Use of Dibenzophosphole Oxides in the Horner Reaction: Stereospecific Formation of (*Z*)-Stilbene from an *erythro*-β-Hydroxyalkylphosphine Oxide

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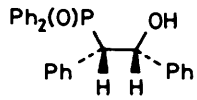
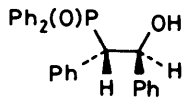
Treatment of the *erythro*-β-hydroxyalkyldibenzophosphole oxide (**6**), derived from (*E*)-stilbene oxide and lithiodibenzophosphole, with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in dimethyl sulphoxide (DMSO) affords (*Z*)-stilbene with high stereospecificity.

In an earlier paper we described the results of an investigation into the preparation of stilbene from the diastereoisomeric 1,2-diphenyl-2-diphenylphosphinoylethan-1-ols (**1**) and (**2**)[1] in order to clarify some details of the work by Horner and Klink[2] on this system. As expected for a *syn* elimination mechanism, treatment of the *threo*-isomer (**2**) with base gave (*E*)-stilbene stereospecifically. However under most conditions, base treatment of the *erythro*-isomer (**1**) also gave predominantly (*E*)-stilbene, together with variable amounts of benzyldiphenylphosphine oxide. This conversion of *erythro*-isomer (**1**) into (*E*)-stilbene was shown to occur *via* fragmentation to $Ph_2POCHLiPh$ and PhCHO followed by recombination to the anion of the *threo*-isomer (**2**) and then elimination. Apparently the combined influence of unfavourable Ph–Ph eclipsing interactions in the *syn*-elimination pathway from (**1**) and the relatively high acidity of benzyldiphenylphosphine oxide conspire to disfavour the formation of (*Z*)-stilbene from (**1**). In contrast, *erythro*-1,2-disubstituted 2-diphenylphosphinoylethan-1-ols with an alkyl group at C-2 give (*Z*)-alkenes stereospecifically on treatment with base.[3]



(**1**)

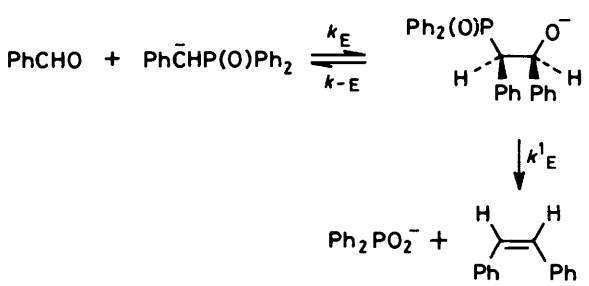


(**2**)

In a similar vein, a recent paper dealing with the diethyl phosphonates analogous to (**1**) and (**2**) has shown that either diastereoisomer, on base treatment under a range of conditions, inevitably gives (*E*)-stilbene.[4]

In order to achieve efficient formation of (*Z*)-stilbene from and *erythro*-precursor of type (**1**) it is thus necessary to favour the phosphinate elimination (k^1_E) relative to the 'reverse aldol' fragmentation (k_{-E}) (Scheme 1).

It is well known that incorporation of P^V into a five-membered ring can lead to markedly enhanced rates of reaction where a trigonal bipyramidal intermediate is involved;[5] and

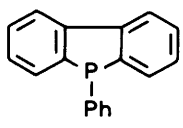


Scheme 1.

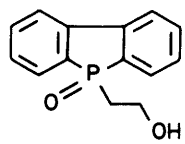
there are a number of cases in the literature where, on starting from, for example, a metallated phosphonate or ylide and an aldehyde, enhanced (*Z*):(*E*) ratios are obtained when the phosphorus atom is incorporated in a five-membered ring.[6] However there do not appear to be any examples of an isolated β-hydroxyalkylphosphine oxide, β-hydroxyphosphonate, or phosphorus betaine where the possible influence of the five-membered ring heterocycle has been explored. Accordingly we decided to investigate a β-hydroxyalkylphosphine oxide of this type.

