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Synthesis of fluorinated pyrazole derivatives from β-alkoxyvinyl trifluoroketones

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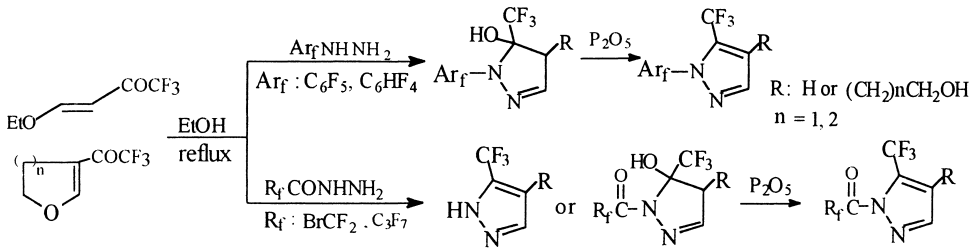
Abstract

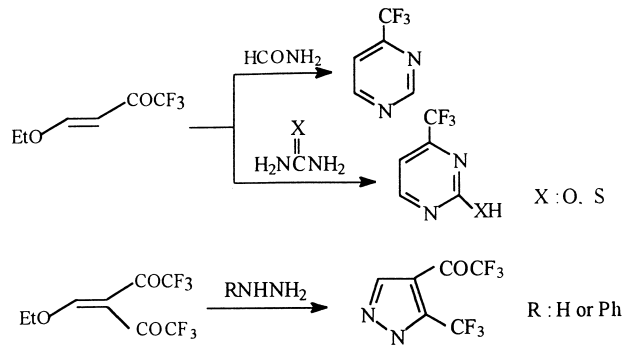
1,1,1-Trifluoro-4-ethoxy-3-butene-2-one, 3-trifluoroacetyl-3, 4-dihydro-2H-pyran or furan reacted readily with pentafluorophenylhydrazine or per(poly)fluoroacectylhydrazine $R_fCO–NHNH_2$ (R_f: $BrCF_2$, C_3F_7) to give *N*-substituted-5-hydroxy-5-trifluoromethyl heterocycles Y−N−N=CH−CH(R)C(OH)CF_3 (Y: H, Ar_f or R_fCO), which were dehydrated by treatment with P_2O_5 or $SOCl_2$ to form *N*-substituted 5-trifluoromethyl pyrazoles Y−N−N=CH−C(R)=CCF_3 (Y: H, Ar_f or R_fCO) in good yields.



Keywords: β-Alkoxyvinyl trifluoromethylketone; Pentafluorophenylhydrazine; Per(poly)fluoroacectyl-hydrazine; Fluorinated pyrazole derivatives

1. Introduction

α,β-Unsaturated ketones with a trifluoromethyl substituent represent interesting building blocks for the synthesis of trifluoromethyl containing compounds, especially heterocyclic systems, which often show high biological activities [1–3]. In recent years, the synthesis of fluorinated *N*-heterocyclic compounds have drawn much more attention, the literature has reported a series of CF_3-substituted pyridines, pyrazoles and quinolines obtained from the reactions of β-ethoxyvinyl-trifluoromethyl ketone or diethylaminomethylene hexafluoromethylacetone $Et_2NCH=C(COCF_3)_2$ with the corresponding nitrogen nucleophiles [4–6], thus:



Jones et al. [7] have reported **2** reacted with hydrazine gave 3-(3-trifluoromethyl-1H-pyrazol-4-yl)propanol and 2-(3-trifluoromethyl-1H-pyrazol-4-yl)ethanol, respectively.

We have also worked with the β-alkoxyvinyltrifluoromethyl ketones and found that they are sensitive to

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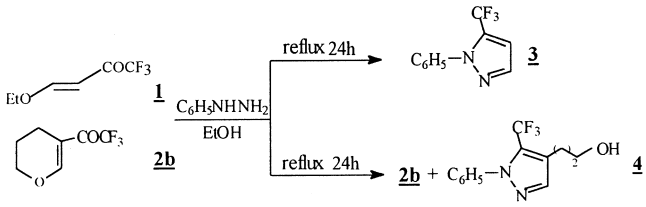
nucleophilic attack, and in some case the products are heterocyclic products containing trifluoromethyl or trifluoroacetyl groups [8].

In continuation of our work on these reactive fluorinated vinylketones we recently found that they reacted readily with hydrazine derivatives to form fluorinated pyrazole derivatives. Herein, we report on this simple method for the preparation of 5-trifluoromethyl pyrazoles from the readily available β-alkoxyvinyltrifluoromethyl ketones.

