Exploiting the Addition of Trimethyl(trifluoromethyl)silane to Functionalized *N*-Benzylimines for the Preparation of Two Novel *x*-Trifluoromethyl *x*-Amino Acids

Anton N. Tkachenko,[a,b] Dmytro S. Radchenko,[a,b] Pavel K. Mykhailiuk,*[a,b] Oleg V. Shishkin,[c,d] Andrei A. Tolmachev,[a,b] Igor V. Komarov[a,b]

[a] Enamine Ltd., Vul. Oleksandra Matrosova 23, 01103 Kyiv, Ukraine

[b] Department of Chemistry, Kyiv National Taras Shevchenko University, Vul. Volodymyrska 64, 01033 Kyiv, Ukraine

[c] SSI, Institute for Single Crystals, National Academy of Science of Ukraine, 60 Lenina Ave., 61001 Kharkiv, Ukraine

[d] Department of Inorganic Chemistry V. N., Karazin Kharkiv National University, Vul. Svobody 4, 61022 Kharkiv, Ukraine
E-mail: Pavel.Mykhailiuk@gmail.com

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Abstract: Straightforward gram-scale syntheses of a novel γ-trifluoromethyl γ-amino acid and a novel ε-trifluoromethyl-ε-amino acid are described. The key step in both syntheses is an acid-catalyzed nucleophilic trifluoromethylation of a cyclic *N*-benzylimine possessing an ester group by using the Ruppert--Prakash reagent [trimethyl(trifluoromethyl)silane]. The strategy provides a potentially general approach for the synthesis of *x*-trifluoromethyl *x*-amino acids.

Key words: amino acids, alkylations, fluorine, peptidomimetics, imines

The replacement of an amide bond with an appropriate bioisostere is a common approach in medicinal chemistry and drug discovery. The natural amide bond is susceptible to enzymatic hydrolysis, facilitating the metabolic degradation of pharmacologically active drug candidates in vivo. The replacement of a scissile amide bond with a surrogate can therefore improve the metabolic stability of a compound. Numerous examples of bioisosteres that retain the geometry of the amide bond found in the parent structure (–CR=CH–) or that present hydrogen bond-accepting properties (–$COCH_2$–) in an appropriate geometry are known. There are, however, fewer examples of amide bond isosteres that preserve both the geometry and the basicity of hydrogen-bond donation of the amide–NH bond.[1]

Recently, the trifluoroethylamine function has been introduced as a novel metabolically stable amide-bond surrogate with several important features (Figure 1). First, because of the electron-withdrawing effect of the trifluoromethyl group, the nitrogen atom in the trifluoroethylamine function is virtually nonbasic, so that the NH_2^+ moiety is not formed under physiological conditions, as is the case with the amide bond. Secondly, a weakly basic nitrogen atom can effectively participate in hydrogen bonding as a hydrogen-atom donor, also in a manner that is similar to the amide bond. Last, but not least, C–CF_3 and C=O bonds are substantially isopolar, which makes the substitution conceptually attractive in terms of electronic effects. In fact, the trifluoroethylamine function has already found a practical application in drug discovery as a structural feature of the highly potent cathepsin K inhibitor Odanacatib, developed in 2008 by Merck and currently undergoing Phase III clinical trials for the treatment of osteoporosis.

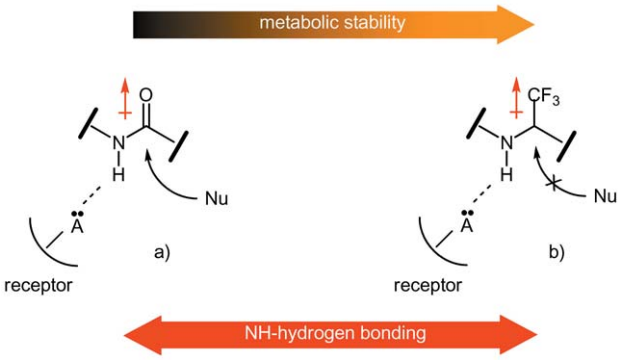

Figure 1 Comparison of the amide bond (a) and the trifluoroethylamine function (b)

The trifluoroethylamine function has also attracted a great deal of attention in biochemistry during the last decade, mainly as a result of the research of Zanda and co-workers,[3] who have synthesized and comprehensively studied the bioactivities and conformations of natural peptide analogues containing β-trifluoromethyl-β-amino acid and γ-trifluoromethyl-γ-amino acid moieties (Figure 2).[4] Several of these compounds were synthesized by incorporation of the appropriately protected *x*-trifluoromethyl *x*-amino acid derivatives into a polypeptide chain. It is noteworthy that the resulting metabolically stable peptidomimetics exhibit unique conformational preferences.

