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Synthesis of Fluorinated Nitrogen Heterocycles as New Drug Scaffolds

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Abstract
The amine compound (N-(2-bromophenyl)-4-methyl-N-(perfluoropyridin-4-yl)benzenesulfonamide) was successfully synthesised which was needed to find a strategy to synthesise fluorinated nitrogen heterocycles. The aim of this study was to make a cyclised product by treating the amine compound with different reagents to effect metalation in the bromophenyl group which could result in S_NAr reaction in the fluorinated ring. However, treating the target compound with Bu-Li or Mg interestingly gave two different compounds which had lost the sulfonyl group. In addition, the reaction of (N-(2-bromophenyl)-4-methyl-N-(perfluoropyridin-4-yl)benzenesulfonamide) with Cu and 2-bromophenyltetrafluoropyridinamine with Cu was unsuccessful due to the recovery of the starting material as a major product and a minor percentage of new compounds had formed.

Keywords: Synthesis, Fluorinated Nitrogen, New Drug, Scaffolds.
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1. Introduction

In the developed world, fluorine is an important element for life; due to the important properties of fluorine atoms as it has high electronegativity, which impacts on the general public as many pharmaceuticals, anaesthetics, agrochemicals, and air conditioning materials depend on the presence of fluorine atoms in their structures [1, 2]. Therefore, fluorinated compounds have a notable record in medicinal chemistry with 20-25% of drugs in the pharmaceutical pipeline containing at least one fluorine atom. There has been rapid progress since the synthesis of 5-fluorouracil (Fig. 1) in 1957, because of its ability to achieve higher metabolic stability, bioavailability and protein-ligand interactions. Thus, the development of new fluorinated compounds (Fig. 2) lead to an increase in the range of synthetic fluorinate building blocks [2, 3]. Moreover, the inclusion of fluorine atoms in a drug allows simultaneous modulation of electronic, lipophilic and steric parameters, which can influence the drugs pharmacokinetics and pharmacodynamics properties [4].

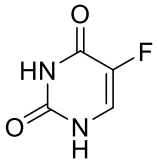


Fig. 1: 5-fluorouracil structure [3]

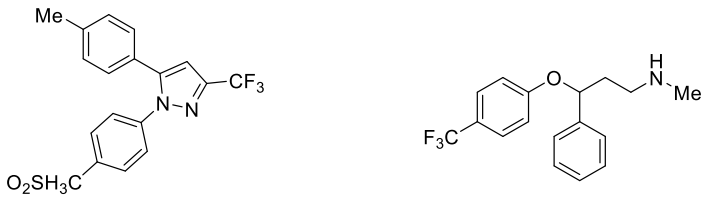
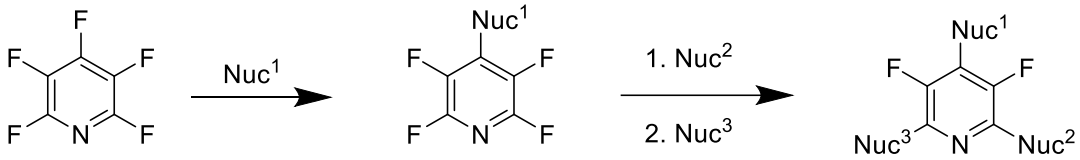
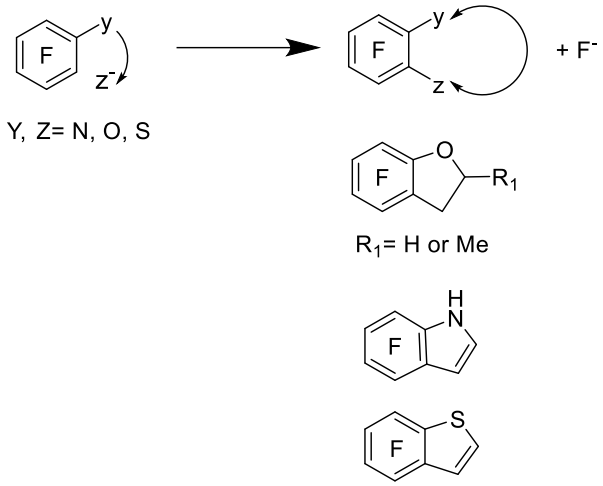


Fig. 2: Different fluorinated compounds

Synthesis of polyfluoro fused-ring heterocycles from fluorinated precursors via nucelophilic substitution of fluorine [5]. Nucleophilic aromatic substitution reactions (S_NAr) (Scheme 1) consisting of replacing the fluorine atom in highly fluorinated heteroaromatic systems by nitrogen, oxygen and sulphur are well reported [5]. The structures in (Scheme 2) can be made by the chemistry indicated [5].

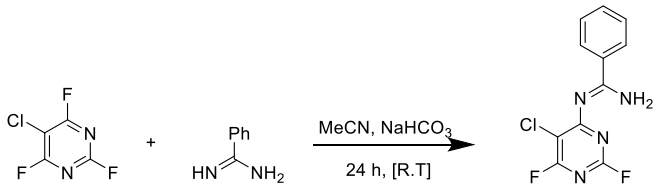


Scheme 1: Regioselective sequential S_NAr reactions of pentafluoropyridine[6]



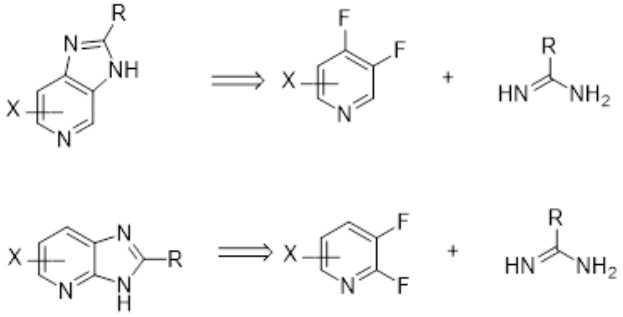
Scheme 2: Heterocycles formed via nucleophilic substitution of fluorine[5]

The reaction of aromatic nucleophilic substitution in polysubstituted pyrimidine derivatives is a major method in making functionalised heterocyclic and aromatic compounds. For example, the compounds have been investigated by Sandford [12] and have been used as scaffolds for drug discovery (Scheme 3) [7].



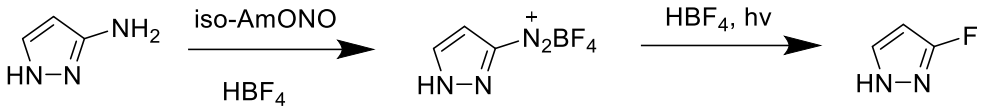
Scheme 3: The reaction of amine nucleophiles with pyrimidine[7]

The aim of Diversity Orientated Synthesis (DOS) strategies is to improve a wide range of structural diversity from polyfunctional starting materials, while Rapid Analogue Synthesis (RAS) is a supplementary approach to synthesise many analogues of biologically active systems. There has been an increasein the synthesis of polyfunctional heterocyclic core scaffolds, for instance, benzopyrans, benzimidozoles and benzofuran systems, which might be valuable to use as privileged structure in parallel synthesis (Scheme 4) [8].



