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Nucleophilic substitutions in 6,7-difluoroquinoxalines

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Abstract

The reactions of 6,7-difluoroquinoxalines with a number of nucleophiles, such as cycloalkylimines, hydrazine, sodium hydroxide and alkoxides have been shown to result in substitution of either one or two fluoro atoms depending on the nature of nucleophiles.

Keywords: Fluoroquinoxalines; Synthesis; ^{1}H, ^{13}C and ^{19}F NMR

1. Introduction

Many organic molecules containing the quinoxaline moiety are known to be biologically active compounds [1,2]. In particular, 6,7-dialkoxy derivatives proved to inhibit tyrosine kinase of some receptors [3,4], while 6,7-dialkyl (alkoxy, halogeno or cyano) substituted 5-nitroquinoxalines are active as glycine receptor antagonists [5]. A series of condensed quinoxalines have been patented as anticancer compounds [6].

Substituted quinoxalines of different types are usually prepared by: (1) condensation reactions of the corresponding *ortho*-phenylenediamines with 1,2-dioxo compounds or (2) by electrophilic or nucleophilic substitution in the quinoxaline nucleus. Substituted *ortho*-phenylenediamines are not always readily accessible, so introduction of a substituent into the pyrazine or benzene moiety of quinoxalines is more attractive. Nucleophilic substitution in halonitroquinoxalines has recently been described by J. Nasielski and coworkers [7–11], who have shown that results of the reaction of 5-chloro-6-nitroquinoxaline with nucleophiles depend on the nature of the nucleophilic reagents [7]. Thus, the reaction of 5-chloro-6-nitroquinoxaline with piperidine results in substitution of the chlorine atom, while in the reaction with sodium methoxide two products are formed, i.e. 5-methoxy-6-nitroquinoxaline and of 5-chloro-6-methoxyquinoxaline (5%). The reaction of 5-chloro-6-nitroquinoxaline with *para*-thiocresol affords 5,6-diarylthio substituted quinoxaline as the only product [8]. Amination of 6-nitro-7-chloro (bromo, iodo) quinoxalines with hydroxyl-amine in the presence of sodium methoxide gave the corresponding 5-amino derivatives, while amination of 6-nitro-7-fluoroquinoxaline under the same conditions was accompanied by the displacement of the 7-fluorine atom with the methoxy group yielding two products, i.e. 5-amino-6-nitro-7-fluoroquinoxaline and 5-amino-7-methoxy-6-nitroquinoxaline (65%) [9–11].

The ability of fluorine atoms in 6,7-difluoroquinoxaline to undergo nucleophilic displacement reactions has not previously been studied, although an enhanced reactivity of fluoroaromatics towards nucleophiles is a well-recognised phenomenon [12].

2. Results and discussion

In this paper we wish to report the results of our studies on the reactivity of 6,7-difluoroquinoxaline (**1**) and 2-methyl-6,7-difluoroquinoxaline (**9**) towards amines, hydrazine hydrate, aqueous sodium hydroxide and alcoholic solutions of potassium hydroxide.

In the reactions of (**1**) with amines the ability of the fluorine atoms to undergo displacement reactions has been found to depend greatly on the nature of nucleophiles. Highly nucleophilic pyrrolidine and hydrazine hydrate react with (**1**) easily on 1 h reflux in acetonitrile or ethanol affording 6-fluoro-7-pyrrolidino- (**2**) and 6-fluoro-7-hydrazino (**5**) derivatives in high yields (Table 1). Morpholine and thiomorpholine react with (**1**) in acetonitrile (reflux for 3 h) only in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 1 and Table 1). All our attempts to carry out

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Table 1
Yields of products in the reactions of 6,7-difluoroquinoxaline (**1**) with nucleophiles

Nucleophile	Preparative and NMR[a] yields (%)	
	Mono-substitution product	Disubstitution product
Pyrrolidine	(**2**) 87	–
Morpholine	(**3**) 77	–
Thiomorpholine	(**4**) 72	–
Hydrazine hydrate	(**5**) 84	–
Sodium hydroxide	(**6**) 67	–
Methanol	(**7a**) 5[a]	(**8a**) 69 + 3[a]
Ethanol	(**7b**) 5[a]	(**8b**) 65 + 2[a]
n-Propanol	(**7c**) 11[a]	(**8c**) 66[a]
n-Butanol	(**7d**) 10[a]	(**8d**) 68 + 2[a]
iso-Butanol	(**7e**) 7[a]	(**8e**) 58 + 7[a]
iso-Propanol	(**7f**) 18	(**8f**) 54
sec-Butanol	(**7g**) 68	–
2,2,3,3-Tetrafluoropropanol	(**7h**) 44 + 5[a]	(**8h**) 25[a]
2,2,2-Trifluoroethanol	(**7i**) 20[a]	–

[a] Determined by ^{1}H NMR.

substitution of a fluorine atom in (**1**) with aniline, benzylamine or diethylamine (even in the presence of DBU) failed and resulted in isolation of the starting material (**1**). On the other hand, a fluorine atom in (**1**) is easily displaced with the hydroxy group on 1 h reflux in 2 N aqueous sodium hydroxide to give 6-fluoro-7-hydroxyquinoxaline (**6**) in 67% yield (Scheme 1).

