Journal of Fluorine Chemistry 130 (2009) 886–893

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Some novel observations on the reaction of 2-hydrazino-3-methylquinoxaline with trifluoromethyl-β-diketones

Ranjana Aggarwal *, Rajiv Kumar, Shiv P. Singh

Department of Chemistry, Kurukshetra University, Kurukshetra 136 119, Haryana, India

ARTICLE INFO

Article history:
Received 17 May 2009
Received in revised form 27 June 2009
Accepted 29 June 2009
Available online 5 July 2009

Keywords:
3-Trifluoromethylpyrazoles
5-Trifluoromethylpyrazoles
5-Trifluoromethyl-5-hydroxypyrazolines
Trifluoromethyl-β-diketones
Triazolo[4,3-*a*]quinoxalines

ABSTRACT

The reaction of 2-hydrazino-3-methylquinoxaline **1** with trifluoromethyl-β-diketones **2** not only yields the expected 5-trifluoromethyl-5-hydroxy-Δ^2-pyrazolines **3a**–**3f** and/or 3-trifluoromethylpyrazoles **4c**–**4f** but also the unexpected products 1,2,4-triazolo[4,3-*a*]quinoxalines **5a**–**5f** and/or 3(5)-trifluoromethyl-1*H*-pyrazoles **6c**–**6f**. Furthermore, the acid-catalyzed dehydration of 5-hydroxypyrazolines **3a**–**3b** resulted in the formation of unexpected **5a**–**5b** along with the expected corresponding pyrazoles **7a**–**7b**. These unprecedented observations provide evidence for the existence of equilibrium between the hydroxypyrazoline **3** and its open chain tautomer, ketoimine **9** in the mechanistic path leading to the formation of pyrazoles **7** and triazoles **5**.

1. Introduction

The reaction of aryl/heteroaryl hydrazines with trifluoromethyl-β-diketones has been studied extensively by us [1–4] and others [5–9] in the last two decades. The reaction between monosubstituted hydrazines and trifluoromethyl-β-diketones typically furnishes three products: 3-trifluoromethylpyrazoles, 5-hydroxy-5-trifluoromethyl-Δ^2-pyrazolines, and their dehydrated products 5-trifluoromethylpyrazoles. It has been established that the ratio of the three products formed in the reaction depends not only upon the relative nucleophilicity of NH and NH_2 of the monosubstituted hydrazine and on the equilibrium ratio of the two enolic forms of β-diketones [1,2] (which in turn depends upon the substituents present on β-diketones and hydrazines) but also on the reaction medium. For instance, reaction of aroyltrifluoroacetones with phenylhydrazine leads to the formation of 5-aryl-3-trifluoromethylpyrazoles an exclusive/major product [2,5] or in varying amount [6] depending upon the solvent and reaction conditions, while the reaction with heteroaryl/*p*-nitrophenylhydrazines resulted in the production of 5-hydroxy-5-trifluoromethyl-Δ^2-pyrazolines as the major product. Similarly, presence of an electron-withdrawing group (NO_2) on the phenyl ring of aroyltrifluoroacetones resulted in the formation of a larger proportion of hydroxypyrazolines [1,2]. On going from neutral to acidic medium, change of regioselectivity has been observed and 5-aryl-3-trifluoromethylpyrazoles have been found to be the major product [1,2]. Also, higher regioselectivity in favour of 5-aryl-3-trifluoromethylpyrazoles has recently been reported by the use of fluorinated alcohols such as 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoro-2-propanol as solvents [6].

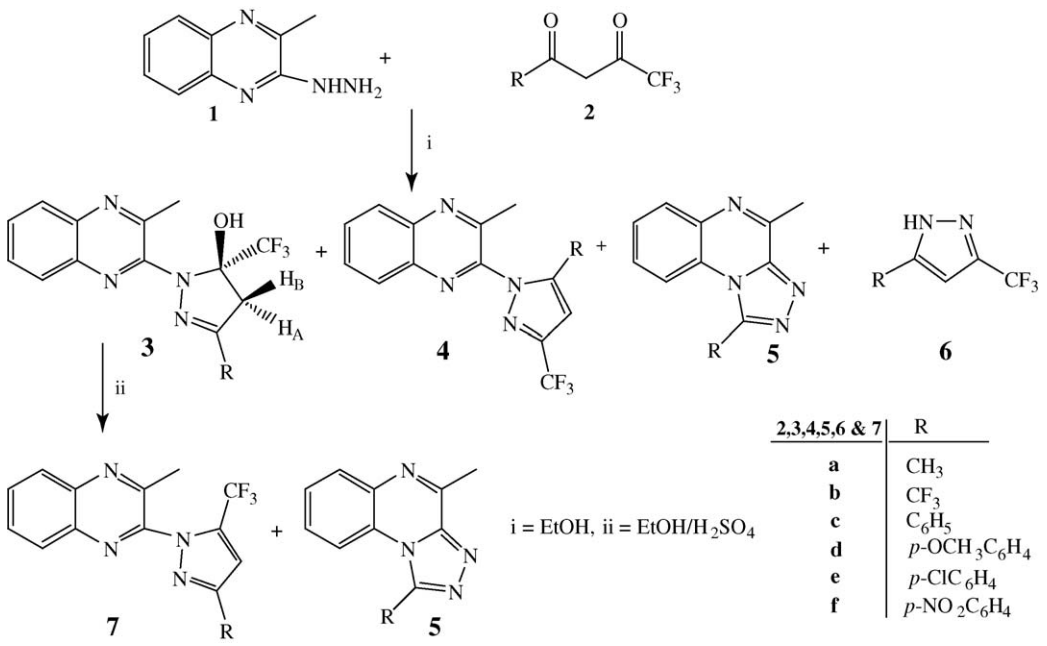
Recent investigation from our laboratory has shown that the reaction between 2-hydrazino-3-methylquinoxaline **1** with aryl-β-diketones leads to the formation of a mixture consisting of regioisomeric pyrazoles along with a small amount of 1,2,4-triazolo[4,3-*a*]quinoxaline [10] rather than the erroneously reported exclusive formation of the latter in the reaction of 2-hydrazino-3-methylquinoxaline with phenyl-1,3-butanedione [11]. Encouraged by these observations and in view of the biological properties associated with pyrazoles bearing trifluoromethyl group [12,13], we now report some novel results of our studies on the reaction of 2-hydrazino-3-methylquinoxaline **1** with trifluoromethyl-β-diketones **2** leading to the formation of 5-hydroxy-5-trifluoromethyl-3-substituted-1-(3-methylquinoxalin-2-yl)-Δ^2-pyrazolines **3**, 3-trifluoromethyl-5-substituted-1-(3-methylquinoxalin-2-yl)pyrazoles **4**, 1-substituted-4-methyl-1,2,4-triazolo[4,3-*a*]quinoxalines **5**, 3(5)-trifluoromethyl-5(3)-substituted-1*H*-pyrazoles **6** and 5-trifluoromethyl-3-substituted-1-(3-methylquinoxalin-2-yl)pyrazoles **7**.

