$CuBr_2$-Promoted Multicomponent Aerobic Reaction for the Synthesis of 1,2,3-Triaroylindolizines

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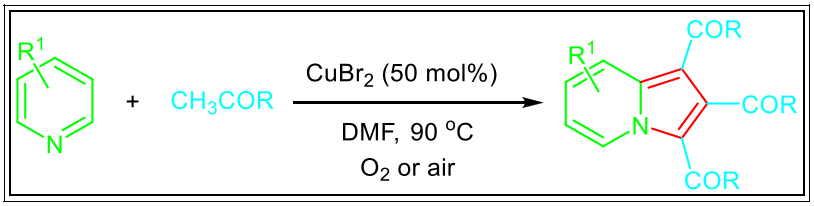

An efficient synthesis of 1,2,3-triaroylindolizines has been developed *via* $CuBr_2$-promoted reaction of three molecules of aromatic methyl ketones and one molecule of pyridine derivative. A wide range of methyl aryl ketones and methyl heteroaryl ketones took part in the reaction and generate 1,2,3-triaroylindolizines in good yields. This protocol also features such advantages as mild reaction conditions and high atom economy and step economy.

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INTRODUCTION

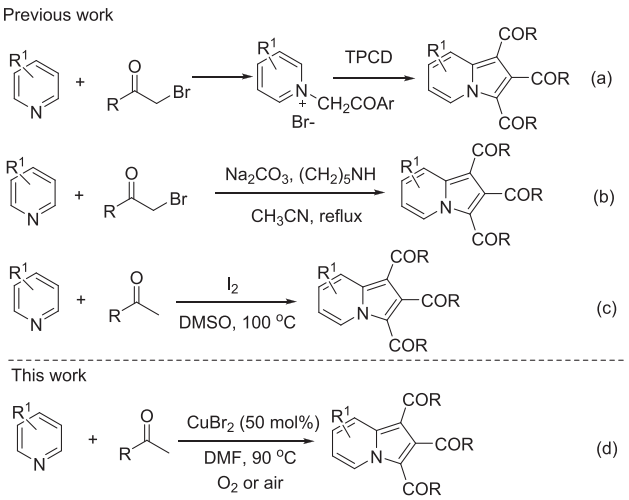
As an important class of nitrogen-containing heterocycles, indolizines exhibit diverse biological activities and have wide application in medicinal [1–8] and material field [9–11]. As the result, great efforts have been made on their synthesis in the past decades [12–16]. Nevertheless, only few routes were disclosed for the synthesis of 1,2,3-triaroylindolizines so far. The existing protocols mainly include (a) cyclization of three molecules of pyridinium bromides in the presence of oxidant TPCD (Scheme 1a) [17]; (b) piperdine-promoted reaction of bromoketones with pyridines (Scheme 1b) [18]; and (c) reaction of pyridines and aromatic methyl ketones in the presence of iodine and dimethyl sulfoxide (Scheme 1c) [19]. The former two protocols (*a* and *b*) employ bromoketones as the reactants that are commercially expensive and need preparation from methyl ketones before use. Besides, low reaction yields and limited substrate scope are also shortcomings of them. Compared with these two protocols, route *c* has higher step economy that utilizes methyl ketones directly as the reactants to form the indolizine products *via* α-ketoaldehyde intermediate. However, three equimolar amount of iodine is required in this reaction that hampers its synthetic value. Therefore, more convenient synthetic methods to 1,2,3-triaroylindolizines from methyl ketones are highly demanded.

Copper-promoted reaction starting from pyridines is an important protocol for the synthesis of indolizine derivatives [20–25]. Also, copper-mediated oxidative halogenation of C–H bond is an important synthetic transformation for the construction of halogenated compound [26–31]. Recently, we have developed an efficient synthesis of indolizines by copper-catalyzed reaction of pyridines, methyl ketones, and alkenoic acid [32]. In this reaction, α-bromoketones are generated from methyl ketones in the presence of copper bromide. We speculated that this protocol can also be applied to the synthesis of 1,2,3-triaroylindolizines. Herein, we reported a convenient $CuBr_2$-promoted four-components reaction of aromatic methyl ketones and pyridines for the synthesis of 1,2,3-triaroylindolizines under oxygen atmosphere (Scheme 1d). Various pyridines and methyl ketones are suitable substrates under the reaction conditions and provided the desired products 1,2,3-triaroylindolizines in moderate to high yields.

RESULTS AND DISCUSSION

At the outset of our work, we chose methyl isonicotinate **1a** and acetophenone **2a** as the model reactants. Initially, by heating **1a** (2.0 mmol), **2a** (1.5 mmol), and $CuBr_2$ (0.5 mmol) in acetonitrile at 90°C for 12 h, we did not obtain any indolizine product (Table 1, entry 1). Other solvents such as dioxane, benzene, dichloroethane, and ethanol were also examined, but no improved result was given (Table 1, entries 2–5). Pleasingly, changing the solvent to dimethylformamide (DMF) led to 1,2,3-triaroylindolizin **3a** in 72% yield (Table 1, entry 6). With

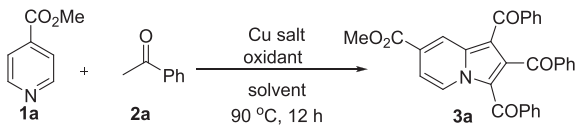
Scheme 1. Synthesis of 1,2,3-triaroylindolizines.



