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I_2-Mediated Oxidative Cyclization for Synthesis of Substituted Indolizines

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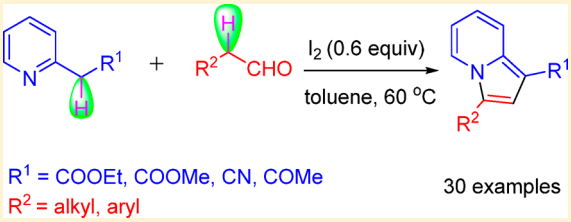
Supporting Information

ABSTRACT: A direct method for the synthesis of substituted indolizines by means of I_2-mediated oxidative tandem cyclization via C−N/C−C bond formation was developed. Various substituted aromatic/aliphatic enolizable aldehydes and 2-pyridylacetates/acetonitrile/acetone proceeded smoothly in this transformation, and the desired products were generated in moderate to good yields.



As well-known fused-ring N-heterocycles, indolizines are ubiquitous scaffolds found in natural products[1] and synthetic drugs.[2] Several indolizines as core structures are found in many pharmacological compounds because of their interesting biological activities, as illustrated in Figure 1.[3]

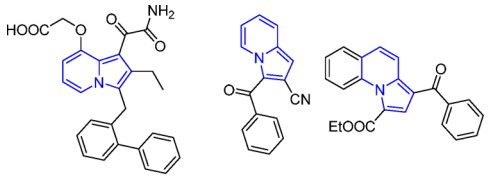


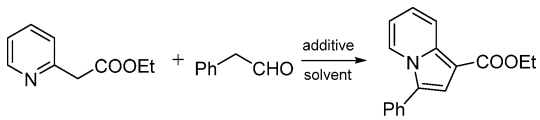
Figure 1. Selected examples of biologically active indolizines.

Substituted indolizines also have been used in materials science for their rich luminescent properties.[4] In the past decades, great progress in the synthesis of substituted indolizines had been achieved. Classical synthetic strategies focused on transition-metal-catalyzed cyclization starting from pyridinium *N*-methylides and pyridines with specific C2 functionalization.[5,6] However, most of those methods have several disadvantages, such as the use of toxic metal compounds, complex substrates, and harsh reaction conditions.

Recently, tandem reactions have emerged as powerful and versatile synthetic tools for the construction of substituted heterocyclic compounds from readily accessible materials.[7] Unfortunately, tandem annulation reactions of pyridine are very rare.[8] Therefore, the problem of how to synthesize substituted indolizines with simple substrates has become a central theme of numerous studies. As part of our continuing studies on the constuction of heterocyclic scaffolds,[9] we spectulated that the core of indolizines could be generated by cyclization of alkylpyridines and aldehydes via an oxidative tandem reaction. On the basis of this hypothesis, ethyl 2-(pyridin-2-yl)acetate (**1a**) and 2-phenylacetaldehyde (**2a**) were subjected to the transformation in DMF at 100 °C catalyzed by I_2. To our delight, the expected product ethyl 3-phenylindolizine-1-carboxylate (**3aa**) was isolated in 15% yield. Herein we report the development of this reaction into a general protocol for the synthesis of substituted indolizines from alkylpyridines and aldehydes.

Encouraged by the above result, substrates **1a** and **2a** were chosen as model compounds for optimization of this cyclization reaction (Table 1). An initial experiment revealed that iodine was

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

entry	additive (equiv)	solvent	T (°C)	yield (%)[b]
1	I_2 (0.1)	DMF	100	15
2	–	DMF	100	–
3	I_2 (0.6)	DMF	100	48
4	I_2 (1.2)	DMF	100	39
5	I_2 (0.6)	DMF	60	52
6	I_2 (0.6)	DMF	rt	33
7	**I_2 (0.6)**	**toluene**	**60**	**71**
8[c]	I_2 (0.6)	toluene	60	48
9	I_2 (0.6)	THF	60	62
10	I_2 (0.6)	CH_3CN	60	57
11	I_2 (0.6)	$ClCH_2CH_2Cl$	60	60
12	I_2 (0.6)	1,4-dioxane	60	32
13	NIS (1.2)	toluene	60	22

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), and additive in 4 mL of solvent under argon for 4 h. [b]Isolated yields. [c]Under air.

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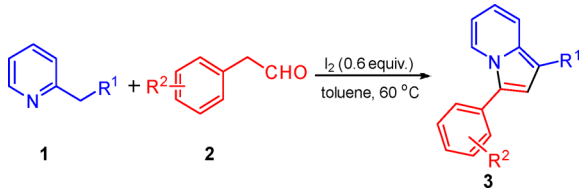
Table 2. Synthesis of Substituted Indolizines from Substituted Aromatic Enolizable Aldehydes and 2-Pyridylacetates/acetonitrile/acetone[a]



entry	1	R^1	2	R^2	product	yield (%)[b]
1	**1a**	COOEt	**2a**	H	**3aa**	71
2	**1a**	COOEt	**2b**	2-Me	**3ab**	66
3	**1a**	COOEt	**2c**	3-Me	**3ac**	78
4	**1a**	COOEt	**2d**	4-Me	**3ad**	60
5	**1a**	COOEt	**2e**	3,4-Me_2	**3ae**	81
6	**1a**	COOEt	**2f**	4-Et	**3af**	67
7	**1a**	COOEt	**2g**	3-OMe	**3ag**	82
8	**1a**	COOEt	**2h**	4-OMe	**3ah**	66
9	**1a**	COOEt	**2i**	3,4-$(OMe)_2$	**3ai**	69
10	**1a**	COOEt	**2j**	3,4,5-$(OMe)_3$	**3aj**	71
11	**1a**	COOEt	**2k**	2-F	**3ak**	68
12	**1a**	COOEt	**2l**	4-F	**3al**	63
13	**1b**	COOMe	**2a**	H	**3ba**	84
14	**1b**	COOMe	**2c**	3-Me	**3bc**	72
15	**1b**	COOMe	**2h**	4-OMe	**3bh**	77
16	**1b**	COOMe	**2j**	3,4,5-$(OMe)_3$	**3bj**	63
17	**1b**	COOMe	**2l**	4-F	**3bl**	78
18	**1c**	CN	**2a**	H	**3ca**	46
19	**1d**	COMe	**2a**	H	**3da**	70

