Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 5062–5070
Tetrahedron

Synthesis and reactions of 5-tributylstannyl-4-fluoro-1*H*-pyrazole

Takeshi Hanamoto,[a,*] Takao Suetake,[a] Yukinori Koga,[a] Toshio Kawanami,[b] Hiroshi Furuno[b] and Junji Inanaga[b]

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

Received 2 February 2007; revised 17 March 2007; accepted 19 March 2007
Available online 24 March 2007

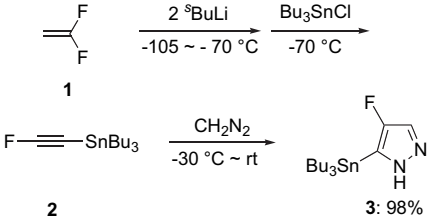
Abstract—The palladium-catalyzed cross-coupling reactions of 5-tributylstannyl-4-fluoro-1*H*-pyrazole with aryl iodides provided high yields of the corresponding 5-aryl-4-fluoro-1*H*-pyrazoles. Furthermore, these cross-coupling reactions proceeded smoothly under an atmosphere of carbon monoxide (CO) to afford the corresponding 5-acyl-4-fluoro-1*H*-pyrazoles as CO-insertion products.

1. Introduction

Synthesis of nitrogen-containing heterocyclic compounds has been a subject of great interest due to the wide application in agrochemical and pharmaceutical fields.[1] Some pyrazole derivatives which belong to this category have certainly been shown to exhibit biological activity.[2] On the other hand, it is well accepted that selective introduction of fluorine to organic compounds often causes a marked effect on structure, stability, reactivity, and biological activity.[3] For instance, Celecoxib is a well-known anti-inflammatory agent on behalf of selectively fluorinated pyrazole derivatives.[4] It is therefore still of importance to develop simple and effective methods for the synthesis of fluorine-containing pyrazoles. Although there are many reports related to the synthesis of pyrazoles in the literature,[5] less study on the synthesis of the fluorine-containing pyrazoles has been examined.[6,7] A general approach to assemble such a fluorinated structural unit may be considered to use the 1,3-dipolar cycloaddition reaction of fluorinated acetylene derivatives and diazomethane. On the basis of this idea, we have recently reported the synthesis of 5-tributylstannyl-4-trifluoromethyl-1*H*-pyrazole and its palladium-catalyzed cross-coupling reactions.[8] Thus, we have demonstrated that tributylstannylpyrazoles bearing fluorines were suitable precursors for the facile preparation of their derivatives. Our next attention was paid to the synthesis of the corresponding ring-fluorinated pyrazoles. There are no reports concerning the cross-coupling reaction of ring-fluorinated stannylpyrazole, although some cross-coupling reactions of stannylpyrazoles with aryl halides have been reported so far.[9] In line with this strategy, we have recently reported a facile method for the preparation of 5-tributylstannyl-4-fluoro-1*H*-pyrazole and its cross-coupling reaction catalyzed by palladium catalyst.[10] As an extension of this work, we continued to examine the palladium-catalyzed carbonylative cross-coupling reaction using the fluorinated pyrazole with aryl halides. In this paper, we wish to report in detail our study on both palladium-catalyzed cross-coupling reaction as well as palladium-catalyzed carbonylative cross-coupling reaction of 5-tributylstannyl-4-fluoro-1*H*-pyrazole with aryl halides.

2. Results and discussion

We previously reported the one-pot preparation of 5-tributylstannyl-4-fluoro-1*H*-pyrazole (**3**) from 1,1-difluoroethylene (**1**) (Scheme 1).[10,11] This method consists of the synthesis of fluoro(tributylstannyl)acetylene (**2**) in situ and its successive 1,3-dipolar cycloaddition reaction with diazomethane. Although attempts to isolate **2** invariably resulted in decomposition owing to its thermal instability, this one-pot process



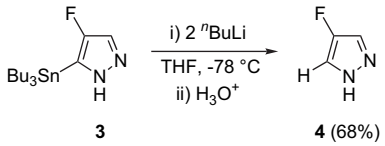
Scheme 1. One-pot synthesis of **3**.

Keywords: Cross-coupling reaction; 1,3-Dipolar cycloaddition; 5-Tributylstannyl-4-fluoro-1*H*-pyrazole; 5-Aryl-4-fluoro-1*H*-pyrazole; 5-Acyl-4-fluoro-1*H*-pyrazole.
* Corresponding author. Tel.: +81 952 28 8704; fax: +81 952 28 8548; e-mail: hanamoto@cc.saga-u.ac.jp

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.117

proceeded cleanly to afford the product (**3**) as a sole adduct in 98% yield. The corresponding regioisomer was not detected by GC–MS analysis in the crude reaction mixture. The fluorinated pyrazole (**3**) thus produced can be stored in the refrigerator at −20 °C at least for one month without deterioration. To reproduce successful reaction the reaction temperature must be kept below −105 °C in a cooling bath, when argon was replaced with 1,1-difluoroethylene (**1**) for the generation of the corresponding lithium species.

The regiochemistry of the cycloaddition was determined as follows. After this isomer was transformed to the corresponding destannylated pyrazole (**4**) via transmetallation–protonation process, the structural assignment was performed on the basis of the comparison of the corresponding ^{19}F NMR chemical shift value in the literature (Scheme 2).[6n]



3 **4** (68%)

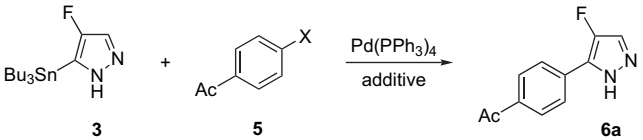
Scheme 2. Destannylation of **3**.

Table 1. DFT calculations of HOMO and LUMO coefficients for diazomethane and (tributylstannyl)fluoroacetylene (**2**)

	HOMO	LUMO+1		HOMO	LUMO
N	0.5366	0.6168	C1(Sn)	0.2990	0.3087
C	−0.5965	0.6264	C2(F)	0.3078	−0.5320

The observed regioselectivity can be explained in terms of HOMO–LUMO interaction as discussed in the literature.[12] We carried out the DFT calculations using Spartan '04 at the B3LYP/6-31G* level of theory.[13] The HOMO coefficient of diazomethane and the LUMO coefficient of (tributylstannyl)fluoroacetylene (**2**) should support the observed regioselectivity in this 1,3-dipolar cycloaddition reaction (Table 1).

