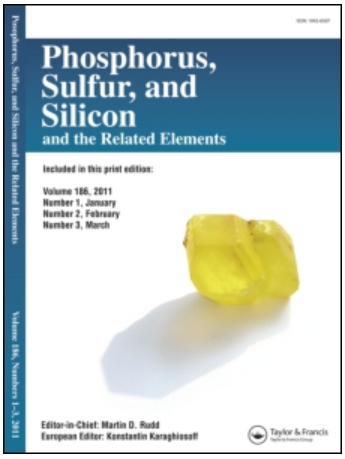

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EVIDENCE FOR SELECTIVE S-ALKYLATION OF AN AMBIDENT ANION OF DICYCLOHEXYLAMMONIUM THIOPHOSPHONATE BY ALKYL HALIDES

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Reaction of the DCHA salt of O-alkyl phenyl phosphonothioic acids **1a–c** with alkyl halides **2a–d** gave exclusively S-derivatives; **3e–h** (85–93%) and **3b–d** (40–43%). The cause for poor yields of the methyl analogues is its ability to participate in the methylation of salt **1a** and give rise by-product O,S-dimethyl phenyl phosphonothiolate (**3a**). Awareness of the unusual pathway for the generation of the by-product has opened a new possibility to adopt this strategy for synthesis of enantiomerically pure thiolates.

Key words: Chiral phosphonothiolates; dicylohexylammonium thiophosphonate anion; resolution; stereospecific synthesis; cross methylation; alkyl halides.

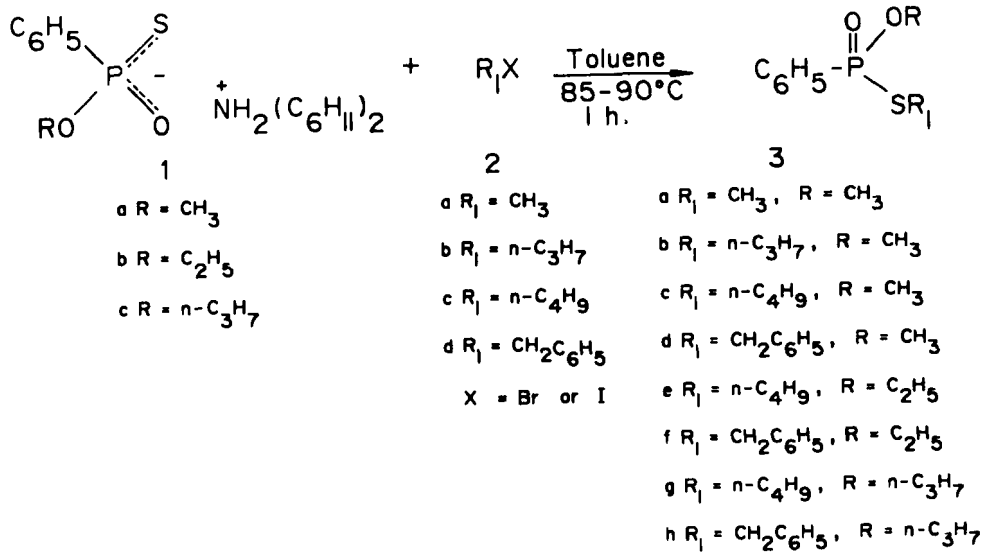
INTRODUCTION

The stereochemistry[1] and biological properties[2–4] of chiral thiolate esters of phosphorus acids are of interest. Generally they are prepared from alkyl halides and thioic acids in presence of a base,[5] its metal,[6] ammonium[7] or dicyclohexylammonium salts.[8] Literature reports reveal that the ambident anion of sodium phosphonothioate[9,10] and potassium phosphorothioate[11] upon reacting with RCH_2Cl lead selectively to S-derivative. Apart from various other factors, metal cations are known to influence the reaction course[12] but the role of dicyclohexylammonium (DCHA) cation is not clear.[8] Here the function of DCHA cation on the mechanism of this reaction is described and its usefulness in the synthesis of enantiomerically pure thiolates is demonstrated.

