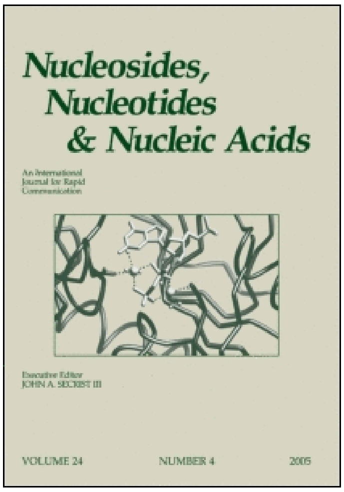

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AN IMPROVED METHOD FOR THE PREPARATION OF METHYL DICHLOROPHOSPHITE. A KEY REAGENT IN THE PHOSPHITE METHOD OF OLIGONUCLEOTIDE SYNTHESIS

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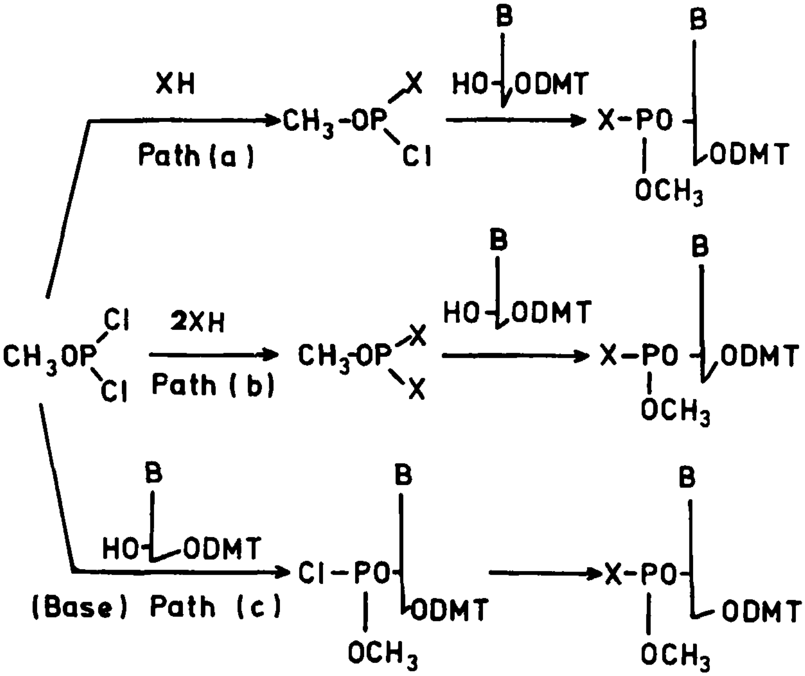
Abstract

The reaction between phosphorus trichloride (PCl_3) and trimethyl phosphite $(CH_3O)_3P$, has been examined by ^{31}Pnmr, in order to achieve a simple and efficient procedure for the formation of methyl dichlorophosphite (CH_3OPCl_2), which is a key intermediate in the synthesis of oligonucleotides. The yield of the reaction was also studied on a preparative scale and it was found that the optimal condition is obtained when the reactants molar ratio is 1:1.

Introduction

Methyl dichlorophosphite is one of the key reagents in the phosphite triester approach to the synthesis of oligodeoxyribonucleotides, introduced by Letsinger(1).



X = Nitroimidazolide (Path c), tetrazolide (Path c and b), dimethylamino (Path a), morpholino (Path a), diisopropylamino (Path a), pyrrolidino (Path a and b)(7).

This phosphitylating agent is currently utilized for various preparations of fully protected deoxynucleosidephosphoramidite intermediates which are essential for the solid-phase oligonucleotide synthesis(2-6).

According to general procedures(8) the synthesis of methyl dicholorophosphite is accomplished by adding methanol to PCl_3 in 1:1 molar ratio at temperature between -10 to -20°C. One of the disadvantages of this method is the formation of HCl which may decrease the yield of the anticipated product via Michaelis-Arbuzov rearrangement (demethylation)(9).

Therefore, a crucial factor in the aforementioned synthesis is the removal of HCl. This is achieved by purging continuously the reaction mixture with a slow stream of nitrogen or argon for a long period of time followed by vacuum. Practically the yields of the product varied between 50% to 20%. In order to simplify the procedure and to increase the yield, we adopted a totally different protocol for the synthesis of CH_3OPCl_2.