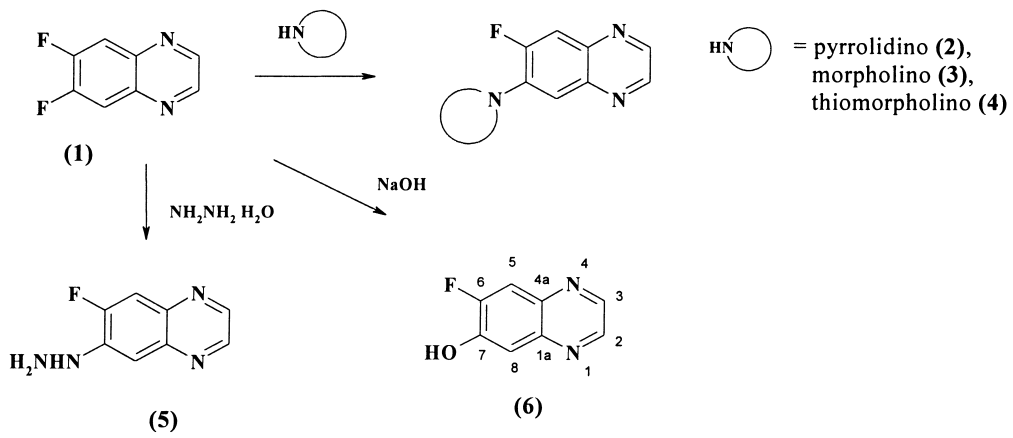
Structures of 6-fluoro-7-substituted quinoxalines (**2–6**) were proved by ^{1}H and ^{19}F NMR. In the ^{1}H NMR spectra of (**2–6**), the doublets of the H5 and H8 atoms are very characteristic due to specific coupling constants ^3J(H5–F6) and ^4J(H8–F6) (Table 2). Two doublets of H2 and H3 atoms of the pyrazine ring demonstrate the coupling constants $^3J(\mathrm{H2-H3}) = 2.1-2.3$ Hz which are typical for pyrazines [13].

The reaction of 6,7-difluoroquinoxaline (**1**) with alcohols (used as solvents) in the presence of potassium hydroxide is controlled mainly by steric hinderance for nucleophilic attack in the substitution of the second fluorine atom (Scheme 2 and Table 1).

Primary linear alcohols (methanol, ethanol, *n*-propanol, *n*-butanol) cause the displacement of both fluorine atoms, yielding 6,7-dialkoxyquinoxalines (**8a–d**) as the major products together with minor 6-fluoro-7-alkoxy-quinoxalines (**7a–d**) formed in 5–11% yields. In the reaction of (**1**) with *iso*-butanol the yield of the mono-substitution product (**7e**) is in the same range (~7%), the reaction with *iso*-propanol results in a 1:3 mixture of mono- and disubstituted products (**7f**) and (**8f**), while the reaction of (**1**) with sec-butanol affords mainly the mono-substitution product, i.e. 6-fluoro-7-(1-methylpropoxy)quinoxaline (**7g**) in 68% yield. 2,2,3,3-Tetrafluoropropanol, which is less nucleophilic and more bulky as compared with propanol, transforms the substrate into mono- and disubstitution products (**7h**) and (**8h**). The same behaviour occurs for 2,2,2-trifluoroethanol affording only the mono-substitution product (**7i**) in 20% yield (Table 1). The products (**8a–d**), (**7f–h**) and (**8f**) were isolated as individual compounds, while (**7a–d**), (**7e**), (**7i**) and (**8h**) were merely identified from the ^{1}H and ^{19}F NMR spectra (Tables 1 and 2).

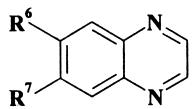
We tried to estimate the transfer of electronic effects of substituents in the pyrazine ring and their influence on the ability of both fluorine atoms in the benzene ring to be displaced by nucleophiles. To do that we studied the reactions of 2-methyl-6,7-difluoroquinoxaline (**9**), bearing the methyl group as the simplest inductive (+I) substituent with pyrrolidine, hydrazine hydrate, aqueous sodium hydroxide and alcohols in the presence of potassium hydroxide.

In contrast to 6,7-difluoroquinoxaline, compound (**9**) reacts with pyrrolidine only in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene, yielding a mixture containing two isomeric mono-substitution products (**10a**) and (**11a**) and the starting material (**9**) (4.5:1:1.7, determined by intensities of H3 resonances at 8.86, 8.59 and 8.45 ppm in the ^{1}H NMR spectra). The reaction of 2-methylquinoxaline (**9**) with hydrazine hydrate is also non-regio-selective and results in two isomeric hydrazino derivatives (**10b**) and (**11b**)



