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The regioselectivity of the formation of 2-pyrazolylthiazoles and their precursors from the reaction of 2-hydrazinothiazoles with 4,4,4-trifluoro-1-hetaryl-1,3-butanediones

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Abstract

Reaction of 2-hydrazinothiazoles **1** with 1-thienyl- and 1-furyl-1,3-butanediones **2a**,**b** in methanol in the presence of hydrochloric acid mainly leads to a mixture of pyrazoles **3** and pyrazolines **4** or pyrazoles **3** and **5** in strong acidic conditions. Isomeric hydrazones **6** and pyrazolines **4** were formed and isolated in these reactions in the absence of hydrochloric acid. It has been shown that the regioselectivity in the reaction of diketones **2** with hydrazine **1** is governed by both the concentration of acid and the nature of substituents in the 1,3-diketones **2**. Cyclization of hydrazones **6** is shown to occur under milder conditions than dehydration for pyrazolines **4**. The new heterocyclic compounds were prepared and fully characterized by NMR spectra and by X-ray analysis for **3c**.

Keywords: Pyrazolylthiazoles; Regioselectivity; 2-Hydrazinothiazoles; 1,3-Diketones; ^{1}H; ^{19}F; ^{13}C NMR

1. Introduction

Heterocyclic compounds bearing a trifluoromethyl group are of special interest as potential pesticides [1] and pharmaceuticals [1–4]. The reaction of trifluoromethyl-1,3-diketones with heterocyclic hydrazines has been shown to be an efficient method to prepare such compounds, where the pyrazole ring is conjugated to other heterocycles [5] and many examples of such type of compounds have recently been reported [5,6]. Tricyclic conjugated compounds containing aromatic and non-aromatic heterocyclic rings are not so common in the literature [5]. Furthermore, different structures have been described for the reaction of similar hydrazines [6–8] and even for the same reagents [7–9]. The reason is that the reaction of 1,3-diketones, and especially those bearing heterocyclic moieties, with hydrazines leads to mixtures of regioisomeric pyrazoles. The most recent advances in this area have been summarized by Singh et al. [5].

There are no data in the literature preceding this work on the influence of the acidity of the reaction medium on the regioselectivity of the condensation of heterocyclic hydrazines with trifluoromethyl 1,3-diketones. Clearly, this correlation could be useful in future process development if any of these compounds emerge as commercial products.

2. Results and discussion

In a previous report, we have described that the reaction of 2-hydrazinothiazoles with 4,4,4-trifluoro-1-aryl-1,3-butanediones (Ar = Ph, 2-naphthyl, 4-ClC_6H_4) to give the selective formation of 2-(3-aryl-5-hydroxy-5-trifluoromethylpyrazolin-1-yl)thiazoles. These compounds in turn undergo dehydration to aromatic 2-(3-aryl-5-trifluoromethylpyrazol-1-yl)-4-thiazoles after reflux in acetic anhydride (Scheme 1) [6]. At the same time, Singh et al. have found that the reaction of these 1,3-diketones with thiazdyl hydrazine generates a product with the opposite regioselectivity [7,8]. Even more surprisingly, for reaction of thiosemicarbazide with diketone **2a**, Singh et al. [7] and Pashkevich et al. [9] have isolated products of opposite regioselectivity from the reaction using identical reagents.

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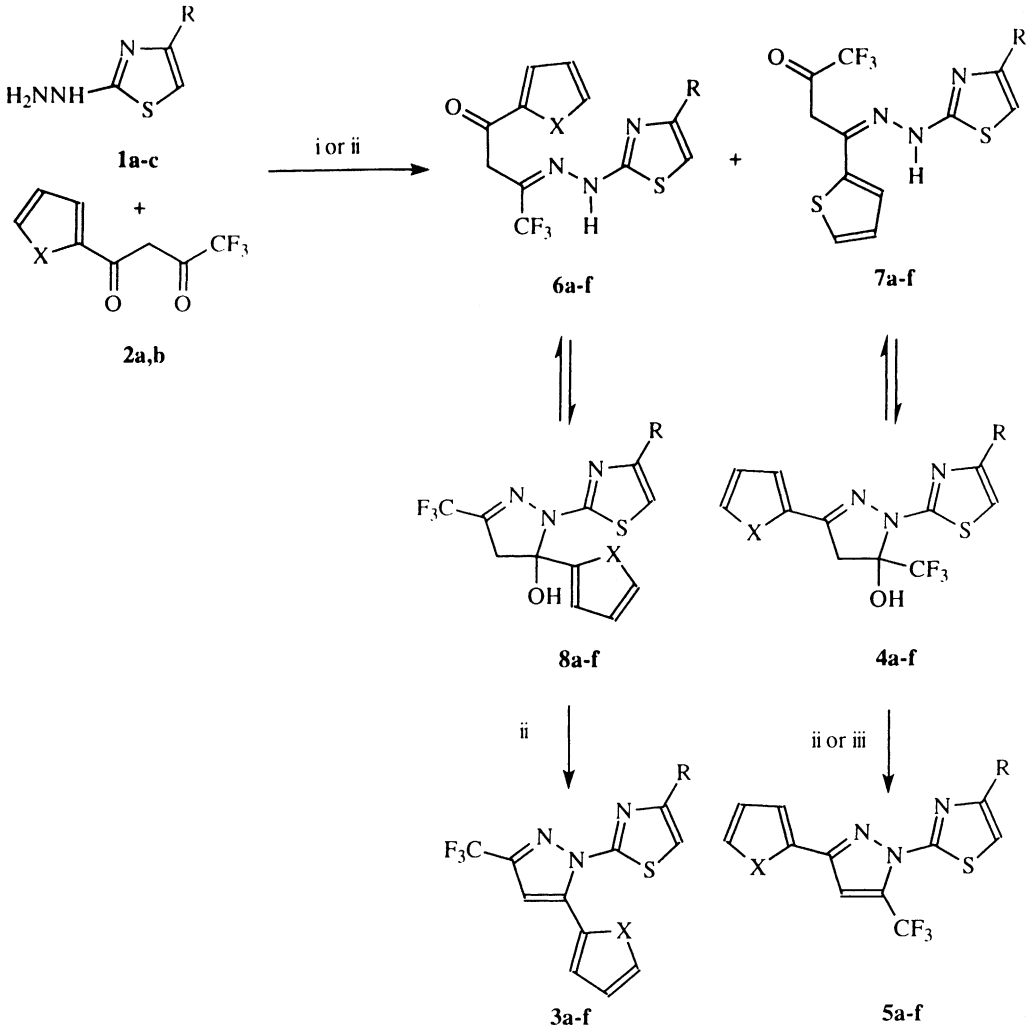

1	R	2	X	3,4,5,6	R	X
a	4-C_6H_4Cl	a	S	a	4-C_6H_4Cl	S
b	Ph	b	O	b	Ph	S
c	COOEt			c	COOEt	S
				c'	COOMe	
				d	4-C_6H_4Cl	O
				e	Ph	O
				f	COOEt	O

Scheme 1. (i) MeOH, reflux (ii) MeOH, HCl, reflux (iii) Ac_2O, reflux.

These results prompted us to carry out a detailed study on the reactions of the 2-hydrazinothiazoles **1a–c** with 1-thienyl-4,4,4-trifluoro-1,3-butanedione **2a**. We have also carried out similar condensation reactions between **1a–c** and 1-furyl-4,4,4-trifluoro-1,3-butanedione **2b**, to generate a series of novel reaction products (Scheme 1).

We have discovered that the reaction of 2-hydrazinothiazole **1a** with diketone **2a** in methanol in the presence of concentrated hydrochloric acid (the molar ratio of **1a** to HCl being 1:0.26), leads to a mixture of 5-hydroxy-5-trifluoromethylpyrazoline **4a**, pyrazole **3a**, and 5-trifluoropyrazole **5a** in a ratio of 26:69:5 as determined from the ^{19}F NMR

Table 1
Quantitative composition of the product mixtures, obtained in the reaction of **1a** with **2a** with different amounts of acid

	Compound					Regioselectivity[a]
	7a (%)	**6a** (%)	**4a** (%)	**3a** (%)	**5a** (%)	
Molar ratio of **1a** to HCl						
1:0	27	18	53	2		0.3
1:0.1			28	67	5	2.0
1:0.26			26	69	5	2.2
1:0.5			25	70	5	2.4
1:100				78	22	3.3
Chemical shift CF_3 (ppm)	94.9	92.7	80.9	98.9	102.0	

[a] The regioselectivity is defined as the ratio of sum of concentration of **6a** and **3a** to the sum of concentration for **7a**, **4a** and **5a**.

spectra (the ratio 5-CF_3/3-CF_3 is 1:2.2). These results are in contrast with the findings of Singh et al. [7]. In the same reaction, using a catalytic amount of HCl, they isolated pyrazole **3a** as the exclusive product. We have also found that the nature and the ratio of these products depend on the amount of acid used (see Table 1). Thus we obtained a mixture of **3a** and **5a** in ratio 3.3:1 with a large excess of HCl (100 molar eq. to **1a**).

