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An Aryne-Based Route to Substituted Benzoisothiazoles

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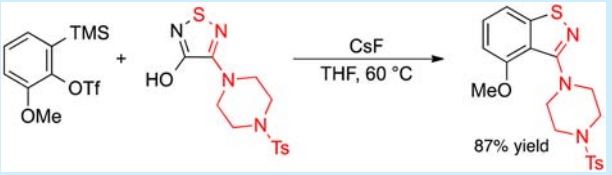
Supporting Information

ABSTRACT: The combination of arynes, generated using fluoride from the corresponding 2-(trimethylsilyl)aryl triflates, and 3-hydroxy-4-aminothiadiazoles leads to the selective formation of 3-amino-substituted benzo[*d*]isothiazoles. Variation of the substitution pattern of the aryne precursor, and of the thiadiazole, is possible, with the target heterocycles being obtained in good to excellent yields. In all cases, use of 3-hydroxy-4-aminothiadiazoles leads to incorporation of the amino-substituent in the product heterocycle.



Substituted benzoisothiazoles are represented in a number of medicinally important molecules, and in particular 3-amino benzoisothiazoles occur in various atypical antipsychotics (AAPs), such as lurasidone, ziprasidone, and perospirone (Figure 1).[1] Synthetic routes to these 3-amino variants generally involve substitution of the corresponding 3-chloro derivative, which in turn is obtained either from cyclization of *bis*(2-cyanophenyl) disulfide[2a] or by chlorination from benzoisothiazolinone.[2b] Both of these approaches require the use of hazardous reagents such as disulfur dichloride, phosphorus pentachloride, or chlorine, and in addition to the safety considerations associated with these reagents, their reactive nature correlates with poor functional group tolerance.

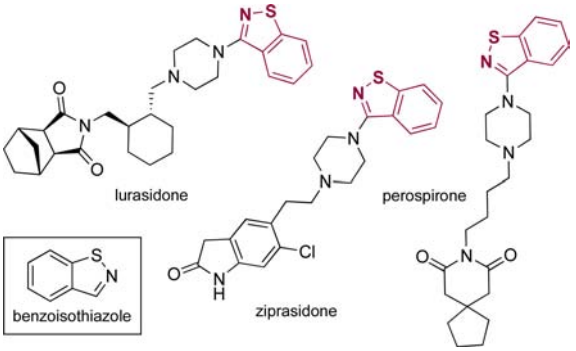
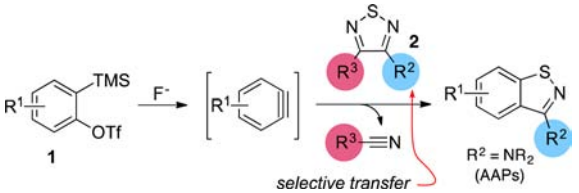


Figure 1. Medicinally relevant benzoisothiazole derivatives.

In addition to developing a more user and environmentally friendly route to benzoisothiazoles which avoids the use of hazardous reagents, we also wanted to introduce convergency and the ability to readily vary the substitution patterns on both the benzene and isothiazole moieties of the core structure. In approaching this threefold challenge, we were drawn to the concept of combining an aryne with an appropriate "S−N═C(R)" fragment in an annulative synthesis, and in particular to the use of 1,2,5-thiadiazoles as suitable addends.[3] In order to target the medicinally relevant 3-amino benzoisothiazole variants directly, we set the challenge of designing suitable asymmetrically substituted 1,2,5-thiadiazoles (**2**) in which only a single substituent, ideally N-based, would be selectively incorporated into the target structure (Scheme 1).

Scheme 1. An Aryne/1,2,5-Thiadiazole Based Route to Benzoisothiazoles



The combination of 3,4-dichloro-1,2,5-thiadiazole and benzyne, generated from benzenediazonium 2-carboxylate, is known to deliver 3-chlorobenzoisothiazole, albeit in only modest yield.[3] We speculated that the use of the Kobayashi benzyne precursor (**1a**),[4] 2-(trimethylsilyl)phenyl triflate, and the associated mild reaction conditions,[4] should allow a higher yielding route to the targeted benzoisothiazoles.[5] Accordingly, we began our study by exploring the reaction of the parent benzyne precursor (**1a**) with commercially available 3,4-dichloro-1,2,5-thiadiazole (**2a**, Table 1). The initial reaction between benzyne precursor **1a** and dichlorothiadiazole, using CsF as the fluoride source with MeCN as solvent at 60 °C, provided 3-chlorobenzoisothiazole (**3a**) in 45% yield (entry 1). Switching to THF as solvent provided a significant boost in yield (entry 2); however, variation of the stoichiometry between the two coupling partners, the reaction time, or temperature all failed to offer any further improvement in yield (entries 2−9). TBAF could also be employed as the fluoride source, with use of a lower reaction temperature allowing a 75% yield of the targeted benzoisothiazole to be achieved (entry 10).

