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Note

New Synthesis of Optically Active *O*-Aryl *O*-Ethyl Phenylphosphonothionates

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The mixed anhydride method was applied to synthesize *O*-aryl *O*-ethyl phenylphosphonothionate. The reaction of *O*, *O*-diethyl phosphorochloridate with *O*-ethyl phenylphosphonothioic acid afforded *O*, *O*-diethyl phosphoric *O*-ethyl phenylphosphonothioic anhydride in a good yield. This anhydride was converted to *O*-aryl *O*-ethyl phenylphosphonothionates by reacting with the appropriate sodium phenoxide. This esterification occurred without racemization and produced optically pure *O*-ethyl *O*-(4-nitrophenyl) phenylphosphonothionate (EPN) and *O*-(4-cyanophenyl) *O*-ethyl phenylphosphonothionate (cyanofenphos).

Key words: stereospecific synthesis; mixed anhydride method; optically active phenylphosphonothionates

Although many organophosphorus insecticides with a chiral phosphorus atom are in use today, it is well known that their insecticidal activity depends on the chirality of the phosphorus atom. For example, (*R*) p(+)-EPN is more active than corresponding (*S*)p(−)-EPN.[1] Figure 1 shows the synthesis of chiral isomers of *O*-aryl *O*-ethyl phenylphosphonothionates by the conventional method.[1] The resolved phosphonothioic acid is converted to the corresponding phosphonochloridothionate by reacting with phosphorus pentachloride or oxalyl chloride. This reaction occurs with inversion of the central phosphorus atom. Reaction of the chloridothionates with phenols gives corresponding thionate esters with additional inversion at the phosphorus center. The enantiomers of EPN,[2] cyanofenphos[3] and leptophos,[4] have been prepared by the conventional method. As this pathway involves two reaction steps of displacement at the phosphorus atom with inversion, some racemization inevitably occurs, particularly in the chlorination process. The author planned to synthesize such optically active phenylphosphonothionates by the mixed anhydride (MA) method which has commonly been used for peptide synthesis. *O*-Ethyl phenylphosphonothioic acid (**1**) was used as the starting material. Ethyl chloroformate, isobutyl chloroformate, isobytyryl chloride, and pivaloyl chloride commonly used for peptide synthesis gave the corresponding anhydrides in good yields, but they did not afford the objective *O*-aryl *O*-ethyl phenylphosphonothionates by reacting with appropriate phenols. It is well known that the phosphorus atom of a phosphonate is more electrophilic than that of the corresponding phosphate because there

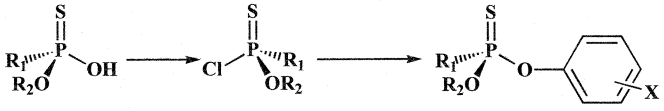

Fig. 1. Conventional Synthesis of Optically Active Phosphonothionate Esters.

is no pπ-dπ overlap between the P–C bond.[5] Consequently, *O*,*O*-diethyl phosphorochloridate was used as the other acid moiety as shown in Fig. 2. The reaction of *O*,*O*-diethyl phosphorochloridate with *O*-ethyl phenylphosphonothioic acid (**1**) in the presence of triethylamine afforded the corresponding mixed anhydride (**2**) in about a 90% yield. The reaction of the anhydride with appropriate phenols gave the objective *O*-aryl *O*-ethyl phenylphosphonothionates (**3**) in about 35% yields. These results may be explained by the higher reactivity of the phosphorus atom at the thiophosphonyl center than that at the phosphoryl center.

The author applied this method to synthesize optically active *O*-aryl *O*-ethyl phenylphosphonothionate as shown in Fig. 3. Optically active *O*-ethyl phenylphosphonothioic acids (**4** and **5**), which were resolved by fractional recrystallization as a brucine salt,[6] were converted to the corresponding mixed anhydrides (**6** and **7**) in about 85% yields. Conversion from the anhydride to the corresponding *O*-aryl *O*-ethyl phenylphosphonothionates (**8** and **9**) was pursued under milder conditions than those used for racemate synthesis. When the reaction was pursued at 30°C, no racemization was apparent in the syntheses of **8a**, **8b**, **9a** and **9b**. The absolute configuration of the central phosphorus atom was determined according to that of (*S*)p(−)-cyanofenphos whose configuration has been defined by an X-ray diffraction analysis.[1,7] The yield in the last step of the reaction seemed too low for a preparative synthesis. However, about 60% of *O*-ethyl phenylphosphonothioic acid could be recovered with little loss of optical purity. In addition, both the enantiomeric *O*-aryl *O*-ethyl phenylphosphonothionate could be obtained from a single enantiomer of the acid by using a combination of the conventional method and the MA method as shown in Fig. 4. These results indicate that this method would be useful for investigating phosphorus stereochemistry and biochemistry.

