Iron-Catalyzed S-Arylation of Benzothiazole with Aryl Iodides under Aqueous Medium: Facile Synthesis of Aryl(2-aminoaryl) Sulfides

Hang Wai Lee, Ka Fu Yung,* Fuk Yee Kwong*

State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong
Fax +85223649932; E-mail: kf.yung@polyu.edu.hk; E-mail: fuk-yee.kwong@polyu.edu.hk

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Abstract: A simple route for facile access of aryl(2-aminoaryl) sulfide was reported. With the aid of iron(III) chloride catalyst and diamine ligand, benzothiazole was efficiently S-arylated with various aryl iodides (19 examples) in water under air atmosphere. This operationally simple protocol provides aryl(2-aminoaryl) sulfides in moderate to good yields.

Key words: S-arylation, iron, catalysis, benzothiazole, water

Diaryl thioethers is a versatile building block for numerous pharmaceutical and biologically active compounds.[1] In particular, aryl(2-aminophenyl) sulfide motif constitutes as bioactive subunit such as G protein coupled receptor,[2] antiviral compounds for treatment of HCV infection,[3] Topoisonmerase I inhibitor (TopoI),[4] and Serotonin transporter imaging agent (Figure 1),[5] in which they have attracted considerable interest. Traditional organic synthesis for preparing aryl(2-aminophenyl) sulfides is the reaction of aryl azide with sulfides.[6] This protocol suffers from regioselectivity as both 2- and 4-amino-substituted products were often resulted. To achieve a better selectivity, an alternative synthesis of nitroaryl sulfides followed by subsequent reduction of the nitro group was reported.[7] In recent decades, transition-metal-catalyzed carbon–sulfur bond formation has emerged as an attractive tool for convergent and modular synthesis.[8] Of the catalytic processes reported, the low-cost and toxic copper-catalyzed[9] C–S bond coupling is one of the most attractive methods. These protocols often employ ArSH and Ar′X as the starting materials.[10] In addition to arylthiols, aryldisulfides have been shown as alternative ArS coupling partner with either specific tris(fluorophenyl)boroxins,[11] general aryltrimethoxysilane,[12] or arylboronic acids[13] to access an array of aryl(2-aminoaryl) sulfides. Yet, polar organic solvents such as DMSO[11] and expensive phosphine ligands (e.g., JohnPhos) were necessary in these reactions.[12] Recently, a thiol surrogate of potassium ethyl xanthogenate was reported.[14] Aryl thiols were generated in situ through the reaction between xanthate and aryl iodides.[15] In fact, 2-aminothiophenols[16] are the more straightforward coupling partners, however, they are easily oxidized under air[17] and thus reaction conditions of under inert atmosphere are generally required. Therefore, an exploration of another user-friendly method that especially allows the S-arylation reaction to be conducted under air would be highly favorable.

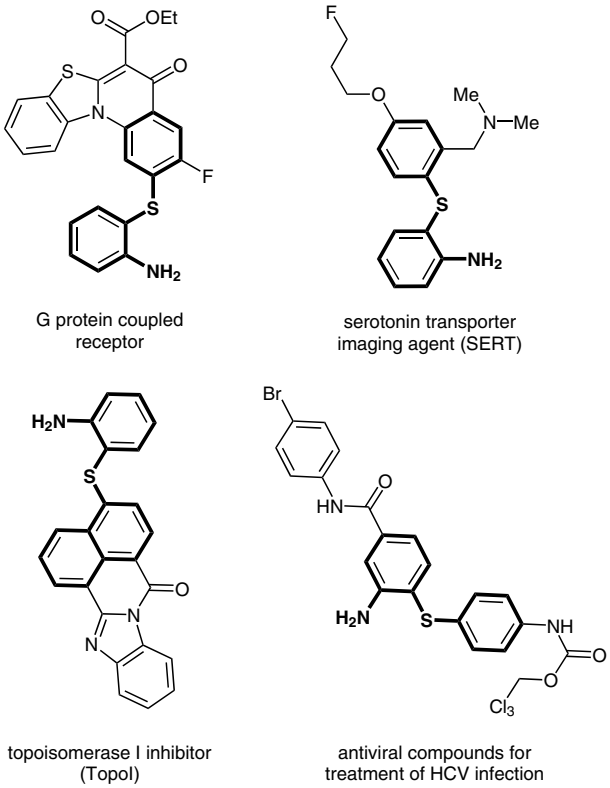

Figure 1 Pharmaceutical and biologically active compounds bearing an aryl(2-aminoaryl) sulfide skeleton

