Convenient Synthesis of 2-Aryl-1-haloindolizines from Pyridinium Salts and 2-Aryl-1,1-dihaloalk-1-enes

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Abstract: 2-Aryl-1-haloindolizines were synthesized from pyridinium salts and 2-aryl-1,1-dihaloalk-1-enes using a DBU/THF system. 2-Aryl-1,1-dihaloalk-1-enes containing electron-withdrawing or -donating groups were efficiently converted into the corresponding 2-aryl-1-haloindolizines in moderate to excellent yields.

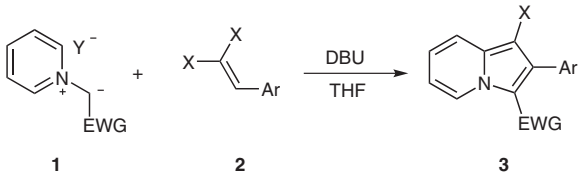
Key words: 2-aryl-1-haloindolizines, pyridinium, 1,1-dihaloalk-1-enes, haloalkyne, 1,3-dipolar cycloaddition

Indolizine is an isomer of indole;[1] its molecular structure, which features 10π-delocalized electrons, has been of theoretical interest for a long time.[2] Additionally, hydrogenated indolizines are key features in the skeletons of many important bioactive natural products, such as tabersonine,[3] strychnine,[4] and vinblastine.[5]

Indolizine derivatives are important heterocyclic compounds, they are widely used in biology as pesticides and medicines. For example, they can be used as pigments,[6] herbicides,[7] potential phospholipase inhibitors,[8] calcium entry blockers,[9] antileishmanial medicines,[10] antiviral drugs,[11] as well as histamine H_3 receptor antagonists;[12] they also display antimycobacterial activity.[13] In addition, they are key intermediates in the preparation of various alkaloids that have important biological activity.[14] Therefore, the synthesis of indolizine derivatives has received increased interest.

Indolizine derivatives can be prepared by various methods. One approach is based on the 1,3-dipolar cycloaddition reaction between pyridinium salts and electron-deficient alkynes or alkenes,[15] but in most cases, only a few terminal alkynes or alkenes, dimethyl acetylenedicarboxylate or dimethyl maleate as well as their analogues could be used in this process.[16] Recently, new synthetic methods have been developed for their preparation,[17] however, these approaches often require a transition metal catalyst. Therefore, it is necessary to develop a convenient synthetic route for the preparation of indolizine derivatives. The classic synthesis of 2-arylindolizines mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the Tsuchiya's procedure is very attractive due to its efficiency,[18] but, unfortunately, the starting materials are not commercially available and they are also not easy to synthesize in the laboratory.

Herein, we report a convenient and metal-free synthesis of a series of new 2-aryl-1-haloindolizines **3** with moderate to excellent yields. The 1,3-dipolar cycloaddition between pyridinium salts **1** and 1,1-dihaloalk-1-enes **2** in a 1,8-diazabicyclo[5.4.0]undec-7-ene–tetrahydrofuran system (Scheme 1) is exploited. To the best of our knowledge, the synthesis of ethyl 2-aryl-1-haloindolizine-3-carboxylates and 2-aryl-1-haloindolizine-3-carbonitriles has not yet been reported.



1 2 3

Scheme 1 Synthesis of 2-aryl-1-haloindolizines

To determine suitable reaction conditions, 1-[(ethoxycarbonyl)methyl]pyridinium bromide (**1a**) and 1-(2,2-dibromovinyl)-4-nitrobenzene (**2a**) were used as model substrates. A mixture of **1a**, **2a**, and DBU in tetrahydrofuran was then heated at 70 °C in a sealed tube using an oil bath. After 12 hours, the product **3a** was isolated in 85% yield. The reaction of **1a** and **2a** using different bases, various mole ratios, different solvents, and various reaction temperatures was investigated. The optimization of this 1,3-dipolar cycloaddition process between **1a** and **2a** is summarized in Table 1.