RESULTS AND DISCUSSION

DCHA phosphonothioates **1a–c** on reaction with alkyl halides **2a–d** gave corresponding esters **3a–h** (Scheme I). Thiolates **3a** and **3e–h** were obtained as the sole product in 85–93% yields, whereas esters **3b–d** were obtained only in 40–43% yields (Table I). A careful chromatographic separation of **1a** and **2b–d** reaction mixtures revealed formation of **3a** and corresponding salts **4a–c** (Scheme II). This evidence indicates the mechanism for formation of a by-product **3a** through a cross reaction involving salt **1a**. Esters **3b–d** formed via a normal reaction pathway.

The participation of esters **3b–d** in methylation of salt **1a** has been attributed mainly to the highly migratory nature of the methyl group of O-methyl, S-alkyl phenylphosphonothiolates **3b–d**. Contrary to this the ethyl or propyl groups of higher homologues **3e–h** showed a nonmigratory character. These results support

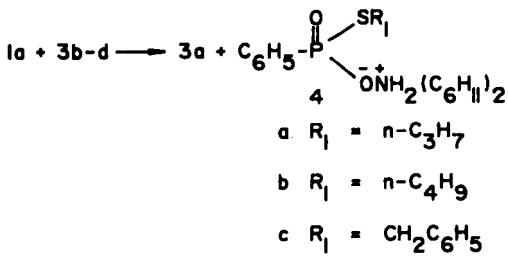


SCHEME I

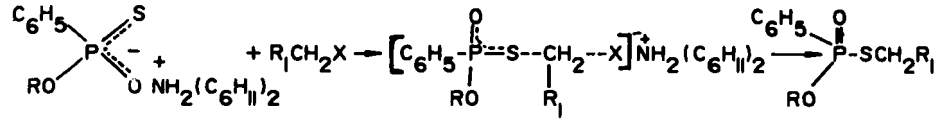
TABLE I

Characterization data of compounds **3a–h**

Entry	Comd.	Yield (%)	bp/mmHg °C	Formula (M^+)	IR(neat) cm^{-1}	^1H NMR (δ ppm)	Mass m/z
1.	**3a**	90	114–116/0.05	$C_8H_{11}O_2PS$ (202)	1230, 1020	2.09(d, 3H), 3.82(d, 3H), 7.45–7.97(br m, 5H)	202(M^+), 156, 155, 77
2.	**3b**	40	160–162/1.5	$C_{10}H_{15}O_2PS$ (230)	1230, 1025	0.90(t, 3H), 1.55–1.71(m, 2H), 2.55–2.92(m, 2H), 3.39 (d, 3H), 7.49–7.99(br m, 5H)	230(M^+), 188, 156, 157, 77
3.	**3c**	43	168–170/1.5	$C_{11}H_{17}O_2PS$ (244)	1230, 1020	0.79(t, 3H), 1.32–1.51(m, 4H), 2.54–2.76(m, 2H), 3.80(d, 3H), 7.37–7.84(br m, 5H)	244(M^+), 188, 156, 155, 77
4.	**3d**	42	180–182/1.5	$C_{14}H_{15}O_2PS$ (278)	1220, 1025	3.86(d, 3H), 4.02(d, 2H), 7.22–7.86(br m, 10H)	278(M^+), 188, 156, 155, 91, 77
5.	**3e**	90	138–140/0.5	$C_{12}H_{19}O_2PS$ (258)	1230, 1020	0.83(t, 3H), 1.1–1.6(m, 7H), 2.04–2.69(m, 2H), 4.06–4.39 (m, 2H), 7.31–7.98(br m, 5H)	258(M^+), 202, 170, 142, 141, 78, 77
6.	**3f**	85	182–184/0.5	$C_{15}H_{17}O_2PS$ (292)	1220, 1020	1.33(t, 3H), 3.88–4.02(m, 2H), 4.07–4.28(m, 2H), 7.20–7.96(br m, 10H)	292(M^+), 170, 142, 141, 91, 77
7.	**3g**	91	147–148/0.5	$C_{13}H_{21}O_2PS$ (272)	1230, 1050	0.90(t, 3H), 1.05–2.58(m, 9H), 2.58–2.79(m, 2H), 4.0–4.18 (m, 2H), 7.50–7.91(br m, 5H)	272(M^+), 175, 143, 142, 141, 77
8.	**3h**	93	188–190/0.5	$C_{16}H_{19}O_2PS$ (306)	1230, 1050	0.91(t, 3H), 1.55–1.71(m, 2H), 3.86–4.11(m, 4H), 7.17–7.93(br m, 10H)	306(M^+), 143, 142, 141, 91, 77



