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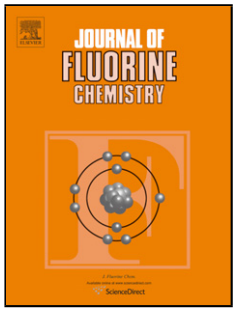

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Synthesis of *N*-substituted sulfonamides containing perhalopyridine moiety as bio-active candidates

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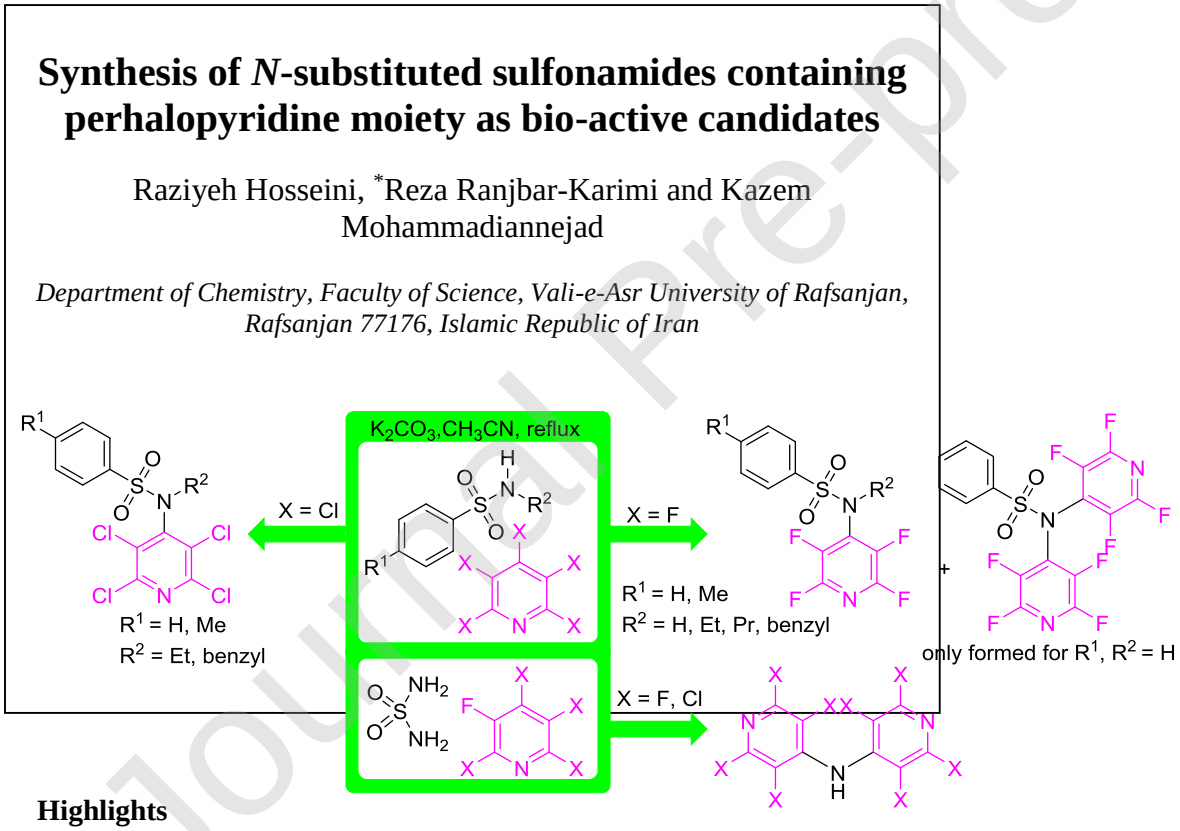
Graphical Abstract



Highlights

- Synthesis of N-substituted sulfonamides containing perhalopyridine moiety
- The reaction of pentafluoropyridine with aryl sulfonamides regioselectivity occurs at the 4-position of pyridine ring by N2 tetrazole ring.
- Synthesis of unexpected bis-perfluoro(chloro)pyridin-4-ylamine

Abstract:

A series of new halogenated aryl sulfonamides, as bio-active candidates, was synthesized from the reaction of the corresponding aryl sulfonamides with pentafluoro- and pentachloropyridines. Surprisingly, unlike aryl sulfonamides, the reaction of sulfamides with pentafluoro- and pentachloropyridines gave unexpected bis-perfluoro(chloro)pyridin-4-ylamines.

Keywords: Pentafluoropyridine, Pentachloropyridine, Sulfonamides, Sulfamide, Nucleophilic Reaction.

1. Introduction

Heteroaromatics bearing halogen atoms are an essential class of heterocyclic compounds with potentially various use in organic chemistry, biochemistry, and pharmaceutical chemistry [1-4]. Among them, perfluorinated pyridines have special interest in organic synthesis because they are suitable precursors for synthesis of substituted perfluoropyridines, ring-fused fluorinated heterocycles as well as macrocycle compounds, as reflected in numerous research studies dedicated to their application [5-9]. In the last few years, we investigated the reaction of various types of ambident nucleophiles as well as equal and unequal bidentate nucleophiles with perfluorinated compounds because of electron deficient property of such systems [10-15], whereas nature of nucleophile, solvent and reaction conditions performed determinative role in their regiochemistry.

