One-Pot Synthesis of Fluoroalkanesulfonyl Substituted Amidines from Ketone, Amine and Fluoroalkanesulfonyl Azides in Mild Conditions

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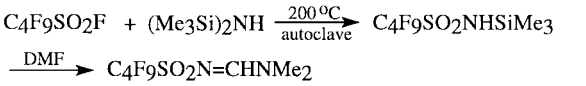
Abstract: A facile one-step method is presented for the synthesis of *N*-per(poly)fluoroalkanesulfonyl amidines in moderate to good yield by reactions of per(poly)fluoroalkanesulfonyl azides, ketone and secondary amine at room temperature. This synthetic methods provide an easy and simple access to *N*-per(poly)fluoroalkanesulfonyl amidines.

Key words: per(poly)fluoroalkanesulfonyl azides, ketone, secondary amine, amidine

Amidines, the nitrogen analogues of carboxylic acids, are structural parts of numerous compounds of biological interest and form important medical and biochemical agents.[1,2] It is well known that introduction of a fluorine atom or fluorine-containing group into an organic molecule changes the chemical or biochemical properties of the original molecule.[3] Thus, fluorine-containing amidines should be expected to be of particular importance.

However, the preparation of fluorine-containing amidines is rarely reported as yet.[4] Niederprum et al. first reported the synthesis of $C_4F_9SO_2N{=}CHNMe_2$ by two reaction steps in very low yield (10%) (Scheme 1).[5] Recently, we prepared these compounds from the reaction of R_fSO_2NHNa with Vilsmaier reagent.[6] (Scheme 2)

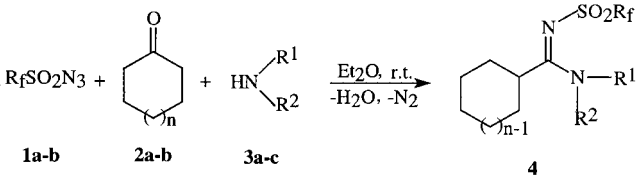


Scheme 1

Scheme 2

During our continuous study on the per(poly)fluoroalkanesulfonyl azides,[7-8] we found that it reacts smoothly with ketones and amines to afford *N*-per(poly)fluoroalkanesulfonyl amidines in good yield. Herein, we wish to report these results.

As shown in Scheme 3, per(poly)fluoroalkanesulfonyl azides **1a–b** were allowed to react with cyclohexanone or cycloheptanone and various secondary amines **3** in absolute diethyl ether to give the one-carbon ring contraction product **4** in good to moderate yield ranging from 48–89% (Table 1). It was found that the use of cyclohexanone led to much better yields, and required shorter reaction times than that of cycloheptanone.[9] Furthermore, the reaction of cyclohexanone did not need the catalysis of activated MS 4A.



Rf = C_4H_9 (**1a**); $IC_2F_4OC_2F_4$ (**1b**)
n = 1 (**2a**); n = 2 (**2b**)
morpholine (**3a**); *N*-methylaniline (**3b**); diethylamine (**3c**)

Scheme 3

Fusco et al. have shown that enamines derived from cyclic ketones react with arenesulfonyl azides mainly under ring contraction with formation of the corresponding amidines.[10,11] However, there are few reports about the synthesis of amidines directly from azides, ketones and amines until now. Enamines were generally prepared by the condensation of ketones with secondary amines,[9] therefore ketones mixed with secondary amines would present an equilibrium between enamine and ketone. Due to the strong electron-withdrawing properties of the fluoroalkanesulfonyl group, per(poly)fluoroalkanesulfonyl azides are more reactive than other organic azides, especially in the reaction with electron-rich olefins.[12,13] As fluoroalkanesulfonyl azides react quickly with enamines, the equilibrium between enamine and ketone should shift to enamines and form the triazoline intermediate by the 1,3-dipolar cycloaddition.[13] When the triazoline ring carries an electron-withdrawing group at the 1-position, it is very labile.[13,14] Thus, the first formed triazolines are not readily isolated, they decompose immediately after their formation to produce amidine **4** through rearrangement and loss of the N_2 at the same time.[15]

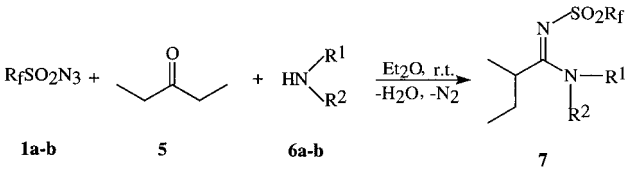
The above one-pot reaction was also extended to the reaction of acyclic ketone (Scheme 4). In the presence of fluoroalkanesulfonyl azides **1**, pentan-3-one reacted with morpholine or pyrrolidine and afforded amidines **7** through ethyl rearrangement. It is noteworthy that there is a big difference between morpholine and pyrrolidine in

