JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

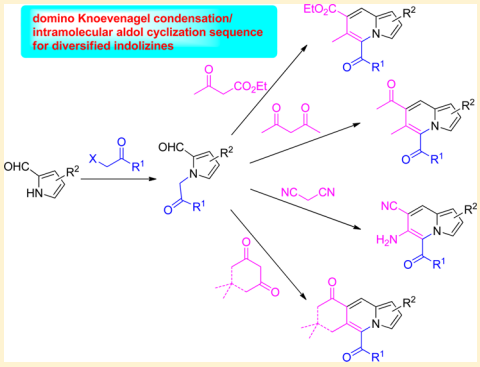
Domino Knoevenagel Condensation/Intramolecular Aldol Cyclization Route to Diverse Indolizines with Densely Functionalized Pyridine Units

Myungock Kim, Youngeun Jung, and Ikyon Kim*

College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, 162-1 Songdo-dong, Yeonsu-gu, Incheon 406-840, Republic of Korea

Supporting Information

ABSTRACT: A highly efficient [4 + 2] annulation route to polysubstituted indolizines is described employing a domino Knoevenagel condensation/intramolecular aldol cyclization process as a key step. Construction of pyridine rings in indolizine skeleton was rapidly achieved from several pyrrole-2-carboxaldehydes in good to excellent yields, leading to indolizines with various substituents at the 5, 6, and 7 positions depending on the reacting active methylene partners.

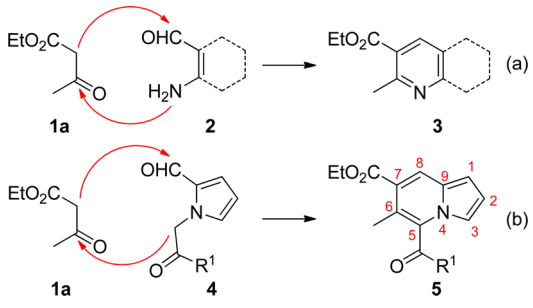


INTRODUCTION

The synthesis of α,β-unsaturated dicarbonyl compounds or related compounds via condensation reaction of aldehydes or ketones with active methylene compounds catalyzed by amines, widely referred to as the Knoevenagel condensation,[1] has been frequently employed as a trigger of domino or cascade processes[2] to form multiple chemical bonds, partly because the resulting α,β-unsaturated dicarbonyl or related functional groups can participate in a range of subsequent transformations with preexisting functional groups. Thus, many successful domino reactions initiated by Knoevenagel condensation[3,4] have been reported including Knoevenagel condensation/hetero-Diels–Alder reactions[5] and Knoevenagel condensation/Michael addition reactions.

As shown in Scheme 1a (Friedländer type annulations), for instance, coupled with the ensuing intramolecular imine formation, Knoevenagel condensation has been used to construct multisubstituted pyridines.[6] In connection with our recent report on a facile cycloaromatization route to indolizines from pyrrole rings,[7,8] we envisioned a mechanistically similar approach to indolizines[9,10] where initial Knoevenagel condensation of **1a** with **4** would induce intramolecular aldol cyclization in a domino fashion to form the highly functionalized pyridine moiety (Scheme 1b).[11]

Scheme 1. Domino Synthesis of Heterocycles



Overall, we expected that **4** readily derived from pyrrole-2-carboxaldehyde serve as four-atom units in these annulation reactions with various active methylene compounds, useful two-carbon units. Recently, Zou and co-workers reported the three-component approach to indolizines from pyrrole-2-carboxaldehyde.[12] Although pyridine unit was assembled with substituents at C5, C6, and C7 positions of indolizine by using Michael reaction/aldol cyclization strategy, substrate scope for two-carbon unit of indolizine was limited to activated acetylenes. We anticipated that use of more easily available active methylene compounds in our domino process gives rise to more diverse indolizines with pyridine moiety decorated at various positions.[13] With this in mind, we decided to investigate a conceptually novel cascade reaction involving Knoevenagel condensation and intramolecular aldol cyclization[14] to construct the pyridine rings. Here we wish to describe our findings.

RESULTS AND DISCUSSION

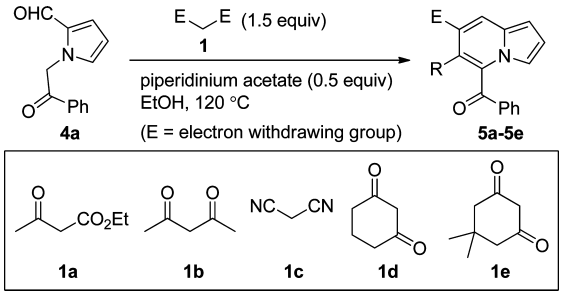
To find the optimal conditions for this annulation, we began our studies by reacting **4a** (50 mg, 0.23 mmol) with **1a** in

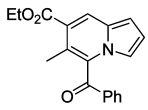
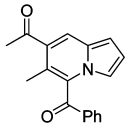
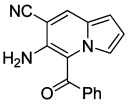
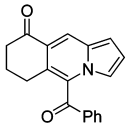
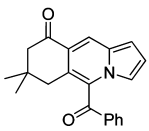
Received: August 16, 2013
Published: September 25, 2013

dx.doi.org/10.1021/jo401801j | J. Org. Chem. 2013, 78, 10395–10404

EtOH as solvent in the presence of various catalysts (triethylamine, morpholine, piperidine, potassium carbonate, proline, and piperidinium acetate). Among the catalysts (0.5 equiv) employed, piperidinium acetate was turned out to be the most effective one, providing **5a** in 98% yield after heating at 120 °C for 24 h.[15] Although morpholine, piperidine, and triethylamine gave the desired product, longer reaction time was required. Surprisingly, very small amount of product was formed with proline, which is widely considered as a catalyst for both Knoevenagel condensation and aldol cyclization. Screening of several solvents (toluene, acetonitrile, dichloroethane, tetrahydrofuran, and ethanol) was also examined with 0.5 equiv of piperidinium acetate, revealing that ethanol is the solvent of choice; either prolonged time was needed to completion, or incomplete conversion was observed in other solvents. Decreasing the reaction temperature to 100 °C led to complete conversion after 48 h (97% yield). Lowering the catalyst loading to 0.3 equiv also resulted in prolonged reaction time for completion. Thus, the reactions of **4a** with several active methylene compounds (**1a**−**1e**, 1.5 equiv) were carried out in EtOH in the presence of piperidinium acetate (0.5 equiv) at 120 °C.[16] As shown in Table 1, the desired indolizines with novel substitution patterns in the pyridine unit were obtained in good to excellent yields. Reactions with 2,4-pentanedione (**1b**) and malononitrile (**1c**) proceeded smoothly to give the corresponding products in 88 and 95% yield, respectively (entries 2 and 3). By using cyclic 1,3-dicarbonyl compounds (**1d** and **1e**), introduction of additional ring in the products was made possible (entries 4 and 5).

Table 1. Domino Synthesis of Novel Indolizines



entry	4	1	product (5)		yield (%)[a]
1	**4a**	**1a**		**5a**	98
2	**4a**	**1b**		**5b**	88
3	**4a**	**1c**		**5c**	95
4	**4a**	**1d**		**5d**	83
5	**4a**	**1e**		**5e**	52

[a]Isolated yields (%).

To further maximize the diversity, several other pyrrole-2-carboxaldehyde derivatives were prepared[17] and exposed to the optimized reaction conditions. To our delight, a wide number of novel indolizines were rapidly constructed in good to excellent yields (Table 2). Reactions with substrates having electron-rich aromatic groups as well as electron-poor aromatic groups at R^1 site furnished the corresponding indolizines in satisfactory yields (entries 1−26). Indolizines containing heterocycle at R^1 position such as thiophene, **5af**−**5ag**, were obtained in good yields as well (entries 27−29). Not only a substrate bearing a polysubstituted benzene ring at R^1 site, **4i**, but also substrates possessing substituent(s) at pyrrole site, **4j**[18] and **4k**,[19] were successfully employed to give the corresponding products (entries 30−37).

To expand the reaction scope of this protocol, other substrates were also investigated. Compound **6** derived from indole-2-carboxaldehyde was allowed to react with malononitrile (**1c**) to give **7** in 77% yield (Scheme 2). When **4e** was exposed to ethyl cyanoacetate, unsymmetrical active methylene compound, in the presence of piperidinium acetate in refluxing EtOH, **8** was obtained as pale orange solid in 52% yield.

Having established an efficient route to novel indolizines with multisubstituted pyridine moiety, postmodification of the resulting indolizines was pursued to add more diversity to this skeleton. Vilsmeier−Haack formylation[20] of **5a** at 0 °C produced monoformylated **9** in 63% yield.[21] Aldol condensation of **5b** with *p*-anisaldehyde and 4-bromobenzaldehyde afforded **10** and **11** in good yields, respectively (Scheme 3).

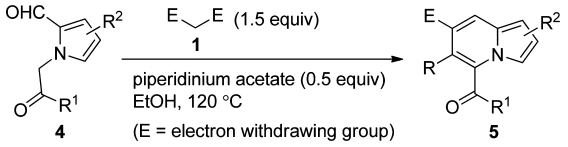
In conclusion, we have developed a facile [4 + 2] annulation route to new indolizines with multisubstituents at the pyridine site by a novel domino Knoevenagel condensation/intramolecular aldol-type cyclization protocol. Operational simplicity, high chemical yields, and easy availability of a variety of active methylene compounds made it possible to rapidly explore a new class of indolizines, a versatile chemical scaffold. In particular, functional groups (esters, ketones, amines, and nitriles) incorporated in the pyridine unit of the resulting indolizines should be useful for diversity-oriented generation of indolizine-based chemical library. Further efforts to extend this method for synthesis of other heterocycles as well as biological evaluation of the synthesized compounds are in progress and will be reported in the near future.

