HETEROCYCLES, Vol 20, No 4, 1983

ABSOLUTE CONFIGURATION AND GRIGNARD REACTION OF CHIRAL 4-ISOPROPYL-3-METHYLOXAZOLIDINES

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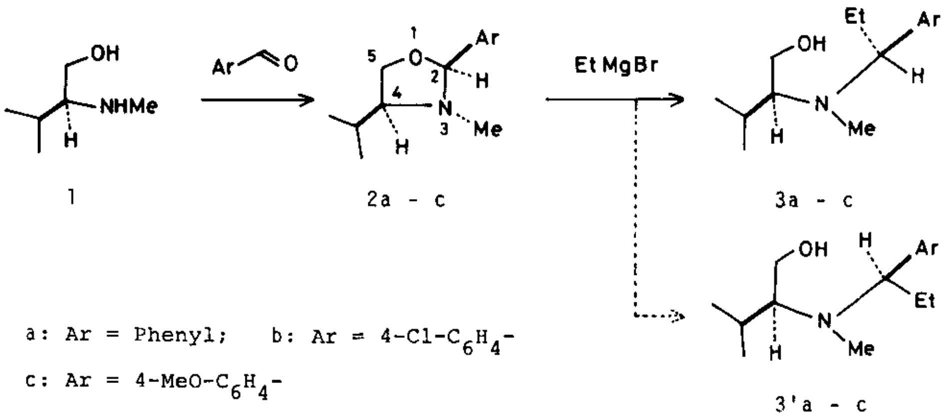
Abstract --- A new chiral 4-isopropyl-3-methyloxazolidines were synthesized by the condensation of *N*-methylvalinol with some aldehydes. The absolute configuration and asymmetric reactions of these compounds were discussed.

The asymmetric heterocyclic compounds play an important role for high stereoselectivity. Recently, the asymmetric reaction with extremely high yield using the chiral oxazolidones derived from (*S*)-valinol was reported.1) This investigation suggested that the isopropyl group of optically active (*S*)-valine produces very high asymmetric induction. Chiral oxazolidine compounds, *e.g.*, 3,4-dimethyl-5-phenyloxazolidines,2) pyrrolidino[1,2-*c*]oxazolidine,3) and 4-ethoxycarbonyl-5-phenyloxazolidine4) were known.



1 2a - c 3a - c 3'a - c

a: Ar = Phenyl; b: Ar = 4-Cl-C_6H_4-
c: Ar = 4-MeO-C_6H_4-

We describe the synthesis of new chiral oxazolidines, *i.e.*, 4-isopropyl-3-methyloxazolidines (2a-c), these absolute configurations, and the stereoselectivity to Grignard reagent.

The new chiral oxazolidines, 2-aryl-4-isopropyl-3-methyloxazolidines (2a-c), were synthesized from (*S*)-*N*-methylvalinol (1) and aromatic aldehydes in benzene using a Dean-Stark trap. In the cases of these compounds, two diastereomers were supposed by the configuration of 2-position carbon atom. However, the proton nuclear magnetic resonance (^{1}H-NMR) spectra of these oxazolidines thus

Table I. Chiral 2-Aryl-4-isopropyl-3-methyloxazolidines (2a-c)

Compd. No.	Ar	bp (° / mmHg)	Yield (%)	MS m/e	^{1}H-NMR ($CDCl_3$) δ N-CH-O (1H,s)	N-CH_3 (3H,s)	$CH(C\underline{H}_3)$2 (6H,d,J=6.8Hz)
2a	Ph	115 / 0.6	83	205	4.68	2.20	0.98, 0.96
2b	4-Cl-C_6H_4-	131 / 0.5	81	239	4.66	2.19	0.96
2c	4-MeO-C_6H_4-	144 / 0.7	82	235	4.62	2.17	0.98, 0.96

Compd. No.		CD and UV (in 95% ethanol) ^1L_a Band	^1L_b Band			$[\alpha]_D$ (*c*, 95% ethanol)
2a	CD	-5.11(212)	-0.26(260)	-0.29(265)	-0.23(278)	-28.4(*c*=0.41)
	UV	203(16.9)	246(3.19)	278*(0.28)	287*(0.22)	
2b	CD	-5.67(216)	-0.32(268)	-0.35(274)	-0.34(282)	-30.7(*c*=0.41)
	UV	216(14.2)	254(4.61)	281*(0.52)	291(0.32)	
2c	CD	-4.54(223)	-0.31(273)	-0.35(278)	-0.30(293)	-32.5(*c*=0.42)
	UV	224(14.0)	271(5.44)	278(4.55)	294*(1.68)	

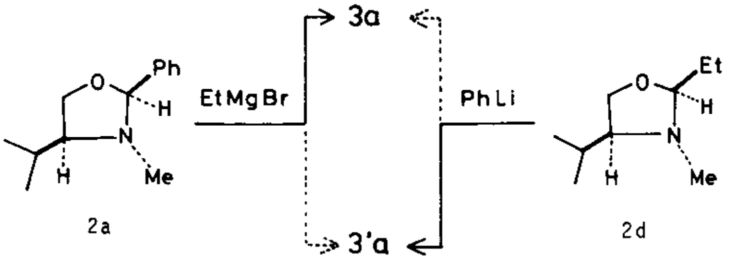
The yields are for isolated products. The MS spectra were recorded with a JEOL JMS-D300 spectrometer, the ^{1}H-NMR spectra with a JEOL FX100 spectrometer, and the UV spectra with a Hitachi 124 spectrometer.