We have found that hydrazine **1a** will slowly react with diketones **2a** in the absence of hydrochloric acid. A mixture of four products including hydrazones **6a** and **7a**, pyrazolines **4a** and pyrazole **3a** is obtained (in a ratio of 9:13.5:26.5:1 according to ^{19}F NMR spectral data). Taking into account that the two series of the products **6** and **3** on one side, and **7**, **4** and **5** on the other side, results from two different reaction pathways from of **1a** with **2a**, we can calculate the regioselectivity for this reaction as the ratio of the sum of the concentrations of **6** and **3** to the sum of the concentrations for **7**, **4** and **5** (see Table 1). It is shown in the Table 1 that the regioselectivity is opposite when we compare the results for the reactions with and without acid. It is also shown that the regioselectivity depends on the amount of HCl used. Products **3a**–**6a** were separated by column chromatography. Compound **7a** was identified in the mixture by ^{19}F NMR spectroscopy. It should be noted that **3a** can be isolated by crystallization from ethanol of the mixture **3a** and **5a** prepared in the presence of hydrochloric acid.

Reactions of hydrazines **1b**,**c** with diketone **2a** in the presence of 0.26 eq. of hydrochloric acid (relative to **1b)** lead to analogous mixtures of compounds **3b**,**c**, **4b**,**c** and **5b**,**c** (see Section 3), which were also separated by column chromatography. The percentage of **5a**–**c** did not exceed 5%. A condensation reaction between **1c** and **2a** is accompanied by transesterification to form **3c′**.

Interestingly, the replacement of the 2-thienyl moiety by the 2-furyl group in 1,3-diketones lead to a difference in regioselectivity. The reaction was carried out under the same conditions. Thus, in reactions of hydrazines **1a**–**c** with 2-furyl diketone **2b** the ratio of 5-CF_3/3-CF_3 products is varied on the substituent in hydrazine moiety at 0.26 eq. of hydrochloric acid relative to **1** between 1.1:1 and 1.25:1, respectively, while for thienyl-containing compounds, the ratio is between 1:2.2 and 1:2.8 (see Section 3). Compounds **4d**–**f** can be easily prepared as pure samples by crystallization of mixtures **4d**–**f**/**3d**–**f** from ethanol.

We have shown that hydrazones **6a**,**c** and pyrazolines **4a**,**c** transform to pyrazoles **3a**,**c** and **5a**,**c**, respectively after reflux in methanol, containing more than 1.5 eq. of hydrochloric acid. The conversion time for **6** was considerably less than that for **4** (0.5–1.5 and 36–54 h, respectively). Complete and fast conversion of **4** to **5** for all samples can be achieved in refluxing acetic anhydride, as described earlier [6].

Regioisomeric pyrazoles **3** and **5** could be readily distinguished by their ^{1}H, ^{19}F and ^{13}C NMR spectra. The signals of the CF_3 groups of compounds **3** in the ^{19}F NMR spectra show up at 98.8–98.9 ppm, which is 3 ppm upfield in comparison with pyrazoles **5** (Table 1). This is in accordance with the data for isomeric pyrazoles described by Singh et al. [5]. Thus, the signals for C_4–H in the ^{1}H NMR spectra of compounds **5** are deshielded 0.3–0.4 ppm in comparison with **3**. Interestingly, the signal of C_3–H corresponding to the furan ring in compound **3f** is shifted downfield (0.5 ppm) in comparison with **5f**. This effect can be explained by a negative anisotropy effect. The same deshielding for **3c** is less than 0.1 ppm.

The isomers **3** and **5** could also be distinguished by their ^{13}C NMR spectroscopic data. The signals belonging to the C_3 and C_5 position of the pyrazole ring resonated at different frequencies. Thus, the C_5 signals for **5a**–**f** were quartets at 131–132 ppm ($^{2}J_{C-CF_3}$ of 40–42 Hz). The C_3 signals for **3a**–**f** appeared as quartets at 143 ppm ($^{2}J_{C-CF_3}$ of 38.2–38.6 Hz). It is interesting to note that some carbon atoms, such as C_4 of the pyrazole ring and C_2 of the thiophene (or furan) ring were sensitive to the change of their chemical environment. The signals for C_4 of the pyrazole ring for compounds **5a**–**c** were deshielded 1.8–2.8 ppm in comparison to **3a**–**c**; for furan-containing derivatives **5d**–**f** and **3d**–**f** this deshielding reaches 3.6–4.5 ppm. The signals for C_2 of the thiophene (or furan) ring of products **5** also are significantly deshielded 7.1–8.3 ppm (respectively 3.6 ppm) in comparison with that for **3**. The CF_3 carbon quartet for **3a**–**f** appeared around 120.5 ppm, whereas the same for **5a**–**f** showed up around 119 ppm.

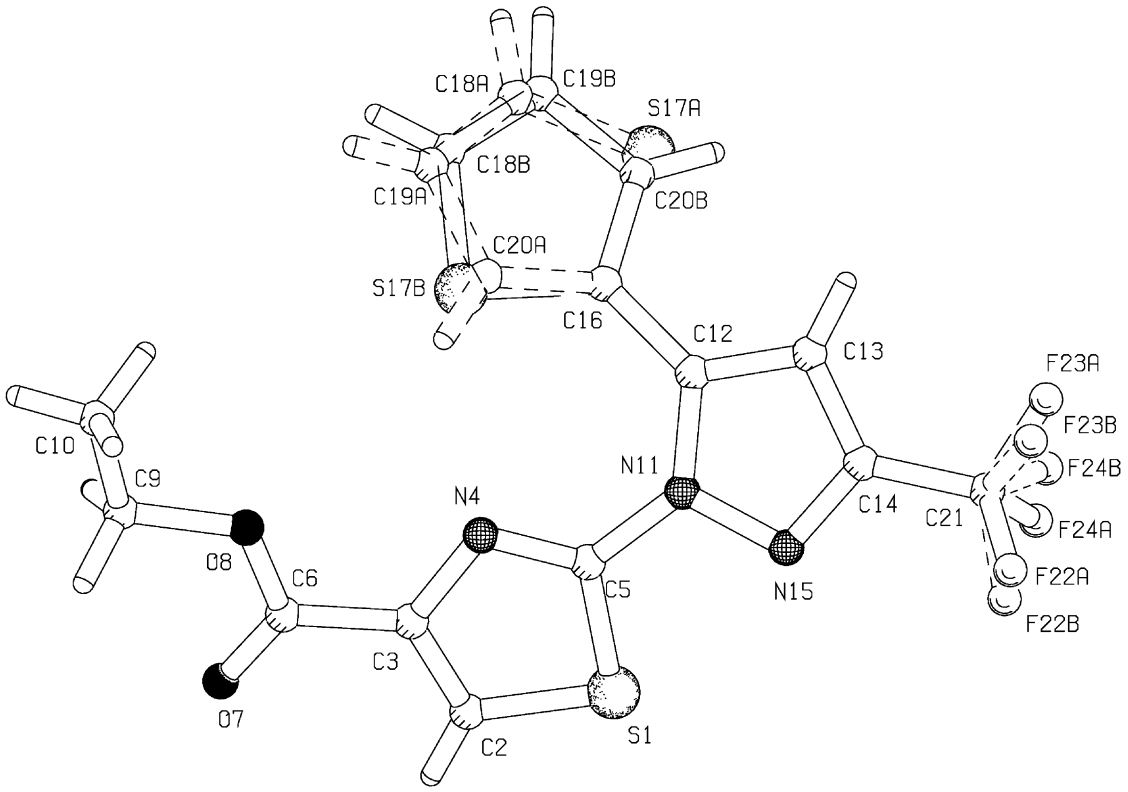

Fig. 1. Molecular structure of 2-(5-(2-thienyl)-3-trifluoromethylpyrazol-1-yl)-4-ethoxycarbonylthiazole **3c**.

Finally, we could remove all doubt about the structure of the two regioisomers by solving the crystal structure of **3c** by X-ray diffraction. The X-ray analysis for the regioisomeric pyrazole of type **5** (R = 4-chlorophenyl, thienyl is substituted by 4-fluorophenyl) has already been reported by us [6]. Two conformations of **3c** are observed in the solid state for both the CF_3 and thiophene substituents (Fig. 1).[2]

The structures of precursors **4** and **6** were also confirmed by spectroscopic methods. The ^{1}H NMR spectra of **4a–f** showed a typical AB pattern for the methylene groups at 3.6 and 4.0 ppm with $^2J_{CH_2}$ coupling of 18–19 Hz. The hydroxyl groups resonated as sharp singlets at 8.3–8.45 ppm. In contrast to **4**, ^{1}H NMR spectra of hydrazones **6a**,**c**,**f** have singlets corresponding to the methylene groups at 4.4 ppm and broad singlets corresponding to the NH group at 12.5 ppm.

