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New types of biorelevant α-functional carboxylic acids and their application for peptide modification

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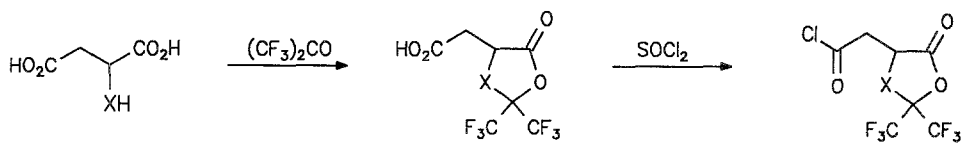
Summary. New methodology for the preparation of L-isoserine and its incorporation into N- and C-terminal position of peptides is described. Furthermore, the new protective group strategy allows regioselective functional group manipulation in multifunctional amino acids like serine and isoserine.

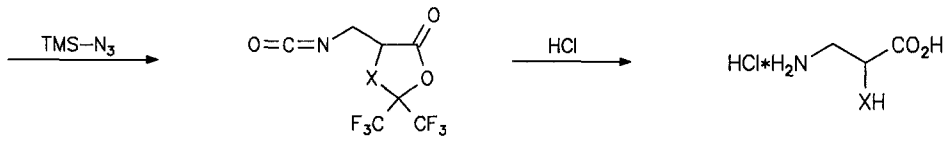
Keywords: Amino acids – Hexafluoroacetone – 2,2-Bis(trifluoromethyl)-1,3-dioxolan-4-ones – 2,2-Bis(trifluoromethyl)-1,3-oxazolidin-5-ones – L-Isoserine – L-Serine – Peptide mimetics

Reaction of α-functional carboxylic acids **1** with hexafluoroacetone (HFA) gives carboxy activated and α-protected carboxylic acid derivatives **2**.

Starting from malic acid as chiral pool precursor or its thio analogue, the isocyanates **4** are obtained on reaction of the acid chloride **3** with trimethylsilyl azide and subsequent Curtius rearrangement of the acyl azide. **4a** can be used for the synthesis of isoserine and its derivates. Via this route, isoserine hydrochloride **5** is formed on hydrolysis of the isocyanate **4a** with 1N HCl at room temperature. The application of this reaction sequence to the synthesis of isocysteine is presently being investigated.



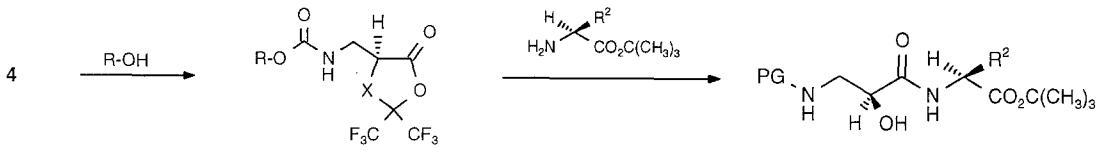
1 X = O,S 2 3



4a X = O
4b X = S

5 X = O

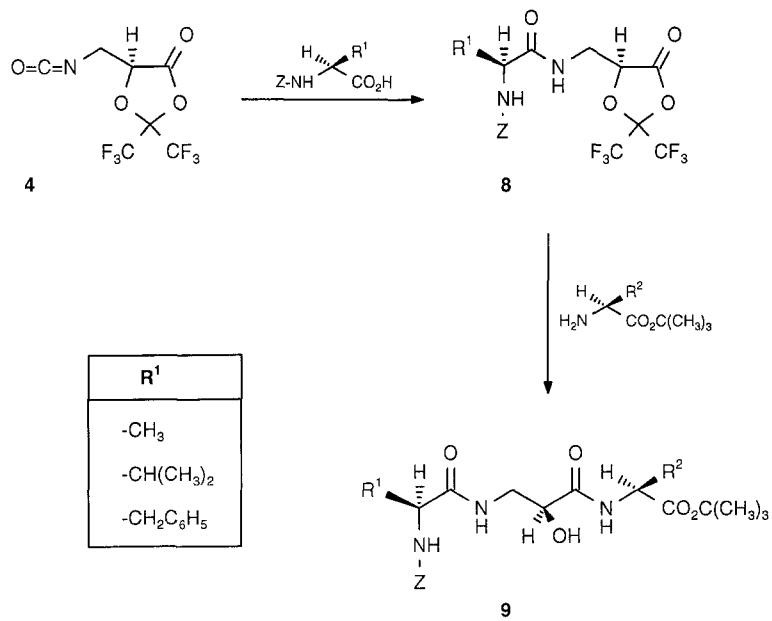
On addition of alcohols, the N-protected isoserine derivative **6** is obtained. Formation of dipeptides **7** can be achieved upon ring opening of the lactone with amino acid esters.



6
X = O

7
PG = BOC, FMOC, Z

Coupling of N-protected amino acids Z-Xaa-OH with the isocyanate **4a** gives fully protected dipeptides **8**. Ring opening of these compounds with amino acid esters provides a preparatively simple route to tripeptides **9** with isoserine in the middle position. It is noteworthy that peptide bond formation and deblocking of the hydroxy group occur in one step (Windeisen, 1993).



