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Domino Reactions Initiated by Copper-Catalyzed Aryl-I Bond Thiolation For the Switchable Synthesis of 2,3-Dihydrobenzothiazinones and Benzoisothiazolones

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Abstract. The three-component reactions of *o*-iodobenzamides, elemental sulfur and dichloromethane (DCM) providing 2,3-dihydro-4*H*-benzo[e][1,3]thiazin-4-ones (2,3-dihydrobenzothiazinones) are accomplished via copper-catalyzed aryl C-I thiolation and subsequent *N*-, *S*-hetero ring formation. In addition, the in situ aryl C-I bond thiolation is also employed for the switchable synthesis of benzo[d]isothiazol-3(2*H*)-ones (benzoisothiazolones) by subjecting *o*-iodobenzamides, elemental sulfur to the copper-catalyzed condition with microwave irradiation.

Keywords: Ullmann C-I thiolation; domino reaction; switchable; 2,3-dihydrobenzothiazinone; benzoisothiazolone

Introduction

The copper-catalyzed Ullmann-type cross coupling reactions between aryl/vinyl halides and a nucleophile represent a classical and reliable strategy in constructing C-C and C-heteroatom (N, O, S *etc*) bonds. Owing to its general applicability in forging new C(sp^2)-C/heteroatom bond as well as the low cost and toxicity of the copper catalyst, the Ullmann cross coupling remains as one of the irreplaceable synthetic tools in both industrial and laboratory synthesis.[1] As an representative application mode, designing domino reactions by making use of the Ullmann cross coupling as the key transformation has in the past decade gained huge success in the synthesis of a massive number of organic products with different structures.[2] For example, by employing the Ullmann C-S coupling as a key transformation, a number of elegant domino reactions showing high efficiency in the synthesis of sulfur containing compounds have been realized. Ma and co-wokers have reported a facile method on benzothiazole synthesis via copper-catalyzed reactions of *N*-acyl *o*-haloanilines and sulfide salts.[3] In addition, the C-S coupling-based domino reactions between *o*-haloanilines and carbon disulfide giving benzothiaozles are also achieved.[4] Bao and co-workers developed the synthetic method toward 2-iminobenzo-1,3-oxathioles via the assemblies of *o*-iodophenols and isothiocyanates.[5] Zeng *et al* have identified the copper-catalyzed one-pot synthesis of phenothiazines via the reactions of aryl *o*-dihalides and o-aminothiphenols via tandem C-N and C-S coupling.[6] Wen and Li *et al* have developed the domino reactions of *o*-bromo-arylisothiocyanates and aroylhydrazides as synthetic route to benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazoles.[7]

Furthermore, the synthesis of 2H-benzo[b][1,4]thiazin-3(4H)-ones,[8] benzothiophenes,[9] 2-aminobenzothiazoles,[10] benzisothiazol-3(2*H*)-ones,[11] 2-(arylthio)arylcyanamides,[12] as well as thiazino[2,3,4-*hi*]indoles[13] have also been reported. In these known reports on domino reactions initiated by the Ullmann C-S coupling, various sulfur sources such as thiophenols, sulfide salts, and isothiocyanates etc have been utilized. Amazingly, as the simplest, cheapest and most abundant sulfur source, the elemental sulfur has not yet been applied to design such type of domino reactions regardless its widespread application on many other C-S bond forming reactions[14] and direct thiolation reactions of aryl halides.[15] In this context, developing Ullmann C-S coupling-based domino reactions using elemental sulfur as the source of sulfur atom is of high merits because of the incomparable atom economy associated with elemental sulfur.

