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One-pot multicomponent synthesis of polysubstituted indolizines

Zhenjun Mao, Xuejian Li, Xufeng Lin *, Ping Lu, Yanguang Wang

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

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ABSTRACT

Concise and efficient four-component tandem approaches to polysubstituted indolizines have been developed under metal-free and mild aerobic conditions in refluxing acetonitrile. The mechanism of the novel reactions was proposed involving the formation of pyridinium ylides and α,β-unsaturated ketones with subsequent 1,3-dipolar cycloaddition and aromatization reaction.

1. Introduction

The chemistry of indolizines has assumed an interesting importance as they widely occur as key structural subunits of many bioactive natural products, organic fluorescent materials, and pharmaceutical substances.[1] As a successful calcium channel blocker antihypertensive drug, Fantofarone is a prime example.[2] Consequently, methods for the synthesis of various types of indolizine derivatives bearing diverse substitution patterns have received much attention.[3] The reactions involved are classified as condensation reactions, 1,3-dipolar cycloadditions, and 1,5-dipolar cyclizations. Recent synthetic strategies also take advantage of a variety of transition-metal catalysts.[4] Whereas these methods have proven very useful for the synthesis of pyrrole derivatives, they generally involve multistep synthetic operations that limit the scope of these reactions. Considering the continued importance of the indolizine core in both biological and chemical fields, new direct approaches remain highly valuable to the contemporary collection of synthetic methods.

Multicomponent reactions (MCRs) have emerged as powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry.[5] Various MCRs have been developed not only for their facileness and efficiency, but also for their economy and ecology in organic synthesis.[6] These features make MCRs well-suited for the easy construction of diversified heterocyclic scaffolds and perfectly amenable to automation for combinatorial synthesis.[7] Actually, three-component reactions have been demonstrated as a straightforward approach to the synthesis of indolizines.[8]

As a part of our ongoing research into heterocyclic synthesis by developing novel MCRs and tandem reaction strategy,[9] we herein report concise and efficient four-component tandem approaches to polysubstituted indolizine derivatives involving the formation of pyridinium ylides and α,β-unsaturated ketones with subsequent 1,3-dipolar cycloaddition and aromatization reaction.

2. Results and discussion

We began our investigations by treating pyridine (**1**) and phenacyl bromide (**2a**) with ethyl glyoxalate (**3**) in the presence of Na_2CO_3 under aerobic conditions in refluxing acetonitrile for 16 h. The resulting polysubstituted indolizine derivative **4a** (ethyl 1,3-dibenzoylindolizine-2-carboxylate) was isolated in 61% yield after workup. Similarly, various 2-bromoacetophenones reacted well under the same conditions to give the corresponding polysubstituted indolizine derivatives **4b**–**4e** in moderate yields, and the results are shown in Table 1 (entries 1–5). 2-Bromoacetophenones with electron-withdrawing groups such as bromo and chloro gave the polysubstituted indolizines in slightly higher yield than those with electrondonating groups such as methoxy and methyl. As expected, aliphatic bromo ketone such as 1-bromobutan-2-one (**2f**) afforded the desired product (**4f**) in low yield (Table 1, entry 6). On the other hand, the replacement of pyridine with quinoline was smoothly transformed into the expected product in good yields (Table 1, entries 7 and 8). The structures of products **4** (**4a**–**h**) were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectra. The typical structure of compound

* Corresponding author. Tel.: +86 571 87952759; fax: +86 571 87953816; e-mail address: lxfok@zju.edu.cn (X. Lin).

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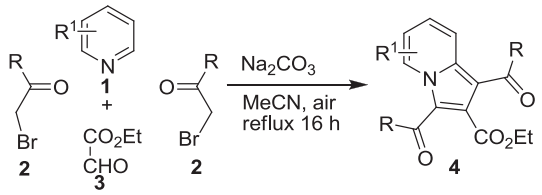
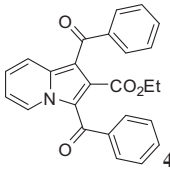
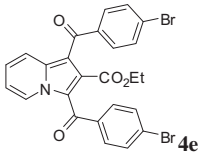
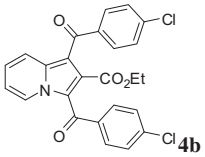
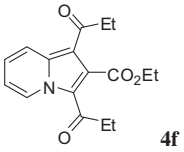
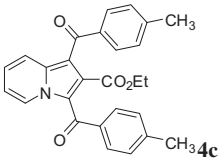
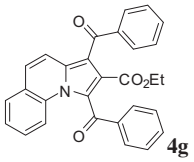
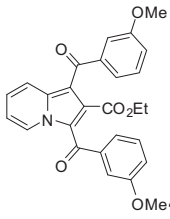
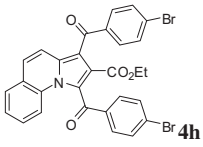
Table 1
Synthesis of indolizines **4**[a]



Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1	 **4a**	61	5	 **4e**	62
2	 **4b**	63	6	 **4f**	32
3	 **4c**	55	7	 **4g**	89
4	 **4d**	58	8	 **4h**	70

[a] Reaction conditions: **3** (1.0 mmol), **2** (2.2 mmol), and **1** (2.5 mmol) and Na_2CO_3 (2.5 mmol) in CH_3CN (5 mL).
[b] Isolated yield based on **3**.