4

8

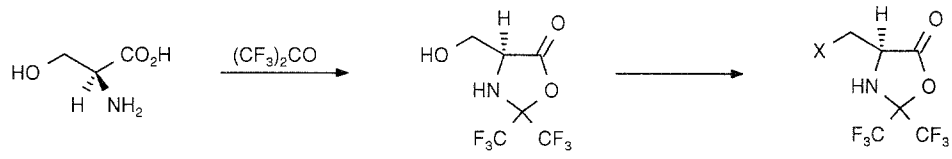
R¹
-CH3
-CH(CH3)2
-CH2C6H5

9

ω-Hydroxy-α-amino acids (e.g. serine **10**) react with hexafluoroacetone to give 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one **11**. The hydroxy group in the

side chain remains unaffected and a variety of regioselective functional group transformations can be applied.

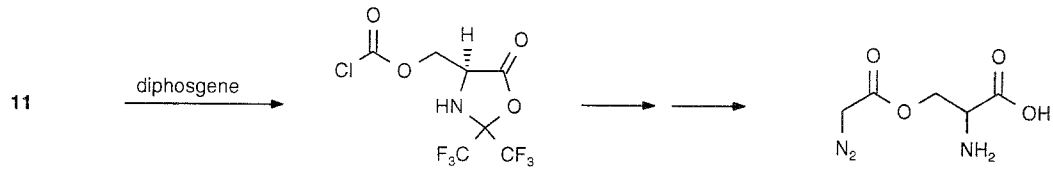
Via this route, e.g. hydroxy/halogen exchange is achieved by reaction of **11** with phosphorpentachloride, phosphorpentabromide or phosphortetraiodide to give the corresponding alanine derivatives **12**.



10 11 12

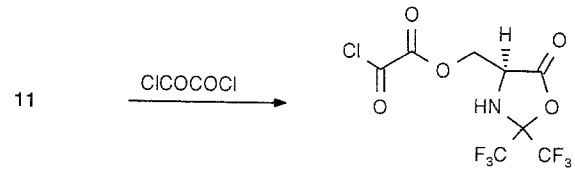
X = Cl, Br, I

The reaction of **11** with diphosgene gives exclusively the open-chain O-chloroformate **13**. This compound represents, inter alia a precursor of azaserine **14**, which exhibits fungicide, bactericide and cytostatic properties.



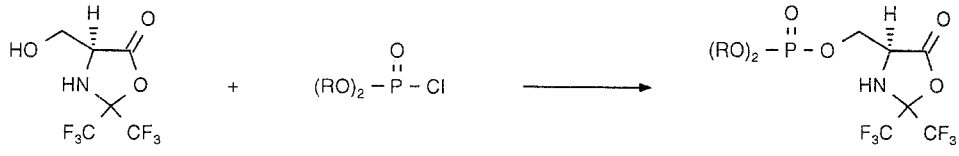
13 14

A variety of biologically active oxalyl derivatives is known among non-proteinogenic amino acids (Thomson et al., 1969). Compound **11** can be transformed directly into the monoester **15** on reaction with oxalylchloride.



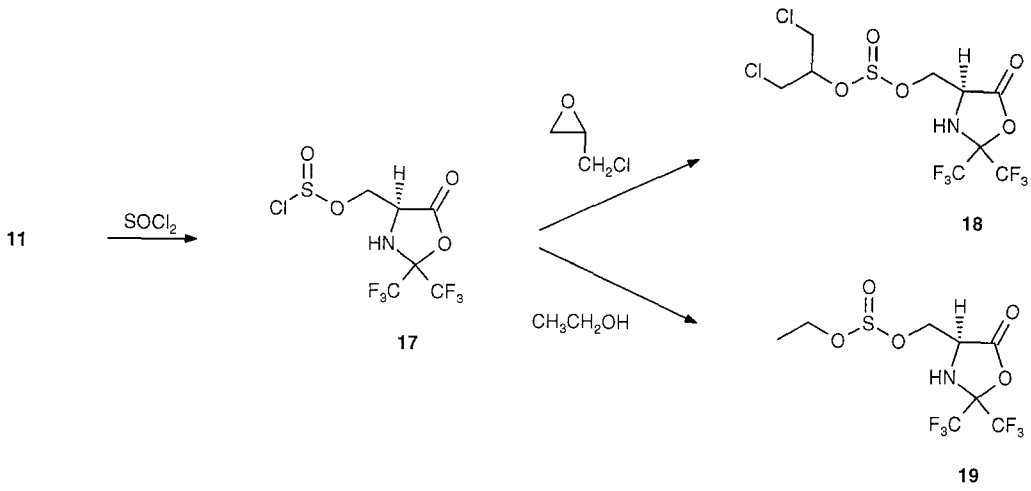
15

Phosphates exhibit enormous importance in biological systems. This class of compounds can be obtained by reaction of **11** with several dialkyl or diaryl chlorophosphates. Deblocking of both functional groups can be achieved in one step on treatment with water/isopropanol at room temperature.



11 16

The reaction of **11** with thionylchloride gives **17**, which can be converted into interesting sulfur containing α-amino acid derivatives of type **18** or **19** (Heistracher, 1989).



References

Heistracher E (1989) Neue Methoden zur Synthese α-funktioneller Carbonsäuren. Dissertation, TU München

Thomson JF, Morris CJ, Smith JK (1969) New naturally occurring amino acids. Annu Rev Biochem 38: 137–158

Windeisen E (1993) Neue Typen biorelevanter α-funktioneller Carbonsäuren und ihre Verwendung zur Modifikation von Peptiden. Dissertation, TU München

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