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# Microwave-assisted sequential one-pot protocol to benzothiadiazin-3-one-1,1-dioxides via a copper-catalyzed N-arylation strategy

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# ABSTRACT

A microwave-assisted, sequential, one-pot protocol has been developed for the synthesis of a variety of benzothiadiazin-3-one-1,1-dioxides. This protocol utilizes a copper-catalyzed N-arylation of  $\alpha$ -bromobenzenesulfonamides with a number of amines to generate the corresponding 2-aminobenzenesulfonamides, which undergo cyclization to the desired sultams using carbonyl diimidazole (CDI). A range of conditions was evaluated for the key C–N bond formation step with tolerance toward functionalized amines.

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### 1. Introduction

The development of protocols for the synthesis of skeletally diverse heterocyclic scaffolds is a critical step in the drug discovery process. The growing demand for libraries of small molecules as potential small molecule therapeutic agents for high-throughput screening presents challenging opportunities in this field. Onepot strategies are highly efficient pathways to rapidly synthesize complex heterocyclic molecules from simple substrates.<sup>1</sup> When coupled with transition metal-catalyzed processes, one-pot processes enable the generation of complex heterocyclic scaffolds from simple building blocks. In this regard,  $\alpha$ -haloarylsulfonamides represent an attractive building block for the production of benzofused sultams.<sup>2,3</sup>

Sultams and their sulfonamide precursors possess a number of advantageous chemical properties making them ideal building blocks for the titled process, the most prominent of these include: (i) click coupling between starting  $\alpha$ -halobenzenesulfonyl chlorides and amines under mild conditions, (ii) the  $\alpha$ -halo group can be utilized in transition metal-catalyzed cross coupling (iii) the  $\alpha$ -halo group enhances the acidity of the aryl sulfonamide N–H enabling Mitsunobu and conventional alkylation reactions to occur under mild conditions, and (iv) the commercial availability of a variety of substituted  $\alpha$ -halo benzenesulfonyl chlorides. Taken collectively, these attributes have guided our efforts to develop a microwave-assisted, sequential one-pot protocol for the synthesis of benzothiazdiazin-3-one-1,1-dioxides based on a pivotal copper-catalyzed N-arylation strategy.

Traditionally, sultams have been synthesized using a number of classical cyclization protocols such as Friedel–Crafts, [3+2] cycloadditions, Diels–Alder reactions, and recently the application of oxa- and aza-Michael reactions.<sup>4</sup> Notably, there have been a number of transition metal-catalyzed protocols reported for the generation of diverse sultams.<sup>3,5</sup>

In addition to their inherent chemical properties, sultams have emerged as important targets for drug discovery due to their potent biological activities. In particular, benzothiadiazin-3-one-1,1dioxides and their derivatives have shown promising activity, including hypoglycemic,<sup>6</sup> anti-HIV,<sup>7</sup> RSV inhibitory activity,<sup>8</sup> as well asand serving as selective antagonists of CXR2 (Fig. 1).<sup>9</sup>



Figure 1. Biologically active benzofuzed sultams.

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# 2. Results and discussion

Since the observation of copper-catalyzed coupling of a arylbromide with an acetanilide by Goldberg in 1907,<sup>10</sup> copper-catalyzed N-arylation represents an effective reaction for the formation of C– N and C–O bonds.<sup>11</sup> Early reports classically required harsh reaction conditions and stoichiometric quantities of copper. Seminal work by Buchwald, Hartwig and Ley reported notable advances in both ligands and reduced reaction temperatures for copper-catalyzed couplings.<sup>12</sup>

Traditionally, benzothiadiazin-3-one-1,1-dioxides have been synthesized in a number of linear protocols.<sup>6–9,13</sup> Envisioning a copper-catalyzed approach to benzothiadiazin-3-one-1,1-dioxides, a variety of conditions were evaluated to probe and subsequently optimize the N-arylation of allyl amine with *N*-allyl-2-bromo-4-fluorobenzenesulfonamide **1** to yield *N*-allyl-2-(allylamino)-4-fluorobenzenesulfonamide **2** (Scheme 1, Table 1).<sup>14</sup> An array of copper sources (Table 1, entries 1–3) and ligands (Table 1, entries 4–7) were initially evaluated followed by a survey of reaction solvent. Under conventional heating, the desired sulfonamide **2**, could be isolated in 92% yield after 6 h.

Further optimization was achieved using microwave irradiation, which reduced reaction times to 11 min at 150 °C with comparable yields (Table 1, entry 8 vs 11).<sup>15</sup> With these results in hand, a number of 2-aminobenzenesulfonamide derivatives were synthesized to demonstrate the versatility of the protocol with a variety of amines, amides, and sulfonamide starting materials (Scheme 2, Table 2).



Scheme 1.