Due to the privileged relevance of sulfur containing molecules with drug discovery and clinical pharmaceuticals, the synthesis of structurally diversified sulfur-containing products keeps attracting extensive interests.[16] The 2,3-dihydrobenzothiazinone is a typical sulfur containing heterocycle motif with well-known application in discovering biologically active lead compounds and

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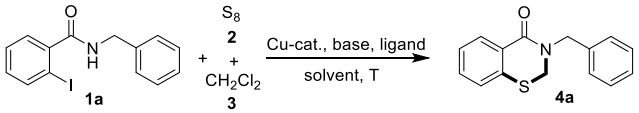
the synthesis of other useful sulfur-based heterocycles.[17] Over the past decades, several different methodologies have been devised for the synthesis of 2,3-dihydrobenzothiazinones. For example, the annulation reactions of 2-mercaptobenzoic acid with imines,[18] the annulation of thioureas with perfluorobenzoyl chlorides or methyl *o*-iodobenzoate,[19] the condensation of 2-mercaptobenzamides with aldehydes,[20] and the cyclization of 2-mercaptobenzamides with alkyl propiolates[21] are predominantly utilized methods. While the employment of the odour smelling thiophenol derivative or sensitive acyl chloride as substrate remains as restriction in the known approaches, developing new synthetic protocols allowing the synthesis of 2,3-dihydrobenzothiazinones without using sensitive of odour chemical is of high urgency. Based on our research interest in developing synthetic methods via Ullmann coupling-based domino reactions and organic reactions employing gem-dihaloakane as building block,[22] we report herein the first domino reaction of *o*-iodobenzamide, elemental sulfur and dichloromethane (DCM) for the synthesis of 2-unsubstituted 2,3-dihydrobenzothiazinones via the sequential transformations of Ullmann-type Ar-I bond thiolation and N-/S-double heteroannulation based on DCM. In addition, modification on the reaction conditions in the absence of DCM allowed the switchable and rapid synthesis of benzoisothiazolones via domino Ar-I thiolation and dehydrogenative N-S bond formation.[23]

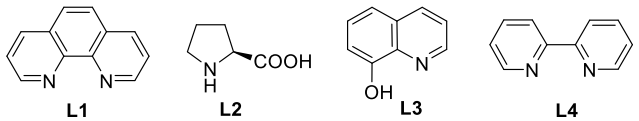
Results and Discussion

At the beginning, the reaction of *N*-benzyl *o*-iodobenzamide **1a**, elemental sulfur **2** and DCM **3** was tentatively employed in the presence of CuBr and Et_3N, by heating at 120 °C in DMSO, the target product **4a** was observed with 23% yield (entry 1, Table 1). The subsequent screening to different Cu(I) and Cu(II) catalysts led to the observation that $CuBr_2$ was a much better catalyst (entries 2-6, Table 1). Variation on the $CuBr_2$ loading revealed that 25 mol% catalyst was proper (entries 7-8, Table 1). Later on, a series of different base additives such as KOH, $NaHCO_3$, Cs_2CO_3, K_3PO_4 were compared for the reaction, and Et_3N remained as the most favourable base additive (entries 9-12, Table 1). Increasing or reducing the loading of Et_3N was both negative to the formation of **4a** (entries 13-14, Table 1). In addition, attempts in employing a ligand turned out to be helpful to improve the yield of **4a**, and 1,10-phenanthroline displayed the best effect (entries 15-18, Table 1). Notably, the parallel reaction conducted in reaction media of different polarity such as DMF, DMAC (*N*,*N*-dimethylacetamide), NMP and xylene gave **4a** with very low or no yield, suggesting the dependence of this reaction on DMSO (entries 19-22, Table 1). Finally, the reaction temperature was also optimized, but the drop on product yield was found in reaction at both higher and lower temperature (entries 23-24, Table 1). A control entry without using base additive provided **4a** with trace amount, suggesting the important role of base in the reaction (entry 25, Table 1). In additional control experiments, no expected reaction takes place when *N*-phenyl *o*-bromobenzamide or *N*-phenyl *o*-chlorobenzamide was used as alternative substrate of **1a**, respectively.

