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SYNTHESIS OF 2-HYDROXY-5-(2',3',5',6'-TETRAFLUORO-PYRIDYLAZO)BENZALDEHYDE AND 2-HYDROXY-5-(2',3',5',6'-TETRAFLUORO-PYRIDYLAZO)PHENYL N-SULPHANILAMIDE-1-IMINE

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ABSTRACT

The present work is aimed mainly to synthesize new fluorinated azo-compounds and Schiff bases. Thus Pentafluoropyridine **1** have been aminated to the compound 4-amino-2,3,5,6-tetrafluoropyridine **2** and then diazotized to the corresponding diazonium **3**. The resulting diazonium ions coupled, *in situ,* to salicylaldehyde giving the corresponding azo-compounds: 2-hydroxy-5-(2',3',5',6'-tetrafluoropyridylazo)benzaldehyde **4** and 2-hydroxy-3-(2',3',5',6'-tetrafluoropyridylazo)benzaldehyde **5** as red crystals in 85 yield. The purity of these azo-compounds were estimated by TLC technique while their structures were established by the usual spectroscopic methods such as A UV, IR, MS and ^{1}H NMR. Fluorinated azo-compound **4** coupled readily to salicylaldehyde resulting a new fluorinated base Schiff: 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)phenyl N- Sulphanilamide-1-imine **6** in 40% yield. The purity of this product was established by its IR, NMR, and Mass spectra.

KEYWORDS: Synthesis, tetrafluoropyridine, Sulphanilamide, fluorinated azo, Schiff base.

I- INTRODUCTION

There is a considerable interest in synthesis of fluorinated compounds because of its use in various areas of life, whether in the pharmaceutical, industrial, cooling systems or in the agricultural fields. In 1997 we reported the synthesis of tetrafluoro-4-nitrosopyridine via oxidation of 4-aminotetrafluoropyridine with peroxytrifluoro acetic acid in dichloromethane [i]. The isolation of this interesting nitrosopyridine has provided a key to the synthesis of bis (tetrafluoro-4-pyridyl) diazene-1-oxide using pentafluorophenyl diazomethane[i, ii]. In related papers the reaction of tetrafluoro-4-nitrosopyridine in combination with diphenyldiazomethane or 1-(4-fluorophenyl diazomethane) has been studied and C, C-diphenyl-N-(tetrafluoro-4-pyridyl)nitrone and C-(4-fluorophenyl)-C-methyl-N-(tetrafluoro-4-pyridyl)nitrone were successfully obtained[iii]. This was followed by diazotation tetrafluoro-4-

nitropyridine derivatives and the resulting fluorinated azo compounds converted to the corresponding fluorinated diazepines[iv].

In 2000, however, a number of 1,3,4-trifluoro-7, 9-dimethyl-11H-pyrido (4,3-c) benzo (1,2) diazepines were synthesized via thermolysis of fluorinated 4-(2,4,6-trimethylphenylazo) pyridines to the corresponding 1,3,4-trifluoro-7, 9-dimethyl-11H-pyrido (4,3-c) benzo (1,2) diazepines[v].

In addition to the synthesis of numerous compounds containing fluorine in our laboratories, recently we reported the synthesis and chemistry of fluorovinyl-containing phosphines and the single crystal X-Ray structure of PPr^{i}_{2} (CF=CF2)[vi]. In 2016, we reported the synthesis and HPLC resolution of isomers of novel phosphorus fluorinated 2,4,6-trimethylphenylazo pyridine[vii].

More recently, we found that 4-aminotetrafluoropyridine coupled readily to the benzaldehyde in THF resulting a new fluorinated Schiff base (E)-Nbenzylidene-2,3,5,6-tetrafluoropyridine-4-amine. This Schiff base was explored in antibacterial activity against both gram-positive and gram-negative bacteria [viii].

We now report that the same transformation can be achieved but this time with extension to the synthesis of new fluorinated azo-compounds and then Fluorinated Sulphanilamide Schiff bases.