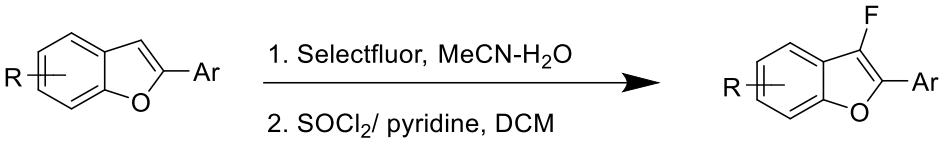
Scheme 4: Strategy for the synthesis of imidazopyridine system[8]

A Recent study investigated the importance of the incorporation of fluorine atoms into pyrazolerings[9]. Therefore, the first synthesis approach, which proved to be one of the most important building blocks for the synthesis of drugs, as it has the ability to increase their biological activity (Scheme 5) [9]. which appears to obtain fluoropyrazoles, is the main synthetic pathways by nucleophilic substitution reactions,



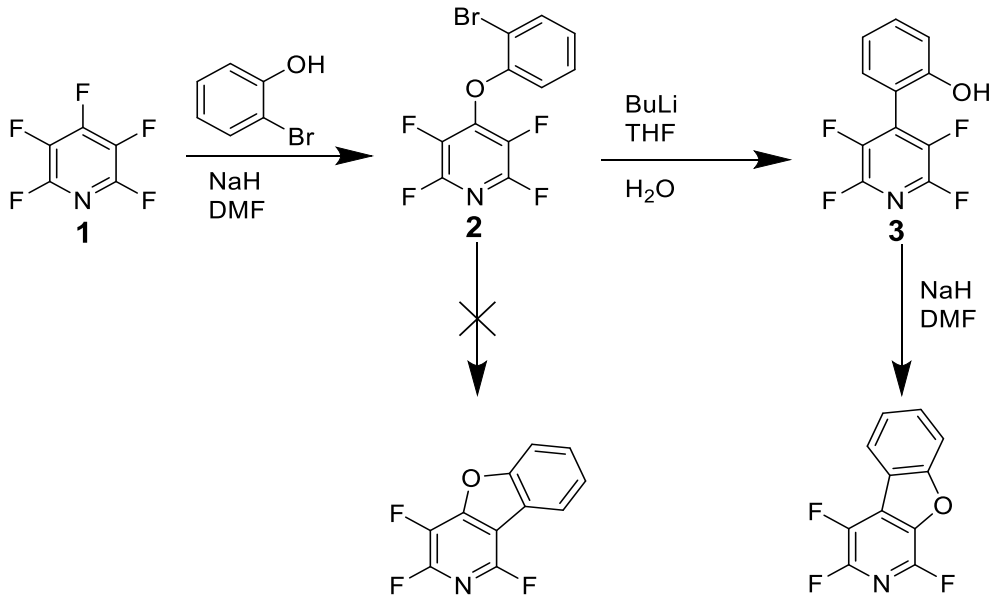
Scheme 5: Fluorine- containing pyrazoles[9]

Moreover, benzo[b]furan rings have recently received denotable attentions [10] and could be the most important finding in medicinal chemistry for drug discovery and development, due to their versatile pharmaceutical activities. An important protocol to generate C(3)-F-substituted of 2-arylbenzo[b]-furans has been reported (Scheme 6) [10].



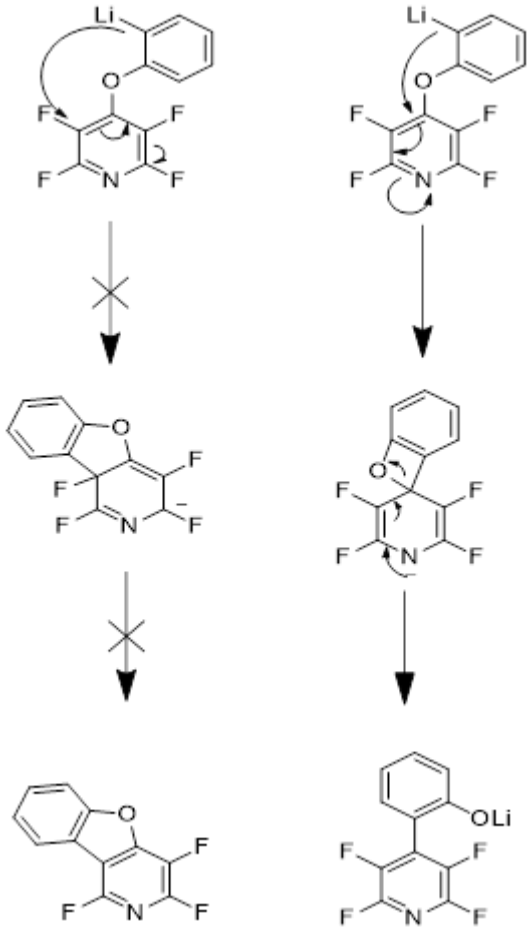
Scheme 6: Fluorination of 2-substituted benzo[b]furans with Selectfluor[10]

The study by J. Gonzales and co-workers [11] investigated the ring closure by the lithiation of bromoaryl ethers and sulfides containing a perfluoroarene ring. In the case of ethers, scheme 2, the compound formed by the lithiation of 2-bromophenyl tetrafluoropyridine-4-yl ether **2** did not as expected to close the furan ring. However, treating the tetrafluoropyridyl ether **2** with *n*-butyllithum in THF at a low temperature provided compound **3**, which was identified by IR and ^{1}H NMR spectroscopy as the presence of an alcohol group, as well as the ^{19}F NMR spectrum showed two pairs of fluorine atoms signals, which means that tetrafluropyridine ring did not reacted with BuLi (Scheme 7) [11].



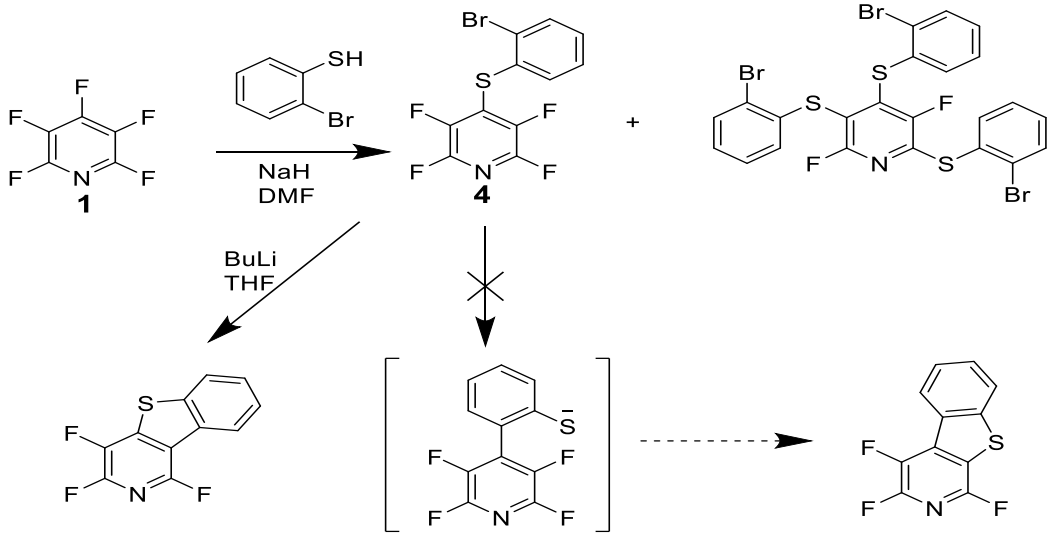
Scheme 7: Formation and Smiles-type rearrangement of ether[11]

Therefore, this reaction is caused by a Smiles type of rearrangement instead of the S_NAr reaction as indicated in (Scheme8) [11].



Scheme 8: Possible reactions pathways for lithiated ether[11]

Secondly, in the case of sulfides (Scheme 9), the lithiation of corresponding sulphides**4**, which were formed from a reaction of pentafluoropyridine with sodium 2-bromobenzenethiolate in DMF, afforded cyclisation of the sulphide to thepyrido-fusedbenzothiophene rather than Smiles type rearrangement (Scheme 9) [11].



