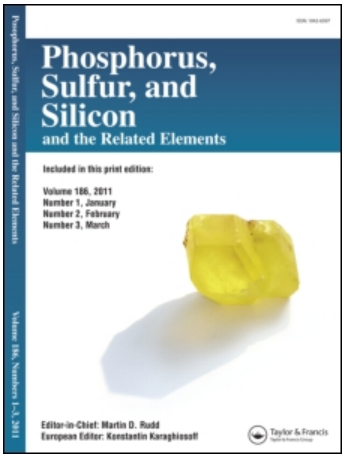

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A CONVENIENT SYNTHESIS OF N-FUNCTIONALIZED PERFLUOROALKANESULFONAMIDES

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This article describes the synthesis of new N-functionalized perfluoroalkanesulfonamides (5) with two sulfonamides functionalities. Perfluoroalkanesulfonyl fluoride underwent a reaction with 2-chloroethylamine hydrochloride or 3-bromopropylamine hydrobromide to give N-(2-chloroethyl or 3-bromopropyl) perfluoroalkanesulfonamides (1). Reaction of (1) with potassium thiocyanate gave N-(2-thiocyanatoethyl or 3-thiocyanatopropyl) perfluoroalkanesulfonamides (3). The sulfonyl chloride derivatives (4) were prepared by reaction of 3 with sulfuryl chloride. In the last step, 4 reacted with ammonia to give the bis sulfonamides derivatives (5). The structures of all new compounds prepared were determined by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopies and by HR-MS.

Keywords Alkylamine salts; N-functionalized perfluoroalkanesulfonamides; perfluoroalkanesulfonyl fluoride

INTRODUCTION

Sulfonamides are an important class of pharmaceutical compounds that exhibit a wide spectrum of biological activities. This functional group constitutes the largest class of antimicrobial drugs, diuretics, carbonic anhydrase inhibitors, anticonvulsants, hypoglycemics, antithyroids agents, and antitumor drugs, and they exhibit a number of other biological activities as well.[1–9] Furthermore, some of them have proved to be useful as herbicides and plaguicides.[10,11] These activities have increased interest in the synthesis of sulfonamides.

The sulfonamides function has been widely studied in the carbohydrogenated compounds around major applications such as hypoglycemic agents, antibiotics, and carbonic anhydrase inhibitors. However investigations on polyfluoroalkanesulfonamides or perfluoroalkanesulfonamides with a long chain have not been carried out in the biological area.

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Generally, these fluorinated sulfonamides have been investigated principally for their toxicity, environmental impact of surfactants, surface treatments for clothes, home furnishings, and paper protection properties.[12–15]

Sulfonamides are usually prepared from substituted sulfonyl chlorides or anhydrides in the presence of a base in an aprotic solvent.[16–18]

The N-functionalized perfluoroalkanesulfonamides may be synthesized from perfluoroalkanesulfonyl azides or from the sulfonyl fluorides with the corresponding primary amine in the presence of a base.[16,19–21]

Recently, we have reported the synthesis of perfluoroalkanesulfonamides, and we have studied the inhibition effects of these compounds on bovine carbonic anhydrase.[22] In continuation of our research on the synthesis of bioactive perfluoroalkanesulfonamides, we describe in this article the multistep synthesis of new N-functionalized perfluoroalkanesulfonamides, which contain two sulfonamide groups, starting from perfluoroalkanesulfonyl fluoride and alkylamine hydrochloridex or hydrobromides.

RESULTS AND DISCUSSION

The N-(2-chloroethyl or 3-bromopropyl) perfluoroalkanesulfonamides (**1**) were prepared from the perfluoroalkanesulfonyl fluorides and suitable amine salts with triethylamine (TEA) in EtOAc at 0°C. It is interesting to note that the synthesis of sulfonamides derivatives (**1**) leads to side products, which were identified as perfluoroalkanesulfonic acid (**2**) (Scheme 1).

In each case, an excellent conversion of perfluoroalkanesulfonyl fluorides into N-(2-chloroethyl or 3-bromopropyl) perfluoroalkanesulfonamides was observed. Recrystallization of these compounds in an ethanol/water mixture (V/V, 90:10) gave the corresponding N-(2-chloroethyl or 3-bromopropyl) perfluoroalkanesulfonamides (**1a–d**) with high purity in moderate to good yields (Table I).

