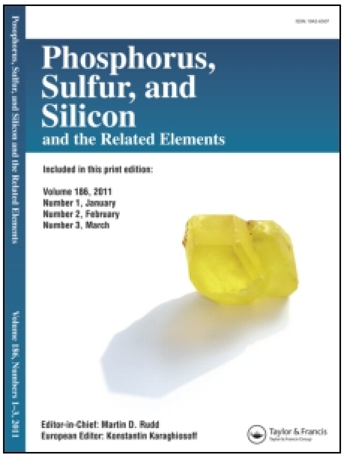

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Synthesis of Some Fluorinated Pyridines Using Tetrabutylammonium Fluoride

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Some bromo- and chloromethyl pyridines were synthesized using radical substitution reactions. Further reaction of these halopyridines with activated tetrabutylammonium fluoride under mild conditions gave the related fluorinated pyridines. The yields of products following recrystallization were of the order of 30–93%. ^{1}H, ^{13}C, *and* ^{19}F *spectroscopies together with elemental analysis were used characterize products.*

Keywords FlurometHyl; pyridine; tetrabutylammonium fluoride

INTRODUCTION

Introduction of fluorine at the methyl site of substituted pyridines has an important role in biological systems due to high NMR sensitivity of ^{19}F and the lake of natural ^{19}F-containing metabolites compared to other nuclei. Alkali metal fluorides have been traditionally used for the synthesis of fluromethylpyridines.[1–8] However preparation of fluorinated pyridines by using alkali metal reagents require vigorous reaction conditions due to their insolubility in organic solvents. Synthesis of fluorinated pyridines under moderate conditions with an associated relatively high yield could be achieved through the use of the alternative fluorinating agents such as tetraalkylammonium fluorides. These reagents provide a soluble form of fluoride in polar aprotic organic solvent systems and their reactions are fast at r.t.[9] The nucleophilicity of the fluoride ion in these situations is increased relative to alkali metal fluoride as a consequence of reducing the effect of ion pairing by replacing the metal ion with a large organic cation. However the difficulty in this approach is that these reagents are very basic and hence

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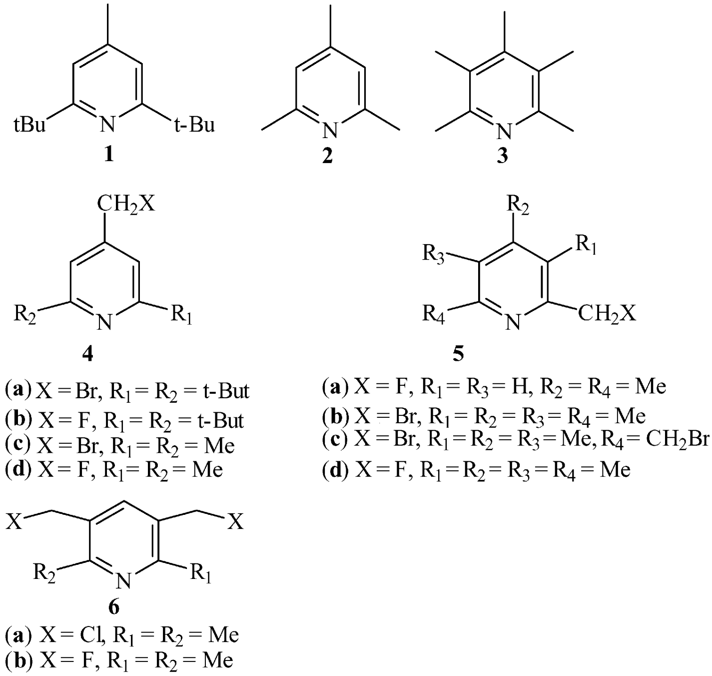
promote an elimination as well as a displacement reaction. The elimination reaction is not significant in this work, as benzylic substitution is required. The purpose of the present work is to extend the preparation method of fluorinated pyridines using Tetrabutylammonium Fluoride (TBAF).