Scheme 9: Formation and cyclisation of sulphides [11]

Following on from the previous work [11], the aim of this study is to establish what happens when analogous amine compounds are used. Does cyclisation or rearrangement occur, and can the strategy be applied to the synthesis of fluorinated nitrogen heterocycles?

The products were to be identified by ^{1}H NMR spectroscopy and other analytical methods such as IR, mass spectroscopy or elemental analysis.

2. Experimental section/MATERIAL AND METHODS

2.1. Generalexperimental procedures

All the starting materials, metals and solvents were used commercially, except for THF, which was distilled from bezophenone sodium under nitrogen atmosphere. Sodium hydride was 60% dispersion in mineral oil. DMSO was purchased dry from a commercial supplier. A 2.5 M solution of *n*-butyllithium in hexane was used.

Melting points were determined on Electrothermal-IA9100. Infrared spectra were recorded on a Perkin-Elmer, spectrum 65 FT-IR spectrophotometer as KBr discs.^{1}H (400 MHz, $CDCl_3$), ^{19}F (376 MHz, $CDCl_3$) NMR spectra were recorded on Bruker DPX 400 instrument. Chemical shifts were given in parts per million (ppm), and *J* values in (Hz) using tetramethylsilane as the internal standard.

TLC was uses on glass backed plates with Merck kiesel gel silica gel 60 F_{254}. To carry out the column chromatography, Merck kiesel 60 silica gel was used. GC-MS was performed on Flison 8060 with a DB5MS column of 30m length and split less injection. The temperature program was 5 min at 50 ºC, ramping to 250 ºC over 10 min, and 250 for 10 min. The headspace temperature was 250 ºC, the interface temperature 250 ºC, and the source temperature 200 ºC. The mass spectroscopy was EI+ with 70eV, full scan per second 50- 500 *m/z*.

2.2. Reaction of 2-bromoaniline with sulfonyl chloride

2-Bromoaniline (1.72 g, 0.01 mol) was dissolved in pyridine (1 mL), and p-toluenesulfonyl chloride (1.90 g, 0.01mol) dissolved in (2 mL) pyridine added, which resulted in a yellow solution, and lefttostir overnight at room temperature for 20h.

Hydrochloric acid (20 ml, 2 M) was added, and the mixture extracted with ethyl acetate (3× 25 mL) to give the organic layers, which were dried over $MgSO_4$, filtered and evaporated to give the product **7** (AH3a) as a yellow solid (2.76 g, 85%), which turned orange after 20min.

m.p: 80ºC. IR: υ_{max}/cm^{-1} (neat) 3294 (N-H), 1474, 1327, 1157, 910. NMR: δ_H(400 MH_Z, $CDCl_3$) 7.65 (3H, t, *J* 7H_Z) 7.55 (1H, dd, *J*2, 1H_Z), 7.21(2H, d, *J*8H_Z), 6.97-6.93 (2H, m) and 2.36 (3H,s).

2.3. Reaction of pentafluoropyridine with methylbenzenesulfonamide

Pentafluoropyridine (1.35 g, 0.008 mol) was added to a suspension of sodium hydride (60% dispersion in mineral oil) (0.32g, 0.008mol) in anhydrous DMF (3 mL), and (1.30 g, 0.004mol) **7** (AH3a) was added to the mixture. The mixture was stirred at room temperature overnight for 20h.

Water (10mL) was added, and the mixture extracted with (20mL ×3) ethyl acetate. The organic layers were dried over $MgSO_4$, filtered and evaporated to give**8**(AH4a), (1.54 g, 100%) as a light brown solid.

m.p: 88- 90ºC. IR: υ_{max}/cm^{-1} (neat) 2950, 1465, 1165, 1095, 1049. NMR: δ_H(400 MH_Z, $CDCL_3$) 8.08-8.04 (1H, m), 7.59 (2H, d, *J*8H_Z), 7.50 (1H, dd, *J*7 and 2 H_Z), 7.48 (1H,td, *J*6 and 2 Hz), 7.31(3H, dd, *J*6 and 2 Hz), 2.98 (1H, s), 2.91 (1H, s) and 2.46 (3H, s). NMR: δ_F(376 MH_Z, $CDCL_3$) 72.8-72.6 (2F, m) and 24(2F, s).

Due to the detection of the starting material when using two equivalents of pentafluoropyridine with one equivalent of **7** in the presence of 1.5 equivalent of sodium hydride, increasing the number of moles for sodium hydride enhanced the chances of the reaction being completed.

2.4. Reaction of benzenesulfonamide8 with *n*-butyllithum

A stirred solution of**8**(AH4a) (0.58g, 0.0015mol) in dry THF (3ml) was cooled to -78ºC and treated dropwise with *n*-butyllithum in hexane (2.5 M, 1 ml). The solution turned dark red. Then, the solution was allowed to warm at room temperature overnight for 18h, with stirring,during which time it changed yellow in colour.

Water (5ml) was added, and the mixture extracted with ethylacetate (20ml×3). The organic layers were dried over $MgSO_4$, filtered and evaporated to give**9**(AH5a) (0.4g) as a yellow solid.

The yellow solid was chromatographed over silica. Elution with light petroleum-ethylacetate (20:1) gave three different fractions **10**, **11** and **12**.

NMR: δ_H(400 MH_Z, $CDCL_3$) 7.12 (2H, d, *J*8Hz) 2.72 (1H, s), 2.41(3H, s), 1.26 (3H, t, *J* 4 Hz). NMR: δ_F(376 MH_Z, $CDCL_3$) 73.25 (2F, q, *J* 27 Hz), 72.82- 72.64 (2F, m), 72.06- 71.89 (2F, m), 33.85 (2F, d, *J*30 Hz), 23.32 (2F, s), 21.14- 20.96 (2F, m). *m/z*Found 241, $C_{11}H_6F_4N_2$, 221, $C_{11}H_5F_4N_2$ and 387, $C_{18}H_{11}BrF_4N_2O_2S$.

Further elution gave **10**, **11** and **12**.

10: Light yellow oil (0.17 g, 15%). NMR: δ_H(400 MH_Z, $CDCL_3$) 7.81 (1H, dd, *J*12 and 8 Hz), 7.39 (2H, d, *J*8 Hz), 7.31(2H, d, *J*4 Hz), 7.29 (1H, s), 7.26- 7.21 (1H, m), 7.09-7.04 (4H, m). NMR: δ_F(376 MH_Z, $CDCL_3$) 71.82 (2F, q, *J* 15 Hz), 68.69- 68.46 (2F, m).

11: Colourless solid (0.12 g, 12%). NMR: δ_H(400 MH_Z, $CDCL_3$) 7.97 (1H, dd, *J*8 and 4 Hz), 7.50 (2H, d, *J*4 Hz), 7.45- 7.38 (2H, m), 7.28 (1H, s), 7.26- 7.17 (2H, m). NMR: δ_F(376 MH_Z, $CDCL_3$) 72.38 (2F, m (AA', BB'), 23.09 (2F, s).

12: Yellow solid (0.08 g, 8%). NMR: δ_H(400 MH_Z, $CDCL_3$) 7.67 (1 H, d, *J*16 Hz), 7.54 (3H, t, *J*12 Hz), 7.42 (3H, d, *J*8 Hz), 7.31 (2H, t, *J*8 Hz), 7.23 (3H, d, *J*12 Hz), 7.14 (3H, d, *J* 8 Hz), 6.34 (1H, s), 4.14 (1H, q, *J*8 Hz), 2.76- 2.45 (3H, m), 2.30 (1H, s). NMR: δ_F(376 MH_Z, $CDCL_3$) 73.28 (1F, t, *J*30 Hz), 33.80 (1F, d, *J*33 Hz), 21.12 (1F, d, *J* 15 Hz). *m/z*Found 241, $C_{11}H_6F_4N_2$ and 221, $C_{11}H_5F_4N_2$.