Table 1 The optimization on reaction condition[a]



entry	catalyst	base	ligand	solvent	yield [%][b]
1	CuBr	Et_3N	no	DMSO	23
2	CuI	Et_3N	no	DMSO	16
3	CuCl	Et_3N	no	DMSO	18
4	$CuBr_2$	Et_3N	no	DMSO	48
5	$Cu(OAc)_2$	Et_3N	no	DMSO	25
6	$CuCl_2$	Et_3N	no	DMSO	15
7[c]	$CuBr_2$	Et_3N	no	DMSO	23
8[d]	$CuBr_2$	Et_3N	no	DMSO	25
9	$CuBr_2$	KOH	no	DMSO	12
10	$CuBr_2$	$NaHCO_3$	no	DMSO	23
11	$CuBr_2$	Cs_2CO_3	no	DMSO	27
12	$CuBr_2$	K_3PO_4	no	DMSO	25
13[e]	$CuBr_2$	Et_3N	no	DMSO	40
14[f]	$CuBr_2$	Et_3N	no	DMSO	38
15	$CuBr_2$	Et_3N	**L1**	DMSO	69
16	$CuBr_2$	Et_3N	**L2**	DMSO	40
17	$CuBr_2$	Et_3N	**L3**	DMSO	36
18	$CuBr_2$	Et_3N	**L4**	DMSO	52
19	$CuBr_2$	Et_3N	**L1**	DMF	nr
20	$CuBr_2$	Et_3N	**L1**	NMP	nr
21	$CuBr_2$	Et_3N	**L1**	DMAC	nr
22	$CuBr_2$	Et_3N	**L1**	xylene	nr
23[g]	$CuBr_2$	Et_3N	**L1**	DMSO	59
24[h]	$CuBr_2$	Et_3N	**L1**	DMSO	62
25	$CuBr_2$	-	**L1**	DMSO	trace



[a]The reaction conditions: **1a** (0.2 mmol), **2** (1.0 mmol), **3** (0.5 mL), copper catalyst (0.05 mmol), base (0.8 mmol), ligand (0.06 mmol) in 2 mL solvent, heated at 120 °C (sealed tube) for 12 h under air atmosphere. [b]Yield of isolated product based on **1a**. [c]The loading of $CuBr_2$ was 20 mol%. [d]The loading of $CuBr_2$ was 30 mol%. [e]The loading of Et_3N was 0.6 mmol. [f]The loading of Et_3N was 1.0 mmol. [g]Heating at 110 °C. [h]Heating at 130 °C.

In the experiments examining the scope of the 2,3-dihydrobenzothiazinone synthesis, a broad range of *o*-iodobenzamides **1** were employed to react with elemental sulfur and dichloromethane under the optimized conditions. As outlined in Table 2, the titled synthesis exhibited general tolerance to the *N*-substituted *o*-iodobenzamides. Generally, *N*-benzyl

