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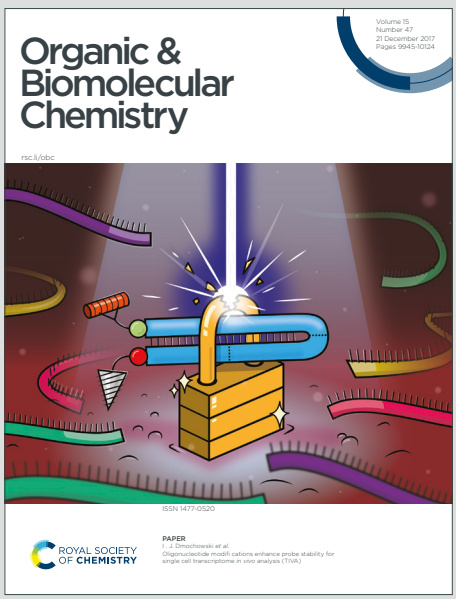

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ARTICLE

Cerium photocatalyzed dehydrogenative lactonization of 2-arylbenzoic acids

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The first cerium photocatalyzed dehydrogenative lactonization of 2-arylbenzoic acids has been developed. This operationally simple protocol allow rapid access to synthetically useful coumarins on a gram scale by employing $CeCl_3$ as a photocatalyst and O_2 as a terminal oxidant. Overall, this deliver an economical and environmentally amiable entry to diversely substituted coumarins, an important structural motifs in bioactive molecules.

Introduction

The Visible-light photocatalysis has emerged as one of the fastest growing field in organic synthesis. In such reactions, a photoactive catalyst absorbs visible light and participates in either single electron transfer (SET) or energy transfer (ET) processes with organic substrates to generate various radical entities under very mild reaction conditions.[1] Most photoredox catalysts at present use are transition metal derived complexes[2] or synthetically elaborate organic dyes,[3a-d] the cost and limited availability[3e] of which can hamper their application for industrial processes. Recently, visible-light induced Ligand to Metal Charge Transfer (LMCT) has gained significant attention for the generation of radical entities by coordination-LMCT-homolysis process[4,5] This strategy substitutes transition metal (Ir, Ru) based photocatalysts for an abundant and inexpensive metal catalyst, thus empower a new plot for the late-stage derivatization of complex molecules.[5]

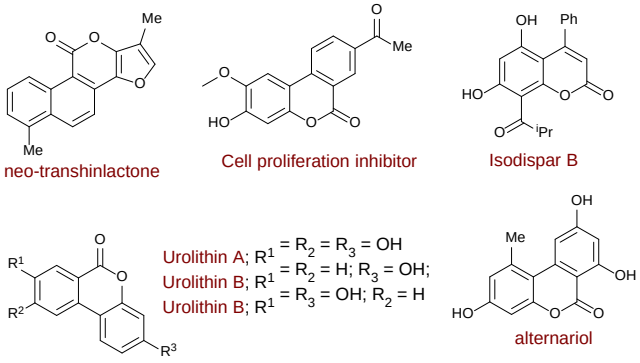

Figure 1. Natural products and pharmaceuticals containing benzo 3,4-coumarins.

Derivatives of benzo-3,4-coumarins are widely found in pharmaceuticals and natural bioactive compounds such as neo-transshinlactone,[6a] cell proliferation inhibitors,[6b] Isodispar B,[6c] alternariol[6d,e] and the urolithin family[7] (Figure 1). Recently, in material science these molecules found an interesting applications.[8] Due to the important synthetic applications of benzo-3,4-coumarins, significant achievements have been made by using C-H activation strategies for their synthesis[9–11]. Among these synthetic protocols, the intramolecular C–H lactonization of 2-arylbenzoic acids has emerged as attractive and efficient method (Figure 2, top). Early methods employing undesirable stoichiometric toxic reactants[12] or UV light[13] have been used for such reactions. Also, transition metal (Pd, Cu) catalyzed procedures have been developed. Recently, a silver-catalyzed method has been described to enable this reaction,