2.5. Reaction of benzenesulfonamide 8 with magnesium

Firstly, the magnesium metal was activatedbefore use; the activation was by washing Mg (0.24 g, 0.01 mol) with HCl (1M) to remove the oxidised layers as the H_2 gas evaporated. Then, washed with water in order to remove the acid, and finally, washed with ethanol followed by light petroleum.

In a round bottom flask and under dry condenser, THF (3 mL) was added dropwise to a suspension of **8** (0.38 g, 0.001 mol), with an activated Mg (0.24 g, 0.01 mol), and a

few crystals of iodine. This experiment was heated under refluxfor 5 h, in order toachieve a reasonable reaction rate, during which time the colour changed to dark red.

Non-reacted magnesium was filtered. Water (10 mL) was added and the mixture extracted with (20mL ×3) ethyl acetate. The organic layers were dried over $MgSO_4$, filtered and evaporated to give **18** and **19** (AH6a), (0.21 g) as a dark brown solid.

IR: υ_{max}/cm^{-1} (neat) 3294, 2924, 2854, 1643, 1535, 1465. NMR: δ_H(400 MH_Z, $CDCL_3$) 7.64 (1H, dd, *J*8 and 2 Hz), 7.41 (2H, t, *J*4 Hz), 7.24 (1H, t, *J*8 Hz), 7.14 (2H, d, *J* 4 Hz), 6.39 (1H, s). NMR: δ_F(376 MH_Z, $CDCL_3$) 70.51 (1F, quintet, *J* 11Hz) 69.77 (2F, quintet,*J* 11Hz) 7.83 (1F, quintet, *J* 11 Hz) 6.69 (2F, quintet, *J* 11 Hz). *m/z*Found 242, $C_{11}N_2F_4H_6$ and 222, $C_{11}N_2F_3H_5$.

2.6. Reaction benzenesulfonamide8 with copper

In a test tube, dimethyl sulfoxide (DMSO) (0.5 mL) was added dropwise to a stirred solution of **8** (AH4a) (0.07 g, 0.0001 mol) with copper (0.12 g, 0.002 mol), and a few crystals of iodine at 160 °C for two hours.

Water (2 mL ×3) was added, and the mixture extracted with (20 mL ×3) diethyl ether. The organic layers were dried over $MgSO_4$, filtered and evaporated to give a compound **20** (AH7a) as pale-yellow oil (0.03 g), which was found to be the starting material recovered.

NMR: δ_H(400 MH_Z, $CDCL_3$) 8.06 (2H, dd, *J*8 and 2 Hz), 7.57 (3H, t, *J*8 Hz), 7.53- 7.49 (2H, m), 7.46 (2H, t, *J*8 Hz), 4.14 (2H, q, *J*8 Hz), 3.01 (1H, s). NMR: δ_F(376 MH_Z, $CDCL_3$) 72.82, 72.77, 72.73, 72.72, 72.68, 72.64, 72.62, 72.58, 72.57, 72.53, 72.49, 24.73, 23.31 (indicated as a mixture).

2.7. Reaction of pentafluoropyridine with 2-bromoaniline to form 2-bromophenyltetrafluoropyridinamine 21 as intermediate, to reaction with copper

A stirred solution of 2-bromoaniline (1.72 g, 0.01 mol) and pentafluoropyridine (2.00 g, 0.02 mol), was treated dropwise by dry tetrahydrofuran (THF) (0.5 mL) at 68 °C for 15 h.

Water (2 mL ×3) was added, and the mixture extracted with (20 mL ×3) ethyl acetate. The organic layers were dried over $MgSO_4$, filtered and evaporated to givethe intermediate**21** (AH9a) as a yellow oil (1.69 g, 53 %).

NMR: δ_H(400 MH_Z, $CDCL_3$) 7.44 (1H, d, *J*4 Hz), 7.16-7.12 (1H, m), 6.78 (1H, q, *J*2 Hz), 6.68- 6.64 (1H, m), 4.18 (1H, q, *J* 8 Hz), 4.08 (1H, s). NMR: δ_F(376 MH_Z, $CDCL_3$) 70.35, 30.25, 7.68, 7.05, 2.24, 2.20 (indicating the mixture)

In a test tube, **21** (AH9a) (1.39 g, 0.004 mol) was added to a suspension of copper (0.63 g, 0.01 mol) and a few crystals of iodine, whichwastreated dropwise by dimethylsulfoxide (DMSO) (0.5 mL) at 160 °C for 3 h.Water (2 mL ×3) was added and the mixtureand extracted with (20 mL ×3) diethyl ether. The organic layers were dried over $MgSO_4$, filtered and evaporated to give the products **22** (AH9b) as a yellow oil (0.8 g).

NMR: δ_H(400 MH_Z, $CDCL_3$) 7.69(1H, d, *J*8 Hz), 7.47 (1H, d, *J*8 Hz), 7.28 (1H, s), 7.15 (1H, t, *J*8 Hz), 6.77 (1H, d, *J*8 Hz), 6.64 (1H, t, *J* 8 Hz), 2.20 (1H, s). NMR: δ_F(376 MH_Z, $CDCL_3$) 70.43, 69.69, 68.65, 15.79, 7.74, 6.99 (indicating the mixture)

