Journal of Fluorine Chemistry 132 (2011) 965–972

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis and antibacterial activity of some 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamides, 3-trifluoromethylpyrazol-1-thiocarboxamides and 4-aryl-2-(5(3)-trifluoromethyl-1-pyrazolyl)thiazoles

Ranjana Aggarwal [a,*], Rajiv Kumar [a], Sunil Kumar [a], Gaurav Garg [b], Ritu Mahajan [b], Jitender Sharma [b]

[a] Department of Chemistry, Kurukshetra University, Kurukshetra – 136 119 Haryana, India
[b] Department of Biotechnology, Kurukshetra University, Kurukshetra – 136 119 Haryana, India

ARTICLE INFO

Article history:
Received 2 May 2011
Received in revised form 22 July 2011
Accepted 27 July 2011
Available online 4 August 2011

Keywords:
5-Hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamides
3-Trifluoromethylpyrazol-1-thiocarboxamides
3/5-Trifluoromethylpyrazolylthiazoles
Trifluoromethyl-β-diketones
Thiosemicarbazide
Antibacterial activity

ABSTRACT

5-Hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamides **3** and 3-trifluoromethylpyrazol-1-thiocarboxamides **4**, regioselectively obtained by the condensation of trifluoromethyl-β-diketones with thiosemicarbazide under neutral and acidic conditions, on further reaction with phenacyl bromides **5** afforded 4-aryl-(5-trifluoromethyl-pyrazol-1-yl)thiazoles **6** and 4-aryl-(3-trifluoromethyl-pyrazol-1-yl)thiazoles **7**, respectively. Five 4,5-dihydropyrazoles (**3a**–**e**) and two pyrazolylthiazoles (**6a** and **6c**) were tested against one Gram-positive and one Gram-negative bacteria to assess their *in vitro* antibacterial activity. Compounds **3a**, **3b** and **3e** showed moderate antibacterial activity against Gram-positive bacterium, *Bacillus pumilus*.

1. Introduction

Heterocyclic compounds bearing trifluoromethyl group play an important role in medicinal and agricultural fields [1–5]. Celecoxib and SC-588 are the selective cyclooxygenase-2 (COX-2) inhibitors with fewer gastrointestinal side effects to traditional NSAIDs and are being used for the treatment of rheumatoid arthritis and osteoarthritis [6,7]. These compounds also act as nuclear factor of activated T-cells (NFAT) transcription factor regulator [8] and are widely used as agrochemicals [9,10]. Pyrazolylthiazoles have been used in cardiovascular diseases as selective inhibitors of fibrinogen-mediated platelet aggregation [11]. Many of these compounds display antinociceptive activity [12], toxicity towards *Candida elegans* [13] and phototoxicity against mosquito larvae [14]. In view of these observations, it was aimed to synthesize a series of pyrazolylthiazoles derivatives bearing trifluoromethyl group on 3 and/or 5 positions of pyrazole ring as potential antibacterical agents. A perusal of literature revealed that the most common route to the synthesis of pyrazolylthiazoles comprised of the reaction of 2-hydrazinothiazoles with β-diketones [15]. But, the reaction suffers with the draw-back of regioselectivity and affords non-separable mixture of regioisomeric pyrazolylthiazoles. There are contradictory reports also in the literature concerning the structure of the products obtained in these reactions. For instance, the reaction between 4-aryl-2-hydrazinothiazoles with β-diketones has been reported to yield thiazolotriazepines [16] instead of isomeric pyrazoles.

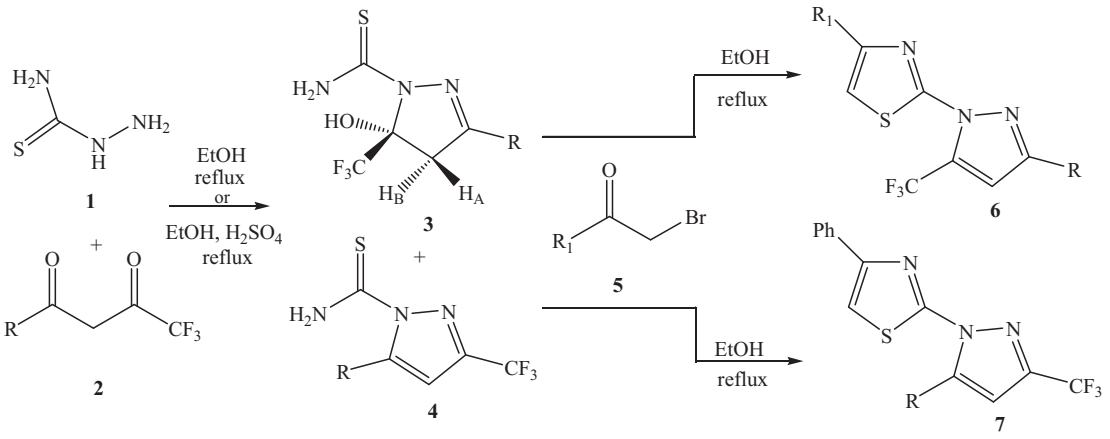
So, in the present investigation, an alternate route has been explored to prepare some new trifluoromethyl substituted pyrazolylthiazoles involving the reaction of 3(5)-trifluoromethyl-5(3)-substituted-pyrazol-1-thiocarboxamides with phenacyl bromides.

2. Result and discussion

Synthesis of 4-aryl-2-(3-substituted-5-trifluoromethyl-1-pyrazolyl)thiazoles **6** and isomeric 4-aryl-2-(5-substituted-3-trifluoromethyl-1-pyrazolyl)thiazoles **7** was accomplished by the reaction of 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamides **3** and 3-trifluoromethylpyrazol-1-thiocarboxamides **4**, respectively with phenacyl bromides **5** (Scheme 1). The key intermediates **3** and **4**, in turn, were obtained by the cyclo-condensation of thiosemicarbazide **1** with trifluoromethyl-β-diketones **2** in equimolar ratio using ethanol as solvent. Whereas the reaction with aliphatic trifluoromethyl-β-diketones **2a**–**b**

* Corresponding author. Tel.: +91 1744 238734; fax: +91 1744 238277.
E-mail address: ranjana67in@yahoo.com (R. Aggarwal).

0022-1139/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2011.07.029



2, 3, 4	R
a	CH_3
b	CF_3
c	C_6H_5
d	p-$CH_3OC_6H_4$
e	p-ClC_6H_4

5	R_1
a	C_6H_5
b	p-$CH_3OC_6H_4$

6	R	R_1
a	CH_3	p-$CH_3OC_6H_4$
b	CF_3	C_6H_5
c	C_6H_5	C_6H_5
d	p-$CH_3OC_6H_4$	C_6H_5
e	p-ClC_6H_4	p-$CH_3OC_6H_4$

7	R
a	C_6H_5
b	p-$CH_3OC_6H_4$
c	p-ClC_6H_4

Scheme 1. Synthesis of 2-(3/5-trifluoromethylpyrazol-1-yl)thiazoles from thiosemicarbazide and trifluoromethyl-β-diketones.

Table 1
Ratio[a] of compounds **3** and **4** in the reaction between **1** and **2**.

Compound	**3** (%)	**4** (%)
a	100	0
b	100	0
c	85	15
d	58	42
e	65	35

[a] The ratio of different products is calculated by ^{1}H NMR spectra of the crude reaction mixture.

yielded a single product, which was identified as 5-hydroxy-5-trifluoromethyl-3-substituted-4,5-dihydropyrazol-1-thiocarboxamides **3a–b**, the reaction with aromatic trifluoromethyl-β-diketones **2c–e** afforded a mixture of two products, which were identified as 5-hydroxy-5-trifluoromethyl-3-substituted-4,5-dihydropyrazol-1-thiocarboxamides **3c–e** as the major and 3-trifluoromethyl-5-substitutedpyrazole-1-thiocaboxamides **4c–e** as the minor product (Scheme 1). 4,5-Dihydropyrazol-1-thiocarboxamides **3** and pyrazol-1-thicarboxamides **4** were purified by column chromatography and the ratio of these two different products was measured by ^{1}H NMR spectroscopy of the crude reaction mixture (Table 1). Formation of these compounds was confirmed on the basis of their IR, NMR (^{1}H, ^{13}C, ^{19}F), mass spectra and elemental analysis.

