

H₂O₂–HBr: A metal-free and organic solvent-free reagent system for the synthesis of arylaldehydes from methylarenes

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Abstract. A novel, practical and environmentally benign approach has been developed for the oxidation of methylarenes using H₂O₂–HBr system in water. Arylaldehydes containing electron-withdrawing groups are isolated in good to high yields. Methylarenes containing electron-donating groups, in contrast, are transformed into bromo-substituted arylaldehyde undergoing a tandem oxidation–bromination process.

Keywords. (H₂O₂–HBr) system; water; environmentally benign procedure; arylaldehydes; methylarenes.

1. Introduction

Arylaldehydes are important industrial materials for the manufacture of odorants, flavours, food and beverage. They serve also as principal intermediates in the production of dyes, optical brighteners, agricultural chemicals and pharmaceuticals.¹ Their direct synthesis from methylarenes is normally accomplished by using transition metal oxidants such as chromium,² or manganese³ compounds. In these cases, the initial oxidation products are often more susceptible to oxidation than the starting material. Once a methyl group is attacked, it is likely to be oxidized to the carboxylic acid.⁴ While such reactions readily give benzoic acids in high yields, they are rather difficult to stop at the aldehyde stage.

Numerous oxidative reagents and processes have been implemented to synthesize benzaldehydes from methylarenes.^{5–28} Nevertheless, from the synthesis standpoint, these procedures generally require multi-step preparation conditions (causing high labour time), special apparatus in some cases, strong oxidants, and operational and practical problems.

Hydrogen peroxide (H₂O₂) is a ‘green’, waste-avoiding oxidant.²⁹ It can oxidize organic compounds with an atom efficiency of 47% and theoretically generates only water as co-product. Notably, H₂O₂ is much easier to handle, especially for batch reactions.

Hence, H₂O₂ is particularly useful for the synthesis of fine chemicals and has found comprehensive application in several oxidation systems.³⁰ Recently, Neumann and co-workers have reported the use of a combination of hydrogen peroxide and hydrohalic acid as a green halogenating agent.³¹ On the other hand, water is one of the greenest solvents one can imagine in terms of cost, availability, safety and environmental impact.³²

The development of waste-free, non-polluting benign systems and more sustainable strategies is one of the main themes of contemporary organic synthesis.³³ So far, our investigations on the oxidation of methylarenes to arylaldehydes consisted in using Br₂/DMSO as a mild catalytic system in a relatively short period of time.³⁴ As part of our program directed towards the development of efficient and practical procedures for the one-pot synthesis of aromatic compounds,^{34–35} we herein wish to report a ‘green’, metal-free and organic solvent-free (H₂O₂–HBr) system for the oxidation of toluene family of derivatives using water as medium.

2. Experimental

All the methylarenes, HBr and H₂O₂ were available commercially. ¹H NMR (80 or 500 MHz) spectra were recorded on a Bruker 80 or 500 MHz spectrometer in CDCl₃ using TMS as internal standard. A GC–MS method for the analysis of mixtures and

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Table 1. Optimization of the reaction time for preparing 4-Cl-Ph-CHO.

Entry	Time (h)	Temperature (°C)	4-Cl-Ph-CHO Yield (%) ^{a,b}	4-Cl-Ph-CH ₂ Br Yield (%) ^{a,b}	4-Cl-Ph-COOH Yield (%) ^{a,b}
1	3.5	85	55	45	–
2	4.5	85	65	35	–
3	5.5	85	87	13	–
4	7.5	85	68	12	20
5	8.5	85	61	10	29
6	11	85	54	4	42
7	14	85	40	–	60

^aGC Yield. ^b4-Cl-Ph-CH₃ : H₂O₂ : HBr (mol ratio) = 1 : 4 : 1.5

Table 2. Optimization of the reaction temperature for preparing 4-Cl-Ph-CHO.