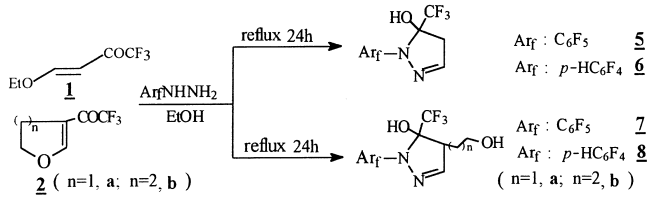
2. Results and discussion

1,1,1-Trifluoro-4-ethoxy-3-butene-2-one $EtOCH{=}CHCOCF_3$ **1**, 3-trifluoroacetyl-3,4-di-hydro-2H-pyrane $CH_2CH_2CH_2OCH{=}CC(O)CF_3$ **2b** reacted smoothly with phenylhydrazine in ethanol to give the corresponding trifluoromethyl substituted pyrazoles. The undehydrated product 4,5-dihydro-1-phenyl-5-(trifluoromethyl)-1H-pyrazol-5-ol was also synthesized in high yield [9] and shows the reaction occurred via two steps.



However, under the same reaction condition treatment **1** or **2** with pentafluorophenyl-hydrazine or tetrafluorophenyl-hydrazine did not give the expected *N*-fluorinated phenyl pyrazole. For example: the product obtained from the reaction of **1** with $C_6F_5NHNH_2$ is a stable colorless solid. It is readily crystallized from CH_2Cl_2 and was characterized (by spectroscopic data and X-ray diffraction analysis) as $C_6F_5N{-}N{=}CHCH_2C(OH){-}CF_3$ **5**. In the ^{19}F NMR spectrum the chemical shift of the CF_3 is at −79.9 ppm indicating that this CF_3 group is bonded to a saturated carbon atom. For compounds **3** or **4** in which the CF_3 group is bonded to a carbon–carbon double bond, the chemical shift of the CF_3 group is at −54.5 and −55.6 ppm, respectively. The molecular structure of **5** is shown in Fig. 1. Selected bond angles and bond lengths are summarized in Table 1.

The differences between the reaction of $C_6H_5NHNH_2$ and $C_6F_5NHNH_2$ with **1** should been due to the different basicities of $C_6H_5NHNH_2$ and $C_6F_5NHNH_2$. In the case of $C_6F_5NHNH_2$ or $HC_6F_4NHNH_2$ it give the undehydrated products, thus:



Compounds **6** and **8a** were identified by ^1H NMR spectroscopy (400 MHz) and by other techniques as appropriate. For example, the ^1H NMR spectrum of **6** displayed the dihydropyrazole 4–CH_2 protons as an AB system (doublets at δ_A 3.49 and δ_B 3.33 with the geminal coupling constant $J = 19$), which corresponds with the work of Singh et al., reported previously [10].

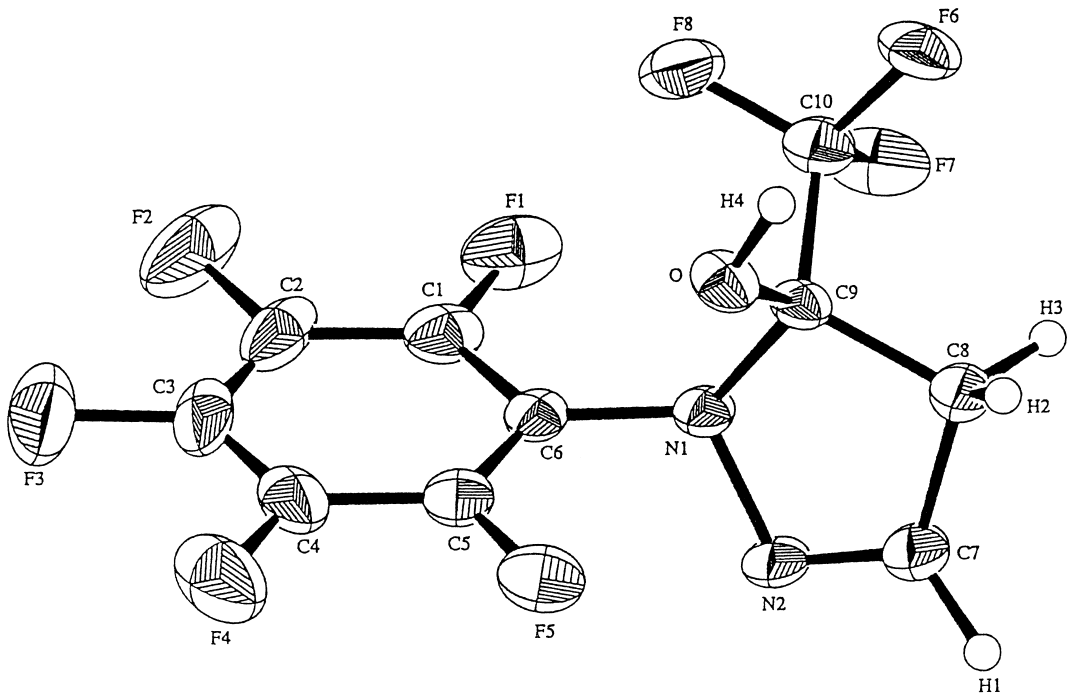
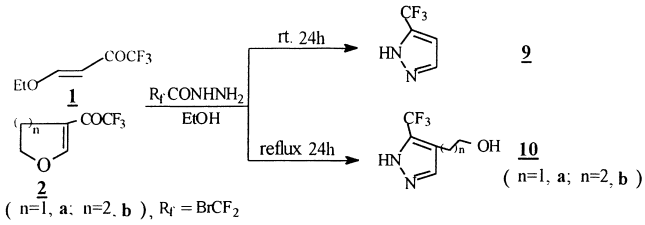
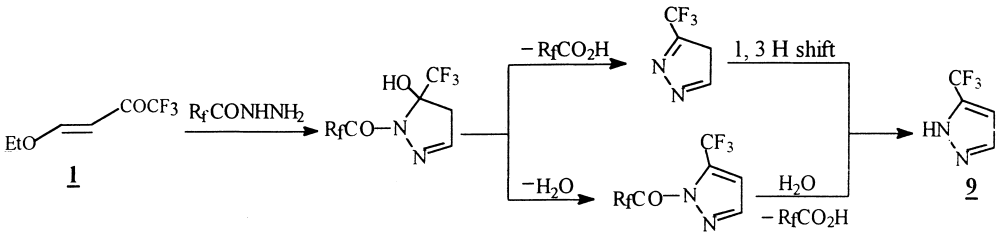


