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Synthesis of new 2-substituted 3-(tri(di)fluoromethyl)-quinoxalines from 3-(trifluoromethyl)quinoxalin-2(1*H*)-one and 3-(tri(di)fluoromethyl)quinoxaline-2-carboxylic acids

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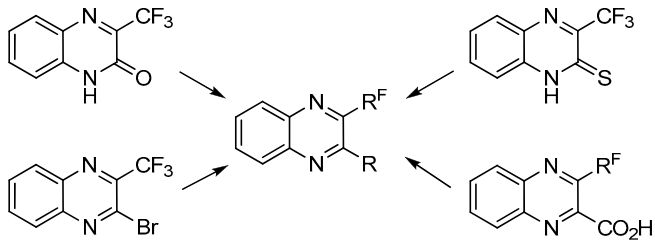


Starting from 3-(trifluoromethyl)quinoxalin-2(1*H*)-one, a wide range of new 2-substituted 3-(trifluoromethyl)quinoxalines were obtained, including amino, bromo, chloro, hydrazino, phenyl, α-furyl, formyl, methylsulfanyl, and methylsulfonyl derivatives. 3-(Tri(di)-fluoromethyl)quinoxaline-2-carboxylic acids were obtained for the first time and used for the synthesis of 2-amino-3-(tri(di)-fluoromethyl)quinoxalines and 2-(2-aminothiazol-4-yl)-3-(trifluoromethyl)quinoxaline.

Keywords: quinoxaline-2-carboxylic acid, quinoxaline-2(1*H*)-thione, quinoxalin-2(1*H*)-one, 2-substituted 3-(tri(di)fluoromethyl)-quinoxalines.

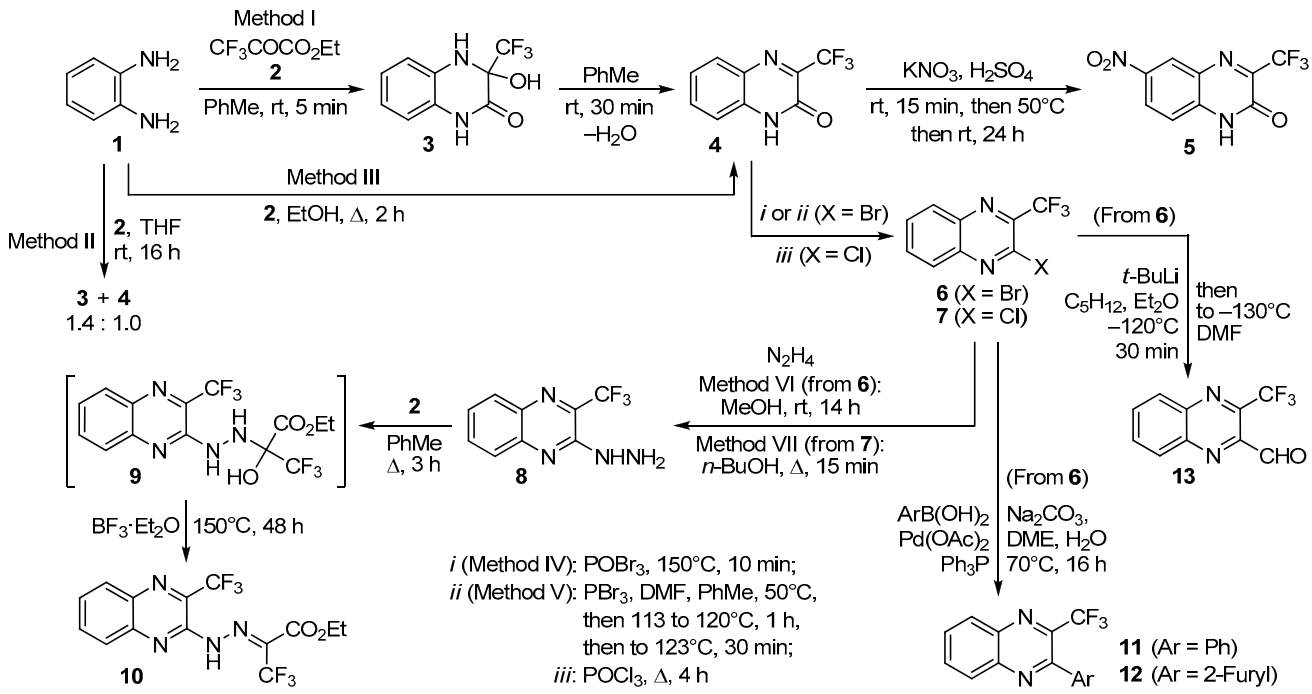
Heterocyclic compounds containing a polyfluoroalkyl group (denoted as R^F), such as a trifluoromethyl group, possess a wide range of useful properties and attract significant interest in the fields of medicinal chemistry and plant protection.[1] However, selective introduction of perfluoroalkyl substituent is a complicated synthetic task that requires a different approach in each particular case. The existing direct fluorination and trifluoromethylation methods for organic compounds[2] do not always succeed, thus it is often more appropriate to use the more flexible synthon approach, employing simple and accessible fluoroorganic synthons.[3]

In the current work, which follows such methodology,[3] we used easily available and highly reactive substrates, trifluoromethyl derivatives of quinoxalin-2(1*H*)-one and quinoxaline-2(1*H*)-thione, as well as 3-(tri(di)fluoro-methyl)quinoxaline-2-carboxylic acids. Functional group transformations in these molecules allowed to substantially expand the range of new quinoxalines containing an R^F group in the pyrazine ring and presenting interest for the synthesis of more complex biologically active compounds.

Quinoxalines are an important type of heterocyclic compounds, some of which have been found to possess strong antitumor, antimicrobial, antibacterial, and antiHIV activity, as well as other biological effects.[4] Trifluoromethyl-containing quinoxalines are also of significant interest in medicinal chemistry as compounds with remarkable biological and physiological properties.[5] Among these compounds are HIV-1 reverse transcriptase inhibitors,[5a] hGLP-1 receptor agonists,[5b] LXR-modulators,[5c] as well as agents with antidiabetic[5d] and anti-inflammatory activity.[5e] The main routes of synthesis for trifluoromethyl derivatives of quinoxaline are condensation of substituted *o*-phenylene-diamines with CF_3-containing α-diketones[6] and α-halo-(nitroso)-β-dicarbonyl compounds.[7] The reactions of hexafluoro-1,2-epoxypropane[5a,8] or alkyltrifluoropyruvates[9] with *o*-phenylenediamine produce 3-(trifluoromethyl)-quinoxalin-2(1*H*)-one, the chemical properties of which remain largely unexplored.[6a]

Synthesis and reactivity of 3-(trifluoromethyl)-quinoxalin-2(1*H*)-one. Initially we studied the reaction of *o*-phenylenediamine (**1**) with ethyl trifluoropyruvate (**2**), leading to 3-(trifluoromethyl)quinoxalin-2(1*H*)-one (**4**), which we propose as a simple and convenient building block for the synthesis of various 2-substituted

Scheme 1



3-(trifluoromethyl)quinoxalines. It was established that performing the reaction in toluene at room temperature for 5 min (method I, Scheme 1) gave at first a precipitate of previously unknown intermediate hydrated form **3**, which could be dehydrated to quinoxalinone **4** (yield 80%) by refluxing in a flask with Dean–Stark trap for 2 h. In tetrahydrofuran, this reaction produced a 1.4:1 mixture of compounds **3** and **4** (method II, Scheme 1), while refluxing in methanol[5c] gave the quinoxalinone **4** in 98% yield (method III, Scheme 1).

The treatment of compound **4** with nitrating mixture gave the expected 6-nitro-3-(trifluoromethyl)quinoxalin-2-(1*H*)-one (**5**) in 88% yield (Scheme 1). Previously this product had been isolated in merely 20% yield from a mixture with 7-nitro-3-(trifluoromethyl)quinoxalin-2(1*H*)-one, obtained from reaction of ethyl trifluoropyruvate (**2**) with 1,2-diamino-4-nitrobenzene.[9b]

The previously unknown 2-bromo-3-(trifluoromethyl) quinoxaline (**6**) was synthesized from the quinoxalinone **4** by two methods and used in this work for most of the following transformations in the pyrazine ring. The reaction of compound **4** with $POBr_3$ during a 10 min heating to 150°C without solvent gave the bromoquinoxaline **6** in 72% yield (method IV, Scheme 1). Even higher yield (85%) was achieved in the reaction with PBr_3 in toluene–DMF mixture (method V, Scheme 1). 2-Chloro-3-(trifluoromethyl)quinoxaline (**7**) was synthesized by refluxing the quinoxalinone **4** with $POCl_3$ for 4 h (46% yield). Even though the reactions of chloroquinoxaline **7** with a range of S-, N-, and C-nucleophiles have been described in the literature,[5d,e] no spectral data or methods for its synthesis were given.

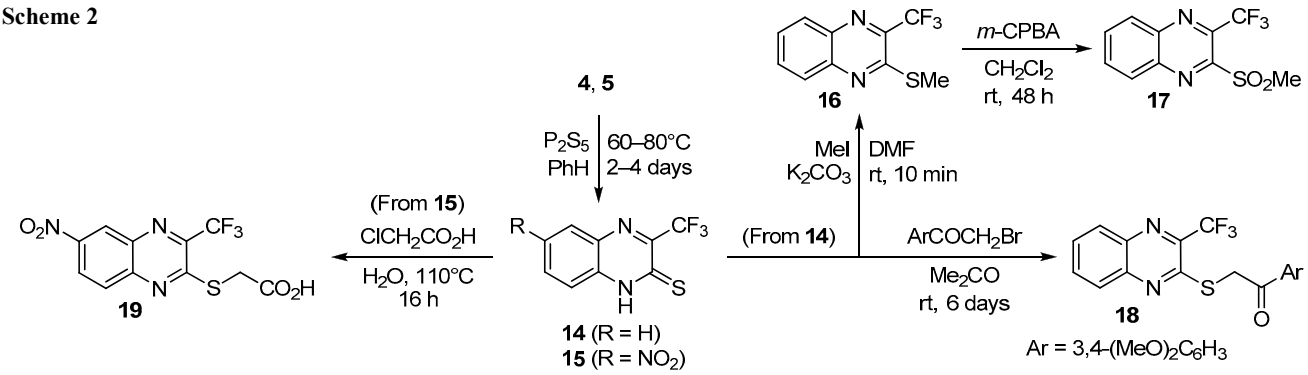
The reaction of hydrazine hydrate with 2-bromoquinoxaline **6** in methanol at room temperature for 14 h or with 2-chloroquinoxaline **7** in refluxing butanol for 15 min gave [(3-trifluoromethyl)quinoxalin-2-yl]hydrazine (**8**) in 72% and 69% yields, respectively. This compound could be subsequently used for reactions with carbonyl compounds (Scheme 1). For example, it was completely converted to the addition product **9** after refluxing for 3 h in toluene with ethyl trifluoropyruvate (**2**) (control by ^{19}F NMR spectroscopy, δ_{CF3} –82.0 and –68.0 ppm). Further heating of the reaction mixture for 48 h at 150°C in the presence of 1 drop of $BF_3 \cdot OEt_2$ caused dehydration of the intermediate **9** to hydrazone **10** (δ_{CF3} –68.6 and –68.2 ppm) in 53% yield.

The Suzuki reaction of bromoquinoxaline **6** with phenyl- and α-furylboronic acids, catalyzed by palladium(II) acetate and triphenylphosphine in dimethoxyethane in the presence of aqueous Na_2CO_3 solution led to the formation of cross-coupling products **11** and **12** in 39% and 81% yields, respectively (Scheme 1). 2-Phenyl-3-(trifluoromethyl)quinoxaline (**11**) was earlier obtained from 1,1,1-trifluoro-3-(2,6-dimethylphenylimino)-3-phenylpropan-2-one and *o*-phenylenediamine.[10]

The substitution of bromine atom with formyl group in quinoxaline **6** could be accomplished by interaction of the latter with a double excess of *tert*-butyllithium at –120°C and subsequent treatment of the lithiated intermediate with excess DMF at –130°C. The reaction product 3-(trifluoromethyl)quinoxaline-2-carbaldehyde (**13**) was isolated by silica gel column chromatography in 16% yield (Scheme 1). The use of such reagents as *n*-BuLi and *i*-PrMgCl gave inferior results, apparently due to alkyl anion addition at the C=N bond of the ring.

Synthesis and reations of 3-(trifluoromethyl)-quinoxaline-2(1*H*)-thione. In order to further modify the quinoxaline system at position 2, compounds **4** and **5** were

Scheme 2

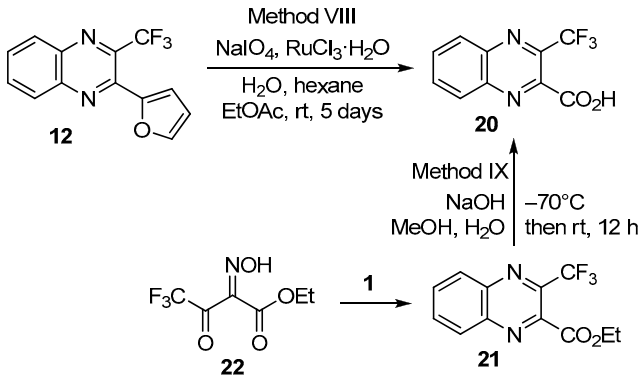


thionated by heating the reaction mixture with P_2S_5 in anhydrous benzene (Scheme 2). The reaction progress was monitored by TLC, and chromatography on a short silica gel column gave the quinoxaline-2(1*H*)-thiones **14** and **15** in 68% and 70% yields, respectively. Treatment of the thione **14** with methyl iodide in anhydrous DMF in the presence of anhydrous potassium carbonate (~20°C, 10 min) led to 2-(methylsulfanyl)-3-(trifluoromethyl)quinoxaline (**16**) in 61% yield. This compound was further oxidized with *m*-chloroperoxybenzoic acid in dichloromethane, producing 2-(methylsulfonyl)-3-(trifluoromethyl)quinoxaline (**17**) in 95% yield. The treatment of compound **14** with 3,4-dimethoxyphenacyl bromide in acetone for 6 days at room temperature gave a 27% yield of the thio derivative **18** by nucleophilic substitution of bromine atom in phenacyl bromide, while the analogous reaction of thione **15** with chloroacetic acid in water (110°C, 16 h) gave {[6-nitro-3-(trifluoromethyl)quinoxalin-2-yl]sulfanyl}acetic acid (**19**) in 43% yield.

Synthesis and reactions of 3-(tri(di)fluoromethyl)-quinoxaline-2-carboxylic acids. We obtained these previously undescribed carboxylic acids by several methods (Schemes 3 and 4). For example, oxidation of the furyl substituent in quinoxaline **12** by the action of $NaIO_4$ in the presence of $RuCl_3 \cdot H_2O$ catalyst over 5 days at room temperature gave 3-(trifluoromethyl)quinoxaline-2-carboxylic acid (**20**) (method VIII, yield 67%). Besides that, the carboxylic acid **20** was synthesized by alkaline hydrolysis of the previously described ester **21** (Method IX, yield 93%), which, in turn, can be obtained by condensation of *o*-phenylenediamine (**1**) with the nitrosation product of ethyl 4,4,4-trifluoro(acetoacetate) **22**[7a] or with ethyl 4,4,4-trifluoro(acetoacetate) in the presence of *N*-bromosuccinimide[7c] (Scheme 3).

We used a method based on the addition of diamine to ketone carbonyl group and the substitution of halogen atom in α-halo-β-ketoester with subsequent oxidation of the dihydropyrazine ring with air oxygen in order to prepare 3-(difluoromethyl)quinoxaline-2-carboxylic acid (**23**). It was established that refluxing α-chloro-β-ketoester **24** with diamine **1** in ethanol gave a mixture of 2-(difluoromethyl)-benzimidazole (**25**) and ethyl 3-(difluoromethyl)quinoxaline-2-carboxylate (**26**) (Scheme 4). Monitoring the reaction by ^{19}F NMR showed that already after 1 h along with the starting ester **24**, conversion of which was 50%, the solution contained a mixture of products **25** and **26**; the

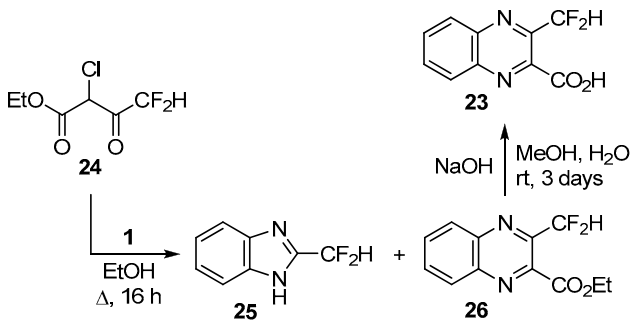
Scheme 3



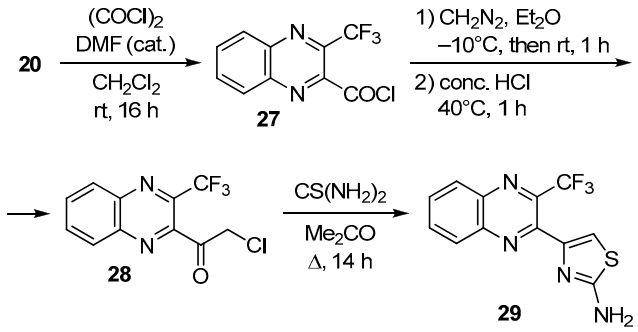
molar ratio of compounds **25** and **26** after 16 h was 3:1, while the ester **24** was virtually absent. Products **25** and **26** were separated by crystallization and column chromatography, and obtained in 21 and 12% yields, respectively, after which the ester **26** was hydrolyzed in methanol solution by the addition of 0.5 M aqueous NaOH, and the target carboxylic acid **23** was isolated in 90% yield.

In order to demonstrate the synthesis of biologically relevant 2-hetaryl-3-(trifluoromethyl)quinoxalines, dichloromethane suspension of the carboxylic acid **20** was treated with oxalyl chloride in the presence of 1 drop of DMF (Scheme 5). The acyl chloride **27** was formed in quantitative yield and reacted first with ether solution of diazomethane, then with conc. HCl, giving the chloro ketone **28** in 76% yield. Further treatment with thiourea in refluxing acetone gave 2-(2-aminothiazol-4-yl)-3-(trifluoromethyl)quinoxaline (**29**) in 71% yield.

Scheme 4

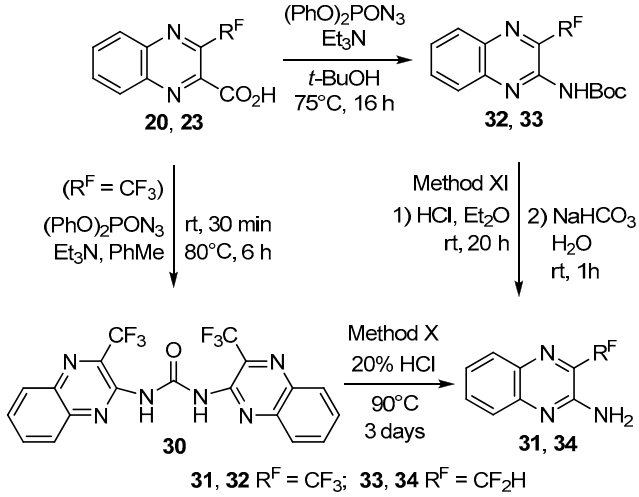


Scheme 5



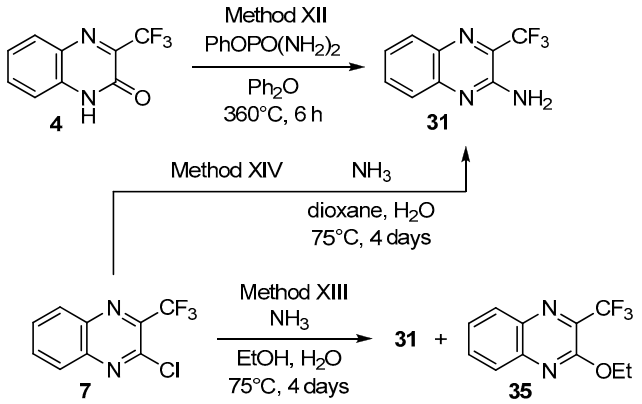
We attempted to transform the carboxyl group of acid **20** into amino group by using a safer modification of Curtius reaction employing diphenylphosphoryl azide[11] and triethylamine in toluene, but obtained only a low yield (15%) of the urea **30**, which was smoothly hydrolyzed to [3-(trifluoromethyl)quinoxalin-2-yl]amine (**31**) upon heating with 20% HCl for 3 days (method X, yield 85%, Scheme 6). Performing this reaction in *t*-butanol with subsequent acidic hydrolysis of the intermediate Boc-amide **32** gave the aminoquinoxaline **31** in 46% yield (method XI). Analogous reaction of 3-(difluoromethyl)quinoxaline-2-carboxylic acid (**23**) through the stage of Boc-amide **33** gave [3-(difluoromethyl)quinoxalin-2-yl]amine (**34**) in 57% yield.

Scheme 6



In conclusion, we should note that the amine **31** may also be obtained in one stage. Thus, treatment of the quinoxalinone **4** with phenyl phosphorodiamidate[12] in diphenyl ether for 6 h at 360°C gave the amine **31** in 56% yield (Method XII, Scheme 7). Compared to the Curtius reaction, this method was preferrable despite the forcing conditions, due to fewer steps and the availability of starting materials. The attempt at substituting chlorine atom with amino group in 2-chloroquinoxaline **7** by the action of 25% aqueous ammonia in ethanol gave a mixture of amine **31** with the ethoxy derivative **35** in 2:1 ratio. The amine **31** could be isolated in 44% yield by recrystallization from heptane (method XIII). Performing this reaction in dioxane gave the target 2-aminoquinoxaline **31** in 55% yield (method XIV).

Scheme 7



The structures of the synthesized compounds were confirmed by elemental analysis, as well as by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy and mass spectrometry.

Thus, we have shown that 3-(trifluoromethyl)-quinoxalin-2(1*H*)-one and tri(di)fluoromethylated quinoxaline-2-carboxylic acids can be used as promising building blocks for the synthesis of a wide range of 2-substituted 3-(tri(di)fluoromethyl)quinoxalines, which may attract interest in the fields of medicinal and agricultural chemistry.

Experimental

^{1}H, ^{13}C, and ^{19}F NMR spectra were acquired on Bruker DPX-200 (compounds **3**, **6**, **8**, **21**, **25**, **26**) and Bruker AC-200 (the rest of the compounds) spectrometers (200, 50, and 188 MHz, respectively) in DMSO-d_6 (compounds **3**, **5**, **14**, **15**, **20**) and $CDCl_3$ (the rest of the compounds). The internal standards were residual solvent proton signals (7.25 ppm for $CDCl_3$, 2.50 ppm for DMSO-d_6), $CDCl_3$ signal (77.0 ppm for ^{13}C nuclei), and $CFCl_3$ signal (0.0 ppm for ^{19}F nuclei). Mass spectra were recorded on a MAT 95 instrument (EI ionization, 70 eV). Elemental analysis was performed on LECO CHN200 analyzer. Melting points were determined on a Jürgens apparatus. The reaction progress, as well as the individuality and identity of the obtained compounds were controlled by TLC on Fluka Analytical plates (60 Å, 254 nm), visualization under UV light. The reaction progress was also controlled by ^{19}F NMR spectroscopy of reaction mixture samples disssolved in $CHCl_3$ with added hexafluorobenzene as internal standard (without lock). Diazomethane was prepared from nitrosomethylurea according to a published procedure[13], oxime **22** was synthesized according to another procedure[14], α-chloro-β-ketoester **24** was synthesized according to procedure[15]. The other reagents were commercially available. Reactions were performed in standard glassware under dry nitrogen atmosphere, using anhydrous solvents (dried according to standard methods: CH_2Cl_2 – by refluxing with P_2O_5; benzene, toluene, Et_2O, and THF – by refluxing with Na and benzophenone). Column chromatography was performed with silica gel from Acros Organics (0.060–0.200 mm, 60 Å).

Reaction of *o*-phenylenediamine (1) with ethyl trifluoropyruvate (2). Synthesis of 3-hydroxy-3-(tri-

fluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (3) and 3-(trifluoromethyl)quinoxalin-2(1*H*)-one (4).

Method I. A suspension of diamine **1** (2.16 g, 20 mmol) in toluene (70 ml) at room temperature was stirred and treated by dropwise addition of the ketoester **2** (3.40 g, 20 mmol). The diamine **1** dissolved with a slight exothermic effect, followed after 5 min by the formation of white precipitate from the greenish solution. An aliquot of the reaction mixture was filtered, giving 100 mg of **3-hydroxy-3-(trifluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (3)**. White powder. Mp 145–147°C. ^{1}H NMR spectrum, δ, ppm: 6.75–7.02 (4H, m, H Ar); 7.40 (1H, s, NH), 7.70 (1H, s, OH); 11.00 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: –80.2. Found, %: C 46.45; H 2.89. $C_9H_7F_3N_2O_2$. Calculated, %: C 46.56; H 3.04.

The reaction mixture was stirred for 30 min at room temperature, then refluxed for 2 h in a flask with a Dean–Stark trap. The precipitate of compound **3** dissolved, a precipitate of quinoxalinone **4** formed and was filtered off, washed with water, and dried. Yield 3.70 g (80%). White powder. Mp >180°C (subl.) (mp 210–211°C).[7a]

Method II. A suspension of diamine **1** (2.16 g, 20 mmol) in THF (25 ml) was stirred and cooled to 5°C, and treated by dropwise addition of the ketoester **2** (3.40 g, 20 mmol). The reaction mixture was slowly brought to room temperature and stirred for 16 h in a sealed vessel. The obtained dark solution was poured into water (200 ml), extracted with $CHCl_3$ (4×30 ml), the combined extracts were dried over $MgSO_4$ and evaporated under vacuum. The residue was dissolved in a 2:1 hexane–Et_2O mixture and cooled to –30°C. The precipitate that formed was filtered off, dried, and recrystallized from toluene. The obtained yellow crystals (1.00 g) were a mixture of compounds **3** and **4** in a 1.4:1.0 molar ratio (according to ^{1}H and ^{19}F NMR data).

Method III. A suspension of diamine **1** (10.80 g, 0.1 mol) in EtOH (85 ml) was stirred at room temperature and treated by dropwise addition of the ketoester **2** (17.00 g, 0.1 mol). The mixture was refluxed for 2 h, the obtained red solution with precipitate was left overnight at room temperature, then the precipitate was filtered off, washed with water (2×25 ml), and dried, giving the quinoxalinone **4** (19.00 g). A second crop of 2.00 g was obtained by concentrating the filtrate. The total yield was 21.00 g (98%). White powder. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.37–7.45 (2H, m, H Ar); 7.72 (1H, t, *J* = 8.1, H Ar); 7.91 (1H, d, *J* = 8.2, H Ar); 13.10 (1H, br. s, NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.33–7.50 (2H, m, H Ar); 7.72 (1H, t, *J* = 7.1, H Ar); 7.99 (1H, d, *J* = 7.9, H Ar); 12.20 (1H, br. s, NH). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –69.2. ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –70.2. Compound **4** was used in the further experiments without additional purification.

6-Nitro-3-(trifluoromethyl)quinoxalin-2(1*H*)-one (5). A solution of quinoxalinone **4** (0.56 g, 2.6 mmol) in conc. H_2SO_4 (10 ml) was stirred and treated by portionwise addition of ground KNO_3 (0.40 g, 3.9 mmol). After stirring for 15 min at room temperature, the mixture was briefly heated to 50°C and then stirred for 24 h at room temperature. The reaction mixture was poured on crushed ice, neutralized with $NaHCO_3$; the impurities were removed by extraction with $CHCl_3$ (2×20 ml), and the aqueous layer was acidified with conc. HCl to pH 2. The product was extracted with CH_2Cl_2 (3×30 ml), the combined extracts were dried over anhydrous Na_2SO_4 and the solution was evaporated. Yield 0.60 g (88%). Yellow powder. Mp 215°C (subl.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.51 (1H, d, *J* = 9.0, H-8); 8.50 (1H, dd, *J* = 9.0, *J* = 2.5, H-7); 8.68 (1H, d, *J* = 2.5, H-5); 13.50 (1H, br. s, NH). ^{19}F NMR spectrum, δ, ppm: –69.5. Compound **5** was used in the further experiments without additional purification.

2-Bromo-3-(trifluoromethyl)quinoxaline (6).

Method IV. A mixture of quinoxalinone **4** (1.5 g, 7.0 mmol) and $POBr_3$ (2.0 g, 7.0 mmol) was heated for 10 min at 150°C. The reaction mixture was then cooled to room temperature, diluted with ice water (100 ml), and stirred for 10 min. The obtained white precipitate was filtered off, washed with water (5 ml), and dried. Yield 1.4 g (72%). Light-yellow crystals.

Method V. A solution of quinoxalinone **4** (17.8 g, 83 mmol) in a mixture of DMF (16 ml) and toluene (150 ml) was heated to 50°C and treated with PBr_3 (33.8 g, 125 mmol). The reaction mixture was stirred and heated in a sealed vessel, while increasing the bath temperature from 113°C to 120°C over 1 h, then to 123°C over 30 min (*Caution, excess pressure caused by HBr!*). The mixture was then cooled to room temperature, the organic layer was decanted, the solid residue was washed with boiling toluene (2×100 ml). The combined toluene solutions were washed with H_2O (70 ml), with saturated aqueous $NaHCO_3$ (3×50 ml), then again with H_2O (70 ml) and saturated aqueous NaCl (70 ml), followed by drying over anhydrous Na_2SO_4 and evaporation. The obtained crude product (22.5 g) was recrystallized from MeOH. Yield 19.6 g (85%). Light-yellow crystals. Mp 150–152°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.86–7.97 (2H, m, H Ar); 8.12 (1H, dd, *J* = 8.2, *J* = 2.4, H Ar); 8.21 (1H, dd, *J* = 8.1, *J* = 2.6, H Ar). ^{19}F NMR spectrum, δ, ppm: –66.8. Mass spectrum, *m*/*z* (I_{rel}, %): 276 $[M(^{79}Br)]^+$ (74), 257 $[M(^{79}Br)–F]^+$ (4), 197 $[M–Br]^+$ (100), 128 $[M–CF_3–Br]^+$ (5), 69 $[CF_3]^+$ (34). Found, %: C 39.00; H 1.35. $C_9H_4BrF_3N_2$. Calculated, %: C 39.02; H 1.46.

2-Chloro-3-(trifluoromethyl)quinoxaline (7). A mixture of quinoxalinone **4** (18.0 g, 84 mmol) and $POCl_3$ (100 ml) was refluxed for 4 h. The reaction mixture was then cooled to room temperature, poured onto crushed ice (500 g), stirred for 30 min, and extrated with EtOAc (3×70 ml). The combined organic extracts were washed with H_2O (2×30 ml) and saturated aqueous NaCl (30 ml), then dried over anhydrous Na_2SO_4, evaporated. The solid residue was recrystallized from a 6:1 hexane–$CHCl_3$ mixture. Yield 9.0 g (46%). White crystals. Mp 105–107°C (subl.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.86–7.99 (2H, m, H Ar); 8.11 (1H, dd, *J* = 8.4, *J* = 1.4, H Ar); 8.23 (1H, dd, *J* = 8.3, *J* = 1.7, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 120.4 (q, *J* = 275.8, CF_3); 128.3, 129.9, 131.4, 133.5 (C-5,6,7,8); 138.9, 142.8, 143.4 (C-2,4a,8a); 140.3 (q, *J* = 35.8, C-3). ^{19}F NMR spectrum, δ, ppm: –67.3. Found, %: C 46.77; H 1.99. $C_9H_4ClF_3N_2$. Calculated, %: C 46.48; H 1.73.

[3-(Trifluoromethyl)quinoxalin-2-yl]hydrazine (8).

Method VI. A solution of bromide **6** (0.60 g, 2.2 mmol) in MeOH (30 ml) was stirred at room temperature and treated by dropwise addition of 100% $N_2H_4 \cdot H_2O$ (0.50 g, 10.0 mmol). The reaction mixture was stirred for 14 h in a sealed vessel at room temperature, poured into H_2O (100 ml), the precipitate that formed was filtered off and dried. Yield 0.36 g (72%).

Method VII. A solution of chloride **7** (0.12 g, 0.5 mmol) in *n*-BuOH (10 ml) was stirred at room temperature and treated by dropwise addition of 100% $N_2H_4 \cdot H_2O$ (0.28 g, 5.6 mmol). The obtained solution was refluxed for 15 min (the reaction progress was controlled by ^{19}F NMR, confirming the complete conversion of chloride **7** to hydrazine **8**). The volatile components were removed under vacuum, the solid residue was dissolved in $CHCl_3$ (15 ml) and washed with H_2O (2×5 ml). The organic phase was dried over anhydrous Na_2SO_4, evaporated, the solid residue was recrystallized from heptane. Yield 0.080 g (69%). Reddish crystals. Mp 152–154°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.20 (2H, br. s, NH_2); 6.70 (1H, br. s, NH); 7.51 (1H, t, *J* = 7.4, H Ar); 7.69–7.88 (2H, m, H Ar); 8.00 (1H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 121.2 (q, *J* = 275.8 , CF_3); 126.3, 126.4, 129.8, 132.6 (C-5,6,7,8); 131.6 (q, *J* = 35.8 , C-3); 135.6, 142.6, 149.9 (C-2,4a,8a). ^{19}F NMR spectrum, δ, ppm: –68.4. Found, %: C 47.22; H 2.98. $C_9H_7F_3N_4$. Calculated, %: C 47.38; H 3.09.

[3-(Trifluoromethyl)quinoxalin-2-yl]hydrazone of ethyl trifluoropyruvate (10). A solution of hydrazine **8** (110 mg, 0.5 mmol) in toluene (25 ml) was stirred and treated with the ketoester **2** (120 mg, 0.7 mmol), followed by refluxing the reaction mixture for 3 h. According to ^{19}F NMR spectrum, the conversion of compound **8** reached 100%, while the reaction mixture contained adduct **9** (δ_{CF3} –82.0 and –68.0 ppm). The mixture was treated with 1 drop of $BF_3 \cdot OEt_2$, stirred, and heated in a sealed vessel at 150°C for 48 h (monitoring of the reaction progress by ^{19}F NMR spectroscopy confirmed the complete conversion of adduct **9** to hydrazone **10**). The reaction mixture was then evaporated to dryness under vacuum, the solid residue was recrystallized from heptane. Yield 100 mg (53%). Red crystals. Mp 135–137°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.43 (3H, t, *J* = 7.1, $OCH_2\underline{CH_3}$); 4.47 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$); 7.75 (1H, t, *J* = 7.3, H Ar); 7.87 (1H, d, *J* = 7.7, H Ar); 8.10–8.16 (2H, m, H Ar); 13.60 (1H, br. s, NH). ^{19}F NMR spectrum, δ, ppm: –68.6; –68.2. Found, %: C 44.50; H 2.81. $C_{14}H_{10}F_6N_4O_2$. Calculated, %: C 44.22 ; H 2.65.

2-Phenyl-3-(trifluoromethyl)quinoxaline (11). A solution of bromide **6** (0.38 g, 1.4 mmol) in dimethoxyethane (15 ml) was treated by the addition of phenylboronic acid (0.20 g, 1.6 mmol), 0.7 M aqueous Na_2CO_3 solution (6 ml), $Pd(OAc)_2$ (0.03 g, 0.14 mmol), and Ph_3P (0.07 g, 0.28 mmol). The reaction mixture was stirred and heated under nitrogen atmosphere at 70°C for 16 h. The brown solution with black precipitate was cooled to room temperature, poured into H_2O (100 ml), and extracted with $CHCl_3$ (3×10 ml). The combined extracts were dried over anhydrous $MgSO_4$, evaporated under vacuum, and the solid residue was recrystallized from heptane. Yield 150 mg (39%). Yellow needles. Mp 115–116°C (mp 115–116°C)[10]. ^1H NMR spectrum, δ, ppm: 7.50–7.55 (3H, m, H Ph); 7.55–7.65 (2H, m, H Ph); 7.85–7.97 (2H, m, H Ar); 8.19–8.28 (2H, m, H Ar). ^{19}F NMR spectrum, δ, ppm: –62.2. Found, %: C 65.54; H 3.05. $C_{15}H_9F_3N_2$. Calculated, %: C 65.70; H 3.31 .

2-(2-Furyl)-3-(trifluoromethyl)quinoxaline (12). A solution of bromide **6** (1.30 g, 4.7 mmol) in dimethoxyethane (50 ml) was treated by addition of (2-furyl)boronic acid (1.05 g, 9.4 mmol), 0.7 M aqueous Na_2CO_3 solution (20 ml), Ph_3P (0.25 g, 0.94 mmol), and $Pd(OAc)_2$ (0.11 g, 0.47 mmol). The reaction mixture was stirred and heated under nitrogen atmosphere at 70°C for 16 h, then cooled to room temperature, poured into H_2O (150 ml), and extracted with Et_2O (3×50 ml). The combined extracts were washed with H_2O (30 ml), saturated NaCl solution (30 ml), dried over Na_2SO_4, and evaporated. Compound **12** was isolated by column chromatography (eluent 1:8 EtOAc–hexane, R_f 0.45). Yield 1.00 g (81%). Yellow crystals. Mp 89–90°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.63 (1H, dd, *J* = 3.0, *J*= 1.5, H-4 Fur); 7.33 (1H, d, *J* = 3.1, H-3 Fur); 7.73 (1H, s, H-5 Fur); 7.78–7.92 (2H, m, H Ar); 8.16–8.20 (2H, m, H). ^{19}F NMR spectrum, δ, ppm: –65.5. Found, %: C 59.20; H 2.81. $C_{13}H_7F_3N_2O$. Calculated, %: C 59.10; H 2.67 .

3-(Trifluoromethyl)quinoxaline-2-carbaldehyde (13). A mixture of pentane (20 ml) and Et_2O (10 ml) was stirred and cooled to –78°C, and treated by dropwise addition of 1.7 M *t*-BuLi solution in pentane (10 ml, 17 mmol). The reaction mixture was cooled to –120°C, a solution of bromide **6** (2.35 g, 8.5 mmol) in Et_2O (10 ml) was added dropwise. The reaction mixture was stirred for 30 min at –120°C, then cooled to –130°C, and treated by dropwise addition of DMF (2.20 g, 30 mmol) in Et_2O (5 ml). The reaction mixture was then poured onto a mixture of ice (100 g) and 1.5 M HCl (20 ml). The organic layer was separated, extracted with Et_2O (3×20 ml); the combined extracts were washed with H_2O (20 ml), saturated NaCl solution (20 ml), dried over Na_2SO_4, and evaporated. Compound **13** was isolated by column chromatography (eluent 1:2 EtOAc–hexane, R_f 0.2) and additionally purified by recrystallization from heptane. Yield 0.30 g (16%). Light-red powder. Mp 113–114°C. ^1H NMR spectrum, δ, ppm: 8.02–8.09 (2H, m, H Ar); 8.29–8.38 (2H, m, H Ar); 10.37 (1H, s, CHO). ^{19}F NMR spectrum, δ, ppm: –64.8. Found, %: C 52.98; H 2.14. $C_{10}H_5F_3N_2O$. Calculated, %: C 53.11; H 2.23.

3-(Trifluoromethyl)quinoxaline-2-thione (14). A suspension of quinoxalinone **4** (1.5 g, 7 mmol) in benzene (50 ml) was stirred and heated to 50°C, and treated by portionwise addition of P_2S_5 (1.6 g, 7 mmol). The reaction mixture was stirred in a sealed vessel at 60°C for 48 h. Monitoring by TLC (1:2 EtOAc–hexane) showed the presence of the starting compound **4** in the mixture, therefore another portion of P_2S_5 (3.0 g, 13.5 mmol) was added, and stirring at 80°C was continued for 72 h. The reaction mixture was filtered through a thin silica gel layer (eluent was THF), the filtrate was evaporated, the solid residue was purified by recrystallization from benzene. Yield 1.1 g (68%). Yellow crystals. Mp 191°C (subl.). ^1H NMR

spectrum, δ, ppm (*J*, Hz): 7.51–7.63 (2H, m, H Ar); 7.81 (1H, t, *J* = 7.2, H Ar); 7.97 (1H, d, *J* = 8.1, H Ar); 14.80 (1H, br. s, NH). ^{19}F NMR spectrum, δ, ppm: –67.4. Found, %: C 46.70; H 2.12. $C_9H_5F_3N_2S$. Calculated, %: C 46.96; H 2.19.

6-Nitro-3-(trifluoromethyl)quinoxaline-2-thione (15). A suspension of quinoxalinone **5** (0.53 g, 2.0 mmol) in benzene (30 ml) was stirred and heated to 60°C, and treated by portionwise addition of P_2S_5 (1.0 g, 4.5 mmol). The reaction mixture was stirred in a sealed vessel at 80°C for 4 days, then evaporated, the residue was dissolved in THF (15 ml), the solution was filtered through a thin silica gel layer (eluent THF). The brown, resinous material obtained after evaporation of the filtrate was purified by chromatography on a short column (eluent $CHCl_3$) and recrystallized from toluene. Yield 0.40 g (70%). Red crystals. Mp 210–212°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.70 (1H, d, *J* = 9.0 , H-8); 8.55 (1H, dd, *J* = 9.0, *J* = 2.5, H-7); 8.73 (1H, d, *J* = 2.5, H-5); 15.10 (1H, br. s, NH). ^{19}F NMR spectrum, δ, ppm: –67.8. Found, %: C 39.59; H 1.59. $C_9H_4F_3N_3O_2S$. Calculated, %: C 39.28; H 1.47.

2-(Methylsulfanyl)-3-(trifluoromethyl)quinoxaline (16). A suspension of anhydrous K_2CO_3 (0.42 g, 3 mmol) in DMF (10 ml) was treated by the addition of thioamide **14** (0.70 g, 3 mmol), then stirred and treated by dropwise addition of MeI (0.26 ml, 0.60 g, 4.3 mmol). Complete conversion of the starting compound **14** was observed by TLC (1:1 EtOAc–hexane) after 10 min. The reaction mixture was poured into H_2O (100 ml), the precipitate that formed was filtered off, washed with H_2O (10 ml), dried, and purified by recrystallization from heptane. Yield 0.45 g (61%). Yellowish crystals. Mp 109–110°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.72 (3H, s, CH_3); 7.69 (1H, t, *J* = 7.1, H Ar); 7.82 (1H, t, *J* = 7.0, H Ar); 7.99 (1H, d, *J* = 8.3, H Ar); 8.10 (1H, d, *J* = 8.2, H Ar). ^{19}F NMR spectrum, δ, ppm: –67.6. Compound **16** was used further without additional purification.

2-(Methylsulfonyl)-3-(trifluoromethyl)quinoxaline (17). A solution of compound **16** (0.40 g, 1.6 mmol) in CH_2Cl_2 (30 ml) was stirred and treated by the addition of *m*-chloroperoxybenzoic acid (0.57 g, 3.2 mmol). The mixture was stirred at room temperature for 48 h and washed with saturated aqueous $NaHCO_3$ solution (20 ml). The organic layer was separated and evaporated. Sulfone **17** was isolated by column chromatography (eluent was 1:2 EtOAc–hexane, R_f 0.5) and additionally purified by recrystallization from 2:1 heptane–toluene. Yield 0.43 g (95%). Flesh colored needles. Mp 148–149°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.55 (3H, s, CH_3); 8.04–8.09 (2H, m, H Ar); 8.20–8.35 (2H, m, H Ar). ^{19}F NMR spectrum, δ, ppm: –63.6. Found, %: C 43.30; H 2.31. $C_{10}H_7F_3N_2O_2S$. Calculated, %: C 43.48; H 2.55.

1-(3,4-Dimethoxyphenyl)-2-{[3-(trifluoromethyl)quinoxalin-2-yl]sulfanyl}ethanone (18). A solution of thioamide **14** (0.21 g, 0.9 mmol) in acetone (5 ml) was treated by the addition of 3,4-dimethoxyphenacyl bromide (0.24 g, 0.9 mmol). The reaction mixture was stirred at room temperature in a sealed vessel for 6 days, poured into H_2O (100 ml), the obtained precipitate of compound **18** was filtered off, dried, and recrystallized from toluene. Yield 0.10 g (27%). Yellowish plates. Mp 170–171°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.82 (3H, s, OCH_3); 3.92 (3H, s, OCH_3); 4.74 (2H, s, SCH_2CO); 6.98 (1H, d, *J* = 8.4, H Ar); 7.49–7.84 (5H, m, H Ar); 8.07 (1H, d, *J* = 8.2, H Ar). ^{19}F NMR spectrum, δ, ppm: –67.3. Found, %: C 55.59; H 3.40. $C_{19}H_{15}F_3N_2O_3S$. Calculated, %: C 55.88; H 3.70.

{[6-Nitro-3-(trifluoromethyl)quinoxalin-2-yl]sulfanyl}-acetic acid (19). A mixture of thioamide **15** (20 mg, 0.07 mmol) and chloroacetic acid (50 mg, 0.5 mmol) in H_2O (5 ml) was heated for 16 h at 110°C. Crystals of carboxylic acid **19** formed after cooling to room temperature were filtered off, dried, and recrystallized from a 3:2 heptane–toluene mixture. Yield 10 mg (43%). Yellow crystals. Mp 180–182°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.16 (2H, s, CH_2); 8.08 (1H, d, *J* = 9.0, H-8); 8.58 (1H, dd, *J* = 9.0, *J* = 1.5 , H-7); 9.05 (1H, d, *J* = 1.5, H-5). ^{19}F NMR spectrum, δ, ppm: –67.7. Found, %: C 39.51; H 1.69. $C_{11}H_6F_3N_3O_4S$. Calculated, %: C 39.65; H 1.81.

3-(Trifluoromethyl)quinoxaline-2-carboxylic acid (20).

Method VIII. A solution of H_5IO_6 (17.3 g, 76 mmol) in H_2O (120 ml) was stirred and cooled with ice, then cold aqueous 0.95 M NaOH solution (80 ml) was added, followed by hexane (100 ml), EtOAc (50 ml), a solution of quinoxaline **12** (2.5 g, 9.5 mmol) in EtOAc (50 ml), and $RuCl_3 \cdot H_2O$ (110 mg, 0.5 mmol). The reaction mixture was then stirred at room temperature for 5 days (monitoring by ^{19}F NMR spectroscopy confirmed the complete conversion of compound **12**). The aqueous phase was separated, extracted with EtOAc (30 ml), the combined organic phases were washed with 5% aqueous Na_2CO_3 solution (3×50 ml). The alkaline aqueous phases were washed with EtOAc (30 ml), acidified with 3 M HCl to pH 3, the product was extracted with EtOAc (2×50 ml), the extracts were washed with H_2O (30 ml), saturated NaCl solution (30 ml), dried over anhydrous Na_2SO_4, and evaporated. The obtained gray crystalline material (1.7 g) was dissolved in H_2O and treated with $NaHCO_3$ with added activated carbon (0.5 g). The mixture was stirred at room temperature for 2 h, filtered through a thin layer of Celite, washed with H_2O (20 ml), the filtrate was acidified with diluted HCl to pH 3, the product was extracted with EtOAc (2×50 ml). H_2O (30 ml), saturated NaCl solution (30 ml), dried over Na_2SO_4, and the solvent was evaporated. Yield 1.55 g (67%).