2. Results and discussion

Results of the reaction between 2-hydrazino-3-methylquinoxaline **1** and a series of trifluoromethyl-β-diketones **2** are

* Corresponding author. Tel.: +91 1744 238734; fax: +91 1744 238277.
E-mail addresses: ranjana67in@yahoo.com (R. Aggarwal), rajivchem@yahoo.com (R. Kumar), shivpsingh@rediffmail.com (S.P. Singh).

0022-1139/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2009.06.021



Scheme 1. Various products obtained from the reaction of trifluoromethyl-β-diketones and 2-hydrazino-3-methylquinoxaline.

summarized in Scheme 1 and the ratio of different products obtained in neutral (EtOH, reflux) and acidic conditions (EtOH, 2–3 drops of H_2SO_4, reflux) has been gathered in Table 1.

Initially, the reaction of **1** with aliphatic trifluoromethyl-β-diketones (**2a**–**2b**) in neutral medium was investigated. The two reaction products were identified as 5-hydroxy-3-methyl/trifluoromethyl-5-trifluoromethyl-1-(3-methylquinoxalin-2-yl)-Δ^2-pyrazolines (**3a**–**3b**) and 1-methyl/trifluoromethyl-1,2,4-triazolo[4,3-*a*]quinoxalines (**5a**–**5b**), an unexpected product. However, similar treatment of **1** with aryl trifluoromethyl-β-diketones (**2c**–**2f**) yielded four products namely: 5-hydroxy-5-trifluoromethyl-3-aryl-1-(3-methylquinoxalin-2-yl)-Δ^2-pyrazolines (**3c**–**3f**), 3-trifluoromethyl-5-aryl-1-(3-methylquinoxalin-2-yl)pyrazoles (**4c**–**4f**), 1-aryl-4-methyl-1,2,4-triazolo[4,3-*a*]quinoxalines (**5c**–**5f**) and another unexpected product, 3(5)-trifluoromethyl-5(3)-aryl-1*H*-pyrazoles (**6c**–**6f**) obtained by C–N bond cleavage (Scheme 1). All the products were purified by column chromatography and the ratio of these different products was measured by ^{1}H NMR spectroscopy of the crude reaction mixture (Table 1).

All the four products have been unambiguously characterized by a combined application of ^{1}H, ^{13}C and ^{19}F NMR spectroscopy. The ^{1}H NMR spectra of **3a**–**3f** displayed one doublet of one proton intensity at about δ 3.7 ($^2J_{H_A-H_B} = 18$ Hz) due to geminal coupling and one doublet of quartet of one proton intensity at about δ 3.5 ($^2J_{H_A-H_B} = 18$ Hz, $^4J_{H_B-CF_3} = 1.2$ Hz) due to geminal coupling as well as coupling with the CF_3 located at position 5. 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 hydroxypyrazolines as these protons observe a difference in coupling with CF_3 located at position 5. Further support for the structure of **3** was provided by ^{13}C NMR spectra, which exhibited signals at δ 48, 94–95 as a quartet ($^2J_{C-F} = 33$ Hz) and 151 ppm for hydroxypyrazolines **3** C_4, C_5 and C_3, respectively (Table 2). Finally, the ^{19}F NMR spectra showed a signal in the range δ −78.99 to −79.14 ppm (Table 3), which is typical for CF_3 bound to saturated carbon. In the case of **3b**, second CF_3 resonates at δ −66.85, which is the typical position of CF_3 located at position 3 of hydroxypyrazoline (Table 3) [14–17].

In ^{1}H NMR spectra of **4**, a singlet of one proton intensity appeared in the range δ 6.9–7.0 indicating that this proton is an aromatic pyrazole proton corresponding to C_4–H. Also, the ^{13}C NMR spectra of **4** showed signals at about δ 104, 145 (q, $^2J_{C-F} = 38$ Hz) and 146 ppm corresponding to C_4, C_3 and C_5, respectively (Table 4) and thus providing the firm evidence in support of the formation of aromatic system. Further support to the position of CF_3 in 3-trifluoromethylpyrazoles **4** was provided by ^{19}F NMR spectrum, 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 (Table 3) [1,2,14–16].

Identity of 1-substituted-4-methyl-1,2,4-triazolo[4,3-*a*]quinoxalines **5** was confirmed on the basis of ^{1}H NMR spectra, an

Table 1
The ratio of different products obtained is calculated by ^{1}H NMR of the crude reaction mixture in neutral (EtOH, reflux) and acidic conditions (EtOH, 2–3 drops of H_2SO_4, reflux)[a].

Compds.	R	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	Dehydration of hydroxypyrazoline (3)
a	CH_3	85(0)	0(9)	15(73)	0(0)	0(18)	80%(**5a**), 20%(**7a**)
b	CF_3	80(0)	0(58)	20(42)	0(0)	0(0)	57%(**5b**), 43%(**7b** or **4b**)
c	C_6H_5	45(0)	34(45)	10(17)	11(15)	0(23)	**7c**
d	*p*-$OCH_3C_6H_4$	35(0)	29(67)	26(<7)	10(12)	0(14)	**7d**
e	*p*-ClC_6H_4	37(0)	33(49)	15(<5)	15(10)	0(36)	**7e**
f	*p*-$NO_2C_6H_4$	70	14	<5	14	0	**7f**

[a] Percentages in parenthesis are for reaction in acidic medium.

Table 2
^{13}C NMR data for 5-hydroxy-5-trifluoromethylpyrazolines **3** (ppm).

Compds.	3a	3b	3c	3d	3e	3f
Pyrazole carbons						
C-3	151.08	141.18(q, $^2J_{C-F}$ = 39Hz)	150.78	149.52	150.13	150.04
C-4	48.08	42.15	44.32	43.36	44.19	43.90
C-5	94.33 (q, $^2J_{C-F}$ = 33 Hz)	95.75 (q, $^2J_{C-F}$ = 33 Hz)	94.68 (q, $^2J_{C-F}$ = 33 Hz)	93.44 (q, $^2J_{C-F}$ = 28.5 Hz)	94.84 (q, $^2J_{C-F}$ = 33 Hz)	95.26 (q, $^2J_{C-F}$ = 33 Hz)
Quinoxaline carbons						
C-2′	151.41	150.08	150.86	149.76	150.54	150.08
C-3′	150.86	149.56	150.18	149.20	149.71	148.44
C-5′, 6′, 7′, 8′	129.70, 128.06, 128.01, 126.56	130.23, 129.23, 128.48, 126.84	130.45, 130.15, 128.44, 125.99	128.98, 127.17, 126.57, 125.45	130.12, 128.49, 127.83, 126.61	130.01, 128.62, 128.40, 126.69
C-4a′, 8a′	138.63, 136.74	139.68, 136.46	137.01, 130.57	136.77, 135.93	138.30, 136.39	139.43, 136.65
Aryl carbons						
C-1″			127.57	122.14	129.63	133.20
C-2″, 6″			128.89	126.76	127.43	126.80
C-3″, 5″			126.25	113.21	129.16	124.16
C-4″			126.61	160.31	136.89	148.30
Other carbons						
Qux-CH_3	24.07	23.72	24.15	23.32	24.18	24.29
CF_3	123.74 (q, $^1J_{C-F}$ = 283.5 Hz)	123.14 (q, $^1J_{C-F}$ = 269.25 Hz)	123.68 (q, $^1J_{C-F}$ = 285 Hz)	124.33 (q, $^1J_{C-F}$ = 285 Hz)	123.6 (q, $^1J_{C-F}$ = 284.25 Hz)	123.47 (q, $^1J_{C-F}$ = 284.25 Hz)
3′-CF_3		119.50 (q, $^1J_{C-F}$ = 261.75 Hz)				
CH_3	15.53					
OCH_3				54.32		

Table 3
^{19}F NMR data for 5-hydroxy-5-trifluoromethylpyrazolines 3,3-trifluoromethylpyrazoles **4** and 5-trifluoromethylpyrazoles **7** (ppm).

