

PHOSPHINYL- AND PHOSPHINOTHIOYLAMINO ACIDS AND PEPTIDES. I.  
PREPARATION OF DIPHENYLPHOSPHINOTHIOYL(Ppt)-AMINO ACIDS

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Diphenylphosphinothioyl(Ppt)-amino acids were prepared under the Schotten-Baumann conditions by use of diphenylphosphinothioyl chloride (Ppt-Cl). Ppt group is cleaved about 4 times faster than *t*-butyloxycarbonyl group. Ppt causes no steric hindrance and no racemization.

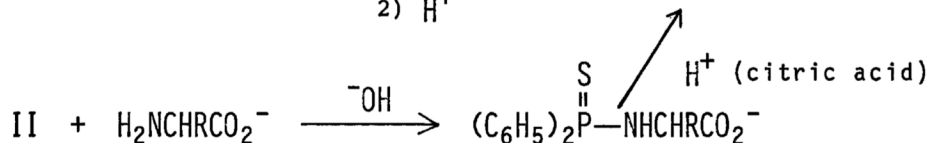
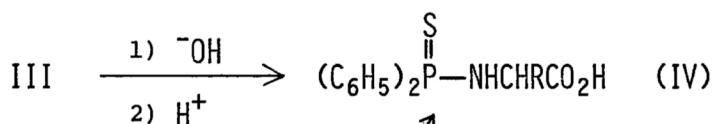
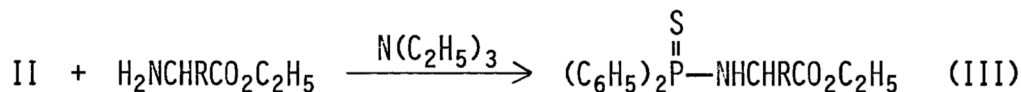
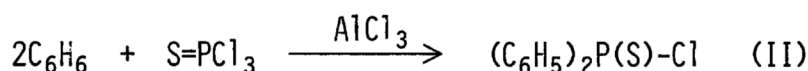
Phosphorus-nitrogen bond is well known to be acid labile, but it is quite stable in alkaline medium. Alkaline hydrolysis of N-diaryloxyphosphinylamino acid esters afforded N-dihydroxyphosphinylamino acid salts.<sup>1)</sup> But, isolation of N-dihydroxyphosphinylamino acids was not possible because of the strong acidity of the dihydroxyphosphinyl group.<sup>2)</sup> In this work it was made possible to isolate amino acid derivatives with P-N bond and free carboxyl group by substitution of the diaryloxyphosphinyl group with diarylphosphinyl- or diarylphosphinothioyl group and utility of these compounds for peptide synthesis was investigated.

When diphenylphosphinyl chloride was treated with ethyl glycinate in the presence of triethylamine, diphenylphosphinylglycine ethyl ester (I), mp 96-97°, was obtained quantitatively. Hydrolysis of I with 1N NaOH in ethanol at room temperature for 30 min and acidification with 5% citric acid solution gave diphenylphosphinylglycine, mp 129-130°, in 93% yield. By the same way diphenylphosphinothioylglycine (IV, R=H), mp 118-119°, was obtained in 75% yield from its ethyl ester (III, R=H).

Measurement of P-N bond cleavage rates of I and III in 80% acetic acid showed that the diphenylphosphinyl group was cleaved faster than the diphenylphosphinothioyl (Ppt) group. Practically Ppt derivatives are more favorable, because diphenylphosphinothioyl chloride (II) is prepared very easily from benzene and thiophosphoryl

chloride by the Friedel-Crafts reaction with use of  $\text{AlCl}_3$  as catalyst.<sup>3)</sup> II can be stored without any decomposition for long time at room temperature. It is also noted that this chloride is almost stable under the strongly alkaline condition used for the Schotten-Baumann reaction.<sup>4)</sup> Then, direct synthesis of Ppt-amino acids starting from free amino acids was tried.

To a solution of glycine (10 mmol) in 2N NaOH were added II (10.5 mmol) and dioxane (10 ml), and the mixture was stirred vigorously. During the reaction pH of the solution was kept at the value given by Schnabel<sup>5)</sup> by the addition of 2N NaOH. To the end of the reaction pH was raised to about 12, dioxane was removed *in vacuo*, and the excess II was extracted with ether. Then, the aqueous layer was acidified to pH 5.5 by 5% citric acid solution and extracted with ether. Acidification of the aqueous layer and extraction were repeated twice. Combined ethereal extracts were washed with saturated NaCl solution, dried with anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated. Addition of dicyclohexylamine (DCHA) gave Ppt-glycine DCHA salt in 94% yield. By the similar way Ppt derivatives of various amino acids were prepared in yields between 65 and 94%. Some properties of the Ppt-amino acids synthesized were summarized in Table 1.



Comparison of cleavage rates between Ppt and *t*-butyloxycarbonyl (Boc) groups was made by using glycine ethyl ester derivatives. Each protected glycine ester was dissolved in 2N HCl/tetrahydrofuran-water (9:1).<sup>6)</sup> Aliquot of the solution was taken and treated with propylene oxide to scavenge the excess HCl. Then, chloride ion of ethyl glycinate hydrochloride produced was determined by titration with 0.1N  $\text{AgNO}_3$  solution. Results are summarized in Table 2. It should be noted that Ppt group was cleaved about 4 times faster than Boc group.

