

ipso-Nitration of Arylboronic Acids with Bismuth Nitrate and Perdisulfate

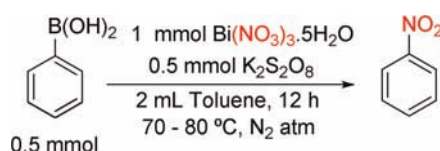
Srimanta Manna, Soham Maity, Sujoy Rana, Soumitra Agasti, and Debabrata Maiti*

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai, 400076, India

dmaiti@chem.iitb.ac.in

Received February 9, 2012

ABSTRACT



An efficient and one pot synthetic method of *ipso*-nitration of arylboronic acids has been developed. The high efficiency, general applicability, and broader substrate scope including heterocycles and functional groups make this method advantageous. Due to its simplicity, we expect to find application of this method in synthesis.

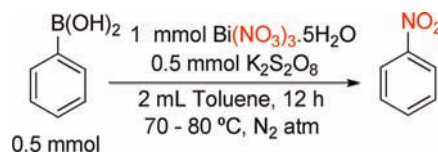
Nitration of aromatic compounds is one of the most widely studied reactions in synthetic chemistry as nitroaromatics are important intermediates for the generation of dyes, plastics, and pharmaceuticals.¹ Commonly nitration is done by a strongly oxidizing mixed acid (HNO₃/H₂SO₄) or with dinitrogen pentoxide, and consequently these methods suffer from regioselectivity and functional group compatibility issues. In this context, nitration of arylboronic acid by *ipso*-substitution² can be considered an efficient method as it circumvents the regioselectivity problem. Arylboronic acids have found applications as synthetic precursors in methods such as Suzuki couplings and Petasis reactions.³ Also hydroxylation⁴ and halogenations^{5–11} have been carried out from an arylboronic acid recently.

The first *ipso*-nitration from an arylboronic acid was reported using a relatively powerful Crivello reagent,¹² and later on a modified protocol was reported using chlorotrimethylsilane–nitrate salt.^{13,14} Nitroaromatics were also prepared from aryl iodides using a copper catalyst involving an Ullmann type reaction.¹⁵ More recently *ipso*-nitration has been reported by using *tert*-butyl nitrite as the nitrating agent.¹⁶ However, these reports suffer from a poor substrate scope.

Further, no example of heterocyclic nitro compounds was found in these reports.^{12–17} In this context, determining an efficient, experimentally simple, and economical nitration method with a broader substrate scope remains a challenging scientific task. Notably conversion of aryl chlorides, triflates, and nonaflates to the corresponding nitro compounds has been reported by using a Pd catalyst.^{14,18}

- (1) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: 2001
- (2) Perrin, C. L.; Skinner, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 3389.
- (3) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
- (4) Prakash, G. K. S.; Chacko, S.; Panja, C.; Thomas, T. E.; Gurung, L.; Rasul, G.; Mathew, T.; Olah, G. A. *Adv. Synth. Catal.* **2009**, *351*, 1567.
- (5) Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141.
- (6) Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2011**, *76*, 7195.
- (7) Wu, H.; Hynes, J. *Org. Lett.* **2010**, *12*, 1192.
- (8) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993.
- (9) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P. P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793.
- (10) Zhang, G. Y.; Lv, G. L.; Li, L. P.; Chen, F.; Cheng, J. *Tetrahedron Lett.* **2011**, *52*, 1993.
- (11) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860.

Scheme 1. *ipso*-Nitration of Arylboronic Acid by Bi(NO₃)₃·5H₂O and Perdisulfate

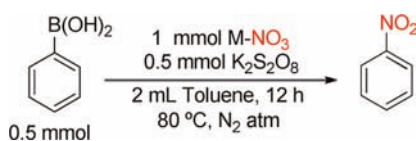


- (12) Salzbrunn, S.; Simon, J.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, 1485.

Herein, we report a simple and convenient method for the conversion of arylboronic acid to nitroarenes using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{S}_2\text{O}_8$ as the nitrating agent (Scheme 1). Bismuth reagents have been extensively used in synthetic chemistry due to their low toxicity and ready availability.¹⁹ Aromatic nitro compounds possessing a variety of electron-donating and -withdrawing functional groups can be synthesized following this protocol. Moreover, the present method showed that some heterocyclic nitro compounds could also be generated in good yield.

