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PREPARATION OF OPTICALLY ACTIVE PHOSPHINE OXIDES BY REGIOSELECTIVE CLEAVAGE OF CYCLIC PHENYLPHOSPHONITE WITH ALKYL HALIDES

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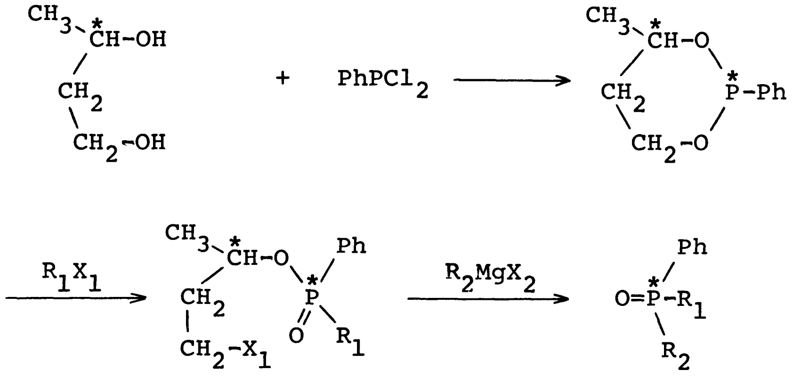
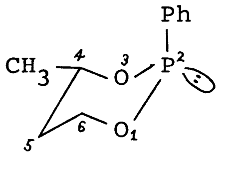
The Arbuzov reaction of (2S, 4S)-4-methyl-2-phenyl-1,3,2-dioxaphosphorinane with various alkyl halides gave the diastereomerically pure phosphinates with regioselective cleavage of the primary carbon-oxygen bond. These phosphinates reacted with Grignard reagents to give optically active phosphine oxides in high optical yields.

Mislow et al.1) have synthesized some optically active phosphine oxides. Their synthetic routes required the fractional recrystallization of diastereomeric menthyl phosphinates which are the precursors of phosphine oxides. Inch et al.2) prepared optically active phosphine oxides via cyclic phosphonates, utilizing carbohydrate derivatives as a chiral source. On the other hand, it has been reported that the Arbuzov reaction of five-3a) or six-membered3b) ring phosphites with alkyl halides gave the acyclic phosphonates resulting from the regioselective ring-cleavage of the primary carbon-oxygen bond. This paper describes the convenient method for the preparation of optically active phosphine oxides, taking advantage of the similar regioselective ring-cleavage of cyclic phenylphosphonite.



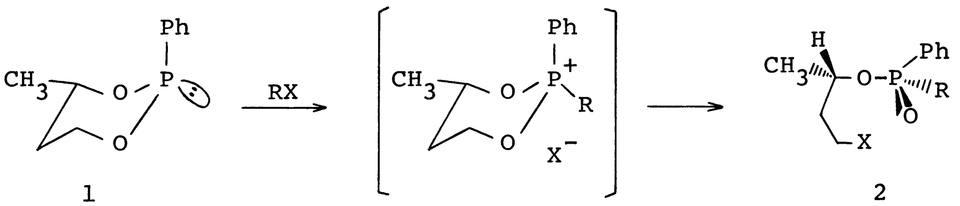
Dichlorophenylphosphine was treated with (S)-1,3-butanediol[4)] in the presence of 4 equiv. triethylamine in ether at 5~10°C under a nitrogen atmosphere to give the cyclic phenylphosphonite (**1**), bp 59~60°C/0.05 mmHg, $[\alpha]_D^{25}$+51.6° (c 5.5, C_6H_6), in 62% yield. This fraction contains almost one diastereomer as below.[5)] The



(2S, 4S)-**1**

conformation and the configuration of **1** were confirmed by comparisons with ^1H-NMR spectra of the related cyclic phosphorus compounds.[6)] The conformation of **1** is the chair form with 4-methyl equatorial and 2-phenyl axial and the absolute configuration of phosphorus atom is shown as S.

The reactions of **1** with various alkyl halides have been carried out in an excess halide without solvents under a nitrogen atmosphere until the complete consumption of **1**. The resulting phosphinate (**2**) was separated by column chromatography (silica gel; benzene-acetone 1 : 1).[7)] The results are shown in Table 1.



1 **2**

Table 1. The Arbuzov Reactions of (2S, 4S)-**1** with Alkyl Halides

Alkyl Halides	Temp (°C)	Time (h)	Phosphinates (**2**)[a)] Yield[b)] (%)	$[\alpha]_D$[c)] (°)
CH_3I	r.t.	≈0	86.4	-10.6
C_2H_5I	60	1.0	71.1	-15.9
n-C_3H_7Br	80	7.5	51.5	-12.3
n-C_4H_9Br	100	3.0	58.0	-8.1
CH_2=$CHCH_2Br$	60	1.0	77.3	+4.7
$PhCH_2Cl$	90	1.5	64.0	-11.8
Ph_3CCl	80	2.0	56.4	-25.0

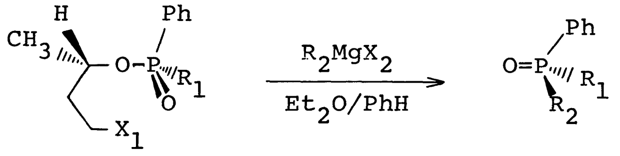
a) All of phosphinates obtained gave satisfactory NMR data.

b) Isolated yield. c) Measured in chloroform.

