Catalytic Oxidative Cleavage of 1,3-Diketones to Carboxylic Acids by Aerobic Photooxidation with Iodine

Norihiro Tada, Motoki Shomura, Lei Cui, Tomoya Nobuta, Tsuyoshi Miura, Akichika Itoh*

Gifu Pharmaceutical University, 1-25-4, Daigaku-nishi, Gifu 501-1196, Japan Fax +81(58)2308105; E-mail: itoha@gifu-pu.ac.jp *Received 29 August 2011*

Abstract: We report the catalytic oxidative cleavage of 1,3-diketones to the corresponding carboxylic acids by aerobic photooxidation with iodine under irradiation with a high-pressure mercury lamp.

Key words: photooxidation, aerobic, iodine, 1,3-diketone, carboxylic acid

Syntheses of carboxylic acids are essential in organic chemistry because carboxylic acids are versatile compounds or intermediates that can be used in various fields, such as pharmaceuticals, agrochemicals, paints, lubricants, liquid crystal polymers, cosmetics, and food additives. Thus, many useful methods have been developed for the preparation of carboxylic acids including (i) oxidation of alkyl benzenes, primary alcohols, and aldehydes, (ii) reaction of organometallic reagents with carbon dioxide, (iii) oxidative cleavage of alkenes, alkynes, and vicinal diols, and (iv) haloform-type reactions, etc.¹ The conversion of 1,3-diketones into carboxylic acids is a supplementary reaction for the preparation of carboxylic acids.² However, it requires a stoichiometric amount of reagents, such as CAN,^{2c} oxone,^{2d} PIDA,^{2h} SnCl₄,²ⁱ heavymetal catalyst [In(OTf)₃,^{2b} and MeReO₃^{2f}], high-tempera-ture water conditions,^{2a} and electrochemical oxidation conditions.^{2e,g} In 1953, conversion of benzoylacetone catalyzed by iodine (only one substrate) was reported, although benzoic acid was obtained only in 18% yield.²ⁱ Thus, the development of a mild and efficient protocol for a metal-free catalytic conversion of 1,3-diketones into the corresponding carboxylic acids is highly desirable. Currently, the effective use of light is one of the most important research topics for the development of new energyconversion protocols and energy-using technologies. Furthermore, molecular oxygen has received considerable attention as an ultimate oxidant because it is photosynthesized by plants, produces little waste, is inexpensive, and has larger atom efficiency than other oxidants. Considering these factors, we have developed various aerobic photooxidation reactions in an oxygen atmosphere and under light irradiation.³ We recently reported the tandem oxidation-rearrangement-oxidative decarboxylation of 1,3diketones to 1,2-diketones in the presence of a catalytic amount of I2.3f In the course of this study, we found that

Advanced online publication: 11.11.2011

DOI: 10.1055/s-0031-1289891; Art ID: U06311ST

© Georg Thieme Verlag Stuttgart · New York

the succeeding oxidation of 1,2-diketones would make it possible to synthesize carboxylic acids from 1,3-diketones. Herein we report a catalytic oxidative cleavage of 1,3-diketones to carboxylic acids by aerobic photooxidation with iodine under light irradiation with a 400 W mercury lamp (Scheme 1).



Scheme 1

To explore this approach, we selected benzoylacetone (1)as a test substrate for the optimization of reaction conditions (Table 1). Among the solvents and catalysts examined, ethyl acetate with I_2 provides benzoic acid (2) most efficiently (Table 1, entries 1-9). After detailed studies on the reaction conditions, we found that the efficient reaction conditions involve I_2 (0.1 equiv) in ethyl acetate for ten hours (entries 1, 10, and 11).⁴ Note that a lower yield of 2 was obtained when other light sources, such as a xenon lamp (500 W) and a fluorescent lamp $(4 \times 22 \text{ W})$, were used instead of a 400 W mercury lamp (Table 1, entries 12 and 13). The fact that compound 2 was not obtained or was obtained only in low yield without iodine, molecular oxygen, and irradiation confirms the requirement of all these conditions for this reaction (Table 1, entries 14–16).

