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# A New Equivalent of the $CF_3S(O)^+$ Cation. Synthesis of Trifluoromethanesulfinates and Trifluoromethanesulfinamides.

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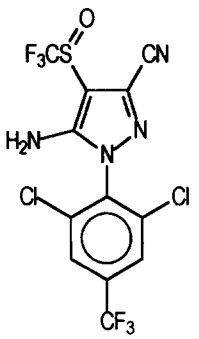
***Abstract :*** The solution of sodium trifluoromethanesulfinate (sodium "triflinate") and phosphoryl chloride (2/1), in AcOEt, behaves like an equivalent of the $CF_3S(O)^+$ cation. It can be used *in situ* to prepare trifluoromethanesulfinates ($CF_3S(O)OR$) or trifluoromethanesulfinamides ($CF_3S(O)NHR$) at room temperature from alcohols or amines, respectively. 

Since a few years, many compounds bearing a trifluoromethanesulfinyl moiety [$CF_3S(O)$] have been described and seem to present interesting biological activities.[1] For example, Fipronil®, a new powerful insecticide, has been recently developed by the Rhône-Poulenc Co.




Fipronil®

Usually, the introduction of a trifluoromethanesulfinyl group into organic compounds is not carried out directly but generally involves either substitutive trifluoromethylation of sulfinyl chlorides with $CF_3SiMe_3/F^-$ [2] or electrophilic reaction of substrates with $CF_3SCl$, a very toxic reagent,[3] both reactions being followed by oxidation. Thus, it would be interesting to elaborate a new efficient reagent which could

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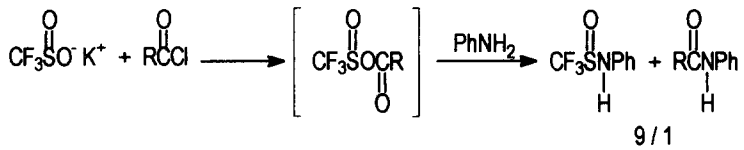
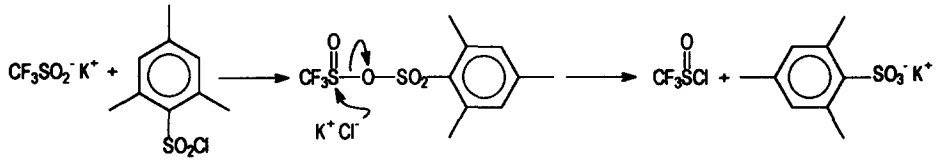
introduce directly the trifluoromethanesulfinyl moiety in order to avoid the use of toxic $CF_3SCl$ or expensive $CF_3SiMe_3$.

To our knowledge, only two examples have been reported by Hendrickson concerning the direct introduction of the $CF_3S(O)$ group.[4,5] In the first one, potassium « triflinate » ($CF_3SO_2^-K^+$) was reacted with an acyl chloride to yield an unstable intermediate which has been opposed to aniline (scheme I).[4] However, this process is not completely chemoselective.




Scheme I

In the second way, $CF_3S(O)Cl$ has been prepared from $CF_3SO_2K$ and a hindered sulfonyl chloride (scheme II), then opposed to an amine to deliver the corresponding trifluoromethanesulfinamide.[5]




Scheme II

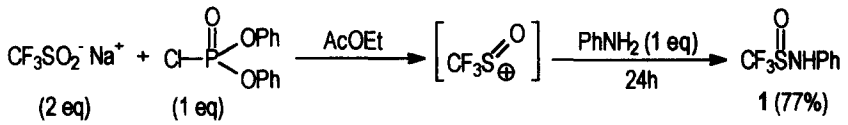
Trifluoromethanesulfinyl chloride has been also prepared from trifluoromethanesulfinic acid and thionyl chloride, phosphorus trichloride or phosphorus pentachloride[6] but $CF_3S(O)OH$ is rather unstable, as $CF_3S(O)Cl$, which, on the other hand, is very volatile ($Eb_{760}$ = 41 °C). Trifluoromethanesulfinyl fluoride, which is more stable than the corresponding chloride, has been already isolated and opposed to nucleophiles.[7-10] But this gaseous reagent is not easily available and does not seem to be very reactive.

