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Palladium-Catalyzed Direct and Regioselective C–H Acyloxylation of Indolizines

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A direct and regioselective C1-acyloxylation of indolizines was developed via palladium-catalyzed C–H functionalization. A series of indolizines were successfully acyloxylated at C1 position with the tolerance of a broad range of ring functional groups. In this reaction, high regioselectivity was achieved in the absence of directing group. This work represents the first example of indolizine acyloxylation via C–H activation.

Introduction

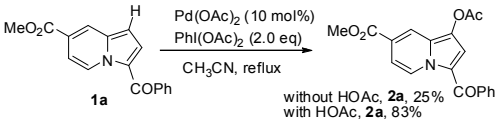
Bridgehead nitrogen heterocycles constitute an important class of compounds because of their intriguing molecular structures and their diversified biological activities.[1] Among them, indolizines have received much attention for decades because the structural fragments of this family are widely found in natural and synthetic biologically active molecules.[2] These molecules have exhibited various pharmaceutical activities[3-8] and are playing an important role in developing new drugs for the treatment of human diseases.[9]

C-1 acyloxylated indolizines are important indolizine derivatives with important biological activities.[10] Although a lot of efforts have been made toward the synthesis of indolizine motif,[11] efficient synthetic routes to C1-acyloxylated indolizines are very limited. The existing synthetic protocols of 1-acyloxylindolizines are mainly restricted to cycloisomerization of propargylic or allylic pyridines,[12] which are usually prepared from organolithium or Grignard reagent and are not easily available. Hence, more simple and convenient synthetic protocols of C1-acyloxylated indolizines are highly desired.

Meanwhile, transition metal-catalyzed direct C–H functionalization has emerged as an important research field of organic chemistry.[13] As an important class of heterocyclic compounds, direct C–H functionalization of indolizines is an important approach for making various substituted indolizines. However, the reported examples usually focused on metal-catalyzed indolizines C–H functionalization at C3 position,[14] whereas examples of indolizines C1 functionalization are rare.[15] Also, although transition metal catalyzed aromatic C-H acyloxylation has long been an interesting area and many important results have been reported,[16] the regioselective C-H acyloxylation using heterocycles as substrate has proven difficult with only a few examples reported so far.[17] Herein, we report an efficient and regioselective synthesis of C1-acyloxylated indolizines via palladium-catalyzed direct acyloxylation of indolizines at C1 position. This work represents the first example of indolizine acyloxylation via C–H activation.

Results and Discussion

Initially, we found that C1-acetoxylated indolizine **2a** could be generated in 25% yield by refluxing indolizine **1a** (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), and 10 mol% $Pd(OAc)_2$ in acetonitrile (10 mL) for 12 h. Subsequently, it was found that adding HOAc (1.0 mmol) into the reaction system could increase the yield of **2a** dramatically (Scheme 1). It illustrated that indolizine **1a** could undergo C–H acetoxylation with high regioselectivity under these reaction conditions.



Scheme 1. Acetoxylation of Indolizine **1a**

Encouraged by this promising result, we began to optimize the reaction conditions. Firstly, various oxidants in place of $PhI(OAc)_2$ were examined and it was found that benzoquinone (BQ), $Cu(OAc)_2$ or AgOAc could not give the acetoxylated product, while *tert*-butyl hydroperoxide (TBHP) and $K_2S_2O_8$ could generate the product in low or modest yield (entry 2–6, Table 1). Solvent effect was then investigated using $PhI(OAc)_2$ as oxidant, and acetonitrile confirmed to be the optimal choice (Table 1, entries 1, 7–10). Regarding catalyst study, 5 mol% $Pd(OAc)_2$ seemed to be the most promising (entry 11–14, Table 1). Noteworthy, both palladium catalyst and

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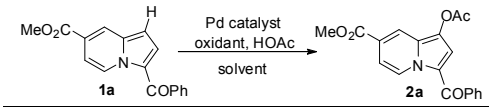
oxidant were crucial to this reaction. Without either $Pd(OAc)_2$ or $PhI(OAc)_2$, no desired product was formed (entry 15–16, Table 1). Further optimization showed the amount of $PhI(OAc)_2$ could be reduced to 1.5 equiv (entry 17–18, Table 1). We finally optimized the reaction temperature and found that decreased reaction temperature led to low conversion and product yield (Table 2, entry 19). Therefore, the optimal reaction conditions should be refluxing indolizine **1a** with 1.5 equiv of $PhI(OAc)_2$ and 2.0 equiv of HOAc in CH_3CN using 5 mol% of $Pd(OAc)_2$ as catalyst.

