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$NaIO_4$-Mediated Selective Oxidation of Alkylarenes and Benzylic Bromides/Alcohols to Carbonyl Derivatives Using Water as Solvent

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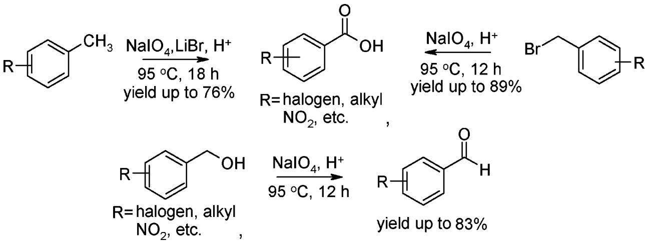
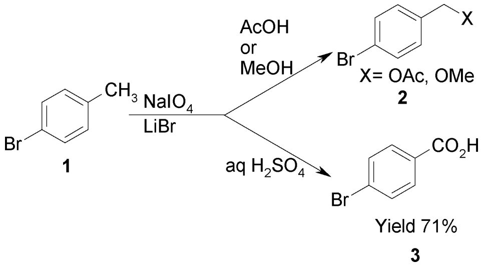


A new transition-metal-free, sodium metaperiodate ($NaIO_4$)-mediated direct oxidation of methylarenes and benzylic bromides to the corresponding aromatic carboxylic acids is described. Under the same reaction conditions, benzylic alcohols are selectively oxidized to afford the corresponding aldehydes in good yields without undergoing overoxidation. Unprecedentedly, oxidation of benzyl bromide, toluene, or benzyl alcohol with $NaIO_4$ underwent nuclear bromination followed by oxidation to give 4-bromobenzoic acid in 60−79% yields.

The oxidation of methylarenes to the corresponding carboxylic acids is of industrial importance because such carbonyl derivatives constitute versatile building blocks in pharmaceutical and polymer industries.[1] A variety of oxometal oxidants[2] such as $KMnO_4$, $Na_2Cr_2O_7$, or CrO_3 in stoichiometric amounts and RuO_4,[3] $Co(OAc)_2$,[4] and more recently Bi[5] salts in catalytic amounts have been employed in such oxidative processes. Among nonoxometal oxidants, HNO_3[6] is commonly used. In particular, RuO_4-catalyzed oxidations of methylarenes to oxygenated derivatives are achieved only for deactivated systems; for activated systems, ring halogenation is often the competitive reaction. Also, oxidations of alkylarenes with HNO_3 have often led to electrophilic ring nitrations. In continuation of our work[7] on $NaIO_4$-mediated reactions, we report herein a novel transition-metal-free method for the oxidation of methylarenes to the corresponding carboxylic acids using $NaIO_4$/LiBr/H^+ combinations.

SCHEME 1. Oxidation of an Alkylarene by $NaIO_4$/LiBr



Recently, we reported that direct oxidation[7b] of alkylarenes produced the corresponding benzylic acetates mediated by $NaIO_4$/LiBr. During our mechanistic investigations, we found that the reaction proceeded through benzylic bromide intermediates, which were subsequently oxidized by $NaIO_4$ to liberate bromine and benzyl cations; solvolysis of the latter gave benzylic acetates **2**. With this information, we believed that solvolysis from the benzyl cation with water, instead of AcOH, should give benzylic alcohol. Surprisingly, when 4-bromotoluene (**1**) was heated with $NaIO_4$ (1 equiv) and LiBr (1 equiv) in 2% aq H_2SO_4, the reaction took a different course to furnish 4-bromobenzoic acid (**3**) in 71% yield (Scheme 1).

Encouraged by this result, we subjected a variety of methylarenes having both electron-donating and -withdrawing groups to oxidation with $NaIO_4$ (1 equiv) and LiBr (1 equiv) in 2% aq H_2SO_4 (15 mL) at 95 °C and successfully obtained carboxylic acids **4** in good yields (Table 1). The use of excess $NaIO_4$ (1.2 equiv) did not improve the yield considerably. The yields were found to be higher in the case of methylarenes with electron-withdrawing groups (NO_2, Cl). When highly activating substituents (NH_2, OH) are present, electrophilic ring bromination took place preferentially. Attempts to improve the yields further by using a combination of solvents (*t*-BuOH/H_2O, THF/H_2O, CH_3CN/H_2O, etc.) were not fruitful. When LiBr was replaced by other halogen sources such as NaCl or KI, no reaction took place. Another interesting feature is that, although methyl groups were selectively oxidized to the corresponding carboxylic acids, benzylic methylene groups were oxidized to ketones; the overoxidation of benzylic methylenes to carboxylic acids with carbon C−C bond cleavage,[8] a common feature noticed in the case of transition-metal oxides, was not observed here (entries m and n, Table 1).