RESULTS AND DISCUSSION

The 2- or 4-position of **1**, **2**, and **3**, for making brominated pyridines, were functionalized by bromine using NBS to give **4a** (93%), **4c** (4%), and **5b** (60%). In contrast reaction of 4-methylpyridine with NBS was unsuccessful. In the reaction of 2,3,4,5,6-pentamethylpyridine, **3**, with NBS, some 2,6-bis(bromomethyl)-3,4,5-trimethylpyridine **5c** were also isolated (Scheme 1). In the case of **2** and **3** it was observed that the 2-bromomethyl compounds were obtained in preference to the 4-derivative. Only a small amount of 4-bromomethyl compound (4–7%) was detected by ^{1}HNMR. As a result an alternative route using 4-(hydroxymethyl)-2,6-dimethylpyridine[10] was adopted for preparation



SCHEME 1

of **4c** (82%). The preference for 2-bromination over 4- is consistent with the lack of success in brominating 4-methylpyridine. All fluorinated compounds were prepared by the reaction of the appropriate substituted bromo- or chloromethylpyridines with activated TBAF as a common fluoride ion source. The ^{1}HNMR spectra of the synthesized compounds are simple and show two distinct aliphatic and aromatic proton rersonances. The aromatic protons resonate at 6.93–7.58 ppm and the methyl protons resonate as a singlet or doublet at 1.35–2.54 ppm. The protons of the CH_2Br and CH_2Cl groups appear as a singlet at 4.32–4.58 ppm. However the CH_2F protons resonate as a doublet at 5.51–5.34 ppm.

EXPERIMENTAL

Activated TBAF was prepared according to the literature.[11] TBAF hydrate (0.30 g) was heated in a 25-mL flask with stirring at 40–45°C under vacuum (1 mm Hg) for 48 h until constant weight (0.20 g) was obtained. Column chromatography was carried out using Merck silica gel #9385 with a loading ratio of 1:60 (crude material:adsorbent). Solvent ratio is given as volume percentages. The precursors **1** and **2** were commercially available and **3** was synthesized according to the literature.[12–14] ^{1}H and ^{13}C NMR spectra were recorded at 25°C on Varian VXRS 300 MHz spectrometer using Me_4Si (TMS) as an internal standard and $CDCl_3$ as a solvent. ^{19}F NMR spectra were referenced to external fluorotrichloromethane in $CDCl_3$. Reaction courses were monitored by thin layer chromatography.

4-(Bromomethyl)-2,6-di-*tert*-butylpyridine (4a)

A mixture of 2,6-di-*tert*-butyl-4-methylpyridine, **1**, (0.21 g, 1.0 mmol), NBS (0.18 g, 1 mmol), and dibenzoyl peroxide (0.025 g, 1 mmol) in dry carbon tetrachloride (15 mL) was refluxed under N_2 for 3 h. The mixture was then cooled in an ice bath and the precipitated succinimide was removed by filtration. The solvent was evaporated to give a brown oily mixture. This mixture was dissolved in carbon tetrachloride (15 mL). NBS (0.036 g, 0.20 mmol) and dibenzoyl peroxide (0.0050 g, 0.021 mmol) added and refluxed under N_2 for another 2 h. The crude product was distilled at 90–110°C/2 mm Hg to give pure compound **4a** (93%).

^{1}H NMR ($CDCl_3$): δ (ppm): 1.35 (18H, s, 2 × t-butyl), 4.38 (2H, s, CH_2Br), 7.09 (2H, s, Ar). ^{13}C NMR ($CDCl_3$): δ (ppm): 30.1 (2 × t-butyl), 32.2 (CH_2Br), 37.7 (2 × C), 115.3 (2 × CH, Ar), 145.7 (1 × C, Ar), 168.4 (2 × C, Ar).

2,6-Di-*tert*-Butyl-4-(Fluoromethyl)pyridine (4b)

A solution of 4-(bromomethyl)-2,6-di-*tert*-butylpyridine, **4a**, (0.15 g, 0.53 mmole) in dry dichloromethane (5.0 mL) was added to activated tetrabutylammonium fluoride (0.15 g, 0.57 mmol) under an inert atmosphere at r.t. The solvent was removed under reduced pressure and the mixture was kept at 25°C for 8 h in a closed vessel. The reaction mixture was extracted with pentane (5 × 10 mL) and the solvent evaporated to give a crude material. Chromatography on silica gel using hexane as an eluent gave the desired compound **4b** (0.057 g, 48%) as a white oily product.

^{1}H NMR ($CDCl_3$): δ (ppm): 1.35 (18H, s, 2 × t-butyl), 5.42 (2H, d, J = 48.0 Hz, CH_2F), 7.18 (2H, s, Ar).

