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THIOLYSIS OF OXAZOLINES: A NEW, SELECTIVE METHOD FOR THE DIRECT CONVERSION OF PEPTIDE OXAZOLINES INTO THIAZOLINES

Peter Wipf*,[1], Chris P. Miller, Srikanth Venkatraman and Paul C. Fritch

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, U.S.A.

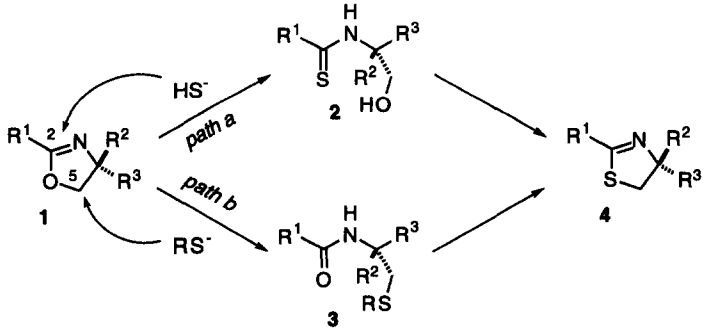
Abstract: A direct oxazoline→thiazoline conversion can be realized by thiolysis of oxazolines with H_2S in methanol/triethylamine, followed by cyclodehydration with Burgess reagent. This protocol is high-yielding, chemoselective, and essentially free of racemization for C(5)-unsubstituted and *trans*-4,5-disubstituted peptide oxazolines. Thioamide intermediates are obtained regioselectively, thus the thiolysis of oxazolines offers an alternative to the thiation of peptides with Lawesson's reagent.

Biosynthetic cyclodehydration of serine, threonine, and cysteine amino acid residues leads to oxazolines and thiazolines. These five-membered heterocycles are a common feature of many biologically active marine natural products and are especially abundant in the *Lissoclinum* family of marine cyclopeptides.[2] A wide range of protocols is available for the oxidation of these heterocycles to the aromatic oxazoles and thiazoles which are popular pharmacophores in medicinal chemistry. Oxazolines and thiazolines are also recently attracting considerable attention as chiral ligands in transition metal catalyzed asymmetric synthesis.[3]

Oxazolines are synthetically more generally accessible than the corresponding thiazolines but are of lower solvolytic stability.[3e,4,5] For structure-activity studies as well as for natural products synthesis, a direct oxazoline→thiazoline conversion would be highly advantageous. In this paper, we present a stereoselective two-step protocol for this transformation.

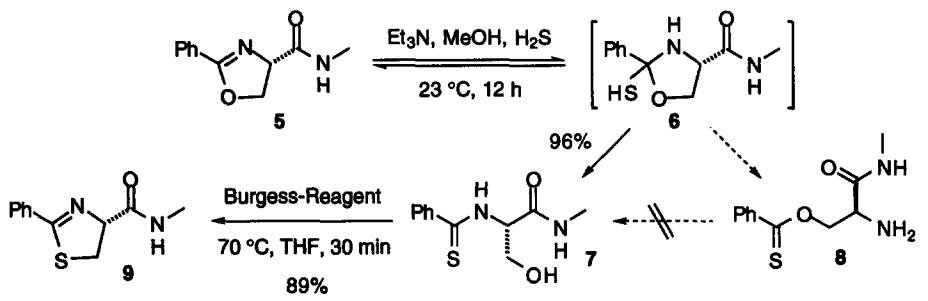
Ring-opening of oxazolines **1** occurs predominantly at C(2) under moderately basic or acidic conditions in protic solvents (Scheme 1, path a).[5b] With strong nucleophiles in aprotic media, irreversible attack at C(5) is favored (path b).[6] Both pathways can be utilized to convert oxazolines into thiazolines,[7] since thioamides **2**[4a] and cysteinamides **3**[4b] can be cyclodehydrated to thiazolines **4**. We chose to further investigate path a, since thiolysis[6a] at C(2) proved to be less dependent on the degree of substitution at C(5).[7]

Scheme 1



Treatment of model oxazoline **5** with a saturated solution of H_2S in methanol at room temperature led to the formation of thioamide **7**, probably via reversible formation of orthoamide **6** (Scheme 2). The presence of triethylamine to buffer the reaction medium was crucial for the success of this transformation; under more acidic conditions the yield of thioamide **7** dropped significantly, possibly due to an alternative breakdown of intermediate **6** to give thionoester **8**.[8] With methanol/triethylamine mixtures ranging from 10:1 to 1:1, the desired thioamide **7** was isolated in quantitative yield. Subsequent cyclodehydration of **7** with Burgess reagent[4a] ($MeO_2CNSO_2NEt_3$) provided thiazoline **9** in 89% yield and established the viability of this novel oxazoline→thiazoline conversion strategy.

