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[¹¹C]Cyanation of Arylboronic Acids in Aqueous Solution

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Abstract

A copper-mediated ¹¹C-cyanation method employing arylboronic acids and [¹¹C]HCN has been developed. This method was applied to the radiochemical synthesis of a wide range of aromatic ¹¹C-nitriles in aqueous solutions. The use of readily accessible arylboronic acids as precursors makes this method complementary to the well-established ¹¹C-cyanation methods that utilize aryl halide precursors.

TOC image

A copper-mediated ¹¹C-cyanation method employing arylboronic acids and [¹¹C]HCN in aqueous solutions has been developed to provide a wide range of aromatic ¹¹C-nitriles.

Positron Emission Tomography (PET) is a highly sensitive non-invasive molecular imaging modality, which can be used to monitor biochemical processes *in vivo*.¹ Carbon-11 (¹¹C; *t*_{1/2} = 20.4 min) is a widely utilized radionuclide in radiotracer synthesis, particularly for labeling small organic, drug-like molecules. This is due to the breadth of functional groups (e.g., ¹¹CH₃, ¹¹CN, ¹¹C=O, etc.) into which carbon-11 could be incorporated. Furthermore, the relative short half-life of carbon-11 allows for repeated *in vivo* PET studies in animals or humans within short time intervals while maintaining a reasonable imaging window.^{2, 3} Carbon-11-labeled radiotracers are predominantly prepared by methylation reactions between –OH, –NH, or –SH groups and [¹¹C]CH₃I^{4, 5} or [¹¹C]CH₃OTf.⁶ Driven by the need to expand beyond ¹¹C-methylation reactions as a mainstay in PET radiopharmaceutical

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production, continued efforts to employ a more diverse library of ^{11}C -synthons remain a focus for several research laboratories,^{7–12} and this topic has been reviewed by us^{13–15} and others.¹⁶ We are particularly interested in the development of new ^{11}C]HCN-labeling methods because nitriles are not only frequently present in biologically active agents but also represents a versatile functional group that can be readily converted to ^{11}C -labeled amides, carboxylic acids or amines.¹⁵ Historically, nucleophilic ^{11}C -cyanation of aliphatic substrates was a subject that received long-term attention and is generally performed *via* the Strecker reaction⁷ or by ring-opening of activated aziridines.¹⁷ The resulting ^{11}C -labeled aliphatic nitriles have been used to prepare ^{11}C -labeled amino acids such as ^{11}C]phenylalanine,¹⁸ ^{11}C]tyrosine,¹⁸ and ^{11}C]aspartic acid (Fig. 1A).¹⁷ Whereas existing methods for introducing ^{11}C]CN[–] into aromatic rings are focused on either nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) reactions with $\text{Cr}(\text{CO})_3$ activated arenes¹⁹ or Pd-catalyzed ^{11}C -cross-coupling reactions with ArBr ,^{20–22} ArI ^{23, 24} or ArOTf ²⁵ substrates (Fig. 1B). Alternatively, copper catalyzed transformation from aryl halide to aryl nitrile in the Rosenmund-von Braun reaction could be employed for ^{11}C -aromatic cyanation (Fig. 1B).²⁶ This method takes advantage of the robust nature and environmentally-benign characteristics of the copper catalyst and obviates the limitation imposed by air/moisture sensitive ligands which are required by Pd-catalyzed reactions. With the increased demand of developing rapid and highly efficient syntheses for ^{11}C -CN-labeled PET tracers, we herein report a novel copper(I)-mediated ^{11}C -cyanation of arylboronic acids in aqueous solution.

Copper-mediated Rosenmund-von Braun type transformations between arylboronic precursors and various coupling partners have been the subject of extensive investigation^{27–29} and their translations into radiochemistry have gained increasing attention. For example, Riss *et al.*³⁰ and our laboratory³¹ developed ^{11}C -carboxylation reactions with arylboronic esters using copper(I) catalysts (Fig. 1C). Mossine *et al.*³² and Preshlock *et al.*³³ reported aromatic ^{18}F -fluorinations using boronic acid/ester precursors, respectively (Fig. 1C). Moreover, Zhang *et al.*³⁴ and Wilson *et al.*³⁵ disclosed aromatic $^{131}\text{I}/^{123}\text{I}$ -iodination reactions involving copper catalysts and boronic acids/esters (Fig. 1C). Inspired by their pioneering work, we envisioned that ^{11}C -aromatic cyanation could be achieved using widely available and easy-handling arylboronic acids³⁶ precursors, ^{11}C -cyanide and copper catalysts.

