

A novel synthesis of 5-perfluorophenyl 4,5-dihydro-1H-pyrazoles in THF or water

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Abstract

5-Perfluorophenyl 4,5-dihydro-1H-pyrazoles were synthesized from 1,3-dipolar cycloaddition reaction of perfluorobenzyl 2,4,6-triisopropylbenzenesulfonylhydrazone and α,β -unsaturated carbonyl compounds or acrylonitrile in THF or water. It was worthy to note that better results were obtained when water was employed as the solvent, which was considered as an effective, economic and environmentally friendly method to synthesize these pyrazole derivatives.

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1. Introduction

The Bamford–Stevens reaction has been widely used to synthesize diazo compounds [1]. Usually, the reaction is carried out in conventional solvent such as benzene, toluene, acetonitrile, dioxane, *N,N*-dimethylformamide, tetrahydrofuran, hexane, ethyl acetate, nitromethane, ether and methyl alcohol [2], which greatly limited their attractiveness from the environmental point of view. Water, being cheap, readily available, nontoxic and environment concerns, results in a safer process and has clear advantages as an environmentally friendly solvent alternative in organic synthesis and is attracting more and more attention [3]. Furthermore, the use of water facilitates the catalyst-product separation, which greatly interest chemists [4].

1H-pyrazoles and 4,5-dihydro-1H-pyrazoles derivatives have been found diverse applications in medicine and agriculture. In particular, they are widely used as antitumor, antibacterial, anti-fungal, anti-parasitic, anti-tubercular and insecticidal agents [5]. Some of these compounds also have anti-inflammatory, anti-diabetic, anesthetic and analgesic properties [6]. Hence, various mild methods capable of generating libraries of heterocycles of this type are very attractive.

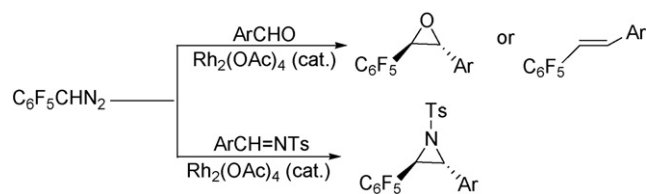
The introduction of fluorine into organic molecules can make a profound and unexpected influence on the physical and biological properties. Recently, there has been growing interest in fluorine-containing aromatic compounds due to the unique physical properties of the fluorine atom [7b]. In our previous work [7], we have reported a catalytic process for the perfluorophenyl diazomethane with activated aryl aldehydes or tosyl imines to give perfluorophenyl-containing epoxides, alkenes or aziridines exclusively with *trans* structure (Scheme 1).

2. Results and discussions

As a part of our continuing study on the chemical transformation of perfluorophenyl diazomethane [7], we recently investigated the reactivity of dipolar cycloaddition of perfluorophenyl diazomethane with α,β -unsaturated carbonyl compounds or acrylonitrile. Initially, perfluorobenzyl 2,4,6-triisopropylbenzenesulfonylhydrazone **1** was treated with 1.2 equiv. quantity of methyl acrylate **2a** in the presence of triethylamine in THF at room temperature to give the corresponding product **3a** in 88% yield (Scheme 2). In the reaction, the perfluorophenyl diazomethane was generated *in situ* by Bamford–Stevens reaction using perfluorobenzyl 2,4,6-triisopropylbenzenesulfonylhydrazone in the presence of

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Scheme 1.

Table 1
Reaction results of **1** with **2**

Entry	Y in 2	Product	Yield (%) ^a		M.P. (°C)
			Method A ^b	Method B ^c	
1	CO ₂ Me (2a)	3a	88	99	130–132
2	CO ₂ Et (2b)	3b	90	99	128–130
3	CO ₂ Bu ^t (2c)	3c	98	99	127–129
4	CO ₂ Bu ⁿ (2d)	3d		99	119–121
5	CO ₂ Bu ⁱ (2e)	3e		99	139–141
6	CN (2f)	3f	94	99	124–126
7	C(O)Me (2g)	3g	95	45	127–129

^a Isolate yield base on **1**.^b Method A: THF as the solvent.^c Method B: water as the solvent.

triethylamine, which avoided the hazard of diazomethane in its handling.

