Methyl α-Iminotrifluoropropionate: A Novel Convenient Building Block for the Preparation of Functionalized Derivatives Bearing a Trifluoroalanine Residue

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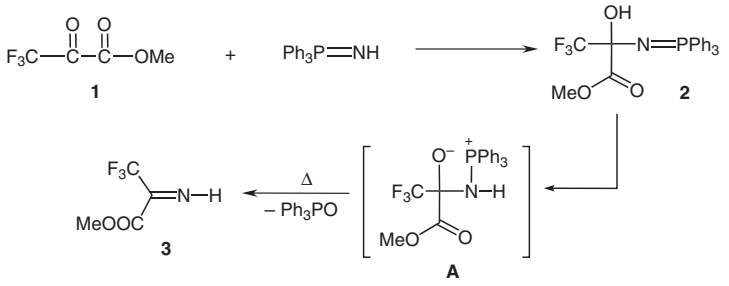
Abstract: A convenient synthesis of methyl α-iminotrifluoropropionate (methyl 3,3,3-trifluoro-2-iminopropanoate, **3**), based on the aza-Wittig reaction of methyl trifluoropyruvate with triphenylphosphine imide, was developed. The synthetic potential of N–H imine **3**, existing as equilibrium mixture (10:1) of *E*/*Z* isomers, in the preparation of functionalized acyclic and heterocyclic derivatives possessing a pharmacophoric trifluoroalanine fragment, is disclosed.

Key words: N–H imines, trifluoropyruvate, trifluoroalanine, iminocarboxylates, cyclization, nucleophilic addition



Scheme 1

Activated imines are valuable building blocks in the synthesis of functionalized nitrogen-containing compounds.[1] Specifically, compounds bearing an alkoxycarbonyl group at the imine carbon atom are convenient precursors of α-amino acids. Trifluoropyruvate imines are especially promising as their functionalization leads to biorelevant α-amino acids possessing the trifluoromethyl group. The latter brings in its unique properties such as high electronegativity, high lipophilicity, and steric demand.[2] For this reason, trifluoropyruvate imines with various substituents at nitrogen atom are widely used in the design of biologically active amino acids derivatives.[3] Surprisingly, the parent α-iminotrifluoropropionate with a free imine N–H group is apparently unknown so far. At the same time, the presence of the =N–H function in this compound offers additional opportunities connected with the possibility of their functionalization by both nucleophilic (at the imine carbon atom) and electrophilic agents (at the nitrogen atom).

A convenient synthetic approach to methyl α-iminotrifluoropropionate (methyl 3,3,3-trifluoro-2-iminopropanoate, **3**), based on the aza-Wittig reaction of commercially available methyl trifluoropyruvate (**1**) with triphenylphosphine imide has been developed (Scheme 1). It is noteworthy that at room temperature the reaction of **1** and triphenylphosphine imide leads initially to a mixture (~1:10) of imine **3** and phosphine imide **2**. The latter results from nucleophilic addition of the imino N–H function of triphenylphosphine imide across highly electrophilic C=O bond of **1**. Imide **2** is stable at room temperature in ethereal or benzene solutions, but upon heating or thermal distillation it cleanly converts into imine **3**. The transformation of **2** into **3** is believed to involve 1,3-proton transfer followed by elimination of triphenylphosphine oxide in the classical aza-Wittig reaction intermediate **A** (Scheme 1).

Imine **3** is quite stable in a dry inert atmosphere and can be easily purified by distillation. In solution ($CDCl_3$, benzene-d_6) iminocarboxylate **3** exists as an equilibrium mixture of *E*/*Z* isomers (*E*/*Z* ~10:1 at 25 °C). Identification of *E*,*Z*-isomers is based on the comparison of ^1H and ^{19}F NMR characteristics with the respective iminophosphonates analogues.[4]

Imine **3** contains a polarized azomethine group and it is a promising building block in the synthesis of amino acid derivatives containing a trifluoromethyl group. Its synthetic potential is demonstrated in Scheme 2. Specifically, reaction with indole leads directly to methyl α-amino-α-

