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Graphical Abstract

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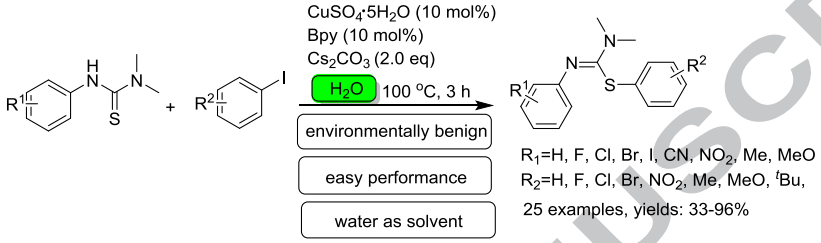

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Facile synthesis of *S*-arylisothioureas *via* the *S*-arylation of arylthioureas with aryl iodides in water

Xing Liu[a+], Hui Zhu[a+], Shi-Bo Zhang[a], Yu Cheng[a], Han-Ying Peng[a], Zhi-Bing Dong[a,b*]

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ABSTRACT

An environmentally benign, simple and highly efficient protocol for the synthesis of *S*-arylisothiourea derivatives has been achieved in good to excellent yields by reacting a series of aryl iodides with arylthioureas, using inexpensive $CuSO_4{\cdot}5H_2O$ as catalyst in water without PTC (phase transfer catalyst). The protocol features easy performance, good to excellent yields, good tolerance towards a variety of functional groups, which could be useful for the preparation of some biologically active compounds.

1. Introduction

Isothioureas are an important class of bioactive and industrially organic compounds with broad applications as antivirals,[1] antihistamines,[2] insecticides,[3] acaricides,[4] and herbicides.[5] *S*-arylisothioureas also show very interesting biological effects, such as antiviral and antianginal[6] activities. In recent years, increasing numbers of *S*-arylisothioureas have been designed and synthesized for biological evaluation, including HIV-1 inhibitors (**A**), anti-infective agent (**B**), central system agents (**C**), and valosine containing protein inhibitor (**D**) (**Figure 1**).[7] Therefore the preparation of *S*-arylisothioureas has received increased attention from synthetic organic chemists and biologists.

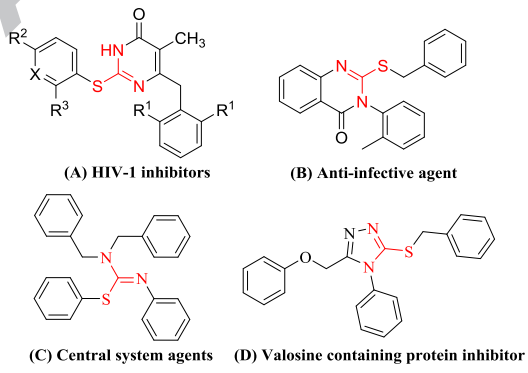


Figure 1. Some biologically active *S*-arylisothioureas.

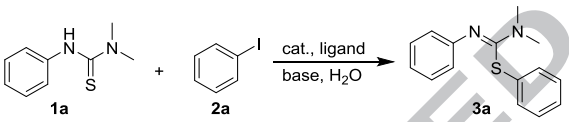
Conventionally, *S*-aryisothioureas have been synthesized *via* the cross-coupling reactions of mercaptothioureas with aryl halides[8] or aryl boronic acids,[9] or the nucleophilic attack of arylthiols.[10] Although these methods are suitable for certain synthesis, there somehow exist some drawbacks such as long reaction time, expensive reagents, low yields of products, high catalyst loading, and large amounts of solid supports, which would eventually result in the generation of a large amount of toxic waste. Several other methods are available for the synthesis of *S*-arylisothioureas, including the *S*-arylation of *N*-phenylthioureas with diazonium salts,[11] the reaction of benzotriazolecarboxiimidamides with aromatic thiols,[12] and the metathesis exchange reaction between isothioureas and aryl isocyanates.[13] Although significant progress has been achieved towards the synthesis of these compounds, development of alternatively inexpensive, non-air sensitive catalytic systems for the preparation of *S*-arylisothioureas is still highly desirable.

In recent decades, the development of environmentally friendly reaction medium, especially water, has been paid much attention because water is nontoxic, low price and widely available.[14] On the other side, significant progress has been made towards the development of copper-catalyzed C-S coupling reactions in water recently.[15] However, PTC (phase transfer catalyst) are normally added in most of the reported protocols.[15] Lately, our group developed protocols for the synthesis of *S*-arylisothioureas in organic phase, as well as the synthesis of the substituted 2-mercaptobenzoheterocycles in water without PTC.[16] For the continuous interest in the C-S coupling reaction,[17] we present here the *S*-arylations of arylthioureas with aryl iodides in water, furnishing the *S*-arylisothioureas by C-S coupling.

