Organometallic Chemistry

DOI: 10.1002/anie.201205156

Electrophilic Trifluoromethanesulfanylation of Organometallic Species with Trifluoromethanesulfanamides**

*François Baert, Julie Colomb, and Thierry Billard**

Dedicated to Dr. Bernard Langlois

More and more applications for fluorinated molecules are being found in various fields, in particular in the fields of medicinal chemistry and agrochemistry.[1] In recent years, there has been growing interest in the association of the trifluoromethyl group with heteroatoms such as CF_3O or CF_3S. The CF_3S moiety is of particular interest, because it has a high hydrophobicity parameter ($\pi_R = 1.44$).[2] Consequently, compounds bearing this group are potentially important targets for applications in pharmaceuticals and agrochemicals.[1e,3]

Numerous methods for the introduction of this group onto organic substrates are described in literature.[4] The main strategies are indirect methods, wherein the CF_3S moiety can be constructed from a precursor already present in the molecule by halogen–fluorine exchange reactions.[5] Another way is through the trifluoromethylation of sulphur-containing compounds. Examples include the nucleophilic[6] and radical trifluoromethylation[7] of disulfides, thiocyanates, and thiols, as well as the electrophilic trifluoromethylation of thiolates.[8] Such strategies may be of interest, but require the preparation of sulfur-precursors, must be fluorinated or trifluoromethylated.

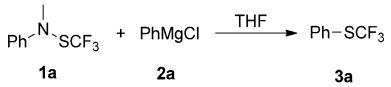
A more elegant approach is the direct trifluoromethanesulfanylation of substrates. However, this method is still limited. Some radical and electrophilic reactions have been performed with CF_3SCl.[9] However, this species is gaseous and highly toxic. Some nucleophilic reactions have previously been realized through the use of stabilized forms of the unstable CF_3S anion, but apart from CF_3SCu the reactivity of these species is relatively limited;[10] such reagents are generally not stable enough to be stored for extended periods. Most recently, metal-catalyzed coupling reactions with CF_3SAg[11] or CF_3SNMe_4[12] have been described. However, the reagents are not very stable and must be prepared before use. Qing et al. have circumvented this main drawback by generating the CF_3SCu reagent in situ from Ruppert's reagent, S_8 and copper salts.[13] Nevertheless, these recent direct trifluoromethanesulfanylations are essentially limited to aromatic compounds. Furthermore, whereas researchers have shown renewed interest in nucleophilic strategies,[11–13] electrophilic methods remain underdeveloped.

We have, recently, described an easy synthesis of a family of reagents that are stable and easy to handle, namely the trifluoromethanesulfanamides.[14] These reagents have already demonstrated their potential in the electrophilic trifluoromethanesulfanylations of alkenes, alkynes,[15a] and electron-rich aromatic compounds.[15b]

Herein, we will extend the application of these reagents to organometallic nucleophiles. In previous papers, the use of Lewis or protic acids has been required to activate the trifluoromethanesulfanamides.[15] However, when the same strategy (with $BF_3{\cdot}Et_2O$ as an activator) has been applied to the reaction of **1a** and phenylmagnesium chloride (**2a**), no reaction was been observed. This was probably due to reaction between the Grignard reagent and the Lewis acid. Supposing that magnesium could play the role of a Lewis acid, the same reaction was performed without additional activator (Table 1).

With this change, the expected product **3a** was obtained in good yield, but with a long reaction time at 13 °C (entries 1 and 2). Increasing the temperature appears to be deleterious for the reaction, probably owing to the thermal degradation of a reaction intermediate. To increase the kinetic reaction, the reacting medium was concentrated. Although temper-

Table 1: Conditions for trifluoromethanesulfanylation of **2a** with **1a**.



1a **2a** **3a**

Entry	[**2a**][a]	*T* [°C]	*t* [h]	**3a** [%][b]
1	0.4	13[c]	3	50
2	0.4	13[c]	31	77[e]
3	0.4	21	8	30[e]
4	0.4	60	4	6[e]
5	2.0	21	8	54[e]
6	2.0	0	3.5	73
7	2.0	0	6	83[e]
8	2.0	0→20[d]	3	86[e]

[a] Final concentration [mol L^{-1}]. [b] Crude yield, as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [c] Ambient temperature in winter. [d] 0 °C for 10 min. then 20 °C. [e] No further reaction progress.