Table 1. Optimization of Reaction Conditions[a]

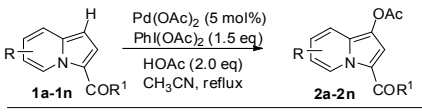


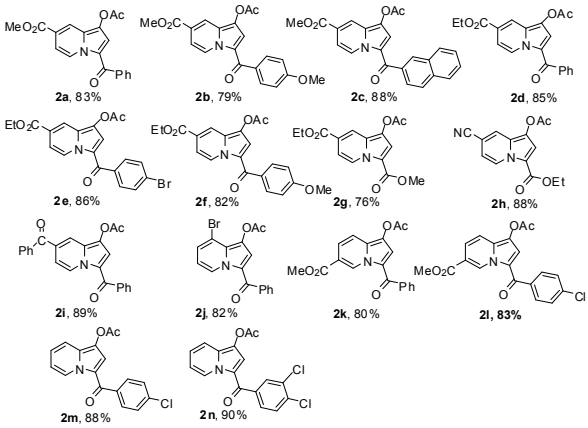
Entry	Pd catalyst (mol%)	Oxidant (equiv)	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	CH_3CN	83
2	$Pd(OAc)_2$ (10)	BQ (2.0)	CH_3CN	0
3	$Pd(OAc)_2$ (10)	AgOAc (2.0)	CH_3CN	0
4	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2.0)	CH_3CN	0
5	$Pd(OAc)_2$ (10)	TBHP (2.0)	CH_3CN	36
6	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.0)	CH_3CN	60
7	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	C_2H_5OH	0
8[c]	$Pd(OAc)_2$(10)	$PhI(OAc)_2$ (2.0)	DMF	0
9[c]	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	Toluene	0
10	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	THF	56
11	$PdCl_2$ (10)	$PhI(OAc)_2$ (2.0)	CH_3CN	78
12	$Pd(TFA)_2$ (10)	$PhI(OAc)_2$ (2.0)	CH_3CN	72
13	$Pd(dba)_2$ (10)	$PhI(OAc)_2$ (2.0)	CH_3CN	36
14	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.0)	CH_3CN	83
15	none	$PhI(OAc)_2$ (2.0)	CH_3CN	0
16	$Pd(OAc)_2$ (5)	none	CH_3CN	0
17	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (1.5)	CH_3CN	83
18	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (1.0)	CH_3CN	51
19[d]	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (1.5)	CH_3CN	33

[a] Reaction conditions: indolizine **1a** (0.5 mmol), oxidant, palladium catalyst, and acetic acid (2.0 equiv), refluxing in solvent for 12 h. [b] Isolated yields. [c] Heated at 80 °C. [d] Heated at 50 °C.

Having the optimized conditions in hand, we then evaluated the generality of our procedure, applying different indolizines **1** to react with acetic acid and $PhI(OAc)_2$ in the presence of $Pd(OAc)_2$ under the optimized conditions. As shown in Table 2, in almost all the cases tested, the acetoxylation process took place smoothly, giving the desired products in high yields. For instance, when indolizines **1b–1i** including ester, cyano, or carbonyl group at C7 were used to carry out this acetoxylation reaction, the corresponding products **2b–2i** could be formed in 76%–89% yields, and a series of functional groups were well tolerated under the reaction conditions. Meanwhile, employing indolizines **1j–1l** with C8 or C6 substituent as substrates also gave the corresponding products **2j–2l** in good yields. Also, high yield of product **2m** or **2n** was isolated when indolizine **1m** or **1n** was used to react with HOAc and $PhI(OAc)_2$ under the optimal condition.

Table 2. C1-Acetoxylation of Indolizines[a,b]

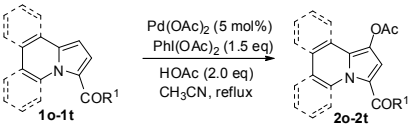


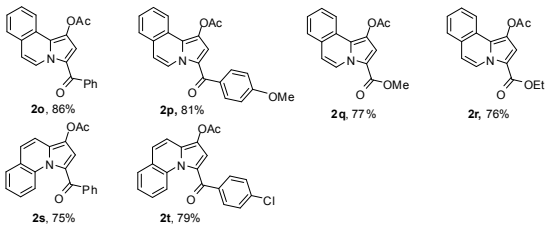


[a] Reaction conditions: indolizines **1a–1n** (0.5 mmol), $PhI(OAc)_2$ (0.75 mmol), $Pd(OAc)_2$ (5 mol%), and acetic acid (1.0 mmol), refluxing in acetonitrile (10 mL) for 12 h. [b] Isolated yields.

We then turned our attention to annulated indolizines and found that either 7,8-annulated indolizines **1o–1r** or 5,6-annulated indolizines **1s–1t** could take part in this reaction smoothly, affording the target products **2o–2t** in good yields. The structure of **2t** was unambiguously established by X-ray crystallography (see supporting information). These showed that our protocol provides a convenient and highly regioselective synthesis of C1-acetoxylated indolizines.

