Synthesis of 2,3,5,6-tetrafluoro-pyridine derivatives from reaction of pentafluoropyridine with malononitrile, piperazine and tetrazole-5-thiol

Khalil Beyki, Reza Haydari* and Malek Taher Maghsoodlou

Abstract
Some pentafluoropyridine derivatives have been synthesized by the reaction of pentafluoropyridine with appropriate C, S and N-nucleophile such as malononitrile, 1-methyl-tetrazole-5-thiol and piperazine. These reactions provided 4-substituted 2,3,5,6-tetrafluoropyridine derivatives in good yields. All the compounds were characterized using $^1$H, $^{13}$C and $^{19}$F-NMR spectroscopy and X-ray crystallography.

Keywords: Pentafluoropyridine, Heterocycle, Nucleophilic Substitution, Synthesis, $^{19}$F-NMR

Background
Pentafluoropyridine and related compounds in which all the hydrogen atom in heterocyclic ring have been replaced by fluorine atoms were synthesized by reaction of potassium fluoride with perchloro heteroaromatic (Ojima 2009). In pharmacology, it is common to substitute hydrogen with fluorine atoms for increases the lipophilicity and biological activity of the compounds (Chambers et al. 2008a, b). Pentafluoropyridine one of the most important perfluoroheteroaromatic compounds have been used for the synthesis of various drug-like systems (Gutov et al. 2010). These systems are highly active towards nucleophilic additions owing to the presence of electronegative fluorine atoms and the presence of the nitrogen heteroatom so all five fluorine atoms in pentafluoropyridine may be substituted by an appropriate nucleophile (Cartwright et al. 2010; Chambers et al. 2005). A nucleophilic substitution reaction of pentafluoropyridine occurs in two-step addition–elimination mechanism, so install nucleophile addition and in the end elimination flour ring nitrogen (Colgin et al. 2012). The site reactivity order of pentafluoropyridine is well known that, the order of activation toward nucleophilic attack follows these quence 4 (Para)-fluorine > 2 (Ortho)-fluorine > 3 (Meta)-fluorine so the reactions of pentafluoropyridine with some nucleophilic occur selectively at the Para position as this site is most activated towards nucleophilic additions to afforded of 4-substituted tetrafluoropyridine (Chambers et al. 2008a, b).

Results and discussion
In this research, we describe nucleophilic substitution of pentafluoropyridine with a wide range of nucleophiles and highlight how the resulting products 4-substituted-2,3,5,6-tetrafluoro-pyridine derivatives. Reaction of pentafluoropyridine 1 with malononitrile 2a under basic conditions ($\text{K}_2\text{CO}_3$) in DMF at reflux gave a 4-(malononitrile)-2,3,5,6-tetrafluoropyridine 6a (Fig. 1).

In basic condition, malononitrile 2a deprotonate and carbon nucleophile of malononitrile attack to Para position of pentafluoropyridine 1 and elimination 4-fluor ring pyridine to give 5a. In 5a, hydrogen malononitrile very acidy so essay deprotonate in base solution to give potassium dicyano (perfluoropyridin-4-yl) methanide 6a (Fig. 2). Purification of 6a was achieved by recrystallization in ethanol/acetonitrile. In crystal 6a, two molecule chelate by potassium ion between flour and nitrogen. Identification of chelate 6a was done by...
19F-NMR analysis, in which the resonance attributed to fluorines located Ortho to ring nitrogen has a chemical shift of -83.5 ppm and -84.4 ppm. The corresponding resonance for fluorines located Meta to ring nitrogen in chelate 6a occurred at -135.4 and -139.4 ppm. Four resonances by 19F-NMR indicate displacement of fluorine atoms attached to the Para position of two pyridine ring. The 1H-NMR spectra of compound 6a consisted of a H broad signal at δ = 7.29 ppm for CH malononitrile. X-ray crystallography confirmed the structure of chelate 6a (Figs. 3, 4). A summary of the crystal data, experimental details and refinement results for 6a is given in Table 1.