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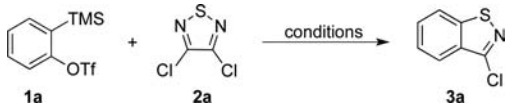
Table 1. Optimization of Reaction Conditions for the Formation of Benzoisothiazole 3a from 1a and 2a[a]



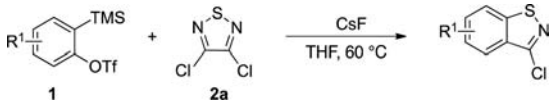
entry	equiv 1a	"F⁻" (equiv)	solvent	time (h)	temp (°C)	yield[b] (%)
1	1.4	CsF (2.8)	MeCN	20	60	45
2	1.4	CsF (2.8)	THF	20	60	76
3	2.0	CsF (4.0)	THF	36	60	45
4	1.4	CsF (2.8)	THF	48	22	43
5[c]	1.0	CsF (2.0)	THF	20	66	33
6[d]	1.0	CsF (2.0)	THF	20	66	32
7	1.0	CsF (3.0)	THF	20	66	55
8	1.0	CsF (2.0)	THF	20	66	40
9	1.0	CsF (4.0)	MeCN	20	82	65
10[e]	1.4	TBAF (2.8)	THF	8	22	75

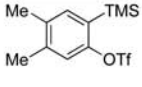
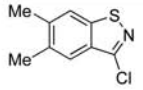
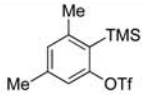
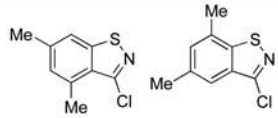
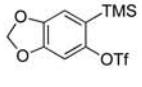
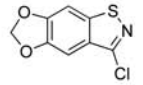
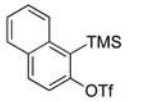
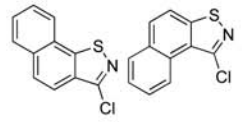
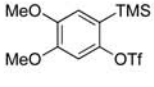
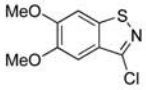
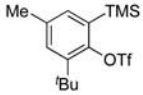
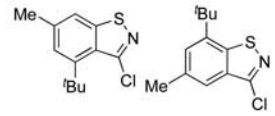
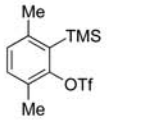
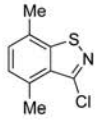
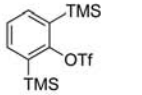
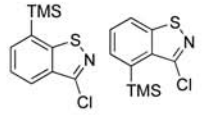
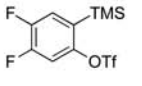
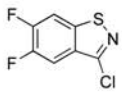
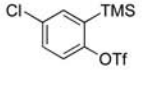
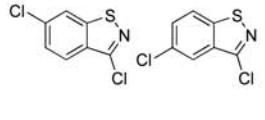
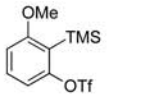
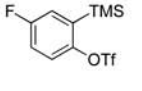
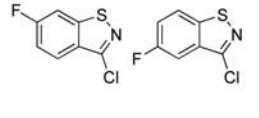
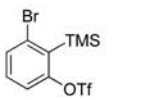
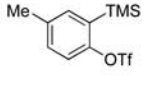
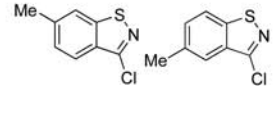
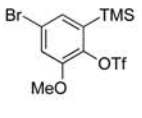
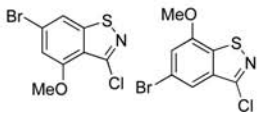
[a]Reaction conditions: **2a** (1.0 equiv), 0.33 M. [b]Isolated yields. [c]**2a** (2.0 equiv). [d]**2a** (3.0 equiv). [e]Reaction temp −55 to 22 °C over 12 h.

