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REGIOSPECIFIC SYNTHESIS OF 1-(3,4-DIHYDRO-2*H*-BENZO[*b*][1,4]OXAZIN-3-YL)INDOLIZINE DERIVATIVES THROUGH A THREE-STEP SEQUENCE FROM 2-ARYLINDOLIZINE

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Abstract – A three-step sequence for the synthesis of new indolizine derivatives containing 1,4-benzoxazine subunits is presented. Two formyl groups were firstly introduced into 2-arylindolizine via Vilsmeier-Haack reaction. Subsequent aldimine condensation gave regiospecific indolizin-1-imine product, which underwent DMAP-catalyzed cascade reaction with α-bromoketones, giving 1-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)indolizine derivatives in moderate to good yields. A wide range of substrates were tolerated in this reaction. The mechanism for DMAP-catalyzed process was briefly discussed with a tentative catalytic cycle proposed.

INTRODUCTION

As an important class of heterocyclic compounds, indolizine (Figure 1) and its derivatives have been found possessing a diversity of biological activities,[1] such as anticancer,[2] antiproliferative,[3] antimycobacterial[4] and so on. For indolizine's peculiar scaffold, the six-membered ring in it was electron-deficient, while the five-membered ring was electron-rich, especially C3 and C1. This characteristic made it possible to modify indolizine and obtain structurally diverse derivatives. Indeed, it has attracted much attention in the last decades. For example, Gevorgyan,[5,6] You,[7,8] and Zhang[9] have succeeded in modifying the structure and synthesized a series of 3-substituted indolizine in the presence of Pd catalyst. Herein, we would like to construct indolizine derivatives with potentially biological activities and expand the library of indolizine based on the electron-rich property on its five-membered ring.

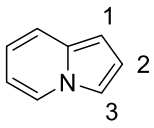
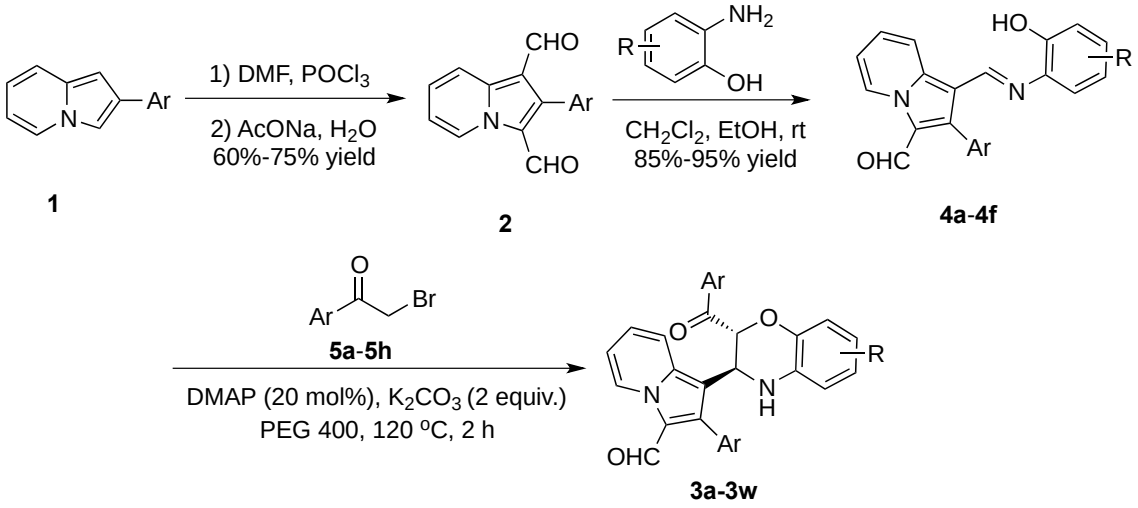


Figure 1. The scaffold of indolizne

Organocatalysis has been widely applied in organic synthesis for the new carbon-carbon/heteroatom bond formation over the last decades.[10] Previously, we developed an efficient synthesis approach for heterocyclic compounds via organocatalytic one-pot cascade and multicomponent reactions from simple and cheap starting materials.[11] With this efficacious strategy, we presumed that indolizine derivatives with benzoxazine heterocyclic substituent could be constructed between Schiff base **4** derived from 2-arylindolizine **1** and α-bromoketones **5**. To our delight, we obtained the desired indolizine derivatives 1-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)indolizines **3** in moderate to good yields (Scheme 1).



