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Synthesis of aryloxyacetonitriles based on arylboronic acids with 2-bromoacetonitrile

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ABSTRACT

A new and efficient protocol for the synthesis of aryloxyacetonitriles based on arylboronic acids with 2-bromoacetonitrile has been developed using eco-friendly hydrogen peroxide as oxidant under metal-free conditions. This method is compatible with arylboronic acid attached sensitive substituent and obtains desired product in moderate to good yield.

Aryl oxyacetonitriles are important organic compounds as versatile precursors in synthesis of pharmaceuticals [1–4]. The nitrile pharmacophore plays a significant role in modulating the biological activities of synthetic medicinal drugs and natural products [5–9]. Additionally, the cyano group can be easily converted to other functional groups, such as carboxyl derivatives, amines, ketones, and various heterocycles [10–14]. Therefore, the concise, cost-effective and environmentally friendly methods for assembling aryloxyacetonitriles should be deserved more attention. In the past few years, the perfluorobutyl iodide-promoted cyanomethylation of phenols with acetonitrile for the synthesis of the aryloxyacetonitriles has been reported in the presence of NaH through a cyanomethyl radical pathway [15] (Scheme 1). More recently, A metal-free direct C(sp3)–H cyanation reaction with cyanobenziodoxolones and anisole derivatives for preparing aryloxyacetonitriles has been developed. In this reaction, cyanobenziodoxolones are both cyanating reagents and oxidants [16] (Scheme 2). However, the direct use of inexpensive, commercially available starting material to undergo reaction has attracted much interest in organic chemistry. Investigation showed that arylboronic acids, which have the advantages of versatile nature, structural diversity, low toxicity, easy availability, greater stability and reactivity, can be easily converted into corresponding phenols by oxidative hydroxylation [17–22]. Cao's work showed that unsymmetrical biaryl ethers were synthesized via a novel Ni-catalyzed cross-coupling reaction of polyfluoroarenes with arylboronic acids and oxygen [23]. Herein, we report the first example of efficient methods for the synthesis of the aryloxyacetonitriles based on arylboronic acids with 2-bromoacetonitrile without transition metal catalyst using H_2O_2 as a green oxidant (Scheme 3).

We started with a model reaction of phenylboric acid 1 (0.5 mmol) with 2-bromoacetonitrile **2** (0.7 mmol), which was conducted in H_2O (3 mL) at 80 °C in the presence of H_2O_2 (0.08 mL), giving 25% yield of 2-phenoxyacetonitrile **3a** (Table 1, entry 1). Consequently, the reaction conditions by varying the ratio of starting materials, solvents, bases, amounts of oxidant, times and temperatures were examined, and the yield of **3a** improved to 74% using NaOH as base in DMF (Table 1, entry 2). This encouraged us to explore the effect of bases and, as a result, the yield of **3a** was poor with other bases (Table 1, entry 8–12). Then, the effects of the ratio of starting materials **1:2** were examined, and relatively high yield at the proportion of 1:1.4 was chosen as the the ratio of starting materials **1:2** (Table 1, entry 2, 13–16). Investigating the effect of the amount of oxidant H_2O_2 on this reaction clearly showed that 0.08 mL was the most appropriate amount for the synthesis of phenyloxyacetonitriles (Table 1, entry 2, 17–19). Further optimizations showed that increasing the reaction time did not improve the yield (Table 1, entries 22) and decreasing or increasing reaction temperature obtained the lower yields (Table 1, entries 20–25). Therefore, the reaction conditions of entry 2 proved to be optimal.

Next, we were interested to demonstrate the general applicability of this method for the synthesis of structurally diverse and challenging aryloxyacetonitriles. As shown in Table 2, aryl-

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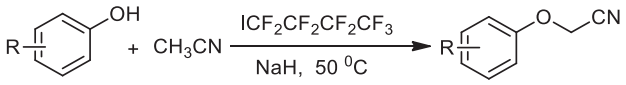
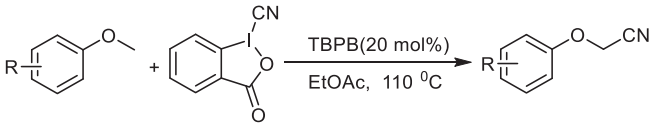
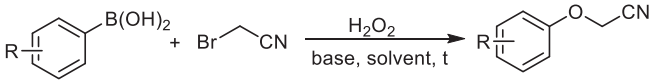


Scheme 1. Radical pathway.



Scheme 2. C(sp3)–H cyanation.



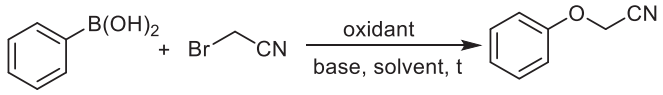
Scheme 3. This work.

boronic acid with electron-withdrawing substituent such as Cl, Br, F, -CN, -COOMe, -NO_2 afford good yield (3b-3h and 3k-3m, Table 2), but arylboronic acid with electron-donating substituent such as -CH_3, -OCH_3 afford moderate yield (3i-3j, Table 2), indicating that both electron-rich and electron-deficient arylboronic acids resulted corresponding product in moderate to good yield, which suggests that the electronic nature of attached substituent has slight influence on reaction process (3a-3m, Table 2). It is noteworthy to observe that arylboronic acid with sensitive functional group, such as thioether group, reacted with 2-bromoacetonitrile under oxidation condition obtained 56% yield of the desired product (3n, Table 2).

