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A FACILE APPROACH TO INDOLIZINES *VIA* TANDEM REACTION

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Abstract – Indolizines were synthesized by a novel tandem reaction at rt. The operation was simple and convenient. Various indolizine derivatives were obtained in good yields. The reaction mechanism was also proposed.

INTRODUCTION

Indolizines have attracted considerable attention from medicinal and organic chemists because of the interesting similarities and diversions in structure to indole.[1] Synthetic indolizines play important roles as calcium entry blockers,[2] potential central nervous system depressants,[3] 5-HT_3 receptor antagonist,[4] histamine H_3 receptor antagonists,[5] cardiovascular agents,[6] and PLA_2 inhibitors.[7] They have also drawn much attention owing to their possible usage as dyes and chemosensors.[8]

Several condensation reactions, 1,3-dipolar cycloadditions, and 1,5-dipolar cyclizations are known to facilitate the formation of indolizines.[9] The most general method is the formation of the five-member ring moiety in the indolizine framework.[1b] Chichibabin-type cyclocondensation requires elevated temperatures and/or extended reaction time and, thus, may not be compatible with some functionality.[10] Also, it provides low to moderate yields of the products.[11] Dipolar cycloaddition of pyridinium ylides with alkynes,[12] cyclopropenone[13] or cyclopropenes[14] is limited to the use of symmetric substrates, producing indolizines with two identical substituents at the pyrrole ring. Therefore new methods for the synthesis of indolizine that allow functional groups variation on indolizine nucleus are highly desirable.

Currently, transition metal-catalyzed C-N bond-forming reactions have become important methods for the preparation of indolizines in both academic and pharmaceutical research areas,[15] most of which are realized by the formation of five-membered ring starting from six-membered pyridine derivatives. The formation of six-membered rings moiety in indolizine framework starting from five-membered ring system is less known.[16] Our previous work[17] prompted us to find a novel method to synthesize the indolizine derivatives. Herein an intramolecular condensation of α-carbon of α, β-unsaturated esters with

aldehydes was discovered and the indolizine derivatives were conveniently synthesized by a novel tandem reaction under very mild conditions. The reaction mechanism was also proposed.

RESULTS AND DISCUSSION

Pyrrole-2-carboxaldehydes **1a-j** were easily prepared as described in the literature.[18] Vilsmeier-Haack reaction of pyrrole resulted in pyrrole-2-carboxaldehyde **1a**. The Vilsmeier-Haack intermediate **7** formed from pyrrole may be acylated under normal Friedel-Crafts reaction conditions or brominated giving the corresponding substituted pyrrole-2-carboxaldehydes **1b-j** in good yields. Pyrrole-2-carboxaldehydes **1a-j** reacted with ethyl γ- bromo-α, β-unsaturated esters in DMF and suitable base at rt and the unexpected products indolizines were obtained.

The effects of solvent and base on the yields of the reaction were evaluated using 4-acetyl-2-pyrrole carboxaldehyde **1d** and **2a** as a model substrate, and the results were summarized in Table 1.

First, aprotic solvents of different polarities such as dichloromethane, tetrahydrofuran, acetone, acetonitrile, and DMF, and protic solvents such as MeOH and EtOH were examined. It was noted that protic and strong polar aprotic solvents were significantly preferred over weak aprotic solvents. The reaction was fastest in MeOH, but it afforded transesterified indolizine byproduct. Second, the choice of base was found to have a significant impact on the reaction. Strong bases such as sodium ethoxide and potassium hydroxide gave no products. Neither did weak bases such as magnesium oxide, potassium bicarbonate, and triethylamine. Carbonate bases, however, were found to be effective. Highest yield was obtained with potassium carbonate. Third, the yield of **3g** increased when **1d** was the limiting reagent and the number of equivalents of **2a** was increased from one to two. However, an additional increase of **2a** to three had no beneficial effect on the yield. Eventually, the desired **3g** was obtained in good yield under conditions of 2 equivalents of **2a** and 2.2 equivalents of potassium carbonate in DMF at rt (entry 1, Table 1). Under these conditions, a variety of differently substituted pyrrole-2-carboxaldehydes **1** with ester, acetyl, benzoyl, and bromine functionalities underwent smooth reaction with **2** to afford indolizines **3** in good yields (Table 2).

The structure of **3g** was further confirmed by X-ray crystallographic analysis as shown in Figure 1.