Entry	Time (h)	Temperature (°C)	4-Cl-Ph-CHO Yield (%) ^{a,b}	4-Cl-Ph-CH ₂ Br Yield (%) ^{a,b}	4-Cl-Ph-COOH Yield (%) ^{a,b}
1	5.5	50	17	47	–
2	5.5	70	20	44	–
3	5.5	85	87	13	–
4	5.5	100	86	14	–

^aGC Yield. ^b4-Cl-Ph-CH₃ : H₂O₂ : HBr (mol ratio) = 1 : 4 : 1.5

pure products was applied; A Fisons instruments gas chromatograph 8000 connected to a mass detector (Trio1000) with 70 eV was used. A 30 m × 0.25 mm column packed with WCOT fused silica CP-sil 5CB-MS was employed. Column temperature was programmed from 80 to 270°C at 10°C/min. Injection was performed at 280°C. The carrier gas was helium and the inlet pressure was 10 psi.

2.1 General procedure for the preparation of arylaldehydes

Toluene derivative (10 mmol) and HBr 48% (2.5 mL, 15 mmol) and 10 mL H₂O were placed in a 25 mL two-necked reaction flask. The obtained mixture was stirred for 20 min and heated up to 85°C (oil bath temperature: 120°C). H₂O₂ 30% (4.5 mL, 40 mmol) was added drop-wise. The heating was continued for 5.5 h. The resulting reaction mixture was cooled and washed with cold KOH 10 wt% solution in water (40 mL) and then extracted by diethyl ether (3 × 20 mL). The organic layer was separated and dried over anhydrous Na₂SO₄. After filtration, the crude reaction mixture was passed through a dry silica gel column (50 g, Art 109385) to obtain the pure products (eluent: light petroleum ether for extracting the starting material and benzylbromide derivative then dichloromethane for ex-

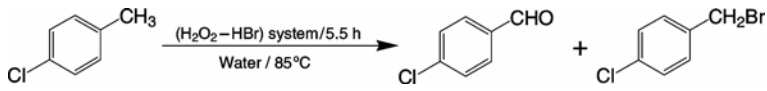
tracting the product). The identification of the isolated products was performed by ¹H NMR and GC-MS spectral analyses.

3. Results and discussion

We have studied the influence of the reaction time, the reaction temperature, the molar ratio of H₂O₂-HBr to toluene derivative and the minimum over-oxidation of the obtained arylaldehyde in order to optimize the reaction conditions for each substrate separately.

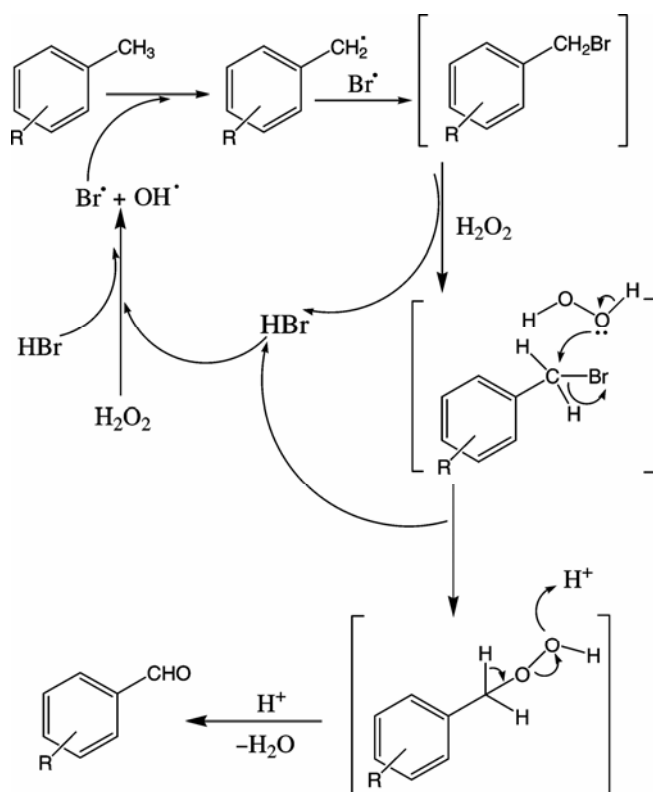
We first screened the reaction conditions for 4-chlorotoluene. The best reaction time and temperature for preparing 4-chlorobenzaldehyde is found to be 5.5 h at 85°C (tables 1 and 2), and the best molar ratio of (H₂O₂-HBr) to 4-chlorotoluene is (4 : 1.5 mol%) (table 3).