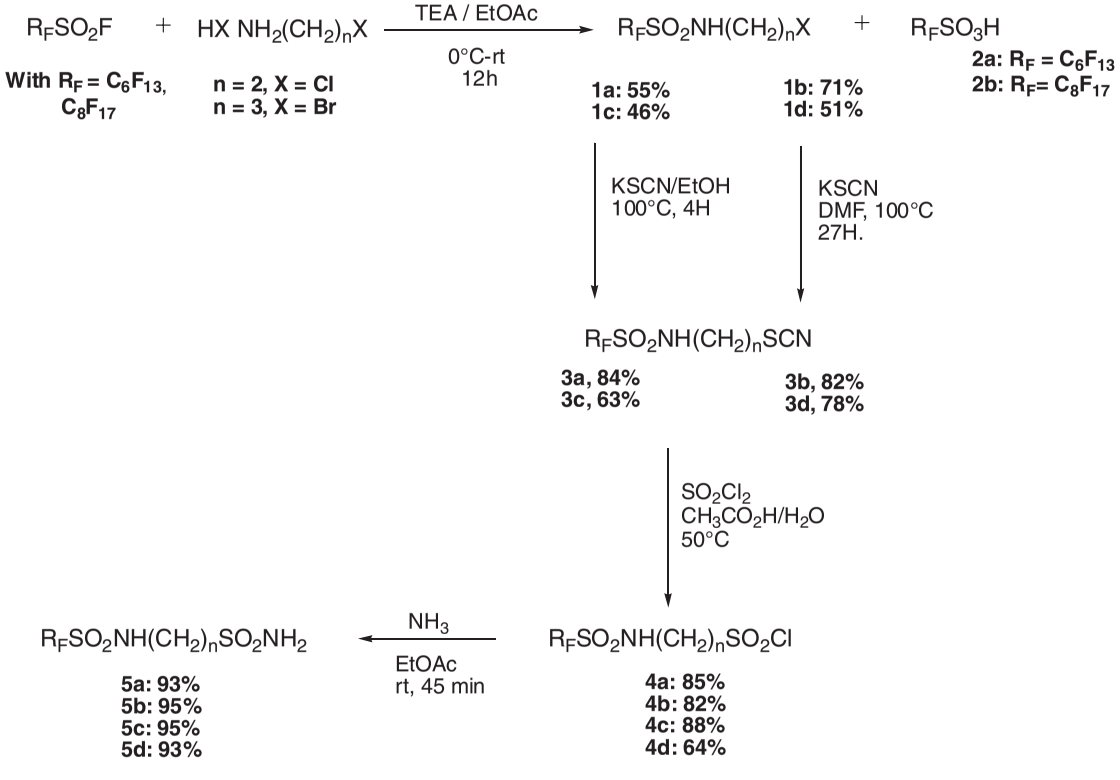
The formation of the perfluoroalkanesulfonic acid (**2**) was probably related to the hydrolysis of the perfluoroalkanesulfonyl fluoride, which did not react in the presence of water and an excess of TEA after the treatment of the crude product. The formation rate was determined as a function of time using ^{19}F NMR spectroscopy (Figure 1).

Table I Preparation of the N-(2-chloroethyl or 3-bromopropyl)-perfluoroalkanesulfonamides

Reactants		Products				
R_FSO_2F	Amine salts	**1**	Conversion[a] (%)	Yield[b] (%)	**2**	Conversion[a] (%)
$C_6F_{13}SO_2F$	$Cl^-\,{}^+NH_3(CH_2)_2Cl$	**b**	93	71	**a**	7
$C_8F_{17}SO_2F$	$Cl^-\,{}^+NH_3(CH_2)_2Cl$	**d**	90	51	**b**	10
$C_6F_{13}SO_2F$	$Br^-\,{}^+NH_3(CH_2)_3Br$	**a**	93	55	**a**	7
$C_8F_{17}SO_2F$	$Br^-\,{}^+NH_3(CH_2)_3Br$	**c**	91	46	**b**	9

[a]The conversions were determined by ^{19}F NMR spectrocopy (d_6-acetone) after treatment of the crude product. They were also determined by the relative integration of the functional CF_2 signal of compounds **1a**, **1b**, **1c**, **1d**, **2a**, and **2b** by the formula (fi/Ni)/(Σfi/Ni) × 100, where fi represents the height integration of the functional CF_2 signal and Ni the number of corresponding atom.

[b]All these compounds **1** were crystallized in ethanol/water (V/V, 90:10) media.



Scheme 1

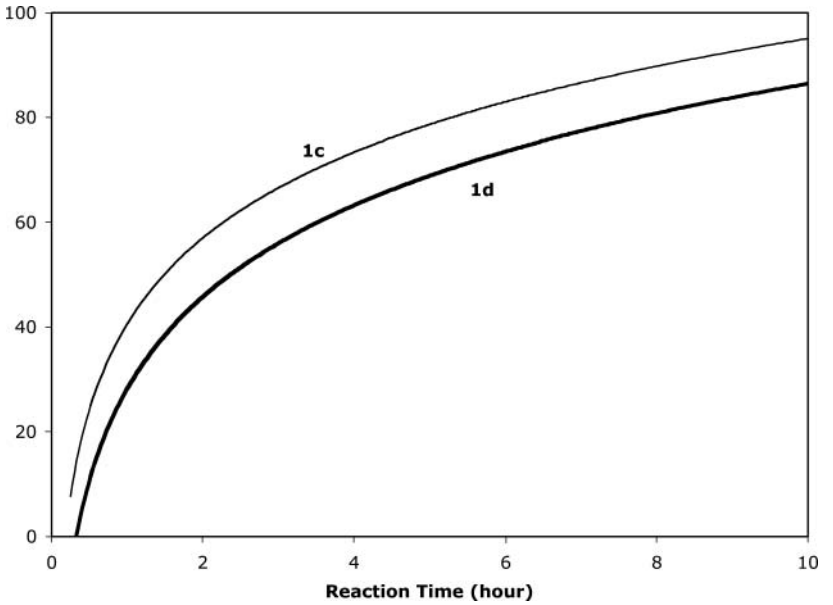


Figure 1 Formation rate of **1c** and **1d**. The conversions were determined by ^{19}F NMR spectroscopy (d_6-acetone) after treatment of the crude product (the residue was diluted with water and EtOAc then washed with 1N HCl and water). They were also determined by the relative integration of the functional $\mathbf{CF_2}$ signal respectively of **1c** and **1d** compared with that of the functional $\mathbf{CF_2}$ signal of $C_8F_{17}SO_2F$.

