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CF₃S-N bond formation under mild conditions. Easy access to trifluoromethanesulfenamides with a versatile reagent

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ABSTRACT

Trifluoromethanesulfenamides (CF₃SN-molecules) are interesting products for further applications. In particular, the presence of the CF₃SN group can contribute to increase their lipophilicity. The better way to obtain such products is the direct trifluoromethylthiolation of the corresponding amines. Herein, an efficient method under mild conditions (room temperature, iodide catalysis) is described to obtain the expected trifluoromethanesulfenamides in a late-stage functionalization. This method is based on the use of the reagent **BB23** (*N*-tosyl, *N*-methyltrifluoromethanesulfenamide), demonstrating the high versatility and polyvalence of this reagent in organofluorine chemistry. Some bioactive elaborated compounds were successfully functionalized.

1. Introduction

Due to the specific properties of the fluorine atom [1,2], fluorinated molecules have found many uses in the last decades in a wide range of applications from materials to life sciences [3–12]. In order to propose new molecules with new properties for targeted applications, the development of new fluorinated groups has been a dynamic research field these last years [13,14]. These new groups have allowed the improvement of specific properties. In particular, lipophilicity is an important targeted parameter to modify the physicochemical properties of molecules [15,16].

To achieve such an objective, the association of the CF₃ moiety with heteroatoms seemed to be a valuable strategy [13,14]. Some years ago, we have shown that the CF₃SN group possesses a high Hansch-Leo lipophilicity parameter which allows to increase the lipophilicity of compounds bearing this group (Table 1) [17].

Despite such interest in such CF₃SN-molecules, the main efficient synthetic approach to such compounds remains essentially the trifluoromethylthiolation of amines with a trifluoromethylthiolating reagent, as recently well reviewed in the literature (Scheme 1) [18].

Some years ago, we developed a family of reagents, namely the trifluoromethanesulfenamides, which are efficient to perform various trifluoromethylthiolations [19–21]. In particular, the **BB23** reagent (*N*-tosyl, *N*-methyltrifluoromethanesulfenamide) has emerged in recent

years as a highly versatile reagent in fluorine organic chemistry that can be used in a wide range of reactions [21].

The use of this reagent to form the CF₃S-N bond by trifluoromethylthiolation of amines has been briefly described previously, but required harsh conditions, requiring prior deprotonation of amines with BuLi (Scheme 1), which is not compatible with sensitive compounds [17,22].

In this context, in order to propose an easy and efficient access to CF₃SN-molecules under mild conditions and to continue to demonstrate the high versatility of the **BB23** reagent in fluorine chemistry, we decided to reinvestigate its ability to trifluoromethylthiolate amines.

2. Results and discussion

In our recent studies on the synthesis of thiocarbamoyl fluorides by reaction of **BB23** with amines in the presence of Bu₄NI [23], we observed the formation of the corresponding trifluoromethanesulfenamide (**2a**) as a by-product (Scheme 2). In this study, we hypothesized that the intermediate species CF₃SI, formed by the reaction of **BB23** with Bu₄NI [24], could react directly with amine to form the corresponding CF₃SN-product (**2a**) (Scheme 2).

Encouraged by this interesting result, we decided to delve into this side-reaction to determine the optimal conditions for obtaining the CF₃SN-product under milder conditions (Table 2).

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Table 1
Hansch-Leo lipophilicity parameter (π_R)
of fluorinated groups.

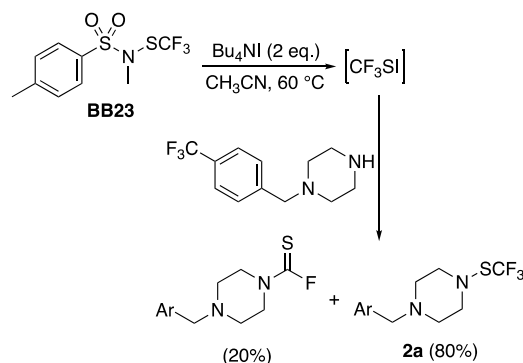
| Group | π_R |
|--------------------|---------|
| CF ₃ | 0.88 |
| CF ₃ O | 1.04 |
| CF ₃ S | 1.44 |
| CF ₃ Se | 1.61 |
| CF ₃ SN | 1.50 |

BB23 seemed to be able to react with the amine without the addition of Bu₄NI at 60 °C for 16 h (entry 1). At 20 °C, the yield was slightly lower (entry 2), but decreased significantly for only 1 h (entry 3). The use of 1 equivalent of Bu₄NI significantly improved the reaction (entry 4). To develop the mildest conditions, only catalytic amounts of Bu₄NI were considered (entries 5–10). With 0.1 equivalent the obtained yields remained good (entries 5–7), but a longer reaction time was required to obtain an excellent result (entry 7). The amount of Bu₄NI could also be reduced to 0.05 equivalent but with slower kinetics (entries 8–10). Good results were also obtained with Bu₄NCl (entry 11) or Bu₄NBr (entry 12), but with lower yields. Finally, alkaline sources of iodide anions can also be used (entries 13–14), but with also lower yields, probably due to lower solubility.