Table 2. Cross-coupling reaction of **3** with 4′-iodoacetophenone (**5**) under a variety of conditions[a]



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

Entry	X	CuTC[b] (mol %)	LiCl (mol %)	Time (h)	Solvent	Temp (°C)	Yield[c] (%)
1	I	5	—	89	DMF	25	44
2	I	5	—	18	DMF	80	Trace
3	I	5	20	37	DMF	25	0
4	I	—	—	13	DMF	100	40
5	I	5	100	39	DMSO	25	28
6	I	5	20	17	DMSO	25	100
7	I	5	—	18	DMSO	25	45
8	I	—	20	2	DMSO	100	100
9	I	—	—	3	DMSO	100	100 (91)[d]
10[e]	I	—	—	2	DMSO	100	84
11	Br	—	—	2	DMSO	100	Trace

[a] All reactions were conducted using **3** (1.0 equiv) with **5** (1.1 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %).
[b] Cu(I) thiophene-2-carboxylate.
[c] GC yield.
[d] Isolated yield in parenthesis.
[e] $PdCl_2(PPh_3)_2$ was used instead of $Pd(PPh_3)_4$.

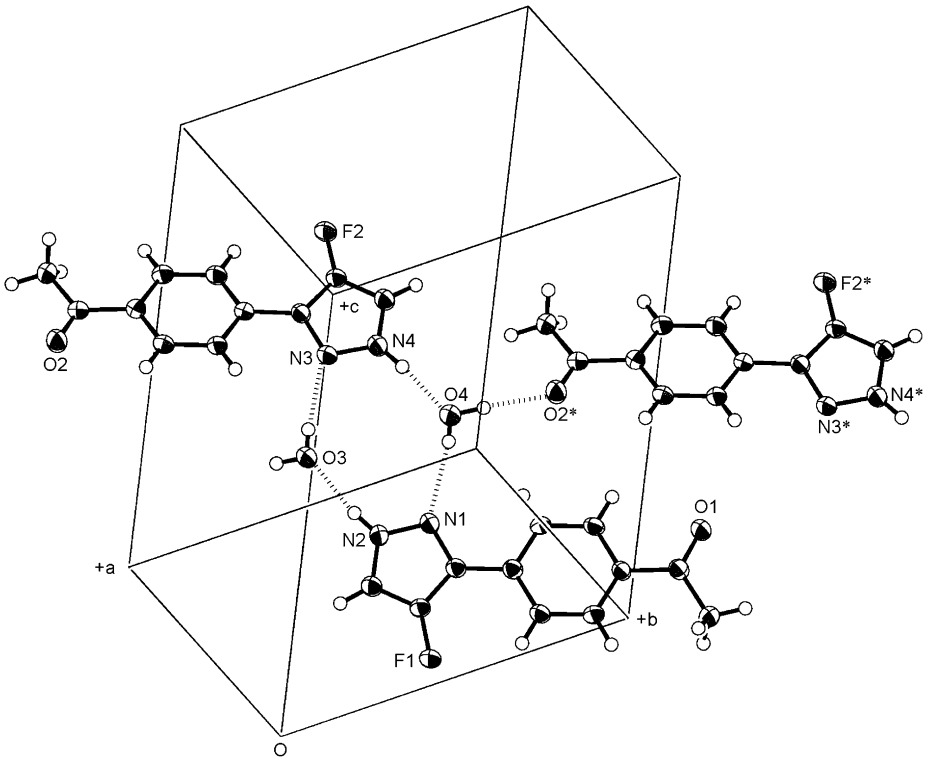


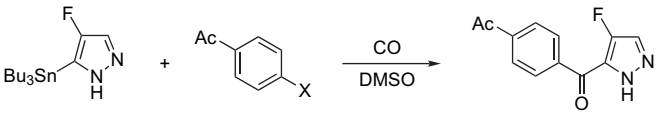
Figure 1. Crystal packing of **6a**. Hydrogen bonds are shown by dotted lines.

With an aim to prove the role of **3** as a versatile precursor for the synthesis of 4-fluoro-5-substituted-pyrazoles, the cross-coupling reaction of the fluoropyrazole (**3**) with 4′-iodoacetophenone (**5**) was next examined under a variety of reaction conditions. As can be seen in Table 2, the best result was obtained when the reaction was conducted in the presence of a catalytic amount of [$Pd(PPh_3)_4$] (5 mol %) in DMSO at 100 °C, affording the corresponding 5-(4′-acetylphenyl)-4-fluoro-1*H*-pyrazole (**6a**) in 91% yield (entry 9).

The structure of **6a** was established on the basis of its X-ray crystallographic analysis. A crystal packing drawing of **6a** is shown in Figure 1. This X-ray analysis added the unambiguous proof to the regiochemistry of the cycloaddition as has been mentioned above.

The features of the reaction are as follows. (1) The use of DMSO as a solvent was essential to the successful reaction.[14] (2) The corresponding aryl bromide was not effective for this coupling reaction. (3) Addition of copper(I) thiophene-2-carboxylate (CuTC) and LiCl as additives to the

Table 4. CO-insertive cross-coupling reaction of **3** with 4′-haloacetophenone (**5**) under a variety of conditions[a]

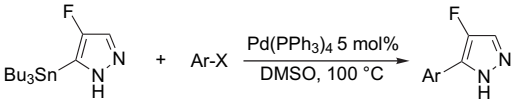


3 **5** **7a**

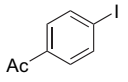
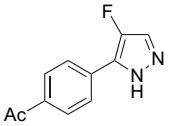
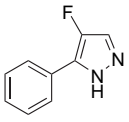
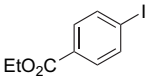
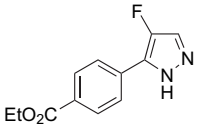
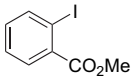
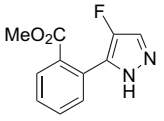
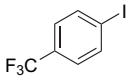
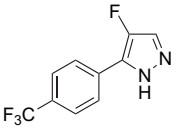
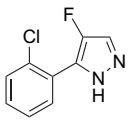
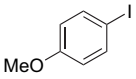
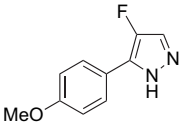
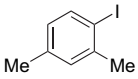
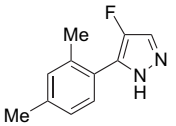
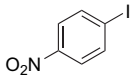
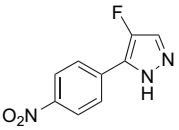
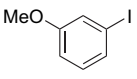
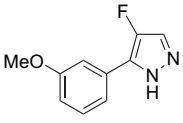
Entry	X	Pd (5 mol %)	Time (h)	Temp (°C)	Yield[b] (%)
1	I	$Pd(PPh_3)_4$	2	60	0
2	I	$Pd(PPh_3)_4$	24	60	4
3	I	$Pd(PPh_3)_4$	24	80	85
4	I	$Pd(PPh_3)_4$	2	100	61
5	I	$PdCl_2(PPh_3)_2$	24	80	82
6	I	$Pd(OAc)_2$	24	80	70
7	I	$Pd(OAc)_2$+4$(PPh_3)_4$	24	80	45
8	Br	$Pd(PPh_3)_4$	24	80	Trace
9[c]	OTf	$Pd(PPh_3)_4$	24	80	32

[a] All reactions were conducted using **3** (1.0 equiv) with **5** (1.1 equiv) in the presence of Pd catalyst (5 mol %).
[b] Isolated yield.
[c] The reaction was carried out in the presence of $^nBu_4NI$ (2.5 eqiuv) under the same conditions.

