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Polyfluoroalkylation of 2-aminothiazoles

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Dedication to Professor Weiyuan Huang on the occasion of his 90th birthday.

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ABSTRACT

An efficient, highly selective method for polyfluoroalkylation of 2-aminothiazole derivatives was described. Interestingly, a defluorinated reductive 2-aminothiazole derivative was obtained in moderate yields when 2-aminothiazole was reacted with $(CF_3)_2CFI$.

1. Introduction

2-Aminothiazole is regarded as a privileged structure motif in medicinal chemistry due to its presence in the numerous pharmaceuticals [1,2] and agrochemicals [3]. The decoration of 2-aminothiazole is, therefore, of great current interests. In particular, the incorporation of fluoroalkyl groups into 2-aminothiazole represents an attractive strategy in this regard (Scheme 1) [2,4,5], since it is well-known that fluorination of less active precursors often leads to potent drugs with enhanced bioavailability, reduced toxicity or improved affinity for the target receptor [6].

In general, fluoroalkyl-substituted 2-aminothiazoles are synthesized through condensation of thiourea with fluoroalkyl-substituted synthons [2,5,7,8] or copper-mediated nucleophilic polyfluoroalkylation of halogen-substituted 2-amino-thiazoles [9]. However, both of these methods suffer from tedious procedures for the preparation of fluoroalkyl-substituted synthons or the halogen-substituted 2-aminothiazoles, the incompatibility of important functional groups and low yields. Direct coupling of 2-aminothiazole with polyfluoroalkyl halides under mild conditions would be more straightforward and efficiency [10]. We speculated that sulfinatodehalogenation reaction, which is firstly developed by Huang [11] and well-known for the polyfluoroalkylation of electron-rich arenes, would provide a highly selective route for the polyfluoroalkylation of 2-aminothiazoles. Herein, we describe a facile procedure for highly selective polyfluoroalkylation of 2-aminothiazole and its derivatives in good yields. Interestingly, an unexpected reduction of sp^3 C–F bond instead of the polyfluoroalkylation of aminotiazole occurred when $(CF_3)_2CFI$ was used.

2. Results and discussion

Reactions of 2-aminothiazole with nonafluoro-1-iodobutane under standard sulfinatodehalogenation conditions ($Na_2S_2O_4$/$NaHCO_3$, CH_3CN/H_2O (4:1), 5–10 °C) gave the coupled products in 80% yield with perfect selectivity at 5-position of 2-aminothiazole (Table 1, entry 3). The reaction was not sensitive to the concentration of the reactants and the acetonitrile/water ratio only slightly affected the yields of the products. Table 1 summarized the reactions of a variety of substituted 2-aminothiazoles with polyfluoroalkyl iodides. Reactions of 2-aminothiazoles with CF_3I, C_2F_5I, n-C_4F_9I, ClC_4F_8I and $IC_2F_4OC_2F_4SO_2F$ occurred to give the corresponding 5-polyfluoroalkyl-2-aminothiazoles in good to excellent yields (Table 1, entries 1-5). 4-Aryl-substituted 2-aminothiazoles also reacted with perfluorobutyl iodides to give the desired products in good yields (Table 1, entries 6–14). Substrates with chloride, nitro or hydroxy group on phenyl ring were compatible under these conditions (Table 1, entries 9–11, 14).

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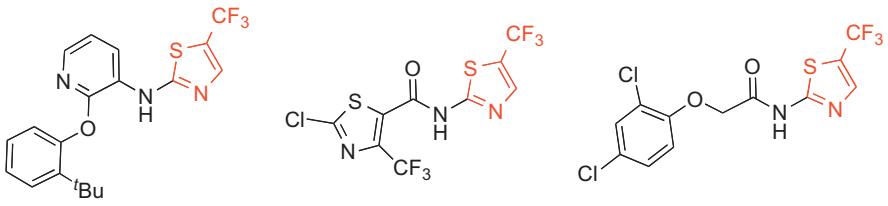
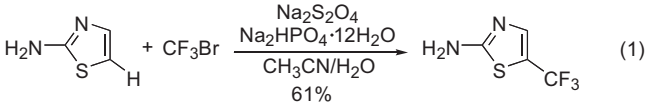


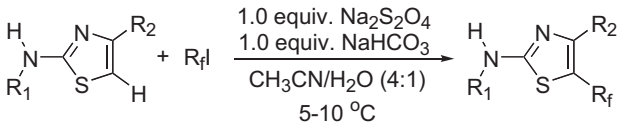
Scheme 1. Example of drug candidates with 2-amino-5-trifluoromethylthiazole moiety.