4a (Table 1, entry 1) was unambiguously confirmed by single-crystal X-ray analysis (Fig. 1).[10]

To explain the mechanism of this one-pot multicomponent tandem reaction, we propose a possible mechanism as shown in Scheme 1. The first step is the formation of phenacylpyridinium bromide **A** from the addition of phenacyl bromide to pyridine. The second step is the nucleophilic attack of a pyridinium ylide **B**, which is generated in situ via deprotonation of **A** on ethyl glyoxalate **3** to afford **C**. Then, the reactive alkene **E** is generated via a 1,2-H shift of **C** followed by elimination of pyridine. Intermediate **E** subsequently reacts with another pyridinium ylide **B** via 1,3-dipolar cycloaddition followed by elimination of H_2O to give the regioselective intermediate **G**. Finally, **G** is oxidized by O_2 in air to give the desired product **4**.

We then tested the reaction between phenacyl bromide and pyridine in the absence of ethyl glyoxalate (**3**) under the similar conditions, and no indolizine was obtained other than pyridinium ylide (**B**). An exploration of several parameters (including base catalyst, solvent, temperature, the sequence of addition of substrates) provided dramatic improvements. Surprisingly, the unexpected product of 1,2,3-triaroylindolizine **5a** was generated in 44% isolated yield after addition of piperidine into this reaction under the similar conditions. The type of compound has previously been accessed only by more cumbersome multistep procedures.[11] We are pleased to find a convenient method for the synthesis of 1,2,3-triaroylindolizines **5** via a four-component reaction with a molecular of pyridine and three phenacyl bromide in the presence of Na_2CO_3 and piperidine under metal-free and mild aerobic conditions in refluxing acetonitrile.

Subsequently, we investigated the reaction scope, as shown in Table 2. A variety of electron-poor and electron-rich 2-bromoacetophenones were found to react to provide the analogous 1,2,3-triaroylindolizines **5** with 35–46% yields (Table 2, entries 1–8). The replacement of pyridine with isoquinoline or quinoline was transformed into the expected products (Table 2, entries 9 and 10). The structures of products **5** (**5a**–**j**) were characterized by ^1H NMR, ^{13}C NMR, IR, MS, and HRMS spectra. The typical structure of compound **5a** (Table 2, entry 1) was unambiguously confirmed by single-crystal X-ray analysis (Fig. 2).[12]

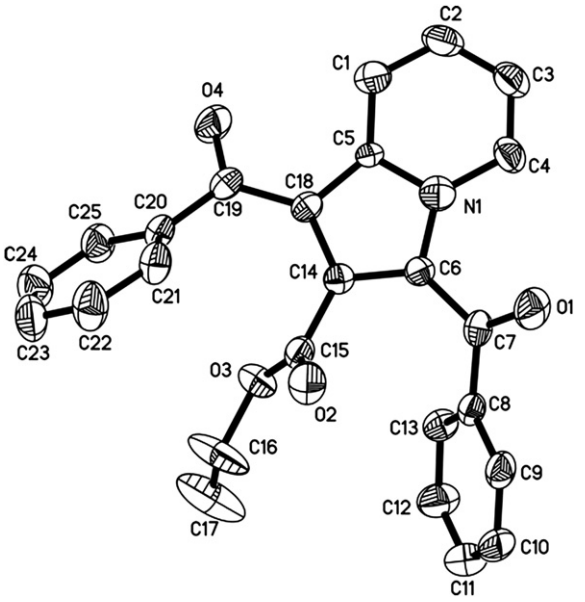
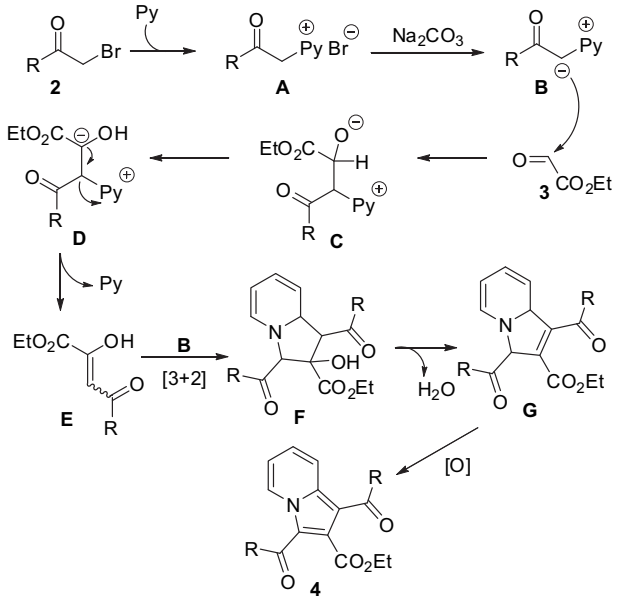


Fig. 1. X-ray crystal structure of **4a**.



