

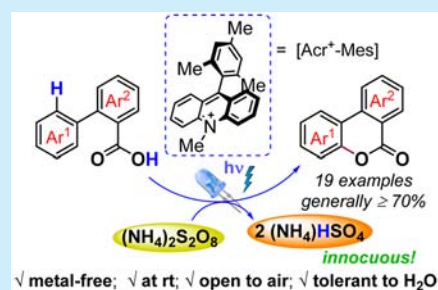
Photocatalytic Dehydrogenative Lactonization of 2-Arylbenzoic Acids

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S Supporting Information

ABSTRACT: A metal-free dehydrogenative lactonization of 2-arylbenzoic acids at room temperature was developed. This work illustrates the first application of visible-light photoredox catalysis in the preparation of benzo-3,4-coumarins, an important structural motif in bioactive molecules. The combination of photocatalyst [Acr⁺-Mes] with (NH₄)₂S₂O₈ as a terminal oxidant provides an economical and environmentally benign entry to different substituted benzocoumarins. Preliminary mechanistic studies suggest that this reaction most likely occurs through a homolytic aromatic substitution pathway.



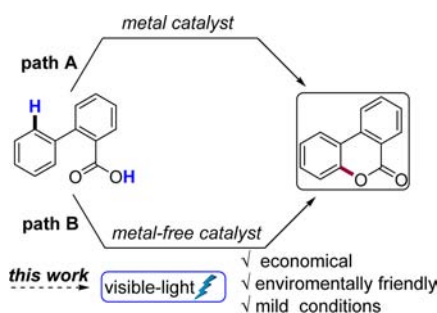
Benzo-3,4-coumarins derivatives are widely found in natural bioactive compounds,¹ as well as key intermediates in the synthesis of natural products,² including some examples with axial chirality.³ Recently, these molecules have also found interesting applications in material science.⁴ The diverse applications of benzocoumarins make them ideal targets to develop novel efficient methods for their preparation.

Carboxylic acids are readily available and versatile starting materials.⁵ Accordingly, the dehydrogenative lactonization of 2-arylbenzoic acids has emerged as a very attractive approach to prepare benzo-3,4-benzocoumarins. Stoichiometric toxic reactants⁶ as well as UV light⁷ have been used with this purpose, limiting the actual applicability of these methodologies. More recently some metal catalyzed procedures have been developed to enable this C–H functionalization/C–O bond formation (Scheme 1, path A). Most of these procedures make use of transition metals such as palladium⁸ or copper based catalysts,⁹ and the large HOMO–LUMO energy gap for these reactions¹⁰ is reflected in reaction temperatures above 75 °C. Very recently, a silver-catalyzed procedure has been reported for this

transformation at room temperature, most likely via SET oxidation-radical cyclization.¹¹ Also very recently, the first organocatalyzed procedure that enables this transformation at room temperature was developed, avoiding the use of toxic and expensive transition metal catalysts (Scheme 1, path B).¹² In this context, we describe herein the first organocatalyzed dehydrogenative lactonization of 2-arylbenzoic acids promoted by visible light.¹³

Photocatalytic decarboxylation of carboxylic acids promoted by visible light, via carboxyl radicals, has recently emerged as a powerful synthetic tool.¹⁴ Given that decarboxylation of aryloxy radicals is slower than their aliphatic homologues,¹⁵ decarboxylation of aryl acids usually requires temperatures above 100 °C.¹⁶ We thus reasoned that a photocatalytic oxidation of 2-arylbenzoic acids at room temperature would provide benzoyloxy radicals that could be trapped by the aryl substituent, which, after subsequent further oxidation, would lead to benzo-3,4-coumarins. For this transformation we selected the 9-mesityl-10-methylacridinium perchlorate ([Acr-Mes]⁺ClO₄),¹⁷ one of the strongest oxidants in the excited state upon irradiation with visible light, among organic photocatalysts. The triplet state, with a microsecond lifetime, is generally proposed as the reactive species in most oxidative transformations. However, the exact nature of the oxidant and its reduction potential is still a matter of debate ($E_{1/2}^{\text{red}} = +1.88$ V¹⁸ or 1.45 V¹⁹ vs SCE). Recent studies have shown that substrates with reduction potentials over +1.88 V can also be oxidized with [Acr⁺-Mes]^{*}, most likely through a short-lived singlet state ($E_{1/2}^{\text{red}} = +2.08$ V vs SCE).²⁰ Regardless the exact nature of the catalytically active species, the [Acr⁺-Mes] has recently proved to be useful for the photocatalytic decarboxylation of aliphatic acids.²¹