DMF as the solvent, the kind of copper salts was then screened. $CuBr_2$ has been found to work the best (Table 1, entries 7–10). Further optimization showed that 0.5 equimolar amount of $CuBr_2$ was enough to assure the high yield of **3a** in oxygen atmosphere, while no **3a** was found in the absence of $CuBr_2$ (Table 1, entry 11–13). Next, we examined the effect of oxidants other than oxygen, including $K_2S_2O_8$, DTBP, and TBHP, but no better results were obtained (Table 1, entries 14–16). In addition, the loading of **1a** could be decreased to 0.75 mmol, but adding extra base could not reduce the amount of **1a** further (Table 1, entries 17–20). Finally, we lowered the reaction temperature to 70°C and found **3a** was formed only in 61% yield (Table 1, entry 21). Therefore, the optimal conditions were heating **1a** (0.75 mmol), **2a** (1.5 mmol), and $CuBr_2$ (0.25 mmol) in DMF at 90°C for 12 h in a sealed tube under oxygen atmosphere.

Table 1

Optimization of reaction conditions[a].



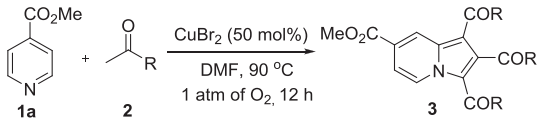
Entry	Solvent	Copper (mmol)	Oxidant (mmol)	Yield (%)[b]
1	CH_3CN	$CuBr_2$ (0.5)	Air	0
2	Dioxane	$CuBr_2$ (0.5)	Air	0
3	Benzene	$CuBr_2$ (0.5)	Air	0
4	DCE	$CuBr_2$ (0.5)	Air	0
5	Ethanol	$CuBr_2$ (0.5)	Air	0
6	DMF	$CuBr_2$ (0.5)	Air	72
7	DMF	CuBr (0.5)	Air	0
8	DMF	CuI (0.5)	Air	0
9	DMF	$CuCl_2$ (0.5)	Air	26
10	DMF	CuCl (0.5)	Air	0
11	DMF	$CuBr_2$ (0.25)	O_2 (1 atm)	72
12	DMF	$CuBr_2$ (0.15)	O_2 (1 atm)	58
13	DMF	None	O_2 (1 atm)	0
14	DMF	$CuBr_2$ (0.25)	$K_2S_2O_8$ (1)	20
15	DMF	$CuBr_2$ (0.25)	DTBP (1)	42
16	DMF	$CuBr_2$ (0.25)	TBHP (1)	15
17[c]	DMF	$CuBr_2$ (0.25)	O_2 (1 atm)	72
18[d]	DMF	$CuBr_2$ (0.25)	O_2 (1 atm)	60
19[e]	DMF	$CuBr_2$ (0.25)	O_2 (1 atm)	Trace
20[f]	DMF	$CuBr_2$ (0.25)	O_2 (1 atm)	Trace
21[g]	DMF	$CuBr_2$ (0.25)	O_2 (1 atm)	61

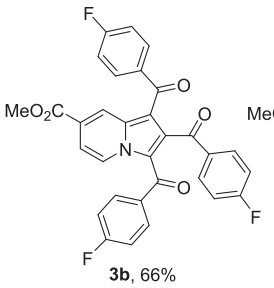
DMF, dimethylformamide.
[a]Conditions: heating **1a** (2.0 mmol), **2a** (1.5 mmol), copper salt, and oxidant at 90°C for 12 h.
[b]Isolated yields based on **2a**.
[c]**1a** (0.75 mmol).
[d]**1a** (0.5 mmol).
[e]**1a** (0.5 mmol), K_2CO_3 (1.0 mmol).
[f]**1a** (0.5 mmol), Et_3N (1.0 mmol).
[g]Heating at 70°C.

With the optimized conditions in hand, we firstly explore the scope of methyl ketones by using various kinds of methyl ketones **2** to react with methyl isonicotinate **1a** under the optimal conditions (Table 2). It showed that a variety of acetophenones **2b**–**2l** containing electron-withdrawing (F, Cl, and CO_2Me) or electron-

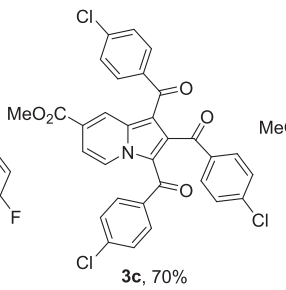
Table 2

Scope of methyl ketones[a,b].