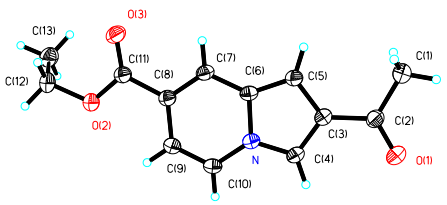
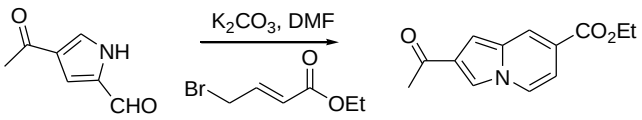


Figure 1. Crystal Structure of **4f**

Table 1. Solvent and Base Effects on the Tandem Reaction



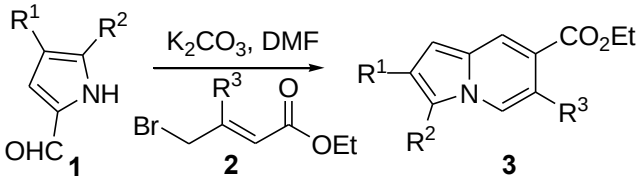
1d **2a** **3g**

Entry	Base (equiv)	Solvent	Time (h)	Isolated Yield (%)
1	K_2CO_3(2.2)	DMF	8	79
2	K_2CO_3(2.2)	MeCN	12	70
3	K_2CO_3(2.2)	acetone	12	53
4	K_2CO_3(2.2)	THF	72	65
5	K_2CO_3(2.2)	DCM	72	0
6	K_2CO_3(2.2)	MeOH	6	75
7	K_2CO_3(2.2)	EtOH	7	73
8	MgO(2.2)	DMF	72	0
9	$KHCO_3$(2.2)	DMF	72	0
10	triethylamine (2.2)	DMF	72	0
11	Na_2CO_3(2.2)	DMF	5	55
12	LiOH(2.2)	DMF	5	63
13	NaOH(2.2)	DMF	0.5	33
14	KOH	DMF	5	0
15	NaOEt	EtOH	5	0

On the basis of the above results and the literature,[16] we proposed the reaction mechanism as follows: Firstly, an intermolecular S_N2 reaction between pyrrole-2-carboxaldehydes **1** and ethyl γ-bromo-crotonates **2** occurs, and the intermediate **4** is formed. Subsequently, intermediate **4** is deprotonated by the existing base to form a γ-carbon anion of the ester, and in turn the electron pair transfers from the γ position to α position. Then the formed β, γ-unsaturated α-carbanion of ester cyclizes with the aldehyde group by intramolecular nucleophilic addition to afford intermediate **5** and then **6**. The final products indolizines **3** can be obtained *in situ* from **6** by eliminating a water. The whole process is shown in Scheme 1.

In summary, we have developed a novel and general method for the synthesis of N-bridgehead indolizines with special substituent on them, especially with an ester group on the pyridine ring under very mild conditions. The operations are simple and convenient. Various indolizine derivatives were obtained using simple procedures in good yields. The reaction mechanism was also proposed.

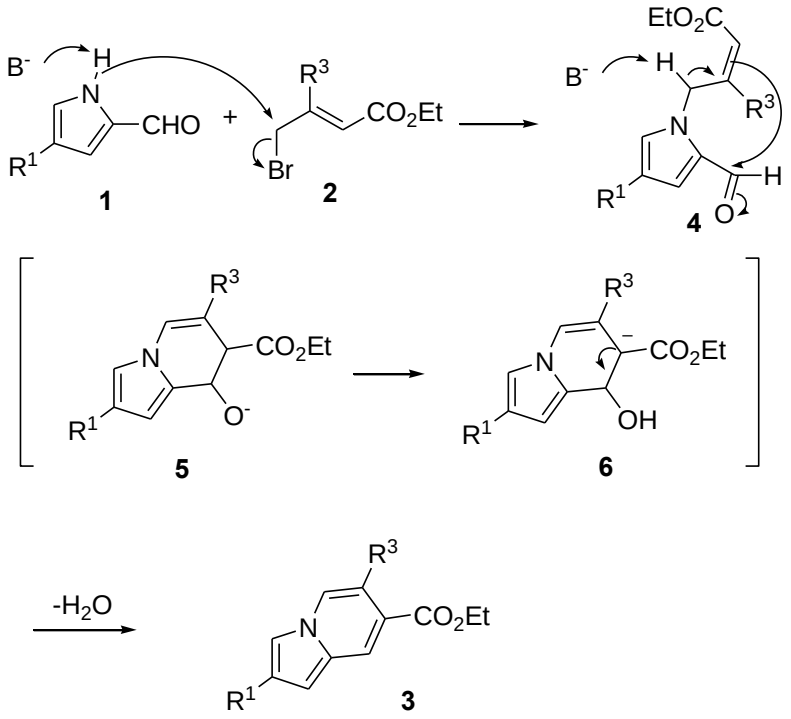
Table 2. Synthesis of Indolizines Derivatives from Pyrroles