Scheme 1.

Scheme 2 shows a plausible reaction mechanism for the multicomponent transformations, starting with the formation of pyridinium ylide **B** and the reactive **H** from the addition of phenacyl bromide to piperidine. A nucleophilic substitution reaction between **B** and **H** affords the pyridinium salt **I**. Subsequently, **I** releases piperidine to generate **J**, which undergoes an elimination of pyridine to give the intermediate **K**. The 1,2,3-triaroylindolizine **5** is finally obtained via 1,3-dipolar cycloaddition between the electron-deficient alkene **K** and another pyridinium ylide **B** followed by aromatization.

3. Conclusion

In summary, we have demonstrated the concise and efficient four-component tandem approaches to polysubstituted indolizines from easily available starting materials by the more general 1,3-dipolar cycloaddition followed by mild aerobic aromatization strategy. This strategy takes advantage of the successful use of pyridinium ylides generated in situ as the dipoles, the electron-deficient alkenes generated in situ as dipolarophiles, and oxygen in air as the oxidizer of aromatization in the reactions.

4. Experimental section

4.1. General

All reagents were purchased from a commercial supplier and used as received. IR spectra were recorded on an ATR spectrometer (neat) and reported in reciprocal centimeters (cm^{-1}). NMR spectra were recorded for ^1H NMR at 400 MHz and for ^{13}C NMR at 100 MHz. For ^1H NMR, tetramethylsilane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), and coupling constant in hertz. For ^{13}C NMR, $CDCl_3$ (δ=77.00) was used as internal standard and spectra were obtained with complete proton decoupling. Low-resolution MS data were obtained using ESI ionization. HRMS data were obtained using EI ionization. Mp data were measured with micro melting point apparatus.

4.2. General procedure for the synthesis of indolizines 4

To a solution of ethyl glyoxylate (1.0 mmol), phenacyl bromide (2.2 mmol), and pyridine (2.5 mmol) in CH_3CN (5 mL) was added Na_2CO_3 (2.5 mmol). The resulting mixture was refluxed for 16 h and then filtered through a Celite plug. The filtrate was concentrated in vacuum and the residue was subjected to a flash chromatography on silica gel with petroleum ether/ethyl acetate (4:1) as eluent to afford the corresponding product **4**.

4.3. General procedure for the synthesis of indolizines 5

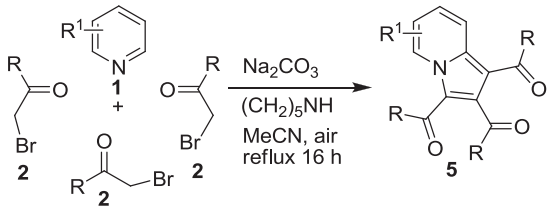
To a solution of phenacyl bromide (1.5 mmol), Na_2CO_3 (2 mmol), and pyridine (1.0 mmol) in CH_3CN (5 mL) was added piperidine (0.5 mmol). The resulting mixture was refluxed for 16 h, and then filtered through a Celite plug. The filtrate was concentrated in vacuum, and the residue was subjected to a flash chromatography on silica gel with petroleum ether/ethyl acetate (3:1) as eluent to afford the corresponding product **5**.

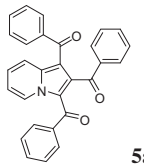
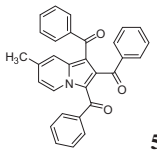
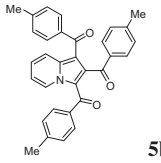
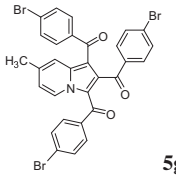
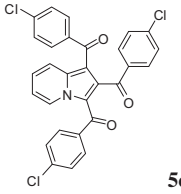
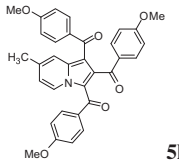
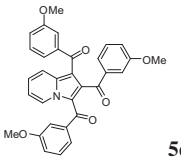
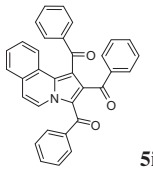
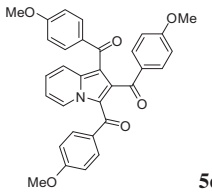
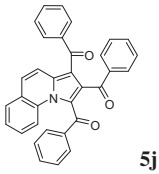
4.4. Characterization data