It is evident from Table 1 that reaction exhibits high level of regioselectivity towards the formation of 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamides **3**. The presence of a trifluoromethyl group on the β-diketones **2** and the thiocarboxamide group on the dinucleophile (thiosemicarbazide) were the determining factors to control the regiochemistry of the reaction along with substituents present on aryl ring of the diketones, which are in accordance with our earlier results [17]. It has also been observed earlier by us that the acidic medium causes the change in the regioselectivity of the reaction. So in the present study, reaction of thiosemicarbazide and β-diketones **2** was also studied in acidic medium to achieve 3-trifluoromethylpyrazol-1-thiocarboxamides **4** as major product. A set of different experiments was carried out by using different acids taking 4,4,4-trifluoro-1-phenylbutane-1,3-dione **2c** as a reference compound (Table 2). The optimum condition for formation of 5-phenyl-3-trifluoromethylpyrazol-1-thiocarboxamide **4c** was found to be 4–5 drops of H_2SO_4 in EtOH (yield 42% as compared to 15% in neutral medium). To check the scope of the reaction, other β-diketones **2** were also made to react with thiosemicabazide **1** under the above said optimized reaction conditions and a change in regioselectivity was observed (Table 2).

In IR spectra of **3** two absorption bands appeared at about 3400 and 3300 cm^{-1} due to N–H stretch and two absorption bands at 3504–3574 and 1600-1620 cm^{-1} indicated the presence of O–H and C=S stretch, respectively. The ^{1}H NMR spectra of **3a–e** displayed one doublet of one proton intensity at about δ 3.3-3.8 (J_{HA-HB} = 18-20 Hz) and one doublet of quartet of one proton intensity at about δ 3.2-3.6 (J_{HA-HB} = 18-20 Hz, $^4J_{HB-CF3}$ = 1-2 Hz). This particular pattern is expected from the two methylene protons (CH_AH_B), respectively (*cis* and *trans* to the CF_3 group) at position 4 of 5-hydroxy-4,5-dihydropyrazoles [17–20]. Compound **3** also exhibited three signals each of one proton intensity at about δ 6.1-6.6, 7.1-7.7 (NH_2) and 7.7-8.5 (OH) which are exchangeable with D_2O indicating the presence of two thiocarboxamide ($CSNH_2$) protons at position 1 and OH proton at position 5, respectively. Further support for the structure of **3** was provided by ^{13}C NMR spectra, which exhibited signals at δ 44–49, 92–93 as a quartet ($^2J_{C-F}$ = 33-34 Hz) and 153–157 ppm corresponding to carbons C_4, C_5 and C_3 (Table 3) respectively. Also, signal at about δ 177 ppm in the ^{13}C NMR spectra demonstrate the presence of C=S group. Finally, the ^{19}F NMR spectra showed a signal

Table 2
The ratio of **3** and **4** in the reaction between **1** and **2** in acidic medium.

Effect of different reaction condition on the ratio of **4c**		Ratio of **3** and **4** using 4–5 drops of H_2SO_4 in EtOH		
Different reaction conditions	**4c** (%)[a]	Compound	**3** (%)[a]	**4** (%)[a]
EtOH	15	**a**	91	9[b]
2 drops HCl in EtOH	17	**b**	100	0
4–5 drops H_2SO_4 in EtOH	42	**c**	58	42
AcOH	33	**d**	40	60
		e	46	54

[a] The ratio of different products is calculated by ^{1}H NMR spectra of the crude reaction mixture.
[b] **4a** cannot be isolated because of poor yields.

Table 3
^{13}C NMR data for 5-hydroxy-5-trifluoromethyl-3-substituted-4,5-dihydropyrazol-1-thiocarboxamides **3**.

Compound	**3a**	**3b**	**3c**	**3d**	**3e**
Pyrazole carbons					
C-3	155.41	156.67 (q, $^2J_{C-F}$ = 33.25 Hz)	153.43	152.96	153.95
C-4	48.03	49.11	44.12	44.52	43.87
C-5	92.53 (q, $^2J_{C-F}$ = 33.75 Hz)	93.33 (q, $^2J_{C-F}$ = 33.75 Hz)	92.71 (q, $^2J_{C-F}$ = 33.25 Hz)	92.96 (q, $^2J_{C-F}$ = 33.75 Hz)	92.87 (q, $^2J_{C-F}$ = 33.50 Hz)
Aryl carbons					
C-1′			134.21	121.66	129.45
C-2′,6′			128.08	128.68	127.52
C-3′,5′			128.84	114.49	128.92
C-4′			131.66	162.49	136.51
Others					
C=S	177.11	178.16	178.76	177.06	178.01
5-CF_3	123.31 (q, $^1J_{C-F}$ = 288.00 Hz)	125.35 (q, $^1J_{C-F}$ = 288.00 Hz)	122.42 (q, $^1J_{C-F}$ = 285.05 Hz)	123.49 (q, $^1J_{C-F}$ = 275.25 Hz)	124.34 (q, $^1J_{C-F}$ = 275.75 Hz)
3-CF_3		119.27 (q, $^1J_{C-F}$ = 275.25 Hz)			
CH_3	15.63				
OCH_3				55.49	

Table 4
^{13}C NMR data for 5-substituted-3-trifluoromethylpyrazol-1-thiocarboxamides **4**.

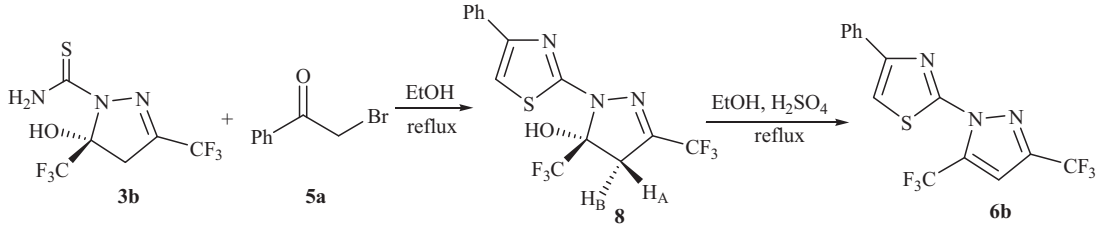
Compound	**4c**	**4d**	**4e**
Pyrazole carbons			
C-3	157.73 (q, $^2J_{C-F}$ = 33.5 Hz)	175.71 (q, $^2J_{C-F}$ = 36 Hz)	177.58 (q, $^2J_{C-F}$ = 36.98 Hz)
C-4	101.33	91.53	92.32
C-5	145.10	144.25	145.94
Aryl carbons			
C-1′	133.47	125.48	131.32
C-2′,6′	127.51	130.00	128.93
C-3′,5′	129.35	114.40	129.43
C-4′	128.12	164.64	140.64
Others			
C=S	176.15	186.18	184.88
3-CF_3	120.24 (q, $^1J_{C-F}$ = 275.25 Hz)	119.27 (q, $^1J_{C-F}$ = 275.25 Hz)	118.95 (q, $^1J_{C-F}$ = 283 Hz)
OCH_3		55.58	

in the range δ −78.44 to −79.11 ppm, which is typical for CF_3 bound to a saturated carbon [17–20].