^{13}C NMR ($CDCl_3$): δ(ppm): 30.1 (2 × t-butyl), 38.0 (2 × C), 82.6 (d, J = 169.2 Hz, CH_2F), 112.7 (d, J = 7.4 Hz, 2 × CH, Ar), 144.8 (d, J = 18.3 Hz, 1 × C, Ar), 168.1 (2×C, Ar).

^{19}F NMR ($CDCl_3$): δ(ppm): −217.4 (t, J = 48.2 Hz, CH_2F).

Anal. cald. for $C_{14}H_{22}FN$: C, 75.4; H, 9.9; F, 8.5; N, 6.3. Found: C, 75.4; H, 9.6; F, 8.2; N, 5.9%.

4-(Bromomethyl)-2,6-Dimethylpyridine (4c)

A solution of 4-(hydroxymethyl)-2,6-dimethylpyridine[10] (1.5 g, 11 mmol) in 48% HBr (35 mL) was refluxed for 4 h. The solvent was evaporated under reduced pressure to give a brown thick paste that was washed with cold absolute ethanol (3 × 15 mL). The residue was dissolved in water (10 mL) and made basic (pH > 10) with sodium hydrogen carbonate. The aqueous solution was extracted with diethyl ether (3 × 20 mL) and dried with $MgSO_4$. After evaporation of the solvent the crude product was chromatographed on silica gel. Elution with chloroform:methanol (9:1) gave the product **4c** as a white oily liquid (1.8 g, 82%).

^{1}H NMR ($CDCl_3$): δ (ppm): 2.52 (6H s, 2 × CH_3), 4.32 (2H, s, CH_2Br), 6.97 (2H, s, Ar).

^{13}C NMR ($CDCl_3$): δ (ppm): 24.4 (2 × CH_3), 30.9 (CH_2Br), 120.1 (2 × CH, Ar), 146.6 (1 × C, Ar), 158.5 (2 × C, Ar).

Anal. cald. for $C_8H_{10}BrN$: C, 48.0; H, 5.7; Br, 39.6; N, 6.8. Found: C, 48.3; H, 5.4; Br, 39.8; N, 6.9%.

4-(Fluoromethyl)-2,6-Dimethylpyridine (4d)

A solution of 4-(bromomethyl)-2,6-dimethylpyridine, **4c**, (0.50 g, 2.5 mmol) in dichloromethane (5 mL) was added to activated TBAF (0.8 g, 3.1 mmol). The solvent was then evaporated in vacuo and the mixture stirred for 8 h at r.t. in a closed vessel. The reaction mixture was extracted with pentane (5 × 5 mL) to give the crude product, which was chromatographed on silica gel. Elution with chloroform: methanol (9:1) afforded the desired compound **4d** as a white oily liquid (0.16 g, 45%).

^{1}H NMR ($CDCl_3$): δ (ppm): 2.54 (6H s, 2 × CH_3), 5.34 (2H, d, J = 47.3 Hz, CH_2F), 6.93 (1H, s, Ar).

^{13}C NMR ($CDCl_3$): δ(ppm): 24.5 (2 × CH_3), 80.6 (d, J = 171.7 Hz, CH_2F), 117.1 (d, J = 6.1 Hz, 2 × CH, Ar) 145.9 (d, J = 17.2 Hz, 1 × C, Ar), 158.2 (2 × C, Ar).

^{19}F NMR ($CDCl_3$): δ(ppm): −222.5 (t, J = 47.3 Hz, CH_2F).

Anal.cald.for $C_8H_{10}FN$: C, 69.1; H, 7.2; F, 13.6; N, 10.1. Found: C, 68.9; H, 7.3; F, 13.8; N, 10.0%.

2-(Fluoromethyl)-4,6-Dimethylpyridine (5a)

2-(bromomethyl)-4,6-dimethylpyridine[15] (0.2 g, 1 mmol) in dry dichloromethane (5.0 mL) was added to activated tetrabutylammonium fluoride (0.31 g, 1.2 mmol) under an inert atmosphere at r.t. The solvent was removed under reduced pressure and the mixture was stirred for 48 h in a closed vessel at r.t. The reaction mixture was extracted with pentane (5 × 10 mL) and the combined extracts were evaporated under reduced pressure to give the crude product. The crude product was chromatographed on silica gel. Elution with a mixture of acetonitrile:dichloromethane:hexane (1:2:1) gave the pure product **5a** (0.050 g, 35%). A 60% yield was achieved by using excess (1:3) of TBAF. b.p. 50–54°C/1 mm Hg.

