ISSN 2321-807X

Synthesis of Fluorinated Pyridines as ^{19}F NMR pH Indicators

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ABSTRACT

This research was undertaken to synthesizes and evaluate 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine and 4-(fluoromethyl)-2,6-dimethylpyridine as indicators of ^{19}F NMR pH. A comparison of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine to 4-(fluoromethyl)-2,6-dimethylpyridine showed that 4-(fluoromethyl)-2,6-dimethylpyridine has a large ^{19}F chemical shift to pH, a suitable pKa value and a good water solubility.

Keywords: Fluorination; fluorinated pyridine derivatives; ^{19}F NMR pH indicators; pKa

Council for Innovative Research

Peer Review Research Publishing System

Journal: Journal of Advances in Chemistry

Vol. 10, No. 3

editorjaconline@gmail.com

www.cirjac.com

ISSN 2321-807X

1. INTRODUCTION

The fluorine atom with its relative small size, natural isotope abundance of 100%, high detection sensitivity, and no natural fluorine compounds offers an attractive option as a pH indicator [1] and a subject for biological NMR studies [2]. Fluorinating reagents have been developed by introducing fluorine or fluorine-containing units into many kinds of compounds [3-6]. Fluorinated pyridines are an important class of fluoroheterocyclic compounds [7-9]. Substitution of a hydrogen atom or a hydroxyl group by a fluorine atom has been largely practiced. Another interest is the introduction of a fluorobebnzaldyhyde moiety into a pyridine ring by a Hantzsch condensation reaction. The introduction of fluorine atoms into pyridine base compounds strongly modifies their properties. In this study, we designed, synthesized and evaluated 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine and 4-(fluoromethyl)-2,6-dimethylpyridine to apply as ^{19}F NMR pH indicators.

2. EXPERIMENTAL

The products were characterized by elemental analysis; IR, ^{1}H NMR, and ^{13}C NMR spectra. ^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker Avance 500 and 300 MHz spectrometers (DRX). It is to be mentioned that, in this paper, ^{1}H and ^{13}C chemical shifts are referenced to TMS, as an internal standard, and ^{19}F to a diluted solution of trifluoroacetic acid (TFA) in a capillary column, as an external reference. The elemental analysis was done by a Costech ECS 4010 CHNS-O analyzer. The melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus. Chromatography columns were prepared from Merck silica-gel powder.

Diethyl-2,6-dimethyl-4-(2-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (a) [10].

A mixture of 2-fluorobenzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and anhydrous ammonium carbonate (1 mmol) was stirred in H_2O (2 mL) at 55–60 °C. After the completion of the reaction (TLC monitoring), the mixture was diluted with cold EtOH (10 mL) and filtered to remove the precipitated product which was further purified by re-crystallization in ethanol to obtain a pure product in the form of a pale yellow solid. Yield: 85%, mp 153-155 °C. IR: 3330 (NH- stretching), 1692 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.19 (t, J = 7.1 Hz, 6 H, 2xCH_3CH_2); 2.32 (s, 6 H, 2×CH_3); 4.00- 4.10 (m, 4 H, 2xO–CH_2CH_3); 5.24 (s, 1 H, CH); 6.42 (s, 1 H, NH); 6.89 (t, J = 9.3 Hz, 1 H_{arom}); 6.98 (t, J = 7.4 Hz, 1 H_{arom}); 7.06-7.10 (m, 1 H_{arom}); 7.31 (dd, J = 7.6 Hz, J = 1.6 Hz, 1 H_{arom}). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.45, 19.63, 34.50, 60.07, 103.24, 115.26 ($^{2}J_{C\text{-}F}$ = 23.4 Hz), 124.03, 128.00 ($^{3}J_{C\text{-}F}$ = 8.2 Hz), 131.65, 145.12, 168.08. ^{19}F-NMR (470 MHz, $CDCl_3$): δ -117.29.