Table 3. C1-Acetoxylation of Annulated Indolizines[a,b]



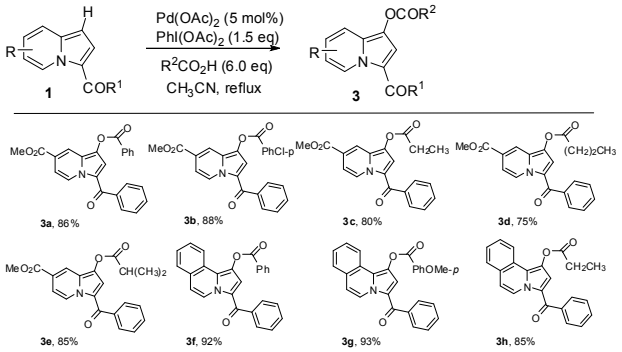


[a] Reaction conditions: annulated indolizines **1o–1t** (0.5 mmol), $PhI(OAc)_2$ (0.75 mmol), $Pd(OAc)_2$ (5 mol%), and acetic acid (1.0 mmol), refluxing in acetonitrile (10 mL) for 12 h. [b] Isolated yields.

We have also investigated the acyloxylation of indolizines **1** with other acids to further extend the utility of this reaction (Table 4). To our delight, by refluxing the mixture of indolizine **1a** with 6.0 equiv of benzoic acid and 1.5 equiv of $PhI(OAc)_2$ in acetonitrile for 12 h in the presence of 5 mol% $Pd(OAc)_2$, we could obtain 1-benzoxyindolizines **3a** exclusively in 86% yield. Other acids as *p*-

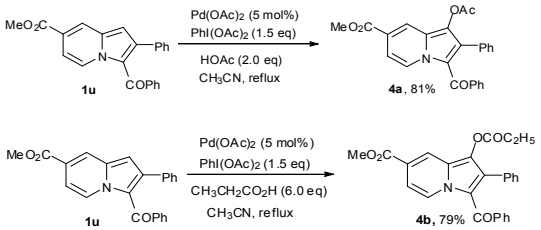
chlorobenzoic acid, *n*-propyl acid, *n*-butyric acid and *i*-butyric acid could also react with indolizine **1a** under the same reaction conditions, leading to 1-acyloxyindolizines **3b–3e** in 75%–88% yields, respectively. Similarly, using annulated indolizine **1o** as acyloxylation substrate to react with different acids under these reaction conditions, the desired products **3f–3h** were obtained in excellent yields.

Table 4. C1-Acyloxylation of Indolizines with other acids[a,b]



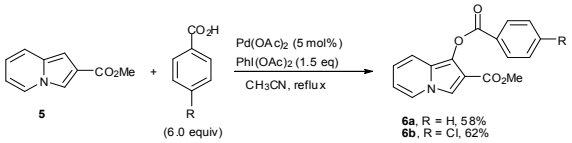
[a] Reaction conditions: indolizine **1a** or **1o** (0.5 mmol), $PhI(OAc)_2$ (0.75 mmol), $Pd(OAc)_2$ (5 mol%), and various acids (3.0 mmol), refluxing in acetonitrile (10 mL) for 12 h. [b] Isolated yields.

In addition, 2,3-disubstituted indolizine **1u** was also tried to undergo this acyloxylated reaction, and it proved to be good substrate, providing the desired C-1 acyloxylated products **4a** and **4b** in high yields, shown in scheme 2.



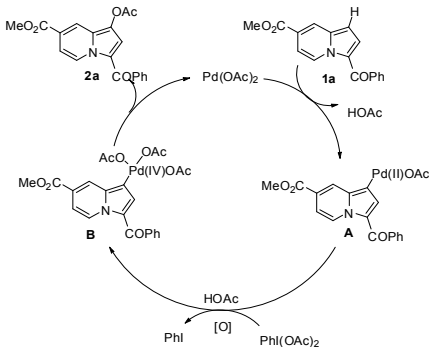
Scheme 2 Acyloxylation of 2,3-disubstituted indolizine **1u**

Furthermore, when the C3-unsubstituted indolizine **5** with an ester functionality at C-2 was used as substrate[18] to react with 6.0 equiv of benzoic acid and 1.5 equiv of $PhI(OAc)_2$ in the presence of 5 mol% $Pd(OAc)_2$, C1-acyloxylated indolizine **6a** or **6b** was found to be formed in modest yield (Scheme 3).



