

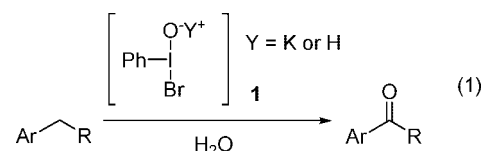
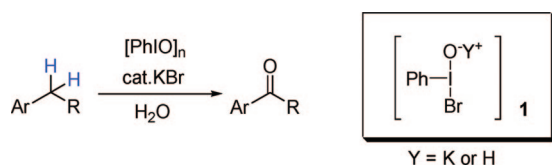
Clean and Efficient Benzylic C–H Oxidation in Water Using a Hypervalent Iodine Reagent: Activation of Polymeric Iodosobenzene with KBr in the Presence of Montmorillonite-K10

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We have found that unreactive and insoluble polymeric iodosobenzene $[\text{PhIO}]_n$ induced aqueous benzylic C–H oxidation to effectively give arylketones, in the presence of KBr and montmorillonite-K10 (M-K10) clay. Water-soluble and reactive species **1** having the unique I(III)–Br bond, *in situ* generated from $[\text{PhIO}]_n$ and KBr, was considered to be the key radical initiator during the reactions.

Development of aqueous-phase reactions is one of the active fields in organic synthesis due to a recent demand for realization of green chemical processes.¹ Benzylic oxidation is a fundamental transformation that is useful for the conversion of alkylarenes into the corresponding carbonyl compounds. Concerning this important transformation, numerous methods have been developed using a variety of oxidants and conditions in organic solvents,² whereas only a few examples performed in water have been described thus far. The photocatalytic TiO_2/O_2 system³ and the methods using a stoichiometric chromate salt⁴ or NaIO_4 ⁵ were examined, but there still exist serious drawbacks such as low yields, complicated procedures, and

competitive side reactions, c.f., ring bromination, for which their applications are strictly limited. Therefore, a survey of a facile and selective new method in water using an alternative suitable oxidant is of great importance.

Recently, hypervalent iodine reagents have received much attention by virtue of their low toxicity, ready availability, and reactivity similar to those of heavy metal oxidants.⁶ In organic solvents, it is known that few active cyclic iodine(III) compounds show radical reactivities to induce benzylic oxidation.⁷ A pentavalent iodine reagent, *o*-iodoxybenzoic acid (IBX), also oxidizes alkylarenes to arylketones in DMSO.⁸ These reported methods, albeit useful and versatile, are restricted in their use in organic solvents because of low solubilities and reactivities of the organoiodine compounds in water. Herein, we now report a promising new method for clean benzylic C–H oxidation in water by utilizing water-soluble and highly reactive oxidant **1**,⁹ *in situ* generated from iodosobenzene $[\text{PhIO}]_n$ and KBr (eq 1).

In our study for developing new environmentally benign oxidation reactions, we have been engaged in the practical utilization of hypervalent iodine reagents in water, especially with trivalent organoiodine compounds.^{9,10} In particular, we have previously found that the activation of the iodosobenzene polymer $[\text{PhIO}]_n$ by inorganic bromide salts in water is a powerful method for the effective and unprecedented hypervalent iodine(III)-induced oxidation of alcohols.⁹ Detailed studies on the mechanism revealed that the reaction involves the generation of a water-soluble species **1** having the unique I(III)–Br bond as a reactive intermediate. On the basis of a previous report and unique reactivity of hypervalent iodine(III)–halogen bonds for initiating radical reactions,¹¹ we assumed that the reaction of **1** in water is the development of a new aqueous benzylic oxidation via the radical pathway (Scheme 1).¹²