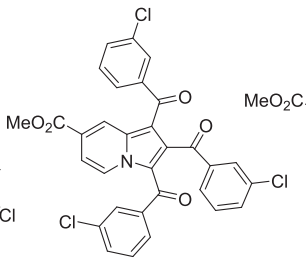




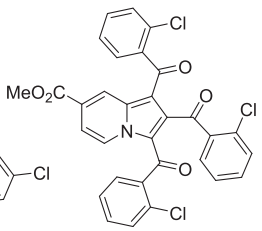
3b, 66%



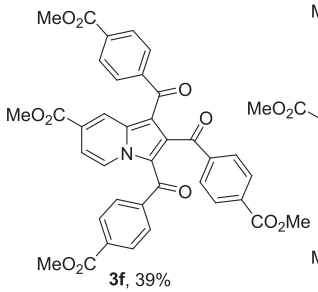
3c, 70%



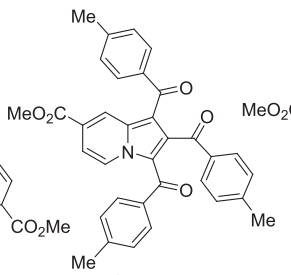
3d, 62%



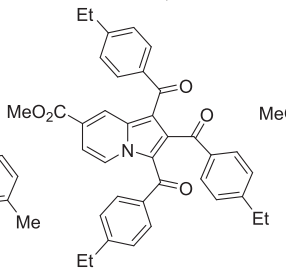
3e, 56%



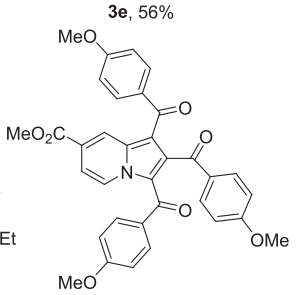
3f, 39%



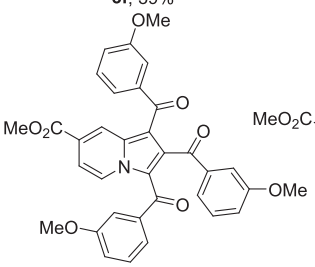
3g, 82%



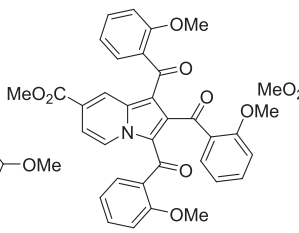
3h, 81%



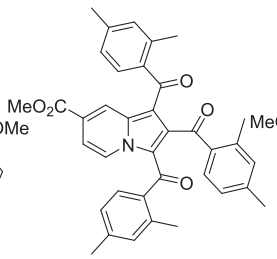
3i, 85%



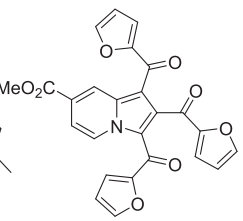
3j, 76%



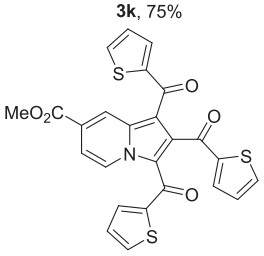
3k, 75%



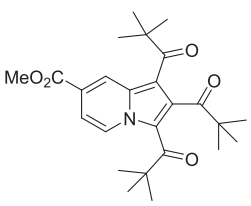
3l, 80%



3m, 70%



3n, 46%



3o, 0%

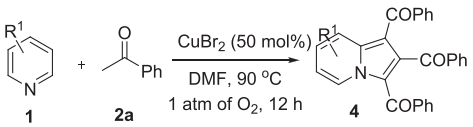
[a]Conditions: **1a** (0.75 mmol), **2** (1.5 mmol), $CuBr_2$ (0.25 mmol), and DMF (5 mL).
[b]Isolated yields based on **2**.

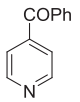
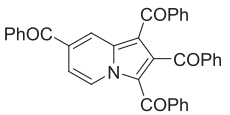
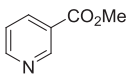
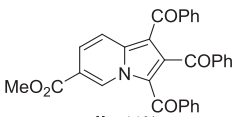
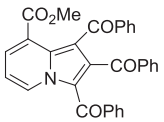
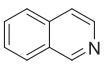
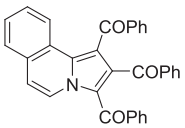
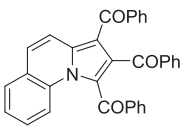
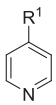
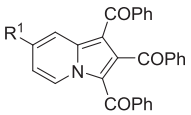
donating groups (Me, Et, and OMe) on the *para*-position, *meta*-position, or *ortho*-position of the Ar ring participate this reaction smoothly, providing the corresponding 1,2,3-traroylindolizines **3b**–**3l** in moderate to good yields. Besides, employing 1-(furan-2-yl)ethanone **2m** or 1-(thiophen-2-yl)ethanone **2n** as reactant, we also isolated the desired product **3m** or **3n** in 70% or 46% yields, respectively. However, when aliphatic methyl ketone **2o** was used to this reaction, the desired product **3o** was not detected.

