DOI: 10.1002/ejoc.200901354

Synthesis of α-Alkynyl-β,β,β-trifluoroalanine Derivatives by Sonogashira Cross-Coupling Reaction

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Keywords: Amino acids / Alkynes / Cross-coupling / Peptidomimetics / Hydrogenation

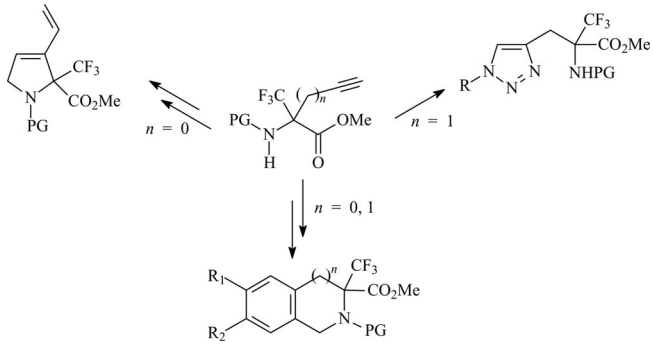
An efficient route to new α-CF_3-α-amino acid derivatives bearing an arylalkynyl moiety at the α-carbon atom has been developed. The method is based on palladium-catalyzed cross-coupling of the corresponding α-propargyl (ethynyl) α-amino esters with aryl halides to afford the amino acid derivatives with an internal triple bond that is suitable for further modifications.

Introduction

Non-proteinogenic α-amino acids have played a crucial role in the development of peptides and peptidomimetics as therapeutic agents.[1] Unsaturated α-amino acids have turned out to be especially important building blocks for these studies due to the diverse reactivities of the multiple bonds and their ability to introduce biologically active functionalities.[2] Thus, such compounds are useful in providing a handle for a range of transformations, especially transition-metal-mediated functionalizations.[3] Among those, metal-catalyzed cross-coupling and metathesis-type reactions including acetylene metathesis[4] have become standard tools in organic synthesis. Moreover, with the advent of the "click chemistry" concept,[5] interest in acetylenic amino acids has been sharply rising. Furthermore, unsaturated α-amino acids currently play an important role in peptide chemistry due to their facile incorporation into protein structures.[3]

On top of this, the introduction of fluorine or fluoroalkyl substituents into biologically relevant compounds has become an important tool in the drug discovery process.[6] Special attention is paid to trifluoromethyl-containing compounds due to the unique properties of the trifluoromethyl group, such as high electronegativity, steric hindrance, and hydrophobic character[7] that can greatly improve the pharmacokinetic properties of potential drugs. Moreover, incorporation of α-trifluoromethyl α-amino acids[8] into key positions of peptides retards their proteolytic degradation, induces secondary structure motifs, and improves lipophilicity,[8c] which enhances absorption in vivo and thus improves the permeability through certain body barriers. Therefore, the synthesis of new members of this special class of $C^{\alpha,\alpha}$-disubstituted amino acids as building blocks for specific peptide modification and as potent inhibitors that block biologically important enzymes, is of current interest.[9]

We have previously described highly efficient syntheses of various α-CF_3-amino acid derivatives based on addition of different C-nucleophiles to acylimines of 3,3,3-trifluoropyruvates.[10] α-Alkynyl α-CF_3-amino esters obtained by this method were successfully applied further in metal-catalyzed reactions, such as ring-closing metathesis, 1,3-dipolar cycloaddition and cyclotrimerization, to afford new families of the corresponding proline,[11] aza-histidine[12] and pipecolic acid derivatives[13] (Scheme 1).



Scheme 1. α-Alkynyl-α-CF_3-amino acids derivatives in metal-catalyzed transformations.

Here, we disclose an efficient synthetic approach to novel α-CF_3-amino acid derivatives bearing an aromatic moiety at the end of an alkyne chain attached to the α-carbon atom. The derivatives were obtained by applying the Sono-

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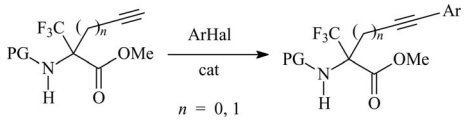
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901354.

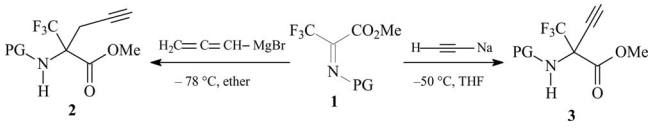
gashira cross-coupling reaction conditions to a combination of the corresponding α-ethynyl- or α-propargyl-containing α-amino esters and aryl halides (Scheme 2).



Scheme 2. Cross-coupling of α-alkynyl-α-CF_3-amino esters with aryl halides.

Results and Discussion

Synthesis of starting α-ethynyl- and α-propargyl-β,β,β-trifluoroalaninates **2** and **3** was accomplished by addition of either sodium acetylenide or allenylmagnesium bromide to electrophilic imines **1**. The reactions proceeded in anhydrous diethyl ether or tetrahydrofuran under mild conditions to give the corresponding amino esters in moderate to good yields (Scheme 3). Some of these compounds were previously described in short communications as mentioned above.[11–13] Here we give some additional examples (Table 1), and provide detailed experimental procedures for all products and their full characterizations (see Exp. Sect.).

