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Metal-Free Synthesis of Functionalized Indolizines via a Cascade Michael/S_N2/Aromatization Reaction of 2-Alkylazaarene Derivatives with Bromonitroolefins

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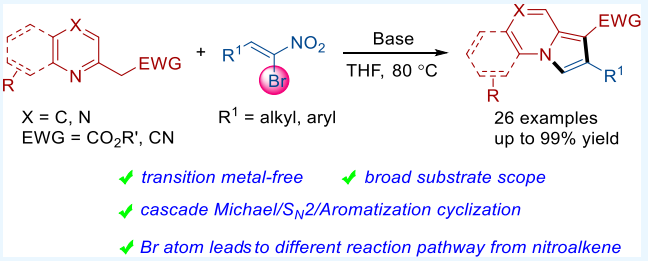
ABSTRACT: A transition metal-free domino Michael/S_N2/aromatization annulation of 2-pyridylacetates with bromonitroolefins has been developed. A wide range of substrates containing various substituted groups was compatible with the present methodology and afforded functionalized indolizines with moderate to excellent yield (up to 99% yield). In addition, the potential practicality of the method stood out through scale-up reactions and further transformations to other valuable compounds. In our view, this study is an essential complement for the rapid construction of indolizine derivatives through a metal-free strategy.



INTRODUCTION

Nitrogen-containing heterocycles are important constituents in a diverse variety of leading compounds and drugs. Statistically, more than 85% of bioactive molecules are heterocycles; above all, the nitrogen atom heterocycle is one of the most frequently and privileged core backbones in their structures.[1] Among them, indolizines are interesting unsaturated heterocycle compounds, which are made by a pyrrole ring and a pyridine ring, in which the nitrogen atom is shared by both rings. Many indolizine derivatives have shown a wide range of important biological activities (Figure 1), for example, anti-inflammatory (**I**),[2] anticancer activity (**II**),[3] vascular endothelial growth factor (VEGF) inhibitor (**III**),[4] as well as phosphodiesterase V inhibitor (**IV**).[5] Additionally, owing to indolizine derivatives possessing appreciable photophysical properties, they have also been investigated for organic light-emitting devices[6] and biological fluorescent probes (**V**).[7]

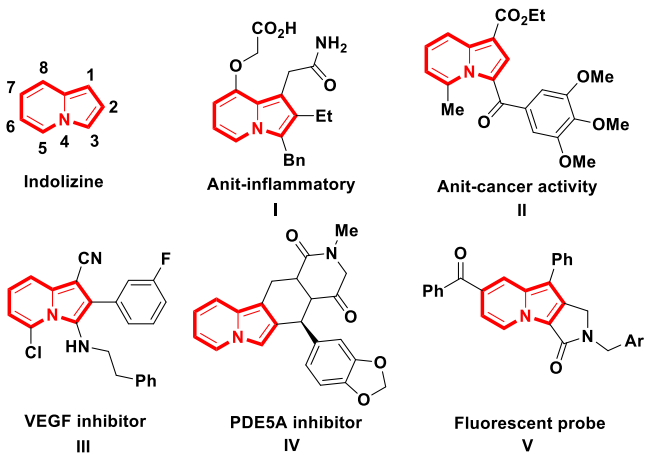


Figure 1. Selected bioactive molecules containing indolizine scaffolds.

Due to the unique bioactivity and physicochemical properties of indolizine derivatives, many methodologies for their synthesis have been developed by the organic chemistry community. Compared to classical methods, for example, the Scholtz and Chichibabin reactions,[8] the main strategies for indolizine derivative synthesis also comprised C−H functionalization of pyridine at the C-2 position,[9] cycloaddition reactions of pyridine analogues with electron-deficient unsaturated alkenes,[9] carbonyl groups,[10] transannulations of pyridotriazoles,[11] pyrrole rings,[12] and intramolecular cycloisomerization reactions (Scheme 1a).[13] Despite the efficiency and practicality of these approaches, they suffer from shortcomings, more or less, such as higher reaction temperatures, limited substrate range, and the use of catalytic quantities and even stoichiometric metal compounds. In particular, the contamination of metal residues in biologically active indolizine derivatives requires extreme care during the purification process, which is tedious and environmentally unfriendly. Therefore, it is highly desirable to develop transition metal-free routes for the synthesis of various substituted indolizines.