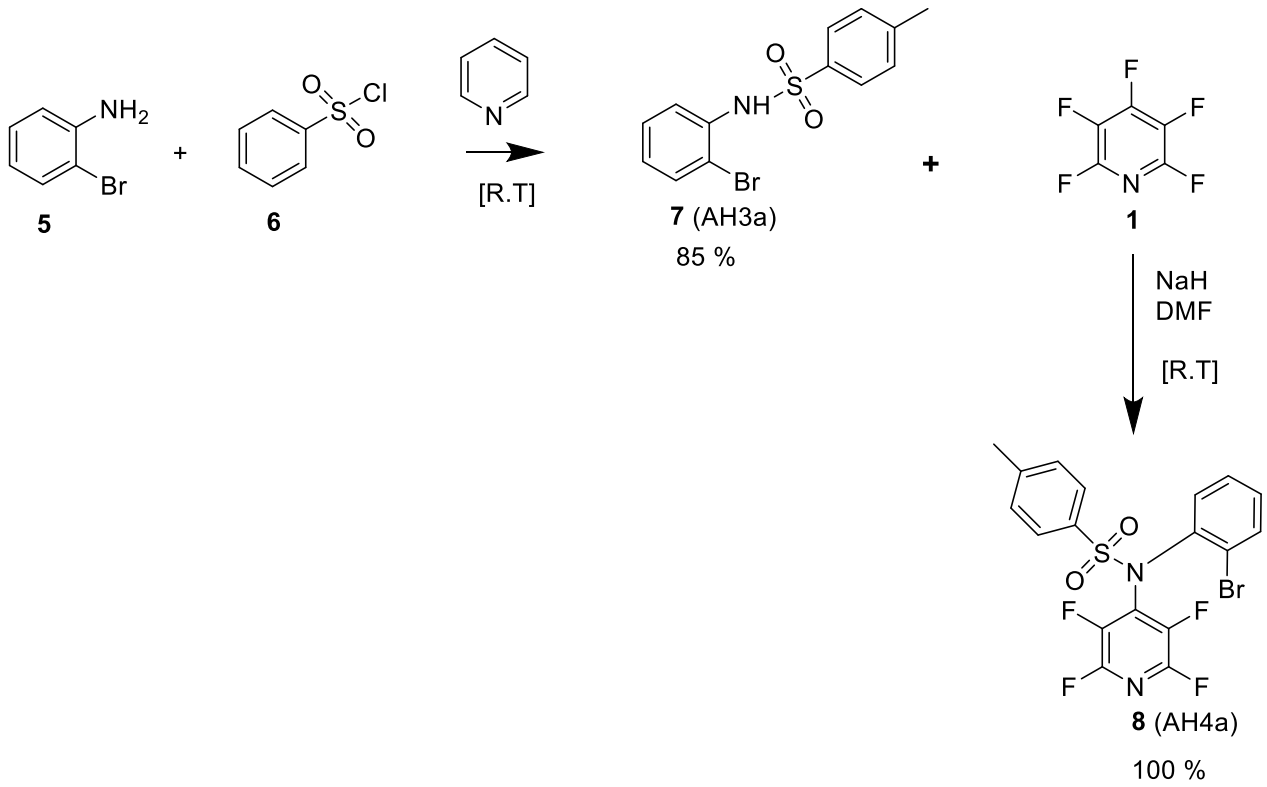
3. Results and Discussion

3.1. Reaction of 2-bromoaniline with sulfonylchloride to formethylbenzenesulfonamide, which then reacted with pentafluoropyridine

The aim of these reactions was the formation of **7** as a starting material to react it with pentafluoropyridine, to synthesis a target compound **8**, which was treated with different reagents to achieve the goal of this study as mentioned before.

This reaction aimed to synthesis of **7** (AH3a) as intermediate by a reaction of 2-bromoaniline **5** with p-toluensulfonyl chloride **6** in the presence of pyridine (base) at room temperature (Scheme 10). The intermediate compound **7** as orange solid was formed in 85% yield and confirmed by its ^{1}H NMR spectrum. In addition, infrared spectroscopy indicated the present of an NH group by showing single peak between 3000- 3300 cm^{-1} and the absent of two signal peaks of NH_2 group of the starting material **5**.

Then, the intermediate compound **7**was reacted successfully withpentafluoropyridine**1** in DMF with the presence of sodium hydride (NaH) at room temperature and successfully gave compound **8**, ((N-(2-bromophenyl)-4-methyl-N-(perfluoropyridin-4-yl)benzenesulfonamide) (AH4a)(Scheme 10). The structure of **8** was confirmed bythe^{19}F NMR spectrum as it showed two peaks (one single sharp peak, and the other was a broad peak) which supported the presence of twopairs of fluorine atoms, as expected (Fig. 3).



Scheme 10: Reaction of **5** with **6** to form methylbenzenesulfonamide**7**, which then reacted with pentafluoropyridine**1**

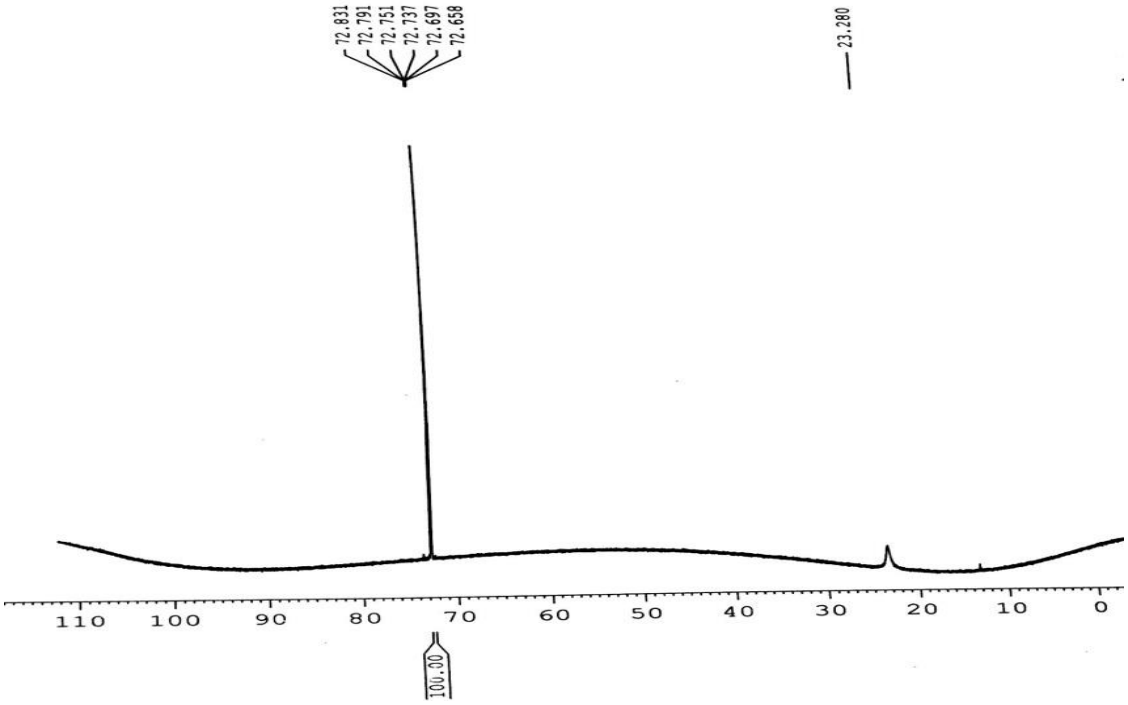


Fig. 3:[19]F NMR spectrum of 2-bromophenylbenzenesulfonamide **8**

3.2. Reaction of 2-bromophenylbenzenesulfonamide8 with *n*-butyllithum

This reaction aimed to discover what happened when using amine compounds with Bu-Li. We expected a cyclisation between the bromine atom with the fluorine atom at C-3 position in the pyridine ring of compound **8** or Smiles type rearrangement structure.

Treatment of **8** (AH4a) with 1.1 equivalent of *n*-butyllithum in dry tetrahydrofuran (THF) at -78 ^{o}C, followed by warming at room temperature gave, after the work-up afforded, a complex mixture**9**(AH5a) (Scheme

