

# Tandem Oxidation/Rearrangement of $\beta$ -Ketoesters to Tartronic Esters with Molecular Oxygen Catalyzed by Calcium Iodide under Visible Light Irradiation with Fluorescent Lamp

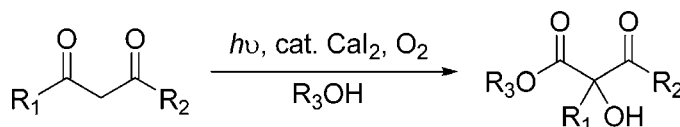
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## ABSTRACT



It was found that  $\beta$ -ketoesters were directly transformed to the corresponding  $\alpha$ -hydroxymalonic esters, tartronic esters, with molecular oxygen catalyzed by calcium iodide under visible light irradiation from fluorescent lamp. This reaction includes tandem oxidation/rearrangement and has received much attention from the viewpoint of reduction of energy consumption, labor, and solvents.

Malonic esters have been important substrates for malonic ester synthesis, a synthetic process used in the synthesis of variety of biologically active compounds.<sup>1</sup> In particular, tartronic esters and hydroxymalonic esters have been studied as biodegradable organic builders for surfactants.<sup>2</sup> The prevalent way for the preparation of tartronic esters is the oxidation of the corresponding malonic esters with heavy metal oxidants (i.e.,  $\text{Pd}(\text{OAc})_4$ ,  $\text{MoOPH}$ ),<sup>3</sup> peracids,<sup>4</sup> or molecular oxygen catalyzed by various metal catalysts (i.e., Mn, Co, Cs, Ce, Pd).<sup>5</sup> However, some problems relating to these reactions, such as low yield,

the necessity of stoichiometric amounts, or environmental high impact catalyst, deserve rectification. With this background, we attempted in photooxidation with molecular oxygen. Some properties of light make it a clean reagent because it has neither shape nor weight that exhausts the residue, and it becomes a most important method for developing environmentally benign processes. Actually, effective use for the light that overflows in our surroundings is an exciting research topic in all fields, including energy. Furthermore, molecular oxygen has recently received much attention since it is photosynthesized by plants and is an effective oxidant of larger atom efficiency than that of other oxidants. Previously, we have reported that alcohols and a methyl group at the aromatic nucleus were oxidized directly to the corresponding carboxylic acids in the presence of catalytic halogen sources in an oxygen atmosphere under UV or vis irradiation.<sup>6</sup> This new oxidation reaction is appealing to the notion of "Green Chemistry"<sup>7</sup> due to nonuse of heavy metals, waste reduction, use of molecular oxygen, and inexpensive acquisition of reagents. In the course of our further study on the extension of the application, we have found that  $\beta$ -ketoesters were directly transformed to the corresponding  $\alpha$ -hydroxymalonic esters, tartronic esters, with molecular

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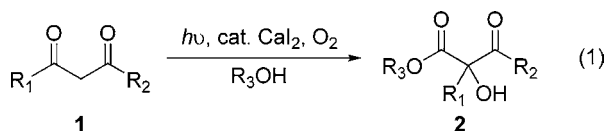
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oxygen catalyzed by calcium iodide under visible light irradiation from a fluorescent lamp (eq 1).



This reaction includes tandem oxidation/rearrangement and has gained much attention from the viewpoint of reduction of energy consumption, labor, and solvents and the development of tandem reactions has been a fertile field in organic synthesis.<sup>8</sup> Herein, we report our detailed study on the scope and limitation of this aerobic photo tandem oxidation/rearrangement.

**Table 1.** Optimization of Catalysts<sup>a</sup>

entry	catalyst	equiv	time (h)	yield <sup>b</sup> (%)
1	LiI	0.2	10	0
2	NaI	0.2	10	0
3	KI	0.2	10	0
4	MgI <sub>2</sub>	0.2	10	65
5	CaI <sub>2</sub>	0.2	10	85
6	CaI <sub>2</sub>	0.2	5	59
7	CaI <sub>2</sub>	0.2	10	0 <sup>c</sup>
8	CaI <sub>2</sub>	0.2	10	0 <sup>d</sup>
9	CaI <sub>2</sub>	0.1	10	8 <sup>e</sup>
10	CaI <sub>2</sub>	0.3	10	80
11	CaI <sub>2</sub>	0.4	10	79
12	SrI <sub>2</sub>	0.2	10	45
13	BaI <sub>2</sub>	0.2	10	24
14	SmI <sub>2</sub>	0.2	10	34
15	TiI <sub>2</sub>	0.2	10	0
16	MnI <sub>2</sub>	0.2	10	0
17	FeI <sub>2</sub>	0.2	10	0
18	CoI <sub>2</sub>	0.2	10	79
19	NiI <sub>2</sub>	0.2	10	81
20	CuI	0.2	10	0
21	ZnI <sub>2</sub>	0.2	10	48
22	AlI <sub>3</sub>	0.2	10	0
23	GeI <sub>4</sub>	0.2	10	0
24	CaCl <sub>2</sub>	0.2	10	0
25	CaBr <sub>2</sub>	0.2	10	0
26	I <sub>2</sub>	0.2	10	0 <sup>f</sup>
27			10	0

