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Efficient Oxidative Cleavage of 1,3-Dicarbonyl Derivatives with Hydrogen Peroxide Catalyzed by Quaternary Ammonium Iodide

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Keywords: Cleavage reactions / Oxidation / Sustainable chemistry / Ketones

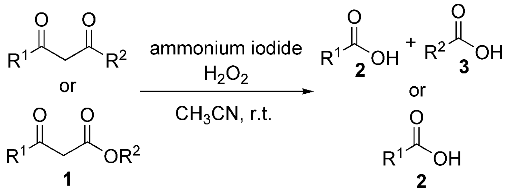
Quaternary ammonium iodide, a metal-free and mild catalyst, was proven to be a successful catalyst in the oxidative cleavage of 1,3-dicarbonyl derivatives with H_2O_2 as terminal oxidant. The mechanistic aspects of these "multistep" catalytic oxidations were discussed in terms of the catalytic cycle of the iodine species and the oxidative cleavage of the α carbon from the dicarbonyl compounds to generate the corresponding carboxylic acids.

Introduction

Carboxylic acids are very important components of numerous biomolecules and synthetic targets of high pharmaceutical value, and many useful methods have been developed to expand the organic synthesis of carboxylic acids.[1] Among these methods, oxidative cleavage of 1,3-dicarbonyl compounds has been paid much attention by chemists.[2] However, these procedures usually require very harsh reaction conditions such as high temperatures, long reaction time, the use of expensive and toxic reagents, and even oxidation with electrocatalysts.

Green chemistry has been developed extensively in the methodology of modern organic synthesis.[3] Metal-free oxidation is one of the best choices in the pharmaceutical industry due to the avoidance of metal contamination.[4] Considered as one of the cleanest terminal oxidants with only water as the byproduct, hydrogen peroxide has attracted more and more attention in modern organic synthesis.[5] In 1996, Espenson and co-workers developed a methylrhenium trioxide catalytic oxidation of cyclic diketones with H_2O_2 to generate a series of carboxylic diacids as final products.[6] It was illustrated that hydrogen peroxide is a nice reagent for oxidative cleavage reactions.

Meanwhile, ammonium iodides are well known as proven nontoxic, readily available, inexpensive, neutral, and mild chemicals that are utilized in many chemical industries.[7] We envisage that ammonium iodides could catalyze the oxidative cleavage reaction of 1,3-dicarbonyl compounds with H_2O_2 as the terminal oxidant. Herein, we present our research on the development of a novel and environmentally friendly method for the oxidative cleavage of 1,3-dicarbonyls to generate carboxylic acids with H_2O_2 in the presence of ammonium iodide catalytic system (shown in Scheme 1). We also describe the possible reaction mechanism and the effect of ammonium iodide on the transformation of carbonyl compounds.



Scheme 1. Oxidative cleavage of 1,3-dicarbonyl compounds to carboxylic acids with H_2O_2 catalyzed by ammonium iodides.

Results and Discussion

Several solvents were initially screened in this oxidative cleavage reaction of **1a** with 30% H_2O_2 (3.0 equiv.) in the solvents with the use of Et_4NI (20 mol-%) as catalyst at room temperature. The oxidation in CH_3CN resulted in a 94% yield of benzoic acid (**2a**) after 15 h, because this solvent is aprotic and polar and has good solubility in water (Scheme 2). However, only 11% of the product was obtained when water was used as the solvent. Other organic solvents such as MeOH, THF, acetone, and dichloromethane gave very poor yields or almost no reaction after 15 h. Consequently, we deemed CH_3CN to be the optimal solvent for this type of oxidation and all further optimizations were performed in this solvent.