Sulfonamides are an important moiety of various range of bioactive molecules and pharmaceutical compounds such as anticancer, antitumor, protease inhibitory, antibacterial, anti-inflammatory, and anticonvulsant activities [16-29]. Furthermore, sulfonamides used as an efficient kind of protective group for amine owing to their facile removal feature [30-32]. On the other hand, sulfonamides containing fluorinated moiety showed improved biological properties [33-40].

Sulfonamides are less nucleophilic than amines due to the electron-withdrawing property of sulfonyl group attached to amino group. Nevertheless, numerous articles focused on them as nucleophile groups for construction structures bearing sulfonamide moiety because of importance such compounds [40-46].

Besides great importance of sulfonamides in the pharmaceutical and agrochemical industries, in continuity with research on nucleophilic reactions of perhalogenated pyridines, we will to report the reaction of some sulfonamides with pentafluoropyridine and pentachloropyridine for preparation of new *N*-perhalopyridyl sulfonamide derivatives.

2. Results and discussion

Sulfonamides **3a-h** were synthesized by the reaction of aliphatic and aromatic amines with aryl sulfonyl chlorides **1a-b** according to the reported procedure (Scheme 1) [47].

The reaction of pentafluoropyridine **4a** with 4-methyl-*N*-propylbenzenesulfonamide **3a** in the presence of potassium carbonate was applied as a model reaction for optimization of reaction conditions (Table 1). At room temperature, the reaction was not successful in any of the solvents. At reflux, the reaction gave high yield in acetonitrile (Table 1, Entry 4), whereas the yields were low in other solvents. Accordingly, the reaction of pentafluoropyridine **4a** with 4-methyl-*N*-propylbenzensulfonamide **3a** under optimized reaction conditions gave 4-methyl-*N*-(perfluoropyridin-4-yl)-*N*-propylbenzenesulfonamide **5a** after washing of the product with ethanol (Table 2). The two resonances observed at -88.6 and -142.6 ppm (ortho and meta fluorine atoms, respectively) by ^{19}F NMR analysis indicated replacement of para fluorine atom to nitrogen ring by sulfonamide moiety. ^{1}H NMR spectrum of this compound showed two doublet peaks at 7.36 ppm and 7.69 ppm for aromatic hydrogens and a singlet peak at 2.46 ppm for methyl attached to benzene ring. It also indicated two triplet peaks at 0.87 and 3.47 ppm and one multiplet peak at 1.46 ppm for propyl hydrogens. In ^{13}C NMR spectrum **5a**, aromatic carbons were located in the range of 127.5-144.8 ppm and aliphatic carbons were located in the range of 10.7-51.6 ppm. Similarly, *N*-perfluoropyridyl sulfonamides **5b-g** were obtained by the reaction of corresponding sulfonamides with pentafluoropyridine **4a** (Table 2). Interestingly, ^{1}H NMR analysis as well as ^{19}F NMR analysis of **5d** showed nitrogen inversion phenomenon. For example, ^{19}F NMR spectrum **5d**

revealed two resonances at -99.0 and -102.8 ppm for ortho fluorine atoms and two resonances at -154.5 and -172.3 ppm for meta fluorine atoms.

In order to expand our research, we performed reaction of some sulfonamides with pentachloropyridine **4b** as electron-poor system. Similar to pentafluoropyridine, anion derived from sulfonamides **3c**, **3f** and **3g** attacked to the 4-position of pyridine ring and produced *N*-perchloropyridyl sulfonamides **5h-j** in good yields (Table 2).

In contrast with **3d**, sulfonamide **3h** on treatment with pentafluoropyridine gave *N*,*N*-bis(perfluoropyridin-4-yl)benzenesulfonamide **6** as major product along with *N*-(perfluoropyridin-4-yl)benzenesulfonamide **5k**, via attacking the anion derived from product **5k** in basic medium to other molecule of pentafluoropyridine (Scheme 3). The absence of absorption band for NH stretching in IR spectrum confirmed the structure of product **6**, while IR spectrum product **5K** showed a broad absorption band at 3426 cm^{-1} for NH stretching.

In continuous our research, we performed the reaction of sulfamide **7** as bidentate nucleophile with pentafluoropyridine. The ^{19}F NMR spectrum of product showed the characteristic bands for 4-substituted tetrafluoropyridine at -93.1 and -153.2 ppm for ortho and meta fluorine atoms. The ^{1}H NMR spectrum showed a broad peak at 10.77 and the ^{13}C spectrum showed bands for the ring carbon atoms which is the characteristic of a 4-substituted tetrafluoropyridine. The elemental analysis indicated that the product had the molecular formula $C_{10}HF_8N_3$. This data suggested that the compound was bis-(2,3,5,6-tetrafluoro-4-pyridyl)amine **8** (Scheme 4). The structure of compound **8** was confirmed by X-ray analysis on a single crystal, as shown in Fig. 1. This compound has been reported previously by a different route [48]. Performance of the reaction without base failed. We repeated the reaction in the presence of different molar ratios of sulfamide and pentafluoropyridine in the presence of the corresponding amounts of base, but the result was the same. Similarly, the reaction of pentachloropyridine **4b** and sulfamide **7** with a different molar ratios and in the presence of potassium carbonate yielded bis(perchloropyridin-4-yl)amine **9** (Scheme 4). A plausible mechanism for formation of **8** is shown in scheme 5. We believe that the first step is the expected nucleophilic substitution-fluorine by nitrogen of sulfamide, to give the first formed intermediate **A** and then, intermediate **A** is converted to anion **B** under basic medium condition of reaction, which attacked another molecule of pentafluoropyridine and gave compound

8 according to a mechanism postulated by Coe and co-workers [48] concerning reactions between pentafluoropyridine and urea. Compound **9** was obtained in same manner.