To evaluate several reaction parameters including copper catalyst, base, and solvent, we initiated our preliminary studies by selecting phenylboronic acids and KCN under the non-radioactive conditions. After a survey of copper catalysts, we found that CuI and CuBr outperformed Cu_2O and $\text{Cu}(\text{OTf})_2$ in cyanation reactions (Table 1, entry 1–4). When 0.55 equiv of CuI catalyst was added to the reaction mixture, 13% and 36% cyanated product were obtained for *para*-Br- and *para*-OMe-phenylboronic acids, respectively (Table 1, entry 1 and 16). Further increasing the temperature did not improve the yield within the 1 hour reaction window (Table 1, entry 5). The presence of base such as $n\text{Bu}_4\text{NOH}$ was essential to this transformation (Table 1, entry 6), therefore we evaluated a variety of inorganic and organic bases. We found that K_2CO_3 and Et_3N were both ineffective for CuI catalyzed reactions. However, NaOH and Cs_2CO_3 promoted the reaction and yielded 13% and 18% of the desired aryl nitrile, respectively (Table 1, entry 7–10). We next screened different solvents and found DMF to be the optimal solvent for this model reaction (Table 1, entry

11–14). It is noteworthy that when a mixture of DMF/water was used, nearly identical yield of the cyanated product was observed (Table 1, entry 15). The use of DMF/water mixture as the solvent was beneficial to the development of our ^{11}C -cyanation reaction because with increased Cs_2CO_3 solubility in aqueous solution, we were able to carry out the trapping of ^{11}C HCN gas in a basic solution of Cs_2CO_3 directly.

Aromatic ^{11}C -cyanation was optimized using **1a** as the model substrate. A 1:2 ratio (mass ratio) of CuI:**1a** mixture was reacted with ^{11}C HCN/ ^{11}C CsCN trapped in a solution of Cs_2CO_3 in 3:1 DMF/water (v/v) mixture at 120 °C for 5 min. A 13% radiochemical conversion (RCC) of **2a** was determined by radioTLC (Table 2, entry 1). Increasing the loading of CuI catalyst (Table 2, entry 2–3) did not affect the RCC of **2a**. However, by elevating the reaction temperature from 120°C to 150°C, the RCC of **2a** was increased to 22% (Table 2, entry 4). The amount of boronic acid substrate was also found to influence the reaction outcome (Table 2, entry 5) and 37% RCC was obtained when the substrate loading was doubled. Further increasing the quantity of the boronic acid substrate was expected to lead to insoluble materials given the limited amount of solvent (200 μL) under the present conditions, therefore we varied alternative parameters to further improve the yield. For example, when the amount of Cs_2CO_3 was doubled from 4 mg to 8 mg, a significant increase of RCC from 37% to 61% was achieved (Table 2, entry 6). Shorter reaction times were apparently not sufficient for a satisfactory RCC (Table 2, entry 7–8). Lastly, a variety of copper ligands were tested and DMEDA was shown to benefit the radiochemical transformation by further improving the RCC to 65% (Table 2, entry 9–13). In addition, we found that an additional amount of Cs_2CO_3 increased the RCC to 70% (Table 2, entry 14). This experimentation led us to determine the optimal molar ratio for the reactants as follows: 1:5:4:4 for CuI/boronic acid/ Cs_2CO_3 /DMEDA, respectively.

Arylboronic acids with different functional groups were reacted with ^{11}C HCN/ ^{11}C CsCN under the optimized conditions established in Table 2 to explore the substrate scope of this transformation. Substrates bearing electron-donating groups such as methoxy and phenyl groups on the *para*-position gave rise to desired products in good RCCs (Fig. 2, 2a and 2b), making this method complementary to existing $\text{S}_{\text{N}}\text{Ar}$ methods where electron-withdrawing groups are necessary to activate the aromatic ring. However, 2,4,6-trimethylphenyl boronic acid is less reactive and afforded 8% RCC (Fig. 2, 2c). This is possibly due to steric hindrance exerted by the *ortho*-substituents. Parent phenylboronic acid and substrates bearing electron-withdrawing groups on the *para*-position were less favored and showed moderate RCCs ranging from 34–50% (Fig. 2, 2d–2g). We were pleased to see halogen-substituted arylboronic acid afforded good RCC of the corresponding nitrile (Fig. 2, 2e), a significant advantage over the Pd-catalyzed methods (i.e., a multi-halogen bearing precursor utilized with the Pd-catalyzed method would raise regioselectivity concerns). Furthermore, *meta*-substituents on the phenyl ring are well tolerated with the radiochemical conditions established herein. Substrates bearing *meta*-amino and *meta*- CF_3 groups both proceed smoothly to afford the ^{11}C -cyanated product (Fig. 2, 2h and 2i). Under our reaction conditions, the unprotected benzamide and aniline (Fig. 2, 2g and 2h) did not interfere with the copper-mediated transformation. This observation holds true for heteroaromatic boronic acids substrates as well. Pyridine-3-boronic acid produced ^{11}C 3-pyridine nitrile with good

conversion (Fig. 2, 2j; >50% RCC). Both quinoline and furan based boronic acids are radiolabeled with ^{11}C -cyanide, albeit in lower RCCs (Fig. 2, 2k and 2i). As a proof-of-concept, we selected **1a** as the substrate and carried out the radiosynthesis and isolation of **2a**. A slightly modified procedure using the reaction mixture (DMF/water) as the ^{11}C]HCN trapping solution was adopted in order to improve the operational-simplicity (see SI). We isolated 0.455 GBq (12.3 mCi) of **2a**, after semi-preparative HPLC purification which resulted in an RCY of 4.2% ($n=2$, non-decay corrected, relative to starting ^{11}C]HCN) and the specific activity was determined to be 16 GBq/ μmol (433 mCi/ μmol) with a total synthesis time of 26 min.

