THE EXPEDITIOUS OXIDATION OF ARYLBORONIC ACIDS TO PHENOLS BY TERTIARY BUTYL HYDROPEROXIDE IN GREEN AQUEOUS ETHANOL

Ayaz Mahmood Dar[a]*, Nisar A Dangroo[b], Shafia Mir[a] and Bashir Ahmad Dar[c]

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An efficient protocol for the synthesis of phenols from arylboronic acids has been developed by using t-butyl hydroperoxide (TBHP) as oxidant in water-ethanol as a binary reaction medium. The reaction is metal and additive free and does not require strong basic conditions. The developed protocol has a broad substrate scope and functional group compatibility. Notably the mild conditions, shorter reaction time, good to excellent yields and eco-friendly reaction medium are some important features of the developed method.

* Corresponding Authors
Tel: +91 990695985
E-Mail: ayazchem09@gmail.com
[a] Department of Chemistry Govt. Degree College Kulgam, J&K, India
[b] Department of Chemistry, Govt. Degree College Sopore, J&K, India
[c] Department of Chemistry, National Institute of Technology, Srinagar, J&K, India

INTRODUCTION

Phenols and their derivatives are found in numerous bioactive natural products and serve as well-known precursors for the synthesis of pharmaceuticals and natural product analogs of therapeutic importance.[1] Consequently, the synthesis of phenols has attracted a considerable impetus and numerous methods have been developed over the years. Among these, copper-catalyzed conversion of diazoarenes, benzynes and aromatic nucleophilic substitutions of aryl halides are the main routes for the synthesis of phenols.[2] Some other strategies utilize palladium-based catalysts using phosphine ligands and copper catalyst using non-phosphine ligands at elevated temperature for the conversion of aryl halides into phenols.[3,4] However, these methods involve prefunctionalization–defunctionalization strategies, rely upon the use of hazardous metal catalysts and harsh reaction conditions which limit their utility due to functional group compatibility problems.

An alternative easy accessible route utilizes arylboronic acids/esters for the synthesis of phenols. The harmless nature of arylboronic acids, their thermal, air and moisture stability make them useful and readily available precursors for the synthesis of phenols.[5,6] In this direction, numerous methods are known for arylboronic acid/ester hydroxylation which include $CuSO_4$-phenanthrolin,[7] H_2O_2-poly (N-vinylpyrrolidone),[8] NH_2OH,[9] potassium per-oxy sulfate,[10] H_2O/H_2O_2,[11] I_2/H_2O_2,[12] PEG400/H_2O_2,[13] Cu_2O NPs,[14] m-CPBA/KOH,[15] TBPH/KOH.[16] These strategies, however, have some demerits such as long reaction times.[9,11] use of strong basic conditions[7] and toxic chlorinated organic solvents.[8] Thus, development of more efficient and environmentally benign and mild synthetic procedure for the synthesis of phenols is still desirable. In our previous communication, we report ipso-hydroxylation of phenyl boronic acids.[17] therefore, in continuation of our previous research endeavors for the development of green and more efficient synthetic methods,[18-20] herein we wish to report a rapid, base-free *ipso*-hydroxylation of arylboronic acids to phenols at room temperature in a green binary reaction medium (water-ethanol) and TBHP as an oxidant/catalyst.

EXPERIMENTAL

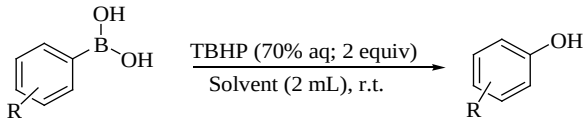
All the melting points were determined on a Kofler apparatus and are uncorrected. The IR spectra were recorded on KBr pellets with Perkin Elmer RXI Spectrophotometer and values are given in cm^{-1}. ^1H and ^{13}C NMR spectra were run in $CDCl_3$ on a JEOL Eclipse (400 MHz) instrument with TMS as internal standard and values are given in ppm (δ). Mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer. Thin layer chromatography (TLC) plates were coated with silica gel G and exposed to iodine vapours to check the homogeneity as well as the progress of reaction. Petroleum ether refers to a fraction of boiling point 60-80 °C. Sodium sulfate (anhydrous) was used as a drying agent. All the chemicals were purchased from Merck India and were used after distillation.

Procedure for ipso-hydroxylation of arylboronic Acid

A reaction flask was charged with 1.0 mmol of arylboronic acid and TBPH (2.0 mmol) in 2 mL of H_2O-C_2H_5OH solvent (1:1) and stirred at room temperature for 8-18 min. The reaction progress and completion was monitored by TLC. After completion, the crude reaction mixture was extracted with ethyl acetate and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by SiO_2 column chromatography (ethyl acetate: hexane) to afford the desired product. The prepared phenols were characterized by comparing the observed spectral data[17] and physical properties.

RESULTS AND DISCUSSION

The base-free *ipso*-hydroxylation of different arylboronic acids in a water-ethanol solvent system in presence of TBHP were completed within a short reaction time of 8-18 min and the phenols were produced in excellent yields. The reaction is shown below (Scheme 1).



Scheme 1. Synthesis of phenols from arylboronic acids.

Table 1. Effect of solvent systems on *ipso*-hydroxylation of arylboronic acid.

