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Application of hexafluoroacetone as protecting and activating reagent in amino acid and peptide chemistry

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Summary. Using hexafluoroacetone as protecting and activating reagent, multifunctional amino acids like aspartic acid can be functionalized regioselectively. This strategy offers i.a. a two-step synthesis for aspartame and preparatively simple access to multifunctional natural and unnatural amino acids, like 4-oxo-L-amino acids, 5-diazo-4-oxo-L-amino acids, 4-substituted L-proline derivatives and various heterocyclic L-amino acids. On application of this strategy to amino diacetic acid N-substituted glycines become readily available.

Keywords: Amino acids – Aspartame – 3-(2-Furoyl)-L-alanine – 5-Diazo-4-oxo-L-norvaline (DONV) – 5-Hydroxy-4-oxo-L-norvaline (HON) – 3-(Thiazol-4-yl)-L-alanines – *cis*-4-Hydroxy-L-proline – *trans*-4-Fluoro-L-proline

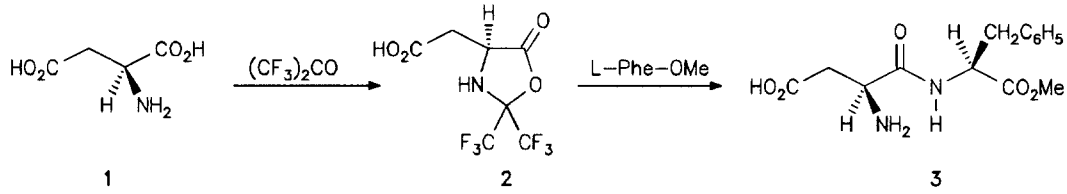
Hexafluoroacetone reacts with α-amino acids to give 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones. This heterocyclization process results in a simultaneous protection of the α-amino and carboxylic group. Furthermore, the carboxylic group is obtained as an activated ester which can be functionalized in various ways on reaction with nucleophiles.

Since additional groups present in the amino acid side chain like $-CO_2H$ or -OH remain unaffected, this method can be applied successfully to regioselective functional group transformations in multifunctional α-amino acids.

In certain cases the application of hexafluoroacetone as protecting and activating reagent is superior to conventional methods. As protection and activation of both functions can be achieved in only one step, the new concept results in a saving of synthetic steps. The oxazolidinone can be cleaved under neutral conditions with water/isopropanol.

Complex protection and activation procedures have been developed for the regioselective functionalization of α-aminodicarboxylic acids (aspartic acid, glutamic acid etc.). The classical synthesis for aspartame requires 7 *steps!*

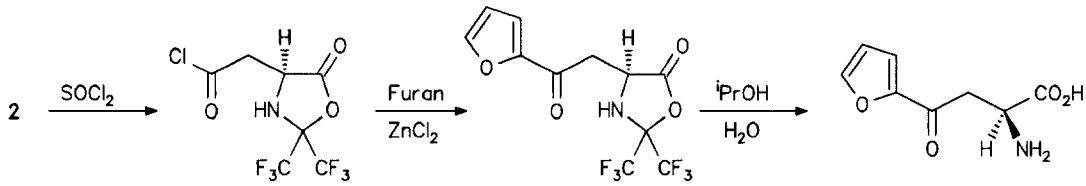
The bis(trifluoromethyl) substituted oxazolidin-5-one **1**, obtained in 86% yield from aspartic acid and hexafluoroacetone, can be transformed directly into aspartame on reaction with L-phenylalanine methylester (72%) (Burger and Rudolph, 1990).



1 2 3

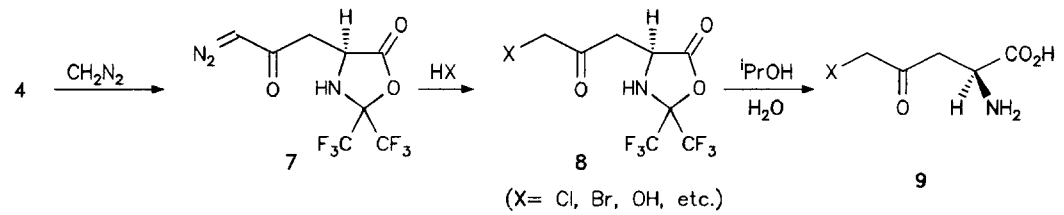
Via this route, a wide variety of α-functionalized aspartic, glutamic, and α-aminoadipic acid derivatives can be synthesized regioselectively. All steps of this reaction sequence occur with complete retention of configuration.

ω-Functionalization can be achieved readily via the acid chloride **4** (Burger et al., 1991a): L-3-(2-furoyl)alanine **6** (*produced by fagopyrum esculentum Moench*) is one of the naturally occuring 4-oxo-amino acids we have synthesized from **4** (Burger et al., 1991b).



