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Synthesis of Aromatic Sulfones from SO₂ and Organosilanes, Under Metal-free Conditions

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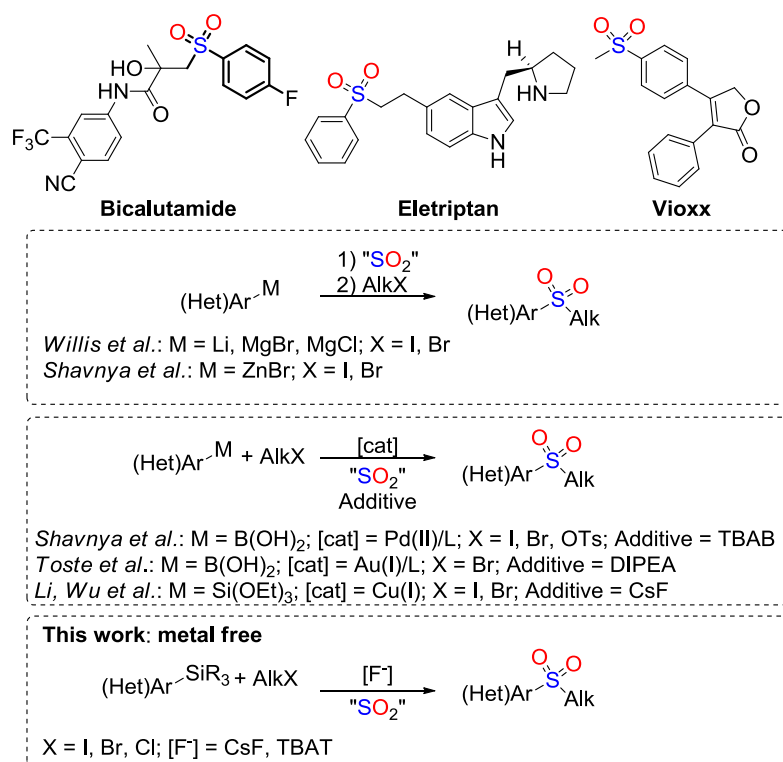
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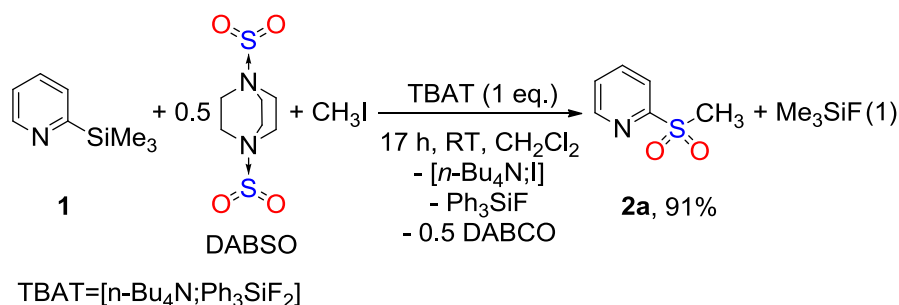
Abstract: The conversion of SO₂ to arylsulfones has been achieved for the first time under metal-free conditions, by reacting SO₂ with (hetero)arylsilanes and alkylhalides, in the presence of a fluoride source. The mechanism of this transformation has been elucidated based on DFT calculations, which highlight the influence of SO₂ in promoting C–Si bond cleavage.

The sulfone functional group (RSO₂R') has found widespread applications in organic chemistry, due to its unique physico-chemical properties (stability, lipophilicity, H-bonding etc.),^[1] and many arylsulfone derivatives are currently exploited as drugs (e.g. bicalutamide, eletriptan and Vioxx)^[2] or herbicides. In recent years, heteroarylsulfones were also shown to exhibit important biological activity.^[3] Whereas classical synthesis of sulfones rely on the oxidation of sulfides or the sulfonylation of arenes under harsh conditions,^[4] the introduction of sulfones in pharmaceuticals has called for the development of mild and step efficient methodologies. An alternative route utilizes SO₂ 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 coworkers, who were able to generate sulfinate anions from SO₂ surrogates (DABCO·(SO₂)₂ (DABSO), K₂S₂O₅, etc.) with arylmagnesium and aryllithium species.^[5] Using stoichiometric or catalytic quantities of metal compounds, the method has then been extended to milder nucleophiles, such as organo-zinc and organo-boron reagents, to improve the tolerance to functional groups.^[6] For example, arylsulfonates could be obtained from boronic acids, using palladium and gold catalysts.^[7] 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 SO₂ surrogates.^[6b] Interestingly, air and moisture stable organosilanes could also be used for the synthesis of sulfones using a copper(I) oxide as catalyst with SO₂ surrogates and alkylhalides.^[8] 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. In this perspective, we report herein the one-step fluoride mediated synthesis of aryl and heteroarylsulfones from aryl and heteroarylsilanes under metal-free conditions.