Compds.	3	4	7
a	−78.99		−58.21
b	−79.14, −66.85	–	−58.25, −66.51
c	−79.02	−62.40	−58.28
d	−78.94	−62.48	−58.23
e	−71.10	−62.45	−58.25
f	−78.93	–	−58.31

alternative synthesis of **5a** [10] and mix Mp. The signal for CH_3 protons on quinoxaline ring is deshielded and appears at about δ 3.1 ppm in ^1H NMR spectra of **5**. Also, in ^{19}F NMR spectrum of **5b**, a sharp singlet for CF_3 appeared at about δ −57.85 ppm. 3(5)-Trifluoromethyl-5(3)-aryl-1*H*-pyrazoles **6** obtained by C–N bond cleavage were identified on the basis of their ^1H NMR spectra, literature Mp., mix Mp. and co-tlc.

5-Hydroxy-5-trifluoromethyl-Δ^2-pyrazolines **3** are resistant to elimination of water under the reaction conditions. However, treatment of **3c**–**3f** in EtOH/H_2SO_4 furnished the dehydrated product i.e. 3-aryl-5-trifluoromethylpyrazoles (**7c**–**7f**) in good yields (Scheme 1). However, surprisingly, **3a** and **3b** under similar reaction conditions afforded a mixture consisting of corresponding pyrazoles (**7a**–**7b**) and 1,2,4-triazolo[4,3-*a*]quinoxalines (**5a**–**5b**) (Table 1).

Structure of compound **7** was established on the basis of ^1H, ^{13}C and ^{19}F NMR spectra. ^1H NMR displayed a singlet of one proton intensity in the range δ 7.1–7.3 ppm corresponding to the pyrazole 4-position [14–17], which is about 0.2 ppm downfield as compared to the corresponding proton in the regioisomer **4**. Also, in ^{13}C NMR spectra signals at δ 107, 135 (q, $^2J_{C-F}$ = 40 Hz) and 150 ppm were assigned to the C_4, C_5 and C_3 positions of **7**, respectively. The two regioisomeric pyrazoles **4** and **7** can be distinguished on the basis of these signals [1,2,14–16]. A comparative ^{13}C NMR data of both the pyrazoles are given in Table 4. In ^{19}F NMR spectra of compound **7**, a signal appears at about −58 ppm indicating that CF_3 is located at position 5 of the pyrazole ring (Table 3).

It was also observed that the position of CH_3 protons signal located at position 3 of quinoxaline ring is significantly affected by the position of trifluoromethyl group on the hydroxypyrazoline/pyrazole ring attached to quinoxaline at position 2. The signal for CH_3 protons is deshielded when CF_3 group is present at position 5, and appeared as a singlet at δ 2.95 (except in the case of **3b** where this CH_3 appears at δ 2.76 ppm) and 2.80 ppm in ^1H NMR spectra of **3** and **7**, respectively. However, this methyl resonates at about δ 2.45 in ^1H NMR spectra of **4**, when the CF_3 group is present at position 3 of pyrazole ring.

We also explored alternate reaction conditions hoping to change the ratio of products by changing the solvent of the reaction from ethanol to THF. When **1** and **2c** were refluxed in THF for 5 h, a mixture consisting of the pyrazoline **3c**, pyrazole **4c** and triazole **5c** was obtained in the percentage ratio 46:42:12 without any trace of **6c**. Further, the reaction between **1** and **2e** was carried out in solvent-free conditions, in a conical flask at 180 °C for 30–35 min, and again pyrazole **6e** was excluded from the reaction mixture and it contained pyrazoline **3e**, pyrazole **4e** and triazole **5e** in the ratio 49:38:13. This result finds precedence in the literature where it has been observed that the 2-hydrazinobenzoxazole on reaction with pentan-2,4-dione in EtOH/HCl results into the formation of 3,5-dimethyl-1*H*-pyrazole. It has been proposed that ethanol acts as a nucleophile and results in the cleavage of C–N bond [18]. Also, pyrazole **4c** was recovered unchanged when it was refluxed in a mixture of EtOH:H_2O (1:1) for 6 h indicating the stability of the pyrazole ring under the reaction conditions. It can thus be concluded that C–N bond cleavage occurs in the intermediate(s) leading to the formation of the pyrazole ring.

The reaction between diketones **2** and hydrazine **1** was also carried out in acidic conditions by adding a few drops of H_2SO_4 to the reaction mixture. Work-up of the reaction mixture showed the predominance of the 3-trifluoromethylpyrazoles **4** obviously due to the change in regioselectivity as has already been observed by us [1,2]. 5-Trifluoromethylpyrazoles 7

Table 4
^{13}C NMR data for 3-trifluoromethylpyrazoles **4** and 5-trifluoromethylpyrazoles **7** (ppm).

Compds.	7a	7b	4c	7c	4d	7d	4e	7e	7f
C-3	152.46	144.25 (q, $^2J_{C-F}$ = 38 Hz)	143.23 (q, $^2J_{C-F}$ = 38.25 Hz)	151.14	144.45 (q, $^2J_{C-F}$ = 37.5 Hz)	151.1	144.53 (q, $^2J_{C-F}$ = 39 Hz)	151.00	150.31
C-4	108.10	106.12	103.65	106.72	104.23	106.4	105.20	106.56	107.23
C-5	130.07 (q, $^2J_{C-F}$ = 37.5 Hz)	132.12 (q, $^2J_{C-F}$ = 39 Hz)	144.58	134.40 (q, $^2J_{C-F}$ = 39 Hz)	146.02	135.01 (q, $^2J_{C-F}$ = 39 Hz)	145.50	135.60 (q, $^2J_{C-F}$ = 39 Hz)	135.81 (q, $^2J_{C-F}$ = 40.5 Hz)
C-2′	152.72	154.74	150.11	152.67	151.52	152.4	151.31	151.57	150.75
C-3′	145.71	147.76	145.65	144.90	146.76	145.01	145.78	144.77	144.51
C-5′, 6′, 7′, 8′	128.74, 129.51, 129.85, 130.32	128.65, 129.55, 129.67, 130.35	130.29, 129.09, 128.12, 127.16	128.41, 129.08, 130.21, 131.23	131.47, 130.27, 129.32, 128.46	128.42, 129.20, 130.13, 131.12	128.27, 128.57, 130.42, 131.60	128.47, 129.57, 130.22, 131.27	128.53, 129.23, 130.44, 131.58
C-9′	139.50	140.11	138.44	139.39	139.77	139.5	139.22	139.37	137.39
C-10′	140.30	140.72	141.01	142.23	142.35	142.4	142.49	142.37	139.32
C-1″			130.90	131.34	120.60	123.90	126.86	126.95	142.51
C-2″, 6″			128.01	128.89	129.70	127.33	129.66	129.21	120.60
C-3″, 5″			127.06	125.99	114.40	114.29	129.20	127.23	124.62
C-4″			128.01	129.22	160.33	160.71	135.65	135.02	148.05
Qux-CH_3	23.45	21.99	20.02	21.93	21.21	21.97	21.39	21.85	21.81
CF_3	123.74 (q, $^1J_{C-F}$ = 267 Hz)	122.57 (q, $^1J_{C-F}$ = 285 Hz)	122.56 (q, $^1J_{C-F}$ = 283.5 Hz)	119.50 (q, $^1J_{C-F}$ = 285 Hz)	122.75 (q, $^1J_{C-F}$ = 277.5 Hz)	119.40 (q, $^1J_{C-F}$ = 275 Hz)	120.91 (q, $^1J_{C-F}$ = 267.5 Hz)	119.46 (q, $^1J_{C-F}$ = 268.5 Hz)	122.84 (q, $^1J_{C-F}$ = 267 Hz)
3′-CF_3		125.84 (q, $^1J_{C-F}$ = 267 Hz)							
CH_3	13.44								
OCH_3					55.26	55.35			

