

Reaction of *N*-Methyl-5-tributylstannyl-4-fluoro-1*H*-pyrazole and Its Application to *N*-Methyl-chromeno[2,3-*d*]pyrazol-9-one Synthesis

Takeshi Hanamoto,^{*†} Eri Hashimoto,[†] Masayuki Miura,[†] Hiroshi Furuno,[‡] and

Junji Inanaga[‡]

Department of Chemistry and Applied Chemistry, Saga University, Honjyo-machi 1, Saga 840-8502, Japan, and Institute for Materials Chemistry and Engineering (IMCE), Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

hanamoto@cc.saga-u.ac.jp

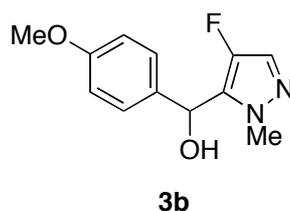
Supporting Information

Table of Contents:

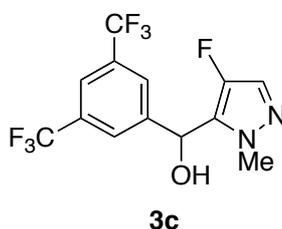
General	S2
Analytical Data for compounds 3b-3j	S2-S6
Preparation of compound 4	S6
ORTEP drawing of compound 3g	S8
Crystal Data for 3g	S9
NMR spectra for compounds 2a, 3a-j, 4, 7, 8, 9	S10-S24

General. Melting points are uncorrected. Infrared (IR) spectra are reported in cm^{-1} . ^1H , ^{19}F and ^{13}C NMR spectra were measured in CDCl_3 solutions. Chemical shifts were given by δ relative to that of an internal Me_4Si (TMS) for ^1H NMR and ^{13}C NMR spectra and benzyldiyne trifluoride ($\text{CF}_3\text{C}_6\text{H}_5$) for ^{19}F NMR spectra.

Compounds 3b-j:

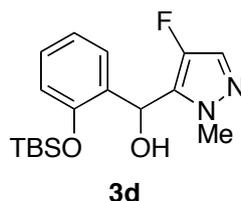


***N*-Methyl-5-[(4'-methoxyphenyl)hydroxymethyl]-4-fluoro-1*H*-pyrazole (3b).** a white solid; yield 87%; mp 95.2-96.0 °C; IR (KBr) 3237, 1608, 1584, 1511, 1444, 1364, 1304, 1248, 1171, 1030, 803 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 3.59 (4H, s), 3.79 (3H, s), 6.00 (1H, s), 6.88 (2H, d, $J = 8.8$ Hz), 7.19 (1H, d, $J = 4.4$ Hz), 7.25 (2H, d, $J = 8.8$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 38.7, 55.3, 65.4 (d, $J = 3.1$ Hz), 114.0, 124.8 (d, $J = 12.5$ Hz), 127.1, 128.4 (d, $J = 12.5$ Hz), 131.8, 147.1 (d, $J = 246.6$ Hz), 159.3; ^{19}F NMR (CDCl_3 , 283 MHz) δ -177.4 (d, $J = 5.2$ Hz); GC-MS m/z 236 (0.8, M^+), 235 (4), 218 (6), 135 (7), 127 (26), 109 (100), 94 (12), 77 (16); Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{FN}_2\text{O}_2$: C, 61.01; H, 5.55; N, 11.86. Found: C, 61.03; H, 5.55; N, 11.78.



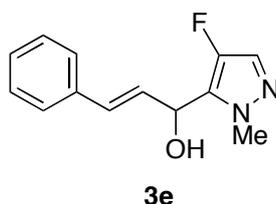
***N*-Methyl-5-[(3',5'-bis(trifluoromethyl)phenyl)hydroxymethyl]-4-fluoro-1*H*-pyrazole (3c).** a white solid; yield 84%; mp 99.8-101.9 °C; IR (KBr) 3251, 1585, 1449, 1409, 1373, 1284, 1168, 1130, 1061, 1014, 901, 844, 809, 704, 684 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 3.62 (3H, s), 3.74 (1H, d, $J = 3.3$ Hz), 6.16 (1H, s), 7.24 (1H, d, $J = 4.4$ Hz), 7.85 (3H, brs); ^{13}C NMR (CDCl_3 , 75