Entry	R^1	R^2	R^3	Product	Isolated Yield(%)
1	H	H	H	**3a**	78
2	H	H	Me	**3b**	76
3	CO_2Me	H	H	**3c**	75
4	CO_2Me	H	Me	**3d**	76
5	Br	Br	H	**3e**	65
6	Br	Br	Me	**3f**	62
7	Ac	H	H	**3g**	79
8	Ac	H	Me	**3h**	76
9	propionyl	H	H	**3i**	81
10	propionyl	H	Me	**3j**	78
11	benzoyl	H	H	**3k**	85
12	benzoyl	H	Me	**3l**	81
13	4-nitrobenzoyl	H	H	**3m**	86
14	4-nitrobenzoyl	H	Me	**3n**	84
15	4-methoxybenzoyl	H	H	**3o**	80
16	4-methoxybenzoyl	H	Me	**3p**	76
17	2-fluorobenzoyl	H	H	**3q**	82
18	2-fluorobenzoyl	H	Me	**3r**	76
19	2,4-dichlorobenzoyl	H	H	**3s**	79
20	2,4-dichlorobenzoyl	H	Me	**3t**	75

EXPERIMENTAL

All reagents and solvents were purchased from Sinopharm Chemical Reagent Co. Ltd and used without further purification unless otherwise noted. Starting materials were prepared according to literatures. Thin-layer chromatography (TLC) was conducted on silica gel 60 F254 plates (Merck KGaA). ^{1}H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer, using $CDCl_3$ or DMSO-d_6 as solvents and tetramethylsilane (TMS) as an internal standard. Melting points were determined on an XD-4 digital micro-melting point apparatus and are uncorrected. IR spectra were recorded with an IR spectrophotometer Avtar 370 FT-IR (Termo Nicolet). Elemental analyses were performed on a Vario EL III (Elementar Analysensysteme GmbH) spectroanalyzer. MS spectra were recorded on a Trace DSQ mass spectrometer.



Scheme 1. Mechanism of the tandem reaction

General procedure for the synthesis and analytical data of 1a-j

Pyrrole-2-aldehydes **1a-j** were easily prepared according to the literature.[18]

1*H*-Pyrrole-2-carbaldehyde (1a) [18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.36 (s, 1H), 7.18 (s, 1H), 7.01 (m, 1H), 6.36 (m, 1H). ^{13}C NMR (75.4 Hz, $CDCl_3$): δ 179.5, 132.9, 126.9, 121.8, 111.4.

Methyl 5-formyl-1*H*-pyrrole-3-carboxylate (1b) [18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.13 (s, 1H), 9.57 (d, 1H, J = 1.2 Hz), 7.71 (dd, 1H, J = 1.2 Hz, 3.0 Hz), 7.40 (dd, 1H, 2.4 Hz, 1.5 Hz), 3.86 (s, 3H). ^{13}C NMR (75.4 Hz, $CDCl_3$): δ 180.0, 164.0, 133.1, 129.7, 121.3, 118.8, 51.6.

4,5-Dibromo-1*H*-pyrrole-2-carbaldehyde (1c) [18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.28 (s, 1H), 9.35 (s, 1H), 6.97 (d, 1H, J = 2.4 Hz). ^{13}C NMR (75.4 Hz, $CDCl_3$): δ 177.7, 133.1, 123.0, 113.0, 101.9.

4-Acetyl-1*H*-pyrrole-2-carbaldehyde (1d) [18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.98 (s, 1H), 9.61 (s, 1H), 7.70 (s, 1H), 7.39 (t, 1H, J = 1.8 Hz), 2.48 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 193.0, 180.2, 133.4, 129.2, 128.0, 120.2, 27.4.