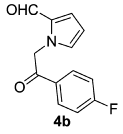
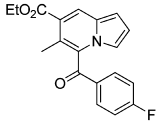
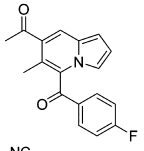
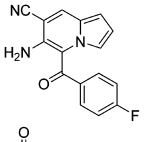
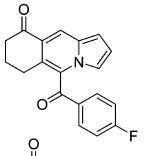
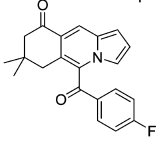
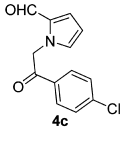
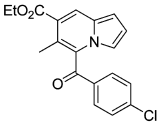
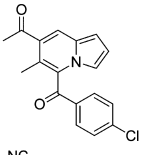
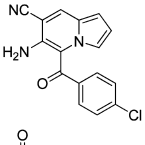
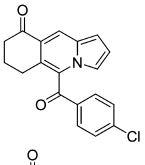
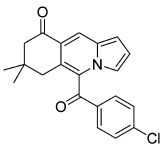
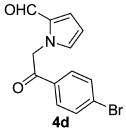
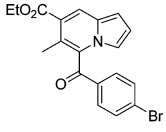
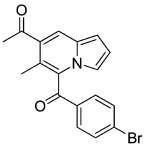
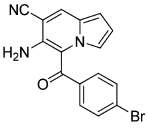
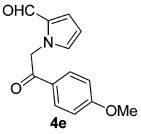
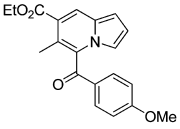
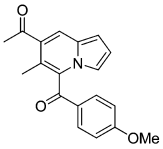
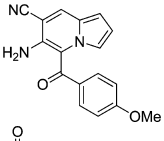
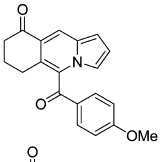
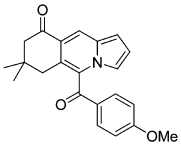
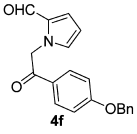
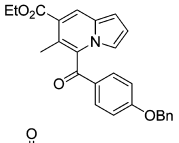
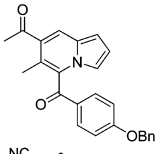
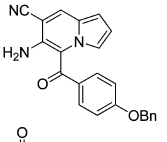
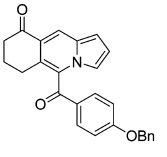
EXPERIMENTAL SECTION

General Methods. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents via distillation using a Büchi rotary evaporator. "Dried" refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230−400 mesh) with hexanes, ethyl acetate, and dichloromethane as eluent. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualizing with UV light. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. IR spectra were recorded on FT-IR using diamond ATR technique and were described as wavenumbers (cm^{-1}). HRMS were measured with electrospray ionization (ESI) and Q-TOF mass analyzer.

dx.doi.org/10.1021/jo401801j | J. Org. Chem. 2013, 78, 10395−10404

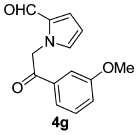
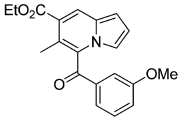
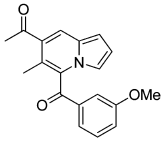
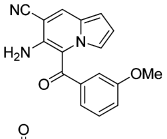
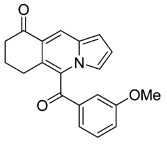
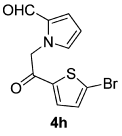
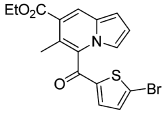
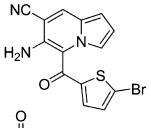
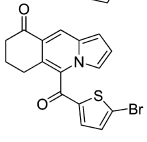
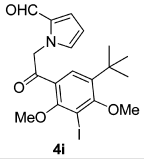
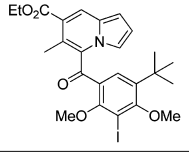
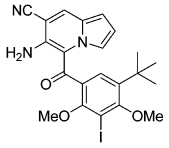
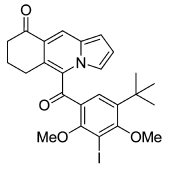
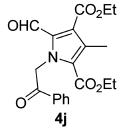
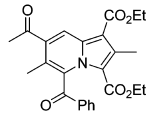
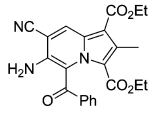
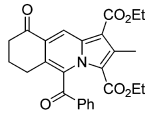
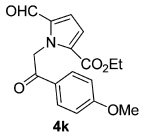
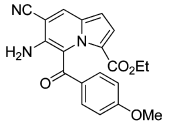
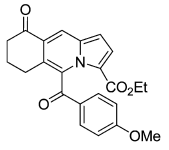
Table 2. Domino Syntheses of Diverse Indolizines



entry	4	1	5	yield (%)[a]
1		1a		5f 60
2	4b	1b		5g 65
3	4b	1c		5h 92
4	4b	1d		5i 58
5	4b	1e		5j 59
6		1a		5k 88
7	4c	1b		5l 61
8	4c	1c		5m 68
9	4c	1d		5n 68
10	4c	1e		5o 67
11		1a		5p 78
12	4d	1b		5q 72
13	4d	1c		5r 77
14		1a		5s 73
15	4e	1b		5t 68
16	4e	1c		5u 96
17	4e	1d		5v 56
18	4e	1e		5w 52
19		1a		5x 70
20	4f	1b		5y 60
21	4f	1c		5z 73
22	4f	1d		5aa 52

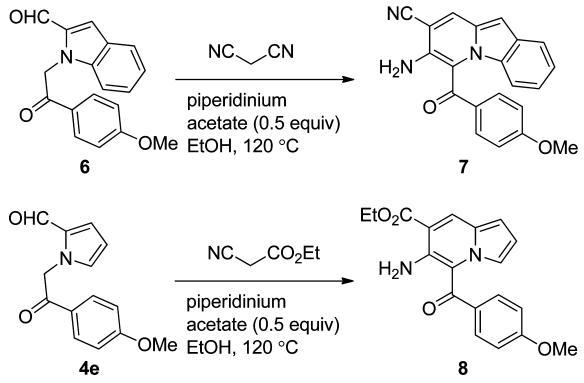
dx.doi.org/10.1021/jo401801j | J. Org. Chem. 2013, 78, 10395−10404

Table 2. continued

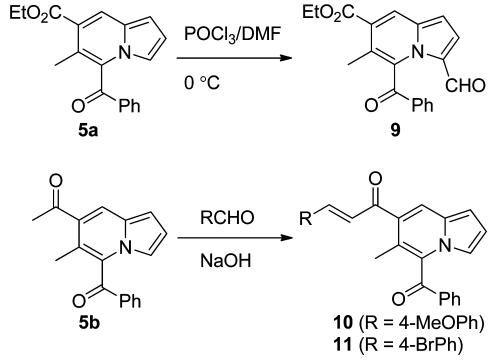
entry	4	1	5	yield (%)[a]
23	 **4g**	**1a**		**5ab** 100
24	**4g**	**1b**		**5ac** 65
25	**4g**	**1c**		**5ad** 86
26	**4g**	**1d**		**5ae** 72
27	 **4h**	**1a**		**5af** 50
28	**4h**	**1c**		**5ag** 75
29	**4h**	**1d**		**5ah** 72
30	 **4i**	**1a**		**5ai** 66
31	**4i**	**1c**		**5aj** 82
32	**4i**	**1d**		**5ak** 54
33	 **4j**	**1b**		**5al** 51
34	**4j**	**1c**		**5am** 83
35	**4j**	**1d**		**5an** 100
36	 **4k**	**1c**		**5ao** 89
37	**4k**	**1d**		**5ap** 97

[a]Isolated yields (%).

Scheme 2. Application of This Domino Protocol to Other Substrates



Scheme 3. Further Functionalization of 5



General Procedure for the Synthesis of 4. To a stirred solution of pyrrole-2-carboxaldehyde (500 mg, 5.258 mmol) in CH_3CN (18 mL) were added K_2CO_3 (1.09 g, 1.5 equiv) and 2-bromoacetophenone (1.26 g, 1.2 equiv) at room temperature. After being stirred for 24 h, the reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (30 mL), and washed with H_2O (30 mL). The water layer was extracted with ethyl acetate (30 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by trituration with mixed solvent (hexanes/ethyl acetate/dichloromethane = 30:1:2 or 10:1:2) to give **4a** (952.9 mg, 85%).

*1-(2-Oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde (**4a**).* White solid: mp 118.7−119.2 °C (952.9 mg, 85%); R_f 0.18 (hexanes/ethyl

dx.doi.org/10.1021/jo401801j | J. Org. Chem. 2013, 78, 10395−10404

acetate/dichloromethane 10:1:2); IR (ATR) ν = 2938, 1701, 1650, 1594, 1400, 1325, 747, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.00 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.04 (d, J = 4.0 Hz, 1H), 6.96 (s, 1H), 6.36 (t, J = 3.2 Hz, 1H), 5.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 180.0, 135.0, 134.0, 132.7, 131.8, 129.0, 128.2, 124.9, 110.5, 54.9; HRMS (ESI-QTOF) calcd for $C_{13}H_{11}NO_2$ 214.0863 ([M + H]$^+$), found 214.0861.

