ChemPubSoc Europe

DOI: 10.1002/ejoc.201600197

EurJOC European Journal of Organic Chemistry

Communication

Trifluoromethylthiolation

Metal-Free Direct Dehydroxytrifluoromethylthiolation of Alcohols via the Umpolung Reactivity of Trifluoromethanesulfenamides

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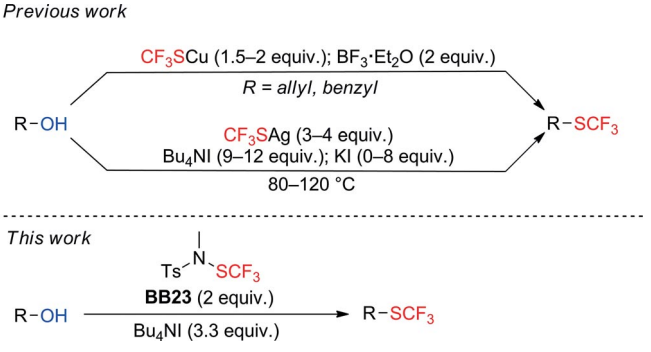
Abstract: A direct dehydroxytrifluoromethylthiolation of alcohols with trifluoromethanesulfenamide has been described. This method, based on the original umpolung reactivity of trifluoromethanesulfenamides, proposes a direct "OH-SCF_3 exchange" under mild and, more especially, metal-free conditions.

Introduction

Because fluorinated compounds are more and more used in various fields of applications,[1] new methods to introduce fluorinated groups into organic molecules are highly desirable.[2] The trifluoromethylthio group has attracted particular attention, notably due to its specific electronic properties (Hammett constants σ_p = 0.50, σ_m = 0.40; Swain–Lupton constants F = 0.36, R = 0.14)[3] and its high lipophilicity (Hansch parameter π_R = 1.44).[4] In the last years, growing efforts have been made to develop efficient reagents and strategies to synthesize trifluoromethylthiolated molecules, with a particular focus on direct approaches using "CF_3S-donor reagents".[2f,5] Many of these methods are based on the nucleophilic substitution of various leaving groups.[5f] However, due to the wide availability of alcohols, a direct "OH-SCF_3 exchange", without prefunctionalization, could constitute a pertinent strategy. Nevertheless, despite such an interest, only two methods have dealt with this direct transformation of a hydroxyl group to a CF_3S moiety, that is, dehydroxytrifluoromethylthiolation reactions. A Lewis acid mediated strategy has been recently developed, it uses an excess amount of CF_3SCu as trifluoromethylthiolating reagent.[6] However, this approach is limited to allylic and benzylic substrates and requires an excess amount of Lewis acid, which could limit the functional-group tolerance. In the same time, an elegant approach using CF_3SAg has been proposed.[7] In this strategy, the trifluoromethylthiolating reagent, in excess, acts both as activating reagent for the alcohol, through the functionalization of the OH group with difluorothiophosgene arising from the decomposition of CF_3SAg, and as CF_3S^- donor to perform the nucleophilic substitution. The scope of this reaction appears the most extended. However, if these two approaches are efficient, the use of an excess amount of metal, inherent to the structure of the used trifluoromethylthiolating reagents, constitutes a major drawback (Scheme 1).



Scheme 1. Different strategies for direct "OH-SCF_3 exchange".

Results and Discussion

We have recently demonstrated the Janus faces of trifluoromethanesulfenamide (**BB23**), which can release the CF_3S^- anion under simple iodide activation.[8] Consequently, this reagent could constitute a valuable metal-free alternative to the CF_3S–metal reagents generally used. Hence, a direct dehydroxytrifluoromethylthiolation, based on Qing's strategy,[7] was envisaged.

Inspired by our previously described results,[8] the reaction conditions were optimized with benzyl alcohol (**1a**) (Table 1).

Good yields were already obtained with 2 equiv. of **BB23** and 2.2 equiv. of Bu_4NI (entry 1). An excess amount of Bu_4NI (3.3 equiv.) slightly improved yield (entry 2). Furthermore, increasing the reaction temperature to 60 °C led to excellent results (entry 3). Afterwards, solvents other than acetone were evaluated under the optimal conditions without success, regardless of their polarity (entries 4–11).

