

A Simple and Highly Selective Biomimetic Oxidation of Alcohols with Hypervalent Iodine(III) Reagent Catalyzed by β -Cyclodextrin in Water

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Abstract A simple, mild and highly efficient biomimetic oxidation of alcohols to the corresponding aldehydes or ketones with hypervalent iodine(III) reagent catalyzed by β -cyclodextrin was reported. β -cyclodextrin serves as a biological catalyst to enhance the reaction remarkably. The oxidation proceeded in water to afford aldehydes or ketones in excellent yields and high selectivity without remarkable over-oxidation to carboxylic acids. Selective oxidation of primary alcohols in the presence of secondary alcohols was also achieved. A possible mechanism for the oxidation was proposed.

Keywords Alcohols · Cyclodextrin · Hypervalent iodine · Catalytic oxidation · Water

1 Introduction

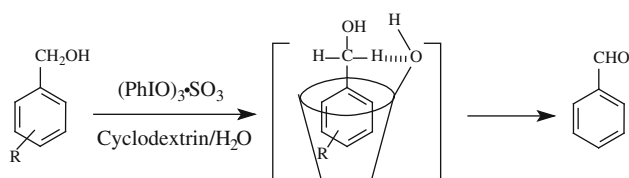
The selective oxidation of alcohols to the corresponding aldehydes or ketones is a fundamental transformation both in laboratory synthesis and industrial production [1, 2]. Numerous oxidizing reagents (for example, CrO_3 , KMnO_4 , MnO_2 , etc.) in stoichiometric amounts have been traditionally employed to accomplish this transformation with considerable drawbacks such as the use of expensive reagents, volatile organic solvents, and discharge of environmentally pernicious wastes [3]. Transition metal-catalyzed oxidations of alcohols using aqueous H_2O_2 or gaseous O_2 as oxidant have also been developed [4–7]. From economic and environmental perspectives, the

development of new catalytic oxidation system is particularly attractive.

β -Cyclodextrin (β -CD), which is cyclic oligosaccharide with hydrophobic cavity, can catalyze chemical reactions by supramolecular catalysis involving reversible formation of host–guest complexes by non-covalent bonding. The complexation depends on the size, shape and hydrophobicity of the guest molecule. Thus, mimicking of biochemical selectivity, which shows shape and substrate selectivity, with the reactions being carried out in water will be superior to chemical selectivity. Due to these attractive features in the biomimetic modelling of chemical reactions, β -cyclodextrin has drawn considerable attention as an efficient catalyst for various organic transformations [8–15].

On the other hand, hypervalent iodine(III) reagents have drawn considerable attention as mild and highly chemoselective oxidizing reagents for various organic transformations [16]. As a result of their nontoxic nature, affordability, and safety profile, hypervalent iodine(III) reagents are nowadays popular reagents for the formation of carbon–carbon bonds, carbon–heteroatom bonds, heteroatom–heteroatom bonds. Activation of carbon–hydrogen bonds, rearrangements and fragmentations can also be induced by these reagents [17]. Therefore, hypervalent iodine compounds offer high potential for the improvement of known reactions, not only from the environmental point of view, they are also potentially interesting reagents for the development of completely new synthetic transformations. Some reviews about the oxidation of alcohols using hypervalent iodine reagents have been published just in the last 10 years [18, 19]. However, typical reactions of common hypervalent iodine reagents are performed in non-recyclable organic solvents such as dichloromethane, dimethyl sulfoxide, and acetone, which

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Scheme 1 Oxidation of alcohols catalyzed by $(\text{PhIO})_3\cdot\text{SO}_3/\beta$ -cyclodextrin in water

have potentially damaging environmental properties. The development of aqueous-phase reactions using environmentally friendly reagents is one of the active fields in organic synthesis due to a recent demand for realization of green chemical processes [20, 21]. From economic and environmental perspectives, the development of reactions in water based on hypervalent iodine reagents have received great attention. Many highly efficient systems for application of hypervalent iodine reagents in water have been developed [22–28].

In continuation of our efforts to develop new applications of hypervalent iodine reagents [29–34], here, we would like to report a facile procedure for the oxidation of alcohols to the corresponding carbonyl compounds with $(\text{PhIO})_3\cdot\text{SO}_3$ catalyzed by β -cyclodextrin in water (Scheme 1).