We began our *ipso*-nitration protocol by studying the reaction of phenylboronic acid with different commercially available nitrate sources (Table 1).²⁰

Table 1. Effect of Different Nitrate Salts in the *ipso*-Nitration of Phenylboronic Acid



entry	nitrate source	temp (°C)	GC yield (%)
1	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$	80	100
2	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$	70	94
3	AgNO_3	100	62
4	$\text{Cd}(\text{NO}_3)_2$	100	51
5	$\text{Mg}(\text{NO}_3)_2$	100	38
6	$\text{NH}_4\text{Ce}(\text{NO}_3)_4$	100	33
7	$\text{Pb}(\text{NO}_3)_2$	80	1
8	NaNO_3	100	1
9	NaNO_2	80	1
10	AgNO_2	80	1

Using $\text{Cd}(\text{NO}_3)_2$ at 100 °C, nitrobenzene was generated in 51% yield after 12 h, while a relatively better result was obtained with AgNO_3 under the same reaction conditions (Table 1). Subsequently, the best result was achieved with 1 mmol of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ at 80 °C (Table 1, entry 1). Later, it was found that an increase in the amount of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ had some detrimental effect, resulting in a lower yield of the nitro product. Other nitrate sources such as NaNO_3 or $\text{Pb}(\text{NO}_3)_2$ and nitrite sources such as NaNO_2 or AgNO_2 failed to give the nitro product.

(13) Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205.

(14) Prakash, G. K. S.; Mathew, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1726.

(15) Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715.

(16) Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 12462.

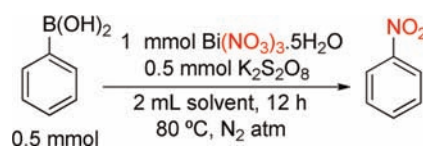
(17) Yang, H. J.; Li, Y.; Jiang, M.; Wang, J. M.; Fu, H. *Chem.—Eur. J.* **2011**, *17*, 5652.

(18) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898.

(19) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373.

(20) See Supporting Information.

Table 2. *ipso*-Nitration of Phenylboronic Acid with Different Solvents



entry	solvent	temp (°C)	GC yield (%)
1	toluene	80	100
2	toluene	100	62
3	<i>o</i> -xylene	80	100
4	benzene	80	90
5	trifluorotoluene	80	70
6	$\text{ClCH}_2\text{CH}_2\text{Cl}$	70	70
7	cyclohexane	60	51
8	DMSO	50	15
9	acetone	40	15
10	DMF	110	1
11	dioxane	90	1

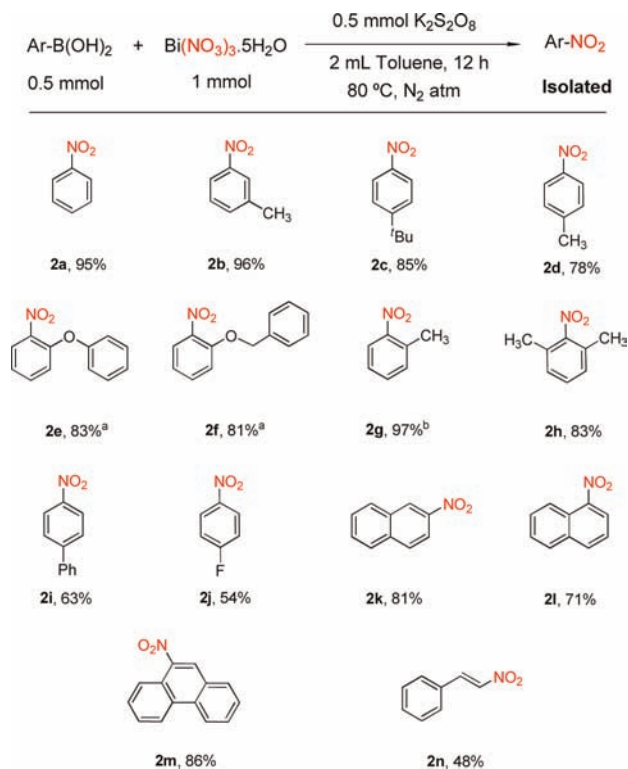
Nonpolar solvents, including toluene and *o*-xylene, were found to give the best results at 80 °C (Table 2, entries 1 and 3, respectively). However, temperatures higher than 80 °C led to lower conversion due to increased protodeboronation reactions.²⁰ While trifluorotoluene and benzene were considerably good solvents, giving 70% and 90% yields of the desired nitro product, respectively, *ipso*-nitration was not observed with dioxane and DMF. Other polar solvents such as acetone and DMSO produced little nitro product. The choice of solvent thus has been restricted to relatively nonpolar hydrocarbon solvents, among which toluene was chosen as the most suitable solvent. While studying the substrate scope we have realized that benzene can also be used as a useful solvent in some *ipso*-nitration reactions.