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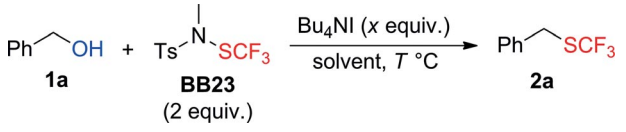
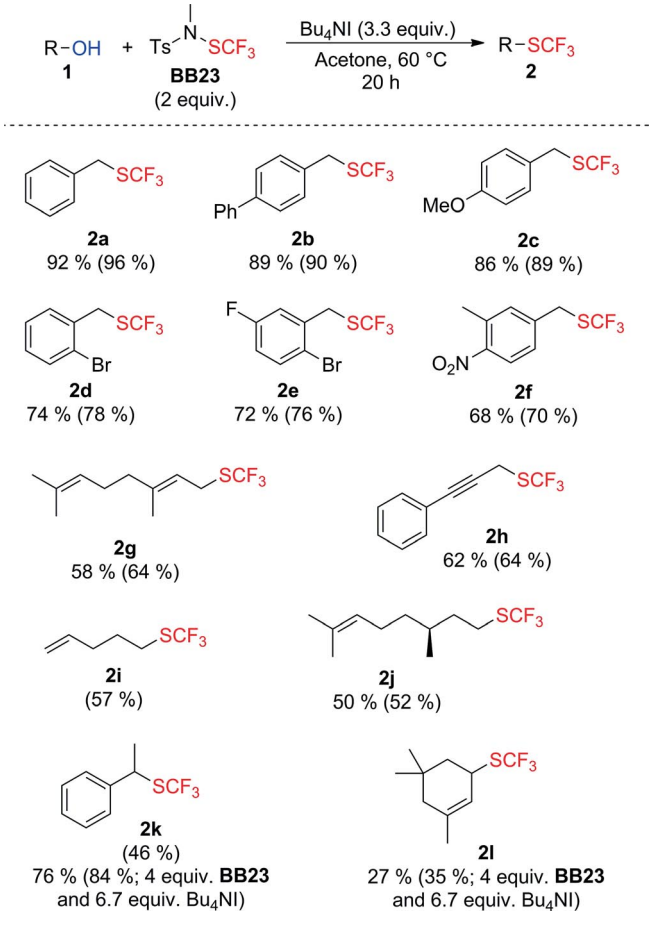
Table 1. Reaction between **BB23** and benzyl alcohol.



Entry	Bu_4NI [equiv.]	Solvent	T [°C]	**2a** [%][a]
1	2.2	acetone	40	80
2	3.3	acetone	40	85
3	3.3	acetone	60	96
4	3.3	CH_3CN	60	64
5	3.3	CH_3CN	80	60
6	3.3	THF	60	58
7	3.3	Diglyme	60	53
8	3.3	Toluene	60	48
9	3.3	DMF	60	56
10	3.3	DMSO	60	50
11	3.3	H_2O	60	36

[a] Yields as determined by ^{19}F NMR spectroscopy by using $PhOCF_3$ as an internal standard.

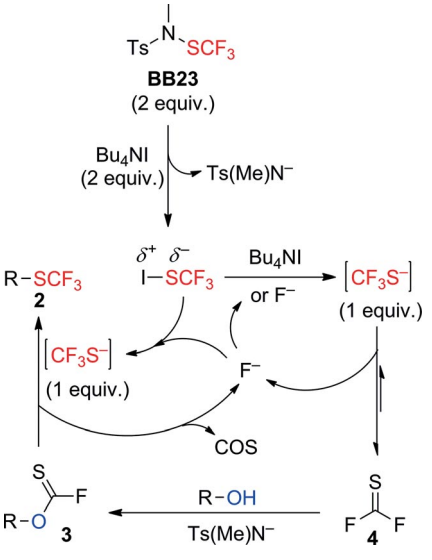
With optimal conditions in hand (entry 3), various alcohols were engaged (Scheme 2). In general, the reaction gave satisfactory to excellent yields. In the benzylic series, good yields were obtained, regardless of the substituents. Indeed, electron donors or acceptors led to similar results. The position of the substituents also does not seem to have significant effects. Allylic and propargylic alcohols provided the corresponding trifluoromethyl sulfides but with lower yields than benzylic alcohols. Less reactive primary aliphatic alcohols also reacted, but only medium yields were then observed.