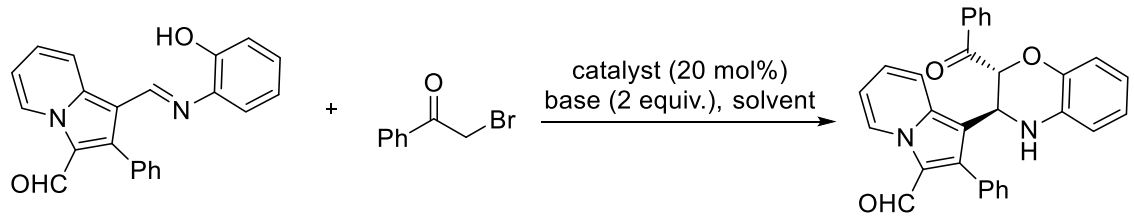
Scheme 1. Synthetic route of 1-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)indolizine derivatives from 2-arylindolizine

RESULTS AND DISCUSSION

Firstly, two formyl groups were introduced into 2-arylindolizine via Vilsmeier-Haack reaction due to the high electron density of the indolizine five-membered ring. 2-Arylindolizine-1,3-dicarbaldehyde **2** was obtained in moderate to good yields as shown in Scheme 1. Subsequently, various 2-aminophenol were used to react with compound **2**, interestingly, compounds **4a**-**4f** were obtained as the sole product in the reaction conditions showed in Scheme 1, which may ascribe to the difference of the electron density of the C1 and C3 formyl groups in compound **2**. This speculation is confirmed by theoretical calculations that the charge distribution of C1 and C3 formyl groups in the most stable conformation of compound **2** was 0.071 and 0.062, respectively.

The typical reaction of 1-(((2-hydroxyphenyl)imino)methyl)-2-phenylindolizine-3-carbaldehyde (**4a**) and 2-bromo-1-phenylethan-1-one (**5a**) was carried out in the presence of 20 mol% DABCO, 2 equiv. K_2CO_3, PEG 400 at 120 °C. After 2 hours, **4a** was consumed completely and a new compound was easily isolated from the reaction system by silica gel column chromatography. Spectral characterization clearly indicated it was the addition-cyclization product **3a** in 71% yield (Table 1, entry 1).

Table 1. Optimization of the reaction conditions[a]



4a **5a** **3a**

Entry	Catalyst	Base	Solvent	Temperature (°C)	Yield (%)[b]
1	DABCO	K_2CO_3	PEG 400	120	71
2	TEA	K_2CO_3	PEG 400	120	26
3	3-HQD	K_2CO_3	PEG 400	120	75
4	DMAP	K_2CO_3	PEG 400	120	80
5	—	K_2CO_3	PEG 400	120	trace
6	DMAP	K_2CO_3	PEG 400	140	80
7	DMAP	K_2CO_3	DMF	120	70
8	DMAP	K_2CO_3	MeCN	reflux	62
9	DMAP	Na_2CO_3	PEG 400	120	78

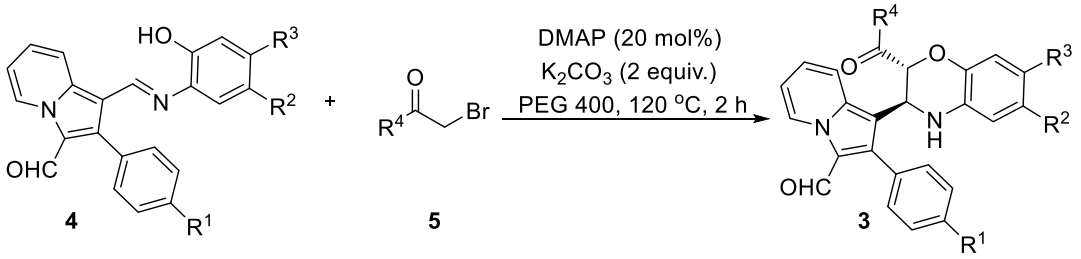
[a]Reaction conditions: **4a** (1.0 mmol), **5a** (1.5 mmol), catalyst (20 mol%) and base (2 equiv.), solvent (5 mL) for 2 h. [b]Isolated yields.

