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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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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 starting with pre-existing aryl frameworks in the substrates. Here we report a new strategy for the 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.

Keywords: air oxidative aromatization; arene construction; 3,4-benzocoumarins; cannabinol; cascade reactions; transition metal-free condiitions

Benzocoumarins constitute a class of unique heterocyclic scaffolds widely present in naturally occurring compounds and synthetic molecules with interesting bioactivities. For example, cannabinol (Figure 1a), which contains a derived dibenzopyran structure from benzocoumarin, is a family member of the cannabinoids[1] that can interact with the G-protein coupled receptors CB1 and CB2,[2] exhibiting a psychotropic effect as well as analgestic,[3] antiemetic[4] and anticonvulsant[5] 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 include alternariol,[7] fasciculiferol,[8] autumnariol,[9] and autumnariniol[9] (Figure 1a). In part due to the potential utilities of these molecules, the synthesis of benzocoumarins remains a long-standing interest in organic chemistry. The dominating methods reported to date require multiple steps with the formation of the lactone ring (B ring as shown in Figure 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 activation,[12] have been widely studied to form the lactone B ring (Figure 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 the C ring (the benzene unit) can pro-

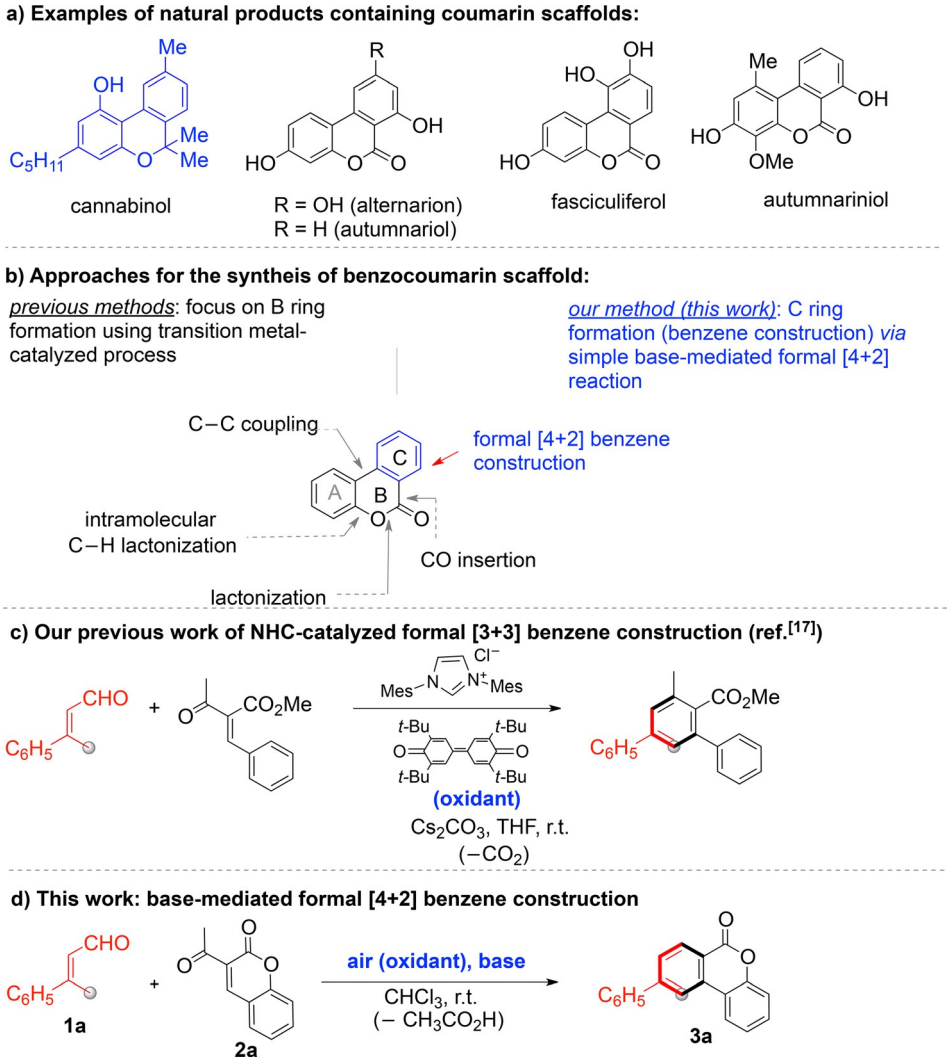


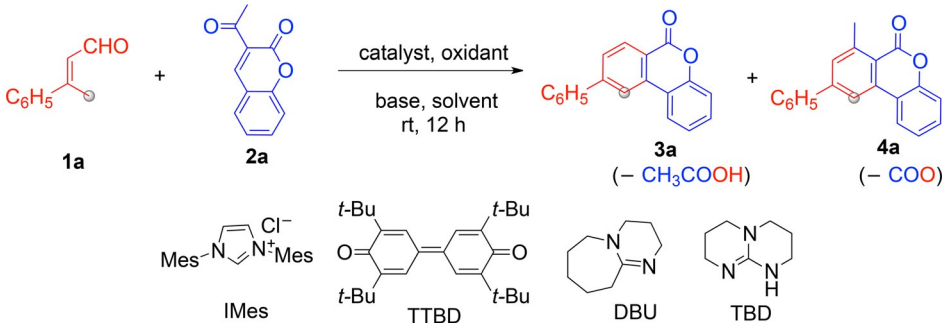
Figure 1. Benzocoumarins and their synthesis.

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

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



Entry	Catalyst	Oxidant	Base	Yield of **3a** [%]	Yield of **4a** [%]
1	IMes	TTBD	Cs_2CO_3	48	31
2	IMes	TTBD	DBU	43	14
3	–	TTBD	Cs_2CO_3	68	0
4	–	air	Cs_2CO_3	10	0
5	–	air	K_2CO_3	trace	0
6	–	air	TBD	12	0
7	–	air	DBU	30	0
8[b]	–	air	DBU	61	0
9[b,c]	–	air	DBU	75	0
10[b,c,d]	–	air	DBU	80	0

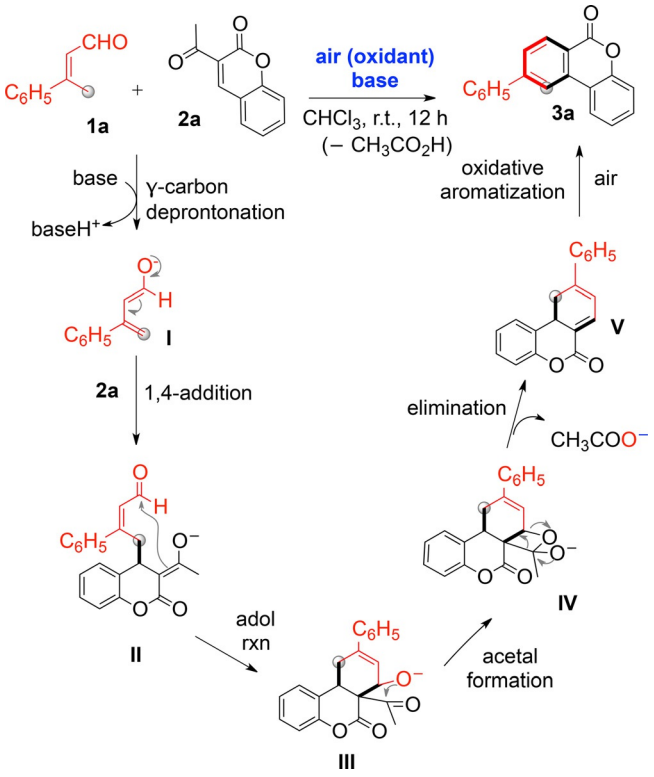
[a] *Reaction conditions:* 0.1 mmol of **1a**, 0.1 mmol of **2a**, 0.10 mmol of base. 0.03 mmol of IMes, 0.2 mmol of TTBD, 1.0 mL of THF. Yields are of isolated products based on **1a**.
[b] With $CHCl_3$ as solvent.
[c] 0.05 mmol of **1a**,0.1 mmol of **2a**, 0.15 mmol of DBU, 0.5 mL of $CHCl_3$.
[d] With 50 mg 4 Å MS.

