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$NaIO_4$-Mediated Selective Oxidative Halogenation of Alkenes and Aromatics Using Alkali Metal Halides

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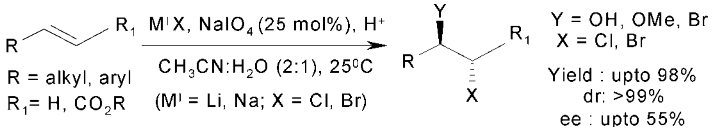
ABSTRACT



$NaIO_4$ oxidizes alkali metal halides efficiently in aqueous medium to halogenate alkenes and aromatics and produce the corresponding halo derivatives in excellent regio and stereoselectivity. The system also demonstrates the asymmetric version of bromo hydroxylation using *β*-cyclodextrin complexes, resulting in moderate ee.

The 1,2-functionalization of olefins by the selective addition of two different functional groups, such as water or alcohols and halogens (halohydroxylation or haloalkoxylation), in a highly regio- and enantioselective manner, remains important and challenging to organic chemists.[1] Such halo derivatives are widely used in the synthesis of pharmaceuticals, dyes, flame-retardants, additives and plasticizers, agrochemicals, and speciality chemicals.[2] Conventional halogenation methods[3] typically use elemental halogens, which are pollutants, and generate hazardous HX as byproducts. Recently, the oxidative halogenation of olefins by metal halides has emerged as an important alternative for the synthesis of such halo derivatives.[4] However, such oxidative halogenations involve the use of heavier metals in stoichiometric amounts, often resulting in poor yield and selectivity. Haloperoxidases, such as vanadium bromoperoxidase (V-BrPO),[5] are known to catalyze the 2e$^-$ oxidation of halides by H_2O_2, resulting in the concomitant halogenation of organic substrates, probably accounting for the biosynthesis of numerous halogenated marine natural products such as terpenes, indoles, phenols, etc. Several catalytic functional mimics of V-BrPO have already been reported.[6]

In this communication, we wish to report that sodium periodate[7] ($NaIO_4$) oxidatively halogenates a variety of olefins and aromatics with alkali metal halides as halogen

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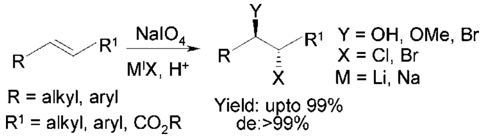
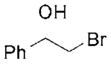
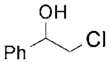
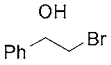
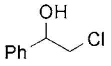
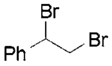
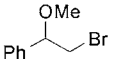
source under mild conditions, in a highly regio- and stereoselective fashion (Scheme 1).

Scheme 1. $NaIO_4$-Mediated Oxidative Halogenation of Alkenes with Metal Halides



When styrene was subjected to oxidative halogenation in the presence of 25 mol % of $NaIO_4$, the corresponding halogenated product was obtained in high yields (Table 1).

Table 1. $NaIO_4$-Mediated Oxidative Halogenation of Styrene Using Metal Halides[a]

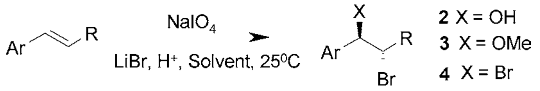
no	metal halide	sol.[b]	product	yield (%)[c]
1	LiBr	A		91[d]
2	LiCl	A		81[d]
3	NaBr	A		86[d]
4	NaCl	A		80[d]
5	LiBr	B		98
6	LiBr	C		57[d]

[a] Conditions: substrate (10 mmol), $NaIO_4$ (25 mol %), metal halides (12 mmol), 30% aqueous H_2SO_4 (0.5 mL, 10 mmol). [b] Solvent 15 mL: A, B, or C [A = CH_3CN/H_2O (2:1), B = AcOH, C = $MeOH/H_2O$ (3:1)]. [c] Isolated yield after column chromatography. [d] 5−10% of the corresponding dihalides are also formed.

In the absence of $NaIO_4$, no reaction took place; lowering the molar ratio of $NaIO_4$ also resulted in the reduced yield. It is found that the use of 25 mol % of $NaIO_4$ and the proper choice of solvent under acidic conditions (H_2SO_4 or HCl) are critical in achieving high conversion level of olefins with excellent product selectivity. Thus, although a mixture of CH_3CN and water at pH = 6.2 (initial pH = 2.17 rose to 6.2 within 10 min) was found to be the best solvent for halohydrin formation, the formation of dibromides was facilitated in the presence of acetic acid as solvent requiring no strong acidic conditions. However, when HIO_4 and PhI(OAc$_2$) were employed in catalytic amounts for the halobromination of styrene with LiBr, mixtures of bromo alcohols and dibromides were obtained in low yield (25%).

