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Formation of Oxazolines and Thiazolines in Peptides by the Mitsunobu Reaction

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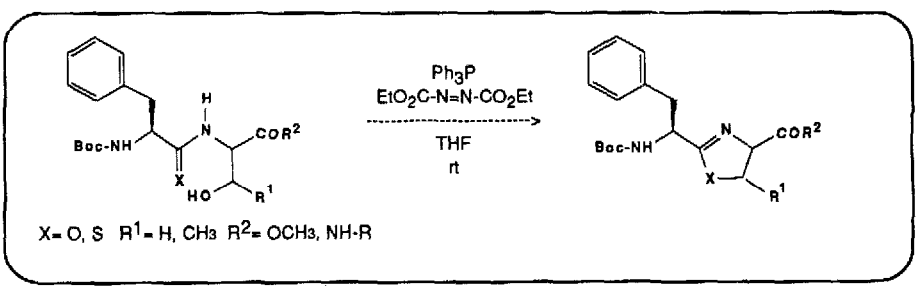
Key Words: β-hydroxy α-amino acids; Peptide-mimics.

Abstract: The Mitsunobu reaction was efficiently used to introduce oxazolines and thiazolines in the peptide backbone. The reaction proceeded from β-hydroxy α-amino acid-containing peptides at room temperature in 58-72% isolated yields.

Oxazolines and thiazolines are found as peptide link modification widespread into metabolites from bacterial and marine invertebrate origin.[1-4] The conformation constraint introduced by these "peptide-mimics" can be used for the design of peptide analogues of pharmacological interest. General synthetic methods to introduce chiral oxazolines and thiazolines in peptide structures need to be developped. Since the oxazoline ring was shown to be acid-sensitive and the thiazoline ring was easily epimerized[5] and opened under basic conditions,[6] these heterocycle systems are preferably introduced at the final stage of the synthesis.[7,8]

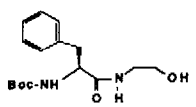
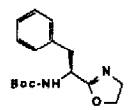
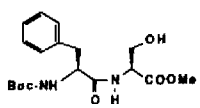
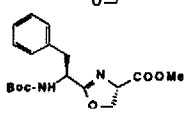
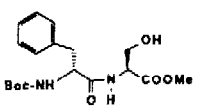
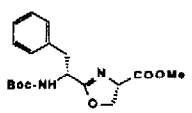
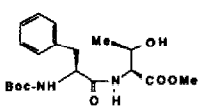
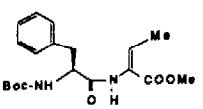
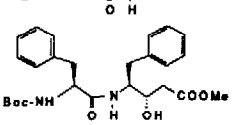
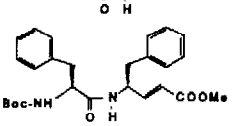
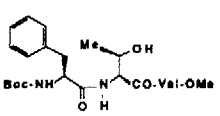
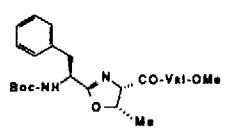
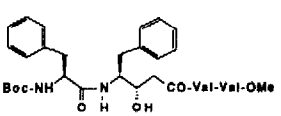
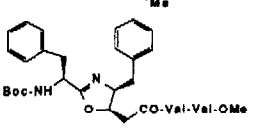
Oxazoline derivatives have been obtained from O-tosyl-N-acyl-hydroxy acid peptides by a β-elimination reaction with Et_3N in THF.[9] Oxazolines were also synthesized from serine-containing peptides by treatment with thionyl chloride followed by silver trifluoromethanesulfonate.[7] On the other hand, a coupling reaction of N-protected imino ethers derived from either serine[10] or cystein[11] can also give the corresponding oxazoline or thiazoline.

We describe herein an efficient method for the construction of oxazoline and thiazoline derivatives from β-hydroxy α-amino acid-containing peptides using the Mitsunobu reaction.[12]



Peptides were synthesized in solution following the Boc strategy with the BOP reagent.[13] The thioamide bond was introduced on silylated hydroxy protected peptides using Lawesson's reagent.[14, 15] Wojciechowska et al. have reported that, under the Mitsunobu reaction, the carbamate-protected serine and threonine methyl esters underwent intramolecular 1,2-dehydration to give the corresponding dehydro-amino acids.[16] Conversely, when the carbamate was replaced by an amide (Table 1: entries 1-3, 6 and 7) the corresponding oxazolines were obtained exclusively and in good yield.

Table 1: Oxazoline formation

Entry	Substrate [a]	Product [b]	Yield (%) [c]	$[\alpha]^{20}_D$ [d]	mp °C
1			62	- 13	76-78
2			61	- 7	81-83
3			60	- 2	87-89
4			63	- 6	98-100
5			60	- 14	146-148
6			59	- 48	122-124
7			58	+ 30	113-115

(a) Reactions performed with 1.5 eq. (entries 1-3) or 2 eq. (entries 4-7) of Ph_3P and DEAD in THF (10ml/mM).

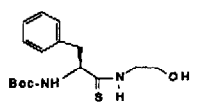
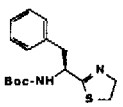
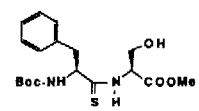
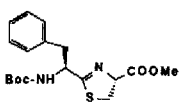
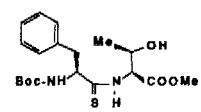
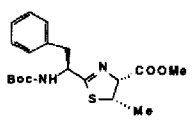
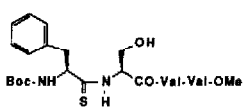
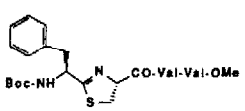
b) The structures were confirmed by ^1H NMR and FAB MS.

(c) All yields refer to pure isolated products.

(d) c=1, MeOH.

This reaction could be explained by the nucleophilicity of the amide function, similarly to the related oxazolone formation during peptide activation.[17] However, the observed 1,2-dehydration of secondary α-amino β-hydroxy esters (Table 1: entries 4 and 5) could result from the acidity of the α-hydrogen. Similarly, the higher nucleophilicity of the thioamide function led to the expected thiazoline formation under Mitsunobu conditions (Table 2).

Table 2: Thiazoline formation

Entry	Substrate [a]	Product [b]	Yield (%) [c]	$[\alpha]^{20}_D$ [d]	mp °C
1			69	+ 2	109-111
2			72	+ 30	98-100
3			65	+ 13	86-88
4			70	+ 15	70-72

(a) Reactions performed with 1 eq. of Ph_3P and DEAD, in THF (10ml/mM).

(b) The structures were confirmed by ^1H NMR and FAB MS.

(c) All yields refer to pure isolated products.

(d) c=1, MeOH.

By starting with both the L- and D- diastereoisomers, Boc-(L)-Phe-Ser-OMe or Boc-(D)-Phe-Ser-OMe (Table 1: entries 2 and 3), no epimerization of the phenylalanine residue had occured. Indeed, the corresponding diastereoisomeric oxazolines could be distinguished by HPLC analysis (column Si Ultrasphere Beckman, 5μ, 4.6 x 250 mm), solvent hexane-ethyl acetate (50-50), retention time: 3.5 min. for entry 2 and 3.9 min. for entry 3.

Assays to extend these modified peptides at the C- and N- terminal are under investigation. This strategy is currently being applied to the synthesis of modified biologically active peptides.

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