Scheme 2. Dehydroxytrifluoromethylthiolations of alcohols. Yields shown are those of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy by using $PhOCF_3$ as an internal standard.

However, the reaction appears to be sensitive to steric hindrance, because only medium yield was observed with 1-phenylethan-1-ol (**1k**). By doubling the amount of trifluoromethylthiolating reagent, good results were then obtained. We can suppose that steric hindrance disfavors the nucleophilic attack compared to the collapse of the intermediate CF_3S^- species into difluorothiophosgene (**4**). The excess amount of reagent used contributes to increase the amount of CF_3S^- anion in the solution and, thus, favors substitution against the degradation. This deleterious steric effect is more crucial with very hindered secondary cyclic alcohol **1l**, with which only modest yields were obtained, even with an excess amount of reagent **BB23**.

From a mechanistic point of view, in the presence of Bu_4NI, the **BB23** reagent forms the CF_3SI species presenting a reverse sulfur polarity,[9] as described previously.[8] This transient species can, then, be activated by iodide or fluoride anions to generate the CF_3S^- anion. This last intermediate partly collapses into difluorothiophosgene (**4**) which can, then, form carbonofluoridothioate **3**, as described previously by Qing et al.[7] The non-degraded CF_3S^- anion can substitute compound **3** to provide the expected trifluoromethylthiolated products **2** (Scheme 3). This intermediate formation of **3** from alcohols has been confirmed by the identification of the compound **3l** in the reaction medium.



Scheme 3. Mechanistic proposal.

In this mechanism proposal (Scheme 3), only 2.2 equiv. of Bu_4NI should be sufficient, as confirmed by the good results already obtained under these conditions (Table 1 – entry 1). However, the better yield observed with 3.3 equiv. of Bu_4NI can be rationalized by the better activation of CF_3SI by iodide than by fluoride, due to a more favorable soft–soft (iodine–iodine) interaction with iodide than the soft–hard (iodine–fluorine) in-

teraction with fluoride. It is noteworthy that no monofluorinated side-products (R–F) have been detected.

Conclusions

Direct dehydroxytrifluoromethylthiolation is a valuable strategy to obtain, rapidly, various trifluoromethylthiolated compounds, avoiding the preliminary transformation of the OH group into a leaving group. The described strategy proposes mild and metal-free conditions, which offer an advantage over the few previously reported methods. Furthermore, this work has confirmed that trifluoromethanesulfenamide reagents constitute a very valuable alternative to generate the CF_3S^- anion and efficiently perform nucleophilic trifluoromethylthiolation without use of any metals. These results reaffirm the "universal reagent" status of trifluoromethanesulfenamides and reinforce their position in the fluorine chemistry toolbox.

Experimental Section

To a flask equipped with a magnetic stirrer were added alcohol **1** (0.3 mmol), trifluoromethanesulfenamide **BB23** (0.60 mmol, 2 equiv.), Bu_4NI (1 mmol, 3.3 equiv.), and acetone (1 mL). The reaction mixture was stirred for 20 h at 60 °C. Conversion was checked by ^{19}F NMR spectroscopy by using $PhOCF_3$ as internal standard. The reaction mixture was partitioned between pentane and water. The aqueous layer was extracted with pentane, and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated to dryness (under moderate vacuum, 800 mbar, at 40 °C). The crude residue was purified by flash chromatography to afford the desired product.

Acknowledgments

We thank the Centre National de la Recherche Scientifique (CNRS) and the French Ministry of Research for their financial support. We also thank the French Fluorine Network for its support.

Keywords: Fluorine · Trifluoromethylthiolation · Alcohols · Nucleophilic substitution · Dehydroxytrifluoromethylthiolation

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Received: February 22, 2016
Published Online: April 5, 2016