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Original article

A regioselective synthesis of pentacyclic compounds containing coumarin, pyrrole, indene without catalysts under microwave irradiation

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ABSTRACT

A concise and efficient approach was developed for the synthesis of pentacyclic compounds containing coumarin, pyrrole, indene in a regioselective manner in good yields *via* the reactions of *N*-substituted 4-aminocoumarin compounds and ninhydrin using microwave irradiation. No catalysts are required in our protocol.

1. Introduction

Coumarin derivatives are regarded as a structurally important class of naturally occurring common compounds and exhibiting a wide range of biological and pharmacological activities [1]. The chromeno[3,4-*b*]pyrrol-4(3*H*)-one scaffold defines the structural core of lamellarin D and ningalin B, which exhibit potent pharmacological properties including antitumour activity, HIV-1 integrase inhibition, multidrug resistance (MDR) reversal and anadlgesic activity [2]. This type of core structure is one of the most important precursors for the antibiotic martinelline, often found in novel drug candidates [3]. Microwave heating has certain benefits compared with conventional heating, such as reaction rate acceleration, lower energy usage and formation of cleaner products, *i.e.*, fewer impurities, consequently microwave-assisted organic synthesis has received a widespread attention [4]. In the past several years, our group and others have developed various protocols that can easily provide access to multifunctionalized chromeno[4,3-*b*]pyrrol-4(1*H*)-one derivatives from readily available starting materials of chemical and pharmaceutical interest [5]. For example, Wang and his co-workers have developed a new protocol for the synthesis of chromeno[4,3-*b*]pyrrol-4(1*H*)-ones by Pd(II)-catalyzed oxidative annulation of 4-aminocoumarin with internal alkynes [6].

Polycyclic compounds with indeno-moieties appropriately substituted on the pyrrolidine ring are an important class of heterocycles, some of which exhibit potent pharmacological properties [7]. In addition, appropriately substituted indenopyrrolidines have been shown to be potent inhibitors of angiotensin converting enzyme (ACE) [8] and evaluated as antagonists of the NMDA receptor [9].

The pharmacologically and biologically importance of chromeno[4,3-*b*]pyrrol-4(1*H*)-ones and appropriately substituted indenopyrrolidines has stimulated the construction of pentacyclic compounds containing coumarin, pyrrole, indene derivatives and led us to generate a new set of dihydroxy chromenoindeno[2,1-*d*]pyrrol analogs. Furthermore, to the best of our knowledge, only one reference exists concerning dihydroxy chromenoindeno[2,1-*d*]pyrrol-ones synthesis. Recently, Pradhan reported on a metallic catalyst, tin oxide (SnO_2) quantum dot (QD), and catalytic protocol for the synthesis of 6*b*,11*b*-dihydroxy-6*b*,7,11*b*,12-tetrahydro-6*H*-chromeno[4,3-*b*]indeno[2,1-*d*]pyrrol-6-ones [10]. We report here the synthesis of 6*b*,11*b*-dihydroxy-12-substituted-6*b*,7,11*b*,12-tetrahydro-6*H*-chromeno-[4,3-*b*]indeno[2,1-*d*]pyrrol-6-ones by a regioselective method with good yields *via* the reactions of *N*-substituted 4-aminocoumarin compounds and ninhydrin without any catalysts utilizing microwave heating.

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2. Experimental

Melting points were determined using a Büchi B-540 capillary melting point apparatus. The Microwave reactor was CEM Discover 908010 with IR-monitored temperature control. Recorded ^{1}H NMR and ^{13}C NMR were obtained on a Varian instrument at 400 and 100 MHz, respectively, with TMS as the internal standard. Mass spectra were measured with Thermo Finnigan LCQ-Advantage instrument, and high resolution mass spectral (HRMS) data were acquired on a Bruker micrOTOF-Q II instrument using ESI techniques.

