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SYNTHESIS OF OPTICALLY ACTIVE 4-HYDROXYALK-2-ENENITRILES; REACTION OF OPTICALLY ACTIVE 2-(p-CHLOROPHENYLSULFINYL)ACETONITRILE WITH ALDEHYDES IN THE PRESENCE OF PIPERIDINE IN ACETONITRILE

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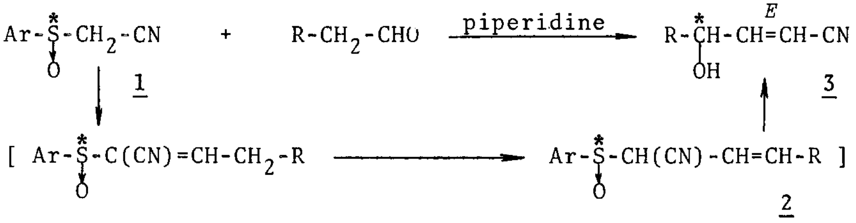
Abstract: Reaction of optically active 2-(p-chlorophenylsulfinyl)acetonitrile ((R)-1a) with aldehydes, in the presence of piperidine in acetonitrile at r.t., gave optically active 4-hydroxyalk-2-enenitriles in good optical and chemical yields. The absolute configuration of (-)-4-hydroxypent-2-enenitrile, predominantly obtained by the reaction of (R)-1a with propanal, was determined to be R.

In the previous papers,[1)] we reported that the reaction of 2-(phenylsulfinyl)acetonitrile with aldehydes and ketones in the presence of piperidine gave 4-hydroxyalk-2-enenitriles which played an important role in our syntheses of some biologically active terpenoids. As an extention of this work, we have been interested in the synthesis of optically active 4-hydroxyalk-2-enenitrile, because it is applicable to syntheses of many biologically active compounds having optically active allylic alcohol functionality.

We report here a chirality transfer reaction of optically active 2-(arylsulfinyl)acetonitrile (1) with aldehyde.



Optically active (R)-2-(arylsulfinyl)acetonitrile ((R)-1) was prepared by treatment of the anion, derived from acetonitrile and lithium diisopropylamide (LDA), with the corresponding optically pure (S)-*l*-menthyl arylsulfinate[2)] at -78 °C in THF. The (R)-2-(arylsulfinyl)acetonitriles, (R)-1a (aryl=p-chlorophenyl) and (R)-1b (aryl=p-tolyl),[3)] were treated with hexanal to give 4-hydroxyoct-2-enenitrile (3b). A considerable substituent effect of the aryl groups and solvent effect of the reaction were observed in the optical yield as shown in Table 1

Table 1 Reaction of (R)-1a and (R)-1b with hexanal to 4-hydroxyoct-2-enenitrile (3b) in the presence of piperidine at r.t.

Reaction Solvent	Chemical Yield/% 3b		Specific Rotation[a] 3b	
	from 1a	from 1b	from 1a	from 1b
acetonitrile	77	64	-25°	-18°
methanol	56	63	-24°	-15°
dimethylsulfoxide	63		-21°	
tetrahydrofuran (THF)	55		-20°	
benzene	83	60	-8°	-7°
1,2-dimethoxyethane		62		-5°

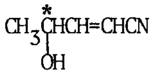
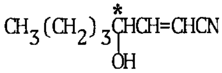
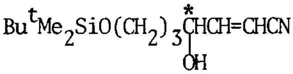
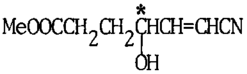
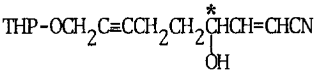
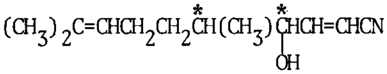
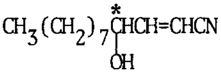
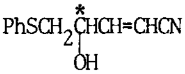
a) $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$)

