Pergamon

Tetrahedron Letters 41 (2000) 3825–3828

TETRAHEDRON
LETTERS

Synthesis of highly fluorinated dipeptide building blocks

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Received 3 March 2000; accepted 30 March 2000

Abstract

A new approach to the synthesis of dipeptides containing up to three trifluoromethyl groups has been developed. The method is based on a [4+1]-cycloaddition reaction of hexafluoroacetone or methyl 3,3,3-trifluoropyruvate derived *N*-acylimines and α-amino acid isocyanides. Acidic hydrolysis of the cycloadducts gives the trifluoromethylated dipeptides in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *N*-acylimines; isocyanides; [4+1]-cycloaddition; α-trifluoromethyl α-amino acid.

Incorporation of α,α-disubstituted α-amino acids into key positions of peptides is an efficient strategy to retard proteolytic degradation and to stabilize secondary structures.[1] Due to the unique properties of the trifluoromethyl group (high electronegativity, high lipophilicity, and high steric demand), α-trifluoromethyl α-amino acids [(α-Tfm) α-amino acids] are a special subclass of α,α-disubstituted α-amino acids. They can improve the profile of bioactive peptides considerably. In this context, incorporation of (α-Tfm) α-amino acids into key positions of peptides is of current biochemical and medicinal interest.[2] Moreover, a sequence of coupled (α-Tfm) α-amino acids incorporated into peptides provides a possibility to form highly fluorinated domains in peptides. Such domains could serve as a suitable tool for the synthesis of peptides with tailor-made lipophilicity.

From the synthetic point of view, the construction of such sequences and their incorporation into peptides is not trivial using conventional peptide chemistry methods (Fig. 1, disconnection 1) because of the strong electronegative influence of the α-CF_3-group on α-amino and the α-carboxylic group reactivity.[3] For example, the common solution phase strategy or protease catalysed peptide synthesis are not applicable for C-terminal introduction of (α-Tfm) α-amino acids into peptides.[4] For these purposes, some special methods for α-amino and α-carboxylic group activation[5] as well as a new type of peptide bond formation[6] (Fig. 1, disconnection 2) have been recently successfully applied.

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0040-4039/00/$ - see front matter
PII: S0040-4039(00)00540-2

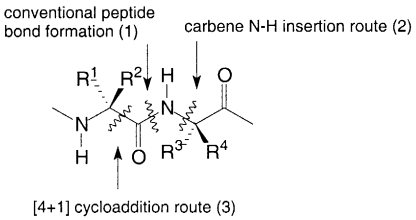
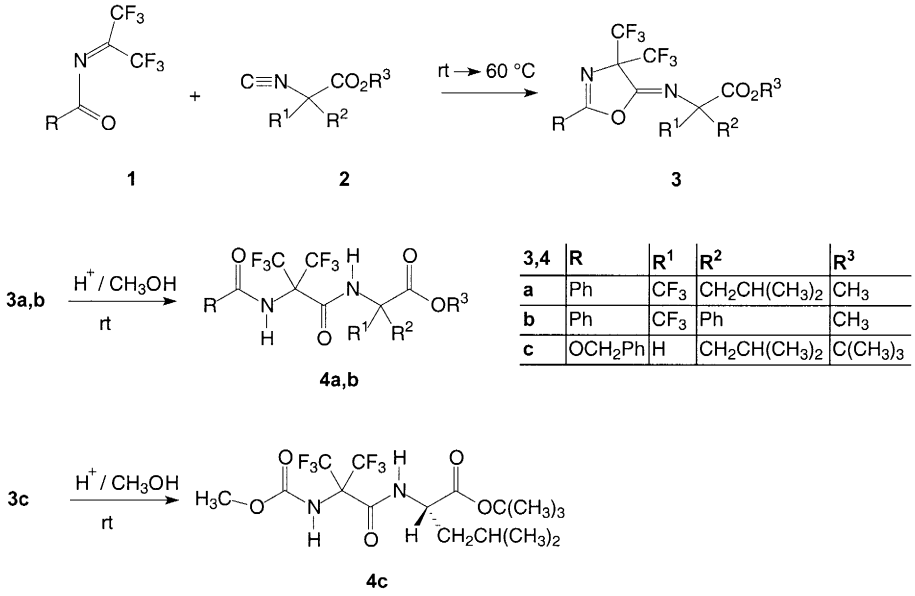


Fig. 1.

