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Reagent Alternatives

Investigation of $(Me_4N)SCF_3$ as a Stable, Solid and Safe Reservoir for $S{=}CF_2$ as a Surrogate for Thiophosgene

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Abstract: While thiophosgene finds widespread usage on a multi-ton scale, its fluorinated counterpart $S{=}CF_2$ is essentially unexplored in synthesis. Using experimental reactivity tests, ReactIR and computational techniques, we herein showcase that the solid $(Me_4N)SCF_3$ functions as a safe reservoir for $S{=}CF_2$. A key feature is that the reactive electrophile is not simply released over time, but instead is liberated under activation with a protic nucleophile. The reactivity of $S{=}CF_2$ is mild, allowing large-scale and late-stage synthetic applications without special reaction control. The mechanism was fully elucidated, including a rationalization of the role of the Me_4N cation and the origins of selectivity.

It has widely been recognized that the introduction of fluorine into organic molecules allows for the modulation of various physical properties.[1] While medicinal chemistry research programs widely make use of these effects, and an arsenal of synthetic methods have also emerged to prepare fluorine-containing compounds, this report capitalizes on fluorine's beneficial impacts on reactivities for the development of safe surrogates.[2]

For example, thiophosgene ($S{=}CCl_2$) finds widespread usage as a coupling agent to access thioureas, isothiocyanates, thiocarbonates as well as a range of valuable heterocycles,[3] and consequently is manufactured on a multi-ton scale.[4] However, thiophosgene is a volatile liquid, highly toxic and reacts vigorously with nucleophiles, requiring careful reaction control. The identification of safe alternatives is therefore of considerable interest. Following the above mentioned impacts of fluorine on properties, the fluorinated analogue of thiophosgene, that is, $S{=}CF_2$, bears significant potential. However, due to difficulties in the preparation and handling,[5] it is essentially unexplored. It is a gas, and reported to generate a complex mixture of compounds upon reaction with itself (Figure 1). Consequently, the storage or handling of $S{=}CF_2$ will not be feasible and instead, a controlled chemical liberation in minute quantities will be required to harness its reactivity benefits.

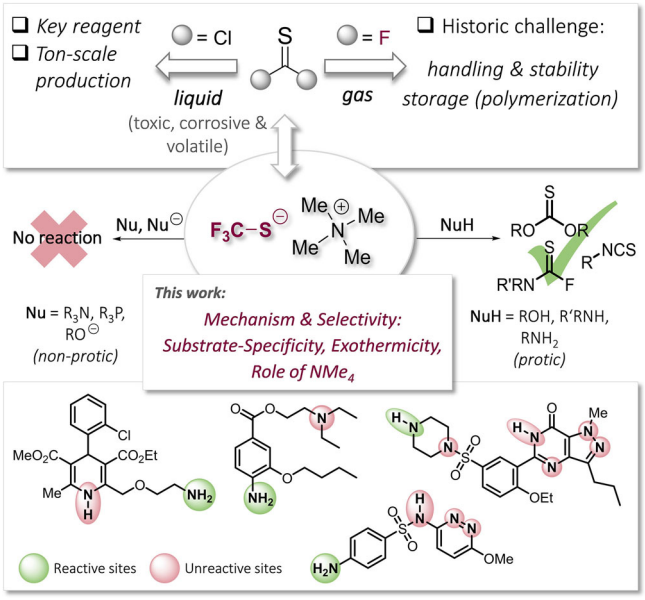

Figure 1. Reactivity pattern of $(Me_4N)SCF_3$ and overview.[6]

We herein report a detailed investigation of the bench-stable and easily accessible solid $(Me_4N)SCF_3$ as a solid reservoir for the controlled release of $S{=}CF_2$. We elucidate the mechanism of liberation with experimental and computational techniques, precise mode of action, and also assess its beneficial reactivity features as compared to thiophosgene.

The bench-stable salt $(Me_4N)SCF_3$ was first synthesized in 2002 by a team at Merck KGaA and Tyrra's group at roughly the same time.[7,8] In recent years, it has become a popular nucleophilic SCF_3 source for catalytic $C{-}SCF_3$ bond formations,[9] for example, it allows for the efficient trifluoromethylthiolation of aryl (pseudo-)halides[10] under transition-metal catalysis. As part of our studies in this area,[11] we recently untapped its potential to access chemistry, which would formally arise from $S{=}CF_2$. We discovered that subjection of the nucleophilic "C=S" source $(Me_4N)SCF_3$ to amines gives rise to the direct and quantitative formation of electrophiles, that is, thiocarbamoyl fluorides or isothiocyanates (see Figure 1).[12] These species serve as key intermediates to various products, including otherwise challenging to access trifluoromethyl amines. Other protic nucleophiles, such as alcohols, also lead to the corresponding thioester derivatives.[12a,13] As opposed to established approaches, a non-volatile solid is used and all by-products can