Next, the scope of pyridines was examined (Table 3). It showed that pyridines with electron-withdrawing groups and annulated pyridines are all good substrates. For example, 4-benzoylpyridine **1b** reacted with methyl

Table 3

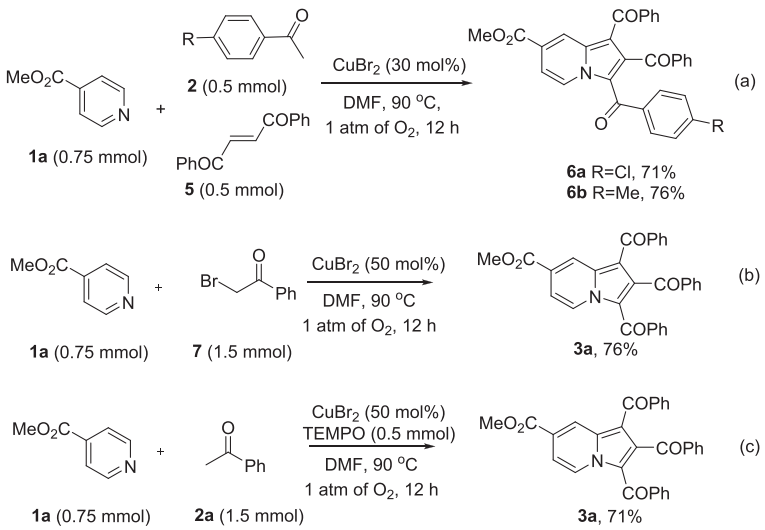
Scope of pyridines[a,b].



Entry	1	Product
1	 **1b**	 **4a,** 62%
2	 **1c**	 **4b,** 41%
		 **4c,** 38%
3	 **1d**	 **4d**, 53%
4	 **1e**	 **4e,** 77%
5[c]	 **1f**, R=H **1g**, R=*t*-Bu	 **4f**, 41% **4g**, 52%

[a]Conditions: **1** (0.75 mmol), **2a** (1.5 mmol), $CuBr_2$ (0.25 mmol), and DMF (5 mL).
[b]Isolated yields based on **2**.
[c]Heating in the air for 18 h.

Scheme 2. Control experiment.

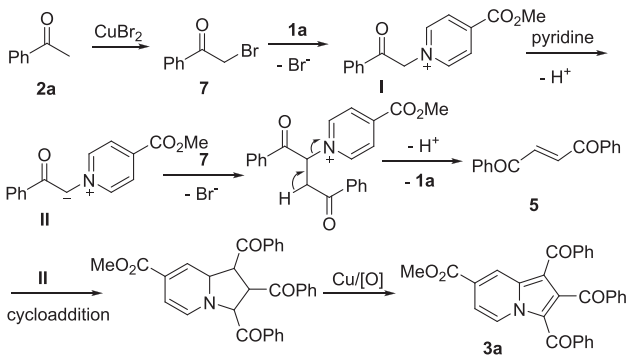


ketones **2** well, forming 1,2,3-triaroylindolizines **4a** in 62% yield. When methyl nicotinate **1c** was employed as reactant, two isomers **4b** and **4c** were isolated in similar yields simultaneously. Also, both isoquinoline **1d** and quinoline **1e** formed the corresponding indolizine products **4d** and **4e** in good yields. For pyridines **1f** and **1g** without substituent or with electron-donating group, higher yields of **4f** and **4g** were obtained in the air than under O_2 atmosphere.

To shed light on the reaction mechanism, several control experiments were carried out (Scheme 2). First, we employed (*E*)-1,2-dibenzoylethylene **5** (0.5 mmol) to react with **1a** (0.75 mmol) and acetophenone **2** (0.5 mmol) in the presence of 30 mol% $CuBr_2$ under oxygen atmosphere and obtained products **6a** and **6b** in 71% and 76% yields, respectively (Scheme 2a). Second, using bromoketone **7** to react with **1a** under the standard conditions, we also got **3a** in good yield (Scheme 2b). These results illustrated that compounds **5** and **7** were the possible reaction intermediates. Third, adding 0.5 mmol of TEMPO into the model reaction did not inhibit the formation of **3a**, which has ruled out the radical mechanism (Scheme 2c).

Based on our experimental results, a plausible mechanism is proposed in Scheme 3. First, the reaction of acetophenone **2a** and $CuBr_2$ generated α-brmoketone **7** that reacted with **1a**, forming pyridinium salt **I** [32]. Then, **I** was transformed to yield **II** with the aid of pyridine. Subsequently, nucleophilic substitution between **II** and **7** followed by β-elimination gave 1,2-dibenzoylethylene **5**. At last, intermediate **5** underwent 1,3-dipolar cycloaddition with **II** and subsequent oxidative aromatization by the aid of copper salt and oxygen, giving the final product **3a**.

Scheme 3. Plausible reaction mechanism.



CONCLUSION

In summary, we have demonstrated an efficient copper-promoted reaction to access 1,2,3-triaroylindolizines from aromatic methyl ketones and pyridines. This protocol needs only 0.5 equimolar amount of copper salt to combine three molecules of acetophenone and one molecule of pyridine derivative together, giving 1,2,3-triaroylindolizines in satisfied yields.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were measured on 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 on 100 MHz with $CDCl_3$ as

solvent. HRMS (ESI) data were obtained in the electron impact mode.

