

Trifluoromethanesulfanylamides as Easy-to-Handle Equivalents of the Trifluoromethanesulfanyl Cation (CF_3S^+): Reaction with Alkenes and Alkynes**

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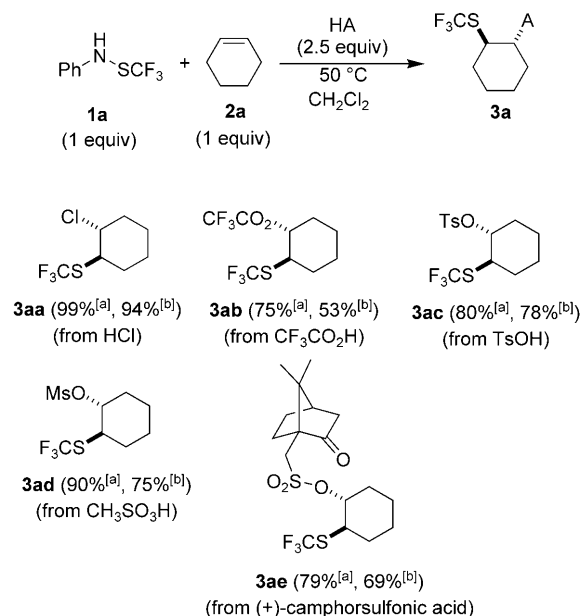
In memory of Lev Yagupolskii

The specific physico-chemical properties of fluorinated molecules are of great interest in a wide range of applications.^[1,2] Consequently, organofluorine chemistry has grown steadily to become, today, a field of tremendous importance with a distinctive role in highly diverse technological applications (for example, fluoropolymers, pharmaceutical and agrochemical products, materials science, and medical imaging).^[3,4] These last years, heteroatom-containing fluorinated groups have attracted special interest, in particular the CF_3S moiety, which exhibits a high hydrophobicity parameter ($\pi_{\text{R}} = 1.44$).^[5] Consequently compounds bearing this group are potentially important targets in the pharmaceutical and agrochemical fields.^[2b,c,6]

Numerous methods are now available to introduce this function to organic substrates.^[7] Essentially three strategies have been developed. The first one consists of constructing the CF_3S moiety from a “precursor”, such as the methylthio group, already present in the molecule. This strategy, which is used on the industrial scale, is based on halogen–fluorine exchange reactions and is limited to aromatic compounds.^[8] The second method is also indirect, since a CF_3 group is grafted onto a sulfur atom of the substrate. This trifluoromethylation approach is not always easy to realize and requires the preliminary synthesis of the sulfur-containing precursor. Examples include the nucleophilic^[9] and radical trifluoromethylation^[10] of disulfides, thiocyanates, and thiols. A few electrophilic trifluoromethylations of thiolates have also been reported.^[11] The third method is the most direct since the CF_3S group is introduced to the molecules directly. Radical and electrophilic hydrogen substitutions have been performed with CF_3SCl ,^[12] which, however, is a very toxic reagent. Some nucleophilic reactions have been also realized

by using stabilized forms of the unstable CF_3S anion, but apart from CF_3SCu the reactivity of these species is relatively limited;^[13] such reagents are generally not stable enough to be stored for extended periods.^[13] Consequently, until now, there has been no efficient and easily available reagent to introduce a CF_3S moiety to molecules directly, in particular in an electrophilic fashion.

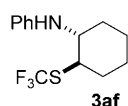
Recently, we have described an easy synthesis of trifluoromethanesulfanylamides (**1**), which are very stable liquid compounds.^[14] As Montevecchi et al. demonstrated that arenesulfonamides can be used for the electrophilic addition of the thiol group to alkenes under Lewis acid activation,^[15] we envisaged using trifluoromethanesulfanylamides (**1**) as new reagents for trifluoromethanesulfanylation. Since under the conditions described by Montevecchi et al. we observed no reaction between **1a** and cyclohexene (**2a**), we tried to activate **1a** by adding a protic acid to induce the electrophilic addition of **1a** to **2a**. The product we obtained, however, did not correspond to that arising from concomitant addition of the anilino part of **1a** but of that of the conjugate base of the acid used (Scheme 1). Only traces of the expected product **3af**



Scheme 1. Addition of **1a** to cyclohexene under protic acid activation. [a] Yield of crude product determined by ^{19}F NMR spectroscopy with an internal standard. [b] Yield of isolated product. Ts = toluene-4-sulfonyl.

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were observed since the nitrogen atom was protonated by the auxiliary acid (that explains why 2.5 equiv of the acid was needed), and consequently, it was not nucleophilic enough.

