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Nucleophilic Substitution in Tetrafluoro-4-nitropyridine Derivatives and the Corresponding Fluorinated Diazepines: HPLC Resolution of Their Isomers

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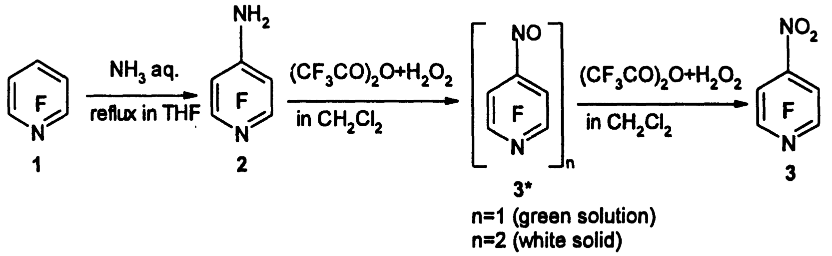
Tetrafluoro-4-nitropyridine derivatives have been synthesized and separated successfully by HPLC. The resulting fluorinated amines and 4-amino-3-chlorotrifluoropyridine have also been diazotized and the resulting diazonium ions coupled to mesitylene giving the corresponding azo-compounds: 2,3,4,6-tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine **(9)** (80%), 3-chloro-2,5,6-trifluoro-4-(2,4,6-trimethylphenylazo)pyridine **(23)** (83%), 2,3,6-trifluoro-4-nitro-5-(2,4,6-trimethylphenylazo)pyridine **(20)** (80%), 2,3,5-trifluoro-4-nitro-6-(2,4,6-trimethylphenylazo)pyridine **(21)** (84%). Treatment of these azo-compounds mentioned earlier with sodium methoxide in methanol/tetrahydro furan gave 3,6-difluoro-2-methoxy-4-nitro-5-(2,4,6-trimethylphenylazo)pyridine **(24)** (37%), 3-fluoro-2,5-dimethoxy-4-nitro-6-(2,4,6-trimethylphenylazo)pyridine **(26)** (49%), 2,3-difluoro-4,5-dimethoxy-6-(2,4,6-trimethylphenylazo)pyridine **(25)** (32%), 3-chloro-2,3,5-trifluoro-6-methoxy-4-(2,4,6-trimethylphenylazo) pyridine **24** (87%), 3-chloro-3,5-difluoro-2,6-dimethoxy-4-(2,4,6-trimethylphenylazo)-pyridine **23** (83%). The two diazepines **25** and **26** were successfully separated by HPLC. The thermolysis of the synthesized azo-compounds in boiling mestylene gave the corresponding diazepines: 1,2,4-trifluoro-7,9-dimethyl-11-H-pyrido[4,3-c]benzo[1,2]diazepine **(15)** (75%), 1,4-difluoro-3-methoxy-7,9-dimethyl-11-H-pyrido[4,3-c]benzo[1,2]diazepine **(32)** (80%) and 3,4-difluoro-1-methoxy-7,9-dimethyl-11-H-pyrido-[4,3-c]benzo[1,2]diazepine **(33)** (9%). The structural diazepine-isomers **32** and **33** were also separated by HPLC.

Key Words: HPLC, 2-Amino-4-nitrotrifluoropyridine, Diazepines, Nucleophilic substitution

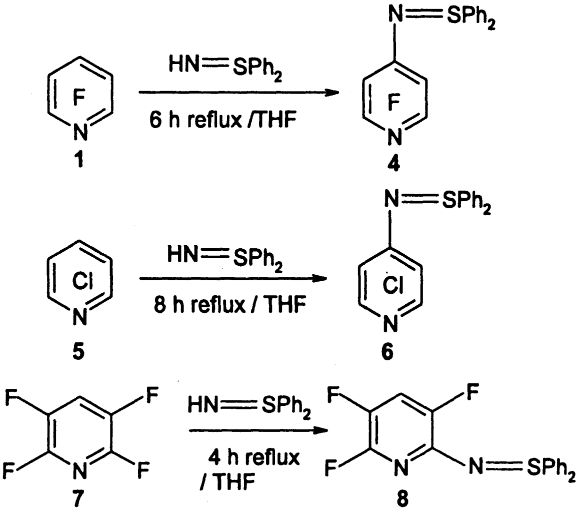
INTRODUCTION

4-Aminotetrafluoropyridine was first prepared in the early 1960's by Banks *et al.*[1] and by Chambers and his co-workers[2] *via* nucleophilic attack of aqueous ammonia on pentafluoropyridine **(1)**. Alty[3] used a modification of these procedures, employing tetrahydro furan (THF) as solvent and obtained 4-aminotetrafluoropyridine **(2)**. Tetrafluoro-4-nitropyridine **(3)** was also prepared by Chambers and his co-workers[4] as shown in **Scheme 1**. In 1987, the isolation of 2,3,5,6-tetrafluoro-4-nitrosopyridine **(3*)** was reported,[5] which provides the key to the synthesis of fluorinated nitrones[5].



Scheme-1

As shown by Chambers *et al.*[6], tetrafluoro-4-nitropyridine (3) undergoes nucleophilic substitution by Nu (charged nucleophiles in case of tetrafluoro-4-nitropyridine) at the 4-position, like 3-chlorotetrafluoropyridine[7] and pentafluoropyridine[1]. The order of ease of displacement of ring fluorine in 3-chlorotetrafluoropyridine, pentafluoropyridine and consequently from tetrafluoro-4-nitropyridine, decreases in the order 4- > 2- (or 6-) ≫ 5- (or 3-)[8, 9]. The nucleophile S, S-diphenylsulphylimine was known to react with various heteroaryl halides[10], as well as polynitrochlorobenzenes[11] in aromatic nucleophilic substitutions to give N-aryl-S, S-diphenylsulphilimine products ($Ph_2S{=}NAr$). Recently, it was reported that halopyridines like pentafluoropyridine (1), pentachloropyridine 5 and 2,3,5,6-tetrafluropyridine (7) undergo ready nucleophilic displacement by Nu ($Ph_2S{=}NH$) at the 4- and 2- (or 6-) positions[12] **(Scheme 2).**

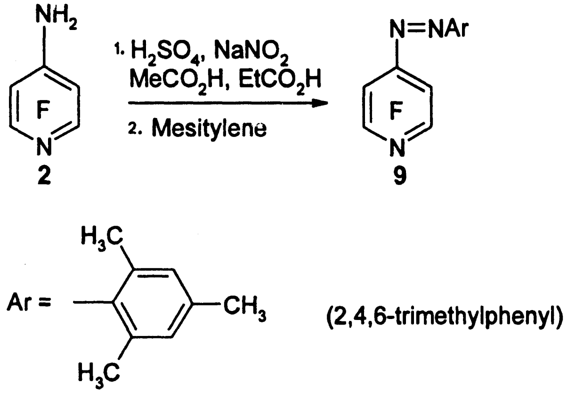


Scheme-2

Banks *et al.*[13] discovered that the tetrafluoropyridine-4-diazonium ion was electrophilic enough to enter into coupling reactions with mesitylene and anisole.

Using the same procedure as Chambers *et al.*[14] but lowering the temperature to –50°C before adding the mesitylene, they obtained 2,3,4,6-tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine (9) in 20% yield. Subsquently, Alty *et al.*[15] found that a much better yield of this azo compound could be achieved using anhydrous HF as the diazotization medium.

In contrast to the previous methods, Alty *et al.*[3] also showed that the diazotization could be achieved by adding the 4-aminotetrafluoropyridine **2** to a solution of sodium nitrite in a mixture of 98% H_2SO_4; CH_3CH_2COOH; subsequent coupling with mesitylene at room temperature gave the azo-compound **9** in 77% yield **(Scheme-3).**



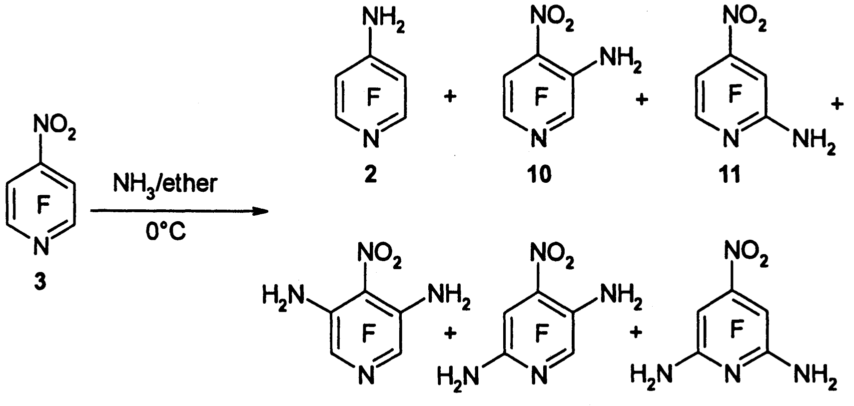
Scheme-3

Herein, the conversion of tetrafluoro-4-nitropyridine into its 4-amino, 3-amino, 2-amino, 3,5-diamino and 2,5-diamino derivatives and then the HPLC separation and diazotization of these amines were described. Furthermore, the nucleophilic substitution in 2,3,4,6-tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine were investigated.