Fig. 1. Molecular structure of **5**.

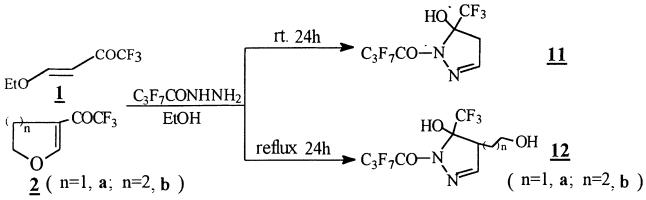
Reactions of **1** with $BrCF_2CONHNH_2$ in ethanol are straightforward yielding 5-trifluoromethyl-stubstituted pyrazoles:



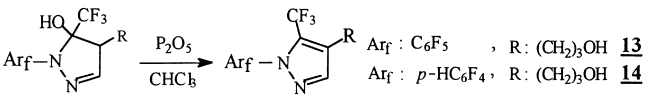
For the formation of compound **9**, a possible reaction path was proposed as follows:



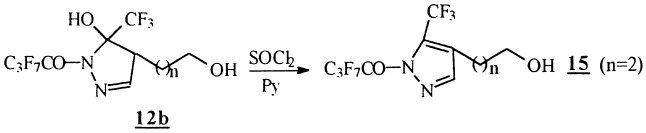
But when **1** or **2** were treated with $C_3F_7CONHNH_2$ the products are: $C_3F_7C(O)N{-}N{=}CH{-}CH(R){-}C(OH)CF_3$.



Treatment of compounds **7b** and **8b** with P_2O_5 or PCl_3 gave. The corresponding dehydrated products *N*-substituted 5-trifluoromethyl pyrazoles:



Under the same reaction conditions, however, the compound **12b** did not form the eliminated product **15**. Treatment of compound **12b** with $SOCl_2$ and pyridine gave. The corresponding dehydrated product *N*-substituted 5-trifluoromethyl pyrazole:



In summary, a series of new fluorinated pyrazole derivatives are prepared from the reaction of β-alkoxyvinyltrifluoromethyl ketone with hydrazine derivatives such as $C_6H_5NHNH_2$, Ar_fNHNH_2 and $R_fCONHNH_2$. In some cases this reaction gave directly the pyrazole product, in other cases a dehydration process with P_2O_5 or $SOCl_2$ is needed.

3. Experimental

Melting points were measured on a Temp-Melt apparatus and are uncorrected. Solvents were dried before use. ^1H NMR and ^{19}F NMR spectra were recorded on a Varian-360 l instrument or Bruker DRX-400 spectrometer with TMS and TFA ($\delta_{CFCl_3} = \delta_{TFA} + 76.8$ ppm) as the internal and external standards and the upfield as negative. IR spectra were obtained with an IR-440 Shimadzu spectrophotometer. Lower resolution mass spectra and high resolution mass spectra (HRMS) were obtained on a Finnigan GC-MS 4021 and Finnigan MAT-8430 instrument, respectively. The X-ray structure analysis was performed with a Rigaku/AFC 7R Diffractometer. Elemental analyses were performed by this Institute. Compounds **1** and **2** were prepared according to the literature methods [12,13].

3.1. Reaction of **1** *with hydrazine derivatives general procedure*

1,1,1-Trifluoro-4-ethoxy-3-butene-2-one (5 mmol) was added dropwise into a 50 ml flask containing a solution of hydrazine (5 mmol) and EtOH (30 ml). After additions

Table 1
Selected bond lengths (Å) and bond angles (°) of compound **5**

Bond length (Å)	
N(1)–N(2)	1.423 (4)
N(2)–C(7)	1.266 (4)
C(7)–C(8)	1.499 (5)
C(8)–C(9)	1.538 (5)
C(9)–N(1)	1.473 (4)
N(2)–C(6)	1.419 (4)
C(9)–C(10)	1.520 (5)
C(9)–O	1.399 (4)
Bond angle (°)	
C(9)–N(1)–N(2)	109.8 (3)
N(1)–N(2)–C(7)	108.8 (3)
N(2)–C(7)–C(8)	114.7 (3)
C(7)–C(8)–C(9)	101.6 (3)
C(8)–C(9)–N(1)	102.7 (4)
C(8)–C(9)–C(10)	112.4 (3)
N(1)–C(9)–C(10)	108.8 (3)
O–C(9)–C(10)	109.4 (3)