2. Results and discussions

Initially, we carried out a set of experiments using *N*-phenylthioureas (**1a**) and iodobenzene (**2a**) as model substrates in water under air using Cu(Ⅱ) salts as the catalyst for optimizing the reaction conditions, and the results are summarized in Table 1. First, bases were screened by using 10 mol% of $CuCl_2$ as the catalyst, 20 mol% of 2,2'-Bipyridine (Bpy) as the ligand, and H_2O as the solvent (entries 1-5). Cs_2CO_3 as the base provided the highest yield of the product at 91% (entry 1). Several copper catalysts were then investigated (entries 6-10), and $CuSO_4{\cdot}5H_2O$ was selected to be the most effective catalyst for the current reaction (entry 10). No reaction could be detected with no catalyst loading (entry 11). When copper salt is replaced by iron salt, no product (**3a**) was obtained (entry 12). Among the ligands tested, *N*,*N*′-dimethylethylenediamine (DMEDA) showed almost no help for reaction, whereas other ligands, such as 1,10-phenantroline, L-proline and pyridine all showed good effect (entries 13-16). 10 mol% of the ligand loading did not affect the yield of the product (entry 17), while the yield of the product was reduced to 81% when 5 mol% of $CuSO_4{\cdot}5H_2O$ was used (entry 18). The screening of the base loading showed that 2 equiv of Cs_2CO_3 was optimal (entries 17, 19-20). In addition, the product yield dropped to 62% when the temperature was reduced to 90 °C (entries 17, 21-22). The later control experiments showed that the Cu(I) was also suitable for the reaction, but less reactive (entry 23). Thus, the optimal reaction conditions were set and were summarized in entry 21 (10 mol% of $CuSO_4{\cdot}5H_2O$, 10 mol% of 2,2'-bipyridine, 2 equiv. of Cs_2CO_3 in water, heating at 100 °C for 3 hours).

Table 1. Screening of the reaction conditions.[a]



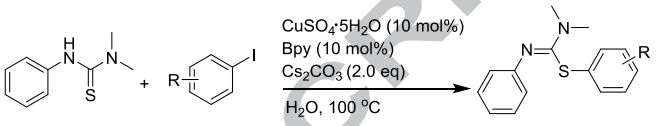
1a 2a 3a

Entry	Catalyst	Base	Ligand	T (°C)	Yield (%)[b]
1	$CuCl_2$	Cs_2CO_3	Bpy	120	91
2	$CuCl_2$	K_2CO_3	Bpy	120	84
3	$CuCl_2$	KOH	Bpy	120	89
4	$CuCl_2$	K_3PO_4	Bpy	120	90
5	$CuCl_2$	NaOH	Bpy	120	84
6	$Cu(OAc)_2$	Cs_2CO_3	Bpy	120	83
7	$Cu(OTf)_2$	Cs_2CO_3	Bpy	120	88
8	$CuBr_2$	Cs_2CO_3	Bpy	120	92
9	$CuCl_2{\cdot}2H_2O$	Cs_2CO_3	Bpy	120	89
10	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	Bpy	120	93
11	--	Cs_2CO_3	--	120	0
12	$FeCl_3{\cdot}6H_2O$	Cs_2CO_3	Bpy	120	0
13	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	1,10-Phen	120	93
14	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	L-proline	120	84
15	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	Py	120	89
16	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	DMEDA	120	trace
17[c]	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	Bpy	120	93
18[d]	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	Bpy	120	81
19[e]	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	Bpy	120	85
20[f]	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	Bpy	120	80
21[g]	**$CuSO_4{\cdot}5H_2O$**	**Cs_2CO_3**	**Bpy**	**100**	**91**
22	$CuSO_4{\cdot}5H_2O$	Cs_2CO_3	Bpy	90	62
23	CuI	Cs_2CO_3	Bpy	100	82