In all styrenic substrates, the incoming hydroxy or methoxy group entered at the benzylic position exclusively (Table 2).

Table 2. $NaIO_4$-Mediated Oxidative Bromination of Olefins[8] with LiBr[a]



		yield (%)[b]		
no.	substrates	2	3	4
1	styrene	91	57	95
2	4-Me styrene	95	78	96
3	4-OMe styrene	90	80	96
4	4-Br styrene	80	76	97
5	4-CH_2Cl styrene	85	78	96
6	α-Me styrene	85	76	95
7	cinnamyl alcohol	80[c]	75[c]	98
8	methyl cinnamate	90[c]	80[c]	98
9	4-Me ethyl cinnamate	95[c]	87[c]	98
10	chromene[d]	95[c]	83[c]	96
11	cyclooctene	85	65	99
12	1-octene	96[e]	84[e]	96
13	indene	98[e]	90[e]	98
14	allybromide	50[e]	46[e]	98
15	acrylamide	0	0	90
16	*N*,*N*-dimethyl acrylamide	0	0	93

[a] Conditions: alkene (10 mmol), LiBr (12 mmol), 30% aqueous H_2SO_4 (0.5 mL, 10 mmol), solvent 15 mL (A, B, or C, see footnote with Table 1). [b] Isolated yield after column chromatography. [c] Only *erythro* products were observed. [d] 2,2-Dimethylchromene. [e] Regioisomers were formed nearly in 1:1 ratio as determined from ^1H and ^{13}C NMR.

Remarkably, in the case of 1,2-disubstituted olefins, *anti*-isomers of the corresponding halo derivatives with dr > 99% (entries 7−10) were obtained exclusively. Electron-deficient substrates such as α,β-unsaturated amides underwent dibromination with 2 molar equiv of LiBr in acetic acid as solvent to afford 1,2-dibromoamides, important precursors to the synthesis of β-lactams.

There has been a growing interest in the past few years in metal halides as alternative to molecular halogens in

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(7) $NaIO_4$ purchased commercially from Aldrich, USA.

(8) **General Experimental Procedure for Bromohydrin or Methoxybromination of Olefins.** To a stirred mixture of olefin (10 mmol), LiBr (12 mmol), and 30% aqueous H_2SO_4 (0.5 mL, 10 mmol) in CH_3CN/H_2O (2:1, 15 mL) for bromohydrin or $MeOH/H_2O$ (3:1, 15 mL) for methoxybromination at 10−15 °C, $NaIO_4$ (25 mol %) was added portionwise. The reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with CH_2Cl_2 (25 mL × 3). The organic layers were washed with dilute solution of Na_2SO_3 and brine. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified by column chromatography packed with silica gel using petroleum ether and ethyl acetate (9:1) as eluent to afford the pure products. **General Experimental Procedure for Dibromination of Olefins.** To a stirred mixture of olefin (10 mmol) and LiBr (12 mmol) in acetic acid (15 mL), $NaIO_4$ (25 mol %) was added portion wise. The reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with CH_2Cl_2 (25 mL × 3). The organic layers were washed with dilute solution of $NaHCO_3$, Na_2SO_3, and brine. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified by column chromatography packed with silica gel using petroleum ether and ethyl acetate (9:1) as eluent to afford the pure products.

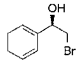
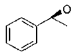
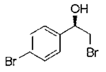
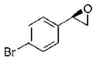
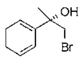
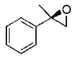
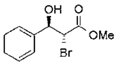
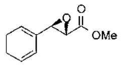
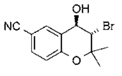
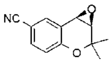
halogenation of aromatic compounds.[9] It is evident from Table 3 that NaCl can be effectively employed as chlorine source for chlorination of aromatics using 25 mol % of $NaIO_4$ under acidic conditions. Importantly, excellent regioselectivity in bromination has been observed with metal bromides rather than chlorides.

Table 3. $NaIO_4$-Mediated Oxidative Halogenation of Arenes with Metal Halides[a]

no.	arenes	halogen source	yield (%)[b]	selectivity[c] 4-x	2-x
1	benzene	NaCl	30	100[d]	
2	toulene	NaCl	39	58	42
3	anisole	NaCl	53	60	40
		NaBr	69	>99	
		LiBr	74	>99	
		Cl_2	83	100[c]	
4	2-nitroanisole	NaCl	59	100[e]	
5	acetophenone	NaCl	75	100[f]	
6	phenol	NaCl	20	75	25

[a] Conditions: $NaIO_4$ (25 mol %), arenes (10 mmol), metal halide (12 mmol), CH_3CN/H_2O (2:1, 15 mL), 30% aqueous H_2SO_4 (0.5 mL, 10 mmol), 80 °C, 3 h. [b] Isolated yield after column chromatography. [c] Determined from GC−MS; X = Cl or Br. [d] Monochlorobenzene. [e] 2-Nitro-4-chloroanisole. [f] α-Chloroacetophenone.