[*] F. Baert, J. Colomb, Dr. T. Billard
Institute of Chemistry and Biochemistry (ICBMS—UMR CNRS 5246) Université de Lyon, Université Lyon 1, CNRS
43 Bd du 11 novembre, 69622 Lyon (France)
E-mail: thierry.billard@univ-lyon1.fr
J. Colomb, Dr. T. Billard
CERMEP—in vivo imaging, Groupement Hospitalier Est
59 Bd Pinel, 69003 Lyon (France)

[**] We thank the CNRS and the Région Rhône-Alpes for their financial support. The French Fluorine Network is also thanked for its support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201205156.

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

ature seems to be deleterious (entry 4), good yields are obtained in a reasonable time at 0 °C (entries 6 and 7). It was noticed that low temperature is crucial only at the time of **2a** addition, afterwards the reaction can be run at 20 °C to achieve a good yield in a short time (entry 8). These optimized conditions have been extended to other Grignard reagents **2** as well (Figure 1).

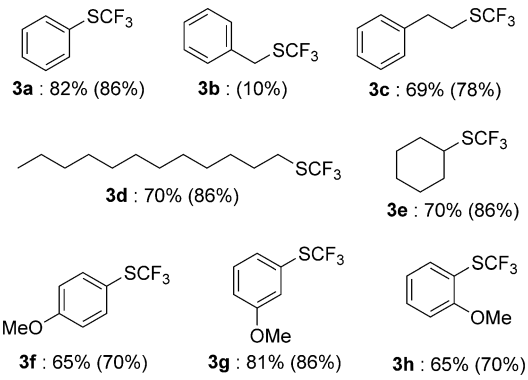
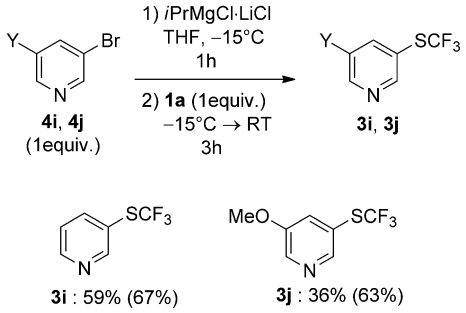


Figure 1. Synthesis of trifluoromethylthioethers from **1a** and **2**. Yields shown are of isolated products; numbers in parentheses are crude yields determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

In general, the reaction gives good yields for aromatic compounds. In the case of **3f** and **3h**, the reactions were slower (an overnight reaction time was required for total conversion). The difference in kinetics could be rationalized by electronic effects. Indeed, in the ortho and para positions, the methoxy group is an electron donor and so contributes to diminishing the electronic density on Mg and, thus, its Lewis acidity. For **3h**, steric hindrance in the ortho position must also play an important role. In the case of **3g**, MeO is electron-withdrawing in the meta position, and so enhances the Lewis acidity of Mg. Good results were also obtained with aliphatic reagents, even with a sterically hindered cyclohexyl group (**3e**). In the case of a benzylic compound (**3b**), the low yield observed could come from a decomposition of **3b** under the basic reaction conditions, by deprotonation of the acidic benzylic protons in the position α to the SCF_3 group.

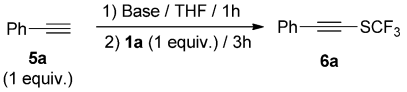
Starting from bromo derivatives **4f,g**, the corresponding Grignard reagents were generated in situ using Turbo-Grignard, as described by Knochel et al.[16] Then the trifluoromethanesulfanamide **1a** was added to provide the expected trifluoromethylthioethers **3f,g** in satisfactory yields (Scheme 1). In the case of **3g**, the modest yield of isolated product comes from the difficulty of separating **3g** from the residual starting material, **4g**.

The reaction between **1a** and deprotonated terminal alkynes has also been envisaged (Table 2). After deprotonation with butyllithium, phenylacetylene reacted with **1a** to provide the expected product **6a** in satisfactory yield. Because of the thermal sensitivity of the alkynyl anion, better yield was obtained by performing the reaction at −78 °C (entries 1 and 2). Phenylacetylene (**5a**) can also be deprotonated with sodium hexamethyldisilazide (NaHMDS), however, a lower



Scheme 1. Reaction of **1a** with Grignard reagents preformed in situ. Yields shown are of isolated products; numbers in parentheses are crude yields determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

Table 2: Conditions for trifluoromethanesulfanylation of **5a** with **1a**.



