An Iodine-Promoted, Mild and Efficient Method for the Synthesis of Phenols from Arylboronic Acids

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Abstract: A mild and efficient methodology for the *ipso*-hydroxylation of arylboronic acids to phenols has been developed using aqueous hydrogen peroxide as oxidizing agent and molecular iodine as catalyst. The reactions were performed at room temperature in short reaction time under metal-, ligand- and base-free conditions.

Key words: arylboronic acid, phenol, hydroxylation, hydrogen peroxide, iodine

Phenol compounds and derivatives have been found in numerous natural products and are well-known precursors for the synthesis of pharmaceuticals, polymers, and naturally occurring compounds.[1] Consequently, the synthesis of phenols continues to attract the attention of organic chemists and a wide variety of methods have been developed their synthesis over the years. Among the approaches, nucleophilic aromatic substitution of aryl halides, copper-catalyzed transformation of diazoarenes, and benzyne protocols are dominant.[2] However, these methods can suffer from disadvantages such as harsh reaction conditions, and diazotization requires conversion of the amino groups into diazoarenes, which is often not compatible with many other functional groups. There are some reports on the conversion of aryl bromides and chlorides into phenols in the presence of palladium-based catalysts and phosphine ligands.[3] Moreover, aryl iodides have been converted into the corresponding phenols in the presence of a copper catalyst using non-phosphine ligands[4] at elevated temperature. In recent years, arylboronic acid derivatives have immerged as one of the most powerful synthons in organic chemistry.[5] Interestingly, although phenols have been found as by-products in many metal-catalyzed reactions of arylboronic acids,[6] there are very few reports available that deal with methodologies for hydroxylation of arylboronic acids. The innocuous nature of arylboronic acids, which are generally non-toxic, stable to heat, air, and moisture, and are availability in a wide range of phenylboronic acid derivatives, make them an interesting and valuable potential precursor of phenols. There are some reports in which $CuSO_4$-phenanthrolin,[7] H_2O_2-poly(*N*-vinylpyrrolidone),[8] NH_2OH,[9] potassium peroxymonosulfate,[10] or aqueous hydrogen peroxide[11] have been effectively utilized for the hydroxylation of arylboronic acid. These strategies, however, have some disadvantages such as long reaction times,[9,11] the use of ligand/base,[7] and the need for toxic chlorinated organic solvents.[8] Thus, the development of catalytic systems that are readily accessible, air and moisture stable, inexpensive, environmentally acceptable, and that can promote these reactions under mild reaction conditions are still desirable. Aqueous hydrogen peroxide is well-known as a stoichiometric, environmentally friendly oxidant that shows a high efficiency per weight of oxidant.[12] Moreover, for a long time, iodine has been recognised as a good catalyst and reagent in organic chemistry.[13] In the present study, we wish to report the use of iodine as an extremely powerful promoter for oxidative *ipso*-hydroxylation of arylboronic acids at room temperature under metal-, ligand- and base-free conditions.

To investigate the effectiveness of hydrogen peroxide (30% aqueous) in the hydroxylation reaction, phenylboronic acid (**1a**; 1 mmol) was chosen as a model substrate and the reactions were performed under aerobic conditions at room temperature; the results are summarized in Table 1. When a mixture of **1a** (1 mmol) and aqueous hydrogen peroxide (2 mL) was stirred at room temperature for 1 h, only a trace amount of phenol (**2a**) was obtained (Table 1, entry 1). The insolubility in water of most of the reagents and substrates restricts their use in water as a solvent. Therefore, we carried out the reaction in acetonitrile and the yield of phenol **2a** was slightly increased (Table 1, entry 2). Interestingly, the yield of **2a** was elevated to 85% within 1 h in the presence of iodine (20 mol%; Table 1, entry 3). We carried out the reaction between phenylboronic acid and aqueous hydrogen peroxide in the presence of various solvents by using iodine as reaction promoter. The reaction was found to proceed in both protic and aprotic solvents, although variations in yields were observed (Table 1, entries 3–9). Similarly, 50% aqueous tetrahydrofuran (THF), aqueous acetonitrile, and aqueous methanol gave comparable results (Table 1, entries 7–9) under the same reaction conditions. However, the use of dichloromethane as solvent provided reduced yields (Table 1, entry 6). We obtained the best result by using iodine and aqueous hydrogen peroxide without using any solvent (Table 1, entry 10). Several test reactions were carried out using different amounts of iodine and hydrogen peroxide to establish the optimal amount of catalyst required for this transformation. It was observed that 5 mol% iodine was sufficient for smooth oxidation of 1.0 mmol of the substrate (Table 1, entries 10–15). The reaction did not proceed in the absence of hydrogen peroxide (Table 1, en-

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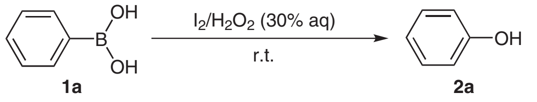
try 16). However, the reaction gave phenol (**2a**) in good yield in the absence of iodine when the reaction time was extended to 36 h (Table 1, entry 17).

