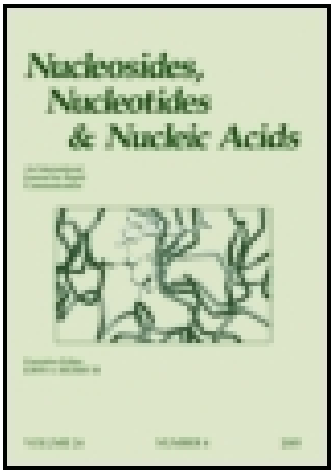

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Studies on Reactions of Nucleoside H-Phosphonates with Bifunctional Reagents. Part III. Further Studies on Transesterification of Nucleoside H-Phosphonate Diesters with Amino Alcohols

Michal Sobkowski [a] , Jacek Stawiński [b] , Anna Sobkowska [a] & Adam Kraszewski [a]

[a] Institute of Bioorganic Chemistry, Polish Academy of Sciences , Noskowskiego, 12/14, 61-704, Pozné, Poland

[b] Department of Organic Chemistry, Arrhenius Laboratory , Stockholm University , S-10691, Stockholm, Sweden

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STUDIES ON REACTIONS OF NUCLEOSIDE H-PHOSPHONATES WITH BIFUNCTIONAL REAGENTS. PART 3. FURTHER STUDIES ON TRANSESTERIFICATION OF NUCLEOSIDE H-PHOSPHONATE DIESTERS WITH AMINO ALCOHOLS

Michał Sobkowski[a], Jacek Stawiński[b], Anna Sobkowska[a] and Adam Kraszewski[a*]

[a] Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznań, Poland.

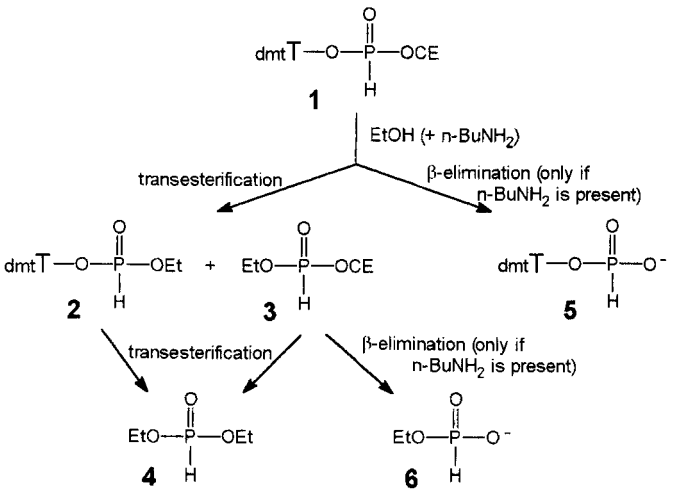
[b] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-10691 Stockholm, Sweden.

Abstract. Reactions of 5'-O-(4,4'-dimethoxytrityl)thymidin-3'-yl 2-cyanoethyl phosphonate with alcohols, amines and amino alcohols in pyridine are described. Transesterification was found to be faster than β-elimination of 2-cyanoethyl group.

INTRODUCTION

H-Phosphonate diesters with nucleophiles undergo several characteristic reactions and the most typical are: transesterification, alkylation, and dealkylation (for review see ref. 1). However, in mild basic conditions often used in natural products chemistry simple dialkyl H-phosphonates appear to be relatively stable.

During our studies on reactions of nucleoside H-phosphonates with bifunctional reagents[2] we have found that nucleoside H-phosphonate diesters could react with amines, alcohols, and amino alcohols giving substitution products at the phosphorus center[3]. It is noteworthy that these reactions proceed under much milder conditions than those required for simple dialkyl H-phosphonate diesters[4-6]. In this paper reactivity of 5'-O-(4,4'-dimethoxytrityl)thymidin-3'-yl 2-cyanoethyl phosphonate diester **1**, which under the reaction conditions may undergo transesterification or β-elimination, is discussed.



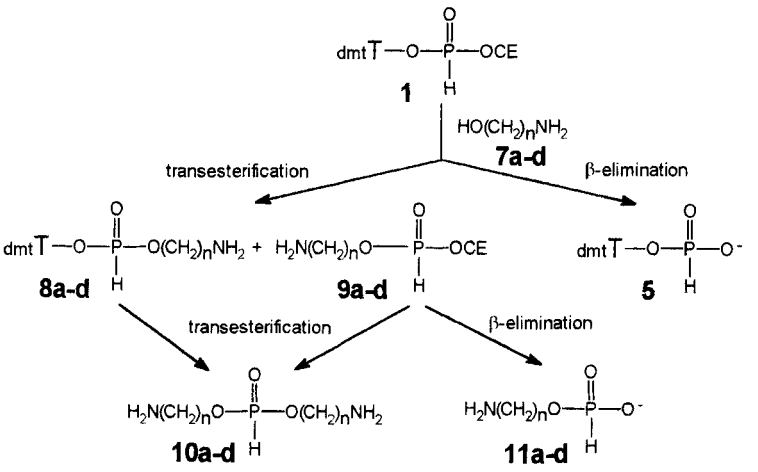
Scheme 1

RESULTS AND DISCUSSION

Reaction with n-butylamine. Compound **1** when treated with n-butylamine within 30 min produced only 5'-O-(4,4'-dimethoxytrityl)thymidin-3'-yl phosphonate monoester **5** as a product of β-elimination of the2-cyanoethyl group.

Reaction with ethanol and a mixture of ethanol and n-butylamine (Scheme 1). The reaction of **1** with ethanol alone was sluggish and after 23 h the reaction mixture consisted of unreacted **1** (32%), 5'-O-(4,4'-dimethoxytrityl)thymidin-3'-yl ethyl phosphonate **2** (42%), 2-cyanoethyl ethyl phosphonate **3**[8] (14%), diethyl phosphonate **4** (7%), and some by-products (5%). The same reaction proceeded much faster in the presence of butylamine and **1** after 2 min reacted completely. At this stage the main compounds observed were the products of transesterification **2** and **3** which underwent further substitution, and after 4 h diethyl phosphonate **4** was found as a final product. The H-phosphonate monoesters **5** and **6** were formed as products of a parallel β-elimination of the 2-cyanoethyl group.

Reactions with amino alcohols ***7a-d*** (Scheme 2). The reaction of **1** with 2-aminoethanol **7a** was very fast and the starting H-phosphonate was consumed in less than 1 min yielding 59% of di(2-aminoethyl) phosphonate **10a**, 23% of 2-aminoethyl 2-cyanoethyl phosphonate **9a**[8], and 18% of **5** (β-elimination of 2-cyanoethyl group). After 4 min **9a** was also converted to **10a** which underwent further transformation to some unidentified compounds. In the case of 3-aminopropan-1-ol **7b**, after 1 min the main product was



Scheme 2

Table 1. The ^{31}P NMR data of the intermediates and the final products.

Compound	Chemical shift[a] (ppm)	$^{1}J_{PH}$ (Hz)	$^{3}J_{PH}$ (Hz)
1	7.72; 7.74	718.4	2.8[b]
3[8]	7.94	693.4	9.3[c]
6	2.57	606.1	8.4[c]
9a[8]	8.29	698.9	8.3[c]
9b[8]	8.37	705.8	d
9c[8]	8.15	d	d
9d[8]	8.16	d	d
11d[8]	2.95	595.1	8.4[e]

[a]Spectra in pyridine with heteronuclear decoupling (0.5% H_3PO_4 in D_2O as an external reference). [b]Doublets of quartets. [c]Doublet of quintets. [d]Not resolved due to overlapping. [e]Doublet of triplets. ^{31}P NMR data for H-phosphonate diesters of type **2**[3], **8**[2], and **10**[3] have been already published.

3-aminopropyl 5'-O-(4,4'-dimethoxytrityl)thymidin-3'-yl phosphonate **8b** (74%) together with 3-aminopropyl 2-cyanoethyl phosphonate **9b**[8] (10%), **5** (12%), and bis(3-aminopropyl) phosphonate **10b** (4%), which became the final product of transesterification after 2 h. For 4-aminobutan-1-ol **7c**, the reaction looked very similar to that of **7b** in the first stage, but compounds **8c** and **10c** were rather unstable and were converted into species which were not further identified. The reaction of **1** with 6-amino-hexan-1-ol **7d** seemed to be slower but it was still fast enough so that **1** could not be registered in time required for recording the first NMR spectra. In this instance also the

products of β-elimination were formed [signals at 2.13 ppm (**5**, 22%) and 2.95 ppm (6-aminohexyl phosphonate **11d**[8], 14%)] but di(6-aminohexyl) phosphonate **10d** was the major product (64%) of transesterification.

From the above experiments it is clear that **1** is much more susceptible to transesterification than 5'-O-(4,4'-dimethoxytrityl)thymidin-3'-yl ethyl phosphonate or even 5'-O-(4,4'-dimethoxytrityl)thymidine-3'-yl 3'-O-(4,4'-dimethoxytrityl)thymidine-5'-yl phosphonate[3]. The reaction is chemoselective to high extent with 2-cyanoethoxy as a preferable leaving group. The ratios of the products **8** to **9** at the early stages of the reaction were ~7:1 for amino alcohols **7b-d** and ~6:1 for **2** to **3**, when using the mixture of ethanol and n-butylamine. In neither case traces of phosphonamidates could be detected in the reaction mixtures.

These properties of 2-cyanoethyl nucleoside H-phosphonate diesters should be kept in mind while working with this type of compounds (e.g. during their transformation towards phosphoesters in the presence of active nucleophiles). On the other hand this fast reaction (particularly with 2-aminoethanol) can be employed for rapid dephosphonylation of diesters, e.g., for the recovery of nucleosides as described recently by Brill[9].

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7 All reactions proceeded in dry pyridine and were monitored by ^{31}P NMR. Concentration of **1** was 0.1 M and the nucleophilic compounds were added in 10-fold molar excess.

8 Assignment of ^{31}P NMR signal to this compound was made according to its predicted magnetic properties.

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