5-Phenyldibenzophosphole (**3**) was prepared essentially according to the literature procedure.[7] Conditions for reductive cleavage of (**3**), hydroxyalkylation with an epoxide and oxidation to the β-hydroxyphosphine oxide were worked out using ethylene oxide. In our hands cleavage was best accomplished using lithium in liquid ammonia (at −78 °C) rather than lithium in tetrahydrofuran (THF);[8] ethylene oxide was added at −35 °C. After oxidation, 2-hydroxyethyldibenzophosphole oxide (**4**) was obtained in 68% yield from (**3**).

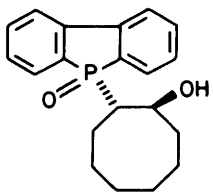
To confirm that 2-hydroxydibenzophosphole oxides could be used for olefin synthesis in a Horner elimination, we prepared the *trans*-2-hydroxycyclo-octyl analogue (**5**) from 1,2-epoxycyclo-octane. Treatment of (**5**) with sodium hydride in dimethyl sulphoxide (DMSO) gave *trans*-cyclo-octene (42%). The yield, though only moderate, showed that stereospecific elimination in this system was a viable process.



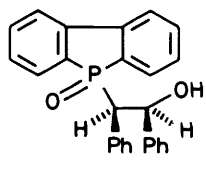
(**3**)



(**4**)



(**5**)



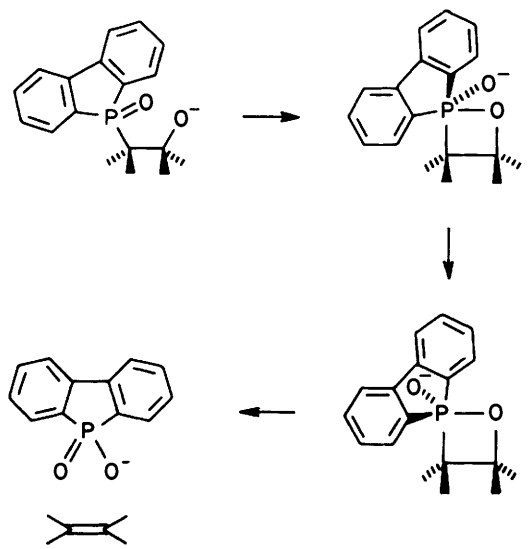
(**6**)

Alkylation of lithiodibenzophosphole, prepared as above in liquid ammonia, with (*E*)-stilbene oxide (8 h at −33 °C), followed by oxidative work-up gave a single β-hydroxyalkylphosphole oxide. Since all previous examples of ring opening of 1,2-disubstituted epoxides, including (*E*)-stilbene oxide, with lithium diphenylphosphide led to clean inversion of configur-

ation,[9] the assignment of the *erythro*-configuration (**6**) to the product would seem to be unequivocal.

Owing to the poor solubility of the phosphole oxide (**6**) in many solvents, elimination experiments were carried out in DMSO. In our previous work,[1] treatment of the *erythro*-isomer (**1**) with sodium hydride in DMSO at 25 °C gave (*E*)-stilbene (78%) and benzyldiphenylphosphine oxide (19%). Treatment of the *erythro*-dibenzophosphole oxide (**6**) under the same conditions gave a mixture of stilbenes (91%) comprising (*Z*)-stilbene (89%) and (*E*)-stilbene (11%). Clearly the desired enhancement of the *syn*-elimination pathway from (**6**) had occurred. Furthermore, previous investigations had shown that the organic base 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) led to optimum formation of (*Z*)-stilbene from (**1**) even though the reverse aldol product predominated. Phosphole oxide (**6**) was therefore treated with DBU in DMSO at 60 °C to give stilbene (93%), shown to be greater than 99% (*Z*)-isomer by g.l.c.

The combination of five-ring phosphine oxide and use of an organic base has thus led to highly stereospecific *syn*-elimination of phosphinate from the *erythro*-β-hydroxyphosphine oxide. Incidentally the experiment gives indirect support for oxaphosphetan intermediates in the elimination reaction. A possible pathway tentatively envisaged is that shown in Scheme 2, involving apical entry of alkoxy O^- with equatorial placement of PO^-, followed by 'pseudorotation' and then olefin formation in which the leading process is cleavage of the apical P–C bond. The 'small ring' effect obviously ensures rapid collapse to the oxaphosphetan before the reverse aldol can take place.



Scheme 2.

