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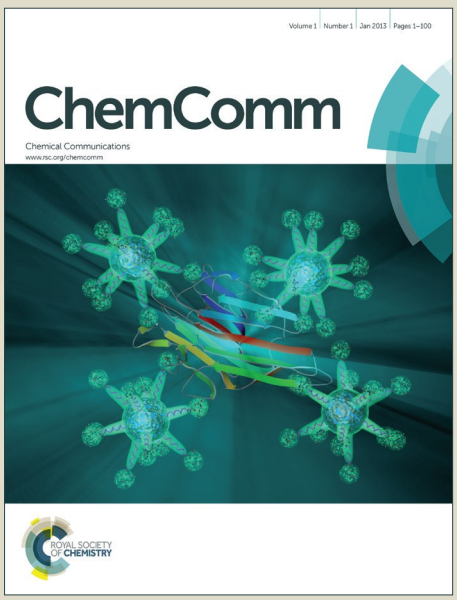

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Thiazolobenzyne: A versatile intermediate for multisubstituted benzothiazoles

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Thiazolobenzyne, which is a benzyne species fused with a thiazole ring, was efficiently generated via an iodine–magnesium exchange reaction of an *ortho*-iodoaryl triflate-type precursor using a trimethylsilylmethyl Grignard reagent as an activator. A wide range of arynophiles reacted efficiently with the thiazolobenzynes generated by this method to afford various multisubstituted benzothiazoles.

Benzothiazole is a heterocycle that is often contained as a core skeleton in a wide range of molecules. These include natural products, such as firefly luciferin, and imaging probes, such as Pittsburgh compound B, which is used as a diagnostic agent for Alzheimer's disease (Fig. 1).[1] Despite the increasing importance of benzothiazoles, methods for synthesizing multisubstituted benzothiazoles are limited.[1] In accordance with our studies to develop selective protein kinase inhibitors such as INDY and TG003,[2] we faced a problem in preparing multisubstituted benzothiazoles.

We assumed that the application of aryne chemistry could be one of the solutions to address this issue because arynes are highly reactive intermediates that are useful for synthesizing diverse aromatic compounds (Fig. 2).[3–9] These include ring-fused multisubstituted arenes that are difficult to prepare using conventional methods (Fig. 2A and 2B). In particular, the chemistry of heterocyclic arynes, such as pyridynes and indolynes, has been well-studied in recent years and a broad range of multisubstituted heteroarenes has become readily accessible.[6,7] We anticipated that thiazole-fused benzyne, i.e., thiazolobenzyne, could be a useful intermediate for preparing multisubstituted benzothiazoles (Fig. 2C).[9] However, despite the potential usefulness of thiazolobenzyne, neither the generation nor the synthetic application of this species has been reported. Moreover, we became interested in the reactivity of thiazolobenzyne, particularly in the characteristic difference between thiazolo[5,4-*c*]benzyne **I** (6,7-thiazolobenzyne) and thiazolo[4,5-c]benzyne **II** (4,5-thiazolobenzyne) (Fig. 2C). Because regioselective reactions of 3,4-ring-fused arynes, such as 6,7-

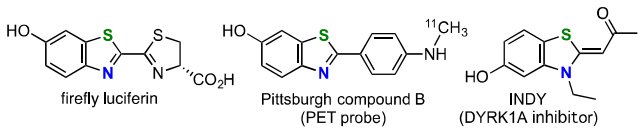

Fig. 1 Various benzothiazole derivatives.

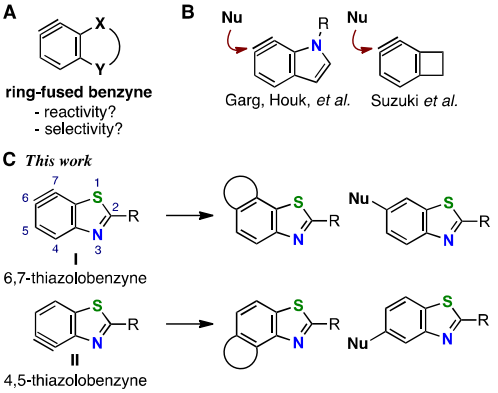

Fig. 2 Thiazolobenzynes: new entries as ring-fused benzynes.

indolyne[7] and 3,4-cyclobutabenzyne,[8] with various arynophiles have been reported (Fig. 2B), we hypothesized that thiazolobenzynes also react with arynophiles in a regioselective manner. Herein, we report an efficient method for the generation of thiazolobenzynes and their use in the synthesis of multisubstituted benzothiazoles.