To optimize the reaction condition, various catalysts, solvents, temperature, and bases were examined and the results are presented in Table 1. It was found that no isolated product was obtained when the reaction proceeded in the absence of catalyst (entry 5). Tertiary amine is critical to this reaction and DMAP was found to be the best catalyst compared to 1,4-diazabicyclo[2.2.2]octane (DABCO), triethylamine (TEA) and 3-hydroxyquinuclidine (3-HQD), giving **3a** in 80% yield (entries 1-4). Then we optimized the temperature condition. As the temperature increased to 140 °C, no obvious improvement in yield was observed (entry 6). PEG 400 turned out to be the promising solvent employed in this reaction for its excellent solubility (entries 4, 7, 8). Furthermore, the effect of base on the reaction was also investigated.

Na_2CO_3 can also promote the reaction smoothly but led to a lightly decrease in yield (entry 9).

Based on the aforementioned experimental results, the optimized reaction condition was settled down as the combination of 20 mol% of DMAP as catalyst, 2 equiv. K_2CO_3 as base, PEG 400 as solvent at 120 °C for 2 h.

Table 2. Substrate scope for the synthesis of indolizine derivatives[a]



Entry	Substrate **4**	Substrate **5**	Product	Yield (%)[b]
1	**4a** (R^1=R^2=R^3=H)	**5a** (R^4=C_6H_5)	**3a**	80
2	**4a**	**5b** (R^4=4-MeC_6H_4)	**3b**	81
3	**4a**	**5c** (R^4=4-EtC_6H_4)	**3c**	82
4	**4a**	**5d** (R^4=4-$MeOC_6H_4$)	**3d**	84
5	**4a**	**5e** (R^4=4-ClC_6H_4)	**3e**	72
6	**4a**	**5f** (R^4=4-BrC_6H_4)	**3f**	75
7	**4a**	**5g** (R^4=4-CNC_6H_4)	**3g**	78
8	**4a**	**5h** (R^4=4-$NO_2C_6H_4$)	**3h**	trace
9	**4b** (R^1=Me, R^2=R^3=H)	**5a**	**3i**	82
10	**4b**	**5b**	**3j**	80
11	**4b**	**5c**	**3k**	81
12	**4b**	**5d**	**3l**	83
13	**4c** (R^1=MeO, R^2=R^3=H)	**5a**	**3m**	65
14	**4c**	**5d**	**3n**	67
15	**4d** (R^1=R^3=H, R^2=Me)	**5a**	**3o**	trace
16	**4e** (R^1=R^2=H, R^3=Me)	**5a**	**3p**	85
17	**4e**	**5b**	**3q**	84
18	**4e**	**5c**	**3r**	86
19	**4e**	**5d**	**3s**	80
20	**4f** (R^1=R^3=Me, R^2=H)	**5a**	**3t**	79
21	**4f**	**5b**	**3u**	80
22	**4f**	**5c**	**3v**	82
23	**4f**	**5d**	**3w**	85

[a]Reactions were carried out with **4** (1.0 mmol), **5** (1.5 equiv), DMAP (20 mol%) and K_2CO_3 (2 equiv.) in PEG 400 (5 mL) at 120 °C for 2 h. [b]Isolated yields.

Using the abovementioned optimized conditions, various 1-(((2-phenolic)imino)methyl)indolizines **4** and α-bromoketones **5** were utilized for assessing the substituent effects on the reaction. All the observed results were summarized in Table 2. Many functionalities were able to survive from this reaction. α-Bromoketones were first examined on this reaction, it was found that electron-donating groups on aromatic ring were smoothly performed to produce the corresponding products giving the desired products **3b**, **3c** and **3d** in good yields (entries 2-4). Weak electron-withdrawing group Cl and Br were all tolerant in this reaction producing **3e** and **3f** in moderate yields (entries 5, 6). It is worth noting that **5g** with strong electron-withdrawing group CN proceeded this reaction successfully giving **3g** in 78% yield (entry 7). In contrast, substrate **5h** with NO_2 group gave no isolated product due to an ionic liquid-based intermediate generation during reaction process and zwitterion ionic properties of NO_2 decreased the nucleophilicity of the active methylene (entry 8). Furthermore various 1-(((2-phenolic)imino)methyl)indolizines **4** were also examined, weak electron-donating R^1 group (Me) showed little influence on this reaction and gave the desired products in all above 80% yield (entries 9-12). In comparison, when R^1 on substrates **4** is strong electron-donating group OMe, the reaction performed to produce the corresponding products **3m** and **3n** in low yields, 65% and 67% respectively (entries 13, 14). It should be noted that the positions of methyl group on substrates **4** has an obvious effect on the reaction. The reaction proceeded smoothly and gave the corresponding products all above 80% yield when R^3 is Me and R^2 is H (entries 16-19). In contrast, no desired product was obtained when R^2 is Me and R^3 is H (entry 15). Substrate **4f** reacted with various of α-bromoaromatic ketone **5** uneventfully and afforded **3t**-**3w** in good yields (entries 20-23).