We now report on an approach, which provides a general access to highly fluorinated dipeptide building blocks containing up to three CF_3-groups. This approach involves formation of the $NHCR^1R^2–CONHR^3R^4CO$ bond (Fig. 1, disconnection 3).

The reaction sequence consists of a [4+1] cycloaddition reaction[7] of *N*-acylimines of trifluoromethyl ketones and isocyanides derived from α-amino acids, followed by hydrolytic ring opening.

Bis(trifluoromethyl)substituted acylimines **1**[8a,b] and methyl 2-isocyanopropionates **2**[9] react at 60°C within 4–6 h to give [4+1] cycloadducts **3**, which can be transformed at rt on treatment with methanol/1N HCl to give dipeptide esters **4** in good yields.[10] (Scheme 1) The fully protected dipeptides **4** possess up to three trifluoromethyl groups.

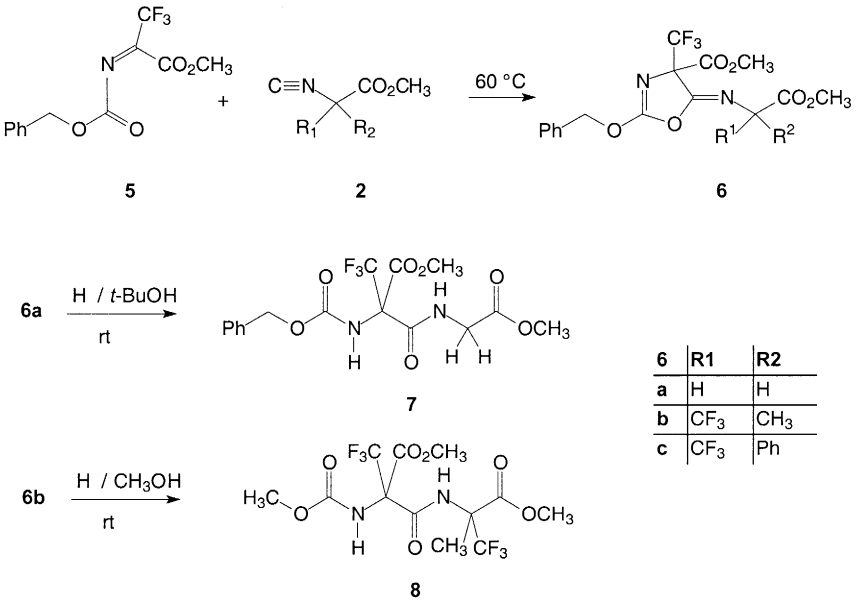


3,4	R	R^1	R^2	R^3
a	Ph	CF_3	$CH_2CH(CH_3)_2$	CH_3
b	Ph	CF_3	Ph	CH_3
c	OCH_2Ph	H	$CH_2CH(CH_3)_2$	$C(CH_3)_3$

Scheme 1.

Likewise, formation of *Z*-protected dipeptide esters can be achieved on the reaction of *N*-acylimine **5**[8c] with isocyanides of type **2**. Ring opening of the [4+1] cycloadducts was performed with 1N HCl in *tert*-butanol to give *Z*-protected dipeptide esters **7**. Ring cleavage with subsequent transesterification (**6**→**8**) was observed on treatment of **6** with methanol/1N HCl (Scheme 2).

In summary, we have developed a new efficient method for the synthesis of highly fluorinated dipeptides. Further investigations on the incorporation of the new building blocks into key positions of biologically active peptides are in progress.