4 5 6

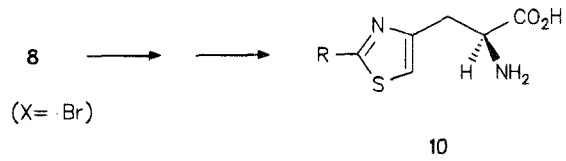
Acid chloride **4** and diazoalkanes react to give derivatives of amino acids **7**, containing a diazofunction in the side chain. Hydrolysis in water/isopropanol at room temperature provides a preparatively simple route to 5-diazo-4-oxo-L-norvaline (DONV) (Weygand et al., 1957). Compounds of type **7** are potential intermediates for the introduction of various functional groups into α-amino acids.



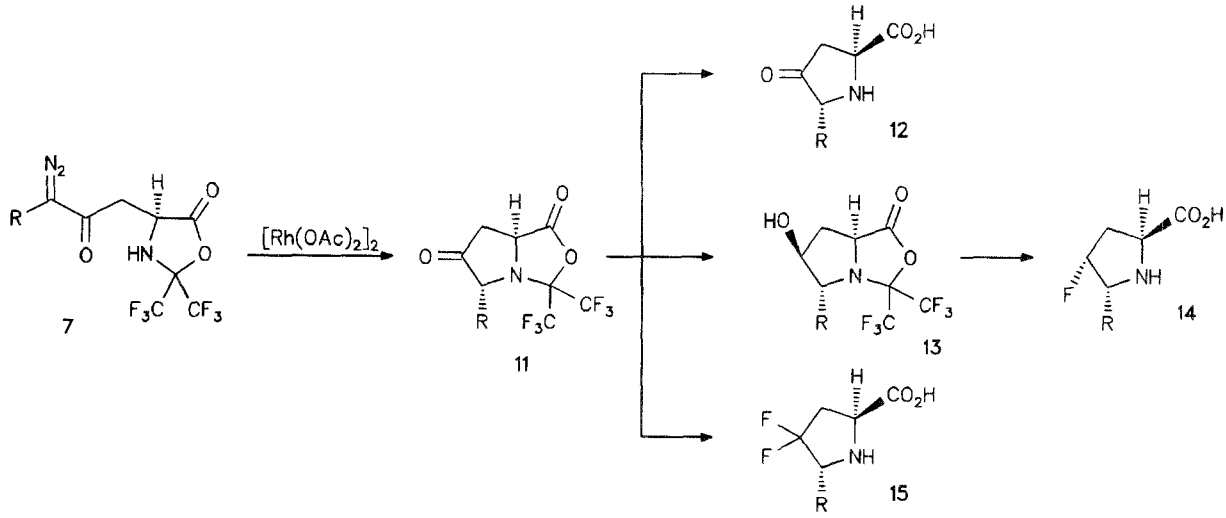
7 8 (X= Cl, Br, OH, etc.) 9

HON **9** (5-hydroxy-4-oxo-L-norvaline, X = OH) is an antibiotic isolated from *streptomyces akiyoshiensis* (Burger et al., 1992a). Amino acids with hetero-

cyclic side chains are obtained from **8** (X = Br) by simple Hantzsch reactions (Burger et al., 1992b).

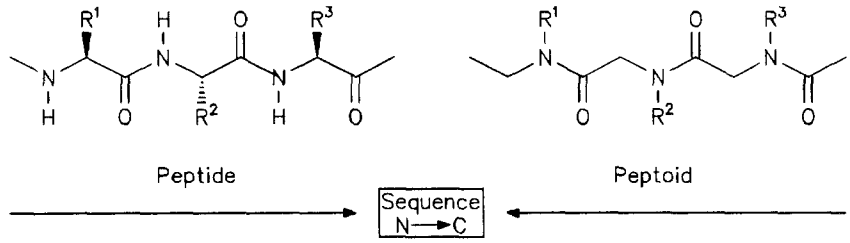


Controlled decomposition of diazo compounds of type **7** with $(Rh(OAc)_2)_2$ results in formation of 4-keto-L-proline derivatives **11** (R = H). Reduction of the latter with $NaBH_3CN$ gives cis-4-hydroxy-L-proline (Burger et al., 1993a). On treatment with DAST, compounds **11** and **13** are transformed into 4,4-difluoro-L-proline **15** (R = H) and trans-4-fluoro-L-proline **14** (R = H), respectively (Burger et al., 1993c). Because of the concave structure of compounds **11**, addition reactions to the carbonyl group occur with high diastereoselectivity.

