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BIS(2,4,6-TRIHALOPHENOXY)TRICHLOROPHOSPHORANES: NOVEL CONDENSING REAGENTS FOR INTERNUCLEOTIDIC PHOSPHOTRIESTER BOND FORMATION VIA ACTIVE PHOSPHOROCHLORIDATE INTERMEDIATES

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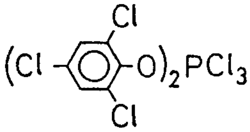
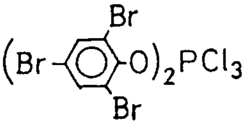
Abstract—New types of reagents, bis(2,4,6-trihalophenoxy)trichlorophosphoranes, were very effective as condensing agents for internucleotidic bond formation in the phosphotriester method. The ^{31}P NMR study showed that the condensation proceeded via phosphorochloridate intermediates.

It has been proved by means of ^{31}P NMR that the condensation using arenesulfonyl chlorides or azolides in the phosphotriester approach proceeded via symmetrical pyrophosphate or/and phosphorazole intermediates.$^{1)}$ In the previous paper,$^{2)}$ we reported a method for the synthesis of oligodeoxyribonucleotides using sterically hindered diaryl phosphorochloridates such as bis(2,4,6-tribromophenyl) phosphorochloridate (TBP). A plausible intermediate in this reaction was suggested to be an unsymmetrical pyrophosphate derivative which was produced from a phosphodiester and TBP.$^{3)}$ In this paper, we wish to report novel condensing reagents, bis(2,4,6-trihalophenoxy)trichlorophosphoranes, which were capable of rapid internucleotidic bond formation via reactive species of phosphorochloridate intermediates.$^{4)}$

Bis(2,4,6-tribromophenoxy)trichlorophosphorane (BTCP)$^{5)}$ is known to be a synthetic precursor of TBP. BTCP is readily obtained by the reaction of phosphorus pentachloride with 2 equiv of 2,4,6-tribromophenol. Since the phosphorane-type reagent might have a potential condensing ability, we investigated the condensation using sterically hindered phosphoranes as condensing reagents in our phosphorothioate approach.$^{6)}$ In this study, bis(2,4,6-trichlorophenoxy)trichlorophosphorane (CTCP) was also synthesized$^{7)}$ and its condensing ability was tested.


CTCP


BTCP

The condensation of triethylammonium S-phenyl 5'-O-(4,4'-dimethoxytrityl)-3-N-benzoylthymidine 3'-phosphorothioate (1) with 3'-O,3-N-dibenzoylthymidine (2) was performed by treatment with a small excess amount of CTCP or BTCP in the presence of 3-nitro-1,2,4-triazole (NT)[8)] (Table 1). When CTCP was employed, the reaction was completed in 5 min and the desired dimer (3) was obtained in 87% yield after silica gel column chromatography. TLC showed that a certain amount of 5'-O-bis(2,4,6-trichlorophenyl)phosphorylthymidine derivative was formed. In the case of BTCP having a more hindered substituent, the side reaction was prevented more effectively and the condensation required 8 min for completion. Thus, the dimer 3 was obtained in 93% yield. These reactions were very rapid compared with those using arenesulfonyl chlorides or diarylphosphoryl chlorides which produced initially pyrophosphate intermediates from phosphodiester components.

From these results, a new type of intermediate was expected in the present phosphorane-mediated condensation. Therefore, we studied the spectroscopic analysis of the present reaction by means of ^{31}P NMR. The phosphodiester 1 and CTCP gave resonance peaks at -11.24 and 55.63 ppm, respectively (Fig. 1). When 1 was mixed with 1.1 equiv of CTCP in pyridine, the two peaks of 1 and CTCP disappeared and several new peaks were observed. The strong peak at 7.31 ppm was assigned to bis(2,4,6-trichlorophenyl) phosphorochloridate (TCP). The minor triplet peaks at -13.93, -13.35, and -12.57 ppm were derived from the symmetrical pyrophosphate formed from bimolecules of 1. The major doublet at -30.00 and -29.85 ppm was determined as the phosphorochloridothioate (4) because CTCP could be regarded as a potential chlorinating agent of phosphates like phosphorus pentachloride and the chlorination gave a pair of diasteromers due to the new chiral center on the phosphorus atom. This conclusion was also supported by the fact that a similar reaction of 1 with BTCP gave the same

