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Domino Aryne Precursor: Efficient Construction of 2,4-Disubstituted Benzothiazoles

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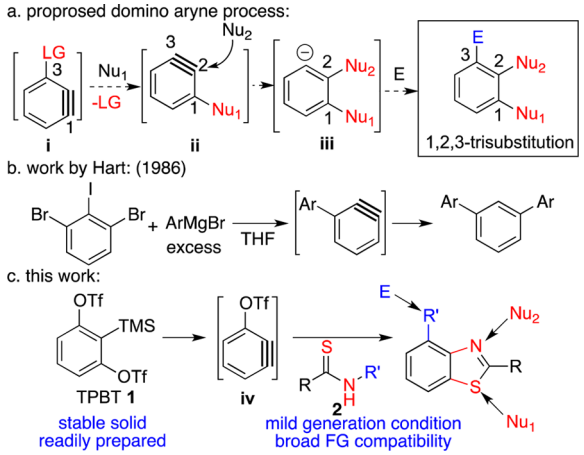
Supporting Information

ABSTRACT: An aryne precursor with a potential to perform domino aryne chemistry was proposed and synthesized. The reaction of this reagent with benzothioamide derivatives could afford 2,4-disubstituted benzothiazole with sequential incorporation of C−S, C−N, and C−C bonds on the consecutive three positions of the aryne precursor.

Arynes are among the most reactive organic species and have been broadly employed in numerous organic syntheses.[1] In particular, the success of Kobayashi reagents,[2] *o*-trimethylsilylphenyl triflates, in recent aryne chemistry is primarily attributed to their convenient and mild aryne generation conditions.[1f,g] Because of the formal triple bond character of arynes, however, normally only 1,2-disubstituted aromatics are attainable via aryne intermediates. The preparation of 1,2,3-trisubstituted benzenes, the structure of which prevails in vast groups of organic compounds, are still beyond the boundary of standard aryne chemistry and have yet to be well-documented.[3] Aryne precursors that can assemble three consecutive functional groups on a benzene ring in "one-pot" fashion, are compatible with various reagents and functional groups, and can perform versatile transformations would largely expand the realm of current aryne chemistry.

To reach the goal for trisubstitution, a domino aryne process can be conceived. As depicted in Scheme 1a, this process could sequentially accept two nucleophiles, namely, Nu1 and Nu2, and an electrophile (E) through two aryne intermediates, **i** and **ii**. The generation of consecutive 1,2- and 2,3-arynes in Scheme 1a could deliver the reaction toward trifunctionalization. To the best of our knowledge, domino aryne pathway was only reported by Hart in the construction of *m*-terphenyls from 2,6-dibromoiodobenzene (Scheme 1b).[4] Utilizing Grignard reagents to generate aryne from polyhalobenzenes, however, falls short of functional group compatibility and restricts the synthetic application of this approach. Herein, we report a reagent that can carry out domino aryne chemistry under mild aryne generation conditions and exhibit its efficient synthesis of 2,4-disubstituted benzothiazoles.

Scheme 1. Proposed Construction of 1,2,3-Trisubstituted Benzene



We started our reagent design with the same generation method as Kobayashi reagents and looked for a suitable leaving group on intermediate **i**. Although several Kobayashi reagents are known to generate intermediate **i** with halogens[5] or sulfamoyloxy ($-OSO_2NMe_2$) group[6] on its 3-position, they have been traditionally employed as directing groups to control the regioselectivity upon nucleophilic reactions[3b] and none of them could conduct the transformation in Scheme 1a. Because of the supreme leaving ability of the triflyloxy (OTf) group, we proposed 2-(trimethylsilyl)-1,3-phenylene bis(trifluoromethanesulfonate) (TPBT) (**1**) as our reagent, which could generate 3-triflyloxybenzyne (**iv**) for our domino aryne process study (Scheme 1c).[7] TPBT **1** is a stable, low melting point solid and could be prepared in gram scale in a batch from 2-bromoresorcinol in an overall yield between 60% and 80% (see Supporting Information (SI) for the preparation procedure).

