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L-Proline catalyzed facile and efficient synthesis of functionalized indol-3-yl pyran derivatives by multi-component reactions

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Abstract A simple and green synthetic method for preparation of functionalized indol-3-yl pyran derivatives was developed. The reactions were carried out by one-pot three-component synthesis of 3-cyanoacetyl indoles, malononitrile/cyanoacetate and various aldehydes/isatins/acenaphthenequinone in the presence of catalytic amount of L-proline. The advantages of this method included straightforward processing, excellent yields, broad substrate scope and environmental friendliness.

Keywords Indol-3-yl pyran · L-Proline catalyst · Multi-component reactions

Introduction

Multi-component reactions (MCRs) has been developed as one of the most powerful tools for the synthesis of structurally complex, biologically active and drug-like compounds [1–3], for their convergence, productivity, easy execution, excellent yields and atom economy characters [4–7].

Jing Wang, Hongzhi Liu and Ren Wen have contributed equally to this work.

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Pyran frame is an example of the 'privileged scaffolds' existing in numerous natural and synthetic products [8–15]. Compounds containing the pyran ring system exhibit important biological or pharmacological activities as hypertensive agents [16], anti-coagulants [17], anticancer agents [18, 19], inhibitors of matrix metalloproteinases [20] and analgesic agents [21]. Another example of the 'privileged scaffolds' is indole framework [22–24]. Among indole derivatives, the 3-substituted indole nucleus are prevalent in numerous natural products which show prominent anticancer, anti-tumour, anti-inflammatory, hypoglycemic, analgesic and anti-pyretic activities [25–30]. Some biologically active 3-substituted indole representatives [31–33] are shown in Fig. 1.

Although a number of methods for the construction of indol-3-yl pyran derivatives have been reported, many of them suffer from some drawbacks, for example, the use of metal catalyst $InCl_3$ [34], relative toxic organic catalyst Et_3N [35] or piperidine under ultrasonic irradiation [36]. Thus, it is still necessary to develop an efficient and relatively low toxic method to construct this type of meaningful heterocyclic compounds.

In recent years, L-proline catalyzed organic reaction has drawn much attentions because of its commercially available, ease of handing and excellent solubility in water and organic solvents characters [37–41]. L-Proline has been proved to be an efficient catalyst in different organic reactions such as asymmetric aldol condensations [42, 43], Mannich reactions [44, 45], Diels–Alder reactions [46], Michael additions [47] and many multicomponent reactions [48–52].

As continuation of our interest in developing new methodologies for the preparation of highly functionalized heterocyclic compounds [53–56], as well as the research for L-proline catalyzed reactions [57], herein we report a simple and

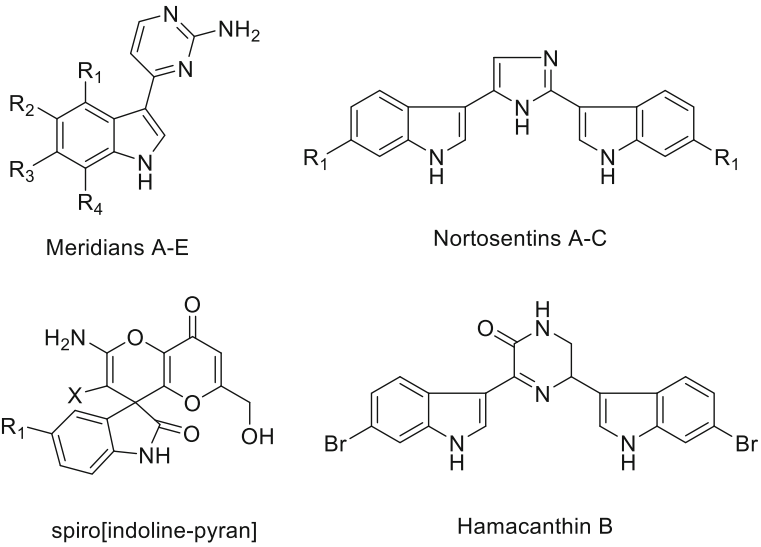
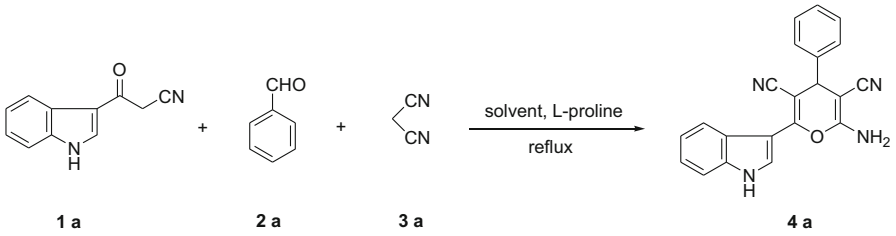


Fig. 1 Representative structure of biologically 3-substituted indoles

efficient protocol for the synthesis of 3-pyranyl indole derivatives catalyzed by L-proline.