Table 1				
Screening	conditions	for	reaction	optimization

Entry <sup>a,d</sup>	[Cu] cat.	Ligand	Solvent	Yield (%)
1	CuI	L-Proline	DMSO	65
2	CuBr	L-Proline	DMSO	55
3	Cu <sub>2</sub> O	L-Proline	DMSO	10
4	CuI	$(CH_2OH)_2$	DMSO	78
5	CuI	1,10-Phenanthroline	DMSO	94
6	CuI	DBU	DMSO	50
7	CuI	(CH <sub>2</sub> NHMe) <sub>2</sub>	DMSO	72
8	CuI	1,10-Phenanthroline	DMF	92
9	CuI	1,10-Phenanthroline	Dioxane	84
10	CuI	1,10-Phenanthroline	DMF	96 <sup>b</sup>
11	CuI	1,10-Phenanthroline	DMF	94 <sup>c</sup>

 $^a$  Reaction conditions: 1 (0.17 mmol), allylamine (0.2 mmol), CuX (0.017 mmol), ligand (0.034 mmol), Cs\_2CO\_3 (0.34 mmol) in solvent (0.5 M) at 100  $^\circ$ C for 6 h.

<sup>b</sup> Microwave irradiation for 22 min at 140 °C.

<sup>c</sup> Microwave irradiation for 11 min at 150 °C.

 $^{\rm d}$  Other bases were also investigated (DBU,  $K_2 CO_3, \ Et_3 N)$  but  $Cs_2 CO_3$  was preferred.



# Table 2

Catalytic N-arylation of  $\alpha$ -bromobenzene sulfonamides<sup>16</sup>

Entry <sup>a</sup>	R <sup>1</sup>	$\mathbb{R}^2$	R <sup>3</sup>	R <sup>4</sup> -NH <sub>2</sub>	Yield (%)
1	Н	Н	Bn	4-MeOBnNH <sub>2</sub>	90
2	Н	Н	Bn	4-ClBnNH <sub>2</sub>	89
3	Н	Н	Bn	Octylamine	94
4	Н	Н	Bn	Phenethylamine	91
5	Н	Н	Bn	Allylamine	96
6	Н	Н	4-MeOBn	Cyclopentylamine	90
7	Н	Н	Ср	4-MeOBnNH <sub>2</sub>	96
8	Н	F	Allyl	Allyl NH <sub>2</sub>	94
9	Н	F	n-Butyl	BnNH <sub>2</sub>	92
10	CF <sub>3</sub>	Н	Allyl	n-Butyl amine	95
11	CF <sub>3</sub>	Н	(CH <sub>2</sub> ) <sub>2</sub> Bn	Propargyl amine	69
12	Н	F	Allyl	EtC(O)NH <sub>2</sub>	80

<sup>&</sup>lt;sup>a</sup> Reaction conditions: sulfonamide (0.17 mmol), amine (0.2 mmol), Cul (0.017 mmol), 1,10-phenanthroline (0.034 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.34 mmol) in dry DMSO (0.5 M) in microwave for 11 min at 150 °C.

With an array of 2-aminobenzenesulonfamides in hand, cyclization to the corresponding benzothiadiazin-3-one-1,1-dioxides with carbonyl diimidazole (CDI) was achieved in excellent yields under thermal conditions (Scheme 3, Table 3).<sup>13b,17</sup>

Finally with both protocols in hand, a sequential, two-step, onepot approach was achieved whereby microwave irradiation afforded the desired benzothiadiazin-3-one-1,1-dioxides in good yield (Scheme 4).<sup>18</sup> To achieve this, the CDI cyclization was conducted under microwave irradiation following the initial copper-catalyzed step in the same microwave vial. This required a change of solvent to DMF which was the optimum compatible solvent for both the Narylation and CDI cyclization steps while maintaining good yields.



Scheme 3. CDI cyclization to benzothiadiazin-3-one-1,1-dioxides.

Table 3					
Entry <sup>a</sup>	$\mathbb{R}^1$	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup> -NH <sub>2</sub>	Yield (%)
1	Н	Н	Bn	4-MeOBnNH <sub>2</sub>	96
2	Н	Н	Bn	Octylamine	96
3	Н	F	Allyl	Allylamine	98
4	Н	Н	Bn	Phenethylamine	94
5	CF <sub>3</sub>	Н	Allyl	n-Butylamine	97
6	Н	Н	4-MeOBn	Cyclopentylamine	92
7	Н	Н	Ср	4-MeOBnNH <sub>2</sub>	93
8	Н	F	n-Butyl	BnNH <sub>2</sub>	97
				-	

 $^a$  Reaction conditions: sulfonamide (0.17 mmol), CDI (0.69 mmol), Et\_3N (0.34 mmol) in dry DMF (0.2 M) at 100  $^\circ$ C for 6 h.



Scheme 4. Sequential one-pot synthesis of benzothiadiazin-3-one-1,1-dioxides.

In conclusion, we have developed a microwave-assisted, copper-catalyzed, sequential, one-pot synthesis of benzothiadiazin-3-one-1,1-dioxides. A variety of derivatives of benzothiadiazin-3one-1,1-dioxides can be rapidly accessed by combining a coppermediated N-arylation followed by cyclization with CDI. Further efforts toward employment of this method in library production will be published in due course.

