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A CONVENIENT METHOD FOR THE SYNTHESIS OF DEOXYRIBONUCLEOSIDE 3'-HYDROGENPHOSPHONATES

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Summary: Appropriately protected 5'-O-dimethoxytrityldeoxyribonucleoside derivatives were converted to the corresponding 3'-hydrogenphosphonates by treatment with phosphinic acid in the presence of mesitylenedisulfonyl chloride via an oxidative phosphonylation process.

Much attention has recently been devoted to the hydrogenphosphonate approach reported by Garegg[1] and Froehler[2] as a promising method for rapid internucleotidic bond formation.[3] Deoxyribonucleoside 3'-hydrogenphosphonates (2) required for this approach have been synthesized by condensation of 3'-unprotected deoxyribonucleoside derivatives (1) with phosphonic acid in the presence of condensing agents[4] or by introduction of phosphitylating agents to the 3'-hydroxyl group of 1 followed by partial hydrolysis.[1,2b,5] In this paper, we wish to report a new method for the synthesis of 2 via a new type of oxidative phosphonylation.

In an attempt to improve our original method[4c] for the synthesis of 2 involving condensation between 1 and phosphonic acid, several experiments were conducted with condensing agents such as acyl chlorides and arenedisulfonyl chlorides in place of 2,4,6-triisopropylbenzenesulfonyl chloride (TPS)[6] which was previously employed for the 3'-phosphonylation[4b,c]. First, pivaloyl chloride (PVC) was examined as the condensing agent since 2 was known to be activated easily by this reagent.[2] When a mixture of 1a (1 mmol) and phosphonic acid (3 mmol) in pyridine (10 ml) was allowed to react with PVC (6 mmol), 1a disappeared within 1 min and two products were formed in a 3:2 ratio. The major product was determined to be the desired product 2a and the minor a dinucleoside hydrogen phosphonate (3a). A lot of attempts were made to obtain 2a more predominantly over 3a under a variety of conditions. In all cases, however, 3a was formed in more than 30% yield. Under these conditions, 1a was coupled competitively with both phosphonic acid and 2a. A similar result was obtained when diphenyl phosphorochloridate[7] was employed. During this study, we have also encountered an extreme example as far as formation of 3a was concerned. As one of possible phosphitylating agents to obtain 2a, tribenzoyl phosphite (4a)[8] was chosen. When a solution of 2a in pyridine was added to a vigorously stirred solution of 1 equiv of 4a in pyridine, the reaction was completed within 1 min to give surprisingly a 1:10 mixture of 2a and 3a.

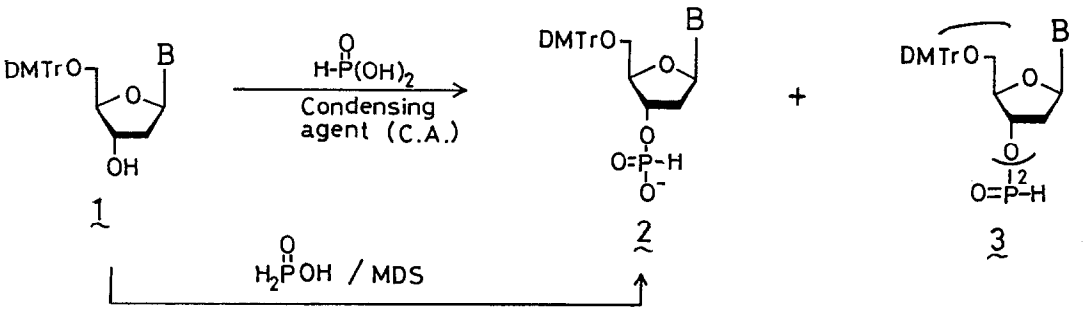
Compound 3a was rapidly converted to a phosphorothioate derivative (5) by addition of 1.2 equiv of elemental sulfur. After removal of the DMTr group, an unprotected 3'-3' linked dithymidine phosphorothioate (6) was obtained in 80% overall yield. A similar result was obtained even when a more hindered acylphosphite (4b) was employed. In our previous paper,[4c] it was reported that 2i can be obtained in 90% yield by reaction of 1i with 4 equiv of phosphonic acid in the presence of 4 equiv of TPS in pyridine. The only problem in this method was difficult separation of 2i from the byproduct, 2,4,6-triisopropylbenzenesulfonic acid, so that paper chromatography was finally required for isolation of 2i. In order to avoid such a problem, we chose a bifunctional condensing reagent, mesitylenesulfonyl chloride (MDS),[9] which could be easily removed as a water-soluble disulfonic acid by extractive workup after hydrolysis. However, reaction of 1b with 3 equiv of phosphonic acid in the presence of 3 equiv of MDS gave a considerable amount (20%) of 3b along with 2b (80%). Now, we understood that in our previous experiment using TPS[4c] one-half of 3i formed simultaneously was converted to 2i during paper chromatography owing to its basic conditions (developing solvent: iPrOH-conc. NH_3-H_2O, 7:1:2, v/v/v) so that 1i was obtained ultimately in a high yield.