In this paper, we describe a new, simpler and more reactive system which reacts readily like a trifluoromethanesulfinyl cation and can be conveniently used for the synthesis of trifluoromethanesulfinates and trifluoromethanesulfinamides.

## Results and discussion

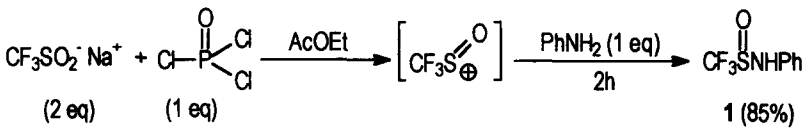
As chlorophosphates are known as useful coupling agents,[10] we first put them in reaction with sodium triflinate ($CF_3SO_2^-Na^+$) to obtain a trifluoromethanesulfinylating reagent. In a first experiment, diphenyl chlorophosphate was reacted with two equivalents of sodium triflinate in ethyl acetate. $^{19}F$ and $^{31}P$ NMR

analyses did not allow us to determine accurately the composition of the crude mixture but after addition of aniline, the corresponding sulfinamide 1 was obtained in a good yield (Scheme III). However, the needed 24 h to proceed completely



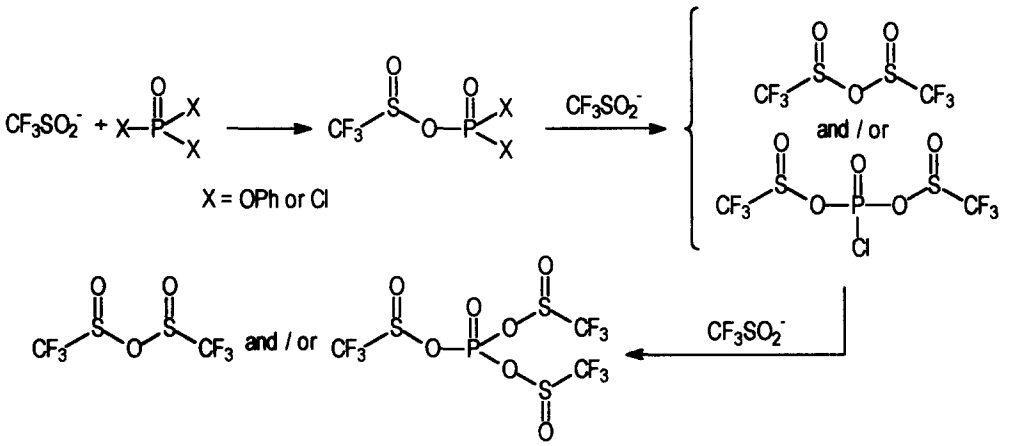

Scheme III

The replacement of diphenylchlorophosphate by phosphoryl chloride resulted in a much faster reaction (85 % after 2 hours - scheme IV).




Scheme IV

As previously, analysis of the mixture, before addition of aniline, did not allow us to determine precisely the reactive species. However, in accordance with spectral data, four reactive species could be considered (scheme V), all of them being potential equivalents of the $CF_3SO^+$ cation.

