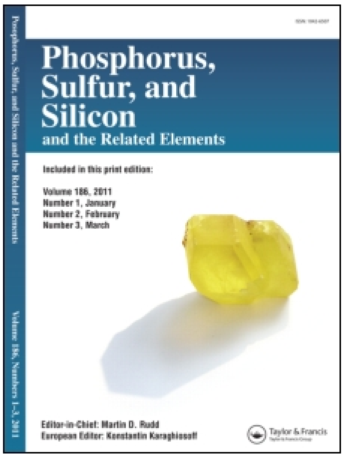

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OPTICALLY ACTIVE PHOSPHINE OXIDES. 6.[1] CONJUGATE ADDITION OF THIOLS AND ALCOHOLS TO (-)-(S)-METHYL-PHENYLVINYLPHOSPHINE OXIDE

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OPTICALLY ACTIVE PHOSPHINE OXIDES. 6.[1] CONJUGATE ADDITION OF THIOLS AND ALCOHOLS TO (−)-(S)-METHYLPHENYLVINYLPHOSPHINE OXIDE

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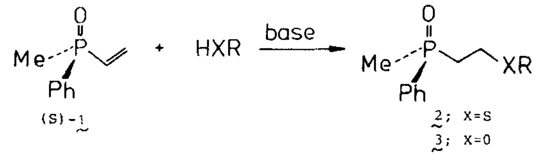
Aliphatic and aromatic thiols have been added to a homochiral methylphenylvinylphosphine oxide, (−)-**1**, to provide the first examples of optically active β-alkylthioethyl and β-arylthioethyl phosphine oxides. The additions have typically required catalysis by base although in case of arylthiols they could have been performed thermally. Base catalyzed addition of alcohols to (−)-**1** have analogously afforded optically active (β-alkoxyethyl)methylphenylphosphine oxides. Exemplary phenylsilane reduction of (−)-(β-ethylthioethyl)-methylphenylphosphine oxide to (−)-(β-ethylthioethyl)methylphenylphosphine demonstrates the facility of transformation of the synthesized adducts into optically active phosphines bearing thioether functions.

INTRODUCTION

The conjugate addition of carbon and heteroatom nucleophiles to vinyl phosphine oxides has early been recognized as a convenient method for preparation of phosphine oxides containing additional functions in the position β to phosphorus.[2] Although deoxygenated compounds of this type have found wide use as mono- and bidenate ligands in transition metal complexes the method, despite its simplicty, has not gained much favour in synthesis.[3] Recent access to enanthiomeric vinyl phospnine oxides[4,5] has reawakened interest in such additions which can now be utilized for production of variously substituted optically active phosphine oxides.[1,4–7] In this paper we wish to report that conjugate addition of thiols and alcohols to a homochiral methylphenylvinylphosphine oxide [4] yields optically active (β-alkylthioethyl)-, (β-arylthioethyl)- and (β-alkoxyethyl)-methylphenylphosphine oxides in a very straightforward fashion (Equation 1). It will also be demonstrated that simple silane reduction of the synthesized (β-alkylthioethyl)methylphenylphosphine oxides can provide novel sulphur containing *P*-chiral phosphines. Phosphine ligands incorporating either ligating or non-ligating sulphur sites are attracting considerable attention.[8]



(1)

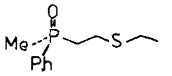
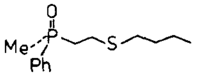
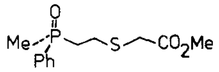
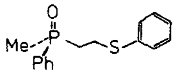
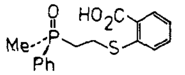
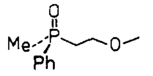
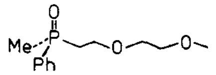
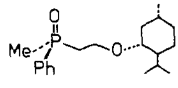
RESULTS AND DISCUSSION

Thiols are known to be good Michael-donors and their conjugate addition to (−)-(S)-methylphenylvinylphosphine oxide **1** was expected to occur readily.[9] We have found that thiophenol can be added to **1** without catalysis. The addition was very slow at room temperature providing only 7% of the adduct after 2 days bu was completed within 4 h at 110°C. Likewise, 2-mercaptobenzoic acid added to 1 thermally although in this case much longer heating (110°C, 2 days) appeared necessary to drive the reaction to completion.

The conjugate addition of aliphatic thiols to **1** could not be realized withou catalysis and typically ca. 5 mol% of an added base was required as a reaction promoter. Ordinary bases like potassium hydroxide, sodium hydride and triethyl amine served the purpose satisfactorily. In a much similar manner, the base catalyzed addition of alcohols to **1** afforded readily optically active (β

TABLE I

Optically active phosphine oxides **2** and **3** prepared by the conjugate addition of thiols and alcohols to (−)-*S*-**1**

Phosphine oxide		Yield[a] (%)	Mp[°C] or[b] bp[°C/Torr]	$[\alpha]_{589}$[c] [deg]	δ ^{31}P NMR[c] [ppm]
2a		97	240/0.45	−21.1	35.2
2b		72	210/0.1	−19.1	35.8
2c		72	210/0.1	−14.6	35.5
2d		84	94–94.5	+6.1	35.2
2e		68	149–150	−2.6[d]	39.2[e]
3a		72	170/0.2	−15.5	35.9
3b		76	220/0.1	+0.5	36.2
3c		47	f	−60.4	35.6

[a] The yields correspond to the isolated and purified material. Crude yields (^{31}P NMR) approached 100% in all cases.

[b] Melting points are uncorrected; boiling points are from Kugelrohr distillations and represent oven temperatures.

[c] In $CHCl_3$ unless indicated otherwise.

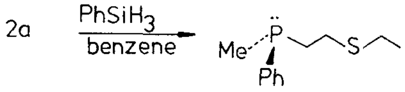
[d] In DMSO.

[e] In DMSO-d_6.

[f] An oil, distillation not attempted.

alkoxyethyl)methylphenylphosphine oxides **3**. The addition was conveniently carried out in an excess of alcohol as solvent or in an aprotic solvent when the alcohol component was less readily available.

As can be seen from the Table the yields of the studied additions are good and the process tolerates some organic functions which offer attractive possibilities for further elaboration of the side chain in the adducts. The potential utility of **2** as precursors to the previously unknown *P*-chiral phosphines bearing thioether functions is also demonstrated by an exemplary phenylsilane reduction of **2a** to the optically active **4** (Equation 2).[10]



4

(2)

It is reasonable to assume that the synthesized compounds **2** and **3** possess the S-configuration at phosphorus and that the initial optical purity of the phosphorus centre in **1** has been preserved during their syntheses. Observation of only one product of the addition of *L*-menthol to **1** corroborates this notion further.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker MSL-300 (300 MHz) or a Tesla (80 or 60 MHz) spectrometer; ^{13}C NMR spectra were taken on the Bruker or the Tesla instrument operating at 75 MHz or 25 MHz, respectively. ^{31}P NMR spectra were obtained either on a Jeol-JNM-FX-60 spectrometer at 24.3 MHz or on the Bruker MSL-300 instrument at 121.4 MHz using 85% H_3PO_4 as external standard. The optical activity measurements were performed on a Perkin Elmer 241 MC photopolarimeter. Gas chromatography analyses were carried out with a Varian Aerograph 2700 instrument with a flame-ionization detector using a 2-m glass column packed with OV-17 on Chromosorb WAW. Mass spectra were recorded on a LKB-2091 mass spectrometer under 15 and 70 eV electron impact conditions. Solvents and commercial reagents were pruified by conventional methods before use. A homochiral (−)-(S)-methylphenylvinylphosphine oxide **1** was obtained from (−)-(methoxycarbonylmethyl)phenylvinylphosphine oxide as described previously.[4] The material mp = 80°C, $[\alpha]_{589} = -80°$ (c, 3.2, $CHCl_3$) was used for the preparation of adducts **2** and **3**. All the adduct (except 2e) were checked for purity by GC and were assessed more than 97% purity. Their mp or bp, optical rotation and ^{31}P NMR data are listed in the Table.

(β-Ethylthioethyl)methylphenylphosphine Oxide **2a**. A solution of 0.33 g (2 mmol) of (−)-**1** in 2 ml of ethylmercaptan containing 0.01 g (0.1 mmol) of triethylamine was kept at room temperature for 2d. After evaporation of an excess of ethylmercaptan and triethylamine the residue was Kugelrohr distilled under reduced pressure to yield 0.44 g (97%) of **2a**. MS *m/e* 228 (M^+), 199, 168, 140 (base), 125, 77. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.13 (*t*, $J = 8$ Hz, 3H); 1.7 (d, $J = 13$ Hz, 3H); 1.95–2.95 (m, 6H); 7.37–7.87 (m, 5H). ^{13}C NMR (25 MHz, $CDCl_3$) δ: 14.6, 15.92 (d, $J = 71.3$ Hz), 23.82 (d, $J = 3.8$ Hz), 26.05, 32.5 (d, $J = 65.7$ Hz), 128.8 (d, $J = 11.3$ Hz), 130.0 (d, $J = 9.4$ Hz), 131.9 (d, $J = 3.8$ Hz), 133.1 (d, $J = 95.7$ Hz).

(β-Butylthioethyl)methylphenylphosphine Oxide **2b**. To a solution of 0.1 g (0.6 mmol) of (−)-**1** and 0.108 g (1.2 mmol of 1-butylmercaptan in 4 ml of benzene was added 0.0017 g (5 mol%) of solid potassium hydroxide and the resulting mixture was heated to reflux for 10 h. After cooling to room temperature the reaction mixture was transferred to a separatory funnel and washed once with 10% HCl aq. and twice with water. The benzene layer was separated and dried over anhydrous magnesium sulphate. After filtration and evaporation of benzene the product was isolated by a short column chromatography on silica gel using chloroform-methanol 20:1 mixture as eluent and was finally purified by a Kugelrohr distillation under reduced pressure to give 0.11 g (72%) of **2b**. MS, *m/e* 256 (M^+), 199, 168, 140 (base), 125. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 0.75 (bt, $J = 6.5$ Hz, 3 H); 1.7 (d,

$J = 12.8$ Hz, 3H); 1.15–1.6 (m, 4H); 1.85–3.1 (m, 6H); 7.33–7.91 (m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 13.6, 16.42 (d, J = 69.6 Hz), 21.94, 24.29, 31.55, 31.96, 32.63 (d, $J = 65.4$ Hz), 128.82 (d, $J = 11.4$ Hz), 130.03 (d, $J = 9.1$ Hz), 131.9, 133.13 (d, $J = 95.7$ Hz).

[β-(Methoxycarbonylmethylthio)ethyl]methylphenylphosphine Oxide **2c**. To a solution of 0.166 g (1 mmol) of (−)-**1** and 0.13 g (1.2 mmol) of methyl mercaptoacetate in 4 ml of benzene was added 0.0017 g (5 mol%) of potassium hydroxide and the resulting mixture was heated to reflux for 10 h. After cooling to room temperature the reaction mixture was transferred to a separatory funnel and washed once with 10% HCl aq. and twice with water. The benzene layer was separated and dried over anhydrous magnesium sulphate. After filtration and evaporation of benzene the crude product was purified by a Kugelrohr distillation under reduced pressure to give 0.195 g (72%) of **2c**. MS, *m/e* 272 (M$^+$), 199, 168, 140 (base), 125, 77. ^{1}H NMR (60 MHz, CDCl$_3$) δ: 1.7 (d, $J = 12.8$ Hz, 3H); 1.93–3.08 (m, 4H); 3.15 (s, 2H); 3.6 (s, 3H); 7.33–7.92 (m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 16.32 (d, J = 69.8 Hz), 25.2 (d, J = 2.6 Hz), 31.96 (d, $J = 65.4$ Hz), 33.54, 52.39, 128.8 (d, $J = 11.7$ Hz), 129.98 (d, $J = 9.5$ Hz), 131.96, 132.34 (d, $J = 97.2$ Hz), 170.49.

Methylphenyl(β-phenylthioethyl)phosphine Oxide **2d**. A solution of 0.33 g (2 mmol) of (−)-**1** and 0.253 g (2.3 mmol) of thiophenol in 4 ml of toluene was heated to reflux for 4 h. After evaporation of the solvent the residue was crystallized from hexane-benzene 1 : 1 mixture to provide 0.47 g (84%) of **2d** as white needles. MS, *m/e* 276 (M$^+$), 167, 140 (base), 125, 77. ^{1}H NMR (80 MHz, CDCl$_3$) δ: 1.64 (d, $J = 12.4$ hz, 3H); 2–2.37 (m, 2H); 2.65–3.38 (m, 2H); 7.24 (bs, 5H); 7.37–8 (m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 16.56 (d, $J = 69.8$ Hz), 26.31, 32.1 (d, $J = 65.9$ Hz), 126.65, 128.85 (d, $J = 11.4$ Hz), 129.11, 129.91, 130.07 (d, $J = 9.3$ Hz), 131.98, 132.97 (d, $J = 95.7$ Hz), 134.88.

[β-(2-Carboxyphenyl)thioethyl]methylphenylphosphine Oxide **2e**. A slurry of 0.166 g (1 mmol) of (−)-**1** and 0.41 g (2.65 mmol) of 2-mercaptobenzoic acid in 3 ml of toluene was heated to reflux for 2d. Toluene was then evaporated and the oily solid residue was repeatedly crystallized from small amounts of dimethoxyethane to provide, in four crops, 0.217 g (68%) of **2e**. MS, *m/e* 320 (M$^+$), 166 (base), 140, 139, 125, 77. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.85 (*d*, $J = 13.2$ Hz, 3H); 2.36–2.52 (m, 2H); 2.9–3.02 (m, 1H); 3.13–3.3 (m, 1H); 7.22–7.27 (m, 2H); 7.46–7.57 (m, 1H); 7.58–7.69 (m, 3H); 7.7–7.95 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 16.98 (d, $J = 69.8$ Hz), 25.4, 31.71 (d, $J = 65.4$ Hz). Only aliphatic carbons are listed; the low field signals could not be assigned with certainty due to solubility problems.

(β-Methoxyethyl)methylphenylphosphine Oxide **3a**. A solution of 0.166 g (1 mmol) of (−)-**1** and 0.0017 g (5 mol%) of potassium hydroxide in 5 ml of methanol was kept at room temperature for 5 days. Excess of methanol was then evaporated and the residue was dissolved in 10 ml of chloroform, washed with 10% HCl aq. (1 × 5 ml) and water (2 × 5 ml), dried over anhydrous magnesium sulphate and filtered. After evaporation of chloroform the residue was Kugelrohr distilled to give 0.145 g (72%) of **3a**. MS, *m/e* 199 (M$^+$ + 1), 168, 140 (base), 125. ^{1}H NMR (80 MHz, CDCl$_3$) δ: 1.74 (d, $J = 13.6$ Hz, 3H); 2–2.38 (m, 2H); 3.25 (s, 3H); 3.35–3.8 (m, 2H); 7.4–7.87 (m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 16.99 (d, $J = 70$ Hz), 32.65 (d, $J = 69.2$ Hz), 58.54, 66.03, 128.64 (d, $J = 11.6$ Hz), 129.89 (d, $J = 9.3$ Hz), 131.7, 133.24 (d, $J = 97.2$ Hz).

[β-(1-Methoxyethoxy)ethyl]methylphenylphosphine Oxide **3b**. To a solution of 0.166 g (1 mmol) of (−)-**1** in 5 ml of 2-methoxyethanol was added a glass rod-tip of sodium hydride (50% suspension in mineral oil) and the resulting mixture was kept at 124°C for 5 h. The mixture was then worked-up as described above for **3a** and gave 0.183 g (76%) of **3b**. MS, *m/e* 243 (M$^+$ + 1); 185, 183, 140, 139 (base), 125, 77. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.74 (d, $J = 13.2$ Hz, 3H); 2.19–2.29 (m, 2H); 3.31 (s, 3H); 3.32–3.62 (m, 5H); 3.75–3.85 (m, 1H); 7.41–7.52 (m, 3H); 7.67–7.74 (m, 2H). ^{13}C NMR 75 MHz, CDCl$_3$) δ: 17.01 (d, $J = 69.9$ Hz), 32.65 (d, $J = 68.9$ Hz), 58.94, 64.63, 70.15, 71.68, 128.61 (d, $J = 11.5$ Hz), 129.93 (d, $J = 9.4$ Hz), 131.64, 133.78 (d, $J = 96.5$ Hz).