II-EXPERIMENTAL

II.1- Methods

Pentafluoropyridine **1** used for the preparation of 4-aminotetrafluoropyridine **2**, salicyaldehyde and sulphanilamide were purchased from ***A***lfa ***A***esar. They were used without further purification. The solvents used were of synthesis grade. They were used without further purification. Thin-chromatography (TLC) was performed using precoated plates (Aluminium foil, silica gel 60 F254 Merck, 0.25mm). Merck 60 silica gel (230-400 mesh) was used for flash chromatography.

All reactions were carried out under atmospheric air conditions. Solutions were dried over anhydrous Magnesium Sulphate ($MgSO_4$) and evaporated under reduced pressure using a rotary evaporator (IKA Evaporator RV 06-ML). Solvents were purified according to standard methods.

II-2. Physical measurements

Compounds 4, 5 and 6:

^{1}H NMR spectra were recorded on BRUCKER AC 400 MHz spectrometer at 0°C, and the chemical shifts are reported in ppm relative to the central line of the singlet for DMSO-d6 at 2.5 ppm. Coupling constants (*J* values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

IR spectra were recorded on SHIMADZU 830-FTIR spectrometer using KBr pellets. Melting points were recorded on a Gallenkamp melting point apparatus, and are uncorrected. Thin Layer Chromatography (TLC) was performed on precooked 0.25 mm silica gel plates 60F254purchased from Merck.

Starting material 4-aminotetrafluoropyridine 2:

Nuclear Magnetic Resonance Spectroscopy (NMR) spectra were normally recorded at 35°C using a Perkin-Elmer R10 or R12 or a Perkin-Elmer Hitachi R20A spectrometer operating at 60 MHz for ^{1}H spectra and 56.4 MHz for ^{19}F spectra. Tetramethylsilane (TMS) was used as reference for ^{1}H spectra; and for ^{19}F spectra, chemical shifts were measured relative to

trifluoroacetic acid (TFA) as an external interchange reference unless otherwise stated. Positive chemical shifts are in ppm downfield of the appropriate reference. Mass spectra were recorded on A.E.I. MS902 double-focusing mass spectrometer at 70 eV (ionization beam energy). The intensities of the peaks are given in terms of relative abundance, with the most intense peak (the base peak) taken as 100%. Ultraviolet spectra were measured using a Cary 118 instrument. Samples were examined as dilute solutions in ethanol. Melting points were determined on a Gallenhamp melting point apparatus and were uncorrected.

II-3. Procedures

II-3.1 Synthesis of fluorinated Schiff base 6

A mixture of sulphanilamide (*p*-aminobenzenesulphonamide) (0.01 mol) and 2-hydroxy-5-(2',3',5',6'-tetrafluoropyridylazo)benzaldehyde **4** (0.01 mol) was dissolved in ethyl alcohol (30 ml). One drop of glacial acetic was added to it and refluxed for 3 hrs. The resulting clear solution was cooled and poured in ice-cold water. The separated solid was filtered and recrystallized from dimethylformamide to give 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)phenyl N- Sulphanil- amide-1-imine **6** (0.004mol, 40% yield). The purity of this product was established by its IR, NMR, and mass spectra.

λmax 209; νmax (cm^{-1}) 1630 ν(C=N), 1510 νC=C, 1320 ν (C-F) and 600 ν(C-Cl). ^{1}H NMR: 1.3 (s, 2H, $-NH_2$), 2.5 (s, 6H, DMSO-d6), 3.4 (br.s, 1H, -OH), 7.2-8.3 (m, 7H, Ar-H) and 10.3 (s, 1H, N=CH).