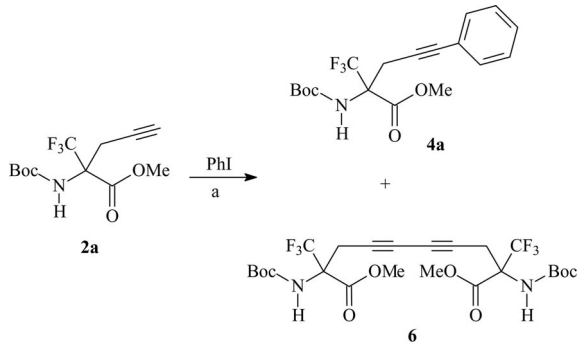


Scheme 3. Synthesis of α-ethynyl(propargyl) trifluoroalaninates **2** and **3**.

Table 1. α-Ethynyl(propargyl) trifluoroalaninates **2** and **3**.

Entry	PG	Product	Yield [%]
1	Boc	**2a**	69
2	Cbz	**2b**	54
3	SO_2Ph	**2c**	55
4	Boc	**3a**	64
5	Cbz	**3b**	67
6	SO_2Ph	**3c**	61

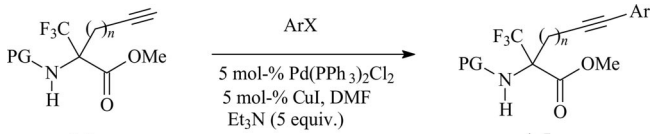
Investigations into the palladium-catalyzed cross-coupling of alkynyl-containing amino esters with aryl halides commenced with the reaction of Boc-protected propargylalaninate **2a** with iodobenzene. Application of conventional conditions for Sonogashira-type coupling initially gave unsatisfactory results. Thus, the reaction of **2a** with iodobenzene performed at room temperature in dichloromethane, in the presence of $PdCl_2(PPh_3)_2$ (5 mol-%), copper iodide (5 mol-%) and an excess of triethylamine (5 equiv.), lead to the desired product **4a** in just 35% yield after column chromatography. Comparable amounts of the homo-coupled derivative **6** (32%), presumably arising from a Glaser-type coupling,[14] was also isolated as a byproduct (Scheme 4).



(a) CH_2Cl_2, 5 mol-% $PdCl_2(PPh_3)_2$, 5 mol-% CuI, 5 equiv. Et_3N, at r.t.

Scheme 4. Reaction of **2a** with phenyl iodide.

Variation of solvent (THF, Et_2O, MeCN), organic base (Et_2NH, iPr_2NEt), catalyst [$PdCl_2(MeCN)_2$, $Pd(PPh_3)_4$] and reaction temperature did not significantly influence the ratio of **4a** and **6** formed in the reaction. However, we were pleased to find that formation of the homo-coupled derivative **6** could be almost completely suppressed (<5%, ^{19}F NMR spectroscopic analysis) by adding a solution of alkyne **2a** in DMF over period of one hour to the iodobenzene/catalyst solution in the same solvent; this procedure allowed the Sonogashira product **4a** to be isolated in a yield of 80%. The reaction was complete in three hours at ambient temperature. These conditions proved to be suitable for the cross-coupling of functionalized aryl iodides with other α-propargyl (and ethynyl)-α-amino acid derivatives bearing a range of protecting groups. The nature of the substituents on the benzene ring did not significantly affect the outcome of the reaction (Scheme 5, Table 2).



Scheme 5. Coupling of α-ethynyl(propargyl) trifluoroalaninates with aryl halides.

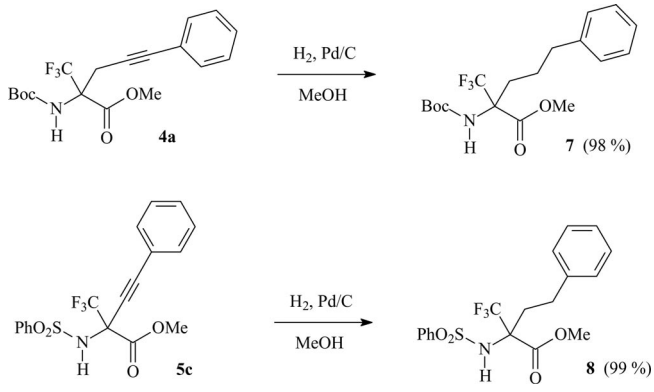
The cross-coupling of *N*-Boc-protected α-propargyl α-amino ester **2a** with aryl bromide required heating at 80 °C and went to completion within two hours to give **4e** in poor yield (entry 6). In this case, homo-coupled compound **6** was isolated as the major product in 35% yield. In the case of 5-bromopyrimidine (entry 9), none of the corresponding product **4h** was detected when the reaction was performed either at room temperature or under heating at 80 °C for eight hours.

To demonstrate one of the possible further synthetic applications of the new amino esters, we performed palladium-catalyzed hydrogenation of the internal triple bond to afford two homologues of α-CF_3-phenylalanine (**7** and **8**), in excellent yields (Scheme 6).

Table 2. Coupling of α-ethynyl(propargyl) trifluoroalaninates **2** and **3** with aryl halides.

