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STEREOSELECTIVE CONVERSION OF ALLYLIC ALCOHOLS TO N-ACYL-trans-4,5-DIALKYLOXAZOLIDINES.[1]

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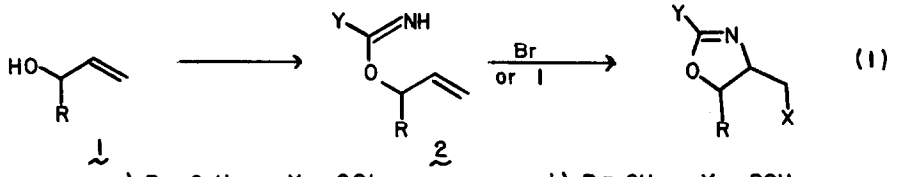
Summary: The stereoselective synthesis of N-acyl-trans-4,5-dialkyloxazolidines (precursors to threo-β-amino alcohols) through a procedure involving amidomethylation of a 2° allylic alcohol followed by mercuric-ion inititated cyclofunctionalization is reported.

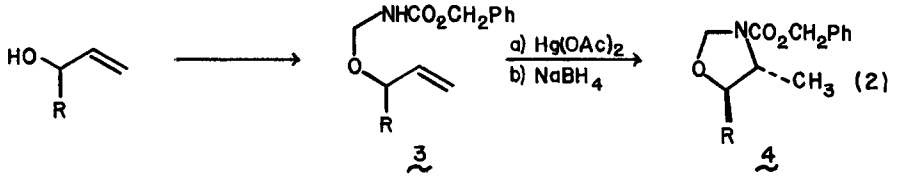
Recent reports on the use of cyclofunctionalization reactions for the conversion of allylic alcohols to vicinal amino alcohols[2] prompt the report of our initial studies in this area. Previous investigations in this area have involved conversion of the allylic alcohols to imidate derivatives and cyclofunctionalization with halogen electrophiles (eq. 1).[2] The cyclizations involving 2-cyclohexenol derivatives gave, as expected, only cis-fused products.[2b,2c] However, the cyclization of acyclic allylic alcohol derivative **2b** gave a 1.4:1 ratio of cis and trans products,[2c] while the cyclization of derivative **2a** was reported to give a 75:25 ratio of isomers with no indication of which product predominated.[2a] We have found that mercuric ion-initiated cyclizations of acylaminomethyl ether derivatives **3** of acyclic allylic alcohols proceed stereoselectively to form trans 4,5-disubstituted oxazolidine derivatives (eq. 2). Since oxazolidines are readily hydrolyzed,[3] these studies illustrate a new method for stereoselective synthesis of acyclic threo-β-amino alcohols from allylic alcohols (**1** --> **5**).



(1)

1 **2**

a) R = C_5H_{11}, Y = CCl_3 b) R = CH_3, Y = SCH_3



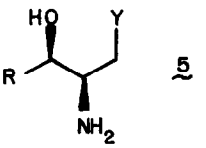
(2)

3 **4**

a) R = CH_3, b) R = $CH(CH_3)_2$, c) R = C_6H_5

$HOCH_2NHCO_2CH_2Ph$

6



5

The ether derivatives **3** were prepared by the reaction of allylic alcohols **1** with N-hydroxymethyl benzylcarbamate (**6**) in CH_2Cl_2 or ether using p-toluenesulfonic acid as catalyst.[4,5] In cases involving amidomethylation of inexpensive alcohols, an excess of the alcohol was used, but more complex alcohols can be converted to these derivatives in good yield[6] using the alcohol as the limiting reagent. Cyclizations of the carbamoyl ethers **3** were not as facile as the previously studied cyclizations of simple δ-alkenyl carbamates to form pyrrolidine derivatives.[7] We found that cyclization proceeded more readily in acetonitrile than in tetrahydrofuran, which had been used in our previous work.[7] Thus, treatment of ether **3** with 1.25-2.0 equivalents of mercuric acetate in acetonitrile for a period of twelve hours followed by the addition of saturated sodium acetate and sodium borohydride gave the disubstituted oxazolidine derivatives **4** in good yield.[4,6] The dimethyl system **4a** was found (^{1}H NMR and HPLC) to contain 25% of the corresponding cis isomer, while the trans isomers **4b** and **4c** were formed with very high stereoselectivity (greater than 95:5 by NMR and HPLC). The assignment of stereochemistry can be made readily by examination of the signals for the methyl groups in the ^{13}C NMR spectra of **4**.[8]

Studies on the application of this method to synthesis of polyfunctional natural products are in progress.[11]

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3. Goldberg, E. P.; Nace, H. R. J. Am. Chem. Soc. **1955** 77, 359-361.
4. Spectral data (IR, ^{1}H NMR, ^{13}C NMR, HRMS) consistent with assigned structures have been obtained for all new compounds.
5. Compound **6** was prepared in 90% yield (mp 86.5-87.5 °C) by the well-documented reaction of amides with formalin: (a) Zaug, H. E.; Martin, W. B. Organic Reactions **1965**, 14, 52. (b) Hellman, H. Ang. Chem. **1957**, 69, 463.
6. Yields have not been optimized for these reactions. Typical yields for formation of **3**: 60-80%. Typical yields for cyclization of **3**: 60-90%.
7. Harding, K. E.; Burks, S. R. J. Org. Chem. **1981**, 46, 3920-3922.
8. The signal for the methyl groups of **4a** appear in the ^{13}C NMR spectrum ($CDCl_3$) at 17.3 ppm, while the signal for the minor isomer appears at 14.1 ppm. The significant upfield shift of the signal for the minor isomer is consistent only with its assignment as the cis isomer.[9] The signals (^{13}C NMR, $CDCl_3$) for the methyl groups of **4b** and **4c** at 18.2 and 17.2 ppm, respectively, are consistent only with their assignment as trans isomers.[9] In addition, the appearance in the ^{1}H NMR spectrum of the signal for the methyl group of **4c** at 1.35 ppm with a small signal (≈3%) at 0.8 ppm confirms the stereochemical assignment for **4c**.[10]
9. Cf. inter alia: (a) Stothers, J. B.; Tan, C. T. Can. J. Chem. **1974**, 52, 308-314. (b) Christl, M.; Reich, H. J.; Roberts, J. D. J. Am. Chem. Soc. **1971**, 93, 3463-3468. (c) Ambuehl, J.; Pregosin, P. S.; Venanzi, L. M.; Consiglio, G.; Bachechi, F.; Zambonelli, L. J. Organomet. Chem. **1979**, 181, 255-269. (d) Parker, K. A.; O'Fee, R. J. Am. Chem. Soc. **1983**, 105, 654-655, footnote 7.
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