Table 1 Study of Reaction Conditions

1 (0.3 m) O O ₂ , h c mol)	v (400 W Hg lamp atalyst (equiv) solvent (5 mL)		он
Entry	Catalyst (equiv)	Solvent	Time (h)	Yield (%) ^a
1	I ₂ (0.1)	EtOAc	10	89
2	NIS (0.1)	EtOAc	10	47
3	LiI (0.1)	EtOAc	10	56
4	CaI ₂ (0.1)	EtOAc	10	19
5	Br ₂ (0.1)	EtOAc	10	44
6	$I_2(0.1)$	hexane	10	66
6	$I_2(0.1)$	hexane	10	66

SYNLETT 2011, No. 19, pp 2896–2900

 Table 1
 Study of Reaction Conditions (continued)

		ov (400 W Hg lamp catalyst (equiv)		ОН
1 (0.3 m	nmol)	solvent (5 mL)	<u> </u>	2
Entry	Catalyst (equiv)	Solvent	Time (h)	Yield (%) ^a
7	I ₂ (0.1)	<i>i</i> -Pr ₂ O	10	49
8	I ₂ (0.1)	MeCN	10	46
9	I ₂ (0.1)	MeOH	10	24
10	I ₂ (0.05)	EtOAc	10	69
11	I ₂ (0.1)	EtOAc	5	57
12	I ₂ (0.1)	EtOAc	10	75 ^b
13	I ₂ (0.1)	EtOAc	10	40 ^c
14	-	EtOAc	10	9
15	I ₂ (0.1)	EtOAc	10	0^d
16	I ₂ (0.1)	EtOAc	10	0 ^e

^a Isolated yields.

^b The reaction was carried out with xenon lamp (500 W).

 $^{\rm c}$ The reaction was carried out with fluorescent lamp (4 \times 22 W).

^d The reaction was carried out under Ar.

^e The reaction was carried out in the dark.

Table 2 Oxidative Cleavage of 1,3-Diketones

		O ₂ , <i>h</i> v (400 W H I ₂ (0.1 equ	Hg lamp) iiv)		
substi (0.3 m	rate mol)	EtOAc (5 mL)), 24 h	product	
Entry	Substra	te	Product		Yield (%) ^a
1	MeO		MeO	ОН	84
2	3		4	ОН	77
3	5			ЭH	89 ^b
4				ОН	91

Table 2 Ovidative Cleavage of 1.3-Diketones (continued)

Table	O_2 , hv (400 V	V Hg lamp)	led)
substr (0.3 mi	rate mol) EtOAc (5 n	nL), 24 h	
Entry	Substrate	Product	Yield (%) ^a
5			69
6		он	57
7		ОН	80°
8			70
9	14 OEt	15 Он	73 ^d
10			61
11			40
12	ОН	ОН	63
13		2	0 ^e
14	22 $ \swarrow_{g}^{O} \qquad 0 \qquad $	2 → → ○ → ○ → ○ → ○ → ○ → ○ → ○ → ○ → ○ →	$0^{\rm f}$

^a Isolated yields.

^b The reaction was carried out for 10 h.

^c Compound 2 (0.48 mmol) was obtained.

^d The reaction was carried out with I_2 (0.2 equiv). ^e Starting material **22** was recovered in 87% yield.

^f Starting material 23 was recovered in 97% yield.

Next, we investigated the scope and limitation of the oxidative cleavage of 1,3-diketones under the optimal reaction conditions (Table 2). When benzoylacetones were used as a substrate, the corresponding carboxylic acids were obtained in good to high yields, regardless of an electron-donating or electron-withdrawing group at the benzene ring (Table 2, entries 1-4). Furthermore, 2-naphthoic acid (10) and 3-thiophenecarboxylic acid (12) were obtained from 9 and 11 in moderate yields (Table 2, entries 5 and 6), respectively. Dibenzoylmethane (13) was also oxidized to benzoic acid (2) in 80% yield (Table 2, entry 7). When 1,3-indandione (14), a cyclic 1,3-diketone, was used, phthalic anhydride (15) was obtained in 70% yield (Table 2, entry 8). 1,3-Keto ester 16 was also converted into benzoic acid (2) in good yield (Table 2, entry 9). Note that 2,4-tridecanedione (17) and 1,3-cyclohexanedione (19), which are aliphatic diketones, also afforded decanoic acid (18) and glutaric acid (20) in moderate yields (Table 2, entries 10 and 11), respectively. In addition, 2-hydroxyacetophenone (21) was oxidized to afford benzoic acid (2) in 63% yield. Under these conditions, acetophenone (22) and didecyl malonate (23) functioned as poor substrates.