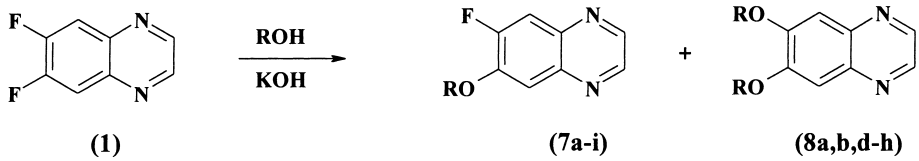
Scheme 1

Table 2
^{1}H NMR spectral data for 6,7-disubstituted quinoxalines in DMSO-d_6



Compound	R6	R7	Chemical shifts (δ) (ppm)					Coupling constants (Hz)		
			H2	H3	H5	H8	R^6 (R^7)	^3J(H2–H3)	^4J(H5–F6)	^4J(H8–F6)
(**2**)	F	Pyrrolidino	8.65 d[a]	8.53 d[a]	7.70 d	7.02 d	3.52 (m, 4H, NCH_2), 1.96 (m, 4H, CH_2)	2.0	13.3	9.0
(**3**)	F	Morpholino	8.84 d[a]	8.77 d[a]	7.81 d	7.49 d	3.83 (m, 4H, OCH_2), 3.22 (m, 4H, NCH_2)	2.0	13.7	9.2
(**4**)	F	Thiomorpholino	8.83 d[a]	8.76 d[a]	7.84 d	7.52 d	3.48 (m, 4H, SCH_2), 2.83 (m, 4H, NCH_2)	2.0	12.7	9.1
(**5**)	F	Hydrazino	8.67 d[a]	8.54 d[a]	7.61 d	7.42 d	4.35 (s br, 2H,NH), 3.31 (s br, 1H, NH)	2.0	12.7	9.1
(**6**)	F	OH	8.79 d[a]	8.73 d[a]	7.82 d	7.45 d	11.15 (s, 1H, OH)	2.0	13.3	9.0
(**7a**)	F	OCH_3	8.87 d[a]	8.81 d[a]	7.87 d	7.65 d	4.05 (s, 3H, CH_3)	2.3	11.8	9.0
(**8a**)	OCH_3	OCH_3	8.69 s	8.69 s	7.40 s	7.40 s	3.97 (s, 6H, CH_3)	–	–	–
(**7b**)	F	OC_2H_5	8.84 d[a]	8.78 d[a]	7.87 d	7.46 d	4.26 (dd, 2H, CH_2), 1.35 (t, 3H, CH_3)	2.3	11.9	8.8
(**8b**)	OC_2H_5	OC_2H_5	8.67 s	8.67 s	7.37 s	7.37 s	4.24 (dd, 4H, CH_2), 1.45 (t, 6H, CH_3)			
(**7c**)	F	$O(CH_2)_2CH_3$	8.86 d[a]	8.84 d[a]	7.88 d	7.63 d	4.25 (t, 2H, OCH_2), 1.90 (m, 2H, CH_2), 1.12 (t, 3H, CH_3)	2.14	11.9	8.8
(**8c**)	$O(CH_2)_2CH_3$	$O(CH_2)_2CH_3$	8.67 s	8.67 s	7.37 s	7.37 s	4.11 (t, 4H, OCH_2), 1.90 (m, 4H, CH_2), 1.12 (t, 6H, CH_3)			
(**7d**)	F	$O(CH_2)_3CH_3$	8.85 d[a]	8.80 d[a]	7.73 d	7.63 d	4.15 (t, 2H, OCH_2), 1.67 (m, 4H, CH_2), 0.97 (t, 3H, CH_3)	2.2	11.9	8.9
(**8d**)	$O(CH_2)_3CH_3$	$O(CH_2)_3CH_3$	8.68 s	8.68 s	7.37 s	7.37 s	4.15 (t, 4H, OCH_2), 1.67 (m, 8H, CH_2), 0.97 (t, 6H, CH_3)			
(**7e**)	F	$OCH_2CH(CH_3)_2$	6.82 d[a]	8.75 d[a]	7.86 d	7.70 d	3.67 (d, 2H, OCH_2), 2.20 (m, 1H, CH), 1.35 (d, 6H, CH_3)	2.1	11.7	8.9
(**8e**)	$OCH_2CH(CH_3)_2$	$OCH_2C(CH_3)_2$	8.66 s	8.66 s	7.35 s	7.35 s	3.98 (d, 4H, OCH_2), 2.25 (m, 2H, CH), 1.10 (d, 12H, CH_3)			
(**7f**)	F	$OCH(CH_3)_2$	8.85 d[a]	8.79 d[a]	7.85 d	7.64 d	5.0 (m, 1H, CH), 1.46 (d, 6H, CH_3)	2.1	11.7	8.8
(**8f**)	$OCH(CH_3)_2$	$OCH(CH_3)_2$	8.67 s	8.67 s	7.40 s	7.40 s	4.82 (m, 2H, CH), 1.37 (d, 12H, CH_3)			
(**7g**)	F	$OCH(CH_3)CH_2CH_3$	8.86 d[a]	8.80 d[a]	7.87 d	7.66 d	4.75 (m, 1H, CH), 1.80 (m, 2H, CH_2), 1.33 (d, 3H, CH_3), 1.07 (t, 3H, CH_3)	2.2	11.8	8.9
(**7h**)	F	$OCH_2(CF_2)_2H$	8.90 d[a]	8.87 d[a]	7.95 d	7.90 d	6.65 (m, 1H, CH), 4.95 (m, 2H, CH_2)	1.8	11.6	8.9
(**8h**)	$OCH_2(CF_2)_2H$	$OCH_2(CF_2)_2H$	8.80 s	8.80 s	7.72 s	7.72 d	6.60 (m, 2H, CH), 4.85 (m, 4H, CH_2)			
(**7i**)	F	OCH_2CF_3	8.91 d[a]	8.86 d[a]	7.96 s	7.89 s	5.12 (m, 2H, CH_2)	1.8	11.6	8.9

[a] The assignments might be interchanged.



(1) (7a-i) (8a,b,d-h)

Scheme 2. R = methyl (a); ethyl (b); *n*-propyl (c); *n*-butyl (d); *iso*-butyl (e); *iso*-propyl (f); sec-butyl (g); 2,2,3,3-tetrafluropropyl (h); 2,2,2-trifluoroethyl (i).

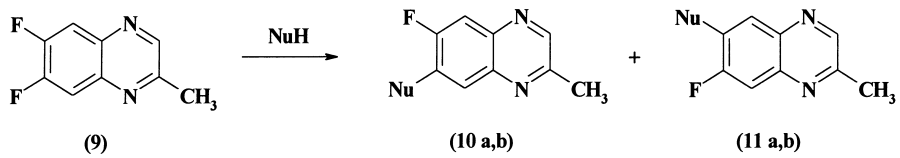
(6:1, according to the ^{1}H NMR spectra, see Table 3 and Scheme 3).

Heating of (**9**) in aqueous 2N sodium hydroxide resulted in no reaction, however treatment of (**9**) with alcoholic solutions of potassium hydroxide gave mono- and disubstitution products (Scheme 4).