Method IX. A solution of ester **21** (2.15 g, 8.0 mmol) in MeOH (70 ml) was cooled to –70°C, stirred, and treated with 1.7 M aqueous solution of NaOH (5 ml). The obtained mixture was stirred at room temperature for 12 h, the obtained red solution was poured onto ice (400 g) and acidified with dilute HCl to pH 1. The obtained yellow precipitate was filtered off, washed with H_2O (10 ml), and dried, giving 1.00 g of carboxylic acid **20**. The filtrate was extracted with EtOAc (2×50 ml). The combined organic extracts were dried with anhydrous $MgSO_4$ and evaporated under vacuum, giving additional 0.80 g of the carboxylic acid **20**. The total yield was 1.80 g (93%). Yellow powder. Mp 170°C (subl.). ^{1}H NMR spectrum, δ, ppm: 8.05–8.21 (2H, m, H Ar); 8.25–8.40 (2H, m, H Ar). ^{19}F NMR

spectrum, δ, ppm: –65.00. Compound **20** was used further without additional purification.

Ethyl 3-(trifluoromethyl)quinoxaline-2-carboxylate (21) was obtained according to a published procedure.[7a] ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.56 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.95–8.00 (2H, m, H Ar); 8.24–8.29 (2H, m, H Ar). ^{19}F NMR spectrum, δ, ppm: –65.0.

The reaction of ethyl 2-chloro-4,4-difluoro-3-oxobutanoate (24) with *o*-phenylenediamine (1). Synthesis of 2-difluoromethyl)benzimidazole (25) and ethyl 3-(difluoromethyl)quinoxaline-2-carboxylate (26). A solution of β-ketoester **24** (2.00 g, 10 mmol) in EtOH (40 ml) was treated with the diamine **1** (1.10 g, 10 mmol) and refluxed for 16 h. The reaction mixture was poured into H_2O (200 ml), extracted with $CHCl_3$ (3×25 ml). The combined extracts were dried over anhydrous $MgSO_4$, and the solvent was removed by evaporation. The oily residue crystallized, its recrystallization from a minimum amount of $CHCl_3$ gave 2-(difluoromethyl)benzimidazole (**25**). Yield 0.35 g (21%). Reddish prisms. Mp 150°C (mp 153°C)[16]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.94 (1H, t, *J* = 53.8, CF_2H); 7.35–7.39 (2H, m, H Ar); 7.69–7.73 (2H, m, H Ar); 10.90 (1H, br. s, NH). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –115.6 (d, *J* = 52.9). The filtrate was separated by column chromatography (eluent CH_2Cl_2), giving ethyl 3-(difluoromethyl)quinoxaline-2-carboxylate (**26**). Yield 0.30 g (12%). Yellowish crystals. Mp 95–97°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.58 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.41 (1H, t, *J* = 54.3, CF_2H); 7.92–7.97 (2H, m, H Ar); 8.24–8.30 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.1 ($OCH_2\underline{C}H_3$); 63.2 ($O\underline{C}H_2CH_3$); 111.3 (t, *J* = 243.1, CF_2H); 129.8, 130.1, 132.5, 132.9 (C-5,6,7,8); 141.6, 142.6, 145.83 (C-2,4a,8a); 145.81 (t, *J* = 24.2, C-3); 164.4 (CO). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –118.8 (d, *J* = 54.9). Compound **26** was used further without additional purification.

3-(Difluoromethyl)quinoxaline-2-carboxylic acid (23). A solution of ester **26** (150 mg, 0.6 mmol) in MeOH (50 ml) was cooled to –20°C and treated with aqueous 0.5 M solution of NaOH (3 ml). The mixture was stirred at room temperature for 3 days, then the solvent was removed by evaporation under vacuum, the solid residue was dissolved in H_2O (30 ml). The solution was washed with Et_2O (5 ml), acidified with dilute HCl to pH 1, the product was extracted with Et_2O (3×15 ml), the combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed by evaporation. Yield 120 mg (90%). Creme colored powder. Mp 149–150°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.89 (1H, t, *J* = 53.8, CF_2H); 7.99–8.11 (2H, m, H); 8.23–8.27 (1H, m, H Ar); 8.36–8.41 (1H, m, H Ar); 10.40 (1H, br. s, CO_2H). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –120.1 (d, *J* = 52.7). Found, %: C 53.72; H 2.95. $C_{10}H_6F_2N_2O_2$. Calculated, %: C 53.58; H 2.70.

3-(Trifluoromethyl)quinoxaline-2-carbonyl chloride (27). A suspension of carboxylic acid **20** (0.15 g, 0.6 mmol) in CH_2Cl_2 (20 ml) was stirred and treated by dropwise addition of $(COCl)_2$ (2.00 g, 15.7 mmol) and 1 drop of DMF. The mixture was stirred overnight at room temperature, the homogenous solution was evaporated to dryness, the residue was dried under vacuum. Yield 0.16 g (100%). Orange solid. ^{1}H NMR spectrum, δ, ppm: 8.03–8.10 (2H, m, H Ar); 8.27–8.35 (2H, m, H Ar). ^{19}F NMR spectrum, δ, ppm: –64.5. Compound **27** was used further without additional purification.

2-Chloro-1-[3-(trifluoromethyl)quinoxalin-2-yl]ethanone (28). A solution of acyl chloride **27** (160 mg, 0.6 mmol) in Et_2O (5 ml) was cooled to –10°C and treated by dropwise addition of diazomethane (126 mg, 3 mmol) in Et_2O (7 ml). The solution was then allowed to warm to room temperature, stirred for 1 h, conc. HCl (12 ml) was cautiously added, and the reaction mixture was stirred for 1 h at 40°C. The obtained solution was neutralized with saturated $NaHCO_3$ solution, extracted with Et_2O (5×5 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated. The residue was triturated with heptane (2 ml) and dried under vacuum. Yield 130 mg (76%). Orange powder. Mp 88–89°C. ^{1}H NMR spectrum, δ, ppm: 5.06 (2H, s, CH_2); 8.00–8.05 (2H, m, H Ar); 8.22–8.32 (2H, m, H Ar). ^{19}F NMR spectrum, δ, ppm: –64.7. Compound **28** was used further without additional purification.

2-(2-Aminothiazol-4-yl)-3-(trifluoromethyl)quinoxaline (29). A mixture of ketone **28** (130 mg, 0.47 mmol) and thiourea (37 mg, 0.47 mmol) in acetone (20 ml) was refluxed for 14 h. The solvent was removed by evaporation; the residue was treated with saturated $NaHCO_3$ solution (15 ml) and extracted with Et_2O (5×5 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, evaporated, and the residue was recrystallized from heptane. Yield 100 mg (71%). Yellow crystals. Mp 166–167°C. ^{1}H NMR spectrum, δ, ppm: 5.20 (2H, br. s, NH_2); 7.10 (1H, s, H-5 thiazole); 7.81–7.95 (2H, m, H Ar); 8.20–8.24 (2H, m, H Ar). ^{19}F NMR spectrum, δ, ppm: –63.2. Found, %: C 48.54; H 2.27. $C_{12}H_7F_3N_4S$. Calculated, %: C 48.65; H 2.38.

[3-(Trifluoromethyl)quinoxalin-2-yl]amine (31).