Experimental

Spectroscopy. Nuclear magnetic resonance spectra

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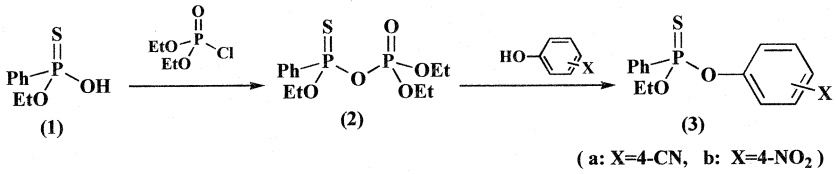

Fig. 2. Synthetic Pathway of *O*-Aryl *O*-Ethyl Phenylphosphonothionates by the MA Method.

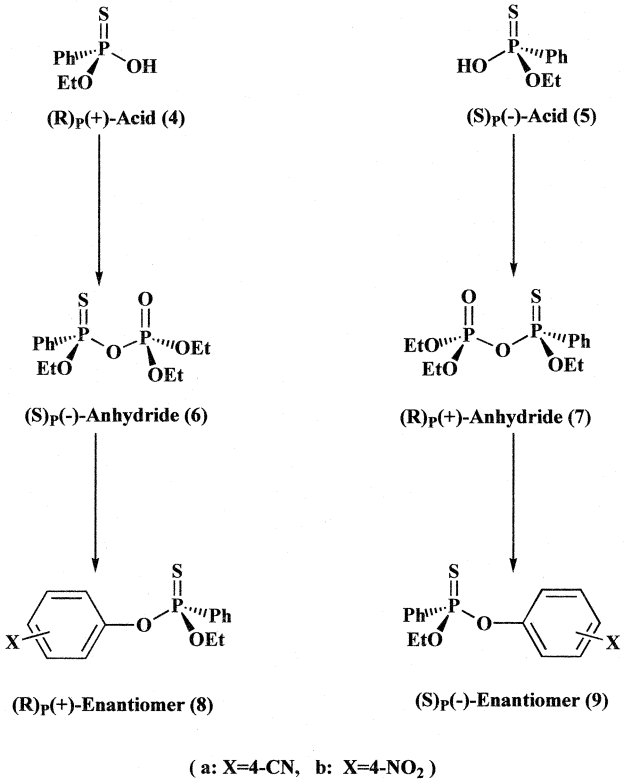

Fig. 3. Synthetic Pathways to Optically Active *O*-Aryl *O*-Ethyl Phenylphosphonothionates by the MA Method.

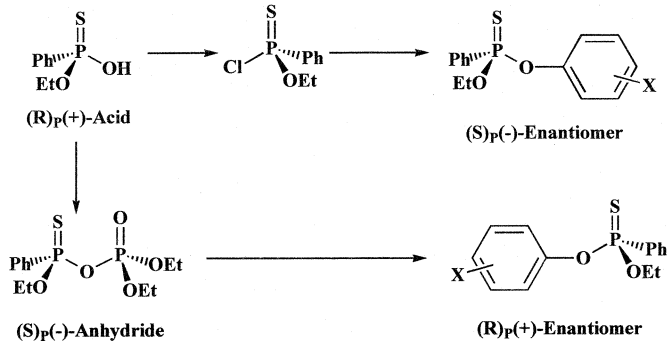

Fig. 4. Synthesis of an Enantiomeric Pair of *O*-Aryl *O*-Ethyl Phenylphosphonothionates from a Single Enantiomer of *O*-Ethyl Phenylphosphonothioic Acid.

were recorded in deutero-chloroform, using tetramethylsilane as an internal standard, with a JEOL EX 90 spectrometer at 90 MHz. Infrared spectra were recorded by a Shimadzu IR-408 spectrometer. Specific optical rotation values were measured in diisopropyl ether solutions in a 1-cm cell by a Union Giken PM-101 digital polarimeter.