RESULTS AND DISCUSSION

In the present work, several fluorinated amino and azo compounds were succeessfully separated using flash column chromatography and modern chromatographic equipment, high pressure liquid chromatography (HPLC) (the organic solvents H_2Cl_2, hexane, were used as mobile phase). As described in Chamber procedure[6], ammonia gas was bubbled through a solution of tetrafluoro-4-nitropyridine **3** in dry ether at 0°C for 4 h **(Scheme-4).** They obtained only two compounds from this reaction 4-aminotetrafluoropyridine **(2)** (27%) and 3-amino-2,5,6-trifluoro-4-nitropyridine **(10)** (48%). The same reaction was repeated in order to prepare the starting material for further work on the synthesis of azo-compounds. As described in the earlier procedure[5], ammonia gas was bubbled through a solution of tetrafluoro-4-nitropyridine **3** in dry ether at 0°C for 4 h. The solution was filtered off *in vacuo*, to leave a dark red solid which was subjected to dry column flash chromatography to give as the first band a yellow/orange material which was shown by ^{19}F NMR spectroscopy to be a mixture of 4-aminotetrafluoropyridine **(2)**, 3-amino-2,5,6-trifluoropyridine **(10)** and 2-amino-3,5,6-trifluoro-4-nitropyridine **11.** Analytical HPLC (60/40 v/v hexane/dichloromethane) also revealed the presence of three components. Semi-preparative HPLC, using the same conditions, gave 4-aminotetrafluoropyridine

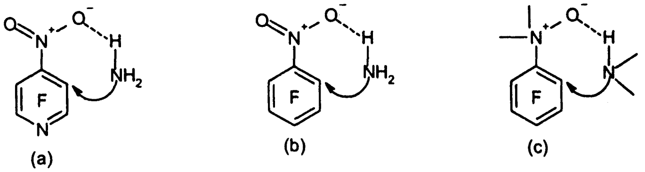
(**2**) (15%), bright yellow 3-amino-2,5,6-trifluoro-4-nitropyridine (**10**) (49%) with a satisfactory elemental analysis (C, H, N, F) and correct spectroscopic properties (IR, NMR and mass) and orange 2-amino-3,5,6-trifluoro-4-nitropyridine (**11**) (19%). The last product is new and was identified by IR spectroscopy [primary amine NH st. in the region 3500–3300 cm^{-1}]. ^{1}H NMR spectrum showed only a broad NH$_2$ absorption at 5.0 ppm, the ^{19}F NMR spectrum comprised three doublet of doublets of equal intensity at –8.0 (F-6), –71.2 (F-5) and 84.1 (F-3) ppm (ext. TFA). The ^{19}F coupling constants were similar to those of compound **10** and the ^{19}F NMR spectrum revealed that two fluorines are β to ring nitrogen and the other is α, *i.e.*, the NH$_2$ substituent lay in position 2 not 3. The ^{19}F NMR chemical shift data of compound **11** showed the expected effect of NH$_2$ on F-3, F-5 and F-6, the absorption for which were shifted to –84.1 (F-3), –71.2 (F-5) and –8.0 (F-6) ppm (relative to TFA) by comparison with F-3 or F-5 and F-6 of the starting material **2**. The mass spectrum of **11** showed a molecular ion at m/z 193, which was also the base peak and the compound possessed a satisfactory elemental analysis (C, H, F, N) (**Scheme 4**).



Scheme-4

The second band eluted by the dry column flash chromatographic separation of the original product was a shiny black solid, shown to be 3,5-difluoro-4-nitropyridine (**12**). This new compound was identified by IR spectroscopy (N—H str. at 3500–3300 cm^{-1}) and ^{1}H NMR (broad NH$_2$ at 5.7 ppm) and ^{19}F NMR (only one absorption at –24.3 ppm, which can be assigned to F-2 and F-6 but not to F-3 and F-5). The mass spectrum showed a molecular ion at m/z 190, which was also the base peak.

A special case[16] of preferred ortho attack occurs in the reaction of pentafluorobenzene with ammonia and to a lesser extent, with other amines in ether[17] (**Scheme 5**), whereas with other reagents, para attack is preferred[14, 18]. The high ortho ratios were attributed to hydrogen bonding (b) of the nucleophile to the nitro group leading to a lower energy transition state for ortho than para substitution, with a steric effect inhibiting such hydrogen bonding. Preferential attack by amines ortho to N-oxide of N-pentafluorophenyl heterocycles has also been attributed to hydrogen bonding (c). Therefore, in the case in question, the 3-amino-2,5,6-trifluoro-4-nitropyridine should be formed as the major product (a); the experimental evidence agrees with this assessment **(Scheme 5).**



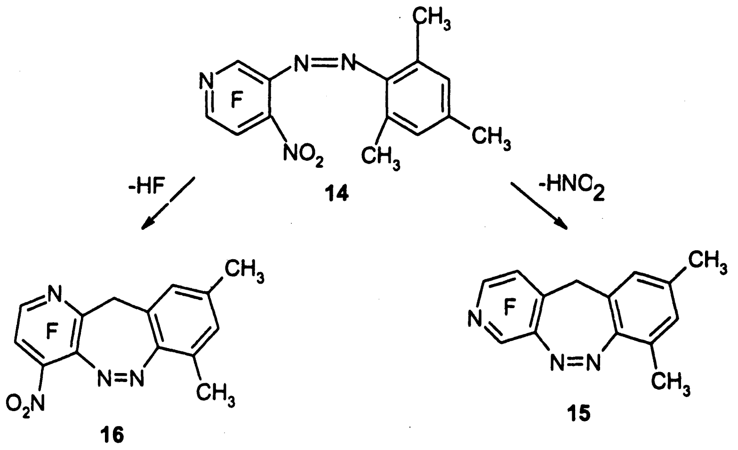
Scheme-5

On the other hand, tetrafluoro-4-nitropyridine (**3**) undergoes nucleophilic substitution by $^{-}$OMe at the 2- or (6-) position. Since sodium methoxide cannot form hydrogen bonds so it was expected to displace the 2,6-fluorines and the 3- or 5-fluorines, consecutively. The experiment carried out confirmed this behaviour.

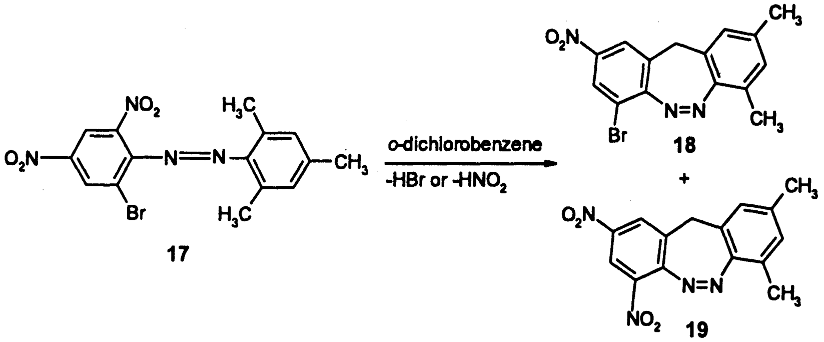
The formation of compound **12** and absence of 2,6-diamino-3,5-difluoro-4-nitropyridine (**13**) and 2,6-diamino-3,5-difluoro-4-nitropyridine (**14**) provides further evidence that nucleophilic substitution in tetrafluoro-4-nitropyridine by NH_3 is directed strongly to ortho position by the nitro group. Also the formation of 4-aminotetrafluoropyridine (**2**) (displacement of nitro group) provides further evidence to what we found when we heated 2,3,6-trifluoro-4-nitro-5-(triphenylazo)pyridine (**14**) in boiling mesitylene for 8 h; and isolated of 1,2,4-trifluoro-7, 9-dimethyl-11H-pyridol [4,3-c] benzo[1,2] diazepine (**15**) was 74%. No product (*i.e.*, **16**) was isolated that could be attributed to the loss of fluorine in the ring closure **(Scheme 6).**

Regarding the nature of the ring substituent lost in the closure, this reaction is analogous to a reaction carried out by Alty[19] which involved heating 2-bromo-4,6-dinitro-2′,4′,6′-trimethylazopyridine (**17**) in boiling *o*-dichlorobenzene for 1 h; this caused 100% conversion of the azo-compound to a material from which the diazepine **18** was obtained in 60% yield; no product was isolated that could be attributed to the loss of bromine **19 (Scheme 7).**

