



Short communication

A green catalytic method for selective synthesis of iodophenols via aerobic oxyiodination under organic solvent-free conditions



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ABSTRACT

A highly efficient catalytic method for aerobic oxyiodination of various phenols catalysed by copper(II) nitrate was achieved under mild conditions using I₂ as an iodinating reagent, molecular oxygen as an oxidant, and water as a solvent. The catalyst shows not only high activity for phenols with either electron-donating or electron-withdrawing groups, but also a remarkable selectivity for the formation of *para*-iodo substituted phenols. This study offers a green method for iodination of aromatic phenols with high atom economy.

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1. Introduction

Iodoarenes are important organic intermediates in synthesis of pharmaceuticals, drugs, oligomers, fine chemicals and functional compounds possessing pharmaceutical and biological activity [1]. The application of iodoarenes in carbon-carbon or carbon-heteroatom bond formation presents a series of classic reactions, such as Heck, Stille and Suzuki coupling [2]. Common methods for their synthesis usually involve aromatic halogenations with a series of iodinating reagents such as iodine [3–6], iodide [6–8] and *N*-iodosuccinimide (NIS) [9–11]. Although great progress has been made, these systems usually involve the use of hazardous, toxic or expensive reagents/equipments, more economic and environmentally friendly methods attract much attention of researchers.

As an alternative solution, oxidative iodination, i.e. oxyiodination, has been developed in the iodination of various aromatic compounds [12–16]. In these processes, oxyiodination reactions are carried out with a combination of iodinating reagents and various oxidants. In general, iodide anions, as an iodinating reagent, are oxidized into active molecular iodines via the oxidation by oxidants. In this way, the iodinating reagents are efficiently incorporated into the products, and the atom economy of iodine atoms is much higher than that in the above mentioned traditional methods. However, the products in these systems often present as a mixture of *ortho*-, *para*- and *multi*-iodo substituted aromatics, from which the separation of desired product is a problem.

Moreover, in many cases, stoichiometric inorganic salts are required, leading to environmental problems due to undesirable by-products.

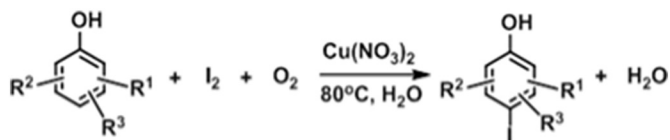
Compared with the studies as described above, oxyiodinations based on mild and environmentally friendly oxidants like hydrogen peroxide and dioxygen are particularly attractive, in that the by-product from these oxidants is only water [17,18]. Although various strategies have been achieved, these processes usually perform in VOC (volatile organic compound) as a solvent [19–21]. According to the points of view in industrial production, the use of water as a solvent possesses some advantages: 1) no organic solvent is cheaper than water; 2) the explosion risk of water-based systems is much lower than those containing VOC in the presence of oxygen or hydrogen peroxide. Thus, it is much desirable to develop novel water-based oxyiodination with environmentally friendly oxidants. Herein, we present a direct, efficient, aerobic oxyiodination of phenols catalysed by copper(II) nitrate, in which iodine is used as an iodinating agent, dioxygen as a final oxidant, and water as a solvent. The current method shows high activity and selectivity in converting phenols to *para*-iodinated phenols. A schematic representation of the reactions is given in Scheme 1.

2. Results and discussion

Oxyiodination was performed in water, and unsubstituted phenol (**1a**) was selected as a model substrate to screen the reaction conditions. The results over various metal salts are summarized in Table 1. In the absence of metal salts, no reaction was observed ever for prolonged time (Table 1, run 1). The salts of Fe²⁺, Fe³⁺, Mn²⁺, Ni²⁺, Co²⁺ and Na⁺ showed no activity (Table 1, run 2–8). Among the tested copper

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Scheme 1. Aerobic oxyiodination of phenols to *para*-iodo substituted phenols under organic solvent-free conditions.

salts, CuSO₄, CuCl₂, Cu(OAc)₂ and CuBr₂ had no effect on the reactions (Table 1, run 9–12), only Cu(NO₃)₂ exhibited remarkable activity (Table 1, run 13). Notably, *para*-iodophenol (**1b**) was preferentially formed in the presence of copper(II) nitrate, and almost no *ortho*-isomer was detected in the reaction. To the best of our knowledge, such a high selectivity in water-based aerobic oxyiodination of phenols has not been reported yet.