Diethyl-2,6-dimethyl-4-(2-fluorophenyl)-pyridine-3,5-dicarboxylate (b) [10].

NaI (0.05 mmol, 0.008 g) was added to a mixture of Hantzsch 1,4-dihydropyridine (1 mmol), H_2O_2 30% (2.2 mmol, 0.25 ml) and acetic acid (3 ml), and the obtained product was stirred at room temperature for an appropriate reaction time. After the completion of the reaction was confirmed by TLC, the product was precipitated by adding ice-water to the reaction mixture. The intended pure pyridine could be collected by simple filtration and subsequent washing with cold water. The crude product was re-crystallized in ethanol to obtain pure product in the form of a pale yellow solid. Yield: 85%, mp 45-47 °C. IR: 2982, 1722, 1557. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.00 (t, J = 7.1 Hz, 6 H); 2.65 (s, 6 H); 4.04 (q, J = 7.1 Hz, 4 H); 7.11 (t, J = 8.6 Hz, 1 H_{arom}); 7.14-7.21 (m, 2 H_{arom}); 7.36-7.40 (m, 1 H_{arom}). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.04, 23.64, 61.73, 115.65 ($^{2}J_{C\text{-}F}$ = 21.2 Hz), 124.13 ($^{3}J_{C\text{-}F}$ = 3.6 Hz), 124.82 ($^{2}J_{C\text{-}F}$ = 16.7 Hz), 127.56, 130.81 ($^{3}J_{C\text{-}F}$ = 7.9 Hz), 131.08 ($^{4}J_{C\text{-}F}$ = 2.6 Hz), 141.45, 156.62, 159.72 ($^{1}J_{C\text{-}F}$ = 246.4 Hz), 167.63. ^{19}F-NMR (470 MHz, $CDCl_3$): δ -114.28.

3,5-Dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine (c) [10].

To a magnetically stirred slurry of $LiAlH_4$ (2.2 mmol, 0.083 g) in anhydrous THF (5.0 mL), a solution of 2,6-dimethyl-4-(2-fluorophenyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.34 g) in anhydrous THF (5.0 mL) was added drop-wise at 0 °C for 5 minutes. The reaction mixture was further stirred magnetically for 2.5 hours at 30 °C. Excess $LiAlH_4$ was quenched by adding a saturated aqueous sodium sulfate solution, and the reaction mixture was filtered. The solid cake was washed with THF, and the filtrate was concentrated under reduced pressure. The latter was extracted with chloroform (2×25 mL) and water (12.5 mL) and dried Na_2SO_4, and the organic layer was concentrated under reduced pressure to give a crud mass, which was then chromatographed over an SiO_2 column using chloroform/ethyl acetate (30:70) as an eluent to give as pale yellow oil. Yield: 83% IR: 3161 (OH-stretching). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.71 (s, 6 H, 2×CH_3), 3.70 (s, 2 H, 2×OH), 4.32-4.45 (m, 4 H, 2×CH_2), 7.22-7.27 (m, 3 H_{arom}), 7.44-7.45 (m, 1 H_{arom}). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.50, 58.67, 115.32 ($^{2}J_{C\text{-}F}$ = 21.0 Hz), 124.08 ($^{4}J_{C\text{-}F}$ = 2.6 Hz), 124.95 (J = 20 Hz), 130.14 ($^{3}J_{C\text{-}F}$ = 3.6 Hz), 130.25 ($^{3}J_{C\text{-}F}$ = 7.9 Hz), 132.07, 143.72, 156.50, 159.59 ($^{1}J_{C\text{-}F}$ = 246 Hz). ^{19}F-NMR (470 MHz, $CDCl_3$): δ -114.69, Anal. Calcd. for $C_{15}H1_6FNO_2$: C, 68.9; H, 6.2, N 7.3 found: C, 69.1; H, 6.2, N 7.1.

2,6-Dimethylpyridine-N-oxide (d).

