HETEROCYCLES, Vol. 4, No. 10, 1976

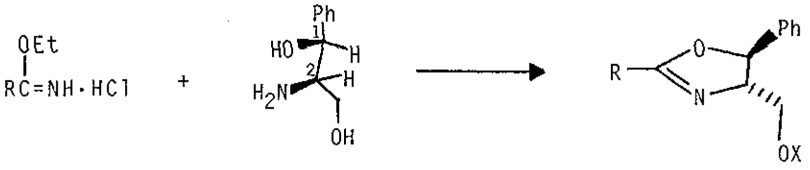
OXAZOLINES XXIV: CHIRAL OXAZOLINES AND THIAZOLINES FROM L-SERINE AND L-CYSTEINE. THEIR POTENTIAL USE IN ASYMMETRIC SYNTHESIS.

A. I. Meyers* and Charles E. Whitten

(Department of Chemistry, Colorado State University, Fort Collins, Colorado)

Summary. The synthesis of S(+)-3-phenylheptanoic acid in >90% ee using a chiral oxazoline derived from L-serine is described.

The utility of chiral oxazolines 2, 3 in asymmetric synthesis has been reported[1] from this laboratory. These reagents

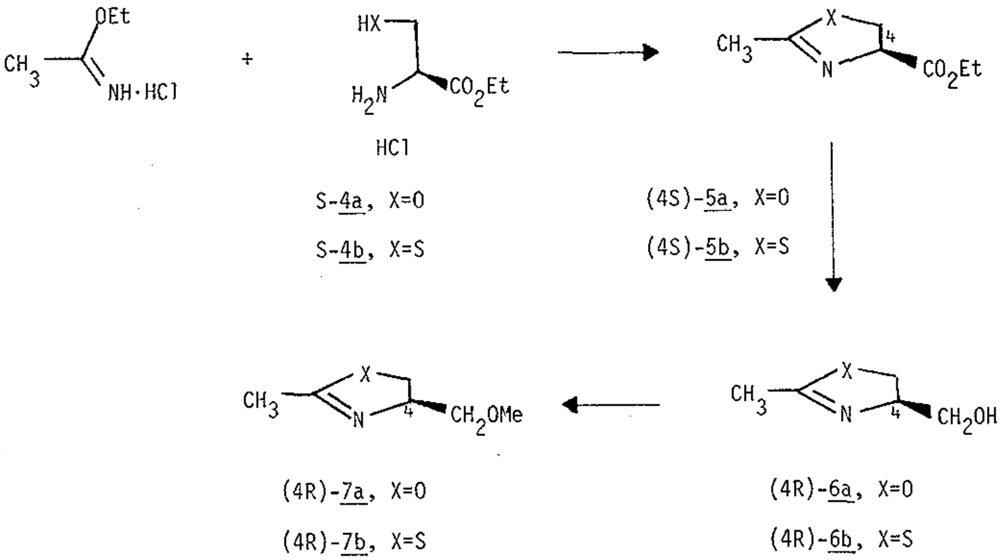


(R = Me, Et, $PhCH_2$) (1S,2S)-1 (4S,5S)-2 X = OH

(4S,5S)-3 X = OMe

were prepared using the aminodiol 1 and various imidates followed by methylation of the hydroxyoxazoline 2. In view of the uncertainty surrounding the continued availability of 1* we have investigated alternative routes to chiral oxazolines from more reliable sources. We now report that the related systems 7a and 7b have been prepared from the naturally occurring amino acids, L-serine and L-cysteine with the former evaluated as a vehicle in the asymmetric synthesis of 3-phenylheptanoic acid, 11.

Treatment of L(S)-serine ester hydrochloride 4a ($[\alpha]_D$ -5.13°) with ethyl acetimidate hydrochloride (2.0 eqiv.