It is known that transformation of phenols over the catalysts of copper complexes is often effected by the anions of catalysts [22], which have been reported in various oxidative transformations of phenols, such as oxidation [23], coupling [24], and bromination [25]. Although the exact roles of nitrate anions remains unknown, many reports on oxidative chlorination, bromination and iodination of aromatic compounds including phenols involved the use of either nitrate or nitrite anions as oxidants or proton donors [26–30]. In our study, when NaNO₃ was added into an aqueous solution of potassium iodide, color of the solution immediately turned purple, which indicated the formation of iodine due to the oxidative capability of nitrate anions. As CuCl₂ and NaNO₃ were combined and performed the reaction for 3 h, 65% of **1a** was converted and the yield for **1b** reached 61% (Table 1, run 14). If CuCl₂ and NaNO₂ were combined, a conversion of 61% for **1a** was achieved and the yield of **1b** was 57% (Table 1, run 15). These results indicate nitrite and nitrate anions play the same roles in this system. As NaNO₃ was replaced with NO₂, a conversion of 95% was achieved for **1a** and the yield of **1b** was 88% (see Supporting information). Because phenol has weak acidity, pH value of the reaction solution is about 6.0 by pH indicator strips. In experiment, when NaNO₂ was added into an aqueous solution containing phenol, the color immediately turned as yellow, which indicated the released NO from NaNO₂ reacts with oxygen to produce NO₂. Thus, we think the oxidation of nitrite to nitrate by oxygen is achieved based on NO/NO₂ cycle, and the recycle of NO/NO₂ and nitrite/nitrate is the same in our case. To clarify the roles of oxygen and nitrate anions, several reactions were run as control experiments (see Supporting information, Table 1S). If phenol was

Table 1
Oxyiodination of **1a** with I₂ over various metal salts.^a

Run	Metal salt	Time (h)	Conversion (%)	Isolated yield ^b (%)
1	–	10	<1	–
2	FeSO ₄	3	<1	–
3	FeCl ₃	3	<1	–
4	MnCl ₂	3	<1	–
5	NiSO ₄	3	<1	–
6	Co(OAc) ₂	3	<1	–
7	Mn(acac) ₂	3	<1	–
8	NaNO ₃	3	<1	–
9	CuCl ₂	3	<1	–
10	Cu(OAc) ₂	3	<1	–
11	CuBr ₂	3	<1	–
12	CuSO ₄	3	<1	–
13	Cu(NO ₃) ₂	3	98	93
14 ^c	CuCl ₂ /NaNO ₃	3	65	61
15 ^d	CuCl ₂ /NaNO ₂	3	61	57

^a Reaction conditions: **1a**: 2 mmol, I₂: 2.2 mmol, metal salt: 5 mol%, O₂: 1 atm, water: 10 ml, 80 °C.

^b Yield for **1b**.

^c CuCl₂: 5 mol%, NaNO₃: 10 mol%.

^d CuCl₂: 5 mol%, NaNO₂: 10 mol%.

treated with 1.0 eq. of NaNO₃ or NaNO₂ in the absence of I₂ under Ar or O₂ atmosphere, no reaction occurred even for prolonged time. As phenol was treated with copper nitrate in the absence of I₂ under Ar atmosphere, trace 4,4'-dihydroxybiphenyl was found after reaction. When the reaction was carried out in the absence of I₂ under O₂ atmosphere, the product was *p*-benzoquinone. These results indicate copper ions activate phenol to form phenoxy radicals, which couples as 4,4'-

