New Routes to Optically Active Phosphorus Compounds. Asymmetric Alkylation of Phosphide Anions

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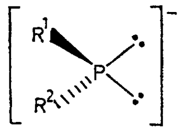
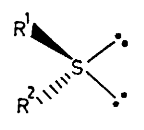
Summary The reaction of sodium methylphenylphosphide with (+)-(*R*)-1-chloroethylbenzene gives (−)-(S_P)-(S_C)-α-methylbenzylmethylphenylphosphine oxide after oxidation; the optical purities at phosphorus and carbon have been determined.

Attempts at asymmetric oxidation of tervalent phosphorus compounds have been singularly unsuccessful,[1] although similar oxidations of amines[2] and sulphides[3] give the corresponding amine oxide and sulphoxide as optically active products. In our search for new routes to optically active phosphorus compounds and in view of the difficulties due to the low rate of tervalent phosphorus inversion, we studied the reactions of the phosphide anions (**1**) which are isoelectronic with sulphides (**2**).

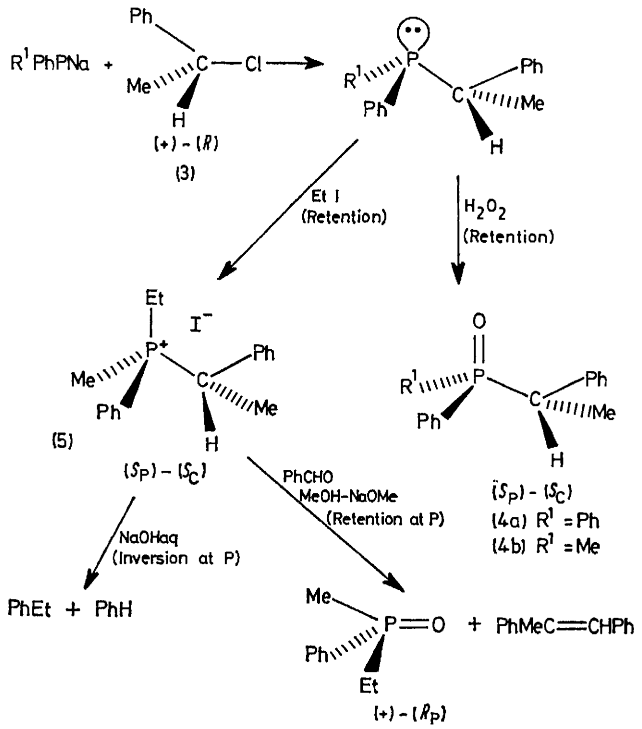
Oxidation of phosphide anions leads to readily racemised products and so reaction with optically active alkyl halides was initially investigated. Reaction of sodium diphenylphosphide with the halide (**3**), $[\alpha]_D^{25}$ + 109·74° (neat), in tetrahydrofuran (THF) at −50° gave, after peroxide oxidation, the oxide (**4a**) (70%), $[\alpha]_D^{25}$ −48·9° (c = 1·0, MeOH), m.p. 156—157°. A similar reaction of sodium methylphenylphosphide with (**3**) gave oxide (**4b**),† $[\alpha]_D^{25}$ −6·9° (c = 1·0, MeOH), as a mixture of diastereoisomers (63:37 by n.m.r. spectroscopy)‡ from which the major diastereoisomer could be obtained pure, $[\alpha]_D^{25}$ −3° (c = 1·0, MeOH), by chromatography on silica gel.



(1)



(2)



In order to determine the optical purity at phosphorus, and hence at carbon, in (**4b**), the reaction product of phosphide with (**3**) was converted into the salt (**5**) by reaction with EtI. Alkaline hydrolysis of (**5**) (inversion at phosphorus) gave a hygroscopic oil and g.l.c. of the reaction mixture showed the presence of both benzene and ethyl benzene; competitive loss of both benzyl and phenyl groups obviously takes place. The Wittig reaction of (**5**) (retention at phosphorus) with benzaldehyde and NaOMe in MeOH gave, after chromatography on silica gel, a high yield of methylstilbene and a colourless oil, $[\alpha]_D^{25}$ + 2·5° (c = 1·0, MeOH), which could not be crystallised, but was identical (i.r. spectroscopy) with an authentic sample of ethylmethylphenylphosphine oxide; comparison with optically pure oxide[5] indicates the R-configuration and 10% optical purity at phosphorus. Attempts to confirm this result through the use of optically active shift reagents failed and resulted only in broad, unresolved n.m.r. spectra.

A further estimation of optical purity in (4**b**) was provided by the use of Mislow's method[5] to obtain (R_P)-(**4b**), $[\alpha]_D^{25}$ + 30·1° (c = 1·0, MeOH), optically pure at phosphorus,§ as a diastereoisomeric mixture (62:38 by n.m.r. spectroscopy) which could be equilibrated to another diastereoisomeric mixture (17:83), $[\alpha]_D^{25}$ −13·9° (c = 1·0, MeOH), by treatment with BuLi and water quenching.¶ These results give the specific rotation of individual diastereoisomers (optically pure at phosphorus) as −31 and +68° respectively. The use of these values in conjunction with the rotations obtained for diastereoisomeric mixtures from the reaction of methylphenylphosphide with (+)-(R)-(**3**) gave the optical purity of (**4b**) as isolated directly from the phosphidehalide reaction after oxidation as 12·8% (S_C)** and 2·8% (S_P). The value for phosphorus is in the region expected for induced asymmetry (see refs. 2 and 3). The low value for carbon could be due to a large S_N1 mechanistic contribution; however, nucleophilic substitutions of (**3**) are largely second-order even in more polar solvents.[6] Racemisation during or after oxidation at neutral pH seems unlikely; this is supported by the similar results obtained from the corresponding sulphide. Base-catalysed racemisation in the initially formed phosphine seems most likely, although experiments involving inverse addition and hence a deficiency of basic phosphide give ambiguous results.

The (S_P) configuration of (**4b**) agrees with that obtained from a study of the Wittig reaction.

We thank the S.R.C. for a fellowship (R.A.N.), and Professor G. M. Whitesides for samples of shift reagents.

(*Received*, 11*th November* 1974; *Com.* 1380.)

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† Satisfactory analyses were obtained for all new compounds.

‡ This value is supported by ratios from ^{31}P n.m.r. spectra. A similar ratio was observed for the corresponding sulphide formed by treatment of the reaction product with sulphur. All diastereoisomer ratios were determined on crude products unless otherwise stated.

§ Recent work indicates that phosphine oxides prepared by this method are not optically pure since some racemisation takes place in the final step; however, they are still 90% optically pure and the error introduced by this assumption is minimal.

¶ Similar treatment of a sample of (**4a**) gives (**4a**) with $[\alpha]_D^{25}$ 0° (MeOH).

** This assumes net inversion at carbon; however the assignment of the (S) configuration to the phosphorus centre is independent of this assumption.

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