A solution of m-CPBA (13.0 g, 75 mmol) in acetone (60 mL) was added to 2,6-dimethylpyridine (5.0 g, 47 mmol) in acetone (60 mL) over 10 minutes. The mixture was stirred for 90 minutes then cooled in ice for 30 minutes. Ice-cold ether (20 mL) was added, and hydrogen chloride gas bubbled through the solution for 10 minutes. The solid was filtered and washed with ether (2x20 mL). Hydrochloride salt was dissolved in water (10 mL), and the aqueous solution was made basic with sodium hydrogen carbonate (pH>10). The aqueous solution was then extracted with chloroform (3x20 mL), and the solvent was evaporated to give 2,6-dimethylpyridine-N-oxide as an oily hygroscopic liquid. Yield: 4.5 g (78%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 6 H, 2xCH_3), 7.01 (d, 2 H_{arom}), 7.60 (t, 1 H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.22, 123.10, 147.50, 157.90.

ISSN 2321-807X

N-Methoxy-2,6-dimethylpyridinium tetrafluoroborate (e) [11].

A solution of 2,6-dimethylpyridine-N-oxide (4.0 g, 32 mmol) in dry dichloromethane (60 ml) was added to trimethyloxonium tetrafluoroborate (4.7 g, 32 mmol). The reaction mixture was stirred for 90 minutes at room temperature. The solvent was removed in vacuous to obtain N-methoxy-2,6-dimethylpyridinium tetrafluoroborate as a white hygroscopic solid. Yield: 6.2 g (85%). ^{1}H-NMR (300 MHz, D_2O):δ 2.70 (s, 6 H, 2xCH_3), 4.21 (s, 3 H, OCH_3), 7.71 (d, *J* = 8.4 Hz, 2 H_{arom}), 8.15 (t, *J* = 8.4 Hz, 1 H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): 16.40, 6750, 123.70, 137.50 157.90.

4-(Hydroxymethyl)-2,6-dimethylpyridine (f).

A solution of N-methoxy-2,6-dimethylpyridinium tetrafluoroborate (6.1 g, 27 mmol) in methanol (70 mL) was heated under reflux. To this mixture was added ammonium persulfate (1.5 g, 6.6 mmol) in water (6 mL). After a 30 minute reflux, a further portion of ammonium persulfate (0.50 g, 2.2 mmol) in water (2 mL) was added, and then heating under reflux continued for another 30 minutes. The mixture was filtered and the solvent was evaporated to give an oily brown liquid (1.7 g), which was chromatographed on a silica gel. Elution with chloroform:methanol (9:1) gave 4-(hydroxymethyl)-2,6-dimethylpyridine as a colourless oily liquid. Yield: 1.5 g (41%) ^{1}H-NMR (300 MHz, D_2O): δ 2.60 (s, 6 H, 2xCH_3), 4.74 (s, 2 H, CH_2OH), 7.47 (s, 2 H_{arom}). ^{13}C-NMR (75 MHz, D_2O): δ 24.53 (2xCH_3), 62.94 (CH_2OH), 121.34 (2xCH_{arom}), 149.08 (1xC_{arom}), 153.12 (2xC_{arom}), Anal. Calc. for $C_8H_{11}NO$: C 70.0, H 8.08, N 10.2, found: C 70.2, H 7.9, N 10.1.

4-(Bromomethyl)-2,6-dimethylpyridine (g).

