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Radiochemistry

Nickel-Mediated Radioiodination of Aryl and Heteroaryl Bromides: Rapid Synthesis of Tracers for SPECT Imaging**

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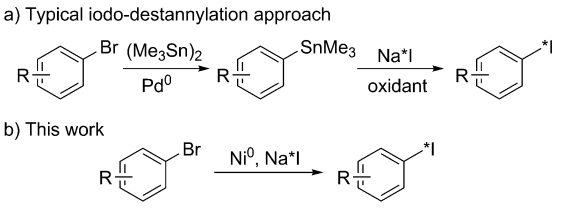
Molecular imaging technologies in combination with radionuclide-labeled molecules allow the noninvasive study of biological processes in vivo at the molecular, cellular, and whole-organ level.[1–3] The development of these techniques has had a significant impact on healthcare with their use in clinical diagnosis, drug development in the preclinical and clinical phase, and biomedical research. In particular, the use of single photon emission computed tomography (SPECT) with radioiodinated probes has found widespread application in biological research (^{125}I) and diagnostic imaging (^{123}I), specifically with diseases associated with the central nervous system.[2,3]

Labeling of small molecules for SPECT imaging using radioiodine is generally restricted to electrophilic aromatic substitution of activated arenes or iodo-demetalation of arenes and alkenes.[1–5] The most commonly used approach is a two-step procedure that involves a palladium(0)-catalyzed stannylation of a halogenated arene or alkene followed by an oxidative iodo-destannylation (Scheme 1a). This method tends to generate iodinated compounds with excellent radiochemical purity and high specific activity.[6] However, there are issues with this approach, such as toxicity concerns associated with the potential of organotin residues in clinical preparations of radioiodinated molecular imaging agents. Furthermore, organotin compounds can be unstable, resulting in unreliable radioiodination reactions. This also restricts the viability of widespread distribution and long-term storage of these precursors in healthcare facilities.

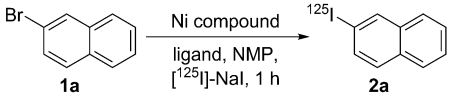


Scheme 1. Radioiodination of aryl bromides.

We now report a nickel-mediated, single-step halogen-exchange reaction for the rapid and direct radioiodination of aryl and heteroaryl bromides that overcomes these limitations (Scheme 1b). As well as exploring the scope of this transformation for the preparation of a range of [^{125}I]-labeled compounds, we also demonstrate its application for the synthesis of 5-[^{123}I]-A85380, a SPECT tracer used for imaging neuronal nicotinic acetylcholine receptors (nAChR) in humans.[7–10]

Optimal reaction conditions for a nickel(0)-mediated halogen-exchange reaction were explored using 2-bromonaphthalene **1a** as a substrate (Table 1). Nickel(0)-mediated halogen-exchange reactions have been reported previously using either zinc[11a] or an electrochemical cell[11b] to reduce a Ni^{II} catalyst to the active Ni^0 species.[12] However, under these reducing conditions, Ullmann-type homocoupled products are also formed. Therefore, based on our previous study of aromatic Finkelstein reactions of aryl bromides,[13] the use of tri-*n*-butylphosphine to mediate the reduction of nickel(II) bromide giving a nickel(0) species for oxidative addition into the C–Br bond, followed by halogen exchange with [^{125}I]-NaI and subsequent reductive elimination was initially investigated.[14] At 160 °C, this approach gave low radiochemical yields (RCYs) of [^{125}I]-2-iodonaphthalene **2a** (entry 2).[15]

Table 1: Optimization of the nickel(0)-mediated radioiodination of 2-bromonaphthalene.[a]



Entry	*T* [°C]	Ni compound/ligand	RCY [%][b]
1	160	–	0
2	160	$NiBr_2$/*n*Bu_3P	7
3	160	$NiBr_2$/dppb	19
4	160	$NiBr_2$	19
5	180	$NiBr_2$	29
6	180	Ni	26
7	180	$[Ni(cod)_2]$	93

[a] All reactions were performed using 2-bromonaphthalene (2 μmol) and 2.5–3.5 MBq [^{125}I]-NaI. [b] Determined by HPLC. NMP = *N*-methyl-2-pyrrolidinone.

