Aerobic Photooxidation of Methyl Group at Aromatic Nucleus with LiBr

Akichika Itoh,* Shouei Hashimoto, Tomohiro Kodama, Yukio Masaki

Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502-8585, Japan E-mail: itoha@gifu-pu.ac.jp Received 27 April 2005

Abstract: A methyl group at the aromatic nucleus was found to be oxidized to the corresponding carboxylic acid directly in the presence of lithium bromide under aerobic photoirradiation.

Key words: photooxidation, methyl group, lithium bromide, aerobic, carboxylic acid

Oxidation reactions are the foundation of synthetic chemistry. Although oxidation reactions have been investigated by many researchers, most of them have involved the use of large quantities of heavy metals which results in the discharge of large amounts of contaminants, and were not at all environmentally benign.¹ With this background in mind, the notion of green chemistry is becoming well established, and the development of environmentally benign processes is the goal of various research projects. The method using hydrogen peroxide or molecular oxygen which possesses a high atomic effect or E-factor as an oxidant is one way consistent with this notion. We have previously reported that in the presence of a mesoporous silica FSM-16 under irradiation by a high-pressure mercury lamp, 4-tert-butylbenzyl bromide could be oxidized to benzoic acid.² We believed that the benzyl radical species, which is generated in situ by the irradiation of UV, traps molecular oxygen, and affords hydroperoxide via a peroxyradical. In this reaction, oxidation is thought to proceed smoothly due to facile elimination of a brominated functional group; however, a similar oxidation reaction would proceed even in the absence of a good releasing group, if an intermediate such as any methyl halide could be formed in situ. Based on tests conducted thus far, we have discovered that 4-tert-butyltoluene (1) was oxidized directly to 4-tert-butyl benzoic acid (2) in an oxygen atmosphere in ethyl acetate in the presence of catalytic lithium bromide (Scheme 1).³ There have been no reports on this point regarding the generalization of photooxidation of organic compounds with alkali metal halides so far.⁴ Now we report our study on generality of this reaction as a new kind of oxidation reaction.



SYNLETT 2005, No. 13, pp 2107–2109 Advanced online publication: 12.07.2005 DOI: 10.1055/s-2005-871942; Art ID: U13105ST © Georg Thieme Verlag Stuttgart · New York Table 1 shows our initial study of the reaction conditions of the aerobic photooxidation, which were carried out using 4-*tert*-butyltoluene (**1**, 50 mg, 0.269 mmol) as a test substrate with several alkali metal halides in various solvents.⁵ Among the solvents and the alkali metal halides examined, ethyl acetate and lithium bromide (0.5 equiv) were found to be suitable for the reaction.^{6,7}

Table 2 shows the results for the oxidation of several substrates under the reaction conditions outlined above.⁸ Although an electron-donating group, such as a *tert*-butyl group or a methoxy group at an aromatic group, in

Table 1 Study of Reaction Conditions of Aerobic Photooxidation

	\widehat{O}	O ₂ -balloo hv (400 W),	n MX	Coc	θH
<i>t</i> -Bu 1	(50 mg)	solvent (5 m	nL) <i>t</i> -Bu	2	
Entry	МХ	Equiv	Solvent	Time (h)	Yield of 2 (%)
1	LiBr	0.5	Hexane	4	7
2	LiBr	0.5	Acetone	4	0
3	LiBr	0.5	MeCN	4	0
4	LiBr	0.5	<i>i</i> -Pr ₂ O	4	9
5	LiBr	0.5	THF	4	0
6	LiBr	0.5	EtOAc	4	90
7	LiBr	0.1	EtOAc	4	25
8	LiBr	0.1	EtOAc	10	51
9	LiBr	0.3	EtOAc	4	81
10	LiBr	0.7	EtOAc	4	64
11	LiBr	1.0	EtOAc	4	22 ^a
12	LiBr	0.5	EtOAc	3	65
13	LiBr	0.5	EtOAc	6	88
14	LiCl	0.5	EtOAc	4	0
15	Lil	0.5	EtOAc	4	0
16	NaBr	0.5	EtOAc	4	0

^a A total of 30% of 4-*tert*-butylbenzaldehyde was obtained and 22% of **1** was recovered. The yield was estimated on the ratio of integral value of 400 MHz NMR analysis.