MHz) δ 38.7, 63.9 (d, $J = 3.1$ Hz), 122.0 (sep, $J = 3.7$ Hz), 123.1 (q, $J = 272.8$ Hz), 125.0 (d, $J = 13.1$ Hz), 126.0 (q, $J = 3.7$ Hz), 127.2 (d, $J = 21.8$ Hz), 132.1 (q, $J = 33.6$ Hz), 142.3 (d, $J = 1.2$ Hz), 147.3 (d, $J = 249.1$ Hz); ^{19}F NMR (CDCl_3 , 283 MHz) δ -64.1 (6F, s), -175.8 (1F, d, $J = 4.9$ Hz); GC-MS m/z 342 (1, M^+), 341 (5), 194 (5), 145 (5), 129 (100), 127 (28), 109 (21), 99 (25), 72 (16); Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{F}_7\text{N}_2\text{O}$: C, 45.63; H, 2.65; N, 8.19. Found: C, 45.66; H, 2.60; N, 8.27.



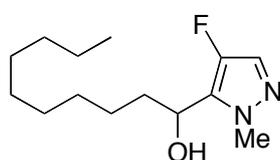
***N*-Methyl-5-[(2'-(*tert*-butyldimethylsilyloxy)phenyl)hydroxymethyl]-4-fluoro-1*H*-pyrazole**

(3d). a white solid; yield 94%; mp 66.3-67.1 °C; IR (KBr) 3201, 2858, 1583, 1493, 1403, 1360, 1279, 1037, 1010, 935, 840 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.20 (3H, s), 0.27 (3H, s), 0.93 (9H, s), 3.74 (3H, s), 4.10 (1H, t, $J = 5.0$ Hz), 6.12 (1H, d, $J = 5.0$ Hz), 6.84 (1H, d, $J = 7.5$ Hz), 6.94 (1H, t, $J = 7.5$ Hz), 7.14 (1H, dd, $J = 4.2, 1.3$ Hz), 7.18 (1H, dd, $J = 7.5, 1.5$ Hz), 7.25 (1H, dt, $J = 7.5, 1.5$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ -4.4, -4.1, 18.1, 25.6, 38.5, 63.0 (dd, $J = 3.1, 1.2$ Hz), 118.2, 121.1, 124.7 (d, $J = 13.1$ Hz), 127.3, 127.6, 129.0, 129.8 (d, $J = 1.2$ Hz), 146.8 (d, $J = 247.9$ Hz), 153.1; ^{19}F NMR (CDCl_3 , 283 MHz) δ -175.7 (d, $J = 3.8$ Hz); GC-MS m/z 280 (3), 279 (20), 278 (33), 179 (9), 178 (9), 161 (3), 133 (3), 116 (6), 77 (16), 75 (100), 57 (11); Anal. Calcd. for $\text{C}_{17}\text{H}_{25}\text{FN}_2\text{O}_2\text{Si}$: C, 60.68; H, 7.49; N, 8.33. Found: C, 60.67; H, 7.54; N, 8.33.



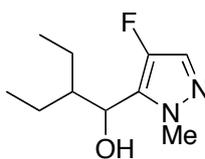
***N*-Methyl-5-[(cinnamyl)hydroxymethyl]-4-fluoro-1*H*-pyrazole (3e).** colorless oil; yield 76%; IR (neat) 3246, 3126, 1587, 1493, 1443, 1406, 1360, 1330, 1307, 1102, 1071, 972, 791, 759,

693 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 3.58 (1H, brs), 3.81 (3H, s), 5.53 (1H, dd, $J = 5.4, 1.2$ Hz), 6.41 (1H, ddd, $J = 16.0, 5.4, 1.2$ Hz), 6.67 (1H, dd, $J = 16.0, 1.2$ Hz), 7.18 (1H, d, $J = 4.4$ Hz), 7.22-7.72 (5H, m); ^{13}C NMR (CDCl_3 , 75 MHz) δ 38.5, 64.5 (d, $J = 3.1$ Hz), 124.7 (d, $J = 24.5$ Hz), 126.6, 127.1 (d, $J = 1.2$ Hz), 127.6 (d, $J = 21.2$ Hz), 128.1, 128.6, 131.6, 135.9, 146.7 (d, $J = 246.6$ Hz); ^{19}F NMR (CDCl_3 , 283 MHz) δ -176.4 (d, $J = 3.9$ Hz); GC-MS m/z 232 (0.4, M^+), 231 (4), 215 (4), 127 (48), 126 (41), 113 (58), 112 (40), 105 (86), 104 (100), 91 (49), 77 (42), 51 (20); Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{FN}_2\text{O}$: C, 67.23; H, 5.64 N, 12.06. Found: C, 67.06; H, 5.77; N, 11.83.



