ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 3993–3995

www.rsc.org/chemcomm

COMMUNICATION

Nickel-catalysed aromatic Finkelstein reaction of aryl and heteroaryl bromides†

Alastair A. Cant,[a] Rajiv Bhalla,[b] Sally L. Pimlott[c] and Andrew Sutherland*[a]

Received 9th February 2012, Accepted 21st February 2012
DOI: 10.1039/c2cc30956d

A fast and efficient nickel-catalysed iodination reaction of aryl and heteroaryl bromides has been developed. The transformation was found to be general for a wide range of substrates and was used for the synthesis of iodo-PK11195, an imaging agent of Alzheimer's disease and iniparib, a compound used in the treatment of breast cancer.

Aryl and heteroaryl iodides are ubiquitous synthetic intermediates used for a wide range of transformations, particularly metal-catalysed cross-coupling reactions.[1] The versatility of the C–I bond makes aryl and heteroaryl iodides essential building blocks in medicinal chemistry, material science and total synthesis. Furthermore, radioiodinated aryl and heteroaryl compounds are important in the field of single photon emission computed tomography (SPECT) imaging for the non-invasive investigation in humans of disease such as cancer and neurological disorders.[2]

Due to their general importance in chemical and medicinal science, a number of methods have been developed for the synthesis of aryl iodides from less reactive aryl bromides and chlorides.[3] Most common procedures involve nickel- or copper-mediated reactions. The first nickel-catalysed reaction was reported by Takagi and co-workers who used nickel(II)-bromide with potassium iodide in HMPA as the solvent.[4] An excess of zinc was required as a reducing agent, resulting in the formation of Ullmann-type homo-coupled bi-aryl species as by-products.[4] Cheng and co-workers reported the efficient synthesis of aryl iodides from aryl bromides but this procedure required stoichiometric amounts of Ni(0) powder.[5] Similar limitations were observed with copper mediated processes[6] until the work of Klapars and Buchwald who demonstrated that a high yielding aromatic Finkelstein reaction could be catalysed by copper(I) iodide using diamine ligands.[7] The scope of this process was found to be general allowing the synthesis of a wide range of aryl and heteroaryl iodides. The only drawback with this reaction was the time for completion of the transformation (22–40 h at 110–130 °C). We were interested in developing a metal-catalysed halogen exchange reaction that would not only allow the general synthesis of aryl and heteroaryl iodides, but one that could be applied for the rapid radioiodination of potential SPECT imaging agents. Herein, we report the development of a nickel-catalysed iodination reaction of aryl and heteroaryl bromides that overcomes previous limitations. As well as demonstrating the scope of this new process with compounds used in SPECT imaging and anti-cancer therapy, we also show that the iodination can be completed in as little as 10 min using microwave accelerated heating.

The programme of research began by investigating the iodination of 2-bromoacetanilide. Iodination of this substrate would have to overcome the steric hinderance of the *ortho*-substituent and possible reduction of the carbon–bromine bond by the adjacent amide hydrogen during oxidative addition of the nickel catalyst. Thus, it was believed that an optimised procedure for this challenging substrate would lead to a general iodination method for a wide range of aryl and heteroaryl bromides. Initially, 2-bromoacetanilide was heated to 140 °C with nickel bromide (10 mol%) and sodium iodide (6 equiv.), however, this gave none of the desired iodide (Table 1, entry 1). A ligand screen was then implemented, with electron rich aryl and alkyl phosphines showing conversion to the iodide (entries 3–7). The best result was obtained with tri-*n*-butylphosphine which gave 2-iodoacetanilide in 49% yield after 16 h (entry 7). It should be noted that several diamine ligands such as DMEDA (entry 2) that were successfully utilised in the Buchwald procedure,[7] gave no iodide product when used in the nickel-catalysed reaction. Having identified a suitable ligand, a temperature screen was performed in an effort to shorten the reaction time. An optimal temperature of 180 °C allowed the isolation of 2-iodoacetanilide in 63% yield after only 3 h (entry 9). During this optimisation study, various amounts of the reduced by-product, acetanilide (6–30%) were also isolated from these reactions. By changing the solvent to NMP, restricted this side-reaction and allowed much cleaner reactions (entry 10).

