Carbene-Catalyzed Formal [5 + 5] Reaction for Coumarin Construction and Total Synthesis of Defucogilvocarcins

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∥∥Supporting Information

ABSTRACT: An N-heterocyclic carbene-catalyzed formal [5 + 5] reaction between enals and furanones that generates multisubstituted coumarins in a single step is reported. Five atoms in each of the substrates are involved in this catalytic process to form a benzene and a lactone ring. The power of the method is further demonstrated in metal-free total syntheses of several natural products (defucogilvocarcins M, E, and V) bearing coumarin as the key structural motif.

Coumarin is a fragrant organic compound made of a benzene ring fused with a six-membered lactone. Substituted coumarins and their derivatives are widely found in natural products,1 bioactive molecules,2 and functional materials.3 For example, chartreusin4 and defucogilvocarcins5 are bioactive compounds containing one or more coumarin moieties (Figure 1a). They are antibiotics isolated from Streptomyces and show anticancer and antibacterial activities. The only differences between defucogilvocarcins M, E, and V are the C-8 substituents in the D ring (Figure 1a). Libraries of diverse C-8 analogues are of high interest in pharmaceutical studies. In the area of materials science, coumarins exhibit strong light absorption properties and high fluorescence quantum yield. They are widely studied for laser devices, organic light emitting diodes (OLEDs), and fluorescent probes.7 Thus, there is a need for the development of short, highly efficient routes to prepare coumarins and their analogues. Examples of widely studied protocols for coumarin synthesis include the Perkin reaction, the Knoevenagel condensation, the Pechmann-Duisberg reaction,8 and the transition-metal-catalyzed coupling.9 In these reported methods, nearly all of the syntheses start with a pre-existing arene unit and require rather tedious steps to install proper substitutes and functional units. The long steps have limited the application of these methods especially for scalable preparation of coumarin-derived complex molecules.

We are interested in developing unusual activation and reaction modes enabled by N-heterocyclic carbene (abbreviated as NHC or carbene) as a key catalyst.10 Inspired by the recent improvement of complex molecules syntheses via novel methods,11 we believe some of our reaction modes shall provide unique advantages in constructing widely used chemical bonds and scaffolds via much shorter routes. Here we report an uncommon reaction mode enabled by carbene organic catalyst to generate substituted coumarins (Figure 1b). In our protocol, carbene-catalyzed remote-activation of α,β-unsaturated aldehydes (enals) initiates a formal [5 + 5] reaction with furanones. Five atoms in each of the two substrates are involved in this process to simultaneously form a benzene and a lactone ring. Our method allows for a single-step access to various coumarins with up to 94% yield. In contrast, literature approaches to this class of multisubstituted coumarins typically require six steps with around 10% overall yield.4b Given the simplicity and shorter route, we expect this approach to be widely applicable for rapid preparation of various coumarins. We also believe that sophisticated natural products bearing multiple rings can be

Figure 1. Multisubstituted coumarins and their synthesis.

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prepared through a concise path by employing our unique reaction mode. Here we demonstrate that bioactive natural products defucogilvocarcins (M, E, and V) and chartreusin analogues can be readily prepared with short steps using our carbene-catalyzed reaction as a key step (Figure 1c).

We started by using enal 3a and furanone 4a as model substrates, quinone\textsuperscript{13} 6 as oxidant, THF (tetrahydrofuran) as solvent, and Cs\textsubscript{2}CO\textsubscript{3} base to search for suitable NHC catalysts (entries 1–5). Triazolium-based NHC catalysts B\textsuperscript{14} and D\textsuperscript{15} with an N-mesityl substituent were found to mediate the formation of 5a with 14% and 5% yield, respectively (entries 2 and 4). We next optimized the reaction conditions using NHC precatalyst B (entries 6–10) and found that by using K\textsubscript{3}PO\textsubscript{4} as base and THF as solvent, the desired product 5a could be obtained in 86% yield (entry 10). The reaction at room temperature took 48 h to complete. A shorter reaction time was possible in 80 °C, albeit with a moderately decreased reaction yield (entry 9). The use of 4 Å molecular sieves was necessary to achieve good yields, likely due to a dehydration process involved in this reaction pathway (see mechanistic pathway in Figure 3). It is worth noting that the choice of bases is critical for this reaction. For example, switching K\textsubscript{3}PO\textsubscript{4} to bases such as DBU and Et\textsubscript{3}N led to little formation of 5a. Additional results from condition optimization are detailed in the Supporting Information.

