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Metal-Free Catalyzed Synthesis of Fluorescent Indolizine Derivatives

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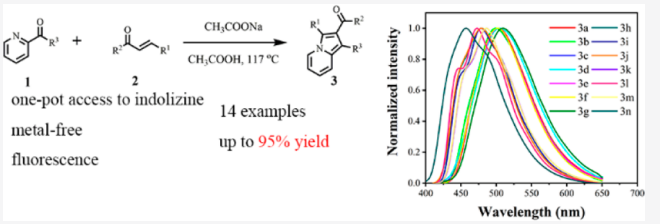
ABSTRACT: A mild and high efficient method to prepare indolizines by two-component reaction with the acid as the catalyst was developed. In this reaction, a new ring efficiently formed in one-step reaction. A wide range of substrates could be applied and the desired products were obtained in 8−95% yields under metal-free conditions. Different indolizine derivatives (compounds **3a**−**3n**) were synthesized by general conditions and microwave irradiation conditions, and compound **3a** gave the best results with an isolated yield of 95% and 82%, respectively. The structures of synthesized compounds were characterized by spectral analysis, and compound **3m** was confirmed by single crystal X-ray analysis. UV−vis absorption and fluorescence properties of these compounds were correlated with substituent groups on indolizine rings.



INTRODUCTION

Heterocyclic compounds play a prominent part in the field of organic and medicinal chemistry. Indolizine is one of the major classes of nitrogen-containing heterocycle. Indolizine skeleton has been embodied in many natural and therapeutic products which have biological activities. As shown in Figure 1, several indolizine derivatives have been reported as antimicrobial,[1] antitubercular,[2] antiproliferative,[3] showing anti-inflammatory activity,[2] and inhibitors of Alzheimer's disease.[4]

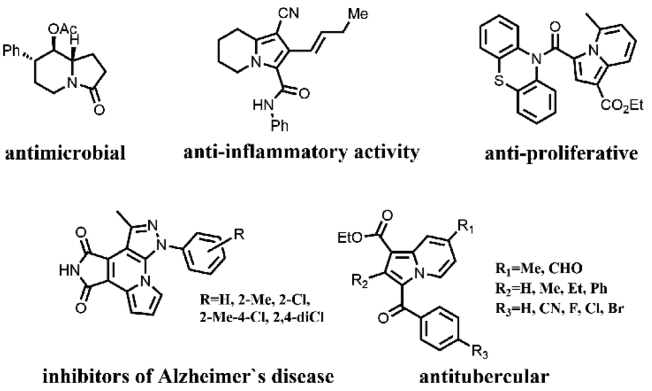


Figure 1. Biologically active molecules that incorporate indolizine.

The importance of fluorescent molecules has been well proved in the past few years. Fluorescent probe, as a fluorescent molecule, has been used extensively in biological science and clinical diagnosis. As a research tool, fluorescent probe has a lot of advantages such as excellent sensitivity, low cost, a large linear range of analysis, and ease of handling. However, most of the fluorescent probes were based on the coumarin,[5,6] 1,8-naphthalene diimide,[7,8] etc. Although indolizine skeleton has favorable properties, it can be only found in few fluorescent sensors.[9,10] Therefore, the development of an efficient method for the construction of indolizines has been received a great deal of attention, particularly in the field of synthetic chemistry and chemical biology. Construction of indolizine derivatives through direct functionalization of C−H bonds with simple and readily available starting substrates is of considerable interest in organic synthesis. Transition-metal-catalyzed direct C−H bond activation is one of the most powerful and useful tools to construct nitrogen-containing heterocycle in the past few years.[11,12] Compared to a transition-metal-catalyzed approach, few metal-free approaches for the synthesis of nitrogen-containing heterocycle have been developed. The reaction accomplished under transition-metal free conditions was advantageous because it avoided the metal contamination in the final product.

A number of synthetic methodologies have been reported for the construction of indolizine derivatives in recent years. As shown in Figure 2, Li's group reported the Rh catalyzed reaction for the synthesis of 3-allylindolizines.[13] Xu's group reported an efficient synthesis method of indolizine derivatives by the cyclization of propargylic pyridines with aroyl chlorides.[14] Shanmugam et al. reported the base-promoted one-pot three-component domino reaction to synthesize indolizine derivatives.[15] Zou et al. developed a one-pot