4-Propionyl-1*H*-pyrrole-2-carbaldehyde (1e) [18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.02 (s, 1H), 9.60 (s, 1H), 7.72 (s, 1H), 7.39 (s, 1H), 2.84 (q, 2H, J = 7.4 Hz), 1.22 (t, 3H, J = 7.4 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 196.4, 180.5, 133.3, 129.6, 127.3, 120.7, 32.9, 8.3.

4-Benzoyl-1*H*-pyrrole-2-carbaldehyde (1f) [18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.78 (s, 1H), 9.62 (s, 1H), 7.87-7.48 (m, 7H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 190.3, 180.6, 138.7, 133.3, 132.3, 131.6, 129.0, 128.5, 126.4, 122.6.

4-(4-Nitrobenzoyl)-1*H*-pyrrole-2-carbaldehyde (1g) [18]

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.99 (s, 1H), 9.65 (s, 1H), 8.37 (d, 2H, J = 8.4 Hz), 8.02 (d, 2H, J = 8.4 Hz), 7.82 (s, 1H), 7.49 (s, 1H). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 188.2, 181.4, 149.6, 144.4, 134.4, 132.7, 130.3, 124.9, 124.2, 121.5.

4-(4-Methoxybenzoyl)-1*H*-pyrrole-2-carbaldehyde (1h) [18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.21 (s, 1H), 9.63 (s, 1H), 7.89 (d, 2H, J = 8.7 Hz), 7.71 (d, 1H, J = 1.2 Hz), 7.45 (s, 1H), 6.99 (d, 2H, J = 8.7 Hz), 3.90 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 188.6, 180.1, 163.1, 133.1, 131.4, 131.3, 130.4, 126.7, 121.9, 113.8, 55.5.

4-(2-Fluorobenzoyl)-1*H*-pyrrole-2-carbaldehyde (1i) [18]

^{1}H NMR (300 MHz, $CDCl_3$: δ 10.38 (s, 1H), 9.60 (d, 1H, J = 0.6 Hz), 7.67-7.42 (m, 4H), 7.29-7.15 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 186.7, 180.3, 161.3, 158.0, 133.4, 133.0, 132.9, 131.2, 130.3, 130.2, 127.8, 127.6, 127.5, 124.4, 124.3, 121.4, 116.6, 116.3.

4-(2,4-Dichlorobenzoyl)-1*H*-pyrrole-2-carbaldehyde (1j) [18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.84 (s, 1H), 9.58 (d, 1H, J = 0.6 Hz), 7.56 (t, 1H, J = 1.5 Hz), 7.49 (d, 1H, J = 0.9 Hz), 7.37-7.33 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 188.0, 180.4, 137.4, 136.7, 133.7, 132.0, 131.7, 130.3, 129.7, 127.1, 126.8, 121.5.

General procedure for the synthesis and analytical data of 3a-3t

To a 100-mL round-bottomed flask were added **1a-j** (6.0 mmol), enoate **2a-b** (7.2 mmol), potassium carbonate (1.60 g, 12.5 mmol) and DMF (30 mL). The mixture was stirred at rt for 6-7 h and then filtered. The filtrate was concentrated by rotary evaporation. The crude products were purified by column chromatography.

Ethyl indolizine-7-carboxylate (3a)

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.89 (d, 1H, J = 7.2 Hz), 7.42 (s, 1H), 7.05 (d, 1H, J = 7.2 Hz), 6.87 (s, 1H), 6.71 (s, 1H), 4.36 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 Hz, $CDCl_3$): δ 166.1, 131.5, 124.3, 123.1, 118.6, 115.3, 115.1, 109.4, 104.4, 60.8, 14.4. IR (KBr) ν = 3103, 3061, 2981, 2936, 1706, 1629, 1520, 1478, 1260, 1199, 1130, 1092, 752 cm^{-1}. HRMS (EI): m/z Calcd. for: $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.2185; Found: 190.2188. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.86; H, 5.84; N, 7.41.

