#### **Metal-Free Reactions**

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# Synthesis of Aromatic Sulfones from SO<sub>2</sub> and Organosilanes Under Metal-free Conditions

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**Abstract:** The conversion of  $SO_2$  into arylsulfones under metal-free conditions was achieved for the first time by reacting  $SO_2$  with (hetero)arylsilanes and alkylhalides in the presence of a fluoride source. The mechanism of this transformation was elucidated based on DFT calculations, which highlight the influence of  $SO_2$  in promoting C–Si bond cleavage.

The sulfone functional group  $(RSO_2R')$  has found widespread applications in organic chemistry owing to its unique physicochemical properties (e.g., stability, lipophilicity, Hbonding),<sup>[1]</sup> and many arylsulfone derivatives are currently exploited as drugs (e.g., bicalutamide, eletriptan, and Vioxx)<sup>[2]</sup> or herbicides. In recent years, heteroarylsulfones have also been shown to exhibit important biological activity.<sup>[3]</sup> Whereas classical syntheses of sulfones rely on the oxidation of sulfides or sulfonylation of arenes under harsh conditions,<sup>[4]</sup> the introduction of sulfones into pharmaceuticals has called for the development of mild and step-efficient methods. An alternative route utilizes SO<sub>2</sub> as a sulfonyl cation/anion synthon via the formation of an intermediate sulfinate anion that undergoes S-alkylation to yield sulfones (Scheme 1). This strategy has been successfully applied by Willis and co-workers, who were able to generate sulfinate anions from SO<sub>2</sub> surrogates (e.g., DABCO·(SO<sub>2</sub>)<sub>2</sub> (DABSO), K<sub>2</sub>S<sub>2</sub>O<sub>5</sub>) with arylmagnesium and aryllithium species.<sup>[5]</sup> Using stoichiometric or catalytic quantities of metal compounds, the method has then been extended to milder nucleophiles, such as organozinc and organoboron reagents, to improve the funtional-group tolerance.<sup>[6]</sup> For example, arylsulfinates were obtained from boronic acids, using palladium and gold catalysts.<sup>[7]</sup> Because arylboronic acids are compatible with alkylhalides, Shavnya et al. demonstrated for the first time in 2015, the preparation of sulfones in a single step from SO<sub>2</sub> surrogates.<sup>[6b]</sup> Interestingly, air- and moisture-stable organosilanes could also be used for the synthesis of sulfones using a copper(I) oxide as catalyst with SO<sub>2</sub> surrogates and alkylhalides.<sup>[8]</sup> In order to circumvent the use of toxic organometallic reagents or metal catalysts, the preparation of sulfones under metal-free conditions is still to be accomplished. With this perspective, we report herein the one-step

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**Scheme 1.** Representative sulfone-containing drugs and trends in state-of-the-art sulfone synthesis from  $SO_2$ .

fluoride-mediated synthesis of aryl and heteroarylsulfones from aryl and heteroarylsilanes under metal-free conditions.

Organosilanes are very mild nucleophiles and a fluoride source or a base is needed to activate the weakly polar C–Si bond and facilitate transmetallation to a metal catalyst.<sup>[9]</sup> Interestingly, we have recently reported the fluoride-mediated carboxylation of heteroarylsilanes with CO<sub>2</sub>, where CO<sub>2</sub> acts both as a reagent and as a catalyst.<sup>[10]</sup> Reasoning that SO<sub>2</sub> is a stronger Lewis acid than CO<sub>2</sub>, we have sought to promote the sulfonylation of 2-(trimethylsilyl)pyridine (1) with the SO<sub>2</sub> adduct DABSO. Addition of DABSO to a CH<sub>2</sub>Cl<sub>2</sub> solution of 1 and methyliodide, in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT) as a fluoride source, resulted in the formation of the expected methylsulfone 1a in more than 90% yield within 17 h at 25 °C (Scheme 2). DABCO, Ph<sub>3</sub>SiF, tetrabutylammonium iodide and Me<sub>3</sub>SiF were formed as byproducts.