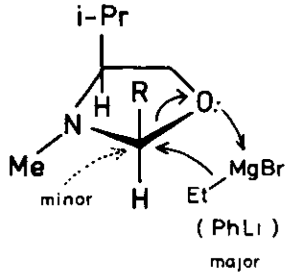
The CD spectra were measured at 20-23 °C using a Jasco J-40 spectropolarimeter; the magnitudes of the bands were calibrated with, as standard, D-10-camphorsulfonic acid at 289 nm and D-pantolactone at 221 nm. The optical rotations were measured at 20-23 °C with a Jasco DIP-180 polarimeter.

obtained in this reaction showed to consist of one diastereomer. The reaction products were distilled under reduced pressure to give 2a-c as colorless oil in high yields. The structures of these compounds were confirmed by the ^{1}H-NMR and mass (MS) spectroscopies. The circular dichroism (CD) spectra of 2a-c showed the negative Cotton effects at the ${}^{1}L_a$ and ${}^{1}L_b$ bands, as shown in Table I, these absorption bands are attributable to aromatic ring chromophore.
The relationship between the Cotton effects and the absolute configurations in the 1-arylalkylamine compounds has been reported, and the aromatic quadrant-sector rule was applied for the determination of the absolute configurations of 1,2-diarylethylamines.5,6) By the consideration of a CPK molecular model, the application of the quadrant-sector rule to these compounds predicts that the negative Cotton effects at the ${}^{1}L_a$ and ${}^{1}L_b$ bands tentatively indicate *S*-configuration at 2-position.

The reactions of 2a-c with ethylmagnesium bromide in ether gave colorless oily products of *N*-(2'-hydroxy-1'-isopropylethyl)-*N*-methyl-1-arylpropylamines (3a-c and 3'a-c) in good yields. These reaction products were elucidated to consist of the mixture of two diastereomers by means of ^{1}H-NMR spectroscopy, and the ratios of the major to minor component in 3a:3'a, 3b:3'b, and 3c:3'c were estimated as 82 : 18%, 79 : 21%, and 90 : 10%, respectively.

The structures of 3a-c were confirmed by the ^{1}H-NMR and MS spectroscopies. The CD spectra of those compounds showed that the Cotton effects of the ${}^{1}L_a$ band are positive, and those of the ${}^{1}L_b$ bands are negative. The Cotton effects of (1*R*, 1'*R*)-*N*-(2'-hydroxy-1'-isopropylethyl)-*N*-methyl-1-phenylpropylamine, which obtained *via* an alternative route using material of known absolute configuration,7) showed negative in the ${}^{1}L_a$ band and positive in the ${}^{1}L_b$ band. Accordingly, the absolute configurations at 2-position of 3a-c were estimated as *S*-configuration.





On the other hand, 2-ethyl-4-isopropyl-3-methyloxazolidine (2d) was synthesized by the condensation of (*S*)-*N*-methylvalinol with propionaldehyde, and the ^{1}H-NMR spectrum of 2d indicated to consist of one diastereomer. Reaction of 2d with phenyllithium in ether gave *N*-(2'-hydroxy-1'-isopropylethyl)-*N*-methyl-1-phenylpropylamine as a colorless oil. The ^{1}H-NMR spectrum of this product showed the mixture of two diastereomers, and the ratio of major to minor product was estimated as 89 : 11%. It was confirmed that the structure of the major product is 3'a, while the minor product is identified with 3a by the ^{1}H-NMR spectroscopy.

The mechanism of this asymmetric reaction may be assumed as follows: First, the magnesium atom of the Grignard reagent attaches to the lone pair of 1-position oxygen from the less sterically hindered side,and then the ethyl anion attacks the 2-position carbon from the same side, because the reaction of 2a-c with ethylmagnesium bromide gave the (1*S*, 1'*S*)-configuration amines (3a-c as the major products). On the other hand, the minor component (3'a-c) is considered to be formed since the ethyl anion would attack the carbon at 2-position from the back side.

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7. This compound was synthesized by the condensation of (*R*)-1-phenylpropylamine with *dl*-2-bromo-3-methyl-1-butanol, followed by *N*-methylation.

Received, 17th January, 1983