The reaction of (**9**) with ethanol yielded isomeric monosubstitution products (**12a**) and (**13a**) ca. 6:1 (87% overall yield) and diethoxy derivative (**14a**) (13% yield). The reaction of (**9**) with 2,2,3,3-tetrafluoropropanol gave monosubstitution product (**12b**) in 40% yield, while 2,2,2-trifluoroethanol did not react with the substrate (**9**).

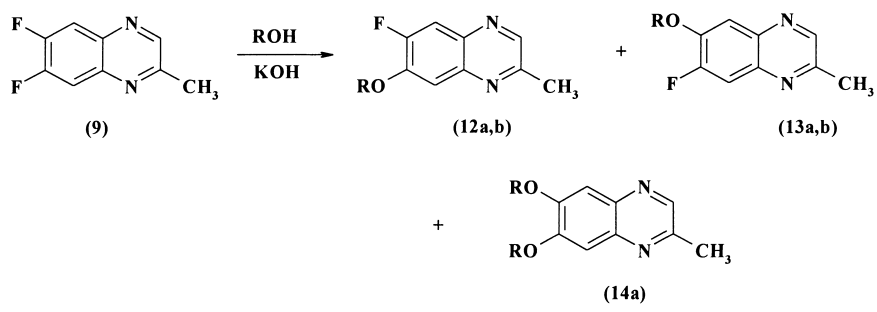
These experimental data indicate that C6 and C7 carbon atoms in 2-methyl-6,7-difluoroquinoxaline (**9**) differ significantly towards nucleophilic attack: the fluorine F7 is more easily displaced by nucleophiles than F6, yielding predominantly 6-fluoro-7-alkoxy substituted 2-methylquinoxalines. Evidence for the structure of (**12a**) was provided by ^{13}C NMR spectra (Table 4). Two resonances, C2 and C3, in the ^{13}C NMR spectrum of 2-methyl-6,7-difluoroquinoxaline (**9**) can be easily distinguished ($^{1}J_{C3-H3}$ = 181.8 Hz). The feature of this system is the existence of long-range couplings ^{6}J(C2–F6) and ^{6}J(C3–F7) (3.2 Hz both), while neither ^{5}J(C3–F6) nor ^{5}J(C2–F7) are observed in the spectra (Table 4). The latter is also substantiated by the ^{13}C NMR spectra of 2-methyl-6-fluoro-7-ethoxyquinoxaline (**12a**): the coupling ^{6}J(C2–F6) is just the same (3.2 Hz) with no coupling between C3 and F6 (Table 4 and Scheme 5). Another important feature of the ^{13}C NMR spectrum of (**12a**) is that the carbon C4a is coupled with both H3 and F6: ^{3}J(C4a−H3) = 10.8 and ^{3}J(C4a−F6) = 11.8 Hz, which enable us to make unequivocal assignments of the ring junction carbon resonances as well as to establish the position of substituents in the benzene ring (Scheme 5). It should be noted that similar values for ^{3}J(C4a–F6) have been measured in the ^{13}C NMR spectra of a number of 6-fluoroquinoxalines, such as 6-fluoro-7-morpholinoquinoxaline (12.0 Hz), 6-fluoro-7-thiomorpholinoquinoxaline (11.3 Hz), and 1-ethyl-6-fluoro-7-morpholinoquinoxalinium tetrafluoroborate (13.0 Hz). The evidence for the structure of the latter salt has been obtained by X-ray analysis [14].

In conclusion, it is worth to note that when using nucleophilic displacement reactions for structural modifications of 6,7-difluoroquinoxalines, one should realise that these reactions are rather sensitive to both electronic effects of



(9) (10 a,b) (11 a,b)

Scheme 3. Nu = pyrrolidino (a); hydrazino (b).

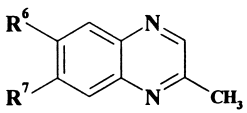


(9) (12a,b) (13a,b) (14a)

R= ethyl (a), 2,2,3,3-tetrafluoropropyl (b)

Scheme 4. R = ethyl (a); 2,2,3,3-tetrafluoropropyl (b).

Table 3
^{1}H NMR spectral data for 2-methyl-6,7-disubstituted quinoxalines in DMSO-d_6



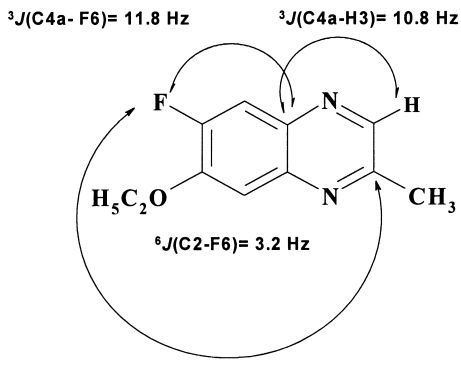
Compound	R6	R7	Chemical shifts (δ) (ppm)					Coupling constants (Hz)			
			C2–CH_3	H3	H5	H8	R^6 (R^7)	^3J (H5–F6)	^4J (H8–F6)	^4J (H5–F7)	^4J (H8–F7)
(**9**)	F	F	2.73	8.68	7.81[a]	7.72[a]		11.1	8.0	7.6	11.2
(**10a**)	F	Pyrrolidino	2.70	8.59	7.55	6.92	3.49 (m, 4H, NCH_2), 1.97 (m, 4H, CH_2)	14.9	9.5	–	–
(**11a**)	Pyrrolidino	F	2.67	8.45	7.54	6.98	3.25 (m, NCH_2), 2.46 (m, CH_2)	–	–	14.9	9.5
(**10b**)	F	$NHNH_2$	2.60	8.45	7.54	7.36	4.30 (br, s, NH), 3.30 (br, s, NH),	12.7	8.9	–	–
(**11b**)	$NHNH_2$	F	2.51	8.59	7.50	7.42	4.30 (br, s, NH), 3.30 (br, s, NH),	–	–	13.0	8.8
(**12a**)	F	OC_2H_5	2.65	8.76	7.81	7.63	4.24 (dd, 2H, CH_2), 1.45 (t, 3H, CH_3)	11.3	7.6	–	–
(**13a**)	OC_2H_5	F	2.66	8.75	7.77	7.53	4.44 (dd, 2H, CH_2), 1.43 (t, 3H, CH_3)	–	–	8.8	11.9
(**12b**)	F	$OCH_2(CF_2)_2H$	2.66	8.76	7.87	7.78	6.62 (m, CH), 4.86 (m, CH_2)	11.6	9.2	–	–
(**13b**)	$OCH_2(CF_2)_2H$	F	2.68	8.80	7.89	7.80	6.62 (m, CH), 4.86 (m, CH_2)	–	–	9.1	11.6
(**14a**)	OC_2H_5	OC_2H_5	2.61	8.58	7.32	7.29	4.44 (dd, 4H, CH_2), 1.43 (t, 6H, CH_3)	–	–	–	–