To the best of our knowledge, the conversion of 1 into 2a represents the first example of the direct sulfonylation of an organosilane reagent under metal-free conditions. Importantly, 1 selectively reacts with SO<sub>2</sub>, and no trace of pyridine or 2-methylpyridine, which would result from quenching of the pyridine anion with protons or MeI, was detected. It is notable that, in the absence of SO<sub>2</sub>, no conversion of 1 was

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**Scheme 2.** Sulfonylation of 2-(trimethylsilyl)pyridine (1) with the SO<sub>2</sub> adduct DABSO.

observed after 17 h at 25 °C, thus suggesting that  $SO_2$  facilitates the C–Si bond scission.<sup>[11]</sup>

As pointed out by Willis et al.,<sup>[12]</sup> DABSO is a practical surrogate for SO<sub>2</sub> since it is bench stable and avoids the manipulation of a toxic and corrosive gas. Nonetheless, 2a could also be successfully obtained in 71% yield upon replacing DABSO with SO<sub>2</sub> gas, thus demonstrating that DABCO does not play an essential role in this transformation. Upon replacing MeI with other organohalides, a large variety of 2-pyridylsulfone derivatives were successfully prepared (Table 1). For example, sulfones 2a-2e were formed in excellent 71-96% yields using primary alkyl halides such as iodomethane, iodoethane, 1-iodohexane, 1bromohexane, allyl iodide, allyl bromide, and benzylbromide (Table 1, entries 1–5). Although TBAT can be easily recycled by adding TBAF to fluorotriphenylsilane,<sup>[13]</sup> the atom efficiency of the present transformation can be improved by utilizing CsF as a fluoride source in a polar solvent such as CH<sub>3</sub>CN. Under these conditions, 2e is isolated in 77% yield (see Supporting Information). This reaction is tolerant of several functional groups, including iodides (2g), esters (2h), ketones (2i), and nitriles (2j; Table 1, entries 7-10). Introducing an electron-donating group (EDG; 3-CH<sub>3</sub>, 5-CH<sub>3</sub> or 6- $CH_3$ ) or an electron-withdrawing group (EWG; 4-CF<sub>3</sub>) onto the pyridine ring of 1 did not significantly influence the reactivity of the organosilane reagent, and sulfones 4a-4d were formed in 64–90% yield, with 4b (5-CH<sub>3</sub>) being the most reactive (Scheme 3).

Disappointingly, trimethylphenylsilane (5) exhibits no reactivity in the presence of DABSO, EtI, and CsF, thus showing that the pyridine ring has a positive influence on the reaction of 1 with SO<sub>2</sub>. In order to promote the metal-free conversion of arylsilanes into aromatic sulfones, we sought to increase the Lewis acidity of silicon to facilitate the activation of the arylsilane by CsF. The sulfonation of triethoxyphenylsilane (6a) with DABSO, EtI, and CsF indeed enables the formation of phenylethylsulfone 7a after 3 h at 80 °C in a low 5% yield. This poor conversion could be attributed to competitive formation of the anion FSO<sub>2</sub><sup>-.[14]</sup> To shift this equilibrium towards the release of the active fluoride and SO<sub>2</sub> sources, the conversion of a variety of aryltriethoxylsilanes possessing EDGs and EWGs (6a-6e) was attempted, with 6 equiv CsF, 3 equiv DABSO, and 4 equiv EtI at 120 °C (Scheme 4). The corresponding arylethylsulfones 7a–7e were successfully isolated in 33-97%, with the electron-deficient  $C_6F_5Si(OEt)_3$  (6e) derivative being the most reactive.

The formation of **2a–2j**, **4a–4d**, and **7a–7e** represents the first metal-free synthesis of sulfones from (hetero)arylsilanes.

 Table 1:
 Synthesis of sulfones by fluoride-mediated sulfonylation of

 2-(trimethylsilyl)pyridine (1) with various electrophiles.

