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Kai-Kai Dong, Qiang Huang

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Metal-Free Synthesis of Novel Indolizines from Chromones and Pyridinium Salts via 1,3-Dipolar Cycloaddition, Ring-opening and Aromatization

Kai-Kai Dong[a,b] , Qiang Huang[a,b,] *

[a] *Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China*
[b] *University of the Chinese Academy of Sciences, Beijing 100049, China*

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* Corresponding author. e-mail: huangqiang65@sina.com

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ABSTRACT

A simple, efficient, and economical synthetic approach to construct a variety of stucturally novel indolizines bearing a phenolic hydroxy group has been developed through 1,3-dipolar cycloaddition of chromones and pyridinium salts. The methodology is tolerant of a wide range of functional groups and applicable to library synthesis

The indolizine structural motif is a class of important nitrogen-containing heterocycles [1] with diverse biological activities [2], such as anti-cancer [3], anti-inflammatory [4], anti-convulsant [5] and inhibitors for phosphodiesterase 4 (PDE4) [6], topoisomerase I and HIV integrase [7] (Figure 1). Besides, indolizine skeleton has also been widely used in fluorescent materials [8]. Therefore, the wide use of this heterocyclic moiety as a preferred scaffold has prompted the exploration of efficient and novel protocols for the synthesis of multisubstituted indolizine derivatives in organic chemistry and material science.

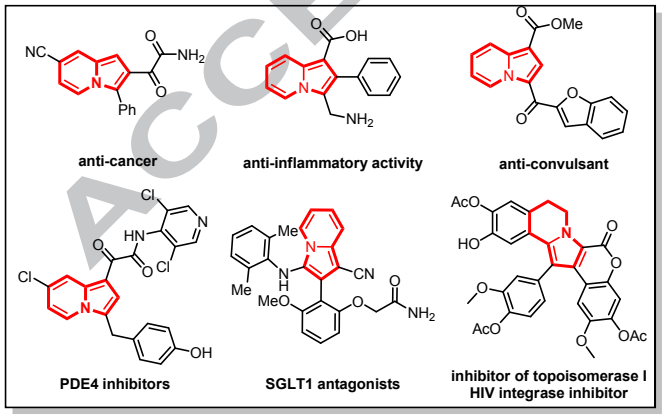


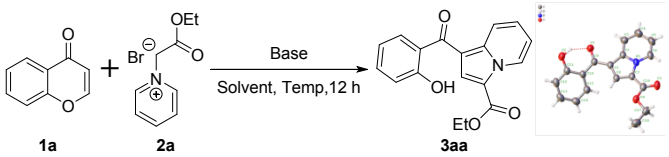
Figure 1. Bioactive indolizines

Generally, Scholtz [9] and Tschitschibabin [10] reactions have become the classical methodologies for the straightforward synthesis of indolizines. Recently, several other synthetic approaches have also been reported [11], such as 1,3-dipolar cycloaddition of activated alkynes or alkenes with pyridinium salts [11a], cyclization of pyridines with alkenyldiazoacetates [11d-e], metal-catalyzed C-H functionalization [11g-h]. Notably, Liu's [12] and Shi's [13] groups successively developed a series of gold(I)-catalyzed synthesis of indolizines via hydroarylation. Among the above methods, the 1,3-dipolar cycloaddition of pyridinium ylides with 1,3-dipolarphiles, such as electron-deficient alkenes and alkynes [14], has emerged as a powerful tool for the construction of indolizines with substituent groups at positions C-1 or C-3 [15]. Despite some great achievements, the 1,3-dipolar cycloaddition of pyridinium ylides with structure-specific alkenes, which could provide a method for the synthesis of indolizines with other types of substituents, remains to be explored.

Chromones are privileged scaffolds that can be converted into valuable functional groups for the purpose of constructing compounds with pharmacological activity [16]. Recent investigations in the C-H bond functionalization and cyclization of chromones have attracted considerable attention [17]. Especially, Yang et al developed a series of approaches to synthesize high-functionalized molecules by chromones as starting materials [17b-f]. Inspired by these remarkable works, here, we believe that chromones may react with pyridinium ylides via 1,3-dipolar cycloaddition, which provided an alternative strategy for the synthesis of complex indolizines derivatives. Herein, a base-promoted synthesis of indolizines from chromones and pyridinium salts was disclosed in this work.