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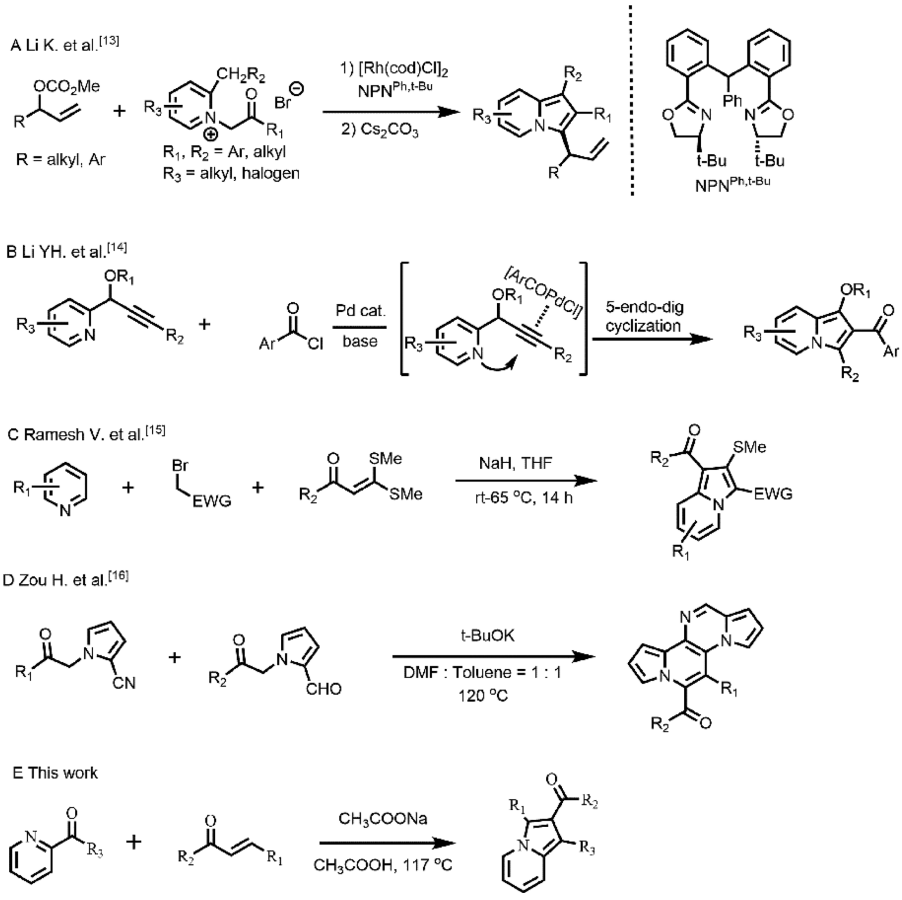


Figure 2. Representative examples and synthetic methods for indolizines.

chemoselective domino condensation method by which a fused pyrrolo−pyrazino−indolizine was formed.[16] However, these methods have some disadvantages such as using expensive and toxic metals as catalysts, reactants being difficult to prepare, and harsh reaction conditions.

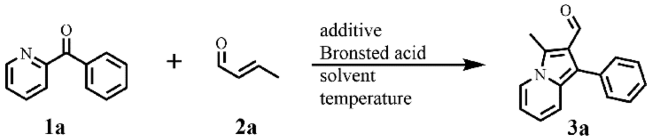
On the basis of previous research,[17] in the interest of green chemistry and atom economy, we report the direct synthesis of functionalized indolizines from pyridinone and α, β-unsaturated aldehydes or ketones under transition-metal-free catalytic conditions. X-ray crystal structures and optical properties of new indolizine derivatives are reported to investigate their potential application in small molecule fluorescent probe.

RESULTS AND DISCUSSION

For the screening of the reaction conditions, we first selected phenyl(pyridin-2-yl)methanone for the condensation with (*E*)-but-2-enal under the influence of an appropriate additive. For optimization of this condensation strategy, we examined the same reaction under different additive and temperature (Table 1). As shown in Table 1, no reaction occurred in the absence of the sodium acetate (Table 1, entry 3). While in the presence of sodium acetate, **3a** was obtained in 89% yield (Table 1, entry 4). Ammonium acetate also exhibited a promising reaction ability, and the yield of **3a** reached 85% (Table 1, entry 1). Sodium ethoxide was proved to be unsuitable for this reaction (Table 1, entry 2). It was found that reflux temperature (117 °C) was enough to ensure a good yield of **3a** (entries 4−8).

From Table 1 we get a better reaction condition, that is compound **1** (2 mmol), compound **2** (6 mmol) in the presence of 1 equiv of sodium acetate in 25 mL of acetic acid at 117 °C (Table 1, entry 5). To extend substrates, we next selected 2-acetylpyridine (**1b**) and (*E*)-but-2-enal as the model substrates with various solvent to screen the optimal reaction conditions, and the details are summarized in Table 2. Initially, by heating the reactants in EtOH at reflux temperature for 4 h in the presence of 3 equiv of acetic acid and 3 equiv of sodium acetate, we did not detect the formation of product **3b** (Table 2, entry 1). Unfortunately, changing solvent such as *N*,*N*-dimethylformamide, acetonitrile, toluene, and dioxane also did not give the desired product **3b** (Table 2, entries 2−5).

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	solvent	additive	temp (°C)	yield[b] (%)
1	CH_3COOH	CH_3COONH_4	117	85%
2	EtOH	EtONa	78	nd[c]
3	CH_3COOH		117	nd[c]
4	CH_3COOH	CH_3COONa	117	89%
5[d]	CH_3COOH	CH_3COONa	117	95%
6	CH_3COOH	CH_3COONa	26	81%
7	CH_3COOH	CH_3COONa	60	76%
8	CH_3COOH	CH_3COONa	100	78%

[a]Conditions: 2 mmol of **1a**, 3 mmol of **2a**, 2 mmol of additive. [b]Isolated yield. [c]Not detected. [d]6 mmol of **2a**.

