JOC Article

Synthesis of Trifluoromethanesulfinamidines and -sulfanylamides

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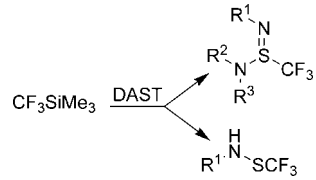

Fluorinated moieties constitute important substituents used in many applications to modify the properties of molecules. The action of DAST onto Ruppert's reagent yields to a not isolable intermediate that can then react with various primary amines to give trifluoromethanesulfinamidines and trifluoromethanesulfanylamides. 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) Groβ, 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.; DiMagno, 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.

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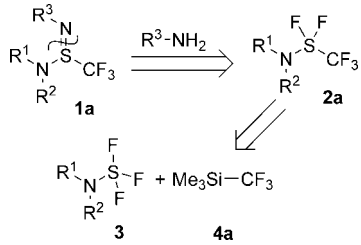
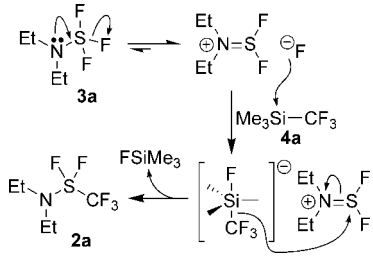
SCHEME 1. Retrosynthetic Scheme of Trifluoromethanesulfinamidines



SCHEME 2. Expected Formation of 2a



Me) was prepared very inconveniently by reaction of CF_3SF_3 and TMS−NMe_2 between −196 and −78 °C.

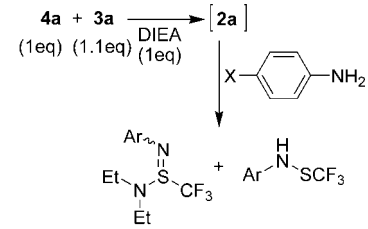
Our rationale came from a work previously reported by one of us and featuring the easy transformation of a naturally occurring alcohol ROH (R = pristinamycin II) into R-Nu upon reaction with DAST and $Bu_4N^+Nu^-$ (Nu = Hal, SCN, ONO, etc.).[9] In these reactions, involvement of the new species Et_2NSF_2-Nu was strongly suspected. On the basis of these results, we envisioned that **2a** ($R^1 = R^2 =$ Et) would be readily formed by mixing **4a** with DAST (**3a**). We supposed that an equilibrium between the covalent and the ionic forms of DAST could take place and generate a fluoride anion, able to activate **4a** (Scheme 2).

However, the first attempts to obtain **2a** led us to an unchanged mixture of **3a** and **4a**. Examination of the ^{19}F NMR spectra of the corresponding DAST solutions did not show any trace of fluoride, which precluded the existence of the expected equilibrium. In order to activate DAST and favor this equilibrium, various additives were tried. Surprisingly, when DAST was mixed with tertiary amines (Et_3N, DIEA, pyridine), the formation of a fluoride anion was observed by ^{19}F NMR, thus suggesting the occurrence of the expected equilibrium. This was further confirmed by the quantitative formation of **2a** when adding **4a** to this mixture. Such activation of DAST by a tertiary amine could be rationalized by the nucleophilic displacement onto the sulfur atom of fluoride by amine.

Nevertheless, **2a** was not stable enough to be isolated. It was very sensitive to hydrolysis and readily led to the corresponding trifluoromethanesulfinamide ($CF_3S(O)NEt_2$). Its utilization in situ was therefore envisaged, by adding a primary amine following its formation.

This reaction was initially tested with aniline and 4-nitroaniline (Scheme 3). In both cases, after 4 h of reaction, ^{19}F NMR monitoring showed the formation of two compounds. In the case of aniline, the ratio between these two products was inverted, after 24 h. The formed compounds were identified as the

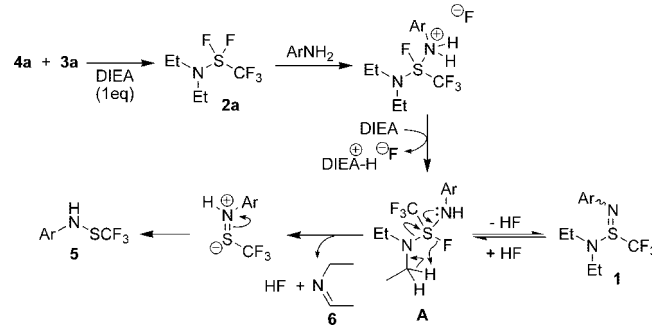
SCHEME 3. Synthesis of 1 and 5[a]



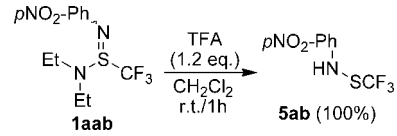
X = H	δ = -71.08 (**1aaa**)	δ = -53.33 (**5aa**)
t = 4h :	65%	30%
t = 24h :	10%	85%
X = NO_2	δ = -70.35 (**1aab**)	δ = -52.71 (**5ab**)
t = 4h :	85%	0%
t = 24h :	80%	4%

[a] Crude yield determined by ^{19}F NMR with internal standard.