II-3.2. Synthesis of two structural isomers 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)benzaldehyde 4

An 86:14 V:V mixture of glacial acetic acid (61.6 cm^2) and propionic acid (8.4 cm^3) was added dropwise to a mechanically stirred solution of dry, powdered sodium nitrite (2.1 g, 30 mmol) in 98% sulphuric acid (60 cm^3). The acetic acid/propionic acid mixture is added as a solubiliser. This proportion does not freeze at 0°C whereas glacial acetic acid freezes at 16°C. This mixture was maintained at 30°C in order to avoid the decomposition of nitrosyl sulphuric acid (revealed by the evolution of brown fumes of NO_2). The temperature of nitrosating medium was then lowered to 0°C by means of an ice-salt bath, and 4-amino-2,3,5,6-tetrafluoropyridine **2** (5g, 30 mmol) was added slowly. Stirring was continued for 1h30 min. At this stage diazotization was shown to be complete, when addition of a small drop of the reaction mixture to M-N,N-diethyltoluidine gave an intense red coloration. Salicylaldehyde (3.66g, 30 mmol) was then added over 15 minute period, so that any temperature rise caused by the coupling reaction would not be too drastic, and also to ensure complete reaction. Addition of the salicylaldehyde resulted in the formation of red slurry. For a 30 minutes period after addition had been completed, the temperature was kept below 0°C to prevent the immediate for 1 hr at room temperature, and then the solution was added to water (1000 cm^3). The red precipitate was filtered off and dried in an air oven at 80°C. Recrystallisation of the crude material from ethanol gave dark pinkish-red needles of fluorinated azo-compound (7.8 g, 26.0 mmol, 87%) which was identified by ^{1}H NMR to be two structural isomers:

2-hydroxy-5-(2',3',5',6'-tetrafluoropyridylazo)benzaldehyde **4** (85%). The purity of this product was established by its IR, NMR, and mass spectra.

IR (KBr), (cm^{-1}): 3500-3300 ν (OH str.), 3150-3050 ν (Ar-H str.), 2850-2750 ν (Aldehyde C-H), 1820-1660 ν (C=O str.), 1600-1565 ν (-N=N- str.), 1450-1190 ν (Py-F str.), 1250 ν (C-O asym str.),1040 ν (C-O sym str.); ^{1}H NMR (DMSO-d6): δ 2.5 (6H, s, DMSO-d6), 3.4 (1H, brs, OH), 7.3-8.5(3H, m, Ar-H), 10.4(1H, s, -CHO); MS: m/z 299 [M^+, 100].

2-hydroxy-3-(2',3',5',6'-tetrafluoropyridylazo)benzaldehyde **5** (15%).
The purity of this product was established by its IR, NMR, and mass spectra.
IR (KBr), cm^{-1}): 3500-3300 ν (OH str.), 3150-3050 ν (Ar-H str.), 2850-2750 ν (Aldehyde C-H), 1820-1660 ν (C=O str.), 1600-1565 ν (-N=N- str.), 1450-1190 ν (Py-F str.), 1250 ν (C-O asym str.),1040 ν (C-O sym str.); ^{1}H NMR (DMSO-d6): δ 2.5 (6H, s, DMSO-d6), 3.4 (1H, brs, OH), 7.3-8.5(3H, m, Ar-H), 10.3 (1H, s, -CHO); MS: m/z 299 [M^+, 100]. This preparation was repeated several times to give enough material for further conversion into fluorinated Schiff base, 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)phenyl N-Sulphanilamide-1-imine **6**.

II-3.3. Synthesis of Starting Material: 4-Amino-2,3,5,6-tetrfluoro-pyridine 2:

Pentafluoropyridine **1** (50 g, 296 mmol) was dissolved in THF (350 cm^3) in a round bottomed flask equipped with a reflux condenser to give a clear solution. On addition of aqueous ammonia (sp.gr. 0.88, 250 cm^3) a cloudy solution was produced and an exothermic reaction ensued. The mixture was then refluxed for 24 hrs. The clear solution produced was poured into water (1000 cm^3) and the whole mixture was extracted with ether (4X 150 cm^3). The extract was dried ($MgSO_4$), evaporated using a rotary evaporator, and the residue freed from the last traces of solvent *in vacue*, to give a pale cream solid. Recrystallisation of this crude material from light petroleum (b.p.80-100°C) gave long white needles of 4-amino2,3,5,6-tetrafluoropyridine **2** (42g, 253 mmol, 85%), m.p. 84-86 °C [lit.[ii,iii] 86°C, lit.[iv] 83.5-84 °C, lit.[v] 85-86°C, lit.[viii] 85-87°C]. The product was identified by comparing its I.R., and NMR spectra with those of an authentic sample.
IR (KBr), cm^{-1}): 3500-3300 ν (NH str.); ^{1}H NMR ($CDCl_3$): δ 5.05 (2H, brs, NH_2); ^{19}F NMR ($CDCl_3$): δ -15.1 (2F, AA'XX', F-2 and F-6), -85.1 (2F, AA'XX', F-3, and F-5) As shown in **Figure-II-1**; MS: m/z 166 [M^+, 100].

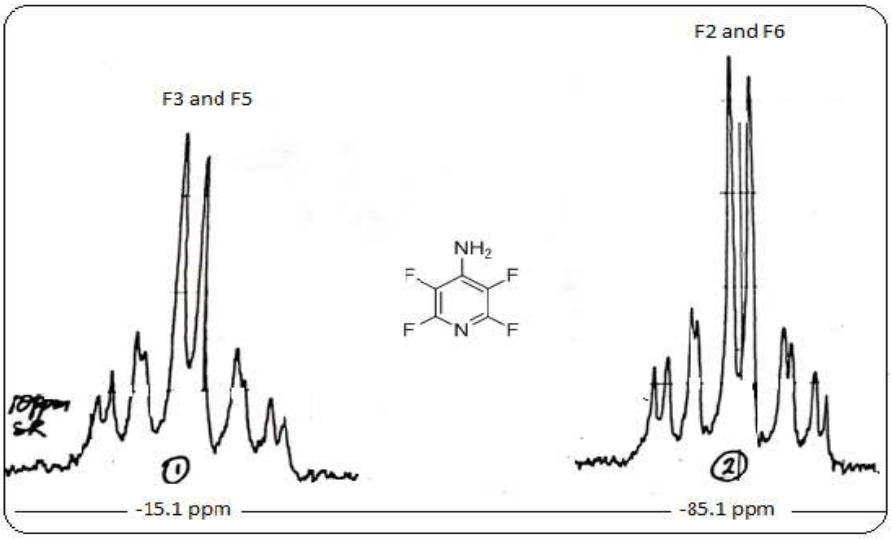


Figure-II.1: The Shape AA'XX' in the two peaks of ^{19}F NMR spectrum of 4-amino2,3,5,6-tetrafluoropyridine **2**