General procedure for the preparation of 3. Methyl isonicotinate **1a** (0.75 mmol), methyl ketone **2** (1.5 mmol), and copper bromide (0.25 mmol) were mixed in 5 mL of DMF in a sealed tube and heated at 90°C for 12 h under oxygen atmosphere. After completion of the reaction, the mixture was cooled to room temperature and separated by flash column chromatography (ethyl acetate/hexane) on silica gel to afford product **3**.

Methyl 1,2,3-tribenzoylindolizine-7-carboxylate (3a). Yellow solid; yield: 176.1 mg (72%); mp: 172–174°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.06 (t, J = 7.6 Hz, 2H), 7.13–7.17 (m, 4H), 7.25–7.39 (m, 7H), 7.45 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 7.2 Hz, 1H), 8.73 (s, 1H), 9.50 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 191.1, 187.7, 164.9, 139.5, 139.4, 138.3, 136.6, 136.3, 132.9, 132.4, 132.3, 128.9, 128.8, 128.7, 128.1, 128.0, 127.3, 123.3, 122.3, 117.8, 114.9, 52.8. HRMS (ESI) *m/z* calcd for $C_{31}H_{22}NO_5$ $[M + H]^+$ 488.1498, found 488.1482.

Methyl 1,2,3-tris(4-fluorobenzoyl)indolizine-7-carboxylate (3b). Yellow solid; yield: 179.2 mg (66%); mp: 178–180°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 6.80 (t, J = 8.4 Hz, 2H), 6.87–6.92 (m, 4H), 7.34–7.44 (m, 4H), 7.51–7.54 (m, 2H), 7.66 (d, J = 7.2 Hz, 1H), 8.68 (s, 1H), 9.46 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 189.3, 186.0, 165.6 (d, J = 256 Hz), 164.3 (d, J = 253 Hz), 165.3 (d, J = 252 Hz), 164.7, 136.3, 135.9, 135.7 (d, J = 3 Hz), 135.5 (d, J = 3 Hz), 135.4 (d, J = 3 Hz), 134.7 (d, J = 3 Hz), 131.5, 131.4, 131.3, 131.2, 131.1, 128.3, 127.3, 123.0, 122.1, 117.5, 115.6, 115.5, 115.4, 115.3, 115.2, 115.1.

HRMS (ESI) *m/z* calcd for $C_{31}H_{19}F_3NO_5$ $[M + H]^+$ 542.1215, found 542.1201.

Methyl 1,2,3-tris(4-chlorobenzoyl)indolizine-7-carboxylate (3c). Yellow solid; yield: 204.9 mg (70%); mp: 168–170°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.09 (d, J = 8.0 Hz, 2H), 7.18–7.27 (m, 6H), 7.32 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 7.2 Hz, 1H), 8.68 (s, 1H), 9.48 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 189.4, 186.1, 164.7, 140.0, 139.1, 129.0, 137.6, 137.4, 136.5, 136.0, 130.2, 130.1, 129.9, 128.6, 128.5, 128.4, 127.4, 122.9, 122.0, 117.4. 115.3. 52.9. HRMS (ESI) *m/z* calcd for $C_{31}H_{19}Cl_3NO_5$ $[M + H]^+$ 590.0329, found 590.0313.

Methyl 1,2,3-tris(3-chlorobenzoyl)indolizine-7-carboxylate (3d). Yellow solid; yield: 183.6 mg (62%); mp: 156–158°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.10–7.27 (m, 6H), 7.28–7.36 (m, 5H), 7.42 (d, J = 7.6 Hz, 1H), 7.72 (dd, J = 7.2, 1.6 Hz, 1H), 8.80 (s, 1H), 9.56 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 189.1, 185.6, 164.4, 140.8, 140.7, 139.2, 136.6, 136.1, 134.8, 134.4, 132.9, 132.1, 132.0, 129.5, 129.4, 128.8, 128.4, 127.9, 127.3, 126.7, 126.6, 122.7, 122.0, 117.0, 115.4, 52.7.HRMS (ESI) *m/z* calcd for $C_{31}H_{19}Cl_3NO_5$ $[M + H]^+$ 590.0329, found 590.0317.

Methyl 1,2,3-tris(2-chlorobenzoyl)indolizine-7-carboxylate (3e). Yellow solid; yield: 166.1 mg (56%); mp: 170–172°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 6.92 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.07–7.23 (m, 8H), 7.32 (td, J = 8.0, 1.2 Hz, 1H), 7.44 (dd, J = 7.6, 0.8 Hz, 1H), 7.75 (dd, J = 7.6, 1.6 Hz, 1H), 8.57 (s, 1H), 10.02 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 188.1, 185.1, 164.6, 140.8, 138.9, 137.9, 137.6, 134.4, 133.6, 133.2, 131.9, 131.5, 131.3, 131.2, 130.2, 129.8, 129.5, 129.0, 128.9, 126.6, 126.2, 126.1, 122.4, 121.8, 116.9, 115.9, 52.9. HRMS (ESI) *m/z* calcd for $C_{31}H_{19}Cl_3NO_5$ $[M + H]^+$ 590.0329, found 590.0346.