Scheme 2

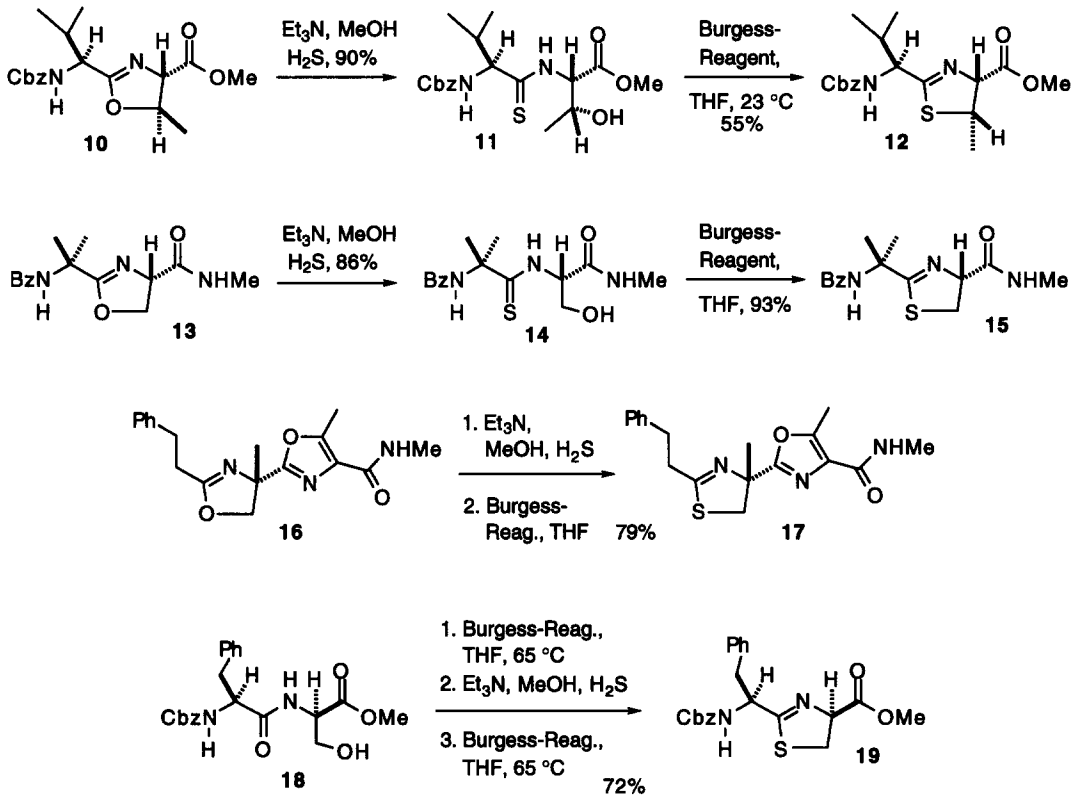


The scope of this process proved to be quite general.[9] The *N*-Cbz-protected valine-threonine oxazoline **10** was converted in 50% overall yield via the thioamide **11** to the dipeptide thiazoline **12** (Scheme 3). Steric hindrance at the C(2) exocyclic position as well as at C(4) and C(5) was tolerated to a very high extent even with substrates containing quarternary carbons. The α-methylalanine and α-methylserine derived thiazolines **15** and **17** were isolated in overall yields of 80% and 79%, respectively. A wide range of functional groups is compatible with the reaction conditions. Starting from dipeptide ester **18**, thiazoline **19** was accessible in 72% yield by Burgess cyclization,[5a] thiolysis, and a second cyclodehydration with Burgess reagent. Racemization at the labile amino acid α-carbons was consistently <3%, as determined by ^1H NMR comparisons of a series of epimers of **18** and **19**.[10]