With acceptable conditions in hand (Table 1, entry 10), the scope of the reaction was evaluated (Scheme 1). With 4a as the model furanone substrate, enals with different substitutes were investigated (5a–I). The reactions were quite general, and placing different substituents on the phenyl ring of 3a was well tolerated. For example, both electron-withdrawing (5c–e) and electron-donating (5b,f–h) substituents could be installed on the phenyl ring of the enal substrates. Different substitution patterns (5f–h) were tolerated, although enal with an ortho-substituent on the phenyl ring gave a lower yield (5h, 45% yield) likely due to steric effects. Replacing the phenyl group with other aryl units such as furan (5i), thiophene (5j), and naphthalenes (5k,l) did not affect the reaction outcomes. With respect to the furanone substrates, substitution on the α- or β-position (R' or R") with methyl group was tolerated (5m–r). Coumarins 5s and 5t were also prepared as key precursors for our total syntheses of defucogilvocarins. Gram-scale synthesis of 5s showed similar results with the standard conditions, giving 1.9 g of 5s in 70% yield. In the preparation of 5t, the corresponding β-alkyl enal was used. In carbene catalysis, it still remains difficult for many of the β-alkyl enals to be effective substrates mostly due to electronic effects. Although the yield for the formation of 5t (40%) is low at this point, it is worth noting that as an key intermediate in syntheses of chartreusin analogues coumarin 5t needs to be prepared in six steps with 10.5% overall yield with the most recent literature method\textsuperscript{12} (also see Figure 1b).

We next explored the potentials of our catalytic reactions for concise total syntheses of several natural products (Figure 2). Defucogilvocarin V (2c) is an antibiotic with antitumor and antibacterial activities. To our knowledge, the most efficient total synthesis of 2c involves nine steps with 16% overall yield from juglone, as reported by Snieckus.\textsuperscript{19} Our total synthesis of 2c involves six steps with 25% overall yield by starting from readily available furanone 4a, as detailed in Figure 2a. Fusion of coumarin 5s and furanone 7 (requires two steps synthesis with known methods\textsuperscript{17}) under Hauser annulation\textsuperscript{18} conditions gave chartreusin analogue 8 in 76% yield. Decarboxylation and successive protection gave 9a in 98% yield. Careful air-free operation is necessary during these two steps likely because the adduct after decarboxylation is unstable under air.\textsuperscript{19} Oxidative cleavage of 9a afforded 10 that underwent Wittig olefination and a spontaneous MOM (−CH\textsubscript{2}OCH\textsubscript{3}) deprotection (during acid workup) to afford defucogilvocarin V (2c). Our six-step total synthesis of 2c is a transition-metal-free process. In contrast, transition-metal catalysts were required in previous approaches based on cross-coupling reactions.\textsuperscript{16} Hydrogenation of 2c gave another natural product defucogilvocarin E (2b)\textsuperscript{20} in 85% yield.

Our catalytic reaction product coumarin 5t could be used as a key substrate for concise total synthesis of defucogilvocarin M (2a), as illustrated in Figure 2b. The conversion of 5t to 2a involved four steps with 62% overall yield. In all these steps (from 5t to 2a), simple crystallization and filtration processes were sufficient to give pure adduct, and column chromatographic purification was not needed. This practical feature allows for scalable syntheses using our approach. The shortest route in the literature for the total synthesis of 2a required seven steps, with five of the steps involving transition-metal-catalyzed reactions.\textsuperscript{21} The use of transition metals may cost additional efforts to remove the residual metal impurities when these methods are used for preparing pharmaceuticals.\textsuperscript{22}

In addition to natural products, our approach provides significant advantages in preparing diverse natural product analogs and libraries of other bioactive molecules. Specifically, our method for coumarin synthesis uses direct benzene construction as a key step.\textsuperscript{12} This allows us to readily incorporate a diverse set of functional groups to coumarins and subsequently to natural product analogues. For example, various C-8 analogs of defucogilvocarins can easily be obtained via similar synthetic routes from our coumarins 5a–I. Additionally, coumarin 5t can be transformed to (1→2)-abeo-chartreusin in three steps via a known method\textsuperscript{1b} (Figure 2c). This analogue has similar antitumor activity with the nature product chartreusin. The
The recent synthesis toward this biologically active compound needs nine steps with a very low yield. The low efficiency of the literature method results from the tedious synthesis of $5t$ via a stepwise substitution approach (six steps, 10.5% yield).

