

A PRACTICAL SYNTHESIS OF (+)-PHOSPHINOTHRICINE

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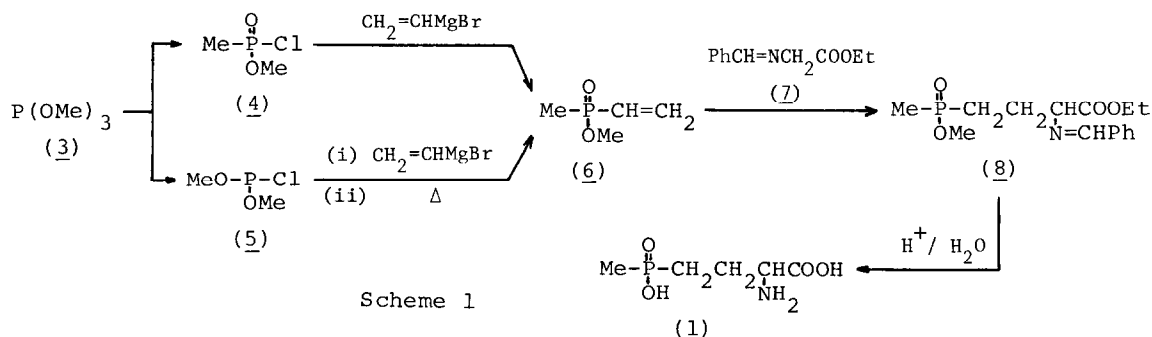
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Summary A practical synthesis of (+)-phosphinothricine from trimethyl phosphite is described.

Phosphinothricine (1), 2-amino-4-(methylphosphino)butanoic acid, was isolated as its alanyl-alanine derivative (2), from the culture filtrates of *Streptomyces viridochromogenes*^{1a)} and *Streptomyces hygroscopicus*.^{1b)} Phosphinothricine and its tripeptide inhibit some enzymatic processes.^{1a,2)} In addition to their antibiotic properties,¹⁾ it was recently reported that they had strong herbicidal activity.^{3e)}

Several synthetic methods of phosphinothricine have been reported,^{3e)} but they have suffered from the inconvenience that the starting material, methyl dichlorophosphine, can not easily be prepared in a large scale. We now report a practical method for preparing phosphinothricine (1) from commercially available trimethyl phosphite (3) (Scheme 1). The key strategy involves the direct introduction of a vinyl function into the phosphorus compounds (4, 5), followed by the addition of glycine Schiff base (7) to the vinyl group of the key intermediate (6).

The key intermediate (6) was prepared from 3 by two routes. Phosphonyl chloride (4) was obtained in good yield by Arbuzov rearrangement of 3 followed by the treatment of the resulting methyl methylphosphinate with phosphorus penta



Scheme 1

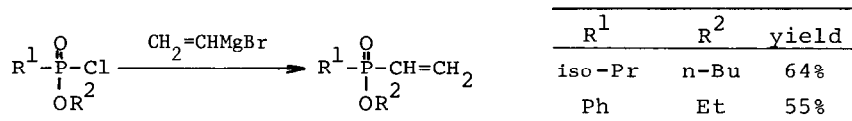
chloride.⁴⁾ Coupling of a vinyl group with phosphorus atom was accomplished also by the addition of vinylmagnesium bromide to 4 in tetrahydrofuran at -20°C to give the desired vinylphosphinate (6, bp $74-76^{\circ}\text{C}/14\text{mmHg}$)⁵⁾ in 61% yield. In another route, phosphorochloridite (5), prepared by treating 3 with phosphorus trichloride, was subjected to alkylative coupling with vinylmagnesium bromide in tetrahydrofuran at -10°C and the resulting vinylphosphonite was heated to afford the key intermediate (6) in 76% yield. A few methods have been reported for preparing alkenyl-phosphonates and -phosphinates.^{3b,6)} However, to our knowledges, this is the first example for preparing vinylphosphinates by the direct introduction of a vinyl group.⁷⁾

The α -amino acid part could be successfully introduced into the vinyl group of 6 by utilizing a Schiff base (7) of glycine ethyl ester as a Michael donor.⁸⁾ Treatment of the Schiff base with 6 in the presence of 0.2 equivalent of potassium hydroxide in ethanol at room temperature afforded the adduct (8),⁵⁾ which was successively refluxed with 6N-hydrochloric acid for 24 hr to give phosphinothricine (1) in 65% yield after purification (Dowex 50X2-400).

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References and Notes

- 1) a) E. Bayel, K. H. Gugel, K. Hägele, H. Hagenmaier, S. Jessipow, W. A. König and H. Zähler, *Helv. Chim. Acta*, **55**, 224 (1972). b) Y. Kondo et al., *Meiji Seika Kenkyu Nempo*, **1973**, 34.
- 2) S. G. Cull-Candy, J. F. Donnellan, R. W. James, and G. G. Lunt, *Nature*, **262**, 408 (1976). b) Wu. Chung, *Can. J. Biochem.*, **55**, 332 (1977).
- 3) a) Y. Ogawa, H. Yoshida, S. Inoue, and T. Niida, *Meiji Seika Kenkyu Nempo*, **1973**, 49. b) H. Gross, and Th. Grouk, *J. Prakt. Chem.*, **318**, 157 (1976). c) E. Gruszecka, P. Mastalerz, and M. Soroka, *Roczn. Chem.*, **49**, 2127 (1975). d) C. Wasielewski, and K. Artczak, *Synthesis*, **1981**, 540. e) K. Weissermel, H. J. Kleiner, M. Finke, and U. H. Felcht, *Angew. Chem. Int. Ed. Engl.*, **20**, 223 (1981). f) A. Suzuki, T. Tsuruoka, K. Mizutani, and S. Inoue, *Meiji Seika Kenkyu Nempo*, **1981**, 33.
- 4) T. M. Balthazor, and R. A. Flores, *J. Org. Chem.*, **45**, 529 (1980).
- 5) NMR(CDCl₃) δ : (6) 1.51 (d, 3H, J=15Hz), 3.65 (d, 3H, J=11Hz), 5.80-6.50 (m, 3H); (8) 1.27 (t, 3H, J=7.5Hz), 1.47 (d, 3H, J=14Hz), 1.5-2.7 (m, 4H), 3.66 and 3.69 (each d, 3H, J=10.5Hz, J=10.5Hz), 4.02 (t, 1H, J=7.0Hz), 4.20 (q, 2H, J=7.5Hz), 7.2-7.9 (m, 5H), 8.30 (s, 1H).
- 6) T. Koizumi, N. Tanaka, M. Iwata, and E. Yoshii, *Synthesis*, **1982**, 917 and references cited therein.
- 7) This procedure could be applicable to other phosphonyl chlorides. For example, the following vinyl phosphinates were directly obtained in a similar method.



- 8) G. Stork, A. Y. W. Leong, and A. M. Touzin, *J. Org. Chem.*, **41**, 3491 (1976).

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