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Synthesis of functionalized benzothiadiazine 1,1-dioxide derivatives *via* intramolecular C-H activation reactions of trichloroacetamidine and benzenesulfonyl chloride

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ABSTRACT

The synthesis of functionalized benzothiadiazine 1,1-dioxide derivatives was achieved through a novel three-component intramolecular C-H activation reaction of trichloroacetonitrile, benzenesulfonyl chloride, and various primary amines. This reaction was performed in the presence of catalytic copper(I) and L-proline as the ligand in tetrahydrofuran at room temperature.

Keywords:
C-H Activation

Copper-catalyzed

Benzothiadiazine 1,1-dioxide

Benzenesulfonyl chloride

Trichloroacetonitrile

Primary amine

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Benzothiadiazine 1,1-dioxide derivatives are the key structural motifs in various biologically active molecules.[1] They have shown antiviral activities against Hepatitis C virus (HCV) (Fig. 1), human herpes virus 6 (HHV-6) and Varicella-Zoster virus (VZV).[2-4] Moreover, benzothiadiazine 1,1-dioxide derivatives have revealed excellent biological activity in the treatment of cancer[5] and the early stages of Alzheimer disease,[6] and have also been used as potassium channel openers (PCOs) that can activate KATP channels[7] (Fig. 1).

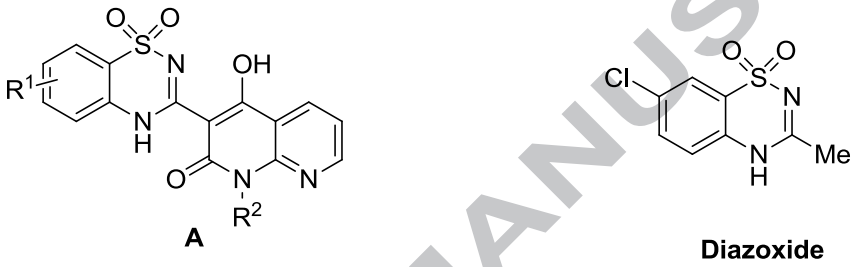


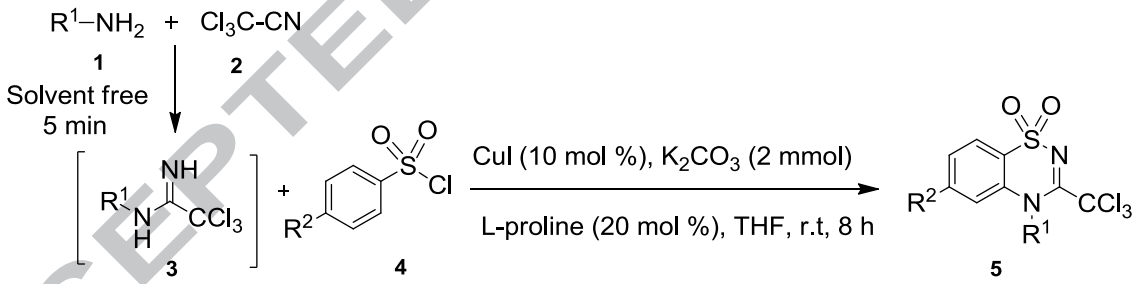
Figure 1. Representative examples of benzothiadiazine 1,1-dioxide derivatives as HCV polymerase inhibitors (**A**) and ATP-sensitive potassium channel openers (Diazoxide).

Recently, many methods have been developed for the synthesis of benzothiadiazines.[8] These methods often require toxic reagents, harsh reaction conditions, expensive catalysts, inconvenient multi-step processes, high temperatures, long reaction times and also produce undesirable by-products. Therefore, the development of an efficient and practical method for the synthesis of functionalized benzothiadiazine 1,1-dioxide derivatives under mild conditions is desirable.

An immense effort has been made to develop efficient strategies for the direct functionalization of C-H bonds using transition-metal catalysis. The intramolecular heterofunctionalization of C-H bonds is an ideal, truly atom-economical approach for the construction of new heterocyclic architectures. A rapidly growing number of different types of

heterocycles, especially those containing nitrogen, have been constructed by applying this novel strategy in recent years.[9] Recently, we reported that quinazoline derivatives could be formed by intramolecular C-H bond functionalization.[10] We were eager to extend our approach to the synthesis of other classes of heterocycles, such as benzothiadiazine 1,1-dioxide derivatives, by copper-catalyzed C-H activation reactions which are of remarkable importance in medicinal chemistry.