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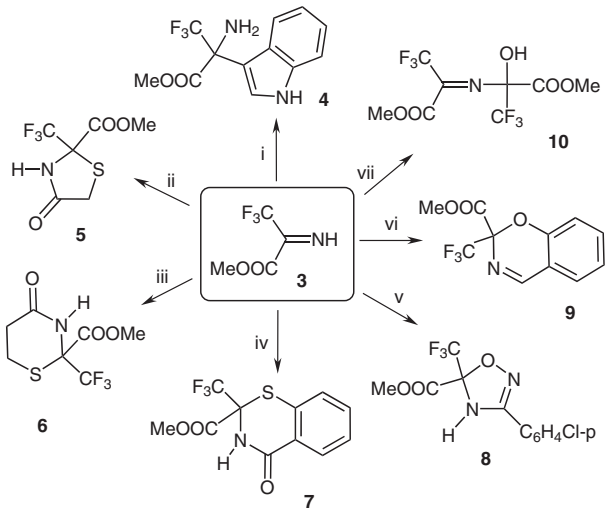
(1*H*-indol-2-yl)trifluoroalanine [methyl 2-amino-3,3,3-trifluoro-2-(1*H*-indol-3-yl)propanoate, **4**] in 90% yield. Cyclocondensations with mercaptoacetic, 3-mercaptopropionic, or thiosalicylic acid allow the preparation of biologically promising thiazolidinone **5**, thiazinanone **6**, or benzothiazine derivatives **7** bearing a trifluoroalanine fragment as part of the five- or six-membered heterocycle. [3+2]-Dipolar cycloaddition with nitrile oxide leads to functionalized dihydro-1,2,4-oxadiazole **8**. Reaction with salicylaldehyde opens the way to 2*H*-1,3-benzoxazines of type **9**. This interesting approach involves most probably addition of the O–H function across the C=N bond of imine **3** followed by the creation of a novel C=N bond by means of intramolecular condensation of the amino and carbonyl groups. The possibility for functionalization at the nitrogen atom of N–H imine **3** is exemplified by reaction with methyl trifluoropyruvate leading to the stable, highly functionalized imine **10**. Note that the two latter reactions are possible only for imines with a free N–H function.



Scheme 2 *Reagents and conditions*: (i) indole, Et_2O, r.t., 90%; (ii) $HSCH_2CO_2H$, Et_2O, r.t., 92%; (iii) $HS(CH_2)_2CO_2H$, Et_2O, r.t., 92%; (iv) thiosalicylic acid, THF, r.t., 95%; (v) 4-$ClC_6H_4C(Cl)$=NOH, Et_3N, Et_2O, –30 °C to r.t., 90%; (vi) salicylaldehyde, *p*-TsOH, benzene, 80 °C, 60%; (vii) $CF_3C(O)CO_2Me$, r.t, 100%.

In summary, a simple and efficient synthesis of methyl α-iminotrifluoropropionate has been developed and its synthetic potential for the preparation of functionalized acyclic and heterocyclic derivatives possessing a pharmacophoric trifluoroalanine fragment has been demonstrated.

IR spectra were obtained with an UR-20 instrument. NMR spectra were recorded on Varian VXR-300 spectrometer (operating frequency 299.95 MHz), ^{19}F and ^{31}P NMR spectra on a Gemini 200 Varian instrument operating at 188.14 and 80.95 MHz, respectively. ^{13}C NMR spectra were obtained on Bruker Avance DRX 500 spectrometer operating at 125.76 MHz. Chemical shifts are reported relative to internal TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) standards. Melting points are uncorrected. Solvents were dried before use according to standard methods. All reactions were carried out under an argon atmosphere in oven-dried glassware.

Methyl 3,3,3-Trifluoro-2-iminopropanoate (3)

Methyl trifluoropyruvate (**1**, 7 g, 45 mmol) was added to a stirred soln of Ph_3P=NH (12.4 g, 45 mmol) in anhyd Et_2O (30 mL) at 0 °C and was allowed to warm to r.t. The solvent was evaporated under reduced pressure to give a mixture (~1:10) of imine **3** and phosphine imide **2**.