Ethyl 6-methylindolizine-7-carboxylate (3b)

Yellow solid: mp 44-45 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.69 (s, 1H), 7.32 (s, 1H), 6.81 (t, 1H, J = 3.0 Hz), 6.63 (d, 1H, J = 3.6 Hz), 4.33 (q, 2H, J = 7.2 Hz), 2.46 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.7, 130.7, 124.0, 123.5, 119.5, 119.3, 117.1, 114.9, 114.0, 103.6, 60.5, 18.9, 14.4. IR (KBr) ν = cm^{-1}. HRMS (EI): m/z Calcd. for: $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.2451; Found: 204.2455. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.96; H, 6.46; N, 6.91.

7-Ethyl 2-methyl indolizine-2,7-dicarboxylate (3c)

Yellow solid: mp 105-107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.86 (t, 2H), 7.13-7.09 (m, 2H), 4.36 (q, 2H, J = 7.2 Hz), 3.89 (s, 3H), 1.39 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.5, 164.9, 131.4, 124.7, 124.2, 121.3, 120.4, 117.9, 111.3, 105.6, 61.1, 51.7, 14.4. IR (KBr) ν= 3137, 2954, 2896, 1711, 1701, 1635, 1495, 1266, 1215, 1165, 1085, 1011, 763, 556 cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{13}H_{14}NO_4$ $[M+H]^+$: 248.2546; Found: 248.2552. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.18; H, 5.33; N, 5.69.

7-Ethyl 2-methyl 6-methylindolizine-2,7-dicarboxylate (3d)

Yellow solid: mp 128-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.78 (d, 2H, J = 0.6 Hz), 7.65 (d, 2H, J = 0.9 Hz), 4.34 (q, 2H, J = 7.2 Hz), 3.89 (s, 3H), 2.45 (d, 2H, J = 0.9 Hz),1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.1, 165.1, 130.7, 125.0, 123.6, 121.5, 120.8, 116.8, 105.0, 60.8, 51.6, 18.9, 14.3. IR (KBr) ν= 3143, 3068, 2944, 1718, 1688, 1640, 1536, 1220, 1154, 1061, 1004, 776, 751 cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{14}H_{16}NO_4$ $[M+H]^+$: 262.2811; Found: 262.2813. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.41; H, 5.77; N, 5.37.

Ethyl 2,3-dibromoindolizine-7-carboxylate (3e)

Yellow solid: mp 78-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.93 (d, 1H, J = 7.5 Hz), 7.23 (dd, 1H, J = 1.5, 7.5 Hz), 6.89 (s, 1H), 4.38 (q, 2H, J = 7.2 Hz), 1.41 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.4, 132.4, 122.7, 121.5, 120.1, 110.8, 107.6, 106.8, 97.9, 61.2, 14.3. IR (KBr) ν= 3120, 2988, 2907, 1711, 1628, 1517, 1463, 1246, 1145, 1018, 752, 744 cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{11}H_{10}Br_2NO_2$ $[M+H]^+$: 348.0106; Found: 348.0107. Anal. Calcd for $C_{11}H_9Br_2NO_2$: C, 38.07; H, 2.61; N, 4.04. Found: C, 38.11; H, 2.62; N, 4.06.

Ethyl 2,3-dibromo-6-methylindolizine-7-carboxylate (3f)

Yellow solid: mp 99-101 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.94 (s, 1H), 7.08 (s, 1H), 4.28 (q, 2H, J = 7.2 Hz), 2.46 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 165.7, 131.6, 122.5, 121.2, 106.9, 106.7, 97.2, 61.1, 18.6, 14.6. IR (KBr) ν= 3123, 2986, 2933, 2898, 1697, 1627, 1517, 1496, 1472, 1423, 1251, 1175, 1131, 1071, 1017, 964, 916, 776, 605cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{12}H_{12}Br_2NO_2$ $[M+H]^+$: 362.0372; Found: 362.0376. Anal. Calcd for $C_{12}H_{11}Br_2NO_2$: C, 39.92; H, 3.07; N, 3.88. Found: C, 39.95; H, 3.08; N,3.88.

Ethyl 2-acetylindolizine-7-carboxylate (3g)

Yellow solid: mp 105-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.88 (t, 2H, J = 3.6 Hz), 7.15 (dd, 1H, J = 1.5 Hz, 7.5 Hz), 7.07 (s, 1H), 4.37 (q, 2H, J = 7.2 Hz), 2.58 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 194.5, 165.4, 131.7, 129.8, 124.9, 124.4, 120.6, 117.1, 111.6, 104.6, 61.2, 27.7, 14.3. IR (KBr) ν = 3129, 3110, 2996, 2977, 1711, 1666, 1629, 1488, 1454, 1219, 1175, 1093, 818, 750, 653 cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.2552; Found: 232.2550. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.52; H, 5.66; N, 6.07.