Benzothiazole can be potentially used as a more economical and stable substitute to 2-aminothiolphenol.[18] Indeed, 2-aminothiophenol would be generated in situ through a ring-opening process of benzothiazole under basic conditions.[19] This intermediate allows the subsequent metal-catalyzed C–S bond formation. Nevertheless, recent reports showed that nitrogen or argon environment with the uses of specific base (n-Bu_4NOH)[19f] and solvent (PEG-600)[19g] were required. To date, it is still a challenge to develop a simple and environmentally benign catalysis for the synthesis of aryl(2-aminoaryl) sulfides. Iron catalysts have become successful in C–S bond-forming reactions over the past few years.[20] In continuing our efforts in iron-catalyzed N-arylation of pyrazoles,[21] we herein report

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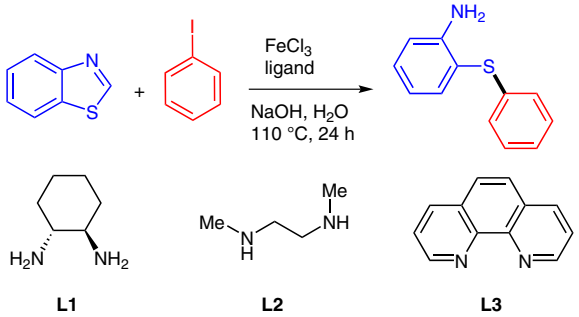
iron(III) chloride associated diamine ligand that facilitate the synthesis of aryl(2-aminoaryl) sulfides.

Benzothiazole and electronically neutral iodobenzene were chosen as the model substrates in our initial investigation (Table 1). A survey of commercially available diamine ligands revealed that *trans*-1,2-diaminocyclohexane (**L1**) was the best ligand while DMEDA and 1,10-Phen provided slightly lower product yields (Table 1, entries 1–3). Control experiment showed that no S-arylation product was afforded in the absence of either ligand or metal (Table 1, entries 4–6). Of the commonly used bases examined, NaOH gave superior performance whereas NaO*t*-Bu and KOH provided slightly lower conversions (Table 1, entries 1, 7, and 8). Further addition of base did not improve the product yield (Table 1, entry 9). Interestingly, solvent screening showed that water gave the best yield for the S-arylation process. Dioxane, DMF, and neat conditions did not promote the reaction (Table 1, entries 10–14). Lower product yield was observed when the reaction was run at 130 °C (Table 1, entry 15).

Table 1 Initial Screenings on the Feasibility of Aqueous Iron-Catalyzed S-Arylation of Benzothiazole[a]



L1 **L2** **L3**

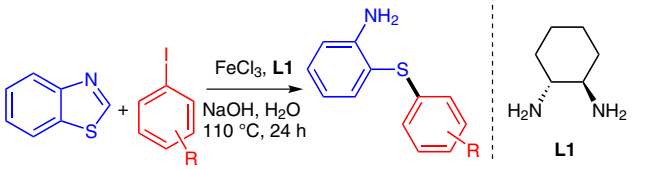
Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	$FeCl_3$/**L1**	NaO*t*-Bu	H_2O	58
2	$FeCl_3$/**L2**	NaO*t*-Bu	H_2O	42
3	$FeCl_3$/**L3**	NaO*t*-Bu	H_2O	56
4	$FeCl_3$/–	NaO*t*-Bu	H_2O	n.r.
5	–/**L1**	NaO*t*-Bu	H_2O	n.r.
6	–	NaO*t*-Bu	H_2O	n.r.
7	$FeCl_3$/**L1**	NaOH	H_2O	60
8	$FeCl_3$/**L1**	KOH	H_2O	54
9[c]	$FeCl_3$/**L1**	NaOH	H_2O	58
10	$FeCl_3$/**L1**	NaOH	dioxane	n.r.
11	$FeCl_3$/**L1**	NaO*t*-Bu	dioxane	n.r.
12	$FeCl_3$/**L1**	NaO*t*-Bu	DMF	n.r.
13	$FeCl_3$/**L1**	NaOH	*t*-BuOH	trace
14	$FeCl_3$/**L1**	NaOH	neat	trace
15[d]	$FeCl_3$/**L1**	NaOH	H_2O	54

[a] Reaction conditions: benzothiazole (1.0 mmol), iodobenzene (1.5 mmol), iron catalyst (20 mol%), diamine ligand (40 mol%), base (3.0 mmol), and solvent (1 mL) were stirred at 110 °C for 24 h under air.
[b] Calibrated GC yields using dodecane as internal standard.
[c] Conditions: 5.0 mmol of NaOH were used.
[d] The reaction was performed at 130 °C.

