Tetrahedron Letters,Vol.26,No.10,pp 1341-1342,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

BENZOTRIAZOL-1-YL DIETHYL PHOSPHATE. A NEW CONVENIENT COUPLING REAGENT FOR THE SYNTHESIS OF AMIDES AND PEPTIDES.

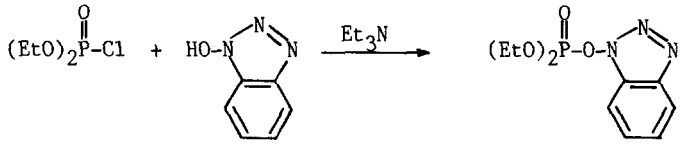
Sunggak Kim,* Heung Chang, and Young Kwan Ko
Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131, Korea

Summary: Benzotriazol-1-yl diethyl phosphate is found to be a new convenient coupling reagent for the synthesis of amides and practically racemization-free peptides.

Among a wide variety of coupling reagents for peptide synthesis, organophosphate types of coupling reagents have attracted a great deal of interest in the synthesis of racemization-free peptides in recent years.[1]

In connection with our research directed toward synthetic utility of active esters and carbonates containing 2-pyridyl and benzotriazol-1-yl moieties,[2] we wish to report the use of a new coupling reagent, benzotriazol-1-yl diethyl phosphate (BDP), for the synthesis of amides and peptides (eq. 1). BDP was conveniently prepared by mixing equimolar amounts of diethyl chlorophosphate, 1-hydroxybenzotriazole, and triethylamine in tetrahydrofuran at room temperature (eq. 2). BDP was obtained in an essentially quantitative yield as an oil after purification by filtration through a short column of silica gel or cellulose and can be stored in a refrigerator for several weeks without any decomposition.[3]

$$RCOOH + R'NH_2 + BDP + Et_3N \longrightarrow RCONHR' \qquad (1)$$



(2)

BDP

Various amides were obtained in high yields by simple mixing carboxylic acids, amines, BDP, and triethylamine in an equimolar ratio in various solvents such as N,N-dimethylformamide, tetrahydrofuran, acetonitrile, and methylene chloride at room temperature. Among the solvents employed, N,N-dimethylformamide gave the best results in terms of the rapidity and the high yield and is generally recommended. The reaction was complete within 20 min in N,N-dimethylformamide at room temperature and the corresponding amides were obtained without contamination of side products. Some typical isolated yields were: $C_6H_5CONHCH_2C_6H_5$, 95%; $C_6H_5CONHC_6H_5$, 96%; C_6H_5CONH-c-C_6H_{11}, 93%; $C_6H_5CH_2CONHC_6H_5$, 96%; $CH_3CH{=}CHCONHC_6H_5$, 95%.

Table 1. Preparation of Peptides with BDP in DMF.[a]

Peptide	Yield, %[b]	mp, °C	$[\alpha]_D$ (c, solvent, °C)[c]
Z-Phe-Gly-OEt	95	109-110	-17.0 (1.7, EtOH, 16)
Z-Phe-Ser-OMe	96	121-122	-5.5 (2.0, DMF, 20)
Z-Val-Gly-OEt	94	166-167	-25.6 (1.8, EtOH, 20)
Z-Val-Tyr-OMe	95	155-156	+14.6 (1.8, pyridine, 16)
Z-Met-Val-OMe	92	103-104	-26.3 (1.0, MeOH, 20)
Boc-Try-Gly-OEt	91	117.5-118	-12.7 (1.0, EtOH, 18)
Boc-Ile-Gly-OEt	96	104	-28.5 (1.4, EtOH, 15)
Boc-Val-Val-OMe	96	166-167	-9.3 (2.0, EtOAc, 18)

[a] The reaction was carried out with equimolar amounts of two amino acid components and BDP using 2.1 equiv of triethylamine in DMF at room temperature for 3 h. [b] The yields refer to isolated products. [c] Melting points and $[\alpha]_D$ values are in accord with reported values.

In order to investigate the usefulness of BDP in the synthesis of racemization-free peptides, we examined the supersensitive Young test and it was found that practically no racemization was observed using N,N-dimethylformamide as a solvent, though it was reported the use of benzotriazol-1-yloxytris(dimethyl)phosphonium hexafluorophosphate (BOP) as a coupling reagent resulted in practically complete racemization during Young test.[4] Thus, to an equimolar mixture of Bz-L-Leu and Gly-OEt·HCl in DMF is added to a solution of 1 equiv of BDP in DMF at 0 °C, followed by the addition of 2.1 equiv of triethylamine. The mixture was stirred at room temperature for 3 h. After usual workup, Bz-L-Leu-Gly-OEt was isolated in 89% yield. mp 156.5-157 °C, $[\alpha]_D^{18}$ -33.0° (2.0, EtOH).[5] When the reaction was carried out in dichloromethane and ethyl acetate under the similar conditions, Bz-L-Leu-Gly-OEt was obtained in 82% ($[\alpha]_D$ -27.8°) and 80% yield ($[\alpha]_D$ -30.4°), respectively.

As shown in Table 1, the reaction was complete within 3 h at room temperature and various dipeptides were obtained in high yields without racemization. The identities of peptides were confirmed by comparison of mp, NMR data, and $[\alpha]_D$ values with reported data.

Acknowledgment: We thank Korea Science and Engineering Foundation for financial support.

References and Notes.

1. For recent examples, see: (a) T. Mukaiyama, N, Morito, and Y. Watanabe, Chem. Lett., 1305 (1979). (b) H. Ogura, S. Nagai, and K. Takeda, Tetrahedron Lett., 1467 (1980). (c) Y. Kiso, T. Miyazaki, M. Satomi, H. Hiraiwa, and T. Akita, J. C. S. Chem. Comm., 1029 (1980).
2. (a) S. Kim and H. Chang, J. C. S. Chem. Comm., 1357 (1983). (b) S. Kim and J. I. Lee, Chem. Lett., 237 (1984). (c) S. Kim and J. I. Lee, J. Org. Chem., 49, 1712 (1984). (d) S. Kim and J. I. Lee, Tetrahedron Lett., 4943 (1984).
3. Distillation in vacuo led to decomposition of BDP.
4. B. Castro, J. R. Dormoy, G. Evin, and C. Selve, Tetrahedron Lett., 1219 (1975).
5. The per cent of L isomer is 97%, based on $[\alpha]_D^{20}$ -34° from Young's report. M. W. Williams and G. T. Young, J. Chem. Soc., 881 (1963).

(Received in Japan 15 December 1984)