Effective Pathway to the α-CF_3-Substituted Azahistidine Analogues

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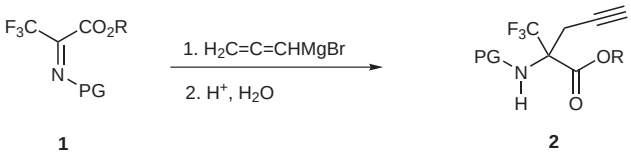
Abstract: An efficient method for the preparation of functionalized α-trifluoromethyl-substituted azahistidine analogues has been developed. The method is based on the regioselective addition of allenylmagnesiumbromide to highly electrophilic imines of trifluoropyruvates and subsequent 1,3-dipolar Huisgen cycloaddition between α-propargyl-α-trifluoromethyl-α-amino esters and organic azides.

Key words: fluorinated imines, amino acids, histidine, click reaction, organic azides

Synthetic α-amino acids play an important role in the area of peptide research and are extensively incorporated into biologically active peptides to restrict their conformational flexibility, enhance proteolytic stability, increase selectivity and improve pharmacokinetics and bioavailability properties of the potential drugs.[1] At the same time, it is known, that the incorporation of α-trifluoromethyl-α-amino acids (α-CF_3-AA) into strategically important positions of peptides retards proteolytic degradation, induces secondary structure motif, and improves lipophilicity[2] enhancing in vivo absorption, thus improving permeability through certain body barriers. Furthermore, ^{19}F NMR spectroscopy represents an efficient tool for conformational studies of fluorine-containing peptides as well as for the elucidation of metabolic processes.[3] The spectra can be recorded even in water and under cell-like conditions. Therefore, the synthesis of new members of this special class of $C^{\alpha,\alpha}$-disubstituted amino acids as building blocks for peptide modification and as suicide inhibitors irreversibly blocking pyridoxal phosphate-dependent enzymes[4] is of current interest.

In previous papers we described the syntheses of α-CF_3-AA derivatives (e.g. such as CF_3-ornithine,[5a] CF_3-arginine,[5b] CF_3-thalidomide[5c]) based on addition of C-nucleophiles to acylimines of 3,3,3-trifluoropyruvates.[6] Unsaturated α-CF_3-AA obtained by this methodology were successfully applied further in ruthenium-mediated metathesis-type reactions to afford a new family of the corresponding proline and pipecolic acid derivatives.[7] Taking into consideration that synthetic design of histidine is not a trivial task and any modification of both imidazole moiety and its amino acid backbone currently represents a great challenge in synthetic biomedicinal chemistry,[8] we wish to disclose herein an efficient approach to functionalized aza analogues of α-CF_3-histidine which is based on the 'click chemistry' conception recently introduced by Sharpless and co-workers.[9] The replacement of the C(2) atom by nitrogen in the imidazole ring to give 1,2,3-triazole could be interesting from the biological activity point of view. This heterocycle functions as a rigid linking unit that can mimic the atom placement and electronic properties of a peptide bond without the same susceptibility to hydrolytic cleavage. Both the N(2) and N(3) triazole atoms can act as hydrogen-bond acceptors, the strong dipole may polarize the C(5) proton to such degree that it can function as a hydrogen-bond donor, like the amide proton.[10] Perhaps due to their ability to mimic certain aspects of a peptide bond, many 1,2,3-triazoles possess varied biological activity, including anti-HIV activity,[11] selective β_3-adrenergic receptor inhibition,[12] antibacterial activity,[13] potent antihistamine activity[14] and more.[15]

The synthesis of starting α-propargyl-α-CF_3-AA derivatives **2**[16] has been accomplished via addition of Grignard reagent generated from propargyl bromide[17] to electrophilic imines **1** under mild conditions. Reactions proceeded in anhydrous diethyl ether or THF at –78 °C to give corresponding amino esters in moderate to good yields (Scheme 1, Table 1).