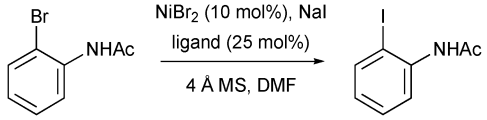
The scope of the reaction was then explored with a range of aryl and heteroaryl bromides (Table 2).[8] The transformation was found to give the corresponding iodides in high yields for *p*-, *m*- and *o*-substituted aryl compounds with electron rich and electron deficient substituents.

Based on previous studies of nickel-catalysed halogen exchange reactions,[3a,4,5] the mechanism likely involves the

[a] *WestCHEM, School of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, UK. E-mail: Andrew.Sutherland@glasgow.ac.uk; Fax: +44 141 330 4888; Tel: +44 141 330 5936*
[b] *GE Healthcare, The Grove Centre, White Lion Road, Amersham, Buckinghamshire HP9 7LL, UK*
[c] *West of Scotland Radionuclide Dispensary, NHS Greater Glasgow and Clyde, Glasgow G11 6NT, UK*

† Electronic supplementary information (ESI) available: Full experimental procedures, spectroscopic data, NMR spectra for all compounds synthesised. See DOI: 10.1039/c2cc30956d

Table 1 Development of the nickel-catalysed iodination reaction of 2-bromoacetanilide



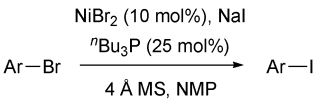
Entry	Ligand	Temp. (°C)	Time (h)	Yield (%)[a]
1	None	140	16	0
2	DMEDA[b]	140	16	0
3	Xantphos	140	16	14
4	Ph_3P	140	16	15
5	dppp	140	16	19
6	dppb	140	16	19
7	$^nBu_3P$	140	16	49
8	$^nBu_3P$	160	16	58
9	$^nBu_3P$	180	3	63
10[c]	$^nBu_3P$	180	3	65

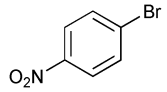
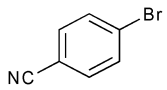
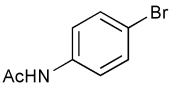
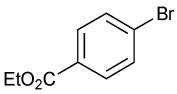
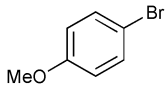
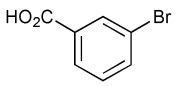
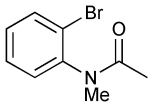
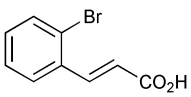
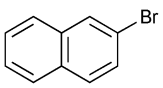
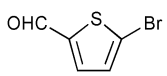
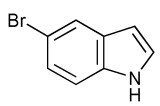
[a] Isolated yields. [b] *N*,*N*′-dimethylethylenediamine. [c] Reaction conducted using NMP as the solvent.

tri-*n*-butylphosphine mediated reduction of Ni(II) to Ni(0) which then oxidatively adds into the carbon–bromine bond.[9] This intermediate can then undergo halogen exchange with the excess iodide.[10] As expected, 4-bromoacetanilide (entry 3) with a distal amide hydrogen atom and *N*-(2-bromophenyl)-*N*-methylacetamide (with no acidic hydrogen, entry 7) gave the corresponding iodides very cleanly with none of the reduced by-product. Heteroaryl bromides such as 5-bromo-2-thiophenecarboxaldehyde (entry 10) and 5-bromoindole (entry 11) were also iodinated cleanly and in good yield. Several of the substrates (entries 3, 7–9 and 11) required longer reaction times for optimal yields. Despite the longer reaction times at high temperatures, the products were isolated very cleanly with minimal decomposition. This was typified by the iodination of more complex substrates such as the translocator protein (TSPO) ligand, I-PK11195 **2** and the PARP inhibitor, iniparib **5**. [^{123}I]-PK11195 **2**, a high affinity ligand for TSPO has been developed for *in vivo* SPECT imaging of human neurodegenerative diseases such as Alzheimer's disease.[11,12] Using the nickel-catalysed iodination reaction at 160 °C, Br-PK11195 **1**[13] was cleanly converted to I-PK11195 **2** in 75% yield (Scheme 1). The preparation of [^{123}I]-PK11195 has been reported using a two-stage synthesis from **1** *via* an organotin derivative.[14] Organotin compounds can be unstable making radioiodination reactions unreliable. In addition, the potential of tin residues in clinical preparations raises toxicity concerns. Using [^{123}I]-sodium iodide with this more direct nickel-catalysed reaction has the potential to provide an alternative route that will reliably allow the radiosynthesis of imaging agents more safely for *in vivo* studies.