Scheme 1. Some representative sulfone-containing drugs and trends in state of the art sulfone synthesis from SO₂.

Organosilanes are very mild nucleophiles and a fluoride source or a base is needed to activate the low polar C–Si bond and facilitate transmetalation to a metal catalyst.^[9] Interestingly, we have recently reported on the fluoride-mediated carboxylation of heteroarylsilanes with CO₂, where CO₂ acts both as a reagent and as a catalyst.^[10] Reasoning that SO₂ is a stronger Lewis acid than CO₂, we have sought to promote the sulfonylation of 2-(trimethylsilyl)pyridine (**1**) with SO₂ adduct DABSO. Addition of DABSO to a CH₂Cl₂ solution of **1** and methyl iodide, in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT) as a fluoride source, resulted in the formation of the expected methylsulfone **2a** in >90% yield within 17 h at 25 °C (Eq. 1). DABCO, Ph₃SiF, tetrabutylammonium iodide and Me₃SiF were formed as byproducts.



To the best of our knowledge, the conversion of **1** to **2a** represents the first example of the direct sulfonylation of an organosilane reagent under metal-free conditions.

Importantly, **1** selectively reacts with SO₂ and no trace of pyridine or 2-methylpyridine was detected, that would result from quenching of the pyridine anion with protons or MeI. It is notable that, in the absence of SO₂, no conversion of **1** was observed after 17 h at 25 °C, thereby suggesting that SO₂ facilitates the C–Si bond scission.^[11]

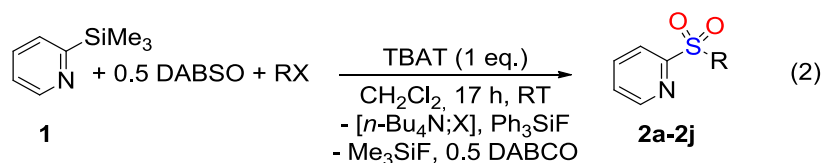


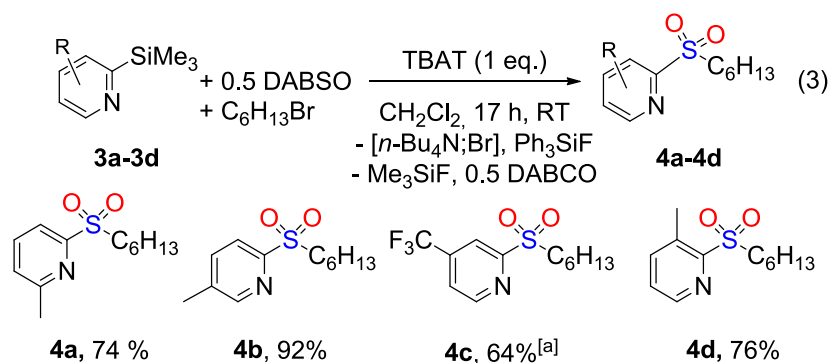
Table 1. Synthesis of sulfones by fluoride mediated sulfonylation of 2-(trimethylsilyl)pyridine (**1**) with various electrophiles (Eq. 2).

Entry	RX	Product	Isolated yield [%]
1	CH ₃ I		91
2	C ₂ H ₅ I		88
	C ₆ H ₁₃ I		96
3	C ₆ H ₁₃ Br		83
	C ₆ H ₁₃ Cl		48
4	C ₃ H ₅ I		95
	C ₃ H ₅ Br		83
5	C ₇ H ₇ Br		71
6	C ₃ H ₇ I		64
7	I(CH ₂) ₄ I		78
8	BrCH ₂ COOC ₂ H ₅		77
9	CH ₃ OC ₆ H ₄ COCH ₂ Br		20 (75) ^a



Reaction conditions: Ar-Si(Me)₃ (0.5 mmol), TBAT (0.5 mmol), RX (0.5 mmol), DABSO (0.25 mmol), CH₂Cl₂ (1 mL). a) NMR yield.