Entry	Ar	PG	*n*	X	Product	Yield [%][a]
1	Ph	Boc	1	I	**4a**	80
2	Ph	Cbz	1	I	**4b**	75
3	(2-Me)Ph	Cbz	1	I	**4c**	88
4	(2-MeO)Ph	Boc	1	I	**4d**	71
5	(4-MeO)Ph	Boc	1	I	**4e**	76
6	(4-MeO)Ph	Boc	1	Br	**4e**	28[b]
7	(2-NO_2)Ph	Boc	1	I	**4f**	72
8		Cbz	1	I	**4g**	83
9		Boc	1	Br	**4h**	0[b]
10	Ph	Boc	0	I	**5a**	77
11	(2-Me)Ph	Boc	0	I	**5b**	76
12	Ph	SO_2Ph	0	I	**5c**	84
13	(2-Me)Ph	SO_2Ph	0	I	**5d**	72
14	(4-Me)Ph	SO_2Ph	0	I	**5e**	91
15	(2-MeO)Ph	Boc	0	I	**5f**	77
16	(2-NO_2)Ph	Cbz	0	I	**5g**	89
17	(2-NH_2)Ph	Cbz	0	I	**5h**	68

[a] After column chromatography on silica gel (hexanes/ethyl acetate). [b] Reactions were performed at 80 °C.



Scheme 6. Hydrogenation of **4a** and **5c**.

Conclusions

In summary, we have developed an efficient method with which to synthesize new α-CF_3-α-amino acid derivatives comprising an arylalkynyl moiety at the α-carbon atom through palladium-catalyzed Sonogashira cross-coupling of the corresponding α-propargyl (ethynyl) α-amino esters with aryl halides. Various N-protected amino esters, which are potentially applicable in a number of pharmaceutical and biochemical areas, were conveniently obtained in moderate to excellent yields. Their synthetic application in ruthenium-catalyzed cyclotrimerization to produce previously unknown bicyclic amino acid derivatives is under current investigation.

Experimental Section

General: 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 argon. Analytical TLC was performed with Merck silica gel 60 F_{254} plates; visualization was accomplished with UV light or spraying with $Ce(SO_4)_2$ solution in 5% H_2SO_4. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM) and ethyl acetate/petroleum ether as eluent. NMR spectra were obtained with Bruker AV-300, AV-400, or AV-600 spectrometers operating at 300, 400, or 600 MHz, respectively, for ^{1}H (TMS reference), at 75, 100, or 150 MHz for ^{13}C, and at 288 MHz for ^{19}F (CF_3COOH reference).

General Procedure for the Synthesis of 2a–c: Allenylmagnesiumbromide,[15] obtained from magnesium (30 mmol) and propargyl bromide (20 mmol) in the presence of $HgCl_2$ (5 mol-%) in diethyl ether (30 mL), was added dropwise to a stirred solution of an imine (10.0 mmol) in dry ether (25 mL) at –78 °C. After 1 h at –70 °C the reaction mixture was warmed to r.t. over 2 h. The reaction was quenched with sat. NH_4Cl and extracted with diethyl ether (2 × 25 mL). The combined organic layer was washed with brine (25 mL), dried with Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (ethyl acetate/hexanes).

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-2-(trifluoromethyl)pent-4-ynoate (2a): Yield: 69%; m.p. 70–71 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.51 [s, 9 H, $C(CH_3)_3$], 2.11 (t, *J* = 2.5 Hz, 1 H, ≡CH), 3.16 (dd, *J* = 16.9, *J* = 2.5 Hz, 1 H, CH_2), 3.76 (m, 1 H, CH_2), 3.95 (s, 3 H, OCH_3), 5.75 (br. s, 1 H, NH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.40 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 20.84, 28.12, 54.24, 64.59 (q, $^2J_{C–F}$ = 28.8 Hz), 72.13, 76.34, 80.97, 123.38 (q, $^1J_{C–F}$ = 288.6 Hz), 153.23, 166.33 ppm. $C_{12}H_{16}F_3NO_4$ (295.26): calcd. C 48.82, H 5.46, N 4.74; found C 48.74, H 5.47, N 4.68.

Methyl 2-[(Benzyloxycarbonyl)amino]-2-(trifluoromethyl)pent-4-ynoate (2b): Yield: 54%; oil. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.09 (t, *J* = 2.5 Hz, 1 H, ≡CH), 3.18 (dd, *J* = 16.2, *J* = 2.5 Hz, 1 H, CH_2), 3.85 (m, 1 H, CH_2), 3.95 (s, 3 H, OCH_3), 5.18 (d_{AB}, *J* = 12.2 Hz, 1 H, OCH_2), 5.24 (d_{AB}, *J* = 12.2 Hz, 1 H, OCH_2), 6.12 (br. s, 1 H, NH), 7.42 (m, 5 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.38 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 20.69, 54.45, 64.87 (q, $^2J_{C–F}$ = 28.8 Hz), 67.29, 72.45, 76.03, 123.30 (q, $^1J_{C–F}$ = 288.6 Hz), 128.14, 128.34, 128.57, 135.85, 153.91, 166.04 ppm. $C_{15}H_{14}F_3NO_4$ (329.28): calcd. C 54.71, H 4.29, N 4.25; found C 55.12, H 4.68, N 4.24.

