Copper-Catalyzed Nitration of Arylboronic Acids with Nitrite Salts Under Mild Conditions: An Efficient Synthesis of Nitroaromatics

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Received June 16, 2011: Revised September 22, 2011: Accepted November 01, 2011

Abstract: Copper-catalyzed nitration of arylboronic acids has been developed with nitrite salts as nitrating agent under mild conditions. This process provides an efficient and practical method for the synthesis of nitro aromatics, due to its simple experimental procedure and its use of convenient and inexpensive copper catalyst.

Keywords: Arylboronic acids, copper catalyst, nitration.

INTRODUCTION

Aromatic nitro compounds have found widespread applications as pharmaceuticals, dyes, industrial materials, and so on [1]. They are also versatile building blocks in organic synthesis [2]. Traditional methods for the synthesis of nitroaromatics are *via* direct electrophilic aromatic substitution in the presence of an excess of nitric acid or a mixture of nitric acid and sulfuric acid [2]. These classic methods, although still widely used in the industry as well as in the laboratory, suffer from issues of poor regioselectivity and arrow functional group compatibility. Moreover, these nitrating agents are also good oxidants, the nitrated compounds are often accompanied by oxidation products. In 2000, Prakash and co-workers firstly reported the *ipso*-nitration of arylboronic acids with Crivello's reagent [3a]. 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 *ipso*-nitrating agent [3b]. Recently, transition-metal-catalyzed nitration of aromatic halide has emerged as a more attractive method to synthesize aromatic nitro compounds. In 2005, Saito and co-workers disclosed a method for the transformation of aryl iodides and bromides to nitroaromatics catalyzed by copper in the presence of *N, N*-dimethylethylenediamine [4]. Buchwald and co-workers in 2009 developed a very efficient palladation-nitration protocol for the regioselective *ipso*-nitration of aryl chlorides, triflates and nonaflates with sodium nitrite [5].

The transition-metal-catalyzed functionalization of arylboronic acids is the most powerful tool for the formation of carbon–carbon and carbon–heteroatom bonds in modern organic synthesis [6]. Apart from the well-known Suzuki-Miyaura cross-coupling [7], there has been a significant development in copper-mediated oxidative coupling of arylboronic acids with heteroatom nucleophiles reported by Chan and Lam [8]. These pioneering reports spurred recent numerous investigations into the copper-catalyzed C-C, C-N, C-O, C-S, C-X and C-P coupling protocols of arylboronic acids with nucleophiles [9]. Here, we report a more convenient and inexpensive copper-catalyzed method for the synthesis of nitroaromatics under mild conditions.

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RESULTS AND DISCUSSION

On the outset of this investigation, we used 4-methylphenylboronic acid **1a** as model substrate with *n*-Bu_4NNO_2 to screen suitable reaction conditions and the results are summarized in Table **1**. When Cu_2O was used catalyst, the nitration of **1a** indeed took place in methanol at room temperature under open air, albeit in low yield (entry 1). Encouraged by this initial result, we proceeded to optimize the proposed reaction. To our delight, the nitration product **2a** was obtained with 61% yield in MeCN (entry 2). Other solvents, such as CH_2Cl_2, THF, dioxane, DMF and DMSO, were unsuitable for this reaction (entries 3-7). Various copper sources were further tested. It was found that the reaction afforded the desired product with lower yields under Cu(I) or Cu(II) catalysts, except for CuO (entries 8-13). The yield of the reaction was significantly improved by increasing the amount of **1a**, due to the competing side reaction of the formation of 4,4'-dimethylbiphenyl and 4-methylphenol (entry 14). Finally, for comparison the reaction was carried out in the absence of Cu_2O, no product **2a** could be detected (entry 15).

Under the optimized conditions, the substrate scope of this reaction was investigated and the results are 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 *ortho*-, *meta*-, and *para*-electron-donating substituted arylboronic acids proceeded smoothly and afforded the corresponding nitro compounds in excellent yields (**2a, c-g**). Higher reactivity was observed for 4-tert-butylphenylboronic acid and 2-naphthylboronic acid (**2f, 2i**). The substituted arylboronic acids bearing electron-deficient groups showed slightly lower reactivity than those bearing electron-rich or neutral groups (**2j-o**). It is particularly noteworthy that bromo and chloro substituents are tolerated in the reaction conditions, which is advantageous for further transformations (**2j, 2k**). The reaction tolerated a wide range of functional groups, such as

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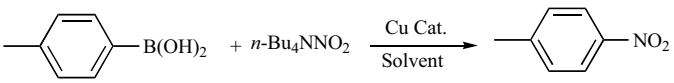
Table 1. Optimization of Copper-Catalyzed Nitration of 1a with *n*-Bu_4NNO_2[a]