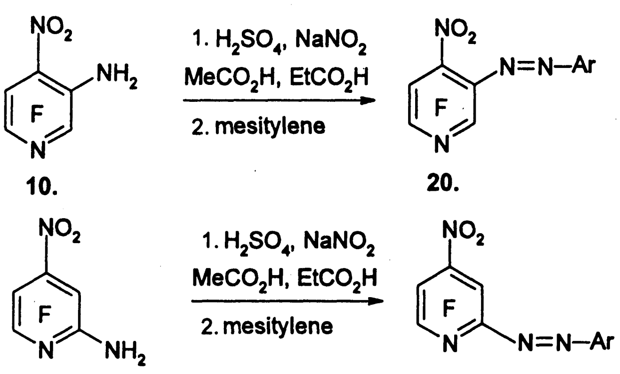
We also examined aqueous ammonia to aminate tetrafluoro-4-nitropyridine (**3**) because it is much easier, cheaper and less dangerous to use than ammonia gas. Thus, tetrafluoro-4-nitropyridine (**3**) (22.5 mmol) was dissolved in THF (250 mL); aqueous ammonia (sp. gr. 0.88, 15 mL) was added dropwise to the solution. Work up of the reaction products yielded the same products which were obtained when ammonia gas was used. Having prepared the amino compounds **2, 10** and **11,** the next step was to diazotize them using the method described by Alty[19] to prepare 2,3,5,6-tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine (**9**) **(Scheme 2),** 2,3,6-trifluoro-5-nitro-4-(2,4,6-trimethylphenylazo)pyridine **(20),** and 2,3,5-trifluoro-6-nitro-4-(2,4,6-trimethylphenylazo)pyridine **(21) (Scheme 8).**



Scheme-6



Scheme-7

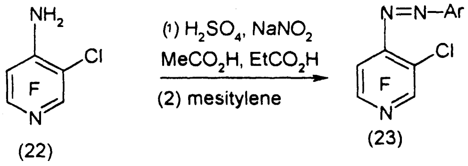


Scheme-8

This involved adding dry powder sodium nitrile (32 mmol) over a 5 min period to a stirred mixture of *ca.* 2.5 : 1 of 3-amino-2,5,6-trifluoro-4-nitropyridine, 2-amino-3,5,6-trifluoro-4-nitropyridine and 4-aminotetrafluoropyridine in anhydrous hydrogen fluoride (AHF) contained in a polythene beaker. After stirring had been continued for 1.5 h at room temperature, an excess of mesitylene was added. This caused an immediate deep-red colour to be formed. Stirring was continued at room temperature until all the AHF had evaporated; then the residual red solid was subjected to dry column flash column chromatography to give new compound 2,3,6-trifluor-4-nitro-5-(2,4,6-trimethylphenylazo)pyridine **(20)** m.p. 114–116°C, in 84% yield. This new azo-compound was identified spectroscopically. Its ^{1}H NMR spectrum was very similar to that of compound **9,** while the ^{19}F NMR spectrum comprised 3 doublet of doublets of equal intensity at +6.03 (F-6), –0.30 (F-2) and –75.0 (F-3) ppm (ext. TFA). The mass spectrum was characteristic of an azo compound; the major breakdown pattern is mesitylene ion at m/z 119 (100%).

A pale brown solid was also isolated as 2,3,5-trifluoro-6-nitro-4-(2,4,6-trimethylphenylazo)pyridine (**21**) in 76% yield, m.p. 165–167°C. Its ^{19}F NMR spectrum showed three fluorines with chemical shifts very different from those characteristic of the starting material 2-amino-3,5,6-trifluoro-4-nitropyridine (**6**); thus, the F-2, F-3 and F-5 absorptions were shifted from –8.0, –71.2 and –84.1 to –2.4, –60.2 and 63.0 ppm, respectively. The ^{1}H NMR spectrum was very similar to those of azo compounds **9** and **20**. The IR spectrum confirmed that the nitro group was still present in the pyridine ring [strong absorption at 1550 and 1350 cm^{-1} ν(NO_2)]. The mass spectrum showed a molecular ion at m/z 324 and base peak at m/z 119.

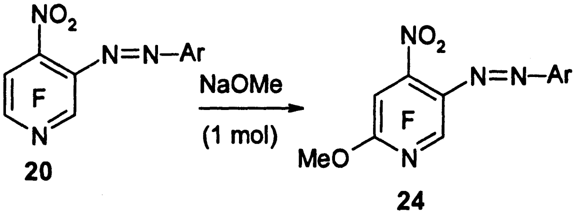
3-Chloro-4-aminotrifluoropyridine (**22**) was successfully diozotized to the corresponding 3-chloro-2,5,6-trifluoro-4-(2,4,6-trimethylphenylazo)pyridine (**23**), m.p. 150–151°C in 83% yield. It was identified by elemental analysis and ^{1}H and ^{19}F NMR assignments for the fluorine spectrum followed by consideration of the work of Lee and Orrel[20]; they showed in pentafluoropyridine and its derivatives that para fluorines (FF) coupling constants are larger than those of the ortho and meta. The mass spectrum showed a molecular ion at m/z 313, and base peak at m/z 119 **(Scheme 9).**



Scheme-9

As part of our studies on the chemistry of fluorinated amino pyridines, we found that the fluorinated pyridine's ring in the azo-compounds undergoes nucleophilic substitution by sodium methoxide at the 2- (or 6-) position. Thus attack by Nu at the 5- (or 3-) position is least preferred. When heated 2,3,6-

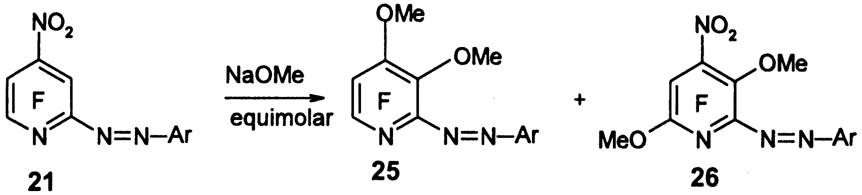
fluoro-5-nitro-4-(2,4,6-trimethylphenylazo)pyridine (**20**) with an approximately equimolar proportion of sodium methoxide in dry methanol for 2 h, it gave 3,6-difluoro-2-methoxy-4-nitro-5-(2,4,6-trimethylphenylazo)pyridine (**24**) (37% yield). **(Scheme 10).** The purity and identity of the novel compound **24** was demonstrated spectroscopically. The IR spectrum showed that the nitro group was still present (NO_2 asym and sym str.). The ^1H NMR spectrum showed 4 absorptions of intensity 3 : 6 : 3 : 2 at 2.30 (4-CH_3), 2.40 (2,6-CH_3), 4.01 (2-OCH_3) and 6.96 (Ar—H). The ^{19}F NMR spectrum exhibited two absorptions at +3.7 (d, F-6) and –75.37 (d, F-3) ppm (relative to TFA), which revealed mono-replacement of an α-fluorine (F-2).



Scheme-10

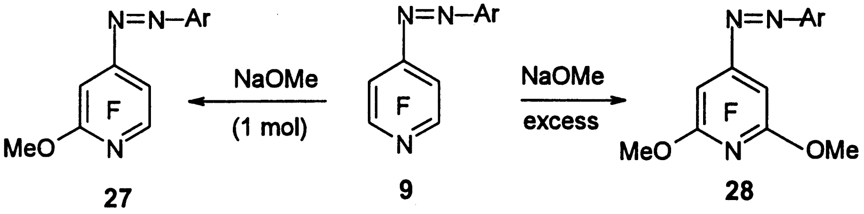
The reaction of tetrafluoro-4-nitropyridine with sodium methoxide in anhydrous methanol has been reported in literature[6] to give 2,3,5-trifluoro-6-methoxy-4-nitropyridine as the major product and tetrafluoro-4-methoxy pyridine as the minor product. This reaction is analogous to a reaction we carried out which involved treating 2,3,5-trifluoro-4-nitro-6-(2,4,6-trimethylphenylazo)pyridine (**21**) with an approximately equimolar proportion of sodium methoxide in methanol, the products isolated are 2,3-difluoro-4,5-dimethoxy-6-(2,4,6-trimethylphenylazo)pyridine (**25**) in 32%. The IR spectrum of this novel compound showed the absence of nitro group. The ^1H NMR spectrum exhibits five absorptions of intensity 3 : 6 : 3 : 3 : 2 at 2.30 (4-CH_3), 2.43 (2,6-CH_3), 4.03 and 4.26 (4,5-OCH_3) and 6.96 (Ar—H) (relative to TMS), revealing replacement of both fluorine (F-2) and nitro substituents, a fact which was revealed by ^{19}F NMR spectroscopy, which proved a two absorptions [–2.8 (d, F-2) and –70.8 (F-3) relative to TFA]. The effect of the presence of two methoxide groups on fluorine-3 (F-3) was to shift the absorption from –63.0 (F-3) to –70.8 ppm in comparison with the starting material. The mass spectrum complied with a normal fragmentation mechanism for azo-compounds.