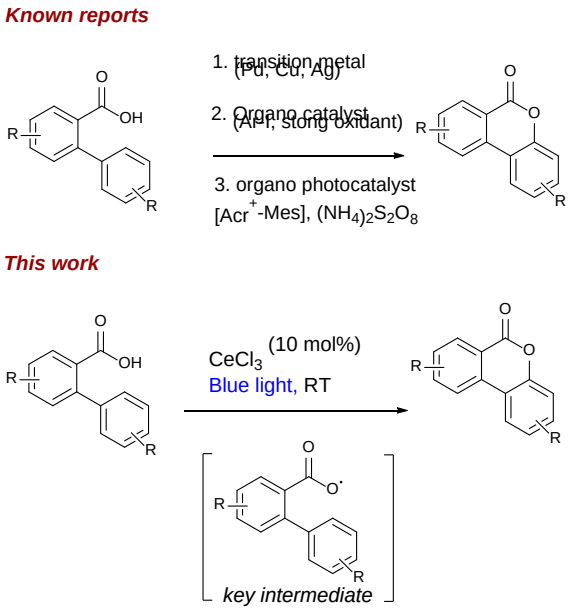

Figure 2. Dehydrogenative lactonization of 2-arylbenzoic acids

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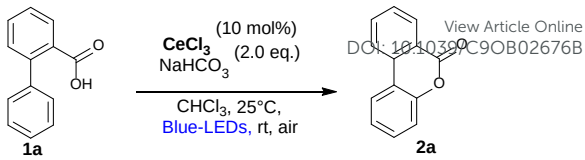
most likely via SET oxidation-radical cyclization.[14] In addition, Martin group reported the first organocatalyzed dehydrogenative lactonization process that avoids the use of expensive transition metal and toxic catalysts[15] However, a common feature associated with all these methods are employing stoichiometric amounts of oxidants [e.g., $PhCO_2OtBu$, $(PhCO_2)_2$, AcOOH, $K_2S_2O_8$, $(NH_4)_2S_2O_8$] that leads to waste generation.Photo catalysis has also provided an alternative strategy for this dehydrogenative lactonization reaction. In 2013, Wei et al. developed the NIS-mediated lactonization of 2-arylbenzoic acids for the synthesis of benzo-3,4-coumarins.[16] In 2015, Gonzalez-Gomez et al. also reported a visible-light photocatalytic intramolecular dehydrogenative lactonization of 2-arylbenzoic acids using $(NH_4)_2S_2O_8$ as the stoichiometric oxidant.[17a] In 2019 Song Ye et al. also reported photocatalytic oxidative lactonization of 2-methyl-1,1'-biaryls using oxygen as the final oxidant.[17b] More recently, three groups described a dual cobalt-photoredox system for the dehydrogenative lactonization of 2-arylbenzoic acids[18]

Results and Discussions

Motivated by the recent work of Zuo[5a] and König[5e] et al., who developed the cerium photocatalyzed 1,5-HAT functionalization of alcohols and the cerium photocatalyzed decarboxylative hydrazination of alkyl carboxylic acids. We wondered how 2-arylbenzoic acids would behave under cerium photocatalysis. Given that decarboxylation of aromatic carboxyl radicals is slower than for their aliphatic homologues,[19] we thus reasoned that homolysis of 2-aryl benzoicacids under cerium photocatalysis would provide benzoyloxy radicals (key intermediate, Figure 2) that could be trapped by the aryl substituent in an intramolecular fashion, further oxidation would generate the benzo-3,4-coumarins (Scheme 2). Herein, we report the first cerium photocatalyzed dehydrogenative lactonization of 2-arylbenzoic acids in the presence of visible light at room temperature, which could provide an alternative robust method for the synthesis of benzo-3,4-coumarins (Figure 2, bottom).

We were pleased to find that the dehydrogenative lactonization of biphenyl-2-carboxylic acid (**1a**) took place efficiently at room temperature upon irradiation with blue LEDs (455 nm) under cerium photocatalysis. Specifically, using $CeCl_3$ (10 mol%) as the photocatalyst and O_2 (air) as the terminal oxidant in the presence of $NaHCO_3$ (2.0 eq) in $CHCl_3$ gave compound **2a** in 90% isolated yield after 20 h (Table 1, entry 1). The reaction using $CeCl_3.7H_2O$ as a photocatalyst works with similar efficiency to give **2a** in 85% yield (Table 1, entry 2), while the yield of **2a** slightly dropped upon use of other cerium salts (Table 1, entry 3 and 4). When $NaHCO_3$ was replaced with K_2CO_3, **2a** was afforded in 66% yield (Table 1, entry 5), where as employing Cs_2CO_3 instead of $NaHCO_3$ caused a drastic reduction in the yield (Table 1, entry 6). The reaction worked with similar efficiency in EtOAc, Acetone and CH_3CN, while other solvents (e.g., DMF or THF) were less effective (Table 1, entries 10-11). The substitution of air for an



