Alkoxide Ion *vs.* Methylthiolate Ion Displacement in the Grignard Reaction on *O*-Alkyl *S*-Methyl Phenylphosphonothiolate

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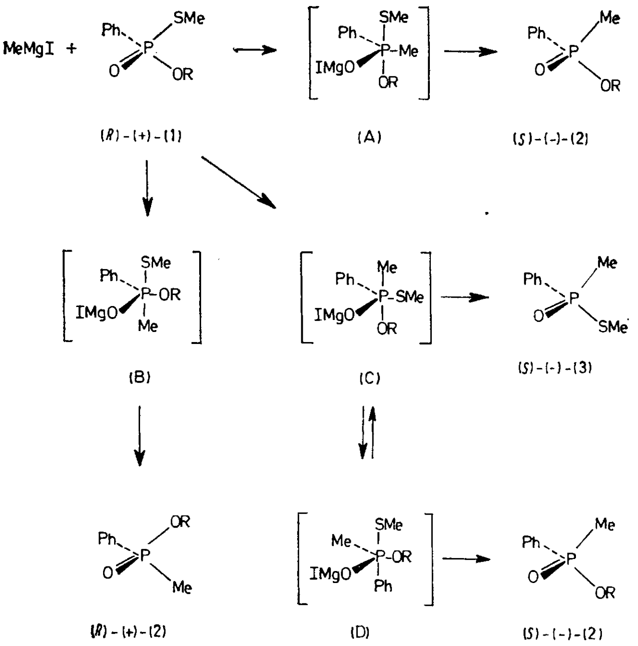
Summary MeMgI reacts with *O*-alkyl *S*-methyl phenylphosphonothiolates to displace either the methylthio group with retention of configuration at phosphorus or the alkoxy group with inversion, the competition depending on the nature of the alkoxy group.

The reactions of MeMgBr with PhP(O)(SMe)(O-menthyl)[1] and PhMgBr with MeP(O)(SMe)(OPr^i)[2] have been shown to proceed by displacement of the MeS group with retention of configuration at phosphorus. We report that the pathway for these reactions is dependent on the nature of the alkoxy group such that displacement of the alkoxy group and not the alkylthio group becomes the dominant reaction with PhP(O)(SMe)(OMe) and proceeds with inversion of configuration at phosphorus.

Optically pure (*R*)-(+) PhP(O)(SMe)(OMe) (**1a**)[3,4] and PhP(O)(SMe)(OPr^i) (**1b**)[4] were treated in separate experiments with 2 equiv. of MeMgI as a filtered solution in benzene at *ca.* 15 °C. In both reactions, products from competitive displacements of the methylthio group or the alkoxy group occurred to give PhP(O)(Me)(OR) (**2**) or PhP(O)(SMe)(Me) (**3**) respectively. In order to evaluate this competititon quantitatively, the reactions were quenched at *ca.* 1 half-life, avoiding the complication of further competitive displacements to give PhP(O)Me$_2$ and analysed directly by ^{1}H n.m.r. spectroscopy. For comparison, the reaction[1] of MeMgBr with $(S)_P$ PhP(O)(SMe)(O-menthyl) (**1c**) was repeated using MeMgI and quenched at partial completion in an attempt to detect the presence of the product (**3**); however, only $(R)_P$ PhP(O)(Me)(O-menthyl) (**2c**) could be detected.

The stereochemistry of products (**2a**; R = Me) from the reaction of (**1a**; R = Me), and (**3**) from the reactions of both (**1a**; R = Me) and (**1b**; R = Pr^i), was determined by ^{1}H n.m.r. spectroscopy in the chiral solvent (+)-1-phenyl-2,2,2-trifluoroethanol. The difference in chemical shift ($\Delta\delta = \delta_R - \delta_S$) between enantiomers was +2·5 Hz for the POMe resonance of (**2a**; R = Me) and +3·3 Hz for the PMe resonance of (**3**) as determined on independently prepared samples of these products. The stereochemistry of (**2b**; R = Pr^i) was determined polarimetrically after treating the product mixture from (**1b**; R = Pr^i), containing (**1b**), (**2b**), and (**3**), with 1 M NaOH in 30% aqueous dioxan, removing (**1b**) and (**3**) by their selective hydrolysis to the corresponding acid anions, and leaving (**2b**) as the neutral ester. The Table lists the yield and the stereochemistry of the products.†

Three important observations can be made from the results: (i) as the size of the alkoxy group is reduced with improved leaving ability, the displacement of the alkoxy group occurs more readily than that of the methylthio group, (ii) although MeS$^-$ would be expected to be a better leaving group than MeO$^-$, displacement of the latter is preferred in the reaction of (**1a**; R = Me), and (iii) in all cases, displacement of the methylthio group occurs with retention of the configuration at phosphorus while displacement of the alkoxy group occurs with inversion.