An inspection of the ^{13}C NMR spectra of **4a–f** showed that the chemical shifts of the C_4 signals for the dihydropyrazoline rings were found at 44.6–45.5 ppm. The signals of C_5 were found back as quartets at 92.3–92.8 ppm with a typical coupling constant $^2J_{CF_3}$ of 33.6 Hz. The signals corresponding to the methylene groups of the hydrazones **6a**,**c** were situated at 36.7 ppm. The CF_3 carbon quartets for **6a**,**c** appeared at 120.9 ppm.

The data obtained in this study allow us to draw some conclusions regarding the mechanism of the reaction of 2-hydrazinothiazoles **1** with 1,3-diketones **2**.

Selevanov et al. proposed a general scheme for the reaction of hydrazines with 1,3-diketones [10]. Stop-flow NMR techniques were used to characterize the intermediates, including β-ketohydrazinocarbinols, the monohydrazones of 1,3-diketones, 3,5-dihydroxypyrazolidines and 5-hydroxypyrazolines from the reaction of 1,3-diketones with hydrazine and methylhydrazine [11]. They have also shown that two pathways, respectively via 3,5-dihydroxypyrazolidines and via hydrazone intermediates may occur, leading to regioisomeric pyrazoles in these reactions. A similar condensation with phenylhydrazine has been shown to take place via hydrazone intermediates only, due to poor nucleophilicity of this reagent [11]. On the other hand, Singh et al. postulated the existence of 3,5-dihydroxypyrazolidines in the reaction of arylhydrazines with 1,3-diketones. Based on semiempirical calculations of the electronic density on the pyrazolidine nitrogens for the dehydration reaction, they rationalized the opposite regioselectivity for the reaction of phenylhydrazine and 2,4-dinitrophenylhydrazine with 1,1,1-trifluoropentane-2,4-dione [5].

In this report, we have shown that reactions of diketones **2** bearing a trifluoromethyl group and a heterocyclic moiety can proceed with participation of either of the carbonyl

[2] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as a supplementary publication number CCDC 161525. 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).

groups to afford, in the absence of acid, mainly hydrazones **6**, **7** and pyrazolines **4**. The formation of the latter most probably took place via a hydrazone intermediate of type **7** that is a regioisomer of **6**. Clearly, the hydrazone **7** is prone to intramolecular cyclization of its NH moiety with the highly reactive CF_3CO group. On the other hand, the hydrazones **6** will be in equilibrium with an unstable pyrazoline **8**. This equilibrium is normally completely shifted to the hydrazone **6** (Scheme 1). The formation of hydrazones **6** and **7** confirms the data of Selevanov [11] that elimination of water from the hydrazinocarbinol group to form a hydrazone takes place more easily than its cyclization to 3,5-dihydroxypyrazolidines. At the same time, our data on the isolation and identification of isomeric hydrazones **6**, **7** does not support the hypothesis of Singh et al. that dehydration of isomeric 3,5-dihydroxypyrazolidines rules the regioselectivity in this reaction. If 3,5-dihydroxypyrazolidines is an intermediate in this reaction then it should eliminate water followed by ring opening to form hydrazones **6** and **7**.

Dehydration of compounds **4** and **6** (via **8**) was carried out in acidic media or with acetic anhydride to form aromatic regioisomeric pyrazoles **5** and **3**. We can assume that this will occur via carbocation intermediates [5], which are more difficult to form in the case of **4**, where the trifluoromethyl group is adjacent to the cationic center. Indeed, in this case it is better to convert the hydroxy group of **4** to a better leaving group (e.g. acetoxy) prior to aromatization.

If the regioselectivity of the reaction of methylhydrazine with various diketones depends mainly on the relative nucleophilicity of nitrogen atoms [10,11] the direction of poor nucleophiles, such as 2-hydrazinothiazoles should be governed by the relative reactivity of the two ketone groups in 1,3-diketones. The observed variation of the regioselectivity of the reaction of hydrazines **1** with diketones **2** upon variation in acid catalyst can shed light on the reasons of contradictory results obtained by different research groups. One can assume that the acid present mainly protonates the carbonyl group of **1** connected with the heterocyclic ring and such activation favors the Michael 1,4-addition, rather than the 1,2-addition of hydrazine [12] which shifts the chemistry in favor of pyrazoles **3**.[3] Further work, testing this hypothesis, is under way.

[3] One referee suggested an alternative explanation for the regioselectivity of the condensation reactions of **1** and **2** by assuming reversibility for all reaction steps. Thus, the condensation products **6** or **7** can revert to the starting materials with the involvement of water. In this case, the product ratio under the reaction conditions without acid represents the thermodynamic stability of the respective products. Acid would influence the equilibrium by taking away products **6** and **8** by irreversibly forming the product **3**. However, isolated products such as **4a** give only **5a** on treatment with acid without the formation of any side products with different regiochemistry. Thus, even if such equilibration is taking place, it is slow compared to the acid-catalyzed formation of the final products and is not likely to have an influence on the regioselectivity.

3. Experimental

^1H, ^{19}F and ^{13}C NMR spectra were recorded at 400, 376 and 100 MHz, respectively on a Bruker AMX 400 in either $(CD_3)_2SO$ or $CDCl_3$ solutions. The internal standard for the ^{19}F spectra was C_6F_6 and for ^1H spectra used Me_4Si. The mass spectra were scanned at 70 eV on an MS 12 mass spectrometer fitted with a direct inlet system. Products were analyzed by TLC on DC-Plastikfolen Kieselgel 60 F 254 plates. Melting point were taken in open capillaries and are uncorrected. The 2-hydrazino-4-*R*-thiazoles (**1a–c**) were prepared by steam distillation of respective hydrobromides of 2-isopropylidenhydrazino-4-*R*-thiazoles, as reported earlier [6]. Commercial samples of **2a**,**b** were used.

*3.1. General procedure 1: reactions of 2-hydrazinothiazoles **1a–c** with diketones **2a,b** in the presence of hydrochloric acid*

*3.1.1. 2-(5-(2-Thienyl)-3-trifluoromethyl-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole (**3a**) and 2-(5-hydroxy-3-(2-thienyl)-5-trifluoromethylpyrazolin-1-yl)-4-(4-chlorophenyl)-thiazole (**4a**)*

A mixture of **1a** (0.6 g, 2.66 mmol) in methanol (30 cm^3), containing hydrochloric acid (0.7 mmol, being a molar ratio of 1:0.26), and **2a** (0.61 g, 2.75 mmol) was refluxed during 3 h. The solvent was completely removed. In the residue, three products **3a**, **4a** and **5a** were present in the ratio of 69:26:5 as determined by the ^{19}F NMR spectral data (the ratio 5-CF_3/3-CF_3 is 1:2.2). Column chromatography using dichloromethane–hexane (1:4) or hexane–ethyl acetate (25:1), separated the mixture of **4a** and **3a**. The first fraction contained **3a**, R_f 0.5 and the second fraction contained **4a**, R_f 0.25. The product **5a** was not separated, but obtained by general procedure 2. 2-(5-(2-Thienyl)-3-trifluoromethyl-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole **(3a)** (0.7 g, 61%); mp 110 °C was described earlier ([7], 110 °C). 2-(5-Hydroxy-3-(2-thienyl)-5-trifluoromethylpyrazolin-1-yl)-4-(4-chlorophenyl)-thiazole (**4a**) (0.28 g, 26%), as white crystals, mp 154–156 °C; ^1H NMR ($(CD_3)_2SO$) δ: 3.72 (d, 1H, $J = 18.6$ Hz, pyrazole 4-H), 4.04 (d, 1H, $J = 18.6$ Hz, pyrazole 4-H), 7.20 (dd, 1H, $J = 5.0$ Hz, thienyl 4-H), 7.49 (d, 2H, $J = 8.4$, phenyl 2-H and 6-H), 7.56 (dd, 1H, $J = 3.6$ Hz, thienyl 5-H), 7.62 (s, 1H, thiazole 5-H), 7.77 (dd, 1H, $J = 5.0$ Hz, thienyl 3-H), 7.94 (d, 2H, $J = 8.4$, phenyl 3-H and 5-H), 8.34 (s, 1H, OH); ^{13}C NMR ($(CD_3)_2SO$) δ: 45.5 (pyrazole 4-C), 92.8 (q, $J_{C-F} = 33.6$ Hz, pyrazole 5-C), 107.6 (thiazole 5-C), 123.1 (q, $J_{C-F} = 284.8$ Hz, CF_3), 127.4 (phenyl 3-C and 5-C), 128.1 (thienyl 4-C), 128.6 (phenyl 2-C and 6-C), 129.7 (thienyl 3-C), 130.5 (thienyl 5-C), 132.1 (phenyl 4-C), 133.0 (thienyl 2-C), 133.3 (phenyl 1-C), 147.7 (pyrazole 3-C), 149.7 (thiazole 4-C), 162.9 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 80.9 (s, CF_3). MS (EI) *m/z*: 429/431 $[M]^+$ (95/46), 411/413 $[M - H_2O]^+$(18/9), 360/362 $[M - CF_3]^+$ (100/46). Anal. Calcd. for $C_{17}H_{11}ClF_3N_3OS_2$: C, 47.50; H, 2.58;

Cl, 8.41; N, 9.78; S, 14.92. Found: C, 47.31; H, 2.50; Cl, 8.31; N, 9.65; S, 14.83.

