Tetrahedron Letters Vol. 21, pp 1467 - 1468 0040-4039/80/0408-1467$02.00/0

A NOVEL REAGENT (N-SUCCINIMIDYL DIPHENYLPHOSPHATE) FOR SYNTHESIS OF ACTIVE ESTER AND PEPTIDE

Haruo Ogura,* Sachiko Nagai, and Kazuyoshi Takeda

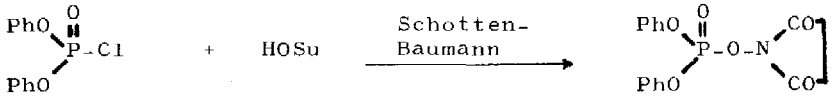
School of Pharmaceutical Sciences, Kitasato University

Shirokane, Minato-ku, Tokyo 108, Japan

N-succinimidyl diphenylphosphate (SDPP) was prepared. This reagent was useful for the preparation of active esters and peptides in stead of dicyclohexylcarbodiimide.

Recently, we reported that N,N'-disuccinimidyl carbonate[1] was used as a reagent for active ester synthesis. Active esters of N-hydroxysuccinimide have been prepared by the dicyclohexylcarbodiimide (DCC) method or the mixed anhydride (MA) method.[2] However, mechanistic studies of the reaction of carboxylic acids with amines mediated by DCC show some trouble in the peptide synthesis.[3,4] In this paper, we described a more convenient method of active ester and peptide synthesis than DCC method, that is preparation of peptide using N-succinimidyl diphenylphosphate (SDPP).

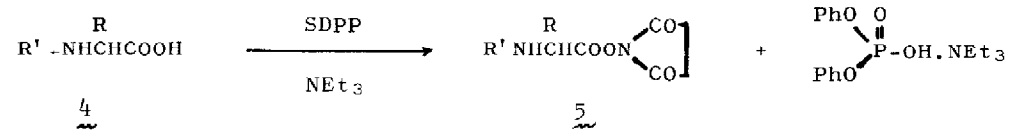
SDPP (3) was prepared by the reaction of diphenylphosphoric chloride (1) with the N-hydroxysuccinimide (HOSu) (2) under the condition of Schotten-Baumann reaction in an aqueous or an organic solution in good yield (60-80%) (Scheme 1). SDPP is white leaves having mp 88-90° and can be kept for several months upon storage in a refrigerator.



1 2 3 (SDPP)

Scheme 1

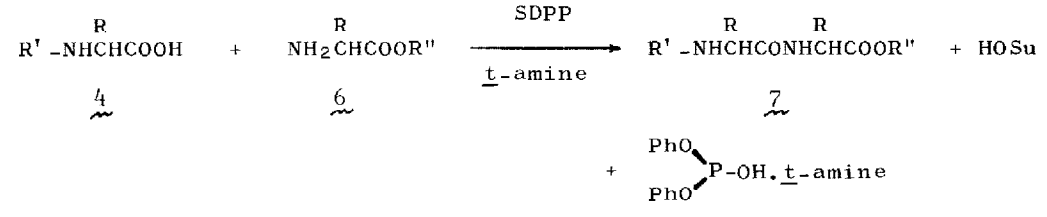
Peptides can be prepared by the following two procedures using SDPP. (A) *Active ester synthesis: From a molar equivalent of* Z- or Boc-alanine (4), SDPP (3), and triethylamine gave active ester (5) in 87% and 88% yield, respectively. In a similar treatment of Z- or Boc- amino acids, further thirteen active esters were obtained in good yields without racemization.



R': $COOCH_2C_6H_5$ (Z) or $COOC(CH_3)_3$ (Boc)

Scheme 2

(B) Direct peptide synthesis: A molar equivalent of Z-valine (carboxyl component; 4), ethyl glycinate (amine component; 6), and triethylamine or N-methylmolphorine with SDPP was treated at room temperature to give Z-Val-Gly-OEt (7) in 89% yield. Similarly, seven dipeptides were prepared in good yields.



R': Z or Boc R": CH_3, C_2H_5

Scheme 3

The phosphonate type coupling reagent is more convenient than DCC for active ester and peptide syntheses.

REFERENCES

1) H. Ogura, T. Kobayashi, K. Shimizu, K. Kawabe, and K. Takeda, Tetrahedron Lett., 4745 (1979).
2) M. Bodanszky, T. S. Klausner, and M. A. Ondetti, "Peptide Synthesis", 2nd Ed., Jone Wiley & Sons, New York, 1976.
3) H. Gross and L. Bilk, Tetrahedron, 24, 6935 (1968).
4) J. Rebek and D. Feitler, J. Am. Chem. Soc., 95, 4052 (1973); 96, 1606 (1974).

(Received in Japan 30 December 1979)