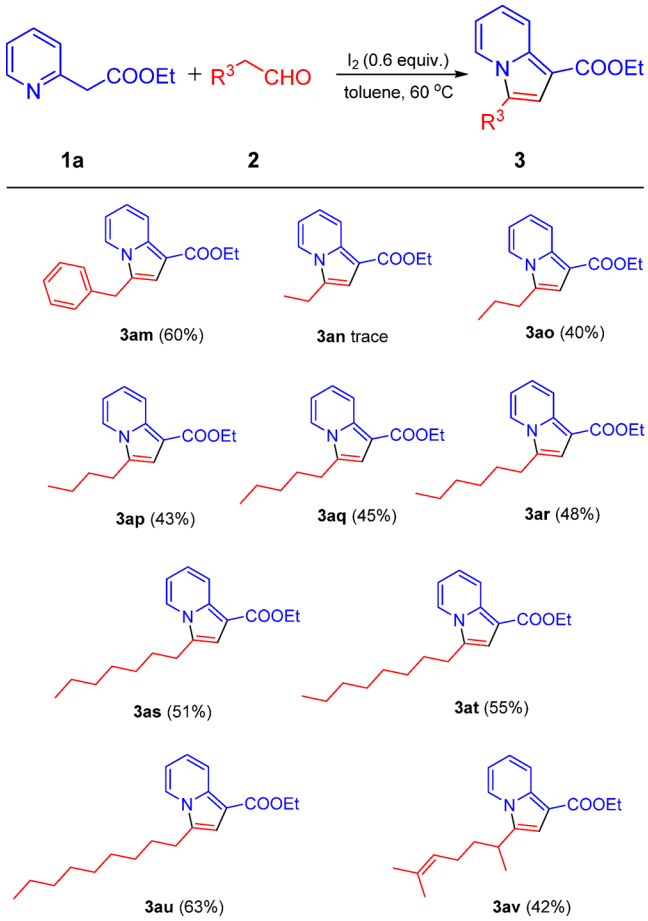
[a]Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), and I_2 (0.6 equiv) in 4 mL of toluene under argon for 4 h. [b]Isolated yields.

an important mediator in this reaction because no target product was detected without iodine (entry 2).[10] A higher yield was obtained with 0.6 equiv of iodine, when the amount of iodine was changed for this reaction (entry 3). The yield increased to 52% when the temperature was lowered to 60 °C in DMF with 0.6 equiv of I_2 (entry 5). Then different solvents were also evaluated for this transformation, and the highest yield (71%) was obtained in toluene at 60 °C under argon (entry 7). After screening of other parameters, we found that the optimal reaction conditions were 0.6 equiv of I_2 in toluene at 60 °C under argon.

The generality of the reaction was examined under the optimized conditions, and the results are illustrated in Table 2. A series of substituted aromatic enolizable aldehydes and 2-pyridylacetates/acetonitrile/acetone were investigated. To our satisfaction, the results indicated that aldehydes with different functionalities on the aryl ring reacted with 2-pyridylacetates/acetonitrile/acetone to generate the desired products in moderate to good yields. Further studies showed that neither the electronic nature nor the steric nature of the aldehyde significantly affected the efficiency of the reaction in terms of the yields of the products. When R^1 of alkylpyridines **1** was changed from −COOEt to −COOMe, the substituted aldehydes displayed better compatibility and performed well in this process (entries 13−17). Notably, when the R^1 group was altered to −CN and −COMe, the desired products **3ca** and **3da** were also formed in 46% and 70% yield, respectively (entries 18 and 19).

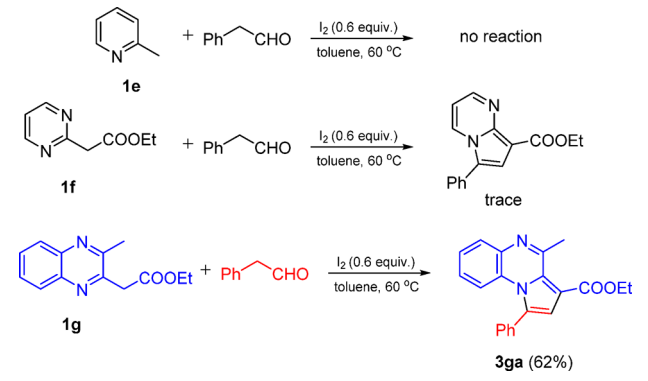
In order to extend the scope of this reaction, further experiments were conducted for the reaction of **1a** and aliphatic aldehydes under optimized conditions, and the results were

Scheme 1. Synthesis of Substituted Indolizines from Ethyl 2-Pyridylacetate and Aliphatic Aldehydes[a]



[a]Reaction conditions: **1a** (1.0 mmol), **2** (1.2 mmol), and I_2 (0.6 equiv) in 4 mL of toluene under argon for 4 h.

