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PII: S0040-4039(14)01951-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.11.058
Reference: TETL 45442

To appear in: *Tetrahedron Letters*

Received Date: 10 September 2014
Revised Date: 11 November 2014
Accepted Date: 13 November 2014

Please cite this article as: Chatterjee, N., Chowdhury, H., Sneh, K., Goswami, A., Hydroxylation of Aryl- and Alkylboronic Acids/Esters Mediated by Iodobenzene Diacetate – An Avenue for Using Organoboronic Acids/Esters as Nucleophiles for Hydroxylation Reactions, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.11.058

Graphical Abstract

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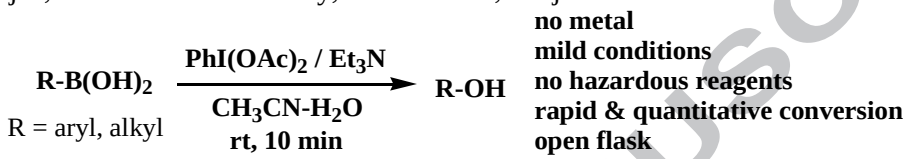

Tetrahedron Letters
journal homepage: www.elsevier.com

Hydroxylation of Aryl- and Alkylboronic Acids/Esters Mediated by Iodobenzene Diacetate – An Avenue for Using Organoboronic Acids/Esters as Nucleophiles for Hydroxylation Reactions

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1. aliphatic alcohols
2. aromatic alcohols
3. hydroxylation
4. hypervalent iodine, DAIB
5. organoboronic acids/esters

ABSTRACT

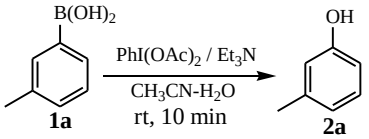
A metal free, mild and highly efficient methodology for *ipso*-hydroxylation of diversely functionalized aryl- and alkylboronic acids/esters mediated by iodobenzene diacetate (DAIB) under ambient temperature has been developed. This protocol is also applicable to *N*-heterocyclic boronic acids and esters. In the course of understanding the mechanism of this protocol, it is anticipated that organoboronic acid/ester, even being an electron demanding moiety, is acting as a nucleophile in presence of DAIB for the hydroxylation reaction.

Phenol is a far-reaching structural unit found in a vast array of natural products and pharmaceuticals and could be present in both monomeric and polymeric forms.[1] Phenol and their derivatives act as key synthetic precursors in constructing aryl ethers and *O*-heterocycles.[2] In medicinal chemistry, they are found to exhibit antitumor, antiviral, antibacterial, cardio-protective, pro-oxidant and antimutagenecity activities.[3] Consequently, efficient access to phenols under mild and eco-friendly conditions, especially in the presence of other functional groups is always of great significance.

The traditional procedures for the syntheses of aromatic alcohols such as activated aromatic nucleophilic substitution methodology and the benzyne protocols have some drawbacks of their own, they normally require harsh conditions to succeed and has problem with the selectivity issues.[4] Over the last few decades, arylboronic acids and their other surrogates have emerged as important moieties in the field of synthetic chemistry.[5] Among the many known metal catalyzed protocols for functional group transformation of arylboronic acids/esters, Cu and Pd catalyzed methods are widely used for hydroxylation of arylboronic acids.[6] However, from pharmaceutical perspective, metal free protocols are always preferred over metal promoted methods. From this point of view, few metal free methodologies for hydroxylation of arylboronic acids have also been achieved.

The classical metal free methodology involves hydrogen peroxide[7] as oxidant in presence of base such as NaOH or Na_2CO_3 and oxone[8] in the absence of base. Recently, Zhu *et al.* has reported aromatic *N*-oxide promoted hydroxylation of arylboronic acids.[9] In addition, other methods involving *m*CPBA,[10] $NaClO_2$-H_2O,[11] HOF-CH_3CN,[12] as oxidants have also been developed. All these methodologies, however, have drawbacks of their own, such as toxicity factors, environmental issues, relatively longer reaction time, non compatibility with C-C double bonds and inaccessibility to alkylboronic acids.