Entry	T [°C]	Base	**6a** [%][a]
1	−78→RT[b]	BuLi	49
2	−78	BuLi	73
3	−78	NaHMDS	58

[a] Crude yield, as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] Deprotonation conducted at −78 °C; reaction run at RT after the addition of **1a**. NaHMDS = sodium hexamethyldisilazide.

yield was observed. This can be rationalized by the lower Lewis acidity of Na, which, consequently, cannot activate **1a** as well as Li can.

In general this method furnishes satisfactory results with aromatic or aliphatic substrates (Figure 2). The commercially available organolithium reagents, which did not need to be preformed, also react with **1a** to give modest to satisfactory yields (**3k**,**l**; volatile products), even with a hindered *tert*-butyl derivative (**3l**; overnight reaction). Surprisingly, product **6b** seems to degrade in the basic medium, as previously observed

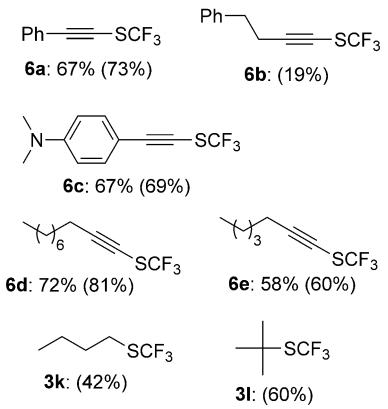


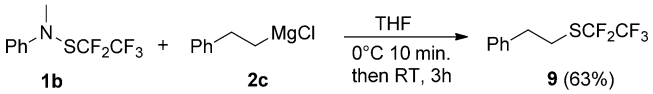
Figure 2. Synthesis of trifluoromethylthioethers **6**. Yields shown are of isolated products; numbers in parentheses are crude yields determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

with **3b**. The formation of **6b** has been tested with LiHMDS as a base instead of BuLi, however, the results s were not reproducible (yields varied between 11% and 40%). These results suggest that **6b** is very sensitive to basic conditions and begins to decompose as soon as it is formed.

The reaction between **1a** and the organozinc reagents Et_2Zn and $EtO_2C(CH_2)_2ZnBr$ has also been tested, but without success. This could be explained by the lower reactivity of organozinc reagents and the poor Lewis acidity of zinc. Furthermore, the possibility of extending this reaction to more fluorinated reagent has been verified. Grignard reagent **2c** reacts with pentafluoromethanesulfanamide **1b**[14] to give the corresponding pentafluoroethylthioether **9** in satisfactory yield (Scheme 2). This result suggests that **1b** and **1a** are similarly reactive.



Scheme 2. Synthesis of a pentafluoroethylthioether with **1b**.

In conclusion, we have demonstrated that trifluoromethanesulfanamides (**1**) easily react with organometallic species such as Grignard or organolithium reagents. These results extend the applications of this new family of reagents, which more and more appears to be a valuable alternative to CF_3SCl for trifluoromethanesulfanylation reactions. Furthermore, their easy handling makes them accessible to the broad community of synthetic chemists who are not organofluorine specialists.

Received: July 2, 2012
Revised: July 31, 2012
Published online: ■■ ■■, ■■■■

Keywords: fluorine · grignard reaction · trifluoromethanesulfanamide · trifluoromethanesulfanylation · trifluoromethylthioether

[1] a) *Bioorganic and Medicinal Chemistry of Fluorine* (Eds.: J.-P. Begue, D. Bonnet-Delpon), Wiley, Hoboken, **2008**; b) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**; c) J. D. Dunitz, *ChemBioChem* **2004**, *5*, 614 – 621; d) J. C. Biffinger, H. W. Kim, S. G. DiMagno, *ChemBioChem* **2004**, *5*, 622 – 627; e) A. Becker, *Inventory of Industrial Fluoro-Biochemicals*, Eyrolles, Paris, **1996**; f) P. Jeschke, *ChemBioChem* **2004**, *5*, 570 – 589; g) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886; h) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; i) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369.

[2] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165 – 195.

[3] a) B. R. Langlois, T. Billard, S. Large, N. Roques, *Fluorinated Bio-active Compounds*, Fluorine Technology, Cheshire, **1999**, Paper 24; b) J. Szmuszkovicz, *J. Med. Chem.* **1966**, *9*, 527 – 536; c) S. C. Cherkofsky (Du Pont de Nemours), US 4267184, **1981** [*Chem. Abstr.* 95:61982].

[4] J. T. Welch, S. Turner-McMullin in *Chemistry of Organic Fluorine Compounds II. A Critical Review* (Eds.: M. Hudlicky, A. E. Pavlath), American Chemical Society, Washington, DC, **1995**, pp. 545 – 614.