Scheme 2. Construction of Substituted Indolizines



shown in Scheme 1. Fortunately, the aliphatic aldehydes could also react well with **1a** in this transformation and form the desired products in moderate yields, except for *n*-butanal. As shown in Scheme 1, the yields slightly increased as the length of the carbon chain increased. Furthermore, aliphatic aldehydes bearing an aryl or alkenyl group were also perfectly tolerated under the optimized conditions, offering the target products **3am** and **3av** in 60% and 42% yield, respectively.

Moreover, some more challenging substrates were also tested for this reaction (Scheme 2). When 2-methylpyridine (**1e**) and

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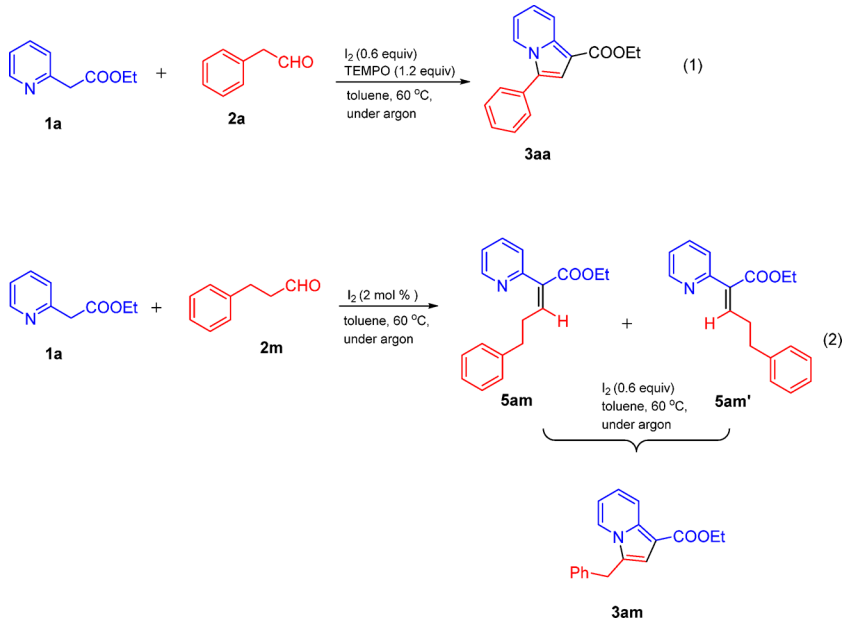
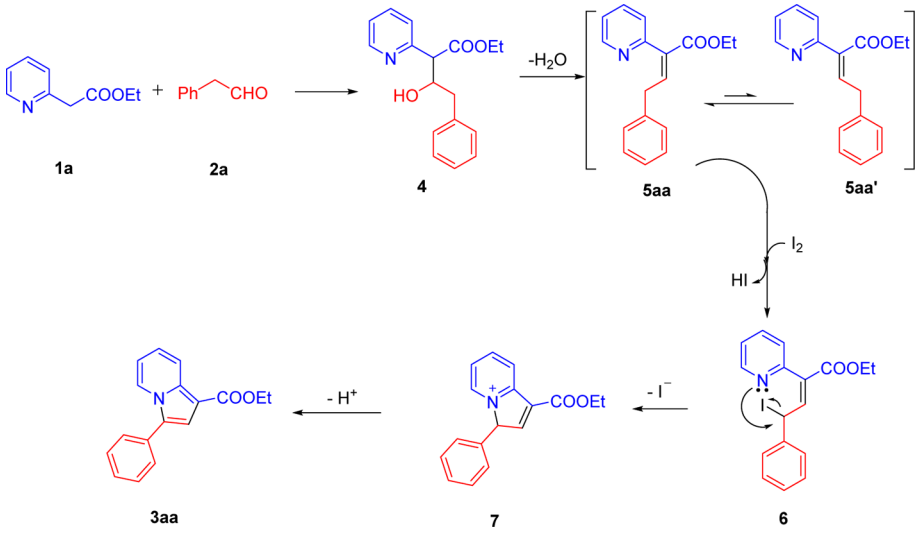
Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism



ethyl 2-(pyrimidin-2-yl)acetate (**1f**) were employed for this transformation, no desired products were isolated. Interestingly, when ethyl 2-(3-methylquinoxalin-2-yl)acetate (**1g**) was subjected to the optimized conditions, the desired compound **3ga** was successfully isolated in 62% yield (Scheme 2).

To probe the mechanism further, some control experiments were performed. First, a radical trapping experiment was performed in the presence of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO). Indeed, upon the addition of 1.2 equiv of TEMPO, the oxidative process was not remarkly suppressed, and no useful intermediate was isolated (Scheme 3, eq 1). Then, when the reaction of substrates **1a** and **2m** were carried out under the standard conditions with 2 mol % I_2, the compounds ethyl (*E*)-5-phenyl-2-(pyridin-2-yl)pent-2-enoate (**5am**) and ethyl (*Z*)-5-phenyl-2-(pyridin-2-yl)pent-2-enoate (**5am′**) were obtained after 4 h, and the **5am**:**5am′** molar ratio was approximately 1:1. Moreover, the desired product **3am** could also be successfully obtained at 60 °C (Scheme 3, eq 2). This indicates that the compounds **5am** and **5am′** are the intermediates of the transformation.

