BRØNSTED ACID-PROMOTED MULTICOMPONENT REACTION FOR THE CONSTRUCTION OF PYRROLOCOUMARIN DERIVATIVES

Zhiwei Chen,* Sunjia Ye, and Xiongfei Zhang

Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, 310014, P. R. China. E-mail: chenzhiwei@zjut.edu.cn

Abstract – An efficient one-pot synthesis of functionalized indole-containing pyrrolocoumarin derivatives via a three-component reaction of 4-aminocoumarins, arylglyoxal monohydrates and indoles promoted by p-TSA in ethanol is described. The attractive features of this protocol are simple starting materials, operational simplicity, short reaction time and moderate to good yields.

Heterocycles are common structural units in natural compounds and many of them exhibit significant pharmacological activities.1 It is well known that the selective and environment amiability synthesis of highly functionalized compound libraries of medicinal motifs is a constant challenge in chemical sciences.2 Among a number of methods available for the construction of heterocyclic frameworks, multicomponent reactions (MCRs) are particularly important.3 Such reactions provide the advantages of high atom economy, simplicity and good synthesis efficiency.

Coumarin derivatives have latent ability to exert noncovalent interactions with the various active sites in organisms and display a wide range of biological activities.4 The pyrrolocoumarins, in particular, are involved in various natural products, such as marine alkaloids ningalin A, ningalin B and lamellarin D which are likely to exhibit interesting biological properties.5 On the other hand, indole nucleus is one of the most common heterocycles found in nature.6 Amongst them, 3-substituted indole is an unique one with significant biological activities and has a venerable value in medical applications.7 Furthermore, indoles are important building blocks that can be used in the synthesis of drug-like compounds.8 Thus, a combination of pyrrolocoumarin and 3-substituted indole could potentially lead to a series of compounds that possess structural and biological interests.

Recently, we have developed a series of new MCRs that provided easy access to heterocycles.9 In this regard, Tu10 and co-workers have developed an efficient protocol for the synthesis of bis-indole derivatives through a one-pot reaction using N-arylenaminones, arylglyoxal monohydrates and indoles.
Lin\textsuperscript{11} and co-workers have reported another three-component reaction for the synthesis of highly functionalized bicyclic pyrrole derivatives in 72-95\% yields. Choudhury\textsuperscript{12} and co-workers described a microwave-assisted MCR of arylglyoxal monohydrates, 4-hydroxycoumarins, and various cyclic 1,3-C,N-binucleophiles in acetic acid providing access to fused five- or six-membered N-heterocycles. Based on the previous works and our continuous interests in the development of functionalized heterocycle libraries, we would like to report another new synthetic method for the synthesis of indole-containing chromeno[4,3-b]pyrrole unit by simple heating 4-aminocoumarins, arylglyoxal monohydrates, and indoles promoted by p-TSA in EtOH.

The initial reaction was conducted by subjecting 4-aminocoumarin (1\textsubscript{a}) to phenylglyoxal monohydrate (2\textsubscript{a}) and 2-methylindole (3\textsubscript{a}) in EtOH at reflux without catalyst for 3 h (entry 1, Table 1). As expected, no desired product was obtained. Fortunately, the reaction was able to produce the targeted product 4\textsubscript{a} in 30\% yield when using FeCl\textsubscript{3} as catalyst (entry 2, Table 1). After a set of Brønsted and Lewis acids were explored as potential catalysts, p-TSA was identified as the optimal catalyst to enable facilitate this procedure (entries 3-6, Table 1). Next, the reaction temperature was examined. It was found that an

\begin{table}[h]
\centering
\caption{Optimization of the reaction condition for the synthesis of compound 4\textsubscript{a}}
\begin{tabular}{lllllll}
\hline
Entry & Catalyst & Loading (mol\%) & Solvent & Temperature (\textdegree{}C) & Time (h) & Yield (\%) \\
\hline
1 & - & - & EtOH & reflux & 3 & n.r. \\
2 & FeCl\textsubscript{3} & 20 & EtOH & reflux & 3 & 30 \\
3 & Y(OTf)\textsubscript{3} & 20 & EtOH & reflux & 3 & 41 \\
4 & MeSO\textsubscript{3}H & 20 & EtOH & reflux & 3 & 56 \\
5 & AcOH & 20 & EtOH & reflux & 3 & 45 \\
6 & p-TSA & 20 & EtOH & reflux & 3 & 63 \\
7 & p-TSA & 20 & EtOH & rt & 3 & trace \\
8 & p-TSA & 20 & EtOH & 60 & 3 & 45 \\
9 & p-TSA & 20 & EtOH & 100 & 3 & 74 \\
10 & p-TSA & 20 & EtOH & 120 & 3 & 72 \\
11 & p-TSA & 10 & EtOH & 100 & 3 & 68 \\
12 & p-TSA & 40 & EtOH & 100 & 3 & 73 \\
13 & p-TSA & 20 & MeOH & 100 & 3 & 67 \\
14 & p-TSA & 20 & toluene & reflux & 3 & trace \\
15 & p-TSA & 20 & [bmim]BF\textsubscript{4} & 100 & 3 & 51 \\
\hline
\end{tabular}
\end{table}
increase in yield was observed under higher temperature, while the reaction got less effectively under lower temperature (entries 6-10, Table 1). In addition, switching the catalyst loading from 10 mol% to 40 mol% had less influence on the reaction yield (entries 11, 12, Table 1). Finally, the reaction solvent was explored, such as [bmim]BF_4, toluene and MeOH, however, no improved yield was afforded (entries 13-15, Table 1). It should be mentioned that protic solvents were proved to be better than aprotic solvents according to the reaction outcomes as shown in Table 1.

