



Calcium iodide catalyzed photooxidative oxylactonization of oxocarboxylic acids using molecular oxygen as terminal oxidant

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ABSTRACT

We developed aerobic photooxidative oxylactonization of oxocarboxylic acids catalyzed by calcium iodide using molecular oxygen as the terminal oxidant under photo irradiation.

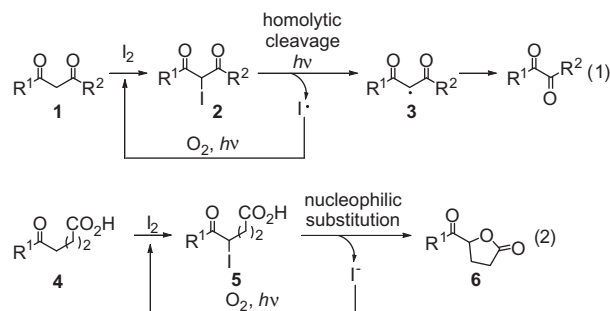
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Molecular oxygen has received much attention as a primary environmentally benign oxidant because it is photosynthesized by plants, produces little waste, is inexpensive, and has greater atom efficiency than other oxidants.¹ From this perspective, we have developed several catalytic photooxidation methods using molecular oxygen as the terminal oxidant.² In the course of our further studies of aerobic photooxidations, we have successfully found the efficient oxylactonization of oxocarboxylic acids to the corresponding oxolactones under aerobic photooxidation conditions using molecular oxygen as the terminal oxidant in combination with photo irradiation.

Lactones are essential structural motifs in organic chemistry because their frameworks are ubiquitously found in many biologically active natural products. Various methods for the preparation of lactones from many types of substrates have been reported, and of these, the oxylactonization of oxocarboxylic acids is one of the most efficient synthetic methods. Several oxylactonizations have been described that use stoichiometric amounts of reagents such as (i) Br₂,³ (ii) (CF₃CO)₂O/hν,⁴ (iii) CuCrO₄,⁵ (iv) lead acetate,⁶ and (v) Koser's reagent and its derivatives.⁷ Recently, the catalytic oxylactonization of oxocarboxylic acids to oxolactones with in situ generated Koser's reagent derivatives has been reported.⁸ Furthermore, Ishihara's group showed that tetrabutylammonium iodide was highly effective as a precatalyst for the oxylactonization of oxocarboxylic acids with 30% aqueous hydrogen peroxide.⁹ However, to the best of our knowledge, there is

no reported catalytic oxylactonization of oxocarboxylic acids that uses molecular oxygen as the terminal oxidant.

Recently, we reported the tandem oxidative conversion of 1,3-diketones **1** to 1,2-diketones in the presence of a catalytic amount of iodine.²⁰ In this reaction, 1,3-diketones **1** are iodinated at the α-position to give iodide **2**, and iodide **2** is then cleaved homolytically to an iodine radical and radical species **3**, which is subsequently converted to 1,2-diketone (Scheme 1, Eq. 1). In contrast, the aerobic photooxidation of the iodine radical or hydrogen iodide, generated by the abstraction of hydride from a substrate or a solvent, to iodine enables iodine-catalyzed oxidative conversion with molecular oxygen as the terminal oxidant. It occurred to us that a successive nucleophilic substitution of the iodine of iodide **5** by the internal carboxylic acid and oxidation of the resulting iodide anion to iodine under aerobic photooxidation conditions would enable



Scheme 1. Aerobic photooxidative oxylactonization with an iodine source.

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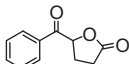
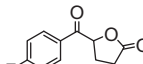
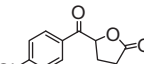
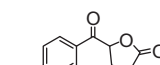
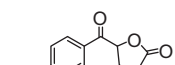
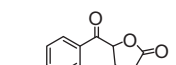
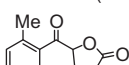
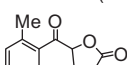
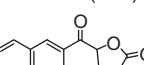
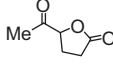
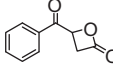
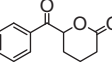
the synthesis of oxolactone **6** from oxocarboxylic acid **4** using molecular oxygen as the terminal oxidant (Scheme 1, Eq. 2).

Initially, to explore the potential of iodine-catalyzed aerobic photooxidative oxylactonization, we chose 4-benzoylbutyric acid (**4a**) as a test substrate to optimize the reaction conditions (Table 1). Although we examined this reaction under the optimized conditions of our previous works,^{21,6} product **6a** was either not obtained or obtained in a low yield (entries 1 and 2). Among the solvents, iodine sources, and additives examined, THF, CaI_2 , and K_2CO_3 appear to be the most suitable, respectively (entries 3–8). As a result of further optimization, the highest yield was obtained using CaI_2 (0.2 equiv), K_2CO_3 (0.1 equiv), and THF (5 mL) under irradiation with a 400-W high-pressure mercury lamp for 20 h (entries 4, 9–11, 15, and 16). Surprisingly, this reaction proceeded even under an air atmosphere (entry 12). In contrast, **6a** was not obtained in an Ar atmosphere or in the dark (entries 13 and 14). Furthermore, note that the reaction proceeded in a good yield even in the presence of the radical scavenger galvinoxyl, indicating that the reaction proceeded by a nonradical mechanism (entry 17).