Scheme 3. Acyloxylation of 2-Esterindolizine **5**

To rationalize the regioselectivity of indolizine C1 acyloxylation reaction, DFT/UB3LYP calculation of the charge density distribution in the 3-acylindolizine and 2-esterindolizine at the 6-31+G (d,p) level had been performed, which illustrated that either with or without the summing up of the charge density at the hydrogen atom to the attached carbon atom, C1 is the most negatively charged carbon atom in 3-acylindolizine or 2-esterindolizine (see supporting information). On the basis of our experimental results, a possible mechanism for this reaction is suggested, as shown in Scheme 4. Initially, electrophilic palladation of indolizine **1a** and subsequent loss of proton afforded Pd(II) intermediate **A**. Then, oxidation of intermediate **A** with $PhI(OAc)_2$ in the presence of HOAc generated Pd(IV) species **B**. Finally, Pd(IV) intermediate **B** underwent reductive elimination to form product **2a** and regenerated Pd(II) catalyst which would continue the catalytic cycle. Acetic acid in this reaction promoted the formation of intermediate **B**, to increase the yield of **2a** greatly.



Scheme 4. Plausible Reaction Mechanism

Conclusions

In conclusion, we have reported an efficient and highly regioselective protocol for direct acyloxylation of indolizines at C1 position via palladium-catalyzed C-H activation. This protocol provided a convenient synthesis to C1-acyloxylated indolizines.

Experimental Section

General: Melting points are uncorrected. ^1H NMR spectra were measured at 400 MHz with $CDCl_3$ as solvent. The chemical shifts (δ) are reported in parts per million relative to the residual deuterated solvent signal, and coupling constants (J) are given in Hertz. ^{13}C NMR spectra were measured at 100 MHz with $CDCl_3$ as solvent. Substrates **1** were prepared according to lit. 19.

General procedure for the preparation of 2: The mixture of indolizine **1** (0.5 mmol), palladium acetate (5 mol%), $PhI(OAc)_2$ (0.75 mmol), and acetic acid (1.0 mmol) was refluxed in acetonitrile (10 ml) for 12 h. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:10) as eluent to give the products **2**.

Methyl 1-acetoxy-3-benzoylindolizine-7-carboxylate (2a): Yellow solid, mp 126–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.98 (s, 3H), 7.37 (s, 1H), 7.45–7.57 (m, 4H), 7.80 (d, *J* = 7.2 Hz, 2H), 8.25 (s, 1H), 9.86 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.4, 168.5, 165.3, 139.8, 131.5, 130.8, 129.1, 129.0, 128.5, 128.4, 127.3, 124.5, 120.3, 118.6, 117.0, 113.0, 52.6, 20.9. HRMS (ESI) *m/z* calcd for $C_{19}H_{16}NO_5$ $[M+H]^+$ 338.1028, found 338.1044.

Methyl 1-acetoxy-3-(4-methoxybenzoyl)indolizine-7-carboxylate (2b): Yellow solid, mp 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.39–7.43 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.24 (s, 1H), 9.78 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.3, 168.5, 165.4, 162.5, 132.2, 131.2, 130.6, 128.0, 127.1, 123.9, 120.3, 118.6, 116.5, 113.7, 112.7, 55.5, 52.6, 20.9. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}NO_6$ $[M+H]^+$ 368.1134, found 368.1144.

Methyl 3-(2-naphthoyl)-1-acetoxyindolizine-7-carboxylate (2c): Yellow solid, mp 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.98 (s, 3H), 7.43 (s, 1H), 7.47 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.54–7.62 (m, 2H), 7.89–7.97 (m, 4H), 8.25–8.26 (m, 1H), 8.31 (s, 1H), 9.88 (dd, *J* = 7.6, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.2, 168.5, 165.3, 137.1, 134.8, 132.5, 130.9, 129.9, 129.2, 128.6, 128.4, 127.9, 127.8, 127.4, 126.8, 125.5, 124.5, 120.5, 118.7, 117.1, 113.1, 52.6, 20.9. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}NO_5$ $[M+H]^+$ 388.1185, found 388.1197.

Ethyl 1-acetoxy-3-benzoylindolizine-7-carboxylate (2d): Yellow solid, mp 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, *J* = 7.2 Hz, 3H), 2.39 (s, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 7.37 (s, 1H), 7.45–7.56 (m, 4H), 7.80 (d, *J* = 7.2 Hz, 2H), 8.23–8.24 (m, 1H), 9.86 (dd, *J* = 7.6, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.3, 168.5, 164.8, 139.8, 131.4, 130.7, 129.0, 128.5, 128.4, 127.2, 124.8, 120.2, 118.4, 117.0, 113.1, 61.6, 20.9, 14.3. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}NO_5$ $[M+H]^+$ 352.1185, found 352.1184.

Ethyl 1-acetoxy-3-(4-bromobenzoyl)indolizine-7-carboxylate (2e): Yellow solid, mp 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, *J* = 7.2 Hz, 3H), 2.39 (s, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 7.34 (s, 1H), 7.47 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.62–7.69 (m, 4H), 8.24–8.25 (m, 1H), 9.83 (dd, *J* = 7.2, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9, 168.4, 164.7, 138.6, 131.6, 130.9, 130.5, 128.8, 127.3, 126.2, 125.2, 119.8, 118.4, 116.7, 113.3, 61.7, 20.9, 14.3. HRMS (ESI) *m/z* calcd for $C_{20}H_{17}BrNO_5$ $[M+H]^+$ 430.0290, found 430.0299.