Methyl 2-[(Phenylsulfonyl)amino]-2-(trifluoromethyl)pent-4-ynoate (2c): Yield: 55%; m.p. 94–95 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.05 (t, *J* = 2.3 Hz, 1 H, ≡CH), 3.18 (dd, *J* = 17.0, *J* = 2.3 Hz, 1 H, CH_2), 3.59 (dd, *J* = 17.0, *J* = 2.3 Hz, 1 H, CH_2), 3.94 (s, 3 H, OCH_3), 6.0 (s, 1 H, NH), 7.53–7.66 (m, 3 H, ArH), 7.97 (d, *J* = 7.8 Hz, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 4.38 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 22.02, 54.72, 67.20 (q, $^2J_{C–F}$ = 28.8 Hz), 73.10, 75.67, 122.49 (q, $^1J_{C–F}$ = 288.6 Hz), 126.97, 128.80, 132.86, 141.55, 165.54 ppm. $C_{13}H_{12}F_3NO_4S$ (335.30): calcd. C 46.57, H 3.61, N 4.18; found C 46.51, H 3.54, N 4.11.

General Procedure for the Synthesis of 3a–c: Sodium acetylide (17.5 mmol, 18% solution in xylol) was added dropwise to a solution of CF_3-imine (17.0 mmol) in anhydrous THF (60 mL) at –78 °C. The reaction mixture was warmed to r.t. over a period of 2 h, treated with 1 N HCl (50 mL) and extracted with diethyl ether (2 × 30 mL). The combined organic layer was washed with brine (50 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate).

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-2-(trifluoromethyl)but-3-ynoate (3a): Yield: 64%; oil. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ =

1.51 [s, 9 H, $C(CH_3)_3$], 2.71 (s, 1 H, ≡CH), 3.97 (s, 3 H, OCH_3), 5.51 (br. s, 1 H, NH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 2.65 (s, 3 F, CF_3) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 28.05, 54.45, 59.98 (q, $^2J_{C-F}$ = 28.7 Hz), 73.56, 75.87, 82.11, 121.93 (q, $^1J_{C-F}$ = 287.5 Hz), 152.96, 163.32 ppm. $C_{11}H_{14}F_3NO_4$ (281.23): calcd. C 46.98, H 5.02, N 4.98; found C 46.68, H 5.00, N 4.62.

Methyl 2-[(Benzyloxycarbonyl)amino]-2-(trifluoromethyl)but-3-ynoate (3b):[16] Yield: 67%; oil. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 2.75 (s, 1 H, ≡CH), 3.95 (s, 3 H, OCH_3), 5.19 (d_{AB}, J = 12.0 Hz, 1 H, OCH_2), 5.23 (d_{AB}, J = 12.0 Hz, 1 H, OCH_2), 5.88 (br. s, 1 H, NH), 7.42 (m, 5 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 2.77 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 54.71, 59.98 (q, $^2J_{C-F}$ = 32.07 Hz), 67.90, 72.99, 76.45, 121.87 (q, $^1J_{C-F}$ = 287.0 Hz), 128.37, 128.53, 128.62, 135.36, 153.7, 163.07 ppm. $C_{14}H_{12}F_3NO_4$ (315.25): calcd. C 53.34, H 3.84, N 4.44; found C 53.31, H 3.88, N 4.37.

Methyl 2-[(Phenylsulfonyl)amino]-2-(trifluoromethyl)but-3-ynoate (3c): Yield: 61%; solid; m.p. 117–118 °C. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.56 (s, 1 H, ≡CH), 3.87 (s, 3 H, OCH_3), 5.88 (br. s, 1 H, NH), 7.47–7.60 (m, 3 H, ArH), 7.92 (d, J = 7.6 Hz, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 2.00 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 55.32, 61.02 (q, $^2J_{C-F}$ = 33.2 Hz), 69.87, 80.09, 121.26 (q, $^1J_{C-F}$ = 287.5 Hz), 127.82, 128.84, 133.33, 140.12, 163.94 ppm. $C_{12}H_{10}F_3NO_4S$ (321.27): calcd. C 44.86, H 3.14, N 4.36; found C 44.61, H 2.97, N 4.17.

General Procedure for the Cross-Coupling Reaction: A mixture of $PdCl_2(PPh_3)_2$ (0.017 mmol), CuI (0.034 mmol), Et_3N (0.25 mL), and aryl halide (0.4 mmol) was stirred in degassed DMF (4 mL) for 30 min. A solution of alkynyl-containing amino ester (0.34 mmol) in the same solvent (2 mL) was added over a period of 1 h to the above catalyst/aryl halide solution, and the resulting mixture was stirred at r.t. until the starting alkyne had completely disappeared (ca. 3 h, detection by TLC analysis). Methylene chloride (30 mL) was added and the mixture was treated with 5% $NaHCO_3$ (20 mL). The organic layer was washed with water (2 × 10 mL), separated and dried with $MgSO_4$. After removing solvent under reduced pressure the crude product was purified by column chromatography on silica gel with ethyl acetate/hexanes as eluent.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-5-phenyl-2-(trifluoromethyl)-pent-4-ynoate (4a): Yield: 80%; oil. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.52 [s, 9 H, $C(CH_3)_3$], 3.37 (d_{AB}, J = 16.8 Hz, 1 H, CH_2), 3.92 (m, 1 H, CH_2), 3.97 (s, 3 H, OCH_3), 5.80 (br. s, 1 H, NH), 7.32–7.38 (m, 3 H, ArH), 7.40–7.45 (m, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.61 (s, 3 F, CF_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 22.04, 28.15, 54.16, 64.80 (q, $^2J_{C-F}$ = 28.7 Hz), 81.00, 81.56, 84.25, 122.79, 123.52 (q, $^1J_{C-F}$ = 288.5 Hz), 128.24, 128.30, 131.73, 153.34, 166.54 ppm. $C_{18}H_{20}F_3NO_4$ (371.36): calcd. C 58.22, H 5.43, N 3.77; found C 58.65, H 5.44, N 3.68.