Entry	Deviation from standard conditions	2a (%)[a]
1	***none***	***95(90)***[b]
2	$CeCl_3 \cdot 7H_2O$ instead of $CeCl_3$	85
3	$(NH_4)_2Ce(NO_3)_6$ instead of $CeCl_3$	60
4	$(^tBu_4)_2CeCl_6$ instead of $CeCl_3$	80
5	K_2CO_3 instead of $NaHCO_3$	66
6	Cs_2CO_3 instead of $NaHCO_3$	25
7	EtOAc instead of $CHCl_3$	92
8	Acetone instead of $CHCl_3$	90
9	CH_3CN instead of $CHCl_3$	85
10	THF instead of $CHCl_3$	62
11	DMF instead of $CHCl_3$	56
12	with 2.0 eq. of $(NH_4)_2S_2O_8$ instead of air	6
13	with O_2 ballon	78
14	Under nitrogen	6
15	without $CeCl_3$	0
16	without light	0

Table 1. Optimization of the reaction conditions. **1a** (0.2 mmol), $CeCl_3$ (10 mol%), $CHCl_3$ (0.1 M) at 25°C, 455 nm blue LED for 20 h. [a]NMR yields using trimethoxy benzene as internal standard. [b]Isolated yield.

oxygen atmosphere afforded, **2a** in 78% yield (Table 1, entry 13), while employing $(NH_4)_2S_2O_8$ instead of air diminished in the yield (Table 1, entry 12). Additionally, control experiments indicated that a light irradiation, catalytic amount of cerium salt and an air atmosphere were required for the reaction to occur. Not even traces of **2a** were detected in the absence of cerium catalyst or the light (Table 1, entries 15 and 16).

With the optimized reaction conditions in hand, we next investigated the substrate scope (Scheme 1). First, the electronic variation in the para position of the Ar^2 ring was studied. The results indicates that ethyl (**1b**), *tert*-butyl (**1c**), phenyl (**1d**) halogens such as fluoro (**1e**), chloro (**1f**), bromo (**1g**), trifluoromethyl (**1h**), trifluoromethoxy (**1i**), groups were all well tolerated, giving benzo-3,4-benzocoumarins in 67–91% yields. Next, the electronic variation in the meta- substitution of the Ar^2 ring was investigated. Electron donating (Me, OMe; **1j** and **1k**) groups provide the corresponding benzo-3,4-coumarins in mixture of regio isomers. While electron-withdrawing (F, Cl; **1l** and **1m**) groups furnished the corresponding benzo-3,4-coumarins as a single regio isomer in moderate to excellent yields (Scheme 1). Notably, this reaction could tolerate functional groups such as ketone (**1n**), amide (**1o**), nitro (**1p**) and benzyloxy (**1x**) give the corresponding benzo-3,4-coumarins as a single regio isomer in moderate to good yields (Scheme 1). Meanwhile, the corresponding benzo-3,4-benzocoumarins (Scheme 1, **1q-t**) were obtained in good regioselectivities with good yields.[20] However, when the ortho position of Ar^2 was substituted, the reaction was significantly inhibited.[20] A naphthalene (**1u**, **1v**), dibenzothiophene (**1aa**), dibenzofuran (**1ab**) ring could also be tolerated in this reaction (Scheme 1). Arylcinnamic acids **1w-1y** was converted to the corresponding coumarin **2w-2y** in good yield, which shows

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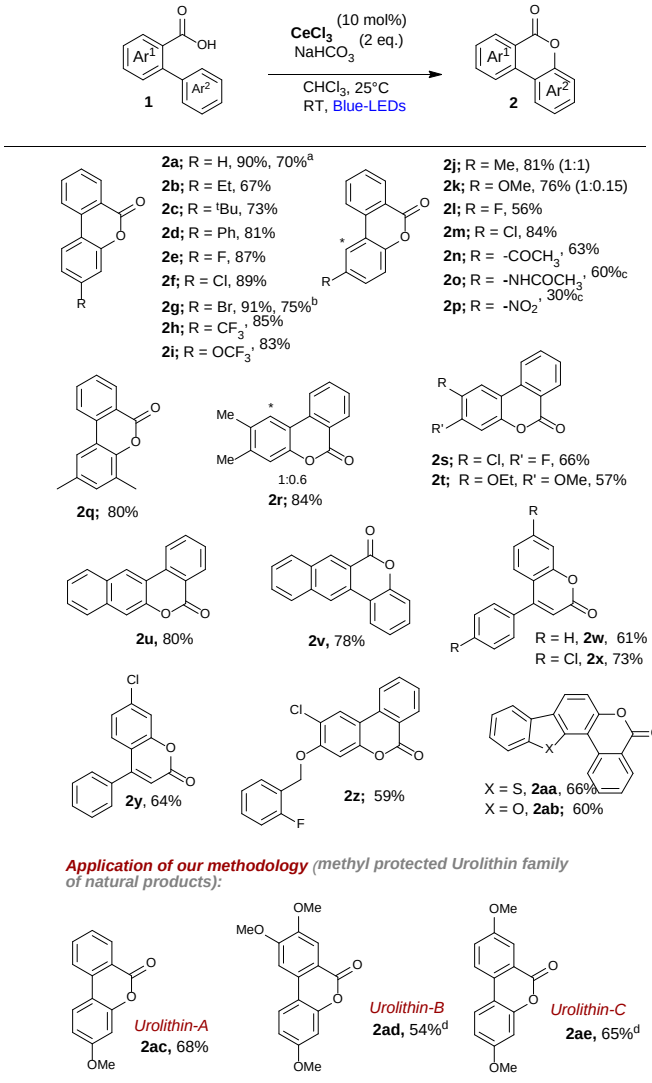
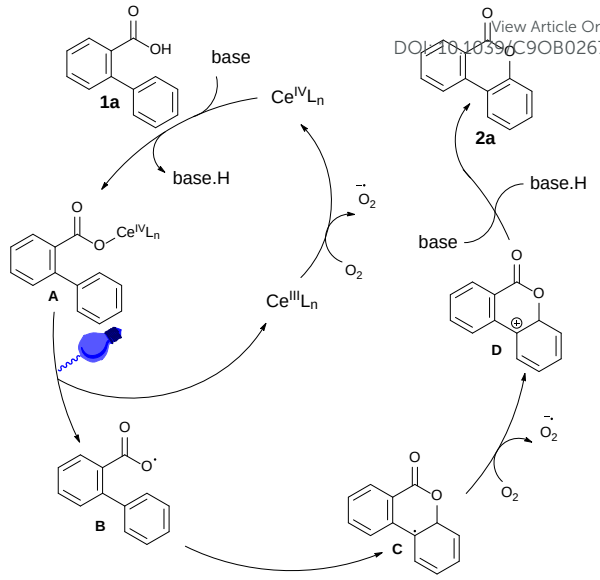


