Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Fluorine Chemistry 124 (2003) 211–217
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

Synthesis of polyfluorophenyl substituted-4,5-dihydropyrazole derivatives via 1,3-dipolar cycloaddition of nitrile imine with ethyl acrylate

Li-Ping Song[a,b], Shi-Zheng Zhu[b,*]

[a]School of Chemistry and Pharmaceutics, East China University of Science and Technology, Shanghai 200237, China
[b]Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai 200032, China

Received 20 May 2003; received in revised form 13 August 2003; accepted 15 August 2003

Abstract

Oxidation of aldehyde 4-chloro-2,3,5,6-tetrafluorophenylhydrazones (**1**) with [bis(acetoxy)iodo]benzene leads to the formation of nitrile imines (**2**) which reacted in situ with ethyl acrylate to produce 3-substituted-1-(4-chloro-2,3,5,6-tetrafluorophenyl)-5-ethoxycarbonyl-4,5-dihydropyrazoles (**3**) in moderate to good yields. The structures of new compounds were fully confirmed by their spectral data, elemental analyses and X-ray diffraction (XRD) analysis. A plausible reaction mechanism for the synthesis of title compounds is presented.

Keywords: 1,3-Dipolar cycloaddition; Nitrile imine; Ethyl acrylate; 4,5-Dihydropyrazole derivatives

1. Introduction

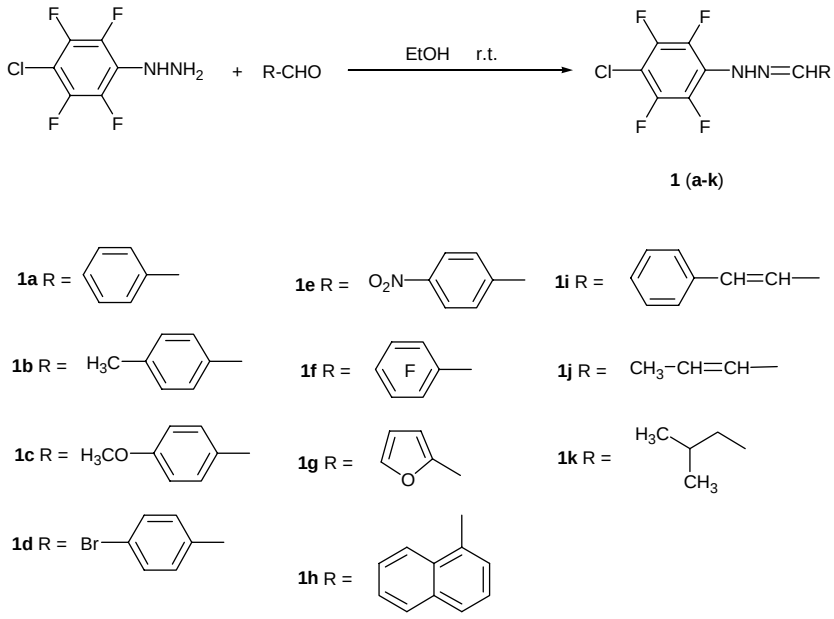
Recently, there has been a growing interest in the synthesis of fluorine-containing heterocyclic compounds because of their potential biological activities [1]. 4,5-Dihydropyrazole derivatives have been studied extensively due to their diverse chemical reactivity, broad spectrum of biological activity and variety of industrial application [2]. In addition, it is known that 4,5-dihydropyrazole derivatives were useful compounds not only as intermediates in the synthesis of pyrazoles, but also as effective chemical bleaching agents, luminescent and fluorescent substances [3]. In terms of biological activity, substituted 4,5-dihydropyrazoles were used as anti-inflammatory or anti-coagulating agent [4]. Thus, the synthesis of 4,5-dihydropyrazole derivatives is of current importance. These compounds were generally prepared via 1,3-dipolar cycloaddition reaction of nitrile imines with alkene [5]. A series of useful methods for generating nitrile imine intermediates in situ have been mentioned by Rai and Hassner [6]. Dehydrogenation of an aldehyde hydrazone with Chloramine-T (CAT) [7], [bis(acetoxy)iodo]benzene [8], polymer supported [bis(acetoxy)iodo]benzene [9], lead tetraacetate [10] or mercuic acetate [11] also lead to nitrile imines. Nitrile imine can also be formed by reaction of α(azobenzyl)hydroperoxide formed on auto oxidation of an aldehyde hydrazone with triethylamine [12]. These results prompted us to use the methodology to aldehyde 4-chloro-2,3,5,6-tetrafluorophenylhydrazones (**1**). In previous work [13], we reported the preparation of 5-cyano-4,5-dihydropyrazoles. In continuation of our studies on the application of nitrile imine, we investigated the reaction of nitrile imine with ethyl acrylate. Herein, we wish to report the generation of nitrile imines from the oxidation of aldehyde 4-chloro-2,3,5,6-tetrafluorophenylhydrazones with [bis(acetoxy)iodo]benzene in situ, and their simultaneous trapping with ethyl acrylate to produce a series of 3-substituted-1-(4-chloro-2,3,5,6-tetrafluorophenyl)-5-ethoxycarbonyl-4,5-dihydropyra-zole derivatives (**3**).

