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Synthesis of Indolizines through Oxidative Linkage of C−C and C−N Bonds from 2-Pyridylacetates

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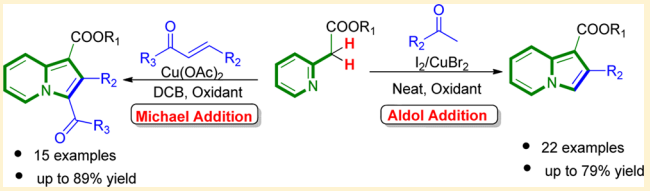
Supporting Information

ABSTRACT: Synthesis of indolizine-1-carboxylates through the Ortoleva−King reaction of 2-pyridylacetate followed by the Aldol condensation under mild reaction conditions has been described. This protocol is compatible with a broad range of functional groups, and it has been also successfully extended to unsaturated ketones, bringing about the regioselective formation of benzoyl-substituted indolizines through Michael addition followed by C−N bond formation, which are difficult to prepare by previous methods in a single step.



Indolizines are the most privileged structural units of heterocycles, and considerable attention has been paid in modern organic synthesis.[1−3] Several molecules bearing the indolizine scaffold have been proven to exhibit remarkable biological activity (Figure 1) like antimicrobial, anti-tubercular,[4]

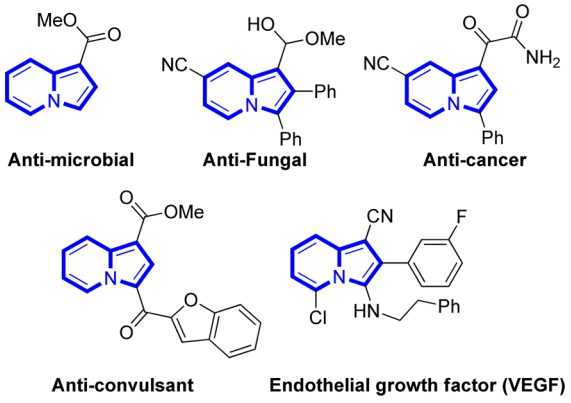
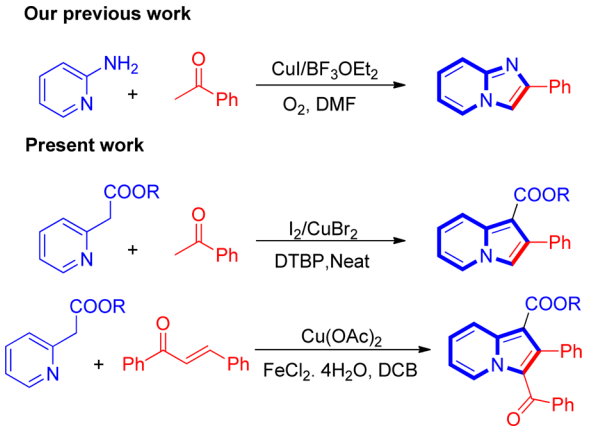


Figure 1. Biologically active Indolizines.

anti-inflammatory,[5] antifungal,[6] antioxidant,[7] anticancer,[8] and inhibitor for vascular endothelial growth factor (VEGF).[9,10] Substituted indolizines have also been used in material science due to their rich luminescent properties.[11−13]

Considering the wide range of biological activities, indolizine derivatives are being used as valuable leads for the design and synthesis of new biologically active analogues. Because of the importance of these molecules, some graceful methods have been developed, which includes 1,3-dipolar cycloaddition of pyridinium *N*-methylides with electron-deficient alkynes or alkenes,[14−17] transition-metal-catalyzed intramolecular cycloisomerization of pyridines,[18−22] copper-catalyzed [3 + 2] cyclization of pyridines with alkenyldiazoacetates,[23] multicomponent approaches,[24−28] copper catalyzed annulation of 2-alkylazaarenes with α,β-unsaturated carboxylic acids,[29] and I_2-mediated oxidative cyclization[30] and cyclization of pyridine derivatives.[31] Recently, we have reported copper-catalyzed aerobic oxidative synthesis of imidazo[1,2-*a*]pyridines from pyridine derivatives.[32] In continuation of our interest in the synthesis of heterocycles, herein we describe the direct synthesis of unsubstituted and substituted indolizine derivatives from commercially accessible pyridines, acetophenones, and chalcones (Scheme 1). The present method

Scheme 1



features a much broader scope on indolizine synthesis, and eliminates the requirement of pyridinium *N*-methylide derivatives.

In continuation of our studies on the synthesis of nitrogen-heterocycles,[33−38] we investigated the reaction of 2-pyridylacetates and acetophenones, as these starting substrates are commercially available. Initially, we performed the reaction of 2-pyridyl ethyl ester **1a** with 4-chloro acetophenone **2a** with a

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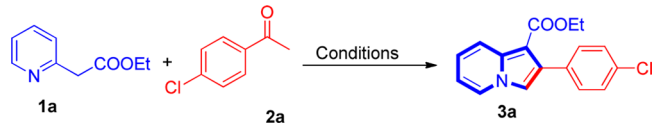
Table 1. Optimization of Conditions for 3a[a]



sample no	catalyst (mol %)	additive (mol %)	oxidant (equiv)	temp (°C)	solvent (mL)	yield (%)
1	CuI (10)	BF_3OEt_2 (10)	Air	65	DMF	5
2	CuI (10)	BF_3OEt_2 (10)	O_2	65	DMF	trace
3	CuI (10)	PivOH (10)	Air	65	DMF	trace
4	CuI (10)	-	Air	65	DMF	trace
5	CuI (10)	BF_3OEt_2 (10)	Air	65	neat	20
6	CuI (10)	$In(OTf)_3$(10)	Air	65	neat	23
7	CuI (10)	$CuBr_2$ (10)	Air	65	neat	32
8	-	$CuBr_2$ (10)	Air	65	neat	trace
9	CuI (10)	$CuBr_2$ (10)	DTBP(1)	65	neat	trace
10	CuI (10)	$CuBr_2$ (10)	DTBP(1)	80	neat	15
11	CuI (20)	$CuBr_2$ (10)	DTBP(1)	80	neat	20
12	**I_2 (20)**	**$CuBr_2$ (10)**	**DTBP**(1)	**80**	**neat**	**68**
13	I_2 (20)	-	DTBP(1)	80	neat	10
14	I_2 (10)	$CuBr_2$ (10)	DTBP(1)	80	neat	50
15	I_2 (30)	$CuBr_2$ (10)	DTBP(1)	80	neat	57
16	I_2 (20)	$CuBr_2$ (10)	TBBP(1)	80	neat	trace
17	I_2 (20)	$CuBr_2$ (10)	TBHP(1)	80	neat	trace
18	I_2 (20)	$CuBr_2$ (10)	$K_2S_2O_8$(1)	80	neat	trace
19	I_2 (20)	$CuBr_2$ (10)	H_2O_2(1)	80	neat	trace
20	I_2 (20)	$CuBr_2$ (10)	DTBP(1)	80	DMF	41
21	I_2 (20)	$CuBr_2$ (10)	DTBP(1)	80	DMA	43
22	I_2 (20)	$CuBr_2$ (10)	DTBP(1)	80	toluene	25
23	KI (20)	$CuBr_2$ (10)	DTBP(1)	80	neat	nr
24	TBAI (20)	$CuBr_2$ (10)	DTBP(1)	80	neat	nr

[a]Conditions: **1a** (0.30 mmol), **2a** (0.90 mmol), catalyst, additive, solvent (0.50 mL), in an oil bath 5 h in argon balloon, isolated yield.