SCHEME II



SCHEME III

alkylation at sulfur atom of ambident anion of salts **1a–c**, and are consistent with the formation of a transition state of the SN^2 type (Scheme III).

The proposed mechanism was confirmed by synthesis of pure enantiomers of model compound **3e**. DCHA salts of resolved O-ethyl phenylphosphonothioic acids[13] (+ or − isomers) on reaction with *n*-butyl bromide gave rise to **+3e** or **−3e** respectively, and possessed specific rotation of equal amounts but opposite signs.

In conclusion, our results indicate that this method is a valuable addition to the synthesis of enantiomerically pure O,S-dialkyl phenylphosphonothiolates bearing alkyl groups other than O-methyl groups.

EXPERIMENTAL

Boiling points and melting points are uncorrected. Melting points are determined with a silicon oil bath. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer. The NMR spectra were recorded on Jeol FX-90Q and EX-90 spectrometer in $CDCl_3$ (unless otherwise indicated) with Me_4Si internal standard and mass spectra on Jeol JMS DX300. Optical rotations were determined with Perkin-Elmer 241 polarimeter. Silica gel (S. Merck) was used for column chromatography. Thin layer chromatography was performed on glass plates coated with Merck Silica gel G. Alkyl halides were obtained from Merck-Schuchardt and DCHA from Aldrich Chemical Company Ltd.

DCHA salt of O-alkyl phenylphosphonothioic acids **1a–c** were prepared according to the published procedure.[13,14]

DCHA salt of O-ethyl phenylphosphonothioic acid (**1b**): Colorless crystals: yield 83%; mp 154°C. (lit[14] mp 143–144°C).

DCHA salt of O-n-propyl phenylphosphonothioic acid (**1c**): Colorless crystals: yield 85%; mp 161–162°C. Anal. Calcd for $C_{21}H_{36}NO_2PS$ (397.55): C, 63.45; H, 9.12; N, 3.52. Found: C, 63.67; H, 9.42; N, 3.14.

O,S-Dimethyl phenylphosphonothiolate (**3a**). Methyl iodide (2.8 g, 0.02 mol) was added in dry toluene (10 mL) to a clear solution of **1a** (3.7 g, 0.01 mol) in (20 mL) dry toluene (obtained by heating and then cooling to room temperature). After addition, the temperature of the reaction mixture was raised

O,S-Dimethyl phenylphosphonothiolate (**3a**). Methyl iodide (2.8 g, 0.02 mol) was added in dry toluene (10 mL) to a clear solution of 1a (3.7 g, 0.01 mol) in (20 mL) dry toluene (obtained by heating and then cooling to room temperature). After addition, the temperature of the reaction mixture was raised

slowly to 85–90°C and stirred continuously for 1 h. After completion of the reaction, the salt was filtered out and the solvent was stripped off. The crude oily liquid, thus obtained, on distillation at 114–116°C (0.05 mmHg) [lit[8] bp 110–112°C (0.08 mmHg)], yields 1.8 g (90%). Spectral data are given in Table I.