Table 3. Cross-coupling reaction of **3** with various aryl iodides[a]



3 **6**

Entry	ArX	Time (h)	Product yield[b] (%)	Entry	ArX	Time (h)	Product yield[b] (%)
1		3	 **6a**: 91	6		4	 **6f**: 99
2		3	 **6b**: 78	7		16	 **6g**: 83
3		3	 **6c**: 92	8		16	 **6h**: 89
4		9	 **6d**: 59	9		3	 **6i**: 94
5		5	 **6e**: 84	10		3	 **6j**: 74

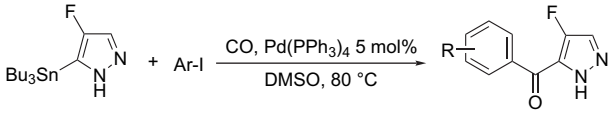
[a] All reactions were conducted using **3** (1 equiv) with aryl halides (1.1–1.3 equiv) in the presence of 5 mol % $Pd(PPh_3)_4$ in DMSO at 100 °C.
[b] Isolated yield.

reaction mixture improved the yield at 25 °C, albeit troublesome procedure (entry 6).[15] (4) The catalytic activity of $PdCl_2(PPh_3)_2$ was slightly inferior to that of $Pd(PPh_3)_4$.

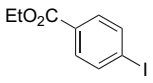
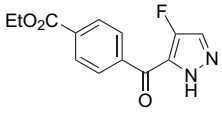
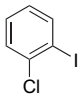
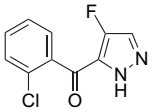
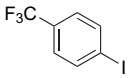
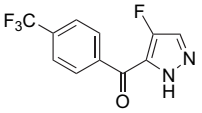
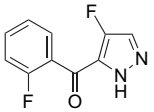
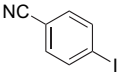
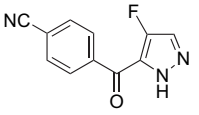
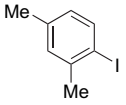
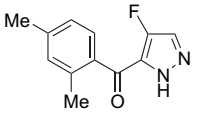
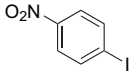
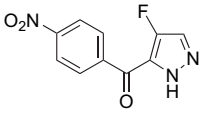
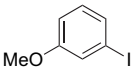
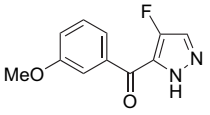
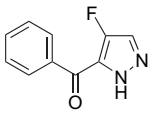
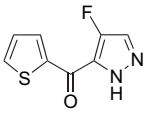
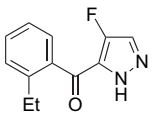
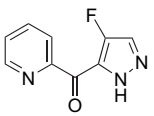
The generality of the coupling reaction was then demonstrated by the synthesis of other 5-aryl-4-fluoro-1*H*-pyrazoles (**6**). These results are summarized in Table 3. Aryl iodides bearing not only an electron-withdrawing group but also an electron-donating group were suitable for the reaction. The substitution patterns on the aromatic ring did not noticeably influence the product yield. The functional group compatibility (ketone, ester, ether, nitro, halide) of the coupling reaction is noteworthy.

After having accomplished the synthesis of 5-aryl-4-fluoro-1*H*-pyrazoles (**6**), we focused our attention on the carbonylative cross-coupling reaction of **3**.[16] We have already investigated the successful carbonylative cross-coupling reaction of the tributyl(1-fluorovinyl)stannane with aryl halides.[17] Thus, the carbonylative cross-coupling reaction of the fluoropyrazole (**3**) with 4′-iodoacetophenone (**5**) was initially examined under a variety of reaction conditions (Table 4). The best result was obtained when the reaction was conducted in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ (5 mol %) in DMSO at 80 °C, affording the corresponding 5-(4′-acetylbenzoyl)-4-fluoro-1*H*-pyrazole (**7a**) in 85% yield (entry 3). These carbonylative coupling reactions required the reaction temperature of 80 °C, and almost no reaction took place at 60 °C (entries 1 and 2). The forced conditions (at 100 °C) resulted in the decreased yield in some degree (entry 4). With regard to the catalytic activity, $PdCl_2(PPh_3)_2$ was comparable to $Pd(PPh_3)_4$, however, $Pd(OAc)_2$ was slightly less effective than $Pd(PPh_3)_4$ (entries 5 and 6). Although the corresponding aryl bromide was less

Table 5. CO-insertive cross-coupling reaction of **3** with various aryl iodides[a]



3 **7**

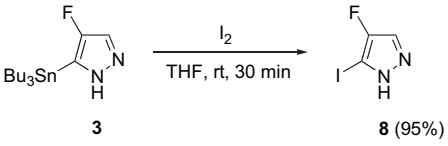
Entry	Ar-I	Product yield[b] (%)	Entry	Ar-I	Product yield[b] (%)
1		 **7b**: 91	7		 **7h**: 36
2		 **7c**: 67	8		 **7i**: 16
3		 **7d**: 62	9		 **7j**: 95
4		 **7e**: 47	10		 **7k**: 74
5		 **7f**: 78	11		 **7l**: 84
6		 **7g**: 83	12		 **7m**: 35

[a] All reactions were conducted using **3** (1 equiv) with aryl iodides (1.1–1.3 equiv) in the presence of 5 mol % $Pd(PPh_3)_4$ in DMSO at 80 °C for 24 h.
[b] Isolated yield.

effective for this carbonylative coupling reaction, the corresponding triflate was also accessible in the presence of $^{n}Bu_4NI$ albeit in low yield (entries 8 and 9).

The generality of the carbonylative coupling reaction was then demonstrated by the synthesis of other 5-acyl-4-fluoro-1*H*-pyrazoles (**7**). These results are summarized in Table 5. The pyrazole (**3**) employed was completely consumed during the reaction, and no ordinary cross-coupling products were detected by GC–MS analysis in the crude reaction mixtures. Although the product yields considerably varied according to the aryl halides employed, these CO-insertion products (**7**) are not easily accessible by other methods.[18] As is the case of the above coupling reaction, the functional group compatibility (ketone, ester, cyano, ether, nitro, halide) of this carbonylative coupling reaction is also noteworthy. It is additionally noted that the relevant heteroaromatic iodides gave the corresponding CO-insertion adducts (entries 11 and 12).

Finally, in addition to the cross-coupling reaction, introduction of iodine to **3** was also examined.[8,9e] The reaction smoothly proceeded to give the corresponding 4-fluoro-5-iodo-1*H*-pyrazole (**8**) in 95% yield (Scheme 3).



3 **8** (95%)

Scheme 3. Synthesis of 4-fluoro-5-iodo-1*H*-pyrazole.