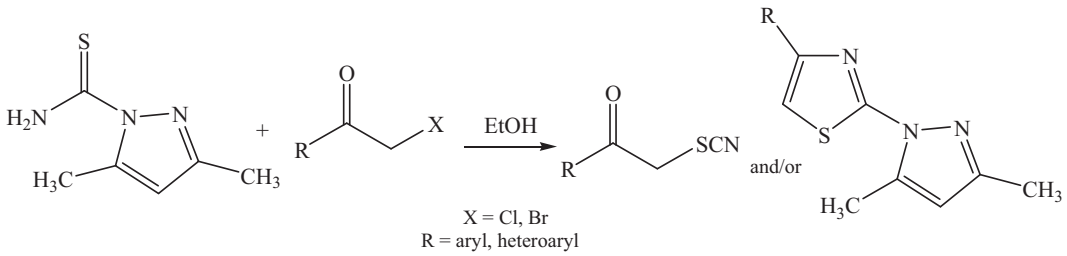
In contrast, the ^1H NMR spectra of 4 showed a singlet of one proton intensity appearing in the range δ 6.5–6.8 corresponding to pyrazole C_4–H. Also, a broad signal at δ 7.15 ppm of two proton intensity, exchangeable with D_2O, showed the presence of thiocarboxamide ($CSNH_2$) group. In the ^{13}C NMR spectra of **4**, signals at about δ 91–101, 157–177 (q, $^2J_{C-F}$ = 33–37 Hz) and 145 ppm correspond to C_4, C_3 and C_5 (Table 4) respectively which provide the firm evidence in support of the formation of aromatic system. Signal at about δ 176–186 ppm shows the presence of C=S group. Further support to the position of CF_3 in 3-trifluoromethylpyrazoles **4** was provided by ^{19}F NMR spectra. A sharp singlet for CF_3 appeared in the range δ −62.26 to −62.58 ppm thus establishing that the CF_3 is bonded to double bond and located at position 3. These are in accordance with the data described in literature [17–20].

Subsequent reaction of 5-hydroxy-5-trifluoromethyl-3-substituted-4,5-dihydropyrazol-1-thiocarboxamides **3** and 3-trifluoromethyl-5-substitutedpyrazole-1-thiocarboxamides **4** with phenacyl bromides **5** provided corresponding 4-aryl-2-(3(5)-substituted-5(3)-trifluoromethyl-1-pyrazolyl)thiazoles **6** and **7**, respectively as exclusive products (Scheme 1). Formation of **6** indicates the formation of thiazole ring is accompanied by simultaneous dehydration of 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazole ring to 5-trifluoromethylpyrazole ring under the reaction conditions. This observation was substantiated by the isolation of intermediate 4-phenyl-2-(5-hydroxy-3,5-*bis*(trifluoromethyl)-4,5-dihydro-1-pyrazolyl)thiazole **8** obtained by the reaction of 5-hydroxy-3,5-*bis*(trifluoromethyl)-4,5-dihydropyrazol-1-thiocarboxamide **3b** with phenacyl bromide **5a**, which was further dehydrated in EtOH–H_2SO_4 to afford corresponding pyrazolylthiazole **6b** as the sole product (Scheme 2). Isolation of the intermediate **8** confirms that there is initial formation of the thiazole ring which is followed by the dehydration of the 4,5-dihydropyrazole ring with the acid (HBr) generated *in situ* during the reaction. Also it was observed in our earlier studies that during the dehydration of 5-hydroxy-5-trifluoromethyl-1-(3-methylquinoxalin-2-yl)-4,5-dihydropyrazoles in acidic medium formation of triazolo[4,3-*a*]quinoxalines took place through ring opening of the 5-hydroxy-4,5-dihydropyrazole [17], however, no such observation was noticed in the present study.

It is interesting to note that, in the present study, the reaction of **3** or **4** with phenacyl bromides did not afford any trace of α-thiocyanatoketone due to C–N bond cleavage, as was reported earlier in the reaction of (3,5-dimethylpyrazol-1-yl)thiocarboxamide with phenacyl bromides and phenacyl chlorides (Scheme 3)



Scheme 2. Isolation of 2-(5-trifluoromethyl-4,5-dihydropyrazol-1-yl)thiazole and its conversion to 2-(5-trifluoromethylpyrazol-1-yl)thiazole.



Scheme 3. Formation of α-thiocyanatoketones and 2-(3,5-dimethylpyrazol-1-yl)thiazoles.

Table 5
^{13}C NMR data for 4-aryl-2-(3(5)-trifluoromethyl-5-substituted-pyrazol-1-yl)thiazoles **6** and **7**.

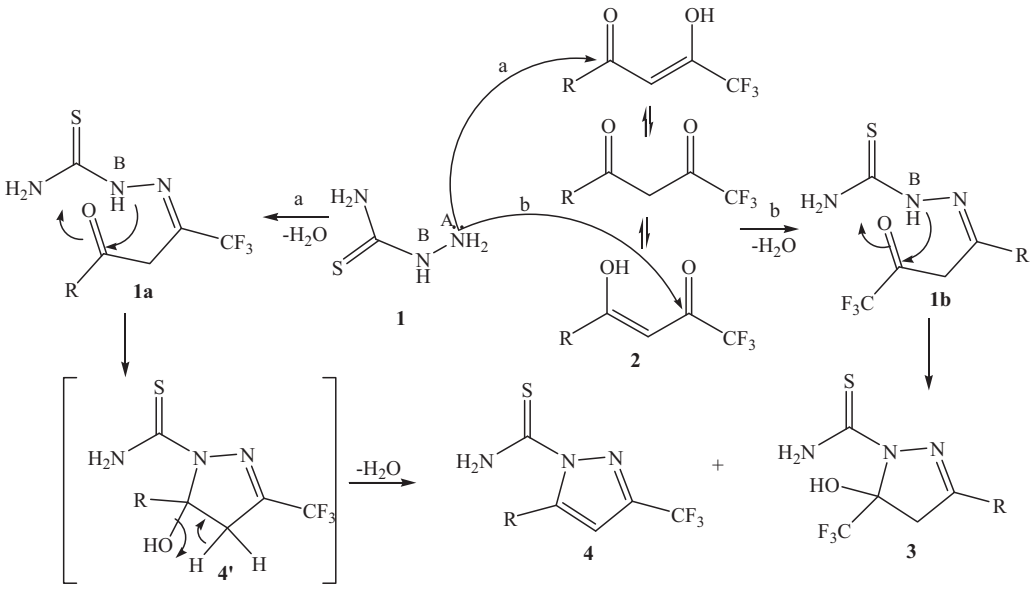
Compound	**6a**	**6b**	**6c**	**6d**	**6e**	**7a**	**7b**	**7c**
Thiazole								
C-2	159.78	158.92	157.93	158.98	158.56	159.54	159.52	159.22
C-4	158.66	133.84	138.47	152.53	152.53	152.47	152.56	152.44
C-5	110.21	110.42	112.12	110.21	113.11	112.45	111.45	112.19
Pyrazole								
C-3′	152.46	152.69 (q, $^2J_{C-F}$ = 38.75 Hz)	151.67	152.78	152.78	144.54 (q, $^2J_{C-F}$ = 39.00 Hz)	144.45 (q, $^2J_{C-F}$ = 39.00 Hz)	143.20 (q, $^2J_{C-F}$ = 38.33 Hz)
C-4′	108.10	109.19	109.34	108.80	109.81	106.23	107.12	106.57
C-5′	134.25 (q, $^2J_{C-F}$ = 33.25 Hz)	133.19 (q, $^2J_{C-F}$ = 41.25 Hz)	132.81 (q, $^2J_{C-F}$ = 40.75 Hz)	133.07 (q, $^2J_{C-F}$ = 41.25 Hz)	133.07 (q, $^2J_{C-F}$ = 41.25 Hz)	147.52	146.23	146.53
Aryl carbons								
C-1″	126.88	130.63	132.54	128.37	133.54	130.90	121.04	120.78
C-2″,6″	127.36	128.94	128.51	127.50	128.48	128.01	131.28	130.99
C-3″,5″	114.14	126.06	125.25	126.05	113.92	127.06	125.97	125.76
C-4″	162.71	128.45	127.32	123.32	162.04	128.01	128.37	128.12
C-1‴			131.94	133.91	128.37	131.34	133.64	128.37
C-2‴,6‴			128.74	128.79	127.50	128.89	128.68	127.55
C-3‴,5‴			124.35	114.33	126.05	125.99	113.56	127.09
C-4‴			127.01	160.69	123.32	129.22	160.65	122.59
Others								
CH_3	13.44							
OCH_3	55.33			55.34	55.45		55.43	
3′-CF_3		119.44 (q, $^1J_{C-F}$ = 267.75 Hz)				122.65 (q, $^1J_{C-F}$ = 265.75 Hz)	120.73 (q, $^1J_{C-F}$ = 267.75 Hz)	120.78 (q, $^1J_{C-F}$ = 262.85 Hz)
5′-CF_3	115.72 (q, $^1J_{C-F}$ = 297.75 Hz)	122.45 (q, $^1J_{C-F}$ = 267.75 Hz)	118.45 (q, $^1J_{C-F}$ = 281.25 Hz)	119.49 (q, $^1J_{C-F}$ = 267.75 Hz)	119.22 (q, $^1J_{C-F}$ = 287.25 Hz)			