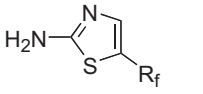
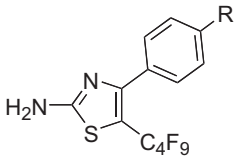
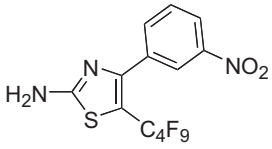
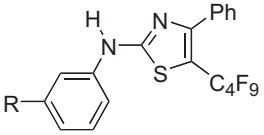
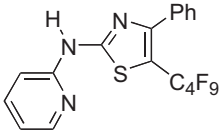
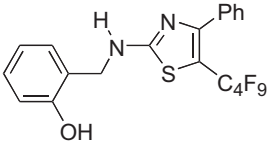
Reaction of 2-aminothiazole with CF_3Br, a much cheaper trifluoromethyl resource than CF_3I, also proceeded smoothly to give 5-trifluoromethyl-2-aminothiazole in 61% yield when the reaction was conducted in an autoclave at 80 °C. The same operation may be applied to the reaction conducted on a 0.2 mol scale (Eq. (1)).



(1)

Table 1
Polyfluoroalkylation of substituted 2-aminothiazoles under sulfinatodehalogenation conditions.[a]

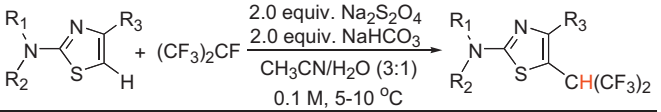


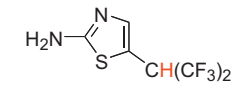
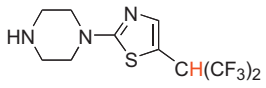
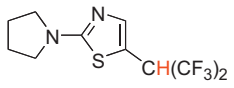
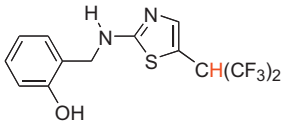
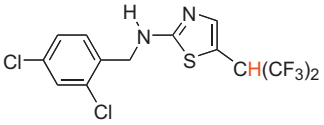
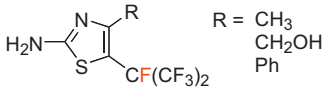
Entry	Product		Yield (%)[b]
1		R_f = CF_3	67
2		CF_2CF_3	60
3		C_4F_9	80
4		C_4F_8Cl	85
5		$C_2F_4OC_2F_4SO_2F$	72
6		R = H	61
7		Me	58[d]
8		OMe	63[d]
9		Cl	75[d]
10			76[e]
11		R = Cl	68[d]
12		CF_3	86[d]
13			90[d]
14			78

[a]Reaction conditions: **1** (1.0 mmol), 1.5 equiv. of R_fI in the presence of 1.0 equiv. of $Na_2S_2O_4$ and 1.0 equiv. of $NaHCO_3$ in 1.5 mL of CH_3CN/H_2O (4/1) at 5–10 °C.
[b]Isolated yields.
[c]CF_3Br was used and the reaction was conducted in an autoclave at 80 °C for 2 h.
[d]DMF/H_2O (4:1) was used as solvent.
[e]Reaction conducted at 0.05 M.