Methyl 2-[(Benzyloxycarbonyl)amino]-5-phenyl-2-(trifluoromethyl)-pent-4-ynoate (4b): Yield: 75%; oil. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 3.40 (d_{AB}, J = 16.9 Hz, 1 H, CH_2), 3.95 (s, 3 H, OCH_3), 4.08 (d_{AB}, J = 16.9 Hz, 1 H, CH_2), 5.15 (d_{AB}, J = 12.2 Hz, 1 H, OCH_2), 5.27 (d_{AB}, J = 12.2 Hz, 1 H, OCH_2), 6.22 (br. s, 1 H, NH), 7.31–7.41 (m, 10 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.63 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 21.79, 54.42, 64.15 (q, $^2J_{C-F}$ = 28.8 Hz), 67.22, 81.30, 84.48, 122.65, 123.51, (q, $^1J_{C-F}$ = 288.6 Hz), 128.09, 128.30, 128.42, 128.59, 131.82, 135.98, 154.07, 166.32 ppm. $C_{21}H_{18}F_3NO_4$ (405.37): calcd. C 62.22, H 4.48, N 3.46; found C 62.34, H 4.41, N 3.36.

Methyl 2-[(Benzyloxycarbonyl)amino]-5-(2-methylphenyl)-2-(trifluoromethyl)pent-4-ynoate (4c): Yield: 88%; oil. ^1H NMR (600.22 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3), 3.40 (d_{AB}, J = 16.4 Hz, 1 H, CH_2), 3.94 (s, 3 H, OCH_3), 4.12 (d_{AB}, J = 16.4 Hz, 1 H, CH_2), 5.13 (d_{AB}, J = 12.1 Hz, 1 H, OCH_2), 5.20 (d_{AB}, J = 12.1 Hz, 1 H, OCH_2), 6.12 (br. s, 1 H, NH), 7.12 (t, J = 7.6 Hz, 1 H, ArH), 7.19 (d, J = 7.6 Hz, 1 H, ArH), 7.23 (t, J = 7.6 Hz, 1 H, ArH), 7.28–7.36 (m, 6 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.61 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 20.56, 21.72, 54.53, 65.18 (q, $^2J_{C-F}$ = 28.8 Hz), 67.22, 83.18, 85.08, 122.41, 123.41 (q, $^1J_{C-F}$ = 287.5 Hz), 125.51, 128.10, 128.31, 128.37, 128.56, 129.4, 132.1, 135.81, 140.27, 153.9, 166.38 ppm. $C_{22}H_{20}F_3NO_4$ (419.40): calcd. C 63.00, H 4.81, N 3.34; found C 63.07, H 4.74, N 3.33.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-5-(2-methoxyphenyl)-2-(trifluoromethyl)pent-4-ynoate (4d): Yield: 71%; solid; m.p. 97–98 °C. ^1H NMR (600.22 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 3.41 (d_{AB}, J = 17.2 Hz, 1 H, CH_2), 3.83 (m, 1 H, CH_2), 3.92 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 5.90 (br. s, 1 H, NH), 6.88 (d, J = 8.2 Hz, 1 H, ArH), 6.90 (t, J = 7.6 Hz, 1 H, ArH), 7.30 (dt, J = 8.47, J = 1.61 Hz, 1 H, ArH), 7.4 (dd, J = 7.6, J = 1.4 Hz, 1 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.89 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 22.70, 28.15, 53.96, 55.71, 64.45 (q, $^2J_{C-F}$ = 27.6 Hz), 77.11, 80.81, 85.58, 110.63, 111.97, 120.36, 123.63 (q, $^1J_{C-F}$ = 287.5 Hz), 129.72, 133.41, 153.44, 160.26, 166.59 ppm. $C_{19}H_{22}F_3NO_5$ (401.38): calcd. C 56.86, H 5.52, N 3.49; found C 56.89, H 5.41, N 3.52.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-5-(4-methoxyphenyl)-2-(trifluoromethyl)pent-4-ynoate (4e): Yield: 76%; oil. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 3.29 (d_{AB}, J = 16.9 Hz, 1 H, CH_2), 3.80 (s, 3 H, OCH_3), 3.81 (m, 1 H, CH_2), 3.91 (s, 3 H, OCH_3), 5.74 (br. s, 1 H, NH), 6.82 (d, J = 8.6 Hz, 2 H, ArH), 7.30 (d, J = 8.6 Hz, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 4.09 (s, 3 F, CF_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 21.97, 28.02, 53.97, 55.13, 64.64 (q, $^2J_{C-F}$ = 28.7 Hz), 79.77, 80.82, 83.98, 113.74, 114.76, 123.43 (q, $^1J_{C-F}$ = 287.6 Hz), 133.01, 153.21, 159.49, 166.46 ppm. $C_{19}H_{22}F_3NO_5$ (401.38): calcd. C 56.86, H 5.52, N 3.49; found C 56.64, H 5.61, N 3.78.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-5-(2-nitrophenyl)-2-(trifluoromethyl)pent-4-ynoate (4f): Yield: 72%; oil. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.49 [s, 9 H, $C(CH_3)_3$], 3.48 (d_{AB}, J = 17.2 Hz, 1 H, CH_2), 3.92 (m, 1 H, CH_2), 4.00 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.90 (br. s, 1 H, NH), 7.50 (m, 1 H, ArH), 7.61 (d, J = 4.4 Hz, 2 H, ArH), 8.07 (d, J = 8.1 Hz, 1 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.38 (s, 3 F, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 22.28, 28.10, 54.38, 64.67 (q, $^2J_{C-F}$ = 28.7 Hz), 79.18, 80.98, 90.42, 118.09, 123.41 (q, $^1J_{C-F}$ = 288.2 Hz), 124.55, 128.76, 132.77, 134.94, 150.00, 153.41, 166.16 ppm. $C_{18}H_{19}F_3N_2O_6$ (416.35): calcd. C 51.93, H 4.60, N 6.73; found C 52.10, H 4.81, N 6.67.