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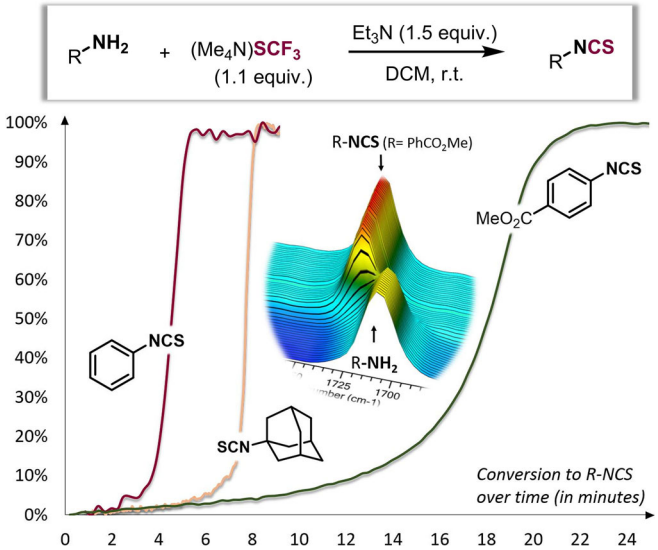
readily be precipitated with low-polarity solvents, allowing the purification of the desired products by filtration. Moreover, our synthetic investigations with primary and secondary amines revealed that there is a distinct selectivity pattern that does not follow the general electrophile–nucleophile reactivity trend. Formally quite nucleophilic sites, such as tertiary amines, heterocycles or deprotonated alcohols remained completely untouched, that is, the starting materials, substrate and $(Me_4N)SCF_3$, remained unchanged. Instead, 'heteroatom–H' sites are the reaction partners. However, of the available 'N–H' units, only the more nucleophilic and hence, less acidic, sites transform (see Figure 1).[12] This substrate specificity hints towards an unusual mechanistic scenario.

Being encouraged by the practicability paired with late-stage synthetic potential, we herein report our study of the mechanism of the transformation.

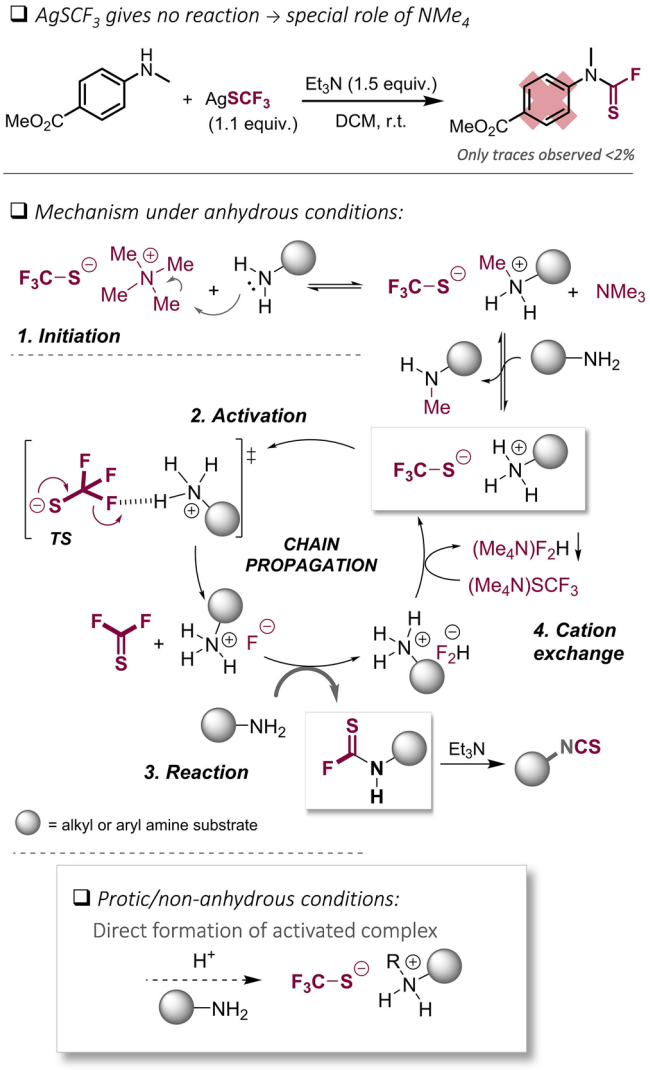
Our investigation began with an in-depth monitoring of the formation of R–NCS from $R–NH_2$ using in situ FTIR spectroscopy (ReactIR©). We investigated three electronically and sterically different primary amines for their propensity to form R–NCS with $(Me_4N)SCF_3$ under anhydrous conditions. The data are shown in Scheme 1. Interestingly, for all three amines, an induction period is observed under these conditions. The reaction profiles are unusual and might imply that a chemical initiation event needs to take place before any conversion can happen. As the initiation phases differ for the three amines (≈3 vs. 6 vs. 10 min), with the least nucleophilic/electron-rich displaying the longest, the initiation is clearly substrate-dependent. Once initiated, relatively rapid and non-exponential conversion to the R–NCS products follows. Such non-exponential growth is frequently associated with autocatalytic reaction behavior. Moreover, as seen in the 3D illustration in Scheme 1, no intermediate was observed en route to the R–NCS product.