Ethyl 1-acetoxy-3-(4-methoxybenzoyl)indolizine-7-carboxylate (2f): Yellow solid, mp 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 3.90 (s, 3H), 4.43 (q, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.39–7.44 (m, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 8.23 (s, 1H), 9.79 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.3, 168.5, 164.9, 162.5, 132.2, 131.2, 130.6, 128.1, 127.1, 124.3, 120.3, 118.5, 116.5, 113.7, 112.7, 61.6, 55.5, 20.9, 14.4. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}NO_6$ $[M+H]^+$ 382.1291, found 382.1298.

Diethyl 1-acetoxyindolizine-3,7-dicarboxylate (2g): White solid, mp 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38–1.44 (m, 6H), 2.40 (s, 3H), 4.37–4.42 (m, 4H), 7.33 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.51 (s, 1H), 8.17–8.18 (m, 1H), 9.35 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 165.1, 161.0, 130.2, 126.9, 125.9, 122.5, 118.8, 113.1, 112.8, 112.0, 61.4, 60.4, 20.9, 14.5, 14.4. HRMS (ESI) *m/z* calcd for $C_{16}H_{18}NO_6$ $[M+H]^+$ 320.1134, found 320.1136.

Methyl 1-acetoxy-7-cyanoindolizine-3-carboxylate (2h): Whiite solid, mp 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.93 (s, 3H), 6.86 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.56 (s, 1H), 7.84 (d, *J* = 1.2 Hz, 1H), 9.39 (dd, *J* = 7.6, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 161.1, 130.2, 126.8, 125.7, 122.6, 117.8, 113.6, 113.5, 112.5, 103.4, 51.8, 20.9. HRMS (ESI) *m/z* calcd for $C_{13}H_{11}N_2O_4$ $[M+H]^+$ 259.0719, found 259.0728.

3,7-Dibenzoylindolizin-1-yl acetate (2i): Yellow solid, mp 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 7.38–7.40 (m, 2H), 7.49–7.65 (m, 6H), 7.81–7.86 (m, 4H), 7.96 (s, 1H), 9.90 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 185.4, 168.4, 139.8, 137.0, 132.8, 131.5, 131.3, 131.2, 129.8, 129.0, 128.6, 128.4, 128.1, 127.4, 120.3, 119.3, 117.0, 113.7, 20.9. HRMS (ESI) *m/z* calcd for $C_{24}H_{18}NO_4$ $[M+H]^+$ 384.1236, found 384.1242.

3-Benzoyl-8-bromoindolizin-1-yl acetate (2j): Yellow solid, mp 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 6.77 (t, *J* = 7.2 Hz, 1H), 7.22 (s, 1H), 7.36 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.47–7.50 (m, 2H), 7.54–7.58 (m, 1H), 7.76–7.79 (m, 2H), 9.94 (dd, *J* = 7.2, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 170.0, 139.9, 131.3, 128.9, 128.4, 128.3, 127.9, 127.1, 119.1, 113.9, 109.7, 21.0. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}BrNO_3$ $[M+H]^+$ 358.0079, found 358.0080.

Methyl 1-acetoxy-3-benzoylindolizine-6-carboxylate (2k): Yellow solid, mp 165–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.98 (s, 3H), 7.43 (s, 1H), 7.49–7.59 (m, 4H), 7.70 (dd, *J* = 9.2, 1.2 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.6 Hz, 2H), 10.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 168.5, 165.6, 139.8, 132.2, 131.4, 129.8, 128.9, 128.6, 128.4, 123.0, 119.2, 118.0, 115.1, 52.5, 20.8. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}NO_5$ $[M+H]^+$ 338.1028, found 338.1037.

Methyl 1-acetoxy-3-(4-chlorobenzoyl)indolizine-6-carboxylate (2l): Yellow solid, mp 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.98 (s, 3H), 7.41 (s, 1H), 7.47–7.53 (m, 3H), 7.71–7.77 (m, 3H), 10.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.3, 168.5, 165.5, 138.1, 137.7, 132.1, 130.3, 130.1, 128.7, 128.6, 123.3, 119.3, 119.0, 118.3, 115.1, 52.5, 20.8. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}ClNO_5$ $[M+H]^+$ 372.0639, found 372.0636.

3-(4-Chlorobenzoyl)indolizin-1-yl acetate (2m): Yellow solid, mp 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 6.97 (t, *J* = 6.8 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.44–7.50 (m, 3H), 7.73 (d, *J* = 8.0 Hz, 2H), 9.92 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.0, 168.7, 138.8, 137.2, 130.5, 130.3, 128.6, 128.3, 128.2, 124.4, 118.2, 116.6, 115.6, 114.7, 20.9. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}ClNO_3$ $[M+H]^+$ 314.0584, found 314.0583.