After identifying the optimum reaction conditions, various reactions were examined with a wide variety of starting materials in order to explore the synthetic scope and the generality of the present protocol. Upon experimentation, it was found that this protocol had a broad substrate scope and functional group tolerance, delivering the corresponding products in moderate to good yields (Table 2). The scope of this reaction was initially explored with a range of indole derivatives 3, 4-aminocoumarin (1a) and phenylglyoxal monohydrate (2a). It was found that the 2-substituted indole with electron-donating group showed better reactivity (entry 1, Table 2) and resulted in higher yields than the one with electron-withdrawing group (entry 2, Table 2). Furthermore, the substitution pattern of the aryl moieties had a slight effect on the efficiency of the reaction as well as the N-substituted indoles, producing the desired products in 47-58% yield (entries 3-6, Table 2). It should be mentioned that indole with methyl at C3 position was employed in this process, but no desired product was obtained due to the C-nucleophilicity at the C2 position is weaker than that of the C3 position.13

Next, the substrate scope with arylglyoxal monohydrates 2 was examined, and the results was shown in Table 2. The electronic nature of the substituents on the phenyl ring of arylglyoxal monohydrates had some influence on the reaction yields. Aryl glyoxal monohydrates substituted with electron-withdrawing groups (4h-m) offered a little bit higher yields than those with electron-donating groups (4n-r) 2-Me, 3-Me, 4-Me, 4-OH 4-OMe, and 3,4-(OCH_2O) (entries 8-19, Table 2). It was noteworthy that the arylglyoxal monohydrates with 2-Cl gave rise to 4g in relatively low yield due to the steric hindrance (entry 7, Table 2). To our delight, 1-naphthylglyoxal monohydrates and 2-thienylglyoxal monohydrates also performed smoothly to give the corresponding products 4t and 4u in 67% and 64% yields, respectively (entries 20, 21, Table 2).

To further investigate the scope of 4-aminocoumarin (1a), 6-substituted and N-substituted 4-aminocoumarins were examined as a replacement for 4-aminocoumarin to synthesize the target products. The electronic nature of the substituents on the phenyl ring of 4-aminocoumarin had no significant influence on the reaction yield (entries 22, 23, Table 2). However, both N-ethyl-4-aminocoumarin and N-phenyl-4-aminocoumarin were carried out in poor performances towards the generation of final products with little yields and hard to separate. It could be assumed that steric effects play the major role when there was a nitrogen substituent at 4-aminocoumarin.
Table 2. Synthesis of substituted pyrrolocoumarin derivatives 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>4</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>H</td>
<td>C₆H₅</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>4a</td>
<td>74</td>
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<tr>
<td>2</td>
<td>H</td>
<td>C₆H₅</td>
<td>H</td>
<td>C₆H₅</td>
<td>H</td>
<td>4b</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>4c</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>4d</td>
<td>57</td>
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<tr>
<td>5</td>
<td>H</td>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>4e</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>C₆H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>4f</td>
<td>47</td>
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<tr>
<td>7</td>
<td>H</td>
<td>2-ClC₆H₄</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>4g</td>
<td>56</td>
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<tr>
<td>8</td>
<td>H</td>
<td>3-ClC₆H₄</td>
<td>H</td>
<td>Me</td>
<td>H</td>
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<td>Me</td>
<td>H</td>
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<td>H</td>
<td>Me</td>
<td>H</td>
<td>4j</td>
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<td>H</td>
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<td>H</td>
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<td>H</td>
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<td>H</td>
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<tr>
<td>19</td>
<td>H</td>
<td>3,4-(OCH₂O)C₆H₃</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>4s</td>
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<tr>
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<td>H</td>
<td>Me</td>
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<td>4t</td>
<td>67</td>
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<td>Me</td>
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<td>4u</td>
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<td>Me</td>
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<td>4v</td>
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<td>H</td>
<td>Me</td>
<td>H</td>
<td>4w</td>
<td>77</td>
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</table>

