2-Polyfluoroalkylchromones

10.* Synthesis of regioisomeric 3-(2-hydroxyaryl)-5-polyfluoroalkyl- and 5-(2-hydroxyaryl)-3-polyfluoroalkylisoxazoles and determination of their structures by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy

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The reactions of 2-hydroxy-2-polyfluoroalkylchroman-4-ones with hydroxylamine yield, through Δ^2-isoxazolines as intermediate products, 3-(2-hydroxyaryl)-5-polyfluoroalkylisoxazoles. Analogous reactions with 2-polyfluoroalkylchromones afford β-diketone monooximes, which in an acidic medium undergo cyclodehydration into 5-(2-hydroxyaryl)-3-polyfluoroalkylisoxazoles. The structures of regioisomeric 3- and 5-polyfluoroalkylisoxazoles were determined using ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy.

Key words: 2-hydroxy-2-polyfluoroalkylchroman-4-ones, 2-polyfluoroalkylchromones, hydroxylamine hydrochloride, 5-hydroxy-5-polyfluoroalkyl-Δ^2-isoxazolines, 5-polyfluoroalkylisoxazoles, β-diketone monooximes, 3-polyfluoroalkylisoxazoles; ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy.

In recent years, much attention has been given to the development of efficient methods for the synthesis of trifluoromethylated heterocycles,[2] which are of interest as potential bioactive compounds.[3] However, information on the regiocontrolled syntheses that afford regioisomeric CF_3-containing heterocycles, including isoxazoles, in good yields is very scarce. Isoxazoles play an important part in medicinal and agricultural chemistry,[4] and the reductive opening of the isoxazole ring affords various polyfunctional compounds.[5,6] It is known[5,7] that the reactions of hydroxylamine with β-diketones bearing a fluorinated substituent at one of the carbonyl groups and with ethers of the enol form of β-diketones (β-alkoxyvinyl trifluoromethyl ketones)[8—10] give, through the formation of 5-hydroxy-5-polyfluoroalkyl-Δ^2-isoxazolines, 5-R^F-isoxazoles, which make them quite accessible compounds, as distinct from their 3-R^F-regioisomers. In addition, 5-trifluoromethylisoxazoles have been synthesized in two steps from perfluoroethyl iodide, monosubstituted acetylenes, and hydroxylamine,[11] while 5-perfluoroalkylisoxazoles, by the reactions of fluorine-containing β-dicarbonyl compounds with nitrile *N*-oxides.[12] Analogous reactions of nitrile *N*-oxides with fluorinated alkynes give a mixture of 4- and 5-perfluoroalkylisoxazoles,[13—16] while those with alkenes yield 5-perfluoroalkylisoxazolines.[16] 3-Trifluoromethyl-Δ^2-isoxazolines and 3-trifluoromethylisoxazoles are obtained by 1,3-dipolar cycloaddition of trifluoroacetonitrile *N*-oxide to alkenes,[17,18] alkynes,[17,18] β-diketones,[19] β-oxo esters,[19] β-acyl pyruvates,[20] and malononitrile.[21] Regioisomeric 3- and 5-trifluoromethylisoxazoles have been synthesized from trifluoroacetylalkynes[22] and a trifluoroacetyl derivative of 4-homoadamantanone,[23] while 3- and 5-trifluoromethyl-Δ^2-isoxazolines, from 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones.[24]

In the present work, the reactions of hydroxylamine with adducts of 2-hydroxyacetophenones and R^FCO_2Et (R^F = CF_3, CF_2CF_2H, and CF_2H) and with 2-polyfluoroalkylchromones obtained from these adducts were studied with the aim of synthesizing regioisomeric 3-(2-hydroxyaryl)-5-polyfluoroalkyl- and 5-(2-hydroxyaryl)-3-polyfluoroalkylisoxazoles. For the first time, we performed comparative analysis of the ^{1}H, ^{19}F, and ^{13}C NMR data for 5-R^F- and 3-R^F-isoxazoles and revealed some of their characteristic spectral features for clearcut distinction between these compounds.

Results and Discussion

Earlier,[25] enol structure **1** has been assigned to adducts of substituted 2-hydroxyacetophenones with ethyl trifluoroacetate; they were shown to react with hydroxylamine to give monooximes **2** containing the oxime group at the aromatic substituent. Later,[26] it was determined

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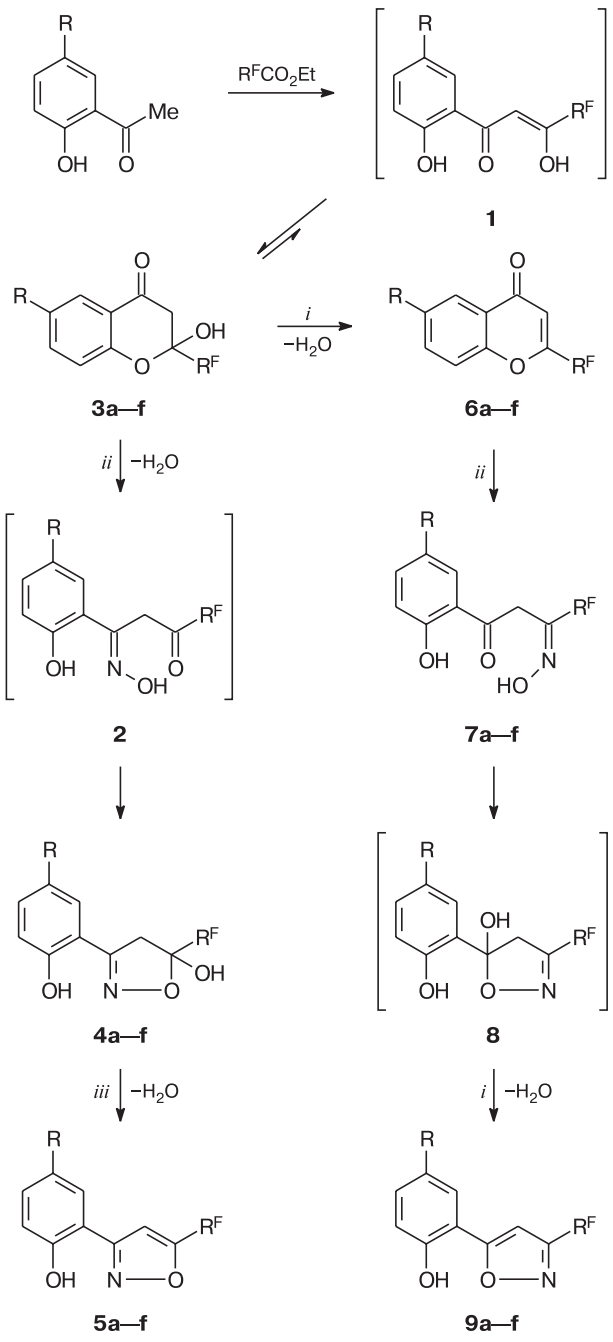
that these adducts have structures of cyclic chromanones **3** both in the crystalline state and in solution. We found that the reactions of hydroxylamine with 2-hydroxy-2-polyfluoroalkylchroman-4-ones **3a—f** (compounds **3c**,**d** containing the $(CF_2)_2H$ group exist in $CDCl_3$ as a mixture of tautomers **1** and **3**), afford 5-R^F-isoxazolines **4** rather than open oximes **2** as believed previously,[25] which is due to a high electrophilicity of the carbonyl C atom bound to the R^F group (Scheme 1). The cyclic structure of compounds **4a—f** was confirmed by ^1H NMR spectra, which show a characteristic AB system of the methylene protons at δ 3.59—3.71 (J_{AB} = 17.7—17.9 Hz) (Table 1). For compounds **4a** and **4e**, the higher-field doublet of the AB system for the *cis*-proton with respect to the R^F group (the proton that is *cis* to the hydroxy group is deshielded more strongly[27]), splits into two quartets ($^4J_{H,F}$ = 1.1 Hz) and two triplets ($^4J_{H,F}$ = 1.5 Hz), respectively.