Table 1

Entry	Azides	Ketones	Amines	Time (h)	Product	Yield %
1	**1a**	cyclohexanone	morpholine	5	**4aaa**	77
2	**1b**	cyclohexanone	morpholine	5	**4baa**	70
3	**1a**	cyclohexanone	*N*-methylaniline	72	**4aab**	81
4	**1b**	cyclohexanone	*N*-methylaniline	72	**4bab**	89
5	**1a**	cyclohexanone	diethylamine	48	**4aac**	48[a]
6	**1b**	cyclohexanone	diethylamine	48	**4bac**	53[a]
7	**1a**	cycloheptanone	morpholine	12	**4aba**	53[a]
8	**1b**	cycloheptanone	morpholine	12	**4bba**	54[a]

[a] 0.4 g of activated MS 4A was used for 1 mmol azides **1**.

the reaction rate and product yield (Table 2). In the case of pyrrolidine, the reaction time is about 1 hour and the yield is 74−85%. However, the reaction of morpholine with **1** needed 2 days under the catalysis of activated MS 4A, and gave lower yields. The difference should be attributed to pyrrolidine being more nucleophilic than morpholine.[9]



morpholine (**6a**); pyrrolidine (**6b**)

Scheme 4

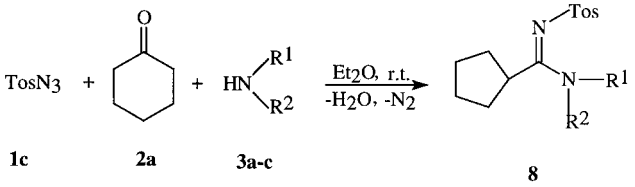
We have also tried the reaction of *p*-toluenesulfonyl azide ($TosN_3$) with cyclohexanone and amines **3a−c** in the same reaction conditions. Fortunately, it gave good reaction results (Scheme 5, Table 3). Because of the low reactivity of $TosN_3$, the reaction rate is slow compared to fluoroalkanesulfonyl azides. Furthermore, it is noteworthy that the presence of MS 4A is indispensable in the case of *N*-methylaniline (Entries 3, 4)

In conclusion, the reaction described herein provides a novel, convenient and one-pot approach to *N*-per(poly)fluoroalkanesulfonyl amidines. The easy procedure and simple workup, availability of reagents and good yield of the products make this method a useful addition to the present methodologies.

Table 2

Entry	Azides	Amines	Time (h)	Product	Yield (%)
1	**1a**	morpholine	48	**7aa**	53
2	**1b**	morpholine	48	**7ba**	43
3	**1a**	pyrrolidine	1	**7ab**	83[a]
4	**1b**	pyrrolidine	1	**7bb**	74[a]

[a] 0.4 g of activated MS 4A is used for 1 mmol azides **1**.



morpholine (**3a**); *N*-methylaniline (**3b**); diethylamine (**3c**)

Scheme 5

All reagents were of analytical grade. IR spectra were obtained with a Perkin−Elmer 983G spectrophotometer using KBr disks. ^1H NMR and ^{19}F NMR spectra were recorded on a Varian-360L or Bruker AM-300 spectrometer instrument with TMS and $CFCl_3$ (with upfield negative) as an internal and external standard, respectively. NMR spectra were recorded using $CHCl_3$ unless otherwise stated. Mass spectra were obtained in a HP 5989a instrument. Elemental analyses were performed at this Institute. Column chromatography was performed using silica gel H, particle size 10−40μ. The per(poly)fluoroalkanesulfonyl azides **1** were prepared by our previously described methods.[7]

***N′*-Perfluorobutanesulfonyl-*N*, *N*-cyclo(ethyleneoxyethylene)-cyclopentanamidine (4aaa); Typical Procedure for 4 and 7**

To a solution of cyclohexanone **2a** (0.118 g, 1.2 mmol) and morpholine (0.113 g, 1.3 mmol) in absolute Et_2O (5 mL), was added fluoroalkanesulfonyl azide **1a** (0.325 g, 1.0 mmol) dropwise with magnetic stirring at r.t. The reaction was completed after 5 h (monitored by TLC). After removal of solvent, the residue obtained was purified by column chromatography (petroleum ether/EtOAc, 6:1, R_f = 0.42) to give the pure product **4aaa** (0.357 g, 77%). All of the

