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SHORT COMMUNICATION

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ipso-Hydroxylation of Arylboronic Acids and Boronate Esters by Using Sodium Chlorite as an Oxidant in Water

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A facile and efficient procedure for the *ipso*-hydroxylation of arylboronic acids to phenols in water was developed. A series of electron-rich and electron-deficient arylboronic acids were smoothly *ipso*-hydroxylated with this protocol to afford products in excellent yields. Moreover, the protocol is amenable to boronate esters. In most cases, the phenolic products were obtained in pure form without any chromatographic purification.

Introduction

The hydroxylation of aromatic compounds remains a challenge in organic chemistry, even though phenols are very useful intermediates for many pharmaceutical molecules, natural products and polymers.[1] Naturally, phenols are produced by plants and microorganisms in response to ecological and physiological pressures such as pathogens, insect attack, UV radiation, and wounding.[2] In industry, phenols are synthesized as raw materials and as additives for industrial wood processing and the chemical industries.[1a] In medicinal chemistry, they are known to exhibit many pharmacological actions including antitumor, antiviral, antibacterial, cardioprotective, pro-oxidant, and antimutagenicity activities.[3] The synthesis of phenols therefore continues to attract the attention of organic chemists, and various methods for their preparation have been developed. Most commonly, phenols are produced by pyrolysis of the sodium salt of benzene sulfonic acid, the Dow process, hydrolysis of diazonium salts, or by the Hock process.[4] However, these methods invariably suffer from disadvantages such as harsh reaction conditions and the production of byproducts. In contrast, aryl iodides, bromides, and chlorides can be converted into phenols by palladium- and copper-catalyzed processes,[5] which involve the use of rare and expensive metal catalysts and sophisticated supporting ligands and additionally require high reaction temperatures and long reaction times. Over the last decade, arylboron reagents have been recognized as valuable alternatives to aryl groups for the synthesis of phenols, because they are readily available, nontoxic, shelf stable, and often react under mild conditions with good functional group tolerance. Moreover, they can be prepared by C–H bond functionalization, which is complementary to the chemistry of aryl halides.[6] The oxidation of arylboronic acids and its derivatives to phenols was first reported by Ainley and Challenger[7a] with alkaline hydrogen peroxide and was later modified by Kuivila[7b] and Olah.[7c] Although this transformation is simple and green, electron-deficient arylboronic acids give low yields and alkaline hydrogen peroxide can lead to undesirable side reactions. To improve this transformation, I_2,[7d] acidic Al_2O_3,[7e] and Amberlite IR-120 resin[7f] have been used as catalysts with H_2O_2 and complexes of poly(*N*-vinylpyrrolidone)/hydrogen peroxide and poly(4-vinylpyridine)/hydrogen peroxide.[7g] Other catalysts/reagents used for the transformation of arylboronic acids into phenols include $CuSO_4$/phenanthroline,[7h] NH_2OH/NaOH,[7i] potassium peroxymonosulfate,[7j] photoredox catalysis with the use of visible light,[7k] and *N*-oxides,[7l] but the search for better methods still continues.[7m,7n] Most of the reported methods are not free from drawbacks such as the use of transition metals with ligands,[7h] harsh reaction conditions,[7j] long reaction times,[7i] chlorinated organic solvents as reaction media,[7l] and expensive reagents.[7k] Consequently, there is a genuine need for the development of new methodologies for *ipso*-hydroxylation of arylboronic acids and its derivatives.

Sodium chlorite ($NaClO_2$), an easily available and inexpensive oxidizing agent, has been extensively used for bleaching and stripping of textiles, pulp, and paper.[8] In addition, its applications have received growing interest of the organic chemistry community in recent years. In organic synthesis, sodium chlorite is frequently used for the Pinnick oxidation of aldehydes,[9] oxidation of allylamines to epoxyamides,[8a] oxidation of alkyl furans to γ-hydroxybutenolides,[10a] epoxidation of olefins,[10b] oxidation of sulfides to sulfoxides,[10c] chlorination of activated arenes[10d] and