On the basis of the results described above, a plausible mechanism is proposed in Scheme 4. First, substrate **1a** reacts with **2a** to produce the aldol condensation intermediate **4**, which generates **5aa** and **5aa′** by a dehydration reaction. In this transformation, **5aa′** is converted to **5aa** via inversion of configuration under the optimized conditions. Then intermediate **6** is formed from **5aa** via electrophilic substitution with iodine. Finally, intermediate **6** undergoes intramolecular nucleophilic substitution to give intermediate **7** and subsequent proton elimination to afford the product **3aa** (Scheme 4).

In summary, we have developed an I_2-mediated direct oxidative cyclization reaction for the synthesis of substituted indolizines. Various aromatic and aliphatic enolizable aldehydes are well-tolerated in this procedure and react with 2-pyridylacetates/acetonitrile/acetone to give the desired products in moderate to good yields.

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EXPERIMENTAL SECTION

General Remarks. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$. All chemical shifts are given as δ values (in ppm) with reference to tetramethylsilane (TMS) as an internal standard. HRMS was performed on an FT-ICRMS instrument using electrospray ionization (ESI). Copies of the ^{1}H NMR and ^{13}C NMR spectra are provided in the Supporting Information. Products were purified by flash chromatography on 200−300 mesh silica gels. All melting points were determined without correction. Commercially available reagents and solvents were used without further purification except as noted.

General Procedure for the Synthesis of the Desired Indolizines 3. An oven-dried Schlenk tube was charged with ethyl 2-(pyridin-2-yl)acetate (**1a**) (1.0 mmol), 2-phenylacetaldehyde (**2a**) (1.2 mmol), and I_2 (0.6 mmol). The Schlenk tube was sealed and then evacuated and backfilled with argon (three cycles). Then 4 mL of toluene was added to the reaction system, and the reaction mixture was stirred at 60 °C for 4 h. After the mixture was cooled to room temperature, the solvent was evaporated with CH_2Cl_2 in vacuo, and the residues were purified by column chromatography, eluting with petroleum ether/EtOAc (20:1), to afford the desired indolizine **3aa**.

*Ethyl 3-Phenylindolizine-1-carboxylate (**3aa**).* White solid (188.2 mg, 71% yield), melting point 61−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.25 (m, 2H), 7.56−7.47 (m, 4H), 7.42−7.38 (m, 1H), 7.31 (s, 1H), 7.09−7.05 (m, 1H), 6.72−6.68 (m, 1H), 4.42−4.36 (q, J = 7.2 Hz, 2H), 1.44−1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 136.4, 131.3, 129.1, 128.6, 128.0, 126.4, 123.4, 122.2, 120.2, 116.1, 112.6, 104.3, 59.5, 14.7; HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$ 266.1176, found 266.1172. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.82; H, 5.75; N, 5.12%.

*Ethyl 3-(o-Tolyl)indolizine-1-carboxylate (**3ab**).* Brown oil (184.1 mg, 66% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.28 (d, J = 12 Hz, 1H), 7.64−7.63 (d, J = 4 Hz, 1H), 7.41−7.32 (m, 4H), 7.28 (s, 1H), 7.11−7.07 (m, 1H), 6.71−6.69 (m, 1H), 4.45−4.40 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.47−1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 138.5, 135.6, 131.5, 130.5, 130.4, 129.0, 126.2, 125.5, 123.7, 121.9, 120.0, 116.2, 112.3, 103.7, 59.5, 19.6, 14.7; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1332, found 280.1330. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.28; H, 6.21; N, 4.96%.

*Ethyl 3-(m-Tolyl)indolizine-1-carboxylate (**3ac**).* Brown oil (217.6 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.17 (m, 2H), 7.32−7.26 (m, 3H), 7.21 (s, 1H), 7.15−7.13 (d, J = 8 Hz, 1H), 7.00−6.96 (m, 1H), 6.64−6.60 (m, 1H), 4.34−4.29 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.36−1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 138.8, 136.3, 131.2, 129.3, 128.9, 128.8, 126.6, 125.6, 123.4, 122.1, 120.1, 116.0, 112.5, 104.2, 59.5, 21.5, 14.7; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1332, found 280.1335. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.54; H, 6.08; N, 5.11%.

*Ethyl 3-(p-Tolyl)indolizine-1-carboxylate (**3ad**).* Green oil (167.4 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.16 (m, 2H), 7.36−7.34 (d, J = 8 Hz, 2H), 7.23−7.19 (m, 3H), 6.99−6.65 (m, 1H), 6.62−6.58 (m, 1H), 4.34−4.28 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.36−1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 138.2, 136.5, 130.0, 128.8, 128.6, 126.7, 123.6, 122.3, 120.4, 116.0, 112.7, 104.3, 59.8, 21.6, 14.9; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1332, found 280.1330. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.35; H, 6.19; N, 4.97%.

*Ethyl 3-(3,4-Dimethylphenyl)indolizine-1-carboxylate (**3ae**).* White solid (225.9 mg, 81% yield), melting point 65−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.23 (m, 2H), 7.30 (s, 1H), 7.25 (s, 3H), 7.06−7.02 (m, 1H), 6.69−6.65 (m, 1H), 4.41−4.36 (q, J = 7.2 Hz, 2H), 2.33 (s, 6H), 1.43−1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 137.4, 136.7, 136.2, 130.3, 129.9, 128.7, 126.7, 126.0, 123.5, 122.0, 120.1, 115.7, 112.4, 104.1, 59.5, 19.9, 19.6, 14.7; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_2$ $[M + H]^+$ 294.1489, found 294.1488. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.63; H, 6.59; N, 4.76%.