As precursors for 6,7- and 4,5-thiazolobenzynes, we chose *ortho*-iodoaryl triflates[10] because they were expected to be easily synthesized. Indeed, thiazolobenzyne precursors **1a** and **1b** with a 4-fluorophenyl group at the 2-position (Scheme 1) were easily prepared from the corresponding 6- and 4-methoxybenzothiazole, respectively. For example, thiazolobenzyne precursor **1a** was efficiently prepared from 6-methoxybenzothiazole in three steps: *ortho*-iodination,

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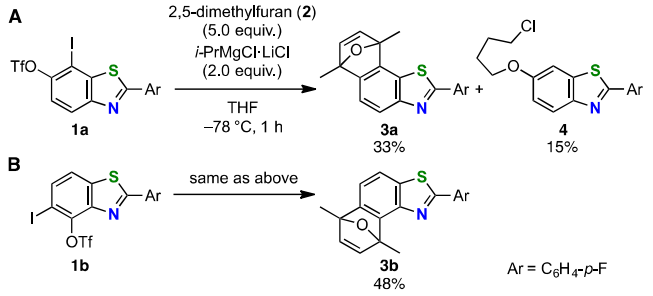
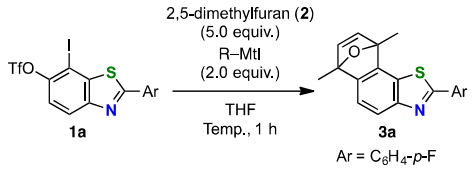
demethylation, and triflylation.[11] Our initial attempts showed that generating thiazolobenzynes from these precursors via iodine–metal exchange reaction triggered by treatment with an organometallic reagent was possible (Scheme 1). However, these attempts also indicated difficulty in achieving an efficient transformation via these species. For example, the treatment of **1a** with isopropylmagnesium chloride–lithium chloride complex in the presence of 2,5-dimethylfuran (**2**) in THF at −78 °C afforded the desired cycloadduct **3a** only in low yield (Scheme 1A). After careful investigation of the products, we identified a side product **4**, which was probably formed via nucleophilic addition of THF to 6,7-thiazolobenzyne. This result indicated the particularly high electrophilicity and instability of thiazolobenzyne species. Similarly, the reaction using 4,5-thiazolobenzyne precursor **1b** under the same conditions afforded the desired cycloadduct **3b** in moderate yield (Scheme 1B).



Scheme 1 Initial attempts.

Table 1 Optimization of reaction conditions

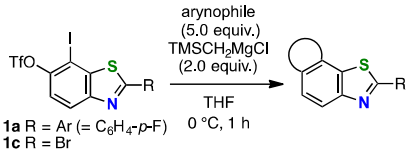


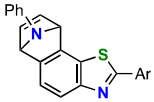
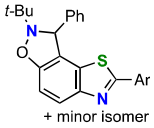
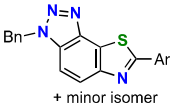
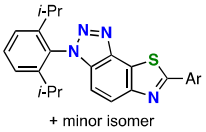
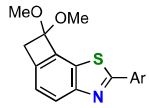
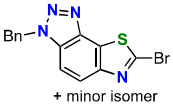
Entry	R–MtI	Temp. (°C)	Yield[a] (%)
1	*n*-BuLi	−78	49
2	*n*-BuMgBr	−78	53
3	*i*-PrMgCl	−78	46
4	*t*-BuMgCl	−78	27
5	PhMgBr	−78	37
6	$TMSCH_2MgCl$	−78	67
7	$TMSCH_2MgCl$	−30	85
8	$TMSCH_2MgCl$	0	91 (89)[b]

[a]Yields based on ^{1}H NMR analysis. [b]Isolated yields in parentheses.