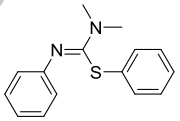
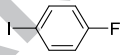
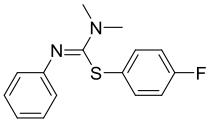
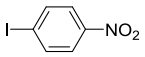
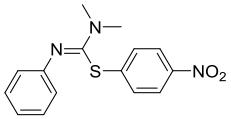
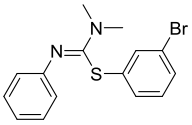
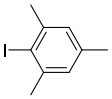
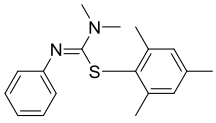
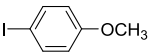
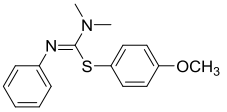
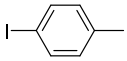
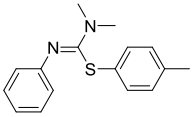
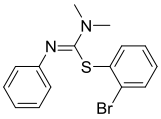
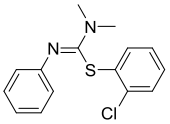
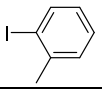
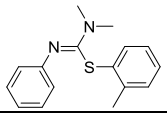
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), Catalyst (10 mol %), ligand (20 mol %), base (2.0 equiv), and H_2O (2 mL) in a sealed tube at 90-120 °C for 3 h. [b]Isolated yield. [c]In the presence of $CuSO_4{\cdot}5H_2O$ (10 mol %) and 1,10-phenanthroline (10 mol %). [d]In the presence of $CuSO_4{\cdot}5H_2O$ (5 mol %) and 1,10-phenanthroline (10 mol %). [e]In the presence of Cs_2CO_3 (1.5 equiv). [f]In the presence of Cs_2CO_3 (1.0 equiv). [g]The optimal reaction conditions: 10 mol% of $CuSO_4{\cdot}5H_2O$, 10 mol% of 2,2'-bipyridine, 2 equiv. of Cs_2CO_3 in water, heating at 100 °C for 3 hours.

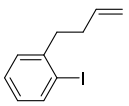
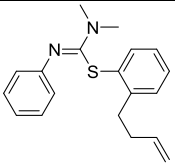
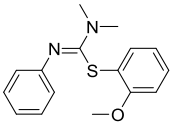
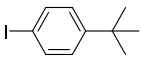
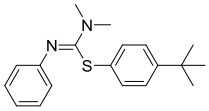
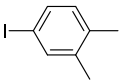
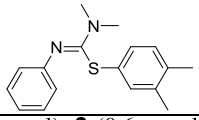
With the above mentioned optimized conditions in hand, we made the investigation of *S*-arylation of arylthiourea by reacting with different aryl iodides and the results are summarized in Table 2. Different aryl iodides reacted with arylthiourea to give the corresponding *S*-arylisothioureas. Electron-withdrawing substituents resulted in good yields. Halide groups such as F, Cl, and Br yielded the desired products in 86-93% yield (entries 2, 4, 8, 9), while strongly electron-withdrawing group (NO_2) gave lower yields (entry 3). For the electron-donating alkyl or methoxy groups, general good yields were obtained. (entries 5-7, 10, 12, 13-14). Due to the possible steric hindrance reason, compound **3k** was obtained in a moderate yield (70%, entry 11).

Table 2. *S*-arylation of arylthiourea with various aryl iodides.[a]



1 2 3

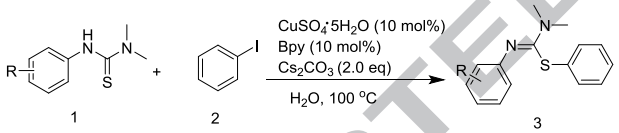
Entry	Aryl iodide	Product		Yield %[b]
1			**3a**	91
2			**3b**	89
3			**3c**	33
4			**3d**	86
5			**3e**	81
6			**3f**	80
7			**3g**	83
8			**3h**	89
9			**3i**	93
10			**3j**	90

11			**3k**	70
12			**3l**	93
13			**3m**	94
14			**3n**	94

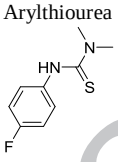
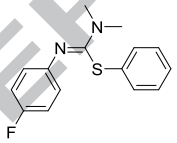
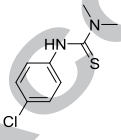
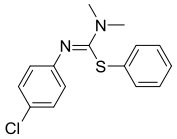
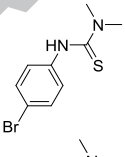
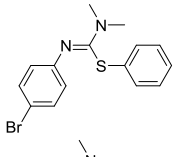
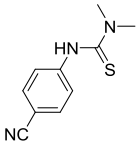
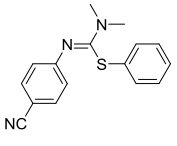
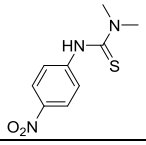
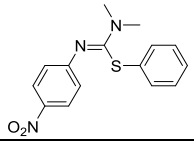
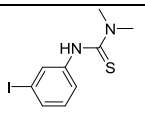
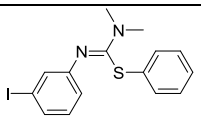
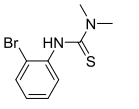
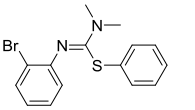
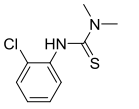
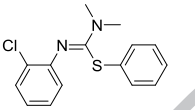
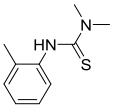
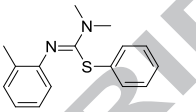
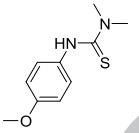
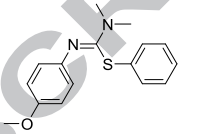
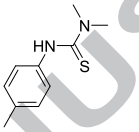
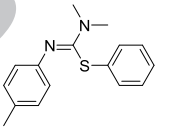
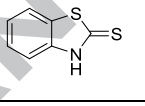
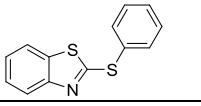
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), $CuSO_4{\cdot}5H_2O$ (10 mol %), 2,2'-bipyridine (10 mol %), Cs_2CO_3 (2.0 equiv), H_2O (2 mL), 100 °C. [b]Isolated yield.

Studies on the scope of the coupling reactions with respect to a wide array of electronically and structurally diverse thioureas were summarized in Table 3. As expected, the reaction showed good functional compatibility. Substrates bearing *ortho* Br or Cl group resulted in moderate yield (entries 7-8). To further illustrate our protocol in the organic synthesis, we explored the benzo-heterocycle substrate (entry 12). It is a pity that the benzo[*d*]thiazole-2(3H)-thione could not be converted to the desired product **3z** under the standard conditions. While the reaction could be proceeded smoothly when TBAB (tetrabutylammonium bromide, 5 mol %) was added.

Table 3. *S*-Arylation of aryl iodide with various arylthioureas.[a]



1 2 3

Entry	Arylthiourea	Product		Yield %[b]
1			**3o**	94
2			**3p**	96
3			**3q**	94
4			**3r**	96
5			**3s**	96
6			**3t**	61
7			**3u**	50
8			**3v**	45
9			**3w**	95
10			**3x**	82
11			**3y**	85
12			**3z**	87[c] trace[d]

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), $CuSO_4{\cdot}5H_2O$ (10 mol %), 2,2'-bipyridine (10 mol %), Cs_2CO_3 (2.0 equiv), H_2O (2 mL), 100 °C. [b]Isolated yield. [c]In the presence of TBAB (tetrabutylammonium bromide, 5 mol %). [d]Without TBAB.

A control experiment was conducted in a N_2 atmosphere, and the model reaction gave only trace of the product, indicating that the oxygen in the air serves as oxidant in the reaction. Although the reaction mechanism is not clear so far, we speculate that the reaction proceeds through an oxidative addition−reductive elimination mechanism via an unstable Cu^{III} intermediate,[18] which is energetically more feasible than other possible mechanisms. The further details and the related applications are still under research in our lab.

3. Conclusion

In summary, we have developed a simple and effective method for the synthesis of a series of *S*-arylisothiourea derivatives by using $CuSO_4{\cdot}5H_2O$ as a catalyst, the reaction was conducted under PTC-free (PTC: phase transfer catalyst) conditions in an aqueous medium. The experimental simplicity, good to excellent yields and environmental friendliness of this protocol, is expected to be useful for the preparation of some biologically active compounds.

Acknowledgments

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Experimental

All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR and capillary GC analysis. NMR spectra were recorded on a Bruker AM400 NMR instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in ppm and coupling constants (J) are given in Hz. All melting points were determined on a RY-1G melting point instrument without correction. High-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95Q or Finnigan 90 mass instrument (ESI). TLC was performed using aluminum plates coated with SiO_2 (Merck 60, F-254) and visualized with UV light at 254 nm. Column chromatography was performed on silica gel (200-300 mesh) with PE-EtOAc as eluent.

Typical procedure for the preparation of aryl-isothioureas (3a)

Aryl thiourea (**1**, 0.5 mmol), aryl iodide (**2**, 0.6 mmol), $CuSO_4{\cdot}5H_2O$ (0.05 mmol), Cs_2CO_3 (2.0 equiv), 2,2'-bypyridine (0.05 mmol) were added in sealed tube equipped with a septum and magnetic stirring bar, H_2O (2.0 mL) was then added. The mixture was stirred at 100 ^oC and checked by TLC until the starting material was finished (about 3h). The reaction was terminated with sat. NH_4Cl solution (3 mL) and then extracted with ethyl acetate. The crude solution was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography to afford the desired product **3a**.

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Highlights:

- **25 *S*-arylisothiourea derivatives are synthesized in good to excellent yields.**
- **Inexpensive $CuSO_4.5H_2O$ serve as catalyst, and water serve as solvent.**
- **No PTC (phase transfer catalyst) is needed.**
- **The protocol features easy performance, good tolerance towards a variety of functional groups.**