Ethyl 2-acetyl-6-methylindolizine-7-carboxylate (3h)

Yellow solid: mp 126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 7.00 (s, 1H), 4.35 (q, 2H, J = 7.2 Hz), 2.56 (s, 3H), 2.46 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 194.6, 166.0, 131.0, 129.5, 125.3, 123.8, 121.8, 121.7, 116.0, 104.1, 60.9, 27.7, 18.9, 14.3. IR (KBr) ν = 3115, 2980, 2923, 1704, 1667, 1636, 1467, 1282, 1229, 1183, 1069, 853, 769, 661 cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.2817; Found: 246.2815. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.59; H, 6.17; N, 5.71.

Ethyl 2-propionylindolizine-7-carboxylate (3i)

Yellow solid: mp 103-104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.87 (d, 2H, J = 6.9 Hz), 7.13 (dd, 1H, J = 1.5 Hz, 7.5 Hz), 7.08 (s, 1H), 4.38 (q, 2H, J = 7.2 Hz), 2.95 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz), 1.24 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 197.6, 165.5, 131.7, 129.4, 124.9, 124.5, 120.5, 116.7, 111.6, 104.4, 61.2, 33.3, 14.4, 8.3. IR (KBr) ν= 3140, 2985, 2970, 1715, 1673, 1630, 1488, 1259, 1160, 1093, 777, 758, 629 cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.2817; Found: 246.2817. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.59; H, 6.17; N, 5.72.

Ethyl 6-methyl-2-propionylindolizine-7-carboxylate (3j)

Yellow solid: mp 111-112 °C. ^{1}H NMR (300 MHz, $CDCl_3$: δ 8.17 (s, 1H), 7.78 (d, 2H, J = 0.6 Hz), 7.66 (s, 1H), 7.01 (s, 1H), 4.35 (q, 2H, J = 7.2 Hz), 2.94 (q, 2H, J = 7.2 Hz), 2.46 (d, 2H, J = 0.9 Hz), 1.40 (t, 3H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 197.7, 166.1, 131.0, 129.1, 124.9, 125.3, 123.8, 121.7, 121.6, 115.7, 103.8, 60.9, 33.2, 30.9, 18.9, 14.3, 8.4. IR (KBr) ν= 3114, 2971, 2937, 1701, 1664, 1479, 1264, 1163, 1082, 791 cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.3083; Found: 260.3088. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.47; H, 6.63; N, 5.42.

Ethyl 2-benzoylindolizine-7-carboxylate (3k)

Yellow solid: mp 108-109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.94-7.88 (m, 4H), 7.62-7.48 (m, 3H), 7.17-7.13 (m, 2H),4.38 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 191.4, 165.4, 139.0, 132.2, 131.6, 129.4, 128.5, 128.4, 124.8, 124.5, 120.7, 118.8, 111.7, 106.5, 61.2, 14.4. IR (KBr) ν= 3056, 2984, 1714, 1633, 1485, 1400, 1274, 1233, 1119, 883, 748, 690 cm^{-1}.

HRMS(EI): m/z Calcd. for: $C_{18}H_{16}NO_3$ $[M+H]^+$: 294.3245; Found: 294.3249. Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.75; H, 5.16; N, 4.77.

Ethyl 2-benzoyl-6-methylindolizine-7-carboxylate (3l)

Yellow solid: mp 142-143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.93-7.90 (t, 2H), 7.78 (s, 1H), 7.69 (s, 1H),7.62-7.48 (m, 3H), 7.06 (s, 1H),4.35 (q, 2H, J = 7.2 Hz), 2.47 (s, 3H),1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 191.5, 166.0, 139.2, 132.1, 130.8, 129.4, 128.3, 128.2, 125.3, 123.8, 121.9, 121.8, 117.8, 105.9, 60.9, 18.9, 14.3. IR (KBr) ν= 3118, 2978, 1707, 1629, 1478, 1395, 1230, 1194, 1119, 1062, 884, 724 cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{19}H_{18}NO_3$ $[M+H]^+$: 308.3511; Found: 308.3514. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.29; H, 5.60; N, 4.55.