2. Results and discussion

Aldehyde 4-chloro-2,3,5,6-tetrafluorophenylhydrazones (**1**) were readily prepared by the reaction of aldehydes and 4-chloro-2,3,5,6-tetrafluorophenylhydrazine in EtOH at room temperature (Scheme 1). After recrystallization from petroleum-ether ethyl acetate, they were purified enough to be used. XRD analysis of compound **1a** showed that due to the fluorine atoms in one of aromatic ring, there exists H···F inter molecular hydrogen bonds between two molecules, resulting in the formation of cross-stacking of two

* Corresponding author. Fax: +86-21-6416-6128.
E-mail address: zhusz@mail.sioc.ac.cn (S.-Z. Zhu).

0022-1139/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2003.08.005



Scheme 1.

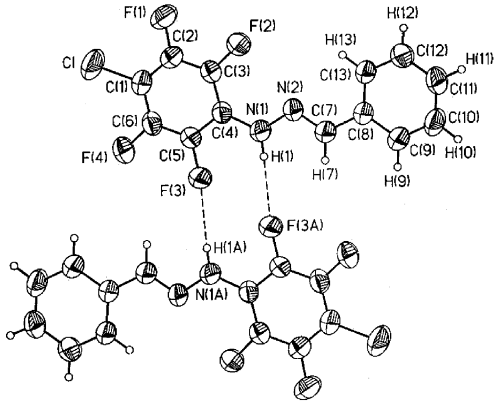


Fig. 1. Molecular structure of **1a**, showing the existence of H···F hydrogen bond.

molecules in the unit cell. Molecular structure of compound **1a** is shown in Fig. 1. The stacking diagram of compound **1a** is shown in Fig. 2. The crystal data and refinement details are summarized in Table 2. Selected bond lengths and bond angles of compound **1a** are listed in Table 3.

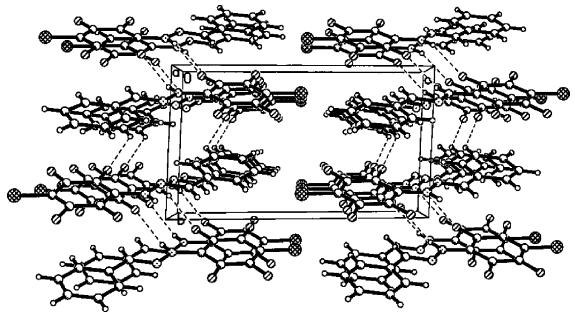
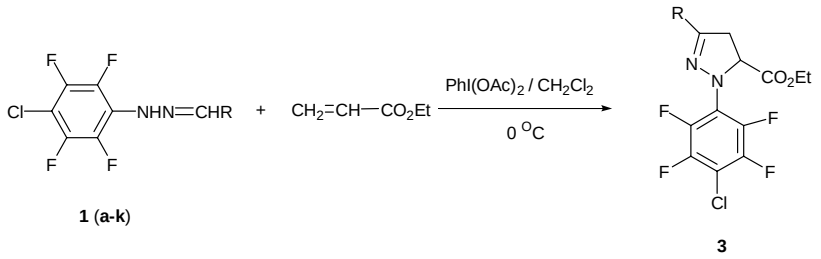


Fig. 2. The stacking diagram of **1a**.

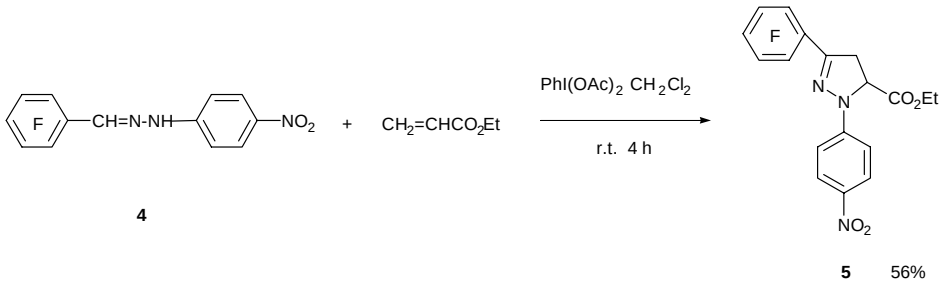
Oxidation of **1** with [bis(acetoxy)iodo]benzene in the presence of ethyl acrylate (Scheme 2) occurred smoothly at 0 °C for 4 h, after general work-up, giving the expected 1,3-disubstituted 5-ethoxycarbonyl-4,5-dihydropyrazoles in moderated to good yields.

