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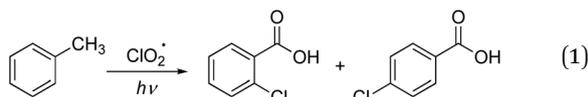
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One-pot chlorocarboxylation of toluenes with chlorine dioxide under photoirradiation†

Shohei Ohno, [ID] [a] Haruyasu Asahara, [ID] [ab] Tsuyoshi Inoue[ab] and Kei Ohkubo [ID] *[bc]

Chlorocarboxylation of toluene was achieved by photoirradiation of a chlorine dioxide radical ($ClO_2^\bullet$) under ambient conditions (298 K and 1 atm). 2- and 4-Chlorobenzoic acids were obtained in a 1 : 1 yield ratio. This is a single step synthesis under metal-free and mild conditions.

The chlorocarboxylation reaction is of practical importance in organic synthesis as chloro and carboxy groups are introduced into the substrate in a single step. In the 1980s, chlorocarboxylation of polymer materials such as polyethylene was performed using toxic dry chlorine gas and/or maleic anhydride at high temperatures (90–110 °C).[1] To the best of our knowledge, there have been no reports of chlorocarboxylation of small molecules thus far.[2,3] However, reactions such as chloroesterification and chlorocarbamoylation in the presence of transition metal catalysts have been reported.[4] The substrates used in these reactions were limited to only alkenes and alkynes; chlorocarboxylation of aromatic compounds have not been reported to date. In this study, we developed a photoinduced chlorocarboxylation of toluene initiated by a chlorine dioxide radical ($ClO_2^\bullet$) at room temperature without the use of a metal catalyst [eqn. (1)]. We hypothesized that $ClO_2^\bullet$ is first photochemically activated to generate $Cl^\bullet$ and O_2, which would react with toluene to produce 2- and 4-chlorobenzoic acids in a 1 : 1 yield ratio.

$$(1)$$

Previous reports have demonstrated the synthesis of 2- and 4-chlorobenzoic acids *via* a two-step process, where chlorination occurs first followed by the oxidation of toluene in the presence of toxic metals.[5] In contrast, our method is green and sustainable as the products are obtained in a single step under metal-free conditions.
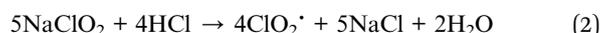
[a]Graduate School of Pharmaceutical Sciences, Osaka University, Yamada-oka 1-6, Suita, Osaka, 565-0871, Japan

[b]Institute for Open and Transdisciplinary Research Initiatives, Osaka University, Yamada-oka 1-6, Suita, Osaka, 565-0871, Japan

[c]Institute for Advanced Co-Creation Studies, Osaka University, Yamada-oka 1-6, Suita, Osaka, 565-0871, Japan. E-mail: ohkubo@irdd.osaka-u.ac.jp

$ClO_2^\bullet$ (50 mM), which is a water-soluble gas and a stable radical at room temperature, was prepared by mixing sodium chlorite ($NaClO_2$, 200 mg, 1.75 mmol) and 35% aq. HCl (100 μL) in aqueous solution (28 mL), as described in a previously reported method.[6-9] The generation of $ClO_2^\bullet$ gas is shown in eqn (2).
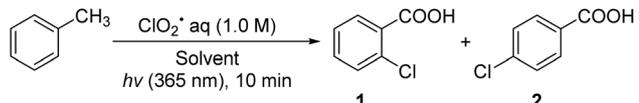
$$5NaClO_2 + 4HCl \rightarrow 4ClO_2^\bullet + 5NaCl + 2H_2O \qquad (2)$$