Entry	Solvent	Time, min	Yield,[a] %
1	Water	10	85
2	Ethanol	10	77
3	Methanol	12	70
4	EtOAc	15	53
5	DMF	15	67
6	CH_3CN	17	62
7	DMSO	12	62
8	Dioxane	18	55
9	DCM	18	60
10	water-ethanol	9	95
11	water-methanol	10	93
12	water-DMSO	15	88
13	water-CH_3CN	13	85
14	water-DMF	16	69
15	ethanol-DMSO	10	77
16	ethanol-DMF	12	70

[a] Isolated yields after purification using column chromatography.

To set up the optimum reaction conditions, phenylboronic acid (**1**) was chosen as a model substrate to evaluate the proposed hydroxylation of aryl boronic acids. The model reaction containing the mixture of (**1**) (1 mmol) and TBHP (70 % aq; 2.0 mmol) when stirred at room temperature in methanol furnished the corresponding phenol with 70% yield notably in a short reaction time of 12 min. We then began to evaluate a range of different solvents like water, ethanol, methanol, ethyl acetate (EtOAc), dimethylformamide (DMF), acetonitrile (ACN), dimethyl sulphoxide (DMSO) and dichloromethane (DCM) and noticed that the nature of the solvents have significant influence on rate and yield of the reaction (Table 1). Protic solvents such as water, methanol and ethanol proved to be better reaction medium than aprotic solvents with better yields (Table 1, entries 1-3) In aprotic solvents such as EtOAc, DMF, ACN, DMSO and DCM moderate yields were obtained with incomplete substrate conversion (Table 1, entries 4-9). Since protic medium particularly water proved to be a better solvent, we then evaluated different combination of water-organic solvents such as water-ethanol, water-methanol, water-ethanol, water-methanol, water-DMSO, Water-ACN and water-DMF to further improve the reaction conditions in terms of yield and reaction rate (Table 1, entries 10-16). It was observed that binary solvent system improved the reaction yield especially when water is one of the co-solvents (Table 1, entry 14). Finally water-ethanol combination was found to be the medium of choice for the proposed model reaction with 95 % yield of the phenol in a short reaction time of 9 min. Additionally this reaction medium offers to synthesize phenols under environmental friendly conditions due to biodegradable nature of ethanol.

Table 2. The *ipso*-hydroxylation reaction of substituted arylboronic acids.

Entry	Substituent	Time, min	Yield, %
1	R = H	8	94
2	R = *p*-F	10	90
3	R = *m*-CH_3	8	92
4	R = *m*-Br	10	88
5	R = *p*-OCH_3	14	95
6	R = *p*-Br	12	89
7	R = *p*-CF_3	13	91
8	R = 2-butyl	15	94
9	R = *p*-NO_2	10	82
10	R = *p*-C_6F_5	16	88
11	R = *o*-NO_2	18	60
12	R = *o*-Cl	10	89
13	R = *p*-F, *o*-CF_3	18	74
14	R = *o*-F	18	87
15	R = *p*-OCF_3	18	90

With the optimized reaction conditions, we evaluated a wide array of electronically and structurally diverse arylboronic acids to check the substrate scope of the developed protocol and found that a variety of functionalities were tolerated (Table 2). In general, arylboronic acid with either electron-withdrawing or electron-donating substituents like -OMe, -CH_3, -CF_3, -NO_2, OCF_3 and -OH underwent the *ipso*-hydroxylation reaction efficiently with excellent yields (Table 2, entries 2, 3, 5, 7, 9, 11 and 15). Ortho substituted arylboronic acids were found to be less reactive than para substituted arylboronic acids (Table 2, entries 2-6, 7, 9, 11, 12-15). Phenylboronic acids bearing bulky substituents, such as phenyl and butyl groups were also examined, and excellent yields of the phenols were obtained (Table 2, entries 8 and 10). Halogen substituted boronic acids like bromo, chloro and fluoro phenylboronic acids were also rapidly transformed into the corresponding products in excellent yield under the optimized conditions (Table 2, entries 2, 4, 6, 12, 13 and 14). Electron rich arylboronic acids (Table 2, entries 3, 5 and 8) gave satisfactory yields within 8-15 min. The optimized protocol was also found to be compatible with heteroaryl boronic acids furnishing good yields (Table 3).

Table 3. The *ipso*-hydroxylation of naphthyl and heteroaryl boronic acid.

No.	Substrate	Product	Time, min	Yield, %
1	1-Naphthyl boronic acid	1-Naphthol	8	93
2	2-Naphthyl boronic acid	2-Naphthol	15	93
3	2-Furyl boronic acid	2-Hydroxy furan	14	82

Mechanistically the reaction is actually a nucleophilic 1, 2-migration of the aryl group from boron to oxygen[21] which leads to the formation of phenols.

CONCLUSION

In conclusion, a mild and efficient prptpcol for the ipso-hydroxylation of arylboronic acids to the corresponding phenol using TBHP as oxidizing agent in water-ethanol solvent has been developed. The developed method has a broad substrate scope and functional group compatibility. Notably mild reaction conditions, shorter reaction time, metal free conditions, devoid of additives such as ligands or bases and finally a green reaction medium are some of the striking features of this protocol.

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