



Catalyst-free *ipso*-nitration of aryl boronic acids using bismuth nitrate[☆]

Rammohan R. Yadav, Ram A. Vishwakarma^{*}, Sandip B. Bharate^{*}

Medicinal Chemistry Division, Indian Institute of Integrative Medicine (Council of Scientific and Industrial Research), Canal Road, Jammu 180001, India

ARTICLE INFO

Article history:

Received 28 July 2012

Revised 27 August 2012

Accepted 28 August 2012

Available online 4 September 2012

Keywords:

*Ips*o-nitration

Aryl boronic acids

Bismuth (III) nitrate

Catalyst-free

Regioselective

ABSTRACT

We report a catalyst-free *ipso*-nitration of aryl boronic acids using bismuth (III) nitrate as nitrating agent. Reaction proceeds in shorter reaction times with moderate to excellent yields. This method is operationally simple, regioselective, and possesses excellent functional group compatibility to synthesize nitroarenes.

© 2012 Elsevier Ltd. All rights reserved.

Nitroarenes are important class of compounds in synthetic organic chemistry as well as in pharmaceutical industry. The electrophilic nitration of arenes is one of the most extensively studied organic reactions, which involves the use of $\text{HNO}_3/\text{H}_2\text{SO}_4$ as a nitrating mixture under harsh reaction conditions. This method suffers from the problem of regioselectivity as it leads to the formation of a mixture of isomers along with oxidation products.¹ Therefore, development of a mild and operationally simple method for regioselective nitration is of great significance in organic synthesis. Research efforts toward regioselective nitration led to the discovery of *ipso*-nitration as a promising approach. There exists significant number of reports on *ipso*-nitration. *Ips*o-nitration is reported on a variety of substrates such as aryl chlorides, triflates, nontriflates, and boronic acids. Fors and Buchwald reported Pd catalyzed *ipso*-nitration of aryl chlorides, triflates, and nontriflates.^{2,3} Saito and Koizumi⁴ reported the conversion of aryl iodides to nitroarenes using Cu catalyst. Likewise, Olah's group^{5,6} along with several others^{7–9} reported the *ipso*-nitration of arylboronic acids.^{6,5,8,9,7} However, the *ipso*-nitration of aryl boronic acids still remains a challenge to achieve a highly efficient, experimentally simple, and economical protocol.

In recent years, aryl boronic acids have been extensively used as versatile synthons in organic transformations mainly for *ipso*-type of reactions, where the boronic acid group has been replaced with a variety of other functional groups such as hydroxy,^{9,10} azido,^{11,9} sulfones,⁹ halo,¹² nitro,^{6,5,8,9,7} and amines.⁹ Olah and co-workers⁶

were the first to report *ipso*-nitration from aryl boronic acids, who used Crivello's reagent (ammonium nitrate/trifluoro acetic anhydride) for this conversion. Crivello's reagent is relatively powerful, therefore dinitration was also observed as well as there was a need to control temperature during the course of reaction to avoid the formation of undesirable side products.⁶ Later the same group⁵ discovered another *ipso*-nitration reagent, $\text{MNO}_3/\text{TMS-Cl}$; however this protocol requires longer reaction times (30–72 h). As an improvement of available methods, Wu et al.⁸ reported a metal-free *ipso*-nitration using *tert*-butyl nitrite in dioxane as solvent in 45–87% yield. This method has poor substrate scope as only phenyl and naphthyl boronic acids were explored and heteroaryl boronic acids were not studied. Further, reaction times of this protocol were also higher (16 h). Fu and co-workers⁹ reported $\text{NaNO}_2/\text{Cu}_2\text{O}/\text{aq-NH}_3$ catalyzed *ipso*-nitration of aryl boronic acids. The method was highly versatile as it was also applicable to other *ipso*-substitutions and was performed under aqueous conditions; however only phenyl boronic acids were studied and reaction times were also longer (35–96 h). Recently Maiti and co-workers⁷ reported the use of $\text{Bi}(\text{NO}_3)_3/\text{perdisulfate}$ as a new nitrating reagent for *ipso*-nitration. This method has a good substrate scope, but requires 12–14 h of reaction time. All literature reports on *ipso*-nitration are summarized in Table 1.