UV-vis absorption ($\lambda_{max} = 358$ nm) and electron spin resonance (ESR) spectroscopy ($g = 2.015$, $a(Cl) = 16$ G) of the aqueous solution confirmed the generation of $ClO_2^\bullet$ gas.[7] Chlorocarboxylation of toluene did not occur in the dark because $ClO_2^\bullet$ cannot be activated without photoirradiation. In contrast, when an LED ($\lambda = 365$ nm, 20 mW cm^{-1}) was used, $ClO_2^\bullet$ was photochemically activated to yield $Cl^\bullet$ radical and singlet oxygen ($(^1O_2^*)$) [eqn (3)].[7]

$$ClO_2^\bullet \xrightarrow{h\nu} Cl^\bullet + {}^1O_2^* \qquad (3)$$

First, we studied the effects of different solvents on the chlorocarboxylation of toluene (Table 1). This reaction does not proceed in solvents with C–H bonds because $ClO_2^\bullet$ reacts with a hydrogen atom from the solvent. When acetone-d_6 (entry 1) was used, 2-chlorobenzoic acid **1** and 4-chlorobenzoic acid **2** were produced in a total yield of 68% (35% and 33%, respectively). This implies that chlorination proceeded selectively at the electron-rich *ortho* and *para* positions. When acetonitrile-d_3 and dimethylformamide-d_6 were used under identical conditions (entries 2 and 3), the product yields (33% and 31%) were comparable to that of entry 1.[10] When methanol-d_4, *N*,*N*-dimethylformamide-d_7, tetrahydrofuran-d_8, benzene-d_6, perfluorocarbons, and carbon tetrachloride were used (entries 4–9), the reaction did not proceed at all.
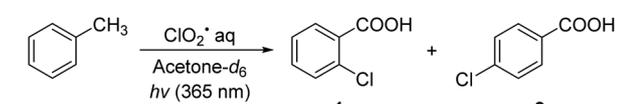
Next, we optimized the reaction conditions—concentration of $ClO_2^\bullet$ and excitation wavelength (Table 2). We observed that the reaction proceeded most efficiently when a 0.05 M $ClO_2^\bullet$ solution was used (entry 2). Other concentrations of $ClO_2^\bullet$ solutions produced the products in lower yields (entries 3, 4 and

Table 1 Solvent effects on the chlorocarboxylation of toluene using $ClO_2^{\cdot}$ gas

Entry	Solvent	Yield (%)[a] 1 : 2
1	Acetone-d_6	35 : 33
2	Acetonitrile-d_3	33 : 31
3	Dimethyl sulfoxide-d_6	32 : 30
4	Methanol-d_6	ND
5	DMF-d_7	ND
6	THF-d_8	ND
7	Benzene-d_6	ND
8	Perfluorohexane	ND
9	Tetrachloromethane	ND

[a] The products were identified and quantified using GC-MS by comparing them with the characterization data of authentic samples; ND = not detected.
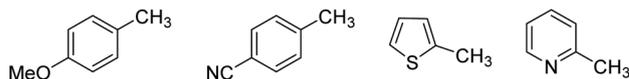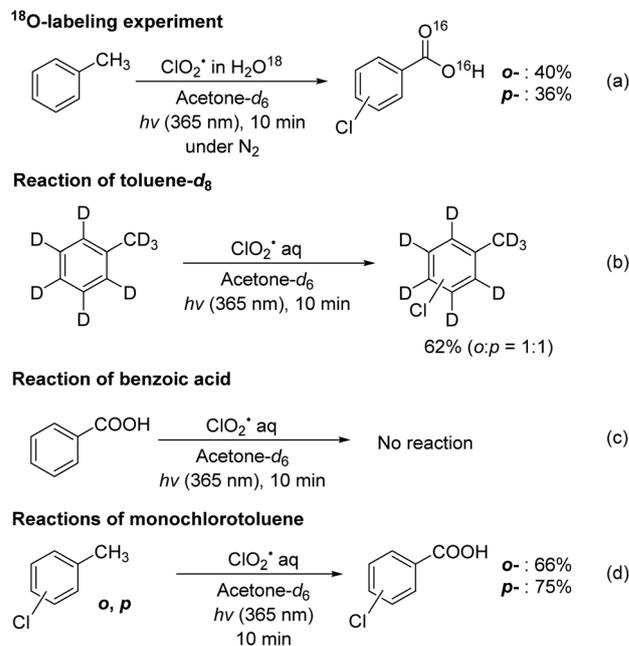
Table 2 Optimization of reaction conditions for the chlorocarboxylation of toluene