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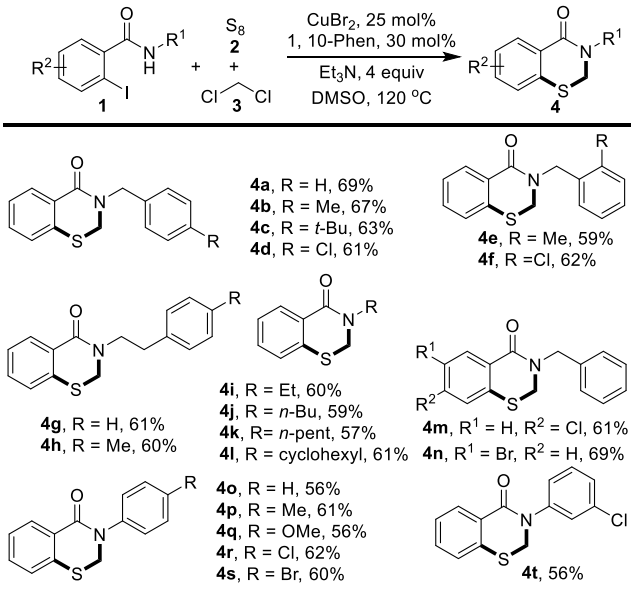
(**4a**-**4f**, Table 2), *N*-phenylethyl (**4g**-**4h**, Table 2), *N*-alkyl (**4i**-**4l**, Table 2) as well as *N*-aryl (**4o**-**4t**, Table 2) functionalized substrates **1** could participate in the synthesis of products **4** with moderate to good yields. When substrate **1** with electron withdrawing substituent on the phenyl ring was utilized, the product was also smoothly afforded (**4m**-**4n**, Table 2). On the other hand, when *N*-benzyl 2-iodo-5-methyl benzamide was used to react with **2** and **3**, complex mixture was provided, indicating the presence of unfavoured side reactions resulted from the electron donating methyl group in the phenyl ring. In addition, the *o*-iodobenzamide without *N*-substitution failed to take part in this domino reaction to yield expected *N*-unsubstituted product. The reaction employing 1,1-dichloroethane as the alternative substrate of DCM was also performed, but not corresponding product of type **4** was observed, either.

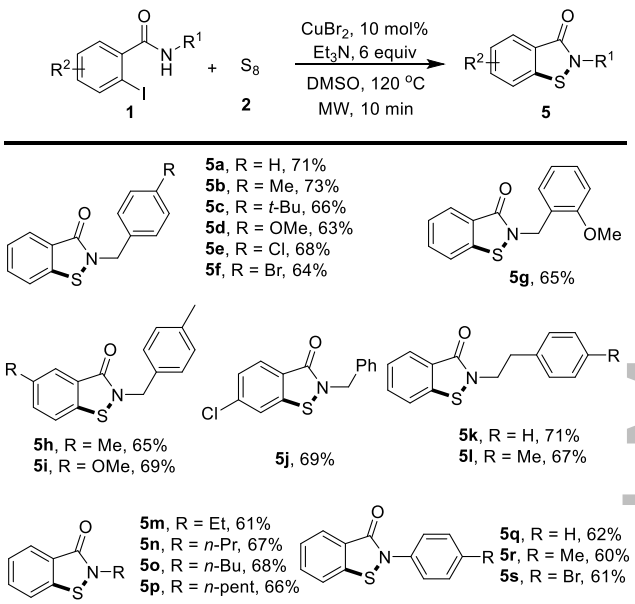
Table 2 Scope on the synthesis of 2,3-dihydrobenzothiazinones[a,b]



[a]General condition: *o*-iodobenzmide **1** (0.2 mmol), sulfur powder **2** (1.0 mmol), DCM **3** (0.5 mL), $CuBr_2$ (0.05 mmol), 1,10-phenanthroline (0.06 mmol), Et_3N (0.8 mmol) and DMSO (2 mL), stirred at 120 °C for 12 h in sealed tube under air atmosphere. [b]Yield of isolated product based on **1**.

Interestingly, when we tried to synthesize and isolate the potential 2-mercaptobenzamide intermediate from the reaction without using DCM, we observed the formation of benzoisothiazolone (see the proposed mechanism in Scheme 1). This result encouraged us to further examine this catalytic system in hope of providing a generally applicable Ar-X bond thiolation approach for the synthesis of benzoisothiazolones. After brief exploration on reaction conditions, the microwave irradiation turned out to be a practical tool enabling highly efficient and rapid synthesis of **5a**. Thus, the scope on this microwave-assisted, copper-catalyzed domino synthesis of benzoisothiazolones was then studied. As shown in Table 3, the method also displayed satisfactory tolerance to the substrates. The benzamides **1** with divergent substitution, including benzyls (**5a**-**5g**, Table 3), phenylethyl (**5k**-**5l**, Table 3), alkyls (**5m**-**5p**, Table 3) as well as aryls (**5q**-**5s**, Table 3) all reacted with elemental sulfur to give corresponding product with moderate to good yields. What's more, the benzamides with a substituent such as methyl, methoxyl and chloro in the phenyl ring were also successfully utilized for the expected synthesis (**5h**-**5j**, Table 1), supporting the general tolerance of the present synthetic method to the *N*-substituted *o*-iodobenzamides via intramolecular dehydrogenative S-N bond formation.[24] However, the employment of *N*-unsubstituted *o*-iodobenzamide for the synthesis of corresponding *NH* benzoisothiazolone was not realized, either.