*Ethyl 3-(4-Ethylphenyl)indolizine-1-carboxylate (**3af**).* White oil (196.3 mg, 67% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.16 (m, 2H), 7.38−7.36 (d, J = 8 Hz, 2H), 7.25−7.23 (d, J = 8 Hz, 2H), 7.20−7.18 (d, J = 8 Hz, 1H), 6.99−6.95 (m, 1H), 6.62−6.58 (m, 1H), 4.34−4.28 (q, J = 7.2 Hz, 2H), 2.67−2.62 (q, J = 7.6 Hz, 2H), 1.36−1.32 (t, J = 7.2 Hz, 3H), 1.24−1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 144.3, 136.2, 128.7, 128.6, 126.6, 123.4, 122.0, 120.2, 115.8, 112.4, 104.2, 59.5, 28.7, 15.5, 14.7; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_2$ $[M + H]^+$ 294.1489, found 294.1493. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.83; H, 6.53; N, 4.71%.

*Ethyl 3-(3-Methoxyphenyl)indolizine-1-carboxylate (**3ag**).* Yellow solid (241.9 mg, 82% yield), melting point 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.17 (m, 2H), 7.35−7.31 (m, 1H), 7.24 (s, 1H), 7.07−7.05 (m, 1H), 7.01−6.97 (m, 2H), 6.88−6.85 (m, 1H), 6.64−6.61 (m, 1H), 4.34−4.29 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 1.36−1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 160.1, 136.4, 132.6, 130.1, 126.3, 123.5, 122.2, 120.8, 120.2, 116.1, 114.2, 113.6, 112.6, 104.3, 59.6, 55.4, 14.7; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_3$ $[M + H]^+$ 296.1281, found 296.1284. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.40; H, 5.71; N, 4.78%.

*Ethyl 3-(4-Methoxyphenyl)indolizine-1-carboxylate (**3ah**).* Brown solid (194.7 mg, 66% yield), melting point 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.19 (m, 2H), 7.46−7.44 (d, J = 8 Hz, 2H), 7.24 (s, 1H), 7.07−7.01 (m, 3H), 6.70−6.66 (m, 1H), 4.41−4.36 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.43−1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 159.8, 136.3, 130.4, 126.5, 123.9, 123.6, 122.2, 120.4, 115.9, 114.8, 112.7, 104.3, 59.7, 55.64, 14.9; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_3$ $[M + H]^+$ 296.1281, found 296.1281. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.31; H, 5.86; N, 4.58%.

*Ethyl 3-(3,4-Dimethoxyphenyl)indolizine-1-carboxylate (**3ai**).* Yellow oil (224.3 mg, 69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.16 (m, 2H), 7.19 (s, 1H), 7.19−6.91 (m, 4H), 6.64−6.60 (m, 1H), 4.35−4.29 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 1.37−1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 149.5, 149.1, 136.1, 126.3, 123.9, 123.4, 122.0, 121.3, 120.2, 115.6, 112.5, 112.3, 111.6, 104.0, 59.5, 56.1, 56.0, 14.7; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_4$ $[M + H]^+$ 326.1387, found 326.1383. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.28; H, 5.93; N, 4.50%.

*Ethyl 3-(3,4,5-Trimethoxyphenyl)indolizine-1-carboxylate (**3aj**).* Yellow solid (252.1 mg, 71% yield), melting point 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.23 (m, 2H), 7.24 (s, 1H), 7.08−7.03 (m, 1H), 6.72−6.68 (m, 3H), 4.41−4.35 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 6H), 1.43−1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 153.8, 138.1, 136.2, 126.7, 126.4, 123.5, 122.1, 120.2, 115.9, 112.6, 106.1, 104.1, 61.0, 59.6, 56.3, 14.7; HRMS (ESI) m/z calcd for $C_{20}H_{22}NO_5$ $[M + H]^+$ 356.1493, found 356.1490. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.46; H, 6.03; N, 3.87%.

*Ethyl 3-(2-Fluorophenyl)indolizine-1-carboxylate (**3ak**).* Green oil (192.4 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−827 (d, J = 8 Hz, 1H), 7.89−7.86 (m, 1H), 7.51−7.46 (m, 1H), 7.45−7.39 (m, 1H), 7.35 (s, 1H), 7.29−7.20 (m, 2H), 7.12−7.08 (m, 1H), 6.75−6.71 (m, 1H), 4.42−4.37 (q, J = 7.2 Hz, 2H), 1.43−1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 161.4, 159.0, 136.5, 132.0 (d, J = 3 Hz, 1C), 130.3−130.2 (d, J = 10 Hz, 1C), 124.8−124.7 (d, J = 10 Hz, 1C), 124.3 (d, J = 4 Hz, 1C), 122.4, 120.5, 120.0, 119.1−118.9 (d, J = 20 Hz, 1C), 117.5, 116.3−116.1 (d, J = 20 Hz, 1C), 112.5, 104.4, 59.6, 14.7; HRMS (ESI) m/z calcd for $C_{17}H_{15}FNO_2$ $[M + H]^+$ 284.1081, found 284.1082. Anal. Calcd for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; N, 4.94. Found: C, 72.00; H, 4.91; N, 5.03%.

