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Aerobic Photooxidation of Toluene Derivatives into Carboxylic Acids with Bromine–Water under Catalyst-Free Conditions

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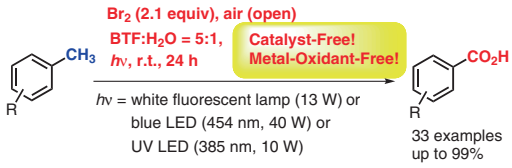

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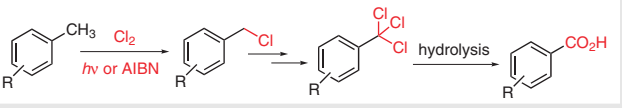
Abstract The photoirradiation of toluene derivatives with two equivalents of bromine in benzotrifluoride–water provided a satisfactory yield of the corresponding benzoic acid derivatives. Either a fluorescent lamp, blue LED (454 nm), or UV LED (385 nm) was used for the photoreaction. The reaction pathway might proceed through the dibromination of benzylic carbon, generation of the benzylic radical via oxidative C–H abstraction, formation of benzoyl bromide, and hydrolysis of carboxylic acid.

Key words oxidation, toluene, benzoic acid, carboxylic acid, bromine, aerobic oxidation, photoreaction

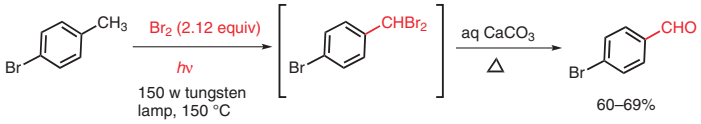
Benzoic acid derivatives are important intermediates in the formation of esters, amides, and acid chlorides for laboratory and industrial applications. The oxidation of the corresponding toluene derivatives is the most common preparation method of benzoic acid derivatives. However, the oxidation of the methyl group in aromatic compounds is limited, except when using toxic metal oxidants, such as $KMnO_4$[1] or Cr(VI).[2] Although oxidation with molecular oxygen has been applied in the industrial field, the method requires high pressures and temperatures.[3] Several studies have demonstrated the formation of benzoic acid derivatives using a catalytic bromide, such as HBr, KBr, CBr_4 with Oxone™, or O_2 under visible or ultraviolet light.[4]

Historically, the chlorination of toluene derivatives followed by hydrolysis has been established and applied in industrial fields. Chlorination involves a radical chain reaction by chloro radicals generated by AIBN or a photoreaction from molecular chlorine.[5] The time-consuming process of chlorination to trichloromethyl derivatives is necessary to yield benzoic acid derivatives (Scheme 1). On the other hand, the bromination of toluene derivatives mainly produced dibromomethyl compounds because the transformation of bulky bromide atoms into tribromomethyl groups is difficult. The hydrolysis of the dibromomethyl compound produces aldehydes.[6–9] The photobromination of 4-bromotoluene investigated in a previous study indicated that 4-bromo(dibromomethyl)benzene produced 4-bromobenzaldehyde (Scheme 2).[6]



Scheme 2 Industrial synthesis of benzoic acids from toluene derivatives via photochlorination and successive hydrolysis

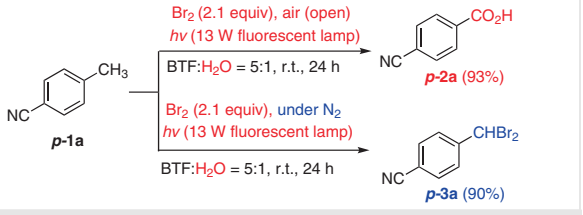
Notably, there are no reports on using toluene derivatives **1** with Br_2 in the presence of water to directly form aromatic carboxylic acids **2** under visible- or UV-light irradiation. Therefore, these reactions were examined under sev-



Scheme 1 Photobromination and hydrolysis of 4-bromotoluene

eral conditions using 1-cyano-4-methylbenzene (*p*-tolunitrile) (***p*-1a**) as the substrate.

