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Cascade Reaction of Isatins with Heterocyclic Ketene Aminals: Synthesis of Imidazopyrroloquinoline Derivatives

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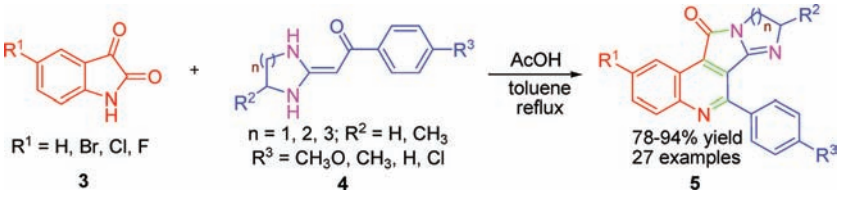
ABSTRACT



A concise and efficient route for the synthesis of highly substituted imidazopyrroloquinoline derivatives by simply refluxing a reaction mixture of different types of isatins and heterocyclic ketene aminals (HKAs) by acetic acid was developed. This method is suitable for combinatorial and parallel syntheses in drug discovery; consequently, a library of highly substituted imidazopyrroloquinoline derivatives was rapidly constructed using the present protocol.

The quinoline derivatives are an important class of heterocyclic pharmaceuticals and bioactive natural products due to their significant and wide-spectrum biological activities. Considerable efforts have been directed toward the construction of quinoline building blocks. These methods include the classic Skraup,[1] Doebner–von Miller,[1b,2] Friedländer,[3] Pfitzinger,[4] Conrad-Limpach,[5] and Combes[2] reactions as well as more recent approaches.[6] Consequently, a number of compounds have been obtained with diverse biological activities. These activities include anticancer[7,8] (TAS-103[9] and 6-aryl-indeno[1,2-*c*]quinoline,[10] Figure 1), antituberculosis agents,[11] antifungal agents,[12]

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anti-inflammatory agents,[13] adenosine receptors,[14] P-selectin agonists,[15] caspase-3 inhibitors,[16] and anti-Alzheimer's drugs,[17] among others.[18] Among these compounds, indenoquinoline derivatives (Figure 1) are the most important compounds, most notably because of their antiproliferative character.[7,9,10] Although there have been many studies on the synthesis of these molecules,[7,19] these methods require multistep syntheses or strict anhydrous conditions.[7,19] Thus, there is a need for the development of concise and effective methods for building up the target compound library.

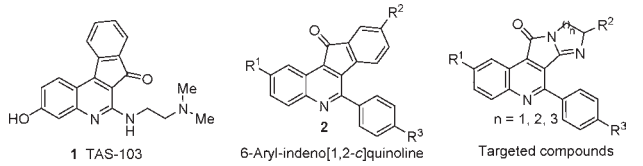


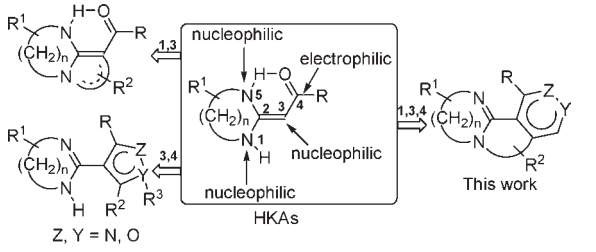
Figure 1. Structures of indenoquinolines derivatives and targeted compounds.

Nowadays, the development of concise and effective one-pot transformations for building up the target compound library is a major change in organic synthesis.[20] A number of strategies have been developed to meet this challenge. In particular, the cascade reaction has received much attention because the ability to undertake more than one synthetic step in the same reaction vessel represents a useful tool for saving time and energy, as well as for reducing the use of organic solvents in the isolation and purification of intermediates.[21] For these reasons, the cascade reaction has been used as a tool for building up the diversity of the compound library.[22]

As a type of versatile synthetic intermediate, heterocyclic ketene aminals (HKAs) are widely used for the synthesis of a variety of heterocyclic and fused heterocyclic compounds,[23,24] including anticancer agents, herbicides, pesticides, antianxious agents, antileishmanial agents and antibacterial and antitherapeutic drugs.[25]