The *trans* configuration of the products supports an *anti* addition involving the opening of an episulfonium intermediate. The choice of the protic acid is crucial. Indeed, no reaction was observed with weak acids such as AcOH and PhCO₂H, which are not able to protonate **1a**. However, the conjugate base of the protic acid must be also sufficiently nucleophilic to open the intermediate episulfonium cation. Thus, triflic acid (TfOH) and sulfuric acid resulted in the degradation of **1a** without formation of any identifiable addition product.

This method has been tested with other alkenes and with TsOH as the protic acid (Method 1 in Figure 1). This reaction

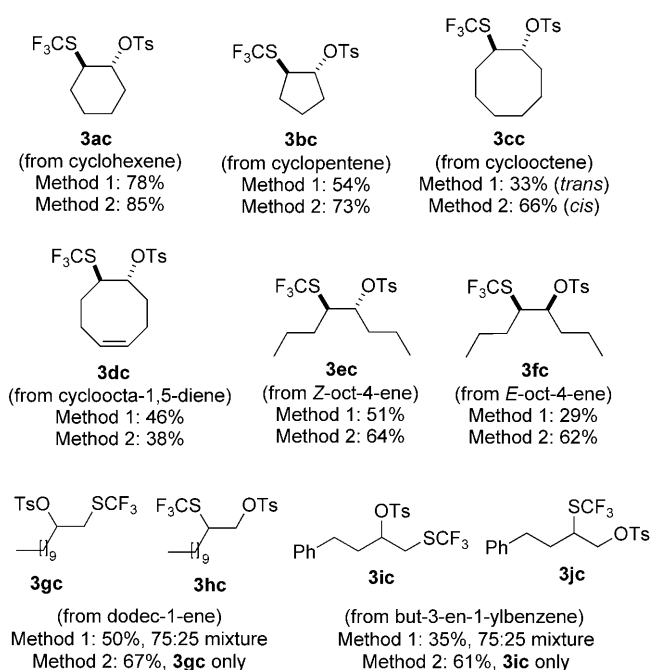
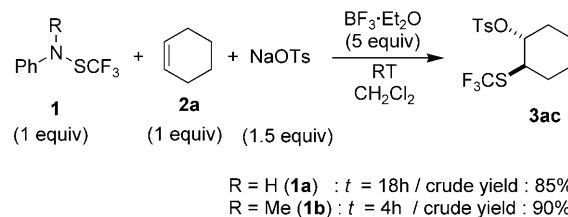


Figure 1. Addition of trifluoromethanesulfanylamides **1** to alkenes (yields of isolated products). Method 1: addition of **1a** under activation by TsOH. Method 2: addition of **1b** under activation by BF₃·Et₂O and in the presence of TsONa.

provided the expected products with satisfactory yields and was stereospecific, since *erythro* or *threo* products were obtained depending on the *Z* or *E* configuration of the starting alkene (cf. **3ec** and **3fc**). The regioselectivity was not complete since a mixture of Markovnikov and anti-Markovnikov compounds was observed (cf. **3gc/3hc** and **3ic/3jc**). This reaction was carried out on a preparative scale in similar yields for the synthesis of 1.4 g of **3ac** (see the Experimental Section).

To improve some of the previous modest yields, we considered Lewis acid activation of **1a**. In this case, since the anilino part of **1a** appeared to be poorly nucleophilic when protonated or complexed by a Lewis acid, an auxiliary nucleophile was added. To obtain the same products as

previously, sodium tosylate was chosen. The experimental conditions were optimized with BF₃·Et₂O (Scheme 2). In this case, the reaction delivered good results at room temperature,



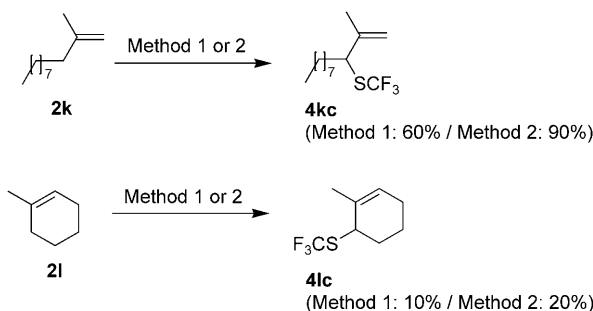
Scheme 2. Reaction of **1** with cyclohexene under Lewis acid activation (yield of crude product determined by ¹⁹F NMR spectroscopy with an internal standard).