1-(2-(4-Fluorophenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (**4b**). White solid: mp 110.6−110.9 °C (717.3 mg, 59%); R_f 0.18 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3114, 2809, 1700, 1652, 1595, 1510, 1481, 1403, 1223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.09−7.98 (m, 2H), 7.23−7.15 (m, 2H), 7.04 (dd, J = 1.6, 4.0 Hz, 1H), 6.96 (s, 1H), 6.36 (dd, J = 2.4, 4.0 Hz, 1H), 5.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 180.0, 132.7, 131.7, 131.0, 130.9, 125.0, 116.4, 116.2, 110.5, 54.7; HRMS (ESI-QTOF) calcd for $C_{13}H_{10}FNO_2$ 232.0768 ([M + H]$^+$), found 232.0769.

1-(2-(4-Chlorophenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (**4c**). White solid: mp 128.9−129.5 °C (703.2 mg, 54%); R_f 0.22 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3043, 1703, 1650, 1588, 1527, 1405, 1365, 1324, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.04 (dd, J = 1.2, 4.0 Hz, 1H), 6.95 (s, 1H), 6.36 (dd, J = 2.4, 4.0 Hz, 1H), 5.75(s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 180.0, 140.5, 133.3, 132.6, 131.7, 129.6, 129.4, 125.0, 110.6, 54.8; HRMS (ESI-QTOF) calcd for $C_{13}H_{10}ClNO_2$ 248.0473 ([M + H]$^+$), found 248.0470.

1-(2-(4-Bromophenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (**4d**). Dark brown solid: mp 139.7−140.5 °C (967.6 mg, 63%); R_f 0.19 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3042, 2802, 1702, 1650, 1584, 1406, 1365, 1323, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.04 (dd, J = 1.6, 4.0 Hz, 1H), 6.95 (s, 1H), 6.36 (dd, J = 2.4, 4.0 Hz, 1H), 5.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 180.0, 133.7, 132.6, 132.4, 131.6, 129.7, 129.3, 125.0, 110.6, 54.8; HRMS (ESI-QTOF) calcd for $C_{13}H_{10}BrNO_2$ 291.9968 ([M + H]$^+$), found 291.9965.

1-(2-(4-Methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (**4e**). Dark purple solid: mp 116.5−116.8 °C (1048.7 mg, 82%); R_f 0.20 (hexanes/ethyl acetate/dichloromethane 7:1:2); IR (ATR) ν = 3068, 2942, 2801, 1683, 1651, 1598, 1571, 1226, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.03 (s, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 6.35 (s, 1H), 5.78 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 180.0, 164.2, 132.8, 131.8, 130.5, 128.0, 124.9, 114.2, 110.4, 55.7, 54.4; HRMS (ESI-QTOF) calcd for $C_{14}H_{13}NO_3$ 244.0968 ([M + H]$^+$), found 244.0968.

1-(2-(4-(Benzyloxy)phenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (**4f**). Brown solid: mp 165.4−165.7 °C (1309.7 mg, 78%); R_f 0.11 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2938, 2825, 1701, 1643, 1597, 1572, 1323, 1229, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.48−7.31 (m, 5H), 7.05 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 4.0 Hz, 1H), 6.95 (s, 1H), 6.35 (dd, J = 2.4, 3.6 Hz, 1H), 5.76 (s, 2H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 180.0, 163.4, 136.2, 132.8, 131.8, 130.5, 128.9, 128.4, 128.1, 127.6, 124.9, 115.1, 110.4, 70.4, 54.5; HRMS (ESI-QTOF) calcd for $C_{20}H_{17}NO_3$ 320.1281 ([M + H]$^+$), found 320.1286.

1-(2-(3-Methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (**4g**). White solid: mp 107.7−108.4 °C (1010.4 mg, 79%); R_f 0.13 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2940, 2803, 1693, 1651, 1593, 1263, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.51 (s, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 6.36 (s, 1H), 5.79 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 180.0, 160.1, 136.2, 132.6, 131.8, 130.0, 124.9, 120.7, 120.5, 112.5, 110.5, 55.6, 55.0; HRMS (ESI-QTOF) calcd for $C_{14}H_{13}NO_3$ 244.0968 ([M + H]$^+$), found 244.0966.

1-(2-(5-Bromothiophen-2-yl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (**4h**). Dark gray solid: mp 124.9−125.4 °C (987.6 mg, 63%); R_f 0.18 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3073, 2830, 1682, 1648, 1523, 1367, 1228 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 2.8 Hz, 1H), 7.02 (s, 1H), 6.98 (s, 1H), 6.35 (s, 1H), 5.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 180.0, 142.7, 132.8, 132.7, 131.7, 125.1, 124.0, 110.7, 54.3; HRMS (ESI-QTOF) calcd for $C_{11}H_8BrNO_2S$ 297.9532 ([M + H]$^+$), found 297.9528.

1-(2-(5-(tert-Butyl)-3-iodo-2,4-dimethoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (**4i**). Brown solid: mp 119.8−120.6 °C (1843.2 mg, 77%); R_f 0.28 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2964, 2870, 1686, 1653, 1578, 1321, 1156, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.84 (s, 1H), 7.04 (s, 1H), 6.90 (s, 1H), 6.34 (s, 1H), 5.74 (s, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 179.9, 165.2, 159.5, 141.6, 132.4, 131.9, 130.3, 125.7, 124.8, 110.3, 92.2, 63.1, 62.4, 58.2, 35.4, 30.9; HRMS (ESI-QTOF) calcd for $C_{19}H_{22}INO_4$ 456.0666 ([M + H]$^+$), found 456.0679.

Diethyl 5-formyl-3-methyl-1-(2-oxo-2-phenylethyl)-1H-pyrrole-2,4-dicarboxylate (**4j**). White solid: mp 78.8−79.1 °C (833.8 mg, 42.7%); R_f 0.29 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2971, 1696, 1663, 1597, 1475, 1270, 1247, 1224, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.00 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 6.46 (s, 2H), 4.40 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 6.8 Hz, 2H), 2.58 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 184.7, 163.9, 161.7, 135.0, 133.9, 133.7, 130.8, 129.0, 128.1, 126.7, 123.9, 61.4, 61.2, 54.0, 14.5, 14.2, 12.6; HRMS (ESI-QTOF) calcd for $C_{20}H_{21}NO_6$ 372.1442 ([M + H]$^+$), found 372.1447.

Ethyl 5-formyl-1-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (**4k**). White solid: mp 104.5−105.2 °C (1326.3 mg, 80%); R_f 0.32 (hexanes/ethyl acetate/dichloromethane 5:1:2); IR (ATR) ν = 2954, 1712, 1682, 1599, 1256, 1230, 1202, 1182, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 4.4 Hz, 1H), 6.99 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.42 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 181.8, 164.1, 161.1, 135.2, 130.4, 128.1, 122.9, 117.3, 114.2, 61.1, 55.7, 53.0, 14.3; HRMS (ESI-QTOF) calcd for $C_{17}H_{17}NO_5$ 316.1179 ([M + H]$^+$), found 316.1182.

Compound **6** was prepared similarly in 62% yield.

1-(2-(4-Methoxyphenyl)-2-oxoethyl)-1H-indole-2-carbaldehyde (**6**). Pale green solid: mp 150.4−151.1 °C (956.1 mg, 62%); R_f 0.18 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2822, 1681, 1658, 1594, 1269, 1233, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.43−7.34 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.02 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 183.2, 164.2, 141.2, 135.7, 130.5, 128.1, 127.5, 126.8, 123.8, 121.4, 118.6, 114.2, 110.2, 55.7, 50.7; HRMS (ESI-QTOF) calcd for $C_{18}H_{15}NO_3$ 294.1125 ([M + H]$^+$), found 294.1125.

General Procedure for the Synthesis of 5. To a solution of **4a** (50 mg, 0.23 mmol) in EtOH (2 mL) were added piperidinium acetate (17 mg, 0.5 equiv) and ethyl acetoacetate (**1a**) (44.5 μL, 1.5 equiv) at room temperature. The reaction was carried out in a 7 mL sealed vial. After being heated at 120 °C for 24 h, the reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexanes:ethyl acetate:dichloromethane = 50:1:2) to give **5a** (70.6 mg, 98%).

Ethyl 5-benzoyl-6-methylindolizine-7-carboxylate (**5a**). Yellow solid: mp 71.5−72.3 °C (70.6 mg, 98.0%); R_f 0.39 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2984, 2902, 1705, 1655, 1428, 1230, 1171, 1163 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 8.30 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.02 (s, 1H), 6.81−6.72 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 166.6, 135.6, 135.0, 131.0, 130.4, 129.7, 129.5, 124.9, 119.5, 117.7, 115.6, 114.4, 104.8, 60.9, 16.9, 14.5; HRMS (ESI-QTOF) calcd for $C_{19}H_{17}NO_3$ 308.1281 ([M + H]$^+$), found 308.1285.

1-(5-Benzoyl-6-methylindolizin-7-yl)ethanone (**5b**). Brown solid: mp 96.0−96.5 °C (56.1 mg, 88%); R_f 0.30 (hexanes/ethyl acetate/

dichloromethane 10:1:2); IR (ATR) ν = 2927, 2853, 1734, 1720, 1660, 1425, 1227, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.89 (d, J = 7.2 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.03 (s, 1H), 6.79 (s, 1H), 6.78 (s, 1H), 2.63 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 193.3, 135.5, 135.1, 130.7,130.6,129.7, 129.5, 127.2, 124.6, 117.3, 115.8, 114.8, 105.4, 28.6, 17.0; HRMS (ESI-QTOF) calcd for $C_{18}H_{15}NO_2$ 278.1176 ([M + H]$^+$), found 278.1181.