The postulated pathway of our reaction is illustrated in Figure 3. Enal $3a$ is converted to unsaturated azolium ester intermediate $I$ under oxidative NHC catalysis.$^{13,24}$ Deprotonation on the γ-carbon of $I$ led to vinyl enolate intermediate $II$. Addition of the nucleophilic carbon of $II$ to furanone $4a$ via a formal 1,6-addition process affords intermediate $III$. Notably, this process is highly regioselective, and the possible 1,4-addition product was not observed. Intermediate $III$ undergoes an analogous intramolecular Claisen-type addition of the furan carbon$^{26}$ to the azolium ester carbonyl carbon to produce a spirocyclic adduct $IV$. Enolization of $IV$ gives $V$. An intramolecular transesterification

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**Scheme 1. Substrate Scope**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td>$a$</td>
<td>tBuOLi, THF, 60 °C to rt</td>
<td>76%</td>
</tr>
<tr>
<td>$b$</td>
<td>1 N NaOH, 1,4-dioxane, 60 °C</td>
<td>78%</td>
</tr>
<tr>
<td>$c$</td>
<td>Me$_3$SO$_2$K, CO$_2$, acetone, 50 °C</td>
<td>98%</td>
</tr>
<tr>
<td>$d$</td>
<td>6 N HCl, MeOH, 50 °C</td>
<td>96%</td>
</tr>
<tr>
<td>$e$</td>
<td>cat. K$_2$OsO$_4$, NaIO$_4$, THF$\rightarrow$H$_2$O, rt</td>
<td>81%</td>
</tr>
<tr>
<td>$f$</td>
<td>MePPh$_3$Br, KHMDS, THF</td>
<td>60%</td>
</tr>
<tr>
<td>$g$</td>
<td>Pd/C, H$_2$ balloon, ethyl acetate, rt</td>
<td>85%</td>
</tr>
</tbody>
</table>

$^a$Isolated yield. $^b$K$_3$PO$_4$ (100 mol %).

**Figure 2. Synthesis of defucogilvocarins and chartreusin analogues.** Reaction conditions: (a) tBuOLi, THF, −60 °C to rt, for $8a$ 76% yield; for $8b$ 78% yield; (b) 1 N NaOH, 1,4-dioxane, 60 °C; (c) Me$_3$SO$_2$K, CO$_2$, acetone, 50 °C, for $9a$ 98% yield (two steps); for $9b$ 83% yield (two steps); (d) 6 N HCl, MeOH, 50 °C, for $9a$ 98% yield (two steps); (e) cat. K$_2$OsO$_4$, NaIO$_4$, THF$\rightarrow$H$_2$O, rt, 81% yield; (f) MePPh$_3$Br, KHMDS, THF, 0 °C, then 6 N HCl, 60% yield; (g) Pd/C, H$_2$ balloon, ethyl acetate, rt, 85%. KHMDS = potassium bis(trimethylsilyl)amide.

**Figure 3.** Postulated reaction pathway.
process of IV gives intermediate VI that readily dehydrates to afford curmarine product 5a. Efforts to detect or trap intermediates IV and VI were unsuccessful at this point.

In summary, we have developed a unique reaction strategy enabled by carbene organic catalysts for the syntheses of multisubstituted coumarins. The catalytic reaction constitutes an unusual formal [S + S] process that simultaneously constructs a substituted benzene fused with a lactone ring. Application of this direct coumarin formation method allows for concise total syntheses of defucogilvocarins and their analogues. We demonstrated that defucogilvocarins M, V, and E could be prepared via short routes and simple operations by using our catalytic reactions. Our study shall inspire advances in developing new catalytic reaction modes that dramatically reduce the synthetic steps for sophisticated functional molecules. Further development of this reaction mode for concise synthesis, and the search for new basic activation modes and unusual chemical bond construction strategies enabled by carbene catalysts are being pursued in our laboratory.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03102.

Experimental procedures and characterization data for the intermediates and products (PDF)

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Notes

The authors declare no competing financial interest.

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