K. Zheng et al.

Letter

Photoinduced Carbon Tetrabromide Initiated Aerobic Oxidation of Substituted Toluenes to Carboxylic Acids

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Received: 17.10.2019 Accepted after revision: 28.11.2019 Published online: 13.12.2019 DOI: 10.1055/s-0039-1691534; Art ID: st-2019-k0567-I

Abstract A mild and metal-free procedure is reported for the aerobic oxidation of substituted toluenes to carboxylic acids by using CBr_4 as initiator under irradiation from a 400 nm blue light-emitting diode.

Key words metal-free synthesis, photooxidation, toluenes, benzoic acids

Aerobic oxidation of toluene and substituted toluenes is one of the most important and most fundamental transformations in organic synthesis,¹ because of the importance and versatility of the corresponding carboxylic acids in the fine-chemical industry.² Although this transformation has found broad applications, it still suffers from some limitations, such as the use of metal catalysts, the need for harsh reaction conditions, and poor selectively.³ In recent years, a great deal of research effort has been devoted to the development of metal-free procedures for aerobic oxidation of substituted toluenes to carboxylic acids as alternatives to the conventional protocols.⁴ Among these, photochemical reactions provide an alternative to classical reactions under thermal control, avoiding the need for harsh reaction conditions and improving the selectively (Scheme 1). Itoh and co-workers developed an aerobic oxidation of substituted toluenes by UV irradiation in the presence of LiBr or HBr.⁵ They also improved the reaction by employing a CBr₄–PPh₃ system as bromine source under visible-light irradiation.⁶ Here, we report a simpler aerobic oxidation of substituted toluenes under visible-light irradiation with CBr₄ as an initiator without the assistance of PPh₃.

We commenced our studies by investigating the aerobic oxidation of toluene (**1a**). In our initial attempt, only a trace amount of benzoic acid was detected under visible-light irradiation by a general-purpose fluorescent lamp or a 460



Scheme 1 Photoinduced aerobic oxidation of substituted toluenes to carboxylic acids

nm light-emitting diode (LED) (Table 1, entries 1 and 2). Notably, an 8% yield of benzaldehyde was obtained when a 460 nm LED was used. Inspired by these results, we decided

Table 1 Optimization of the Reaction Conditions^a

	Me 1a	O ₂ (balloon) CBr ₄ (10 mol%) MeCN, rt visible light	COOH + 2a 3	CHO
Entry	Catalyst	Light source	Yield ^b (%) of $2a$	Yield (%) of 3
1	CBr ₄	fluorescent lamp	trace	trace
2	CBr ₄	460 nm LED	trace	8
3	CBr ₄	440 nm LED	38	26
4	CBr ₄	400 nm LED	70	21
5°	CBr ₄	400 nm LED	98 (96) ^d	2
6 ^e	-	400 nm LED	-	-
7	CCl_4	400 nm LED	-	-

 a Reaction conditions: toluene 1a (0.5 mmol), catalyst (10 mol%), MeCN (10 mL), 60 W 400 nm LED, O_2 balloon, rt, 24 h.

^b GC yields with 1,4-dioxaneas internal standard.

° 48 h.

^d Isolated yield.

^e No catalyst.

K. Zheng et al.

to test LEDs with a shorter wavelength. To our delight, by using a 440 nm LED, the desired benzoic acid (**2a**) and benzaldehyde (**3**) were formed in yields of 38 and 26%, respectively (entry 3). A further reduction in the wavelength of the light to 400 nm increased the yield of benzoic acid (**2a**) to 70% (entry 4). Moreover, prolonging the reaction time to 48 hours increased the yield to 96% (entry 5). Control experiments suggested that CBr₄ was essential for a successful aerobic oxidation of toluene (entry 6), as structurally similar CCl₄ gave no reaction (entry 7).

With the optimized reaction conditions in hand,⁷ we next investigated the scope of the scope (Scheme 2). A diverse array of methylarenes with a variety of functional groups (tert-butyl, methoxy, fluoro, chloro, bromo, iodo, nitro, nitrile, bromomethyl, or acyl) were tolerated in this reaction. Generally, para-substituted methylarenes, which gave products 2a-k in yields of 72-96%, were more effective substrates than their meta- or ortho-substituted analogues, which gave products **2l-q** in yields of 41-68%. Notably, whereas the methyl group of 4-(bromomethyl)toluene (1i) was smoothly oxidized, the bromomethyl group was unaffected by the reaction conditions, possibly due to the steric effect of the neighboring bromine atom. The terminal methyl group of a propionyl group was also tolerated to afford the corresponding product 2r in good yield. Furthermore, we found that 4-methylbenzophenone could be oxidized to the acid **2s**, but with modest efficiency (63% yield).