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_2CO_3 or Et_3N 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-triazabicylo[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 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_3COOH 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**.[21] Subsequent intramolecular acetal formation gives **IV**. Elimination of an acetate[16c,22] 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**.

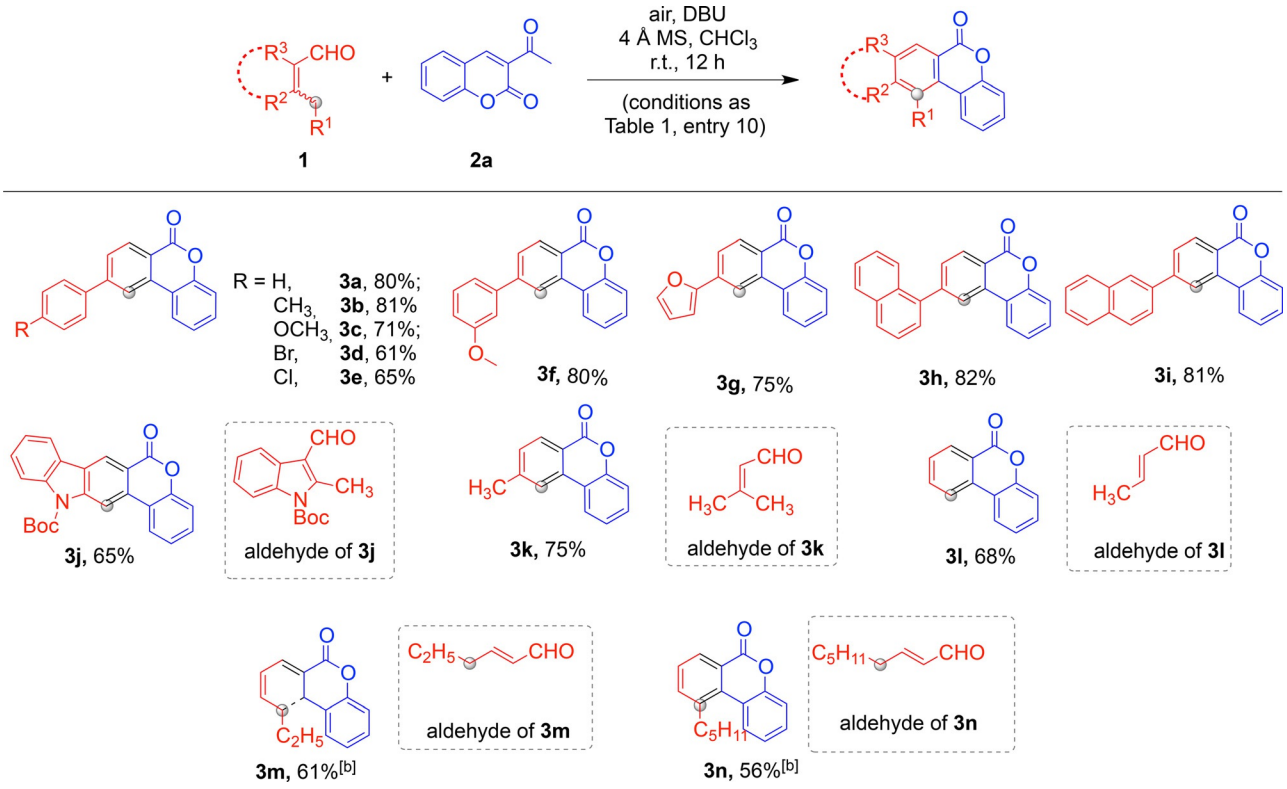
We next evaluated the scope of the substrates (using conditions as in Table 1, entry 10). With 3-acetylcoumarin **2a** as the model electrophile, several representative enal substrates were examined (Table 2). We first studied enals with an aryl and a methyl substituent at the β-carbon (products **3a–c**). Different



Scheme 1. Postulated pathway.