The relative configuration of product **3c** was unambiguously confirmed by the X-ray crystallographic analysis (Figure 2).[12]

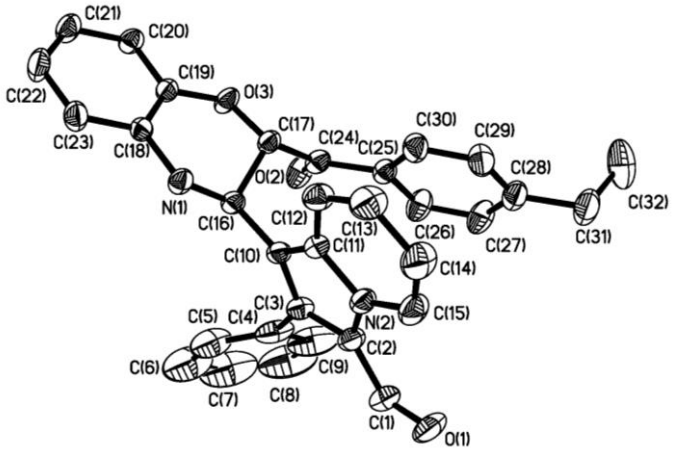
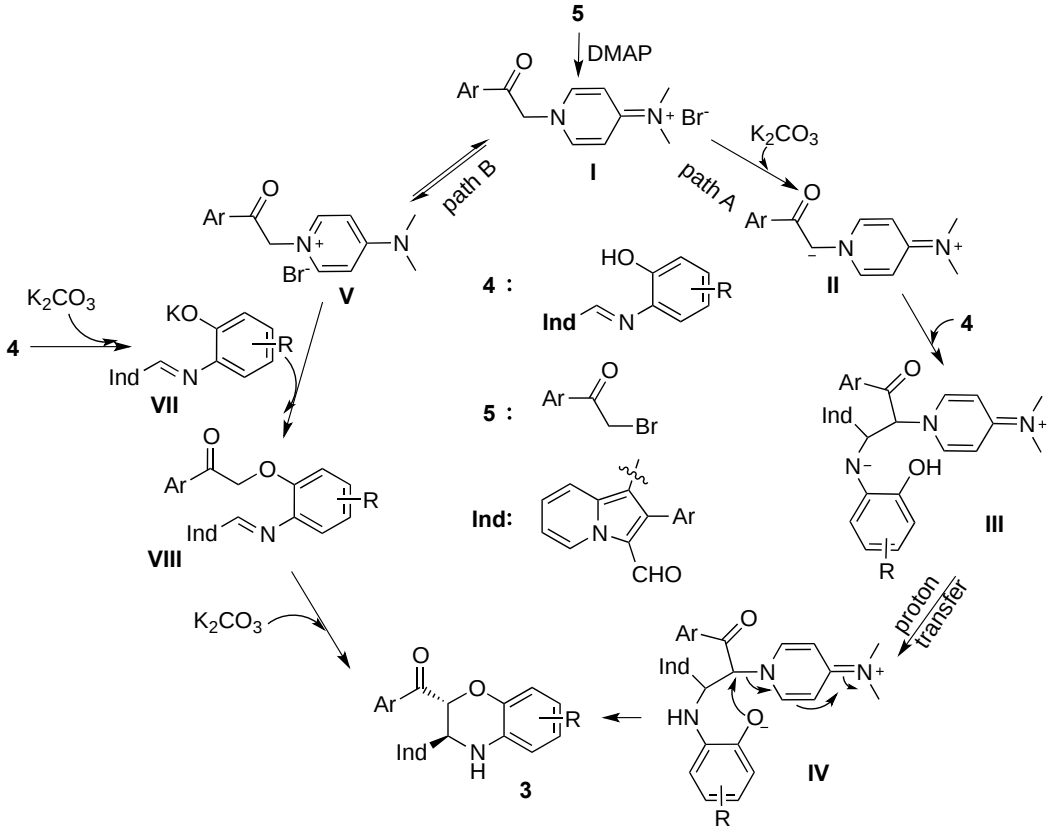