The N-(3-bromopropyl) perfluoroalkanesulfonamides **1a** and **1c** reacted with potassium thiocyanate in absolute ethanol at 100°C for 4 h and yielded the desired N-(3-thiocyanatopropyl) perfluoroalkanesulfonamides **3a** and **3c** in good yields (Scheme 1).

We also employed similar conditions (1.5 eq. of potassium thiocyanate in absolute ethanol at 100°C for 4 h) for the synthesis of N-(2-thiocyanatoethyl) perfluoroalkanesulfonamides **3b** and **3d**, but unfortunately the starting material **1b** and **1d** still remained unreacted (Scheme 1). The chlorine atom was a less suitable leaving group than the bromine atom.

In order to find out the optimum conditions, the reactions of **1d** with potassium thiocyanate were examined under various reaction conditions (Table II). In each case, the formation of **3b** and **3d** were determined by ^1H NMR spectroscopy. When more than 1.5 eq. of potassium thiocyanate in ethanol (protic and polar solvent), in acetone (aprotic and polar solvent), or acetonitrile (aprotic and polar solvent) were used, there was no formation of the desired product (**3b** and **3d**). However, when we used 1.5 eq. of potassium thiocyanate in DMF (solvent with a high dielectric constant) at 100°C for 27 h, the reaction was complete. DMF is a basic solvent that solvates specifically the K^+ ions and leads to more reactivity of the nucleophile ^-SCN. It is interesting to note that the reaction time is the same regardless of the length of the F-alkylated chain studied (Table II).

The N-(2-thiocyanatoethyl or 3-thiocyanatopropyl) perfluoroalkanesulfonamides (**3**) react with sulfuryl chloride in a mixture of acetic acid/water at 50°C to lead to the corresponding alkanesulfonyl chloride derivatives (**4a–d**) in good yields according to a method developed in our laboratory.

In the last step, the N-functionalized perfluoroalkanesulfonamides (**5a–d**) were prepared by reaction of **4** with gaseous ammonia in EtOAc in good yields. Compounds **5a–d**

Table II Preparation of the N-(2-thiocyanatoethyl)-perfluoroalkanesulfonamides

Reactants				Products	
1 (1 eq.)	KSCN (eq.)	Solvent	Reaction time (h)	**3**	Conversion[a] (%)
1d	1.5	Ethanol	1	**3d**	0
1d	1.5	Ethanol	4	**3d**	0
1d	1.5	Ethanol	12	**3d**	0
1d	1.5	Ethanol	22	**3d**	0
1d	10	Ethanol	22	**3d**	0
1d	10	Ethanol	100	**3d**	0
1d	1.5	Acetone	4	**3d**	0
1d	1.5	Acetone	25	**3d**	0
1d	10	Acetone	25	**3d**	0
1d	1.5	Acetonitrile	4	**3d**	0
1d	1.5	Acetonitrile	25	**3d**	0
1d	10	Acetonitrile	25	**3d**	0
1d	1.5	DMF	23	**3d**	92
1d	1.5	DMF	27	**3d**	100
1b	1.5	DMF	23	**3b**	93
1b	1.5	DMF	27	**3b**	100

[a]The conversions were determined by ^{1}H NMR spectroscopy (d_6-acetone) after treatment of the crude product (the residue was diluted with water and EtOAc and washed with water). They were also determined by the relative integration of the functional C**H$_2$** signal of **3b** and **3d** compared, respectively, with that of the functional C**H$_2$** signal of **2b** and **2d**.

were recrystallized in an ethanol/water mixture (V/V, 90:10) and were characterized by ^{19}F, ^{1}H, ^{13}C NMR spectroscopies and HRMS (Scheme 1).

CONCLUSION

In summary, we prepared new N-functionalized perfluoroalkanesulfonamides, which contain two sulfonamides function by a multistep reaction starting from perfluoroalkanesulfonyl fluoride and alkylamine hydrochlorides or hydrobromides. They were obtained in good yields, and they were characterized by ^{19}F, ^{1}H, and ^{13}C NMR spectroscopies and HRMS.

EXPERIMENTAL

Moisture-sensitive reactions were carried out under dry nitrogen. Different perfluoroalkyl sulfonyl fluorides were prepared according to a method developed in our laboratory.[23,24] Solvents were distilled from the appropriate drying agents immediately prior to use.

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 300.13 MHz, 282.37 MHz, and 75.46 MHz, respectively, with a Bruker Avance 300 spectrometer; the chemical shifts are given in ppm relative to Me_4Si for the ^{1}H and ^{13}C, and CCl_3F for ^{19}F, as internal standards. Coupling constants were given in Hz. Mass spectra and HRMS were recorded on a Jeol SX 102 spectrometer.

