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ARTICLE TYPE

One-pot cascade reactions of 1-arylpenta-3,4-dien-2-ones leading to 2-arylphenols and dibenzopyranones

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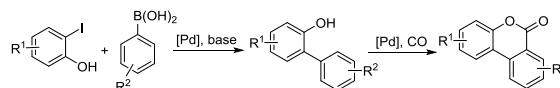
A one-pot cascade reaction of 1-arylpenta-3,4-dien-2-ones with activated ketones allowed for an efficient and sustainable synthesis of 2-arylphenols. Moreover, this reaction was found to be also compatible and combinable with Pd-catalyzed C-H activation and carbonylation of the *in situ* formed 2-arylphenols, thus resulting in a highly convenient and atom-economy synthesis of dibenzopyranones.

Cascade reactions are emerging as attractive tools in organic chemistry since they combine two or more chemical steps in one pot and enable the construction of complex molecules from simple and easily available starting materials.^{1,2}

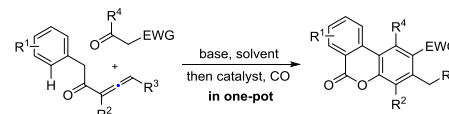
The dibenzopyranone unit has been found in a wide range of natural products, pharmaceuticals and functional materials.³ Due to their importance, the search for novel and efficient synthesis of dibenzopyranones remains a hot topic in synthetic community.⁴ Recently, Inamoto⁵, Shi,⁶ and Chuang⁷ have independently developed an elegant approach toward dibenzopyranones through metal-catalyzed CO insertion of 2-arylphenols. While this C-H activation and carbonylation process itself was atom-economy compared with classical coupling methods starting from pre-functionalized substrates, a retroactive look of this method revealed that the 2-arylphenols used therein were in most cases prepared beforehand by Pd-catalyzed coupling between *o*-iodo phenols and arylboronic acids (Scheme 1). The necessity of step by step operation and the pre-introduction and subsequent loss of the stoichiometric amounts of boronic acid and iodide functions may compromise the sustainability of this strategy.

Allene derivatives are valuable intermediates in synthetic chemistry owing to their diverse reactivity.⁸ Among them, the electron-deficient allenic ketones have been proved as good electrophiles for conjugate addition with active methylene compounds. More interestingly, this conjugate addition is often followed by simultaneous cyclization(s) to afford various cyclic compounds. This has been well pioneered by Ma's synthesis of α -pyrones from the tandem reaction of allenic ketones with diethyl malonate.⁹ Our own efforts have also resulted in some efficient synthesis of benzoic and heterocyclic compounds through reactions of allenic ketones with different nucleophiles.¹⁰ Inspired by these results, we found a new synthesis of 2-arylphenols *via* a base-promoted Michael addition of activated ketones onto the readily obtainable 1-arylpenta-3,4-dien-2-ones followed by an intramolecular aldol condensation, a process that allows for the synthesis of a wide range of 2-arylated phenols. Interestingly, this

Stepwise synthesis of dibenzopyranones from pre-functionalized substrates, ref. 5-7



One-pot synthesis of dibenzopyranones from 1-phenylpenta-3,4-dien-2-ones, this work

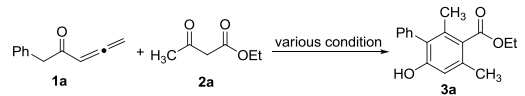


Scheme 1 Michael addition/aldol condensation/C-H activation/carbonylation leading to dibenzopyranones from allenic ketones

tandem process was found to be compatible and combinable with a palladium-catalyzed C-H activation and carbonylation of the *in situ* formed 2-arylphenol, thus resulting in a highly convenient one-pot process toward dibenzopyranones featured with atom economy and operational simplicity as shown in Scheme 1.¹¹