Figure 2. X-Ray crystal structure of product **3c**

A possible mechanistic explanation was also proposed to rationalize the formation of **3** as outlined in Scheme 2. Catalyst DMAP displaces the halogen of α-bromoketones **5** to generate the corresponding ammonium salt intermediate **I** which would then undergo along with path A or path B to generate thermodynamically stable compound **3** and regenerated catalyst DMAP for the next catalytic cycle.[13]



Scheme 2. Possible mechanism for the synthesis of 1-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-indolizine derivatives

In summary, a direct synthetic approach for the preparation of 1-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)indolizine derivatives through a double formylation, regiospecific Schiff-base formation and organocatalysis cycloaddition three step sequence was reported here. The reaction formed the corresponding indolizine derivative products in good yields under moderate reaction conditions without column chromatography purification of intermediate product. These novel compounds enriched the indolizine library, which may have potential biological and pharmacological activities. The tertiary amine-catalyzed cascade reaction developed in our laboratory proved to be an effective strategy and would be used to synthesize more heterocycles.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker instrument (300 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows:

chemical shift, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Bruker instrument (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. HRMS values were obtained using (ESI) mass spectrometer (TOF). IR spectra of liquid compounds were recorded neat and KBr plates were used for solid compounds. Melting points were measured using a hot stage apparatus and are reported uncorrected.

General procedure for the synthesis of indolizine-1,3-dicarbaldehyde 2. $POCl_3$ (5.2 mL, 57 mmol) was added dropwise to DMF (35 mL) in an ice bath. After finishing addition, 2-phenylindolizine (4.4 g, 22.8 mmol) was added and the ice bath was removed. The mixture was warmed to room temperature and stirred for 2 h. Then the temperature was raised to 60 ºC and the mixture was stirred for an additional 3 h. The reaction mixture was cooled to room temperature and slowly poured into saturated aqueous AcONa (200 mL). Dark green solid dissociated from the water phase immediately. The mixture was further stirred for 3 h. Finally, the precipitated product was filtered to afford the desired product without further purification.

General procedure for the synthesis of Schiff bases 4. *o*-Aminophenol (0.74 g, 6.8 mmol) and 2-(*p*-tolyl)indolizine-1,3-dicarbaldehyde (1.788 g, 6.8 mmol) were added into EtOH (20 mL) and CH_2Cl_2 (5 mL), the reaction mixture was stirred at room temperature. The reaction was monitored by TLC. Upon the completion of this reaction, the solid compound was filtered and washed with EtOH to give the desired product.

General procedure for the synthesis of indolizine derivatives 3. DMAP (25 mg, 0.2 mmol) and K_2CO_3 (276 mg, 2 mmol) were added to a solution of 1-(((2-hydroxyphenyl)imino)methyl)-2-arylindolizine-3-carbaldehyde (1.0 mmol), α-bromoketones (1.5 mmol), and 5 mL PEG 400. The reaction mixture was stirred at 120 ºC for 2 h. Upon completion of this reaction, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and washed with water. Organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica-gel (200-300 mesh) to afford the product **3**.

1-**(2-Benzoyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizine-3-carbaldehyde (3a).** Yellow solid; yield: 80%; mp 192-194 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (s, 1H, NH), 4.96 (d, *J* = 7.8 Hz, 1H, CH), 5.55 (d, *J* = 7.8 Hz, 1H, CH), 6.74 (t, *J* = 8.1 Hz, 2H, ArH), 6.86-6.97 (m, 3H, ArH), 7.15-7.43 (m, 9H, ArH), 7.64 (d, *J* = 7.2 Hz, 2H, ArH), 7.94 (d, *J* = 8.7 Hz, 1H, ArH), 9.28 (s, 1H, CHO), 9.71 (d, *J* = 6.3 Hz, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.8, 78.5, 109.6, 114.7, 115.3, 117.2, 118.4, 119.3, 120.8, 122.2, 126.0, 128.1, 128.2, 128.6, 128.7, 130.6, 133.1, 133.3, 135.0, 136.6, 141.3, 142.9, 143.6, 178.3, 194.5 ppm; IR (KBr): υ 3360, 3057, 2358, 2339, 1670, 1635, 1597, 1498, 1371, 1246, 746, 727, 680 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{23}N_2O_3$ $[M+H]^+$: 459.1630, found: 459.1638.

ACKNOWLEDGEMENTS

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12. CCDC 1410567 contains the supplementary crystallographic data for compound **3c**.
13. See the Supporting Information.