*4.4.1. Ethyl-1,3-dibenzoylindolizine-2-carboxylate (**4a**).* Light yellow solid, mp 130–131 °C; IR (neat) ν 2977, 1709, 1603, 1487, 1420, 1383, 1223, 1052, 1020, 891, 862, 793, 761, 697, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, J=7.2 Hz, 1H), 8.15 (d, J=9.2 Hz, 1H), 7.69–7.67 (m, 4H), 7.51–7.46 (m, 2H), 7.42–7.35 (m, 5H), 7.11–7.08 (m, 1H), 3.10 (q, J=7.2 Hz, 2H), 0.73 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 187.1, 164.1, 140.2, 140.0, 138.0, 132.2, 132.1, 130.2, 128.6, 128.6, 128.2, 128.2, 127.6, 127.5, 121.0, 119.8, 116.2, 113.3, 61.5, 13.2 ppm; MS (ESI): m/z ($[M+H]^+$): 398; HRMS (EI): m/z calcd for ($C_{25}H_{19}NO_4$): 397.1314; found: 397.1317.

*4.4.2. Ethyl-1,3-bis(4-chlorobenzoyl)indolizine-2-carboxylate (**4b**).* Light yellow solid, mp 171–172 °C; IR (neat) ν 2987, 1727, 1617, 1586, 1491, 1423, 1382, 1219, 1080, 1052, 1013, 868, 830, 776, 750, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, J=7.2 Hz, 1H), 8.11 (d, J=9.6 Hz, 1H), 7.64 (dd, J=8.4, 2.0 Hz, 4H), 7.44–7.35 (m, 5H), 7.14–7.10 (m, 1H), 3.26 (q, J=7.2 Hz, 2H), 0.80 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 185.7, 164.0, 138.7, 138.6, 138.4, 138.2, 138.0, 130.1, 130.0, 129.8, 128.6, 128.6, 127.8, 127.6, 120.8,

Table 2
Synthesis of indolizines **5**[a]



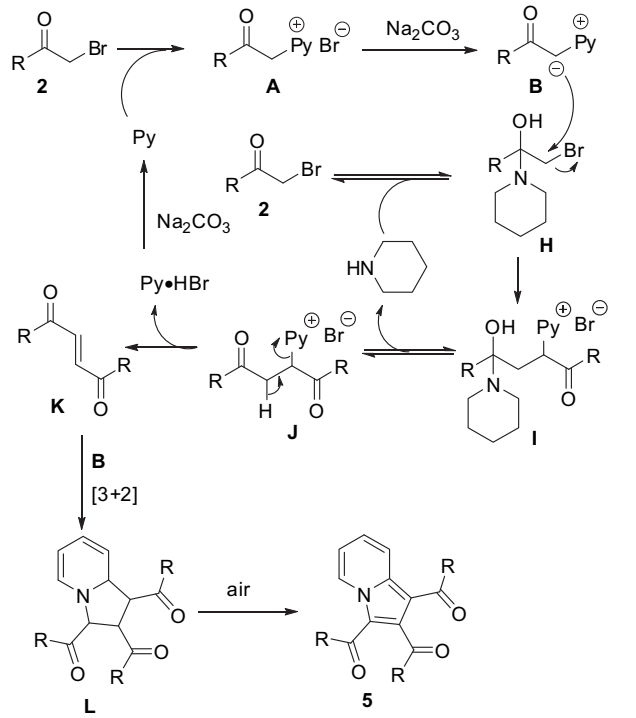
Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1	 **5a**	44	6	 **5f**	42
2	 **5b**	47	7	 **5g**	40
3	 **5c**	36	8	 **5h**	46
4	 **5d**	45	9	 **5i**	35
5	 **5e**	43	10	 **5j**	33

[a] Reaction conditions: **2** (1.5 mmol) and **1** (1.0 mmol), piperidine (0.5 mmol) and Na_2CO_3 (2.0 mmol) in CH_3CN (5 mL).
[b] Isolated yield based on **2**.

119.7, 116.5, 113.0, 61.8, 13.3 ppm; MS (ESI): *m*/*z* ([M+H]$^+$): 466; HRMS (EI): *m*/*z* calcd for ($C_{25}H_{17}Cl_2NO_4$): 465.0535; found: 465.0534.