catalytic amount of copper(I) iodide and $BF_3{\cdot}Et_2O$ as additive based on our previous results,[32] only 5% of product **3a** formation was observed in 5 h in open air (Table 1, entry 1). Traces of product formation were observed under oxygen atmosphere (entry 2) and with other additives (entries 3 and 4). In the reaction under neat conditions, 20% of **3a** was obtained (entry 5). Further, with other additives, the yield was raised to 32% (entries 6 and 7). No improvement of yield was observed in the absence of CuI, with other oxidant (DTBP) and increase of temperature to 80 °C (entries 8−11). However, using elemental iodine as catalyst in the place of copper iodide and DTBP as oxidant at 80 °C, 68% of **3a** was isolated (Table 1, entry 12). Under the same conditions but without additive ($CuBr_2$), the yield was dropped to 10% (entry 13). By increasing the amount of iodine, with other iodine sources (KI, and TBAI), oxidants (TBHP, TBBP, $K_2S_2O_8$, and H_2O_2), and other solvents tested were either poorly effective or entirely ineffective for the present transformation (Table 1, entries 14−24). As the cooperation of the I_2−$CuBr_2$ source showed the best reactivity, it was chosen as the best combination for further reactions (Table 1, entry 12).

To demonstrate the efficiency and to explore the scope of the optimized conditions for the synthesis of indolizines, different 2-pyridylacetates were investigated with acetophenone derivatives (Table 2). The oxidative annulation of other 2-pyridylacetates such as −COOMe, −COO^{i}Pr, −COO^{n}Bu, −COO^{t}Bu, and −COOCy, reacted well with 4-chloroacetophenone and produced the corresponding indolizine esters **3b**−**3f** in moderate to good yields. One of the product **3b** was further confirmed by single crystal XRD analysis (Figure 2). Although this route was only realized for a particular class of substrates (2-pyridylacetate based), for the formation of C−N bonds it represents a major development for the annulation strategy to obtain indolizine derivatives under mild conditions without the requirement of pyridinium-*N*-methylides.

Then, the generality of this reaction was extended with more functionalized acetophenones **2** with various 2-pyridylacetate **1**. The reaction was found to be very facile with both electron-rich and electron-deficient acetophenones. The reaction of ethyl 2-(pyridin-2-yl) acetate (**1a**), with neutral, electron rich, and deficient groups at the *para* position of acetophenone (Me, Et, OMe, Br) provided the desired products **3g**−**3k** in moderate yields. There was no steric effect observed in the case of 2,6-methoxyacetophenone as it also gave 57% yield of desired product **3l**. Attempts were made with substrates having halogens at the *ortho* position of acetophenones, and obtained corresponding halo products **3m**−**3r** in 52−76% yields. It may be noted that halide (Cl, Br, and F) substituted indolizine derivatives were well tolerated, and these products could be further useful in traditional cross-coupling reactions. We found that the present system is applicable to 2-acetylthiophene, to afford the desired product **3s** in moderate yield. Delightfully, the present system is also applicable to 2-(pyridin-2-yl) acetonitrile, and the nitrile substituted products **3t** and **3u** were obtained in 50% and 54% yield. Reaction of **1a** with propiophenone gave the desired product **3v** in moderate yield. In the case of aliphatic ketone like acetone, no reaction was observed **3w** (the substrate decomposed).

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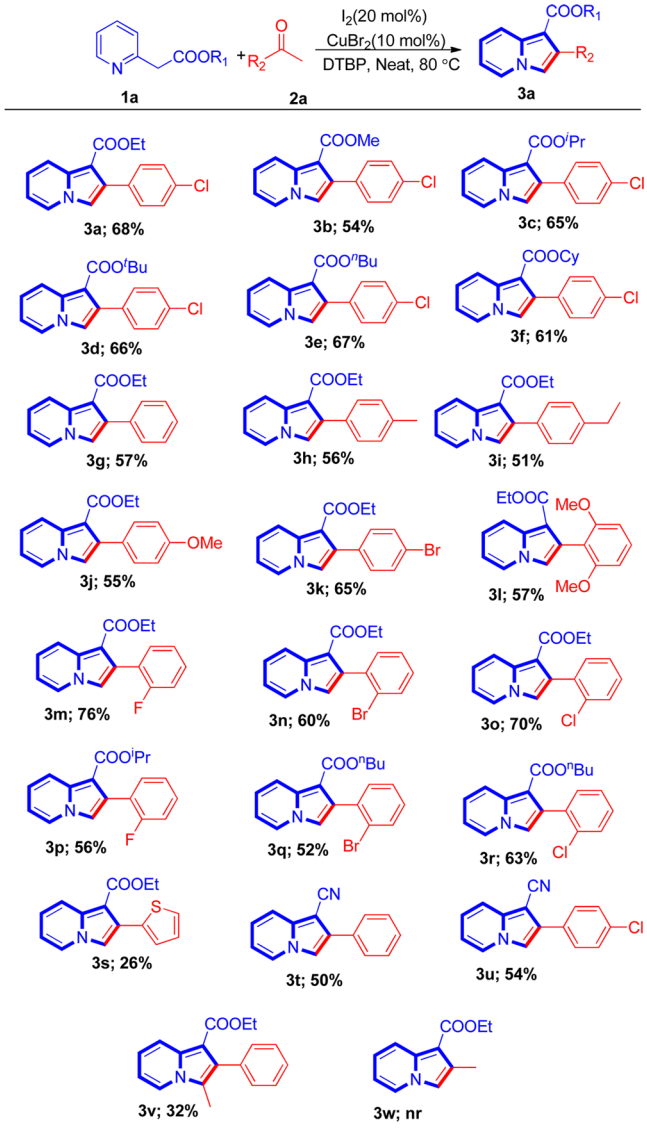
Table 2. Substrate Scope of Various 2-Pyridylacetate and Different Acetophenones[a]



[a]Conditions: **1** (0.30 mmol), **2** (0.90 mmol), I_2 (20 mol %), $CuBr_2$ (10 mol %), DTBP (0.30 mmol) in an oil bath 5 h, at 80 °C h in argon balloon, isolated yield.

Then, to establish the reaction mechanism, some control experiments were performed (Scheme 2). When 2-ethylpyridine **6** was reacted with acetophenone **2a** under the optimized conditions, no product formation was observed. When the same reaction was carried out in the presence of 1.0 equiv I_2, it resulted in <5% of yield. Further, the reaction was performed by the addition of AgOAc under optimized conditions, to confirm the role of catalytic iodine, but no product formation was observed. To confirm whether α-bromo/iodoacetophenone gives the desired product under the optimized reaction conditions, we performed the reaction of **1a** with both α-iodoacetophenone (**2aa**) and α-bromo acetophenone (**2ab**), respectively, in the former case 70% of **3a** was isolated and in the latter one traces of product were observed. These observations indicate that catalytic iodine plays a crucial role in generating α-iodoacetophenone as intermediate in the present transformation.

