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Facile and Clean Oxidation of Alcohols in Water Using Hypervalent Iodine(III) Reagents**

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Tomohiro Maegawa, and Yasuyuki Kita*

Oxidation of alcohols to carbonyl compounds is a pivotal reaction in organic chemistry and numerous methods using a variety of reagents and conditions have been developed. Recent demand for eco-conscious chemical processes has encouraged the development of several clean and practical oxidation reactions,^[1] and awaits further development of high-yielding, clean, safe, and economical methods for the oxidation of alcohols. Hypervalent iodine reagents have been used extensively in organic syntheses as a result of their low toxicity, ready availability, and easy handling.^[2] For example,

the highly utilized pentavalent iodine reagents such as Dess–Martin periodinane (DMP)^[3] and *o*-iodoxybenzoic acid (IBX)^[4] oxidize alcohols mildly and efficiently to carbonyl compounds in high yields in organic solvents such as CH₂Cl₂, DMSO, and acetone. However, despite their utility, iodine(V) reagents are potentially explosive, cannot be stocked, and the generated iodine(III) species are usually not utilized (only iodine(V) species can be used for the oxidation of alcohols). Therefore, a facile and efficient use of the readily available and relatively stable iodine(III) reagents in place of iodine(V) reagents has been long desired. In contrast to oxidations with iodine(V)-based reagents, only a few examples of the oxidation of alcohols using iodine(III) reagents have been described.^[5] Existing methods are limited to organic solvents and usually involve activation of Ru or Yb catalysts^[5a,b] or of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)^[5c] by an iodine(III) co-oxidant. As an exception, readily oxidizable benzylic alcohol derivatives do not require catalysts.^[6, 13a] We have been studying the activation of hypervalent iodine reagents using several additives and solvents,^[7] and report herein an efficient oxidation of alcohols using iodosobenzene (PhI=O) with an inexpensive inorganic salt, KBr, in water under neutral conditions. This method was extended to an environmentally benign polymer-supported (diacetoxyiodo)benzene (PSDIB) oxidation procedure.

Various aqueous oxidation reactions have been developed since economic and environmental concerns encourage the use of water as a reaction medium.^[8] Very recently we have achieved a novel catalytic activation of PhI=O using a cationic surfactant, cetyltrimethylammonium bromide (CTAB), under neutral conditions. Its low solubility in water and in most organic solvents normally limits the reactivity of PhI=O, however, our micellar and reversed micellar systems have expanded the choice of solvents (from nonpolar solvents to water) for hypervalent iodine oxidation.^[9] In this study we first examined the oxidation of alcohols using PhI=O–CTAB in water, by the CTAB-catalyzed (20 mol %) oxidation of 2-octanol (**1e**) in water to give 2-octanone (**2e**) in 67 % yield. Thus, we re-examined the activation of PhI=O in this reaction with a variety of additives including alkali metal salts. The addition of bromide salts such as NaBr, KBr, and LiBr was found to activate PhI=O remarkably to give **2e** in good yields (94 % yield (KBr)), while salts other than bromide (NaX: X = F, Cl, I, HSO₄, BF₄, HCO₃, ClO₄, OAc, NO₃) did not catalyze the reaction effectively.^[10] We therefore chose KBr, the most economical alkali metal bromide, for further studies. The oxidation of activated alcohols such as benzylic or allylic alcohols proceeds quantitatively just by activating PhI=O with a small amount of water (10 equiv.), and without addition of KBr (Table 1, entries 1–3). With benzyl alcohol (**1a**), the reaction rate is enhanced remarkably by adding a catalytic amount of KBr. In contrast, a catalytic amount of KBr is indispensable for the oxidation of saturated primary and secondary alcohols. This PhI=O–KBr system is applicable to the oxidation of a variety of primary and secondary alcohols bearing functional groups such as ether, ester, sulfonamide, and azido groups (see Table 1). Oxidation of primary alcohol **1k** only yields carboxylic acid **2k** (52 % yield) and none of the corresponding aldehyde when using 1.1 equivalents of PhI=O.

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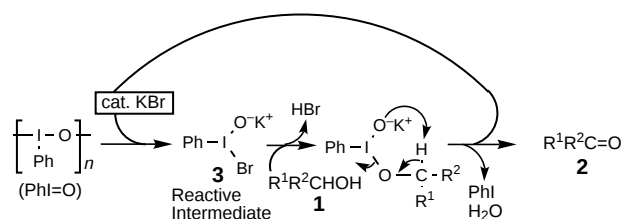
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Table 1. Oxidation of alcohols **1** with $\text{PhI}=\text{O}-\text{KBr}$ in H_2O .

