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# CHIRAL PHENYLPHOSPHONIC ESTERS, THEIR PREPARATION VIA ETHYL N-[CHLORO-(PHENYL)THIOPHOSPHONYL] L-PROLINATE AND THEIR ABSOLUTE CONFIGURATIONS

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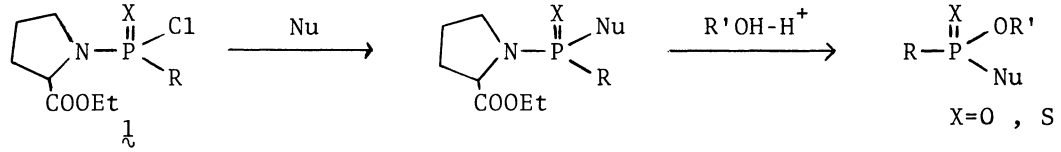
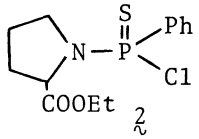
Diastereomerically pure ethyl N-[chloro(phenyl)thiophosphonyl]-L-prolinate was prepared. From this intermediate various optically active phenylphosphonic acid derivatives have been obtained in high optical yields. Their absolute configurations have been determined by the chemical correlation.

During the course of our investigation aimed to establish the utility of ethyl L-prolinate as a chiral source of optically active organophosphorus compounds,[1] it occurred to us that phosphorus amide monochloride 1, if being isolated as a diastereomerically pure form, could become a quite useful intermediate: A variety of chiral phosphorus compounds could be obtained from 1 after the single diastereomeric separation.




This paper describes the successful results obtained during the investigations along this line in the case of phenylthiophosphonic derivatives, which comprise the separation of diastereomeric phenylthiophosphonic monochloride 2 and its stereospecific conversion to various chiral phosphonic acid derivatives.[2] Furthermore,

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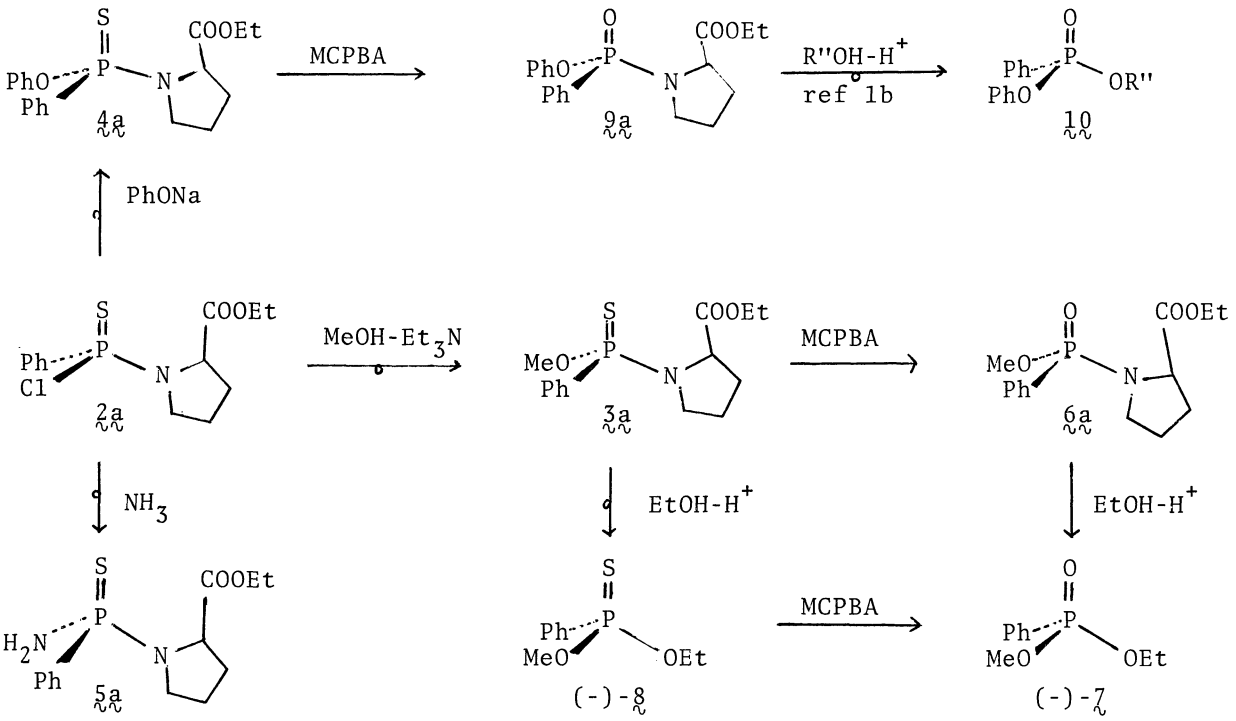
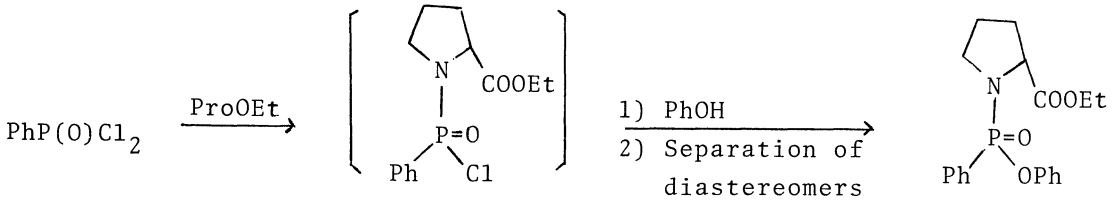
absolute configurations of the compounds derived from 2 have been determined by the chemical correlation with (-)-O,S-dimethyl phenylphosphonothioate[3].