*Ethyl 3-(4-Fluorophenyl)indolizine-1-carboxylate (**3al**).* White oil (178.3 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.28 (d, J = 8 Hz, 1H), 8.21−8.19 (d, J = 8 Hz, 1H), 7.54−7.51 (m, 2H), 7.30−7.28 (d, J = 8 Hz, 1H), 7.24−7.19 (m, 2H), 7.11−7.07 (m, 1H), 6.75−6.71 (m, 1H), 4.44−4.39 (q, J = 7.2 Hz, 2H), 1.46−1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 163.7, 161.2, 136.2, 130.6−130.5 (d, J = 10 Hz, 2C), 127.4−127.3 (d, J = 10 Hz, 1C), 125.3, 123.1, 122.2, 120.2, 116.3−116.1 (m, 1C), 112.7, 104.3, 59.6, 14.6; HRMS (ESI) m/z

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calcd for $C_{17}H_{15}FNO_2$ $[M + H]^+$ 284.1082, found 284.1085. Anal. Calcd for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; N, 4.94. Found: C, 72.25; H, 5.05; N, 4.92%.

*Methyl 3-Phenylindolizine-1-carboxylate (**3ba**).* Yellow solid (210.8 mg, 84% yield), melting point 87−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.25 (m, 2H), 7.55−7.48 (m, 4H), 7.42−7.38 (m, 1H), 7.29 (s, 1H), 7.09−7.05 (m, 1H), 6.72−6.68 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 136.4, 131.2, 129.1, 128.6, 128.0, 126.5, 123.4, 122.3, 120.1, 116.0, 112.6, 103.9, 50.9; HRMS (ESI) m/z calcd for $C_{16}H_{14}NO_2$ $[M + H]^+$ 252.1019, found 252.1016. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.31; H, 5.11; N, 5.43%.

*Methyl 3-(m-Tolyl)indolizine-1-carboxylate (**3bc**).* Green oil (190.8 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.24 (m, 2H), 7.39−7.32 (m, 3H), 7.25 (s, 1H), 7.22−7.20 (d, J = 8 Hz, 1H), 7.08−7.04 (m, 1H), 6.71−6.67 (m, 1H), 3.91 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 138.8, 136.4, 131.1, 129.3, 128.9, 128.8, 126.6, 125.6, 123.5, 122.2, 120.1, 115.9, 112.5, 103.8, 50.9, 21.5; HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$ 266.1176, found 266.1175. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.86; H, 5.76; N, 5.14%.

*Methyl 3-(4-Methoxyphenyl)indolizine-1-carboxylate (**3bh**).* Black solid (216.4 mg, 77% yield), melting point 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.19 (m, 2H), 7.46−7.44 (d, J = 8 Hz, 2H), 7.22 (s, 1H), 7.08−7.02 (m, 3H), 6.71−6.67 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 159.5, 136.1, 130.2, 126.3, 123.5, 123.3, 122.1, 120.1, 115.5, 114.5, 112.5, 103.6, 55.4, 50.9; HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_3$ $[M + H]^+$ 282.1125, found 282.1129. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.48; H, 5.35; N, 4.96%.

*Methyl 3-(3,4,5-Trimethoxyphenyl)indolizine-1-carboxylate (**3bj**).* White solid (214.8 mg, 63% yield), melting point 176−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31−8.25 (m, 2H), 7.27 (s, 1H), 7.10−7.06 (d, J = 16 Hz, 1H), 6.74−6.71 (m, 3H), 3.93−3.92 (d, J = 4 Hz, 6H), 3.90 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 153.7, 138.1, 136.3, 126.6, 126.4, 123.5, 122.2, 120.1, 115.7, 112.7, 106.1, 103.7, 60.9, 56.3, 50.9; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_5$ $[M + H]^+$ 342.1336, found 342.1334. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.92; H, 5.69; N, 4.25%.

*Methyl 3-(4-Fluorophenyl)indolizine-1-carboxylate (**3bl**).* Yellow solid (209.8 mg, 78% yield), melting point 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27−8.25 (d, J = 8 Hz, 1H), 8.19−8.17 (d, J = 8 Hz, 1H), 7.51−7.48 (m, 2H), 7.25 (s, 1H), 7.21−7.17 (m, 2H), 7.10−7.06 (m, 1H), 6.73−6.69 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 164.0, 161.5, 136.6, 130.9−130.8 (d, J = 10 Hz, 2C), 127.6−127.5 (d, J = 10 Hz, 1C), 125.6, 123.4, 122.6, 120.4, 116.6−116.3 (d, J = 30 Hz, 1C), 113.0, 104.2, 51.2; HRMS (ESI) m/z calcd for $C_{16}H_{13}FNO_2$ $[M + H]^+$ 270.0925, found 270.0927. Anal. Calcd for $C_{16}H_{12}FNO_2$: C, 71.37; H, 4.49; N, 5.20. Found: C, 71.29; H, 4.54; N, 5.23%.

*3-Phenylindolizine-1-carbonitrile (**3ca**).* Yellow oil (100.3 mg, 46% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.26 (d, J = 8 Hz, 1H), 7.69−7.67 (d, J = 8 Hz, 1H), 7.52−7.50 (m, 4H), 7.47−7.42 (m, 1H), 7.10−7.06 (m, 1H), 7.04 (s, 1H), 6.76−6.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4 130.2, 129.3, 128.7, 128.6, 127.0, 123.8, 122.4, 118.2, 116.9, 116.3, 113.1, 82.3; HRMS (ESI) m/z calcd for $C_{15}H_{11}N_2$ $[M + H]^+$ 219.0917, found 219.0917. Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84. Found: C, 82.41; H, 4.64; N, 12.95%.