To demonstrate the proposed domino process with TPBT **1**, we designed protected benzothioamides **2** as the substrates (Scheme 1c), on which the sulfur[8] and nitrogen[9] atoms correspond to Nu_1 and Nu_2, respectively. We also envisioned that a carbonyl group migration from carbamide would take place in the final stage, which has been accomplished previously in aryne chemistry.[9a,c,10] When **2a** and **2b** were treated with TPBT **1**, to our surprise, two different products, **3a** and **4a**, respectively, were obtained (Scheme 2). When pivaloyl (Piv) group was employed, the reaction gave 2,4-disubstituted benzothiazole **3a** in 51% yield (see SI for its crystal structure); whereas with acetyl protected **2b**, 2-phenylbenzothiazole (**4a**) was found to be the product in 36% isolated yield. The formation of **4a** from **2b** is in contrast with aryne acyl-alkylation reactions, which give readily acetyl group migration.[11]

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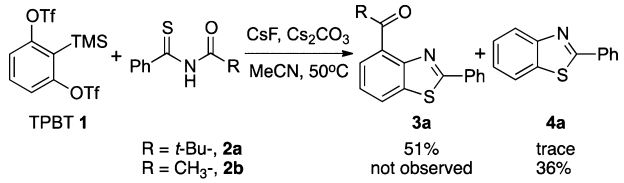
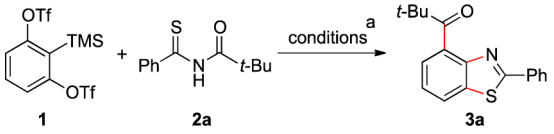
Scheme 2. Initial Tests



This preliminary study indicates that by varying the protecting groups on benzothioamide **2** the reaction path can be altered. Intriguingly, it is the first mild and direct domino aryne chemistry to incorporate three functional groups on a benzene ring with strict 1−2−3 sequence. In view of the broad spectrum of biological activities of benzothiazoles, such as antitumor, antimicrobial, anticonvulsant, antidiabetic, and anti-inflammatory activities,[12,13] in addition with the antitumor property of benzothiazole-4-carboxamides as poly(ADP-ribose) polymerase (PARP) inhibitors,[12a] our method could provide a quick structural diversification on both the 2- and 4-positions of a benzothiazole core. Although the syntheses of benzothiazoles have been well documented,[12a,14] preparing 2,4-disubstituted benzothiazoles with the core of **3a** usually requires multistep manipulation.[13]

As shown in Table 1, different solvents were screened first (entries 1−6), and dioxane was found to be the best solvent

Table 1. Optimization Conditions to Make 3a



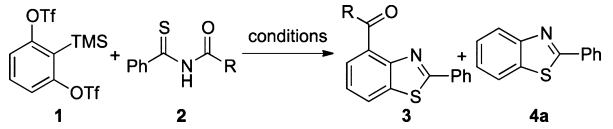
entry	F (equiv)	solvent	temp (°C)	3a[b] (%)
1	CsF (3.0)	MeCN	80	71
2	CsF (3.0)	toluene	80	40
3	CsF (3.0)	tol./MeCN[c]	80	60
4	CsF (3.0)	THF	50	40
5	CsF (3.0)	DCM	rt	47
6	**CsF (3.0)**	**dioxane**	**80**	**82**
7	no	dioxane	80	0
8	CsF (3.0)	dioxane	100	73
9	CsF (3.0)	dioxane	50	69
10	CsF (3.0)	dioxane	rt	52
11[d]	CsF (3.0)	dioxane	80	71
12	KF (5.0), 18-c-6 (2.0)	dioxane	80	trace
13	KF (3.0), 18-c-6 (2.0)[e]	dioxane	80	63
14	TBAT(1.5)[f]	dioxane	80	51
15	TBAF (5.0)[e]	dioxane	80	23

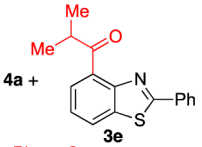
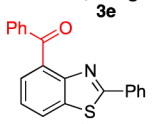
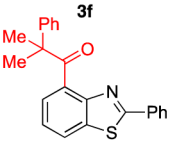
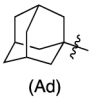
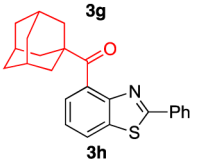
[a]Conditions: slow addition of TPBT **1** (0.6 mmol) in solvent (10 mL) to **2** (0.4 mmol) in solvent (30 mL) over 8 h. [b]Isolated yield. [c]Tol./MeCN = 1:1. [d]TPBT **1** (0.2 mmol) was used. [e]With K_2CO_3 (3.0 equiv). [f]TBAT = tetrabutylammonium difluorotriphenylsilicate.

(entry 6). In the absence of CsF, no **3a** was observed (entry 7), and the optimal temperature is 80 °C (entries 8−10). Further study revealed that CsF is the best fluoride source (entries 12−15). Finally, the optimal condition is slow addition of TPBT **1** via a syringe pump at 80 °C in dioxane (condition A), and **3a** was obtained in 82% yield (entry 6).

