Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c5ob00337g

Received 18th February 2015,
Accepted 13th March 2015

DOI: 10.1039/c5ob00337g

www.rsc.org/obc

A novel transition metal free [bis-(trifluoroacetoxy)-iodo]benzene (PIFA) mediated oxidative *ipso* nitration of organoboronic acids†

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A mild, convenient and transition metal free methodology for oxidative *ipso* nitration of diversely functionalized organoboronic acids, including heteroaryl- and alkylboronic acids, has been developed at ambient temperature using a combination of [bis-(trifluoroacetoxy)]iodobenzene (PIFA) – *N*-bromosuccinimide (NBS) and sodium nitrite as the nitro source. It is anticipated that the reaction proceeds through *in situ* generation of NO_2 and O-centred organoboronic acid radicals followed by the formation of an O–N bond *via* combination of the said radicals. Finally transfer of the NO_2 group to the aryl moiety occurs through 1,3-aryl migration to provide the nitroarenes.

Over the last century nitroarenes have been considered as versatile structural motifs because of their wide range of applications in pharmaceuticals, pesticides, dyes, agrochemicals and polymers (Fig. 1).[1] They also play a vital role in the development of mechanistic concepts.[2,3] Therefore, developing novel methodologies to access variedly functionalized nitroarenes always have a great research importance.

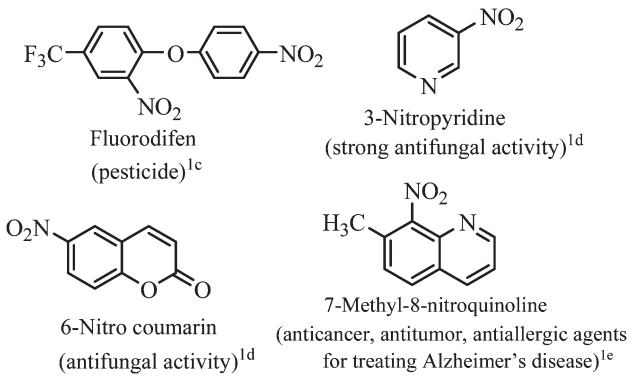

Fig. 1 Selected biologically active nitro compounds.

The traditional approach of synthesizing nitroarenes is the direct electrophilic nitration of the arenes. Such electrophilic nitration methods usually require the use of excess mixed acids (c.HNO_3–c.H_2SO_4) or a mixture of conc. HNO_3 and dinitrogen pentoxide as the nitrating agent.[3] However, these approaches suffer from several drawbacks, such as limited substrate scope, poor regioselectivity and formation of various undesired by-products.[4] To overcome these difficulties, some notable efforts have been made towards regioselective syntheses of nitroarenes under mild reaction conditions.[5]

Recently, our group has reported a novel methodology for *ipso* hydroxylation of organoboronic acids/esters mediated by $PhI(OAc)_2$.[6] Likewise, *ipso* nitration of the arylboronic acids can be considered as a useful alternative methodology for synthesizing nitroarenes as it completely circumvents the regioselectivity problem and very often can be performed under mild reaction conditions. First transition metal free *ipso* nitration of arylboronic acids was achieved using a relatively strong oxidant the Crivello reagent.[7] Later, several other transition metal free methodologies for *ipso* nitration of the arylboronic acids have been developed using a chlorotrimethylsilane–nitrate salt,[8] *tert*-butyl nitrite (TBN),[9] and bismuth nitrate–perdisulphate[10] (Scheme 1). However, despite their noticeable advancements, these protocols suffer from long reaction time, higher reaction temperature and the use of hazardous reagents. Furthermore, it could also be mentioned that none of the literature so far reported, has documented the *ipso* nitration of the alkylboronic acids and very few have reported the *ipso* nitration with heteroaryl boronic compounds.