Table 3

Entry	Azides	Amines	Product	Yield (%)
1	**1c**	morpholine	**8a**	76
2[a]	**1c**	*N*-methylaniline	**8b**	57
3[b]	**1c**	*N*-methylaniline	–[c]	0
4[a]	**1c**	diethylamine	**8c**	59

[a] 0.4 g of activated MS 4A was used for 1 mmol azides **1**.
[b] No MS 4A was used.
[c] The structures of all compounds prepared were confirmed by spectroscopic methods and elemental analysis. The IR spectra of compounds **4** and **7** showed strong absorption of C=N at 1560 cm^{-1}.

products **4** and **7** are oily compounds except product **4aba**, which is a white crystalline solid.

4aaa
IR (KBr): ν = 1540 (C=N), 1478 (SO_2), 1120−1236 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.85 (m, 2H), 3.73 (m, 4H), 3.60 (m, 2H), 3.55 (m, 1H), 2.12 (m, 2H), 1.87 (m, 4H), 1.70 (m, 2H).

^{19}F NMR ($CDCl_3$): δ = −79.9 (s, 3F), −113.0 (m, 2F), −120.8 (m, 2F), −125.8 (m, 2F).

MS: *m/z* (%) = 465 (M^++1, 17.53), 245 (M^+-R_f, 2.85), 181 ($M^+-SO_2R_f$, 3.63), 86 ($C_4H_8NO^+$, 100.00), 69 (CF_3^+ or $C_5H_9^+$, 25.54).

4baa
IR (KBr): ν = 1540 (C=N), 1478 (SO_2), 1080−1360 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): 3.85 (m, 2H), 3.73 (m, 4H), 3.60 (m, 2H), 3.55 (m, 1H), 2.12 (m, 2H), 1.87 (m, 4H), 1.70 (m, 2H).

^{19}F NMR ($CDCl_3$): δ = −62.8 (s, 2F), −80.4 (t, 2F, $^4J_{FF}$ = 17 Hz), −84.7 (t, 2F, $^4J_{FF}$ = 17 Hz), −116.0 (s, 2F).

MS: *m/z* (%) = 589 (M^++1, 55.87), 245 (M^+-R_f, 2.76), 181 ($M^+-SO_2R_f$, 2.62), 86 ($C_4H_8NO^+$, 100.00), 69 ($C_5H_9^+$, 13.57).

4aab
IR (KBr): ν = 1540 (C=N), 1478 (SO_2), 1140−1238 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.52 (m, 3H), 7.18 (m, 2H), 3.35 (s, 3H), 2.72 (m, 1H), 2.20 (m, 2H), 1.85 (m, 2H), 1.70 (m, 2H), 1.38 (m, 2H).

^{19}F NMR ($CDCl_3$): δ = −80.1 (s, 3F), −112.2 (m, 2F), −120.8 (m, 2F), −125.3 (m, 2F).

MS: *m/z* (%) = 485 (M^++1, 8.52), 265 (M^+-R_f, 4.26), 201 ($M^+-SO_2R_f$, 100.00), 106 ($C_7H_8N^+$, 62.66), 69 (CF_3^+ or $C_5H_9^+$, 66.25).

4bab
IR (KBr): ν = 1538 (C=N), 1474 (SO_2), 1080−1230 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.52 (m, 3H), 7.18 (m, 2H), 3.35 (s, 3H), 2.72 (m, 1H), 2.20 (m, 2H), 1.85 (m, 2H), 1.70 (m, 2H), 1.38 (m, 2H).

^{19}F NMR ($CDCl_3$): δ = −61.9 (s, 2F), −79.6 (t, 2F, $^4J_{FF}$ = 17 Hz), −83.8 (t, 2F, $^4J_{FF}$ = 17 Hz), −116.8 (s, 2F).

MS: *m/z* (%) = 609 (M^++1, 1.82), 265 (M^+-R_f, 7.90), 201 ($M^+-SO_2R_f$, 100.00), 106 ($C_7H_8N^+$, 36.37), 69 ($C_5H_9^+$, 24.63).

4aac
IR (KBr): ν = 1542 (C=N), 1490 (SO_2), 1140−1227 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.55 (q, 2H, *J* = 7.1 Hz), 3.48 (q, 2H, *J* = 7.1 Hz), 3.30 (m, 1H), 2.22 (m, 2H), 1.95 (m, 4H), 1.65 (m, 2H), 1.33 (t, 3H, *J* = 7.1 Hz), 1.21 (t, 3H, *J* = 7.1 Hz).