2 Experimental

2.1 Instruments and Reagents

Gas chromatography (GC) analysis was performed on an Agilent GC-6820 chromatograph equipped with a $30\text{ m} \times 0.32\text{ mm} \times 0.5\text{ }\mu\text{m}$ HP-Innowax capillary column and a flame ionization detector. GC–MS spectra were recorded on Thermo Trace DSQ GC–MS spectrometer using TRB-5MS ($30\text{ m} \times 0.25\text{ mm} \times 0.25\text{ }\mu\text{m}$) column. $(\text{PhIO})_3\cdot\text{SO}_3$ was prepared from commercially available $\text{PhI}(\text{OAc})_2$ and $\text{NaHSO}_4\cdot\text{H}_2\text{O}$ by a procedure described in the literature [35, 36]. Other reagents (AR grade) were obtained from commercial resources and used without further purification. Products were all known compounds and were identified by comparing of their physical and spectra data with those reported in the literature.

2.2 Typical Procedure for Oxidation of Alcohols

2.2.1 Oxidation of Alcohols with $(\text{PhIO})_3\cdot\text{SO}_3$

β -Cyclodextrin (0.57 g, 0.5 mmol) was dissolved in H_2O (15 mL) at $60\text{ }^\circ\text{C}$ for several minutes, and then alcohol (1 mmol) was added slowly with stirring. To this was added $(\text{PhIO})_3\cdot\text{SO}_3$ (0.30 g, 0.4 mmol) portion-wise over a period of 10 min. The mixture was stirred at $60\text{ }^\circ\text{C}$ for

several hours while checking the reaction progress by gas or thin-layer chromatography. After completion, the mixture was extracted with ethyl acetate ($3 \times 10\text{ mL}$) and analyzed by GC–MS. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 10/1) to afford the analytically pure product. The aqueous phase was removed by decantation and lyophilized to obtain the β -CD.

2.2.2 Oxidation of Alcohols with $(\text{PhIO})_3\cdot\text{SO}_3$ Generated In Situ

β -Cyclodextrin (0.57 g, 0.5 mmol) was dissolved in H_2O (15 mL) at $60\text{ }^\circ\text{C}$ for several minutes, followed by addition of alcohol (1 mmol) with stirring. Then $\text{PhI}(\text{OAc})_2$ (0.35 g, 1.1 mmol) and $\text{NaHSO}_4\cdot\text{H}_2\text{O}$ (0.15 g, 1.1 mmol) were added and stirred at $60\text{ }^\circ\text{C}$ for several hours while checking the reaction progress by gas or thin-layer chromatography. After the completion of the reaction, the mixture obtained was treated as above to afford the corresponding pure product.

3 Results and Discussion

The initial experiments were carried out using 4-nitrobenzyl alcohol as the model substrate. First, a range of hypervalent iodine reagents such as $\text{PhI}(\text{OAc})_2$, $\text{PhI}(\text{OH})\text{OTs}$, PhIO_2 , PhICl_2 , $\text{PhI}(\text{OCOCF}_3)_2$, and PhIO were used as oxidant in the reaction, however, all of them were not satisfactory probably due to their poor solubility in water (Table 1, entries 1–6). Recently, Zhdankin and co-workers [35, 36] have reported a mild and efficient method for the preparation of oligomeric iodosylbenzene sulfate $(\text{PhIO})_3\cdot\text{SO}_3$. This sulfate can find practical application as a readily available, stable, and water-soluble hypervalent iodine reagent with a reactivity pattern similar to iodosylbenzene [37, 38]. It was found that in the case of $(\text{PhIO})_3\cdot\text{SO}_3$ as oxidant, desired product was obtained in 49% yield (Table 1, entry 7). Encouraged by this result, we evaluated the effects of three species of CDs on the reaction, in hopes of promoting the oxidation. Fortunately, β -CD serves as a good catalyst to enhance the reaction remarkably (Table 1, entry 9). In the same conditions, α -CD and γ -CD show no catalytic activity (Table 1, entries 8 and 10). It might be concluded that the oxidation with CDs as catalyst is highly shape-selective, owing to the different interior cavity sizes of these CDs. With regard to the dosage of β -CD, use of more β -CD accelerated the reaction rate (Table 1, entries 9, 11, and 12). It is well known that the presence of an appropriate catalyst (Lewis acid, bromide or iodide anions, transition metal complex)