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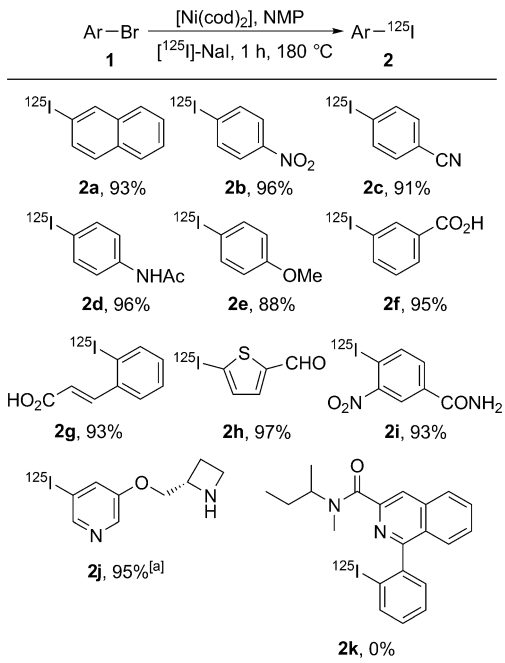
Attempted iodination using other phosphine ligands, such as bis(diphenylphosphinobutane) (dppb), gave similar results (entry 3). Several attempts using nickel bromide without an exogenous ligand and increasing the reaction temperature to 180 °C did not result in any substantial improvement in radiochemical yield (entries 4 and 5).

Although we were aware that the presence of the bromide ion from the nickel complex could interfere with the equilibrium of the halogen exchange, our previous success with nickel(II) bromide during our non-radioactive study demonstrated that iodination could be achieved using an excess of NaI.[13] However, these initial results from the development of a radioiodination reaction showed that when the iodide ion, in this case [^{125}I]-NaI, is the limiting reagent, the equilibrium of halogen exchange is inhibited by the presence of an excess of bromide ions. Therefore, we next investigated non-halogen-containing sources of nickel(0). While nickel powder gave low conversion because of poor solubility, the reaction with bis(1,5-cyclooctadiene)nickel(0) was successful. At 180 °C, with a reaction time of one hour, [^{125}I]-2-iodonaphthalene **2a** was produced in a radiochemical yield of 93 % (entry 7).[16]

The reaction conditions identified for the radioiodination of 2-bromonaphthalene were evaluated for the preparation of a range of [^{125}I]-iodinated aryl and heteroaryl compounds (Scheme 2). Electron-rich and electron-deficient *o*-, *m*-, and *p*-substituted aryl compounds (**2a**–**2h**) were all compatible and converted in excellent radiochemical yield under the standard reaction conditions. While the temperature required for this transformation is higher than that for other radioiodination methods,[6,7] analysis by radio-HPLC showed clean



Scheme 2. Scope of the [Ni(cod)$_2$]-mediated radioiodination. Reactions were performed using substrate (20 μmol) and [^{125}I]-NaI (2.5–3.5 MBq). Radiochemical yields were determined by HPLC. [a] After deprotection of N-Boc group with TFA.