*4.4.3. Ethyl-1,3-bis(4-methylbenzoyl)indolizine-2-carboxylate (**4c**).* Light yellow solid, mp 153–154 °C; IR (neat) ν 2922, 1719, 1603, 1492, 1427, 1381, 1222, 1176, 1050, 1015, 897, 866, 825, 775, 750, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J*=6.8 Hz, 1H), 8.07 (d, *J*=8.8 Hz, 1H), 7.62–7.60 (m, 4H), 7.51–7.46 (m, 2H), 7.36–7.32 (m, 1H), 7.20–7.17 (m, 4H), 7.05 (t, *J*=6.8 Hz, 1H), 3.22 (q, *J*=7.2 Hz, 2H), 2.37 (s, 6H), 0.76 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 186.9, 164.2, 142.9, 142.8, 137.6, 137.6, 137.4, 129.6, 128.9, 128.8, 127.4, 126.9, 121.2, 119.7, 115.9, 113.5, 61.3, 21.5, 13.2 ppm; MS (ESI): *m*/*z* ([M+H]$^+$): 426; HRMS (EI): *m*/*z* calcd for ($C_{27}H_{23}NO_4$): 425.1627; found: 425.1631.

*4.4.4. Ethyl-1,3-bis(3-methoxybenzoyl)indolizine-2-carboxylate (**4d**).* Light yellow solid, mp 145–146 °C; IR (neat) ν 2938, 1711, 1623, 1580, 1490, 1427, 1385, 1242, 1201, 1176, 1045, 921, 851, 771, 702, 655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, *J*=7.2 Hz, 1H), 8.19 (d,



Scheme 2.

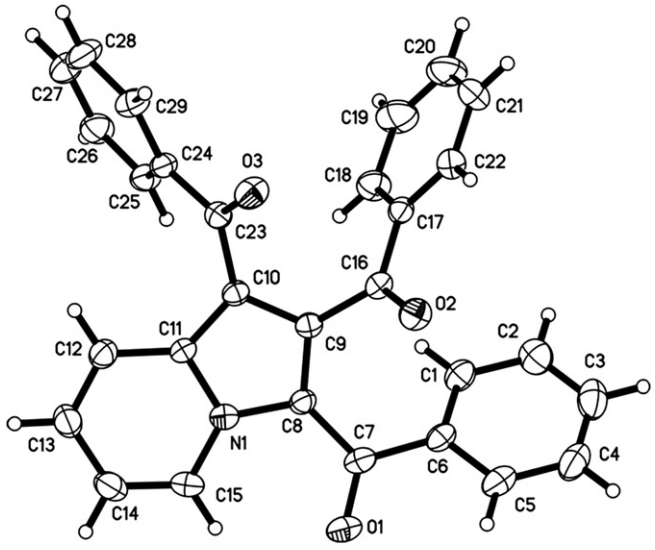


Fig. 2. X-ray crystal structure of **5a**.

J=8.4 Hz, 1H), 7.42 (t, *J*=8.0 Hz, 1H), 7.29–7.21 (m, 4H), 7.12–7.09 (m, 2H), 7.05–7.04 (m, 1H), 7.03–7.02 (m, 2H), 3.79 (s, 6H), 3.18 (q, *J*=7.2 Hz, 2H), 0.77 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 186.8, 164.2, 159.4, 159.3, 141.4, 141.3, 138.1, 130.3, 129.3, 129.2, 127.6, 121.3, 121.2, 120.9, 119.1, 118.9, 116.3, 113.2, 112.6, 112.5, 61.5, 55.3, 13.1 ppm; MS (ESI): *m*/*z* ([M+H]$^+$): 458; HRMS (EI): *m*/*z* calcd for ($C_{27}H_{23}NO_6$): 457.1525; found: 457.1507.

4.4.5. Ethyl-1,3-bis(4-bromobenzoyl)indolizine-2-carboxylate (***4e***). Light yellow solid, mp 178–179 °C; IR (neat) ν 3093, 1726, 1617, 1492, 1423, 1383, 1217, 1108, 1056, 1007, 955, 898, 845, 774, 728, 676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, *J*=7.2 Hz, 1H), 8.11 (d, *J*=8.8 Hz, 1H), 7.56–7.51 (m, 8H), 7.44–7.40 (m, 1H), 7.11 (t, *J*=7.2 Hz, 1H), 3.25 (q, *J*=7.2 Hz, 2H), 0.80 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 185.8, 164.0, 138.8, 138.6, 138.0, 131.5, 131.5, 130.1, 130.1, 129.9, 127.9, 127.6, 127.2, 127.1, 120.7, 119.7, 116.5, 112.3, 61.8, 13.2 ppm; MS (ESI): *m*/*z* ([M+H]$^+$): 554; HRMS (EI): *m*/*z* calcd for ($C_{25}H_{17}Br_2NO_4$): 552.9524; found: 552.9518.