Scheme 1. Catalytic Dehydrogenative Lactonization of 2-Arylbenzoic Acids



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We were pleased to find that the dehydrogenative lactonization of 2-phenylbenzoic acid (**1a**) took place efficiently upon irradiation with blue LEDs at room temperature, using [Acr-Mes]ClO₄ as the photocatalyst and air as the terminal oxidant (Table 1, entry 1).²² The reaction worked with similar

Table 1. Reaction Optimization

1 (X)	entry	solvent ^a	oxidant (equiv)	yield ^b
1a (H)	1	A	air (1 atm) ^c	70% (60%) ^d
	2	A	O ₂ (1 atm)	60%
	3	A	air (1 atm)	82% ^c
1b (F)	4	A	air (1 atm)	45%
	5	A	<i>t</i> -BuOOH (1)	73%
	6	A	AcOOH (1)	66%
	7	B	(NH ₄) ₂ S ₂ O ₈ (1.2)	70%
	11	B	(NH ₄) ₂ S ₂ O ₈ (1.2)	46%
1c (OMe)	8	A	air (1 atm)	n.d. ^f
	9	A	<i>t</i> -BuOOH (1)	<10%
	10	A	AcOOH (1)	<10%
	11	B	(NH ₄) ₂ S ₂ O ₈ (1.2)	46%
	12	B	(NH ₄) ₂ S ₂ O ₈ (3)	73%

1a: X = H
1b: X = F
1c: X = OMe

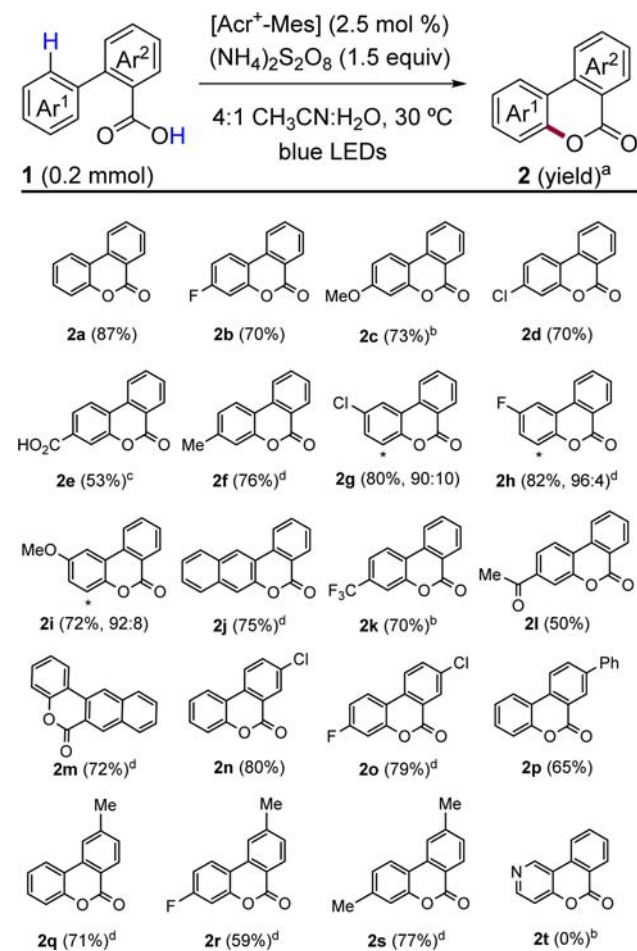
2a: X = H
2b: X = F
2c: X = OMe

^aA: 1:1 DCE/CH₃CN. B: 4:1 CH₃CN/H₂O. ^bIsolated yields at 0.2 mmol scale. ^cThe reaction was opened to air via a needle. ^dAt 2 mmol scale, after 48 h. ^eThe reaction was irradiated with sunlight over 8 h, without stirring; see Supporting Information. ^fNot detected after 48 h.

