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An Efficient Synthesis of Pyrrolo[2,3,4-*kl*]acridin-1-one Derivatives Catalyzed by L-Proline

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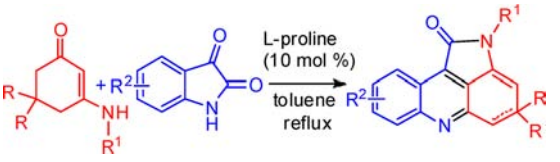
ABSTRACT



An efficient domino approach for the synthesis of novel pyrrolo[2,3,4-*kl*]acridin-1-one derivatives has been established. This reaction represents the first facile conversion of an isatin to a pyrrolo[2,3,4-*kl*]acridin-1-one via a C–N bond cleavage reaction without the need for a multistep reaction process.

Functionalized heterocyclic building blocks are of great importance to both medicinal and organic chemists, and their synthesis continues to represent a challenge from both an academic and industrial perspective.[1] The acridine derivatives are an important class of heterocyclic pharmaceuticals and bioactive natural products because of their significant and wide spectrum of biological activities. Acridine derivatives display a broad range of biological properties including antiparasitic,[2] antibacterial,[3] and antitumor activity.[4]

In 1990, three novel pentacyclic alkaloids, Plakinidines A, B, and C (Figure 1), were isolated from a *Plakortis* sponge.[5] Plakinidines A and B exhibited in vitro activity against *Nippostrongylus brastiliensis*, and Plakinidine A showed activity against reverse transcriptase. These alkaloids possess a unique heterocyclic pyrrolo[2,3,4-*kl*]acridine parent ring system (Figure 1). Although there have been many studies on the synthesis of these molecules,[6,7] these methods require multistep syntheses. Thus, there is a need for the development of concise and efficient methods for the construction of this heterocyclic skeleton and its analogues.

Nowadays, the development of concise and effective one-pot transformations for the construction of target compound libraries represents a major challenge in organic synthesis.[8] A number of strategies have been developed to overcome this

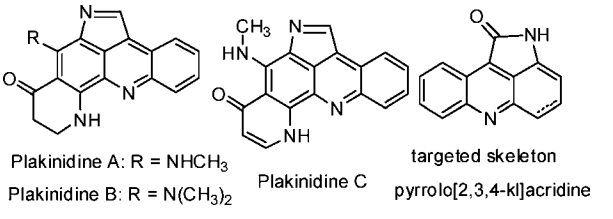


Figure 1. Structures of pyrrolo[2,3,4-*kl*]acridine derivatives and the targeted skeleton.

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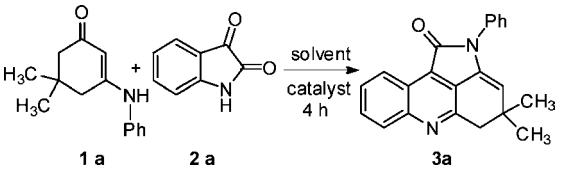
challenge, and the domino reaction in particular has received considerable attention. Reactions of this type offer a wide range of possibilities for the efficient construction of highly complex molecules in a single process consisting of several steps, thus avoiding the requirement for complicated purification stages and therefore allowing for considerable savings in the use of both solvents and reagents. For these reasons, the domino reaction has been used as a tool for delivering high levels of diversity in targeted compound libraries.[9]

Small organic molecules such as the cinchona alkaloids, L-proline, and their derivatives are readily available commercial catalysts and have been used in various transformations with excellent yields.[10] For example, L-proline has been used in enamine-based direct catalytic asymmetric Aldol,[11] Mannich,[12] Michael,[13] Diels–Alder,[14] α-amination,[15] and Knoevenagel type reactions,[16] as well as an unsymmetric Biginelli reaction.[17] Recently, L-proline and its derivatives have been used in domino reactions;[18] we also reported the synthesis of a series of heterocycles using domino reactions catalyzed by L-proline.[19] In the current paper, we report a novel domino reaction for the synthesis of pyrrolo[2,3,4-*kl*]acridine derivatives using L-proline as the catalyst. The attractive features of the current domino reaction include the novel construction of the pyrrolo[2,3,4-*kl*]acridine skeleton and the direct C–N bond cleavage of an isatin, both of which were easily achieved without the need for multistep operations.