3f

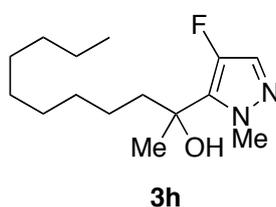
***N*-Methyl-5-(1'-hydroxydecanyl)-4-fluoro-1*H*-pyrazole (3f).** colorless oil; yield 72%; IR (neat) 3338, 2926, 2855, 1584, 1466, 1439, 1364, 1306, 1195, 1068, 1003, 821 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.88 (3H, t, $J = 6.4$ Hz), 1.26 (14H, brs), 1.80-2.05 (3H, m), 3.88 (3H, s), 4.75-4.85 (1H, m), 7.23 (1H, d, $J = 4.2$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.1, 22.6, 25.8, 29.2, 29.5, 29.7, 31.8, 35.4 (d, $J = 3.0$ Hz), 38.5, 65.1 (d, $J = 2.5$ Hz), 124.9 (d, $J = 13.1$ Hz), 128.7 (dd, $J = 21.1, 1.9$ Hz), 146.7 (d, $J = 246.0$ Hz); ^{19}F NMR (CDCl_3 , 283 MHz) δ -176.2 (d, $J = 5.2$ Hz); GC-MS m/z 256 (2, M^+), 255 (3), 130 (26), 129 (100), 128 (44), 113 (8), 101 (9), 57 (4); Anal. Calcd. for $\text{C}_{14}\text{H}_{25}\text{FN}_2\text{O}$: C, 65.59; H, 9.83 N, 10.93. Found: C, 65.54; H, 9.89; N, 10.74.



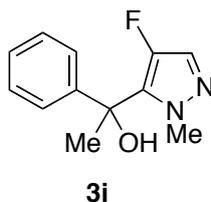
3g

***N*-Methyl-5-[2'-ethyl-1'-hydroxybutyl]-4-fluoro-1*H*-pyrazole (3g).** a white solid; yield 71%; mp 70.1-70.9 $^{\circ}\text{C}$; IR (KBr) 3251, 2970, 2872, 1581, 1445, 1366, 1332, 1299, 1040, 1007, 855,

805, 692 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.81 (3H, t, $J = 7.5$ Hz), 0.95 (3H, t, $J = 7.3$ Hz), 1.10-1.40 (2H, m), 1.40-1.90 (2H, m), 1.80-1.90 (1H, m), 2.04 (1H, brs, $J = 5.4$ Hz), 3.86 (3H, s), 4.68 (1H, dd, $J = 9.0, 5.4$ Hz), 7.23 (1H, d, $J = 4.4$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 9.9, 10.5, 20.9, 21.2, 38.6, 44.5 (d, $J = 1.2$ Hz), 66.7 (d, $J = 3.7$ Hz), 124.6 (d, $J = 13.1$ Hz), 129.0 (d, $J = 21.8$ Hz), 146.8 (d, $J = 244.8$ Hz); ^{19}F NMR (CDCl_3 , 283 MHz) δ -176.6 (d, $J = 4.9$ Hz); GC-MS m/z 200 (0.1, M^+), 199 (2), 152 (2), 129 (95), 128 (100), 113 (6), 100 (4), 54 (4); Anal. Calcd. for $\text{C}_{10}\text{H}_{17}\text{FN}_2\text{O}$: C, 59.98; H, 8.56 N, 13.99. Found: C, 59.78; H, 8.48; N, 13.80.