Scheme 1. Dehydrogenative lactonization of 2-aryl benzoic acids. Reaction conditions as given in Table 1 (entry 1). Isolated yields, average of at least two independent runs. [a]Reaction performed at 5.0 mmol. [b]Reaction performed at 3.6 mmol scale. [c]Mixture of DMSO and $CHCl_3$ (1:1) was used as a solvent. [d]Acetone was used as a solvent. *other regio isomer.

further synthetic application of our lactonization. To show potential application of our methodology, a gram-scale synthesis of this lactonization was performed. A 5 mmol and 3.6 mmol portion of **1a** and **1g** could be cyclized to **2a** and **2g** in 70% and 75% yield. This result indicated that the cerium photocatalyzed dehydrogentaive lactonization had great potential in a practical organic synthesis.

To further demonstrate the synthetic utility of our methodology, we targeted the synthesis of the methyl protected urolithin family of natural products (Scheme 1). Starting from commercially available starting materials, we synthesized substituted 2-aryl benzoic acids, then applied our dehydrogenative lactonization to convert compounds (**1ac-1ae**) to cyclized products (**2ac-2ae**) in good yields.[20,21] The efficiency of our dehydrogenative lactonization reaction



Scheme 2. Proposed mechanism for the dehydrogenative lactonization

prompted us to conduct some preliminary mechanistic studies.[20] As anticipated, ON/OFF experiments revealed that our reaction required a continuous visible light irradiation to proceed.[20] The inhibition of catalysis upon addition of TEMPO further indicate that the reaction proceeds via radical intermediates.

Based on the investigations of Zuo[5a] and König[5d,e] et al., we propose that the dehydrogenative lactonization of 2-arylbenzoic acids to benzo-3,4-coumarins occurs via benzoyloxy radical generation upon ligand-to-metal-charge-transfer (LMCT). The detailed mechanistic proposal is shown in Scheme 2. By oxidation of $CeCl_3$ with O_2, a cerium(IV) species is generated. Next the co-ordination of aryl carboxylic acid with Ce^{IV} forms complex **A**, which undergoes the photoinduced Ce-O(CO) homolytic cleavage and regenerates the catalytically competent Ce^{III} species and carboxyl radical **B.** Followed by an intramolecular attack by the carboxyl radical[22] to the aryl substituent generate the cyclized intermediate **C**. Which further undergoes a single electron transfer (SET) process with O_2, **C** would be converted to cation intermediate **D**. Finally, a deprotonation process, from **D** would deliver the desired product **2**.

Conclusions

In conclusions, we have developed a general procedure for the catalytic dehydrogenative lactonization of 2-aryl carboxylic acids using an inexpensive cerium photocatalyst under transition metal free conditions. This operationally simple protocol allows for the efficient synthesis of benzo-3,4-coumarins derivatives and has been applied to the family of natural products. We further demonstrated the application of our methodology by a gram scale reaction, which is an important industrial application.

Conflicts of interest

There are no conflicts to declare

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