Therefore, the optimal conditions selected were 0.1 equivalent of Bu₄NI, at 20 °C for 16 h (entry 7).

These optimal conditions were then applied to various amines (Scheme 3).

The reaction gave good yields with aliphatic amines (**2a-c,i**), whereas only moderate to low yields were observed with aniline derivatives (**2d-e**). This could be explained by the lower nucleophilicity of anilines. Such a difference in reactivity favors the chemoselectivity of the reaction, as illustrated with compound **2f**, where only the aliphatic nitrogen was trifluoromethylthiolated in the presence of an aromatic nitrogen. Surprisingly, the reaction with tryptoline **1g** gave a mixture of mono- and bis-trifluoromethylthiolated products (ratio 58:42). A good yield of bis-trifluoromethylthiolated compound **2g** was obtained by using 2 equivalents of **BB23**. Contrary to aniline, the low nucleophilic aromatic nitrogen was able to react well under these conditions. This phenomenon was confirmed by the good yield obtained with indole **2h**.



Scheme 2. Formation of CF₃SN-product during the thiocarbonyl fluoride formation. Yields determined by ¹⁹F NMR spectroscopy with PhCF₃ as internal standard.

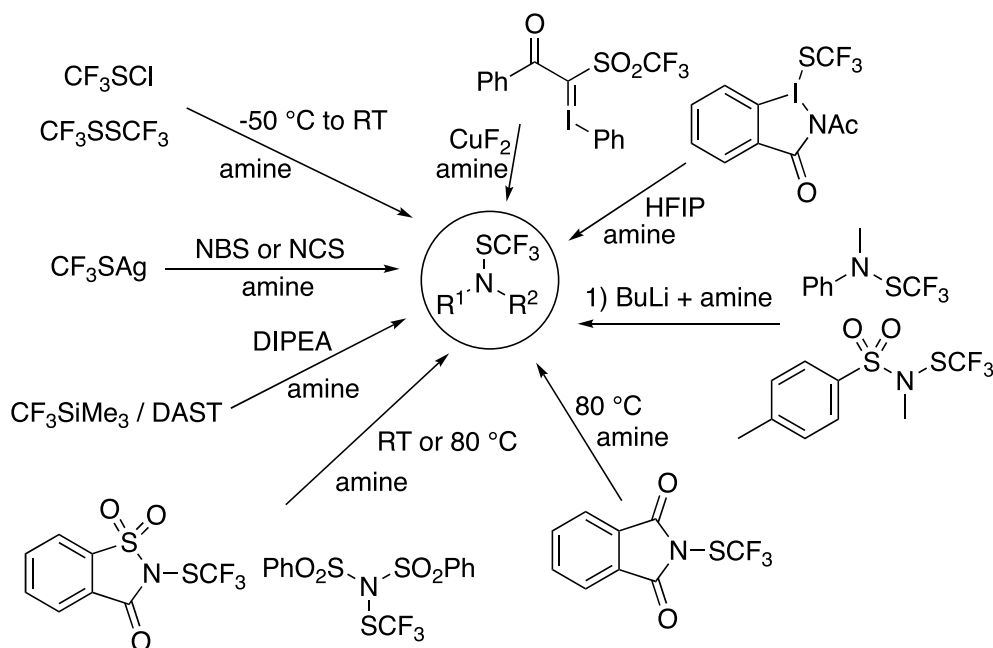
This higher reactivity of the heteroaromatic nitrogen could be rationalized by the higher acidity of the hydrogen carried by the nitrogen atom, which could interact with the sulfonamide anion released during the formation of CF₃SI, thus enhancing the nucleophilicity of the nitrogen (Scheme 4). Hydrochloride salts have also been directly involved in the reaction (**2i-j**), but required the addition of 1 equivalent of DIPEA (diisopropylethylamine). More sophisticated bioactive compounds have also been successfully trifluoromethylthiolated as illustrated by the Fluoxetine (**2j**), Sildenafil (**2k**) and Vonoprazan (**2l**) derivatives. Finally, ephedrine (an amino-alcohol) was chemoselectively trifluoromethylthiolated in a satisfactory yield (**2m**).