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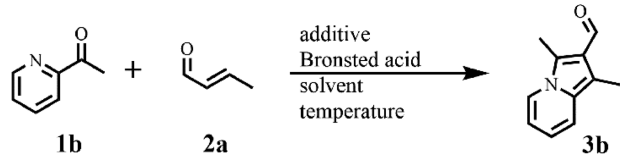
Table 2. Screening of Conditions for Model Reaction with 1b and 2a[a]



1b 2a 3b

entry	solvent	Brønsted acid (6.0 mmol)	additive (6.0 mmol)	temp (°C)	yield[b] (%)
1	CH_3CH_2OH	CH_3COOH	CH_3COONa	78	nd[c]
2	DMF	CH_3COOH	CH_3COONa	153	nd[c]
3	CH_3CN	CH_3COOH	CH_3COONa	81	nd[c]
4	toluene	CH_3COOH	CH_3COONa	111	nd[c]
5	dioxane	CH_3COOH	CH_3COONa	101	nd[c]
6	dioxane	CF_3COOH	CH_3COONa	101	nd[c]
7	CH_3COOH		CH_3COONa[d]	117	55%
8	CH_3COOH		CH_3COONa	117	56%
9	CH_3COOH		CH_3COONa[e]	117	52%

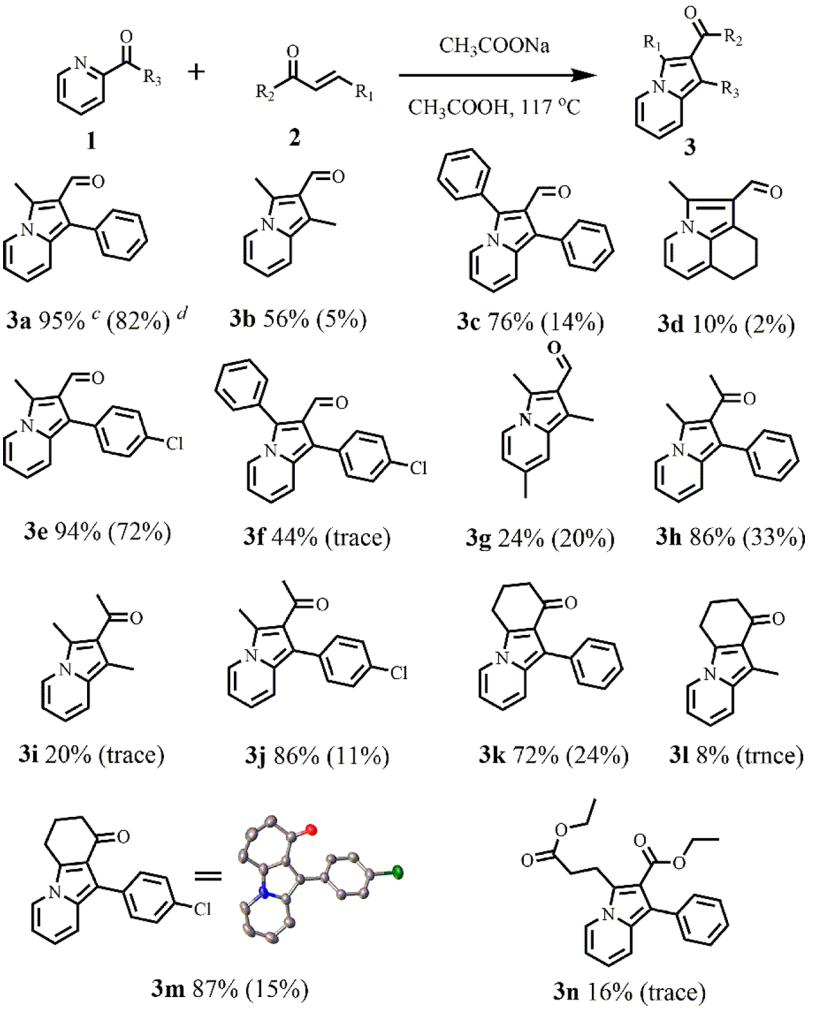
[a]2 mmol of **1b**, 6 mmol of **2a**, [b]Isolated yield. [c]Not detected. [d]2 mmol. [e]10 mmol.

However, using acetic acid as the solvent, product **3b** was isolated with the yield of 55% (Table 2, entry 7). Further research found that the amount of sodium acetate has no obvious impact on the yields of **3b** (Table 2, entries 7−9). Thus, the model reaction was carried out employing compound **1b** (2 mmol), compound **2a** (6 mmol) in the presence of 3 equiv of sodium acetate in 25 mL of acetic acid at 117 °C (Table 2, entry 8).

With the optimized conditions in hand, the substrate scope of this reaction was tested (Scheme 1). Products **3a**−**3n** could be obtained in 8−95% yields under the optimal conditions. As evidenced in Scheme 1, when R_3 was aryl group, both α, β-unsaturated aldehydes and ketone participated in this reaction readily, affording the desired indolizine derivatives in good to excellent yields. When substituent R_3 was alkyl, the yields of desired indolizine derivatives were low.

