Methyltrifluoropyruvate imines possessing *N*-oxalyl and *N*-phosphonoformyl groups—precursors to a variety of α-CF_3-α-amino acid derivatives

Hanna Skarpos,[a] Daria V. Vorob'eva,[b] Sergey N. Osipov,*[b] Irina L. Odinets,[b] Eli Breuer[c] and Gerd-Volker Röschenthaler*[a]

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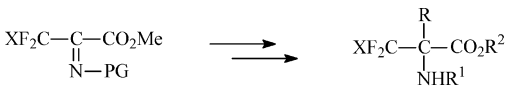
Convenient routes to methyl 2-oxalylimino- and 2-(phosphonoformimido)-3,3,3-trifluoropropanoates have been elaborated, based on the reaction of methyl trifluoropyruvate with ethyl oxamate or diethyl carbamoylphosphonate, respectively, followed by dehydration. The compounds obtained are useful synthetic intermediates toward a variety of novel 3,3,3-trifluoroalanine derivatives that are potential drug candidates.

1. Introduction

Peptides modified by non-proteinogenic amino acids are useful building blocks for drug discovery. Therefore, the development of new synthetic pathways to unnatural amino acids containing different functionalities remains a constant challenge. In this connection, hydroxamic acid derivatives including *N*-oxalylamino acids have attracted considerable attention due to their high activity in inhibiting medically important metalloenzymes.[1] For example oxaloglycine and its derivatives are known to inhibit prolyl hydroxylase[2] involved in the biosynthesis of collagen. The hyperactivity of the enzyme leads to the accumulation of large amounts collagen in different organs and tissues that causes the life-threatening fibrotic diseases such as pulmonary fibroses, liver and renal fibrosis *etc.* Furthermore, phosphonoformate (PFA, Foscarnet) is an effective antiviral compound clinically used in the treatment of herpetic diseases and of AIDS.[3] Incorporation of the PFA backbone into amides and amino acids is a promising strategy used currently for the development of new drug candidates based on selective inhibition of important enzymes including MMPs (matrix metalloproteinases).[4] The capacity of oxamic and phosphonoformic acid moieties for bidentate metal binding presumably plays a role in metalloenzyme inhibition. On the other hand, α-amino acids containing the trifluoromethyl (Tfm) group[5] are of particular interest due to the unique characteristics of the trifluoromethyl group, such as high electronegativity, electron density, steric hindrance and hydrophobicity.[6] The advantages of peptides modified by Tfm-amino acid include enhanced proteolytic stability, affinity for lipid bilayer membranes, as well as stabilization of secondary supramolecular structures[7] owing to the ability of the fluorine atom to form hydrogen bonds.[8,9]

Previously we have developed an effective strategy for the synthesis of α-halodifluoromethyl-substituted α-amino acid derivatives (including peptides) based on the amidoalkylation of different nucleophiles with highly electrophilic imines of methyl 3-halo-3,3-difluoropyruvates (Scheme 1).[10]



X = F, Cl, Br, H
PG = Boc, Cbz, SO_2R, C(O)R; R = Alk, Ar, Alkenyl, Alkynyl;
R^1 = H, Xaa; R^2 = H, Yaa

Scheme 1

In this communication, we report the synthesis of novel imines of methyl trifluoropyruvate bearing oxalyl and phosphonoformyl groups at the nitrogen atom, and their subsequent transformations into the corresponding amino acid derivatives (see Scheme 2). The resulting α-Tfm-α-amino acids possessing *N*-oxalyl and *N*-phosphonoformyl groups are potentially useful candidate molecules for the design of novel inhibitors of medically important enzymes.

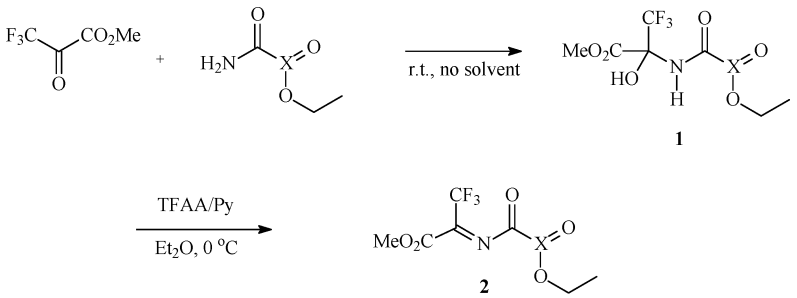
2. Results and discussion

We found that methyl trifluoropyruvate (MTFP)[11] had reacted readily with ethyl oxamate and diethyl carbamoylphosphonate at room temperature in the absence of any solvent, to give, in high yields, the stable adducts **1** which could be dehydrated by standard procedure[10] to afford the corresponding imines **2** (Scheme 2).

Similar to the other acylimines[10b] of MTFP, the imines **2** can interact smoothly with organometallic reagents at −78 °C in anhydrous THF or diethyl ether. The nucleophilic addition to the C=N double bond proceeded regiospecifically and resulted in the alkylation of the α-carbon atom, to give the corresponding α-amino acid derivatives **3** in moderate to good yields (Scheme 3, Table 1).