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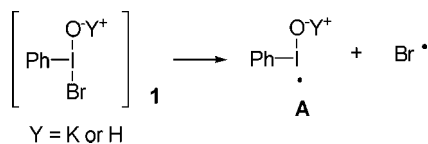
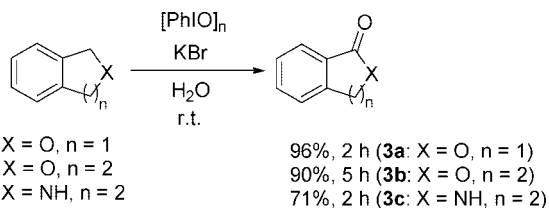
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SCHEME 1. Radical Formation from 1 via Homolytic Cleavage of the Labile I(III)–Br Bond in Water

SCHEME 2. Aqueous Benzylic Oxidation of Aromatic Compounds Having Activated Benzyl Groups


Accordingly, by the simple mixing of aromatic compounds **2a–c** having activated benzyl groups, $[\text{PhIO}]_n$ (3 equiv) and KBr (0.2 equiv for **2a**, 1 equiv for **2b** and **2c**) in water (0.2 M) at room temperature, the starting suspensions of the reaction mixtures became clear and the desired **3a–c** were successfully produced in good yields as a result of the selective oxidation at the benzyl positions adjacent to the heteroatoms (Scheme 2). Under these mild reaction conditions, aryl ring oxidation or further oxidation of the aryl ketone was not observed. As mentioned in the Introduction, organoiodine(III) compounds are generally not very reactive by nature in water, and hence neither the reactions with $[\text{PhIO}]_n$ nor $\text{PhI}(\text{OAc})_2$ in the absence of KBr resulted in the formation of the oxidation products **3a–c**. In the present aqueous system, the benzamide **3c** rather than the corresponding imine of **2c** was formed.¹³ The observed yields and reaction rates in water were compatible to those of the methods using organoiodine oxidants in organic solvent systems.^{7,8}

However, when we tried to apply the reaction using other compounds without any activated benzyl groups, that is, ethylbenzene derivatives, the arylketones were obtained in low yields (less than 20% conversion of ethylbenzenes). We then attempted to use several common Lewis acids in the hypervalent iodine(III)-induced reactions,⁶ such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$, TMSOTf, and TMSBr, for the purpose of activation of $[\text{PhIO}]_n$. In fact, the addition of these acids allowed the conversion of the substrates to be enhanced, but undesired ring bromination usually accompanied the benzylic oxidation. Under such situations, we further explored more suitable reaction conditions using 4-bromoethylbenzene **4a** as the model case (Table 1).

Although a good yield of the ketone **5a** was obtained at the elevated temperature of 80 °C with drastic improvement in the conversion of **4a**, a large amount of **4a** was still recovered from the $[\text{PhIO}]_n/\text{KBr}$ combination (entries 1 and 2). Therefore, alternative mild activators not causing any undesired side reactions were further investigated. Taking into account the nature of the anion parts of the acid additives, we specifically focused on utilizing solid Brønsted acid catalysts, such as heteropoly acids (HPA) and montmorillonitic clays, for the reactions.¹⁴ These solid acids are known to be environmentally

TABLE 1. Optimization of the Reaction Conditions^a

entry	bromide	additive	conversion (%) ^b	5a (%) ^b
1 ^c	KBr	none	17	6
2	—	—	73	39 ^d
3	—	$\text{H}_3[\text{PW}_{12}\text{O}_{40}]^e$	99	70 ^d
4	—	M-K10 ^e	100	72 ^d
5	—	M-KSF ^e	99	61
6	—	Nafion NR50 ^e	99	34
7	—	Amberlyst 15-H ^e	99	38
8	$\text{Bu}_4\text{N}^+\text{Br}^-$	M-K10 ^e	20	trace
9	$\text{Bu}_4\text{P}^+\text{Br}^-$	—	24	trace

^a Reactions were performed using 3 equiv of $[\text{PhIO}]_n$ and 1 equiv of the bromides and additives unless otherwise noted. ^b Determined by ¹H NMR. ^c Reaction was performed at r.t. ^d Isolated yield. ^e 100 mg/mL of H₂O.