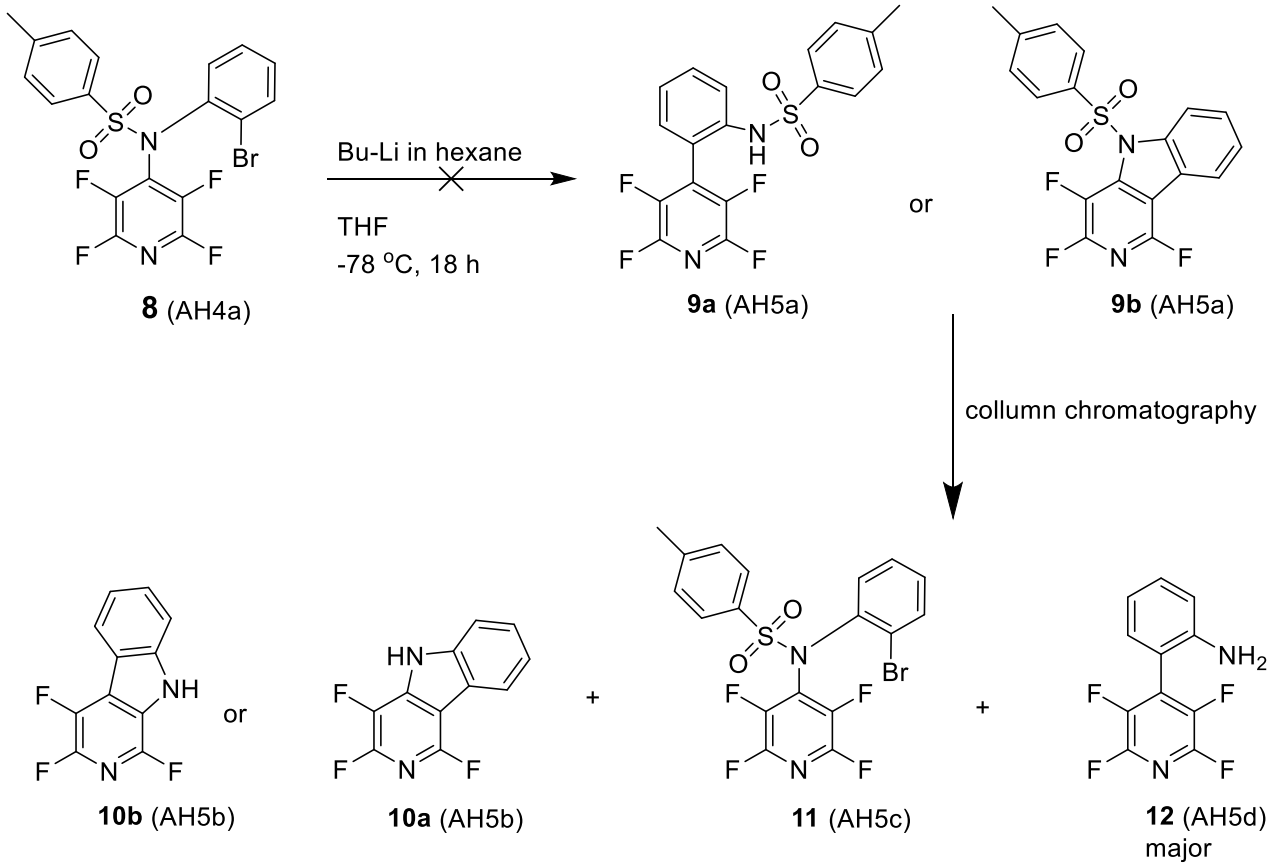
11), which was not as expected to form a compound by cyclisation or Smiles type rearrangement (Scheme 12).

The mechanism of cyclisation was expected to occur by replacement of the bromine atom to form a carbanion which then may attack at C-3 or C-4 of the pyridine ring. Moreover, Smiles type rearrangement would lead to the intermediate **14** which on protonation during work-up would generate the aniline derivative **16**. Alternatively, direct cyclisation of the carbanion **13** would give the tricyclic ring **15**.

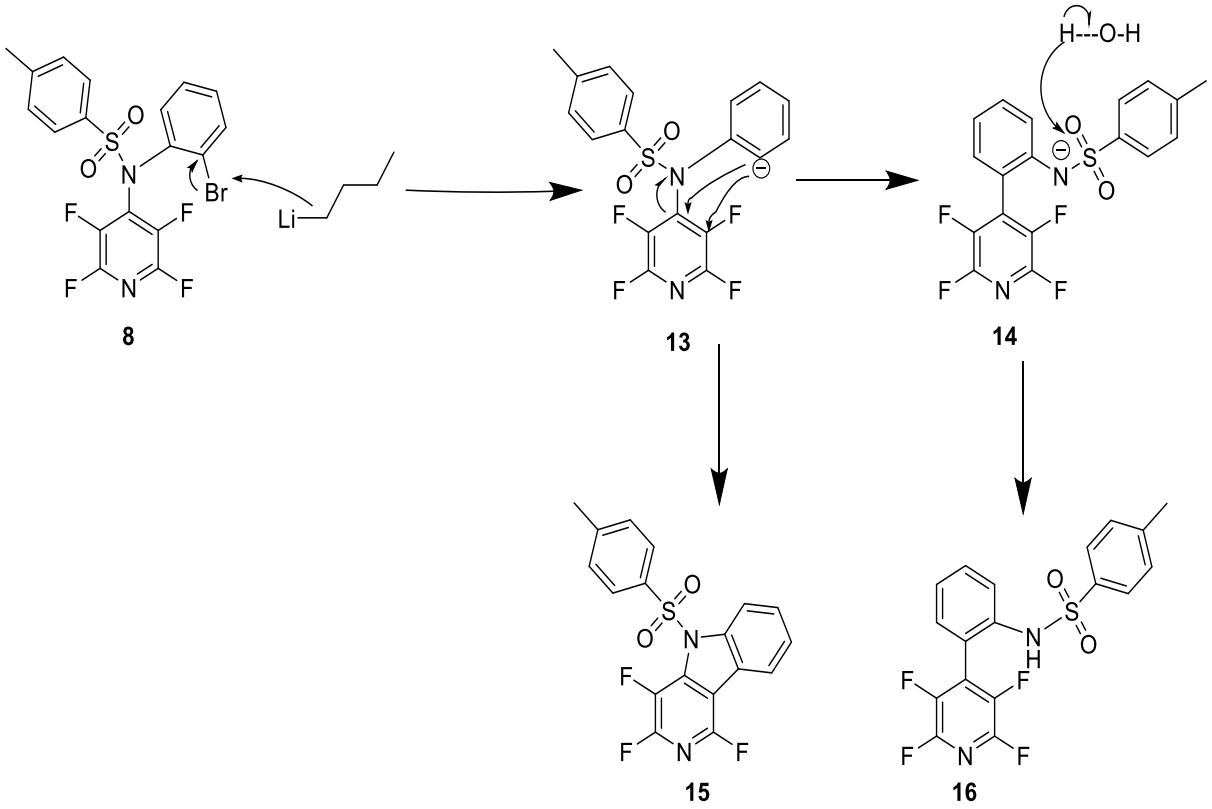
Thin layer chromatography and ^{19}F NMR spectrum of **9a,b** indicated that there are three different compounds. One of them is the starting material, which was supported by mass spectrometry withm/z of 387 corresponding to $C_{18}H_{11}BrF_4N_2O_2S$.

Due to the good yield 85%, this mixture could easily be separated by column chromatography to identify the components. Therefore, the mixture was separated by column chromatography to give three different fractions **10a or 10b**, **11** and **12**(Scheme7), which were analysed spectroscopically. ^1H NMR analysis of **10** suggested that the cyclisation had occurred with loss of the sulfonyl group. Further work may determine the orientation of the cyclisation (**10a** or **10b**) as indicated in (Scheme 11).

Moreover, ^{19}F NMR spectrum of **12** suggested that the reaction had undergone a Smiles type rearrangement with loss of the sulfonyl group giving **12**, but there were other minor peaks which suggested there was another compound present. The major compound was confirmed as structure **12**by mass spectrometry with m/z of241, $C_{11}H_6F_4N_2$ and the other component had a mass m/z of 221, $C_{11}H_5F_4N_2$ which indicated the presence of cyclisation structure (**10a** or **10b**) occurred with loss of the sulfonyl group. Finally, ^{19}F NMR spectrum of **11** may suggest the starting material was recovered.