With these optimized reaction conditions with the iodine source, the scope and limitations of the reaction were explored using a series of oxocarboxylic acids (Table 2).¹⁰ Electron-deficient and electron-rich substrates gave the corresponding oxolactones (**6b**, **6c**, **6d**, **6e**, and **6f**) in good yields. Sterically hindered substrates possessing two methyl groups on the aromatic ring gave the corresponding oxolactones (**6g** and **6h**) in modest yields. 4-(2-Naphthoyl)butyric acid (**4i**) gave the corresponding oxolactone (**6i**) in good yield. Unfortunately, 4-acetylbutyric acid (**4j**), 3-ben-

Table 2

Scope and limitations^a

$\text{substrate (0.3 mmol)} \xrightarrow[\text{THF}]{\text{O}_2, h\nu \text{ (400-W Hg lamp)} \text{CaI}_2 \text{ (0.2 equiv)} \text{K}_2\text{CO}_3 \text{ (0.1 equiv)}} \text{product}$		
 6a 63% (20 h)	 6b 74% (10 h)	 6c 64% (20 h)
 6d 58% (70 h)	 6e 65% (40 h)	 6f 58% (70 h)
 6g 36% (20 h)	 6h 24% (20 h)	 6i 57% (70 h)
 6j 7% (20 h)	 6k 0% (20 h)	 6l 16% (40 h)

^a Isolated yields. Substrate (0.3 mmol), CaI_2 (0.2 equiv), K_2CO_3 (0.1 equiv), THF (5 mL), with O_2 balloon, and irradiation with a 400-W high pressure mercury lamp.

Table 1

Study of reaction conditions with an iodine source^a

$\text{4a} \xrightarrow[\text{solvent, 20 h}]{\text{O}_2, h\nu \text{ (400-W Hg lamp)} \text{iodine source additive}}$				
Entry	Iodine source (equiv)	Additive (equiv)	Solvent	Yield ^b (%)
1	I_2 (0.2)	$\text{Ca}(\text{OH})_2$ (0.5)	EtOAc	0 ^c
2	CaI_2 (0.2)	—	MeOH	4 ^c
3	CaI_2 (0.2)	—	THF	25
4	CaI_2 (0.2)	K_2CO_3 (0.2)	THF	57
5	I_2 (0.2)	K_2CO_3 (0.2)	THF	52
6	NIS (0.2)	K_2CO_3 (0.2)	THF	50
7	CaI_2 (0.2)	$\text{Ca}(\text{OH})_2$ (0.5)	THF	49
8	CaI_2 (0.2)	Et_3N (0.2)	THF	25
9	CaI_2 (0.1)	K_2CO_3 (0.2)	THF	54
10	CaI_2 (0.2)	K_2CO_3 (0.1)	THF	74 (63)
11	CaI_2 (0.2)	K_2CO_3 (0.05)	THF	58
12	CaI_2 (0.2)	K_2CO_3 (0.1)	THF	67 ^d
13	CaI_2 (0.2)	K_2CO_3 (0.1)	THF	0 ^e
14	CaI_2 (0.2)	K_2CO_3 (0.1)	THF	0 ^f
15	CaI_2 (0.2)	K_2CO_3 (0.1)	THF	43 ^c
16	CaI_2 (0.2)	K_2CO_3 (0.1)	THF	65 ^g
17	CaI_2 (0.2)	K_2CO_3 (0.1)	THF	72 ^h

^a Reaction conditions: **4a** (0.3 mmol), iodine source, additive, solvent (5 mL), with O_2 balloon, and irradiation with a 400-W high pressure mercury lamp for 20 h.

^b ¹H NMR yields. Number in parentheses denotes isolated yield.

^c This reaction was carried out through irradiation with four of 22-W fluorescent lamp.

^d This reaction was carried out under an air atmosphere.

^e This reaction was carried out under an Ar atmosphere.

^f This reaction was carried out in the dark.

^g This reaction was carried out through irradiation with a 500-W Xe lamp.

^h This reaction was carried out in the presence of galvinoxyl (1.0 equiv).

zoylpropionic acid (**4k**), and 5-benzoylpentanoic acid (**4l**) were poor substrates.