provided that an excess of BF₃·Et₂O (5 equiv) was used. The yield was improved and the reaction time was dramatically decreased when *N*-methyl-trifluoromethanesulfanylamide (**1b**) was used. (The nitrogen atom of **1b** is more nucleophilic and, consequently, more easily complexed by the Lewis acid.) Furthermore, with **1b**, the addition of *N*-methylaniline as a side reaction was not observed. Lewis acids other than BF₃·Et₂O were evaluated with **1b** as reagent. Ti(O*i*Pr)₄, Cu(OTf)₂, Yb(OTf)₃, La(OTf)₃, and In(OTf)₃ gave no results. Chlorinated Lewis acids such as TiCl₄, SnCl₄, and ClSiMe₃ provided exclusively the chlorinated product **3aa** (crude yields: 60%, 46%, and 84%, respectively). The expected product **3ac** was obtained with (Bu)₂BOTf and TfOSiMe₃, but with lower yields than those resulting from BF₃·Et₂O (crude yield: 40% and 45% respectively). Since BF₃·Et₂O appeared to be the best choice for the auxiliary nucleophile, the same alkenes as those previously used were tested under these new conditions (Method 2 in Figure 1).

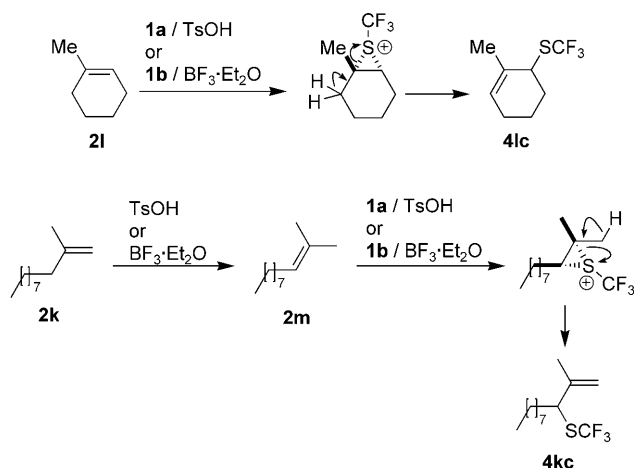
Generally, better yields were observed with Method 2. The reaction was always stereospecific (cf. **3ec** and **3fc**) but also regioselective since only Markovnikov products were obtained (cf. **3gc** and **3ic**). More surprisingly, the addition onto cyclooctene provided the *cis* product rather than the *trans* previously obtained.^[16] Such differences between the two methods are not really well understood at the moment. This reaction was carried out on a preparative scale in similar yields for the synthesis of 1.5 g of **3ac** (see the Experimental Section).

When more hindered alkenes were used as substrates, formal allylic trifluoromethanesulfanylation was observed with both methods (Scheme 3). In the case of **4lc**, hindrance of the intermediate episulfonium cation by the adjacent methyl group prevents the approach of the nucleophile and favors deprotonation (Scheme 4). The same phenomenon was observed in the case of **4kc** and can be explained by the isomerization of the starting olefin **2k** in situ to give the tetrasubstituted olefin **2m** before formation of the episulfonium cation (Scheme 4). Indeed, a quantitative isomerization of **2k** into **2m** was observed under acidic conditions and **4kc** was also obtained in the same yield by reaction of preformed **2m** with either **1a** or **1b**.

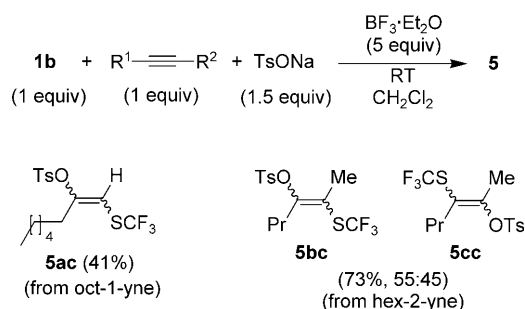
As these reagents were efficient in reactions with olefins, we evaluated their reactivity towards some alkynes



Scheme 3. Reaction with hindered alkenes.



Scheme 4. Mechanism of the formal allylic trifluoromethanesulfanylation.

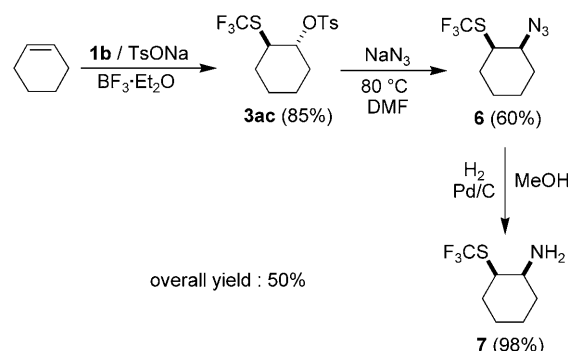


Scheme 5. Reaction of **1b** with alkynes.

(Scheme 5). Since the best results with alkenes were obtained with **1b** under BF₃·Et₂O activation, these conditions were applied to alkynes. The reaction gave satisfactory yields, but the regiochemistry was not controlled in the case of internal alkynes since an equal amount of the two regioisomers was obtained (**5bc** and **5cc**). The reaction was stereoselective since only one stereoisomer was obtained. The stereochemistry of the products could not be determined, but as an *anti* addition was observed with olefins, the *E* configuration can be reasonably postulated.