Table 1 Optimization studies for the conversion of 4-nitrobenzyl alcohol

Entry	Oxidant	Catalyst (equiv)	Additive	Temperature (°C)	Yield (%) ^a
1	PhI(OAc) ₂	–	–	r.t.	–
2	PhI(OH)OTs	–	–	r.t.	14
3	PhIO ₂	–	–	r.t.	–
4	PhICl ₂	–	–	r.t.	–
5	PhI(OCOCF ₃) ₂	–	–	r.t.	22
6	PhIO	–	–	r.t.	27
7	(PhIO) ₃ ·SO ₃	–	–	r.t.	49
8	(PhIO) ₃ ·SO ₃	α-CD (0.1)	–	r.t.	46
9	(PhIO) ₃ ·SO ₃	β-CD (0.1)	–	r.t.	76
10	(PhIO) ₃ ·SO ₃	γ-CD (0.1)	–	r.t.	44
11	(PhIO) ₃ ·SO ₃	β-CD (0.5)	–	r.t.	83
12	(PhIO) ₃ ·SO ₃	β-CD (1.0)	–	r.t.	85
13	(PhIO) ₃ ·SO ₃	β-CD (0.5)	KBr	r.t.	81
14	(PhIO) ₃ ·SO ₃	β-CD (0.5)	Et ₂ O·BF ₃	r.t.	77
15	(PhIO) ₃ ·SO ₃	β-CD (0.5)	3 Å MS	r.t.	80
16	(PhIO) ₃ ·SO ₃	β-CD (0.5)	–	60	94
17	PhI(OAc) ₂	β-CD (0.5)	NaHSO ₄ ·H ₂ O	60	92

Reactions were performed by using 4-nitrobenzyl alcohol (1 mmol), oxidant (1.1 mmol), catalyst (0.5 mmol), H₂O (15 mL) at 60 °C for 3 h unless otherwise noted

^a GC–MS yield

can effectively depolymerize (PhIO)_n generating the reactive monomeric species [39]. However, addition of KBr, Et₂O·BF₃ or 3 Å molecular sieves to accelerate the depolymerization did not improve the oxidation (Table 1, entries 13–15). In addition, increasing the temperature is beneficial to the reaction (Table 1, entry 16). A further study showed that (PhIO)₃·SO₃ can be generated in situ from PhI(OAc)₂ and NaHSO₄·H₂O, used conveniently without isolation for the oxidation (Table 1, entry 17).

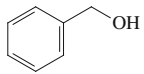
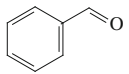
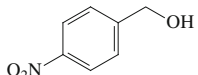
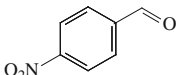
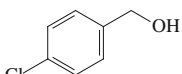
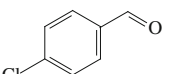
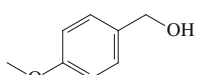
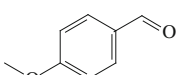
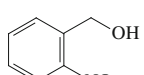
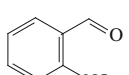
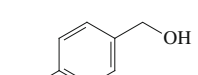
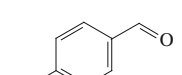
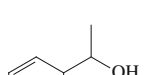
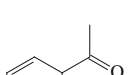
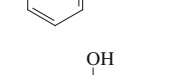
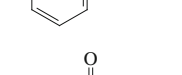
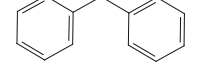
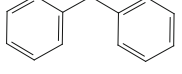
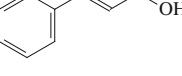
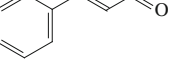
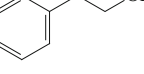
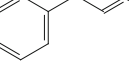
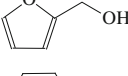
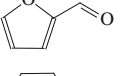
In order to evaluate the versatility of this novel catalytic system, we applied the procedure to the oxidation of a wide range of alcohols. Excellent chemoselectivity was observed under the present system. We detected no phenol oxidation products (Table 2, entry 6), which are well known to form in reactions with aryl-λ³-iodanes. For the oxidation of primary alcohol, no noticeable over-oxidation of aldehyde to carboxylic acid was detected. Allylic alcohol such as cinnamyl alcohol (Table 2, entry 9) was also oxidized efficiently without any observable reaction at the double bond functionality. In the present research benzylic alcohols underwent smooth oxidation (Table 2, entries 1–7). The electronic properties of the substituents in the aromatic ring had remarkable influence on the rate of the oxidation of benzyl alcohols. Strong electron withdrawing groups, such as nitro group, improve the oxidation of alcohol (Table 2, entry 2). Strong electron-donating groups, such as –OCH₃ group, lowered the reaction rate (Table 2, entry 4). However, the yield of the oxidation of 2-nitrobenzyl

alcohol was not satisfactory, indicating that the space configuration of guest molecules is more important for smooth conversion than the influence from electron effect in the present catalytic system. This could be further supported by the fact that the existence of any group on the aromatic ring decreased the reactivity more or less (Table 2, entries 1–6).

In spite of the good results with benzylic alcohols, the oxidation of cycloalkyl and aliphatic alcohols under the same conditions gave quite low yields (Table 1, entries 12–13). Cyclohexanol exhibited low reactivity towards the oxidation, which may be explained by the bulk of the cyclohexyl group, with chair and boat conformations occupying more space than an aromatic group. The other possible reason might attribute to the inactive of the hydroxyl group in virtue of the absence of electron cloud conjugation.