To clarify the reaction mechanism, we assayed the peroxides in solution and found that 2-tetrahydrofuryl hydroperoxide (**7**, 0.17 mmol) is generated in THF under the optimized conditions (Table 3, entry 1). Furthermore, **7** (0.51 mmol) was generated in the absence of a substrate, a catalyst, and an additive, and **7** (0.13 mmol) was generated in the presence of oxygen only in the dark (entries 2 and 4).¹¹ Thus, we examined the reaction using THF, which was irradiated with 400-W Hg lamp for 20 h beforehand as the solvent, and found that the reaction proceeded in a good yield under an optimized condition (Table 4, entry 1). In contrast, the reaction did not proceed in the absence of calcium iodide (entry 2). Without light irradiation or molecular oxygen, **6a** was obtained in low yields (entries 3–5). These results suggest that the iodide anion was oxidized to iodine partly by 2-tetrahydrofuryl hydroperoxide, generated from THF under aerobic photooxidation conditions,¹² and partly by light irradiation and molecular oxygen. Note that H_2O_2 was a poor oxidant under this condition, and **6a**

Table 3

Assay of 2-tetrahydrofuryl hydroperoxide

$\text{(5 mL)} \xrightarrow[\text{20 h}]{\text{conditions}} \text{7}$		
Entry	Conditions	7 ^a (mmol)
1	$\text{O}_2, h\nu$ (400-W Hg lamp), 4a (0.3 mmol) CaI_2 (0.2 equiv), K_2CO_3 (0.1 equiv)	0.17 (0.17)
2	$\text{O}_2, h\nu$ (400-W Hg lamp)	0.51 (0.59)
3	Ar, $h\nu$ (400-W Hg lamp)	0.01
4	O_2	0.13

^a Determined by iodometry. Numbers in parentheses were determined by ¹H NMR using internal standard.

Table 4
Effect of 2-tetrahydrofuryl hydroperoxide^a

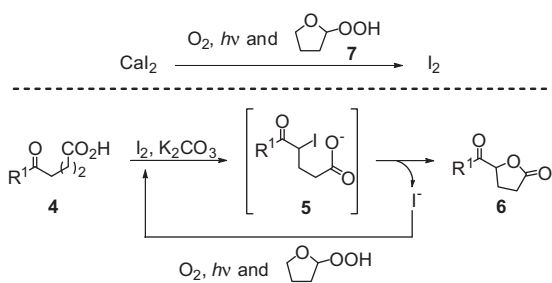
$\text{O}_2, h\nu$ (400-W Hg lamp)
 Cal_2 (0.2 equiv)
 K_2CO_3 (0.1 equiv)
 THF, 20 h

Entry	Change from standard conditions	Yield ^b (%)	
		6a	4a
1	—	67	6
2	Without Cal_2 and K_2CO_3	0	95
3	In the dark	39	55
4	Under Ar	20	53
5	In the dark, under Ar	9	90
6 ^c	H_2O_2 (1.2 equiv) was added, in the dark	8	72

^a Reaction conditions: **4a** (0.3 mmol), Cal₂ (0.2 equiv), K₂CO₃ (0.1 equiv), THF (5 mL). Before using, THF was irradiated with a 400-W high pressure mercury lamp with O₂ balloon for 20 h. This THF include 2-tetrahydrofuryl hydroperoxide (0.51 mmol) (Table 3, entry 2)), with O₂ balloon, and irradiation with a 400-W high pressure mercury lamp for 20 h.

^b ¹H NMR yields.

^c THF was used without previous irradiation under an oxygen atmosphere.



Scheme 2. Plausible path.

was obtained in a low yield (entry 6). These results indicate the following reaction mechanism (Scheme 2): (1) Calcium iodide is oxidized to iodine with light and molecular oxygen or 2-tetrahydrofuryl hydroperoxide (7). (2) The enolate of the oxocarboxylic acid **4** is formed with potassium carbonate, and reacts with iodine to form iodide **5**. (3) Iodide **5** cyclizes to form oxolactone **6** in the presence of potassium carbonate. (4) The reoxidation of the iodide anion to iodine completes the catalytic cycle, thus enabling the iodine-catalyzed reaction.

In conclusion, we have developed convenient methods for the direct synthesis of oxolactones from oxocarboxylic acids catalyzed by calcium iodide. This method is of great value from a green chemistry perspective and organic synthesis because of its use of molecular oxygen as the terminal oxidant.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.11.014>.

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- Typical procedure:** A solution of substrate (0.3 mmol), Cal₂ (0.2 equiv), and K₂CO₃ (0.1 equiv) in dry THF (5 mL) in a Pyrex test tube with O₂ balloon is stirred and irradiated externally with 400-W high pressure mercury lamp at room temperature for the indicated time. The temperature of the reaction mixture at the final stage of this reaction was about 50 °C. The product is quenched with 0.5 M aq Na₂S₂O₃. Then the solution is acidified with 0.5 M aq HCl and extracted with EtOAc. The product is purified by PTLC.
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