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A Simple Route to Chiral Phosphonothionates from Diastereomeric Phosphonamidothionates.

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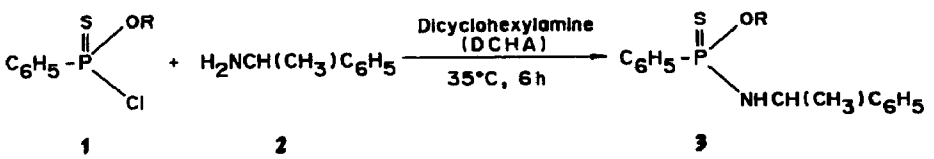
Abstract: Optical isomers of phosphonothionates have been prepared by acid catalyzed alcoholysis of resolved phosphonamidothionates in high optical purity.

Chiral organophosphorus compounds, exhibit differential toxicity[1] and metabolism[2] in living organisms. Moreover, these compounds find application in elucidating organic and enzymatic reaction mechanisms[3,4]. The only procedure available to-date for the preparation of these compounds is through conversion of resolved phosphonothioic acids into their chlorides followed by reaction with phenols[5]. However, this method involves multisteps and consequently affords poor yields. Recently stereoselective P-O and P-N bond cleavage was adopted for preparation of chiral esters[6]. To our knowledge this methodology has never been considered for the synthesis of insecticides. In this communication the utility of stereospecific P-N bond cleavage for the synthesis of pure enantiomers of cyanofenphos (O-ethyl, O-4-cyanophenyl phenyl phosphonothionate) an insecticide and related compounds are described.

Reported procedure[7] provided good yield of intermediates **1a-c**. This prompted us to examine the reaction with optically active isomers R(+) and S(-)- α -methyl benzylamine **2** (eq. 1).



(eq. 1)

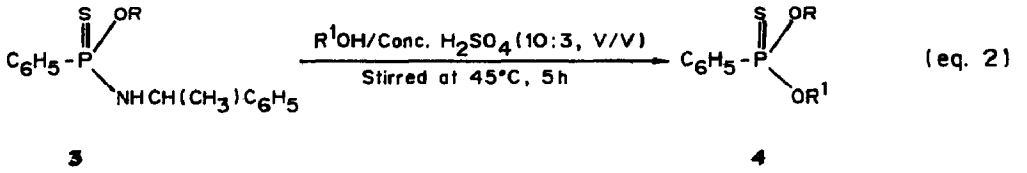
1 **2** **3**

a : R = 4-CN-C_6H_4, b : R = 4-Cl-C_6H_4, c : R = C_6H_5

The following procedure for preparation of O-4-cyanophenyl phenyl phosphonamidothionate 3 is representative. To **1a** (6.0g,20 mmol) taken in a flask containing dry benzene (50ml) was added slowly a solution of S(-)-isomer of **2** (2.4g, 20mmol) and DCHA (3.6g, 20mmol) in dry benzene (50 ml), with stirring. The reaction mixture was stirred at 35°C for another 6 h and DCHA salt thus formed was filtered. Solvent was removed under vacuum and the residual liquid so obtained was cleaned up by column chromatography on silica gel with eluent; benzene/hexane (8:2) Evaporation of collected fractions afforded **3** (6.3 g, 83% yield) as viscous liquid . This was dissolved in hexane/ether (10:3) and kept aside overnight which upon rubbing the sides of flask gave white cystalline solid **3a** (1.8 g , 28% yield).

Determination of specific rotation and ^{31}P NMR by Perkin Elmer polarimeter model 241 and 90 MHz spectrometer model Jeol EX90 respectively showed hundred percent purity of diastereomer P(-)C(-). Isomer P(+)C(+) was obtained by reacting R(+)- α -methylbenzylamine with **1a** as described above. Though the synthesis of diastereomer of **3b, c** was done in a similar manner the resolution was obtained through fractional crystallization in petroleum ether (40-60°C). Microanalysis, IR, ^{1}H NMR and ^{31}P NMR spectroscopy was used to characterize the products[8]. Physical data and specific rotation of resolved isomers **3a-c** are summarized in table 1.

Acid catalyzed methanolysis/ethanolysis of **3a-c** resulted in products[9] **4a-e** through stereospecific P-N bond cleavage as represented (eq .2).



3 **4** (eq. 2)

An evidence for high stereospecificity was brought by comparing observed specific rotation with reported values[3]. Products **4a-e** were characterized by IR and ^{1}H NMR spectral data[10]. Physical data and specific rotation of enantiomers **4a-e** are given in table 1.

The present method thus provided an easy access to chiral isomers of cyanofenphos, an important neurotoxic esterase inhibitor.