^{19}F NMR ($CDCl_3$): δ = −79.9 (s, 3F), −112.2 (m, 2F), −119.9 (m, 2F), −125.0 (m, 2F).

MS: *m/z* (%) = 451 (M^++1, 9.90), 167 (M^++1−SO_2R_f, 3.37), 72 (Et_2N^+, 100.00), 69 (CF_3^+, 66.25), 67 ($C_5H_7^+$, 6.10).

4bac
IR (KBr): ν = 1542 (C = N), 1490 (SO_2), 1140−1227 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.55 (q, 2H, *J* = 7.1 Hz), 3.48 (q, 2H, *J* = 7.1 Hz), 3.30 (m, 1H), 2.22 (m, 2H), 1.95 (m, 4H), 1.65 (m, 2H), 1.33 (t, 3H, *J* = 7.1 Hz), 1.21 (t, 3H, *J* = 7.1 Hz).

^{19}F NMR ($CDCl_3$): δ = −62.6 (s, 2F), −80.3 (t, 2F, $^4J_{FF}$ = 17Hz), −84.7 (t, 2F, $^4J_{FF}$ = 17 Hz), −115.8 (s, 2F).

MS: *m/z* (%) = 575 (M^++1, 0.37), 231 (M^+-R_f, 3.18), 167 (M^++1−SO_2R_f, 3.54), 72 (Et_2N^+, 100.00), 69 (CF_3^+, 66.25).

4aba: mp 97−98 °C
IR (KBr): ν = 1541 (C=N), 1475 (SO_2), 1005−1295 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.76 (s, 8H), 3.10 (m, 1H), 2.16 (s, 2H), 1.95 (m, 4H), 1.73 (m, 2H), 1.27 (m, 2H).

^{19}F NMR ($CDCl_3$): δ = −79.8 (s, 3F), −112.2 (m, 2F), −120.0 (m, 2F), −125.2 (m, 2F).

MS: *m/z* (%) = 479 (M^++1, 17.60), 259 (M^+-R_f, 2.34), 195 ($M^+-SO_2R_f$, 4.21), 86 ($C_4H_8NO^+$, 100.00), 69 (CF_3^+, 25.54).

4bba
IR (KBr): ν = 1541 (C=N), 1449 (SO_2), 1094−1230 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.76 (s, 8H), 3.10 (m, 1H), 2.16 (s, 2H), 1.95 (m, 4H), 1.73 (m, 2H), 1.27 (m, 2H).

^{19}F NMR ($CDCl_3$): δ = −64.8 (s, 2F), −80.3 (t, 2F, $^4J_{FF}$ = 17 Hz), −84.6 (t, 2F, $^4J_{FF}$ = 17 Hz), −125.7 (s, 2F).

MS: *m/z* (%) = 603 (M^++1, 17.60), 259 (M^+-R_f, 3.09), 195 ($M^+-SO_2R_f$, 4.20), 86 ($C_4H_8NO^+$, 100.00), 83 ($C_6H_{10}^+$, 8.53).

7aa
IR (KBr): ν = 1542 (C = N), 1487 (SO_2), 1123−1274 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (m, 2H), 3.76 (m, 6H), 3.48 (m, 1H), 1.82 (m, 1H), 1.70 (m, 1H), 1.38 (d, 3H, *J* = 11 Hz), 1.05 (t, 3H, *J* = 7.0 Hz).

^{19}F NMR ($CDCl_3$): δ = −80.0 (s, 3F), −113.8 (m, 2F), −120.2 (m, 2F), −125.3 (m, 2F).

MS: *m/z* (%) = 453 (M^++1, 6.50), 424 ($M^+-C_2H_4$, 2.71), 217 (M^+-OR_f, 4.29), 86 ($C_4H_8NO^+$, 100.00), 69 (CF_3^+, 66.25).

7ba
IR (KBr): ν = 1541 (C=N), 1489 (SO_2), 1095−1226 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (m, 2H), 3.76 (m, 6H), 3.48 (m, 1H), 1.82 (m, 1H), 1.70 (m, 1H), 1.38 (d, 3H, *J* = 11 Hz), 1.05 (t, 3H, *J* = 7.0 Hz).

^{19}F NMR ($CDCl_3$): δ = −62.9 (s, 2F), −80.3 (t, 2F, $^4J_{FF}$ = 17 Hz), −84.8 (t, 2F, $^4J_{FF}$ = 17 Hz), −116.3 (s, 2F).