Isoxazolines **4a—f** are resistant to dehydration; they were converted into 5-R^F-isoxazoles **5a—f** in 59—93% yields only by the reactions with $SOCl_2$ in boiling toluene in the presence of pyridine for 5—10 min. The reaction duration should not be extended because of possible side reactions at the aromatic ring. Attempts at dehydrating compounds **4** both with conc. H_2SO_4 at ~20 °C for a day or at 70 °C for 0.5 h and with several drops of conc. HCl in boiling acetic acid failed. Isoxazolines **4** were recovered upon the dilution of the reaction mixture with ice water.

The reactions of hydroxylamine with 2-polyfluoroalkylchromones **6a—f** obtained by the dehydration of chromanones **3a—f** involve the C(2) atom rather than the carbonyl group, as in the case of the latter. The opening of the pyrone ring gives monooximes **7a—f** (Scheme 1). In these compounds, the oxime group is adjacent to the electron-withdrawing R^F group, which decreases the nucleophilicity of the oxime OH group and stabilizes the open form **7**. Earlier,[24] it was shown that aliphatic analogs of oximes **7** in the crystalline state and in $CDCl_3$ exist as 3-trifluoromethyl-Δ^2-isoxazolines, while in DMSO-d_6 they exist as an equilibrium mixture of the oxime and isoxazoline forms. The ^1H NMR spectra of aromatic oximes **7a—f** in $CDCl_3$ (see Table 1) show only one set of signals corresponding to their open form **7** (a singlet for the CH_2 group appears at δ 4.18—4.26), while the cyclic isoxazoline form **8** was not detected, which is due to a lower reactivity of the carbonyl group conjugated with the aromatic ring (see Ref. 24). The existence of compounds **7a—f** in the open rather than cyclic form was also confirmed by the chemical shifts of signals for the benzene protons in isomeric compounds **4** and **7**. Signals for the most strongly deshielded H(4) and H(6) protons in oximes **7** are shifted downfield by 0.14—0.16 and 0.58—0.63 ppm, respectively, compared to those for isoxazolines **4** (see Table 1).

Scheme 1



	R^F	R		R^F	R
a	CF_3	H	**d**	$(CF_2)_2H$	Me
b	CF_3	Me	**e**	CF_2H	H
c	$(CF_2)_2H$	H	**f**	CF_2H	Me

i. AcOH, HCl; *ii*. $NH_2OH \cdot HCl$, AcONa, EtOH, H_2O; *iii*. $SOCl_2$, PhMe, Py

This can be associated with an anisotropic effect of the C=O group in compounds **7**. The chemical shifts of signals for the H(3) and H(5) protons (whose shielding is

Table 1. ^{1}H NMR and IR spectra of isoxazolines **4a—f** and monooximes **7a—f**

Compound	^{1}H NMR ($CDCl_3$, δ, J/Hz)								IR, ν/cm^{-1}
	CH_3	CH_2	H(3)	H(4)	H(5)	H(6)	OH	R^F	
4a		3.71[a,b] (J = 17.7, Δδ = 0.17)	7.07 (dd, J_o = 8.3, J_m = 0.9)	7.39 (ddd, J_o = 8.3, 7.3, J_m = 1.6)	6.96 (ddd, J_o = 7.8, 7.3, J_m = 0.9)	7.16 (dd, J_o = 7.8, J_m = 1.6)	3.9[c] br.s; 9.1[d] br.s		1580, 1610, 1625, 3350
4b	2.29 s	3.70[a] (J = 17.7, Δδ = 0.17)	6.96 (d, J_o = 8.4)	7.18 (dd, J_o = 8.4, J_m = 1.6)		6.93[e] (d, J_m = 1.0)	3.7[c] br.s; 9.07[d] s		1580, 1610, 1630, 3350
4c		3.70[a] (J = 17.9, Δδ = 0.34)	7.05 (dd, J_o = 8.3, J_m = 1.0)	7.37 (ddd, J_o = 8.3, 7.3, J_m = 1.6)	6.94 (ddd, J_o = 7.8, 7.3, J_m = 1.0)	7.14 (dd, J_o = 7.8, J_m = 1.6)	[f]	6.15 (tt, ^2J = 52.8, ^3J = 5.6)	1570, 1605, 1625, 3345
4d	2.29 s	3.69[a] (J = 17.9, Δδ = 0.35)	6.95 (d, J_o = 8.4)	7.17 (dd, J_o = 8.4, J_m = 1.7)		6.91[e] (d, J_m = 1.4)	3.91[c] s; 9.13[d] s	6.15 (tt, ^2J = 52.8, ^3J = 5.7)	1580, 1610, 1635, 1655, 3200, 3430
4e		3.59[a,g] (J = 17.7, Δδ = 0.21)	7.06 (dd, J_o = 8.4, J_m = 1.0)	7.37 (ddd, J_o = 8.4, 7.0, J_m = 1.6)	6.95 (ddd, J_o = 7.8, 7.0, J_m = 1.0)	7.16 (dd, J_o = 7.8, J_m = 1.6)	3.63[c]; 9.40[d]	5.95 (t, ^2J = 54.9)	1575, 1605, 1620, 3350
4f	2.30 s	3.59[a] (J = 17.7, Δδ = 0.21)	6.95 (d, J_o = 8.4)	7.17 (dd, J_o = 8.4, J_m = 1.9)		6.95[e] s	3.50[c] s; 9.20[d] s	5.94 (t, ^2J = 55.0)	1580, 1610, 1630, 3350
7a		4.24 s	7.02 (dd, J_o = 8.5, J_m = 0.9)	7.53 (ddd, J_o = 8.5, 7.2, J_m = 1.5)	6.95 (ddd, J_o = 8.1, 7.2, J_m = 0.9)	7.74 (dd, J_o = 8.1, J_m = 1.5)	8.51[h] s; 11.68[d] s	−70.8 s[i]	1590, 1625, 1645, 1670, 3350
7b	2.33 s	4.23 s	6.92 (d, J_o = 8.5)	7.33 (dd, J_o = 8.5, J_m = 1.7)		7.51[e] s	8.81[h] s; 11.51[d] s		1575, 1615, 1635, 3280, 3390
7c		4.26 s	7.02 (dd, J_o = 8.5, J_m = 1.0)	7.52 (ddd, J_o = 8.5, 7.1, J_m = 1.4)	6.95 (ddd, J_o = 8.1, 7.1, J_m = 1.0)	7.75 (dd, J_o = 8.1, J_m = 1.4)	8.26[h] s; 11.70[d] s	6.17 (tt, ^2J = 52.8, ^3J = 5.1)	1580, 1635, 1665, 3200, 3450
7d	2.33 s	4.25 s	6.92 (d, J_o = 8.5)	7.33 (dd, J_o = 8.5, J_m = 2.0)		7.52[e] (d, J_m = 1.1)	8.37[h] s; 11.53[d] s	6.17 (tt, ^2J = 52.8, ^3J = 5.1)	1595, 1620, 1640, 1670, 3320
7e		4.20 s	7.02 (dd, J_o = 8.5, J_m = 1.0)	7.52 (ddd, J_o = 8.5, 7.1, J_m = 1.6)	6.95 (ddd, J_o = 8.1, 7.1, J_m = 1.0)	7.79 (dd, J_o = 8.1, J_m = 1.6)	8.15[h] s; 11.78[d] s	6.22 (t, ^2J = 54.5)	1585, 1620, 1645, 3200, 3400
7f	2.33 s	4.18 s	6.92 (d, J_o = 8.5)	7.33 (dd, J_o = 8.5, J_m = 2.0)		7.55[e] (d, J_m = 1.2)	7.86[h] s; 11.59[d] s	6.22 (t, ^2J = 54.5)	1590, 1625, 1645, 3180, 3470