[21,22]. This observation suggests that C–N bond cleavage is dependent not only on the nature of R_1 and leaving group in phenacyl bromides **5** but also on nature of ring system attached to the thiocarboxamide group as well as on the substitutents present on pyrazole and pyrazoline rings.

In the ^{1}H NMR spectra of compounds **6**, two singlets of one proton intensity appeared at about δ 6.6-7.1 and 7.1-7.3 ppm thus, corresponding to protons at position-4 of pyrazole and position-5 of thiazole ring, respectively. In the ^{13}C NMR spectra of compounds **6**, signals at about δ 109, 133 (q, $^2J_{C-F}$ = 33-41 Hz) and 152 ppm correspond to carbons C_4, C_5 and C_3 of pyrazole (Table 5) respectively. In the ^{19}F NMR spectra of **6**, a singlet at about δ −59 ppm confirms that CF_3 is located at position-5 of the pyrazole ring [17–20].

The ^{1}H NMR spectra of compounds **7** displayed a singlet of one proton intensity in the range of δ 6.6–6.7 ppm corresponding to the pyrazole 4-position, which is about 0.4 ppm upfield as compared to the corresponding proton in the regioisomer **6** [17–20]. An another signal of one proton intensity in the range δ 7.3–7.4 ppm (sometime merge with protons of aryl ring) was also observed in the ^{1}H NMR spectra of compound **7** which shows the formation of thiazole nucleus. Also, in ^{13}C NMR spectra, signals at about δ 106, 143 (q, $^2J_{C-F}$ = 38-39 Hz) and 146 ppm were assigned to the C_4, C_3 and C_5 positions of the pyrazole ring of **7**, respectively (Table 5). The two regioisomeric pyrazoles **6** and **7** can be distinguished on the basis of quartet for carbon attached to CF_3 group, which is about 10 ppm downfield in **7** as compared to that in **6**. This shows that CF_3 is present at C_3 and C_5 of pyrazole ring in **7** and **6**, respectively. The ^{13}C NMR data of both the regioisomeric pyrazoles are given in Table 5. Further support to the position of CF_3 in 3-trifluoromethylpyrazoles **7** was provided by ^{19}F NMR spectra, a sharp singlet for CF_3 appeared at about δ −62 ppm showing that CF_3 is bonded to double bond and located at position-3 [17–20].

A plausible mechanism for the formation of these products is given in Scheme 4. Initially, nucleophilic attack of nitrogen (N_AH_2) on either carbonyl (path **a** or **b**) gave the corresponding thiosemicarbazones **1a** and **1b**. Relative possibility of this attack depends upon the ratio of two enol forms of the diketones **2** in equilibrium. As established earlier in our previous reports, with aliphatic substituents present on diketones, initial attack of nitrogen takes place entirely on carbonyl remote to trifluoromethyl group. However, with aromatic substituents possibility of attack on trifluoromethyl carbonyl begins to increase. Thiosemicarbazones **1a** and **1b** further cyclized by the nucleophilic attack of other nitrogen (N_BH) on the other carbonyl centre to give the corresponding 5-hydroxy-4,5-dihydropyrazoles **3** and 5-hydroxy-4,5-dihydropyrazoles **4**′. Later undergoes ready dehydration in reaction medium to give the corresponding pyrazoles **4**. However, dehydration of 5-hydroxy-4,5-dihydropyrazoles **3** is not so facile



Scheme 4. Plausible mechanism for the formation of **3** and **4**.

due to presence of electron-withdrawing trifluoromethyl group and these intermediates were isolated in all cases.

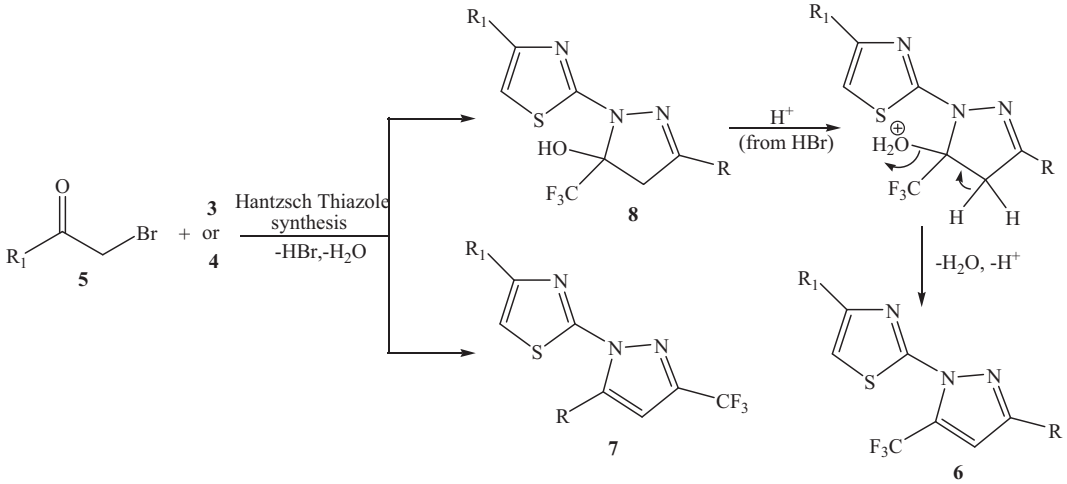
Mechanism of further cyclization of thiocarboxamide group with phenacyl bromides **5** involves three steps as established for Hantzsch thiazole synthesis. There is initial nucleophilic displacement of bromide by the attack of sulphur with the loss of HBr, cyclization in the second step by the attack of nitrogen on the carbonyl carbon and in last step; dehydration to give the corresponding thiazoles **6** and **7**. Acid (HBr) formed during the first step of reaction acts as a catalyst for the *in situ* dehydration of 5-hydroxy-4,5-dihydropyrazole **8** to give the corresponding pyrazolylthiazoles **6** (Scheme 5).

3. Biological assay

Medium used for the antibacterial testing was nutrient agar media (NAM) of the following composition: peptone 5 g; beef extract 3 g; sodium chloride 5 g; agar 2% and final volume of the media was adjusted to 1 l with distilled water and autoclave at 15 lbs/in^2.