In summary, we have demonstrated the facile one-pot synthesis of **3** via 1,3-dipolar cycloaddition reaction of **2** with diazomethane in excellent yield. The regiochemistry of the cycloaddition was confirmed by chemical transformation and X-ray crystallographic analysis. The cross-coupling reactions of **3** and a variety of aryl iodides smoothly proceeded to give the corresponding 5-aryl-4-fluoro-1*H*-pyrazoles in high yields. Furthermore, similar reactions were conducted under an atmosphere of carbon monoxide to afford the corresponding 5-acyl-4-fluoro-1*H*-pyrazoles.

3. Experimental

3.1. 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 benzylidyne trifluoride ($CF_3C_6H_5$) for ^{19}F NMR spectra.

3.1.1. Preparation of 5-(4′-acetylphenyl)-4-fluoro-1*H*-pyrazole (6a). To a solution containing 117.1 mg (0.312 mmol) of pyrazole **3**[10] and 4′-iodoacetophenone (85 mg, 0.345 mmol) in DMSO (1 mL) was added $Pd(PPh_3)_4$ (18.1 mg, 5 mol %), and the whole mixture was heated to 100 °C. After being stirred for 3 h, the resulting mixture was quenched with ethyl acetate and water, and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. To the residue was added ether (ca. 5 mL) and saturated aqueous KF solution (ca. 5 mL), and the mixture stirred vigorously for a few minutes. The ethereal layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate/triethylamine=200/20/1 then 200/200/1) to give the desired compound (**6a**) as a white solid (57.7 mg, 91%): mp 159.2–160.8 °C; IR (KBr) 3158, 3108, 2951, 1668, 1607, 1416, 1362, 1269, 941, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.64 (3H, s), 7.55 (1H, d, J=4.2 Hz), 7.91 (2H, d, J=8.4 Hz), 8.02 (2H, d, J=8.4 Hz), 10.40 (1H, br s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 26.6, 125.8, 128.9, 136.4, 148.0 (d, J=250.4 Hz), 197.7; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −176.2 (1F, s); GC–MS m/z 204 (37, M^+), 189 (100), 188 (49), 161 (24), 134 (50), 108 (36). Anal. Calcd for $C_{11}H_9FN_2O$: C, 64.70; H, 4.44; N, 13.72. Found: C, 64.60; H, 4.56; N, 13.57.

3.1.2. 5-(4′-Ethoxycarbonylphenyl)-4-fluoro-1*H*-pyrazole (6b). White solid; yield 78%; mp 99.1–100.9 °C; IR (KBr) 3106, 1285, 1712, 1694, 1557, 1484, 924, 859 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (3H, t, J=7.2 Hz), 4.40 (2H, q, J=4.2 Hz), 7.53 (1H, d, J=3.5 Hz), 7.87 (2H, d, J=8.3 Hz), 8.10 (2H, d, J=8.3 Hz), NH proton is missing; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 61.1, 125.5 (d, J=3.7 Hz), 129.8, 130.1, 133.7, 149.2 (d, J=249.1 Hz), 166.3; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −176.3 (1F, s); GC–MS m/z 234 (1, M^+), 233 (32), 188 (100), 160 (14), 134 (35), 107 (53), 75 (6). Anal. Calcd for $C_{12}H_{11}FN_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.58; H, 4.73; N, 12.02.

3.1.3. 4-Fluoro-5-(4′-trifluoromethylphenyl)-1*H*-pyrazole (6c). White solid; yield 92%; mp 109.2–110.1 °C; IR (KBr) 3180, 2962, 1596, 1417, 1335, 1165, 1072, 937, 848, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (1H, d, J=3.7 Hz), 7.63 (2H, d, J=7.7 Hz), 7.85 (2H, d, J=7.7 Hz), 10.82 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 119.5 (d, J=23.0 Hz), 122.2, 125.8 (q, J=3.7 Hz), 126.0, 126.1, 130.2 (q, J=33.0 Hz), 133.8 (d, J=12.5 Hz), 147.7 (d, J=249.7 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −64.0 (3F, s), −176.6 (1F, s); GC–MS m/z 230 (13, M^+), 229 (100), 175 (9), 145 (26), 144 (36), 133 (9). Anal. Calcd for $C_{10}H_6F_4N_2$: C, 52.18; H, 2.63; N, 12.17. Found: C, 52.49; H, 2.67; N, 12.12.

3.1.4. 4-Fluoro-5-(4′-methoxylphenyl)-1*H*-pyrazole (6d). White solid; yield 59%; mp 91.7–92.5 °C; IR (KBr) 3238, 1614, 1587, 1546, 1463, 1243, 1185, 1039, 929, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.84 (3H, s), 6.93 (2H, d, J=8.3 Hz), 7.45 (1H, d, J=4.4 Hz), 7.66 (2H, d, J=8.3 Hz), 11.25 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.2, 114.2, 121.6 (d, J=4.4 Hz), 127.2, 127.3, 132.8, 146.6 (d, J=246.0 Hz), 159.5; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −179.6 (1F, d, J=4.4 Hz); GC–MS m/z 192 (100, M^+), 191 (26), 177 (55), 176 (11), 149 (66), 101 (11), 75 (12). Anal. Calcd for $C_{10}H_9FN_2O$: C, 62.49; H, 4.72; N, 14.58. Found: C, 62.33; H, 4.69; N, 14.56.

3.1.5. 4-Fluoro-5-(4′-nitrophenyl)-1*H*-pyrazole (6e). Yellow solid; yield 84%; mp 195.1–196.1 °C; IR (KBr) 3269, 3156, 1603, 1504, 1346, 1330, 856 cm^{-1}; ^1H NMR

($CDCl_3$, 300 MHz) δ 7.57 (1H, d, J=4.6 Hz), 8.04 (2H, dt, J=9.0, 2.2 Hz), 8.30 (2H, dt, J=9.0, 2.2 Hz), 10.03 (1H, br s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 124.1, 126.4 (d, J=3.7 Hz), 147.2, 148.2 (d, J=251.3 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −175.4 (1F, d, J=4.6 Hz); GC–MS m/z 207 (100, M^+), 206 (13), 177 (40), 149 (32), 134 (56), 107 (11), 75 (50), 50 (17). Anal. Calcd for $C_9H_6FN_3O_2$: C, 52.18; H, 2.92; N, 20.28. Found: C, 52.31; H, 2.99; N, 20.10.

3.1.6. 4-Fluoro-5-phenyl-1*H*-pyrazole (6f). White solid; yield 99%; mp 82.5–83.3 °C; IR (KBr) 3166, 3140, 2890, 1600, 1532, 1447, 1363, 1187, 1097, 940, 759, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.47 (3H, m), 7.50 (1H, d, J=4.4 Hz), 7.76 (2H, dt, J=7.5 Hz), 10.35 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 121.1, 125.9 (d, J=3.7 Hz), 128.3, 128.9, 129.1, 147.2 (d, J=247.9 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −178.2 (1F, s); GC–MS m/z 162 (51, M^+), 161 (100), 133 (11), 108 (47), 107 (68), 106 (18), 104 (15), 77 (67), 76 (35), 51 (22). Anal. Calcd for $C_9H_7FN_2$: C, 66.66; H, 4.35; N, 17.27. Found: C, 66.38; H, 4.44; N, 17.04.