6-Amino-5-benzoylindolizine-7-carbonitrile (**5c**). Orange solid: mp 155.2−155.6 °C (57.1 mg, 95%); R_f 0.36 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3381, 3276, 2922, 2216, 1620, 1570, 1460, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.57−7.49 (m, 3H), 7.42 (t, J = 7.2 Hz, 2H), 6.87 (s, 1H), 6.73 (d, J = 4.0 Hz, 1H), 6.48 (dd, J = 2.8, 3.6 Hz, 1H), 6.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 141.2, 138.2, 132.5, 131.6, 129.3, 128.3, 128.2, 123.5, 116.6, 114.3, 113.0, 108.9, 93.4; HRMS (ESI-QTOF) calcd for $C_{16}H_{11}N_3O$ 262.0975 ([M + H]$^+$), found 262.0974.

5-Benzoyl-7,8-dihydropyrrolo[1,2-b]isoquinolin-9(6H)-one (**5d**). Brown solid: mp 92.2−92.6 °C (55.2 mg, 83%); R_f 0.18 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2926, 2868, 1735, 1671, 1593, 1256, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.15 (s, 1H), 6.89 (d, J = 3.2 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H), 2.71−2.61 (m, 4H), 2.09−1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 192.4, 135.9, 135.0, 132.4, 129.62, 129.58, 128.0, 122.4, 122.3, 122.2, 116.5, 115.7, 107.3, 39.3, 26.2, 22.9; HRMS (ESI-QTOF) calcd for $C_{19}H_{15}NO_2$ 290.1176 ([M + H]$^+$), found 290.1178.

5-Benzoyl-7,7-dimethyl-7,8-dihydropyrrolo[1,2-b]isoquinolin-9(6H)-one (**5e**). Yellow gum (38.0 mg, 52%): R_f 0.31 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2955, 2927, 2869, 1734, 1665, 1596, 1260, 1220, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.08 (s, 1H), 6.89 (d, J = 3.6 Hz, 1H), 6.82 (dd, J = 2.8, 4.0 Hz, 1H), 2.53 (s, 2H), 2.49 (s, 2H), 0.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 192.4, 135.6, 135.1, 132.3, 129.65, 129.60, 121.8, 121.4, 120.6, 116.5, 115.7, 107.2, 52.5, 39.2, 33.1, 28.3; HRMS (ESI-QTOF) calcd for $C_{21}H_{19}NO_2$ 318.1489 ([M + H]$^+$), found 318.1490.

Ethyl 5-(4-fluorobenzoyl)-6-methylindolizine-7-carboxylate (**5f**). Brown gum (44.9 mg, 60%): R_f 0.33 (hexanes/ethyl acetate/dichloromethane 20:1:2); IR (ATR) ν = 3073, 2979, 1708, 1666, 1591, 1228, 1169, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.97−7.86 (m, 2H), 7.21−7.09 (m, 2H), 7.00 (s, 1H), 6.78 (s, 1H), 6.76 (s, 1H), 4.36 (q, J = 6.8 Hz, 2H), 2.32 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 166.6, 165.7, 132.6, 132.5, 131.1, 125.1, 119.5, 117.8, 117.0, 116.7, 115.8, 114.4, 105.0, 61.0, 16.8, 14.5; HRMS (ESI-QTOF) calcd for $C_{19}H_{16}FNO_3$ 326.1187 ([M + H]$^+$), found 326.1187.

1-(5-(4-Fluorobenzoyl)-6-methylindolizin-7-yl)ethanone (**5g**). Yellow gum (44.1 mg, 65%): R_f 0.27 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2926, 1700, 1665, 1592, 1227, 1152, 845, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.98−7.86 (m, 2H), 7.22−7.09 (m, 2H), 7.02 (s, 1H), 6.80 (s, 2H), 2.64 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 191.6, 132.6, 132.5, 130.6, 127.3, 124.7, 117.4, 117.0, 116.8, 115.9, 114.8, 105.5, 28.6, 17.0; HRMS (ESI-QTOF) calcd for $C_{18}H_{14}FNO_2$ 296.1081 ([M + H]$^+$), found 296.1064.

6-Amino-5-(4-fluorobenzoyl)indolizine-7-carbonitrile (**5h**). Red solid: mp 135.6−135.8 °C (59.1 mg, 92%); R_f 0.23 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3411, 3297, 2924, 2215, 1736, 1595, 1565, 1312, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.60−7.49 (m, 2H), 7.15−7.04 (m, 2H), 6.88 (s, 1H), 6.75 (d, J = 4.0 Hz, 1H), 6.51 (s,1H), 6.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 141.1, 134.2, 131.6, 131.05, 130.96, 128.4, 123.4, 116.6, 116.4, 114.5, 109.0; HRMS (ESI-QTOF) calcd for $C_{16}H_{10}FN_3O$ 280.0881 ([M + H]$^+$), found 280.0882.

5-(4-Fluorobenzoyl)-7,8-dihydropyrrolo[1,2-b]isoquinolin-9(6H)-one (**5i**). Yellow solid: mp 109.8−110.5 °C (41.0 mg, 58%); R_f 0.20 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2938, 1735, 1701, 1592, 1233, 1220, 1158, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.97−7.86 (m, 2H), 7.24−7.15 (m, 2H), 7.14 (s, 1H), 6.91 (d, J = 3.2 Hz, 1H), 6.85 (t, J = 2.8 Hz, 1H), 2.73−2.59 (m, 4H), 2.12−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 190.8, 132.5, 132.44, 132.42, 127.6, 122.5, 122.3, 122.2, 117.1, 116.8, 116.7, 115.6, 107.4, 39.2, 26.2, 22.8; HRMS (ESI-QTOF) calcd for $C_{19}H_{14}FNO_2$ 308.1081 ([M + H]$^+$), found 308.1084.

5-(4-Fluorobenzoyl)-7,7-dimethyl-7,8-dihydropyrrolo[1,2-b]-isoquinolin-9(6H)-one (**5j**). Orange gum (45.5 mg, 59%): R_f 0.20 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2925, 2853, 1734, 1701, 1582, 1177, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.97−7.85 (m, 2H), 7.22−7.13 (m, 2H), 7.07 (s, 1H), 6.90 (d, J = 4.4 Hz, 1H), 6.83 (t, J = 3.2 Hz, 1H), 2.52 (s, 2H), 2.49 (s, 2H), 1.00 (s, 6H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 132.6, 132.5, 132.3, 121.9, 121.3, 120.6, 117.1, 116.9, 116.6, 115.6, 107.4, 52.5, 39.3, 33.2, 28.3; HRMS (ESI-QTOF) calcd for $C_{21}H_{18}FNO_2$ 336.1394 ([M + H]$^+$), found 336.1401.

Ethyl 5-(4-chlorobenzoyl)-6-methylindolizine-7-carboxylate (**5k**). Orange gum (69.2 mg, 88%): R_f 0.47 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2980, 2934, 1706, 1669, 1585, 1428, 1224, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.00 (s, 1H), 6.82−6.77 (m, 1H), 6.77−6.73 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 2.31 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 166.6, 141.7, 134.0, 131.1, 129.9, 125.1, 119.4, 118.0, 115.8, 114.4, 105.0, 61.0, 16.9, 14.5; HRMS (ESI-QTOF) calcd for $C_{19}H_{16}ClNO_3$ 342.0891 ([M + H]$^+$), found 342.0897.

1-(5-(4-Chlorobenzoyl)-6-methylindolizin-7-yl)ethanone (**5l**). Brown solid: mp 114.9−115.4 °C (43.7 mg, 61%); R_f 0.26 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2967, 2926, 1736, 1701, 1584, 1423, 1231, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.01 (s, 1H), 6.80 (s, 2H), 2.64 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 192.1, 141.8, 133.9, 131.1, 130.6, 130.2, 130.0, 127.2, 124.8, 117.6, 116.0, 114.8, 105.6, 28.6, 17.1; HRMS (ESI-QTOF) calcd for $C_{18}H_{14}ClNO_2$ 312.0786 ([M + H]$^+$), found 312.0784.

6-Amino-5-(4-chlorobenzoyl)indolizine-7-carbonitrile (**5m**). Orange solid: mp 142.9−143.4 °C (46.3 mg, 68%); R_f 0.25 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3382, 2922, 2217, 1702, 1577, 1460, 1313, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 6.86 (s, 1H), 6.75 (d, J = 4.4 Hz, 1H), 6.50 (dd, J = 2.4, 4.2 Hz, 1H), 6.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 141.6, 138.6, 136.4, 131.8, 129.8, 129.6, 128.3, 123.7, 116.4, 114.4, 112.7, 109.2, 93.4; HRMS (ESI-QTOF) calcd for $C_{16}H_{10}ClN_3O$ 296.0585 ([M + H]$^+$), found 296.0582.

5-(4-Chlorobenzoyl)-7,8-dihydropyrrolo[1,2-b]isoquinolin-9(6H)-one (**5n**). Brown solid: mp 99.2−100.1 °C (50.6 mg, 68%); R_f 0.19 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3085, 2925, 1753, 1735, 1582, 1260, 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.14 (t, J = 0.8 Hz, 1H), 6.91 (d, J = 4.4 Hz, 1H), 6.84 (dd, J = 2.4, 4.2 Hz, 1H), 2.69−2.61 (m, 4H), 2.07−1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 191.2, 141.7, 134.2, 132.4, 131.0, 130.0, 127.4, 122.7, 122.6, 122.1, 116.7, 115.7, 107.5, 39.2, 26.2, 22.8; HRMS (ESI-QTOF) calcd for $C_{19}H_{14}ClNO_2$ 324.0786 ([M + H]$^+$), found 324.0778.

