This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Catalyst-free tandem Michael addition/decarboxylation of (thio)coumarin-3-carboxylic acids with indoles: facile synthesis of indole-3-substituted 3,4-dihydro(thio)coumarins

Zhuzhou Shao, Lubin Xu, Liang Wang, Hongtao Wei and Jian Xiao*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

The tandem Michael addition/decarboxylation of (thio)coumarin-3-carboxylic acids with indoles has been developed and the biologically important indole-3-substituted dihydrocoumarins were obtained in good to excellent yields under catalyst-free conditions.

Both indoles and 4-dihydrocoumarins are the privileged structures of a large number of heterocyclic compounds in nature. The derivatives of the compounds of these two families exhibit a broad spectrum of biological and pharmacological properties, which exist in numerous drugs and biologically active natural products. Due to the high significance of these two classes of compounds in drug discovery, the synthesis of the compounds containing both of these two moieties is highly desirable. However, up to now, only few methods are available for the synthesis of indole-3-substituted dihydrocoumarins. In 2006, Tang et al reported a Mg(OTf)₂-catalyzed tandem reaction involving consecutive Michael additions between indoles, 3-nitrocoumarins and methyl vinyl ketones which gave rise to multi-functionalized 3,4-dihydrocoumarins. Recently, Mattson disclosed conjugate addition of indoles to coumarins using urea palladacycles as a hybrid catalyst to prepare this motif. Besides conjugate addition, multicomponent reaction can also be employed to produce indole-3-substituted dihydrocoumarins.

Srivastava et al reported a saccharin-based functional ionic liquid mediated multicomponent reaction involving Knoevenagel condensation and Michael addition to yield the indole-3-substituted dihydrocoumarins efficiently. Despite the above protocols to prepare indole-3-substituted dihydrocoumarins, there are still drawbacks such as the lack of substrate generality and use of expensive catalyst and reagents. Thus the avoidance of use of precious catalyst and materials is highly desirable for organic chemists. During our great interest in manipulation of coumarin derivatives, we have developed a facile catalyst-free tandem addition/decarboxylation of 2-alkylazaarenes with (thio)coumarin-3-carboxylic acids via sp² C-H activation for efficient construction of azaraenes substituted 3,4-dihydro(thio)coumarins. As a continuation of this work and development of efficient and green manner to construct biologically active molecules, herein we present a facile catalyst-free tandem Michael addition/decarboxylation reaction to construct indole-3-substituted dihydrocoumarins in one step from simple and readily available indoles and coumarin-3-carboxylic acids (Scheme 1).

Our initial study commenced with the conjugate addition of 2-methylindole 1a with coumarin-3-carboxylic acid 2a in the presence of 10 mol% Sc(OTf)₃ (Table 1, entry 1). To our delight, the decarboxylative product 3a was obtained in dioxane at 120°C in high yield (96%). However, if CH₃CO₂H (10 mol%) was exploited as catalyst, product 3a was afforded only in very low yield (Table 1, entry 2). The most intriguing result was that when this reaction was conducted under catalyst-free condition, the desired product 3a could be obtained in excellent yield (98%) after isolation (Table 1, entry 3), which was superior to that using Lewis acids or Bronsted acids as catalysts. The employment of other solvents, e.g. THF, DMF, CF₃CH₂OH, DCE and toluene, led to inferior yields (Table 1, entries 4-9), which demonstrated that the option of solvent was critical this reaction. Furthermore, the lower temperature was detrimental to the yield of the transformation (Table 1, entries 10-11). With the optimized conditions, the reaction could be carried out at 120°C in dioxane to give the desired product 3a in 96% yield (Table 1, entry 1).

Table 1 Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OTf)₃</td>
<td>dioxane</td>
<td>120</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CO₂H</td>
<td>dioxane</td>
<td>120</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>dioxane</td>
<td>120</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>THF</td>
<td>120</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>DMSO</td>
<td>120</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>DMF</td>
<td>120</td>
<td>59</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>CF₃CH₂OH</td>
<td>120</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>DCE</td>
<td>120</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>toluene</td>
<td>120</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>dioxane</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>dioxane</td>
<td>80</td>
<td>72</td>
</tr>
</tbody>
</table>

* Reactions were conducted with 1a (0.4 mmol), 2a (0.2 mmol), catalyst (10 mol%) in 1 mL solvent for 48 h. Isolated yield.
Organic & Biomolecular Chemistry Accepted Manuscript

Scheme 2 Substrate scope of indoles and coumarin-3-carboxylic acids a,b

Reactions were conducted with indoles 1 (0.75 mmol), coumarin-3-carboxylic acid 2 (0.3 mmol) in 2 mL dioxane at 120 °C for 48 h. a The yields indicated are the isolated yield by column chromatography.

Encouraged by the success of coumarins-3-carboxylic acid, we extended the substrate scope to thiocoumarin-3-carboxylic acid since thiocoumarin derivatives also exhibit a broad spectrum of pharmacological properties.9,10 Gratifyingly, when thiocoumarin-3-carboxylic acid 4 was allowed to react with indoles 1, the corresponding indole-3-substituted 3, 4-dihydrothiocoumarins 5 could be isolated in good to excellent yield (Scheme 3).

Scheme 3 Reaction of thiocoumarin-3-carboxylic acids with indoles a,b

Reactions were conducted with indoles 1 (0.75 mmol), thiocoumarin-3-carboxylic acid 4 (0.3 mmol) in 2 mL dioxane at 120 °C for 48 h. a The yields indicated are the isolated yield by column chromatography. b Reaction time was 30 h.

To elucidate the reaction mechanism, control experiments were carried out with ethyl coumarin-3-carboxylate 6a, 3-acetyl coumarin 6b, coumarin-3-phenylsulfone 6c, coumarin 6d and 2H-chromene-3-carboxylic acid 6e under the standard condition. Remarkably, no reaction occurred and all the substrates remained intact even in the presence of TFOH catalyst or the reaction temperature was raised to 140 °C. Thus it can be concluded that the carboxyl group in C-3 position of coumarin was indispensable for the success of this reaction.11 The failure of the reaction of 2H-chromene-3-carboxylic acid 6e might be rationalized that without synergistic activation of alkene by carboxylic group and lactone moiety, Michael acceptor is not electrophilic enough for the conjugate addition.
According to the experimental results, a possible mechanism was proposed as follows: the alkenne of coumarin-3-carboxylic acid is rendered electrophilic synergistically by carboxylic group and lactone moiety, while hydrogen bond formation between nitrogen atom and hydroxyl group not only render alkene more electrophilic but also bring the indole close to electron deficient double bond for subsequent conjugate addition to afford intermediate A. A subsequent rearomatization followed by decarboxylation furnishes the product 3.

Scheme 5 Proposed mechanism.

Conclusions

In summary, we present a facile catalyst-free tandem Michael addition/decarboxylation of indoles with (thio)coumarin-3-carboxylic acids for the efficient construction of indole-3-substituted 3,4-dihydro(thio)cumarins. A broad scope of coumarins, thiocoumarins and indoles has been defined and the coupled products were isolated in good to excellent yields. This tandem reaction provides an efficient and novel protocol to construct this biologically important architecture without catalyst in one step.

Acknowledgement. We are grateful to the National Natural Science Foundation of China (No. 21102142) and the Outstanding Young Scientist Award Foundation of Shandong Province (No. BS2011YY007, BS2013YY002). Financial support from Talents of High Level Scientific Research Foundation (No. 631223) of Qingdao Agricultural University is also gratefully acknowledged.

Notes and references