Then, the following experiments were carried out by using (R)-1a in acetonitrile. To a solution of (R)-1a (200 mg, 1 mmol) and piperidine (0.2 ml, 2 mmol) in dry acetonitrile (4 ml) was added aldehyde (1.0-1.5 mmol,[4] acetonitrile solution) over a period of 1.5 h[5] with stirring at room temperature.[6] After completion of the addition of aldehyde, diluted tartaric acid was added to the reaction mixture.[7] The mixture was extracted with ether to give a crude product, which was purified by column chromatography on silica gel. Specific rotation was measured by a Union Automatic Digital Polarimeter (PM-101) in chloroform at 20 °C. The enantiomeric composition (optical purity) was determined by ^1H and ^{13}C NMR spectra after conversion of the alcohol to the corresponding MTPA ester by treatment with acyl chloride derived from (+)-2-methoxy-2-(trifluoromethyl)phenylacetic acid ((+)-MTPA).[8] The chemical and optical yields of 4-hydroxyalk-2-enenitriles obtined by the reaction of (R)-1a with aldehydes were listed in Table 2.

The absolute configuration of (-)-4-hydroxypent-2-enenitrile ((-)-3a) predominantly obtained from (R)-1a was proved to be R by the following procedure. The alcohol ((-)-3a) was converted to tert-butyldimethylsilyl ether by the usual way (Bu^tMe_2SiCl, imidazole, DMF) and then to (+)-2-tert-butyldimethylsilyloxypropanal ($[\alpha]_D^{20}$+6° (c 1.0, $CHCl_3$)) by ozonolysis (O_3, -78 °C, Me_2S). (S)-(-)-2-Tert-butyldimethylsilyloxypropanal ($[\alpha]_D^{20}$-11° (c 1.0, $CHCl_3$)) was derived from (S)-ethyl lactate by silylation followed by DIBAH reduction (CH_2Cl_2, -78 °C).

(+)-4-Hydroxyoct-2-enenitrile ((+)-3b, $[\alpha]_D^{20}$+25°) was also obtained by the same reaction of hexanal with (S)-1a derived from (R)-(+)-*d*-menthyl p-chlorophenylsulfinate.[9]

Table 2 Reaction of (R)-1a with aldehydes in acetonitrile at r.t.

Aldehydes	Reaction Time (h)	Product[a]		Yield/%	$[\alpha]_D^{20}$[b] (% ee)[c]
CH_3CH_2CHO	1.5	 $CH_3\overset{*}{\underset{OH}{C}}HCH=CHCN$	3a	61	-28° (50)
$CH_3(CH_2)_4CHO$	1.5	 $CH_3(CH_2)_3\overset{*}{\underset{OH}{C}}HCH=CHCN$	3b	77	-25° (75)
$Bu^tMe_2SiO(CH_2)_4CHO$	1.0	 $Bu^tMe_2SiO(CH_2)_3\overset{*}{\underset{OH}{C}}HCH=CHCN$	3c	57	+7.6°
$MeOOC(CH_3)_3CHO$	2.0	 $MeOOCCH_2CH_2\overset{*}{\underset{OH}{C}}HCH=CHCN$	3d	71	+5.6° (76)
$THP\text{-}OCH_2C\equiv C(CH_2)_3CHO$	2.0	 $THP\text{-}OCH_2C\equiv CCH_2CH_2\overset{*}{\underset{OH}{C}}HCH=CHCN$	3e	54	-17° (80)[d]
$(CH_3)_2C=CHCH_2CH_2\overset{*}{C}H(CH_3)CH_2CHO$	1.5	 $(CH_3)_2C=CHCH_2CH_2\overset{*}{C}H(CH_3)\overset{*}{\underset{OH}{C}}HCH=CHCN$	3f	56	-30° (80)[e]
$CH_3(CH_2)_8COSiMe_3$	2.0	 $CH_3(CH_2)_7\overset{*}{\underset{OH}{C}}HCH=CHCN$	3g	71	-22° (74)
$PhSCH_2CH_2CHO$	1.0	 $PhSCH_2\overset{*}{\underset{OH}{C}}HCH=CHCN$	3h	53[f]	-8.5° (60)

a) Geometry of the products was specifically *E* (*Z* isomer was not detected).[1]

b) (c 1.0, $CHCl_3$).

c) Determined by ^1H and ^{13}C NMR spectra of (+)-MTPA ester of 3 unless otherwise noted.

d) THP=2-tetrahydropyranyl; It was impossible to detect the isomers depend on the THP, and only two isomers were observed NMR spectroscopycally.