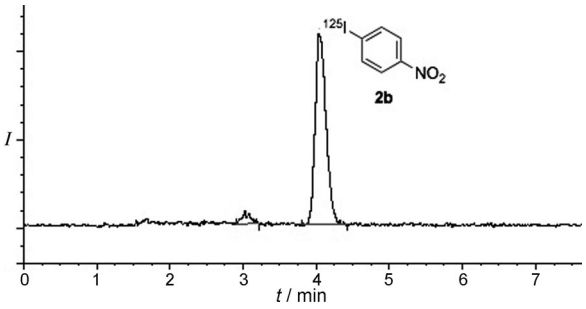


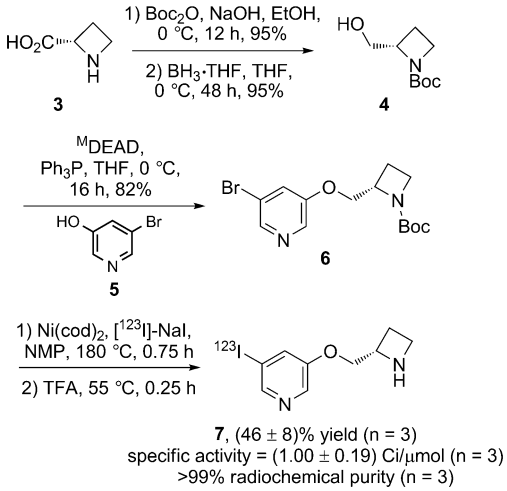
Figure 1. Chromatogram obtained by analytical radio-HPLC of the reaction mixture from the radioiodination of 4-bromonitrobenzene (**1b**), showing a yield of radioiodide incorporation of 96 %.

reactions with no side products from processes such as S_NAr reactions (see Figure 1). [^{123}I]- and [^{125}I]-SPECT imaging agents are generally prepared in low micromole quantities and so the scalability of this transformation was investigated.[2,3] The nickel(0)-mediated radioiodination of substrates **2a**–**2h** was also performed at a 4 μmol scale of substrate. These reactions gave the [^{125}I] products in similar radiochemical yields (85–91 %) as observed with the reaction on a 20 μmol scale. Further studies using 2-bromonaphthalene **2a** at 0.4 and 0.2 μmol were also implemented and consistently afforded [^{125}I]-2-iodonaphthalene in high radiochemical yields.[17] Another important issue in developing new radiolabeling methods for molecular imaging is that the targets can be quickly and easily purified and are not contaminated with by-products or reagents. For all the reactions described in this manuscript, purification was easily achieved using standard HPLC methods. Several of the purified products were then analyzed by atomic absorption spectroscopy for the presence of nickel. Within the detection level of this method (2.5 mg kg^{-1}), nickel species could not be detected in any of these samples.

As well as exploring the scope of radioiodination for the synthesis of standard [^{125}I]-aryl iodides, application of this transformation to the preparation of more functionalized compounds and imaging agents that are currently used clinically was also investigated. Iniparib, the first poly(ADP-ribose) polymerase (PARP) inhibitor to proceed to phase III clinical trials for the treatment of triple-negative breast cancer was rapidly produced in radioiodinated form using the nickel-mediated halogen-exchange reaction.[18] Reaction of 4-bromo-3-nitrobenzamide using [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) and [^{125}I]-NaI gave [^{125}I]-iniparib **2i** in 93 % radiochemical yield. This result now allows access to a new SPECT imaging agent for the development of novel PARP inhibitors. The nickel-mediated radioiodination reaction was also employed for the preparation of 5-[^{125}I]-A85380 **2j**, a SPECT tracer used for imaging neuronal nicotinic acetylcholine receptors (nAChR) in humans.[7–10] Radioiodination of (2*S*)-3-bromo-5-{[1-(*tert*-butoxycarbonyl)-2-azetidinyl]-methoxy}pyridine followed by removal of the *tert*-butyloxycarbonyl (Boc) protecting group mediated by trifluoroacetic acid (TFA) gave 5-[^{125}I]-A85380 **2j** in 95 % radiochemical yield. Some limitations using the nickel-mediated radioiodination reaction were also discovered. For example, attempted

radioiodination of Br-PK11195 to give [^{125}I]-PK11195 **2k**, a SPECT imaging agent of the translocator protein (TSPO),[19] returned none of the expected [^{125}I] product. In this case, the halogen-exchange reaction with [Ni(cod)$_2$] is likely restricted by the steric congestion associated with the *o*-substituted bromobenzene moiety.[20]

