Synthesis of 2-*n*-Butyl-3-fluoropyrrole Derivatives

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A new series of *N*-substituted 2-*n*-butyl-3-fluoropyrroles were prepared by a simple one-pot reaction designed of retrosynthesis. α,α-Difluoro-γ-iodo-γ-(trimethylsilyl)propyl *n*-butyl ketone, a component precursor molecule to 2-*n*-butyl-3-fluoropyrroles, was prepared with Cu(0) catalyst. It reacted with various primary amines to yield *N*-substituted 2-*n*-butyl-3-fluoropyrroles. The products were synthesized *via* a one-pot reaction scheme between α,α-Difluoro-γ-iodo-γ-(trimethylsilyl) propyl *n*-butyl ketone and primary amines in excess (≥ 5 molar equivalence), which eliminate the need of KF required in obtaining *n*-butyl-1*H*-3-fluoropyrrole. The yield of products depended reversely on spatial bulkness around *N*-binding carbon.

Key Words: *N*-Substituted 2-*n*-butyl-3-fluoropyrroles, α,α-Difluoro-iodomethyl *n*-butylketone, 2,α,α-Difluoro-γ-iodo-γ-(trimethylsilyl)propyl *n*-butylketone, 2-Butyl-3,3-difluoro-5-trimethylsilyl pyrroline

Introduction

Organic compounds with fluorine atoms have been known to enhance physiological activities.[1,2,3] It has been reported that C-F bond is stable enough to survive through biological systems, acts as a receiver for hydrogen bond,[4] and has increased lipophilicity.[5] Recently, selective fluorination on pyrroles has drawn much attention as an efficient method for modifying and improving the reactivity and selectivity of organic molecules, which have not only medical applications such as anti-microbial,[6] anti-tumor,[7] hypertension,[8-11] *etc.* but industrial applications of chemistry as well.[12-16] In general, the reactions of xenon with pyrrole derivatives, 1,3-dipolarcyclo addition, and ring extension of a 2-azido-3,3-difluorocyclobutane are reported as synthetic methods to prepare α-fluoropyrrole derivatives. In order to prepare β-fluoropyrrole, reaction of bromopyrroles with NFSi (*N*-fluoro-o-benzen-edisulfomide), photosynthesis of pyrrole-α-diazonium tetrafluoroborate, *etc.* have been reported.[17,18] There are, on the contrary, much less of examples with β-fluoropyrrole derivatives than those with α-analogues, possibly because of lack of suitable synthetic strategy yet. Recently, we have noticed that the report of Qiu *et al.* on the synthesis of β-fluoropyrrole would be a great method in making. That is, the detailed chemistry of α,α-difluoro-iodomethylketone needs to be explored further, which would generalize the synthesis of branched *N*-substituted pyrroles of pharmaceutical importance.

In general, when an electron withdrawing group is attached to the α,β-unsaturated system, photochemical reactions induce α,α-difluoro-iodomethylketone being added to the unsaturated bond. In the case that an electron donating group such as 1-pentane is substituted, Pd(0) has been used the most extensively.[19] Thus, Qiu, *et al.* let α,α-difluoro-α-iodomethyl *n*-butylketone and α,α-difluoro-α-iodomethyl *n*-hexylketone be added to trimethylvinylsilane either in the presence of catalytic amount of palladium(0) or *via* UV irradiation to obtain α,α-difluoro-γ-iodo-γ-trimethylsilyl *n*-butylketone and α,α-difluoro-γ-iodomethyl *n*-hexylketone, respectively.[17,18] These molecules underwent a further reaction with aqueous ammonium hydroxide to yield 2-alkyl-3,3-difluoro-γ-trimethylsilyl pyrrolines that were in sequence converted to β-fluoropyrroles.[20] It is, however, a tremendous challenge to scale up both Pd(0) catalytic reaction or photochemical one to obtain those starting molecules. Therefore, Cu(0) catalyst has been tried for large scale preparation of them, and it was successful in our previous work.[21] In this study, we obtained *N*-substituted 2-*n*-butyl-3-fluoropyrrole derivatives by reacting primary amines with α,α-difluoro-γ-iodo-γ-(trimethylsilyl)propyl *n*-butyl ketone, in one pot reaction with high yield.

