Electrophilic Reagents

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Straightforward One-Pot Synthesis of Trifluoromethyl Sulfonium Salts**

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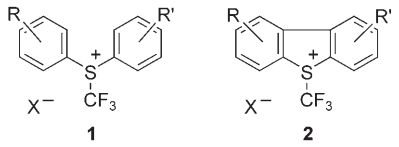
The trifluoromethyl group[1] has found widespread use in medicinal,[2] agrochemical,[3] and materials science.[4] Thanks to recent progress in these fields and the skill of organic chemists, methodologies for the direct introduction of the trifluoromethyl group are now available through radical, nucleophilic, or electrophilic approaches.[5] Being the newest, the electrophilic route is the least developed at this time and is scarcely used in the laboratory.[6] However, over the past two decades, electrophilic trifluoromethylation has been made possible by the development of various trifluoromethyl sulfide based reagents. In a pioneering study, Yagupolskii et al. described the preparation of trifluoromethylsulfonium compounds **1** and their reactivity towards some simple nucleophiles (Scheme 1).[7] More recently, Shreeve and co-



Scheme 1. Trifluoromethylating reagents.

workers proposed an alternative route to related reagents with improved electrophilic power.[8] In the meantime, Umemoto and Ishihara succeeded in the preparation of sulfonium salts of type **2**, with a dibenzothiophenium skeleton.[9] The last two research groups clearly demonstrated that the reactivity of both types of reagents **1** or **2** is enhanced by the presence of electron-withdrawing substituents R and R′, such as fluorinated or nitro groups, on the aromatic nucleus.

Although S-(trifluoromethyl) dibenzothiophenium tetrafluoroborate (**2**; $R = R' = H$, $X = BF_4$) is now commercially available, its use and that of related reagents suffers from the

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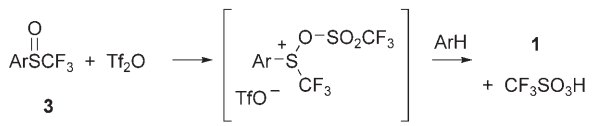
major drawback of their relatively complex synthesis. They are prepared in multistep sequences using either the now-banned ozone-depleting greenhouse gas CF_3Br[10] or expensive silver fluoride,[8] or even lengthier syntheses.[9b] Herein, we propose a multicomponent-reaction process for the preparation of compounds of type **1**.

A close examination of the literature shows that the cornerstone of the previously described syntheses is the formation of an intermediate trifluoromethyl sulfoxide **3**, precursor of the targeted sulfonium compounds **1** or **2** (Scheme 2).



Scheme 2. Mechanism of the formation of the sulfonium compounds.

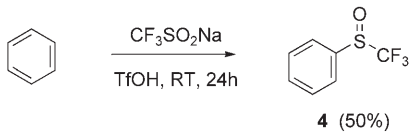
The mechanism proposed by Shreeve and co-workers[8] for the formation of sulfonium **1** involves activation of the sulfoxide function by trifluoromethanesulfonic anhydride ($(CF_3SO_2)_2O$), followed by intermolecular condensation with an arene and concomitant production of trifluoromethanesulfonic acid (CF_3SO_3H; Scheme 2).

In this context, we recently reported an efficient preparation of various aryl trifluoromethyl sulfoxides **3** by treatment of aromatic compounds with a mixture of potassium trifluoromethanesulfinate (CF_3SO_2K), trifluoromethanesulfonic anhydride, and trifluoromethanesulfonic acid.[11] This study could be considered to be the first improvement in the preparation of sulfonium compounds of type **1** as it decreases the number of necessary steps that lead to the synthesis of aryl trifluoromethyl sulfoxides **3**. However, only polymeric material was produced when the methodology was applied to the simplest benzene case.

A reappraisal of this work led us to suspect that the presence of both trifluoromethanesulfonic acid and trifluoromethanesulfonic anhydride at the beginning of the experiment may be deleterious to the outcome of the reaction.