Having fully optimized reaction conditions in hand, we next set out to explore the substrate scope of the $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}/\text{K}_2\text{S}_2\text{O}_8$ catalyzed transformation of arylboronic acids to nitroaromatics. With various alkyl and aryl substituted arylboronic acids, nitrated products were obtained in good to excellent yields (Scheme 2, **2b–2d**, **2g–2i**). Sterically demanding arylboronic acids with 2-methyl (**2g**) and 2,6-dimethyl (**2h**) substituents resulted in the desired nitro product in excellent yields. *ortho*-Phenoxy (**2e**) and *ortho*-benzyloxy (**2f**) substituted nitroarenes were also synthesized in 83% and 81% yields, respectively, following the standard protocol. A recent report described the generation of cyclized dibenzo[*b,d*]furan derivatives from 2-aryloxyarylboronic acids by using $\text{AgNO}_3/$

(21) We have observed the solvent nitration product in a few cases. For example, PhCH_2NO_2 was isolated in ~10% yield from toluene. Toluene as substrate/solvent (without arylboronic acid) resulted in the formation of PhCH_2NO_2 and PhCO_2H and other solvent oxidized products. Benzene as a substrate/solvent (without arylboronic acid) gave nitrobenzene in 38% yield. However in the presence of arylboronic acid, only 5–10% of nitrobenzene formation was detected.

(22) Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628.

Scheme 2. *ipso*-Nitration of Arylboronic Acids

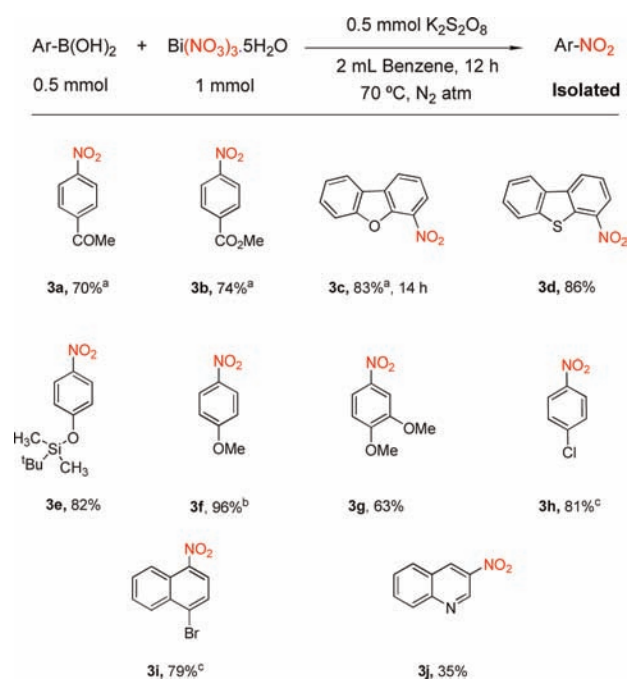


^a Benzene, molecular sieves, 70 °C. ^b GC yield.

$\text{K}_2\text{S}_2\text{O}_8$ at 60 °C.²² However, using the present reaction conditions in a benzene medium and with molecular sieves, we found the desired nitrated product in 83% yield (**2e**); not even a trace of dibenzo[*b,d*]furan was detected. The naphthalene-2-boronic acid (**2k**) resulted in the desired nitro product in good yield. The more sterically demanding arenes such as 1-naphthaleneboronic acid (**2l**) and 9-phenanthreneboronic acid (**2m**) furnished the expected nitro products in 71% and 86% yield, respectively.