3.1.2. 2-(5-(2-Thienyl)-3-trifluoromethylpyrazol-1-yl)-4-phenylthiazole (**3b**) and 2-(5-hydroxy-3-(2-thienyl)-5-trifluoromethylpyrazolin-1-yl)-4-phenylthiazole (**4b**)

Following the general procedure 1, three products **3b**, **4b** and **5b** were obtained in a ratio 25.7:10.7:1 as determined by the ^{19}F NMR spectral data (the ratio 5-CF_3/3-CF_3 is 1:2.2). The mixture of **3b** and **4b** was separated by column chromatography on silica, using hexane–ethyl acetate (28:1) as the eluent. The first fraction contained **3b**, R_f 0.5, the second was **4b**, R_f 0.25. Compound **5b** was obtained by general procedure 2. 2-(5-(2-Thienyl)-3-trifluoromethylpyrazol-1-yl)-4-phenylthiazole (**3b**) (0.46 g, 45%); mp 62 °C was described earlier ([7], 62 °C). 2-(5-Hydroxy-3-(2-thienyl)-5-trifluoromethylpyrazolin-1-yl)-4-phenylthiazole (**4b**) (0.3 g, 31%), as white solid, mp 153–155 °C; ^{1}H NMR ($(CD_3)_2SO$) δ: 3.73 (d, 1H, $J = 18.6$ Hz, pyrazole 4-H), 4.03 (d, 1H, $J = 18.6$ Hz, pyrazole 4-H), 7.19 (dd, 1H, $J = 5.0$ Hz, thienyl 4-H), 7.31 (dd, 1H, $J = 8.4$ Hz, phenyl 4-H), 7.42 (dd, 2H, $J = 8.4$ Hz, phenyl 3-H and 5-H), 7.54 (dd, 1H, $J = 3.7$ Hz, thienyl 5-H), 7.55 (s, 1H, thiazole 5-H), 7.77 (dd, 1H, $J = 5.0$ Hz, thienyl 3-H), 7.92 (d, 2H, $J = 8.4$ Hz, phenyl 2-H and 6-H), 8.31 (s, 1H, OH); ^{13}C NMR ($(CD_3)_2SO$) δ: 45.5 (pyrazole 4-C), 92.8 (q, $J_{C-F} = 33.6$ Hz, pyrazole 5-C), 106.9 (thiazole 5-C), 123.0 (q, $J_{C-F} = 283.8$ Hz, CF_3), 125.7 (phenyl 3-C and 5-C), 127.7 (phenyl 4-C), 128.1 (thienyl 4-C), 128.6 (phenyl 2-C and 6-C), 129.7 (thienyl 3-C), 130.4 (thienyl 5-C), 132.1 (phenyl 4-C), 133.1 (thienyl 2-C), 134.4 (phenyl 1-C), 147.5 (pyrazole 3-C), 151.0 (thiazole 4-C), 162.7 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) d: 80.8 (s, CF_3). MS (EI) m/z: 395 $[M]^+$ (88), 377 $[M - H_2O]^+$(7), 326 $[M - CF_3]^+$ (100). Anal. Calcd. for $C_{17}H_{12}F_3N_3OS_2$: C, 51.64; H, 3.06; N, 10.63; S, 16.21. Found: C, 51.43; H, 3.02; N, 10.42; S, 16.33.

3.1.3. 2-(5-(2-Thienyl)-3-trifluoromethylpyrazol-1-yl)-4-ethoxycarbonylthiazole (**3c**), 2-(5-(2-thienyl)-3-trifluoromethylpyrazol-1-yl)-4-methoxycarbonylthiazole (**3c′**) and 2-(5-hydroxy-3-(2-thienyl)-5-trifluoromethylpyrazolin-1-yl)-4-ethoxycarbonylthiazole (**4c**)

Following the general procedure 1, three products **3c**, **3c′** and **4c** (the concentration of **5c** less then 1%) were obtained in a ratio 1:2.84 (compounds **3c** and **3c′** have the same chemical shifts of CF_3 groups) as determined by the ^{19}F NMR spectral data. This reaction was accompanied by transesterification of **3c** to **3c′**. The mixture of hexane–ethyl acetate (10:1) has been used for separating **3c** (R_f 0.5) and **3c′** (R_f 0.45), and continuing the elution with a mixture of hexane–ethyl acetate (10:2.5) afforded **4c** (R_f 0.3). 2-(5-(2-Thienyl)-3-trifluoromethylpyrazol-1-yl)-4-ethoxycarbonylthiazole (**3c**) (0.5 g, 50%), as white solid, mp 102–104 °C; ^{1}H NMR ($(CD_3)_2SO$) δ: 1.32 (t, 3H, $J = 7.0$ Hz, Et), 4.32 (q, 2H, $J = 7.0$ Hz, Et), 7.18 (dd, 1H, $J = 4.7$ Hz, thienyl 4-H), 7.44 (s, 1H, pyrazole 4-H), 7.69 (d, 1H, $J = 3.5$ Hz, thienyl 3-H), 7.79 (d, 1H, $J = 5.1$ Hz, thienyl 5-H), 8.62 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 14.0 (Me), 61.1 (OCH_2), 107.1 (pyrazole 4-C), 120.5 (q, $J_{C-F} = 284.0$ Hz, CF_3), 127.2 (pyrazole 5-C), 127.6 (thienyl 4-C), 130.0 (thienyl 3-C), 130.7 (thiazole 5-C), 131.3 (thienyl 5-C), 140.6 (thienyl 2-C), 143.0 (thiazole 4-C), 143.5 (q, $J = 38.4$ Hz, pyrazole 3-C), 158.2 (thiazole 2-C), 159.9 (CO); ^{19}F NMR ($CDCl_3$) d: 98.8 (s, CF_3). MS (EI) m/z: 373 $[M]^+$ (100), 354 $[M - F]^+$(7), 344 $[M - Et]^+$ (12), 328 $[M - OEt]^+$(20), 301 $[M - COOEt]^+$(38). Anal. Calcd. for $C_{14}H_{10}F_3N_3O_2S_2$: C, 45.04; H, 2.70; N, 11.25; S, 17.17. Found: C, 44.97; H, 2.68; N, 11.33; S, 17.03. 2-(5-(2-Thienyl)-3-trifluoromethylpyrazol-1-yl)-4-methoxycarbonylthiazole (**3c′**) (0.15 g, 15%), as white solid, mp 128–130 °C; ^{1}H NMR ($(CD_3)_2SO$) δ: 3.86 (s, 3H, OCH_3), 7.18 (dd, 1H, $J = 4.7$ Hz, thienyl 4-H), 7.44 (s, 1H, pyrazole 4-H), 7.66 (d, 1H, $J = 3.5$ Hz, thienyl 3-H), 7.79 (d, 1H, $J = 5.1$ Hz, thienyl 5-H), 8.66 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) d: 52.3 (OCH_3), 107.0 (pyrazole 4-C), 120.5 (q, $J_{C-F} = 283.8$ Hz, CF_3), 127.2 (pyrazole 5-C), 127.8 (thienyl 4-C), 130.0 (thienyl 3-C), 130.9 (thiazole 5-C), 131.0 (thienyl 5-C), 140.6 (thienyl 2-C), 142.7 (thiazole 4-C), 143.5 (q, $J = 38.4$ Hz, pyrazole 3-C), 158.1 (thiazole 2-C), 160.3 (CO); ^{19}F NMR ($CDCl_3$) δ: 98.8 (s, CF_3). MS (EI) m/z: 359 $[M]^+$ (100), 328 $[M - OMe]^+$(16), 301 $[M - COOMe]^+$(17), 290 $[M - CF_3]^+$ (7). Anal. Calcd. for $C_{13}H_8F_3N_3O_2S_2$: C, 43.45; H, 2.24; N, 11.69; S, 17.84. Found: C, 43.32; H, 2.16; N, 11.75; S, 17.69. 2-(5-Hydroxy-3-(2-thienyl)-5-trifluoromethylpyrazolin-1-yl)-4-ethoxycarbonylthiazole (**4c**) (0.35 g, 34%), as yellow crystals, mp 107–109 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 1.32 (t, 3H, $J = 7.1$ Hz, Et), 3.71 (d, 1H, $J = 18.7$ Hz, pyrazole 4-H), 4.04 (d, 1H, $J = 18.7$ Hz, pyrazole 4-H), 4.28 (q, 2H, $J = 7.1$ Hz, Et), 7.20 (dd, 1H, $J = 4.7$ Hz, thienyl 4-H), 7.54 (dd, 1H, $J = 3.7$ Hz, thienyl 5-H), 7.78 (dd, 1H, $J = 5.0$ Hz, thienyl 3-H), 7.99 (s, 1H, thiazole 5-H), 8.31 (s, 1H, OH); ^{13}C NMR ($(CD_3)_2SO$) δ: 14.1 (Me), 45.3 (pyrazole 4-C), 60.4 (OCH_2), 92.7 (q, $J_{C-F} = 33.6$ Hz, pyrazole 5-C), 122.5 (thiazole 5-C), 122.9 (q, $J_{C-F} = 283.3$ Hz, CF_3), 128.1 (thienyl 4-C), 129.9 (thienyl 3-C), 130.7 (thienyl 5-C), 132.8 (thienyl 2-C), 143.2 (thiazole 4-C), 148.1 (pyrazole 3-C), 160.7 (CO), 162.8 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) d: 80.8 (s, CF_3). MS (EI) m/z: 391 $[M]^+$ (96), 346 $[M - OEt]^+$ (11), 322 $[M - CF_3]^+$ (98). Anal. Calcd. for $C_{14}H_{12}F_3N_3O_3S_2$: C, 42.96; H, 3.09; N, 10.74; S, 16.38. Found: C, 43.05; H, 2.98; N, 10.65; S, 16.42.