The method is not only applicable to aromatic aldehyde bearing electron-donating substituent or electron-withdrawing substituent, but also α,β-unsaturated aromatic aldehyde, fused aromatic aldehyde and heterocyclic aldehyde. However, the results showed that the electron-withdrawing substituted group on phenyl ring affected the reaction activity of nitrile imine. For example, in most cases, the reactions were carried out at 0 °C, and TLC analysis showed the reaction was completed within 4 h. In the case of **1e**, under the same conditions, treatment of **1e** with [bis(acetoxy)iodo]benzene in the presence of ethyl acrylate, the starting material **1e** was not disappeared completely within 4 h at 0 °C (monitored by TLC). The completion of reaction must be carried out at room temperature for another 3 h, which means the reaction occurred at higher temperature when **1e** was used as starting material. Furthermore, by comparison, the alternative compound pentafluoroaledhyde 4-nitro-phenylhydrazone (**4**) was synthesized to be investigated the relation between the reaction condition and electronic effect of substituent on phenyl group. Similar result was observed by mean of reaction of pentafluoroaledhyde 4-nitro-phenylhydrazone (**4**) with [bis(acetoxy)iodo]benzene in the presence of ethyl acrylate (Scheme 3). Expected compound **5** was obtained in 56% yield after 4 h stirring at room temperature. The different reaction condition can be attributed to the strong electron-withdrawing effect of nitro group.

On the other hand, it was noted that in the cases of **1j** and **1k**, when the aliphatic aldehyde hydrazones were used as starting materials, the yields of the expected products were



Scheme 2.



Scheme 3.

rather lower (see Table 1, entries 10, 11). This can be attributed to the unstability of nitrile imine intermediate, in which there were no aromatic cycles conjugated in the dipole system. The reaction conditions and reaction results are summarized in Table 1.

It is known that 1,3-dipolar cycloaddition reaction of nitrile imines to acrylonitrile is a regioselective reaction, yielding 5-cyano-4,5-dihydropyrazoles exclusively [14]. The same regioselective reaction was observed when ethyl acrylate was employed. The structures of the products were fully confirmed by their elemental analyses and spectral data. For instance, in their ^{1}H NMR spectra, the five-position proton in the 4,5-dihydropyrazole was found as doublet of doublet in the region δ 5.00–5.20, whereas the four-position protons in the compound **3** were found as ABX system in the region δ 3.50–3.70. The mass spectra of compound **3** showed a very similar fragmentation pattern, and in most cases, the base peak was $M^+ - CO_2Et$ peak. The ^{19}F NMR spectra of 4,5-dihydropyrazole showed a very similar pattern in the region δ −140 to −141 and −146 to −147 for the four fluorine atoms, respectively. It should be indicated that, the reaction of trifluoroacetonitrile phenylimine with allyloxybenzene gave two regio-isomeric products in the ratio of 7:1, approximately [15]. However, in our cases, the title compounds were obtained exclusively, without the formation of regio-isomeric products. The structure of 4,5-dihydropyrazole **3** was further confirmed by XRD analysis. A fine crystal of **3i** suitable for X-ray diffraction (XRD) analysis was obtained from chromatography following recrystallization from petroleum-ethyl acetate. Fig. 3 shows the molecular

Table 1
Preparation of compounds **3**

Entry	R	Condition[a]		Product	Yield (%)[b]
		Temperature (°C)	Time (h)		
1	C_6H_5–	0	4	**3a**	65
2	*p*-$CH_3C_6H_4$–	0	4	**3b**	53
3	*p*-$CH_3OC_6H_4$–	0	4	**3c**	51
4	*p*-BrC_6H_4–	0	4	**3d**	56
5	*p*-$O_2NC_6H_4$–	RT	3	**3e**	54
6	C_6F_5–	0	4	**3f**	71
7	Furfuryl–	0	4	**3g**	62
8	Naphthyl-1–	0	4	**3h**	69
9	C_6H_5CH=CH–	0	4	**3i**	56
10	Propenyl–	0	4	**3j**	25
11	iso-Butyl–	0	4	**3k**	20

[a] All reactions were carried out in CH_2Cl_2.
[b] Isolated yield based on **1**.

