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## Novel and efficient synthesis of *p*-quinones in water via oxidative demethylation of phenol ethers using hypervalent iodine(III) reagents

Hirofumi Tohma, Hironori Morioka, Yu Harayama, Miki Hashizume and Yasuyuki Kita\*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

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Abstract—A new method for preparing p-quinone derivatives from phenol ether derivatives in water using the hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA) was developed. The present reaction proceeds in good to excellent yields under mild reaction conditions. This oxidation is expected to be environmentally benign since it uses recyclable poly-bis(trifluoroacetoxyiodo)styrene (PBTIS) in water. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of quinones is important in organic chemistry because they are not only useful intermediates, but also many are pharmacologically active compounds.1 Among various preparations of quinone derivatives,<sup>2</sup> oxidative dealkylation (especially demethylation) of hydroquinone dimethyl ethers is one of the most effective methods. This is because methyl ethers of phenol derivatives are stable under various reaction conditions and can be converted to the desired quinones in the later stages of a synthetic scheme. Thus far, oxidative demethylation has been achieved by using cerium(IV) ammonium nitrate (CAN),<sup>3</sup> nitric acid,<sup>4</sup> silver(II) oxide (AgO)-mineral acid,5 manganese dioxide  $(MnO_2)$ -nitric acid,<sup>6</sup> cobalt(III) fluoride  $(CoF_3)^7$  and NBS-H<sub>2</sub>SO<sub>4</sub>.<sup>8</sup> However, total syntheses of naturally occurring complex quinones sometimes need milder reaction conditions and the pharmaceutical and agrochemical industries are seeking environmentally benign methods free of metal waste. Hypervalent iodine reagents have been used extensively in organic syntheses as a result of their low toxicity, ready availability and easy handling.9 As a continuation of our studies on hypervalent iodine chemistry, we have already reported various oxidation reactions of phenol and phenol ether derivatives using phenyliodine(III) bis(trifluoroacetate) (PIFA) and phenyliodine(III) diacetate (PIDA).<sup>10</sup> Among them, we have developed efficient oxidation reactions of p-alkoxyphenols leading to p-quinone monoacetals<sup>11a</sup> and p-quinones<sup>11b</sup> using PIFA in the

presence of alcohols and H<sub>2</sub>O. These involve the reactions of phenols, in which the phenolic oxygen reacts with the iodine center of PIFA. Although similar preparative methods of quinones from phenols using iodine(III) reagents have also been reported,<sup>12</sup> the oxidative demethylation of phenol ethers that have no phenolic OH groups (hydroquinone dimethyl ethers) using hypervalent iodine reagents has never been reported, probably due to their low reactivity in comparison with metal oxidants. Very recently, we have shown that iodine(III) reagents can be remarkably activated in water by micellar effect<sup>13</sup> or hydrophobic effect.<sup>14</sup> We report herein the first example of oxidative demethylation reaction of hydroquinone dimethyl ether derivatives in water using PIFA or poly-bis(trifluoroacetoxyiodo)styrene (PBTIS) in the absence of additives.

First, we examined the oxidation of 1,4-dimethoxybenzene (1a) using PIFA. Interestingly, after optimization of the reaction conditions, the reaction was found to proceed smoothly in water (containing a small amount of MeOH as a co-solvent) to give *p*-benzoquinone (2a) quantitatively,<sup>15</sup> while either deficiency or absence of water caused side reactions<sup>16</sup> as well as low yield of 2a.

Next, we compared this reaction with typical oxidative demethylation methods using CAN or  $AgO-HNO_3$  (Table 1).

Although hypervalent iodine oxidations required long reaction time in all cases, Table 1 shows that the present reaction gave the best results when PIFA or

<sup>\*</sup> Corresponding author. Tel.: +81-6-6879-8225; fax: +81-6-6879-8229; e-mail: kita@phs.osaka-u.ac.jp

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Table 1. Comparison with other methods using CAN or AgO



<sup>a</sup> 2.5 v/v% MeOH in H<sub>2</sub>O.

<sup>b</sup> 3a was mainly obtained (see Refs. 3 and 5).

PIDA was used<sup>17</sup> even in the oxidation of **1b**, which was converted to dimeric product **3a** when using CAN or AgO. Incidentally, the oxidation reaction that uses CAN in water was not effective for oxidative demethylation (entry 3, Table 1).

The present method is applicable to a variety of substituted phenol ethers (1a-m) and affords the corresponding *p*-quinones (2a-m) in high yields as shown in Table 2.

Interestingly, *p*-quinones were obtained selectively even when using *ortho*-substituted phenol ethers (**1g**, **h**) (entries 7–8, Table 2). Furthermore, oxidation of indole derivatives also proceeded to give pharmacologically important indoloquinone derivatives in good yields (entries 12, 13, Table 2). However, the oxidation of *meta*-substituted phenol ethers (**1n**–**p**) did not yield quinones but yielded the corresponding diaryliodonium salts (**4a–c**) in high yields (entries 14–16, Table 2).