<sup>a</sup> Reaction conditions: a mixture of **1a** (0.3 mmol) and catalyst (0.2 equiv) in MeOH (5 mL) was irradiated with fluorescent lamp for 10 h in an oxygen atmosphere. <sup>b</sup> Yield of isolated product. <sup>c</sup> The reaction was carried out in the dark. <sup>d</sup> The reaction was carried out in an argon atmosphere. <sup>e</sup> The mixture of  $\alpha,\beta$ -diketoester and its hydrated species **3a** was obtained in 73% yield. <sup>f</sup> **3a** was obtained in 43% yield.

Table 1 shows the results of the optimization of reaction conditions for the transformation of methyl 3-oxoheptanoate (**1a**), a test substrate, to dimethyl 2-butyl-2-hydroxymalonate (**2aa**).<sup>9</sup> Among the catalysts we examined, 0.2 equiv of CaI<sub>2</sub> was found to produce **2aa** in highest yield, although several metal iodides could give **2aa**. On the other hand, other calcium halides, CaCl<sub>2</sub>, CaBr<sub>2</sub>, and I<sub>2</sub>, were not effective for this reaction (entries 1–3, 15–17, 20, and 22–26). The fact that **2aa** was not obtained without the addition of CaI<sub>2</sub>, irradiation, or molecular oxygen shows the necessity of all conditions for this reaction (entries 7, 8, and 27).

**Table 2.** Transformation of  $\beta$ -Dicarbonyl Compounds to  $\alpha$ -Hydroxy- $\beta$ -keto Esters<sup>a</sup>

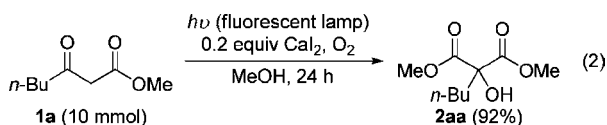
entry	substrate <b>1</b>	solvent	product <b>2</b>	yield (%) <sup>b</sup>
1	<b>1a</b>	MeOH	<b>2aa</b> : R = Me	85
2	<b>1a</b>	EtOH	<b>2ab</b> : R = Et	80
3	<b>1a</b>	<i>i</i> -PrOH	<b>2ac</b> : R = <i>i</i> -Pr	71
4	<b>1b</b>	MeOH	<b>2aa</b> : R <sub>1</sub> = R <sub>2</sub> = Me	79 <sup>c,d</sup>
5	<b>1b</b>	EtOH	<b>2ba</b> : R <sub>1</sub> = R <sub>2</sub> = Et	81
6	<b>1b</b>	<i>i</i> -PrOH	<b>2bb</b> : R <sub>1</sub> = Et, R <sub>2</sub> = <i>i</i> -Pr	71
7	<b>1c</b>	MeOH	<b>2c</b>	78
8	<b>1d</b>	MeOH	<b>2d</b>	66 <sup>e</sup>
9	<b>1e</b>	MeOH	<b>2e</b>	72 <sup>c</sup>
10	<b>1f</b>	MeOH	<b>2f</b>	88
11	<b>1g</b>	MeOH	<b>2ga</b>	57 <sup>e,f</sup>
12	<b>1h</b>	MeOH	<b>2h</b>	70
13	<b>1i</b>	MeOH	<b>2ia</b> : R <sub>1</sub> = Ph, R <sub>2</sub> = Me <b>2ib</b> : R <sub>1</sub> = Me, R <sub>2</sub> = Ph	26 <sup>g</sup> 26 <sup>g</sup>

