2-Pyridon-1-yl Diphenyl Phosphate. A Useful New Reagent for the Synthesis of Amides and Peptides

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2-Pyridon-1-yl diphenyl phosphate is found to be a useful coupling agent for the synthesis of amides and practically racemization-free peptides.

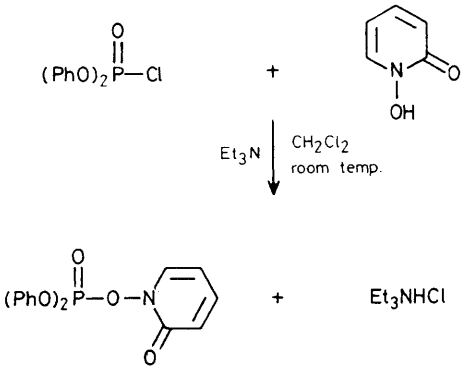
Among a large number of coupling agents for peptide synthesis,[1] phosphorus-based coupling agents have attracted a great deal of recent attention.[2] In the course of our work in developing new effective coupling agents,[3] we have found that 2-pyridon-1-yl diphenyl phosphate is easily prepared by simply mixing equimolar amounts of 1-hydroxy-2(1*H*)-pyridone,[4] Et_3N, and diphenyl chlorophosphate in CH_2Cl_2 at room temperature for 30 min (equation 1). The reagent is obtained as colourless crystals (m.p. 76—77 °C) in essentially quantitative yields (90—95%) after purification through a short column of silica gel and can be stored in a refrigerator for a long period of time without any decomposition.

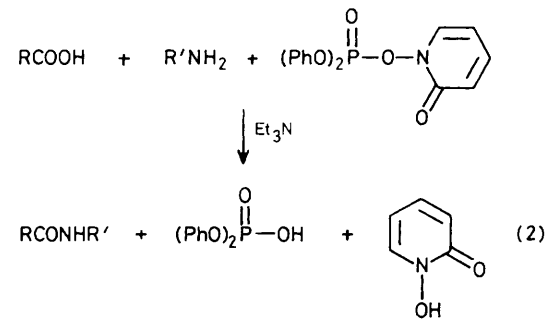
Reaction of carboxylic acids with equimolar amounts of amines, the reagent, and Et_3N in CH_2Cl_2 occurred cleanly and rapidly at room temperature within 30 min, yielding the corresponding amides in high yields (equation 2). When t-butylamine was used as the amine component, the reaction required 1 h for completion of the reaction. Some typical isolated yields were: $PhCH_2CONHCH_2Ph$, 85%; $Ph_2CHCONH$-c-C_6H_{11}, 93; PhCONH-c-C_6H_{11}, 97; $PhCONHCH_2Ph$, 91; $PhCONHCMe_3$, 88.

Furthermore, reaction of carboxylic acids with equimolar amounts of the reagent and Et_3N in various solvents such as CH_2Cl_2 and *N,N*-dimethylformamide (DMF) at room temperature gave the synthetically useful carboxylate esters of 1-hydroxy-2(1*H*)-pyridone in essentially quantitative yields. It was shown that these active esters were cleanly converted into the amides and esters by treatment with amines and alcohols, respectively.[5]

In order to study the effectiveness of the reagent in peptide synthesis, the supersensitive Young test was examined under various conditions. Among solvents and amine bases employed in this study, the combination of Et_3N and DMF gave the best results in terms of the degree of racemization and the high yield and is generally recommended for the synthesis of racemization-free peptides. Thus, reaction of the reagent with an equimolar mixture of Bzl–L-Leu† and Gly–OEt·HCl in the presence of 2 equiv. of Et_3N in DMF at room temperature gave Bzl–L-Leu–Gly–OEt{m.p. 156—156.5 °C, $[\alpha]_D^{20}$ −33.3° (*c* 1.6, EtOH)} in 93% yield. The amount of L isomer is 98%, based on $[\alpha]_D^{20}$ −34° from Young's report.[6] When the reaction was carried out in CH_2Cl_2 and EtOAc under similar conditions, Bz–L-Leu–Gly–OEt was obtained in 90 ($[\alpha]_D^{20}$ −25.9°) and 81% yield ($[\alpha]_D^{20}$ −21.3°), respectively. Furthermore, various dipeptides were obtained in high yields without observable racemization using 2-pyridon-1-yl diphenyl phosphate and Et_3N in DMF and the reaction was complete within 3 h at room temperature. Some typical isolated yields were: Boc-Ile–Val–OMe, 88%; Boc–Val–Val–OMe, 88; Boc–Phe–Gly–OEt, 89; Boc–Try–Gly–OEt, 90; Boc–Thr–Phe–OMe, 87; Z–Val–Gly–OEt, 94; Z–Val–Val–OMe, 88; Z–Val–Tyr–OMe, 93; Z–Pro–Phe–OMe, 85.† The identities of dipeptides obtained were confirmed by comparison of m.p.s, $[\alpha]_D$ values, and spectral data with reported data.

† Bzl = benzyl, Boc = t-butoxycarbonyl, Z = benzyloxycarbonyl.





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References

1 E. Gross and J. Meienhofer, 'The Peptides, Analysis, Synthesis, Biology,' vol. 1, Academic Press, New York, 1979, and references cited therein.
2 For recently developed reagents, see: H. Ogura, S. Nagai, and K. Takeda, *Tetrahedron Lett.*, 1980, 1467; T. Miyazaki, M. Satoni, H. Hiraiwa, and T. Akita, *J. Chem. Soc., Chem. Commun.*, 1980, 1029; T. Mukaiyama, K. Kamekawa, and Y. Watanabe, *Chem. Lett.*, 1981, 1367; R. Ramage, C. P. Ashton, D. Hopton, and M. J. Parrott, *Tetrahedron Lett.*, 1984, 4825; M. Miyake, M. Kirisawa, and N. Tokutake, *Chem. Lett.*, 1985, 123; R. D. Tung and D. H. Rich, *J. Am. Chem. Soc.*, 1985, **107**, 4342.
3 For our recent reports, see: S. Kim, H. Chang, and Y. K. Ko, *Tetrahedron Lett.*, 1985, 1341; S. Kim and K. Y. Yi, *ibid.*, 1985, 1661; S. Kim and Y. K. Ko, *J. Chem. Soc., Chem. Commun.*, 1985, 473.
4 A. R. Katritzky, *J. Chem. Soc.*, 1957, 191; M. Hamana and M. Yamazaki, *Yakugaku Zasshi*, 1961, **81**, 612.
5 L. A. Paquette, *J. Am. Chem. Soc.*, 1965, **87**, 5186.
6 M. W. Williams and G. T. Young, *J. Chem. Soc.*, 1963, 881.