In continuation of our efforts toward the development of simple and efficient synthetic methodologies,^{11b,13} and in an effort to develop an efficient catalyst-free *ipso*-nitration protocol, we found that bismuth (III) nitrate alone acts as an efficient reagent for *ipso*-nitration of aryl boronic acids (Fig. 1). Advantages of the present protocol over previous methods are shorter reaction times and good substrate scope and most importantly no catalyst required.

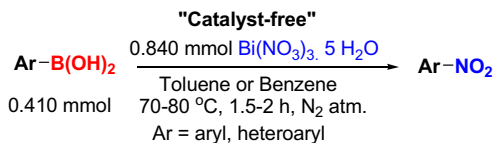
[☆] IIIM Publication Number. IIIM/1489/2012.

^{*} Corresponding authors. Tel.: +91 191 2569111; fax: +91 191 2569333.

E-mail addresses: ram@iiim.ac.in (R.A. Vishwakarma), sbharate@iiim.ac.in (S.B. Bharate).

Table 1Literature reports on *ipso*-nitration of aryl and heteroaryl boronic acids and present work

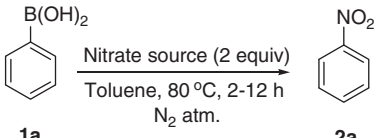
$\text{Ar}-\text{B}(\text{OH})_2 \xrightarrow{\text{Nitrating agent/cat.}} \text{Ar}-\text{NO}_2$				
Sr. no.	Nitrating source and catalyst	Solvent/reaction time	Examples (yields)	Reference
1	$\text{NH}_4\text{NO}_3/(\text{CF}_3\text{CO})_2\text{O}$	ACN, -35°C , 2–6 h	8 (23–78)	Olah's group (2000) ⁶
2	$\text{MNO}_3/\text{TMS-Cl}$ $\text{M} = \text{NH}_4, \text{Ag}$	DCM, rt, 30–72 h	9 (20–98)	Olah's group (2004) ⁵
3	<i>tert</i> -Butyl nitrite	Dioxane, 80°C , 16 h	10 (45–87)	Wu's group (2011) ⁸
4	$\text{NaNO}_2, \text{Cu}_2\text{O}, \text{NH}_3 \cdot \text{H}_2\text{O}$	H_2O , rt, 36–48 h	12 (44–70)	Fu's group (2011) ⁹
5	$\text{Bi}(\text{NO}_3)_3/\text{K}_2\text{S}_2\text{O}_8$	Toluene, 12–14 h, $70\text{--}80^\circ\text{C}$	26 (35–96)	Maiti's group (2012) ⁷
6	$\text{Bi}(\text{NO}_3)_3$	Toluene, 1.5–2 h, 80°C	15 (70–90)	Present work

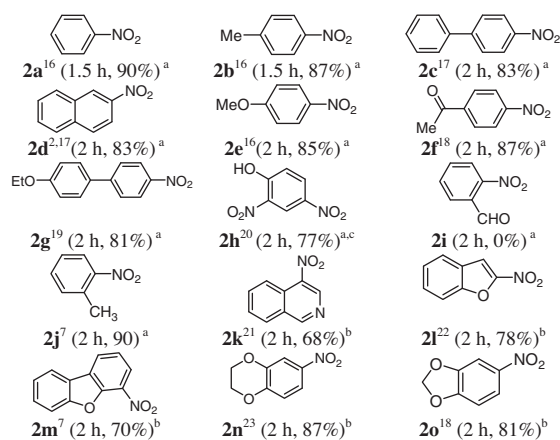
**Figure 1.** Catalyst-free *ipso*-nitration of aryl and heteroaryl boronic acids using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$.