[a] The assignments might be interchanged.

Table 4
^{13}C NMR spectral data for some quinoxalines in $CDCl_3$

Characteristics		Compounds		
δ (ppm)	^{n}J (Hz)	**7h**	**9**	**12a**
C2		144.56	154.03	152.87
	^{1}J(C2–H2)	183.1	–	–
	^{2}J(C2–H3)	11.2	10.0	10.2
	^{6}J(C2–F6)	3.1	3.2	3.2
C3		144.03	145.97	143.85
	^{1}J(C3–H3)	183.4	181.8	181.1
	^{2}J(C3–H2)	11.3	–	–
	^{6}J(C3–F7)		3.2	–
C5		114.08	114.78[a]	112.96
	^{1}J(C5–H5)	167.2	167.7	165.6
	^{2}J(C5–F6)	18.2	17.1	18.5
	^{3}J(C5–F7)	–	1.7	–
	^{4}J(C5–H8)	–	1.5	–
C6		154.05	151.58	153.96
	^{1}J(C6–F6)	258.1	255.2	255.3
	^{2}J(C6–H5)	6.0	6.0	5.9
	^{3}J(C6–F7)	–	16.2	–
	^{4}J(C6–H8)	10.1	9.0	10.2
C7		148.49	152.29	150.36
	^{1}J(C7–F7)	–	256.2	–
	^{2}J(C7–H8)	[b]	6.1	[b]
	^{2}J(C7–F6)	14.5	15.9	[b]
	^{3}J(C7–H5)	[b]	9.1	[b]
C8		110.54	114.33[a]	108.64
	^{1}J(C8–H8)	164.4	167.8	162.5
	^{2}J(C8–F7)	–	17.2	–
	^{3}J(C8–F6)	2.0	1.6	2.9
	^{4}J(C8–H5)	–	1.5	–
C1a		140.83	139.35	140.37
	^{2}J(C1a–H8)	3.2	[b]	2.9
	^{3}J(C1a–H2)	9.8	–	–
	^{3}J(C1a–F7)	–	10.9	–
	^{3}J(C1a–H5)	6.5	[b]	6.5
C4a		139.53	138.01	136.39
	^{2}J(C4a–H5)	2.9	[b]	2.7
	^{3}J(C4a–H3)	11.2	[b]	10.8
	^{3}J(C4a–F6)	11.5	12.3	11.8
	^{3}J(C4a–H8)	6.4	[b]	6.7
Others			22.34 (CH_3)	22.38 (CH_3), 14.32, 64.81 (OC_2H_5)

[a] The assignments might be interchanged.
[b] Difficult to measure due to overlap of multiplets.



Scheme 5

substituents which are present even in the pyrazine ring as well as to nucleophilic character and effective volume of the reagents.

3. Experimental

Melting points are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solutions (1–5 wt.%) using a Bruker WP-80 (80 MHz for ^{1}H, 75 MHz for ^{19}F) and a Bruker DRX-500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) spectrometers. Chemical shifts are given in ppm and were calculated for proton and carbon spectra relative to

the solvent signals used as the internal standards: $CDCl_3$ ($\delta_H = 7.240$, $\delta_C = 76.900$), DMSO-d_6 ($\delta_H = 2.500$, $\delta_C = 39.500$), whereas fluorine chemical shifts were determined by using addition of hexafluorobenzene as the internal standard ($\delta_F = 0.000$). Fluorine resonances were taken from proton coupled spectra.

3.1. Preparation of 6-fluoro-7-pyrrolidinoquinoxaline (2)

Pyrrolidine (284 mg; 0.33 cm^3; 0.004 mol) was added to a solution of 6,7-difluoroquinoxaline (**1**) (332 mg; 0.002 mol) in acetonitrile (5 cm^3) and the mixture was refluxed for 1 h, cooled to room temperature and poured into water (20 cm^3). The precipitate was separated by filtration and recrystallised from 50% aqueous ethanol to give 6-fluoro-7-pyrrolidinoquinoxaline (**2**), (380 mg; 87%) mp 88–89°C. ^{16}F NMR (DMSO): δ, −117.95 (dd, F6, J = 13.3 and 9.0 Hz) ppm.

	C	H	N
Calculated for $C_{12}H_{12}FN_3$	66.34	5.57	19.34
Found	66.45	5.68	19.03

3.2. Preparation of 6-fluoro-7-morpholinoquinoxaline (3)

Morpholine (390 mg; 0.3 cm^3; 0.004 mol) was added to a solution of 6,7-difluoroquinoxaline (**1**) (332 mg; 0.002 mol) and DBU (610 mg; 0.6 cm^3; 0.002 mol) in acetonitrile (5 cm^3) and the reaction mixture was refluxed for 3 h, cooled to room temperature and treated with acetic acid to adjust pH 6–7 and extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent gave a solid which was recrystallised from water to give 6-fluoro-7-morpholinoquinoxaline (**3**), (360 mg; 77%) mp 103–104°C (lit. mp 101–102°C [14]. ^{19}F NMR (DMSO): δ, −116.18 (dd, F6, J = 13.7 and 9.2 Hz) ppm.