We commenced our study by choosing chromone **1a** and 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium **2a** as our model substrates to examine the optimal reaction conditions (Table 1). To our delight, when the reaction was performed in DMF by using DBU as base, the desired product **3aa** was obtained in 52% yield, and the structure of **3aa** was confirmed by single crystal XRD analysis (Table 1, entry 1). Solvent screening found that 1,4-dioxane was to be the best choice (Table 1, entries 1-5). Subsequently, various bases were investigated. When other bases were added in the system, such as Et_3N, DIPEA, K_2CO_3, DMAP, DBACO and TBD, the reaction efficiency was not obviously improved (Table 1, entries 6-11). However, none of product was detected when the reaction was performed in the absence of base, which indicated that the base plays a key role in the present transformation (Table 1, entry 12). Further investigation for the amount of base and reaction temperature did not give improved yield of **3aa** (Table 1, entries 13-16).

Table 1. Optimization of reaction conditions[a]



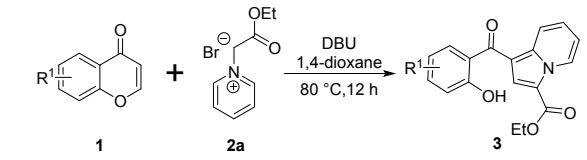
1a **2a** **3aa**

Entry	Base	Solvent	T (°C)	Yields (%)[b]
1	DBU	DMF	80	52
2	DBU	DMSO	80	72
3	DBU	NMP	80	78
4	DBU	toluene	80	76
5	**DBU**	**1,4-dioxane**	**80**	**81**
6	Et_3N	dioxane	80	70
7	DIPEA	dioxane	80	76
8	K_2CO_3	dioxane	80	56
9	DBACO	dioxane	80	38
10	DMAP	dioxane	80	30
11	TBD	dioxane	80	NR
12	-	dioxane	80	NR
13[c]	DBU	dioxane	80	49
14[d]	DBU	dioxane	80	76
15	DBU	dioxane	70	70
16	DBU	dioxane	90	74

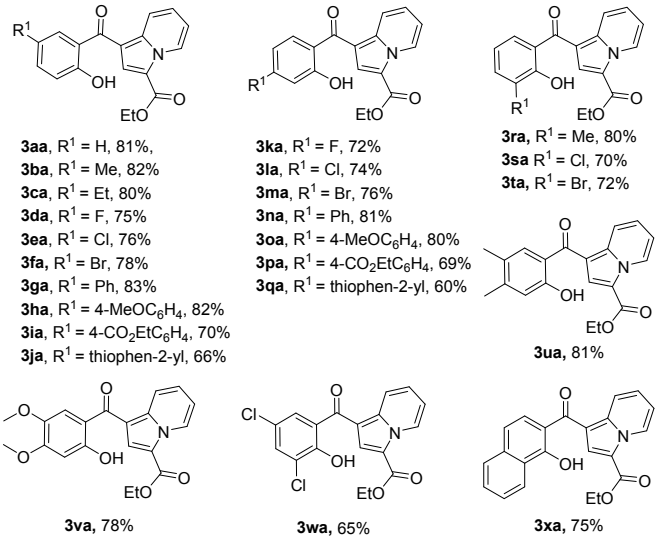
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), , Base (1.0 mmol), Solvent (3.0 mL), 12 h. NR = no reaction. [b] Isolated yields based on **1a**; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DBACO: 1,4-diazabicyclo[2.2.2]octane; TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [c] 0.5 mmol DBU. [d] 1.25 mmol DBU. NR means no reaction.