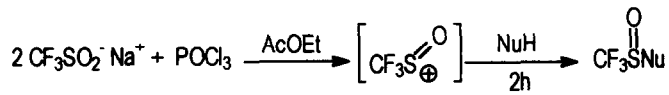


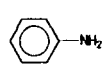
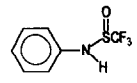
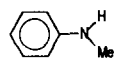
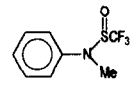
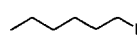
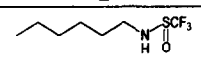
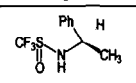
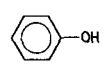
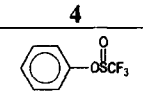
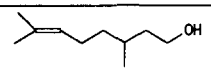
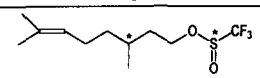
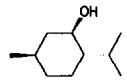
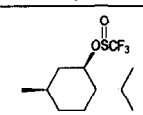
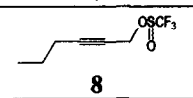

Scheme V

Nevertheless, the best results were obtained with two equivalents of $CF_3SO_2Na$ vs. $POCl_3$ and aniline (yield 1 = 85%) : yields were far lower with one equivalent of $CF_3SO_2Na$ (yield 1 = 33%) but were not significantly improved with three equivalents of this reagent (yield 1 = 90%). Thus, in our opinion,

$(CF_3SO_2)_2O$ could be the most efficient component of the reactive system, concerning trifluoromethanesulfinylation of aniline.

Even if we were not able to precise the exact structure of this sulfinylating reagent, it seemed to be very efficient and was then opposed to some other amines and alcohols. The corresponding trifluoromethane- sulfinamides and sulfinates were obtained as well (Table I).




| Entry | NuH | Product | Yield (%) [a] |
|---|---|---|---|
| 1 |  |  **1** | 84 (80) |
| 2 |  |  **2** | 80 (70) |
| 3 |  |  **3** | 41 (38)<br>80 (75) [b] |
| 4 |  |  **4** | 25 (21)<br>66 (60) [b]<br>2 diastereomers (46/54) |
| 5 |  |  **5** | 76 (73) |
| 6 |  |  **6** | 90 (83)<br>2 diastereomers (57/43) |
| 7 |  |  **7** | 90 (85)<br>2 diastereomers (55/45) |
| 9 |  |  **8** | 70 (67) |

[a] crude yields determined by NMR $^{19}F$. Isolated yields in parentheses.
[b] with one equivalent of added Diisopropyl Ethyl Amine.

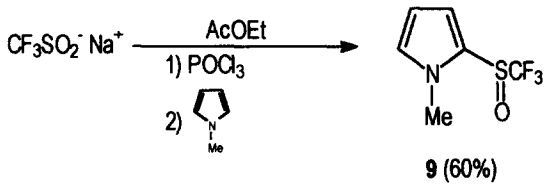
Table I

It can be noticed that chiral substrates, like citronellol (entry 6), menthol (entry 7) and 1-phenylethylamine (entry 4) led to two diastereomers because of the chiral character of the sulfinyl group. These diastereomers can be probably separated by chromatography (work in progress).

The lower yields obtained with primary amines, like hexylamine (entry 3) and 1-phenylethylamine (entry 4), were consistent with the fact that these substrates behave as bases and were neutralized by acidic phosphoric species resulting from the reaction. Consequently, the trifluoromethanesulfinylation of these substrates was repeated in the presence of one equivalent of diisopropylethylamine (DIEA) : as expected, yields increased dramatically (up to 80% for **3** and 66% for **4**) as shown in Table I.

Table I also shows, from these preliminary experiments, that our trifluoromethanesulfinylation reagent is compatible with aromatic nuclei (even activated ones), alkenes and alkynes. The wider scope and limitations of this technique is, nevertheless, under study in our laboratory.

We also used it towards N-methyl pyrrole and obtained the corresponding α-sulfoxyde regioselectively and in a fair yield (scheme VI).




**9** (60%)

Scheme VI

Trifluoromethanesulfinylation of other carbon nucleophiles is also under study.

In conclusion, the system $CF_3SO_2Na$ / $POCl_3$ can be considered as an efficient and cheap equivalent of the $CF_3S(O)^+$ cation which can be used *in situ* and reacts rapidly at room temperature with amines and alcohols, as well as with carbon nucleophiles, to provide trifluoromethanesulfinamides, trifluoromethanesulfinates or trifluoromethyl sulfoxides.