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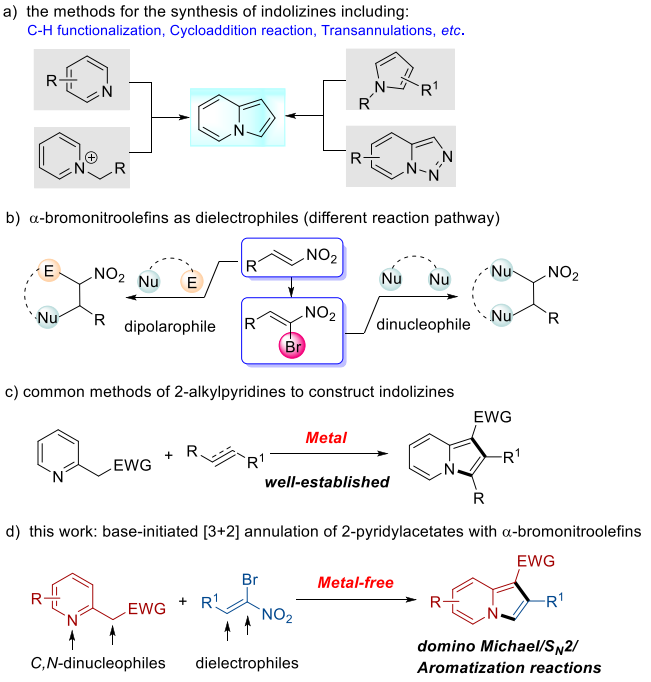
Scheme 1. Synthetic Strategies for Indolizines and Our Design



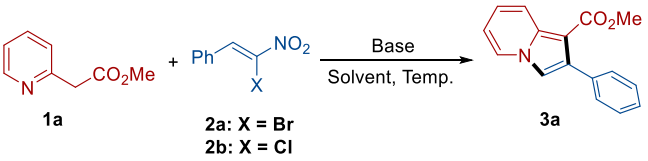
Nitroalkenes are a class of versatile building blocks in modern organic synthesis, which can be used to form diverse C−C and C−X bonds.[14] In addition, owing to the bromine atom possessing strongly electronegative and the repulsion effect of its lone-pair electrons, the C═C of nitroalkene is easily polarized.[15] So we believe that when introducing a bromine atom into nitroalkenes, bromonitroolefins exhibit different reaction paths compared with nitroalkenes. Recently, [2 + *n*] annulations with brominated nitroalkenes as dielectrophiles have been reported (Scheme 1b).[16] On the other hand, the construction of indolizines through 2-alkylpyridines' reaction with alkenes or alkynes is well established[10] but often requires catalytic quantities and even stoichiometric metal compounds. Moreover, the inherent 1,3-dinucleophile features of 2-alkylpyridine could make it a type of useful *C,N*-dinucleophile that reacts with 1,*n*-dielectrophiles to access aza-heterocycles (Scheme 1c).[17]

Based on these achievements, coupled with our interest in constructing pharmacologically active indolizine derivatives, we envisioned that the [3 + 2] annulations of 2-alkylpyridines with *α*-brominated nitroalkenes might be carried out without a metal catalyst. In this work, we reveal a versatile method to synthesize poly-substituted indolizine compounds from 2-alkylpyridines with bromonitroolefins through cascade Michael/S_N2/aromatization reactions without metal catalysts (Scheme 1d).