When methyl iodide was used as a halide, the ring-opening reaction took place instantaneously. The reactions of secondary or tertiary halides except triphenylmethyl chloride with 1 did not give the corresponding products under mild conditions. Generally, the Arbuzov reaction proceeds by the nucleophilic attack of the nonbonding electron pair of the phosphorus atom onto the carbon of alkyl halide followed by the S_N2 reaction of the displaced anion on an alkyl group of the resulting quasiphosphonium intermediate.[8)] Thus, the ring-opening reaction of this phosphonite would proceed with a complete stereospecificity.

2 was converted to phosphine oxide (3) with Grignard reagent (5 equiv.) according to the procedure of Mislow.[1)] Optically active 3 was isolated by column chromatography on silica gel (eluent, chloroform-methanol 5 : 1). The results are summarized in Table 2. The absolute configurations of phosphine oxides obtained

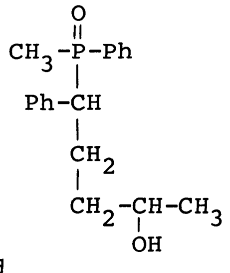
Table 2. The Reaction of Phosphinates (2) with Grignard Reagents



2 3

Run	R_1X_1	R_2X_2	Temp (°C)	Time (h)	Phosphine Oxides (3)[a)] Yield[b)] (%)	$[\alpha]_D$[c)] (°)	O.Y.[d)] (%)	Config.
1	CH_3I	$PhCH_2Cl$	70	9.0	32.7	+34.6	77	R
2	$PhCH_2Cl$	CH_3I	80	6.0	10.3[e)]	-42.4	94	S
3	C_2H_5I	CH_3I	80	30.0	56.6	-22.6	100	S
4	n-C_3H_7Br	CH_3I	80	33.0	65.7	-19.5	100	S
5	CH_3I	n-C_3H_7Br	70	4.0	22.3	+14.8	76	R
6	CH_3I	n-C_4H_9Br	80	5.0	38.0	+16.7	—[f)]	R[g)]

a) All of phosphine oxides gave satisfactory NMR and IR data. b) Isolated yield. c) Measured in methanol. d) Optical yields were calculated from the maximum rotations of phosphine oxides reported[1)] by considering the optical purity of starting diol (88.5%, ref. 4). e) The low yield is partly due to the formation of a by-product of which structure is assigned as 4. f) Maximum rotation has not been reported. g) Presumed configuration.



$$CH_3-\overset{\overset{O}{\|}}{P}(-Ph)-CH(Ph)-CH_2-CH_2-CH(OH)-CH_3$$

4

have been established.1) Accordingly, the nucleophilic attack of Grignard reagents at phosphorus in 2 proceeded with inversion of configuration, being consistent with Mislow's results.1) Particularly, the reaction of 2 with methylmagnesium iodide afforded the corresponding phosphine oxide with almost complete stereospecificity.

The present synthetic processes described herein make the separations of diastereomers unnecessary and give phosphine oxides in high optical yields. Further applications in the versatility of optically active cyclic phenylphosphonite as the chiral intermediate are now under way.

References

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3) a) A. E. Arbuzov and V. M. Zoroastrova, Chem. Abstr., 42, 4932g (1948).
b) This work has been presented in part at 45th Meeting of Chemical Society of Japan, April 3, 1982, "Abstracts of paper" 3G02.

4) The specific rotation of (S)-1,3-butanediol used is +26.5° (c 7.5, EtOH) (optical purity 88.5%). For the maximum rotation ($[\alpha]_D$+29.9°), see K. Hintzer, B. Koppenhoefer, and V. Schurig, J. Org. Chem., 47, 3850 (1982), and for the preparation of this diol, see M. Segi, M. Takebe, S. Masuda, T. Nakajima, and S. Suga, Bull. Chem. Soc. Jpn., 55, 167 (1982).

5) ^{1}H-NMR spectrum of 1 showed a single doublet at δ 1.26 ppm (J=6.1 Hz) for the methyl proton. If 1 is a mixture of diastereomeric phenylphosphonite, two doublets corresponding to the methyl protons should be recorded on ^{1}H-NMR spectrum, respectively.

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7) Attempts to isolate 2 by distillation under reduced pressure were unsuccessful because of the thermal unstability of 2.

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