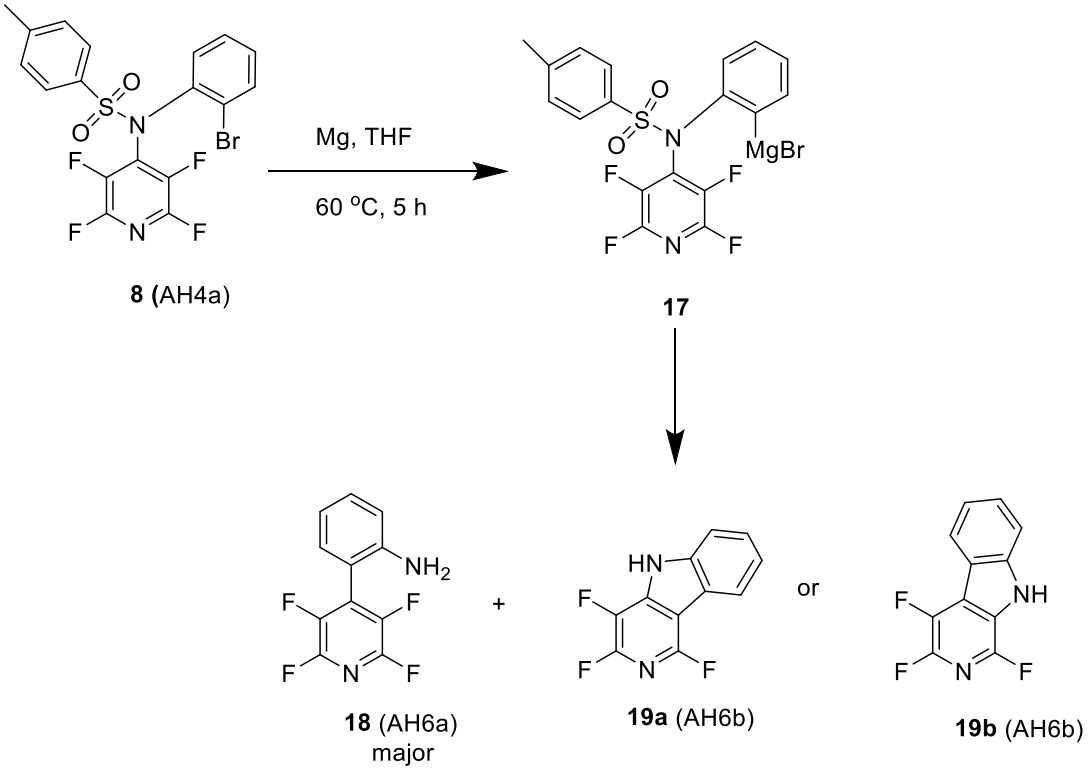
Scheme 11: Reaction of 2-bromophenylbenzenesulfonamide**8**with Bu-Li



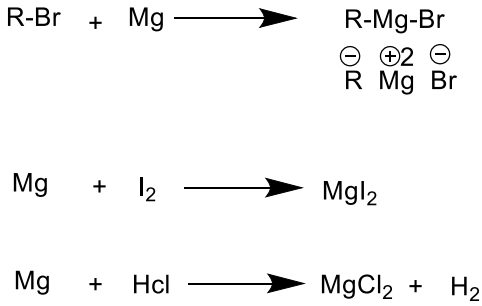
Scheme 12: Mechanism of cyclisation and Smiles type rearrangement

3.3. Reaction of2-bromophenylbenzenesulfonamide8 with magnesium

The reaction of 2-bromophenylbenzenesulfonamide**8** with BuLi resulted in the formation of interesting products as the loss of the sulfonyl group had occurred. Therefore, the reaction of **8** (AH4a) with excess equivalent of magnesium in dry tetrahydrofuran (THF) with heating until 70 ^{o}C was attempted. The reaction gave a complex mixture **18**+ **19** (AH6a) (Scheme13). The magnesium was used after activating it by washing with hydrochloric acid before making the Grignard reagent (Scheme 14). The data analysis to identify the structure formed involved ^{19}F NMR spectroscopy, which indicated that there might be one major product**18**, as the spectrum showed two sharp signals (Fig. 4). GC-MS confirmed a mass *m/z* of 242, $C_{11}H_6F_4N_2$corresponding to **18**. Also, fromthe^{1}H NMR analysis, the major compound could be the Smiles type rearrangement product with loss of the sulfonyl group, due to the presence of N-H peak and the absence of a tosylmethyl group peak. As well as this, the proton signals appear to be at meta, para and ortho position. In addition, gas chromatography- mass spectrometry (GC-MS) method supported that the compound**19**could be a cyclisation product with loss of the sulfonyl group, which has a mass *m/z* of 222, $C_{11}H_5F_3N_2$ (Scheme 13).



Scheme 13: Reaction of 2-bromophenylbenzenesulfonamide**8** with magnesium



Scheme 14: Grignard reagent

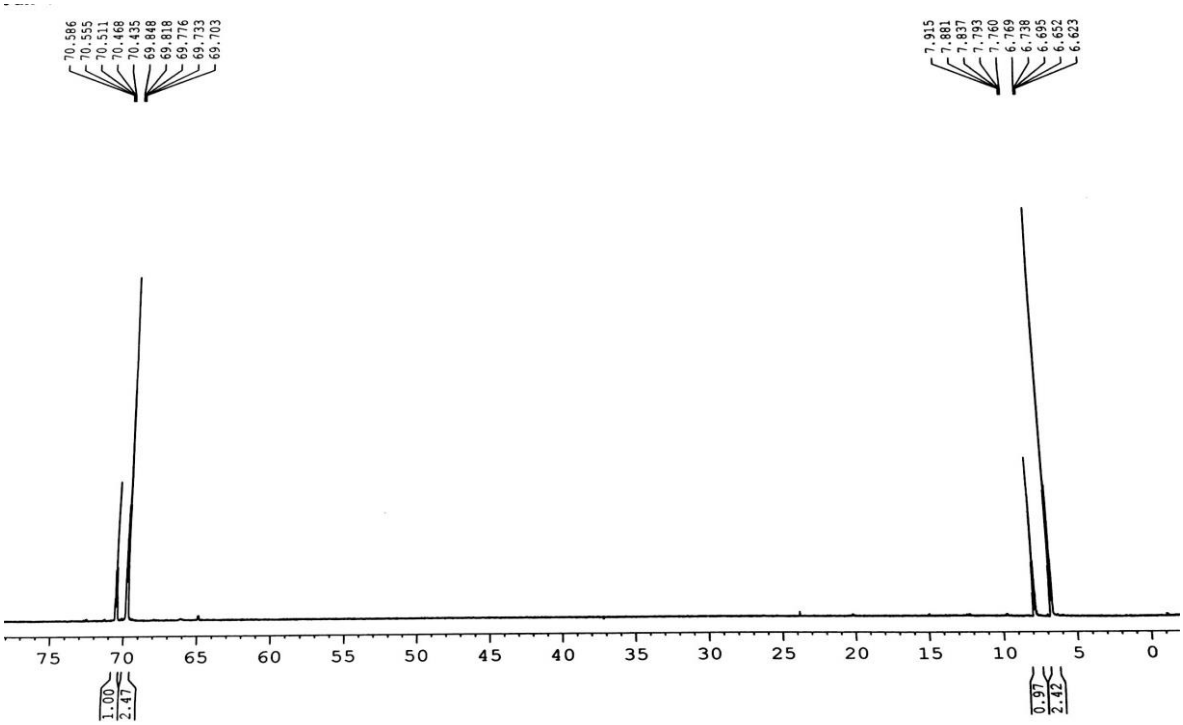


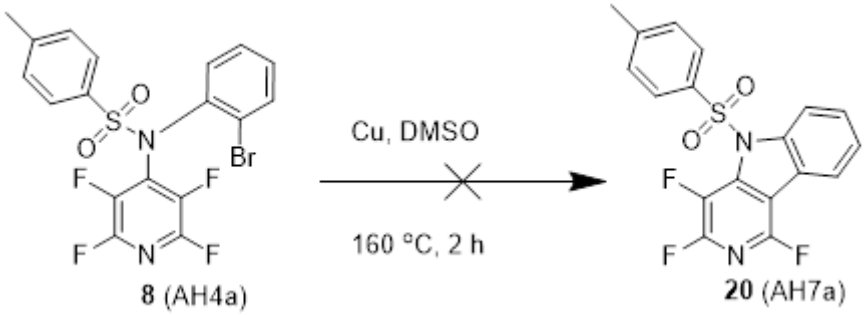
Fig. 4: ^{19}F NMR spectrum of **18** and **19**

3.4. Reaction of2-bromophenylbenzenesulfonamide 8 with copper

As a result of a complex mixture produced by adding *n*-butyllithum or magnesium metal to **8** (AH4a), the aim of this reaction was to find a better metal to react successfully with **8**.