Table 1. Optimizing the Reaction Conditions for the Synthesis of **3a**



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

entry	solvent	catalyst (mol %)	*t* (°C)	yield[a] (%)
1	ethanol	—	reflux	trace
2	ethanol	L-proline (10)	reflux	23
3	acetonitrile	L-proline (10)	reflux	22
4	chloroform	L-proline (10)	reflux	52
5	THF	L-proline (10)	reflux	33
6	1,4-dioxane	L-proline (10)	reflux	20
7	DMF	L-proline (10)	80	40
8	water	L-proline (10)	80	trace
9	toluene	L-proline (10)	80	82
10	toluene	piperidine (10)	80	57
11	toluene	phenylalanine (10)	80	49
12	toluene	L-proline (5)	80	80
13	toluene	L-proline (15)	80	74
14	toluene	L-proline (20)	80	70
15	toluene	L-proline (10)	40	11
16	toluene	L-proline (10)	60	20
17	toluene	L-proline (10)	100	84
18	toluene	L-proline (10)	reflux	90

[a] Yield was determined by HPLC-MS.

We initially evaluated the domino reaction of the enaminone **1a**, which was derived from the reaction of aniline with 5,5-dimethylcyclohexane-1,3-dione, and isatin **2a**. The reaction mixture, which was composed of a 1:1 mixture of **1a** to **2a**, was tested under a variety of different conditions. The results are summarized in Table 1.

The optimization process revealed that the reaction could not proceed in ethanol under catalyst-free conditions (Table 1, entry 1). Pleasingly, when the reaction was conducted in the presence of L-proline (10 mol %) in ethanol, the target compound **3a** was obtained in 23% yield (Table 1, entry 2). To improve the yield, different solvents were evaluated. The results indicated that toluene provided much better results than ethanol, acetonitrile, chloroform, tetrahydrofuran (THF), 1,4-dioxane, *N,N*-dimethylformamide (DMF), and water (Table 1, entries 2–9). Several other organocatalysts were also evaluated for their catalytic efficiency in the current reaction. In all cases, 10 mol % of the catalyst was used and the reaction was carried out in toluene at 80 °C. The results revealed that L-proline provided a superior catalytic effect to piperidine and phenylalanine (Table 1, entries 10–11). These results indicated that the presence of both secondary nitrogen and carboxylic acid groups may be essential for better catalytic activity.

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Having identified L-proline as the best organocatalyst for the transformation, we proceeded to evaluate the amount of L-proline required for this reaction. The results revealed that increasing the amount of L-proline from 5 to 10 mol % led to an increase in the yield from 80% to 82% (Table 1, entries 12 and 9). The use of 10 mol % of L-proline in toluene was effective in pushing this reaction forward, and the addition of larger amounts of the catalyst did not improve the yields. To identify the optimum reaction temperature, the reaction was carried out with 10 mol % L-proline at 40, 60, 80, and 100 °C and reflux temperature, providing the product **3a** in yields of 11%, 20%, 82%, 84%, and 90% (Table 1, entries 15−18 and 9), respectively. Thus, the optimum conditions required the use of 10 mol % L-proline in a toluene solvent at reflux.

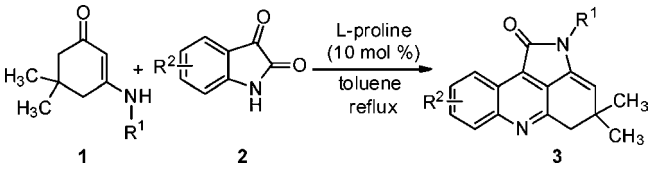
With the optimal conditions in hand (toluene, reflux, 10 mol % L-proline), we proceeded to investigate the substrate scope of the transformation. As shown in Table 2, methyl, bromo, chloro, and fluoro substituents on the isatin ring, and *n*-butyl, naphthalene-1-yl, and phenyl groups bearing either electron-withdrawing or electron-donating groups on the enaminone ring, were well tolerated under the reaction conditions, leading to the final products in satisfactory yields (up to 93%). Under the standard conditions, 4-chloroisatin (Table 2, **3y**) remained intact and only the starting materials were recovered. This failure to react was attributed to the effect of steric hindrance upon the reactivity of the carbonyl group.