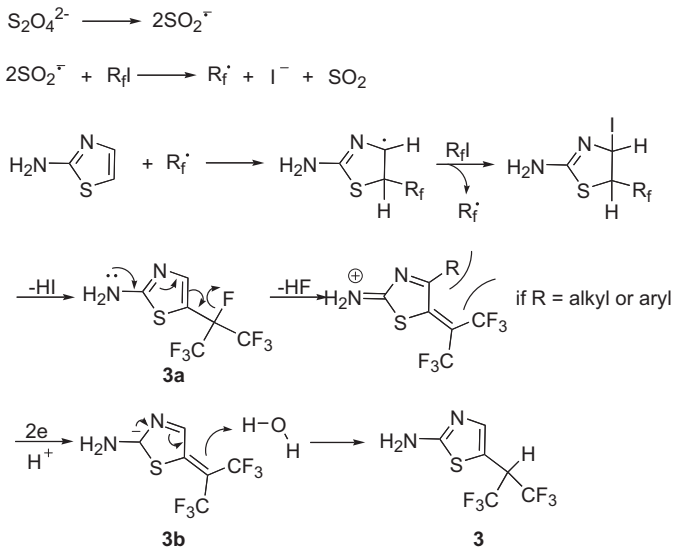
Interestingly, when $(CF_3)_2CFI$ was used under standard sulfinatodehalogenation conditions, unexpected C–F bond reduced products **3** instead of the perfluoroalkylated derivative were isolated. A number of other N-substituted 2-aminothiazoles also reacted with $(CF_3)_2CFI$ to afford the reductive defluorinated products in good yields (Table 2, entries 1–5) [8]. Reactions of 4-alkyl or aryl-substituted 2-aminothiazoles, however, gave the

Table 2
Reductive polyfluoroalkylation of substituted 2-aminothiazoles under sulfinatodehalogenation conditions.[a]



entry	product		yield (%)[b]
1			78
2			78
3			74
4			78
5			60
6		R = CH_3	67
7		CH_2OH	79
8		Ph	85[c]

[a]Reaction conditions: **1** (1.0 mmol), 1.5 equiv. of R_fI in the presence of 2.0 equiv. of $Na_2S_2O_4$ and 2.0 equiv. of $NaHCO_3$ in 10.0 mL of CH_3CN/H_2O (3/1) at 5–10 °C.
[b]Isolated yields.
[c]DMF/H_2O (4:1) was used as solvent.



Scheme 2. Proposed mechanism for the formation of reductive defluorinated product **3**.

perfluoroalkylated products in good yields. Increasing the amount of $Na_2S_2O_4$ or longer reaction time did not lead to the reductive defluorinated products. This result is important because recently heptafluoroisopropyl substituted aniline derivatives showed high insecticidal effect on diamondback moth [12].

While defluorination of polyfluoroalkyl-substituted arenes followed by nucleophilic attack from water have been well documented in the literature [13], very few reductive defluorinations of polyfluoroalkyl-substituted arenes under mild conditions have been reported previously [14]. We then studied the reaction in more detail. Careful monitoring of the reaciton by TLC and ^{19}F NMR spectroscopy revealed that perfluoroalkylation product **3a** was formed as the only product after 30 min. However, compound **3a** was not stable under sulfinatodehalogenation conditions and slowly converted to compound **3** within 3 h. Compound **3a**, which was not stable on silica gel or neutral aluminum oxide, was purified by extraction with diethyl ether and drying over Na_2SO_4, followed by removing the solvent under vacuum [15]. Treatment of isolated **3a** with $Na_2S_2O_4/NaHCO_3$ in CH_3CN/H_2O (4:1) at 5–10 °C leads to **3** quantitatively. The yield of the same reaction under oxygen atmosphere was much lower.

Based on these observations, we postulate that compound **3a** was formed initially under sulfinatodehalogenation conditions (Scheme 2). Intramolecular elimination of hydrogen fluoride from **3a**, followed by two-electron reduction in the presence of $Na_2S_2O_4$ gave an anionic intermediate **3b**. Protonation of intermediate **3b** afforded compound **3**. In the presence of oxygen, the two-electron oxidation process was prohibited. When 4-alkyl or aryl-substituted 2-aminothiazoles were used, elimination of hydrogen fluoride was much slower possibly due to the steric hindrance between the trifluoromethyl group and the 4-substituent group (Scheme 2).