Table 2
Preparation of fluorinated pyrazole derivatives

Entry	Reactants	Reaction condition	Product	mp (°C)	Yield(%)
1	**1** + $C_6H_5NHNH_2$	EtOH, reflux, 24 h	**3**	–[a]	79
2	**1** + $C_6F_5NHNH_2$	EtOH, reflux, 24 h	**5**	130–132	80
3	**1** + $HC_6F_4NHNH_2$	EtOH, rt, 24 h	**6**	140–142	72
4	**1** + $BrCF_2CONHNH_2$	EtOH, rt, 24 h	**9**	47–48[b]	78
5	**1**+$BrCF_2CONHNH_2$	DMSO, rt, 24 h	**9**	47–48[b]	73
6	**1** + $C_3F_7CONHNH_2$	EtOH, rt, 24 h	**11**	56–58	62
7	**2a** + $C_6F_5NHNH_2$	EtOH, reflux, 24 h	**7a**	134–136	71
8	**2a** + $HC_6F_4NHNH_2$	EtOH, reflux, 24 h	**8a**	130–132	70
9	**2a** + $BrCF_2CONHNH_2$	EtOH, reflux, 24 h	**10a**	114–116[c]	66
10	**2a** + $C_3F_7CONHNH_2$	EtOH, reflux, 24 h	**12a**	128–130	55
11	**2b** + $C_6H_5NHNH_2$	EtOH, reflux, 24 h	**4** (**2b**)	–[a]	36 (40)
12	**2b** + $C_6F_5NHNH_2$	EtOH, reflux, 24 h	**7b**	122–124	46
13	**2b** + $HC_6F_4NHNH_2$	EtOH, reflux, 24 h	**8b**	172–174	55
14	**2b** + $BrCF_2CONHNH_2$	EtOH, reflux, 24 h	**10b**	90–92[c]	61
15	**2b** + $C_3F_7CONHNH_2$	EtOH, reflux, 24 h	**12b**	50–52	47
16	**7b**	$CHCl_3/P_2O_5$	**13**	–[a]	68
17	**8b**	$CHCl_3/P_2O_5$	**14**	106–108	65
18	1**2b**	$CHCl_3/SOCl_2$/py	**15**	144–146	66

[a] Liquid at room temperature.
[b] Product **9** is known compound, see [11].
[c] Products **10a** and **10b** are known compounds, see [10], melting points were measured after recrystallization with petroleum and ethyl acetate.

this reaction mixture was refluxed in EtOH for 24 h, the solvent was evaporated, and the obtained crude product was purified by column chromatography to give the pure product. The reaction yields are shown in Table 2.

3.1.1. 5-Hydroxy-1-pentafluorophenyl-5-trifluoromethyl-4,5-dihydropyrazole, ***5***

IR (ν_{max}, cm^{-1}): 3612 (s, O–H), 2955 (m, C–H), 1509 (s, C=N), 1199, 1152 (vs, C–F); ^1H NMR (90 MHz, $(CD_3)_2CO$) δ (ppm): 6.98 (s, ^1H, pyrazole 3-H), 3.28 (s, 2H pyrazole 4-H), 3.20 (br, 1H, OH); ^{19}H NMR (56.4 MHz, $(CD_3)_2CO$) δ (ppm): −79.9 (s, CF_3); −142.9 (d, Ar–F, F2, F6), −155.5 (t, Ar–F, F-4), −164.9(t, Ar–F, F3, F5); MS (*m/z*, %): 320 (M^+, 6.32), 319 (M^+–H, 36.62), 302 (M^+–H_2O, 6.81), 251 (M^+–CF_3, 100.00), 181 ($C_6F_5N^+$, 90.88), 167 ($C_6F_5^+$, 36.18); HRMS for $C_{10}H_4F_8N_2O$: Calculated: 320.01959; Found: 320.02354.

3.1.1.1. Crystal structure analysis. $C_{10}H_4ON_2F_8$: MW = 320.14, monoclinic, space group $p2_1/c$ (#14), $a = 10.924$ (4) Å, $b = 9.437$ (4) Å, $c = 11.813$ (4) Å, $\beta = 114.99(2)^\circ$, $V = 1103.7$ (7) $Å^3$, $Z = 4$, $D_c = 1.927$ g/cm^3, $F(000) = 632.00$. Radiation, Mo Kα ($\lambda = 0.71069$ Å). Crystal dimension, 0.20 mm × 0.20 mm × 0.30 mm. Intensity data were collected at 20°C with a Ragaku AFC 7R diffractometer using graphite-monochromated Mo Kα radiation ($\mu = 2.18\ cm^{-1}$). A total of 2826 independent reflection were measured in the range $18.7 < 2\theta < 21.4^\circ$.The structure was solved by direct methods and referred using Fourier techniques. The nonhydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of full matrix least-square refinement was based on 1384 observed reflections ($I > 2.00\sigma(I)$) and 191 variable parameters. The final R and R_w value were 0.052 and 0.054, respectively. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation Table 1.