HPLC analysis. HPLC analysis was carried out with a Shimadzu LC-6A equipped with an SPD-6AUV detector and a Chromatopak C-R3A recorder. The product (1 mg) was dissolved in acetone (1 ml), and 1 μl was injected. A Chiralcel OJ stainless steel column (Daisel Chemical; 44.6 × 250 mm) was used, the mobile phase consisting of a hexane-2-propanol mixture (9:1, v/v). The flow rate was 0.9 ml/min, and the absorbance at 254 nm was measured. The areas of all peaks were integrated, and the optical purity of the products was calculated from the corresponding peak areas.

Synthesis. O-Ethyl phenylphosphonothioic acid was prepared and resolved by fractional recrystallization as the brucine salt according to the method in the previous report. Each salt was treated with dilute hydrochloric acid to afford the corresponding enantiomers whose specific rotation values were +15.1° and −15.2°, respectively.[6]

O,O-Diethyl phosphoric O-ethyl phenylphosphonothioic anhydride (**2**). *O,O*-Diethyl phosphorochloridate (0.05 mol, 8.6 g) in dry THF (25 ml) was added dropwise to a mixture of *O*-ethyl phenylphosphonothioic acid (**1**, 0.05 mol, 10.1 g) and triethylamine (0.05 mol, 5.1 g) while stirring at room temperature. Stirring was continued at room temperature for 3 hr. The reaction mixture was concentrated *in vacuo*, and the residue was fractionated with dichloromethane and water. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a slightly yellow oil. The product was purified by column chromatography on silica gel to afford the anhydride (**2**, 15.0 g) in an 89% yield. n_D^{20} 1.5120, IR ν_{max} (neat) cm^{-1}: 1285, 1030, 830; NMR δ_H ($CDCl_3$): 1.01–1.56 (9H, t, CH_3), 3.77–4.63 (6H, m, CH_2), 7.17–8.23 (5H, m, aromatic).

Racemic O-(4-cyanophenyl) O-ethyl phenylphosphonothionate (**3a**). A mixture of the mixed anhydride (**2**, 0.01 mol, 3.4 g), cyanophenol (0.01 mol, 1.2 g) and potassium carbonate (0.01 mol, 1.4 g) in dry acetone was refluxed for 70 min. The reaction mixture was concentrated *in vacuo*, fractionated with ether and water, and then the ethereal layer was dried over anhydrous sodium sulfate. The organic layer was evaporated *in vacuo* to give a slightly yellow residue which was purified by

column chromatography on silica gel to afford *O*-(4-cyanophenyl) *O*-ethyl phenylphosphonothionates (**3a**, 1.07 g) in a 35.3% yield. mp 82.9°C; IR ν_{max} (neat) cm^{-1}: 2245, 1603, 1500, 1220, 1030, 905; NMR δ_H ($CDCl_3$): 1.35 (3H, t, J=7 Hz, CH_3), 4.00–4.59 (2H, m, CH_2), 7.84–8.26 (9H, m, aromatic). Racemic EPN (**3b**) was prepared by the same procedure in a 32.4% yield, n_D^{20} 1.5978; IR ν_{max} (neat) cm^{-1}: 1598, 1520, 1350, 1220, 1030, 907; NMR δ_H ($CDCl_3$): 1.37 (3H, t, J=7 Hz, CH_3), 4.01–4.55 (2H, m, CH_2), 7.08–8.26 (9H, m, aromatic).

(S)p(−)-O,O-Diethyl phosphoric O-ethyl phenylphosphonothioic anhydride (**6**). *O,O*-Diethyl phosphorochloridate (0.025 mol, 4.3 g) in dry THF (25 ml) was added dropwise to a mixture of *(R)*p(+)-*O*-ethyl phenylphosphonothioic acid (**4**, 0.025 mol, 5.0 g) and triethylamine (0.026 mol, 2.6 g) while stirring at 0°C. Stirring was continued at below 5°C for 3 hr. The reaction mixture was concentrated *in vacuo*, and the obtained residue was fractionated with dichloromethane and water. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a slightly yellow liquid. This liquid was purified by column chromatography on silica gel to afford (−)-*O*, *O*-diethyl phosphoric *O*-ethyl phenylphosphonothioic anhydride (**6**, 7.1 g, 84.2%) as a colorless oil. $[\alpha]_D^{20}$ −16.8° (c=0.5, diisopropyl ether), optical purity >99.9%ee, retention time 8.8 min, n_D^{20} 1.5122; IR ν_{max} (neat) cm^{-1}: 1285, 1030, 830; NMR δ_H ($CDCl_3$); 1.07–1.56 (9H, t, CH_3), 3.77–4.63 (6H, m, CH_2), 7.17–8.23 (5H, m, aromatic). The *(R)*p(+)-anhydride (**7**) was prepared by the same procedure in a 85.3% yield. $[\alpha]_D^{20}$ 16.3° (c=0.43, diisopropyl ether), optical purity >99.9%ee, retention time 12.9 min, n_D^{20} 1.5121; IR ν_{max} (neat) cm^{-1}: 1285, 1030, 830; NMR δ_H ($CDCl_3$): 1.07–1.56 (9H, t, CH_3), 3.77–4.63 (6H, m, CH_2), 7.17–8.23 (5H, m, aromatic).