3. Conclusion

In summary, we have developed a highly selective protocol for the polyfluoroalkylation of 2-aminothiazole derivatives in good yields under mild conditions. Careful control of the reaction conditions enables us to obtain either reductive defluorinated 2-aminothiazole derivatives or polyfluoroalkylated products when $(CF_3)_2CFI$ was used. Expansion of the scope of the reaction to other heterocycles that are important for pharmaceuticals and agrochemicals are ongoing in our laboratory.

4. Experimental

4.1. General information

All solvents were purified by standard method. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on 300 or 400 MHz, 100 MHz, and 282 MHz spectrometer, respectively. ^1H NMR and ^{13}C NMR chemical shifts were determined relative to an internal standard TMS at δ 0.0 and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as an external standard. All reactions were monitored by TLC or ^{19}F NMR. Flash column chromatography was carried out using 300–400 mesh silica gel at medium pressure. Melting points were determined on a SGW X-4 apparatus and were uncorrected. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

4.2. Typical procedure for the polyfluoroalkylation of 2-aminothiazoles under sulfinato-dehalogenation conditions

Sodium dithionite (1.0 mmol) was added in one portion to a mixture of 2-aminothiazole (1.0 mmol), $NaHCO_3$ (1.0 mmol) and polyfluoroalky iodide (1.5 mmol) in acetonitrile/water (4:1/v:v) at 5–10 °C under Ar atmosphere. The mixture was stirred until complete conversion of starting material as indicated by TLC analysis. Acetonitrile was removed under reduced pressure and water (5 mL) was added. The mixture was extracted with ethyl acetate (4.0 mL × 3) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (petroleum/ethyl acetate) to give the product.

4.2.1. 5-(Trifluoromethyl)thiazol-2-amine [7] (Table 1, entry 1)

The general procedure conducted with sodium dithionite (174 mg, 1.0 mmol), 2-aminothiazole (100 mg, 1.0 mmol), $NaHCO_3$ (84 mg, 1.0 mmol) and CF_3I (294 mg, 1.5 mmol) in 5.2 mL acetonitrile and 1.3 mL water gave 112 mg (67%) of the product as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 7.38 (s, 1H), 5.82 (br, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −54.90 (s, 3F).

4.2.2. 5-(Perfluoroethyl)thiazol-2-amine (Table 1, entry 2)

The general procedure conducted with sodium dithionite (174 mg, 1.0 mmol), 2-aminothiazole (100 mg, 1.0 mmol), $NaHCO_3$ (84 mg, 1.0 mmol) and CF_3CF_2I (294 mg, 1.5 mmol) in 5.2 mL acetonitrile and 1.3 mL water gave 131 mg (60%) of the product as a light yellow solid. Mp: 26–27 °C. ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 7.40 (s, 1H), 5.45 (br, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −83.87 (m, 3F), −103.30 (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 141.8 (t, J = 6.6 Hz), 123.0–109.1. MS (ESI positive ion): 218.9 (M+1); HRMS (ESI) calcd for $C_5H_4F_5N_2S^{+1}$ (M+H): 219.00099. Found: 219.00145. IR (thin film) δ 3297, 3166, 1622, 1552, 1506, 1347, 1289, 1208, 1121, 1076, 936, 747 cm^{-1}.

4.3. Preparation of 5-(trifluoromethyl)thiazol-2-amine from CF_3Br

Sodium dithionite (70 g, 0.4 mol), 2-aminothiazole (20 g, 0.2 mol) and $Na_2HPO_4{\cdot}12H_2O$ (76 g, 0.1 mol) in 150 mL acetonitrile/180 mL water was added into a 1.0 L autoclave, and then it was sealed and evacuated followed with the introduction of CF_3Br (90 g, 0.6 mmol). The reaction mixture was heated to 80 °C for 3 h. The work up was the same as that aforementioned to give 5-(trifluoromethyl)thiazol-2-amine in 61% yield.