3.1. In vitro antibacterial assay

The newly synthesised compounds **3a–e**, **6a** and **6c** were screened for their antibacterial activity against Gram-positive bacteria i.e. *Bacillus pumilus* (MTCC 7411) and Gram-negative bacteria i.e. *Escherichia coli* (MTCC 1652) using disc diffusion assay technique [23,24] and minimum inhibition concentration (MIC) method. Standard antibiotics Gentamicin, Ciprofloxacin were used for the comparison against the antibacterial activities shown by the compounds (Tables 6 and 7). Compounds **3a**, **3b** and **3e** were found to be active against *B. pumilus* at 4 mg/ml concentration. However, no compound showed any activity against *E. coli* at this concentration. The zone of inhibition of compounds **3a**, **3b** and **3e** against *B. pumilus* were 15 mm, 12 mm and 6 mm, respectively and the zone of inhibition of standard antibiotics Gentamicin and Ciprofloxacin were 27 mm and 38 mm, respectively against *B. pumilus* and 28 mm and 25 mm against *E. coli*. The MIC of compounds **3a**, **3b** and **3e** was found to be 400 μg/ml, 400 μg/ml and 500 μg/ml, respectively against the *B. pumilus* where as no



Scheme 5. Plausible mechanism for the formation of **6**, **7** and **8**.

Table 6
In vitro antibacterial activity of **3** and **6** by disc diffusion method.

S. no.	Compound	Diameter of growth of inhibition zone (mm)[a]	
		Bacillus pumilus	*Escherichia coli*
1	**3a**	15	–
2	**3b**	12	–
3	**3c**	–	–
4	**3d**	–	–
5	**3e**	6	–
6	**6a**	–	–
7	**6c**	–	–
	Gentamicin	27	28
	Ciprofloxacin	38	25

(–) indicates no activity at 4 mg/ml.
[a] Means of three replicates, including diameter of disc.

Table 7
Minimum inhibitory concentration (MIC) (μg/ml) of **3a**–**b**, **e**.

S. no.	Compound	*Bacillus pumilus*	*Escherichia coli*
1	**3a**	400	–
2	**3b**	400	–
3	**3e**	500	–
	Gentamicin	10	10
	Ciprofloxacin	5	5

(–) indicates no activity.

zone of inhibition was appeared unless a concentration of 4 mg/ml was used against in case of *E. coli*. However, compounds **3c**–**d**, **6a** and **6c** did not show any zone of inhibition against either of bacteria at 4 mg/ml concentration. The MIC of Ciprofloxacin and Gentamicin was 5 μg/ml and 10 μg/ml, respectively against both *B. pumilus* and *E. coli*.

4. Conclusion

A regioselective synthesis of isomeric (5(3)-trifluoromethylpyrazol-1-yl)thiazoles **6** and **7** was developed. The highlights of the present study are: (i) cyclo-condensation of thiosemicarbazide **1** with trifluoromethyl-β-diketones **2** to form 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamides **3** as major product in neutral conditions, (ii) reversal of regioselectivity during the reaction of **1** and **2** in acidic medium afforded pyrazole-1-thiocarboxamides **4** as significant or major product, (iii) the reaction of 4,5-dihydropyrazol-1-thiocarboxamides **3** and pyrazole-1-thiocarboxamides **4** with phenacyl bromides **5** to give isomeric (5(3)-trifluoromethylpyrazol-1-yl)thiazoles **6** and **7**, respectively as exclusive product, (iv) isolation of intermediate 2-(5-trifluoromethyl-4,5-dihydropyrazol-1-yl)thiazole **8** provides an insight in the mechanistic pathway.

5. Experimental

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. IR spectra were recorded on a Buck Scientific IR M500 instrument. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker instrument at 300 MHz and 75 MHz, respectively. ^{19}F NMR spectra were run on DRX 300 and DPX 400 at 282 and 376 MHz, respectively, using deuteriochloroform as a solvent. The internal standard for ^{19}F spectra was fluorotrichloromethane, setting the $CFCl_3$ signal at δ 0.0. High resolution mass spectra (HRMS) were measured in EI mode on a Kratos MS-50 spectrometer at MS Facilities at UCSF, USA. Elemental analysis was performed at SAIF, Lucknow, India. The compounds gave satisfactory analytical results (within ±0.4 of the calculated values).

5.1. General procedure for the preparation of 5-hydroxy-5-trifluoromethyl-3-alkyl-4,5-dihydropyrazol-1-thiocarboxamides 3a–b

An ethanolic solution (30 ml) of thiosemicarbazide **1** (0.9 g 10 mmol) and trifluoromethyl-β-diketones **2a**–**b** (10 mmol) was refluxed for 6 h. The progress of reaction was monitored with the help of TLC. When the reaction was complete, solvent was distilled off under vacuum. ^{1}H NMR spectra and TLC of reaction mixture showed the presence of single product **3a**–**b**.

5.1.1. 5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamide 3a

Mp. 174–176 °C; Yield 92% IR (cm^{-1}): 3403, 3285 (NH_2), 3574 (O–H), 1605 (C=S), 1477 (C=N); ^{1}H NMR ($CDCl_3$) δ: 2.09 (s, 3H, CH_3), 3.26 (dq, 1H, J_{HA-HB} = 18.9 Hz, $^4J_{HB-CF3}$ = 1.2 Hz 4-H_B), 3.37 (d, 1H, J_{HA-HB} = 18.9 Hz, 4-H_A), 6.23 (bs, 1H, NH, exchangeable with D_2O), 7.14 (bs, 1H, NH, exchangeable with D_2O), 7.95 (bs, 1H, 5-OH, exchangeable with D_2O); ^{19}F NMR ($CDCl_3$) δ: −78.51 (5-CF_3); HRMS (*m*/*z*): 227.0343 (M+), $C_6H_8F_3N_3OS$ requires 227.0340.

5.1.2. 5-Hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydropyrazol-1-thiocarboxamide 3b

Mp. 122–125 °C; Yield 91%; IR (cm^{-1}): 3415 (NH_2), 3310 (NH_2), 3504 (O–H), 1612 (C=S), 1475 (C=N); ^{1}H NMR ($CDCl_3$) δ: 3.47 (dq, 1H, J_{HA-HB} = 19.6 Hz, $^4J_{HB-CF3}$ = 1.4 Hz, 4-H_B), 3.63 (d, 1H, J_{HA-HB} = 19.6 Hz, 4-H_A), 6.55 (bs, 1H, NH, exchangeable with D_2O), 7.19 (bs, 1H, NH, exchangeable with D_2O), 7.75 (bs, 1H, 5-OH, exchangeable with D_2O); ^{19}F NMR ($CDCl_3$) δ: −78.75 (5-CF_3), −62.42 (3-CF_3); Elemental Analysis: Found: C, 25.51; H, 1.84; N, 14.84; $C_6H_5F_6N_3OS$ requires C, 25.63; H, 1.79; N, 14.94.

5.2. General procedure for the preparation of 5-hydroxy-5-trifluoromethyl-3-aryl-4,5-dihydropyrazol-1-thiocarboxamides 3c–d and 3-trifluoromethyl-5-arylpyrazol-1-thiocarboxamides 4c–d

An ethanolic solution (30 ml) of thiosemicarbazide **1** (0.9 g, 10 mmol) and trifluoromethyl-β-diketones **2c**–**d** (10 mmol) was refluxed for 6 h. The progress of reaction was monitored with the help of TLC. When the reaction was complete, solvent was distilled off under vacuum. The ^{1}H NMR spectra and TLC of reaction mixture showed the presence of two products in the ratio given in Table 1. Column chromatographic separation using silica gel (100–200 mesh) with petroleum ether:ethyl acetate (99:1) afforded **4**, further elution of column with petroleum ether:ethyl acetate (97:3) afforded **3**.