As shown in Figure 3, substrates with both electron-withdrawing groups and electron-donating groups on the pyridine ring (e.g., $-COCH_3$, $-OCH_3$, $-CH_3$) have also been examined under the current conditions; however, the reactions

Scheme 1. Substrate Scope[a,b]



[a]General heat method reaction conditions: **1** (2 mmol), **2** (6 mmol), and sodium acetate (6 mmol) in acetic acid (25 mL) at 117 °C. [b]Microwave-assisted synthesis reaction conditions: a mixture of **1** (2 mmol), **2** (6 mmol), and sodium acetate (6 mmol) in acetic acid (25 mL) was placed into the microwave reactor and irradiated at 110 °C for 30 min. [c]Isolated yields of general heat method. [d]Isolated yields of microwave-assisted synthesis method.

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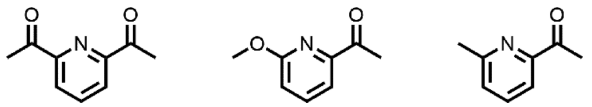


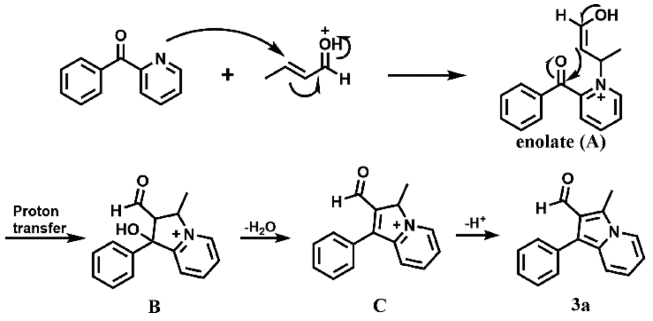
Figure 3. Unreacted compounds.

are messy and no desired products can be isolated, which might be attributed to the steric effects.

The microwave-assisted reactions have many advantages, so we attempted to synthesize the indolizine derivatives under microwave irradiation conditions. On the basis of the previously investigated reaction, different indolizine derivatives (compounds **3a**−**3n**) were synthesized under microwave condition, and some examples got good yields. Compounds **3a** gave the best results with an isolated yield of 82%.

A plausible mechanism was described for the reaction of phenyl(pyridin-2-yl)methanone (**1a**) and (*E*)-but-2-enal (**2a**) as a model case in Scheme 2. The initial Michael addition of

Scheme 2. Plausible Mechanism



the pyridyl nitrogen onto protonated (*E*)-but-2-enal led to the formation of enolate (**A**). The intramolecular aldol reaction of enolate (**A**) followed by the proton transfer gave intermediate **B**. Subsequent removal of the H_2O produced intermediate **C** that should be highly acidic. Finally, the desired product **3a** was obtained by the deprotonation of intermediate **C**.

The UV−vis spectrum characteristics of compounds **3a**−**3n** measured in acetonitrile, dimethyl sulfoxide, and dichloromethane solutions with the concentration of 1.2×10^{-4} M, respectively, are summarized in Table 3. As shown in Table 3, compounds **3a**−**3n** display similar maximum absorption ranging from 390 to 409 nm. It can be found that compounds with aldehyde in C-2 position of indolizine moiety have red shift than that with the ketone group.

The maximum molar extinction coefficients of **3a**−**3n** in acetonitrile, dimethyl sulfoxide, and dichloromethane are different. Although the difference is less, it can be observed that the enhancement order is generally ε (acetonitrile) < ε (dimethyl sulfoxide) < ε (dichloromethane).

Fluorescence spectral characteristics of compounds **3a**−**3n** in acetonitrile, dimethyl sulfoxide, and dichloromethane solution with the concentration of 5×10^{-6} M were investigated. Most of the products showed an emission band centered between 470 and 510 nm (Table 4).

Table 4. Maximum Wavelength (nm) of Excitation and Fluorescence Emission of Compounds 3a−3n[a]

	acetonitrile		dimethyl sulfoxide		dichloromethane	
compound	λ_{ex} (nm)	λ_{em} (nm)	λ_{ex} (nm)	λ_{em} (nm)	λ_{ex} (nm)	λ_{em} (nm)
3a	398	500	401	503.5	401	500.5
3b	405	495	404	499.5	405	498
3c	395	497	397	502.5	396	497
3d	399	505	397	504.5	399	503.5
3e	397	498	400	502.5	399	499.5
3f	393	498	397	502	395	497
3g	394	507	398	509.5	405	508
3h	390	475.5	391	479.5	391	478.5
3i	391	478	394	478.5	394	479.5
3j	389	475	390	479	390	477.5
3k	393	482.5	395	486	394	485.5
3l	392	470	394	472.5	394	473.5
3m	392	482	394	486	394	486
3n	382	454	383	457	382	456.5

[a]Slits: 15 nm/5 nm.