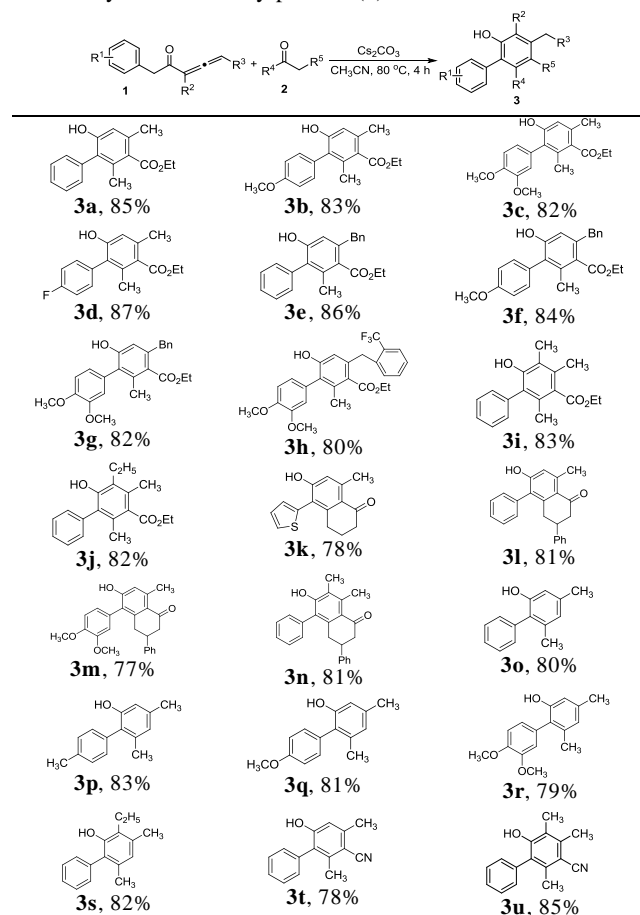
Initially, 1-phenylpenta-3,4-dien-2-one (**1a**) and ethyl 3-oxobutanoate (**2a**) were selected as model substrates for our study (Table 1). We found that the reaction of **1a** and **2a** proceeded smoothly under the promotion of 1 equiv of K_2CO_3 in CH_3CN at 80 °C for 4 h to generate ethyl 6-hydroxy-2,4-dimethyl-[1,1'-bi(phenyl)]-3-carboxylate (**3a**) in 78% yield (Table 1, entry 1). Following studies on the effect of different bases showed that Cs_2CO_3 gave the best yield and its optimum dosage turned out to be 1 equiv (entries 2-8). In the absence of a base, no reaction was observed (entry 9). In following studies, we found temperature higher or lower than 80 °C did not improve the yield of **3a** (entries 10 and 11). Furthermore, changing CH_3CN to EtOH, DMF, THF, DCE or toluene as the reaction medium gave slightly decreased yield (entries 12-16). In summary of the optimization, treatment of **1a** and **2a** with 1 equiv of Cs_2CO_3 in CH_3CN at 80 °C for 4 h gave **3a** in a yield of 85% (entry 2).

To confirm the generality of this one-pot synthesis of 2-arylphenols (**3**), we examined a variety of 1-arylpenta-3,4-dien-2-ones (**1**) under the optimized reaction conditions. The results in Table 2 showed that **1** with either electron-donating or electron-withdrawing group(s) on the aryl ring underwent this cascade process smoothly to give **3** in good to excellent yields. Notably, fluoride was compatible with the reaction conditions (**3d**). In addition, reactions of **1** bearing methyl, ethyl or aryl group on the internal or terminal position of the allene moiety proceeded effectively to afford 2-arylphenols with diverse substitution patterns (**3e-3j**, **3n**, **3s**, **3u**). As a further aspect, with 1-thioenyl