<sup>a</sup> Reaction conditions: a mixture of substrate (0.3 mmol) and catalyst (0.2 equiv) in solvent (5 mL) was irradiated with a fluorescent lamp for 10 h in an oxygen atmosphere. <sup>b</sup> Yield of isolated product. <sup>c</sup> The reaction was carried out in the presence of CaI<sub>2</sub> (0.5 equiv). <sup>d</sup> The products (R<sub>1</sub> = R<sub>2</sub> = Me; **2aa**: 5.6%, R<sub>1</sub> = Et, R<sub>2</sub> = Me; **2ab**: 29%) were obtained in the presence of CaI<sub>2</sub> (0.2 equiv). <sup>e</sup> The reaction was carried out for 24 h. <sup>f</sup> Methyl 4-nitrobenzoate (**2gb**) was also obtained in 17% yield. <sup>g</sup> Estimated by <sup>1</sup>H NMR. Methyl 2-hydroxy-2-phenylacetate (**2ic**) was also isolated in 12% yield.

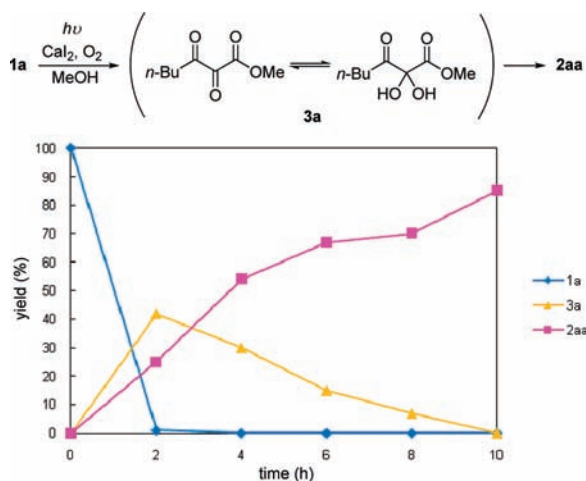
Table 2 shows the scope and limitation of this transformation of a variety of  $\beta$ -ketoesters under the optimal reaction conditions mentioned above. The reaction of methyl 3-oxoheptanoate (**1a**) and ethyl 3-oxoheptanoate (**1b**) gave the corresponding  $\alpha$ -hydroxy- $\beta$ -keto esters (**2aa–2bb**), which possess the ester group derived by transesterification with solvent, in high yield (entries 1–3, 5, and 6). On the other hand, although the reaction of **1b** in MeOH afforded the mixed products (**2aa**, **2ab**), the sole product (**2aa**) was obtained in 79% yield by increasing CaI<sub>2</sub> to 0.5 equiv (entry 4). This reaction was also applicable to the  $\beta$ -dicarbonyl compounds which possess bulky groups, such as *i*Pr (**1c**) or *t*Bu (**1d**), and gave the corresponding malonic esters **2c** and **2d** in good yields (entries 7, 8). In addition, the reaction of ethyl 3-oxo-3-phenylpropanoate (**1e**) and methyl 3-(4-methoxyphenyl)-3-oxopropanoate (**1f**), which possess an electron-donating group at the aromatic nucleus, gave the corresponding tartronic esters (**2e** and **2f**) in good to excellent yields, respectively, and methyl 3-(4-nitrophenyl)-3-oxopropanoate

(**1g**), which possesses an electron-withdrawing group at the aromatic nucleus gave the corresponding **2ga** in modest yield (entries 9–11). Fortunately, this reaction was also effective for heterocyclic compounds, and methyl nicotinoylacetate (**1h**) afforded the corresponding tartronic ester **2h** in good yield (entry 12). Furthermore, benzoylacetone (**1i**), without an ester group, was reactive for this tandem reaction condition and gave the mixed products **2ia** and **2ib** (entry 13).

The developed protocol was easily scaled up; the reaction of **1a** and 0.2 equiv of  $\text{CaI}_2$  in MeOH (150 mL) was irradiated with a fluorescent lamp for 24 h in an oxygen atmosphere on a 10 mmol scale, and dimethyl 2-butyl-2-hydroxymalonate (**2aa**) was obtained in 92% yield (eq 2).



