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3-Thioaryne Intermediates for the Synthesis of Diverse Thioarenes

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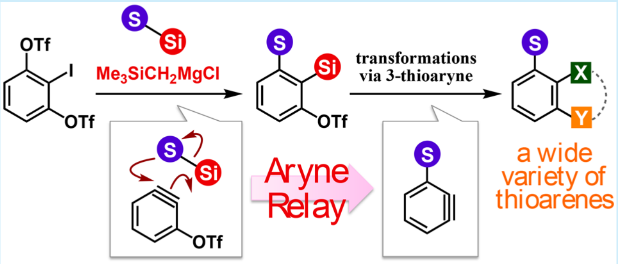
Supporting Information

ABSTRACT: The synthetic utility of 3-thioaryne intermediates has been demonstrated through an aryne relay approach. The efficient synthesis of *o*-silylaryl triflate-type 3-thioaryne precursors has been achieved by the regioselective silylthiolation of 3-(triflyloxy)arynes with silyl sulfides. Various 3-thioarynes were successfully generated from these precursors and reacted with various arynophiles to afford diverse multisubstituted aryl sulfides. Further derivatizations of the products enabled easy access to the novel sulfur-containing π-extended heterocycles, which demonstrates the utility of this method.



Sulfur-containing aromatic compounds are widely used in various research fields, such as materials science[1] and medicinal chemistry.[2,3] Various efficient synthetic methods for thioarenes such as aryl sulfides have been extensively developed, which include the nucleophilic displacement of disulfides with carbon nucleophiles, nucleophilic aromatic substitution of electron-deficient aryl halides, and transition metal-catalyzed coupling reactions of aryl halides or boronic acids with disulfides or thiosulfonates.[4,5] Nevertheless, sterically congested multisubstituted aryl sulfides are often difficult to synthesize because of the demanding reaction conditions and catalyst poisoning caused by the sulfur atoms. To provide an alternative means of synthesis for aryl sulfides, we conceived a concept of using aryne intermediates substituted with a thio group. However, despite the recent marked rise in synthetic aryne chemistry that has enabled the convenient preparation of a wide range of aromatic compounds via various aryne intermediates,[6,7] only a few transformations via sulfanylaryne species have been studied.[8] Therefore, their potential as synthetic intermediates remains largely unexplored. This is probably due to the time-consuming, linear, and multistep routes required for the synthesis of 3-sulfanylaryne precursors. Herein, we report a facile method for preparing various 3-thioaryne precursors and demonstrate their utility for the synthesis of multisubstituted aryl sulfides.

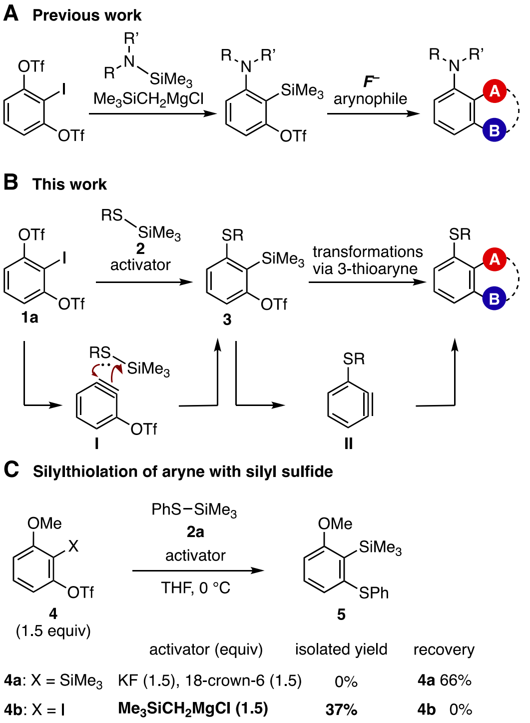


Figure 1. Background of this study. (A) Our previous study. (B) Concept of the proposed study: synthesis of aryl sulfides via 3-(triflyloxy)benzyne (**I**) and 3-sulfanylbenzyne **II** by an aryne relay chemistry. (C) Attempts at silylthiolation of 3-methoxybenzyne with silyl sulfide **2a**.

