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Green and Rapid Access to Benzocoumarins via Direct Benzene Construction through Base-Mediated Formal [4+2] Reaction and Air Oxidation

Chengli Mou†‡§, Tingshun Zhu†, Pengcheng Zheng†‡, Song Yang†, Bao-An Song*, †, Yonggui Robin Chi*, †,‡

†Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China; ‡Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information Placeholder

ABSTRACT: Benzocoumarin is an important structural motif widely found in natural products and synthetic molecules. Traditional methods for the synthesis of Benzocoumarins and their derivatives require multiple steps, typically with an intramolecular ester forming reaction to make the lactone ring as the last step. Another major method involves transition metal-catalyzed coupling or carbon-hydrogen bond activation reactions by starting with pre-existing aryl frameworks in the substrates. Here we report a new strategy for green and rapid access to benzocoumarins and their derivatives. Our method uses readily available unsaturated aldehydes and coumarins as the substrates and air as the green oxidant. The overall reaction proceeds through a formal [4+2] process to construct a new benzene ring and thus to afford benzocoumarines in essentially a single step. No metal catalysts were used; no toxic or expensive reagents were involved. The power of our new approach is further demonstrated in a concise formal total synthesis of cannabinol, a bioactive natural product.

Benzocoumarin is a class of unique heterocyclic scaffolds widely present in naturally occurring compounds and synthetic molecules with interesting bioactivities. For example, cannabinol (Scheme 1a), which contains a derived dibenzopyran structure from benzocoumarin, is a family member of cannabinoïds that can interact with the G-protein coupled receptors CB1 and CB2, exhibiting psychotrophic effect, analgesic, antiemetic, and anticonvulsant properties. Notably, natural cannabinoids shows poor selectivities in differentiating the two receptors, and synthetic analogs with better selectivities are being actively pursued. Other important examples of bioactive benzocoumarin-type natural products includes alternariol, fasiculiflor, automnariol, and automnarinio(Scheme 1a). In part due to the potential utilities of these molecules, the synthesis of benzocoumarins remains a lasting interest in organic chemistry. The dominated methods reported to date require multiple steps with the formation of the lactone ring (B ring as shown in Scheme 1b) as the key step. Transition metal-catalyzed reactions, such as carbon-carbon couplings of two aryl rings, CO insertion, and carbon-hydrogen bond activations, have been widely studied to form the lactone B ring (Scheme 1b). Metal-free approaches have also been explored, typically through a low yielding process involving condensation of salicylaldehyde and cyclohexanone followed by pyran formation and aromatization. In contrast to the B-ring forming approaches that involve multiple steps and catalysts/reagents that are expensive and/or toxic, strategies that focus on the construction of C ring (the benzene unit) can provide new opportunities. Unfortunately, such approaches are rarely studied likely because in organic
synthesis the construction of new benzene ring is often avoided. In 2008, Deiters\textsuperscript{14} developed an Ru-catalyzed [2+2+2] trimerization method for the synthesis 3,4- benzocoumarins. In 2010, Bodewell\textsuperscript{15} developed an amine catalyzed inverse electron demand [4+2] Diels-Alder reaction for access to these compounds.\textsuperscript{16} 

Our laboratories are interested in new strategies for direct construction of aromatic rings that can provide unusual short synthetic routes for functional molecules. We recently report N-heterocyclic carbene organic catalyst-mediated formal [3+3] reaction\textsuperscript{17} and unsaturated aldehyde-carbon activation\textsuperscript{18} for the synthesis of benzene unit. Here we report a new strategy for the construction of benzene framework as the C-ring in benzocoumarins and their derivatives (Scheme 1b and 1c). Our present method uses enals and coumarins as the starting materials. Enals are commercially available with low cost or easily accessible; coumarins are either commercially available or can be readily prepared in one step via condensation of salicylaldehyde and ethyl acetoacetate (see SI).\textsuperscript{19} In our approach a simple base (DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene) is used, and no expensive or toxic catalysts/reagents are involved.