2.1. General procedure for the preparation of 4-(n-butylamino)-2H-chromen-2-one

A mixture of 4-hydroxycoumarin (0.01 mol) and *n*-butylamine (0.02 mol) was stirred for 6 h in 50 mL of ethoxyethanol at reflux. The solvent was then evaporated under vacuum and the crude product was rinsed with diethyl ether to obtain pure 4-(*n*-butylamino)-2*H*-chromen-2-one.

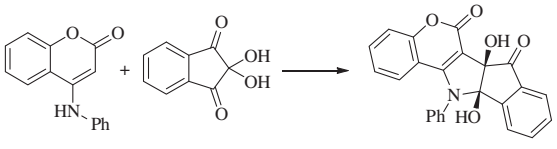
2.2. General procedure for the preparation of 4-(phenylamino)-2H-chromen-2-one

A mixture of 4-hydroxycoumarin (0.01 mol) and aniline (0.05 mol) was stirred at 185 °C for 45 min. The resulting mixture was dissolved in methanol (20 mL) and the solution treated with 0.1 molar aqueous sodium hydroxide (40 mL) under stirring. After 30 min, the resulting precipitate was collected and recrystallized from ethanol to obtain pure 4-(phenylamino)-2*H*-chromen-2-one.

2.3. General procedure for the preparation of dihydrochromenoindeno [1,2-b]pyrroles

Substituted 4-aminocoumarin (**1**) (1 mmol), ninhydrin (**2**) (1 mmol), and toluene (7 mL) were introduced into a 10 mL initiator microwave reaction vial. Subsequently, the reaction vial was closed, stirred for 15 s, then the reaction mixture was stirred at 110 °C for 45 mins under microwave irradiation using a CEM Discover microwave reactor The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to r.t. The crude product was collected by filtration. The pure product was obtained by recrystallization from ethanol.

Table 1
Optimization of the reaction conditions.[a]

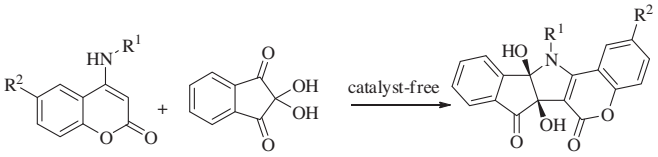


1a **2** **3a**

Entry	Solvent	Catalyst	Loading (mol%)	Temp. (°C)	Time (min)	Yield (%)[b]
1	MeOH	AcOH	10	60	90	trace
2	EtOH	AcOH	10	78	90	30
3	MeCN	AcOH	10	80	90	35
4	Toluene	AcOH	10	110	45	90
5	Glycol	AcOH	10	170	60	40
6	Toluene	*p*-TSA	10	110	70	60
7	Toluene	$KHSO_4$	10	110	50	80
8	Toluene	AcOH	20	110	55	88
9	Toluene	AcOH	40	110	60	90
10	Toluene	none	0	110	45	90

[a] All the reactions were performed with **1a** (1 mmol), **2** (1 mmol), and solvent (7 mL).
[b] Isolated yields based on **1a**.

Table 2
Synthesis of various substituted dihydrochromenoindeno [1,2-*b*]pyrroles.[a]



1 **2** **3**

Entry	R^1	R^2	Time (min)	Products	Yield (%)[b]
1	$-C_6H_5$	H	45	**3a**	85
2	$4\text{-}FC_6H_4$	H	50	**3b**	73
3	$4\text{-}ClC_6H_4$	H	45	**3c**	78
4	$4\text{-}BrC_6H_4$	H	48	**3d**	78
5	$2\text{-}ClC_6H_4$	H	48	**3e**	80
6	$2\text{-}CH_3CO_2C_6H_4$	H	50	**3f**	75
7	$2,4\text{-}diClC_6H_3$	H	55	**3g**	70
8	$2\text{-}MeC_6H_4$	H	40	**3h**	92
9	$2\text{-}C_2H_5C_6H_4$	H	40	**3i**	90
10	$2\text{-}MeOC_6H_4$	H	40	**3j**	90
11	$4\text{-}MeC_6H_4$	H	40	**3k**	92
12	$4\text{-}C_2H_5C_6H_4$	H	40	**3l**	91
13	$4\text{-}MeOC_6H_4$	H	40	**3m**	78
14	Bn	H	40	**3n**	88
15	*n*-Bu	H	40	**3o**	78
16	$4\text{-}ClC_6H_4$	–Me	40	**3p**	88
17	$4\text{-}ClC_6H_4$	$-C(CH_3)_3$	40	**3q**	87
18	H	H	40	**3r**	90