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**Experimental section**

All reagents were used as received. $^1H$, $^{19}F$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ at 300, 188 and 75 MHz respectively, unless stated otherwise.

Chemical shifts are given in ppm relative to TMS ($^1H$, $^{13}C$) or $CFCl_3$ ($^{19}F$), used as internal references. Coupling constants are given in hertz. Mass spectra were recorded at 70 eV. Flash-chromatographies were performed on silica gel MERCK Geduran SI 60.

**Reaction of aniline with sodium triflinate and diphenyl chlorophosphate.**

To a solution of 0.33g (2 mmol) of sodium triflinate (purity 95%) in 2 mL of ethyl acetate was added, at room temperature, 220µL (1 mmol) of diphenyl chlorophosphate. The resulted mixture was stirred for 5 min, then 1 mmol of aniline was dropped on it. The reaction mixture was stirred for 24 h, then deposited on the top of a chromatography column and eluted with a mixture of petroleum ether and ether (4/1).

**Reaction of amines and alcohols with sodium triflinate and phosphoryl chloride. General procedure.**

To a solution of 0.33g (2 mmol) of sodium triflinate (purity 95%) in 2 mL of ethyl acetate was added, at room temperature, 95µL (1 mmol) of phosphoryl chloride. The resulted mixture was stirred for 5 min, then 1 mmol of nucleophile (dissolved in ethyl acetate, if necessary) was added. The reaction mixture was stirred for 2 h, then treated in the usual way (*vide infra*) or directly deposited on chromatography column and eluted.

***N*-Phenyl trifluoromethanesulfinamide (1).**

White solide after purification by flash chromatography with petroleum ether/ether (4/1) as eluent and further recrystallization in petroleum ether.

$^1$H NMR : 7.05-7.51 (massif ; 5H) ; 6.73 (s ; 1H). $^{13}$C NMR : 138.13 ; 129.86 ; 125.44 ; 123.68 (q ; $^1J_{C\text{-}F}$ = 333.4 Hz) ; 120.32. $^{19}$F NMR : -78.12. Mass spectrum : m/z = 140 ($M^{+\bullet}$-$CF_3$) ; 92 ; 77 ; 65 ; 39. Melting point : 64°C. HRMS ($CI^+$) calcd for $C_7H_7F_3NOS$ : $MH^+$=210.02004 ; Found : $MH^+$= 210.02005.

***N*-Methyl-*N*-phenyl trifluoromethanesulfinamide (2).**

Yellow liquid after purification by flash chromatography with petroleum ether/ether (9/1) as eluent.

$^1$H NMR : 7.35-7.42 (massif ; 2H) ; 7.17-7.26 (massif ; 3H) ; 3.25 (q ; 3H ; $^5J_{H\text{-}F}$ = 1.5 Hz). $^{13}$C NMR : 143.12 ; 129.74 ; 126.02 ; 124.35 (q ; $^1J_{C\text{-}F}$ = 342.2 Hz) ; 122.06 ; 31.11(q ; $^4J_{C\text{-}F}$ = 1.1 Hz). $^{19}$F NMR : -74.02. Mass spectrum : m/z = 223 ($M^{+\bullet}$) ; 154 ; 106 ; 77 ; 69 ; 51 ; 39. HRMS ($CI^+$) calcd for $C_8H_9F_3NOS$ : $MH^+$=224.03569 ; Found : $MH^+$= 224.03573.

***N*-*n*-Hexyl trifluoromethanesulfinamide (3).**

Yellow liquid after extraction of the crude mixture with water and ether and drying on $CaCl_2$.