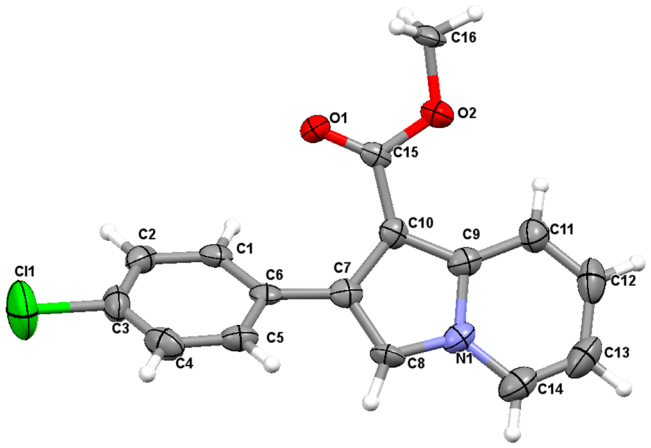
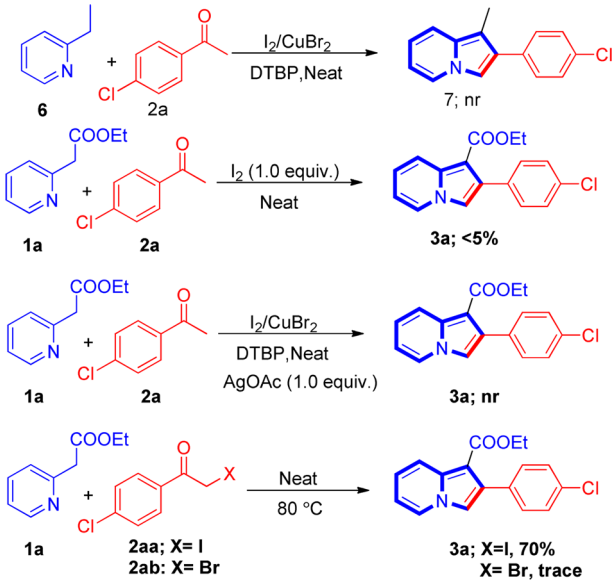
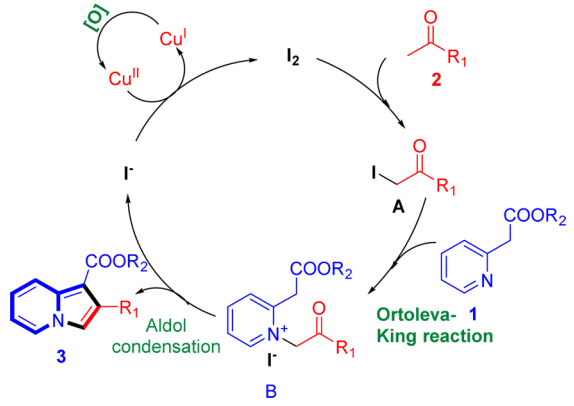


Figure 2. Crystal structure of **3b** (40% probability factor for the thermal ellipsoids).

Scheme 2. Control Experiments



Scheme 3. Plausible Reaction Mechanism



Based on the above control experiments and literature reports,[39−41] we proposed a plausible reaction mechanism as shown in Scheme 3. Initially, acetophenone **2** reacts with molecular iodine and generates α-iodoacetophenone **A** in situ, which will react with 2-pyridylacetate **1** and generates another

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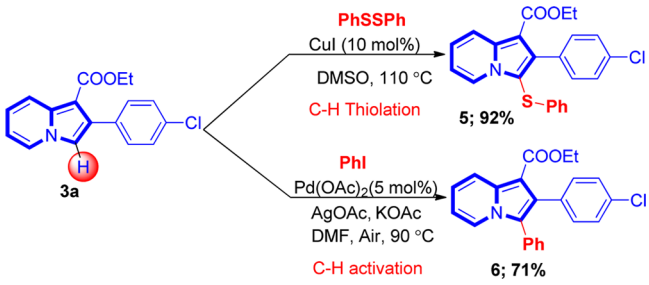
intermediate **B** through Ortoleva–King reaction. Intermediate **B** undergoes aldol condensation and yields the desired product **3**. The eliminated iodide ion (I^-) gets converted to molecular iodine to continue the cycle in the presence of copper and oxidant.

As the handful of indolizines were obtained under mild conditions, we thought of introducing substituents regioselectively at C-3 position of **3a**, to obtain the corresponding functionalized indolizine derivatives **5** and **6** (Scheme 4).

Scheme 4. Functionalization of 3-Unsubstituted Indolizines



Generally, the insertion of acyl/benzoyl groups to azo-heterocycles is a difficult task and often requires forcible reaction conditions.[42−44] To overcome these difficulties, we took on the challenge to obtain directly benzoylated indolizines from chalcones and 2-pyridylacetates under copper catalysis (for detailed investigation see Table S2) and good yields of desired products were obtained under these optimized conditions (Table 3).

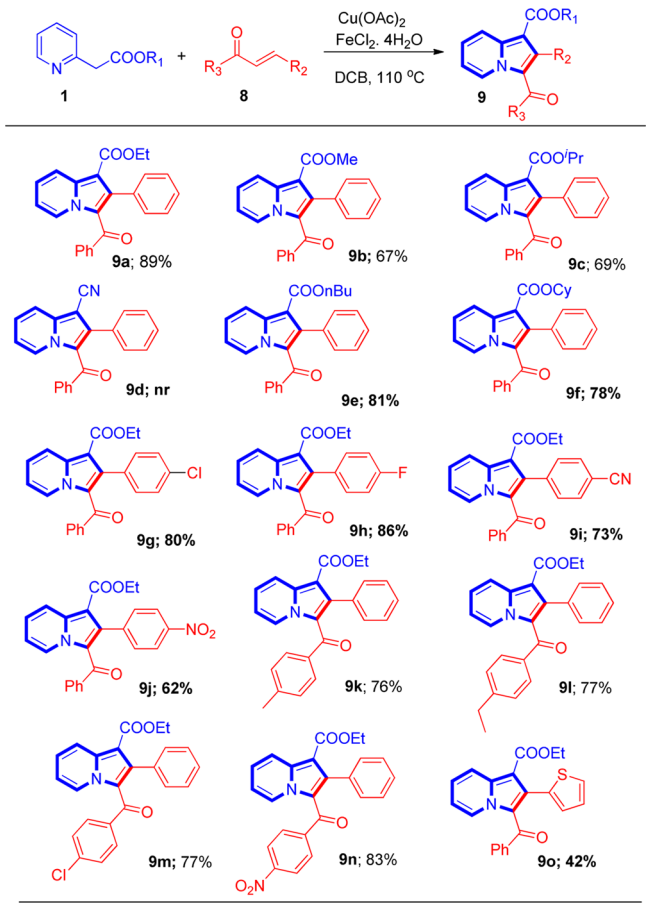
To the best of our knowledge, no reports exist to access these highly substituted indolizines from commercially available starting substrates in one pot under mild conditions. Chalcone **8a** was reacted with different 2-pyridylacetates such as−COOEt, −COOMe, −COO^{i}Pr, −COO^{n}Bu, −COO^{t}Bu, and −COOCy, and obtained the corresponding indolizines **9a**−**9f** in moderate to good yields. The product **9a** was further confirmed by single crystal XRD analysis (Figure S1). The presence of electron donating and withdrawing substituents in both phenyl rings of chalcones reacted well with 2-pyridylacetate and afford the corresponding products **9g**−**9n** in good yields (62−86%). The heteroatom substituted chalcone (*E*)-1-phenyl-3-(thiophen-2-yl)-prop-2-en-1-one was also reactive and produced the substituted indolizine **9o** in moderate yield. Unfortunately, the present system is not applicable for ethylcinnamate (**9p**) and it was not included in Table 3.

In conclusion, we have developed a new method for the synthesis of indolizine-1-carboxylates by the cooperative (I_2−$CuBr_2$) catalysis under mild reaction conditions. This protocol is compatible with a broad range of functional groups, and these molecules were selectively functionalized at the C-3 position to obtain sulfenylated and arylated products. In addition, copper-catalyzed synthesis of aroylated indolizines in a single step was also investigated.