Therefore, the reaction of **8** with copper metal in DMSO at 160 ºC was studied (Scheme 15). However, none of the product expected was formed, as only the starting material was recovered in this experiment. The reason for this could be the reaction conditions, for example: temperature, time or solvents. ^{19}F NMR spectrum supported that the starting material **8** recovered, which showed one sharp single peak and one broad peak (Fig. 5).

However, the ^{1}H NMR spectrum showed that there were minor peaks formed which may suggest that anew product had started to form in a small percentage, but it was difficult to identify the structure, due to the small peaks' signals.



Scheme 15: Reaction of 2-bromophenylbenzenesulfonamide **8** with copper

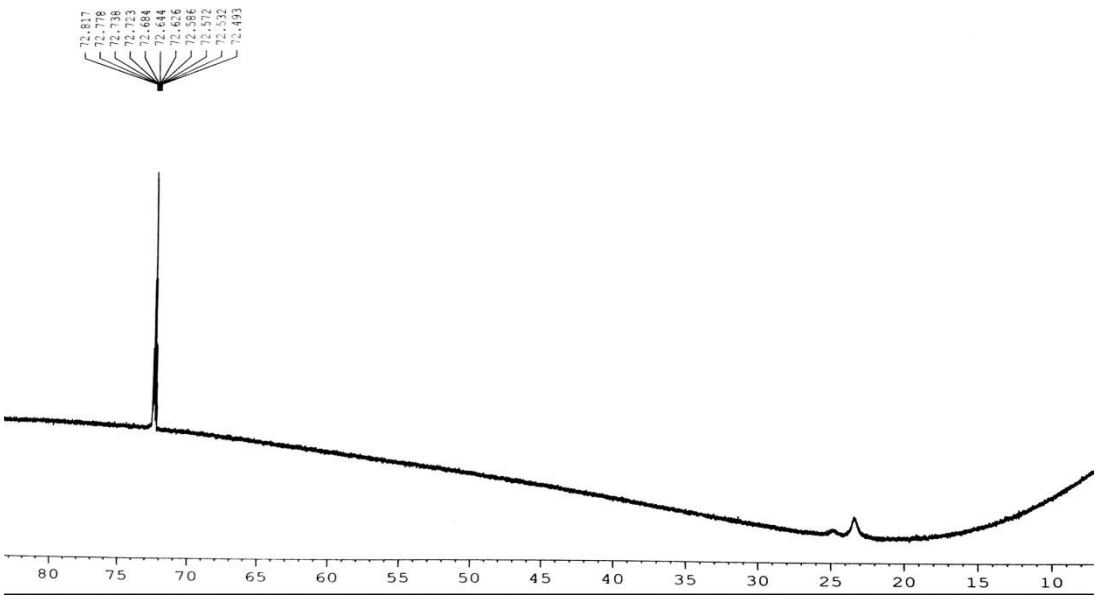


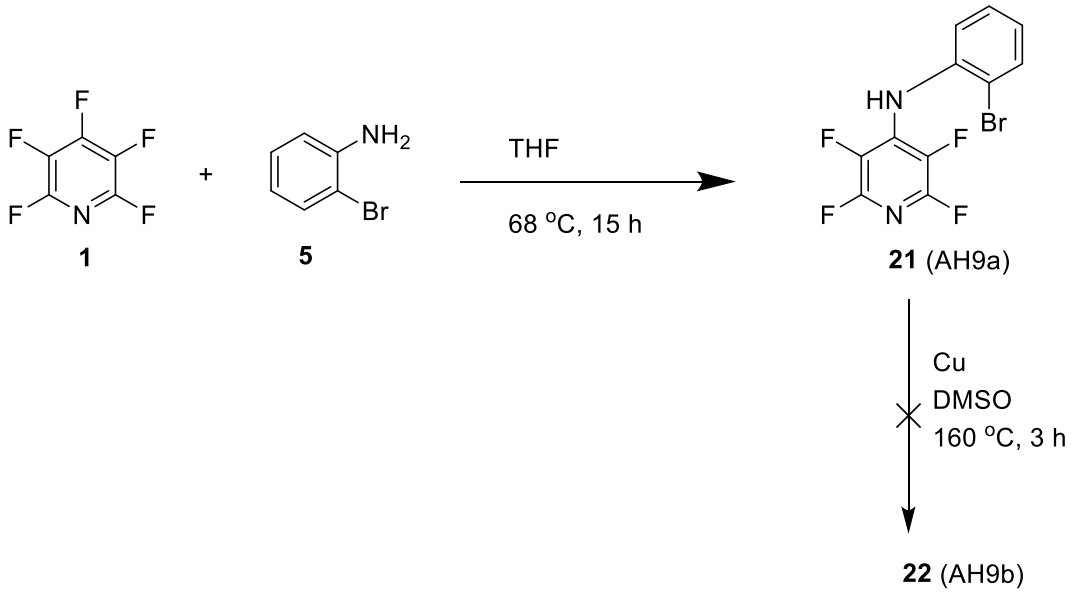
Fig. 5:^{19}F NMR spectrum of **20**

3.5. Reaction of pentafluoropyridine with2-bromoaniline to form an intermediate 21, for reaction with copper

Due to the unexpected products from previous reactions such as loss of the sulfonyl group, the aim of these reactions was to synthesise an intermediate **21** (AH9a) which does not contain the sulfonyl group, by a reaction of pentafluoropyridine**1** with 2-bromoaniline **2** in tetrahydrofuran (THF) at 68 ^{o}C (Scheme 16). This intermediate compound **21** was isolated as yellow oil and confirmed by ^{1}H NMR and ^{19}F NMR analysis.

Then, the intermediate 2-bromophenyltetrafluoropyridinamine**21** was reacted with copper in DMSO at 160 ^{o}C, for three hours (Scheme 16). After the work-up, the product **22** (AH9b) was obtained as a yellow oil. Unfortunately, ^{1}H NMR analysis indicated that there were minor percentages formed of a new compound. On the other hand, the major product identified was the starting material.

It is clear from this experiment that the starting material was recovered, which may suggest that changing the conditions of the reaction, possibly by increasing the time, may increase the amount of product formed.



Scheme 16: Synthesis of 2-bromophenyltetrafluoropyridinamine**21**, and reacted with copper

4. Conclusion

To sum up, this study has shown that amine compound ((N-(2-bromophenyl)-4-methyl-N-(perfluoropyridin-4-yl)benzenesulfonamide) **8** was successfully synthesised, which was used to identify a strategy to the synthesis of fluorinated nitrogen heterocycles. Benzenesulfonamidetreated with *n*-butyllithum or magnesium metal gave an interesting result, showing that loss of the sulfonyl group occurred with both cyclisation

and Smiles type rearrangement products forming. However, treatment of benzenesulfonamide with copper metal gave only the starting material recovered with a small percentage of a new product forming.

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