Melting points were recorded at atmospheric pressure, unless otherwise stated, on a Stuart Scientific SMP3 apparatus and were uncorrected.

Synthesis of $R_FSO_2NH(CH_2)_nX$ (1): General Procedure (GP1)

To a suspension of 3-bromopropylamine hydrobromide or 2-chloroethylamine hydrochloride (1 eq.) in anhydrous ethyl acetate, triethylamine (2 eq.) and perfluoroalkanesulfonyl fluoride (0.9 eq.) were added at 0°C. The mixture was then stirred at room temperature for 12 h, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by crystallization from EtOH/H_2O (90:10).

Synthesis of N-(3-bromopropyl)-perfluorohexanesulfonamide 1a. Compound **1a** (11.73 g, 55%) was obtained from 3-bromopropylamine hydrobromide (10.0 g, 45.7 mmol) according to the GP1.

Mp: 89–90°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ:2.21 (m, 2H, C**H$_2$**CH$_2$Br), 3.62 (m, 4H, C**H$_2$**CH$_2$C**H$_2$**Br), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.80 (m, 2F, CF$_3$C**F$_2$**), −123.30 (m, 2F, CF$_3$CF$_2$C**F$_2$**), −122.36 (m, 2F, C**F$_2$**(CF$_2$)$_2$SO$_2$), −120.97 (m, 2F, C**F$_2$**CF$_2$SO$_2$), −113.58 (m, 2F, C**F$_2$**SO$_2$), −81.66 (m, 3F, C**F$_3$**); ^{13}C NMR (75.46 MHz, d_6-acetone): δ:30.6 (**C**H$_2$), 34.1 (CH$_2$-**C**H$_2$-CH$_2$), 43.7 (**C**H$_2$), 108–120 (**C$_6$**F$_{13}$); MS (FAB$^-$) m/z: 518.

Synthesis of N-(2-chloroethyl)-perfluorohexanesulfonamide 1b. Compound **1b** (12.63 g, 71%) was obtained from 2-chloroethylamine hydrochloride (5.0 g, 43.1 mmol) according to the GP1.

Mp: 100–101°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ:3.65 (m, 4H, (C**H$_2$**)$_2$), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.77 (m, 2F, CF$_3$C**F$_2$**), −123.30 (m, 2F, CF$_3$CF$_2$C**F$_2$**), −122.37 (m, 2F, C**F$_2$**(CF$_2$)$_2$SO$_2$), −120.94 (m, 2F, C**F$_2$**CF$_2$SO$_2$), −113.60 (m, 2F, C**F$_2$**SO$_2$), −81.68 (m, 3F, C**F$_3$**); ^{13}C NMR (75.46 MHz, d_6-acetone): δ: 42.9 (**C**H$_2$), 44.8 (**C**H$_2$), 108–120 (**C$_6$**F$_{13}$); MS (FAB$^-$) m/z: 460.

Synthesis of N-(3-bromopropyl)-perfluorooctanesulfonamide 1c. Compound **1c** (11.76 g, 46%) was obtained from 3-bromopropylamine hydrobromide (10.0 g, 45.7 mmol) according to the GP1.

Mp: 100–101°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ:2.21 (m, 2H, C**H$_2$**CH$_2$Br), 3.63 (m, 4H, C**H$_2$**CH$_2$C**H$_2$**Br), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.80 (m, 2F, CF$_3$C**F$_2$**), −123.25 (m, 2F, CF$_3$CF$_2$C**F$_2$**), −122.36 (m, 6F, (C**F$_2$**)$_3$(CF$_2$)$_2$SO$_2$), −120.97 (m, 2F, C**F$_2$**CF$_2$SO$_2$), −113.52 (m, 2F, C**F$_2$**SO$_2$), −81.68 (m, 3F, C**F$_3$**); ^{13}C NMR (75.46 MHz, d_6-acetone): δ:30.5 (**C**H$_2$), 34.2 (CH$_2$-**C**H$_2$-CH$_2$), 43.7 (**C**H$_2$), 108–120 (**C$_8$**F$_{17}$); MS (FAB$^-$) m/z: 618.

Synthesis of N-(2-chloroethyl)-perfluorooctanesulfonamide 1d. Compound **1d** (21.97 g, 51%) was obtained from 2-chloroethylamine hydrochloride (10 g, 86.2 mmol) according to the GP1.

Mp: 120–121°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 3.75 (m, 4H, (C**H$_2$**)$_2$), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.86 (m, 2F, CF$_3$C**F$_2$**(CF$_2$)$_6$-), −123.41 (m, 2F, CF$_3$CF$_2$C**F$_2$**(CF$_2$)$_5$-), −122.40 (m, 6F, CF$_3$(CF$_2$)$_2$(C**F$_2$**)$_3$(CF$_2$)$_2$-), −121.01 (m, 2F, CF$_3$(CF$_2$)$_5$C**F$_2$**CF$_2$-), −113.73 (m, 2F, CF$_3$(CF$_2$)$_6$C**F$_2$**-), −81.86 (m, 3F, C**F$_3$**(CF$_2$)$_7$); ^{13}C NMR (75.46 MHz, d_6-acetone): δ: 44.1 (**C**H$_2$), 46.9 (**C**H$_2$), 108–120 (**C$_8$**F$_{17}$); MS (FAB$^-$) m/z: 560.

