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Copper-mediated nucleophilic radiobromination of aryl boron precursors: Convenient preparation of a radiobrominated PARP-1 inhibitor

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ABSTRACT

The copper-mediated nucleophilic radiobromination of aryl boron precursors with a radiobromide ion is a novel radiolabeling method that is efficient and robust. High radiochemical conversion (RCC) was observed using a variety of solvents, temperatures and catalysts. The reaction is also clean and is feasible for purification to obtain high chemical and radiochemical purity. This method provides a very useful route for the preparation of radiobrominated pharmaceuticals, including a radiobromine labeled PARP-1 inhibitor, and it is a valuable addition to the family of copper-mediated radiolabeling processes.

Introduction

Radiobromine-labeled compounds can be used for positron emission tomography (PET) imaging (i.e. ^{76}Br) and for radiation therapy (i.e. ^{77}Br), making the radiobrominated pharmaceutical a theranostic pair for radiotherapy and PET imaging. Radiobromine has some advantages over radiofluorine (^{18}F) and radioiodine:[1] unlike bromine, fluorine only has one radioisotope (^{18}F) that is useful for PET imaging; bromine is smaller in size than iodine, and the C—Br bond is stronger than the C-I bond, leading to greater in vivo stability and potentially better pharmacokinetic and pharmacodynamics properties for the brominated compounds; the accumulation of radioiodide in the thyroid is also not a problem for radiobromide.[2] Among the bromine radioisotopes, [^{76}Br] bromide and [^{77}Br] bromide can be produced practically by a medical cyclotron in high specific activity by the $^{76/77}$Se(p,n)$^{76/77}$Br nuclear reaction on a ^{76}Se- or ^{77}Se-enriched Cu_2Se target.[3] ^{76}Br (55% β^+, 45% EC, $t_{1/2}$ = 16 h) is used mainly for PET imaging; ^{77}Br (99% EC, $t_{1/2}$ = 57 h) is an Auger electron emitter and can be used for radiotherapy. Auger electron radiation is very short range and thus is highly toxic when in close proximity to DNA strands but causes little damage outside the nucleus; this renders Auger electron radiation therapy a promising approach for the treatment of cancer.[4]

Oxidative electrophilic radiobromination (Fig. 1a) is a commonly used method.[1] However, due to the high reactivity of the brominating intermediate under no-carrier-added (NCA) conditions, this oxidative method for radiolabeling may not always afford the desired product.[5] The copper-catalyzed halogen-exchange reaction is a nucleophilic substitution approach, but generally requires high temperatures and is seldom used (Fig. 1b).[6] Recently, we reported that radiobromination of iodonium precursors by nucleophilic substitution gave high radiochemical conversion (RCC), but it produced two major radioactive products (Fig. 1c).[7] Significant progress has also been reported for copper-mediated nucleophilic substitution of aryl boron precursors with [^{18}F]fluoride, radioiodides and [^{11}C]HCN, reactions that proceeded with high RCC.[8–12] Herein, we report the radiobromination of aryl boron precursors using copper-mediated nucleophilic substitution (Fig. 1d).

Results and discussion

^{76}Br and ^{77}Br were produced and isolated as bromide ions in water (1–1.5 mL). Normally, the bromide is thoroughly dried at

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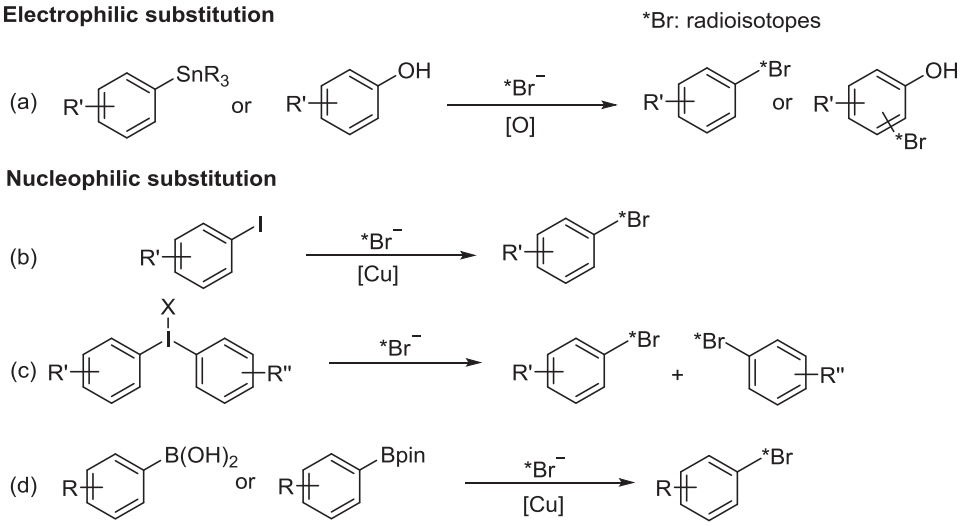
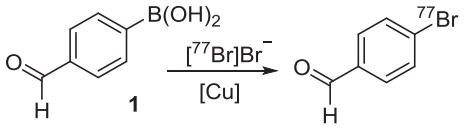