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## Supplementary data

Supplementary data associated with this article Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.090.

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- 15. While final yields obtained with DMSO, using DMF gave results within 5% experimental error. However it was found that under microwave conditions at 150 °C, a small amount of by-product was formed from the addition of dimethylamine into the 4-F position of the benzene ring in a S<sub>N</sub>Ar mechanism. It is proposed that a small amount of dimethylamine is produced from the decomposition of DMF under these conditions and hence DMSO is a better solvent for such substrates.
- 16. General procedure for the N-arylation of α-bromobenzenesulfonamides: Into a microwave reaction vial was added sulfonamide (0.17 mmol, 1 equiv), Cul (0.017 mmol, 0.1 equiv), 1,10-phenanthroline (0.034 mmol, 0.2 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.34 mmol, 2 equiv), dry DMSO or DMF (0.5 M), and amine (0.2 mmol, 1.2 equiv). The reaction was heated in the microwave (Biotage initiator, www.biotage.com) at 150 °C for 11 min. After such time, the crude reaction was purified by flash chromatography [hexane/EtOAc, 8:2] to afford the desired product as a solid. Table 2, entry 8. FTIR (neat): 3400, 1579, 1301, 1149, 547 cm<sup>-1</sup>; mp 178–181 °C: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.73 (dd, *J* = 8.5, 6.6 Hz, 1H), 6.42 (ddd, *J* = 13.5, 9.7, 2.0 Hz, 2H), 6.19 (s, 1H), 5.98–5.83 (m, 1H), 5.67 (qt, *J* = 15.0, 7.5 Hz, 1H), 5.25 (dd, *J* = 19.5, 13.8 Hz, 2H), 5.12 (dd, *J* = 25.7, 13.7 Hz, 2H), 4.67 (t, *J* = 5.6 Hz, 1H), 3.88–3.74 (m, 2H), 3.52 (t, *J* = 5.8 Hz, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 167.8, 165.8, 147.9 (d, *J*<sub>C</sub>=F = 13.1 Hz), 133.2, 132.7, 117.8, 116.9, 103.5, 103.3, 99.6, 99.4, 46.1; HRMS calcd for C<sub>12</sub>H<sub>16</sub>FN<sub>2</sub>O<sub>2</sub>S (M+H)<sup>+</sup> 271.0917; found 271.0923.
- General procedure for the synthesis of benzothiadiazin-3-one-1,1-dioxides via CDI cyclization: To a round-bottomed flask was added sulfonamide (0.17 mmol, 1 equiv), dry DMF (0.2 M), Et<sub>3</sub>N (0.34 mmol, 2 equiv) and CDI (0.69 mmol, 4 equiv). The reaction mixture was heated at 100 °C for 6 h, cooled to rt and concentrated under reduced pressure. The crude oil was diluted in CH<sub>2</sub>Cl<sub>2</sub>, washed with 1 M HCl (aq, 5 mL), water (5 mL), and dried (MgSO<sub>4</sub>). Subsequent filtration and concentration yielded a crude oil which was purified by flash chromatography [hexane/EtOAc, 7:3] to afford the desired product as clear oil. (Table 3, entry 3). FTIR (neat): 3400, 1575, 1310, 1149 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.92–7.83 (m, 1H), 7.03–6.94 (m, 2H), 6.04–5.88 (m, 2H), 5.39–5.30 (m, 2H), 5.29–5.19 (m, 2H), 4.69–4.59 (m, 2H), 4.52–4.46 (m, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 166.7, 164.6, 150.2, 138.8 (dd, *J*<sub>C-F</sub> = 10.8 Hz), 131.6, 130.7, 125.3, 119.2, 118.0, 111.1, 104.7, 104.4, 48.5, 44.8; HRMS calcd for C<sub>13</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>5</sub>S (M+H)<sup>\*</sup> 297.0709; found 297.0712.
- 18. General one-pot procedure for the synthesis of benzothiadiazin-3-one-1,1-dioxides: Into a microwave reaction vial (0.5–2.0 ml) was added sulfonamide (0.17 mmol, 1 equiv), Cul (0.017 mmol, 0.1 equiv), 1,10-phenanthroline (0.034 mmol, 0.2 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.34 mmol, 2 equiv), dry solvent (0.5 M), and amine (0.2 mmol, 1.2 equiv). The reaction was heated in the microwave (Biotage initiator, www.biotage.com) at 150 °C for 11 min. After such time Et<sub>3</sub>N (0.34 mmol, 2 equiv) and CDI (0.69 mmol, 4 equiv) was added directly to the microwave vial. The reaction mixture was heated at 150 °C for 11 min, cooled to rt and concentrated under reduced pressure. The crude oil was diluted in CH<sub>2</sub>Cl<sub>2</sub>, washed with 1 M HCl (aq, 5 mL), water (5 mL) and dried (MgSO<sub>4</sub>). Subsequent filtration and concentration yielded a crude oil, which was purified by flash chromatography [hexane/EtOAc, 7:3] to afford the desired product.