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Research Article

An Efficient Synthesis of Phenols via Oxidative Hydroxylation of Arylboronic Acids Using $(NH_4)_2S_2O_8$

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A mild and efficient method for the *ipso*-hydroxylation of arylboronic acids to the corresponding phenols was developed using $(NH_4)_2S_2O_8$ as an oxidizing agent. The reactions were performed under metal-, ligand-, and base-free conditions.

1. Introduction

Phenol and its derivatives are present in numerous natural products (e.g., aromatic steroids, cannabinoids, macrolides, quinines, terpenoids, lignans, and alkaloids) and serve as key synthetic intermediates for the construction of complex structures [1–5]. In medicinal chemistry, they are known to exhibit many pharmacological actions including antitumor, antiviral, antibacterial, cardioprotective, and antimutagenic activities [6–10]. The development of methods for accessing such structural motifs, therefore, remains an area of intensive research. In laboratory-scale synthesis, phenols are routinely prepared through the nucleophilic substitution of an activating aryl halide [11] in a copper-catalyzed transformation of a diazoarene [12] or through the Pd-catalyzed conversion of an aryl halide to a phenol using phosphine ligands [13]. These methods, however, often suffer from several drawbacks, such as poor functional group compatibility, narrow substrate scope, harsh reaction conditions, and difficulties in obtaining the starting materials, which limit their utility and applicability. Phenols have been identified as by-products in many metal-catalyzed reactions of arylboronic acids [14]; however, only a few reports have described methodologies for the hydroxylation of arylboronic acids. Although the oxidation of arylboronic acid is not a popular or economical approach for preparing phenols, it provides access to phenols that may be difficult to obtain by other means [15].

In recent years, arylboronic acid derivatives have emerged as one of the most efficient and powerful synthetic precursors for facile regioselective functional group transformations [16]. They are innocuous (generally nontoxic and stable to heat, air, and moisture) and available in a wide range of structures and often react under mild conditions with good functional group tolerance, making them an interesting and valuable potential precursor for phenols. The oxidation of arylboronic acids and their derivatives to phenols with alkaline hydrogen peroxide was first reported by Ainley and Challenger [17] and was later modified by Kuivila [18] and Simon et al. [19]. Although this transformation is simple and green, when electron-deficient arylboronic acids and sensitive substituents are present, give low yields and alkaline hydrogen peroxide can lead to undesirable side reactions.

In this context, some reports have described the preparation of phenols from arylboronic acid using oxone [20, 21], $Cu(OAc)_2$–H_2O_2 [19], NH_2OH [22], H_2O_2-poly(*N*-vinylpyrrolidone) [23], $CuSO_4$–phenanthroline [24], $CuCl_2$–micellar systems [25], I_2–H_2O_2 [26], photoredox catalysis [27], electrochemical reactions [28], N-oxides [29], Amberlite IR-120–H_2O_2 [30], Al_2O_3–H_2O_2 [31], MCPBA [32], and $NaClO_2$ [33]. Although these methods often provide good yields, in the majority of cases, these strategies have some disadvantages such as harsh reaction conditions, long time reactions, the use of transition metals with ligands or base, chlorinated organic solvents as reaction media, or expensive

reagents. Thus the developments of protocols that are readily accessible, air and moisture stable, inexpensive, and environmentally acceptable and that can promote these reactions under mild reaction are still desirable.

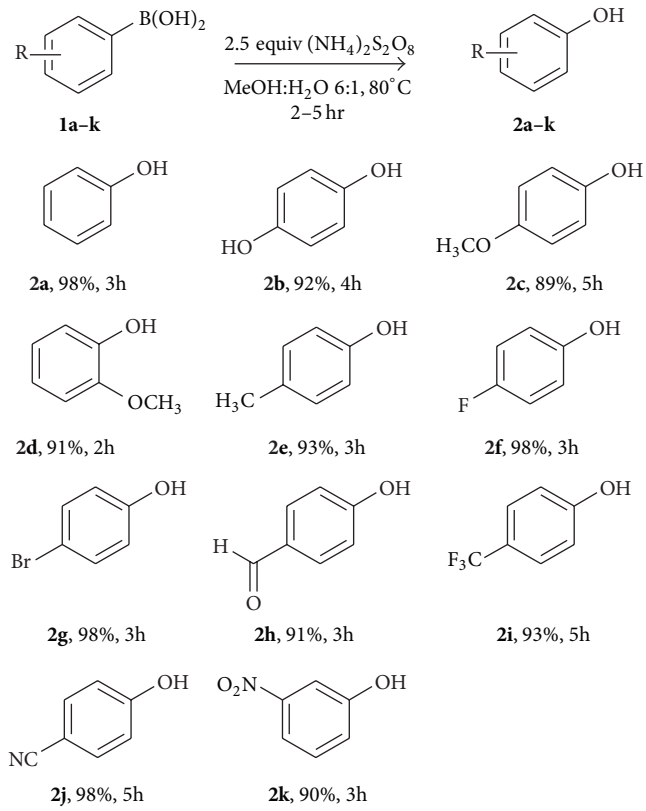
The present study sought to develop an efficient conversion of substituted arylboronic acids to substituted phenols by an oxidative hydroxylation reaction using $(NH_4)_2S_2O_8$ under metal-, ligand-, and base-free conditions. Ammonium peroxodisulfate is an inexpensive easily available reagent, a "green" oxidizer that is widely used in industry for bleaching and waste water treatment. However, only scanty literature is available that describes its applications in organic synthesis. The compound has been used to accomplish certain oxidations of alkenes [34], benzyl alcohols [35], and substituted aromatics [36].

