. (b) Schreiber, S. L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science* **2000**, *287*, 1964−1969.

(5) (a) Burke, M.; Schreiber, S. L. A Planning Strategy for Diversity-Oriented Synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58. (b) Kim, M.; Jung, Y.; Kim, I. Domino Knoevenagel Condensation/Intramolecular Aldol Cyclization Route to Diverse Indolizines with Densely Functionalized Pyridine Units. *J. Org. Chem.* **2013**, *78*, 10395−10404. (c) Wang, L.; Song, X.; Guo, F.; Xu, L.; Hu, F.; Guo, F.-W.; Li, S.-S. Diversity-oriented synthesis of indole-fused scaffolds and bis(indolyl)methane from tosyl-protected tryptamine. *Org. Biomol. Chem.* **2024**, *22*, 2824−2834.

(6) (a) Yang, Y.; Yang, W. Divergent synthesis of N-heterocycles by Pd-catalyzed controllable cyclization of vinylethylene carbonates. *Chem. Commun.* **2018**, *54*, 12182−12185. (b) Sakakibara, Y.; Murakami, K. Switchable Divergent Synthesis Using Photocatalysis. *ACS Catal.* **2022**, *12*, 1857−1878. (c) Koyama, R.; Anada, M.; Sueki, S.; Makino, K.; Kojima, T.; Kawasaki-Takasuka, T.; Mori, K. Divergent synthesis of multi-substituted phenanthrenes via an internal redox reaction/ring expansion sequence. *Chem. Commun.* **2024**, *60*, 3822−3825.

(7) CCDC 2354336 and 2354339 contain the supplementary crystallographic data for **4a** and **5a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, V. M.; Aubé, J. HFIP in Organic Synthesis. *Chem. Rev.* **2022**, *122*, 12544−12747.

(9) (a) Acheson, R. M.; Woollard, J. Addition reactions of heterocyclic compounds. Part LX. Reactions of 2-substituted pyridines with acetylenic esters leading to quinolizines and pyrrolo-[2,1,5-*cd*]indolizines. *J. Chem. Soc., Perkin Trans.* **1975**, *1*, 740−743. (b) Forti, L.; Gelmi, M. L.; Pocar, D.; Varallo, M. Convenient Synthesis of 4-Oxo-4*H*-quinolizines. *Heterocycles* **1986**, *24*, 1401−1410. (c) den Heeten, R.; van der Boon, L. J. P.; Broere, D. L. J.; Janssen, E.; de Kanter, F. J. J.; Ruijter, E.; Orru, R. V. A. Concise Synthesis of Highly Substituted Benzo[*a*]quinolizines by a Multicomponent Reaction/Allylation/Heck Reaction Sequence. *Eur. J. Org. Chem.* **2012**, *2*, 275−280. (d) Rosas-Sánchez, A.; Toscano, R. A.; López-Cortés, J. G.; Ortega-Alfaro, M. C. An Expedient Approach to Synthesize Fluorescent 3-Substituted 4*H*-quinolizin-4-ones via (η^4-vinylketene)-Fe$(CO)_3$ Complexes. *Dalton Trans.* **2015**, *44*, 578−590. (e) Chen, Z.; Liu, T.; Ma, X.; Liang, P.; Long, L.; Ye, M. One-Pot Sonogashira Coupling and Annulation Reaction: An Efficient Route toward 4*H*-Quinolizin-4-ones. *Synlett* **2019**, *30*, 863−867. (f) Fang, J.-W.; Liao, F.-J.; Qian, Y.; Dong, C.-C.; Xu, L.-J.; Gong, H.-Y. One-Pot Synthesis of 3-Substituted 4*H*-Quinolizin-4-ones via Alkyne Substrate Control Strategy. *J. Org. Chem.* **2021**, *86*, 3648−3655. (g) Qiu, D.; Su, Y. A dearomatization−rearomatization strategy for construction of 4*H*-quinolizin-4-ones via C−H bond functionalization of pyridines. *Org. Chem. Front.* **2014**, *11*, 2319−2325.