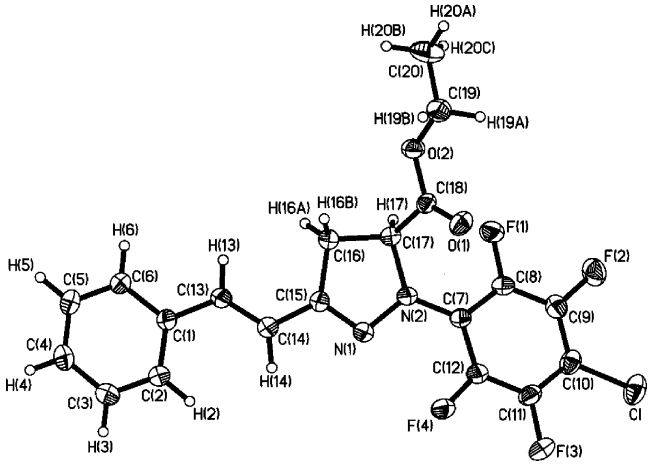


Fig. 3. Molecular structure of compound **3i**.

Table 2
Crystal data and details of structural determination for **1a** and **3i**

	Compound **1a**	Compound **3i**
Formula	$C_{13}H_7ClF_4N_2$	$C_{20}H_{15}ClF_4N_2O_2$
Formula weight	306.66	426.79
Crystal size (mm^3)	0.578 × 0.498 × 0.156	0.156 × 0.467 × 0.311
Crystal system	Triclinic	Monoclinic
Space group	*P*-1 (no. 2)	$P2_1/n$ (no. 14)
a (Å)	6.432(1)	9.245(2)
b (Å)	7.531(1)	21.544(4)
c (Å)	12.887(1)	9.824(2)
α (°)	92.22(1)	90.00
β (°)	96.17(1)	105.76(3)
γ (°)	90.87(1)	90.00
V ($Å^3$)	620.04(14)	1884.0(7)
Z	2	4
D_{calcd}	1.621	1.505
2θ range (°)	2–50	2–50
μ (mm^{-1})	0.347	0.261
F(0 0 0)	304	872
Total reflections	4128	5368
Unique reflections	2850 ($R_{int} = 0.0182$)	4315 ($R_{int} = 0.0335$)
Observed reflections ($I > 2\sigma(I)$)	1735	2205
Data/restraints/parameters	2850/0/183	4315/0/286
Goodness of fit on F^2	1.078	0.947
Final *R* indices ($I > 2\sigma(I)$)	$R_1 = 0.0574$, $wR_2 = 0.1375$	$R_1 = 0.0672$, $wR_2 = 0.1489$
R indices (all data)	$R_1 = 0.0862$, $wR_2 = 0.1616$	$R_1 = 0.1306$, $wR_2 = 0.1843$

Data were collected at 293(2) K on Bruker P4 diffractometer with graphite monochromator and Mo Kα radiation ($\lambda = 0.71073$ Å). Refinement method: full-matrix least-squares on F^2.

structure of compound **3i**. The crystal data and refinement details are summarized in Table 2. Selected bond lengths and bond angles of compound **3i** are listed in Table 3.

A plausible mechanism for the generation of nitrile imines is analogous to the oxidation of the aldehyde hydrazones with lead tetracetate [8] as well as mercuric acetate [11] and is illustrated in Scheme 4.

In summary, a series of 3-substituted-1-(4-chloro-2,3,5,6-tetrafluorophenyl)-5-ethoxycarbonyl-4,5-dihydropyrazoles (**3**) were prepared by oxidation of aldehyde 4-chloro-2,3,5,6-tetrafluorophenylhydrazones (**1**) with [bis(acetoxy)iodo]benzene in the presence of ethyl acrylate. The biological activity of typical compounds was measured,

Table 3
Selected bond lengths (Å) and bond angles (°) of compounds **1a** and **3i**

Compound **1a**		Compound **3i**	
Bond length (Å)			
C(4)–N(1)	1.372(3)	N(1)–N(2)	1.389(3)
N(1)–N(2)	1.364(2)	N(2)–C(17)	1.466(4)
N(2)–C(7)	1.276(3)	C(16)–C(17)	1.529(4)
C(7)–C(18)	1.456(3)	C(15)–C(16)	1.492(4)
N(1)–H(1)	0.860	N(1)–C(15)	1.291(4)
F(3)···H(1A)	2.323	C(14)–C(15)	1.444(4)
F(3)···H(1A)–N(1A)	3.103	C(17)–C(18)	1.512(4)
		N(2)–C(7)	1.377(4)
Bond angle (°)			
N(4)–N(1)–N(2)	102.9(2)	C(15)–N(1)–N(2)	108.2(2)
N(1)–N(2)–C(7)	115.4(2)	N(1)–N(2)–C(17)	112.2(2)
N(2)–C(7)–C(8)	121.7(2)	N(2)–C(17)–C(16)	102.9(2)
F(3)···H(1A)–N(1A)	151.01	C(17)–C(16)–C(15)	102.2(2)
		C(16)–C(15)–N(1)	114.4(3)