3-(3,4-Dichlorobenzoyl)indolizin-1-yl acetate (2n): Yellow solid, mp 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 6.99 (td, *J* = 7.2, 0.8 Hz, 1H), 7.23–7.26 (m, 2H), 7.50–7.63 (m, 3H), 7.87 (d, *J* = 2.0 Hz, 1H), 9.90 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.3, 168.7, 140.2, 135.3, 132.8, 130.9, 130.8, 130.4, 128.6, 128.3, 128.0, 124.8, 117.8, 116.5, 115.7, 115.0, 20.9. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{12}Cl_2NO_3$ $[M+H]^+$ 348.0194, found 348.0193.

3-Benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl acetate (2o): Yellow solid, mp 131–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.33 (s, 1H), 7.47–7.61 (m, 5H), 7.71 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.83 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.43 (d, *J* = 8.4 Hz, 1H), 9.58 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 168.5, 140.2, 131.5, 131.3, 129.1, 128.3, 127.9, 127.8, 126.8, 125.1, 125.0, 124.1, 123.8, 120.1, 117.3, 113.8, 21.3. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}NO_3$ $[M+H]^+$ 330.1130, found 330.1139.

3-(4-Methoxybenzoyl)pyrrolo[2,1-*a*]isoquinolin-1-yl acetate (2p): Yellow solid, mp 142–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (s,

3H), 3.89 (s, 3H), 6.99 (td, *J* = 6.8, 2.0 Hz, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.34 (s, 1H), 7.53–7.58 (m, 2H), 7.69 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.86 (td, *J* = 8.8, 2.0 Hz, 2H), 8.42 (d, *J* = 7.6 Hz, 1H), 9.49 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.5, 168.5, 162.4, 132.7, 131.4, 129.0, 127.8, 127.7, 126.8, 125.1, 124.6, 124.2, 123.7, 120.3, 116.7, 113.6, 113.5, 55.5, 21.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}NO_4$ $[M+H]^+$ 360.1236, found 360.1248.

Methyl 1-acetoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (2q): White solid, mp 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.91 (s, 3H), 6.98 (d, *J* = 7.6 Hz, 1H), 7.50–7.55 (m, 3H), 7.66 (d, *J* = 7.6 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 9.20 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 161.6, 130.9, 128.0, 127.7, 127.3, 126.8, 124.5, 124.1, 123.4, 123.3, 113.1, 112.8, 112.1, 51.3, 21.4. HRMS (ESI) *m/z* calcd for $C_{16}H_{14}NO_4$ $[M+H]^+$ 284.0923, found 284.0931.

Ethyl 1-acetoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (2r): White solid, mp 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, *J* = 7.2 Hz, 3H), 2.48 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.48–7.66 (m, 3H), 7.65 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 9.20 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 161.3, 130.9, 128.0, 127.7, 127.2, 126.7, 124.5, 124.1, 123.3, 123.2, 113.0, 112.7, 112.5, 60.2, 21.4, 14.5. HRMS (ESI) *m/z* calcd for $C_{17}H_{16}NO_4$ $[M+H]^+$ 298.1079, found 298.1087.

1-Benzoylpyrrolo[1,2-*a*]quinolin-3-yl acetate (2s): Yellow solid, mp 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.19 (s, 1H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.39–7.44 (m, 2H), 7.52 (t, *J* = 8.0 Hz, 3H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.71 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.2, 168.6, 139.0, 133.1, 132.4, 130.2, 130.1, 129.4, 129.3, 128.8, 128.3, 128.2, 125.4, 125.1, 125.0, 124.5, 120.1, 119.6, 114.2, 20.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}NO_3$ $[M+H]^+$ 330.1130, found 330.1130.

1-(4-Chlorobenzoyl)pyrrolo[1,2-*a*]quinolin-3-yl acetate (2t): Yellow solid, mp 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.17 (s, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.48–7.55 (m, 3H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 168.6, 138.7, 137.4, 133.1, 131.4, 129.7, 129.5, 128.9, 128.6, 128.4, 125.6, 125.2, 124.1, 120.1, 119.6, 114.2, 20.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClNO_3$ $[M+H]^+$ 364.0740, found 364.0742.

General procedure for the preparation of 3: The mixture of indolizine **1** (0.5 mmol), palladium acetate (5 mol%), $PhI(OAc)_2$ (0.75 mmol), and organic acid (3.0 mmol) was refluxed in acetonitrile (10 ml) for 12 h. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:10) as eluent to give the products **3**.