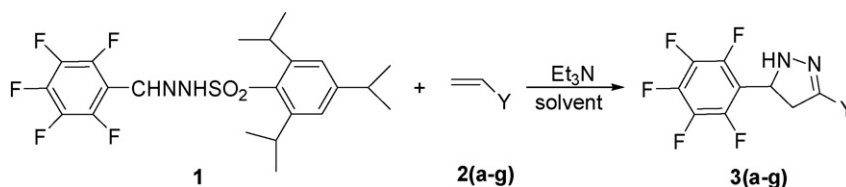
The configuration of product **3a** was fully characterized by various spectra. From its MS, it is clearly showed the molecular ion peak at 294 (M^+) and basic peak at 194 ($C_6F_5CHN_2^+$) in EI. The ¹H NMR spectrum of **3a** showed a broad peak at $\delta = 6.38$ (s, NH), and the no equal ring CH₂ at 3.14 and 3.43, respectively, they couple with each other ($J = 17$ Hz). Another ring proton is 5.40 ppm. ¹⁹F NMR spectrum of **3a** exhibited a

typical perfluorophenyl group at $\delta = -141.5$, -153.4 and -160.8 ppm in the 2:1:2 integral. Its infrared spectrum has the strong absorption of N–H at 3277 cm^{-1} .

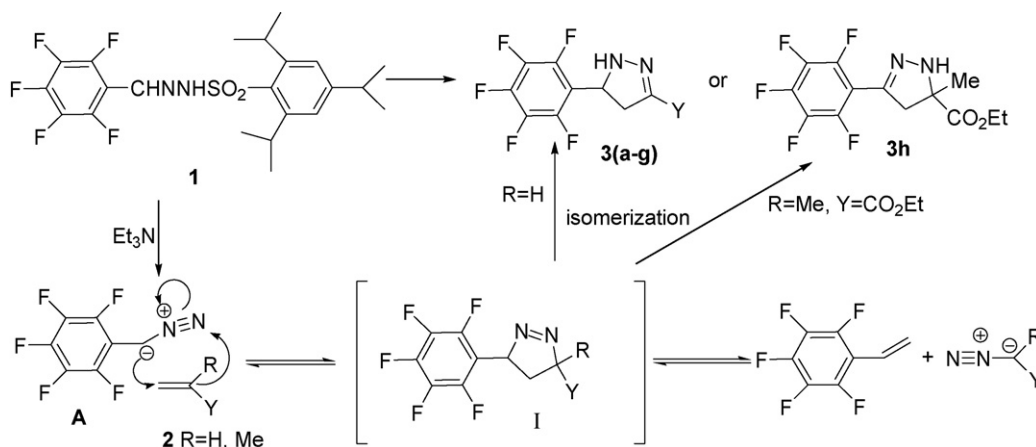
Under the prompting of such good result mentioned above, we examined a variety of alkenes under the same reaction conditions. However, only the terminal alkenes bearing electron-withdrawing group such as acrylate, acrylonitrile and vinyl ketone could give the desired products in high yields. Other terminal alkenes bearing electron-donating groups such as ethyl vinyl ether and butyl vinyl ether, styrene and push-pull alkenes did not gave the desired products. The results were summarized in Table 1 (Method A).

The reaction mechanism is proposed as follows (Scheme 3) [8]. Firstly, triethylamine was added to a colorless solution of **1** in THF, then there appeared an intense yellow coloration, indicating the formation of a diazo compound **A** which reacted with α,β -unsaturated carbonyl compounds or acrylonitrile **2** to form 1,3-dipolar cycloaddition product 5-(perfluorophenyl)-4,5-dihydro-3H-pyrazole-3-carboxylate **I**. The intermediate **I** was unstable, which, on one hand, isomerized quickly to the corresponding product **3**, on the other hand decompose to diazo compound and dipolarophile by two routes. The corresponding products (**3a–g**) were colorless crystals. However, when they were dissolved in organic solvents for a few hours, the colorless solution gradually changed to primrose. It was worth to notice that in the case of ethyl methacrylate **2h**, because of the methyl group, the product was ethyl 5-methyl-3-(perfluorophenyl)-4,5-dihydro-1H-pyrazole-5-carboxylate, and it was buff liquid. Its ¹H NMR spectra clearly conformed to its structure.

