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SYNTHESIS VIA OXAZOLINES IX. AN ASYMMETRIC SYNTHESIS OF 2-METHOXY AND 2-CHLOROALKANOIC ACIDS

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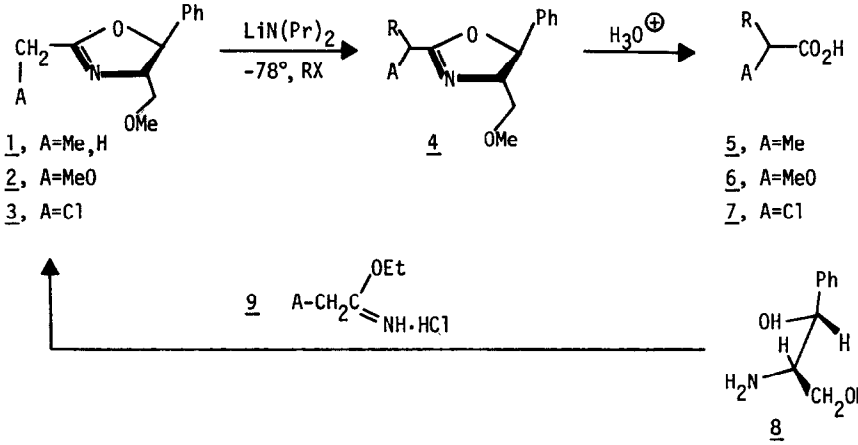
In several previous reports we have described the utility of chiral non-racemic 2-oxazolines 1 as precursors in asymmetric syntheses of 2-methylalkanoic acids[1] (5), 3-hydroxy and 3-methoxyalkanoic acids,[2] and 3-alkylalkanoic acids.[3] In addition, the ability of 1 to act as a chiral ligand in lithium aluminum hydride[4] and Grignard[5] additions to carbonyl groups has also been demonstrated.

We now report that two additional chiral oxazolines 2 and 3 may serve as useful precursors to optically active 2-methoxy and 2-chloroalkanoic acids (Table 1). The 2-methoxymethyl oxazoline 2 [bp 128°/0.5 mm, $[\alpha]_D$ -90.0° (c 11.3, $CHCl_3$)] was prepared from commercially available[6] 1S,2S-(+)-1-phenyl-2-amino-1,3-propanediol and the ethyl imidate of



1, A=Me,H
2, A=MeO
3, A=Cl

4

5, A=Me
6, A=MeO
7, A=Cl

9

8

methoxyacetonitrile 9 (A=MeO) (CH_2Cl_2, 25°) affording trans-2-methoxymethyl-4-hydroxymethyl-5-phenyloxazoline [mp 48-49°, $[\alpha]_D$ -121° (c 11.2, $CHCl_3$)] which was then transformed into its methyl ether (NaH, MeI, THF). Metalation of 2 with 1.0 equiv of lithium diisopropylamide at -78° (THF) followed by addition of methyl iodide (-78°) gave 4 (R=Me, A=OMe) in high yield. However, acidic cleavage (3N HCl, 95°, 3-4 h) produced 2-methoxypropionic acid in only 11-12%

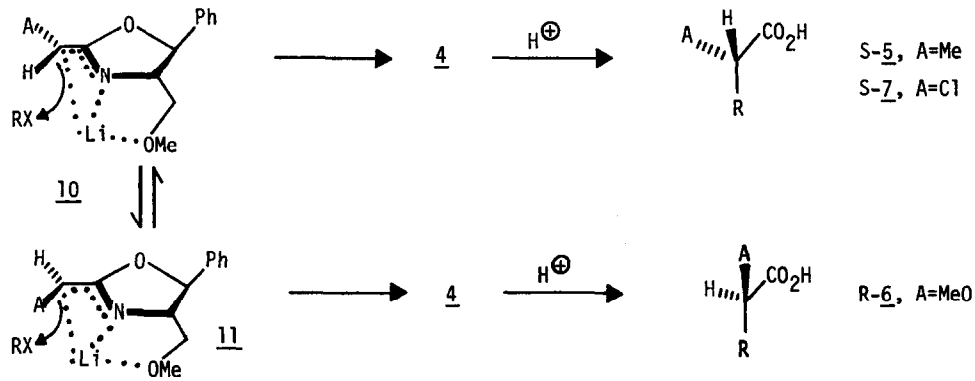
TABLE 1 Asymmetric Synthesis of 2-methoxy and 2-chloroalkanoic acids

