Tetrahedron Letters No. 40, pp 3851 - 3854.
©Pergamon Press Ltd. 1979. Printed in Great Britain.
0040-4039/79/1001-3851$02.00/0

A NOVEL DEHYDRODIPEPTIDE SYNTHESIS BY THE REACTION OF α-TRIETHOXYPHOSPHINIMINO-α-ALKENOATES WITH L-LEUCYL CHLORIDES

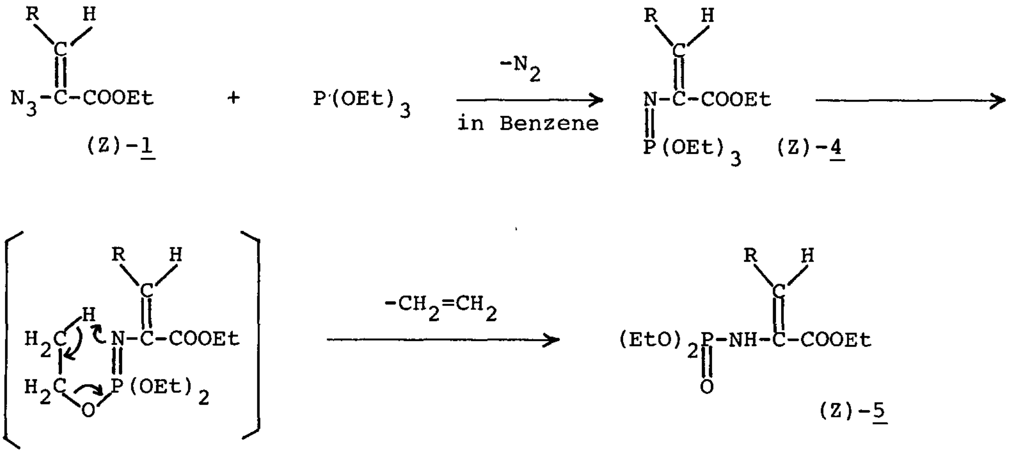
Yasuchika Yonezawa, Chung-gi Shin,* Mitsunori Kiyohara, and Juji Yoshimura†
Laboratory of Organic Chemistry, Kanagawa University, Kanagawaku, Yokohama 221
†Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology, Midoriku, Yokohama 227, Japan

Summary: A new useful method for the synthesis of dehydropeptide by the reaction of L-leucyl chloride with α-triethoxyphosphinimino-α-alkenoic acids, derived from ethyl α-azido-α-alkenoates and triethyl phosphite, is described.

We have previously reported the facile synthesis of ethyl (Z)-α-azido-α-alkenoate (1) from ethyl (E)-α-alkenoate by three steps[1,2] and the subsequent reduction of 1 to ethyl (Z)-α-amino-α-alkenoate (2).[2,3] Although many reports have been published on the reaction of saturated azido compounds, the synthesis and the reaction of α,β-unsaturated α- and β-azidocarboxylic acid esters (1 and 3) has scarcely appeared in literature.[4-6] Moreover, no attention was paied to the reactivity of the azidoolefins utilizing trivalent organic phosphorus reagents, except the reaction of ethyl β-azidocrotonate (3) with triphenyl phosphine.[7]

In this paper, we wish to report a novel synthesis of α-dehydroamino acid (DHA) and its dipeptide (DHP) N-protected with a phosphoryl group *via* an α-phosphinimino-α-alkenoic acid derivative.

To a solution of 1 (0.03 mol) in dry benzene (30 ml) was added triethyl phosphite (0.03 mol) dropwise with stirring at 10 °C. The reaction solution was kept at room temperature for 2.5 h and then concentrated under reduced pressure to give a residual syrup, which was subsequently distilled in *vacuo*. The colorless syrup obtained in *ca.* 80% yield was assigned to be ethyl (Z)-α-triethoxyphosphinimino-α-alkenoate (4). When 4 was allowed to stand at room temperature for about 5 weeks or a solution of 4 in benzene-ethyl acetate (3 : 1 v/v) was passed through a silica gel column, the elimination of ethylene occurred spontaneously to give ethyl (Z)-α-(diethyl phosphonyl)amino-α-alkenoate (5) as colorless needles in *ca.* 87% yield. The configuration of 5 was proved by the independent



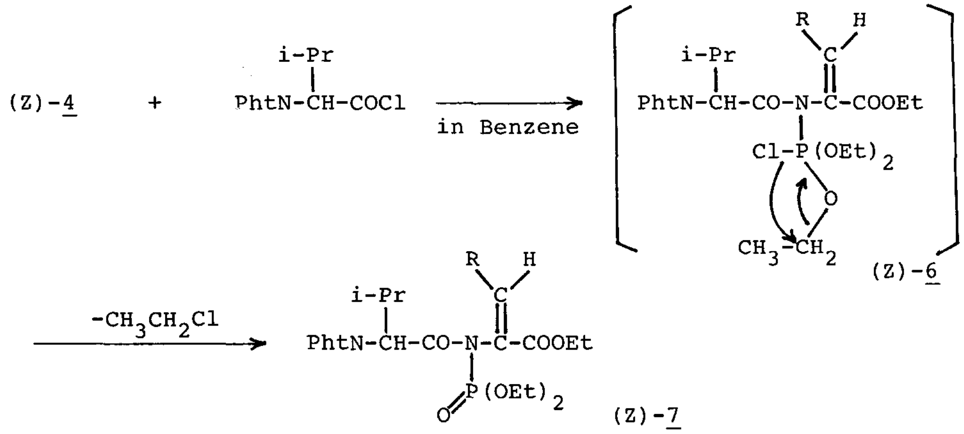
a; $R=CH_3$, b; $R=C_2H_5$, c; $R=n\text{-}C_3H_7$, d; $R=i\text{-}C_3H_7$, e; $R=C_6H_5$

Table 1. Yields, physical constants and NMR data of 4 and 5.

