



Copper-catalyzed conversion of aryl and heteroaryl bromides into the corresponding iodide



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ABSTRACT

An efficient method for the synthesis of aryl and heteroaryl iodides is described in this study. The reactions of aryl and heteroaryl bromides with potassium iodide proceeded smoothly in the presence of a copper catalyst under mild reaction conditions to produce the corresponding iodides in satisfactory to excellent yields.

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1. Introduction

Aryl and heteroaryl iodides are ubiquitous synthetic intermediates. The most famous application of these iodides in organic chemistry is used as raw materials for the formation of new C–C bonds through coupling reactions [1]. Aryl iodides are generally more reactive than bromides, chlorides, and fluorides because they have a weaker C–I bond, and aryl iodides can be readily employed in medicinal chemistry, material science, and total synthesis as essential building blocks [2]. A number of methods have been developed for the synthesis of aryl iodides from less reactive aryl bromides and chlorides via Finkelstein-type halide exchange reaction [3]. Most common procedures involve nickel- or copper-mediated reactions. Therefore, the production of the corresponding aryl iodides between aryl bromides and copper(I) iodide or nickel(0) powder has been thoroughly investigated and widely employed for this purpose [4]. However, these reactions often require high temperatures (>150 °C) and use excess CuI or Ni(0). In 1978, Takagi and co-workers first reported the nickel-catalyzed reaction using nickel(II)-bromide with potassium iodide in hexamethylphosphoramide (HMPA) solvent [5]. Recently, Klars and Buchwald reported a mild and efficient Cu(I)-catalyzed

method for the conversion of aryl bromides to aryl iodides using diamine ligands in 1,4-dioxane solvent, which is the first example of bromide–iodide exchange reaction catalyzed by copper (I) iodide catalyst [6]. The bromide–iodide exchange reaction involving the use of catalytic amounts of nickel or copper offers several advantages over previous methods that using excess Cu or Ni [7,8], such as mild conditions, broad scope of substrate, and high yield. The only weak point of these catalytic reactions is the use of toxic or carcinogenic solvents, such as HMPA, *N*-methylpyrrolidine (NMP), *N*-dimethylformamide (DMF), acetonitrile (MeCN), and 1,4-dioxane, which does not meet the requirements of sustainable development.

In the course of our research on copper-catalyzed aryl bromide–chloride exchange reaction (Figs. 1 and 2, Eq. (1)) [9], we found that the bromide–iodide exchange reaction between aryl and heteroaryl bromides with potassium iodide can also be performed by utilizing copper(I) oxide (Cu₂O) as the catalyst (Fig. 1, Eq. (2)). The results are reported in this paper.

2. Experimental

2.1. General information

Solvents were dried and degassed before use by standard procedures. ¹H and ¹³C NMR spectra were recorded on either a Varian Inova-400 spectrometer (400 MHz for ¹H, 100 MHz for ¹³C) or a Bruker Avance II-400 spectrometer (400 MHz for ¹H, 100 MHz

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for ^{13}C); CDCl_3 and TMS were used as a solvent and an internal standard, respectively. The chemical shifts are reported in ppm downfield (δ) from TMS, and the coupling constants J are given in Hz. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. GC analysis was performed on an Agilent Technologies 7820A GC system. The products were separated on a 30 m length by 0.320 mm id, HP-5. Nitrogen was employed as the carrier gas, with a constant column flow of 0.8 mL/min. The injector temperature was held constant at 250 °C. The GC oven temperature program was as follows: start from 60 °C, ramp 20 °C/min to 140 °C, ramp 5 °C/min to 180 °C, and then ramp 25 °C/min to 300 °C, hold for 3 min. TLC was carried out on SiO_2 (silica gel 60 F₂₅₄, Merck), and the spots were located with UV light or iodoplatinate reagent. Flash chromatography was carried out on SiO_2 (silica gel 60, 200–300 mesh). The starting materials **1a–1o** and **3a–3g** are commercially available.

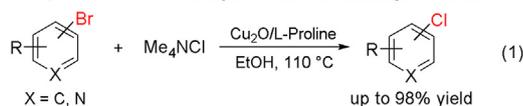
2.2. General procedure for aryl and heteroaryl bromide–iodide exchange reaction

A Schlenk tube was charged with Cu_2O (7.2 mg, 10 mol%), L-proline (11.5 mg, 20 mol%), aryl (or heteroaryl) bromide (**1** or **3**, 0.50 mmol), potassium iodide (KI) (249 mg, 0.75 mmol), and EtOH (1.5 mL) under nitrogen atmosphere. The Schlenk tube was sealed with a teflon valve, and then the reaction mixture was stirred at 110 °C for a period (the reaction progress was monitored by GC analysis). After the reaction was completed, GC yield of high volatile product was determined using an appropriate internal standard (chlorobenzene or 1-chloro-4-methylbenzene) or the solvent was removed under reduced pressure. The residue obtained was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) to afford aryl iodides **2a–2o** or heteroaryl iodides **4a–4g**.