Oxazoline	RX	% 4	$[\alpha]_{589}^{25}$	%ee (%O.P.)[a,b]	Configuration[c]	Overall Yield (%)[d]
			2-Methoxyalkanoic Acids (6)			
2	MeI	93	+ 9.1 (neat)	12 (11)	R	42
	Me_2SO_4	91	+17.7 "	23 (22)	R	52
	MeOTs	90	+32.6 "	42 (41)	R	48
2	EtI	96	+18.4 (neat)	23	(R)	62
	Et_2SO_4	91	+25.5 "	32	(R)	45
2	n-PrI	95	+16.2 (neat)	22	(R)	60
	n-BuI	97	+15.3 "	22	(R)	65
	n-BuI	95	+17.5 "	25[e]	(R)	65
			2-Chloroalkanoic Acids (7)			
3	MeI[f]	85	- 0.3 (c 10.9, MeOH)	(2)[b]	S	55
	Me_2SO_4[f]	90	- 0.4 (c 10.5, MeOH)	(3)	S	57
3	EtI[f]	90	- 1.04 (c 10.6, MeOH)	(11)[b]	S	60
3	n-BuI[f]	94	- 3.30 (c 10.9, MeOH)	(28)[b]	S	62

a) % enantiomeric excess was determined for all the 2-methoxyalkanoic acids by converting them to their methyl esters 9 and employing chiral shift reagent Eu-Optishift I [tris-(3-trifluoromethylhydroxymethylene)-d-camphorato europium III]; b) Optical purities given in parentheses were based upon highest rotation available; 6 (R=Me) $[\alpha]_D^{25}$ -77.6°, P. A. Levene and R. E. Marker, J. Biol. Chem., 102, 297 (1933); 7 (R=Me, $[\alpha]_D^{27}$ -13.9°), (R=Et, $[\alpha]_D^{27}$ -9.7°), (R=n-Bu, $[\alpha]_D^{27}$ -11.7°), W. Gaffield and W. G. Galetto, Tetrahedron, 27, 915 (1971); c) Configurations in parentheses are not specifically known and are presumed to be R only on the basis that all were dextrorotary isomers; d) Distilled products gave satisfactory elemental analyses. The high volatility of these compounds was partly responsible for the lower yields; e) Alkylation with n-butyl iodide performed at -98°; f) Two equivalents of hexamethyl phosphoramide were added to the alkyl iodide prior to introduction into the anion solution.

optical purity. Surprisingly, repetition of the alkylation using methyl tosylate gave the methoxy acid in 42% optical yield. This pronounced effect of the leaving group in methyl electrophiles has also been observed in other asymmetric alkylations.[7] However, in the case of ethyl iodide versus ethyl sulfate or tosylate, the optical yields were somewhat less spectacular. Although not shown in the table, as the alkyl group became larger (n-Pr or n-Bu), the optical yields of the methoxy acids were virtually the same regardless whether the iodide, sulfate or tosylate was employed. Lowering the alkylation temperature to -98° also failed to significantly increase the optical yields (Table 1, footnote e). Since only the R-2-methoxypropionic acid has been previously reported, it was necessary to utilize chiral shift reagents to determine the enantiomeric composition of the other derivatives. The acids failed to exhibit clean peak separations and they were, therefore, transformed into their corresponding methyl esters using 3-methyl-1-(p-tolyl triazene)[8] in ether. The enantiomeric composition (%ee in Table 1) was readily determined by the cleanly resolved (12-15 Hz) OMe singlets of the ether function. Of interest is the excellent agreement shown by the nmr technique (%ee) and the rotation data (% O.P.) for 2-methoxypropionic acid (42% and 41%, respectively). The methoxy amino alcohol 8 [mp 49-51°, ether (-78°), $[\alpha]_D$ +24.2° (c 10, $CHCl_3$)][1] recovered from the acid hydrolysis of 4 was treated with the ethyl imidate of chloroacetonitrile 9 (A=Cl) producing the chloromethyloxazoline 3 [chromatographed on alumina I, ethyl acetate, $[\alpha]_D$ -84.1° (c 11, $CHCl_3$)]. Attempts at purification by distillation resulted in considerable loss of material. Treatment of 3 with lithium diisopropylamide (1.0 equiv) at -78° produced a deep red anion solution which was quenched with deuterium oxide to give the monodeuteriated oxazoline 4 (R=D, A=Cl), confirmed by nmr. However, addition of alkyl iodides resulted in little or no alkylation at -98° to -40°. If the reaction was allowed to warm to ambient, alkylation occurred (80-90%) furnishing 4 (A=Cl). Hydrolysis to the 2-chloro acids 7 gave products which were all nearly racemic. Prior mixing of the electrophiles with 2.0 equiv of HMPA provided a more polar medium for alkylation and these reactions did indeed occur at -78°. The chloro oxazolines obtained under these conditions (85-94%) were hydrolyzed to the chloro acids and a noticeable improvement in some optical yields was realized. It is clear from these results that there are many

complex factors operating in the asymmetric syntheses derived from oxazolines. The significant differences in optical yields of acids 5 (60-80%), 6 (22-42%), and 7 (2-28%) must be the result of considerable differences in the rigidity of the intermediate lithio salts (10, 11) and their subsequent transition states during alkylation. Alkylation is presently assumed to occur from the bottomside of 10 and 11 in order to also explain the pronounced effect of the leaving groups (iodide vs. tosylate) in Table 1.



When A is Me or Cl, it appears that the approach of RX to 10 enroute to the transition state would possess fewer non-bonded interactions than the approach of RX to 11. On the other hand, when A=MeO, the donating ability of oxygen may hold this group partially bonded to the lithium in a cisoid fashion (11) and cause this mode of approach to be favored. This tentative explanation is consistent with the configuration of the acids observed. Obviously, more detailed studies will be required prior to reaching a firm conclusion.[9]

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