When **1a** reacted with **2a** in the presence of DBU (3 equiv) as a base in tetrahydrofuran solvent (70 °C, 12 h), the desired product **3a** was smoothly generated in 85% yield (entry 3). Changing the base to cesium carbonate, potassium carbonate, or DBU with potassium carbonate decreased the yields to 65%, 60%, and 80%, respectively (entries 1, 2, and 4). Using the conditions of entry 3 but at a temperature of 25 °C did not yield **3a** (entry 5). Changing the solvent to *N*,*N*-dimethylformamide and dimethyl sulfoxide decreased the yields to 30% and 5%, respectively (entries 6 and 7). Using a molar ratio of **1a** to **2a** 1:2

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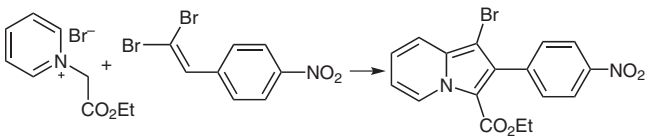
Table 1 Optimization of the Synthesis of **3a**



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

Entry	**1a** (mmol)	**2a** (mmol)	Base (3 equiv)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	0.15	0.15	Cs_2CO_3	THF	70	12	65
2	0.15	0.15	K_2CO_3	THF	70	12	60
3	0.15	0.15	DBU	THF	70	12	85
4	0.15	0.15	DBU + K_2CO_3[b]	THF	70	12	80
5	0.15	0.15	DBU	THF	25	6	0
6	0.15	0.15	DBU	DMF	70	12	30
7	0.15	0.15	DBU	DMSO	70	12	5
8	0.15	0.30	DBU[c]	THF	90	12	95
9	0.15	0.30	DBU[c]	THF	70	12	90

[a] Isolated yield.
[b] DBU (1.5 equiv) + K_2CO_3 (1.5 equiv).
[c] DBU (4.5 equiv).

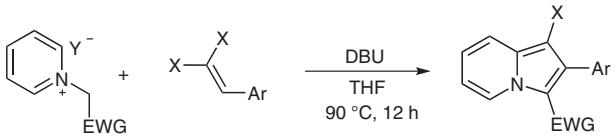
with DBU in tetrahydrofuran at 90 °C gave the major product **3a** in 95% yield (entry 8).

Hence, the optimum reaction conditions are 1:2 mol ratio of **1a** to **2a**, DBU (4.5 equiv) the base in tetrahydrofuran solvent, 90 °C reaction temperature, and 12 hours of reaction time (entry 8). Under these optimized conditions, the substrate scope was investigated. Apparently, these newly developed conditions are applicable to a series of 2-aryl-1-haloindolizines (Table 2).

Table 2 shows that 1,1-dihaloalk-1-enes **2** carrying either an electron-withdrawing group (such as nitro **2a**, halogens **2b–f**, trifluoromethyl **2g**, cyano **2h**, and methoxycarbonyl **2i**) or an electron-donating substituent (such as methyl **2k**, and methoxy **2l**) all proceeded smoothly with moderate to excellent yields.

Higher yields were obtained when 1,1-dihaloalk-1-enes **2** carried an electron-withdrawing group. Generally speaking, a higher yield was obtained using substrates **2** that have an electron-withdrawing group (hence a stronger electron-withdrawing inductive effect). Higher yields were also obtained when the substrates had a substituent in the *para*-position than in the *ortho*-position, cf. **2c** and **2d**, because of steric hindrance. 1,1-Dihaloalk-1-enes **2** bearing a *meta* group also produced good yields, but these were still lower than those bearing a *para* group, cf. **2e** and **2f**. An electron-withdrawing group at the *para*-position has a stronger electron-withdrawing inductive effect than a group at the *meta*-position. Compared with **1a**, the presence of a strong electron-withdrawing group on pyridinium salt **1b** decreased the yield of the indolizines **3** (cf. **3a** and **3o** with and **3p** and **3q**).