From the structural point of view phosphinothioyl groups are very bulky and have electron-withdrawing effect. Bulky trityl group causes steric hindrance<sup>7)</sup> and tosyl-

Table 1. Diphenylphosphinothioyl (Ppt) Derivatives of Amino Acids

Ppt-derivatives of	mp, °C	$[\alpha]_D$ , degree	$R_f(A)^*$	$R_f(B)^*$
Glycine	118-119		0.53	0.87
<u>L</u> -Alanine DCHA salt	177-178	- 3.7 (cl, EtOH)	0.55	0.87
<u>L</u> -Leucine DCHA salt	137-138	-15.0 (cl, EtOH)	0.52	0.91
<u>L</u> -Valine DCHA salt	149-151	-10.0 (cl, EtOH)	0.53	0.93
<u>L</u> -Phenylalanine DCHA salt	190-191	+ 8.7 (cl, EtOH)	0.54	0.89
<u>L</u> -Proline DCHA salt	194-195	-40.0 (cl, EtOH)	0.52	0.90
<u>L</u> -Methionine DCHA salt	145-146	- 1.2 (cl, MeOH)	0.52	0.88
S-Benzyl- <u>L</u> -cysteine DCHA salt	170-171	+22.5 (cl, MeOH)	0.52	0.92
<u>L</u> -Asparagine	163-164	- 5.0 (cl, MeOH)	0.31	0.76
<u>L</u> -Glutamine DCHA salt	172-174	+ 8.7 (cl, EtOH)	0.31	0.77

\*) TLC by Kieselgel 60 F 254. Solvent system: A; chloroform:methanol:acetic acid =95:5:3. B; n-butanol:acetic acid:water=4:1:1.

Table 2. Removal of Protecting Groups by 2N HCl/THF-H<sub>2</sub>O(9:1)

Time (min)	5	10	30	60	120	240	$k \times 10^{-3} \text{ (min}^{-1}\text{)}$
Ppt-Gly-OEt	22	36	67	85	95	(%)	38.0
Boc-Gly-OEt		7	20	42	65	86	8.8

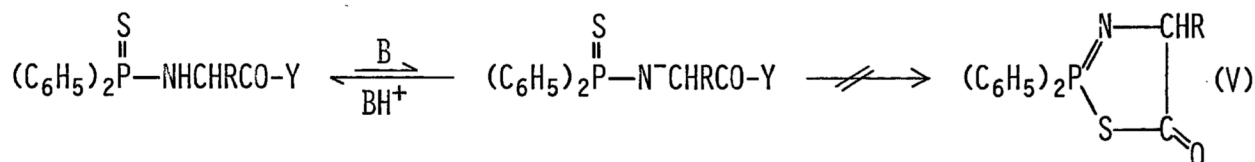
amino acids are reported to yield peptides in low yields by the mixed anhydride method.<sup>8)</sup> Acetyl- and benzoylamino acids are prone to racemize. In order to check the reactivity and tendency of racemization of the Ppt-amino acids peptide synthesis by use of Ppt-amino acids was tried. Ppt-amino acids could be coupled by DCC, mixed anhydride and oxidation-reduction condensation methods without any problem as shown in Table 3. NMR spectrum of Ppt-L-Val-L-Val-OMe obtained showed only one ester methyl proton signal ( $\delta_{TMS}$  3.68ppm(CDCl<sub>3</sub>)), while two signals ( $\delta_{TMS}$  3.63 and 3.68ppm) were observed in the case of Ppt-DL-Val-L-Val-OMe. These data are consistent with the result reported by Davies, et al. for the benzoyl derivatives.<sup>9)</sup> From these results it can be said that Ppt protecting group causes no steric hindrance and no racemization. These facts would be explained by the relatively weak electron-withdrawing effect of diphenylphosphinothioyl group<sup>10)</sup> and unstability of the cyclic structure (V) corresponding to the oxazolone.

Table 3. Peptide Synthesis by Use of Ppt-amino Acids

Ppt-peptides	Method	Solvent	Yield, %	$[\alpha]_D$ , deg.	mp, °C
Ppt-Gly-Gly-OEt	DCC	CH <sub>2</sub> Cl <sub>2</sub>	86		98.5 -99.5
Ppt- <u>L</u> -Ala-Gly-OEt	DCC	CH <sub>2</sub> Cl <sub>2</sub>	86	-37.5 (c2, EtOH)	94.0 -95.0
Ppt- <u>L</u> -Leu-Gly-OEt	DCC	CH <sub>2</sub> Cl <sub>2</sub>	85	-40.0 (c2, EtOH)	110.0-111.0
Ppt- <u>L</u> -Pro- <u>L</u> -Val-OMe	DCC	CH <sub>2</sub> Cl <sub>2</sub>	91	-70.3 (c2.4, EtOH)	oil
Ppt- <u>L</u> -Val- <u>L</u> -Phe-OBzl	Ph <sub>3</sub> P + (2-PyS) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	86	-40.0 (c1, EtOH)	119.5-120.5
Ppt- <u>L</u> -Val- <u>L</u> -Val-OMe	mixed anhydride	THF	90	-50.0 (c1, MeOH)	132.0-133.0
Z- <u>L</u> -Pro- <u>L</u> -Leu-Gly-OEt*	DCC	CHCl <sub>3</sub>	72	-77.8 (c2.3, EtOH)	148.0-149.0
			[lit. <sup>11)</sup>	-79.8 (c2.5, EtOH)	148-149]

Abbreviations: DCC=dicyclohexylcarbodiimide, (2-PyS)<sub>2</sub>=2,2'-dithiodipyridine.

\*) HCl-L-Leu-Gly-OEt was obtained from Ppt-L-Leu-Gly-OEt by treating with 4N HCl/dioxane and neutralized with triethylamine.



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#### References

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