Over the last two decades, organic hypervalent iodine has been widely utilized as a green and potential oxidant in various fields of organic synthesis including functionalization of different organic compounds,[11] but much less attention has been devoted to generate nitro radicals through 1 electron oxidation of simple sodium or potassium nitrite[12] utilizing

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ob00337g

Previous work:

$$\text{R-B(OH)}_2 \xrightarrow{\text{reaction conditions}} \text{R-NO}_2$$

reaction conditions

1. TMSCl-MNO_3 (M = Ag, NH_4); ***RT, 30-72 h*; R = aryl; ref.8**
2. *t*-BuONO; ***80 ^{0}C, 16 h*; R = aryl; ref.9**
3. $Bi(NO_3)_3$ - $K_2S_2O_8$; ***80 ^{0}C, 12 h*; R = aryl, heteroaryl; ref.10**

This work:

$$\text{R-B(OH)}_2 \xrightarrow{\text{reaction conditions}} \text{R-NO}_2$$

reaction conditions

PIFA-NBS-$NaNO_2$; ***RT, 3 h;* R = aryl, heteroaryl, alkyl**

Scheme 1 *ipso* Nitration of organoboronic acids under various reaction conditions.

the hypervalent iodine reagents. Recently, Kloeckner *et al.* reported an efficient [bis-(trifluoroacetoxy)]iodobenzene (PIFA) mediated generation of a nitro radical through 1 electron oxidation from $NaNO_2$.[13]

Taking this lead, we herein report a highly efficient PIFA mediated oxidative regioselective nitration of aryl-, alkyl- and heteroarylboronic acids which are expected to have biological importance. This is not only an efficient alternative to other *ipso* nitrations of the organoboronic acids but also to the best of our knowledge, the first example of using PIFA–NBS–$NaNO_2$ combination to generate nitroarenes under transition metal free conditions.

To start the initial investigation, 3-methylphenylboronic acid (**1b**) was chosen as the model substrate for obtaining 3-nitrotoluene (**2b**). An initial screening of the organoiodine(III) species revealed that the reagents **I**, **II** and **III** failed to provide the desired nitroarenes irrespective of the presence or absence of any additive, whereas, with **IV**, the *ipso* nitration of the organoboronic acids was successfully achieved in the presence of NBS as an additive (Fig. 2).

Table 1 summarizes the optimization results of PIFA mediated *ipso* nitration of organoboronic acids in open air and at ambient temperature.

It was observed that, for the reaction to be successful, the presence of both PIFA and NBS are essential; in the absence of any one of the reagents, the reaction could not be made possible (entries 1–3). The presence of an additive (NBS) is not only

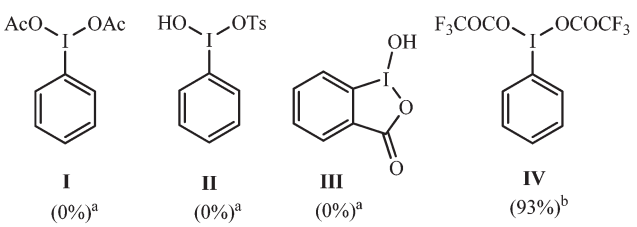
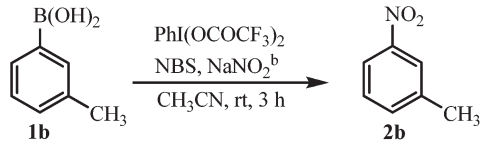


Fig. 2 Different organoiodine(III) reagents employed. [a] No nitration took place with these reagents. [b] Isolated yield.

