Synthesis of Phosphirane Oxide Derivatives Promoted by Introduced Phenylsulfinyl Groups and Their Pummerer Reaction

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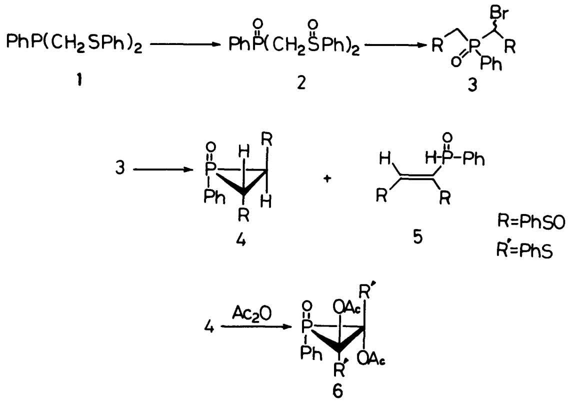
Synopsis. Phosphirane oxide derivatives were first successfully synthesized in good yield under mild conditions wherein carbon-carbon bond formation was promoted by two phenylsulfinyl groups on the α and α' carbons of the phosphorus atom. A structure determination of the formed phosphirane oxide derivatives as well as the stereochemistry of the Pummerer reaction product revealed a trans geometry for the phosphirane oxide.

In the field of three-membered heterocycles, many papers concerning aza and thia analogues have been published; however, little is known about the syntheses of phosphiranes via reactions of phosphides with epoxides2) and via the formation of two carbon–phosphorus bonds were reported.3) This paper describes the first attempt to introduce activating groups, such as phenylsulfinyl groups, on the α and α' carbons of phosphorus atom in order to promote regioselectivity in a coupling reaction leading to phosphirane oxides via carbon-carbon bond formation.

Results and Discussion

Compound **1** was prepared by a reaction of phenylphosphonous dichloride with a Grignard reagent of chloromethyl phenyl sulfide. Phosphine **1** was oxidized with hydrogen peroxide to give compound **2**, the bromonation of which was then carried out with an *N*-bromosuccinimide/bromine/pyridine system4) to afford α-bromophosphine oxide **3**. Compound **3** consisted of diastereomers, being used for a further transformation without separation. The treatment of **3** with a variety of bases, such as DBU and triethylamine, in tetrahydrofuran at room temperature brought about dehydrobromination to afford a phosphirane oxide **4**. When DBU, a strong dehydrobromination reagent, was used an olefinic product **5** was obtained as the major product (yield of **4** and **5** were 3 and 73%, respectively).

Phosphiranes have been known to be unstable towards bases and heat; therefore, it may be difficult to produce phosphirane as the sole product.1,2) The amount of the olefinic product which was formed as the by-product depended on the base, since the base catalyzed a ring opening of the phosphirane oxide **4** to open the three-membered ring. Therefore, the major product was an olefinic type when a strong dehydrobromination reagent such as DBU was used. On the other hand, triethylamine remarkably improved the formation of phosphirane oxide **4** by a 1,3-elimination of hydrogen bromide (yield of **4** and **5** were 75 and 3%, respectively). Quast and Heuschmann5) obtained a single stereoisomer of a phosphirane oxide having a configuration where the C–H vs. C–H was syn and P=O vs. C–H was an anti form from the diastereomeric α-bromo precursor. Four isomers can possibly exist for the phosphirane oxide **4**; however, the substituent R's (PhSO) should be anti to each other, as shown in the Scheme since only the Z-isomer **5** was produced in the ring-opening transformation of the phosphirane oxide **4**. The vinyl proton of compound **5** showed small values for the H–P coupling constant6) in the ^{1}H NMR spectrum (J_{HCCP}=15.0 Hz), indicating a Z-geometry (as cis for H–C=C–P or R–C=C–R bond) compared with the large coupling constant for the E-isomer.6) Since the cleavage of the carbon–phosphorus bond of phosphirane oxide 4 having trans R's proceeds in a conrotatory fashion from the Woodward–Hoffmann rule (as shown in the literature7)) the cis-geometry for the phenylsulfinyl groups on the carbon–carbon double bond to form the Z-isomer **5** should be brought about in consequence of the three-membered ring opening.



Scheme.

