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First and second generation of trifluoromethanesulfenamide reagent: A trifluoromethylthiolating comparison☆

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ABSTRACT

Trifluoromethylthiolation of molecules is a more and more studied reaction. In particular, the direct electrophilic trifluoromethylthiolation plays an important role in this chemistry. Among the various developed reagents, trifluoromethanesulfenamides constitute an efficient family of reagents. However, no systematic comparison of these two generations has been realized. In this paper, the difference of reactivity of these reagents is studied towards various nucleophiles.

1. Introduction

With the fluorine discovery [1], Moissan has open the way to a fascinating chemistry which led to the design of new compounds with specific and particular properties for a large panel of various applications [2–5]. In particular, fluorinated molecules have found a crucial place in life sciences due to their original physico-chemical properties [6–12]. In this specific field of applications, the trifluoromethylthio group appeared to be very contributive. Indeed, this substituent is one of the most lipophilic fluoroalkyl groups, with a Hansch parameter $\pi_R = 1.44$ [13]. Such important physico-chemical property greatly contributes to enhancing molecules biodisponibility by favoring the transmembrane permeation [6,7,14–18].

This growing interest for the CF_3S group has largely contributed to the recent developments of new methodologies and new reagents to introduce this moiety onto organic molecules [19–21]. More specifically, a particular focus was recently laid on direct methods of trifluoromethylthiolation which are more elegant and practical in a synthetic point of view [19,20,22,23].

Such recent strategies have required the development of new shelf-stable reagents. More specifically, new electrophilic trifluoromethylthiolating reagents [24–30] were highly required to replace CF_3SCl, the only reagent available until recently, but very toxic [31].

2. Results and discussion

One of the first developed reagents was the 1st generation of trifluoromethanesulfenamide **1** [25,32–36]. Recently, the 2nd generation of trifluoromethanesulfenamide **2** has been introduced to realize more difficult reactions [29,37,38] (Fig. 1). A reactivity comparison between these reagents could be interesting to well rationalize the choice of the better trifluoromethanesulfenamide reagent.

The first reaction described was the electrophilic addition onto alkenes (Table 1) [32]. With Brønsted acids, the reagent **1a** gave the best results compared to **1b** (entries 1–2, 4–5). This is particularly clear with TFA since no addition product was observed (entries 4–5). This could be explained by the bigger counter ion of trifluoroacetate (N-Me anilinium) which strongly contribute to decrease its already weak nucleophilicity. With **2**, no reaction was

☆ In honor of Véronique Gouverneur, with congratulations.

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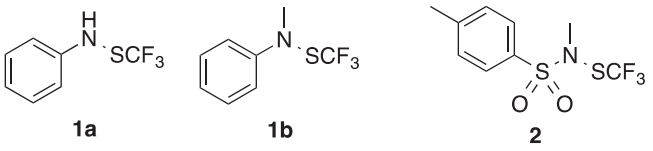


Fig. 1. 1st and 2nd generation of trifluoromethanesulfenamide.

observed with TsOH or TFA (entries 3, 6) because of the lower basicity of the nitrogen atom which could not be easily protonated by these too weak acids. This protonation step being crucial to activate the reagents, no reactions can occur in these conditions. With TfOH, all the reagents are reactive, even if the more basic reagents **1** stays more efficient (entries 7–9). It should be noticed that an increased temperature gave lower yields (entries 10–11), the degradation of activated reagents being more rapid than the electrophilic attack onto cyclohexene. With Lewis acid activation, same observations have been made. Strong Lewis acid such as $BF_3{\cdot}Et_2O$ succeeded to activate all the reagents (entries 12–14), but more efficiently **1**, whereas weak Lewis acid $ClSiMe_3$ seemed able to activate only **1b** (entries 15–16).

Friedel-Crafts reactions have been then studied (Table 2) [33,38]. With dimethoxybenzene (**5a**), reactions were observed with all the reagents with TsOH as activator, with a better yield obtained with **1a** (entries 1–3). The product formation by using **2** proves that TsOH, contrary to the previous observation with cyclohexene (Table 1, entry 3), could activate this one. Consequently, the reagent activation seems to be not the lone determining parameter, and the nucleophilicity of the nucleophile appears also to be important. Hence, the couple activator/nucleophilicity must be taken in consideration. Triflic acid could also promote this reaction, even at room temperature, with better results by using **2** (entries 4–7). Catalytic reaction was also possible with TfOH but only with the more reactive reagent **2**, subject to heat at 80 °C (entries 8–10). As with cyclohexene, $BF_3{\cdot}Et_2O$ was a better activator with **1b** than with **2** (entries 11–13).

