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SHORT COMMUNICATION

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Copper-Catalyzed Domino Reactions for the Synthesis of Phenothiazines

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A method for the one-pot synthesis of phenothiazines from benzothiazoles and aryl *ortho*-dihalides was explored. Preliminary work on the mechanism of the reaction suggested that it follows a domino process, including the hydrolysis of benzothiazoles followed by C–S coupling and C–N coupling. The low loading of the catalyst system (5 mol-% for both copper and ligand), the mild experimental conditions (90 °C, 12 h), and the use of a green reaction medium make this synthesis very attractive to academia and industry.

Introduction

The phenothiazine family of compounds has played a significant role in chemistry, life sciences, and materials science since its first member was prepared by Bernthsen in 1883.[1] Up to now, over 5000 phenothiazine derivatives have been obtained, most of which exhibit valuable bioactivities, such as neuroleptic, anticancer, antiemetic, antihistaminic, antipruritic, reversing multidrug resistance (MDR), antibacterial, and analgesic properties; they have been described in several reviews.[2] For example, over 100 phenothiazines have been used as neuroleptics in clinical settings.

The unique features of phenothiazines, including electron-rich sulfur and nitrogen heteroatoms as well as a nonplanar ring with a butterfly conformation in the ground state, can impede molecular aggregation and the formation of intermolecular excimers.[3] Therefore, phenothiazines have been introduced as scaffolds for various metal-free organic dyes for use in dye-sensitized solar cells (DSSCs),[4] lithium-ion batteries,[5] photocatalytic hydrogen production,[6] nonlinear optical devices,[7] organic light-emitting diodes (OLEDs),[8] polymer light-emitting diodes (PLEDs),[7] molecular wires,[9] and so on.[10]

Several methods for the synthesis of phenothiazines have been previously reviewed.[11] The conventional methods can be roughly classified into the following categories: (1) heating of suitable substituted diphenylamines with sulfur, (2) Smiles rearrangement of 2-amino-2-nitrodiphenyl sulfides followed by ring closure, (3) transition-metal-catalyzed intramolecular cyclization of 2-amino-2′-halodiphenyl sulfides, and (4) other specific methods, including cyclization of 2-aminothiophenols with cyclohexanones under an atmosphere of oxygen,[12] cyclization with benzoquinones,[13] reductive cyclization of 2-nitrodiphenyl sulfides with triethyl phosphite,[14] and thermal cyclization of aryl azides with 1,2,3-benzothiadiazole.[15] However, drawbacks and challenges of these methods still remain. The cyclization of diphenylamines with sulfur produces isomeric substituted phenothiazines, which makes it difficult to isolate the desired product even though iodine is used as a catalyst.[16] The cyclization of diphenyl sulfides involving a Smiles rearrangement was developed to overcome this issue, but its steric hindrance and difficult four-step route have limited its applications.[17] The functionalization of phenothiazine affords substituted phenothiazines, but the process often suffers from poor regioselectivity.[7,18] Moreover, the most clear drawback of these conventional methods is the lack of availability of the starting materials. Several tactics, such as using new types of starting materials and/or using a tandem reaction pathway, have recently been able to circumvent these issues. In 2008, a palladium-catalyzed, three-component approach to synthesize promazine was reported.[19] Since then, the transition-metal-catalyzed synthesis of phenothiazines has attracted significant attention. In 2010, Ma et al.[20] reported the first copper-catalyzed synthesis of phenothiazines in good to high yields from 2-iodoanilines and 2-bromobenzenethiols. Using this protocol, the catalyst loading could reach 20 mol-%. The reaction temperature must be sequentially held at 90 °C for 24–48 h and then at 110 °C for 48–96 h. In 2012, Zeng et al.[21] used aryl *ortho*-dihalides and *ortho*-aminobenzenethiols as starting materials to form phenothiazines in a one-pot synthesis but still needed a high loading of CuI (30 mol-%), a high temperature (120 °C), and long reaction time (48 h). Interestingly, Abele et al.[22] developed a new pathway toward phenothiazines by using 2-aminobenzothiazoles as the starting materials. However, the high reaction temperature (170 °C), narrow substrate scope, and relatively low yields in most cases make this method less practical.