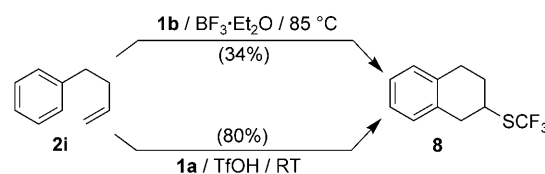
The products obtained constitute valuable building blocks for further syntheses of compounds bearing the CF₃S moiety.

Indeed, the presence of the tosyl group allows further functionalizations, as illustrated by the synthesis of *syn* 2-trifluoromethylsulfanyl cyclohexyl amine (**7**), which was obtained in a good overall yield of 50% over 3 steps (Scheme 6). Because of the S_N2 process of the reactions, the observed diastereoselectivity is complete and the *cis* product is formed exclusively.



Scheme 6. Synthesis of **7** from cyclohexene.

Finally, the possibility of inducing electrophilic cyclization has been also investigated. For this purpose, but-3-en-1-ylbenzene (**2i**) was reacted with **1b** and BF₃·Et₂O (without an auxiliary nucleophile) or with **1a** and triflic acid, the conjugate base of which was not nucleophilic enough to compete with the π system (Scheme 7). In this case, Lewis acid activation was not the best way since the optimal yield, under heating, was only 34%. In contrast, triflic acid activation gave a good yield of **8** at room temperature.



Scheme 7. Electrocyclic cyclization of **2i** to give **8**.

To conclude, trifluoromethanesulfanylamides **1a** and **1b** are valuable and stable reagents; they are easy to obtain^[14] and easy to handle, and efficiently effect electrophilic trifluoromethanesulfanylation. These new reagents constitute the first alternative to CF₃SCl and will open opportunities in the synthesis of compounds bearing the CF₃S moiety. Furthermore, because they are easy to handle, they are accessible to the broad community of synthetic chemists beyond organofluorine specialists. Further studies of their reactivity and applications are in progress and will be published in due course.

Experimental Section

Typical procedure: Synthesis of **3ac**:

Method 1: To a solution of **1a** (965 mg, 5 mmol) in dichloromethane (10 mL) was added cyclohexene **2a** (507 μL, 5 mmol) then TsOH (2.38 g, 12.5 mmol). The reaction mixture was heated for 24 h.

The organic phase was washed with water and dried over Na_2SO_4 . After removing solvent in vacuo, the crude was purified by flash chromatography (eluent: pentane/acetone 70:1) to afford **3ac** (1.38 g, 3.9 mmol) as a colorless oil.

Method 2: To a solution of **1b** (1.035 mg, 5 mmol) in dichloromethane (10 mL) was added cyclohexene **2a** (507 μL , 5 mmol) then sodium tosylate (1.5 g, 7.7 mmol). The resulting suspension was stirred vigorously at room temperature. After 5 min of stirring, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3.2 mL, 25 mmol) was then added dropwise. The reaction mixture stirred for further 4 h before Et_2O and H_2O were added. The organic phase was washed with aqueous HCl (2N) and dried over Na_2SO_4 . After the solvent had been removed in vacuo, the crude was purified by flash chromatography (eluent: pentane/acetone 70:1) to afford **3ac** (1.5 g/4.24 mmol) as a colorless oil.

^1H NMR: δ = 7.80 (d, $^3J(\text{H,H})$ = 8.1, 2H), 7.35 (d, $^3J(\text{H,H})$ = 8.1, 2H), 4.49 (ddd, $^3J(\text{H,H})$ = 6.6, $^3J(\text{H,H})$ = 6.6, $^3J(\text{H,H})$ = 3.6, 1H), 3.29 (ddd, $^3J(\text{H,H})$ = 6.9, $^3J(\text{H,H})$ = 6.9, $^3J(\text{H,H})$ = 4.2, 1H), 2.44 (s, 3H), 2.22 (m, 1H), 2.03 (m, 1H), 1.69–1.65 (m, 3H), 1.48–1.44 ppm (m, 3H). ^{13}C NMR: δ = 145.4, 134.0, 130.9 (q, $^1J(\text{C,F})$ = 306), 130.2, 128.3, 80.7, 45.9, 30.4, 30.1, 23.3, 21.9, 21.8 ppm. ^{19}F NMR: δ = –40.06 ppm (s). Elemental analysis calcd (%) for $\text{C}_{14}\text{H}_{17}\text{F}_3\text{O}_3\text{S}_2$: C 47.45, H 4.83, S 18.09; found: C 47.43, H 4.87, S 17.93.

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