Further examination of the chemistry of imines **2** has revealed that these compounds are sufficiently powerful electrophiles to alkylate π-donor aromatic compounds such as furan, pyrrole, indole, *N*,*N*-dimethylaniline, and pyrazolone. Thus, the various

[a]*Institute for Inorganic and Physical Chemistry, The University of Bremen, Leobener Str., D-28334, Germany. E-mail: gvr@chemie.uni-bremen.de*
[b]*A.N. Nesmeyanov Institut of Organoelement compounds, Russian Academy of Sciences, 119991, Moscow, Vavilov str. 28, Russia. E-mail: osipov@ineos.ac.ru; Fax: +7 095 135 5085*
[c]*The Department of Medicinal Chemistry, The School of Pharmacy, The Hebrew University of Jerusalem, P.O. Box 12065, Jerusalem, 91120, Israel*



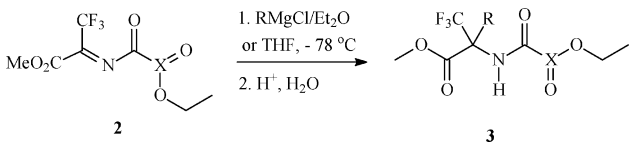
X = C (**1a** - 98 %, **2a** - 82 %), P-OEt (**1b** - 97 %, **2b** - 72 %)

Scheme 2

Table 1 Reaction of **2** with Grignard reagents *via* Scheme 3

Entry	Product	R	X	Yield[a] (%)
1	**3a**	Me	C	65
2	**3b**	Me	P-OEt	58
3	**3c**	Ph	C	52
4	**3d**	Ph	P-OEt	49
5	**3e**	CH_2Ph	C	59
6	**3f**	CH_2Ph	P-OEt	55
7	**3g**	Allyl	C	43
8	**3h**	Allyl	P-OEt	48

[a] Isolated yields after the purification by column chromatography.



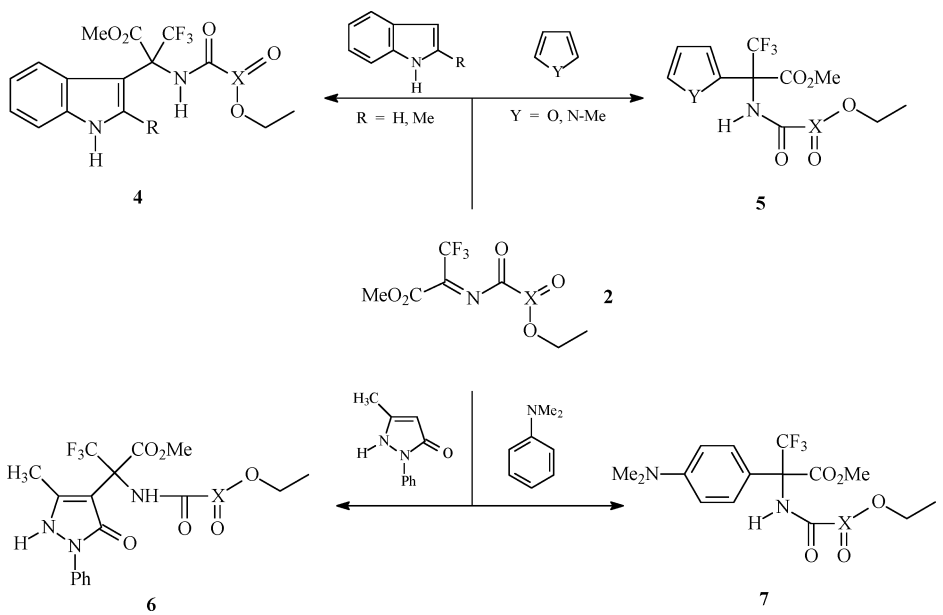
Scheme 3

α-aryl and α-heteroaryl substituted α-Tmf-amino acids could easily be prepared as indicated (Scheme 4, Table 2).

The reactions with indoles, 1-phenyl-3-methylpyrazol-5-one, furan, *N*-methylpyrrole and *N*,*N*-dimethylaniline proceeded under mild conditions (entries 4–7 and 10,11), or at moderate heating (entries 3,8,9) to yield the corresponding α-aryl(hetaryl)-β,β,β-trifluoroalanine derivatives **4–7**. In the aromatic rings, the C-amidoalkylation had been directed consistently and regioselectively to the sites of maximal π-electron density.

Due to the strong electrophilic nature, the reduction of C=N double-bond of the imines **2** could also be easily accomplished using 1.5 equivalents of $NaBH_4$ (Scheme 5) in anhydrous ether at room temperature. Under these conditions the reduction of *N*-oxalyl imine **2a** lead to the desired trifluoroalanine derivative **8** in 69% yield, while in the case of phosphorus-containing imine **2b**, the unexpected azirine derivative **9** was obtained in preparative yield. The structure of **9** has been unambiguously confirmed by the NMR, IR and HRMS data. The formation of azirine **9** is being tentatively rationalized by assuming the tautomerization of the initially formed reduction product **A** to the enol **B**, followed by dehydration. However; the actual mechanism of this reaction is not quite clear.

In conclusion, the results reported in this paper offer a convenient pathway to a variety of novel *N*-oxalyl and

