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Reactions of 6-(tri- and 6-(difluoromethyl))comanic acids and their ethyl esters with aniline and its 2-substituted derivatives

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ABSTRACT

Reactions of 6-(tri- and 6-(difluoromethyl))comanic acids with aniline, o-phenylenediamine and o-aminophenol were investigated. R^F-containing derivatives of 4-pyridones, benzodiazepines and quinoxalinones were synthesized. Electrophilic properties of 6-(trifluoromethyl)comanic acid were evaluated.

1. Introduction

Fluorine-containing organic compounds have attracted much interest because of their unique chemical properties and biological activities [1]. Among those, trifluoromethylated and other fluoroalkylated pyrones belong to a peculiar group of fluorinated compounds. In spite of some representatives of R^F-pyrones were described earlier, their chemical properties till investigated very poorly [2]. Recently we described regioselective solvent-sensitive reactions of such CF_3-pyrones as 6-(trifluoromethyl)comanic acid and its derivatives with phenylhydrazine [2f], which lead to trifluoromethylated 3-(pyrazolyl)indoles [2p]. It is known, that 5-methyl-2-(trifluoromethyl)-4*H*-pyran-4-one reacts with methylamine in methanol to give the corresponding pyridone, 1,5-dimethyl-2-(trifluoromethyl)-4(1*H*)-pyridin-4-one [2c], however, there are no data in literature about reactions of 2-R^F-4-pyrones with aromatic amines. With the aim to develop approaches for the preparation of fluorine-containing heterocycles on the basis of pyrone compounds, we studied reactions of 6-tri(di)fluoromethyl-comanic acids and their ethyl esters with such aromatic amines as aniline, *o*-phenylenediamine (*o*-PhDA) and *o*-aminophenol under various reaction conditions.

2. Results and discussion

We have found that 2-R^F-4-pyrones **1a–d** [2g] (derivatives of 4-pyrone-2-carboxylic (comanic) acid) react with aniline and *o*-aminophenol by heating the mixtures in a protic solvent under acidic conditions (HCl or H_2SO_4) to give the corresponding 2-R^F-1-arylpyridin-4(1*H*)-ones **2a–h** in 21–65% yield (Scheme 1). Pyridonecarboxylic acids **2a**,**b** were also synthesized in 74–70% yield by saponification of esters **2e**,**f** with KOH. Pyridones **2** are the first representatives of 2-tri(di)fluoromethylated *N*-aryl-4-pyridones and they are fluorine-containing analogs of pharmaceutically important pyridone compounds [3a–c], which were prepared using the reactions of such non-fluorinated 4-pyrones as comanic [3a] or chelidonic acid (its derivatives) with anilines [3b–g]. In all cases, described reactions of non-fluorinated 4-pyrones with aniline and their 2-substituted analogs give 4-pyridones [3a–g] or their annulated derivatives [3h–j]. In the last case (when *o*-PhDA or *o*-aminophenols were used as nucleophiles), the reactions were followed by intramolecular cyclization due to the attack of the second nucleophilic atom on the ester carbonyl group, resulting in the formation of pyrido[2,1-*c*]benzoxazine and pyrido[1,2-*a*]quinoxaline derivatives [3h–j].

We have shown, that in contrast to those non-fluorinated 4-pyrones, 2-CF_3(CF_2H)-4-pyrones **1a–d** react with *o*-PhDA in the presence of a strong acid to give R^F-bearing benzodiazepines **3a–d** (Scheme 1). Nevertheless, besides the benzodiazepines, quinoxalin-2(1*H*)-one derivatives were formed in the reaction of **1** with *o*-PhDA, which were precipitated from the reaction mixtures as low

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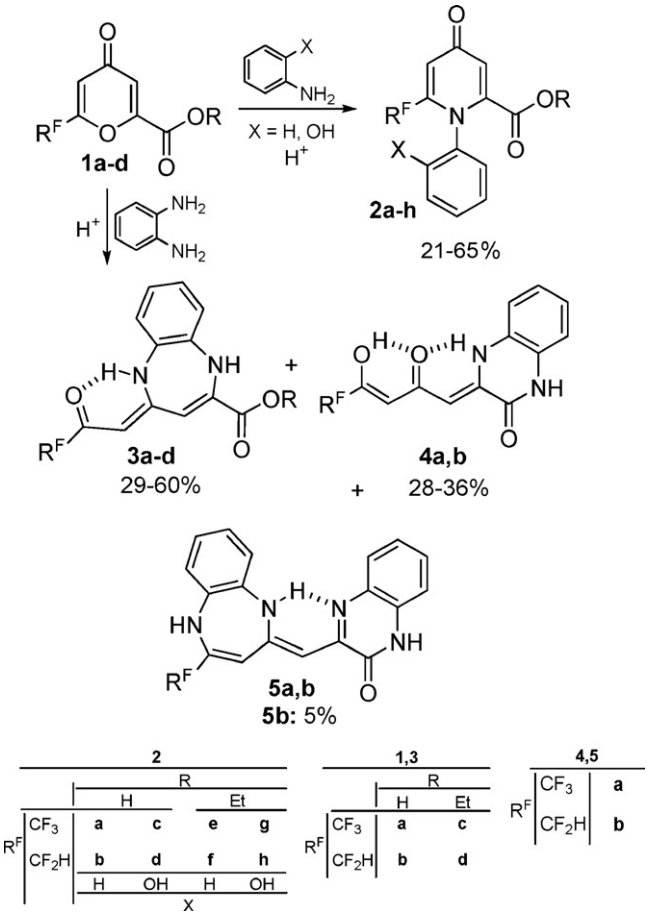
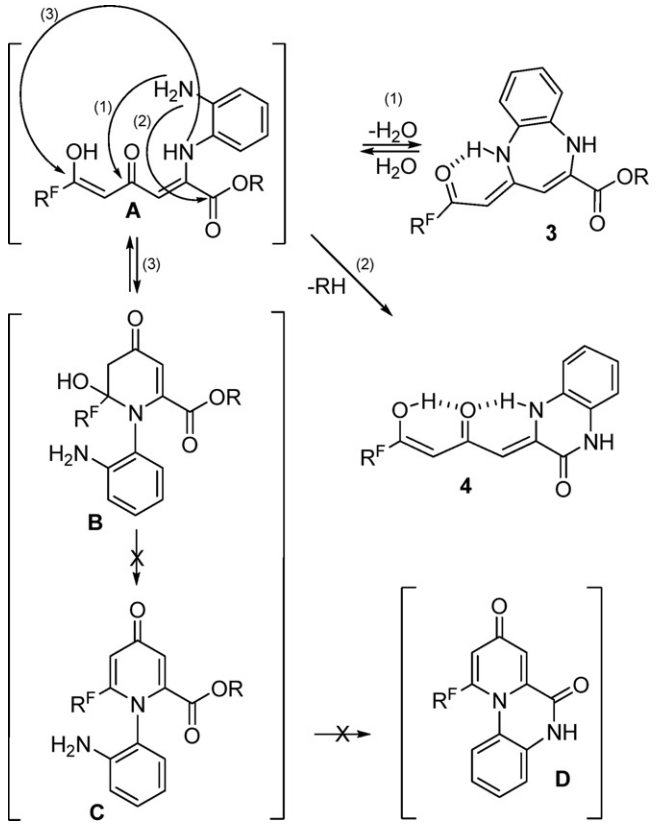


Scheme 1.