From Figure 4 and Table 4 it can be found that the maximum emission spectra of compounds in three different solvents are also mainly depended on the groups in C-2 position of indolizine moiety. Thus, compounds with an aldehyde group at C-2 position of indolizine have red shift than

Table 3. Maximum Absorption Wavelength (λ_{max}) and Maximum Molar Extinction Coefficients (ε_{max}) of 3a−3n in Acetonitrile, Dimethyl Sulfoxide, and Dichloromethane

	acetonitrile		dimethyl sulfoxide		dichloromethane	
compound	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})
3a	404.5	3625	408	3725	408	3783
3b	404.5	2208	407.5	2267	407.5	2467
3c	398.5	4458	402	4558	401.5	4708
3d	399.5	1892	401.5	2008	403	2033
3e	403	3917	406.5	4200	406.5	4158
3f	397.5	4975	400.5	5100	400.5	5317
3g	406	1783	409.5	1900	409.5	1942
3h	389	3767	392	3783	391.5	4242
3i	396	2258	400.5	2342	399.5	2383
3j	388.5	4258	390.5	4450	391	4600
3k	396.5	4350	398.5	4525	399.5	4783
3l	396.5	2633	399.5	2850	400	2975
3m	395.5	4842	390.5	4450	398.5	5492
3n	375	3792	377	3958	377.5	4150

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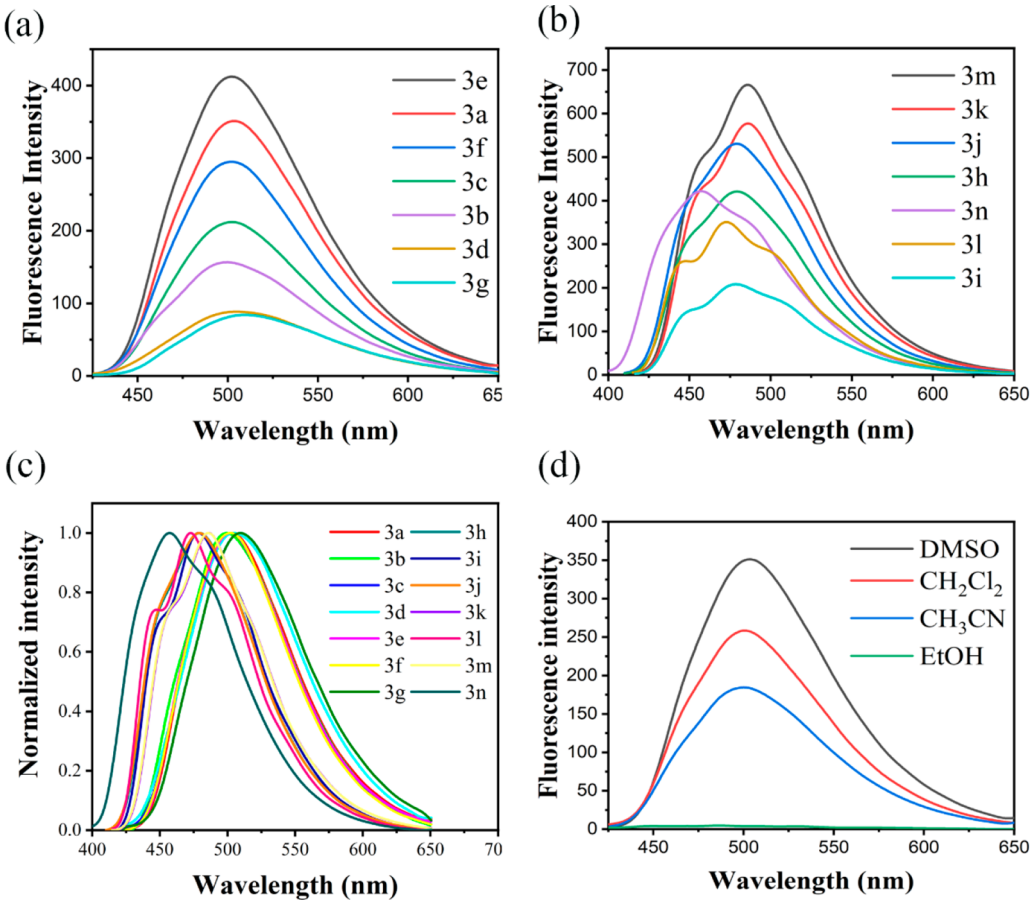

Figure 4. (a, b) Fluorescence spectra of compounds **3a−n** in dimethyl sulfoxide (5×10^{-6} M). (c) Normalized fluorescence spectra of compounds **3a−n** in dimethyl sulfoxide (5×10^{-6} M). (d) Fluorescence spectra of compounds **3a** in different solutions (5×10^{-6} M).

that without aldehyde group. For example, it can be seen from Figure 5 that compound **3a** with the aldehyde group at C-2

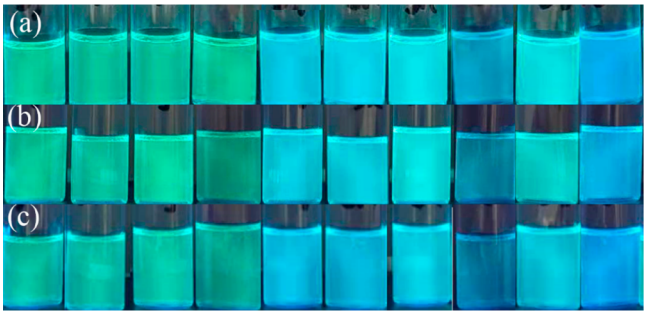

Figure 5. Visual fluorescence color photograph of compounds (from left to right: **3a**, **3c**, **3e**, **3f**, **3h**, **3j**, **3k**, **3l**, **3m**, **3n**) in three different solvents. (a) Dimethyl sulfoxide. (b) Dichloromethane. (c) Acetonitrile. (UV lamp, 365 nm).

position of indolizine moiety has a red shift compared with **3h**. The intensity of fluorescence was also correlated with substituents on indolizine moiety. Generally, fluorescence intensity of compounds with the aldehyde group at C-2 position of indolizine was weaker than others in three different solvents, respectively.