Next, we focused on the screening of the ammonium salt catalyst system mentioned above for the oxidative cleavage of β-diketone **1a**. As shown in Table 1, other tetraalkyl-

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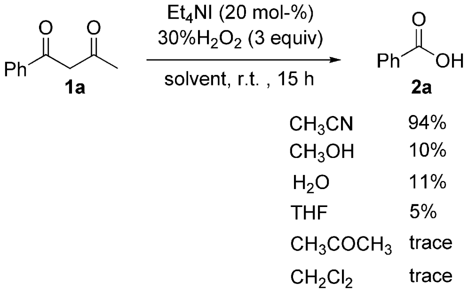
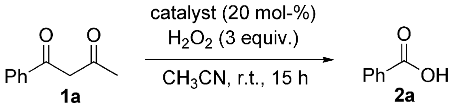


Scheme 2. Solvent effect in the oxidative cleavage of β-diketones.

ammonium iodides resulted in comparable high yields, and methyltriethylammonium iodide was the best catalyst in this system (Table 1, Entries 2–4). Interestingly, the combination of trialkylamine/methyl iodide in situ also gave satisfactory results, but trialkylamine/ethyl iodide showed poor reactivity as a result of the difficulty in forming ammonium iodide at room temperature (Table 1, Entries 5 and 6).[7] Ammonium bromides, triethylamine, and hydroiodic acid failed to catalyze the oxidative cleavage reaction. (Table 1, Entries 7–10).

Table 1. Versatile catalyst for oxidative cleavage of **1a** with H_2O_2.

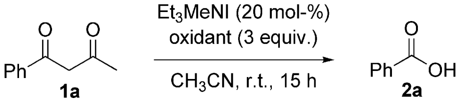


Entry	Catalyst	Yield[a] [%]
1	Et_4NI	94
2	Bu_4NI	88
3	Et_3MeNI	95
4	Me_3OctNI[b]	95
5	Et_3N/MeI	95
6	Et_3N/EtI	58
7	Et_4NBr	NR
8	Bu_4NBr	NR
9	Et_3N	NR
10	HI	NR
11	Et_3N/HI	95

[a] Isolated yield. NR = no reaction. [b] Oct = octyl.

In addition, other oxidants were investigated in the catalytic oxidative cleavage reaction of β-diketone **1a** with Et_3MeNI as the catalyst. As demonstrated in Table 2, benzoyl peroxide (Table 2, Entry 2) gave a comparable yield of 87%, whereas other oxidants, such as *t*BuOOH, NaClO, and $NaIO_4$ (Table 2, Entries 3–5) produced only moderate yields. Surprisingly, a very low yield of the corresponding acid was obtained with urea–hydrogen peroxide complex as the oxidant (Table 2, Entry 6). Among all the oxidants tested, 30% aqueous H_2O_2 gave the best result after 15 h at room temperature.

Table 2. Various oxidants for the oxidative cleavage reaction of **1a** catalyzed by ammonium iodide.



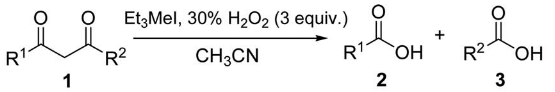
Entry	Oxidant	Yield[a] [%]
1	H_2O_2	95
2	benzoyl peroxide	87
3	*t*BuOOH	60
4	NaClO	50
5	$NaIO_4$	51
6	H_2O_2·urea	24

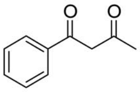
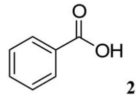
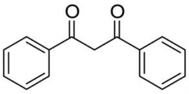
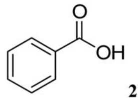
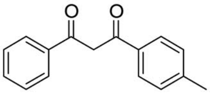
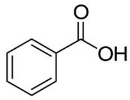
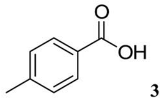
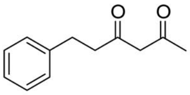
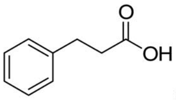
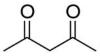
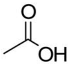
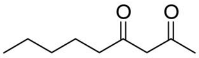
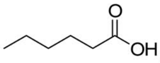
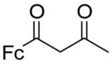
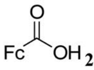
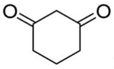
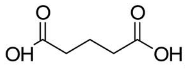
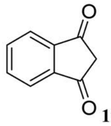
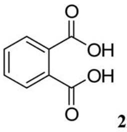
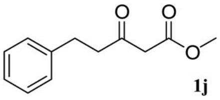
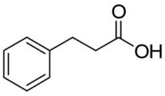
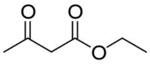
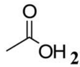
[a] Isolated yield.