To improve the efficiency of the reaction between **1a** and **2**, we aimed for better conditions (Table 1). After extensive screening of activators, the trimethylsilylmethyl Grignard reagent delivered the best result among various organometallic reagents examined (entries 1–6). Similar to our previous reports, the modest ability of the trimethylsilylmethyl Grignard reagent for iodine–magnesium exchange due to its low nucleophilicity must have contributed to the significant improvement of the reaction efficiency via the generation of aryne species with particularly high reactivity.[5] Further improvement in the yield of cycloadduct **3a** was achieved by performing the reaction at higher temperatures (entries 7 and 8); the best result was obtained when the reaction was performed at 0 °C (entry 8).

Table 2 Cycloadditions of 6,7-thiazolobenzyne



Entry		Arynophile		Product		Yield[a] (%)
1	**1a**		**5**		**6**	86
2	**1a**		**7**	 + minor isomer	**8** + **8'**	96[b] (80:20)
3	**1a**	BnN_3	**9**	 + minor isomer	**10** + **10'**	70[b,c,d] (94:6)
4	**1a**		**11**	 + minor isomer	**12** + **12'**	73[b] (91:9)
5	**1a**		**13**		**14**	82[e]
6	**1c**	BnN_3	**9**	 + minor isomer	**15**	75[b,c,f] (86:14)

[a]Isolated yields, unless otherwise noted. Ratio of regioisomers shown in parentheses. [b]Yields as a mixture of regioisomers. [c]Yield based on ^{1}H NMR analysis. [d]The major product was isolated in 66% yield. [e]Regioisomer was not detected. [f]The major product was isolated in 56% yield.

Under optimized conditions, various ring-fused benzothiazoles were efficiently prepared from 6,7-thiazolobenzyne precursor **1a** (Table 2). The Diels–Alder reaction of 6,7-thiazolobenzyne with *N*-phenylpyrrole (**5**) (entry 1) and [2+3] and [2+2] cycloadditions with a variety of arynophiles, such as nitrone **7**, azides **9** and **11**, and ketene acetal **13**, proceeded with high efficiencies (entries 2–5). High regioselectivities observed in these cases indicated that the most nucleophilic atom of the arynophiles predominantly attacked the 6-position of 6,7-thiazolobenzyne to form new bonds. The structure of the major isomer of the triazole-fused product **10** was confirmed by X-ray crystallographic analysis.[11] Notably, 6,7-thiazolobenzyne bearing a bromo group at the 2-position was also successfully generated from precursor **1c**, leaving the organometallic reagent-susceptible bromo group intact, as demonstrated in the reaction with azide **9** (entry 6). The obtained cycloadduct **15** would be further transformed to various C2-substituted benzothiazoles by taking advantage of the C2-bromo group, easily widening the available benzothiazoles by this method.

The method was also applicable for the generation and cycloaddition of 4,5-thiazolobenzyne bearing an aryne triple bond adjacent to the nitrogen atom (Table 3). Using the same conditions for the generation of 6,7-thiazolobenzyne from **1a**, various ring-fused benzothiazoles were prepared from the 4,5-thiazolobenzyne

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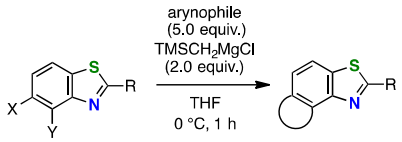
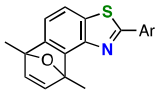
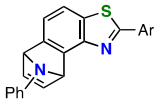
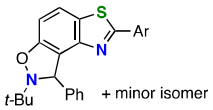
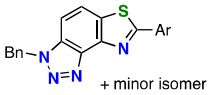
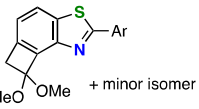
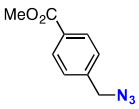
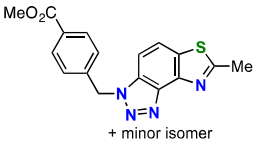
precursor **1b** in high yields with high regioselectivities (entries 1–5). Notably, the reaction of 2-methyl-4,5-thiazolobenzyne, which was generated from **1d**, with azide **20** proceeded smoothly without affecting the methyl and ester groups, demonstrating the mildness of the reaction conditions (entry 6).