Table 1 Optimization of reaction conditions[a]



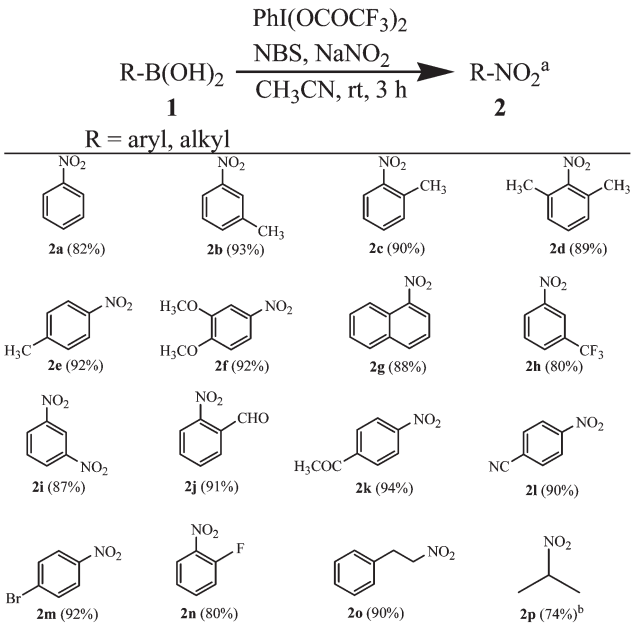
Entry	Eq. of PIFA	Additive	Eq. of the additive	Solvent	Yield[c] (%)
1	2.0	—	—	CH_3CN	n.r[d]
2	4.0	—	—	CH_3CN	n.r[d]
3	—	NBS	2.1	CH_3CN	n.r[e]
4	2.0	NBS	1.1	CH_3CN	52
5	3.0	NBS	1.1	CH_3CN	64
6	3.0	NBS	2.1	CH_3CN	93[f]
7	3.0	NBS	2.1	CH_3CN	92[g]
8	3.0	NBS	2.1	CH_2Cl_2	76

[a] Optimized reaction conditions: **1a** (0.5 mmol, 1.0 eq.), $PhI(OCOCF_3)_2$ (1.5 mmol, 3.0 eq.), $NaNO_2$ (1.5 mmol, 3.0 eq.), NBS (1.05 mmol, 2.1 eq.), CH_3CN (5 mL), rt, 3 h, open air. [b] All optimization reactions were carried out with 3.0 equiv. of $NaNO_2$. [c] Isolated yield. [d] No nitration took place either by stirring the reaction mixture for 24 h at room temperature or on heating at 60 °C for 6 h. [e] No nitration was observed either by stirring the reaction mixture for 24 h at room temperature or on heating at 60 °C for 6 h, however, bromination took place on heating the mixture at 60 °C for 6 h. [f] These reaction conditions were taken as optimized reaction conditions. [g] The reaction was carried out under an argon atmosphere.

essential for nitration to happen but also the amount of the additive is important for better conversion of the organoboronic acids to the nitroarenes (entries 1–6). Keeping the amount of NBS fixed (1.1 eq.), increase in the amount of PIFA from 2.0 eq. to 3.0 eq. enhances the yield of the reaction a bit (entries 4 and 5) while increasing the amount of NBS from 1.1 eq. to 2.1 eq. (PIFA 3.0 eq.) resulted in almost quantitative nitration of the *m*-tolylboronic acid (entries 5 and 6). However, changing the solvent from acetonitrile to dichloromethane resulted in a comparatively lower yield probably owing to the lower solubility of $NaNO_2$ in dichloromethane (entry 8). In this context it could be mentioned that performing the reaction in an inert environment did not change the reaction outcome by any extent (entry 7).

Having optimized the reaction conditions, the investigations were conducted in other substrates in order to outline the substrate scope of this PIFA mediated nitration methodology and the results are summarized in Scheme 2.

