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# Generation of the $CF_3$ radical from trifluoromethylsulfonium triflate and its trifluoromethylation of styrenes†

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**The $CF_3$ radical was generated from the reaction of *S*-(trifluoromethyl)diphenylsulfonium triflate with $Na_2S_2O_4$ or $HOCH_2SO_2Na$ under suitable conditions without further reduction. Based on this, a method for the synthesis of α-trifluoromethylated ketones has been successfully developed.**

Trifluoromethylated compounds are increasingly important in organic and medicinal chemistry.[1] A series of trifluoromethylating reagents have been designed and synthesized to transfer the trifluoromethyl group into organic compounds.[1,2] *S*-(Trifluoromethyl)diarylsulfonium salts, which were first prepared by Yagupolskii and then developed by Umemoto, Shreeve, Ishihara and Shibata, have been successfully used for the electrophilic trifluoromethylation of nucleophiles.[3] To the best of our knowledge, however only few novel applications beyond the electrophilic reactions of these trifluoromethylating reagents have been published so far.[3–5] In our previous work, we found that *S*-(trifluoromethyl)diphenylsulfonium triflate could be reduced by metals.[5b] On the basis of this observation, we developed a convenient method for the synthesis of trifluoromethylated heteroaromatics under mild conditions using an *S*-(trifluoromethyl)diphenylsulfonium salt and copper as the reagent mixture.[5b] The intermediacy of a $CuCF_3$ species was confirmed in this trifluoromethylation reaction, and the $CF_3$ radical ($^\bullet CF_3$) was assumed to be the most probable precursor to the $CF_3$ anion ($CF_3^-$), although it could not be captured by radical acceptors when metals were present in the reaction mixture.

In order to obtain the $CF_3$ radical and to avoid its further reduction and thus expand its application, we investigated the reaction of *S*-(trifluoromethyl)diphenylsulfonium triflate with the reducing agents $Na_2S_2O_4$ and $HOCH_2SO_2Na$.[6] We were pleased to find that the $CF_3$ radical generated from the trifluoromethylsulfonium salt had a sufficient lifetime to be captured by styrenes. This is the first example of the generation of the $CF_3$ radical from a trifluoromethylsulfonium salt initiated by $Na_2S_2O_4$ or $HOCH_2SO_2Na$. Herein, we report the details.

As shown in Table 1, *S*-(trifluoromethyl)diphenylsulfonium triflate reacted with styrene at room temperature or at 0 °C in the presence of two equivalents of $Na_2S_2O_4$ to provide **2a** in 26% yield (entries 1 and 2, Table 1). This product is completely different from that obtained in the reaction between olefins and the $CF_3$ radical derived from $CF_3I$ and $Na_2S_2O_4$, $SmI_2$ or $Et_3B$.[6g–k] The reaction temperature and the amount of reductant influence the reaction. For example, reducing the reaction temperature to −15 °C, gave the desired product **2a** in a lower 19% yield (entry 3, Table 1), and using one instead of two equivalents of $Na_2S_2O_4$ gave the product **2a** in only 14% yield (entry 4, Table 1). Similar results were found in the reaction of **1a** with *S*-(trifluoromethyl)diphenylsulfonium triflate and $HOCH_2SO_2Na{\cdot}2H_2O$ (entries 9–11, Table 1). The use of larger excesses of $HOCH_2SO_2Na{\cdot}2H_2O$ from 6 equiv. to 11 equiv. in this reaction, however, led to no increase in the yield of **2a** (entries 12 and 13, Table 1). The amount of the sulfonium salt also has an influence on the reaction (entries 11–14, Table 1). For example, treatment of *S*-(trifluoromethyl)diphenylsulfonium triflate (2 equiv.) with **1a** (1 equiv.) in the presence of $HOCH_2SO_2Na{\cdot}2H_2O$ (6 equiv.) at 0 °C afforded **2a** in 36% yield (entry 12, Table 1), while the use of three equivalents of the sulfonium salt under the same conditions provided **2a** in 42% yield (entry 14, Table 1). Moreover, the use of an excess of styrene in this reaction resulted in a 40% yield of the product (entry 15, Table 1).