3. Conclusion

In conclusion, we have demonstrated that aryl sulfonamides successfully react with pentafluoro- and pentachloropyridine to give new *N*-perhalopyridyl sulfonamides as bio-active candidates. In contrast with aryl sulfonamides, the reaction of sulfamide with pentafluoro- and pentachloropyridine gave unexpected bis-perfluoro(chloro)pyridin-4-ylamine.

4. Experimental

All the solvents and starting materials were obtained commercially (Merck). Solvents were dried using the procedures recommended in the literature and distilled before use. ^{1}H NMR spectra were recorded at 500 MHz. ^{13}C NMR spectra were recorded at 125 MHz. ^{19}F NMR spectra were recorded at 470 and 282 MHz. The elemental analyses for C, H, and N were performed using Heraeus CHN-O rapid analyzer. TLC analysis was performed on silica gel TLC plates (Merck).

Reaction of sulfonamides with perhalopyridines; General procedure

A mixture of sulfonamide **3** or sulfamide **7** (1 mmol) and perhalopyridine **4** (1 mmol) in the presence of K_2CO_3 (1 mmol) in CH_3CN (5 mL) was stirred at reflux for 12 h. The reaction mixture was poured on 10 mL water and extracted with chloroform (2× 30 mL), then organic phase dried over $MgSO_4$ and solvent evaporated. The pure product was obtained after washing with ethanol.

*4-methyl-N-(perfluoropyridin-4-yl)-N-propylbenzenesulfonamide (**5a**)*

Yield: 88% (0.32 g); yellow solid; mp 79-86 °C. (Found: C, 49.67; H, 3.83; N, 7.70. $C_{15}H_{14}F_4N_2O_2S$ requires: C, 49.72; H, 3.89; N, 7.73%). IR (KBr): ν = 1164 and 1361 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.35 (d, 2H, *J* = 8.51 Hz, Ar-H), 3.47 (t, 2H, *J* = 7.3 Hz, N$\underline{CH_2}$), 2.46 (s, 3H, CH_3), 1.45 (sext, 2H, *J* = 7.3 Hz, $CH_2\underline{CH_2}CH_3$), 0.87 (t, 3H, *J* = 7.3 Hz, $CH_2\underline{CH_3}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.9 (Ar-C), 143.7 (dm, *J* = 234.7 Hz, C2,6-py), 141.0 (dm, *J* = 262.0 Hz, C3,5-py), 134.6 (Ar-C), 130.0 (Ar-CH), 127.6 (Ar-CH), 51.6 (N$\underline{CH_2}$), 21.9 (CH_3), 21.6 (CH_2), 10.7 ($CH_2\underline{CH_3}$) ppm. ^{19}F NMR ($CDCl_3$, 470.33 MHz): δ = -88.6 (m, 2F, F2,6-py), -142.8 (m, 2F, F3,5-py).

*N-ethyl-4-methyl-N-(perfluoropyridin-4-yl)benzenesulfonamide (**5b**)*

Yield: 85% (0.29 g); yellow solid; mp 57-61 °C. (Found: C, 48.17; H, 3.41; N, 7.99. $C_{14}H_{12}F_4N_2O_2S$ requires: C, 48.28; H, 3.47; N, 8.04%). IR (KBr): ν = 1163 and 1363 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.36 (d, 2H, *J* =8.2 Hz, Ar-H), 3.56 (q, 2H, *J* =7.3 Hz, N$\underline{CH_2}$), 2.47 (s, 3H, CH_3), 1.11 (t, 3H, *J* = 7.2 Hz, $CH_2\underline{CH_3}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.9 (Ar-C), 143.7 (dm, *J* = 235.2 Hz, C2,6-py), 141.1 (dm, *J* = 264.8 Hz, C3,5-py), 135.5 (Ar-C), 130.0 (Ar-CH), 127.6 (Ar-CH), 45.0 (N$\underline{CH_2}$), 22.0 (CH_3), 13.9 ($CH_2\underline{CH_3}$). ^{19}F NMR ($CDCl_3$, 470.33 MHz): δ = -88.5 (m, 2F, F2,6-py), -143.1 (m, 2F, F3,5-py).

