Photocatalytic Dehydrogenative Lactonization of 2-Arylbenzoic Acids

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Supporting Information Placeholder

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 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, as well as key intermediates in the synthesis of natural products, including some examples with axial chirality. Recently, these molecules have also found interesting applications in material science. 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. Accordingly, the dehydrogenative lactonization of 2-arylbenzoic acids has emerged as a very attractive approach to prepare benzo-3,4-benzocoumarins. Stoichiometric toxic reactants as well as UV light 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 palladium or copper based catalysts and the large HOMO-LUMO energy gap for these reactions 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. Also very recently, the first organocatalyzed dehydrogenative lactonization of 2-arylbenzoic acids promoted by visible-light.

Scheme 1. Catalytic Dehydrogenative Lactonization of 2-Arylbenzoic Acids

Photocatalytic decarboxylation of carboxylic acids promoted by visible-light, via carboxyl radicals, has recently emerged as a powerful synthetic tool. Given that decarboxylation of aroyloxy radicals is slower than their aliphatic homologues, decarboxylation of aroyc acids usually requires temperatures...
above 100 °C. We thus reasoned that a photocatalytic oxidation of 2-arylbenzoic acids at room temperature, would provide benzoyleoxy 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]), 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}^{red} = +1.88 V^{16} or 1.45 V^{17} vs SCE). Recent studies have shown that substrates with reduction potentials over +1.88 V can also be oxidized with [Acr²-Mes]*, most likely through a short-lived singlet state (E_{1/2}^{red} = + 2.08 V vs SCE).²⁰ Regardless the exact nature of the catalytically active specie, the [Acr⁻-Mes] has recently proved to be useful for the photocatalytic decarboxylation of aliphatic acids.¹¹

### Table 1: Reaction Optimization

<table>
<thead>
<tr>
<th>(X)</th>
<th>entry</th>
<th>solvent</th>
<th>oxidant (equiv)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H)</td>
<td>1</td>
<td>A</td>
<td>air (1 atm)²</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>A</td>
<td>O₃ (1 atm)</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>A</td>
<td>air (1 atm)</td>
<td>82%</td>
</tr>
<tr>
<td>(F)</td>
<td>4</td>
<td>A</td>
<td>air (1 atm)</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>A</td>
<td>t-BuOOH (1)</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>A</td>
<td>AcOOH (1)</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>B</td>
<td>(NH₄)₂S₂O₈ (1.2)</td>
<td>70%</td>
</tr>
<tr>
<td>(OME)</td>
<td>8</td>
<td>A</td>
<td>air (1 atm)</td>
<td>n.d.</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>A</td>
<td>t-BuOOH (1)</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>A</td>
<td>AcOOH (1)</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>B</td>
<td>(NH₄)₂S₂O₈ (1.2)</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>B</td>
<td>(NH₄)₂S₂O₈ (3)</td>
<td>73%</td>
</tr>
</tbody>
</table>

²A: 1:1 DCE/CH₃CN; B: 4:1 CH₃CN/MeOH. O: isolated yields at 0.2 mmol scale. c The reaction was opened to air via a needle. d At 2 mmol scale, after 48 h. e The reaction was irradiated with sunlight over 8 h, without stirring, see Supporting Information. f Not detected after 48 h.

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 photocatalyst and air as terminal oxidant (Table 1, entry 1).²² The reaction worked with similar efficiency in DCE, CH₃CN or mixture of 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, took longer (48 h) and the isolated yield was slightly slower (60%).²⁵ 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 45% yield was obtained for compound 2b and no reaction was observed for 1c. After examined 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 equivalent was sufficient for both substrates (entries 7 and 11), the addition of 3 equivalents of this oxidant accelerate 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, non-toxic, easily removed from reaction mixtures and generates innocuous by-products upon reduction (most likely HSO₄⁻).

### Scheme 2. Substrate Scope

We isolated yields of reactions run on 0.2 mmol scale until complete conversion by TLC (see details in SI).³ Is equiv of (NH₄)₂S₂O₈ were used. ³Air (1 atm) was used as oxidant and a 1:1 CH₃CN/DCE/MeOH mixture. ⁴4:1 DCE/H₂O. *Minor regioisomer.
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 equivalents of (NH₄)₂S₂O₈ were used, although 3 equivalents were necessary for the less reactive substrates (2e and 2k). Although most reaction were run in CH₃CN/H₂O, in some cases better results were obtained in a DCE/H₂O mixture (2f, 2g, 2i, 2m, 2o, 2q, 2r, 2s). Presumably, in DCE/H₂O overoxidization is minimized due to a lower concentration of the stoichiometric oxidant in the organic phase. In the case of dicarboxylic acid 1e, an organic solvent mixture was used to dissolve the substrate and the desired reaction took place in 53% yield using air as 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 ºC and similar to the one obtained with a silver catalyst at room temperature. Unfortunately, 2-(3'-pyridyl)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 formed by single electron transfer (SET) or SET/deprotonation processes. The catalyst turnover would be possible by oxidation with persulfate anion ([Ac⁺·Mes] cat.) or a stoichiometric oxidant in the organic phase. In the presence of TEMPO, the reaction is completely inhibited (< 5%), indicating that the reaction pathway is not via SET. To gather more information on the reaction pathway, lactone 2a was opened in the presence of MeI and KOH, and the obtained ester was hydrolyzed (Scheme 5). Acid 1u was 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. The preferred addition at the ipso-position should result from a 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
ASSOCIATED CONTENT

Supporting Information
Experimental procedures, characterization data and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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REFERENCES

(22) The internal temperature of the irradiated reaction mixture was found to be in the range 30–35 °C.