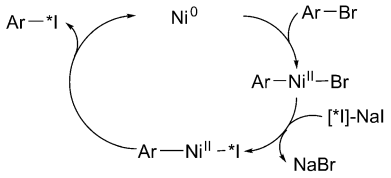
Having demonstrated the scope of [^{125}I] radioiodination typically used in preclinical imaging development, we wanted to show that this approach could also be utilized for the effective preparation of [^{123}I]-labeled compounds for clinical applications. This was achieved with a short five-step synthesis of 5-[^{123}I]-A85380, the SPECT tracer used for imaging nAChRs (Scheme 3). Because of the issues associated with



Scheme 3. Radiosynthesis of 5-[^{123}I]-A85380 (**7**). n = number of independent experiments.

previous syntheses of the bromo-substituted precursor of 5-[^{123}I]-A85380,[8] a new approach was developed during these studies. Under standard conditions, the amino group of commercially available (2*S*)-2-azetidinecarboxylic acid (**3**) was protected with an N-Boc group, followed by chemoselective reduction of the carboxylic acid with borane. Incorporation of the 5-bromo-3-pyridinol moiety is normally achieved using a Mitsunobu reaction, however, problems associated with purification led to the isolation of the coupled product in only modest yields.[8] In this study, this obstacle was overcome using a low-molecular-weight MPEG-supported version of diethyl azodicarboxylate (^{M}DEAD; reported by Hartley and co-workers), which can be removed at the end of the reaction by solid-phase extraction with silica gel.[21] In the first example of the use of this technology for the preparation of an ether, the Mitsunobu reaction of alcohol **4** with 5-bromo-3-pyridinol **5** in the presence of ^{M}DEAD gave the coupled product **6** in 82% yield. The key radioiodination reaction was then performed under our optimized conditions using [^{123}I]-NaI (74 MBq, 237.4 Ci μmol^{-1}). Purification of the iodinated product by HPLC followed by TFA-mediated removal of the Boc protecting group gave 5-[^{123}I]-A85380 **7** in 46% isolated radiochemical yield, with a radiochemical purity of higher than 99% and with a specific activity of 1.0 Ci μmol^{-1}. Identification of the product was confirmed using HPLC by co-injection with a cold sample of 5-I-A85380. The more traditional two-step synthesis of **7** involving formation of an organotin intermediate from **6** followed by an oxidative [^{123}I] iodo-destannylation reaction produces isolated **7** in comparable radiochemical yields (40–61%) and radiochemical purity (> 95%) but generally with higher specific activities (1.7–149 Ci μmol^{-1}).[7,8,9a] However, the synthesis of the organotin precursor from **6** gives yields of only 42–44%,[8,22] and subsequent iodo-destannylation using chloramine-T as the oxidant produces a non-radioactive chloropyridine by-product, which decomposes further during the radiochemical synthesis to give a nonseparable, highly potent nAChR ligand.[7] Therefore, the use of our single-step, nickel-mediated radioiodination gives **7** in significantly higher overall yield without any purification issues.

A proposed reaction mechanism that is consistent with the known chemistry of nickel(0)[11,23] and our data is shown in Scheme 4. In this pathway, the electron-rich nickel(0) per-



Scheme 4. Proposed mechanism for the radioiodination of aryl bromides with nickel(0).

forms an oxidative addition with the aryl bromide, giving a nickel(II) species. In the presence of radiolabeled sodium iodide, a halogen exchange takes place. The resulting Ar–Ni^{II}–*I species then undergoes reductive elimination to form the radioiodinated aryl iodide product and regenerate Ni^{0}. In transition-metal-catalyzed halogen-exchange reactions, an excess of the halide nucleophile is normally added to drive the equilibrium of the process. In our case, where sodium iodide is the limiting reagent, the equilibrium is likely assisted by the formation of the sodium bromide by-product.