(β-Menthoxyethyl)methylphenylphosphine Oxide **3c**. To a solution of 0.1 g (0.6 mmol) of (−)-**1** and 1 g (6.4 mmol) of L-menthol in 5 ml of benzene was added a glass rod-tip of sodium hydride (50% suspension in mineral oil) and the resulting mixture was heated to reflux for 6 h. The mixture was then worked-up as described above for **3a** and gave 0.092 g (47%) of **3c**. MS, *m/e* 323 (M$^+$ + 1), 185 (base), 183, 168, 140, 139. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.61–0.93 (m, 3H); 0.63 (d, $J = 6.9$ Hz, 3H); 0.77 (d, $J = 7.1$ Hz, 3H); 0.83 (d, $J = 6.6$ Hz, 3H); 1.03–1.12 (m, 1H); 1.17–1.29 (m, 1H); 1.3–1.57 (m, 2H); 1.94–2.08 (m, 2H); 2.09–2.28 (m, 2H); 2.88–2.95 (m, 1H); 3.36–3.48 (m, 1H); 3.84–4.01 (m, 1H); 7.23–7.47 (m, 3H); 7.49–7.7 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 16.37, 17.09 (d, $J = 69.9$ Hz), 20.95, 22.28, 23.45, 25.73, 39.87, 31.54, 33.26 (d, $J = 69.2$ Hz); 34.54, 40.41, 48.29, 61.69, 79.66, 128.63 (d, $J = 11.6$ Hz); 129.92 (d, $J = 9.4$ Hz); 131.62, 134.17 (d, $J = 96.7$ Hz).

(β-Ethylthioethyl)methylphenylphosphine **4**. To a deaerated solution of 0.2 g (0.88 mmol) of **2a** in 1 ml of benzene was added via syringe an excess (0.5 g, 4.6 mmol) of freshly distilled phenylsilane and the resulting mixture was heated to reflux under argon atmosphere until ^{31}P NMR monitoring of the reaction indicated practically complete reduction of **2a** (34 h). Benzene and unreacted phenylsilane were then removed under reduced pressure and the product was isolated from the residue by Kugelrohr distillation. **4**: 0.102 g (54.5%), bp = 90–95°C/0.3 Torr (oven temperature). The distillate was dissolved in $CHCl_3$ (under argon) and transferred into a polarimeter cell for the optical rotation measurement; $[\alpha]_{589} = -10.4°$ (c, 2.1, $CHCl_3$). The sample recovered from the optical rotation measurement was subsequently dissolved in $CDCl_3$ and subjected to spectral analysis. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13 (t, $J = 7.4$ Hz, 3H), 1.44 (s, 3H), 2.01–2.1 (m, 2H), 2.45 (q, $J = 7.4$ Hz, 2H), 2.41–2.55 (m, 2H), 7.29–7.34 (m, 3H), 7.4–7.54 (m, 2H). ^{13}C NMR (25 MHz, $CDCl_3$) δ: 10.59 (d, $J = 3.8$ Hz), 14.63, 25.83, 27.35 (d, $J = 13.2$ Hz), 29.0 (d, $J = 5.6$ hz), 128.7 (d, $J = 7.5$ hz), 129.5, 131.6 (d, $J = 15$ Hz). ^{31}P NMR (24.3 MHz, $CDCl_3$) δ: −29.9. Phosphine **4** was found to be very easily oxidized. The recorded spectra indicated some contamination of the sample by a slowly increasing amount of **2a**. The sample was finally authenticated by its reoxidation with aqueous hydrogen peroxide which provided the expected phosphine oxide **2a** as the main product.

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