With the best reaction conditions in hand, we began to study the substrate scope of the chromones **1**. As illustrated in Table 2, both electron-donating and electron-withdrawing substituted chromones at C-6, C-7 and C-8 position were smoothly transformed into the desired products (**3aa-3ta**) in good yields. Notably, aryl and heteroaryl substituted chromones could also give the desired products in 60-83% yield (**3ga-3ja** and **3na-3qa**). In addition, the steric hindrance of substituent had no detrimental effect on the synthesis of indolizines (**3ra-3ta**). Importantly, the halogens such as fluoro-, chloro- or bromo- substitutions on the chromone rings were well tolerated to give the corresponding indolizines in good yields (**3da-3fa, 3ka-3ma** and **3sa-3ta**). Multi-substituted chromones were also suitable for the reaction leading to more complex indolizines in 65-81% yield (**3ua-3xa**)

Table 2. The substrate scope of chromones [a,b]



1 2a 3



3aa, R^1 = H, 81%,
3ba, R^1 = Me, 82%
3ca, R^1 = Et, 80%
3da, R^1 = F, 75%
3ea, R^1 = Cl, 76%
3fa, R^1 = Br, 78%
3ga, R^1 = Ph, 83%
3ha, R^1 = 4-$MeOC_6H_4$, 82%
3ia, R^1 = 4-$CO_2EtC_6H_4$, 70%
3ja, R^1 = thiophen-2-yl, 66%

3ka, R^1 = F, 72%
3la, R^1 = Cl, 74%
3ma, R^1 = Br, 76%
3na, R^1 = Ph, 81%
3oa, R^1 = 4-$MeOC_6H_4$, 80%
3pa, R^1 = 4-$CO_2EtC_6H_4$, 69%
3qa, R^1 = thiophen-2-yl, 60%

3ra, R^1 = Me, 80%
3sa R^1 = Cl, 70%
3ta, R^1 = Br, 72%

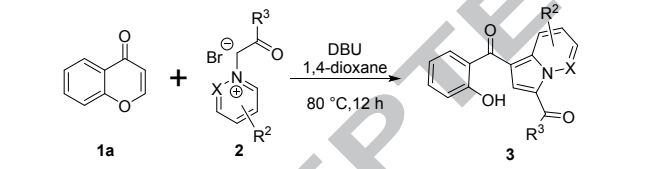
3ua, 81%

3va, 78% **3wa,** 65% **3xa,** 75%

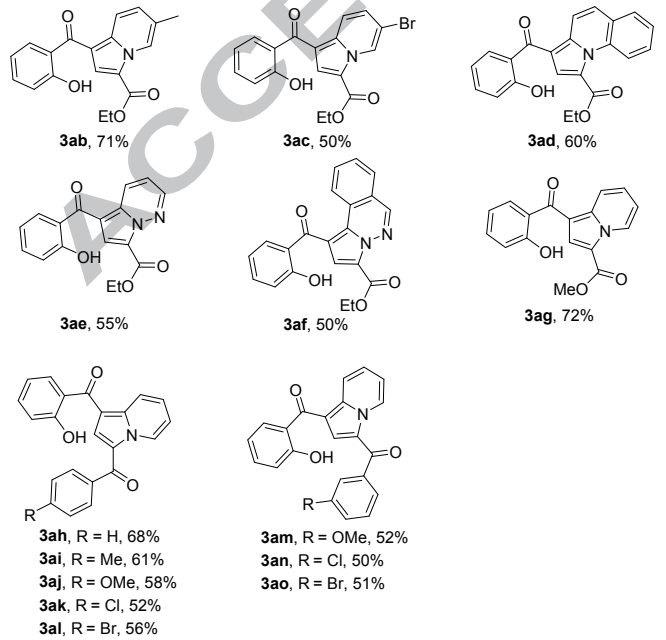
[a] Reagents and reaction conditions: chromone derivatives **1** (0.5 mmol), **2a** (0.55 mmol), DBU (1.0 mmol), 1,4-dioxane (3.0 mL), 80 °C, 12 h. [b] isolated yields.