Successful nitrations of diversely substituted arylboronic acids demonstrated the excellent functional group (*e.g.* halide, nitro, aldehyde, keto and nitrile) compatibility of the protocol developed in the present work. The nitrations of the *ortho*-substituted arylboronic acids to the corresponding nitroarenes (**2c**, **2d**, **2j** and **2n**) indicated that the steric effect plays a negligible role in the reaction outcome. It is noteworthy that the nitration process developed herein works equally well with arylboronic acids, having either an electron donating or withdrawing group. It is important to mention that arylboronic acids with an oxidation sensitive functional group such as



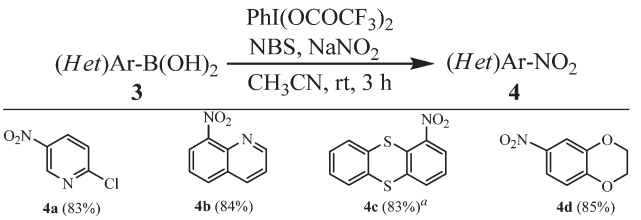
Scheme 2 PIFA mediated *ipso*-nitration of aryl- and alkylboronic acids. [a] Reaction conditions: **1** (0.5 mmol), $PhI(OCOCF_3)_2$ (1.5 mmol), $NaNO_2$ (1.5 mmol), NBS (1.05 mmol), CH_3CN (5 mL), rt, 3 h, open air. [b] The reaction with **1p** was carried out on the 2.0 mmol scale.

aldehyde (**2j**) also endured the reaction conditions employed, without undergoing over-oxidation. The smooth transformation of halide-substituted arylboronic acids to the corresponding halo substituted nitroarenes (**2m** and **2n**), synthons for further functionalization, makes this protocol further versatile.

Encouraged by these results, the alkylboronic acids were also employed for nitration reactions to judge the spectrum of this methodology (Scheme 2). Surprisingly, there is no documentation so far on the synthesis of nitroalkanes through *ipso* substitution of the alkylboronic acids/esters. Greatly, through this newly developed protocol, both primary and secondary nitroalkanes (**2o** and **2p**) were successfully synthesized in high yields. On the other hand, organoboronates could not be transformed to their corresponding nitro compounds through this protocol.

Equally stimulating was the observation that the methodology developed herein, can conveniently nitrate the heteroarylboronic acids in excellent yields, which were otherwise in general hard to achieve (Scheme 3). However, compound **4c** was always obtained with an inseparable impurity associated with it.

There could be several possible mechanistic rationales for this regioselective nitration of the organoboronic acids. As it is known that PIFA reacts with $NaNO_2$ to generate the nitro radical,[12,13] the choice of NBS was made with this consideration that if the combination of PIFA–NBS, with arylboronic acids could generate an aryl radical, then these two radicals may combine to provide nitroarenes in a single pot.



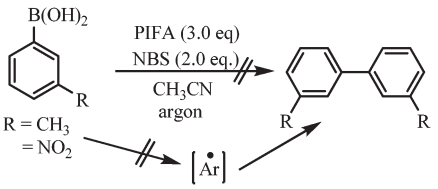
Scheme 3 PIFA mediated *ipso* nitration of heteroarylboronic acids. Reaction conditions: **3** (0.5 mmol), $PhI(OCOCF_3)_2$ (1.5 mmol), $NaNO_2$ (1.5 mmol), NBS (1.05 mmol), CH_3CN (5 mL), rt, 3 h, open air. [a] The reported yield is along with the impurity associated with the compound.

The radical scavenging experiment with TEMPO confirms the radical mechanistic pathway of the nitration reactions presented in this work.[14] On the other side, the reaction between arylboronic acids and PIFA–NBS (Scheme 4) did not afford any biaryl compounds which clearly suggests that the aryl radical is not getting formed during the course of the reaction. Hence the combination of aryl radical and nitro radical to generate nitroarenes might not be the probable mechanism.

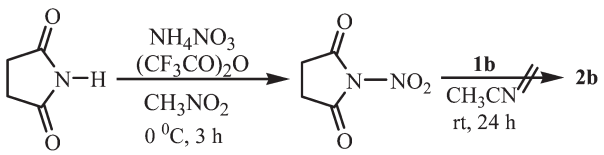
Another possibility could be such that in the presence of PIFA, NBS could readily react with the nitro radical to form *N*-nitrosuccinimide which then reacts with arylboronic acids in the same fashion as proposed by Petasis *et al.* for the bromination of organoboronic acids/esters by NBS.[15]

However, the reaction between *m*-tolylboronic acid (**1b**) and *N*-nitrosuccinimide, synthesized separately following the reported literature procedure,[16] did not afford the corresponding *m*-nitrotoluene (**2b**) (Scheme 5). Also we did not observe the formation of *N*-nitrosuccinimide in GCMS when we performed a separate reaction between NBS and $NaNO_2$ in the presence of PIFA.