Methyl 1,2,3-tri(4-(methoxycarbonyl)benzoyl)indolizine-7-carbo-xylate (3f). Yellow solid; yield: 129.9 mg (39%); mp: 169–171°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 9H), 4.03 (s, 3H), 7.56 (s, 1H), 7.79 (dd, J = 7.2, 1.6 Hz, 1H), 7.84 (dd, J = 8.0, 1.2 Hz, 4H), 8.13–8.19 (m, 7H), 9.31 (s, 1H), 10.02 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 184.9, 166.2, 166.1, 164.8, 142.9, 142.7, 139.5, 134.3, 133.0, 132.9, 130.3, 130.0, 129.9, 129.7, 129.5, 128.7, 128.6, 128.5, 123.2, 122.4, 115.8, 52.8, 52.4, 52.3. HRMS (ESI) *m/z* calcd for $C_{37}H_{28}NO_{11}$ $[M + H]^+$ 662.1662, found 662.1646.

Methyl 1,2,3-tris(4-methylbenzoyl)indolizine-7-carboxylate (3g). Yellow solid; yield: 215.9 mg (82%); mp: 210–212°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.29 (s, 3H), 2.33 (s, 3H), 3.96 (s, 3H), 6.87 (d, J = 8.0 Hz, 2H), 6.94–6.98 (m, 4H), 7.17 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 7.2 Hz, 1H), 8.69 (s, 1H), 9.40 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 190.9, 187.5, 165.0, 143.7, 143.2, 136.9, 136.7, 136.3, 136.2, 135.9, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 127.4, 127.1, 123.5, 122.3, 118.0, 114.5, 52.7, 21.7, 21.6, 21.5. HRMS (ESI) *m/z* calcd for $C_{34}H_{28}NO_5$ $[M + H]^+$ 530.1967, found 530.1982.

Methyl 1,2,3-tris(4-ethylbenzoyl)indolizine-7-carboxylate (3h). Yellow solid; yield: 231.8 mg (81%); mp: 135–137°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09–1.23 (m, 9H), 2.51–2.62 (m, 6H), 3.95 (s, 3H), 6.86 (d, J = 8.0 Hz, 2H), 6.95 (t, J = 8.0 Hz, 4H), 7.16 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.60 (dd, J = 7.2, 0.8 Hz, 1H), 8.71 (s, 1H), 9.43 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 190.9, 187.6, 165.0, 149.8, 149.3, 137.2, 137.1, 136.5, 136.3, 136.0, 129.1, 129.0, 128.9, 127.6, 127.5, 127.4, 127.1, 123.5, 122.3, 118.1, 114.6, 52.7, 29.0, 29.0, 28.9, 28.8, 15.5, 15.3, 15.2. HRMS (ESI) *m/z* calcd for $C_{37}H_{34}NO_5$ $[M + H]^+$ 572.2437, found 572.2420.

Methyl 1,2,3-tris(4-methoxybenzoyl)indolizine-7-carboxylate (3i). Yellow solid; yield: 245.7 mg (85%); mp: 159–161°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 3.96 (s, 3H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.65–6.68 (m, 4H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.56 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.68 (s, 1H), 9.32 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 189.8, 186.4, 185.1, 163.3, 163.2, 163.1, 135.7, 135.6, 132.3, 132.2, 132.0, 131.3, 131.2, 131.0, 127.0, 126.9, 123.4, 122.3, 117.9, 114.3, 113.4, 113.3, 112.9, 55.5, 55.4, 55.3. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{34}H_{28}NO_8$: 578.1815, found 578.1795.

Methyl 1,2,3-tris(3-methoxybenzoyl)indolizine-7-carboxylate (3j). Yellow solid; yield: 220.3 mg (76%); mp: 137–139°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.66 (s, 6H), 3.98 (s, 3H), 6.63 (s, 1H), 6.86–7.04 (m, 10H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.80 (s, 1H), 9.48 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 190.7, 187.3, 164.7, 159.2, 159.1, 140.7, 140.6, 139.7, 136.3, 136.2, 129.0, 128.9, 128.8, 127.8, 127.0, 123.2, 122.3, 122.2, 121.7, 121.6, 119.9, 119.4, 119.3, 117.6, 114.8, 112.2, 112.1, 111.3, 55.1, 55.0, 52.6. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{34}H_{28}NO_8$: 578.1815, found 578.1810.

Methyl 1,2,3-tris(2-methoxybenzoyl)indolizine-7-carboxylate (3k). Yellow solid; yield: 215.8 mg (75%); mp: 162–164°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 3H), 3.55 (s, 3H), 3.56 (s, 3H), 3.98 (s, 3H), 6.46 (d, *J* = 8.4 Hz, 1H), 6.52 (t, *J* = 7.6 Hz, 1H), 6.60–6.68 (m, 4H), 7.02–7.09 (m, 4H), 7.16 (td, *J* = 7.6, 1.6 Hz, 1H), 7.27–7.34 (m, 1H), 7.66 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.89–8.90 (m, 1H), 9.97 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 188.3, 186.6, 165.3, 159.1, 157.0, 156.9, 143.2, 137.2, 134.3, 131.8, 131.7, 131.0, 129.6, 129.4, 128.8, 128.5, 126.0, 122.5, 119.9, 119.7, 119.6, 117.1, 114.9, 111.1, 110.7, 55.5, 55.4, 55.3, 52.8. HRMS (ESI) *m/z* calcd for $C_{34}H_{28}NO_8$: 578.1815, found 578.1796.