(R)p(+)-O-Aryl O-ethyl phenylphosphonothionates (**8a** and **8b**). A mixture of the *(S)*p(−)-anhydride (**6**, 0.01 mol, 3.4 g) and appropriate equimolar sodium phenoxide in dry THF was stirred at 30°C for 2 hr. The reaction mixture was concentrated *in vacuo* to give crude products. These products were fractionated with dichloromethane and water, and the organic layer was dried over anhydrous sodium sulfate. The organic layer was evaporated *in vacuo* to give a residue which was purified by column chromatography on silica gel to afford corresponding *(R)*p(+)-*O*-aryl *O*-ethyl phenylphosphonothionates (**8a** and **8b**) in 10.5% and 14.4% yields, respectively. **8a**: mp 103.1°C, $[\alpha]_D^{20}$ 39.9, (c=0.52, diisopropyl ether), optical purity >99.9%ee, retention time 28.3 min; IR ν_{max} (neat) cm^{-1}: 2245, 1603, 1500, 1220, 1030, 905; NMR δ_H ($CDCl_3$): 1.35 (3H, t, J=7 Hz, CH_3), 4.00–4.59 (2H, m, CH_2), 7.84–8.26 (9H, m, aromatic); Anal. Found: C, 59.62; H, 4.56; N, 4.49%. Calcd. for $C15H_{14}NO_2PS$: C, 59.40; H, 4.65; N, 4.62%.

(S)p(−)-Isomer (**8b**): n_D^{20} 1.5983, $[\alpha]_D^{20}$ 35.8° (c=0.4, diisopropyl ether), optical purity 99.8%ee, retention time 25.3 min; IR ν_{max} (neat) cm^{-1}: 1598, 1520, 1350, 1220, 1030, 907; NMR δ_H ($CDCl_3$): 1.37 (3H, t, J=7 Hz, CH_3), 4.01–4.55 (2H, m, CH_2), 7.08–8.26 (9H, m, aromatic). Anal. Found: C, 51.88; H, 4.46; N, 4.49%. Calcd. for $C_{14}H_{14}NO_4PS$: C, 52.01; H, 4.36; N, 4.33%.

(S)p(−)-O-Aryl O-ethyl phenylphosphonothionates (**9a** and **9b**). The *(S)*p(−)-isomers (**9a** and **9b**) were prepared by the same procedure as that just described. **9a**: yield 11.2%, mp 102.8°C, $[\alpha]_D^{20}$ −39.5° (c=0.7, diisopropyl ether), optical purity >99.9%ee, retention time 33.6 min; IR ν_{max} (neat) cm^{-1}: 2245, 1603, 1500, 1220, 1030, 905; NMR δ_H ($CDCl_3$): 1.35 (3H, t, J=7 Hz, CH_3), 4.00–4.59 (2H, m, CH_2), 7.84–8.26 (9H, m, aromatic). Anal. Found: C, 59.57; H, 4.76; N, 4.39%. Calcd. for $C_{15}H_{14}NO_2PS$: C, 59.40; H, 4.65; N, 4.62%. **9b**: yield 15.3%, $[\alpha]_D^{20}$ −35.1° (c=0.6, diisopropyl ether), optical purity >99.9%ee, retention time 31.4 min, n_D^{20} 1.5981; IR ν_{max} (neat) cm^{-1}: 1598, 1520, 1350, 1220, 1030, 907; NMR δ_H ($CDCl_3$): 1.37 (3H, t, J=7 Hz, CH_3), 4.01–4.55 (2H, m, CH_2), 7.08–8.26 (9H, m, aromatic). Anal. Found: C, 51.84; H, 4.56; N, 4.41%. Calcd. for $C_{14}H_{14}NO_4PS$: C, 52.01; H, 4.36; N, 4.33%.

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