[5] a) J. Swarts, *Bull. Acad. R. Med. Belg.* **1892**, *24*, 309; b) L. M. Yagupolskii, M. S. Marenets, *Zh. Obshch. Khim.* **1959**, *29*, 278 – 283; c) O. Scherer, *Angew. Chem.* **1939**, *52*, 457 – 459; d) B. Langlois, M. Desbois, *Ann. Chim. Farm.* **1984**, 729 – 741; e) R. Janin, L. Saint-Jalmes (Rhône – Poulenc), EP 96400375, **1996** [*Chem. Abstr.* 125:246885]; f) T. Umemoto, S. Ishihara, M. Harada (Daikin), JP 97207900, **1999** [*Chem. Abstr.* 130:209495].

[6] a) W. R. Dolbier, Jr., C. Pooput, M. Médebielle, *Org. Lett.* **2004**, *6*, 301 – 303; b) S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848 – 8856; c) B. Quiclet-Sire, R. N. Saisic, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 9057 – 9058; d) T. Billard, B. R. Langlois, G. Blond, *Tetrahedron Lett.* **2001**, *42*, 2473 – 2475; e) T. Billard, B. R. Langlois, *Tetrahedron Lett.* **1996**, *37*, 6865 – 6868; f) T. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65 – 68.

[7] a) R. N. Haszeldine, R. B. Rigby, A. E. Tipping, *J. Chem. Soc. Perkin Trans. 1* **1972**, 2180 – 2182; b) L. Z. Gandel'sman, V. N. Boiko, *Ukr. Khim. Zh. (Russ. Ed.)* **1977**, *43*, 1224 – 1225 [*Chem. Abstr.* 88:89253]; c) V. N. Boiko, G. M. Shchupak, N. V. Ignat'ev, L. M. Yagupolskii, *Zh. Org. Khim.* **1979**, *15*, 1245 – 1253 [*Chem. Abstr.* 91:157378]; d) V. Soloshonok, V. Kukhar, Y. Pastrait, V. Nazaretian, *Synlett* **1992**, 657 – 659; e) V. I. Popov, V. N. Boiko, L. M. Yagulpolskii, *J. Fluorine Chem.* **1982**, *21*, 365 – 369; f) V. G. Koshechko, L. A. Kiprianova, L. I. Fileleeva, *Tetrahedron Lett.* **1992**, *33*, 6677 – 6678; g) C. Wakselman, M. Tordeux, *J. Chem. Soc. Chem. Commun.* **1984**, 793 – 794; h) C. Wakselman, M. Tordeux, *J. Org. Chem.* **1985**, *50*, 4047 – 4051; i) C. Wakselman, M. Tordeux, J. L. Clavel, B. Langlois, *J. Chem. Soc. Chem. Commun.* **1991**, 993 – 994; j) M. Tordeux, C. Wakselman, B. Langlois, *J. Org. Chem.* **1989**, *54*, 2452 – 2453; k) J. L. Clavel, B. Langlois, E. Laurent, N. Roidot, *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *59*, 463 – 466; l) B. Langlois, N. Roidot, D. Montègre, *J. Fluorine Chem.* **1994**, *68*, 63 – 66; m) B. Langlois, T. Billard, N. Roques, *J. Org. Chem.* **1999**, *64*, 3813 – 3820.

[8] a) I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem.* **2007**, *119*, 768 – 771; *Angew. Chem. Int. Ed.* **2007**, *46*, 754 – 757; b) L. M. Yagupolskii, N. V. Kondratenko, G. N. Timofeeva, *Zh. Org. Khim.* **1984**, *20*, 115 – 118 [*Chem. Abstr.* 100:191494]; c) T. Umemoto, S. Ishihara, *Tetrahedron Lett.* **1990**, *31*, 3579; d) T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, *115*, 2156 – 2164.