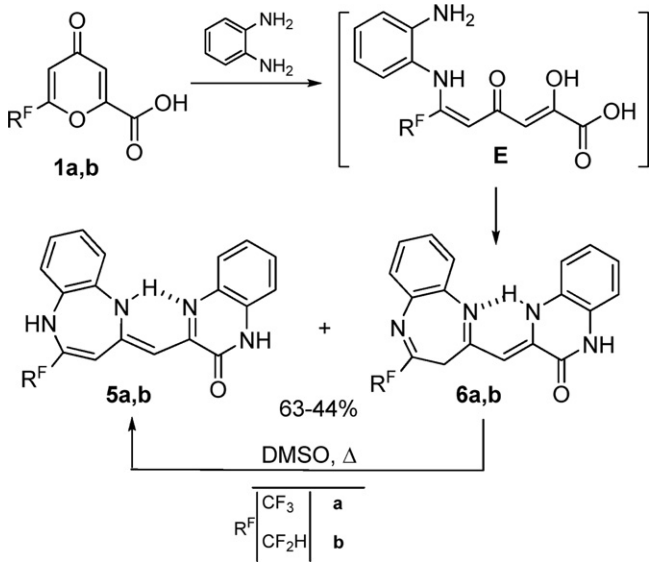
Scheme 2.

soluble red solids. NMR spectra and elemental analysis of these residues showed that in the case of the carboxylic acids (**1a**,**b**) they are almost pure (*Z*)-(5,5,5-trifluoro- and (*Z*)-(5,5-difluoro-2,4-dioxopentylidene))-1,2,3,4-tetrahydro-2-quinaxolinones **4a**,**b**, whereas a red residue, prepared from ester **1c**, is a mixture of **4a** and (*Z*)-3-[(2-(trifluoromethyl)-1*H*-benzo[*b*][1,4]diazepin-4-yl)methylene]-3,4-dihydroquinoxalin-2(1*H*)-one **5a** (Scheme 1). In the case of ethyl 6-(difluoromethyl)comanoate **1d** the red residue consisted of only (*Z*)-3-[(2-(difluoromethyl)-1*H*-benzo[*b*][1,4]diazepin-4-yl)methylene]-3,4-dihydroquinoxalin-2(1*H*)-one **5b**.

The main and common intermediate in the reactions of **1** with anilines for strongly acidic conditions, most probably, is enaminodione **A** (Scheme 2), which is formed by nucleophilic attack at the C-2 carbon of the pyrone ring. Intermediates **A** then could be transformed either into benzodiazepines **3** through path (1) or into quinoxalinones **4** through path (2). The reaction (1) is a reversible process due to facile ring opening of labile seven-membered diazepine ring. This supposition was confirmed by heating of **3c** in AcOH/HCl, which gave **4a** in 31% yield. On the other hand, the alternative reaction pathway (2) leads to the formation of stable six-membered pyrazine ring. Thus, benzodiazepines **3** can be considered as kinetically controlled products, whereas compounds **4** are thermodynamically controlled ones (Scheme 2).

Neither the corresponding 4-pyridone nor pyrido[1,2-*a*]quinoxaline derivatives were detected in crude samples of **3**. The reason which prevents the formation of pyridones and pyrido[2,1-*c*]quinoxalines (structures **C** and **D**, Scheme 2) from R^F-pyrones **1** and *o*-PhDA can be explained by relatively slow dehydratation of intermediate R^F-hemiaminals **B** (dehydratation of trifluoromethylated cyclic hemiaminals occurs not so rapidly [4]) in comparison with reactions (1) and (2). Theoretically, intermediate **A** could give compounds **5** via quinoxalinones **4**. However, **4a** did not react with excess *o*-PhDA (heating the reagents in EtOH with or without HCl). Vice versa, treatment of **5a** with HCl led to hydrolysis of the diazepine moiety and formation of **4a** (46%). This result excludes **A** as an intermediate by the formation of **5**.

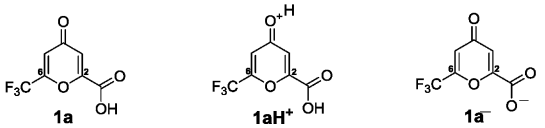
We have found that compounds **5** can be prepared more selectively by treatment of 4-pyrone-2-carboxylic acids **1a**,**b** with *o*-PhDA in the absence of a strong acid. According to the ^{1}H NMR spectra, the crude products are mixtures of **5** and their diimine



Scheme 3.

Table 1
Electroaccepting power (ω^+) of **1a**, **1aH$^+$** and **1a$^-$**, and regional electrophilicity (ω_k^+) of atoms C-2 and C-6.

6-(Trifluoromethyl)comanic acid (**1a**), its protonated (**1aH$^+$**) and deprotonated (**1a$^-$**) forms



	1a	**1aH$^+$**	**1a$^-$**
Electroaccepting power ω^+ (eV)			
ω^+	6.832	35.143	0.273
Regional electrophilicity ω_k^+ (eV) of atoms C-2 (ω_2^+) and C-6 (ω_6^+)			
ω_2^+	0.544	3.486	0.0144
ω_6^+	0.327	2.520	0.0293

tautomers **6** (**5a**:**6a** = 21:79; **5b**:**6b** = 65:35) (Scheme 3). To transform partially **6** into more conjugated tautomers **5** the mixtures were heated in DMSO at 80–120 °C. The syntheses of compounds **5** and **6** confirm that in the absence of a strong acid *o*-PhDA attacks carbon C-6 of the pyrone ring rather than carbon C-2 (formation of intermediate **E**, Scheme 3). This supposition was proved theoretically and experimentally.

There are three possible reactive forms that can react with *o*-PhDA in the case of carboxylic acid **1a**: pyrone form **1a**, protonated form **1aH$^+$** and anionic form **1a$^-$** (Table 1). The reactivity of the C-2 and C-6 carbons of the pyrone ring can be described using indices of reactivity calculated with computational methods such as Density Functional Theory (DFT) [5a]. Parr et al. [5b], promoted by the work of Maynard et al. [5c] have determined the electrophilicity index that measures the energy changes of an electrophile when it becomes saturated with electrons, by considering the case when an electrophile (electrophilic ligand) is immersed in idealized zero-temperature free electron sea of zero chemical potential. In this case the electrophile (electrophilic species) becomes saturated with electrons when its chemical potential becomes equal to the chemical potential of the sea. The energy change becomes

$$\Delta E = -\frac{\mu^2}{2\eta} < 0,$$

and it was suggested as the definition of electrophilicity (ω) (the global electrophilicity index) as

$$\omega = \frac{\mu^2}{2\eta}, \tag{1}$$

where μ is the chemical potential and η is the chemical hardness. Gázquez et al. have proposed the following expression for electroaccepting power (ω^+) to describe electrophilic properties of molecules (chemical systems) [5d]:

$$\omega^+ = \frac{(I+3A)^2}{16(I-A)} \tag{2}$$

where I is the ionization potential, and A is the electron affinity. Using Koopmans' theorem [5e] the ionization potential and electron affinity can be replaced by the HOMO and LUMO energies:

$$I = -E_{\mathrm{HOMO}} \quad \text{and} \quad A = -E_{\mathrm{LUMO}} \tag{3}$$

The calculated LUMO energies of **1a** (−3.50 eV), **1a$^-$** (0.10 eV) and **1aH$^+$** (−8.85 eV) show ability of the forms to accept electrons from nucleophiles.

Electroaccepting power (ω^+) is a global reactivity index. This index can be specified for each atom in a molecule by Fukui functions [5f] via expression (4) [5g]:

$$\omega_k^+ = f_k^+ \omega^+ \tag{4}$$

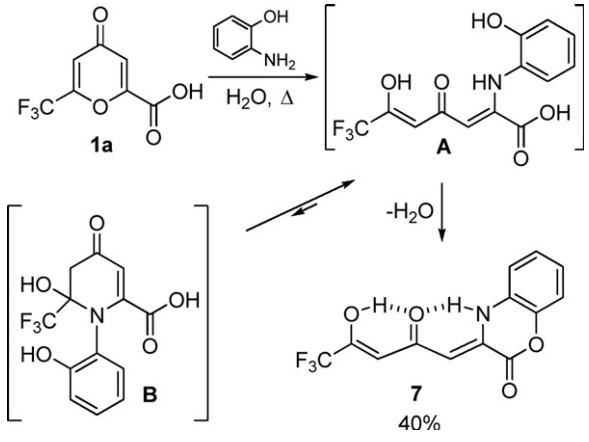
where index ω_k^+ is the regional electrophilicity condensed to atom k in a molecule, and f_k^+ is the condensed Fukui function [5h] at atom k for a nucleophilic attack, which is given by

$$f_k^+ = q_k(N+1) - q_k(N) \tag{5}$$

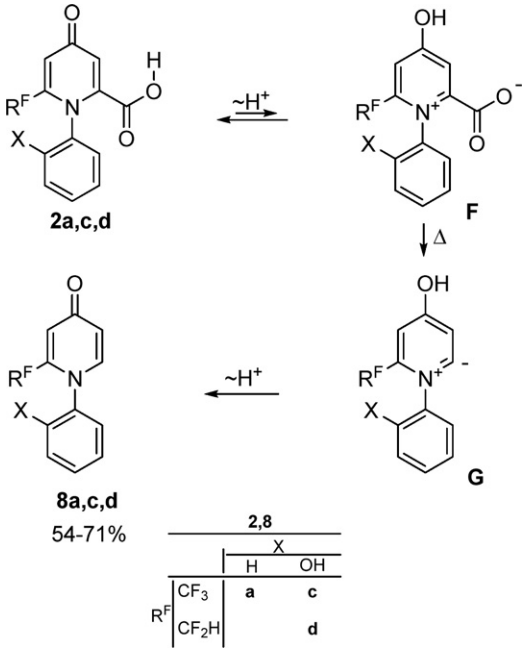
where N is the total number of electrons in the reference molecule, $q_k(N)$ and $q_k(N+1)$ denote the atomic population on atom k in the molecule with N and $N+1$ electrons.