[a] Center of the AB system.
[b] Each signal of the higher-field part of the AB system is split into a quartet with $^4J_{H,F}$ = 1.1 Hz.
[c] A signal for the hemiketal OH proton in DMSO-d_6 appears at δ 8—9.
[d] For the phenolic OH proton.
[e] The broadening of the signal is due to *o*-benzyl splitting with $^4J_{H(6),CH_3} \approx 0.5$ Hz.
[f] Hemiketal and phenolic OH protons were not detected.
[g] Each signal of the higher-field part of the AB system is split into a triplet with $^4J_{H,F}$ = 1.5 Hz.
[h] For the oxime OH proton.
[i] The ^{19}F NMR spectrum with reference to $CFCl_3$.

mainly determined by the effect of the 2-hydroxy substituent) remain virtually the same; therefore, the phenolic OH group is not involved in the ring-chain tautomerism resulting in a chromanone structure of type **3**. It is worth noting that compounds **7a—f** exist in $CDCl_3$ as *E*-isomers (**7a**: ^{19}F NMR, δ: −70.8 (CF_3)). According to the literature data,[28—30] a signal for this group in trifluoromethylated oximes and hydrazones appears at δ −64 to −66 for *Z*-isomers and at δ −67 to −71 for *E*-isomers.

Oximes **7a—f** are dehydrated under milder conditions compared to isoxazolines **4a—f**. Their cyclodehydration in boiling acetic acid with a few drops of conc. HCl gave 3-R^F-isoxazoles **9a—f** in 86—98% yields within 3—5 min. Unlike regioisomeric 5-R^F-isoxazoles **5a—f**, the latter are high-melting substances and insoluble in most organic solvents.

Thus, the direction of the nucleophilic attack changes in passing from chromanones **3** to chromones **6**. This makes it possible to obtain regioisomeric 5- and 3-polyfluoroalkylisoxazoles **5** and **9**. Note that chromanones **3a—c** and chromones **6a—c** regiospecifically react with $NH_2OH \cdot HCl$ to give products **4a—c** and **7a—c**, which are converted into regioisomers **5a—c** and **9a—c**. However, the regioselectivity decreases when passing from trifluoromethyl and tetrafluoroethyl derivatives to difluoromethylchromanones **3e**,**f** and -chromones **6e**,**f**. Thus the reactions of compounds **3e**,**f** with $NH_2OH \cdot HCl$ afford products containing, along with isoxazolines **4e**,**f**, oximes **7e**,**f** (2—3%) (^{1}H NMR data). Chromone **6e** yields a mixture of compounds **7e** and **4e** in the 94 : 6 ratio, while difluoromethylchromone **6f** containing a donor methyl group in position 6 proved to react even less regioselectively, giving isoxazoline **4f** (12%) along with oxime **7f**. The cyclization of compound **7d** yielded a mixture of isoxazole **9d** and chromone **6d** in the 7 : 3 ratio (^{1}H NMR data); this outcome suggests that an alternative reaction direction involving the phenolic OH group and the C=N bond is more pronounced in this case.

The high regioselectivity of the above reactions is characteristic of only 2-polyfluoroalkylchromanones and -chromones since 2-nonsubstituted chromones,[31—33] 2-methylchromones,[32,34] and flavones[35,36] react with hydroxylamine ambiguously to give a complex mixture of products usually including isomeric isoxazoles or one of them. Nonfluorinated analogs of isoxazoles **5** and **9**, namely, 3-(2-hydroxyaryl)-5-methyl- and 5-(2-hydroxyaryl)-3-methylisoxazoles, have been described previously.[32,34,37]

As a rule, the IR spectra of 5-R^F-isoxazoles **5** usually contain two medium-intensity absorption bands at 1590—1630 cm^{-1}, while those of 3-R^F-isoxazoles **9** show three absorption bands at 1580—1620 cm^{-1} (Table 2). Obviously, these data preclude reliable assignment of the compound under study to one or the other series. Unlike the IR spectra of regioisomeric isoxazoles **5** and **9**, their ^{1}H, ^{19}F, and ^{13}C NMR spectra in $CDCl_3$ have a number of characteristic features, which enable one to easily distinguish between these compounds (Tables 2—4). In this respect, for trifluoromethylated isoxazoles ^{19}F NMR spectroscopy proved to be least informative, while ^{13}C NMR spectroscopy was most informative.

^{19}F NMR spectra. The ^{19}F NMR spectra of 5-CF_3-isoxazole **5a** and 3-CF_3-isoxazole **9a** show a signal for the trifluoromethyl group at δ −65.1 (d, $^4J_{F,H}$ = 0.9 Hz) and δ −64.4 (s), respectively. Earlier,[5,22] close values have been reported for 3-phenyl- and 3-hexyl-5-trifluoromethylisoxazoles (δ −65.0) and for 5-hexyl-3-trifluoromethylisoxazole (δ −64.0),[22] although the 5-CF_3-isomers gave no doublet signals for the CF_3 group. In nonsubstituted 5-trifluoromethylisoxazole, a signal for this group appears at δ −64.6 (dd, $^4J_{F,H(4)} \approx {}^5J_{F,H(3)} \approx 1$ Hz),[10] while for disubstituted 5-CF_3-isoxazoles a singlet was observed at δ −63.5 to −64.4.[12,38] Hence, the chemical shift of a signal for the CF_3 group provides no reliable criterion for the distinction between 5- and 3-CF_3-isoxazoles. Whereas a signal for this group in regioisomeric *N*-substituted 5- and 3-CF_3-pyrazoles appears at δ ~−58 and ~−62, respectively,[39] which is used as an argument while proving the structures of trifluoromethylated pyrazoles.[40,41] The constant $^4J_{F,H}$ = 0.8—1.0 Hz can be useful only for 4-nonsubstituted isoxazoles. It should be kept in mind that although the presence of a spin-spin coupling between the H(4) proton and the polyfluoroalkyl F atoms makes it possible to sufficiently strictly classify a compound among 5-R^F-isoxazoles, its absence does not yet indicate that this compound is a 3-R^F-isoxazole.