Table 2
Results for oxyiodination of various substrates with I₂.^a

Run	Substrate	Time (h)	Product	Conversion (%)	Isolated Yield (%)
1	1a	3	1b	98	93
2	2a	3	2b	98	82
3	3a	2.5	3b	97	90
4	4a	2.5	4b	96	91
5 ^b	5a	6	5b	96	83
6 ^b	6a	6	6b	95	78
7 ^b	7a	6	7b	97	88
8 ^b	8a	6	8b	92	84
9 ^b	9a	6	9b	95	89
10	10a	10	10b	93	89
11	11a	10	11b	96	86
12 ^b	12a	12	12b	92	85
13	13a	12	13b	0	0
14	14a	12	14b	0	0

^a Reaction conditions: **1a**: 2 mmol, I₂: 2.2 mmol, metal salt: 5 mol%, O₂: 1 atm, water: 10 ml, 80 °C.

^b 5 mol% of tetra-butyl ammonium bromide was added.

dihydroxybiphenyl under inert atmosphere and combines with oxygen to form *p*-benzoquinone under O₂ atmosphere in the absence of I₂. Obviously, oxygen is a radical scavenger in the absence of I₂. In the presence of I₂ and O₂, I₂ preferentially reacts with phenol and oxygen plays the role of an oxidant. Although nitrate anions are not active centers for phenol, they significantly accelerate the reactions. Thus, we consider nitrate anion is likely a co-catalyst, which possibly activate I₂ to promote the reactions.

The optimized results are listed in Table 2S (see Supporting information). When I₂ was replaced with HI, reactions also proceeded smoothly, and a yield of 88% was achieved for **1b** in 12 h. As dioxygen was replaced with air, a high yield of 91% was obtained at 80 °C for 10 h. Studies indicate that common organic solvents, such as methanol, are also effective, but water is undoubtedly the best alternative. Based on the optimized conditions, complete conversion was achieved, and a high yield of 93% for **1b** was obtained with 5 mol% of catalyst at 80 °C for 3 h. Because iodine is easy to sublime, part of iodine is always out of the reaction system and aggregates as iodine bulk on the top of glassware. The aggregated iodine bulk was collected, and it is around 1.20–1.25 mmol according to titration test. Thus, the iodine involved in the reactions is 0.95–1.00 mmol. Since the substrate of **1a** is 2.0 mmol, the utilization of iodine atoms is ≥93% and iodine involved in the reactions is almost quantitatively incorporated into the product. Therefore, the current approach demonstrates a high atom economy. When we enlarged the reaction scale to 50 times in the absence of any VOCs, a conversion of **1a** was 95% with a yield of **1b** at 90%. The reaction proceeded well without VOC (see Supporting information).

In further experiments, various substituted phenols were examined under similar conditions (Table 2). In fact, phenols with electron donating groups at *meta*-position can be easily iodinated, and *para*-iodophenols were produced in good yield in 3 h (Table 2, run 2–4). A yield of 82% was achieved for **2b** from *m*-cresol (**2a**), and a 90% yield for **3b** was obtained from 3,5-dimethylphenol (**3a**). As for 2,3,5-trimethylphenol (**4a**), the yield of **4b** reached as high as 91%. When phenols with electron donating groups grafted at *ortho*-position were used, no reaction was observed even the reaction time was prolonged to 6 h. In order to increase the solubility of these phenols in water, the phase-transfer reagent, such as tetra-butyl ammonium bromide, was added into the system. Iodination proceeded smoothly and the reaction was completed after 6 h (Table 2, run 5–9). A yield for **5b** was 83% from *o*-cresol (**5a**), and a yield of 78% for **6b** was obtained from 2-tert-butylphenol (**6a**). The yield of **7b** was 88% from 2,6-dimethylphenol (**7a**). As for 2,6-di-isopropylphenol (**8a**) and 2,6-di-tert-butylphenol (**9a**), the yield for **8b** and **9b** reached 84% and 89%, respectively. Compared with unsubstituted phenol (**1a**) or phenols with electron donating groups at *ortho*-position, the reaction speed of phenols with electron donating groups at *ortho*-position is slower under the same conditions. Phenols with electron withdrawing groups can also be successfully iodinated in our system (Table 2, run 10–12). Iodination of 2-chlorophenol (**10a**) gave **10b** in 89% yield, and the yield of **11b** from 2-bromophenol (**11a**) was 86% for 10 h. While 2,4-dichlorophenol (**12a**) was iodinated as **12b** in a high yield of 85% in 12 h, no iodination was observed for 4-chlorophenol (**13a**) and 4-bromophenol (**14a**) (Table 2, run 13–14). Compared with unsubstituted phenol (**1a**) or phenols with electron donating groups, the iodination of phenols with electron withdrawing groups proceeded at slower speed under the same conditions. In above reactions, only trace of *ortho*- or *meta*-isomer was observed, and no *multi*-iodo substituted products were found. The preferential formation of *para*-iodo substituted phenols by our method is remarkably selective.