Method X. A suspension of carboxylic acid **20** (0.35 g, 1.45 mmol) in toluene (20 ml) at room temperature was treated with Et_3N (0.15 g, 1.45 mmol) and diphenylphosphoryl azide (0.40 g, 1.45 mmol). The reaction mixture was stirred for 30 min at room temperature, then heated at 80°C for 6 h. Toluene was evaporated, the residue was treated with $CHCl_3$ (30 ml) and H_2O (10 ml). The organic phase was washed with $NaHCO_3$ solution (2×10 ml), dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was recrystallized from toluene, giving ***N*,*N*'-bis-[3-(trifluoromethyl)quinoxalin-2-yl]urea (30)**. Yield 0.05 g (15%). Yellow crystals. Mp 221–222°C (subl.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.80 (2H, td, *J* = 8.0, *J* = 1.0, H Ar); 7.93 (2H, td, *J* = 8.0, *J* = 0.8, H Ar); 8.10 (2H, d, *J* = 8.0, H Ar); 8.19 (2H, d, *J* = 8.0, H Ar); 10.00 (2H, br. s, 2NH). ^{19}F NMR spectrum, δ, ppm: –66.1. Mass spectrum, *m*/*z* (I_{rel}, %): 452 $[M]^+$ (8), 239. $[M–HetNH_2]^+$ (44), 213 $[HetNH_2]^+$ (100), 144 $[HetNH_2–CF_3]^+$ (14), 69 $[CF_3]^+$ (4). The obtained urea **30** (0.05 g) was combined with filtrate, treated with 20% HCl solution (15 ml), and the obtained mixture was stirred at 90°C for 3 days (control by ^{19}F NMR

spectroscopy confirmed the complete conversion of urea **30** into the amine **31**). The reaction mixture was neutralized with aqueous $NaHCO_3$, the product was extracted with Et_2O (3×15 ml), the combined extracts were washed with H_2O (5 ml), dried over anhydrous Na_2SO_4, and evaporated. Compound **31** was isolated by column chromatography (eluent 1:2 EtOAc–hexane, R_f 0.6) and additionally purified by recrystallization from heptane. Yield 0.04 g (85%). Bright-yellow needles. Mp 82°C (subl.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.30 (2H, br. s, NH_2); 7.47–7.55 (1H, m, H Ar); 7.67–7.71 (2H, m, H Ar); 7.99 (1H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 121.5 (q, *J* = 274.7, CF_3); 126.0, 126.4, 129.8, 132.7 (C-5,6,7,8); 131.6 (q, *J* = 34.7, C-3); 135.9, 143.0, 148.7 (C-2,4a,8a). ^{19}F NMR spectrum, δ, ppm: –68.5. Found, %: C 50.60; H 2.71. $C_9H_6F_3N_3$. Calculated, %: C 50.71; H 2.84.

Method XI. Carboxylic acid **20** (100 mg, 0.41 mmol) and diphenylphosphoryl azide (125 mg, 0.45 mmol) were added to a mixture of Et_3N (50 mg, 0.51 mmol) and *t*-BuOH (5 g). The obtained mixture was stirred at 75°C for 16 h, then the volatile components were removed under vacuum. The residue was partitioned between Et_2O (25 ml) and H_2O (25 ml), the organic layer was separated, while aqueous layer was extracted with Et_2O (2×10 ml). The combined organic extracts were washed with aqueous 5% solution of citric acid (10 ml), saturated solutions of $NaHCO_3$ (2×10 ml) and NaCl (5 ml), dried over anhydrous Na_2SO_4, and evaporated. The brown, resinous precipitate was washed with hexane (2×10 ml) and the combined hexane fractions were evaporated. ***tert*-Butyl[3-(trifluoromethyl) quinoxalin-2-yl]carbamate (32)** was obtained as yellowish, semicrystalline material. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.56 (9H, s, $C(CH_3)_3$); 7.22–7.41 (3H, m, H Ar); 8.09 (1H, d, *J* = 8.3 , H Ar). ^{19}F NMR spectrum, δ, ppm: –66.2. Saturated HCl solution in Et_2O (10 ml) was added to this compound, the obtained mixture was stirred at room temperature for 20 h. The precipitated hydrochloride of amine **31** (80 mg) was filtered off, dissolved in H_2O (5 ml), treated with saturated aqueous $NaHCO_3$ solution (10 ml), and stirred for 1 h. The product was extracted with Et_2O (3×5 ml), the combined extracts were dried over anhydrous Na_2SO_4 and evaporated, giving pure amine **31**. Yield 50 mg (46%).

Method XII. A mixture of quinoxalinone **4** (1.62 g, 7.5 mmol) and phenyl phosphorodiamidate (3.90 g, 22.7 mmol) was added to molten Ph_2O (50 ml), which was free of dissolved gases. The obtained mixture was stirred on a sand bath at 360°C (the reaction did not proceed at lower temperatures) for 6 h under nitrogen atmosphere, cooled to room temperature, and treated with Et_2O (50 ml). The precipitate was filtered off, washed with Et_2O (20 ml), and discarded, while the filtrate was acidified with saturated HCl solution in Et_2O (40 ml), maintained for 1 day at room temperature, the precipitate formed was filtered off, washed with Et_2O (20 ml), and dried, giving a gray amorphous product (1.30 g). This product was dissolved by treating three times with conc. HCl (3×50 ml) at 50–60°C over 1 h. The obtained yellow solution was washed with heptane (50 ml) and filtered. The filtrate was basified with solid Na_2CO_3, extracted with Et_2O (2×40 ml), the combined extracts were washed with H_2O (20 ml) and saturated aqueous NaCl solution (20 ml), dried over Na_2SO_4, and evaporated, giving the amine **31**. Yield 0.90 g (56 %).

Method XIII. Aqueous 25% ammonia solution (3.5 ml) was added to a suspension of chloride **7** (0.25 g, 1.1 mmol) in EtOH (5 ml). The mixture was stirred in a sealed vessel at 75°C for 4 days and poured into H_2O (100 ml). The precipitate that formed was filtered off, washed with H_2O (5 ml) and dried, giving 0.18 g of yellowish powder containing compounds **31** and **35** in 2:1 molar ratio. **2-Ethoxy-3-(trifluoromethyl)quinoxaline (35)**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.63 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.60–7.77 (2H, m, H Ar); 7.85 (1H, t, *J* = 8.8, H Ar); 8.09 (1H, d, *J* = 8.2, H Ar). ^{19}F NMR spectrum, δ, ppm: –68.7. Recrystallization of the obtained mixture of compounds **31** and **35** from heptane afforded the pure amine **31**. Yield 100 mg (44%) .

Method XIV. Aqueous 25% ammonia solution (5.5 ml) was added to a solution of chloride **7** (0.25 g, 1.1 mmol) in dioxane (5 ml). The obtained mixture was stirred in a sealed vessel at 75°C for 4 days. The reaction mixture was then poured into H_2O (100 ml), the precipitate formed was filtered off, washed with H_2O (5 ml), and dried, giving the amine **31** (80 mg). The filtrate was extracted with $CHCl_3$ (3×5 ml), giving additional 50 mg of the amine **31**. Total yield 130 mg (55%).

Compound 34 was obtained from carboxylic acid **23** (80 mg, 0.36 mmol) according to method XI for compound **31** through the stage of forming Boc-amide **33**. Yield 40 mg (57%).

***tert*-Butyl[3-(difluoromethyl)quinoxalin-2-yl]carbamate (33)**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, $C(CH_3)_3$); 6.91 (1H, t, *J* = 54.2, CF_2H); 7.20–7.38 (1H, m, H Ar); 7.60–7.78 (2H, m, H Ar); 8.01 (1H, d, *J* = 7.4, H Ar). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –116.6 (d, *J* = 54.9).

[3-(Difluoromethyl)quinoxalin-2-yl]amine (34). Light-yellow crystals. Mp 138–139°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.50 (2H, br. s, NH_2); 6.77 (1H, t, *J* = 54.3, CF_2H); 7.42–7.50 (1H, m, H Ar); 7.63–7.70 (2H, m, H Ar); 7.90 (1H, d, *J* = 8.2, H Ar). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –118.5 (d, *J* = 53.9). Found, %: C 55.65; H 3.80. $C_9H_7F_2N_3$. Calculated, %: C 55.39; H 3.62.

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