To expand the scope of the current method, *N*-substituted 3-aminocyclohex-2-enone (**4**) was examined as a replacement for the *N*-substituted 3-amino-5,5-dimethylcyclohex-2-enone (**1**). Surprisingly, the desired 4,5-dihydropyrrolo[2,3,4-*kl*]acridine derivatives **3** were not obtained under the optimized conditions and the corresponding oxidation products pyrrolo[2,3,4-*kl*]acridine derivatives **5** were obtained instead in good yields (Table 3). The reaction pathways could therefore been controlled by varying the enaminones with a different substituted pattern to give a series of novel 4,5-dihydropyrrolo[2,3,4-*kl*]acridin-1-ones and pyrrolo[2,3,4-*kl*]acridin-1-ones selectively.

The structures of the products were identified from their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra. The structures of compounds **3b** and **5m** were further confirmed by X-ray analysis (Figures 2 and 3).

In accordance with reports from the literature,[20] we have proposed a mechanism for the current L-proline-catalyzed domino reaction (Scheme 1). The initial nucleophilic reaction of L-proline on the isatin affords intermediate **6**, which is subsequently attacked by enaminone to give intermediate **7**. Intermediate **7** undergoes imine-enamine tautomerization to give intermediate **8**, which subsequently reacts in an intramolecular cyclization and ring-opening sequence to give compound **10**. Intramolecular

Table 2. Preparation of Compounds **3**

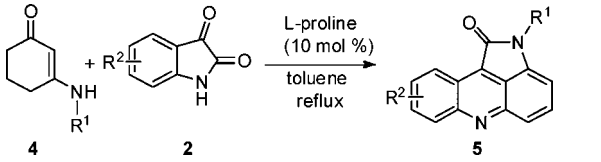


1 2 3

product	R^1	R^2	time (h)	yield[a] (%)
3a	C_6H_5	H	2	90
3b	C_6H_5	5-F	2	92
3c	C_6H_5	6-Cl	2	87
3d	C_6H_5	5-Br	1.5	89
3e	4-BrC_6H_4	5-Br	2	93
3f	4-BrC_6H_4	6-Br	2	82
3g	4-BrC_6H_4	H	2.5	90
3h	4-BrC_6H_4	6-Cl	2	87
3i	4-BrC_6H_4	5-CH_3	2	89
3j	4-BrC_6H_4	5-F	2	90
3k	4-$CH_3C_6H_4$	5-Cl	3	84
3l	4-$CH_3C_6H_4$	6-Br	2	91
3m	4-$CH_3C_6H_4$	5-Br	3	90
3n	4-$CH_3C_6H_4$	H	2.5	85
3o	4-$NO_2C_6H_4$	6-Cl	4.5	80
3p	4-$NO_2C_6H_4$	5-Cl	4.5	82
3q	4-$NO_2C_6H_4$	5-F	4	78
3r	4-$NO_2C_6H_4$	H	4	78
3s	3-Cl-4-FC_6H_3	5-Br	2.5	92
3t	3-Cl-4-FC_6H_3	H	2.5	90
3u	3-Cl-4-FC_6H_3	5-Cl	2.5	80
3v	*n*-C_4H_9	H	2.5	90
3w	*n*-C_4H_9	6-Br	2	90
3x	naphthalene-1-yl	5-Br	3	90
3y	C_6H_5	4-Cl	4.5	NR

[a] Yield was isolated yield.

Table 3. Preparation of Compounds **5**



4 2 5

product	R^1	R^2	time (h)	yield[a] (%)
5a	2,4-$(CH_3)_2C_6H_3$	5-F	2	80
5b	2,4-$(CH_3)_2C_6H_3$	H	2	84
5c	2,4-$(CH_3)_2C_6H_3$	6-Cl	2	78
5d	4-$CH_3OC_6H_4$	7-CF_3	2	78
5e	*n*-C_4H_9	5-CH_3	1.5	80
5f	4-$NO_2C_6H_4$	H	3	60
5g	C_6H_5	5-Cl	2.5	82
5h	C_6H_5	5-Br	2.5	79
5i	C_6H_5	H	2.5	81
5j	4-$CH_3C_6H_4$	5-Cl	2	80
5k	naphthalene-1-yl	H	1.5	82
5l	naphthalene-1-yl	5-Br	1.5	76
5m	2-ClC_6H_4	5-F	2	76

[a] Yield was isolated yield.

