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PENTAFLUOROPHENYL DIPHENYLPHOSPHINATE
A NEW EFFICIENT COUPLING REAGENT IN PEPTIDE CHEMISTRY

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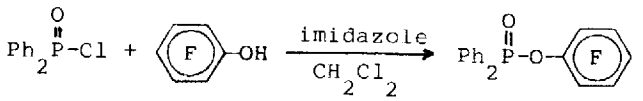
Abstract: Pentafluorophenyl diphenylphosphinate was found to be a new efficient coupling reagent for the racemization-free synthesis of peptides. It has been applied in both the solution and the solid phase peptide synthesis.

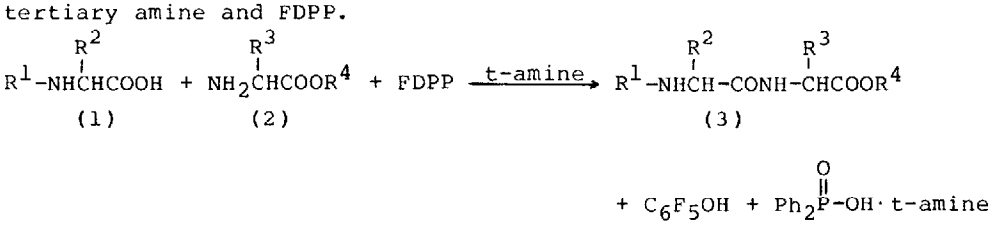
Diphenylphosphinic mixed anhydrides have been used in the peptide chemistry[1]. Pentafluorophenyl ester has also been used in both the solution[2] and the solid phase peptide synthesis[3]. However, the preactivation of amino acids or preparation of active esters was necessary. We have synthesized a new reagent, pentafluorophenyl diphenylphosphinate (FDPP), which is prepared from diphenylphosphinic chloride and pentafluorophenol, and found that it can directly be used as an efficient coupling reagent for peptide synthesis without racemization.

FDPP can conveniently be prepared by mixing equimolar amounts of diphenylphosphinic chloride, pentafluorophenol and imidazole in CH_2Cl_2 at room temperature[4]. It can be kept for several months upon storage in a refrigerator.



(FDPP)

Using FDPP as a coupling reagent, peptides can easily be prepared in good yields by simply mixing carboxyl component(1), amine component(2), tertiary amine and FDPP.



(1) (2) (3)

Of several solvents examined, DMF was found to be the best. Moni-

toring by HPLC, the reactions were shown to be completed (yield>95%) within 0.5 h. Many peptides were synthesized with excellent yields as shown in Table 1.

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

peptide	yield(%)[b]	mp (°C)	$[\alpha]_D$(C,solvent,°C)[c]
Boc-Cys(Bzl)-Trp-OMe	98	160-162	-12.6(1,MeOH,25)
Boc-Trp-Trp-OMe	96	180-182	-15.3(1,MeOH,25)
Boc-Phe-Phe-OMe	99	118-120	-13.1(1,MeOH,25)
Boc-Leu-Trp-OMe	91	86-88	-14.4(1,MeOH,25)
Z-Gly-Phe↓Val-OMe[d]	86	94-96	-16.9(1,EtOH,25)
Boc-Tyr(Bzl)-Gly-OEt	94	126-128	-1.4(1,MeOH,15)
Boc-Phe-Leu-OMe	94	102-103	-24.9(1,MeOH,15)
Boc-Phe-Met-OMe	81	86-88	-20.4(1,MeOH,18)
Boc-Tyr(Bzl)-Gly↓Gly-OEt[d]	83	101-103	+10.9(1,MeOH,15)
Boc-Tyr(Bzl)-Gly-Gly↓Phe-Met-OMe[d]	91	153-154	-7.5(1,MeOH,15)

a. The reactions were performed with equimolar amounts of a carboxyl component, an amino component hydrochloride and 3 equiv. diisopropylethylamine (DIEA) using 1.2 equiv. of reagent FDPP in DMF at room temperature for 1.5 h. b. The yields refer to isolated products. c. Melting points and $[\alpha]_D$ values are in accord with reported values and all the products are confirmed by elemental analysis. d. The arrow indicates a coupling site.

Although many conventional reagents, such as, DCCI, BOP[5] and HBTU[6] etc., have successfully been used for peptide synthesis, the racemization occurs to large extents if no additives are used. Using HPLC[7] (the coupling of Z-Gly-Phe-OH and Val-OMe·HCl) and Young test[8] (the coupling of Bz-Leu-OH and Gly-OEt·HCl), extent of racemization was examined with our reagent. Almost no racemization was observed in both methods. Comparing with other methods, including our previous reagent, pentafluorophenyl diphenylphosphate (FDP)[9], the racemization in FDPP method was the lowest as shown in Table 2.

In order to evaluate the application of the FDPP reagent in peptide chemistry, Leu-enkephalin was synthesized in solution. Each coupling was carried with FDPP and the yield of each coupling product was over 90%. The HPLC profile showed that the product is identical with the authentic sample.