The mechanism of ^{11}C]cyanation of arylboronic acids is proposed as follows: CuI underwent ligand exchange with ^{11}C -cyanide in the presence of ligand to afford Cu(I) intermediate **3**. Intermediate **3** was subsequently converted to Cu(III) intermediate **4** under the aerobic oxidative condition. Intermediate **4** participated in a transmetallation reaction with the borate complex to give rise to intermediate **5**. After reductive elimination, cyanated product **2d** was formed and Cu(I) species was regenerated to complete the catalytic cycle.

In conclusion, we have developed a copper-mediated ^{11}C -aromatic cyanation reaction using readily available boronic acids in aqueous solutions. This method is applicable to a broad range of arylboronic acids and complementary to existing methods for ^{11}C -aromatic cyanation. Carbon-11 labeled **2a** was synthesized and isolated using this approach as a proof-of-concept. Efforts to improve specific activity and application of this method to the synthesis other ^{11}C -labeled radiotracers are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A: Aliphatic ^{11}C -Cyanation Strategy B: Aromatic ^{11}C -Cyanation Strategy

C: Cu-Mediated Radiochemical Transformations with Arylboronic Acid/Ester

Fig. 1.
Cyanation Strategies and Utility of Boronic Precursors in Radiochemical Transformations.

Fig. 2.
Substrate Scope of the ^{11}C -Aromatic Cyanation Reactions.

Scheme 1. Proposed Mechanism for Copper-mediated ^{11}C -Aromatic Cyanation.

Table 1

Preliminary Screening of Aromatic Cyanation.

Entry	R	Base	Cu catalyst	Solvent	Yield ^[a] (%)
1	Br	nBu ₄ NOH	CuI	DMF	13
2	Br	nBu ₄ NOH	CuBr	DMF	12
3	Br	nBu ₄ NOH	Cu ₂ O	DMF	not observed
4	Br	nBu ₄ NOH	Cu(OTf) ₂	DMF	not observed
5/b/	Br	nBu ₄ NOH	CuI	DMF	11
6	Br	None	CuI	DMF	trace
7	Br	NaOH	CuI	DMF	13
8	Br	Et ₃ N	CuI	DMF	not observed
9	Br	K ₂ CO ₃	CuI	DMF	not observed
10	Br	Cs ₂ CO ₃	CuI	DMF	18
11	Br	Cs ₂ CO ₃	CuI	1,4-dioxane	not observed
12	Br	Cs ₂ CO ₃	CuI	MeCN	not observed ^[c]
13	Br	Cs ₂ CO ₃	CuI	DMA	9
14	Br	Cs ₂ CO ₃	CuI	DMSO	4
15	Br	Cs ₂ CO ₃	CuI	DMF:H ₂ O=1:1	18
16	OMe	nBu ₄ NOH	CuI	DMF	36
17	OMe	Cs ₂ CO ₃	CuI	DMF	33
18	OMe	Cs ₂ CO ₃	CuI	DMF:H ₂ O=1:1	36

^[a]The reactions were carried out at 60 °C and stopped at 1 h.; isolated yields are reported.;

[c] The desired cyanated product was not observed, but the homocoupling product of the boronic acid was isolated instead.

[b] The reaction was carried out at 90 °C;

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Table 2

Optimization of Aromatic ^{11}C -Cyanation of Boronic Acids.

Entry	CuI (mg)	$p\text{MeOPhB(OH)}_2$ (mg)	CS_2CO_3 (mg)	Additive	T ($^\circ\text{C}$)	Time (min)	RC $^{[a]}$ (%)
1	1	2	4	none	120	5	13
2	2	2	4	none	120	5	13
3	4	2	4	none	120	5	10
4	1	2	4	none	150	5	22
5	1	4	4	none	150	5	37
6	1	4	8	none	150	5	61
7	1	4	8	none	150	1	13
8	1	4	8	none	150	3	23
9	1	4	8	Pyridine (2 μL)	150	5	24
10	1	4	8	1,10-Phenanthroline (2 mg)	150	5	64
11	1	4	8	Bis-pyridine (2 μL)	150	5	37
12	1	4	8	TMEDA $^{[b]}$ (2 μL)	150	5	45
13	1	4	8	DMEDA $^{[d]}$ (2 μL)	150	5	65
14 $^{[d]}$	1	4	16	DMEDA (2 μL)	150	5	70

$^{[a]}$ Radiochemical conversion and product identity were determined by radioTLC and radioHPLC, respectively;

$^{[b]}$ TMEDA = N,N,N',N'-Tetramethylethylenediamine;

$^{[c]}$ DMEDA = N,N'-dimethylethylenediamine;

$^{[d]}$ Molar ratio for the optimal reaction condition: CuI (5.25 μmol): Boronic acid (26 μmol): CS_2CO_3 (24 μmol): DMEDA (19 μmol) = 1:5:4:4