In summary, a single-step method for generating [^{123}I]- and [^{125}I]-SPECT imaging agents has been developed using a rapid nickel(0)-mediated halogen-exchange reaction of aryl and heteroaryl bromides. The transformation was compatible with a wide range of electron-rich and electron-deficient *o*-, *m*-, and *p*-substituted aryl compounds and was utilized for the preparation of biologically active compounds, such as iniparib, a PARP inhibitor, and 5-I-A85380, a SPECT tracer for imaging nAChRs in humans. The novel features of this approach include the generation of these compounds directly from readily accessible, nontoxic, stable precursors as well as a short reaction time that allows facile preparation and purification of these SPECT imaging agents within the relatively long half-lifes of the isotopes involved (^{123}I: 13.2 h, ^{125}I: 59.4 days). We expect this method to be widely utilized for the synthesis and development of SPECT radioligands, and, although outside the scope of this study, the transformation also has the potential for [^{131}I] labeling of

compounds for application in radiotherapy. Further studies to extend the scope of this transformation for the preparation of other imaging agents are currently underway.

Experimental Section

A solution of [^{123}I]-NaI in 0.05 M NaOH (74 MBq, 237.4 Ci μmol^{-1}) in a 2 mL reaction vial was blown to dryness under a stream of argon. [Ni(cod)$_2$] (0.5 mg, 1.8 μmol) was added, followed by a solution of (2*S*)-3-bromo-5-{[1-(*tert*-butoxycarbonyl)-2-azetidinyl]methoxy}pyridine (**6**) (1.5 mg, 4.4 μmol) in NMP (40 μL). The mixture was vortexed and heated at 180 °C for 0.75 h. After cooling to room temperature, the reaction mixture was diluted with a solution of acetonitrile (30 μL) in water (470 μL). A small sample was removed for analytical HPLC to assess the incorporation of radioiodide. The crude product was purified by semipreparative HPLC to separate the 5-[^{123}I]-Boc-A85380 from precursor **6**. The fraction containing 5-[^{123}I]-Boc-A85380 **7** was evaporated to dryness, reconstituted in acetonitrile (3 × 200 μL) and transferred to a conical-bottom vial. The intermediate product was blown to dryness under a stream of argon. Trifluoroacetic acid (300 μL) was then added, the mixture was vortexed and heated at 55 °C for 0.25 h to effect deprotection. The final product was blown to dryness under a stream of argon, then reconstituted in 0.9 % saline to afford 5-[^{123}I]-A85380 **7** in (46 ± 8) % isolated radiochemical yield, with specific activity of (1.00 ± 0.19) Ci μmol^{-1} (n = 3). Quality control was performed by analytical HPLC and radiochemical purity was higher than 99 % (n = 3). The identity of the product was confirmed by co-injection with a cold sample of 5-I-A85380.