friendly heterogeneous catalysts possessing soft counteranions, in which negative charges of the oxygen atoms are highly dispersed over the entire sheets of the molecules.¹⁵ During our investigations, $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$ and montmorillonite-K10 (M-K10) were found to be the most suitable as mild catalysts, and the benzylic oxidation proceeded with complete conversion of **4a** to give the corresponding ketone **5a** in better yields (entries 3 and 4). A slightly more acidic phyllosilicate mineral clay, M-KSF, gave an inferior result compared to M-K10 (entry 5). The nature of the counteranion in the additives seems to be important, as the addition of sulfonated acidic resins, ex. Nafion NR-50 and Amberlyst 15-H, led to a decrease in the yield of the benzylic oxidation product **5a** (entries 6 and 7). With regard to the bromide source, an interesting fact is revealed that the replacement of KBr with other organic bromides, $\text{Bu}_4\text{N}^+\text{Br}^-$ (entry 8) and $\text{Bu}_4\text{P}^+\text{Br}^-$ (entry 9), gave disappointing results;¹⁶ in these unsuccessful cases, the generation of molecular bromine (Br_2) was assumed by the rapid color change of the solutions from orange to dark brown. Under the optimized reaction conditions in entry 4,¹⁷ $[\text{PhIO}]_n$ was the best oxidant versus the other iodine(III) and iodine(V) compounds ($\text{PhI}(\text{OAc})_2$, $\text{PhI}(\text{O}-\text{COCF}_3)_2$, $\text{PhI}(\text{OH})\text{OTs}$, Dess-Martin Periodinane and PhIO_2).

In this context, the optimized reaction conditions expanded the scope of the substrates (Table 2). Another linear alkylbenzene **4b** gave the product **5b** in a good yield (entry 2). Cyclic compounds, such as indan **4c** and tetralin **4d**, afforded the corresponding arylketones **5c** and **5d** in high yields (entries 3 and 4). This reaction system was mild enough to be suitable for the conversion of **4e** bearing an acetoxy group (entry 5).

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(16) Formation of bisacetoxy bromate(I) was proposed by the reaction of $\text{PhI}(\text{OAc})_2$ and $\text{Bu}_4\text{N}^+\text{Br}^-$: (a) Kirschning, A.; Hashem, M. A.; Monenschein, H.; Rose, L.; Schoning, K.-U. *J. Org. Chem.* **1999**, *64*, 6522. (b) Kirschning, A.; Jesberger, M.; Monenschein, H. *Tetrahedron Lett.* **1999**, *40*, 8999. (c) Monenschein, H.; Sourkouni-Argirusi, G.; Schuboth, K. M.; O'Hare, T.; Kirschning, A. *Org. Lett.* **1999**, *1*, 2101.

(17) Due to the easy removal of the added M-K10 from the reaction mixtures by simple filtration through celite, we have selected M-K10 rather than the water-soluble heteropoly acid.

(12) Recently, we have reported a new lactone forming method using $\text{ArI}(\text{OAc})_2$ and powdered KBr in organic solvent via benzylic C–H activation: Dohi, T.; Takenaga, N.; Goto, A.; Maruyama, A.; Kita, Y. *Org. Lett.* **2007**, *9*, 3129.

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TABLE 2. [PhIO]_n/KBr/MK-10 System for Benzylic Oxidation of Alkylbenzene Derivatives 4^a

