Acceleration of Norrish Type I Reaction with Molecular Oxygen and Catalytic CBr_4

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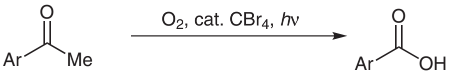
Abstract: We report a useful method for facile synthesis of aryl carboxylic acids from aryl ketones by aerobic photooxidation using the inexpensive and easily handled CBr_4 as catalyst. This procedure is applicable to inert compounds under usual photo-irradiation conditions, and appears very attractive from the view point of new method of expansion of Norrish Type I reaction.

Key words: Norrish Type I, photooxidation, carbon tetrabromide, aerobic, carboxylic acid

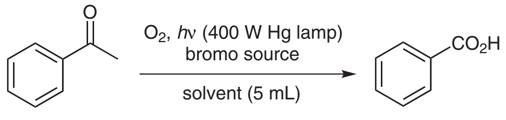
Functionalized aromatic carboxylic acids are widely used as key intermediates of pharmaceutical chemicals and as monomers of special polymers. Although several groups reported the syntheses of these aromatic carboxylic acids from aryl methyl ketones, these oxidation reactions either essentially involve the use of large quantities of heavy metals and complex organic compounds under strongly basic conditions or result in modest yields.[1] Due to an increasing demand for more environmentally benign synthesis, molecular oxygen has received much attention as an ultimate oxidant, since it, theoretically, produces only water with a certain suitable catalyst, is rather inexpensive and of larger atom efficiency than that of other oxidants.[2] With these perspectives, we have examined a new oxidation method with molecular oxygen and found direct aerobic photooxidation of methyl groups at the aromatic nucleus and primary alcohols to the corresponding carboxylic acids in good yields in the presence of a catalytic amount of the bromo source.[3] Our method is interesting in terms of use of molecular oxygen, heavy-metal-free waste reduction, inexpensive acquisition of reagents, and environmentally low-impact solvent, and, in the course of our further study of this photooxidation, we also found that aryl methyl ketones were oxidized to aromatic carboxylic acids successfully under similar conditions (Scheme 1).



Scheme 1

A cleavage of the bond between carbonyl group and α-carbon of carbonyl compound under photo-irradiation conditions is generally known as the Norrish Type I reaction;[4] however, this reaction is inert when using aryl ketones, such as acetophenone, as starting material because of its low excitation energy and instability of the phenyl and primary alkyl radical species, which will be generated by α-cleavage. However our method seems applicable to a wider range of substrates than that under usual Norrish

Table 1 Study of Reaction Conditions for Aerobic Photooxidation



1a (0.3 mmol) **2a**

Entry	Bromo source	Amount (equiv)	Solvent	Time (h)	Yield of **2a** (%)[a]
1	CBr_4	0.2	hexane	10	trace
2	CBr_4	0.2	PhH	10	trace
3	CBr_4	0.2	CH_2Cl_2	10	12
4	CBr_4	0.2	MeCN	10	12
5	CBr_4	0.2	i-Pr_2O	10	14
6	CBr_4	0.2	MeOH	10	30
7	CBr_4	0.2	EtOAc	10	73
8	CBr_4	0.1	EtOAc	10	37
9	CBr_4	0.3	EtOAc	10	27
10	CBr_4	0.2	EtOAc	12	82
11	–		EtOAc	12	0
12	CBr_4	0.2	EtOAc	12	0[b]
13	CBr_4	0.2	EtOAc	10	0[c]
14	Br_2	0.2	EtOAc	10	20
15	aq HBr	0.2	EtOAc	10	26
16	LiBr	0.2	EtOAc	10	trace
17	$MgBr_2{\cdot}OEt_2$	0.2	EtOAc	10	0
18	$BrCCl_3$	0.2	EtOAc	10	22
19	NBS	0.2	EtOAc	10	trace

[a] All yields are for pure, isolated products.
[b] The reaction was carried out in the dark.
[c] The reaction was carried out under Ar.

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Type I reaction conditions. Herein, we describe the detailed study of our improvement of the conventional Norrish Type I reaction conditions.