(10) (a) Chen, K.-P.; Chen, Y.-J.; Chuang, C.-P. Ethyl α-Nitrocinnamates in the Synthesis of Highly Functionalized Isoxazoles. *Eur. J. Org. Chem.* **2010**, *2010*, 5292−5300. (b) Yang, Y.; Gao, M.; Deng, C.; Zhang, D.-X.; Wu, L.-M.; Shu, W.-M.; Wu, A.-X. Synthesis of trisubstituted isoxazoles via in situ trapping strategy from α-nitro carbonyl compounds and methyl ketones or terminal aryl alkenes. *Tetrahedron* **2012**, *68*, 6257−6262. (c) Rathor, S. S.; Patel, A. K.; Samanta, S. Organocatalyzed diastereoselective cyclization of β-alkyl nitroolefins with alkylidene malononitriles: new approach to azetidine nitrones and isoxazoles. *Org. Chem. Front.* **2024**, *11*, 1782−1789.

(11) CCDC 2354335 contains the supplementary crystallographic data for **3b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) We thanked the reviewer for suggesting this experiment.

(13) Joshi, D. R.; Seo, Y.; Heo, Y.; Park, S.-H.; Lee, Y.; Namkung, W.; Kim, I. Domino [4 + 2] Annulation Access to Quinone−Indolizine Hybrids: Anticancer *N*-Fused Polycycles. *J. Org. Chem.* **2020**, *85*, 10994−11005.

(14) Zhou, X.; Chen, A.; Du, W.; Wang, Y.; Peng, Y.; Huang, H. Palladium−Catalyzed Hydrocarbonylative Cyclization Enabled by Formal Insertion of Aromatic C−N Bonds into Pd−Acyl Bonds. *Org. Lett.* **2019**, *21*, 9114−9118.

(15) Shukla, M. R.; Patra, S.; Verma, M.; Sadasivam, G.; Jana, N.; Mahangare, S. J.; Vidhate, P.; Lagad, D.; Tarage, A.; Cheemala, M.; Kulkarni, C.; Bhagwat, S.; Chaudhari, V. D.; Sayyed, M.; Pachpute, V.; Phadtare, R.; Gole, G.; Phukan, S.; Sunkara, B.; Samant, C.; Shingare, M.; Naik, A.; Trivedi, S.; Marisetti, A. K.; Reddy, M.; Gholve, M.; Mahajan, N.; Sabde, S.; Patil, V.; Modi, D.; Mehta, M.; Nigade, P.; Tamane, K.; Tota, S.; Goyal, H.; Volam, H.; Pawar, S.; Ahirrao, P.; Dinchhana, L.; Mallurwar, S.; Akarte, A.; Bokare, A.; Kanhere, R.; Reddy, N.; Koul, S.; Dandekar, M.; Singh, M.; Bernstein, P. R.; Narasimham, L.; Bhonde, M.; Gundu, J.; Goel, R.; Kulkarni, S.; Sharma, S.; Kamboj, R. K.; Palle, V. P. Discovery of a Potent and Selective PI3Kδ Inhibitor (*S*)-2,4-Diamino-6-((1-(7-fluoro-1-(4-fluorophenyl)-4-oxo-3-phenyl-4*H*-quinolizin-2-yl)ethyl)amino)-pyrimidine-5-carbonitrile with Improved Pharmacokinetic Profile and Superior Efficacy in Hematological Cancer Models. *J. Med. Chem.* **2020**, *63*, 14700−14723.

(16) Zahara, A. J.; Haines, B. E.; Wilkerson-Hill, S. M. Programmed Heterocycle Synthesis Using Halomuconononitriles as Pyridinimine Precursors. *Org. Lett.* **2024**, *26*, 2976−2981.

https://doi.org/10.1021/acsomega.4c05375
ACS Omega 2024, 9, 38126−38141