A mechanistic possibility is that an $S{=}CF_2$ electrophile is liberated. For $KSCF_3$, it has previously been suggested that the salt might be unstable and might release $S{=}CF_2$ upon elimination of KF.[5] This hypothesis was subsequently also used to try and rationalize the transformations of R–OH with $AgSCF_3$ to $R–SCF_3$.[13] However, our NMR spectroscopic studies of $(NMe_4)SCF_3$ suggest that it is stable and remains untouched by itself as a solid and in solution until the amine reaction partner is added. Moreover, our observed "N–H" selectivity and lack of reactivity of formally more nucleophilic sites are inconsistent with a simple, direct release of $S{=}CF_2$ from the salt precursor. Similarly, the observed initiation phase in the ReactIR profile and non-exponential growth is also inconsistent with a spontaneous release of $S{=}CF_2$ from $(NMe_4)SCF_3$. Instead, the data suggest a substrate-induced transformation.

To gain additional support we also tested $AgSCF_3$ for its potential to transform a secondary amine to a thiocarbamoyl fluoride. This salt was previously also suggested to potentially release $S{=}CF_2$ upon AgF elimination.[13] However, when we mixed $AgSCF_3$ with methyl 4-(methylamino)benzoate, at best traces of thiocarbamoyl fluoride product (≤2%) was observed and starting material remained (see Scheme 2). This



Scheme 1. ReactIR reaction profiles of aniline, 1-adamantanamine and methyl 4-aminobenzoate with $(Me_4N)SCF_3$ under anhydrous conditions.



Scheme 2. a) Test whether $AgSCF_3$ would also be effective. b) Proposed mechanism for the formation of isothiocyanates with $(NMe_4)SCF_3$ under anhydrous vs. protic conditions.

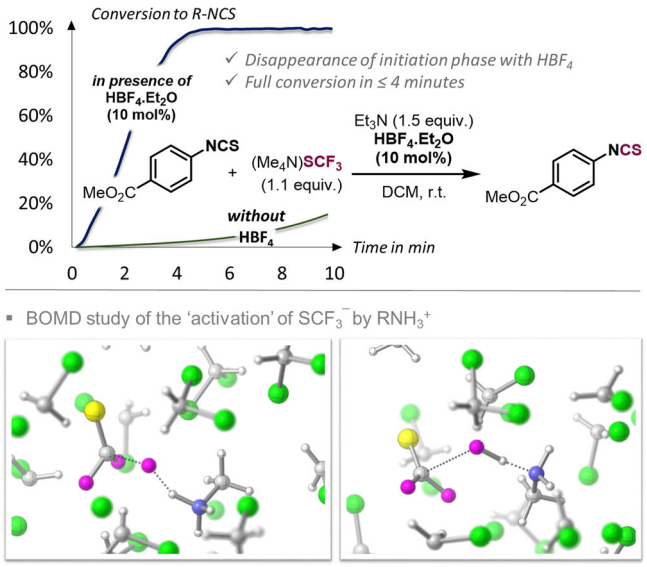
observation refutes the spontaneous liberation of $S{=}CF_2$ and reinforces a special role of the tetraalkylammonium cation.

On the basis of these observations, we propose the mechanism in Scheme 2. A reasonable substrate-induced initiation would arise from an initial Me-transfer between the $(Me_4N)SCF_3$ and the amine site in the substrate. This process[14] would only be efficient for more nucleophilic "N–H" sites and would now render the N-methylated substrate acidic. The latter species could equilibrate further to the proton-exchanged counterpart (e.g. H_3NR^+). These acidic species could then trigger the conversion of the SCF_3^- anion to $S{=}CF_2$ under concomitant formation of ammonium fluoride. Once generated, the $S{=}CF_2$ would then serve as electrophile to the 'N–H' moiety to give a thiocarbamoyl fluoride and ammonium bifluoride. NEt_3-triggered conversion to R–NCS would subsequently take place.