^{1}H NMR spectra. The H(4) proton of the isoxazole ring gives a quartet ($^4J_{H,F}$ = 0.9 and 0.7 Hz, respectively) in the spectra of 5-CF_3-isoxazoles **5a**,**b** and a triplet ($^4J_{H,F}$ = 1.0 Hz) in the spectra of 5-H$(CF_2)_2$-isoxazoles **5c**,**d**, whereas for 3-R^F-isoxazoles **9a—d** its signal does not split but appears as a singlet. The H(4) proton in difluoromethylisoxazoles **5e**,**f** and **9e**,**f** manifests itself as a singlet at any arrangement of the double bonds in the ring (see Table 2); this is probably due to a decreased population of rotamers in which the H(4) atom and the fluorine atoms are spatially close. This is evidence in favor of the spatial mechanism of ^{1}H...^{19}F spin-spin coupling transfer. In the literature, the H(4) proton in both 5-CF_3-3-Ph-[5,11] and 3-CF_3-5-Ph-isoxazoles[18] is reported to give a singlet; however, we found that a signal for the H(4) proton in 3-phenyl-, 3-styryl-, 3-(2-thienyl)-, and 3-*tert*-butyl-5-CF_3-isoxazoles is split into a quartet with $^4J_{H,F}$ = 0.8—0.9 Hz. A signal for this proton has been described for nonsubstituted 5-CF_3-isoxazole (dq, $^3J_{H,H} \approx {}^4J_{H,F} \approx 1.0$ Hz)[10] and 3-CF_3-isoxazole (d, $^3J_{H,H}$ = 1.8 Hz)[17]. The constants $^4J_{H,F}$ = 0.7—1.0 Hz found for 5-R^F-isoxazoles correlate well with the data for trisubstituted alkenes with geminal alkoxy and trifluoromethyl groups ($^4J_{H,F}$ = 0.7—1.1 Hz, regardless of the configuration of the double bond).[42] It should also be noted that the spectra of compounds **5a** and **9a** in DMSO-d_6 show a singlet for the H(4) proton.

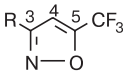
The data in Table 3 indicate that a signal for the H(4) proton in 3-trifluoromethylisoxazole is shielded more strongly ($\Delta\delta_{H(4)}$ = 0.55 ppm) than the corresponding signal for 5-trifluoromethylisoxazole. Apparently, this is

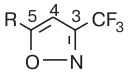
Table 2. ^{1}H NMR and IR spectra of 5-R^F-isoxazoles **5a—f** and 3-R^F-isoxazoles **9a—f**

Compound	^{1}H NMR ($CDCl_3$, δ, *J*/Hz)								IR, ν/cm^{-1}
	CH_3	=CH	H(3)	H(4)	H(5)	H(6)	OH	R^F	
5a		7.13 (q, $^4J_{H,F}$ = 0.9)	7.11 (ddd, J_o = 8.4, J_m = 1.1, J_p = 0.3)	7.40 (ddd, J_o = 8.4, 7.3, J_m = 1.6)	7.01 (ddd, J_o = 7.8, 7.3, J_m = 1.1)	7.51 (ddd, J_o = 7.8, J_m = 1.6, J_p = 0.3)	8.97 s	−65.1[a] (d, $^4J_{F,H}$ = 0.9)	1590, 1610, 1625, 3190
5a[b]		7.72 s	7.06 (dd, J_o = 8.3, J_m = 1.0)	7.39 (ddd, J_o = 8.3, 7.3, J_m = 1.7)	6.95 (ddd, J_o = 7.8, 7.3, J_m = 1.0)	7.75 (dd, J_o = 7.8, J_m = 1.7)	10.46 s		
5b	2.34 s	7.12 (q, $^4J_{H,F}$ = 0.7)	7.01 (d, J_o = 8.4)	7.21 (dd, J_o = 8.4, J_m = 2.0)		7.28[c] (d, J_m = 1.6)	8.77 s		1595, 1625, 3210
5c		7.11 (t, $^4J_{H,F}$ = 1.0)	7.11 (dd, J_o = 8.3, J_m = 1.1)	7.40 (ddd, J_o = 8.3, 7.3, J_m = 1.6)	7.01 (ddd, J_o = 7.8, 7.3, J_m = 1.1)	7.51 (dd, J_o = 7.8, J_m = 1.6)	9.01 s	6.13 (tt, ^2J = 53.1, ^3J = 2.8)	1595, 1630, 3280
5d	2.34 s	7.11 (t, $^4J_{H,F}$ = 1.0)	7.00 (d, J_o = 8.4)	7.20 (dd, J_o = 8.4, J_m = 2.1)		7.30[c] (d, J_m = 2.1)	8.80 s	6.12 (tt, ^2J = 53.1, ^3J = 2.8)	1595, 1635, 3300
5e		7.00 s	7.11 (dd, J_o = 8.4, J_m = 0.9)	7.39 (ddd, J_o = 8.4, 7.1, J_m = 1.5)	7.00 (ddd, J_o = 7.8, 7.1, J_m = 0.9)	7.51 (dd, J_o = 7.8, J_m = 1.5)	9.14 s	6.83 (t, ^2J = 53.6)	1580, 1625, 3160, 3240
5f	2.34 s	6.99 s	7.00 (d, J_o = 8.3)	7.19 (dd, J_o = 8.3, J_m = 1.8)		7.29[c] s	8.94 s	6.82 (t, ^2J = 53.6)	1590, 1630, 3140, 3250
9a		7.01 s	6.95 (dd, J_o = 8.2, J_m = 1.0)	7.38 (ddd, J_o = 8.2, 7.4, J_m = 1.6)	7.08 (ddd, J_o = 7.9, 7.4, J_m = 1.0)	7.88 (dd, J_o = 7.9, J_m = 1.6)	5.90 s	−64.4[a] s	1580, 1600, 1620, 3230
9a[b]		7.30 s	7.09 (dd, J_o = 8.3, J_m = 1.0)	7.41 (ddd, J_o = 8.3, 7.2, J_m = 1.7)	7.00 (ddd, J_o = 8.0, 7.2, J_m = 1.0)	7.85 (dd, J_o = 8.0, J_m = 1.7)	10.94 s		
9b	2.35 s	6.99 s	6.84 (d, J_o = 8.3)	7.17 (dd, J_o = 8.3, J_m = 1.9)		7.67[c] (d, J_m = 1.7)	5.69 s		1580, 1605, 1625, 3210
9c		7.00 s	6.95 (dd, J_o = 8.2, J_m = 1.0)	7.37 (ddd, J_o = 8.2, 7.4, J_m = 1.6)	7.07 (ddd, J_o = 7.9, 7.4, J_m = 1.0)	7.86 (dd, J_o = 7.9, J_m = 1.6)	5.99 s	6.18 (tt, ^2J = 53.1, ^3J = 4.0)	1575, 1605, 1625, 3200, 3440
9d	2.35 s	6.99 s	6.85 (d, J_o = 8.3)	7.16[d] (ddq, J_o = 8.3, J_m = 2.1)		7.64[c] (d, J_m = 1.5)	5.94 s	6.17 (tt, ^2J = 53.1, ^3J = 4.0)	1585, 1615, 1630, 3240
9e		6.96 s	6.96 (dd, J_o = 8.2, J_m = 0.9)	7.36 (ddd, J_o = 8.2, 7.4, J_m = 1.6)	7.06 (ddd, J_o = 7.9, 7.4, J_m = 0.9)	7.83 (dd, J_o = 7.9, J_m = 1.6)	6.11 s	6.82 (t, ^2J = 53.8)	1580, 1620, 3190
9f	2.34 s	6.93 s	6.85 (d, J_o = 8.3)	7.15[e] (ddq, J_o = 8.3, J_m = 2.2)		7.61[c] (d, J_m = 1.5)	5.91 s	6.82 (t, ^2J = 53.8)	1580, 1600, 1625, 3230, 3550