EXPERIMENTAL SECTION

General Experimental Section. All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. The spectra were recorded in $CDCl_3$ as solvent. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), etc.; and coupling constants (*J*) were given in Hz. Chemical shifts are reported in ppm relative to TMS as an internal standard. The peaks around

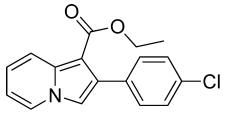
Table 3. Substrate scope of various 2-pyridylacetates with different chalcones[a]



[a]Conditions: **1** (0.60 mmol), **8** (0.20 mmol), catalyst (0.04 mmol), oxidant (0.40 mmol), solvent (1.0 mL), in an oil bath 12 h at 110 °C in argon balloon, isolated yield.

delta values of ^{1}H NMR (7.26) and ^{13}C NMR (77.0) correspond to deuterated solvent chloroform. The mass analyzer type TOF used for the HRMS measurements. Mass spectra were obtained using the electrospray ions impact (ESI) ionization method. Progress of the reactions was monitored by thin layer chromatography (TLC). All products were purified through column chromatography using silica gel 100−200 mesh size using hexane/ethyl acetate as eluent unless otherwise indicated.

*Typical Procedure for the Synthesis of Ethyl 2-(4-chlorophenyl)-indolizine-1-carboxylate (**3a**).* 49.5 mg (0.300 mmol) of ethyl 2-(pyridin-2-yl)acetate **1a**, 138.6 mg (0.900 mmol) of 4-chloroacetophenone (**2a**), I_2 (0.060 mmol, 15.2 mg), $CuBr_2$ (0.030 mmol, 6.6 mg), and DTBP (0.300 mmol) were placed in a reaction tube. The tube containing the above mixture was heated in an oil bath at 75−80 °C for 5 h under an argon atmosphere (balloon). After completion of the reaction, it was allowed to attain room temperature and added 20 mL of saturated ($Na_2S_2O_3$) hypo solution, extracted with EtOAc (20 mL × 2), and the solvent removed under reduced pressure. The remaining crude product was then purified through column chromatography using silica gel (5% EtOAc/hexane) to afford **3a**; 68% (60.5 mg) yield:



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 7.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H),

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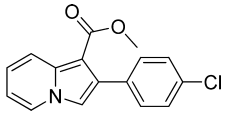
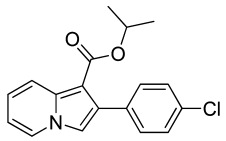
7.22 (s, 1H), 7.07 (t, J = 6.5 Hz, 1H). 6.73 (t, J = 6.5 Hz, 1H), 4.27 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 136.7, 133.4, 133.0, 131.4, 131.1, 127.6. 125.6, 120.3, 113.6, 112.7, 101.4, 59.4, 14.3. HRMS calcd for $C_{17}H_{15}ClNO_2$: 300.0791. Found: 300.0784.

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



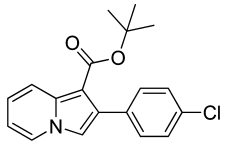
(Eluent: 5% EtOAc/hexane); 54% yield (46 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.5 Hz, 1H), 7.98 (d, J = 6.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.23 (s, 1H), 7.10−7.07 (m, 1H), 6.74 (t, J = 6.5 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 136.8, 133.4, 133.1, 131.5, 131.1, 127.8, 125.5, 122.7, 120.3, 113.7, 112.8, 101.1, 50.6. HRMS calcd for $C_{16}H_{13}ClNO_2$: 286.0635. Found: 286.0638.

*Isopropyl 2-(4-Chlorophenyl)indolizine-1-carboxylate (**3c**).*



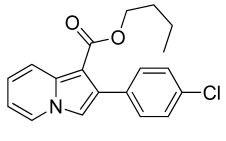
(Eluent: 5% EtOAc/hexane); 65% yield (60.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 7.0 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.20 (s, 1H), 7.07−7.04 (m, 1H), 6.71 (t, J = 6.5 Hz, 1H), 5.5 (septet, J = 6.5 Hz, 1H), 1.24 (d, J = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 135.6, 132.5, 131.9, 130.2, 126.5, 124.5, 121.5, 119.3, 112.5, 111.7, 100.8, 65.7, 21.0. HRMS calcd for $C_{18}H_{17}ClNO_2$: 314.0948. Found: 314.0952.

*tert-Butyl 2-(4-chlorophenyl)indolizine-1-carboxylate (**3d**).*



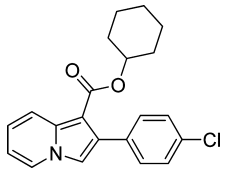
(Eluent: 5% EtOAc/hexane); 66% yield (65.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 7.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.09 (s, 1H), 6.95 (t, J = 6.5 Hz, 1H), 6.61 (t, J = 6.5 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 135.5, 132.8, 131.8, 130.2, 130.1, 126.8, 124.4, 121.3, 119.2, 112.3, 111.8, 27.4. HRMS calcd for $C_{19}H_{19}ClNO_2$: 328.1104. Found: 328.1092.

*Butyl 2-(4-Chlorophenyl)indolizine-1-carboxylate (**3e**).*



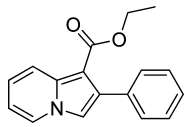
(Eluent: 5% EtOAc/hexane); 67% yield (66.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 7.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.10 (s, 1H), 6.99−6.96 (m, 1H), 6.79 (t, J = 6.5 Hz, 1H). 4.10 (t, J = 6.5 Hz, 2H), 1.49 (sextet, J = 6.5 Hz, 2H), 1.19 (sextet, J = 6.5 Hz, 2H). 0.79 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 136.7, 133.5, 132.9, 131.3, 131.1, 127.6, 125.4, 122.6, 120.3, 113.6, 112.7, 101.4, 63.3, 30.7, 19.2, 13.6. HRMS calcd for $C_{19}H_{19}ClNO_2$: 328.1104. Found: 328.1093.

*Cyclohexyl 2-(4-Chlorophenyl)indolizine-1-carboxylate (**3f**).*



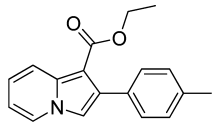
(Eluent: 5% EtOAc/hexane); 61% yield (65.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 7.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.19 (s, 1H), 7.06−7.03 (m, 1H), 6.70 (t, J = 6.5 Hz, 1H). 4.49 (septet, J = 4.0 Hz, 1H), 1.89−1.86 (m, 2H), 1.63−1.60 (m, 2H), 1.52−1.49 (m, 2H), 1.44−1.30 (m, 4H), 1.26−1.22 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 136.6, 133.5, 132.9, 131.4, 131.1, 127.4, 125.4, 122.9, 120.3, 113.5, 112.6, 101.8, 71.7, 31.8, 15.4, 13.7. HRMS calcd for $C_{21}H_{21}ClNO_2$: 354.1261. Found: 354.1254.

*Ethyl 2-Phenylindolizine-1-carboxylate (**3g**).*



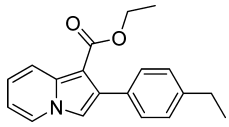
(Eluent: 5% EtOAc/hexane); 57% yield (45 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 9.0 Hz, 1H), 7.99 (d, J = 7.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 7.0 Hz, 2H), 7.31 (t, J = 7.0 Hz, 1H), 7.20 (s, 1H), 7.03 (t, J = 7.5 Hz, 1H). 6.68 (t, J = 6.5 Hz, 1H), 4.25 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 136.7, 134.9, 132.6, 129.8, 127.4, 126.9, 125.4 122.3, 120.2, 113.6, 112.5, 101.5, 59.2, 14.2. HRMS calcd for $C_{17}H_{16}NO_2$: 266.1181. Found: 266.1188.