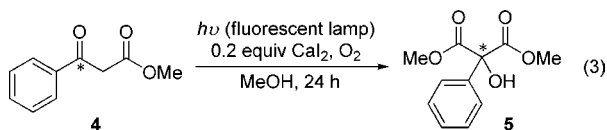
In order to examine the mechanism of this reaction, we studied the time-course of this transformation (Figure 1). The



**Figure 1.** Time-course of transformation of  $\beta$ -ketoesters to tartronic esters.

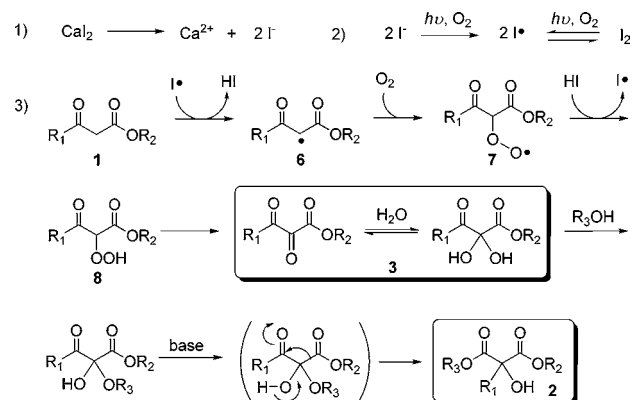
mixture of  $\alpha,\beta$ -diketoester and its hydrated species **3a**, which we could obtain as an intermediate, increased for 2 h and gradually decreased with increasing yield of **2aa** (Table 1, entry 9).<sup>10</sup> In addition, **2aa** was obtained in 90% yield when **3a** was used as a substrate under the conditions mentioned above.<sup>11</sup>

Furthermore,  $^{13}\text{C}$ -enriched substrate **4** produced **5** under the same reaction conditions (eq 3).



Scheme 1 shows a proposal for a reaction mechanism for the conversion of  $\beta$ -ketoesters to tartronic esters, which

### Scheme 1. Plausible Path of Transformation of $\beta$ -Ketoesters to Tartronic Esters



is postulated by considering all of the results mentioned above, the change of the solution color to yellow, and the necessity of continuous irradiation, catalytic amount of  $\text{CaI}_2$ , and molecular oxygen. At first,  $\beta$ -ketoester **1** is transformed to radical species **6** through abstraction of hydrogen by the iodo radical, which is formed from  $\text{I}^-$  in situ. The resulting species **6** traps molecular oxygen to generate hydroperoxide **8** through peroxy radical **7**, and this hydroperoxide **7** is transformed to **3**. The resulting **3** is attacked by alcohol and rearranged to produce tartronic

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(9) A typical procedure follows: A dry methanol solution (5 mL) of **1a** (0.3 mmol) and  $\text{CaI}_2$  (0.06 mmol) in a Pyrex test tube equipped with an  $\text{O}_2$  balloon was irradiated under stirring conditions for 10 h with four of 22 W fluorescent lamps, which was set from the test tube in the distance of 80 mm. The reaction mixture was concentrated under the reduced pressure, dissolved in ethyl acetate, and washed with sodium thiosulfate and brine. The organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The pure product **2aa** was obtained by preparative TLC.

(10) Oxidation of  $\beta$ -dicarbonyl compounds to tricarbonyl compounds: (a) Schank, K.; Leider, R.; Lick, C.; Glock, R. *Helv. Chim. Acta* **2004**, 87, 869–924. (b) Carnell, A. J.; Johnstone, R. A. W.; Parsy, C. C.; Sanderson, W. R. *Tetrahedron Lett.* **1999**, 40, 8029–8032. (c) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. *Tetrahedron Lett.* **1993**, 34, 167–170. (d) Adam, W.; Prechtel, F. *Chem. Ber.* **1991**, 124, 2369–2372. (e) Wasserman, H. H.; Pickett, J. E. *Tetrahedron* **1985**, 41, 2155–2162. (f) Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, 47, 891–892. (g) Bigelow, L. A.; Hanslick, R. S. *Org. Synth.* **1933**, 13, 38–40. (h) Muller, R. *Chem. Ber.* **1933**, 66B, 1668–1670. (i) Astin, S.; Newman, A. C. C.; Riley, H. L. *J. Chem. Soc.* **1933**, 391–394. (j) Dox, A. W. *Org. Synth.* **1925**, 4, 27–29.

(11) Benzilic acid rearrangement of  $\alpha,\beta$ -diketoesters, see: (a) Dahn, H.; Dao, L. H.; Hunma, R. *Helv. Chim. Acta* **1982**, 65, 2458–2463. (b) Dahn, H.; Gowal, H.; Schlunke, H. P. *Helv. Chim. Acta* **1970**, 53, 1598–1605, and references cited therein.

ester **2**. Iodine is regenerated from an iodo radical or hydrogen iodide.

In conclusion, we report a novel and facile tandem oxidation/rearrangement of  $\beta$ -ketoesters to tartronic esters, which is the first successful synthetic method with molecular oxygen catalyzed by calcium iodide under visible light

irradiation. Further applications of this system to the other reactions are now in progress in our laboratory.

**Supporting Information Available:** Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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