4.4.6. Ethyl-1,3-dipropionylindolizine-2-carboxylate (***4f***). Yellow liquid; IR (neat) ν 2979, 2938, 1728, 1643, 1492, 1427, 1383, 1232, 1180, 1160, 1113, 1056, 1020, 900, 816, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (d, *J*=7.6 Hz, 1H), 8.39 (d, *J*=9.2 Hz, 1H), 7.47 (t, *J*=7.6 Hz, 1H), 7.47 (t, *J*=6.8 Hz, 1H), 4.55 (q, *J*=7.2 Hz, 2H), 2.91–2.85 (m, 4H), 1.46 (t, *J*=7.2 Hz, 3H), 1.27–1.21 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 191.5, 167.9, 137.2, 129.8, 129.3, 128.5, 120.1, 119.8, 116.0, 113.0, 62.7, 34.5, 33.0, 13.9, 8.2, 8.0 ppm; MS (ESI): *m*/*z* ([M+Na]$^+$): 330; HRMS (EI): *m*/*z* calcd for ($C_{17}H_{19}NO_4$):301.1314; found: 301.1409.

4.4.7. Ethyl-1,3-dibenzoylpyrrolo[1,2-a]quinoline-2-carboxylate (***4g***). Light yellow solid, mp 181–182 °C; IR (neat) ν 2990, 1705, 1639, 1427, 1228, 1204, 1228, 1204, 1178, 1061, 977, 931, 861, 796, 726, 681, 642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J*=7.2 Hz, 2H), 7.85 (d, *J*=6.8 Hz, 2H), 7.75–7.68 (m, 3H), 7.61–7.60 (m, 1H), 7.52–7.46 (m, 3H), 7.44–7.35 (m, 5H), 3.57 (q, *J*=7.2 Hz, 2H), 0.67 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 190.7, 163.2, 139.9, 137.7, 134.8, 134.2, 132.4, 129.7, 129.3, 129.1, 129.0, 128.9, 128.3, 127.9, 125.8, 125.7, 122.3, 117.8, 117.8, 115.1, 61.0, 13.1 ppm; MS (ESI): *m*/*z* ([M+H]$^+$): 448; HRMS (EI): *m*/*z* calcd for ($C_{29}H_{21}NO_4$): 447.1471; found: 447.1465.

4.4.8. Ethyl-1,3-bis(4-bromobenzoyl)pyrrolo[1,2-a]quinoline-2-carboxylate (***4h***). Light yellow solid, mp 190–191 °C; IR (neat) ν 2982, 1715, 1649, 1581, 1429, 1394, 1207, 1170, 1112, 1065, 975, 924, 844, 799, 738, 689, 636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J*=8.8 Hz, 2H), 7.75–7.68 (m, 4H), 7.65–7.61 (m, 3H), 7.58–7.43 (m, 2H), 7.40–7.37 (m, 3H), 3.68 (q, *J*=7.2 Hz, 2H), 0.75 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 189.7, 163.0, 138.6, 136.4, 134.9, 132.4, 132.3, 131.6, 131.0, 130.6, 129.8, 129.5, 129.1, 127.6, 127.5, 126.1, 125.9, 125.4, 121.8, 117.5, 117.5, 114.7, 61.2, 13.2 ppm; MS (ESI): *m*/*z* ([M+H]$^+$): 604; HRMS (EI): *m*/*z* calcd for ($C_{29}H_{19}Br_2NO_4$): 602.9681; found: 602.9683.

4.4.9. Indolizine-1,2,3-triyltris(phenylmethanone)[11c] (***5a***). Light yellow solid, mp 203–204 °C; IR (neat) ν 2926, 1661, 1636, 1610, 1495, 1476, 1448, 1421, 1370, 1340, 1222, 1174, 1072, 1048, 922, 744, 701, 646, 631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J*=6.8 Hz, 1H), 8.04 (d, *J*=8.8 Hz, 1H), 7.46–7.42 (m, 3H), 7.40–7.32 (m, 4H), 7.28–7.24 (m, 3H), 7.16–7.12(m, 5H), 7.03 (t, *J*=7.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 191.3, 187.6, 139.9, 139.8, 138.4, 138.1, 136.9, 132.7, 131.9, 131.8, 128.8, 128.7, 128.7, 127.9, 127.9, 127.6, 122.2, 119.7, 116.1, 115.1 ppm; MS (ESI): *m*/*z* ([M+H]$^+$): 430; HRMS (EI): *m*/*z* calcd for ($C_{29}H_{19}NO_3$): 429.1365; found: 429.1353.