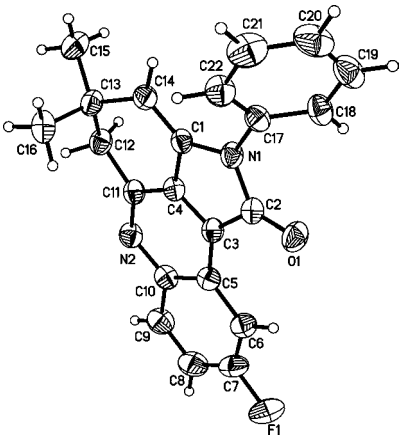


Figure 2. Molecular structure of compound **3b**.

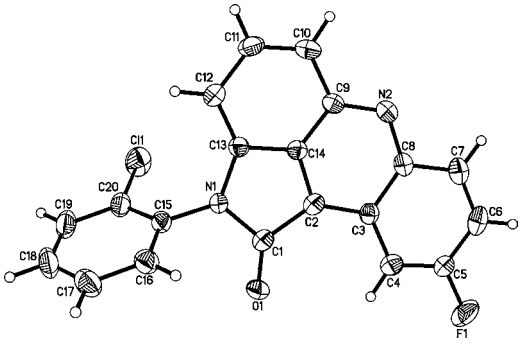


Figure 3. Molecular structure of compound **5m**.

imine formation then leads to the formation of intermediate **12**, which loses the molecule L-proline to give the desired product **3**. When R is H in compound **3**, the product **3** would be oxidized by oxygen in the air to give product **5**.

In conclusion, we have developed a procedure for the facile synthesis of a variety of potentially biologically active pyrrolo[2,3,4-*kl*]acridines based on a novel domino reaction. Using this method, a diverse collection of pyrrolo-[2,3,4-*kl*]acridine derivatives was rapidly constructed with excellent yields by simply refluxing a mixture of isatins and enaminones in toluene in the presence of an L-proline catalyst.

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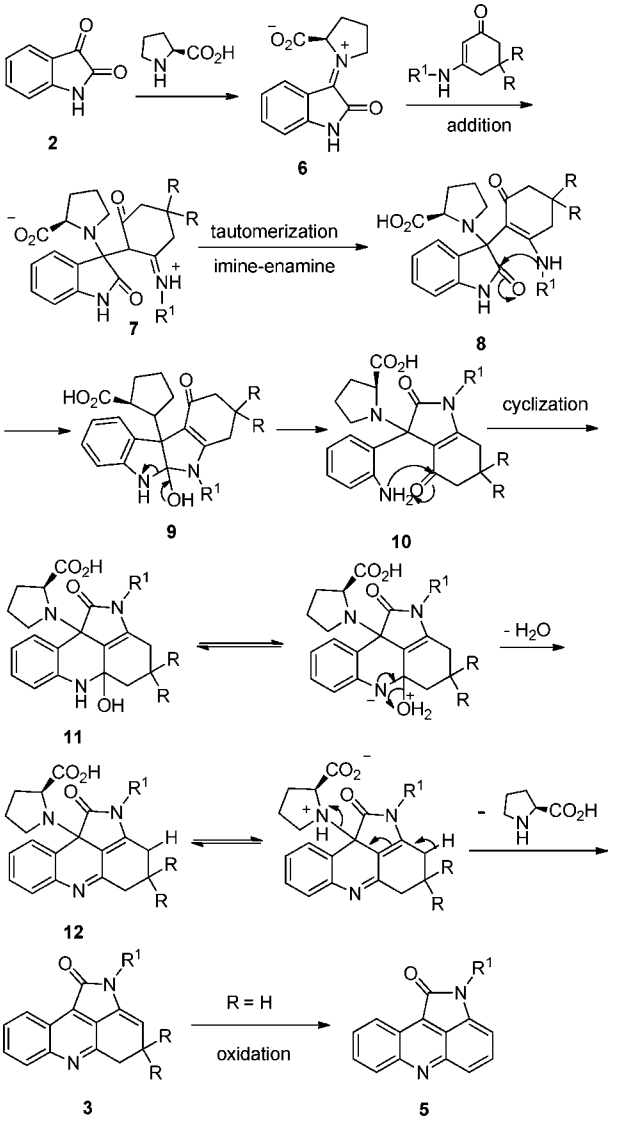
Scheme 1. Proposed Mechanism of the Domino Reaction



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Supporting Information Available. Experimental procedures, spectroscopic data for all compounds **3** and **5**, and crystal data for compounds **3b** and **5m**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.