*Ethyl 2-(p-Tolyl)indolizine-1-carboxylate (**3h**).*



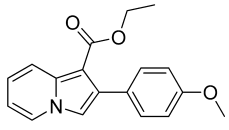
(Eluent: 5% EtOAc/hexane); 56% yield (47 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 6.5 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.14−7.09 (m, 3H), 6.93 (t, J = 7.0 Hz, 1H), 6.58 (t, J = 6.5 Hz, 1H). 4.25 (q, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9. 136.6, 132.6, 131.8, 129.7, 128.2, 125.4, 122.2, 120.2, 113.5, 112.4, 101.4, 59.2, 21.1, 14.2. HRMS calcd for $C_{18}H_{18}NO_2$: 280.1338. Found: 280.1324.

*Ethyl 2-(4-Ethylphenyl)indolizine-1-carboxylate (**3i**).*



(Eluent: 5% EtOAc/hexane); 51% yield (45.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 6.5 Hz, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.13−7.11 (m, 3H), 6.95−6.92 (m, 1H), 6.58 (t, J = 6.5 Hz, 1H), 4.18 (q, J = 7.5 Hz, 2H), 2.60 (q, J = 7.5 Hz, 2H). 1.20−1.14 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 143.0, 136.6, 132.0, 129.7, 127.0, 125.4, 122.2, 120.2, 113.5, 112.4, 101.4, 59.2, 28.5, 15.5, 14.2. HRMS calcd for $C_{19}H_{20}NO_2$: 294.1494. Found: 294.1490.

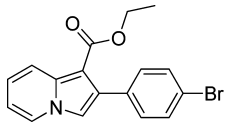
*Ethyl 2-(4-Methoxyphenyl)indolizine-1-carboxylate (**3j**).*



DOI: 10.1021/acs.joc.5b00477
J. Org. Chem. 2015, 80, 6846−6855

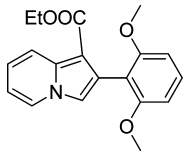
(Eluent: 5% EtOAc/hexane); 55% yield (48.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 7.0 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.19 (s, 1H), 7.03 (t, J = 6.5 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H), 6.69 (t, J = 6.5 Hz, 1H), 4.27 (q, J = 7.5 Hz, 2H), 3.83 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 158.8, 136.6, 130.9, 127.1, 125.4, 122.2, 120.2, 113.4, 113.0, 112.4, 101.3, 59.2, 52.2, 14.3. HRMS calcd for $C_{18}H_{18}NO_3$: 296.1287. Found: 296.1275.

*Ethyl 2-(4-Bromophenyl)indolizine-1-carboxylate (**3k**).*



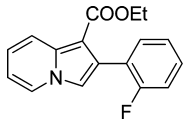
(Eluent: 5% EtOAc/hexane); 65% yield (66.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 6.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.19 (s, 1H), 7.06–7.03 (m, 1H), 6.71 (t, J = 6.5 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 136.7, 133.8, 130.5, 125.4, 122.6, 121.1, 120.2, 113.5, 112.7, 101.2, 59.3, 14.2. HRMS calcd for $C_{17}H_{15}BrNO_2$: 344.0286. Found: 344.0298.

*Ethyl 2-(2,6-Dimethoxyphenyl)indolizine-1-carboxylate (**3l**).*



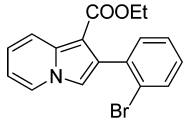
(Eluent: 5% EtOAc/hexane); 57% yield (56.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.13 (s, 1H), 6.91 (t, J = 7.0 Hz, 1H), 6.79–6.76 (m, 3H), 6.5 (t, J = 6.5 Hz, 1H), 4.08 (t, J = 7.5 Hz, 2H), 3.68 (s, 3H), 3.61 (s, 3H), 1.05 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 151.6, 136.0, 127.9, 125.4, 125.3, 121.9, 119.9, 117.2, 113.6, 112.6, 112.2, 111.2, 102.9, 58.9, 55.9, 55.5, 14.0. HRMS calcd for $C_{19}H_{20}NO_4$: 326.1394. Found: 326.1383.

*Ethyl 2-(2-Fluorophenyl)indolizine-1-carboxylate (**3m**).*



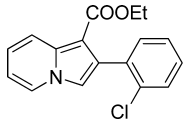
(Eluent: 5% EtOAc/hexane); 76% yield (61.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.5 Hz, 1H), 7.95 (d, J = 7.0 Hz, 1H), 7.38–7.29 (m, 2H), 7.24 (s, 1H, 7.16–7.08 (m, 2H), 7.05–7.02 (m, 1H), 6.68 (t, J = 6.5 Hz, 2H), 4.22 (q, J = 7.5 Hz, 2H), 1.63 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 161.3, (d, J = 245 Hz), 136.3, 131.8, 128.9, (d, J = 7.7 Hz), 125.5, 125.3, 123.2, 123.0, 122.3, 120.1, 115.0, (d, J = 22.5 Hz), 113.9, 112.5, 102.6, 59.2, 14.0. HRMS calcd for $C_{17}H_{15}FNO_2$: 284.1087. Found: 284.1081.

*Ethyl 2-(2-Bromophenyl)indolizine-1-carboxylate (**3n**).*



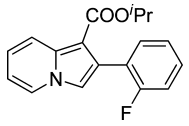
(Eluent: 5% EtOAc/hexane); 60% yield (61.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.33–7.29 (m, 2H), 7.21–7.17 (m 2H), 7.07–7.04 (m, 1H), 6.71 (t, J = 6.5 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 1.07 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 136.8, 135.9, 131.9, 131.5, 130.8, 128.5, 126.4, 125.6, 124.7, 122.4, 120.1, 113.5, 112.6, 102.8, 59.1, 13.9. HRMS calcd for $C_{17}H_{15}Br\ NO_2$: 344.0286. Found: 344.0298.

*Ethyl 2-(2-Chlorophenyl)indolizine-1-carboxylate (**3o**).*



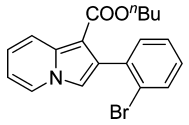
(Eluent: 5% EtOAc/hexane); 70% yield (62.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 7.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.33–7.24 (m, 3H), 7.20 (s, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.70 (t, J = 7.0 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 136.0, 134.6, 134.3, 131.5, 129.0, 128.8, 128.4, 125.8, 125.6, 122.4, 120.0, 113.6, 112.6, 102.8, 59.1, 13.9. HRMS calcd for $C_{17}H_{15}Cl\ NO_2$: 300.0791. Found: 300.0782.

*Isopropyl 2-(2-Fluorophenyl)indolizine-1-carboxylate (**3p**).*



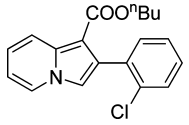
(Eluent: 5% EtOAc/hexane); 56% yield (49.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 7.0 Hz, 1H), 7.38–7.30 (m, 2H), 7.24 (s, 1H), 7.16–7.08 (m, 2H), 7.04 (t, J = 7.0 Hz, 1H), 6.68 (t, J = 6.5 Hz, 1H), 5.13 (septet, J = 6.0 Hz, 1H), 1.16 (d, J = 6.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 161.3, (d, J = 244 Hz), 136.2, 131.8, 128.8, (d, J = 7.7 Hz), 125.4, 125.3, 123.4, 123.2, 123.2, 122.2, 120.1, 115.0, (d, J = 22.2 Hz), 113.7, 112.5, 103.0, 67.4, 21.8. HRMS calcd for $C_{18}H_{17}FNO_2$: 298.1243. Found: 298.1231.

