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Direct Thioamination of Arynes via Reaction with Sulfilimines and Migratory *N*-Arylation

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Supporting Information

ABSTRACT: A novel method for preparing a diverse range of *o*-sulfanylanilines is described. Direct thioamination of arynes with sulfilimines gives *o*-sulfanylanilines, involving C−N and C−S bond formations and migratory *N*-arylation.

Arenes with sulfur and nitrogen substituents at *ortho*-positions with respect to each other play important roles in a broad range of fields, including materials science and medicinal chemistry.[1,2] In particular, *o*-sulfanylaniline is a core structure of a variety of heteroaromatics, such as benzothiazoles, phenothiazines, and benzothiazepines, which are frequently found in pharmaceuticals and drug candidates.[2,3] Despite the importance of *o*-sulfanylanilines, only a limited number of synthetic methods have been reported, and the need to develop more efficient approaches remains. Herein we report a straightforward synthetic method for *o*-sulfanylanilines through direct thioamination of aryne species with sulfilimines.

During the course of our studies on aryne chemistry,[4] we unexpectedly found that an *o*-sulfanylaniline was produced from the reaction of an aryne[5,6] with a sulfilimine[7] (Figure 1). Initially, we intended to achieve a simple amination of arynes[8] via the formation of a C−N bond using a sulfilimine as an amino source, followed by hydrolysis of the adduct (Figure 1A). However, for example, the reaction of *S*,*S*-diphenylsulfilimine (**2a**) with 3-methoxybenzyne, which was generated by the treatment of *o*-silylaryl triflate **1a**[9] with cesium fluoride, did not afford the desired *N*-arylsulfilimine **3** (Figure 1B). Instead, *o*-sulfanylaniline **4a** was obtained in low yield. The structure of **4a** bearing a phenylthio and phenylamino group was confirmed by X-ray crystallographic analysis (Figure 1C). This result indicated that C−S bond formation simultaneously proceeded with the anticipated C−N bond formation between the electrophilic aryne carbon and the nucleophilic nitrogen.[8] Furthermore, one of the phenyl groups of the sulfilimine seemed likely to have migrated from sulfur to nitrogen during the reaction. Owing to the limited number of reports on thioamination of arynes,[10−12] we embarked on a study to optimize this promising and mechanistically interesting synthetic transformation.

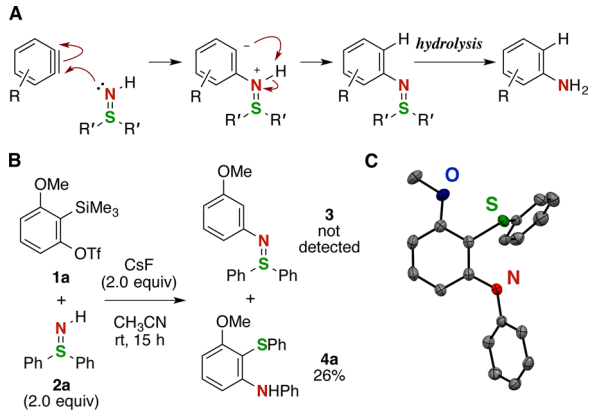

Figure 1. Unexpected reaction between an aryne and a sulfilimine. (A) An initial plan: synthesis of anilines via amination of arynes with sulfilimines. (B) The reaction between 3-methoxybenzyne generated from precursor **1a** with sulfilimine **2a**. (C) X-ray crystal structure of **4a**. Hydrogen atoms are omitted for clarity.

Vigorous screening of reaction conditions for the generation of an aryne species from **1a** greatly improved the yield of **4a** (Table 1). Treatment of aryne precursor **1a** with potassium fluoride and 18-crown-6-ether in the presence of sulfilimine **2a** (2.0 equiv) in tetrahydrofuran at 60 °C afforded the desired product **4a** in high yield and as a single regioisomer (entry 1). Performing the reaction at room temperature or in the absence of crown ether considerably decreased the yield of **4a** (entries 2 and 3). An alternative method for generating aryne efficiently from *o*-silylaryl triflate using cesium carbonate[4i] and 18-crown-6 also afforded **4a** in good yield (entry 4). Other conventional methods that use tetrabutylammonium fluoride or tetrabutylammonium difluoro(triphenyl)silicate as an activator were less effective (entries 5 and 6).

Using either of the two optimized conditions, various *o*-sulfanylaniline derivatives **4b**−**k** were prepared from reactions of sulfilimine **2a** with a variety of arynes, which were generated from *o*-silylaryl triflates **1** (Table 2). Unsubstituted benzyne reacted with **2a** to yield *N*-phenyl-*o*-(phenylthio)aniline (**4b**) in

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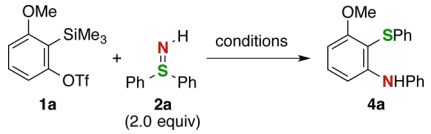
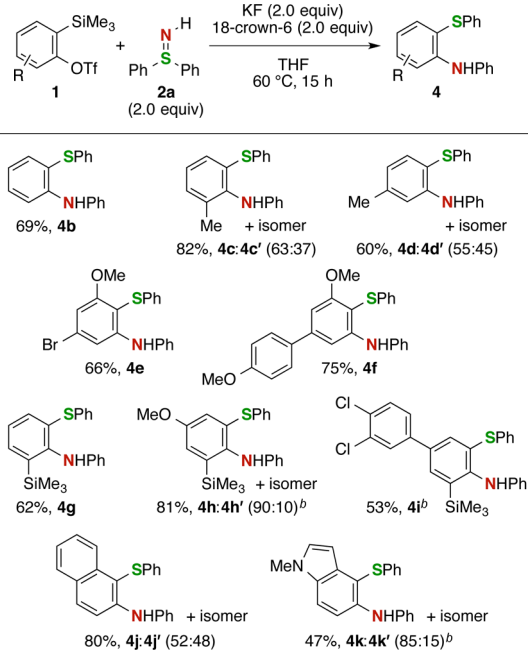
Table 1. Optimization of the Reaction Conditions



entry	conditions[a]	yield (%)[b]
1	KF, 18-crown-6, THF, 60 °C, 15 h	77[c]
2	KF, 18-crown-6, THF, rt, 15 h	17
3	KF, THF, 60 °C, 15 h	2
4	Cs_2CO_3, 18-crown-6, THF, rt, 15 h	69[c]
5	*n*-Bu_4NF, THF, 0 °C, 1 h	trace
6	*n*-$Bu_4N[Ph_3SiF_2]$, THF, rt, 24 h	41

[a]See Supporting Information for details. [b]Yields based on ^1H NMR analysis by using 1,1,2,2-tetrachloroethane as an internal standard, unless otherwise noted. [c]Isolated yield.

Table 2. Reactions of Various Arynes with Sulfilimine 2a[a]

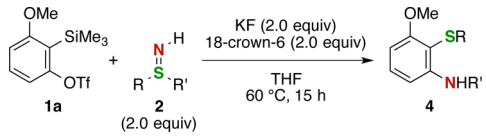


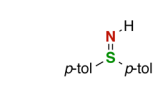
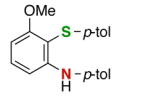
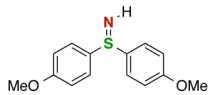
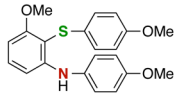
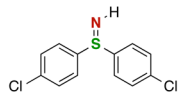
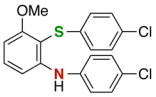
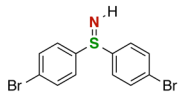
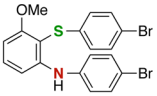
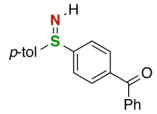
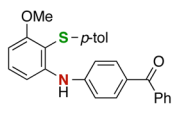
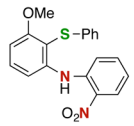
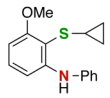
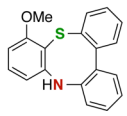
[a]Isolated yields are shown. [b]Conditions: Cs_2CO_3 (2.0 equiv), 18-crown-6 (2.0 equiv), THF, rt, 15 h.

good yield. 3-Methylbenzyne and 4-methylbenzyne also participated in the reactions to afford regioisomeric mixtures **4c**/**4c′** and **4d**/**4d′**, respectively, with low regioselectivities. Conversely, the reaction of 3-methoxybenzyne afforded 3-phenylamino-2-(phenylthio)anisole (**4a**) in a regioselective manner (Table 1). Similar selectivity was observed for the reactions of 5-substituted 3-methoxyarynes that were generated from the corresponding precursors, which were easily prepared from 3-methoxybenzyne precursor **1a** via the C−H borylation.[4j,13] For example, thioaminated products **4e** and **4f** with bromo or *p*-anisyl groups, respectively, were selectively obtained in good yields. Reactions of 3-(trimethylsilyl)arynes resulted in the opposite regioselectivity to that of 3-methoxyarynes, which were similar to those of reported reactions with other arynophiles.[14] Thus, thioaminated arylsilanes **4g**−**i** were prepared in good yields with high to exclusive regioselectivities. The regioselectivities observed in the reactions between sulfilimines and 3-methoxyarynes or 3-silylarynes can be rationalized by their distorted structures.[14c] Furthermore, while 1,2-naphthalyne reacted with **2a** to afford regioisomers **4j** and **4j′** in almost equal proportions, moderate selectivity was observed for the reaction of the more distorted 4,5-indolyne, which agrees with previous reports.[15]

A variety of sulfilimines such as **2b**−**j** also reacted efficiently with 3-methoxybenzyne to afford an array of *o*-sulfanylaniline derivatives **4l**−**t** (Table 3). Not only sulfilimines with electron-

Table 3. Reactions of 3-Methoxybenzyne with Various Sulfilimines



entry	sulfilimine	2	product	4	yield (%)[a]
1		**2b**		**4l**	69
2[b]		**2c**		**4m**	54
3		**2d**		**4n**	67
4		**2e**		**4o**	71
5		**2f**		**4p**	66
6		**2g**		**4q**	60
7		**2h**		**4r**	50
8		**2i**		**4s**	43
9		**2j**		**4t**	73

[a]Isolated yields. [b]Conditions: Cs_2CO_3 (2.0 equiv), 18-crown-6 (2.0 equiv), THF, rt, 16 h.

rich aryl groups such as **2b** and **2c** (entries 1 and 2) but also those with electron-deficient aryl groups such as **2d** or **2e** (entries 3 and 4) participated in the reaction. Remarkably, the reaction of unsymmetrical sulfilimine **2f** having both an electron-rich *p*-tolyl and an electron-deficient *p*-benzoylphenyl group with 3-methoxybenzyne selectively afforded benzoylphenyl-migrated product **4p**, and the tolyl-migrated isomer was not detected (entry 5, Figure 2). A similar trend was observed

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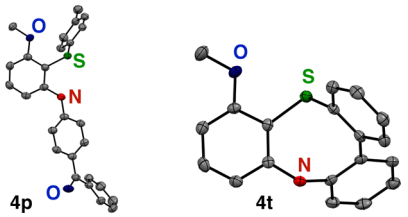
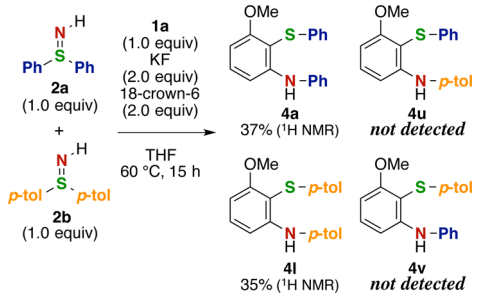


Figure 2. X-ray crystal structures of **4p** and **4t**. Hydrogen atoms and solvent molecules are omitted for clarity.

for *S*-(*o*-nitrophenyl)-*S*-phenylsulfilimine (**2g**) that afforded nitrophenyl-migrated product **4q** exclusively (entry 6). These results indicate that the more electron-deficient aryl group attached to the sulfur atom is prone to migrate to the nitrogen atom, which proceeds at the *ipso*-position of the aryl group. Besides diaryl sulfilimines, *S*-alkyl-*S*-arylsulfilimines also participated in the reaction, expanding the reaction's scope. For example, the reaction of *S*-cyclopropyl-*S*-phenylsulfilimine (**2h**) afforded 2-cyclopropylthio-3-(phenylamino)anisole (**4r**) via a selective rearrangement of the phenyl group (entry 7). Intriguingly, the reaction of *S*-methyl-*S*-*p*-tolylsulfilimine (**2i**) furnished 2-(4-tolylthio)-*m*-anisidine (**4s**) wherein the methyl group was lost during the reaction (entry 8). Notably, the reaction using cyclic sulfilimine **2j** afforded a unique eight-membered thiazocine derivative **4t** in high yield via a ring expansion (entry 9, Figure 2).