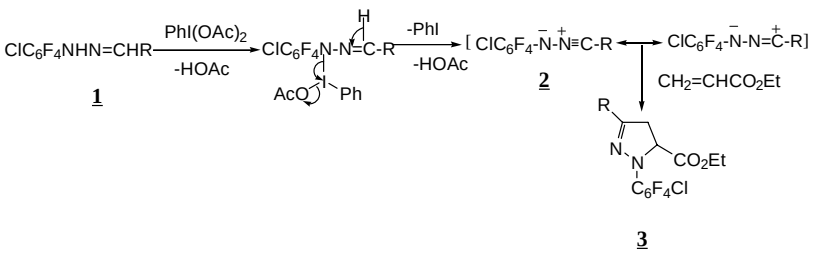
indicating polyfluorophenyl substituted-4,5-dihydropyrazole derivatives have moderate biological activity as embryotoxic, uricosuric, interleukin antagonist, complement inhibitor and metabolic, etc. A further chemical transformation of the new compounds **3** is under investigation.

3. Experimental

Melting points were measured on a Temp-Melt apparatus and are uncorrected. Solvents were dried before use. ^{1}H NMR and ^{19}F NMR spectra were recorded on a Bruker AM-300 spectrometer with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectra or high resolution mass spectra (HRMS) were obtained on a Finnigan GC-MS 4021 or a Finnigan MAT-8430 instrument respectively. Elemental analyses were performed by this Institute. X-ray diffraction crystal structure analysis was obtained on Bruker P4 instrument. [Bis(acetoxy)iodo]benzene was purchased from Acros.

3.1. A general procedure for the preparation of 4,5-dihydropyrazoles

A solution of [bis(acetoxy)iodo]benzene (0.322 g, 1 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a 20 ml



Scheme 4.

flask containing aldehyde 4-chloro-2,3,5,6-tetrafluorophenylhydrazone (**1**) (1 mmol) and ethyl acrylate (5 ml). After stirring at 0 °C for 4 h, TLC analysis shown the reaction was completed. The reaction mixture was then concentrated under vacuum. To the residue was added 20 ml of CH_2Cl_2 and the organic layer was washed with 5% aq. Na_2CO_3 solution (10 ml), brine (10 ml), and dried with anhydrous $MgSO_4$. After evaporation of the solvent, the crude material was purified by column chromatography on silica gel using petroleum-ethyl acetate as eluent. The reaction yields are shown in Table 1.

*3.1.1. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-phenyl-4,5-dihydropyrazole (**3a**)*

m.p. 116–118 °C; IR (KBr): *v* 2996, 1731, 1636, 1506, 1488, 1220, 1165, 1112 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 7.71–7.67 (m, 2H, Ar–H), 7.42–7.39 (m, 3H, Ar–H), 5.02 (dd, $J = 11.7$ Hz, $J = 7.2$ Hz, 1H, pyrazole 5-H), 4.16 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.69–3.50 (m, ABX system, 2H, pyrazole 4-H), 1.20 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.4 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −147.8 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 402/400 $[M]^+$ (7/19), 329/327 $[M - CO_2Et]^+$ (33/100), 77 $[C_6H_5]^+$ (7); Anal. Calcd. for $C_{18}H_{13}ClF_4N_2O_2$: C, 53.95; H, 3.27; N, 6.99. Found: C, 54.09; H, 3.21; N, 6.88.

*3.1.2. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-(4-methylphenyl)-4,5-dihydropyrazole (**3b**)*

m.p. 118–120 °C; IR (KBr): *v* 2992, 1733, 1634, 1486, 1216, 1162, 1107 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 7.57 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.21 (d, $J = 8.4$ Hz, 2H, Ar–H), 5.01 (dd, $J = 12.0$ Hz, $J = 7.2$ Hz, 1H, pyrazole 5-H), 4.16 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.67–3.48 (m, ABX system, 2H, pyrazole 4-H), 2.38 (s, 1H, Ar–CH_3), 1.19 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.5 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −147.8 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 416/414 $[M]^+$ (7/18), 343/341 $[M - CO_2Et]^+$ (34/100), 91 $[CH_3Ph]^+$ (14); Anal. Calcd. for $C_{19}H_{15}ClF_4N_2O_2$: C, 55.02; H, 3.65; N, 6.75. Found: C, 55.04; H, 3.45; N, 6.61.