^{1}H NMR ($CDCl_3$): δ (ppm): 2.34 (3H, s, CH_3), 2.51 (3H, s, CH_3), 5.42 (2H, d, J = 47.2 Hz, CH_2F), 6.94 (1H, s, Ar), 7.09 (1H, s, Ar).

^{13}C NMR ($CDCl_3$): δ (ppm): 21.1 (CH_3), 24.2 (CH_3), 84.7 (d, J = 168.7 Hz, CH_2F), 118.6 (d, J = 5.8 Hz, CH, Ar), 123.6 (CH, Ar), 148.4 (C, Ar), 155.5 (d, J = 20.3 Hz, C, Ar), 157.9 (C, Ar).

^{19}F NMR ($CDCl_3$) : δ (ppm): −220.4 (t, J = 47.1 Hz, CH_2F).

Anal. cald. for $C_8H_{10}FN$: C, 69.1; H, 7.2; F, 13.6; N, 10.1. Found: C, 68.9; H, 7.3; F, 13.7; N, 10.1%.

2-(Bromomethyl)-3,4,5,6-Tetramethylpyridine (5b)

A mixture of 2,3,4,5,6-pentamethylpyridine, **3**, (0.80 g, 4.8 mmol), NBS (0.90 g, 5 mmol), and dibenzoyl peroxide (0.025 g, 0.10 mmol) in dry carbon tetrachloride (20 mL) was refluxed under N_2 atmosphere for 3 h. The mixture was cooled in an ice bath and the precipitated succinimide removed by filtration. The solvent was evaporated in vacuo at r.t. to give a brown oily crude product.

^{1}H NMR spectroscopy showed that the product is a mixture of 70% 2-(bromomethyl)-3,4,5,6-tetramethylpyridine ($\delta = 4.55$ ppm, CH_2Br) and 20% 2,6-bis(bromomethyl)-3,4,5,-trimethylpyridine ($\delta = 4.51$ ppm, CH_2Br). Chromatography on silica gel and elution with acetonitrile:hexane:dichloromethane (2:1:1) gave 2-(bromomethyl)-3,4,5,6-tetramethylpyridine **5b** (0.54 g, 60%).

^{1}H NMR ($CDCl_3$) : δ (ppm): 2.20 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.52 (3H, s, CH_3), 2.60 (3H, s, CH_3), 4.55 (2H, s, CH_2Br).

^{13}C NMR ($CDCl_3$): δ(ppm): 14.8 (CH_3), 15.5 (CH_3), 21.3 (CH_3), 24.7 (CH_3), 30.8 (CH_2Br), 122.9 (C, Ar), 125.1 (C, Ar), 144.8 (C, Ar), 154.9 (C, Ar), 156.7 (C, Ar).

Anal. cald. for $C_{10}H_{14}BrN$: C, 52.6; H, 6.1; Br, 35.2; N, 6.1. Found: C, 52.9; H, 6.2; Br, 34.8; N, 5.9%. 2,6-bis(bromomethyl)-3,4,5-trimethylpyridine **5c** was also isolated (0.32 g 30%).

^{1}H NMR ($CDCl_3$) : δ(ppm): 2.41 (3H, s, CH_3), 2.59 (6H, s, 2 × CH_3), 4.51 (2H, s, 2 × $CHBr_2$).

^{13}C NMR ($CDCl_3$) : δ (ppm): 15.5 (2 × CH_3), 21.3 (CH_3), 31.4 (2 × CH_2Br), 127.1 (2 × C, Ar), 144.8 (C, Ar), 156.7 (2 × C, Ar).

Anal. cald. for $C_{10}H_{13}Br_2N$: C, 39.1; H, 4.2; Br, 52.1; N, 4.6. Found: C, 38.9; H, 4.2; Br, 51.8; N, 4.9%.

2-(Fluoromethyl)-3,4,5,6-Tetramethylpyridine (5d)

A solution of 2-(bromomethyl)-3,4,5,6-tetramethylpyridine, **5b**, (0.60 g, 2.6 mmol) in dry dichloromethane (5 mL) was added to activated TBAF (1.1 g, 4.2 mmol). The solvent was removed under reduced pressure and the reaction mixture was stirred for 8 h at 25°C in a closed vessel. The product was extracted with dry pentane (5 × 5 mL) then evaporated to give a crude yellow oily product. Distillation at 150°C/ 22 Hg gave white crystals of 2-(fluoromethyl)-3,4,5,6-tetramethylpyridine **5d** (0.2 g, 45%).