5-(4-Chlorobenzoyl)-7,7-dimethyl-7,8-dihydropyrrolo[1,2-b]-isoquinolin-9(6H)-one (**5o**). Brown gum (54.2 mg, 67%): R_f 0.13 (hexanes/ethyl acetate/dichloromethane 20:1:2); IR (ATR) ν = 2956, 2927, 1734, 1701, 1585, 1261, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.06 (s, 1H), 6.90 (d, J = 3.6 Hz, 1H), 6.82 (dd, J = 2.4, 3.4 Hz, 1H), 2.52 (s, 2H), 2.49 (s, 2H), 1.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 191.2, 141.8, 134.0, 132.3, 131.0, 130.0, 128.4, 122.05, 120.8, 116.6, 115.6, 107.5, 52.5, 46.1, 39.3, 33.2, 28.3; HRMS (ESI-QTOF) calcd for $C_{21}H_{18}ClNO_2$ 352.1099 ([M + H]$^+$), found 352.1095.

*Ethyl 5-(4-bromobenzoyl)-6-methylindolizine-7-carboxylate (**5p**).* Brown gum (69.3 mg, 78%): R_f 0.51 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2980, 2928, 1708, 1668, 1582, 1429, 1257, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.62(d, J = 8.8 Hz, 2H), 7.00 (s, 1H), 6.81−6.77 (m, 1H), 6.77−6.74 (m, 1H), 4.36 (q, J = 6.8 Hz, 2H), 2.31 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ192.1, 166.6, 134.5, 132.9, 131.1, 131.1, 130.6, 129.9, 125.2, 119.5, 118.1, 115.8, 114.4, 105.0, 61.0, 16.9, 14.5; HRMS (ESI-QTOF) calcd for $C_{19}H_{16}BrNO_3$ 386.0386 ([M + H]$^+$), found 386.0385.

*1-(5-(4-Bromobenzoyl)-6-methylindolizin-7-yl)ethanone (**5q**).* Yellow solid: mp 108.7−109.2 °C (59.0 mg, 72%); R_f 0.39 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2970, 2926, 1749, 1699, 1581, 1422, 1216, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.80 (s, 2H), 2.63 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 192.3, 134.4, 132.9, 131.1, 130.7, 130.6, 130.2, 127.2, 124.8, 117.7, 116.0, 114.8, 105.6, 28.6, 17.0; HRMS (ESI-QTOF) calcd for $C_{18}H_{14}BrNO_2$ 356.0281 ([M + H]$^+$), found 356.0282.

*6-Amino-5-(4-bromobenzoyl)indolizine-7-carbonitrile (**5r**).* Orange solid: mp 161.3−161.7 °C (60.2 mg, 77%); R_f 0.24 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3396, 2922, 2853, 2216, 1708, 1573, 1456, 1310, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.86 (s, 1H), 6.75 (dd, J = 0.8, 4.0 Hz, 1H), 6.51 (dd, J = 2.4, 4.4 Hz, 1H), 6.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ187.8, 141.6, 136.9, 132.5, 131.8, 129.9, 128.3, 127.2, 123.7, 116.4, 114.4, 112.7, 109.2, 93.4; HRMS (ESI-QTOF) calcd for $C_{16}H_{10}BrN_3O$ 340.0080 ([M + H]$^+$), found 342.0072.

*Ethyl 5-(4-methoxybenzoyl)-6-methylindolizine-7-carboxylate (**5s**).* Brown gum (56.6 mg, 73%): R_f 0.32 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2977, 2933, 1705, 1657, 1593, 1427, 1237, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.03 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.82−6.75 (m, 1H), 6.75−6.70 (m, 1H), 4.36 (q, J = 6.8 Hz, 2H), 3.88 (s, 3H), 2.32 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 166.7, 165.1, 132.3, 131.0, 130.7, 128.6, 124.7, 119.5, 117.1, 115.6, 114.7, 114.3, 104.6, 60.9, 55.8, 16.8, 14.5; HRMS (ESI-QTOF) calcd for $C_{20}H_{19}NO_4$ 338.1387 ([M + H]$^+$), found 338.1384.

*1-(5-(4-Methoxybenzoyl)-6-methylindolizin-7-yl)ethanone (**5t**).* Yellow gum (48.1 mg, 68%): R_f 0.31 (hexanes/ethyl acetate/dichloromethane 7:1:2); IR (ATR) ν = 2927, 2850, 1736, 1674, 1595, 1422, 1239, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.04 (s, 1H), 6.94 (d, J = 8.4 Hz, 2H), 6.78 (s, 2H), 3.88 (s, 3H), 2.64 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 191.6, 165.2, 132.3, 131.1, 130.5, 128.5, 127.3, 124.3, 116.8, 115.7, 114.7, 105.2, 55.8, 28.6, 16.9; HRMS (ESI-QTOF) calcd for $C_{19}H_{17}NO_3$ 308.1281 ([M + H]$^+$), found 308.1285.

*6-Amino-5-(4-methoxybenzoyl)indolizine-7-carbonitrile (**5u**).* Orange solid: mp 131.4−132.2 °C (64.3 mg, 96%); R_f 0.35 (hexanes/ethyl acetate/dichloromethane 5:1:2); IR (ATR) ν = 3440, 3329, 2923, 2217, 1703, 1584, 1312, 1261, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 4.0 Hz, 1H), 6.53 (dd, J = 2.4, 3.8 Hz, 1H), 5.83 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 163.5, 139.3, 131.0, 130.8, 130.1, 128.4, 122.6, 116.7, 114.5, 114.4, 113.5, 108.2, 93.8, 55.6; HRMS (ESI-QTOF) calcd for $C_{17}H_{13}N_3O_2$ 292.1081 ([M + H]$^+$), found 292.1076.

*5-(4-Methoxybenzoyl)-7,8-dihydropyrrolo[1,2-b]isoquinolin-9(6H)-one (**5v**).* Yellow solid: mp 112.2−112.8 °C (41.1 mg, 56%); R_f 0.21 (hexanes/ethyl acetate/dichloromethane 7:1:2); IR (ATR) ν = 2934, 1735, 1677, 1595, 1421, 1250, 1230, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.15 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.88 (s, 1H), 6.84 (s, 1H), 3.89 (s, 3H), 2.75−2.59 (m, 4H), 2.09−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 190.8, 165.2, 132.3, 128.6, 122.2, 122.0, 121.4, 116.5, 115.5, 114.8, 107.1, 55.8, 39.3, 26.0, 22.9; HRMS (ESI-QTOF) calcd for $C_{20}H_{17}NO_3$ 320.1281 ([M + H]$^+$), found 320.1278.

*5-(4-Methoxybenzoyl)-7,7-dimethyl-7,8-dihydropyrrolo[1,2-b]-isoquinolin-9(6H)-one (**5w**).* Brown solid: mp 116.9−117.6 °C (41.5 mg, 52%); R_f 0.17 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2956, 2936, 1700, 1664, 1597, 1421, 1256, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.09 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 3.6 Hz, 1H), 6.81 (s, 1H), 3.89 (s, 3H), 2.54 (s, 2H), 2.48 (s, 2H), 1.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 190.7, 165.3, 132.3, 129.3, 128.6, 121.4, 119.8, 116.4, 115.4, 114.9, 107.0, 55.8, 52.6, 39.2, 33.1, 28.3; HRMS (ESI-QTOF) calcd for $C_{22}H_{21}NO_3$ 348.1594 ([M + H]$^+$), found 348.1612.

*Ethyl 5-(4-(benzyloxy)benzoyl)-6-methylindolizine-7-carboxylate (**5x**).* Yellow gum (66.6 mg, 70%): R_f 0.26 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2979, 2931, 1705, 1657, 1571, 1229, 1162, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.45−7.33 (m, 5H), 7.01 (d, J = 8.8 Hz, 3H), 6.77 (dd, J = 2.4, 4.0 Hz, 1H), 6.73 (dd, J = 0.8, 3.6 Hz, 1H), 5.13 (s, 2H), 4.35 (q, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 166.8, 164.3, 135.9, 132.3, 131.1, 130.8, 128.9, 128.8, 128.5, 127.7, 124.7, 119.6, 117.2, 115.6, 115.5, 114.4, 104.6, 70.5, 60.9, 16.8, 14.5; HRMS (ESI-QTOF) calcd for $C_{26}H_{23}NO_4$ 414.1700 ([M + H]$^+$), found 414.1706.

*1-(5-(4-(Benzyloxy)benzoyl)-6-methylindolizin-7-yl)ethanone (**5y**).* Yellow gum (52.9 mg, 60%): R_f 0.20 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2981, 1698, 1657, 1592, 1423, 1237, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.86 (d, J = 7.2 Hz, 2H), 7.45−7.33 (m, 5H), 7.03 (d, J = 5.2 Hz, 2H), 7.00 (s, 1H), 6.77 (s, 2H), 5.13 (s, 2H), 2.63 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 191.6, 164.4, 135.9, 132.3, 131.1, 130.6, 128.9, 128.8, 128.5, 127.6, 127.4, 124.3, 116.8, 115.75, 115.6, 114.8, 105.2, 70.5, 28.6, 16.9; HRMS (ESI-QTOF) calcd for $C_{25}H_{21}NO_3$ 384.1594 ([M + H]$^+$), found 384.1609.

*6-Amino-5-(4-(benzyloxy)benzoyl)indolizine-7-carbonitrile (**5z**).* Orange solid: mp 169.4−169.8 °C (61.7 mg, 73%); R_f 0.17 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3412, 2922, 2217, 1736, 1599, 1562, 1316, 1296, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.46−7.31 (m, 5H), 7.02 (s, 1H), 6.98 (s, 1H), 6.96 (s, 1H), 6.71 (d, J = 3.6 Hz, 1H), 6.53 (s, 1H), 5.80 (s, 2H), 5.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 162.6, 139.3, 136.2, 131.0, 130.8, 130.4, 128.8, 128.5, 127.7, 122.6, 116.7, 115.4, 114.45, 113.5, 108.2, 93.7, 70.4; HRMS (ESI-QTOF) calcd for $C_{23}H_{17}N_3O_2$ 368.1394 ([M + H]$^+$), found 368.1392.