With our optimized reaction conditions in hand, we next examined the substrate scope of this S-arylation reaction (Table 2). A range of aryl iodides were tested and they proceeded smoothly to give the corresponding products in good yields. Functional groups such as bromo, chloro, and enolizable keto and nitro groups were compatible under these reaction conditions (Table 2, entries 4–9). In particular, the intact chloro and bromo group is beneficial for further functionalization at a later stage using other cross-coupling protocols.

The nitro group was tolerated during the course of reaction (55% yield), thus providing a complementary method to the reported copper catalyst system,[22] which gave the desired product in only 35% yield (Table 2, entry 5). Particularly noteworthy is that this S-arylated product can undergo further reduction and acylation to form potential antiviral compounds.[23] Moreover, (2-aminophenyl)-3-nitrophenylsulfide is a useful substructure of the nitroquinoxalinedone core, which can be used as neuronal death inhibitors for treatment of HCV infection.[24] *ortho*-Substituted aryl iodides were applicable substrates for the S-arylation (Table 2, entries 10–14). More sterically hindered 2-iodocumene furnished the product with comparable yield to that of 2-iodotoluene (Table 2, entry 12 vs. 14).

Table 2 Iron-Catalyzed S-Arylation of Benzothiazole with Aryl Iodides[a]



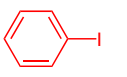
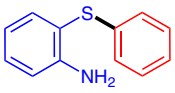
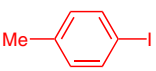
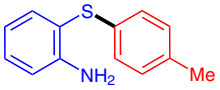
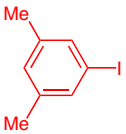
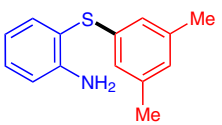
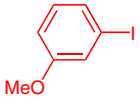
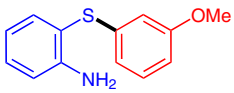
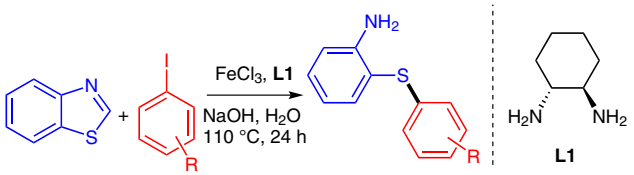
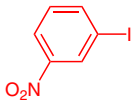
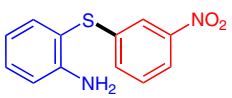
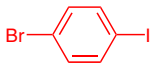
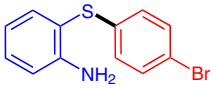
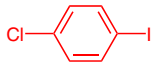
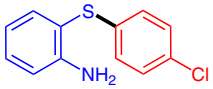
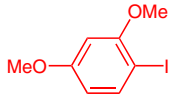
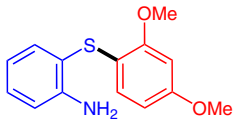
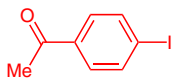
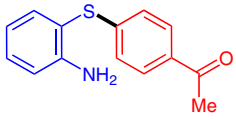
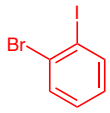
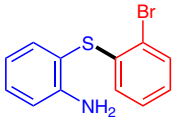
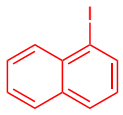
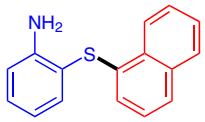
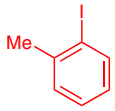
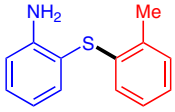
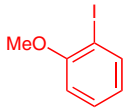
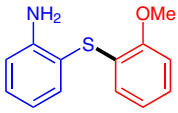
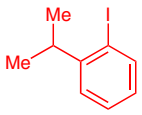
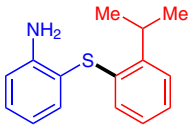
Entry	ArI	Product	Yield (%)[b]
1			60
2			61
3			54
4			53

Table 2 Iron-Catalyzed S-Arylation of Benzothiazole with Aryl Iodides[a] (continued)

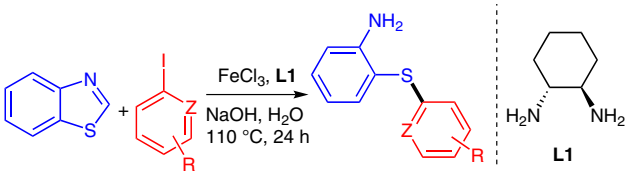


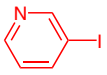
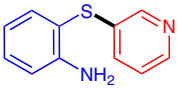
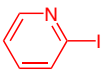
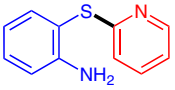
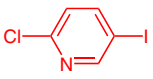
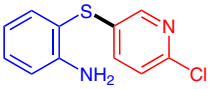
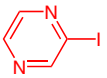
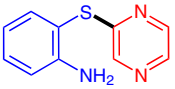
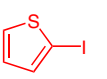
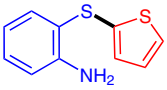
Entry	ArI	Product	Yield (%)[b]
5			55 35[c]
6			64
7			62
8			50
9			43
10			53
11			51
12			52
13			64
14			60

