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Further Studies on Oxazoline and Thiazoline Oxidations. A Reliable Route to Chiral Oxazoles and Thiazoles

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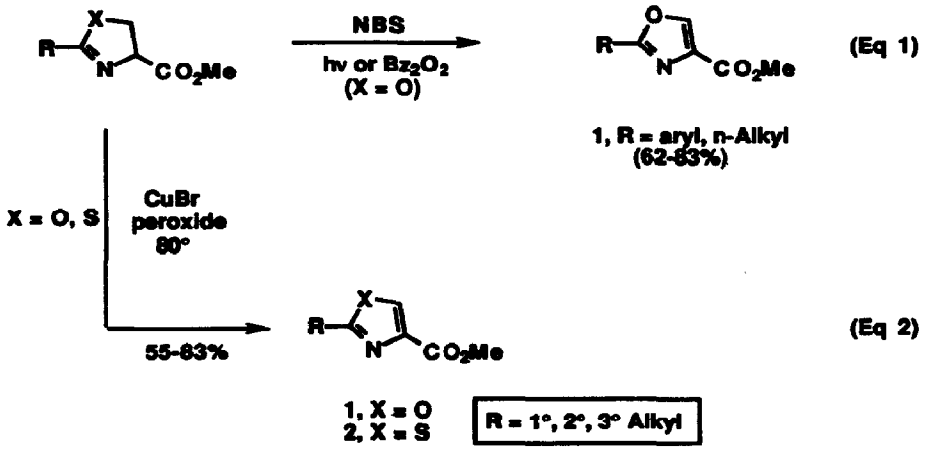
Summary: *Oxazoles and thiazoles containing amino groups and stereocenters at the 2-(α) position are reached without racemization during aromatization.*

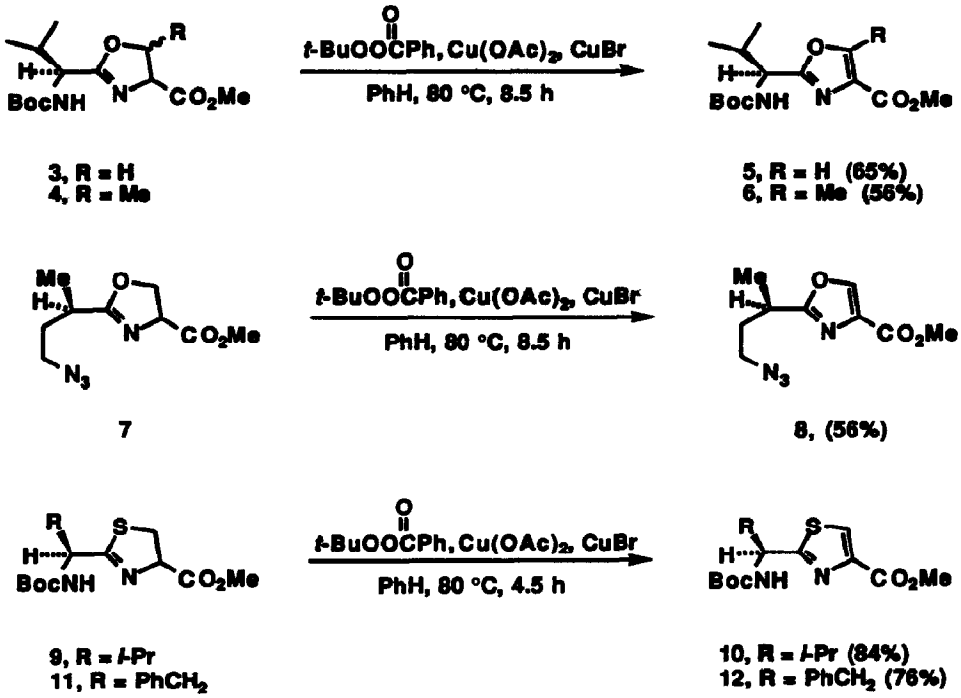
The presence of oxazoles and thiazoles as masked dehydropeptides in a number of important, naturally occurring molecules, continues to fuel intensive research regarding their acquisition.[1] In a recent report[2] we described two methods (eq 1, 2) to oxidize a variety of 2-alkyl and 2-aryl oxazolines or thiazolines to their dehydro derivatives **1** and **2**, respectively. We found,



however, that the NBS-hv route was only successful if the 2-substituent was a primary alkyl or aryl group. Radical halogenation occurred if the 2-substituent was tertiary at the α-position giving rise to mainly brominated product. This limitation was nicely avoided when the oxidations were