The solvent effect on the fluorescence behavior of all compounds was studied. Taking **3a** as an example, its maximum emission wavelength is 500, 503.5, and 500.5 nm in acetonitrile, dimethyl sulfoxide and dichloromethane, respectively. No significant differences were observed in the maximum emission wavelength in these solvents. Interestingly, the effects of solvents on the fluorescence intensities of **3a−3n** are obvious. It can be observed that the fluorescence intensities order is generally: $F_{\text{acetonitrile}} < F_{\text{dichloromethane}} < F_{\text{dimethyl sulfoxide}}$. However, when the compound is dissolved in ethanol, fluorescence quenching occurs.

CONCLUSION

In summary, a simple, one-pot, metal-free reaction for the preparation of indolizines has been established. By using this approach, a series of indolizines were synthesized in good yields (up to 95%). These examples demonstrate that the Brønsted acid-catalyzed synthesis of indolizine derivatives has a wide applicability. All obtained the indolizine derivatives exhibited interesting optical properties in solution, with a wide variety of fluorescent emissions (467−510 nm). On the basis of these promising emission properties, further studies are in progress to test these indolizine derivatives as fluorescent probe.

EXPERIMENTAL SECTION

General Experimental Methods. All solvents and raw materials were used as received from commercial suppliers without further purification. ^{1}H NMR (400 MHz) and ^{13}C{^{1}H} NMR (101 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer, with DMSO-d_6 or $CDCl_3$ as solvent. Thin-layer chromatography (TLC) was conducted on silica gel 60 F_{254} plates (Merck KGaA) and column chromatography was conducted over silica gel (mesh 200−

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300). IR spectra were measured by using the IR spectrophotometer Tensor II FT-IR (Bruker Optics). Melting points were determined on a XD-4 digital micro melting point apparatus. High-resolution mass spectrometry (HRMS) was obtained on an Impact II spectrograph (Bruker). Fluorescence measurements were carried out on a PerkinElmer LS-55 luminescence spectrophotometer. Quartz cuvettes with a 1 cm path length and 3 mL volume were used for all measurements. UV−vis spectra were recorded with the U-4100 spectrophotometer (Hitachi). Microwave reactions were conducted in a Milestone Start Synth Microwave Reactor. For single-crystal X-ray diffraction, intensity data and cell parameters were recorded at 293 K on a Bruker Apex II single crystal diffractometer employing Cu K_α (λ = 1.54184 Å) and a CCD area detector. Starting materials **1** and **2** were purchased from common chemical suppliers and used without further purification.

Photophysical Characterization of the Compounds. The stock solutions of compound **3a−3n** (10^{-3} M) in dimethyl sulfoxide were prepared. Test solutions (1.2×10^{-4} M) were made in dimethyl sulfoxide, dichloromethane, and acetonitrile, respectively, for UV−vis spectra. The diluted solutions (5×10^{-6} M) in dimethyl sulfoxide, dichloromethane, acetonitrile, and ethanol, respectively, were used for fluorescence measurements.

Synthesis of Compounds 3a−3n by General Heat Method. A mixture of phenyl(pyridin-2-yl)methanone (2 mmol), conjugated unsaturated aldehyde or ketone (6 mmol), and sodium acetate (6 mmol) in acetic acid (25 mL) was stirred at 117 °C in the oil bath. After 10−20 h, the reaction mixture was cooled to room temperature and the acetic acid was removed by evaporation under reduced pressure. The obtained crude product was purified via column chromatography on silica gel (CH_2Cl_2) to give desired compounds **3a−3n** in 8−95% yield.

Microwave-Assisted Synthesis of Compounds 3a−3n. A mixture of phenyl(pyridin-2-yl)methanone (2 mmol), conjugated unsaturated aldehyde or ketone (6 mmol), and sodium acetate (6 mmol) in acetic acid (25 mL) was placed into the microwave reactor and irradiated at 110 °C for 30 min. Sealed reaction vessels were used, and the reaction temperature was monitored by external surface sensor. Power of the START SYNTH MW synthesizer was 750−1000 W. After cooling to room temperature, the acetic acid was removed by evaporation under reduced pressure. The desired compounds **3a−3n** were obtained in 5−82% yield by purification via column chromatography on silica gel (CH_2Cl_2).

Crystal Structure. Suitable single crystals of **3m** for X-ray structural analysis were obtained by slow solvent evaporation from mixed solution of dichloromethane and *n*-hexane at room temperature for 7 days.

*3-Methyl-1-phenylindolizine-2-carbaldehyde (**3a**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 447 mg, 95% yield, yellow solid; Mp 86−88 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.13 (dt, J = 5.4, 1.4 Hz, 1H), 7.52−7.41 (m, 5H), 7.41−7.31 (m, 1H), 6.86−6.76 (m, 2H), 2.76 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.2, 133.1, 130.9, 129.5, 128.7, 126.9, 124.3, 121.9, 121.4, 119.7, 118.0, 117.6, 113.8, 10.4; IR (KBr) = ν 1668, 1532, 1495 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{14}NO$ (M+H)$^+$: 236.1070; found: 236.1078.

