Trifluoromethylthiolation

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Base-Catalyzed Electrophilic Trifluoromethylthiolation of Terminal Alkynes**

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Because of its intrinsic properties, and more particularly its high lipophilicity,[1] the trifluoromethanesulfenyl group (CF_3S) is of considerable interest for the design of bioactive compounds, in particular in medicinal chemistry and agrochemistry.[2] Indeed, it is now accepted that incorporation of this CF_3S moiety onto organic molecules greatly contributes to enhancing their transmembrane permeation, thus increasing their biodisponibility.[3]

Numerous methods to introduce this group onto organic substrates are described in the literature.[4] They typically involve halogen–fluorine exchange reactions, often under harsh conditions,[5] or the trifluoromethylation of sulfur-containing compounds.[6–8] However, both of these methods require the preliminary preparation of the precursors.

A more elegant approach is the trifluoromethylthiolation of substrates by the direct formation of a C–SCF_3 bond.[9] In recent years, several elegant nucleophilic strategies have emerged using stabilized forms of the unstable CF_3S anion.[10,11] However, these transition-metal-catalyzed methods are based on the use of reagents which, generally, are not very stable and must be prepared before utilization, and could require stoichiometric amounts of metal.[10] Qing et al., inspired by the previous works of Kirsch et al.,[12a] have circumvented the drawback of the instability of "CF_3S^-" species by generating it in situ from the Ruppert reagent and S_8.[12b] Nevertheless, all of these reactions are restricted to the formation of C_{sp^2}–SCF_3 bonds, and, in general, with aromatic substrates, starting from boronic or halogenated derivatives. Direct electrophilic trifluoromethylthiolation reactions are less developed because of the lack of efficient reagents. Although gaseous CF_3SCl has been used to react with some nucleophiles,[4a,13] its high toxicity constitutes a real limitation to its convenient use. Recently, three new reagents have been described for efficient electrophilic trifluoromethylthiolation.[10] Some sulfenylation reactions of sp^2 aromatic C–H bonds have been performed by employing the commercially available, but expensive, reagent, CF_3SSCF_3.[14] However, only one CF_3S moiety of the reagent is consumed. Inspired by the Togni reagent, a trifluoromethylthiolated hypervalent iodine reagent has been described and has been shown to have interesting reactivity.[15] However, its synthesis appears to be not so easy to perform and its stability seems limited. Furthermore, the recent emphasis on the explosive character of trifluoromethylated hypervalent iodine reagents[16] suggests that such a derivative may pose a similar danger. Finally, stable trifluoromethanesulfenamides have also demonstrated their potential in electrophilic trifluoromethylthiolation reactions of various classes of compounds.[17]

Surprisingly, among all of these recent efficient methods, the construction of C_{sp}–SCF_3 bonds has, to date, been rarely described,[10] despite the fact that alkynes constitute very valuable building blocks for the synthesis of various molecules, in particular in medicinal chemistry,[18] and are involved in the development of click chemistry.[19]

Qing et al. have performed the oxidative trifluoromethylthiolation of terminal alkynes using their CF_3TMS and S_8 system, which requires an excess of the expensive Ruppert reagent.[20] For their part, Shen et al. have applied their trifluoromethylthiolated hypervalent iodine reagent to copper-mediated coupling reactions with a few terminal alkynes under basic conditions. However, this method requires an excess (2 equiv) of alkynes.[15] In each case, mainly aromatic alkynes were used. We have also recently described the trifluoromethylthiolation of lithium alkynides with trifluoromethanesulfenamide **1a**.[17b]

However, all of these methods require basic conditions (excess of KF, K_2CO_3, or organolithium reagents), which could be incompatible with some of the trifluoromethylthioethers obtained, owing to the high acidic character of protons in the α position of the CF_3S group. We observed this drawback with the trifluoromethylthiolation of but-3-yn-1-ylbenzene (**2f**) which led to low yields. Furthermore, degradation of the resulting trifluoromethylthioether **3f** under the basic reaction conditions has been observed.[17b] This same reason could reasonably explain the low yields obtained under the conditions used by Qing et al.[20]

When the trifluoromethylthiolation of lithium alkynides is performed with trifluoromethanesulfenamide **1a**, a lithium amide (Li-**1a**) is generated. Because the pKa of such an anion is around 31 and the pK_a of terminal alkynes is around 29,[21] the amide Li-**1a** could generate lithium alkynides by deprotonation of terminal alkynes. In this way, the formation of

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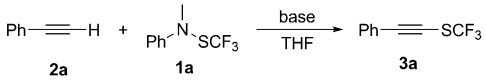
Table 1: Conditions for the trifluoromethylthiolation of **2a** with **1a**.