Experimental Section

General. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Jeol JNM-ECP (500 MHz) and Brüker AC-300 (300 MHz) spectrometer as solution in $CDCl_3$ Chemical shift are expressed in parts per million (ppm) downfield from internal standard, tetramethylsilane. ^{19}F NMR spectra were referenced relative to an internal $CFCl_3$. HRMS and MS spectra were obtained at 70 eV in electron impact mode on Shimadzu GC 17A-QP5000.

3,3-Difluoro-1-iodo-1-trimethylsilyl-4-octanone (3): To a solution of α,α-difluoroiodomethyl ketone **1** (2.62 g, 10 mmol) and activated copper powder (0.1 g, 1.5 mmol) in dried acetonitrile (10 mL), vinyltrimethylsilane **2** (1.20 g, 12 mmol) was dropped under N_2 gas (Scheme 2), and the mixture was heated at 60 °C for 15 hr. The reaction mixture was cooled down to room temperature. The reaction mixture was quenched by addition of water and extracted with methylene chloride (10 mL × 3). The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$ and evaporated in vacuo. Separation of the resulting residue by column chromatography on silica gel afforded compound **3** (3.06 g, 94%) as a liquid. ^{1}H-NMR($CDCl_3$) δ 3.08 (dd, J =10.54 Hz, 3.21 Hz, 1H), 2.73 (m, 2H), 2.59 (m, 2H), 1.61 (quintet, J = 7.33 Hz, 2H), 1.34 (sextet, J = 7.33 Hz, 2H), 0.90 (t, J = 7.33 Hz, 3H), 0.12 (s,

9H). ^{19}F-NMR ($CFCl_3$) δ -109.15 (ddd, J = 261.01 Hz, 16.06 Hz). ^{13}C-NMR ($CDCl_3$) δ -2.04 (s), 4.89 (s), 13.82 (s), 22.11 (s), 24.76 (s), 36.63 (s), 37.08 (t, J = 23.99 Hz), 117.60 (t, J = 254.31 Hz), 201.15 (t, J = 31.19 Hz). IR (CCl_4) 2917, 2904, 1760, 1448 cm^{-1}. GC-MS (m/e, relative intensity) 55.00 (54.27), 57.05 (97.45), 73.05 (100.00), 85.10 (54.89), 101.05 (6.33), 143.05 (12.35), 151.05 (10.97), 157.10 (8.31), 185.00 (7.73), 235.20 (2.84), 362.15 (0.75).

2-Butyl-3,3-difluoro-5-trimethylsilylpyrroline (6): Ammonium hydroxide solution (4.93 g, 80 mmol, 28% aqueous solution) was added to 3,3-difluoro-1-iodo-1-trimethylsilyl-4-octanone (3.62 g, 10 mmol) in a round bottom flask. The reaction mixture was stirred for 10 hr at room temperature. The reaction mixture was quenched by addition of water and the aqueous solution was extracted with methylene chloride (10 mL × 3). The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$ and evaporated in vacuo. Flash chromatography on silica gel 60F-254 using ethylacetate/hexane (3:1) afforded the title compound (**5a**) (1.34 g, 95%) as a liquid. ^{1}H- NMR ($CDCl_3$) δ 3.69 (m, 1H), 2.46 (m, 1H), 2.41 (m, 2H), 2.20 (m, 1H), 1.63 (quintet, J = 7.79 Hz, 2H), 1.39 (sextet, J = 7.33 Hz, 2H), 0.92 (t, J = 7.79 Hz, 3H), 0.06 (s, 9H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -95.37 (ddd, J = 288.93 Hz, 21.67 Hz, 9.03 Hz, 1H), -93.88 (dddd, J = 267.26 Hz, 19.86 Hz, 9.03 Hz, 9.03 Hz, 1H). ^{13}C- NMR ($CDCl_3$) δ 167.15 (t, J = 27.35 Hz), 130.60 (t, J = 251.92 Hz), 59.81 (s), 34.74 (t, J = 23.03 Hz), 28.63 (s), 27.18 (s), 22.63 (s), 13.81 (s), -3.73 (s). IR (CCl_4) 34.78, 3062, 1678, 786 cm^{-1}. GC-MS (m/e, relative intensity) 236 (M^-, 19.36), 176 (1.22), 164 (2.57), 150 (1.31), 134 (1.98), 122 (4.19), 106 (4.52), 102 (2.19), 73 (100), 55 (7.20) HRMS obsd. 233.14093, $C_{11}H_{21}NF_2Si$; calcd. 233.141133.