4.4.10. Indolizine-1,2,3-triyltris(p-tolylmethanone)[11c] (***5b***). Light yellow solid, mp 208–209 °C; IR (neat) ν 2917, 1656, 1602, 1472, 1418, 1376, 1228, 1172, 1049, 1025, 847, 802, 769, 748, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J*=7.2 Hz, 1H), 7.95 (d, *J*=9.2 Hz, 1H), 7.40–7.33 (m, 3H), 7.27 (d, *J*=8.4 Hz, 2H), 7.07 (t, *J*=6.8 Hz, 1H), 6.95 (dd, *J*=12.4, 8.0 Hz, 4H), 6.84 (d, *J*=7.6 Hz, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 191.0, 187.4, 143.4, 142.6, 142.5, 137.7, 137.3, 137.2, 136.8, 136.3, 129.1, 128.9, 128.8, 128.7, 128.5, 128.4, 127.9, 127.0, 122.3, 119.6, 115.7, 115.3, 21.6, 21.5, 21.4 ppm; MS (ESI): *m*/*z* ([M+H]$^+$): 472; HRMS (EI): *m*/*z* calcd for ($C_{32}H_{25}NO_3$): 471.1834; found: 471.1841.

4.4.11. Indolizine-1,2,3-triyltris((4-chlorophenyl)methanone)[11c] (***5c***). Light yellow solid, mp 203–204 °C; IR (neat) ν 1668, 1612,

1488, 1464, 1416, 1221, 1168, 1085, 1050, 996, 896, 877, 775, 735, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, J=7.2 Hz, 1H), 7.96 (d, J=8.8 Hz, 1H), 7.27 (t, J=8.0 Hz, 4H), 7.20–7.15 (m, 5H), 7.06 (d, J=8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 189.5, 185.9, 139.7, 138.6, 138.5, 138.1, 138.1, 137.9, 136.6, 136.5, 130.2, 130.1, 129.9, 128.5, 128.5, 128.3, 128.2, 121.8, 119.6, 116.5, 114.9 ppm; MS (ESI): m/z ($[M+H]^+$): 532; HRMS (EI): m/z calcd for ($C_{29}H_{16}Cl_3NO_3$): 531.0196; found: 531.0204.

4.4.12. Indolizine-1,2,3-triyltris((3-methoxyphenyl)methanone) (***5d***). Light yellow liquid; IR (neat) ν 2938, 2836, 1662, 1621, 1583, 1487, 1427, 1376, 1317, 1263, 1202, 1176, 1033, 911, 849, 763, 729, 687, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, J=6.8 Hz, 1H), 8.10 (d, J=9.2 Hz, 1H), 7.43(t, J=7.6 Hz, 1H), 7.15–7.00 (m, 5H), 6.96–6.81 (m, 7H), 6.67 (s, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.59 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 191.1, 187.3, 159.3, 159.1, 141.3, 140.0, 138.1, 137.0, 129.0, 128.8, 128.0, 127.6, 122.5, 122.3, 121.7, 119.9, 119.8, 119.0, 116.2, 115.2, 112.5, 112.5, 111.5, 55.2, 55.2, 55.1 ppm; MS (ESI): m/z ($[M+H]^+$): 520; HRMS (EI): m/z calcd for ($C_{32}H_{25}NO_6$): 519.1682; found: 519.1671.

4.4.13. Indolizine-1,2,3-triyltris((4-methoxyphenyl)methanone)[11c] (***5e***). Light yellow solid, mp 209–210 °C; IR (neat) ν 2936, 2839, 1595, 1573, 1492, 1423, 1377, 1311, 1252, 1232, 1165, 1052, 1024, 905, 847, 773, 728, 695, 645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J=7.2 Hz, 1H), 7.96 (d, J=8.8 Hz, 1H), 7.50 (d, J=8.8 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.35–7.31 (m, 3H), 7.04 (t, J=7.2 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 190.1, 186.5, 163.1, 162.8, 162.8, 137.5, 136.2, 132.8, 132.7, 132.2, 131.2, 131.0, 130.9, 127.7, 126.6, 122.2, 119.6, 115.5, 115.1, 113.2, 113.2, 113.2, 55.4, 55.3 ppm; MS (ESI): m/z ($[M+H]^+$): 520; HRMS (EI): m/z calcd for ($C_{32}H_{25}NO_6$): 519.1682; found: 519.1700.

4.4.14. (7-Methylindolizine-1,2,3-triyl)tris(phenylmethanone) (***5f***). Light yellow solid, mp 205–206 °C; IR (neat) ν 2923, 1617, 1489, 1416, 1374, 1338, 1227, 1175, 1050, 1009, 926, 796, 739, 698, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (d, J=7.2 Hz, 1H), 7.91 (s, 1H), 9.40 (d, J=8.0 Hz, 2H), 7.33–7.28 (m, 4H), 7.26–7.22 (m, 3H), 7.14–7.08 (m, 4H), 7.02–6.98 (m, 3H), 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 191.6, 187.5, 140.1, 140.1, 139.6, 138.7, 138.4, 137.2, 132.6, 131.8, 131.7, 129.0, 128.7, 128.7, 128.1, 127.9, 127.8, 127.5, 121.8, 118.8, 118.4, 114.1, 21.6 ppm; MS (ESI): m/z ($[M+H]^+$): 444; HRMS (EI): m/z calcd for ($C_{30}H_{21}NO_3$): 443.1521; found: 443.1510.