[a] The ^{19}F NMR spectrum with reference to $CFCl_3$.
[b] In DMSO-d_6.
[c] The broadening of the signal is due to *o*-benzyl splitting with $^4J_{H(6),CH_3} \approx 0.5$ Hz.
[d] $^4J_{H(4),CH_3} = 0.5$ Hz.
[e] $^4J_{H(4),CH_3} = 0.6$ Hz.

Table 3. Chemical shifts of the signal for the H(4) proton in 3-R-5-CF_3- and 5-R-3-CF_3-isoxazoles in $CDCl_3$





R	$\delta_{H(4)}$	$^4J_{H,F}$/Hz	Reference	R	$\delta_{H(4)}$	Reference
H	6.65 dq	~1.0	10	H	6.10 d	17
Ph	6.98 s		11	Ph	6.67[a] s	18
Ph	7.00 q	0.9	[b]			
5a	7.13 q	0.9	[b]	**9a**	7.01 s	[b]

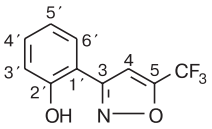
[a] In CCl_4.
[b] This study.

partially due to the electron-withdrawing effect of the CF_3 group, which is more pronounced in the 5-CF_3-isomer containing an adjacent double bond. As expected, in the spectra of 5(3)-phenyl-3(5)-CF_3-isoxazoles, this signal is shifted downfield since the H(4) proton is deshielded by the benzene ring, especially in the 3-CF_3-isomer, which reduces $\Delta\delta_{H(4)}$ to 0.33 ppm. When the phenyl substituent contains an *o*-hydroxy group (compounds **5a** and **9a**), the rings are conjugated more efficiently through an intramolecular hydrogen bond, which will hinder the rotation about the C(1′)—C(3/5) bond and thus stabilize the coplanar conformer. As a result, the H(4) protons in regioisomeric isoxazoles **5** and **9** are deshielded to a larger extent; again, this effect is more pronounced for the 3-CF_3-isomer, and $\Delta\delta_{H(4)}$ is reduced to 0.12—0.13 ppm for **5a**,**b** and **9a**,**b**. An analogous pattern is characteristic of the other 5(3)-R^F-isoxazoles ($\Delta\delta_{H(4)}$ = 0.11—0.12 ppm for $R^F = (CF_2)_2H$ and $\Delta\delta_{H(4)}$ = 0.14—0.16 ppm for $R^F = CF_2H$). Because of this, $\delta_{H(4)}$ cannot be regarded as a reliable criterion for identification of a regioisomer belonging to the (*o*-hydroxyaryl)isoxazole series if only one is present. However, if both regioisomers are available, then the lower-field signal will most probably be related to 5-R^F-isoxazole. This rule is also true for solutions in DMSO-d_6; for compounds **5a** and **9a**, $\Delta\delta_{H(4)}$ = 0.42 ppm (see Table 2). Earlier,[43] it has been found that a signal for the H(4) proton is shifted downfield by 0.23—0.46 ppm when passing from 1-R-3-CF_3- to 1-R-5-CF_3-pyrazoles.

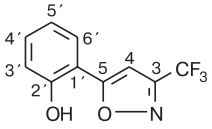
In $CDCl_3$, the phenolic proton in isoxazoles **9a**—**f** gives a singlet at δ 5.7—6.1, which disappears immediately upon the addition of CD_3CO_2D. In the spectra of compounds **5a**—**f**, an analogous signal is significantly shifted downfield (δ 8.8—9.1), and this proton slowly exchanges for deuterium with CD_3CO_2D, indicating its involvement in intramolecular hydrogen bonding *via* the N atom of the isoxazole ring. Based on these data, one can conclude that the O—H...N= hydrogen bond occurring in 5-R^F-isoxazoles **5** is stronger than the O—H...O bond in 3-R^F-isoxazoles **9**. Thus, the chemical shift of a signal for the phenolic proton is quite indicative in $CDCl_3$ and can be useful while determining the structures of regioisomeric (*o*-hydroxyaryl)isoxazoles.

The aromatic protons in isomeric isoxazoles also manifest themselves differently. A signal for the H(6) proton in compounds **9a**—**f** is shifted downfield by

Table 4. ^{13}C NMR spectra of isoxazoles **5a** and **9a** (δ, *J*/Hz)