3.1.7. 4-Fluoro-5-(2′-methoxycarbonylphenyl)-1*H*-pyrazole (6g). White solid; yield 83%; mp 96.9–99.0 °C; IR (KBr) 3316, 3170, 2953, 1728, 1587, 1435, 1296, 1263, 1129, 1092, 767, 720, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.81 (3H, s), 7.41–7.63 (4H, m), 7.87 (1H, d, J=7.7 Hz), 10.26 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.3, 119.1 (d, J=21.2 Hz), 128.4, 128.8 (d, J=3.7 Hz), 130.1, 130.25, 130.28, 130.4, 131.7, 147.1 (d, J=146.0 Hz), 168.5; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −177.5 (1F, d, J=5.8 Hz); GC–MS m/z 220 (11, M^+), 189 (19), 188 (100), 133 (14), 132 (97), 131 (29), 106 (16), 75 (6), 50 (7). Anal. Calcd for $C_{11}H_9FN_2O_2$: C, 60.00; H, 4.12; N, 12.72. Found: C, 60.21; H, 4.42; N, 12.22.

3.1.8. 5-(2′-Chlorophenyl)-4-fluoro-1*H*-pyrazole (6h). White solid; yield 89%; mp 70.6–71.5 °C; IR (KBr) 3161, 3134, 2945, 1585, 1529, 1452, 1427, 1190, 1078, 937, 758, 741, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.59 (5H, m), 11.09 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 120.3, 126.8, 127.8 (d, J=3.7 Hz), 129.99, 130.18, 131.05 (d, J=2.5 Hz), 132.8, 147.1 (d, J=247.9 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −175.3 (1F, s); GC–MS m/z 196 (100, M^+), 195 (12), 134 (25), 133 (12), 107 (16), 102 (9), 75 (12). Anal. Calcd for $C_9H_6ClFN_2$: C, 54.98; H, 3.08; N, 14.25. Found: C, 55.31; H, 3.20; N, 14.07.

3.1.9. 4-Fluoro-5-(2′,4′-dimethylphenyl)-1*H*-pyrazole (6i). White solid; yield 94%; mp 90.2–91.3 °C; IR (KBr) 3157, 3087, 2927, 1608, 1527, 1445, 1357, 1098, 941, 817, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (3H, s), 2.36 (3H, s), 7.05–7.26 (3H, m), 7.45 (1H, d, J=4.6 Hz), 10.44 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8 (d, J=3.7 Hz), 21.1, 121.8, 124.9, 129.52, 129.57, 131.3, 136.8, 138.8, 146.8 (d, J=244.8 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −177.2 (1F, s); GC–MS m/z 190 (100, M^+), 189 (17), 175 (13), 162 (30), 148 (21), 146 (11), 115 (11), 77 (10). Anal. Calcd for $C_{11}H_{11}FN_2$: C, 69.46; H, 5.83; N, 14.73. Found: C, 69.43; H, 5.88; N, 14.74.

3.1.10. 4-Fluoro-5-(3′-methoxylphenyl)-1*H*-pyrazole (6j). White solid; yield 74%; mp 53.2–55.0 °C; IR (KBr) 3168, 3139, 2915, 1627, 1601, 1538, 1471, 1435, 1296, 1248, 1209, 1176, 1064, 1035, 941, 837, 768, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.85 (3H, s), 6.89–6.94 (1H, m), 7.32–7.39 (3H, m), 7.50 (1H, d, J=4.6 Hz), 10.33 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.1, 111.1, 114.0, 118.3, 121.1 (d, J=20.6 Hz), 129.9, 130.2, 133.2, 147.1 (d, J=247.9 Hz), 159.8; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −177.2 (1F, d, J=4.6 Hz); GC–MS m/z 192 (100, M^+), 191 (33), 163 (19), 162 (22), 149 (24), 120 (6), 101 (7), 77 (13), 63 (4). Anal. Calcd for $C_{10}H_9FN_2O$: C, 62.49; H, 4.72; N, 14.58. Found: C, 62.57; H, 4.82; N, 14.47.

3.1.11. Preparation of 5-(4′-acetylbenzoyl)-4-fluoro-1*H*-pyrazole (7a).[19] To a solution containing 91.0 mg (0.243 mmol) of pyrazole **3** and 4′-iodoacetophenone (65.2 mg, 0.265 mmol) in DMSO (1 mL) was added a catalytic amount of $Pd(PPh_3)_4$ (14.1 mg, 5 mol %). After argon in the flask was replaced with carbon monoxide (balloon), the whole mixture was heated to 80 °C. After being stirred for 24 h at this temperature, the resulting mixture was cooled to room temperature. After removal of remaining carbon monoxide, the reaction mixture was quenched with hexane/ethyl acetate=3/1 solution and brine, and then extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. To the residue was added hexane/ethyl acetate=3/1 solution (ca. 5 mL) and saturated aqueous KF solution (ca. 5 mL), and the mixture stirred vigorously for a few minutes. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Florisil column chromatography (hexane/ethyl acetate/triethylamine=200/20/1, then 200/200/1) to give the desired compound (**7a**) as a white solid (48.0 mg, 85%): mp 175.9–176.6 °C; IR (KBr) 3269, 3148, 3117, 1657, 1574, 1504, 1470, 1278, 1143, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.67 (3H, s), 7.59 (1H, d, J=5.3 Hz), 8.04 (4H, br s), 10.66 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −176.4 (1F, s); GC–MS m/z 232 (0.4, M^+), 216 (100), 133 (46), 113 (65), 107 (19), 104 (31), 90 (24), 76 (62), 57 (24), 50 (32). Anal. Calcd for $C_{12}H_9FN_2O_2$: C, 62.07; H, 3.91; N, 12.06. Found: C, 61.70; H, 4.10; N, 11.97.

3.1.12. 5-(4′-Ethoxycarbonylbenzoyl)-4-fluoro-1*H*-pyrazole (7b). White solid; yield 91%; mp 149.6–150.3 °C; IR (KBr) 3188, 1717, 1634, 1567, 1448, 1280, 1201, 1023, 915, 831, 746, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (3H, t, J=7.2 Hz), 4.43 (2H, q, J=7.2 Hz), 7.58 (1H, d, J=4.6 Hz), 8.00–8.10 (2H, m), 8.15–8.20 (2H, m), 10.61 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −168.3 (1F, s); GC–MS m/z 262 (3.3, M^+), 261 (30), 216 (100), 188 (48), 148 (46), 133 (40), 113 (74), 112 (90), 104 (56), 76 (69), 75 (79), 50 (43). Anal. Calcd for $C_{13}H_{11}FN_2O_3$: C, 59.54; H, 4.23; N, 10.68. Found: C, 59.67; H, 4.52; N, 10.27.