3. Results and discussions

In the initial studies conducted, the halogen exchange reaction of 1-bromo-4-methylbenzene (**1b**) was used as a model to optimize the reaction conditions. The optimization included the selection of the most suitable iodine source, iodine source loading, and the amount of solvent. The results are shown in Table 1. Several iodine sources, including Me_4NI , NaI, and KI, were initially tested in ethanol (EtOH) at 110 °C using Cu_2O and L-proline as precatalyst and ligand, respectively (entries 1–3) [10]. Among the iodine sources tested, KI exhibited a higher reactivity than the others. The effect of KI loading on the yield of **2b** was evaluated (entries 1, 4, and 5). A decreased yield of **2b** was obtained when 2.5 or 3.5 equivalents of KI were employed (entry 4, 91%; entry 5, 64%). The effect of the amount of solvent on the yield of **2b** was finally screened (entries 1, 6–9). The yield of **2b** increased with increasing amount of solvent. Product **2b** was obtained in 95% yield when 1.5 mL EtOH and 3.0 equiv KI were utilized. Therefore, the subsequent reactions

Our previous work: Catalytic Br and Cl-exchange reaction



This work: Catalytic Br and I-exchange reaction

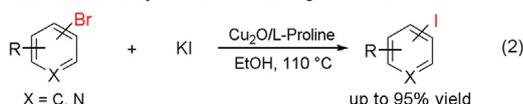


Fig. 1. Preparation of aryl iodide and chloride from bromide.

Table 1
Reaction condition screening.^a

Entry	I source	Solvent (mL)	Yield (%) ^b
1	Me_4NI	EtOH (1.0)	26
2	NaI	EtOH (1.0)	47
3	KI	EtOH (1.0)	92
4 ^c	KI	EtOH (1.0)	91
5 ^d	KI	EtOH (1.0)	64
6	KI	EtOH (0.5)	82
7	KI	EtOH (0.7)	85
8	KI	EtOH (1.2)	90
9	KI	EtOH (1.5)	95

^a Reaction conditions: 1-bromo-4-methylbenzene (**1b**, 0.25 mmol, 42.8 mg), iodine source (3.0 equiv), Cu_2O (10 mol%, 3.6 mg), L-proline (20 mol%, 5.8 mg), and EtOH (0.5–1.5 mL) in a sealed tube.

^b GC yield; chlorobenzene was used as an internal standard.

^c 2.5 equivalents of KI were used.

^d 3.5 equivalents of KI were used.

of aryl (**1a–1o**) and heteroaryl (**3a–3g**) bromides with KI were performed in the presence of Cu_2O and L-proline as precatalyst and ligand, respectively, in EtOH at 110 °C.

The reactions of aryl bromides **1a–1o** with KI were performed under optimized conditions, and the results are summarized in Table 2. The reaction of bromobenzene (**1a**), the simplest aryl bromide, was completed within 30 h to offer the corresponding product, iodobenzene (**2a**), in 91% yield (entry 1). The reactions of both electron-rich (**1b–1e**) and electron-deficient (**1f–1h**) aryl bromides proceeded smoothly to produce aryl iodides **2b–2h** in good to excellent yields (entries 2–8). The electronic properties of the substituents linked to the benzene ring did not strongly affect the reactivity of aryl bromide. 1-Iodo-4-nitrobenzene (**2i**) was also obtained in good yield (85%) from the reaction of phenyl bromide **1i**, which bears a strong electron-withdrawing group nitro (NO_2) on *para*-position (entry 9). 4-Iodobenzonitrile (**2j**) was obtained along with an ester product, ethyl 4-iodobenzoate (**2g**), in 80% and 15% yields, respectively, from the reaction of 4-bromobenzonitrile (**1j**) with KI in the EtOH medium (entry 10). As expected, the chloride atom remained in the iodinated product molecule when 1-chloro-4-bromobenzene (**1k**) was examined (entry 11, 94% yield). 1-Iodo-4-(trifluoromethyl) benzene (**2l**) was produced when 1-bromo-4-(trifluoromethyl) benzene (**1l**) was treated for 30 h (entry 12, 95% yield). The reaction of 1-bromo-2-methylbenzene (**1m**) only gave 28% yield of product 1-iodo-2-methylbenzene (**2m**) (entry 13). The relatively low reactivity of *ortho*-substituted aryl bromide was attributed to the steric effect. The reactions of 5-bromo-1*H*-indole (**1n**) and 1-bromonaphthalene (**1o**) were finally investigated, and the corresponding products **2n** and **2o** were obtained in good to excellent yields (entries 14 and 15, 82% and 92% yields, respectively).

The successful acquisition of aryl iodides from Cu(I)-catalyzed aryl bromide–iodide exchange reactions encouraged the current authors to examine heteroaryl bromide–iodide exchange reactions. The results are summarized in Table 3. The reaction of 2-bromopyridine (**3a**) with KI proceeded smoothly to produce the desired product, 2-iodopyridine (**4a**), in 88% yield (entry 1). 2-Iodo-5-nitropyridine (**4b**) was obtained along with C–N coupling product **5** in 56% and 20% yields, respectively, from the reaction of 2-bromo-5-nitropyridine (**3b**) with KI (entry 2). This result indicated that the electron-deficient heteroaryl bromide could undergo a Cu(I)-catalyzed C–N coupling reaction. The product 6-iodonicotinonitrile **4c** was obtained in 80% yield

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