Although synthetic approaches to β-trifluoromethyl-β-amino acids are quite well elaborated and comprehensively documented in the literature,[5] the chemistry of γ-trifluoromethyl-γ-amino acids and their higher homologues has attracted significantly less attention.[6] In this context, we decided to develop a general strategy for the practical synthesis of *x*-trifluoromethyl *x*-amino acids that might be

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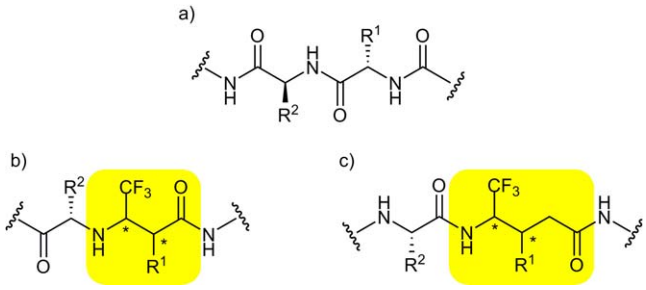


Figure 2 Structures of (a) a natural peptide, (b) peptidomimetics containing a β-trifluoromethyl-β-amino acid residue, and (c) a γ-trifluoromethyl-γ-amino acid residue[3]

useful as building blocks for the preparation of novel peptidomimetics containing trifluoroethylamine functions. Here we detail our preliminary results on the synthesis of two representative compounds, the γ-trifluoromethyl-γ-amino acid **1** and the ε-trifluoromethyl-ε-amino acid **2** (Figure 3) through the addition of trimethyl(trifluoromethyl)silane to the corresponding functionalized *N*-benzylimines.

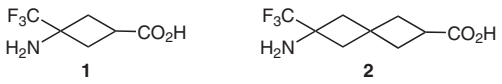
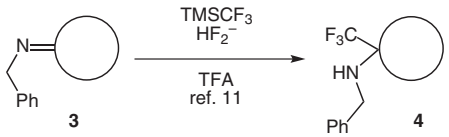


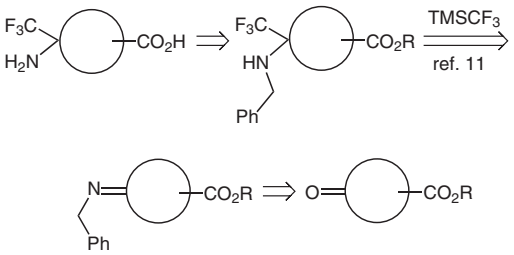
Figure 3 Structure of γ-trifluoromethyl-γ-amino acid **1** and ε-trifluoromethyl-ε-amino acid **2**.

Among the various approaches available for the incorporation of a trifluoromethyl group into organic molecules,[7] nucleophilic trifluoromethylation by using the Ruppert–Prakash reagent [trimethyl(trifluoromethyl)silane] has attracted the most attention recently.[8] However, the application of trimethyl(trifluoromethyl)silane has generally been limited to fluoride anion mediated addition to aldehydes or ketones to provide the corresponding trifluoromethyl-substituted alcohols. The synthesis of pharmacologically attractive amines containing trifluoromethyl groups from trimethyl(trifluoromethyl)silane and imines has received little attention because of the significantly lower reactivity of imines compared with ketones and aldehydes.[9,10] It was only in 2008 that a smooth reaction of a nonactivated *N*-alkylimine with trimethyl(trifluoromethyl)silane under acidic conditions was reported in the literature, when the conversion of cyclic *N*-benzylimines **3** into the corresponding derivatives **4** in good yields was described (Scheme 1).[11]



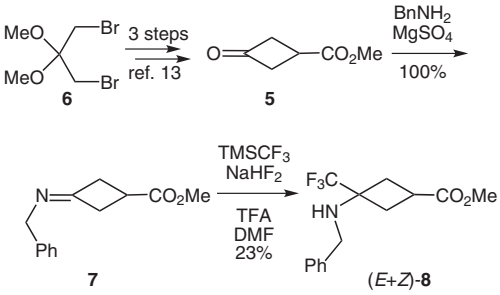
Scheme 1 Acid-catalyzed addition of trimethyl(trifluoromethyl)silane to cyclic *N*-benzylimines

Because an *N*-benzyl group can usually be cleaved by hydrogenation over palladium/carbon catalyst in quantitative yield, we realized that the transformation discussed above might be applicable in preparation of functionalized α-trifluoromethyl-substituted primary amines.[12] In particular, if the original imine structure contains an ester group, a trifluoromethyl-containing amino acid should be obtained as the reaction product (Scheme 2). The ester-functionalized imines should, in turn, be obtainable from the corresponding keto acid derivatives.



Scheme 2 Retrosynthetic approach to *n*-trifluoromethyl *n*-amino acids

To test this hypothesis, we chose the simplest stable cyclic ketone, cyclobutanone, as a model core structure. The conformable substrate **5** was prepared from commercially available dibromide **6** by a three-step procedure, following the literature protocol[13] (Scheme 3). The reaction of keto ester **5** with benzylamine in the presence of an excess of dry magnesium sulfate as a dehydrating agent in dichloromethane at room temperature smoothly gave the imine **7** in near-quantitative yield. Next, we examined the key synthetic step, the acid-catalyzed nucleophilic trifluoromethylation of imine **7** by Ruppert–Prakash reagent. In their original report, Dilman et al.[11] described three different procedures for the trifluoromethylation of imines. Adopting the first of these procedures, we examined the reaction of compound **7** with trimethyl(trifluoromethyl)silane (1.5 equivalents) in acetonitrile in the presence of *N*,*N*-dimethylformamide (3 equivalent), sodium hydrogen fluoride ($NaHF_2$; 0.75 equivalents), and trifluoroacetic acid (1.25 equivalents). The required product **8** was isolated as a mixture of two stereoisomers **8** (*Z*/*E* = 3:1) in 23% unoptimized yield. Separation of the isomers by column chromatography was not possible at this stage, as the compounds had identical R_f values.

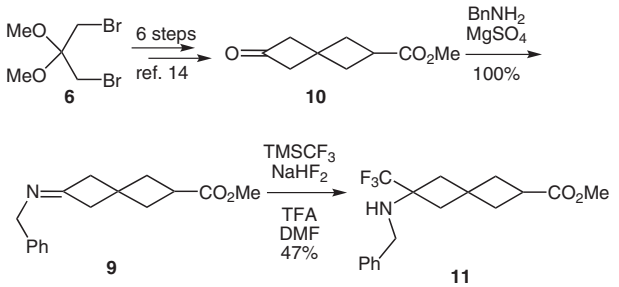


Scheme 3 Synthesis of intermediate **8**

We then tested Dilman's second procedure by attempting the reaction of imine **7** and trimethyl(trifluoromethyl)silane (2 equivalents) in acetonitrile in the presence of sodium hydrogen fluoride (1.0 equivalents) and trifluoroacetic acid (1.5 equivalents). After a standard workup, we unexpectedly obtained ketone **5** as the major product, and the formation of amine **8** was not observed. Obviously, imine **7** did not react with trimethyl(trifluoromethyl)silane under these conditions, so that after the addition of water during the workup, hydrolysis of the imine to give ketone **5** occurred. An attempted synthesis of amine **8** by following Dilman's third procedure using trimethyl(trifluoromethyl)silane (3 equivalents), sodium hydrogen fluoride (1.5 equivalents), triflic acid (1.6 equivalents) was not effective either, as ketone **5** was formed once more. The results of the two last experiments confirmed the importance of the presence of both *N*,*N*-dimethylformamide and trifluoroacetic acid in the reaction mixture.

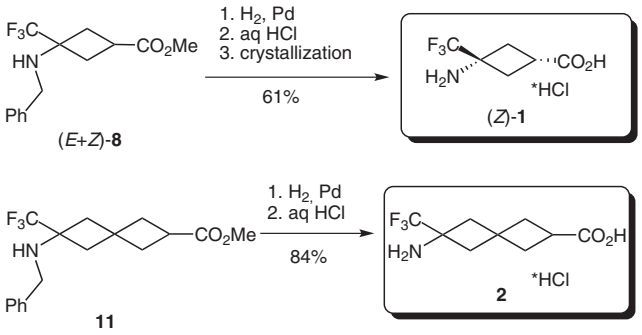
The low isolated yield of the target product **8** in the first experiment was caused by the formation of a number of unidentified side products. Although the compounds were not isolated in a pure state, we assumed that their formation was caused by the proximity of the electrophilic methyl ester group to the reaction center.

To confirm this hypothesis, we performed a model reaction of the functionalized imine **9** with trimethyl(trifluoromethyl)silane (Scheme 4). The intrinsic restriction on the conformation of compound **9** imparted by the presence of the spirocyclobutane core ensured that the carboxymethyl and imine moieties were located at distal positions to one another, thereby eliminating any possible intramolecular interaction between them. Imine **9** was efficiently synthesized from ketone **10** in a quantitative yield by using magnesium sulfate as a dehydrating agent. Compound **10**, in turn, was obtained from dibromide **6** in six steps following the literature protocol.[14] The addition of trimethyl(trifluoromethyl)silane to compound **9** under the conditions used for the successful preparation of intermediate **8** did, indeed, give the required amine **11** in 47% isolated yield. Although the yield of product **11** was not excellent, it was twice that of compound **8**, thereby demonstrating the importance of the geometry of the substrate in relation to the outcome of the reaction.



Scheme 4 Synthesis of intermediate **11**

Finally, we converted intermediates **8** and **11** into the target amino acids **1** and **2**, respectively, by following standard synthetic protocols (Scheme 5). Cleavage of the *N*-benzyl group in **8** by hydrogenation over palladium/carbon catalyst followed by acidic hydrolysis of the methyl ester group and subsequent crystallization gave the diastereomerically pure amino acid (*Z*)-**1**·HCl in 61% yield. Amino acid **2**·HCl was analogously prepared from precursor **11** by a two-step procedure in 84% yield.



Scheme 5 Synthesis of amino acids (*Z*)-**1** and **2**

Even though the unoptimized yield for the key transformation of imines **7** and **9** into amines **8** and **11**, respectively, was quite moderate, the experimental procedures were completely reproducible so that 3–5 g batches of the target amino acids could be conveniently obtained in one synthesis run. Note that compounds **1** and **2** can also be considered as trifluoromethyl-substituted conformationally restricted analogues of γ-aminobutyric acid (GABA).[15]

To determine a stereochemical configuration of the isomer of amino acid **1**, we performed an X-ray diffraction study. The required monocrystals were obtained by slow evaporation of a dilute aqueous solution of the amino acid hydrochloride. The crystallographic analysis revealed that the isolated isomer has the *Z*-configuration, with the amino group and the carboxyl group in a *cis*-configuration to one another (Figure 4).

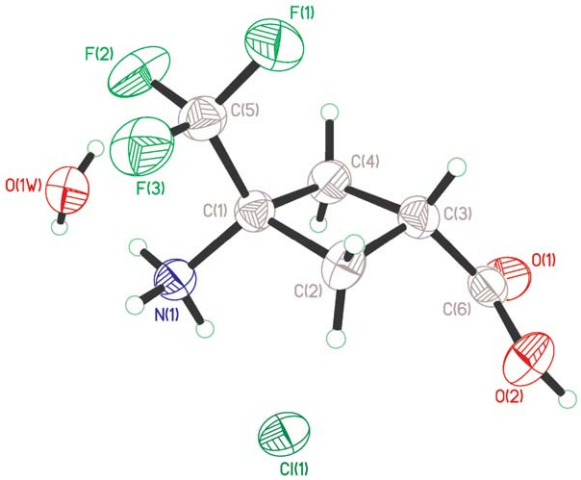


Figure 4 Structure of compound (*Z*)-**1** according to X-ray diffraction data; thermal ellipsoids are shown at the 50% probability level

Compound *(Z)*-**1** exists in the crystal phase as a chloride of the organic cation in the form of monohydrate. The cyclobutane ring adopts a folded conformation with a folding angle of 11.8°.

In summary, we synthesized the novel γ-trifluoromethyl-γ-amino acid **1** and the novel ε-trifluoromethyl-ε-amino acid **2**. The key step in the syntheses was the acid-catalyzed nucleophilic trifluoromethylation of the cyclic functionalized *N*-benzylimines **7** and **9** by Ruppert–Prakash reagent [trimethyl(trifluoromethyl)silane]. The yield of the key transformation appears to depend on the spatial proximity of the imine and ester group to one another. Further studies on the evaluation of the applicability of the reported procedure in the synthesis of various *x*-trifluoromethyl *x*-amino acids are ongoing.

Solvents were purified according to standard procedures. Imines **7** and **9** were synthesized under argon. Compounds **5** and **10** were synthesized according to literature procedures.[13,14] Other starting materials were provided by Enamine Ltd. Column chromatography was performed by using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on either a Bruker Avance 500 spectrometer at 500, 470, or 125 MHz, respectively, or on a Varian Unity Plus 400 spectrometer at 400, 377, and 101 MHz, respectively. Signals in the ^{13}C NMR spectra were assigned by means of DEPT experiments. Chemical shifts are reported in ppm downfield from TMS (^{1}H and ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on Hewlett-Packard GC/MS 5890/5972 instrument by electronic ionization (EI).

Methyl 3-(Benzylimino)cyclobutanecarboxylate (7)

A suspension of keto ester **5** (20.7 g, 0.162 mol), $BnNH_2$ (18.6 mL, 0.170 mol), and dry powdered $MgSO_4$ (97.2 g, 0.81 mol) in CH_2Cl_2 (500 mL) was stirred vigorously at r.t. for 96 h. The precipitate was filtered off, washed with CH_2Cl_2 (200 mL), and discarded. The combined organic phase was concentrated under vacuum to give a yellow oil; yield: 35 g (0.162 mol, quant); purity ~90%. The product was used in the next step without additional purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.17–3.32 (m, 5 H), 3.75 (s, 3 H, C*H*$_3$), 4.43 (s, 2 H, PhC*H*$_2$), 7.22–7.38 (m, 5 H, Ph).

Methyl 3-(Benzylamino)-3-(trifluoromethyl)cyclobutanecarboxylate (8)

TFA (16.0 mL, 0.209 mol) was added to a mixture of imine **7** (35.0 g, 0.162 mol) and $NaHF_2$ (8.1 g, 0.131 mol) in MeCN (300 mL) and DMF (37 mL, 0.49 mol) at 0 °C, and the suspension was stirred for 5 min. $TMSCF_3$ (34.5 g, 0.243 mol) was added and the mixture was stirred at r.t. for 12 h before sat. aq Na_2CO_3 (60 mL) was added and the mixture was stirred for a further 5 min. The mixture was then diluted with H_2O (500 mL) and extracted with EtOAc (3 × 300 mL). The combined organic phases were washed with H_2O and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography [hexane–EtOAc (3:1)] to give a yellow oil; yield: 10.7 g (0.037 mol, 23%); inseparable 1:3 mixture of *E*- and *Z*-isomers: R_f = 0.25.

^{1}H NMR (500 MHz, DMSO-d_6): δ (isomeric mixture) = 1.67 (br s, 1 H, NH, *E* + *Z*), 2.21 [dd, 0.5 H, *J* = 12.5, 9.0 Hz, (C*H*H)$_2$, *E*], 2.46 [dd, *J* = 11.0, 7.0 Hz, 1.5 H, (C*H*H)$_2$, *Z*], 2.63–2.68 (m, 2 H, (CH*H*)$_2$, *Z* + *E*), 3.13 (quin, *J* = 9.0 Hz, 0.75 H, CH, *Z*), 3.41 (quin, *J* = 9.0 Hz, 0.25 H, CH, *E*), 3.75 (s, 3 H, CH_3), 3.84 (1.5 H, s, $PhCH_2$, *Z*), 3.88 (0.5 H, s, $PhCH_2$, *E*), 7.25–7.43 (m, 5 H, C_6H_5, *E* + *Z*).

^{13}C NMR (125 MHz, $CDCl_3$): δ (isomeric mixture) = 29.87 [d, ^2J(C,F) = 2.5 Hz, CH_2, *E*], 30.69, 31.73 [2 s, CH, *Z* + *E*], 30.96 [d, ^2J(C,F) = 1.3 Hz, CH_2, *Z*], 47.16, 47.47 (2 s, NCH_2, *Z* + *E*), 51.88, 51.97 (2 s, CH_3, *Z* + *E*), 57.61 [q, ^2J(C,F) = 27.5 Hz, *C*CF_3, *E*], 58.21 [q, ^2J(C,F) = 27.5 Hz, *C*CF_3, *Z*r], 126.22 [q, ^1J(C,F) = 282.5 Hz, CF_3, *E*], 127.13, 127.17 [2 s, CH, Ph, *Z* + *E*], 127.34 [q, ^1J(C,F) = 283.8 Hz, CF_3, *Z*], 127.84, 128.00 [2 s, CH, Ph, *Z* + *E*], 128.42, 128.47 (2 s, CH, Ph, *Z* + *E*), 140.18, 140.44 (2 s, *tert*-C, Ph, *Z* + *E*), 174.90, 174.51 (2 s, *C*$OOCH_3$, *Z* + *E*).

^{19}F NMR (470 MHz, $CDCl_3$): δ (isomeric mixture) = –78.89 (s, CF_3, major, *Z*), –77.55 (s, CF_3, major, *E*).

MS: *m/z* = 287 (M^+).

(*Z*)-3-Amino-3-(trifluoromethyl)cyclobutanecarboxylic Acid Hydrochloride [(*Z*)-1·HCl]

A soln of ester **8** (5.7 g, 0.020 mol) and 12 M aq HCl (0.5 mL) in MeOH (120 mL) was hydrogenated at r.t. and 10 atm for 12 h by using 10% Pd/C (100 mg) as the catalyst. The soln then was filtered and the filtrate was concentrated under vacuum. The residue was treated with 6 M aq HCl (100 mL) and the mixture was refluxed for 1 h. The soln was then concentrated under vacuum to give a tarry residue that was crystallized from MeCN (20 mL) and H_2O (5 mL). The white solid was filtered off and dried in air to give the pure amino acid hydrochloride as the monohydrate; yield: 2.9 g (0.012 mol, 61%); mp > 200 °C.

Crystals of compound (*Z*)-**1**·HCl suitable for X-ray diffraction studies were obtained by slow evaporation of a dilute aq soln of the compound.

^{1}H NMR (500 MHz, D_2O): δ = 2.63–2.74 [m, 2 H, (C*H*H)$_2$], 2.81–2.91 [m, 2 H, (CH*H*)$_2$], 3.23 (quin, *J* = 9.0 Hz, 1 H, CH).

^{13}C NMR (125 MHz, D_2O): δ = 29.74 [s, $(CH_2)_2$], 30.31 (s, CH), 53.59 [q, ^2J(C,F) = 33.9 Hz, *C*CF_3], 124.58 [q, ^1J(C,F) = 280.3 Hz, CF_3], 176.96 (s, COOH).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –78.85 (s, CF_3).

Anal. Calcd for $C_6H_8F_3NO_2·H_2O·HCl$: C, 30.33; H, 4.67; N, 5.89. Found: C, 30.11; H, 4.89; N, 6.11.

X-ray Diffraction Details for (*Z*)-1·HCl·H_2O

Colorless crystals of (*Z*)-**1**·HCl·H_2O ($C_6H_9NO_2F_3^+$ Cl^-·H_2O) were monoclinic. At 293 K, *a* = 6.2722(6), *b* = 6.5628(3), *c* = 12.2478(8) Å, *β* = 96.704(6)°, *V* = 500.71(6) Å^3, M_r = 237.61, *Z* = 2, space group $P2_1$, d_{calc} = 1.576 g/cm^3, μ(MoKα) = 0.410 mm^{-1}, *F*(000) = 244. Intensities of 3101 reflections (1680 independent, R_{int} = 0.014) were measured on an Xcalibur-3 diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 50°). The structure was solved by direct method using the SHELXTL package.[16] Positions of the hydrogen atoms were located from electron density difference maps and refined by isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for nonhydrogen atoms using 1617 reflections was converged to wR_2 = 0.051 [R_1 = 0.020 for 1582 reflections with $F > 4\sigma(F)$, *S* = 1.057]. The final atomic coordinates, and crystallographic data for (*Z*)-**1**·HCl·H_2O have been deposited with the accession number CCDC 842686, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

Methyl 6-(Benzylimino)spiro[3.3]heptane-2-carboxylate (9)

A suspension of ester **10** (18.6 g, 0.111 mol), $BnNH_2$ (12.6 mL, 0.115 mmol), and dry powdered $MgSO_4$ (66 g, 0.550 mmol) in CH_2Cl_2 (500 mL) was vigorously stirred at r.t. for 96 h. The precipitate was filtered off, washed with CH_2Cl_2 (200 mL), and discarded. The combined organic phases were concentrated under vacuum to

give a brown oil; yield: 28.5 g (0.110 mol, quant); purity ~90%. The product was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ (isomeric mixture) = 2.33–2.63 [m, 4 H, $(CH_2)_2$], 2.94–3.20 [m, 5 H, $(CH_2)_2$, CH], 3.71 (s, 3 H, CH_3), 4.40–4.41 (2 s, 2 H, $PhCH_2$, *E* + *Z*), 7.21–7.42 (m, 5 H, C_6H_5).