S-4a, X=O

S-4b, X=S

(4S)-5a, X=O

(4S)-5b, X=S

(4R)-7a, X=O

(4R)-7b, X=S

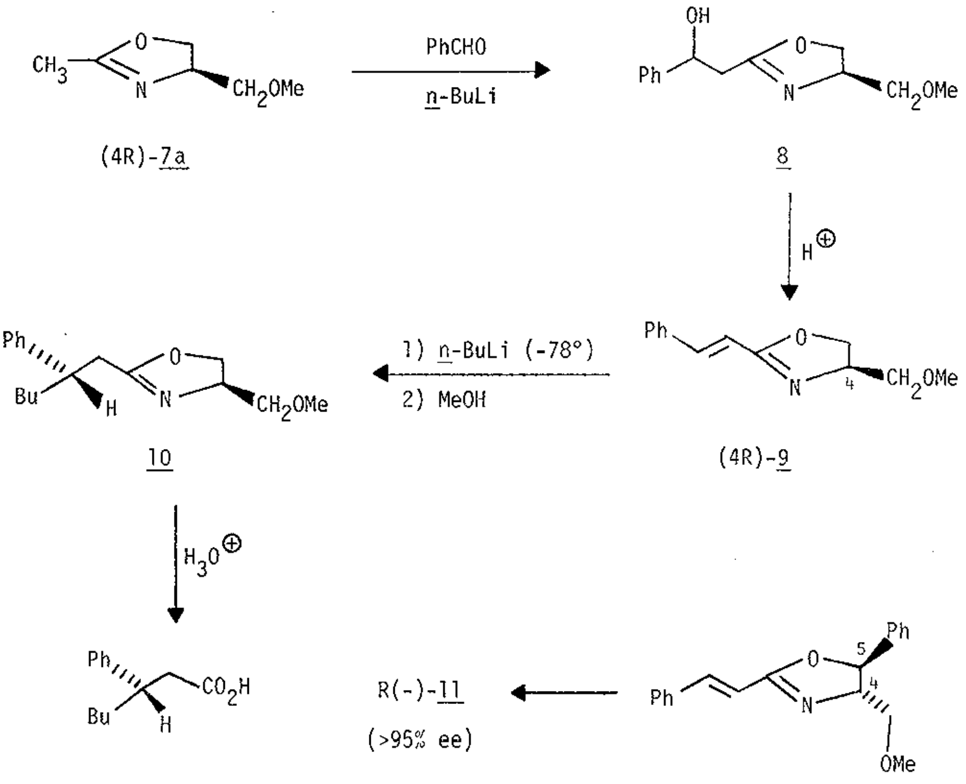
(4R)-6a, X=O

(4R)-6b, X=S

Et_3N, $CHCl_2$, 25°) gave (4S)-(+)-2-methyl-4-carboethoxy-2-oxazoline 5a in 75% yield ($[\alpha]_D$ +182.3° (10, $CHCl_3$), bp 98-100° (11 mm)). Reduction of 5a using bis-(2-methoxyethoxy)aluminum hydride in benzene-ether at 0° furnished (4R)-(+)-2-methyl-4-hydroxymethyl-2-oxazoline 6a in 73% yield ($[\alpha]_D$ +157.0° (10,

$CHCl_3$), bp 56-59° (0.03 mm). Methylation of 6a was accomplished using NaH-MeI in THF affording 68% of (4R)-(+)-2-methyl-4-methoxymethyl-2-oxazoline 7a ($[\alpha]_D$ +108° (10.7, $CHCl_3$), bp 56-59° (8 mm)). The enantiomeric purity of 7a was determined using the chiral shift reagent [*tris*-[(trifluoromethyl hydroxymethylene)-d-camphorato]europium III] and found to be 80±2%. In a similar sequence, L(S)-cysteine ester hydrochloride 4b (Aldrich) and ethyl acetimidate hydrochloride gave 82% of (4S)-(+)-5b ($[\alpha]_D$ +137° (10.5, $CHCl_3$)). Chiral shift reagent determinations, as above, indicated that 5b was 85% enantiomerically pure. Reduction, using sodium borohydride (H_2O·EtOH, 1:1, 0° to 25°), furnished the hydroxymethyl derivative (4R)-(+)-6b with less than 2% racemization ($[\alpha]_D$ +141° (10.4, $CHCl_3$)) and this product was converted (NaH-MeI) to the methyl ether (4R-(+)-7b ($[\alpha]_D$ +101.5° (10, $CHCl_3$)) in 73% yield. The enantiomeric purity of 7b was determined by chiral shift reagents and found to be 82±3%, thus confirming that the reduction and methylation steps proceeded with no more than 2-3% racemization.

Of prime concern in this study was the ability of 7a to function as efficiently as 3 in asymmetric syntheses. The following scheme was investigated in this regard. The oxazoline 7a was elaborated (*n*-BuLi, PhCHO, -78°) to the β-hydroxy adduct 8 in 97% yield (7:3 mixture of diastereomers) and then dehydrated (TFA, benzene, 80°) to the trans-alkenyloxazoline (4R)-9 (51%, $[\alpha]_D$ +101° (8, $CHCl_3$), bp 121-124° (0.03 mm)). Following the procedure previously reported[2] for 1,4-addition to chiral oxazolines, 9 was treated with n-butyllithium in THF at -78° and after 2 hr was quenched with methanol. The addition product 10 (92% crude yield) was not purified further but was directly hydrolyzed in 3M sulfuric acid (6h, 95°) to yield S(+)-3-phenylheptanoic acid (52%, $[\alpha]_{578}$ +25.5° (8, C_6H_6)). The pure acid has an $[\alpha]_{578}$ -34.4° (8, C_6H_6)[2] and thus the asymmetric yield of S(+)-11 is 77%. However, correcting for the enantiomeric purity of 5a of only 80±2%, S(+)-11 was obtained in 96±4% ee. This agrees well with the 95% of R(-)-11 achieved using the alkenyl oxazoline 12 which was derived from the aminodiol 1 and the oxazoline 3.[2] Since 5a has the 4R-configuration and 3 has the 4S-configuration, the phenylheptanoic acids from each route should have opposite configurations. This, indeed, turns out to be the case which suggests that the mechanisms operating from either oxazoline (5a or 3) are probably identical. This preliminary experiment amply demonstrates that the versatile oxazoline[3] and thiazoline[4] systems can now be obtained from a more ready source, namely natural amino acids and that they appear to function in an equally efficient manner toward forming chiral organic compounds. Studies are in progress to prepare chiral oxazolines and thiazolines of complete enantiomeric purity.



(4R)-7a

8

(4R)-9

10

S(+)-11 (>90% ee)

R(-)-11 (>95% ee)

(4S,5SO-12

Acknowledgement Financial support from the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

REFERENCES AND NOTES

* Aminodiol _1_ has been sold by Parke-Davis as a by-product in the manufacture of the anti-biotic "Chloromycetin". However, this drug is under limited production and its future availability is uncertain.

1. A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, J. Am. Chem. Soc., 98, 567 (1976).
2. A. I. Meyers and C. E. Whitten, J. Am. Chem. Soc., 97, 6266 (1975).
3. For a recent review on "Oxazolines in Synthesis", see A. I. Meyers and E. D. Mihelich, Angew. Chem. Int. Ed., 15, 270 (1976).
4. A. I. Meyers and J. L. Durandetta, J. Org. Chem., 40, 2021, 2025 (1975).

Received, 10th September, 1976