(obviously formed by the dehydration of hydroxypyrazolines **3**), triazoles **5** and pyrazoles **6** were other isolable products. In a typical reaction between **1** and **2a**, three products namely: 3-trifluoromethylpyrazole **4a**, triazole **5a** and 5-trifluoromethylpyrazole **7a** were observed in the ratio 9:73:18. While with symmetrical diketone **2b**, only two products **4b** (or **7b**) and **5b** were observed. However, with aryl diketones **2c**–**2e**, as expected, four products **4**, **5**, **6** and **7** were observed (Table 1). A graphical representation of the composition of different products formed in neutral and acidic media has been indicated in Fig. 1.

The plausible mechanism for the formation of these products is given in Scheme 2. With 1,1,1-trifluoropentane-2,4-diones **2a** only two products **3a** and **5a** were formed. Since, in diketone **2a**, $COCF_3$ carbonyl is known to exist predominantly in enolized form A [19–21] so that terminal nitrogen of hydrazine attacks on the carbonyl carbon remote to CF_3 (pathway a) generating hydrazone **8**. It is worth mentioning here that nucleophilicity of nitrogen attached to the quinoxaline ring (NH) is poor due to electron-withdrawing nature of quinoxaline ring. Thus the possibility of the first nucleophilic attack of this nitrogen is almost negligible. There may now be competition between two possibilities of cyclization of hydrazone **8**. One of the routes through the intermediacy of **9** and **10** leads to the formation of triazole **5** and other gives hydroxypyrazoline **3**. The fact that triazoles (**5a**–**5b**) were also obtained during dehydration of hydroxypyrazolines (**3a**–**3b**) can only be explained if hydroxypyrazoline **3** ring opens up and exists in equilibrium with its open chain tautomer ketoimine **9**. It thus looks attractive to speculate that during the dehydration of **3**, pyrazoline ring opened up and again cyclized along the other path to give the fused triazole **5**. Existence of equilibrium between hydroxypyrazoline and ketoimine, established by the ^1H NMR of the supercooled reaction mixture of 1-hydrazinophthalazine with β-diketones, has also been reported by Zimmer and Amer [22]. Since the diketone **2b** is symmetrical, the reaction leads to formation of only two products **3b** and **5b** through the same path.

However, in the case of aroyltrifluoroacetones (**2c**–**2f**) ratio of enol tautomer B increases due to extended conjugation between the C=C–C=O and arenes [19–21]. The terminal nitrogen (NH_2) of quinoxaline then attacks on the CF_3 carbonyl (pathway b) and further cyclization gives rise to the regioisomer **4**.

An interesting correlation between product composition and the substituent effect on β-diketones was also noted e.g. strong electron-withdrawing group like *p*-NO_2 present on arenes of the diketone increases the ratio of hydroxypyrazoline **3e** up to 70%, which is minimum in the case of *p*-methoxyphenyltrifluoromethyl-β-diketone where **3d** was formed only to the extent of 35%. The percentage of triazole **5** also decreases when the electron-withdrawing substituents are present on the aryl ring. As the cleaved pyrazoles **6** were formed only with aryldiketones **2c**–**2f**, this indicates that its formation may take place by initial attack on the $COCF_3$ carbonyl (pathway b) or may be due to slow reaction rate of diketones **2c**–**2f**.

In acidic medium, the ratio of 5-trifluoromethylpyrazole **7** (dehydrated product of 5-hydroxy-5-trifluoromethylpyrazoline **3**) decreases and that of corresponding regioisomeric 3-trifluoromethylpyrazole **4** increases which is maximum (67%) when *p*-OMe group is present on arene of β-diketones. The change in regioselectivity in acidic medium may be either due to alteration of electrophilicity of carbonyl group of β-diketones [23] or may be due to change in nucleophilicity of the nitrogens of the hydrazine. As, more basic nitrogen (NH_2) will be protonated more easily than less basic one (NH) [1,2,24].