	Yield (%)	Bp °C/mmHg[a]	NMR, δ in $CDCl_3$ Olefinic-H	(J_{Hz})		Yield (%)	Mp °C	NMR, δ in $CDCl_3$ Olefinic-H	(J_{Hz})	$NH^{d)}$
4a	83	105-107/0.5	5.99dq	(4.0) (6.9)	5a	87	47-48[b]	6.50dq	(2.6), (7.0)	4.78
4b	63	111-115/0.5	5.92dt	(4.1) (7.0)	5b	86	30-31[b]	6.37dt	(2.6), (7.0)	4.80
4c	92	113-119/0.5	5.93dt	(4.1) (7.0)	5c	81	46-47[b]	6.42dt	(2.6), (7.0)	4.73
4d	75	115-119.0.7	5.77dd	(4.5) (8.3)	5d	88	40-42[b]	6.19dd	(2.5), (10.0)	4.70
4e	89	syrup	6.70d	(8.0)	5e	91	70-71[c]	7.23s,		4.80

a) Colorless syrup. b) Colorless needles from hexane. c) Colorless needles from cyclohexane. d) Broad singlet.

synthesis of 5 from (Z)-2 and diethyl phosphorochloridate by the usual method. In a similar manner, the reaction of 1 with ethyl diphenylphosphinite gave ethyl (Z)-α-diphenylethoxyphosphinimino-α-alkenoate as the initial product, which was immediately transformed on a silica gel column into the expected ethyl (Z)-α-(diphenylphosphinyl)amino-α-alkenoate in *ca.* 70% overall yield. In the Table 1, only triethoxyphosphinimino and (diethyl phosphoryl)amino derivatives are listed.



a; R=CH_3, b; R=C_2H_5, c; R=n-C_3H_7, d; R=i-C_3H_7, e; R=C_6H_5. PhtN=phthalimino.

Table 2. Yields, physical constants, and spectral data of 7.

	Yield (%)	Mp °C	IR, cm^{-1} in KBr COOEt	NHCO	C=C	P=O P-O-P	NMR, δ in $CDCl_3$ Olefinic-H (J_{Hz}) (J_{Hz})	N-CH- (J_{Hz})	$[\alpha]_D^{25}$
7a	70	syrup[a)]	1740,	1720,	1620,	1270 1050	7.02dq (2.0) (7.0),	4.70 (8.0),	0[c)]
7b	66	79-80.5[b)]	1740,	1720,	1620,	1270 1040	6.90dt (2.0) (7.0),	4.70 (8.0),	-60.2
7c	67	98-99.5[b)]	1740,	1710,	1653,	1280 1030	7.00dt (2.0) (7.6),	4.77 (7.2),	-55.2
7d	64	syrup[a)]	1740,	1720,	1615,	1270 1040	6.75dd (2.2) (11.0),	4.80 (8.0),	-45.3
7e	60	119-120[b)]	1735,	1710,	1640,	1265 1050	7.35-7.84 [Ph + H],	4.42 (8.0),	-40.4

a) Colorless. b) Colorless prisms from cyclohexane. c) Obtained from racemic N-phthalylleucyl chloride and 4.

On the other hand, more interestingly, a one step formation of dehydrodipeptide from 4 and N-phthalyl-L-α-amino acid chloride could be achieved; for example, a solution of 4 (0.04 mol) and N-phthalyl-L-leucyl chloride, prepared by the reaction of N-phthalyl-L-leucine (0.02 mol) with thionyl chloride (8 ml) by the usual way, in dry benzene (30 ml) was stirred at room temperature for 12 h. The reaction solution was concentrated under reduced pressure to give a residual syrup, which was purified on a silica gel column using benzene-ethyl acetate (5 : 1 v/v) as eluent to give colorless prisms or syrups assigned to be ethyl N-phthalyl-L-leucyl-N-(diethyl phosphoryl)amino-α-alkenoate (7). In the Table 2, yields and physical constants are listed.

N-Phosphoryl-DHA and its peptides, especially N-diphenylphosphinyl (Dpp) derivatives,[8)] will be useful for the synthesis of peptides containing DHA.

From the NMR spectrum of 4, 5, and 7, the long range couplings between phosphorus and vinyl proton were observed as sharp doublets by the values of *ca.* 4.2, 2.6, and 2.1 Hz, respectively, as shown in Tables 1 and 2. As shown in Schemes, the formation of DHA and DHP was attributed to an Arbusov-type reaction of 4 and 6 formed only as an unstable intermediate, which yielded 5 and 7, respectively.

The structure of all new compounds were supported by spectroscopic data and satisfactory results in elemental analysis.

References

1) C. Shin, Y. Yonezawa, and J. Yoshimura, *Chem. Lett.*, **1976**, 1063.

2) C. Shin, Y. Yonezawa, K. Unoki, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **52**, 1657 (1979).

3) C. Shin, Y. Yonezawa, and J. Yoshimura, *Chem. Lett.*, **1976**, 1095.

4) A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968).

5) H. Hemetsberger, D. Knittel, and H. Weidmann, *Monat. Chem.*, **100**, 1599 (1969).

6) C. Shin, Y. Yonezawa, and J. Yoshimura, *Tetrahedron Lett.*, **1974**, 7.

7) G. R. Harvey and K. W. Ratts, *J. Org. Chem.*, **31**, 3907 (1966).

8) M. Ueki and S. Ikeda, *Chem. Lett.*, **1976**, 827.

(Received in Japan 6 June 1979)