The nickel-catalysed iodination reaction was also used as the key step in a new synthesis of iniparib **5**. Iniparib was the first poly-ADP-ribose-polymerase (PARP) inhibitor to commence phase III clinical trials for the treatment of triple negative breast cancer.[15,16] Reaction of commercially available 4-bromobenzonitrile (**3**) with potassium nitrate and sulfuric acid gave 4-bromo-3-nitrobenzamide (**4**) in 74% yield (Scheme 2).[17] Nickel-catalysed iodination of **4** was found to proceed at 140 °C and after 16 h, gave iniparib **5** in 54% yield.

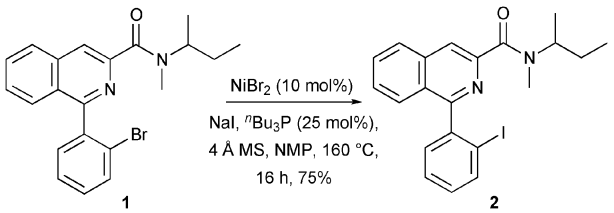
Table 2 Scope of the nickel-catalysed iodination reaction



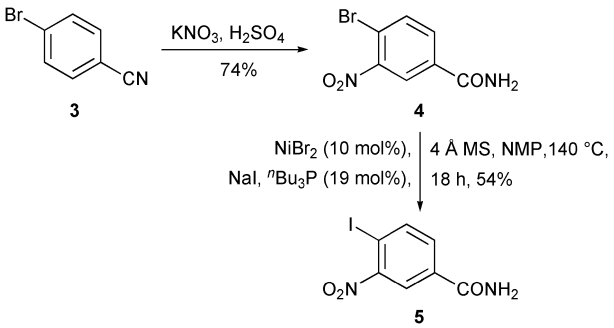
Entry	Bromide	Temp. (°C)	Time (h)	Yield (%)[a]
1		180	3	87
2		180	3	84
3		180	16	83
4		180	3	57
5		160	3	67
6		180	3	77
7		190	7	70
8		140	16	86
9		180	16	74
10		160	3	65
11		160	16	64

[a] Isolated yields.

As the nickel-catalysed iodination reaction was able to produce the desired iodides more quickly at higher temperatures while still maintaining good yields, it was proposed that faster reaction times could be achieved using microwave irradiation to promote the process.[18] Furthermore, the optimal solvent for the iodination reaction, NMP, has a relatively good tanδ (0.275) and so is effective at transforming electromagnetic energy into heat. Therefore, a preliminary study was conducted with a number of aryl bromides to investigate the efficiency of a microwave promoted reaction (Table 3).[19] Even at temperatures of up to 200 °C, many of the substrates were converted to the corresponding iodides in comparable yields to that of the conventional heated

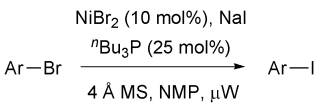


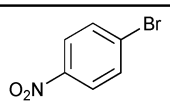
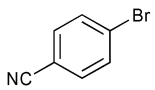
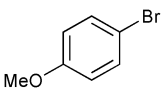
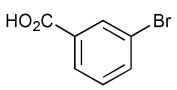
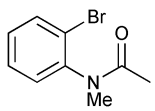
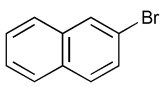
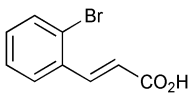
Scheme 1 Nickel-catalysed iodination of Br-PK11195 **1**.



Scheme 2 Two-step synthesis of iniparib **5**.

Table 3 Microwave accelerated iodination reactions



Entry	Bromide	Temp. (°C)	Time (min)	Yield (%)[a]
1		200	30	74
2		200	10	67
3		160	10	49
4		160	10	72
5		200	30	51
6		180	10	68
7		160	60	30

[a] Isolated yields.

process. More importantly, the reactions were found to be complete in times ranging from 10 to 30 min (entries 1–6). The only drawback with microwave heating is that not all functional groups are tolerated. This was exemplified by 2-bromocinnamic acid (entry 7) which under microwave heating produced the corresponding iodide in only 30% yield (*cf.* Table 2, entry 8).[20] Nevertheless, this rapid iodination procedure has the potential for application in the development of a wide range of radioiodinated SPECT imaging agents.

In summary, an efficient nickel-catalysed aromatic Finkelstein reaction has been developed for the general iodination of aryl and heteroaryl bromides. The procedure was applicable for the synthesis of relatively complex targets such as the translocator protein ligand, I-PK11195 **2** and the anti-cancer compound, iniparib **5**. These reactions could be greatly accelerated using microwave irradiation and application of this protocol for the radioiodination of potential SPECT imaging agents is currently underway.

Financial support from the Scottish Funding Council, SINAPSE and GE Healthcare Ltd is gratefully acknowledged.

Notes and references

1 (*a*) *Metal-Catalysed Cross-Coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, New York, 1998; (*b*) N. Kambe, T. Iwasaki and J. Terao, *Chem. Soc. Rev.*, 2011, **40**, 4937.
2 S. L. Pimlott and A. Sutherland, *Chem. Soc. Rev.*, 2011, **40**, 149.
3 (*a*) T. D. Sheppard, *Org. Biomol. Chem.*, 2009, **7**, 1043 and references therein; (*b*) A. C. Bissember and M. G. Banwell, *J. Org. Chem.*, 2009, **74**, 4893 and references therein.
4 (*a*) K. Takagi, N. Hayama and T. Okamoto, *Chem. Lett.*, 1978, 191; (*b*) K. Takagi, N. Hayama and S. Inokawa, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3691.
5 S. H. Yang, C. S. Li and C. H. Cheng, *J. Org. Chem.*, 1987, **52**, 691.
6 For a general review, see: J. Lindley, *Tetrahedron*, 1984, **40**, 1433.
7 A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 14844.
8 After optimisation of the iodination of aryl and heteroaryl bromides, several aryl chlorides and aryl fluorides were explored as possible substrates. However, neither of these substrate classes showed any reactivity.
9 To rule out a S_NAr type reaction mechanism, several of the reactions in Table 1 were repeated in the absence of nickel bromide and tri-*n*-butylphosphine. However, no conversion to the iodides, even at elevated temperatures and extended reaction times was observed.
10 The proposed mechanism seems highly plausible by the observation that Ni(0) powder in the absence of any phosphine ligands also catalyses iodination of aryl bromides under our conditions, although in lower yields.
11 A. M. Scarf, L. M. Ittner and M. Kassiou, *J. Med. Chem.*, 2009, **52**, 581 and references therein.
12 J. J. Versijpt, F. Dumont, K. J. V. Laere, D. Decoo, P. Santens, K. Audenaert, E. Achten, G. Slegers, R. A. Dierckx and J. Korf, *Eur. Neurol.*, 2003, **50**, 39.
13 L. Stevenson, S. L. Pimlott and A. Sutherland, *Tetrahedron Lett.*, 2007, **48**, 7137.
14 S. L. Pimlott, L. Stevenson, D. J. Wyper and A. Sutherland, *Nucl. Med. Biol.*, 2008, **35**, 537.
15 E. C. Y. Woon and M. D. Threadgill, *Curr. Med. Chem.*, 2005, **12**, 2373.
16 (*a*) J. Mendeleyev, E. Kirsten, A. Hakam, K. G. Buki and E. Kun, *Biochem. Pharmacol.*, 1995, **50**, 705; (*b*) J. O'Shaughnessy, C. Osbourne, J. E. Pippen, M. Yoffe, D. Patt, C. Rocha, I. C. Koo, B. M. Sherman and C. Bradley, *N. Engl. J. Med.*, 2011, **364**, 205.
17 M. Schöpff, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 3435.
18 C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250.
19 A microwave mediated halogen exchange reaction for the synthesis of aryl chlorides and aryl bromides using stoichiometric amounts of nickel chloride and nickel bromide, respectively has been previously reported: R. K. Arvela and N. E. Leadbeater, *Synlett*, 2003, 1145.
20 The build up of pressure within the sealed vessel during microwave heating of 2-bromocinnamic acid suggests that under these conditions, the compound undergoes decarboxylation.