(	SiMe <sub>3</sub> N + 0.5 DABSO + F	RX TBAT (1 equiv) CH <sub>2</sub> Cl <sub>2</sub> , 17 h, RT - [ <i>n</i> -Bu₄N;X], Ph <sub>3</sub> SiF - Me <sub>3</sub> SiF, 0.5 DABCO	0,0 S∵R N 2a–2j
Entry	RX	Product	Isolated yield [%
1	CH₃I	0,0 N 2a	91
2	C <sub>2</sub> H <sub>5</sub> I	O S N 2b	88
3	C <sub>6</sub> H <sub>13</sub> I C <sub>6</sub> H <sub>13</sub> Br C <sub>6</sub> H <sub>13</sub> CI	0,50 ,N 2c	96 83 48
4	$C_3H_5I$ $C_3H_5Br$	0,50 S N 2d	95 83
5	C <sub>7</sub> H <sub>7</sub> Br	S N 2e	71
6	C <sub>3</sub> H <sub>7</sub> I	$ \begin{array}{c} 0, \\ 0, \\ S \\ 0 \\ 1 \end{array} $ 2f	64
7	I(CH <sub>2</sub> ) <sub>4</sub> I	N 2g	78
8	BrCH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>	°, s, o 0 N 2h	77
9	CH₃OC <sub>6</sub> H₄COCH₂Br		20 (75) <sup>[a]</sup>
10	Br(CH <sub>2</sub> ) <sub>3</sub> CN	S CN N 2j	90

Reaction conditions: Ar-Si(Me)<sub>3</sub> (0.5 mmol), TBAT (0.5 mmol), RX (0.5 mmol), DABSO (0.25 mmol),  $CH_2Cl_2$  (1 mL). [a] NMR yield.

From a mechanistic viewpoint, experiments showed that, in the presence of a fluoride source, the C–Si bond scission of (hetero)arylsilanes does not take place in the absence of SO<sub>2</sub>. Second, a marked difference in reactivity was observed between pyridyl- and phenylsilane derivatives, with the latter being less reactive. To address these questions, DFT calculations were performed for the sulfonylation of 2-(trimethylsilyl)pyridine (1) and trimethylphenylsilane (5) with SO<sub>2</sub>, Me<sub>3</sub>SiF<sub>2</sub><sup>-</sup>, and MeI (Scheme 5 and the Supporting Information).

The simplest pathway would rely on a fluoride transfer from the fluoride source to the organosilane and subsequent

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*Scheme 3.* Synthesis of (hexylsulfonyl)pyridine. Reaction conditions: Ar-Si(Me)<sub>3</sub> (0.5 mmol), TBAT (0.5 mmol), C<sub>6</sub>H<sub>13</sub>Br (0.5 mmol), DABSO (0.25 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL). [a] NMR yield



**Scheme 4.** Synthesis of arylsulfone. Reaction conditions: ArSi(OEt)<sub>3</sub> (0.1 mmol), CsF (0.6 mmol), Etl (0.4 mmol), DABSO (0.3 mmol), CH<sub>3</sub>CN (1 mL).

C-Si bond cleavage of the hypervalent intermediate (8) to release the free pyridyl or phenyl anion (Scheme 5a). Nevertheless, this sequence can be discarded since it involves unstabilized carbanions ( $\Delta G > 28.7 \text{ kcal mol}^{-1}$ ) and transition states lying at least 35.6 kcalmol<sup>-1</sup> higher than the starting materials. Since SO<sub>2</sub> has a positive influence on the early stages of the reaction, its role in the formation of 8 and the activation of the organosilane was investigated computationally (Scheme 5b).  $SO_2$  is a potent electrophile and it readily abstracts a fluoride anion from Me<sub>3</sub>SiF<sub>2</sub><sup>-</sup> to yield the stable  $FSO_2^{-}$  anion, as observed experimentally ( $\Delta G = -12.7$  kcal  $\text{mol}^{-1}$ ;  $\Delta G^{\pm}(\mathbf{TS}_3) = 6.3 \text{ kcal mol}^{-1}$ ). The stable FSO<sub>2</sub><sup>-</sup> can then act as a fluoride-transfer agent, and a transition state (TS4) was located that connects phenylsilane 5 to the sulfinate anion 9 in the presence of a second molecule of SO<sub>2</sub>. TS4 lies only 20.4 kcal mol<sup>-1</sup> above the starting materials and its low energy is attributed to the strong electrophilic character of SO<sub>2</sub>, which is able to stabilize the charge build up on the aryl ring upon cleavage of the C-Si bond. Indeed, the highest occupied molecular orbital (HOMO) of TS4 shows a large delocalization of the carbon lone pair onto the SO<sub>2</sub> fragment, with a minimum structural perturbation of  $SO_2$  (OSO = 114.4° vs. 117.6° in free SO<sub>2</sub>, mean S–O bond lengths of 1.47 Å vs. 1.45 Å in free SO<sub>2</sub>; Scheme 5 c). The so-formed arylsulfinate anion 9  $(-28.0 \text{ kcal mol}^{-1})$  could then undergo S-alkylation via transition state **TS5**  $(-11.5 \text{ kcal mol}^{-1})$  to afford the final sulfone product  $(-47.8 \text{ kcal mol}^{-1})$ . This pathway helps rationalize the positive effect of SO<sub>2</sub> in the activation of the organosilane reagent. Nonetheless, it fails to account for the difference in reactivity between 1 and 5, since similar energy barriers are computed for the two substrates (20.0 vs.  $20.4 \text{ kcal mol}^{-1}$ ).