MS: *m/z* (%) = 577 (M^++1, 3.76), 548 ($M^+-C_2H_4$, 6.54), 233 (M^+-R_f, 7.48), 86 ($C_4H_8NO^+$, 100.00), 56 ($C_4F_8^+$, 23.65).

7ab
IR (KBr): ν = 1542 (C=N), 1487 (SO_2), 1123−1274 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.75 (m, 2H), 3.55 (m, 6H), 2.10−1.85 (m, 4H), 1.70 (m, 2H), 1.42 (d, 3H, *J* = 7.0 Hz), 0.98 (t, 3H, *J* = 7.4 Hz).

^{19}F NMR ($CDCl_3$): δ = −79.4 (s, 3F), −110.3 (m, 2F), −116.7 (m, 2F), −122.1 (s, 2F).

MS: *m/z* (%) = 437 (M^++1, 34.96), 217 (M^+-R_f, 7.19), 153 ($M^+-SO_2R_f$, 2.68), 70 ($C_4H_8N^+$, 100.00), 69 (CF_3^+, 20.41).

7bb
IR (KBr): ν = 1542 (C=N), 1487 (SO_2), 1123−1274 (C-F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.75 (m, 2H), 3.55 (m, 6H), 2.10−1.85 (m, 4H), 1.70 (m, 2H), 1.42 (d, 3H, *J* = 7.0 Hz), 0.98 (t, 3H, *J* = 7.4 Hz).

^{19}F NMR ($CDCl_3$): δ = −63.8 (s, 2F), −80.0 (t, 2F, $^4J_{FF}$ = 17 Hz), −85.1 (t, 2F, $^4J_{FF}$ = 17 Hz), −116.6 (s, 2F).

MS: *m/z* (%) = 561 (M^++1, 40.55), 532 ($M^+-C_2H_4$, 3.07), 217 (M^+-R_f, 10.34), 153 (M^+-SO_2R_f, 3.21), 70 ($C_4H_8N^+$, 100.00).

8a
White solid: mp 148−149 °C (Lit[10] 145 °C).

IR (KBr): ν = 2965 (C–H), 1597 (m), 1541 (C=N), 1475 (SO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.79 (d, 2H, *J* = 8.2 Hz), 7.25 (d, 2H, *J* = 8.2 Hz), 4.12 (m, 1H), 3.71 (m, 4H), 3.46 (m, 4H), 2.40 (s, 3H), 2.10 (m, 2H), 1.26 (m, 6H).

MS: *m/z* (%) = 337 (M^++1, 3.15), 295 (M^++1−C_3H_6, 6.91), 181 (M^+−Tos, 8.44), 169 ($TosN^+$, 3.47), 155 (Tos^+, 25.36), 91 ($C_7H_7^+$, 53.69), 86 ($C_4H_8NO^+$, 100.00), 69 ($C_5H_9^+$, 12.08).

8b
White solid: mp 91−92 °C.

IR (KBr): ν = 2947 (C–H), 1597 (m), 1541 (C=N), 1471 (SO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.91 (d, 2H, *J* = 8.2 Hz), 7.41 (m, 3H), 7.26 (d, 2H, *J* = 7.8 Hz), 7.18 (d, 2H, *J* = 8.2 Hz), 3.35 (s, 3H), 2.88 (m, 1H), 2.40 (s, 3H), 2.28 (m, 2H), 1.73 (m, 4H), 1.35 (m, 2H).

MS: *m/z* (%) = 356 (M^+, 0.52), 250 (M^+−$C_7H_8N^+$, 5.43), 201 (M^+−Tos, 37.19), 155 (Tos^+, 100.00), 106 ($C_7H_8N^+$, 41.87), 91 ($C_6H_5N^+$, 97.18), 77 ($C_6H_5^+$, 16.13).

8c
White solid: mp 83−84 °C.

IR (KBr): ν = 2975 (C–H), 1540 (C=N), 1478 (SO_2) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.82 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 2H, *J* = 8.1 Hz), 3.81 (m, 1H), 3.38 (m, 4H), 2.39 (s, 3H), 2.02 (m, 2H), 1.98 (m, 4H), 1.67 (m, 2H), 1.21 (m, 3H), 1.10 (m, 3H).

MS: *m/z* (%) = 323 (M^++1, 43.41), 250 (M^+−$C_4H_{10}N^+$, 5.85), 215 (M^+−OC_7H_7, 3.21), 167 (M^+−Tos, 11.47), 155 (Tos^+, 23.08), 91 ($C_7H_7^+$, 51.55), 72 ($C_4H_{10}N^+$, 100.00).

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