The degree of reaction progress and selectivity of methyl group oxidation depends on the reaction time. Although the overall yields increase by prolonging the reaction time, at the same time, aromatic carboxylic acid is produced as by-product (table 1). It is noteworthy that the best reaction time found for preparing each arylaldehyde varies according to substrate. As shown in table 3, during the course of the reaction, a few benzylbromide derivatives are produced as by-product. The reaction time is optimized

Table 3. Optimization of the molar ratio of H₂O₂-HBr to 4-Cl-Ph-CH₃ for preparing 4-Cl-Ph-CHO.


Entry	4-Cl-Ph-CH ₃ : H ₂ O ₂ : HBr (mol. ratio)	4-Cl-Ph-CHO Yield (%) ^a	4-Cl-Ph-CH ₂ Br Yield (%) ^a	4-Cl-Ph-COOH Yield (%) ^{a,b}
1	1 : 4 : 0.5	25	30	–
2	1 : 4 : 1	21	45	–
3	1 : 4 : 1.5	87	13	–
4	1 : 4 : 2	70	20	10
5	1 : 2 : 1.5	23	69	–
6	1 : 3 : 1.5	29	60	–
7	1 : 4 : 1.5	87	13	–
8	1 : 5 : 1.5	66	15	19
9	1 : 6 : 1.5	53	19	28

^a GC Yield. ^b Over-oxidation of the arylaldehyde to aromatic carboxylic acid

**Scheme 1.** Proposed mechanism for the formation of arylaldehydes containing electron-withdrawing groups.

in the way that no or negligible over-oxidation of arylaldehyde to the corresponding aromatic carboxylic acid occurs.

Our investigation revealed that the presence of H₂O₂-HBr in hot water leads easily to the generation of benzylbromides followed by their conversion to

the corresponding aldehydes. As shown in scheme 1, HBr reacts with H₂O₂ to produce free bromine. The generated bromine continues the bromination process and H₂O₂ oxidizes it to give the corresponding aldehydes resulting in moderate to good yields. In the heterogeneous reaction media, the over-oxidation of arylaldehyde may occur (table 3, Entry 4) because molecular bromine can oxidize aldehydes to their corresponding carboxylic acids; consequently, the optimized condition requires the partial consumption of the liberated HBr all along the reaction. Thus, its molar ratio cannot be predicted and is determined empirically according to the nature of substrate. In order to prove the proposed mechanism, we carried out the reaction of 4-chlorobenzylbromide under the same reaction conditions which led to the formation of 4-chlorobenzaldehyde.

The crude reaction mixture was subjected to a standard aqueous quench, and purified by flash column chromatography. The isolated products were quantitatively pure as judged by TLC, ¹H NMR and GC-MS spectral analyses.

These preliminary results led us to expand the generality of this novel green system to various substrates. The reaction conditions and yields of the products (i.e. aromatic aldehydes) are given in table 4. These results indicate that products in entries 1–9 were directly synthesized from methyl substituted aromatic compounds using (H₂O₂-HBr) system in hot water.

Moderate to good isolated yields are obtained for halotoluenes (table 4, Entries 1–5). Moreover, for some substrates having extremely limited solubility

Table 4. (H₂O₂-HBr) system for the oxidation of methylarenes in water.

Entry	Substrate 1	Product 2	Time (h)	1 : H ₂ O ₂ : HBr (mol. ratio)	Yield (%) ^{a,b}	
					2	3
1			5.5	1 : 4 : 1.5	82	13
2			5.5	1 : 4 : 1.5	57	12
3			5.5	1 : 4 : 1.5	67	33
4			5.5	1 : 4 : 1.5	73	22
5			5.5	1 : 4 : 1.5	42	31
			19 ^c	1 : 4.5 : 2 ^c	51	30
6			5.5	1 : 4 : 1.5	14	31
			24 ^c	1 : 5.5 : 3.5 ^c	47	14
7			5.5	1 : 4 : 1.5	5	15
			24 ^c	1 : 5.5 : 3.5 ^c	38	23
8			8 ^c	1 : 6 : 2.5 ^c	35 ^d	45 ^d
9			8 ^c	1 : 5 : 2.5 ^c	23 ^e	36 ^e

^aIsolated yield.