3.1.4. 2-(5-(2-Furyl)-3-trifluoromethylpyrazol-1-yl)-4-(4-chlorophenyl) thiazole (**3d**) and 2-(3-(2-furyl)-5-hydroxy-5-trifluoromethylpyrazolin-1-yl)-4-(4-chlorophenyl) thiazole (**4d**)

Following the general procedure 1, three products **3d**, **4d** and **5d** in a ratio 2.8:2.0:1 as determined by the ^{19}F NMR spectral data were obtained (a ratio 5-CF_3/3-CF_3 is 1.07:1).

The mixture of **3d** and **4d** was chromatographically separated, using hexane–ethyl acetate (26:1) as the eluent. The first fraction contained **3d**, R_f 0.5, the second contained **4d**, R_f 0.25. Compound **5d** was obtained by the method, described in general procedure 2. 2-(5-(2-Furyl)-3-trifluoromethylpyrazol-1-yl)-4-(4-chlorophenyl) thiazole (**3d**) (0.30 g, 28%), as white crystals, mp 127–129 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 6.71 (dd, 1H, $J = 3.5$ Hz, furyl 4-H), 7.15 (d, 1H, $J = 3.4$ Hz, furyl 3-H), 7.41 (s, 1H, pyrazole 4-H), 7.53 (d, 2H, $J = 8.6$ Hz, phenyl 2-H and 6-H), 7.88 (d, 2H, $J = 8.6$ Hz, phenyl 3-H and 5-H), 7.91 (d, 1H, $J = 1.8$ Hz, furyl 5-H), 8.23 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 106.6 (pyrazole 4-C), 111.8 (furyl 4-C), 113.3 (thiazole 5-C), 115.7 (furyl 3-C), 120.4 (q, $J_{C-F} = 269.6$ Hz, CF_3), 127.4 (phenyl 3-C and 5-C), 128.9 (phenyl 2-C and 6-C), 132.0 (phenyl 4-C), 133.0 (phenyl 1-C), 136.4 (pyrazole 5-C), 141.1 (furyl 2-C), 143.3 (q, $J = 38.6$ Hz, pyrazole 3-C), 145.0 (furyl 5-C), 150.1 (thiazole 4-C), 158.6 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 98.8 (s, CF_3). MS (EI) *m/z*: 395/397 $[M]^+$ (100/40), 376/378 $[M - F]^+$ (5/2), 366/368 $[M - CHO]^+$ (33/14). Calcd. for $C_{17}H_9ClF_3N_3OS$: C, 51.59; H, 2.29; Cl, 8.96; N, 10.62; S, 8.10. Found: C, 51.86; H, 2.16; Cl, 8.85; N, 10.48; S, 8.03. 2-(3-(2-Furyl)-5-hydroxy-5-trifluoromethylpyrazolin-1-yl)-4-(4-chlorophenyl) thiazole (**4d**) (0.4 g, 36%), as white crystals, mp 142–144 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 3.61 (d, 1H, $J = 18.7$ Hz, pyrazole 4-H), 3.94 (d, 1H, $J = 18.7$ Hz, pyrazole 4-H), 6.70 (m, 1H, furyl 4-H), 7.07 (d, 1H, $J = 3.4$ Hz, furyl 3-H), 7.48 (d, 2H, $J = 8.4$ Hz, phenyl 2-H and 6-H), 7.61 (s, 1H, thiazole 5-H), 7.92 (m, 1H, furyl 5-H), 7.94 (d, 2H, $J = 8.4$ Hz, phenyl 3-H and 5-H), 8.30 (s, 1H, OH); ^{13}C NMR ($(CD_3)_2SO$) δ: 44.7 (pyrazole 4-C), 92.3 (q, $J_{C-F} = 33.5$ Hz, pyrazole 5-C), 107.5 (thiazole 5-C), 112.2 (furyl 4-C), 114.1 (furyl 3-C), 123.0 (q, $J_{C-F} = 284.7$ Hz, CF_3), 127.4 (phenyl 3-C and 5-C), 128.5 (phenyl 2-C and 6-C), 132.1 (phenyl 4-C), 133.3 (phenyl 1-C), 143.0 (furyl 2-C), 145.1 (pyrazole 3-C), 145.1 (pyrazole 3-C), 145.7 (furyl 5-C), 149.7 (thiazole 4-C), 163.0 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 80.9 (s, CF_3). MS (EI) *m/z*: 413/415 $[M]^+$ (84/34), 395/397 $[M - H_2O]^+$ (7/4), 344/346 $[M - CF_3]^+$ (100/41). Anal. Calcd. for $C_{17}H_{11}ClF_3N_3O_2S$: C, 49.34; H, 2.68; Cl, 8.57; N, 10.15; S, 7.75. Found: C, 49.25; H, 2.49; Cl, 8.54; N, 10.03; S, 7.63.

*3.1.5. 2-(5-(2-Furyl)-3-trifluoromethylpyrazol-1-yl)-4-phenylthiazole (**3e**) and 2-(3-(2-furyl)-5-hydroxy-5-trifluoromethylpyrazolin-1-yl)-4-phenyl) thiazole (**4e**)*

