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PEPTIDE SYNTHESIS WITH POLYMERIC TRIPHENYLPHOSPHINE/2,2'-DIPYRIDYL DISULFIDE[1]

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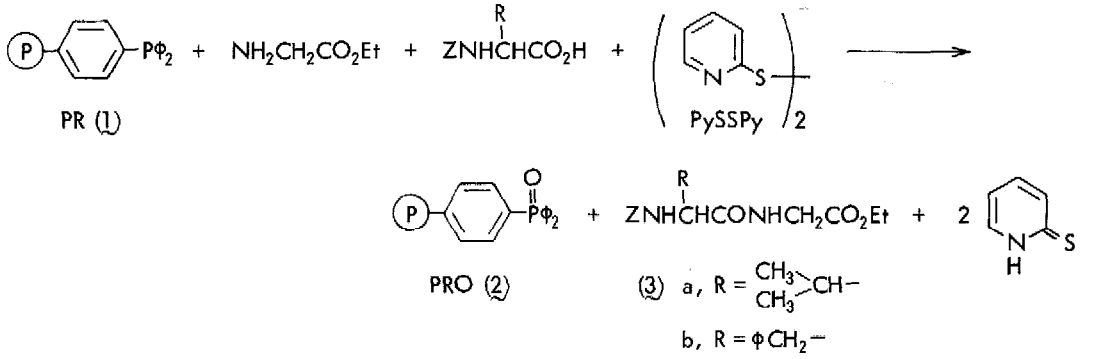
Although a number of peptide preparations have been successfully obtained by the Merrifield procedure,[2] the use of insoluble reagents bound to polymers (anti-Merrifield method) is only currently receiving attention. Some workers have pointed out the advantage of utilizing these polymeric reagents not only in peptide but also organic syntheses.[3] The main advantage of this procedure is that the excess reagent and other reaction products are removed simply by filtration and the recovered polymer can be recycled to the original reagent in most cases.

We wish to report a successful synthesis of dipeptides by the Mukaiyama procedure[4] using a polymeric triphenylphosphine-type reagent (1) and 2,2'-dipyridyl disulfide as shown in the following scheme:*



Polymeric triphenylphosphine (1) was prepared according to the method developed by Relles and Schluenz;[5] cross-linked polystyrene (Amberlite XE-305)[6] was brominated using a catalytic amount of

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* The following abbreviations are used: (P) for a copolymer of polystyrene and divinylbenzene, PR for polymeric triphenylphosphine (1), PRO for polymeric triphenylphosphine oxide (2), and PySSPy for 2,2'-dipyridyl disulfide.

ferric chloride followed by treatment with lithium diphenylphosphide to afford PR (1). Phosphorus content, determined by elemental analysis, was generally 2.6-2.9 mmol/g in the resin-substituted triphenylphosphine (1).

The following is a general procedure for the preparation of dipeptides. A solution of Z-Valine (2 mmol) and PySSPy (3 mmol) in 20 ml of methylene dichloride was added to a suspension of ethyl glycinate hydrochloride (2 mmol), triethylamine (2 mmol) and PR (1) (4 mmol) in 10 ml of methylene dichloride and the mixture was heated to reflux for 24 hours. Polymer beads were filtered and thoroughly washed with methylene dichloride and ethanol. The filtrate combined with the washings was evaporated to afford a pale yellow solid which was dissolved in methylene dichloride. The solution obtained was washed successively with dil. hydrochloric acid, aqueous sodium bicarbonate solution, and water, then dried. After evaporation of the solvent, the residue was treated with Norit and recrystallized from a mixture of n-hexane and acetone to give needles, mp 162-164°C, in 83.7% yield.

The Table lists the results of several reaction conditions. The best result was obtained when two equivalents of PR (1) and 1.5 equivalents of PySSPy to each amino acid were used. Use of two equivalents of each PR (1) and PySSPy to amino acid did not improve the yield of dipeptide (3a). For comparison, the dipeptide (3a) also was prepared by the recently reported procedure of Appel et al.[8] (PR (1)/CCl_4 in acetonitrile), in which we used methylene dichloride as the reaction solvent instead of the reported acetonitrile. The result is also included in the Table.

Reduction of PRO (2) with an excess of trichlorosilane[9] in anhydrous benzene followed by treatment with 30% aqueous sodium hydroxide afforded the regenerated PR (1), which was easily confirmed by the disappearance of the infrared P=O absorption at 1185 cm^{-1} (KBr)[10] shown in Fig. 1 and 2. This ir band provides a convenient indication of regeneration of the reagent (1) before use. The regenerated reagent (1) was again used to prepare the dipeptide (3a), showing that its activity was completely restored by the reduction as seen in the Table. The yield of 3a was better with this regenerated PR (1). The advantage of this peptide synthesis method lies in its facile removal of PRO (2).

Further investigations of this procedure concerning racemization and solvent effects are now in progress.

Table. Preparation of Dipeptides[a]

Dipeptide	Molar ratio [PR (1) / amino acid]	Molar ratio [PySSPy / amino acid]	Mp,[b] °C	Yield,[b] %
Z-Val-Gly-OEt (3a)[c]	2	1	158-159	67
	3	1	161-163	71
	2	1.5	162-164	83.7 (78.1)[d]
	2	2	163-164	82.6
	3	CCl_4[e]	162-163	76.3
	2[f]	1.5	162-164	87.6 (81.1)[d]
Z-Phe-Gly-OEt (3b)[c]	2	1	102-104	65
	2	1.5	102-104	82.7 (78.1)[d]

[a] All reactions were carried out in boiling methylene dichloride.

[b] Yields and mp indicated here are the values after one recrystallization and all melting points are uncorrected.

[c] Pure material for 3a had mp 164-165°C and $[\alpha]_D^{25.5}$ -4.9 ± 0.4 (c = 1, EtOAc) and that for 3b showed mp 105-107°C and $[\alpha]_D^{25.5}$ -17.1 ± 0.1 (c = 5, EtOH).[7]

[d] The values in parentheses are the yields for pure materials.

[e] One equivalent of CCl_4 instead of PySSPy was used.[8]

[f] The regenerated PR (1) was used (see text).

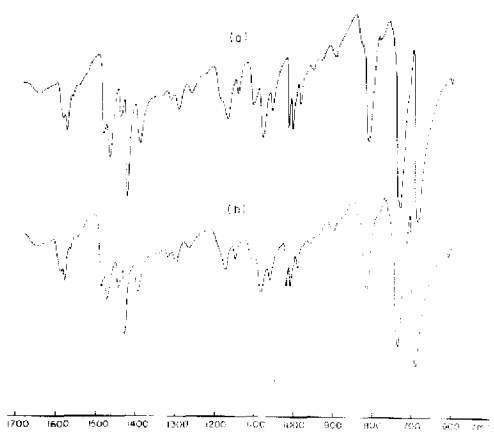

Fig. 1. a: Freshly prepared PR (1).
b: Regenerated PR (1) by reduction of PRO (2) (see text).

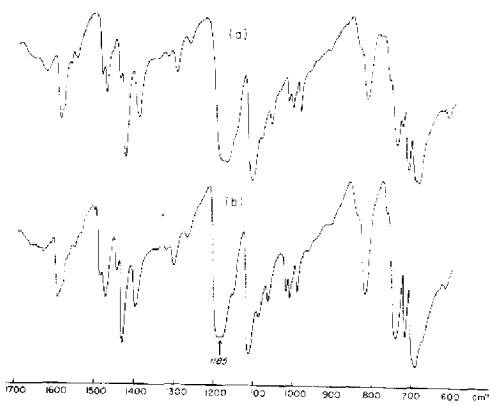

Fig. 2. a: PRO (2) prepared by oxidation of PR (1) with peracetic acid.[5]
b: The recovered PRO (2).

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