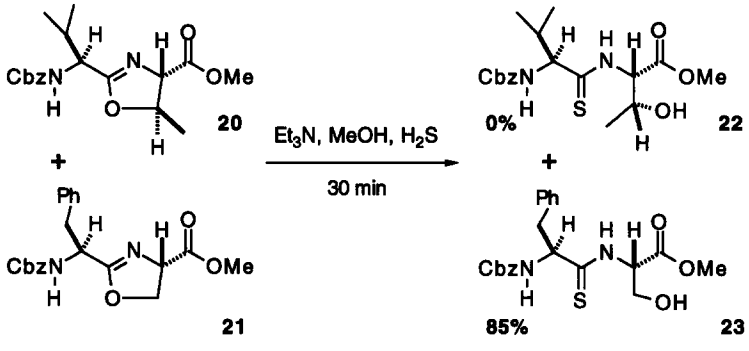
The formation of thioamides such as **11** and **14** demonstrates that this methodology is also applicable for the regiospecific preparation of ψ[CSNH] peptide bond isosteres. Especially with sterically hindered substrates, these peptidase-resistant peptide mimetics are difficult to prepare by direct amide thionation. Treatment of the *N*-benzoyl-Aib-Ser-NHMe precursor of oxazoline **13** with Lawesson reagent, for example, would lead to a mixture of thioamides and require a protection of the side-chain hydroxyl group.[11] In contrast, thiolytic cleavage of peptide oxazolines reliably leads to thioamide formation next to the β-hydroxy-α-amino acid residue.

Thiolysis of threonine-derived oxazolines in MeOH/Et_3N mixtures requires considerably longer exposure to H_2S than thiolysis of C(5)-unsubstituted serine-derived oxazolines (1-3 days vs. 1-3 hours). This can be used for the chemoselective conversion of serine-oxazolines to thioamides (and, subsequently, to thiazolines) in the presence of threonine-oxazolines (Scheme 4). Thiolysis of a 1:1 mixture of **20** and **21** for 30 min at room temperature led to the isolation of 85% of thioamide **23**. Oxazoline **20** was recovered quantitatively from the reaction mixture.

Scheme 3



Scheme 4



An application of this protocol for the synthesis of both oxazoline- and thiazoline-containing *Lissoclinum* peptides and other marine natural products will be reported in due course.

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9. The preparation of 5-methyl-2-((4*R*)-4-methyl-2-phenethyl-4,5-dihydro-thiazol-4-yl)-oxazole-4-carboxylic acid methyl amide (17) is representative: A solution of 70 mg (0.22 mmol) of **16** in 2 mL of MeOH/Et_3N (2:1) was saturated with H_2S and stirred at room temperature for 3 d. CAUTION! H_2S is a toxic gas and has to be handled in a well-vented hood! Excess H_2S, MeOH and Et_3N were removed by evaporation in vacuo through a solution of bleach, and the residue was chromatographed on SiO_2 (EtOAc/Hexanes, 4:1) to yield 83 mg of 2-[(1*S*)-2-hydroxy-1-methyl-1-(3-phenyl-thiopropionylamino)-ethyl]-5-methyl-oxazole-4-carboxylic acid methylamide that was directly used for the next step: R_f 0.4 (EtOAc).

   A solution of 83 mg (0.22 mmol) of thioamide in 2.0 mL of THF was treated with 170 mg (0.67 mmol) of Burgess reagent and stirred at room temperature for 3.5 h. The reaction mixture was quenched with 0.5 mL of MeOH, concentrated in vacuo and chromatographed on SiO_2 (EtOAc/Hexanes, 3:2) to yield 55 mg (79%) of **17**: R_f 0.5 (EtOAc); $[\alpha]_D$ 40.2° (*c* 0.73, $CHCl_3$, 25 °C); IR (neat) 1653, 1619, 1561, 1549, 1518, 1489, 1441, 1401, 1368, 1327, 1186, 1142, 1102, 994, 741 cm^{-1}; ^1H NMR δ 7.37-7.20 (m, 5 H), 6.94 (bs, 1 H) 3.26, 3.95 (AB, 2 H, J = 11.2 Hz), 3.02-2.94 (m, 5 H), 2.89-2.83 (m, 2 H), 2.65 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR δ 171.3, 162.5, 162.4, 153.4, 140.1, 129.1, 128.5, 128.4, 79.5, 42.7, 36.0, 33.7, 25.6, 24.7, 11.8; MS (EI) *m/z* (relative intensity) 343 (M^+, 100), 328 (10), 310 (15), 297 (7), 212 (43), 179 (70), 162 (10), 153 (25), 137 (10), 123 (10), 112 (8), 105 (10), 98 (20), 91(75), 69 (25), 57 (75); HRMS (EI) *m/z* calcd for $C_{18}H_{21}N_3O_2S$: 343.1354, found 343.1322.
10. Recently, however, we have detected significant epimerization at C(4) of a *cis*-4,5-disubstituted oxazoline under prolonged exposure to thiolysis reaction conditions.
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