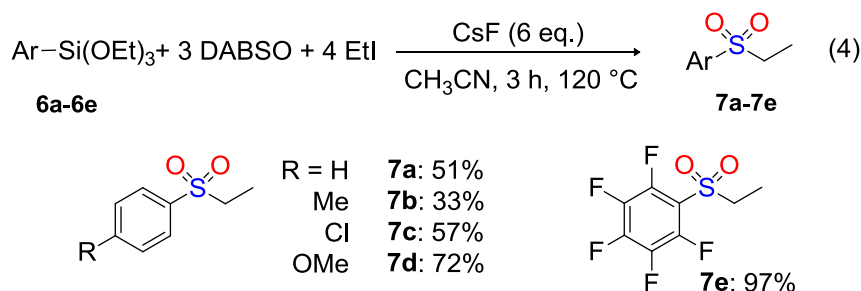
As pointed out by Willis *et al.*, DABSO is a practical surrogate for SO₂, as it is bench-stable and avoids the manipulation of a toxic and corrosive gas.^[12] Nonetheless, **2a** could also be successfully obtained in 71% yield by replacing DABSO with SO₂ gas, highlighting that DABCO does not play an essential role in this transformation. Replacing MeI with other organo-halides, a large variety of 2-pyridylsulfone derivatives were successfully prepared (Eq. 2, Table 1). For example, sulfones **2a-2e** were formed in excellent 71-96% yields using primary alkyl halides such as iodomethane, iodoethane, 1-iodohexane, 1-bromohexane, allyl-iodide and -bromide and benzylbromide respectively (Table 1, entries 1-5). Although TBAT can be easily recycled by addition of TBAF to fluorotriphenylsilane,^[13] the atom efficiency of the present transformation can be improved by utilizing CsF as a fluoride source, in a polar solvent such as CH₃CN. Under these conditions **2e** is isolated in 77% yield (see SI). This reaction is tolerant towards several functional groups such as iodides (**2g**), esters (**2h**), ketones (**2i**) and nitriles (**2j**) (Table 1, entries 7-10). Introducing, an electron donating (3-CH₃, 5-CH₃ or 6-CH₃) (EDGs) or withdrawing (4-CF₃) (EWGs) group on the pyridine ring of **1** did not influence significantly the reactivity of the organosilane reagent and sulfones **4a-4d** were formed in 64-90% yield, with **4b** (5-CH₃) being the most reactive (Scheme 2).



Scheme 2. Synthesis of (hexylsulfonyl)pyridine. Reaction conditions: Ar-Si(Me)₃ (0.5 mmol), TBAT (0.5 mmol), C₆H₁₃Br (0.5 mmol), DABSO (0.25 mmol), CH₂Cl₂ (1 mL). [a] NMR yield determined with mesitylene as internal standard.

