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A SHORT, STEREOSPECIFIC SYNTHESIS OF DIHYDROOXAZOLES FROM SERINE AND THREONINE DERIVATIVES

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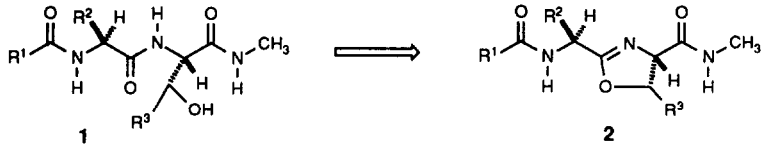
Abstract: Cyclization of serine and threonine derivatives with Burgess reagent provides a one-step, stereospecific access to 4,5-dihydrooxazoles. Noteworthy features of this new methodology include mild experimental conditions, and the absence of β-lactam, aziridine, or dehydroamino acid side products.

As a part of our program for the preparation of peptide mimetics, we were interested in the direct preparation of 4,5-dihydrooxazoles **2** from β-hydroxy-α-amino acids **1** (Scheme I). A considerable number of methods to effect this transformation had been reported previously.[1] However, none of the published procedures appeared of general scope, and the formation of significant amounts of eliminated compounds, β-lactams, and aziridines, were very common side reactions.[2] Indeed, whereas the Mitsunobu-type cyclization[1h,m] of Cbz-glycyl-*allo*-threonine N-methyl amide with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) **3** provided us with the desired dihydrooxazole **4** in 64 % yield, the analogous reaction with Cbz-glycyl-threonine N-methyl amide (**5**) led to the formation of aziridine **6** besides 28% of recovered starting material. Only dehydroamino acid **8**,[3] finally, was isolated in the Mitsunobu reaction of N-benzoyl threonine methyl ester (**7**) (Scheme II).

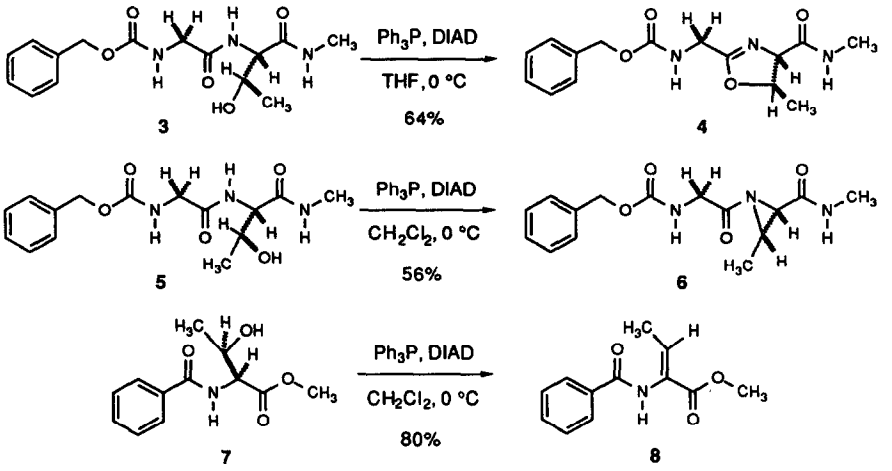
Scheme I



1 **2**

Attempts to induce cyclization with neat or diluted thionyl chloride at 0 °C,[1a,b] or via the corresponding tosylates or mesylates,[1a,3a,d] led to the quantitative recovery of starting material or the formation of the desired dihydrooxazole in <25% overall yield. Therefore, we turned our attention to the investigation of alternative protocols to effect a more selective intramolecular substitution. Among the methods we had tested previously, the cyclization of β-sulfonate derivatives derivatives of threonine and serine led to the least amount of side products, even though the overall yield of the two-step protocol was less than acceptable. Alternatively, direct treatment of the hydroxy amino acid precursors with Burgess reagent[4] (methyl N-(triethylammoniosulfonyl)carbamate) was envisioned to provide both for a reactive alcohol derivative and for an intramolecular base to facilitate the cyclization process.

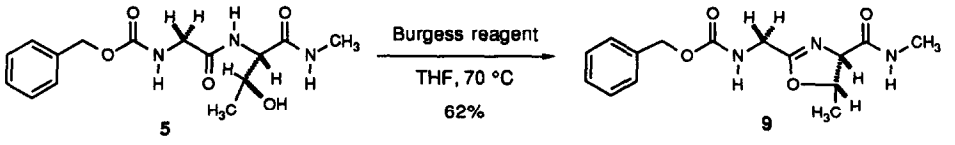
Scheme II



Indeed, treatment of threonine derivative **5** with 1.10 equiv of Burgess reagent at room temperature, followed by a short heating period, led to the isolation of the desired dihydrooxazole as the sole product in this transformation. After a short chromatographic workup, heterocycle **9** was obtained in 62% yield (Scheme III). More significantly, this new methodology proved to to be of very general scope. Table I summarizes our results with a variety of serine and threonine derivatives. Yields range between 62 to 85% and are to a large extent unoptimized. No side products were observed, and TLC examination of the crude reaction mixtures revealed very clean dihydrooxazole formation. Even with methyl esters **7** and **10**, no elimination product was detected.