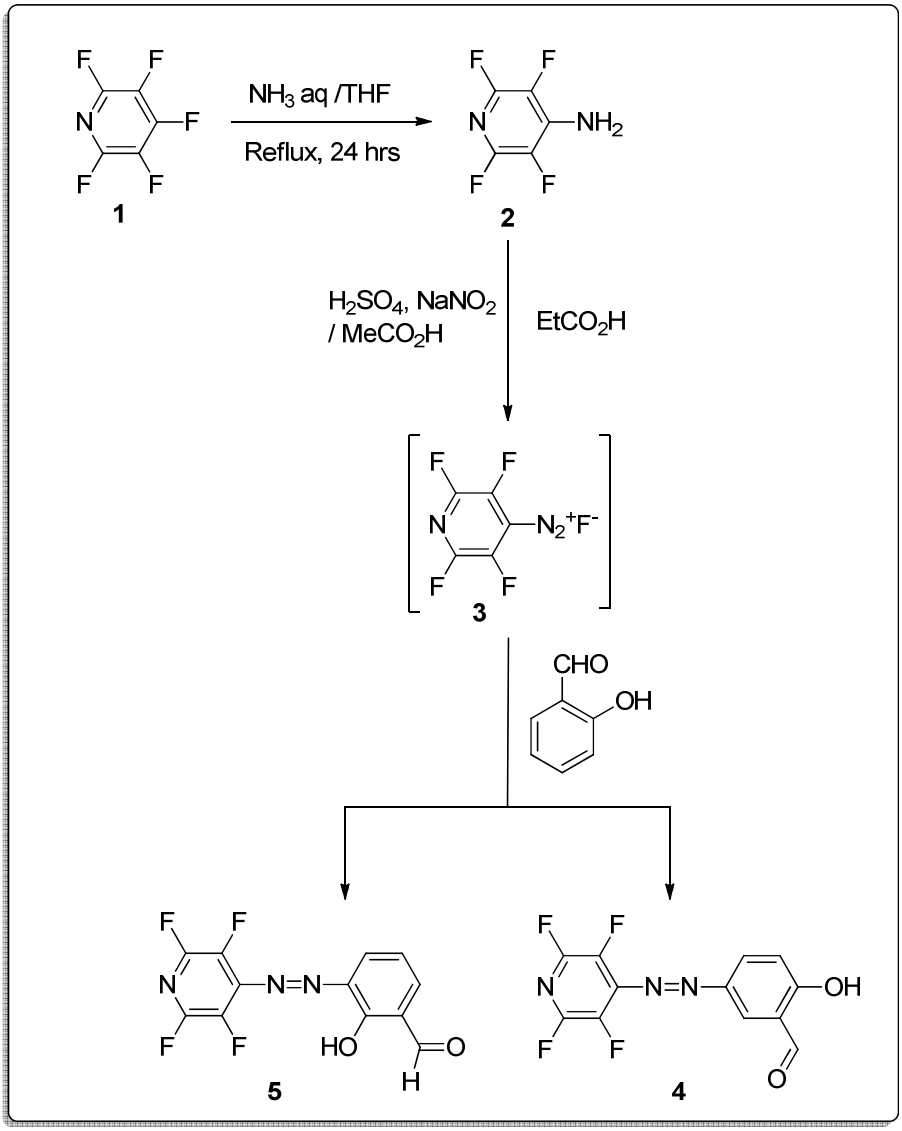
The preparation was repeated several times in order to produce large quantities of starting material for conversion into: 2-hydroxy-5-(2',3',5',6'-tetrafluoropyridylazo)benzaldehyde **4** and 2-hydroxy-3-(2',3',5',6'-tetrafluoropyridylazo)benzaldehyde **5**.

III-RESULTS AND DISCUSSION

The strategy we have adopted for the synthesis of two structural isomers 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)benzaldehyde **4** and 2-hydroxy-3-(2',3',5',6'-tetrafluoro-

pyridylazo)benzaldehyde **5** and fluorinated Schiff base, 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)phenyl N- Sulphanil- amide-1-imine **6** Consists of the following steps: (a) synthesis of starting 4-amino-2,3,5,6- tetrafluoro pyridine **2** via amination of pentafluoropyridine **1**.

(b) This starting 4-amino-2,3,5,6- trifluoro pyridine **2** was diazotized to the corresponding diazonium salt **3** which was coupled, *in situ*, to salicylaldehyde to obtain fluorinated azo compounds **4** and **5 (Scheme-III-1).**



Scheme-III-1: Synthesis of fluorinated azo compounds **4** and **5**

The diazotation procedure utilized by Bank and co- workers[ix] was able to successfully diazotize 4-amino Alkyl (Aryl) pyridines at room temperature using dry powdered sodium nitrite in a medium of anhydrous hydrogen fluoride (AHF), and the resulting 3,5,6- trifluoro -2- Alkyl (Aryl) pyridyl -4- diazonium ion was coupled, *in situ*, to a variety of aromatic agents, including mesitylene.