3.1.13. 4-Fluoro-5-(4′-trifluoromethylbenzoyl)-1*H*-pyrazole (7c). White solid; yield 67%; mp 154.8–156.3 °C; IR (KBr) 3155, 1651, 1574, 1446, 1337, 1066, 1017, 956, 914, 860, 820, 783, 699, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (1H, d, J=4.6 Hz), 7.78 (2H, d, J=8.3 Hz), 8.12 (2H, d, J=8.3 Hz), NH proton is missing; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −64.4 (3F, s), −165.9 (1F, s); GC–MS m/z 258 (0.9, M^+), 257 (26), 173 (35), 172 (57), 145 (84), 144 (100), 113 (69), 112 (65), 95 (30), 75 (26),

57 (26). Anal. Calcd for $C_{11}H_6F_4N_2O$: C, 51.17; H, 2.34; N, 10.85. Found: C, 51.46; H, 2.56; N, 10.64.

3.1.14. 5-(4′-Cyanobenzoyl)-4-fluoro-1*H*-pyrazole (7d). White solid; yield 62%; mp 207.5–210.0 °C; IR (KBr) 3243, 2231, 1651, 1568, 1348, 1284, 1144, 957, 918, 849, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.59 (1H, d, J=4.6 Hz), 7.75–7.85 (2H, m), 8.13 (2H, d, J=8.1 Hz), 10.50 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −170.4 (1F, s); GC–MS m/z 215 (8, M^+), 214 (18), 187 (5), 130 (76), 129 (76), 113 (43), 102 (100), 101 (81), 75 (30), 51 (17). Anal. Calcd for $C_{11}H_6FN_3O$: C, 61.40; H, 2.81; N, 19.53. Found: C, 61.05; H, 2.86; N, 19.17; HRMS (FAB) m/z calcd for $C_{11}H_7FN_3O$: 216.0572 ($M+H^+$). Found: 216.0573.

3.1.15. 4-Fluoro-5-(4′-nitrobenzoyl)-1*H*-pyrazole (7e). Pale yellow solid; yield 47%; mp 186.0–188.5 °C; IR (KBr) 3255, 1652, 1520, 1457, 1348, 1285, 1148, 919, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (1H, d, J=4.4 Hz), 8.21 (2H, d, J=7.9 Hz), 8.36 (2H, d, J=7.9 Hz), 10.48 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −169.4 (1F, s); GC–MS m/z 235 (3, M^+), 234 (22), 217 (17), 149 (39), 113 (79), 112 (100), 104 (56), 103 (71), 76 (49), 75 (67), 50 (39). Anal. Calcd for $C_{10}H_6FN_3O$: C, 51.07; H, 2.57; N, 17.87. Found: C, 51.28; H, 2.62; N, 17.94.

3.1.16. 5-Benzoyl-4-fluoro-1*H*-pyrazole (7f). White solid; yield 78%; mp 151.0–153.8 °C; IR (KBr) 3148, 3161, 1651, 1569, 1450, 1347, 1280, 1201, 1145, 957, 913, 817, 738, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.70 (3H, m), 7.57 (1H, d, J=4.6 Hz), 7.95–8.10 (2H, m), NH proton is missing; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −167.8 (1F, s); GC–MS m/z 190 (3, M^+), 189 (16), 162 (3), 112 (9), 105 (73), 104 (100), 77 (56), 76 (58), 51 (25), 50 (21); HRMS (FAB) m/z calcd for $C_{10}H_8FN_2O$: 191.0620 ($M+H^+$). Found: 191.0621.

3.1.17. 5-(2′-Ethylbenzoyl)-4-fluoro-1*H*-pyrazole (7g). White solid; yield 83%; mp 121.1–123.0 °C; IR (KBr) 3224, 3147, 3111, 2965, 2932, 2874, 1659, 1643, 1566, 1442, 1350, 1275, 1151, 915, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (3H, t, J=7.5 Hz), 2.80 (2H, q, J=7.5 Hz), 7.25–7.40 (2H, m), 7.42–7.51 (2H, m), 7.53 (1H, d, J=4.6 Hz), 10.97 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −165.4 (1F, s); GC–MS m/z 217 (7, M^+-1), 202 (24), 197 (24), 132 (37), 131 (30), 104 (84), 103 (100), 102 (65), 77 (98), 76 (50), 51 (35); HRMS (FAB) m/z calcd for $C_{12}H_{12}FN_2O$: 219.0933 ($M+H^+$). Found: 219.0909.

3.1.18. 5-(2′-Chlorobenzoyl)-4-fluoro-1*H*-pyrazole (7h). White solid; yield 36%; mp 158.0–161.0 °C; IR (KBr) 3237, 1650, 1574, 1445, 1356, 1290, 1148, 1061, 957, 915, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.53 (4H, m), 7.55 (1H, d, J=3.3 Hz), 11.01 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −166.3 (1F, s); GC–MS m/z 225 (4, M^+), 223 (14), 188 (29), 139 (89), 138 (79), 113 (71), 111 (100), 75 (71), 74 (43), 50 (31). Anal. Calcd for $C_{10}H_6ClFN_2O$: C, 53.47; H, 2.69; N, 12.47. Found: C, 53.65; H, 2.82; N, 12.35.

3.1.19. 4-Fluoro-5-(2′-fluorobenzoyl)-1*H*-pyrazole (7i). White solid; yield 16%; mp 155.3–156.9 °C; IR (KBr) 3202, 3143, 3110, 1651, 1643, 1633, 1612, 1573, 1454, 1351, 1294, 1145, 957, 915, 828, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15–7.35 (2H, m), 7.50–7.70 (2H, m), 7.55 (1H, d, J=4.2 Hz), 10.77 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −114.8 (1F, s), −166.5 (1F, s); GC–MS m/z 207 (11, M^+-1), 123 (77), 122 (100), 112 (13), 98 (36), 94 (51), 75 (15), 74 (21). Anal. Calcd for $C_{10}H_6F_2N_2O$: C, 57.70; H, 2.91; N, 13.46. Found: C, 57.66; H, 2.96; N, 13.67.

3.1.20. 4-Fluoro-5-(2′,4′-dimethylbenzoyl)-1*H*-pyrazole (7j). White solid; yield 95%; mp 136.5–137.6 °C; IR (KBr) 3191, 1636, 1569, 1346, 1202, 1159, 963, 890, 797 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.39 (3H, s), 2.46 (3H, s), 7.05–7.20 (2H, m), 7.45–7.55 (1H, m), 7.52 (1H, d, J=4.2 Hz), 10.73 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −165.9 (1F, s); GC–MS m/z 217 (9, M^+-1), 197 (21), 133 (42), 132 (67), 105 (63), 104 (100), 103 (61), 78 (48), 77 (66), 76 (51). Anal. Calcd for $C_{12}H_{11}FN_2O$: C, 66.05; H, 5.08; N, 12.84. Found: C, 65.90; H, 5.25; N, 12.65.