Presumably this stratagem of using the phosphole oxide could be employed in other cases where successful Horner elimination is foiled by 'reverse-aldol' reaction (k_{-E} step in Scheme 1).

We tried briefly to compare the nucleophilicity of the lithium derivatives of diphenylphosphine and dibenzophosphole by treating a mixture of approximately 1 equiv. of each with 1 equiv. of (*E*)-stilbene oxide in liquid ammonia. After oxidative work-up the diphenylphosphine oxide (**1**) was isolated while the dibenzophosphole was converted into the corresponding phosphinic acid. Apparently, under the above conditions, lithium diphenylphosphide is effectively the better nucleophile.

Experimental

2-*Hydroxyethyldibenzophosphole Oxide*.—Lithium pieces (*ca.* 0.3 g) were added gradually to a stirred suspension of 5-phenyldibenzophosphole[7] (3.67 g, 14 mmol) in liquid ammonia (100 ml) at −78 °C until the mixture was a yellow–green. The mixture was then allowed to warm up to −35 °C, and ethylene oxide (1.76 g, 0.04 mol) in ether (20 ml) was added dropwise over 10 min. After a further 1 h the ammonia was evaporated off. Acetic acid (4 ml) and hydrogen peroxide solution (30%; 20 ml) were added and the mixture was stirred at 0 °C for 3 h. Aqueous sodium hydroxide (50 ml) and dichloromethane (75 ml) were added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (×3) and the combined organic layers were dried ($MgSO_4$) and evaporated to give a solid (2.98 g). Recrystallisation of this from ethyl acetate gave the *phosphole oxide* (**4**) (2.34 g, 68%), m.p. 172—175 °C (Found: C, 68.5; H, 5.2; P, 12.45. $C_{14}H_{13}O_2P$ requires C, 68.85; H, 5.35; P, 12.7%); δ($CDCl_3$) 2.35 (2 H, d of t, J_{PH} 11.5 and J_{HH} 6 Hz, 1-H), 3.68 (1 H, s, OH), 4.17 (2 H, d of t, J_{PH} 17 and J_{HH} 6 Hz, 2-H), and 7.3—8.05 (8 H, m).

trans-2-*Hydroxycyclo-octyldibenzophosphole Oxide*.—Lithium pieces (*ca.* 0.4 g) were added gradually to a stirred suspension of 5-phenyldibenzophosphole (4.9 g, 19 mmol) in liquid ammonia (100 ml) at −78 °C until the resulting mixture was yellow–green. After warming to −33 °C, 9-oxa-*cis*-bicyclo-[6.1.0]nonane (2.52 g, 20 mmol) in ether (40 ml) was added dropwise over 10 min. The mixture was stirred for 6 h at −33 °C and the ammonia was allowed to evaporate off. The ether was evaporated, and the residue was stirred with acetic acid (4 ml) and aqueous hydrogen peroxide (30%; 20 ml) at 0 °C for 3 h. Aqueous sodium hydroxide (1M; 50 ml) was added and the product was isolated by extraction with dichloromethane (3 × 75 ml). Evaporation of the dried ($MgSO_4$) extract and crystallisation of the residue from ethyl acetate–light petroleum (b.p. 40—60 °C) (1:1) gave the *phosphole oxide* (**5**) (3.27 g, 50%), m.p. 144—146 °C (Found: C, 73.6; H, 7.05; P, 9.65. $C_{20}H_{23}O_2P$ requires C, 73.6; H, 7.1; P, 9.5%); δ($CDCl_3$) 0.75—2.05 (12 H, m, ring methylenes), 2.62 (1 H, m, 1-H), 4.48 (1 H, m, 2-H), 5.32 (1 H, s, OH), and 7.3—8.0 (8 H, m).