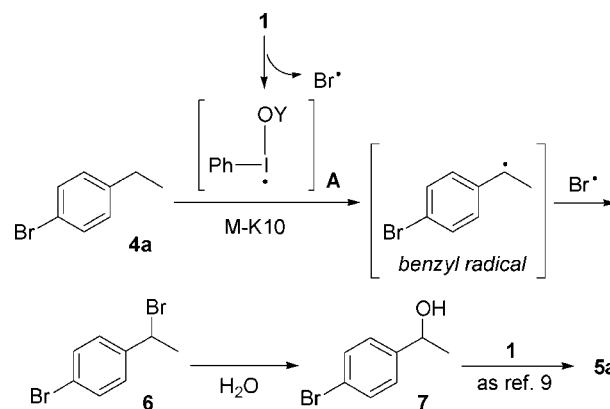
entry	substrate	product	yield, ^b time	entry	substrate	product	yield, ^b time
1			72%, 24 h	8			43%, 24 h
2			70%, 24 h	9 ^c			94%, 3 h
3			72%, 24 h	10			83%, 24 h
4			82%, 24 h	11 ^{c,d}			68%, 8 h
5			55%, 24 h	12			57%, 24 h
6			68%, 24 h	13			87%, 24 h
7			59%, 24 h	14			68%, 24 h

^a Reactions were performed using 3 equiv of [PhIO]_n, 1 equiv of KBr, and M-K10 (100 mg/mL) in H₂O (0.1M) at 80 °C unless otherwise noted. ^b Isolated yield after purification. ^c Reaction was performed at r.t. ^d In the absence of M-K10.

No hydrolysis of **4e** and the product **5e** was observed. The selective benzylic oxidation occurred in the substrate **4f** having other reactive C–H bonds of the cyclopropane (entry 6).¹⁸ In 4-ethyltoluene **4g**, the secondary benzyl group was chemoselectively oxidized (entry 7). The presence of an electron-withdrawing group at the aryl ring somewhat lowered the rate of the reaction and yield (entry 8). On the other hand, the diphenylmethane motif was less subject to the ring substitution effect (entries 9 and 10). Surprisingly, the benzylic oxidation was preferred to the sulfide oxidation as shown in the substrate **4k** (entry 11). Fluorene **4l**, diarylmethanes **4m** and **4n** including a heteroaromatic ring also provided the oxidation products in good yields (entries 12–14). These results clearly show the versatility of the present aqueous system over the previous ones performed in water using a metal catalyst or inorganic oxidants.^{3–5}

A plausible explanation for the reaction mechanism is exemplified by the transformation of 4-bromoethylbenzene **4a** (Scheme 3). First, as we previously confirmed,⁹ polymeric iodosobenzene [PhIO]_n was depolymerized in water by the aid of KBr that generated the reactive species **1**. The added M-K10

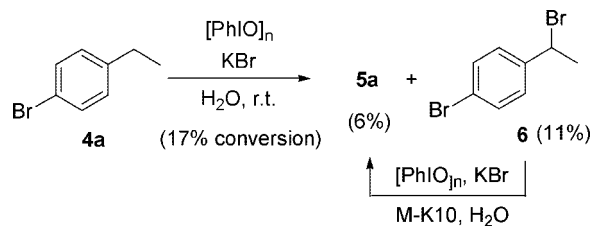
SCHEME 3. Proposed Reaction Mechanism



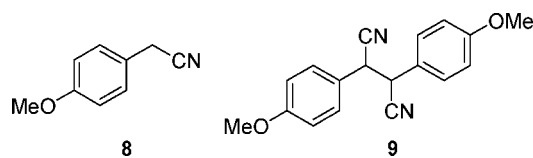
seems to assist in the efficient formation and activation of **1**. The reactive **1** could produce the iodanyl radical **A**¹⁹ by facile homolytic cleavage of the labile I(III)–Br bond, initiating the radical reaction with **4a**. Thus, selective abstraction of the benzylic hydrogen atom in **4a** by the iodine-centered radical **A** would produce the corresponding benzyl radical. Indeed, when the reaction was performed in organic solvents, radical coupling

(18) It is known that the cyclopropylbenzyl radicals are more stable than the corresponding ring-opened forms: (a) Bowry, V. W.; Luszytk, J.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1990**, 923. (b) Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **2000**, *122*, 2988.