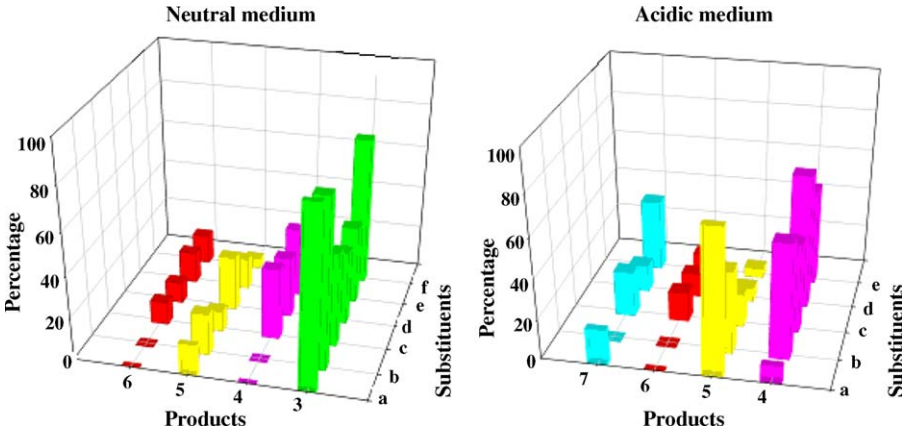
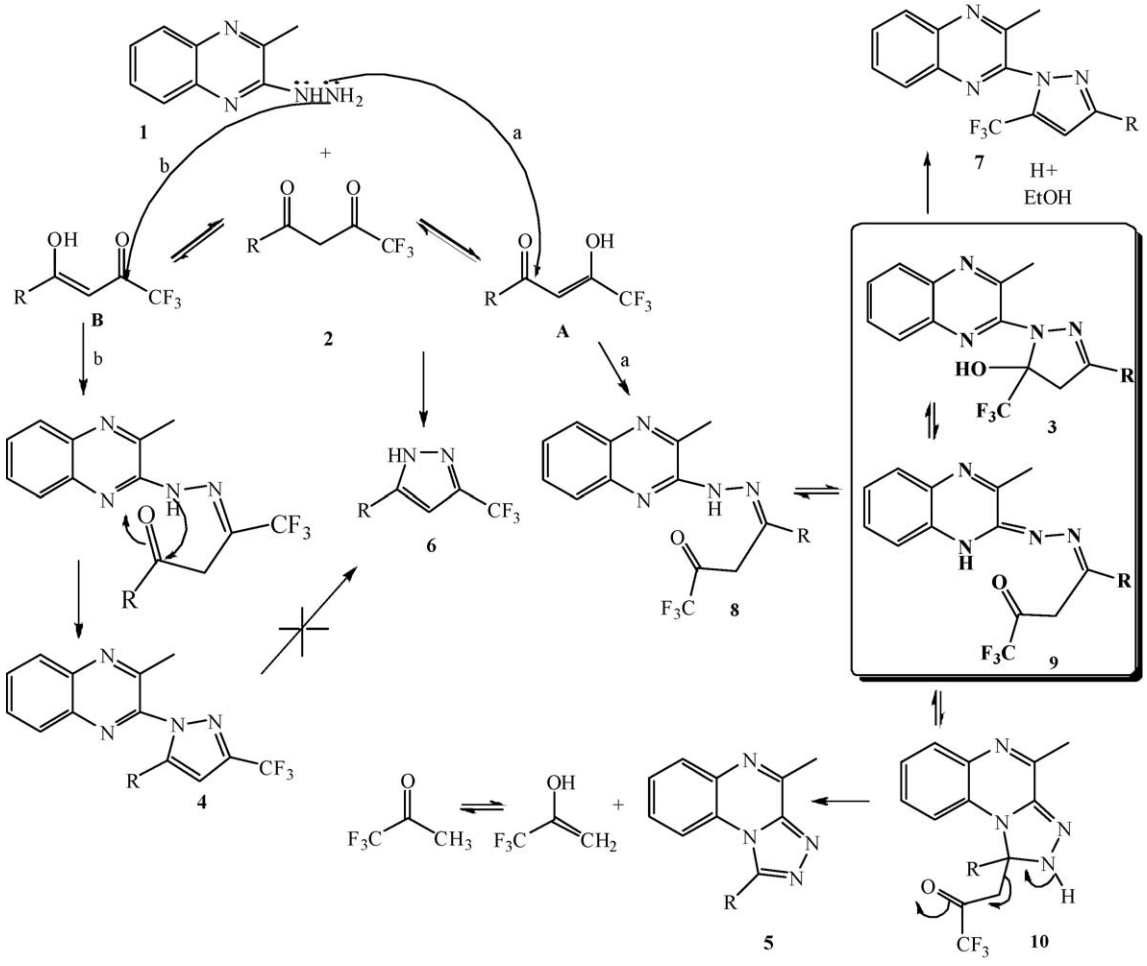


Fig. 1. Graphical representation of percentage of different products in neutral and acidic medium.



Scheme 2. Plausible mechanism for the formation of **3**, **4**, **5**, **6** and **7**.

3. Conclusion

In summary, we have studied the reaction of 2-hyrazino-3-methylquinoxaline **1** with trifluoromethyl-β-diketones **2** in different reaction conditions. The reaction resulted in the formation of the unexpected products 1-substituted-4-methyl-1,2,4-triazolo[4,3-*a*]quinoxalines **5** and 3(5)-trifluoromethyl-5(3)-substituted-1*H*-pyrazoles **6** in addition to the expected 5-hydroxy-3-substituted-1-(3-methylquinoxalin-2-yl)-5-trifluoromethyl-Δ^2-pyrazolines **3**, 3-trifluoromethyl-5-substituted-1-(3-methylquinoxalin-2-yl)pyrazoles **4** and 5-trifluoromethylpyrazole **7**. Through the unprecedented formation of triazolo[4,3-*a*]quinoxaline **5** while dehydration of hydoxypyrazoline **3** in acidic medium, we propose the existence of equilibrium between 5-hydroxy-5-trifluoromethylpyrazoline **3** and its open chain tautomer **9**. The study also shows the role of ethanol as a solvent in C–N bond cleavage which results into the production of cleaved pyrazoles **6**.

4. Experimental

The IR spectra of the compounds were recorded on Buck Scientific IR M-500 spectrophotometer using KBr pellets (ν_{max} in cm^{-1}), ^1H and ^{13}C NMR spectra on a Bruker instrument at 300 and 75 MHz, respectively; chemical shifts are expressed in δ-scale downfield from TMS as an internal standard. ^{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. Elemental analyses were performed at Sophisticated Analytical Instrument Facility Central Drug Research Institute, Lucknow, India.

Fluorinated β-diketones **2a**–**2c** are available commercially and other **2d**–**2f** were prepared according to the literature procedure [25,26]. 2-Hydrazino-3-methylquinoxaline **1** was also synthesized according to the literature procedure [11].

*4.1. General procedure for the preparation of 5-hydroxy-3-substituted-1-(3-methylquinoxalin-2-yl)-5-trifluoromethyl-Δ²-pyrazolines **3a**–**3b**, and 1-substituted-4-methyl-1,2,4-triazolo[4,3-a]quinoxalines **5a**–**5b***

An ethanolic solution (30 ml) of 2-hydrazino-3-methylquinoxaline **1** (0.35 g, 2 mmol) and trifluoromethyl-β-diketones **2a**–**2b** (2 mmol) was refluxed for 6 h. The reaction was monitored by tlc. On completion of reaction solvent was evaporated completely. The tlc and ^1H NMR of the reaction mixture showed the formation of products in the ratio given in Table 1. Column chromatography separation using silica gel (100–200 mesh) with petroleum ether:ethyl acetate (99:1) afforded **3**, and further elution with petroleum ether:ethyl acetate (90:10) afforded **5**.

*4.1.1. 5-Hydroxy-3-methyl-1-(3-methylquinoxalin-2-yl)-5-trifluoromethyl-Δ²-pyrazoline **3a***

(67%) Mp. 116–118 °C; IR: (KBr, cm^{-1}) 3448 ν(O–H), 1501 ν(C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.13 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.10 (dq, 1H, $^2J_{H_A-H_B}$ = 18 Hz, $^4J_{H_B-CF_3}$ = 1.2 Hz, 4-H_B), 3.38 (d, 1H, $^2J_{H_A-H_B}$ = 18 Hz, 4-H_A), 7.59–7.67 (m, 2H, 6′, 7′-H), 7.75–7.78 (m, 1H, 5′-H), 7.96–7.99 (m, 1H, 8′-H), 8.9 (bs, 1H, 5′-OH, exchangeable with D_2O); MS (EI) m/z: 311 $[M+1]^+$. Anal. Calcd. for $C_{14}H_{13}F_3N_4O$: C, 54.19; H, 4.22; N, 18.06. Found: C, 54.53; H, 3.99; N, 19.05.