	C	H	N
Calculated for $C_{12}H_{12}FN_3O$	61.79	5.19	18.02
Found	61.76	5.20	18.20

3.3. Preparation of 6-fluoro-7-thiomorpholinoquinoxaline (4)

Thiomorpholine (412 mg; 0.4 cm^3; 0.04 mol) was added to a mixture of 6,7-difluoroquinoxaline (**1**) (332 mg; 0.002 mol) and DBU (610 mg; 0.6 cm^3; 0.02 mol) in acetonitrile (5 cm^3) and the reaction mixture was refluxed for 5 h, cooled to room temperature and poured into water (20 cm^3). The crystalline precipitate was isolated by filtration. Recrystallisation from 50% aqueous ethanol gave 6-fluoro-7-thiomorpholinoquinoxaline (**4**), (360 mg; 72%) mp 111–113°C. ^{19}F NMR (DMSO): δ, −131.5 (dd, F6 J = 12.7 and 9.1 Hz) ppm.

	C	H	N
Calculated for $C_{12}H_{12}FN_3S$	57.81	4.85	16.85
Found	57.49	4.69	16.85

3.4. Preparation of 6-fluoro-7-hydrazinoquinoxaline (5)

6,7-Difluoroquinoxaline (**1**) (332 mg; 0.002 mol) was added to a solution of hydrazine hydrate (98%) (0.6 ml; 0.012 mol) in ethanol (5 cm^3) and the reaction mixture was refluxed for 0.5 h to produce yellow crystals. The mixture was cooled to room temperature, and the crystals were isolated by filtration followed by recrystallisation from ethanol to give 6-fluoro-7-hydrazinoquinoxaline (**5**), (300 mg; 84%) mp 225°C (decomp.). ^{19}F NMR (DMSO): δ, −125.8 (ddd, F6, JF–H = 12.7 and 9.1 Hz, JF−NH = 1.8 Hz) ppm.

	C	H	N
Calculated for $C_8H_7FN_4$	53.93	3.96	31.45
Found	53.72	4.11	31.60

3.5. Preparation of 6-fluoro-7-hydroxyquinoxaline (6)

6,7-Difluoroquinoxaline (**1**) (1.66 g; 0.01 mol) was added to a 2N solution of NaOH (10 cm^3), the reaction mixture was refluxed for 1 h, cooled to room temperature, and treated with acetic acid to adjust pH to 6–7. The precipitate obtained was separated by filtration. Recrystallisation from ethanol gave 6-fluoro-7-hydroxyquinoxaline (**6**), (1.1 g; 67%) mp 220–230°C (decomp.). ^{19}F NMR (DMSO): δ, −127.0 (dd, F6, J = 13.3 and 9.0 Hz) ppm.

	C	H	N
Calculated for $C_8H_5FN_2O$	58.54	3.07	17.07
Found	57.86	3.01	16.90

3.6. Reaction of 6,7-difluoroquinoxaline (1) with alcohols in the presence of potassium hydroxide

3.6.1. Methanol

6,7-Difluoroquinoxaline (**1**) (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in methanol (60 cm^3) and the reaction mixture was refluxed for 1 h. The solvent was distilled off and the solid residue was suspended in cold water (20 cm^3), filtered off and dried. Recrystallisation from acetic acid gave 6,7-dimethoxyquinoxaline (**8a**), (4.3 g; 69%) mp 148–149°C (lit. mp 150–151°C [15]).

	C	H	N
Calculated for $C_{10}H_{10}N_2O_2$	63.15	5.30	14.73
Found	63.29	5.36	14.84

The mother liquor was evaporated to dryness to give a solid (0.45 g) containing additional 6-fluoro-7-methoxyquinoxaline (**7a**) and 6,7-dimethoxyquinoxaline (**8a**) in the ratio 1.5:1 (^{1}H NMR). Overall yields of (**7a**) and (**8a**) are given in Table 1. ^{19}F NMR of (**7a**) (DMSO): δ, −128.55 (dd, F6, J = 11.8 and 8.9 Hz) ppm.

3.6.2. Ethanol

6,7-Difluoroquinoxaline (**1**), (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in ethanol (60 cm^3) and the reaction mixture was refluxed for 1 h. Cooling to room temperature resulted in a solid which was isolated by filtration. Recrystallisation from acetonitrile (20 cm^3) gave 6,7-diethoxyquinoxaline (**8b**), (4.7 g; 65%) mp 125–126°C.

	C	H	N
Calculated for $C_{12}H_{14}N_2O_2$	66.03	6.47	12.80
Found	66.45	6.68	13.03

The mother liquor was evaporated to dryness to give a solid (0.55 g) containing 6-fluoro-7-ethoxyquinoxaline (**7b**) and 6,7-diethoxyquinoxaline (**8b**) in the ratio 2.5:1 (from ^{1}H NMR spectra). Overall yields of (**7b**) and (**8b**) are given in Table 1. ^{19}F NMR of (**7b**) (DMSO): δ, −126.95 (dd, F6, $J = 11.8$ and 8.7 Hz) ppm.