Table 2 Synthesis of 2-Aryl-1-haloindolizines **3**

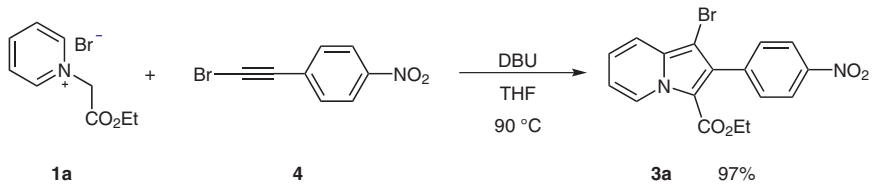


1a Y = Br, EWG = CO_2Et **2** **3**
1b Y = Cl, EWG = CN

Entry	Pyridinium salt **1**	1,1-Dihaloalk-1-ene **2**	X	Ar	Product	Yield (%)
1	**1a**	**2a**	Br	4-$O_2NC_6H_4$	**3a**	95
2	**1a**	**2b**	Br	4-FC_6H_4	**3b**	63
3	**1a**	**2c**	Br	4-ClC_6H_4	**3c**	85
4	**1a**	**2d**	Br	2-ClC_6H_4	**3d**	44
5	**1a**	**2e**	Br	4-BrC_6H_4	**3e**	76
6	**1a**	**2f**	Br	3-BrC_6H_4	**3f**	72
7	**1a**	**2g**	Br	4-$F_3CC_6H_4$	**3g**	62
8	**1a**	**2h**	Br	4-NCC_6H_4	**3h**	54
9	**1a**	**2i**	Br	4-$MeO_2CC_6H_4$	**3i**	46
10	**1a**	**2j**	Br	Ph	**3j**	40
11	**1a**	**2k**	Br	4-MeC_6H_4	**3k**	36
12	**1a**	**2l**	Br	4-$MeOC_6H_4$	**3l**	31
13	**1a**	**2n**	Br	3-pyridyl	**3m**	45
14	**1a**	**2m**	Br	2-naphthyl	**3n**	35
15	**1a**	**2o**	Cl	4-$O_2NC_6H_4$	**3o**	72
16	**1b**	**2a**	Br	4-$O_2NC_6H_4$	**3p**	80
17	**1b**	**2o**	Cl	4-$O_2NC_6H_4$	**3q**	67

We also used compound **1a** and 1,1-dibromo-4,8-dimethylnona-1,7-diene in a attempt to synthesize ethyl 1-bromo-2-(2,6-dimethylhept-5-enyl)indolizine-3-carboxylate, but unfortunately it was unsuccessful. The result indicated that it was hard for alkyl-substituted 1,1-dihaloalk-1-enes to react with compound **1a** to prepare 2-alkyl-1-haloindolizines.

To elucidate the probable reaction mechanism, the reaction of 1-(2,2-dibromovinyl)-4-nitrobenzene (**2a**) was performed in the presence of DBU, and the expected 1-(2-bromoethynyl)benzene (**4**) was obtained. Then pyridinium salt **1a** reacted with compound **4** using DBU as a base to generate indolizine **3a** in 97% yield in tetrahydrofuran solvent at 90 °C (Scheme 2). Based on the experimental data, a probable mechanism for the synthesis of 2-aryl-1-haloindolizines **3** is proposed.



1a 4 3a 97%

Scheme 2 1,3-Dipolar cycloaddition between **1a** and **4**

A haloalkyne was obtained by the elimination of hydrogen bromide from 1,1-dihaloalk-1-enes **2** using DBU as a base. Pyridinium salt **1** was deprotonated by DBU to give the corresponding ylide, which acted in a dipolar manner to react with the haloalkyne. Hence, 2-aryl-1-haloindolizines **3** were generated via 1,3-dipolar cycloaddition.

In conclusion, we have synthesized a series of novel 2-aryl-1-haloindolizines with moderate to excellent yields by the reaction of pyridinium salts and 1,1-dihaloalk-1-enes in the presence of the mild base DBU. The synthesis of a series of new 1,2,3-trisubstituted indolizines was convenient and metal-free. These indolizines are important heterocyclic compounds used in medicinal and biological research.