Table 1 shows the results of the study of the reaction conditions for aerobic photooxidation using acetophenone (**1a**) as test substrate.[5] Among our data, better results were obtained when using 0.2 equivalents of CBr_4 as bromo source and EtOAc as solvent (entries 1–10 and 14–19). The fact that benzoic acid (**2a**) was not obtained without CBr_4, irradiation or molecular oxygen shows the necessity of all for this reaction (entries 11–13).

Table 2 presents the scope and limitation of this oxidation under the optimized reaction conditions mentioned above. The corresponding carboxylic acids were obtained in good to better yield regardless of an electron-donating or electron-withdrawing group at aromatic nucleus (entries 1–5). Moreover, propiophenone (**1f**), isobutyrophenone (**1g**), and 2,2-dimethylpropiophenone (**1h**) were oxidized to benzoic acid (**2a**) in good to moderate yields (entries 6–8). We also found that α-phenethyl alcohol (**1i**) was oxidized directly to **2a** in 73% yield; however, 2-naphthoic acid was obtained in low yield when using 2-naphthophenone (**1j**) as starting material (entries 9 and 10). Since the corresponding carboxylic acids were not obtained or obtained only in low yield when using **1a**, **1f**, and **1g** as substrates under usual Norrish Type I reaction conditions, only photo-irradiation, our procedure is complementary to conventional Norrish Type I reaction.

The detailed mechanism has not been clarified yet; as shown in Scheme 2, we infer the corresponding carboxylic acid was produced via acyl radical **5**. The first step involves abstraction of hydrogen radical from aryl alkyl ketone with bromo radical, generated from CBr_4, to produce phenacyl radical **3**. Positive evidence remains elusive; however, we think there are two paths, a and b, which involve cleavage of carbon–carbon bond of phenacyl bromide **4**[6] and 1,2-diketone **8** correspondingly.[7] Because of the stability of its generated radical species, 8% and 37% of **2a** were obtained correspondingly when using **1g** and **1h** under the usual Norrish reaction condition (Table 2, entries 7 and 8). Compounds **1h** and **1j** produced **2a** and **2j** correspondingly in lower yield due to its steric hindrance and formation of many unidentified products.

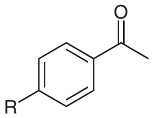
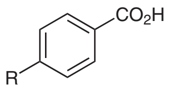
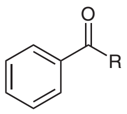
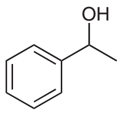
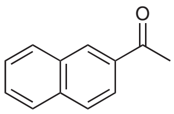
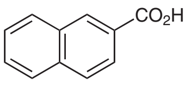
In conclusion, we report a useful method for facile synthesis of aryl carboxylic acids from aryl ketones by aerobic photooxidation using inexpensive and easily handled CBr_4 as catalyst. This procedure is applicable to inert compounds under usual photo-irradiation conditions, and appears very attractive from the view point of new method of expansion of Norrish Type I reaction. Further studies on use of the bromo source catalyst and additional applications are now in progress in our laboratory.

References and Notes

(1) (a) Kajigaeshi, S.; Nakagawa, T.; Nagasaki, N.; Fujisaki, S. *Synthesis* **1985**, 674. (b) Moriarty, R. M.; Prakash, I.; Penmasta, R. *J. Chem. Soc., Chem. Commun.* **1987**, 202. (c) Olah, G. A.; Ramos, M. T.; Wang, Q.; Surya Prakash, G. K. *Synlett* **1991**, 41. (d) Kathó, A.; Beck, M. T. *Synlett* **1992**, 165. (e) Gurunath, S.; Sudalai, A. *Synlett* **1999**, 559. (f) Zabjek, A.; Petriè, A. *Tetrahedron Lett.* **1999**, *40*, 6077. (g) Minisci, F.; Recupero, F.; Fontana, F.; Bjørsvik, H. R.; Liguori, L. *Synlett* **2002**, 610.