*3.1.3. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-(4-methoxyphenyl)-4,5-dihydropyrazole (**3c**)*

m.p. 120–122 °C; IR (KBr): *v* 2996, 1730, 1637, 1608, 1489, 1265, 1218, 1165, 1111 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 7.63 (d, $J = 9.0$ Hz, 2H, Ar–H), 6.92 (d, $J = 9.0$ Hz, 2H, Ar–H), 4.98 (dd, $J = 11.4$ Hz, $J = 7.2$ Hz, 1H, pyrazole 5-H), 4.16 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.84 (s, 1H, $ArOCH_3$), 3.66–3.47 (m, ABX system, 2H, pyrazole 4-H), 1.20 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.5 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −147.8 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 432/430 $[M]^+$ (9/25), 359/357 $[M - CO_2Et]^+$ (35/100), 148 $[C_6F_4]^+$ (18); Anal. Calcd. for $C_{19}H_{15}ClF_4N_2O_3$: C, 52.98; H, 3.51; N, 6.50. Found: C, 53.02; H, 3.36; N, 6.31.

*3.1.4. 3-(4-Bromophenyl)-1-(4-chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-4,5-dihydropyrazole (**3d**)*

m.p. 136–138 °C; IR (KBr): *v* 2992, 1731, 1637, 1502, 1487, 1219, 1161, 1106 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 7.57–7.51 (m, 4H, Ar–H), 5.03 (dd, $J = 11.7$ Hz, $J = 7.2$ Hz, 1H, pyrazole 5-H), 4.16 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.66–3.48 (m, ABX system, 2H, pyrazole 4-H), 1.20 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.2 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −147.7 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 482/480/478 $[M]^+$ (5/21/16), 409/407/405 $[M - CO_2Et]^+$ (26/100/78), 328/326 $[M - CO_2Et–Br]^+$ (8/25); Anal. Calcd. for $C_{18}H_{12}BrClF_4N_2O_2$: C, 45.07; H, 2.52; N, 5.84. Found: C, 45.03; H, 2.45; N, 5.88.

*3.1.5. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-(4-nitrophenyl)-4,5-dihydro-pyrazole (**3e**)*

m.p. 118–120 °C; IR (KBr): *v* 2986, 1737, 1638, 1597, 1573, 1505, 1489, 1343, 1157, 1107 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 8.14 (d, $J = 9.0$ Hz, 2H, Ar–H), 7.73 (d, $J = 9.0$ Hz, 2H, Ar–H), 5.05 (dd, $J = 12.0$ Hz, $J = 7.2$ Hz, 1H, pyrazole 5-H), 4.08 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.62–3.43 (m, ABX system, 2H, pyrazole 4-H), 1.12 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −141.9 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −147.7 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 447/445 $[M]^+$ (6/16), 374/372 $[M - CO_2Et]^+$ (35/100), 328/326 $[M - CO_2Et–NO_2]^+$ (11/33); Anal. Calcd. for $C_{18}H_{12}ClF_4N_3O_4$: C, 48.50; H, 2.71; N, 9.43. Found: C, 48.68; H, 2.78; N, 9.35.

*3.1.6. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-(pentafluorophenyl)-4,5-dihydropyrazole (**3f**)*

m.p. 106–108 °C; IR (KBr): *v* 1733, 1530, 1484, 1224, 1157, 1115, 1107 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 5.01 (dd, $J = 11.7$ Hz, $J = 6.9$ Hz, 1H, pyrazole 5-H), 4.17 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.76–3.60 (m, ABX system, 2H, pyrazole 4-H), 1.23 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.3 (d, $J = 15.0$ Hz, 2F, $C_6F_5–$, F2, F6), −141.7 (d, $J = 15, 0$ Hz, 2F, $ClC_6F_4–$, F2, F6), −147.3 (d, $J = 15.0$ Hz, 2F, $ClC_6F_4–$, F3, F5), −152.5 (t, $J = 24.0$ Hz, 1F, $C_6F_5–$, F4), −161.2 to −161.3(m, 2F, $C_6F_5–$, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 492/490 $[M]^+$ (4/13), 419/417 $[M - CO_2Et]^+$ (33/100), 197 $[ClC_6F_4]^+$ (6); Anal. Calcd. for $C_{18}H_8ClF_9N_2O_2$: C, 44.06; H, 1.64; N, 5.71. Found: C, 44.15; H, 1.62; N, 5.65.

*3.1.7. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-(furfur-2-yl)-4,5-dihydropyrazole (**3g**)*

m.p. 110–112 °C; IR (KBr): ν 3149, 2994, 1731, 1639, 1505, 1486, 1217, 1173, 1111 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 7.52 (d, $J = 1.6$ Hz, 1H, furfuryl-H), 6.68 (d, $J = 3.6$ Hz, 1H, furfuryl-H), 6.50–6.49 (m, 1H, furfuryl-H), 4.96 (dd, $J = 11.1$ Hz, $J = 7.8$ Hz, 1H, pyrazole 5-H), 4.17 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.64–3.50 (m, ABX system, 2H, pyrazole 4-H), 1.20 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.2 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −147.2 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 392/390 $[M]^+$ (11/32), 319/317 $[M - CO_2Et]^+$ (33/100); Anal. Calcd. for $C_{16}H_{11}ClF_4N_2O_3$: C, 49.19; H, 2.84; N, 7.17. Found: C, 49.41; H, 2.75; N, 7.12.