Ethyl 2-(4-nitrobenzoyl)indolizine-7-carboxylate (3m)

Yellow solid: mp 163-164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38-8.35 (m, 2H), 8.24 (s, 1H), 8.07-8.04 (m, 2H), 7.93-7.88 (m, 2H), 7.22-7.19 (dd, 1H, J = 1.8, 7.2 Hz), 7.09 (s, 1H), 4.39 (q, 2H, J = 7.2 Hz), 1.41 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 189.5, 165.2, 149.8, 144.1, 132.0, 130.1, 127.6, 125.0, 124.5, 123.6, 121.4, 118.8, 112.2, 106.2, 61.3, 14.3. IR (KBr) ν= 3139, 3113, 2985, 1724, 1642, 1600, 1526, 1480, 1348, 1296, 1241, 1178, 1122, 848, 746cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{18}H_{15}N_2O_5$ $[M+H]^+$: 339.3221; Found: 339.3226. Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.96; H, 4.18; N, 8.26.

Ethyl 6-methyl-2-(4-nitrobenzoyl)indolizine-7-carboxylate (3n)

Yellow solid: mp 164-165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37-8.35 (d, 2H, J = 8.1 Hz), 8.20 (s, 1H), 8.06-8.03 (d, 2H, J = 8.1 Hz), 7.78 (s, 1H), 7.71 (s, 1H), 7.01 (s, 1H),4.36 (q, 2H, J = 7.2 Hz), 2.48 (s, 1H),1.41 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 189.5, 165.8, 149.7, 144.3, 131.2, 130.1, 127.2, 125.2, 123.8, 123.6, 122.6, 122.5, 117.7, 105.6, 61.0, 18.9, 14.3. IR (KBr) ν= 3141, 3109, 2981, 2939, 2849, 1709, 1639, 1599, 1524, 1476, 1384, 1349, 1277, 1252, 1128, 1069, 846, 710cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{19}H_{17}N_2O_5$ $[M+H]^+$: 353.3487; Found: 353.3488. Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.79; H, 4.57; N, 7.96.

Ethyl 2-(4-methoxybenzoyl)indolizine-7-carboxylate (3o)

Yellow solid: mp 158-159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.99-7.94 (m, 2H), 7.91-7.87 (m, 2H), 7.17-7.14 (dd, 1H, J = 1.5, 7.2 Hz), 7.11 (s, 1H), 7.02-6.97 (m, 2H), 4.38 (q, 2H, J = 7.2 Hz), 3.90 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 190.0, 165.5, 163.0, 131.8, 131.6, 131.4, 128.9, 124.8, 124.4, 120.5, 118.4, 113.6, 111.5, 106.4, 61.2, 55.5, 14.4. IR (KBr) ν= 3135, 2984, 2937, 2839, 1712, 1627, 1602, 1575, 1490, 1278, 1248, 1233, 1175, 1120, 1028, 848, 759cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.3505; Found: 324.3510. Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.63; H, 5.31; N, 4.32.

Ethyl 2-(4-methoxybenzoyl)-6-methylindolizine-7-carboxylate (3p)

Yellow solid: mp 132-133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.97-7.94 (d, 2H, J = 7.8 Hz), 7.77 (s, 1H), 7.69 (s, 1H), 7.04 (s, 1H), 7.00-6.97 (d, 2H, J = 7.8 Hz), 4.35 (q, 2H, J = 7.2 Hz), 3.90 (s, 3H), 2.47 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 190.1, 166.1, 163.0, 131.8, 130.7, 128.5, 125.2, 123.7, 121.7, 121.6, 117.4, 113.6, 105.8, 60.8, 55.5, 18.9, 14.4. IR (KBr) ν= 3124, 2978, 2936, 2837, 1710, 1629, 1602, 1574, 1474, 1394, 1277, 1228, 1172, 1118, 1072, 1028, 888, 847, 777, 751, 705cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{20}H_{20}NO_4$ $[M+H]^+$: 338.3771; Found: 338.3775. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.24; H, 5.66; N, 4.15.