5a



9a

Compound	C(3)	C(4)	C(5)	CF_3	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	C(6′)
5a[a]	162.5 (t, ^3J_H = ^2J_H = = 4.5)	103.3 (dq, ^1J_H = 187.0, ^3J_F = 2.1)	158.3 (qd, ^2J_F = 42.9, ^2J_H = 8.5)	117.8 (qd, ^1J_F = 270.7, ^3J_H = 0.5)	111.8 (dd, $^3J_H \approx$ 7.6, $^3J_H \approx$ 6.0)	156.6 (tm, $^3J_H \approx$ 8.0)	118.0 (dd, ^1J_H = 161.0, ^3J_H = 6.5)	132.8 (ddd, ^1J_H = 160.0, ^3J_H = 8.8, ^2J_H = 1.4)	120.2 (ddd, ^1J_H = 163.3, ^3J_H = 8.1, ^2J_H = 0.8)	128.0 (ddd, ^1J_H = 157.6, ^3J_H = 8.7, ^2J_H = 1.4)
9a[b]	156.1 (q, ^2J = 38.0)	100.0	169.1	119.9 (q, ^1J = 271.1)	113.4	153.1	116.9	132.4	121.5	127.9
9a[c]	155.1 (qd, ^2J_F = 37.1, ^2J_H = 5.4)	99.9 (dd, ^1J_H = 191.7, ^4J_H = 1.1)	169.3 (ddd, ^3J_H = 8.7, ^2J_H = 4.5, ^4J_H = 2.0)	119.8 (q, ^1J_F = 271.0)	112.4 (br.s)	155.2 (t, $^3J_H \approx$ 8.9)	116.6 (dd, ^1J_H = 160.4, ^3J_H = 7.7)	132.7 (ddd, ^1J_H = 160.4, ^3J_H = 8.9, ^2J_H = 1.7)	119.6 (dd, ^1J_H = 163.5, ^3J_H = 7.8)	127.0 (ddd, ^1J_H = 161.0, ^3J_H = 8.5, ^2J_H = 2.0)

[a] In $CDCl_3$.
[b] In $CDCl_3$ with proton decoupling (**9a** is insoluble in $CDCl_3$).
[c] In DMSO-d_6.

0.32—0.39 ppm compared to its position in the spectra of **5a**—**f**, while a signal for the H(3) proton is shifted upfield by 0.15—0.17 ppm. However, when $CDCl_3$ is replaced by DMSO-d_6, the chemical shifts of the aromatic protons in, *e.g.*, regioisomeric compounds **9a** and **5a** become virtually identical ($\Delta\delta$ = 0.02—0.10 ppm). The same relates to signals for the phenolic proton, which forms intermolecular hydrogen bonds with polar DMSO-d_6 molecules (δ 10.94 for **9a** and δ 10.46 for **5a**). Thus, the above signals are useless while distinguishing between these regioisomers. If one takes into account that the isoxazole proton in both isomers gives a singlet while recording their spectra in this solvent, then $\delta_{H(4)}$ is the sole criterion for their identification ($\delta_{H(4)}$ 7.30 for **9a** and $\delta_{H(4)}$ 7.72 for **5a**) (see Table 2).

Regioisomeric isoxazoles **5c**,**d** and **9c**,**d** containing the $(CF_2)_2H$ group can be easily distinguished by the coupling constants $^3J_{H,F}$ = 2.8 and 4.0 Hz for **5c**,**d** and **9c**,**d**, respectively (the chemical shifts of signals for the tetrafluoroethyl proton differ only by 0.05 ppm). Note that $^3J_{H,F}$ of isoxazoles **5c**,**d** is exactly half as high as that of isoxazolines **4c**,**d** (5.6 versus 2.8 Hz), while the cyclodehydration of oximes **7** into isoxazoles **9** decreases its value from 5.1 to 4.0 Hz. The $^3J_{H,F}$ values determined for the isoxazole systems supplement the data reported in Ref. 44 (in this paper, variations in the constant $^3J_{H,F}$ of the $(CF_2)_2H$ group with the nearest environment of its adjacent carbon atom have been analyzed and some generalization made).

^{13}C NMR spectra. In the proton-decoupled ^{13}C NMR spectra of isoxazoles **5a** and **9a** (see Table 4), the coupling constants $^nJ_{C,F}$ (n = 1—3) are of primary note. The direct constants $^1J_{C,F}$ for compounds **5a** and **9a** are almost the same (270.7 and 271.1 Hz, respectively), while the constant $^2J_{C,F}$ decreases from 42.9 to 38.0 Hz in passing from **5a** to **9a**, which is probably characteristic of regioisomeric 5- and 3-CF_3-isoxazoles and can be of diagnostic interest for their ^{13}C NMR identification. Indeed, $^2J_{C,F}$ = 42.1 Hz in 3-phenyl-5-trifluoromethylisoxazole,[11] while for various disubstituted 5- and 3-CF_3-isoxazoles, this constant has been reported to be 40—45 and 36—39 Hz, respectively.[12,21,23,38] Moreover, a similar decrease in $^2J_{C,F}$ has been noted earlier for *N*-substituted 5(3)-CF_3-pyrazoles. For example, for the C(5) and C(3) atoms in 3,5-bis(trifluoromethyl)-1-(4-methylquinolin-2-yl)pyrazole the $^2J_{C,F}$ values are 42.9 and 38.6 Hz, respectively.[39] However, the constant $^2J_{C,F}$ in this series of pyrazoles more strongly depends on the nature of substituents, and the C(5) and C(3) atoms in, *e.g.*, 3,5-bis(trifluoromethyl)-1-(4-nitrophenyl)pyrazole are characterized by the same value (40.0 Hz).[41] On the whole, the constant $^2J_{C,F}$ for *N*-substituted 5-CF_3-pyrazoles ranges from 38 to 43 Hz,[12,38,39,45] while that for 3-CF_3-pyrazoles is known to vary from 36 to 40 Hz.[21,38,39,45] Hence, this constant still tends to decrease, but the overlap of the above ranges makes this constant a less valuable criterion for the distinction between regioisomeric trifluoromethylpyrazoles. It is also noteworthy that a signal for the C(4) atom in isoxazole **9a** appears as a singlet at δ 100.0, while the corresponding signal in the ^{13}C NMR spectrum of compound **5a** is a quartet (δ 103.3, $^3J_{C,F}$ = 2.1 Hz). Such a coupling constant is obviously lower than those for other compounds with the *cis*-H—C=C—CF_3 fragment (alkenes and six-membered nitrogen- and oxygen-containing heterocycles, $^3J_{C,F}$ = 2.8—7.1 Hz)[42,46] and lies in the range characteristic of the *trans*-fragment (alkenes, $^3J_{C,F}$ = 1.5—3.3 Hz).[42,46]

The ^{13}C NMR spectra recorded without proton decoupling and the literature data for similar systems[11,47,48] (with consideration of the constants $^nJ_{C,H}$ (n = 1—4)) were used to assign signals for the benzene C atoms and the isoxazole carbon atom having no C—F coupling. While comparing the chemical shifts of signals for the C(3)—C(5) atoms in 3,5-diphenylisoxazole ($\delta_{C(3)}$ 162.2, $\delta_{C(4)}$ 98.3, and $\delta_{C(5)}$ 169.3),[47] 3-phenyl-5-trifluoromethylisoxazole ($\delta_{C(3)}$ 162.7, $\delta_{C(4)}$ 103.5, and $\delta_{C(5)}$ 159.4),[5,11,49] and compounds **5a** and **9a** (see Table 4), one can note that the C(5) atom bearing a trifluoromethyl group instead of the phenyl group is shielded by ~10 ppm, while the C(4) atom becomes deshielded by ~5 ppm. An analogous replacement at the C(3) atom causes shielding of this atom by ~6 ppm and deshielding of the C(4) atom by ~2 ppm. The direct constant $^1J_{C(4),H}$ (191.7 Hz for **9a**) is indicative of an increased electron deficiency of the isoxazole ring containing the trifluoromethyl group.[50] Note a decrease in $^2J_{C,H}$ (along with $^2J_{C,F}$) from 8.5 to 5.4 Hz for the same carbon atom in compound **9a** compared to **5a**. In addition, unlike a quartet for the trifluoromethyl C atom in isoxazole **9a**, the corresponding signal for compound **5a** appears as a quartet of doublets due to additional splitting at the vicinal hydrogen atom with $^3J_{C,H}$ = 0.5 Hz. Earlier,[46] it has been reported that compounds with the *cis*-H atom relative to the CF_3 group have $^3J_{C,H}$ = 1.8—8.0 Hz.

