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

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Benzocoumarins constitute a class of unique heterocyclic scaffolds widely present in naturally occurring compounds and synthetic molecules with interesting bioactivities. For example, cannabino (Figure 1a), which contains a derived dibenzopyran structure from benzocoumarin, is a family member of the cannabino-oids that can interact with the G-protein coupled receptors CB1 and CB2, exhibiting a psychotropic effect as well as 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.

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vide new opportunities. Unfortunately, such approaches are rarely studied likely because in organic synthesis the construction of a new benzene ring is often avoided. In 2008, Deiters[14] developed an Ru-catalyzed [2+2+2] trimerization method for the synthesis 3,4-benzocoumarins. In 2010, Bodewell[15] developed an amine-catalyzed inverse electron demand [4+2] Diels–Alder reaction for access to these compounds.[16]

Our laboratories are interested in new strategies for the direct construction of aromatic rings that can provide unusual short synthetic routes for functional molecules. We recently report the N-heterocyclic carbene–organic catalyst-mediated formal [3+3] reaction[17] (Figure 1c) and unsaturated aldehyde δ-carbon activation[18] for the synthesis of the benzene unit.[19] Here we report a new strategy for the construction of the benzene framework as the C-ring in benzocoumarins and their derivatives (Figure 1b and d). Our present method uses enals and coumarins as the starting materials. Enals are commercially available or easily accessible; coumarins are either commercially available or can be readily prepared in one step via condensation of salicylaldehyde and ethyl acetoacetate (see the Supporting information).[20] 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 cannabinol.

We started by using enal 1a and 3-acetylcoumarin 2a as the model substrates (Table 1). To our surprise, under the standard [3+3] benzene construction conditions[17] the desired product 4a was obtained in only 31% yield, together with a “demethyl” product 3a in 48% yield (Table 1, entry 1). Use of a stronger base such as DBU can even decrease the formation of 4a (Table 1, entry 2). Further study showed that the NHC catalyst was not necessary in the formation of
3a (Table 1, entry 3). And we were also delighted to find that air could replace TTBD (3,3',5,5'-tetra-tert-butyl-[1,1'-bi(cyclohexylidene)]-2,2',5,5'-tetraene-4,4'-dione) as a cheap and green oxidant in the reaction, albeit in lower yield (Table 1, entry 4). Under these air oxidation conditions, K$_2$CO$_3$ or Et$_3$N could barely mediate the reaction (Table 1, entries 5 and 6). 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 as suitable choice and only low yields of 3a could be obtained due to the rapid hydrolysis of 2a under the reaction conditions (Table 1, entry 6) for the result with LDA, see the Supporting Information). After further evaluation of the bases (see the Supporting Information) we found that DBU could mediate the reaction with the formation of 3a in 30% yield (Table 1, entry 7). Solvents could significantly affect the reaction yields (see the Supporting Information) and the use of CHCl$_3$ as solvent could give 3a in 61% yield (Table 1, entry 8). In all cases, hydrolysis of 2a was the main side reaction. When two equivalents of 2a were used, product 3a could be obtained in 75% yield (Table 1, entry 9). The reaction yield could be further improved to 80% by the addition of molecular sieves (Table 1, entry 10).

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 or aryl substituents, albeit with lower yields under the current conditions optimized for substrate 2a (see the Supporting Information). The ketone moiety of 2a could also be replaced with an ester unit (see the Supporting Information).

The postulated reaction pathway of the reaction is illustrated in Scheme 1. Deprotonation of the γ-CH of enal substrate 1a in the presence of a base gives a dienolate intermediate 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. Subsequent intramolecular acetal formation gives IV. Elimination of an acetate 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 next evaluated the scope of the substrates (using conditions as in Table 1, entry 10). With 3-ace-tylcoumarin 2a as the model electrophile, several representative enal substrates were examined (Table 2). We first studied enals with an aryl and am ethyl substituent at the b-carbon (products 3a–c). Different

### Table 1. Optimization of the reaction conditions.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Base</th>
<th>Yield of 3a [%]</th>
<th>Yield of 4a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IMes</td>
<td>TTBD</td>
<td>Cs$_2$CO$_3$</td>
<td>48</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>IMes</td>
<td>TTBD</td>
<td>DBU</td>
<td>43</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>TTBD</td>
<td>Cs$_2$CO$_3$</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>air</td>
<td>Cs$_2$CO$_3$</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>air</td>
<td>K$_2$CO$_3$</td>
<td>trace</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>air</td>
<td>TBD</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>air</td>
<td>DBU</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
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<td></td>
<td>air</td>
<td>DBU</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>air</td>
<td>DBU</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>air</td>
<td>DBU</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.1 mmol of 1a, 0.1 mmol of 2a, 0.10 mmol of base, 0.03 mmol of IMes, 0.2 mmol of TTBD, 1.0 mL of THF. Yields are of isolated products based on 1a.
[b] With CHCl$_3$ as solvent.
[c] 0.05 mmol of 1a, 0.1 mmol of 2a, 0.15 mmol of DBU, 0.5 mL of CHCl$_3$.
[d] With 50 mg 4Å MS.
substituents (3d, 3e) or different substituent patterns (3f) on the β-phenyl ring of enals could all be tolerated. Replacement of the phenyl unit of the enal with a naphthyl (3h, 3i) or heteroaryl (3g) unit worked well too. In all cases, the E/Z mixture of the enals could be directly used without affecting the reaction outcomes. Notably, in addition to enals, aryl aldehydes bearing side alkyl substituents with an 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, the substituent (R1) 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 1). For the reaction 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 1 when the reaction was carried out under air).

Scheme 1. Postulated pathway.

Table 2. Scope of aldehydes.[a]

<table>
<thead>
<tr>
<th>R</th>
<th>3a, 80%; 3b, 81%; 3c, 71%; 3d, 81%; 3e, 66%</th>
<th>3f, 80%; 3g, 75%; 3h, 82%; 3i, 81%; 3j, 65%</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>aldehyde of 3j</td>
<td>aldehyde of 3k</td>
</tr>
<tr>
<td>R2</td>
<td>aldehyde of 3m</td>
<td>aldehyde of 3n</td>
</tr>
</tbody>
</table>

[a] Reaction conditions as in Table 1 entry 10. Yields are of isolated products.

[b] Reaction was carried out at 50°C to give the dihydride of benzocoumarin, which successively oxidized by DDQ (1 equiv.) in refluxing CH2Cl2 to give the product, yields are total isolated yields of the two steps, see the Supporting Information for details.
With enal 1a as a model nucleophile, several substituted 3-acetylcoumarins were then examined (Table 3). Installing different substituents on the benzene ring of substrate 2 was well tolerated (3o–t) without further optimization of the conditions. Our reaction provides a new approach for the rapid synthesis of benzocoumarin-containing functional molecules. Here we demonstrate the utility of our method through a formal total synthesis of cannabinol, \[\text{Scheme 2}.\]

Experimental Section

General Procedure for the Synthesis of 3,4-Benzocoumarins 3

To a dry Schlenk tube equipped with a magnetic stir bar, were added aldehyde 1a (0.1 mmol), coumarin 2a (0.2 mmol), 4 Å MS (50 mg) and DBU (0.15 mmol). Freshly anhydrous CHCl₃ (0.5 mL) was added, and the reaction mixture was stirred at room temperature until the aldehyde was completely consumed (for 12 h, monitored by TLC). The reaction mixture was concentrated under reduced pressure. The resulting crude residue was purified \[\text{via} \text{column chromatography on silica gel (hexane/EtOAc) to afford the desired 3,4-benzocoumarin derivative product 3.}\]

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References