Next, we modified this system to develop a practical and clean procedure for oxidative demethylation using a polymer-supported hypervalent iodine(III) reagent. Polymer-supported hypervalent iodine reagents<sup>18</sup> are expected to be useful for pharmaceutical and agrochemical industries due to their versatility, low toxicity and high yields. Recently, Togo et al.<sup>19</sup> and Ley et al.<sup>20</sup> demonstrated that poly-(diacetoxyiodo)styrene (PDAIS) shows similar reactivity to PIDA and utilized it as a replacement for previously reported iodine(III) reagents. We have reported on a new and facile activation of PDAIS and PBTIS in water as well as in CH<sub>2</sub>Cl<sub>2</sub> and developed an environmentally benign oxidation of alcohols<sup>21</sup> as well as an efficient biaryl coupling reaction.<sup>22</sup> As an extension of our studies on the practical utility of hypervalent iodine reagents, we then investigated the use of recyclable poly-(diacyloxyiodo)styrene for oxidative demethylation. As a result, *p*-quinones were obtained in good yields when using PBTIS in water, while the reaction proceeded much more slowly than when PIFA was used (Table 3).

Tabl	e 2.	. Synth	esis of	<i>p</i> -	quinor	nes vi	ia	oxidative	demethyla-
tion	of	phenol	ethers	in	water	using	g	PIFA	



<sup>*a*</sup>Reactions were performed with 4.0 equiv. PIFA. <sup>*b*</sup>Reactions were performed with 1.5 equiv. PIFA. <sup>*d*</sup>Yield in parenthesis is based on the consumed starting material.

**Table 3.** Synthesis of *p*-quinones via oxidative demethylation using PBTIS and the efficiency of recycled PBTIS

Entry	Substrate	Product	Reaction time (h)	Yield (%)
1	1b	2b	16	74
2	1c	2c	12	71
3	1i	2i	24 (cycle 1)	95
4	1i	2i	27 (cycle 2)	95
5	1i	2i	32 (cycle 3)	94

All reactions were carried out in  $H_2O:MeOH$  using 4.0 equiv. PBTIS at 20°C.



Scheme 1. Proposed mechanism of oxidative demethylation using I(III) reagents.

The resin (poly iodostyrene) is readily recoverable and recyclable. The resin was recovered nearly quantitatively by filtering the resulting mixture. The recovered resin was easily reoxidized by pertrifluoroacetic acid  $(30\% \text{ H}_2\text{O}_2 \text{ and } (\text{CF}_3\text{CO})_2\text{O})^{23}$  and the regenerated PBTIS was found to maintain its activity (entries 3–5, Table 3).

A plausible reaction mechanism for the preparation of p-quinones from hydroquinone dimethyl ethers is shown in Scheme 1. Abstraction of highly acidic  $\alpha$ -hydrogen of the phenyliodonio group induces aromatization to yield stable diaryliodonium salts **4** in the oxidation of *meta*-substituted phenol ethers, while phenyliodonio group acts as an excellent leaving group<sup>24</sup> in the oxidation of *para*-substituted phenol ethers. It seems reasonable to assume that hydrophobic aggregation between the iodine(III) species and the substrate promotes the reaction progression in water.

In summary, using PIFA in water allowed us to develop a facile and efficient synthetic method for obtaining p-quinone derivatives via oxidative demethylation of hydroquinone dimethyl ethers. Furthermore, we succeeded in a practical application of this method by utilizing a polymer-supported hypervalent iodine reagent, PBTIS, under mild reaction conditions. Hence, hypervalent iodine reagents show promise in replacing highly toxic metal oxidants and should become useful

tools for the syntheses of various biologically active natural products containing a quinone structure. Synthetic application of this method is now underway in our laboratory.

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- 15. General experimental procedures are as follows. *PIFA*oxidation in water: To a stirred suspension of 1 (0.20 mmol) in H<sub>2</sub>O (1.0 mL) containing a small amount of MeOH (25.0  $\mu$ L), PIFA (0.30 or 0.80 mmol) was added as a solid at room temperature. The mixture was stirred under the same conditions. Extraction of the reaction mixture with AcOEt followed by column chromatography (SiO<sub>2</sub>/n-hexane–AcOEt) gave pure **2**.

Although the reaction also proceeded in water, the addition of a small amount of MeOH (<20% MeOH in H<sub>2</sub>O) was found to be more effective for an enhancement of the reaction rate. Addition of excess amount of MeOH deactivated PIFA.

*PBTIS*—oxidation in water: To a stirred suspension of 1 (0.20 mmol) in H<sub>2</sub>O (1.0 mL) containing a small amount of MeOH (25.0  $\mu$ L), PBTIS (0.80 mmol) was added as a solid at room temperature. The mixture was stirred under the same conditions. The reaction mixture was filtered, and the residue (recovered resin) was washed with AcOEt. The filtrate was extracted with AcOEt, then purified by column chromatography (SiO<sub>2</sub>/*n*-hexane–AcOEt) to give pure **2**.

- Trifluoroacetoxylation and/or dimerization of 1a also proceeded in such cases.
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- 23. Regeneration of PBTIS: To a stirred suspension of recovered poly iodostyrene (87% iodinated polystyrene based on elemental analysis) (400 mg) in  $(CF_3CO)_2O$  (20.0 mL) 30%  $H_2O_2$  aq. (5.0 mL) was added dropwise at 0°C. The mixture was stirred for 30 hours at room temperature. Et<sub>2</sub>O was added to the reaction mixture to precipitate the polymer. The mixture was filtered and the precipitate was washed with Et<sub>2</sub>O. The product was dried under vacuum to give PBTIS. Poly iodostyrene was readily prepared from polystyrene standard (Mw=50,000 purchased from Aldrich) by treatment with  $I_2/I_2O_5/50\%H_2SO_4/nitroben-zene under reflux.<sup>18a</sup>$
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