A solution of 2-(hydroxymethyl)-2,6-dimethylpyridine (1.5 g, 11 mmol) in 48% HBr (35 mL) was heated under reflux for 4 hours. The solvent was evaporated in vacuo to give a brown thick paste which was washed with cold absolute ethanol (3x15 mL), then dissolved in water (10 mL) and made basic (pH>10) with solid sodium hydrogen carbonate. The aqueous solution was extracted with ether (3x20 mL) and dried ($MgSO_4$). After evaporation of the solvent *in vacuo* the crude product (2.2 g) was chromatographed on a silica gel. Elution with chloroform:methanol (9:1) gave 4-(bromomethyl)-2,6-dimethylpyridine as a white oily liquid. Yield: 1.8 g (82%). ^{1}H-NMR (300MHz, $CDCl_3$): δ 2.52 (s, 6 H, 2xCH_3), 4.32 (s, 2 H, CH_2Br), 6.97 (s, 2 H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.45 (2xCH_3), 30.92 (CH_2Br), 120.12 (2xCH_{arom}), 146.65 (1xC_{arom}), 158.56 (2xC_{arom}). Anal. Calc. for $C_8H_{10}BrN$: C 48.3, H 5.4, N 6.9, found: C 48.0, H 5.6, N 6.8.

4-(Fluoromethyl)-2,6-dimethylpyridine (h).

A solution of 4-(bromomethyl)-2,6-dimethylpyridine (0.50 g, 2.5 mmol) in dichloromethane (5 mL) was added to activate TBAF (0.80 g, 3.1 mmol). The solvent was then evaporated immediately in vacuous and the mixture was stirred for 8 hours at room temperature in a closed vessel. The reaction mixture was extracted with pentane (3x5 mL) to give a crude product (0.30 g) which was chromatographed on a silica gel. elution with chloroform/methanol (9:1) gave 4-(fluoromethyl)-2,6-dimethylpyridine as a white oily liquid. Yield: 0.16 g (45%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 6 H, 2xCH_3), 5.34 (d, 2 H, *J* = 47.3 Hz, CH_2F), 6.93 (s, 2 H_{arom}). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.54 (2xCH_3), 80.68 (d, *J* = 171.7 Hz, CH_2F), 117.12 (d, *J* = 6.1 Hz, 2xCH_{arom}), 145.90 (d, *J* = 17.2 Hz, 1xC_{arom}), 158.23 (2xC_{arom}). ^{19}F-NMR (282.2 MHz, $CDCl_3$): δ -222.52 (t, *J* = 47.3 Hz, CH_2F). Anal. Calc. for $C_8H_{10}FN$: C 68.9, H 7.3, N 10.0, found: C 69.1, H 7.2, N 10.1.

3. RESULTS AND DISCUSSTION

The electronic effect of protonation and deprotonation on the nitrogen of a pyridine ring is communicated to carbons 2 and 4 *via* a 6- electron system. Thus, a NMR active nucleus situated at 2 - or 4 – of a pyridine ring would be expected to experience significant changes due to pH variation in the electronic environment. To achieve this goal, the initial candidate for the synthesis of these target molecules was 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine (Scheme 1).

Scheme 1. **Synthesis of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine**

The ^{19}F NMR chemical shift of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine as a function of pH values are shown in Fig. 1 [12]. Acidity determinations were carried out in an aqueous solution within a pH range from 2.0 to 10.0 that consisted of one singlet. The direction of the ^{19}F signals showed progressive shifts to higher magnetic fields with decreasing pH values, which is in contrast to what is observed normally, reflecting some parameters such as the paramagnetic effect of fluorine atoms. However, the direction of ^{19}F chemical shift with pH was not crucial in this study.

ISSN 2321-807X

The averaged pKa value of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine was found to be 5.3 [13]. The low pH sensitivity (~ o.6 ppm) due to the distance of the fluorine from the nitrogen site and the pKa value (5.3) meant that 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine was unsuitable as a pH indicator.