Table 1: Optimization of reaction conditions[a]



1a **2a**

entry	oxidant	base	equiv. of base	time	yield (%) **2a**[b]
1	$PhI(OAc)_2$	no base	-	6 h	trace
2	$PhI(OAc)_2$	Et_3N	1.0	10 min	65
3	**$PhI(OAc)_2$**	**Et_3N**	**2.0**	**10 min**	**97**
4	$PhI(OAc)_2$	Et_3N	2.0	10 min	96[c]
5	$PhI(OCOCF_3)_2$	no base	-	6 h	trace
6	$PhI(OCOCF_3)_2$	Et_3N	1.0	10 min	64
7	$PhI(OCOCF_3)_2$	Et_3N	2.0	10 min	96[d]

[a]reaction conditions: **1a** (0.5 mmol), $PhI(OAc)_2$ (0.75 mmol), Et_3N (1.0 mmol), CH_3CN (5 mL), H_2O (11 µL, 0.6 mmol), rt, 10 min, open flask;

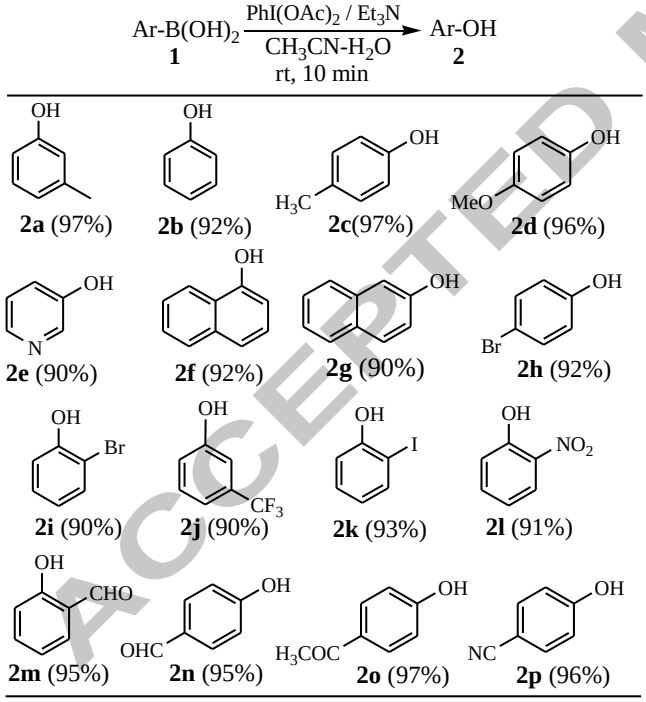
[b]isolated yield;

[c]the reaction was carried out under argon atmosphere;

[d]the reactions gave comparable yields both with PIFA and DAIB, as DAIB is cheaper and more air stable compared to PIFA, former was preferred to be used as an oxidant.

Hypervalent iodine reagent is widely considered as a unique and powerful oxidant with no toxic or environmental issues and is sufficiently stable to heat, air and moisture.[13] However, to the best of our knowledge, no substantial documentation of hypervalent iodine mediated hydroxylation of aryl/alkylboronic acids has been made so far. Herein, we reveal the first iodobenzene diacetate (DAIB) mediated general route for hydroxylation of both aryl- and alkylboronic acids and esters including *N*-heteroaryl ones.

Table 1 summarizes the optimization results of $PhI(OAc)_2$ (DAIB) mediated hydroxylation of arylboronic acids in open air, under ambient temperature. 3-Methylphenlylboronic acid (**1a**) was chosen as the model substrate in optimization of the reaction conditions for obtaining *m*-cresol (**2a**). An initial optimization revealed that in the absence of a base no hydroxylation occurred, irrespective of oxidants and solvents used (entries 1, 5). Triethylamine is found to be the most effective base for smooth progress of this reaction, while other bases such as pyridine and diisopropylamine could not give satisfactory results (not shown in the table). The amount of base plays an important role for quantitative conversion of the organoboronic acids (entries 2, 3, 6, 7).