Initially, ***p*-1a** was treated with Br_2 (2.1 equiv) and water in (trifluoromethyl)benzene (BTF) with irradiation from a 13 W fluorescent lamp and vigorous stirring in an air atmosphere for 24 h. Some solids were precipitated and dissolved in ethyl acetate (EtOAc) and aqueous NaOH. Thereafter, the aqueous alkaline layer was separated and acidified with dil. HCl, which was extracted using EtOAc. An excellent yield (93%) of the desired carboxylic acid ***p*-2a** was obtained in its pure form from the EtOAc extract after evaporation. The presence of molecular oxygen was essential for obtaining carboxylic acid ***p*-2a**. A 90% yield of dibromomethyl compound *p*-(dibromomethyl)benzonitrile (***p*-3a**), was produced in an inert atmosphere rather than ***p*-2a** (Scheme 3).



Scheme 3 Reaction of **1a** with Br_2 and H_2O in BTF and irradiation with a fluorescent lamp

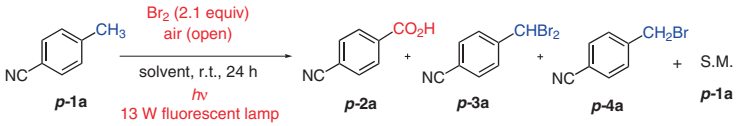
The solvent effects of this photoinduced aerobic oxidation through Br_2 and H_2O were examined using ***p*-1a** as the substrate (Table 1). In BTF without H_2O, the monobrominated compound ***p*-4a** was the main compound produced, whereas a certain amount of unreacted***p*-1a** was recovered (entry 2). Significantly, a similar result was obtained in H_2O without BTF, in which the desired ***p*-2a** was not produced (entry 3). An acceptable yield of carboxylic acid ***p*-2a** was produced in halogenated solvents (BTF, chlorobenzene, *p*-chloroBTF, CH_2Cl_2, and CCl_4) with H_2O (entries 1, 4–7), and the best result was obtained in BTF (entry 1). In benzene–H_2O, the yield of ***p*-2a** was low, with dibromide ***p*-3a** as the major product. The reaction advanced slowly in polar solvents (EtOAc, MeCN, and DMF) with H_2O not producing the desired ***p*-2a** (entries 9–11).

The reactions of several toluene derivatives **1** under optimized conditions (2 equiv of Br_2 in BTF and H_2O) were conducted with vigorous stirring for 24 h under photoirradiation.

A 13 W fluorescent lamp, 40 W blue LED (454 nm), or 10 W UV LED (385 nm) was used for irradiation. A considerable amount of solid precipitate was produced in all cases; the reaction mixture was subjected to the same procedure as that for **1a**. The corresponding carboxylic acid derivatives **2** were obtained in high yields in most cases; the compounds obtained were sufficiently pure and did not require further purification (Tables 2–4).[10]

Thereafter, control experiments were performed to elucidate the reaction mechanism. As shown in Scheme 3 and Table 1, both O_2 and H_2O are essential in entry 2 for producing the desired carboxylic acid **2**; the corresponding dibromide **3** was produced instead of **2** without either O_2 or H_2O.

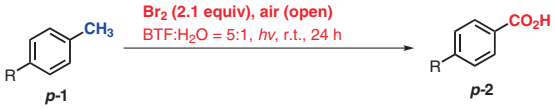
Table 1 Examination of Solvents Effects



Entry	Solvent	Carboxylic acid ***p*-2a**[a]	Dibromide ***p*-3a**[b]	Monobromide ***p*-4a**[b]	S. M. ***p*-1a**[b]
1	BTF:H_2O = 5:1	93%	0%	0%	0%
2	BTF	4%	0%	64%	20%
3	H_2O	0%	0%	79%	1%
4	chlorobenzene:H_2O = 5:1	76%	13%	1%	0%
5	*p*-chloroBTF:H_2O = 5:1	90%	0%	0%	0%
6	CH_2Cl_2:H_2O = 5:1	70%	19%	trace	0%
7	CCl_4:H_2O = 5:1	85%	0%	0%	0%
8	Benzene:H_2O = 5:1	28%	42%	5%	0%
9	EtOAc:H_2O = 5:1	0%	0%	49%	32%
10	MeCN:H_2O = 5:1	0%	0%	19%	65%
11	DMF:H_2O = 5:1	0%	0%	0%	quant.

[a] Isolated yield, [b] ^{1}HNMR yield.