The proposed mechanism of the reaction is summarized in Scheme 4.

The reagent **BB23** reacts with the iodide anion (from Bu₄NI) to form the transient CF₃SI species and releases a sulfonamide anion. The amine, eventually activated by interaction with sulfonamide, can then react with the highly electrophilic CF₃SI to give the expected product **2**.

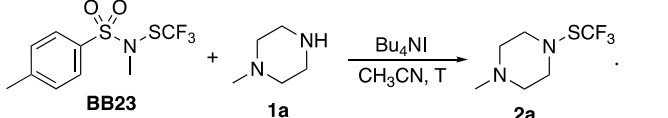
3. Conclusion

In conclusion, this work confirms the high versatility of the reagent **BB23** and confirms its high polyvalence in the toolbox of organofluorine chemistry. The results described provide an efficient method to obtain



Scheme 1. Synthesis of CF₃SN-product by trifluoromethylthiolation of amines.

Table 2
Optimization of the formation of 2a.



| Entry | Bu ₄ NI (eq.) | T (°C) | t (h) | 2a ^a |
|-------|---------------------------|--------|-------|-----------------|
| 1 | – | 60 | 16 | 62 |
| 2 | – | 20 | 16 | 54 |
| 3 | – | 20 | 1 | 33 |
| 4 | 1 | 20 | 1 | 75 |
| 5 | 0.1 | 20 | 1 | 67 |
| 6 | 0.1 | 20 | 4 | 82 |
| 7 | 0.1 | 20 | 16 | 90 |
| 8 | 0.05 | 20 | 1 | 54 |
| 9 | 0.05 | 20 | 4 | 68 |
| 10 | 0.05 | 20 | 16 | 80 |
| 11 | 0.1 (Bu ₄ NCl) | 20 | 16 | 78 |
| 12 | 0.1 (Bu ₄ NBr) | 20 | 16 | 88 |
| 13 | 0.1 (KI) | 20 | 16 | 76 |
| 14 | 0.1 (CsI) | 20 | 16 | 84 |

^a Yields determined by ¹⁹F NMR spectroscopy with PhCF₃ as internal standard.

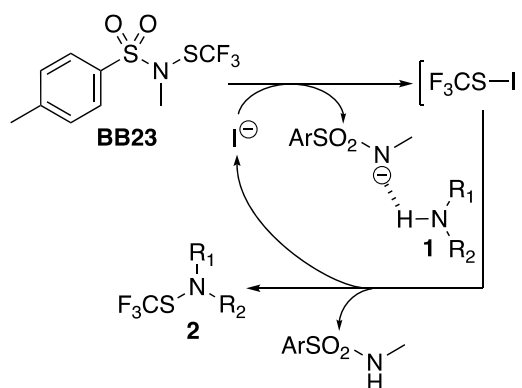
various CF₃SN-molecules under mild conditions by late-stage functionalization of the corresponding amine. This method has also allowed the trifluoromethylthiolation of various bioactive amines (from commercial drugs).