Scheme

Of the three possible modes for reaction of MeMgI with (**1**) shown in the Scheme, only the pathway involving initial

Table. The reaction of PhP(O)(SMe)(OR) with MeMgI.[a]

	PhP(O)(SMe)(OR) (**1**)			Ph(P)(O)(Me)(OR) (**2**)			PhP(O)(SMe)(Me) (**3**)		
	R	Config.	$[\alpha]_D$	Yield/%[c]	Config.	%e.e.[d]	Yield/%[c]	Config.	%e.e.[d]
(**1a**)	Me	(*R*)[e]	+120°	25	(*S*)[f]	88	75	(*S*)[g]	>95
(**1b**)	Pr^i	(*R*)[e]	+119°	80	(*S*)[h]	>95[i]	20	(*S*)[g]	>95
(**1c**)	Menthyl	$(S)_P$[j]	−141°	100	$(R)_P$[j]	>95	0[k]	—	—

[a] In benzene at 15 °C. [b] Rotations in benzene (*c* 2·0—4·0). [c] % of total phosphinate and phosphinothioate products. [d] % Excess enantiomer = 100 × [(*S*) − (*R*)]/[(*S*) + (*R*)]. [e] Ref. 4. [f] Ref. 5. [g] Refs. 1, 6, and 7. [h] Refs. 2 and 6. [i] Optically pure (*S*) (**2b**) was assumed[4] to have $[\alpha]_D = -54°$. [j] Ref. 1. [k] Not detected by ^{1}H n.m.r. spectroscopy.

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† Similar product ratios were obtained with ether as solvent and the stereochemistry of the reactions was independent of solvent (ether *vs.* benzene), progress of the reaction (36—65% completion), or mole ratio of MeMgI to (**1**) (1·0—4·6).

formation of the intermediate (C) is consistent with the above results. Loss of magnesium alkoxide directly from (C), resulting in the formation of (**3**) with inversion of configuration, is competitive with isomerization to, *e.g.*, (D) which rapidly loses MgSMe to form (**2**) with retention. The degree of competition is determined by the leaving ability of the alkoxide ion and, to a lesser extent,[5] by the steric preference for the more bulky alkoxy-group to occupy the less hindered equatorial position as in (D). This scheme parallels that advanced[7] for the alkaline hydrolysis of alkoxy(alkylthio)phosphonium salts. The small amount of (*R*)-(**2a**) may arise *via* the intermediate (B). When (**1**) contains more bulky alkoxy groups, attack on phosphorus away from the bulky group to form (C) becomes more favourable and formation of (B) becomes non-competitive.

An alternative to the above explanation, consistent with the stereochemistry observed, involves (*S*)-(**2**) being formed *via* (A) rather than (D), while (*S*)-(**3**) results *via* the intermediate (C). This alternative, however, is inconsistent with the observation that (**1b**), containing the more bulky Pr^{i}O group, gives a better yield of (**2b**) than does (**1a**). Steric factors would predict that as the alkoxy group in (**1**) is increased in size from MeO to Pr^{i}O to menthoxy, attack of the methyl group to form (A) should be increasingly hindered, relative to attack to form (C), resulting in a smaller amount of (**2**), not more as was observed. Thus, the formation of (A) is only a minor pathway.

From thermodynamic considerations, the apicophilicity of an alkoxy group is much greater than that of a methyl group and is comparable with that of a methylthio group.[8,9] Thus the relative thermodynamic stabilities of intermediates (A)—(C) would be in the approximate order (A) $>$ (B) or (C). Our observations suggest a kinetic order for formation of (C) $>$ (B) or (A), widely different from the thermodynamic predictions. Of major importance is the resulting conclusion that although (A), formed by equatorial attack of the methyl group on tetrahedral phosphorus, should be several kcal more stable than (C), a strong preference for axial attack of the nucleophile exists and overrides the thermodynamic factors. The origin of the preferred formation of (C) over (B) cannot be explained with our present understanding but parallels the observations made in the hydrolysis of phosphonium salts, a parallel perhaps not surprising if an initial complexation of (**1**) with magnesium occurs in the Grignard reaction to form a phosphonium-like species.[10]

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