RESULTS AND DISCUSSION

Consequently, our investigation started with methyl 2-pyridylacetate **1a** and bromonitroolefin **2a** as the starting substrates to obtain the optimal conditions, and the results are concluded (Table 1). Initially, we used organic bases as the promoters, such as DBU, Et_3N, and DIPEA, which failed to promote the cascade Michael/S_N2/aromatization reactions (Table 1, entries 1−3). Interestingly, we find that indolizine **3a** can be isolated with a 64% yield under the presence of the inorganic compound Na_2CO_3 (Table 1, entry 4). And then, several other inorganic bases with different alkalis were tested, and Na_2CO_3 remained the best base. When $NaHCO_3$, NaOAc, K_2CO_3, K_3PO_4, and Cs_2CO_3 were screened, the yields of indolizine **3a** significantly dropped (Table 1, entries 5−9). The molar ratio of the reactant, which can adjust the value of the equilibrium constant K and affect the equilibrium state of the reaction, is very important in chemical synthesis for obtaining the target compounds with a high yield and purity.[18] Thus, we further screen the molar ratio of **1a** with **2a** (Table 1, entries 10−11). When the molar ratio of **2a** with **1a** is 1:1.5, the indolizine compound **3a** is obtained in a good yield of 75%. Moreover, a wide range of common solvents were examined to obtain the optimal reaction media (Table 1, entries 12−17). The results revealed that a protic polar solvent, such as MeOH, seemed to be inappropriate. Interestingly, the reaction can afford the targeted product with a slightly increased yield in the THF solvent (Table 1, entry 12 vs entries 13−17). Afterward, other reaction parameters, including the reaction temperature, the quantity of base, and concentration, were investigated. An outstanding yield was produced at higher temperatures (Table 1, entry 18), but further raising the reaction temperature to 100 °C could not improve the yield (Table 1, entry 19). In addition, either increasing or decreasing the amount of the base led to inferior results (Table 1, entries 20−21). Moreover,

Table 1. Optimization of the Domino Reaction Conditions[a]



entry	base	temp (°C)	solvent	yield (%)[b]
1	DBU	60	toluene	—
2	Et_3N	60	toluene	—
3	DIPEA	60	toluene	—
4	Na_2CO_3	60	toluene	64
5	$NaHCO_3$	60	toluene	20
6	NaOAc	60	toluene	48
7	K_2CO_3	60	toluene	18
8	K_3PO_4	60	toluene	20
9	Cs_2CO_3	60	toluene	<5
10[c]	Na_2CO_3	60	toluene	75
11[d]	Na_2CO_3	60	toluene	70
12[c]	Na_2CO_3	60	THF	80
13[c]	Na_2CO_3	60	dioxane	53
14[c]	Na_2CO_3	60	CH_3CN	15
15[c]	Na_2CO_3	60	MeOH	<5
16[c]	Na_2CO_3	60	DCM	47
17[c]	Na_2CO_3	60	acetone	26
18[c]	Na_2CO_3	80	THF	86
19[c]	Na_2CO_3	100	THF	75
20[c,e]	Na_2CO_3	80	THF	35
21[c,f]	Na_2CO_3	80	THF	76
22[c,g]	Na_2CO_3	80	THF	81
23[c,h]	Na_2CO_3	80	THF	78

[a]Unless noted otherwise, reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), and base (1.5 equiv) in the solvent (1.0 mL) at 60 °C in a sealed tube for 12−24 h. [b]Isolated yields. [c]The equivalent ratio of **2a** with **1a** is 1:1.5. [d]The equivalent ratio of **1a** with **2a** is 1:1.5. [e]0.5 equiv of base. [f]2.5 equiv of base. [g]2.0 mL of the solvent. [h]The nitroolefin substrate is **2b**.