An unprecedented transformation occurred when toluene was subjected to oxidation under the same reaction conditions

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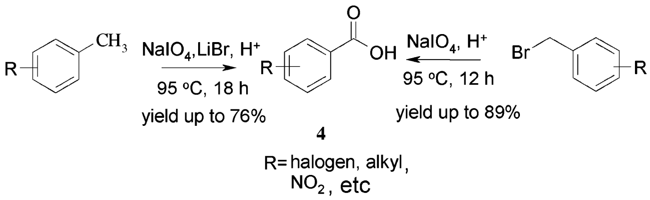
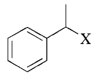
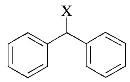
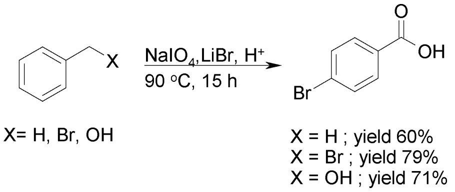
TABLE 1. NaIO$_4$/LiBr-Mediated Oxidation of Alkylarenes and Benzylic Bromides in Acidic Medium[a]



entry	R	yield of **4** (%)[b]	
		X = H	X = Br
a	4-Br	71, 30[c]	81
b	4-Cl	73	79
c	2-Cl	72	76
d	4-NO$_2$	76	89 (78)[d]
e	4-C (CH$_3$)$_3$	63	73
f	4-Me	70	78[e]
g	3,4-Cl	73	88
h	2,3-Cl	75	84
i	3-NO$_2$	69	81
j	4-Ph	70	83
k	4-F	g	86
l	4-CO$_2$Me	g	83[f]
m[i]	 X	72	87
n[i]	 X	76	85[h]

[a] See Experimental Section for procedure. [b] Isolated yield. [c] 50 mol % of NaIO$_4$ and LiBr were employed. [d] KIO$_3$ (1.2 equiv) was employed as the oxidant. [e] Terephthalic acid was obtained in 4% yield. [f] Methyl ester is hydrolyzed to form terephthalic acid. [g] Reactions were not done. [h] Yield was 83% with 50 mol % of NaIO$_4$. [i] Corresponding ketones were obtained.

SCHEME 2. Unprecedented Oxidation with Nuclear Bromination Mediated by NaIO$_4$



(NaIO$_4$/LiBr/H$^+$) giving 4-bromobenzoic acid in 60% isolated yield instead of the expected unsubstituted benzoic acid. We also found a similar observation when either benzyl bromide or benzyl alcohol was subjected to oxidation, although other methylarenes gave only the expected unsubstituted benzoic acids. Additional 2-methoxybenzyl bromide under the same reaction conditions gave 5-bromo-2-methoxybenzaldehyde in 18% yield. It may be explained that the intermediate benzyl alcohol, formed by solvolysis, probably underwent nuclear bromination at the para position with Br$_2$ before, itself, being oxidized to carboxylic acids (Scheme 2). To explain this observation, the following experiments have been carried out: (1) when 2-nitrotoluene was subjected to oxidation under this reaction condition, 2-nitrobenzoic acid (54%) was obtained, as a side-chain oxidized product; (2) *o*-xylene under the same experimental condition gave only 4-bromo-1 and 2-dimethylbenzene, a ring-brominated product; (3) a simple competitive experiment was carried out with a mixture of toluene and 2-chlorotoluene where we obtained only 4-bromo- and 2-chlorobenzoic acid, respectively. Notably, we observed that the electrophilic ring bromination was observed only in electron-rich methylarenes with an unblocked, sterically favorable para position. However, the presence of electron-withdrawing groups such as Br, Cl, NO$_2$, etc. probably deactivates the ring and also facilitates the oxidation of the intermediate species thereby shortening their lifetime thus resulting in no ring bromination. Ortho bromination was not observed possibly because of the steric nature of the bromonium ion.