As part of our previous study based on synthetic aryne chemistry, we developed a facile method for synthesizing *o*-silylaryl triflate-type 3-aminoaryne precursors via the regioselective silylamination of 3-(triflyloxy)arynes (Figure 1A).[9c] It was proven that it is possible to synthesize a diverse range of aniline derivatives from these precursors via the generation of 3-aminoarynes. The key to the success was the use of a silylmethyl Grignard reagent for generating 3-(triflyloxy)arynes[9,10] from 1,3-bis(triflyloxy)-2-iodoarenes, which enabled the iodine−magnesium exchange reaction without any undesired cleavage of the weak N−Si bonds of the *N*-silylamines.[11,12] On the basis of the results of this previous work, we anticipated that *o*-silylaryl triflate-type 3-thioaryne

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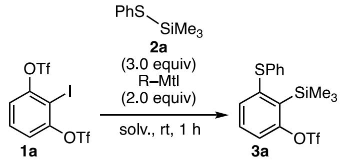
precursors would be obtained by regioselective silylthiolation[13,14] of 3-(triflyloxy)arynes **I** with silyl sulfides **2** (Figure 1B).

Although there was still some concern that the weak S−Si bonds of the silyl sulfides would be cleaved, our initial study of the silylthiolation of an aryne with a silyl sulfide provided an encouraging result (Figure 1C). Unfortunately, our attempts to achieve the silylthiolation of 3-methoxybenzyne generated from *o*-silylaryl triflate **4a** with phenyl trimethylsilyl sulfide (**2a**) under the conditions reported for the thiostannylation of arynes did not afford desired *o*-sulfanylarylsilane **5**, and a significant amount of starting material **4a** remained unreacted.[12a] This unfavorable result would be caused by the activation of the silyl group of silyl sulfide **2a** by the fluoride anion prior to that of aryne precursor **4a**. On the contrary, when the reaction was performed using *o*-iodoaryl triflate-type 3-methoxybenzyne precursor **4b** by treatment with a (trimethylsilyl)methyl Grignard reagent, desired product **5** was obtained, albeit in a low yield. These results indicate that the soft reactivity of the (trimethylsilyl)methyl Grignard reagent sufficiently triggered the iodine−magnesium exchange reaction even in the presence of silyl sulfide **2a** with a weak S−Si bond.

On the basis of these preliminary results and our scenario, we screened for the reaction conditions that efficiently promoted the silylthiolation of 3-(triflyloxy)benzyne generated from 1,3-bis(triflyloxy)-2-iodobenzene (**1a**) (Table 1). As expected, the reaction between **1a** and silyl sulfide **2a** under conditions similar to those for silylamination, using (trimethylsilyl)methylmagnesium chloride as an activator in ether, afforded the desired 3-(phenylthio)-2-(trimethylsilyl)phenyl triflate (**3a**) in a high yield (entry 1). Among the conditions tested, the use of dichloromethane as a solvent yielded the best result (entry 4). Using more nucleophilic activators instead of (trimethylsilyl)methylmagnesium chloride decreased the yield of **3a** (entries 5−7).

Table 1. Optimization of the Reaction Conditions



entry	R-metal	solvent	yield (%)[a]
1	Me_3SiCH_2MgCl	Et_2O	76
2	Me_3SiCH_2MgCl	THF	46
3	Me_3SiCH_2MgCl	toluene	77
4	Me_3SiCH_2MgCl	CH_2Cl_2	81 (79)[b]
5	*n*-BuLi	CH_2Cl_2	35
6	*i*-PrMgCl·LiCl	CH_2Cl_2	47
7	PhMgBr	CH_2Cl_2	61

[a]Yields based on ^{1}H NMR analysis, unless otherwise noted. [b]Isolated yield.

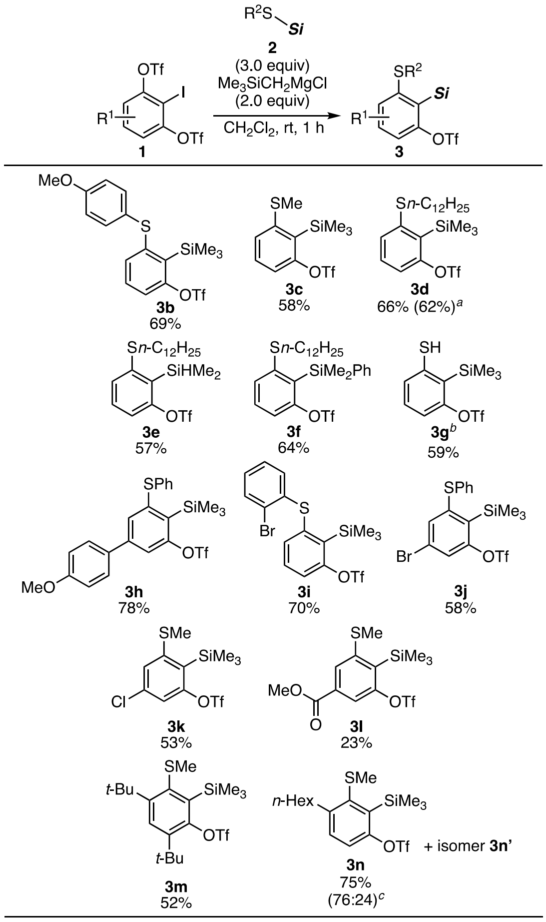
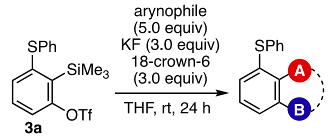