Methyl 2-[(Benzyloxycarbonyl)amino]-5-pyridin-2-yl-(trifluoromethyl)pent-4-ynoate (4g): Yield: 83%; oil. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 3.40 (d_{AB}, J = 17.0 Hz, 1 H, CH_2), 3.91 (s, 3 H, OCH_3), 4.00 (d_{AB}, J = 17.0 Hz, 1 H, CH_2), 5.11 (d_{AB}, J = 12.3 Hz, 1 H, OCH_2), 5.21 (d_{AB}, J = 12.3 Hz, 1 H, OCH_2), 6.18 (br. s, 1 H, NH), 7.19–7.38 (m, 7 H, ArH), 7.58 (dt, J = 7.8, J = 1.8 Hz, 1 H, ArH), 8.54 (d, J = 4.3 Hz, 1 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 4.07 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 21.71, 54.58, 64.83 (q, $^2J_{C-F}$ = 28.8 Hz), 67.25, 81.78, 83.72, 123.03, 123.32, (q, $^1J_{C-F}$ = 287.5 Hz), 127.44, 128.17, 128.28, 128.56, 135.87, 136.14, 142.66, 149.88, 154.03, 166.07 ppm.

$C_{20}H_{17}F_3N_2O_4$ (406.36): calcd. C 59.11, H 4.22, N 6.89; found C 59.29, H 4.15, N 6.96.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-4-phenyl-2-(trifluoromethyl)-but-3-ynoate (5a): Yield: 77%; m.p. 112–113 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.52 [s, 9 H, $C(CH_3)_3$], 3.98 (s, 3 H, OCH_3), 5.56 (br. s, 1 H, NH) 7.35–7.46 (m, 3 H, ArH), 7.53–7.56 (m, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 2.82 (s, 3 F, CF_3) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 28.07, 54.21, 60.50 (q, $^2J_{C–F}$ = 31.8 Hz), 78.71, 81.90, 87.03, 122.30 (q, $^1J_{C–F}$ = 287.0 Hz), 128.37, 129.58, 132.15, 152.98, 163.71 ppm. $C_{17}H_{18}F_3NO_4$ (357.33): calcd. C 57.14, H 5.08, N 3.92; found C 57.04, H 5.05, N 3.90.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-4-(2-methylphenyl)-2-(trifluoromethyl)but-3-ynoate (5b): Yield: 76%; m.p. 74–75 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.53 [s, 9 H, $C(CH_3)_3$], 2.49 (s, 3 H, CH_3), 3.98 (s, 3 H, OCH_3), 5.55 (br. s, 1 H, NH), 7.18–7.28 (m, 2 H, ArH), 7.31–7.36 (m, 1 H, ArH), 7.5 (dd, J = 7.7, J = 1.1 Hz, 1 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 2.82 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 20.35, 28.06, 54.17, 60.68 (q, $^2J_{C–F}$ = 31.0 Hz), 81.84, 82.55, 86.21, 120.62, 122.34 (q, $^1J_{C–F}$ = 287.5 Hz), 125.55, 129.54, 129.57, 132.29, 141.35, 152.96, 163.82 ppm. $C_{18}H_{20}F_3NO_4$ (371.36): calcd. C 58.22, H 5.43, N 3.77; found C 58.14, H 5.51, N 3.74.