5.2.1. 5-Hydroxy-3-phenyl-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamide 3c

Mp. 130–132 °C; Yield 65%; IR (cm^{-1}): 3412, 3291 (NH_2), 3568 (O–H), 1602 (C=S), 1472 (C=N); ^{1}H NMR ($CDCl_3$) δ: 3.66 (dq, 1H, J_{HA-HB} = 18.6 Hz, $^4J_{HB-CF3}$ = 1.3 Hz, 4-H_B), 3.82 (d, 1H, J_{HA-HB} = 18.6 Hz, 4-H_A), 6.28 (bs, 1H, NH, exchangeable with D_2O), 7.32 (bs, 1H, NH, exchangeable with D_2O), 7.44–7.54 (m, 3H, 3′,4′,5′-H), 7.58 (m, 2H, 2′,6′-H), 8.00 (bs, 1H, 5-OH, exchangeable with D_2O); ^{19}F NMR ($CDCl_3$) (: −79.11 (5-CF_3); Elemental Analysis: Found: C, 45.53; H, 3.34; N, 14.32; $C_{11}H_{10}F_3N_3OS$ requires C, 45.67; H, 3.48; N, 14.53.

5.2.2. 5-Phenyl-3-trifluoromethylpyrazol-1-thiocarboxamide 4c

Mp. 100–102 °C; Yield 10%; IR (cm^{-1}): 3012, 1503; ^{1}H NMR ($CDCl_3$) δ: 6.82 (s, 1H, 4-H), 7.16 (bs, 2H, NH_2, exchangeable with D_2O), 7.34 (m, 3H, 3′,4′,5′-H), 7.61 (m, 2H, 2′,6′-H); ^{19}F NMR ($CDCl_3$) δ: −62.45 (3-CF_3); Elemental Analysis: Found: C, 48.51; H, 2.84; N, 15.77; $C_{11}H_8F_3N_3S$ requires C, 48.70; H, 2.97; N, 15.79.

*5.2.3. 5-Hydroxy-3-(p-methoxyphenyl)-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamide **3d***

Mp. 160–165 °C; Yield 45%; IR (cm^{-1}): 3405, 3275 (NH_2), 3578 (O–H), 1614 (C=S), 1476 (C=N); ^1H NMR ($CDCl_3$) δ: 3.56 (dq, 1H, J_{HA-HB} = 18.6 Hz, $^4J_{HB-CF3}$ = 1.2 Hz 4-H_B), 3.76 (d, 1H, J_{HA-HB} = 18.6 Hz, 4-H_A), 3.80 (s, 3H, OCH_3), 6.19 (bs, 1H, NH, exchangeable with D_2O), 6.89 (dd, 2H, J = 9.0 Hz, J = 1.8 Hz, 3′,5′-H), 7.20 (bs, 1H, NH, exchangeable with D_2O), 7.58 (dd, 2H, J = 9.0 Hz, J = 1.8 Hz, 2′,6′-H), 8.58 (bs, 1H, 5-OH, exchangeable with D_2O); ^{19}F NMR ($CDCl_3$) δ: −78.44 (5-CF_3); HRMS (m/z): 319.0611 (M+), $C_{12}H_{12}F_3N_3O_2S$ requires 319.0602.

*5.2.4. 5-(p-Methoxyphenyl)-3-trifluoromethylpyrazol-1-thiocarboxamide **4d***

Mp. 112–114 °C; Yield 25%; IR (cm^{-1}): 3034, 1512; ^1H NMR ($CDCl_3$) δ: 3.92 (s, 3H, OCH_3), 6.52 (s, 1H, 4-H), 7.0 (dd, 2H, J = 6.9 Hz, J = 1.8 Hz, 3′, 5′-H), 7.14 (bs, 2H, NH_2, exchangeable with D_2O), 7.96 (dd, 2H, J = 6.9 Hz, J = 1.8 Hz, 2′, 6′-H); ^{19}F NMR ($CDCl_3$) δ: −62.58 (3-CF_3); Elemental Analysis: Found: C, 47.53; H, 3.23; N, 13.77; $C_{12}H_{10}F_3N_3OS$ requires C, 47.84; H, 3.35; N, 13.95.

*5.2.5. 5-Hydroxy-3-(p-chlorophenyl)-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamide **3e***

Mp. 140–142 °C; Yield 52%; IR (cm^{-1}): 3431, 3264 (NH_2), 3573 (O–H), 1610 (C=S), 1463 (C=N); ^1H NMR ($CDCl_3$) δ: 3.57 (dq, 1H, J_{HA-HB} = 18.6 Hz, $^4J_{HB-CF3}$ = 1.2 Hz 4-H_B), 3.71 (d, 1H, J_{HA-HB} = 18.6 Hz, 4-H_A), 6.29 (bs, 1H, NH, exchangeable with D_2O), 7.22 (bs, 1H, NH, exchangeable with D_2O), 7.37 (dd, 2H, J = 9.0 Hz, J = 2.3 Hz, 3′,5′-H), 7.56 (dd, 2H, J = 9.0 Hz, J = 2.3 Hz, 2′,6′-H), 7.90 (bs, 1H, 5-OH, exchangeable); ^{19}F NMR ($CDCl_3$) δ: −79.04 (5-CF_3); Elemental Analysis: Found: C, 40.67; H, 2.64; N, 12.54; $C_{11}H_9ClF_3N_3OS$ requires C, 40.81; H, 2.80; N, 12.98.

*5.2.6. 5-(p-Chlorophenyl)-3-trifluoromethylpyrazol-1-thiocarboxamide **4e***

Mp. 114–116 °C; Yield 24%; IR (cm^{-1}): 3032, 1508; ^1H NMR ($CDCl_3$) δ: 6.76 (s, 1H, 4-H), 7.13 (bs, 2H, NH_2, exchangeable with D_2O), 7.46 (d, 2H, J = 8.3 Hz, 3′, 5′-H), 7.53 (d, 2H, J = 8.3 Hz, 2′, 6′-H); ^{19}F NMR ($CDCl_3$) δ: −62.26 (3-CF_3); Elemental Analysis: Found: C, 43.12; H, 2.34; N, 13.67; $C_{11}H_7ClF_3N_3S$ requires C, 43.22; H, 2.31; N, 13.75.

*5.3. General procedure for the reaction between thiosemicarbazide **1** and trifluoromethyl-β-diketones **2** in acidic conditions*

To an ethanolic solution (30 ml) of thiosemicarbazide **1** (0.9 g, 10 mmol) 4–5 drops of H_2SO_4 were added followed by trifluoromethyl-β-diketones **2c**–**d** (10 mmol) and was refluxed for 6 h. The progress of reaction was monitored with the help of TLC. When the reaction was complete, solvent was distilled off under vacuum. Reaction mixture thus obtained by neutralized by aq. NaOH and was extracted by ethyl acetate (3 × 20 ml). The combined organic extracts were dried over anhyd. sodium sulphate, filtered and concentrated. The ^1H NMR spectra and TLC of reaction mixture showed the presence of two products in the ratio given in Table 2. Data of compounds **3** and **4** has already been given above.

*5.4. Preparation of 4-aryl-2-(3-substituted-5-trifluoromethyl-1-pyrazolyl)thiazoles **6a, c–e***

To a solution of **3** (1 mmol) in ethanol (20 ml) was added **5** (1 mmol). The reaction mixture was refluxed for 3 h. The progress of reaction was monitored with the help of TLC. When the reaction was complete, solvent was evaporated to reduce the volume, which was neutralized by sodium bicarbonate and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried over anhyd. sodium sulphate, filtered and concentrated to give **6**.