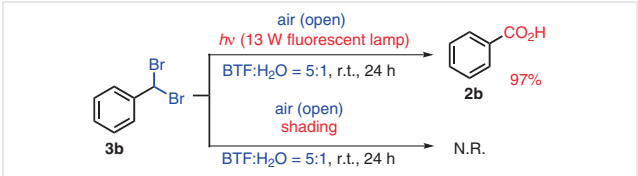
Table 2 Oxidation of *para*-Substituted Toluenes



Entry	Substrate	Product	Isolated yield (%)
1	*p*-1a	*p*-2a	93[a] 99[b]
2	1b	2b	95[a] 98[b] 88[c]
3	*p*-1c	*p*-2c	95[a] 98[b] 95[c]
4	*p*-1d	*p*-2d	96[a]
5	*p*-1e	*p*-2e	81[c]
6	*p*-1f	*p*-2f	80[c]
7	*p*-1g	*p*-2g	90[a] 96[c]
8	*p*-1h	*p*-2h	91[a]
9	*p*-1i	*p*-2i	90[a,d]
10	*p*-1j	*p*-2j	90[a]
11	*p*-1k	*p*-2k	79[a,e]
12	*p*-1l	*p*-2l	90[a]
13	*p*-1m	*p*-2m	91[a]
14	*p*-1n	*p*-2n'	90[a,e]
15	*p*-1o	*p*-2o'	95[a,e]
16	*p*-1p	complex mixture	
17	*p*-1q	complex mixture	
18	*p*-1r	complex mixture	

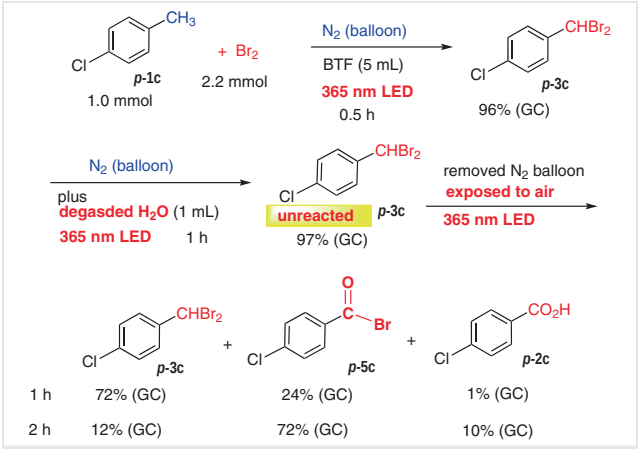
[a] White fluorescent lamp (13 W) or
[b] Blue LED (454 nm, 40 W) or
[c] UV LED (385 nm, 10 W)
[d] Br_2 (4.2 equiv), 48 h, [e] Br_2 (3.1 equiv).

We estimated that **3** was the reaction intermediate between **1** and **2** under these reaction conditions. Therefore, (dibromomethyl)benzene (**3b**) was treated with H_2O in BTF in an air atmosphere by vigorously stirring for 24 h with or without irradiation from a 13 W fluorescent lamp (Scheme 4). Benzoic acid (**2b**) was produced in an almost quantitative yield with photoirradiation. Conversely, **3b** did not react and was quantitatively recovered for reactions performed in the dark.



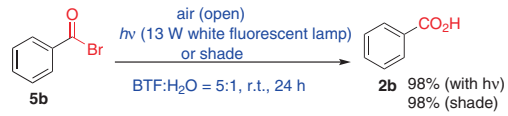
Scheme 4 Examination of the effect of light energy on the reaction

Third, a solution of 4-chlorotoluene (***p*-1c**) and bromine in BTF (without H_2O) was irradiated with a 365 nm UV lamp after freeze substitution with nitrogen. The bromination was fast at 96% of 4-chloro(dibromomethyl)benzene (***p*-3c**) after 0.5 h. Nitrogen-substituted H_2O was added to the mixture, which was then irradiated for 1 h. GC analysis revealed the presence of 97% of ***p*-3c**. The nitrogen balloon was removed (open air), and irradiation continued. After 1 h, a GC analysis revealed 72% of (***p*-3c**) and 24% of 4-chlorobenzoyl bromide (***p*-5c**). 4-Chlorobenzaldehyde was not detected. The control experiment is shown in Scheme 5.