Air is used as the green oxidant. The utility of our method is further demonstrated in a concise formal total synthesis of cannabidiol.

The postulated reaction pathway of our designed reaction is further illustrated in Scheme 1c. Deprotonation of the γ-carbon of enal substrate 1a in the presence of a base gives a dienolate I. Michael-type addition of the enal γ-carbon of intermediate I to coumarin 2a forms intermediate II that undergoes intramolecular aldol reaction to form tricyclic intermediate III.\textsuperscript{20} Subsequent intramolecular acetal formation gives IV. Elimination of an acetate\textsuperscript{16c,21} from IV affords intermediate V that then undergoes spontaneous oxidative aromatization (with air as the oxidant) to complete the reaction cycle and give 3,4-benzocoumarin product 3a.

We started by using enal 1a and 3-acteyl-coumarin 2a as the model substrates (Table 1). When Cs\textsubscript{2}CO\textsubscript{3} was used as the base, we were delighted to find proposed product 3a in 10\% yield (entry 1). K\textsubscript{2}CO\textsubscript{3} or Et\textsubscript{3}N could barely mediate this reaction (entries 2-3), and in such cases the substrates (nearly all 1a and most 2a) remained unreacted. Strong bases such as TBD (1,5,7- Triazabicyclo[4.4.0]dec-5-ene) and LDA (Lithium diisopropylamide) were not a suitable choice and only low yields of 3a could be obtained due to the rapid hydrolysis of 2a under the reaction condition (entry 4). After further evaluation of the bases (see SI) we found DBU could mediate the reaction with the formation of 3a in 30\% yield (entry 5). Solvents could significantly affect the reaction yields (see SI) and the use of CHCl\textsubscript{3} as a solvent could give 3a in 61\% yield (entry 6). In all cases, hydrolysis of 2a was the main side reaction. When two equivalents of 2a was used, product 3a could be obtained in 75\% yield (entry 7). The reaction yield could be further improved by the addition of molecular sieve (entry 8).

![Scheme 1. Benzocoumarins and their synthesis.](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R. Conditions</th>
<th>yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>CH\textsubscript{3}- (2a), THF, Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>2a, THF, K\textsubscript{2}CO\textsubscript{3}</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>2a, THF, Et\textsubscript{3}N</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>2a, THF, TBD</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>2a, THF, DBU</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>2a, CHCl\textsubscript{3}, DBU</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>2a, CHCl\textsubscript{3}, DBU</td>
<td>75</td>
</tr>
<tr>
<td>8\textsuperscript{b}</td>
<td>2a, CHCl\textsubscript{3}, DBU</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>C\textsubscript{3}H\textsubscript{5}- (2b),CHCl\textsubscript{3}-DBU</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>C\textsubscript{3}H\textsubscript{5}- (2c),CHCl\textsubscript{3}-DBU</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>(CH\textsubscript{3})\textsubscript{3}C\textsubscript{2}H\textsubscript{2}(CHCl\textsubscript{3})-DBU</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>CH\textsubscript{3}(2e),CHCl\textsubscript{3},DBU</td>
<td>45</td>
</tr>
<tr>
<td>13</td>
<td>OCH\textsubscript{3}- (2f),CHCl\textsubscript{3},DBU</td>
<td>32</td>
</tr>
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\textsuperscript{7} Reaction conditions: 0.1 mmol of 1a, 0.1 mmol of 2a, 0.10 mmol of base. Yields are isolated yields based on 1a. \textsuperscript{8} 0.1 mmol of 2a, 0.05 mmol of 1a, 0.15 mmol of base. \textsuperscript{9} with 4Å MS 50 mg.
Notably, the CH$_3$ group in the ketone moiety of substrate 2a (released as CH$_3$COOH after the reaction) could be replaced with other alkyl (such as entry 9-11) or aryl (C$_6$H$_5$, entry 12) substituents, albeit with dropped yields under current condition optimized for substrate 2a. The ketone moiety of 2a could also be replaced with an ester unit (e.g., R = OCH$_3$, 2f, entry 13).