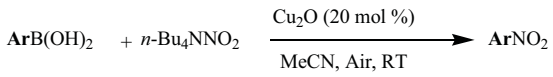


1a **2a**

Entry	Cu Cat.	Solvent	Yield(%)[b]
1	Cu_2O	MeOH	35
2	Cu_2O	MeCN	61
3	Cu_2O	CH_2Cl_2	15
4	Cu_2O	THF	18
5	Cu_2O	Dioxane	Trace
6	Cu_2O	DMF	Trace
7	Cu_2O	DMSO	Trace
8	CuI	MeCN	31
9	CuBr	MeCN	37
10	CuCl	MeCN	40
11	CuO	MeCN	/
12	$Cu(OAc)_2$	MeCN	21
13	$Cu(OTf)_2$	MeCN	26
14[c]	**Cu_2O**	**MeCN**	**75**
15[d]	/	MeCN	/

[a]Unless otherwise noted, the reaction conditions are as follows: 4-methylphenylboronic acid **1a** (1.5 equiv), *n*-Bu_4NNO_2 (0.3 mmol), Cu Cat. (20 mol %), in anhydrous solvent (2 mL), at room temperature, under open air. [b]Isolated yield. [c]4-methylphenylboronic acid **1a** (2 equiv). [d]The reaction was carried out in the absence of Cu_2O.

Table 2. Copper-Catalyzed Nitration of Arylboronic Acids 1a-p with *n*-Bu_4NNO_2[a]

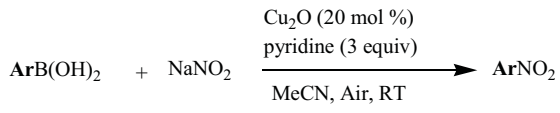


1a-p **2a-p**

Entry	$ArB(OH)_2$ (1)	Product (2)	Yield (%)[b]
1	*p*-MeC_6H_4 **1a**	**2a**	75
2	C_6H_5 **1b**	**2b**	61
3	*o*-MeC_6H_4 **1c**	**2c**	70
4	*m*-MeC_6H_4 **1d**	**2d**	72
5	*3,5*-$Me_2C_6H_3$ **1e**	**2e**	80
6	*p*-^{t}BuC_6H_4 **1f**	**2f**	87
7	*p*-$MeOC_6H_4$ **1g**	**2g**	78
8	4-Me-1-naphthyl **1h**	**2h**	65
9	2-naphthyl **1i**	**2i**	88
10	*p*-BrC_6H_4 **1j**	**2j**	51
11	*p*-ClC_6H_4 **1k**	**2k**	57
12	*m*-CNC_6H_4 **1l**	**2l**	48
13	*p*-$CHOC_6H_4$ **1m**	**2m**	60
14	*p*-$MeO_2CC_6H_4$ **1n**	**2n**	53
15	*p*-$CF_3C_6H_4$ **1o**	**2o**	30
16	2-thiophyl **1p**	**2p**	Trace

[a]Unless otherwise noted, the reaction conditions are as follows: arylboronic acid **1a-p** (2.0 equiv), *n*-Bu_4NNO_2 (0.3 mmol), Cu_2O (20 mol %), MeCN (2 mL), at room temperature, under open air. [b]Isolated yield.

Table 3. Copper-Catalyzed Nitration of Arylboronic Acids with Sodium Nitrite[a]



1 **2**

Entry	ArB(OH)$_2$ (1)	Product (2)	Yield (%)[b]
1	*p*-MeC$_6$H$_4$ **1a**	**2a**	81
2	C$_6$H$_5$ **1b**	**2b**	68
3	*o*-MeC$_6$H$_4$ **1c**	**2c**	72
4	*m*-MeC$_6$H$_4$ **1d**	**2d**	78
5	*p*-^{t}BuC$_6$H$_4$ **1f**	**2f**	88
6	*p*-MeOC$_6$H$_4$ **1g**	**2g**	80
7	*p*-BrC$_6$H$_4$ **1j**	**2j**	55
8	*p*-ClC$_6$H$_4$ **1k**	**2k**	60
9	*m*-CNC$_6$H$_4$ **1l**	**2l**	50
10	*p*-CHOC$_6$H$_4$ **1m**	**2m**	68

[a]Unless otherwise noted, the reaction conditions are as follows: arylboronic acid **1** (2.0 equiv), $NaNO_2$ (0.3 mmol), Cu_2O (20 mol %), Pyridine(3.0 equiv), MeCN (2 mL), at room temperature, under open air. [b]Isolated yield.

bromo, chloro, cyano, aldehyde, ester, and trifluoromethyl groups (**2j-o**). However, the application of this process is problematic for the nitration of sulfur-containing heteroaromatic boronic acid (**2p**). The reason for the failure of the reaction is less clear.

Next, we preceeded to apply sodium nitrite as nitrating agent, which is genernally low solubility in organic solvents. Under the optimized conditions, the nitration product **2a** of 4-methylphenylboronic acid **1a** was obtained with 62% yield**.** As we all know, base could promote the transmetalation of arylboronic acids. Pyridine was found the most suitable base to promote the reaction with 81% yield, while the addition of inorganic bases, such as K_2CO_3, Cs_2CO_3 and K_3PO_4, inhibited the reactivity of the substrate. A series of arylboronic acids were then subjected to this optimized reaction conditions. As shown in Table **3**, the reaction also gave cross coupling products in moderate to good yields.