4. Experimental section

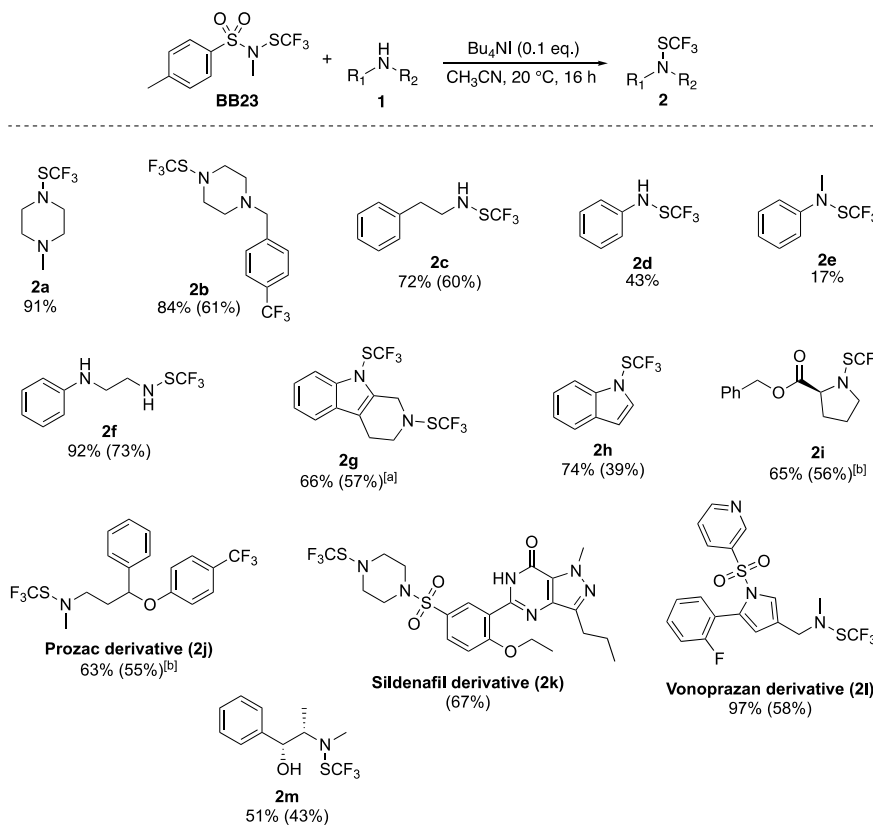
Typical procedure for the synthesis of trifluoromethanesulfenamides (2):
In a 10 mL vial, **BB23** (145 mg, 0.5 mmol, 1 equiv.) is dissolved in

anhydrous acetonitrile (1 mL) and the amine **1** (0.5 mmol, 1 equiv.) is added. Tetrabutylammonium iodide (18.5 mg, 0.05 mmol, 0.1 equiv.) is added and the reaction mixture is stirred at room temperature for 16 h. The yield is determined by ¹⁹F NMR using α,α,α-trifluorotoluene (PhCF₃) as an internal standard. After completion of the reaction, the reaction mixture is transferred to a separatory funnel and water (10 mL) and dichloromethane (10 mL) are added. The aqueous layer is extracted with dichloromethane (3 × 10 mL). The organic layers are combined and dried using MgSO₄, filtered and concentrated under vacuum. The crude obtained is purified using flash chromatography to afford the desired compound.

Supplementary materials: Experimental section and copies of NMR spectra of all the synthesized compounds.



Scheme 4. Proposed mechanism.



Scheme 3. Trifluoromethylthiolation of various amines. Yields determined by ¹⁹F NMR spectroscopy with PhCF₃ as internal standard (in parentheses isolated yields). [a] with 2 eq. of **BB23** and 0.2 eq. of Bu₄NI. [b] From the hydrochloride salt, with 1 eq. of DIPEA.

CRedit authorship contribution statement

Clément Delobel: Methodology, Investigation. **Fabien Toulgoat:** Supervision, Project administration, Methodology. **Thierry Billard:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jfluchem.2024.110353](https://doi.org/10.1016/j.jfluchem.2024.110353).