To gain more insight into the reaction mechanism, we conducted a crossover experiment using a mixture that contained an equimolar amount of sulfilimines **2a** and **2b** in the reaction with 3-methoxybenzyne (Scheme 1). The products

Scheme 1. Crossover Experiment

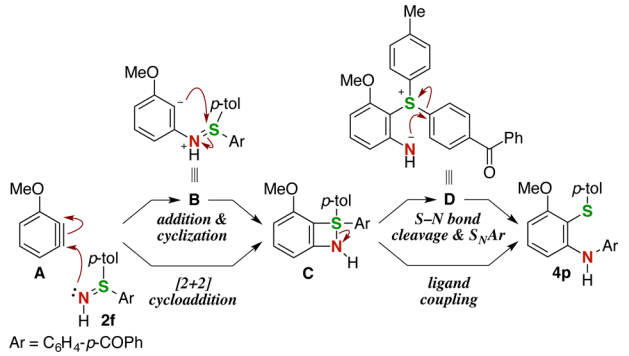


obtained were *o*-sulfanylanilines **4a** and **4l**, and crossover products **4u** or **4v** were not detected. This result suggests that rearrangement of the aryl group from the arylthio group proceeded in an intramolecular manner.

Based on the experimental results, we currently consider the reaction to proceed through a four-membered ring intermediate **C**, which is produced either via nucleophilic addition of sulfilimine to the aryne followed by cyclization or via a direct [2+2] cycloaddition (Scheme 2).[6k,m] Cleavage of the S−N bond of **C** and subsequent intramolecular *ipso*-substitution at the more electron-deficient aryl group provided the *N*-arylated product. However, the possibility of a pathway involving direct ligand coupling on the sulfur of **C** cannot be excluded.[16]

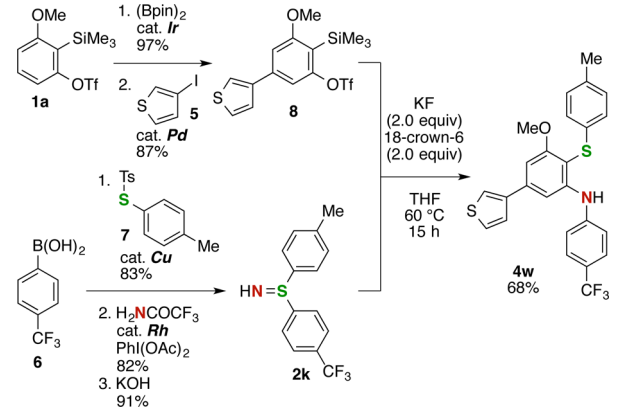
The synthetic utility of this method was further demonstrated in combination with other methods for preparing diverse multisubstituted *o*-silylaryl triflates[4j] and sulfides via copper-catalyzed thiolation of organoborons[17] that we recently developed. This method allowed for modular synthesis of

Scheme 2. Plausible Reaction Mechanisms



multisubstituted *o*-sulfanylanilines. As an example, four readily available components, namely aryne precursor **1a**, aryl iodide **5**, arylboronic acid **6**, and thiosulfonate **7**, were easily assembled in high efficiency to afford multiarylated *o*-sulfanylaniline **4w** (Scheme 3). A wide variety of multisubstituted *o*-sulfanylanilines can be easily synthesized by replacing each component with another compound.[18]

Scheme 3. Modular Synthesis of Multiarylated *o*-Sulfanylaniline[a]



[a]Isolated yields are shown.

In summary, we have developed a novel method for preparing a diverse range of *o*-sulfanylanilines via direct thioamination of arynes with sulfilimines. Further applications of the method to the synthesis of diverse sulfur and nitrogen containing aromatics are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10557.

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

X-ray crystallographic data for **4a** (CCDC 1428754) (CIF)

X-ray crystallographic data for **4p** (CCDC 1428753) (CIF)

X-ray crystallographic data for **4t** (CCDC 1428752) (CIF)

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Notes

The authors declare no competing financial interest.

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