Table 1 Optimization of Reaction Conditions for Iodine-Mediated *ipos*-Hydroxylation[a]

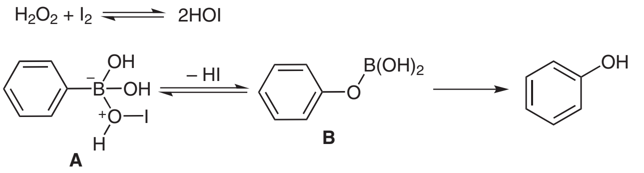


Entry	Oxidant	Solvent	Catalyst	Time (min)	Yield (%)[b]
1	H_2O_2	–	–	60	04
2	H_2O_2	MeCN	–	60	07
3	H_2O_2	MeCN	I_2 (20 mol%)	50	85
4	H_2O_2	MeOH	I_2 (20 mol%)	50	82
5	H_2O_2	THF	I_2 (20 mol%)	50	81
6	H_2O_2	CH_2Cl_2	I_2 (20 mol%)	70	75
7	H_2O_2	THF–H_2O (1:1)	I_2 (20 mol%)	50	85
8	H_2O_2	MeCN–H_2O (1:1)	I_2 (20 mol%)	50	80
9	H_2O_2	MeOH–H_2O (1:1)	I_2 (20 mol%)	50	82
10	H_2O_2	–	I_2 (20 mol%)	45	92
11	H_2O_2	–	I_2 (15 mol%)	45	90
12	H_2O_2	–	I_2 (10 mol%)	45	90
13	H_2O_2	–	I_2 (5 mol%)	45	93
14	H_2O_2	–	I_2 (3 mol%)	60	85
15	H_2O_2	–	I_2 (5 mol%)	60	80[c,d]
16	H_2O	–	I_2 (20 mol%)	60	trace
17	H_2O_2	–	–	36 h	80[c]

[a] Reagents and conditions: phenylboronic acid (1 mmol), H_2O_2 (30% aq, 2 mL), solvent (2 mL), ca 28 °C.
[b] Isolated yields.
[c] The reaction did not reach completion.
[d] H_2O_2 (1 mL) was used

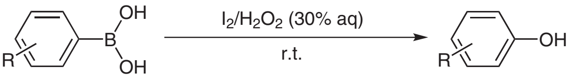
To evaluate the scope and limitations of the current procedure, the reactions of a wide array of electronically diverse arylboronic acids were examined using iodine as catalyst (Table 2).[14] In general, arylboronic acids with either electron-withdrawing or electron-donating substituents such as OMe, Me, Cl, COMe, NO_2, CHO, NH_2, OH (Table 2, entries 2–12) underwent the *ipso*-hydroxylation reaction in good yields (80–93%). It was observed that a variety of substituents were tolerated on the aromatic substrate. The reaction was also compatible with heteroarylboronic acid (Table 2, entry 13).

A mechanistic path for the reaction is proposed in Scheme 1, following the mechanism proposed by Kuivila[15] and Kianmehr.[9] It is reported that the reaction between hydrogen peroxide and iodine in neutral medium leads to the formation of hypoiodous acid (HOI).[16] Hypoiodous acid could then react with phenylboronic acid to form adduct **A**. Removal of HI and subsequent phenyl migration to the oxygen generates adduct **B**. Finally, hydrolysis of adduct B leads to the formation of phenol. Excess hydrogen peroxide in the reaction medium facilitates the regeneration of iodine from hydroiodic acid.



Scheme 1

Table 2 Iodine-Catalyzed Synthesis of Phenols[a]



Entry	R	Time (min)	Yield (%)[b,c]
1	H	45	93
2	*p*-OMe	45	91
3	*o*-OMe	30	90
4	*m*-OMe	45	91
5	*o*-Me	30	92
6	*p*-Me	30	92
7	*p*-Cl	50	90
8	*p*-COMe	60	91
9	*o*-NO_2	35	87
10	*p*-CHO	50	88
11	*p*-NH_2	60	85
12	*p*-OH	50	84
13	thiophene-2-boronic acid	120	80

[a] Reagents and conditions: $ArB(OH)_2$ (1 mmol), I_2 (5 mol%), H_2O_2 (30% aq, 2 mL), ca 28 °C.
[b] Yield of isolated product.
[c] All compounds were characterized by ^1H NMR, ^{13}C NMR, FT-IR and MS.

In conclusion, we have developed a mild and efficient methodology for the *ipso*-hydroxylation of arylboronic acids to the corresponding phenol using aqueous hydrogen peroxide as oxidizing agent and molecular iodine as catalyst. Advantages of the protocol are that it operates at room temperature under mild reaction conditions in short reaction time without requiring metal, ligand or base.

Acknowledgment

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(14) **Hydroxylation of Arylboronic Acids; General Procedure**: A 50 mL round-bottom flask was charged with arylboronic acid (1 mmol), 30% aqueous H_2O_2 (2 mL) and iodine (5 mol%) and the reaction mixture was stirred at room temperature. After completion of the reaction (TLC) the reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (3 × 15 mL). The ether extract was washed with sodium thiosulfate solution (10 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane or diethyl ether/hexane) or by crystallization. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR and MS and by comparison with authentic samples. Analytical data of phenol (**2a**): colorless solid; mp 41–42 °C (Lit.[17] 41–42 °C). ^{1}H NMR ($CDCl_3$): $\delta = 7.25–7.19$ (m, 2 H), 6.93–6.88 (m, 1 H), 6.81–6.78 (m, 2 H), 5.08 (s, 1 H); ^{13}C NMR ($CDCl_3$): $\delta = 153.0$, 127.5 (2C), 120.0, 114.5 (2C)

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