^bAll products were characterized by ¹H NMR and GC-MS spectral analyses.

^cIn order to improve the yield of 2, the reaction time and the molar ratio of (H₂O₂-HBr) system to each toluene derivative were optimized separately.

^dThe formation of the expected product did not occur. Instead of Ph-CHO, the reaction resulted in the formation of 4- and 2-Br-Ph-CHO (overall yield = 35%) and 4- and 2-Br-Ph-CH₂Br (overall yield = 45%).

^eThe formation of the expected product did not occur. Instead of 1-naphthaldehyde, the reaction resulted in the formation of 4-Br-1-naphthaldehyde (yield = 23%) and 4-Br-1-CH₂Br-naphthalene (yield = 36%).

in water, increased amounts of H₂O₂-HBr were used in order to improve the reaction yield (table 4, Entry 6, 7). In other words, when the phenyl ring is deactivated with an electron withdrawing group such as NO₂, the rate of the reaction may be increased by

addition of a more concentrated aqueous solution of HBr and H₂O₂.

Direct synthesis of 2-, 3-, 4-nitrobenzaldehydes from their corresponding methylarenes still remains a great challenge from an industrial vantage point.

According to literature, 4-nitrotoluene fails to give 4-nitrobenzaldehyde as product even in long (18 h)²⁸ and extremely long reaction times (138 h).²¹ As a remarkable advantage of this work, 4-nitrobenzaldehyde (table 4, Entry 6, yield = 47%) and 3-nitrobenzaldehyde (table 4, Entry 7, yield = 38%) are prepared and isolated in 24 h.

On the other hand, the oxidation protocol enables the tandem oxidation–bromination of phenyl nuclei containing a methyl group such as toluene and 1-methylnaphthalene. Toluene and 1-methylnaphthalene failed to give benzaldehyde and 1-naphthaldehyde. Instead, the reaction resulted in the formation of the corresponding 4-bromo- and 2-bromo-arylaldehyde. Despite the fact that H₂O₂ or HBr does not solely work on the oxidation of methylarenes under the reaction conditions, it seems difficult to selectively oxidize toluene and 1-methylnaphthalene into benzaldehyde and 1-naphthaldehyde without their concomitant bromination. As shown in table 4, 4-bromo- and 2-bromo-benzaldehyde are directly synthesized from toluene (Entry 8, overall yield = 35%), and 1-methylnaphthalene is directly transformed into 4-bromo-1-naphthaldehyde (Entry 9, yield = 23%) after 8 h at 85°C. Nevertheless, the major products formed from toluene are 4-bromo- and 2-bromo-benzylbromide (overall yield = 45%) and 2- and 4-bromo-toluene (overall yield = 20%). In addition, 1-methylnaphthalene gives 4-bromo-1-(bromomethyl)naphthalene (yield = 36%) and 2- and 4-bromo-1-methylnaphthalene (overall yield = 41%) as major products under the reaction conditions.

4. Conclusion

Methylarenes were successfully oxidized to arylaldehydes using an aqueous H₂O₂–HBr system without added catalyst in hot water. Water is used as a green solvent contributing to reduce the harmful effects of conventional organic solvents on the environment. The green halogenating agent also has a lower impact on the environment since bromine is generated *in situ* from H₂O₂ and HBr. Moreover, the use of H₂O₂ as an oxidant gives water as the only by-product. All these advantageous features make the procedure metal-free, organic waste-free and organic solvent-free and therefore a good alternative to the existing oxidation methods. Furthermore, the aqueous H₂O₂–HBr system could be used for tandem oxidation–bromination of toluene and 1-methylnaphthalene. This is while H₂O₂ or HBr does not solely work on the oxidation of these compounds.

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