1 **2**

Scheme 1 Synthesis of α-propargyl-α-CF_3-AA derivatives

Table 1 α-Propargyl-α-CF_3-AA Derivatives

Entry	R	PG	Product	Yield (%)
1	Me	Cbz	**2a**	69
2	Me	Boc	**2b**	54
3	Me	Ts	**2c**	74
4	Me	SO_2Ph	**2d**	55
5	Me	CO_2Et	**2e**	41
6	Et	Cbz	**2f**	40
7	Et	Boc	**2g**	61

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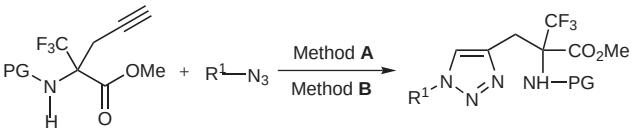
The usual procedure for regioselective Cu(I)-catalyzed alkyne–azide coupling, that is the best 'click' reaction to date, involves the use of a copper salt in conjugation with an added organic or inorganic base. The catalyst can be directly introduced as a Cu(I) salt or generated in situ by reduction of Cu(II) salts,[10] usually in organoaqueous systems. Application of these protocols to amino acid and peptide chemistry has recently begun,[18] but to the best of our knowledge fluorinated amino acids have not been utilized for such kind of transformations.

For the synthesis of the CF_3-substituted azahistidines **3** we applied both of above-mentioned methods, namely: A) the usage of CuI as a catalyst in organic solvent (THF) in the presence of organic base (DIPEA); B) the generation of Cu(I) in situ from $CuSO_4$ and sodium ascorbate in water–alcohol media (Scheme 2, Table 2).



Scheme 2 Synthesis of α-CF_3 azahistidine derivatives. *Reagents and conditions*: Method **A**: CuI (10 mol%), DIPEA (3 equiv), THF; Method **B**: $CuSO_4$ (5 mol%), Na-ascorbate (30 mol%), H_2O–*t*-BuOH.

Table 2 α-CF_3-Histidine Derivatives

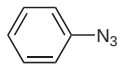
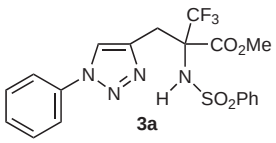
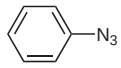
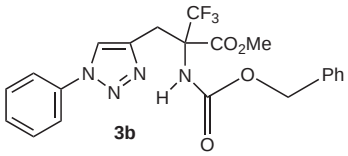
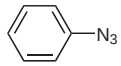
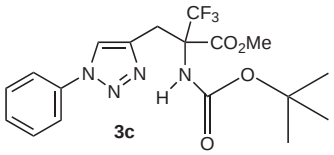
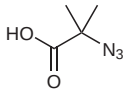
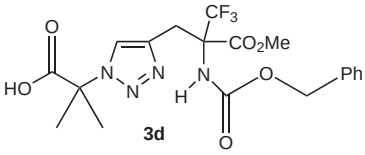
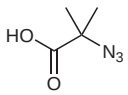
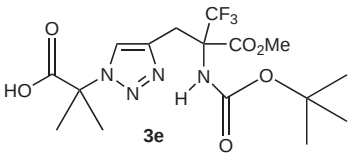
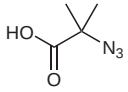
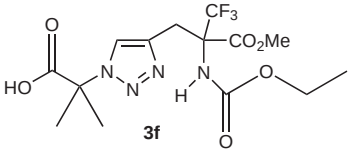
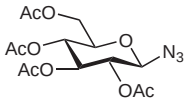
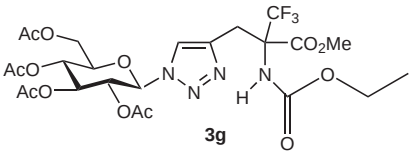
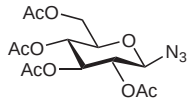
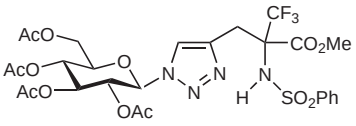
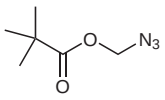
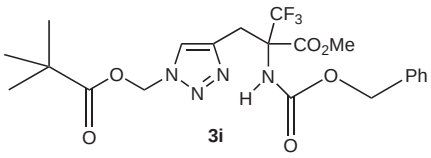
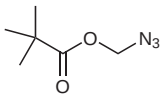
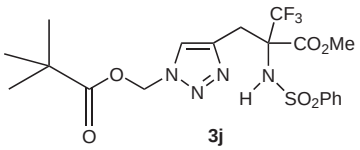
Entry	R^1-N_3	Product	Method	Yield (%)
1		 **3a**	B	89
2		 **3b**	A	79
3		 **3c**	A	77
4		 **3d**	A	85
5		 **3e**	A	83
6		 **3f**	A/B	78/84
7		 **3g**	A/B	82/92