*5.4.1. 4-(p-Methoxyphenyl)-2-(3-methyl-5-trifluoromethylpyrazol-1-yl)thiazole **6a***

Mp. 110–112 °C; Yield 82%; IR (cm^{-1}): 3154, 1497; ^1H NMR ($CDCl_3$)δ: 2.30 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.61 (s, 1H, 4′-H), 6.88 (d, 2H, J = 8.7 Hz, 3″,5″-H), 7.09 (s, 1H, 5-H), 7.84 (d, 2H, J = 8.7 Hz, 2″,6″-H); ^{19}F NMR ($CDCl_3$) δ: −58.33 (5′-CF_3); Elemental Analysis: Found: C, 53.15; H, 3.44; N, 12.48; $C_{15}H_{12}F_3N_3OS$ requires C, 53.09; H, 3.56; N, 12.38.

*5.4.2. 4-Phenyl-2-(3-phenyl-5-trifluoromethylpyrazol-1-yl)thiazole **6c***

Mp. 118–122 °C; Yield 76%; IR (cm^{-1}): 3255, 1482; ^1H NMR ($CDCl_3$) δ: 7.11 (s, 1H, 4′-H), 7.16 (s, 1H, 5-H), 7.32–7.47 (m, 6H, 3″,4″,5″,3‴,4‴,5‴-H), 7.78–7.81 (m, 2H, 2″,6″-H), 7.84–7.86 (m, 2H, 2‴,6‴-H); ^{19}F NMR ($CDCl_3$) δ: −59.01 (5′-CF_3); Elemental Analysis: Found: C, 61.22; H, 3.12; N, 11.24; $C_{19}H_{12}F_3N_3S$ requires C, 61.45; H, 3.26; N, 11.31.

*5.4.3. 4-Phenyl-2-(3-(p-methoxyphenyl)-5-trifluoromethylpyrazol-1-yl)thiazole **6d***

Mp. 130–132 °C; Yield 86%; IR (cm^{-1}): 3145, 1495; ^1H NMR ($CDCl_3$) δ: 3.89 (s, 3H, OCH_3), 7.01 (d, 2H, J = 9.0 Hz, 3‴, 5‴-H), 7.14 (s, 1H, 4′-H), 7.36 (s, 1H, 5-H), 7.37–7.40 (m, 1H, 4″-H), 7.44–7.49 (m, 2H, 3″,5″-H), 7.84 (d, 2H, J = 9.0 Hz, 2‴, 6‴-H), 7.94–7.96 (m, 2H, 2″,6″-H); ^{19}F NMR ($CDCl_3$) δ: −59.13 (5′-CF_3); Elemental Analysis: Found: C, 59.52; H, 3.43; N, 10.53; $C_{20}H_{14}F_3N_3S$ requires C, 59.84; H, 3.52; N, 10.47.

*5.4.4. 4-(p-Methoxyphenyl)-2-(3-(p-chlorophenyl)-5-trifluoromethylpyrazol-1-yl)thiazole **6e***

Mp. 124–126 °C; Yield 82%; IR (cm^{-1}): 3355, 1492; ^1H NMR ($CDCl_3$) δ: 3.88 (s, 3H, OCH_3), 6.99 (d, 2H, J = 8.7 Hz, 3″, 5″-H), 7.18 (s, 1H, 4′-H), 7.24 (s, 1H, 5-H), 7.46 (d, 2H, J = 8.4 Hz, 3‴, 5‴-H), 7.84 (d, 2H, J = 8.4 Hz, 2‴, 6‴-H), 7.88 (d, 2H, J = 8.7 Hz, 2″, 6″-H); ^{19}F NMR ($CDCl_3$) δ: −58.97 (5′-CF_3); Elemental Analysis: Found: C, 55.23; H, 2.92; N, 9.45; $C_{20}H_{13}ClF_3N_3S$ requires C, 55.11; H, 3.01; N, 9.64.

*5.5. Preparation of 4-aryl-2-(5-substituted-3-trifluoromethyl-1-pyrazolyl)thiazoles **7a–c***

To a solution of **4** (1 mmol) in ethanol (20 ml) was added **5** (1 mmol). The reaction mixture was refluxed for 3 h. The progress of reaction was monitored with the help of TLC. When the reaction was complete, solvent was evaporated to reduce the volume, which was neutralized by sodium bicarbonate and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried over anhyd. sodium sulphate, filtered and concentrated to give **7**.

*5.5.1. 4-Phenyl-2-(5-phenyl-3-trifluoromethylpyrazol-1-yl)thiazole **7a***

Mp. 115–116 °C; Yield 82%; IR (cm^{-1}): 3354, 1497; ^1H NMR ($CDCl_3$) δ: 6.76 (s, 1H, 4′-H), 7.33–7.37 (m, 7H, 5,3″,4″,5″,3‴,4‴,5‴-H), 7.75–7.83 (m, 4H, 2″,6″,2‴6‴-H); ^{19}F NMR ($CDCl_3$) δ: −62.34 (3′-CF_3); Elemental Analysis: Found: C, 61.40; H, 3.22; N, 11.45; $C_{19}H_{12}F_3N_3S$ requires C, 61.45; H, 3.26; N, 11.31.

*5.5.2. 4-Phenyl-2-(5-(p-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl)thiazole **7b***

Mp. 110–112 °C; Yield 78%; IR (cm^{-1}): 3352, 1490; ^1H NMR ($CDCl_3$) δ: 3.89 (s, 3H, OCH_3), 6.71 (s, 1H, 4′-H), 7.01 (d, 2H, J = 8.7 Hz, 3‴,5‴-H), 7.31–7.36 (m, 4H, 3″,4″,5″,5-H), 7.53 (d, 2H,

J = 8.7 Hz, 2‴,6‴-H) 7.64–7.67 (m, 2H, 2″,6″-H); ^{19}F NMR ($CDCl_3$) δ: −62.44 (3′-CF_3); Elemental Analysis: Found: C, 59.23; H, 3.92; N, 10.45; $C_{20}H_{14}F_3N_3OS$ requires C, 59.84; H, 3.52; N, 10.47.

5.5.3. 4-Phenyl-2-(5-(p-chlorophenyl)-3-trifluoromethylpyrazol-1-yl)thiazole ***7c***

Mp. 124–126 °C; Yield 86%; IR (cm^{-1}): 3357, 1494; ^{1}H NMR ($CDCl_3$) δ: 6.72 (s, 1H, 4-H), 7.42–7.45 (m, 3H, 5, 3‴,5‴-H), 7.53–7.58 (m, 4H, 3″,5″, 2‴,6‴-H), 7.63–7.66 (m, 4″-H), 7.97–8.01 (m, 2H, 2″,6″-H); ^{19}F NMR ($CDCl_3$) δ: −62.37 (3′-CF_3); Elemental Analysis: Found: C, 56.55; H, 2.62; N, 10.45; $C_{19}H_{11}ClF_3N_3S$ requires C, 56.23; H, 2.73; N, 10.35.