Melting points were recorded using a WRS-2A melting point apparatus and are uncorrected. IR spectra were obtained on a Nexus FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz spectrometer. Chemical shifts were reported relative to internal TMS [δ = 0.00 (^{1}H) and $CDCl_3$ [δ = 77.0 (^{13}C)]. MS data were measured with a Varian-310 mass spectrometer. HRMS were determined using a Finnigan-NAT GC/MS/DS 8430 spectrometer. Flash column chromatography was performed on 300–400 mesh silica gel. Pyridinium salts and 1,1-dihaloalk-1-enes were prepared according to literature procedures.[19–22]

2-Aryl-1-haloindolizines 3; General Procedure

A mixture of the pyridinium salt (0.15 mmol), the 1,1-dihaloalk-1-ene (0.30 mmol), and DBU (0.675 mmol) in THF was placed in a sealed tube. The tube was heated at 90 °C for 12 h using an oil bath. After the reaction was completed (TLC monitoring), the mixture was cooled to r.t. The solvent was then evaporated in vacuo. The resulting residue was purified by flash column chromatography (petroleum ether–EtOAc, 10:1) to yield 2-aryl-1-haloindolizines **3**.

Ethyl 1-Bromo-2-(4-nitrophenyl)indolizine-3-carboxylate (3a)

Yellow solid; mp 171.2–171.5 °C.

IR (KBr): 2962, 1679, 1593, 1531, 1505, 1464, 1349, 1226, 855, 740, 677 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 7.2 Hz, 1 H), 8.37 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.53 (d, *J* = 9.6 Hz, 1 H), 7.16 (t, *J* = 7.8 Hz, 1 H), 6.93 (t, *J* = 7.0 Hz, 1 H), 4.50 (q, *J* = 7.0, 7.2 Hz, 2 H), 1.50 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 146.7, 140.1, 134.8, 131.0 (2 C), 130.6, 127.9, 124.2, 123.8 (2 C), 116.4, 115.2, 113.8, 111.2, 60.7, 14.4.

MS (ESI): *m*/*z* (%) = 390 [(M + 2)$^+$, 38], 388 (M$^+$, 40).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{13}{}^{79}BrN_2O_4$: 388.0058; found: 388.0060.

Ethyl 1-Bromo-2-(4-fluorophenyl)indolizine-3-carboxylate (3b)

Yellow green solid; mp 124.1–125.0 °C.

IR (KBr): 2979, 1678, 1606, 1536, 1508, 1455, 1369, 1351, 1307, 1222, 1185, 1121, 753, 567 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.45 (d, *J* = 7.2 Hz, 1 H), 7.40–7.35 (m, 3 H), 7.10 (t, *J* = 8.4 Hz, 2 H), 6.97 (t, *J* = 7.8 Hz, 1 H), 6.76 (t, *J* = 7.0 Hz, 1 H), 4.39 (q, *J* = 7.2, 6.8 Hz, 2 H), 1.39 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2 (d, *J* = 245.4 Hz, 1 C), 161.2, 134.9, 132.2 (d, *J* = 8.0 Hz, 2 C), 128.8 (d, *J* = 3.1 Hz, 1 C), 127.6, 123.1, 116.8, 116.7, 115.5 (d, *J* = 21.5 Hz, 2 C), 113.3, 111.8, 111.4, 60.4, 14.5.

MS (ESI): *m*/*z* (%) = 363 [(M + 2)$^+$, 27], 361 (M$^+$, 28).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{13}{}^{79}BrFNO_2$: 361.0113; found: 361.0115.

Ethyl 1-Bromo-2-(4-chlorophenyl)indolizine-3-carboxylate (3c)

Light yellow solid; mp 105.6–106.3 °C.

