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Transition-Metal-Free Thioamination of Arynes Using Sulfenamides

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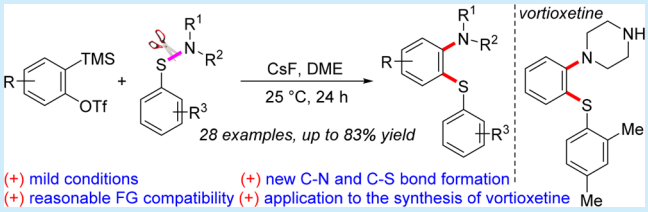
Supporting Information

ABSTRACT: The insertion of arynes into the S−N σ-bond of sulfenamides allowing the synthesis of *o*-sulfanylaniline derivatives with reasonable functional group compatibility is presented. The aryne generated from 2-(trimethylsilyl)aryl triflates using CsF in DME was the key for the success of this transition-metal-free thioamination reaction, which involves new C−N and C−S bond formations in a single step under mild conditions. Moreover, the synthetic potential of this method was demonstrated by the synthesis of the antidepressant drug vortioxetine.



o-Sulfanylanilines are aromatic compounds bearing nitrogen and sulfur atoms on adjacent carbons and are important molecules having broad range of applications in medicinal chemistry and materials science.[1] Some of important pharmaceuticals and drug molecules such as benzothiazepines, benzothiazoles, and phenothiazines have *o*-sulfanylanilines as the core structure.[2] For example, the phenothiazine-containing drug chlorpromazine is used to treat psychotic disorders including schizophrenia (Figure 1).[3] Moreover, the FDA-approved antidepressant drug vortioxetine (sold as Trintellix) contains *o*-sulfanylaniline moiety,[4] and the benzothiazole-derived drug riluzole (marketed as Rilutek and Teglutik) is used in the treatment of amyotrophic lateral sclerosis.[5] In addition, the benzothiazepine-containing drug diltiazem (calcium channel blocker) is used in the treatment of hypertension and angina.[6] Given the significance of functionalized *o*-sulfanylanilines in medicine, development of new synthetic routes to these molecules is highly important.[7]

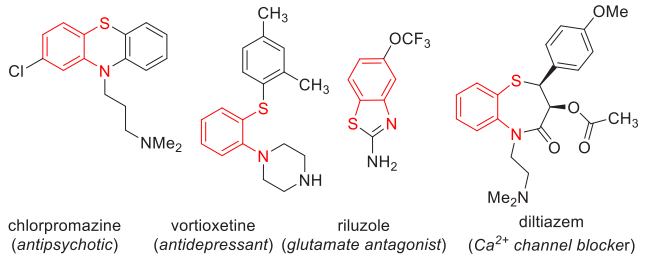
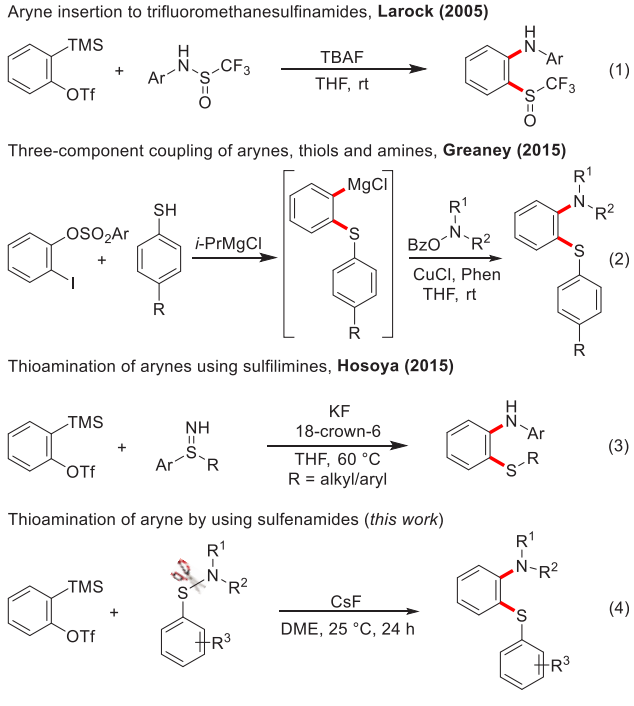


Figure 1. Selected medicinally important *o*-sulfanylaniline containing scaffolds.