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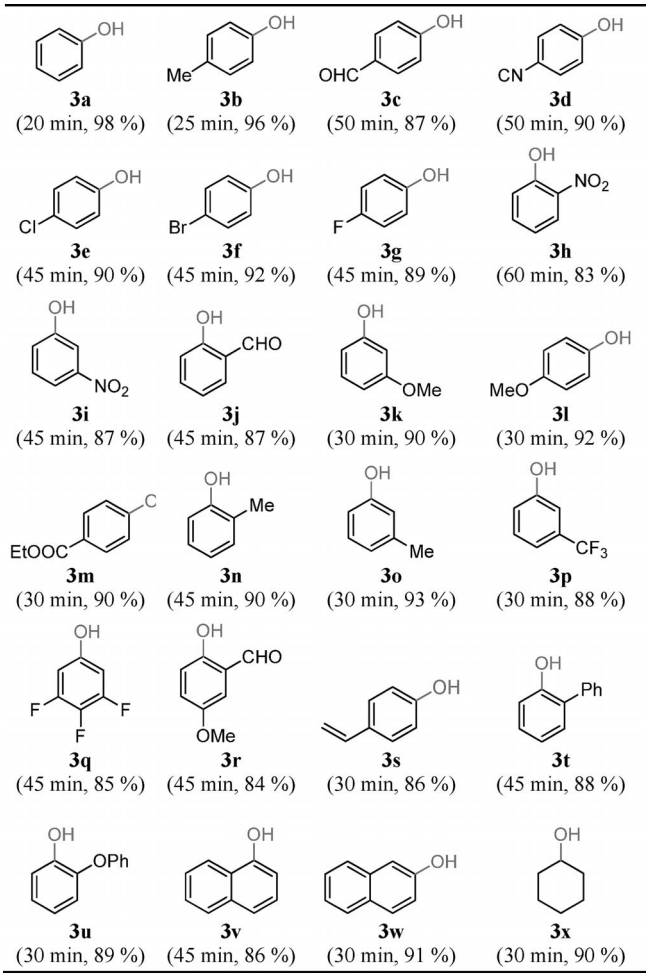
ketones,[10e] oxidation of saturated hydrocarbons,[10f] oxidation of primary alcohols to the corresponding carboxylic acids in the presence of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO),[10g] and the dihydroxylation of olefins with osmium as a catalyst.[10] Nevertheless, to the best of our knowledge, the use of sodium chlorite for the conversion of arylboronic acid into phenol has not yet been reported.

Results and Discussion

In the context of our ongoing interest in the chemistry of organoboron compounds,[11] we report here a novel and simple procedure for the direct conversion of boronic acids into phenols by using $NaClO_2$ as the oxidizing agent in water at room temperature. To understand the versatility and applicability of our protocol, a wide array of substituted arylboronic acids were smoothly converted into their corresponding phenols (Table 1).

Table 1. *ipso*-Hydroxylation of arylboronic acids.[a]

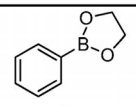
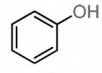
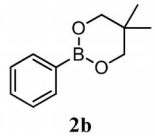
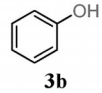
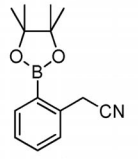
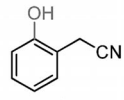
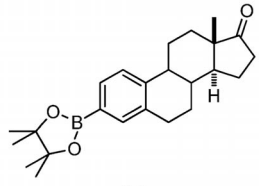
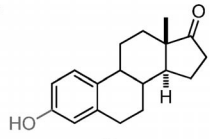


[a] The reaction was carried out with **1** (1 mmol), water (5 mL), and $NaClO_2$ (1.2 mmol) at room temperature.

The reaction of arylboronic acids **1** with sodium chlorite took place under very mild conditions at room temperature; expected products **3** and **4** were afforded in excellent yields. Both electron-rich and electron-poor arylboronic acids afforded the corresponding phenols in excellent yields. However, arylboronic acids bearing electron-poor groups required longer reaction times than arylboronic acids bearing electron-rich groups. The reaction conditions notably showed a great tolerance to a range of functional groups including alkoxy, acetyl, halo, nitrile, and nitro moieties. Sterically hindered arylboronic acids **1h**, **1n**, **1t**, and **1u** gave the desired products in 83–92% yield. Naphthalene-1-boronic acid (**1v**) and naphthalene-2-boronic acid (**1w**) were smoothly oxidized to their corresponding *ipso*-hydroxylated products. Importantly, oxidation-prone substituents such as nitrile (as in **1d**) and vinyl (as in **1s**) groups were well tolerated and oxidized products were not formed.[10b] Remarkably, the aldehyde group (as in **1c** and **1j**) remained intact under the reaction conditions, and Pinnick oxidized products were not formed.[9]

Having established the *ipso*-hydroxylation reaction for a wide range of aromatic and acyclic boronic acid derivatives (i.e., **1a**–**x**), we examined the scope of the *ipso*-hydroxylation of other boronic acid surrogates (Table 2).