Table 3 Cycloadditions of 4,5-thiazolobenzyne



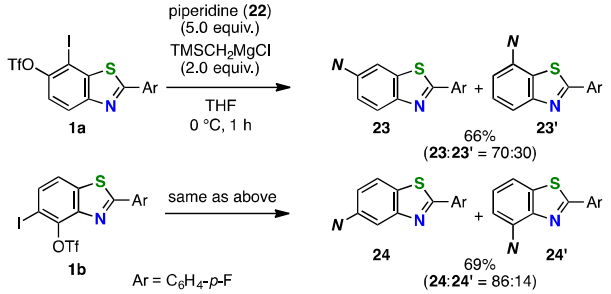
1b X = I, Y = OTf, R = Ar (= C_6H_4-*p*-F)
1d X = OTf, Y = I, R = Me

Entry	1	Arynophile		Product		Yield[a] (%)
1	**1b**		**2**		**3b**	91
2	**1b**		**5**		**16**	78
3	**1b**		**7**		**17** + **17'**	94[b] (93:7)
4	**1b**	BnN_3	**9**		**18** + **18'**	85[b] (87:13)
5	**1b**		**13**		**19** + **19'**	94[b] (89:11)
6	**1d**		**20**		**21** + **21'**	93[b] (77:23)

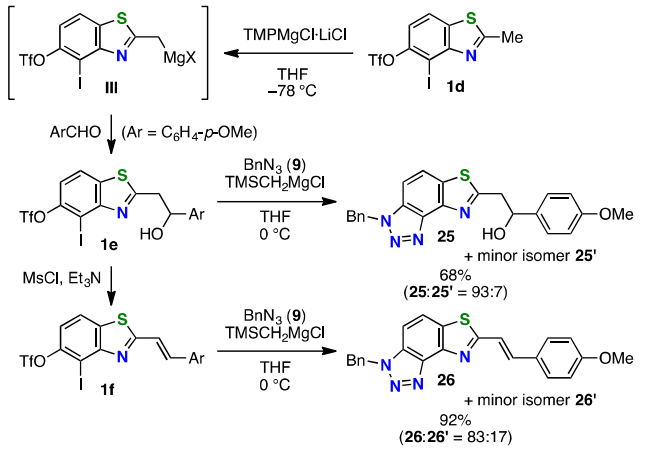
[a]Isolated yields. Ratio of regioisomers shown in parentheses. [b]Yields as a mixture of regioisomers.

Generation of thiazolobenzyne from **1a** or **1b** in the presence of piperidine (**22**) afforded 6- or 5-piperidinobenzothiazole, **23a** or **24a**, respectively, as a major product, indicating that the addition of the nucleophile predominantly proceeded at the 6- or 5-position of 6,7- or 4,5-thiazolobenzyne, respectively (Scheme 2). These results were in good agreement with regioselectivities observed in cycloadditions of thiazolobenzynes with unsymmetrical arynophiles (Table 2, entries 2–5 and Table 3, entries 3–6).

Derivatization of a simple thiazolobenzyne precursor further expanded the scope of synthesizable benzothiazole derivatives by this method. For example, modification of the C2-methyl group of 4,5-thiazolobenzyne precursor **1d** via metalation and subsequent reaction of generated carbanion **III** with an electrophile rendered functionalized thiazolobenzyne precursors such as **1e** and **1f** easily available (Scheme 3). Thiazolobenzynes bearing a hydroxy or styryl group were efficiently generated from these precursors and reacted successfully with an arynophile, demonstrating the synthetic utility of this method.



Scheme 2 Addition of an amine to thiazolobenzynes. *N* = piperidinyl.