Table 1 Optimization studies for the formation of **3a**^a


| Entry | Base | Solvent | T (°C) | Yield (%) ^b |
|----------------|---------------------------------|--------------------|--------|------------------------|
| 1 | K ₂ CO ₃ | CH ₃ CN | 80 | 78 |
| 2 | Cs ₂ CO ₃ | CH ₃ CN | 80 | 85 |
| 3 | NaOH | CH ₃ CN | 80 | 50 |
| 4 | Na ₂ CO ₃ | CH ₃ CN | 80 | 56 |
| 5 | Et ₃ N | CH ₃ CN | 80 | trace |
| 6 ^c | Cs ₂ CO ₃ | CH ₃ CN | 80 | 71 |
| 7 ^d | Cs ₂ CO ₃ | CH ₃ CN | 80 | 48 |
| 8 ^e | Cs ₂ CO ₃ | CH ₃ CN | 80 | 29 |
| 9 | - | CH ₃ CN | 80 | - |
| 10 | Cs ₂ CO ₃ | CH ₃ CN | 100 | 83 |
| 11 | Cs ₂ CO ₃ | CH ₃ CN | 40 | 58 |
| 12 | Cs ₂ CO ₃ | EtOH | reflux | 76 |
| 13 | Cs ₂ CO ₃ | DMF | 80 | 80 |
| 14 | Cs ₂ CO ₃ | THF | reflux | 81 |
| 15 | Cs ₂ CO ₃ | DCE | 80 | 83 |
| 16 | Cs ₂ CO ₃ | toluene | 80 | 80 |

^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), base (0.5 mmol), solvent (5 mL), 4 h; ^b Isolated yield; ^c 1 mmol of base; ^d 0.25 mmol of base; ^e 0.1 mmol of base.

Table 2 Synthesis of 2-arylphenols (**3**)^{a, b}

^a Reaction conditions: 0.5 mmol of **1**, 0.6 mmol of **2**, 0.5 mmol of Cs₂CO₃, 5 mL of CH₃CN, 80 °C, 4 h; ^b Isolated yield.

allenic ketone, **3k** was obtained successfully. Next, the scope of the ketone substrates (**2**) was studied. In addition to β-ketoester, β-diketone or β-cyanoketone reacted with **1** smoothly to give **3k-3u** in good yields. Interestingly, from the reactions of cyclohexane-1,3-dione, dibenzochromenones (**3k-3n**) were obtained. With pentane-2,4-dione as a substrate, on the other hand, the reactions went through a more sophisticated process to give the corresponding deacetylated 2-arylphenols (**3o-3s**).¹²

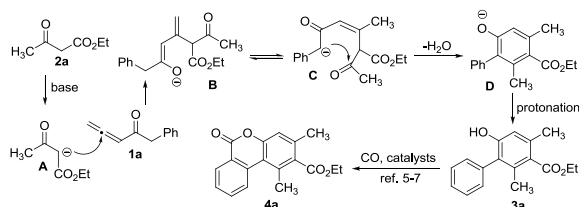
With the establishment of a simple and sustainable synthesis of 2-arylphenols, its compatibility and combinability with the Pd-catalyzed C-H activation and carbonylation required for the formation of dibenzopyranones was studied. Thus, **1a** and **2a** was treated with 1 equiv of Cs₂CO₃ in CH₃CN at 80 °C for 4 h. To the resulting mixture were added Pd(OAc)₂ (10 mol%) and AgOAc (3 equiv). It was then stirred at 80 °C under CO atmosphere.⁷ From this one-pot reaction, the desired ethyl 1,3-dimethyl-6-oxo-6H-benzo[*c*]chromene-2-carboxylate (**4a**) was obtained in a yield of 36%. Considering that water formed along with **3a** may have adverse effect on the formation of **4a**, anhydrous Na₂SO₄ was added as a dehydrating agent. In this case, the yield could be improved to 68%. Notably, the two phases of this cascade process were well compatible in that not only was it unnecessary to isolate the intermediating 2-phenylphenol, but also was it needless to change or remove the solvent or the base promoter.