When phenylthiophosphonic dichloride was treated with ethyl L-prolinate (1 equiv) in the presence of $Et_3N$ (1 equiv) in THF at room temperature, a mixture of diastereomeric monochloride 2 was obtained in about 90 % yield. The mixture was separated by column chromatography (silica gel; benzene-ethyl acetate 50:1) to give the corresponding pure diastereomer 2a , bp 165°/0.15 mmHg, mp 53-54° (hexane), $[\alpha]_D^{10}$+24.3° (c 0.92) in 48 % yield; and 2b, bp 150°/0.02 mmHg, $[\alpha]_D^{20}$-52.1° (c 1.9) in 5 % yield. Because of the low yield and the low stereospecificity in the displacement reaction of 2b[4], only 2a was employed for further reactions. When 2a was subjected to methanolysis (2 h at reflux) under the presence of $Et_3N$ (1 equiv), the methyl ester 3a, bp 155°/0.02 mmHg, $[\alpha]_D^{18}$-122.6° (c 1.0), was obtained in 88 % yield. Corresponding ethyl, propyl, and sec-butyl esters were also obtained in 70-85 % yields under the same reaction conditions. Furthermore the diastereomerically pure phenyl ester 4a, mp 68-69.9° (cyclohexane), $[\alpha]_D^{28}$-51.5°(c 1.8) and amide 5a, mp 64-65° (hexane), $[\alpha]_D^{17}$ -67.5° (c 1.8) were obtained in 90 and 95 % yield, respectively, by the reaction of 2a with PhONa (4 equiv in THF at room temp.) and aq. $NH_4OH$ (Schottenbauman condition).

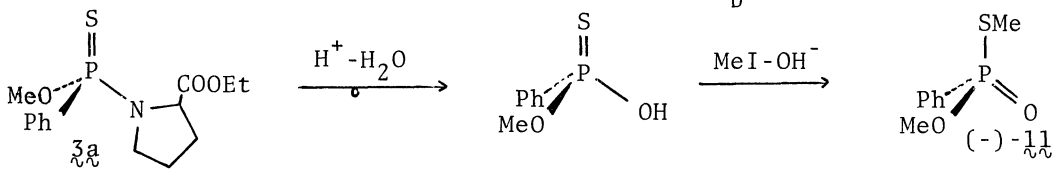



Scheme I

Conversion of P=S to P=O and the acid-catalyzed P-N bond cleavage reaction of 3a were then carried out. When 3a was treated with m-chloroperbenzoic acid (MCPBA) in dichloromethane at room temp., the corresponding amidate 6a, bp 155°/0.02 mmHg, $[\alpha]_D^{16}$-98.9° (c 1.8) was obtained in 70 % yield. The acid-catalyzed ethanolysis (1 M $H_2SO_4$-EtOH, 48 h at r. t.) of 6a afforded in 40 % yield (-)-ethyl methyl phenylphosphonate 7, bp 85°/0.03 mmHg, $[\alpha]_D^{13}$-3.74° (c 1.8), whose optical purity was determined as more than 98 % by NMR using chiral shift reagent Eu(tfmc)$_3$[5]. The acid-catalyzed ethanolysis (0.5 M $H_2SO_4$-EtOH, 2h at 70°) of 3a afforded (-)-ethyl methyl phenylthiophosphonate 8, bp 73°/0.03 mmHg, $[\alpha]_D^{12}$-7.36° (c 2.8) in 58 % yield. Reaction of MCPBA with (-)-8 also gave (-)-ethyl methyl phenylphosphonate 7, $[\alpha]_D^{14}$-3.58° (c 2.5)[6]. The phenyl ester 4a reacted with MCPBA to give the corresponding oxo compound 9a[7], bp 190°/0.03 mmHg, $[\alpha]_D^{26}$-44.3° (c 1.8), which was in all respects identical with one of the diastereomers prepared by us previously[1b].