*N-benzyl-4-methyl-N-(perfluoropyridin-4-yl)benzenesulfonamide (**5c**)*

Yield: 75% (0.31 g); white solid; mp 78-88 °C. (Found: C, 55.57; H, 3.40; N, 6.78. $C_{19}H_{14}F_4N_2O_2S$ requires: C, 55.61; H, 3.44; N, 6.83%). IR (KBr): ν = 1170 and 1369 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.40 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.22-7.24 (m, 3H, Ar-H), 7.18-7.20 (m, 2H, Ar-H), 4.70 (s, 2H, N$\underline{CH_2}$), 2.50 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.2 (Ar-C), 143.5 (dm, *J* = 227.4 Hz, C2,6-py), 140.8 (dm, *J* = 260.2 Hz, C3,5-py), 135.2 (Ar-C), 133.4 (Ar-C), 130.2 (Ar-CH), 128.9 (Ar-CH), 128.8 (Ar-CH), 128.3 (Ar-CH), 127.7 (Ar-CH), 52.4 (N$\underline{CH_2}$), 22.3 (CH_3). ^{19}F NMR ($CDCl_3$, 470.33 MHz): δ = -88.9 (m, 2F, F2,6-py), -142.4 (m, 2F, F3,5-py).

*4-methyl-N-(perfluoropyridin-4-yl)benzenesulfonamide (**5d**)*

Yield: 70% (0.22 g); white solid; mp 80-97 °C. (Found: C, 44.97; H, 2.49; N, 8.73. $C_{12}H_8F_4N_2O_2S$ requires: C, 45.00; H, 2.52; N, 8.75%). IR (KBr): ν = 3442 (NH), 1146 and 1384 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 7.772 and 7.769 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1.14H, Ar-H), 7.48 (d, *J* = 6.8 Hz, 0.61H, Ar-H), 7.10 (d, *J* = 7.9 Hz, 1.19H, Ar-H), 6.96 (d, *J* = 7.9 Hz, 0.63H, Ar-H), 2.29 (s, 1.83 H, CH_3), 2.25 (s, 0.99H, CH_3), The signal of NH was not observed due to the broadening. ^{13}C NMR (125 MHz, DMSO-d_6/$CDCl_3$): δ = 144.2 (dm, J = 231.0 Hz, C2,6-py), 140.1 (dm, J = 242.5 Hz, C3,5-py), 139.3 (Py-C), 128.6 (Ar-CH), 128.3 (Ar-CH), 126.5 (Ar-CH), 125.9 (Ar-CH), 21.3 (CH_3). ^{19}F NMR (DMSO, 470.33 MHz): δ = -99.0, -102.8 (m, 2F, F2,6-py), -154.5, -172.3 (m, 2F, F3,5-py) ppm.

*N-(perfluoropyridin-4-yl)-N-propylbenzenesulfonamide (**5e**)*

Yield: 60% (0.21 g); yellow solid; mp 84-88 °C. (Found: C, 48.23; H, 3.45; N, 7.98. $C_{14}H_{12}F_4N_2O_2S$ requires: C, 48.28; H, 3.47; N, 8.04%). IR (KBr): ν = 1166 and 1362 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.68 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.57 (t, 2H, *J* = 7.8 Hz, Ar-H), 3.50 (t, 2H, *J* = 7.4 Hz, N-$\underline{CH_2}$), 1.47 (sext, 2H, *J* = 7.4 Hz, $CH_2\underline{CH_2}CH_3$), 0.88 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.8 (dm, *J* = 241.7 Hz, C2,6-py), 142.2 (m, C4-py), 140.9 (dm, *J* = 256.3 Hz, C3,5-py), 138.3 (Ar-C), 133.8 (Ar-CH), 129.4 (Ar-CH), 127.5 (Ar-CH), 51.7 ($N\underline{CH_2}$), 21.9 ($CH_2\underline{CH_2}CH_3$), 10.6 (CH_3). ^{19}F NMR (470.33 MHz, $CDCl_3$): δ = -88.4 (m, 2F, F2,6-py), -142.8 (m, 2F, F3,5-py).

*N-ethyl-N-(perfluoropyridin-4-yl)benzenesulfonamide (**5f**)*

Yield: 80% (0.27 g); white solid; mp 101-116 °C. (Found: C, 46.65; H, 2.97; N, 8.35. $C_{13}H_{10}F_4N_2O_2S$ requires: C, 46.71; H, 3.02; N, 8.38%). IR (KBr): ν = 1164 and 1350 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.68 (t, 1H, *J* =7.5 Hz, Ar-H), 7.57 (t, 2H, *J* = 7.6 Hz, Ar-H), 3.61 (q, 2H, *J* = 7.3 Hz, $N\underline{CH_2}$), 1.13 (t, 3H, *J* = 7.3 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.1 (dm, J = 232.3 Hz, C2,6-py), 142.3 (dm, J = 251.6 Hz, C3,5-py), 138.6 (Py-C), 138.5 (Ar-C), 133.8 (Ar-CH), 129.4 (Ar-CH), 127.0 (Ar-CH), 44.7 ($N\underline{CH_2}$), 13.92 (CH_3). ^{19}F NMR ($CDCl_3$, 470.33 MHz): δ = -88.3 (m, 2F, F2,6-py), -143.1 (m, 2F, F3,5-py).