IR (KBr): 2925, 1678, 1591, 1532, 1503, 1455, 1369, 1347, 1307, 1224, 1185, 1122, 820, 733, 657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (d, *J* = 7.2 Hz, 1 H), 7.40–7.35 (m, 5 H), 6.98 (t, *J* = 7.8 Hz, 1 H), 6.77 (t, *J* = 6.8 Hz, 1 H), 4.39 (q, *J* = 7.0, 7.2 Hz, 2 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 134.8, 133.3, 131.8 (2 C), 131.4, 128.7 (2 C), 127.7, 123.3, 116.7, 116.4, 113.4, 112.0, 111.3, 60.5, 14.5.

MS (ESI): *m*/*z* (%) = 381 [(M + 4)$^+$, 12], 379 [(M + 2)$^+$, 48], 377 (M$^+$, 37).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{13}{}^{79}Br^{35}ClNO_2$: 376.9819; found: 376.9818.

Ethyl 1-Bromo-2-(2-chlorophenyl)indolizine-3-carboxylate (3d)

Tan oil.

IR (KBr): 2927, 1678, 1600, 1536, 1459, 1369, 1354, 1342, 1308, 1223, 1188, 1122, 754, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (d, *J* = 7.2 Hz, 1 H), 7.57 (d, *J* = 4.0 Hz, 1 H), 7.40 (s, 3 H), 7.19 (d, *J* = 8.8 Hz, 1 H), 7.06 (t, *J* = 7.2 Hz, 1 H), 6.87 (t, *J* = 6.4 Hz, 1 H), 4.48 (q, *J* = 6.4, 6.8 Hz, 2 H), 1.49 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 135.3, 134.9, 133.5, 131.9, 129.8, 129.4, 127.7, 126.7, 123.0, 117.3, 115.5, 113.2, 112.5, 111.8, 60.4, 14.5.

MS (ESI): *m*/*z* (%) = 381 [(M + 4)$^+$, 10], 379 [(M + 2)$^+$, 45], 377 (M$^+$, 33).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{13}{}^{79}Br^{35}ClNO_2$: 376.9819; found: 376.9820.

Ethyl 1-Bromo-2-(4-bromophenyl)indolizine-3-carboxylate (3e)

Yellow solid; mp 102.2–103.1 °C.

IR (KBr): 2978, 1678, 1591, 1457, 1368, 1343, 1307, 1223, 1185, 1122, 819, 753, 655, 502 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.55 (d, *J* = 7.2 Hz, 1 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 9.2 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.08 (t, *J* = 7.8 Hz, 1 H), 6.87 (t, *J* = 6.4 Hz, 1 H), 4.48 (q, *J* = 7.0, 7.2 Hz, 2 H), 1.49 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 134.7, 132.1 (2 C), 131.9, 131.7 (2 C), 127.7, 123.3, 121.5, 116.7, 116.4, 113.4, 112.1, 111.2, 60.5, 14.5.

MS (ESI): *m*/*z* (%) = 425 [(M + 4)$^+$, 48], 423 [(M + 2)$^+$, 80], 421 (M$^+$, 50).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{13}{}^{79}Br_2NO_2$: 420.9313; found: 420.9315.

Ethyl 1-Bromo-2-(3-bromophenyl)indolizine-3-carboxylate (3f)
Tan solid; mp 89.4–90.2 °C.

IR (KBr): 2925, 1678, 1595, 1454, 1368, 1348, 1307, 1223, 1186, 1123, 750, 700, 651 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (d, *J* = 7.2 Hz, 1 H), 7.58 (s, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.38 (t, *J* = 9.8 Hz, 2 H), 7.28 (t, *J* = 7.8 Hz, 1 H), 7.00 (t, *J* = 7.8 Hz, 1 H), 6.78 (t, *J* = 6.8 Hz, 1 H), 4.39 (q, *J* = 7.2, 6.8 Hz, 2 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 135.1, 134.8, 133.3, 130.3, 130.0, 129.2, 127.7, 123.5, 122.4, 116.7, 116.1, 113.5, 112.1, 111.3, 60.5, 14.5.

MS (ESI): *m*/*z* (%) = 425 [(M + 4)$^+$, 50], 423 [(M + 2)$^+$, 85], 421 (M$^+$, 53).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{13}{}^{79}Br_2NO_2$: 420.9313; found: 420.9312.