The preferred ortho and para attack occurs in the reaction of 4-amino-2,3,5,6- tetrafluoro pyridine **2** with salicylaldehyde were attributed to the presence of the hydroxyl group (*ortho-*

para directing group). The high *para* ratio was attributed to the steric effect inhibiting. Therefore, in this case, fluorinated azo-compounds **4** should be formed as the major product.

The IR spectrum of **3** confirmed the absence of amino group at 3500-3300 and the presence of (-N=N- str.) at 1600-1565. The ^{1}HNMR spectrum showed 4 absorptions δ 2.5 (6H, s, DMSO-d6), 3.4 (1H, brs, OH), 7.3-8.5 (3H, m, Ar-H), 10.4 (1H, s, -CHO). The spectroscopic data of **5** were very similar to those of azo compounds **4 (Figure-III.1)**.

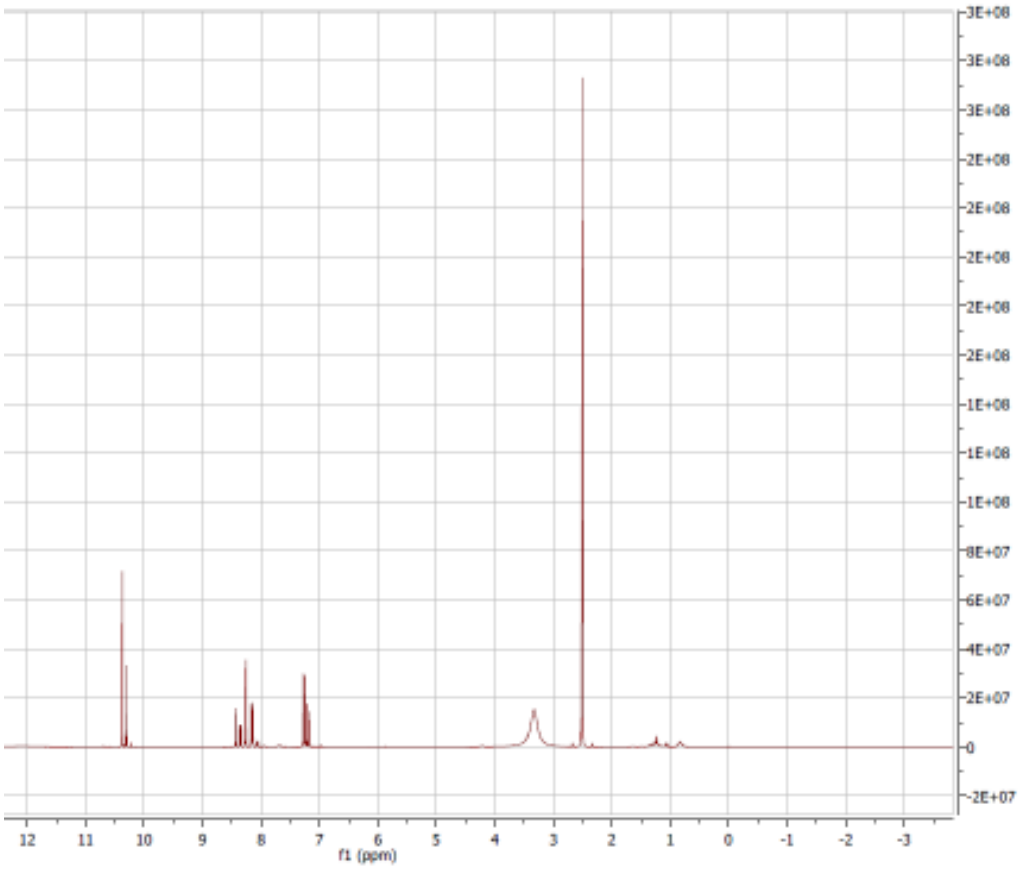
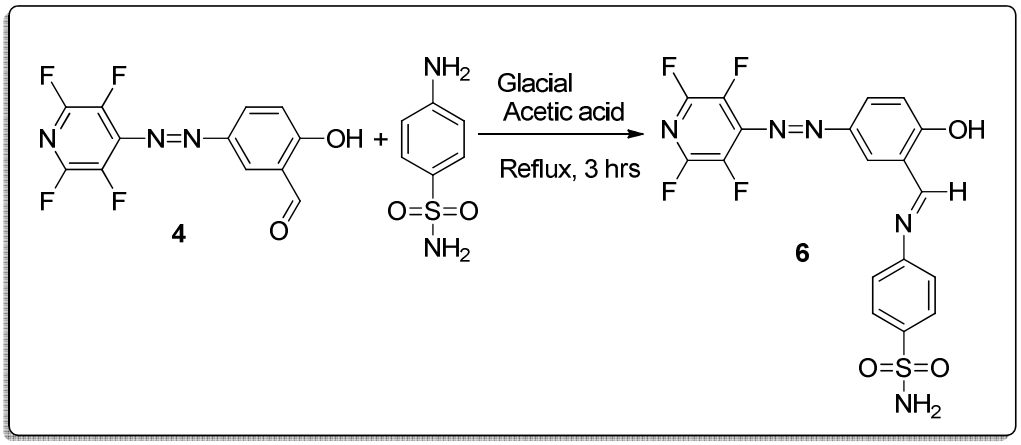