Base-sensitive functional groups such as keto with an acidic alkyl group (Scheme 3, **3a**) and ester (**3b**) functional groups were well tolerated. Note that a previous report incorporating $\text{AgNO}_3/\text{TMS}-\text{Cl}$ as the nitrating agent gave low yields of nitro aromatic products for electron-deficient arylboronic acids.¹³ Furthermore, the previous method also suffers from the generation of variable amounts of aryl chlorides depending on the electronic properties of arylboronic acids and the nature of the solvent. Nitroaromatics containing an electron-donating substituent at the para- and meta-positions were also obtained in good yields (**3f** and **3g**). Moreover, the heterocyclic nitro derivatives of dibenzo[*b,d*]furan and dibenzo[*b,d*]thiophene were also synthesized in excellent yields (83% and 86%, **3c** and **3d**). A TBDMS protected 4-hydroxyphenylboronic acid produced a nitro compound in 82% isolated yield (**3e**). Next we focused on synthesizing halogenated nitroarenes. The importance of halogenated nitro compounds arises from the fact that these can be further functionalized and are often found as suitable coupling

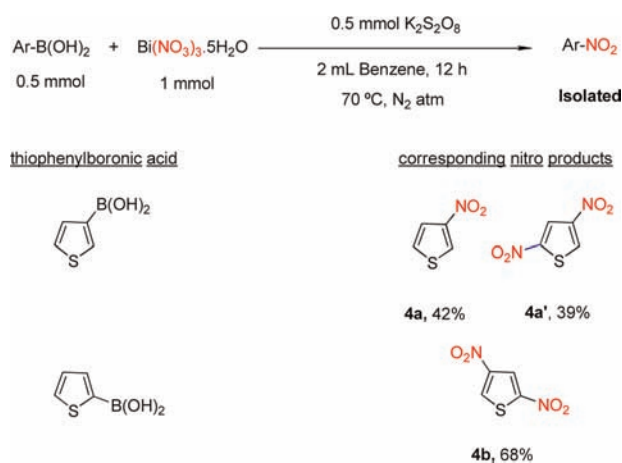
Scheme 3. *ipso*-Nitration of Functionalized and Heterocyclic Arylboronic Acids



^a Molecular sieves. ^b GC yield. ^c 80 °C.

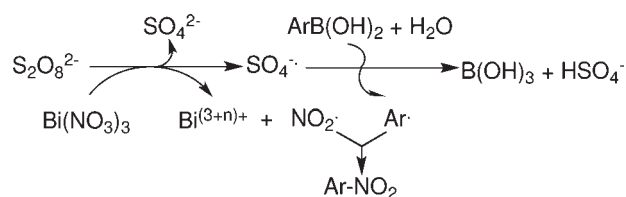
partners in a number of coupling reactions. Even aryl halides were employed as the precursor to synthesize the nitro compounds by Pd and Cu catalyzed methods.^{15,18} In this context, we found that halogenated nitroarenes can be synthesized by the current method in considerably good yields (**3h** and **3i**).

Scheme 4. *ipso*-Nitration of Thiophenylboronic Acids



Thiopheneboronic acids were also investigated to generate the nitro products following our standard reaction conditions (Scheme 4). While 3-thiophenylboronic acid gave 42% and 39% yields of the mono- and 2,4-dinitro

Scheme 5. Proposed Mechanism for *ipso*-Nitration of Arylboronic Acid



product, respectively (**4a** and **4a'**), a 68% yield of 2,4-dinitrothiophene (**4b**) was observed from 2-thiophenylboronic acid. We have applied the present nitration protocol either with thiophene or 2-nitro thiophene as a substrate, but no corresponding (< 1%) nitro product was observed from the reaction mixture.²⁰

Unfortunately, nitrogen-based heteroaromatic 3-nitro quinoline can only be synthesized in 35% yield despite our best efforts (Scheme 3, **3j**). An alternative pathway to synthesize nitro derivatives of quinoline is currently being pursued in our laboratory due to their importance in synthetic chemistry.

(23) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.

A radical-based mechanism has been proposed for the *ipso*-nitration of an arylboronic acid (Scheme 5) following literature precedence.^{22,23} To verify the radical nature of the reaction, commonly used radical scavengers like TEMPO, hydroquinone, and thiourea were used under the standard reaction conditions. Addition of hydroquinone or TEMPO with $\text{PhB}(\text{OH})_2$ resulted in the formation of the desired PhNO_2 product in 5% and 14% yields, respectively, whereas 95% PhNO_2 has been isolated without the scavenger (Scheme 2, **2a**). With thiourea, 3% PhNO_2 has been detected.²⁰

In summary, we have developed an efficient and one pot synthetic method of *ipso*-nitration from arylboronic acids. The high efficiency, general applicability, and broader substrate scope, including heterocycles and functional groups, make this method advantageous.

Acknowledgment. This activity is supported by CSIR (P81102) India.

Supporting Information Available. Experimental procedures and characterization data for all new and known compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.