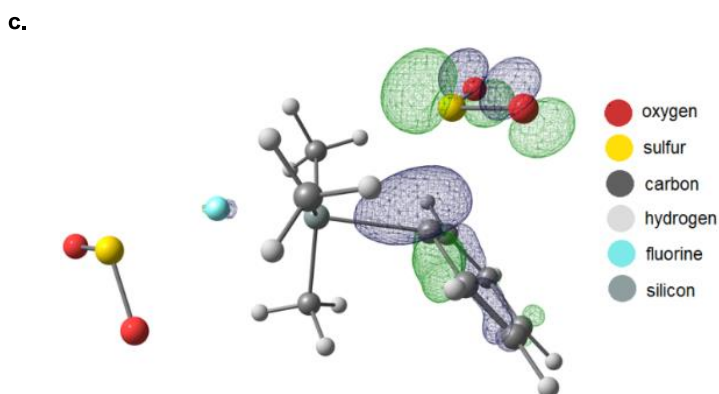
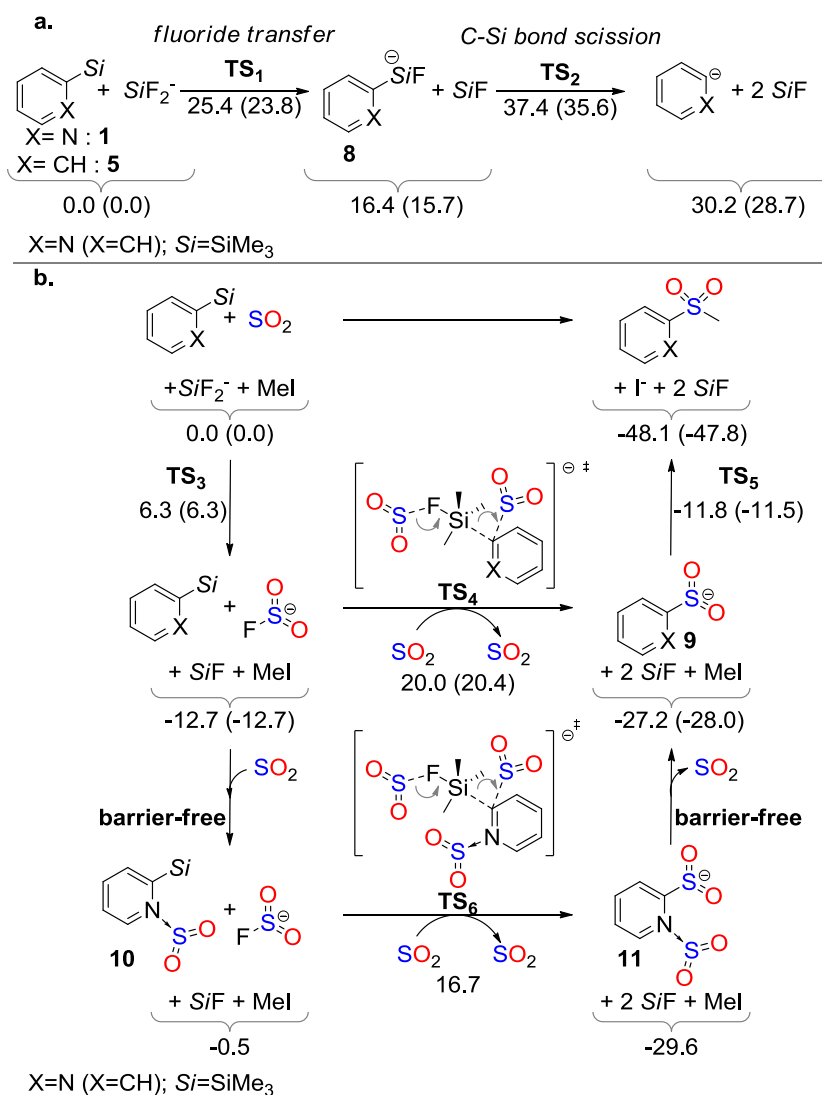
Disappointingly, trimethylphenylsilane (**5**) exhibits no reactivity in the presence of DABSO, EtI and CsF, thereby showing that the pyridine ring has a positive influence on the reaction of **1** with SO₂. In order to promote the metal-free conversion of arylsilanes to aromatic sulfones, we sought 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 the competitive formation of the anion FSO_2^- .^[14] To shift this equilibrium towards the release of the active fluoride and SO_2 sources, the conversion of a variety of aryltriethoxysilanes possessing EDGs and EWGs groups (**6a-6e**) was attempted, with 6 equiv. CsF, 3 equiv. DABSO and 4 equiv. EtI, at 120 °C (Scheme 3). The corresponding arylethylsulfones **7a-7e** were successfully isolated in 33-97% with the electron deficient $\text{C}_6\text{F}_5\text{Si}(\text{OEt})_3$ (**6e**) derivative being the most reactive.



Scheme 3. Synthesis of arylsulfone. Reaction conditions: silane (0.1 mmol), CsF (0.6 mmol), EtI (0.4 mmol), DABSO (0.3 mmol), CH_3CN (1 mL).

The formation of **2a-2j**, **4a-4d** and **7a-7e** represents the first examples of a metal-free synthesis of sulfones from (hetero)arylsilanes. From a mechanistic viewpoint, experiments showed that, in the presence of a fluoride source, the C–Si bond scission of arylsilanes does not take place in the absence of SO_2 . Second, a marked difference in reactivity was observed between pyridyl- and phenyl-silane derivatives, 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_2 , $\text{Me}_3\text{SiF}_2^-$ and MeI (Scheme 4 and SI).



