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Rajendra D. Patil [a], Sukalyan Bhadra [b], Subbarayappa Adimurthy [a] & Brindaban C. Ranu [b]

[a] Central Salt and Marine Chemicals Research Institute, Council of Scientific and Industrial Research, G. B. Marg, Bhavnagar, Gujarat, India

[b] Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata, India

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GREEN OXIDATION OF METHYLARENES TO BENZOIC ACIDS WITH BROMIDE/BROMATE IN WATER

Rajendra D. Patil,[1] Sukalyan Bhadra,[2]
Subbarayappa Adimurthy,[1] and Brindaban C. Ranu[2]
[1]*Central Salt and Marine Chemicals Research Institute, Council of Scientific and Industrial Research, G. B. Marg, Bhavnagar, Gujarat, India*
[2]*Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata, India*

An efficient and convenient procedure has been developed for the oxidation of methylarenes to the corresponding benzoic acids using a bromide/bromate-based reagent system in water. Regeneration and reusability of the bromide/bromate reagent is demonstrated.

Keywords: Benzoic acids; bromide/bromate; methylarenes; oxidation

INTRODUCTION

The oxidation of methyl aromatics into the corresponding benzoic acids is an important transformation in organic synthesis as these carbonyl derivatives constitute versatile building blocks in pharmaceutical and polymer industries.[1] A variety of oxidizing agents such as $KMnO_4$, CrO_3, $Na_2Cr_2O_7$, TiO_2, $NaIO_4$, and HNO_3 are available to effect this key reaction.[2–6] However, these metallic reagents are often required in stoichiometric amounts, and these procedures are associated with environmental pollution because of the large amounts of hazardous metallic wastes. Moreover, purification of the reaction products is often very tedious because of the difficulty in separation of the metal residues from the product. Despite the industrial importance of this process and ever-growing environmental concerns, efficient catalytic systems have been rarely described.[7] Recently, WO_3/70% *tert*-butyl hydroperoxide (TBHP)/aqueous NaOH has been reported.[8] Although several methods are known for the synthesis of aromatic carboxylic acids, preparation under mild conditions without use of heavy-metal catalysts and generation of waste is an ultimate goal in view of technical, economical, and industrial aspects. As a part of our continuing activities to develop green procedures that avoid hazardous reagents,[9] we report herein a novel, heavy-metal-free, and recyclable reagent system for the oxidation of methylarenes to

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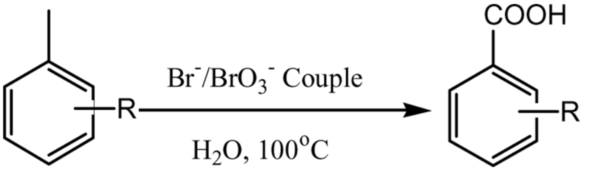
Address correspondence to Subbarayappa Adimurthy, Central Salt and Marine Chemicals Research Institute, Council of Scientific and Industrial Research, G. B. Marg, Bhavnagar 364 002, Gujarat, India. E-mail: sadimurthy@yahoo.com



Scheme 1. Oxidation of methyl arenes to benzoic acids.

their corresponding benzoic acids using a bromide/bromate reagent under mild conditions in an open atmosphere with water as solvent (Scheme 1).

RESULTS AND DISCUSSION

To gain more insight into this process, the oxidation of methylarenes with bromide/bromate under an aqueous acidic medium was investigated. In our earlier studies, we showed that the reactions of bromide/bromate and acid in a 2:1:3 molar ratio [Eq. (1)] generates the reactive species BrOH.[9] We think that this species is also responsible for the oxidation of methylarenes.

$$2Br^- + BrO_3^- + 3\ H^+ \rightarrow 3BrOH \tag{1}$$

A study for the oxidation of toluene by this reagent in different organic solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$, CCl_4, and CH_3OH demonstrated that the best result with regard to the formation of carboxylic acid was achieved using water as solvent. To optimize the reaction parameters, such as the amount of reagent system and reaction temperature, the reaction of toluene was investigated under various conditions as illustrated in Table 1. The best yield was obtained using 3 equivalents of bromide/bromate/acid in a 2:1:3 molar ratio (Table 1, entry 3).

The present transformation, **1** to **2**, proceeds through the intermediates of benzyl alcohol **4** and aldehyde **3** [Eqs. (2)–(4)]. Thus, this transformation needs 3 equivalents of the reagent [Eq. (5)].

$$ArCH_3 + BrOH \rightarrow ArCH_2OH + HBr \tag{2}$$

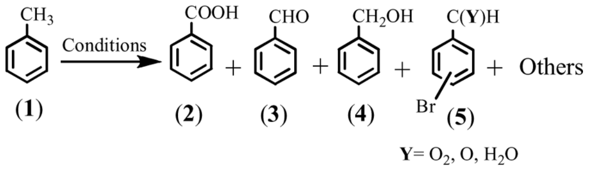
$$ArCH_2OH + BrOH \rightarrow ArCHO + HBr + H_2O \tag{3}$$

$$ArCHO + BrOH \rightarrow ArCO_2H + HBr \tag{4}$$

$$ArCH_3 + 3BrOH \rightarrow ArCO_2H + 3HBr + H_2O \tag{5}$$

It clearly indicates that the intermediates **3** and **4** could be avoided completely by using 3 equivalents of the reagent, and the desired product **2** was obtained in 72% isolated yield (Table 1, entry 3). When the reaction was conducted at room temperature, it took a prolonged period of time to consume the total reagent and undesired products were formed (Table 1, entry 4). This indicates that the selective activation of aromatic alkyl C-H group at room temperature will be difficult without any metal catalyst.[4,10] It is further observed that in the absence of visible light, nuclear