Fig. 1. Radiobromination of aromatic compounds.

elevated temperature under a flow of argon or nitrogen,[7] however, in this study the bromide ion in water was used directly without drying. To determine the best reaction conditions, we followed a typical protocol reported for the radiofluorination of aryl boron precursors, using $Cu(OTf)_2(Py)_4$ as the catalyst and 4-formylphenylboronic acid (**1**) as the model compound.[8,9] First, we explored solvents commonly used in radiochemistry (acetonitrile, DMSO, DMF, and DMA). All of the solvents afforded almost quantitative RCC (Table 1), however, multiple side-products were observed in acetonitrile. The precursor proved to be stable in the other solvents, and only one side-product was observed in small amounts. DMSO gave the best performance and was used in all subsequent evaluations.

The temperature dependence of the radiobromination RCC was studied. Labeling was complete at room temperature, which resulted from using large amounts of reagents (Table 2). Temperatures of 80 °C or 110 °C were used for subsequent experiments to ensure that the reaction would be complete within 20 min. When the amount of boron precursor was reduced to less than 1 mg, a practical amount for the preparation of radiopharmaceuticals, RCC still remained high (Table 3), and subsequent experiments were performed on the same scale (6 μmol boron reagent). The high RCC clearly benefits from the high efficiency of the nucleophilic substitution with the bromide ion and the stability of the

Table 1
Effect of solvent on RCC.[a]



Entry	Solvent	RCC (%)[b]
1	Acetonitrile	98
2	DMSO	98
3	DMF	98
4	DMA	98

[a] **1** (9 mg, 60 μmol), $Cu(OTf)_2(Py)_4$ (18 mg, 26.5 μmol), [^{77}Br]bromide (0.1 mCi in 5 μL water), solvent (1 mL), 110 °C/20 min.
[b] Water (1 mL) was added to the reaction mixture in order to solubilize any free [^{77}Br]bromide in the reaction vessel; RCC was measured by radio-TLC (silica gel/ethyl acetate), and the reaction mixture was analyzed by radio-HPLC.

Table 2
Effect of temperature on radiobromination.[a]

Entry	Temperature (°C)	RCC (%)[b]
1	110	98
2	80	98
3	65	97
4	RT	97

[a] See Table 1 for the reaction conditions (Solvent: DMSO).
[b] Reaction time: 20 min, except for RT (40 min).

Table 3
Effect of reaction concentration on radiobromination.[a]

Entry	**1**/$Cu(OTf)_2(Py)_4$ (mg/mg)	RCC (%)
1	9/18	98
2	4.5/9	98
3	1.8/3.6	98
4	0.9/1.8	98
5	0.36/0.72	96

[a] DMSO (1 mL), 110 °C/20 min.

Table 4
Effect of water content on radiobromination.[a]

Entry	Water (μL)	DMSO (μL)	RCC (%)
1	10	500	98
2	25	500	98
3	50	500	97
4	100	500	94
5	500	500	92[b]

[a] **1** (0.9 mg, 6 μmol), $Cu(OTf)_2(Py)_4$ (1.8 mg, 2.65 μmol), [^{77}Br]bromide (0.1 mCi in 5 μL water), DMSO (0.5 mL), 80 °C/20 min.
[b] 76% as the desired product and 16% as 4-bromobenzoic acid, determined by HPLC.

Table 5
Effect of carrier addition on radiobromination.[a]

Entry	**1** (μmol)	Bromide (μmol)[b]	RCC (%)
1	6	0.01	98
2	6	0.1	98
3	6	1	41[c]

[a] See Table 4 for the reaction conditions.
[b] NaBr in water (1 μL).
[c] 110 °C/20 min.