Herein, we report a novel, simple and efficient protocol for the synthesis of various functionalized benzothiadiazine 1,1-dioxide derivatives *via* the copper-catalyzed C-H activation reactions of trichloroacetamidines[11] and benzenesulfonyl chlorides (see Scheme 1). Compared with conventional methods, this method has considerable advantages such as mild conditions, easy work-up, uses readily-available starting materials including the catalyst, and results in highly pure products in good yields.



Scheme 1. Synthesis of various benzothiadiazine 1,1-dioxide derivatives *via* the Cu-catalyzed intramolecular C-H activation reactions of trichloroacetamidines and benzenesulfonyl chlorides.

Benzylamine, trichloroacetonitrile and benzenesulfonyl chloride were initially chosen as model substrates to optimize the reaction conditions, including the catalyst, base and solvent, at room temperature. As shown in Table 1, the copper salts CuI, CuBr, CuCl, $Cu(OAc)_2$ and $CuSO_4$ (10 mol% amount) were tested. CuI was found to be the most effective catalyst. Also THF was

the best solvent for the reaction; K_2CO_3 proved to be most effective among several bases tested, Cs_2CO_3, KOH, KO*t*-Bu, K_2CO_3 and NaOH. Combining these parameters resulted in the use of THF, 10 mol% of CuI as the catalyst, 2.0 mmol of K_2CO_3 as the base, 20 mol% of L-proline as the ligand, 1.5 mmol of benzenesulfonyl chloride, 1.0 mmol of trichloroacetonitrile and 1.0 mmol of benzylamine (Table 1, entry 1).

Table 1. Optimization of reaction conditions for the formation of product **5a** (R^1 = Bn, R^2 = H) from 1.5 mmol of benzenesulfonyl chloride, 1.0 mmol of trichloroacetonitrile, 1.0 mmol of benzylamine, 10 mol% of copper salt as the catalyst, 2.0 mmol of base, and 20 mol% of L-proline as the ligand at room temperature.

Entry	Catalyst	Solvent	Base	Yield **5a** (%)[a]
1[b]	**CuI**	**THF**	**K_2CO_3**	**80**
2	CuI	MeCN	KO*t*-Bu	63
3	CuI	DMF	NaOH	19
4	CuI	THF	Cs_2CO_3	70
5	CuCl	MeCN	KOH	38
6	CuCl	THF	K_2CO_3	64
7	CuBr	MeCN	Cs_2CO_3	59
8	CuBr	DMF	K_2CO_3	62
9	CuBr	DMF	NaOH	25
10	$Cu(OAc)_2$	MeCN	Cs_2CO_3	31
11	$Cu(OAc)_2$	DMF	KO*t*-Bu	20
12	$Cu(OAc)_2$	MeCN	K_2CO_3	36
13	$CuSO_4$	THF	K_2CO_3	29
14	$CuSO_4$	DMF	Cs_2CO_3	15
15	$CuSO_4$	MeCN	K_2CO_3	10

[a] Reaction time 8 h.
[b] 5 mol% catalyst, reaction time was 12 h.

Using the optimized conditions described above, various benzothiadiazine 1,1-dioxide derivatives were then synthesized from trichloroacetonitrile, benzenesulfonyl chlorides and primary amines with various electron-withdrawing or electron-donating substituents on the aromatic rings (see Table 2).

