NEW METHOD OF SYNTHESIZING N-ALKOXYCARBON-

YLALKYLPHOSPHORAMIDITES

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The transamidation reaction is well known as a method of synthesizing amides of acids of trivalent phosphorus [1-4]. It appeared to us to be of interest to use transamidation for the synthesis of esters of amino acids having a phosphorus grouping with a trivalent phosphorus atom attached to the nitrogen atom [5,6]. The presence of such a phosphorus grouping in the molecule makes it possible to carry out a number of reactions for the synthesis of new types of amino acid esters substituted on the nitrogen. These reactions include the Arbuzov and Perkow rearrangements, oxidation, the addition of sulfur, tranesterification, etc.

In accordance with what has been said, amino acid esters react with N-dialkylphosphoramidites in accordance with the equation

(RO)₂PNR₂' + H₂NCH₂COOR" \rightarrow (RO)₂PNHCH₂COOR" + NHR₂'

with a yield of 60-80% of theoretical. The compounds obtained undergo the Arbuzov rearrangement with the formation of N-phosphinylsubstituted amino acid esters. The N-alkoxycarbonylalkylphosphoramidites readily add sulfur giving the corresponding phosphorothioates with good yields. The study of the other reactions of the N-alkoxycarbonylalkylphosphoramidites is continuing.

EXPERIMENTAL

<u>Transamidation of Dialkyl N-Dialkylphosphoramidites</u>. <u>Diethyl N-Ethoxycarbonyl-methylphosphoramidite</u>. An Arbuzov flask was charged with 46 g of diethyl N-diethylphosphoramidite and 24.5 g of glycine ethyl ester. The reaction mixture was slowly heated to 140°C, and 17.2 g of diethylamine was evolved (theoretical amount 24.8 ml). The reaction product was twice distilled in vacuum from an Arbuzov flask. This gave 36.8 g of pure diethyl N-ethoxycarbonylmethylphosphoramidite, yield 69.3%, b.p. 69-71° (0.1 mm); n_D^{20} 1.4439; d_4^{20} 1.0571. Found %: C 43.03; H 8.26; P 13.86; N 6.19. MR 56.02. $C_8H_{18}O_4PN$. Calculated %: C 43.04; H 8.07; P 13.9; N 6.27. MR 56.06. Literature [5]: b.p. 85-86° (2 mm); n_D^{20} 1.4442; d_4^{20} 1.0575.

The following compounds were obtained similarly:

 $\begin{array}{c} \underline{\text{Dipropyl N-Ethoxycarbonylmethylphosphoramidite;}}_{1.4467;\ d_{4}^{20}\ 1.0264.\ Found\ \%:\ C\ 46.68;\ H\ 8.75;\ P\ 12.14;\ N\ 5.35.\ MR\ 65.30.\ C_{10}H_{22}O_{4}PN.\ Calculated\ \%:\ C\ 47.8;\ H\ 8.7;\ P\ 12.3;\ N\ 5.5.\ MR\ 65.29. \end{array}$

<u>Diisopropyl N-Ethoxycarbonylmethylphosphoramidite</u>; yield 71.4%; b.p. 70.5-71° (1 mm); n_D^{20} 1.4390; d_4^{20} 1.007. Found %: P 12.28; N 5.50. MR 65.56. $C_{10}H_{22}O_4PN$. Calculated %: P 12.28; N 5.57. MR 65.294.

 $\frac{\text{Dibutyl N-Ethoxycarbonylmethylphosphoramidite; yield 77.7\%; b.p. 98-101° (1 mm);}{n_D^{20} 1.4468; d_4^{20} 1.0074. Found \%: P 11.1. MR 73.97. C_{12}H_{26}O_4PN. Calculated \%: P 11.25. MR 74.521.}$

<u>Diisopropyl N-Isopropoxycarbonylmethylphosphoramidite;</u> yield 59.3%; b.p. 80.5-81° (1 mm); n_D^{20} 1.4379; d_4^{20} 0.9893. Found %: P 11.22; N 5.32. MR 70.3. $C_{11}H_{24}O_4PN$. Calculated %: P 11.6; N 5.2. MR 69.912.

 $\frac{\text{Dibutyl N-(4-Ethoxycarbonylmethylphenyl)phosphoramidite; b.p. 175-177° (1 mm).}{\text{Found \%: C 60.36; H 8.37; P 8.57; N 4.16. C_{18}H_{30}O_4PN. Calculated \%: C 60.84; H 8.29; P 8.57; N 3.94.}$

A. E. Arbuzov Institute of Organic and Physical Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 4, pp. 939-940, April, 1967. Original article submitted October 21, 1966. Is omerization of Diethyl Ethoxycarbonylmethylphosphoramidite. A mixture of 11.8 g of diethyl N-ethoxycarbonylmethylphosphoramidite and 5.3 g of ethyl iodide was placed in a glass tube filled with argon. The tube was sealed and heated at 70°C for 10 h. When there was no further diminution in volume, the tube was opened and the light yellow liquid was subjected to molecular distillation and then to vacuum distillation from an Arbuzov flask. This gave ethyl N- (ethoxycarbonylmethyl)ethylphosphonamidate, b.p. 127° ($1 \cdot 10^{-3}$ mm). The pure product crystallized; m.p. 45-47°; yield 69%. Found %: P 13.56; N 6.28. C₈H₁₈O₄PN. Calculated %: P 13.9; N 6.27.

<u>Diethyl N-ethoxycarbonylmethylphosphorothioamidate</u>. Five grams of diethyl Nethoxycarbonylmethylphosphoramidite was mixed with 0.71 g of sulfur. The temperature rose to 60° and the sulfur dissolved completely. The resulting product was distilled in vacuum. This gave diethyl Nethoxycarbonylmethylphosphorothioamidate, b.p. 126-127° (1 mm); n_D^{20} 1.4711; d_4^{20} 1.1474. Found %: C37.87; H 7.08. P 11.92; N 5.42. $C_8H_{18}O_4PN$. Calculated %: C 37.64; H 7.62; P 12.15; N 5.49.

CONCLUSIONS

1. The reaction of dialkyl N-dialkylphosphoramidites with alkyl esters of α -amino acids leads to their transamidation.

2. The transamidation products undergo an isomerization reaction with alkyl halides.

3. The transamidation products add sulfur to the trivalent phosphorus.

LITERATURE CITED

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