2-Butyl-3-fluoropyrrole (5a): 2-butyl-3,3-difluoro-5-trimethyl silyl pyrroline (2.33 g, 0.01 mole) and potassium fluoride (1.16 g, 0.02 mole) were added to DMSO (15 mL) in a round bottom flask and stirred at 100 °C for 15 hr. The reaction mixture was quenched by adding and the aqueous solution extracted with diethyl ether (10 mL × 3). The combined organic extracts were wash with water then brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography on silica gel 60F-254 using diethylether/*n*-hexane (1:4) afforded (**5b**) (1.34 g, 95%), as a liquid. ^{1}H-NMR ($CDCl_3$, TMS) δ 7.45 (s, broad, 1H), 6.35 (dd, J = 7.4 Hz, 3.2 Hz, 1H), 5.89 (t, J = 3.0 Hz, 1H), 2.56 (t, J = 7.5 Hz, 2H), 1.61-1.51 (quintet, J = 7.33 Hz, 2H), 1.41-1.28 (sextet, J = 7.33 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -172.13 (s). ^{13}C- NMR ($CDCl_3$, TMS) δ 148.52 (d, J = 234.2 Hz), 114.51 (d, J = 26.0 Hz), 112.42 (d, J = 7.6 Hz), 97.23 (d, J = 17.4 Hz), 34.45 (s), 23.80 (s), 22.35 (s), 13.80 (s). FTIR (CCl_4) 3489, 2960, 2933, 11613, 146, 1414, 780 cm^{-1}. GC-MS (m/e, relative intensity) 141 (M^-, 27.86), 142 (M^++1, 3.57), 111 (2.21), 98 (100), 71 (9.43), 57 (7.37), 51 (5.08), 41 (3.38). HRMS obsd. 141.0936, $C_8H_{12}NF$; calcd. 141.095376.

General procedure for synthesis of compounds 5b-5h. 3,3-difluoro-1-iodo-1-trimethylsilyl-4-octanone (3.62 g, 10 mmol) and methylamine (3.78 g, 50 mmol, 40% aqueous solution) were added to 5 mL of acetonitile in a round bottom flask. The reaction mixture was stirred for 10 hr at a room temperature. The reaction mixture was quenched by addition of water and extracted with methylene chloride (10 mL × 3). The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Separation of the resulting residue by column chromato-graphy on silica gel (ethyl acetate/hexane) afforded compound **5b** (1.42 g, 92%) as a liquid.

2-Butyl-3-fluoro-1-methylpyrrole (5b): ^{1}H-NMR ($CDCl_3$) δ 6.23 (dd, J = 5.04 Hz, 3.21 Hz, 1H), 5.18 (d, J = 2.75 Hz, 1H), 3.47 (s, 3H), 2.55 (t, J = 7.56 Hz, 2H), 1.54 (quintet, J = 7.33 Hz, 2H), 1.35 (sextet, J = 7.33 Hz, 2H), 0.93 (t, J = 7.33 Hz, 3H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -168.84 (s). ^{13}C-NMR ($CDCl_3$) δ 148.71 (d, J = 234.17 Hz), 116.14 (d, J = 7.68 Hz), 115.95 (d, J = 23.99 Hz), 94.93 (d, J = 17.27 Hz), 34.35 (s), 31.43 (d, J = 1.92 Hz), 22.54 (d, J = 1.92 Hz), 22.54 (d, J = 1.92 Hz), 22.37 (s), 13.87 (s). IR (CCl_4) 3449, 2934, 2876, 1450, 1361 cm^{-1}. GC-MS (m/e, relative intensity) 155 (M^+, 16.06), 113 (7.13), 112 (100.00), 99 (1.05), 98 (1.12), 84 (1.47), 71 (2.43), 65 (4.03), 59 (2.40), 57 (4.37), 51 (5.08). HRMS obsd. 155.11098, $C_9H_{14}NF$; calcd. 155.111027.