Table 2 α-CF_3-Histidine Derivatives (continued)

Entry	R^1-N_3	Product	Method	Yield (%)
8		 **3h**	B	89
9		 **3i**	B	80
10		 **3j**	B	88

Thus, we found that 1,3-dipolar Huisgen cycloaddition reaction of propargyl-containing amino esters **2** with various available azides at room temperature for 6–8 hours readily provided functionalized α-CF_3 azahistidines **3**.[19] In spite of the fact that both methods give good to excellent results, route **B** is preferable due to a simpler isolation procedure (in all cases column chromatography was not needed).

To obtain free α-CF_3 azahistidine **6**, *N*-pivaloylmethyl derivative **3j** was selected as the most suitable precursor. We found that the pivaloylmethyl group could be selectively removed under basic conditions within few minutes at room temperature in methanol; more prolonged exposure of **3j** in 5% KOH–MeOH solution resulted in simultaneous ring and carboxylic function deprotection. Finally, the Cbz protective group of **5** was quantitatively removed via Pd-catalyzed hydrogenation in methanol to afford the desired free amino acid **6**[20] (Scheme 3).

In conclusion, we have developed an effective pathway to functionalized aza analogues of α-CF_3-histidine via Cu(I)-catalyzed 'click' reaction of α-propargyl substituted α-CF_3-AA derivatives with different azides. The free amino acid can be easily synthesized by step-wise deprotection of the corresponding cycloadduct bearing the pivaloylmethyl moiety.

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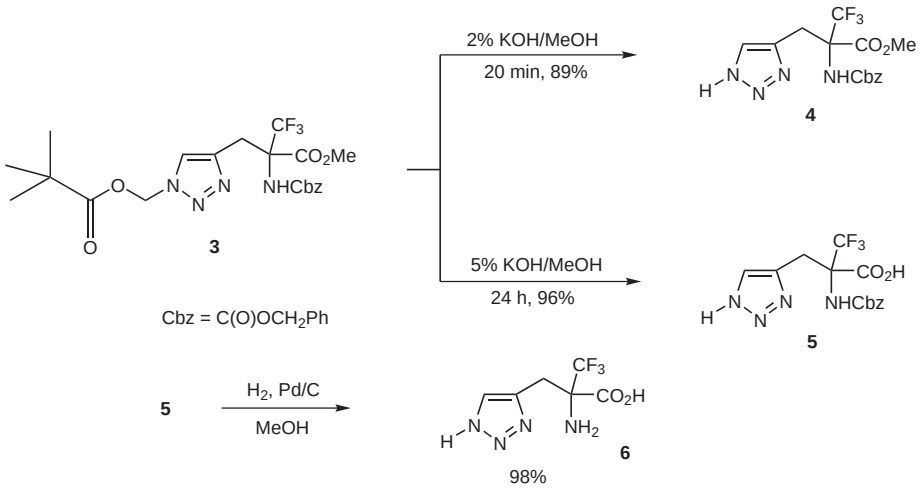

Scheme 3 Deprotection of α-CF_3 azahistidine

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(16) **General Procedure for the Preparation of 2.**
Allenylmagnesiumbromide[17] (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 to r.t. within 2 h. The reaction was quenched with 1 N HCl and extracted with Et_2O (2 × 25 mL). The combined organic layer was 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 (EtOAc–PE).
Data for Compounds 2a,b.
Compound **2a**: oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 1 H, ≡CH), 3.10 (d, J_{AB} = 16.6 Hz, 1 H, CH_2), 3.71 (d, J_{AB} = 16.6 Hz, 1 H, CH_2), 3.96 (s, 3 H, OCH_3), 5.22 (m, 2 H, OCH_2), 6.10 (s, 1 H, NH), 7.43 (m, 5 H, Ph). ^{19}F NMR (282 MHz, $CDCl_3$): δ (TFA) = 3.38 (s, 3 F, CF_3). Anal. Calcd for $C_{15}H_{14}F_3NO_4$ (%): C, 54.71; H, 4.29; F, 17.33. Found: C, 55.02; H, 4.38; F, 16.99.
Compound **2b**: mp 70–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.06 (s, 1 H, ≡CH), 3.10 (d, J = 16.9 Hz, 1 H, CH_2), 3.71 (m, 1 H, CH_2), 3.90 (s, 3 H, OCH_3), 5.70 (s, 1 H, NH). ^{19}F NMR (282 MHz, $CDCl_3$): δ (TFA) = 3.44 (s, 3 F, CF_3). Anal. Calcd for $C_{12}H_{16}F_3NO_4$: C, 48.81; H, 5.47; N, 4.74. Found: C, 48.74; H, 5.47; N, 4.68.