Scheme 3 Diversification of a simple thiazolobenzyne precursor.[11]

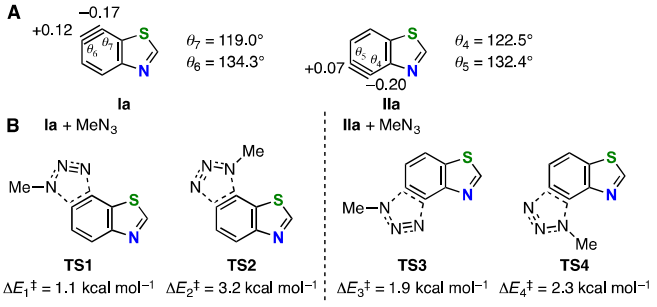


Fig. 3 Computational studies using a DFT method (M11-L/6-31G(d)).[11] (A) Optimized structures of 6,7-thiazolobenzyne (**Ia**) and 4,5-thiazolobenzyne (**IIa**). The numbers denotes the charge distribution of **Ia** and **IIa**. (B) Analysis of the reaction pathway for cycloadditions of **Ia** and **IIa** with methyl azide.

Theoretical studies based on density functional theory (DFT) provided insights into the particularly high reactivity of thiazolobenzynes and the regioselectivity observed in their reactions with arynophiles (Fig. 3). Using the GAMESS-US program package,[12] we analyzed the geometric/electronic structures of thiazolobenzynes and their reactivity with methyl azide at the M11-L/6-31G(d) level of the theory.[11] Optimized geometry structures of thiazolobenzynes **Ia** and **IIa** were in good agreement with those previously reported by Paton, Houk, Garg, and coworkers;[13] the calculated values of the internal angles at C6 and C5 in the optimized structures of 6,7-thiazolobenzyne (**Ia**) and 4,5-thiazolobenzyne (**IIa**) were larger than that of C7 and C4, respectively, indicating that the structures of these arynes are highly distorted (Fig. 3A). Furthermore, population

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analysis[11,14] revealed that C6 of **Ia** and C5 of **IIa** are the more electrophilic carbons. The considerable distortion of **Ia** bearing the aryne triple bond adjacent to the sulfur atom can be attributed to the electronic effect derived from the increased p-character of the C–S bond[15] as well as the strain effect elicited by the fused ring, which is similar to the case of cyclobutabenzyne proposed by Suzuki and coworkers.[8a] For the case of **IIa** bearing the aryne triple bond adjacent to the nitrogen atom, in addition to the strain effect, the electronnegativity of the nitrogen atom must have contributed to eliciting the distortion, as with the case of 6,7-indolyne.[7]

Transition state (TS) structures for the cycloadditions of **Ia** and **IIa** with methyl azide were obtained at the same level of the theory (Fig. 3B). The difference in the calculated activation energies for the distal cycloadditions via **TS1** or **TS3** was 2.1 or 0.4 kcal/mol less, respectively, than the proximal cycloadditions via **TS2** or **TS4**, which was in good agreement with the observed selectivity (Table 2, entry 3 vs Table 3, entry 4).

In summary, we have developed an efficient method for generating thiazolobenzynes. The method has been applied to the synthesis of various multisubstituted benzothiazoles. Further studies to expand the scope of the method and its application to the synthesis of bioactive compounds are now in progress.

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Notes and references

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data including copies of NMR spectra, details for computational studies, and the X-ray crystallographic data for **10** (CCDC 1481578). See DOI: 10.1039/c000000x/

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Thiazolobenzyne: A versatile intermediate for multisubstituted benzothiazoles

Suguru Yoshida, Takahisa Yano, Yoshitake Nishiyama, Yoshihiro Misawa, Masakazu Kondo, Takeshi Matsushita, Kazunobu Igawa, Katsuhiko Tomooka and Takamitsu Hosoya*

Thiazolobenzynes were efficiently generated via an iodine–magnesium exchange reaction of *ortho*-iodoaryl triflate-type precursors using a trimethylsilylmethyl Grignard reagent as an activator, which enabled facile synthesis of various multisubstituted benzothiazoles.