To clarify the reaction mechanism, the time course of the oxidative cleavage of **13** was studied (Figure 1). It was revealed that dibenzoyliodomethane (**25**), triketone (**26**, including its monohydrate), benzil (**27**), and glyoxylic acid

(28) were detected by ¹H NMR.⁵ When 26 and 28 were used as substrates under the optimal conditions, benzoic acid (2) was obtained in high yield (Scheme 2, equations 1 and 3). These results suggest that 26 and 28 are intermediates in this reaction. On the other hand, when 27 was used as the substrate under the optimal conditions, benzoic acid (2) was only afforded in 13% yield and 87% yield of recovered 27 (Scheme 2, equation 2). In contrast, 27 was converted into benzoic acid (2, 33%) and perbenzoic acid (29, 30%) without I_2 (Scheme 2, equation 5). Note that in the oxidative cleavage of 13, iodobenzene and iodinated ethyl acetate were detected by GC-MS in the later stages of this reaction. These results probably indicated that benzil (27) is a minor intermediate, and oxidative conversion of 27 reached completion in the later stages of the reaction in the presence of low I_2 concentration.⁶ Moreover, 26 and 28 were also oxidized to benzoic acid and perbenzoic acid without I_2 (Scheme 2, equations 4 and 6).

Scheme 3 shows a plausible path of this reaction, which is postulated by considering the requirement of continuous irradiation, a catalytic amount of I_2 , and molecular oxygen for the oxidative cleavage of 1,3-diketones. 1,3-Diketone **13** was initially oxidized to triketone **26** and its monohydrate by aerobic photooxidation with catalytic amount of iodine.^{3f,7,8} Triketone **26** was transferred to benzil (**27**),^{3f,9} glyoxylic acid (**28**),¹⁰ and perbenzoic acid (**29**) under light irradiation and in the presence of oxygen. Moreover, ben-



Scheme 2 Study of reaction intermediate

Synlett 2011, No. 19, 2896-2900 © Thieme Stuttgart · New York



Scheme 3 Plausible path



Figure 1 Time course of oxidative cleavage of 1,3-diketones

zil $(27)^{11}$ and glyoxylic acid $(28)^{12}$ were converted into perbenzoic acid (29). Finally, perbenzoic acid (29) was reduced to benzoic acid (2). Iodine was regenerated by aerobic photooxidation of hydrogen iodide.

In conclusion, we have developed the catalytic oxidative cleavage of 1,3-diketones to carboxylic acids through iodine-catalyzed aerobic photooxidation under light irradiation with a 400 W mercury lamp. This mild and efficient reaction is significantly important because of the use of inexpensive molecular iodine as the catalyst and molecular oxygen as the terminal oxidant.

References and Notes

- (a) Larock, R. C. Comprehensive Organic Transformations, 2nd ed.; Wiley-VCH: New York, **1999**, 1625. (b) Smith, M. B.; March, J. March's Advanced Organic Chemistry, 6th ed.; John Wiley and Sons: Hoboken, **2007**, 1745.
- (2) (a) Hirashita, T.; Kuwahara, S.; Okochi, S.; Tsuji, M.; Araki, S. *Tetrahedron Lett.* 2010, *51*, 1847. (b) Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. *Angew. Chem. Int. Ed.* 2007, *46*, 7793. (c) Zhang, Y.; Jiao, J.; Flowers, R. A. II. *J. Org. Chem.* 2006, *71*, 4516. (d) Ashford, S. W.; Grega, K. C. *J. Org. Chem.* 2001, *66*, 1523. (e) Cho, L. Y.; Romero, J. R. *Quim. Nova* 1998, *21*, 144. (f) Abu-Omar, M. M.; Espenson, J. H. *Organometallics* 1996, *15*, 3543. (g) Wermeckes, B.; Ye, S.; Beck, F. *Chem. Lett.* 1992, 609. (h) Podolešov, B. *J. Org. Chem.* 1984, *49*, 2644. (i) Perfetti, B. M.; Levine, R. *J. Am. Chem. Soc.* 1953, *75*, 626.
- (3) (a) Hirashima, S.; Nobuta, T.; Tada, N.; Miura, T.; Itoh, A. Org. Lett. 2010, 12, 3645. (b) Nobuta, T.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. Synlett 2010, 2335. (c) Tada, N.; Ban, K.; Hirashima, S.; Miura, T.; Itoh, A. Org. Biomol. Chem. 2010, 8, 4701. (d) Nobuta, T.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. Tetrahedron Lett. 2010, 51, 4576. (e) Kanai, N.; Nakayama, H.; Tada, T.; Itoh, A. Org. Lett. 2010, 12, 1948. (f) Tada, N.; Shomura, M.; Nakayama, H.; Miura, T.; Itoh, A. Synlett 2010, 1979. (g) Hirashima, S.; Itoh, A. J. Synth. Org. Chem. Jpn. 2008, 66, 748. (h) Nakayama, H.; Itoh, A. Synlett 2008, 675. (i) Nakayama, H.; Itoh, A. Tetrahedron Lett. 2008, 49, 2792. (j) Hirashima, S.; Itoh, A. Photochem. Photobiol. Sci. 2007, 6, 521. (k) Hirashima, S.; Itoh, A. Green Chem. 2007, 9, 318. (1) Nakayama, H.; Itoh, A. Tetrahedron Lett. 2007, 48, 1131. (m) Nakayama, H.; Itoh, A. Chem. Pharm. Bull. 2006, 54, 1620. (n) Itoh, A.; Kodama, T.; Masaki, Y.; Inagaki, S. Synlett 2002, 522. (o) Itoh, A.; Kodama, T.; Inagaki, S.; Masaki, Y. Org. Lett. 2001, 3, 2653. (p) Itoh, A.; Kodama, T.; Masaki, Y. Chem. Lett. 2001, 686.