In order to develop a catalyst-free *ipso*-nitration, we investigated different nitrate sources using phenyl boronic acid (**1a**) as a model substrate. Toluene was chosen as the reaction medium for optimization studies (Table 2). Nitrate sources such as zirconium nitrate, potassium nitrate, sodium nitrate, ceric ammonium nitrate, silver nitrate, bismuth subnitrate, and bismuth (III) nitrate were used. Among different nitrate sources, bismuth (III) nitrate was found to be the best for *ipso*-nitration, showing the formation of nitrobenzene (**2a**) in 90% yield (entry 7). However, Maiti and co-workers⁷ recently reported a combination of 2 equiv bismuth (III) nitrate with 1 equiv potassium persulfate for *ipso*-nitration of aryl boronic acids. To check whether the addition of persulfate has any added advantage in this reaction, we performed the *ipso*-nitration of phenyl boronic acid (**1a**) using a $\text{Bi}(\text{NO}_3)_3$ /persulfate catalytic system in toluene at 80°C for 12 h, which led to the formation of nitrobenzene (**2a**) in 90% yield. This result indicated that addition of potassium persulfate does not have any added advantage and further optimization, revealed that a reaction time of 2 h is enough to produce excellent yields of the product (entry 10). Thus, reaction conditions, 2 equiv of bismuth (III) nitrate in toluene as a solvent, reflux at 80°C for 2 h were chosen for further studies. Further solvent optimization studies¹⁴ revealed that only toluene and benzene were efficient.

With optimal conditions in our hand, the scope of catalyst-free *ipso*-nitration of aryl boronic acids with $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ was explored with a variety of substrates in order to establish the generality of the methodology. The substrate scope for different substituted phenyl boronic acids and heteroaryl boronic acids is shown in Figure 2. Electron donating groups such as methyl and methoxy containing aryl boronic acids participated well in this reaction (products **2b**, **2e**, **2j**). Aryl boronic acids substituted with electron withdrawing group such as acetyl also produced excellent yield (product **2f**). Ortho-substituted, sterically hindered boronic acids also participated well in this reaction (e.g. product **2j**), however 2-formyl phenyl boronic acid did not undergo *ipso*-nitration using our reaction conditions (product **2i**). Like phenyl boronic acids, 2-naphthyl boronic acid (product **2d**) and biphenyl boronic acids (products **2c**, **2g**) also produced good yields of respective nitro products. When 4-hydroxyl phenyl boronic acid was treated with $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ in toluene, 2,4-dinitrophenol (**2h**) was formed as the only product in 77% yield, however we could not see formation of 4-nitro phenol. Phenols are prone to direct *ortho* or *para*-nitration and a bismuth nitrate catalyzed *ortho*-nitration of

Table 2Optimization of nitrate source for *ipso*-nitration of phenyl boronic acid (**1a**)^a

			
Entry	Nitrate source	Time	Yield ^b (%)
1	$\text{Zr}(\text{NO}_3)_4$	8	0
2	$\text{Bi}_5\text{O}(\text{OH})_9(\text{NO}_3)_4$	8	5
3	KNO_3	8	0
4	NaNO_3	8	0
5	$\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$	8	0
6	AgNO_3	8	0
7	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$	8	90
8 ^c	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O} + \text{K}_2\text{S}_2\text{O}_8$	12	90
9 ^c	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O} + \text{K}_2\text{S}_2\text{O}_8$	2	85
10	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$	2	85

^a Reagents and conditions: **1a** (0.410 mmol, 1 equiv) and nitrate source (0.82 mmol, 2 equiv) in toluene (2 ml) at 80°C for 2–12 h.^b Isolated yields.^c Potassium persulfate (0.41 mmol, 1 equiv) was used as per Maiti and co-workers (2012) report.⁷**Figure 2.** Nitroarenes synthesized using optimized protocol²⁴ (reaction time and yields are mentioned in the bracket; ^a toluene was used as solvent; ^b benzene was used as solvent; ^c 4-hydroxy phenyl boronic acid was starting material for preparation of **2h**).