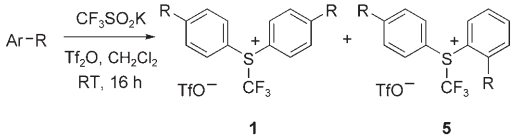
In a first trial, we observed that phenyltrifluoromethyl sulfoxide **4** could be isolated in a satisfactory yield when starting from benzene provided that trifluoromethanesulfonic anhydride was not used (Scheme 3).[12] We assume that this improved procedure can be readily generalized to the synthesis of other aryl trifluoromethyl sulfoxides of type **4**.

However, as shown in Scheme 2, the presence of trifluoromethanesulfonic anhydride is essential for the preparation of sulfonium salts **1**. In a second trial, we thus replaced trifluoromethanesulfonic acid with trifluoromethanesulfonic anhydride. We were very pleased to find that this improvement, with dichloromethane as the solvent, resulted in the straightforward preparation of *S*-(trifluoromethyl)diaryl sulfonium trifluoromethanesulfonates **1** and **5** in a one-pot procedure with low-to-good yields depending on the substrate (Table 1). With an electron-donating substituent on the aromatic ring (entry 1), the yield of isolated product is good, although associated with incomplete *ortho*/*para* selectivity. Benzene itself gave rise to compound **1b**, already synthesized by Shreeve and co-workers in three steps, in a satisfactory yield (entry 2).[8] Even with less activated substrates (entries 3–5) new trifluoromethyl sulfonium compounds **1c–e** could be prepared in fair (**1c**,**d**) to low (**1e**) yield. All compounds have been fully characterized (see the Supporting Information).



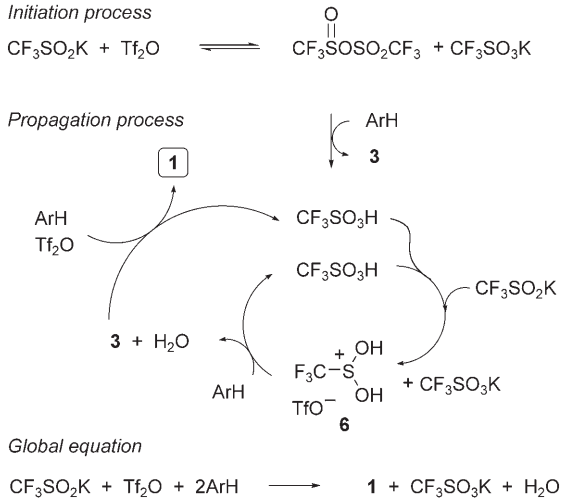
Scheme 3. One-step synthesis of phenyltrifluoromethyl sulfoxide **4**.

Table 1: One-pot synthesis of trifluoromethyl sulfonium compounds



Entry	R	Compound	Yield of isolated product [%]	1/5
1	Me	**1a**	73	85:15
2	H	**1b**	60	100:0
3	Cl	**1c**	50	100:0
4	F	**1d**	46	100:0
5	OCF_3	**1e**	15	100:0

The mechanism of this transformation seems rather intriguing, and we propose a possible pathway in Scheme 4. We assume that the process can be divided in two parts, the first being the formation of sulfoxide **3**, the second its transformation into sulfonium **1**. Reaction between potassium trifluoromethanesulfinate and trifluoromethanesulfonic anhydride can produce a mixed sulfonate sulfinate anhydride.[13] This species may be activated enough to react with the aromatic substrate by a Friedel–Crafts-like electrophilic



Scheme 4. Proposed mechanism for the formation of the sulfonium compounds **1**.

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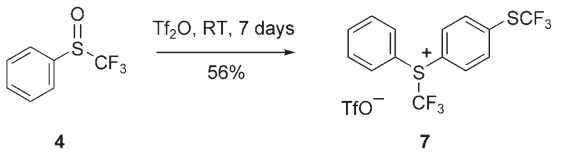
substitution. This first reaction is presumably the slower step and may be considered as an initiation process that generates trifluoromethanesulfonic acid and sulfoxide **3**. The acid thus formed may then lead to sulfoxide **3** by the intermediate **6**, as shown in our earlier work.[11] The second part of the mechanism is presumed to be analogous to the one proposed by Shreeve and co-workers (Scheme 2). At this point, the requisite two equivalents of acid necessary for the twofold protonation of potassium trifluoromethanesulfinate (to give **6**) are produced by the propagation reaction. Some experimental observations are in favor of this mechanism. The reaction is inhibited by a base such as 2,6-di-*tert*-butyl-4-methylpyridine. Moreover, in some cases, small quantities of sulfoxide are isolated from the reaction mixture. This last point will be discussed later. The global equation shows that trifluoromethanesulfonic acid does not appear in the reaction equation. The stoichiometry used for the reagents (one equivalent for each) may appear to be in contradiction with this equation. Nevertheless, these conditions gave the best results with respect to the yield of isolated product.[14]

