

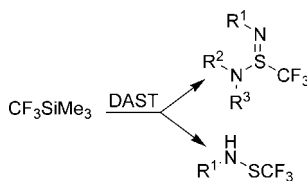
Synthesis of Trifluoromethanesulfinamidines and -sulfanylamides

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Fluorinated moieties constitute important substituents used in many applications to modify the properties of molecules. The action of DAST onto Ruppert's reagent yields to a not isolable intermediate that can then react with various primary amines to give trifluoromethanesulfinamidines and trifluoromethanesulfanylamides. Such compounds were unknown until now and constitute interesting new families of fluorinated molecules.

Introduction

Fluorine occupies a specific place among all elements of the periodic classification because of its high electronegativity and its specific properties. This singular nature of the fluorine atom, combined with the unique physical and chemical properties that fluorine imparts to compounds that contain it, explains the importance of organofluorine chemistry.¹ Indeed, the specific physicochemical properties of fluorinated organic compounds are of huge interest in a wide range of applications.^{1,2} Consequently, organofluorine chemistry has been steadily growing to become, today, a field of great importance with a distinctive role in highly diverse technological developments (fluoropolymers, pharmaceutical and agrochemical products, materials science, etc.).^{3,4}

These past years, heteroatomic fluorinated groups have attracted a growing interest. The most popular representative of such moieties is the perfluoroalkylsulfonylimidyl group, which has found applications as electrolytes for lithium batteries, as ionic liquids,⁵ as Lewis acid catalysts,⁶ and as intermediates for bioactive molecules.⁷

Surprisingly, among these nitrogen- and sulfur-containing groups, trifluoromethanesulfinamidines **1** have never been described and studied until now.

In our quest for new fluorinated groups exhibiting specific physicochemical properties for biological applications or materials, we focused our interest on the synthesis of such trifluoromethanesulfinamidines.

Results and Discussion

In our retrosynthetic strategy, the use of commercially available, easy to handle reagents was the *sine qua non* condition.

Such considerations led us to envisage the preparation of **1a** starting from Ruppert's reagent (**4a**) and DAST derivatives (**3**), via a trifluoromethyl difluorosulfur intermediate (**2a**) (Scheme 1). To our knowledge, preparation of the later type of compounds has only been reported once:⁸ compound **2** ($R^1 = R^2 =$

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(1) (a) Groß, U.; Rüdiger, S. In *Organo-Fluorine Compounds*; Baasner, B., Hagemann, H., Tatlow, J. C., Eds.; Thieme: Stuttgart, 1999; Vol. E10a, Houben-Weyl: Methods of Organic Chemistry; pp 18–26. (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11. (c) Hiyama, T. *Organofluorine Compounds: Chemistry and Properties*; Springer-Verlag: Berlin, 2000. (d) Dunitz, J. D. *ChemBioChem* **2004**, *5*, 614–621. (e) Biffinger, J. C.; Kim, H. W.; DiMaggio, S. G. *ChemBioChem* **2004**, *5*, 622–627.

(2) (a) Filler, R.; Kobayashi, Y.; Yagulpolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993. (b) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (c) Hiyama, T. *Organofluorine Compounds: Chemistry and Properties*; Springer-Verlag: Berlin, 2000; Chapter 5, pp 137–182. (d) Becker, A. *Inventory of Industrial Fluoro-Biochemicals*; Eyrolles: Paris, 1996.

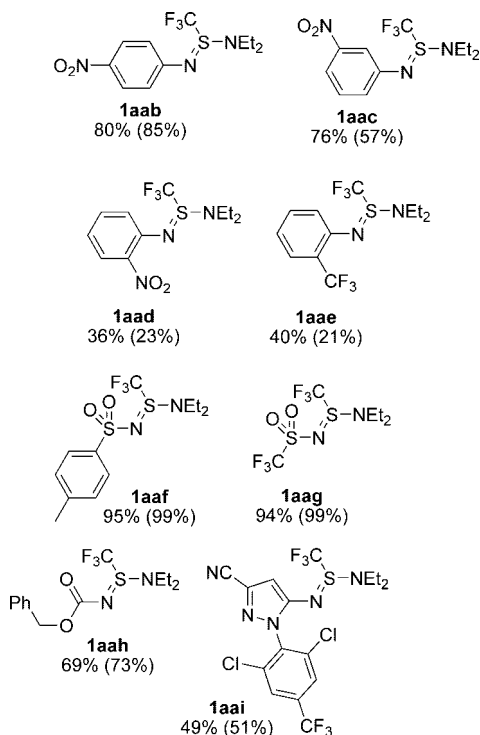
(3) Dolbier, W. R., Jr. *J. Fluorine Chem.* **2005**, *126*, 157–163.