Methyl 1,2,3-tris(2,4-dimethylbenzoyl)indolizine-7-carboxylate (3l). Yellow solid; yield: 229.2 mg (80%); mp: 130–132°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.10 (s, 6H), 2.14 (s, 3H), 2.19 (s, 3H), 2.29 (s, 3H), 3.97 (s, 3H), 6.49 (d, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.72 (s, 2H), 6.79 (s, 1H), 6.87 (t, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.73 (s, 1H), 9.76 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 191.2, 189.2, 165.0, 142.8, 141.1, 140.7, 140.6, 140.0, 137.3, 137.0, 136.9, 136.8, 136.1, 134.0, 133.3, 132.2, 131.3, 131.2, 129.2, 128.6, 128.0, 125.6, 125.5, 125.2, 123.5, 122.2, 118.2, 114.9, 21.5, 21.4, 21.2, 21.1, 19.5, 19.4. HRMS (ESI) *m/z* calcd for $C_{37}H_{34}NO_5$: 572.2437, found 572.2460.

Methyl 1,2,3-tri(furan-2-carbonyl)indolizine-7-carboxylate (3m). Yellow solid; yield: 159.6 mg (70%); mp: 164–166°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 6.42–6.43 (m, 3H), 6.98 (d, *J* = 3.6 Hz, 1H), 7.10 (dd, *J* = 10.0, 3.6 Hz, 2H), 7.26–7.29 (m, 2H), 7.48 (d, *J* = 0.8 Hz, 1H), 7.59 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.82 (s, 1H), 9.28 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 177.1, 173.4, 164.9, 153.4, 153.0, 152.6, 146.9, 146.5, 146.1, 135.9, 133.4, 127.6, 126.7, 122.4, 122.3, 119.2, 118.4, 116.4, 114.8, 112.8, 112.6, 112.5, 52.7. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{25}H_{16}NO_8$: 458.0876, found 458.0890.

Methyl 1,2,3-tri(thiophene-2-carbonyl)indolizine-7-carboxylate (3n). Yellow solid; yield: 117.2 mg (46%); mp: 208–210°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 6.85–7.01 (m, 3H), 7.36 (d, *J* = 2.0 Hz, 2H), 7.43 (d, *J* = 2.8 Hz, 1H), 7.56–7.59 (m, 4H), 8.72 (s, 1H), 9.18 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 182.4, 178.9, 164.9, 146.2, 145.1, 144.7, 135.4, 135.3, 134.8, 134.4, 134.3, 134.2, 134.0, 133.9, 128.1, 127.7, 127.6, 127.4, 126.7, 123.2, 122.3, 117.5, 114.7, 52.8. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{25}H_{16}NO_5S_3$: 506.0191, found 506.0177.

General procedure for the preparation of 4. Pyridines **1** (0.75 mmol), acetophenone **2a** (1.5 mmol), and copper bromide (0.25 mmol) were mixed in 5 mL of DMF in a sealed tube and heated at 90°C for 12 h under oxygen atmosphere. After completion of the reaction, the mixture was cooled to room temperature and separated by flash column chromatography (ethyl acetate/hexane) on silica gel to afford product **4**.

Indolizine-1,2,3,7-tetrayltetrakis(phenylmethanone) (4a). Yellow solid; yield: 165.9 mg (62%); mp: 210–212°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, *J* = 7.6 Hz, 2H), 7.12–7.17 (m, 4H), 7.26–7.44 (m, 9H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.83 (d, *J* = 7.6 Hz, 2H), 8.40 (s, 1H), 9.55 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 191.2, 191.1, 187.7, 139.4, 139.3, 138.2, 136.7, 136.3, 136.0, 134.7, 133.1, 132.9, 132.4, 132.3, 130.1, 129.8, 128.8, 128.7, 128.1, 128.0, 127.6, 123.4, 123.0, 118.0, 115.3. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{36}H_{24}NO_4$: 534.1705, found 534.1688.

Methyl 1,2,3-tribenzoylindolizine-6-carboxylate (4b). Yellow solid; yield: 100.8 mg (41%); mp 206–208°C.^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.06 (t, *J* = 7.6 Hz, 2H), 7.15–7.20 (m, 4H), 7.27–7.30 (m, 3H), 7.36–7.40 (m, 4H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.99 (d, *J* = 9.6 Hz, 1H), 10.23 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 190.9, 187.5, 164.8, 139.4, 138.2, 138.1, 138.9, 132.9, 132.3, 131.7, 128.8, 128.7, 128.2, 128.1, 128.0, 126.5, 123.0, 119.7, 119.2, 52.7. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{31}H_{22}NO_5$: 488.1498, found 488.1507.