The second product was 3-fluoro-2,5-dimethoxy-4-nitro-6-(2,4,6-trimethylphenylazo)pyridine (**26**). The NMR (^{19}F, ^1H) analyses were consistent for this compound, but the elemental analysis failed to identify this compound **(Scheme 9).** The IR spectrum showed that the nitro group was also still present (NO_2 asym and sym str). The ^1H NMR spectrum showed 5 absorptions of intensity 3 : 6 : 3 : 3 : 2 at 2.30 (4-CH_3), 2.40 (2, 6-CH_3), 4.50 (2-OCH_3) 4.65 (6-OCH_3) and 6.96 (Ar—H). The ^{19}F NMR spectrum exhibited one absorption at –71.8 (1F, s, F-5) ppm (relative to TFA), which revealed di-replacement of an α-fluorine (F-2) and an α-fluorine (F-6) **(Scheme 11).**



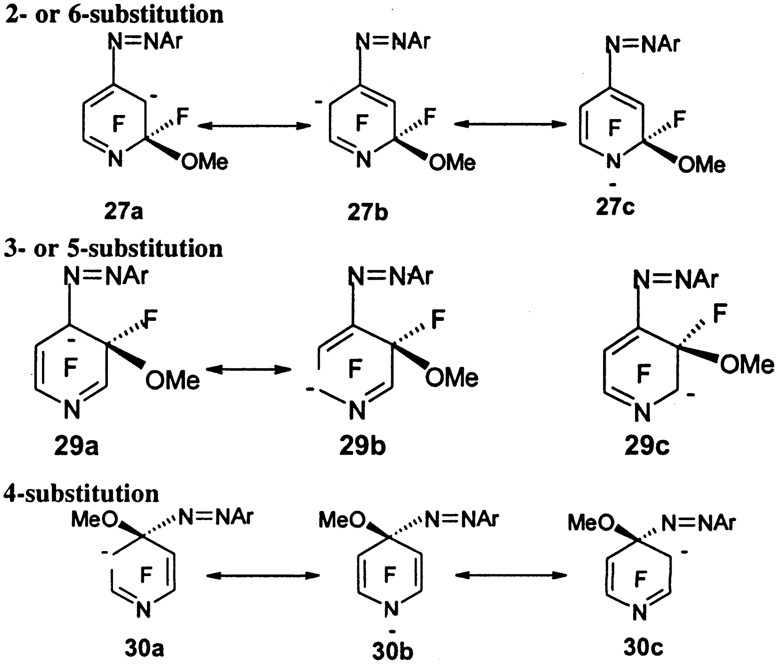
Scheme-11

However, when 2,3,5,6-tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine (**9**) is heated with an equimolar amount and excess of sodium methoxide in methanol, it gave respectively 2,3,5-trifluoro-6-methoxy-4-(2,4,6-trimethylphenylazo)-pyridine (**27**) (87% yield) and 3,5-difluoro-2,6-dimethoxy-4-(2,4,6-trimethyl-phenylazo)pyridine (**28**) (83% yield) **(Scheme 12)**.



Scheme-12

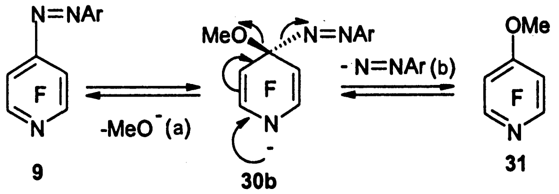
The formation of compounds **27** and **28** provides further evidence that nucleophilic substitution in azo-compound **9** by Nu (NaOMe) is directed strongly to ortho positions. This can be interpreted in terms of the relative stabilities of the transition states involved in the rate determining steps for substitution at the different positions, using the σ-complexes as models for the states **(Scheme 13)**.



Scheme-13

The cases where the negative charge resides on the carbon of a C-F group are destabilized by the I_π-repulsive effect of fluorine. These forms in which the ring nitrogen carries the negative charge, resulting from the attack by Nu ($^-$OMe) are stabilized with respect to those which do not. Thus, attack by $^-$OMe at the 5- (or 3-) position is least preferred. Substitution at the 4-position has a faster rate than that at the 6- (or 2-) position, reflecting the higher stability of hybrids **27a–c** when compared with **29a–c.** This is attributable to the relative stabilities of the para-quinonoid forms **30b** and **29b. 30b** is more stable, since in this case, the negative charge resides on the ring nitrogen, rather than on the less electronegative ring carbon **29b.** The para-quinonoid forms **30a** and **30b** and **29a** and **29c.**

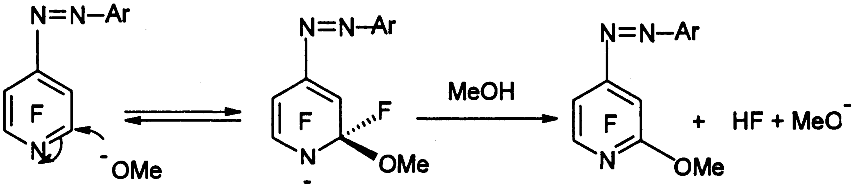
The species **30** can regain the aromatic condition by either $^-$OMe (a) or $^-$N=N—Ar (b) acting as a leaving group, the former resulting in recovery of the starting material **9**, the latter resulting in the formation of product **31.** Ar—N=N$^-$ is a poor leaving group, so the equilibrium tends to lie over to the left $^-$OMe, being a better leaving group, is lost a lot more often than Ar—N=N$^-$ (**Scheme 14**). The experimental evidence agrees with this assessment.



9 30b 31

Scheme-14

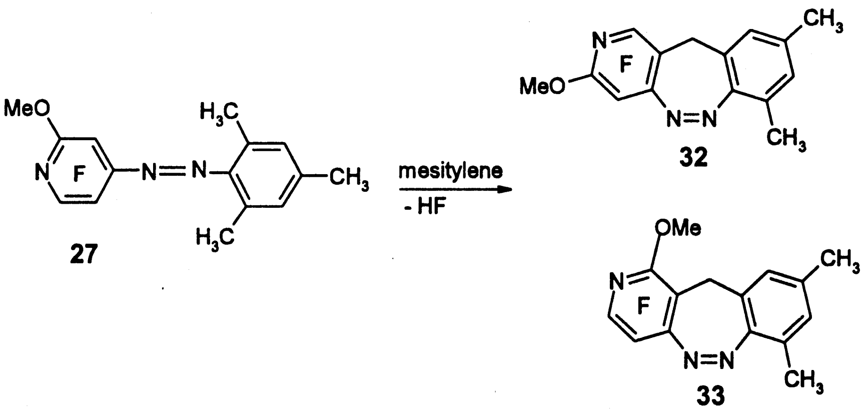
As we might have expected, the azo-compound **9** requires no more than its own inbuilt capacity for electron withdrawal and is itself attacked by powerful nucleophiles, *e.g.*, by $^-$OMe (sodium methoxide) in methanol. The F$^-$ leaving group is helped off by MeOH, HF being evolved and $^-$OMe regenated (**Scheme 15**).



9 27C 27

Scheme-15

Like the thermal ring-closure of fluorinated azo-compound **9**, clearly, the thermolysis of azo-compound **27** may yield the diazepine **32** (*via* elimination of HF-3), **33** (*via* elimination of HF-5), or mixture of both these isomers (**Scheme 16**).



Scheme-16

The high temperature requires for displacement of F-3 or F-5 on pyridine ring of previous azo-compounds provides further evidence that nucleophilic attack by Nu at the 5- or (3-) is least preferred.

Conclusions

In summary, tetrafluoro-4-nitropyridine derivatives have been synthesized in high yields. The resulting fluorinated amines and 4-amino-3-chlorotrifluoropyridine have also been diazotized and the resulting diazonium ions coupled to mesitylene giving the corresponding azo-compounds in high yields. The order of ease of displacement of pyridine-ring fluorine or NO_2 either in tetrafluoro-4-nitropyridine derivatives, azo-compounds and diazpines decreases are in the order 4- > 2- (or 6-) ≫ 5- (or 3-) except a special case of preferred ortho attack (to the nitro group) occurs in the reaction of 4-nitrotetrafluoropyridine with ammonia. The high ortho ratios were attributed to hydrogen bonding of the nucleophile to the nitro group. The structural isomers in either fluorinated amines, fluorinated azo-compounds or diazepines were separated successfully by HPLC.