Ethyl 1-Bromo-2-[4-(trifluoromethyl)phenyl]indolizine-3-carboxylate (3g)
Yellow-green solid; mp 97.1–98.0 °C.

IR (KBr): 2961, 1679, 1617, 1500, 1459, 1369, 1351, 1324, 1225, 1166, 1123, 756, 743, 654 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.48 (d, *J* = 7.2 Hz, 1 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 1 H), 7.01 (t, *J* = 7.8 Hz, 1 H), 6.79 (t, *J* = 6.8 Hz, 1 H), 4.40 (q, *J* = 7.0, 7.2 Hz, 2 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 136.8, 134.9, 130.7 (2 C), 129.3 (q, *J* = 32.3 Hz, 1 C), 127.8, 126.9 (q, *J* = 269.8 Hz, 1 C), 125.4 (q, *J* = 3.7 Hz, 2 C), 123.6, 116.6, 116.1, 113.6, 112.3, 111.2, 60.6, 14.5.

MS (ESI): *m*/*z* (%) = 413 [(M + 2)$^+$, 77], 411 (M$^+$, 79).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{18}H_{13}{}^{79}BrF_3NO_2$: 411.0082; found: 411.0083.

Ethyl 1-Bromo-2-(4-cyanophenyl)indolizine-3-carboxylate (3h)
Yellow solid; mp 145.1–146.1 °C.

IR (KBr): 2918, 2849, 2223, 1679, 1606, 1459, 1367, 1349, 1229, 1125, 754, 549 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, *J* = 7.2 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.8 Hz, 1 H), 7.13 (t, *J* = 7.8 Hz, 1 H), 6.91 (t, *J* = 7.0 Hz, 1 H), 4.49 (q, *J* = 7.2, 6.8 Hz, 2 H), 1.49 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 138.0, 134.7, 132.3 (2 C), 131.0 (2 C), 127.9, 124.0, 119.0, 116.4, 115.5, 113.7, 112.6, 111.1, 110.8, 60.6, 14.4.

MS (ESI): *m*/*z* (%) = 370 [(M + 2)$^+$, 35], 368 (M$^+$, 37).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{18}H_{13}{}^{79}BrN_2O_2$: 368.0161; found: 368.0163.

Ethyl 1-Bromo-2-[4-(methoxycarbonyl)phenyl]indolizine-3-carboxylate (3i)
Yellow solid; mp 131.4–132.3 °C.

IR (KBr): 2925, 1722, 1678, 1608, 1498, 1459, 1369, 1349, 1308, 1277, 1224, 1179, 1123, 750, 708, 658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (d, *J* = 7.2 Hz, 1 H), 8.17 (d, *J* = 7.6 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.10 (t, *J* = 7.6 Hz, 1 H), 6.88 (t, *J* = 7.0 Hz, 1 H), 4.49 (q, *J* = 7.2, 6.8 Hz, 2 H), 3.98 (s, 3 H), 1.49 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 161.1, 137.8, 134.9, 130.4 (2 C), 129.7 (2 C), 128.8, 127.8, 123.6, 116.7, 116.5, 113.6, 112.3, 111.2, 60.5, 52.2, 14.5.

MS (ESI): *m*/*z* (%) = 403 [(M + 2)$^+$, 46], 401 (M$^+$, 47).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{19}H_{16}{}^{79}BrNO_4$: 401.0263; found: 401.0265.

Ethyl 1-Bromo-2-phenylindolizine-3-carboxylate (3j)
Yellow-green oil.

IR (KBr): 2960, 2928, 1678, 1603, 1453, 1369, 1354, 1343, 1308, 1224, 1186, 1122, 734, 701, 659 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.55 (d, *J* = 7.2 Hz, 1 H), 7.54–7.49 (m, 5 H), 7.42 (d, *J* = 6.8 Hz, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H), 6.85 (t, *J* = 6.8 Hz, 1 H), 4.49 (q, *J* = 7.0, 7.2 Hz, 2 H), 1.49 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 134.9, 132.9, 130.5 (2 C), 128.4 (2 C), 127.6, 127.4, 123.0, 117.8, 117.0, 113.3, 111.8, 111.3, 60.4, 14.5.