4.4. Characterization of 5-(perfluoropropan-2-yl)thiazol-2-amine

Sodium dithionite (261 mg, 1.5 mmol) in one portion was added to a mixture of 2-aminothiazole (100 mg, 1.0 mmol), $NaHCO_3$ (252 mg, 3.0 mmol) and $(CF_3)_2CFI$ (443 mg, 1.5 mmol) in 5.2 mL acetonitrile and 1.3 mL water at 5–10 °C under argon. The mixture was stirred until complete conversion of starting material as indicated by TLC analysis (within 30 min). Acetonitrile was removed under reduced pressure (Caution: the temperature of the water bath of the rotvap maintained below 15 °C. Otherwise, higher temperature resulted in the decomposition of the product). The mixture was extracted with diethyl ether (4.0 mL × 1) and the organic layers were dried over Na_2SO_4. The solvent was removed under vacuum to give a white solid in 76% yield, 204 mg. The white solid was pure as indicated by ^1H NMR spectroscopy and Mass Spectroscopy. Note: The title product was stable for months when stored at -20 °C. *5-(perfluoropropan-2-yl)thiazol-2-amine:* White solid, isolated yield: 76%. ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 7.33 (s, 1H), 5.44 (br, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.93 (d, J = 9.3 Hz, 6F), −167.60 (m, 1F). MS (ESI positive ion): 269.0 (M+1); HRMS (ESI) calcd for $C_6H_4F_7N_2S^{+1}$ (M+H): 268.9978. Found: 268.9977.

4.5. Typical procedure of the reductive polyfluoroalkylation of substituted 2-aminothiazoles

Sodium dithionite (2.0 mmol) was added in one portion to a mixture of 2-aminothiazole (1.0 mmol), $NaHCO_3$ (2.0 mmol) and polyfluoroalky iodide (1.5 mmol) in 10.0 mL acetonitrile/water (3:1/v:v) at 5–10 °C under Ar atmosphere. The mixture was stirred until complete conversion of starting material as indicated by TLC or ^{19}F NMR analysis. Acetonitrile was removed under reduced pressure and water (5 mL) was added. The mixture was extracted with ethyl acetate (4.0 mL × 3) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (petroleum/ethyl acetate) to give the product.

4.5.1. 5-(1,1,1,3,3,3-Hexafluoropropan-2-yl)thiazol-2-amine (Table 2, entry 1)

The general procedure conducted with sodium dithionite (348 mg, 2.0 mmol), 2-aminothiazole (100 mg, 1.0 mmol), $NaHCO_3$ (168 mg, 2.0 mmol) and $(CF_3)_2CFI$ (443 mg, 1.5 mmol) in 7.5 mL acetonitrile and 2.5 mL water gave 194 mg (78%) of the product as a white solid. Mp 67–68 °C. ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 7.13 (s, 1H), 5.23 (br, 2H), 4.16–4.32 (Septet, J = 7.9 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.31 (d, J = 7.9 Hz, 1F). ^{13}C NMR (100 MHz, CDCl3) δ 170.3, 142.3, 122.3 (q, J = 210.9 Hz, CF_3), −109.7, 48.2 (t, J = 31.0 Hz, –CH–). MS (ESI positive ion): 250.9 (M+1); HRMS (ESI) calcd for $C_6H_5F_6N_2S^{+1}$ (M+H): 251.0078. Found: 251.0072. IR (thin film) 3468, 3287, 3122, 2678, 1630, 1556, 1528, 1513, 1353, 1278, 1233, 1188, 1149, 1095, 1050, 902, 863, 738, 692, 533 cm^{-1}.