With the optimal conditions to make **3a** in hand, we examined the reaction outcomes with other protecting groups. It was found that whenever there is a α-hydrogen on the carbonyl group, such as acetyl, phenylacetyl, diphenylacetyl, and dimethylacetyl groups, **4a** was found the dominant product (entries 1−4, Table 2). Since **4a** could also react with aryne, excess amount of

Table 2. Reaction with Various R Groups



entry	R		condition	products	yield[c] 3 (%)	4a (%)
1	Me-	(**2b**)	B[a]	**4a**	0	54
2	$PhCH_2$-	(**2c**)	B	**4a**	0	59
3	Ph_2CH-	(**2d**)	B	**4a**	0	50
4	Me_2CH-	(**2e**)	B	**4a** +  **3e**	14	48
5	Bz-	(**2f**)	A[b]	 **3f**	55	0
6	Me_2PhC-	(**2g**)	A	 **3g**	80	0
7	 (Ad)	(**2h**)	A	 **3h**	72	0

[a]Condition B: slow addition of TPBT **1** (0.3 mmol) in dioxane (10 mL) to a mixture of **2** (0.9 mmol), K_2CO_3 (1.8 mmol), and 18-c-6 (0.9 mmol) in dioxane (40 mL). [b]Condition A: slow addition of TPBT **1** (0.6 mmol) in dioxane (10 mL) to **2** (0.4 mmol) and CsF (2.0 mmol) in dioxane (30 mL) over 8 h. [c]Isolated yield.

thioamides was used in these reactions. Dimethylacetamide **2e** could also produce 1,4-disubstituted benzothiazole **3e** in 14% yield, along with **4a** in 48% yield (entry 4). In the absence of α-H, thioamides with benzoyl, dimethylphenylacetyl, and 1-adamantylcarbonyl could all produce the corresponding carbonyl migration products (entries 5−7, Table 2). Other functional groups either gave unstable thioamides (with trifluoroacetyl or *p*-toluene-sulfonyl) or received no desired product (with *t*-butoxycarbonyl) under the reaction conditions.

As shown in Table 3, further study on the reaction scope reveals that various protected thioamides, both aromatic and aliphatic, could react with TPBT **1**. When aromatic thioamides were employed, both electron donating groups (**3i**, **3j**, and **3p**) and electron withdrawing groups (**3k**−**3o**) could give the desired products in moderate to high yields. Heteroaromatic rings, such as thiophene, could give the corresponding product **3q** in 71% yield. Moreover, aliphatic analogues could also afford the desired products, albeit with lower efficiency (**3r** and **3s**). At last, when 1,3-bis(benzothioamide) **2t** was employed, the corresponding bisbenzothiazole **3t** was obtained in 41% yield.

To further expand the scope of our method, we turned to convert the *t*-butyl ketone on **3a** to either acid or amide via Baeyer−Villiger oxidation or Beckmann rearrangement, respectively. Satisfyingly, under Baeyer−Villiger oxidation conditions,

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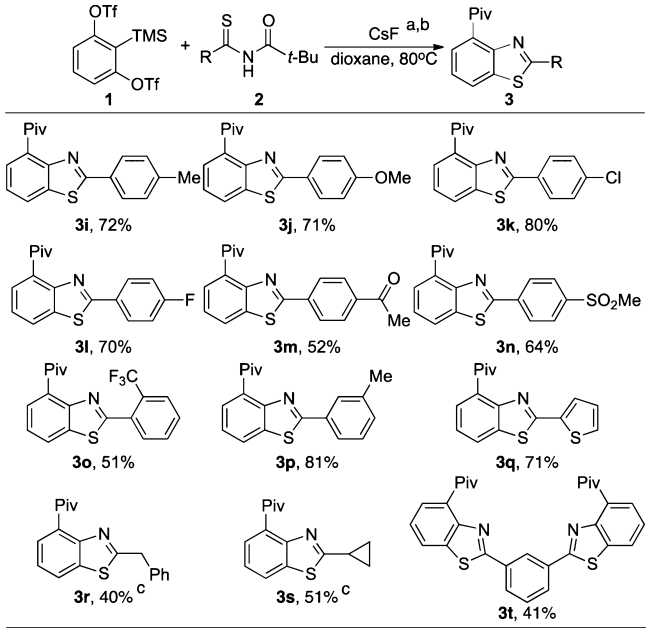
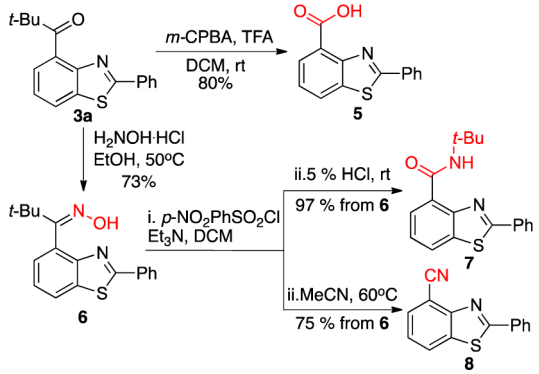
Table 3. Substrate Scope for the Preparation of 3