The disubstituted methylarenes **1t** and **1u** also performed well in this reaction. Perhaps most importantly, this transformation is not limited to substituted toluenes; for example, 1-bromo-2-methylnaphthalene readily underwent this aerobic oxidation to give acid **2v** in 53% yield. However, none of the reactions was scaled to above 0.5 mmol because of concerns regarding the formation of potentially explosive peroxide and hydroperoxide intermediates.⁷

The aerobic oxidation of toluene was then monitored over a period of 48 hours. GC analysis showed that benzaldehyde was the main product during the first ten hours, but this was later consumed to form benzoic acid (Figure 1).



Figure 1 Monitoring the aerobic oxidation of toluene

To gain more insights into the reaction pathway for the aerobic oxidation, we treated benzaldehyde with O₂ under various conditions (Table 2). The reaction of benzaldehyde under the optimized reaction conditions gave a 97% conversion into 2a, demonstrating its competency as an intermediate (Table 2, entry 1). Control experiments revealed that the reaction efficiency was reduced significantly in the absence of visible-light irradiation (entries 2 and 3). In contrast, the reaction under visible-light irradiation in the absence of CBr₄ was moderately successful (entry 4), suggesting that the interaction between light and CBr4 might promote the photoinduced oxidation. Notably, no acyl bromide was detected when the reaction was conducted in the presence of 4 Å molecular sieves (entry 5), indicating that acyl bromides might be not involved as intermediates.⁶ The decrease in the yield might be due to the opacity of the solution caused by the addition of the molecular sieves.

Based on these experiments and on previous results, a plausible mechanism is proposed in Scheme 3. Under irradiation and/or activation by a charge-transfer (CT) complex of toluene with CBr_4 ,⁸ homolysis of CBr_4 gives a tribromomethyl radical and a bromo radical. The reaction of toluene with the bromo radical gives a benzyl radical (I) and initiates a chain oxidation process.⁹ The reaction of the benzyl radical (I) with dioxygen yields benzyl hydroperoxide

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 Table 2
 Control Experiments

K. Zheng et al.

	CHO O ₂ (ba 3	diloon)	
Entry	Catalyst	Light	Yield ^b (%)
1	CBr ₄	400 nm	97
2	CBr ₄	-	5
3	-	-	1
4	-	400 nm	23
5°	CBr ₄	400 nm	64

 a Reaction conditions: PhCHO (3; 0.5 mmol), CBr_4 (10 mol%), MeCN (10 mL), 60 W 400 nm LED, O_2 balloon, rt, 48 h.

^b GC vields with 1,4-dioxane as internal standard.

^c 4 Å molecular sieves added.

(**II**), which is then transformed into benzaldehyde (**3**).^{9b} Finally, benzaldehyde (**3**) is further oxidized to benzoic acid (**2**) on prolonging the reaction time.¹⁰



Scheme 3 Plausible mechanism

In conclusion, we have developed a simple and effective method for the photoinduced aerobic oxidation of substituted toluenes to benzoic acids under mild metal-free conditions. The method uses easily handled CBr_4 as the only initiator and a 400 nm LED as a source of visible light. The transformation exhibits a broad scope and good functional-group compatibility.

Funding Information

This work was supported by the National Key Research and Development Program of China (2017YFC0210900).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691534.