substra	hv (400 W), LiBr (0.5	O ₂ -balloon equiv)	product	
(50 m	g) EtOAc	(5 mL)		
Entry	Substrate	Time (h)	Product	Yield (%)
1	t-Bu	4	соон	90
2	MeO	6	2 MeO	73
3	3	12	4 COOH OMe	49
4	5	12	б Соон	76
5	7	24	8 NC COOH	80
6	9 ₀₂ N	36	10 COOH	78
7	11 Ph	24	12 Ph	88
8	13	48	14	63
9	15	48	16 COOH	22
	17		18	

Table 2 Aerobic Photooxidation for Aromatic Methyl Groups

general, enhanced the reaction rate, an electron-withdrawing group, such as a cyano or a nitro group, retarded this oxidation (entries 1, 2, 4–6). 2-Methoxytoluene ($\mathbf{5}$) was found to afford the corresponding benzoic acid $\mathbf{6}$ in moderate yield due to the steric hindrance of the methoxy group (entry 3).

The mechanism of this reaction has not yet been determined. However, the pale yellow coloration of the suspension suggests that bromine is generated in situ from lithium bromide under UV irradiation.⁹ Because the color

Synlett 2005, No. 13, 2107–2109 © Thieme Stuttgart · New York

fades as the reaction proceeds, we believe that the radical species **19** is generated by abstraction of a hydrogen radical with a bromo radical, formed under irradiation from bromine. The radical species traps molecular oxygen to afford the peroxyradical **20**, which gives hydroperoxide **21** and regenerates the bromo radical (Scheme 2).

In conclusion, we have found a useful method for the synthesis of benzoic acids with lithium bromide, which uses safe and inexpensive reagents, under aerobic UV irradiation. This novel method is thought to be convenient in view of the non-requirement of environmentally detrimental heavy metals and halogenated solvents.



Scheme 2

References

- Comprehensive Organic Transformations: A Guide to Functional Group Preparations; Larock, R. C., Ed.; Wiley-VCH: New York, 1999.
- (2) Itoh, A.; Kodama, T.; Inagaki, S.; Masaki, Y. Org. Lett. 2000, 2, 2455.
- (3) Photooxidation of alkylbenzene in the presence of alkyl bromides or hydrogen bromide under oxygen has been previously reported, see: Nakada, M.; Fukushi, S.; Hirota, M. Bull. Chem. Soc. Jpn. 1990, 63, 944.
- (4) Regarding photooxidation with alkali metal halides, the conversion of CO to CO₂ and H₂ to H₂O in the presence of hydrogen exposed to over 200 nm of ultraviolet light has been previously reported, see: Ryabchuk, V. *Catal. Today* **2000**, *58*, 89.
- (5) A typical procedure follows: a solution (5 mL) of the 4-tertbutyltoluene (50 mg) and LiBr in dry EtOAc was stirred and irradiated at r.t. with a 400-W high-pressure mercury lamp externally for the indicated time. The reaction mixture was concentrated under reduced pressure, and 1% NaOH aqueous solution was added. The aq soln was washed with Et₂O, and acidified with 2 N HCl aq soln, and then extracted again with Et₂O. The organic layer was washed with brine and dried over Na₂SO₄, and concentrated under reduced pressure. The product was pure without further purification.
- (6) No product (2) was detected when the reaction was carried out in the absence of UV irradiation or LiBr, which indicates the necessity of both LiBr and light for this reaction.
- (7) The reaction did not proceed with the irradiation in short time, for example 1 h, for the initiation of the reaction.

(8) A typical procedure follows: a solution (5 mL) of the substrate (0.269 mmol) and LiBr (0.5 equiv) in dry EtOAc was stirred and irradiated at r.t. with a 400-W high-pressure mercury lamp externally for the indicated time. The reaction mixture was concentrated under reduced pressure, and 1% NaOH aq soln was added. The aq soln was washed with Et_2O , acidified with 2 N HCl aq soln, and then extracted again with Et_2O . The organic layer was washed with brine and dried over Na_2SO_4 , and concentrated under reduced pressure. The product was pure without further purification.

(9) Catalytic bromine oxidized 1 to 2 in 21% yield under similar conditions.