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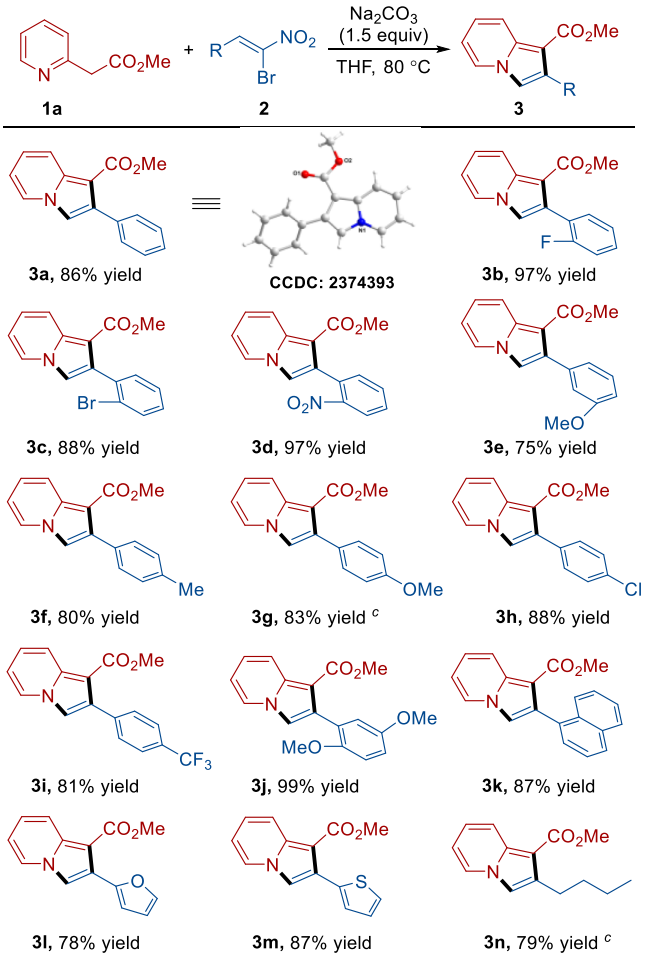
no improved result was obtained when the concentration was changed (Table 1, entry 22). At last, replacing the halogens with chlorine atoms also did not deliver better data (Table 1, entry 23). Overall, the optimal reaction condition is employing 2-alkylazaarene **1a** (0.15 mmol), bromonitroolefin **2a** (0.1 mmol), and Na_2CO_3 as a base (1.5 equiv) in THF (1.0 mL) at 80 °C for 24 h (Table 1, entry 18).

Under the optimal catalytic conditions (Table 1, entry 18), we probed the scope of bromonitroolefins **2**. As summarized in Scheme 2, it can be seen that a series of aryl (**3b**−**3j**),

Scheme 2. Substrate Scope for the Domino Cyclization of 2-Alkylazaarene 1a with Bromonitroolefins[ab]

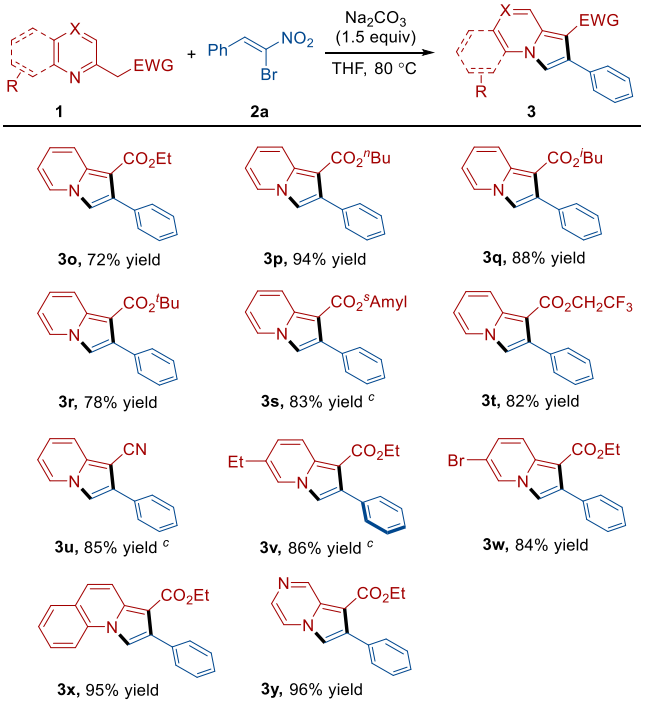


[a]Unless noted otherwise, reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol), and Na_2CO_3 (1.5 equiv) in THF (1.0 mL) at 80 °C in a sealed tube for 24 h. [b]Isolated yields. [c]The reaction time is 48 h.