3.6.3. n-Propanol

6,7-Difluoroquinoxaline (**1**) (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in *n*-propanol (60 cm^3). Evaporation of the solvent to dryness left a solid which was suspended in a cold water (20 cm^3), filtered off and dried. Recrystallisation from 30% ethanol gave a mixture of 6-fluoro-7-propoxyquinoxaline (**7c**) and 6,7-dipropoxyquinoxaline (**8c**) in the ratio 1:6 (from ^{1}H NMR spectra). Yields of (**7c**) and (**8c**) are given in Table 1. ^{19}F NMR of (**7c**) (DMSO): δ, −127.35 (dd, F6, $J = 11.8$ and 8.0 Hz) ppm.

3.6.4. n-Butanol

6,7-Difluoroquinoxaline (**1**) (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in *n*-butanol (60 cm^3) and the reaction mixture was refluxed for 1 h. Evaporation of the solvent under reduced pressure left a solid, which was suspended in cold water (20 cm^3), filtered off and dried. Recrystallisation from acetonitrile gave 6,7-dibutoxyquinoxaline (**8d**), (6.2 g; 68%) mp 70–71°C (lit. mp 65–67°C [16]).

	C	H	N
Calculated for $C_{16}H_{22}N_2O_2$	70.04	8.08	10.21
Found	69.96	8.26	10.20

The mother liquor was evaporated to dryness to give a solid (1.3 g) containing 6-fluoro-7-ethoxyquinoxaline (**7d**) and 6,7-diethoxyquinoxaline (**8d**) in the ratio 5:1 (from ^{1}H NMR spectra). Overall yields of (**7d**) and (**8d**) are given in Table 1. ^{19}F NMR (DMSO): δ, −127.18 (dd, F6, $J = 11.8$ and 8.9 Hz) ppm.

3.6.5. iso-Butanol

6,7-Difluoroquinoxaline (**1**) (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in *iso*-butanol (60 cm^3) and the reaction mixture was refluxed for 1 h. Evaporation of the solvent to dryness left a solid which was suspended in cold water (20 cm^3), filtered off and dried. Recrystallisation from ethanol gave 6,7-di(2-methylpropoxy)quinoxaline (**8e**), (5.3 g; 58%) mp 57–58°C.

	C	H	N
Calculated for $C_{16}H_{22}N_2O_2$	70.04	8.08	10.21
Found	69.86	8.00	10.14

The mother liquor was evaporated to dryness to give a solid (1.3 g) containing additional 6-fluoro-7-(2-methylpropoxy)quinoxaline (**7e**) and 6,7-di(2-methylpropoxy)quinoxaline (**8e**) in the ratio 1:1 (from ^{1}H NMR spectra). Overall yields of (**7e**) and (**8e**) are given in Table 1.

3.6.6. iso-Propanol

6,7-Difluroquinoxaline (**1**) (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in *iso*-propanol (60 cm^3) and the reaction mixture was refluxed for 1 h. Evaporation of the solvent under reduced pressure left a solid which was suspended in cold water (20 cm^3), filtered off, dried and recrystallised from acetonitrile to give 6-fluoro-7-(*iso*-propoxy)quinoxaline (**7f**), (1.2 g; 18%) mp 97–98°C.

	C	H	N
Calculated for $C_{14}H_{18}N_2O_2$	68.27	7.36	11.38
Found	68.45	7.68	11.70

^{19}F NMR of (**7f**) (DMSO): δ, −126.35 (dd, F6, $J = 11.8$ and 8.9 Hz) ppm.

Evaporation of acetonitrile from the mother liquor left a solid which was recrystallised from aqueous 50% ethanol to give 6,7-di(*iso*-propoxy)quinoxaline (**8f**), (4.4 g; 54%) mp 63–64°C.

	C	H	N
Calculated for $C_{14}H_{18}N_2O_2$	68.27	7.36	11.38
Found	68.45	7.68	11.70

3.6.7. sec-Butanol

6,7-Difluoroquinoxaline (**1**) (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in sec-butanol (60 cm^3) and the reaction mixture was refluxed for 1 h. Evaporation of the solvent left a solid which was suspended in cold water (20 cm^3), filtered off, dried and recrystallised from aqueous 50% ethanol to give 6-fluoro-7-(1-methylpropoxy)quinoxaline (**7g**), (4.8 g; 68%) mp 51–52°C.

	C	H	N
Calculated $C_{12}H_{13}FN_2O$	65.44	5.95	12.73
Found	65.52	5.83	12.78

^{19}F NMR of (**7g**) (DMSO): δ, −127.35 (dd, F6, $J = 11.8$ and 8.9 Hz) ppm.

3.6.8. 2,2,3,3-Tetrafluoropropanol

6,7-Difluoroquinoxaline (**1**) (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in 2,2,3,3-tetrafluoropropanol (60 cm^3) and the reaction mixture was refluxed for 1 h. Evaporation of the solvent left a solid which was recrys-

tallised from *iso*-propanol to give 6-fluoro-7-(2,2,3,3-tetrafluoropropoxy)quinoxaline (**7h**), (4.0 g; 44%), mp 125–126°C.

	C	H	N
Calculated for $C_{11}H_7F_5N_2O$	49.33	3.10	9.59
Found	49.52	3.23	9.45

^{19}F NMR (DMSO): δ, −126.35 (dd, 1F, F6, J = 11.6, 8.9 Hz), −124.85 (br, 2F), −138.65 (dd, 1F), −139.32 (br, 1F) ($CH_2CF_2CF_2H$) ppm.

The mother liquor was evaporated to dryness to give a solid (3.4 g) containing 6-fluoro-7-(2,2,3,3-tetrafluoropropoxy)quinoxaline (**7h**) and 6,7-di(2,2,3,3-tetrafluoropropoxy)quinoxaline (**8h**) in the ratio 1:5 (from ^{1}H and ^{19}F NMR spectra).