Besides the generation of **2a**, $CF_3H$ and $CF_3CF_3$ were formed in these reactions ($CF_3SO_2Na$ could not be completely excluded, however). The presence of these by-products was determined by $^{19}F$ NMR spectra according to a literature method.[7] No residual styrene **1a** was detected by TLC and GC analysis of the reaction mixtures, except for the reaction shown as entry 15 in Table 1. The polymerization of styrene might occur under the reaction conditions, leading to a complete loss of **1a**. The formation of $CF_3H$ and $CF_3CF_3$ is important evidence that the $CF_3$ radical is generated from *S*-(trifluoromethyl)diphenylsulfonium triflate and is not further reduced to the $CF_3$ anion by $Na_2S_2O_4$ or $HOCH_2SO_2Na$.

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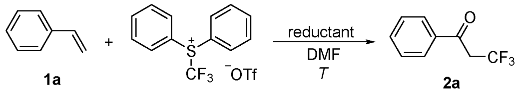
**Table 1** Screening for optimal conditions for the oxidative-trifluoromethylation of styrene[a]



| Entry | Reductant (R) | **1a** : $[Ph_2SCF_3]^+$ $[OTf]^-$ : R[b] | Time (h) | $T$/°C | Yield (**2a**,%)[c] |
|---|---|---|---|---|---|
| 1 | $Na_2S_2O_4$ | 1 : 1 : 2 | 5 | r.t. | 26 |
| 2 | $Na_2S_2O_4$ | 1 : 1 : 2 | 6 | 0 | 26 |
| 3 | $Na_2S_2O_4$ | 1 : 1 : 2 | 6 | −15 | 19 |
| 4 | $Na_2S_2O_4$ | 1 : 1 : 1 | 11 | r.t. | 14 |
| 5[d] | $Na_2S_2O_4$ | 1 : 1 : 2 | 5 | r.t. | 14 |
| 6[e] | $Na_2S_2O_4$ | 1 : 1 : 2 | 6 | 0 | 14 |
| 7[f] | $Na_2S_2O_4$ | 1 : 1 : 2 | 6 | 0 | 22 |
| 8[g] | $Na_2S_2O_4$ | 1 : 1 : 2 | 5 | r.t. | 0 |
| 9 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 2 | 5 | r.t | 22 |
| 10 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 2 | 5 | 0 | 28 |
| 11 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 3 | 5 | 0 | 34 |
| 12 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 2 : 6 | 5 | 0 | 36 |
| 13 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 2 : 11 | 5 | 0 | 36 |
| 14 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 3 : 6 | 5 | 0 | 42 |
| 15 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 4 : 1 : 3 | 6 | 0 | 40 |

[a] The reaction was conducted in air. [b] Molar ratio. [c] Determined by $^{19}F$ NMR and TLC analysis. [d] 6 equivalents of $H_2O$ were added. [e] 6 equivalents of $H_2O^{18}$ were added. [f] The solvent was dried. [g] The reaction was conducted under a nitrogen atmosphere.

Although we have made extensive efforts to try to improve the yield of **2a**, the generation of $CF_3H$ and $CF_3CF_3$ and the polymerization of styrene could not be completely suppressed. In fact, α-trifluoromethylated ketones (*e.g.* $RCOCH_2CF_3$) are difficult to synthesize.[8] Ando *et al.* reported that treatment of α,*β*-unsaturated ketones with $CF_3I$ in the presence of $Et_2Zn$ and $RhCl(PPh_3)_3$ could give α-trifluoromethylation products in moderate yield.[8b] Furthermore, trimethyl(1-phenylvinyloxy)-silane reacts with $CF_3I$ in the presence of $RhCl(PPh_3)_3$ to provide **2a** in 32% yield.[8c] The requirement for an expensive catalyst limits the use of these methods, making the methodology that we report in this paper highly significant.