Based on the known stereochemical course[8] of the reactions utilized, it is possible to assign by the chemical correlation the absolute configurations of all compounds obtained from 2a. As the key chiral compound for this purpose we noticed O,S-dimethyl phenylphosphonothioate 11[3], which is to our best knowledge the only phenylphosphonic acid derivative of the known absolute configuration.
When 3a was hydrolyzed under the acidic condition (0.1 M $H_2SO_4$-EtOH-$H_2O$(3:1), 0.5 h at 75°) and then methylated with methyl iodide (1 M NaOH-$CH_3I$, 1 h at r. t.), the desired O,S-dimethyl phenylphosphonothioate 11, bp 110°/0.5 mmHg, was obtained in 62 % yield. From the observed specific rotation of $[\alpha]_D^{22}$-106.3°[9] (c 0.43, benzene),




the absolute configuration of 11 was determined as S, and hence the absolute configurations of compounds 1~10 were deduced as shown in Scheme I. The results described herein may provide a general route to the preparation of chiral phenylphosphonic acid derivatives with the desired absolute configurations and may also confirm the versatility of ethyl L-prolinate as the chiral source for organophosphorus compounds.

References and Notes

1) a) T. Koizumi, Y. Kobayashi, H. Amitani, and E. Yoshii, J. Org. Chem., 42, 3459 (1977). b) T. Koizumi, H. Amitani, and E. Yoshii, Tetrahedron Lett., 1978, 3741. c) T. Koizumi, H. Amitani, and E. Yoshii, Synthesis, 1979, 110.

2) All optically active compounds were identified after microdistillation (bath temp. are described) or recrystallization and gave satisfactory elemental analyses and spectral data. All $[\alpha]_D$ measurements were taken in $CCl_4$ unless otherwise noted.

3) K. E. DeBruin, and D. M. Johnson, J. Chem. Soc., Chem. Commun., 1975, 753.

4) The displacement reactions of 2b were not stereospecific but afforded the diastereomeric mixture of the substitution products. Comparing the TLC and/or NMR spectra of the products from 2a and 2b, the stereospecificity of reactions of 2 was analyzed. For example, NMR spectrum of 3a showed P-OMe doublet at δ3.75 ppm(J= 14 Hz), whereas the corresponding diastereomeric mixture 3a, b (1:2.3) derived from 2b exhibited a pair of P-OMe doublet at δ3.65 and 3.75 ppm (J=14 Hz).

5) $Eu(hfc)_3$ was not effective in this case.

6) Although the chiral shift reagent method was not effective with 8, its optical purity was calculated as no less than 96 % by the optical rotation and NMR shift reagent analysis of 7 obtained from the MCPBA oxidation of 8.

7) The oxo compound 9a was identical with the compound 4b in reference 1b.

8) The stereochemical course of the P(S)-Cl substitution, P-N cleavage, and P=S to P=O conversion have been established as the followings. P-Cl cleavage with inversion: J. Mikołajczyk, J. Omelańczuk, and M. Para, Tetrahedron, 28, 3855(1972). P-N bond cleavage with inversion of configuration: T. Koizumi, Y. Kobayashi, and E. Yoshii, Chem. Pharm. Bull., 24, 834(1976); T. Koizumi, Y. Kobayashi, and E. Yoshii, Heterocycles, 9, 1723(1978); Y. Kobayashi, T. Koizumi, and E. Yoshii, Chem. Pharm. Bull., 27, 1641(1979). P=S to P=O conversion reaction with retention of configuration: A. W. Herriott, J. Amer. Chem. Soc., 93, 3304(1971).

9) Although the $[\alpha]_D$ of (+)-(R)-11 was recorded as +120° in reference 3, the value has been corrected as +81° according to the recent private communication by Prof. DeBruin, to whom we are grateful for giving us the information.

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