Recently, water as the green solvent for chemical reactions has attracted considerable attention because of cost, safety and environment concerns. This prompted us to investigate whether



Scheme 2.



Scheme 3.

Table 2
Selected bond lengths (Å) and angles (°) of compound **3a** and **3f**

Compound 3a		Compound 3f	
Bond lengths (Å)	Angles (°)	Bond lengths (Å)	Angles (°)
C ₆ –C ₇ : 1.513(3)	C ₆ –C ₇ –N ₁ : 109.48(17)	C ₁ –C ₇ : 1.507(4)	C ₁ –C ₇ –N ₁ : 110.6(2)
C ₇ –N ₁ : 1.477(3)	C ₇ –N ₁ –N ₂ : 113.05(17)	C ₇ –N ₁ : 1.473(3)	C ₇ –N ₁ –N ₂ : 114.0(2)
N ₁ –N ₂ : 1.342(2)	N ₁ –N ₂ –C ₉ : 109.75(16)	N ₁ –N ₂ : 1.334(3)	N ₁ –N ₂ –C ₉ : 108.5(2)
N ₂ –C ₉ : 1.291(3)	N ₂ –C ₉ –C ₈ : 113.71(17)	N ₂ –C ₉ : 1.292(3)	N ₂ –C ₉ –C ₈ : 114.5(2)
C ₉ –C ₈ : 1.507(3)	C ₉ –C ₈ –C ₇ : 101.19(17)	C ₉ –C ₈ : 1.494(4)	C ₉ –C ₈ –C ₇ : 101.3(2)
C ₈ –C ₇ : 1.554(3)	C ₈ –C ₇ –C ₆ : 115.80(16)	C ₈ –C ₇ : 1.542(4)	C ₈ –C ₇ –C ₁ : 116.5(2)
C ₉ –C ₁₀ : 1.463(3)	C ₁₀ –C ₉ –C ₈ : 128.27(18)	C ₉ –C ₁₀ : 1.423(4)	C ₁₀ –C ₉ –C ₈ : 124.5(2)
	C ₁₀ –C ₉ –N ₂ : 118.02(17)		C ₁₀ –C ₉ –N ₂ : 120.6(3)
Angle of phenyl ring-five membered: 89.37°		Angle of phenyl ring-five membered: 87.05°	

this reaction could occur in water. Subsequently, we attempted the reaction of **1** with 1.2 equiv. quantity of methyl acrylate **2a** in the presence of triethylamine in water at room temperature. Fortunately, the corresponding 1,3-dipolar cycloaddition product was obtained in quantitative yield though the reaction system was not homogenous. The results were summarized in Table 1 (Method B).

Excited by the above results, we would like to know whether the reaction could also occur without triethylamine. Accordingly, **1** was treated with 1.2 equiv. quantity of methyl acrylate **2a** in water at room temperature for more than 1 week. Unfortunately, the start materials were unchangeable (monitored by TLC) and **1** was reclaimed (Table 1, entry 2), which showed that the reaction could not occur absolutely without base.

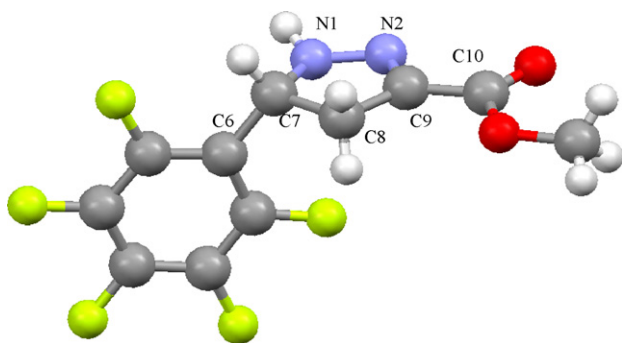


Fig. 1. Crystal structure of **3a**.