Table 1. Oxidation of toluene (**1**) with $Br^-/BrO_3^-/H^+$ reagent under different conditions



Run	Reagent (eqv.)	Conv (%)[a]	**2**	**3**	**4**	**5**	Others
1	1.0	100	22.6	10.7	25.4	10.2	Rest
2	2.0	100	41.1	7.3	22.4	9.6	Rest
3	**3.0**	100	**90 (72)[b]**	—	—	**4.6**	**Rest**
4[c]	3.0	100	9.0	4.4	—	26.4	59.4[d]
5[e]	3.0	100	32.6	—	—	58.6	Rest

Notes. Conditions: 10.86 mmol of **1**, $Br^-/BrO_3^-/H^+$ are in a 2:1:3 molar ratio, water, 100 °C, 8.00 h, in visible light. Product distribution is based on GC area percentages.

[a] GC-MS.

[b] Isolated yield.

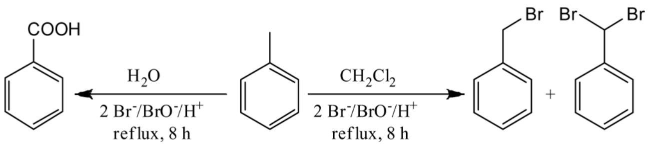
[c] Reaction carried out at rt for 16 h.

[d] Constituted with multinuclear brominated and oxidized products not mentioned in the table.

[e] Without visible light.

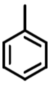
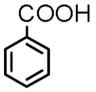
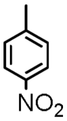
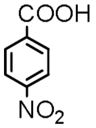
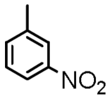
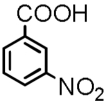
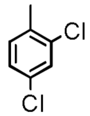
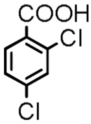
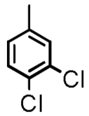
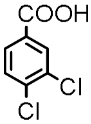
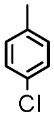
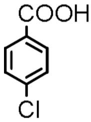
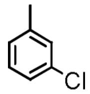
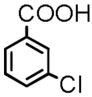
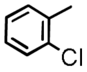
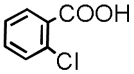
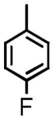
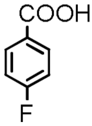
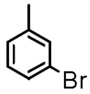
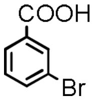
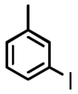
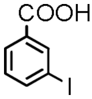
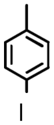
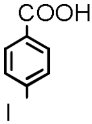
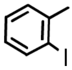
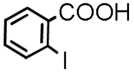
brominated products were formed (Table 1, entry 5). Presumably, the presence of visible light is necessary to initiate the reaction if it proceeds via a free-radical mechanism.[11] To check whether the present transformation proceeds via the benzylic bromide mechanism,[6e] we performed the reaction of toluene under the same conditions in dichloromethane and water. In the former case, benzylic brominated products **6** and **7** were formed, and in the latter case, the desired product benzoic acid **2** (Scheme 2) was produced. Thus, the transformation of toluene to benzoic acid is facilitated in water rather than in organic solvents. Based on all these observations, the oxidations were carried out in water at 100 °C using 3 equivalents of reagent system. The isolation of the product is very simple. The completion of the reaction is indicated by the disappearance of the color of the reactive species $BrOH/Br_2$. The reaction mixture was allowed to cool to room temperature, and the solid was filtered. The solid was washed with cold water and dried to get the product.

Several substituted methylarenes were subjected to oxidation by this procedure to provide the corresponding benzoic acids in good yields. The results are summarized in Table 2. The position of substitution (*o, m, p*) does not affect the oxidation process. The hindered *o*-substituted toluenes (Table 2, entries 8 and 13) were also



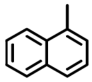
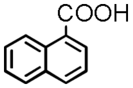
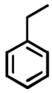
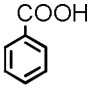
Scheme 2. Effect of H_2O and CH_2Cl_2 on oxidation of toluene.