*Butyl 2-(2-Bromophenyl)indolizine-1-carboxylate (**3q**).*



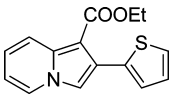
(Eluent: 5% EtOAc/hexane); 52% yield (58 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.32–7.29 (m, 2H), 7.21–7.18 (m, 2H), 7.08–7.05 (m, 1H), 6.73 (t, J = 6.5 Hz, 1H), 4.10 (t, J = 6.5 Hz, 2H), 1.39 (q, J = 6.5 Hz, 2H). 1.10 (sextet, J = 6.5 Hz, 2H), 0.79 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 136.9, 136.0, 132.0, 131.5, 130.7, 128.5, 126.4, 125.6, 124.7, 122.4, 120.1, 113.5, 112.6, 102.8, 63.2, 30.5, 19.1, 13.7. HRMS calcd for $C_{19}H_{19}BrNO_2Na$: 395.0497. Found: 395.0497.

*Butyl 2-(2-Chlorophenyl)indolizine-1-carboxylate (**3r**).*



(Eluent: 5% EtOAc/hexane); 63% yield (62.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 7.0 Hz, 1H), 7.544–7.42 (m, 1H), 7.34–7.32 (m, 1H), 7.39–7.24 (m, 2H0, 7.18 (s, 1H), 7.06 (t, J = 7.0 Hz, 1H), 6.70 (t, J = 7.0 Hz, 1H), 4.10 (t, J = 6.5 Hz, 2H), 1.14 (d, J = 6.5 Hz, 2H). 1.12 (sextet, J = 6.5 Hz, 2H), 0.80 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 136.1, 134.7, 134.3, 131.5, 128.9, 128.8, 128.3, 125.8, 125.5, 124.4, 120.0, 113.6, 112.6, 102.9, 63.2, 30.5, 19.0, 13.6. HRMS calcd for $C_{19}H_{19}ClNO_2$: 328.1104. Found: 328.1111.

*Ethyl 2-(thiophen-2-yl)indolizine-1-carboxylate (**3s**).*



(Eluent: 5% EtOAc/hexane); 26% yield (20.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 7.0 Hz, 1H),

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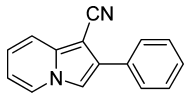
J. Org. Chem. 2015, 80, 6846–6855

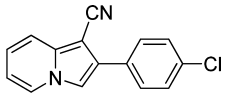
7.42 (d, J = 3.5 Hz, 1H), 7.36 (s, 1H), 7.31 (d, J = 5.0 Hz, 1H), 7.08–7.02 (m, 2H), 6.69 (t, J = 7.0 Hz, 1H), 4.35 (q, J = 7.0 Hz, 2H). 1.34 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 136.8, 135.5, 127.8, 126.6, 125.3, 124.8, 122.5, 120.3, 114.0, 112.8, 102.4, 59.4, 14.4. HRMS calcd for $C_{15}H_{14}NO_2S$: 272.0745. Found: 272.0738.

*2-Phenylindolizine-1-carbonitrile (**3t**).*



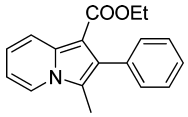
(Eluent: 5% EtOAc/hexane); 50% yield (33 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 9.0 Hz, 1H), 7.46–7.43 (m, 3H), 7.35 (t, J = 7.5 Hz, 1H), 7.07–7.04 (m, 1H), 6.75 (t, J = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 132.2, 131.7, 128.9, 128.0, 127.3, 126.0, 122.5, 117.7, 117.0, 113.2, 111.1, 80.0. HRMS calcd for $C_{15}H_{11}N_2$: 219.0922. Found: 219.0910.

*2-(4-Chlorophenyl)indolizine-1-carbonitrile (**3u**).*



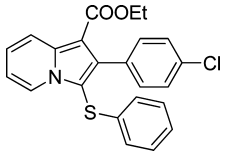
(Eluent: 5% EtOAc/hexane); 53% yield (40 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 7.0 Hz, 1H), 7.60–7.59 (m, 2H), 7.54 (d, J = 9.0 Hz, 1H), 7.33–7.31 (m, 3H), 6.99 (t, J = 7.0 Hz, 1H), 6.68 (t, J = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 133.9, 130.7, 130.5, 129.1, 128.4, 126.0, 122.8, 117.7, 116.8, 113.4, 111.1, 80.0. HRMS calcd for $C_{15}H_{10}ClN_2$: 253.0533. Found: 253.0536.

*Ethyl 3-Methyl-2-phenylindolizine-1-carboxylate (**3v**).*



(Eluent: 5% EtOAc/hexane); 32% yield (27 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 7.0 Hz, 1H), 7.33–7.26 (m, 5H), 7.00 (t, J = 8.5 Hz, 1H), 6.73 (t, J = 6.5 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 2.25 (s, 3H), 1.05 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 135.5, 135.4, 130.6, 1289.6, 127.2, 126.6, 122.5, 121.4, 120.0, 119.5, 112.4, 101.6, 59.0, 14.1, 9.7. HRMS calcd for $C_{18}H_{18}NO_2$: 280.1334. Found: 280.1336.

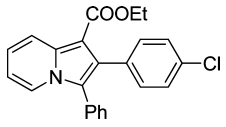
*Ethyl 2-(4-Chlorophenyl)-3-(phenylthio)indolizine-1-carboxylate (**5**).*[45]



To a round-bottomed flask containing organic disulfide (0.10 mmol), appropriate **3a** (0.20 mmol), CuI (3.0 mol %), was added DMSO (0.5 mL). The reaction mixture was allowed to stir at 110 °C for 10 h under atmospheric air the solutions were cooled to room temperature, diluted with ethyl acetate (10 mL), and washed with water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residues were purified by chromatography on silica gel using 3% ethyl acetate/hexane as the eluent and to afford **5**; 92% (75 mg) yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 9.0 Hz, 1H), 8.32 (d, J = 7.0 Hz, 1H), 7.33–7.29 (m, 5H), 7.23 (t, J = 8.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.84–6.79 (m, 3H), 4.23(q, J = 7.5 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 139.0, 138.4, 135.7, 133.48, 133.40, 133.7, 131.7, 129.2, 127.5, 127.4, 125.7, 125.3, 124.7, 124.6, 124.5, 120.0, 113.5, 110.1, 103.2, 59.5, 14.1. HRMS calcd for $C_{23}H_{19}ClNO_2$ S: 408.0825. Found: 408.0811.

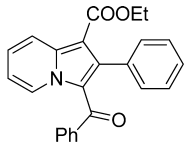
*Ethyl 2-(4-Chlorophenyl)-3-phenylindolizine-1-carboxylate (**6**).*[46]



A mixture of **3a** (0.300 mmol), iodobenzene (0.300 mmol), $Pd(OAc)_2$ (3.0 mg, 5 mol %), AgOAc (50.0 mg, 0.300 mmol), KOAc (59.0 mg, 0.600 mmol) in DMF (2 mL) was stirred at 90 °C under N_2 for 12 h. Afterward, the mixture was cooled to room temperature and filtered through a pad of Celite. The crude product was dissolved in Et_2O (20 mL), washed with water (2 × 10 mL) and brine (10 mL), and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography to obtain the desired product. (Eluent: 5% EtOAc/hexane); 71% yield (79.5 mg) isolated.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (t, J = 7.5 Hz, 1H), 7.96 (d, J = 7.0 Hz, 1H), 7.30–7.24 (m, 3H), 7.71–7.08 (m, 6H). 7.04–7.01 (m, 1H), 6.61 (t, J = 6.5 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 136.0, 133.4, 132.5, 132.2, 130.8, 129.8, 129.1, 128.9, 128.2, 127.4, 127.3, 124.7, 123.2, 122.8, 122.7, 120.2, 112.7, 102.4, 59.3, 14.2. HRMS calcd for $C_{23}H_{19}ClNO_2$ S: 376.1104. Found: 376.1103.