*N-benzyl-N-(perfluoropyridin-4-yl)benzenesulfonamide (**5g**)*

Yield: 70% (0.28 g); yellow solid; mp 95-97 °C. (Found: C, 54.50; H, 3.08; N, 7.00. $C_{18}H_{12}F_4N_2O_2S$ requires: C, 54.55; H, 3.05; N, 7.07%). IR (KBr): ν = 1172 and 1355 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.73 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.62 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.23 – 7.27 (m, 3H, Ar-H), 7.17-7.20 (m, 2H, Ar-H), 4.71 (s, 2H, $N\underline{CH_2}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.7(Ar-C), 143.5 (dm, *J* = 243.4 Hz, C2,6-py), 140.8 (dm, *J* = 263.8 Hz, C3,5-py), 134.0 (Ar-CH), 133.3 (Ar-C), 130.0 (Ar-CH), 128.9 (Ar-CH), 128.3 (Ar-CH), 127.7 (Ar-CH), 51.3 ($N\underline{CH_2}$). ^{19}F NMR ($CDCl_3$, 470.33 MHz): δ = -88.7 (m, 2F, F2,6-py), -142.4 (m, 2F, F3,5-py).

*N-benzyl-4-methyl-N-(perchloropyridin-4-yl)benzenesulfonamide (**5h**)*

Yield: 75% (0.36 g); white solid; mp 109-110 °C. (Found: C, 47.81; H, 2.87; N, 5.85. $C_{19}H_{14}Cl_4N_2O_2S$ requires: C, 47.92; H, 2.96; N, 5.88%). IR (KBr): ν = 1168 and 1360 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.36 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.25 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.20 (t, 2H, *J* = 7.2 Hz, Ar-H), 7.16 (d, 2H, *J* = 7.2 Hz, Ar-H), 4.75 (s, 2H, N$\underline{CH_2}$), 2.49 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.0 (Ar-C), 146.2 (Ar-C), 144.3 (Ar-C), 136.7 (Ar-C), 133.1 (Ar-CH), 132.8 (Ar-C), 129.82 (Ar-CH), 129.78 (Ar-CH), 128.9 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 122.7 (Ar-C), 53.5 (N$\underline{CH_2}$), 22.3 (CH_3) ppm.

*N-ethyl-N-(perchloropyridin-4-yl)benzenesulfonamide (**5i**)*

Yield: 87% (0.35 g); white solid; mp 114-116 °C. (Found: C, 39.00; H, 2.50; N, 6.93. $C_{13}H_{10}Cl_4N_2O_2S$ requires: C, 39.03; H, 2.52; N, 7.00%). IR (KBr): ν = 1170 and 1356 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, 2H, *J* = 7.1 Hz, Ar-H), 7.65 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.55 (t, 2H, *J* = 7.8 Hz, Ar-H), 3.68 (q, 2H, *J* = 7.3 Hz, N$\underline{CH_2}$), 1.15 (t, 3H, *J* = 7.3 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.2 (Ar-C), 146.5 (Ar-C), 139.8 (Ar-C), 133.5 (Ar-CH), 133.2 (Ar-C), 129.2 (Ar-CH), 127.8 (Ar-CH), 45.6 (N$\underline{CH_2}$), 14.1 (CH_3).

*N-benzyl-N-(perchloropyridin-4-yl)benzenesulfonamide (**5j**)*

Yield: 82% (0.38 g); yellow solid; mp 110-111 °C. (Found: C, 46.69; H, 2.51; N, 5.94. $C_{18}H_{12}Cl_4N_2O_2S$ requires: C, 46.78; H, 2.62; N, 6.06%) IR (KBr): ν = 1165 and 1357 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.68 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.58 (t, 2H, *J* = 7.8 Hz, Ar-H), 7.24-7.27 (m, 1H, Ar-H), 7.21 (t, 2H, *J* = 7.8 Hz, Ar-H), 7.16 (d, 2H, *J* = 8.1 Hz, Ar-H), 4.78 (s, 2H, N$\underline{CH_2}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.0 (Ar-C), 146.0 (Ar-C), 139.9 (Ar-C), 133.7 (Ar-CH), 133.1 (Ar-C), 132.7 (Ar-C), 129.8 (Ar-CH), 129.3 (Ar-CH), 128.9 (Ar-CH), 128.5 (Ar-CH), 128.0 (Ar-CH), 52.0 (N$\underline{CH_2}$).

*N-(perfluoropyridin-4-yl)benzenesulfonamide (**5k**)*

Yield: 45% (0.14 g); white solid; decomposed at 290 °C. (Found: C, 43.09; H, 1.87; N, 7.10. $C_{11}H_6F_4N_2O_2S$ requires: C, 43.14; H, 1.97; N, 9.15%). IR (KBr): ν = 3426 (NH), 1165 and 1384 (SO_2) cm^{-1}. ^1H NMR (500 MH_z, DMSO-d_6): δ = 7.72-7.74 (m, 2H, Ar-H), 7.39-

7.43 (m, 3H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 147.7 (Ar-C),144.4 (dm, *J* = 238.6 Hz, C2,6-py), 141.9 (m, C4-py), 135.5 (dm, *J* = 257.3 Hz, C3,5-py), 130.2 (Ar-CH), 128.5 (Ar-CH), 125.8 (Ar-CH). ^{19}F NMR (470 MHz, DMSO,): δ = -99.0 (m, 2F, F2,6-py), -154.5 (m, 2F, F3,5-py).