3.1.2. 5-Hydroxy-1-(2,3,5,6, tetrafluorophenyl)-5-trifluoromethyl-4,5-dihydropyrazole, ***6***

IR (ν_{max}, cm^{-1}): 3100 (m, O–H), 1510 (s, C=N), 1195, 1145 (vs, C–F); ^1H NMR (400 MHz,$(CD_3)_2CO$) δ (ppm): 7.57 (m, 1H, H–C_6F_4), 7.15 (s, 1H, pyrazole 3–H), 3.49 (d, 1H, $J = 19$ Hz, pyrazole 4–H), 3.33 (d, 1H, $J = 19$ Hz, pyrazole 4–H), 3.22 (br, 1H, OH); ^{19}F NMR (56.4 MHz, $CDCl_3 + (CD_3)_2CO)\delta$ (ppm): −79.4 (s, CF_3); −140.8 (d, Ar–F, F2, F6), −143.4(d, Ar–F, F3, F5); MS (*m/z*, %): 302 (M^+, 35.60), 285 (M^+–OH, 6.68), 233 (M^+–CF_3, 100.00), 163 ($HC_6F_4N^+$, 49.42), 149 ($HC_6F_4^+$, 13.75), 69 (CF_3^+, 14.13); Elemental analyses for $C_{10}H_5F_7N_2O$: Anal. Calculated: N, 9.27%; H, 1.66%; C, 39.74%; Found: N, 9.16%; H, 1.71%; C, 39.69%.

3.1.3. 1-Heptafluorobutanoyl-5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazole, ***11***

IR (ν_{max}, cm^{-1}): 3400 (s, O–H), 1705 (s, C=O), 1490 (s, C=N), 1168 (vs, C–F); ^1H NMR (60 MHz, $(CD_3)_2CO$) δ (ppm): 7.30 (s, 1H, pyrazole 3-H), 5.10 (br, 1H, O–H), 3.46 (s, 2H, pyrazole 4-H) ^{19}F NMR (56.4 MHz, $(CD_3)_2CO$) δ (ppm): −79.6 (s, CF_3), −80.3 (s, CF_3); −113.6 (s, CF_2), −124.3 (s, CF_2); MS (*m/z*, %): 350 (M^+, 0.8), 333 (M^+–OH, 16.23), 281 (M^+–CF_3, 22.23), 169 ($C_3F_7^+$, 36.18), 69 (CF_3^+, 100.00); Elemental analyses for $C_8H_4F_{10}N_2O_2$: Anal.

Calculated: N, 8.00%; H, 1.14%; C, 27.43%; Found: N, 7.69%; H, 1.11%; C, 27.31%.

3.2. Reaction of **2** with hydrazine derivatives general procedure

3-Trifluoroacetyl-3,4-dihydro-2H-pyran or furan (5 mmol) was added into a 50 ml flask containing a solution of hydrazine (5 mmol) and EtOH (30 ml). This reaction mixture was refluxed in EtOH for 24 h, the solvent was evaporated and the crude product was purified by column chromatography.

3.2.1. 4-(3-Hydroxypropyl)-1-phenyl-5-trifluoromethylpyrazole, **4**

IR (ν_{max}, cm^{-1}): 3394 (s, O–H), 2949 (m, C–H), 1597 (vs, C=C), 1499 (s, C=N), 1129, 1099 (vs, C–F); ^{1}H NMR (90 MHz, $CDCl_3$) δ (ppm): 7.70 (s, 1H, pyrazole 3-H), 7.57 (m, 5H, Ar–H), 3.73 (t, 2H, CH_2–O), 3.73 (br, 1H, OH), 2.85 (t, 2H, pyrazole–CH_2), 1.99 (m, 2H, CH_2CH_2); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ (ppm): −54.5 (s, CF_3); MS (*m/z*, %): 270 (M^+, 68.31), 252 (M^+–H_2O, 69.75), 225 (M^+–CH_2CH_2OH, 100.00), 201 (M^+–CF_3, 9.25), 183 (M^+–CF_3–H_2O, 23.94); HRMS for $C_{13}H_{13}F_3N_2O$: Calculated: 270.0980; Found: 270.0988.