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(19) **Typical Procedure for the Preparation of 3.**
Method A. A mixture of organic azide (1.0 mmol), amino ester **2** (1.0 mmol), DIPEA (3.0 mmol) and CuI (0.1 mmol) in THF (10 mL) was stirred at r.t. for 6–8 h. The resulted reaction mixture was treated with 1 N HCl (15 mL), and extracted with Et_2O (3 × 15 mL). Combined organic layers were 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 (EtOAc–PE).
Method B. Organic azide (2.0 mmol) and amino ester **2** (2.0 mmol) were suspended in 1:1 H_2O–*t*-BuOH (8 mL). To this was added $CuSO_4 \cdot 5H_2O$ (5 M solution, 0.1 mmol, 5 mol%) and sodium ascorbate (0.6 mmol). The mixture was stirred at r.t. for 24 h, at which time TLC (silica, PE–EtOAc) indicated complete conversion. The resulted solution was concentrated under reduced pressure (rotary evaporator). The residue was dissolved in 30 mL of brine and then extracted with CH_2Cl_2 (3 × 30 mL). Combined organic layers were washed with 5% aq NH_4OH (2 × 10 mL), dried over $MgSO_4$, filtered and solvent was removed under vacuum to give analytically pure product.
Data for Compounds 3a,g.
Compound **3a**: mp 158–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (d, 1 H, CH_2, J_{AB} = 15.0 Hz), 4.03 (s, 3 H, OCH_3), 4.16 (d, 1 H, CH_2, J_{AB} = 15.0 Hz), 6.18 (s, 1 H, NH),

7.53–7.90 (m, 10 H, Ar), 8.22 (s, 1 H, H-triazole). ^{19}F NMR (282 MHz, $CDCl_3$): δ (TFA) = 5.38 (s, 3 F, CF_3). Anal. Calcd for $C_{19}H_{17}F_3N_4O_4S$ (%): C, 50.22; H, 3.77; N, 12.33. Found: C, 50.07; H, 3.84; N, 12.28.

Compound **3g**: mp 78–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 and 1.88 (2 × s, 3 H, OAc), 2.12 (m, 9 H, 3 × OAc), 3.67 (dd, *J* = 14.8, 2.5 Hz, 1 H, CH), 3.95 and 3.98 (2 × s, 3 H, OMe), 4.02 (m, 1 H, CH), 4.26 (m, 3 H, CH, CH_2), 5.11–5.51 (m, 5 H, 3 × CH, OCH_2), 5.78 (t, $^2J_{H–H}$ = 8.9 Hz, 1 H), 6.09 (br s, 1 H, NH), 7.45 (m, 6 H, 1 H-triazole, 5 H-Ar). ^{19}F NMR (282 MHz, $CDCl_3$): δ (TFA) = 3.87 (br s, 3 F, CF_3). Anal. Calcd for $C_{29}H_{33}F_3N_4O_{13}$: C, 49.58; H, 4.73; N, 7.97. Found: C, 49.12; H, 4.57; N, 7.57.

(20) **Data for Compound 6.**

Mp 216–217 °C. ^{1}H NMR (300 MHz, D_2O): δ = 3.38 (d, J_{AB} = 15.3 Hz, 1 H), 3.64 (d, J_{AB} = 15.3 Hz, 1 H), 7.73 (s, 1 H, H-triazole). ^{19}F NMR (282 MHz, D_2O): δ (TFA) = 3.55 (s, 3 F, CF_3). ^{13}C NMR (150.9 MHz, D_2O): δ = 26.5, 65.3 (q, $^2J_{C–F}$ = 25.4 Hz), 123.5 (q, $^1J_{C–F}$ = 228.9 Hz), 128.1, 137.9, 166.0. Anal. Calcd for $C_6H_7F_4N_4O_2$: C, 32.15; H, 3.15; N, 25.00. Found: C, 32.12; H, 3.04; N, 24.67.