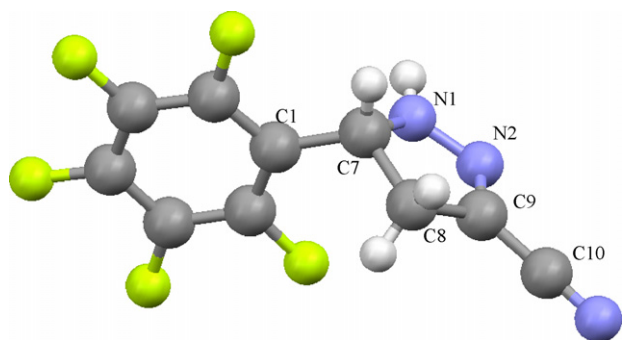


Fig. 2. Crystal structure of **3f**.

The structure of **3a** and **3f** were further confirmed by the X-ray crystal diffraction analysis (Figs. 1 and 2). It is noteworthy that the torsion angle of phenyl and five membered ring was almost 90°. The selected bond lengths and angles of compound **3a** and **3f** were summarized in Table 2.

3. Conclusions

In summary, we described a novel method to synthesize the 5-perfluorophenyl 4,5-dihydro-1H-pyrazoles through the Bamford–Stevens reaction and dipolar cycloaddition reaction in THF or water. We were excited to find that the corresponding reactions of **1** and **2** proceeds very efficiently in a water suspension medium and that 4,5-dihydro-1H-pyrazole derivatives **3** are obtained in quantitative, simple operation and easier product work-up can be achieved. This methodology is superior from the point of view of yield and is more environmentally friendly than the reported methods.

4. Experimental

Melting points were measured in a SGW[®]X-4 micro-melting point apparatus and were uncorrected. ¹H and ¹⁹F NMR spectra were recorded in CDCl₃ (unless mentioned in text), Bruker AM-300 spectrometer with Me₄Si and CFCl₃ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectrum or high-resolution mass spectra (HRMS) were obtained on a Finnigan GC-MS 4021 or a Finnigan MAR-8430 instrument using the electron impact ionization technique (70 eV), respectively. The X-ray structural analysis was performed with a Rigaku/AFC 7R Diffractometer. Elemental analyses were performed by this institute.

4.1. General procedure for the reaction in THF

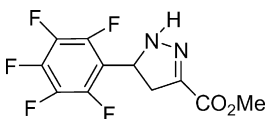
To a mixture of **2** (1.2 equiv.) and Et₃N (51 mg, 0.5 mmol, 1.0 equiv.) in THF (2 mL), a solution of **1** (238 mg, 0.5 mmol) in THF (2 mL) was added dropwise over 2 h by the means of a syringe pump at room temperature. After addition, the reaction mixture was stirred for another 1 h until complete consumption

of starting material as judged by TLC analysis. Removal of the solution in vacuo, and the residue was purified by silica gel chromatography using ethyl ester-hexane as eluent to afford the desired products **3**.

4.2. General procedure for the reaction in water

To a suspension of a mixture of **1** (238 mg, 0.5 mmol) and **2** (1.2 equiv.) in water (2 mL), Et₃N (51 mg, 0.5 mmol, 1.0 equiv.) was added dropwise with vigorous stirring over 42 min. After addition, the reaction mixture was stirred for another 1 h at room temperature until complete consumption of starting material as judged by TLC analysis. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 × 8 mL) and the combined organic phases were washed with brine and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure using a rotary evaporator to afford the desired products **3**. The yield was almost quantitative. The crude crystals thus obtained were recrystallized from ethyl ester and hexane to give pure **3** as colorless crystal.

4.2.1. Methyl 5-(perfluorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate **3a**



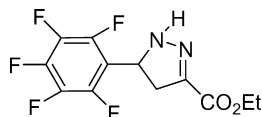
IR (ν_{\max} , cm⁻¹): 3277, 1689, 1551, 1501, 1444, 1358, 1254, 1131, 1012, 953, 874, 750. ¹H NMR δ (ppm): 6.38 (s, 1H), 5.40 (dd, $J_1 = 10$ Hz, $J_2 = 13$ Hz, 1H), 3.88 (s, 3H), 3.43 (dd, $J_1 = 13$ Hz, $J_2 = 17$ Hz, 1H), 3.14 (dd, $J_1 = 10$ Hz, $J_2 = 17$ Hz, 1H). ¹⁹F NMR δ (ppm): -141.5~-141.6 (m, 2F), -153.4 (t, $J = 21$ Hz, 1F), -160.8~-161.0 (m, 2F). ¹³C NMR δ (ppm): 162.6, 145.2 (dm, $J = 253.7$ Hz), 141.5, 141.1 (dm, $J = 248.2$ Hz), 137.7 (dm, $J = 252.8$ Hz), 114.3 (t, $J = 15$ Hz), 54.0, 52.3, 37.3. MS m/z (ion, %): 294 (M⁺, 68), 234 (28), 194 (100), 168 (12), 127 (12), 95 (43). Anal. Calcd for C₁₁H₇F₅N₂O₂: C; 44.91, H; 2.40, N; 9.52%. Found: C; 44.89, H; 2.39; N; 9.56%.