The results of the calculations of global and regional electrophilicity of **1a** and its protonated, and deprotonated forms are compiled in Table 1. Protonation of **1a** (ω^+ = 6.832 eV) dramatically increases electrophilicity of the pyrone system to value 35.143 eV (protonated form **1aH$^+$**). Deprotonation of **1a** to anion **1a$^-$** moderately decreases ω^+ to value 0.273 eV. According to Table 1, atoms C-2 in **1a** and **1aH$^+$** possess a higher the regional electrophilicity ($\omega_2^+ = 0.544$ eV for **1a** and 3.486 eV for **1aH$^+$**) than atoms C-6 in the same structures ($\omega_6^+ = 0.327$ and 2.520 eV, respectively). Atoms C-2 and C-6 in anion **1a$^-$** possess the lowest values of the regional electrophilicity (0.0144 and 0.0293 eV, respectively), and these values show that in contrast to **1a** and **1aH$^+$**, electrophilicity of carbon C-6 in the anion is about 2.0 times higher than electrophilicity of carbon C-2. Since the relative electrophilicity (ω_2^+/ω_6^+) decreases from **1a** to **1a$^-$** ($1.66 < 1.38 < 0.49$), the formation of intermediates type of **E** (attacking at the C-6 carbon) becomes more likely in accordance with this series. Therefore, treatment of compounds **1a**,**b** with *o*-PhDA without adding any strong acid leads to the formation of **5** or **6** (via the carboxylate anions), whereas conducting the reactions of **1** with aromatic amines in a strongly acidified medium gives **2** or **3** (via attacking at the C-2 carbon and the formation of **A**). The decrease of the relative electrophilicity from **1a** to **1aH$^+$** (1.66 versus 1.38) explains the appearance of some amounts of **5** in strongly acidified media due to the existence of trace concentrations of the protonated forms of **1**.

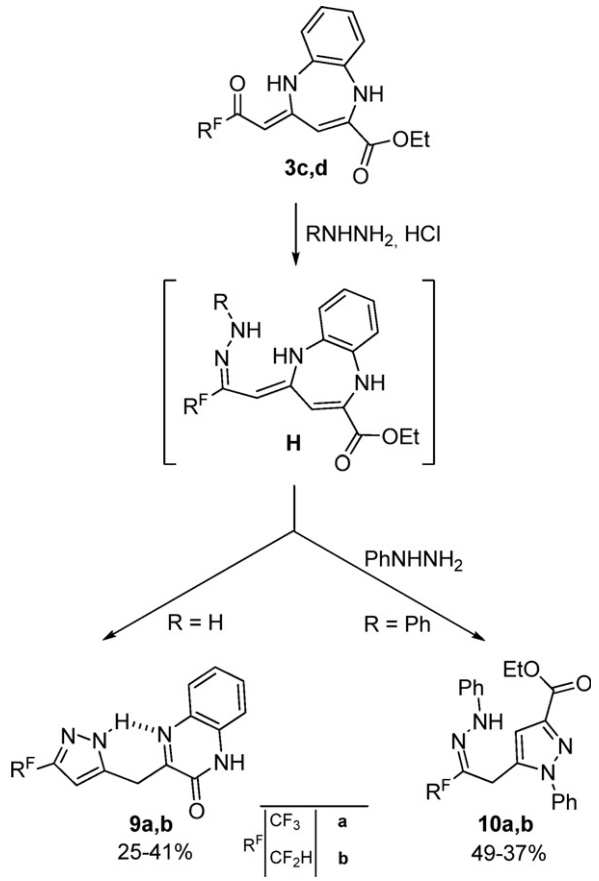
Heating pyrone **1a** with a weaker than *o*-PhDA nucleophile, *o*-aminophenol in water without addition of a strong acid led to the formation of (*Z*)-(5,5,5-trifluoro-2,4-dioxopentylidene)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one **7** in 40% yield (Scheme 4). Probably, nucleophilicity of *o*-aminophenol not enough to attack effectively the C-6 atom of **1a$^-$** with $\omega_6^+ = 0.0293$ eV, and this nucleophile attacks mainly more electrophilic atom C-2 of more reactive substrate **1aH$^+$**, which must be presented in the reaction mixture as one of the forms of the equilibrium protonation–deprotonation process, with $\omega_2^+ = 3.486$ eV, leading to **7** (instead of



Scheme 4.



Scheme 5.



Scheme 6.

2c, which is formed in acidified media). The low yield (40%) of compound **7** can be explained by the formation of side products, which were not isolated, and, therefore, not identified. Quinoxalinones **4** and their structurally closest analogue, benzoxazinone **7**, are fluorine-containing representatives of important groups of compounds, (*Z*)-(2-oxoalkylidene)-1,2,3,4-tetrahydro-2-quinaxolones and (*Z*)-(2-oxoalkylidene)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-ones, many derivatives of which possess antimicrobial activities [6].

Pyridone **2c**, which was isolated in acidified media (Scheme 1), or the corresponding oxazepine were not detected in crude compound **7**. These facts arise from slow dehydratation of cyclic tautomer **B** into pyridone **2c** in low-acid media and lower stability of the oxazepine ring (in comparison with the diazepine ring). 6-(Difluoromethyl)comanic acid **1b** do not give detectible amounts of the corresponding CF_2H-containing benzoxazinone in the reaction with *o*-aminophenol.

6-R^F-4-pyridon-2-carboxylic acids **2a**,**c**,**d** easily decarboxylate by melting to give 2-R^F-pyridones **8a**,**c**,**d** in 54–71% yield (Scheme 5), and only *N*-phenyl-2-(difluoromethyl)-4-pyridone **8b** cannot be synthesized via decarboxylation due to the formation of a complex mixture of products. Such behavior of **2b** can be explained by relatively high acidity of the hydrogen connected to the $-CF_2-C{=}C-CO$ moiety. A likely pathway for this facile decarboxylation involves the formation of intermediate betaines **F** and **G** [7]. The corresponding basic intermediate type of **G** derived from **2b** could react with this acidic hydrogen leading to side products. The electron-withdrawing R^F group should promote the decarboxylation due to additional stabilization of the negative charge at the carbons of the pyridine ring. In the ^{19}F NMR spectrum of pyridone **8d** two nonequivalent fluorines appeared as doublets of doublets at δ 41.9 and 46.3 ($^2J_{F,F}$ 303.3 Hz, $^2J_{H,F}$ 53.0 Hz), due to a high energy barrier for rotation around the C–N bond.

Benzodiazepines **3** are chemically active substrates toward nucleophiles. Thus, reactions of **3c**,**d** with hydrazine and phenylhydrazine in the presence of HCl occur with destruction of the diazepine ring to produce different pyrazole derivatives (**9a**,**b** and **10a**,**b**) (Scheme 6). It is more likely that these reactions proceed through intermediate hydrazones **H**. Recyclization of the *N*-unsubstituted intermediate hydrazones leads to the formation of [(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methyl]-1,2,3,4-tetrahydro-2-quinaxolones **9**. The more sterically hindered nucleophilic nitrogen atom of the *N*-phenylhydrazone intermediates, probably, unable to attack intramolecularly the diazepine ring. Instead, this intermediate reacts with excess phenylhydrazine with loss of *o*-PhDA to give pyrazole-phenylhydrazones **10** (**10a** earlier was prepared rapidly from pyrone **1c** and $PhNHNH_2$ [2f]).