[a] All the reactions were performed with **1** (1 mmol), **2** (1 mmol) in toluene (7 mL) by microwave heating at 110 °C.
[b] Isolated yields based on **1**.

3. Results and discussion

Initially, we conducted this synthesis by reacting 4-phenylamino coumarin (**1a**) with ninhydrin (**2**) to serve as the model to establish the optimal condition. The various attempts are summarized in Table 1. Taking solubility of reactants into consideration, we initially utilized polar protic solvents, such as MeOH, EtOH, MeCN and glycol. We investigated the model reaction under catalyst-free conditions as well as with catalysts such as AcOH, $KHSO_4$, *p*-TSA.

In the preliminary experiment, the reaction was performed in methanol at 60 °C with AcOH as catalyst and yielded a trace of **3a** (Table 1, entry 1). The reaction scarcely proceeded to give the desired product, even at enhanced temperatures. Subsequently,

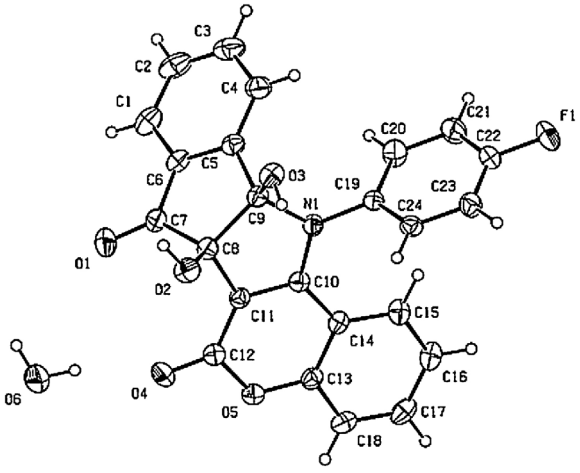


Fig. 1. X-ray crystallographic analysis of the product **3b**.

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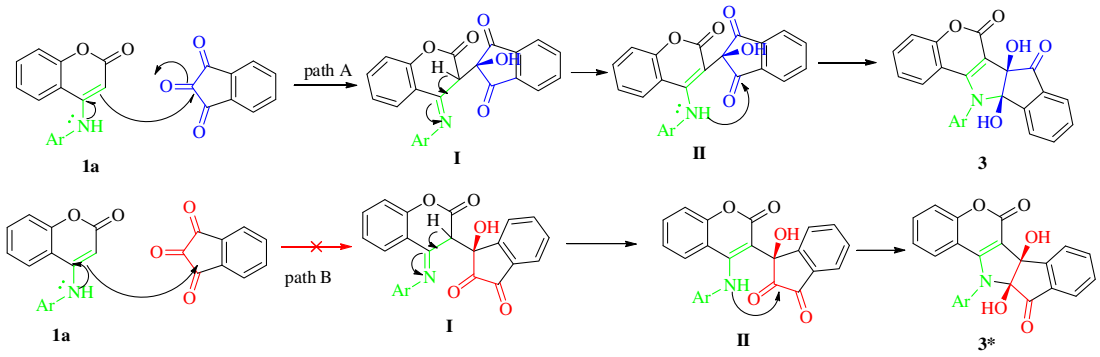

Scheme 1. Proposed mechanism.

the reaction was repeated many times in different solvents, such as MeCN, toluene and glycol and afforded the product, yields 30%, 35%, 90% and 40%, respectively (entries 2–5). Toluene provided a higher yield than other organic solvents, therefore toluene was chosen as the solvent for further reactions. The addition of catalysts such as *p*-TSA, $KHSO_4$, however, did not improve the yields of the product (entries 6 and 7).