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[1] a) S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501 – 1516; b) P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem.* **2008**, *120*, 9136 – 9172; *Angew. Chem. Int. Ed.* **2008**, *47*, 8998 – 9033.
[2] M. J. Adam, D. S. Wilbur, *Chem. Soc. Rev.* **2005**, *34*, 153 – 163.
[3] S. L. Pimlott, A. Sutherland, *Chem. Soc. Rev.* **2011**, *40*, 149 – 162.
[4] R. H. Seevers, R. E. Counsell, *Chem. Rev.* **1982**, *82*, 575 – 590.
[5] The synthesis of ^{125}I-labeled 5-iodo-1,2,3-triazoles as biological probes has been recently reported using a copper-catalyzed reaction of azides and alkynes with electrophilic iodine: R. Yan, K. Sander, E. Galante, V. Rajkumar, A. Badar, M. Robson, E. El-Emir, M. F. Lythgoe, R. B. Pedley, E. Årstad, *J. Am. Chem. Soc.* **2013**, *135*, 703 – 709.
[6] For example, see: S. L. Pimlott, L. Stevenson, D. J. Wyper, A. Sutherland, *Nucl. Med. Biol.* **2008**, *35*, 537 – 542.
[7] A. G. Horti, A. O. Koren, K. S. Lee, A. G. Mukhin, D. B. Vaupel, A. S. Kimes, M. Stratton, E. D. London, *Nucl. Med. Biol.* **1999**, *26*, 175 – 182.
[8] J. L. Musachio, V. L. Villemagne, U. A. Scheffel, R. F. Dannals, A. S. Dogan, F. Yokoi, D. F. Wong, *Nucl. Med. Biol.* **1999**, *26*, 201 – 207.
[9] a) S. L. Pimlott, M. Piggott, J. Patterson, J. Cavanagh, D. J. Wyper, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 350 – 353; b) J. T. O'Brien, S. J. Colloby, S. Pakrasi, E. K. Perry, S. L. Pimlott, D. J. Wyper, I. G. McKeith, E. D. Williams, *J. Neurol. Neurosurg. Psychiatry* **2007**, *78*, 356 – 362.
[10] E. M. Mitsis, K. M. Reech, F. Bois, G. D. Tamagnan, M. G. MacAvoy, J. P. Seibyl, J. K. Staley, C. H. van Dyck, *J. Nucl. Med.* **2009**, *50*, 1455 – 1463.
[11] a) K. Takagi, N. Hayama, S. Inokawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691 – 3695; b) G. Meyer, Y. Rollin, J. Perichon, *Tetrahedron Lett.* **1986**, *27*, 3497 – 3500.
[12] A nickel-mediated oxidative fluorination reaction has been reported recently for the preparation of positron emission tomography (PET) imaging agents: E. Lee, J. M. Hooker, T. Ritter, *J. Am. Chem. Soc.* **2012**, *134*, 17456 – 17458.
[13] A. A. Cant, R. Bhalla, S. L. Pimlott, A. Sutherland, *Chem. Commun.* **2012**, *48*, 3993 – 3995.
[14] Aromatic Finkelstein reaction of aryl bromides using copper catalysis has also been reported: A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14844 – 14845.
[15] Radiochemical yield refers to the yield of a radiochemical procedure expressed as a fraction of the activity originally present.
[16] The use of [Ni(cod)$_2$] is critical for the success of the radioiodination. For example, repeating the reaction of entry 5 in Table 1 ($NiBr_2$ at 180 °C) with two equivalents of the cod ligand results in a similar yield (33 %). This result shows that Ni^0 is important for an efficient process and that in the optimized reaction (Table 1, entry 7), the role of the cod ligand is to facilitate solubilization of the nickel species.
[17] At 0.4 and 0.2 μmol scale, [^{125}I]-2-iodonaphthalene **2a** was produced in 87 % and 76 % radiochemical yields, respectively.
[18] a) E. C. Y. Woon, M. D. Threadgill, *Curr. Med. Chem.* **2005**, *12*, 2373 – 2392; b) J. Mendeleyev, E. Kirsten, A. Hakam, K. G. Buki, E. Kun, *Biochem. Pharmacol.* **1995**, *50*, 705 – 714; c) J. O'Shaughnessy, C. Osbourne, J. E. Pippen, M. Yoffe, D. Patt, C. Rocha, I. C. Koo, B. M. Sherman, C. Bradley, *N. Engl. J. Med.* **2011**, *364*, 205 – 214.
[19] a) A. M. Scarf, L. M. Ittner, M. Kassiou, *J. Med. Chem.* **2009**, *52*, 581 – 592; b) J. J. Versijpt, F. Dumont, K. J. Van Laere, D. Decoo, P. Santens, K. Audenaert, E. Achten, G. Slegers, R. A. Dierckx, J. Korf, *Eur. Neurol.* **2003**, *50*, 39 – 47.
[20] The only other substrate that failed to undergo radioiodination during this study was *o*-bromoaniline, the reaction of which gave a mixture of starting material and aniline. In this case, the presence of adjacent acidic amine hydrogen atoms likely facilitates the reduction of the C–Br bond on oxidative addition of Ni^0.
[21] M. Figlus, A. C. Tarruella, A. Messer, S. L. Sollis, R. C. Hartley, *Chem. Commun.* **2010**, *46*, 4405 – 4407.
[22] A. O. Koren, A. G. Horti, A. G. Mukhin, D. Gündisch, A. S. Kimes, R. F. Dannals, E. D. London, *J. Med. Chem.* **1998**, *41*, 3690 – 3698.
[23] T. D. Sheppard, *Org. Biomol. Chem.* **2009**, *7*, 1043 – 1052.