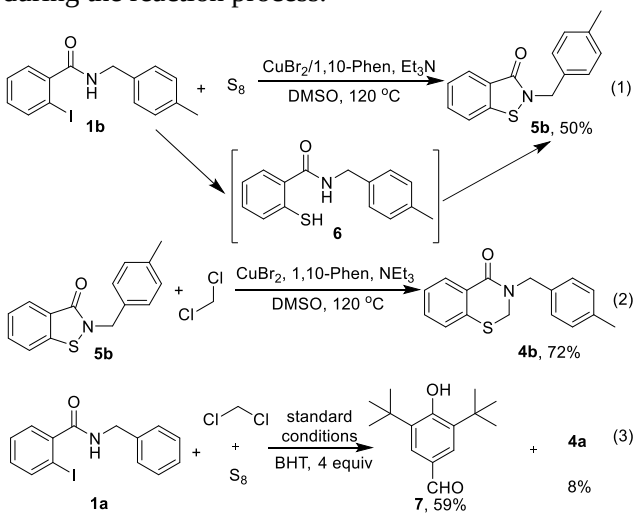
Table 3 Scope on the synthesis of benzoisothiazolones[a,b]



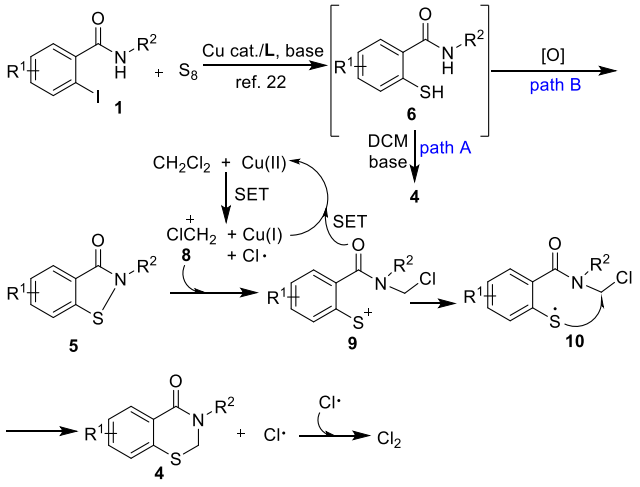
[a]General condition: *o*-iodobenzmide **1** (0.2 mmol), sulfur powder **2** (1.0 mmol), $CuBr_2$ (0.02 mmol), Et_3N (1.2 mmol) and DMSO (2 mL), irradiated at 120 °C with MW for 10 min in sealed tube under air atmosphere. [b]Yield of isolated product based on **1**.

In further investigation, related control experiments were designed and executed to probe the potential reaction pathway. At first, the *o*-iodobenzamide **1b** as well as elemental sulfur was employed to react under the standard heating condition without employing DCM. Instead of the 2-mercaptobenzamide **6**, the product **5b** was directly obtained from this reaction (eq 1), suggesting that **6** was unstable under the present conditions. In addition, subjecting **5b** with DCM under standard reaction conditions smoothly given six-membered heterocyclic product **4b** (eq 2), supporting that **5b** could act as an intermediate during the formation of products **4**. Actually, the analysis by GC observed the formation of **5a** in the reaction synthesizing **4a** (see SI). In addition, the control experiment of **1a**, sulfur powder and DCM provided **4a** with only 8% yield in the presence of radical

scavenger HBT, and the compound **7** resulting from the oxidation of BHT was obtained with 59% yield (eq 3), implying that free radical was generated during the reaction process.[25]



