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THE REACTION OF HEXAMETHYL PHOSPHORIC TRIAMIDE (HMPT) WITH PHOSPHORYL CHLORIDE : A REEXAMINATION. APPLICATION TO A NOVEL PREPARATION OF BOP REAGENT FOR PEPTIDE COUPLING

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Summary : The reaction of hexamethyl phosphoric triamide with phosphoryl chloride at R.T. gave actually a chlorophosphonium salt. This reaction is illustrated in a novel preparation of BOP reagent for peptide coupling in good conditions.

The preparation of our BOP reagent for peptide coupling that we had previously described[1] involves in its first step the reaction of HMPT with phosgene, according to the following scheme :

$$Y_3PO + COCl_2 \longrightarrow \underset{\underline{1}}{Y_3\overset{+}{P}Cl,\ Cl^-} + CO_2 \xrightarrow{BO^-,\ \overset{+}{H}NEt_3} BOPY_3^+,\ Cl^- + HNEt_3^+,\ Cl^-$$

$$Y = N(CH_3)_2 \qquad B = \text{N-benzotriazolyl} \qquad \xrightarrow[H_2O]{KPF_6} BOPY_3^+,\ PF_6^- \ (BOP)$$

The use of phosgene may in some cases constitute a drawback for this preparation. Hence, we were looking for a more convenient access to chlorophosphonium salts 1.

In a related study, we needed a ^{31}P NMR reference sample of $(Me_2N)_2P(O)Cl$; as this compound was not in our collection, we decided to produce it in the NMR tube by the well-known reaction of redistribution between HMPT and $POCl_3$[2] :

$$2\ Y_3PO + Cl_3PO \longrightarrow \underset{\underline{2}}{3\ Y_2P(O)Cl}$$

We actually observed at R.T. that no peak appeared in the expected region for 2 (+30 ppm)[3], but two equivalent peaks developed on the spectrum ; the first one at +53 ppm corresponding to the chlorophosphonium cation $Y_3\overset{+}{P}Cl$; the second one at +10.5 ppm revealed to be the dichlorophosphate anion $Cl_2PO_2^-$, identical to the anion of the Vilsmeier complex formed in the reaction of DMF and $POCl_3$[4].

A minor complex could be detected in some solvents (CH_2Cl_2 -20°, CH_3CN 0°), that decreased gradually as the first two peaks increased ; this complex appeared as two doublets (-17.8 ppm and +25.5 ppm, J_{P-O-P} = 27 Hz)[7] indicating a two phosphorus system to which we assign formula 3. The formation of an intermediate complex had been observed previously[5] to

which no developed formula was assigned. The covalent chloride 2 appeared only after heating.

Hence the reaction of HMPT on $POCl_3$ may be detailed as follows :

$$Y_3P{=}O + Cl_3PO \longrightarrow Cl^-,\ \underset{3}{Y_3\overset{+}{P}\text{-}O\text{-}P(O)Cl_2} \rightleftharpoons \underset{4}{ClPY_3^+},\ Cl_2PO_2^- \xrightarrow{\Delta} 2$$

We did not try to make clear the mechanism of formation of 2 from 3 or 4.

In a preparative scale, we performed the reaction in CH_2Cl_2 as solvent, adding slowly HMPA on $POCl_3$ at $\theta < 20°C$. The reaction is fast. The addition of a solution of anhydrous HCl in ether induced the precipitation of salt 1

$$Y_3\overset{+}{P}Cl,\ Cl_2PO_2^- + HCl \longrightarrow \underset{1}{Y_3\overset{+}{P}Cl},\ Cl^- + HOP(O)Cl_2$$

whereas the chlorophosphoric acid could be washed out with ether.

Addition of water solution of KPF_6 or $KClO_4$ to salt 1 gave the chlorophosphonium hexafluorophosphate or perchlorate[6], in almost quantitative yield.

Hence we got the reaction we looked for the preparation of BOP : one molar equivalent of triethylamine was added to the complex 4 followed by gradual introduction of anhydrous hydroxybenzotriazole (dried by azeotropic distillation with benzene) as a triethylammonium salt in CH_2Cl_2. The $O_2PCl_2^-$ anion does not interfere in this reaction. Just after the addition the reaction mixture was poured into iced water buffered with 1.5 molar equivalent of triethylamine. The organic layer was twice extracted with water, and the aqueous extracts were washed with ether. Then one molar equivalent of KPF_6 solution in water was added inducing the precipitation of the crude BOP (80 %) which could be recristallysed from acetone-ether (M.P. : 145-147°C).

References and notes

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7) ^{31}P NMR spectra were obtained at 36.4 MHz (BRUKER 90 Apparatus with F.T.). Chemical shifts upfield from external H_3PO_4 (10 % in $(CD_3)_2CO$) are quoted as negative.

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