EXPERIMENTAL

General experimental procedures

Nuclear magnetic resonance (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 ^1H NMR spectra and 54.6 MHz for ^{19}F NMR spectra. Tetramethylsilane (TMS) was used as a reference for ^1H NMR spectra and for ^{19}F NMR 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 solution in methanol. Melting points were determined on a Gallenhamp melting point apparatus and were uncorrected. High pressure liquid chromatography (HPLC) was carried out using a hybrid system consisting of high pressure pump (laboratory data control LDC model), an injector fitted with a 20 mL sample loop and using partisil 10, (25 cm × 5 mm i.d.) or silica ODS (20 cm × 5 mm i.d.) columns. The apparatus was connected to a Hewlett Packard 3352C data handling system *via* a 19652A A/D converter. For preparative scale HPLC partisil 20, (30 cm × 8 mm i.d.) was employed. Elemental analyses for carbon and hydrogen were carried out using standard techniques. Nitrogen was determined by the Pregl-Dumas method and fluorine calorimetrically (using the alizarin fluorine blue complexan which changes its colour from red to blue in the presence of F^- ions) and chlorine by potentiometer titration (silver nitrate method), following decomposition of samples by the Schoniger oxygen-flask method.

Synthesis of fluorinated aminopyridines

4-Amino-2,3,5,6-tetrafluoropyridine (2)

Pentafluoropyridine (50 g, 296 mmol) was dissolved in THF (350 mL) in a round-bottomed flask equipped with a reflux condenser to give a clear solution. On addition of aqueous ammonia (sp.gr. 088, 250 mL) a cloudy solution was produced and an exothermic reaction ensued. The mixture was then refluxed for 18 h. The clear solution produced was poured into water (1000 mL) and the whole mixture was extracted with ether (3 × 150 mL). The extract was dried ($MgSO_4$), evaporated using a rotary evaporator and the residue freed from the last traces of solvent *in vacuo*, to give a pale cream solid. Recrystallization of this crude material from light petroleum (b.p. 80–100°C) gave long white needles of 4-aminotetrafluoropyridine (40 g, 241 mmol, 81%), m.p. 84–86°C Lit.[4, 6] IR (KBr cm^{-1}): 3500–3300 ν(NH str.); ^1H ($CDCl_3$): δ 5.05 (2H, br s, NH_2); ^{19}F ($CDCl_3$): δ 15.1 (2F, m, F2 and F6), –85.1 (2F, m and F5).

Tetrafluoro-4-nitropyridine (3)

A mixture of methylene chloride (120 mL), trifluoroacetic anhydride (27 mL) and 85% hydrogen peroxide (12 mL) was refluxed and stirred for 15 min. A solution of 4-aminotetrafluoropyridine (10 g, 59.17 mmol) in methylene chloride (60 mL) was then added to the refluxing solution and the mixture immediately became yellow and changed to bright green (formation of 4-nitrosotetrafluoropyridine) in a few minutes. Hydrgen peroxide (6 mL) was added after a further 20 min, followed 3 h later by more hydrogen peroxide (6 mL) and trifluoroacetic anhydride (6 mL). After 6–7 h, the solution had become yellow. When the solution had been heated for a total of 22 h, water (100 mL) was added, the methylene chloride layer was separated, washed three times with water, dried ($MgSO_4$), and the solvent was distilled off through a short vigreux column. Distillation of the residual liquid (from P_2O_5) afforded pale yellow tetrafluoro-4-

nitropyridine (7.2 g, 36.73 mmol, 61%), b.p. 152–154°C Lit.[6]. IR (KBr, cm^{-1}): 1550 and 1350 $\nu(NO_2)$; ^{19}F ($CDCl_3$) : δ –4.5 (2F, m, F2 and F6), –67.9 (2F, m and F5).

3-Chloro-1,5,6-trifluoro-4-aminopyridine (22)

The compound was prepared in a similar fashion to that described above using 3-chloro-tetrafluoropyridine (10.0 g, 53.9 mmol), THF (150 mL) and aqueous ammonia (sp.gr. 0.88, 60 mL). The isolated product as a white solid was recrystallized from light petroleum (b.p. 80–100°C) to give white crystals of 3-chloro-1,5,6-trifluoro-4-aminopyridine (9.5 g, 52.0 mmol, 96%), m.p. 116–118°C; IR (KBr, cm^{-1}): 3500–3300 ν(NH str.); ^1H ($CDCl_3$) : δ 5.15 (2H, brs, NH_2); ^{19}F ($CDCl_3$) : $\delta + 2.9$ (1F, dd, J = 22.8, 12.7 Hz, F-2), –14.1 (1F, dd, J = 20.3, 12.7 Hz, F-6), –87.8 (1F, dd, J = 22.8, 20.3 Hz, F-5).

Amination of tetrafluoro-4-nitropyridine

(1) Using ammonia gas: Ammonia was bubbled through a solution of tetrafluoro-4-nitropyridine (10 g, 51 mmol) in dry ether (150 mL) at 0°C for 4 h. The solution was filtered *in vacuo* to leave a dark red solid (9.0 g) which was subjected to dry column flash chromatografy [silica (70 × 55 mm), light petroleum, b.p. 40–60°C : dichloromethane] to give:

Band 1: A yellow orange material which was shown by ^{19}F NMR spectroscopy to be a mixture of 4-aminotetrafluoropyridine, 3-amino-2,5,6-trifluoro-4-nitropyridine and 2-amino-3,5,6-trifluoro-4-nitropyridine. The pure components were separated by HPLC [sample column = partisil 10 silica (25 × 0.8 cm); mobile phase = 60% hexane/40% CH_2Cl_2; $\lambda = 254$ nm; pressure = 250–550 p.s.i.; inject = 0.3 mL/value; flow rate = 5 mL/min; c-speed = 1 cm/min] to give:

(i) 4-aminotetrafluoropyridine (2): A white solid (1.28 g, 7.7 mmol, 15%); the product was identified by comparison to its IR and 19F NMR spectra with that of an authentic sample.

(ii) 3-Amino-2,5,6-trifluoro-4-nitropyridine (10): This product was obtained as a bright yellow solid (4.85 g, 25 mmol, 49%), m.p. 82–84°C; IR (KBr, cm^{-1}): 3500–3300 ν(NH str.), 1550 and 1350 $\nu(NO_2)$; UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 400 (3965.75); λ_{min} (ε): 304 (237.94); ^1H ($CDCl_3$): δ 5.5 (2H, br s, NH_2); ^{19}F ($CDCl_3$): δ (1F, dd, J = 30.46, 13.96 Hz, F-6), –25.8 (1F, dd, J = 20.30, 13.96 Hz, F-2), –27.7 (1F, dd, J = 30.46, 20.3 Hz, F-5); m/z (FAB): 193 (M^+, 100), 148 [(P + 1), 7.0], 147 ($P = C_5H_2F_3N_2^{+}$, 81.1), 146 (18.1), 120, (72.9), 75 (20.3), 42 (33.3), 41 (34.2). Anal. Calcd for $C_5H_2N_2O_2F_3$: C, 31.1; H, 1.0; F, 29.5; N, 21.8; Found: C, 30.9, H, 0.8; F, 29.5; N, 22.0.

(iii) 2-Amino-3,5,6-trifluoro-4-nitropyridine (11): Obtained as an orange solid (1.9 g, 9.84 mmol, 19%), m.p. 42–44°C; IR (KBr, cm^{-1}): 3500–3300 ν(NH str.), 1550 and 1350 $\nu(NO_2)$; ^1H ($CDCl_3$): δ 5.15 (2H, br s, NH_2); ^{19}F ($CDCl_3$): δ 8.0 (1F, dd, J = 29.6, 22.9 Hz, F-6), –71.2 (1F, dd, J = 29.6, 13.1 Hz, F-5), –84.1 (1F, dd, J = 29.6, 13.1 Hz); m/z (FAB): 195 [$(M + 2)^+$, 0.4), 194 [$(M + 1)^+$, 9.4], 193 (M^+, 100), 148 [(P + 1), 7.5], 147 (P = $CH_2F_3N_2^+$, 9.5), 120 (49.4), 97 (13.6), 93 (19.3), 75 (20.0), 42 (59.4), 41 (CHN_2^+, 99). Anal. Calcd. for $C_5H_2O_2F_3N_3$: C, 31.1; H, 1.0; F, 29.5; N, 21.8; Found: C, 31.1; H, 1.0; F, 29.7; N, 21.5.

Band 2: 3,5-Diamino-2, 6-difluoro-4-nitropyridine (14):

Resulted as shiny black (0.3 g, 1.58 mmol, 3%), m.p. 151–153°C; IR (KBr, cm^{-1}): 3500–3300 ν(NH str.), 1550 and 1350 ν(NO_2); UV λ_{max} (cm^{-1} $mol^{-1}L$) in ethanol: 272 (4773.28), 331 (4540.40), 475 (3725.49); λ_{min} (ε): 256 (3143.38), 295 (1746.32), 380 (698.53); ^1H ($CDCl_3$): δ 5.70 (4H, br s, 3,5-NH_2); ^{19}F ($CDCl_3$): δ –24.30 (2F, s, F-2 and F-6), m/z (FAB): 190 (M^+, 100), 144 (35.2), 124 (15.7), 117 (12.2), 104 (14.1), 97 (24.8), 71 (23.8), 70 (26.0), 46 (NO_2^+, 9.3), 30 (NO_2^+, 17.0). Anal. Calcd. for $C_5H_4N_4O_2F_2$: C, 31.6; H, 2.1; N, 29.5; F, 20.0; Found: C, 31.7; H, 2.1; N, 29.4; F, 20.2.