*3.1.8. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-(naphth-1-yl)-4,5-dihydropyrazole (**3h**)*

m.p. 96–98 °C; IR (KBr): ν 2982, 1755, 1638, 1506, 1489, 1191, 1138, 1109 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 9.25 (d, $J = 8.4$ Hz, 1H, naphthyl-H), 7.88 (d, $J = 8.4$ Hz, 2H, naphthyl-H), 7.66–7.45 (m, 4H, naphthyl-H), 5.07 (dd, $J = 12.3$ Hz, $J = 6.0$ Hz, 1H, pyrazole 5-H), 4.17 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.93–3.66 (m, ABX system, 2H, pyrazole 4-H), 1.21 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −141.9 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −147.7 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 452/450 $[M]^+$ (10/29), 379/377 $[M - CO_2Et]^+$ (34/100), 127 $[C_{10}H_7]^+$ (63); Anal. Calcd. for $C_{22}H_{15}ClF_4N_2O_2$: C, 58.61; H, 3.35; N, 6.21. Found: C, 58.73; H, 3.31; N, 6.10.

*3.1.9. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-styryl-4,5-dihydropyrazole (**3i**)*

m.p. 148–150 °C; IR (KBr): ν 2997, 1740, 1637, 1507, 1491, 1212, 1133, 1121 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 7.50–7.49 (m, 2H, Ar–H), 7.41–7.32 (m, 3H, Ar–H), 7.12 (d, $J = 16.5$ Hz, 1H, =CH–), 6.74 (d, $J = 16.5$ Hz, 1H, =CH–), 5.03 (dd, $J = 11.1$ Hz, $J = 6.9$ Hz, 1H, pyrazole 5-H), 4.18 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.58–3.42 (m, ABX system, 2H, pyrazole 4-H), 1.22 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.5 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −148.3 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 428/426 $[M]^+$ (10/29), 355/353 $[M - CO_2Et]^+$ (33/100), 103 $[C_6H_5CH{=}CH]^+$ (24), 77 $[C_6H_5]^+$ (16); Anal. Calcd. for $C_{20}H_{15}ClF_4N_2O_2$: C, 56.28; H, 3.54; N, 6.56. Found: C, 56.17; H, 3.40; N, 6.41.

*3.1.10. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3-propenyl-4,5-dihydropyrazole (**3j**)*

m.p. 72–74 °C; IR (KBr): ν 3134, 2999, 1744, 1638, 1509, 1493, 1214, 1181, 1119 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 6.43 (d, $J = 15.6$ Hz, 1H, =CH–), 6.05–5.93 (m, 1H, =CH–), 4.89 (dd, $J = 11.4$ Hz, $J = 7.5$ Hz, 1H, pyrazole 5-H), 4.16 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.41–3.23 (m, ABX system, 2H, pyrazole 4-H), 1.92 (d, $J = 6.9$ Hz, 3H, $–CH_3$), 1.20 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.8 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −148.2 (d, 2F, $J = 15.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 366/364 $[M]^+$ (6/17), 293/291 $[M - CO_2Et]^+$ (34/100); Anal. Calcd. for $C_{15}H_{13}ClF_4N_2O_2$: C, 49.40; H, 3.59; N, 7.68. Found: C, 49.40; H, 3.52; N, 7.60.

*3.1.11. 1-(4-Chloro-2,3,5,6-tetrafluoro)phenyl-5-ethoxycarbonyl-3(2-methylpropyl)-4,5-dihydropyrazole (**3k**)*

sticky oil; IR (liquid film): ν 2960, 1744, 1636, 1493, 1200, 1168, 1027 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 4.74 (dd, $J = 10.8$ Hz, $J = 7.8$ Hz, 1H, pyrazole 5-H), 4.14 (q, $J = 7.2$ Hz, 2H, $–OCH_2–$), 3.24–3.07 (m, ABX system, 2H, pyrazole 4-H), 2.26 (d, $J = 7.8$ Hz, 2H, $–CH_2–$), 2.05–1.90 (m, $J = 6.6$ Hz, 1H, –CH–, 1.19 (t, $J = 7.2$ Hz, 3H, $–CH_3$), 0.99 (d, $J = 6.6$ Hz, 6H, $2 \times CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −143.1 (d, 2F, $J = 18.0$ Hz, Ar–F, F2, F6), −147.7 (d, 2F, $J = 18.0$ Hz, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 382/380 $[M]^+$ (3/7), 309/307 $[M - CO_2Et]^+$ (22/63), 57 $[C_4H_9]^+$ (41), 43 $[C_3H_7]^+$ (100); HRMS Calcd. for $C_{16}H_{17}ClF_4N_2O_2$: 380.09147. Found: 380.08944.