In view of our interest in the transition-metal-free aryne reactions,[8,9] we envisioned that the cleavage of the S−N σ-bonds in sulfenamides and stitching the two fragments at the C−C triple bond of arynes could result in straightforward access to *o*-sulfanylanilines.[10] The synthesis of *o*-sulfanylaniline using aryne as the aryl source was demonstrated by Larock in 2005 via the insertion of arynes into the S−N bond of trifluoromethanesulfenamides (Scheme 1, eq 1).[11,12] Notably, the presence of a CF_3 group on sulfinamide was necessary for the reaction, which increases the N−H acidity and also the electrophilicity of the sulfinyl moiety. Later in 2015, Greaney and co-workers uncovered the aryne three-component coupling triggered by thiols and *O*-benzoyl *N*,*N*-dialkylhydroxylamines as the third component for the construction of *o*-sulfanylanilines (eq 2).[13] Moreover, employing sulfilimines,

Scheme 1. Synthesis of *o*-Sulfanylaniline Derivatives



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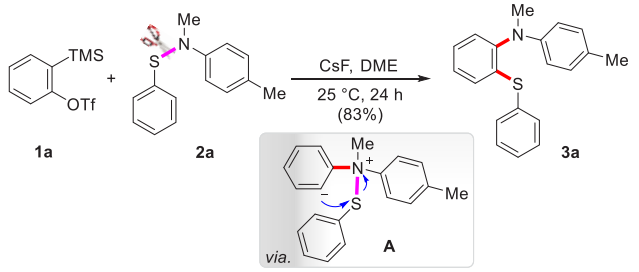
Hosoya and co-workers reported the thioamination of arynes for *o*-sulfanylaniline synthesis resulting in C−N and C−S bond formation as well as a migratory *N*-arylation (eq 3).[14] Herein, we demonstrate a mild and simple insertion of arynes into the S−N σ-bond of sulfenamides for the synthesis of diverse *o*-sulfanylaniline derivatives (eq 4).[15,16]

The present studies were initiated by the treatment of the unsubstituted aryne generated in situ from 2-(trimethylsilyl) aryl triflate **1a**[17] (using excess CsF) with the sulfenamide **2a** in DME as solvent. Interestingly, a facile insertion reaction occurred under these conditions, leading to formation of the *o*-sulfanylaniline derivative **3a** in 83% yield (Scheme 2).[18] The

Scheme 2. Thioamination of Aryne Using Sulfenamides

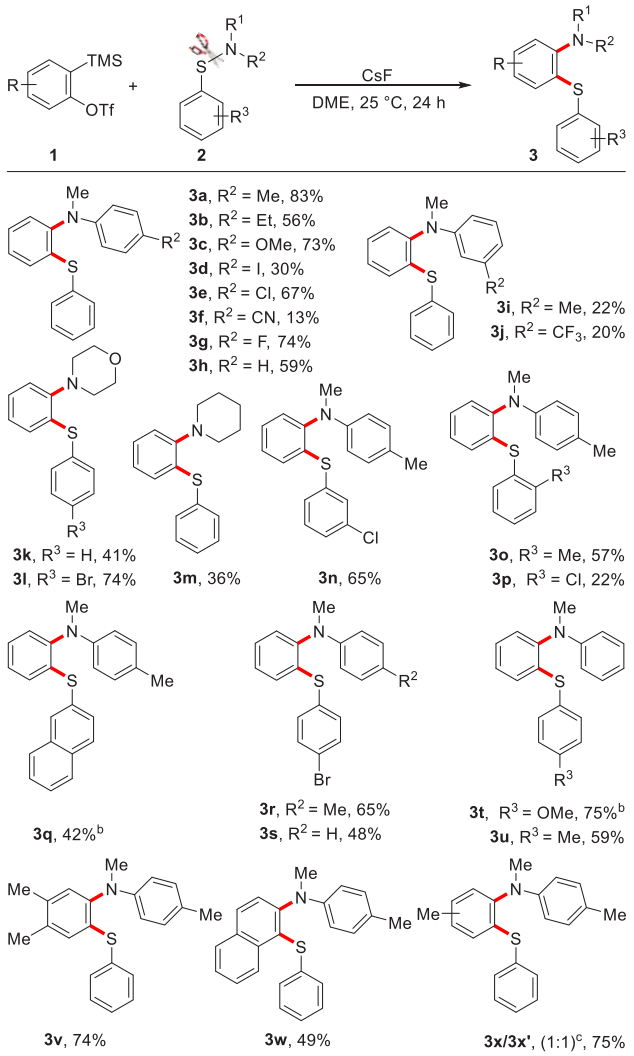


other fluoride sources such as KF (along with 18-crown-6 additive) and TBAF provided a reduced yield of **3a** and DME was found to be the best solvent for this transformation. The reaction proceeds via the nucleophilic addition of sulfenamide nitrogen to the in situ generated aryne from **1a**, leading to the formation of the aryl anion intermediate **A**, which is subsequently added to the sulfur resulting in the formation of **3a**.[19]