*5-(4-(Benzyloxy)benzoyl)-7,8-dihydropyrrolo[1,2-b]isoquinolin-9(6H)-one (**5aa**).* Orange gum (47.3 mg, 52%): R_f 0.17 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2978, 2933, 1707, 1670, 1580, 1428, 1255, 1204, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.45−7.32 (m, 5H), 7.14 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 4.0 Hz, 1H), 6.83 (dd, J = 2.4, 3.6 Hz, 1H), 5.14 (s, 2H), 2.73−2.59 (m, 4H), 2.09−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 164.4, 135.9, 132.35, 132.26, 128.9, 128.6, 127.6, 122.3, 122.0, 121.5, 116.5, 115.7, 115.5, 107.1, 70.5, 39.3, 26.0, 22.9; HRMS (ESI-QTOF) calcd for $C_{26}H_{21}NO_3$ 396.1594 ([M + H]$^+$), found 396.1609.

*Ethyl 5-(3-methoxybenzoyl)-6-methylindolizine-7-carboxylate (**5ab**).* Yellow gum (77.6 mg, 100%): R_f 0.40 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2925, 1734, 1701, 1593, 1256, 1224, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.53 (s, 1H), 7.39−7.30 (m, 2H), 7.24−7.15 (m, 1H), 7.02 (s, 1H), 6.81−6.76 (m, 1H), 6.76−6.72 (m, 1H), 4.36 (q, J = 6.8 Hz, 2H), 3.86 (s, 3H), 2.32 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 166.7, 160.5, 137.0, 131.1, 130.5, 124.9, 122.7, 121.7, 119.5, 117.7, 115.7, 114.4, 113.0, 104.8, 60.9, 55.7, 16.9, 14.5; HRMS (ESI-QTOF) calcd for $C_{20}H_{19}NO_4$ 338.1387 ([M + H]$^+$), found 338.1382.

*1-(5-(3-Methoxybenzoyl)-6-methylindolizin-7-yl)ethanone (**5ac**).* Yellow solid: mp 128.1−128.8 °C (45.9 mg, 65%); R_f 0.20 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2970, 2938, 1701, 1657, 1593, 1423, 1259, 1208, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.53 (s, 1H), 7.39−7.30 (m, 2H), 7.23−7.17

dx.doi.org/10.1021/jo401801j | J. Org. Chem. 2013, 78, 10395−10404

(m, 1H), 7.03 (s, 1H), 6.79 (s, 2H), 3.86 (s, 3H), 2.64 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 193.2, 160.5, 136.9, 130.8, 130.6, 130.5, 127.2, 124.6, 122.7, 121.8, 117.3, 115.8, 114.8, 113.0, 105.4, 55.7, 28.6, 17.0; HRMS (ESI-QTOF) calcd for $C_{19}H_{17}NO_3$ 308.1281 ([M + H]$^+$), found 308.1287.

*6-Amino-5-(3-methoxybenzoyl)indolizine-7-carbonitrile (**5ad**).* Orange solid: mp 123.4−123.8 °C (57.6 mg, 86%); R_f 0.20 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3422, 3319, 2932, 2214, 1622, 1574, 1301, 1256, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.07−7.04 (m, 3H), 6.91 (s, 1H), 6.72 (d, J = 3.6 Hz, 1H), 6.48 (s, 1H), 6.26 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 160.4, 141.3, 139.6, 131.6, 130.4, 128.3, 123.5, 120.3, 118.7, 116.6, 114.3, 113.1, 112.6, 109.0, 93.3, 55.6; HRMS (ESI-QTOF) calcd for $C_{17}H_{13}N_3O_2$ 292.1081 ([M + H]$^+$), found 292.1085.

*5-(3-Methoxybenzoyl)-7,8-dihydropyrrolo[1,2-b]isoquinolin-9(6H)-one (**5ae**).* Orange solid: mp 149.3−149.6 °C (52.9 mg, 72%); R_f 0.20 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2927, 2854, 1734, 1671, 1592, 1422, 1253, 1203, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.50 (s, 1H), 7.36 (d, J = 7.2 Hz, 2H), 7.21 (d, J = 6.8 Hz, 1H), 7.16 (s, 1H), 6.88 (s, 1H), 6.83 (s, 1H), 3.86 (s, 3H), 2.73−2.58 (m, 4H), 2.09−1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 192.3, 160.6, 137.2, 132.4, 130.6, 128.0, 122.5, 122.4, 122.21, 122.17, 121.7, 116.5, 115.7, 113.1, 107.3,55.7, 39.3, 26.1, 22.8; HRMS (ESI-QTOF) calcd for $C_{20}H_{17}NO_3$ 320.1281 ([M + H]$^+$), found 320.1294.

*Ethyl 5-(5-bromothiophene-2-carbonyl)-6-methylindolizine-7-carboxylate (**5af**).* Orange gum (45.1 mg, 50%): R_f 0.15 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2980, 2927, 1707, 1646, 1579, 1402, 1236, 1198 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.25 (d, J = 4.0 Hz, 1H), 7.15 (s, 1H), 7.09 (d, J = 4.0 Hz, 1H), 6.81 (dd, J = 2.8, 3.8 Hz, 1H), 6.75 (d, J = 4.0 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 166.5, 144.4, 135.9, 132.2, 131.1, 129.6, 126.2, 125.4, 119.4, 118.1, 115.8, 114.4, 105.1,61.0, 17.2, 14.5; HRMS (ESI-QTOF) calcd for $C_{17}H_{14}BrNO_3S$ 391.9951 ([M + H]$^+$), found 391.9952.

*6-Amino-5-(5-bromothiophene-2-carbonyl)indolizine-7-carbonitrile (**5ag**).* Red solid: mp 177.4−178.0 °C (59.7 mg, 75%); R_f 0.29 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3433, 3320, 2923, 2213, 1736, 1561, 1454, 1311, 1263 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.43 (s, 1H), 7.12 (d, J = 4.0 Hz, 1H), 6.98 (d, J = 4.0 Hz, 1H), 6.75 (d, J = 4.0 Hz, 1H), 6.61 (dd, J = 4.0, 2.8 Hz, 1H), 5.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 143.7, 139.2, 132.2, 131.4, 131.3, 128.6, 122.8, 122.4, 116.4, 114.5, 113.0, 108.7, 93.9; HRMS (ESI-QTOF) calcd for $C_{14}H_8BrN_3OS$ 345.9644 ([M + H]$^+$), found 345.9622.

*5-(5-Bromothiophene-2-carbonyl)-7,8-dihydropyrrolo[1,2-b]-isoquinolin-9(6H)-one (**5ah**).* Orange solid: mp 134.4−134.8 °C (62.0 mg, 72%); R_f 0.18 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3101, 2885, 1735, 1671, 1508, 1401, 1260, 1229, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.26 (s, 2H), 7.11 (d, J = 3.6 Hz, 1H), 6.92−6.88 (m, 1H), 6.88−6.84 (m, 1H), 2.75 (t, J = 5.6 Hz, 2H), 2.66 (t, J = 6.0 Hz, 2H), 2.05 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 183.0, 144.2, 135.8, 132.4, 132.3, 127.0, 126.5, 122.7, 122.1, 116.7, 115.5, 107.6, 39.2, 26.3, 22.8; HRMS (ESI-QTOF) calcd for $C_{17}H_{12}BrNO_2S$ 373.9845 ([M + H]$^+$), found 373.9831.

*Ethyl 5-(5-(tert-butyl)-3-iodo-2,4-dimethoxybenzoyl)-6-methylindolizine-7-carboxylate (**5ai**).* Brown gum (83.4 mg, 66%): R_f 0.30 (hexanes/ethyl acetate/dichloromethane 20:1:2); IR (ATR) ν = 2927, 2855, 1711, 1649, 1572, 1254, 1198, 1164, 1077 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.80 (s, 1H), 7.11 (s, 1H), 6.78 (s, 1H), 6.74 (d, J = 3.6 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 3.52 (s, 3H), 2.35 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 166.7, 166.3, 160.8, 141.7, 132.4, 131.3, 131.1, 126.5, 124.9, 119.6, 117.6, 115.6, 114.5, 104.9, 93.2, 62.4, 62.4, 60.9, 35.4, 30.9, 16.7, 14.5; HRMS (ESI-QTOF) calcd for $C_{25}H_{28}INO_5$ 550.1085 ([M + H]$^+$), found 550.1089.

*6-Amino-5-(5-(tert-butyl)-3-iodo-2,4-dimethoxybenzoyl)-indolizine-7-carbonitrile (**5aj**).* Orange solid: mp 138.4−140.2 °C (94.9 mg, 82%); R_f 0.23 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3481, 3403, 2933, 2208, 1719, 1561, 1302, 1222, 1202, 1073 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.33 (s, 1H), 6.85 (s, 2H), 6.74 (d, J = 1.6 Hz, 1H), 6.73 (s, 1H), 6.47 (t, J = 3.2 Hz, 1H), 3.9 (s, 3H), 3.60 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 163.5, 157.1, 142.8, 142.1, 132.3, 128.5, 128.4, 128.4, 122.9, 116.6, 114.5, 113.9, 109.9, 92.6, 92.4, 62.8, 62.5, 35.3, 31.0; HRMS (ESI-QTOF) calcd for $C_{22}H_{22}IN_3O_3$ 504.0779 ([M + H]$^+$), found 504.0780.