*1-(3-Phenylindolizin-1-yl)ethanone (**3da**).* Yellow solid (164.5 mg, 70% yield), melting point 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47−8.45 (d, J = 8 Hz, 1H), 8.23−8.21 (d, J = 8 Hz, 1H), 7.49−7.42 (m, 4H), 7.37−7.33 (m, 1H), 7.13−7.07 (m, 2H), 6.72−6.69 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 135.9, 131.1, 129.2, 128.7, 128.2, 126.4, 123.8, 123.2, 121.1, 116.5, 113.6, 28.0; HRMS (ESI) m/z calcd for $C_{16}H_{14}NO$ $[M + H]^+$ 236.1070, found 236.1074. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.73; H, 5.56; N, 5.88%.

*Ethyl 3-Benzylindolizine-1-carboxylate (**3am**).* Red oil (167.4 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33−8.30 (m, 1H), 7.83−7.81 (d, J = 8 Hz, 1H), 7.42−7.33 (m, 4H), 7.28 (d, J = 1.6 Hz, 1H), 7.19 (s, 1H), 7.15−7.11 (m, 1H), 6.78−6.74 (m, 1H), 4.49−4.44 (q, J = 7.2 Hz, 2H), 4.31 (s, 2H), 1.52−1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 136.9, 136.1, 128.8, 128.4, 126.8, 123.5, 123.1, 121.5, 120.0, 116.0, 112.3, 103.1, 59.4, 32.4, 14.7; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1332, found 280.1334. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.52; H, 6.08; N, 5.12%.

*Ethyl 3-Propylindolizine-1-carboxylate (**3ao**).* Green oil (92.4 mg, 40% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (d, J = 8 Hz, 1H), 7.85−7.83 (d, J = 8 Hz, 1H), 7.04−7.00 (m, 2H), 6.75−6.72 (m, 1H), 4.39−4.34 (q, J = 7.2 Hz, 2H), 2.78−2.74 (t, J = 7.2 Hz, 2H), 1.85−1.76 (m, 2H), 1.42−1.39 (t, J = 7.2 Hz, 3H), 1.07−1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 135.7, 125.5, 122.7, 121.1, 120.0, 113.8, 112.1, 102.9, 59.4, 27.8, 20.2, 14.7, 14.0; HRMS (ESI) m/z calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$ 232.1332, found 232.1331. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.81; H, 7.38; N, 6.03%.

*Ethyl 3-Butylindolizine-1-carboxylate (**3ap**).* Green oil (105.4 mg, 43% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (d, J = 8 Hz, 1H), 7.85−7.83 (d, J = 8 Hz, 1H), 7.04−7.00 (m, 2H), 6.76−6.72 (m, 1H), 4.39−4.33 (q, J = 7.2 Hz, 2H), 2.80−2.76 (t, J = 7.2 Hz, 2H), 1.80−1.72 (m, 2H), 1.52−1.39 (m, 5H), 1.00−0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 135.6, 125.7, 122.7, 121.0, 120.0, 113.7, 112.1, 102.8, 59.3, 29.0, 25.4, 22.6, 14.7, 13.9; HRMS (ESI) m/z calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$ 246.1489, found 246.1485. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.87; N, 5.74%.

*Ethyl 3-Pentylindolizine-1-carboxylate (**3aq**).* Green oil (116.6 mg, 45% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (d, J = 8 Hz, 1H), 7.85−7.83 (d, J = 8 Hz, 1H), 7.04−7.00 (m, 2H), 6.76−6.72 (m, 1H), 4.39−4.33 (q, J = 7.2 Hz, 2H), 2.79−2.75 (t, J = 7.2 Hz, 2H), 1.82−1.74 (m, 2H), 1.45−1.38 (m, 7H), 0.94−0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 135.7, 125.8, 122.7, 121.0, 120.0, 113.7, 112.1, 102.8, 59.4, 31.6, 26.6, 25.7, 22.5, 14.7, 14.0; HRMS (ESI) m/z calcd for $C_{16}H_{22}NO_2$ $[M + H]^+$ 260.1645, found 260.1642. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.08; H, 8.19; N, 5.36%.

*Ethyl 3-Hexylindolizine-1-carboxylate (**3ar**).* White solid (131.0 mg, 48% yield), melting point 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.17 (m, 1H), 7.82−7.80 (d, J = 8 Hz, 1H), 7.03−6.98 (m, 2H), 6.73−6.70 (m, 1H), 4.39−4.33 (q, J = 7.2 Hz, 2H), 2.76−2.73 (t, J = 7.6 Hz, 2H), 1.79−1.72 (m, 2H), 1.43−1.27 (m, 9H), 0.91−0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 135.8, 125.9, 122.8, 121.2, 120.1, 113.8, 112.2, 103.0, 59.5, 31.8, 29.3, 27.0, 25.9, 22.7, 14.8, 14.2; HRMS (ESI) m/z calcd for $C_{17}H_{24}NO_2$ $[M + H]^+$ 274.1802, found 274.1801. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.75; H, 8.52; N, 5.33%.

*Ethyl 3-Heptylindolizine-1-carboxylate (**3as**).* Yellow oil (146.4 mg, 51% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (d, J = 8 Hz, 1H), 7.84−7.82 (d, J = 8 Hz, 1H), 7.04−7.00 (m, 2H), 6.75−6.71 (m, 1H), 4.39−4.34 (q, J = 7.2 Hz, 2H), 2.78−2.74 (t, J = 7.2 Hz, 2H), 1.80−1.73 (m, 2H), 1.45−1.28 (m, 11H), 0.91−0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 135.6, 125.7, 122.6, 121.0, 120.0, 113.6, 112.0, 102.8, 59.3, 31.7, 29.4, 29.1, 26.9, 25.7, 22.6, 14.7, 14.0; HRMS (ESI) m/z calcd for $C_{18}H_{26}NO_2$ $[M + H]^+$ 288.1958, found 288.1961. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.27; H, 8.79; N, 4.79%.