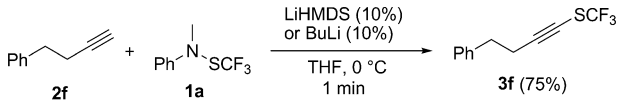
Entry	Base (mol%)	T [°C]	t	Yield of **3a** [%][a]
1	BuLi (10)	−40	3 h	81
2	LiHMDS (10)	−40	3 h	85
3	BuLi (10)	0	3 h	84
4	LiHMDS (10)	0	3 h	85
5	BuLi (5)	0	3 h	54
6	LiHMDS (5)	0	3 h	60
7	BuLi (10)	20	3 h	80
8	LiHMDS (10)	20	3 h	82
9	LiHMDS (10)	0	30 min	87
10	LiHMDS (10)	0	1 min	89
11	BuLi (10)	0	1 min	88
12	LDA (10)	0	1 min	90

[a] Yield of unisolated product, as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

a C_{sp}–SCF_3 bond should be performed only with a catalytic amount of base to generate the first lithium species (Table 1).

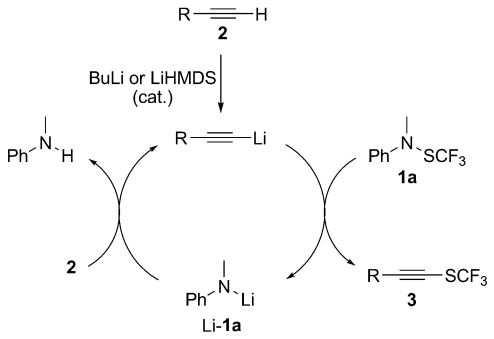
As expected, with only a 10 mol% loading of lithiated base, the expected product **3a** was obtained with good yield. The nature of the initial base does not play an important role, as similar results were observed with BuLi, lithium hexamethyldisilazide (LiHMDS), or lithium diisopropylamine (LDA). Whereas a 5 mol% loading of base give satisfactory yields (Table 1, entries 5–6), the use of 10 mol% appears to be optimal (entries 3–4). The influence of temperature is also negligible, as comparable results were obtained from −40 °C to 20 °C (entries 1–8), although the best yields were observed at 0 °C. A kinetic study (entries 2, 9, 10) has shown that this reaction is very rapid, as total conversion and excellent yields were obtained in 1 min (entries 10–12). This certainly constitutes the fastest trifluoromethylthiolation of terminal alkynes.

Under these conditions, the amount of base remains low and should be compatible with compounds sensitive to basic conditions. To confirm this hypothesis, but-3-yn-1-ylbenzene (**2f**) which gave rise to low yields under stoichiometric conditions was tested in these catalytic conditions (Scheme 1).

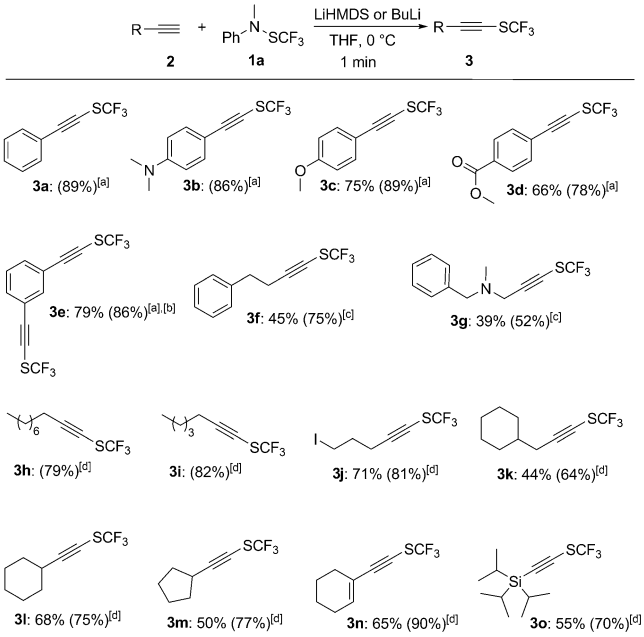


Scheme 1. Trifluoromethylthiolation of **2f**.

As hypothesized, the expected product **3f** was obtained with good yield. However, when LiHMDS was used, degradation of **3f** was observed over the time in the reacting mixture; this is certainly due to the basic character of the HMDS generated during the reaction. With the use of BuLi, which generates butane, no degradation of **3f** was noticed. The following mechanism shown in Scheme 2 could thus be envisaged for this trifluoromethylthiolation of terminal



Scheme 2. Mechanism for the base-catalyzed trifluoromethylthiolation of terminal alkynes with **1a**.