MS (ESI): *m*/*z* (%) = 345 [(M + 2)$^+$, 28], 343 (M$^+$, 30).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{17}H_{14}{}^{79}BrNO_2$: 343.0208; found: 343.0210.

Ethyl 1-Bromo-2-*p*-tolylindolizine-3-carboxylate (3k)
Yellow-green oil.

IR (KBr): 2924, 2854, 1678, 1509, 1454, 1369, 1351, 1309, 1224, 1188, 1121, 816, 753, 663, 505 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.45 (d, *J* = 7.2 Hz, 1 H), 7.40 (d, *J* = 9.2 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 6.94 (t, *J* = 7.4 Hz, 1 H), 6.74 (t, *J* = 7.0 Hz, 1 H), 4.38 (q, *J* = 7.0, 7.2 Hz, 2 H), 2.36 (s, 3 H), 1.39 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 137.1, 134.9, 130.3 (2 C), 129.9, 129.2 (2 C), 127.6, 122.8, 117.7, 117.1, 113.2, 111.7, 111.4, 60.4, 21.3, 14.5.

MS (ESI): *m*/*z* (%) = 359 [(M + 2)$^+$, 92], 357 (M$^+$, 95).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{18}H_{16}{}^{79}BrNO_2$: 357.0365; found: 357.0368.

Ethyl 1-Bromo-2-(4-methoxyphenyl)indolizine-3-carboxylate (3l)
Yellow-green oil.

IR (KBr): 2927, 2852, 1678, 1612, 1454, 1369, 1351, 1307, 1288, 1248, 1223, 1188, 1121, 835, 755, 639, 579 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.44 (d, *J* = 7.2 Hz, 1 H), 7.38 (d, *J* = 9.2 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 6.94 (t, *J* = 7.8 Hz, 3 H), 6.74 (t, *J* = 6.8 Hz, 1 H), 4.38 (q, *J* = 7.0, 7.2 Hz, 2 H), 3.80 (s, 3 H), 1.39 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 158.9, 135.0, 131.6 (2 C), 127.6, 125.1, 122.8, 117.5, 117.1, 114.0 (2 C), 113.2, 111.6, 111.5, 60.3, 55.3, 14.5.

MS (ESI): *m*/*z* (%) = 375 [(M + 2)$^+$, 78], 373 (M$^+$, 80).

HRMS: *m/z* $[M]^+$ calcd for $C_{18}H_{16}{}^{79}BrNO_3$: 373.0314; found: 373.0315.

Ethyl 1-Bromo-2-(3-pyridyl)indolizine-3-carboxylate (3m)
Yellow-green solid; mp 120.3–121.2 °C.

IR (KBr): 3078, 2933, 2851, 1678, 1630, 1460, 1367, 1342, 1324, 1223, 1200, 1125, 809, 752, 711, 690, 566 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.50 (d, *J* = 7.2 Hz, 1 H), 8.72 (s, 1 H), 8.58 (d, *J* = 2.8 Hz, 1 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.47 (q, *J* = 5.2, 2.4 Hz, 1 H), 7.40 (d, *J* = 9.2 Hz, 1 H), 7.05 (t, *J* = 7.6 Hz, 1 H), 6.83 (t, *J* = 6.8 Hz, 1 H), 4.40 (q, *J* = 7.2, 6.8 Hz, 2 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 148.4, 145.6, 141.8, 140.1, 134.9, 130.5, 128.0, 124.3, 116.1, 113.9, 112.8, 112.5, 111.5, 60.7, 14.4.

MS (ESI): *m/z* (%) = 346 $[(M + 2)^+$, 59], 344 $(M^+$, 62).

HRMS: *m/z* $[M]^+$ calcd for $C_{16}H_{13}{}^{79}BrN_2O_2$: 344.0161; found: 344.0164.