^{1}H NMR ($CDCl_3$) : δ (ppm): 2.21 (3H s, CH_3), 2.33 (3H, d, $J = 2.1$ Hz, CH_3), 2.51 (3H, d, $J = 3.3$ Hz, CH_3), 2.59 (3H, d, $J = 2.1$ Hz, CH_3), 5.51 (2H, d, $J = 48.2$ Hz, CH_2F).

^{13}C NMR ($CDCl_3$): δ (ppm): 15.1 (CH_3), 15.4 (CH_3), 22.2 (CH_3), 23.5 (CH_3), 79.2 (d, $J = 172.3$ Hz, CH_2F), 125.2 (d, $J = 22.7$ Hz, C, Ar), 128.1 (C, Ar), 146.1 (C, Ar), 154.2 (d, $J = 6.3$ Hz, C, Ar), 156.7 (C, Ar).

^{19}F NMR ($CDCl_3$): δ (ppm): −206.9 (t, $J = 48.1$ Hz, CH_2F).

Anal. cald. for $C_8H_{14}FN$: C, 71.8; H, 8.4; F, 11.4; N, 8.4. Found: C, 71.8; H, 8.4; F, 11.4; N, 8.3%.

3,5-Bis(chloromomethyl)-2,6-Dimethylpyridine (6a)

Freshly distilled thionyl chloride (5.0 g) was added to the 3,3-bis(hydroxymethyl)-2,6-dimethylpyridine (0.90 g, 5.4 mmol) and cooled at 0°C. The mixture was kept at 0°C for 15 min and then heated under reflux for 1 h. The excess thionyl chloride was removed in vacuo to give a thick brown paste. Ice-cooled water (10 mL) was added and the mixture was made basic ($pH > 11$) with 10% sodium hydroxide solution. The cream precipitate was extracted with diethyl ether to give a crude product (0.89 g, 81%), which was purified by distillation at 150–160°C/1 mm Hg to give white crystals **6a** b.p.: 150°C/1 mm Hg.

^1H NMR ($CDCl_3$): δ(ppm): 2.61 (6H, s, 2 × CH_3), 4.58 (4H, s, 2 × CH_2Cl), 7.54 (1H, s, Ar). ^{13}C NMR ($CDCl_3$) : δ (ppm): 24.2 (2 × CH_3), 45.9 (2 × CH_2Cl), 131.4 (2 × C, Ar), 141.0 (CH, Ar), 159.6 (2 × C, Ar).

3,5-Bis(fluoromethyl)-2,6-Dimethylpyridine (6b)

A solution of 3,5-bis(chloromomethyl)-2,6-dimethylpyridine, **6a**, (0.12 g, 0.59 mmol) in dichloromethane (2 mL) was added to the activated TBAF (0.22 g, 0.84 mmol). The solvent was removed in vacuo and the mixture stirred for 48 h at 25°C in a closed vessel. The reaction mixture was extracted with dry pentane (5 × 5 mL) and the organic extracts were evaporated in vacuo to give a yellow oily crude product. Chromatography silica gel and elution with acetonitrile:hexane:dichloromethane (2:3:5) gave 3,5-bis(fluoromethyl)-2,6-dimethylpyridine, **6b**, (0.045, 45%).

^1H NMR ($CDCl_3$) : δ (ppm): 2.56 (6H, s, 2 × CH_3), 5.41 (4H, d, $J = 48.3$ Hz, 2 × CH_2F), 7.58 (H, s, Ar).

^{13}C NMR ($CDCl_3$): δ(ppm): 21.6 (2 × CH_3), 81.8 (d, $J = 167.4$ Hz, 2 × CH_2F), 127.1 (d, $J = 16.5$ Hz, 2 × C, Ar), 136.4 (d, $J = 7.5$ Hz, CH, Ar), 156.9 (2 × C, Ar).

Anal. cald. for $C_9H_{11}F_2N$: C, 63.2; H, 6.4; F, 22.2; N, 8.2. Found: C, 62.8; H, 6.6; F, 22.1; N, 7.9%.

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