Scheme 4. Computed reaction pathways as calculated by DFT. Level of theory: PBE0/G-D3/ 6-311+G(d) for all atom types / 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 SO₂. Values given in parenthesis correspond to the conversion of PhSiMe₃ (**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 a strong electron delocalization over the SO₂-fragment.

The simplest pathway would rely on a fluoride transfer from the fluoride source to the organosilane and subsequent C–Si bond cleavage of the hypervalent intermediate (**8**) to release the free pyridyl or phenyl anion (Scheme 4a). Nevertheless, this sequence can be discarded as it involves the unstabilized carbanions ($\Delta G > 28.7 \text{ kcal.mol}^{-1}$) and transition states lying at least $35.6 \text{ kcal.mol}^{-1}$ higher than the starting materials. As SO_2 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 4b). SO_2 is a potent electrophile and it readily abstracts a fluoride anion from $\text{Me}_3\text{SiF}_2^-$ to yield the stable FSO_2^- anion, as observed experimentally ($\Delta G = -12.7 \text{ kcal.mol}^{-1}$; $\Delta G^\ddagger(\text{TS}_3) = 6.3 \text{ kcal.mol}^{-1}$). The stable FSO_2^- can then act as a fluoride transfer agent and a transition state (**TS**₄) was located that connects phenylsilane **5** to the sulfinate anion **9**, in the presence of a second molecule of SO_2 . **TS**₄ only lies $20.4 \text{ kcal.mol}^{-1}$ above the starting materials and its low energy is attributed to the strong electrophilic character of SO_2 , 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 **TS**₄ shows a large delocalization of the carbon lone pair onto the SO_2 fragment, with a minimum structural perturbation of SO_2 ($\text{OSO} = 114.4^\circ$ vs. 117.6° in free SO_2 , mean S–O bond lengths of 1.47 \AA vs. 1.45 \AA in free SO_2) (Scheme 4c). The so-formed arylsulfinate anion **9** ($-28.0 \text{ kcal.mol}^{-1}$) could then undergo S-alkylation *via* transition state **TS**₅ ($-11.5 \text{ kcal.mol}^{-1}$) to afford the final sulfone product ($-47.8 \text{ kcal.mol}^{-1}$). This pathway helps rationalize the positive effect of SO_2 in the activation of the organosilane reagent. Nonetheless, it fails to account for the difference in reactivity between **1** and **5**, as similar energy barriers are computed for the two substrates (20.0 vs $20.4 \text{ kcal.mol}^{-1}$).

Reasoning that the nitrogen atom of the pyridyl ring could also interact with SO_2 , the formation of adduct **10** was computed. Interestingly, sulfonylation of **1** leading to **10** is barrier-less and only slightly endergonic ($\Delta G = 12.2 \text{ kcal.mol}^{-1}$). The sulfonylation of the C–Si bond, in the presence of FSO_2^- , then proceeds *via* **TS**₆ to yield sulfinate **11**. Decoordination of SO_2 from **11** is again barrier-free and it releases the expected sulfinate anion **9**. Importantly, **TS**₆ displays similar features to **TS**₄ and the extra stabilization provided by the N– SO_2 interaction translates into a $3.3 \text{ kcal.mol}^{-1}$ stabilization of **TS**₆ compared to **TS**₄. Overall, these mechanistic trends unveil a multiple catalytic influence of SO_2 in the sulfonylation of **1** and **5**. 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** by 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 low lying π^* vacant orbital perpendicular to the (O,S,O) plane and polarized towards the sulfur atom, SO_2 is poised towards 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 could be facilitated by SO_2 , such as the sulfonylation of C–H, N–H or N–Si bonds, 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 SO₂ or a surrogate, the activation of the organosilane being promoted by a fluoride source. Mechanistic investigations show that SO₂ is an excellent electrophile, able to synchronize a fluoride mediated C–Si bond cleavage with C–S bond formation.

Experimental Section

Detailed descriptions of experimental and computational methods are given in the Supporting Information.

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Keywords: SO₂ • organosilanes • sulfones • metal-free • DFT calculations

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