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

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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 photo-reaction. 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 KMnO4 or Cr(VI). Although oxidation with molecular oxygen has been applied in the industrial field, the method requires high pressures and temperatures. Several studies have demonstrated the formation of benzoic acid derivatives using a catalytic bromide, such as HBr, KBr, CBr₄ with Oxone™, or O₂ 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.3 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).

Notably, there are no reports on using toluene derivatives 1 with Br₂ 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-
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 Br2 and H2O in BTF and irradiation with a fluorescent lamp](image)

The solvent effects of this photoinduced aerobic oxidation through Br$_2$ and H$_2$O were examined using p-1a as the substrate (Table 1). In BTF without H$_2$O, 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$_2$O 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$_2$Cl$_2$, and CCl$_4$) with H$_2$O (entries 1, 4–7), and the best result was obtained in BTF (entry 1). In benzene–H$_2$O, 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$_2$O not producing the desired p-2a (entries 9–11).

![Table 1 Examination of Solvents Effects](image)

| Entry | Solvent | Carboxylic acid p-2a | Dibromide Monobromide p-3a | S. M. p-1a
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>BTF:H$_2$O = 5:1</td>
<td>93%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>BTF</td>
<td>4%</td>
<td>0%</td>
<td>64%</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$O</td>
<td>0%</td>
<td>0%</td>
<td>79%</td>
</tr>
<tr>
<td>4</td>
<td>chlorobenzene:H$_2$O = 5:1</td>
<td>76%</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>5</td>
<td>p-chloroBTF:H$_2$O = 5:1</td>
<td>90%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>CH$_2$Cl$_2$:H$_2$O = 5:1</td>
<td>70%</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>CCl$_4$:H$_2$O = 5:1</td>
<td>85%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>Benzene:H$_2$O = 5:1</td>
<td>28%</td>
<td>42%</td>
<td>5%</td>
</tr>
<tr>
<td>9</td>
<td>EtOAc:H$_2$O = 5:1</td>
<td>0%</td>
<td>0%</td>
<td>49%</td>
</tr>
<tr>
<td>10</td>
<td>MeOH:H$_2$O = 5:1</td>
<td>0%</td>
<td>0%</td>
<td>19%</td>
</tr>
<tr>
<td>11</td>
<td>DMF:H$_2$O = 5:1</td>
<td>0%</td>
<td>0%</td>
<td>49%</td>
</tr>
</tbody>
</table>

* Isolated yield, *b* 1HNMR yield.

The reactions of several toluene derivatives 1 under optimized conditions (2 equiv of Br$_2$ in BTF and H$_2$O) 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$_2$O 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$_2$O.
We estimated that 3 was the reaction intermediate between 1 and 2 under these reaction conditions. Therefore, (dibromomethyl)benzene (3b) was treated with H₂O 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.

Third, a solution of 4-chlorotoluene (p-1c) and bromine in BTF (without H₂O) 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 H₂O 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.

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).
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.

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 H₂O 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.
References and Notes


(10) Typical Experimental Procedure
A 100 mL Pyrex flask was charged with 1-cyano-4-methylbenzene (p-1a, 586 mg, 5.0 mmol) and Br2 (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 NaHCO3 and EtOAc. The alkaline aqueous layer was successively extracted using EtOAc and washed with H2O and brine. After drying over anhydrous Na2SO4, 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.1 mp 221 °C). 1H NMR (400 MHz, CD3OD): δ = 8.11 (d, J= 8.4 Hz, 2 H), 7.79 (d, J = 8.4 Hz, 2 H). 13C NMR (101 MHz, CD3OD): δ = 167.9, 135.9, 133.3, 131.2, 118.9, 117.1.