phenols has been reported in the literature.¹⁵ Heterocyclic nitroarenes such as 3-nitro isoquinoline (**2k**), 2-nitrobenzofuran (**2l**), 1-nitro dibenzofuran (**2m**), 6-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-boronic acid (**2n**), and 5-nitro-benzo[d][1,3]dioxole-5-boronic acid (**2o**) were also synthesized using our protocol (Fig. 2). Boronic acids such as indole-5-boronic acid, pyridine-4-boronic

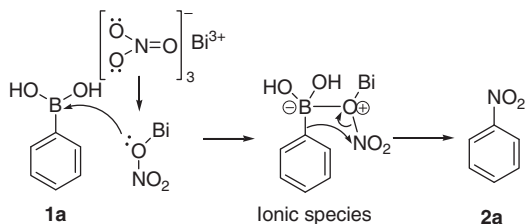


Figure 3. Proposed mechanism for *ipso*-nitration of aryl boronic acids by $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$.

acid, and cyclohexyl boronic acid (not shown) have not participated in this reaction. All the synthesized nitroarenes are known in the literature and were characterized by comparison of their melting point, ^1H NMR, GC–MS, and IR data with literature values.^{16,17,2,18–23,7}

Next, we sought to determine the mechanism of *ipso*-nitration by $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$. The plausible mechanism of *ipso*-nitration is depicted in Figure 3. Maiti and coworkers⁷ propose a free-radical mechanism for $\text{Bi}(\text{NO}_3)_3/\text{K}_2\text{S}_2\text{O}_8$ catalyzed *ipso*-nitration. To check whether the present catalyst-free *ipso*-nitration also occurs via free-radical mechanism, reaction of phenyl boronic acid **1a** was performed in the presence of free-radical scavengers TEMPO and thiourea. The reaction took place smoothly in the presence of TEMPO and thiourea, thus ruling out the possibility of free radical mechanism. The fact that aliphatic boronic acid (e.g. cyclohexyl boronic acid) did not participate in this reaction, indicates that the aromatic ring plays an important electronic role in the *ipso*-nitration. We presume that bismuth nitrate produces in situ $\text{Bi}-\text{O}-\text{NO}_2$ species. Since, boron is known to be highly oxophilic in nature, it is likely that through electronic interaction between boronic acid group and the $\text{Bi}-\text{O}-\text{NO}_2$ species, there is formation of ionic species which helps the nitration to occur at *ipso*-position as depicted in Figure 3.

In conclusion, we have developed a simple, efficient, and economical protocol for *ipso*-nitration of aryl and heteroaryl boronic acids in shortest reaction times. Most importantly, the present protocol is catalyst-free, making it more ecofriendly, economical, and feasible for large scale synthesis of nitroarenes.

Acknowledgments

R.R.Y. is thankful to CSIR for the award of Junior Research Fellowship. Authors thank analytical department, IIIM for NMR and MS analysis of our compounds.

Supplementary data

Supplementary data (spectral data of all compounds) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.08.121>.