*1,3-Dimethylindolizine-2-carbaldehyde (**3b**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 193 mg, 56% yield, yellow solid; Mp 56−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.59 (dd, J = 7.1, 1.1 Hz, 1H), 7.33 (dt, J = 9.1, 1.3 Hz, 1H), 6.63−6.50 (m, 2H), 2.68 (s, 3H), 2.53 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 188.3, 129.8, 125.3, 122.3, 121.6, 119.1, 116.1, 112.9, 110.0, 9.7, 9.0; IR (KBr) = ν 3112, 2921, 1662, 1532, 1511, 1431, 738 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{11}H_{12}NO$ (M+H)$^+$: 174.0913; found: 174.0908.

*1,3-Diphenylindolizine-2-carbaldehyde (**3c**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 452 mg, 76% yield, yellow solid; Mp 169−170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.99 (dt, J = 7.3, 1.0 Hz, 1H), 7.71−7.53 (m, 5H), 7.54−7.43 (m, 5H), 7.41−7.32 (m, 1H), 6.89 (dd, J = 9.2, 6.3 Hz, 1H), 6.74 (td, J = 7.0, 1.3 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 187.4, 132.8, 131.1, 130.4, 130.3, 130.1, 129.2, 129.0, 128.3, 128.2, 126.6, 122.9, 121.3, 120.6, 118.8, 114.8, 114.1; IR (KBr) = ν 1678, 1601, 1521, 1482, 752, 698 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{16}NO$ (M+H)$^+$: 298.1226; found: 298.1236 $C_{21}H_{15}NOK$ (M+K)$^+$: 336.0785; found: 336.0735.

*2-Methyl-8,9-dihydro-7H-pyrrolo[3,2,1-ij]quinoline-1-carbaldehyde (**3d**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 40 mg, 10% yield, yellow solid; Mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 6.50 (t, J = 6.8 Hz, 1H), 6.23 (d, J = 6.3 Hz, 1H), 3.09 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.1 Hz, 2H), 2.67 (s, 3H), 2.02 (p, J = 6.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.8, 132.7, 130.3, 125.0, 121.1, 118.7, 114.2, 112.8, 110.7, 27.8, 23.4, 22.2, 9.8; IR (KBr) = ν 2937, 1652, 1538, 1501, 1453, 767 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{14}NO$ (M+H)$^+$: 200.1070; found: 200.1076.

*1-(4-Chlorophenyl)-3-methylindolizine-2-carbaldehyde (**3e**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 507 mg, 94% yield, yellow solid; Mp 102−105 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.14 (dt, J = 6.7, 1.3 Hz, 1H), 7.54−7.49 (m, 2H), 7.48−7.42 (m, 3H), 6.89−6.77 (m, 2H), 2.76 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 188.3, 132.5, 132.0, 131.7, 131.2, 129.0, 128.4, 126.1, 123.3, 120.4, 119.4, 118.3, 113.5, 9.7; IR (KBr) = ν 1668, 1528, 1489 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{13}ClNO$ (M+H)$^+$: 270.0680; found: 270.0699.

*1-(4-Chlorophenyl)-3-phenylindolizine-2-carbaldehyde (**3f**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 292 mg, 44% yield, yellow solid; Mp 177−179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.01 (dt, J = 7.2, 1.1 Hz, 1H), 7.73−7.57 (m, 5H), 7.55−7.36 (m, 5H), 6.92 (m, 1H), 6.75 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 187.4, 132.1, 131.8, 131.3, 131.2, 131.1, 130.3, 129.3, 129.1, 128.1, 128.0, 123.0, 121.3, 121.1, 118.6, 114.1, 112.8; IR (KBr) = ν 1679, 1594, 1524, 1483 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{15}ClNO$ (M+H)$^+$: 332.0837; found: 332.0821.

*1,3,7-Trimethylindolizine-2-carbaldehyde (**3g**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 88 mg, 24% yield, yellow solid; Mp 40−41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 1.4 Hz, 1H), 6.38 (dd, J = 7.3, 1.7 Hz, 1H), 2.65 (s, 3H), 2.49 (s, 3H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 188.3, 129.9, 126.1, 124.9, 122.4, 121.1, 116.7, 115.8, 107.9, 21.2, 9.7, 9.0.; IR (KBr) = ν 2914, 1671, 1542, 1503, 1433 1382, 773 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{12}H_{14}NO$ (M+H)$^+$: 188.1070; found: 188.1060.

*1-(3-Methyl-1-phenylindolizin-2-yl)ethan-1-one (**3h**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 428 mg, 86% yield, yellow solid; Mp 117−119 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12−8.04 (m, 1H), 7.51−7.43 (m, 2H), 7.35 (tt, J = 7.9, 1.3 Hz, 3H), 7.32−7.24 (m, 1H), 6.82−6.70 (m, 2H), 2.61 (s, 3H), 2.05 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 198.1, 134.9, 130.1, 128.6, 126.6, 124.8, 123.1, 122.6, 118.5, 118.1, 113.3, 112.6, 31.3, 10.2; IR (KBr) = ν 1657, 1596, 1527, 1494 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{16}NO$ (M+H)$^+$: 250.1226; found: 250.1234.