(4) Schofield, H. *J. Fluorine Chem.* **1999**, *100*, 7–11.

(5) Bonhote, P.; Dias, A.-P.; Papageorgiou, N.; Kalyanasundaram, K.; Gratzel, M. *Inorg. Chem.* **1996**, *35*, 1168–1178.

(6) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H.; Maruta, M. *Synlett* **1996**, 171–172.

(7) Vij, A.; Kirschmeier, R. L.; Schreeve, J. M.; Verma, R. D. *Coord. Chem. Rev.* **1997**, *158*, 413–432.

SCHEME 6. Trifluoromethanesulfinamidines (**1**)^a

^a Isolated yield. In parentheses: crude yield determined by ¹⁹F NMR with internal standard.

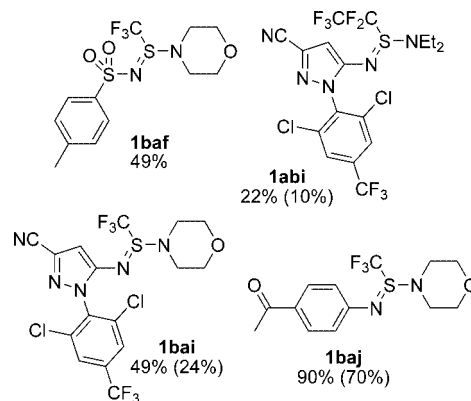
Because of the high electron-withdrawing character of NO₂ moiety, the protonation of the imino nitrogen in **1aab** should be disfavored by inductive effect, explaining the greater stability of **1aab** compared to that of **1aaa**. The intermediate **A** could also undergo an intramolecular rearrangement, which would yield trifluoromethanesulfinamidine **1** with elimination of HF and imine **6**.

In order to substantiate this mechanism, we first checked the effective possibility to transform isolated **5** into **1** under acidic conditions.

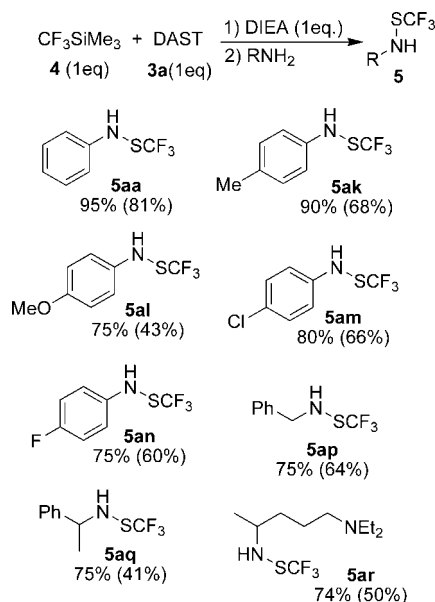
With 1.2 equiv of trifluoroacetic acid, **1aab** has been rapidly and quantitatively transformed into **5ab**, at room temperature, confirming the role of an acidic catalysis in this transformation. To confirm that, within the reaction mixture, released HF was sufficient to cause the formation of **5**, the same reaction was conducted with 2 equiv of DIEA in order to neutralize all acidic species. After 4 h of reaction, starting from aniline, **1aaa** was the only formed product and no trace of **5aa** could be detected.

To assert unambiguously the proposed mechanism, the acidic transformation of isolated **1aab** was conducted in CD₂Cl₂ and monitored by ¹H NMR. Formation of imine **6** was detected, and after hydrolysis with D₂O, disappearance of the characteristic signals of **6** and apparition of acetaldehyde confirmed this observation. A similar monitoring of the complete reaction, from the point where aniline is added to **2a**, was also realized, and the same observations (in particular the formation of acetaldehyde) were noted.

With such a methodology in hand, various trifluoromethanesulfinamidines (**1**) were then synthesized (Scheme 6). Only those trifluoromethanesulfinamidines arising from amines bearing electron-withdrawing groups could be isolated. In the other cases, even if the trifluoromethanesulfinamidines could be detected in the NMR spectra of the crude mixtures, they were too unstable to be isolated. Also noteworthy was the observation

SCHEME 7. Other Fluorinated Sulfinamidines (**1**)^a

^a Isolated yield. In parentheses: crude yield determined by ¹⁹F NMR with internal standard.