2-Butyl-1-ethyl-3-fluoropyrrole (5c): The product was obtained with 89% yield (1.51 g). ^{1}H-NMR ($CDCl_3$) δ 6.29 (dd, J = 5.04 Hz, 3.21 Hz, 1H), 5.84 (d, J = 3.21 Hz, 1H), 3.77 (q, J = 7.33 Hz, 2H), 2.55 (t, J = 7.33 Hz, 2H), 1.55 (quintet, J = 7.33 Hz, 2H), 1.37 (sextet, J = 7.33 Hz, 2H), 1.34 (t, J = 7.33 Hz, 2H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -168.84 (s). ^{13}C-NMR ($CDCl_3$) δ 148.65 (d, J = 234.17 Hz), 115.17 (d, J = 23.99 Hz), 114.04 (d, J = 7.67 Hz), 95.19 (d, J = 16.31 Hz), 41.69 (s), 31.62 (s), 22.56 (d, J = 2.88 Hz), 22.46 (s), 16.58 (s), 13.86 (s). IR (CCl_4) 2986, 2958, 1209 cm^{-1}. GC-MS (m/e, relative intensity) 169 (M^+, 100.00), 111 (1.96), 98 (25.97), 84 (1.56), 74 (1.10), 71 (4.49), 59 (2.99), 57 (5.13), 51 (6.60). HRMS obsd. 169.12650, $C_{10}H_{16}NF$; calcd. 169.126677.

2-Butyl-1-propyl-3-fluoro-pyrrole (5d): The product was obtained with 82% yield (1.51 g). ^{1}H-NMR ($CDCl_3$) δ 6.28 (dd, J = 5.04 Hz, 3.21 Hz, 1H), 5.84 (d, J = 3.21 Hz, 1H), 3.67 (t, J = 7.33 Hz, 2H), 2.55 (t, J = 7.33 Hz, 2H), 1.71 (sextet, J = 7.33 Hz, 2H), 1.55 (quintet, J = 7.33 Hz, 2H), 1.37 (sextet, J = 7.33 Hz, 2H), 0.94 (t, J = 7.33 Hz, 3H), 0.92 (t, J = 7.33 Hz, 3H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -168.96 (s). ^{13}C-NMR ($CDCl_3$) δ 148.77 (d, J = 235.13 Hz), 115.46 (d, J = 23.99 Hz), 115.11 (d, J = 7.68 Hz), 95.12 (d, J = 16.31 Hz), 49.00 (s), 31.72 (s), 24.82 (d, J = 2.88 Hz), 22.60 (s), 14.01 (s), 11.41 (s). IR (CCl_4) 2934, 2878, 1367 cm^{-1}. GC-MS (m/e, relative intensity) 183 (M^-, 25.43), 154 (8.79), 140 (100.00), 124 (2.84), 112 (11.24), 98 (76.86), 51 (22.34). HRMS obsd. 183. 14059, $C_{11}H_{18}NF$; calcd. 183.142327.

2-Butyl-*N*-butyl-3-fluoropyrrole (5e): The product was obtained with 77% yield (1.52 g). ^{1}H-NMR ($CDCl_3$) δ 6.26 (dd, J = 5.04 Hz, 3.21 Hz, 1H), 5.81 (d, J = 3.21 Hz, 1H), 3.69 (t, J = 7.33 Hz, 2H), 2.53 (t, J = 7.33 Hz, 2H), 1.65 (quintet, J = 7.33 Hz, 2H), 1.53 (quintet, J = 7.33 Hz, 2H), 1.35 (sextet, J = 7.33 Hz, 2H), 1.31 (sextet, J = 7.33 Hz, 2H), 0.93 (t, J = 7.33 Hz, 3H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -168.93 (s). ^{13}C-NMR ($CDCl_3$) δ 148.74 (d, J = 234.17 Hz), 115.42 (d, J = 23.99 Hz), 115.04 (d, J = 6.72 Hz), 95.11 (d, J = 16.31 Hz), 47.09 (s), 33.67 (s), 31.70 (s), 22.75 (d, J = 2.88 Hz), 22.58 (s), 20.12 (s), 13.90 (s). IR (CCl_4) 3422, 2936, 2854, 1450, 1375, 1261 cm^{-1}. GC-MS (m/e, relative intensity) 197 (M^-, 25.23), 155 (11.11),