Reaction of 1-methyl-tetrazole-5-thiol 2b with pentafluoropyridine 1 in acetonitrile at reflux temperature and recrystallisation in ethanol gave 2-ethoxy-3,5,6-trifluoro-4-((1-methyl-1H-tetrazol-5-yl)thio)pyridine 5b (Fig. 5). In 1-methyl-1H-tetrazole-5-thiol, sulfur atom more nucleophilic than other atoms, so install attack at the Para position of the pyridine ring to give 4b. Purification of 4b was achieved by recrystallization in ethanol (accessible and non-toxic solvent). In hot EtOH, Ethoxy group attack at ortho position of 2,3,5,6-tetrafluoro-4-(1-methyl-1H-tetrazol-5-ylthio)pyridine 4b to give 5b (Fig. 6). Identification of 5b was done from 19F-NMR analysis in which the resonance attributed to displacement of fluorine atoms attached only at the Para and ortho position of the pyridine ring. The corresponding resonance for F-3,5 (Meta) in 5b occurs at -131 and -154 ppm and F-6 (ortho) at -88 ppm. Other spectroscopic techniques were consistent with the structures proposed. The protons of the methyl group, were observed at δ = 4.13 ppm. The molecular structure of the 2-ethoxy-3,5,6-trifluoro-4-((1-methyl-1H-tetrazol-5-yl)thio)pyridine obtained has been determined by X-ray.
crystallography (Figs. 7, 8). A summary of the crystal data, experimental details and refinement results for 5b is given in Table 1.

Also, we examined the reaction of pentafluoropyridine 1 with piperazine 2c in the presence of sodium carbonate in CH3CN solvent gave 1,4-bis(perfluoropyridin-4-yl)piperazine 3c (Fig. 9). In basic condition, two nitrogen of the piperazine deprotonation and attack to Para position of pentafluoropyridine and elimination of 4-fluor pyridine ring to give 3e.

Table 1 Crystal data for 6a, 5b and 3c

| Compound | 6a    | 5b    | 3c    |
|----------|-------|-------|-------|
| Formula  | C8F4KN3 | C9H6F2N2OS | C14H6F8N4 |
| Formula weight | 253.21 | 291.26 | 384.24 |
| Wavelength | 0.71073 | 0.71073 | 0.71073 |
| Crystal system | Monoclinic | Monoclinic | Orthorhombic |
| Space group | C2/c | P 21/n | P bc a |
| Unit cell dimensions (Å) | | | |
| a = 11.882 (2) | a = 9.0254 (9) | a = 8.8425 (5) |
| b = 18.857 (4) | b = 7.5269 (8) | b = 11.0779 (4) |
| c = 7.7561 (15) | c = 17.9941 (19) | c = 14.5459 (7) |
| α = 90 | a = 90 | a = 90 |
| β = 108.369 (3) | β = 90 | β = 90 |
| γ = 90 | y = 90 | y = 90 |
| Volume Å³ | 1649.2 (6) | 1206.9 (2) | 1424.86 (12) |
| Z | 8 | 4 | 4 |
| Density (calculated) g cm⁻³ | 2.040 | 1.603 | 1.791 |
| F(000) | 992 | 592 | 768 |
| Crystal size | 0.469 × 0.196 × 0.165 | 0.309 × 0.240 × 0.151 | – |
| Θ range for data | 2.99°–32.57° | 0.999°–1.000° | 3.264°–28.311° |
| Index range | | | |
| −17 < h < 17 | −12 < h < 12 | −11 < h < 11 |
| −12 < k < 12 | −10 < k < 10 | −25 < l < 25 |
| −11 < l < 11 | | |
| Absorption coefficient mm⁻¹ | 0.682 | 0.307 | 0.184 |
| Parameters/restraints | 0 | 0 | 0 |
| Final R1, wR2 (Obs. data) | 0.0249, 0.0781 | 0.0503, 0.0411 | 0.0500, 0.1435 |
| Final R1, wR2 (all data) | 0.0277, 0.0781 | 0.1207, 0.1122 | 0.0690, 0.1681 |
| Goodness of fit on F² (S) | 1.468 | 1.035 | 1.295 |
Purification of 3c was achieved by recrystallization in acetonitrile. The structure of compounds 3c was confirmed by X-ray crystallography and by NMR spectroscopic data. In particular, $^{19}$F-NMR spectroscopy shows the chemical shift of fluorine atoms attached to the Ortho and Meta position are observed respectively at $-97.3$ and $-160.5$ ppm. In $^1$H-NMR, the protons of CH$_2$ piperazine, was observed at $\delta = 4.3$ ppm. The $^{13}$C-NMR spectrum of compound 3c showed 4 distinct resonances in agreement with the proposed structure. The structure of 3c was confirmed by X-ray crystallography (Figs. 11, 12).

**Conclusion**

In conclusion, we showed that pentafluoropyridine can successfully react with a variety of nucleophiles to afford of 4-substituted tetrafluoropyridine. The regioselectivity of nucleophilic substitution in this process may be explained by high nucleophilicity of sulfur, nitrogen or oxygen and activating influence of pyridine ring nitrogen that significantly activate the Para and Ortho sites to itself.

