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Further study of peptide synthesis using 1,3,4-trimethyl-Δ^3-phospholene-1,1-dichloride as a coupling reagent.

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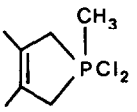
We have recently described[1] the use of the cycloadduct 1 of 2,3-dimethyl-buta-1,3-diene and methylphosphonous dichloride[2] as a coupling reagent in peptide synthesis. We showed that it provides a convenient method for stepwise condensation, but the question of its use for fragment condensation remained open since the Young test gave 47% racemization whereas the coupling of Z-Val-Val-OH with H_2N-Val-OMe yielded the pure tripeptide as the sole product. We should like now to report on our new results with reagent 1 which establish that it can be employed also for fragment coupling at least with valine, leucine or phenylalanine as the C-terminal residue of the fragment.

The first piece of evidence came from the identification of the Z-Val-Val-Val-OMe tripeptide from fragment condensation (Table, entry 1) as the pure L-L-L isomer, by comparison with the product of stepwise elongation via Boc-Val-Val-OMe (entry 2).



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The results of the Anderson test[3] were satisfactory. Coupling of Z-glycyl-L-phenylalanine with ethyl glycinate (entry 3) gave an excellent yield of the tripeptide containing at least 92% of the L-isomer.

Two other tripeptides have been synthesized by the fragment condensation method (entries 4 and 5). The second one is the protected C-terminal tripeptide of oxytocin[5] and the synthetic precursor of the related glycinamide Pro-Leu-Gly-NH_2, a hypothalamic hormone : melanocyte-stimulating-hormone-release-inhibiting factor (MRIF)[6].

Entries 6 to 9 give examples of coupling of aminoacids carrying functional groups. It is obvious from the last two ones that phenolic or alcoholic hydroxyls have to be protected prior to coupling.

The experimental procedure for the synthesis of peptide 5 is given as a typical example. Z-Proline and Leucine methyl ester hydrochloride 2 mmoles each) were dissolved in 50 ml CH_2Cl_2 distilled over P_2O_5[10,11]. Triethylamine (6 mmoles) was added, followed by 2.2 mmoles of 1 added in solid state and by ∿ 1 mmole of

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Table. Preparation of peptides by means of reagent 1.

N°	Peptide a)b)	Yield %	M.p.°C	$[\alpha]_D^{21\pm1}$ (C solvent)	Literature M.p.°C	Literature $[\alpha]_D$	ref.
1	Z-Val-Val¦Val-OMe c)	90	215-217	-15.2 2 DMF			
2	Z-Val¦Val-Val-OMe	88	216-217	-15 2 DMF			
3	Z-Gly-Phe¦Gly-OEt	93	118-120	-12.4 2 EtOH	118-119	-13.5	3a
					120-120.5	-13.1	3b
4	Z-Gly-Leu¦Leu-OMe	86	133-134	-46.5 2 MeOH	133-134	-47.4	4
5	Z-Pro-Leu¦Gly-OEt	95	148-149	-88.1 1 EtOH	150-152	-83.2	5
6	Z-Asp-Phe-OMe d) OBz	78	118-119	- 9.8 4 MeOH	119-120	-10	7
7	Z-Asn-Gly-OEt	85	186-188	-35.2 0.5 EtOH	186-187	-35	8
8	Boc-Tyr-Phe-OMe c)	52	140-141	+27.6 2 $CHCl_3$			
9	Z-Ser-Gly-OEt	30	100-102	- 5.2 1 EtOH	103	- 5	9

a) All aminoacids have the L-configuration. b) The dotted line indicates the site of last coupling. c) Not yet prepared to our knowledge; structure confirmed by ^1H NMR spectrometry. d) Asp-Phe-OMe has a sweetening potency of 100-200 times sucrose[7].

N-methylimidazole. The mixture was stirred for 90 min; after 30 min it became homogeneous. The solution was concentrated in vacuum, diluted with AcOEt, C_6H_6 and 5% aq. HCl and the organic layer successively washed with aq. HCl, sat. NaCl, sat. $NaHCO_3$ (twice) and sat. NaCl. Drying followed by evaporation gave the crude protected dipeptide in 96% yield, m.p. 75-76° (AcOEt-Hex), $[\alpha]_D^{22}$ -69.5°, c = 1.4 EtOH; reported[5] : m.p. 76.5-78° $[\alpha]_D^{21}$ -69°, c = 1 EtOH. It was saponified by means of aq. alcoh. NaOH at r.t. according to [5] and the crude acid obtained in 90% yield coupled with glycine ethyl ester hydrochloride following the above procedure. The over-all yield of Z-Pro-Leu-Gly-OEt was 82%.

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References and notes.

1. E. Vilkas, M. Vilkas and J. Sainton, Nouv.J.de Chimie, to be published.
2. L.D. Quin, J.P. Gratz and T.P. Barket, J.Org.Chem., 33, 1034 (1968).
3a. J.C. Sheehan and G.P. Hess, J.Amer.Chem.Soc., 77, 1067 (1955).
b. G.W. Anderson and F.M. Callahan, J.Amer.Chem.Soc., 80, 2902 (1958).
4. R.W. Young, K.H. Wood, R.J. Joyce and G.W. Anderson, J.Amer.Chem.Soc., 78, 2126 (1956).
5. W.D. Cash, J.Org.Chem., 26, 2136 (1961).
6. A. Vivas and M.E. Celis, Proceedings of the 4th Amer. Peptide Symp., p. 777, R. Wetter and J. Meienhofer, ed. (1975).
7. R.H. Mazur, J.M. Schlatter and A.H. Goldkamp, J.Amer.Chem.Soc., 91, 2684 (1969).
8. G.R. Pettit, Synthetic Peptides, p.92, Van Nostrand Reinhold Comp. (1970).
9. B. Castro, J.R. Dormoy, G. Evin and C. Selve, Tetrahedron Letters, 1219 (1975)
10. Use of dichloromethane only kept over $CaCl_2$ gives lower yields of condensation product.
11. When the components are incompletely soluble in CH_2Cl_2, DMF can be added.