Results and discussion

Initially, the three-component reaction of 3-cyanoacetyl indole **1** (1), benzaldehyde **2** (1), and malononitrile **3** (1) (Scheme 1) was studied as a model reaction. As shown in Table 1, different solvents (entries 1–6) were employed to find the optimal



Scheme 1 The model reaction

Table 1 Optimization of reaction conditions for the synthesis of **4** (1, 1, 1)

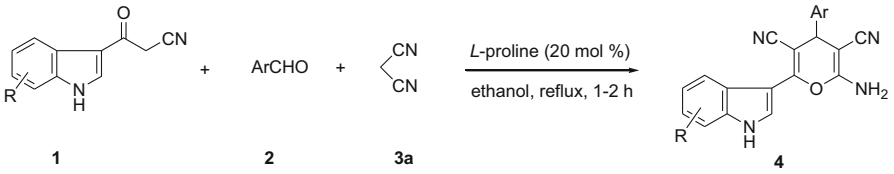
Entry	Solvent	Catalyst (mol%)	Temp (°C)	Yield[a,b] (%)
1	DMF	L-Proline (20)	Reflux	61
2	Dichloromethane	L-Proline (20)	Reflux	40
3	Acetonitrile	L-Proline (20)	Reflux	63
4	Water	L-Proline (20)	Reflux	20
5	Methanol	L-Proline (20)	Reflux	82
6	Ethanol	L-Proline (20)	Reflux	88
7	Ethanol	None	Reflux	Trace
8	Ethanol	L-Proline (5)	Reflux	52
9	Ethanol	L-Proline (10)	Reflux	76
10	Ethanol	L-Proline (50)	Reflux	88
11	Ethanol	L-Proline (20)	60	72
12	Ethanol	L-Proline (20)	40	58
13	Ethanol	L-Proline (50)	20	35
14	Ethanol	Piperidine(20)	Reflux	80
15	Ethanol	Et_3N(20)	Reflux	83
16	Ethanol	$InCl_3$(20)	Reflux	87 [34]
17	Ethanol	Glycine	Reflux	43
18	Ethanol	Alanine	Reflux	38
19	Ethanol	Sarcosine	Reflux	33

[a] Isolated yields

[b] All the reactions were carried out for 1 h

reaction media. The results indicated that ethanol was found to be the ideal solvent for this domino reaction which afforded maximum yield (entry 6). We also evaluated the amount of L-proline required for this reaction. It was shown that 20 mol% L-proline was necessary to complete the reaction and provided the highest yield (88%); while 5 or 10 mol% L-proline was not enough (52 or 76% yield respectively), and 50 mol% L-proline did not lead to much more increase in terms of the reaction yield (entries 6–10). Moreover, the reaction was carried out under different temperatures, as showed in Table 1, with the temperature dropping, the yields of products were decreased (entries 11–13).

Compared to some reported catalysts, such as $InCl_3$ [34], Et_3N [35] and piperidine [36], although the model reaction could be catalyzed under the optimal condition and good yields (80–87%) were obtained (Table 1, entries 14–16), L-proline employed in this work manifested the advantages of higher yield (88%),



Scheme 2 The synthesis of 3-pyranyl indole derivatives **4** (entries 1–17)

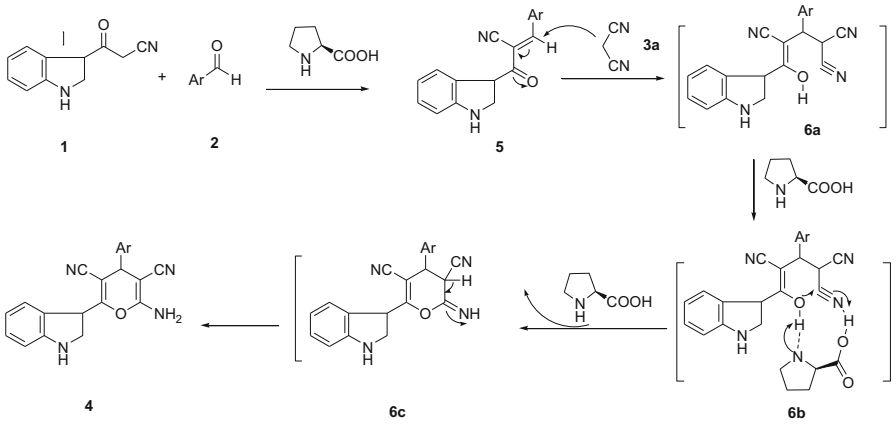
Table 2 The synthesis of 3-pyranyl indole derivatives **4**