Next, we further investigated the scope of various pyridinium salts under the standard conditions. As illustrated in Table 3, various pyridinium salts **2** could generate the corresponding products smoothly in moderate yields (**3ab-3ao**). Compared with the electron-donating substituted pyridinium salts, electron-withdrawing substituted pyridinium salts showed lower reaction activity in the system (**3ab** and **3ac**). Notably, other types of aza-aromatic rings could afford the target indolizines in moderate to good yields (**3ad-3ag**). To our delight, pyridinium salts derived from α-halo aryl ketones reacted well with **1a**, generating the more complex products in moderate to good yields (**3ah-3ao**). These results indicated that this method could be very suitable for constructing structural diversity molecules base on chromones motif.

Table 3. The substrate scope of pyridinium salts [a]



1a 2 3



3ab, 71% **3ac**, 50% **3ad**, 60%

3ae, 55% **3af**, 50% **3ag**, 72%

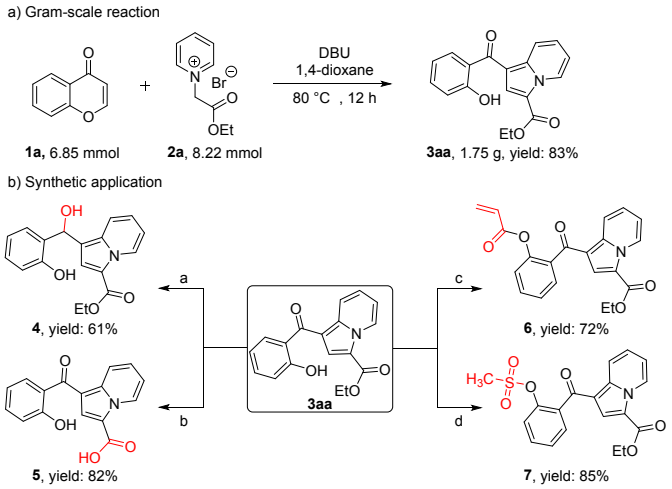
3ah, R = H, 68%
3ai, R = Me, 61%
3aj, R = OMe, 58%
3ak, R = Cl, 52%
3al, R = Br, 56%

3am, R = OMe, 52%
3an, R = Cl, 50%
3ao, R = Br, 51%

[a] Reagents and reaction conditions: **1a** (0.5 mmol), **2** (0.55 mmol), DBU (1.0 mmol), 1,4-dioxane (3.0 mL), 80 °C, 12 h, isolated yields.

To demonstrate the potential application of the method, a gram-scale reaction was carried out under the standard conditions. As seen from Scheme 1, to our delight, the reaction proceeded smoothly and afforded the desired product **3aa** in 83% yield (Scheme 1a). Moreover, the valuable functionalization of the product **3aa** was further investigation. For instance, the ketone group could be reduced to alcohol to generate **4** easily. Hydrolysis of the ester moiety in **3aa** generated **5** with free carboxyl group. Importantly, the phenolic group could be modified with acryloyl chloride and methanesulfonyl chloride (MsCl) to deliver potential biologically valuable acrylate **6** and sulfonate **7** (Scheme 1b).

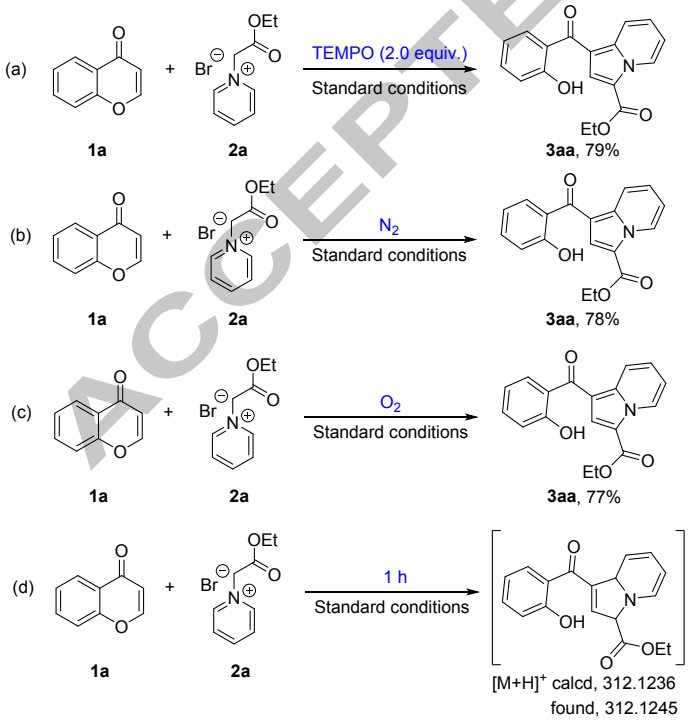
Scheme 1. Gram-scale reaction and synthetic applications