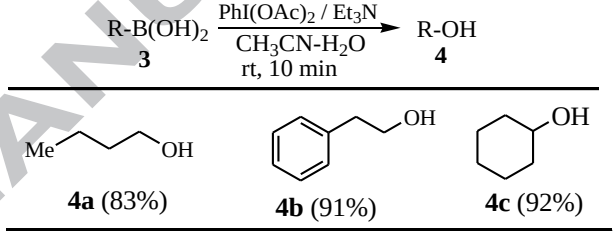


Scheme 1: *ipso*-Hydroxylation of aromatic boronic acids

Increasing the amount of base from 1.0 equiv. to 2.0 equiv. resulted in a dramatic shift in the reaction outcome leading to almost quantitative hydroxylation (entries 2-3, 6-7). In the course of optimization of oxidant, it was noticed that the reaction goes equally well with bis(trifluoroacetoxy)iodo-benzene (PIFA) (entries 6, 7). However, DAIB being cheaper and relatively more air-stable compared to PIFA, the former was chosen as a suitable oxidant for this methodology. It is important to mention that the reaction can also proceed quantitatively under an inert environment (entry 4), clearly demonstrating no involvement of molecular oxygen in the aforesaid hydroxylation process.

Having optimized the reaction conditions, we subsequently explored the substrate scope of the hydroxylation methodology and the results are summarized in Scheme 1. Successful hydroxylations of diversely substituted arylboronic acids exhibit excellent compatibility towards various functional groups (*e.g.* halide, nitro, aldehyde, keto and nitrile). The smooth hydroxylations of the *ortho*-substituted arylboronic acids to corresponding aromatic alcohols (**2k**, **2l**, **2m**) clearly indicate that steric effect has no significant role in the reaction outcome. It is noticed that arylboronic acids having electron donating and withdrawing groups show similar reactivity towards hydroxylation.

It is important to mention that arylboronic acids with oxidation sensitive functional group such as aldehydes (**2m**, **2n**) tolerate the reaction conditions without suffering over-oxidation. *N*-Heterocyclic boronic acid can also be applied for hydroxylation to 3-hydroxy pyridine (**2e**) by this protocol. Interestingly, halide substituted arylboronic acids can be converted to corresponding halo- substituted alcohols (**2h**, **2i**, **2k**), which are precursors of further functionalization.

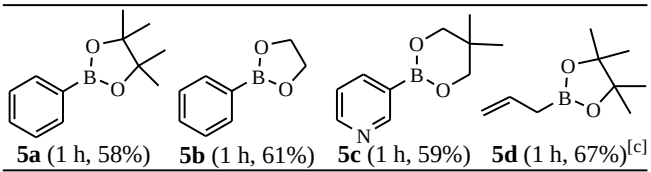


reaction conditions: **3** (2.0 mmol), $PhI(OAc)_2$ (3.0 mmol), Et_3N (4.0 mmol), CH_3CN (5 mL), H_2O (44 µL, 2.4 mmol), rt, 10 min, open flask;

Scheme 2: *ipso*-Hydroxylation of alkylboronic acids

Encouraged by these results, the protocol was applied to alkylboronic acids to obtain aliphatic alcohols (Scheme 2). In general, aliphatic alcohols, especially primary alcohols are hard to synthesize through oxidative methods as they are prone to get over-oxidized easily.[14] Interestingly, the newly developed protocol did not exhibit such problem. This protocol, in a similar way to arylboronic acids, goes equally well with alkylboronic acids. Excellent yields were obtained for both primary (**4a**, **4b**) and secondary alcohols (**4c).**

Remarkably, not only the aromatic/aliphatic boronic acids, but other alkyl/arylboronates also were found suitable for hydroxylation in this method (Figure 1). However, unlike aryl/alkylboronic acids, the reactions with the organoboronates were relatively sluggish with moderate yields. It should be indicated that reaction did not go to completion either at room temperature or on heating at 40 ^{0}C for 4 h. In this context, it is to be mentioned that this methodology is found to be compatible with the olefinic moiety without causing any oxidation to the C-C double bond of **5d**.