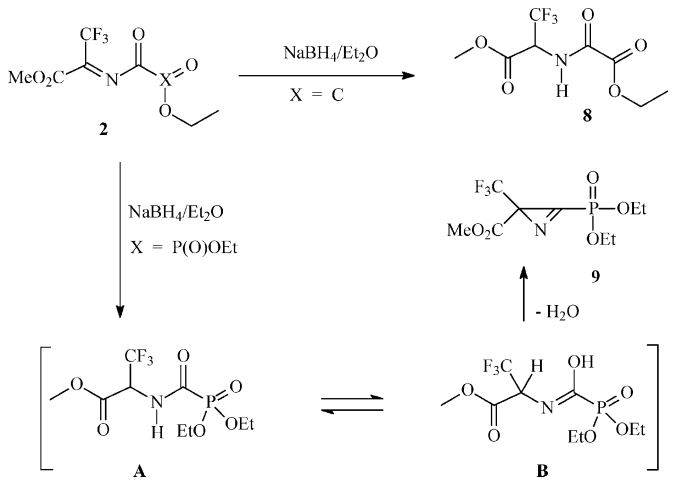


Scheme 4

Table 2 Results of reactions with aromatic π-donors shown in Scheme 4

Entry	Product	R	X	Y	Reaction temperature/°C	Yield[a] (%)
1	**4a**	H	C	—	RT	93
2	**4b**	H	P-OEt	—	RT	85
3	**4c**	Me	C	—	60	62
4	**4d**	Me	P-OEt	—	60	50
5	**5a**	—	C	O	0 → RT	39
6	**5b**	—	P-OEt	O	0 → RT	40
7	**5c**	—	C	N-Me	0 → RT	38
8	**5d**	—	P-OEt	N-Me	0 → RT	42
9	**6a**	—	C	—	60	76
10	**6b**	—	P-OEt	—	60	55
11	**7a**	—	C	—	−40 → *RT*	46
12	**7b**	—	P-OEt	—	−40 → *RT*	43

[a] Isolated yields after purification by column chromatography.



Scheme 5

N-phosphonoformyl derivatives of α-Tfm-α-amino acids—potential inhibitors of medically important enzymes. In addition, the novel amino acid derivatives herein reported could find further applications as building blocks for the modification of other biologically active peptides. The new compounds reported in this study will be examined for MMP inhibitory activity.

3. Experimental

General remarks

All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. Reactions were performed under an atmosphere of dry nitrogen. Analytical TLCs were performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light or spraying by $Ce(SO_4)_2$ solution in 5% H_2SO_4. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. NMR spectra were obtained on a Bruker DPX-200 spectrometer operating at 200.13 MHz for ^{1}H (TMS), 188.31 MHz for ^{19}F ($CFCl_3$), 80.99 MHz for ^{31}P (H_3PO_4) and 50.32 MHz ^{13}C (TMS). HRMS spectra were obtained on a Varian MAT CH7A instrument at 70 eV. IR spectra were recorded in a thin layer on a Fourier-spectrometer "Magna-IR750" (Nicolet), resolution 2 cm^{-1}, 128 scans. The assignment of the absorption bands in IR spectra was made according to ref. 12.

General procedure for the preparation of hemiamidals 1

A mixture of MTFP (10 mmol) and ethyl oxamate (or diethyl carbamoylphosphonate; 10 mmol) was kept at room temperature for 16 h. The crude solid product was washed with petroleum ether to give analytically pure hemiamidals **1**.

2-(Ethoxyoxalyl-amino)-3,3,3-trifluoro-2-hydroxy-propionic acid methyl ester (1a). Yield: 98% (white solid), mp 58–61 °C. ^{1}H NMR ($CDCl_3$) δ: 8.11 (s, 1H), 5.42 (s, 1H), 4.41 (q, 2H, $^3J_{HH} = 7.1$ Hz), 3.90 (s, 3H), 1.42 (t, 3H, $^3J_{HH} = 7.1$ Hz). ^{19}F NMR ($CDCl_3$) δ: −81.7 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 16.6, 55.2, 65.5, 80.5 (q, $^2J_{CF} = 29.5$ Hz), 121.6 (q, CF_3, $^1J_{CF} = 285.0$ Hz), 156.1, 158.3, 159.1. HRMS calculated for $C_8H_{10}F_3NO_6$ (M^+) 273.0460, found 273.0462.

2-(Diethylphosphonoformamido)-3,3,3-trifluoro-2-propionic acid methyl ester (1b). Yield: 97% (white solid), mp 69–72 °C. ^{1}H NMR ($CDCl_3$) δ: 8.51 (s, 1H), 5.32 (s, 1H), 4.20 (m, 4H), 3.93 (s, 3H), 1.4 (t, 6H, $^3J_{HH} = 7.0$ Hz). ^{19}F NMR ($CDCl_3$) δ: −75.5 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −1.9 (m). ^{13}C NMR ($CDCl_3$) δ: 16.6 and 16.7, 55.3, 65.6 and 65.7, 80.5 and 80.6 (both q, $^2J_{CF} = 29.0$ Hz), 122.5 and 122.6 (both q, CF_3, $^1J_{CF} = 286.0$ Hz), 165.5 (d, $^1J_{CP} = 123.0$ Hz), 170.2. HRMS calculated for $C_9H_{15}F_3NO_7P$ (M^+) 337.0538, found 337.0539.

General procedure for the preparation of imines 2

Trifluoroacetic anhydride (4.5 mL, 31.9 mmol) was added at 0 °C to a vigorously stirred solution of a hemiamidal (29.0 mmol) in dry ether (100 mL) over a period of 0.5 h. After stirring for 0.5 h, pyridine (5.2 mL, 64.0 mmol) was added slowly. Stirring was continued for additional 2 h. The reaction mixture was cooled down to −20 °C and the precipitated pyridinium trifluoroacetate was filtered off under an inert gas atmosphere. The filtrate was concentrated in vacuum and triturated with petroleum ether (3 × 100 mL) to dissolve the imine and separate it from residual pyridinium trifluoroacetate. The combined petroleum ether solutions were evaporated to give **2** which was additionally purified by distillation in the case of **2a**. Imine **2b** proved to be

unstable under distillation conditions; therefore it was used further as a crude product (purity *ca.* 90% according the NMR data).