Entry	Substrate	Product	KBr [equiv.]	Time [h]	Yield [%] ^[a]
1	$\text{Ph}-\text{CH}_2\text{OH}$ 1a	PhCO_2H 2a	none	30	quant. ^[b]
2	$\text{C}_6\text{H}_5\text{OH}$ 1b	$\text{C}_6\text{H}_5\text{O}$ 2b	none	6	78(94) ^[c, d]
3	$\text{C}_6\text{H}_4\text{OH}$ 1c	$\text{C}_6\text{H}_4\text{O}$ 2c	none	24	87
4	1c	2c	0.2	2	quant.
5	$\text{PhCH}(\text{OH})\text{Et}$ 1d	PhCOEt 2d	1.0	4	quant. ^[d]
6	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1e	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C(=O)CH}_3$ 2e	none	48	trace
7	1e	2e	0.2	24	94 ^[d]
8	1e	2e	1.0	8	98 ^[d]
9	$\text{PhCOOCH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1f	$\text{PhCOOCH}_2\text{CH}_2\text{C(=O)CH}_3$ 2f	1.0	4	quant.
10	$\text{C}_6\text{H}_{11}\text{OH}$ 1g	$\text{C}_6\text{H}_{11}\text{O}$ 2g	1.0	3	quant. ^[d]
11	$\text{TsNCH}_2\text{CH}_2\text{OH}$ 1h	$\text{TsNCH}_2\text{CH}_2\text{O}$ 2h	1.0	24	86
12	L-menthol 1i	L-menthone 2i	1.0	7	quant. ^[d]
13	3 β -cholestanol 1j	5 α -cholestan-3-one 2j	1.0	4	quant.
14	$\text{Ph}-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1k	$\text{Ph}-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ 2k	none	48	trace
15	1k	2k	0.2	2	92 ^[b]
16	$\text{BnOCH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1l	$\text{BnOCH}_2\text{CH}_2\text{CO}_2\text{H}$ 2l	0.2	2	76 ^[b]
17	$\text{EtO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1m	$\text{EtO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$ 2m	0.2	2	92 ^[b]
18	$\text{N}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ 1n	$\text{N}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ 2n	0.2	2	90 ^[b]

[a] Yields of isolated products unless otherwise noted. [b] 2.2 equiv. $\text{PhI}=\text{O}$ was used. [c] Yield in parenthesis is based on the consumed starting material. [d] Yields were determined by GC.

A plausible mechanism for the catalytic activation of $\text{PhI}=\text{O}$ with KBr is depicted in Scheme 1. Polymeric iodoso-benzene is initially depolymerized by the addition of KBr to form a highly reactive intermediate **3**, which reacts with alcohols **1** to yield the corresponding carboxylic acids or ketones with regeneration of KBr. Although another mechanism mediated by Br^+ may be possible, **3** is more likely to be the reactive species since only a trace amount of **2e** was obtained even with an excess of either aqueous H_2O_2 or aqueous NaOCl in the presence of KBr. Thus, the activation of $\text{PhI}=\text{O}$ with KBr involving **3** is very different from the mechanism involving transition metals or TEMPO, since in

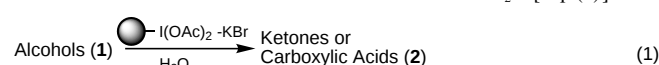


Scheme 1. Catalytic activation of $\text{PhI}=\text{O}$ with KBr.

the latter cases, the metal oxide or *N*-oxoammonium salt works as the reactive species.

Next, we modified this system to develop a practical and clean procedure for the oxidation of alcohols using a polymer-supported hypervalent iodine(III) reagent. Solid and polymer-supported reagents have applications in combinatorial chemistry, and the use of such operationally simple and environmentally benign reagents is becoming more and more important in the pharmaceutical and agrochemical industries. Several polymer-bound oxidants have been reported,^[11] and polymer-supported hypervalent iodine reagents should be a welcome addition as a result of their versatility, low toxicity, and high yields. Recently, Togo et al.^[12] and Ley et al.^[13] demonstrated that PSDIB [see Eq. (1)]^[14] shows similar reactivity to (diacetoxyiodo)benzene and utilized it in organic solvents as a replacement for previously reported iodine(III) reagents. A method for the oxidation of alcohols using DMP with a thiosulfate resin was recently reported by Parlow et al.,^[15] but, this required an excess amount of reagent. We re-examined the oxidation using PSDIB in water. The oxidation of saturated secondary alcohols using 1.1 equivalents of PSDIB and 0.2 equivalents of KBr proceeded in water at room temperature in a few hours to give the corresponding carbonyl compounds **2** in excellent yields, while the addition of 1.0 equivalents of NaHCO_3 was necessary for primary alcohol **1k**^[16] (Table 2). Furthermore, the iodinated resin could be regenerated and recycled successfully. We also unexpectedly found that water is a suitable solvent for PSDIB-induced oxidation, and that PSDIB is considerably

Table 2. Oxidation of alcohols **1** with PSDIB–KBr in H_2O [Eq. (1)].