heteroaryl (**3k**−**3m**), and alkyl (**3n**) substrates were tolerated to the cascade Michael/S_N2/aromatization reactions to afford indolizine derivatives. In general, the substrates containing a halogen or nitro at the ortho-position of the phenyl ring showed high reactivity and delivered the target products in higher yields (**3b**−**3d**). Moreover, the electron-donating group at the meta-position of the phenyl ring also provides the targeted indolizine product **3e** in good yield. In addition, either electron-donating or -withdrawing groups at para-positions of phenyl ring also reacted smoothly with 2-alkylpyridine **1a**, and the adducts **3f**−**3i** were produced in good yield (80−88%). It is noteworthy that the 2,5-MeO-disubstituted substrates could generate the desired product **3j** nearly equivalently. The 2-naphthyl substituted substrate **2k** delivered the product **3k** in a good yield. Further investigations demonstrated that the bromonitroolefin bearing S- and O-atom heteroaryl groups can also be used as the partner to react with methyl 2-pyridylacetate **1a** to obtain products **3l** and **3m** in 78% and 87% yields, respectively. Intriguingly, a brominated nitroalkene including an alkyl group, for example, *n*-Bu, was also found to be a suitable nitroalkene in good yield for 48 h (**3n**, 79% yield), possibly due to its lower activity compared to an aryl group. Moreover, the relative configuration of the targeted indolizine **3a** was unambiguously determined by X-ray crystallographic analysis; thus, the spare indolizine products were determined by analogy.

Next, we also screened the scope of 2-alkylazaarenes under the optimal reaction conditions. At first, we investigated the different substituents on the ester moiety, and the results are listed in Scheme 3. Fortunately, the ester group could be

Scheme 3. Substrate Scope for the Domino Cyclization of 2-Alkylazaarenes with Bromonitroolefin 2a[ab]



[a]Unless noted otherwise, reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol), and Na_2CO_3 (1.5 equiv) in THF (1.0 mL) at 60 °C in a sealed tube for 24 h. [b]Isolated yields. [c]The reaction time is 48 h.

converted into ethyl- or butyl-esters, all of which react well with *α*-brominated nitroalkene **2a** to deliver their respective products **3o** and **3p** in good yield. A sterically hindered isobutyl, *tert*-butyl, or *sec*-amyl group ($CH_3(CH)$-$CH_2CH_2CH_3$) on the ester was also compatible with the reaction to obtain the adducts **3q**−**3s** in moderate to good yield (78%−88%). Moreover, with introduction of a CF_3 functional group into the ester group, the corresponding product **3t** was obtained in good yield. In addition, when using 2-(pyridine-2-yl)acetonitrile as the *C*,*N*-dinucleophile substrate to react with **2a**, the indolizine targeted compound **3u** was

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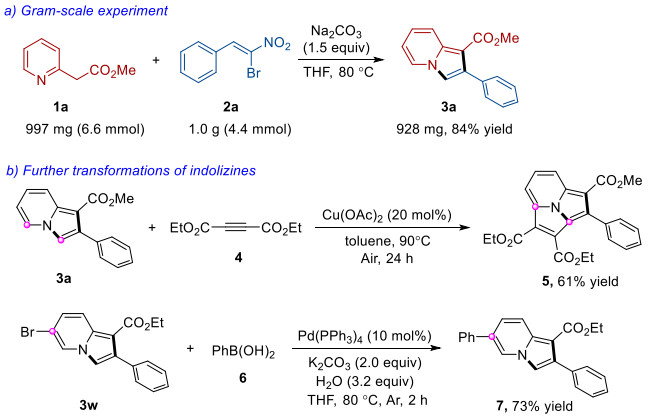
isolated with an 85% yield, although the time was extended to 48 h. Furthermore, it was found that the substrates bearing an electron-rich (Et) or electron-deficient (Br) group at the C5-position of the pyridine ring were also tolerated and delivered the indolizine targeted compounds **3v** and **3w** with good yields (86% and 84%), respectively. Additionally, when using ethyl 2-(isoquinolin-1-yl)acetate **2x** as the *C,N*-dinucleophile, the π-extended indolizine compound **3x** was generated in an excellent yield (95%). Ultimately, when the pyridine ring of the indolizine was changed to a pyrazine ring, the [3 + 2] annulation reaction also smoothly happened to give product **3y** with a 96% yield.