[9] a) J. F. Harris, F. W. Stacey, *J. Am. Chem. Soc.* **1961**, *83*, 840 – 845; b) J. F. Harris, *J. Am. Chem. Soc.* **1962**, *84*, 3148 – 3153; c) J. F. Harris, *J. Org. Chem.* **1966**, *31*, 931 – 935; d) W. Sheppard, S. Andreades, J. F. Harris, *J. Org. Chem.* **1964**, *29*, 898 – 900; e) J. Ippen, B. Baasner, A. Marhold, E. Kysela, S. Dutzmann, P. Reinecke (Bayer A.G.), DE 3836161, **1990** [*Chem. Abstr.* 113:167366]; f) W. A. Sheppard, *J. Org. Chem.* **1964**, *29*, 895 – 898; g) K. Sivasankaran, K. S. Rao, K. R. Ratnam, M. S. Mithyantha, K. S. Bhat (Rallis India), IN 178903, **1997** [*Chem. Abstr.* 140:375162]; h) S. C. Cherkofsky (Du Pont de Nemours), US 80159236, **1981** [*Chem. Abstr.* 96:104081]; i) K. Bogdanowicz-Szwed, B. Kawalek, M. Lieb, *J. Fluorine Chem.* **1987**, *35*, 317 – 327; j) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, W. G. Wagner, H. D. Durst, *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 1021 – 1031; k) A. Haas, U. Niemann, *Chem. Ber.* **1977**, *110*, 67 – 77.

[10] a) E. H. Man, D. D. Coffmann, E. L. Muetterties, *J. Am. Chem. Soc.* **1959**, *81*, 3575 – 3577; b) G. A. R. Brandt, H. J. Emeléus, R. N. Haszeldine, *J. Chem. Soc.* **1952**, 2198 – 2205; c) J. F. Harris, *J. Org. Chem.* **1967**, *32*, 2063 – 2074; d) A. Haas, W. Hinsken, *J. Fluorine Chem.* **1985**, *28*, 303 – 317; e) H. J. Emeléus, D. E. McDuffie, *J. Chem. Soc.* **1961**, 2597 – 2599; f) L. M. Yagulpolskii, O. D. Smirnova, *Zh. Org. Khim.* **1972**, *8*, 1990 – 1991 [*Chem. Abstr.* 78:15699]; g) N. V. Kondratenko, V. P. Sambur, *Ukr. Khim. Zh.* **1975**, *41*, 516 – 519 [*Chem. Abstr.* 83:58321]; h) M.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Hanack, A. Khünle, *Tetrahedron Lett.* **1981**, *22*, 3047 – 3048; i) D. J. Adams, J. H. Clark, *J. Org. Chem.* **2000**, *65*, 1456 – 1460; j) L. M. Yagulpolskii, N. V. Kondratenko, V. P. Sambur, *Synthesis* **1975**, 721 – 723; k) L. M. Yagulpolskii, N. V. Kondratenko, A. A. Kolomeitsev, V. I. Popov, *Synthesis* **1985**, 667 – 669; l) J. H. Clark, C. W. Jones, A. P. Kybett, M. A. Mc Clinton, J. M. Miller, D. Bishop, R. J. Blade, *J. Fluorine Chem.* **1990**, *48*, 249 – 253; m) D. Remy, K. E. Rittle, C. A. Hunt, M. B. Freedmann, *J. Org. Chem.* **1976**, *41*, 1644 – 1646; n) W. Tyrra, D. Naumann, B. Hoge, Y. L. Yaguploskii, *J. Fluorine Chem.* **2003**, *119*, 101 – 107; o) J. H. Clark, H. Smith, *J. Fluorine Chem.* **1993**, *61*, 223 – 231.

[11] G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450 – 7452; *Angew. Chem. Int. Ed.* **2011**, *50*, 7312 – 7314.

[12] C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183 – 185.

[13] C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem.* **2012**, *124*, 2542 – 2545; *Angew. Chem. Int. Ed.* **2012**, *51*, 2492 – 2495.

[14] A. Ferry, T. Billard, B. R. Langlois, E. Bacque, *J. Org. Chem.* **2008**, *73*, 9362 – 9365.

[15] a) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem.* **2009**, *121*, 8703 – 8707; *Angew. Chem. Int. Ed.* **2009**, *48*, 8551 – 8555; b) A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160 – 163.

[16] A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396 – 3399; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333 – 3336.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

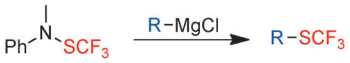
These are not the final page numbers!

Communications

Organometallic Chemistry

F. Baert, J. Colomb, T. Billard* ——— ▮▮▮▮–▮▮▮▮

Electrophilic Trifluoromethanesulfanylation of Organometallic Species with Trifluoromethanesulfanamides



It's so easy! Direct trifluoromethanesulfanylation reactions remain difficult to perform because of the lack of reagents which are stable and easy to handle. Trifluoromethanesulfanamides are reagents which, in combination with readily available Grignard reagents, can be used by those without experience in fluorine chemistry to easily synthesize trifluoromethylthioethers.

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim