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EXPLORATION OF FLUORAL HYDRAZONES DERIVED FROM CARBOHYDRAZIDES FOR THE SYNTHESIS OF TRIFLUOROMETHYLATED HETEROCYCLES

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Dedicated to Professor Dr. Victor Snieckus on the occasion of his 77th birthday

Abstract – The reaction of fluoral hydrate with carbohydrazides in methanol in the presence of molecular sieves (4 Å) gave the desired *N*-acylated fluoral hydrazones (**3a–f**) in fair yields. Treatment of the latter with mercaptoacetic acid in benzene led to the corresponding 2-trifluoromethyl-1,3-thiazolidinone derivatives (**4a–f**), whereas the reaction with acetic anhydride gave 3-acetyl-2,3-dihydro-2-trifluoromethyl-1,3,4-oxadiazoles (**5a–f**). The structures of each type of product have been established by X-ray crystallography.

INTRODUCTION

In the synthesis of fluorine-containing organic compounds, fluoral hydrate and fluoral ethyl hemiacetal play an important role. Of special importance are the imines of fluoral, which are available via reactions of fluoral hemiacetals with primary amines.² The initially formed fluoral amins are relatively stable compounds, and the elimination of water is performed by adding molecular sieves or by azeotropic removal of water.

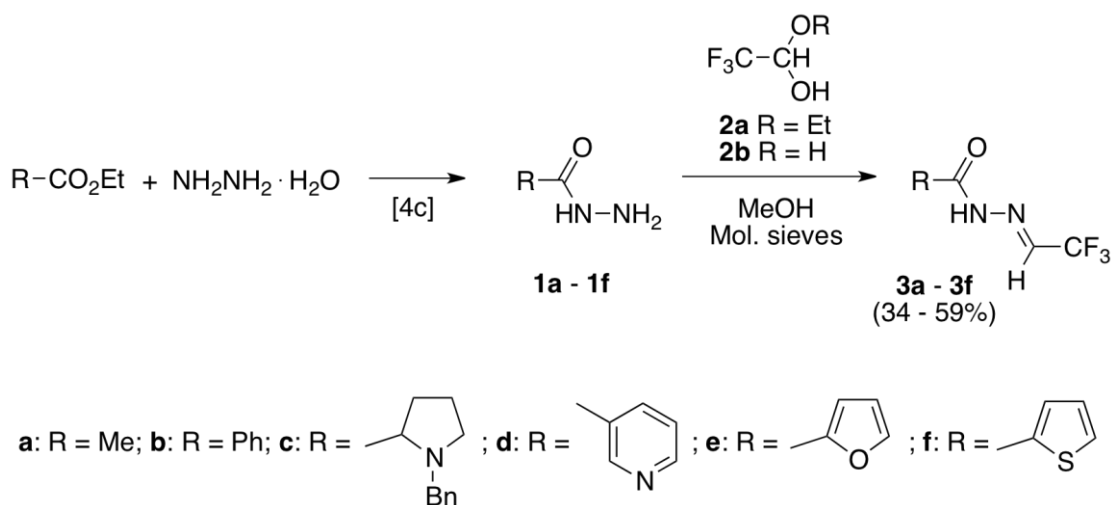
Carbohydrazides and their hydrazones are widely applied in the synthesis of diverse heterocycles.³ Recently, we published a series of papers in which heterocyclizations of some hydrazones derived from imidazole carboxylic acid and proline, respectively, were used as starting materials.⁴ To the best of our knowledge, there are only a few publications dealing with preparations of carbohydrazide hydrazones

derived from fluoral.⁵ Moreover, there are no known reports on their applications as starting materials for heterocyclization reactions.

The aim of the present study was the synthesis of fluoral hydrazones derived from carbohydrazides and subsequent reactions leading to trifluoromethylated heterocycles.

RESULTS AND DISCUSSION

The preparation of the starting hydrazides (**1**) was performed in a typical manner using the corresponding carboxylic esters and hydrazine hydrate.^{4c} In preliminary experiments, hydrazide (**1a**, R = Me) was reacted with fluoral hemiacetal (**2a**) or fluoral hydrate (**2b**) in methanol in the presence of molecular sieves (4Å). In the case of **2a**, only a moderate yield of the required hydrazone (**3a**) was obtained (Scheme 1). On the other hand, the reaction with **2b** occurred smoothly with complete conversion after 2 h. Based on this observation, all other hydrazides were converted into the hydrazones using **2b**. All fluoral hydrazones (**3**) were obtained as pure products. The spectroscopic properties proved the structures. For example, in the case of **3d**, the ¹³C-NMR spectrum in DMSO-*d*₆ showed the signals of the C=O and C=N groups at 162.8 and 135.1 ppm, respectively. The signal of the CF₃ group appeared at 120.6 ppm as a quartet (¹J_{C,F} = 269 Hz), and in the ¹⁹F-NMR spectrum at -66.2 ppm. The data are consistent with the presence of a single isomer in DMSO solution at room temperature. In contrast, the NMR data of **3a** in DMSO-*d*₆ showed that in this case two isomers existed in a ratio of ca. 2:1. For example, in the ¹⁹F-NMR spectrum, two signals appeared at -65.9 ppm for the major and at -66.1 ppm for the minor isomer.⁶ In all other cases studied (**3b-f**), the spectra in DMSO-*d*₆ confirmed that only one isomer was present in the solution.



Scheme 1

Finally, the structure of **3c** was established by X-Ray crystallography (Figure 1). The space group permits the compound in the crystal to be enantiomerically pure, but the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was based on the known (*S*)-configuration of the molecule. The pyrrolidine ring adopts an envelope conformation with N(1) as the envelope flap and the benzyl group in an *exo* orientation. The CF₃ group is disordered over two equally occupied orientations. The amide N(2)–H group forms an intermolecular hydrogen bond with the amide O(1)-atom of a neighboring molecule and thereby links the molecules into extended chains, which run parallel to the [100] direction. This pattern can be described by a graph set motif⁸ of C(4).

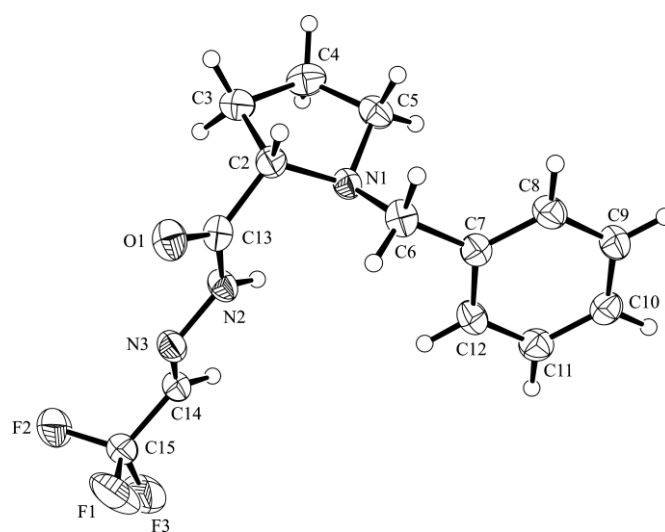
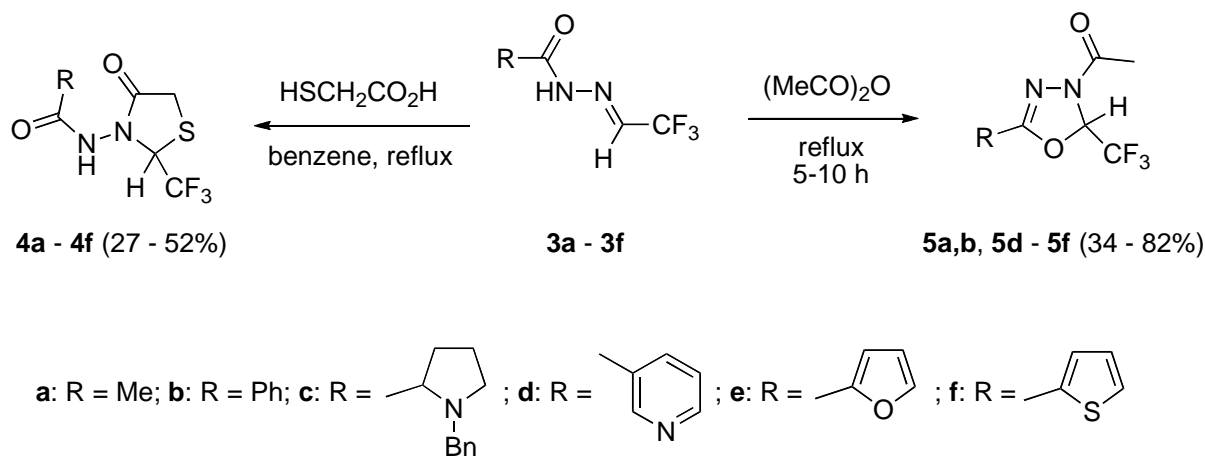


Figure 1. ORTEP plot⁷ of the molecular structure of one conformation of **3c** (arbitrary numbering of the atoms; 50% probability ellipsoids)

Heterocyclizations of hydrazones derived from carbohydrazides using acetic anhydride or mercaptoacetic acid, to yield 3-acetyl-1,3,4-oxadiazole derivatives and 3-acylamino-1,3-thiadiazolidin-4-ones, respectively, have been applied for the preparation of biologically active products.^{9,10} We used both types of heterocyclization reactions starting with fluoral hydrazones (**3**) (Scheme 2).

In a typical procedure, a solution of hydrazone (**3**) in benzene was heated with an equimolar amount of mercaptoacetic acid in a Dean-Stark apparatus. After evaporation of the solvent, the crude products were analyzed (¹H-NMR). The heterocyclization led to the expected 1,3-thiazolidin-4-ones (**4**), and in the case of **4c**, a mixture of two diastereoisomers was formed. In this case, chromatographic separation and subsequent fractional crystallization gave the major isomer as a pure compound. The structures of products (**4**) were proposed on the basis of the spectroscopic data. The presence of the CF₃ group was evidenced by the characteristic signals in the ¹³C- and ¹⁹F-NMR spectra (124.0–126.8 and –(75.8–77.8)

ppm, resp.). In the case of **4b**, the structure was unambiguously established by X-Ray crystallography (Figure 2a).



Scheme 2

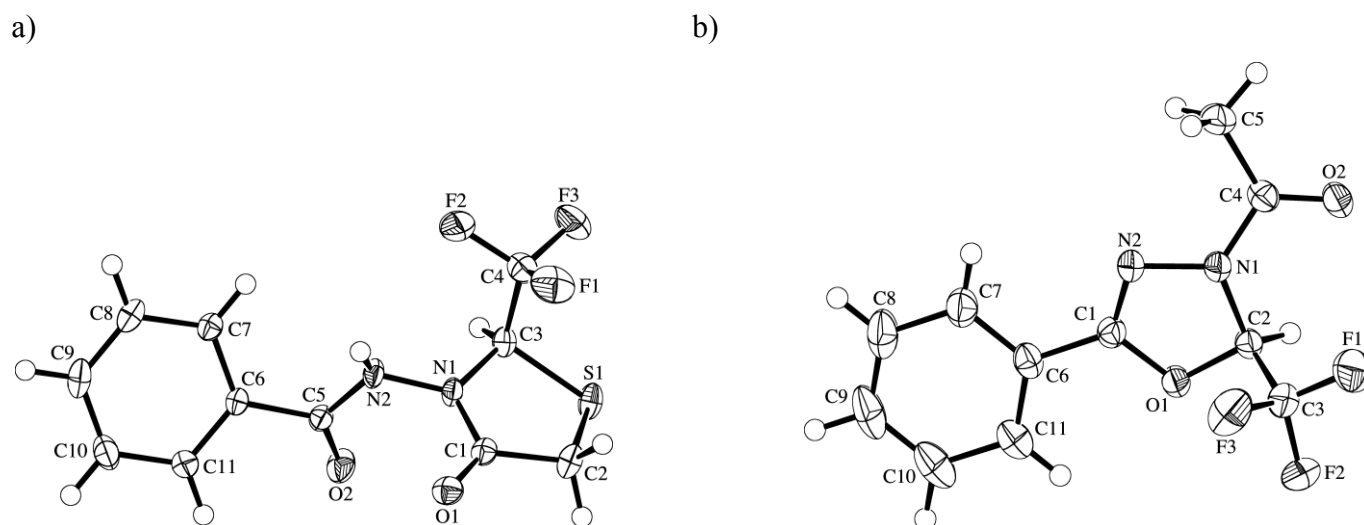


Figure 2. ORTEP plots⁷ of the molecular structures of a) **4b** and b) **5b** (arbitrary numbering of the atoms; 50% probability ellipsoids)

Since the space group of **4b** is centrosymmetric, the compound in the crystal is racemic. The five-membered ring adopts an envelope conformation with S(1) as the envelope flap. An unusual feature of this structure is that the amide H-atom (H–N(2)) is not coplanar with the amide group and the N(2)-atom shows distinct pyramidalization. The N(2)–C(5) bond is also a little longer (1.3694(14) Å) than a usual amide N–C bond. This must be a consequence of participation of the ring N(1)-atom in the delocalization scheme. The amide group (N(2)–H) forms an intermolecular hydrogen bond with the

amide O(1)-atom of the five-membered ring of a neighboring molecule and thereby links pairs of molecules into centrosymmetric dimers. The hydrogen bonding can be described with a graph set motif of $R_2^2(10)$.

The synthesis of 2,3-dihydro-1,3,4-oxadiazoles (**5**) was performed by refluxing hydrazones (**3**) in acetic anhydride. The crude products were analyzed by ^1H -NMR spectroscopy. The expected compounds were obtained as single products, but in the case of the proline derivative (**3c**), decomposition leading to a complex mixture of unidentified products was observed. In all other cases, crystalline products were obtained after chromatographic purification and crystallization. Again, characteristic signals of the CF_3 group were found in the ^{13}C - and ^{19}F -NMR spectra in narrow regions (119.7–121.0 and at -82.3 ppm, resp.). The structure of **5b** was also confirmed by X-Ray crystallography (Figure 2b).

The space group of **5b** is also centrosymmetric, and therefore the compound in the crystal is racemic. The five-membered ring is almost planar. The acetyl group at N(1) and the phenyl ring at C(1) are nearly coplanar with the heterocyclic ring (torsion angle $\text{C}(2)\text{--N}(1)\text{--C}(4)\text{--O}(2) = -12.7(2)^\circ$ and $\text{N}(2)\text{--C}(1)\text{--C}(6)\text{--C}(7) = 8.7(2)^\circ$, respectively).

CONCLUSIONS

The described results show that the little known fluoral hydrazones of aliphatic and aromatic carbohydrazides can be prepared from commercially available fluoral hydrate and the corresponding carbohydrazides in the presence of molecular sieves. The isolated hydrazones easily undergo heterocyclization reactions with mercaptoacetic acid and acetic anhydride leading to trifluoromethylated 1,3-thiazolidin-4-ones (**4**) and 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles (**5**), respectively. Keeping in mind that the presence of fluorinated alkyl groups in an organic molecule significantly changes the physicochemical and biological properties,¹¹ the application of fluoral-derived hydrazones is of potential importance not only for the synthesis of 1,3-thiazolidin-4-ones and 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles but also for other systems available via heterocyclization of carbohydrazide hydrazones.³ Diverse derivatives of type **4** and **5** are known as biologically active systems with a wide spectrum of activities.

EXPERIMENTAL

General remarks. Melting points were determined in a capillary using a Melt-Temp. II (Aldrich) apparatus, and they are uncorrected. The IR spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions in cm^{-1} . The ^1H -, ^{13}C -, and ^{19}F -NMR spectra were measured on a Bruker Avance III (600, 150, and 564 MHz, resp.) instrument using solvent signals as reference. Chemical shifts (δ) are given in ppm and coupling constants J in Hz. Assignments of signals in ^{13}C -NMR spectra were made on

the basis of HMQC experiments. ESI-MS: Varian 500 MS LC Ion Trap spectrometer; HR-ESI-MS: Bruker maXis spectrometer.

Starting materials. All solvents and reagents are commercially available and were used as received. The carbohydrazides (**1a-f**) were prepared from the corresponding esters by treatment with excess hydrazine hydrate according to published procedures (acetic acid hydrazide (**1a**, 55%),^{12a} benzoic acid hydrazide (**1b**, 67%),^{12b} (2*S*)-1-benzylpyrrolidine-2-carbohydrazide (**1c**, 82%),^{4c} picolinic acid hydrazide (**1d**, 37%),^{12c} furane-2-carbohydrazide (**1e**, 66%),^{12d} thiophene-2-carbohydrazide (**1f**, 8%).^{12e}

Synthesis of fluoral hydrazones (3a–3f). – **General procedure.** A solution of 1 mmol of the corresponding hydrazide (**1**) and 1 mmol (116 mg) of fluoral hydrate (**2b**) in 1 mL of MeOH was placed in a glass tube. After addition of freshly dried molecular sieves (4 Å), the tube was closed and heated in an oil bath to 75 °C for 24 h. Then, the mixture was cooled, filtered, and washed with a portion of MeOH. The solvent of the combined solutions was evaporated, and the crude products obtained were purified by column chromatography or on preparative thin layer plates (SiO₂). Hydrazones (**3**) were isolated as crystalline materials. Analytically pure samples were obtained after recrystallization.

***N*-[(2,2,2-Trifluoroethylidene)amino]acetamide (3a).** Solvent for chromatography: AcOEt. Yield: 79 mg (51%). Colorless solid, mp 107–114 °C (Et₂O/hexane). IR (KBr): 3226*s* (NH), 1670*vs* (C=O), 1560*m*, 1374*m*, 1361*m*, 1261*s*, 1195*s*, 1139*s*, 1009*m*, 703*m*. ¹H-NMR (DMSO-*d*₆): *isomer A*: 2.13 (*s*, 3H, CH₃); 7.50 (*q*, ³*J*_{H,F} = 3.8 Hz, 1H, CH–CF₃); 11.72 (*br. s*, NH); *isomer B*: 1.99 (*s*, 3H, CH₃); 7.85 (*br. q*, ³*J*_{H,F} ≈ 2.6 Hz, 1H, CH–CF₃); 11.89 (*br. s*, NH). ¹³C-NMR (DMSO-*d*₆): 19.9 (CH₃(*A*)); 21.8 (CH₃(*B*)); 120.5 (*q*, ¹*J*_{C,F} = 269.0 Hz, CF₃(*A*)); 120.8 (*q*, ¹*J*_{C,F} = 268.3 Hz, CF₃(*B*)); 129.0 (*q*, ²*J*_{C,F} = 36.5 Hz, CH–CF₃(*A*)); 132.8 (*q*, ²*J*_{C,F} = 36.8 Hz, CH–CF₃(*B*)); 167.2 (C=O(*B*)); 172.7 (C=O(*A*)). ¹⁹F-NMR (DMSO-*d*₆): –66.1 (*d*, ³*J*_{H,F} = 2.6 Hz, CF₃(*B*)); –65.9 (*d*, ³*J*_{H,F} = 3.8 Hz, CF₃(*A*)). The NMR spectra in CDCl₃ show only one set of signals: ¹H-NMR (CDCl₃): 2.32 (*s*, 3H, CH₃); 7.15 (*q*, ³*J*_{H,F} = 3.4 Hz, 1H, CH–CF₃); 9.70 (*br. s*, NH). ¹⁹F-NMR (CDCl₃): –67.5 (*d*, ³*J*_{H,F} = 3.3 Hz, CF₃). ESI-MS: 154 (*M*⁺, 100); HR-ESI-MS (MeOH/CH₂Cl₂+NaI): 177.02469 (calcd. 177.02438 for C₄H₅F₃N₂NaO, [*M*+Na]⁺).

***N*-[(2,2,2-Trifluoroethylidene)amino]benzamide (3b).** Solvent for chromatography: hexane/AcOEt 7:3. Yield: 76 mg (35%). Colorless solid, mp 198–200 °C (Et₂O/hexane). IR (KBr): 3196*s* (NH), 3058*m*, 3009*w*, 1662*vs* (C=O), 1548*m*, 1356*s*, 1261*s*, 1141*s*, 1078*m*, 923*w*, 694*m*. ¹H-NMR (DMSO-*d*₆): 7.54–7.57 (*m*, 2 arom. H); 7.63–7.65 (*m*, 1 arom. H); 7.89–7.90 (*m*, 2 arom. H); 8.05 (*br. s*, CH–CF₃); 12.39 (*br. s*, NH). ¹³C-NMR (DMSO-*d*₆): 120.8 (*q*, ¹*J*_{C,F} = 269.0 Hz, CF₃); 128.0, 128.8, 132.4 (5 arom.

CH); 132.7 (1 arom. C); 134.3 (br. *q*, CH–CF₃); 164.2 (C=O). ¹⁹F-NMR (DMSO-*d*₆): –66.1 (*s*, CF₃). ESI-MS: 216 (*M*⁺, 77); 215 ([*M*–1]⁺, 100); HR-ESI-MS (MeOH/CH₂Cl₂+NaI): 239.04033 (calcd. 239.04027 for C₉H₇F₃N₂NaO, [*M*+Na]⁺).

(2*S*)-1-Benzyl-*N*-[(2,2,2-trifluoroethylidene)amino]pyrrolidine-2-carboxamide (3c). Solvent for chromatography: pentane/AcOEt 3:2. Yield: 100 mg (34%). Colorless solid, mp 114–120 °C (CH₂Cl₂/hexane). IR (KBr): 3235*s* (NH), 1693*vs* (C=O), 1632*m*, 1525*s*, 1456*m*, 1359*s*, 1320*m*, 1254*m*, 1171*m*, 1141*s*, 1100*s*, 1003*m*, 864*m*, 761*m*, 700*m*. ¹H-NMR (CDCl₃): 1.73–1.87 (*m*, 2 H(prot)); 1.96–1.99 (*m*, 1 H(prot)); 2.25–2.32 (*m*, 1 H(prot)); 2.46–2.51 (*m*, 1 H(prot)); 3.12 (*t*, *J*_{H,H} = 7.4 Hz, HC(2)(prot)); 3.34–3.56 (*m*, 1 H(prot)); 3.68 and 3.80 (*AB*, ²*J*_{H,H} = 12.8 Hz, 2H, CH₂–Ph); 7.28–7.35 (*m*, 5 arom. H); 8.42 (br. *d*, CH–CF₃); 10.40 (br. *s*, NH). ¹³C-NMR (CDCl₃): 24.2, 30.7, 54.5, 60.1, 67.1 (4 CH₂, CH(prot)); 120.2 (*q*, ¹*J*_{C,F} = 269.9 Hz, CF₃); 127.7, 128.7, 128.8 (5 arom. CH); 137.1 (*q*, ²*J*_{C,F} = 38.4 Hz, CH–CF₃); 137.6 (1 arom. C); 172.5 (C=O). ¹⁹F-NMR (CDCl₃): –68.5 (*s*, CF₃). HR-ESI-MS (MeOH/CHCl₃+NaI): 300.13187 (calcd. 300.13182 for C₁₄H₁₇F₃N₃O, [*M*+H]⁺).

***N*-[(2,2,2-Trifluoroethylidene)amino]pyridine-3-carboxamide (3d).** Solvent for chromatography: AcOEt. Yield: 64 mg (29%). Colorless solid, mp 160–162 °C (CH₂Cl₂/pet.ether). IR (KBr): 3201*s* (NH), 3066*m*, 2961*w*, 1663*vs* (C=O), 1591*m*, 1552*m*, 1360*s*, 1270*s*, 1150*s*, 1077*m*, 929*w*, 707*m*. ¹H-NMR (DMSO-*d*₆): 7.59 (br. *s*, 1 arom. H); 8.06 (br. *s*, 1 arom. H); 8.24 (br. *s*, 1 arom. H); 8.79 (br. *s*, 1 arom. H); 9.05 (br. *s*, CH–CF₃); 12.55 (br. *s*, NH). ¹³C-NMR (DMSO-*d*₆): 120.6 (*q*, ¹*J*_{C,F} = 269.0 Hz, CF₃); 123.8 135.8; 148.9; 153.1 (4 arom. CH); 128.3 (1 arom. C); 135.1 (*q*, ²*J*_{C,F} ≈ 39.0 Hz, CH–CF₃); 162.8 (C=O). ¹⁹F-NMR (DMSO-*d*₆): –66.2 (*d*, ³*J*_{H,F} = 2.4 Hz, CH–CF₃). ESI-MS: 217 (*M*⁺, 100); HR-ESI-MS (MeOH/CH₂Cl₂+NaI): 218.05352 (calcd. 218.05357 for C₈H₇F₃N₃O, [*M*+H]⁺).

***N*-[(2,2,2-Trifluoroethylidene)amino]furan-2-carboxamide (3e).** Solvent for chromatography: pentane/AcOEt 1:1. Yield: 70 mg (34%). Colorless solid, mp 184–187 °C (CH₂Cl₂). IR (KBr): 3261*s* (NH), 3115*m*, 3082*m*, 1675*vs* (C=O), 1637*m*, 1571*m*, 1551*m*, 1470*s*, 1362*s*, 1288*s*, 1274*s*, 1197*s*, 1176*s*, 1139*s*, 1086*m*, 958*w*, 767*m*, 601*m*. ¹H-NMR (DMSO-*d*₆): 6.73–6.74 (*m*, 1 arom. H); 7.36–7.37 (*m*, 1 arom. H); 7.99–8.00 (*m*, 1 arom. H, CH–CF₃); 12.32 (br. *s*, NH). ¹³C-NMR (DMSO-*d*₆): 112.5, 146.9 (3 arom. CH); 120.8 (*q*, ¹*J*_{C,F} = 270.0 Hz, CF₃); 134.0 (1 arom. C); 145.7 (br. *s*, CH–CF₃); 155.3 (C=O). ¹⁹F-NMR (DMSO-*d*₆): –66.1 (*d*, ³*J*_{H,F} = 3.4 Hz, CF₃). HR-ESI-MS (MeOH+NaI): 229.01941 (calcd. 229.01953 for C₇H₅F₃N₂NaO₂, [*M*+Na]⁺).

***N*-[(2,2,2-Trifluoroethylidene)amino]thiophene-2-carboxamide (3f).** Solvent for chromatography:

pentane/AcOEt 1:1. Yield: 179 mg (81%). Colorless solid, mp 126 °C (decomp., CH₂Cl₂/hexane). IR (KBr): 3242_s (NH), 3044_m, 1646_{vs} (C=O), 1567_m, 1417_m, 1355_m, 1263_s, 1130_{vs}, 1072_m, 899_w, 720_m. ¹H-NMR (DMSO-*d*₆): 7.24–7.25 (*m*, 1 arom. H); 7.79–7.97 (*m*, 2 arom. H, CH–CF₃); 12.42 (br. *s*, NH). ¹³C-NMR (DMSO-*d*₆): 120.6 (*q*, ¹*J*_{C,F} = 270.0 Hz, CF₃); 128.3, 129.5, 131.7 (3 arom. CH); 134.2 (br. *s*, CH–CF₃); 138.1 (1 arom. C), 162.3 (C=O). ¹⁹F-NMR (DMSO-*d*₆): –67.2 (*d*, ³*J*_{H,F} = 3.4 Hz, CF₃). HR-ESI-MS: (MeOH + NaI): 244.99650 (calcd. 244.99669 for C₇H₅F₃N₂NaOS, [M+Na]⁺).

Synthesis of trifluoromethylated 1,3-thiazolidin-4-ones (4a–4f). – General procedure. A solution of 1 mmol of the corresponding hydrazone **3** and 1 mmol (94 mg) of mercaptoacetic acid in dry benzene was heated in a Dean-Stark apparatus until the separation of water ceased (5–18 h). Then, benzene was evaporated and the residue was treated with a saturated aqueous NaHCO₃ solution. The mixture was extracted with CH₂Cl₂ (3×), the organic layers were combined and dried over anhydrous MgSO₄. After filtration, the solvents were evaporated and the residue analyzed by ¹H-NMR. The crude products were purified by crystallization. In the case of **4c**, the mixture of two diastereoisomeric products was separated by thin layer chromatography and the main product was obtained as a pure substance by additional crystallization.

***N*-(4-Oxo-2-trifluoromethyl-1,3-thiazolidin-3-yl)acetamide (4a).** Yield: 113 mg (50%). Colorless solid, mp 138–140 °C (Et₂O/pet. ether). IR (KBr): 3283_s (NH), 3006_m, 2972_m, 1717_{vs} (C=O), 1681_{vs} (C=O), 1522_m, 1397_s, 1270_s, 1227_s, 1187_s, 1175_s, 1110_{vs}, 873_m, 670_m. ¹H-NMR (CDCl₃): 2.10 (*s*, 3H, CH₃); 3.53 (*A* part of *AB*, ²*J*_{H,H} = 15.8 Hz, 1H of CH₂); 3.73 (*B* part of *AB* × *d*, ²*J*_{H,H} = 15.8 Hz, ⁴*J*_{H,H} = 1.5 Hz, 1H of CH₂); 5.07 (*dq*, ³*J*_{H,F} = 5.6 Hz, ⁴*J*_{H,H} = 1.5 Hz, CH–CF₃); 7.85 (br. *s*, NH). ¹³C-NMR (CDCl₃): 20.6 (CH₃); 28.3 (CH₂); 59.1 (*q*, ²*J*_{C,F} = 34.5 Hz, CH–CF₃); 124.1 (*q*, ¹*J*_{C,F} = 279.2 Hz, CF₃); 168.5, 169.6 (2 C=O). ¹⁹F-NMR (CDCl₃): –76.0 (br. *d*, ³*J*_{H,F} = 5.6 Hz, CF₃). HR-ESI-MS (MeOH/CH₂Cl₂+NaI): 251.00748 (calcd. 251.00725 for C₆H₇F₃N₂NaO₂S, [M+Na]⁺).

***N*-(4-Oxo-2-trifluoromethyl-1,3-thiazolidin-3-yl)benzamide (4b).** Yield: 124 mg (43%). Colorless solid, mp 161–163 °C (Et₂O/hexane). IR (KBr): 3246_s (NH), 2996_m, 2974_w, 1728_{vs} (C=O), 1683_{vs} (C=O), 1517_m, 1396_m, 1284_s, 1251_s, 1191_{vs}, 1129_{vs}, 753_m, 699_m, 645_m. ¹H-NMR (DMSO-*d*₆): 3.69 (*A* part of *AB*, ²*J*_{H,H} = 15.4 Hz, 1H of CH₂); 3.91 (*B* part of *AB* × *d*, ²*J*_{H,H} = 15.4 Hz, ⁴*J*_{H,H} = 1.5 Hz, 1H of CH₂); 5.59 (br. *q*, ³*J*_{H,F} = 5.8 Hz, CH–CF₃); 7.52–7.55 (*m*, 2 arom. H); 7.61–7.64 (*m*, 1 arom. H); 7.88–7.89 (*m*, 2 arom. H); 11.15 (br. *s*, NH). ¹³C-NMR (CDCl₃): 28.5 (CH₂); 59.3 (*q*, ²*J*_{C,F} = 33.6 Hz, CH–CF₃); 124.1 (*q*, ¹*J*_{C,F} = 279.0 Hz, CF₃); 127.5, 128.8, 132.9 (5 arom. CH); 130.5 (1 arom. C); 165.6, 170.3 (2 C=O). ¹⁹F-NMR (CDCl₃): –76.0 (br. *d*, ³*J*_{H,F} = 5.7 Hz, CF₃). HR-ESI-MS (MeOH/CH₂Cl₂+NaI): 313.02294

(calcd. 313.02290 for $C_{11}H_9F_3N_2NaO_2S$, $[M+Na]^+$).

(2S)-1-Benzyl-N-(4-oxo-2-trifluoromethyl-1,3-thiazolidin-3-yl)pyrrolidine-2-carboxamide (4c).

Yield: 93 mg (49%; pure major isomer). Colorless solid, mp 126–128 °C (CH_2Cl_2 /hexane). IR (KBr): 3264s (NH), 1725vs (C=O), 1687s (C=O), 1485s, 1385m, 1320m, 1254m, 1200s, 1158s, 1124s, 1028m, 986m, 700m, 677m. 1H -NMR ($CDCl_3$): 1.73–1.75 (m, 1 CH(prol)); 1.78–1.86 (m, 1 CH(prol)); 1.88–1.94 (m, 2 CH(prol)); 2.23–2.27 (m, 1 CH(prol)); 2.36–2.39 (m, 1 CH(prol)); 3.00 (t, $^3J_{H,H} = 7.4$ Hz, HC(2)(prol)); 3.53 (A part of AB, $^2J_{H,H} = 15.7$ Hz, 1H of CH_2); 3.75 (B part of AB \times d, $^2J_{H,H} = 15.7$ Hz, $^4J_{H,H} = 1.4$ Hz, 1H of CH_2); 3.49 and 4.14 (AB, $J_{H,H} = 12.6$ Hz, CH_2 -Ph); 5.21 (m, 1H, CH-CF₃); 7.28–7.37 (m, 5 arom. H); 9.28 (br. s, NH). ^{13}C -NMR ($CDCl_3$, 150 MHz): 24.0, 28.2, 30.6, 53.2, 59.6 (5 CH_2); 58.5 (q, $^2J_{C,F} = 34.3$ Hz, CH-CF₃); 66.5 (CH(prol)); 124.0 (q, $^1J_{C,F} = 280.1$ Hz, CF₃); 127.5, 128.6, 129.2 (5 arom. CH); 137.8 (1 arom. C); 168.7, 173.3 (2 C=O). ^{19}F -NMR ($CDCl_3$): -75.8 (br. s, CF₃). HR-ESI-MS (MeOH+NaI): 374.11448 (calcd. 374.11446 for $C_{16}H_{19}F_3N_3O_2S$, $[M+H]^+$).

N-(4-Oxo-2-trifluoromethyl-1,3-thiazolidin-3-yl)pyridine-3-carboxamide (4d). Yield: 80 mg (27%). Colorless solid, mp 202–204 °C (CH_2Cl_2 /hexane). IR (KBr): 3432m (NH), 2958m, 1740vs (C=O), 1678vs (C=O), 1595m, 1297s, 1268s, 1254m, 1219m, 1197m, 1178s, 1114vs, 652m. 1H -NMR ($CDCl_3$): 3.60 (A part of AB, $^2J_{H,H} = 15.7$ Hz, 1H of CH_2); 3.80 (B part of AB \times d, $^2J_{H,H} = 15.8$ Hz, $^4J_{H,H} = 1.5$ Hz, 1H of CH_2); 5.21 (dq, $^3J_{H,F} = 5.5$ Hz, $^4J_{H,H} = 1.5$ Hz, CH-CF₃); 7.42–7.44 (m, 1 arom. H); 8.13–8.15 (m, 1 arom. H); 8.41–8.44 (m, 1 arom. H); 8.80–8.82 (m, 1 arom. H); 9.05 (d, $J = 1.5$ Hz, NH). ^{13}C -NMR (CD_3OD): 30.2 (CH_2); 61.3 (q, $^2J_{C,F} = 34.5$ Hz, CH-CF₃); 124.0, 138.5, 150.4, 152.7 (4 arom. CH); 126.8 (q, $^1J_{C,F} = 279.0$ Hz, CF₃); 130.4 (1 arom. C); 167.3, 172.6 (2 C=O). ^{19}F -NMR (CD_3OD): -77.8 (d, $^3J_{H,F} = 5.4$ Hz, CF₃). ESI-MS: 291.1 (M^+ , 100). HR-ESI-MS (MeOH+NaI): 314.01808 (calcd. 314.01815 for $C_{10}H_8F_3N_3NaO_2S$, $[M+Na]^+$).

N-(4-Oxo-2-trifluoromethyl-1,3-thiazolidin-3-yl)furan-2-carboxamide (4e). Yield: 146 mg (52%). Colorless solid, mp 200–206 °C (CH_2Cl_2 /hexane). IR (KBr): 3216m (NH), 1713vs (C=O), 1697vs and 1679vs (C=O), 1588m, 1478m, 1299s, 1228m, 1203m, 1181s, 1132vs, 869m, 764m, 660m. 1H -NMR ($CDCl_3$): 3.63 (A part of AB, $^2J_{H,H} = 15.9$ Hz, 1H of CH_2); 3.89 (B part of AB \times d, $^2J_{H,H} = 15.9$ Hz, $^4J_{H,H} = 1.5$ Hz, 1H of CH_2); 5.16 (dq, $^3J_{H,F} = 5.3$ Hz, $^4J_{H,H} = 1.5$ Hz, CH-CF₃); 6.57–6.59 (m, 1 arom. H); 7.28–7.30 (m, 1 arom. H); 7.53–7.54 (m, 1 arom. H); 8.18 (br. s, NH). ^{13}C -NMR (CD_3OD): 30.1 (CH_2); 61.5 (q, $^2J_{C,F} = 34.1$ Hz, CH-CF₃); 114.2, 118.6, 148.5 (3 arom. CH); 126.8 (q, $^1J_{C,F} = 279.2$ Hz, CF₃); 147.8 (1 arom. C); 160.0, 172.5 (2 C=O). ^{19}F -NMR (CD_3OD): -77.7 (d, $^3J_{H,F} = 5.3$ Hz, CF₃). HR-ESI-MS (MeOH+NaI): 303.00238 (calcd. 303.00217 for $C_9H_7F_3N_2NaO_3S$, $[M+Na]^+$).

***N*-(4-Oxo-2-trifluoromethyl-1,3-thiazolidin-3-yl)thiophene-2-carboxamide (4f)**. Yield: 142 mg (48%). Colorless solid, mp 152 °C (decomp., CH₂Cl₂/hexane). IR (KBr): 3253 m (NH), 2981 w , 1721 vs (C=O), 1664 vs (C=O), 1534 m , 1416 m , 1294 s , 1262 s , 1191 s , 1177 s , 1116 s , 871 w , 722 s , 653 w . ¹H-NMR (CDCl₃): 3.58 (*A* part of *AB*, ²*J*_{H,H} = 15.8 Hz, 1H of CH₂); 3.78 (*B* part of *AB* × *d*, ²*J*_{H,H} = 15.8 Hz, ⁴*J*_{H,H} = 1.5 Hz, 1H of CH₂); 5.20 (*dq*, ³*J*_{H,F} = 5.3 Hz, ⁴*J*_{H,H} = 1.5 Hz, CH–CF₃); 7.10–7.11 (*m*, 1 arom. H); 7.57–7.59 (*m*, 1 arom. H); 7.65–7.66 (*m*, 1 arom. H); 8.27 (br. *s*, NH). ¹³C-NMR (CDCl₃): 28.5 (CH₂); 59.5 (*q*, ²*J*_{C,F} = 33.8 Hz, CH–CF₃); 124.1 (*q*, ¹*J*_{C,F} = 280.1 Hz, CF₃); 128.1, 130.4, 132.3 (3 arom. CH); 134.1 (1 arom. C); 160.3, 170.3 (2 C=O). ¹⁹F-NMR (CDCl₃): –76.0 (*d*, ³*J*_{H,F} = 5.3 Hz, CF₃). HR-ESI-MS (MeOH+NaI): 318.97906 (calcd. 318.97932 for C₉H₇F₃N₂NaO₂S₂, [M+Na]⁺).

Synthesis of trifluoromethylated 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles (5a,b,d–f). – **General procedure.** A solution of 1 mmol of the corresponding hydrazone **3** in excess acetic anhydride (5 mL) was heated at reflux until complete conversion of the starting material (5–10 h). The progress of the reaction was monitored by TLC. When the reaction was finished, excess acetic anhydride was distilled off under reduced pressure, and the crude material obtained was analyzed by ¹H-NMR. Isolation of pure products was achieved either by crystallization or by preparative thin layer chromatography followed by crystallization.

3-Acetyl-2,3-dihydro-5-methyl-2-trifluoromethyl-1,3,4-oxadiazole (5a). Yield: 161 mg (82%). Colorless solid, mp 40–42 °C (pentane/pet. ether). IR (KBr): 2931 w , 2860 w , 1692 vs (C=O), 1646 s (C=N), 1425 s , 1373 s , 1242 m , 1150 s , 1044 m , 856 m , 623 m , 594 m . ¹H-NMR (CDCl₃): 2.12 (*s*, 3H, CH₃); 2.26 (*s*, 3H, CH₃); 6.34 (*q*, ³*J*_{H,F} = 4.1 Hz, CH–CF₃). ¹³C-NMR (CDCl₃): 10.8 (CH₃); 21.2 (CH₃); 84.4 (*q*, ²*J*_{C,F} = 37.5 Hz, CH–CF₃); 120.8 (*q*, ¹*J*_{C,F} = 285.0 Hz, CF₃); 156.5 (C=N); 169.9 (C=O). ¹⁹F-NMR (CDCl₃): –82.3 (*d*, ³*J*_{H,F} = 3.3 Hz, CF₃). HR-ESI-MS (MeOH+NaI): 219.03463 (calcd. 219.03518 for C₆H₇F₃N₂NaO₂, [M+Na]⁺).

3-Acetyl-2,3-dihydro-5-phenyl-2-trifluoromethyl-1,3,4-oxadiazole (5b). Solvent for chromatography: hexane/AcOEt 4:1. Yield: 186 mg (72%). Colorless solid, mp 74–76 °C (pet. ether). IR (KBr): 2966 w , 1683 v (C=O), 1642 m (C=N), 1418 s , 1398 s , 1288 s , 1272 s , 1187 s , 1168 vs , 1155 vs , 1058 m , 1029 m , 864 m , 856 m , 771 m , 717 m , 688 m , 644 m . ¹H-NMR (CDCl₃): 2.39 (*s*, 3H, CH₃); 6.54 (*q*, ³*J*_{H,F} = 4.1 Hz, CH–CF₃); 7.46–7.88 (*m*, 5 arom. H). ¹³C-NMR (CDCl₃): 21.4 (CH₃); 84.8 (*q*, ²*J*_{C,F} = 38.1 Hz, CH–CF₃); 120.9 (*q*, ¹*J*_{C,F} = 284.3 Hz, CF₃); 123.1 (1 arom. C); 127.2, 128.9, 132.3 (5 arom. CH); 156.2 (C=N); 169.9 (C=O). ¹⁹F-NMR (CDCl₃): –82.3 (*d*, ³*J*_{H,F} = 3.3 Hz, CF₃). HR-ESI-MS (MeOH/CH₂Cl₂+NaI): 281.05093 (calcd. 281.05083 for C₁₁H₉F₃N₂NaO, [M+Na]⁺).

3-Acetyl-2,3-dihydro-5-(pyridin-3-yl)-2-trifluoromethyl-1,3,4-oxadiazole (5d). Yield: 143 mg (55%). Colorless solid, mp 80–82 °C (CH₂Cl₂/hexane). IR (KBr): 1691_{vs} (C=O), 1644_m (C=N), 1412_s, 1262_s, 1194_s, 1158_s, 1106_m, 894_m, 852_m, 698_m, 642_m. ¹H-NMR (CDCl₃): 2.40 (*s*, 3H, CH₃); 6.57 (*q*, ³*J*_{H,F} = 4.1 Hz, CH-CF₃); 7.41–7.43 (*m*, 1 arom. H); 8.13–8.15 (*m*, 1 arom. H); 8.77–8.78 (*m*, 1 arom. H); 9.10–9.11 (*m*, 1 arom. H). ¹³C-NMR (CDCl₃): 21.3 (CH₃); 85.0 (*q*, ²*J*_{C,F} = 38.3 Hz, CH-CF₃); 119.7 (*q*, ¹*J*_{C,F} = 283.7 Hz, CF₃); 123.5 (1 arom. C); 123.5, 134.3, 148.3, 152.9 (4 arom. CH); 154.2 (C=N); 169.8 (C=O). ¹⁹F-NMR (CDCl₃): –82.3 (*d*, ³*J*_{H,F} = 3.4 Hz, CF₃). ESI-MS: 258 ([*M*–1]⁺, 100); HR-ESI-MS (MeOH/CH₂Cl₂+NaI): 282.04581 (calcd. 282.04608 for C₁₀H₈F₃N₃NaO₂, [*M*+Na]⁺); 260.06363 (calcd. 260.06414 for C₁₀H₉F₃N₃O₂, [*M*+H]⁺).

3-Acetyl-5-(furan-2-yl)-2,3-dihydro-2-trifluoromethyl-1,3,4-oxadiazole (5e). Yield: 161 mg (65%). Colorless solid, mp 75–77 °C (pentane). IR (KBr): 2979_m, 1682_{vs} (C=O), 1646_m (C=N), 1482_s, 1391_s, 1275_s, 1165_{vs}, 1011_m, 854_m, 766_m, 708_m, 646_m, 593_w. ¹H-NMR (CDCl₃): 2.38 (*s*, 3H, CH₃); 6.51 (*q*, ³*J*_{H,F} = 4.1 Hz, CH-CF₃); 6.57–6.58 (*m*, 1 arom. H); 7.06–7.07 (*m*, 1 arom. H); 7.62–7.63 (*m*, 1 arom. H). ¹³C-NMR (CDCl₃): 21.3 (CH₃); 84.7 (*q*, ²*J*_{C,F} = 39.0 Hz, CH-CF₃); 112.1, 116.0, 146.6 (3 arom. CH); 121.0 (*q*, ¹*J*_{C,F} = 285.0 Hz, CF₃); 138.4 (1 arom. C); 149.1 (C=N); 169.9 (C=O). ¹⁹F-NMR (CDCl₃): –82.3 (*d*, ³*J*_{H,F} = 3.4 Hz, CF₃). HR-ESI-MS (MeOH+NaI): 271.02978 (calcd. 271.03010 for C₉H₇F₃N₂NaO₃, [*M*+Na]⁺).

3-Acetyl-2,3-dihydro-5-(thiophen-2-yl)-2-trifluoromethyl-1,3,4-oxadiazole (5f). Yield: 89 mg (34%). Colorless solid, mp 90 °C (decomp., hexane). IR (KBr): 2967_m, 1679_{vs} (C=O), 1642_m (C=N), 1445_s, 1411_s, 1265_s, 1164_{vs}, 1035_m, 853_m, 722_m, 708_m, 643_m, 597_w. ¹H-NMR (CDCl₃): 2.40 (*s*, 3H, CH₃); 6.55 (*q*, ³*J*_{H,F} = 4.1 Hz, CH-CF₃); 7.16–7.18 (*m*, 1 arom. H); 7.58–7.59 (*m*, 1 arom. H); 7.68–7.69 (*m*, 1 arom. H). ¹³C-NMR (CDCl₃): 21.3 (CH₃); 84.8 (*q*, ²*J*_{C,F} = 38.5 Hz, CH-CF₃); 120.8 (*q*, ¹*J*_{C,F} = 283.5 Hz, CF₃); 123.6 (1 arom. C); 128.0, 131.0, 131.2 (3 arom. CH); 153.4 (C=N); 169.9 (C=O). ¹⁹F-NMR (CDCl₃): –82.3 (*d*, ³*J*_{H,F} = 3.4 Hz, CF₃). HR-ESI-MS (MeOH+NaI): 287.00700 (calcd. 287.00725 for C₉H₇F₃N₂NaO₂S, [*M*+Na]⁺).

X-Ray Crystal-Structure Determination of 3c, 4b, and 5b (Figures 1 and 2).¹³ All measurements for **3c** were made on a Nonius KappaCCD area detector diffractometer¹⁴ using graphite-monochromated MoK α radiation ($\lambda = 0.71073$ Å) and an Oxford Cryosystems Cryostream 700 cooler, and those for **4b** and **5b** on an Agilent Technologies SuperNova area-detector diffractometer¹⁵ using MoK α (**4b**) or CuK α (**5b**; $\lambda = 1.54184$ Å) radiation from a micro-focus X-ray source and an Oxford Instruments Cryojet XL cooler. Data reduction was performed with HKL Denzo and Scalepack¹⁶ (**3c**) and CrysAlisPro¹⁵ (**4b** and **5b**),

respectively. The intensities were corrected for Lorentz and polarization effects, and in the cases of **4b** and **5b**, an empirical absorption correction using spherical harmonics¹⁵ was applied. Equivalent reflections, other than the Friedel pairs for **3c**, were merged. The data collection and refinement parameters are given below. Views of the molecules are shown in Figures 1 and 2. The structures were solved by direct methods using SHELXS97,¹⁷ which revealed the positions of all non-H-atoms. The CF₃ group of **3c** is disordered over two nearly equally occupied orientations. Two sets of positions were defined for the F-atoms and the site occupation factor of the major conformation of the group refined to 0.502(6). Similarity restraints were applied to the chemically equivalent C–F and F...F distances, while neighboring F-atoms from each conformation were restrained to have similar atomic displacement parameters. The non-H-atoms were refined anisotropically. The amide H-atoms of **3c** and **4b** were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms in each structure were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the methyl group of **5b**). The refinement of each structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\sum w(F_o^2 - F_c^2)^2$. Corrections for secondary extinction were applied. Neutral atom scattering factors for non-H-atoms were taken from ref.¹⁸, and the scattering factors for H-atoms were taken from ref.¹⁹ Anomalous dispersion effects were included in F_c ;²⁰ the values for f' and f'' were those of ref.²¹ The values of the mass attenuation coefficients are those of ref.²² All calculations were performed using the SHELXL97 program.¹⁷

Crystal data for **3c**: Crystallized from hexane/CH₂Cl₂, C₁₄H₁₆F₃N₃O, $M = 299.30$, colorless, needle, crystal dimensions 0.10 × 0.13 × 0.23 mm, orthorhombic, space group $P2_12_12_1$, $Z = 4$, reflections for cell determination 1957, 2θ range for cell determination 4–55°, $a = 5.1299(1)$ Å, $b = 15.0924(3)$ Å, $c = 18.6500(4)$ Å, $V = 1443.93(5)$ Å³, $D_X = 1.377$ g·cm⁻³, $\mu(\text{MoK}\alpha) = 0.115$ mm⁻¹, $T = 160(1)$ K, ϕ and ω scans, $2\theta_{\text{max}} = 55^\circ$, total reflections measured 22075, symmetry independent reflections 3296, reflections with $I > 2\sigma(I)$ 2421, reflections used in refinement 3293, parameters refined 223, restraints 66, final $R(F)$ ($I > 2\sigma(I)$ reflections) = 0.0509, $wR(F^2)$ (all data) = 0.1285 ($w = [\sigma^2(F_o^2) + (0.0568P)^2 + 0.4765P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$, goodness of fit 1.018, secondary extinction coefficient 0.015(3), final $\Delta_{\text{max}}/\sigma = 0.001$, $\Delta\rho$ (max; min) = 0.47; -0.26 e Å⁻³.

Crystal data for **4b**: Crystallized from Et₂O/hexane, C₁₁H₉F₃N₂O₂S, $M = 290.26$, colorless, prism, crystal dimensions 0.10 × 0.15 × 0.22 mm, triclinic, space group $P\bar{1}$, $Z = 2$, reflections for cell determination 8405, 2θ range for cell determination 4–61°, $a = 8.7000(3)$ Å, $b = 8.8660(3)$ Å, $c = 8.8889(3)$ Å, $\alpha = 63.283(4)^\circ$, $\beta = 81.807(3)^\circ$, $\gamma = 89.503(3)^\circ$, $V = 605.00(4)$ Å³, $D_X = 1.593$ g·cm⁻³, $\mu(\text{MoK}\alpha) = 0.305$ mm⁻¹,

$T = 160(1)$ K, ω scans, $2\theta_{\max} = 60.9^\circ$, transmission factors (min; max) 0.934; 1.000, total reflections measured 15137, symmetry independent reflections 3379, reflections with $I > 2\sigma(I)$ 2917, reflections used in refinement 3379, parameters refined 177, restraints 0, final $R(F)$ ($I > 2\sigma(I)$ reflections) = 0.0306, $wR(F^2)$ (all data) = 0.0796 ($w = [\sigma^2(F_o^2) + (0.0346P)^2 + 0.1802P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$, goodness of fit 1.052, secondary extinction coefficient 0.012(2), final $\Delta_{\max}/\sigma = 0.001$, $\Delta\rho$ (max; min) = 0.36; -0.28 e \AA^{-3} .

Crystal data for **5b**: Crystallized from petroleum ether, $C_{11}H_9F_3N_2O_2$, $M = 258.20$, colorless, prism, crystal dimensions $0.12 \times 0.20 \times 0.25$ mm, monoclinic, space group $P2_1/n$, $Z = 4$, reflections for cell determination 6567, 2θ range for cell determination $10\text{--}149^\circ$, $a = 8.88944(13)$ \AA , $b = 7.43167(12)$ \AA , $c = 17.7441(3)$ \AA , $\beta = 94.8117(16)^\circ$, $V = 1168.11(3)$ \AA^3 , $D_X = 1.468$ $\text{g}\cdot\text{cm}^{-3}$, $\mu(\text{CuK}\alpha) = 1.181$ mm^{-1} , $T = 160(1)$ K, ω scans, $2\theta_{\max} = 148.8^\circ$, transmission factors (min; max) 0.255; 1.000, total reflections measured 11304, symmetry independent reflections 2338, reflections with $I > 2\sigma(I)$ 2163, reflections used in refinement 2338, parameters refined 165, restraints 0, final $R(F)$ ($I > 2\sigma(I)$ reflections) = 0.0309, $wR(F^2)$ (all data) = 0.0843 ($w = [\sigma^2(F_o^2) + (0.0428P)^2 + 0.3239P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$, goodness of fit 1.050, secondary extinction coefficient 0.0021(4), final $\Delta_{\max}/\sigma = 0.001$, $\Delta\rho$ (max; min) = 0.23; -0.18 e \AA^{-3} .

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