With suitable reaction conditions for the synthesis of benzoisothiazole **3a** identified (Table 1, entry 2), we next explored the generality of these conditions for variously substituted benzyne precursors (**1**), in combination with dichlorothiadiazole **2a**, to target a range of 3-chloro benzoisothiazoles (Table 2). A series of symmetrically substituted benzyne precursors combined effectively with the dichlorothiadiazole, delivering the desired Cl-substituted heterocycles as single compounds in good yields (entries 1–4), although the electron-poor difluoro-derivative was less efficient (entry 5). Of the remaining benzyne precursors, the 6-methoxy (entry 6) and 3-bromo (entry 7) variants delivered single benzoisothiazole products,[6,7] and the 4-bromo-6-methoxy precursor generated the 6-bromo-4-methoxy-substituted adduct as the major isomer with 8:1 selectivity (entry 8). All other unsymmetrically substituted aryne precursors that were explored delivered adducts as mixtures of regioisomers (entries 9–15). Notable among these examples were the 4-Me-6-^{t}Bu (entry 11) and 6-trimethylsilyl (entry 12) substrates, which despite the significant steric demands associated with these substitution patterns, still generated mixtures of regioisomeric adducts with poor selectivity.[8]

Having established that a broad range of substituted aryne precursors could effectively participate in reactions with the dichlorothiadiazole, we returned to the issue of identifying

Table 2. Synthesis of 3-Chlorobenzoisothiazoles Using Thiadiazole 2a[a]



entry	precursor (1)	product(s)	yield (%)/(ratio)	entry	precursor (1)	product(s)	yield (%)/(ratio)
1			96	9			83 (1:1)[b]
2			96	10			97 (2.5:1)
3			93	11			82 (2:1)[b]
4			67	12			64 (2:1)
5			52	13			76 (1:1.9)[b]
6			70	14			68 (1:2)[b]
7			40	15			64 (1:1)[b]
8			78 (8:1)				

[a]Reaction conditions: **1** (1.4 equiv), **2a** (1.0 equiv), 0.33 M. Isolated yields. [b]Regioisomers inseparable.

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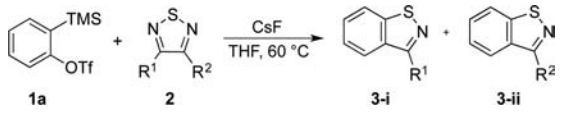
asymmetrically substituted thiadiazole substrates that would allow the selective incorporation of a single substituent into the products (Scheme 1). We prepared a range of asymmetric thiadiazoles[9] and explored their reactivity with the parent aryne precursor **1a** (Table 3). To compare the reactivity of Cl versus

Table 3. Evaluation of Asymmetrically Substituted Thiadiazole Derivatives in Combination with Aryne Precursor 1a[a]



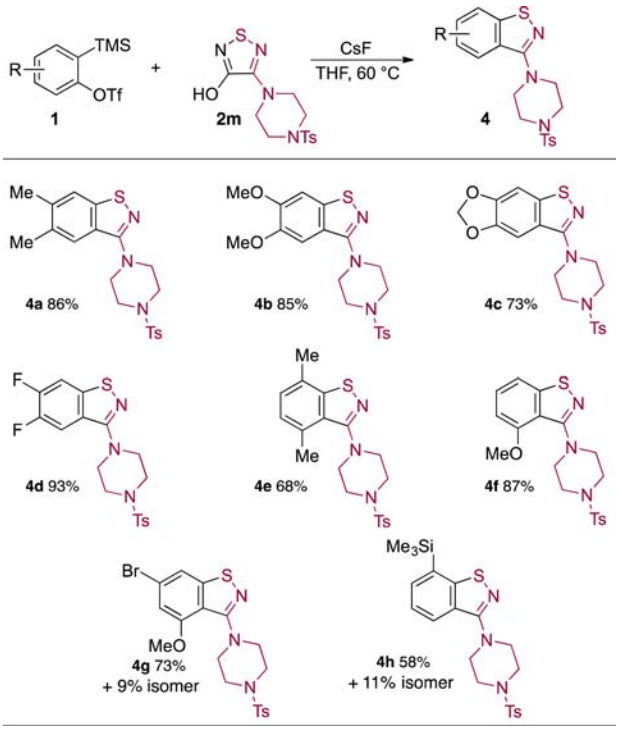
entry	thiadiazole	R^1	R^2	3-(i):(ii)	yield (%)
1	**2b**	OMe	OMe	-	81
2	**2c**	OMe	Cl	1:3	75
3	**2d**	OMe	SMe	1:1	61[b]
4	**2e**	OMe	SO_2Me	1:20	24
5	**2f**	Cl		3:1	83
6	**2g**	OMe		2:3	86
7	**2h**	OH		1:>20	96
8	**2i**	OH		1:>20	83
9	**2j**	OH		1:>20	78
10	**2k**	OH		1:>20	93
11	**2l**	OH		1:>20	73
12	**2m**	OH		1:>20	85

[a]Reaction conditions: **1a** (1.4 equiv), **2** (1.0 equiv), 0.33 M. Isolated yields. [b]Products inseparable.