The structure of HKAs can be described as follows (Scheme 1), with the conjugation of electro-donating amino groups and the electron-withdrawing carbonyl group, with a highly polarized double bond (C=C).[26] This leads to the electron density of the α-carbon (C3) being higher than that of the secondary amino groups (N1 and N5). As a result, they can serve as bis-nucleophiles (C3 and N1 as nucleophilic sites) and react with bis-electronphiles to synthesize the fused heterocyclic compounds.[23,24] In addition to this, they can be reacted with 1,3-dipoles to form 1,2,3-triazoles or isoxazoles.[25b,27] However, incorporation of the two nucleophilic sites N1 and C3 and the electronphile site C4 (C=O) through a one-pot protocol via the cascade reaction to form polycyclic frame compounds has not been reported to date (Scheme 1).

Scheme 1. Routes Based on the Cascade Reaction of HKAs through the Three Reaction Sites (N1, C3 and C4) to Give Polycyclic Compounds



To explore the cascade reaction of HKAs through the three reaction sites (N1, C3 and C4), we designed and synthesized the target compounds based on the scaffold of compound **1**. We hypothesized that modifying the indeno ring of **1** by incorporating heteroatoms and the HKA rings (n = 1, 2, 3) could lead to analogs with improved

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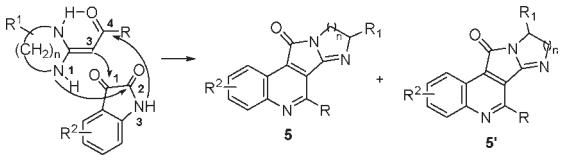
properties such as antiproliferative characteristics and better log *P* values (Scheme 2).

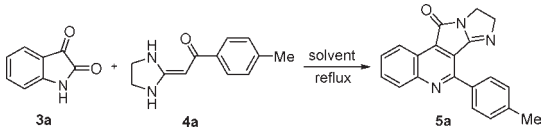
Scheme 2. Routes Based on the Cascade Reaction of HKAs to Produce Imidazopyrroloquinolines



In this communication, we report a novel synthetic method to produce imidazopyrroloquinoline derivatives **5** by refluxing isatins **3** and HKAs **4** catalyzed by acetic acid, forming the target compounds with good to excellent yields (78−94%).

First, we evaluated the cascade reaction of isatins **3** and the HKAs **4**. The mixture, which was composed of a 1.1:1 ratio of **3a** to **4a**, was treated under various conditions (Table 1, entries 1−20). This demonstrated that the reactions could not proceed in some solvents such as acetonitrile, THF or 1,4-dioxane under catalyst-free conditions (Table 1, entries 1, 2 and 4). We obtained the target compound **5a** in the absence of catalysts in toluene with a low yield (52%). The catalyst AcOH promoted the reactions in different solvents (Table 1, entries 5, 9, 13 and 17). The results indicated that the best reaction conditions for the synthesis of imidazopyrroloquinolines were toluene as the solvent and acetic acid as the catalyst under reflux for 4 h with an isolated product with a good yield (78%) (Table 1, entry 13).

Table 1. Optimizing the Reaction Conditions for the Synthesis of **5a**



entry	solvent	catalyst	*t* [°C]	time [h]	yield [%][a]
1	acetonitrile	–	reflux	4	n.r.
2	THF	–	reflux	4	n.r.
3	toluene	–	reflux	4	52
4	dioxane	–	reflux	4	n.r.
5	acetonitrile	AcOH	reflux	4	67
6	acetonitrile	$ZnCl_2$	reflux	4	69
7	acetonitrile	$H_3PW_{14}O_4$	reflux	4	n.r.
8	acetonitrile	TFA	reflux	4	15
9	THF	AcOH	reflux	4	28
10	THF	$ZnCl_2$	reflux	4	n.r.
11	THF	$H_3PW_{14}O_4$	reflux	4	n.r.
12	THF	TFA	reflux	4	5
13	toluene	AcOH	reflux	4	78
14	toluene	$ZnCl_2$	reflux	4	n.r.
15	toluene	$H_3PW_{14}O_4$	reflux	4	n.r.
16	toluene	TFA	reflux	4	45
17	dioxane	AcOH	reflux	4	70
18	dioxane	$ZnCl_2$	reflux	4	12
19	dioxane	$H_3PW_{14}O_4$	reflux	4	n.r.
20	dioxane	TFA	reflux	4	6

[a] Isolated yield based on HKA **4a**. n.r. = no reaction.