Figure-III.1: ^{1}H NMR spectrum of the two structural isomers 2-hydroxy-5-(2',3',5',6'-tetrafluoropyridylazo) benzaldehyde **4** and 2-hydroxy-3-(2',3',5',6'-tetrafluoropyridylazo) benzaldehyde **5.**

(c) Carbonyl compound was added to the fluorinated azo-compound resulted from step two to obtain the corresponding fluorinated Schiff base **6.**

In general, the nucleophilic addition reactions on carbonyl compounds which make it possible to create carbon-nitrogen double bonds are generally carried out with acidic and sometimes basic catalysts[x]. Several tests were carried out, by playing on the operating conditions brought to the reaction medium; confirm the obtaining of the condensation product. So the strategy we adopted for the synthesis of Schiff's base was to condense the fluorinated carbonyl compound, 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)benzaldehyde **4** with sulphanilamide (*p*-aminobenzenesulphonamide) in the presence of a catalytic amount of acetic acid under reflux in ethanol.

The reaction is the result of the nucleophilic attack of the amine nitrogen on the carbonyl of the aldehyde. This leads to the formation of the carbon-nitrogen double bond (-C=N-), and the formation of imine **6** after removal of a molecule of water, as shown in **(Scheme III.2).**



Scheme-III-2: Fluorinated base Schiff: 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)phenyl N- Sulphanilamide-1-imine **6**

The addition is all the easier as the nucleophilic character of the nitrogen reactants (the amine) is high. Conversely, amines, weak nucleophiles, more easily add on the aldehydes in the presence of an acid whose role is to activate the carbonyl group of this function. The removal of water is relatively easy in this case. This shows the importance of pH for these reactions[xi].

The purity of fluorinated Schiff base **6** was confirmed by the following spectroscopic data: IR confirmed the persistence of the absorption band of the azomethine function (C=N) near 1654 cm^{-1}. As expected, no N-H vibration band attributable to the primary amine used as reagents (3518-3442 cm^{-1}) is detected. The UV-vis spectrum is recorded in the range (200-800 nm) in dimethylsulfoxide medium (DMSO). The spectrum has an absorption band located at 264 nm is attributable to the transition $\pi \rightarrow \pi^*$ chromophore azomethine (C=N). The ^1H NMR spectrum shows a chemical shift at 1.3 and 2.5 ppm which are attributed respectively to the $-SO_2-NH_2$ and DMSO-d6 protons, while the 3.4 and 10.3 ppm chemical shifts are attributed respectively to the (OH) and (-N=CH-) protons. The chemical shifts at 7.2-8.3 ppm corresponding to the Ar-H protons **Figure-III.2.**