Thus, we developed the new method for the synthesis of regioisomeric fluorine-containing isoxazoles from 2-hydroxyacetophenones and polyfluorocarboxylates. The structures of the compounds obtained were determined by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy. Analysis of the essential NMR features of 5- and 3-R^F-isoxazoles showed that these regioisomers can be most reliably distinguished using ^{13}C NMR spectroscopy. In particular, the constant $^2J_{C,F}$ is of diagnostic value for structure determination of trifluoromethylated isoxazoles. The 3(5)-aryl-5(3)-polyfluoroalkylisoxazoles obtained are of interest both as compounds with potential biological activity and as starting reagents for construction of more complex heterocyclic systems with fluorinated substituents.

Experimental

IR spectra were recorded on an IKS-29 instrument (Vaseline oil). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (400.13 and 100.62 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. ^{19}F NMR spectra were recorded on a Tesla BS-587A instrument (75.3 MHz) with $CFCl_3$ as the internal standard. The ^{1}H NMR spectra of the starting compounds **3c—f** and **6c**,**d**,**f** were recorded on Bruker WM-250 and Tesla BS-587A instruments (250 and 100 MHz, respectively).

Compounds **3a**,**b** and **6a**,**b**,**e** have been characterized earlier.[25,51,52] Chromanones **3c—f** and chromones **6c**,**d**,**f** were obtained as described in Ref. 53, while 3-phenyl(styryl, 2-thienyl, or *tert*-butyl)-5-trifluoromethylisoxazoles were prepared by the known procedures.[5,54] The ^{1}H, ^{19}F, and ^{13}C NMR data and IR spectra of compounds **4a—f** and **7a—f** are given in Table 1; those for compounds **5a—f** and **9a—f** are presented in Tables 2 and 4. The ^{1}H NMR data and IR spectra of chromanones **3c—f** and chromones **6c**,**d**,**f** are given in Table 5. The yields, melting points, and elemental analysis data of the compounds obtained are summarized in Table 6. The yields are given for non-recrystallized products since their melting points remained virtually unchanged upon recrystallization.

5-Hydroxy-3-(2-hydroxyaryl)-5-R^F-Δ^2-isoxazolines (4a—f) and 1-(2-hydroxyaryl)-3-R^F-propane-1,3-dione 3-oximes (7a—f) (general procedure). Chromanone **3** or chromone **6** (2 mmol), hydroxylamine hydrochloride (4 mmol), and sodium acetate (6 mmol) were dissolved with heating in 5 mL of aqueous ethanol (water : ethanol = 1 : 1). The resulting solution was refluxed for 1 h, cooled, and diluted with water. The crystalline

Table 5. ^{1}H NMR and IR spectra of chromanones **3c—f** and chromones **6c,d,f**

Compound	^{1}H NMR ($CDCl_3$, δ, *J*/Hz)									IR, ν/cm^{-1}
	CH_3	CH_2	=CH	H(5)	H(6)	H(7)	H(8)	OH	R^F	
3c[a,b]		3.09[c] (J = 16.7, Δδ = 0.15)		7.89 (dd, J_o = 7.6, J_m = 1.5)	7.13 (t, J_o = 7.3)	7.56 (ddd, J_o = 8.3, 7.0, J_m = 1.5)	7.02 (d, J_o = 8.3)	4.00 s	6.27 (tt, ^2J = 52.7, ^3J = 5.9)	1585, 1610, 1680, 3220
3d[d,e]	2.30 s	3.04[c] (J = 16.9, Δδ = 0.15)		7.64[f] (d, J_m = 1.6)		7.35[f] (dd, J_o = 8.4, J_m = 1.6)	6.90 (d, J_o = 8.4)	4.36 (br.s)	6.25 (tt, ^2J = 52.7, ^3J = 5.9)	1585, 1620, 1670, 3300
3e[a]		2.96[c], J = 16.8, Δδ = 0.08)		7.86 (dd, J_o = 7.9, J_m = 1.7)	7.08 (t, J_o = 7.5)	7.54 (ddd, J_o = 8.6, 7.0, J_m = 1.7)	7.02 (d, J_o = 8.6)	4.15 s	5.85 (t, ^2J = 55.0)	1580, 1610, 1685, 3340
3f [d,g]	2.30 s	2.94 s		7.65[f] (d, J_m = 1.6)		7.35[f] (dd, J_o = 8.4, J_m = 2.1)	6.91 (d, J_o = 8.4)	3.95 s	5.83 (t, ^2J = 55.0)	1580, 1620, 1675, 3200, 3330
6c[d,h]			6.71 s	8.19 (dd, J_o = 7.8, J_m = 1.8)	7.45 (ddd, J_o = 7.6, J_m = 0.9)	7.74 (ddd, J_o = 7.8, J_m = 1.8)	7.51 (dd, J_o = 8.2, J_m = 0.9)		6.15 (tt, ^2J = 52.9, ^3J = 3.6)	1615, 1645, 1660
6d[d]	2.45 s		6.69 s	7.96 br.s		7.54 (dd, J_o = 8.5, J_m = 2.1)	7.38 (d, J_o = 8.5)		6.14 (tt, ^2J = 53.0, ^3J = 3.8)	1620, 1640, 1660
6f [d]	2.43 s		6.55 s	7.93 br.s		7.51 (dd, J_o = 8.6, J_m = 2.0)	7.35 (d, J_o = 8.6)		6.43 (t, ^2J = 53.8)	1615, 1640, 1665, 3110

