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A mild conversion of arylboronic acids and their pinacolyl boronate esters into phenols using hydroxylamine

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Abstract—Hydroxylamine was found to be a mild reagent for conversion of arylboronic acids and their pinacolyl boronate esters into phenols. This procedure works on most arylboronic acids at room temperature, yielding phenols in moderate to good yields, and efficiently on arylboronates also yielding phenols in good yields.

1. Introduction

Phenols serve as synthetic building blocks and intermediates for the construction of important molecules ranging from polymers to pharmaceuticals[1] and due to the importance of their derivatives, much attention has been focused on their synthesis.[2] One of the key features of organoboranes is that they can be prepared containing a wide variety of functional substituents. Boronic acids and esters are mild organic Lewis acids and their reactivity profile, coupled with their stability and ease of handling, make them a particularly attractive class of synthetic intermediates.[3] Although the oxidation of arylboronic acids is not a popular or economical approach for preparing phenols, it gives access to phenols that might be difficult to obtain by other means. It was recently reported that a one-pot C–H borylation/oxidation sequence gives access to *meta*-substituted phenols that would be difficult to obtain by other methods.[4] To the best of our knowledge there are only a few methods described in the literature for the conversion of arylboronic acids into phenols. Treatment of arylboronic acids and esters with alkaline hydrogen peroxide was first reported by Ainley and Challenger[5] and later modified by Petasis and co-workers[6] but when sensitive substituents are present, alkaline hydrogen peroxide can lead to undesirable side reactions. Milder oxidants such as oxone[7] and sodium perborate[8] can also be employed for the oxidation of boronic acid derivatives. However, a new general, mild and easy to handle reagent for conversion of arylboronic acids and esters to phenols is still required.

We were aware of a variety of different *ipso*-substitution reactions of arylboronic acids.[9] Considering the mechanism proposed by Kuivila,[10] Scheme 1, we were interested in using a substitute for hydrogen peroxide with similar structure but different oxidative properties.

Hydroxylamine is cheap and easy to handle as its hydrochloride salt so we considered the reactions of arylboronic acids with hydroxylamine, produced in situ from hydroxylammonium chloride and sodium hydroxide. The results are summarized in Table 1 (entries 12–21). As can be seen from the Table, the corresponding phenols were typically obtained in moderate to good yields. However, in the case of arylboronic acids having strongly electron-withdrawing groups, the yields were lower. Ethanol or water could be used as the solvent. Boronic acids are often best handled as ester derivatives, in which the two hydroxyl groups are masked, and hence are less polar and easier to handle, using boronate esters instead of boronic acids may also influence the efficiency of the reaction.[11] This Letter also describes our efforts to use boronate esters in this reaction and the results are summarized in Table 1 (entries 1–11). As can be seen from the Table, in most cases the products were obtained in good to excellent yields. The best results were obtained with those involving derivatives containing electron-donating groups.

Keywords: Arylboronic acid; Arylboronate ester; Phenol; Hydroxylamine.
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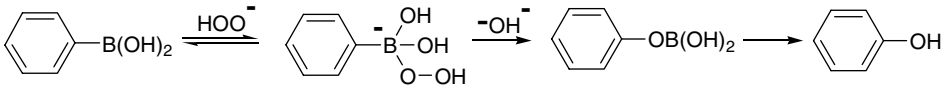
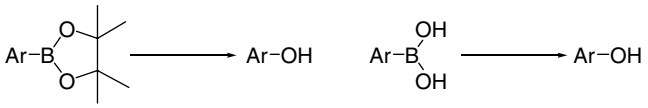


Scheme 1.