Entry	Compound		Product	Time (h)	Yield[a] (%)
	1(R)	2(Ar)			
1	H	C_6H_5	**4a**	1.0	88
2	H	4-Cl-C_6H_4	**4b**	1.0	80
3	H	2-Cl-C_6H_4	**4c**	1.5	77
4	H	2-Br-C_6H_4	**4d**	1.5	75
5	H	2,4-$(Cl)_2$-C_6H_3	**4e**	2.0	79
6	H	3-NO_2-C_6H_4	**4f**	1.5	70
7	H	4-CH_3-C_6H_4	**4g**	1.0	85
8	H	4-OCH_3-C_6H_4	**4h**	1.5	84
9	H	2-OCH_3-C_6H_4	**4i**	1.5	74
10	H	2,3-$(OCH_3)_2$-C_6H_3	**4j**	2.0	71
11	H	2-Naphthyl	**4k**	1.5	77
12	5-Br	4-Cl-C_6H_4	**4l**	1.0	79
13	5-Br	4-OCH_3-C_6H_4	**4m**	1.5	77
14	2-CH_3	4-Cl-C_6H_4	**4n**	1.0	78
15	2-CH_3	4-OCH_3-C_6H_4	**4o**	1.5	73
16	1-CH_3-2-C_6H_5	4-Cl-C_6H_4	**4p**	1.5	74
17	1-CH_3-2-C_6H_5	4-OCH_3-C_6H_4	**4q**	2.0	71

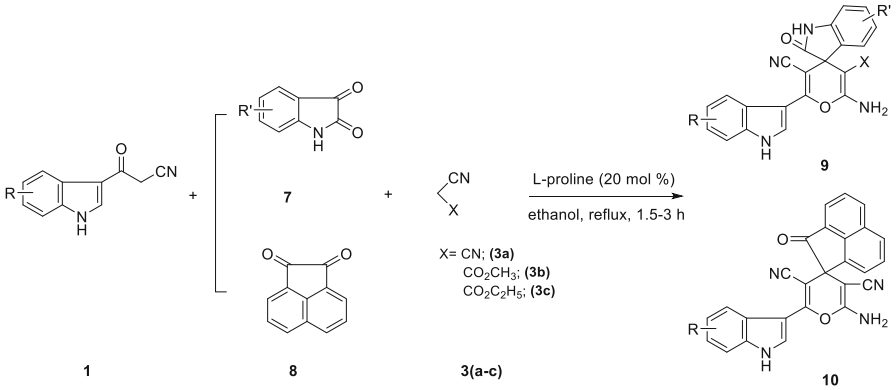
[a] Isolated yield

easy handling and green procedure characters. Furthermore, some other amino acids, for example, glycine, alanine and sarcosine were also tested as a catalyst in the experiment, the reaction performed to some extent with lower to moderate yields (Table 1, entries 17–19).

Under the optimal conditions, the generality of the reaction was investigated with 3-cyanoacetyl indoles **1**, various aldehydes **2** and malononitrile **3a** in ethanol with catalyst L-proline (20 mol%) (Scheme 2). The results were summarized in Table 2 (entries 1–11). It was shown that, the method was not only suitable to aromatic aldehydes with electron-withdrawing groups (entries 2–6), but also to the aromatic aldehydes with electron-donating groups (entries 7–10), as well as 2-naphthaldehyde (entry 11). Moreover, when different substituted 3-cyanoacetyl indoles **1** were employed in the reaction under the optimized reaction conditions, the desired 3-pyranyl indole derivatives **4** (entries 12–17) were also obtained with satisfied yields.