SCHEME 4. Mechanism of Formation of 1 and 5



SCHEME 5. Transformation of 1 into 5 in Acidic Conditions



expected trifluoromethanesulfinamidines (**1**) and the trifluoromethanesulfanylamides (**5**). Product **1aaa** turned out to be too unstable under the aqueous conditions of the workup to be isolated. Its identity was only ascertained on the basis of the ^{19}F NMR spectrum of the crude reaction mixture by analogy between its NMR shift and that of its congeners.

Considering these results, we reasonably supposed that sulfanylamides (**5**) stemmed from the in situ transformation of sulfinamidines (**1**). Since product **1aab**, arising from *p*-NO_2 aniline, underwent far more slowly the same transformation and because of the acidity of the reaction mixture, the hypothesis of the protonation of **1** was postulated as the starting point of the subsequent transformation into **5**. Such hypothesis was in accordance with the previously described transformation of sulfimides into sulfanylamides under acidic conditions.[10] Consequently, a mechanism is proposed in Scheme 4.

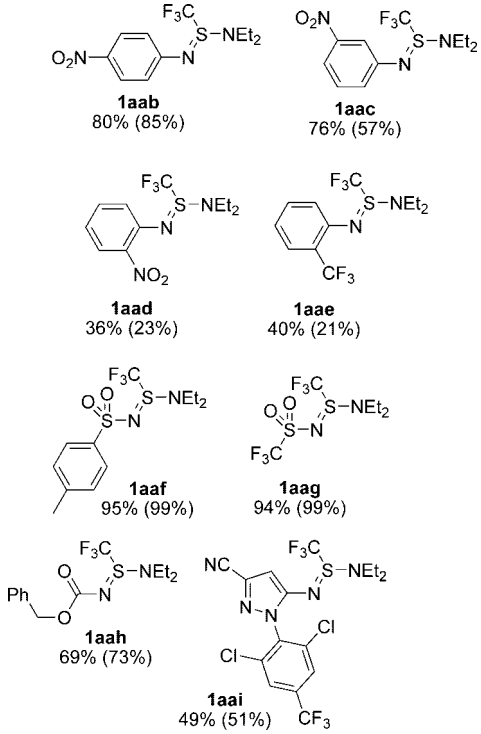
In our mechanism (Scheme 4), the intermediate resulting from the reaction of primary amine onto **2a** could eliminate HF, which is neutralized by the DIEA, to generate the second intermediate **A**. This one would then eliminate a second equivalent of HF to yield trifluoromethanesulfanylamide **5**. This second equivalent of HF could react with **5** to regenerate the intermediate **A**.

(8) Sprenger, G. H.; Cowley, A. H. *J. Fluorine Chem.* **1976**, *7*, 333–346.

(9) (a) Achard, D.; Bacqué, E.; Barrière, J. C.; Bouquerel, J.; Desmazeau, P.; Grisoni, S.; Leconte, J. P.; Ribeill, Y.; Ronan, B. WO 2001002427. (b) Bacqué, E.; Barrière, J. C.; Berthaud, N. *Curr. Med. Chem.: Anti-Infect. Agents* **2005**, *4*, 185–217.

(10) Claus, P. K.; Silbernagel, W.; Franek, W.; Rieder, W. *Monatsh. Chem.* **1985**, *116*, 841–850.

SCHEME 6. Trifluoromethanesulfinamidines (1)[a]



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

Because of the high electron-withdrawing character of NO_2 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**.

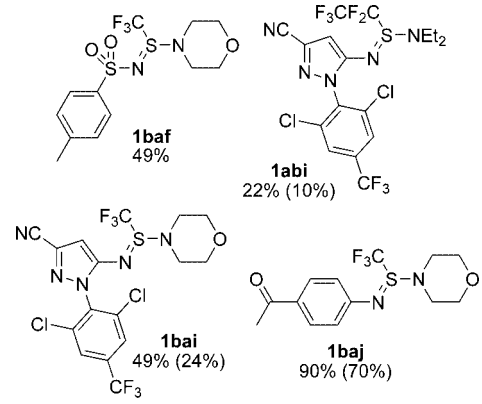
In order to substantiate this mechanism, we first checked the effective possibility to transform isolated **5** into **1** under acidic conditions.