*4.1.2. 5-Hydroxy-1-(3-methylquinoxalin-2-yl)-3,5-bis(trifluoromethyl)-Δ²-pyrazoline **3b***

(75%) Mp. 84–86 °C; IR: (KBr, cm^{-1}) 3455 ν(O–H), 1505 ν(C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.76 (s, 3H, CH_3), 3.31 (d, 1H, $^2J_{H_A-H_B}$ = 18.6 Hz, 4-H_B), 3.54 (d, 1H, $^2J_{H_A-H_B}$ = 18.6 Hz, 4-H_A), 7.61–7.64 (m, 2H, 6′, 7′-H), 7.72–7.75 (m, 1H, 5′-H), 7.94–7.97 (m, 1H, 8′-H), 8.6 (bs, 1H, 5′-OH, exchangeable with D_2O); MS (EI) m/z: 365 $[M+1]^+$. Anal. Calcd. for $C_{14}H_{10}F_6N_4O$: C, 46.16; H, 2.77; N, 15.38. Found: C, 46.10; H, 2.85; N, 16.02.

*4.1.3. 1-Trifluoromethyl-4-methyl-1,2,4-triazolo[4,3-a]quinoxaline **5b***

(19%) Mp. 190–92 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.10 (s, 3H, CH_3), 7.54–7.57 (m, 2H, 6′, 7′-H), 7.99–8.02 (m, 1H, 5′-H), 8.06–8.09 (m, 1H, 8′-H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −57.85 (s, CF_3).

*4.2. General procedure for the preparation of 5-hydroxy-3-aryl-1-(3-methylquinoxalin-2-yl)-5-trifluoromethyl-Δ²-pyrazolines **3c**–**3f**, 3-trifluoromethyl-5-aryl-1-(3-methylquinoxalin-2-yl)pyrazoles **4c**–**4f**, 3(5)-trifluoromethyl-5(3)-arylpyrazoles **6c**–**6f** and 1-aryl-4-methyl-1,2,4-triazolo[4,3-a]quinoxalines **5c**–**5f***

2-Hyrazino-3-methylquinoxaline **1** (0.35 g, 2 mmol) was slowly added to the corresponding trifluoromethyl-β-diketone **2** (2 mmol) in the ethanol (30 ml), and the mixture was refluxed for 6 h. The reaction was monitored by tlc. The solvent was evaporated and the tlc and ^1H NMR of residue showed the formation of products in the ratio given in Table 1. Column chromatography separation using silica gel (100–200 mesh) with petroleum ether:ethyl acetate (99:1) afforded **3**, further elution of column with petroleum ether:ethyl acetate (98:2) afforded **4**, elution with petroleum ether:ethyl acetate (96:4) afforded **6** and further elution with petroleum ether:ethyl acetate (90:10) afforded **5**.

*4.2.1. 5-Hydroxy-1-(3-methylquinoxalin-2-yl)-3-phenyl-5-trifluoromethyl-Δ²-pyrazoline **3c***

(43%) Mp. 144–146 °C; IR: (KBr, cm^{-1}) 3550 ν(O–H), 1565 ν(C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.96 (s, 3H, CH_3), 3.53 (dq, 1H, $^2J_{H_A-H_B}$ = 18.6 Hz, $^4J_{H_B-CF_3}$ = 1.2 Hz, 4-H_B), 3.69 (d, 1H, $^2J_{H_A-H_B}$ = 18.6 Hz, 4-H_A), 7.38–7.40 (m, 3H, 3″, 4″, 5″-H), 7.59–7.75 (m, 5H, 5′, 6′, 7′, 2″, 6″-H), 7.99–8.01 (m, 1H, 8′-H), 8.80 (bs, 1H, 5′-OH, exchangeable with D_2O); MS (EI) m/z: 373 $[M+1]^+$. Anal. Calcd. for $C_{19}H_{15}F_3N_4O$: C, 61.29; H, 4.06; N, 15.05. Found: C, 61.26; H, 4.02; N, 14.89.

*4.2.2. 5-Hydroxy-1-(3-methylquinoxalin-2-yl)-3-(p-methoxyphenyl)-5-trifluoromethyl-Δ²-pyrazoline **3d***

(31%) Mp. 94–96 °C; IR: (KBr, cm^{-1}) 3480 ν(O–H), 1509 ν(C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.00 (s, 3H, CH_3), 3.58 (d, 1H, $^2J_{H_A-H_B}$ = 18 Hz, 4-H_B), 3.74 (d, 1H, $^2J_{H_A-H_B}$ = 18 Hz, 4-H_A), 3.88 (s, 3H, OCH_3), 6.97 (d, 2H, 3″, 5″-H, *J* = 8.7 Hz), 7.66–7.69 (m, 4H, 6′, 7′, 2″, 6″-H), 7.78–7.81 (m, 1H, 5′-H), 8.03–8.05 (m, 1H, 8′-H), 8.60 (bs, 1H, 5′-OH, exchangeable with D_2O; MS (EI) m/z: 403 $[M+1]^+$. Anal. Calcd. for $C_{20}H_{17}F_3N_4O_2$: C, 59.70; H, 4.26; N, 13.92. Found: C, 59.65; H, 4.21; N, 13.90.

*4.2.3. 5-Hydroxy-1-(3-methylquinoxalin-2-yl)-3-(p-chlorophenyl)-5-trifluoromethyl-Δ²-pyrazoline **3e***

(29%) Mp. 110–112 °C; IR: (KBr, cm^{-1}) 3406 ν(O–H), 1511 ν(C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.96 (s, 3H, CH_3), 3.57 (d, 1H, $^2J_{H_A-H_B}$ = 18 Hz, 4-H_B), 3.74 (d, 1H, $^2J_{H_A-H_B}$ = 18 Hz, 4-H_A), 7.43 (d, 2H, *J* = 8.7 Hz, 3″, 5″-H), 7.65–7.69 (m, 4H, 6′, 7′, 2″, 6″-H), 7.78–7.81 (m, 1H, 5′-H), 7.99–8.01 (m, 1H, 8′-H), 8.81 (bs, 1H, 5′-OH, exchangeable with D_2O); MS (EI) m/z: 407/409 $[M+1]^+$. Anal. Calcd. for $C_{19}H_{14}ClF_3N_4O$: C, 56.15; H, 3.47; N, 13.79. Found: C, 56.20; H, 3.35; N, 13.54.

*4.2.4. 5-Hydroxy-1-(3-methylquinoxalin-2-yl)-3-(p-nitrophenyl)-5-trifluoromethyl-Δ²-pyrazoline **3f***

(64%) Mp. 173–176 °C; IR: (KBr, cm^{-1}) 3466 ν(O–H), 1551 ν(C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.88 (s, 3H, CH_3), 3.53 (dq, 1H, $^2J_{H_A-H_B}$ = 18 Hz, $^4J_{H_B-CF_3}$ = 1.5 Hz, 4-H_B), 3.71 (d, 1H, $^2J_{H_A-H_B}$ = 18 Hz, 4-H_A), 7.57–7.64 (m, 2H, 6′, 7′-H), 7.72–7.75 (m, 1H, 5′-H), 7.78 (d, 2H, *J* = 8.7 Hz, 2″, 6″-H), 7.92–7.95 (m, 1H, 8′-H), 8.23 (d, 2H, *J* = 8.7 Hz, 3″, 5″-H), 8.67 (bs, 1H, 5′-OH, exchangeable with D_2O); MS (EI) m/z: 418 $[M+1]^+$. Anal. Calcd. for $C_{19}H_{14}F_3N_5O_3$: C, 54.54; H, 3.38; N, 16.78. Found: C, 54.49; H, 3.34; N, 16.85.