Methyl 1,2,3-tribenzoylindolizine-8-carboxylate (4c). Yellow solid; yield: 93.1 mg (38%); mp 215–216°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H), 7.05 (t, *J* = 7.6 Hz, 2H), 7.11–7.14 (m, 3H), 7.23 (t, *J* = 7.2 Hz, 3H), 7.26–7.42 (m, 6H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.83 (d, *J* = 7.2 Hz, 1H), 9.76 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 187.1, 165.3, 139.9, 138.4, 138.3, 136.4, 132.7, 132.6, 132.4, 131.9, 130.5, 129.3, 128.9, 128.8, 128.7, 128.1, 127.9, 127.8, 123,7, 121.4, 117.2, 114.3, 51.8. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{31}H_{22}NO_5$: 488.1498, found 488.1483.

Pyrrolo[2,1-a]isoquinoline-1,2,3-triyltris(phenylmethanone) (4d). Yellow solid; yield: 127.5 mg (53%); mp 210–212°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07–7.12 (m, 4H), 7.22–7.45 (m, 11H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 1H), 9.10 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 191.7, 187.5, 140.3, 139.0, 138.4, 133.7, 133.5, 132.5, 132.3, 131.9, 129.6, 129.5, 129.1, 128.8, 128.7, 128.5, 128.3, 128.1, 127.9, 127.4, 125.2, 124.2, 123.9, 123.6, 118.7, 115.9. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{33}H_{22}NO_3$: 480.1600, found 480.1648.

Pyrrolo[1,2-a]quinoline-1,2,3-triyltris(phenylmethanone) (4e). Yellow solid; yield: 184.2 mg (77%); mp 172–174°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.19 (m, 4H), 7.29–7.36 (m, 6H), 7.41–7.48 (m, 5H), 7.55 (d, *J* = 9.6 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.84–7.91 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 191.5, 189.6, 140.2, 138.7, 137.7, 136.1, 134.0, 132.5, 132.4, 132.3, 132.0, 129.7, 129.3, 129.1, 128.9, 128.7, 128.1, 128.0, 127.4, 125.8, 125.5, 118.7, 117.9, 116.0. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{33}H_{22}NO_3$: 480.1600, found 480.1652.

Indolizine-1,2,3-triyltris(phenylmethanone) (4f). Yellow solid; yield: 87.6 mg (41%); mp: 202–204°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, *J* = 7.2 Hz, 2H), 7.13–7.16 (m, 5H), 7.25–7.29 (m, 3H), 7.34–7.46 (m, 7H), 8.04 (d, *J* = 8.8 Hz, 1H), 9.64 (dd, *J* = 7.2, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 191.4, 187.7, 140.0, 139.9, 138.4, 138.1, 137.0, 132.7, 132.0, 131.9, 128.9, 128.8, 128.7, 128.6, 128.1, 128.0, 127.9, 127.7, 122.2, 119.8, 116.2, 115.2. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{29}H_{20}NO_3$: 430.1443, found 430.1458.

(7-tert-Butylindolizine-1,2,3-triyl)tris(phenylmethanone) (4g). Yellow solid; yield: 126.7 mg (52%); mp: 212–213°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 7.02 (t, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 4H), 7.20–7.28 (m, 4H), 7.31–7.34 (m, 4H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.99 (s, 1H), 9.57 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 191.6, 187.5, 152.4, 140.2, 140.1, 138.8, 138.5, 137.3, 132.7, 131.9, 131.7, 128.8, 128.7, 128.1, 128.0, 127.9, 127.7, 121.8, 115.6, 114.7, 114.5, 35.3, 30.3. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{33}H_{28}NO_3$: 486.2069, found 486.2079.

General procedure for the preparation of 6. Methyl isonicotinate **1a** (2.0 mmol), methyl ketone **2** (0.5 mmol), alkene **5** (0.5 mmol), and copper bromide (0.15 mmol) were mixed in 5 mL of DMF in a sealed tube and heated at 90°C for 12 h under oxygen atmosphere. After completion of the reaction, the mixture was cooled to room temperature and separated by flash column chromatography (ethyl acetate/hexane) on silica gel to afford product **6**.

Methyl 1,2-dibenzoyl-3-(4-chlorobenzoyl)indolizine-7-carboxylate (6a). Yellow solid; yield: 185.8 mg (71%); mp 185–187°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.14–7.20 (m, 4H), 7.27–7.31 (m, 4H), 7.36–7.40 (m, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.65 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.71 (s, 1H), 9.50 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 191.0, 186.3, 164.8, 139.2, 138.7, 138.2, 137.8, 136.7, 136.5, 133.1, 132.5, 130.1, 128.9, 128.7, 128.4, 128.2, 128.1, 127.3, 122.9, 122.2, 118.0, 115.1, 52.8. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{31}H_{21}ClNO_5$: 522.1108, found 522.1120.

Methyl 1,2-dibenzoyl-3-(4-methylbenzoyl)indolizine-7-carboxylate (6b). Yellow solid; yield: 191.3 mg (76%); mp 169–171°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.96 (s, 3H), 6.86 (d, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 4H), 7.25–7.31 (m, 4H), 7.33–7.39 (m, 2H), 7.45 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.62 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.72 (s, 1H), 9.41 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 191.1, 187.4, 165.0, 143.4, 139.4, 138.4, 136.8, 136.2, 136.1, 132.8, 132.4, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 127.8, 127.1, 122.3, 117.7, 114.7, 52.7, 21.5. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{32}H_{24}NO_5$: 502.1654, found 502.1637.

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