Synthesis of of $R_FSO_2NH(CH_2)_nSCN$ (3): General Procedure (GP2)

These compounds were prepared by reaction of potassium thiocyanate (1.5 eq.) with either **1a** and **1c** (1 eq.) in absolute ethanol or **1b** and **1d** in DMF at 100°C, for 4 h and 27 h,

respectively. After completion and cooling, all volatile parts of the mixture were removed in vacuo. The residue was dissolved in EtOAc and washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to yield the corresponding alkyl thiocyanates, which were used in the next step without any purification.

Synthesis of N-(3-thiocyanatopropyl)-perfluorohexanesulfonamide 3a. Compound **3a** (5.05 g, 84%) was prepared starting from **1a** (6.3 g, 12.1 mmol) in absolute ethanol (60 mL) according to the GP2.

Mp: 84–86°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 2.21 (m, 2H, $CH_2C\mathbf{H_2}CH_2$), 3.25 (m, 2H, $C\mathbf{H_2}SCN$), 3.55 (m, 2H, $NHC\mathbf{H_2}$), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.78 (m, 2F, $CF_3C\mathbf{F_2}$), −123.30 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.36 (m, 2F, $C\mathbf{F_2}(CF_2)_2S$), −120.96 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.59 (m, 2F, $C\mathbf{F_2}S$), −81.68 (m, 3F, $C\mathbf{F_3}$); ^{13}C NMR (75.46 MHz, d_6-acetone): δ: 31.4 ($\mathbf{C}H_2SCN$), 31.6 ($\mathbf{C}H_2$), 43.0 ($NH\mathbf{C}H_2$), 112.7 (S**C**N), 108–120 ($\mathbf{C_6}F_{13}$); MS (FAB$^-$) m/z: 497.

Synthesis of N-(2-thiocyanatoethyl)-perfluorohexanesulfonamide 3b. Compound **3b** (4.77 g, 82%) was prepared starting from **1b** (5.6 g, 12.1 mmol) in DMF (50 mL) according to the GP2.

Mp: 115–117°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 3.25 (m, 2H, $C\mathbf{H_2}SCN$), 3.65 (m, 2H, $NHC\mathbf{H_2}$), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.90 (m, 2F, $CF_3C\mathbf{F_2}$), −123.43 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.48 (m, 2F, $C\mathbf{F_2}(CF_2)_2S$), −121.04 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.54 (m, 2F, $C\mathbf{F_2}S$), −81.89 (m, 3F, $C\mathbf{F_3}$); ^{13}C NMR (75.46 MHz, d_6-acetone): δ: 34.7 ($\mathbf{C}H_2SCN$), 44.6 ($NH\mathbf{C}H_2$), 112.0 (S**C**N), 107–121 ($\mathbf{C_6}F_{13}$); MS (FAB$^-$) m/z: 522.

Synthesis of N-(3-thiocyanatopropyl)-perfluorooctanesulfonamide 3c. Compound **3c** (5.65 g, 63%) was prepared starting from **1c** (9.22 g, 14.9 mmol) in absolute ethanol (65 mL) according to the GP2.

Mp: 121–122°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 2.22 (m, 2H, $CH_2C\mathbf{H_2}CH_2$), 3.25 (m, 2H, $C\mathbf{H_2}SCN$), 3.55 (m, 2H, $NHC\mathbf{H_2}$), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.80 (m, 2F, $CF_3C\mathbf{F_2}$), −123.25 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.36 (m, 6F, $(C\mathbf{F_2})_3(CF_2)_2S$), −120.97 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.59 (m, 2F, $C\mathbf{F_2}S$), −81.68 (m, 3F, $C\mathbf{F_3}SCN$); ^{13}C NMR (75.46 MHz, d_6-acetone): δ: 30.7 ($\mathbf{C}H_2SCN$), 31.1 ($\mathbf{C}H_2$), 42.7 ($NH\mathbf{C}H_2$), 111.6 (S**C**N), 108–120 ($\mathbf{C_8}F_{17}$); MS (FAB$^-$) m/z: 597.

Synthesis of N-(2-thiocyanatoethyl)-perfluorooctanesulfonamide 3d. Compound **3d** (5.0 g, 78%) was prepared starting from **1d** (6.2 g, 11.1 mmol) in DMF (55 mL) according to the GP2.

Mp: 118–120°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 3.38 (m, 2H, $C\mathbf{H_2}SCN$), 3.77 (m, 2H, $NHC\mathbf{H_2}$), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.77 (m, 2F, $CF_3C\mathbf{F_2}$), −123.28 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.25 (m, 6F, $(C\mathbf{F_2})_3(CF_2)_2S$), −120.90 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.43 (m, 2F, $C\mathbf{F_2}S$), −81.69 (m, 3F, $C\mathbf{F_3}$);^{13}C NMR (75.46 MHz, d_6-acetone): δ: 34.7 ($\mathbf{C}H_2SCN$), 44.6 ($NH\mathbf{C}H_2$), 111.8 (S**C**N), 108–120 ($\mathbf{C_8}F_{17}$); MS (FAB$^-$) m/z: 583.

Synthesis of of $R_FSO_2NH(CH_2)_nSO_2Cl$ (4): General Procedure (GP3)

Compounds **3a–d** dissolved in a mixture of acetic acid (5 eq.) and water (1.5 eq.) were stirred for 30 min at 50°C. Sulfuryl chloride (SO_2Cl_2, 10 eq.) was added dropwise to the reaction mixture at 50°C. This reaction was accompanied by a strong emission of gases (SO_2 and Cl_2), which were trapped with an aqueous solution of NaOH (1 M). The excess of

SO_2Cl_2, present in the media, was hydrolyzed by the dropwise addition of water. The crude product was extracted three times with EtOAc. The combined organic extracts were washed three times with water, dried over anhydrous Na_2SO_4, and concentrated, giving a crude material alkanesulfonyl chlorides (**4a–d**), which could be used without any purification.

Synthesis of N-(3-sulfonylchloridepropyl)-perfluorohexanesulfonamide 4a. Compound **4a** (4.59 g, 85%) was obtained from **3a** (5.0 g, 10 mmol) according to the GP3. The excess of SO_2Cl_2 was hydrolyzed by the addition of water (25 mL).

Mp: 114–119°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 2.41 (m, 2H, $CH_2C\mathbf{H_2}CH_2$), 3.65 (m, 2H, $NHC\mathbf{H_2}$), 4.22 (m, 2H, $C\mathbf{H_2}SO_2Cl$), 8.50 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.81 (m, 2F, $CF_3C\mathbf{F_2}$), −123.27 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.35 (m, 2F, $C\mathbf{F_2}(CF_2)_2S$), −120.94 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.48 (m, 2F, $C\mathbf{F_2}S$), −81.63 (m, 3F, $C\mathbf{F_3}$);^{13}C NMR (75.46 MHz, d_6-acetone): δ: 26.6 ($\mathbf{C}H_2$), 42.8 ($NH\mathbf{C}H_2$), 62.8 ($\mathbf{C}H_2SO_2Cl$), 108–120 ($\mathbf{C_6}F_{13}$).

Synthesis of N-(2-sulfonylchlorideethyl)-perfluorohexanesulfonamide 4b. Compound **4b** (4.28 g, 82%) was obtained from **3b** (4.77 g, 9.9 mmol) according to the GP3. The excess of SO_2Cl_2 was hydrolyzed by the addition of water (20 mL).

Mp: 104–106°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 4.10 (m, 2H, $NHC\mathbf{H_2}$), 4.45 (m, 2H, $C\mathbf{H_2}SO_2Cl$);^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.76 (m, 2F, $CF_3C\mathbf{F_2}$), −123.28 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.34 (m, 2F, $C\mathbf{F_2}(CF_2)_2S$), −120.91 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.44 (m, 2F, $C\mathbf{F_2}S$), −81.66 (m, 3F, $C\mathbf{F_3}$);^{13}C NMR (75.46 MHz, d_6-acetone): δ: 39.8 ($NH\mathbf{C}H_2$), 64.7 ($\mathbf{C}H_2SO_2Cl$), 108–120 ($\mathbf{C_6}F_{13}$).

Synthesis of N-(3-sulfonylchloridepropyl)-perfluorooctanesulfonamide 4c. Compound **4c** (5.09 g, 88%) was obtained from **3c** (5.42 g, 9.06 mmol) according to the GP3. The excess of SO_2Cl_2 was hydrolyzed by the addition of water (25 mL).

Mp: 116–118°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 2.41 (m, 2H, $C\mathbf{H_2}CH_2SO_2Cl$); 3.63 (m, 2H, $NHC\mathbf{H_2}$); 4.15 (m, 2H, $C\mathbf{H_2}SO_2Cl$); 8.52 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.73 (m, 2F, $CF_3C\mathbf{F_2}$), −123.25 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.26 (m, 6F, $(C\mathbf{F_2})_3(CF_2)_2S$), −120.91 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.45 (m, 2F, $C\mathbf{F_2}S$), −81.64 (m, 3F, $C\mathbf{F_3}$);^{13}C NMR (75.46 MHz, d_6-acetone): δ: 25.41 ($\mathbf{C}H_2$), 41.60 ($NH\mathbf{C}H_2$), 61.59 ($\mathbf{C}H_2SO_2Cl$), 108–120 ($\mathbf{C_8}F_{17}$).

Synthesis of N-(2-sulfonylchlorideethyl)-perfluorooctanesulfonamide 4d. Compound **4d** (2.74 g, 64%) was obtained from **3d** (4 g, 6.85 mmol) according to the GP3. The excess of SO_2Cl_2 was hydrolyzed by the addition of water (20 mL).

Mp: 134–136°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 4.12 (m, 2H, $NHC\mathbf{H_2}$); 4.42 (m, 2H, $C\mathbf{H_2}SO_2Cl$); 8.71 (m, 1H, $SO_2N\mathbf{H}$); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.70 (m, 2F, $CF_3C\mathbf{F_2}$), −123.22 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.27 (m, 6F, $(C\mathbf{F_2})_3(CF_2)_2S$), −120.83 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.35 (m, 2F, $C\mathbf{F_2}S$), −81.64 (m, 3F, $C\mathbf{F_3}$);^{13}C NMR (75.46 MHz, d_6-acetone): δ: 40.55 ($NH\mathbf{C}H_2$), 65.08 ($\mathbf{C}H_2SO_2Cl$), 108–120 ($\mathbf{C_8}F_{17}$).

Synthesis of of $R_FSO_2NH(CH_2)_nSO_2NH_2$ (5): General Procedure (GP4)

The compounds **4a–d** were dissolved in ethyl acetate (30 mL), and gaseous NH_3 was bubbled through the solution for 15 min at room temperature. The mixture was stirred at room temperature for 30 min, then filtered. The organic layer was washed three times with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified by crystallization from EtOH/H_2O (90:10) to give the title compound.

Synthesis of N-(3-propylsulfonamide)-perfluorohexanesulfonamide 5a. Compound **5a** (3.55 g, 93%) was obtained from **4a** (4 g, 7.41 mmol) according to the GP4.

Mp: 138–140°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 2.15 (m, 2H, $CH_2C\mathbf{H_2}CH_2$), 3.23 (m, 2H, $C\mathbf{H_2}SO_2NH_2$), 3.61 (m, 2H, $NHC\mathbf{H_2}$), 6.30 (m, 2H, $N\mathbf{H_2}$), 8.41 (m, 1H, N**H**);^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.75 (m, 2F, $CF_3C\mathbf{F_2}$), −123.28 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.34 (m, 2F, $C\mathbf{F_2}(CF_2)_2S$), −120.94 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.51 (m, 2F, $C\mathbf{F_2}S$), −81.64 (m, 3F, $C\mathbf{F_3}$);^{13}C NMR (75.46 MHz, d_6-acetone): δ: 25.3 ($\mathbf{C}H_2CH_2$), 43.0 ($NH\mathbf{C}H_2$), 51.8 ($\mathbf{C}H_2SO_2$), 108–119 ($\mathbf{C_6}F_{13}$); MS (FAB$^-$) m/z:519; HRMS calcd for $C_9H_8O_4N_2F_{13}S_2$: 518.9645; found 518.9635.

Synthesis of N-(2-ethylsulfonamide)-perfluorohexanesulfonamide 5b. Compound **5b** (3.90 g, 95%) was obtained from **4b** (4.28 g, 8.14 mmol) according to the GP4.

Mp: 149–151°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 3.42 (m, 2H, $NHC\mathbf{H_2}$), 3.85 (m, 2H, $C\mathbf{H_2}SO_2NH_2$), 6.60 (m, 3H, N**H**, $N\mathbf{H_2}$); ^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.75 (m, 2F, $CF_3C\mathbf{F_2}$), −123.27 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.32 (m, 2F, $C\mathbf{F_2}(CF_2)_2S$), −120.92 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.51 (m, 2F, $C\mathbf{F_2}S$), −81.61 (m, 3F, $C\mathbf{F_3}$); ^{13}C NMR (75.46 MHz, d_6-acetone): δ: 40.4 ($\mathbf{C}H_2$), 55.4 ($\mathbf{C}H_2$), 108–119 ($\mathbf{C_6}F_{13}$); MS (FAB$^+$) m/z:507; HRMS calcd for $C_8H_8O_4N_2F_{13}S_2$: 506.9718; found 506.9735.

Synthesis of N-(3-propylsulfonamide)-perfluorooctanesulfonamide 5c. Compound **5c** (3.22 g, 95%) was obtained from **4c** (3.62 g, 5.66 mmol) according to the GP4.

Mp: 158–160°C; ^{1}H NMR (300.13 MHz, d_6-DMSO): δ: 1.90 (m, 2H, $CH_2C\mathbf{H_2}CH_2$), 3.01 (m, 2H, $C\mathbf{H_2}SO_2NH_2$), 3.32 (m, 2H, $NHC\mathbf{H_2}$), 6.85 (m, 2H, $N\mathbf{H_2}$), 9.65 (m, 1H, N**H**); ^{19}F NMR (282.37 MHz, d_6-DMSO): δ: −126.62 (m, 2F, $CF_3C\mathbf{F_2}$), −123.17 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.13 (m, 6F, $(C\mathbf{F_2})_3(CF_2)_2S$), −120.69 (m, 2F, $C\mathbf{F_2}CF_2S$); −113.49 (m, 2F, $C\mathbf{F_2}S$); −81.40 (m, 3F, $C\mathbf{F_3}$);^{13}C NMR (75.46 MHz, d_6-DMSO): δ: 25.5 ($CH_2\mathbf{C}H_2CH_2$), 42.8 ($NH\mathbf{C}H_2$), 52.0 ($\mathbf{C}H_2SO_2$), 108–120 ($\mathbf{C_8}F_{17}$); MS (FAB$^-$) m/z: 619; HRMS calcd for $C_{11}H_8O_4N_2F_{17}S_2$: 618.9654; found 618.9641.

Synthesis of N-(2-ethylsulfonamide)-perfluorooctanesulfonamide 5d. Compound **5d** (2.25 g, 93%) was obtained from **4d** (2.5 g, 4 mmol) according to the GP4.

Mp: 161–162°C; ^{1}H NMR (300.13 MHz, d_6-acetone): δ: 3.43 (m, 2H, $NHC\mathbf{H_2}$), 3.83 (m, 2H, $C\mathbf{H_2}SO_2NH_2$), 6.50 (m, 3H, N**H**, $N\mathbf{H_2}$);^{19}F NMR (282.37 MHz, d_6-acetone): δ: −126.71 (m, 2F, $CF_3C\mathbf{F_2}$), −123.22 (m, 2F, $CF_3CF_2C\mathbf{F_2}$), −122.24 (m, 6F, $(C\mathbf{F_2})_3(CF_2)_2S$), −120.86 (m, 2F, $C\mathbf{F_2}CF_2S$), −113.49 (m, 2F, $C\mathbf{F_2}S$), −81.61 (m, 3F, $C\mathbf{F_3}$);^{13}C NMR (75.46 MHz, d_6-acetone): δ: 39.1 ($\mathbf{C}H_2$), 54.2 ($\mathbf{C}H_2$), 108–120 ($\mathbf{C_8}F_{17}$); MS (FAB$^+$) m/z:607; HRMS calcd for $C_{10}H_8O_4N_2F_{17}S_2$: 606.9815; found 606.9825.

REFERENCES

1. N. Anand, In *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed., M. E. Wolff, Ed. (J. Wiley & Sons, New York, 1996), vol. 2, pp. 527–544.
2. L. Bouissane, S. El Kazzouli, S. Léonce, B. Pfeiffer, E.M. Rakib, and M. Khouili, *Bioorg. Med. Chem.*, **14,** 1078–1088 (2006).
3. G. Melagraki, A. Afantinis, S H. Arimveis, O. Iglessi-Markopoulou, and C. T. Supuran, *Bioorg. Med. Chem.*, **14,** 1108–1114 (2006).
4. D. Mandloi, S. Joshi, P. V. Khadikar, and N. Khosla, *Bioorg. Med. Chem.*, **17,** 15–40 (2005).
5. D. Vullo, B. Steffansen, B. Brodin, C. T. Supuran, A. Scozzafava, and C. U. Nielsen, *Bioorg. Med. Chem.*, **14,** 2418–2427 (2006).
6. A. Sherif, F. Rostom, *Bioorg. Med. Chem.*, **14,** 6475–6485 (2006).

7. M. A Santos, S. M. Marques, T. Tuccinardi, P. Carelli, L. Panelli, and A. Rossello, *Bioorg. Med. Chem.*, **14,** 7539–7550 (2006).
8. S. Joshi, N. Khosla, and P. Tiwari, *Bioorg. Med. Chem.*, **12,** 571 (2004).
9. P. R. Hanson, D. A. Probst, R. E. Robinson, and M. Yau, *Tetrahedron Lett.*, **40,** 4761–4764 (1999).
10. R. J. Cremlyn, M. J. Frearson, and S. Graham, *Phosphorus, Sulfur, and Silicon*, **107,** 205–217 (1995).
11. K. Fujii, K. Hatano, K. Tsutsumiuchi, A. Ooka, Y. Nakamoto, and H. Umeyama, JP Patent, 2000136179 A2 (2000).
12. G.-L. Li, L.-Q. Zheng, and J.-X. Xiao, *J. Fluorine Chem.*, **130,** 674–681 (2009).
13. H.-J. Lehmler, V. V. V. N. S. Rama Rao, D. Nauduri, J. D. Vargo, and S. Parkin, *J. Fluorine. Chem.*, **128**(6), 595–607 (2007).
14. E. Kissa, *Fluorinated Surfactants and Repellents*, Surfactant Science Series, vol. 97 (Marcel Dekker, New York, 2001).
15. R. Cremlyn, *Organosulfur Chemistry: An Introduction* (John Wiley and Sons, New York, 1996).
16. K. Strancar, D. Blanot, and S. Gobec, *Bioorg. Med. Chem. Lett.*, **16,** 343–348 (2006).
17. H. G. Khorana, *Can. J. Chem.*, **31,** 585–588 (1953).
18. H.-J. Lehmler, *Chemosphere*, **58,** 1471–1496 (2005).
19. Y. Xu and S. Zhu, *Tetrahedron*, **57,** 4337–4341 (2001).
20. R. E. Banks, B. E. Smart, J. C. Tatlow, Eds., *Organofluorine Chemistry: Principles and Commercial Applications* (Plenum Press, New York, 1994).
21. S. Benefice-Malouet, H. Blancou, R. Teissedre, and A. Commeyras, *J. Fluorine Chem.*, **31,** 319–332 (1986).
22. H. Blancou, F. D. Guillen, and Z. Benfodda, WO Patent, 2006067330 (2006).
23. H. Blancou and F. D. Guillen, WO Patent, 2002081431 (2002).
24. H. Blancou and F. D. Guillen, WO Patent, 2002081081 (2002).