OMe substituents we evaluated the dimethoxythiadiazole (**2b**, entry 1), which proved to show comparable reactivity to the dichloro-derivative (Table 1, entry 2). Perhaps unsurprisingly therefore, reaction of a 3-OMe-4-Cl-thiadiazole (**2c**) provided the targeted benzoisothiazoles as a 3:1 mixture, with the Cl-derivative being the major compound (entry 2). A 3-OMe-4-SMe combination showed no selectivity; however, a 3-OMe group partnered with a 4-SO_2Me group selectively delivered the SO_2Me-substituted product, albeit in a poor 24% yield (entry 4). A morpholino-substituent partnered with either a Cl- or a OMe-group was poorly selective (entries 5 and 6). The breakthrough result was achieved when a morpholino group was partnered against a OH-group; the morpholino unit was transferred exclusively in 96% yield (entry 7). Following this encouraging result, a number of 3-dialkylamino-4-hydroxy-thiadiazoles were prepared and evaluated, with all examples delivering the 3-aminobenzoisothiazoles in good yields and with excellent selectivities (entries 8–12).

Given the frequent occurrence of the 3-aminobenzoisothiazole scaffold in medicinal chemistry, we next explored the combination of thiadiazole **2m**, featuring a piperazine substituent, with a range of substituted aryne precursors (Scheme 2). Pleasingly, the use of symmetrically substituted

Scheme 2. Preparation of Substituted 3-Aminobenzoisothiazoles Using Thiadiazole 2m[a]



[a]Reaction conditions: **1** (1.4 equiv), **2** (1.0 equiv), 0.33 M. Isolated yields.

benzyne precursors delivered the expected 3-aminobenzo-isothiazoles (**4a–e**) in good yields, demonstrating that a range of electron-donating, -withdrawing, and -neutral substituents could be incorporated effectively. The use of unsymmetric precursors allowed the selective formation of a 3-amino-4-methoxybenzoisothiazole (**4f**), together with a 4-methoxy-6-bromo (**4g**, 8:1) and a 7-trimethylsilyl (**4h**, 5:1) variant, although the latter two examples were obtained along with small amounts of the regioisomeric adducts.

Thiadiazoles featuring C-based substituents at C3 and/or C4 proved to be difficult to access, thus limiting entry to the corresponding C-substituted benzoisothiazoles, which were a variant of the heterocycles that we wished to explore. To address this issue we investigated a cascade reaction sequence whereby an initially formed 3-Cl benzoisothiazole is reacted in situ with a nucleophilic species, allowing substitution of the Cl group. As shown in Scheme 3, addition of a malonate nucleophile to the *in situ* formed 3-Cl benzoisothiazole **3a**, in a one-pot two-step process, generated C-substituted benzoiso-thiazole **5** in 68% yield, along with 11% of the corresponding 3-aminobenzothiophene **6**.[10]

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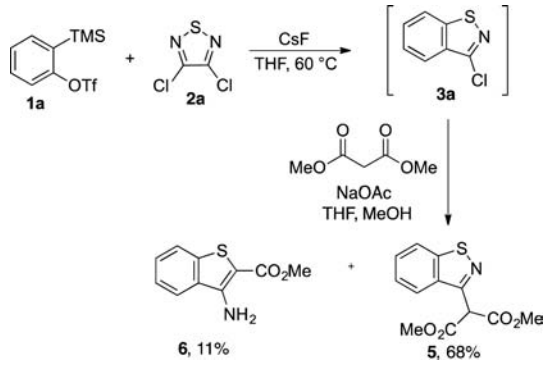
Scheme 3. Cascade Process for the Formation of C-Substituted Benzoisothiazole 5



In conclusion, we have shown that a range of thiadiazoles can be combined effectively with benzyne precursors to deliver the corresponding 3-substituted benzoisothiazoles. In particular, the use of 3-(dialkyl)amino-4-hydroxythiadiazoles allows the selective formation of 3-(dialkyl)amino-substituted benzoisothiazoles, with the formal loss of a molecule of cyanic acid as a byproduct. Good variation of the benzyne precursor was possible, allowing the efficient preparation of a broad range of 3-aminobenzoisothiazoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02347.

Experimental procedures and full characterization for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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