For a solid phase synthesis, we also set Leu-enkephalin as a target molecule. The chloromethyl resin was used as the support. The reaction

was carried out for 2 h. with 3 equiv. Boc-amino acid, FDPP and 9 equiv. diisopropylethylamine. The FDPP method is superior to DCCI method also in solid phase synthesis since there is no problem of insouble by-product such as DCU in the washing step. The coupling yield was over 98.5% estimated by quantitative ninhydrin method[10](Table 3). The product showed the same retention time in HPLC as the authentic sample and the product synthesized in solution.

Table 2. Comparison of racemizations of different methods[a]

Reagent		FDPP	FDP	HBTU	BOP	DCCI
HPLC	DL%	0.0	5.4	9.0	9.6[b]	18.8
Young test	$[\alpha]_D$	-34.0	-27.0	-25.4	-20.5	-9.0
	DL%	0.0	20.6	25.4[c]	39.8[d]	73.6

a. All the reaction conditions were the same as in Table 1, except that one equiv. DIEA was used in DCCI method. b. Lit. 11: DL%=11.4%, BOP/HOBt: DL%=3.4%. c. Lit.12: $[\alpha]_D$=-25.6(3.1,EtOH), DL%=24.8%. d. Lit. 6: $[\alpha]_D$=-13.5(EtOH), DL%=60%.

Table 3. Coupling efficiency in the solid phase synthesis of Leu-enkephalin using FDPP

Step	Boc-Phe	Boc-Gly	Boc-Gly	Boc-Tyr(Bzl)
coupling yield	99.4%	99.4%	98.8%	98.6%

Thus FDPP reagent was proved to be an efficient reagent for peptide synthesis particularly because of the following facts: (1) very low or no racemization; (2) no problem of insouble by-product such as DCU; (3) excellent synthetic yield and high coupling speed; (4) simplicity of the coupling procedure. FDPP can directly be used in coupling reaction without the preactivation in the mixed anhydride method or the preparation of pentafluorophenyl active esters in the ester method; (5) simple preparation of the reagent.

References and notes:

1. a) A.G. Jackson, G.W. Kenner, G.A. Moore, R. Ramage, W.D. Thorpe, Tetrahedron Lett., **40**, 3627 (1976). b) R. Ramage, D. Hopton, M.J.

Parrott, R.S. Richardson, G.W. Kenner, G.A. Moore, J. Chem. Soc. Perkin Trans. I., 461 (1985).

2. a) J. Kovacs, G.L. Mayers, R.H. Johnson, R.E. Cover, U.R. Ghatak, J. Chem. Soc. Chem. Commun., 53 (1970). b) J. Kovacs, L. Kisfaludy, M. Q. Ceprini, J. Am. Chem. Soc. **89**, 183 (1967). c) L. Kisfludy, I. Schon, Synthesis, 325 (1983).
3. a) E. Atherton, R.C. Sheppard, J. Chem. Soc. Chem. Commun., 165 (1985). b) E. Atherton, L.R. Cameron, R.C. Sheppard, Tetradron, **44**, 843 (1988).
4. Preparation of FDPP: A solution of imidazole (1.07g, 15.7mmol) in anhydrous CH_2Cl_2 (20ml) was added dropwise to a stirred solution of diphenylphosphinic chloride (2.89g, 15.7mmol) in anhydrous CH_2Cl_2 (30 ml) at room temperature. The reaction mixture was stirred for 1 h after the addition was complete. After removal of imidazole HCl salt by filtration, the filtrate was concentrated in vacuo. After purification by a short column of silical gel and drying over P_2O_5 for 2 days, FDPP (6.0g, ~100%) was obtained and solidified (Distillation in vacuo led to decomposition of FDPP). mp: 46-49°C. M^+: 384. ^{31}P(acetone-d_6): 36.07(s).
5. a) B. Castro, J.R. Dormoy, G. Evin, C. Selve, Tetrahedron Lett., **14**, 1219 (1975). b) A. Fournier, C.-T. Wang, A.M. Felix, Int. J. Peptide Protein Res., **31**, 86 (1988).
6. V. Dourtoglou, J.C. Ziegler, B. Gross, Tetrahedron Lett., 15, 1269 (1978).
7. C. Van der Auwera, S. Van Damme, M.J.O. Anteunis, Int. J. Peptide Protein Res., **29**, 464 (1987).
8. M.W. Williams, G.T. Young, J. Chem. Soc., 881 (1963).
9. a) M.I. Kabachnik, L.S. Zakharov, I.Yu. Kudryavtsev, A.P. Kharchenko, G.P. Tataurov, L.I. Korobeinikova, Izv. Akad. Nauk SSSR, Ser. Khim., **4**, 896 (1979). b) S. Chen, J. Xu, to be published.
10. V.K. Sarin, S.B.H. Kent, J.P. Tam, R.B. Merrifield, Anal. Biochem, **117**, 147 (1981).
11. R. Steinauer, F.M.F. Chen, N.L. Benoiton, Int. J. Peptide Protein Res. **34**, 295 (1989).
12. B. Castro, J.R. Dormoy, G. Evin, C. Selve, J. Chem. Res. 182 (1977).

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