erythro-2-*Hydroxy*-1,2-*diphenylethyldibenzophosphole Oxide*.—Lithium pieces (*ca.* 0.7 g) were added gradually to a stirred suspension of 5-phenyldibenzophosphole (13 g, 50 mmol) in liquid ammonia (250 ml) at −78 °C until a yellow–green colour persisted. After the mixture had warmed to −33 °C, (*E*)-stilbene oxide (9.8 g, 50 mmol) in ether (150 ml) was added and stirring continued at −33 °C for 8 h. Removal of ammonia and ether by evaporation was followed by oxidation with hydrogen peroxide (30%; 60 ml) in acetic acid (12 ml) (0 °C, 4 h). After addition of aqueous sodium hydroxide (100 ml) the product was isolated with dichloromethane (3 × 100 ml) as a solid. Recrystallisation of this from benzene gave the *phosphole oxide* (**6**) (13.1 g, 66%), m.p. 224—228 °C (Found: C, 78.6; H, 5.3; P, 7.75. $C_{26}H_{21}O_2P$ requires C, 78.75; H, 5.35; P, 7.8%); δ[$(CD_3)_2SO$] 4.19 (1 H, dd, J_{PH} 19, J_{HH} 4 Hz, 1-H), 5.93 (1 H, ddd, $J_{PH} \sim J_{H,OH} \sim J_{H,H} \sim 4$ Hz), 6.4 (1 H, d, $J_{H,OH}$ 4 Hz), and 6.55—8.15 (18 H, m).

trans-*Cyclo-octene*.—Sodium hydride in oil suspension (80%, 0.4 g) was washed with light petroleum under nitrogen and *trans*-2-hydroxycyclo-oct-1-yldibenzophosphole oxide (1.25 g) in DMSO (40 ml) was added with stirring. After 1.5 h at 18 °C, water (100 ml) was added to the dark solution. Extraction of the product with light petroleum (b.p. 30—40 °C) was followed by washing of the extracts with water. Evaporation of the dried ($MgSO_4$) solution under reduced pressure at 0 °C gave *trans*-

cyclo-octane (0.18 g, 42%) which was identified by its n.m.r. spectrum.[10]

Stilbene from erythro-2-*Hydroxy*-1,2-*diphenylethyldibenzophosphole Oxide.*—(a) Sodium hydride in oil suspension (80%, 1 g) was washed with light petroleum (b.p. 30—40 °C) under nitrogen and the dibenzophosphole oxide (4.3 g, 11 mmol) in DMSO was added with stirring. After 3.5 h, dilution with water (200 ml) was followed by extraction with light petroleum (b.p. 40—60 °C; 3 × 100 ml). The combined organic extracts were washed with water (3 × 100 ml), dried ($MgSO_4$), and evaporated to give the mixture of stilbenes as an oil (1.8 g, 91%) shown by g.l.c. to comprise 89% (*Z*)- and 11% (*E*)-isomer.

(b) DBU (0.8 g, 5 mmol) in DMSO (10 ml) was added to the dibenzophosphole oxide (0.97 g, 2.5 mmol) in DMSO (20 ml) with stirring. After 3 h at 60 °C the product was isolated as in (a) above to give an oil (0.41 g, 93%) shown by g.l.c. to be (*Z*)-stilbene containing only a trace (*ca.* 1%) of (*E*)-isomer; $\delta(CDCl_3)$ 6.6 (2 H, s, =CH) and 7.2 (10 H, s, ArH).

Competitive Reaction of Lithium Diphenylphosphide and Lithiated Dibenzophosphole with (E)-*Stilbene Oxide.*—A mixture of triphenylphosphine (2.35 g, 9 mmol) and 5-phenyldibenzophosphole (2.35 g, 9 mmol) were stirred in liquid ammonia (100 ml) at −78 °C and lithium pieces were gradually added until a yellow–green colour persisted. After the mixture had warmed to −33 °C, (*E*)-stilbene oxide (1.765 g, 9 mmol) in ether (50 ml) was added and stirring was continued for 8 h. The ammonia and ether were removed by evaporation, and the residue was oxidised with hydrogen peroxide (30%, 20 ml)–acetic acid (4 ml) at 0 °C (3 h). Aqueous sodium hydroxide (1M; 50 ml) and dichloromethane (75 ml) were added and the organic layer was separated and combined with further dichloromethane extracts (3 × 75 ml) of the aqueous layer. The solution was dried ($MgSO_4$) and evaporated to give a solid (2.96 g, 82%) identified by n.m.r. ($CDCl_3$) as *erythro*-2-hydroxy-1,2-diphenylethyldiphenylphosphine oxide.[1] Examination of the n.m.r. spectrum in $(CD_3)_2SO$ confirmed the absence of dibenzophosphole oxide.

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