*N,N-bis(perfluoropyridin-4-yl)benzenesulfonamide (**6**)*

Yield: 50% (0.23 g); white solid; mp 150-156 °C. (Found: C, 42.17; H, 1.05; N, 9.15. $C_{16}H_5F_8N_3O_2S$ requires: C, 42.21; H, 1.11; N, 9.23%). IR (KBr): ν = 1164 and 1300 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.73-7.75 (m, 2H, Ar-H), 7.41-7.43 (m, 3H, Ar-H). The signal of NH was not observed due to the broadening. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 147.7 (Ar-C), 144.4 (dm, *J* = 233.9 Hz, C2,6-py), 141.8 (m, C4-py), 137.6 (dm, *J* = 258.3 Hz, C3,5-py), 130.2 (Ar-H), 128.5 (Ar-CH), 125.8 (Ar-CH). ^{19}F NMR (470 MHz, DMSO): δ = -89.3 (m, F2,6-py), -153.9 (m, F3,5-py).

*bis(perfluoropyridin-4-yl)amine (**8**)*

Yield: 75% (0.24 g); white solid; mp 143-145 °C (144-146 °C)[48]. (Found: C, 38.14; H, 0.41; N, 13.25. $C_{10}HF_8N_3$ requires: C, 38.11; H, 0.32; N, 13.33%). IR (KBr): ν 3306 (NH) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.77 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 143.5 (dm, *J* = 235.4 Hz, C2,6-py), 135.2 (dm, *J* = 253.9 Hz, C3,5-py), 132.8 (m, C4-py). ^{19}F NMR (282 MHz, DMSO-d_6) δ = -93.1 (m, 2F, F2,6-py), -153.2 (m, 2F, F3,5-py).

*bis(perchloropyridin-4-yl)amine (**9**)*

yield 45% (0.20 g); white solid; mp 147-150 °C (Found: C, 26.78; H, 0.15; N, 9.34. $C_{10}HCl_8N_3$ requires: C, 26.89; H, 0.23; N, 9.41%). IR (KBr): ν 3386 (NH) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.38 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 151.3 (C2,6-py), 144.6 (Hz, C3,5-py), 112.1 (m, C4-py).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] B.E. Smart, J. Fluorine Chem. 109 (2001) 3-11.

[2] D.F. Halpern, G. Vernice, Chemistry of organic fluorine compounds II, eds. M. Hudlicky, A.E. Pavlath, American Chemical Society, Washington D.C. 1995, pp. 172.

[3] I. Ojima, Fluorine in medicinal chemistry and chemical biology, John Wiley & Sons, 2009.

[4] J.T. Welch, Tetrahedron, 43 (1987) 3123-3197.

[5] R.D. Chambers, J. Hutchinson, W.K.R. Musgrave, J. Chem. Soc. (1964) 3736-3739.

[6] R.E. Banks, J.E. Burgess, W.M. Cheng, R.N. Haszeldine, J. Chem. Soc. (1965) 575-581.

[7] G. Sandford, R. Slater, D.S. Yufit, J.A. Howard, A. Vong, J. Org. Chem. 70 (2005) 7208-7216.

[8] A. Baron, G. Sandford, R. Slater, D.S. Yufit, J.A. Howard, A. Vong, J. Org. Chem. 70 (2005) 9377-9381.

[9] R.D. Chambers, A. Khalil, C.B. Murray, G. Sandford, A.S. Batsanov, J.A. Howard, J. Fluorine Chem. 126 (2005) 1002-1008.

[10] R. Ranjbar-Karimi, A. Poorfreidoni, H.R. Masoodi, J. Fluorine Chem. 180 (2015) 222-226.

[11] R. Ranjbar-Karimi, E. Heidari, J. Fluorine Chem. 154 (2013) 47-52.

[12] R. Ranjbar-Karimi, M. Mousavi, J. Fluorine Chem. 131 (2010) 587-591.

[13] A. Poorfreidoni, R. Ranjbar-Karimi, Tetrahedron Lett. 57 (2016) 5781-5783.

[14] R. Ranjbar-Karimi, A. Darehkordi, F. Bahadornia, A. Poorfreidoni, J. Heterocycl. Chem. 55 (2018**)** 2516-2521.

[15] R. Ranjbar-Karimi, A. Karbakhsh-Ravari, A. Poorfreidoni. J. Iran. Chem. Soc. 14 (2017) 2397-2405.

[16] T. Han, M. Goralski, N. Gaskill, E. Capota, J. Kim, T.C. Ting, Y. Xie, N.S. Williams, D. Nijhawan, Science, 356 (2017) eaan7977.

[17] T. Uehara, Y. Minoshima, K. Sagane, N.H. Sugi, K.O. Mitsuhashi, N. Yamamoto, H. Kamiyama, K. Takahashi, Y. Kotake, M. Uesugi, Nat. Chem. Biol. 13 (2017) 675-680.

[18] M.M. Ghorab, F.A. Ragab, H.I. Heiba, A.M. Soliman, Eur. J. Med. Chem. 117 (2016) 8-18.

[19] M.M. Ghorab, M.A. Shaaban, H.M. Refaat, H.I. Heiba, S.S. Ibrahim, Eur. J. Med. Chem. 53 (2012) 403-407.