SCHEME 8. One-Pot Synthesis of **5**^a

^a Isolated yield. In parentheses: crude yield determined by ¹⁹F NMR with internal standard.

that selected sulfonamides and carbamates afforded in good yields isolable trifluoromethanesulfinamidines (see **1aaf**, **1aag**, and **1aah**).

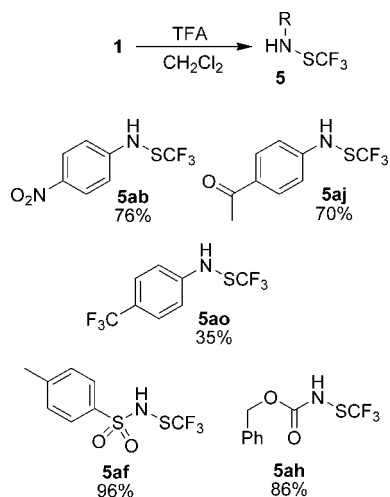
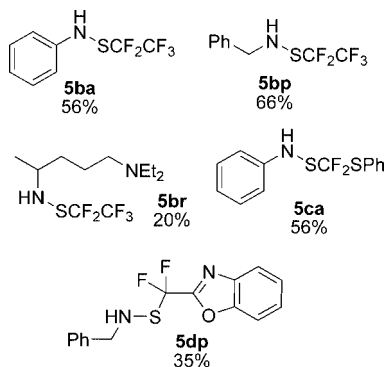
Similar products were also synthesized following reaction of morpholino-DAST with **4a** or that of DAST with pentafluoroethylsilane (Scheme 7).

Since our methodology afforded very easily trifluoromethanesulfinamidines (**5**), we next focused our interest onto these products. Only a few representatives of this family have been previously described in the literature and reported to have agrochemical applications.¹¹ However, their preparations from very volatile and toxic CF₃SCl¹² or CF₃SSCF₃¹³ have limited their production. On the other hand, nonfluorinated analogues are well documented and display various interesting biological

(11) For example: (a) Schallner, O.; Schwarz, H.-G.; Hoischen, D.; Linker, K.-H.; Drewes, M. W.; Dahmen, P.; Feucht, D.; Pontzen, R. (Bayer AG) *WO 2002006277*, 2002; *Chem. Abstr.* **2002**, 136, 118455. (b) Maurer, F.; Gayer, H.; Gerdes, P.; Heinemann, U.; Krueger, B.-W.; Markert, R.; Stenzel, K.; Haenssler, G.; Mauler-Machnik, A. (Bayer AG) *DE 19925780*, 2000; *Chem. Abstr.* **2000**, 132, 166019.

(12) Kolasa, A.; Lieb, M. *J. Fluorine Chem.* **1995**, 70, 45–47.

(13) Peach, M. E. *Can. J. Chem.* **1967**, 45, 429–432.

SCHEME 9. Synthesis of 5 from 1 under Acidic Conditions^a^a Isolated yields.**SCHEME 10. Other Fluorinated Sulfanylamides 5 with Various Fluorinated Moieties**

properties,¹⁴ suggesting that our compounds **5** might also find interesting applications, in particular, in the field of life science.

Trifluoromethanesulfanylamides (**5**) were obtained following two procedures. When the intermediary sulfinamidines **1** were unstable, products **5** were directly isolated following reaction of **2** with primary amines (Scheme 8).

In the case of the stable sulfinamidines, compounds **5**, including the *N*-sulfonyl and *N*-benzyloxycarbonyl analogues, were synthesized by acidic transformation of the corresponding purified **1** (Scheme 9).

Whereas the formation of **5ab**, **5aj**, and **5ao** required only 1.2 equiv of TFA and 1 h at room temperature, more drastic conditions were needed for **5af** and **5ah** (3.5 equiv TFA/50 °C/24 h), certainly because of the higher deactivation of the nitrogen atom. Moreover, **1aag** could never be transformed probably because of the incapacity of its imino nitrogen to be protonated.

Related sulfanylamides, bearing different fluorinated moieties R_F, such as CF₂CF₃, CF₂SPh, and CF₂-2-benzoxazolyl, were also synthesized by the same methodology, starting from R_F-TMS and DAST (Scheme 10).

Conclusion

In conclusion, we have described a method to prepare, very easily, two new families of fluorinated compounds, namely, the trifluoromethanesulfinamidines (**1**) and the trifluoromethanesulfanylamides (**5**). The interest of our methodology lies in its easy implementation that does not require any expertise in fluorine chemistry. These two families of compounds should be of great interest in various fields of applications, from conception of materials to drug design. Exploration of the reactivity and of the potential applications of compounds **1** and **5** are under studies in our laboratory and will be published in due course.