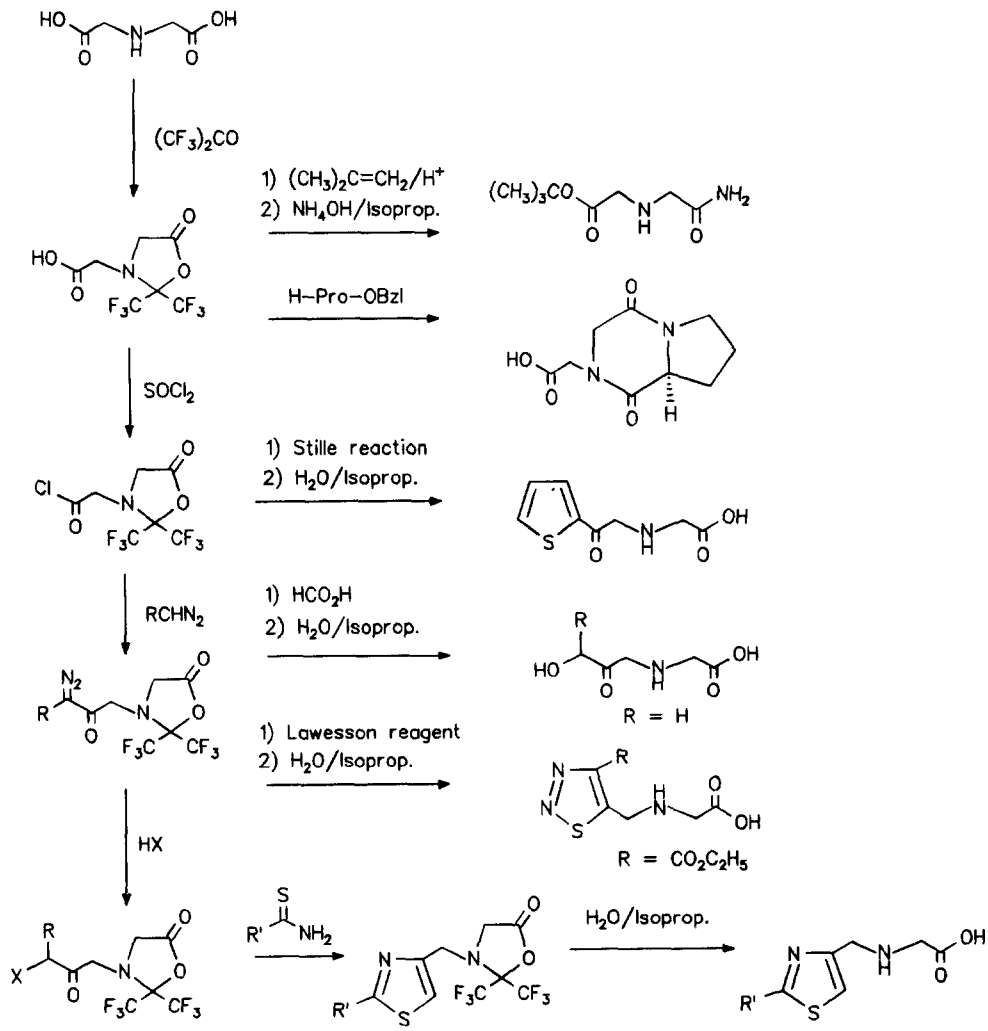


L-Proline is a constituent of a wide variety of peptide hormones (bradykinin, angiotensin, thyroliberin etc.) and peptide drugs (captopril, enalapril etc.). In the tse tse fly, proline is the sole energy source for the flight. The first step of this energy producing process – the oxidation of proline to give 1-pyrroline-5-carboxylic acid – is catalyzed by proline dehydrogenase. Inhibition of this enzyme may be a strategy to control this insect. Therefore, the development of methodology for the stereoselective functionalization of proline is of current interest, *inter alia* for peptide and drug modification, and design of enzyme inhibitors.

Oligomers of N-substituted glycines, named "peptoids", represent a new class of polymers which are not found in nature. They are synthetically accessible and have been shown to possess significant biological activity and proteolytic stability (Simon et al., 1992; Kessler, 1993).



Consequently, the development of new synthetic routes to N-substituted glycines is of current interest. The application of the above strategy to amino diacetic acid offers the possibility to construct the amino acid side chain at the nitrogen atom. N-Substituted glycine derivatives with variable substituent patterns now become readily available in a preparatively simple way (Burger et al., 1993b).



X = Cl, Br ; R = H ; R' = alkyl, aryl

Hydrophobic interactions are known to play an important role in binding of substrates or inhibitors to the active site of an enzyme. Considering this aspect, substitution of hydrogen atoms in the side chain of amino acids and other biorelevant compounds by lipophilic substituents is a promising strategy. The application of hexafluoroacetone as protecting group for amino acids seems to be an interesting concept for the introduction of many functional groups, including fluorine and trifluoromethyl groups into the side chain.

Acknowledgements

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