Reagents and conditions: a. $NaBH_4$, $CeCl_3$, MeOH, 0 °C - RT, 5 h; b. 2N NaOH solution, V_{THF} :V_{MeOH} = 2 : 1, 0 °C - RT, 16 h; c. Acryloyl Chloride, Et_3N, DCM, 0 °C - RT, 1.5 h; d. MsCl, Et_3N, DCM, 0 °C - RT, 4 h.

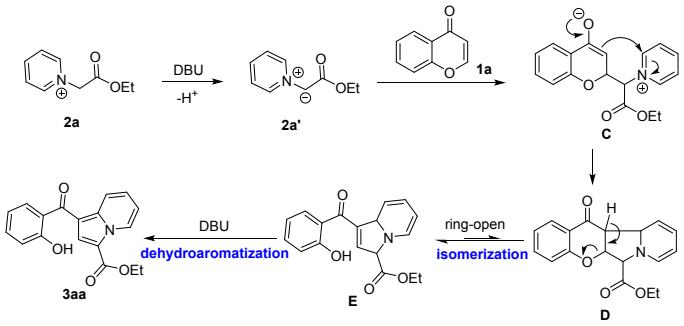
In order to illustrate the reaction pathway, a series of control experiments were conducted. When the free radical scavenger 2,2,6,6-tetramethyl-piperidinyloxyl (TEMPO) was added in the model reaction, the reaction did not be inhibited obviously (Scheme 2a), which precluded the free radical process involved in the reaction. Next, the reaction was carried out under N_2 or O_2. It was observed that the reaction efficiency kept almost consistent (Scheme 2b and c). The result showed that O_2 was not involved in the process of the reaction. However, no reaction occurred in the absence of DBU (Table 1, entry 12), indicating DBU as base played a key role in the dehydrogen process. HRMS experiment was performed to detect the possible intermediate, a Michael addition intermediate was found by LC-HRMS analysis (Scheme 2d).

Scheme 2 control experiments



Basing on the above results and previous reports [18], a proposed mechanism was illustrated in Scheme 3. First, the pyridinum salt **2a** was converted to the corresponding ylide **2a'** in the presence of DBU via the hydrogen-transfer reaction. Subsequently, the regioselective 1,3-dipolar cycloaddition occurred between the electron-deficient C=C bond of **1a** and **2a'**, forming a Michael addition intermediate **D**. Unstable **D** readily was converted into intermediate **E** via the ring-open isomerization. Finally, the desired product 3aa was produced by dehydroaromatization in the presence of DBU [19].

Scheme 3. Plausible reaction mechanism



In conclusion, we have developed a novel method for the synthesis of complex indolizines bearing a phenolic hydroxyl group from various chromones and halogenated pyridinium salts via 1,3-dioplar cycloaddition under the mild conditions. This protocol is compatible with a wide range of functional groups and represents a simple, efficient, and economical method of producing biologically active indolizines derivatives with moderate to good yields. Moreover, the obtained products could be easily functionalized under the suitable conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.****

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Metal-Free Synthesis of Novel Indolizines from Chromones and Pyridinium Salts via 1,3-Dipolar Cycloaddition, Ring-opening and Aromatization

Kai-Kai Dong, Qiang Huang

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- High-functionalization
- 42 examples, up to 83%

1. Metal- free synthesis
2. Wide substrate scope
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4. High-functionaliztion