[20] Y. Kwon, J. Song, H. Lee, E.Y. Kim, K. Lee, S.K. Lee, S. Kim, J. Med. Chem. 58 (2015) 7749-7762.

[21] A. Nocentini, C.T. Supuran, Expert Opin. Ther. Pat. 28 (2018) 729-740.

[22] İ. Gulçin, P. Taslimi, Expert Opin. Ther. Pat. 28 (2018) 541-549.

[23] A.K. Ghosh, H.L. Osswald, G. Prato, J. Med. Chem. 59 (2016) 5172-5208.

[24] S. Konda, S. Raparthi, K. Bhaskar, R.K. Munaganti, V. Guguloth, L. Nagarapu, D.M. Akkewar, Bioorg. Med. Chem. Lett. 25 (2015) 1643-1646.

[25] S.S. Swain, S.K. Paidesetty, R.N. Padhy, Biomed. Pharmacother. 88 (2017) 181-193.

[26] C. De Monte, S. Carradori, A. Gentili, A. Mollica, D. Trisciuoglio, C.T. Supuran, Curr. Med. Chem. 22 (2015) 2812-2818.

[27] V. Gorantla, R. Gundla, S.S. Jadav, S.R. Anugu, J. Chimakurthy, S.K. Nidasanametla, R. Korupolu, New J. Chem. 41 (2017) 13516-13532.

[28] J. Li, J. Lou, Z. Wang, T. Wang, Y. Xiao, X. Hu, P. Liu, X. Hong, Eur. J. Med. Chem. 92 (2015) 370-376.

[29] M. Aggarwal, B. Kondeti, R. McKenna, Expert Opin. Ther. Pat. 23 (2013) 717-724.

[30] X. Lin, H. Dorr, J. M. Nuss, Tetrahedron Lett. 41 (2000) 3309-3313.

[31] M.A. Schmidt, R.W. Stokes, M.L. Davies, F. Roberts, J. Org. Chem. 82 (2017) 4550-4560.
[32] P.K. Chinthakindi, A. Benediktsdottir, A. Ibrahim, A. Wared, C.J. Aurell, A. Pettersen, E. Zamaratski, P.I. Arvidsson, Y. Chen, A. Sandstrom, Eur. J. Org. Chem. (2019) 1045-1057.
[33] J. Wang, M. Sanchez-Rosello, J.L. Acena, C. del Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, Chem. Rev. 114 (2013) 2432-2506.
[34] C. Isanbor, D. O'Hagan, J. Fluorine Chem. 127 (2006) 303-319.
[35] M. Ceruso, D. Vullo, A. Scozzafava, C.T. Supuran, Bioorg. Med. Chem. 21 (2013) 6929-6936.
[36] K.L. Kirk. J. Fluorine Chem. 127 (2006) 1013-1029.
[37] T. Fujiwara, D. O'Hagan, J. Fluorine Chem. 167 (2014) 16-29.
[38] M. Ceruso, D. Vullo, A. Scozzafava, C.T. Supuran, J. Enzyme Inhib. Med. Chem. 29 (2014) 686-689.
[39] M.M. Ghorab, F.A. Ragab, H.I. Heiba, R.K. Arafa, E.M. El-Hossary, Med. Chem. Res. 20 (2011) 388-400.
[40] M. al-Rashida, M. Ashraf, B. Hussain, S.A. Nagra, G. Abbas, Bioorg. Med. Chem. 19 (2011) 3367-3371.
[41] H. Qin, N. Yamagiwa, S. Matsunaga, M. Shibasaki, Angew. Chem. Int. Ed. 46 (2007) 409-413.
[42] M.V. Pham, B. Ye, N. Cramer, Angew. Chem. Int. Ed. 51 (2012) 10610-10614.
[43] A. Martinez-Asencio, D.J. Ramón, M. Yus, Tetrahedron Lett. 51 (2010) 325-327.
[44] J.K. Laha, S. Sharma, N. Dayal, Eur. J. Org. Chem. 17 (2015) 7885-7891.
[45] M. Yamagishi, K. Nishigai, T. Hata, H. Urabe, Org. Lett. 13 (2011) 4873-4875.
[46] M. Yamagishi, K. Nishigai, A. Ishii, T. Hata, H. Urabe, Angew. Chem. Int. Ed. 51 (2012) 6471-6474.
[47] X. Deng, N.S. Mani. Green Chem. 8 (2006) 835-838.
[48] P.L. Coe, A.J. Rees, J. Whittaker, J. Fluorine Chem. 107 (2001) 13-22.