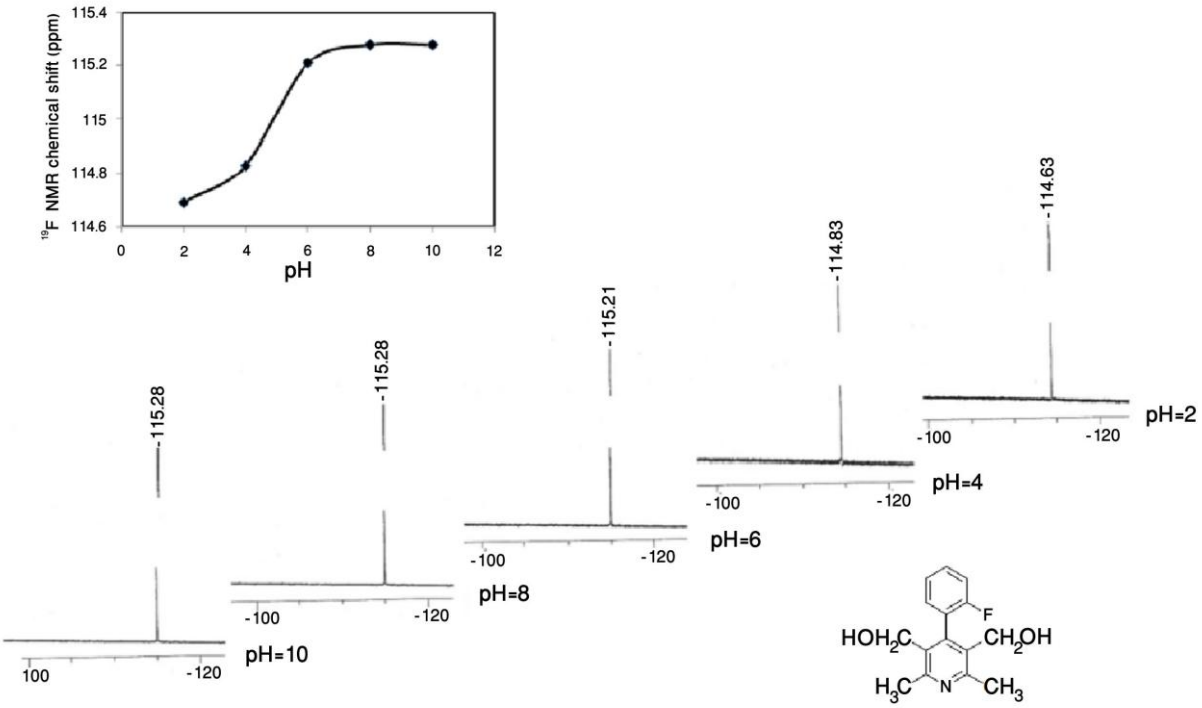

Fig. 1 ^{19}F NMR signals of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine at different pH values

To make a comparison with 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine, the synthesis of 4-(fluoromethyl)-2,6-dimethylpyridine was undertaken (Scheme 2).

Scheme 2. Synthesis of 4-(fluoromethyl)-2,6-dimethylpyridine

The ^{19} F NMR of 4-(fluoromethyl)-2,6-dimethylpyridine showed large chemical shift differences between acid and base forms (Fig. 2) [12]. In contrast to what is observed normally, the signals showed progressive shifts to higher magnetic fields with a decrease of pH, reflecting some parameters which uniquely influence fluorine atoms. The average pKa value for 4-(fluoromethyl)-2,6-dimethylpyridine was found to be 6.3 [13]. Water solubility, suitable pKa value and large ^{19}F chemical shift sensitivity to pH (~2.6 ppm) make a suitable pH indicator out of 4-(2-fluorophenyl)-2,6-dimethylpyridine.