Entry	$ClO_2^{\cdot}$ aq. (M)	Excitation wavelength (nm)	Yield (%)[a] 1 : 2
1	1.0	365	35 : 33
2	0.05	365	40 : 36
3	0.25	365	39 : 35
4	0.5	365	38 : 35
5	1.5	365	33 : 31
6	0.05	405	39 : 35

[a] The products were identified and quantified using GC-MS by comparing them with the characterization data of authentic samples.

Fig. 1 Chlorocarboxylation of other aromatic compounds.

Fig. 2 Control experiments to elucidate the reaction mechanism of the chlorocarboxylation of toluene.

5) than those obtained for entry 2. However, the reaction proceeded well even with visible light ($\lambda = 405$ nm) (entry 6). Therefore, the optimal conditions were 0.05 M $ClO_2^{\cdot}$ and an excitation wavelength of 365 nm.

Subsequently, we attempted the chlorocarboxylation of other substrates (Fig. 1). When an electron-donating group-bearing toluene (*p*-methoxy toluene) was used di- or trichlorination occurred instead of the desired reaction. In contrast, when an electron-withdrawing group-bearing toluene (*p*-cyano toluene) was used, the reaction did not proceed and the starting material was recovered. Furthermore, the desired reaction did not proceed when electron-rich or electron-deficient heterocycles (2-methyl thiophene and 2-methyl pyridine, respectively) were used as substrates.

Finally, control experiments were performed to investigate the reaction mechanism (Fig. 2). First, the reaction was examined using ^{18}O-labeled water (H_2O^{18}) under nitrogen atmosphere; however, no labeled product was observed [Fig. 2(a)]. This result suggests that the carboxylate oxygen atoms in the product were not derived from water. In contrast, when the reaction was conducted in toluene-d$_8$, only monochlorinated toluene was obtained without any carboxylated products [Fig. 2(b)]. This result suggests that the carboxylation step in chlorocarboxylation begins with hydrogen abstraction at the benzyl position of toluene. Moreover, when we studied the chlorination of benzoic acid under $ClO_2^{\cdot}$ photoreaction conditions, chlorination did not occur [Fig. 2(c)]. The reactions of 2- and 4-chlorotoluene yielded the corresponding chlorocarboxylic acids in good yields (66% and 75%, respectively) [Fig. 2(d)]. These results indicate that the chlorocarboxylation of toluene begins with chlorination, in which a chlorine radical attacks the aromatic ring.

Based on these experimental results, we propose the following mechanism (Scheme 1).:[11] First, the photoirradiation of $ClO_2^{\cdot}$ produces a $Cl^{\cdot}$ radical and singlet O_2. Then the $Cl^{\cdot}$ radical attacks toluene to generate an aryl radical. Subsequently, another $Cl^{\cdot}$ radical abstracts a hydrogen from the aryl radical to produce chlorotoluene. Next, another hydrogen abstraction from chlorotoluene generates a benzyl radical.

Scheme 1 Plausible reaction mechanism for the chlorocarboxylation of toluene using $ClO_2^{\cdot}$. $h\nu$ represents photo-irradiation and [O] represents autoxidation.

This benzyl radical reacts with a singlet oxygen in the solution to form a peroxy radical intermediate. This peroxy radical releases one oxygen atom to form chlorobenzyl alcohol and chlorobenzaldehyde, which are then oxidized through Pinnick oxidation or autoxidation to yield the final product, chlorobenzoic acid.

In conclusion, for the first time in the literature, we demonstrated that $ClO_2^{\cdot}$ is an efficient reagent for the chlorocarboxylation of toluene in a single step. A plausible mechanism was proposed based on control experiments. This single-step synthesis of chlorobenzoic acids under metal-free conditions is a green and sustainable method that has potential applications in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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