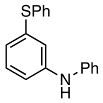
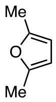
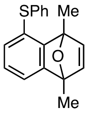
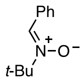
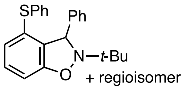
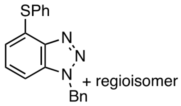
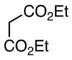
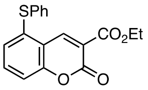
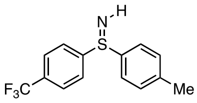
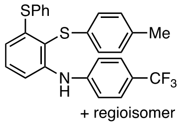
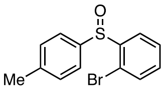
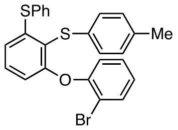
Figure 2. Synthesis of various 3-sulfanylaryne precursors. [a]The yield when the reaction was performed using **1a** (10.0 mmol) and **2d** (2.0 equiv) is shown in parentheses. [b]Bis(trimethylsilyl) sulfide was used as a silyl sulfide. [c]See the Supporting Information for details.

Various 3-sulfanylaryne precursors **3b−n** were successfully obtained by the regioselective silylthiolation of 3-(triflyloxy)arynes with silyl sulfides under the optimized conditions (Figure 2). A wide range of trimethylsilyl sulfides, such as 4-methoxyphenyl, methyl, and dodecyl trimethylsilyl sulfides **2b−d** could be used for the silylthiolation of 3-(triflyloxy)benzyne, affording the corresponding 3-sulfanyl-2-(trimethylsilyl)aryl triflates **3b−d** in good yields. In addition, sulfides having a dimethylsilyl or dimethylphenylsilyl group participated in the reaction to afford 3-sulfanyl-2-silylaryl triflate **3e** or **3f**, respectively. Notably, the reaction between 3-(triflyloxy)benzyne and bis(trimethylsilyl) sulfide afforded 3-mercapto-2-(trimethylsilyl)phenyl triflate (**3g**), wherein the trimethylsilyl group on the sulfur was removed during the reaction or workup procedures without further C−S bond formation with 3-(triflyloxy)benzyne. Furthermore, the silylthiolation of 5-(4-anisyl)-3-(triflyloxy)benzyne proceeded to give 3-sulfanylaryne precursor **3h** in a high yield. The reactions using substrates bearing a bromo group at either the aryne precursor or the sulfide also proceeded uneventfully to give desired products such as **3i** and **3j**, leaving the bromo group untouched. Additionally, treatment of 3-(triflyloxy)aryne precursors bearing electron-withdrawing a chloro or methoxycarbonyl group with (trimethylsilyl)methylmagnesium chloride in the presence of methyl trimethylsilyl sulfide afforded 3-sulfanylaryne precursor **3k** or **3l**, respectively, albeit in low to moderate yields. The silylthiolation of 4,6-di(*tert*-butyl)-3-(triflyloxy)benzyne also took place to provide desired *o*-silylaryl triflate **3m** despite the steric hindrance of the *tert*-butyl groups. The reaction using 1,3-bis(triflyloxy)-4-(*n*-hexyl)-2-iodobenzene afforded a mixture of 3-sulfanylaryne precursor **3n** and its isomer **3n′** with moderate selectivity.[9b] The scalability of the reaction was demonstrated in the gram-scale synthesis of **3d** performed using 10 mmol of **1a**.

We then examined the reactions of 3-(phenylthio)benzyne with various arynophiles by generating the aryne intermediate from precursor **3a** under the typical conditions using a fluoride anion source as an activator (Table 2).[15] For example, treating a mixture of **3a** and aniline (**6**) in tetrahydrofuran (THF) with potassium fluoride and 18-crown-6-ether at room temperature for 24 h afforded diarylamine **7** as a single isomer in high yield (entry 1). The Diels−Alder reaction of 3-(phenylthio)benzyne with 2,5-dimethylfuran (**8**) took place uneventfully to afford cycloadduct **9** in high yield (entry 2). Nitrone **10** and benzyl azide (**12**) also reacted with 3-(phenylthio)benzyne to afford cycloadducts **11** and **13** in good yields with moderate selectivity (entries 3 and 4). The three-component coupling reaction of 3-(phenylthio)benzyne, diethyl malonate (**16**), and *N*,*N*-dimethylformamide (DMF) proceeded to provide 5-thiocoumarin **15** as the sole product, which exhibited unique fluorescence properties, including a large Stokes shift (entry 5).[9c,16,17] Furthermore, the direct thioamination[12k] and oxythiolation[12t] of 3-(phenylthio)benzyne with sulfilimine **16** and sulfoxide **18** proceeded smoothly, resulting in the selective formation of 1,2-dithiophenyl aniline **17** and 1,2-dithiophenyl ether **19**, respectively.

Table 2. Reactions of 3-(Phenylthio)benzyne with Various Arynophiles

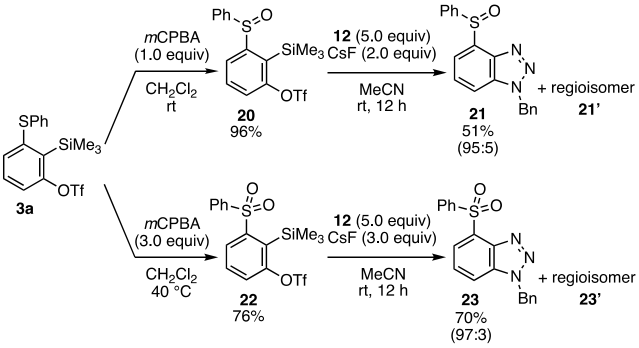


entry	arynophile		product		yield (%)
1	H_2NPh	**6**		**7**	80
2		**8**		**9**	90
3		**10**		**11** + **11′**	86 (87:13)[a]
4[b]	N_3Bn	**12**		**13** + **13′**	90 (88:12)[a]
5[c]		**14** + DMF		**15**	78
6[d]		**16**		**17** + **17′**	58 (92:8)[a]
7[e]		**18**		**19**	41

[a] Ratios of regioisomers determined on the basis of ^{1}H NMR analysis are shown in parentheses. [b] The reaction was performed using 2.0 equiv of CsF as an activator in a MeCN solution. [c] The reaction was performed using 1.5 equiv of **14** and 3.0 equiv of $Bu_4NPh_3SiF_2$ as an activator in a DMF solution. [d] The reaction was performed using 2.0 equiv of **16** at 60 °C for 21 h. [e] The reaction was performed using 2.0 equiv of **18** at 110 °C for 20 h.

We next examined the 3-sulfinyl- and 3-sulfonylbenzyne species paying particular attention to the effect of electron-withdrawing groups on their reactivity. Their precursors **20** and **22** were prepared by the oxidation of 3-(phenylthio)-benzyne precursor **3a** using equimolar and excess amounts of *m*CPBA, respectively (Scheme 1). The generation of 3-(phenylsulfinyl)benzyne from **20** in the presence of benzyl azide (**12**) under the same conditions for the reaction of 3-(phenylthio)benzyne with **12** (Table 2, entry 4) selectively afforded benzotriazole **21** along with a small amount of regioisomer **21′**. Similarly, 3-sulfonylbenzyne generated from **22** reacted with **12** to afford cycloadducts **23** and **23′** in good yields with high selectivity.

Scheme 1. Preparation and Transformation of 3-Sulfinyl- and 3-Sulfonylbenzyne Precursors



To gain insight into the regioselectivity observed in the cycloaddition of 3-sulfanyl-, 3-sulfinyl-, and 3-sulfonylbenzyne with an azide, the optimized structures of 3-(phenylthio)-benzyne (**III**), 3-(phenylsulfinyl)benzyne (**IV**), and 3-(phenylsulfonyl)benzyne (**V**), respectively, were calculated on the basis of density functional theory (DFT) at the B3LYP/6-311+G(d,p) level of theory using the Spartan '16 program (Figure 3).[17,18] The order of the difference in the internal angles at the aryne carbons ($\Delta\theta_{1-2} = \theta_1 - \theta_2$) in the optimized structures was found to be **III** (6.1°) < **V** (8.5°) < **IV** (9.9°), indicating that the structures of **IV** and **V** are more distorted than that of **III**. This order was in good agreement with the higher regioselectivity observed for the reaction of **IV** or **V** with azide **12** (Scheme 1) than that of **III** (Table 2, entry 4). For those benzynes bearing a sulfur atom, C1 of the benzyne triple bond is more electron-deficient due to the increased p