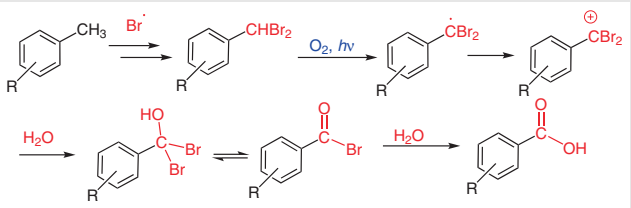
Scheme 5 Stepwise control experiment through the oxidation of toluene derivatives into carboxylic acids

Furthermore, a separate experiment on the hydrolysis of benzoyl bromide (**5b**) was conducted with and without light. The results indicated that light was not necessary for the hydrolysis of benzoyl bromide to carboxylic acid (Scheme 6).



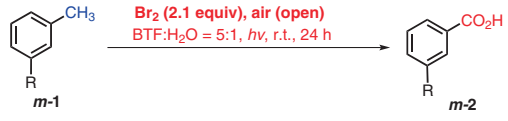
Scheme 6 Examination of the effect of photoenergy for the hydrolysis of benzoyl bromide

Based on the above evidence, a plausible mechanism for the direct oxidation of toluene derivatives with bromine–water under photoirradiation is depicted in Scheme 7.



Scheme 7 Plausible photooxidation pathway with bromine–water from toluene derivatives to the carboxylic acids

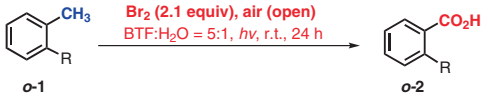
Table 3 Oxidation of *meta*-Substituted Toluenes



Entry	Substrate	Product	Isolated yield (%)
1	*m*-1a	*m*-2a	94[a] 97[c]
2	*m*-1c	*m*-2c	99[a]
3	*m*-1d	*m*-2d	94[a]
4	*m*-1e	*m*-2e	93[a]
5	*m*-1f	*m*-2f	90[a]
6	*m*-1g	*m*-2g	94[a]
7	*m*-1h	*m*-2h	90[a]
8	*m*-1n	*m*-2n'	90[a,d]

[a] White fluorescent lamp (13 W) or
[b] Blue LED (454 nm, 40 W) or
[c] UV LED (385 nm, 10 W)
[d] Br_2 (4.2 equiv), 48 h.

Table 4 Oxidation of *ortho*-Substituted Toluenes



Entry	Substrate	Product	Isolated yield (%)
1	*o*-1a	*o*-2a	83[c]
2	*o*-1c	*o*-2c	78[c]
3	*o*-1e	*o*-2e	79[c]
4	*o*-1g	*o*-2g	91[a]
5	*o*-1s	*o*-2s	91[a]
6	*o*-1n	*o*-2n'	90[a,d]
7	*o*-1i	complex mixture	

[a] White fluorescent lamp (13 W) or
[b] Blue LED (454 nm, 40 W) or
[c] UV LED (385 nm, 10 W)
[d] Br_2 (4.2 equiv), 48 h, [e] Br_2 (3.1 equiv).

The key step is the radical fission of the C–H bond in the dibromide by photoactivated molecular oxygen, where it was successively oxidized into a dibromomethyl cation, followed by a dose of H_2O to form the acyl bromide. The rate-determining step of the whole reaction was the hydrolysis of acyl bromide into carboxylic acid.

This facile procedure for the oxidation of toluene derivatives into benzoic acids using readily available inexpensive reagents under catalyst-free conditions can be considered a convenient method for laboratory and industrial applications.

Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1887-7885.

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(10) **Typical Experimental Procedure**

A 100 mL Pyrex flask was charged with 1-cyano-4-methylbenzene (***p*-1a**, 586 mg, 5.0 mmol) and Br_2 (840 mg, 10.5 mmol) in BTF (30 mL) and water (6 mL). The attached reflux condenser was open air, and the flask was irradiated with a 13 W white fluorescent lamp at intervals of 5 cm with vigorous stirring for 24 h. The reaction mixture was combined with saturated aqueous $NaHCO_3$ and EtOAc. The alkaline aqueous layer was then separated and acidified with diluted HCl. The solution was successively extracted using EtOAc and washed with H_2O and brine. After drying over anhydrous Na_2SO_4, it was concentrated to produce 4-cyanobenzoic acid (***p*-2a**, 684 mg, 93%) colorless crystals. The sample was sufficiently pure, and further purification was not performed.

4-Cyanobenzoic Acid (*p*-2a)

Mp 222 °C (lit.[11] mp 221 ℃). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.11 (d, *J*= 8.4 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (101 MHz, CD_3OD): δ = 167.9, 135.9, 133.3, 131.2, 118.9, 117.1.

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