It is known that the oxidative transformations of phenols catalysed by copper compounds usually involve the oxidation of phenolate by Cu(II) to phenoxy radical [31]. However, phenoxy radicals are extremely active and the reaction proceeds too fast to observe the intermediate, our attempts to obtain the electron paramagnetic resonance of phenoxy radicals were failed. Although the results shown in control experiments

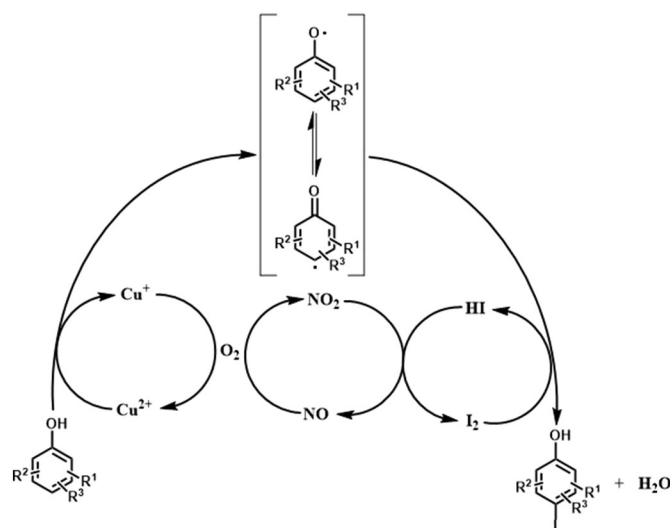


Fig. 1. A possible mechanism of the aerobic oxyiodination of aromatic phenols catalysed by copper(II) nitrate.

are indirect evidences, we think phenoxy radical involves in our system. Besides those results, the following evidences also support this hypothesis: 1) when 2,3,6-tri-methylphenol was treated with 1.0 eq. of copper(II) nitrate in the absence of I₂ under Ar atmosphere, a yield of 60% was detected for 2,2',3,3',5,5''-hexamethyl-4,4''-dihydroxybiphenyl; 2) if a free radical scavenger, 2,6-di-tert-butyl-4-methyl phenol, was added into the above reactions, almost no products were found in the reactions; 3) as we took a little solution (about 1 ml) from the reaction mixtures as the reaction ran for 1.5 h, and performed the precipitation reaction using silver nitrate as a precipitator for I⁻, precipitation of silver iodide was observed. Thus, although the details of reaction mechanism are not clear so far, a possible mechanism is shown in Fig. 1: Cu²⁺ oxidizes phenols to produce phenoxy radicals, which react with I₂ to form *p*-iodophenol and HI; HI is oxidized by NO₂ to I₂ with the formation of NO; and the reduced Cu⁺ and NO are re-oxidized by dioxygen back to Cu²⁺ and NO₂, respectively. The reaction is recycled as above described until I₂ is exhausted.

3. Conclusion

A simple, green, and efficient method has been developed for aerobic oxyiodination of aromatic phenols using dioxygen and iodine under organic solvent-free conditions. Copper(II) nitrate showed very high catalytic activity and selectivity for the direct iodination of various phenols to *para*-iodophenols with dioxygen in water. A wide range of phenol derivatives were tested, containing either electron-donating or electron-withdrawing groups, which suggested that this method is suitable to synthesize various *para*-iodophenols.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.catcom.2017.01.019>.

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