Methyl 4-Phenyl-2-[(phenylsulfonyl)amino]-2-(trifluoromethyl)but-3-ynoate (5c): Yield: 84%; m.p. 118–120 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, OCH_3), 6.06 (br. s, 1 H, NH), 7.30–7.38 (m, 4 H, ArH), 7.45 (t, J = 9.0 Hz, 3 H, ArH), 7.58 (t, J = 7.4 Hz, 1 H, ArH), 7.98 (d, J = 7.3 Hz, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 1.97 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 55.30, 61.74 (q, $^2J_{C–F}$ = 33.2 Hz), 74.97, 91.18, 120.23, 121.53 (q, $^1J_{C–F}$ = 287.5 Hz), 127.72, 128.29, 128.83, 129.89, 132.16, 133.00, 140.39, 164.65 ppm. $C_{18}H_{14}F_3NO_4S$ (397.37): calcd. C 54.41, H 3.55, N 3.52; found C 54.49, H 3.50, N 3.53.

Methyl 4-(2-Methylphenyl)-2-[(phenylsulfonyl)amino]-2-(trifluoromethyl)but-3-ynoate (5d): Yield: 72%; m.p. 104–106 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 3.98 (s, 3 H, OCH_3), 6.08 (br. s, 1 H, NH), 7.17–7.25 (m, 3 H, ArH), 7.31–7.34 (m, 1 H, ArH), 7.42 (t, J = 7.9 Hz, 2 H, ArH), 7.56 (t, J = 7.3 Hz, 1 H, ArH), 7.96 (d, J = 7.3 Hz, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 1.94 (s, 3 F, CF_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 20.11, 55.19, 61.71 (q, $^2J_{C–F}$ = 33.0 Hz), 78.66, 90.54, 120.09, 121.58 (q, $^1J_{C–F}$ = 287.6 Hz), 125.45, 127.76, 128.73, 129.56, 129.87, 132.34, 132.93, 140.36, 141.66 164.74 ppm. $C_{19}H_{16}F_3NO_4S$ (411.40): calcd. C 55.47, H 3.92, N 3.40; found C 55.61, H 3.85, N 3.23.

Methyl 4-(4-Methylphenyl)-2-[(phenylsulfonyl)amino]-2-(trifluoromethyl)but-3-ynoate (5e): Yield: 91%; m.p. 125–127 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 3.97 (s, 3 H, OCH_3), 6.04 (br. s, 1 H, NH), 7.17–7.25 (m, 3 H, ArH), 7.19 (q, J = 8.23 Hz, 4 H, ArH), 7.45 (t, J = 7.7 Hz, 2 H, ArH), 7.58 (t, J = 7.3 Hz, 1 H, ArH), 7.97 (d, J = 7.5 Hz, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 1.93 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 21.62, 55.24, 61.76 (q, $^2J_{C–F}$ = 33.2 Hz), 74.3, 91.49, 117.17, 121.54 (q, $^1J_{C–F}$ = 287.5 Hz), 127.74, 128.80, 129.03, 132.07, 132.94, 140.27, 140.42 164.75 ppm. $C_{19}H_{16}F_3NO_4S$ (411.40): calcd. C 55.47, H 3.92, N 3.40; found C 55.59, H 3.79, N 3.41.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-4-(2-methoxyphenyl)-2-(trifluoromethyl)but-3-ynoate (5f): Yield: 77%; m.p. 94–96 °C. ^{1}H NMR (600.22 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 3.84 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 5.51 (br. s, 1 H, NH), 6.85 (d, J = 8.4 Hz, 1 H, ArH), 6.89 (t, J = 7.5 Hz, 1 H, ArH), 7.32 (dt, J = 9.0, J = 1.8 Hz, 1 H, ArH), 7.41 (dd, J = 7.5, J = 1.5 Hz, 1 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 2.85 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 28.05, 54.01, 55.83, 60.54 (q, $^2J_{C–F}$ = 31.0 Hz), 81.77, 82.44, 83.90, 110.01, 110.92, 120.37, 122.41 (q, $^1J_{C–F}$ = 287.5 Hz), 131.13, 134.01, 152.98, 160.86, 163.72 ppm. $C_{18}H_{20}F_3NO_5$ (387.36): calcd. C 55.81, H 5.20, N 3.62; found C 55.74, H 5.17, N 3.64.

Methyl 2-[(Benzyloxy)carbonyl]amino-4-(2-nitrophenyl)-2-(trifluoromethyl)but-3-ynoate (5g): Yield: 89%; oil. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, OCH_3), 5.20 (d_{AB}, J = 12.1 Hz, 1 H, OCH_2), 5.25 (d_{AB}, J = 12.1 Hz, 1 H, OCH_2), 6.14 (s, 1 H, NH), 7.41 (br. s, 5 H, ArH), 7.56–7.72 (m, 3 H, ArH), 8.15 (dd, J = 7.3, J = 0.7 Hz, 1 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.33 (s, 3 F, CF_3) ppm. ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ = 54.48, 60.87 (q, $^2J_{C–F}$ = 31.3 Hz), 67.04, 86.28, 115.10, 122.62 (q, $^1J_{C–F}$ = 286.8 Hz), 125.45, 128.45, 128.88, 131.71, 134.42, 135.58, 136.56, 149.82, 155.05, 163.23 ppm. $C_{20}H_{15}F_3N_2O_6$ (436.34): calcd. C 55.05, H 3.46, N 6.42; found C 55.34, H 3.18, N 6.48.

