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Copper-Catalyzed Synthesis of 1,2,4-Benzothiadiazine 1,1-Dioxide Derivatives by Coupling of 2-Halobenzenesulfonamides with Amidines

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Abstract: We have developed a simple and practical copper-catalyzed method for the synthesis of 1,2,4-benzothiadiazine 1,1-dioxide derivatives *via* cascade reactions of substituted 2-halobenzenesulfonamides with amidines, and the method is of value for the construction of this kind of molecules with biological and medicinal activities.

Keywords: 1,2,4-benzothiadiazine 1,1-dioxides; copper; cyclization; *ortho*-substituent effect; synthetic methods

Introduction

Benzothiadiazine 1,1-dioxide derivatives have been used as ATP-sensitive potassium channel openers that can activate channels (such as diazoxide in Figure 1),[1] and they have been shown to reduce the AMPA receptor desensitization[2] and improve the impaired synaptic transmission of functions, which are useful action in the treatment of early stages of Alzheimer's disease.[3] Cyclothiazid[4] and IDRA 21[5] have been demonstrated to be among the most potent compounds that enhance synaptic transmission by removal of AMPA receptor desensitization.[6] Some cyclothiazide derivatives exhibit physico-chemical characteristics which should facilitate the crossing of the blood-brain barrier and have potential application in the treatment of attention disorders in children as well as senile dementias. In addition, some of the benzothiadiazine derivatives (such as **A** in Figure 1) have also been shown to possess antiviral activities[7] particularly against human herpes virus 6 (HHV-6), human cytomegalovirus (H-CMV) and Varicella-Zoster virus (VVZ), and they have been also reported as heterocyclic inhibitors of PDE7 with concurrent inhibitory activity at PDE4 and PDE3.[8]

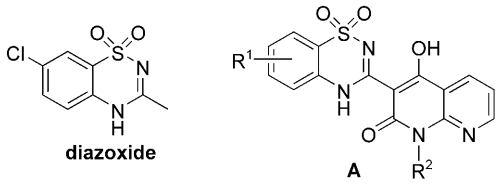
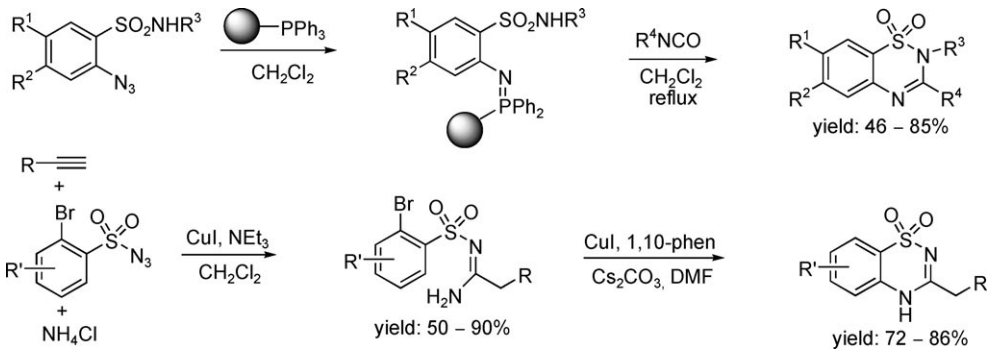


Figure 1. Examples of benzothiadiazine 1,1-dioxide derivatives as ATP-sensitive potassium channel openers or HCV polymerase inhibitors.

Although some methods have been developed for synthesis of benzothiadiazine 1,1-dioxides derivatives,[1b–e,7e,9] these routes are often troublesome and some of the starting materials are not readily available (Scheme 1). It is highly desirable to develop more convenient and efficient approaches. In the past decade, copper-catalyzed Ullmann N-arylations have made great progress,[10] and the N-arylation strategy has been used to make N-heterocycles.[11] Recently, we have developed some efficient copper catalyst sys-



Scheme 1. Examples for synthesis of benzothiadiazine-1,1-dioxide derivatives.[9a,d]

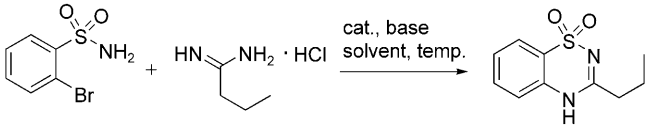
tems for use in N-arylations,[12] and some of N-heterocycles have been constructed *via* the Ullmann coupling.[13] As a continuation of our research, herein, we report a simple and efficient copper-catalyzed method for synthesis of benzothiadiazine 1,1-dioxide derivatives without addition of any ligand or additive.