Following the general procedure 1, three products **3e**, **4e** and **5e** in a ratio 3.4:3.2:1 as determined by the ^{19}F NMR spectral data were obtained (the ratio 5-CF_3/3-CF_3 is 1.25:1). The mixture of **3e** and **4e** was chromatographically separated, using dichloromethane–hexane (1:2) as the eluent. The first fraction contained **3e**, R_f 0.5, the second contained **4e**, R_f 0.25. Compound **5e** was obtained by the method, described in general procedure 2. 2-(5-(2-Furyl)-3-trifluoromethylpyrazol-1-yl)-4-phenylthiazole (**3e**) (0.3 g, 27%), as white crystals, mp 76–78 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 6.71 (dd, 1H, $J = 3.4$ Hz, furyl 4-H), 7.16 (d, 1H, $J = 3.4$ Hz, furyl 3-H), 7.38 (m, 1H, phenyl 4-H), 7.41 (s, 1H, pyrazole 4-H), 7.46 (dd, 2H, $J = 7.2$ Hz, phenyl 3-H and 5-H), 7.86 (d, 2H, $J = 7.2$ Hz, phenyl 2-H and 6-H), 7.91 (m, 1H, furyl 5-H), 8.20 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 106.6 (pyrazole 4-C), 111.9 (furyl 4-C), 113.3 (thiazole 5-C), 115.1 (furyl 3-C), 120.5 (q, $J_{C-F} = 268.7$ Hz, CF_3), 125.8 (phenyl 3-C and 5-C), 128.6 (phenyl 4-C), 130.0 (phenyl 2-C and 6-C), 133.2 (phenyl 1-C), 136.5 (pyrazole 5-C), 141.2 (furyl 2-C), 143.4 (q, $J = 38.2$ Hz, pyrazole 3-C), 145.1 (furyl 5-C), 151.5 (thiazole 4-C), 158.5 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 98.7 (s, CF_3). MS (EI) *m/z*: 361 $[M]^+$ (100), 342 $[M - F]^+$ (5), 332 $[M - CHO]^+$ (36). Anal. Calcd. for $C_{17}H_{10}F_3N_3OS$: C, 56.51; H, 2.79; N, 11.63; S, 8.87. Found: C, 56.45; H, 2.65; N, 11.54; S, 8.75. 2-(3-(2-Furyl)-5-hydroxy-5-trifluoromethylpyrazolin-1-yl)-4-phenyl) thiazole (**4e**) (0.5 g, 42%), as yellow crystals, mp 146–148 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 3.60 (d, 1H, $J = 18.6$ Hz, pyrazole 4-H), 3.93 (d, 1H, $J = 18.6$ Hz, pyrazole 4-H), 6.70 (m, 1H, furyl 4-H), 7.07 (d, 1H, $J = 3.3$ Hz, furyl 3-H), 7.31 (dd, 1H, $J = 8.4$ Hz, phenyl 4-H), 7.42 (dd, 2H, $J = 8.4$ Hz, phenyl 3-H and 5-H), 7.55 (s, 1H, thiazole), 7.91 (m, 1H, furyl 5-H), 7.92 (d, 2H, $J = 8.4$ Hz, phenyl 2-H and 6-H), 8.31 (s, 1H, OH); ^{13}C NMR ($(CD_3)_2SO$) δ: 44.7 (pyrazole 4-C), 92.4 (q, $J_{C-F} = 33.2$ Hz, pyrazole 5-C), 106.8 (thiazole 5-C), 112.3 (furyl 4-C), 114.1 (furyl 3-C), 123.1 (q, $J_{C-F} = 284.7$ Hz, CF_3), 125.7 (phenyl 3-C and 5-C), 127.7 (phenyl 4-C), 128.6 (phenyl 2-C and 6-C), 134.4 (phenyl 1-C), 142.9 (furyl 2-C), 145.2 (pyrazole 3-C), 145.7 (furyl 5-C), 150.9 (thiazole 4-C), 162.0 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 80.9 (s, CF_3). MS (EI) *m/z*: 379 $[M]^+$ (81), 361 $[M - H_2O]^+$ (11), 311 $[M - CF_3]^+$ (100). Anal. Calcd. for $C_{17}H_{12}F_3N_3O_2S$: C, 53.82; H, 3.19; N, 11.08; S, 8.45. Found: C, 53.77; H, 3.06; N, 11.04; S, 8.36.

*3.1.6. 2-(5-(2-Furyl)-3-trifluoromethylpyrazol-1-yl)-4-ethoxycarbonylthiazole (**3f**) and 2-(5-hydroxy-3-(2-furyl)-5-trifluoromethylpyrazolin-1-yl)-4-ethoxycarbonylthiazole (**4f**)*

Following the general procedure 1, three products **3f**, **4f** and **5f** in a ratio 7.7:7.8:1 as determined by the ^{19}F NMR spectral data were obtained (the ratio 5-CF_3/3-CF_3 is 1.15:1). Compounds **3f** and **4f** were separated using a mixture of dichloromethane and hexane (1:2). The first fraction contained **3f** (R_f 0.5) and the second was **4f** (R_f 0.45). Compound **5f** was obtained by the method, described in general procedure 2. 2-(5-(2-Furyl)-3-trifluoromethylpyrazol-1-yl)-4-ethoxycarbonylthiazole (**3f**) (0.25 g, 22%), as white crystals, mp 108–110 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 1.34 (t, 3H, $J = 7.1$ Hz, Et), 4.34 (q, 2H, $J = 7.1$ Hz, Et), 6.70 (dd, 1H, $J = 3.5$ Hz, furyl 4-H), 7.40 (s, 1H, pyrazole 4-H), 7.68 (d, 1H, $J = 3.5$ Hz, furyl 3-H), 7.92 (d, 1H,

$J = 1.7$ Hz, furyl 5-H), 8.57 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 14.1 (Me), 61.1 (OCH_2), 105.8 (pyrazole 4-C), 112.1 (furyl 4-C), 114.7 (furyl 3-C), 120.5 (q, $J_{C-F} = 284.0$ Hz, CF_3), 129.5 (thiazole 5-C), 137.1 (pyrazole 5-C), 141.4 (furyl 2-C), 142.9 (thiazole 4-C), 143.5 (q, $J = 38.4$ Hz, pyrazole 3-C), 145.4 (furyl 5-C), 159.0 (thiazole 2-C), 160.0 (CO); ^{19}F NMR ($CDCl_3$) δ: 98.7 (s, CF_3). MS (EI) *m/z*: 357 $[M]^+$ (100), 338 $[M - F]^+$ (9), 329 $[M - Et]^+$ (27), 312 $[M - OEt]^+$ (26). Anal. Calcd. for $C_{14}H_{10}F_3N_3O_3S$: C, 47.06; H, 2.82; N, 11.76; S, 8.97%. Found: C, 46.95; H, 2.69; N, 11.68; S, 8.90. 2-(5-Hydroxy-3-(2-furyl)-5-trifluoromethylpyrazolin-1-yl)-4-ethoxycarbonylthiazole (**4f**) (0.55 g, 46%), as yellow crystals, mp 68–70 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 1.32 (t, 3H, $J = 7.1$ Hz, Et), 3.59 (d, 1H, $J = 18.7$ Hz, pyrazole 4-H), 3.92 (d, 1H, $J = 18.7$ Hz, pyrazole 4-H), 4.27 (q, 2H, $J = 7.1$ Hz, Et), 6.69 (dd, 1H, $J = 3.4$ Hz, furyl 4-H), 7.08 (d, 1H, $J = 3.4$ Hz, furyl 3-H), 7.92 (d, 1H, $J = 1.4$ Hz, furyl 5-H), 7.98 (s, 1H, thiazole 5-H), 8.38 (s, 1H, OH); ^{13}C NMR ($(CD_3)_2SO$) δ: 14.1 (Me), 44.6 (pyrazole 4-C), 60.4 (OCH_2), 92.3 (q, $J_{C-F} = 34.2$ Hz, pyrazole 5-C), 112.1 (furyl 4-C), 114.4 (furyl 3-C), 122.4 (thiazole 5-C), 122.9 (q, $J_{C-F} = 284.8$ Hz, CF_3), 143.2 (furyl 2-C), 143.5 (thiazole 4-C), 145.0 (pyrazole 3-C), 145.9 (furyl 5-C), 160.7 (CO), 163.0 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 80.9 (s, CF_3). MS (EI) *m/z*: 375 $[M]^+$ (88), 357 $[M - H_2O]^+$ (7), 330 $[M - OEt]^+$ (12), 306 $[M - CF_3]^+$ (100). Anal. Calcd. for $C_{14}H_{12}F_3N_3O_4S$: C, 44.80; H, 3.22; N, 11.20; S, 8.54. Found: C, 44.72; H, 3.10; N, 11.02; S, 8.38.

*3.2. General procedure 2: dehydration of **4a–f** to **5a–f** in acetic anhydride*

*3.2.1. 2-(3-(2-Thienyl)-5-trifluoromethylpyrazol-1-yl)-4-(4-chlorophenyl)thiazole (**5a**)*

Compound **4a** (0.3 g, 0.7 mmol) in acetic anhydride (5–7 cm^3) was refluxed for 3 h. The solvent was removed and the residue was crystallized from ethanol. **5a** (0.25 g, 87%) was obtained as white crystals, mp 165–167 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 7.22 (dd, 1H, $J = 5.0$ Hz, thienyl 4-H), 7.51 (d, 2H, $J = 8.5$ Hz, phenyl 2-H and 6-H), 7.71 (d, 1H, $J = 5.0$ Hz, thienyl 5-H), 7.79 (d, 1H, $J = 3.6$ Hz, thienyl 3-H), 7.86 (s, 1H, pyrazole 4-H), 7.87 (d, 2H, $J = 8.5$ Hz, phenyl 3-H and 5-H), 8.15 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 110.4 (pyrazole 4-C), 113.7 (thiazole 5-C), 119.0 (q, $J_{C-F} = 268.8$ Hz, CF_3), 127.3 (phenyl 3-C and 5-C), 127.3 (phenyl 4-C), 128.0 (thienyl 4-C), 128.1 (thienyl 3-C), 128.2 (thienyl 5-C), 129.0 (phenyl 2-C and 6-C), 131.5 (q, $J = 40.0$ Hz, pyrazole 5-C), 132.2 (pyrazole 3-C), 133.0 (phenyl 1-C), 148.4 (thienyl 2-C), 150.1 (thiazole 4-C), 158.2 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 102.1 (s, CF_3). MS (EI) *m/z*: 411/413 $[M]^+$ (100/43), 342/344 $[M - CF_3]^+$ (3/1). Calcd. for $C_{17}H_9ClF_3N_3S_2$: C, 49.58; H, 2.20; Cl, 8.61; N, 10.20; S, 15.57. Found: C, 49.45; H, 2.05; Cl, 8.55; N, 10.02; S, 15.46.