Importantly, a trace amount of methylated amine would be fully sufficient to initiate the overall transformation. This mechanism would account for the fact that (i) the tetraalkylammonium ion is key for reactivity, that (ii) "nucleophilic N–H" units are required, (iii) the occurrence of a substrate-dependent initiation phase and (iv) the non-exponential evolution of product under anhydrous reaction conditions.

To gain further insight, we applied QM studies as a first approximation to evaluate the feasibility of the initiation process.[15] As a representative example, we studied 1-adamantanamine. At CPCM (DCM) B3LYP-D3/def2-tzvp level of theory, the methyl transfer between $^+NMe_4$ and RNH_2 to generate RNH_2Me^+ was energetically slightly uphill with a reaction free energy ($\Delta_r G$) of 2.5 kcal mol^{-1}. From here further Me^+/H^+ exchanges could in principle take place in a dynamic equilibrium to generate RNH_3^+ and $RNHMe_2^+$ ($\Delta_r G = 3.1$ kcal mol^{-1}). While these energetics will not allow quantitative Me/proton transfers, they are in agreement with the prerequisite for an initiation (i.e. requiring only a trace). However, as we did not involve the SCF_3^- counter anion and hence ion-pairing in these considerations, the results must not be taken as more than a first indication. We hence sought for additional experimental support.

Mechanistically, the generation of an acidic amine appears to be key for the liberation of $S{=}CF_2$. In our current mechanistic picture, the observed initiation time stems from the propensity to allow for H/Me-transfers. If this mechanistic picture is indeed true, we would expect the formation of a trace amount of methylated amine resulting from initial Me-transfer. Using a secondary amine, we were indeed able to detect a trace of R_2NMe upon mass spectrometric analysis (see Supporting Information). Moreover, given that in situ generation of an acidic species appears to be key, the addition of an external proton should also trigger the chain reaction, but without the substrate-dependent initial lag time. Thus, we undertook another experiment, in which we added $HBF_4{\cdot}Et_2O$ to the reaction of methyl 4-aminobenzoate with $(Me_4N)SCF_3$. This led to a complete disappearance of the previously observed initiation phase and the product started to form immediately (see Scheme 3). Similarly, using reaction conditions that are not completely anhydrous, that is, with technical grades solvents



Scheme 3. Test experiment in the presence of $HBF_4{\cdot}Et_2O$ and ReactIR profile of the reaction with observed disappearance of the initiation phase (top). BOMD simulations (bottom) of $S{=}CF_2$ release from $(H_3NMe)SCF_3$. Colour code of atoms: Cl (green), C (grey), S (yellow), F (pink), N (blue), H (white).

that are not dried prior to use under open-flask reaction conditions, the initiation phase equally disappeared, consistent with small amounts of protonated amine that could function in the SCF_3 anion activation. On the contrary, a mixture of amine (1.0 equiv), $AgSCF_3$ (1 equiv), Et_3N (1.5 equiv) and $HBF_4{\cdot}Et_2O$ (10 mol%) gave only traces of product. These observations would be consistent with our proposed mechanism (see Scheme 2). With $AgSCF_3$, the required counter-cation exchange to form an activated complex and later from $(RNH_3)^+(F_2H)^-$ to $(RNH_3)^+(SCF_3)^-$ would not likely happen, and the crucial proton for activation of SCF_3^- would not be propagated.

With all experimental observations accounted for in our mechanistic model, the final open question is, how the $S{=}CF_2$ electrophile is released. To assess this, we turned to computations. Ion pair reactivity of $R{-}NH_3^+$ and F_3CS^- is challenging to investigate with static, gas-phase QM techniques. Thus, we turned to DFT-based (BLYP-D3) MD, that is, Born–Oppenheimer molecular dynamics (BOMD).[16] The advantage is that this methodology, in principle, maps all possible pathways at atomic resolution from a given reactant complex under more realistic conditions, that is, with explicit solvent.