Methyl 3-benzoyl-1-(benzoyloxy)indolizine-7-carboxylate (3a): Yellow solid, mp 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 7.50–7.58 (m, 7H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.83–7.85 (m, 2H), 8.25 (dd, *J* = 8.4, 1.6 Hz, 2H), 8.31 (d, *J* = 0.4 Hz, 1H), 9.90 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.4, 165.3, 164.2, 139.8, 134.0, 131.5, 130.9, 130.3, 129.0, 128.8, 128.7, 128.4, 127.3, 124.5, 120.4, 118.6, 117.1, 113.1, 52.6. HRMS (ESI) *m/z* calcd for $C_{24}H_{18}NO_5$ $[M+H]^+$ 400.1185, found 400.1195.

Methyl 3-benzoyl-1-(4-chlorobenzoyloxy)indolizine-7-carboxylate (3b): Yellow solid, mp 183–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.49–7.57 (m, 7H), 7.83 (d, *J* = 7.2 Hz, 2H), 8.19 (d, *J* = 7.6 Hz, 2H), 8.30 (s, 1H), 9.90 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.4, 165.3, 163.4, 140.7, 139.7, 131.6, 131.5, 130.7, 129.2, 129.0, 128.6, 128.4, 127.4, 127.1, 124.6, 120.4, 118.5, 117.1, 113.1, 52.6. HRMS (ESI) *m/z* calcd for $C_{24}H_{17}ClNO_5$ $[M+H]^+$ 434.0795, found 434.0791.

Methyl 3-benzoyl-1-(propionyloxy)indolizine-7-carboxylate (3c): Yellow solid, mp 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.6 Hz, 3H), 2.69 (q, *J* = 7.6 Hz, 2H), 3.98 (s, 3H), 7.39 (s, 1H), 7.44–7.51 (m, 3H), 7.54–7.58 (m, 1H), 7.79–7.82 (m, 2H), 8.23–8.24 (m, 1H), 9.86 (dd, *J* = 7.2, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.3, 172.1, 165.3, 139.8, 131.4, 130.9, 129.0, 128.5, 128.4, 127.3, 124.3, 120.2, 118.6, 117.0, 113.0, 52.6, 27.5, 9.0. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}NO_5$ $[M+H]^+$ 352.1185, found 352.1180.

Methyl 3-benzoyl-1-(butyryloxy)indolizine-7-carboxylate (3d): Yellow solid, mp 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, *J* = 7.2 Hz, 3H), 1.80–1.86 (m, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 7.39 (s, 1H), 7.45–7.58 (m, 4H), 7.80 (dd, *J* = 8.4, 1.6 Hz, 2H), 8.23 (d, *J* = 0.8 Hz, 1H), 9.86 (dd, *J* = 7.2, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.3, 171.2, 165.3, 139.8, 131.5, 130.9, 129.0, 128.5, 128.4, 127.3, 124.3, 120.2, 118.6, 117.0, 113.0, 52.6, 36.0, 18.4, 13.7. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}NO_5$ $[M+H]^+$ 366.1341, found 366.1340.

Methyl 3-benzoyl-1-(isobutyryloxy)indolizine-7-carboxylate (3e): Yellow solid, mp 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, *J* = 6.8 Hz, 6H), 2.87–2.94 (m, 1H), 3.98 (s, 3H), 7.40 (s, 1H), 7.45–7.58 (m, 4H), 7.80 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.21 (s, 1H), 9.86 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.3, 174.7, 165.3, 139.8, 131.4, 131.0, 128.9, 128.5, 128.4, 127.3, 124.3, 120.2, 118.5, 117.0, 113.0, 52.6, 34.1, 19.0. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}NO_5$ $[M+H]^+$ 366.1341, found 366.1345.

3-Benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl benzoate (3f): Yellow solid, mp 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 7.6 Hz, 1H), 7.41 (s, 1H), 7.48–7.62 (m, 7H), 7.70–7.74 (m, 2H), 7.86 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.32 (dd, *J* = 8.4, 1.6 Hz, 2H), 8.45–8.47 (m, 1H), 9.62 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 164.6, 140.2, 134.0, 131.5, 131.3, 130.2, 129.2, 129.1, 128.9, 128.3, 128.0, 127.9, 126.8, 125.6, 125.2, 124.1, 123.9, 120.3, 117.6, 113.8. HRMS (ESI) *m/z* calcd for $C_{26}H_{18}NO_3$ $[M+H]^+$ 392.1287, found 392.1275.

3-Benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl 4-methoxybenzoate (3g): Yellow solid, mp 191–193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 3H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.38 (s, 1H), 7.48–7.57 (m, 5H), 7.72–7.74 (m, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 8.28 (d, *J* = 8.8 Hz, 2H), 8.44–8.46 (m, 1H), 9.62 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 164.2, 140.2, 132.4, 131.6, 131.3, 129.2, 129.1, 128.3, 127.9, 127.8, 126.8, 125.2, 124.1, 123.9, 121.3, 120.3, 117.8, 114.2, 113.8, 55.6. HRMS (ESI) *m/z* calcd for $C_{27}H_{20}NO_4$ $[M+H]^+$ 422.1392, found 422.1379.