[a] For an operating frequency of 250 MHz.
[b] According to the ^{1}H and ^{19}F NMR data, this compound exists as a mixture of **3c** (88%) and **1c** (12%). For **1c**: ^{1}H NMR, δ: 6.10 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 52.8 Hz, $^3J_{H,F}$ = 5.0 Hz); 6.73 (s, 1 H, =CH); 6.96 (t, 1 H, H(5), J_o = 7.8 Hz); 7.72 (d, 1 H, H(6), J_o = 7.8 Hz); 11.57 (s, 1 H, OH phenol); 14.36 (br.s, 1 H, OH enol); signals for the H(3) and H(4) protons coincide with those for the H(6) and H(7) protons of the cyclic form **3c**. ^{19}F NMR ($CFCl_3$), δ: −139.0 (dt, 2 F, CF_2H, $^2J_{F,H}$ = 52.7 Hz, $^3J_{F,F}$ = 7.1 Hz); −126.6 (dt, 2 F, CF_2, $^3J_{F,F}$ = 7.1 Hz, $^3J_{F,H}$ = 4.9 Hz).
[c] Center of the AB system.
[d] For a operating frequency of 100 MHz.
[e] According to the ^{19}F NMR data, the compound exists as a mixture of **3d** (92%) and **1d** (8%). For **1d**: ^{19}F NMR ($CFCl_3$), δ: −138.9 (dt, 2 F, CF_2H, $^2J_{F,H}$ = 52.8 Hz, $^3J_{F,F}$ = 7.1 Hz); −126.4 (dt, 2 F, CF_2, $^3J_{F,F}$ = 7.1 Hz, $^3J_{F,H}$ = 4.9 Hz).
[f] The broadening of the signal is due to *o*-benzyl splitting with $^4J_{H(6),CH_2} \approx 0.5$ Hz.
[g] ^{19}F NMR ($CFCl_3$), δ: −135.8 (the AB part of the ABX system, 2 F, CF_2H, $^2J_{F,F}$ = 287.4 Hz, $^2J_{F,H}$ = 54.9 Hz).
[h] ^{19}F NMR ($CFCl_3$), δ: −136.9 (dt, 2 F, CF_2H, $^2J_{F,H}$ = 53.0 Hz, $^3J_{F,F}$ = 5.4 Hz); −122.9 (dt, 2 F, CF_2, $^3J_{F,F}$ = 5.4 Hz, $^3J_{F,H}$ = 3.4 Hz).

Table 6. Main physicochemical characteristics of compounds **3c—f**, **4a—f**, **5a—f**, **6c,d,f**, **7a—f**, and **9a—c,e,f**

Compound	Yield (%)	M.p. /°C	Molecular formula	Found / Calculated (%)		
				C	H	N
3c	70	117—118	$C_{11}H_8F_4O_3$	50.08 50.01	3.34 3.05	—
3d	68	113—114	$C_{12}H_{10}F_4O_3$	51.67 51.81	3.73 3.62	—
3e	84	123—124	$C_{10}H_8F_2O_3$	56.16 56.08	3.64 3.77	—
3f	48	126—127	$C_{11}H_{10}F_2O_3$	57.77 57.90	4.39 4.42	—
4a	90	122—123	$C_{10}H_8F_3NO_3$	48.54 48.59	3.42 3.26	—[a]
4b[b]	94	141—142	$C_{11}H_{10}F_3NO_3$	50.48 50.58	3.70 3.86	—[c]
4c	90	89—90	$C_{11}H_9F_4NO_3$	47.28 47.32	2.99 3.25	4.92 5.02
4d	96	85—86	$C_{12}H_{11}F_4NO_3$	48.89 49.16	3.57 3.78	4.51 4.78
4e	75	126—127	$C_{10}H_9F_2NO_3$	52.27 52.41	4.04 3.96	6.20 6.11
4f	83	151—152	$C_{11}H_{11}F_2NO_3$	54.24 54.32	4.60 4.56	5.72 5.76
5a	65	98—99	$C_{10}H_6F_3NO_2$	52.35 52.41	2.72 2.64	6.03 6.11
5b	59	84—85	$C_{11}H_8F_3NO_2$	54.44 54.33	3.42 3.32	5.69 5.76
5c	85	48—49	$C_{11}H_7F_4NO_2$	50.58 50.59	2.66 2.70	5.49 5.36
5d	93	60—61	$C_{12}H_9F_4NO_2$	52.45 52.37	3.14 3.30	5.19 5.09
5e	72	73—74	$C_{10}H_7F_2NO_2$	56.77 56.88	3.27 3.34	6.48 6.63
5f	82	62—63	$C_{11}H_9F_2NO_2$	58.55 58.67	4.05 4.03	5.93 6.22
6c	91	100—101	$C_{11}H_6F_4O_2$	53.55 53.67	2.52 2.46	—
6d	94	95—96	$C_{12}H_8F_4O_2$	55.37 55.40	3.03 3.10	—
6f	90	95—96	$C_{11}H_8F_2O_2$	62.76 62.86	3.90 3.84	—
7a	87	118—119	$C_{10}H_8F_3NO_3$	48.54 48.59	3.27 3.26	5.84 5.67
7b	91	142—143	$C_{11}H_{10}F_3NO_3$	50.79 50.58	3.71 3.86	5.22 5.36
7c	92	93—94	$C_{11}H_9F_4NO_3$	47.02 47.32	3.08 3.25	4.96 5.02
7d	31	102—103	$C_{12}H_{11}F_4NO_3$	49.15 49.16	3.58 3.78	4.65 4.78
7e[d]	67	109—112	$C_{10}H_9F_2NO_3$	52.61 52.41	4.13 3.96	6.37 6.11
7f[e]	90	132—135	$C_{11}H_{11}F_2NO_3$	54.31 54.32	4.49 4.56	6.05 5.76
9a	92	213—215	$C_{10}H_6F_3NO_2$	52.42 52.41	2.66 2.64	6.26 6.11
9b	97	subl. >210	$C_{11}H_8F_3NO_2$	54.59 54.33	3.51 3.32	5.92 5.76
9c	91	161—163	$C_{11}H_7F_4NO_2$	50.56 50.59	2.60 2.70	5.48 5.36
9e	86	173—176	$C_{10}H_7F_2NO_2$	57.05 56.88	3.26 3.34	6.50 6.63
9f	86	162—164	$C_{11}H_9F_2NO_2$	58.64 58.67	4.25 4.03	6.45 6.22

[a] Found (%): F, 22.86. Calculated (%): F, 23.06.
[b] Ref. 25: m.p. 140 °C.
[c] Found (%): F, 21.96. Calculated (%): F, 21.82.
[d] The content of isoxazoline **4e** in oxime **7e** is 6%.
[e] The content of isoxazoline **4f** in oxime **7f** is 12%.

product (in some cases, gradually solidifying oil) that formed was filtered off, washed with water, dried, and recrystallized from hexane—chloroform for isoxazolines **4** and from ethanol—water (2 : 1) for oximes **7**.

3-(2-Hydroxyaryl)-5-R^F-isoxazoles (5a—f) (general procedure). Isoxazoline **4** (4 mmol) was dissolved with slight heating in 3 mL of toluene. Then two drops of pyridine and thionyl chloride (0.6 mL, 1.0 g, 8.1 mmol) were added. The reaction mixture was refluxed for 5—10 min. All volatile substances were removed *in vacuo* (water-jet pump), and the solid residue was recrystallized from hexane with a small amount of chloroform.

5-(2-Hydroxyaryl)-3-R^F-isoxazoles (9a—f) (general procedure). Three to five drops of conc. HCl were added to 2 mL of glacial acetic acid. Oxime **7** (0.8 mmol) was dissolved in the resulting mixture. The reaction mixture was refluxed for 3—5 min, cooled, and diluted with water. The precipitate that formed was filtered off and dried.

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