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Table 6
Effect of the amount of catalyst-$Cu(OTf)_2(Py)_4$.[a]

Entry	$Cu(OTf)_2(Py)_4$ (mg)	RCC (%)
1	0.9	95
2	0.45	93
3	0.18	56
4	0.09	59

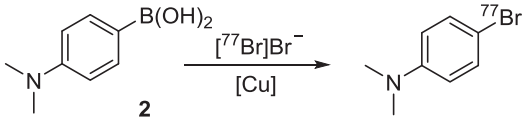
[a] **1** (0.9 mg, 6 μmol), [^{77}Br]bromide (0.1 mCi in 5 μL water), DMSO (0.5 mL), 80 °C/20 min.

Table 7
Effect of the type of copper (II) catalyst.[a]

Entry	[Cu]	RCC (%)
1	None	0
2	$Cu(OTf)_2(Py)_4$	98
3	$Cu(OTf)_2$	99
4	$CuSO_4{\cdot}5H_2O$	92

[a] **1** (0.9 mg, 6 μmol), catalyst (2.65 μmol), [^{77}Br]bromide (0.1 mCi in 10 μL water), DMSO (0.5 mL), 110 °C/20 min.

Table 8
Efficacy of catalysts in radiobromination.[a]



Entry	[Cu]	Temp/Time	RCC (%)
1	$Cu(OTf)_2(Py)_4$	80 °C/20 min	14
		105 °C/10 min	92[b]
2	$Cu(OTf)_2$	80 °C/20 min	0
		105 °C/10 min	30[b]

[a] **2** (6 μmol), catalyst (2.65 μmol), [^{77}Br]bromide (0.1 mCi in 10 μL water), DMSO (0.5 mL).
[b] After 80 °C/20 min, the reaction was further heated at 105 °C for 10 min.

reagents under the base-free conditions. It has been shown previously that water is well tolerated in the nucleophilic substitution reaction with bromide using aryl iodonium salts as precursors.[7] Using 1:1 DMSO/water, RCC remained high (>90%) (Table 4). However, a radioactive by-product was observed in this model reaction that appeared to be 4-bromobenzoic acid, the oxidation product of 4-bromobenzaldehyde, according to HPLC. The water tolerance for this radiobromination is in sharp contrast to that of radiofluorination, which afforded no RCC in the presence of water (data not shown). As water is tolerated, radiobromination using aryl boron precursors can be carried out in aqueous solution, which is advantageous because it reduces the overall time and manipulations involved in the radiolabeling process. It also lowers the radiation exposure to a radiochemist and increases the reliability of the radiochemistry.

Carrier-added radiobromination was also carried out in order to simulate large-scale radiolabeling. RCC remained high even with the addition of 0.1 μmol of carrier (Table 5). This result also indicates the high efficiency of the nucleophilic substitution of the boron precursor with the bromide ion.

$Cu(OTf)_2(Py)_4$ is an efficient catalyst for the nucleophilic radiobromination of aryl boron precursors (Table 6). Pleasingly, reducing the catalyst loading to 0.1 mg (0.13 μmol) still gave over 50% RCC within 20 min. Other copper catalysts, $Cu(OTf)_2$ and $CuSO_4$-

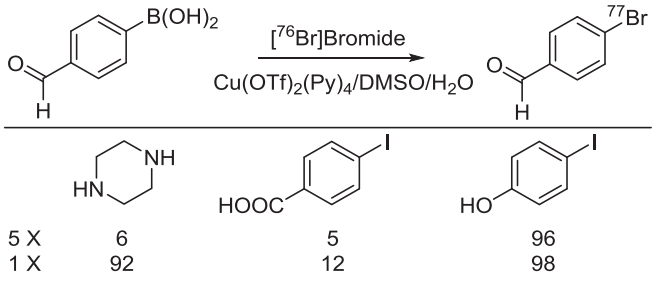


Fig. 3. Influence of reactive groups on radiobromination. (X = 1 equivalent in molarity).