Table 1. Conversion of arylboronic acids and esters into phenols using $NH_2OH{\cdot}HCl$:NaOH (1.1 equiv:1.5 equiv and 1.5 equiv:2.0 equiv, respectively) in ethanol at room temperature[a]



1 **2**

Entry	Ar, **1**	Time (h)	Yield (%)	Entry	Ar, **2**	Time (h)	Yield (%)
1	Phenyl, **1a**	23	57	12	Phenyl, **2a**	26	68
2	4-Bromophenyl, **1b**	18	81	13	4-Bromophenyl, **2b**	24	53
3	3,5-Dimethylphenyl, **1c**	18	94	14	3,5-Dimethylphenyl, **2c**	25	82
4	3-Methylphenyl, **1d**	18	92	15	3-Methylphenyl, **2d**	23	86
5	3-Fluorophenyl, **1e**	25	67	16	4-Chlorophenyl, **2e**	48	48
6	4-Chlorophenyl, **1f**	48	63	17	2-Naphthyl, **2f**	26	46
7	2-Naphthyl, **1g**	48	71	18	3-Nitrophenyl, **2g**	48	Trace
8	3-Nitrophenyl, **1h**	48	52	19	4-Fluorophenyl, **2h**	26	32
9	2,4-Dichlorophenyl, **1i**	23	69	20	4-Methoxyphenyl, **2i**	27	91
10	4-Methoxyphenyl, **1j**	48	86	21	4-Acetylphenyl, **2j**	24	—
11	4-Acetylphenyl, **1k**	48	—				

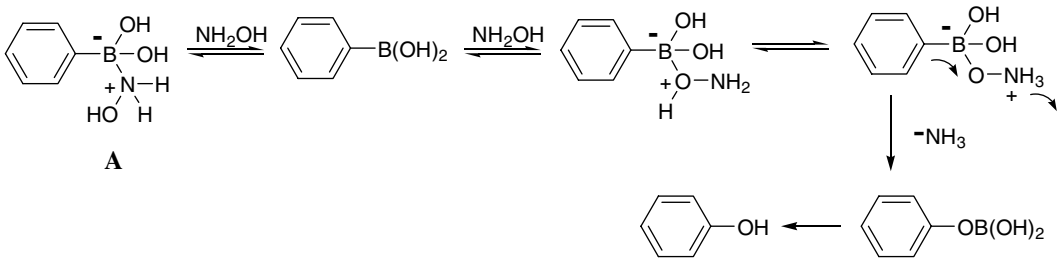
[a] All the products and starting arylboronic esters are known compounds apart from **1e** and **1i**. These were characterized by physical and spectral analysis (see Supplementary data).

To investigate the reaction mechanism, we first considered the source of phenolic oxygen. For this reason, the reactions were conducted in the absence of oxygen, under a nitrogen atmosphere, and in degassed solvent. Under the above mentioned conditions no difference was observed in the yields and times of the reactions. To make sure that only the hydroxylamine oxygen was the source for phenolic oxygen, the reactions were repeated using hydrazinium hydroxide. Under these conditions no phenolic compound was observed. Also, addition of NaOH was necessary and the reactions failed to proceed with hydroxylammonium chloride alone. A mechanistic rationalization is provided in Scheme 2, following the mechanism proposed by Kuivila.[10] Another possibility is that the products arise from addition of the nitrogen of hydroxylamine to boron (**A** in Scheme 2) followed by phenyl migration to the oxygen of hydroxylamine through a four membered TS. This was explored using H_2NOCH_3 in place of hydroxylamine, however, with this reagent the reaction failed to proceed and the expected anisole derivatives were not observed.

In summary, we have successfully carried out the conversion of arylboronic acids and esters into phenols in good yields using hydroxylamine hydrochloride and sodium hydroxide, which is an easy to handle reagent system, under very mild reaction conditions.

2. Typical procedure

To a solution of arylboronic acid (1.0 equiv) or arylboronic ester (1.0 equiv) in ethanol, hydroxylammonium chloride (1.1 equiv or 1.5 equiv) and sodium hydroxide (1.5 equiv or 2.0 equiv) were added and the mixture was stirred at room temperature for 18–48 h. The reaction progress was monitored by TLC. Work-up of the reaction involved evaporating the solvent under reduced pressure, then extraction with dichloromethane. The solvent was removed under vacuum and the product was purified by column chromatography (silica gel, Merck 230–400 mesh) using hexane–ethyl acetate (9:1) as eluent. Formation of the required pinacolyl esters was easily achieved by reaction of the boronic acids with pinacol in ether.[12]



A

Scheme 2.

Acknowledgements

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Supplementary data

Characterization data of **1i** and **1e**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.069.

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