Results and Discussion

2-Bromobenzenesulfonamide and butyramidine hydrochloride were initially chosen as the model substrates to optimize reaction conditions including the catalysts, bases and solvents under a nitrogen atmosphere. As shown in Table 1, reaction temperature was investigated using CuI as the catalyst, Cs_2CO_3 as the base and DMF as the solvent under a nitrogen atmosphere (entries 1–3), yield of the target product reached a maximum when the temperature was raised to 110 °C (entry 3). Three copper catalysts were tested at 110 °C (entries 3–5), and CuBr showed the best activity (entry 4). The reaction gave the same yield as the result in entry 4 when proline was used as the ligand (entry 6). Several bases, Cs_2CO_3, K_3PO_4 and K_2CO_3, were screened, and Cs_2CO_3 proved to be most effective (compare entries 4, 7 and 8). The effect of solvents was also investigated (compare entries 4, 9–11), and DMF was the best choice (entry 4).

We then investigated the scope of copper-catalyzed couplings of the substituted 2-halobenzenesulfonamides with amidine hydrochlorides under the optimized catalytic conditions determined above. As shown in Table 2, the substrates examined provided good to excellent yields. For the substituted 2-halobenzenesulfonamides, electron-withdrawing as well as electron-donating substituents did not significantly affect the catalytic activity. Reactions of 2,5-dibromobenzenesulfonamide with amidines only took place on the *ortho*-site C–Br bond of the sulfonamide group, the 5-site C–Br bond remained intact, and the result showed the *ortho*-substituent effect of the sulfonamide group during N-arylations (entries 13–15). It is

Table 1. Copper-catalyzed coupling of 2-bromobenzenesulfonamide with butyramidine hydrochloride: optimization of conditions.[a]



1a 2b 3b

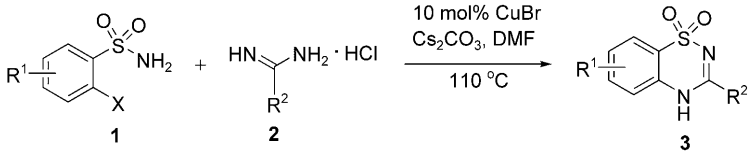
Entry	Catalyst	Base	Solvent	Temp. [°C]	Yield [%][b]
1	CuI	Cs_2CO_3	DMF	50	50
2	CuI	Cs_2CO_3	DMF	80	70
3	CuI	Cs_2CO_3	DMF	110	77
4	**CuBr**	**Cs_2CO_3**	**DMF**	**110**	**80**
5	$CuCl_2$	Cs_2CO_3	DMF	110	75
6	CuBr	Cs_2CO_3	DMF	110	80[c]
7	CuBr	K_3PO_4	DMF	110	55
8	CuBr	K_2CO_3	DMF	110	68
9	CuBr	Cs_2CO_3	DMSO	110	70
10	CuBr	Cs_2CO_3	toluene	110	0
11	CuBr	Cs_2CO_3	1,4-dioxane	110	77

[a] *Reaction conditions:* under nitrogen atmosphere, reaction time (5 h). 2-Bromobenzenesulfonamide (1 mmol), butyramidine hydrochloride (1.2 mmol), catalyst (0.1 mmol), base (1.5 mmol), solvent (2 mL).
[b] Isolated yield.
[c] L-Proline (0.2 mmol) as the ligand was added.

worthwhile to note that the copper-catalyzed couplings of the substituted 2-halobenzenesulfonamides with amidines were performed in the absence of ligand and additive, this result also illustrates the *ortho*-substituent effect.

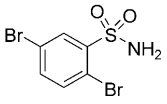
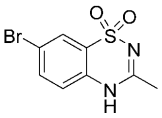
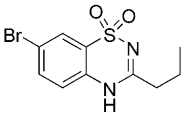
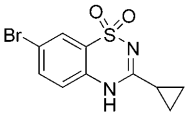
We also explored the formation mechanism of 1,2,4-benzothiadiazine 1,1-dioxide derivatives. Coupling of benzenesulfonamide (**4**) with butyramidine hydrochloride (**2b**) did not work under our standard condition (Scheme 2 A), and reaction of ^{15}N-labeled 2-bromo-4-trifluoromethylbenzenesulfonamide (**1f**) with butyramidine hydrochloride (**2b**) led to fully ^{15}N-

Table 2. Copper-catalyzed synthesis of benzothiadiazines-1,1-dioxides derivatives.[a]