To propose a plausible reaction mechanism, we began our investigation by testing the reaction of phenylglyoxal monohydrate (2a) and 2-methylindole (3a) initially. However, none of the expected intermediate was observed during the reaction, instead the compound 5 was afforded (Scheme 1). It was found that the intermediate A could be detected when we lowered the reaction temperature, suggesting that intermediate A might immediately react with nucleophiles at high temperature, making it difficult to detect. We next added 4-aminocoumarin (1a) to the resulting mixture and the target product 4a was obtained fortunately (Scheme 1). If necessary, intermediate A can be separated and then react with 1a in the same condition to afford the target product 4a in 86% yields.
Based on the above observation and previous reports,\textsuperscript{10,14} a plausible pathway for the formation of 3-(2-methyl-1\(H\)-indol-3-yl)-2-phenylchromeno[4,3-\(b\)]pyrrol-4(1\(H\))-one (4\(a\)) is proposed in Scheme 2. Initially, intermediate A is formed by the condensation of phenylglyoxal monohydrate (2\(a\)) and 2-methylindole (3\(a\)) promoted by \(p\)-TSA. Next, nucleophilic attack upon the protonated form of intermediate A by 4-aminocoumarin (1\(a\)) gives intermediate C, which was subsequently converted into intermediate D. Moreover, intermediate D undergoes intramolecular cyclization followed by dehydration to afford the target product 4\(a\).
In conclusion, we have described a Brønsted acid-promoted multicomponent reaction for the construction of indole-containing pyrrolocoumarin derivatives from easily accessible starting materials. The reaction is operationally simple and offers moderate to good yields of the target products. Further investigation on biological activity studies of these compounds is in progress at our lab.

EXPERIMENTAL
Melting points were determined using a Büchi B-540 capillary melting point apparatus. IR spectra were recorded with a Thermo Nicolet AVATAR 370 spectrophotometer in KBr. 1H NMR and 13C NMR were recorded with Varian instrument at 600 and 150 MHz, respectively, and TMS was used as internal standard. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. High resolution mass spectral (HRMS) analyze were measured on a Bruker microTOF-Q II instrument using ESI techniques. The preparation of 4-aminocoumarins 1 and arylglyoxal monohydrates 2 were according to the literature procedure. All other chemicals used in this study were commercially available.

General procedure for the synthesis of indole-containing pyrrolocoumarin derivatives 4: In a 10 mL reaction tube, 4-aminocoumarins 1 (1 mmol), arylglyoxal monohydrates 2 (1.1 mmol) and indoles 3 (1.1 mmol), p-TSA (34 mg, 0.2 mmol), and EtOH (3 mL) were mixed and then capped. The mixture was heated for 3 h at 100 °C (oil bath). Upon completion of the reaction, monitored by TLC, the reaction solution was transferred to a 100 mL single-necked flask. Water (30 mL) was add to it. After being stirred for 3 h, the solution was filtered. The residue was purified by column chromatography (CH2Cl2/MeOH, 180:1 v/v) to afford target product 4. Spectral data for 4a and 4e were as follows:

3-(2-Methyl-1H-indol-3-yl)-2-phenylchromeno[4,3-b]pyrrol-4(1H)-one (4a): Pale yellow powder. mp 189-191 °C. IR (KBr): 3421, 1695, 1507 cm -1. 1H NMR (600 MHz, DMSO-d6): δ = 12.74 (s, 1H), 11.00 (s, 1H), 8.34 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.41 (m, 4H), 7.33-7.25 (m, 3H), 7.22 (t, J = 7.2 Hz, 1H), 6.97 (t, J = 8.4 Hz, 2H), 6.79 (t, J = 7.2 Hz, 1H), 2.09 (s, 3H). 13C NMR (150 MHz, DMSO-d6): δ = 157.7, 151.8, 136.0, 136.0, 134.3, 134.3, 132.5, 129.1, 128.8, 127.7, 127.4, 124.4, 122.2, 120.4, 119.0, 118.8, 117.1, 114.3, 113.8, 110.9, 109.2, 104.6, 12.6. MS (ESI): m/z = 391 [M + H]+. HRMS-ESI: calcd for C26H18N2NaO2 [M + Na]+: 413.1266; found 413.1250.

3-(5-Bromo-1H-indol-3-yl)-2-phenylchromeno[4,3-b]pyrrol-4(1H)-one (4e): White powder. mp 272-274 °C. IR (KBr): 3439, 1667, 1507 cm -1. 1H NMR (600 MHz, DMSO-d6): δ = 12.80 (s, 1H), 11.41 (d, J = 1.8 Hz, 1H), 8.33 (dd, J = 7.8, 1.4 Hz, 1H), 7.51-7.38 (m, 7H), 7.36-7.31 (m, 2H), 7.31-7.27 (m, 1H), 7.16 (dd, J = 8.4, 1.8 Hz, 1H), 7.12 (d, J = 1.8 Hz, 1H). 13C NMR (150 MHz, DMSO-d6): δ = 157.9, 151.8, 136.0, 135.1, 134.2, 132.2, 129.3, 129.2, 128.9, 128.3, 128.0, 127.9, 124.5, 123.7, 122.3, 122.2, 117.1, 114.2, 113.9, 113.4, 111.7, 108.5, 106.9. MS (ESI): m/z = 455 [M + H]+. HRMS-ESI: calcd for C25H15BrN2NaO2 [M + Na]+: 477.0215; found 477.0213.
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REFERENCES


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