[a]Conditions: slow addition of TPBT **1** (0.6 mmol) in dioxane (10 mL) to **2** (0.4 mmol) and CsF (2.0 mmol) in dioxane (30 mL) over 8 h. [b]Isolated yield. [c]Cs_2CO_3 (2.0 mmol) was used instead of CsF.

benzothiazole **3a** could be oxidized to carboxylic acid **5** in 80% yield (Scheme 3). Moreover, both benzamide **7** and benzonitrile

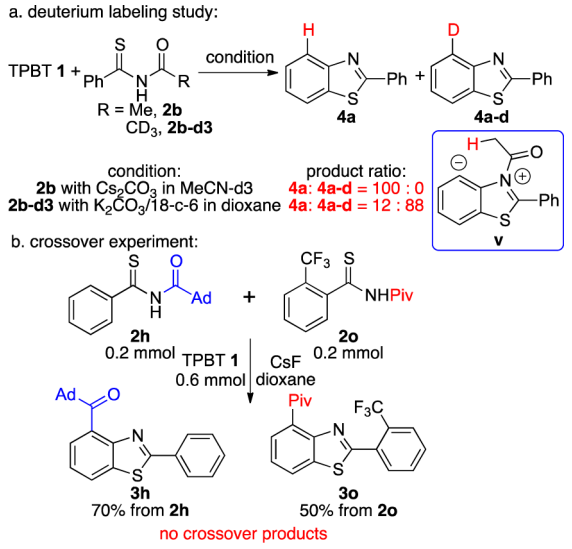
Scheme 3. Synthetic Applications of 3a



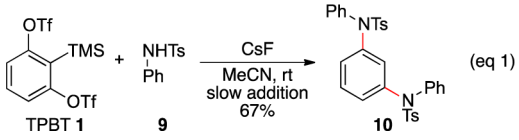
8 were obtained in 97% and 75% yields, respectively, from oxime **6**. The successful achievement of acid **5**, amide **7**, and benzonitrile **8**, the structures of which belong to a series of biologically active compounds,[13] indicates that our methodology is versatile in structural diversification.

To elucidate the hydrogen source of the 4-position in **4a**, deuterium labeling studies were carried out (Scheme 4a). When **2b** reacted with TPBT **1** in acetonitrile-d_3, surprisingly, **4a**−**d** was not observed. In contrast, when **2b**-d_3 was treated with TPBT **1** in dioxane, **4a**−**d** was obtained with 88% deuteration on its 4-position. These observations indicate that the 4-hydrogen on **4a** originates from the intramolecular 1,5-hydrogen abstraction via intermediate **v** as a major pathway (Scheme 4a). In addition, crossover experiment with **2h** and **2o** as a mixture gave only two products, **3h** and **3o**, respectively (Scheme 4b). The absence of crossover products in this experiment suggests that the carbonyl group migration step is solely intramolecular.

Scheme 4. Mechanistic Study



While demonstrated for benzothiazole synthesis, our reagent has great potential for use with other nucleophiles as well. For example, when TPBT **1** was treated with *N*-tosylated aniline **9** in the presence of CsF, 1,3-diaminated product **10** could be achieved in 67% isolated yield (eq 1). This example indicates that the reaction mode of double nucleophile attack on our TPBT reagent is general when it combines with different types of nucleophiles.



In summary, a series of 2,4-disubstituted benzothiazoles is prepared from aryne precursor TPBT **1**, whose conversion involves a domino aryne mechanism. By varying the carbonyl groups, either 2-substituted or 2,4-disubstituted benzothiazoles were obtained. A sequential formation of C−S, C−N, and C−C bonds on the 1,2,3-positions of the TPBT **1** benzene ring was achieved. This method is versatile, and the 2,4-disubstituted benzothiazole product could be further converted to other derivatives. Our ongoing projects focus on the development of the other useful synthetic applications of TPBT **1**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details for all chemical reactions and measurements and X-ray single crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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