Reductants such as $Na_2SO_3$, $NaHSO_3$, $P(NEt_2)_3$ and $P(OEt)_3$ were also tested for their suitability in the reaction. However, none of the desired product was formed in most cases, as determined by $^{19}F$ NMR spectroscopy and TLC analysis (entries 1–4, Table 2). When $Na_2S_2O_3{\cdot}5H_2O$ was used as the reductant, **2a** was obtained in 11% yield, which is lower than the yields obtained with $Na_2S_2O_4$ or $HOCH_2SO_2Na{\cdot}2H_2O$. It was also found that the solvent greatly influenced the reaction. When DMF was replaced by DMSO, MeOH, THF or acetone, only a trace of **2a** was formed (entries 6, 8, 10 and 12, Table 2), while none of the required product was formed when $CH_3CN$, $H_2O$ or DCM were used as the solvent (entries 7, 9 and 11, Table 2). This indicated that DMF is the most suitable solvent for the reaction.

To explore the scope of the reaction, as well as its suitability for the preparation of substituted α-trifluoromethylated ketones, various styrenes were allowed to react with *S*-(trifluoromethyl)diphenylsulfonium triflate in the presence of $HOCH_2SO_2Na{\cdot}2H_2O$. As shown in Table 3, styrenes with electron-withdrawing and electron-donating groups on the phenyl ring were all transformed into the corresponding oxidative-trifluoromethylation products (entries 1–9, Table 3). The position of the substituent had some influence on the reaction. On replacement of the *meta*-substituted styrene (**1b**) with the *para*-substituted analogue (**1c**), the oxidative-trifluoromethylated product (**2c**) was obtained in higher yield (entries 1 and 2, Table 3).When *ortho*-nitro-substituted styrene was used instead of **1b**, almost none of the desired product was obtained (not shown). 1-Vinylnaphthalene was also found to be a suitable substrate for this reaction. (entry 10, Table 3). Aliphatic olefins do not seem to be suitable substrates for this reaction (*e.g.* entry 11, Table 3).

Based on the results achieved above, we propose the following mechanism for the reaction (Scheme 1). The *S*-(trifluoromethyl)diphenylsulfonium triflate is first reduced by $Na_2S_2O_4$ or $HOCH_2SO_2Na$ *via* single electron transfer (SET) to form the intermediate **3**.[6k] The $CF_3$ radical is then formed *via* rapid decomposition of intermediate **3** and can be captured by styrenes to give **4** with hardly any over-reduction to form the $CF_3$ anion. Finally, the intermediate **4** is oxidized to produce the observed product. As expected, $Ph_2S$ was formed in the reaction and could be isolated by column chromatography after workup. The final step in this sequence, an oxidative process, surprised us because it unexpectedly happened in the presence of $Na_2S_2O_4$ or $HOCH_2SO_2Na$ which are always used as reductants. Moreover, the addition of six equivalents of water to the reaction mixture of **1a** with *S*-(trifluoromethyl)diphenylsulfonium triflate and $Na_2S_2O_4$ led to a lower yield of the product (entry 5, Table 1), while the addition of $H_2O^{18}$ instead of $H_2O$ led to a product which did not contain an $O^{18}$ atom (entry 6, Table 1). When the