3.2.2. 5-Hydroxy-4-(2-hydroxyethyl)-1-pentafluorophenyl-5-trifluoromethyl-4,5-dihydropyrazole, **7a**

IR (ν_{max}, cm^{-1}): 3280 (s, O–H), 2800 (m, C–H), 1500 (s, C=N), 1180, 1168 (vs, C–F); ^{1}H NMR (60MHz, $(CD_3)_2CO$) δ (ppm): 6.86 (s, 1H, pyrazole 3-H), 3.55 (t, 2H, O–CH_2), 3.55 (br, 1H, OH), 2.85 (br, 1H, OH), 1.90 (m, 1H, pyrazole 4-H), 1.73 (m, 2H, pyrazole–CH_2); ^{19}F NMR (56.4 MHz, $(CD_3)_2CO$) δ (ppm): −81.9 (s, CF_3); −144.8 (d, Ar–F, F2, F6), −157.8 (t, Ar–F, F4), −166.8 (t, Ar–F, F3, F5); MS (*m/z*, %): 364 (M^+, 43.59), 346 (M^+–H_2O, 29.34), 295 (M^+–CF_3^+, 100.00), 181 ($C_6F_5N^+$, 73.62), 167 ($C_6F_5^+$, 40.95), 69 (CF_3^+, 56.12); Elemental analyses for $C_{12}H_8F_8N_2O_2$: Anal. Calculated: N, 7.69%; H, 2.20%; C, 39.56%; Found: N, 7.62%; H, 2.18%; C, 39.80%.

3.2.3. 5-Hydroxy-4-(3-hydroxypropyl)-1-pentafluorophenyl-5-trifluoromethyl-4,5-dihydro-pyrazole **7b**

IR (ν_{max}, cm^{-1}): 3370 (s, O–H), 2954 (m, C–H), 1522 (s, C=N), 1260, 1056 (vs, C–F); ^{1}H NMR (90 MHz, $(CD_3)_2CO$) δ (ppm): 6.65 (s, 1H, pyrazole 3-H), 3.14 (t, 2H, CH_2O), 3.14 (br, 1H, OH), 2.92 (br, 1H, OH), 1.55 (m, 1H, pyrazole 4-H), 1.35 (m, 4H, CH_2CH_2); ^{19}F NMR (56.4 MHz, $(CD_3)_2CO$) δ (ppm): −80.8 (s, CF_3); −144.1 (d, Ar–F, F2, F6), −157.5 (t, Ar–F, F4), −166.4 (t, Ar–F, F3, F5); MS (*m/z*, %): 378 (M^+, 4.15), 360 (M^+–H_2O, 5.33), 309 (M^+–CF_3, 39.02), 181 ($C_6F_5N^+$, 40.70), 167 ($C_6F_5^+$, 23.94), 41 ($C_3H_5^+$, 100.00); Analysis for $C_{13}H_{10}F_8N_2O_2$: Calculated: N, 7.41%; H, 2.64%; C, 41.27%; Found: N, 7.08%; H, 2.41 %; C, 41.10%.

3.2.4. 5-Hydroxy-4-(2-hydroxyethyl)-1-(2,3,5,6-tetrafluorophenyl)-5-trifluoromethyl-4,5-dihydro-pyrazole, **8a**

IR (ν_{max}, cm^{-1}): 3300 (s, O–H), 3050 (m, H–C_6F_4) 1500(s, C=N), 1180, 1145 (vs, C–F); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ (ppm): 7.57 (m, 1H, H–C_6F_4), 7.21 (s, 1H, pyrazole 3-H), 3.80 (m, 2H, CH_2–O), 3.80 (br, 1H, –OH), 3.17 (br, 1H, OH), 2.20 (m, 1H, pyrazole 4-H), 2.12 (m, 2H, pyrazole–CH_2); ^{19}F NMR (56.4 MHz, $CDCl_3 + (CD_3)_2CO$) δ (ppm): −80.8 (s, CF_3); −141.3 (d, Ar–F, F2, F6), −143.8 (s, Ar–F, F3, F5); MS (*m/z*, %): 346 (M^+, 36.36), 328 (M^+–H_2O, 24.74), 277 (M^+–CF_3, 96.59), 259 (M^+–CF_3–H_2O, 90.26), 163 ($HC_6F_4N^+$, 100.00), 149 ($HC_6F_4^+$, 46.65), 69 (CF_3^+, 77.04); Elemental analyses for $C_{12}H_9F_7N_2O_2$: Anal. Calculated: N, 8.09%; H, 2.60%; C, 41.62%; Found: N, 8.02%; H, 2.56%; C, 41.78%.

3.2.5. 5-Hydroxy-4-(3-hydroxypropyl)-1-(2,3,5,6-tetrafluorophenyl)-5-trifluoromethyl-4,5-di-hydropyrazole, **8b**

IR (ν_{max}, cm^{-1}): 3320 (s, O–H), 3050 (m, H–C_6F_4), 2990 (m, C–H), 1500 (s, C=N), 1185, 1155 (vs, C–F); ^{1}H NMR (60 MHz, $CDCl_3 + (CD_3)_2CO$) δ (ppm): 7.20 (m, 1H, H–C_6F_4), 6.94 (s, 1H, pyrazole 3-H), 3.73 (t, 2H, CH_2–O), 3.50 (br, 1H, –OH), 3.02 (br, 1H, OH), 2.01 (m, 1H, pyrazole 4-H), 1.83 (m, 4H, CH_2CH_2); ^{19}F NMR (56.4 MHz, $CDCl_3$+ $(CD_3)_2CO$) δ (ppm): −79.8 (s, CF_3); −140.8 (t, Ar–F, F2, F6), −143.3 (s, Ar-F, F3, F5); MS (*m/z*, %): 360 (M^+, 8.26), 342 (M^+–H_2O, 8.91), 291 (M^+–CF_3, 100.00), 273 (M^+–CF_3–H_2O, 90.26), 163 ($HC_6F_4N^+$, 75.34), 149 ($HC_6F_4^+$, 29.71), 69 (CF_3^+, 77.04), 41 ($C_3H_5^+$, 24.97); Elemental analyses for $C_{13}H_{11}F_7N_2O_2$ Anal. Calculated: N, 7.78%; H, 3.06%; C, 43.33%; Found: N, 7.74%; H, 3.10%; C, 43.26%.