Using aqueous ammonia: Tetrafluoro-4-nitropyridine was also aminated using aqueous ammonia in similar method described for pentafluoropyridine. Work up of the reaction products yielded the same products which were obtained when ammonia gas was used, with different yields: 4-aminotetrafluoropyridine (12%), 3-amino-2,5,6-trifluoro-4-nitropyridine (38%), 2-amino-3,5,6-trifluoro-4-nitropyridine (15%) and 3,5-diamino-2,6-difluoro-4-nitropyridine (4%).

4-Amino-2,3,5-trifluoro-6-methoxypyridine

To a solution of 4-aminotetrafluoropyridine (10 g, 0.06 mol) in methanol (50 mL) was added during 30 min, a solution (50 mL) of methanolic sodium methoxide (30% w/v, 10.84 g, 0.06 mol). The mixture was stirred under reflux for 18 h. The product was poured into water and the mixture was extracted with ether (3 × 150 mL). The extract was dried ($MgSO_4$), evaporated using a rotary evaporator and the pure product freed from the last traces of solvent *in vacuo,* to give white 4-amino-2,3,5-trifluoro-6-methoxypyridine (10.0 g, 55.62 mmol, 93%), m.p. 92–93°C Lit.[6] 92.5–93°C; IR (KBr, cm^{-1}): 1450–1190 ν(Py-F), 1250 ν(C—O asym str.) and 1040 ν(C—O sym str.); UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 230 (7569.59); ^1H ($CDCl_3$): δ 3.9 (3H, s, —OCH_3), 4.5 (2H, br s, —NH_2; ^{19}F ($CDCl_3$): δ –17.80 (1F, dd, J = 25.0, 22.0 Hz, F-2), –87.80 (1F, dd, J = 25.23, 4.63 Hz, F-3), –93.3 (1F, dd, J = 22.00, 4.63 Hz, F-5). Anal. Calcd. for $C_6H_5N_2OF_3$: C, 40.4; H, 2.8; F, 32.0; N, 15.7; Found: C, 40.2; H, 2.6; F, 32.2; N, 15.9.

Synthesis of azo-compounds

2,3,6-triflouro-4-nitro-5-(2,4,6-trimethylphenlazo)pyridine (20)

In a typical experiment, dry powdered sodium nitrite (1.30 g, 18.76 mmol) was added over a period of 5 min to 3-amino-2,5,6-trifluoronitropyridine (3.62 g, 18.76 mmol) in 300 mL contained in a polythene beaker. After stirring had been continued for 1.5 h at room temperature, mesitylene (2.26 g, 18.76 mmol) was added, which caused an immediate deep-red colour to be formed. Stirring was continued at room temperature until all the AHF evaporated, then the red precipitate was isolated following addition of the mixture to water (750 mL).

After being dried (oven, 70°C), the resulting red solid was recrystallized from ethanol to give bright red needles of 2,3,6-triflouro-4-nitro-5-(2,4,6-trimethylphenlazo)pyridine (5.1 g, 17.76 mmol, 84%), m.p. 114–116°C; IR (KBr, cm^{-1}): 1600 ν(—N=N—str.); UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 360 (2050.00), 482 (1169.07), λ_{min} (ε): 270 (4175.26), 435 (835.05); ^{19}H ($CDCl_3$): δ 2.20 (3H, s, 4-CH_3), 2.38 (6H, s, 2, 6-CH_3), 6.94 (2H, s, 3, 5-H); ^{19}F ($CDCl_3$): δ +6.03 (1F, dd, J = 27.5, 12.7 Hz, F-6), –0.30 (1F, dd, J = 21.2, 12.7 Hz, F-2), –75.0 (1F, dd, J = 12.7, 21.2 Hz); m/z (FAB): 325 [(M + 1), 1.9], 324 (M^+, 10.7), 307 (6.1), 277 (16.0), 234 (4.5), 120 [(B + 1), 10.1], 119 [C_9H_{11}(B), 100.0)], 117 (7.1), 91 (31.9), 77 (16.1), 41 (14.3), 29 (6.3). Anal. Calcd. for $C_{14}H_{11}N_4O_2F_3$: C, 51.8; H, 3.4; N, 17.3; F, 17.6; Found: C, 50.9; H, 3.3; N, 17.3; F, 17.6.

2,3,5-Trifluoro-4-nitro-6-(2,4,6-trimethylphenylazo)pyridine (21)

The compound was prepared in a similar method to that described for 2,3,6-triflouro-4-nitro-5-(2,4,6-trimethylphenlazo)pyridine using 2-amino-3,5,6-trifluoronitropyridine (1.42 g, 7.36 mmol), AHF (150 mL) and mesitylene (0.90 g, 7.36 mmol) and resulted in a red solid which was recrystallized from ethanol to give bright red needles of 2,3,5-triflouro-4-nitro-6-(2,4,6-trimethylphenlazo)pyridine (1.81 g, 5.59 mmol, 76%), m.p 165–167°C; IR (KBr, cm^{-1}): 1600 (—N=N—str.); 1550 and 1350 $\nu(NO_2)$; ^1H ($CDCl_3$): δ 2.34 (3H, s, 4-CH_3), 2.51 (6H, s, 2, 6-CH_3), 7.05 (2H, s, 3, 5-H); ^{19}F ($CDCl_3$): δ –2.4 (1F, dd, J = 30.0, 25.0 Hz, F-2), –60.2 (1F, dd, J = 30.0, 3.8 Hz, F-5), –63.0 (1F, dd, J = 25.0, 3.8 Hz, F-3); m/z (FAB): 325 [(M + 1), 5.2], 324 (M^+, 30.9), 277 (5.0), 147 (4.9), 120 [(B + 1), 14.7], 119 [$C_9H_{11}^+$ (B), 100], 91 (22.5), 29 (61.9). Anal. Calcd. for $C_{14}H_{11}N_4O_2F_3$: C, 51.8; H, 3.4; N, 17.3; F, 17.6; Found: C, 52.1; H, 3.6; N, 17.1; F, 18.0.

2,3,5,6-Tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine (9)

This compound was also prepared in a similar method to that described for 2,3,6-triflouro-5-nitro-4-(2,4,6-trimethylphenlazo)pyridine using 4-amino-2,3,5,6-tetrafluoropyridine (3.0 g, 18.06 mmol), AHF (300 mL) and mesitylene (2.21 g, 18.06 mmol) and resulted in a red solid which was recrystallized from ethanol to give bright red needles of 2,3,5,6-tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine (4.27 g,14.39 mmol, 80%), m.p 143°; IR (KBr, cm^{-1}): 1600 ν(—N=N— Str.); ^1H ($CDCl_3$): δ 2.35 (3H, s, 4-CH_3), 2.50 (6H, s, 2, 6-CH_3), 7.05 (2H, s, 3, 5-H); ^{19}F ($CDCl_3$): δ –11.2 (2F, m, F-3, F-6), –75 (2F, m, F-3, F-5); m/z (FAB): 297 (M^+, 78.9), 296 (6.8), 277 (13.3), 147 (24.8), 119 ($C_9H_{11}^+$, 100), 58 (55.7), 44 (36.7), 40 (24.4). Anal. Calcd. for $C_{14}H_{11}N_3F_4$: C, 56.6 ; H, 3.7; N, 14.1; F, 25.6; found: C, 56.9; H, 3.8; N, 14.0; F, 25.3.

3-Chloro-2,5,6-trifluoro-4-(2,4,6-trimethylphenylazo)pyridine (23)

An 86 : 14 (v/v) mixture (30 mL) of glacial acetic and propionic acid was added dropwise to a stirred solution of dry powdered sodium nitrite (0.95 g, 13.77 mmol) in 98% sulphuric acid (30 mL) [made by heating the sulphuric acid to *ca.*

70°C to completely dissolve the sodium nitrite] kept at 30°C by means of an ice bath. The resulting nitrosating medium was cooled to 0°C, then treated with 4-amino-3-chloro-2,5,6-trifluoropyridine (2.5 g, 13.70 mmol); stirring was continued for 2 h. Addition of mesitylene (1.66 g, 13.83 mmol) gave a red precipitate which was isolated by addition of the mixture to water (1000 cm^3) after it had been stirred for 3 h at room temperature. After being dried (oven, 70°C), the resulting red solid was recrystallized from petroleum ether (b.p. 80–100°C) to give orange red needles of 3-chloro-2,5,6-trifluoro-4-(2,4,6-trimethylphenylazo)-pyridine (3.56 g, 11.37 mmol, 83%), m.p. 150–151°C; IR (KBr, cm^{-1}): 565 ν(—N═N—str.), 1450–1190 ν(Py—F) and 1250–1070 ν(Ar—Cl); UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 460 (561.87), λ_{min} (ε): 408 (327.76); ^{1}H (CDCl$_3$): δ 2.40 (3H, s, 4-CH$_3$), 2.55 (6H, s, 2,6-CH$_3$); ^{19}F (CDCl$_3$): δ +5.0 (1F, dd, J = 29.3, 13.7 Hz, F-2), –8.6 (1F, dd, J = 20.3, 13.7 Hz, F-6), –78.5 (1F, dd, J = 29.3, 20.3 Hz, F-5); m/z (FAB): 313 (M$^+$, 33.8), 312 (2.2), 279 (Q + 1, 3.3), 278 [($C_{14}H_{11}F_3N_3^+$ (Q), 20.4], 120 (B + 1, 12.5), 119 [C_9H_{11}(B), 100], 91 (48.3). Anal. Calcd. for $C_{14}H_{11}N_3ClF_3$: C, 53.6; H, 3.5; N, 13.4; Cl, 11.3; Found: C, 53.3; H, 3.5; N, 13.2; Cl, 11.1.