In order to overcome the formation of undesired byproduct 3b, phosphinic acid as a precursor of the phosphonate group which existed as a monobasic acid in a lower oxidation state than phosphonic acid, was allowed to react with 1b in the presence of pivaloyl chloride or MDS in pyridine. In the case of the former condensing agent, the 3'-phosphinylaton proceeded rapidly but the subsequent air-oxidaiton or iodine oxidation resulted in a complex mixture. However, the latter gave directly the 3'-phosphonate 2b as a sole nucleotidic product which was isolated in 76% yield by silica gel column chromatography. It should be noted that under these conditions not only the 3'-phosphinylation but also the oxidation proceeded without formation of the 3'-3' linked

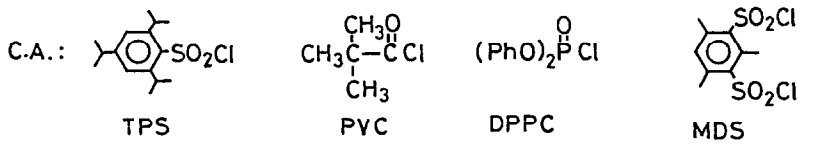
Table 1. The conditions and results of the oxidative phosphonylation of 1

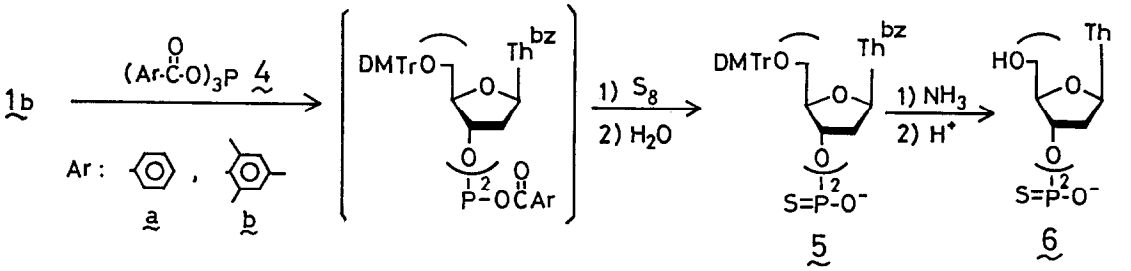
Nucleoside	H_3PO_2 equiv	MDS equiv	Time min	Yield of 2 %	^{31}P NMR($CDCl_3$-Py,2:1,v/v) ppm from 85% H_3PO_4
1a	6	3	12	79	2.88
	6	3	45	91[a]	
1b	6	3	60	96[b]	3.05
	6	3	30	76	
1c	6	3	15	67	1.94
1d	6	3	30	66	2.37
1e	6	3	15	58	3.29
1f	6	3	30	69	2.49
1g	6	3	30	98[a]	2.81
1h	6	3	30	69	1.38

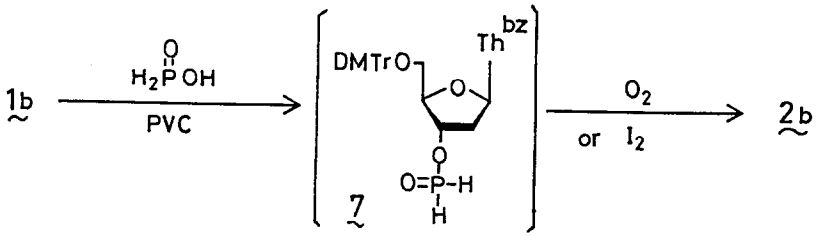
[a] The reaction was carried out in the presence of 1,2,4-triazole.
[b] This coumpound was obtained without chromatographic purification.
[c] Compounds 1d, 1f, and 1h were reported in our previous paper.[10] TBTr and bibe refer to the 4,4',4"-tris(benzoyloxy)trityl and 1,2-bis(benzoyloxy)ethylene groups, respectively.



B: Th (a), Th^bz (b), Cy^bz (c), Cy^TBTr (d), Ad^bz (e), Ad^TBTr (f), Gu^DPC·pro (g), Gu^TBTr·bibe (h), Th (The 5'OH is protected with MMTr in this case) (i)







byproduct 3b. In a similar manner, other deoxyribonucleoside 3'-phosphonates derivatives (1a,c-h) were obtained in 58-75% yields. A considerable loss of material on silica gel was observed probably because of their relatively strong polarity. In our hand, the same tendency was also observed in a 1 mmol scale

in the case of the use of salicylchlorophosphite as the phosphitylating agent reported by van Boom et al.[5b] We felt that these deoxyribonucleoside 3'-hydrogenphosphonates should be isolated by reverse-phase chromatography as suggested by van Boom.[5b] Since TLC gave essentially one spot after the oxidative phosphonylation, 2a could be obtained as relatively pure powder in 96% yield by the extractive workup followed by precipitation from its methylene chloride solution into hexane. The ^{31}P NMR of this sample was almost the same as that of 2a obtained by silica-gel column chromatography. This new type of oxidative phosphonylation took place exothermically. It is also found that, when triazole (1.2 equiv to phosphinic acid) was added to the reaction mixture to control the exothermic reaction, somewhat cleaner and moderate 3'-phosphonylation took place. In this manner, for example, compounds 2a and 2g were prepared in 91% and 96% yields, respectively, without chromatographic separation. As reported in a previous paper,[5a] the present reaction might involve an intramolecular oxygen transfer of activated mixed-anhydride species drived from the reaction of MDS with phosphinic acid or nucleoside phosphinate ester derivative (7). Mechanistic consideration will be required as the future subject.

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