Encouraged by the above results, we then studied the generality of this novel synthesis of dibenzopyranone. The results listed in Table 3 showed that all the substrates tested could be successfully converted into the corresponding products in good yields (**4a-4r**). The R¹ unit of **1** could be neutral H, electron-donating methyl, methoxy or electron-withdrawing fluoro group and the R² and R³ units could be H, alkyl or aryl group. Meanwhile, the R⁵ fragment of **2** could be an ester, keto or

ciano group. The inclusion of these versatile functional groups makes further structural manipulations of **4** easy to implement. Interestingly, starting from 1-thienonyl allenic ketone, thieno[3,2-*c*]pyran-4-one (**4h**) with potential anti-cancer activity could be conveniently obtained.¹³ It is worth to be noted this cascade reaction was regio-selective and favored the formation of less sterically hindered products **4c**, **4j** and **4o**.

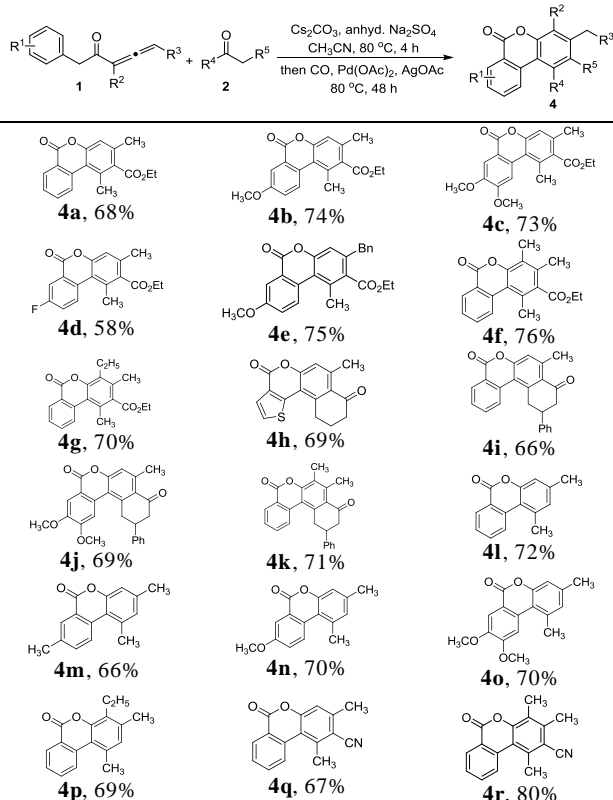
Based on the above observations and previous reports, plausible pathways to account for the formation of **3a** and **4a** was proposed in Scheme 2. Initially, base triggers the cascade process by deprotonating **2a** to give anion **A**, which then undergoes a Michael addition onto **1a** to afford the second anion **B**. Tautomerization of **B** affords the third anion **C**. Next, an intramolecular aldol type reaction followed by tautomerization takes place with **C** to give intermediate **D**. Protonation of **D** affords 2-phenylphenol **3a**. In the presence of CO and catalysts, a C-H activation and carbonylation cascade occurs with the *in situ* formed **3a** to give dibenzopyranone **4a**.⁵⁻⁷

In summary, a novel and efficient method for the synthesis of 2-arylphenols through Michael addition and intramolecular aldol condensation of the easily obtainable 1-arylbuta-3,4-dien-2-ones with activated ketones has been developed. Moreover, this convenient and sustainable synthesis of 2-arylphenols was found to be also compatible and combinable with a metal-catalyzed C-H activation and CO-insertion to give diversely substituted dibenzo-



Scheme 2 Plausible mechanisms for the formation of **3a** and **4a**

Table 3 One-pot syntheses of dibenzopyranones (**4**)^{a, b}



^a Reaction conditions: 0.2 mmol of **1**, 0.24 mmol of **2**, 0.2 mmol of Cs₂CO₃, 0.2 mmol of anhydrous Na₂SO₄, 4 mL of CH₃CN, 80 °C, 4 h; then, CO (1 atm), 0.02 mmol of Pd(OAc)₂, 0.6 mmol of AgOAc, 80 °C, 48 h; ^b Isolated yield.

pyranones with good efficiency. These novel methodologies are complementary to previously reported synthetic procedures and enable easy and sustainable accesses to poly-substituted phenols and dibenzopyranones.

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Notes and references

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