154 (100.00), 140 (9.35), 138 (1.40), 126 (5.91), 124 (5.40), 113913.76), 112 (52.74), 98 (41.60), 84 (3.27), 71 (5.10), 57 (11.58), 55 (11.90), 51 (7.35). HRMS obsd. 197.15643, $C_{12}H_{20}NF$; calcd. 197.157977.

2-Butyl-2-cyclopentyl-3-fluoropyrrole (5f): The product was obtained with 68% yield (1.42 g). ^{1}H-NMR ($CDCl_3$) δ 6.36 (dd, J = 4.58 Hz, 3.67 Hz, 1H), 5.86 (d, J = 2.75 Hz, 1H), 4.30 (quintet, J = 7.33 Hz, 1H), 2.58 (t, J = 7.33 Hz, 2H), 1.74 (m, 2H), 1.67 (m, 2H), 1.54 (quintet, J = 7.33 Hz, 2H), 1.37 (sextet, J = 7.33 Hz, 2H), 0.93 (t, J = 7.33 Hz, 3H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -169.75 (s). ^{13}C-NMR ($CDCl_3$) δ 148.65 (d, J = 235.13 Hz), 115.97 (d, J = 23.99 Hz), 111.23 (d, J = 7.68 Hz), 95.44 (d, J = 16.32 Hz), 56.93 (s), 33.86 (s), 31.95 (s), 24.44 (s), 22.82 (d, J = 2.88 Hz), 22.58 (s), 14.02 (s). IR (CCl_4) 3413, 2962, 1477, 1319 cm^{-1}. GC-MS (m/e, relative intensity) 209 (M^+, 18.95), 180 (4.54), 167 (8.65), 166 (68.20), 124 (3.60), 112 (2.57), 99 (7.52), 98 (100.00), 69 (6.62), 57 (4.00), 51 (6.21). HRMS obsd. 209.15752, $C_{13}H_{20}NF$; calcd. 209.157977.

2-Butyl-1-cyclohexyl-3-fluoropyrrole (5g): The product was obtained with 68% yield (1.52 g). ^{1}H-NMR ($CDCl_3$) δ 6.36 (dd, J = 4.58 Hz, 3.21 Hz, 1H), 5.85 (d, J =3.21 Hz, 1H), 3.66 (dddd, J = 8.25 Hz, 8.25 Hz, 3.67 Hz, 3.67 Hz, 1H), 2.56 (t, J = 7.56 Hz, 2H), 1.93-1.87 (m, 4H), 1.64-1.52 (m, 4H), 1.48-1.35 (m, 4H), 0.94 (t, J = 7.33 Hz, 3H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -170.26 (s). ^{13}C-NMR ($CDCl_3$) δ 148.42 (d, J = 234.17 Hz), 114.95 (d, J = 23.99 Hz), 111.40 (d, J = 6.72 Hz), 95.21 (d, J = 17.27 Hz), 55.22 (s), 34.72 (s), 32.04 (s), 26.20 (s), 25.65 (s), 22.57 (d, J = 2.88 Hz), 22.50 (s), 14.01 (s). IR (CCl_4) 3425, 2886, 2798, 1425 cm^{-1}. GC-MS (m/e, relative intensity) 223 (M^+, 19.04), 194 (2.32), 181 (9.88), 180 (71.72), 166 (2.22), 142 (3.23), 112 (3.11), 98 (100.00), 83 (6.45), 81 (5.48), 71 (2.65), 55 (31.16). HRMS obsd. 223.14762, $C_{14}H_{22}NF$; calcd. 223.173627.