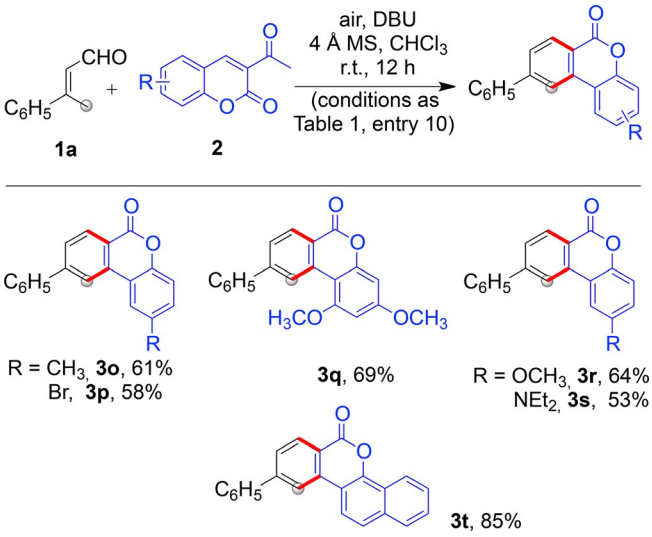
substituents (**3d**, **3e**) or different substituent patterns (**3f**) on the β-phenyl ring of enals could all be tolerated. Replacement of the phenyl unit of the enal with a naphthyl (**3h**, **3i**) or heteroaryl (**3g**) unit worked well too. In all cases, the *E*/*Z* mixture of the enals could 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 (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 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).

Table 2. Scope of aldehydes.[a]



[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 CH_2Cl_2 to give the product, yields are total isolated yields of the two steps, see the Supporting Information for details.

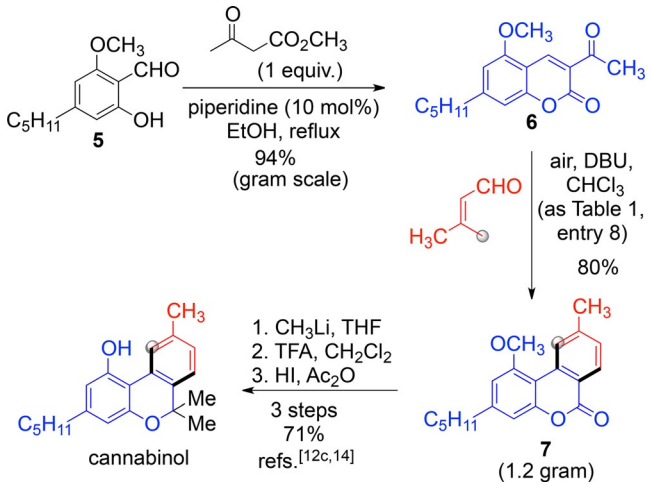
Table 3. Scope of the 3-acetylcoumarins.[a]



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

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,[1] a bioactive natural product that was found to exhibit several interesting bioactivities[3–5] (Scheme 2). Briefly, Knoevenagel condensation of aldehyde **5** and methyl acetoacetate efficiently gave 3-acetylcoumarin **6** in 94% yield (gram scale). Reaction of **6** with 3,3-dimethylacrolein (enal substrate) *via* our formal [4+2] benzene forming process under standard conditions effectively gave 1.2 grams of adduct **7** in 80% yield. Adduct **7** could be transformed to cannabinol *via* a 3-step protocol (with 71% overall yield) as previously reported.[12c,14] Our method is operationally simple and green; and it involves shorter routes when compared to previous methods. For example, Deiters'[14] 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].



Scheme 2. Synthesis of cannabinol.

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 cannabionol. The benzocoumarin moiety 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.

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 $CHCl_3$ (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 *via* column chromatography on silica gel (hexane/EtOAc) to afford the desired 3,4-benzocoumarin derivative product **3**.

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