4.5.2. (2-Amino-5-(perfluoropropan-2-yl)thiazol-4-yl)methanol (Table 2, entry 7)

The general procedure conducted with sodium dithionite (134 mg, 0.8 mmol), 2-aminothiazole (50 mg, 0.4 mmol), $NaHCO_3$ (65 mg, 0.8 mmol) and $(CF_3)_2CFI$ (171 mg, 0.6 mmol) in 3.0 mL acetonitrile and 1.0 mL water gave 90 mg (79%) of the product as a white solid. Mp: 110–111 °C. ^1H NMR (300 MHz, DMSO-d_6/TMS) δ 7.60 (s, 2H, –N**H**$_2$), 5.08 (t, J = 6.0 Hz, 1 H, –O**H**), 4.29 (dd, J = 2.1, 5.7 Hz, 2H, –C**H**$_2$–). ^{19}F NMR (282 MHz, DMSO-d_6) δ −75.70 (d, J = 8.2 Hz, 6F), −172.62 (m, 1F). ^{13}C NMR (100 MHz, DMSO-d_6/TMS) δ 169.8, 157.6, 120.6 (qd, J = 286.6, 28.5, Hz), 98.3 (d, J = 24.7 Hz), 58.1 (d, J = 8.8 Hz). MS (ESI positive ion): 299.0 (M+1); HRMS (ESI) calcd for $C_7H_6F_7N_2O_1S^{+1}$ (M+H): 299.0084. Found: 299.0089. IR (thin film) 3450, 3281, 3135, 2939, 1630, 1537, 1509, 1312, 1218, 1095, 1041, 949, 913, 721 cm^{-1}.

4.5.3. 5-(Perfluoropropan-2-yl)-4-phenylthiazol-2-amine (Table 2, entry 8)

The general procedure conducted with sodium dithionite (2.0 g, 11.4 mmol), 2-aminothiazole (1.0 g, 5.7 mmol), $NaHCO_3$ (960 mg, 11.4 mmol) and $(CF_3)_2CFI$ (2.52 g, 8.6 mmol) in 20.0 mL DMF and 10.0 mL water gave 1.66 g (85%) of the product as a white solid. Mp: 132–133 °C. ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 7.37 (m, 5H), 5.70 (br, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.10 (d, J = 10.4 Hz, 6F), −174.33 (m, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 156.2, 135.0 (d, J = 2.2 Hz), 129.0 (d, J = 2.9 Hz), 128.6, 127.7, 120.3 (qd, J = 285.1, 27.2 Hz, CF_3), 102.0 (d, J = 22.6 Hz), 89.4–93.4 (m). MS (ESI positive ion): 345.0 (M+1); HRMS (ESI) calcd for $C_{12}H_8F_7N_2S^{+1}$ (M+H): 345.0291. Found: 345.0302. IR (thin film) 3461, 3279, 3097, 2970, 1631, 1527, 1298, 1206, 1159, 1068, 969, 934, 922, 777, 754, 723, 706, 663, 596 cm^{-1}.

4.6. Reductive defluorination of 4-methyl-5-(perfluoropropan-2-yl)thiazol-2-amine

A solution of sodium dithionite (123 mg, 0.7 mmol) and 4-methyl-5-(perfluoropropan-2-yl)thiazol-2-amine (100 mg, 0.4 mmol) in 1.2 mL acetonitrile and 1.2 mL water was heated to 60 °C under argon. The mixture was stirred until complete conversion of starting material as indicated by TLC analysis. Acetonitrile was removed under reduced pressure and water (5 mL) was added. The mixture was extracted with ethyl acetate (4.0 mL × 3) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (petroleum/ethyl acetate) to give 55 mg (60%) of the product as a white solid. 5-(1,1,1,3,3,3- hexafluoropropan-2-yl)-4-methylthiazol-2-amine. Mp: 104–105 °C. ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 5.61 (br, 2H), 4.30 (m, J = 7.8 Hz, 1H), 2.20 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.70 (d, J = 7.3 Hz, 6F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 151.3, 122.6 (q, J = 281.4 Hz), 102.9, 47.8 (septet, J = 31.0 Hz), 14.98. MS (ESI positive ion): 265.0 (M+1); HRMS (ESI) calcd for $C_7H_7F_6N_2S^{+1}$ (M+H): 265.0229. Found: 265.0227. IR (thin film) 3469, 3231, 3080, 2927, 1613, 1574, 1533, 1509, 1348, 1331, 1271, 1224, 1203, 1171, 1091, 965, 897, 867, 734, 695, 622, 530, 449 cm^{-1}.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.07.005.

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