Methyl 6-(Benzylamino)-6-(trifluoromethyl)spiro[3.3]heptane-2-carboxylate (11)

TFA (10.9 mL, 0.143 mol) was added to a mixture of imine **9** (28.5 g, 0.110 mol) and $NaHF_2$ (5.5 g, 0.088 mol) in MeCN (300 mL) and DMF (25 mL, 0.33 mol) at 0 °C, and the suspension was stirred for 5 min. $TMSCF_3$ (23.5 g, 0.165 mol) was added and the mixture was stirred at r.t. for 12 h then sat. aq Na_2CO_3 (50 mL) was added and the mixture was stirred for a further 5 min. The mixture was diluted with H_2O (500 mL) and extracted with EtOAc (3 × 300 mL). The combined organic phases were washed with H_2O and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography [hexane–EtOAc (3:1)] to give a colorless oil; yield: 17.0 g (0.052 mol, 47%); R_f = 0.3.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.58 (br s, 1 H, NH), 2.08 (d, *J* = 12.0 Hz, 1 H), 2.14 (d, *J* = 12.5 Hz, 1 H), 2.27–2.50 (m, 6 H), 3.06 (quin, *J* = 8.5 Hz, 1 H, CH), 3.70 (s, 3 H, CH_3), 3.81 (s, 2 H, $PhCH_2$), 7.25–7.41 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.86 (s), 33.54 (s), 37.81 (s), 39.34 (s), 39.59 (s), 40.17 (s), 47.33 (s), 51.66 (s, CH_3), 56.75 [q, ^2J(C,F) = 28.9 Hz, *C*CF_3], 127.06 (s, CH, Ph), 127.09 [q, ^1J(C,F) = 285.3 Hz, CF_3], 127.89 (s, CH, Ph), 128.41 (s, CH, Ph), 140.63 (s, *tert*-C, Ph), 175.65 (s, *C*$OOCH_3$).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –78.44 (br s, CF_3).

MS: *m/z* = 327 (M^+).

6-Amino-6-(trifluoromethyl)spiro[3.3]heptane-2-carboxylic Acid Hydrochloride (2·HCl)

A soln of ester **11** (8.2 g, 0.025 mol) and 6 M aq HCl (0.5 mL) in MeOH (150 mL) was hydrogenated at r.t. at 10 atm for 12 h using 10% Pd/C (100 mg) as the catalyst. The soln was filtered, and the filtrate was concentrated under vacuum. 6 M aq HCl (100 mL) was added to the residue and the mixture was refluxed for 1 h. The soln was then concentrated under vacuum and the residue was triturated with MeCN (20 mL). The white solid was filtered off and dried in air; yield: 5.45 g (0.021 mmol, 84%); mp >200 °C.

^{1}H NMR (500 MHz, D_2O): δ = 2.13–2.32 (m, 4 H), 2.36 (d, *J* = 15.2 Hz, 1 H), 2.43 (d, *J* = 14.8 Hz, 1 H), 2.55 (dd, *J* = 14.8, 2.8 Hz, 1 H), 2.66 (dd, *J* = 14.4, 2.4 Hz, 1 H), 2.93 (quin, *J* = 8.2 Hz, 1 H, C*H*).

^{13}C NMR (125 MHz, D_2O): δ = 31.80 (s), 32.27 (s), 37.13 (s), 37.19 (s), 38.38 (s), 38.81 (s), 53.13 [quin, ^2J(C,F) = 32.7 Hz, *C*CF_3], 124.61 [quin, ^1J(C,F) = 279.1, CF_3], 180.0 (s, COOH).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –79.01 (br s, CF_3).

Anal. Calcd for $C_9H_{12}F_3NO_2$·HCl: C, 41.63; H, 5.05; N, 5.39. Found: C, 41.33; H, 5.00; N, 5.22.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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