2. Materials and Methods

Arylboronic acids were obtained from Aldrich Chemical Co. Reagents and solvents were of the highest quality available and used as received. Flash chromatography purification was performed on silica gel 60 (230–400 mesh). All products are known compounds and were characterized by comparing the physical and NMR data to published information. NMR spectra were recorded at 200 and 400 MHz, chemical shift in ppm relative to TMS as an internal standard. Microwave heated reactions were performed in a CEM Discover reactor.

2.1. General Procedure for the Hydroxylation of Arylboronic Acid. To a solution of 50 mg arylboronic acid (0.41 mmol, 1.0 equiv.) in 3 cm^3 MeOH : H_2O (6 : 1) was added 2.5 equiv. $NH_4S_2O_8$, and the mixture was stirred at 80°C for the time indicated in Scheme 1. The reaction progress was monitored by TLC, and the reaction was determined to have reached completion when the starting material had been completely consumed. The solvent was evaporated under reduced pressure and extracted with AcOEt. The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the compound was purified by column chromatography using hexane : AcOEt (9 : 1) as an eluent. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and MS and by comparison with the properties of known samples.

2.2. General Procedure for the Hydroxylation of Arylboronic Acid under Microwave Irradiation. To a solution of 50 mg arylboronic acid (0.41 mmol, 1.0 equiv.) in 3 cm^3 MeOH : H_2O (6 : 1) was added 2.5 equiv. $NH_4S_2O_8$, and the mixture was stirred at 105°C and 300 W for 15 min. The solvent was evaporated under reduced pressure and extracted with AcOEt. The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the compound was purified by column chromatography using hexane : AcOEt (9 : 1) as an eluent. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and MS and by comparison to the properties of known samples.



Scheme 1: The hydroxylation reactions of **1a–1k**. Yield of the isolated product. All compounds were characterized by ^{1}H NMR and ^{13}C NMR.

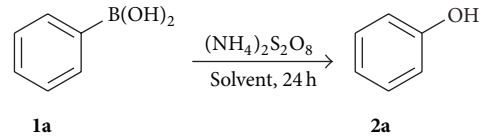


Figure 1

3. Results and Discussion

Our study began by optimizing the reaction conditions. The effectiveness of $(NH_4)_2S_2O_8$ toward oxidative hydroxylation was explored using phenylboronic acid **1a** as a model substrate, Figure 1. Mixtures of **1a** and $(NH_4)_2S_2O_8$ (1.0 equiv.) were prepared in several solvents by stirring at 0°C for 24 h. The phenol **2a** was not obtained at all. In the same reaction at room temperature, only low yields of **2a** were observed. Increasing the reaction temperature to 50°C or 80°C provided a range of yields, although the reaction did not reach completion. As shown in Table 1, the reaction proceeded in both protic and aprotic solvents, and the yield tended to vary with the solvent.

Several test reactions were carried out using different amounts of $(NH_4)_2S_2O_8$ to establish the optimal amount of catalyst required for this transformation. MeOH : H_2O in a 6 : 1 ratio was employed as the solvent. It was found that 2.5 equiv. (Table 2, entry 4) was necessary to achieve the

Table 1: Effects of the solvent and temperature on the hydroxylation of **1a**[a].

Entry	Solvent	Temperature (°C)	**2a** yield[b] (%)
1	Toluene : H_2O 6 : 1	50	23
		80	53
2	Dioxane : H_2O 6 : 1	50	28
		80	47
3	Acetone : H_2O 6 : 1	50	33
		80	52
4	AcCN : H_2O 6 : 1	50	30
		80	45
5	MeOH : H_2O 6 : 1	50	32
		80	65
6	H_2O	50	4
		80	13

[a]Reactions conditions: **1a** (0.41 mmol), $(NH_4)_2S_2O_8$ (1.0 equiv.), solvent 3 mL, and 24 h. [b]Yield determined by ^{1}H NMR.

Table 2: Effects of $(NH_4)_2S_2O_8$ on the hydroxylation of **1a**[a].