$^1$H NMR : 4.5 (broad s ; 1H) ; 3.24 (m ; 2H) ; 1.6 (quint ; 2H ; J = 7 Hz) ; 1.3 (massif ; 6H) ; 0.88 (t ; 3H ; J = 6.7 Hz). $^{13}$C NMR : 123.6 (q ; $^1J_{C\text{-}F}$ = 334.5 Hz) ; 43.3 ; 31.2 ; 30.9 ; 26.1 ; 22.45 ; 13.9. $^{19}$F NMR: -77.9. Mass spectrum : m/z = 148 ($M^{+\bullet}$-$CF_3$) ; 85 ; 69 ; 57 ; 43 ; 29. HRMS ($CI^+$) calcd for $C_7H_{15}F_3NOS$ : $MH^+$=218.08264 ; Found : $MH^+$= 218.08288.

**N-(1-phenylethyl) trifluoromethanesulfinamide (4).**

Yellow liquid (two diastereomers mixture : 46/54) after extraction with ether and brine and drying on $CaCl_2$. $^1$H NMR (200 MHz) : 7.26-7.42 (massif ; 5H) ; 4.75 (broad s ; 1H) ; 4.71 (broad q ; 1H, J=6.5 Hz) ; 1.62 (d ; 3H) ; 1.60 (d, 3H). $^{13}$C NMR (50 MHz) : 142.07 ; 141.58 ; 129.00 ; 128.96 ; 128.28 ; 126.67 ; 126.33 ; 123.68 (q ; $^1J_{C-F}$ = 333 Hz) ; 54.57 ; 54.28 ; 24.19 ; 23.79. $^{19}$F NMR : -78.24 (46%) and -78.29 (54%). Mass spectrum : m/z = 168 ($M^{+\bullet}$-$CF_3$) ; 105 ; 79 ; 77 ; 69. HRMS ($CI^+$) calcd for $C_9H_{11}F_3NOS$ : $MH^+$=238.05134 ; Found : $MH^+$= 238.05164.

**Phenyl trifluoromethanesulfinate (5).**

Yellow liquid after purification by flash chromatography with petroleum ether/ether (9/1) as eluent. $^1$H NMR (200 MHz) : 7.2-7.45 (massif). $^{13}$C NMR (50 MHz) : 152.03 ; 130.46 ; 127.29 ; 122.79 (q ; $^1J_{C-F}$= 335.7 Hz) ; 120.83. $^{19}$F NMR : -79.7. Mass spectrum : m/z = 210 ($M^{+\bullet}$) ; 141 ; 93 ; 77 ; 65 ; 39. HRMS ($CI^+$) calcd for $C_7H_5F_3O_2S$ : $MH^+$=210.99624 ; Found : $MH^+$= 210.99698.

**3,7-dimethyl-6-octenyl trifluoromethanesulfinate (6).**

Colorless liquid (two diastereomers mixture : 57/43) after purification by flash chromatography with petroleum ether as eluent.

$^1$H NMR : 5.06 (m ; 1H) ; 4.1-4.4 (m ; 2H) ; 0.8-2.0 (massif ; 7H) ; 1.66 (broad s ; 3H) ; 1.58 (broad s ; 3H) ; 0.90 and 0.91 (2 d ; 3H ; J = 6.4 Hz). $^{13}$C NMR : *Maj.* : 131.45 ; 124.18 ; 122.88 (q ; $^1J_{C-F}$ = 338.5 Hz) ; 67.40 ; 36.68 ; 36.54 ; 28.86 ; 25.5 ; 25.21 ; 18.99 ; 17.43. *Min.* : 131.45 ; 124.18 ; 122.88 (q ; $^1J_{C-F}$ = 338.5 Hz) ; 67.44 ; 36.77 ; 36.50 ; 28.86 ; 25.50 ; 25.22 ; 19.05 ; 17.43. $^{19}$F NMR : -79.04 (57%) and -79.1 (43%). Mass spectrum : m/z = 272 ($M^{+\bullet}$) ; 203 ; 138 ; 123 ; 109 ; 95 ; 81 ; 69 ; 55 ; 41. HRMS ($CI^+$) calcd for $C_{11}H_{20}F_3O_2S$ : $MH^+$=273.11361 ; Found : $MH^+$= 273.11234.

