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

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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 benzocoumarins 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 cannabinoids¹ that can interact with the G-protein coupled receptors CB1 and CB2,² exhibiting psychotropic effect, analgesic,³ antiemetic⁴ and anticonvulsant⁵ properties. Notably, natural cannabinoids shows poor selectivities in differentiating the two receptors, and synthetic analogs with better selectivities are being actively pursued.⁶ Other important examples of bioactive benzocoumarin-type natural products includes alternariol,⁷ fasciculiferol,⁸ autumnariol,⁹ and autumnariniol⁹ (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,¹⁰ CO insertion,¹¹ and carbon-hydrogen bond activations,¹² 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.¹³

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

Scheme 1. Benzocoumarins and their synthesis.

synthesis the construction of new benzene ring is often avoided. In 2008, Deiters¹⁴ developed an Ru-catalyzed [2+2+2] trimerization method for the synthesis 3,4- benzocoumarins. In 2010, Bodewell¹⁵ 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 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] reaction¹⁷ and unsaturated aldehyde-carbon activation¹⁸ 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).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 cannabinol.

The postulated reaction pathway of our designed reaction is further illustrated in Scheme 1c. 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**.²⁰ Subsequent intramolecular acetal formation gives **IV**. Elimination of an acetate^{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-acetyl-coumarin **2a** as the model substrates (Table 1). When Cs_2CO_3 was used as the base, we were delighted to find proposed product **3a** in 10% yield (entry 1). K_2CO_3 or Et_3N 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_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).

Table 1. Optimization of reaction condition. ^a

entry	R, Conditions	yield (%)
1	CH_3 (2a), THF, Cs_2CO_3	10
2	2a , THF, K_2CO_3	trace
3	2a , THF, Et_3N	NR
4	2a , THF, TBD	12
5	2a , THF, DBU	30
6	2a , CHCl_3 , DBU	61
7 ^b	2a , CHCl_3 , DBU	75
8 ^{b,c}	2a , CHCl_3 , DBU	80
9	C_2H_5 (2b), CHCl_3 , DBU	66
10	C_3H_7 (2c), CHCl_3 , DBU	75
11	$(\text{CH}_3)_2\text{CH}$ (2d), CHCl_3 , DBU	82
12	C_6H_5 (2e), CHCl_3 , DBU	45
13	OCH_3 (2f), CHCl_3 , DBU	32

^a Reaction conditions: 0.1 mmol of **1a**, 0.1 mmol of **2a**, 0.10 mmol of base. Yields are isolated yields based on **1a**. ^b 0.1 mmol of **2a**, 0.05 mmol of **1a**, 0.15 mmol of base. ^c with 4 Å MS 50 mg.

Notably, the CH₃ group in the ketone moiety of substrate **2a** (released as CH₃COOH after the reaction) could be replaced with other alkyl (such as entry 9-11) or aryl (C₆H₅, 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 = OCH₃, **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

Scheme 2. Scope of aldehyde^a

^a Reaction conditions as in Table 1 entry 8. Yields are isolated yields. ^b Reaction was carried out in 50°C to give dihydride benzocoumarin, which successively oxidized by DDQ (1 equiv.) in refluxing CH₂Cl₂ to give the product, yields were total isolated yields of two steps, see supporting information for detail.

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 (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 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

Scheme 3. Scope of 3-acetyl coumarin^a

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,¹ a bioactive natural product that was found to exhibit several interesting bioactivities³⁻⁵ (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.^{12c,14} Our method is operationally simple and green; and it involves shorter routes when compared to previous methods. For example, Deiters's¹⁴ 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)^{12c,15b}.

In conclusion, we have developed a new approach for the

Scheme 4. Synthesis of Cannabionol.

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 cannabionol. 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>.

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Notes

The authors declare no competing financial interest.

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- ♣ direct arene construction
- ♣ catalyst free, mild condition

- ♣ routine solvent and base
- ♣ readily available starting material