Experimental Section

Typical Procedure. Synthesis of *N,N*-Diethyl-1,1,1-trifluoro-*N'*-(4-nitrophenyl)methane Sulfinimidamide 1aab. A flame-dried double-necked vessel was successively charged, under nitrogen, with diisopropylethylamine (14 mL, 80 mmol) and anhydrous dichloromethane (80 mL). The resulting mixture was cooled to −20 °C before addition of diethylaminosulfurtrifluoride (5.5 mL, 44 mmol), followed by the addition of trimethylsilyltrifluoromethane (5.9 mL, 40 mmol) or trimethylsilylpentafluoroethane (7.7 mL, 40 mmol) in 20 min intervals. After 1 h under stirring at −20 °C, aniline (1equiv) was added at 0 °C. The reaction medium was then warmed to room temperature and kept under stirring for a further 4 h. The reaction medium was then washed with 6% aqueous NaHCO₃. The organic phase was dried over Na₂SO₄ and evaporated in vacuo. The crude residue was simply washed with pentane or purified by chromatography over silica gel (eluent = pentane/acetone 30/1) in the presence of 0.5% of Et₃N to afford the corresponding **1aab**: orange solid, mp 40–41 °C. ¹H NMR: δ 7.97 (m, 2H), 6.78 (m, 2H), 3.31 (q, ³J(H,H) = 7.3, 4H), 1.11 (t, ³J(H,H) = 7.2, 6H). ¹³C NMR: δ 123.8 (q, ⁴J(C,F) = 1.1), 140.9, 125.7, 123.8 (q, ¹J(C,F) = 329), 119.7, 41.0, 13.8. ¹⁹F NMR: δ −70.85. Anal. Calcd for C₁₁H₁₄F₃N₃O₂S: C 42.71, H 4.56, N 13.59, S 10.37. Found: C 42.82, H 4.63, N 13.87, S 10.14.

Typical procedure: Synthesis of *N*-[(Trifluoromethyl)thio]-aniline 5aa. A flame-dried double-necked vessel was successively charged, under nitrogen, with diisopropylethylamine (7 mL, 40 mmol) and anhydrous dichloromethane (80 mL). The resulting mixture was cooled to −20 °C before addition of diethylaminosulfurtrifluoride (5.5 mL, 44 mmol), followed by the addition of trimethylsilyltrifluoromethane (5.9 mL, 40 mmol) or trimethylsilylpentafluoroethane (7.7 mL, 40 mmol) in 20 min intervals. After 1 h under stirring at −20 °C, aniline (1equiv) was added at 0 °C. The reaction medium was then cooled to room temperature and kept under stirring overnight. After this period, the reaction medium was washed with distilled water. The organic phase was dried over Na₂SO₄ and evaporated in vacuo. The crude residue was purified by chromatography over silica gel to afford the corresponding sulfanylamides **5aa**: yellow oil. ¹H NMR: δ 7.35 (m, 2H), 7.15 (m, 2H), 7.06 (m, 1H), 5.09 (NH). ¹³C NMR: δ 145.5, 129.8 (q, ¹J(C,F) = 315), 129.7, 122.3, 115.6. ¹⁹F NMR: δ −53.33. Anal. Calcd for C₇H₆F₃NS: C 43.52, H 3.13, N 7.25 S 16.60. Found: C 43.55, H 3.08, N 7.36, S 16.24

Acknowledgment. We thank the CNRS and the Sanofi-Aventis Co. for financial support.

Supporting Information Available: Experimental procedures, full spectral data for all new compounds, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) For example: (a) Sharon, A.; Pratap, R.; Vatsyayan, R.; Maulik, P. R.; Roy, U.; Goel, A.; Ram, V. *J. Bioorg. Med. Chem. Lett.* **2005**, *15*, 3356–3360. (b) Turos, E.; Coates, C.; Shim, J.-Y.; Wang, Y.; Leslie, J. M.; Long, T. E.; Reddy, G. S. K.; Ortiz, A.; Culbreath, M.; Dickey, S.; Lim, D. V.; Alonso, E.; Gonzalez, J. *Bioorg. Med. Chem.* **2005**, *13*, 6289–6308. (c) Dou, Q. P.; Turos, E.; Smith, D. M. *U.S. 2004167115*, 2004; *Chem. Abstr.* **2004**, *141*, 185091.