Ethyl 1-Bromo-2-(2-naphthyl)indolizine-3-carboxylate (3n)
Yellow-green oil.

IR (KBr): 3055, 2926, 1678, 1601, 1453, 1370, 1342, 1330, 1305, 1222, 1118, 817, 745, 651, 559 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.48 (d, *J* = 7.2 Hz, 1 H), 7.87 (d, *J* = 7.2 Hz, 2 H), 7.82 (q, *J* = 5.8, 3.2 Hz, 2 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.47–7.43 (m, 3 H), 6.97 (t, *J* = 7.8 Hz, 1 H), 6.77 (t, *J* = 7.0 Hz, 1 H), 4.40 (q, *J* = 7.0, 7.2 Hz, 2 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 135.1, 133.5, 132.6, 130.4, 129.4, 128.5, 128.0 (2 C), 127.8, 127.7, 126.2, 126.1, 123.2, 117.7, 117.0, 113.4, 111.9, 111.5, 60.4, 14.5.

MS (ESI): *m/z* (%) = 395 $[(M + 2)^+$, 47], 393 $(M^+$, 48).

HRMS: *m/z* $[M]^+$ calcd for $C_{21}H_{16}{}^{79}BrNO_2$: 393.0365; found: 393.0368.

Ethyl 1-Chloro-2-(4-nitrophenyl)indolizine-3-carboxylate (3o)
Yellow solid; mp 171.2–172.1 °C.

IR (KBr): 2924, 1679, 1593, 1509, 1475, 1349, 1257, 1228, 1190, 1105, 855, 800, 755 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, *J* = 6.8 Hz, 1 H), 8.37 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 6.95 (t, *J* = 6.4 Hz, 1 H), 4.49 (q, *J* = 6.6, 7.2 Hz, 2 H), 1.49 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 146.6, 139.2, 134.2, 130.6 (2 C), 127.9, 127.6, 124.4, 123.9 (2 C), 116.3, 113.9, 112.8, 111.4, 60.6, 14.5.

MS (ESI): *m/z* (%) = 346 $[(M + 2)^+$, 20], 344 $(M^+$, 58).

HRMS: *m/z* $[M]^+$ calcd for $C_{17}H_{13}{}^{35}ClN_2O_4$: 344.0565; found: 344.0566.

1-Bromo-2-(4-nitrophenyl)indolizine-3-carbonitrile (3p)
Reddish-brown solid; mp 229.2–230.1 °C.

IR (KBr): 3100, 2203, 1595, 1518, 1338, 854, 744, 678 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 6.8 Hz, 1 H), 8.25 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 9.2 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 6.92 (t, *J* = 6.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 146.2, 140.9, 127.7 (2 C), 126.0, 124.5 (2 C), 124.3, 121.8, 118.2, 114.3, 113.1, 110.2, 93.7.

MS (ESI): *m/z* (%) = 343 $[(M + 2)^+$, 46], 341 $(M^+$, 48).

HRMS: *m/z* $[M]^+$ calcd for $C_{15}H_8{}^{79}BrN_3O_2$: 340.9782; found: 340.9785.

1-Chloro-2-(4-nitrophenyl)indolizine-3-carbonitrile (3q)
Yellow solid; mp 250.0–251.0 °C.

IR (KBr): 3078, 2252, 2126, 1590, 1503, 1343, 824, 762, 617 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 8.4 Hz, 2 H), 8.30 (d, *J* = 6.8 Hz, 1 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.65 (d, *J* = 8.8 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.02 (t, *J* = 6.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 137.9, 133.7, 130.0 (2 C), 125.5, 124.9, 124.2 (2 C), 122.2, 117.5, 114.7, 111.9, 111.4, 104.5.

MS (ESI): *m/z* (%) = 299 $[(M + 2)^+$, 17], 297 $(M^+$, 50).

HRMS: *m/z* $[M]^+$ calcd for $C_{15}H_8{}^{35}ClN_3O_2$: 297.0306; found: 297.0308.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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