Under optimized conditions, other five-member HKAs served as substrates to react with different isatins (**3a**−**3d**). As a result, we obtained polycyclic quinolines (**5a**−**5i**), including a 2,3-dihydropyrrolo[1,2-*a*]imidazol-5-one skeleton, with good yields (78−85%) (Table 2, entries 1−9). To explore the feasibility of substrates, the six-member HKAs were reacted with different isatins (**3a**−**3d**) under the same conditions. The target compounds (**5j**−**5y**), including a 3,4-dihydropyrrolo[1,2-*a*]pyri-midin-6(2*H*)-one skeleton, were formed with excellent yields (82−94%) (Table 2, entries 10−25). We believe that the ring size can influence the yields of the reaction. Consequently, the seven-member HKAs were able to react with isatins **3** in toluene, catalyzed by AcOH, to produce polycyclic quinolines (**5z**−**5a′**) with good yields (Table 2, entries 26−27).

The cascade reaction has very high regional selectivity (Table 2, entries 4−7), and the position of the methyl group of compounds **5d**−**5g** can be tested by ^{15}N−H HMBC correlation data of compound **5d** (See Supporting Information). As a result, we only obtained the target product **5** in the form of compounds **5d**−**5g** (Scheme 2) (Table 2, entries 4−7).

To verify the structure of the imidazopyrroloquinoline derivatives, **5l** was selected as a representative compound and characterized by X-ray crystallography (CCDC 829402, Figure 2).

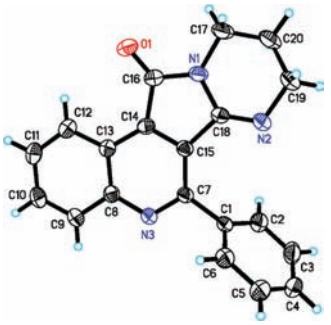
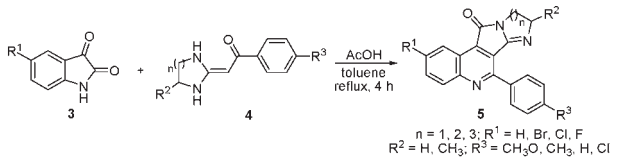


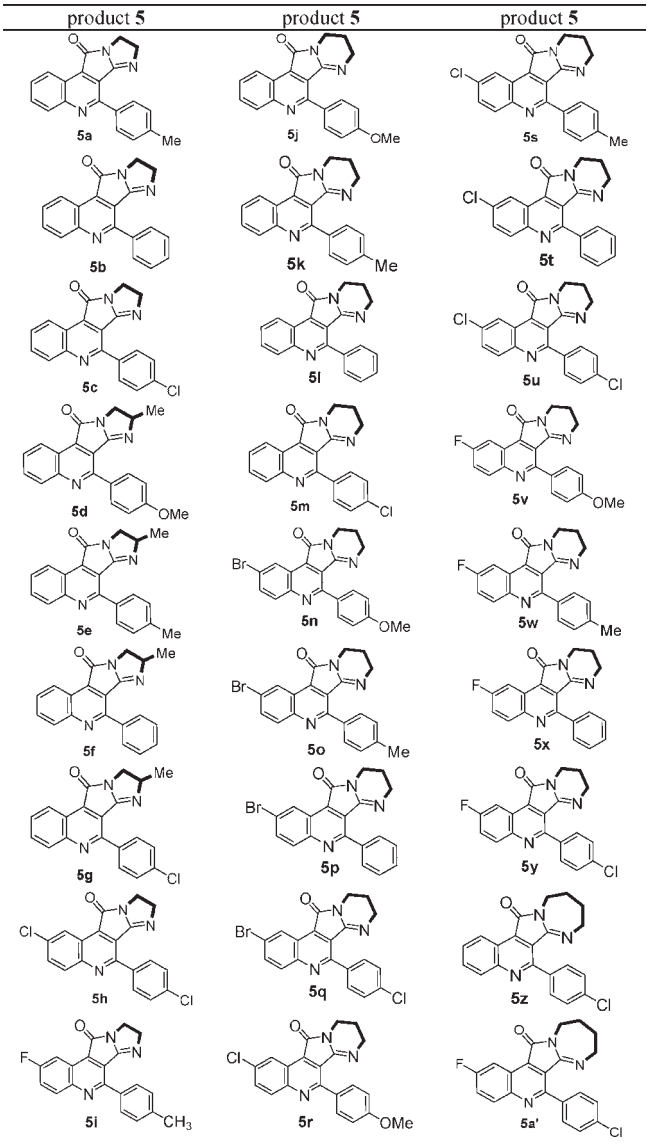
Figure 2. Molecular structure of **5l**. Ellipsoids set at 30% probability.