EXPERIMENTAL

Copper catalysts and arylboronic acids were purchased from Accela ChemBio Co. Ltd. Chloroform-*d* was purchased from Cambridge Isotope Laboratories. All solvents were distilled prior to use. For chromatography, 200-300 mesh silica gel (Qingdao, China) was employed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measure on Bruker 300 M spectrometers. $CDCl_3$ was used as solvent with tetramethylsilane (TMS) as internal standard.

General Procedure for the Nitration of Arylboronic Acids

Under open air, a reaction tube was charged with arylboronic acids (2.0 equiv), $NaNO_2$ (20.7 mg, 0.3 mmol) or *n*-Bu_4NNO_2 (84.6mg, 0.3 mmol), Cu_2O (8.64 mg, 20 mol %), or pyridine (71.1 mg, 3.0 equiv), and dry MeCN (2 mL). The mixture was kept stirring at room temperature for 8-12 h. After completion of the reaction, removal of the solvent under reduced pressure gave a crude product, which was purified on silica gel (Petroleum ether/EtOAc) to afford the products.

Spectral Data for the Products

1-methyl-4-nitrobenzene 2a, [10] (Table 2, entry 1)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.08 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.0, 144.5, 129.8, 123.5, 21.6.

1-nitrobenzene 2b, [11] (Table 2, entry 2)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.18 (d, *J* = 9.0 Hz, 2H), 7.68 (t, *J* = 9.0 Hz, 1H), 7.51 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ =146.5, 134.6, 129.3, 123.4.

1-methyl-2-nitrobenzene 2c, [12] (Table 2, entry 3)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.95 (d, *J* = 9.0 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.32 (t, *J* = 3.0 Hz, 2H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.1, 133.6, 133.0, 132.7, 126.9, 124.6, 20.4.

1-methyl-3-nitrobenzene 2d, [13] (Table 2, entry 4)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.00 (d, *J* = 6.0 Hz, 2H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.40 (d, *J* = 6.0 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.3, 139.7, 135.3, 129.0, 123.9, 123.8, 120.6, 21.2.

1,3-dimethyl-5-nitrobenzene 2e, [5] (Table 2, entry 5)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.81 (s, 2H), 7.28 (s, 1H), 2.39 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.2, 139.4, 136.2, 121.1, 21.1.

1-tert-butyl-4-nitrobenzene 2f, [5] (Table 2, entry 6)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.13 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.8, 146.1, 126.2, 123.3, 35.4, 31.0.

1-methoxy-4-nitrobenzene 2g, [14] (Table 2, entry 7)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.18 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.5, 141.5, 125.9, 114.0, 55.9.

1-methyl-4-nitronaphthalene 2h, [15] (Table 2, entry 8)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.66 (d, *J* = 9.0 Hz, 1H), 8.15 (q, *J* = 9.0 Hz, 2H), 7.77~7.65 (m, 2H), 7.40 (d, *J* = 9.0 Hz, 1H), 2.81(s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.3, 133.1, 128.9, 127.1, 125.1, 125.0, 124.7, 124.2, 123.9, 123.6, 20.2.

2-nitronaphthalene 2i, [5] (Table 2, entry 9)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.74 (s, 1H), 8.18 (q, *J* = 3.0 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.64 (q, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.4, 135.8, 131.8, 129.9, 129.7, 129.5, 128.0, 127.9, 124.6, 119.2.

1-bromo-4-nitrobenzene 2j, [13] (Table 2, entry 10)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.10 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.4, 132.6, 130.0, 125.0.

1-chloro-4-nitrobenzene 2k, [13] (Table 2, entry 11)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.15 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.4, 141.3, 129.5, 124.9.

3-nitrobenzonitrile 2l, [9b] (Table 2, entry 12)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.53 (s, 1H), 8.48 (d, *J* = 6.0 Hz, 1H), 8.01 (d, *J* = 6.0 Hz, 1H), 7.75 (t, *J* = 9.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.1, 137.6, 130.7, 127.6, 127.2, 116.5, 114.0.

4-nitrobenzaldehyde 2m, [16] (Table 2, entry 13)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 10.13 (s, 1H), 8.37 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.4, 151.2, 140.0, 130.5, 124.3.

methyl 4-nitrobenzoate 2n, [5] (Table 2, entry 14)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.28 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.4, 150.7, 135.4, 130.8, 123.8, 52.8.

1-(trifluoromethyl)-4-nitrobenzene 2o, [11] (Table 2, entry 15)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.37(d, *J* = 6.0 Hz, 2H), 7.85 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.0, 136.3, 135.8, 126.8, 126.8, 126.7, 126.7, 124.7, 124.0, 121.1, 119.0.

CONCLUSION

In summary, we have developed a new, simple, efficient approach to the synthesis of nitroaromatics by copper-catalyzed coupling of arylboronic acids with nitrite salts under mild conditions. This process provides an attractive alternative to the traditional nitration protocol. Further investigation of the detailed mechanism and the scope of substrates is currently underway in our lab.

ACKNOWLEDGEMENT

We are grateful for the financial support by Lishui University Opening Foundation for advanced talents.

CONFLICT OF INTEREST

Declared none.

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