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Green and controllable metal-free nitrification and nitration of arylboronic acids

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Abstract

A novel and green nitrating reagent has been developed for the nitrification and nitration of arylboronic acids, which can be controlled by the reaction conditions. The process provides an attractive alternative to the traditional nitration protocols.

Keywords: Nitrification; Nitration; Arylboronic acids

Aromatic nitro compounds are versatile building blocks in organic synthesis [1]. They have also found widespread applications as pharmaceuticals, dyes, and materials [2]. Traditional methods for the synthesis of nitroaromatics are via direct electrophilic aromatic substitution in the presence of mixtures of nitric and sulfuric acid, or dinitrogen pentoxide. However, these methods suffer from issues of arrow functional group compatibility and poor regioselectivity. Further, these nitrating agents are also good oxidants, which lead to oxidation of some substrates. Therefore, the development of a new and safe nitro source in the nitration reaction with a broad substrate scope remains an extremely attractive yet challenging task for organic chemists. In 2000, Prakash and co-workers firstly reported the *ipso*-nitration of arylboronic acids with the combination of ammonium nitrate and trifluroacetic anhydride as a nitro source [3]. The same group in 2004 made further modifications to the nitration protocol by using inorganic nitrate salt and chlorotrimethylsilane, which acted as a selective and efficient nitrating agent [4]. An interesting copper-catalyzed nitration of aryl iodides and bromides using n-Bu_4NNO_2 as a nitrating agent was discovered by Saito's group [5]. In 2009, Buchwald developed an efficient palladation-nitration protocol for the regioselective *ipso*-nitration of aryl chlorides, triflates and nonaflates with more convenient and inexpensive $NaNO_2$ as a nitrating agent [6]. Very recently, inorganic nitrate or nitrite salts as nitrating agents have been reported on the basis of the metal-catalyzed chelation-assisted C–H bond nitration [7]. Although significant advances were achieved in the transition metal-catalyzed nitration of haloarenes or arenes for the synthesis of nitroarenes, critical issues remains regarding the presence of metal impurities in the final product, which may restrict their practical application.

Therefore, alternative efficient metal-free process for nitration attracts attentions. In 2009, Savinov developed a novel procedure for selective and efficient nitration of phenols using *tert*-butyl nitrite as a nitrating agent [8].

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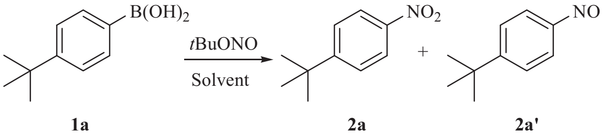
Table 1
Optimization of nitration of 4-*tert*-butylphenylboronic acid **1a** with *tert*-butyl nitrite.[a].



Entry	Solvent	Oxidant	Temp. (°C)	Time (h)	Yield (%)[b]	**2a/2a′**[c]
1	THF	Air	rt	24	32	28:72
2	CH_2Cl_2	Air	rt	24	54	24:76
3	MeCN	Air	rt	24	78	22:78
4	MeCN	N_2	rt	24	85	7:93
5	MeCN	H_2O_2	rt	24	36[d]	–
6	MeCN	O_2	rt	24	82	30:70
7	MeCN	Air	40	18	80	89:11
8	MeCN	Air	50	12	82	>95:5
9[e]	MeCN	Air	50	12	83	>95:5
10[f]	MeCN	Air	50	12	85	>95:5

[a] Unless otherwise noted, the reaction conditions are as follows: 4-*tert*-butylphenylboronic acid **1a** (0.5 mmol), *t*BuONO (1.5 equiv.), in anhydrous solvent (2 mL), under open air.
[b] Isolated yield.
[c] the ratios were determined by GC–MS.
[d] Isolated yield of **2a**.
[e] *t*BuONO (2 equiv).
[f] *t*BuONO (3 equiv).

Arylboronic acids have been widely used in organic synthesis for functional group transformations, due to commercial availability and excellent stability to air and moisture [9]. Herein, we report a simple and controllable procedure for nitrification and nitration of arylboronic acids using *tert*-butyl nitrite as a nitrating agent.

On the outset of this investigation, we used 4-*tert*-butylphenylboronic acid **1a** as model substrate with *tert*-butyl nitrite as a nitrating agent to screen suitable reaction conditions. The results were summarized in Table 1. When the reaction was carried out in THF at the room temperature in air, the inspiring result was obtained that the ratio of **2a** and **2a′** is 28–72 detected by GC–MS after 24 h (Table 1, entry 1). Encouraged by this initial result, we proceeded to optimize the reaction conditions. The yields of the reaction significantly increased in CH_2Cl_2 and MeCN, but the ratio of **2a** and **2a′** slightly changed (Table 1, entries 2 and 3). As is well known, nitroso compounds can be easily transfered into nitro compounds under oxidant conditions. Thus, we wanted to obtain single nitration product **2a** or nitrification product **2a′** *via* controlling the reaction conditions. To our delight, when the reaction was carried out under N_2 at the room temperature in MeCN, nitrification product **2a′** was exclusively obtained with 85% yield (Table 1, entry 4). On the other hand, when H_2O_2 was used as oxidant, the mixture products were detected by GC-Mass, including 4-*tert*-butylphenol, 4-*tert*-butyl-2-nitrophenol and **2a** (Table 1, entry 5). The reaction was carried out under O_2 balloon, affording the mixture products **2a** and **2a′** with 82% yield (Table 1, entry 6). Interestingly, the nitration product **2a** was exclusively obtained with excellent yields by increasing the reaction temperature (Table 1, entries 7 and 8). In addition, the yields of the reaction were slightly improved by increasing the amount of *tert*-butyl nitrite (Table 1, entries 9 and 10).

Because nitroso compounds are poisonous and rarely used in organic synthesis, we only investigated the nitration reactions of a series of arylboronic acids. The results were summarized in Table 2. It was observed that the reaction was marginally affected by electronic effects of the substituents of arylboronic acids. The reaction with electron-donating substituted arylboronic acids proceeded smoothly and afforded the corresponding nitro compounds in good yields (Table 2, entries 1–10). Moreover, it was found that the yields were obviously affected by the steric hindrance of arylboronic acids. The yields of *para*-electron-donating substituted arylboronic acids were higher than that of *ortho*-, *meta*-substituted arylboronic acids (Table 2, entries 2–4). However, the substituted arylboronic acids bearing electron-deficient groups showed lower reactivity (Table 2, entries 11–13). For examples, 1-chloro- and 1-trifluoromethyl-4-nitrobenzenes were obtained with 52% and 26% yields from 4-chloro- and 4-trifluoro- methylphenylboronic acid,