*5-(5-(tert-Butyl)-3-iodo-2,4-dimethoxybenzoyl)-7,8-dihydropyrrolo[1,2-b]isoquinolin-9(6H)-one (**5ak**).* Yellow solid: mp 158.4−159.3 °C (66.0 mg, 54%); R_f 0.18 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2923, 1734, 1675, 1572, 1402, 1259, 1202, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.76 (s, 1H), 7.32 (s, 1H), 6.89 (d, J = 3.6 Hz, 1H), 6.85 (t, J = 4.0 Hz, 1H), 3.98 (s, 3H), 3.49 (s, 3H), 2.69 (t, J = 6.0 Hz, 2H), 2.64 (t, J = 6.0 Hz, 2H), 2.08−1.96 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 189.7, 166.1, 160.3, 141.9, 132.5, 130.8, 129.5, 127.0, 123.2, 122.8, 122.1, 116.6, 116.0, 107.6, 93.1, 62.7, 62.5, 39.2, 35.4, 30.9, 26.3, 22.9; HRMS (ESI-QTOF) calcd for $C_{25}H_{26}INO_4$ 532.0979 ([M + H]$^+$), found 532.1008.

*Diethyl 7-acetyl-5-benzoyl-2,6-dimethylindolizine-1,3-dicarboxylate (**5al**).* Pale yellow solid: mp 83.8−84.4 °C (51.1 mg, 51%); R_f 0.15 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2925, 1688, 1639, 1616, 1533, 1327, 1230, 1172, 1103, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.85 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 3.99 (q, J = 7.2 Hz, 2H), 2.68 (s, 3H), 2.66 (s, 3H), 2.15 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 167.8, 137.2, 133.3, 129.2, 128.7, 128.5, 127.9, 124.9, 121.0, 114.6, 111.8, 74.0, 66.2, 60.9, 30.4, 14.3; HRMS (ESI-QTOF) calcd for $C_{25}H_{25}NO_6$ 436.1755 ([M + H]$^+$), found 436.1790.

*Diethyl 6-amino-5-benzoyl-7-cyano-2-methylindolizine-1,3-dicarboxylate (**5am**).* Yellow gum (80.1 mg, 83%); R_f 0.16 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3456, 3343, 2929, 2220, 1734, 1719, 1689, 1313, 1250, 1203 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 6.01 (s, 2H), 4.44 (q, J = 7.2 Hz, 2H), 4.02 (q, J = 7.2 Hz, 2H), 2.53 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 164.2,161.5, 139.6, 135.8, 135.6, 132.8, 130.9, 129.5, 128.7, 128.4, 123.1, 115.5, 114.7, 110.3, 101.5, 61.1, 60.7, 14.6, 14.2, 12.5; HRMS(ESI-QTOF) calcd for $C_{23}H_{21}N_3O_5$ 420.1554 ([M + H]$^+$), found 420.1582.

*Diethyl 5-benzoyl-2-methyl-9-oxo-6,7,8,9-tetrahydropyrrolo[1,2-b]isoquinoline-1,3-dicarboxylate (**5an**).* Yellow solid: mp 169.6−169.9 °C (102.9 mg, 100%); R_f 0.09 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2989, 2926, 1735, 1683, 1663, 1607, 1255, 1212, 1171 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 4.47 (q, J = 7.2 Hz, 2H), 4.03 (q, J = 7.2 Hz, 2H), 2.76−2.64(m, 4H), 2.67 (s, 3H), 2.05−1.95(m, 2H), 1.49 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 189.5, 164.4, 161.9, 137.1, 136.8, 136.7, 134.0, 131.3, 129.14, 129.08, 128.4, 127.1, 122.0, 119.8, 109.9, 61.0, 60.5, 39.0, 27.2, 22.6, 14.65, 14.3, 12.6; HRMS (ESI-QTOF) calcd for $C_{26}H_{25}NO_6$ 448.1755 ([M + H]$^+$), found 448.1799.

*Ethyl 6-amino-7-cyano-5-(4-methoxybenzoyl)indolizine-3-carboxylate (**5ao**).* Orange solid: mp 156.4−156.8 °C (74.4 mg, 89%); R_f 0.32 (hexanes/ethyl acetate/dichloromethane 5:1:2); IR (ATR) ν = 3416, 3334, 2958, 2225, 1735, 1694, 1282, 1254, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.16 (s, 1H), 7.14 (d, J = 4.0 Hz, 2H), 6.78 (d, J = 4.0 Hz, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 5.82 (s, 2H), 4.03 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 162.8, 160.9, 138.9, 131.4, 130.5, 129.2, 129.0, 124.4, 121.3, 115.9, 114.7, 113.8, 108.7, 98.7, 60.8, 55.5, 14.3; HRMS (ESI-QTOF) calcd for $C_{20}H_{17}N_3O_4$ 364.1292 ([M + H]$^+$), found 364.1314.

*Ethyl 5-(4-methoxybenzoyl)-9-oxo-6,7,8,9-tetrahydropyrrolo[1,2-b]isoquinoline-3-carboxylate (**5ap**).* Yellow solid: mp 162.1−162.6 °C (87.3 mg, 97%); R_f 0.24 (hexanes/ethyl acetate/dichloromethane 5:1:2); IR (ATR) ν = 2927, 1701, 1686, 1657, 1594, 1335, 1218, 1168, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.68 (d, J = 6.4 Hz, 2H), 7.47 (s, 1H), 6.92 (s, 2H), 6.90 (s, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.87 (s, 3H), 2.75 (br s, 2H), 2.66 (t, J = 5.2 Hz, 2H), 2.00 (t, J = 5.6 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 188.3, 163.8, 160.8, 137.0, 131.5, 131.2, 130.4, 125.9, 125.8, 123.5, 121.8, 120.3, 114.2, 108.2, 60.7, 55.6, 39.0, 27.0, 22.7, 14.4; HRMS (ESI-QTOF) calcd for $C_{23}H_{21}NO_5$ 392.1492 ([M + H]$^+$), found 392.1496.

Compounds **7** and **8** were prepared by using the similar procedure for **5**.

*7-Amino-6-(4-methoxybenzoyl)pyrido[1,2-a]indole-8-carbonitrile (**7**).* Red solid: mp 120.7−121.3 °C (60.5 mg, 77%); R_f 0.17 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3305, 2923, 2215, 1719, 1595, 1307, 1248, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.40 (s, 2H), 7.17 (d, J = 8.4 Hz, 1H), 7.14−7.07 (m, 2H), 6.97 (t, J = 8.4 Hz, 1H), 6.69 (s, 1H), 6.67 (s, 1H), 5.48 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 187.3, 163.6, 132.2, 131.0, 130.8, 129.7, 129.1, 123.6, 122.4, 122.0, 116.1, 114.6, 114.3, 101.2, 100.0, 55.5; HRMS (ESI-QTOF) calcd for $C_{21}H_{15}N_3O_2$ 342.1237 ([M + H]$^+$), found 342.1240.

*Ethyl 6-amino-5-(4-methoxybenzoyl)indolizine-7-carboxylate (**8**).* Pale orange solid: mp 153.2−153.9 °C (40.5 mg, 52%); R_f 0.16 (hexanes/ethyl acetate/dichloromethane 5:1:2); IR (ATR) ν = 3331, 2931, 1720, 1673, 1582, 1263, 1241, 1199, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 4.4 Hz, 1H), 7.81 (s, 1H), 7.02 (s, 2H), 6.99 (s, 1H), 6.50 (s, 1H), 5.47 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 164.7, 164.1, 139.3, 131.6, 130.6, 127.8, 127.0, 120.1, 117.0, 114.5, 112.7, 94.1, 62.2, 55.8, 52.6, 14.3; HRMS (ESI-QTOF) calcd for $C_{19}H_{18}N_2O_4$ 339.1339 ([M + H]$^+$), found 339.1348.

Synthesis of 9. A solution of $POCl_3$ (75.8 μL, 0.81 mmol, 5 equiv) in DMF (0.5 mL) was stirred at 0 °C for 1 h. To a stirred solution of **5a** (50 mg, 0.163 mmol) in dried CH_2Cl_2 (2 mL) was dropwise added a mixture of $POCl_3$ and DMF mixture at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched by saturated aqueous $NaHCO_3$ solution (3 mL), diluted with CH_2Cl_2 (5 mL), and washed with H_2O (2 mL). The water layer was extracted with ethyl acetate (5 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexanes/ethyl acetate/dichloromethane = 30:1:2) to give **9** (34.6 mg, 63%).

*Ethyl 5-benzoyl-3-formyl-6-methylindolizine-7-carboxylate (**9**).* White solid: mp 168.6−169.4 °C (34.6 mg, 63%); R_f 0.14 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 3095, 2926, 1705, 1671, 1643, 1301, 1237, 1203, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.28 (s, 1H), 7.87 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.52−7.43 (m, 3H), 6.88 (d, J = 4.8 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 2.30 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 176.0, 165.7, 138.2, 137.9, 134.6, 133.6, 129.0, 129.0, 127.6, 127.5, 127.4, 123.4, 122.2, 107.4, 61.7, 17.2, 14.3; HRMS (ESI-QTOF) calcd for $C_{20}H_{17}NO_4$ 336.1230 ([M + H]$^+$), found 336.1242.