***N*-Methyl-5-(2'-hydroxydecan-2'-yl)-4-fluoro-1*H*-pyrazole (3h).** a white solid; yield 72%; mp 33.0-34.2 $^{\circ}\text{C}$; IR (KBr) 3323, 2927, 2855, 1569, 1467, 1371, 1303, 1134, 1060, 1001, 822 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.88 (3H, t, $J = 6.4$ Hz), 1.24 (14H, brs), 1.63 (3H, d, $J = 2.8$ Hz), 1.80-1.90 (2H, m), 2.15-2.35 (1H, m), 3.97 (3H, s), 7.19 (1H, d, $J = 3.7$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.1, 22.6, 24.1, 27.9 (d, $J = 5.0$ Hz), 29.2, 29.5, 29.7, 31.8, 40.5, 42.0 (d, $J = 2.5$ Hz), 71.8 (d, $J = 4.3$ Hz), 125.0 (d, $J = 14.9$ Hz), 130.7 (d, $J = 18.7$ Hz), 145.9 (d, $J = 245.4$ Hz); ^{19}F NMR (CDCl_3 , 283 MHz) δ -172.5 (s); GC-MS m/z 270 (3, M^+), 143 (3), 130 (21), 129 (100), 128 (32), 113 (7), 101 (7), 57 (4); Anal. Calcd. for $\text{C}_{15}\text{H}_{27}\text{FN}_2\text{O}$: C, 66.63; H, 10.07 N, 10.36. Found: C, 66.68; H, 10.07; N, 10.37.



***N*-Methyl-5-(1'-phenyl-1'-hydroxyethyl)-4-fluoro-1*H*-pyrazole (3i).** a white solid; yield 74%; mp 81.0-81.6 °C; IR (KBr) 3261, 3187, 1569, 1397, 1370, 1310, 1199, 1070, 768, 701 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.92 (3H, d, *J* = 5.0 Hz), 3.37 (3H, s), 3.93 (1H, brs), 7.17 (1H, d, *J* = 4.0 Hz), 7.20-7.35 (5H, m); ¹³C NMR (CDCl₃, 75 MHz) δ 31.9 (d, *J* = 6.9 Hz), 39.3, 71.9 (d, *J* = 3.7 Hz), 124.6, 124.7, 124.8, 127.2, 128.3, 131.0 (d, *J* = 19.3 Hz), 145.2 (d, *J* = 1.2 Hz), 147.1 (d, *J* = 246.6 Hz); ¹⁹F NMR (CDCl₃, 283 MHz) δ -172.0 (quin, *J* = 4.5 Hz); GC-MS *m/z* 220 (6, M⁺), 204 (14), 127 (100), 126 (22), 105 (18), 77 (25), 51 (11); Anal. Calcd. for C₁₂H₁₃FN₂O: C, 65.44; H, 5.95 N, 12.72. Found: C, 65.49; H, 5.96; N, 12.62.

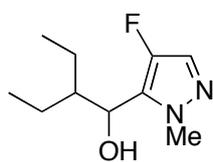
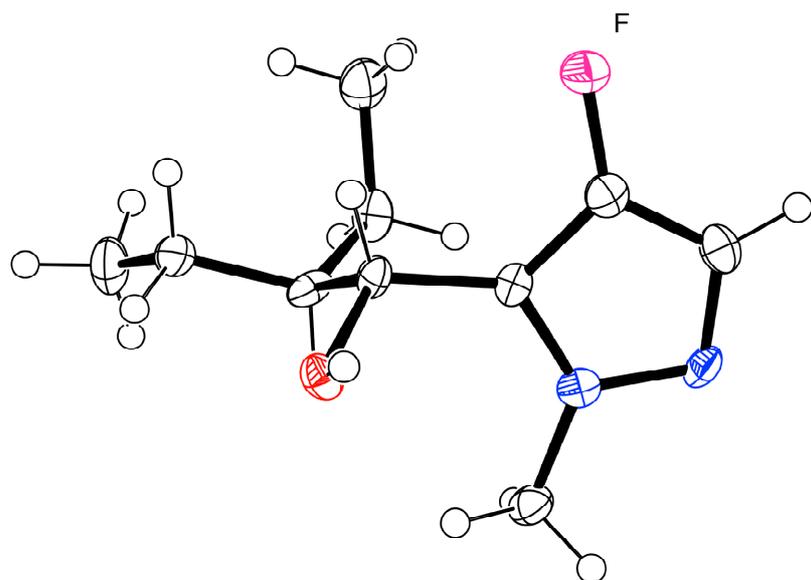