3.1.21. 4-Fluoro-5-(3′-methoxylbenzoyl)-1*H*-pyrazole (7k). White solid; yield 74%; mp 148.1–149.7 °C; IR (KBr) 3209, 3157, 1651, 1645, 1568, 1456, 1349, 1283, 1158, 1136, 1038, 992, 876, 815, 768, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.88 (3H, s), 7.15–7.30 (2H, m), 7.40–7.65 (2H, m), 7.58 (1H, d, J=4.6 Hz), 11.44 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −165.3 (1F, s); GC–MS m/z 220 (5, M^+), 219 (50), 135 (70), 134 (100), 113 (21), 112 (30), 107 (61), 106 (77), 76 (53). Anal. Calcd for $C_{11}H_9FN_2O_2$: C, 60.00; H, 4.12; N, 12.72. Found: C, 59.72; H, 4.15; N, 12.55.

3.1.22. 4-Fluoro-5-(thiophen-2-yl)-1*H*-pyrazole (7l). White solid; yield 84%; mp 147.6–149.8 °C; IR (KBr) 3193, 3147, 1634, 1574, 1505, 1455, 1410, 1361, 1275, 1138, 1042, 898, 829, 786, 760, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21 (1H, dd, J=3.9, 1.1 Hz), 7.58 (1H, d, J=4.4 Hz), 7.77 (1H, dd, J=5.0, 1.1 Hz), 8.18 (1H, d, J=3.9 Hz), 10.83 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −165.7 (1F, s); GC–MS m/z 196 (2, M^+), 195 (20), 112 (16), 111 (100), 110 (93), 83 (12), 57 (10); HRMS (FAB) m/z calcd for $C_8H_6FN_2OS$: 197.0185 ($M+H^+$). Found: 197.0184.

3.1.23. 4-Fluoro-5-(pyridin-2-yl)-1*H*-pyrazole (7m). White solid; yield 35%; mp 159.1–162.9 °C; IR (KBr) 3183, 1667, 1557, 1491, 1439, 1410, 1348, 1219, 1103, 1004, 946, 910, 845, 816, 742, 713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53 (1H, d, J=4.2 Hz), 7.60 (1H, ddd, J=7.7, 5.0, 1.3 Hz), 7.99 (1H, dt, J=5.0, 1.3 Hz), 8.31 (1H, dm, J=7.7 Hz), 8.75 (1H, dm, J=5.0 Hz), 13.30 (1H, br s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −165.0 (1F, s); GC–MS m/z 190 (2, M^+-1), 163 (51), 113 (58), 112 (49), 107 (28), 79 (43), 78 (100), 51 (58). Anal. Calcd for $C_9H_6FN_3O$: C, 56.55; H, 3.16; N, 21.98. Found: C, 56.70; H, 3.18; N, 21.83.

3.1.24. Preparation of 4-fluoro-5-iodo-1*H*-pyrazole (8). To a solution containing 181.9 mg (0.312 mmol) of pyrazole **3** in THF (3 mL) was added iodine (150.0 mg, 0.59 mmol), and the whole mixture was stirred at room temperature for 30 min. The resulting mixture was quenched with aqueous

$NaHSO_3$ solution, and extracted with hexane/ether=3/1 solution. The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=9/1, then 1/1) to give the desired compound (**8**) as a white solid (97.2 mg, 95%): mp 132.5–133.4 °C; IR (KBr) 3147, 3113, 2915, 1574, 1568, 1403, 1338, 1188, 1076, 1056, 934, 794, 658 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46 (1H, d, J=5.1 Hz), 12.27 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 80.9, 116.8, 151.9 (d, J=246.7 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −171.9 (1F, br s); GC–MS m/z 213 (M^++2, 4), 212 (M^++1, 100), 211 (M^+, 9), 185 (19), 127 (26), 85 (9), 58 (44), 57 (10), 56 (10). Anal. Calcd for $C_3H_2FIN_2$: C, 17.00; H, 0.95; N, 13.22. Found: C, 17.38; H, 0.98; N, 13.18.

3.2. Crystal data for 6a

($C_{11}H_9FN_2O\cdot H_2O$): M=222.22, T=93(2) K, triclinic, space group $P\bar{1}$, a=8.329(15), b=11.137(17), c=11.87(3) Å, α=76.62(7)°, β=73.46(7)°, γ=82.32(7)°, V=1024(3) Å^3, Z=4, Dx=1.441 Mg m^{-3}, μ=0.113 mm^{-1}, λ=0.71075 Å, θ_{max}=27.48°, 11,589 measured reflections, 4612 independent reflections, 308 refined parameters, GOF=1.019, $R[F^2>2\sigma(F^2)]$=0.0778, $wR(F^2)$=0.2160. The intensity data were collected on a Rigaku RAXIS-RAPID diffractometer. The structure was solved by direct methods (SHELXS-97[20]) and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedures on F^2 for all reductions (SHELXL-97[21]). All hydrogen atoms were positioned geometrically and refined as riding. CCDC-258756 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/const/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223 336 033, or deposit@ccdc.cam.ac/uk).

Acknowledgements

We are most grateful to Professor Masayuki Koikawa at Saga University for his execution and valuable discussion on the DFT calculations. We also greatly thank F-Tech Co. Ltd for a gift of 1,1-difluoroethylene.