ISSN 2321-807X

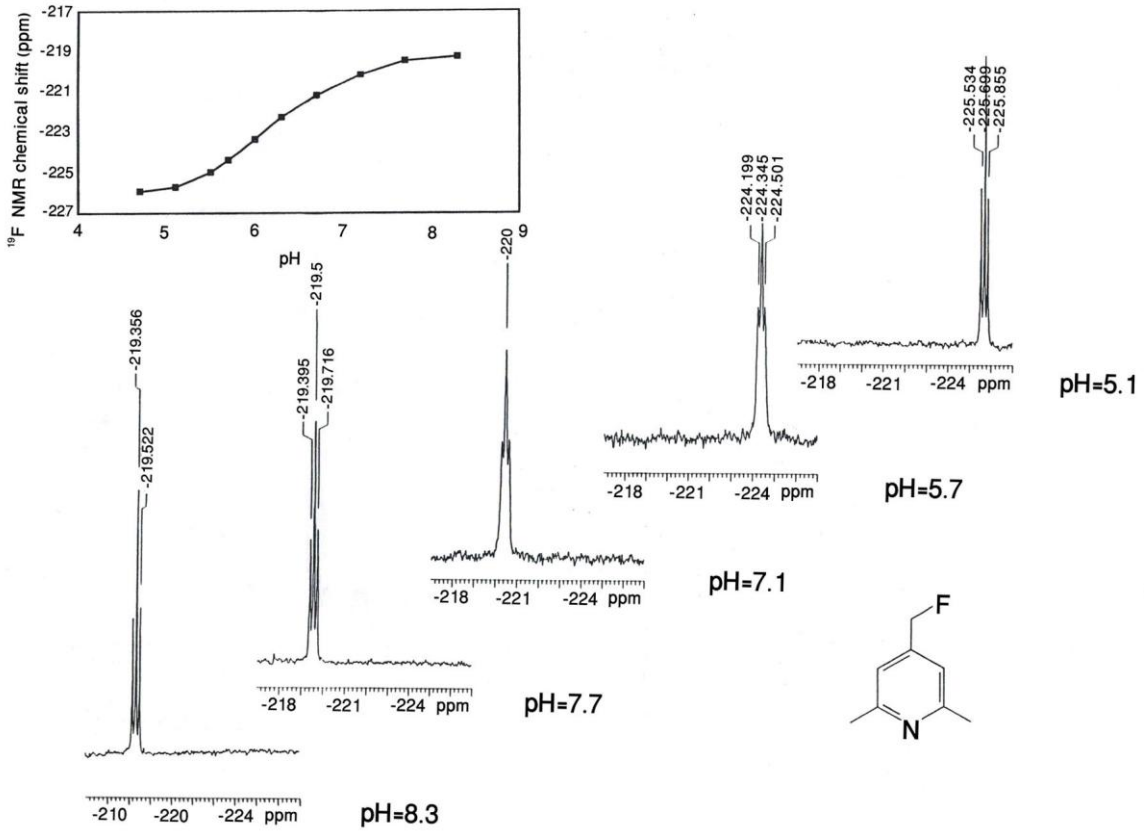

Fig. 2 ^{19}F NMR signals of 4-(fluoromethyl)-2,6-dimethylpyridine at different pH values

CONCLUSIONS

This paper reports the synthesis of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine and 4-(fluoromethyl)-2,6-dimethylpyridine and chractrization of their pH sensitivity. The results indicate that ^{19}F NMR pH sensitivity, pKa and water solubility of 4-(fluoromethyl)-2,6-dimethylpyridine are higher than those of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine.

ACKNOWLEDGEMENT

The authors thank the Research Council of Yazd University for the financial support.

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[12] A solution of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine (3 mmol) in D2O was titrated between acid and base forms and monitored by ^{19}F NMR. The pH was initially set at 2 by adding DCl (0.1 M) and then driven to pH 10 by adding NaOD (0.1 M). The ^{19}F NMR signals at different pH values were recorded.

^{19}F NMR signals of 4-(fluoromethyl)-2,6-dimethylpyridine at different pH values were recorded as described above. A plot of ^{19}F chemical shift versus pH of 4-(fluoromethyl)-2,6-dimethylpyridine is presented in Fig.2.

[13] To a solution of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine (3 mmol) in water was added NaOH (0.1 M) at a pH of 12. The solution was then titrated to pH 1 with HCl (0.1 M). The pH of the solution was measured at regular intervals using a pH electrode and a meter. The pKa was calculated at 8 different pH values about the point of inflection using the equation:

Acidity determination of 4-(fluoromethyl)-2,6-dimethylpyridine was carried out as described above.