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**Scheme 5.** Computed reaction pathways as calculated by DFT. Level of theory: PBE0/G-D3/ 6-311 + G(d) for all atom types, to account for solvation PCM = THF. Values given correspond to Gibbs free energies with respect to the starting material ( $\Delta G = 0.0 \text{ kcal mol}^{-1}$ ). a) fluoride-mediated activation of silanes 1 and 5 in the absence of SO<sub>2</sub>. Values given in parenthesis correspond to the conversion of PhSiMe<sub>3</sub> (5). b) Proposed mechanism for the metal-free sulfonylation of silanes 1 and 5. c) Representation of the HOMO in TS4 with X = CH (5) showing strong electron delocalization over the SO<sub>2</sub><sup>-</sup> fragment.

Reasoning that the nitrogen atom of the pyridyl ring could also interact with SO<sub>2</sub>, the formation of adduct **10** was computed. Interestingly, sulfonylation of **1** to give **10** is barrier-free and only slightly endergonic ( $\Delta G = 12.2$  kcal mol<sup>-1</sup>). Sulfonylation of the C–Si bond in the presence of FSO<sub>2</sub><sup>-</sup> then proceeds via **TS6** to yield sulfinate **11**. Decoordination of SO<sub>2</sub> from **11** is again barrier-free and it releases the expected sulfinate anion **9**. Importantly, **TS6** displays similar features to **TS4**, and the extra stabilization provided by the N-SO<sub>2</sub> interaction translates into a 3.3 kcal mol<sup>-1</sup> stabilization of

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TS6 compared to TS4. Overall, these mechanistic trends reveal that SO<sub>2</sub> catalytically influences the sulfonylation of 1 and 5 on multiple levels. First,  $SO_2$  behaves as an efficient fluoride carrier via the reversible formation of  $FSO_2^{-}$ . Second, it facilitates the C-Si bond cleavage of 1 through reversible coordination to the N atom of the pyridine ring. This kinetic behavior is attributed to the electronic and geometric structure of  $SO_2$ . With a bent structure and a lowlying  $\pi^*$  vacant orbital perpendicular to the (O,S,O) plane and polarized towards the sulfur atom, SO<sub>2</sub> is poised for nucleophilic attack. In fact, we computed that the elongation of the S-O bonds does not exceed 9.8% and the bending of the O-S-O angle remains small (9.7%) upon formation of  $FSO_2^{-}$ , 9, 10, and 11. These findings suggest that the sulfonylation of other mild nucleophiles, for example the sulfonylation of C-H, N-H, or N-Si bonds, could be facilitated by SO<sub>2</sub> under metal-free conditions.

In conclusion, we have shown that sulfones can be accessed under metal-free conditions for the first time from both heteroaryl and arylsilanes in the presence of  $SO_2$  or a surrogate, with the activation of the organosilane being promoted by a fluoride source. Mechanistic investigations show that  $SO_2$  is an excellent electrophile that is able to synchronize fluoride-mediated C–Si bond cleavage with C–S bond formation.

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#### **Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** density functional calculations · metal-free reactions · organosilanes · SO<sub>2</sub> · sulfones

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### Metal-Free Reactions

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Synthesis of Aromatic Sulfones from  $SO_2$  and Organosilanes Under Metal-free Conditions



**SOO good**: The conversion of SO<sub>2</sub> into (hetero)arylsulfones under metal-free conditions was achieved by reacting SO<sub>2</sub> with (hetero)arylsilanes and alkylhalides in the presence of a fluoride source. The

mechanism of this transformation was elucidated based on DFT calculations, which highlight the influence of  $SO_2$  in promoting C–Si bond cleavage.