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 CD_2Cl_2 and monitored by ^1H NMR. Formation of imine **6** was detected, and after hydrolysis with D_2O, 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.

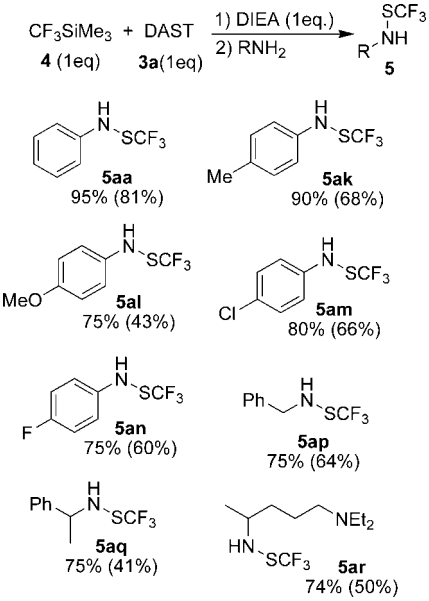
With such a methodology in hand, various trifluoromethanesulfinamidines (**1**) were then synthesized (Scheme 6). Only those trifluoromethanesulfinamidines arising from amines bearing electron-withdrawing groups could be isolated. In the other cases, even if the trifluoromethanesulfinamidines could be 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 ^{19}F NMR with internal standard.

SCHEME 8. One-Pot Synthesis of 5[a]



[a] Isolated yield. In parentheses: crude yield determined by ^{19}F 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).

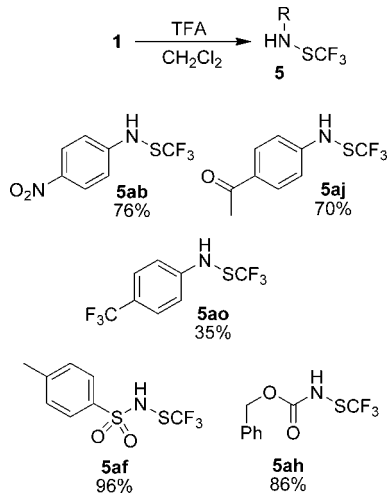
Since our methodology afforded very easily trifluoromethanesulfinamides (**5**), we next focused our interest onto these products. Only a few representatives of this family have been previously described in the literature and reported to have agrochemical applications.[11] However, their preparations from very volatile and toxic CF_3SCl[12] or CF_3SSCF_3[13] 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.

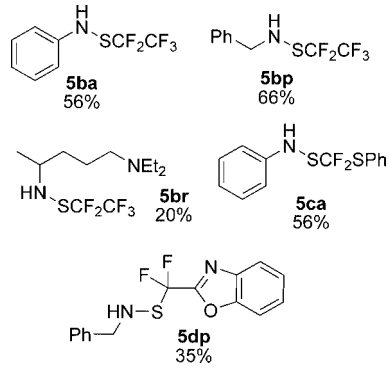
(13) Peach, M. E. *Can. J. Chem.* **1967**, *45*, 429–432.

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 CF_2CF_3, CF_2SPh, and CF_2-2-benzoxazolyl, were also synthesized by the same methodology, starting from R_F-TMS and DAST (Scheme 10).

(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.

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 $NaHCO_3$. The organic phase was dried over Na_2SO_4 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 Et_3N to afford the corresponding **1aab**: orange solid, mp 40−41 °C. ^{1}H 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). ^{13}C 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. ^{19}F NMR: δ −70.85. Anal. Calcd for $C_{11}H_{14}F_3N_3O_2S$: 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 Na_2SO_4 and evaporated in vacuo. The crude residue was purified by chromatography over silica gel to afford the corresponding sulfanylamides **5aa**: yellow oil. ^{1}H NMR: δ 7.35 (m, 2H), 7.15 (m, 2H), 7.06 (m, 1H), 5.09 (NH). ^{13}C NMR: δ 145.5, 129.8 (q, ^1J(C,F) = 315), 129.7, 122.3, 115.6. ^{19}F NMR: δ −53.33. Anal. Calcd for $C_7H_6F_3NS$: 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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