3.2.6. 4-(2-hydroxyethyl)-5-trifluoromethylpyrazole, **10a**

IR (ν_{max}, cm^{-1}): 3230 (s, O–H), 3100 (s, N–H), 2779 (s, C–H), 1458 (s, C=N), 1140, 1050 (vs, C–F); ^{1}H NMR (60 MHz, $CDCl_3 + (CD_3)_2CO$) δ (ppm): 7.53 (s, 1H, pyrazole 3-H), 3.67 (t, 2H, CH_2O), 2.83 (t, 2H, pyrazole–CH_2), 2.13 (br, 1H, –OH); ^{19}F NMR (56.4 MHz, $CDCl_3$+ $(CD_3)_2CO$) δ (ppm): −59.8 (s, CF_3); MS (*m/z*, %): 180 (M^+, 13.2), 149 (M^+–CH_2OH, 100.00), 111 (M^+–CF_3, 2.01), 69 (CF_3^+, 12.19); Elemental analyses for $C_6H_7F_3N_2O$: Anal. Calculated: N, 15.56%; H, 3.89%; C, 40.00%; Found: N, 15.36%; H, 3.89%; C, 40.25%.

3.2.7. 4-(3-Hydroxypropyl)-5-trifluoromethylpyrazole, **10b**

IR (ν_{max}, cm^{-1}): 3100 (s, O–H, N–H), 2880 (s, C–H), 1480 (s, C=N), 1250, 1140 (vs, C–F); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 7.79 (s, 1H, pyrazole 3-H), 4.06 (t, 2H, CH_2O), 3.09 (m, 2H, pyrazole–CH_2), 2.24 (m, 2H, CH_2CH_2), 1.53 (br, 1H, –OH); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ (ppm): −59.8 (s, CF_3); MS (*m/z*, %): 195 ($M^+ + 1$, 28.19), 176 (M^+–H_2O, 96.33), 149 (M^+–CH_2CH_2OH, 100.00), 69 (CF_3^+, 12.49); Elemental analyses for $C_7H_9F_3N_2O$: Anal. Calculated: N, 14.43%; H, 4.64%; C, 43.30%; Found: N, 14.26%; H, 4.59%; C, 43.09%.

3.2.8. 1-Heptafluorobutanoyl-5-hydroxy-4-(2-hydroxyethyl)-5-trifluoromethyl-4,5-dihydro-pyrazole, ***12a***

IR (ν_{max}, cm^{-1}): 3200 (s, O–H), 1705 (s, C=O), 1200, 1160 (vs, C–F); ^1H NMR (60 MHz, $CD_3Cl + (CD_3)_2CO$) δ (ppm): 7.90 (d, 1H, pyrazole 3-H), 4.00 (br, 1H, OH), 4.00 (t, 2H, CH_2O), 3.20 (m, 1H, pyrazole 4-H), 3.20 (br, 1H, OH), 2.10 (m, 2H, pyrazoleCH_2); ^{19}F NMR (56.4 MHz, $CD_3Cl + (CD_3)_2CO$) δ (ppm): −80.6 (s, CF_3), −83.3 (s, CF_3); −120.6 (s, CF_2), −126.8 (s, CF_2); MS (*m/z*, %): 395 ($M^+ + 1$, 4.22), 377 (M^+–OH, 68.57), 280 (M^+–CF_3–CH_2CH_2OH, 23.68), 169 ($C_3F_7^+$, 12.58), 83 ($C_3H_3N_2O^+$, 49.11), 69 (CF_3^+, 77.48), 68 ($C_2N_2O^+$, 100); Elemental analyses for $C_{10}H_8F_{10}N_2O_3$: Anal. Calculated: N, 7.11 %; H, 2.03%; C, 30.46%; Found: N, 7.10%; H, 2.11%; C, 30.17%.