We started our MD from a reactant complex consisting of $Me{-}NH_3^+$ and F_3CS^-, embedded in 14 DCM molecules. We ran 20 trajectories at BLYP-D3/6-31G level of theory at room temperature for about one picosecond, of which nine progressed to the product. We subsequently verified the results also at B3LYP-D3/6-31G(d) level of theory.[16] Snapshots of the key transformations are illustrated in Scheme 3. We observed that $S{=}CF_2$ is indeed formed. Interestingly, the release of $S{=}CF_2$ occurs under fluoride transfer, following $^+R_2N{-}H{\cdots}F{-}CF_2S^-$ interaction and not through initial protonation at the formally negative sulfur in the SCF_3 anion. This observation is in line with our calculation of the p*K*a of $HSCF_3$, which is predicted to be only 2.7 and, as such, is acidic.[17]

These data present a compelling reactivity picture for the release of S=CF_2 from $(Me_4N)SCF_3$ in the presence of protic nucleophiles and we next explored the practicability of employing $(Me_4N)SCF_3$ as a surrogate for thiophosgene. We found the transformation of $(Me_4N)SCF_3$ with amines to be very efficient in a range of solvents, that is, DCM, toluene, EtOAc, acetone, THF, MeCN, MTBE, CPME.[12b] All side-products that are formed in the reaction are solids, allowing their precipitation with low polarity solvents. An open question is the heat generated by the reaction of S=CF_2 (and its release) as compared to thiophosgene. We performed a direct reactivity comparison of the coupling of thiophosgene versus $(Me_4N)SCF_3$ with methyl 4-aminobenzoate at 10 mmol scale (ca. 1.5 g). Both reagents were added in one portion to the respective solutions of amine and triethylamine in DCM. While this resulted in vigorous and uncontrolled reactivity for thiophosgene (see Figure 2) that rapidly released so much heat that DCM started boiling (>15 °C temperature increase in a few seconds), the reaction with $(Me_4N)SCF_3$ showed only a slow warming of 5 °C over a period of 20 minutes.

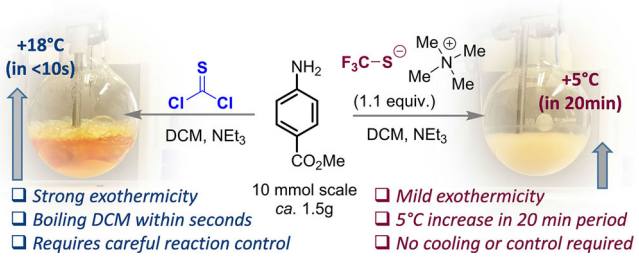


Figure 2. Assessment of heat generation in the reactions of thiophosgene (left) versus $(Me_4N)SCF_3$ (right) to give the corresponding R–NCS (i.e. methyl 4-isothiocyanatobenzoate).

Moreover, a differential scanning calorimetry analysis (DSC) of the $(Me_4N)SCF_3$ salt from 10 °C to 160 °C showed that no exotherm is observed, indicating that the salt is safe to use up to 160 °C (see Supporting Information for additional information).

In summary, a mechanistic study of the mode of action and selectivity of the solid reagent, $(Me_4N)SCF_3$, as a safe surrogate for thiophosgene was conducted. Our studies suggest that an S=CF_2 electrophile is generated in a controlled fashion upon activation with a protic nucleophile. Under anhydrous conditions, the process is likely initiated by a substrate-dependent series of Me- and proton transfers from the NMe_4 cation, consistent with its crucial role in the transformation ($AgSCF_3$ gives no reaction). This substrate-dependent initiation phase will disappear in the presence of exogenous $HBF_4{\cdot}Et_2O$ (10 mol%) or non-anhydrous conditions. In contrast to previous literature statements, $(Me_4N)SCF_3$ is stable as a solid and in solution under anhydrous conditions, liberating the S=CF_2 not by itself in an equilibrium, but under chemical activation and direct fluoride transfer, following $^{+}R_3N{-}H{\cdots}F{-}CF_2S^{-}$ interaction. A systematic comparison with S=CCl_2 revealed much less exothermic reactivity of the fluorinated analogue, requiring no reaction control even at larger scale.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: computational chemistry · fluorine · late-stage functionalization · reaction mechanisms · thiophosgene

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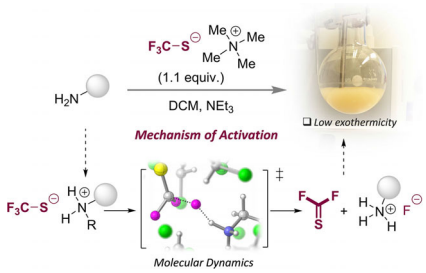

Experiments and computations showcase the solid $(Me_4N)SCF_3$ functioning as a safe reservoir for S=CF_2 and shed light on the mechanism of activation.