According to the results from the controls experiments, the general mechanisms for the reactions providing products **4** and **5** are proposed (Scheme 1). First, in the presence of copper catalyst and elemental sulfur, the Ar-I bond undergoes the typical Ullmann-type thiolation to give thiol functionalized benzamide **6**.[26] This intermediate, as observed in the experiments, can be quickly transformed into products **5** under the catalytic conditions of both microwave irradiation or conventional heating. Subsequently, in the presence of DCM, two reaction pathways may take place. One is the direct double nucleophilic substitution of the SH and NH group to DCM promoted by the base additive (path A). On the other hand, since compounds **5** can also be transformed into products **4** (Eq 2), another possible pathway involving in the ring opening of the heterocycle in **5** is also possible (path B). This pathway might be initiated by the single electron transfer (SET) between Cu(II) and DCM which produces Cu(I), Cl· radical and $ClCH_2^+$ cation **8**. This cation coupling **5** to trigger the ring opening[27] to provide *N*-chloromethylated S^+ cation intermediate **9**. This cation then incorporate Cu(I) to give free radical intermediate **10** and regenerate Cu(II) via SET.



Scheme 1 The proposed reaction mechanism

The intramolecular free radical substation on **10** gives rise to product **4** and Cl· radical. Simultaneously, the homo-coupling of the Cl· yielding molecular chlorine takes place as the free radical chain expiration step.

Conclusion

In summary, we have developed for the first time the domino reactions on the synthesis of 2,3-dihydrobenzothiazinones and switchable synthesis of benzoisothiazolones based on the key transformation of Ullmann-type Ar-I bond thiolation. The easy availability, stable, operator friendly, and low cost of all the reagents constitute the individual advantages of the present methods. In addition, the interesting ring opening of the benzoisothiazolones observed in the experiment can be useful clue in understanding and devising more divergent reactions involving the C-heteroatom bond cleavage based on these featured transformations.

Experimental Section

General procedure for dihydrobenzothiazinones 4

To a 10 mL test tube equipped with stirring bar and condenser was charged with *o*-iodobenzamide **1** (0.2 mmol), sulfur powder **2** (1.0 mmol), DCM **3** (0.5 mL), $CuBr_2$ (0.05 mmol), 1,10-phenanthroline (0.06 mmol), Et_3N (0.8 mmol) and DMSO (2 mL). The test tube was sealed with Teflon cap, and the resulting mixture was stirred at 120 °C for 12 h. Upon completion (TLC), the reaction mixture was allowed to cool down to room temperature, and H_2O (5 mL) was added to the vessel. The resulting suspension was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined and dried over Na_2SO_4. After filtration, the solution obtained therein was employed to reduced pressure to remove the solvent. The residue was subjected to silica gel column chromatography to give pure products by using mixed petroleum ether and ethyl acetate (v / v = 10:1).

General procedure for benzoisothiazolones 5

To a 10 mL microwave reaction tube equipped with stirring bar was charged with *o*-iodobenzamide **1** (0.2 mmol), sulfur powder **2** (1.0 mmol), CuBr (0.02 mmol), Et_3N (1.2 mmol) and DMSO (2 mL). The tube was then sealed, and the resulting mixture was subjected to microwave irradiation at 120 °C in a NOVA-2S microwave reactor for 10 min. After stopping the irradiation, the reaction mixture was allowed to cool down to room temperature, and H_2O (5 mL) was added to the vessel. The resulting suspension was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined and dried over Na_2SO_4. After filtration, the solvent was removed from the solution under reduced pressure. The residue was subjected to silica gel column chromatography to give pure products by using mixed petroleum ether and ethyl acetate (v / v = 10:1).

Acknowledgements

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