In the case of indole (**5b**), same results than with **5a** were observed when TsOH was used as the catalyst (entries 14–16). Nevertheless, because of the nitrogen atom of **5b**, no reaction was observed with TfOH (entry 17). By using $ClSiMe_3$, in acetonitrile, good yields were observed with **2** (entry 19), contrary to the case of cyclohexene (Table 1, entry 16). This confirms the necessity to consider both activator and nucleophilicity to analyze results. Catalytic amount of $ClSiMe_3$ could be used both with **1b** and **2** to trifluoromethylthiolate indole (**5b**) (entries 20–21), which is more nucleophile than **5a**.

When less electron-rich aromatic compounds were considered, no reactions where observed with **1b** or **1a**, only **2** with TfOH (or $ClSiMe_3$ if the aromatic compound contents a nitrogen atom) was able to perform aromatic trifluoromethylthiolation [38].

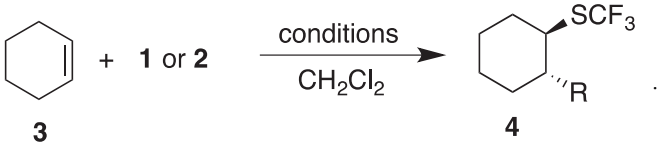
Trifluoromethylthiolation of Grignard reagent constitutes also a convenient way to obtain various trifluoromethylthioethers (Table 3) [34].

With Grignard compounds, **2** was systematically the better trifluoromethylthiolating reagent. More particularly, in the case of benzyl Grignard (**7b**), a degradation of the resulting product **8b** was observed in the reacting medium by using **1b** whereas **8b** seemed stable when obtained from **2**. This lets suggest that the released amide during the reaction contribute to the degradation of **8b** (because of the acidic benzylic hydrogens in α position of SCF_3). Therefore, if the *N*-methylanilide arising from **1b** is basic enough, the sulfonamide coming from **2** is a too weak base to contribute to this degradation.

In the same strategy, terminal alkynes have been also trifluoromethylthiolated in presence of lithium base (Table 4).

When the alkynes were previously deprotonated with 1 eq. of BuLi, similar results than for Grignard reagents were obtained (entries 1–4). With non base-sensitive trifluoromethylthiolated alkyne (**10a**), both reagents gave similar yields (entries 1–2) whereas with more sensitive product (**10b**), in situ degradation was observed with **1b** and not with **2** (entries 3–4). However, this trifluoromethylthiolation could also work with catalytic amount of BuLi but only by using **1b**. With **2** the generated sulfonamide anion is not basic enough to deprotonate the terminal alkynes and, thus, to catalyze the reaction.

Table 1
Electrophilic addition onto alkenes



Entry	Reagent	Conditions	*T* (°C)	**4** (%)[a]
1	**1a**	TsOH (2.5 eq.)	50	**4a**: X = OTs (80)
2	**1b**	TsOH (2.5 eq.)	50	**4a**: X = OTs (70)
3	**2**	TsOH (2.5 eq.)	50	**4a**: X = OTs (0)
4	**1a**	TFA (2.5 eq.)	50	**4b**: X = O_2CCF_3 (75)
5	**1b**	TFA (2.5 eq.)	50	**4b**: X = O_2CCF_3 (0)
6	**2**	TFA (2.5 eq.)	50	**4b**: X = O_2CCF_3 (0)
7	**1a**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	RT	**4c**: X = O_2CPh (69)
8	**1b**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	RT	**4c**: X = O_2CPh (71)
9	**2**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	RT	**4c**: X = O_2CPh (54)
10	**1b**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	50	**4c**: X = O_2CPh (50)
11	**2**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	50	**4c**: X = O_2CPh (35)
12	**1a**	$BF_3{\cdot}Et_2O$ (5.0 eq.)/TsONa (1.5 eq.)	50	**4a**: X = OTs (85)
13	**1b**	$BF_3{\cdot}Et_2O$ (5.0 eq.)/TsONa (1.5 eq.)	RT	**4a**: X = OTs (90)
14	**2**	$BF_3{\cdot}Et_2O$ (5.0 eq.)/TsONa (1.5 eq.)	RT	**4a**: X = OTs (0)
15	**1b**	$ClSiMe_3$ (5.0 eq.)	RT	**4d**: X = Cl (84)
16	**2**	$ClSiMe_3$ (5.0 eq.)	RT	**4d**: X = Cl (0)

[a] Crude yield determine by ^{19}F NMR using $PhOCF_3$ as an internal standard. All the compounds were isolated with yields in accordance with titration.