*3.1.12. 5-Ethoxycarbonyl-1-(4-nitrophenyl)-3-pentafluorophenyl-4,5-dihydropyrazole (**5**)*

m.p. 148–150 °C; IR (KBr): ν 2992, 1751, 1595, 1508, 1488, 1317, 1112 cm^{-1}; ^1H NMR spectral data (300 MHz, $CDCl_3$): δ 8.18 (d, $J = 9.3$ Hz, 2H, Ar–H), 7.13 (d, $J = 9.3$ Hz, 2H, Ar–H), 4.98 (dd, $J = 12.9$ Hz, $J = 5.4$ Hz, 1H, pyrazole 5-H), 4.26 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.91–3.57 (m, ABX system, 2H, pyrazole 4-H), 1.26 (t, $J = 7.2$ Hz, 3H, $–CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −137.9 (d, 2F, $J = 15.0$ Hz, Ar–F, F2, F6), −151.6 (t, 1F, $J = 21.6$ Hz, Ar–F, F4), −160.9 to −161.1 (m, 2F, Ar–F, F3, F5); EIMS (probe) 70 eV, *m/z* (rel. int.): 429 $[M]^+$ (20), 356 $[M - CO_2Et]^+$ (100), 310 $[M - CO_2Et\text{-}NO_2]^+$, (54); Anal. Calcd. for $C_{18}H_{12}F_5N_3O_4$: C, 50.36; H, 2.82; N, 9.79. Found: C, 50.39; H, 2.78; N, 9.83.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 204060–204061. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

The authors thank the National Natural Science Foundation of China (NNSFC) (Nos. 20032010 and 20072049) and Innovation Foundation of Chinese Academy of Sciences for financial support.

References

[1] (a) R. Filler, in: R.E. Banks (Ed.), Organofluorine Chemicals and their Industrial Application, Ellis Horwood, London, 1979, p. 123;
(b) J.T. Welch, Tetrahedron 43 (1987) 3123–3197.

[2] (a) J. Elgeuro, in: A.R. Katritzky, C.W. Rees (Eds.), Comprehensive Heterocyclic Chemistry, vol. 5, Pergamon Press, New York, 1984, p. 167;
(b) S.R. Kotha, G.V. Subbaraju, Indian J. Heterocycl. Chem. 5 (1996) 173–178.

[3] A.N. Kost, I.I. Grandberg, A.R. Katritzky, A.J. Boulton (Eds.), Advances in Heterocyclic Chemistry, vol. 6, Academic Press, New York, 1966, p. 347.

[4] L. Garanti, G. Molteni, P. Casati, J. Chem. Soc., Perkin Trans. 1 (2002) 2504–2580.

[5] (a) P. Caramell, P. Grunanger, A. Padwa (Ed.), 1,3-Dipolar Cycloaddition Chemistry, vol. 1, Wiley, New York, 1984, p. 291;
(b) R. Huisgen, R. Grashey, J. Sauer, in: S. Patai (Ed.), Chemistry of Alkenes, Interscience, New York, 1964, p. 806ff.

[6] K.M.L. Rai, A. Hassner, Synth. Commun. 19 (1989) 2799–2807, and references cited therein.

[7] (a) R. Herrera, A. Nagarajan, M.A. Morales, F. Mendez, H.A. Jimenez-Vazquez, L.G. Zepeda, J. Tamariz, J. Org. Chem. 66 (2001) 1252–1263;
(b) V. Padmavathi, A. Sharmila, A. Balaiah, A.S. Reddy, D.B. Reddy, Synth. Commun. 31 (2001) 2119–2126.

[8] D.W. Chen, Z.C. Chen, Synth. Commun. 25 (1995) 1617–1626.

[9] X. Huang, Q. Zhu, Synth. Commun. 31 (2001) 111–115.

[10] W.A.F. Gladstone, J.B. Aylward, R.O.C. Norman, J. Chem. Soc. (c) (1969) 2587–2598.

[11] K.M.L. Rai, N. Linganna, Synth. Commun. 27 (1997) 3737–3744.

[12] T. Tezuka, T. Otsuka, Chem. Lett. (1988) 1751–1754.

[13] L.P. Song, S.Z. Zhu, J.L. Huang, Chin. J. Chem. 20 (2002) 1274–1278.

[14] H.K. Hasseneen, H.A. Ead, N.M. Elwan, A.S. Shawali, Heterocycles 27 (1988) 2857–2862.

[15] K. Tanak, S. Maeno, K. Mitsuhashi, Chem. Lett. (1982) 543–546.