6	R1	R2
a	H	H
b	CF_3	CH_3
c	CF_3	Ph

Scheme 2.

Acknowledgements

This work was supported by Deutsche Forschungsgemeinschaft (Innovationskolleg), Stiftung Volkswagenwerk, and Fonds der Chemischen Industrie.

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10. The synthesis of **3a** and **4a** is representative: **3a**: A mixture of *N*-acylimine **1**[8] (1.35 g, 5 mmol) and methyl 2-isocyano-4-methyl-2-trifluoromethyl-pentanoate **2a** (1.12 g, 5 mmol) in dry toluene (25 ml) was stirred at 60°C for 4–6 h. After disappearance of the starting material (^{19}F NMR analysis), the solvent was evaporated in vacuo. The residue was purified

by flash chromatography on silica gel (eluent: chloroform/hexanes). Yield: 1.67 g (68%); m.p. 57–58°C; IR (KBr) ν 1775, 1765, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, *J*=6.6 Hz, 3H), 0.99 (d, *J*=6.6 Hz, 3H), 1.88–1.95 (m, 1H), 2.15 (dd, *J*=14.7, 6.8 Hz, 1H), 2.30 (dd, *J*=14.7, 5.4 Hz, 1H), 3.78 (s, 3H), 7.52–7.56 (m, 2H), 7.66–7.71 (m, 1H), 7.99–8.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.43, 24.00, 24.04, 41.53, 53.30, 71.48 (d, *J*=27.5 Hz), 77.12 (qq, *J*=30.7, 30.7 Hz), 120.55 (q, *J*=284.7 Hz), 123.80 (q, *J*=285.9 Hz), 123.48, 129.00, 129.21, 134.70, 149.31, 166.78, 168.06; ^{19}F NMR ($CDCl_3$) δ 5.03 (s, 3F), 5.09 (q, *J*=9.1 Hz, 3F), 5.69 (q, *J*=9.1 Hz, 3F); $C_{19}H_{17}F_9N_2O_3$ (492.32): calcd C 46.35, H 3.48, N 5.69%; found: C 46.85, H 3.54, N 5.89%. **4a**: A solution of **3a** (0.50 g, 1 mmol) in methanol (3 ml) was stirred with 4 drops of 1N HCl at rt. The progress of the reaction was monitored by ^{19}F NMR. After evaporation of the solvent, the residue was dissolved in methylene chloride and washed with $NaHCO_3$ solution, with water and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by flash chromatography on silica gel (eluent: ethyl acetate/hexanes). Yield 0.33 (65%); m.p. 89–91°C; IR (KBr) ν 3370, 1755, 1730, 1705, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (d, *J*=6.6 Hz, 3H), 0.99 (d, *J*=6.6 Hz, 3H), 1.85–1.88 (m, 1H), 2.03 (dd, *J*=14.2, 10.4 Hz, 1H), 2.99 (dd, *J*=14.2, 3.5 Hz, 1H), 3.86 (s, 3H), 7.14 (s, 1H), 7.46–7.52 (m, 2H), 7.56–7.61 (m, 1H), 7.81–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.73, 23.50, 23.80, 36.24, 54.23, 66.76 (d, *J*=29.1 Hz), 67.95 (qq, *J*=29.2, 29.2 Hz), 121.51 (q, *J*=288.0 Hz), 123.64 (q, *J*=288.7 Hz), 127.26, 128.96, 132.52, 132.88, 156.76, 165.95, 168.18; ^{19}F NMR ($CDCl_3$) δ 3.22 (s, 3F), 9.17 (q, *J*=9.7 Hz, 3F), 10.16 (q, *J*=9.7 Hz, 3F); $C_{19}H_{19}F_9N_2O_4$ (510.33): calcd C 44.71, H 3.75, N 5.49%; found: C 45.11, H 3.72, N 5.63%.