4.4.15. (7-Methylindolizine-1,2,3-triyl)tris((4-bromophenyl)methanone) (***5g***). Light yellow solid, mp 215–216 °C; IR (neat) ν 3084, 1610, 1583, 1480, 1419, 1253, 1225, 1171, 1068, 1005, 908, 844, 784, 729, 676, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, J=6.8 Hz, 1H), 7.83 (s, 1H), 7.37–7.31 (m, 6H), 7.21–7.14 (m, 6H), 7.02 (d, J=6.8 Hz, 1H), 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 189.9, 185.9, 140.3, 138.8, 138.6, 138.6, 137.0, 136.7, 131.4, 131.3, 131.2, 130.3, 130.1, 130.0, 128.5, 127.7, 127.1, 126.8, 121.5, 119.1, 118.3, 113.8, 21.6 ppm; MS (ESI): m/z ($[M+H]^+$): 678; HRMS (EI): m/z calcd for ($C_{30}H_{18}Br_3NO_3$): 676.8837; found: 676.8837.

4.4.16. (7-Methylindolizine-1,2,3-triyl)tris((4-methoxyphenyl)methanone) (***5h***). Light yellow solid, mp 214–215 °C; IR (neat) ν 2837, 1658, 1593, 1484, 1416, 1312, 1253, 1229, 1161, 1020, 956, 841, 804, 774, 734, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (d, J=6.8 Hz, 1H), 7.82 (s, 1H), 7.46 (d, J=8.8 Hz, 2H), 7.37 (d, J=9.2 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 6.90 (d, J=7.2 Hz, 1H), 6.64 (d, J=8.8 Hz, 4H), 6.55 (d, J=8.4 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 190.3, 186.3, 163.1, 162.6, 162.6, 138.4, 138.2, 136.4, 132.9, 132.9, 132.2, 131.1, 130.9, 127.1, 121.8, 118.2, 118.1, 114.0, 113.1, 113.1, 55.4, 55.3, 21.4 ppm; MS (ESI): m/z ($[M+H]^+$): 534; HRMS (EI): m/z calcd for ($C_{33}H_{27}NO_6$): 533.1838; found: 533.1844.

4.4.17. Pyrrolo[2,1-a]isoquinoline-1,2,3-triyltris(phenylmethanone)[11c] (***5i***). Light yellow solid, mp 223–224 °C; IR (neat) ν 1654, 1627, 1596, 1490, 1472, 1451, 1391, 1269, 1227, 1175, 1029, 997, 956, 910, 796, 730, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J=7.2 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 7.79 (d, J=7.2 Hz, 2H), 7.73 (d, J=7.2 Hz, 1H), 7.54(t, J=7.2 Hz, 1H), 7.51–7.21 (m, 11H), 7.12–7.06 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 191.6, 187.4, 140.3, 139.0, 138.4, 133.6, 133.4, 132.4, 132.2, 131.9, 129.6, 129.0, 128.7, 128.4, 127.9, 127.3, 125.2, 124.2, 123.9, 118.7, 115.9 ppm; MS (ESI): m/z ($[M+H]^+$): 480; HRMS (EI): m/z calcd for ($C_{33}H_{21}NO_3$): 479.1521; found: 479.1535.

4.4.18. Pyrrolo[1,2-a]quinoline-1,2,3-triyltris(phenylmethanone) (***5j***). Light yellow solid, mp 213–214 °C; IR (neat) ν 1676, 1641, 1597, 1500, 1448, 1420, 1315, 1262, 1231, 1177, 999, 956, 808, 738, 717, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J=9.6 Hz, 1H), 7.85–7.83 (m, 2H), 7.80–7.78 (m, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.54 (d, J=10.0 Hz, 1H), 7.49–7.41 (m, 5H), 7.39–7.28 (m, 6H), 7.19–7.10 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 191.4, 189.5, 140.2, 138.7, 137.7, 136.1, 133.9, 132.4, 132.4, 132.0, 129.7, 129.3, 129.1, 128.8, 128.7, 128.6, 128.1, 128.0, 128.0, 127.3, 125.5, 118.7, 117.9, 116.0 ppm; MS (ESI): m/z ($[M+H]^+$): 480; HRMS (EI): m/z calcd for ($C_{33}H_{21}NO_3$): 479.1521; found: 479.1525.

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Supplementary data

Copies of the ^1H, ^{13}C NMR spectra. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.083.

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10. CCDC 825915 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
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