Synthesis of Novel 3-Amino-5-trifluoromethylazoles: A Convenient Method of Obtaining *N*-(Azol-3-yl)amines

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Abstract: A convenient method to obtain 10 3-amino-5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazoles and 18 3-amino-5-trifluoromethyl-1*H*-pyrazoles by cyclocondensation reaction of 4-amino-4-ethoxy-1,1,1,-trifluorobut-3-en-2-ones [$CF_3COCH=C(OEt)NHR$, where R = H, Me, Et, CH_2CH_2OH, CMe_2Et, CH_2Ph, Ph, 4-$NH_2C_6H_4$, 4-AcC_6H_4, 4-$NO_2C_6H_4$, 5-methylisoxazol-3-yl, thiazol-2-yl, CH_2CO_2Et, $CH(Ph)CO_2Me$, $CH(i\text{-}Bu)CO_2Et$] with hydroxylamine, hydrazine and phenylhydrazine is reported.

Key words: isoxazoles, pyrazoles, enones, amines, azolylation

There is an extensive range of methods used to prepare amines (alkylation, dealkylation and acylation of amines).[1] One particularly convenient method for the synthesis of new amines could be the *azolylation* of primary amines. Amines and their derivatives have fundamental importance as natural products, pharmacological agents, fine chemicals and dyes. We were mainly interested in obtaining amines containing azoles (Figure 1). Many of these heterocyclic compounds have interesting biological activities. Pyrazoles and isoxazoles are heterocyclic compounds with extensive biological properties.[2,3] Their importance as active drugs for medical applications can be evaluated by the fact that they represent 3% of the compounds in the MDL Drug Report (MDDR-3D, 99.2) and 1.6% of the entries in the Comprehensive Medicinal Chemistry (CMC-3D 99.1).[4] The search for new azole structures is a matter of great relevance, as a comprehensive library of these compounds for biological studies is very much desired. Pyrazoles and isoxazoles are of considerable interest due to their herbicidal, fungicidal, insecticidal, analgesic, antipyretic and anti-inflammatory properties.[5,6]

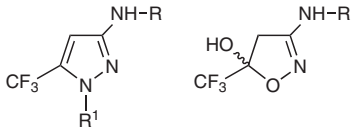

Figure 1 Aminoazoles

The presence of a trifluoromethyl group into cyclic compounds especially at a strategic position of drug molecules has become an important aspect of pharmaceutical research owing to the unique physical and biological properties of fluorine.[7a] The steric requirement of the fluorine atom resembles that of hydrogen (van der Waals radii: CF_3 = 1.35 Å versus CH_3 = 1.29 Å). Thus substitution of a methyl by a trifluoromethyl group in a drug candidate usually allows the trifluoromethylated analogue to be comparable in size and follow similar drug-protein interactions of the parent methyl compound. However, the strong covalent bonding of C–F bond (116 kcal/mol) versus that of the C–H bond (100 kcal/mol)[7b] can often avoid unwanted metabolic transformations. The high electronegativity of fluorine enables a trifluoromethyl group to decrease the electron density and the basicity or enhance the electrophilicity of the neighboring functional groups within a molecule. In many systems, the substitution of methyl group by a trifluoromethyl group results in added lipophilicity [π (CF_3) = 1.07 versus π (CH_3) = 0.50],[7c] which may lead to easier absorption and transportation of the molecules within biological systems and thereby improve the overall pharmacokinetic properties of drug candidates. Our contribution to this library focuses on the preparation of the aminoazoles depicted in Figure 1. The synthetic route leading to the new 3-aminopyrazoles and 3-isoxazoles is another result of our continuous study of the chemical properties of 1,1,1-trihalo-4-methoxyalk-3-en-2-one compounds,[8] which are important halogen-containing building blocks that can be employed in the preparation of many heterocyclic compounds, e.g., isoxazoles, pyrazoles, pyrazolium chlorides, pyrrolidines, pyrimidines, thiazines, diazepines, thiazoles, selenazoles and quinolines.[8] Some aminopyrazoles have been prepared from β-ketonitrile,[9] cyanoethylene compounds[10] or by the [4+1] cyclocondensation of α-haloketene hydrazones with isocyanides.[11] All these methods show only NH_2 as a substituent group on the heterocycle requiring an extra step (N-alkylation or N-acylation) to obtain different amines. Stachel[12] has used benzoylketene *O*,*N*-acetal blocks as a precursor to the synthesis of some non-trifluoromethyl substituted aminoazoles. The aim of this work is to report an efficient method for the preparation of new amines containing an *N*-(azol-3-yl) group (Scheme 1).

1,1,1-Trihalo-4-methoxyalk-3-en-2-ones were easily transformed into β-enamino ketones upon reaction with

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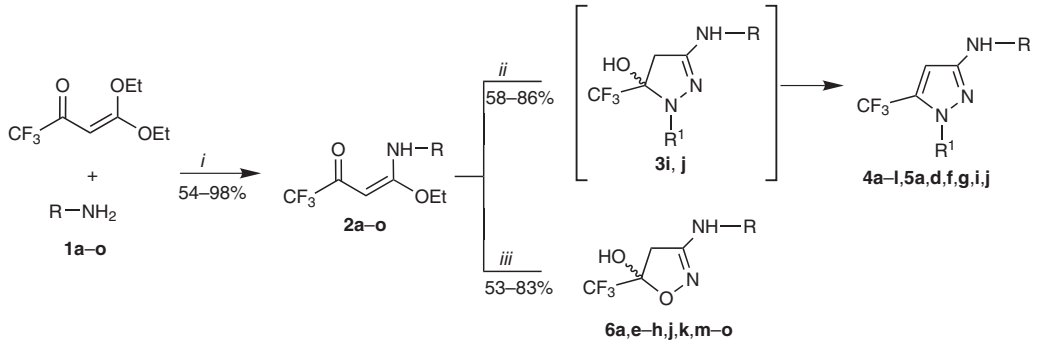


Scheme 1 *Reagents and conditions*: *i*: a) MeCN, 25 °C, 2 h (**1a**–**g**, R–NH_2); b) MeCN, Et_3N, 25 °C, 2 h (**1h**–**l**, R–NH_2·HCl); c) EtOH, H_2O, pyridine, 40 °C, 48 h (**1m**–**o**, R–NH_2·HCl); *ii*: NH_2NHR^1·HCl, Et_3N, EtOH, reflux, 8 h; *iii*: NH_2OH·HCl, pyridine, MeOH, reflux, 4 h

amines.[13] The β-ethoxy-β-enamino ketones **2**, the key precursors for the preparation of the new aminoazoles described in this work, were similarly prepared from 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one (Scheme 1 and Table 1). We have found one report in the literature[14] describing a procedure to obtain compounds **2** by stirring 1,1,1-trifluoro-4,4-dimethoxy but-3-en-2-one and the corresponding alkyl amine **1** at room temperature in acetonitrile for 18 hours. We significantly improved the efficiency of this reaction in solvent-free conditions. Higher yields of **2** were obtained after two hours of continuous stirring. In cases involving volatile amines **1a**,**b**, aqueous solutions of the amines were used. The experiment leading to **2a** was carried out using gaseous ammonia, since it gave better yields when compared to the experiment involving an aqueous solution. Some amines **1h**–**l** were liberated from the corresponding ammonium salts, and this was accomplished by a reaction with pyridine (or triethylamine). Compounds **2m**–**o** were prepared from the corresponding amino esters in reactions that require long reaction times (48 h). In every case, the stereochemistry of the enamino ketones **2** was assigned based on ^{1}H NMR spectroscopy. The downfield peak of the amino protons (10–12 ppm) suggests the existence of hydrogen bonding, and therefore a *cis*-relationship between NH and the C=O groups has been deduced (*E*-configuration).

In a second step, this work involved the cyclocondensation reaction of enaminones **2** with the dinucleophile hydrazine and hydroxylamine. Considering that the main objectives of this work are: (*i*) to show the wide scope of synthetic strategies used in the azolylation of amines; and (*ii*) to show the large number of compounds that can be synthesized, we selected enaminones **2a**–**e**,**g**,**j**,**k**,**m**–**o** to react with hydroxylamine, enaminones **2a**–**l** to react with hydrazine, and enaminones **2a**,**d**,**f**,**g**,**i**,**j** to react with phenylhydrazine. The reagents, products and yields of isolated products are shown in Table 1.

The cyclocondensation of *N*-alkyl and *N*-aryl enaminones **2** and hydrazine (reaction *ii,* entries 1–12, Table 1) and/or phenylhydrazine (reaction *ii,* entries 13–20, Table 1) were carried out at a molar ratio of 1.0:1.2 using triethylamine and ethanol as the solvent under reflux. Product formation was monitored by TLC, and the optimal reaction time was 4–8 hours. These reactions occur with exclusive displacement of the ethoxy substituent because of the primary amino groups' poor ability to act as leaving groups. The correct regiochemistry of the cyclocondensation cannot be distinguished using the non-labeled hydrazine reagent, but from reactions with phenylhydrazine, we have observed an exclusive coupling of the *N*-phenylamino group to the carbonyl carbon of the enaminone. This assignment is based on the ^{1}H NMR spectra of the products obtained from enaminones **2i** and **2j**, reactions which allowed the intermediate 3-*N*-arylamino-5-hydroxy-5-trifluoromethyl-1-phenyl-4,5-dihydropyrazoles, **3i**,**j** (not isolated, entries 17 – 18, Table 1). The observance of two doublets in the ^{1}H NMR of **3i**,**j** [**3i**, δ = 2.67 (*J* = 19 Hz); 2.39 (*J* = 19 Hz); **3j**, δ = 3.43 (*J* = 17 Hz); 3.05 (*J* = 17 Hz)] is in perfect agreement with values reported in the literature for analogous 1,5-isomers of 4,5-dihydropyrazoles.[15a,b] The regiochemistry of the cyclocondensation reaction can, therefore, be understood by the acid–base concept. In both cases, cyclization to pyrazoles and dihydroisoxazoles, we found the harder basic site of the dinucleophile, phenylhydrazine or hydroxylamine bonded to the harder carbonyl carbon acidic site of the enaminone **2**. The 4,5-dihydropyrazole intermediates **3i**,**j** were detected only in these cases. Aromatic pyrazole products **5** were produced from reactions with all the other amines depicted in Table 1.

The cyclocondensation of the β-enamino ketones **2** with hydroxylamine was examined (reaction *iii,* entries 21–30, Scheme 1 and Table 1). The reaction was carried out at a molar ratio of 1.0:1.2 using pyridine and methanol as the solvent under reflux. Product formation was monitored by TLC, and the optimal reaction time was 4 hours.

The reactions regiospecifically produced the 3-amino-4,5-dihydroisoxazole derivatives **6a**,**e**–**g**,**j**,**k**,**m**–**o**, which are derived from exclusive coupling (amino group to olefinic carbon and hydroxyl group to carbonyl carbon) between the enaminone **2** and hydroxylamine. The pair of doublets (H-4) observed in the ^{1}H NMR spectra centered near 3.0 and 3.4 ppm, with *J* = 17 Hz and the quartet (C-5) observed in the ^{13}C NMR near 100 ppm with $^2J_{C,F}$ = 33 Hz are typical spectroscopic data for 4,5-dihydroisoxazoles.[15c,d]

Table 1 Aminoazoles **3**–**6** Prepared

Entry	R	R^1	Reagents		Product	Yield (%)[a]
1	H	H	**2a**	+ NH_2NH_2·HCl	**4a**	69
2	Me	H	**2b**	+ NH_2NH_2·HCl	**4b**	78
3	Et	H	**2c**	+ NH_2NH_2·HCl	**4c**	65
4	CH_2CH_2OH	H	**2d**	+ NH_2NH_2·HCl	**4d**	81
5	CMe_2Et	H	**2e**	+ NH_2NH_2·HCl	**4e**	58
6	CH_2Ph	H	**2f**	+ NH_2NH_2·HCl	**4f**	73
7	Ph	H	**2g**	+ NH_2NH_2·HCl	**4g**	80
8	4-$NH_2C_6H_4$	H	**2h**	+ NH_2NH_2·HCl	**4h**	62
9	4-AcC_6H_4	H	**2i**	+ NH_2NH_2·HCl	**4i**	68
10	4-$NO_2C_6H_4$	H	**2j**	+ NH_2NH_2·HCl	**4j**	72
11	5-methylisoxazol-3-yl	H	**2k**	+ NH_2NH_2·HCl	**4k**	75
12	thiazol-2-yl	H	**2l**	+ NH_2NH_2·HCl	**4l**	69
13	H	Ph	**2a**	+ NH_2NHPh·HCl	**5a**	74
14	CH_2CH_2OH	Ph	**2d**	+ NH_2NHPh·HCl	**5d**	86
15	CH_2Ph	Ph	**2f**	+ NH_2NHPh·HCl	**5f**	59
16	Ph	Ph	**2g**	+ NH_2NHPh·HCl	**5g**	70
17	4-AcC_6H_4	Ph	**2i**	+ NH_2NHPh·HCl	**3i**	–[b]
18	4-$NO_2C_6H_4$	Ph	**2j**	+ NH_2NHPh·HCl	**3j**	–[b]
19	4-AcC_6H_4	Ph	**2i**	+ NH_2NHPh·HCl	**5i**	69
20	4-$NO_2C_6H_4$	Ph	**2j**	+ NH_2NHPh·HCl	**5j**	76
21	H	–	**2a**	+ NH_2OH·HCl	**6a**	81
22	CMe_2Et	–	**2e**	+ NH_2OH·HCl	**6e**	75
23	CH_2Ph	–	**2f**	+ NH_2OH·HCl	**6f**	70
24	Ph	–	**2g**	+ NH_2OH·HCl	**6g**	70
25	4-$NH_2C_6H_4$	–	**2h**	+ NH_2OH·HCl	**6h**	71
26	4-$NO_2C_6H_4$	–	**2j**	+ NH_2OH·HCl	**6j**	74
27	5-methylisoxazol-3-yl	–	**2k**	+ NH_2OH·HCl	**6k**	59
28	CH_2CO_2Et	–	**2m**	+ NH_2OH·HCl	**6m**	53
29	$CH(Ph)CO_2Me$	–	**2n**	+ NH_2OH·HCl	**6n**	72
30	CH(*i*-Bu)CO_2Et	–	**2o**	+ NH_2OH·HCl	**6o**	64

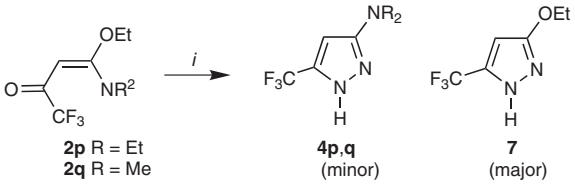
[a] Yields of isolated and purified products.
[b] Product not isolated.

The 3-amino-4,5-dihydroisoxazole products **6** are stable compounds and they were not converted to the aromatic isoxazoles. However, the aromatization of **6** can be obtained easily by stirring these compounds in concentrated sulfuric acid for a few hours at room temperature.[15c]

The dehydration reaction of both 4,5-dihydroazoles is an elimination reaction where the stability of its activated complex depends on the participation of the electron pair of the neighbor heteroatom atom present in the azole ring. Thus, based on the experimental data[15] we believe that the easier dehydration of 4,5-dihydropyrazoles compared to

4,5-dihydroisoxazole is caused by the larger electron-donating strength of the nitrogen atom (N-1) in the pyrazole ring than the oxygen atom (O-1) in the oxazole ring.

The reactions of **2** with hydrazine and phenylhydrazine show interesting additional details, depending on the hydrazine reagent used and the substitution pattern of the amino substituent in the enaminone **2**. The 4-(dialkylamino)-4-ethoxy-1,1,1-trifluorobut-3-en-2-ones **2p** and **2q** obtained from 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one and aqueous diethylamine and dimethylamine, react with hydrazine hydrochloride in triethylamine to afford a mixture of the 3-aminopyrazoles **4p**,**q** and the 3-ethoxypyrazole **7** (Scheme 2). Competition between the ethoxy and the *N*,*N*-dialkylamino groups to act as the actual leaving group seems to determine the product.



2p R = Et
2q R = Me

4p,**q** (minor)

7 (major)

Scheme 2 *Reagents and conditions*: *i*: $NH_2NH_2 \cdot HCl$, Et_3N, EtOH, reflux, 8 h

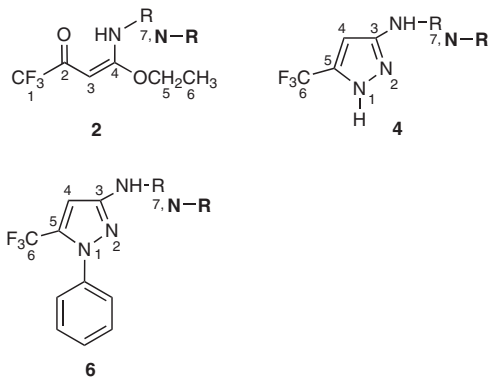
To summarize, we have achieved an efficient procedure to synthesize 3-aminoazoles from β-ethoxy-β-enamino ketones. Specifically, 3-amino-5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazoles and 3-amino-5-trifluoromethylpyrazoles were obtained in good yields. The reaction is regiospecific, with the attachment of the harder basic site of the dinucleophile to the carbonyl carbon atom of the enaminone, and no signs of other isomers were detected. Also, the reaction described in this paper is a very practical and easy method for the preparation of secondary *N*-(azol-3-yl) amines.

Unless otherwise indicated, all solvents were used as obtained from commercial suppliers without further purification. All melting points were measured using a Reichert-Thermovar melting-point microscope and are uncorrected. Yields listed are of isolated and purified compounds. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.63 MHz, respectively) at 298 K with a digital resolution of ±0.01 ppm. $CDCl_3$, acetone-d_6 or DMSO-d_6 (0.5 M) were used as solvents containing TMS as in internal standard. All spectra were acquired in a 5 mm tube, at natural abundance. Atom numbering for NMR spectral assignments is shown in Figure 2.

Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and He was used as the carrier gas.

(*E*)-4-Amino-4-ethoxy-1,1,1-trifluorobut-3-en-2-ones 2a–g; General Procedure

The appropriate amine (5 mmol, gaseous ammonia or aqueous solution for volatile amines, Scheme 1), was added to 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one (1.06 g, 5 mmol) in MeCN (20 mL) at r.t. The mixture was stirred for 2 h and then the solvent was evaporated in vacuo. The residue was extracted with $CHCl_3$ (2 × 20 mL), washed with H_2O (3 × 20 mL), dried ($MgSO_4$) and filtered, and the solvent was evaporated in vacuum. The crude compounds **2a**–**d**,**f**,**g** were obtained with good purity, and **2e** was purified by chromatography on a silica gel column with $CHCl_3$ as an eluent.



2 **4** **6**

Figure 2 Atom numbering in compounds **2**, **4** and **6** for NMR assignments

(*E*)-4-Amino-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (2a)
Yield: 4.35 mmol (87%); mp 76–77 °C.

^1H NMR: see Ref. 14.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9 (q, $^2J_{C,F}$ = 32 Hz, C-2), 171.6 (C-4), 117.8 (q, $^1J_{C,F}$ = 286 Hz, C-1), 73.4 (C-3), 65.2 (C-5), 14.0 (C-6).

MS: *m*/*z* (%) = 183 (M^+, 100), 155 (77), 100 (99), 69 (61).

(*E*)-4-Ethoxy-1,1,1-trifluoro-4-(methylamino)but-3-en-2-one (2b)
Yield: 4.30 mmol (86%); mp 95–96 °C.

^1H NMR: see Ref. 14.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1 (q, $^2J_{C,F}$ = 33 Hz, C-2), 169.8 (C-4), 117.7 (q, $^1J_{C,F}$ = 286 Hz, C-1), 71.9 (C-3), 65.2 (C-5), 29.9 (C-7), 13.3 (C-6).

MS: *m*/*z* (%) = 197 (M^+, 69), 128 (66), 100 (100), 69 (61).

(*E*)-4-Ethoxy-4-(ethylamino)-1,1,1-trifluorobut-3-en-2-one (2c)
Yield: 4.00 mmol (80%); mp 84–86 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.49 (br, 1 H, NH), 5.11 (s, 1 H, H-3), 4.17 (q, 2 H, *J* = 7 Hz, H-5), 3.38 (quin, 2 H, *J* = 7 Hz, H-7), 1.42 (t, 3 H, *J* = 7 Hz, H-6), 1.23 (t, 3 H, *J* = 7 Hz, N–R).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0 (q, $^2J_{C,F}$ = 32 Hz, C-2), 169.5 (C-4), 117.9 (q, $^1J_{C,F}$ = 286 Hz, C-1), 72.3 (C-3), 65.4 (C-5), 35.2 (C-7), 14.3 (N–R), 13.9 (C-6).

MS: *m*/*z* (%) = 211 (M^+, 68), 69 (100).

(*E*)-4-Ethoxy-1,1,1-trifluoro-4-(2-hydroxyethylamino)but-3-en-2-one (2d)
Yield: 4.35 mmol (87%); mp 100–102 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.48 (br, 1 H, NH), 5.01 (s, 1 H, H-3), 4.16 (q, 2 H, *J* = 7 Hz, H-5), 3.68 (t, 2 H, *J* = 7 Hz, N–R), 3.45 (t, 2 H, *J* = 7 Hz, H7), 1.41 (t, 3 H, *J* = 7 Hz, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (q, $^2J_{C,F}$ = 32 Hz, C-2), 169.5 (C-4), 117.8 (q, $^1J_{C-F}$ = 286 Hz, C-1), 72.6 (C-3), 65.5 (C-5), 59.8 (N–R), 42.3 (C-7), 13.5 (C-6).

MS: *m*/*z* (%) = 227 (M^+, 20), 69 (100).

(*E*)-4-Ethoxy-1,1,1-trifluoro-4-(*tert*-pentylamino)but-3-en-2-one (2e)
Yield: 4.25 mmol (85%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.67 (br, 1 H, NH), 5.07 (s, 1 H, H-3), 4.18 (q, 2 H, *J* = 7 Hz, H-5), 1.72 (q, 2-H, *J* = 7 Hz, N–R), 1.44 (t, 3-H, *J* = 7 Hz, H-6), 1.36 (s, 6 H, N–R), 0.92 (t, 3 H, *J* = 7 Hz, N–R).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (q, $^2J_{C,F}$ = 32 Hz, C-2), 169.7 (C-4), 118.1 (q, $^1J_{C,F}$ = 285 Hz, C-1), 72.7 (C-3), 65.4 (C-5), 55.6 (C-7), 34.1 (N–R), 26.7 (N–R), 13.9 (C-6), 8.1 (N–R).

MS: *m*/*z* (%) = 253 (M^+, 44), 224 (69), 184 (49), 114 (100), 86 (75), 58 (100).

(*E*)-4-(Benzylamino)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (2f)
Yield: 3.50 mmol (70%); mp 62–63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.83 (br, 1 H, NH), 7.23–7.39 (m, 5 H, C_6H_5), 5.13 (s, 1 H, H-3), 4.48 (d, 2 H, *J* = 7 Hz, H-7), 4.13 (q, 2 H, *J* = 7 Hz, H-5), 1.36 (t, 3 H, *J* = 7 Hz, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7 (q, $^2J_{C,F}$ = 33 Hz, C-2), 169.1 (C-4), 136.5, 128.6, 128.3, 127.5 (C_6H_5), 118.3 (q, $^1J_{C,F}$ = 286 Hz, C-1), 72.6 (C-3), 65.4 (C-5), 44.7 (C-7), 14.0 (C-6).

MS: *m*/*z* (%) = 273 (M^+, 23), 244 (23), 204 (21), 106 (61), 91 (100).

(*E*)-4-Anilino-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (2g)
Yield: 4.15 mmol (83%); oil.

^{1}H NMR: see Ref. 14.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3 (q, $^2J_{C,F}$ = 33 Hz, C-2), 167.7 (C-4), 135.9, 129.3, 127.4, 122.1 (C_6H_5), 117.9 (q, $^1J_{C,F}$ = 286 Hz, C-1), 73.6 (C-3), 66.2 (C-5), 14.0 (C-6).

MS: *m*/*z* (%) = 259 (M^+, 67), 231 (27), 162 (57), 144 (44), 93 (100).

(*E*)-4-Amino-4-ethoxy-1,1,1-trifluorobut-3-en-2-ones 2h–l; General Procedure
The appropriate amine hydrochloride (5.2 mmol, Scheme 1) was added to a solution of the 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one (5 mmol) and Et_3N (1.06 g, 5.2 mmol) in MeCN (10 mL). The mixture was stirred at r.t. for 2 h and extracted with CH_2Cl_2 (2 × 20 mL). The combined CH_2Cl_2 extracts were washed with water (2 × 20 mL) and evaporated. When necessary, the products were recrystallized from *n*-hexane.

(*E*)-4-(4-Aminoanilino)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (2h)
Yield: 2.75 mmol (55%); mp 120–121 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.23 (br, 1 H, NH), 7.28–6.64 (m, 5 H, C_6H_5), 5.23 (s, 1 H, H-3), 4.23 (q, 2 H, *J* = 7 Hz, H-5), 3.66 (br, 2 H, NH_2), 1.43 (t, 3 H, *J* = 7 Hz, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 (q, $^2J_{C,F}$ = 33 Hz, C-2), 167.4 (C-4), 144.5, 126.8, 123.9, 116.7 (C_6H_5), 118.5 (q, $^1J_{C,F}$ = 289 Hz, C-1), 73.4 (C-3), 66.0 (C-5), 14.1 (C-6).

MS: *m*/*z* (%) = 274 (M^+, 100), 229 (18), 205 (74), 177 (36), 132 (63).

(*E*)-4-(4-Acetylanilino)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (2i)
Yield: 3.95 mmol (79%); mp 132–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.55 (br, 1 H, NH), 7.95–7.43 (m, 5 H, C_6H_5), 5.32 (s, 1 H, H-3), 4.33 (q, 2 H, *J* = 7 Hz, H-5), 2.59 (s, 3 H, H-12), 1.54 (t, 3 H, *J* = 7 Hz, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1 (N–R), 176.2 (q, ^1J = 33 Hz, C-2), 167.9 (C-4), 151.4, 133.7, 130.8, 121.3 (C_6H_5), 120.7 (q, ^1J = 289 Hz, C-1), 74.9 (C-3), 66.9 (C-5), 26.4 (N–R), 14.1 (C-6).

MS: *m*/*z* (%) = 301 (M^+, 84), 258 (100), 189 (54), 110 (36), 69 (58).

(*E*)-4-Ethoxy-1,1,1-trifluoro-4-(4-nitroanilino)but-3-en-2-one (2j)
Yield: 3.85 mmol (77%); mp 110–112 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 12.39 (br, 1 H, NH), 7.99–6.83 (m, 5 H, C_6H_5), 5.45 (s, 1 H, H-3), 4.30 (q, 2 H, *J* = 7 Hz, H-5), 1.54 (t, 3 H, *J* = 7 Hz, H-6).

^{13}C NMR (100 MHz, acetone-d_6): δ = 175.3 (q, $^2J_{C,F}$ = 33 Hz, C-2), 167.2 (C-4), 141.3, 128.4, 125.1, 120.6 (C_6H_5) 118.1 (q, $^1J_{C,F}$ = 286 Hz, C-1), 73.8 (C-3), 66.7 (C-5), 12.7 (C-6).

MS: *m*/*z* (%) = 304 (M^+, 60), 276 (41), 235 (50), 207 (47), 108 (93), 69 (100).

(*E*)-4-Ethoxy-1,1,1-trifluoro-4-[(5-methylisoxazol-3-yl)amino]but-3-en-2-one (2k)
Yield: 3.50 mmol (70%); mp 118–120 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 12.54 (br, 1 H, NH), 6.45 (s, 1H, N–R), 5.49 (s, 1 H, H-3), 4.48 (q, 2 H, *J* = 7 Hz, H-5), 2.41 (s, 3 H, N–R), 1.52 (t, 3H, *J* = 7 Hz, H-6).

^{13}C NMR (100 MHz, acetone-d_6): δ = 176.8 (q, $^2J_{C,F}$ = 33 Hz, C-2), 171.5 (C-4), 168.4, 156.9, 94.5, 12.1 (C, isoxazolyl), 118.1 (q, $^1J_{C,F}$ = 286 Hz, C-1), 74.4 (C-3), 68.3 (C-5), 13.8 (C-6).

MS: *m*/*z* (%) = 264 (M^+, 52), 195 (85), 167 (33), 125 (100).

(*E*)-4-Ethoxy-1,1,1-trifluoro-4-(1,3-thiazol-2-ylamino)but-3-en-2-one (2l)
Yield: 3.70 mmol (74%); mp 150–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.88 (br, 1 H, NH), 7.32 (d, 1 H, *J* = 4 Hz, N–R), 6.92 (d, 2 H, *J* = 4 Hz, N–R), 5.19 (s, 1 H, H-3), 4.25 (q, 2 H, *J* = 7 Hz, H-5), 1.47 (t, 3 H, *J* = 7 Hz, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4 (q, ^2J = 34 Hz, C-2), 164.8 (C-4), 155.8, 138.5, 114.8 (C, thiazolyl), 117.1 (q, ^1J = 286 Hz, C-1), 73.6 (C-3), 67.6 (C-5), 13.6 (C-6).

MS: *m*/*z* (%) = 266 (M^+, 42), 197 (56), 127 (100), 101 (57), 69 (68).

(*E*)-4-Amino-4-ethoxy-1,1,1-trifluorobut-3-en-2-ones 2m–o; General Procedure
The appropriate solution of amino ester hydrochloride (5.2 mmol) in a mixture (20:1) of EtOH–H_2O (5 mL) was added to a solution of the 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one (1.06 g, 5 mmol) and pyridine (410 mg, 5.2 mmol) in EtOH (20 mL). The mixture was stirred at 40 °C for 48 h and extracted with $CHCl_3$ (2 × 20 mL). The combined $CHCl_3$ extracts were washed with H_2O (2 × 10 mL). The residue obtained after evaporation of $CHCl_3$ was recrystallized from a mixture of *n*-hexane–EtOAc (4:1).

4-Ethoxy-4-[ethyl (L)-glycinate]-1,1,1-trifluorobut-3-en-2-one (2m)
Yield: 3.75 mmol (75%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.66 (br, 1 H, NH), 5.15 (s, 1 H, H-3), 4.27 (q, 2 H, *J* = 7 Hz, H-5), 4.14 (q, 2 H, *J* = 7 Hz, N–R), 4.09 (d, 2 H, *J* = 7 Hz, H-7), 1.41 (t, 3 H, *J* = 7 Hz, H-6), 1.29 (t, 3 H, *J* = 7 Hz, N–R).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3 (q, $^2J_{C,F}$ = 33 Hz, C-2), 169.7 (N–R), 168.0 (C-4), 117.8 (q, $^1J_{C,F}$ = 286 Hz, C-1), 72.6 (C-3), 65.8 (C-7), 61.5 (C-5), 42.1 (N–R), 14.0 (N–R), 13.9 (C-6).

MS: *m*/*z* (%) = 269 (M^+, 66), 200 (80), 168 (100), 139 (69).

(*E*)-4-Ethoxy-1,1,1-trifluoro-4-[methyl (L)-phenylglycinate]but-3-en-2-one (2n)
Yield: 3.55 mmol (71%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.26 (br, 1 H, NH), 7.38 (s, 5 H, C_6H_5), 5.40 (d, 2 H, *J* = 7 Hz, H-7), 5.28 (s, 1 H, H-3), 4.11 (q, 2 H, *J* = 7 Hz, H-5), 3.69 (s, 3 H, N–R), 1.31 (t, 3 H, *J* = 7 Hz, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C,F}$ = 33 Hz, C-2), 169.8 (N–R), 169.0 (C-4), 136.2 (N–R), 129.1, 128.8, 127.1, 124.3 (C_6H_5) 118.9 (q, $^1J_{C,F}$ = 286 Hz, C-1), 73.2 (C-3), 66.2 (C-7), 62.6 (C-5), 58.6 (N–R), 14.3 (C-6).

MS: *m*/*z* (%) = 331 (M^+, 5), 272 (100), 244 (5), 106 (63), 79 (15).

(*E*)-4-Ethoxy-1,1,1-trifluoro-4-[ethyl (L)-leucinate]but-3-en-2-one (2o)
Yield: 3.70 mmol (74%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.26 (br, 1 H, NH), 7.38 (s, 5 H, C_6H_5), 5.40 (m, 1 H, H-7), 5.28 (s, 1 H, H-3), 4.11 (q, 2 H, *J* = 7 Hz, H-5), 1.31 (t, 3 H, *J* = 7 Hz, H-6), 1.70 (m, 3 H, N–R), 0.96 (d, 6 H, *J* = 7 Hz, N–R).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C,F}$ = 33 Hz, C-2), 171.0 (N–R), 169.8 (C-4), 118.9 (q, $^1J_{C,F}$ = 286 Hz, C-1), 72.5 (C-3), 65.8 (C-5), 62.3 (N–R), 52.1 (C-7), 40.9 (N–R), 22.4 (N–R), 21.5 (N–R), 21.3 (N–R), 13.7 (C-6), 13.5 (N–R).

MS: *m*/*z* (%) = 325 (M^+, 17), 252 (100), 224 (19), 139 (23), 86 (73), 69 (28).

3-Amino-5-trifluoromethyl-1*H*-pyrazoles 4a–l; 5a,d,f,g,i,j; General Procedure
Hydrazine hydrochloride (144 mg, 2.1 mmol) [or phenylhydrazine hydrochloride (304 mg, 2.1 mmol)] and Et_3N (212 mg, 2.1 mmol) were added to a stirred solution of **2** (2 mmol) in EtOH (15 mL) at r.t. The mixture was stirred under reflux for 8 h and then extracted with $CHCl_3$ (2 × 20 mL). The combined $CHCl_3$ extracts were washed with H_2O (2 × 10 mL) and evaporated. The oily residue was purified by chromatography (silica gel 230-400 mesh) with $CHCl_3$ or $CHCl_3$–MeOH (1%) as eluent.

3-Amino-5-trifluoromethyl-1*H*-pyrazole (4a)
Yield: 1.38 mmol (69%); mp 82–84 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (s, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3 (C-3), 141.9 (q, $^2J_{C,F}$ = 38 Hz, C-5), 121.8 (q, $^1J_{C,F}$ = 268 Hz, C-6), 88.3 (C-4).

MS: *m*/*z* (%) = 151 (M^+, 100), 132 (49), 103 (49), 75 (36), 52 (47).

3-(Methylamino)-5-trifluoromethyl-1*H*-pyrazole (4b)
Yield: 1.56 mmol (78%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 (s, 1 H, H-4), 2.71 (s, 3 H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2 (C-3), 142.2 (q, $^2J_{C,F}$ = 37 Hz, C-5), 121.3 (q, $^1J_{C,F}$ = 268 Hz, C-6), 84.8 (C-4), 31.4 (C-7).

MS: *m*/*z* (%) = 165 (M^+, 100), 144 (56), 102 (18), 75 (38), 67 (61), 52 (39).

3-(Ethylamino)-5-trifluoromethyl-1*H*-pyrazole (4c)
Yield: 1.30 mmol (65%); oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 5.63 (s, 1 H, H-4), 3.17 (q, 2 H, *J* = 7 Hz, H-7), 1.22 (t, 3 H, *J* = 7 Hz, N–R).

^{13}C NMR (100 MHz, acetone-d_6): δ = 150.3 (C-3), 141.5 (q, $^2J_{C,F}$ = 37 Hz, C-5), 120.9 (q, $^1J_{C,F}$ = 268 Hz, C-6), 83.4 (C-4), 38.9 (C-7), 13.6 (N–R).

MS: *m*/*z* (%) = 179 (M^+, 61), 164 (100), 144 (77), 102 (12), 75 (29), 52 (40).

5-Trifluoromethyl-3-(2-hydroxyethylamino)-1*H*-pyrazole (4d)
Yield: 1.62 mmol (81%); mp 124–126 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 5.58 (s, 1 H, H-4), 3.59 (t, 2 H, *J* = 7 Hz, N–R), 3.12 (t, 2 H, *J* = 7 Hz, H-7).

^{13}C NMR (100 MHz, acetone-d_6): δ = 152.3 (C-3), 142.5 (q, $^2J_{C,F}$ = 37 Hz, C-5), 123.0 (q, $^1J_{C,F}$ = 268 Hz, C-6), 85.0 (C-4), 61.4 (N–R), 48.2 (C-7).

MS: *m*/*z* (%) = 195 (M^+, 22), 164 (100), 144 (63), 66 (38).

5-Trifluoromethyl-3-(*tert*-pentylamino)-1*H*-pyrazole (4e)
Yield: 1.16 mmol (58%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.69 (s, 1 H, H-4), 1.48 (q, 2 H, *J* = 7 Hz, N–R), 1.11 (s, 6 H, N–R), 0.86 (t, 3 H, *J* = 7 Hz, N–R).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2 (C-3), 142.3 (q, $^2J_{C,F}$ = 37 Hz, C-5), 122.2 (q, $^1J_{C-F}$ = 268 Hz, C-6), 88.2 (C-4), 54.1 (C-7), 33.4 (N–R), 26.6 (N–R), 8.2 (N–R).

MS: *m*/*z* (%) = 221 (M^+, 28), 206 (30), 192 (100), 151 (71), 71 (72), 55 (51).

3-(Benzylamino)-5-trifluoromethyl-1*H*-pyrazole (4f)
Yield: 1.46 mmol (73%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 5 H, C_6H_5), 5.63 (s, 1 H, H-4), 4.24 (s, 2 H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0 (C-3), 141.9 (q, $^2J_{C,F}$ = 37 Hz, C-5), 137.9, 128.6, 127.5, 117.0 (C_6H_5), 121.9 (q, $^1J_{C,F}$ = 268 Hz, C-6), 85.6 (C-4), 49.2 (C-7).

MS: *m*/*z* (%) = 241 (M^+, 86), 222 (16), 164 (22), 91 (100), 65 (60).

3-Anilino-5-trifluoromethyl-1*H*-pyrazole (4g)
Yield: 1.60 mmol (80%); mp 81–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–6.96 (m, 5 H, C_6H_5), 6.25 (s, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0 (q, $^2J_{C,F}$ = 37 Hz, C-5), 141.3 (C-3), 141.7, 129.6, 121.9, 116.5 (C_6H_5), 120.9 (q, $^1J_{C,F}$ = 267 Hz, C-6), 91.9 (C-4).

MS: *m*/*z* (%) = 227 (M^+, 100), 208 (10), 178 (8), 157 (10), 77 (23).

3-(4-Aminoanilino)-5-trifluoromethyl-1*H*-pyrazole (4h)
Yield: 1.24 mmol (62%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 – 6.64 (m, 5 H, C_6H_5), 5.98 (s, 1 H, H-4), 5.83 (br, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8 (C-3), 141.3 (q, $^2J_{C,F}$ = 38 Hz, C-5), 142.0, 133.0, 127.7, 116.4 (C_6H_5), 121.0 (q, $^1J_{C,F}$ = 269 Hz, C-6), 89.1 (C-4).

MS: *m*/*z* (%) = 242 (M^+, 100), 223 (12), 172 (10), 145 (19), 119 (39), 65 (36).

3-(4-Acetylanilino)-5-trifluoromethyl-1*H*-pyrazole (4i)
Yield: 1.36 mmol (68%); mp 123–125 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.90–7.17 (m, 5 H, C_6H_5), 6.47 (s, 1 H, H-4), 2.48 (s, 3 H, N–R).

^{13}C NMR (100 MHz, acetone-d_6): δ = 197.7 (N–R), 149.3, 146.0 (C-3), 141.8 (q, $^2J_{C,F}$ = 37 Hz, C-5), 149.3, 132.4, 130.8, 115.7 (C_6H_5), 123.1 (q, $^1J_{C,F}$ = 269 Hz, C-6), 94.9 (C-4), 27.2 (N–R).

MS: *m*/*z* (%) = 269 (M^+, 53), 254 (100), 206 (9), 157 (20), 129 (9), 90 (11).

5-Trifluoromethyl-3-(4-nitroanilino)-1*H*-pyrazole (4j)
Yield: 1.44 mmol (72%); mp 133–135 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.58–7.71 (m, 5 H, C_6H_5), 6.84 (s, 1 H, H-4).

^{13}C NMR (100 MHz, acetone-d_6): δ = 150.4 (C-3), 140.9 (q, $^2J_{C,F}$ = 38 Hz, C-5), 138.2, 126.9, 126.6, 114.9 (C_6H_5), 122.1 (q, $^1J_{C,F}$ = 268 Hz, C-6), 95.7 (C-4).

MS: *m*/*z* (%) = 272 (M^+, 100), 242 (37), 157 (30), 90 (20), 75 (20).

5-Trifluoromethyl-3-[(5-methylisoxazol-3-yl)amino]-1*H*-pyrazole (4k)
Yield: 1.50 mmol (75%); mp 164–166 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 6.30 (s, 1 H, N–R), 5.91 (s, 1 H, H-4), 2.34 (s, 3 H, N–R).

^{13}C NMR (100 MHz, acetone-d_6): δ = 170.1, 160.6, 98.5, 12.0 (C, isoxazolyl), 151.8 (C-3), 140.4 (q, $^2J_{C,F}$ = 37 Hz, C-5), 123.5 (q, $^1J_{C,F}$ = 269 Hz, C-6), 95.5 (C-4).

MS: *m*/*z* (%) = 232 (M^+, 100), 218 (21), 202 (39), 175 (51), 151 (37).

5-Trifluoromethyl-3-(thiazol-2-ylamino)-1*H*-pyrazole (4l)
Yield: 1.38 mmol (69%); mp 200 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.24 (d, 1 H, *J* = 4 Hz, N–R), 6.87 (d, 1 H, *J* = 4 Hz, N–R), 6.38 (s, 1 H, H-4).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.9, 137.8, 109.1, (C, thiazolyl), 144.3 (C-3), 139.3 (q, $^2J_{C,F}$ = 37 Hz, C-5), 121.6 (q, $^1J_{C,F}$ = 266 Hz, C-6), 89.9 (C-4).

MS: *m*/*z* (%) = 234 (M^+, 100), 202 (43), 175 (62), 151 (40), 52 (25).

3-Amino-5-trifluoromethyl-1-phenyl-1*H*-pyrazole (5a)
Yield: 1.48 mmol (74%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.28 (m, 5 H, C_6H_5), 5.75 (s, 1 H, H4), 2.82 (br, 2 H, NH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9 (C-3), 142.8 (q, $^2J_{C,F}$ = 37 Hz, C-5), 130.2, 129.5, 126.7, 124.6 (C_6H_5), 123.5 (q, $^1J_{C,F}$ = 268 Hz, C-6), 88.0 (C-4).

MS: *m*/*z* (%) = 227 (M^+, 100), 208 (13), 131 (21), 92 (23), 77 (51).

5-Trifluoromethyl-3-[(2-hydroxyethyl)amino]-1-phenyl-1*H*-pyrazole (5d)
Yield: 1.72 mmol (86%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.18 (m, 5 H, C_6H_5), 5.64 (s, 1 H, H-4), 3.64 (t, 2-H, *J* = 5 Hz, N–R), 3.18 (t, 2-H, *J* = 5 Hz, H-7).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4 (C-3), 142.6 (q, $^2J_{C,F}$ = 37 Hz, C-5), 129.6, 128.9, 128.6, 119.8 (C_6H_5), 120.1 (q, $^1J_{C,F}$ = 269 Hz, C-6), 84.9 (C-4), 60.2 (N–R), 47.5 (C-7).

MS: *m*/*z* (%) = 271 (M^+, 66), 240 (100), 220 (46), 213 (78), 77 (94).

3-(Benzylamino)-5-trifluoromethyl-1-phenyl-1*H*-pyrazole (5f)
Yield: 1.18 mmol (59%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 – 7.29 (m, 10 H, 2 C_6H_5), 5.74 (s, 1 H, H-4), 4.25 (s, 2 H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6 (C-3), 142.7 (q, $^2J_{C,F}$ = 38.1 Hz, C-5), 132.5, 129.0–124.6 (2 C_6H_5), 121.2 (q, $^1J_{C,F}$ = 269.1 Hz, C-6), 85.7 (C-4), 49.7 (C-7).

MS: *m*/*z* (%) = 317 (M^+, 25), 298 (3), 91 (100), 77 (21), 65 (14).

3-Anilino-5-trifluoromethyl-1-phenyl-1*H*-pyrazole (5g)
Yield: 1.40 mmol (70%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.42 (m, 10 H, 2 C_6H_5), 6.38 (s, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7 (C-3), 142.2 (q, $^2J_{C,F}$ = 39 Hz, C-5), 137.8, 132.4, 129.7, 116.6 (C_6H_5), 120.9 (q, $^1J_{C,F}$ = 267, C-6), 92.8 (C-4).

MS: *m*/*z* (%) = 303 (M^+, 100), 167 (9), 128 (9), 116 (9), 77 (78), 51 (35).

3-(4-Acetylanilino)-5-trifluoromethyl-1-phenyl-1*H*-pyrazole (5i)
Yield: 1.38 mmol (69%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–6.93 (m, 10 H, 2 C_6H_5), 6.54 (s, 1 H, H-4), 2.54 (s, 3 H, N–R).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6 (N–R), 149.2 (C-3), 142.4 (q, $^2J_{C,F}$ = 38 Hz, C-5), 139.0, 131.5, 129.3, 114.9 (C_6H_5), 122.3 (q, $^1J_{C,F}$ = 268 Hz, C-6), 98.5 (C-4), 25.9 (N–R).

MS: *m*/*z* (%) = 345 (M^+, 26), 330 (100), 232 (6), 205 (8), 77 (40).

5-Trifluoromethyl-3-(4-nitroanilino)-1-phenyl-1*H*-pyrazole (5j)
Yield: 1.52 mmol (76%); oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.98–7.40 (m, 10 H, 2 C_6H_5), 6.60 (s, 1 H, H-4).

^{13}C NMR (100 MHz, acetone-d_6): δ = 156.9 (C-3), 143.9 (q, $^2J_{C,F}$ = 38 Hz, C-5), 138.8, 131.2, 127.4, 113.6 (C_6H_5), 122.5 (q, $^1J_{C,F}$ = 267 Hz, C-6), 99.9 (C-4).

MS: *m*/*z* (%) = 348 (M^+, 100), 318 (14), 205 (12), 77 (63), 51 (24).

3-Amino-5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazoles 6a,e–h,j,k,m–o; General Procedure
Hydroxylamine hydrochloride (144 mg, 2.1 mmol) and pyridine (166 mg, 2.1 mmol) were added to a stirred solution of **2** (2 mmol) in MeOH (15 mL) at r.t. The mixture was stirred at 40 °C for 4 h and extracted with CH_2Cl_2 (2 × 20 mL). The combined CH_2Cl_2 extracts were washed with H_2O (2 × 10 mL). The crude product obtained by removal of solvent was recrystallized from a mixture of *n*-hexane–EtOAc (9:1).

3-Amino-5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole (6a)
Yield: 1.62 mmol (81%); mp 85–87 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 5.36 (br, 2 H, NH_2), 3.44 (d, 1 H, *J* = 17 Hz, H-4a), 3.06 (d, 1 H, *J* = 17 Hz, H-4b).

^{13}C NMR (100 MHz, acetone-d_6): δ = 158.2 (C-3), 123.1 (q, $^1J_{C,F}$ = 282 Hz, C-6), 102.6 (q, $^2J_{C,F}$ = 33 Hz, C-5), 43.2 (C-4).

MS: *m*/*z* (%) = 170 (M^+, 66), 153 (9), 138 (13), 101 (100), 69 (52), 55 (33).

5-Trifluoromethyl-5-hydroxy-3-(*tert*-pentylamino)-4,5-dihydroisoxazole (6e)
Yield: 1.50 mmol (75%); mp 100–101 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 5.21 (s, 1 H, OH), 3.42 (d, 1 H, *J* = 17 Hz, H-4a), 3.05 (d, 1 H, *J* = 17 Hz, H-4b), 1.71 (q, 2 H, *J* = 7 Hz, N–R), 1.31 (s, 6 H, N–R), 0.83 (t, 3 H, *J* = 7 Hz, N–R).

^{13}C NMR (100 MHz, acetone d_6): δ = 156.0 (C-3), 123.8 (q, $^1J_{C,F}$ = 282 Hz, C-6), 101.3 (q, $^2J_{C,F}$ = 33 Hz, C-5), 54.7 (C-7), 45.1 (C-4), 32.3 (N–R), 26.3 (N–R), 8.5 (N–R).

MS: *m*/*z* (%) = 240 (M^+, 33), 211 (35), 170 (100), 101 (62), 71 (81), 55 (42).

3-(Benzylamino)-5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole (6f)
Yield: 1.40 mmol (70%); mp 88–90 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.39–7.25 (m, 5 H, C_6H_5), 5.96 (s, 1 H, OH), 4.31 (d, 2 H, *J* = 6 Hz, H-7), 3.53 (d, 1 H, *J* = 18 Hz, H-4a) 3.15 (d, 1 H, *J* = 18 Hz, H-4b).

^{13}C NMR (100 MHz, acetone-d_6): δ = 158.3 (C-3), 139.7, 130.1, 127.4, 122.7, 118.3 (C_6H_5), 123.7 (q, $^1J_{C,F}$ = 282 Hz, C-6), 102.8 (q, $^2J_{C,F}$ = 33 Hz, C-5), 47.7 (C-7), 43.5 (C-4).

MS: *m*/*z* (%) = 260 (M^+, 12), 106 (11), 91 (100), 77 (9), 65 (10).

3-Anilino-5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole (6g)
Yield: 1.40 mmol (70%); mp 72–73 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.24 (br, 1 H, NH), 7.39–6.82 (m, 5 H, C_6H_5), 3.88 (d, 1 H, *J* = 17 Hz, H-4a), 3.26 (d, 1 H, *J* = 17 Hz, H-4b).

^{13}C NMR (100 MHz, acetone-d_6): δ = 154.9 (C-3), 123.6 (q, $^1J_{C,F}$ = 282 Hz, C-6), 102.5 (q, $^2J_{C,F}$ = 33 Hz, C-5), 140.7, 129.5, 122.1 118.4 (C_6H_5), 44.4 (C-4).

MS: *m*/*z* (%) = 246 (M^+, 100), 229 (6), 214 (22), 131 (71), 92 (33), 77 (54).

3-(4-Aminoanilino)-5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole (6h)
Yield: 1.42 mmol (71%); mp 102–104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–6.62 (m, 4 H, C_6H_5), 3.57 (d, 1 H, *J* = 17 Hz, H-4a), 3.12 (d, 1 H, *J* = 17 Hz, H-4b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8 (C-3), 123.7 (q, $^1J_{C,F}$ = 282 Hz, C-6), 101.7 (q, $^2J_{C,F}$ = 33 Hz, C-5), 146.8, 136.9, 120.8, 115.5 (C_6H_5), 44.6 (C-4).

MS: *m*/*z* (%) = 261 (M^+, 100), 243 (15), 229 (22), 146 (32), 107 (77).

5-Trifluoromethyl-5-hydroxy-3-(4-nitroanilino)-4,5-dihydroisoxazole (6j)
Yield: 1.48 mmol (74%); mp 141–142 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 9.10 (br, 1 H, NH), 8.21–7.68 (m, 4 H, C_6H_5), 3.81 (d, 1 H, *J* = 17 Hz, H-4a), 3.37 (d, 1 H, *J* = 17 Hz, H-4b).

^{13}C NMR (100 MHz, acetone-d_6): δ = 155.6 (C-3), 124.5 (q, $^1J_{C-F}$ = 282 Hz, C-6), 103.2 (q, $^2J_{C-F}$ = 33 Hz, C-5), 143.3, 127.9, 127.4, 119.2 (C_6H_5), 45.1 (C-4).

MS: *m*/*z* (%) = 291 (M^+, 100), 273 (22), 243 (11), 162 (14), 132 (42), 76 (33).

5-Trifluoromethyl-5-hydroxy-3-[(5-methylisoxazol-3-yl)amino]-4,5-dihydroisoxazole (6k)
Yield: 1.18 mmol (59%); mp 87–89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (br, 1 H, NH), 5.98 (s, 1 H, N–R), 3.47 (d, 1 H, *J* = 18 Hz, H-4a), 3.06 (d, 1 H, *J* = 18 Hz, H-4b), 2.41 (s, 3 H, N–R)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 160.2, 96.6, 12.4 (C, isoxazolyl), 154.3 (C-3), 123.6 (q, $^1J_{C,F}$ = 284 Hz, C-6), 103.1 (q, $^2J_{C,F}$ = 33 Hz, C-5), 43.7 (C-4).

MS: *m*/*z* (%) = 251 (M^+, 91), 219 (23), 182 (100), 149 (24), 108 (47).

5-Trifluoromethyl-5-hydroxy-3-[ethyl (L)-glycinate)]-4,5-dihydroisoxazole (6m)
Yield: 1.06 mmol (53%); mp 98–100 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 4.14 (q, 2 H, *J* = 7 Hz, N–R), 3.87 (s, 2 H, H-7), 3.48 (d, 1 H, *J* = 17 Hz, H-4a), 3.12 (d, 1 H, *J* = 17 Hz, H-4b), 1.22 (t, 3 H, *J* = 7 Hz, N–R).

^{13}C NMR (100 MHz, acetone-d_6): δ = 170.7 (N–R), 166.2 (C-3), 123.3 (q, $^1J_{C,F}$ = 282 Hz, C-6), 103.9 (q, $^2J_{C,F}$ = 33 Hz, C-5), 67.1 (N–R), 45.2 (C-4), 40.8 (C-7), 14.5 (N–R).

MS: *m*/*z* (%) = 256 (M^+, 30), 183 (100), 102 (25).

5-Trifluoromethyl-5-hydroxy-3-[methyl (L)-phenylglycinate]-4,5-dihydroisoxazole (6n)
Yield: 1.44 mmol (72%); mp 64–67°C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.45–7.33 (m, 5 H, C_6H_5), 5.17 (s, 1 H, H-7), 3.67 (s, 3 H, N–R), 3.54 (d, 1 H, *J* = 18 Hz, H-4a), 3.22 (d, 1 H, *J* = 18 Hz, H-4b).

^{13}C NMR (100 MHz, acetone-d_6): δ = 172.1 (N–R), 157.2 (C-3), 137.9, 129.7, 127.9, 117.3 (C_6H_5), 123.7 (q, $^1J_{C,F}$ = 283 Hz, C-6), 103.1 (q, $^2J_{C,F}$ = 31 Hz, C-5), 60.7 (N–R), 52.8 (C-7), 43.3 (C-4).

MS: *m*/*z* (%) = 259 (M^+ – 59 [CO_2Me], 100), 104 (21), 77 (13).

5-Trifluoromethyl-5-hydroxy-3-[ethyl (L)-leucinate]-4,5-dihydroisoxazole (6o)
Yield: 1.28 mmol (64%); mp 91–93 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (q, 3 H, *J* = 7 Hz, N–R), 3.52 (t, 1 H, *J* = 7 Hz, H-7), 3.41 (d, 1 H, *J* = 17 Hz, H-4a), 3.16 (d, 1 H, *J* = 17 Hz, H-4b), 1.70–1.30 (m, 3 H, N–R), 0.96 (d, 6 H, N–R).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2 (N–R), 157.1 (C-3), 122.1 (q, $^1J_{C,F}$ = 285 Hz, C-6), 102.2 (q, $^2J_{C,F}$ = 33 Hz, C-5), 61.6 (N–R), 54.7 (C-7), 42.7 (C-4), 41.4 (N–R), 24.9 (N–R), 22.6 (N–R), 22.1 (N–R), 14.2 (N–R).

MS: *m*/*z* (%) = 312 (M^+, 7), 280 (38), 256 (48), 239 (100), 210 (92), 197 (67), 183 (71), 171 (23), 69 (31).

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