O,S-dialkyl phenylphosphonothiolates (**3b–h**) *and isolation of the salts* **4a–c**. *General procedure.* To a stirred solution of **1a** (3.7 g, 0.01 mol) in dry toluene (20 mL) a solution of *n*-propyl iodide (2.2 g, 0.012 mol) was added in dry toluene (10 mL) at 85–90°C. After stirring the reaction mixture for 1 h the solid salt was filtered out and the solvent was evaporated under reduced pressure. The crude product so obtained was dissolved in dry benzene (3 mL) and subjected to sequential column chromatography on silica gel. Elution with benzene-hexane (1:1) afforded O-methyl, S-*n*-propyl phenylphosphonothiolate (**3b**) as oily liquid. The yields, boiling points and spectral data are listed in Table I. Further elution with benzene-acetone (1:1) afforded salt **4a**. Recrystallization with hexane gave a colorless solid mp 155°C. IR (KBr), 1200 cm $^{-1}$, ^{1}H NMR δ 0.77–0.93 (t, 3H), 1.1–2.43 (br m, 24H), 2.51–2.70 (m, 2H), 2.95 (br, s, 2H), 7.26–7.98 (br m, 5H). Anal. Calcd for $C_{21}H_{36}NO_2PS$ (397.55): C, 63.45; H, 9.12. Found: C, 63.80; H, 8.86.

Compounds **3c–d** and **4b–c** were isolated from the reaction mixtures by a similar procedure. The physical properties of **3c–d** are cited in Table I, and those of **4b–c** are as follows:

4b: mp 138°C. IR(KBr), 1200 cm^{-1}, ^{1}H NMR δ 0.74–0.91 (t, 3H), 1.10–2.25 (br m, 26H), 2.48–2.70 (m, 2H), 2.95 (br s, 2H), 7.28–7.99 (br m, 5H). Anal. Calcd for $C_{22}H_{38}NO_2PS$ (411.58): C, 64.20; H 9.30. Found C, 63.89; H, 8.97.

4c: Recrystallization with hexane-benzene (8:2) mp 168°C. IR (KBr), 1200 cm^{-1}, ^{1}H NMR δ 0.75–2.18 (br m, 22H), 2.90 (br s, 2H), 3.83 (d, 2H), 7.09–8.10 (br m, 10H). Anal. Calcd for $C_{25}H_{36}NO_2PS$ (445.59): C, 67.39; H, 8.14. Found C, 67.28; H, 7.99.

Since the esters **3e–h** reported were formed as single products they were isolated by distillation under vacuum. The yields, boiling points and spectral data are given in Table I.

(+)-O-ethyl, S-n-butyl phenylphosphonothiolate (**+3e**). A solution of *n*-butyl bromide (1.6 g, 0.012 mol) in dry toluene (10 mL) was added dropwise to a stirred solution of the DCHA salt of (+)-O-ethyl phenylphosphonothioic acid $[\alpha]^{20}D$ + 9.11° (c = 5, CH_3OH), (3.83 g, 0.01 mol) in dry toluene (20 mL) at 85–90°C. After stirring for 1 h, the salt was filtered off and the solvent was evaporated under reduced pressure. The crude product was purified on a silica gel column using benzene-acetone (8:2) as the eluent to obtain 1.5 g (74%) of the product; $[\alpha]^{20}D$ + 76.35° (c = 5, $CHCl_3$).

(−)-O-ethyl, S-n-butyl phenylphosphonothiolate (**−3e**): This compound was prepared as described above from DCHA salt of (−)-O-ethyl phenylphosphonothioic acid, $[\alpha]^{20}D$ − 9.23° (c = 5, CH_3OH), and possessed $[\alpha]^{20}D$ − 76.52° (c = 5, $CHCl_3$).

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