Methoxylation of 2,3,6-trifluoro-4-nitro-5-(2,4,6-trimethylphenylazo)-pyridine

To a cold (0°C), stirred solution of 2,3,6-trifluoro-4-nitro-5-(2,4,6-trimethylphenylazo)pyridine (0.7 g, 2.30 mmol) in methanol (15 mL) was added (during 15 min) a solution of methanolic sodium methoxide (30% w/v, 0.42 g, 2.30 mmol) in methanol (15 mL). The mixture was then stirred for 15 min. Water was added and the mixture extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated (rotary evaporated) to leave a red brown solid. This was subjected to dry-column flash chromatography [silica (45 × 50 mm), light petroleum b.p. 40–60°C)/CH_2Cl_2] to give impure material which was subjected to HPLC [column; spherisorb 10 μm silica 25 cm × 8 mm id (semi-prep.) 25 cm × 5 mm id (analytical); mobile phase: 85% hexane, 15% CH_2Cl_2, 5 mL/min (semi-prep) 2 mL/min (analytical); detection: UV, 280 nm] to give:

(i) 3-Fluoro-2,5-dimethoxy-4-nitro-6-(2,4,6-trimethylphenylazo)pyridine (26)

As a pale red solid (0.39 g, 1.08 mmol, 47%), m.p 124–126°C; IR (KBr, cm^{-1}): 2990 ν(CH$_2$ asym str.), 2860–2850 ν(CH$_2$ sym str.), 1600–1565 ν(—N═N—str.), 1550 and 1350 ν(NO$_2$), 1250 ν(C—O asym str.) and 1040 ν(C—O sym str.); ^{1}H (CDCl$_3$): δ 2.30 (3H, s, 4-CH$_3$), 2.43 (6H, s, 2, 6-CH$_3$), 4.50 (3H, s, 2-OCH$_3$), 4.65 (3H, s, 6-OCH$_3$), 6.95 (2H, s, Ar—H); ^{19}F (CDCl$_3$: δ –71.8 (1F, s, F-3); the NMR (^{19}F, ^{1}H) analysis were consistent for this compound, but the elemental analysis failed to identify this compound. Anal. Calcd. for $C_{16}H_{17}N_4O_4F$: C, 53.7; H, 4.2; N, 15.0; F, 7.8; Found: C, 55.2; H, 4.9; N, 16.1; F, 5.5.

(ii) 2,3-Difluoro-4,5-dimethoxy-6-(2,4,6-trimethylphenylazo)pyridine (25)

As a bright red solid (0.24 g, 0.75 mmol, 32%), IR (KBr, cm^{-1}): 1600 ν(—N═N—str.), 1250 ν(C—O asym str.) and 1040 ν(C—O sym str.); ^{1}H (CDCl$_3$): δ 2.30 (3H, s, 4-CH$_3$), 2.43 (6H, s, 2, 6-CH$_3$), 4.03 (3H, s, 2-OCH$_3$), 4.26 (3H, s, 5-OCH$_3$), 6.96 (2H, s, Ar—H); ^{19}F (CDCl$_3$): δ –2.8 (1F, d, J = 22.8 Hz, F-2), –70.8 (1F, d, J = 22.8, Hz, F-3); m/z (FAB): 321 (M$^+$, 10.9), 175 (4.9), 147 (9.2), 20 (B + 1, 10.3), 119 [C$_9$H$_{11}$(B), 100], 91 (21.6). Anal. Calcd. for C$_{16}$H$_{12}$N$_3$O$_2$F$_2$: C, 59.7; H, 5.3; N, 13.0; F, 11.8; Found: C, 59.7; H, 5.6; N, 12.9; F, 10.3.

3,6-Difluoro-2-methoxy-4-nitro-5-(2,4,6-trimethylphenylazo)pyridine (24)

Using a similar method to that described above an approximately equimolar portion of sodium methoxide (30% w/v; 0.40 g, 2.22 mmol)/2,3,6-trifluoro-4-nitro-5-(2,4,6-trimethylphenylazo)pyridine (0.70 g, 2.16 mmol). The dark red solid was purified by dry-column flash chromatography [using 40 : 60 (v/v) mixture of dichloromethane : light petroleum (40–60°C)] to give a bright red solid of 3,6-difluoro-2-methoxy-4-nitro-5-(2,4,6-trimethylphenylazo)pyridine (0.27 g, 0.80 mmol, 37%), m.p. 175–177°C; IR (KBr, cm^{-1}): 2990 ν(CH$_2$ asym. str.), 1600 ν(—N═N— str.), 1550 and 1350 ν(NO$_2$), 2990 ν(C—O sym str.) and 1040 (C—O sym str.); ^{1}H (CDCl$_3$): δ 2.30 (3H, s, 4-CH$_3$), 2.40 (6H, s, 2, 6-CH$_3$), 4.01 (3H, s, 2-OCH$_3$), 6.96 (2H, s, Ar—H); ^{19}F (CDCl$_3$): δ +3.7 (1F, dd, J = 26.6 Hz, F-6), –75.37 (1F, d, J = 26.6, Hz, F-3); m/z (FAB): 337 (M + 1, 2.1), 336 (M$^+$, 10.9), 149 (4.3), 134 (29.9), 119 (C$_9$H$_{11}^+$, 100), 91 (23.9), 77 (1.9), 57 (92.5).

2,3,5-Trifluoro-6-methoxy-4-(2,4,6-trimethylphenylazo)pyridine (27)

This compound was prepared in a similar method to that described for 4-amino-2,3,5-trifluoro-6-methoxypyridine using equimolar portion of 2,3,5,6-tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine (4 g, 13.5 mmol) and a solution of methanolic sodium methoxide (30% w/v, 2.43 g, 13.5 mmol) and resulted in a red solid which was purified by dry-column flash chromatography [using 30 : 70 (v/v) mixture of dichloromethane : light petroleum (40–60°C)] to give red needles of 2,3,5-trifluoro-6-methoxy-4-(2,4,6-trimethylphenylazo)pyridine (3.6 g, 11.7 mmol, 87%), m.p. 110–112°C; IR (KBr, cm^{-1}): 1600–1565 ν(—N═N—str.), 1450–1190 ν(Py—F), 1250 ν(C—O asym str.) and 1040 ν(C—O sym str.); UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 238 (9566.91), 328 (19312.50), 452 (66.47); λ_{min} (ε): 226 (8330.88), 268 (329.41), 410 (477.13); ^{1}H (CDCl$_3$): δ 2.34 (3H, s, 4-CH$_3$), 2.48 (6H, s, 2, 6-CH$_3$), 4.04 (3H, s, —OCH$_3$), 7.07 (2H, s, Ar—H); ^{19}F (CDCl$_3$): δ –14.80 (1F, dd, J = 28.0, 23.0 Hz, F-2), –75.80 (1F, dd, J = 28.0, 3.4 Hz, F-3), –84.50 (1F, dd, J = 23.0, 3.4 Hz, F-5), m/z (FAB): 11(M + 2, 0.3), 310 (M + 2, 4.0), 309 (M$^+$, 24.6), 294 (3.9), 120 (B + 1, 10.3), 119 (B═C$_9$H$_{11}$, 100), 91 (7.9), 79 (1.4), 41 (2.4). Anal. Calcd. for C$_{16}$H$_{17}$N$_3$O$_2$F$_2$: C, 58.2; H, 4.5; F, 18.4; N, 13.6; Found: C, 58.0; H, 4.5; F, 18.3; N, 13.4.