To study its scope, we subjected several benzylic bromides to oxidation with NaIO$_4$/H$^+$ conditions. Indeed, such oxidations of benzylic bromides with NaIO$_4$ produced the corresponding carboxylic acids in high yields (71−89%). Although a variety of reagents are known[9] to oxidize organic halides to aldehydes, no *practical* method[10] exists, to the best of our knowledge, for the direct one-step conversion of benzylic bromides to the corresponding carboxylic acids. As can be seen from Table 1, several benzylic bromides with both electron-withdrawing and -donating groups underwent oxidation with NaIO$_4$/H$^+$ conditions to give the corresponding carboxylic acids in excellent yields. Secondary benzylic bromides were also oxidized to give the

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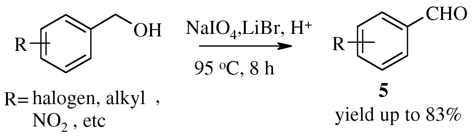
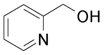
corresponding ketones in 87% yield (entries m and n, Table 1). The use of a substoichiometric amount of $NaIO_4$ (50 mol %) generally gave poor yields of carboxylic acids except in the case of bromodiphenylmethane (entry n), which gave a comparable yield of benzophenone (83%) due to the easy oxidizability of the C−Br bond. However, benzyl chloride was resistant to undergo oxidation under the reaction conditions, probably because of the higher bond strength of the C−Cl bond. KIO_3 was also found to oxidize benzylic bromide to give benzoic acid in high yields (entry d, Table 1). The prolonged oxidation of 4-methylbenzyl bromide led to successive oxidation of benzyl bromide as well as methyl to give 4% terephthalic acid (entry f, Table 1).

We also observed that when benzyl alcohol was subjected to oxidation with $NaIO_4$ (1 equiv) in the presence of acidic medium *without LiBr* benzaldehyde was exclusively obtained in 79% yield with no formation of benzoic acid. To study the generality of the reaction, a variety of primary benzylic alcohols were subjected to oxidation with $NaIO_4/H^+$ conditions, and the results are presented in Table 2. Among the various solvents screened, H_2O was found to give the best results. However, secondary benzylic alcohols as well as aliphatic alcohols were resistant to oxidation under the reaction conditions. The present protocol is mild and selective as compared to the reported literature procedures, which involve transition metals,[11] hypervalent iodine compounds,[12] and other halogen-related systems.[13]

We observed that the oxidation of methylarenes to carboxylic acids proceeds through intermediates such as benzyl bromide, benzyl alcohol, and benzaldehyde in that order, confirmed by GC-MS analysis, during the oxidation process of toluene with $NaIO_4/LiBr/H^+$ combinations. Following the concept of side-chain bromination of alkylarenes using metal halide in the presence of an oxidizing agent[14] (H_2O_2, TeO_2, etc.) as reported by others and us,[7b] we believe that $NaIO_4$ oxidizes LiBr in the presence of acid to liberate molecular bromine that brominates the side chain of alkylarenes to give the corresponding benzylic bromides (eqs 1−3). Similar to inorganic halides (LiBr), benzylic bromides are solvolyzed with water in the presence of $NaIO_4$ in acidic medium at elevated temperature (95 °C) to give benzylic alcohols (eq 4).

TABLE 2. Oxidation of Benzylic Alcohols to Benzaldehydes by $NaIO_4$ in Acidic Medium[a]



entry	R	yield of **5** (%)[b]
a	H	79
b	4-Br	83
c	4-Cl	80
d	4-F	77
e	4-Me	78
f	4-NO_2	67
g	3-NO2	65
h	2-Cl	71
i	4-OMe	21
j		44[c,d]

[a] Reaction conditions: alcohol (3 mmol), $NaIO_4$ (3 mmol), 2% aq H_2SO_4 in water (15 mL), 95 °C, 8 h. [b] Isolated yields after column chromatographic purification. [c] Yield by GC. [d] 2-Pyridinemethanol was employed for oxidation.