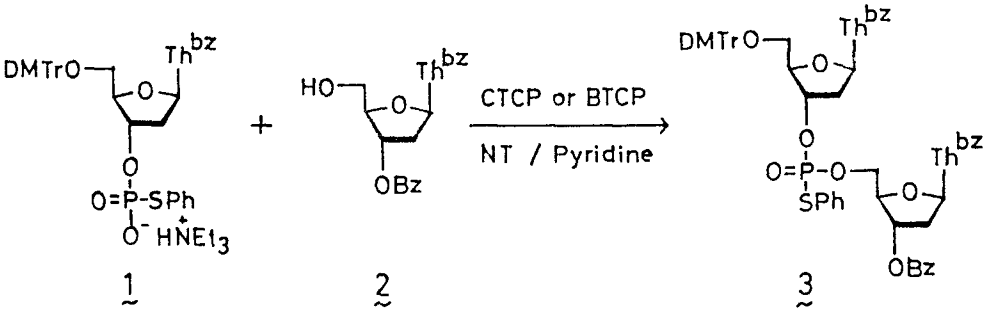


Table 1. The results of the coupling reactions using CTCP and BTCP

1/2	CTCP	BTCP	NT	time (min)[a]	yield of 3 (%)
1.2	1.2	-	1.3	10	87
1.2	-	1.3	3.9	12	93

[a] Times when the reactions were quenched. These condensations were completed within shorter times as described in the text.

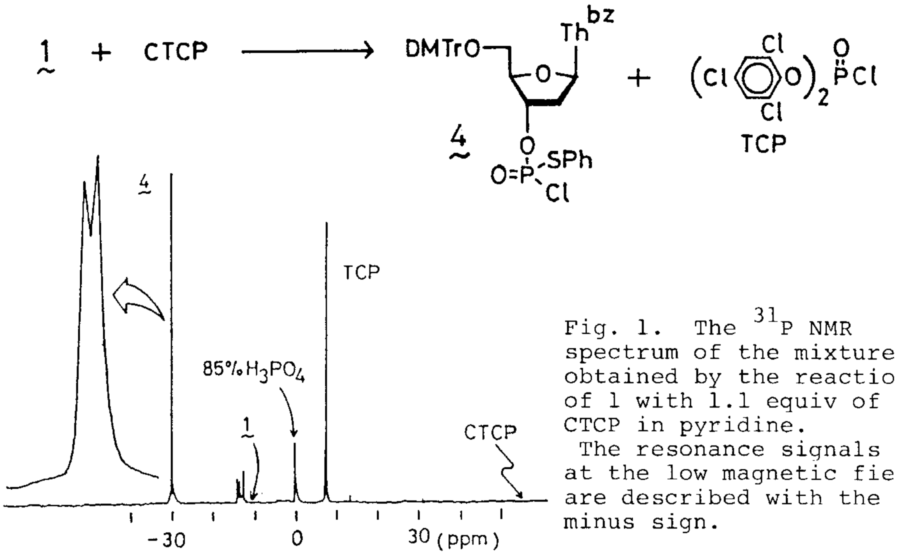


Fig. 1. The ^{31}P NMR spectrum of the mixture obtained by the reaction of 1 with 1.1 equiv of CTCP in pyridine. The resonance signals at the low magnetic field are described with the minus sign.

diastereomeric peaks of 4. This new active species could react directly or via a phosphoronitrotriazole intermediate with the hydroxyl component to give the fully protected dimer 3.

Quite recently, Garegg et al.[9)] reported that a similar type of intermediate existed as one of the minor components in the equilibrium mixture obtained by reaction of a phosphodiester with an arenesulfonyl chloride. It is of great interest that the phosphodiester component could be converted irreversibly and stoichiometrically by the phosphorane reagent to the highly reactive phosphorochloridate intermediate.

A preliminary study showed that other phosphodiester components such as triethylammonium 2-chlorophenyl deoxyribonucleoside 3'-phosphates appropriately protected could be also converted to the corresponding phosphorochloridate intermediates. The synthetic utility of this intermediate has recently been demonstrated by us in the first successful synthesis of phosphorothioates of the triester-type from phosphodiesters and thiols.[10)] The phosphorane reagents described in this paper would be useful not only in nucleotide chemistry but also in general organic synthesis.

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7) Anschütz reported that bis(2,4,6-trichlorophenyl) phosphorochloridate (TCP) (lit. m.p. 126-129 °C) was directly obtained by the reaction of phosphorus pentachloride with 3 equiv of 2,4,6-trichlorophenol. (R. Anschütz, Ann. 454, 106 (1927)). It was, however, found by our detailed study that this reaction gave CTCP in place of TCP as in the case of the synthesis of BTCP.4) Therefore, the reagent which we described as TCP in the previous paper2) was now found to be contaminated with a considerable amount of CTCP. This finding led us to study the condensation using the phosphorane-type reagent. CTCP: m.p. 122 °C (benzene-hexane, 2:1, v/v); ^{31}P NMR (pyridine) 55.63 ppm. Anal. Calcd for $C_{12}H_4O_2Cl_9P$: C, 27.19; H, 0.76; Cl, 60.18. Found: C, 27.36; H, 0.70; Cl, 59.99.

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