Results and discussion

The exchange reaction between triphenylphosphite and PCl_3, tributylphosphite and PCl_3, or 2-trichlorobenzodioxaphosphorane and diethylphosphorochloridite has been described previously in the literature(10). Extension of this reaction to trimethylphosphite indeed leads to the required product:

$$(CH_3O)_3P + 2PCl_3 \longrightarrow 3CH_3OPCl_2$$

From Table 1 it is inferred that although the required stoichiometric ratio of reactants is: PCl_3 (A)/$(CH_3O)_3P$(D)=2:1, an excess of phosphorustrichloride (A) does not bring the reaction to completion. When the reactants ratio A/D was 1.1:1, the desired product B was 57% (Experiment 2). However, when the ratio A/D was 2:1 and 3:1 the yield of B was only 45% and 33% respectively (Experiments 3 and 4).

It is worthy of note that the yield of the reactions conducted at 55°C was inferior to that conducted at 26°C. Although at 55°C a significant increase in the relative ratio of B was observed, a side reaction (yellow precipitation) affected the yield of B. The total amount of A+B+C in experiments 2,3 and 4 at 55°C has been decreased to 29%, 53% and 39% of the theoretical value, respectively.

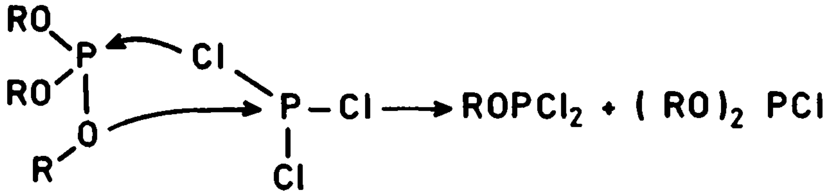
Relative ratio (in%) of reactants and products as a function of time in the reaction of PCl_3 + $(CH_3O)_3P$; Temp=26°C

PCl_3 (A); CH_3O-PCl_2 (B); $(CH_3O)_2-PCl$ (C); $(CH_3O)_3-P$ (D)

	No 1				No 2				No 3				No 4			
time min	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
0	33			66	52			48	66			33	75			25
20		27	46	27	8	40	52		40	21	39		55	15	30	
40		22	56	22	8	40	52									
60		19	63	18	8	40	52		40	21	39		55	15	30	
80		16	70	14	8	41	51									
120		14	74	12	7	43	50		40	21	39		55	15	30	
160		13	76	11	7	43	50									
240		10	82	8					36	29	35		55	15	30	
1200		10	82	8	0	57	43		28	45	27		50	25(a)	25(a)	

All compounds in the reaction mixture were characterized by ^{31}P NMR using H_3PO_4 as an external standard. The chemical shift of A, B, C and D are: 220, 181, 169 and 142 ppm respectively.

[a] The Percentage of B and C calculated from the maximal anticipated amount of B is 33%.



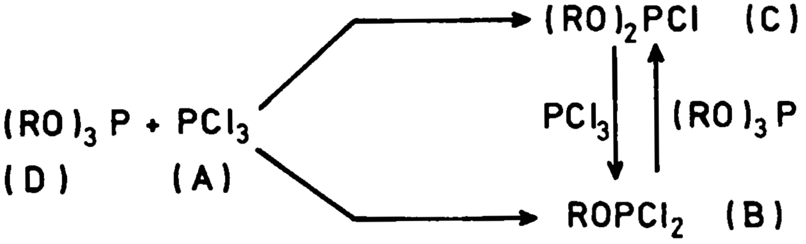
SCHEME 1

The yield of compound B was also tested on a preparative scale at three reactants ratios A|D=2:1, 1:1 and 1:2 according to the following procedure. To three round bottom flasks were added 0.5 mole of trimethylphosphite (D) and 1, 0.5 and 0.25 moles, respectively, of phosphorus trichloride (A). The solutions were stirred at room temperature and kept under nitrogen for 20-24h, then distilled under normal pressure using a Vigreux column (10cmx1cm I.D.). The fraction in the boiling range of 90-97°C was redistilled and the product B was collected at 93°C-95°C. The purity of B was established by ^{31}P and ^{13}C nmr (δ ^{13}C for B and D are 53.4 and 49 ppm). For the reactants ratio (A/D) 2:1, 1:1 and 1:2, the yield of B after the second distillation was 40%, 55% and 12%, respectively. Thus, it seems likely that the best conditions for the synthesis of compound B in substantial yield are those of experiment 2 at 26°C.

The exchange reaction between trialkylphosphite and PCl_3 is assumed to proceed via a four center mechanism.

$(RO)_2PCl$ and $ROPCl_2$ may react further with $(RO)_3P$ and PCl_3 as is depicted in Scheme 2.

Table 1 implies that the pathway B —> C in scheme 2 is favored over that of C —> B. This is inferred from the following: (a) an excess of PCl_3 does not increase the yield of B (experiments 3 and 4); (b) in experiments



SCHEME 2

2,3, and 4 where the ratio A|D is 1:1, 2:1 and 3:1 the percentage of C is greater than B, at least for the first 160-240 min.

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