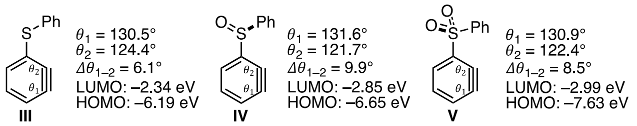


Figure 3. Optimized structures of 3-(phenylthio)benzyne (**III**), 3-(phenylsulfinyl)benzyne (**IV**), and 3-(phenylsulfonyl)benzyne (**V**) obtained using a DFT method [B3LYP/6-311+G(d,p)].

character of the C−S bond, as in the cases of thiazolobenzyne[11e] and thienobenzyne.[11f]

The utility of 3-sulfanylbenzynes was showcased in the synthesis of novel sulfur-containing π-extended heterocycles (Figure 4).[19] The Diels−Alder reaction of 3-(2-bromophenyl)thiobenzyne, generated from **3i**, with furan **8** and subsequent deoxygenative aromatization using sodium iodide and chloro(trimethyl)silane[20] furnished naphthalene **24** (Figure 4A). The oxidation of **24** followed by the palladium-catalyzed cyclization[21] afforded tetracyclic dibenzothiophene derivative **25**. Moreover, bisarene-fused 1,4-dithiin **28** was easily prepared by the C−H sulfanylation of arylsulfoxide via the Pummerer-type activation reported by Yorimitsu and co-workers[22] and subsequent cyclization through 3-sulfanylbenzyne. Indeed, diaryl sulfide **27** was synthesized by treating 2-benzothienyl methyl sulfoxide (**26**) and *o*-silylaryl triflate **3c** with triflic anhydride and trifluoroacetic anhydride (Figure 4B). The subsequent intramolecular addition of the methylthio group to 3-sulfanylbenzyne generated from **27** proceeded efficiently to afford tetracyclic compound **28** containing a 1,4-dithiin structure.[23]

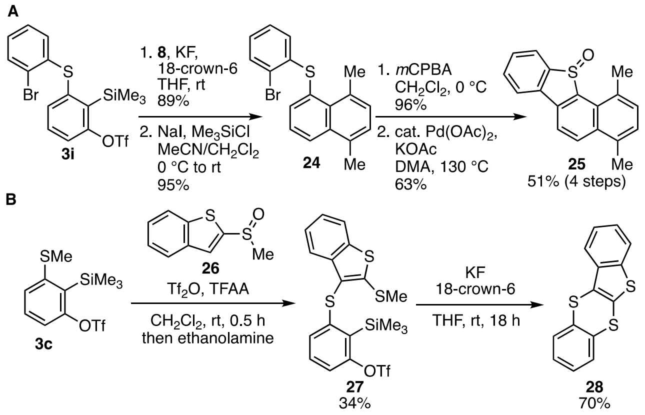


Figure 4. Synthesis of sulfur-containing π-extended heterocycles via 3-sulfanylbenzyne species. (A) Synthesis of dibenzothiophene derivative **25**. (B) Synthesis of bisarene-fused 1,4-dithiin **28**.

In summary, we demonstrated the synthetic utility of 3-thioaryne species through aryne relay chemistry that consists of the practical synthesis of aryne precursors by the regioselective silylthiolation of 3-(triflyloxy)arynes and efficient generation/transformation of 3-thioarynes. The key to the success of this approach was the use of a silylmethyl Grignard reagent as an activator to trigger the generation of 3-(triflyloxy)arynes from *o*-iodoaryl triflate-type precursors. The low nucleophilic characteristic of the silylmethyl Grignard reagent enabled the iodine−magnesium exchange reaction without affecting the weak S−Si bond of silyl sulfides. As demonstrated in this study, 3-thioarynes would serve as versatile intermediates for the synthesis of diverse multisubstituted thioarenes. We are currently undertaking further studies expanding the scope and exploring the potential synthetic application of the method.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01862.

Experimental procedures and characterization of new compounds, including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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