References

- [1] B.E. Smart, Fluorine substituent effects (on bioactivity), *J. Fluorine Chem.* 109 (2001) 3–11, [https://doi.org/10.1016/S0022-1139\(01\)00375-X](https://doi.org/10.1016/S0022-1139(01)00375-X).
- [2] P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, 2013.
- [3] P. Jeschke, The unique role of halogen substituents in the design of modern agrochemicals, *Pest Manage. Sci.* 66 (2010) 10–27, <https://doi.org/10.1002/ps.1829>.
- [4] R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, Organic fluorine compounds: a great opportunity for enhanced materials properties, *Chem. Soc. Rev.* 40 (2011) 3496–3508, <https://doi.org/10.1039/C0CS00221F>.
- [5] N.A. Meanwell, Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design, *J. Med. Chem.* 61 (2018) 5822–5880, <https://doi.org/10.1021/acs.jmedchem.7b01788>.
- [6] M. Inoue, Y. Sumii, N. Shibata, Contribution of organofluorine compounds to pharmaceuticals, *ACS Omega* 5 (2020) 10633–10640, <https://doi.org/10.1021/acsomega.0c00830>.
- [7] B. Ameduri, S. Fomin (Eds.), *Book Fascinating Fluoropolymers and their Applications*, Elsevier, Amsterdam, Netherlands, 2020.
- [8] Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, Current contributions of organofluorine compounds to the agrochemical industry, *iScience* 23 (2020) 101467, <https://doi.org/10.1016/j.isci.2020.101467>.
- [9] J. Lv, Y. Cheng, Fluoropolymers in biomedical applications: state-of-the-art and future perspectives, *Chem. Soc. Rev.* 50 (2021) 5435–5467, <https://doi.org/10.1039/D0CS00258E>.
- [10] C. Zhang, K. Yan, C. Fu, H. Peng, C.J. Hawker, A.K. Whittaker, Biological utility of fluorinated compounds: from materials design to molecular imaging, therapeutics and environmental remediation, *Chem. Rev.* 122 (2022) 167–208, <https://doi.org/10.1021/acs.chemrev.1c00632>.
- [11] D. Janasik, T. Krawczyk, 19F MRI probes for multimodal imaging, *Chem. Eur. J.* 28 (2022) e202102556, <https://doi.org/10.1002/chem.202102556>.
- [12] Y. Wang, Z. Li, Y. Hou, Z. Hao, Q. Zhang, Y. Ni, Y. Lu, Z. Yan, K. Zhang, Q. Zhao, F. Li, J. Chen, Emerging electrolytes with fluorinated solvents for rechargeable lithium-based batteries, *Chem. Soc. Rev.* 52 (2023) 2713–2763, <https://doi.org/10.1039/D2CS00873D>.
- [13] D. Cahard, J.A. Ma (Eds.), *Book Emerging Fluorinated Motifs: Synthesis, Properties and Applications*, Wiley, Weinheim, Germany, 2020.
- [14] K.J. Szabo, N. Selander (Eds.), *Book Organofluorine Chemistry: Synthesis, Modeling, and Applications*, Wiley, Weinheim, Germany, 2021.
- [15] A. Leo, C. Hansch, D. Elkins, Partition coefficients and their uses, *Chem. Rev.* 71 (1971) 525–616, <https://doi.org/10.1021/cr60274a001>.
- [16] C. Hansch, A. Leo, S.H. Unger, K.H. Kim, D. Nikaitani, E.J. Lien, Aromatic substituent constants for structure-activity correlations, *J. Med. Chem.* 16 (1973) 1207–1216, <https://doi.org/10.1021/jm00269a003>.
- [17] S. Alazet, K. Ollivier, T. Billard, Direct electrophilic N-trifluoromethylthiolation of amines with trifluoromethanesulfenamide, *Beilstein J. Org. Chem.* 9 (2013) 2354–2357, <https://doi.org/10.3762/bjoc.9.270>.
- [18] X. Guo-Liang, J. Shang-Hua, S. Xiangdong, F. Behmgham, Recent trends in direct trifluoromethylthiolation of NH bonds, *J. Fluorine Chem.* 235 (2020) 109524, <https://doi.org/10.1016/j.jfluchem.2020.109524>.
- [19] Q. Glenadel, S. Alazet, F. Baert, T. Billard, Multigram Scale Syntheses of First and Second Generation of Trifluoromethanesulfenamide Reagents, *Org. Process Res. Dev.* 20 (2016) 960–964, <https://doi.org/10.1021/acs.oprd.6b00062>.
- [20] F. Toulgoat, T. Billard, Towards CF₃S group: from trifluoromethylation of sulfides to direct trifluoromethylthiolation, in: H. Groult, F. Leroux, A. Tressaud (Eds.), *Modern Synthesis Processes and Reactivity of Fluorinated Compounds: Progress in Fluorine Science*, Elsevier Science, London, United Kingdom, 2017, pp. 141–179.
- [21] F. Toulgoat, F. Liger, T. Billard, Chemistry of OCF₃, SCF₃, and SeCF₃ functional groups, in: K. Szabó, N. Selander (Eds.), *Organofluorine Chemistry: Synthesis, Modeling, and Applications*, Wiley-VCH, Weinheim, Germany, 2021, pp. 49–97.
- [22] Q. Glenadel, S. Alazet, T. Billard, First and second generation of trifluoromethanesulfenamide reagent: a trifluoromethylthiolating comparison, *J. Fluorine Chem.* 179 (2015) 89–95, <https://doi.org/10.1016/j.jfluchem.2015.06.007>.
- [23] C. Delobel, E. Chefdeville, F. Toulgoat, T. Billard, Deep study of thiocarbamoyl fluorides: synthesis and properties, *Adv. Synth. Catal.* 366 (2024) 3474–3480, <https://doi.org/10.1002/adsc.202400412>.
- [24] Q. Glenadel, M. Bordy, S. Alazet, A. Tlili, T. Billard, Metal-free direct nucleophilic perfluoroalkylthiolation with perfluoroalkanesulfenamides, *Asian J. Org. Chem.* 5 (2016) 428–433, <https://doi.org/10.1002/ajoc.201600003>.