DOI: 10.1002/adsc.200800461

Copper(I)-Catalyzed One-Pot Synthesis of 2-Iminobenzo-1,3-oxathioles from *ortho*-Iodophenols and Isothiocyanates

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Received: July 25, 2008; Published online: November 4, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800461.

Abstract: A novel and efficient formation of 2-iminobenzo-1,3-oxathioles from readily available precursors *via* a copper(I)-catalyzed one-pot cascade process has been developed. Various 2-iminobenzo-1,3-oxathioles, which might be useful in pharmaceutical and biochemical areas, were conveniently synthesized in good to excellent yields.

Keywords: copper(I) catalysis; 2-iminobenzo-1,3-oxathioles; intramolecular C–S bond formation; *ortho*-iodophenol; one-pot reactions

The 1,3-oxathiole motifs are found in a variety of useful heterocyclic derivatives applied as biologically active compounds[1] and pharmaceutical products[2] (Figure 1, **A**–**D**). For example, oxathiolone-fused chalcones **A** have been studied for their antibacterial, antifungal and tuberculostatic activities,[1a] oxathiolones **B** are used as neuroprotective agents,[2a] compound **C** with an imino group is found to be an agrochemical pesticide,[1b] and 2-imino-1,3-oxathioles **D** might possess fungicidal activity.[1c] Among the 1,3-oxathiole derivatives, 2-imino-1,3-oxathioles have been demonstrated to be important in the context of potential pharmaceutical or biochemical activities.[2b,3]

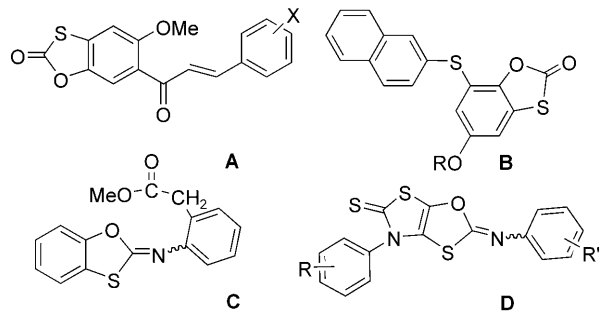


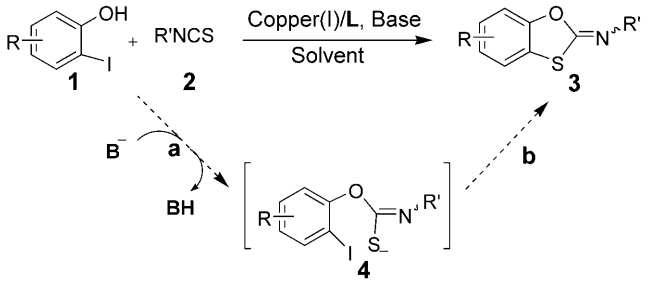
Figure 1. Several 1,3-oxathiole derivatives reported as biologically active compounds and pharmaceutical products.

Only a few methods have been reported for the synthesis of 2-imino-1,3-oxathioles, particularly for the assembly of 2-iminobenzo-1,3-oxathioles.[1b,3a,4] Kulka reported the preparation of *N*-acyl-2-imino-1,3-oxathioles from *O*-alkyl acylcarbamothioates and 2-chloro ketones.[4d] One approach to 2-iminobenzo-1,3-oxathioles utilized the Rh(II)-catalyzed reaction of α-diazocarbonyl compounds with isothiocyanates.[4b] They also could be derived from benzo-1,3-oxathiole-2-thiones,[1b] or synthesized by [4+1] cycloaddition.[3a] However, these approaches might be limited due to their narrow scopes, special or expensive metal catalysts and reagents, unsatisfactory efficiencies, or the tedious mutistep manipulation. Therefore, concise and efficient methods to give these heterocyclic motifs are still in demand.

Batey et al. have reported Cu- or Pd-catalyzed intramolecular C–S cross-coupling for the preparation of benzothiazoles.[5] Recently, one-pot strategies for the synthesis of various useful heterocyclic compounds based on the copper-catalyzed C(aryl)–X (X=N, C, O, etc.) bond formation have been studied.[6–8] They have received much attention because of their more convenient "one-pot" manipulations and good efficiencies. For example, indazoles could be efficiently formed *via* CuO-catalyzed *N*-arylation of hydrazines followed by intramolecular dehydration.[6e] Several benzimidazoles were synthesized *via* aryl amination/condensative cyclization processes.[6a–d] Also, C–C coupling/cyclization methods for the synthesis of indoles[7a–d,f,g] and C–C coupling/intramolecular C–O coupling protocols for the formation of benzofurans[8c] have also been disclosed during the recent years.

To the best of our knowledge, there is no report about the formation of 2-imino-1,3-oxathioles *via* a one-pot copper-catalyzed coupling process. Herein we have designed a novel and efficient one-pot cascade reaction to synthesize 2-iminobenzo-1,3-oxathioles:

ortho-iodophenol would undergo the intermolecular addition/intramolecular C–S coupling process with isothiocyanate in the Cu(I)-ligand-base system. Our proposed approach is summarized in Scheme 1. In the

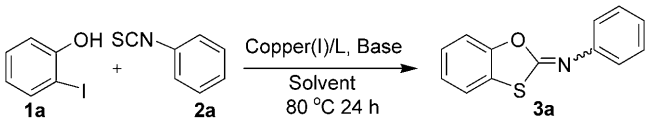


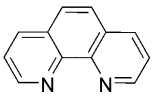
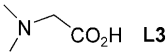
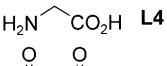
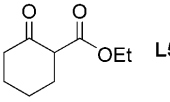
Scheme 1. Proposed one-pot synthesis of 2-iminobenzo-1,3-oxathioles *via* intermolecular addition/intramolecular C–S coupling.

presence of a proper base, the nucleophilic oxygen of *ortho*-iodophenol **1** would attack the carbon atom of NCS on isothiocyanatobenzene **2**, and intermediate **4** could be formed (step **a**).[9] In the presence of a proper copper(I) catalyst and ligand, **4** might convert into the product **3** *via* an intramolecular C–S coupling (step **b**). In the latter step, the sulfur atom would take priority over nitrogen atom in the assaulting action.

In our preliminary experiments, 2-iodophenol **1a** and isothiocyanatobenzene **2a** were chosen as the model substrates. Our reaction was originally carried out in DME with CuI (10 mol%) as the catalyst, 1,10-phenanthroline (20 mol%) as the ligand and Cs_2CO_3 (2.0 equiv.) as the base at 80 °C[10] under an N_2 atmosphere. To our delight, the starting materials disappeared and the anticipated product **3a** was obtained in moderate yield after 24 h (Table 1, entry 1). The IR specrum of **3a** showed a strong absorption at 1655 cm^{-1}, this indicated the presence of an imino group. In the ^{13}C NMR spectrum, the carbon atom of imino group appeared at $\delta = 160.3$ ppm. Other structural characterizations were also carried out and its structure could be established (^1H NMR, MS and elemental analysis). We also tried a two-step procedure during our original research. A mixture of **1a** (1.0 mmol), **2a** (1.0 mmol) and Cs_2CO_3 (2.0 mmol) in DME (2.0 mL) was stirred at 80 °C without any catalyst and ligand. The mixture was analyzed by TLC every 20 min. Both of the starting materials were consumed completely within 1.0 h. Then CuI (10 mol%) and **L1** (20 mol%) were added immediately. The mixture was stirred for 24 h at 80 °C and the same desired product **3a** was isolated in 63% yield (Table 1, entry 1). Comparing the two methods, the former one is superior for its concise single-step manipulation and better yield. Therefore, the former procedure was

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



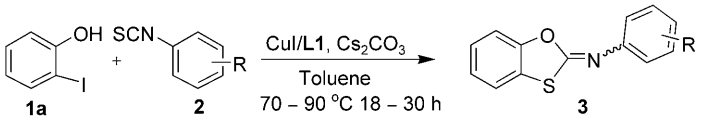
Entry	Copper(I)	Ligand	Base	Sovent	Yield [%][b]
1	CuI	 **L1**	Cs_2CO_3	DME	69, 63[c]
2	CuI	**L1**	Cs_2CO_3	DMF	16
3	CuI	**L1**	Cs_2CO_3	CH_3CN	84
4	CuI	**L1**	Cs_2CO_3	Dioxane	92
5	CuI	**L1**	Cs_2CO_3	Toluene	97, 72[d], 97[e]
6	CuI	L-Proline **L2**	Cs_2CO_3	Toluene	23
7	CuI	 **L3**	Cs_2CO_3	Toluene	93
8	CuI	 **L4**	Cs_2CO_3	Toluene	22
9	CuI	 **L5**	Cs_2CO_3	Toluene	trace
10	CuI	–	Cs_2CO_3	Toluene	trace
11	CuI	**L1**	K_3PO_4	Toluene	89
12	CuI	**L1**	K_2CO_3	Toluene	88
13	CuI	**L1**	Na_2CO_3	Toluene	7
14	–	**L1**	Cs_2CO_3	Toluene	n.d.[f]
15	CuBr	**L1**	Cs_2CO_3	Toluene	70
16	CuCl	**L1**	Cs_2CO_3	Toluene	73
17	Cu_2O	**L1**	Cs_2CO_3	Toluene	16

[a] *Reaction conditions:* 2-iodophenol **1a** (1.0 mmol), isothiocyanatobenzene **2a** (1.0 mmol), copper source (0.1 mmol), ligand (0.2 mmol) and base (2.0 mmol, 2.0 equiv.) in solvent (2.0 mL) under N_2, at 80 °C for 24 h.
[b] Isolated yield.
[c] A subsequential procedure was conducted.
[d] The reaction temperature was 65 °C.
[e] The reaction temperature was 90 °C.
[f] The desired product was not detected (n.d.).

selected and the corresponding optimization was conducted as follows.

Firstly, we investigated the influence of solvents while other conditions were settled (Table 1, entries 1–5). When DMF was used, the result deteriorated (entry 2). The yields were greatly enhanced both in CH_3CN and dioxane (entries 3 and 4). Toluene seemed to be the best solvent (entry 5). Decreasing the reaction temperature gave an obviously lower yield, while hardly any change was observed at a slightly higher temperature (entry 5). Several ligands were tested (entries 6–10). L-Proline and glycine were not suitable for this process. *N,N*-Dimethylglycine was good, but 1,10-phenanthroline proved to be better. Ethyl 2-oxocyclohexanecarboxylate, which performed

Table 2. CuI-catalyzed one-pot synthesis of 2-iminobenzo-1,3-oxathioles from 2-iodophenol **1a** and aryl isothiocyanates **2a–2h**.[a]



1a 2 3

Entry	*ortho*-Iodophenol	Isothiocyanate	Product	Temperature/Time	Yield [%][b]
1	**1a**	**2a**	**3a**	80 °C/24 h	97
2		**2b**	**3b**	80 °C/24 h	91
3		**2c**	**3c**	80 °C/24 h	89
4		**2d**	**3d**	80 °C/30 h	88
5		**2e**	**3e**	80 °C/24 h or 90 °C/30 h	69 or 86
6		**2f**	**3f**	75 °C 20 h	91
7		**2g**	**3g**	70 °C 18 h	92
8		**2h**	**3h**	80 °C 20 h	93

[a] *Reaction conditions: ortho*-iodophenol (1.0 mmol), isothiocyanate (1.0 mmol), CuI (0.1 mmol), **L1** (0.2 mmol) and Cs_2CO_3 (2.0 mmol, 2.0 equiv) in toluene (2.0 mL) under N_2.

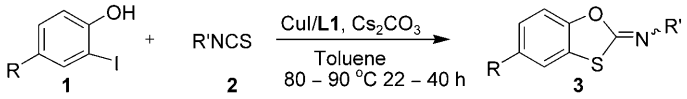
[b] Isolated yield.

as an efficient and versatile ligand in our previous work,[11] was also tested. However, the ligand seemed unsuitable in this process (entry 9). Hardly any anticipated product was observed without a ligand (entry 10). Different bases were examined (entry 5, entries 11–13), and Cs_2CO_3 showed as the optimal base. In a blank experiment, the reaction did not proceed in the absence of copper catalyst (entry 14). When the copper source was switched to CuBr, CuCl or Cu_2O (entries 15–17), the yield decreased (entry 17). Therefore, the optimized conditions were to use a combination of CuI (10 mol%) and 1,10-phenanthroline (20 mol%) in the presence of Cs_2CO_3 (2.0 equiv.) as base in toluene.

With the optimal conditions established, we then tried to investigate the scope of this methodology. Firstly, the reactions of 2-iodophenol **1a** with various substituted isothiocyanates **2** were examined (Table 2, entries 1–8). The isothiocyanates bearing both electron-donating groups (*p*-Me, *m*-Me and *o*-Me) and electron-withdrawing groups (*m*-Cl, *m*-CF_3 and *p*-Br) seemed to be reactive and the products were obtained in good to excellent yields (entries 2–4 and entries 6–8). Strong electron-donating substituents on the isothiocyanate might do harm to the reaction and decrease its reactivity (entry 5). However, once the temperature was raised, the yield improved obviously.

Encouraged by the above results, we further investigated the scope and the generality of the method by varying the *ortho*-iodophenols, which could be facilely derived from the *para*-substituted phenols (Table 3, entries 1–13). To our delight, generally the reactions proceeded successfully in moderate to excellent yields, although higher temperatures and longer times were required. The isothiocyanates bearing electron-withdrawing groups as well as weak electron-donating

Table 3. CuI-catalyzed one-pot synthesis of 2-iminobenzo-1,3-oxathioles from substituted *ortho*-iodophenols and isothiocyanates.[a]



R = Me, *t*-Bu,Cl; R' = Aryl, Alkyl

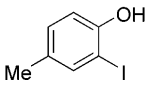
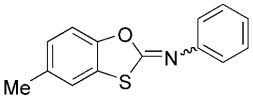
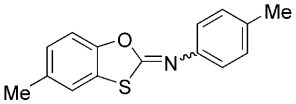
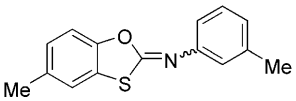
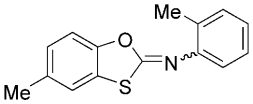
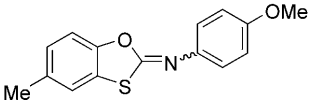
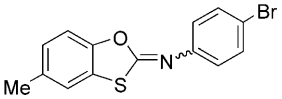
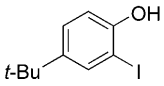
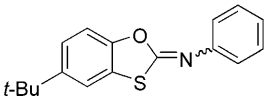
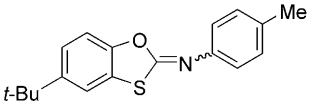
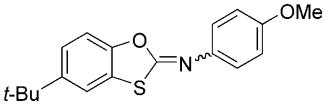
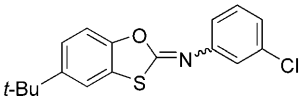
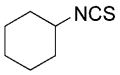
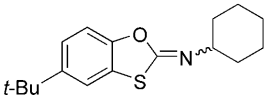
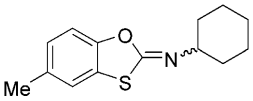
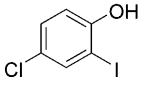
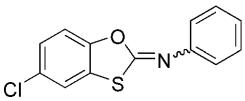
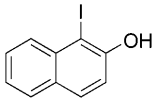
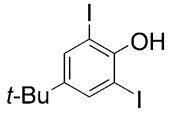
Entry	*ortho*-Iodophenol	Isothiocyanate	Product	Temperature/Time	Yield [%][b]
1	**1b** 	**2a**	**3j** 	85 °C/26 h	96
2	**1b**	**2b**	**3j** 	85 °C/30 h	90
3	**1b**	**2c**	**3k** 	80 °C/26 h	86
4	**1b**	**2d**	**3l** 	85 °C/30 h	84
5	**1b**	**2e**	**3m** 	90 °C/30 h	63
6	**1b**	**2h**	**3n** 	80 °C/22 h	81
7	**1c** 	**2a**	**3o** 	85 °C/26 h	94
8	**1c**	**2b**	**3p** 	85 °C/28 h	86
9	**1c**	**2e**	**3q** 	90 °C/30 h	67
10	**1c**	**2f**	**3r** 	85 °C/24 h	85
11	**1c**	**2i** 	**3s** 	90 °C/30 h	75[c,d]
12	**1b**	**2l**	**3t** 	90 °C/30 h	64[c,e]
13	**1d** 	**2a**	**3u** 	90 °C/40 h	52
14	**1e** 	**2a**	–	90 °C/36 h	–[f]

Table 3. (Continued)

Entry	*ortho*-Iodophenol	Isothiocyanate	Product	Temperature/Time	Yield [%][b]
15	**1f** 	**2a**	–	80 °C/30 h	–[f]

[a] *Reaction conditions: ortho*-iodophenol (1.0 mmol), isothiocyanate (1.0 mmol), CuI (0.1 mmol), **L1** (0.2 mmol) and Cs_2CO_3 (2.0 mmol, 2.0 equiv.) in toluene (2.0 mL) under N_2.
[b] Isolated yield.
[c] The amount of the isothiocyanate **2i** was 1.1 equiv.
[d] A mixture of *anti* and *syn* isomers was obtained (the isomeric ratio was about 89:11, approximately as determined by ^{1}H NMR).
[e] A mixture of *anti* and *syn* isomers was obtained (the isomeric ratio was about 86:14, approximately as determined by ^{1}H NMR).
[f] A complicated mixture was obtained.

groups gave satisfactory results (entries 2–4, 6, 8 and 10), while that bearing the strong electron-donating group *p*-MeO reacted slowly and a lower yield was obtained (entries 5 and 9). In comparison with aryl isothiocyanates, alkyl isothiocyanates seemed less reactive (entries 11 and 12). The *ortho*-iodophenol with a *p*-Cl substituent seemed less reactive and only gave a moderate yield, for its ability to attack the electrophilic carbon of NCS was weaker and step **a** might be influenced (entry 13). 1-Iodonaphthalen-2-ol **1e** was tried under the similar conditions. Unfortunately no desired product was detected (entry 14). Probably the steric hindrance of the naphthyl ring influenced the intramolecular coupling process (step **b**). Finally, a diiodide **1f** was also tested. However, only a complex mixture was obtained and so further isolation was unexecuted (entry 15). We thought this might due to the complicated intermolecular reactions, as well as the steric hindrance.

In summary, we have designed and developed a novel, efficient and concise method for copper(I)-catalyzed one-pot synthesis of 2-iminobenzo-1,3-oxathioles. A simple "one-pot" operation was conducted, readily available starting materials were employed and relatively mild conditions were applied. Various 2-iminobenzo-1,3-oxathioles, which might be potentially applicable in the pharmaceutical and biochemical areas, were conveniently synthesized in moderate to excellent yields. The reaction also performed as a good example for intramolecular C(aryl)–S cyclization by copper(I) catalysis.

Experimental Section

General Procedure

An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, Cs_2CO_3 (652 mg, 2.0 mmol), CuI (19 mg, 0.10 mmol, 10 mol%), 1,10-Phen·H_2O (40 mg, 0.20 mmol, 20 mol%) and *ortho*-iodophenol **1** (1.0 mmol). The tube was evacuated and backfilled with N_2 (this procedure was repeated 3 times). Under a counter flow of N_2, toluene (1.0 mL) was added by syringe and the mixture was pre-stirred for about 0.5 h at room temperature. Then a solution of isothiocyanate **2** (1.0~1.1 mmol) in toluene (1.0 mL) was added *via* syringe under a counter flow of N_2. The tube was sealed and the mixture was allowed to stir at the temperature indicated in Table 2. The reaction was monitored by TLC. After the starting material was consumed completely and the bottom dot was unchanged, the reaction was stopped and cooled to room temperature. The reaction mixture was directly passed through celite. After being rinsed with further 30 mL of Et_2O, the combined filtrate was concentrated by rotatory evaporation. The residue was purified by column chromatography on silica gel to give the pure product. For more details, see Supporting Information.

Acknowledgements

This work was financially supported by the Specialized Research Fund for the Doctoral Program Foundation of Higher Education of China (No. 2060335036).

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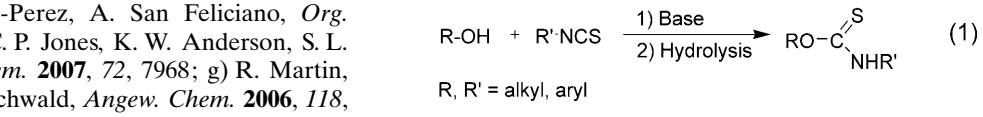

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