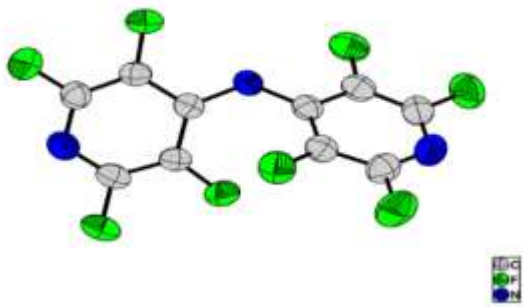
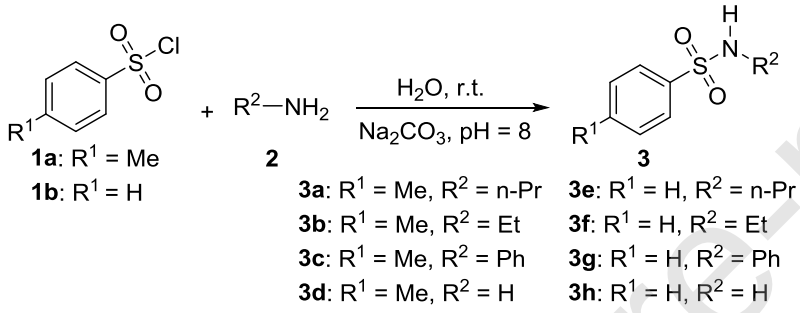
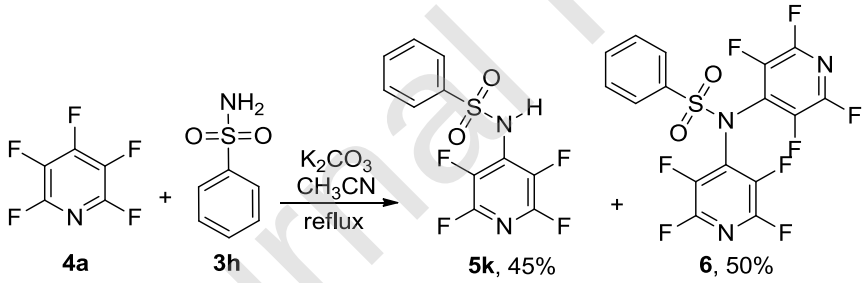


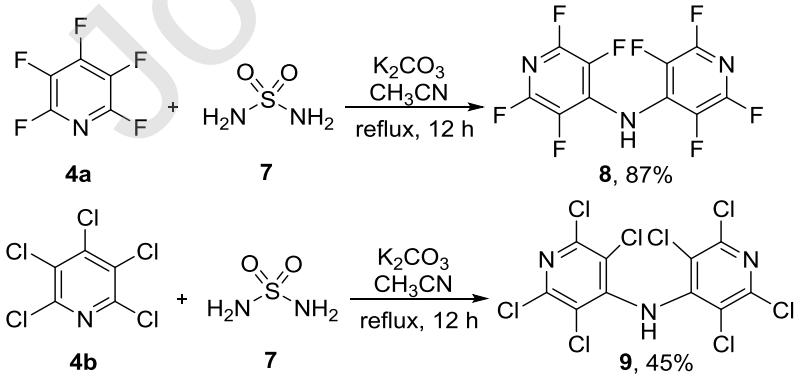
Fig. 1. The molecular structure of **8**



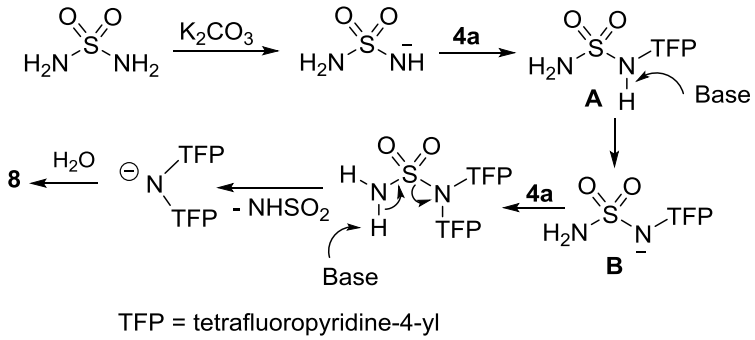
Scheme 1. Synthesis of sulfonamides **3a-h**



Scheme 3. The reaction of sulfonamide **3h** with pentafluoropyridine

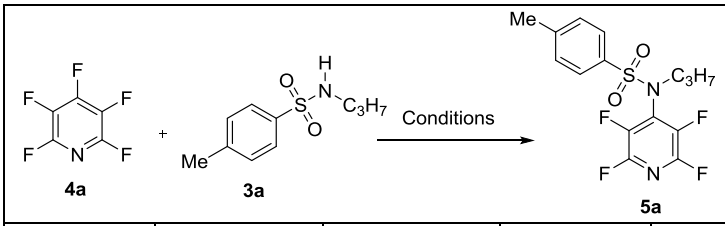


Scheme 4. The reaction of sulfamide with pentafluoro- and pentachloropyridine



Scheme 5. Proposed explanation for the formation of **8**

Table 1: Effect of solvent and temperature on the reaction of pentafluoropyridine **4a** and 4-methyl-*N*-propylbenzensulfonamide **3a**



Entry	Solvent	Temperature	Time (h)	Yield (%)
1	THF	r.t.	12	trace
2	THF	reflux	15	40
3	CH_3CN	r.t.	10	trace
4	CH_3CN	reflux	12	88
5	EtOH	r.t.	12	n.r.
6	EtOH	reflux	17	30
7	Acetone	r.t.	12	trace
8	Acetone	reflux	13	20

[a] **Reaction conditions: 4a** (1.0 mmol), **3a** (1.0 mmol), K_2CO_3 (1.0 mmol), solvent (5.0 ml).

Table 2: Synthesis of *N*-perfluoropyridyl sulfonamides and *N*-perchloropyridyl sulfonamides