3-Benzoylpyrrolo[2,1-*a*]isoquinolin-1-yl propionate (3h): Yellow solid, mp 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H), 2.78 (q, *J* = 7.2 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.35 (s, 1H), 7.48–7.59 (m, 5H), 7.72 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.83 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.44 (dd, *J* = 7.6, 1.2 Hz, 1H), 9.58 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 172.0, 140.2, 131.6, 131.3, 129.1, 128.3, 127.9, 127.8, 126.8, 125.1, 125.0, 124.1, 123.9, 120.1, 117.3, 113.7, 28.0, 9.1. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}NO_3$ $[M+H]^+$ 344.1287, found 344.1284.

General procedure for the preparation of 4: The mixture of 2,3-disubstituted indolizine **1u** (0.5 mmol), palladium acetate (5 mol%), $PhI(OAc)_2$ (0.75 mmol), and organic acid (3.0 mmol) was refluxed in acetonitrile (10 ml) for 12 h. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:10) as eluent to give the products **4**.

Methyl 1-acetoxy-3-benzoyl-2-phenylindolizine-7-carboxylate (4a): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.98 (s, 3H), 7.01–7.04 (m, 7H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.40–7.43 (m, 3H), 8.12–8.13 (m, 1H), 9.64 (dd, *J* = 7.6, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.2, 169.6, 165.4, 139.1, 131.3, 131.2, 130.4, 129.8, 129.5, 128.7, 127.9, 127.8, 127.5, 127.3, 127.0, 124.5, 119.3, 118.6, 112.7, 52.6, 20.5. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}NO_5$ $[M+H]^+$ 414.1341, found 414.1343.

Methyl 3-benzoyl-2-phenyl-1-(propionyloxy)indolizine-7-carboxylate (4b): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.6 Hz, 3H), 2.55 (q, *J* = 7.6 Hz, 2H), 3.97 (s, 3H), 6.99–7.04 (m, 7H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.41 (dd, *J* = 7.6, 0.8 Hz, 3H), 8.11 (d, *J* = 0.8 Hz, 1H), 9.64 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.2, 173.0, 165.4, 139.1, 131.4, 131.2, 130.4, 129.9, 129.5, 128.8, 127.9, 127.7, 127.5, 127.3, 126.9, 124.4, 119.3, 118.6, 118.5, 112.6, 52.6, 27.3, 9.2. HRMS (ESI) *m/z* calcd for $C_{26}H_{22}NO_5$ $[M+H]^+$ 428.1498, found 428.1491.

Procedure for the preparation of Compound 5: compound **5** was prepared according to literature 18.

Methyl indolizine-2-carboxylate (5): White solid, mp 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 6.52 (t, *J* = 6.8 Hz, 1H), 6.67 (t, *J* = 6.8 Hz, 1H), 6.82 (s, 1H), 7.34 (d, *J* = 9.2 Hz, 1H), 7.79 (s, 1H), 7.84 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 132.7, 125.3, 120.2, 118.1, 115.8, 112.2, 100.4, 51.4. HRMS (ESI) *m/z* calcd for $C_{10}H_{10}NO_2$ $[M+H]^+$ 176.0712, found 176.0714.

Procedure for the preparation of 6: The mixture of 2-esterindolizine **5** (0.5 mmol), palladium acetate (5 mol%), $PhI(OAc)_2$ (0.75 mmol), and acid (3.0 mmol) was refluxed in acetonitrile (10 ml) for 12 h. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:10) as eluent to give the products **6**.

Methyl 1-benzoylindolizine-2-carboxylate (6a): White solid, mp 139–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 3H), 6.53 (td, *J* = 7.2, 1.2 Hz, 1H), 6.64–6.68 (m, 1H), 7.26–7.28 (m, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 8.28 (dd, *J* = 8.0, 0.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 163.8, 135.9, 133.5, 130.4, 128.6, 125.0, 117.9, 117.1, 113.3, 112.7, 111.4, 51.4. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}NO_3$ $[M+H]^+$ 280.0974, found 280.0979.

Methyl 1-(4-chlorobenzoyl)indolizine-2-carboxylate (6b): White solid, mp 121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 3H), 6.52–6.55 (m, 1H), 6.65–6.69 (m, 1H), 7.25–7.27 (m, 1H), 7.51 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.72 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 8.21 (dt, *J* = 8.4, 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 163.8, 140.1, 131.8, 129.0, 127.9, 125.0, 124.1, 118.1, 117.1, 113.4, 112.8, 111.2, 51.5. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}ClNO_3$ $[M+H]^+$ 314.0584, found 314.0576.

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