A proposed mechanism of the acetic acid-catalyzed cascade reaction is depicted in Scheme 3. First, the α-*C* of the ketene *N*,*N*-acetals **4** added to the carbonyl group of compound **3** to afford **6**. The intermediate **6** was followed by imine-enamine tautomerization to produce **7**. Intermediate **7** seized one proton of AcOH to form **8**. Intermediate **8**, through intramolecular cyclization, dehydration,

Table 2. Preparation of Imidazopyrroloquinoline Derivative **5**[a]



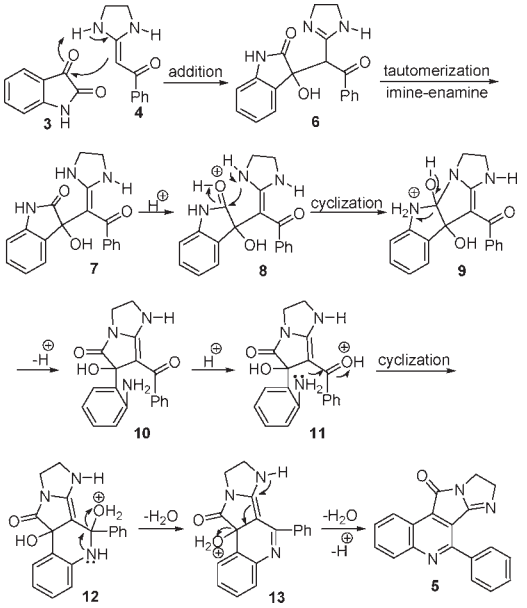
entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
product	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	5m	5n	5o	5p	5q	5r	5s	5t	5u	5v	5w	5x	5y	5z	5a'
yield (%)[b]	78	81	79	84	85	80	83	82	84	85	87	91	92	82	85	86	83	87	86	88	90	89	91	93	94	85	89



[a] Reaction conditions: Isatin **3** (2.2 mmol), HKA **4** (2 mmol), acetic acid (0.4 mL) and toluene (15 mL), at refluxed temperature, and reaction time of 4 h. [b] Isolated yield based on HKA **4.**

and ring-opening reactions formed **10**. Protonation of compound **10** produced **11**. Subsequently, the NH_2 attacked the intramolecular carbonyl group to form intermediate **12**, which, through losing H_2O and proton transfer, produced **13**. Finally, **13** lost a proton and a molecule of H_2O to result in the target product **5**.

Scheme 3. Proposed Mechanism of the Cascade Reaction



In conclusion, we developed a procedure for the simple synthesis of a variety of potential, biologically active imidazopyrroloquinoline based on the cascade reaction. Using this method, a molecularly diverse imidazopyrroloquinoline derivatives library was rapidly constructed with good yields by simply refluxing a reaction mixture of isatins and HKAs in toluene, catalyzed by AcOH.

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Supporting Information Available. Detailed experimental procedures and spectral data for all new compounds and X-ray structural data of **5l**. This material is available free of charge via the Internet at http://pubs.acs.org.