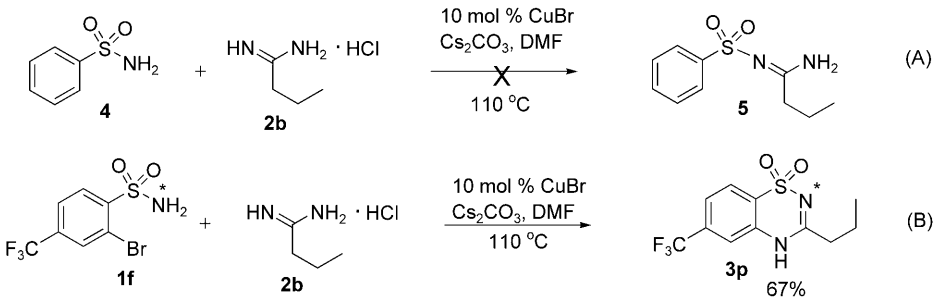


Entry	1	2	Product	Yield [%][b]
1	**1a**	**2a**	**3a**	77
2	**1a**	**2b**	**3b**	80
3	**1a**	**2c**	**3c**	75
4	**1b**	**2a**	**3d**	70[c]
5	**1b**	**2b**	**3e**	65[c]
6	**1b**	**2c**	**3f**	75[c]
7	**1c**	**2a**	**3g**	81
8	**1c**	**2b**	**3h**	78
9	**1c**	**2c**	**3i**	80
10	**1d**	**2a**	**3j**	77[c]
11	**1d**	**2b**	**3k**	75[c]
12	**1d**	**2c**	**3l**	80[c]

Table 2. (Continued)

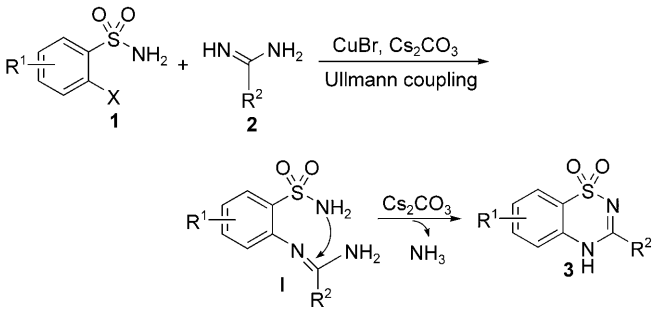
Entry	1	2	Product	Yield [%][b]
13	**1e** 	**2a**	**3m** 	70[d]
14	**1e**	**2b**	**3n** 	68[d]
15	**1e**	**2c**	**3o** 	65[d]

[a] *Reaction conditions:* under nitrogen atmosphere, reaction temperature (110 °C), reaction time (5 h). **1** (1 mmol), **2** (1.2 mmol), CuBr (0.1 mmol), Cs_2CO_3 (1.5 mmol), DMF (2 mL).
[b] Isolated yield.
[c] Reaction time (10 h).
[d] Reaction time (12 h).



Scheme 2. Reaction of butyramidine hydrochloride with benzenesulfonamide (**4**) (A) or ^{15}N-labeled 2-bromo-4-trifluoromethyl-benzenesulfonamide (**1f**) (B) under the optimized catalytic conditions.

labeled 6-trifluoromethyl-3-propyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**3p**) whose structure was elucidated by ^{1}H, ^{13}C, ^{15}N NMR and high resolution mass spectrometry (see Supporting Information)



Scheme 3. Possible formation mechanism of 1,2,4-benzothiadiazine 1,1-dioxide derivatives.

(Scheme 2B). The result implied that nucleophilic attack of the amino group in the amidine to sulfomamide was impossible. A possible formation mechanism for 1,2,4-benzothiadiazine 1,1-dioxide derivatives is proposed in Scheme 3 on the basis of the results above. Ullmann coupling of the substituted 2-halobenzenesulfonamide and the amidine produced intermediate **I** and, in the presence of base (Cs_2CO_3), nucleophilic attack of the amino group of the sulfonamide to the amidine in **I** affords the target product **3** while releasing ammonia.

Conclusions

We have developed an efficient method for the synthesis of 1,2,4-benzothiadiazine 1,1-dioxide derivatives. The couplings were performed using readily available starting materials (substituted 2-halobenze-

nesulfonamides and amidine hydrochlorides) and inexpensive catalyst (CuBr), and no ligand or additive was required. The present method shows simple, economical and practical advantages over the previous methods.

Experimental Section

General Procedure for Copper-Catalyzed Synthesis of 1,2,4-Benzothiadiazine 1,1-Dioxide Derivatives (3a–p) and 5

Substituted 2-halobenzenesulfonamide (**1a–f**, 1 mmol) was added to a two-neck, round-bottom flask charged with amidine hydrochloride (**2**, 1.2 mmol), Cs_2CO_3 (1.5 mmol, 489 mg) and DMF (2 mL) at room temperature. After a 10 min stirring under a nitrogen atmosphere, CuBr (0.1 mmol, 14.3 mg) was added to the flask. The reaction temperature was raised to 110 °C, and the mixture was allowed to stir under a nitrogen atmosphere for the required time (see Table 2). After completion of the reaction, the resulting solution was filtered, and the solvent of the filtrate was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to provide the desired product.

Acknowledgements

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