*3.2.2. 2-(3-(2-Thienyl)-5-trifluoromethylpyrazol-1-yl)-4-phenylthiazole (**5b**)*

Following the general procedure 2, the compound **5b** (0.26 g, 90%) was obtained as white crystals, mp 176–178 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 7.22 (dd, 1H, $J = 5.0$ Hz, thienyl 4-H), 7.39 (m,1H, phenyl 4-H), 7.50 (dd, 2H, $J = 7.3$ Hz, phenyl 3-H and 5-H), 7.72 (dd, 1H, $J_{5-4} = 5.0$ Hz, $J_{5-3} = 1.1$ Hz, thienyl 5-H), 7.80 (dd, 1H, $J_{3-4} = 3.6$ Hz, $J_{3-5} = 1.2$ Hz, thienyl 3-H), 7.86 (s, 1H, pyrazole 4-H), 7.98 (d, 2H, $J = 7.3$ Hz, phenyl 2-H and 6-H), 8.10 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 109.3 (pyrazole 4-C), 112.0 (thiazole 5-C), 118.4 (q, $J_{C-F} = 284.2$ Hz, CF_3), 124.6 (phenyl 3-C and 5-C), 127.0 (phenyl 4-C), 127.1 (thienyl 4-C), 127.2 (thienyl 3-C), 127.5 (thienyl 5-C), 128.0 (phenyl 2-C and 6-C), 130.8 (q, $J = 42.0$ Hz, pyrazole 5-C), 131.3 (pyrazole 3-C), 132.3 (phenyl 1-C), 147.3 (thienyl 2-C), 150.4 (thiazole 4-C), 157.0 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 102.1 (s, CF_3). MS (EI) *m/z*: 377 $[M]^+$ (100). Anal. Calcd. for $C_{17}H_{10}F_3N_3S_2$: C, 54.10; H, 2.67; N, 11.13; S, 16.99. Found: C, 53.95; H, 2.61; N, 11.00; S, 16.87.

*3.2.3. 2-(3-(2-Thienyl)-5-trifluoromethylpyrazol-1-yl)-4-ethoxycarbonylthiazole (**5c**)*

Following the general procedure 2, the compound **5c** (0.24 g, 83%) was obtained as white crystals, mp 175–177 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 1.31 (t, 3H, $J = 7.0$ Hz, Et), 4.33 (q, 2H, $J = 7.0$ Hz, Et), 7.22 (dd, 1H, $J = 4.5$ Hz, thienyl 4-H), 7.72 (d, 1H, $J = 4.6$ Hz, thienyl 5-H), 7.80 (d, 1H, $J = 3.1$ Hz, thienyl 3-H), 7.87 (s, 1H, pyrazole 4-H), 8.46 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 14.1 (Me), 61.2 (OCH_2), 110.5 (pyrazole 4-C), 118.9 (q, $J_{C-F} = 284.0$ Hz, CF_3), 128.1 (thienyl 4-C), 128.2 (thienyl 3-C), 128.2 (thienyl 5-C), 128.2 (thiazole 5-C), 132.1 (pyrazole 3-C), 132.2 (q, $J = 42.0$ Hz, pyrazole 5-C), 143.3 (thiazole 4-C), 148.6 (thienyl 2-C), 158.3 (thiazole 2-C), 159.9 (CO); ^{19}F NMR ($CDCl_3$) δ: 102.1 (s, CF_3). MS (EI) *m/z*: 373 $[M]^+$ (100), 354 $[M - F]^+$ (4), 344 $[M - Et]^+$ (3), 328 $[M - OEt]^+$ (18), 301 $[M - COOEt]^+$ (32). Anal. Calcd. for $C_{14}H_{10}F_3N_3O_2S_2$: C, 45.04; H, 2.70; N, 11.25; S, 17.17. Found: C, 44.97; H, 2.67; N, 11.34; S, 17.00.

*3.2.4. 2-(3-(2-Furyl)-5-trifluoromethylpyrazol-1-yl)-4-(4-chlorophenyl)thiazole (**5d**)*

Following the general procedure 2, the compound **5d** (0.25 g, 87%) was obtained as pink crystals, mp 147–149 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 6.70 (dd, 1H, $J =$ 3.4 Hz, furyl 4-H), 7.16 (d, 1H, $J = 3.4$ Hz, furyl 3-H), 7.56 (d, 2H, $J = 8.5$ Hz, phenyl 2-H and 6-H), 7.71 (s, 1H, pyrazole 4-H), 7.88 (d, 1H, $J = 1.2$ Hz, furyl 5-H), 7.97 (d, 2H, $J = 8.5$ Hz, phenyl 3-H and 5-H), 8.15 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 110.2 (pyrazole 4-C), 110.5 (furyl 4-C), 112.0 (furyl 3-C), 113.8 (thiazole 5-C), 119.1 (q, $J_{C-F} = 270.1$ Hz, CF_3), 127.3 (phenyl 3-C and 5-C), 128.9 (phenyl 2-C and 6-C), 131.6 (q, $J = 40.0$ Hz, pyrazole 5-C), 132.1 (phenyl 4-C), 133.0 (phenyl 1-C), 144.5 (furyl 5-C),

144.8 (pyrazole 3-C), 145.0 (furyl 2-C), 150.1 (thiazole 4-C), 158.3 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 102.1 (s, CF_3). MS (EI) *m/z*: 395/397 $[M]^+$ (100/41), 376/378 $[M - F]^+$ (3/1), 366/368 $[M - CHO]^+$ (23/10). Calcd. for $C_{17}H_9ClF_3N_3OS$: C, 51.59; H, 2.29; Cl, 8.96; N, 10.62; S, 8.10. Found: C, 51.89; H, 2.15; Cl, 8.75; N, 10.49; S, 8.00.

*3.2.5. 2-(3-(2-Furyl)-5-trifluoromethylpyrazol-1-yl)-4-phenylthiazole (**5e**)*

Following the general procedure 2, the compound **5e** (0.25, 87%). was obtained as white crystals, mp 162–164 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 6.69 (m, 1H, furyl 4-H), 7.16 (d, 1H, $J = 3.0$ Hz, furyl 3-H), 7.38 (m, 1H, phenyl 4-H), 7.47 (dd, 2H, $J = 7.2$ Hz, phenyl 3-H and 5-H), 7.70 (s, 1H, pyrazole 4-H), 7.88 (m, 1H, furyl 5-H), 7.96 (d, 2H, $J = 7.2$ Hz, phenyl 2-H and 6-H), 8.09 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 110.2 (pyrazole 4-C), 110.6 (furyl 4-C), 112.1 (furyl 3-C), 113.1 (thiazole 5-C), 119.2 (q, $J_{C-F} = 268.6$ Hz, CF_3), 125.7 (phenyl 3-C and 5-C), 128.5 (phenyl 4-C), 128.9 (phenyl 2-C and 6-C), 131.7 (q, $J = 41.5$ Hz, pyrazole 5-C), 133.3 (phenyl 1-C), 144.6 (furyl 5-C), 144.8 (pyrazole 3-C), 145.1 (furyl 2-C), 151.4 (thiazole 4-C), 158.2 (thiazole 2-C); ^{19}F NMR ($CDCl_3$) δ: 102.1 (s, CF_3). MS (EI) *m/z*: 361 $[M]^+$ (100), 342 $[M - F]^+$ (3), 332 $[M - CHO]^+$ (25). Anal. Calcd. for $C_{17}H_{10}F_3N_3OS$: C, 56.51; H, 2.79; N, 11.63; S, 8.87. Found: C, 56.47; H, 2.69; N, 11.58; S, 8.79.