The product of a Pummerer reaction8) of the phosphirane oxide **4** (i.e., compound **6**) gave additional strong information regarding the structure of compound **4**. If the Pummerer reaction product **6** has a trans configuration for two acetoxyl groups or for two phenylthio groups, the two methyl protons of the acetoxyl groups should be observed separately from the two singlet signals in the ^{1}H NMR spectrum. On the other hand, if the configuration of **6** is cis for these two groups, the two methyl protons should be observed as one singlet, owing to the symmetry. The treatment of compound **4** with acetic anhydride afforded a crystalline phosphirane oxide derivative **6** which had two acetoxyl groups on the α and α' positions of the phosphorus atom. The ^{1}H NMR spectrum of compound **6** clearly showed two kinds of acetoxyl signals at δ 3.00 and 3.32 (three protons each). These observations clearly established the structure of phosphirane oxide **4** to be either (2*S*, 3*S*) or (2*R*, 3*R*) as shown in the scheme. The sp^3 α and α' carbon signals of the phosphorus atom were observed downfield (69.5 and 73.6 ppm) compared with various published reports[2,5] regarding ^{13}C NMR spectrum, since the carbon atoms are connected to oxygen and sulfur atoms.

Experimental

Apparatus. The IR spectra were measured on a Japan Spectroscopic Co., Ltd. JASCO A-3 spectrophotometer; the ^{1}H NMR spectra were run on a Hitachi R-24B (60 MHz) spectrameter; the mass spectra were measured by a Hitachi RMU, DMG, GC-MS spectrometer; the high-performance liquid chromatography was carried out using a Japan Spectroscopic Co., Ltd. UNIFLOW-211 and melting points were measured on a Yanagimoto Seisakusho micro melting-point apparatus.

Synthesis of Bis(phenylthiomethyl)phenylphosphine (1). A Grignard reagent was prepared from chloromethyl phenyl sulfide (3.7 g, 23.4 mmol) and magnesium metal (0.57 g, 23.4 mg atom) in freshly distilled tetrahydrofuran or ether (30 ml) under a dry nitrogen atmosphere. Phenylphosphonous dichloride (2.0 g, 11.2 mmol) in tetrahydrofuran (20 ml) was added to a solution of the Grignard reagent and the resulting solution was stirred for 5 h at room temperature. An aqueous solution of ammonium chloride (20 ml) was added to the reaction mixture; then, the solution was extracted with ether (3×30 ml). The organic layer was washed with water (3×10 ml). and dried over anhydrous sodium sulfate; the solvent was then evaporated. The residue was separated by column chromatography on silica gel (eluent: hexane) to afford compound **1** as colorless crystals in 45% yield, mp 71—72 °C (from ethanol). ^{1}H NMR (CDCl$_3$) δ=2.92 (s, 4H, 2CH$_2$) and 6.98 (br s, 15H, 3Ph).

Found: C, 74.54; H, 5.96%. Calcd for $\mathrm{C_{20}H_{19}PS}$: C, 74.51; H, 5.94%.

Synthesis of Bis(phenylsulfinylmethyl)phenylphosphine Oxide (2). A 30% aqueous solution of hydrogen peroxide (0.37 g) was added to a solution of compound **1** (0.5 g, 1.55 mmol) in acetic acid (10 ml) and was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 0.5 h, followed by the usual work-up. Isolation of the product by column chromatography on silica gel (eluent: benzene/ethyl acetate=1/1 in v/v) afforded compound **2** as a white crystalline material in 80% yield, mp 125—127 °C. ^{1}H NMR (CDCl$_3$) δ=2.92 and 3.20 (s×2, 4H, 2CH$_2$), and 7.36—7.43 (m, 15H, 3Ph). IR ($\nu_{\max}^{\mathrm{KBr}}$) cm^{-1}, 1100 (P=O) and 1150 (S=O).

Found: C, 64.82; H, 5.15%. Calcd for $\mathrm{C_{20}H_{19}PSO_3}$: C, 64.85; H, 5.17%.

Synthesis of 3. After the addition of a dichloromethane (20 ml) solution of bromine (0.25 g, 1.59 mmol), *N*-bromosuccinimide (0.14 g, 0.76 mmol), and pyridine (1 ml) to a solution of compound **2** (0.28 g, 0.76 mmol) in dichloromethane (10 ml), the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into water (30 ml) and the organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and then the solvent was evaporated. The separation of the product by thin-layer chromatography on silica gel afforded a crystalline compound **3** in 60% yield, mp 119—124 °C. Compound **3** was a mixture of diastereoisomers which were detected by an HPLC retention time of 4.2 and 4.4 min (eluent: chloroform/methanol=20/1 in v/v) at the ratio of 1.5 to 1.0, respectively. ^{1}H NMR (CDCl$_3$) δ=3.09—3.81 (m, 2H, CH$_2$), 4.81—5.30 (m, 1H, CH-Br), and 7.43—7.85 (m, 15H, 3Ph); IR ($\nu_{\max}^{\mathrm{KBr}}$) cm^{-1}, 1100 (P=O), 1160 (S=O), and 690 (C-Br); MS, *m/z*, 480 (M$^+$) and 482 (M$^+$+2).