3,5-Difluoro-2,6-dimethoxy-4-(2,4,6-trimethylphenylazo)pyridine (28)

This compound was prepared in a similar method to that described for 4-amino-2,3,5-trifluoro-6-methoxypyridine using a molar ratio of 3 : 1 sodium methoxide : 2,3,5,6-tetrafluoro-4-(2,4,6-trimethylphenylazo)pyridine. The dark red solid was purified by dry-column flash chromatography [using 40 : 60 (v/v) mixture of dichloromethane : light petroleum (40–60°C)] to give red needles of 3,5-difluoro-2,6-dimethoxy-4-(2,4,6-trimethylphenylazo)pyridine (83% yield), m.p. 151–153°C; IR (KBr, cm^{-1}): 1600–1565 ν(—N═N— str.), 1450–1190 ν(Py—F), 1250 ν(C—O asym str.) and 1040 ν(C—O sym str.); UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 247 (1312.50), 340 (1062.50), 435 (1037.44); λ_{min} (ε): 236 (1062.50), 280 (565.50), 400 (688.89); ^{1}H ($CDCl_3$): δ 2.30 (3H, s, 4-CH_3), 2.43 (6H, s, 2, 6-CH_3), 4.00 (3H, s, —OCH_3), 6.96 (2H, s, Ar—H); ^{19}F ($CDCl_3$): δ −84.8 (2F, s, F-3 and F-5); m/z (FAB): 11(M + 2, 1.1), 322 (M + 1, 9.0), 321 (M^+, 49.8), 320 (15.2), 306 (15.8), 290 (18.8), 119 (B═C_9H_{11}, 100), 91 (7.9), 79 (1.4), 41 (2.4). Anal. Calcd. for $C_{16}H_{17}N_3O_2F_2$: C, 59.8; H, 5.3; F, 11.8; N, 13.1; Found: C, 59.5; H, 5.4; F, 11.6; N, 13.1.

Synthesis of fluorinated diazepines

(i) 1,2,4-Trifluoro-7,9-dimethyl-11-H-pyrido[4,3-c]benzo[1,2]diazepine (15)

In a typical experiment 2,3,6-trifluoro-4-nitro-5-(2,4,6-trimethylphenylazo)-pyridine (1.8 g, 5.55 mmol) was refluxed in mesitylene (30 mL) for 7.5 h. Removal of the mesitylene by distillation (rotary evaporator, 80°C, < 1 mm Hg) revealed a yellow-brown oil which was purified by dry-column flash chromatography [silica (45 × 50 mm), light petroleum (b.p. 40–60°C) : dichloromethane] to give:

(i) Unreacted azo compound (0.07 g, 0.2 mmol, 4%, 96% conversion), identified by comparison to its TCL value, m.p. and ^{19}F NMR spectrum with those of an authentic sample; (ii) a yellow component which was recrystallized from aqueous ethanol to give orange needles of 1,2,4-trifluoro-7,9-dimethyl-11-H-pyrido[4,3-c]benzo[1,2]diazepine[0.98 g, 4.11 mmol, 74% (75% based on 100% conversion of azo compound)], m.p. 149–151°C; IR (KBr, cm^{-1}): 1600–1565 (—N═N— str.) and 1450–1260 ν(Py—F), ν(Py—F); UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 335 (7782.68), 428 (889.44); λ_{min} (ε): 290 (3494.27), 385 (597.20); ^{1}H ($CDCl_3$): δ 2.30 (3H, s, 7—CH_3), 2.54 (3H, s, 9-CH_3), 3.54 (2H, s, 11-CH_2), 6.89 (1H, s, 8-H), 7.10 (1H, s, 10-H); ^{19}F ($CDCl_3$): δ +2.3 (1F, dd, J = 28.8, 12.7 Hz, F-4), −5.8 (1F, dd, J = 21.6, 12.7 Hz, F-2), −7.5 (1F, dd, J = 28.8, 21.6 Hz, F-1); m/z (FAB) 278 (M + 1, 16.8), 277 (M^+, 100), 249 (6.2), 235 (11.5), 234 (79.4), 233 (79.4), 214 (11.9). Anal. Calcd. for $C_{14}H_{10}N_3F_3$: C, 60.6; H, 3.6; F, 20.6; N, 15.2. Found: C, 60.9; H, 3.6; F, 21.0; N, 15.4.

Thermolysis of 2,3,5-trifluoro-6-methoxy-4-(2,4,6-trimethylphenylazo) pyridine (27): Using a similar method to that described for the diazepine mentioned earlier, 2,3,5-trifluoro-6-methoxy-4-(2,4,6-trimethylphenylazo)-pyridine (2.0 g, 6.5 mmol) was dissolved in mesitylene (30 cm^3) in a round-bottomed flask equipped with a reflux condenser. The solution was refluxed and the progress of the reaction was followed by thin-layer chromatography. Eventually the solution turned brown. After 12 h refluxing, TLC analysis showed that most of the starting material had been converted to a yellow product, so the solvent (mesitylene) was removed at oil pump pressure using a rotary evaporator. The dark brown residue was subjected to dry-column flash chromatography [silica (45 × 50 mm) light petroleum ether (b.p. 40–60°C) : dichloromethane] to give:

(i) Unreacted azo compound (0.07 g, 0.23 mmol, 96% conversion), identified by comparing its TLC R_f value with that of an authentic sample.

(ii) A yellow orange component (1.64 g, 5.7 mmol, 87%) which was shown by ^{19}F NMR spectroscopy to contain two isomers; these were separated by HPLC [particle diameter 50 × 8 mm i.d. dichloromethane : hexane 50 : 50; flow rate 4 mL/min ultraviolet detection at 254 nm; 1 mL injection volume]. The first was a yellow-orange solid, found to be:

(ii) 1,4-Difluoro-3-methoxy-7,9-dimethyl-11-H-pyrido[4,3-c]benzo[1,2]-diazepine

33 [1.46 g, 5 mmol, 77% (80% based on 100% conversion of the azo-compound)], m.p. 194–196°C; IR (KBr, cm^{-1}): 2925 ν(CH_2 asym str.), 2860–2850 ν(CH_2, str.), 1600–1560 ν(—N═N— str.), 1480–1190 ν(Py—F), 1250 ν(C—O asym str.) and 1040 ν(C—O sym str.); UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 250 (9241.28), 336 (7981.10), 436 (1075.35); λ_{min} (ε): 238 (7981.10), 282 (2520.35), 400 (688.89); ^1H ($CDCl_3$): δ 2.30 (3H, s, 7-CH_3), 2.55 (3H, s, 9-CH_3), 3.32 (2H, s, 11-CH_2), 3.95 (3H, s, 1-OCH_3), 6.85 (1H, s, 8-H), 7.10 (1H, s, 10-H); ^{19}F ($CDCl_3$): δ –14.20 (1F, d, J = 23.3 Hz, F-1), –85.50 (1F, d, J = 23.3, F-4); m/z (FAB) 289 (M^+, 72.7), 247 (B + 1, 15.3, 264 (B═$C_{14}H_{10}F_2NO^+$, 100), 231 (7.1), 231 (7.1), 230 (8.0), 218 (9.2), (216 (10.9). Anal. Calcd. for $C_{15}H_{13}N_3OF_2$: C, 62.3; H, 4.5; F, 13.1; N, 14.5; Found: C, 62.4; H, 4.3; F, 13.1; N, 14.4.

(iii) 3,4-difluoro-1-methoxy-7,9-dimethyl-11-H-pyrido[4,3-c]benzo[1,2]-diazepine

As a second isomer which was also a yellow-orange solid [0.18 g, 0.6 mmol, 7% (9% based on 100% conversion of the azo-compound)], m.p. 190–192°C; IR (KBr, cm^{-1}): 2990 ν(CH_2 asym str.), 2860–2850 ν(CH_2. stretch.), 1600–1565 ν(—N═N— str.), 1450–1190 ν(Py—F), 1250 ν(C—O asym str.) and 1040 ν(C—O sym str.); UV λ_{max} (cm^{-1} mol^{-1} L) in ethanol: 247 (1312.50), 340 (1062.50), 435 (1037.47; λ_{min} (ε): 236 (1062.50), 280 (562.50), 406 (796.60); ^1H ($CDCl_3$): δ 2.30 (3H, s, 7-CH_3), 2.54 (3H, s, 9-CH_3), 3.32 (2H, s, 11CH_2), 3.97 (3H, s, 1-OCH_3), 6.83 (1H, s, 8-H), 7.08 (1H, s, 10-H); ^{19}F ($CDCl_3$): δ –5.0 (1F, d, J = 28.76 Hz, F-3), –76.3 (1F, d, J = 28.76, F-4); m/z (FAB) 289 (M^+, 76.2), 247 (B + 1, 13.1, 264 (B═$C_{14}H_{10}F_2NO^+$, 100), 230 (8.9), 218 (11.3), 203 (8.7). Anal. Calcd. for $C_{15}H_{13}N_3OF_2$: C, 62.3; H, 4.5; F, 13.1; N, 14.5; Found: C, 62.4; H, 4.5; F, 13.4; N, 14.4.

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