Having these reaction conditions in hand, we then examined the substrate scope of this thioamination reaction (Scheme 3). Sulfenamides synthesized from *N*-methylaniline derivatives bearing electron-releasing, -neutral, and -withdrawing substituents at the 4-position and the 3-position of the ring underwent the S−N insertion reaction to aryne leading to the formation of the *o*-sulfanylaniline derivatives in moderate to good yields (**3a**−**j**). In the case of the cyano-substituted substrate, the yield of the desired product **3f** was only 13%. Moreover, the morpholine- and piperidine-derived sulfenamides underwent smooth insertion to aryne to afford the corresponding *o*-sulfanylaniline derivatives in moderate to good yields (**3k**−**m**). Sulfenamides synthesized from substituted benzenethiols having substituents at various positions of the benzene ring are tolerated well under the present reaction conditions, and in each case the desired product was formed in moderate to good yields (**3n**−**u**). Notably, the 2-naphthalenethiol-derived sulfenamide resulted in smooth conversion to the corresponding product **3q** in 42% yield. Disappointingly, sulfenamide substrates bearing −OH and −CHO groups did not afford the expected insertion products under the present conditions.

The tolerance of the present reaction with differently substituted arynes is also examined. The symmetrical 4,5-dimethylaryne generated from the corresponding precursor reacted with **2a**, resulting in the formation of the *o*-sulfanylaniline **3v** in 74% yield. Interestingly, the unsymmetrical naphthalyne furnished a single regioisomer **3w** in 49% yield. Furthermore, the insertion of the sulfenamide **2a** onto the unsymmetrical 4-methylaryne resulted in the formation of

Scheme 3. Substrate Scope of the Reaction[a]



[a]General reaction conditions; **1** (1.1 mmol), **2** (0.5 mmol), CsF (2.2 mmol), DME (2.0 mL), 25 °C and 24 h. Yields of isolated products are given. [b]Reaction performed on 0.25 mmol scale of **2**. [c]The regioisomer ratio was determined by ^{1}H NMR of crude mixture.

an inseparable mixture of regioisomers **3x** and **3x′** in 75% yield and 1:1 ratio.

To gain insight into the mode of addition of sulfenamides (nucleophilic addition via nitrogen center or sulfur center) to arynes, we have performed a few mechanistic experiments. When the reaction was performed using the unsymmetrical 3-methoxybenzyne generated from **1e** and sulfenamide **2r** under the present conditions, the reaction afforded the single regioisomer **3y** in 53% yield (Scheme 4, eq 5). The structure of **3y** was further confirmed by single-crystal X-ray analysis. Given the fact that nucleophilic addition on 3-methoxybenzyne is more favored at the 1-position than the 2-position,[20] the selective formation of **3y** with nitrogen at the 1-position is a clear indication that the present insertion reaction proceeds via the tertiary nitrogen center of sulfenamides.[21] This was further confirmed by the reaction of sulfenamide **2c** with 3-methoxy benzyne to furnish **3z** in 74% yield. Moreover, when the reaction of **2a** was conducted using the domino aryne precursor **1f**[22] under the present conditions, the insertion product **3aa** was formed in 45% yield with the second −OTf