**Table 2** Reductants and solvents used for the oxidative-trifluoromethylation of styrene[a]

| Entry | Reductant (R) | **1a** : $[Ph_2SCF_3]^+[OTf]^-$ : R[b] | Solvent | Time (h) | $T$/°C | Yield (**2a**, %)[c] |
|---|---|---|---|---|---|---|
| 1 | $Na_2SO_3$ | 1 : 1 : 2 | DMF | 5 | r.t. | Trace |
| 2 | $NaHSO_3$ | 1 : 1 : 2 | DMF | 5 | r.t. | 0 |
| 3 | $P(NEt_2)_3$ | 1 : 1 : 2 | DMF | 6 | r.t. | 0 |
| 4 | $P(OEt)_3$ | 1 : 1 : 2 | DMF | 6 | r.t. | 0 |
| 5 | $Na_2S_2O_3{\cdot}5H_2O$ | 1 : 1 : 2 | DMF | 5 | r.t. | 11 |
| 6 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 3 | DMSO | 5 | 0 | Trace |
| 7 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 3 | $CH_3CN$ | 5 | 0 | 0 |
| 8 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 3 | MeOH | 5 | 0 | Trace |
| 9 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 3 | $H_2O$ | 5 | 0 | 0 |
| 10 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 3 | THF | 5 | 0 | Trace |
| 11 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 3 | DCM | 5 | 0 | 0 |
| 12 | $HOCH_2SO_2Na{\cdot}2H_2O$ | 1 : 1 : 3 | Acetone | 5 | 0 | Trace |

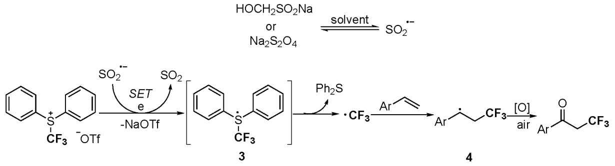
[a] The reaction was conducted in air. [b] Molar ratio. [c] Determined by $^{19}F$ NMR and TLC analysis.

**Table 3** The oxidative-trifluoromethylation of styrenes[a]

1b-l 2b-k

| Entry | Ar | Yield (%)[b] |
|---|---|---|
| 1 | $m$-$NO_2C_6H_4$ (**1b**) | 21 (**2b**) |
| 2 | $p$-$NO_2C_6H_4$ (**1c**) | 25 (**2c**) |
| 3 | $m$-$PhC_6H_4$ (**1d**) | 23 (**2d**) |
| 4 | $p$-$PhC_6H_4$ (**1e**) | 33 (**2e**) |
| 5 | $o$-$ClC_6H_4$ (**1f**) | 21 (**2f**) |
| 6 | $p$-$ClC_6H_4$ (**1g**) | 31 (**2g**) |
| 7 | $p$-$BrC_6H_4$ (**1h**) | 30 (**2h**) |
| 8 | $p$-$MeC_6H_4$ (**1i**) | 31 (**2i**) |
| 9 | $p$-$MeOC_6H_4$ (**1j**) | 39 (**2j**) |
| 10 | 1-Naphthyl (**1k**) | 31 (**2k**) |
| 11 | $n$-$C_8H_{17}$ (**1l**) | Complex |

[a] The molar ratio of **1b–l** : $[Ph_2SCF_3]^+[OTf]^-$ : $HOCH_2SO_2Na{\cdot}2H_2O$ is 1 : 2 : 6. [b] Isolated yield.



**Scheme 1** Proposed mechanism for the oxidative-trifluoromethylation of styrenes by $S$-(trifluoromethyl)diphenylsulfonium salt.

reaction was run under a nitrogen atmosphere, however, none of the product was formed (entry 8, Table 1). It seems that the oxygen atom in these products comes from $O_2$.

In summary, we have discovered that $S$-(trifluoromethyl)-diphenylsulfonium triflate can react with $Na_2S_2O_4$ or $HOCH_2SO_2Na$ under suitable conditions to generate the $CF_3$ radical without further reduction. Based on this, a convenient method for the synthesis of α-trifluoromethylated ketones has been successfully developed. We propose that the $S$-(trifluoromethyl)diphenylsulfonium triflate is reduced by $Na_2S_2O_4$ or $HOCH_2SO_2Na$ *via* a SET mechanism, and that the $CF_3$ radical is the key intermediate which reacts with styrene to produce, after oxidation, α-trifluoromethylated ketones. Investigations into the details of the oxidation process in this reaction are currently underway.

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