Table 1. N-(α-methylbenzyl)phosphonamidothionate

Product No.	R	yield (%)	Diastereomer	$[\alpha]^{20}_D$ (C=5, $CHCl_3$)	mp °C	Molecular Formula
3a	4-CN-C_6H_4	26	P(+)C(+)	+36.45	89-90	$C_{21}H_{19}N_2OPS$
		28	P(-)C(-)	-36.50	89-90	(378.43)
3b	4-Cl-C_6H_4	27	P(+)C(+)	+46.80	87-88	$C_{20}H_{19}NOPSCl$
		24	P(-)C(-)	-47.00	87-88	(387.85)
3c	C_6H_5	25	P(+)C(+)	+58.40	84-85	$C_{20}H_{20}NOPS$
		27	P(-)C(-)	-58.60	84-85	(353.42)

Table 2. Optically Active Phosphonothionates

Product No.	R	R^1	Yield (%)	$[\alpha]^{20}_D$ ($CHCl_3$)	mp °C	Molecular Formula
4a	4-CN-C_6H_4	C_2H_5	63	(R):+37.7 [33.5, C=4.0][3]	100-101	$C_{15}H_{14}NO_2PS$ (303.31)
			66	(S):-38.1 (-33.7, C=3.0)[3]		
4b	4-CN-C_6H_4	CH_3	60	(R):+46.7	60-61	$C_{14}H_{12}NO_2PS$
			58	(S):-45.8		(289.29)
4c	4-Cl-C_6H_4	C_2H_5	57	(R):+29.3	Liquid	$C_{14}H_{14}O_2PSCl$
			60	(S):-29.4		(312.75)
4d	4-Cl-C_6H_4	CH_3	64	(R):+37.8	Liquid	$C_{13}H_{13}O_2PSCl$
			65	(S):-38.1		(299.73)
4e	C_6H_5	CH_3	54	(R):+27.1	Liquid	$C_{13}H_{13}O_2PS$
			56	(S):-27.7		(264.28)

3 Specific rotations under parentheses are reported values.

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8. **3a**:IR(KBr) 3360, 2240,1225cm^{-1};^{1}H NMR (90MHz,$CDCl_3$): δ1.46(d,3H, J=6.49 Hz), 3.7(t,1H, J=9.74Hz), 4.58(m,1H,NH), 7.07-8.01(br,m 14H);^{31}P NMR (90MHz, $CDCl_3$): δ75.2; Anal. Calcd:C,66.65;H,5.06;N,7.40 Found: C,67.04; H,5.08;N,7.13
   3b:IR (KBr) 3300, 1200 cm^{-1};^{1}H NMR (90MHz,$CDCl_3$):δ1.47(d,3H, J=6.83 Hz), 3.53 (t,1H,J=9.40 Hz), 4.51 (m, 1H,NH), 7.05-8.01 (br,m, 14H), ^{31}P NMR (90MHz, $CDCl_3$): δ76.61; Anl.Calcd: C, 61.93; H, 4.94; N, 3.61 Found: C,61.90;H,4.95; N,3.28
   3c :IR (KBr)3300, 1200 cm^{-1} ^{1}H NMR (90MHz,$CDCl_3$): δ1.43 (d,3H,J=6.89Hz), 3.53(t, 1H, J=9.79 Hz), 4.51(m,1H,NH); 7.00 -8.01 (br,m, 15H);^{31}P NMR(90MHz,$CDCl_3$): δ73.98; Anal Calcd: C,67.97; H,5.70;N,3.96. Found : C, 67.70; H,5.55;N.3.47
9. **4a**: P(-)C(-) diastereomer of **3a** (0.4g, 1.05 mmol) was stirred with a mixture (20ml) of ethanol/Conc. H_2SO_4 (10:3 v/v) at 45°C for 5h. Reaction mixture was diluted with water (20ml) and extracted with two portions of 30ml each with ethyl ether. Ether layer was first washed with 3% $NaHCO_3$ solution (10ml) and twice with water (each 10ml). Ether was evaporated off and the crude product was purified by column chromatography on silica gel using benzene/hexane (8:2). Evaporation of solvent under reduced pressure yielded **4a** (0.21 g,66% yield) m.p. 100-101°C.
10. **4a**: IR (KBr) 2230,1215,1040cm^{-1};^{1}H NMR (90MHz,$CDCl_3$): δ1.37(t,3H,J=7.1Hz), 4.28 (m,2H), 7.14-8.05(br,m,9H)
    4b: IR (KBr) 2230,1220,1050cm^{-1}; ^{1}H NMR (90MHz,$CDCl_3$): δ3.85 (d,3H,J=14.18 Hz); 7.13-8.01 (br,m,9H)
    4c: IR(KBr) 1210, 1035cm^{-1}; ^{1}H NMR(90MHz,$CDCl_3$): δ1.42 (t.3H, J=7.05Hz), 4.24 (m,2H), 7.00-8.12 (br,m,9H)
    4d: IR(KBr) 1210, 1040cm^{-1}; ^{1}H NMR(90MHz, $CDCl_3$): δ3.82 (d 3H, J=13.85Hz), 7.03-8.11 (br,m,9H)
    4e: IR(KBr) 1200, 1040cm^{-1}; ^{1}H NMR (90MHz,$CDCl_3$): δ3.82(d,3H,J=12.92Hz), 7.01-8.11 (br,m,10H)

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