e) % de.[10]

f) Reaction in the presence of piperidine did not give the desired product, then diethylaluminum piperidide was used as a base.[11]

This chirality transfer reaction is interesting by the following facts: (1) The chirality at sulfur atom is transfered to α-position of aldehyde-carbonyl group with the Wittig-type two carbon homologation to the carbonyl carbon: (2) In the case of the reaction of 1a with aldehyde, the optical yield is high.[12]

Study on synthesis of optically active allylic alcohols is now in progress.[13]

References and Notes

1) J. Nokami, T. Mandai, Y. Imakura, K. Nishiuchi, M. Kawada, and S. Wakabayashi, Tetrahedron Lett., 22, 4489 (1981); T. Ono, T. Tamaoka, Y. Yuasa, T. Matsuda, J. Nokami, and S. Wakabayashi, J. Am. Chem. Soc.,

106, 7890 (1984).

2) (S)-*l*-Menthyl p-chlorophenylsulfinate; $[\alpha]_D^{20}$-186° (c 1.0, $CHCl_3$). (S)-*l*-Menthyl p-tolylsulfinate; $[\alpha]_D^{20}$-203° (c 1.0, $CHCl_3$) (lit. $[\alpha]_D$ -198° (acetone) [K. Mislow et al., J. Am. Chem. Soc., 87, 1958 (1965)]).

3) (R)-2-(p-Chlorophenylsulfinyl)acetonitrile ((R)-1a); $[\alpha]_D^{20}$+131° (c 1.0, $CHCl_3$), +241° (c 1.0, ethanol); mp 58-59 °C. (R)-2-(p-Tolylsulfinyl)acetonitrile ((R)-1b); $[\alpha]_D^{20}$+145° (c 1.0, $CHCl_3$), +261° (c 1.0, ethanol); mp 61-62 °C (lit. $[\alpha]_D$+252° (ethanol); mp 72 °C [T. Numata, O. Itoh, T. Yoshimura, and S. Oae, Bull. Chem. Soc. Jpn., 56, 257 (1983)]).

4) When 0.5 mmol of hexanal was used, the same result ($[\alpha]_D^{20}$-25°) was obtained.

5) When hexanal was added within a few minutes, 3b was obtained in lower chemical and optical yields.

6) A low temperature reaction did not give the product in satisfactory chemical yield.

7) The same results were obtained, when the reaction was continued for additional 5 h before the workup.

8) J. A. Dale and H. S. Mosher, J. Am. Chem. Soc., 95, 512 (1973).

9) (S)-1a; $[\alpha]_D^{20}$-131° (c 1.0, $CHCl_3$). (R)-*d*-Menthyl p-chlorophenylsulfinate; $[\alpha]_D^{20}$+185° (c 1.0, $CHCl_3$).

10) An assumed % de was measured (62 % de) by ^{13}C NMR spectra, though the optical purity of the citronellal ($[\alpha]_D^{20}$+13.0° (c 2.0, $CHCl_3$)) is not clear. However, it can be estimated that the optical purity of citronellol ($[\alpha]_D^{27}$+3.63° (neat)) derived from the citronellal (reduced by $NaBH_4$) is ca. 78% ee based on the reported specific rotation ($[\alpha]_D^{20}$-4.67° (neat)) for 96.6% ee of (S)-(-)-citronellol [M. Hirama, T. Noda, and S. Ito, J. Org. Chem., 50, 127 (1985)]. The same reaction of (S)-1a[9] with the citronellal afforded (+)-3f ($[\alpha]_D^{20}$+17.0° (c 1.0, $CHCl_3$)) with the same assumed % de. Then, it is considered that the chirality transfer reaction proceeds with 80% de for each enantiomers of citronellal.

11) To a solution of (R)-1a (1 mmol) and diethylaluminum piperidide (2 mmol, prepared by treatment of lithium piperidide with diethylaluminum chloride) in dry benzene was added 3-phenylthiopropanal (1 mmol, benzene solution) over a period of 1 h at 0 °C.

12) In the case of the reaction of (R)-1a with cyclopentanone, cyclohexanone, and 6-methylhept-5-en-2-one, the optical yields were not so high (15-20% de).

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