^{19}F NMR (benzene-d_6): δ = –80.4.

^{31}P NMR (benzene-d_6): δ = 4.2.

Distillation of imine **3** and phosphine imide **2** gives imine **3** as a yellow liquid; yield: 5.6 g (80%); bp 108–109 °C.

IR (film): 1720, 1750 (C=N, C=O), 3250, 3270 cm^{-1} (NH).

(*E*)-3

^1H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, CH_3O), 12.24 (1 H, NH).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.75 (s, CH_3O), 118.66 (q, $^1J_{CF}$ = 278 Hz, CF_3), 156.65 (s, C=O), 156.84 (q, $^2J_{CF}$ = 36.5 Hz, C=N).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –71.1.

(*Z*)-3

^1H NMR (300 MHz, $CDCl_3$): δ = 3.99 (s, 3 H, CH_3O), 11.80 (1 H, NH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.9.

Anal. Calcd for $C_4H_4F_3NO_2$: C, 30.98; H, 2.60; N, 9.03. Found: C, 31.02; H, 2.62; N, 8.99.

Methyl 2-Amino-3,3,3-trifluoro-2-(1*H*-indol-3-yl)propanoate (4)

The mixture of indole (0.08 g, 0.65 mmol) and imine **3** (0.1 g, 0.65 mmol) in Et_2O (2 mL) was left at r.t. for 10 h. The solvent was evaporated under vacuum and the residue was triturated (hexane); yield: 0.16 g (90%).

Physicochemical constants of compound **4** are in agreement with the literature data.[5]

Methyl 4-Oxo-2-(trifluoromethyl)thiazolidine-2-carboxylate (5) and Methyl 4-Oxo-2-(trifluoromethyl)-1,3-thiazinane-2-carboxylate (6); General Procedure

Mercaptoacetic acid or 3-mercaptopropionic acid (1 mmol) was added to a stirred soln of the imine **3** (1 mmol) in Et_2O (2 mL). After reacting at r.t. for 8 h the solvent was evaporated under vacuum and the residue was triturated (hexane) to give compounds **5** or **6**.

Thiazolidine-2-carboxylate 5

White solid; yield: 0.21 g (92%); mp 133–134 °C.

IR (KBr): 1730, 1775 (C=O), 3200 cm^{-1} (NH).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.56 (d, $^2J_{HAHB}$ = 15.3 Hz, 1 H), 3.80 (d, $^2J_{HBHA}$ = 15.3 Hz, 1 H) (SCH_AH_B), 3.93 (s, 3 H, CH_3O), 7.32 (br s, 1 H, NH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –77.9.

Anal. Calcd for $C_6H_6F_3NO_3S$: C, 31.45; H, 2.64; S, 13.99. Found: C, 31.38; H, 2.62; S, 13.94.

Methyl 4-Oxo-2-(trifluoromethyl)-1,3-thiazinane-2-carboxylate (6)

White solid; yield: 0.22 g (92%); mp 83–84 °C.

IR (KBr): 1680, 1760 (C=O), 3200 cm^{-1} (NH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67–2.88 (m, 3 H), 3.21–3.30 (m, 1 H) (SCH_2CH_2), 3.93 (s, 3 H, CH_3O), 7.34 (br s, 1 H, NH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –76.0.

Anal. Calcd for $C_7H_8F_3NO_3S$: C, 34.57; H, 3.32; S, 13.18. Found: C, 34.62; H, 3.28; S, 13.21.

Methyl 4-Oxo-2-(trifluoromethyl)-3,4-dihydro-2*H*-1,3-benzothiazine-2-carboxylate (7)

Thiosalicylic acid (0.23 g, 1.5 mmol) was added to a stirred soln of the imine **3** (0.23 g, 1.5 mmol) in THF (2 mL) and was allowed to react overnight. The solvent was evaporated under vacuum and the residue was crystallized (Et_2O, 3 mL) to give a white solid; yield: 0.41 g (95%); mp 138–139 °C.