The structures of the synthesized compounds were confirmed by ^1H, ^{19}F, ^{13}C NMR and IR spectroscopy, and elemental analysis. In the ^1H NMR spectra of pyridones **2** the pyridone protons (H-3 and H-5) appeared either as two characteristic doublets at field in a δ 6.50–6.85 range (^4J 2.7 Hz) or as a singlet at about δ 6.6 (in the cases when the protons H-3 and H-5 have identical chemical shifts). In the ^{19}F NMR spectra of the pyridones the signal of the trifluoromethyl group appeared at about δ 100.0.

The characteristic triplet at δ 5.30 (J 1.9 Hz) of the diazepine CH proton (coupling to two NH protons) in the ^1H NMR spectrum of benzodiazepine **3c** confirms the 1*H*,5*H*-1,5-benzodiazepinic structure of compounds **3** [8]. Similar buried triplet at δ 5.24 was observed in the ^1H NMR spectrum of **5a**. In the ^{13}C NMR spectrum of benzodiazepine **3a** the trifluoromethyl and carbonyl carbons of the side chain appeared as quartets at δ 117.1 ($^1J_{C,F}$ 289.1 Hz) and 175.7 ($^2J_{C,F}$ 32.4 Hz), respectively, confirming that the trifluoromethyl substituent is attached to the carbonyl group. In the ^{13}C NMR spectrum of **5a** three characteristic quartets of the trifluoromethyl (δ 120.9, $^1J_{C,F}$ 275.7 Hz) and diazepine (δ 133.4, $^2J_{C,F}$ 30.8 Hz; δ 98.1, $^3J_{C,F}$ 5.2 Hz) carbons were observed, confirming the CF_3-diazepine structure of **5**. In the ^1H NMR spectra of the diimine tautomers **6a**,**b** the methylene protons appeared as singlets at δ 3.67–3.50 [9]. According to the ^{19}F NMR spectra the trifluoromethyl group in **5a** appeared at δ 94.1, whereas the same substituent in diimine tautomer **6a** appeared at δ 90.6.

Compounds **3–7** and **9** possess near-planar structures due to intramolecular hydrogen bond stabilizing effect (in the ^{1}H NMR spectra the hydrogen bonded NH protons appeared as low-field signals at about δ 11.2–13.2).

3. Conclusion

Thus, we have shown the versatile reactivity of 2-CF_3(CF_2H)-4-pyrones toward aromatic amines, synthesized the first representatives of 2-tri(di)fluoromethylated *N*-phenyl-4-pyridones, novel CF_3(CF_2H)-containing benzodiazepines, quinoxalinones and (*Z*)-3-[(1*H*-benzo[*b*][1,4]diazepin-4-yl)methylene]-3,4-dihydroquinoxalin-2(1*H*)-ones, and explained possible reasons of the regioselectivitiy of the reactions. Electrophilic properties of such 2-R^F-4-pyrones as 6-(tri(di)fluoromethyl)comanic acids and their ethyl esters were evaluated.

4. Experimental

4.1. General

^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on Bruker AVANCE DRX-400 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) downfield from TMS, shifts for ^{19}F NMR spectra are reported in ppm downfield from internal C_6F_6. Coupling constants (*J*) are given in hertz (Hz). Infrared spectra (IR) were recorded on Nicolet 6700 spectrometer, equipped with attenuated total reflection accessory (ATR), absorbance frequencies are given at maximum of intensity in cm^{-1}. Density Functional Theory (DFT) calculations of **1a**, **1aH$^+$** and **1a$^-$** have been performed using the PRIRODA [10a,b] program. A generalized gradient approximation (GGA) exchange-correlation density functional by Perdew, Burke and Ernzerhoff (PBE) [11] was used with double-zeta-polarized quality. Correlation-consistent Gaussian basis set: (2*s*,2*p*,1*d*)/(10*s*,7*p*,3*d*) for C and O atoms; (2*s*,1*p*)/(6*s*,2*p*) for H atoms [12]. The electroaccepting power (ω^+) was evaluated using Eq. (2). The Koopmans' theorem [5e] was utilized to calculate values of the ionization potential (*I*) and electron affinity (*A*) of the pyrone structures (Eq. (3)). The regional electrophilicity indices (ω_k^+) of atoms C-2 and C-6 (ω_2^+ and ω_6^+) were evaluated using Eq. (4). The condensed Fukui functions were calculated from the Mulliken population of atoms C-2 and C-6 in the molecule with *N* and *N* + 1 electrons (Eq. (5)).

4.2. 6-(Trifluoromethyl)-1,4-dihydro-4-oxo-1-phenylpyridine-2-carboxylic acid (**2a**)

Method A. Aniline (140 mg, 1.5 mmol) and conc. HCl (0.5 mL) were added to a solution of **1a** [2g] (250 mg, 1.2 mmol) in 40% aqueous EtOH (4 mL). The mixture was refluxed for 24 h, excess EtOH was distilled off, and the residue was diluted with H_2O (3 mL). The resulting residue was filtered and crystallized from aqueous EtOH to give **2a** (75 mg, 30%) as white solid, mp 186–187 °C. Method B. KOH (54 mg, 0.96 mmol) was added to a suspension of **2e** (100 mg, 0.32 mmol) in H_2O (2.0 mL). The mixture was stirred at ambient temperature for 1 h, filtered, and the cooled filtrate quenched with 15% HCl until pH ≈ 1–2. The residue was filtered, washed with water and dried to give **2a** (67 mg, 74%) as white solid, mp 186–187 °C; δ_H (400 MHz, DMSO-d_6) 6.61 (1H, d, *J* 2.7 Hz, CH), 6.83 (1H, d, *J* 2.7 Hz, CH), 7.48–7.57 (5H, m, Ph), 14.2 (1H, br s, CO_2H); ν_{max} (ATR) 1720, 1638, 1484 cm^{-1}; δ_F (376.5 MHz, DMSO-d_6) 102.2 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 117.2 (C-3), 117.9 (q, $^3J_{C,F}$ 4.2 Hz, C-5), 119.6 (q, $^1J_{C,F}$ 275.1 Hz, CF_3), 128.7, 129.4, 130.4, 137.1, 138.4 (q, $^2J_{C,F}$ 32.8 Hz, C-6), 147.68, 162.6 (CO), 176.6 (CO) [Found: C, 55.14; H, 2.62; N, 4.92. $C_{15}H_{12}F_3NO_3$ requires C, 55.13; H, 2.85; N, 4.95%].

4.3. 6-(Difluoromethyl)-1,4-dihydro-4-oxo-1-phenylpyridine-2-carboxylic acid (**2b**)

Method A. A mixture of **1b** (39 mg, 0.21 mmol), aniline (21 mg, 0.22 mmol) and conc. HCl (0.1 mL) was refluxed in 40% aqueous EtOH (0.8 mL) for 1.5 days. Then excess EtOH was distilled off, the resulting mixture was diluted with water, the residue was filtered, washed with water and dried to give **2b** (11 mg, 21%) as gray solid, mp 187–188 °C. Method B. KOH (47 mg, 0.84 mmol) was added to a suspension of **2f** (68 mg, 0.23 mmol) in H_2O (1.5 mL). The mixture was stirred at ambient temperature for 1 h, filtered, and the cooled filtrate quenched with 15% HCl until pH ≈ 1–2. The residue was filtered, washed with water (2 mL) and dried to give **2b** (42 mg, 70%) as white solid, mp 187–188 °C; ν_{max} (ATR) 3547, 1642, 1590, 1459, 1376 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.55 (1H, t, $^2J_{H,F}$ 52.6 Hz, CF_2H), 6.56 (1H, d, *J* 2.7 Hz, CH), 6.59 (1H, d, *J* 2.7 Hz, CH), 7.46–7.55 (5H, m, Ph), 13.5–15.0 (1H, br s, CO_2H); δ_F (376.5 MHz, DMSO-d_6) 45.0 (d, $^2J_{H,F}$ 52.6 Hz, CF_2H) [Found: C, 55.06; H, 3.79; N, 4.93. $C_{13}H_9F_2NO_3{\cdot}H_2O$ requires C, 55.13; H, 3.91; N, 4.95%].