3j

***N*-Methyl-5-phenylthio-4-fluoro-1*H*-pyrazole (3j).** colorless oil; yield 80%; IR (neat) 1582, 1561, 1479, 1441, 1426, 1348, 987, 825, 740, 689 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.81 (3H, s), 7.05-7.35 (5H, m), 7.45 (1H, d, *J* = 5.0 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 37.4, 116.8 (d, *J* = 27.4 Hz), 125.5, 126.7, 127.3, 129.4, 134.3 (d, *J* = 1.9 Hz), 152.2 (d, *J* = 250.1 Hz); ¹⁹F NMR (CDCl₃, 283 MHz) δ -172.0 (d, *J* = 4.2 Hz); GC-MS *m/z* 208 (38, M⁺), 207 (72), 192 (21), 118 (85), 109 (43), 77 (100), 72 (46), 69 (33), 51 (96); Anal. Calcd. for C₁₀H₉FN₂S: C, 57.67; H, 4.36 N, 13.45. Found: C, 57.79; H, 4.39; N, 13.24.

***N*-Methyl-3-ethoxycarbonyl-5-phenylthio-4-fluoro-1*H*-pyrazole (4).** To a solution containing 64.9 mg (0.31 mmol) of **3j** in THF (3 mL) was added BuLi [240 μL (0.37 mmol), 1.58 M in hexane solution] by means of syringe at -78 °C. After stirring for 10 min at this temperature, 0.39 mL (0.41 mmol) of ethyl chloroformate was add to the mixture. The mixture was stirred for 1 hr and quenched with water, and extracted with hexane/ethyl acetate = 3/1. Additional extraction was repeated twice. The combined organic layer was dried over Na₂SO₄, and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 150/50/1) to give the desired compound **4** as a white solid (45.3 mg, 52%): mp 49.8-50.4 °C; IR (KBr) 1733, 1725, 1553, 1367, 1269, 1149, 1078, 741, 690 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.41 (3H, t, $J = 7.2$ Hz), 3.81 (3H, s), 4.44 (2H, q, $J = 7.2$ Hz), 7.05-7.35 (5H, m); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.2, 38.2, 61.2, 119.8 (d, $J = 27.4$ Hz), 127.3, 128.0, 129.1 (d, $J = 5.6$ Hz), 133.1 (d, $J = 1.9$ Hz), 152.0 (q, $J = 262.8$ Hz), 160.2 (d, $J = 4.4$ Hz); ^{19}F NMR (CDCl_3 , 283 MHz) δ -157.6 (s); GC-MS m/z 280 (1, M^+), 279 (4), 110 (100), 109 (42), 99 (82), 77 (28), 65 (13), 51 (14); Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{FN}_2\text{O}_2\text{S}$: C, 55.70; H, 4.67; N, 9.99. Found: C, 55.82; H, 4.63; N, 10.06.



3g

FIGURE 1. X-ray crystal structure of **3g** with thermal ellipsoids shown at the 50% probability level.

Crystal Data for 3g: (C₁₀H₁₇FN₂O): $M = 200.26$, $T = 93(2)$ K, monoclinic, space group $P21/c$, $a = 7.539(4)$ Å, $b = 10.017(5)$ Å, $c = 14.621(9)$ Å, $V = 1103.9$ Å³, $Z = 4$, $D_x = 1.205$ Mg m⁻³, $m = 0.090$ mm⁻¹, $l = 0.71073$ Å, $q_{\max} = 27.48^\circ$, 10091 measured reflection, 2518 independent reflections, 136 refined parameters, GOF = 1.059, $R[F^2 > 2s(F^2)] = 0.0439$, $wR(F^2) = 0.1077$. The intensity data were collected on a Rigaku RAXIS-RAPID diffractometer. The structure was solved by direct methods (SIR2002¹) and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedures on F^2 for all reductions (SHELXL97²). All hydrogen atoms were positioned geometrically and refined as riding. CCDC-678892 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

(1) Burla, M. C.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **2003**, *36*, 1103.

(2) Sheldrick, G. M. *SHELXL-97, Program for refinement of crystal structures*; University of Göttingen.