4.2.1.1. X-ray data of **3a**. C₁₁H₇F₅N₂O₂: MW = 294.19, CCDC no. 632046, monoclinic, space group: P2(1)/c, $a = 12.4056(18)$ Å, $b = 7.5033(11)$ Å, $c = 13.628(2)$ Å; $\alpha = 90.00^\circ$, $\beta = 115.458(3)^\circ$, $\gamma = 90.00^\circ$; $V = 1145.4(3)$ Å³, $Z = 4$, $D_c = 1.706$ g/cm³, $F(000) = 592$. Radiation, Mo K α ($\lambda = 0.71073$ Å). Crystal dimension, 0.501 mm × 0.453 mm × 0.307 mm.

Intensity data were collected at 293(2) K with a Bruker P4 four-circle diffractometer with graphite monochromator and Mo K α radiation ($\lambda = 0.71073$ Å). A total of 2615 independent reflection were measured in range $1.82 < \theta < 28.23^\circ$. The structure was solved by directed methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of fullmatrix least-square refinement was based on F^2 . The final R and wR value were 0.0457 and 0.1084,

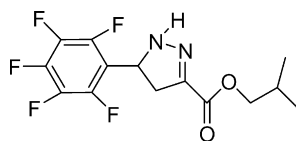
respectively. All calculations were performed using the SHELX-97 program.

4.2.2. Ethyl 5-(perfluorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate **3b**



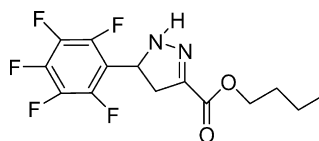
IR (ν_{\max} , cm⁻¹): 3328, 2986, 1699, 1556, 1527, 1500, 1406, 1338, 1289, 1245, 1120, 1012, 985, 945, 872, 750. ¹H NMR δ (ppm): 6.39 (s, 1H), 5.39 (dd, $J_1 = 10$ Hz, $J_2 = 13$ Hz, 1H), 4.33 (q, $J = 4$ Hz, 2H), 3.42 (dd, $J_1 = 13$ Hz, $J_2 = 17$ Hz, 1H), 3.13 (dd, $J_1 = 10$ Hz, $J_2 = 17$ Hz, 1H), 1.37 (t, $J = 7$ Hz, 3H). ¹⁹F NMR δ (ppm): -141.8~-141.9 (m, 2F), -153.9 (t, $J = 20$ Hz, 1F), -161.3~-161.4 (m, 2F). MS m/z (ion, %): 308 (M⁺, 56), 263 (27), 234 (35), 194 (100), 168 (9), 141 (21), 95 (48). Anal. Calcd for C₁₂H₉F₅N₂O₂: C; 46.76, H; 2.94, N; 9.09%. Found: C; 46.82, H; 2.98; N; 9.07%.