Therefore, the development of a novel synthetic approach to phenothiazines under mild conditions, including

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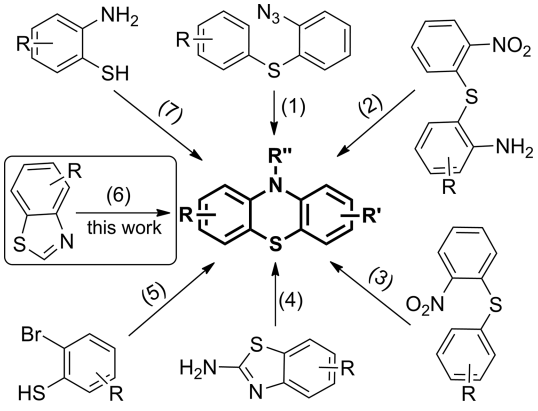
a lower catalyst loading, a lower temperature, and shorter times, as well as a broad substrate scope is highly desired.

Modern synthesis management must seek ideal procedures in which the formation of several bonds can occur in one pot without the addition of any further reagents or catalysts and without changing the reaction conditions. This concept has been well defined as a domino process, which has been applied in many modern syntheses of organic compounds.[23]

In continuation of our interest[24] in finding more effective synthetic approaches to phenothiazines, we herein report a novel domino reaction to synthesize phenothiazines from benzothiazoles and aryl *ortho*-dihalides, as shown in Scheme 1.



Scheme 1. Typical starting materials for the synthesis of phenothiazines. (1) See ref.[15] (2) See ref.[17] (3) See ref.[14] (4) See ref.[22] (5) See ref.[19,20] (6) The starting material in this work. (7) See ref.[12,13,21]

Results and Discussion

Inspired by Abele's method[22] of preparing phenothiazines by using 2-aminobenzothiazoles as alternative starting materials and considering that benzothiazoles can be reliably prepared from various sources[25] with more stability than *ortho*-aminobenzenethiols, we speculated that developing a new synthesis protocol by replacing 2-aminobenzothiazoles with benzothiazoles to increase atom economy would be a challenge. Fortunately, Xu et al.[26] and Han et al.[27] reported the copper-catalyzed direct ring-opening arylation of benzothiazoles with aryl iodides to afford 2-aminoaryl sulfides. Hence, we hypothesized that benzothiazoles would be good starting materials in reactions with aryl *ortho*-dihalides instead of aryl iodides to afford 2-[(2-halophenyl)thio]anilines, a key intermediate for the further synthesis of phenothiazines through copper-catalyzed intramolecular C–N coupling. We began our study by using benzothiazole and 1-bromo-2-iodobenzene as starting materials and Xu's[26] and Han's[27] ligand-free, copper-catalyzed protocols; however, only 2-[(2-bromophenyl)-thio]aniline rather than the expected phenothiazine was obtained. In this case, further intramolecular C–N coupling should be the key to obtaining the target phenothiazine. We assumed that using some type of ligand might be helpful; thus, we screened several typical copper-based catalytic systems for C–N coupling, such as copper/proline,[20] copper/*N*,*N*′-dimethylethylamine,[28] and our previously reported system.[24,29] The copper/*N*-methoxy-1*H*-pyrrole-2-carboxamide (**L1**) catalyst system was found to be the most effective to perform the model reaction to provide phenothiazine in 60% yield, which encouraged us to further optimize the reaction conditions.