A plausible mechanistic pathway has been proposed based on reported literature [24–25], It is assumed that initially H_2O_2 interacts with phenylboronic acid to form an adduct (**A**) which upon rearrangement and subsequent water loss gave adduct (**B**). In the presence of NaOH, hydrolysis of B afforded the sodium phenolate (**C**). Finally, the reaction of $BrCH_2CN$ with C afforded the target compound **3a** (Scheme 4).

In summary, we have developed the first synthetic method of aryloxyacetonitriles using arylboric acids with 2-bromoacetonitrile as reaction substrates in the presence of H_2O_2. The main advantage of this method is H_2O_2 as an eco-friendly oxidant, good compatibility of sensitive groups and metal-free conditions in a relatively short reaction time. Further studies to expand application of this method in drug synthesis are underway in our laboratory.

Table 1
Optimization of the reaction conditions.[a]

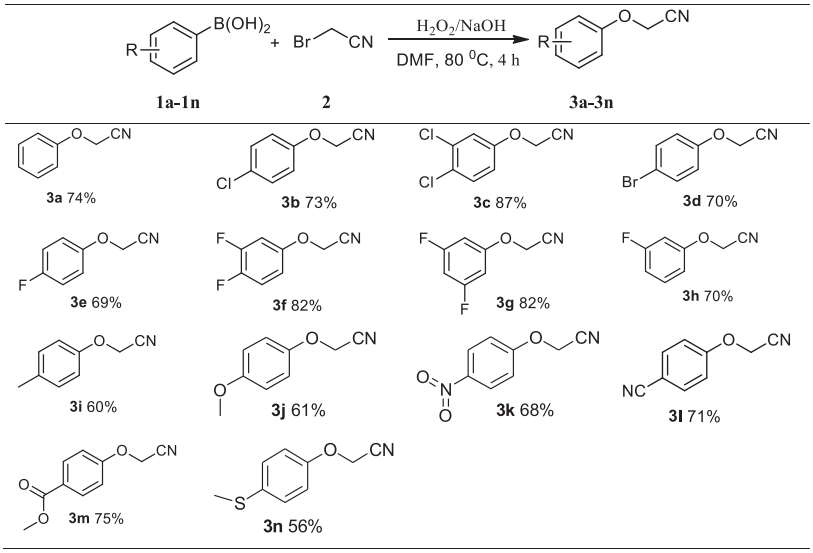


1 2 3a

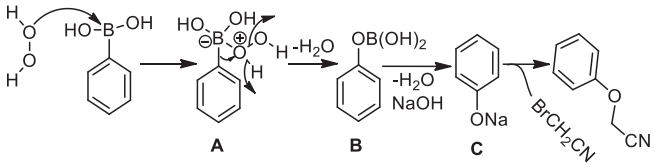
1			2		3a		
Entry	Solvent	Base	Ratio of **1:2**	30% aq·H_2O_2(mL)	Time (h)	Temperature (^{0}C)	Yield(%)[b]
1	H_2O	NaOH	1:1.4	0.08	4	80	25
2	DMF	NaOH	1:1.4	0.08	4	80	74
3	DMSO	NaOH	1:1.4	0.08	4	80	61
4	EtOH	NaOH	1:1.4	0.08	4	80	trace
5	THF	NaOH	1:1.4	0.08	4	80	54
6	1,4-dioxane	NaOH	1:1.4	0.08	4	80	0
7	DMF/H_2O(1:1)	NaOH	1:1.4	0.08	4	80	45
8	DMF	$NaHCO_3$	1:1.4	0.08	4	80	17
9	DMF	K_2CO_3	1:1.4	0.08	4	80	24
10	DMF	Cs_2CO_3	1:1.4	0.08	4	80	39
11	DMF	KOH	1:1.4	0.08	4	80	42
12	DMF	NEt_3	1:1.4	0.08	4	80	trace
13	DMF	NaOH	1:1.2	0.08	4	80	62
14	DMF	NaOH	1:1.6	0.08	4	80	60
15	DMF	NaOH	1:2.0	0.08	4	80	65
16	DMF	NaOH	1.2:1	0.08	4	80	67
17	DMF	NaOH	1:1.4	0.04	4	80	51
18	DMF	NaOH	1:1.4	0.06	4	80	68
19	DMF	NaOH	1:1.4	0.1	4	80	67
20	DMF	NaOH	1:1.4	0.08	1	80	66
21	DMF	NaOH	1:1.4	0.08	2	80	71
22	DMF	NaOH	1:1.4	0.08	6	80	73
23	DMF	NaOH	1:1.4	0.08	4	40	42
24	DMF	NaOH	1:1.4	0.08	4	60	67
25	DMF	NaOH	1:1.4	0.08	4	100	48

[a] Reaction conditions: phenylboric acid **1** (0.5 mmol), 2-bromoacetonitrile **2** (0.7 mmol), base (0.8 mmol), 3 mL solvent, in air.
[b] Isolated yield.

Table 2
Synthesis of aryloxyacetonitriles based on arylboronic acids.[a]



[a] Reaction conditions: arylboric acid **1** (0.5 mmol), 2-bromoacetonitrile **2** (0.7 mmol), NaOH (0.8 mmol), 3 mL DMF, 80 °C, in air, isolated yield.



Scheme 4. Plausible mechanism for synthesis of aryloxyacetonitriles.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152331.

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