Scheme 3 Proposed mechanism for the formation of compounds **4**



Scheme 4 The synthesis of spiro-pyran derivatives **8** and **9** (entries 18–27)

Based on the above results, a plausible mechanism for the formation of compound **4** was proposed (Scheme 3). It was suggested that L-proline may catalyze the Knoevenage condensation reaction of 3-cyanoacetyl indole **1** and aldehydes **2** to

Table 3 The synthesis of spiro-3-pyranyl indole derivatives **5** and **6**

Entry	Compound				Product	Time (h)	Yield[a] (%)
	1(−*R*)	7(−*R*′)	8	3(−*X*)			
18	H	H	–	CN	**9a**	2	85
19	H	5-F	–	CN	**9b**	2	84
20	H	5-Br	–	CN	**9c**	2	79
21	H	5-CH_3	–	CN	**9d**	2	83
22	H	H	–	CO_2Me	**9e**	1.5	76
23	H	H	–	CO_2Et	**9f**	1.5	79
24	H	–	8	CN	**10a**	3	75
25	5-Br	–	8	CN	**10b**	2	83
26	2-CH_3	–	8	CN	**10c**	3	71
27	1-CH_3-2-C_6H_5	–	8	CN	**10d**	3	75

[a] Isolated yield

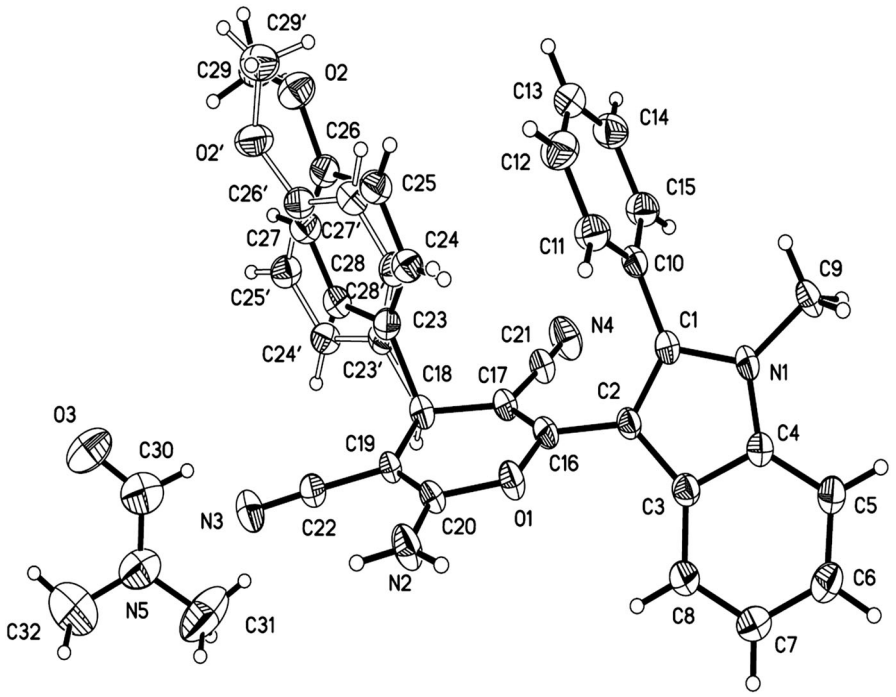


Fig. 2 The crystal structure of **4q** with DMF solvent molecule

form the intermediate **5** which could be observed during the experiment procedure. Then, the Michael addition was taken place between **5** and malononitrile **3a** to give the intermediate **6a**. Finally, with the catalysis of L-proline, the O-atom of the intermediate **6a** attacked the nitrile group, which followed by intramolecular cyclization and a subsequent H-atom shift, leaded to the final product **4**.

To further explore the potential of this protocol for diverse heterocycle synthesis, we replaced aldehydes and malononitrile by isatins **7**/acenaphthenequinone **8** and cyanoacetate **3** (2–3), respectively (Scheme 4). The corresponding spiro-3-pyranyl derivatives **9** and **10** were synthesized smoothly, and the results are summarized in Table 3 (entries 18–27). As illustrated in Table 3, this method is not only suitable to different substituted isatins, but also applicable to acenaphthenequinone. Moreover, the reaction could proceed smoothly when the malononitrile was replaced by cyanoacetate.

All the products were characterized by melting points, IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral determination. Furthermore, the structure of **4q** was established by X-ray crystallographic analysis (Fig. 2). The detailed experimental procedure and characterization data can be found in the supplementary file in the online version.

Conclusion

In conclusion, we have developed an efficient and relatively low toxic protocol for the synthesis of 3-pyranyl indole derivatives via the three-component reaction of 3-cyanoacetyl indoles, aldehydes/isatins/acenaphthenequinone and malononitrile/cyanoacetate in the presence of catalytic amount of L-proline (20 mol%). In view of the additive effect that incorporating two biologically potential moieties into a single molecule may enhance the biological activity of the compounds, further biomedical screening work is in progress in our laboratories.

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