efficiency in DCE, CH₃CN, or a mixture of these two solvents, while other solvents (e.g., CHCl₃, EtOAc, or DMF) were less suitable. The replacement of air for an oxygen atmosphere, as well as the addition of basic 2,6-lutidine (not shown in Table 1), did not improve the results. When the reaction was scaled up to 2 mmol, it took longer (48 h) and the isolated yield was slightly slower (60%).²³ Remarkably, compound **2a** was obtained in 82% isolated yield after 8 h of sunlight irradiation in an open tube without stirring (entry 3). Unfortunately, when 2-arylbenzoic acids **1b** and **1c**, with different electronic demands, were submitted to the conditions described in entry 1, only a 45% yield was obtained for compound **2b** and no reaction was observed for **1c**. After examining different oxidants and conditions (entries 5, 6, 9 and 10), we found that (NH₄)₂S₂O₈ was a competent oxidant for both substrates. Although about 1 equiv was sufficient for both substrates (entries 7 and 11), the addition of 3 equiv of this oxidant accelerates the reaction of **1c** (entry 12). It is worth noting that the reactions are run in organic/aqueous solvent mixtures, which increase the solubility of (NH₄)₂S₂O₈, and can be run in open flasks. Moreover, this stoichiometric oxidant is cheap, nontoxic, easily removed from reaction mixtures, and generates innocuous byproducts upon reduction (most likely HSO₄⁻).

To evaluate the scope of the reaction, a variety of 2-arylbenzoic acids were submitted to the optimized reaction conditions. Different 4'-substituted acids bearing electron-donor or electron-withdrawing groups furnished the corresponding benzocoumarins in good yields (Scheme 2). Generally, 1.5 equiv of (NH₄)₂S₂O₈ were used, although 3 equiv were necessary for the less reactive substrates (**2c** and **2k**). Although most reactions were run in CH₃CN/H₂O, in

Scheme 2. Substrate Scope

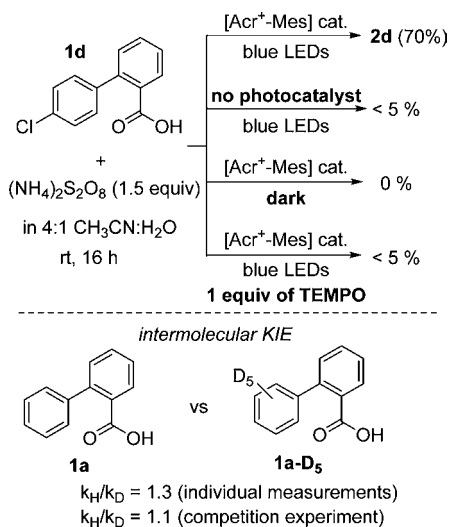


^aIsolated yields of reactions run on 0.2 mmol-scale until complete conversion by TLC (see details in S1). ^b3 equiv of (NH₄)₂S₂O₈ were used. ^cAir (1 atm) was used as oxidant and a 1:1:1 CH₃CN/DCE/MeOH mixture. ^d4:1 DCE/H₂O. * = Minor regioisomer.

some cases better results were obtained in a DCE/H₂O mixture (**2f**, **2h**, **2j**, **2m**, **2o**, **2q**, **2r**, **2s**). Presumably, in DCE/H₂O overoxidation is minimized due to a lower concentration of the stoichiometric oxidant in the organic phase. In the case of diacid **1e**, an organic solvent mixture was used to dissolve the substrate and the desired reaction took place in 53% yield using air as the terminal oxidant. For 3'-substituted acids, the corresponding benzocoumarins (**2g**, **2h**, **2i**) were obtained in good yields and with regioselectivities ranging from 90:10 to 96:4. It is worth mentioning that the regioselectivity obtained for benzocoumarin **2i** under our conditions (92:8) is higher than the one reported for this compound using a copper catalyst at 75–85 °C⁹ and similar to the one obtained with a silver catalyst at room temperature.¹¹ Unfortunately, 2-(3'-pyridinyl)benzoic acid (**1t**) did not react under the established reaction conditions. Other heterocyclic substrates have not been systematically examined yet.