Methyl 2-[*N*-(2-ethoxyoxalyl)imino]-3,3,3-trifluoropropanoate (2a). Yield: 82% (colorless liquid), bp 95–97 °C/0.5 Torr. IR (thin layer) ν/cm^{-1}: 1034 (C–O–C), 1638 (C=N), 1756, 1760 and 1765 (C=O). ^{1}H NMR ($CDCl_3$) δ: 4.41 (q, 2H, $^3J_{HH} = 6.9$ Hz), 4.08 (s, 3H), 1.42 (t, 3H, $^3J_{HH} = 6.9$ Hz). ^{19}F NMR ($CDCl_3$) δ: −71.3 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 14.2, 55.6, 64.4, 122.6 (q, CF_3, $^1J_{CF} = 279.0$ Hz), 154.7, 156.3 (q, *C*=N–CF_3, $^2J_{CF} = 35.1$ Hz), 160.4, 167.3. HRMS calculated for $C_8H_8F_3NO_5$ (M^+) 255.0457, found 255.0461.

Methyl 2-[(*N*-diethylphosphonoformyl)]imino]-3,3,3-trifluoropropanoate (2b). Yield: 75% (pale yellow oil). IR (thin layer) ν/cm^{-1}: 1022, 1046 (P–O–C, C–O–C), 1270 (P=O), 1651 (C=N), 1759 and 1769 (C=O). ^{1}H NMR ($CDCl_3$) δ: 4.33 (m, 4H), 4.07 (s, 3H), 1.69 (t, 6H, $^3J_{HH} = 6.8$ Hz). ^{19}F NMR ($CDCl_3$) δ: −71.3 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −2.2 (m). ^{13}C NMR ($CDCl_3$) δ: 16.0 and 16.3, 55.3, 63.2 and 63.5, 122.9 and 123.2 (both q, CF_3, $^1J_{CF} = 282.0$ Hz), 151.2, 155.1 and 155.4 (both q, $^2J_{CF} = 33.0$ Hz), 164.8 (d, $^1J_{CP} = 120.0$ Hz), 168.2. An analytically pure sample was not obtained.

General procedure for the preparation of 3

The Grignard reagent (solution in THF, 10.0 mmol) was added dropwise to a stirred solution of an imine (10.0 mmol) in dry THF (25 mL) at −78 °C. After 1 h at −78 °C the reaction mixture was allowed to warm up to room temperature within 2 h. The reaction mixture was quenched with 1 M HCl and extracted with ether (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate–hexanes).

Methyl 2-{*N*-(2-ethoxyoxalyl)amino}-3,3,3-trifluoro-2-methylpropanoate (3a). Yield: 65% (oil). ^{1}H NMR ($CDCl_3$) δ: 7.70 (s, 1H), 4.44 (m, 2H), 3.81 (s, 3H), 1.82 (s, 3H), 1.43 (t, 3H, $^3J_{HH} = 7.2$ Hz). ^{19}F NMR ($CDCl_3$) δ: −77.3 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 14.2, 15.9, 54.0, 59.3 (q, $^2J_{CF} = 30.2$ Hz), 64.1, 123.3 (q, CF_3, $^1J_{CF} = 281.0$ Hz), 158.5, 164.3, 165.4. HRMS calculated for $C_9H_{12}F_3NO_5$ (M^+) 271.0667, found 271.0668.

Methyl 2-(diethylphosphonoformamido)-3,3,3-trifluoro-2-methylpropanoate (3b). Yield: 58% (oil). ^{1}H NMR ($CDCl_3$) δ: 7.81 (s, 1H), 4.22 (m, 4H), 3.85 (s, 3H), 1.85 (s, 3H), 1.42 (t, 6H, $^3J_{HH} = 6.8$ Hz). ^{19}F NMR ($CDCl_3$) δ: −77.2 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −1.8 (m). ^{13}C NMR ($CDCl_3$) δ: 16.0 and 16.2, 16.9, 54.7, 59.9 and 60.1 (both q, $^2J_{CF} = 28.8$ Hz), 64.0 and 64.2, 121.8 and 122.0 (both q, CF_3, $^1J_{CF} = 283.0$ Hz), 163.5 (d, $^1J_{CP} = 122.0$ Hz), 165.4. HRMS calculated for $C_{10}H_{17}F_3NO_6P$ (M^+) 335.0745, found 335.0747.

Methyl *N*-(ethoxyoxalyl)-3,3,3-trifluoro-2-phenylalaninate (3c). Yield: 52% (white solid), mp 64–69 °C. ^{1}H NMR ($CDCl_3$) δ: 8.21 (s, 1H), 7.53 (s, 5H), 4.40 (q, 2H, $^3J_{HH} = 7.0$ Hz), 3.93 (s, 3H), 1.42 (t, 3H, CH_3, $^3J_{HH} = 7.0$ Hz). ^{19}F NMR ($CDCl_3$) δ: −72.2 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 14.1, 53.2, 64.0, 66.3 (q, $^2J_{CF} = 29.8$ Hz), 122.2 (q, CF_3, $^1J_{CF} = 285.0$ Hz), 127.5, 128.3, 129.5, 136.6, 157.3, 164.3, 165.4. HRMS calculated for $C_{14}H_{14}F_3NO_5$ (M^+) 333.0824, found 333.0826.

Methyl *N*-(diethylphosphonoformyl)-3,3,3-trifluoro-2-phenylalaninate (3d). Yield: 49% (pale yellow solid), mp 74–78 °C. ^{1}H NMR ($CDCl_3$) δ: 7.92 (s, 1H), 7.61 (s, 5H), 4.30 (m, 4H), 3.91 (s, 3H), 1.23 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −72.1 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −1.6 (m). ^{13}C NMR ($CDCl_3$) δ: 16.1 and 16.3, 54.2, 62.0 and 62.3, 65.0 and 65.2, (both q, $^2J_{CF} = 28.2$ Hz), 121.1 and 121.3 (both q, CF_3, $^1J_{CF} = 281.0$ Hz), 127.2, 128.1, 129.3, 133.7, 164.5 (d, $^1J_{CP} = 121.3$ Hz), 165.0. HRMS calculated for $C_{15}H_{19}F_3NO_6P$ (M^+) 397.0902, found 397.0904.