*4.2.5. 1-(3-Methylquinoxalin-2-yl)-5-phenyl-3-trifluoromethylpyrazole **4c***

(30%) Mp. 122–124 °C; IR: (KBr, cm^{-1}) 3116, 1498; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.50 (s, 3H, CH_3), 6.91 (s, 1H, 4-H), 7.26–7.30 (m, 5H, 2″, 3″, 4″, 5″, 6″-H), 7.77–7.90 (m, 2H, 6′, 7′-H), 8.04–8.15 (m, 2H, 5′, 8′-H); MS (EI) m/z: 355 $[M+1]^+$. Anal. Calcd. for $C_{19}H_{13}F_3N_4$: C, 64.77; H, 3.70; N, 15.81. Found: C, 64.36; H, 3.68; N, 15.47.

*4.2.6. 1-(3-Methylquinoxalin-2-yl)-5-(p-methoxyphenyl)-3-trifluoromethylpyrazole **4d***

(19%) Mp.118–120°C; IR: (KBr, cm^{-1}) 3120, 1501; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.46 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.78 (d,

2H, 3″, 5″-H, J = 8.4 Hz), 6.84 (s, 1H, 4-H), 7.17 (d, 2H, 2″, 6″-H, J = 8.4 Hz), 7.88–7.90 (m, 2H, 6′, 7′-H), 8.08–8.15 (m, 2H, 5′, 8′-H); MS (EI) m/z: 385 $[M+1]^+$. Anal. Calcd. for $C_{20}H_{15}F_3N_4O$: C, 62.50; H, 3.93; N, 14.58. Found: C, 62.49; H, 3.85; N, 13.50.

4.2.7. 1-(3-Methylquinoxalin-2-yl)-5-(p-chlorophenyl)-3-trifluoromethylpyrazole **4e**

(28%) Mp. 130–132 °C; IR: (KBr, cm^{-1}) 3116, 1498; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.62 (s, 3H, CH_3), 6.99 (s, 1H, 4-H), 7.28 (d, 2H, 3″, 5″-H, J = 8.4 Hz), 7.35 (d, 2H, 2″, 6″-H, J = 8.4 Hz), 7.89–7.97 (m, 2H, 6′, 7′-H), 8.09–8.12 (m, 1H, 5′-H), 8.20–8.22 (m, 1H, 8′-H); MS (EI) m/z: 389/391 $[M+1]^+$. Anal. Calcd. for $C_{19}H_{12}ClF_3N_4$: C, 58.76; H, 3.11; N, 14.93. Found: C, 58.69; H, 3.14; N, 14.51.

4.3. General procedure for the preparation of 1-(3-methylquinoxalin-2-yl)-3-alkyl-5-trifluoromethylpyrazoles **7a–7b**

An ethanolic solution of 5-hydroxy-3-substituted-1-(3-methylquinoxalin-2-yl)-5-trifluoromethyl-Δ^2-pyrazoline **3a** or **3b** (1 mmol), 2–3 drops of H_2SO_4 were added and refluxed for 4–5 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 anhydrous sodium sulphate, filtered and concentrated to give **7a–7b** and **5a–5b** ratio calculated from their ^1H NMR is given in Table 1. Column chromatography separation using silica gel (100–200 mesh) with petroleum ether:ethyl acetate (98:2) as eluent afforded **7**, and further elution with petroleum ether:ethyl acetate (90:10) afforded **5**.

4.3.1. 1-(3-Methylquinoxalin-2-yl)-3-methyl-5-trifluoromethylpyrazole **7a**

(17%) Mp. 92–94 °C; IR: (KBr, cm^{-1}) 3125, 1509; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.35 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 6.64 (s, 1H, 4-H), 7.68–7.79 (m, 2H, 6′, 7′-H), 7.99–8.01 (m, 1H, 5′-H), 8.04–8.07 (m, 1H, 8′-H); MS (EI) m/z: 293 $[M+1]^+$. Anal. Calcd. for $C_{14}H_{11}F_3N_4$: C, 57.53; H, 3.79; N, 19.17. Found: C, 57.43; H, 3.74; N, 19.15.

4.3.2. 1-(3-Methylquinoxalin-2-yl)-3,5-bis(trifluoromethyl)pyrazole **7b**

(29%) Mp. 100–102 °C; IR: (KBr, cm^{-1}) 3156, 1548; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.72 (s, 3H, CH_3), 7.21 (s, 1H, 4-H), 7.80–7.92 (m, 2H, 6′, 7′-H), 8.09–8.12 (m, 1H, 5′-H), 8.16–8.18 (m, 1H, 8′-H); MS (EI) m/z: 347 $[M+1]^+$. Anal. Calcd. for $C_{14}H_8F_6N_4$: C, 48.57; H, 2.33; N, 16.18. Found: C, 49.21; H, 2.45; N, 17.01.

4.4. General procedure for the preparation of 1-(3-methylquinoxalin-2-yl)-3-aryl-5-trifluoromethylpyrazoles **7c–7f**

To an ethanolic solution of 5-hydroxy-3-substituted-1-(3-methylquinoxalin-2-yl)-5-trifluoromethyl-Δ^2-pyrazolines **3** (1 mmol), 2–3 drops of H_2SO_4 were added and refluxed for 4–5 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 anhydrous sodium sulphate, filtered and concentrated to give **7**.

4.4.1. 1-(3-Methylquinoxalin-2-yl)-3-phenyl-5-trifluoromethylpyrazole **7c**

(85%) Mp. 94–96 °C; IR: (KBr, cm^{-1}) 3201, 1499; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.78 (s, 3H, CH_3), 7.23 (s, 1H, 4-H), 7.41–7.49 (m, 3H, 3″, 4″, 5″-H), 7.80–7.90 (m, 4H, 6′, 7′, 2″, 6″-H), 8.08–8.11 (m, 1H, 5′-H), 8.13–8.15 (m, 1H, 8′-H); MS (EI) m/z: 355 $[M+1]^+$. Anal. Calcd. for $C_{19}H_{13}F_3N_4$: C, 64.40; H, 3.70; N, 15.81. Found: C, 64.35; H, 3.72; N, 15.31.

4.4.2. 1-(3-Methylquinoxalin-2-yl)-3-(p-methoxyphenyl)-5-trifluoromethylpyrazole **7d**

(83%) Mp. 96–98 °C; IR: (KBr, cm^{-1}) 3220, 1503; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.80 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 7.00 (d, 2H, 3″, 5″-H, J = 8.7 Hz), 7.17 (s, 1H, 4-H), 7.79–7.89 (m, 4H, 6′, 7′, 2″, 6″-H), 8.09–8.12 (m, 1H, 5′-H), 8.15–8.18 (m, 1H, 8′-H); MS (EI) m/z: 385 $[M+1]^+$. Anal. Calcd. for $C_{20}H_{15}F_3N_4O$: C, 62.50; H, 3.93; N, 14.58. Found: C, 62.40; H, 3.91; N, 14.36.