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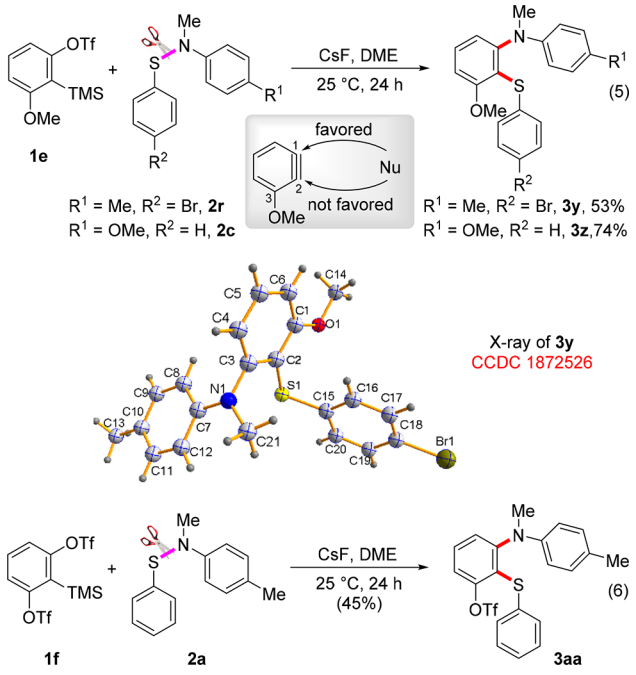
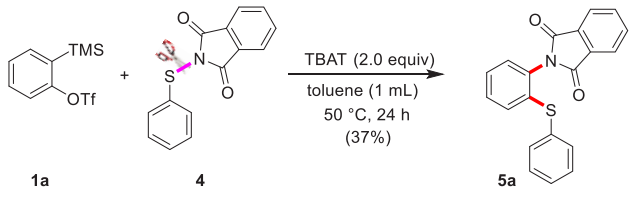
Scheme 4. Studies on the Mechanism of the Reaction



group intact (eq 6). This is an indication that the initially formed aryl anion intermediate in this case prefers addition to sulfur and, hence, S−N bond rupture leading to the formation of **3aa**, in preference to the generation of the second aryne intermediate.

The present aryne insertion into the S−N σ-bond was not only limited to sulfenamides but could be applicable to *N*-(sulfanyl)phthalimide derivatives. Thus, treatment of aryne generated from **1a** using TBAT as the fluoride source with the phthalimide derivative **4** resulted in the formation of the insertion product **5a** in 37% yield (Scheme 5). Toluene was found to be the solvent of choice, and the reaction was performed at 50 °C.

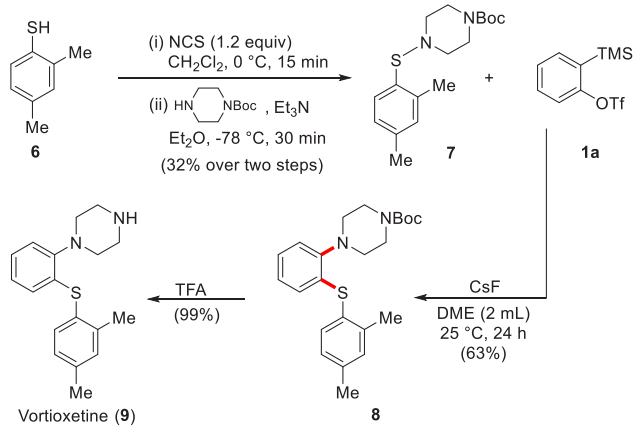
Scheme 5. Aryne Insertion into *N*-(Sulfanyl)phthalimides



Finally, we have demonstrated the application of the aryne insertion into the S−N σ-bond strategy to the synthesis of the FDA-approved antidepressant drug vortioxetine (sold as Trintelli).[23] The key sulfenamide derivative **7** was synthesized in two steps starting from commercially available 2,4-dimethylbenzenethiol **6** and protected piperazine derivative (Scheme 6). Treatment of **7** with aryne generated from **1a** under the present reaction conditions resulted in the formation of the *o*-sulfanylaniline **8** in 63% yield. Deprotection of the Boc group using TFA afforded the vortioxetine **9**. It may be mentioned that the synthesis of the drug has been achieved without the aid of transition metals.[13]

In conclusion, we have demonstrated a transition-metal-free and mild insertion of arynes into the S−N σ-bond of

Scheme 6. Aryne Insertion Route to Vortioxetine



sulfenamides resulting in the synthesis of *o*-sulfanylaniline derivatives. This thioamination reaction of arynes involves formation of new C−N and C−S bonds in a single-step operation. Moreover, the utility of this methodology has been demonstrated by the synthesis of the antidepressant drug vortexetine. Further studies on related aryne insertion reactions are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03966.

Details on experimental procedures, characterization, and NMR spectra of sulfanylanilines derivatives (PDF)

Accession Codes

CCDC 1872526 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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