Methyl *N*-(ethoxyoxalyl)-α-(trifluoromethyl)phenylalaninate (3e). Yield: 59% (oil). ^{1}H NMR ($CDCl_3$) δ: 7.92 (s, 1H), 7.22 (m, 4H), 4.33 (q, 2H, $^3J_{HH} = 7.2$ Hz), 4.24 (d, 1H, $J_{HH} = 14.0$ Hz), 3.90 (s, 3H), 3.55 (d, 1H, $J_{HH} = 14.0$ Hz), 1.36 (t, 3H, $^3J_{HH} = 7.2$ Hz). ^{19}F NMR ($CDCl_3$) δ: −73.4 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 14.0, 35.9, 53.8, 63.8, 65.1 (q, $^2J_{CF} = 28.5$ Hz), 122.9 (q, CF_3, $^1J_{CF} = 288.2$ Hz), 125.4, 127.2, 131.4, 136.5, 155.1, 162.3, 166.2. HRMS calculated for $C_{15}H_{16}F_3NO_5$ (M^+) 347.0980, found 347.0981.

Methyl *N*-(diethylphosphonoformyl)-α-(trifluoromethyl)phenylalaninate (3f). Yield: 55% (oil) ^{1}H NMR ($CDCl_3$) δ: 7.71 (s, 1H), 7.13 (m, 4H), 4.26 (m, 4H), 4.11 (m, 1H), 3.92 (s, 3H), 3.57 (d, 1H, $J_{HH} = 7.0$ Hz), 1.32 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −73.4 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −1.3 (m). ^{13}C NMR ($CDCl_3$) δ: 15.9 and 16.1, 34.5, 55.3, 61.7 and 62.0, 65.2 and 65.5, (both q, $^2J_{CF} = 29.1$ Hz), 122.0 and 122.3 (both q, CF_3, $^1J_{CF} = 284.1$ Hz), 127.4, 129.5, 130.3, 134.9, 158.6, 162.7 (d, $^1J_{CP} = 120.3$ Hz). HRMS calculated for $C_{16}H_{21}F_3NO_6P$ (M^+) 411.1058, found 411.1059.

Methyl 2-(ethoxyoxalylamino)-2-(trifluoromethyl)pent-4-enoate (3g). Yield: 43% (oil). ^{1}H NMR ($CDCl_3$) δ: 7.93 (s, 1H), 5.22 (m, 2H), 4.99 (m, 1H), 4.36 (q, 2H, $^3J_{HH} = 7.2$ Hz), 3.88 (s, 3H), 3.63 (m, 1H), 2.97 (m, 1H), 1.43 (t, 3H, $^3J_{HH} = 7.2$ Hz). ^{19}F NMR ($CDCl_3$) δ: −73.2 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 13.7, 38.2, 53.3, 62.9, 70.2 (q, $^2J_{CF} = 29.8$ Hz), 121. 7, 122.3 (q, CF_3, $^1J_{CF} = 282.2$ Hz), 132.4, 153.6, 160.3, 165.8. HRMS calculated for $C_{11}H_{14}F_3NO_5$ (M^+) 297.0824, found 297.0826.

Methyl 2-{(diethylphosphonoformyl)amino}-2-(trifluoromethyl)-pent-4-enoate (3h). Yield: 48% (oil). ^{1}H NMR ($CDCl_3$) δ: 7.75 (s, 1H), 5.19 (m, 2H), 4.87 (m, 1H), 4.23 (m, 4H), 3.92 (s, 3H), 3.51 (m, 1H), 2.98 (m, 2H), 1.35 (t, 6H, $^3J_{HH} = 7.0$ Hz). ^{19}F NMR ($CDCl_3$) δ: −73.2 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −1.4 (m). ^{13}C NMR ($CDCl_3$) δ: 15.8 and 16.0, 36.9, 53.9, 62.5 and 62.7, 69.0 and 69.2, (both q, $^2J_{CF} = 29.7$ Hz), 120.9, 122.5 and 122.7 (both q, CF_3, $^1J_{CF} = 282.1$ Hz), 131.5, 156.7, 162.7 (d, $^1J_{CP} = 120.9$ Hz). HRMS calculated for $C_{12}H_{19}F_3NO_6P$ (M^+) 361.0902, found 361.0903.

Methyl *N*-(ethoxyoxalyl)-3,3,3-trifluoro-2-(1*H*-indol-3-yl)-alaninate (4a). A mixture of indole (8.0 mmol) and imine (8.0 mmol) in anhydrous diethyl ether (10 ml) was stirred at RT overnight. The white precipitate was filtered off, washed with ether to give analytically pure **4a**. Yield: 93%, mp 178–180 °C. ^{1}H NMR ($CDCl_3$) δ: 8.62 (s, 1H), 8.43 (s, 1H), 7.84 (d, 1H, $J_{HH} = 7.8$ Hz), 7.33 (m, 4H), 4.44 (q, 2H, $^3J_{HH} = 6.9$ Hz), 3.86 (s, 3H), 1.45 (q, 2H, $^3J_{HH} = 6.9$ Hz). ^{19}F NMR ($CDCl_3$) δ: −72.2 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 13.9, 53.8, 64.1, 75.8 (q, $^2J_{CF} = 30.2$ Hz), 112.2, 118.4, 118.9, 120.3, 120,4, 125.6 (q, CF_3, $^1J_{CF} = 280.1$ Hz), 128.1, 129.3, 136.4, 155.6, 160.8, 164.3. HRMS calculated for $C_{16}H_{15}F_3N_2O_5$ (M^+) 372.0933, found 372.0934.

Methyl *N*-(diethylphosphonoformyl)-3,3,3-trifluoro-2-(1*H*-indol-3-yl)alaninate (4b). Obtained from indole and **2b** following the procedure for **4a**. Yield: 85% (white solid), mp 108–110 °C. ^{1}H NMR ($CDCl_3$) δ: 8.90 (s, 1H), 8.23 (s, 1H), 7.63 (d, 1H, J_{HH} = 7.8 Hz), 7.43 (m, 4H), 4.21 (m, 4H), 3.82 (s, 3H), 1.3 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −72.2 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −1.2 (m). ^{13}C NMR ($CDCl_3$) δ: 16.6 and 16.7, 54.5, 65.4 and 65.5, 65.7 (m), 105.3, 112.5, 119.2, 121.2, 123.2, 124.6, 124.9 (q, CF_3, $^1J_{CF}$ = 280.1 Hz), 127.0, 129.3, 136.4, 165.6 (d, $^1J_{CP}$ = 122.3 Hz), 168.2. HRMS calculated for $C_{17}H_{20}F_3N_2O_6P$ (M^+) 436.1011, found 436.1010.

General procedure for the preparation of indoles 4c,d

A mixture of 2-methylindole (8.0 mmol) and appropriate imine (8.0 mmol) in anhydrous $CHCl_3$ was heated at 60–70 °C for 6–8 hours. The solvent was removed under reduced pressure; the product was isolated by flash chromatography on silica gel (eluent: ethyl acetate–hexanes).

Methyl *N*-(ethoxyoxalyl)-3,3,3-trifluoro-2-(2-methyl-1*H*-indol-3-yl)alaninate (4c). Yield 62%. (white solid), mp 107–109 °C. ^{1}H NMR ($CDCl_3$) δ: 8.80 (s, 1H), 8.71 (s, 1H), 7.65 (br. s, 1H), 7.38 (m, 1H), 7.26 (m, 2H), 4.42 (q, 2H, $^3J_{HH}$ = 7.1 Hz), 3.92 (s, 3H), 2.46 (s, 3H), 1.43 (t, 3H, $^3J_{HH}$ = 7.1 Hz). ^{19}F NMR ($CDCl_3$) δ: −71.2 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 11.9, 13.8, 54.8, 64.5, 65.1 (q, $^2J_{CF}$ = 28.2 Hz), 111.8, 113.9, 118.5, 120.1, 121.1, 125.6 (q, CF_3, $^1J_{CF}$ = 281.1 Hz), 128.6, 136.2, 141.4, 158.5, 164.8, 167.3. HRMS calculated for $C_{17}H_{17}F_3N_2O_5$ (M^+) 386.1089, found 386.1090.

Methyl *N*-(diethylphosphonoformyl)-3,3,3-trifluoro-2-(2-methyl-1*H*-indol-3-yl)alaninate (4d). Yield 50%. (pale yellow oil). ^{1}H NMR ($CDCl_3$) δ: 8.69 (s, 1H), 8.55 (s, 1H), 7.35 (br. s, 1H), 7.21 (m, 1H), 7.18 (m, 2H), 4.26 (m, 4H), 3.92 (s, 3H), 2.48 (s, 3H), 1.39 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −71.8 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −2.4 (m). ^{13}C NMR ($CDCl_3$) δ: 13.4, 16.2 and 16.4, 53.9, 62.4 and 62.6, 64.5 and 64.6 (both q, $^2J_{CF}$ = 30.8 Hz), 106.2, 113.5, 117.4, 121.2, 122.8, 126.6, 127.0 (q, CF_3, $^1J_{CF}$ = 283.0 Hz), 135.4, 145.5, 165.2 (d, $^1J_{CP}$ = 123.5 Hz), 167.2. HRMS calculated for $C_{18}H_{22}F_3N_2O_6P$ (M^+) 450.1167, found 450.1168.

General procedure for the preparation of furans 5a,b and pyrroles 5c,d

To a 0 °C solution of the corresponding furan or pyrrole (8.0 mmol) in ether (10 ml) a solution of imine **2a** (4.0 mmol) in 5 ml of ether was added. The mixture was allowed to warm up to rt and was stirred until ^{19}F NMR spectrum indicated the full conversion of imine **2a**. The solvent was removed under reduced pressure. The crude residue was purified by flash chromatography eluting with AcOEt–hexanes.

Methyl *N*-(ethoxyoxalyl)-3,3,3-trifluoro-2-(2-furyl)alaninate (5a). Yield: 39% (white solid), mp 74–79 °C. ^{1}H NMR ($CDCl_3$) δ: 8.22 (s, 1H), 7.43 (m, 1H), 6.62 (d, 1H, J_{HH} = 3.2 Hz), 6.43 (m, 1H, J_{HH} = 2.8 Hz), 4.45 (q, 2H, $^3J_{HH}$ = 7.2 Hz), 3.83 (s, 3H), 1.47 (t, 3H, $^3J_{HH}$ = 7.2 Hz). ^{19}F NMR ($CDCl_3$) δ: −73.3 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 14.2, 53.9, 63.5, 64.0 (q, $^2J_{CF}$ = 29.0 Hz), 104.8, 109.7, 121.9 (q, CF_3, $^1J_{CF}$ = 278.1 Hz), 139.8, 151.5, 157.8, 165.9, 166.3. HRMS calculated for $C_{12}H_{12}F_3NO_6$ (M^+) 323.0617, found 323.0619.