With those optimizations mentioned above, the substrate generality was examined next, and the results are presented in Table 3. In this case, Et_3MeNI was chosen as the standard catalyst. All 1,3-diphenyl- and 1,3-dialkyl-substituted propan-1,3-diones or their derivatives, including **1a**–**f**, were transformed into the corresponding carboxylic acids **2** and **3** in very satisfactory yields from 88 to 98% under the same condition (Table 3, Entries 1–6). However, ferrocenyl-substituted substrate **1g** gave only 10% yield of the product after a reaction time of 15 h. It was supposed that the ferrocenyl group in substrate **1g** could decompose hydrogen peroxide in the system (Table 3, Entry 7),[8] and it seemed that cyclic diketone substrates such as **1h**,**i** required a higher reaction temperature (55 °C) and a longer reaction time to give satisfactory yields (Table 3, Entries 8 and 9). Oxidative cleavage of β-keto esters **1j** and **1k** was also investigated and resulted in the formation of hydrocinnamic acid and acetic acid in 73 and 90% yield under the optimized catalytic conditions, respectively (Table 3, Entries 10 and 11).

On the basis of some related literature,[9] the mechanism of this ammonium iodide catalyzed oxidative cleavage of 1,3-dicarbonyl compounds was proposed as shown in Scheme 3. Because ammonium bromide and Et_3N could not catalyze this reaction under the same conditions, it was believed that an iodine species was essential for the oxidative cleavage (Table 1). Key intermediate 2-iodo derivative **I** was obtained from iodination of starting material **1** and the quaternary ammonium iodide catalyst in the presence of H_2O_2, which could be detected by TLC in the system.[9a,9b] At the same time, quaternary ammonium iodide decomposed into a tertiary amine and an olefin through a Hofmann elimination reaction.[10] Intermediate **I** reacted with amine, which was also produced from ammonium iodide in situ, to generate quaternary ammonium iodide **II**.[9f,11] Intermediate **II** could be observed by the ^1H NMR spectroscopy, whereas **I** and triethylamine were mixed in $CDCl_3$. Consequently, advanced intermediate **III** could be formed from another molecule of H_2O_2; meanwhile, the trialkylammonium iodide is also generated in this step as the effective catalytic species, which was confirmed by the result of the oxidative cleavage catalyzed by Et_3N/HI (Table 1, Entry 11). In the following procedure, product **2** and intermediate **IV** were obtained by the first C–C bond cleavage of the α carbon of the dicarbonyl compounds. Finally, formic acid and corresponding carboxylic acid **3** would be the final products of the cleaved α carbon with the oxidation of **IV** by H_2O_2.[2c,2e,12] To gain insight into this oxidation, especially the cleavage of the α carbon from the dicarbonyl com-

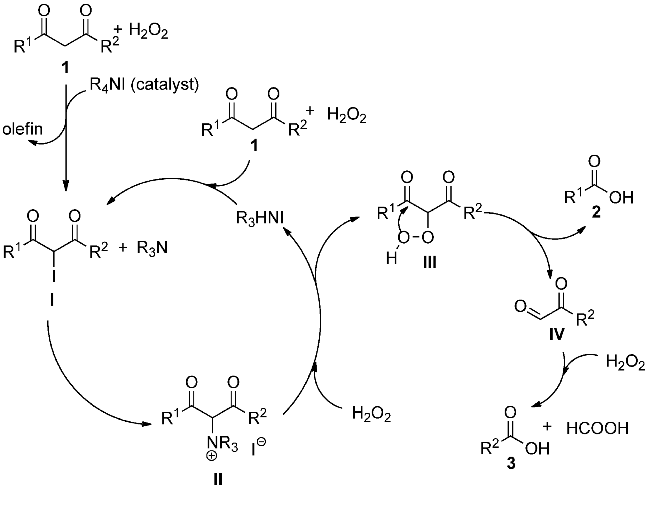
Table 3. Substrate scope for the iodine-catalyzed oxidative cleavage of 1,3-dicarbonyls with H_2O_2.



