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AN INVESTIGATION OF THE MITSUNOBU REACTION IN THE PREPARATION OF PEPTIDE OXAZOLINES, THIAZOLINES, AND AZIRIDINES

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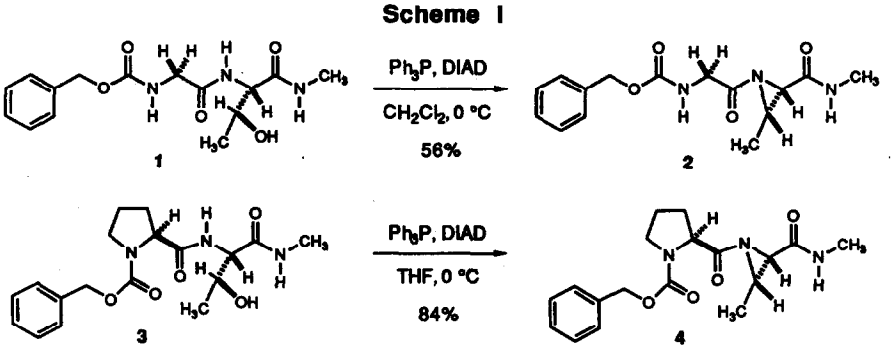
Abstract: The diisopropyl azodicarboxylate-triphenylphosphine mediated cyclization of serine and *allo*-threonine derivatives provides peptide oxazolines, whereas cyclization of threonine containing substrates leads to N-acyl aziridines. In the thiopeptide series, only thiazolines are obtained. The presence of a moderately strong base is necessary for the formation of aziridines from threonine peptides.

A recent communication in this journal[1] concerning the use of the Mitsunobu reaction[2] for the preparation of peptide oxazolines and thiazolines prompts us to disclose our own synthetic and mechanistic investigations of this process. Oxazolines and thiazolines are present in many biologically active natural products,[3] and the use of these heterocyclic units as scaffolding devices in peptide sequences leads to the stabilization of reverse turn secondary structure.[4] Chiral oxazolines are also widely applied as powerful tools in asymmetric synthesis.[5] Among the protocols that were developed for the synthesis of these compounds,[6] cyclization of β-hydroxy amides with Mitsunobu or related systems has been successfully applied to serine-containing peptide segments.[1,7]

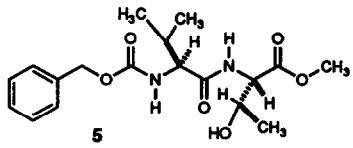
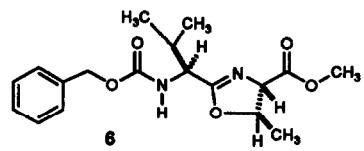
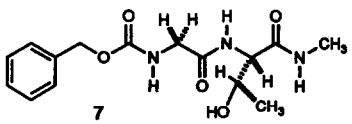
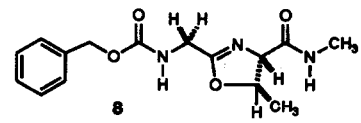
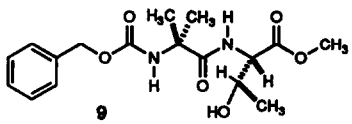
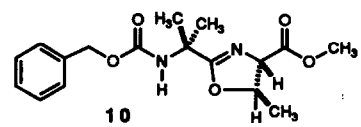
In contrast to the report by Galeotti and co-workers,[1] however, we found that cyclization of threonine derivatives under Mitsunobu conditions results in *aziridine* rather than oxazoline formation (Scheme I). With both Cbz-glycyl-threonine N-methyl amide (**1**) and Cbz-prolyl-threonine N-methyl amide (**3**), cyclization with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine gave the peptide aziridines **2** and **4** in 56% and 84% yield, respectively.[8] No oxazoline was detected.[9] These results are in accord with reports from the laboratories of Bose and Okawa, who isolated only aziridines in addition to β-lactams or dehydroamino acids in the Mitsunobu cyclization of threonine and (2*SR*,3*RS*) phenylserine derivatives.[7c,10] Therefore, the formation of *cis*-oxazolines with threonine containing peptides and related hydroxy amides with secondary alcohol functionalities, as reported by Galeotti et al.,[1] appears highly unlikely under Mitsunobu conditions.

Scheme I



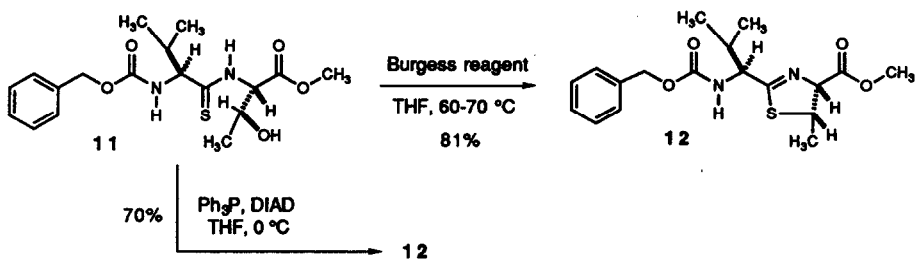
However, the treatment of *allo*-threonine containing peptides with Ph_3P/DIAD yields the corresponding oxazoline derivatives! Our results for the *allo*-threonine series are summarized in Table I. *Trans*-oxazolines were obtained in 64-83% yield, but no aziridine formation was detected. The presence of sterically hindered amino acid residues (Val, Aib) in the peptide sequence had no significant effect on the rate of cyclization or the yield of the isolated heterocycles.

Table I. Reaction of *allo*-threonine derivatives with Mitsunobu reagent.

Peptide	Oxazoline	Yield [%]
 **5**	 **6**	83
 **7**	 **8**	64
 **9**	 **10**	73

With thiopeptide **11**, prepared in 62% yield by treatment of the O-silylated peptide with Lawesson's reagent[11] followed by desilylation, treatment with Burgess reagent (methyl N-(triethylammoniosulfonyl)carbamate)[6a] provides the expected *cis*-thiazoline **12** in 81% yield (Scheme II). Interestingly, Mitsunobu-type cyclization leads now also to thiazoline formation.

Scheme II



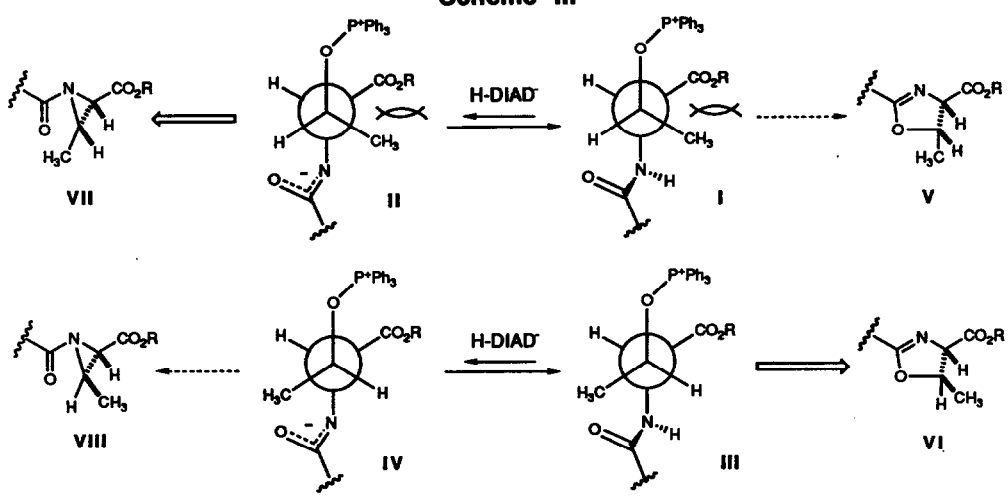
11 → **12**

The significant difference in the reaction pathway of threonine and *allo*-threonine derivatives is unique to the Mitsunobu conditions and is not observed in the analogous cyclizations with Burgess reagent or via sulfonate displacement.[6a,12] Presumably partly responsible for this effect is the destabilizing *gauche* interaction of threonine α-carboxyl and β-methyl groups in conformation **I** leading to *cis*-oxazoline **V** (Scheme III).[13] These substituents are in an antiperiplanar orientation in *allo*-threonine residues, which are therefore smoothly converted into *trans*-oxazolines (**III**→**VI**). Additionally, deprotonation of the amide-NH by the reduced DIAD anion (H-DIAD$^-$) present in the Mitsunobu reaction mixture generates a small amount of anions **II** and **IV**. Both **II** and **IV** are far

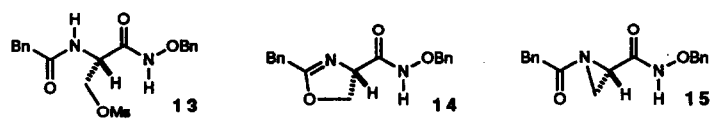
more reactive toward E_i cyclization, and with amide anions an intramolecular alkylation is expected to result predominantly in N-alkylation and aziridine formation.[14] Due to relatively low concentration of H-DIAD$^-$, however, this secondary pathway is only competitive if the rate of the initial cyclization of the neutral amide is reduced.[15] Therefore, aziridines **VII** are observed with threonine peptides via **II**, and oxazolines **VI** are formed from *allo*-threonine residues.[16]

In weakly basic or neutral systems,[17] cyclization can only occur via conformations **I** and **III**, and exclusively oxazolines **V** and **VI** are isolated for both threonine and *allo*-threonine peptides, even though generally higher reaction temperatures are necessary. With thiopeptide **11**, the increased nucleophilicity of the thioamide group results in an enhanced rate of S-alkylation and cyclization to thiazolines in both basic and neutral media.