Burgess reagent has previously been applied for the dehydration of secondary and tertiary alcohols to olefins,[5] and the conversion of amides to nitriles.[6] Primary alcohols are generally transformed into N-alkylated urethanes, presumably because a S_N2 pathway becomes energetically more favorable as compared to the Ei counterpart.[7] In contrast, intramolecular substitution of sulfonate **20** leads to the exclusive formation of heterocycle **21** rather than elimination product with both serine (R^2=H) and threonine (R^2=CH_3) derivatives (Scheme IV). A reaction mechanism involving dehydroamino acid **22** or aziridine **23** appears highly unlikely. Neither 5-endo-trig cyclization[8] of **22** nor rearrangement of **23** to **21** would be expected to occur rapidly with overall retention at the α-carbon and inversion of configuration at the β-carbon under these reaction conditions.[9]

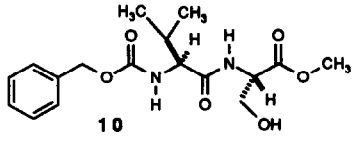
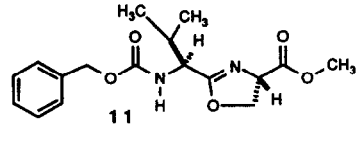
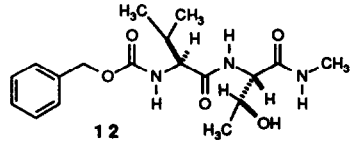
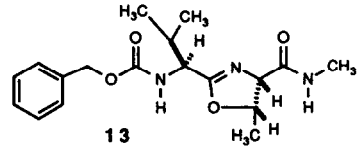
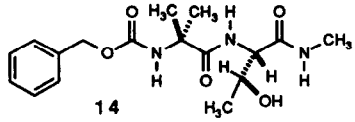
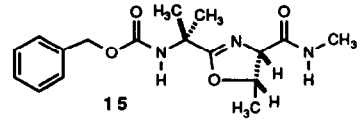
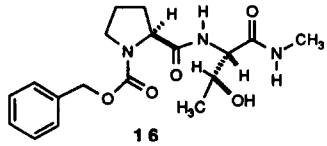
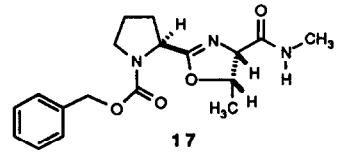
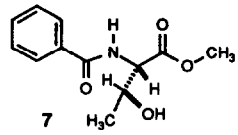
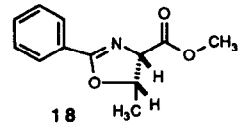
Scheme III



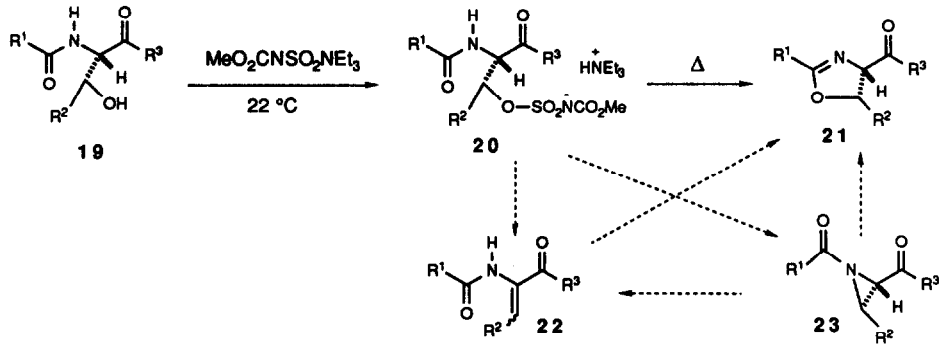
Dihydrooxazoles are important as synthetic intermediates[10] and form an integral part of many biologically active natural products.[11] Generally, tedious multi-step sequences have been used for the preparation of these heterocycles.[12] Cyclization of hydroxy amino acids with Burgess reagent provides a new, single-step approach for the synthesis of dihydrooxazoles from serine and

threonine derivatives. The absence of β-lactam, dehydroamino acid, or azirine side products, and the mild, neutral reaction conditions allow the successful application of this protocol even with highly functionalized, easily epimerizable substrates.

Table I. Reaction of threonine and serine derivatives with Burgess reagent.[13,14,15]

Hydroxy amide	Dihydrooxazole	Yield [%]
 10	 11	74
 12	 13	73
 14	 15	64
 16	 17	66
 7	 18	85

Scheme IV



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3. According to NMR analysis, **8** was formed as a single isomer and assigned the (Z)-stereochemistry, in accordance to a trans E_2 elimination; cf. (a) Srinivasan, A.; Stephenson, R. W.; Olsen, R. K. *J. Org. Chem.* **1977**, *42*, 2256. (b) Ogura, H.; Sato, O.; Takeda, K. *Tetrahedron Lett.* **1981**, *22*, 4817.
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13. Hydroxy amides were synthesized by dicyclohexylcarbodiimide (DCC) or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDCI) coupling of the N-Cbz-protected amino acid with the appropriate amino ester or methyl amide in THF.
14. Yields refer to purified and spectroscopically fully characterized (300 MHz ^{1}H NMR, 75 MHZ ^{13}C NMR, MS, HRMS, IR, $[\alpha]_D$) compounds.
15. A typical protocol for the cyclization with Burgess reagent is as follows: A solution of 0.16 mmol of the dipeptide in 3 mL of dry THF in a Pyrex tube was flushed with nitrogen and 0.176 mmol (1.1 eq.) of the Burgess reagent was added in small portions. The tube was capped, and the reaction mixture was heated at 70°C in an oil bath for 0.7-2.5 h. The solution was allowed to cool to room temperature and evaporated onto silica gel. Chromatographic purification of the residue led to the isolation of the desired 4,5-dihydrooxazoles in 62-85% yield.

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