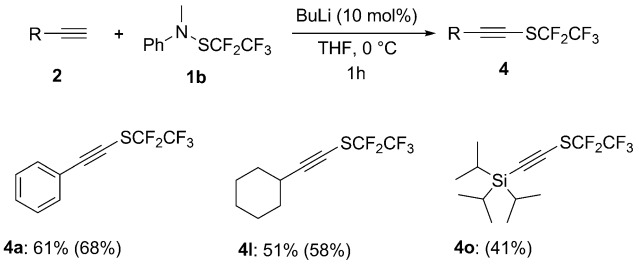


Scheme 3. Synthesis of trifluoromethylthioethers from **1a** and **2**. [a] LiHMDS (10 mol%). [b] with **1a** (2 equiv). [c] BuLi (10 mol%). [d] LiHMDS (20 mol%). Yields shown are of isolated products; values in parentheses are yields of unisolated products, as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

alkynes. These conditions have been extended to other terminal alkynes **2** as well (Scheme 3).

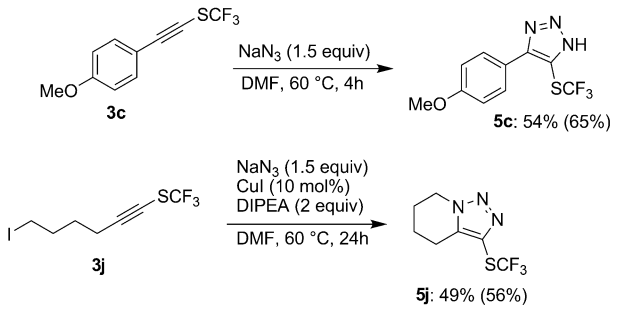
The reaction gives good to excellent yields. Because of the high reactivity of lithium species, the reaction is highly sensitive to moisture and consequently has to be conducted under dry conditions in an inert atmosphere. Because of the well-known volatility of trifluoromethylthiolated compounds, yields of isolated product are often lower than the conversion (as determined by titration). A wide range of functional groups are compatible with the reaction conditions, even ones which are base sensitive. Aromatic or aliphatic alkynes give similar results. However, because of the more basic character of aliphatic alkynides and, consequently, their higher sensitivity to moisture, a loading of 20 mol% of LiHMDS is recommended to favor the catalytic cycle (ca. 55% yield was obtained with only 10 mol%). As previously observed, in the

case of products that are very sensitive to basic conditions, BuLi should be preferred to LiHMDS (products **3f–g**). In the case of the bis(alkynyl) compounds **2e**, using two equivalents of reagent **1a** favored the formation of the bis(CF_3S) product **3e**. With only one equivalent of **1a**, an inseparable mixture of mono and bis adducts (62:38) was observed. The silylated alkyne **2o** is also compatible with these reaction conditions and the product **3o** is a valuable fluorinated building block for further synthetic applications, for example, in the Sonogashira coupling, after desilylation. The possibility of extending this reaction to more fluorinated reagent has been also verified (Scheme 4).



Scheme 4. Synthesis of pentafluoroethylthioethers with **1b**. Yields shown are of isolated products; values in parentheses are yields of unisolated products, as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

Good yields of pentafluoroethylthiolated products were observed with aromatic, aliphatic, or silylated alkynes. Because of the higher steric hindrance of the pentafluoroethyl group, reagent **1** appeared less reactive and, consequently, 1 h (instead of 1 min.) was required to obtain good yields. This reaction constitutes, to our knowledge, one of the rare examples of the pentafluoroethylthiolation of terminal alkynes, which has otherwise only been described in three patents, and without clear explanations of the reaction.[22] To illustrate the high synthetic potential of these fluorinated building-blocks, two [3+2] cycloaddition reactions with azide have been performed (Scheme 5). These two examples gave rise to satisfactory, non-optimized, yields. In case of **3j**, a bicyclic core was obtained by a two-step, one-pot, process: [3+2] cycloaddition followed by intramolecular alkylation.



Scheme 5. [3+2] cycloaddition with trifluoromethylthioalkynes. Yields shown are of isolated products; values in parentheses are yields of unisolated products, as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. DIPEA = diisopropylethyl amine.

In conclusion, we have developed a base-catalyzed trifluoromethylthiolation of terminal alkynes using a stable and readily accessed trifluoromethanesulfenamide reagent. This method provides a simple and rapid synthesis of various alkynyl trifluoromethyl sulfides in mild conditions, using a very small amount of a common metal (Li), and is compatible with various functional groups. Furthermore, this strategy has been extended to pentafluoroethylthiolation, leading to relatively unexplored alkynyl pentafluoroethyl sulfides. Because of the high potential utility of such fluorinated alkynyl sulfides, as illustrated by two examples of 1,3-dipolar cyclization, this catalytic method employing valuable fluoroalkanesulfenamides should find application in various fields, and is already used in our laboratory for the design of fluorinated drugs that target the central nervous system.

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