(4) **Typical Procedure** A solution of benzoylacetone (1, 0.3 mmol) and I_2 (0.03 mmol) in dry EtOAc (5 mL) in a Pyrex test tube, purged with an O_2 balloon, was stirred and irradiated externally with 400 W high-pressure mercury lamp for 10 h. The reaction

Synlett 2011, No. 19, 2896-2900 © Thieme Stuttgart · New York

mixture was concentrated under reduced pressure. The pure product 2 was obtained by preparative TLC.

- (5) These compounds were identified by comparison with authentic samples, and yields were determined by ¹H NMR with internal standard.
- (6) Benzil(27) was obtained as major product in the presence of 0.5 equiv of Ca(OH)₂ under visible-light irradiation. See ref. 3f.
- (7) Oxidation of β-dicarbonyl compounds to tricarbonyl compounds, see: (a) Schank, K.; Leider, R.; Lick, C.; Glock, R. *Helv. Chim. Acta* 2004, 87, 869. (b) Carnell, A. J.; Johnstone, R. A. W.; Parsy, C. C.; Sanderson, W. R. *Tetrahedron Lett.* 1999, 40, 8029. (c) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. *Tetrahedron Lett.* 1993, 34, 167. (d) Adam, W.; Prechtl, F. *Chem. Ber.* 1991, *124*, 2369. (e) Wasserman, H. H.; Pickett, J. E. *Tetrahedron* 1985, 41, 2155. (f) Jung, M. E.; Shishido, K.; Davis, L. H. J. Org. Chem. 1982, 47, 891. (g) Bigelow, L. A.; Hanslick, R. S. Org. Synth. 1933, *13*, 38. (h) Müller, R. *Ber. Dtsch. Chem. Ges. B* 1933, 66, 1668. (i) Astin, S.; Newman, A. C. C.; Riley, H. L. J. Chem. Soc. 1933, 391. (j) Dox, A. W. Org. Synth. 1925, 4, 27.
- (8) Since the reaction did not proceed when using methylene blue, a singlet-state molecular oxygen generator, instead of iodine, singlet-state molecular oxygen is probably not an active species for this reaction.
- (9) Benzilic acid rearrangement of triketone to benzil, see:
 (a) Gurumurthy, R.; Narasimhan, K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1979**, *18*, 4. (b) Roberts, J. D.; Smith, D. R.; Lee, C. C. J. Am. Chem. Soc. **1951**, *73*, 618.
- (10) Cleavage of vicinal tricarbonyl, see: Mecinović, J.; Hamed, R. B.; Schofield, C. J. Angew. Chem. Int. Ed. 2009, 48, 2796.
- (11) Photooxidation of α-diketones, see: (a) Sawaki, Y. *Tetrahedron* 1985, 41, 2199. (b) Sawaki, Y.; Foote, C. J. Org. Chem. 1983, 48, 4934. (c) Sawaki, Y. Bull. Chem. Soc. Jpn. 1983, 56, 3464. (d) Biro, C. W. Chem. Commun. 1968, 1537.
- (12) Photochemical decarboxylation of α-keto acid, see:
 (a) Defoin, A.; Defoin-Straatmann, R.; Kuhn, H. J. *J. Labelled Compd. Radiopharm.* 1982, *19*, 891. (b) Leermakers, P. A.; Vesley, G. F. *J. Am. Chem. Soc.* 1963, *85*, 3776.
 (c) Corson, B. B.; Sanborn, N. E.; Van Ess, P. R. *J. Am. Chem. Soc.* 1930, *52*, 1623.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.