4.4. 6-(Trifluoromethyl)-1,4-dihydro-4-oxo-1-(2-hydroxyphenyl)pyridine-2-carboxylic acid (**2c**)

A solution of **1a** (200 mg, 2.12 mmol), *o*-aminophenol (120 mg, 2.29 mmol) and conc. HCl (0.5 mL) in H_2O (2 mL) was refluxed for 6 h. The residue was filtered and crystallized from aqueous EtOH to give **2c** (180 mg, 62%) as white powder, mp 177–178 °C. ν_{max} (ATR) 2940, 2712, 1751, 1633, 1601, 1556, 1465 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.59 (1H, d, *J* 2.7 Hz, H-3), 6.82 (1H, d, *J* 2.7 Hz, H-5), 6.87 (1H, t, *J* 7.7 Hz, H-5′), 6.94 (1H, d, *J* 8.1 Hz, H-6′), 7.33 (1H, td, *J* 7.7, 1.4 Hz, H-4′), 7.37 (1H, d, *J* 8.1 Hz, H-3′), 10.37 (1H, s, OH); δ_F (376.5 MHz, DMSO-d_6) 100.1 (s, CF_3) [Found: C, 52.64; H, 2.60; N, 4.71. $C_{13}H_8F_3NO_4$ requires C, 52.19; H, 2.70; N, 4.68%].

4.5. 6-(Difluoromethyl)-1,4-dihydro-4-oxo-1-(2-hydroxyphenyl)pyridine-2-carboxylic acid (**2d**)

A solution of acid **1b** (150 mg, 0.79 mmol), *o*-aminophenol (90 mg, 0.82 mmol) and conc. HCl (0.25 mL) in H_2O (2 mL) was refluxed for 3 h. The residue was filtered and crystallized from aqueous EtOH to give **2d** (92 mg, 48%) as white crystals, mp 179–180 °C; ν_{max} (ATR) 3067, 1630, 1462 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.47 (1H, t, $^2J_{H,F}$ 52.8 Hz, CF_2H), 6.55 (1H, d, *J* 2.7 Hz, H-3 (H-5)), 6.58 (1H, d, *J* 2.7 Hz, H-5 (H-3)), 6.89 (1H, t, *J* 7.6 Hz, arom.), 6.97 (1H, d, *J* 8.6 Hz, arom.) 7.30–7.37 (2H, m, arom.), 10.21–10.65 (1H, br s, OH); δ_F (376.5 MHz, DMSO-d_6) 44.9 (d, $^2J_{H,F}$ 52.5 Hz, CF_2H) [Found: C, 54.44; H, 3.34; N, 4.88. $C_{13}H_9F_2NO_4{\cdot}0.33\ H_2O$ requires C, 54.36; H, 3.39; N, 4.88%].

4.6. Ethyl 6-(trifluoromethyl)-1,4-dihydro-4-oxo-1-phenylpyridine-2-carboxylate (**2e**)

Method A. Aniline (100 mg, 1.1 mmol) and conc. HCl (0.2 mL) were added to a solution of ethyl 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylate **1c** [2g] (250 mg, 1.06 mmol) in EtOH (3 mL). The mixture was refluxed for 24 h, the solvent was evaporated, and the residue was quenched with water (10 mL). The resulting residue was filtered and crystallized from petroleum ether (10 mL) to give compound **2e** (150 mg, 47%) as white crystals, mp 100–101 °C. The use H_2SO_4 instead of HCl as a strong acid (refluxing a mixture of **1c** (400 mg, 1.69 mmol) and H_2SO_4 (0.8 mL) in EtOH (4 mL) for 18 h) allows preparation of **2e** in 65% yield; ν_{max} (ATR) 1736, 1641, 1595, 1586, 1487 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.1 Hz, CH_3), 4.00 (2H, q, *J* 7.1 Hz, CH_2), 6.76 (1H, d, *J* 2.7 Hz, H-3), 6.96 (1H, d, *J* 2.7 Hz, H-5), 7.37 (2H, d, *J* 8.0 Hz, H-2′, H-6′), 7.47 (2H, dd, *J* 7.5, 8.0 Hz, H-3′, H-5′), 7.54 (1H, t, *J* 7.5 Hz, H-4′); δ_F

(376.5 MHz, DMSO-d_6) 102.2 (s, CF_3) [Found: C, 57.66; H, 3.72; N, 4.41. $C_{15}H_{12}F_3NO_3$ requires C, 57.88; H, 3.89; N, 4.50%].

4.7. Ethyl 6-(difluoromethyl)-1,4-dihydro-4-oxo-1-phenylpyridine-2-carboxylate (**2f**)

A mixture of **1d** (150 mg, 0.69 mmol), aniline (80 mg, 0.86 mmol) and conc. H_2SO_4 (0.2 mL) in EtOH (2 mL) was refluxed for 30 h. After cooling to ambient temperature, the mixture was diluted with water, the residue was filtered and crystallized from a mixture of petroleum ether and toluene (1:1) to give **2f** (100 mg, 50%) as white solid, mp 129–130 °C; ν_{max} (ATR) 1728, 1637, 1578, 1489, 1404 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 0.88 (3H, t, *J* 7.1 Hz, CH_3), 3.93 (2H, q, *J* 7.1 Hz, CH_2), 6.58 (1H, t, $^2J_{H,F}$ 52.5 Hz, CF_2H), 6.62 (2H, s, H-3, H-5), 7.47–7.58 (5H, m, Ph); δ_F (376.5 MHz, DMSO-d_6) 44.9 (d, $^2J_{H,F}$ 52.5 Hz, CF_2H) [Found: C, 61.30; H, 4.39; N, 4.80. $C_{15}H_{13}F_2NO_3$ requires C, 61.43; H, 4.47; N, 4.78%].

4.8. Ethyl 6-(trifluoromethyl)-1,4-dihydro-4-oxo-1-(2-hydroxyphenyl)pyridine-2-carboxylate (**2g**)

A solution of **1c** (500 mg, 2.1 mmol), *o*-aminophenol (250 mg, 2.29 mmol) and H_2SO_4 (1 mL) in EtOH (6 mL) was refluxed for 24 h. Then the reaction mixture was diluted with H_2O (20 mL), the residue was filtered, washed with H_2O and crystallized from aqueous EtOH to give **2g** (450 mg, 65%) as white crystals, mp 188–189 °C; ν_{max} (ATR) 1751, 1631, 1601, 1555, 1509 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 0.92 (3H, t, *J* 7.1 Hz, CH_3), 3.95 (2H, qd, *J* 7.1, 1.6 Hz, CH_2), 6.65 (1H, d, *J* 2.7 Hz, H-3), 6.85 (1H, d, *J* 2.7 Hz, H-5), 6.88 (1H, t, *J* 7.5 Hz, arom.), 6.95 (1H, d, *J* 8.2 Hz, arom.), 7.33–7.40 (2H, m, arom.), 10.45 (1H, s, OH); δ_F (376.5 MHz, DMSO-d_6) 100.0 (d, *J* 1.0 Hz, CF_3) [Found: C, 54.74; H, 3.84; N, 4.31. $C_{15}H_{12}F_3NO_3$ requires C, 55.05; H, 3.70; N, 4.28%].