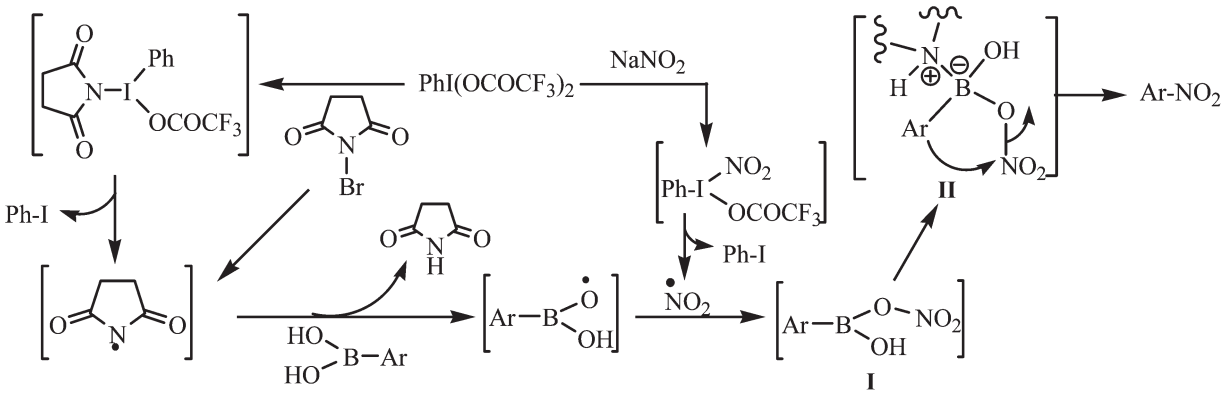
As the reaction proceeds through the radical pathway (already confirmed through the TEMPO experiment) and the reaction occurs at ambient temperature which is much faster



Scheme 4 Attempted synthesis of biphenyl derivatives.



Scheme 5 Synthesis of *N*-nitrosuccinimide and its reaction with **1b**.



Scheme 6 Proposed reaction mechanism.

compared to other *ipso* nitrations, an intramolecular nitro transfer along with a radical pathway seems logical for the reaction to proceed.

Based on these experimental facts and reasoning, it could be proposed that organoboronic acids in the presence of NBS and PIFA generate O-centred radicals which react readily with the nitro radical, generated through one electron oxidation of $NaNO_2$ in the presence of PIFA, to form the metastable species **I**. Finally the nitroarenes are produced *via* nitro transfer to the aryl moiety through 1,3-aryl migration from the tetra-coordinated 'ate' species **II** which is most probably formed from **I** through coordination by the succinimide (Scheme 6).

In conclusion, we have developed a novel method for *ipso* nitration of organoboronic acids using a combination of PIFA–NBS and $NaNO_2$. The method is applicable for aryl-, heteroaryl-, and alkylboronic acids and provides nitro compounds at ambient temperature in a significantly less reaction time exhibiting a wide range of functional group tolerance. In this context, it could be mentioned that the chemistry associated with the reaction pathway of this nitration reaction could be utilized in future for different functional group transformations of the organoboronic acids. The simplicity, high efficiency, use of easily available inexpensive reagents and also the chemistry associated with it are the salient features of this method.

Acknowledgements

We are grateful to CSIR, New Delhi, India for their generous financial support and IIT Ropar for infrastructural facilities. NC and DB would like to thank IIT Ropar and UGC, New Delhi, respectively, for their fellowship.

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