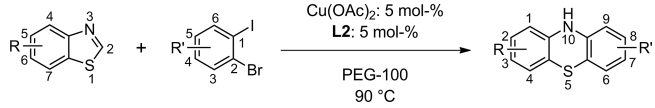
This promising result encouraged us to explore the reaction parameters, mainly including different copper sources, ligands, bases, and solvents, as well as their proportions. The optimized conditions, consisting of $Cu(OAc)_2$ (5 mol-%)/*N*-(benzyloxy)-1*H*-pyrrole-2-carboxamide (**L2**, 5 mol-%), benzothiazole (100 mol-%), aryl *ortho*-dihalide (120 mol-%), and NaOH (400 mol-%) in polyethylene glycol (PEG)-100 (2 g) at 90 °C for 12 h were identified. Although the loadings of both $Cu(OAc)_2$ (5 mol-%) and **L2** (5 mol-%) for the reaction are fairly low, both are necessary for the reaction to proceed effectively. Moreover, PEG-100 was chosen as the solvent mainly because of its environmentally friendly properties and its high efficiency.

After developing an effective protocol for the preparation of phenothiazines, the selection of other benzothiazoles and aryl *ortho*-dihalides was pursued to demonstrate the scope of this novel domino reaction (Table 1).

As an initial observation, good to high yields of phenothiazines were obtained from the reaction of benzothiazoles with aryl *ortho*-dihalides with relatively high functional group tolerance. Thus, benzothiazoles containing either electron-donating (Table 1, entries 7–18) or electron-withdrawing (Table 1, entries 19–22) groups and aryl *ortho*-dihalides bearing either electron-donating (Table 1, entries 4–6, 10–12, 16–18, 22) or electron-withdrawing (Table 1, entries 2, 3, 8, 9, 14, 15, 20, 21) groups afforded the desired products in good yields. However, benzothiazoles with very strong electron-withdrawing groups, for example, $-NO_2$ (Table 1, entry 23), were not successful and basic labile substrates would be problematic under the experimental conditions.

The most involved mechanisms for Ullmann couplings are based on either one-electron redox processes through radical intermediates, which proceed through a Cu^I/Cu^{II} catalytic cycle, or two-electron redox processes operating through a Cu^I/Cu^{III} catalytic cycle.[30] Because the addition of a radical trapping agent, for example, an equivalent of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or *N*-methylimidazole, into the reaction mixture did not clearly delay the reaction, the mechanism likely favors a two-electron redox process, that is, abiding by the Cu^I/Cu^{III} catalytic cycle. Overall, suggesting that the first step is a direct ring-opening arylation of **1a** with **2a** to form **4a** would be reasonable according to the work of Xu[26] and Han[27] (Scheme 2). We successfully isolated **4a** in 20% yield from the reaction mixture, which was quenched within 2 h at 90 °C. UV spectroscopy showed that neither **4a** nor **3a** was found in the reaction mixture if all starting materials and catalysts were simply mixed at room temperature. After heating at 90 °C

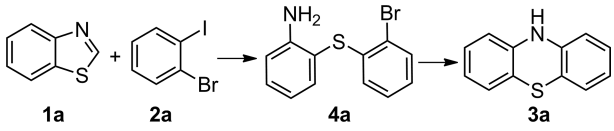
Table 1. Synthesis of phenothiazines.[a]