5.6. Preparation of 4-phenyl-2-(3,5-bis-trifluoromethylpyrazol-1-yl)thiazole ***6b*** *via isolation of 4-Phenyl-2-(5-hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydro pyrazol-1-yl)thiazole* ***8***

5.6.1. Preparation of 4-phenyl-2-(5-hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydro pyrazol-1-yl)thiazole ***8***

To a solution of **3b** (0.281 g, 1 mmol) in ethanol (20 ml) was added **5a** (0.199 g, 1 mmol). The reaction mixture was refluxed for 3 h. The progress of reaction was monitored with the help of TLC. When the reaction was complete, solvent was evaporated to reduce the volume. A yellow colored solid was obtained on standing, which was neutralized by sodium bicarbonate and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried over anhyd. sodium sulphate, filtered and concentrated to give **8**. Mp. 122–124 °C; Yield 0.3 g, 80%; IR (cm^{-1}): 3573 (O–H), 1463 (C=N); ^{1}H NMR ($CDCl_3$) δ: 3.38 (d, 1H, J_{HA-HB} = 18.6 Hz, 4′-H_B), 3.56 (d, 1H, J_{HA-HB} = 18.6 Hz, 4′-H_A), 6.97 (s, 1H, 5-H), 7.10 (bs, 1H, 5′–OH, exchangeable with D_2O), 7.24–7.29 (m, 1H, 4″-H), 7.31–7.35 (m, 2H, 3″,5″-H), 7.65–7.68 (m, 2H, 2″, 6″-H); ^{13}C NMR ($CDCl_3$) δ: 42.05 (C-4′), 93.99 (q, $^2J_{C-F}$ = 34.50 Hz, C-5′), 106.38 (C-5), 119.10 (q, $^1J_{C-F}$ = 271.50 Hz, 3-CF_3), 122.81 (q, $^1J_{C-F}$ = 270.75 Hz, 5-CF_3), 125.96 (C-3″, 5″), 128.48 (C-4″), 128.83 (C-2″, 6″), 128.93 (C-4), 133.47 (C-1″), 142.06 (q, $^2J_{C-F}$ = 39.75 Hz, C-3′), 163.69 (C-2); ^{19}F NMR ($CDCl_3$) δ: −78.55 (5′-CF_3), −62.18 (3′-CF_3); Elemental Analysis: Found: C, 44.12; H, 2.34; N, 11.11; $C_{14}H_9F_6N_3OS$ requires C, 44.10; H, 2.38; N, 11.02.

5.6.2. Preparation of 4-phenyl-2-(3,5-bis-trifluoromethylpyrazol-1-yl)thiazole ***6b***

To an ethanolic solution of **8** (0.19 g, 0.0005 mol), 2–3 drops of H_2SO_4 were added and refluxed for 5 h. The reaction was monitored by TLC. On completion, reaction mixture was neutralized using aq. NaOH and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried over anhyd. sodium sulphate, filtered and concentrated to give **6b**. Mp. 114–118 °C; Yield 90%; IR (cm^{-1}): 3154, 1497; ^{1}H NMR ($CDCl_3$) δ: 7.17 (s, 1H, 4′-H), 7.39–7.43 (m, 1H, 4″-H), 7.46–7.50 (m, 3H, 5, 3″,5″-H), 7.92–7.95 (m, 2H, 2″,6″-H); ^{19}F NMR ($CDCl_3$) δ: −58.45 (5′-CF_3), −62.25 (3′-CF_3); Elemental Analysis: Found: C, 46–51; H, 1.92; N, 11.45; $C_{14}H_7F_6N_3S$ requires C, 46.29; H, 1.94; N, 11.57.

Acknowledgements

We thank the Council of Scientific and Industrial Research and University Grants Commission, New Delhi for financial assistance. Thanks are also due to Sophisticated Analytical Instrument facility, Central Drug Research Institute, Lucknow, India for providing elemental analysis. We are also grateful to UCSF Mass Spectrometry Facility, University of California, San Fransisco, USA for providing high resolution mass spectral data. We also thank Prof. S.P. Singh for helpful suggestions.

References

[1] M.W. Dryden, T.M. Denenberg, S. Bunch, Vet. Parasitol. 93 (2000) 69–75.
[2] F. Leroux, O. Lefebvre, M. Schlosser, Eur. J. Org. Chem. 314 (2006) 3147–3151.
[3] F.H. Arthur, J. Econ. Entomol. 95 (2002) 1314–1318.
[4] K.L. Kees, J.J. Fitzgerald, K.E. Steiner, J. Mattes, B. Mihan, T. Tosi, D. Mondoro, L. McCaleb, J. Med. Chem. 39 (1996) 3920–3958.
[5] S. Buscemi, A. Pace, A. Piccionello, G. Macaluso, N. Vivona, J. Org. Chem. 70 (2005) 3288–3291, and references cited therein.
[6] S.R. Bertenshaw, J.T. Talley, D.J. Rogier, M.J. Graneto, C.M. Koboldt, Y. Zhang, Bioorg. Med. Chem. Lett. 6 (1996) 2827–2830.
[7] T.D. Penning, J.J. Talley, S.R. Bertenshaw, J.S. Carter, P.W. Collins, S. Docter, M.J. Graneto, L.F. Lee, J.W. Malecha, J.M. Miyashiro, R.S. Rogers, D.J. Rogier, S.S. Yu, G.D. Anderson, E.G. Burton, J.N. Cogburn, S.A. Gregory, C.M. Koboldt, W.E. Perkins, K. Seibert, A.W. Veenhuizen, Y.Y. Zhang, P.C. Isakson, J. Med. Chem. 40 (1997) 1347–1365.
[8] S.W. Djuric, N.Y. BaMaung, A. Basha, H. Liu, J.R. Luly, D.J. Madar, R.J. Sciotti, N.P. Tu, F.L. Wagenaar, P.E. Wiedeman, X. Zhou, S. Ballaron, J. Bauch, Y.W. Chen, X.G. Chiou, T. Fey, D. Gauvin, E. Gubbins, G.C. Hsieh, K.C. Marsh, K.W. Mollison, M. Pong, T.K. Shaughnessy, M.P. Sheets, M. Smith, J.M. Trevillyan, U. Warrior, C.D. Wegner, G.W. Carter, J. Med. Chem. 43 (2000) 2975–2981.
[9] Eur. Pat. Appl. EP 819 690, Chem. Abstr. 128 (1998) 140726.
[10] US Patent 5 698 708, Chem. Abstr. 128 (1998) 75398.
[11] P.J. Sanfilippo, M.J. Urbanski, K.N. Beers, A. Ecardt, R. Falotico, M.H. Ginsberg, S. Offord, J.B. Press, J. Tighe, K. Tomko, P. Andrade-Gordon, J. Med. Chem. 38 (1995) 34–41.
[12] C.R. Prokopp, M.A. Rubin, P.D. Sauzem, A.H. de Souza, D.B. Berlese, R.V. Lourega, M.N. Muniz, H.G. Bonacorso, N. Zanatta, M.A.P. Martins, C.F. Mello, Braz. J. Med. Biol. Res. 39 (2006) 795–799.
[13] B.A. Donohue, E.L. Michelotti, J.C. Reader, V. Reader, M. Stirling, C.M. Tice, J. Comb. Chem. 4 (2002) 23–32.
[14] S.P. Singh, L.S. Tarar, Indian J. Chem. 29 (1990) 342–346.
[15] A.B. Denisova, V.Y. Sosnovskikh, W. Dehaen, S. Toppet, L.V. Meervelt, V.A. Bakulev, J. Fluorine Chem. 115 (2002) 183–192.
[16] M.P. Mahajan, S.M. Sondhi, N.K. Ralhan, Aust. J. Chem. 30 (1977) 2053–2056.
[17] R. Aggarwal, R. Kumar, S.P. Singh, J. Fluorine Chem. 130 (2009) 886–893.
[18] V. Kumar, S.P. Singh, R. Aggarwal, J. Fluorine Chem. 127 (2006) 880–888.
[19] S.P. Singh, D. Kumar, B.G. Jones, M.D. Threadgill, J. Fluorine Chem. 94 (1999) 199–203.
[20] L. Song, S. Zhu, J. Fluorine Chem. 111 (2001) 201–205.
[21] S.P. Singh, S. Sehgal, L. Singh, S.N. Dhawan, Indian J. Chem. 26 (1987) 154–155.
[22] S.P. Singh, S. Sehgal, P.K. Sharma, Indian J. Chem. 29 (1990) 533–538.
[23] A.W. Bauer, W.M.M. Kirby, J.C. Sherris, Am. J. Clin. Pathol. 45 (1966) 493–496.
[24] N.V. Shinde, M. Himaja, S.K. Bhosale, M.V. Ramana, D.M. Sakarkar Indian, J. Pharm. Sci. 70 (2008) 827–831.