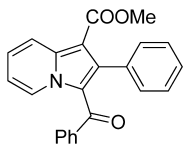
Typical Procedure for the Synthesis of Ethyl 3-Benzoyl-2-Phenylindolizine-1-Carboxylate (9a).



99.0 mg (0.600 mmol) of ethyl 2-(pyridin-2-yl)acetate **1a**, 41.6 mg (0.200 mmol) of (*E*)-chalcone (**8a**), $Cu(OAc)_2$ (0.040 mmol), $FeCl_2{\cdot}4H_2O$ (0.400 mmol), and dichlorobenzene (1.0 mL) were placed in a reaction tube. The tube containing the above mixture was heated in an oil bath at 110 °C for 12 h under an argon atmosphere (balloon). After completion of the reaction, it was allowed to attain room temperature and the reaction mixture filtered using Celite pad and washed with EtOAc. The crude product left after the removal solvent of under reduced pressure was purified through column chromatography using silica gel (10% EtOAc/hexane) to afford **9a**; 89% yield (68 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (d, J = 6.5 Hz, 1H), 8.47 (d, J = 9.0 Hz, 1H), 7.40 (t, J = 8.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.14 (t, J = 7.0 Hz, 1H), 7.08 (t, J = 3.5 Hz, 2H). 7.03–6.98 (m, 6H), 4.16 (q, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 164.3, 140.2, 139.2, 139.1, 133.8, 131.1, 130.8, 129.0, 128.0, 127.3, 127.0, 126.9, 126.6, 122.2, 119.6, 114.7, 104.7, 59.6, 13.4. HRMS calcd for $C_{24}H_{20}NO_3$: 370.1443. Found: 370.1441.

*Methyl 3-Benzoyl-2-phenylindolizine-1-carboxylate (**9b**).*



(Eluent: 10% EtOAc/hexane); 67% yield (47.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, J = 7.5 Hz, 1H), 8.36 (d, J = 9.0 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.0 Hz, 2H), 7.03 (t, J = 7.5 Hz, 1H), 7.02–7.00 (m, 2H), 6.96–6.91 (m, 6H), 3.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3, 164.6, 140.2, 139.2, 139.0, 133.6, 131.1, 131.0, 129.1, 128.0, 127.3, 127.1, 126.7, 122.3, 119.7, 114.8, 104.3, 51.8. HRMS calcd for $C_{23}H_{18}NO_3$: 356.1287. Found: 356.1295.

*Isopropyl 3-Benzoyl-2-phenylindolizine-1-carboxylate (**9c**).*

DOI: 10.1021/acs.joc.5b00477
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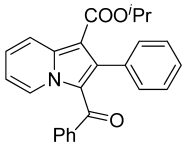
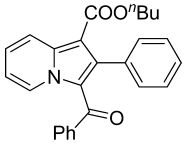


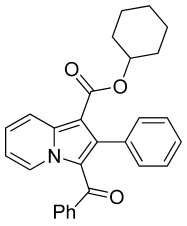
(Eluent: 10% EtOAc/hexane); 69% yield (53 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (d, J = 7.0 Hz, 1H), 8.48 (d, J = 9.0 Hz, 1H), 7.40 (d, J = 7.0 Hz, 1H), 7.35 (d, J = 7.0 Hz, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.08−7.06 (m, 2H), 7.03−6.97 (m, 6H), 5.07 (septet, J = 6.0 Hz, 2H), 1.07 (d, J = 6.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 163.8, 140.1, 139.3, 139.1, 134.0, 131.1, 130.8, 122.1, 119.6, 114.7, 105.2, 67.0, 21.6. HRMS calcd for $C_{25}H_{22}NO_3$: 384.1600. Found: 384.1579.

*Butyl 3-Benzoyl-2-phenylindolizine-1-carboxylate (**9e**).*



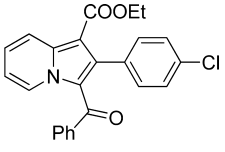
(Eluent: 10% EtOAc/hexane); 81% yield (64 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, J = 7.0 Hz, 1H), 8.49 (d, J = 9.0 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 7.0 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.08−7.07 (m, 2H), 7.03−6.97 (m, 6H), 4.09 (t, J = 6.5 Hz, 2H), 1.39 (quintet, J = 6.5 Hz, 2H), 1.09 (sextet, J = 6.5 Hz, 3H), 0.78 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 164.5, 140.1, 139.2, 133.9, 131.0, 130.8, 129.0, 127.9, 127.3, 127.1, 126.9, 126.6, 122.2, 119.6, 114.8, 104.7, 63.6, 30.4, 19.0, 13.6. HRMS calcd for $C_{26}H_{24}NO_3$: 398.1756. Found: 398.1758.

*Cyclohexyl 3-Benzoyl-2-phenylindolizine-1-carboxylate (**9f**).*



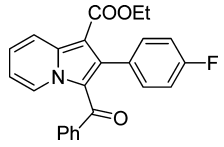
(Eluent: 10% EtOAc/hexane); 78% yield (66 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (d, J = 7.0 Hz, 1H), 8.49 (d, J = 9.0 Hz, 1H), 7.40 (t, J = 7.0 Hz, 1H), 7.34 (d, J = 7.5 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.08−7.07 (m, 2H), 7.03−6.97 (m, 6H), 4.88−4.85 (m, 1H), 1.75−1.73 (m, 2H), 1.48−1.42 (m, 2H), 1.26−1.11 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 163.8, 141.1, 139.3, 139.1, 134.0, 131.1, 130.8, 129.0, 127.9, 127.8, 127.0, 126.9, 126.7, 122.2, 119.7, 114.7,105.1, 72.1, 31.4, 25.2, 23.5. HRMS calcd for $C_{28}H_{26}NO_3$: 424.1913. Found: 424.1897.

*Ethyl 3-Benzoyl-2-(4-chlorophenyl)indolizine-1-carboxylate (**9g**).*



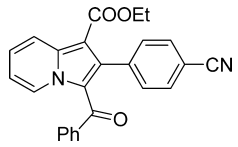
(Eluent: 10% EtOAc/hexane); 80% yield (64.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (d, J = 7.0 Hz, 1H), 8.46 (d, J = 9.0 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.06−6.94 (m, 7H), 4.18 (q, J = 7.0 Hz, 2H), 1.12 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.0. 164.0, 139.2, 139.1, 138.9, 133.0, 132.4, 132.3, 130.9, 128.9, 128.0, 127.5, 127.3, 126.8, 122.2, 119.7, 115.0, 104.6, 59.7, 13.9. HRMS calcd for $C_{24}H_{19}ClNO_3$: 404.1053. Found: 404.1056.

*Ethyl 3-Benzoyl-2-(4-fluorophenyl)indolizine-1-carboxylate (**9h**).*



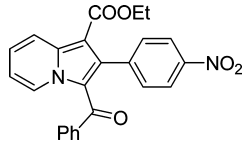
(Eluent: 10% EtOAc/hexane); 86% yield (66.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (d, J = 7.0 Hz, 1H), 8.46 (d, J = 9.0 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.33 (d, J = 7.0 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.05−7.02 (m, 5H), 6.68 (t, J = 5.5 Hz, 2H), 4.18 (q, J = 7.0 Hz, 2H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.0. 164.1, 162.8, (d, J = 245 Hz), 139.2, 139.1, 132.78, (d, J = 7.8 Hz), 131.1, 131.0, 129.8, 129.0, 128.0, 127.4, 127.2, 122.3, 119.7, 114.9, 113.7, (d, J = 21.5 Hz), 104.6, 59.6, 13.9. HRMS calcd for $C_{24}H_{19}FNO_3$: 388.1349. Found: 388.1364.