$$8Br^- + NaIO_4 + 8H^+ \rightarrow 4Br_2 + 4H_2O + I^- + Na^+ \quad (1)$$

$$4ArCH_3 + 4Br_2 \rightarrow 4ArCH_2Br + 4HBr \quad (2)$$

$$ArCH_3 + 2Br^- + (1/4)NaIO_4 + 2H^+ \rightarrow ArCH_2Br + (1/4)I^- + H_2O + HBr + (1/4)Na^+ \quad (3)$$

$$8ArCH_2Br + NaIO_4 + 8H^+ + 8H_2O \rightarrow 8ArCH_2OH + 4Br_2 + I^- + 4H_2O + Na^+ \quad (4)$$

The fact that the reagent $NaIO_4/H^+$ alone did not oxidize secondary alcohols, whereas the $NaIO_4/LiBr/H^+$ combination did, led to our belief that benzylic alcohols were directly

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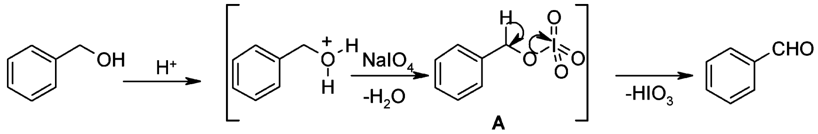
SCHEME 3. Oxidation of Alcohols to Aldehydes



oxidized to the corresponding carboxylic acids with Br_2 via a free radical pathway[15] (eqs 5−10).

$$Br_2 \rightarrow 2Br^{\bullet} \tag{5}$$

$$ArCH_2OH + Br^{\bullet} \rightarrow Ar\dot{C}HOH + HBr \tag{6}$$

$$Ar\dot{C}HOH + Br_2 \rightarrow ArCHO + Br^{\bullet} + HBr \tag{7}$$

$$ArCHO + Br^{\bullet} \rightarrow Ar\dot{C}O + HBr \tag{8}$$

$$Ar\dot{C}O + Br_2 \rightarrow ArCOBr + Br^{\bullet} \tag{9}$$

$$ArCOBr + H_2O \rightarrow ArCO_2H + HBr \tag{10}$$

The probable pathway for the oxidation of primary benzylic alcohol to aldehyde in the absence of LiBr is shown in Scheme 3. The species A formed by reaction of benzyl alcohol with $NaIO_4$ undergoes oxidation to give benzaldehyde. As the further oxidation of aldehydes to acids was not observed, we conclude that $NaIO_4$ was not capable of oxidizing aldehydes to carboxylic acids.

We have developed a mild procedure for the direct conversion of methylarenes and benzyl bromides to the corresponding carboxylic acids in high yields using $NaIO_4/LiBr/H_2SO_4$ conditions. In the absence of LiBr, $NaIO_4$ oxidizes benzylic alcohols to the corresponding benzaldehydes selectively under an acidic medium. An unprecedented oxidation at the benzylic position coupled with nuclear bromination had occurred when toluene, benzyl bromide, or benzyl alcohol was subjected to oxidation with $NaIO_4/LiBr/H^+$/95 °C conditions to give 4-bromobenzoic acid in up to 79% yield.

Experimental Section

Procedure for the Oxidation of Alkylarene. To a mixture of alkylarene (3 mmol), $NaIO_4$ (3 mmol), and LiBr (3.3 mmol) was added 2% aq H_2SO_4 (15 mL). The reaction mixture was heated at 95 °C (using an oil bath) for 18 h. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (40 mL × 3), and the combined organic phase was washed with saturated sodium thiosulfate solution and water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product; it was washed with cold *n*-hexane and recrystallized from suitable solvents to afford pure product.

Procedure for the Oxidation of Benzylic Halide. Benzylic halides were subjected to the reaction conditions as given above but without LiBr.

Procedure for the Oxidation of Primary Benzylic Alcohols. To a mixture of benzylic alcohols (3 mmol) and $NaIO_4$ (3 mmol) was added 2% aq H_2SO_4 (15 mL). The reaction mixture was heated at 95 °C (using an oil bath) for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (40 mL × 3), and the combined organic phase was washed with saturated sodium thiosulfate solution and water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product, which was purified by column chromatography packed with silica gel using *n*-hexane and ethyl acetate (9:1) as eluent to afford pure aldehydes.

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Supporting Information Available: Experimental procedures as well as spectral data for the selected compounds are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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