Entry	Substrate	Product	KBr [equiv.]	Time [h]	Yield [%] ^[a]
1	1a	2a	0.2	24	quant. ^[c]
2	1d	2d	0.2	4	quant. ^[b]
3	1e	2e	0.2	7	quant. ^[b]
4	1i	2i	0.2	20	86 ^[b]
5	1k	2k	1.0	24	90 ^[c, d]

[a] Yields of isolated products unless otherwise noted. [b] Yields were determined by GC. [c] 2.5 equiv. PSDIB was used. [d] In the presence of

stable in water.^[17] Since both water and Br^- are indispensable for the reaction progression, this reaction might also be proceeding via a reactive intermediate similar to **3**, being formed by ligand exchange of diacetate.^[18]

The positive features of the present method are summarized as follows: 1) ease of operation; 2) facile recycling of the polymer-supported iodine(III) reagent; the recovered resin (polyiodostyrene) is easily reoxidized with peracetic acid (30% H_2O_2 and Ac_2O)^[14] and can be used repeatedly without loss of activity; 3) excellent yields; 4) environmental consciousness: no organic solvent is used in the reaction and only a small amount is needed in the workup.

In summary, we have achieved a clean and efficient oxidation of alcohols using $\text{PhI}=\text{O}$ or PSDIB with KBr in water. The present procedure will provide a facile and environmentally benign method for the catalytic activation

of a variety of sluggishly reactive and/or sparsely soluble hypervalent iodine reagents in water under neutral conditions. Further studies on the application of this system are now in progress.

Experimental Section

Method A (for primary alcohols): $\text{PhI}=\text{O}$ (0.44 mmol; Tokyo Chemical Industry Co., Ltd.) was added at room temperature to a stirred mixture of **1** (0.20 mmol) and KBr (0.04 mmol) in water (1.0 mL), and the mixture was stirred for 2 h. The resulting mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4 , evaporated in vacuo, and the residue was purified by column chromatography ($\text{EtOAc}/n\text{-hexane}$) to give pure **2**. Intermolecular esterification through nucleophilic attack on the initially formed aldehyde also proceeds under the conditions of Method B.

Method B (for secondary alcohols): Water (2.0 mmol) was added dropwise to a stirred mixture of **1** (0.2 mmol), $\text{PhI}=\text{O}$ (0.22 mmol), and KBr (0.2 mmol). The mixture was stirred or sonicated for several hours while checking the reaction progress by gas or thin-layer chromatography. After completion, $n\text{-hexane}$ was added to the mixture, and then filtered. Evaporation of the solvent under vacuum afforded a crude product that was further purified by column chromatography ($\text{Et}_2\text{O}/n\text{-hexane}$) to give pure **2**.

Method C (for the oxidation with PSDIB): PSDIB (22 mmol), used without any pretreatment, was added at room temperature to a stirred suspension of **1** (20 mmol) and KBr (14 mmol) in water (40 mL), and the mixture was then sonicated for several hours. The resulting mixture was filtered and the residue containing **2** was washed with water to remove KBr, then extracted with $n\text{-hexane}$ or MeOH, and the filtrate was evaporated to give **2**. The product was purified by column chromatography, when necessary.

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- [17] Even after stirring PSDIB in water for 4 d, the addition of **1e** and KBr to this suspension gave **2e** in 68% yield.
- [18] **2e** was obtained only in 8% yield, when the reaction was performed with PSDIB in CH_2Cl_2 (containing 4-Å molecular sieves) in the presence of 20 mol% NEt_4Br as a bromide ion source. However, addition of a catalytic amount of water to the above mentioned mixture enhanced the yield of **2e** to 51%.

Total Synthesis of (+)-Concanamycin F**

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Malcolm D. McLeod, and Thomas Trieselmann

The concanamycin group of macrolides, first isolated from a culture of *Streptomyces diastatochromogenes* Sp. S45 by Kinashi and co-workers and typified by concanamycin A (**1**, Figure 1)^[1a–d] and its aglycone, concanamycin F (**2**),^[1e,f] exhibit potent inhibition of vacuolar (H^+) ATPase activity.^[2] The

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