4.9. Ethyl 6-(difluoromethyl)-1,4-dihydro-4-oxo-1-(2-hydroxyphenyl)pyridine-2-carboxylate (**2h**)

A mixture of **1d** (200 mg, 0.92 mmol), *o*-aminophenol (110 mg, 1.0 mmol) and H_2SO_4 (0.4 mL) was refluxed in EtOH (3 mL) for 48 h. Then the mixture was diluted with H_2O (10 mL), the residue was filtered and crystallized from aqueous EtOH to give **2h** (108 mg, 40%) as white crystals, mp 210–211 °C; ν_{max} (ATR) 3010, 1741, 1624, 1602, 1541 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 0.92 (3H, t, *J* 7.1 Hz, CH_3), 3.96 (2H, q, *J* 7.1 Hz, CH_2), 6.51 (1H, t, $^2J_{H,F}$ 52.8 Hz, CF_2H), 6.60 (2H, s, H-3, H-5), 6.91 (1H, t, *J* 7.6 Hz, arom.), 6.99 (1H, d, *J* 8.1 Hz, arom.), 7.33–7.38 (2H, m, arom.), 10.49 (1H, s, OH); δ_F (376.5 MHz, DMSO-d_6) 44.89 (d, $^2J_{H,F}$ 52.5 Hz, CF_2H) [Found: C, 58.26; H, 4.14; N, 4.47. $C_{15}H_{13}F_2NO_4$ requires C, 58.25; H, 4.24; N, 4.53%].

4.10. (Z)-4-(2-Oxo-3,3,3-trifluoropropyliden)-1,5-dihydro-1,5-benzodiazepin-2-carboxylic acid (**3a**) and (Z)-(5,5,5-trifluoro-2,4-dioxopentylidene)-1,2,3,4-tetrahydro-2-quinaxolone (**4a**)

A mixture of **1a** (250 mg, 1.20 mmol), *o*-PhDA (140 mg, 1.29 mmol) and conc. HCl (0.5 mL) was refluxed in H_2O (4 mL) for 30 min. The residue was filtered, dried, treated with hot EtOH (15 mL). Hot filtration gave **4a** (100 mg, 28%) as red solid, mp 272–273 °C. After evaporation of excess the solvent from the filtrate, **3a** was isolated by filtration (105 mg, 29%) as black solid, mp 243–244 °C; **3a:** ν_{max} (ATR) 3320, 1710, 1638, 1616, 1572 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 5.26 (1H, buried t, CH), 5.48 (1H, s, CH), 6.50 (1H, dd, *J* 7.3, 1.7 Hz, arom.), 6.77–6.86 (2H, m, arom.), 6.92 (1H, dd, *J* 7.5, 1.8 Hz, arom.), 7.97 (1H, s, NH), 11.22 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 86.9 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 92.8 (CH), 98.8 (CH), 117.1 (q, $^1J_{C,F}$ 289.1 Hz, CF_3), 122.6, 122.7, 125.3, 126.2, 130.4, 135.1, 144.8, 163.3, 164.2, 175.7 (q, $^2J_{C,F}$ 32.4 Hz, CO) [Found: C, 52.24; H, 3.00; N, 9.36. $C_{13}H_9F_3N_2O_3$ requires C, 52.36; H, 3.04; N, 9.39%]. For data of **4a**, please see Section 4.14.

4.11. (Z)-4-(2-Oxo-3,3-difluoropropyliden)-1,5-dihydro-1,5-benzodiazepin-2-carboxylic acid (**3b**) and (Z)-3-[(2-(difluoromethyl)-1H-benzo[b][1,4]diazepin-4-yl)methylene]-3,4-dihydroquinoxalin-2(1H)-one (**4b**)

A mixture of **1b** (150 mg, 0.79 mmol), *o*-PhDA (93 mg, 0.86 mmol) and conc. HCl (0.3 mL) in H_2O (1.5 mL) was refluxed for 30 min. The residue was filtered, washed with water and dried to give a mixture of **3b** and **4b** (130 mg, 59%, ratio **3b**:**4b** = 28:72), mp ~225 °C; δ_H (400 MHz, DMSO-d_6) **3b** (28%) 5.24 (1H, buried t, CH), 5.37 (1H, s, CH), 6.12 (1H, t, $^2J_{H,F}$ 54.5 Hz, CF_2H), 6.49 (1H, m, arom.), 6.79 (2H, m, arom.), 6.93 (1H, m, arom.), 7.88 (1H, d, *J* 0.6 Hz, NH), 11.36 (1H, s, NH); **4b** (72%) 6.04 (1H, s, CH), 6.06 (1H, s, CH), 6.13 (1H, t, $^2J_{H,F}$ 53.4 Hz, CF_2H), 7.10–7.18 (3H, m, arom.), 7.58 (1H, d, *J* 7.5 Hz, arom.), 12.08 (1H, s, NH), 12.58 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) **3b** (28%) 36.8 (d, $^2J_{H,F}$ 54.5 Hz, CF_2H); **4b** (72%) 37.1 (d, $^2J_{H,F}$ 53.4 Hz, CF_2H).

4.12. Ethyl (Z)-4-(2-oxo-3,3,3-trifluoropropyliden)-1,5-dihydro-1,5-benzodiazepin-2-carboxylate (**3c**)

A mixture of **1c** (1.0 g, 4.2 mmol), *o*-PhDA (500 mg, 4.62 mmol) and conc. HCl (1.0 mL) was stirred in EtOH (10 mL) at 50 °C for 3 h. After cooling the reaction mixture to ambient temperature, the residue was filtered, washed with water and dried. Benzodiazepine **3c** was extracted from this residue by hot CCl_4 (25 mL) and separated from insoluble in this solvent a mixture of compounds **4a** and **5a** (~200 mg) by hot filtration. After evaporation of CCl_4 from the extract, the residue was crystallized from EtOH to give **3c** (830 mg, 60%) as black crystals, mp 157–158; ν_{max} (ATR) 3329, 1708, 1624, 1606, 1559, 1491 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.28 (3H, t, *J* 7.1 Hz, CH_3), 4.25 (2H, q, *J* 7.1 Hz, CH_2), 5.29 (1H, t, *J* 1.9 Hz, H-3), 5.54 (1H, s, CH), 6.52 (1H, dd, *J* 7.4, 1.9 Hz, H-6), 6.83 (2H, qn d, *J* 7.4, 1.8 Hz, H-7, H-8), 6.92 (1H, dd, *J* 7.5, 1.9 Hz, H-9), 8.06 (1H, d, *J* 1.6 Hz, NH), 11.22 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 86.9 (s, CF_3) [Found: C, 55.24; H, 3.77; N, 8.52. $C_{15}H_{13}F_3N_2O_3$ requires C, 55.22; H, 4.02; N, 8.59%].

4.13. Ethyl (Z)-2-(2-oxo-3,3-difluoropropyliden)-1,5-dihydro-1,5-benzodiazepin-4-carboxylate (**3d**)

A mixture of **1d** (150 mg, 0.69 mmol), *o*-PhDA (82 mg, 0.76 mmol) and conc. HCl (0.3 mL) was stirred in EtOH (1.5 mL) for 6 h at 50 °C. After cooling, the reaction mixture was diluted with H_2O (5 mL), the residue was filtered, washed with H_2O and dried to give a crude sample of **3d** containing traces of **5b**. To separate **3d** from **5b** by extraction the crude product was treated with CCl_4 (15 mL), the mixture was filtered to give the extract of **3d** and the residue of **5b** (15 mg, 5%). The solvent was evaporated from the extract and the residue was crystallized from EtOH to give analytically pure **3d** (85 mg, 40%) as black crystals, mp 150–151 °C; ν_{max} (ATR) 3326, 1708, 1637, 1619, 1559, 1488 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, CH_3), 4.25 (2H, q, *J* 7.1 Hz, CH_2), 5.28 (1H, s, CH), 5.44 (1H, s, CH), 6.14 (1H, t, $^2J_{H,F}$ 54.5 Hz, CF_2H), 6.52 (1H, m, arom.), 6.80–6.84 (2H, m, arom.), 6.95 (1H, m, arom.), 7.98 (1H, s, NH), 11.35 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 36.7 (d, *J* 54.5 Hz, CF_2H) [Found: C, 58.07; H, 4.53; N, 8.81. $C_{15}H_{14}F_2N_2O_3$ requires C, 58.44; H, 4.58; N, 9.09%].