It is known that β-CD and substrates can form host–guest complex. This complexation depends on the size, shape and hydrophobicity of the guest molecule. For example, the steric hindrance of the diphenyl group might account for the lack of reactivity of diphenylmethanol, which is too large to enter into the hydrophobic cavity of β-CD during the reaction (Table 2, entry 8). This could be further evidenced that the oxidation of straight-chain aliphatic alcohol. The oxidation exhibited low reactivity most probably due to the impossibility of formation of a steady intermediate owing to the long distance between alcohol

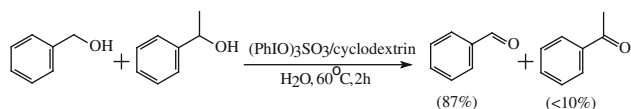
Table 2 β -cyclodextrin catalyzed oxidation of alcohols

Entry	Alcohols	Products	Catalytic system ^a	Time (h)	Yield (%) ^b
1			A	2	92 (1st) 90 (2nd) 91 (3rd)
2			B	3	90
			A	3	94
3			B	3	92
			A	4	90
4			B	5	88
			A	6	82
5			B	5	76
			A	7	70
6			B	4	86
			A	5	89
7			B	4	87
			A	5	85
8			B	8	37
			A	10	26
9			B	6	90
			A	8	87
10			B	8	76
			A	10	64
11			B	5	83
			A	6	80
12 ^c			B	8	58
			A	10	47
13 ^c	$n\text{-C}_{11}\text{H}_{23}\text{-CH}_2\text{OH}$	$n\text{-C}_{11}\text{H}_{23}\text{-CHO}$	B	10	Trace
			A	10	Trace

^a Catalytic system A: $(\text{PhIO})_3\cdot\text{SO}_3/\beta\text{-cyclodextrin}$, B: $\text{PhI}(\text{OAc})_2/\text{NaHSO}_4\cdot\text{H}_2\text{O}/\beta\text{-cyclodextrin}$ ^b Yields of isolated products unless otherwise noted^c Yields were determined by GC-MS

and β -CD (Table 2, entry 13). By compare with the oxidation of benzyl alcohol, cinnamyl alcohol, and phenethyl alcohol (Table 2, entries 1, 9 and 10), it can also conclude that increase the methylene group in the substrate might retard the host-guest complex intermediate formation by hydrogen bonding.

Next, we modified this system to develop a practical and clean procedure for the oxidation of alcohols with $(\text{PhIO})_3\cdot\text{SO}_3$ generated in situ from $\text{PhI}(\text{OAc})_2$ and $\text{NaHSO}_4\cdot\text{H}_2\text{O}$. The use of $\text{PhI}(\text{OAc})_2$ and $\text{NaHSO}_4\cdot\text{H}_2\text{O}$ instead of $(\text{PhIO})_3\cdot\text{SO}_3$ in the oxidation led to similar results, albeit a little longer reaction time was needed. This



Scheme 2 Competitive oxidation of primary and secondary alcohols

was advantageous because of its similar reactivity to $(\text{PhIO})_3\text{SO}_3$ but with the additional advantages of simple workup procedure.

At the end of the reaction, the β -CD was recovered by precipitation with ethyl acetate, the aqueous phase was removed by decantation and lyophilized to obtain the β -CD. The recycled β -CD was reused for three times with no loss of activity or selectivity, and only 1.6% loss of weight was observed after three times recycling (Table 2, entry 1). Therefore, from the point of view on the greener chemical processes, the use of this catalytic system do not lead to two major sources of waste: organic solvent and catalyst.

Scheme 2 shows the result of the competitive oxidation of primary and secondary alcohol. 1 equivalent oxidant was used in this competitive reaction. The competing oxidation of an equimolecular mixture of benzyl alcohol and 1-phenylethanol resulted in 87% yield of benzaldehyde and less than 10% yield of acetophenone. This result suggest that chemoselective oxidation of primary alcoholic functionality in the presence of secondary alcoholic functionality is possible with the present system.

4 Conclusions

In summary, a simple, mild and highly efficient biomimetic oxidation of alcohols with $(\text{PhIO})_3\text{SO}_3/\beta$ -cyclodextrin in water has been developed, which allowed the oxidation of alcohols to aldehydes or ketones in excellent yields and high selectivity without remarkable over-oxidation to carboxylic acids. It is noteworthy to mention that the catalyst could easily be recycled and reused without loss of activity and the oxidant could also be generated in situ.

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