4.2.3. Isobutyl 5-(perfluorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate **3c**



IR (ν_{\max} , cm⁻¹): 3298, 2969, 1734, 1655, 1506, 1386, 1310, 1255, 1124, 993, 826, 788, 753. ¹H NMR δ (ppm): 5.39 (dd, $J_1 = 10$ Hz, $J_2 = 13$ Hz, 1H), 4.28 (t, $J = 7$ Hz, 2H), 3.42 (dd, $J_1 = 13$ Hz, $J_2 = 17$ Hz, 1H), 3.14 (dd, $J_1 = 10$ Hz, $J_2 = 17$ Hz, 1H), 1.77~1.68 (m, 2H), 1.47~1.39 (m, 2H), 0.96 (t, $J = 7$ Hz, 3H). ¹⁹F NMR δ (ppm): -141.3~-141.4 (m, 2F), -153.4 (t, $J = 20$ Hz, 1F), -160.8~-161.0 (m, 2F). MS m/z (ion, %): 336 (M⁺, 20), 280 (94), 263 (93), 234 (64), 194 (100), 168 (9), 141 (21), 57 (35), 41 (55). Anal. Calcd for C₁₄H₁₃F₅N₂O₂: C; 50.01, H; 3.90, N; 8.33%. Found: C; 49.98, H; 3.92; N; 8.23%.

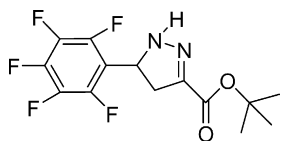
4.2.4. Butyl 5-(perfluorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate **3d**



IR (ν_{\max} , cm⁻¹): 3283, 2966, 1574, 1523, 1503, 1456, 1362, 1253, 1172, 1120, 1037, 1006, 950, 881, 756. ¹H NMR δ (ppm): 5.40 (dd, $J_1 = 10$ Hz, $J_2 = 13$ Hz, 1H), 4.06 (d, $J = 7$ Hz, 2H), 3.43 (dd, $J_1 = 13$ Hz, $J_2 = 17$ Hz, 1H), 3.15 (dd, $J_1 = 10$ Hz, $J_2 = 17$ Hz, 1H), 2.10~2.02 (m, 1H), 0.98 (d, $J = 7$ Hz, 6H). ¹⁹F NMR δ (ppm): -141.4~-141.5 (m, 2F), -153.5 (t, $J = 21$ Hz, 1F), -160.89~-161.1 (m, 2F). MS m/z (ion, %): 336 (M⁺, 28),

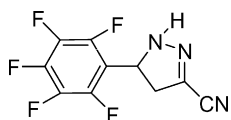
280 (65), 263 (55), 234 (47), 194 (67), 168 (4), 57 (35), 41 (100). Anal. Calcd for $C_{14}H_{13}F_5N_2O_2$: C; 50.01, H; 3.90, N; 8.33%. Found: C; 50.05, H; 3.88; N; 8.24%.

4.2.5. *tert*-butyl 5-(perfluorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate **3e**



IR (ν_{\max} , cm^{-1}): 3292, 2991, 1665, 1562, 1524, 1452, 1436, 1393, 1368, 1256, 1139, 1036, 1008, 953, 750. ^1H NMR δ (ppm): 5.35 (dd, $J_1 = 10$ Hz, $J_2 = 13$ Hz, 1H), 4.23 (s, 1H), 3.38 (dd, $J_1 = 10$ Hz, $J_2 = 17$ Hz, 1H), 3.11 (dd, $J_1 = 10$ Hz, $J_2 = 17$ Hz, 1H), 1.56 (s, 9H). ^{19}F NMR δ (ppm): $-141.7 \sim -141.8$ (m, 2F), -154.2 (t, $J = 20$ Hz, 1F), $-161.5 \sim -161.7$ (m, 2F). MS m/z (ion, %): 336 (M^+ , 3), 280 (35), 263 (12), 234 (18), 194 (18), 168 (2), 57 (100), 41 (50). Anal. Calcd for $C_{14}H_{13}F_5N_2O_2$: C; 50.01, H; 3.90, N; 8.33%. Found: C; 50.19, H; 3.92; N; 8.24%.

4.2.6. 5-(Perfluorophenyl)-4,5-dihydro-1H-pyrazole-3-carbonitrile **3f**

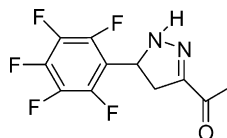


IR (ν_{\max} , cm^{-1}): 3358, 2230, 1507, 1389, 1121, 1011, 952, 874. ^1H NMR δ (ppm): 6.51 (s, 1H), 5.44 (dd, $J_1 = 10$ Hz, $J_2 = 13$ Hz, 1H), 3.40 (dd, $J_1 = 13$ Hz, $J_2 = 17$ Hz, 1H), 3.09 (dd, $J_1 = 10$ Hz, $J_2 = 17$ Hz, 1H). ^{19}F NMR δ (ppm): $-141.4 \sim -141.5$ (m, 2F), -152.3 (t, $J = 21$ Hz, 1F), $-160.1 \sim -160.3$ (m, 2F). MS m/z (ion, %): 261 (M^+ , 90), 194 (100), 181 (55), 168 (21), 94 (60). Anal. Calcd for $C_{10}H_4F_5N_3$: C; 45.99, H; 1.54, N; 16.09%. Found: C; 46.30, H; 1.48; N; 16.15%.