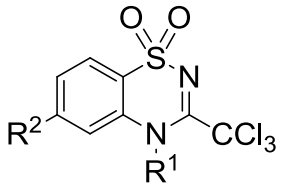


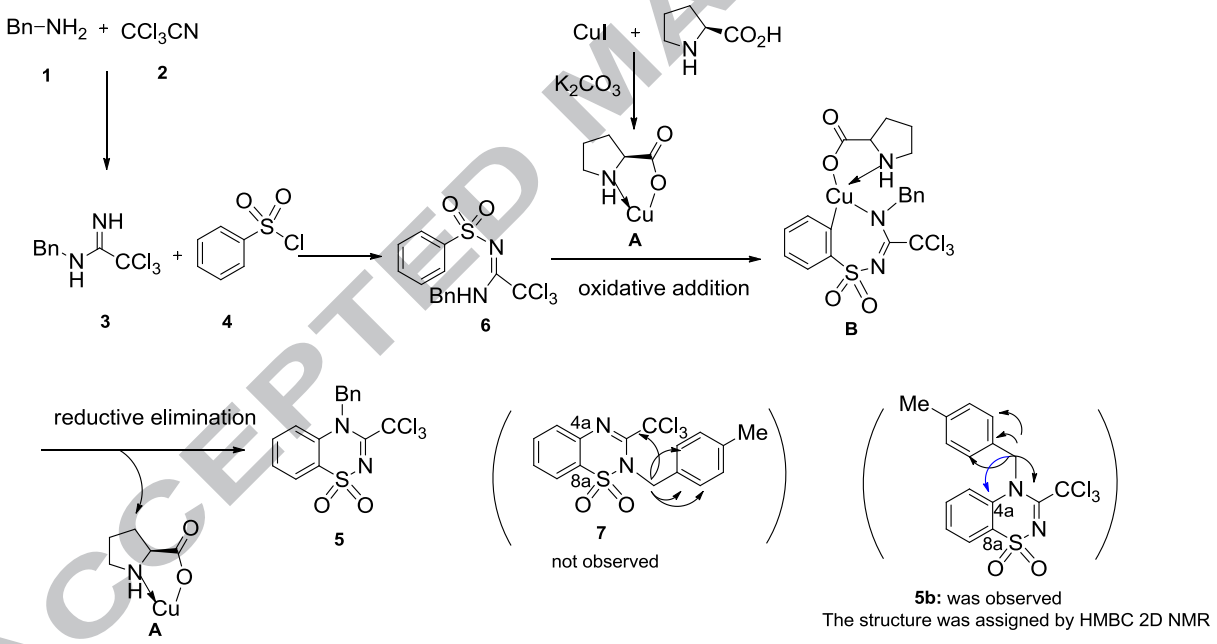
Table 2. Synthesis of various benzothiadiazine 1,1-dioxide derivatives.

Compound	R^1	R^2	Yield **5** (%)
5a	Bn	H	80
5b	4-Me-$CH_2C_6H_4$	H	84
5c	4-Br-$CH_2C_6H_4$	Me	78
5d	4-MeO-$CH_2C_6H_4$	Me	83
5e	Ph	Me	81
5f	4-Me-C_6H_4	NO_2	86
5g	4-Cl-C_6H_4	NO_2	76
5h	4-Br-C_6H_4	NO_2	75
5i	2-Cl-C_6H_4	H	70

The structures of compounds **5a-i** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **5a** exhibited one singlet for the CH_2 group (δ = 4.61 ppm) along with characteristic multiplets for the phenyl protons. The ^{13}C NMR spectrum of **5a** displayed 12 signals in agreement with the proposed structure. The NMR spectra of other compounds were similar to those of **5a**, except for the substituents, and showed characteristic signals in the appropriate regions of the spectra. The mass spectrum of **5a** displayed the molecular ion peak at *m*/*z* = 389.

A possible reaction mechanism is shown in Scheme 2. It is proposed that trichloroacetamidine derivative **3** formed from benzylamine **1** and trichloroacetonitrile **2**, undergoes nucleophilic substitution by benzenesulfonyl chloride **4** to give *N*-sulfonyl trichloroacetamidine **6**. Reaction of CuI with L-proline produced a five-membered chelate **A**.

Oxidative addition of the chelated Cu(I) with compound **6** in the presence of K_2CO_3 led to intermediate **B** stabilized by the amidine nitrogen atom which may coordinate to Cu. Reductive elimination of **B** afforded product **5** regenerating the catalyst chelate **A**. Since trichloroacetamidine derivative **3** possesses two nucleophilic sites, formation of an alternative product, namely 2-benzyl-3-(trichloromethyl)-2*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide **7**, is also possible. Structure **7**, can be ruled out by studying the HMBC 2D NMR spectrum of the products. The presence of a cross peak through the CH_2 at δ_H = 4.88 ppm with the C-*4a* group at 140.0 ppm (in HMBC) confirmed structure **5**. Such a connection should not be present in structure **7**. Key HMBC connectivity is also shown in the ESI.



Scheme 2. Possible mechanism for the formation of compound **5.**

In conclusion, a novel protocol for the one-pot synthesis of various benzothiadiazine 1,1-dioxide derivatives *via* the three-component, intramolecular C-H activation reaction of

benzenesulfonyl chlorides and trichloroacetamidines catalyzed by copper(I) iodide in THF at room temperature is described. Readily, available starting materials, including the catalyst, the use of mild conditions and the ease of purification resulting in high yields makes this reaction a suitable method for the synthesis of various benzothiadiazine 1,1-dioxide derivatives.

Acknowledgements

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Highlights

•Novel synthesis of benzothiadiazine 1,1-dioxide.

•CuI catalyzed the efficient synthesis of benzothiadiazine 1,1-dioxide.

•Intramolecular C-H activation reactions of benzenesulfonylchlorides and trichloroacetamidines.

Graphical Abstract

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