4.4.3. 1-(3-Methylquinoxalin-2-yl)-3-(p-chlorophenyl)-5-trifluoromethylpyrazole **7e**

(85%) Mp. 104–106 °C; IR: (KBr, cm^{-1}) 3145, 1495; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.70 (s, 3H, CH_3), 7.12 (s, 1H, 4-H), 7.36 (d, 2H, 3″, 5″-H, J = 8.4 Hz), 7.74 (d, 2H, 2″, 6″-H, J = 8.4 Hz), 7.77–7.82 (m, 2H, 6′, 7′-H), 8.00–8.03 (m, 1H, 5′-H), 8.06–8.09 (m, 1H, 8′-H); MS (EI) m/z: 389/391 $[M+1]^+$. Anal. Calcd. for $C_{19}H_{12}ClF_3N_4$: C, 58.76; H, 3.11; N, 14.43. Found: C, 58.64; H, 3.05; N, 14.75.

4.4.4. 1-(3-Methylquinoxalin-2-yl)-3-(p-nitrophenyl)-5-trifluoromethylpyrazole **7f**

(90%) Mp. 128–130 °C; IR: (KBr, cm^{-1}) 3201, 1518; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.79 (s, 3H, CH_3), 7.34 (s, 1H, 4-H), 7.82–7.93 (m, 2H, 6′, 7′-H), 8.07 (d, 2H, 2″, 6″-H, J = 8.7 Hz), 8.10–8.19 (m, 2H, 5′, 8′-H), 8.35 (d, 2H, 3″, 5″-H, J = 8.7 Hz); MS (EI) m/z: 400 $[M+1]^+$. Anal. Calcd. for $C_{19}H_{12}F_3N_5O_2$: C, 57.15; H, 3.03; N, 17.54. Found: C, 57.12; H, 3.09; N, 17.68.

4.5. General procedure of the reaction performed under acidic condition $EtOH/H_2SO_4$

To an ethanolic solution of **2** (2 mmol) was added two drops of H_2SO_4 and stirred for a while, then **1** (0.35 g, 2 mmol) was added to this solution and refluxed for 5 h. Reaction was monitered by tlc. On completion of reaction solvent was evaporated completely. The tlc and ^1H NMR of the reaction mixture showed the formation of products in the ratio given in Table 1. Different products formed were identified from their NMR spectra as described above.

4.6. Reaction between 1,1,1-trifluoromethyl-4-(p-chlorophenyl)butan-2,4-dione **2e** and 2-hydrazino-3-methylquinoxaline **1** under solvent-free condition

1 (0.35 g, 2 mmol) and **2e** (0.5 g, 2 mmol) were ground vigorously using a pestle and mortar. The contents were transferred to a conical flask and heated to 180–90 °C for 30–35 min. The reaction was monitored by tlc. The tlc and ^1H NMR of reaction mixture showed the formation of three products 5-trifluoromethyl-5-hydroxypyrazoline **3e**, 3-trifluoromethylpyrazole **4e** and 1-(*p*-chlorophenyl)triazolo[4,3-*a*]quinoxaline **5e** in a percentage ratio 49:38:13. Spectral data have already been given above.

Acknowledgements

We thank the Council of Scientific and Industrial Research, New Delhi for financial assistance and a Senior Research Fellowship to Rajiv Kumar. Thanks are also due to SAIF, CDRI, Lucknow, India for providing ^{19}F NMR spectra, mass spectrometry and elemental analysis.

References

[1] V. Kumar, R. Aggarwal, S.P. Singh, Heterocycles 75 (2008) 2893–2929.
[2] S.P. Singh, V. Kumar, R. Aggarwal, J. Elguero, J. Heterocycl. Chem. 43 (2006) 1003–1014.
[3] S.P. Singh, D. Kumar, H. Batra, R. Naithani, I. Rozas, J. Elguero, Can. J. Chem. 78 (2000) 1109–1120.

[4] S.P. Singh, J.K. Kapoor, D. Kumar, M.D. Threadgill, J. Fluorine Chem. 83 (1997) 73–79.
[5] T. Norris, R. Colon-Cruz, D.H.B. Ripin, Org. Biomol. Chem. 13 (2005) 1844–1849.
[6] S. Fustero, R. Román, J.F. Sanz-Cervera, A. Simón-Fuentes, A.C. Cuñat, S. Villanova, M. Murguía, J. Org. Chem. 73 (2008) 3523–3529.
[7] V. Montoya, J. Pons, J. Garcia-Anton, X. Solans, M. Font-Bardia, J. Ros, J. Fluorine Chem. 128 (2007) 1007–1011.
[8] S.K. Singh, M.S. Reddy, S. Shivaramakrishna, D. Kavitha, R. Vasudav, J.M. Babu, A. Sivalakshmidevi, Y.K. Rao, Tetrahedron Lett. 45 (2004) 7679–7682.
[9] J.W. Lyga, R.M. Patera, J. Heterocycl. Chem. 27 (1990) 919–921.
[10] R. Aggarwal, G. Sumran, R. Kumar, S.P. Singh, ARKIVOC xv (2007) 292–302.
[11] D. Shiho, S. Tagami, J. Am. Chem. Soc. 82 (1960) 4044–4054.
[12] M. Biava, G.C. Porretta, A. Cappelli, S. Vomero, F. Manetti, M. Botta, L. Sautebin, A. Rossi, F. Makovec, M. Anzini, J. Med. Chem. 48 (2005) 3428–3432.
[13] M.M. Ahlstrom, M. Ridderstrom, I. Zamora, K. Luthman, J. Med. Chem. 50 (2007) 4444–4452.
[14] V. Kumar, S.P. Singh, R. Aggarwal, J. Fluorine Chem. 127 (2006) 880–888.
[15] L. Song, S. Zhu, J. Fluorine Chem. 111 (2001) 201–205.
[16] S.P. Singh, D. Kumar, B.G. Jones, M.D. Threadgill, J. Fluorine Chem. 94 (1999) 199–203.
[17] S.P. Singh, R. Aggarwal, D. Kumar, Indian J. Chem. 32b (1993) 843–847.
[18] S.P. Singh, D. Kumar, D. Kumar, R.P. Kapoor, Indian J. Chem. 34b (1995) 682–685.
[19] C.L. Bumgardner, J.C. Sloop, J. Fluorine Chem. 56 (1992) 141–146.
[20] S.R. Salman, R.D. Farrant, J.C. Lindon, Mag. Res. Chem. 28 (1990) 645–650.
[21] J. Elguero, G.I. Yranzo, J. Chem. Res. (S) (1990) 120–121.
[22] H. Zimmer, A. Amer, Heterocycles 26 (1987) 1177–1182.
[23] A.B. Denisova, V.Y. Sosnovskikh, W. Dehaen, S. Toppet, L.V. Meervelt, V.A. Bakulev, J. Fluorine Chem. 115 (2002) 183–192.
[24] H. An, S. Eum, M. Koh, S.K. Lee, S.B. Park, J. Org. Chem. 73 (2008) 1752–1761.
[25] M.J. Uddin, P.N. Rao, K. Praveen, E.E. Knaus, Bioorg. Med. Chem. 11 (2003) 5273–5280.
[26] K.T. Potts, J. Bhattacharya, S.L. Smith, A.M. Ihrig, C.A. Girard, J. Org. Chem. 37 (1972) 4410–4415.