Synthesis of Aromatic Sulfones from SO\textsubscript{2} and Organosilanes, Under Metal-free Conditions

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Abstract: The conversion of SO\textsubscript{2} to arylsulfones has been achieved for the first time under metal-free conditions, by reacting SO\textsubscript{2} 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 SO\textsubscript{2} in promoting C–Si bond cleavage.

The sulfone functional group (RSO\textsubscript{2}R') 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 SO\textsubscript{2} 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 SO\textsubscript{2} surrogates (DABCO·(SO\textsubscript{2})\textsubscript{2} (DABSO), K\textsubscript{2}S\textsubscript{2}O\textsubscript{5}, 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, arylsulfinates could be obtained from boronic acids, using palladium and gold catalysts.\[7\] Because arylboronic acids are compatible with alkylhalides, Shavnya \textit{et al.} demonstrated for the first time, in 2015, the preparation of sulfones in a single step from SO\textsubscript{2} 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 SO\textsubscript{2} 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 heteroaryl sulfones 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 transmetallation to a metal catalyst.\textsuperscript{[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.\textsuperscript{[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 methyliodide, in the presence of tetrabutylammonium triphenylfluorosilicate (TBAT) as a fluoride source, resulted in the formation of the expected methylsulfone 1a 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 SO$_2$ 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 SO$_2$, no conversion of 1 was observed after 17 h at 25 °C, thereby suggesting that SO$_2$ facilitates the C–Si bond scission.$^{[11]}$

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\text{Scheme 1. Synthesis of sulfones by fluoride mediated sulfonylation of 2-} (\text{trimethylsilyl})\text{pyridine (1) with various electrophiles (Eq. 2).}
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**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 | ![Image](2a.png) | 91 |
| 2     | C$_2$H$_5$I | ![Image](2b.png) | 88 |
|       | C$_6$H$_{13}$I | ![Image](2c.png) | 96 |
| 3     | C$_6$H$_{13}$Br | ![Image](2d.png) | 83 |
|       | C$_6$H$_{13}$Cl | ![Image](2e.png) | 48 |
|       | C$_3$H$_5$I | ![Image](2f.png) | 95 |
| 4     | C$_3$H$_5$Br | ![Image](2g.png) | 83 |
| 5     | C$_7$H$_7$Br | ![Image](2h.png) | 71 |
| 6     | C$_3$H$_7$I | ![Image](2i.png) | 64 |
| 7     | I(CH$_2$)$_4$I | ![Image](2j.png) | 78 |
| 8     | BrCH$_2$COOC$_2$H$_5$ | ![Image](2k.png) | 77 |
| 9     | CH$_3$OC$_6$H$_4$COCH$_2$Br | ![Image](2l.png) | 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-iiodohexane, 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 CH₂CN. 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$_2^-$.[1,4] To shift this equilibrium towards the release of the active fluoride and SO$_2$ sources, the conversion of a variety of aryltrialkoxy silanes 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 C$_6$F$_5$Si(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$_3$CN (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$_2$, Me$_3$SiF$_2^-$ and Mel (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 SO$_2$. Values given in parenthesis correspond to the conversion of PhSiMe$_3$ (5). b) Proposed mechanism for the metal-free sulfonylation of silanes 1 and 5. c) Representation of the HOMO in TS$_4$ with X = CH (5) showing a strong electron delocalization over the SO$_2$-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 (ΔG=28.7 kcal.mol⁻¹) and transition states lying at least 35.6 kcal.mol⁻¹ higher than the starting materials. As SO₂ 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). SO₂ is a potent electrophile and it readily abstracts a fluoride anion from Me₃SiF₂⁺ to yield the stable FSO₂⁻ anion, as observed experimentally (ΔG=−12.7 kcal.mol⁻¹; ΔG‡(TS₃)=6.3 kcal.mol⁻¹). The stable FSO₂⁻ 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 SO₂. TS₄ only lies 20.4 kcal.mol⁻¹ above the starting materials and its low energy is attributed to the strong electrophilic character of SO₂, 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 SO₂ fragment, with a minimum structural perturbation of SO₂ (O=114.4° vs. 117.6° in free SO₂, mean S–O bond lengths of 1.47 Å vs. 1.45 Å in free SO₂) (Scheme 4c). The so-formed arylsulfinate anion 9 (−28.0 kcal.mol⁻¹) could then undergo S-alkylation via transition state TS₅ (−11.5 kcal.mol⁻¹) to afford the final sulfone product (−47.8 kcal.mol⁻¹). This pathway helps rationalize the positive effect of SO₂ 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 kcal.mol⁻¹).

Reasoning that the nitrogen atom of the pyridyl ring could also interact with SO₂, the formation of adduct 10 was computed. Interestingly, sulfonylation of 1 leading to 10 is barrier-less and only slightly endergonic (ΔG=12.2 kcal.mol⁻¹). The sulfonylation of the C–Si bond, in the presence of FSO₂⁻, then proceeds via TS₆ to yield sulfinate 11. Decoordination of SO₂ 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–SO₂ interaction translates into a 3.3 kcal.mol⁻¹ stabilization of TS₆ compared to TS₄. Overall, these mechanistic trends unveil a multiple catalytic influence of SO₂ in the sulfonylation of 1 and 5. First, SO₂ behaves as an efficient fluoride carrier via the reversible formation of FSO₂⁻. 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 SO₂. With a bent structure and a low lying π* vacant orbital perpendicular to the (O,S,O) plane and polarized towards the sulfur atom, SO₂ 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 FSO₂⁻, 9, 10 and 11. These findings suggest that the sulfonylation of other mild nucleophiles could be facilitated by SO₂, 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 SO$_2$ or a surrogate, the activation of the organosilane being promoted by a fluoride source. Mechanistic investigations show that SO$_2$ 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.

**Acknowledgements**

For financial support of this work, we acknowledge CEA, CNRS, the CHARMMMAT Laboratory of Excellence and the European Research Council (ERC Starting Grant Agreement n.336467). We thank CINES (project c2016086494) for computational time. T.C. thanks the Foundation Louis D. – Institut de France for its support.

**Keywords:** SO$_2$ • organosilanes • sulfones • metal-free • DFT calculations

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