Scheme III



Our mechanistic model implies that aziridine formation from threonine peptides is only possible in the presence of bases of equal or higher strength than H-DIAD$^-$. To test this hypothesis, the Mitsunobu reaction mixture was buffered by addition of 5 equiv of triethylamine hydrochloride. Whereas oxazoline formation from *allo*-threonine derivatives was slower but otherwise unchanged, aziridine formation from threonines was completely inhibited. On the other hand, the presence of a sufficiently strong base should induce amide deprotonation and thus aziridine formation with other β-hydroxy-α-amino acids and O-leaving groups. This has indeed already been observed by Krook and Miller:[18] Treatment of serine mesylate **13** with $KHCO_3$ in hot dichloroethane led to oxazoline **14**. With KOBu^t in THF, however, aziridine **15** was isolated in 47% yield.



In conclusion, our study demonstrates the specific formation of synthetically useful aziridine and oxazoline derivatives from threonine and *allo*-threonine peptides under Mitsunobu conditions. Cyclization of thiopeptides results in thiazoline formation. Destabilizing *gauche* interactions and the presence of moderate to strong base determine the course of these reactions.[19]

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8. With the corresponding methyl esters, the major products of the Mitsunobu cyclization were the (*Z*)-dehydroamino acid derivatives;[6a] the formation of (*E*)-dehydropeptides[1] was not observed.
9. The aziridine ring structures in **2** and **4** were assigned on the basis of characteristic ^1H and ^{13}C NMR spectral data (**2**): ^1H δ 3.2 (H_α, J_{cis}=7Hz), 2.8 (H_β); ^{13}C δ 181 (OCN), 42, 38 (C_α, C_β). For the corresponding *cis*-oxazoline:[6a] ^1H δ 4.6 (H_α, J_{cis}=10Hz), 5.1 (H_β); ^{13}C δ 170 (OCN), 80, 71 (C_α, C_β).
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15. As a consequence, base-mediated E_2 elimination via α-deprotonation is also increasingly competitive in these substrates: Threonine ester lead exclusively to the corresponding dehydroamino acids, whereas with *allo*-threonine ester only 0-15% of E_2 elimination products are isolated.
16. For a discussion of basicity effects in the Mitsunobu cyclization of peptides to β-lactams, see: (a) Miller, M. J.; Mattingly, P. G. *Tetrahedron* **1983**, *39*, 2563. (b) Ref. 10a.
17. E.g. Burgess conditions,[6a] or elimination of tosylates.[12]
18. Krook, M. A.; Miller, M. J. *J. Org. Chem.* **1985**, *50*, 1126.
19. A typical protocol for the preparation of *trans*-oxazolines from *allo*-threonines with Mitsunobu reagent is as follows: A solution of Cbz-Aib-*a*Thr-OMe (200 mg, 0.56 mmol) and Ph_3P (290 mg, 1.1 mmol) in 10 mL of THF was treated at 0° C dropwise with DIAD (225 µL, 1.1 mmol). After 1 h, the reaction mixture was evaporated. The crude residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:2.3) to yield Cbz-Aib-*trans*-Oxa(5-Me)-OMe (138 mg, 73%) as an oil: IR (neat) 3335, 2971, 1688, 1638, 1537, 1483, 1449, 1372, 1329, 1227, 1190, 1165, 1127, 1051, 1003, 721, 689 cm^{-1}; ^1H NMR δ 7.41-7.24 (m, 5H), 5.73 (br s, 1H), 5.09, 5.05 (AB, 2H, J=12Hz), 4.87-4.83 (m, 1H), 4.26 (d, 1H, J=7Hz), 3.76 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.38 (d, 3H, J=6Hz); ^{13}C NMR δ 172.4, 171.2, 154.5, 136.5, 128.4, 128.0, 79.8, 74.2, 66.3, 52.6, 25.4, 25.1, 20.7; MS (EI) *m/z* (rel. intensity) 334 (M^+, 24), 275 (8), 185 (90), 167 (20), 146 (15), 108 (15), 91 (100), 84 (40), 65 (15); $[\alpha]_D$=85.6° (c=1.8, CH_2Cl_2, 22 °C).

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