Optically Active Trivalent Phosphorus Acids Esters: An Approach by Asymmetric Synthesis

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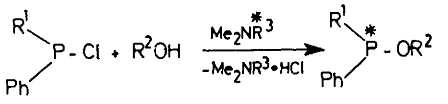
Summary The reaction of chiral P^{III} chlorides with achiral alcohols or thiols in the presence of optically active tertiary amines gives the hitherto unknown optically active trivalent phosphorus acids esters, the absolute configuration and optical purity of which was determined chemically by conversion into known phosphine oxides or phosphonodithioates.

Trigonal-pyramidal, three-co-ordinate phosphorus compounds with three different ligands, $R^1R^2R^3P$:, are chiral at phosphorus and can in principle be resolved into enantiomers or prepared in optically active forms, although very few optically active compounds of this type have been obtained so far. Most information is available on the optically active tertiary phosphines first prepared by Horner in 1961.[1] Recently Benschop *et al.*[2] have synthesized optically active *O*-trimethylsilyl *O*-isopropyl methylphosphonite, the first example of an optically active trivalent phosphorus compound containing a phosphorus–oxygen bond. However, the presence of the trimethylsilyl group is a serious limitation for studies on organophosphorus reaction mechanisms since nucleophilic reagents prefer to react at silicon rather than phosphorus.

We report a general approach to simple, hitherto unknown, optically active trivalent phosphorus esters based on asymmetric reaction between chiral P^{III}-chlorides and achiral alcohols or thiols in the presence of optically active tertiary amines.†

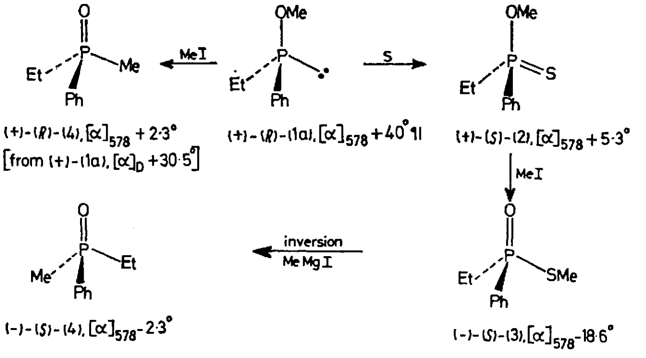


* = optically active centre

(**1a**) $R^1 = Et$, $R^3 = Me$, $[\alpha]_{578} + 30{\cdot}5°$‡
(**1b**) $R^1 = Et$, $R^2 = Pr^n$, $[\alpha]_{578} + 17{\cdot}1°$
(**1c**) $R^1 = Me$, $R^2 = Me$, $[\alpha]_{578} + 15{\cdot}8°$
(**1d**) $R^1 = Me$, $R^2 = Pr^n$, $[\alpha]_{578} + 27{\cdot}2°$
$R^3 = (-)\text{-PhCHMe-}$

We have prepared the optically active phosphinites (**1**) by the reaction of asymmetric chlorophosphines with simple alcohols in the presence of (—)-NN-dimethyl-(1-phenyl ethyl)amine at *ca.* —70° in ether solution under nitrogen. The usual work-up (filtration under N_2, removal of ether) gave the crude esters (**1**) which were purified by distillation under reduced pressure (2 mmHg). Their purity was checked by ^{31}P-n.m.r. spectroscopy.

The chirality at phosphorus in the ester (+)-(**1a**) follows from chemical correlation with (—)-(*S*)- or (+)-(*R*)-methylethylphenylphosphine oxide (**4**) (Scheme **1**).