Table 2. *ipso*-Hydroxylation of other boronic acid surrogates.[a]

Entry	Substrate	Product	Time [min]	Yield [%]
1	 **2a**	 **3a**	45	92
2	 **2b**	 **3b**	45	90
3	 **2c**	 **4a**	45	91
4	 **2d**	 **4b**	60	88

[a] The reaction was carried out with **1** (1 mmol), water (5 mL), and $NaClO_2$ (1.2 mmol) at room temperature in water.

Under the standard reaction conditions, phenylboronic esters **2a**–**d** afforded phenols **3a**, **3b**, **4a**, **4b** in excellent yields. Boronate derivative **2c** was efficiently converted into the corresponding *ipso*-hydroxylated product without affecting the benzylic nitrile group. Steroidal boronate estrone derivative **2d** afforded estrone **4b** in excellent yield. Requisite starting boronic ester **2d** was easily prepared from the corresponding triflate through a palladium-catalyzed cross-

coupling reaction with pinacolborane.[12] Additionally, the *ipso*-hydroxylation of phenylboronic acid was performed on a gram scale (1.5 g), and the desired phenol was obtained in excellent yield (91%).

A proposed reaction mechanism is depicted in Figure 1. To investigate the role of sodium chlorite as the source of phenolic oxygen, we carried out the oxidation of **1a** independently under anaerobic conditions. To our surprise, *ipso*-hydroxylation reactions under these conditions also afforded desired phenol **3a** in 92% yield. It was assumed that aerial oxygen had no role to play in the oxidation reaction, as the anaerobic conditions showed no difference in the yield and time of the reaction. It is proposed that $NaClO_2$ is the sole oxidant for the conversion of phenylboronic acid into phenol during the oxidation reaction. Nucleophilic attack of $NaClO_2$ on the boronic acid generates intermediate [**I**] (Figure 1, path A). Subsequent migration of the aryl group from boron to oxygen generates boronate ester [**III**]. The ^{-}OCl species generated from intermediate [**I**] reacts with another molecule of phenylboronic acid (Figure 1, path B) to generate intermediate [**II**], which leads to [**III**] with loss of a molecule of NaCl. In the presence of water, boronate ester intermediate [**III**] is hydrolyzed to phenol **3a**. To support our mechanism, we independently attempted the hydroxylation of phenylboronic acid with NaOCl (4% solution), and the desired hydroxylated product phenol was obtained in good yield (65%).[13]

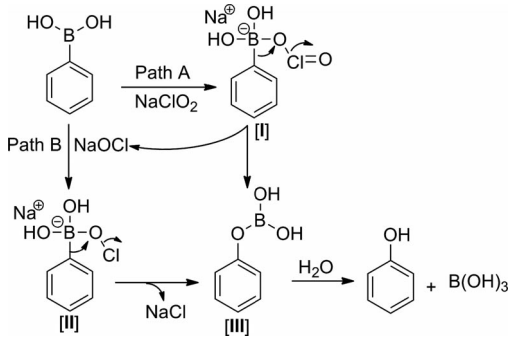


Figure 1. Proposed reaction mechanism and intermediates.

Conclusions

In conclusion, we developed a simple catalyst-free procedure for the *ipso*-hydroxylation of arylboronic acids and their derivatives to phenols by using sodium chlorite as the oxidant. Our method has the advantage of broad functional group compatibility for both electron-rich and electron-poor substituents. In addition, our procedure is amenable to boronate esters. The reaction strategy is facile and clean, as the phenolic products were obtained in pure form and did not require chromatographic purification. Our procedure is operationally simple, practical, inexpensive, and scalable, and it allows *ipso*-hydroxylation of arylboronic acids to substituted phenols with excellent scope under mild conditions.

Experimental Section

General Experimental Procedure for the *ipso*-Hydroxylation of Arylboronic Acid to Phenol: A test tube was charged with phenylboronic acid **1** (1 mmol). Water (5 mL) was then added. Subsequently, sodium chlorite (1.2 mmol) was added into the reaction mixture. The mixture was stirred at room temperature for about 20 min until TLC showed that the starting material had been consumed. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic fraction was dried and concentrated. Phenol **3** was obtained without any chromatographic purification.

Supporting Information (see footnote on the first page of this article): Experimental details, spectroscopic data, copies of the ^{1}H NMR and ^{13}C NMR spectra of all final products

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