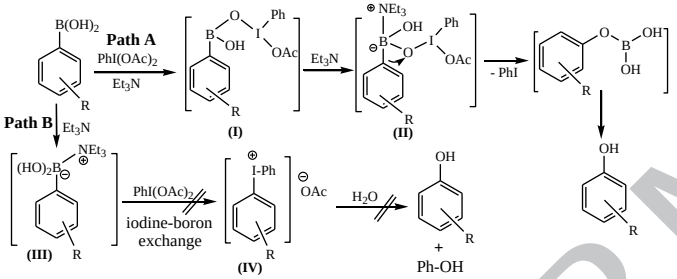


[a]reaction conditions: organoboron compound **5** (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), Et_3N (1.0 mmol), CH_3CN (5 mL), H_2O (11 µL, 0.6 mmol), rt, 1 h, open flask; [b]the reaction did not go to completion in any of the cases even on heating at 40 ^{0}C for 4 h; [c]the reaction with **5d** was carried out in 2.0 mmol scale.

Figure 1: *ipso*-Hydroxylation of other boronic acid surrogates[a,b]

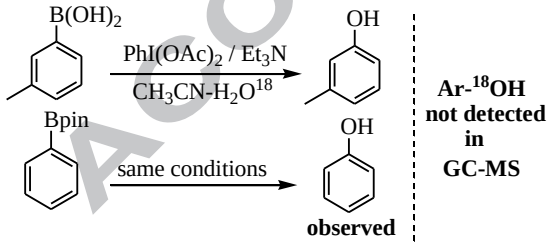
A probable mechanistic pathway is shown in scheme 3. Quantitative hydroxylation of the arylboronic acid under inert environment rules out the involvement of molecular oxygen in the oxidation procedure. Therefore, two pathways can be proposed for this type of hydroxylation reaction. In pathway A, nucleophilic attack of the organoboron specie to DAIB took place to produce another meta-stable hypervalent iodine species (**I**), which in presence of Et_3N transformed to the tetra coordinated boron compound (**II**). The subsequent intra-molecular [1,2] aryl shift of compound (**II**) results in formation of the desired phenol. Similarly, it can be mentioned that in the case of organoboronic esters, they are first converting to the corresponding boronic acids in presence of DAIB prior to the hydroxylation reactions.[15] However, in the presence of a base the conversion of boronic esters to acids is not getting complete.

The second possibility (pathway B) is that the arylboronic acid is first converted to tetra coordinated species (**III**) with Et_3N and subsequently underwent iodine-boron exchange[16] to produce iodonium salt (**IV**); which on further reaction with water could transform to phenol and expected aromatic alcohol. However, under these circumstances, formation of phenol was not observed along with the desired aromatic alcohols.



Scheme 3: Plausible mechanistic pathway

In order to establish which pathway is operating in a more accurate manner, two separate reactions were performed with *m*- tolylboronic acid and phenylboronic acid pinacol ester in anhydrous acetonitrile in presence of 6.0 equiv. of H_2O^{18} (Scheme 4). In neither of the cases, aromatic alcohol containing isotopic oxygen (Ar-^{18}OH) was traced in GC-MS. Therefore, it could be concluded that reaction proceeds through nucleophilic attack of the organoboronic species to DAIB, followed by intra-molecular [1,2] aryl migration.



Scheme 4: H_2O^{18} -isotope labeling experiment

In conclusion, we have developed the first general route, mediated by DAIB to synthesize diversely functionalized aromatic and aliphatic alcohols from aryl/alkylboronic acids/esters. It is an open flask reaction completing in less than 10 minutes at room temperature. A notable feature of this protocol is that among the two electron demanding species (arylboronic acid and $PhI(OAc)_2$) involved in the reaction, arylboronic acid in spite of being an electron deficient compound, can be predicted to act as a nucleophile.[17] To the best of our knowledge, it is a unique study in the field of hydroxylation of aryl/alkylboronic acids and their other surrogates. Further investigations in the direction of detailed mechanistic studies and the scope of using hypervalent iodine as catalyst for the hydroxylation reaction are currently underway.

Acknowledgments

We would like to express our gratitude to Professor Sentaro Okamoto, Kanagawa University, Yokohama, Japan, for his valuable feedback in preparing the manuscript. We are grateful to CSIR, New Delhi, India for their generous financial support and IIT Ropar for infrastructural facilities. NC and HC would like to thank IIT Ropar for their fellowship.

Supplementary Material

Supplementary data (general procedure for synthesis, characterization data and copies of ^{1}H and ^{13}C NMR spectra of all the compounds) associated with this article can be found, in the online version, at

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