Methyl 4-(2-Aminophenyl)-2-[(benzyloxy)carbonyl]amino-2-(trifluoromethyl)but-3-ynoate (5h): Yield: 68%; oil. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 4.01 (s, 3 H, OCH_3), 4.60 (br. s, 2 H, NH_2), 5.22 (br. s, 2 H, OCH_2), 6.07 (br. s, 1 H, NH), 6.67–6.74 (m, 2 H, ArH), 7.22 (m, 1 H, ArH), 7.32 (s, 1 H, ArH), 7.43 (br. s, 5 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 2.71 (s, 3 F, CF_3) ppm. ^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 54.93, 60.69 (q, $^2J_{C–F}$ = 33.2 Hz), 67.76, 82.51, 85.78, 104.7, 114.3, 117.2, 122.18 (q, $^1J_{C–F}$ = 287.5 Hz), 128.32, 128.48, 128.64, 131.04, 132.19, 135.52, 149.88, 153.76, 163.98 ppm. $C_{20}H_{17}F_3N_2O_4$ (406.36): calcd. C 59.11, H 4.22, N 6.89; found C 58.99, H 4.20, N 6.75.

Dimethyl 2,9-Bis[(*tert*-butoxycarbonyl)amino]-2,9-bis(trifluoromethyl)deca-4,6-diynedioate (6): Yield: 32%; m.p. 150–152 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.51 [s, 18 H, 2 × $C(CH_3)_3$], 3.26 (d_{AB}, J = 16.5 Hz, 2 H, 2 × CH_2), 3.82 (m, 2 H, 2 × CH_2), 3.94 (s, 3 H, 6 × OCH_3), 5.71 (br. s, 2 H, 2 × NH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.27 (s, 6 F, 2 × CF_3) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.80, 28.08, 54.36, 64.48 (q, $^2J_{C–F}$ = 29.3 Hz), 68.17, 70.31, 81.23, 123.19 (q, $^1J_{C–F}$ = 287.9 Hz), 153.24, 166.02 ppm. $C_{24}H_{30}F_6N_2O_8$ (588.50): calcd. C 48.98, H 5.14, N 4.76; found C 49.01, H 5.27, N 4.58.

Hydrogenation of the Triple Bond: Alkynyl-containing amino ester (0.26 mmol) was dissolved in methanol (10 mL), and palladium on carbon (0.016 mmol, 10%) was added to the solution. The resulting suspension was degassed twice and then stirred under a hydrogen atmosphere for 3 h. The catalyst was filtered off through a Celite plug, and the solvent was removed under reduced pressure to give the pure product.

Methyl *N*-(*tert*-Butoxycarbonyl)-6-phenyl-2-(trifluoromethyl)norleucinate (7): Yield: 98%; oil. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.43 (m, 1 H, CH_2), 1.46 [s, 9 H, $C(CH_3)_3$], 1.63–1.75 (m, 1 H, CH_2), 2.13 (dt, J = 13.3, J = 4.1 Hz, 1 H, CH_2), 2.58–2.68 (m, 2 H, CH_2), 2.70 (m, 1 H, CH_2), 3.81 (s, 3 H, OCH_3), 5.51 (br. s, 1 H, NH), 7.15–7.32 (m, 5 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 3.20 (s, 3 F, CF_3) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.24, 28.01, 28.48, 35.24, 53.64, 65.72 (q, $^2J_{C–F}$ = 28.5 Hz), 80.47, 123.95 (q, $^1J_{C–F}$ = 287.9 Hz), 125.93, 128.18, 128.30, 141.23, 153.05, 167.40 ppm. $C_{18}H_{24}F_3NO_4$ (375.39): calcd. C 57.59, H 6.44, N 3.73; found C 57.81, H 6.64, N 3.74.

Methyl 5-Phenyl-*N*-(phenylsulfonyl)-2-(trifluoromethyl)norvalinate (8): Yield: 99%; oil. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.53 (m,

2 H, CH_2), 2.96 (m, 1 H, CH_2), 3.11 (m, 1 H, CH_2), 3.86 (s, 3 H, OCH_3), 6.13 (br. s, 1 H, NH), 7.27–7.41 (m, 5 H, ArH), 7.53–7.66 (m, 3 H, ArH), 7.99 (d, J = 8.2 Hz, 2 H, ArH) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 4.78 (br. s, 3 F, CF_3) ppm. ^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 29.84, 31.97, 54.50, 68.52 (q, $^2J_{C–F}$ = 28.8 Hz), 123.05 (q, $^1J_{C–F}$ = 287.5 Hz), 126.51, 126.76, 128.59, 128.68, 128.84, 132.78, 139.81, 141.66, 166.70 ppm. $C_{18}H_{18}F_3NO_4S$ (401.40): calcd. C 53.86, H 4.52, N 3.49; found C 54.19, H 4.53, N 3.44.

Supporting Information (see footnote on the first page of this article): NMR spectra for all new compounds.

Acknowledgments

This work was financially supported by the Russian Foundation of Basic Research (07-03-00593, 07-03-92171) and a GDRE-project between France and Russia.

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Received: November 24, 2009
Published Online: January 27, 2010