IR (KBr): 1695, 1780 (C=O), 3200 cm^{-1} (NH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.02 (s, 3 H, CH_3O), 7.00 (br s, 1 H, NH), 7.29 (d, $^3J_{HH}$ = 8.4 Hz, 1 H, Ar), 7.34 (t, $^3J_{HH}$ = 8.4 Hz, 1 H, Ar), 7.48 (t, $^3J_{HH}$ = 8.4 Hz, 1 H, Ar), 8.17 (d, $^3J_{HH}$ = 8.4 Hz, 1 H, Ar).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –77.0.

Anal. Calcd for $C_{11}H_8F_3NO_3S$: C, 45.36; H, 2.77; S, 11.01. Found: C, 45.42; H, 2.81; S, 10.98.

Methyl 3-(4-Chlorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2,4-oxadiazole-5-carboxylate (8)

4-Chloro-*N*-hydroxybenzenecarboximidoyl chloride (0.3 g, 1.7 mmol) was added to a stirred soln of imine **3** (0.22 g, 1.4 mmol) and Et_3N (1.17 g, 0.24 mL, 1.7 mmol) in Et_2O (5 mL) at –30 °C and was allowed to warm to r.t. After reacting at r.t. for 3 h the precipitated solid was filtered off. The solvent was evaporated under vacuum and the residue was crystallized (heptane) to give white crystals; yield: 0.39 g (90%); mp 97–98 °C.

IR (KBr): 1610 (C=N), 1760 (C=O), 3160 cm^{-1} (NH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, MeO), 6.18 (br s, 1 H, NH), 7.43 (d, $^3J_{HH}$ = 8.4 Hz, 2 H, Ar), 7.67 (d, $^3J_{HH}$ = 8.4 Hz, 2 H, Ar).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –82.4.

Anal. Calcd for $C_{11}H_8ClF_3N_2O_3$: C, 42.81; H, 2.61; Cl, 11.49; N, 9.08. Found: C, 42.79; H, 2.64; Cl, 11.54; N, 9.02.

Methyl 2-(Trifluoromethyl)-2*H*-1,3-benzoxazine-2-carboxylate (9)

A mixture of imine **3** (0.2 g, 1.3 mmol) and salicylaldehyde (0.16 g, 1.3 mmol) was left at r.t. for 10 h, and then *p*-TsOH·H_2O (10 mg, 0.05 mmol) was added; the mixture was heated in benzene (5 mL) under reflux for 2 h. The solvent was evaporated under vacuum and the residue was triturated (hexane) to give a yellow oil; yield: 0.2 g (60%).

IR (KBr): 1650 (C=N), 1770 cm^{-1} (C=O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, CH_3O), 6.99 (d, $^3J_{HH}$ = 8.4 Hz, 1 H, Ar), 7.05 (t, $^3J_{HH}$ = 8.4 Hz, 1 H, Ar), 7.26 (d, $^3J_{HH}$ = 8.4 Hz, 1 H, Ar), 7.45 (t, $^3J_{HH}$ = 8.4 Hz, 1 H, Ar), 8.35 (s, 1 H, CH=N).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –79.5.

Anal. Calcd for $C_{11}H_8F_3NO_3$: C, 50.98; H, 3.11; N, 5.40. Found: C, 51.09; H, 3.12; N, 5.32.

Methyl 3,3,3-Trifluoro-2-hydroxy-2-[(1,1,1-trifluoro-3-methoxy-3-oxopropan-2-ylidene)amino]propanoate (10)

The mixture of imine **3** (0.27 g, 1.75 mmol) and methyl trifluoropyruvate (**1**, 0.27 g, 1.75 mmol) was left at r.t. for 12 h to produce oily adduct **10**; yield: 0.54 g (100%).

IR (film): 1730, 1760, 1780 (C=N, C=O), 3350 cm^{-1} (OH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, CH_3O), 3.98 (s, 3 H, CH_3O), 4.60 (br s, 1 H, OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.1 (CF_3C=N), –79.6 (CF_3COH).

Anal. Calcd for $C_8H_7F_6NO_5$: C, 30.88; H, 2.27; N, 4.50. Found: C, 30.74; H, 2.31; N, 4.48.

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