References and Notes

- (a) Sheldon, R. A.; Kochi, J. K. Metal-Catalyzed Oxidations of Organic Compounds: Mechanistic Principles and Synthetic Methodology Including Biochemical Processes; Academic Press: New York, **1981**. (b) Simandi, L. Catalytic Activation of Dioxygen by Metal Complexes; Kluwer Academic: Boston, **1992**. (c) Henry, P. M. Palladium Catalyzed Oxidation of Hydrocarbons; Reidel: Dordrecht, **1980**.
- (2) (a) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. Angew. Chem. Int. Ed. 2018, 57, 1688. (b) Li, Q.; Meng, L.; Zhou, S.; Deng, X.; Wang, N.; Ji, Y.; Peng, Y.; Xing, J.; Yao, G. Eur. J. Med. Chem. 2019, 180, 509. (c) Oliveira, C.; Bagetta, D.; Cagide, F.; Teixeira, J.; Amorim, R.; Silva, T.; Garrido, J.; Remiao, F.; Uriarte, E.; Oliveira, P. J.; Alcaro, S.; Ortuso, F.; Borges, F. Eur. J. Med. Chem. 2019, 174, 116. (d) Zhang, Z.; Hao, K.; Li, H.; Lu, R.; Liu, C.; Zhou, M.; Li, B.; Meng, Z.; Hu, Q.; Jiang, C. Eur. J. Med. Chem. 2019, 181, 111564.
- (3) (a) Miki, J.; Osada, Y.; Tachibana, Y.; Shikada, T. *Catal. Lett.* 1995, 30, 263. (b) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. J. Org. Chem. 1997, 62, 6810. (c) Yamazaki, S. Org. Lett. 1999, 1, 2129. (d) Rogovin, M.; Neumann, R. J. Mol. Catal. A: Chem. 1999, 138, 315. (e) Bandyopadhyay, R.; Biswas, S.; Bhattacharyya, R.; Guha, S.; Mukherjee, A. K. Chem. Commun. 1999, 1627. (f) Das, B. K.; Clark, J. H. Chem. Commun. 2000, 605. (g) Fraga-Dubreuil, J.; Garcia-Verdugo, E.; Hamley, P. A.; Vaquero, E. M.; Dudd, L. M.; Pearson, I.; Housley, D.; Partenheimer, W.; Thomas, W. B.; Whiston, K.; Poliakoff, M. Green Chem. 2007, 9, 1238. (h) Wang, J.-Q.; He, L-N. New J. Chem. 2009, 33, 1637. (i) Nakamura, R.; Obora, Y.; Ishii, Y. Adv. Synth. Catal. 2009, 351, 1677. (j) Cui, L.-Q.; Liu, K.; Zhang, C. Org. Biomol. Chem. 2011, 9, 2258. (k) Hu, Y.; Zhou, L; Lu, W. Synthesis 2017, 49, 4007.
- (4) (a) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. J. Org. Chem. 1995, 60, 3934. (b) Paul, S.; Nanda, P.; Gupta, R. Synlett 2004, 531. (c) Lu, T.; Mao, Y.; Yao, K.; Xu, J.; Lu, M. Catal. Commun. 2012, 27, 124. (d) Liu, G.; Tang, R.; Wang, Z. Catal. Lett. 2014, 144, 717. (e) Ozen, R. Asian J. Chem. 2014, 26, 941. (f) Heidari, M.; Sedrpoushan, A.; Mohannazadeh, F. Org. Process Res. Dev. 2017, 21, 641.
- (5) (a) Itoh, A.; Hirashima, S.-i. *Synthesis* **2006**, 1757. (b) Itoh, A.; Hashimoto, S.; Kodama, T.; Masaki, Y. *Synlett* **2005**, 2107.
- (6) Sugai, T.; Itoh, A. Tetrahedron Lett. 2007, 48, 9096.
- (7) Arylcarboxylic Acids 1a-v; General Procedure

CAUTION: The reaction is inherently explosive in nature because significant concentrations of peroxide and hydroperoxide intermediates are generated. Appropriate precautions should be adopted. The reaction should not be scaled up. A solution of the appropriate substrate **1** (0.5 mmol) and CBr₄ (0.05 mol) in anhyd MeCN (10 mL) was stirred in a roundbottom flask fitted with an O₂ balloon, and irradiated externally with a 60 W 400 nm LED at rt. When the reaction was complete (TLC), the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel). **Benzoic Acid (2a)**

White solid; yield: 58.6 mg (96%); mp: 120–121 °C; R_f = 0.73 (50% EtOAc–PE). ¹H NMR (500 MHz, CDCl₃): δ = 8.34–8.02 (m, 2 H), 7.71–7.54 (m, 1 H), 7.48 (t, J = 7.9 Hz, 2 H).

- (8) King, J. W.; Quinney, P. R. J. Chromatogr. **1970**, 49, 161.
- (9) (a) Tripathi, S.; Singh, S. N.; Yadav, L. D. S. RSC Adv. 2016, 6, 14547. (b) Sandhiya, L.; Zipse, H. Chem. Eur. J. 2015, 21, 14060.
- (10) Sankar, M.; Nowicka, E.; Carter, E.; Murphy, D. M.; Knight, D. W. Bethell D.; Hutchings, G. J. *Nat. Commun.* **2014**, 5, doi: 10.1038/ncomms 4332.