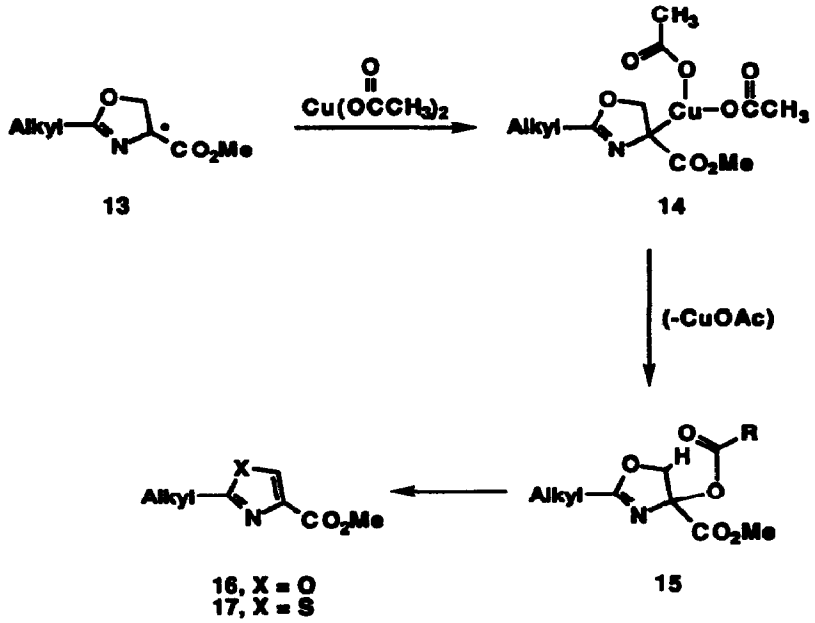
performed (eq 2) using a copper-mediated peroxide process, introduced years ago by Kharasch and Sosnovsky.[3] This route to 1 and 2 did not limit the nature of the side chain to aryl or n-alkyl, but also allowed 2 ° or 3 ° hydrogens to survive at the α-position. We now report further progress in the oxidative route to 1,3-oxazoles and thiazoles which bear the requisite functionality for incorporation into a variety of natural products. Thus, chirality and sensitive amino and azido functions have been shown to survive this oxidation, with a slight modification in procedure.

The enantiomerically pure (chiral hplc) oxazolines and thiazolines 3,[4] 4,[5] 7,[1h] 9,[6] were subjected to the copper (I) initiated decomposition of *t*-butyl perbenzoate as described in our earlier report.[2] We found that the oxidation to oxazoles 5, 6, and 7 did indeed occur but the



reaction proceeded in lower yields (25-30%) and required longer time than the simple alkyl or aryl substituted oxazolines in equation 2. In an effort to enhance the process, we felt that addition of a Cu (II) species (e.g. $Cu(OAc)_2$) may serve to increase the solubility of the oxazoline in the benzene

solution and also allow for a higher copper ion concentration which could lead to a faster rate of oxidation and/or ligand transfer[7] between the presumed radical 13 and the Cu (II) salts. We presently assume this leads to the Cu (III) species 14 *via* oxidative addition and then reductively



eliminates to the acyloxy oxazoline 15. Syn elimination, on warming, would then produce the oxazole 16 (or thiazole, 17). Evidence for this pathway was acquired when the oxidation was performed using the equivalent ratios: CuBr (1.1), $Cu(OAc)_2$ (1.1), and *t*-butyl perbenzoate (1.5) in refluxing benzene for the time specified in the schemes. In this manner, the yields of oxazoles and thiazoles increased to 55-65% and 76-84%, respectively. The reaction times were also significantly decreased to 4-8 h (*vs.* 12-14 h).[8] Additional support for the mechanism above was obtained when we isolated (in 8% yield) the adduct ester 15 (R = Ph) from an oxidation run that was performed at 60 °C in benzene rather than at reflux. Presumably, the benzoate ester eliminates somewhat slower than acetate, thus allowing for its isolation. The structure of the

benzoate **15**, derived from the valine derivative **3** (Alkyl = side chain in **3**), was supported by ^{1}H, ^{13}C, DEPT 135, and 90 spectra; subsequent warming of the solution gave the oxazole **5**, as expected.

In summary, we have found a method to reliably and reproducibly oxidize chiral functionalized oxazolines, and thiazolines, on a scale, thus far, between 20 mg and 350 mg, which should smooth the way for continuing efforts on total synthesis of natural products containing these systems.

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8. All compounds gave completely satisfactory analytical data and comparison with authentic samples was also used to verify structure and purity. Enantiomeric purity of **5**, **10**, **12** was further supported by chiral hplc analyses using a Chiracel OD column and elution with i-PrOH-Hexane (5:95).

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