Entry	Substrate	Product	t [h]	T [°C]	Yield[a] [%]
1	 **1a**	 **2a**	15	r.t.	95
2	 **1b**	 **2b**	15	r.t.	94
3	 **1c**	 **2c**	15	r.t.	98[b]
		 **3c**	15	r.t.	98[b]
4	 **1d**	 **2d**	15	r.t.	88
5	 **1e**	 **2e**	15	r.t.	94[b]
6	 **1f**	 **2f**	15	r.t.	90
7	 **1g**	 **2g**	15	r.t.	10[c]
8	 **1h**	 **2h**	23	55	94
9	 **1i**	 **2i**	15	55	92
10	 **1j**	 **2j**	15	55	73
11	 **1k**	 **2k**	15	55	90[b]

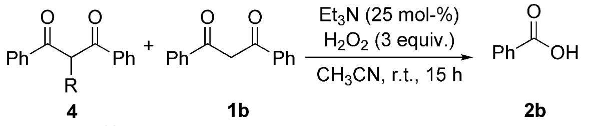
[a] Isolated yield. [b] GC yield. [c] Fc = ferrocenyl.

pounds, a mechanistic study was performed in the following context. It seemed that as the catalyst, the iodine species cycled between I^- and I^+ without the formation of a high-valence iodine species that could also be employed in this type of reaction.[2c] To confirm and clarify the type of catalyst for this transformation, several control experiments were investigated. Because substrate dibenzoylmethane (**1b**) gave the same carboxylic acid product as a result of its symmetric structure, we chose **1b** as the test compound to facilitate the following mechanistic study. Meanwhile, 2-iodo-1,3-diphenylpropane-1,3-dione (**4b**) was synthesized according to a reported procedure.[9a] As a control test, **4b** was subjected to Et_3N (1 equiv.) and 30% H_2O_2 (3 equiv.) for 15 h at room temperature, resulting in a yield of 90% for the target carboxylic acid. Moreover, the silver mirror reaction was detected after treatment of the reaction mixture with Tollens' reagent.[13] This showed that HCOOH existed in the system after the oxidative cleavage reaction that is catalyzed by ammonium iodide with H_2O_2 as oxidant.



Scheme 3. Plausible mechanism for the ammonium iodide catalyzed oxidative cleavage of 1,3-dicarbonyl compounds.

Furthermore, 25 mol-% (based on **1b**) of **4b** combined with 25 mol-% (based on **1b**) of Et_3N could serve as an efficient catalyst for the target oxidative cleavage of **1b** with 30% H_2O_2 (Scheme 4). As a comparison, 2-monosubstituted derivatives **4c** (bromide) and **4d** (chloride) at 25 mol-% loading could not turn over the catalytic cycle but gave the target product in less than 20% yield (yields were based on the benzoyl group). In terms of the verification experiments, it was believed that an iodide functionalization of the 1,3-dicarbonyl compounds took place first to generate key intermediate 2-iodo derivative **I**.[14] These results proved that this intermediate is definitely in the catalytic cycle.



R = I, **4b**, 94 % yield
R = Br, **4c**, 17 % yield
R = Cl, **4d**, 12 % yield
(yields based on the benzoyl group)

Scheme 4. Control experiments with catalytic monosubstituted dicarbonyl compounds.

Conclusions

In summary, a metal-free, mild, and environmentally friendly method for the conversion of diketones and keto esters into carboxylic acids was developed; the process is catalyzed by quaternary ammonium iodide with H_2O_2 as the terminal oxidant. The mechanistic aspects of these "multistep" catalytic oxidations were discussed in terms of the catalytic cycle of the iodine species and the oxidative cleavage reaction of the α carbon from the dicarbonyl compounds to generate the corresponding carboxylic acids.

Experimental Section

Materials: Et_3MeNI was prepared by following reported procedures.[7] Compounds **1d**, **1f**, and **1j** were prepared by treating acetylacetone with the corresponding halides under treatment of NaH and BuLi.[15] Compounds **1c** and **1g** were prepared according to the literature.[16] All other substrates were purchased and used without further purification.