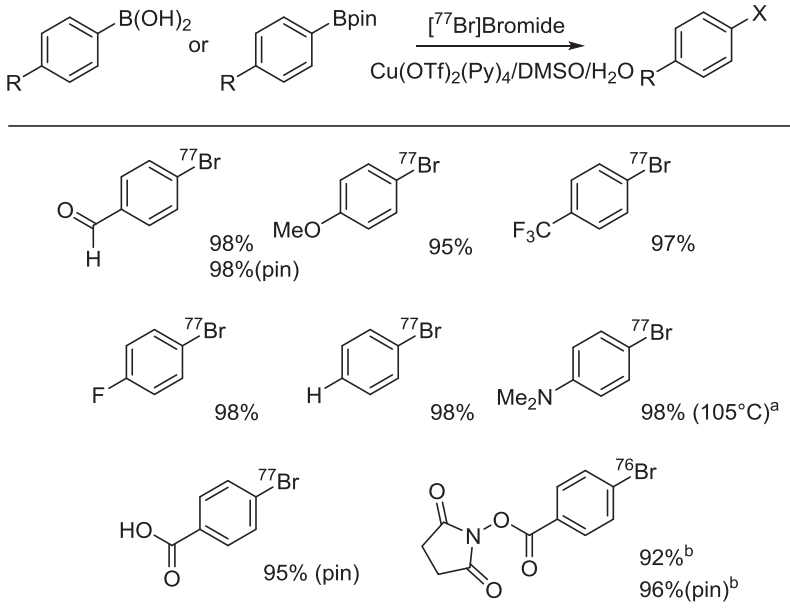


Fig. 2. Copper-mediated radiobromination of model compounds. Reaction condition: precursor (6 μmol), $Cu(OTf)_2(Py)_4$ (2.65 μmol), [^{77}Br]bromide (0.1 mCi in 5–10 μL water), DMSO (500 μL), 80 °C/20 min (except as noted). Note: (a) RCC was 16% at 80 °C/20 min; (b) In addition, 4-bromobenzoic acid was observed in 5% and 3% (pin), respectively.

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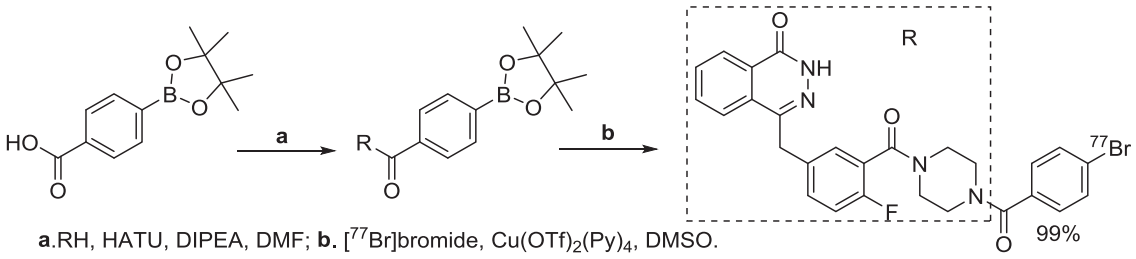

Fig. 4. Synthesis of the boronic ester precursor and radiosynthesis of the olaparib derivative.

·5H_2O, also afforded high RCC. No RCC was obtained in the control reaction without copper (Table 7). The catalytic efficacy of the nucleophilic radiobromination reaction was studied using a less reactive boron precursor, 4-(dimethylamino)phenylboronic acid (**2**). $Cu(OTf)_2(Py)_4$ is more efficient in catalyzing the radiobromination with the less reactive precursor, though required a higher temperature to complete the reaction (Table 8). The optimal performance of $Cu(OTf)_2(Py)_4$ is consistent with that reported for copper-mediated radiofluorination of aryl boron precursors.[8,9]

The radiobromination of other aryl boron precursors is shown in Fig. 2. All the reactions afforded very high RCC using 6 μmol of the precursor at 80 °C or 110 °C. Only the dimethylamine-substituted precursor required 110 °C to complete the reaction, most likely due to the strong electron-donating property of dimethylamino group. Boron precursors appear to be stable under these base-free conditions. Even the base-liable NHS ester can be labeled directly in high yield under these conditions. Only tiny amounts of by-product, presumably the protonated compound,[13] was observed at 80 °C. At 110 °C, more by-product was detected but still remained minimal. In the copper-mediated radiofluorination of aryl boron precursors, one of the major by-products is the protonated material, which may coelute with the fluorinated product upon HPLC, making effective purification a major challenge.[13] By contrast, the brominated product is well separated from the protonated by-product, enabling the final radiobrominated product to be more readily obtained in high chemical and radiochemical purity.