Entry	Benzothiazole	Aryl *ortho*-dihalide	Phenothiazine	Yield[b] [%]
1	**1a**: R = H	**2a**: R′ = H	**3a**: R = H, R′ = H	70
2	**1a**: R = H	**2b**: R′ = 4-Cl	**3b**: R = H, R′ = 8-Cl	53
3	**1a**: R = H	**2c**: R′ = 4-F	**3c**: R = H, R′ = 8-F	60
4	**1a**: R = H	**2d**: R′ = 4-Me	**3d**: R = H, R′ = 8-Me	70
5	**1a**: R = H	**2e**: R′ = 5-Me	**3e**: R = H, R′ = 7-Me	72
6	**1a**: R = H	**2f**: R′ = 5-OMe	**3f**: R = H, R′ = 7-OMe	52
7	**1b**: R = 6-OMe	**2a**: R′ = H	**3f**: R = 3-OMe, R′ = H	65
8	**1b**: R = 6-OMe	**2b**: R′ = 4-Cl	**3g**: R = 3-OMe, R′ = 8-Cl	51
9	**1b**: R = 6-OMe	**2c**: R′ = 4-F	**3h**: R = 3-OMe, R′ = 8-F	45
10	**1b**: R = 6-OMe	**2d**: R′ = 4-Me	**3i**: R = 3-OMe, R′ = 8-Me	53
11	**1b**: R = 6-OMe	**2e**: R′ = 5-Me	**3j**: R = 3-OMe, R′ = 7-Me	69
12	**1b**: R = 6-OMe	**2f**: R′ = 5-OMe	**3k**: R = 3-OMe, R′ = 7-OMe	48
13	**1c**: R = 6-Me	**2a**: R′ = H	**3e**: R = 3-Me, R′ = H	70
14	**1c**: R = 6-Me	**2b**: R′ = 4-Cl	**3l**: R = 3-Me, R′ = 8-Cl	61
15	**1c**: R = 6-Me	**2c**: R′ = 4-F	**3m**: R = 3-Me, R′ = 8-F	58
16	**1c**: R = 6-Me	**2d**: R′ = 4-Me	**3n**: R = 3-Me, R′ = 8-Me	60
17	**1c**: R = 6-Me	**2e**: R′ = 5-Me	**3o**: R = 3-Me, R′ = 7-Me	75
18	**1c**: R = 6-Me	**2f**: R′ = 5-OMe	**3j**: R = 3-Me, R′ = 7-OMe	70
19[c]	**1d**: R = 5-Cl	**2a**: R′ = H	**3b**: R = 2-Cl, R′ = H	50
20[c]	**1d**: R = 5-Cl	**2b**: R′ = 4-Cl	**3p**: R = 2-Cl, R′ = 8-Cl	46
21[c]	**1d**: R = 5-Cl	**2c**: R′ = 4-F	**3q**: R = 2-Cl, R′ = 8-F	52
22[c]	**1d**: R = 5-Cl	**2e**: R′ = 5-Me	**3l**: R = 2-Cl, R′ = 7-Me	56
23	**1e**: R = 6-NO_2	**2a**: R′ = H	**3r**: R = 3-NO_2, R′ = H	–[d]

[a] Reaction conditions: benzothiazole (1 mmol), aryl *ortho*-dihalide (1.2 mmol), $Cu(OAc)_2·H_2O$ (5 mol-%), **L2** (5 mol-%), NaOH (4 mmol), PEG-100 (2 g), N_2, 90 °C, 12 h. [b] Yield of isolated product. [c] 15 h. [d] No reaction.

for 2 h, **4a** was found to be the major product in the mixture with a trace amount of **3a** present. The roles of **3a** and **4a** were gradually reversed until **3a** was detected as the major species after 12 h. This result, along with the direct conversion of **4a** into **3a** in 72% yield under the experimental conditions, confirmed that the reaction of benzothiazoles with aryl *ortho*-dihalides underwent a successive one-pot, two-step process.