In addition to the aromatic starting material, fine analysis of the crude mixture has revealed the presence of small quantities of aryl trifluoromethyl sulfoxides **3** (as mentioned above), but also reduced aryl trifluoromethyl sulfides, in larger quantities. Part of the aryl trifluoromethyl sulfoxide seems to be reduced in situ, presumably by trifluoromethanesulfonic anhydride. This reagent is better known for its oxidative properties,[13a,15] but some examples of its reducing power have been reported.[13b,16] To the best of our knowledge, no explanation has been proposed yet for this behavior.[17]

This reduction process is peculiarly illustrated by the formation of trifluoromethylthio-substituted sulfonium **7** by treatment of sulfoxide **4** with an excess of neat trifluoromethanesulfonic anhydride (Scheme 5).



Scheme 5. Preparation of sulfonium **7** in neat Tf_2O.

We suppose that in the first step one equivalent of sulfoxide is reduced to its corresponding sulfide, which can further react with an activated form of the sulfoxide to generate the observed sulfonium **7** (see Scheme 2). We have no experimental evidence for such a mechanism, except the isolation (besides **7**) of nonpolar sulfide derivatives, which result from the reduction of phenyltrifluoromethyl sulfoxide **4** in the reaction medium. Nevertheless, this reaction constitutes a new route to interesting sulfonium derivatives and can be generalized to prepare various aryl trifluoromethyl sulfoxides.

In summary, we have developed a very short and efficient synthesis of aryl trifluoromethyl sulfonium salts, important electrophilic trifluoromethylating reagents. Our strategy allows the preparation of target compounds in a one-pot process for routine laboratory applications. We are currently applying this methodology to more elaborate aromatic compounds, especially biphenyl derivatives, to synthesize new and hopefully more reactive reagents.

Experimental Section

General procedure for the synthesis of sulfonium compounds as exemplified by the preparation of **1b**: Benzene (1.14 mL, 12.8 mmol, 1 equiv) and trifluoromethanesulfonic anhydride (2.14 mL, 12.8 mmol, 1 equiv) were added under argon to a suspension of potassium trifluoromethanesulfinate (2.2 g, 12.8 mmol) in dichloromethane (2 mL, 64 mmol, 5 equiv). The reaction mixture is filtered after 16 h, diluted with CH_2Cl_2 (30 mL), washed with water (3 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane/methanol (90:10) as the eluent to give 1.76 g (70 %) of a slightly colored powder. Recrystallization from pentane/ethyl acetate (2:8) afforded 1.5 g (60 %) of **1b** as a white solid. M.p. 99.6–100 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.27$ (d, $J = 8.8$ Hz, 4 H), 7.8 ppm (d, 4 H); ^{19}F NMR ($CDCl_3$, 188 MHz): $\delta = -50.7$ (m, 3 F, SCF_3), −79.0 ppm (m, 3 F, SO_2CF_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 145.0$, 134.6, 132.7, 123.0 (q, $J = 328.2$, CF_3), 120.6 (q, $J = 320.0$, CF_3), 114.8 ppm; pos. ESI MS: (m/z): 323 [M^+]; elemental analysis (%) calcd for $C_{14}H_8Cl_2F_6O_3S_2$: C 35.53, H 1.70; found: C 35.51, H 1.69.[18]

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[14] It should be remembered that water is also formed in this process and may concurrently be protonated by trifluoromethanesulfonic acid and/or hydrolyze trifluoromethanesulfonic anhydride; moreover, although the initiation process is no longer rate determining, it may nevertheless continue to participate in the reaction.
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[17] Studies are also ongoing to develop a better understanding of the mechanism of the reduction reaction.
[18] See the Supporting Information for full experimental details, characterization data, and ^{1}H, ^{19}F, and ^{13}C NMR spectra.

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