Table 4. $NaIO_4$-Mediated Asymmetric Oxidative Bromohydroxylation of β-CD Complexes of Styrenes[a] and Conversion to Their Epoxides[b]

	bromohydrin (%)		epoxide (%)		
no	product	yield[c]	product[d]	Yield[c]	ee[e]
1		55		90	25
2		60		90	22
3		58		78	41
4		50		85	55
5		64		89	20

[a] Conditions: β-CD complex of the corresponding styrenes (10 mmol), $NaIO_4$ (25 mol %), LiBr (12 mmol), 30% aqueous H_2SO_4 (0.5 mL, 10 mmol), CH_3CN/H_2O 2:1 (25 mL), 25 °C, 12 h. [b] 1,2-Bromo alcohol (2 mmol), K_2CO_3 (4 mmol), acetone (10 mL), 25 °C, 24 h. [c] Isolated yield after column chromatography. [d] Absolute configurations assigned on the basis of the sign of the optical rotation. [e] Determined from chiral HPLC analysis.

Table 4 shows the asymmetric version of bromohydroxylation of β-cyclodextrin (β-CD) complexes of styrenic substrates followed by their conversion into the corresponding chiral epoxides. Thus, when β-cyclodextrin complexes[10] of the styrenic substrates were subjected to oxidative bromination under the reaction conditions ($NaIO_4$, LiBr, H^+), the corresponding chiral bromohydrins were obtained in good yields. Subsequently, these bromohydrins were converted under basic conditions into their respective epoxides in high yields and moderate enantioselectivity.

The cyclic voltammetry (CV, Figure 1) of the reaction shows, for the forward oxidation scan at 500 mV/s, an irreversible oxidation peak at $Ep_a = 0.565$ V [$Br^- \rightarrow Br_2$ eq 1] and, for the reverse reduction scan, three irreversible reduction peaks at Ep_c = 0.720, 0.490, and 0.390 V corresponding to the reduction of IO_4^-, IO_3^-, and I_2, respectively [eqs 2−4].[11] Thus, CV reveals that X_2 (X = Br, Cl) generated in situ from metal halides by oxidation with $NaIO_4$ rapidly halogenates olefins or aromatic to produce the halo derivatives. The fact that such halogenations take place in *anti* fashion in the case of 1,2-disubstituted olefins probably proves the involvement of bromonium ions.

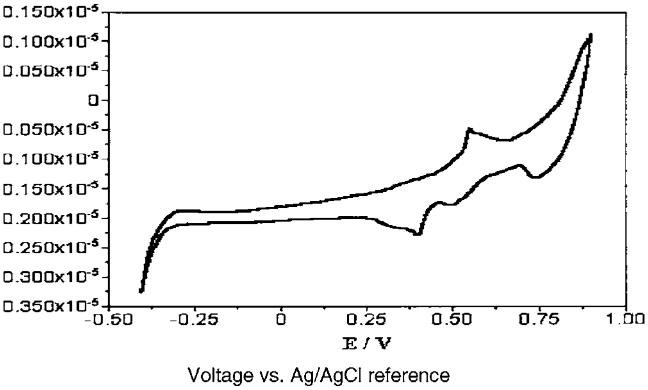


Figure 1. CV of reaction mixture containing $NaIO_4$ (25 mol %), styrene (10 mmol), LiBr (12 mmol), 30% aqueous H_2SO_4 (0.5 mL, 10 mmol), CH_3CN/H_2O 2:1 (20 mL) at 25 °C.

$$2Br^- \rightarrow Br_2 + 2e^- \qquad (1)$$

$$IO_4^- + 2H^+ + 2e^- \rightarrow IO_3^- + H_2O \qquad (2)$$

$$IO_3^- + 6H^+ + 6e^- \rightarrow I^- + 3H_2O \qquad (3)$$

$$I_2 + 2e^- \xrightarrow{\text{fast}} 2I^- \qquad (4)$$

In conclusion, we have shown that a stable, commercially available $NaIO_4$ oxidizes alkali metal halides efficiently in

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aqueous medium to halogenate alkenes and aromatics and produce the corresponding halo derivatives in excellent regio- and diastereoselective fashion. The present system also demonstrates the asymmetric version of bromo hydroxylation using a β-cyclodextrin complex of the respective styrenes, although with low enantiomeric excess. Efforts to improve the chiral version of bromohydroxylation are continuing in our laboratory.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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