*Ethyl 3-Benzoyl-2-(4-cyanophenyl) indolizine-1-carboxylate (**9i**).*



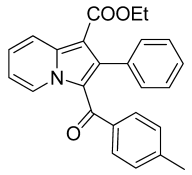
(Eluent: 10% EtOAc/hexane); 73% yield (58 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, J = 7.0 Hz, 1H), 8.48 (d, J = 9.0 Hz, 1H), 7.93−7.88 (m, 1H), 7.48−7.45 (m, 2H), 7.30−7.27 (m, 4H), 7.24−7.18 (m, 3H), 7.10−7.02 (m, 3H), 4.17 (q, J = 7.0 Hz, 2H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.6, 163.7, 139.3, 139.1, 139.0, 137.9, 131.7, 131.3, 130.1, 128.9, 128.6, 128.1, 127.9, 127.6, 122.1, 119.8, 118.7, 115.3, 110.5, 104.6, 59.9, 13.9. HRMS calcd for $C_{25}H_{19}N_2O_3$: 395.1396. Found: 395.1402.

*Ethyl 3-Benzoyl-2-(4-nitrophenyl)indolizine-1-carboxylate (**9j**).*



(Eluent: 10% EtOAc/hexane); 62% yield (51.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (d, J = 7.0 Hz, 1H), 8.49 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.0 Hz, 1H), 7.32 (d, J = 7.0 Hz, 2H), 7.25 (d, J = 7.5 Hz, 2H), 7.16 (t, J = 7.0 Hz, 1H), 7.10 (t, J = 7.0 Hz, 1H), 7.02 (t, J = 7.5 Hz, 2H), 4.18 (q, J = 7.0 Hz, 2H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.6, 163.7, 146.4, 141.4, 139.1, 139.0, 137.5, 132.1, 131.9, 131.3, 128.9, 128.1, 127.7, 127.6, 122.1, 121.7, 119.8, 115.4, 104.6, 59.9, 13.9. HRMS calcd for $C_{24}H_{19}N_2O_5$: 415.1294. Found: 415.1310.

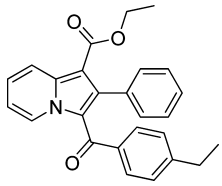
*Ethyl 3-(4-Methylbenzoyl)-2-phenylindolizine-1-carboxylate (**9k**).*



(Eluent: 10% EtOAc/hexane); 76% yield (58 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (d, J = 7.0 Hz, 1H), 8.45 (d, J = 9.0 Hz, 1H), 7.37 (t, J = 7.0 Hz, 1H), 7.27 (d, J = 7.0 Hz, 2H), 7.09−6.98 (m, 5H), 6.80 (d, J = 7.0 Hz, 2H), 4.16 (q, J = 7.0 Hz, 2H), 2.18 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 164.4, 140.5, 139.7, 139.0, 136.5, 134.0, 131.2, 129.3, 128.0, 127.9, 126.8, 126.7, 122.5, 119.7, 114.6, 104.4, 59.6, 21.3, 13.9. HRMS calcd for $C_{25}H_{22}NO_3$: 384.1600. Found: 384.1611.

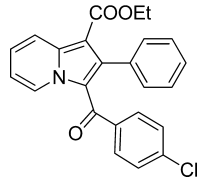
DOI: 10.1021/acs.joc.5b00477
J. Org. Chem. 2015, 80, 6846−6855

*Ethyl 3-(4-Ethylbenzoyl)-2-phenylindolizine-1-carboxylate (**9l**).*



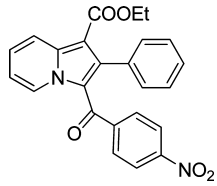
(Eluent: 10% EtOAc/hexane); 77% yield (61.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (d, J = 7.0 Hz, 1H), 8.37 (d, J = 9.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 7.0 Hz, 2H), 7.00−6.98 (m, 2H), 6.93−6.88 (m, 4H), 6.73 (d, J = 7.0 Hz, 2H), 4.03 (q, J = 7.0 Hz, 2H), 2.40 (q, J = 7.0 Hz, 2H), 1.03−0.98 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 164.3, 147.6, 139.9, 139.0, 136.7, 134.0, 131.1, 129.3, 127.9, 126.8, 126.6, 122.4, 119.6, 114.6, 104.5, 59.6, 28.7, 15.2, 13.8. HRMS calcd for $C_{26}H_{24}NO3$:398.1756. Found: 398.1762.

*Ethyl 3-(4-Chlorobenzoyl)-2-phenylindolizine-1-carboxylate (**9m**).*



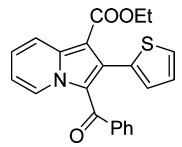
(Eluent: 10% EtOAc/hexane); 77% yield (63 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, J = 7.0 Hz, 1H), 8.47 (d, J = 9.0 Hz, 1H), 7.43 (t, J = 7.0 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 7.09−7.00 (m, 5H), 6.96 (d, J = 8.5 Hz, 2H), 4.16 (q, J = 7.0 Hz, 2H), 1.16 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7, 164.4, 140.4, 139.3, 137.7, 137.6, 133.1, 130.3, 128.0, 127.5, 127.4, 127.1, 126.8, 122.0, 119.7, 115.0, 104.9, 59.7, 13.8. HRMS calcd for $C_{24}H_{19}ClNO_3$: 404.1053. Found: 404.1052.

*Ethyl 3-(4-Nitrobenzoyl)-2-phenylindolizine-1-carboxylate (**9n**).*



(Eluent: 5% EtOAc/hexane); 83% yield (70 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (d, J = 7.0 Hz, 1H), 8.52 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.0 Hz, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.13 (t, J = 7.0 Hz, 1H), 7.03−6.96 (m, 5H), 4.14 (q, J = 7.0 Hz, 2H), 1.13 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6, 163.9, 148.1, 145.3, 141.3, 139.8, 133.6, 131.0, 129.5, 128.5, 128.4, 127.5, 126.9, 124.4, 121.7, 119.8, 115.0, 105.8, 59.8, 13.8. HRMS calcd for $C_{24}H_{19}N_2O_5$: 415.1294. Found: 415.1302.

*Ethyl 3-Benzoyl-2-(thiophen-2-yl)indolizine-1-carboxylate (**9o**).*



(Eluent: 5% EtOAc/hexane); 42% yield (32 mg); ^{1}H NMR (500 MHz,$CDCl_3$) δ 9.47 (d, J = 7.0 Hz, 1H), 8.43 (d, J = 9.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.27−7.24 (m, 1H), 7.14−7.08 (m, 3H), 7.01 (t, J = 7.0 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 6.60−6.58 (m, 1H), 4.25 (q, J = 7.0 Hz, 2H), 1.20 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 164.0, 139.3, 138.9, 133.8, 131.4, 131.2, 130.7, 128.7, 127.59, 127.51, 126.9, 125.9, 123.0, 119.7, 114.8, 105.2, 59.8, 14.0. HRMS calcd for $C_{22}H_{18}NO_3S$: 376.1007. Found: 376.1014.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds. Crystallographic data for compound **3b** (CCDC-1017738) and **9a** (CCDC-1051936) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00477.

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Notes

The authors declare no competing financial interest.

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