*1-(1,3-Dimethylindolizin-2-yl)ethan-1-one (**3i**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 74 mg, 20% yield, yellow solid; Mp 88−91 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00−7.91 (m, 1H), 7.51−7.44 (m, 1H), 6.68−6.57 (m, 2H), 2.62 (s, 3H), 2.52 (s, 3H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 196.9, 128.7, 124.3, 122.6, 122.4, 118.4, 115.8, 112.0, 107.5, 31.8, 10.8; IR (KBr) = ν 3096, 2916, 1728, 1646, 1425, 738 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{12}H_{14}NO$ (M+H)$^+$: 188.1070; found: 188.1066.

*1-(1-(4-Chlorophenyl)-3-methylindolizin-2-yl)ethan-1-one (**3j**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 486 mg, 86% yield, yellow solid; Mp 175−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 6.8, 1.4 Hz, 1H), 7.42−7.34 (m, 2H), 7.33−7.22 (m, 3H), 6.65 (m, 1H), 6.62−

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6.57 (m, 1H), 2.63 (s, 3H), 2.12 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 199.3, 133.9, 132.6, 131.6, 129.4, 128.7, 125.3, 123.0, 121.9, 118.6, 118.1, 112.9, 112.7, 31.6, 10.4; IR (KBr) = ν 1662, 1586, 1567, 1489 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{15}ClNO$ $(M+H)^+$: 284.0837; found: 284.0840.

*10-Phenyl-3,4-dihydropyrido[1,2-a]indol-1(2H)-one (**3k**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 376 mg, 72% yield, yellow solid; Mp 143−144 °C; (113−115 °C[17]). The NMR data match those of the reported molecule.[17] ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.1 Hz, 1H), 7.55 (d, J = 7.0 Hz, 2H), 7.49 (d, J = 9.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 6.67 (m, 1H), 6.61 (td, J = 6.7, 1.4 Hz, 1H), 3.01 (t, J = 6.3 Hz, 2H), 2.68−2.59 (m, 2H), 2.33 (p, J = 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 194.8, 133.8, 133.3, 130.1, 129.6, 127.7, 126.0, 123.6, 119.4, 119.0, 118.5, 112.6, 111.4, 54.9, 22.8, 20.7.

*10-Methyl-3,4-dihydropyrido[1,2-a]indol-1(2H)-one (**3l**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 31 mg, 8% yield, yellow solid; Mp 113−114 °C; (123−125 °C[17]). The NMR data match those of the reported molecule.[17] ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 7.1, 1.2 Hz, 1H), 7.32 (dt, J = 9.2, 1.3 Hz, 1H), 6.61−6.46 (m, 2H), 2.92 (t, J = 6.2 Hz, 2H), 2.64−2.57 (m, 2H), 2.54 (s, 3H), 2.26 (p, J = 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.4, 131.0, 130.1, 122.0, 121.1, 119.3, 116.1, 112.2, 107.9, 39.5, 23.6, 21.3, 9.7.

*10-(4-Chlorophenyl)-3,4-dihydropyrido[1,2-a]indol-1(2H)-one (**3m**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 515 mg, 87% yield, yellow solid; Mp 179−181 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dt, J = 7.1, 1.2 Hz, 1H), 7.52−7.46 (m, 2H), 7.43 (dt, J = 9.2, 1.2 Hz, 1H), 7.39−7.33 (m, 2H), 6.75−6.66 (m, 1H), 6.62 (td, J = 6.7, 1.3 Hz, 1H), 3.01 (t, J = 6.3 Hz, 2H), 2.68−2.60 (m, 2H), 2.32 (p, J = 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 195.7, 132.6, 132.4, 132.3, 131.7, 130.6, 128.1, 122.3, 119.8, 119.6, 119.0, 116.2, 113.1, 111.8, 39.8, 23.4, 21.5; IR (KBr) = ν 1667, 1521, 1434 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{15}ClNO$ $(M+H)^+$: 296.0837; found: 296.0841.

*Ethyl 3-(3-ethoxy-3-oxopropyl)-1-phenylindolizine-2-carboxylate (**3n**).* Purified by flash chromatography (silica gel, dichloromethane) to give the desired product: 117 mg, 16% yield, yellow oily; ^1H NMR (400 MHz, DMSO-d_6) δ 8.29−8.22 (m, 1H), 7.47−7.35 (m, 2H), 7.37−7.25 (m, 4H), 6.81−6.69 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.53−3.44 (m, 2H), 2.68−2.60 (m, 2H), 1.15 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.9, 165.7, 135.0, 130.7, 130.1, 127.7, 126.8, 126.3, 122.0, 119.4, 117.7, 115.8, 115.4, 112.7, 60.7, 60.0, 32.9, 20.4, 14.2, 13.9; IR (KBr) = ν 2977, 1727, 1700, 1272, 1185 cm^{-1}; HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{24}NO_4$ $(M+H)^+$: 366.1700; found: 366.1693.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01292.

^1H and $^{13}C\{^1H\}$ NMR, IR spectra, and HRMS spectra of compounds, UV−vis absorption and fluorescence emission spectra of the compounds (PDF)

Accession Codes

CCDC 2085860 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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