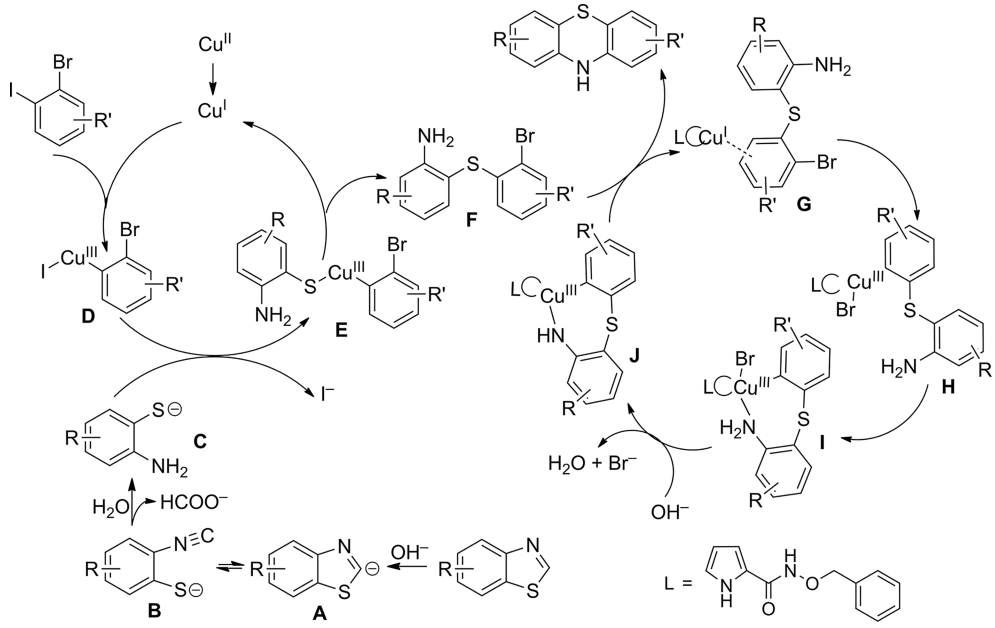


Scheme 2. The domino process of the model reaction.

In the Cu^{I}/Cu^{III} catalytic cycle, the activation of the aryl halide may occur before coordination of the nucleophile to Cu^{I}, or the coordination of the nucleophile may occur before oxidative addition.[30] To understand our reaction in more detail, 3 equivalents of aniline were added to the intramolecular cyclization of **4a** to phenothiazine. If the activation of the aryl halide were to occur before coordination of the nucleophile, we would expect to obtain mainly **3a** because intramolecular C–N coupling is faster than intermolecular C–N coupling. If the coordination of the nucleophile were to occur before oxidative addition, we would expect to obtain a large quantity of the product 2-[(2-aminophenyl)thio]-*N*-phenylaniline from the reaction of **4a** with aniline because there is a higher probability that aniline would be coordinated. The fact that **3a** was mainly obtained in the reaction indicates that the activation of the aryl halide occurs before coordination of the nucleophile in our reaction. Hence, a plausible mechanism is suggested and is shown in Scheme 3.

Conclusions

In conclusion, we established a novel method to synthesize phenothiazines from benzothiazoles and aryl *ortho*-dihalides through one-pot, tandem copper/*N*-(benzyloxy)-1*H*-pyrrole-2-carboxamide-catalyzed reactions. The novel domino process, that is, hydrolysis of benzothiazoles followed by C–S coupling and C–N coupling, plays a substantial role in the synthesis. Moreover, the use of a green solvent (polyethylene glycol-100), the low catalyst loading (5 mol-% for both copper and ligand), and the mild experimental conditions (90 °C, 12 h) make this protocol useful for the synthesis of phenothiazines, although the limited substrate scope has not been thoroughly investigated. Moreover, our preliminary work on this mechanism may be beneficial for the further establishment of more powerful methods for the synthesis of phenothiazines.



Scheme 3. Proposed mechanism.

Experimental Section

General Procedure for the Synthesis of the Phenothiazines: $Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.05 mmol), **L2** (10.8 mg, 0.05 mmol), benzothiazole (1.0 mmol), aryl *ortho*-dihalide (1.2 mmol), NaOH (160 mg, 4.0 mmol), PEG-100 (2.0 g), and a magnetic stir bar were added to a 10 mL sealed vial. The mixture was stirred in an oil bath pre-heated to 90 °C for 12 or 15 h. After allowing the mixture to cool to room temperature, the mixture was extracted with ethyl acetate (3×30 mL) and water (30 mL). The combined organic phase was washed with brine (90 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product.

Acknowledgments

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