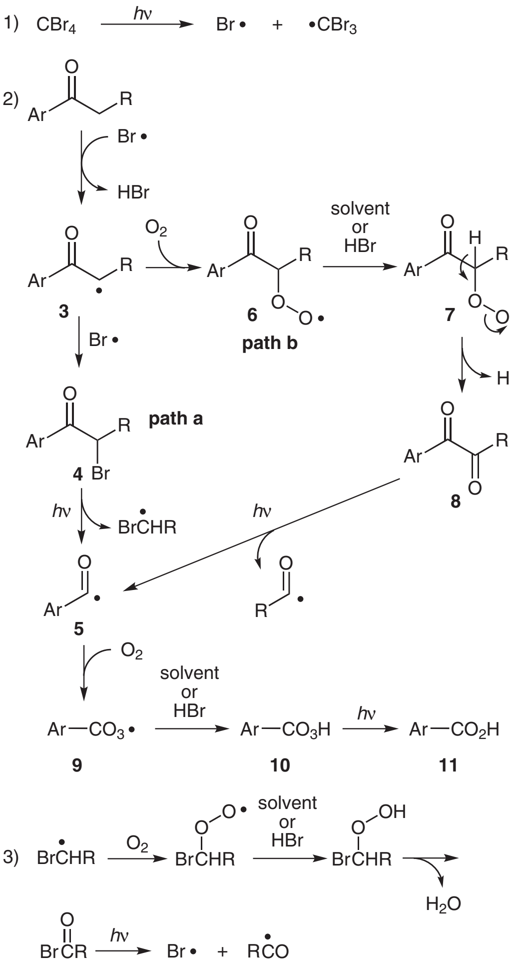
Table 2 Aerobic Photooxidation of Aryl Alkyl Ketones

$$\underset{\text{(0.3 mmol)}}{\textbf{substrate}} \xrightarrow[\text{EtOAc (5 mL)}]{\substack{O_2,\ h\nu \text{ (400 W Hg lamp)} \\ CBr_4 \text{ (0.2 equiv)}}} \textbf{product}$$

Entry	Substrate		Time (h)	Product, yield (%)[a]	
1		**1a** R = H	12		**2a** 82
2		**1b** R = *t*-Bu	12		**2b** 79
3		**1c** R = OMe	12		**2c** 87
4		**1d** R = Cl	12		**2d** 83
5		**1e** R = CN	24		**2e** 88
6		**1f** R = Et	18		**2a** 66
7		**1g** R = *i*-Pr	12		**2a** 77 (8)[b]
8		**1h** R = *t*-Bu	12		**2a** 39 (37)[b]
9		**1i**	12		**2a** 73
10		**1j**	12		**2j** 20

[a] All yields are for pure, isolated products.

[b] The reaction was carried out without CBr_4.



Scheme 2 Plausible path of aerobic photooxidation of aryl methyl ketones

(2) For example, see: Lenoir, D. *Angew. Chem. Int. Ed.* **2006**, *45*, 3206; and references cited therein.

(3) (a) Itoh, A.; Hashimoto, S.; Kodama, T.; Masaki, Y. *Synlett* **2005**, 2107. (b) Itoh, A.; Hashimoto, S.; Masaki, Y. *Synlett* **2005**, 2639. (c) Hirashima, S.; Itoh, A. *Synthesis* **2006**, 1757. (d) Hirashima, S.; Hashimoto, S.; Masaki, Y.; Itoh, A. *Tetrahedron* **2006**, *62*, 7887. (e) Hirashima, S.; Itoh, A. *Photochem. Photobiol. Sci.* **2007**, *6*, 521. (f) Hirashima, S.; Itoh, A. *Green Chem.* **2007**, *9*, 318. (g) Hirashima, S.; Itoh, A. *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 748.

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(5) **Typical Procedure**
A solution of acetophenone (**1a**, 0.3 mmol) and CBr_4 (0.06 mmol) in dry EtOAc (5 mL) in a pyrex test tube, purged with an O_2 balloon, was stirred and irradiated externally with a 400 W high-pressure mercury lamp for 12 h. The reaction mixture was concentrated in vacuo, and 10% NaOH aq solution was added. The aqueous solution was washed with Et_2O, and then acidified with 2 N HCl aq solution, which was extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$, and concentrated in vacuo. The product was pure without further purification.

(6) 4-Bromobenzoic acid was obtained in 82% yield when the reaction was carried out using *p*-bromophenacyl bromide as substrate without CBr_4 under photo-irradiation.

(7) Benzoic acid was obtained in 76% and 48% yield correspondingly when the reaction was carried out using phenylglyoxal and benzil as substrate under these reaction conditions.