Next, the model reaction was studied in toluene using different amounts of AcOH and found that higher amounts of AcOH did not increase the yield significantly (Table 1, entries 8 and 9). Interestingly when this reaction was carried out with 1 mmol of each reactant in 7 mL of toluene in the absence of catalysts at 110 °C under microwave irradiation for 45 min, a maximum yield of 90% of the product **3a** was obtained (Table 1, entry 10). The pure product was obtained as a pale yellow solid by recrystallization from ethanol.

With the optimized conditions in hand, we next decided to ascertain the scope and generality of this method by using various readily available starting materials. The results are presented in Table 2. As usual, the reactions can be finished in 40–55 min. A range of valuable substituted dihydrochromenoindeno [1,2-*b*]pyrroles can be synthesized in good yields. We found that reactants may not only be *N*-arylenaminones (R_1, entries 2–4) which possess electron-withdrawing substituents such as fluoro, chloro and bromo groups at the *para*-position of the benzene ring, but also analogs (R_1, entries 8–13) having electron-donating substituents such as methyl, ethyl and methoxyl groups which gave the corresponding dihydrochromenoindeno [1,2-*b*]pyrroles derivatives **3h–m** in good yields. In addition to *N*-aryl substitutents, *N*-aliphatic groups and 6-aliphatic groups were also found to be suitable and provide the corresponding dihydrochromenoindeno[1,2-*b*]pyrroles derivatives in 78%–90% yields of the products (Table 2, entries 14–17).

This protocol confirms the great scope of functionalities, such as fluoro, chloro and bromo, which intimates the potential opportunity of their further chemical exploitation and utilization. The various structures of products were in accord with ^{1}H NMR and ^{13}C NMR and mass spectral data. The structure of **3b** was further confirmed by X-ray crystallographic analysis (Fig. 1). The detail data has been deposited in Table S1 in Supporting information.

On the basis of the above results together with the related reports [11–13], a plausible mechanistic pathway for the formation of the product is proposed in Scheme 1. This transformation arises from the initial nucleophilic addition of *N*-substituted 4-aminocoumarin compounds to ninhydrin leading to intermediate **I**. The *N*-substituted 4-aminocoumarin compounds presumably add chemoselectively over the more electrophilic middle carbonyl of the indanetrione (Scheme 1, Path A), which is in equilibrium with its hydrate, ninhydrin. Intermediate **I** undergoes successive imine–enamine tautomerization to furnish intermediate **II**, followed by annulation *via* the reaction of the amino group with one of the carbonyl group, resulting in the formation of product **3**.

The reason for the regioselectivity of this transformation is that only the single regioisomer (**3**) is detected. The regiosomer (**3***) could arise from the interaction of the *N*-substituted 4-aminocoumarin compound with one of the edge carbonyls of the indanetrione, followed by hydride migration and intramolecular cyclization (Scheme 1, Path B). Furthermore, the structure of **3** shows the both hydroxyl groups in a *cis*-relationship, confirmed by X-ray structure of compound **3b** in Table 2, which is explicable by spatial restrictions imposed, generated by the annulation of intermediate **II**. The spatial restrictions can orient the addition of the arylamino group on one of the carbonyls from the side opposite to the originally generated hydroxyl group.

4. Conclusion

In conclusion, this investigation describes a facile and precise protocol for the synthesis of a series of novel dihydrochromenoindeno [1,2-*b*]pyrroles in good yields *via* the reaction of substituted 4-aminocoumarin and ninhydrin in an equimolar ratio in the absence of catalysts at 110 °C. The simple work-up procedure without column chromatographic purification, the absence of catalysts, and the excellent yields of products render this method particularly attractive. As shown in this investigation, the reactions have high regioselectivity and one C–C and one C–N bond formed in a single synthetic operation.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.04.009.

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