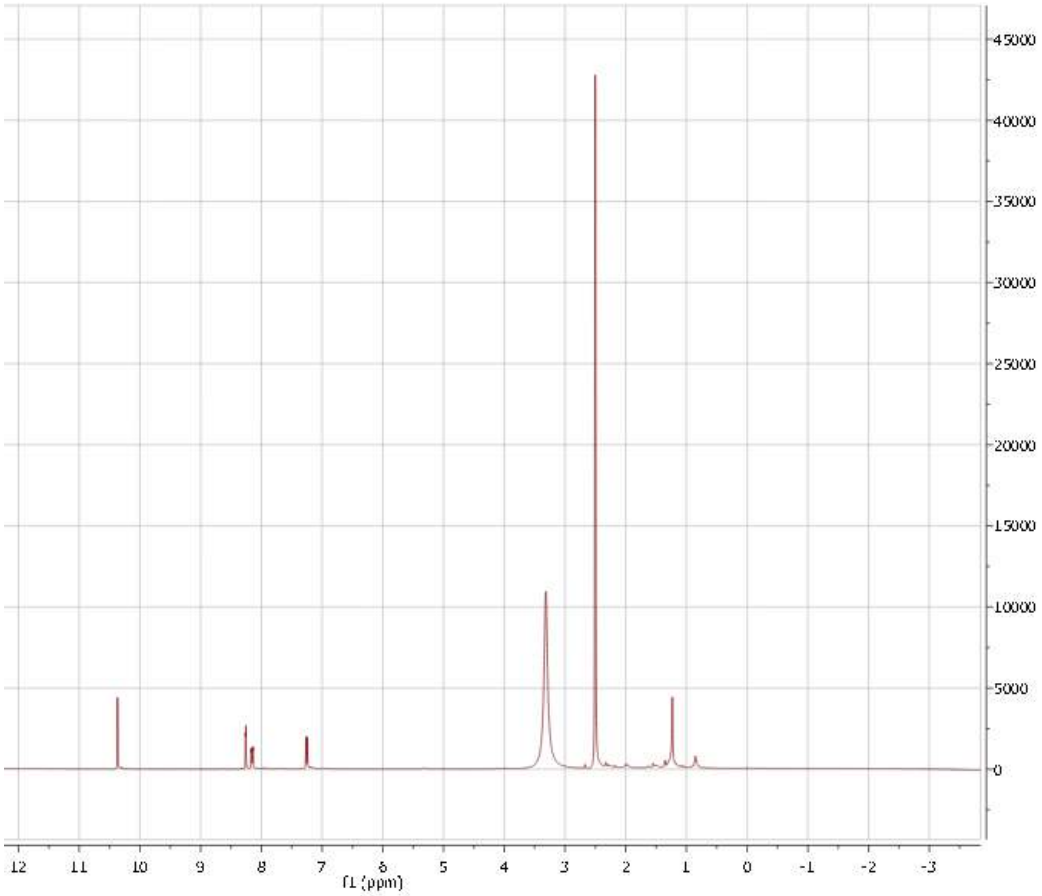


Figure-III.2: ^{1}H NMR spectrum of fluorinated Schiff base **6**

IV- CONCLUSIONS

The azo-compounds: 2-hydroxy-5-(2',3',5',6'-tetrafluoropyridylazo)benzaldehyde **4** and 2-hydroxy-3-(2',3',5',6'-tetrafluoropyridylazo) benzaldehyde **5** were successfully synthesized in excellent yields from 4-aminotetrafluoropyridine. The previous resulting azo-compounds coupled readily to salicylaldehyde resulting a new fluorinated base Schiff: 2-hydroxy-5-(2',3',5',6'-tetrafluoro-pyridylazo)phenyl N- Sulphanilamide-1-imine 6 moderate yields (40% yield). The purity of all these products were established by their IR, NMR, and mass spectra.

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