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Visible light mediated oxidative lactonization of 2-methyl-1,1'biaryls for the synthesis of benzocoumarins

Received 00th January 20xx, Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

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Published on 26 March 2019. Downloaded by University of Edinburgh on 3/26/2019 10:34:09 AM.

A visible light mediated oxidative lactonization of 2-methyl-1,1'biaryls was developed, giving benzocoumarins in good yields. The reaction features multiple C-H functionalization with oxygen as the final oxidant. The corresponding 2-aldehdyes, alcohols and carboxylic acids of the 1,1'-biaryls also worked well for the reaction.

Benzo-3,4-coumarin is the core structure of many natural products with unique biological activities,¹ such as Urolithin A² Alternariol³ and Atenuisol⁴ (Fig. 1). In addition, benzocoumarin can serve as key intermediate for the synthesis of various natural products.⁵ Recently, these molecules have also found applications in smart materials.⁶



Many methods have been developed for the synthesis of benzo-3,4-coumarin, including the classical intramolecular esterification of 2'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid,⁷ Baeyer-Villiger oxidation of fluorenones⁸ and oxidation of benzylic C-H bonds in 6*H*-benzo[*c*]chromenes.⁹ Recently, the transition metal-catalyzed coupling and C-H functionalized reaction have been reported for the synthesis of benzo-3,4-coumarins from readily available biphenyl compounds

(Scheme 1). The lactonization of 2'-halo-1,1'-biaryl-2-carboxylic acids was reported under copper-catalyzed¹⁰ or base-mediated conditions (path a).¹¹ The dehydrogenative lactonization of 2-arylbenzoic acids was realized under transitional metals^{12, 5c} or photocatalysis¹³ (path b). In addition, the metal-catalyzed oxidative aryl C–H lactonization of 2-arylbenzaldehyde was successfully demonstrated (path c).¹⁴ Furthermore, the metal-catalyzed oxidative carbonylation of 2-arylphenol was also established (path d).¹⁵ Despite of these advances, two or one functional group is required for the reaction (paths a-d). In this communication, we report a photocatalyzed oxidative lactonization of 2-methyl-1,1'-biphenyls (path e), which features metal-free C-H functionalization without the requirement of functional groups.



Inspired by the photocatalyzed oxidative $C(sp^3)$ -H functionalization by Fukuzumi¹⁶ and Cibulka,¹⁷ we were interested in the synthesis of benzo-3,4-coumarins from 2-methyl-1,1'-biphenes under photocatalysis. The reaction 5-chloro-2-methyl-1,1'-biphenyl (**1a**) with O₂ (balloon) as oxidant was irradiated with blue LEDs in the presence of [Acr-Mes]ClO₄ as the photocatalyst and HCl as co-catalyst (Table 1). We were encouraged to find that the reaction in acetonitrile gave the desired product benzocoumarin **2a** in 33% yield without chlorinated byproducts (Table 1, entry 1). Water as the co-

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Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/x0xx00000x

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solvent was then investigated, and the yield was improved to 50% when MeCN/H₂O (2:1) was used as the mixed solvent (entries 2-5). Increasing the loading of HCl to 2 equivalents led to slight improvement of the yield (entry 6). Better yield (65%) was realized when the loading of photocatalyst was increased to 4 mol% (entry 7).

Table 1 Reaction optimization.^a



^a Reaction conditions: **1a** (0.3 mmol), PC (x mol %), HCl (4M in 1,3-dioxane, y equiv.), oxygen (balloon), blue LEDs, solvent (1 mL), RT, 48 h. ^b Isolated yield.



With the optimized reaction conditions in hand, a series of 2-methyl-1,1'-biaryls was then investigated for the reaction (Scheme 2). It was found that biaryls with electron-





The success of photocatalyzed oxidative lactonization of 2methyl-1,1'-biphenyls under mild condition promoted us to investigate the reaction of corresponding 2-aldehyde, alcohol and carboxylic acid (scheme 3). It was found that the reaction of 2-aldehyde-biaryls **3** with electron-withdrawing group went smoothly to give the products (**2d** and **2g**, **2d**) in good yields. Interestingly, the one with electron-donating group (methyl) worked as well (**2j**). Notably, the reaction of 3'-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde showed perfect regioselectivity to give the oxidative lactonization product (**2k**) exclusive at the para-position. The reaction of 2alcohol-biaryls **4** gave the desired products (**2g** and **2i**) in reasonable yields. Finally, the reaction of 2-phenylbenzoic acid (**5**) gave benzocoumarin **2b** in high yield (85%).

To classify the mechanism of the photocatalyzed dehydrogenative lactonization reaction, some control experiments were carried out (Scheme 4). It was found that no reaction occurred when light or photocatalyst was absent (reactions a & b). The yield of product was dramatically decreased without the addition of hydrochloride (reaction c). The reaction was totally prohibited when two equivalence of

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TEMPO was added as the radical inhibit (reaction d). Finally, the oxidation of benzaldehyde and benzyl alcohol under the standard conditions afforded benzoic acid in good yields (reactions e & f).



Scheme 4 Control experiments

Based on the experimental results and literature reports,^{16b-d, 18} a plausible mechanism of the reaction is described in Fig. 2. Irradiation of the photocatalyst gives its electron-transfer state $({\sf Acr}^{{\scriptscriptstyle\bullet}}{\sf -Mes}^{{\scriptscriptstyle\bullet}{\scriptscriptstyle+}})^{19}$ that can oxidize ${\sf Cl}^{\scriptscriptstyle-}$ to Cl[•]. A hydrogen of the methyl group of 1,1'-biphenyl is abstracted by Cl^{*} to afford benzyl radical I. It should be noted that the benzyl radical I can also be directly generated via the single electron transfer with excited photocatalyst when no hydrochloride is added according to control experiment (Scheme 4, reaction c). The oxidation of benzyl radical by oxygen affords peroxyl radical II, which is decomposed under oxygen to give aldehyde 3 and alcohol 4 via the disproportionation. Further photocatalyzed oxidation of aldehyde 3 and alcohol 4 leads to acid 5, which could be detected by TLC during the reaction. Next, the benzoyloxy radical III is generated from the acid, followed by intramolecular 6-endo-trig radical addition^{13, 20} to give the cyclic radical IV. The radical is finally oxidized to benzocoumarin 2 via hydrogen atom abstraction (HAT) or SET/deprotonation processes.



In conclusion, the visible-light photocatalytic tandem multiple C-H oxidation and dehydrogenative lactonization of 2-methyl-1,1'-biaryls was developed to give benzocoumarins in good yields. This methodology features multiple C-H functionalization using O_2 as the final oxidant under mild conditions. In addition, the corresponding aldehydes, alcohol and acid of the 1,1'-biaryls also worked for the reaction.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos 21425207, 21521002 and 21702208), and the Chinese Academy of Sciences is greatly acknowledged.

Conflicts of interest

The authors declare no conflicts of interest

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A visible light mediated C-H lactonization of 2-methyl-1,1'-biaryls with oxygen as the

oxidant was developed, giving benzocoumarins in good yields.

View Article Online DOI: 10.1039/C9OB00529C