Synthesis of 10 and 11. To a mixture of **5b** (50 mg, 0.18 mmol) and benzaldehyde (1.05 equiv) in EtOH (1 mL) was dropwise added a solution of NaOH (1 equiv) in H_2O (1 mL) at room temperature. After being stirred at rt for 24 h, the reaction mixture was acidified with 10% HCl, concentrated in vacuo, and extracted with dichloromethane (5 mL) two times. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexanes/ethyl acetate/dichloromethane = 30:1:2) to give **10** (55.3 mg, 78%).

*(E)-1-(5-Benzoyl-6-methylindolizine-7-yl)-3-(4-methoxyphenyl)-prop-2-en-1-one (**10**).* Yellow solid: mp 139.0−139.7 °C (55.3 mg, 78%); R_f 0.38 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2922, 2837, 1719, 1649, 1567, 1282, 1228, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.89 (s, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 16.0 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.50 (t, J = 7.6 Hz, 2H), 7.15 (d, J = 16.0 Hz, 1H), 7.04 (s, 1H), 6.95 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 2.4, 4.0 Hz, 1H), 6.73 (d, J = 3.2, 1H), 3.87 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 161.9, 145.5, 135.7, 135.1, 131.0, 130.8, 130.4, 129.8, 129.54, 129.48, 127.5, 123.7, 122.5, 117.1, 115.5, 114.6, 114.3, 104.2, 55.6, 16.1; HRMS (ESI) calcd for $C_{26}H_{22}NO_3$ 396.1594 ([M + H]$^+$), found 396.1605.

*(E)-1-(5-Benzoyl-6-methylindolizine-7-yl)-3-(4-bromophenyl)-prop-2-en-1-one (**11**).* Yellow solid: mp 148.3−148.9 °C (42.2 mg, 52.7%); R_f 0.49 (hexanes/ethyl acetate/dichloromethane 10:1:2); IR (ATR) ν = 2923, 2854, 1719, 1649, 1422, 1291, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), δ 7.92 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.60 (d, J = 16.0 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.54−7.44 (m, 4H), 7.29 (d, J = 16.0 Hz, 1H), 7.06 (s, 1H), 6.79 (dd, J = 2.4, 3.6 Hz, 1H), 6.76 (d, J = 3.6 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 192.2, 143.7, 135.6, 135.1, 133.8, 132.4, 131.1, 130.6, 129.9, 129.8, 129.6, 128.9, 126.1, 125.0, 123.1, 117.1, 115.7, 114.7, 104.9, 16.2; HRMS (ESI) calcd for $C_{25}H_{19}BrNO_2$ 444.0594 ([M + H]$^+$), found 444.0599.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of compounds **4**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +82 32 749 4515. Fax: +82 32 749 4105. E-mail: ikyonkim@yonsei.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by Nano-Material Technology Development Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012M3A7B4049656).

■ DEDICATION

This paper is dedicated to Professor Deukjoon Kim on the occasion of his retirement.

■ REFERENCES

(1) (a) Knoevenagel, E. *Chem. Ber.* **1896**, *29*, 172. (b) Knoevenagel, E. *Chem. Ber.* **1894**, *27*, 2345.

(2) For selected books and reviews on domino or tandem reactions, see: (a) Ho, T.-L. *Tandem Organic Reactions*; John Wiley & Sons: New York, 1992. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (d) Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (e) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (f) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (g) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442.

(3) For reviews on Knoevenagel condensation-initiated domino processes, see: (a) Tietze, L. F.; Kettschau, G.; Gewart, J. A.; Schuffenhauer, A. *Curr. Org. Chem.* **1998**, *2*, 19. (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. (c) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (d) Tietze, L. F.; Rackelmann, N. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; p 121.

(4) For recent papers on domino reactions triggered by Knoevenagel condensations, see: (a) Tratrat, C.; Giorgi-Renault, S.; Husson, H.-P. *Org. Lett.* **2002**, *4*, 3187. (b) Clarke, P. A.; Martin, W. H. C. *Org. Lett.* **2002**, *4*, 4527. (c) Sabitha, G.; Reddy, G. S. K. K.; Rajkumar, M.;

Yadav, J. S.; Ramakrishna, K. V. S.; Kunwar, A. C. *Tetrahedron Lett.* **2003**, *44*, 7455. (d) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S.; Barbas, C. F., III *J. Org. Chem.* **2004**, *69*, 5838. (e) Kumar, A.; Maurya, R. A. *Tetrahedron* **2007**, *63*, 1946. (f) Ramachary, D. B.; Kishor, M. *J. Org. Chem.* **2007**, *72*, 5056. (g) Verma, R. K.; Verma, G. K.; Shukla, G.; Nagaraju, A.; Singh, M. S. *ACS Comb. Sci.* **2012**, *14*, 224. (h) Vilches-Herrera, M.; Knepper, I.; de Souza, N.; Villinger, A.; Sosnovskikh, V. Y.; Iaroshenko, V. O. *ACS Comb. Sci.* **2012**, *14*, 434. (i) Li, M.; Lv, X.-L.; Wen, L.-R.; Hu, Z.-Q. *Org. Lett.* **2013**, *15*, 1262. (j) Jeyachandran, V.; Kumar, R. R.; Ali, M. A.; Choon, T. S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2101.

(5) Kim, I.; Kim, S. G.; Choi, J.; Lee, G. H. *Tetrahedron* **2008**, *64*, 664. For a recent review on synthesis of heterocycles by domino Knoevenagel condensation/hetero-Diels–Alder reactions, see: Majumdar, K. C.; Taher, A.; Nandi, R. K. *Tetrahedron* **2012**, *68*, 5693.

(6) (a) Toche, R. B.; Bhavsar, D. C.; Kazi, M. A.; Bagul, S. M.; Jachak, M. N. *J. Heterocycl. Chem.* **2010**, *47*, 28. (b) Wang, K.; Herdtweck, E.; Dömling, A. *ACS Comb. Sci.* **2012**, *14*, 316. (c) Shen, Q.; Wang, L.; Yu, J.; Liu, M.; Qiu, J.; Fang, L.; Guo, F.; Tang, J. *Synthesis* **2012**, *44*, 389. (d) Siddiqui, Z. N. *Tetrahedron Lett.* **2012**, *53*, 4974.

(7) Lee, J. H.; Kim, I. *J. Org. Chem.* **2013**, *78*, 1283.

(8) For our efforts towards N-fused bicyclic heterocycles, see: (a) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863. (b) Kim, I.; Won, H. K.; Choi, J.; Lee, G. H. *Tetrahedron* **2007**, *63*, 12954. (c) Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 8976. (d) Choi, J.; Lee, G. H.; Kim, I. *Synlett* **2008**, 1243. (e) Kim, I.; Choi, J.; Lee, S.; Lee, G. H. *Synlett* **2008**, 2334. (f) Kim, K.; Kim, I. *J. Comb. Chem.* **2010**, *12*, 379. (g) Kim, I.; Kim, K. *Org. Lett.* **2010**, *12*, 2500. (h) Cho, H.; Kim, I. *Tetrahedron* **2012**, *68*, 5464. (i) Jung, Y.; Kim, I. *Tetrahedron* **2012**, *68*, 8198.

(9) For general reviews, see: (a) Flitsch, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. *4*, p 443. (b) Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, *46*, 5237.

(10) For recent work towards indolizines, see: (a) Waldmann, H.; Eberhardt, L.; Wittstein, K.; Kumar, K. *Chem. Commun.* **2010**, *46*, 4622. (b) Barluenga, J.; Lonzi, G.; Riesgo, L.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2010**, *132*, 13200. (c) Ziyaadini, M.; Hazeri, N.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Willis, A. C. *Tetrahedron Lett.* **2011**, *52*, 5774. (d) Mao, Z.; Li, X.; Lin, X.; Lu, P.; Wang, Y. *Tetrahedron* **2012**, *68*, 85. (e) Kucukdisli, M.; Opatz, T. *Eur. J. Org. Chem.* **2012**, 4555. (f) Delcamp, J. H.; Yella, A.; Holcombe, T. W.; Nazeeruddin, M. K.; Grätzel, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 376. (g) Khoroshilov, G. E.; Tverdokhleb, N. M.; Brovarets, V.; Babaev, E. V. *Tetrahedron* **2013**, *69*, 4353.

(11) Reports on postfunctionalization of the pyridine ring of indolizine core have been scarce. See: Kuznetsov, A. G.; Bush, A. A.; Rybakov, V. B.; Babaev, E. V. *Molecules* **2005**, *10*, 1074.

(12) Zhu, H.; Stöckigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011**, *13*, 2792.

(13) While this manuscript is in preparation, Opatz's report on use of α,β-unsaturated carbonyl compounds as three-carbon units for pyridine ring annulation appeared. See: Kucukdisli, M.; Opatz, T. *J. Org. Chem.* **2013**, *78*, 6670.

(14) It should be mentioned that no domino Knoevenagel condensation/intramolecular aldol type cyclization sequence has been disclosed yet to the best of our knowledge.

(15) Similar yield of **5a** was obtained when the reaction was run with 700 mg of **4a**.

(16) We found that most cases required overnight stirring to complete the reaction except the reactions with malononitrile (**1c**), which were usually finished within 3 h. Even though complete consumption of the starting materials was checked in some cases by TLC analysis before 24 h, overnight stirring at 120 °C was necessary for conversion of the intermediate formed initially by Knoevenagel condensation to the final product via intramolecular aldol cyclization.

(17) See the Experimental Section for details.

(18) Thyrann, T.; Lightner, D. A. *Tetrahedron Lett.* **1995**, *36*, 4345.

(19) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245.

(20) (a) Liang, F.; Hu, J.; Zhang, L.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2001**, *38*, 853. (b) Ohta, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *J. Org. Chem.* **2009**, *74*, 8143.

(21) Raising the reaction temperature above 0 °C produced a mixture of mono- and diformylated products in variable yields.