4.2.6.1. X-ray data of **3f**. $C_{10}H_4F_5N_3$: MW = 261.16, CCDC no. 632045, monoclinic, space group: $P2(1)/n$, $a = 15.2700(19)$ Å, $b = 5.2118(6)$ Å, $c = 39.706(5)$ Å; $\alpha = 90.00^\circ$, $\beta = 102.178(4)^\circ$, $\gamma = 90.00^\circ$; $V = 3088.9(7)$ Å³, $Z = 12$, $D_c = 1.685$ g/cm³, $F(000) = 1560$. Radiation, Mo K α ($\lambda = 0.71073$ Å). Crystal dimension, 0.30 mm \times 0.20 mm \times 0.10 mm.

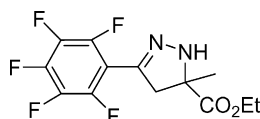
Intensity data were collected at 273(2) K with a Bruker P4 four-circle diffractometer with graphite monochromator and Mo K α radiation ($\lambda = 0.71073$ Å). A total of 2404 independent reflection were measured in range $2.10 < \theta < 25.00^\circ$. The structure was solved by directed methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of fullmatrix least-square refinement was based on F^2 . The final R and wR value were 0.0475 and 0.0955, respectively. All calculations were performed using the SHELX-97 program.

4.2.7. 1-(5-(Perfluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)ethanone **3g**



IR (ν_{\max} , cm^{-1}): 3314, 1641, 1541, 1499, 1418, 1347, 1241, 1132, 1020, 994, 949, 874, 802, 767. ^1H NMR δ (ppm): 6.38 (s, 1H), 5.38 (dd, $J_1 = 10$ Hz, $J_2 = 13$ Hz, 1H), 3.36 (dd, $J_1 = 13$ Hz, $J_2 = 17$ Hz, 1H), 3.05 (dd, $J_1 = 10$ Hz, $J_2 = 17$ Hz, 1H), 2.46 (s, 3H). ^{19}F NMR δ (ppm): $-141.8 \sim -141.9$ (m, 2F), -153.5 (t, $J = 20$ Hz, 1F), $-160.8 \sim -161.0$ (m, 2F). MS m/z (ion, %): 278 (M^+ , 9), 263 (5), 235 (8), 194 (9), 181 (2), 168 (1), 111 (17), 43 (100). Anal. Calcd for $C_{10}H_7F_5N_2O_2$: C; 47.49, H; 2.54, N; 10.07%. Found: C; 47.53, H; 2.58; N; 10.01%.

4.2.8. Ethyl 5-methyl-3-(perfluorophenyl)-4,5-dihydro-1H-pyrazole-5-carboxylate **3h**



IR (ν_{\max} , cm^{-1}): 3346, 2986, 1738, 1651, 1525, 1495, 1314, 1274, 1183, 1097, 990, 809, 765. ^1H NMR δ (ppm): 6.67 (s, 1H), 4.25 (q, $J = 7$ Hz, 2H), 3.66 (d, $J = 17$ Hz, 1H), 3.00 (d, $J = 17$ Hz, 1H), 1.61 (s, 3H), 1.31 (t, $J = 7$ Hz, 3H). ^{19}F NMR δ (ppm): $-139.5 \sim -139.6$ (m, 2F), -154.0 (t, $J = 20$ Hz, 1F), $-162.0 \sim -162.2$ (m, 2F). MS m/z (ion, %): 323 (M^+ , 1), 249 (20), 195 (65), 167 (15), 73 (2), 43 (48). HRMS-EI (70 eV, m/z): calcd for $C_{13}H_{11}F_5N_2O_2$: 322.0741. Found: 322.0756.

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