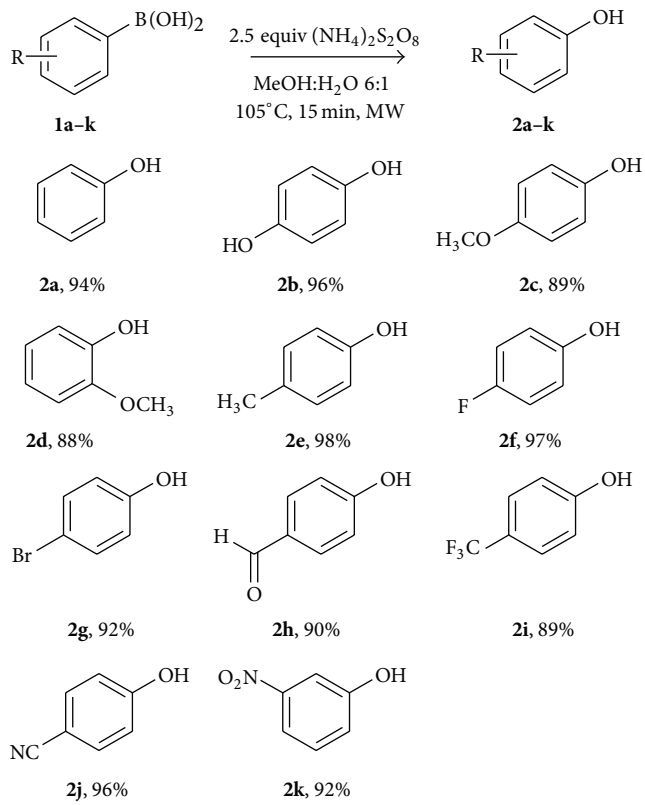
Entry	$(NH_4)_2S_2O_8$ (equiv.)	Time (h)	**2a** yield[b,c] (%)
1	0.0	3	Nr
		10	Nr
		24	Nr
2	1.0	3	39[b,c]
		10	52[b,c]
		24	65[b,c]
3	2.0	3	64[b,c]
		10	79[b,c]
		24	85[b,c]
4	2.5	3	98[d]

[a]Reaction conditions: **1a** (0.41 mmol), MeOH : H_2O 6 : 1 (3 mL), and 80°C. [b]The reaction did not reach completion. [c]Yield determined by ^{1}H NMR of the crude reaction product. [d]Yields obtained after chromatographic purification. Nr: no reaction.

smooth oxidation of 1.0 equiv. of the substrate **1a**. Essentially no product **2a** was obtained from the reaction in the absence of $(NH_4)_2S_2O_8$ (Table 2, entry 1).

The scope and limitations of the current procedure were evaluated by treating a wide array of electronically diverse arylboronic acids with 2.5 equiv. $(NH_4)_2S_2O_8$ in MeOH : H_2O (6 : 1) at 80°C. By using different arylboronic acid **1b–1k**, the method proved to be compatible with a wide range of substrates and **1b–1k** were converted into the corresponding products **2b–2k** in good to excellent yields. In contrast with the traditional nucleophilic substitution of aryl halides, the method preferred to offer the electron-rich phenols easily.

Over the past 25 years, microwave chemistry techniques have been recognized as a powerful method for performing challenging reactions in short amounts of time with a high yield and high purity. We therefore focused on reducing the reaction time using microwave irradiation. Here also, we chose MeOH : H_2O as our reaction medium because of its polarity, which is suitable for microwave heating.



Scheme 2: Hydroxylation reaction of **1a–1k** under microwave irradiation. Reaction conditions: **1a** (0.41 mmol, 1 equiv.), MeOH : H_2O 6 : 1 (3 mL), $(NH_4)_2S_2O_8$ (2.5 equiv.), 105°C, 300 W, and 15 min. Yield of the isolated product. All compounds were characterized by ^{1}H NMR and ^{13}C NMR.

Using the established conditions, we irradiated the diverse arylboronic acid substrates (1 equiv.) in the presence of ammonium peroxodisulfate (2.5 equiv.) in MeOH : H_2O (6 : 1, 3 mL) at 105°C, 300 W for 15 min. The Discover LabMate model reactor from CEM Corporation connected to an IR thermometer for temperature monitoring and control was used. The MW parameters were set at 105°C and 300 W power with a 15 min reaction time, excluding the time taken to reach the temperature ("ramp time"). The "ramp time" was approximately 1 min without the use of the "cooling mode" option. Then the power was zeroed and the irradiation was automatically applied periodically to keep the temperature stable at 105°C for the time of the reaction. Stirring was applied during MW irradiation. The results are summarized in Scheme 2.

4. Conclusions

We developed a mild, efficient, and comparatively cheap method for synthesizing phenols via oxidative hydroxylation of arylboronic acids using $(NH_4)_2S_2O_8$. The reaction was applied to arylboronic acids with either electron-withdrawing or electron-donating substituents. The substrates underwent an *ipso*-hydroxylation reaction in good yields (88–98%). The

reactions were performed under metal-, ligand-, and base-free conditions. This transformation is broadly compatible with a variety of functional groups.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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