*Ethyl 3-Octylindolizine-1-carboxylate (**3at**).* Yellow oil (165.6 mg, 55% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (d, J = 8 Hz, 1H), 7.85−7.83 (d, J = 8 Hz, 1H), 7.04−7.00 (m, 2H), 6.76−6.74 (m, 1H), 4.39−4.34 (q, J = 7.2 Hz, 2H), 2.79−2.75 (t, J = 7.2 Hz, 2H), 1.81−1.73 (m, 2H), 1.57 (s, 2H), 1.46−1.28 (m, 11H), 0.90−0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 135.6, 125.8, 122.7, 121.0, 120.0, 113.7, 112.1, 102.8, 59.3, 31.9, 29.5, 29.4, 29.2, 26.9, 25.7, 22.6, 14.7, 14.1; HRMS (ESI) m/z calcd for $C_{19}H_{28}NO_2$ $[M + H]^+$ 302.2115, found 302.2118. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.76; H, 9.10; N, 4.68%.

*Ethyl 3-Nonylindolizine-1-carboxylate (**3au**).* Green oil (198.5 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (d, J = 8 Hz, 1H), 7.84−7.83 (d, J = 4 Hz, 1H), 7.04−7.00 (m, 2H), 6.76−6.72 (m, 1H),

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4.39−4.33 (q, J = 7.2 Hz, 2H), 2.79−2.75 (t, J = 7.6 Hz, 2H), 1.81−1.73 (m, 2H), 1.44−1.28 (m, 15H), 0.90−0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 135.6, 125.8, 122.7, 121.0, 120.0, 113.6, 112.1, 102.8, 59.4, 31.9, 29.50, 29.49, 29.43, 29.3, 26.9, 25.7, 22.7, 14.7, 14.1; HRMS (ESI) m/z calcd for $C_{20}H_{30}NO_2$ $[M + H]^+$ 316.2271, found 316.2271. Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.23; H, 9.21; N, 4.49%.

*Ethyl 3-(6-Methylhept-5-en-2-yl)indolizine-1-carboxylate (**3av**).* Green oil (125.6 mg, 42% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.19 (d, J = 1 Hz, 1H), 7.88−7.87 (d, J = 4 Hz, 1H), 7.05−6.99 (m, 2H), 6.74−6.71 (m, 1H), 5.14−5.09 (m, 1H), 4.39−4.34 (q, J = 7.2 Hz, 2H), 3.08−2.99 (m, 1H), 2.08−2.02 (m, 2H), 1.68 (s, 3H), 1.65−1.60 (m, 2H), 1.50 (s, 3H), 1.43−1.39 (m, 3H), 1.35−1.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 135.7, 132.3, 130.9, 123.8, 122.7, 121.0, 120.1, 112.1, 112.0, 103.0, 59.4, 35.4, 29.4, 25.7, 25.6, 19.1, 17.6, 14.7; HRMS (ESI) m/z calcd for $C_{19}H_{26}NO_2$ $[M + H]^+$ 300.1958, found 300.1960. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.34; H, 8.36; N, 4.73%.

*Ethyl 4-Methyl-1-phenylpyrrolo[1,2-a]quinoxaline-3-carboxylate (**3ga**).* Yellow solid (204.6 mg, 62% yield), melting point 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 1H), 7.52−7.48 (m, 5H), 7.40−7.33 (m, 2H), 7.18 (s, 1H), 7.12−7.08 (m, 1H), 4.43−4.37 (q, J = 7.2 Hz, 2H), 3.05 (s, 3H), 1.43−1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 154.1, 137.0, 133.6, 131.4, 129.6, 129.3, 129.0, 128.9, 127.2, 126.4, 126.2, 125.7, 119.6, 116.9, 112.9, 60.8, 25.9, 14.3; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_2$ $[M + H]^+$ 331.1441, found 331.1440. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.36; H, 5.51; N, 8.37%.

*Ethyl (E)-5-Phenyl-2-(pyridin-2-yl)pent-2-enoate (**5am**).* Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50−8.48 (m, 1H), 7.58−7.54 (m, 1H), 7.27−7.08 (m, 7H), 6.72−6.68 (m, 1H), 4.29−4.23 (q, J = 7.2 Hz, 2H), 2.80−2.77 (m, 2H), 2.72−2.66 (m, 2H), 1.27−1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 154.9, 149.2, 141.2, 139.6, 136.4, 135.3, 128.5, 128.4, 126.1, 122.3, 121.3, 60.9, 35.3, 31.8, 14.3; HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_2$ $[M + H]^+$ 282.1489, found 282.1492. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.89; H, 6.73; N, 4.86%.

*Ethyl (Z)-5-Phenyl-2-(pyridin-2-yl)pent-2-enoate (**5am′**).* Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57−8.45 (m, 1H), 7.59−7.55 (m, 1H), 7.19−7.08 (m, 6H), 7.03−6.97 (m, 2H), 4.17−4.11 (q, J = 7.2 Hz, 2H), 2.71−2.67 (m, 2H), 2.40−2.34 (m, 2H), 1.19−1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 154.7, 149.2, 145.6, 140.9, 135.9, 134.2, 128.40, 128.36, 126.1, 124.9, 122.2, 60.9, 34.8, 31.2, 14.2; HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_2$ $[M + H]^+$ 282.1489, found 282.1490. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.95; H, 6.83; N, 4.87%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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