Ethyl 2-(2-fluorobenzoyl)indolizine-7-carboxylate (3q)

Yellow solid: mp 102-103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.86-7.82(m, 2H), 7.64-7.49 (m, 2H), 7.29-7.13 (m, 3H), 7.08 (s, 1H), 4.37 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 188.3, 165.3, 161.5, 158.1, 132.8, 132.7, 131.8, 130.3, 129.3, 128.3, 128.1, 124.9, 124.6, 124.2, 124.1, 120.8, 118.9, 116.5, 116.3, 111.9, 106.0, 61.2, 14.3. IR (KBr) ν= 3069, 2999, 2984, 2937, 1702, 1647, 1612, 1575, 1493, 1400, 1329, 1270, 1213, 1141, 1127, 1019, 886, 825, 754cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{18}H_{15}FNO_3$ $[M+H]^+$: 312.315; Found: 312.315. Anal. Calcd for $C_{18}H_{14}FNO_3$: C, 69.45; H, 4.53; N, 4.50. Found: C, 69.46; H, 4.53; N, 4.51.

Ethyl 2-(2-fluorobenzoyl)-6-methylindolizine-7-carboxylate (3r)

Yellow solid: mp 115-117 °C. 1H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.71-7.47 (m, 4H), 7.28-7.15 (m, 2H), 7.00 (s, 1H), 4.34 (q, 2H, J = 7.2 Hz), 2.45 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 188.3, 165.9, 161.5, 158.1, 132.6, 132.5, 131.0, 130.3, 130.2, 128.9, 128.5, 128.2, 125.4, 124.1, 124.0, 123.7, 122.1, 122.0, 117.8, 116.5, 116.2, 105.4, 60.8, 18.8, 14.3. IR (KBr) ν= 3141, 3065, 2975, 2929, 1704, 1697, 1656, 1637, 1614, 1521, 1475, 1449, 1232, 1124, 1064, 891, 745cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{19}H_{17}FNO_3$ $[M+H]^+$: 326.3416; Found: 326.3222. Anal. Calcd for $C_{19}H_{16}FNO_3$: C, 70.14; H, 4.96; N, 4.31. Found: C, 70.18; H, 4.98; N, 4.32.

Ethyl 2-(2,4-dichlorobenzoyl)indolizine-7-carboxylate (3s)

Yellow solid: mp 137-138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.84 (d, 1H, J = 7.2 Hz), 7.72 (s, 1H), 7.50 (s, 1H), 7.42 (d, 2H, J = 8.1 Hz), 7.35 (d, 2H, J = 8.1 Hz), 7.15 (d, 1H, J = 7.2 Hz), 7.00 (s, 1H), 4.37 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 189.3, 165.2, 137.7, 136.5, 132.2, 132.1, 130.2, 129.9, 128.6, 127.6, 125.0, 124.6, 121.1, 119.0, 112.1, 105.9, 61.3, 14.3. IR (KBr) ν= 3123, 3085, 2989, 2902, 1705, 1648, 1630, 1586, 1550, 1479, 1390, 1293, 1232, 1127, 1102, 1021, 887, 834, 766, 751cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{18}H_{14}Cl_2NO_3$ $[M+H]^+$: 363.2147; Found: 363.2149. Anal. Calcd for $C_{18}H_{13}Cl_2NO_3$: C, 59.69; H, 3.62; N, 3.87. Found: C, 59.72; H, 3.63; N, 3.88.

Ethyl 2-(2,4-dichlorobenzoyl)-6-methylindolizine-7-carboxylate (3t)

Yellow solid: mp 153-154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.64-7.62 (m, 2H), 7.50 (d, 1H, J = 1.8 Hz), 7.43-7.33 (m, 2H), 6.92 (s, 1H), 4.35 (q, 2H, J = 7.2 Hz), 2.45 (s, 3H), 1.40 (t, 3H, J = 7.2

Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 189.4, 165.9, 137.9, 136.4, 132.2, 131.3, 130.1, 129.8, 128.2, 126.8, 125.4, 123.8, 122.4, 122.3, 117.8, 105.4, 60.9, 18.8, 14.3. IR (KBr) ν= 3143, 3065, 2983, 2902, 1708, 1656, 1637, 1588, 1521, 1475, 1383, 1340, 1284, 1231, 1125, 1103, 1064, 891, 857, 754cm^{-1}. HRMS(EI): m/z Calcd. for: $C_{19}H_{16}Cl_2NO_3$ $[M+H]^+$: 377.2412; Found: 377.2408. Anal. Calcd for $C_{19}H_{15}Cl_2NO_3$: C, 60.65; H, 4.02; N, 3.72. Found: C, 60.67; H, 4.03; N, 3.72.

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