Scheme 1

(+)-*O*-Methyl ethylphenylphosphinite (**1a**), $[\alpha]_{578} + 40°$,§ prepared as above was treated *in situ* with sulphur to afford (+)-*O*-methyl ethylphenylphosphinothionate (**2**), $[\alpha]_{578} + 5{\cdot}5°$, which was in turn converted into (—)-*S*-methyl ethylphenylphosphinothiolate (**3**), $[\alpha]_{578} - 18{\cdot}6°$, by the Pishschimuka reaction with MeI. Reaction of (—)-(**3**) with MeMgI gave (—)-(*S*)-methylethylphenylphosphine oxide (**4**), $[\alpha]_{578} - 2{\cdot}3°$ (MeOH, 10% optical purity).[3]

Since sulphur addition to P^{III}-compounds proceeds with retention of configuration at phosphorus[4] and during the thiono–thiolo isomerization (**2**) → (**3**) there is no bond breaking around phosphorus[5] and since reactions of Grignard reagents with phosphinothiolates occur with predominant inversion of configuration,[6] the chirality at phosphorus in (+)-(**1a**) is assigned as (*R*). Independent support of this conclusion comes from the reaction of (+)-(**1a**), $[\alpha]_{578} + 30{\cdot}5°$, with MeI ¶ affording directly the (+)-(*R*) phosphine oxide (**4**), $[\alpha]_{578} + 2{\cdot}3°$ (MeOH), a reaction which proceeds with retention of configuration at phosphorus.

Although the optical purity of the phosphine oxide (**4**) so formed is 10% the extent of the asymmetric induction in the reaction discussed here is expected to be higher since the Arbusov reaction as well as the conversion of phosphino-

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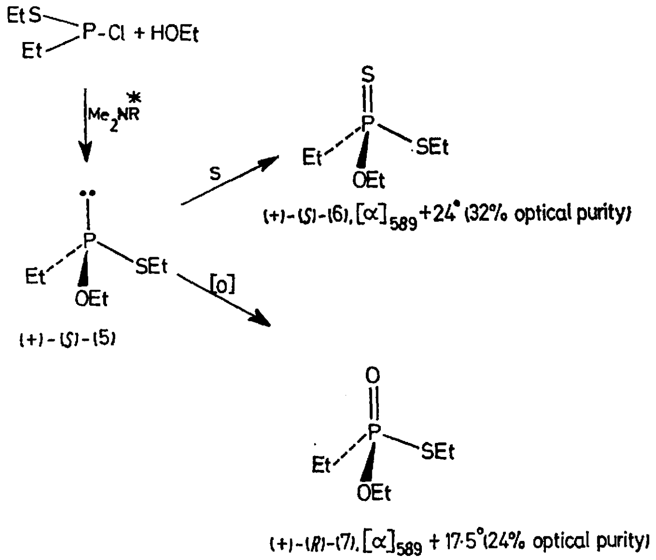
† Optically active tertiary amines have recently been used in the synthesis of optically active sulphinic esters (M. Mikołajczyk and J. Drabowicz, *J.C.S. Chem. Comm.*, 1974, 547).

‡ Rotations refer to neat compounds unless otherwise noted.

§ Since we did not isolate this sample, its rotation value was calculated based on the conversion of the isolated ester (+)-(**1a**), $[\alpha]_{578} + 30{\cdot}5°$, into (—)-(**3**), $[\alpha]_{578} - 14{\cdot}2°$, *via* (+)-(**2**). This indicates that some loss of optical activity takes place during isolation procedure.

¶ The ester (+)-(**1a**) was added dropwise to refluxing MeI.



SCHEME 2

The distilled esters (+)-(*S*)-(**6**) and (+)-(*R*)-(**7**) were further purified by g.l.c.

thiolates into phosphine oxides take place with some loss of stereospecificity.[6] The configuration at phosphorus in (+)-(**1c**) and (+)-(**1d**) was similarly assigned as (*R*).

Reaction of *S*-ethyl ethylphosphonochloridite with ethanol in the presence of (−)-*NN*-dimethyl-(1-phenylethyl)amine gave the optically active (+)-*O*-ethyl *S*-ethyl ethylphosphonite (**5**). It was converted without isolation into (+)-(*S*)-*O*-ethyl *S*-ethyl ethylphosphonodithionate (**6**), $[\alpha]_{578}$ + 24° (32% optical purity),[7,8] and (+)-(*R*)-*O*-ethyl *S*-ethyl ethylphosphonothiolate (**7**), $[\alpha]_{589}$ + 17·5° (24% optical purity),[8,9] by treatment with sulphur and *m*-chloroperbenzoic acid, respectively.

Since both reactions occur with retention of configuration, the chirality at phosphorus in the starting ester (**5**) should be (*S*). The extent of asymmetric induction observed in the last case is relatively high, *ca.* 30%.

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