We next evaluated the scope of the substrates (using condition as in Table 1, entry 8). With 3-acetyl-coumarin 2a as the model electrophile, several representative enal substrates were examined (Scheme 2). We first studied enals with an aryl and a methyl substituent at the β-carbon (product 3a-c). Different substituents (3d-e) or different substituent patterns (3f) on the β-phenyl ring of enals could all be tolerant. Replacement of the phenyl unit of enal with a naphthyl (3h-i) or heteroaryl (3g) unit worked well too. In all cases, an E/Z mixture of the enals could be directly used without affecting the reaction outcomes. Notably, in addition to enal, aryl aldehyde bearing side alkyl substituent with acidic proton (such as indole-derived aldehyde) could be used as well (3j). Next we found that enals with alkyl substituents at the β-carbon (3k-n) could react effectively as well. For example, the β-phenyl group of 2a could be replaced with a methyl unit to afford product 3k in 75% yield. Enals with a single substituent at the enal β-carbon (3l-n) could also be used. Notably, substituents (R$^1$) on the γ-carbon of the enal led to reduced reactivity of the enal substrate and enhanced the difficulty of the oxidative aromatization process (e.g., V to 3a. Scheme 1c). For the reaction in forming products 3m and 3n, an elevated reaction temperature (50°C) was used; and the use of DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) as an oxidant was necessary for the oxidative aromatization step to finally form 3m and 3n (the reaction stopped at intermediate V as illustrated in Scheme 1c when the reaction was carried out under air).

With enal 1a as a model nucleophile, several substituted 3-acetyl-coumarins were then examined (Scheme 3). Installing different substituents on the benzene ring of substrate 2 was well tolerated (3o-t) without further condition optimization.

Our reaction provides a new approach for rapid synthesis of benzocoumarin-containing functional molecules. Here we demonstrate the utility of our method through a formal total synthesis of cannabionol, a bioactive natural product that was found to exhibit several interesting bioactivities (Scheme 4). Briefly, Knoevenagel condensation of aldehyde 5 and methyl acetoacetate efficiently gave 3-acetyl coumarin 6 in 94% yield (gram scale) as the substrate. Reaction of 6 with 3,3-dimethyl acrolein (enal substrate) via our formal [4+2] benzene forming process under standard condition effectively gave 1.2 gram of adduct 7 in 80% yield. Adduct 7 could be transformed to cannabionol via a 3-step protocol (with 71% overall yield) previously reported. Our method is operationally simple and green; and it involves shorter routes when compared to previous methods. For example, Deiters's elegant total synthesis of cannabionol reported in 2008 used 5 steps, including a Ru-catalyzed [2+2+2] trimerization process, in transforming substrate 5 to the adduct 7 (our method involves 2 steps) and 71% yield.

In conclusion, we have developed a new approach for the
rapid synthesis of benzocoumarin derivatives. Instead of functionalizing pre-existing aromatic frameworks, here we construct a new benzene ring via a formal [4+2] process. All substrates are commercially available or easily accessible, and air is used as a green oxidant. The utility of our method was further demonstrated in a formal total synthesis of a natural product cannabinol. Benzocoumarin is a common scaffold in both natural products and functional synthetic molecules. Given the operational simplicity and high efficiency, our synthetic approach via new benzene formation is expected to find wide applications for both small and large scale synthesis.

ASSOCIATED CONTENT
Supporting Information
Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION
Corresponding Author
*E-mail: robinchi@ntu.edu.sg.
Author Contributions
‡These authors contributed equally.

Notes
The authors declare no competing financial interest.

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REFERENCES
- direct arene construction
- catalyst free, mild condition
- routine solvent and base
- readily available starting material