To demonstrate the synthetic potential and utility of the cascade Michael/S_N2/aromatization reactions, we conducted the domino reaction at a scale−up reaction under optimal reaction conditions. The result is exhibited in Scheme 4; the

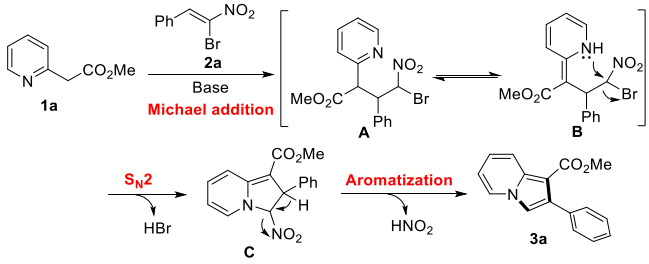
Scheme 4. Gram-Scale Experiment and Further Transformations



domino reaction was conducted on a gram-scale, generating the corresponding indolizine product **3a** with an 84% yield, and there was no obvious loss of yield compared with the 0.1 mmol scale. Moreover, we also have an interest in evaluating the synthetic usefulness of these indolizines. Initially, we treated the **3a** with diethyl acetylenedicarboxylate 4 at 90 °C with $Cu(OAc)_2$ (20 mol %) under air in toluene, which resulted in the formation of pyrrolo[2,1,5-*cd*]indolizine **5** with a 61% yield as a result of the oxidative [8 + 2]-cycloaddition reaction. Furthermore, when **3w** was subjected to the classical Suzuki−Miyaura coupling reaction, the coupling product **7** was smoothly delivered in a 73% yield under the catalyst $Pd(PPh_3)_4$ (10 mol %) at 80 °C. Compounds **5** and **7** possess a large conjugate group, which have the potential to be developed into fluorescent probes.

Having explored the cascade multiple-step reaction, we were intrigued by the reaction mechanism. As illustrated in Scheme 5, based on the previous reports,[10] a possible pathway for the synthesis of indolizine derivatives was proposed. At first, the cascade reaction started with a Michael addition of methyl 2-(pyridin-2-yl)acetate **1a** to bromonitroolefin **2a** to deliver intermediate **A**, and then intermediate **A** could further give **B** through tautomerization. Subsequently, intramolecular nucleophilic substitution led to the formation of intermediate **C**, which further upon elimination of the nitro group (free of one molecule of nitrite) delivered the target product **3a**.

Scheme 5. Possible Reaction Pathway



CONCLUSIONS

In conclusion, we herein report a highly efficient strategy for the construction of poly-substituted indolizine compounds from commercially accessible 2-pyridylacetates and bromonitroolefins. A wide range of substrates containing various substituted groups, including withdrawing or donating groups, were compatible under the present methodology and obtained the functionalized indolizines in moderate to excellent yield. Compared to previous reports, the merit of the present strategy includes transition metal-free catalysts, simple operation, excellent group tolerance, and a broad substrate scope. Meanwhile, the potential practicality of this method was identified by a gram-scale experiment and further transformations of the products to other valuable compounds. We think that this study is an important complement for the rapid synthesis of biologically indolizine derivatives through a metal-free strategy.

EXPERIMENTAL SECTION

General Procedure for Preparation of Indolizines 3a−3z. The reaction was performed with 2-alkylazaarenes **1** (0.15 mmol), bromonitroolefins **2** (0.1 mmol), and Na_2CO_3 (0.15 mmol) in THF (1.0 mL) at 80 °C for 24 or 48 h in a sealed tube. The reaction mixture was concentrated, and then the residue was subjected to column chromatography directly using petroleum ether/EtOAc (most use v/v = 8/1 to 4:1) as the eluent to afford the desired products **3**.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c09295.

X-ray crystal data for compound **3a** (CIF)

Experimental procedures, characterization data, and spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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