4.14. (Z)-(5,5,5-Trifluoro-2,4-dioxopentylidene)-1,2,3,4-tetrahydro-2-quinaxolone (**4a**)

Method A. The residue isolated by hot filtration (Method 4.10) of the extract of **3a** was analytically pure compound **4a** (100 mg, 28%), red solid, mp 272–273 °C. Method B. Benzodiazepine **3c**

(150 mg, 0.46 mmol) was refluxed in a mixture of AcOH (1 mL) and conc. HCl (1 mL) for 30 min. Then the reaction mixture was diluted with water (3 mL), the residue was filtered and crystallized from AcOH to give **4a** (42 mg, 31%) as red solid. Method C. Alternatively, **4a** was prepared by refluxing a mixture of **1c** (250 mg, 1.06 mmol), *o*-PhDA (125 mg, 1.15 mmol) and H_2SO_4 (0.5 mL) in EtOH (3 mL) for 4 h. After cooling the reaction mixture was diluted with H_2O (5 mL), the residue was filtered and crystallized from AcOH (12 mL) to give **4a** (140 mg, 36%) as red solid. Method D. Alternatively **4a** was prepared by hydrolysis of the mixture **5a**–**6a** (21:79) with aqueous HCl. A mixture of **5a**–**6a** (80 mg, 0.22 mmol) and aqueous HCl (20%, 2 mL) was refluxed for 30 min. The residue was filtered and crystallized from AcOH to give **4a** (31 mg, 46%). Hydrolysis of pure **5a** in the same conditions gives **4a** in 60% yield as red solid; ν_{max} (ATR) 2860, 1678, 1605, 1542 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.15 (1H, s, CH), 6.32 (1H, s, CH), 7.13–7.20 (3H, m, arom.), 7.64 (1H, d, *J* 7.7 Hz, arom.), 12.15 (1H, br s, NH), 12.50 (1H, br s, OH); δ_F (376.5 MHz, DMSO-d_6) 89.0 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 92.4 (CH), 99.5 (CH), 115.4, 117.1, 118.5 (q, $^1J_{C,F}$ 277.4 Hz, CF_3), 123.6, 123.7, 124.8, 126.8, 145.7, 154.9 (CONH), 160.4 (buried q, C-CF_3), 188.5 (CO) [Found: C, 52.28; H, 2.91; N, 9.40. $C_{13}H_9F_3N_2O_3$ requires C, 52.36; H, 3.04; N, 9.39%].

4.15. (Z)-3-[(2-(Trifluoromethyl)-1H-benzo[b][1,4]diazepin-4-yl)methylene]-3,4-dihydroquinoxalin-2(1H)-one (**5a**) and its diimine tautomer (**6a**)

A mixture of **1a** (250 mg, 1.2 mmol) and *o*-PhDA (290 mg, 2.7 mmol) was refluxed in EtOH (4 mL) for 30 min, the residue was filtered and washed with EtOH to give a mixture of **6a** and **5a** (280 mg, 63%) as red solid, mp 325–327 °C; ν_{max} (ATR) 2845, 1666, 1620, 1604, 1589 cm^{-1}; δ_H (400 MHz, DMSO-d_6) **5a** (21%) 5.24 (1H, buried t, CH), 6.03 (1H, s, CH), 6.76–6.89 (3H, m, arom.), 7.00 (1H, dd, *J* 7.8, 1.2 Hz, arom.), 7.19–7.28 (2H, m, arom.), 7.36 (1H, td, *J* 7.8, 1.2 Hz, arom.), 7.71 (1H, dd, *J* 7.9, 1.0 Hz, arom.), 8.36 (1H, s, NH), 12.20 (1H, s, NH); **6a** (79%) 3.67 (2H, s, CH_2), 5.98 (1H, s, CH), 7.22 (2H, t, *J* 7.8 Hz, arom.), 7.28–7.33 (2H, m, arom.), 7.43–7.48 (3H, m, arom.), 7.70 (1H, d, *J* 7.8 Hz, arom.), 12.16 (1H, s, NH), 13.11 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) **5a** (21%) 94.1 (s, CF_3); **6a** (79%) 90.6 (s, CF_3) [Found: C, 61.44; H, 3.51; N, 15.09. $C_{19}H_{13}F_3N_4O$ requires C, 61.62; H, 3.54; N, 15.13%]. To transform **6a** into **5a** the mixture of the tautomers (100 mg) was heated in DMSO (4 mL) at 120 °C for 30 min. Then the mixture was diluted with water (10 mL), the residue was filtered, dried and crystallized from acetone (25 mL) to give **5a** (65 mg, 65%) as red crystals, mp 334–336 °C; (ATR) 3433, 1714, 1656, 1632 cm^{-1}; δ_C (100 MHz, DMSO-d_6) 97.4 (CH), 98.1 (q, $^3J_{C,F}$ 5.2 Hz, CH), 115.0, 120.9 (q, $^1J_{C,F}$ 275.7 Hz, CF_3), 121.2, 121.3, 122.9, 123.4, 123.9, 126.1, 127.7, 130.1, 130.6, 131.6, 132.3, 133.4 (q, $^2J_{C,F}$ 30.8 Hz, C-CF_3), 147.9, 154.6, 155.0. The use ratio **1a**:*o*-PhDA = 1:1 gives 38% yield of the mixture of tautomers **5a** and **6a**.

4.16. (Z)-3-[(2-(Difluoromethyl)-1H-benzo[b][1,4]diazepin-4-yl)methylene]-3,4-dihydroquinoxalin-2(1H)-ones (**5b**) and its diimine tautomer (**6b**)

A mixture of **1b** (70 mg, 0.37 mmol) and *o*-PhDA (80 mg, 0.74 mmol) was refluxed in EtOH (2.5 mL) for 30 min. After heating the residue was filtered and washed with EtOH to give a mixture of **5b** and **6b** (57 mg, 44%) as red powder, mp 317–319 °C; ν_{max} (ATR) 2994, 2895, 1710, 1668, 1619, 1601, 1503, 1474 cm^{-1}; δ_H (400 MHz, DMSO-d_6) **5b** (65%) 4.96 (1H, buried t, CH), 5.86 (1H, s, CH), 6.35 (1H, t, $^2J_{H,F}$ 54.1, CF_2H), 6.72–6.86 (3H, m, arom.), 6.93 (1H, dd, *J* 7.9, 1.6 Hz, arom.), 7.19–7.26 (2H, m, arom.), 7.33 (1H, td, *J* 7.6, 1.4 Hz, arom.), 7.68 (1H, dd, *J* 8.0, 1.2 Hz, arom.), 8.19 (1H, buried d, NH), 12.15 (1H, buried d, NH); **6b** (35%) 3.50 (2H, s, CH_2), 5.92 (1H, s, CH), 6.62 (1H, t, $^2J_{H,F}$ 54.5 Hz, CF_2H), 7.18–7.45 (7H, m, arom.), 7.68 (1H, d, *J* 7.5 Hz, arom.), 12.13 (1H, s, NH), 13.11 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) **5b** (65%) 41.8 (d, $^2J_{H,F}$ 54.4 Hz, CF_2H); **6b** (35%) 44.5 (d, $^2J_{H,F}$ 54.0 Hz, CF_2H); To transform **6b** into **5b** the mixture of the tautomers (40 mg) was heated in DMSO (1.6 mL) at 80 °C for 4 h. Then the mixture was diluted with water (10 mL), the residue was filtered, dried and crystallized from acetone to give analytically pure **5b** (22 mg, 55%) as red solid, mp 317–319 °C.

4.17. (Z)-(5,5,5-Trifluoro-2,4-dioxopentylidene)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**7**)

A mixture of **1a** (250 mg, 1.2 mmol) and aminophenol (145 mg, 1.3 mmol) was refluxed in EtOH (3 mL) for 1 h. After cooling the mixture to ambient temperature the residue was filtered and crystallized from EtOH to give **7** (145 mg, 40%) as yellow powder, mp 206–208 °C; ν_{max} (ATR) 3116, 1749, 1668, 1622, 1614 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 5.11 (1H, s, CH), 6.66 (1H, s, CH), 6.80 (1H, d, *J* 7.7 Hz, arom.), 6.94 (1H, td, *J* 7.5, 0.8 Hz, arom.), 7.08 (1H, d, *J* 7.5 Hz, arom.), 7.21 (1H, tt, *J* 7.7, 0.9 Hz, arom.), 10.64 (1H, s, NH) [Found: C, 52.07; H, 2.56; N, 4.64. $C_{13}H_8F_3NO_4$ requires C, 52.19; H, 2.70; N, 4.68%].