The robustness of the nucleophilic radiobromination of boron reagents was studied by spiking in other reagents with functional groups that are typically detrimental to nucleophilic substitution or may cause other side reactions. As shown in Fig. 3, a phenol group had little or no effect on the radiobromination RCC or the formation of by-products. The carboxylic acid group reduced the RCC significantly, even with the addition of only one equivalent. This is different from the result for 4-bromobenzoic acid (Fig. 2), which was used as a pinacol ester instead of a boronic acid. A stoichiometric amount of a secondary amine (piperazine) has little effect on RCC, also a fivefold excess led to a significant decrease in RCC. However, the boron precursor is not very stable under these conditions with the N—H group, according to HPLC analysis. In the radiofluorination reports, the presence of nitrogen in the aryl precursor, especially amines containing the N—H group, reduce RCCs to very low levels.[14] Because many pharmaceuticals contain nitrogen, this observation suggests the broad applicability of this method for the preparation of radiobrominated pharmaceuticals.

Olaparib is a clinical drug, targeting poly (ADP-ribose) polymerase-1 (PARP-1) for the treatment of cancer. Fluorine-18 and radioiodine-labeled derivatives of olaparib have been synthesized using multiple-steps or unconventional methods as potential imaging or therapeutic agents.[15–17] A radiobromine-labeled derivative of olaparib was synthesized by us previously, using a tedious two-step route that proceeded in very low yield.[7] By contrast, using our current method and starting from the corresponding boronic acid precursor (1 mg), we were able to produce the radiobromine-labeled derivative in aqueous DMSO in 99% RCC (n = 2) (Fig. 4). Most significantly, the precursor is stable, and the desired product is well separated from other minimal amount of by-products, ensuring that the final product can be purified in high chemical and radiochemical purity and in high specific activity (See Fig. S2).

Conclusion

We have developed a novel radiobromination method using copper-mediated nucleophilic substitution of aryl boron precursors and the radiobromide ion. This method is highly efficient and robust, affording the radiobrominated product in high RCC under a variety of conditions. The method is also ideal for purification, providing radiobromine-labeled pharmaceuticals with high chemical and radiochemical purity and high specific activity. Using this method, a bromo-derivative of olaparib was synthesized in high RCC with feasible purification as a potential radiopharmaceutical for PARP-1. This method provides a very useful route for radiobromination and is a valuable addition to the family of copper-mediated radiolabeling processes.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.024.

References

1. Maziere B, Loch C. *Appl Radiat Isot*. 1986;37:703–713.
2. Roland DJ, McCarthy TJ, Welch MJ. In: Welch MJ, Redvanly CS, editors. *Handbook of Radiopharmaceuticals Radiochemistry and Applications*. Chichester: Wiley; 2003:441–465.
3. Tang L. *Q J Nucl Med Mol Imag*. 2008;52:121–133.
4. Buchegger F, Perillo-Adamer F, Dupertuis YM, Delaloye AB. *Eur J Nucl Med Mol Imag*. 2006;33:1352–1363.
5. Zhou D, Zhou H, Jenks CC, Lewis JS, Katzenellenbogen JA, Welch MJ. *Bioconjug Chem*. 2009;20:808–816.
6. Moerlein SM, Hwang DR, Welch MJ. *Int J Rad Appl Instrum A*. 1988;39:369–372.
7. Zhou D, Kim S-H, Chu W, Voller T, Katzenellenbogen JA. *J Labelled Comp Radiopharm*. 2017;60:450–456.
8. Zischler J, Kolks N, Modemann D, Neumaier B, Zlatopolskiy BD. *Chem Eur J*. 2017;23:3251–3256.
9. Tredwell M, Preshlock SM, Taylor NJ, et al. *Angew Chem Int Ed*. 2014;53:7751–7755.
10. Ma L, Placzek MS, Hooker JM, Vasdev N, Liang SH. *Chem Commun*. 2017;53:6597–6600.
11. Zhang P, Zhuang R, Guo Z, Su X, Chen X, Zhang X. *Chem Eur J*. 2016;22:16783–16786.
12. Wilson TC, McSweeney G, Preshlock S, et al. *Chem Commun*. 2016;52:13277–13280.

13. Mossine AV, Brooks AF, Ichiishi N, Makaravage KJ, Sanford MS, Scott PJH. *Sci Rep*. 2017;7:233.
14. Taylor NJ, Emer E, Preshlock S, et al. *J Am Chem Soc*. 2017;139:8267–8276.
15. Zmuda F, Malviya G, Blair A, et al. *J Med Chem*. 2015;58:8683–8693.
16. Carney B, Carlucci G, Salinas B, et al. *Mol Imag Bio*. 2016;18:386–392.
17. Salinas B, Irwin CP, Kossatz S, et al. *EJNMMI Res*. 2015;5:123.