References and notes

1. Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell: Oxford, UK, 2000.
2. (a) Wei, F.; Zhao, B.-X.; Huang, B.; Zhang, L.; Sun, C.-H.; Dong, W.-L.; Shin, D.-S.; Miao, J.-Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6342–6347; (b) Cottineau, B.; Chenault, J.; Guillaumet, G. *Tetrahedron Lett.* **2006**, *47*, 817–820; (c) Bekhit, A. A.; Adbel-Aziem, T. *Bioorg. Med. Chem.* **2004**, *12*, 1935–1945; (d) Popsavin, M.; Torovic, L.; Sapic, S.; Stankov, S.; Kapor, A.; Tomic, Z.; Popsavin, V. *Tetrahedron* **2002**, *58*, 569–580; (e) Okada, I.; Fukuchi, T. *J. Pesticide Sci.* **2000**, *25*, 310–320; *Chem. Abstr.* **2000**, *133*, 218748; (f) Torrens, A.; Castrillo, J. A.; Redondo, J. *Synlett* **1999**, 765–767; (g) Hueso-Rodríguez, J. A.; Berrocal, J.; Gutiérrez, B.; Farré, A. J.; Frigola, J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 269–272; (h) Yamamoto, S.; Sato, T.; Morimoto, K.; Makino, K. *J. Heterocycl. Chem.* **1991**, *28*, 1849–1852.
3. (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, UK, 2004; (b) Hiyama, T. *Organofluorine Compounds*; Springer: Berlin, 2000; (c) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995.
4. (a) Liu, H.; Huang, X.; Shen, J.; Luo, X.; Li, M.; Xiong, B.; Chen, G.; Shen, J.; Yang, Y.; Jiang, H.; Chen, K. *J. Med. Chem.* **2002**, *45*, 4816–4827; (b) Price, M. L. P.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2000**, *122*, 9455–9466; (c) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365.
5. Elguero, J. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984.
6. For some reports of 4-fluoropyrazole derivatives, see: (a) Chanteau, F.; Plantier-Royon, R.; Portella, C. *Synlett* **2004**, 512–516; (b) Sloop, J. C.; Bumgardner, C. L.; Loehle, W. D. *J. Fluorine Chem.* **2002**, *118*, 135–147; (c) Bouillon, J.-P.; Didier, B.; Dondy, B.; Doussot, P.; Plantier-Royon, R.; Portella, C. *Eur. J. Org. Chem.* **2001**, 187–192; (d) Zhang, Q.; Lu, L. *Tetrahedron Lett.* **2000**, *41*, 8545–8548; (e) Funabiki, K.; Ohtsuki, T.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **1995**, 239–240; (f) Shi, X.; Ishihara, T.; Yamanaka, H.; Gupton, J. T. *Tetrahedron Lett.* **1995**, *36*, 1527–1530; (g) Dondy, B.; Doussot, P.; Portella, C. *Tetrahedron Lett.* **1994**, *35*, 409–412; (h) Bumgardner, C.; Sloop, J. C. *J. Fluorine Chem.* **1992**, *56*, 141–146; (i) Molines, H.; Wakselman, C. *J. Org. Chem.* **1989**, *54*, 5618–5620; (j) Ishihara, T.; Okada, Y.; Kuroboshi, M.; Shinozaki, T.; Ando, T. *Chem. Lett.* **1988**, 819–822; (k) Kagaruki, S. R. F.; Kitazume, T.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3221–3222; (l) Fabra, F.; Fos, E.; Vilarrasa, J. *Tetrahedron Lett.* **1979**, 3179–3180; (m) Fabra, F.; Vilarrasa, J.; Coll, J. *J. Heterocycl. Chem.* **1978**, *15*, 1447–1449; (n) Reichardt, C.; Halbritter, K. *Justus Liebigs Ann. Chem.* **1975**, 470–483.
7. For some reports of 3- and 5-fluoropyrazole derivatives, see: (a) Volle, J.-N.; Schlosser, M. *Eur. J. Org. Chem.* **2000**, 823–828; (b) Chi, K.-W.; Kim, S.-J.; Park, T.-H.; Gatilov, Y. V.; Bagryanskaya, I. Y.; Furin, G. G. *J. Fluorine Chem.* **1999**, *98*, 29–36; (c) Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T. *J. Org. Chem.* **1996**, *61*, 2763–2769; (d) Ikeda, I.; Kogame, Y.; Okahara, M. *J. Org. Chem.* **1985**, *50*, 3640–3642.
8. Hanamoto, T.; Hakoshima, Y.; Egashira, M. *Tetrahedron Lett.* **2004**, *45*, 7573–7576.
9. (a) Fray, M. J.; Allen, P.; Bradley, P. R.; Challenger, C. E.; Closier, M.; Evans, T. J.; Lewis, M. L.; Mathias, J. P.; Nichols, C. L.; Po-Ba, Y. M.; Snow, H.; Stefaniak, M. H.; Yuong, H. V. *Heterocycles* **2006**, *67*, 489–494; (b) Li, J. J.; Carson, K. G.; Trivedi, B. K.; Yue, W. S.; Ye, Q.; Glynn, R. A.; Miller, S. R.; Connor, D. T.; Roth, B. D.; Luly, J. R.; Low, J. E.; Heilig, D. J.; Yang, W.; Qin, S.; Hunt, S. *Bioorg. Med. Chem. Lett.* **2003**, *11*, 3777–3790; (c) Calle, M.; Cuadrado, P.; González-Nogal, A. M.; Valero, R. *Synthesis* **2001**, 1949–1958; (d) Yagi, K.; Ogura, T.; Numata, A.; Ishii, S.; Arai, K. *Heterocycles* **1997**, *45*, 1463–1466; (e) Sakamoto, T.; Shiga, F.;

Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1992**, *33*, 813–818.
10. Hanamoto, T.; Koga, Y.; Kido, E.; Kawanami, T.; Furuno, H.; Inanaga, J. *Chem. Commun.* **2005**, 2041–2043.
11. These substituted pyrazoles are inevitably mixtures due to their rapid tautomerization. The structure of **3** signified one form.
12. (a) Kobayashi, Y.; Yamashita, T.; Takahashi, K.; Kuroda, H.; Kumadaki, I. *Chem. Pharm. Bull.* **1984**, *32*, 4402–4409; (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons, L3: New York, NY, 1976; (c) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301–7315.
13. Wavefunction, Inc. *Spartan '04 Windows*; Wave function: 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA, 2004.
14. Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
15. (a) Tivola, P. B.; Deagostino, A.; Prandi, C.; Venturello, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 437–441; (b) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.
16. Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500–7506.
17. Hanamoto, T.; Handa, K.; Mido, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2497–2502.
18. For some reports of acylpyrazole derivatives, see: (a) Jung, M. E.; Min, S.-J.; Houk, K. N.; Ess, D. *J. Org. Chem.* **2004**, *69*, 9085–9089; (b) Mallouk, S.; Bougrin, K.; Doua, H.; Benhida, R.; Soufiaoui, M. *Tetrahedron Lett.* **2004**, *45*, 4143–4148; (c) Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Tetrahedron* **2002**, *58*, 2397–2404; (d) Tsuge, O.; Kanemasa, S.; Suzuki, T.; Matsuda, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2851–2860; (e) Kano, K.; Scarpetti, D.; Warner, J. C.; Anselme, J.-P.; Springer, J. P.; Arison, B. H. *Can. J. Chem.* **1986**, *64*, 2211–2219; (f) Doyle, M. P.; Colsman, M. R.; Dorow, R. L. *J. Heterocycl. Chem.* **1983**, *20*, 943–946; (g) El-Kholy, I. E.; Mishrikey, M. M.; Fuid-Alla, H. M.; Nashed, M. A. *J. Heterocycl. Chem.* **1979**, *16*, 849–853; (h) Severin, T.; Adhikary, P.; Bräutigam, I. *Chem. Ber.* **1976**, *109*, 1179–1183.
19. The ^{13}C NMR spectra of compounds **7a–7m** were not successfully measured due to their low solubility in $CDCl_3$ solutions.
20. Sheldrick, G. M. *SHELXS-97, Program for Solution of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.
21. Sheldrick, G. M. *SHELXL-97, Program for Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.