4.18. 2-(Trifluoromethyl)-1-phenylpyridin-4(1H)-one (**8a**)

Acid **2a** (50 mg, 0.18 mmol) was molten and kept at its mp. After CO_2 evolution had ceased, the residue was collected by hexane and crystallized from a mixture of hexane and toluene to give **8a** (24 mg, 57%) as white solid, mp 114–115 °C; ν_{max} (ATR) 1639, 1590, 1571, 1492 cm^{-1} δ_H (400 MHz, DMSO-d_6) 6.33 (1H, d, *J* 7.5 Hz, H-5), 6.75 (1H, s, H-3), 7.57 (5H, s, Ph), 7.80 (1H, d, *J* 7.5 Hz, H-6), δ_F (376.5 MHz, DMSO-d_6) 101.7 (s, CF_3) [Found: C, 60.09; H, 3.26; N, 5.71. $C_{12}H_8F_3NO$ requires C, 60.26; H, 3.37; N, 5.86%].

4.19. 2-(Trifluoromethyl)-1-(2-hydroxyphenyl)pyridin-4(1H)-one (**8c**)

Acid **2c** (100 mg, 0.33 mmol) was molten and kept at its mp. After CO_2 evolution had ceased, the residue was collected by toluene and crystallized from this solvent to give **8c** (46 mg, 54%) as white crystals, mp 193–194 °C; ν_{max} (ATR) 3081, 1632, 1554, 1545, 1512, 1461, 1398 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.31 (1H, dd, *J* 7.7, 2.7 Hz, H-5), 6.72 (1H, d, 2,7 Hz, H-3), 6.92 (1H, td, *J* 7.7, 0.8 Hz, arom.), 7.03 (1H, dd, *J* 8.2, 0.8 Hz, arom.), 7.34–7.44 (2H, m, arom.), 7.67 (1H, d, *J* 7.7 Hz, H-6), 10.42 (1H, s, OH); δ_F (376.5 MHz, DMSO-d_6) 99.5 (s, CF_3) [Found: C, 56.39; H, 3.13; N, 5.49. $C_{12}H_8F_3NO_2$ requires C, 56.48; H, 3.16; N, 5.49%].

4.20. 2-(Difluoromethyl)-1-(2-hydroxyphenyl)pyridin-4(1H)-one (**8d**)

Acid **2d** (86 mg, 0.30 mmol) was molten and kept at its mp. After CO_2 evolution had ceased, the residue was collected by toluene and crystallized from this solvent to give **8d** (52 mg, 71%) as gray powder, mp 207–209 °C; ν_{max} (ATR) 1635, 1599, 1541, 1514, 1455 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.24 (1H, dd, *J* 7.4, 1.9 Hz, H-5), 6.49 (1H, buried d, H-3), 6.53 (1H, t, $^2J_{H,F}$ 52.9 Hz, CF_2H); 6.95 (1H, t, *J* 7.5 Hz, H-5′), 7.06 (1H, d, *J* 8.0 Hz, H-6′), 7.34–7.42 (2H, m, H-3′, H-4′), 7.61 (1H, d, *J* 7.6 Hz, H-6), 10.50 (1H, s, OH); δ_F (376.5 MHz, DMSO-d_6) 41.9 (1F, dd, $^2J_{F,F}$ 303.3 Hz, $^2J_{H,F}$ 53.0 Hz, CFFH), 46.3 (1F, dd, $^2J_{F,F}$ 303.3 Hz, $^2J_{H,F}$ 53.0 Hz, CFFH) [Found: C, 60.88; H, 3.78; N, 5.75. $C_{12}H_9F_2NO_2$ requires C, 60.76; H, 3.82; N, 5.90%].

4.21. General procedure for 3-{[3-(R^F)-1H-pyrazol-5-yl]methyl}quinoxalin-2(1H)-ones (**9a**,**b**)

A mixture of benzodiazepine **3c** or **3d** (0.32 mmol) and $N_2H_4 \cdot 2HCl$ (50 mg, 0.48 mmol) was refluxed in EtOH (2 mL) for

1 h. Then the mixture was diluted with water, and the residue was crystallized from AcOH to give **9**.

*4.21.1. 3-{[3-(Trifluoromethyl)-1H-pyrazol-5-yl]methyl}quinoxalin-2(1H)-one (**9a**)*

Yield 25%, white solid, mp >300 °C (subl.); ν_{max} (ATR) 3237, 1663, 1612, 1572, 1555, 1487, 1464 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.21 (2H, s, CH_2), 6.35 (1H, s, CH), 7.27–7.32 (2H, m, arom.), 7.52 (1H, td, *J* 7.7, 1.0 Hz, arom.), 7.72 (1H, d, *J* 8.0 Hz, arom.), 12.48 (1H, s, NH), 13.15 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 102.3 (s, CF_3) [Found: C, 52.68; H, 3.08; N, 18.82. $C_{13}H_9F_3N_4O$ requires C, 53.07; H, 3.08; N, 19.04%].

*4.21.2. 3-{[3-(Difluoromethyl)-1H-pyrazol-5-yl]methyl}quinoxalin-2(1H)-one (**9b**)*

Yield 41%, white solid, mp 289–290 °C; ν_{max} (ATR) 3230, 1664, 1612, 1553, 1483, 1399 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.21 (2H, s, CH_2), 6.35 (1H, s, CH), 6.92 (1H, t, $^2J_{H,F}$ 54.6 Hz), 7.29 (1H, t, *J* 7.8 Hz, arom.), 7.31 (1H, d, *J* 7.8 Hz, arom.), 7.52 (1H, tt, *J* 7.7, 1.0 Hz, arom.), 7.72 (1H, d, *J* 8.0 Hz, arom.), 12.48 (1H, br s, NH), 13.15 (1H, br s, NH); δ_F (376.5 MHz, DMSO-d_6) 52.6 (d, $^2J_{H,F}$ 52.6 Hz, CF_2H) [Found: C, 56.55; H, 3.63; N, 20.14. $C_{13}H_{10}F_2N_4O$ requires C, 56.52; H, 3.65; N, 20.28%].

*4.22. General procedure for ethyl 5-[3,3,3-tri(2,2-di)fluoro-2-(phenylhydrazono)propyl]-1-phenyl-1H-pyrazole-3-carboxylates (**10**)*

A mixture of **3c** or **3d** (0.32 mmol) and $PhNHNH_2 \cdot HCl$ (170 mg, 0.70 mmol) was refluxed in a solvent (2 mL) for 1 h. After cooling, the reaction mixture was diluted with H_2O, the residue was filtered and crystallized.

*4.22.1. Ethyl 5-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1H-pyrazole-3-carboxylate [2f] (**10a**)*

The reaction mixture was refluxed in AcOH. Crude product was crystallized from toluene to give **10a** (49%) as white powder, mp 198–200 °C. For spectral data see Ref. [2f].

*4.22.2. Ethyl 5-[3,3-difluoro-2-(phenylhydrazono)propyl]-1-phenyl-1H-pyrazole-3-carboxylate (**10b**)*

The reaction mixture was refluxed in EtOH. Crude product was crystallized from toluene to give **10b** (37%) as white powder, mp 186–187 °C; ν_{max} (ATR) 3243, 1718, 1616, 1600, 1498 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.26 (3H, t, *J* 7.1 Hz, CH_3), 3.93 (2H, s, CH_2), 4.26 (2H, q, *J* 7.1 Hz, CH_2), 6.47 (1H, s, CH), 6.48 (1H, t, $^2J_{H,F}$ 54.8 Hz, CF_2H), 6.88 (1H, t, *J* 7.3 Hz, arom.), 7.16 (2H, d, *J* 7.6 Hz, arom.), 7.27 (2H, t, *J* 7.9 Hz, arom.), 7.54 (1H, tt, *J* 7.0, 2.0 Hz, arom.), 7.59–7.66 (4H, m, arom.), 10.05 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 48.2 (d, $^2J_{H,F}$ 54.8 Hz, CF_2H) [Found: C, 63.07; H, 4.83; N, 13.96. $C_{21}H_{20}F_2N_4O_2$ requires C, 63.31; H, 5.06; N, 14.06%].

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