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SCHEME 4. Detection of Benzyl Bromide **6**

homodimers were sometimes obtained, that is, the dimer **9** from the compound **8**. The resulting benzyl radical was probably trapped by the persistent bromo radical *in situ* giving rise to the stable benzyl bromide intermediate **6**. The conversion of the bromide intermediate **6** to the alcohol **7** and subsequent oxidation of **7** by the second molecule of the oxidant **1**⁹ would conclude the series of benzylic oxidation processes to afford the observed arylketone **5a**.



At ambient temperature, the reaction of **4a** could proceed quite slowly. We thus stopped the reaction at the 17% conversion of the substrate **4a** and checked the products by GC and ^1H NMR (Scheme 4). These measurements revealed that the formation of benzyl bromide **6** along with a small amount of the final arylketone product **5a**. Upon heating, both the reaction mixture and isolated **6** afforded the arylketone **5a** in good yields under the standard reaction conditions of $[\text{PhIO}]_n/\text{KBr}/\text{M-K10}$. Alcohol **7** was also detected as the sole product from the reaction mixture of the isolated **6** and M-K10 in water at 80 °C (confirmed by GC and ^1H NMR) in the absence of $[\text{PhIO}]_n$ and KBr. From these observations, we now propose the above-mentioned reaction mechanism, although further study is required to make the conclusion.

In summary, we have achieved an aqueous benzylic C–H oxidation using $[\text{PhIO}]_n/\text{KBr}$ in the presence of M-K10, as efficient, clean and environmentally benign reactions. A water-soluble and reactive iodine(III) species **1** containing the labile I(III)–Br bond acts as an effective radical initiator, so that this $[\text{PhIO}]_n/\text{KBr}$ system improves several drawbacks of the hypervalent iodine(III) reagents using in water, that is, low solubilities

and reactivities. Further studies on the application of this aqueous system are now in progress in our laboratory.

Experimental Section

Typical Procedure for Experiment in Scheme 2. To a suspension of **2a** (24.0 mg, 0.2 mmol) in H_2O (1 mL) was added $[\text{PhIO}]_n$ (132.0 mg, 0.6 mmol) and KBr (23.8 mg, 0.2 mmol) at room temperature. The mixture was then stirred for 2 h. The resulting reaction mixture was quenched by aqueous saturated NaHCO_3 , and extracted with CH_2Cl_2 . The organic phase was dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel gave 3*H*-isobenzofuran-1-one **3a** (25.8 mg, 0.19 mmol) in 96% yield: white crystals; mp 75–76 °C; ^1H NMR (300 MHz, CDCl_3) δ 5.34 (s, 2H), 7.50–7.57 (m, 2H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.94 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 69.6, 122.0, 125.5, 125.6, 128.9, 133.9, 146.4, 171.1; IR (KBr) cm^{-1} : 1765, 1468, 1288, 1219, 1053, 1005, 912, 743.

Gram Scale Preparation of 5m. To a suspension of the substrate **4m** (2.52 g, 15.0 mmol) in water (75 mL) was added iodosobenzene $[\text{PhIO}]_n$ (9.90 g, 45.0 mmol), and the resulting suspension was vigorously stirred for 5 min. The reaction flask was then placed in an ultrasonic bath for a minute with stirring. M-K10 (3.75 g) was added to the mixture, and warmed to 80 °C. KBr (1.80 g, 15.0 mmol) was added, and the mixture was vigorously stirred for 24 h. After cooling to room temperature, the reaction mixture was filtered through celite and the solvent was removed under vacuum. Purification of the residue by column chromatography on silica gel gave diphenylmethanone **5m** (2.38 g, 13.1 mmol) in 87% yield: colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 7.47 (t, $J = 7.5$ Hz, 4H), 7.58 (t, $J = 7.2$ Hz, 2H), 7.78–7.81 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 128.2, 130.0, 132.3, 137.4, 196.7; IR (KBr) cm^{-1} : 3059, 1659, 1599, 1578, 1447, 1275, 1177, 920, 810, 638.

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Supporting Information Available: Experimental details and spectroscopic data of the reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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