References and notes

- Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
- Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898–12899.
- Prakash, G. K. S.; Mathew, T. *Angew. Chem., Int. Ed.* **2010**, *1726*–1728.
- Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715–4717.
- Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205–2207.
- Salzbrunn, S.; Simon, J.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, 1485–1487.
- Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *Org. Lett.* **2012**, *14*, 1736–1739.
- Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 12462–12463.
- Yang, H.; Li, Y.; Jiang, M.; Wang, J.; Fu, H. *Chem. Eur. J.* **2011**, *17*, 5652–5660.
- 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*, 1567–1574.
- (a) Tao, C.-Z.; Cui, X.; Liu, A.-X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 3525–3529; (b) Mohammed, S.; Padala, A. K.; Dar, B. A.; Singh, B.; Sreedhar, B.; Vishwakarma, R. A.; Bharate, S. B. *Tetrahedron* **2012**, *68*, 8156–8162.
- (a) Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141–142; (b) Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2011**, *76*, 7195–7203; (c) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993–5996; (d) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P. P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793–3807; (e) Zhang, G. Y.; Lv, G. L.; Li, L. P.; Chen, F.; Cheng, J. *Tetrahedron Lett.* **2011**, *52*, 1993–1995; (f) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860–2863.
- (a) Bharate, S. B.; Mudududdla, R.; Bharate, J. B.; Battini, N.; Battula, S.; Yadav, R. R.; Singh, B.; Vishwakarma, R. A. *Org. Biomol. Chem.* **2012**, *10*, 5143–5150; (b) Singh, P. P.; Gudup, S.; Ambala, S.; Singh, U.; Dadhwal, S.; Singh, B.; Sawant, S. D.; Vishwakarma, R. A. *Chem. Commun.* **2011**, *47*, 5852–5854; (c) Singh, P. P.; Gudup, S.; Aruri, H.; Singh, U.; Ambala, S.; Yadav, M.; Sawant, S. D.; Vishwakarma, R. A. *Org. Biomol. Chem.* **2012**, *10*, 1587–1597; (d) Jain, S. K.; Meena, S.; Singh, B.; Bharate, J. B.; Joshi, P.; Singh, V. P.; Vishwakarma, R. A.; Bharate, S. B. *RSC Adv.* **2012**. <http://dx.doi.org/10.1039/c2ra21154h>.
- Solvents such as toluene, benzene, acetonitrile, acetone, DMF, DCM, methanol, isopropanol, THF, and dioxane were investigated in the presence of bismuth (III) nitrate as nitrating agent for *ipso*-nitration of aryl boronic acids. Benzene and toluene were found to be the most suitable solvents. In other solvents, such as ACN, acetone, DMF, and DCM, reaction did not proceed at all. No product was formed in isopropanol and dioxane, however small amount (<5%) of product formation was observed in MeOH and THF. Thus study indicated that polar solvents are not suitable. Non-polar solvents such as benzene and toluene were the best among all solvents investigated. Thus, the choice of solvent was restricted to toluene or benzene.
- Bose, A.; Sanjoto, W. P.; Villarreal, S.; Aguila, H.; Banik, B. K. *Tetrahedron Lett.* **2007**, *48*, 3945–3947.
- Aridoss, G.; Laali, K. K. *J. Org. Chem.* **2011**, *76*, 8088–8094.
- Joseph, P. J. A.; Priyadarshini, S.; Kantam, M. L.; Maheswaran, H. *Tetrahedron Lett.* **2012**, *53*, 1511–1513.
- Alagiri, K.; Prabhu, K. R. *Tetrahedron* **2011**, *67*, 8544–8551.
- Lan, P.; Berta, D.; Porco, J. A.; South, M. S.; Parlow, J. J. *J. Org. Chem.* **2003**, *68*, 9678–9686.
- Imoto, M.; Matsui, Y.; Takeda, M.; Tamaki, A.; Taniguchi, H.; Mizuno, K.; Ikeda, H. *J. Org. Chem.* **2011**, *76*, 6356–6361.
- Katritzky, A. R.; Scriven, E. F. V.; Majumder, S.; Akhmedova, R. G.; Vakulenko, A. V.; Akhmedov, N. G.; Murugan, R.; Abboud, K. A. *Org. Biomol. Chem.* **2005**, *3*, 538–541.
- Tromelin, A.; Demerseman, P.; Royer, R. *Synthesis* **1985**, 1074–1076.
- Panchenko, P. A.; Fedorov, Y. V.; Fedorova, O. A.; Perevalov, V. P.; Jonusauskas, G. *Russ. Chem. Bull., Int. Ed.* **2009**, *58*, 1233–1240.
- General procedure for ipso-nitration of aryl and heteroaryl boronic acids*: The mixture of aryl boronic acid (50 mg, 1 equiv) and bismuth (III) nitrate (2 equiv) in toluene or benzene (2 mL) was refluxed for 1.5–2 h. Reaction mixture was allowed to cool to room temperature and was filtered through Whatman filter paper. Residue was washed with ethyl acetate followed by DCM. Combined organic layers were evaporated on a rotary evaporator. Crude product was purified by silica gel column chromatography (#100–200) using EtOAc/hexane (1:99 to 5:95) as mobile phase.