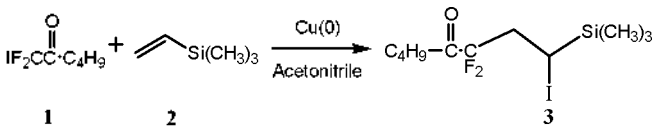
2-Butyl-1-benzyl-3-fluoropyrrole (5h): The product was obtained with 88% yield (2.04 g). ^{1}H- NMR ($CDCl_3$) δ 7.31 (t, J = 7.79 Hz, 2H), 7.25 (t, J = 7.33 Hz, 1H), 7.22 (t, J = 7.33 Hz, 2H), 6.32 (dd, J = 4.58, 3.21 Hz, 1H), 5.90 (d, J = 2.75 Hz, 1H), 4.95 (s, 2H), 2.45 (t, J = 7.33 Hz, 2H), 1.43 (m, 2H), 1.32 (m, 2H), 0.84 (t, J = 7.33 Hz, 3H). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -169.71 (s). ^{13}C- NMR ($CDCl_3$) δ 148.51 (d, J = 234.17 Hz), 138.65 (s), 128.65 (s), 127.68 (s), 126.47 (s), 117.15 (d, J = 23.99 Hz), 116.43 (d, J = 6.72 Hz), 95.93 (d, J = 17.27 Hz), 31.49 (s), 22.78 (d, J = 2.89 Hz), 22.40 (s), 13.92 (s). IR (CCl_4) 2934, 2840, 2760, 2058, 1361 cm^{-1}. GC-MS (m/e, relative intensity) 231.25 (M^-, 17.21), 188 (38.52), 140 (2.21), 91 (100.00), 89 (2.66), 65 (18.27), 63 (2.47), 57 (2.21), 51 (3.88). HRMS obsd. 231.12864, $C_{14}H_{22}NF$; calcd. 231.14233.

Results and Discussion

In our method, α,α-difluoro-iodomethyl *n*-butylketone (**1**) was prepared from chlorodifluoroacetate acid by Grignard reaction[22] and Reformasky reaction.[23] Compound **1** in acetonitrile was added to trimethylvinylsilane (**2**) in the presence of catalytic amount of Cu(0) (15 mol%) to result α,α-difluoro-γ-iodo-γ-trimethylsilylpropyl *n*-butylketone (**3**) with a yield of *ca.* 94%. Previously α,α-difluoro-γ-iodo-γ-substituted ketones were obtained by the reaction of the corresponding iododifluoromethyl ketones with vinyltrimethylsilane using Pd(0) as a catalyst.[24] However, Cu(0) catalyst is much more useful than Pd(0) because it is less sensitive against oxygen, thereby, allowing simple reaction conditions. (Scheme 1) Furthermore, in order to optimize the yield of addition, the reaction of α,α-difluoroiodomethyl butyl ketones with trimethylvinylsilane was tested in a variety of solvents. Among the employed solvents, acetonitrile resulted in the best yield. It is noted that the very strong coordinative solvents such as DMSO, DMF and THF gave rather poor yields although *n*-hexane did no reaction.

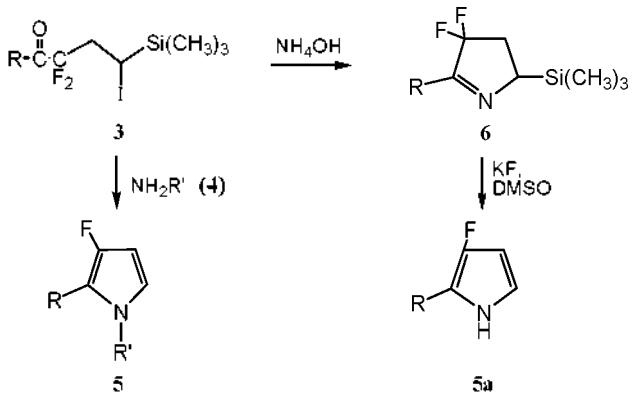
In sequence, *N*-alkyl-2-butyl-3-fluoropyrrole derivatives (**5**) were obtained by the reaction of **3** with primary amines (**4**) in high yields. A reaction mechanism postulated is summarized in Scheme 3. In these reactions, primary amines were used in excess in order to remove hydroxy and trimethylsilyl group along with hydride. When compound **3** reacted with only ammonium hydroxide (28% aqueous solution), 2-*n*-butyl-3,3-difluoro-5-trimethylsilylpyrrolidine (**6**) was obtained first. If ammonium hydroxide was added more than 10 eq., and/or the temperature elevated up to 60 °C for 24 hr, 2-*n*-butyl-3-fluoropyrrole (**5a**) was obtained only with a poor yield. This is because the nucleophilicity of ammonium hydroxide is presumably not high enough to remove the trimethylsilyl group.