Found: C, 49.57: H, 3.69%. Calcd for $\mathrm{C_{20}H_{18}PS_2BrO_3}$: C, 49.90; H, 3.77%.

Synthesis of 1-Phenyl-2,3 -bis(phenylsulfinyl)phosphirane 1-Oxide (4). A solution of compound **3** (0.1 g, 0.21 mmol) and an excess amount of triethylamine (3 ml) in tetrahydrofuran 5 ml) was stirred for 12 h at room temperature. The solvent was evaporated and the residue was separated by thin-layer chromatography on silica gel (eluent: benzene/ethyl acetate=1/1 in v/v) to afford the phosphirane oxide, **4**, and the olefinic product, **5**, in 75 and 3% yields, respectively. The phosphirane oxide, **4**, (syrup): ^{1}H NMR (CDCl$_3$) δ=4.34 (dd, J_{PCH}=7.5 Hz, 2H, 2CH) and 7.55—7.93 (m, 15H, 3Ph); IR ($\nu_{\max}^{\mathrm{KBr}}$) cm^{-1}, 1450 (P–C$_{\mathrm{arom}}$), 1130 (P=O), 1050 (S=O), and 700 (P–C); MS *m/z*, 400 (M$^+$).

Found: C, 60.11; H, 4.31%. Calcd for $\mathrm{C_{20}H_{17}O_3PS_2}$: C, 59.99; H, 4.28%.

The olefinic product,**5**,(syrup): ^{1}H NMR (CDCl$_3$) δ=6.10 (d, J_{HCCP}=15.0 Hz, 1H, $\mathrm{^{P}\backslash C{=}C/^{H}}$), 7.00 (d, J_{HP}=444.0 Hz, 1H, PH), and 7.2—7.6 (m, 15H, 3Ph); IR ($\nu_{\max}^{\mathrm{neat}}$) cm^{-1}, 2350 (P–H), 1580 and 840 (C=C); MS *m/z*, 400 (M$^+$).

Pummerer Reaction of Phosphirane Oxide Derivative 4 with Acetic Anhydride. A solution of phosphirane oxide **4** (0.1 g, 0.25 mmol), acetic anhydride (0.06 g, 0.55 mmol), and a trace of *p*-toluenesulfonic acid in dichloromethane (5 ml) was stirred for 12 h at room temperature; then, the solvent was evaporated. The isolation of the crude product by thin-layer chromatography on silica gel afforded (2*S*, 3*S* or 2*R*, 3*R*)-1-phenyl-2,3-diacetoxy-2,3-bis(phenylthio)phosphirane 1-oxide (**6**) in 85% yield, mp 135—136 °C. ^{1}H NMR (CDCl$_3$) δ=3.00, 3.32 (s, 6H, 2OAc), and 7.52 (m, 15H, 3Ph); ^{31}P NMR (CDCl$_3$) δ_{P}=−62.7 ppm (from 85% H$_3$PO$_4$); ^{13}C NMR (CDCl$_3$) δ=34.2 (s, CH$_3$), 34.5 (s, CH$_3$), 69.5 (d, J_{CP}=37.8 Hz, C$^{\alpha}$), 73.6 (d, J_{CP}=35.2 Hz,C$^{\alpha'}$, 127.4 (P-arom), 128.1 (P-arom), 129.3 (P and S arom), 129.5 (S-arom), 130.4 (S-arom), 140.9 (S-arom), 143.3 (P-arom), 226.3 (s, $\underline{\mathrm{C}}$=O), 230.3 (s, $\underline{\mathrm{C}}$=O); IR ($\nu_{\max}^{\mathrm{KBr}}$) cm^{-1}, 1590 (C=O), 1450 (P–Ph), 1150 (P=O), 750 (C–S–C), and 690 (C–P); MS *m/z*, 484 (M$^+$).

Found: C, 59.52; H, 4.34%. Calcd for $\mathrm{C_{24}H_{21}O_5PS_2}$: C, 59.50; H, 4.37%.

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