*3.2.6. 2-(3-(2-Furyl)-5-trifluoromethylpyrazol-1-yl)-4-ethoxycarbonylthiazole (**5f**)*

Following the general procedure 2, the compound **5f** (0.24 g, 84%) was obtained as white crystals, mp 182–184 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 1.32 (t, 3H, $J = 7.1$ Hz, Et), 4.32 (q, 2H, $J = 7.1$ Hz, Et), 6.69 (dd, 1H, $J = 3.5$ Hz, furyl 4-H), 7.17 (d, 1H, $J_{3-4} = 3.5$ Hz, $J_{3-5} = 0.6$ Hz, furyl 3-H), 7.71 (s, 1H, pyrazole 4-H), 7.88 (d, 1H, $J = 1.7$ Hz, furyl 5-H), 8.46 (s, 1H, thiazole 5-H); ^{13}C NMR ($(CD_3)_2SO$) δ: 14.1 (Me), 61.0 (OCH_2), 110.3 (pyrazole 4-C), 110.8 (furyl 4-C), 112.1 (furyl 3-C), 118.9 (q, $J_{C-F} = 269.6$ Hz, CF_3), 128.2 (thiazole 5-C), 131.8 (q, $J = 41.0$ Hz, pyrazole 5-C), 143.3 (thiazole 4-C), 144.7 (furyl 5-C), 144.9 (pyrazole 3-C), 145.0 (furyl 2-C), 158.4 (thiazole 2-C), 160.0 (CO); ^{19}F NMR ($CDCl_3$) δ: 102.0 (s, CF_3). MS (EI) *m/z*: 357 $[M]^+$ (100), 338 $[M - F]^+$ (3), 329 $[M - Et]^+$ (5), 312 $[M - OEt]^+$ (22). Anal. Calcd. for $C_{14}H_{10}F_3N_3O_3S$: C, 47.06; H, 2.82; N, 11.76; S, 8.97%. Found: C, 46.97; H, 2.73; N, 11.70; S, 8.91.

*3.3. General procedure 3: reaction of **1a–c** and **2a,b** in the absence of hydrochloric acid*

*3.3.1. Compound **4a** and 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione-3-(N-(4-(4-chlorophenyl)-1,3-thiazol-2-yl)hydrazone (**6a**)*

A mixture of **1a** (0.2 g, 0.89 mmol) and **2a** (0.21 g, 0.95 mmol) in methanol (15 cm^3) was refluxed during 10 h. The solvent was completely removed. The residue indicated the formation of four products **6a**, **7a**, **4a** and **3a** in ratio of 9:13.5:26.5:1. as determined by the ^{19}F NMR spectrum. Column chromatography, using hexane–ethyl acetate (10:1), separated the mixture of **6a** and **4a** only. **7a** is not stable and transforms to **4a** on silica gel. Compound **3a** was not obtained by this method because of low concentration. The first fraction contained **4a** (60%) R_f 0.4, identical to the product obtained according to procedure 1. The second fraction contained **6a**, R_f 0.25. 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione-3-(*N*-(4-(4-chlorophenyl)-1,3-thiazol-2-yl)hydrazone (**6a**) (0.23 g, 16%) was obtained as orange crystals, mp 55–57 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 4.54 (s, 2H, CH_2), 7.31 (dd, 1H, $J = 4.8$ Hz, thienyl 4-H), 7.45 (d, 2H, $J = 8.6$ Hz, phenyl 2-H and 6-H), 7.46 (s, 1H, thiazolyl 5-H), 7.85 (d, 2H, $J = 8.6$ Hz, phenyl 3-H and 5-H), 8.08 (d, 1H, $J = 4.9$ Hz, thienyl 5-H), 8.09 (d, 1H, $J = 3.9$ Hz, thienyl 3-H), 12.31 (bs, 1H, NH); ^{13}C NMR ($(CD_3)_2SO$) δ: 36.7 (CH_2), 106.4 (thiazole 5-C), 121.1 (q, $J = 273.1$ Hz, CF_3), 128.8 (thienyl 4-C), 132.2 (thienyl 2-C), 134.5 (thienyl 3-C), 135.3 (thienyl 5-C), 142.2 (thiazole 4-C), 161.5 (thiazole 2-C), 185.3 (CO); ^{19}F NMR ($CDCl_3$) δ: 92.5 (s, CF_3). MS (EI) *m/z*: 429/431 $[M]^+$ (31/15), 411/413 $[M - H_2O]^+$ (14/8), 360/362 $[M - CF_3]^+$ (11/4). Anal. Calcd. for $C_{17}H_{11}ClF_3N_3OS_2$: C, 47.50; H, 2.58; Cl, 8.41; N, 9.78; S, 14.92. Found: C, 47.31; H, 2.50; Cl, 8.31; N, 9.65; S, 14.83.

*3.3.2. Compound **4c** and ethyl-2-((3-oxo-3-(2-thienyl)-1-(trifluoromethyl)propylidene)hydrazono)-1,3-thiazole-4-carboxylate (**6c**)*

A mixture of **1c** (1 g, 5.34 mmol) and **2a** (1.2 g, 5.40 mmol) in ethanol (40 cm^3) was refluxed during 7 h. The crystalline solid that separated out on cooling, was collected, washed with a little ethanol, dried and recrystallized from ethanol to give hydrazone **6c** as yellow crystals. The filtrate mainly contained a mixture of **4c** and **6c** (TLC) and was not further investigated. Ethyl-2-((3-oxo-3-(2-thienyl)-1-(trifluoromethyl)propylidene)hydrazono)-1,3-thiazole-4-carboxylate (**6c**) (1.1 g (52%), mp 77–75 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 1.32 (t, $J = 7.0$ Hz, 3H, Me), 4.23 (q, $J = 7.0$ Hz, 2H, OCH_2), 4.40 (s, 2H, CH_2), 7.23 (dd, 1H, $J = 4.9$ Hz, thienyl 4-H), 7.72 (s, 1H, thiazolyl 5-H), 7.93 (d, 1H, $J = 5.0$ Hz, thienyl 5-H), 7.98 (d, 1H, $J = 3.8$ Hz, thienyl 3-H), 12.45 (bs, 1H, NH); ^{13}C NMR ($(CD_3)_2SO$) δ: 14.0 (Me), 36.5 (CH_2), 60.2 (OCH_2), 120.8 (thiazole 5-C), 120.9 (q, $J = 272.9$ Hz, CF_3), 128.8 (thienyl 4-C), 134.5 (thienyl 3-C), 135.3 (thienyl 5-C), 142.1 (thienyl 2-C), 142.8 (thiazole 4-C), 160.7 (thiazole 2-C), 167.8 (CO), 185.0 (CO); ^{19}F NMR ($CDCl_3$) δ: 92.5 (s, CF_3). MS (EI) *m/z*: 391 $[M]^+$ (11), 373 $[M - H_2O]$ (3), 358 $[M - CHF_2]$ (5), 322 $[M - CF_3]$ (8). Anal. Calcd. for $C_{14}H_{12}F_3N_3O_3S_2$: C, 42.96; H, 3.09; N, 10.74; S, 16.38. Found: C, 43.05; H, 2.98; N, 10.65; S, 16.42.

*3.3.3. Compound **4f** and ethyl-2-((3-oxo-3-(2-furyl)-1-(trifluoromethyl)propylidene)hydrazono)-1,3-thiazole-carboxylate (**6f**)*

A mixture of **1c** (0.4 g, 2.14 mmol) and **2b** (0.46 g, 2.23 mmol) in methanol (20 cm^3) was refluxed during

5 h. The crystalline solid that separated out on cooling, was collected and dried to give 5-hydroxypyrazoline **4f** as white crystals, yield 0.3 g (37%), mp 68–70 °C. The filtrate was completely evaporated and was separated by column chromatography, using dichloromethane as the eluent. The first fraction contained **4f**, R_f 0.5, the second afforded **6f**, R_f 0.25. Ethyl-2-((3-oxo-3-(2-furyl)-1-(trifluoromethyl)propylidene)-hydrazono)-1,3-thiazole-carboxylate (**6f**) (0.13 g, 16%), mp 52–54 °C was obtained as orange crystals. ^{1}H NMR ($(CD_3)_2SO$) δ: 1.30 (t, $J = 7.1$ Hz, 3H, Me), 4.20 (q, $J = 7.1$ Hz, 2H, OCH_2), 4.34 (s, 2H, CH_2), 6.79 (d, 1H, $J = 3.4$ Hz, furyl 4-H), 7.56 (d, 1H, $J = 3.1$ Hz, furyl 3-H), 7.88 (d, 1H, $J = 1.8$ Hz, furyl 5-H), 8.06 (s, 1H, thiazole 5-H), 12.15 (bs, 1H, NH). MS (EI) *m/z*: 375 $[M]^+$ (64), 357 $[M - H_2O]$ (5), 330 $[M - OEt]$ (11), 306 $[M - CF_3]$ (100). Anal. Calcd. for $C_{14}H_{12}F_3N_3O_4S$: C, 44.80; H, 3.22; N, 11.20; S, 8.54. Found: C, 44.72; H, 3.10; N, 11.02; S, 8.38.

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