Table 2. Oxidation of alkylarenes to the corresponding benzoic acids

Entry	Substrate	Time (h)	Product	Yield (%)[a]	Mp (Lit. mp) (°C)	Ref.
1		8		72	122 (121–125)	12
2		5		84	236 (237–240)	12
3		9		69	137 (139–141)	12
4		7		82	167 (163–165)	13
5		8		83	212 (208–209)	14
6		5		75	238 (238–241)	12
7		6		70	155 (153–157)	12
8		6		73	142 (138–140)	12
9		10		73	180 (182–184)	12
10		7		70	160 (155–158)	12
11		8		66	189 (185–187)	12
12		9		67	268 (270–273)	12
13		10		63	164 (160–162)	12

(*Continued*)

Table 2. Continued

Entry	Substrate	Time (h)	Product	Yield (%)[a]	Mp (Lit. mp) (°C)	Ref.
14		9		71	155 (157–160)	12
15		10		64	122 (121–125)	12

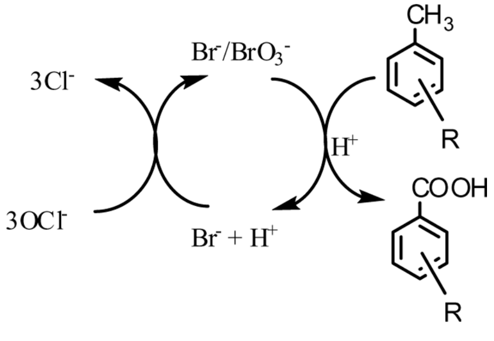
[a] Isolated yields of pure products (^{1}H and ^{13}C NMR).

oxidized without any difficulty. In general, the deactivated methylarenes were more facile in this oxidation process. The highly deactivated toluenes such as nitrotoluenes were not always easy to oxidize.[6a] The unactivated arenes such as α-methyl naphthalene (Table 2, entry 14) and ethyl benzene (Table 2, entry 15) also produced the corresponding carboxylic acids. However, oxidations of highly activating methylarenes were not encouraged, being associated with considerable amounts of ring brominated products.

Because bromide is not consumed as such in the oxidation process, both the bromide/bromate ions ended up in the aqueous effluent as total bromide ions, and we reoxidized a part of the bromide ion with NaOCl to bromate to regenerate the reagent to its original form [Eq. (6)] under ambient conditions (Scheme 3). Sodium chloride produced in the course of regeneration caused no problem in the oxidation reactions. The regenerated reagent was successively used for oxidation of methylarenes under similar conditions. For a representative example, 4-nitrotoluene was subjected to oxidation by this regenerated reagent system with three consecutive cycles, and the results (Table 3) are same as with the fresh reagent.

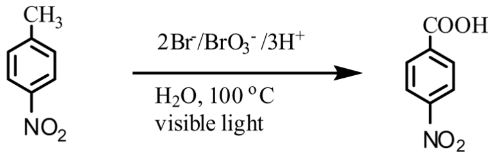
$$3Br^- + 3\ OCl^- \rightarrow 2Br^- + BrO_3^- + 3Cl^- \qquad (6)$$

In conclusion, we have developed a very simple and efficient procedure for the oxidation of methylarenes to the corresponding benzoic acids using an inexpensive



Scheme 3. Regeneration of bromide/bromate.

Table 3. Oxidation of *p*-nitrotoluene with regenerated reagent



Cycle	Time (h)	Yield (%)[a]
1	5.0	84
2	7.0	76
3	7.0	72

[a] Isolated yield.

and easily available bromide/bromate reagent system. The most significant and green feature of this methodology is the simple operation in water and use of no hazardous organic solvent or toxic reagent in the entire process. The recyclability of the reagent also adds to its green merit. Thus, this cost-effective and environmentally friendly procedure is a practical alternative to the existing ones and will find useful applications in academia as well as industry.

EXPERIMENTAL

General Experimental Procedure for the Oxidation of Methylarenes to Benzoic Acids: Representative Procedure for 4-Nitrobenzoic Acid (Table 2, Entry 2)

An aqueous solution of NaBr (3.00 g, 29.1 mmol) and H_2SO_4 (2.14 g, 21.8 mmol) was added at 100 °C (oil bath) to a stirred solution of 4-nitrotoluene (2.0 g, 14.5 mmol), water (20 ml), and $NaBrO_3$ (2.20 g, 14.5 mmol) during a period of 3 h in the presence of visible light. Stirring was continued for 2 h until the brown color disappeared at the same temperature. The reaction mixture was allowed to attain room temperature (25 °C). The solid separated was filtered off, washed with water, and dried to afford 4-nitrobenzoic acid (2.03 g, 84%). Recrystallization from hot water provided the analytically pure sample. The spectroscopic data [infrared (IR), ^1H NMR, and ^{13}C NMR)] are in good agreement with the reported values.[6e] The aqueous part left after workup of the first cycle was neutralized and thereafter treated with NaOCl solution (81.5 ml of 4% available chlorine) to oxidize 1/3 of total Br^- into BrO_3^- and to regenerate the original 2:1 Br^-/BrO_3^- couple. Fresh 4-nitrotoluene (2.0 g, 14.5 mmol) was added to it, followed by H_2SO_4 (2.14 g, 21.8 mmol) at 100 °C (oil bath) during a period of 3 h, and stirring was continued for 4 h. After workup (as mentioned previously), pure 4-nitrobenzoic acid was obtained (1.84 g, 76%). A similar procedure was followed for the third cycle. All of the products are known compounds and were easily identified by comparison of their spectroscopic data with the reported values.[12]

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