3.6.9. 2,2,2-Trifluoroethanol

6,7-Difluoroquinoxaline (**1**) (5 g; 0.33 mol) was added to a solution of KOH (5 g; 0.89 mol) in 2,2,2-trifluoroethanol (60 cm^3) and the reaction mixture was refluxed for 1 h, evaporated to dryness to gave solid, containing starting 6,7-difluoroquinoxaline (**1**) and 6-fluoro-7-(2,2,2-trifluoroethoxy)quinoxaline (**7i**) in the ratio 4:1 (from ^{1}H and ^{19}F NMR spectra). ^{19}F NMR (DMSO): δ, −127.48 (dd, F6, J = 11.6, 8.8 Hz), −139.25 (t, 3F, CF_3) ppm (**7i**).

*3.7. Preparation of 6,7-difluoro-2-methylquinoxaline (**9**)*

4,5-Difluoro-1,2-phenylenediamine (10 g; 0,069 mol) was added to a solution of *iso*-nitrosoacetone (5 g; 0.07 mol) in ethanol (20 cm^3) and the reaction mixture was refluxed for 15 min, cooled to room temperature and poured into water (50 cm^3). The precipitate was filtered off and recrystallised from aqueous 33% ethanol to give 6,7-difluoro-2-methylquinoxaline (**9**), (7.2 g; 60%), mp 125–126°C. ^{19}F NMR (DMSO): δ, −135.25 (ddd, J = 34.2, 11.1 and 8.0 Hz), −144.35 (ddd, J = 34.2, 11.2 and 7.6 Hz) ppm.

	C	H	N
Calculated for $C_9H_6F_2N_2$	60.00	3.36	15.55
Found	60.05	3.33	15.60

3.8. Reactions of 6,7-difluoro-2-methylquinoxaline with nucleophiles

3.8.1. Pyrrolidine

Pyrrolidine (284 mg; 0.33 cm^3; 0.004 mol) was added to a solution of 6,7-difluoro-2-methylquinoxaline (**9**) (100 mg; 0.00056 mol) and DBU (100 mg; 0.1 ml; 0.0006 mol) in acetonitrile (2 cm^3) and the reaction mixture was refluxed for 3 h. Evaporation of the solvent to dryness left a solid, which was recrystallised from water to give a mixture of the starting compound, 6-fluoro-7-pyrrolidino-2-methylquinoxaline (**10a**) and 6-pyrrolidino-7-fluoro-2-methylquinoxaline (**11a**) in the ratio 1:4.5:1.7 (from ^{1}H and ^{19}F NMR spectra). ^{19}F NMR (DMSO): δ, −120.18 (br) (**10a**), −118.43 (br) (**11a**) ppm.

3.8.2. Hydrazine hydrate

6,7-Difluoro-2-methylquinoxaline (**9**) (300 mg; 0.00168 mol) was added to a solution of hydrazine hydrate (98%) (0.6 ml; 0.012 mol) in ethanol (5 cm^3) and the mixture was refluxed for 2 h to form yellow crystals. The mixture was cooled to room temperature and the crystalline precipitate was filtered off and recrystallised from ethanol to give a mixture of 6-fluoro-7-hydrazino-2-methylquinoxaline (**10b**) and 6-hydrazino-7-fluoro-2-methylquinoxaline (**11b**) in the ratio 6:1 (from ^{1}H and ^{19}F NMR spectra) (250 mg; 78%).

	C	H	N
Calculated for $C_9H_9FN_4$	56.24	4.72	29.15
Found	56.72	4.51	29.45

^{19}F NMR (DMSO): δ, −127.85 (br) (**10b**), −126.48 (br) (**11b**) ppm.

3.8.3. Ethanol

6,7-Difluoro-2-methylquinoxaline (**9**) (0.5 g; 0.0028 mol) was added to a solution of KOH (0.6 g; 0.011 mol) in ethanol (10 cm^3) and the reaction mixture was refluxed for 1 h. Evaporation of the solvent left a solid which was recrystallised from 30% ethanol to give 6-fluoro-7-ethoxy-2-methylquinoxaline (**12a**), (300 mg; 49%) mp 111–112°C.

	C	H	N
Calculated for $C_{11}H_{11}FN_2O$	64.07	5.38	13.58
Found	64.25	5.58	13.43

^{19}F NMR (DMSO): δ, −129.13 (dd, F6, J = 11.6 and 8.9 Hz) ppm.

The mother liquor was evaporated to dryness to give a solid (100 mg), containing an additional amount of 6-fluoro-7-ethoxy-2-methylquinoxaline (**12a**), 6-ethoxy-7-fluoro-2-methylquinoxaline (**13a**) and 6,7-diethoxy-2-methylquinoxaline (**14a**) in the ratio 2:1:1 (from ^{1}H and ^{19}F NMR spectra). ^{19}F NMR (DMSO): δ, −129.13 (dd, F6, J = 11.6 and 8.9 Hz) (**12a**), 129.13 (br) (**13a**) ppm.

3.8.4. 2,2,3,3-Tetrafluoropropanol

6,7-Difluoro-2-methylquinoxaline (**9**) (0.5 g; 0.003 mol) was added to a solution of KOH (0.6 g; 0.011 mol) in 2,2,3,3-tetrafluoropropanol (10 cm^3) and the reaction mixture was refluxed for 1 h. Evaporation of the solvent left a solid which was crystallised from 30% ethanol to give the product (400 mg) containing 6,7-difluoro-2-methylquinoxaline (**9**), 6-fluoro-7-(2,2,3,3-tetrafluoropropoxy)-2-methylquinoxaline (**12b**) and 6-(2,2,3,3-tetrafluoropropoxy)-7-fluoro-2-methylquinoxaline (**13b**) in the ratio 4:2:1 (from ^{1}H and ^{19}F NMR spectra). ^{19}F NMR (DMSO): δ, −129.35 (br, t) (**12b**), −127.75 (br) (**13b**) ppm.

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