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Peptide Modification by Introduction of α-Trifluoromethyl α-Amino Acids via 4-Trifluoromethyl-1,3-oxazolidin-2,5-diones[1]

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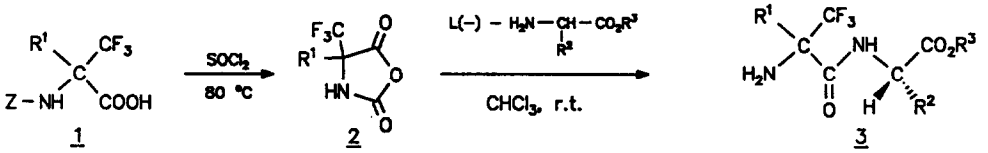
Key Words: α-Trifluoromethyl α-amino acids, Leuchs anhydrides, peptide modification

Abstract: α-Trifluoromethyl substituted α-amino acids can be introduced into the N-terminal position of peptides on carboxyl group activation via Leuchs anhydrides.

One major disadvantage of peptides being used as therapeutic agents is their rapid degradation by peptidases. The replacement of natural amino acids by non natural amino acids is a widely used strategy for stabilization of the scissible peptide bond and for increasing activity by improving the interactions with the receptor site.[2] α,α-Dialkyl α-amino acids are interesting, because of the conformational restrictions they induce which promote the helical structure in peptides.[3] α-Trifluoromethyl α-amino acids (TFM amino acids) are of special interest in this context. The introduction of fluorine in biorelevant systems often leads to reduced metabolism and higher transport rates *in vivo*.[4]

The presence of a trifluoromethyl group in the α-position of the amino acid skeleton strongly influences, electronically and sterically, reactivity of the amino and carboxylic functions (Pk values: Ala pk (CO_2H) = 2.34, pk (NH_2) = 9.87; TFM-Ala pk (CO_2H) = 1.98, pk (NH_2) = 5.91).[5] Some standard carboxylic group activation methods (mixed anhydride, DCC/HOBt) fail to give satisfactory results.

On reaction of Z-TFM α-amino acids **1**[6] with phosphorus oxychloride, phosphorus pentachloride, diphosgene or thionyl chloride at elevated temperatures, 4-trifluoromethyl-1,3-oxazo-



1 **2** **3**

table 1: Characteristic data of compounds **2**:

	R^1	yield	mp (°C)	IR (KBr)	^{19}F-n.m.r. ($CDCl_3$)
2a	$-CH_3$	48 %	56	3300, 1880, 1795	0.4 (s)
2b	$-CH_2-CH(CH_3)_2$	82 %	59	3300, 1870, 1795	1.1 (s)
2c	$-CH_2C_6H_5$	34 %	95	3380, 1865, 1790	- 0.6 (s)
2d	$-C_6H_5$	84 %	90	3260, 1860, 1790	3.4 (s)

table 2: Characteristic data of compounds **3**:

	R^1	R^2	R^3	yield	IR (film)	^{19}F-n.m.r ($CDCl_3$)
3a	$-C_6H_5$	-H	$-CH_2C_6H_5$	92 %	1740, 1680	5.1 (s)
3b	$-CH_2-CH(CH_3)_2$	-H	$-CH_2C_6H_5$	97 %	1740, 1675	1.0 (s)
3c	$-CH_3$	$-CH_2C_6H_5$	$-C(CH_3)_3$	62 %	1735, 1690	0.6/0.7 (s)
3d	$-CH_2-CH(CH_3)_2$	$-CH_2C_6H_5$	$-C(CH_3)_3$	74 %	1730, 1680	0.0/0.1 (s)

lidin-2,5-diones **2** (TFM Leuchs anhydrides)[7] and benzylchloride are formed. Optimum yields of **2** (34 - 84%, table 1) are obtained on heating compounds **1** using thionyl chloride as solvent.

Nucleophilic ring opening reactions of non-fluorinated analogues of **2** require careful pH control to avoid oligopeptide formation.[8] The presence of a trifluoromethyl group at C-4 causes a marked decrease in the nucleophilicity of the amino group and increases steric hindrance.[9] No oligomerization products have been observed in all aminolytic reactions of compounds **2** studied so far. Dipeptides with various TFM amino acids have been synthesized in high yields (table 2) by aminolysis of **2** with amino acid esters.[10] TFM Leuchs anhydrides **2** are therefore the derivatives of choice for the introduction of a wide variety of TFM amino acids into the N-terminal position of a peptide chain. Only a few dipeptides containing DL-trifluoroalanine have hitherto been described.[11]

Further aspects of carboxyl group activation in TFM amino acids and their incorporation into peptides of biological interest will be reported in subsequent publications.

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7. General procedure: 10 mmol of **1** is dissolved in 20 ml thionyl chloride and the mixture is heated at reflux overnight. After evaporation of the thionyl chloride, the crude product is washed 3 times with dry hexane. Compounds **2** are obtained analytically pure, as a colourless crystalline solids.
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10. General procedure: 5 mmol of **2** and 10 mmol of an amino acid ester are dissolved in 20 ml of dry chloroform. The mixture is stirred overnight at r.t. and the solvent is evaporated to dryness under reduced pressure. The crude product **3** is purified by flash-chromatography (SiO_2, eluent: AcOEt), giving **3** as colourless oils.
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