3.2.9. 1-Heptafluorobutanoyl-5-hydroxy-4-(3-hydroxypropyl)-5-trifluoromethyl-4,5-dihydro-pyrazole, ***12b***

IR (ν_{max}, cm^{-1}): 3100 (s, O–H), 1710 (s, C=O), 1160, 1100 (vs, C–F); ^1H NMR (60 MHz, CD_3Cl) δ (ppm): 7.90 (d, 1H, pyrazole 3-H), 4.60 (br, 1H, O–H), 4.05 (m, 2H, CH_2O), 2.45 (m, 1H, OH), 2.30 (m, 1H, pyrazole 4-H), 1.95 (m, 4H, CH_2CH_2); ^{19}F NMR (56.4 MHz, CD_3Cl) δ (ppm): −79.7 (s, CF_3), −83.2 (s, CF_3); −120.2 (s, CF_2), −125.8 (s, CF_2); MS (*m/z*, %): 408 (M^+, 3.72), 391 (M^+–OH, 24.52), 294 (M^+–CF_3–CH_2CH_2OH, 8.62), 239 (M^+–C_3F_7, 7.02), 169 ($C_3F_7^+$, 36.18), 97 ($C_4H_5N_2O^+$, 59.65), 69 (CF_3^+, 100.00), 41 ($C_3H_5^+$, 46.77); Elemental analyses for $C_{11}H_{10}F_{10}N_2O_3$: Anal. Calculated: N, 8.00%; H, 1.14%; C, 27.43%; Found: N, 7.69%; H, 1.11%; C, 27.31%.

3.3. General procedure for the preparation of fluorinated pyrazole derivatives by a dehydration process

At room temperature 1-substituted-5-(trifluoromethyl)-5-hydroxy-4,5-dihydro pyrazole (2 mmol) was added into a 25 ml flask containing a mixture of P_2O_5 (2.5 mmol) and chloroform (15 ml). After reflux for 8 h, the residue was removed by filtration. The solvent was washed with water and dried with anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography.

3.3.1. 4-(3-Hydroxypropyl)-1-pentafluorophenyl-5-trifluoromethylpyrazole, ***13***

IR (ν_{max}, cm^{-1}): 3420 (s, O–H), 2950 (m, C–H), 1510 (s, N=H), 1255, 1050 (vs, C–F); ^1H NMR (60 MHz, $CDCl_3$) δ (ppm): 8.07 (s, 1H, pyrazole 3-H), 4.10 (t, 2H, CH_2O), 3.13 (m, 2H, pyrazole–CH_2), 2.30 (m, 2H, CH_2CH_2), 2.30 (br, 1H, OH); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ (ppm): −57.2 (s, CF_3); −144.7 (d, Ar–F, F2, F6), −149.3 (t, Ar–F, F4), −160.6 (t, Ar–F, F3, F5); MS (*m/z*, %): 360 (M^+, 0.65), 342 (M^+–H_2O, 100.00), 315 (M^+–CH_2CH_2OH, 42.53), 273 (M^+–H_2O–CF_3, 25.80), 167 ($C_6F_5^+$, 5.96), 69 (CF_3^+, 11.42); HRMS for $C_{13}H_8F_8N_2O$: Calculated: 360.05089; Found: 360.05306.

3.3.2. 4-(3-Hydroxypropyl)-1-(2,3,5,6-tetrafluorophenyl)-5-trifluoromethylpyrazole, ***14***

IR (ν_{max}, cm^{-1}): 3410 (s, O–H), 3070 (m, H–C_6F_4), 2980 (m, C–H), 1500 (s, C=N), 1184, 1139 (vs, C–F), ^1H NMR (60 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 1H, pyrazole 3-H), 7.50 (m, 1H, H–C_6F_4), 3.30 (t, 2H, CH_2O), 2.96 (t, 2H, pyrazole–CH_2), 2.13 (m, 2H, CH_2CH_2), 2.13 (br, 1H, OH); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ (ppm): −61.8 (s, CF_3); −136.8 (t, Ar–F, F2, F6), −144.8 (s, Ar–F, F3, F5); MS (*m/z*, %): 342 (M^+, 100.00), 324 (M^+–H_2O, 1.34), 273 (M^+–CF_3, 12.13), 163 ($HC_6F_4N^+$, 25.94), 149 ($HC_6F_4^+$, 28.01), 69 (CF_3^+, 23.51); HRMS for $C_{13}H_9F_7N_2O$: Calculated: 342.06031; Found: 342.05654.

3.3.3. 4-(3-Hydroxypropyl)-1-heptafluorobutanoyl-5-trifluoromethylpyrazole, ***15***

IR (ν_{max}, cm^{-1}): 3180, 3050 (m, =CH), 1700 (s, C=O), 1210, 1130 (vs, C–F); ^1H NMR (90 MHz, $(CD_3)_2CO$) δ (ppm): 8.20 (s, 1H, pyrazole 3-H), 3.90 (t, 2H, CH_2O), 2.60 (s, 1H, OH), 1.63 (m, 4H, CH_2CH_2); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ (ppm): −61.8 (s, CF_3), −79.4 (s, CF_3); −119.8 (s, CF_2), −126.1 (s, CF_2); MS (*m/z*, %): 391 ($M^+ + 1$, 45.26), 390 (M^+, 43.76), 177 ($M^+ + 1$–C_3F_7CO–OH, 100.00), 169 ($C_3F_7^+$, 21.30), 108 ($M^+ + 1$–C_3F_7CO–OH–CF_3, 70.16), 69 (CF_3^+, 54.29); HRMS for $C_{12}H_8F_{10}O_2N_2$: Calculated: 390.04261, Found: 390.04264.

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