**(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl trifluoromethanesulfinate (7).**

Colorless liquid (two diastereomers mixture : 55/45) after purification by flash chromatography with petroleum ether as eluent.

$^1$H NMR : 4.24 and 4.22 (2 td partially superposed ; 1H ; $J_{ax\text{-}eq}$ = 4.6 Hz ; $J_{ax\text{-}ax}$ = 11.3 Hz and $J_{ax\text{-}eq}$ = 4.8 Hz ; $J_{ax\text{-}ax}$ = 11.0 Hz) ; 0.8-2.2 (massif ; 9H) ; 0.92 (m ; 6H) ; 0.78 and 0.75 (2 d ; 3H ; J = 7 Hz). $^{13}$C NMR: *Maj.* : 122.67 (q ; $^1J_{C-F}$ = 335.6 Hz) ; 85.24 ; 47.98 ; 42.76 ; 33.60 ; 31.82 ; 25.20 ; 22.96 ; 21.69 ; 20.59 ; 15.29. *Min.* : 122.60 (q ; $^1J_{C-F}$ = 334.7 Hz ; $CF_3$) ; 84.38 ; 47.79 ; 42.07 ; 33.62 ; 31.72 ; 25.36 ; 23.15 ; 21.73 ; 20.53 ; 15.47. $^{19}$F NMR: *Maj.* : -80.42(55%) and -81.05 (45%). GC-MS : m/e = *First diastereomer* : 139 ($M^{+\bullet}$-$CF_3SO_2$) ; 97 ; 83 ; 69 ; 57 ; 55 ; 43 ; 41. *Second diastereomer* : 139 ($M^{+\bullet}$-$CF_3SO_2$) ; 97 ; 83 ; 69 ; 57 ; 55; 43 ; 41. HRMS ($CI^+$) calcd for $C_{11}H_{20}F_3O_2S$ : $MH^+$=273.11361 ; Found : $MH^+$= 273.11439.

**2-Hexynyl trifluoromethanesulfinate (8)**

Yellow liquid after extraction with ether and brine and drying on $CaCl_2$.

$^1$H NMR : 4.9 (dt ; 1H ; $^2J$ = 15.1 Hz ; $^5J$ = 2.1 Hz) ; 4.8 (dt ; 1H ; $^2J$ = 15.1 Hz ; $^5J$ = 2.1 Hz ) ; 2.25 (tt ; 2H ; $^3J$ = 7.1 Hz ; $^5J$ = 2.1 Hz) ; 1.56 (sext ; 2H ; $^3J$ = 7.1 Hz) ; 1.25 (t ; 3H ; $^3J$ = 7.1 Hz). $^{13}$C NMR : 123.1 (q ; $^1J_{C\text{-}F}$ = 337.1 Hz) ; 92.7 ; 72.34 ; 57.42 ; 21.73 ; 20.85 ; 13.42. $^{19}$F NMR : -79.19. Mass spectrum : m/z = 145 ($M^{+\cdot}$-$CF_3$) ; 81 ; 79 ; 69 ; 53 ; 41 ; 39 ; 29. HRMS ($CI^+$) calcd for $C_7H_{10}F_3O_2S$ : $MH^+$=215.03536 ; Found : $MH^+$= 215.03620.

**1-methyl-2-(trifluoromethanesulfinyl)-1*H*-pyrrole (9)**

Yellow oil

$^1$H NMR : 6.94 (dd ; J = 1.6 Hz ; J = 2.7 Hz) ; 6.86 (dd ; J = 4.08 Hz; J = 1.6 Hz) ; 6.27 (dd ; J = 2.7 Hz ; J = 4.08 Hz) ; 3.9 (s). $^{13}$C NMR : 131.57 ; 124.93 (q ; $^1J_{C\text{-}F}$ = 336 Hz) ; 119.43 ; 109.77 ; 35.4. $^{19}$F NMR : -73.17.

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