Like previously reported method,[24] when **3** was treated with ammonium hydroxide at room temperature, **6** was obtained as intermediate, which on further treatment with potassium fluoride gave rise **5**. Interestingly, addition of primary amines on **3**, however, did not stop at **6**, but proceeded all the way to **5** (one-pot reaction). (Scheme 2) To our best knowledge, there was no report on the reaction of **3** with primary amines. Furthermore, excess of primary amines ($\geq$ 4 eq.) was required



1 **2** **3**

Scheme 1

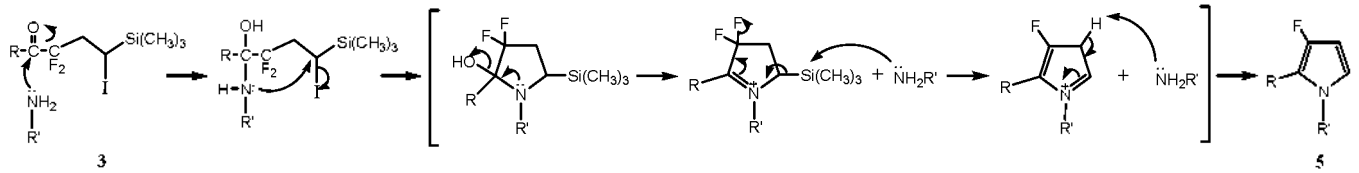


3 **6** **5** **5a**

R : (*n*-butyl)

R' : H(**a**), methyl(**b**), ethyl(**c**), propyl(**d**), *n*-butyl(**e**), cyclopentyl(**f**), cyclohexyl(**g**), benzyl(**h**)

Scheme 2



Scheme 3

Table 1. Synthesis of *N*-alkyl 2-*n*-butyl pyrrole

Entry	Substrate	Reactants	Products	Yields[a]
1	**3**	**4a**	**5a**	95
2	**3**	**4b**	**5b**	92
3	**3**	**4c**	**5c**	89
4	**3**	**4d**	**5d**	82
5	**3**	**4e**	**5e**	77
6	**3**	**4f**	**5f**	68
7	**3**	**4g**	**5g**	68
8	**3**	**4h**	**5h**	88

[a]Combined yields of isolated products after flash chromatography.

to complete this one-pot reaction. The stoichiometry of this reaction was described in Scheme 3. In addition, the bulkness of *N*-substituents affected the yields of products inversely. The structure of *N*-substituents *vs* the yields of **5** was noted in Table 1. Crowded amine could not afford a nucleophilic attack on iodine bearing carbon with ease as illustrated in Scheme 3.

Conclusions

In summary, a new series of *N*-substituted 2-*n*-butyl-3-fluoropyrrole derivatives with high yield were synthesized in one-pot reaction using simple and convenient synthetic strategy. α,α-Difluoro-γ-iodo-γ-(trimethylsilyl)propyl *n*-butyl ketone (**3**), the precursor molecule for 2-*n*-butyl-3-fluoropyrroles, was prepared by the reaction of α,α-difluoro-iodomethyl *n*-butylketone with trimethylvinylsilane in the presence of catalytic amount of Cu(0). Use of catalytic amount of Cu(0) in the reaction of α,α-difluoro-iodomethyl *n*-butylketone (**1**) with trimethylvinylsilane (**2**) was far more practical than those of photochemical and Pd(0) method. A noble series of *N*-substituted 2-*n*-butyl-3-fluoropyrroles were formed by the reaction of **3** with primary amines through one-pot scheme. The driving force of our one-pot reactions stems from the high basicity of primary amines enough for abstracting fluorine atom and silyl group.

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References and Notes

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