**Experimental**

All materials and solvents were purchased from Merck and Aldrich and were used without any additional purification. The melting points of the products were determined in open capillary tubes using BAMSTEAB Electrothermal apparatus model 9002. The $^1$H NMR spectra were recorded at 300 MHz. The $^{13}$C-NMR spectra were recorded at 75 MHz. The $^{19}$F-NMR spectra were recorded at 282 MHz. In the $^{19}$F-NMR spectra, up field shifts were quoted as negative and referenced to CFCl$_3$. Mass spectra were taken by a Micro mass Platform II: EI mode (70 eV). Silica plates (Merck) were used for TLC analysis.

**Preparation of 2-(perfluoropyridin-4-yl)malononitrile 6a**

Pentafluoropyridine 1 (0.1 g, 0.6 mmol), malononitrile 2a (0.04 g, 0.6 mmol) and potassium carbonate (0.11 g, 1.0 mmol) were stirred together in DMF (5 mL) at reflux temperature for 3 h. The reaction mixture was evaporated to dryness than the solid product was recrystallized from acetonitrile to give 2-(perfluoropyridin-4-yl) malononitrile (0.22 g, 86 %) as a red crystals; mp 260 °C dec. $^{19}$F NMR (acetone): $^1$H NMR (acetone): $\delta$ (ppm) 7.79
Preparation of 2-ethoxy-3,5,6-trifluoro-4-((1-methyl-1H-tetrazol-5-yl)thio)pyridine 5b

Pentafluoropyridine 1 (0.1 g, 0.6 mmol), 1-methyl-1H-tetrazole-5-thiol 2b (0.09 g, 0.6 mmol) and sodium hydrogencarbonate (0.11 g, 1.0 mmol) were stirred together in CH₃CN (5 mL) at reflux temperature for 4 h (monitored by TLC). The solvent was evaporated; water (5 mL) was added and extracted with dichloromethane and ethyl acetate (3 × 5 mL). Solvent evaporation and recrystallisation from ethanol gave 2-ethoxy-3,5,6-trifluoro-4-((1-methyl-1H-tetrazol-5-yl)thio)pyridine 5b (0.2 g, 75 %) as a white crystal; mp 130 °C dec. ¹H NMR (acetone): δ (ppm) 1.37 (3H, m, CH₃), 3.90 (3H, s, N-CH₃), 4.3 (2H, m, CH₂); ¹⁹F NMR (acetone): δ (ppm) −88.6 (1F, m, F-2), −131.4 (1F, m, F-3), −154.8 (1F, m, F-5); ¹³C NMR (acetone): δ (ppm) 14.6, 35.5, 63.2, 64.4, 139.2, 140.5, 142.6, 143.7, 145.9 ppm. MS (EI), m/z (%)= 292 (M⁺), 263, 235, 219, 180, 132, 100, 83, 43.

Preparation of 1,4-bis(perfluoropyridin-4-yl)piperazine 3c

Pentafluoropyridine 1 (0.1 g, 0.6 mmol), piperazine 2c (0.03 g, 0.5 mmol) and sodium hydrogencarbonate (0.11 g, 1.0 mmol) were stirred together in CH₃CN (5 mL) at reflux temperature for 5 h. After complicated reaction, the solvent was evaporated; water (5 mL) was added and extracted with dichloromethane and ethyl acetate (3 × 5 mL). Solvent evaporation and recrystallisation from CH₃CN gave 1,4-bis(perfluoropyridin-4-yl)piperazine 3c (0.2 g, 52 %) as a white crystal; mp 288 °C dec. ¹H NMR (acetone): δ (ppm) 4.30 (8H, s, CH₂); ¹⁹F NMR (acetone): δ (ppm) −97.3 (4F, m, F-2,6), −160.5 (4F, s, CH₂).
m, F-3,5). $^{13}$C-NMR (acetone): δ (ppm) 60.3, 123.7, 127.1, 131.3 ppm. MS (EI), m/z (%) = 384 (M$^+)$, 317, 292, 263, 235, 219, 180, 152, 132, 116, 100, 83, 63, 43.

Authors’ contributions
KB, RH and MTM were involved in the study design and manuscript preparation, data collection, data analysis and revisions. All authors read and approved the final manuscript.

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Competing interests
None declared under financial, general, and institutional competing interests. I wish to disclose a competing interest(s) such as those defined above or others that may be perceived to influence the results and discussion reported in this paper.
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