[a] Reaction conditions: benzothiazole (1.0 mmol), aryl iodide (1.5 mmol), $FeCl_3$ (20 mol%), *trans*-1,2-diaminocyclohexane (40 mol%), NaOH (3.0 mmol), and H_2O (1 mL) were stirred at 110 °C for 24 h under air.
[b] Isolated yield.
[c] Benzothiazole (0.5 mmol), aryl iodide (1.0 mmol), copper powder (10 mol%), Cs_2CO_3 (1.0 mmol), and ethylene glycol (2 mL) were stirred at 140 °C for 6 h under N_2.

To further evaluate the efficacy of this catalyst system, we continued to examine the S-arylation with heteroaryl iodides (Table 3). Moderate to good yields of the corresponding products were obtained. 2-Chloro-6-iodopyridine was found to be a feasible substrate for the reaction (Table 3, entry 3). This product gives opportunity for further structural modification using established cross-coupling of aryl chlorides. Thienyl substrate furnished the desired product smoothly (Table 3, entry 5).

Table 3 Iron-Catalyzed S-Arylation with Heteroaryl Iodides[a]



Entry	ArI	Product	Yield (%)[b]
1			58
2			43
3			50
4			42
5			60

[a] Reaction conditions: benzothiazole (1.0 mmol), heteroaryl iodide (1.5 mmol), $FeCl_3$ (20 mol%), *trans*-1,2-diaminocyclohexane (40 mol%), NaOH (3.0 mmol), and H_2O (1 mL) were stirred at 110 °C for 24 h under air.
[b] Isolated yield.

In summary, we have developed a simple protocol for facile preparation of aryl(2-aminophenyl) sulfides. This inexpensive, air-stable, and green reaction system is found to promote the S-arylation in an open-to-air vessel. Moderate to good functional group compatibility was found under the stated reaction conditions. This protocol potentially provides a more complementary access to the S-containing pharmaceutically useful intermediates. Further investigation is currently underway.

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(25) **General Procedure for the Iron-Catalyzed S-Arylation of Benzothiazole with Aryl Iodides**
$FeCl_3$ (32 mg, 20 mol%), *trans*-1,2-diaminocyclohexane (48 μL, 40 mol%), benzothiazole (108 μL, 1.0 mmol), (hetero)aryl iodide (1.5 mmol), NaOH (0.12 g, 3.0 mmol), and H_2O (1.0 mL) were loaded into a reaction tube equipped with a septum in the presence of Teflon-coated magnetic stirrer bar on bench-top under air. The tube was then placed into a preheated oil bath (110 °C) and stirred for 24 h. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to r.t. EtOAc was added for product extraction. The organic layer was separated, and the aqueous layer was further washed with EtOAc (3× ca. 10 mL). The organic part was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230–400 mesh) to afford the desired product (see Supporting Information for details).
2-Aminophenyl Phenyl Sulfide (Table 2, Entry 1)
Yellow liquid; R_f = 0.6 (EtOAc–hexane, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 (br s, 2 H), 6.81–6.85 (m, 2 H), 7.18 (t, *J* = 7.6 Hz, 3 H), 7.27–7.32 (m, 3 H), 7.52–7.55 (dd, *J* = 6.8, 1.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.39, 115.44, 118.8, 125.5, 126.5, 129.0, 131.2, 136.9, 137.5, 148.9 (see Supporting Information for details).
(2-Aminophenyl) 3-Pyridyl Sulfide (Table 3, Entry 1)
Brown solid; R_f = 0.5 (EtOAc–hexane, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.39 (br s, 2 H), 6.71–6.77 (m, 2 H), 7.06–7.09 (q, *J* = 4.8 Hz, 1 H), 7.20–7.24 (td, *J* = 8.0, 1.6 Hz, 1 H), 7.27–7.29 (dt, *J* = 6.4, 1.6 Hz, 1 H), 7.42–7.44 (dd, *J* = 7.6, 1.2 Hz, 1 H), 8.30–8.32 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.38 (d, *J* = 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.4, 115.5, 118.8, 123.7, 131.6, 133.8, 134.2, 137.4, 146.4, 147.5, 149.0 (see Supporting Information for details).