Methyl *N*-(diethylphosphonoformyl)-3,3,3-trifluoro-2-(2-furyl)-alaninate (5b). Yield: 40% (oil). ^{1}H NMR ($CDCl_3$) δ: 8.07 (s, 1H), 7.42 (m, 1H), 6.63 (d, 1H, J_{HH} = 3.4 Hz), 6.42 (m, 1H), 4.25 (m, 4H), 3.88 (s, 3H), 1.43 (t, 6H, $^3J_{HH}$ = 7.1 Hz). ^{19}F NMR ($CDCl_3$) δ: −73.3 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −1.8 (m). ^{13}C NMR ($CDCl_3$) δ: 16.1 and 16.3, 54.3, 62.2 and 62.4, 65.7 and 65.9 (both q, $^2J_{CF}$ = 31.3 Hz), 100.8, 108.5, 121.8 122.1 (both q, CF_3, $^1J_{CF}$ = 280.0 Hz), 140.4, 143.2, 164.7 (d, $^1J_{CP}$ = 122.5 Hz), 166.1. HRMS calculated for $C_{13}H_{17}F_3NO_7P$ (M^+) 387.0695, found 387.0694.

Methyl *N*-(ethoxyoxalyl)-3,3,3-trifluoro-2-(1-methyl-1*H*-pyrrol-2-yl)alaninate (5c). Yield: 38% (white solid), mp 95–97 °C. ^{1}H NMR ($CDCl_3$) δ: 8.21 (s, 1H), 7.63 (s, 1H), 6.64 (d, 1H, J_{HH} = 2.4 Hz), 6.25 (s, 1H), 4.46 (q, 2H, $^3J_{HH}$ = 6.8 Hz), 3.82 (s, 3H), 3.75 (s, 3H), 1.42 (t, 3H, $^3J_{HH}$ = 6.8 Hz). ^{19}F NMR ($CDCl_3$) δ: −73.3 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 14.3, 36.9, 53.8, 64.2, 67.5 (q, $^2J_{CF}$ = 34.0 Hz), 107.5, 114.6, 119.8, 121.5, 123.5 (q, $^1J_{CF}$ = 286.0 Hz), 155.6, 160.3, 165.7. HRMS calculated for $C_{13}H_{15}F_3N_2O_5$ (M^+) 336.0933, found 336.0934.

Methyl α-(diethylphosphonoformamido)-α-(trifluoromethyl)-1*H*-pyrrole-3-acetate (5d). Yield: 42% (oil). ^{1}H NMR ($CDCl_3$) δ: 8.52 (s, 1H), 7.54 (s, 1H), 6.63 (d, 1H, J_{HH} = 2.6 Hz), 6.24 (s, 1H), 4.33 (m, 4H), 3.82 (s, 3H), 3.65 (s, 3H), 1.36 (t, 6H, $^3J_{HH}$ = 7.2 Hz). ^{19}F NMR ($CDCl_3$) δ: −73.3 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −1.1 (m). ^{13}C NMR ($CDCl_3$) δ: 16.3 and 16.4, 40.1, 53.8, 61.2 and 61.4, 62.0 and 62.2 (both q, $^2J_{CF}$ = 28.1 Hz), 104.4, 105.2, 120.3 123.5 (q, CF_3, $^1J_{CF}$ = 279.7 Hz), 135.2, 158.6, 165.8 (d, $^1J_{CP}$ = 122.5 Hz). HRMS calculated for $C_{14}H_{20}F_3N_2O_6P$ (M^+) 400.1011, found 400.1010.

Methyl *N*-(ethoxyoxalyl)-3,3,3-trifluoro-2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)alaninate (6a). Obtained from 1-phenyl-4 methylpyrazole and **2a** following the procedure for **4a**. Yield: 76% (white solid), mp 84–88 °C. ^{1}H NMR (DMSO) δ: 12.10 (s, 1H), 7.62 (m, 2H), 7.51–7.37 (m, 3H), 4.35 (q, 2H, $^3J_{HH}$ = 7.2 Hz), 3.78 (s, 3H), 2.24 (s, 3H), 1.41 (t, 3H, $^3J_{HH}$ = 7.2 Hz). ^{19}F NMR (DMSO) δ: −76.3 (s, CF_3). ^{13}C NMR (DMSO) δ: 11.7, 14.6 and 14.7, 54.2, 62.8 (m), 64.2 and 64.3, 119,5, 121.5, 122.6 (q, CF_3, $^1J_{CF}$ = 272.0 Hz), 127.3, 135.3, 140.5, 156.2, 158.3, 159.6, 161.2, 165.2. HRMS calculated for $C_{18}H_{18}F_3N_3O_6$ (M^+) 429.1148, found 429.1147.

Methyl *N*-(diethylphosphonoformyl)-3,3,3-trifluoro-2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)alaninate (6b). Yield: 55% (pale yellow solid), mp 164–168 °C. ^{1}H NMR (DMSO) δ: 13.11 (s, 1H), 7.92 (m, 2H), 7.30–7.19 (m, 3H), 4.15 (m, 4H), 3.63 (s, 3H), 1.91 (s, 3H), 1.37 (t, 6H, $^3J_{HH}$ = 7.0 Hz). ^{19}F NMR (DMSO) δ: −76.3 (s, CF_3). ^{31}P NMR (DMSO) δ: −0.7 (m). ^{13}C NMR ($CDCl_3$) δ: 12.2, 16.3 and 16.5, 53.3, 64.4 and 64.6, 67.8 (q, $^2J_{CF}$ = 29.3 Hz), 107.0, 121.4, 124.8 (q, CF_3, $^1J_{CF}$ = 280.0 Hz), 125.1, 129.3, 139.5, 160.7, 162.3, 163.5, 164.7 (d, $^1J_{CP}$ = 122.5 Hz). HRMS calculated for $C_{19}H_{23}F_3N_3O_7P$ (M^+) 493.1226, found 493.1225.

Methyl 2-[4-(dimethylamino)phenyl]-*N*-(ethoxyoxalyl)3,3,3-trifluoroalaninate (7a). To a chilled (−40 °C) solution of *N*,*N*-dimethylaniline (8.0 mmol) in ether (10 ml) a solution of imine **2a** (8.0 mmol) in 5 ml of ether was added. The mixture was allowed to warm to RT and stirred until the ^{19}F NMR spectrum

indicated the full conversion of the imine **2a**. The solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica eluting with AcOEt–hexanes. Yield: 46% (oil). ^{1}H NMR ($CDCl_3$) δ: 7.80 (s, 1H), 7.32 (d, 2H, $J_{HH} = 9.0$ Hz), 6.85 (d, 2H, $J_{HH} = 9.0$ Hz), 4.2 (q, 2H, $^3J_{HH} = 7.0$ Hz), 4.03 (s, 3H), 2.95 (s, 6H), 1.44 (t, 6H, $^3J_{HH} = 7.0$ Hz). ^{19}F NMR ($CDCl_3$) δ: −71.3 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 14.1, 40.4, 55.8, 63.6, 70.5 (q, $^2J_{CF} = 31.0$ Hz), 113.5, 121.5, 121.6, 123.4 (q, CF_3, $^1J_{CF} = 281.0$ Hz), 125.6, 128.8, 128.9, 149.5, 160.1, 161.3, 165.7. HRMS calculated for $C_{16}H_{19}F_3N_2O_5$ (M^+) 376.1246, found 376.1247.

Methyl *N*-(diethylphosphonoformyl)-2-[4-(dimethylamino)-phenyl]-3,3,3-trifluoroalaninate (7b). Obtained from *N*,*N*-dimethylaniline and imine **2b** following the procedure for **7a**. Yield: 43% (oil). ^{1}H NMR (CD_3CN) δ: 7.93 (s, 1H), 7.34 (d, 2H, $J_{HH} = 9.0$ Hz), 6.78 (d, 2H, $J_{HH} = 9.0$ Hz), 4.13 (m, 4H), 3.76 (s, 3H), 2.91 (s, 6H), 1.33 (t, 6H, $^3J_{HH} = 7.2$ Hz). ^{19}F NMR (CD_3CN) δ: −71.3 (s, CF_3). ^{31}P NMR (CD_3CN) δ: 3.8 (m). ^{13}C NMR ($CDCl_3$) δ: 16.1 and 16.3, 39.9, 53.5, 61.2 and 61.3, 64.8 and 64.9 (both q, $^2J_{CF} = 28.3$ Hz), 111.4, 120.3, 122.9 and 123.0 (both q, CF_3, $^1J_{CF} = 285.0$ Hz), 127.1, 150.7, 161.5, 163.4 (d, $^1J_{CP} = 124.1$ Hz). HRMS calculated for $C_{17}H_{24}F_3N_2O_6P$ (M^+) 440.1324, found 440.1325.

General procedure for the reactions of 2 with $NaBH_4$

To a 0 °C solution of imine **2** (8.0 mmol) in ether (10 ml) a sodium borohydride (6.0 mmol, powder from Aldrich) was carefully added. The resulting suspension was stirred overnight at rt under nitrogen. The reaction mixture was quenched with 1 M HCl and extracted with ether (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate–hexanes).

Methyl *N*-(ethoxyoxalyl)-3,3,3-trifluoroalaninate (8). Yield: 69% (oil). ^{1}H NMR ($CDCl_3$) δ: 8.23 (s, 1H), 6.15 (m, 1H), 4.35 (m, 2H), 3.79 (s, 3H), 1.36 (t, 3H, $^3J_{HH} = 7.2$ Hz). ^{19}F NMR ($CDCl_3$) δ: −72.0 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 14.0, 53.5, 59.9 (q, $^2J_{CF} = 32.0$ Hz), 64.6, 125.4 (q, CF_3, $^1J_{CF} = 288.2$ Hz), 159.1, 161.4, 167.7. HRMS calculated for $C_8H_{10}F_3NO_5$ (M^+) 257.0511, found 257.0512.

Methyl 3-(diethylphosphonyl)-2-(trifluoromethyl)-2*H*-azirine-2-carboxylate (9). Yield: 57% (oil). IR (thin layer) ν/cm^{-1}: 1025, 1046 (P–O–C, C–O–C), 1271 (P=O), 1652 (C=O), 1765 (C=N). ^{1}H NMR ($CDCl_3$) δ: 4.34 (m, 4H), 4.12 (s, 3H), 1.4 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −62.7 (s, CF_3). ^{31}P NMR ($CDCl_3$) δ: −3.2 (m). ^{13}C NMR ($CDCl_3$) δ: 16.4 and 16.5, 60.4, 64.9 and 64.8, 105.9 and 105.8 (both q, $^2J_{CF} = 40.9$ Hz), 120.5 and 120.6 (both q, CF_3, $^1J_{CF} = 267.0$ Hz), 146.5 (d, $^1J_{CP} = 278.3$ Hz), 158.9. HRMS calculated for $C_9H_{13}F_3NO_5P$ (M^+) 303.0483, found 303.0482.

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