To gain insight into the reaction pathway, some control experiments and preliminary mechanistic studies were carried out (Scheme 3). When substrate **1d** was submitted to the reaction conditions described in Scheme 2, but in the absence of light or photocatalyst, as well as in the presence of TEMPO (1 equiv), the reaction was completely inhibited (<5%). These experiments suggest a photoredox process where radicals are

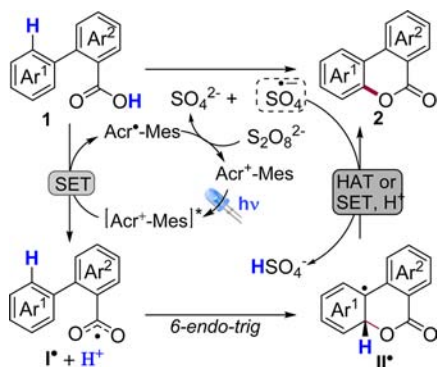
Scheme 3. Preliminary Mechanistic Investigations



likely involved. We also determined the intermolecular kinetic isotopic effect [see Supporting Information (SI) for details] by measuring the individual initial rates of **1a** and **1a-D₅** ($k_{\text{H}}/k_{\text{D}} = 1.3$) and by competition experiments ($k_{\text{H}}/k_{\text{D}} = 1.1$). These results suggest that the C–H bond cleavage might not be the turnover-determining step in the catalytic process.²⁴

Based on our preliminary mechanistic investigations, we tentatively proposed a reaction pathway (Scheme 4) where the

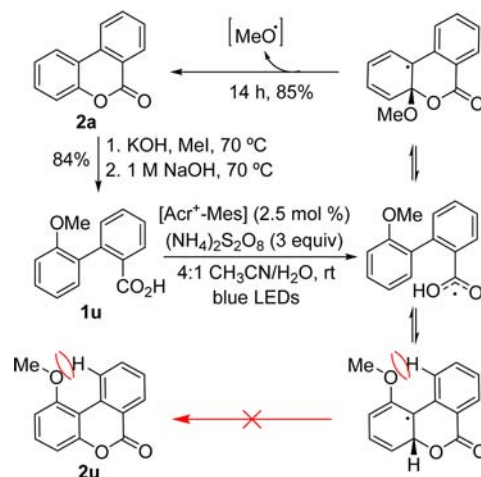
Scheme 4. Plausible Mechanism



activated photocatalyst might generate the benzyloxy radical **I**[•] via single electron transfer (SET). The cyclization should follow a 6-endo-trig approach²⁵ to give intermediate **II**[•], which is finally oxidized to product **2** via hydrogen atom abstraction (HAT) or SET/deprotonation processes. The catalyst turnover would be possible by oxidation with a persulfate anion (or atmospheric oxygen for **2a** and **2e**), generating the sulfate radical-anion [SO₄^{•-}] that can still act as an oxidant in the final aromatization step or in the turnover of the catalyst. This is in line with the observation that only 1 equiv of persulfate is required for most substrates. Based on our kinetic isotopic experiments, and on the high oxidation capacity of the excited photocatalyst that should favor a highly exergonic and fast SET process to generate **I**[•], we speculate that the cyclization is the turnover-determining step. For electron-rich substrates, a different pathway based on the formation of aromatic radical-cations seems also plausible, but the regioselectivity observed

for substrate **2i** is not in accordance with this proposal (see SI for more details). Other mechanisms might also come into play.

To gather more information on the reaction pathway, lactone **2a** was opened in the presence of MeI and KOH,^{9a} and the obtained ester was hydrolyzed (Scheme 5). Acid **1u** was

Scheme 5. Lactone Ring Opening of **2a** and Ring Closing under Photocatalysis

submitted to the photocatalytic dehydrogenative lactonization, and compound **2a** was obtained as a single product in excellent yield. This result is in accordance with the homolytic aromatic substitution pathway depicted in Scheme 4, and other authors have observed similar results using other different oxidants for 2'-substituted-2-arylbenzoic acids.²⁶ The preferred addition at the *ipso*-position should result from kinetic and/or thermodynamic control at the cyclization step, presumably due to steric hindrance between OMe and H₁₀ in **2u**.

In summary, we have developed a visible-light photocatalytic dehydrogenative lactonization of 2-arylbenzoic acids. This method provides a general and convenient access to benzo-3,4-coumarins under mild (room temperature), robust (tolerant to water and air), and environmentally friendly (benign reagents and residues) conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02269.

Experimental procedures, characterization data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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