Procedure for the Oxidation of β-Dicarbonyl Compounds 1 by Using Et_3MeNI as the Catalyst: 30% H_2O_2 (170 mg, 1.5 mmol) was added to a solution of the β-dicarbonyl compound (0.5 mmol) and Et_3MeNI (24.3 mg, 0.1 mmol) in CH_3CN (2.5 mL). The solution was stirred at room temperature or 55 °C for 15–23 h. A saturated aqueous solution of $Na_2S_2O_3$ (1 mL) was added to the reaction mixture. The mixture was extracted with diethyl ether. The organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography by using silica gel as the stationary phase.

Procedure for the Oxidation of 2-Iodo-1,3-diphenylpropane-1,3-dione (4b): 30% H_2O_2 (170 mg, 1.5 mmol) was added to a solution of 2-iodo-1,3-diphenylpropane-1,3-dione (175 mg, 0.5 mmol) and Et_3N (50.5 mg, 0.5 mmol) in CH_3CN (2.5 mL). The solution was stirred at room temperature for 15 h. A saturated aqueous solution of $Na_2S_2O_3$ (1 mL) was added to the reaction mixture. The mixture was extracted with diethyl ether. The organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography by using silica gel as the stationary phase. Benzoic acid was obtained as a white solid (110.1 mg, 90%).

Procedure for the Oxidation of 1,3-Diphenylpropane-1,3-dione by Using 2-Iodo-1,3-diphenylpropane-1,3-dione (4b) as the Catalyst: 30% H_2O_2 (170 mg, 1.5 mmol) was added to a solution of 1,3-diphenylpropane-1,3-dione (89.6 mg, 0.4 mmol), 2-iodo-1,3-diphenylpropane-1,3-dione (35 mg, 0.1 mmol), and Et_3N (10.1 mg, 0.1 mmol) in CH_3CN (2.5 mL). The solution was stirred at room temperature for 15 h. A saturated aqueous solution of $Na_2S_2O_3$ (1 mL) was added to the reaction mixture. The mixture was extracted with diethyl ether. The organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography by using silica gel as the stationary phase. Benzoic acid was obtained as white solid (114.8 mg, 94% based on the benzoyl group).

Procedure for the Silver Mirror Test After Oxidation Cleavage: 30% H_2O_2 (170 mg, 1.5 mmol) was added to a solution of the β-dicarbonyl (0.5 mmol) and Et_3MeNI (24.3 mg, 0.1 mmol) in CH_3CN (2.5 mL). The solution was stirred at room temperature or 55 °C for 15–23 h. A saturated aqueous solution of $Na_2S_2O_3$ was added to the reaction mixture until the color of mixture changed from brown to colorless. The mixture was poured into a clean test tube containing Tollens' reagent. The test tube was then immersed in a hot water bath for a few minutes until the silver mirror appeared.

Supporting Information (see footnote on the first page of this article): ^1H NMR spectrum of intermediate **II** and the procedure for the identification of olefin formation in the first step of the mechanism.

Acknowledgments

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[1] For some examples, see: a) L. D. Arnold, J. C. Drover, J. C. Vederas, *J. Am. Chem. Soc.* **1987**, *109*, 4649–4659; b) C. G. Stuckwisch, G. V. Bailey, *J. Org. Chem.* **1963**, *28*, 2362–2363; c) H. L. Cohen, G. F. Wright, *J. Org. Chem.* **1953**, *18*, 432–446; d) S. A. DiBiase, R. P. Wolak, D. M. Dishong, G. W. Gokel, *J. Org. Chem.* **1980**, *45*, 3630–3634; e) M. S. Newman, R. M. Wise, *J. Am. Chem. Soc.* **1956**, *78*, 450–454; f) L. Anzalone, J. A. Hirsch, *J. Org. Chem.* **1985**, *50*, 2128–2133; g) R. C. Fusan, B. A. Bull, *Chem. Rev.* **1934**, *15*, 275–309; h) J. Owen, J. L. Simonsen, *J. Chem. Soc.* **1932**, *134*, 1424–1429; i) J. L. Simonsen, *J. Chem. Soc.* **1922**, *121*, 2292–2299.

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