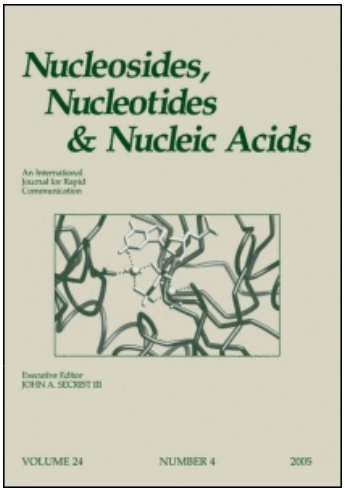

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STUDIES ON ARYL H-PHOSPHONATES. SYNTHESIS OF NUCLEOSIDE N-ALKYLPHOSPHONAMIDATES

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Abstract: The aminolysis of aryl nucleoside H-phosphonate diesters with various amines was studied. The new simple and efficient method of synthesis of nucleoside phosphonamidates is described.

INTRODUCTION

Chemistry and synthetic applications of alkyl H-phosphonamidates have until now been relatively little explored. In nucleotide chemistry, so far there are only few reports on this type of nucleoside derivatives which were used as intermediates in the transformation of nucleoside phosphordiamidites into nucleoside H-phosphonates or phosphates[1]. In the last year Hata *et al.*[2] showed that nucleoside H-phosphonamidates can be also useful synthons for the introduction of 3'-terminal nucleosides onto oligonucleotides.

So far, nucleoside phosphonamidates have been obtained *via* controlled hydrolysis of the corresponding tervalent phosphorus derivatives[3], *e. g.* nucleoside phosphordiamidites[1]. This approach seems to be limited by a rather poor availability of stable phosphitylating reagents - bis(alkylamino)chlorophosphine[1,4] for synthesis of starting phosphordiamidites. Thus, we attempted to develop of versatile method of synthesis of nucleoside phosphonamidates bearing various alkylamino residues which in consequence should provide deeper insight in the chemistry and properties of this type of nucleotide derivatives.

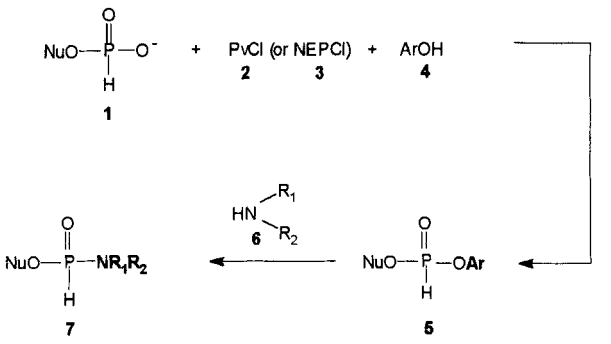
RESULTS AND DISCUSSION

Searching for an efficient method of synthesis of nucleoside phosphonamidates, first the reaction of a standard coupling of nucleoside H-phosphonates with appropriate amines were studied. Two different coupling agents *i. e.* pivaloyl chloride[5] (PvCl) and 2-chloro-5,5-dimethyl-2-oxo-2λ^5-1,3,2-dioxaphosphinane[6] (NEPCl), have been used for the activation of nucleoside H-phosphonates, and the course of particular reactions was monitored by ^{31}P NMR. From these experiments became apparent that formation of the desired nucleoside phosphonamidates depends on the ratio of the rate of reaction of amines with activated H-phosphonate and the rate of aminolysis of coupling agent. In most instances the last reaction prevailed, so that presently we cannot recommend this approach for synthesis of phosphonamidates.

During our studies on transesterification[7] of nucleoside H-phosphonate diesters, we found that nucleoside p-chlorophenyl H-phosphonate diester **5** easily undergo aminolysis with butylamine (**6a**) to produce rapidly and quantitatively the corresponding nucleoside phosphonamidate **7a**. This observation prompted us to investigate the reaction of aminolysis of aryl H-phosphonate diesters and to try to develop it into a versatile method for synthesis of nucleoside phosphonamidates of type **7**. Aryl nucleoside H-phosphonates of type **5** could be easily obtained using a standard coupling of nucleoside H-phosphonate of type **1** and p-chlorophenol (**4**) in the presence of **2** or **3** as coupling reagents. In both cases reactions proceeded rapidly (1 - 2 min) and quantitatively (^{31}P NMR) toward H-phosphonate diester **5**. Due to susceptibility to nucleophilic substitution of aryloxy residue of aryl H-phosphonate diester by different nucleophiles[7], **5** was not isolated and was used directly for aminolysis. The primary and secondary amines which have been used in aminolysis reactions were of a rather narrow range of pKa values (10.6 - 11.3[8]) but they were differently sterically hindered with alkyl substituents.

Using the standard procedure (see later), the aminolysis of **5** with nonhindered primary and secondary amines **6a**,**b**,**d** proceeded smoothly and quantitatively (^{31}P NMR and TLC) toward nucleoside phosphonamidates **7a**,**b**,**d** which were isolated with silica gel column chromatography with 40 - 70% yields. In the above experiments the results were identical irrespective of the coupling agent used. In aminolysis with amines **6c**,**e** and **6f** carrying bulky alkyl substituents the composition of products was different and depended on the route of synthesis of the intermediate substrate **5**.

When nucleoside aryl H-phosphonate diester **5** was produced in a condensation prompted with NEPCl and after treatment with amines **6c** and **6e** the aminolysis proceeded toward the corresponding nucleoside phosphonamidates **7c** and **7e**. When diisopropylamine was used in the same reaction, the aminolysis did not take place and the



6, 7 a; R_1 = H, R_2 = butyl
b; R_1 = H, R_2 = *i*-propyl
c; R_1 = H, R_2 = *t*-butyl
d; R_1 = methyl, R_2 = butyl
e; R_1 = R_2 = butyl
f; R_1 = R_2 = *i*-propyl

Nu - protected nucleoside. Pv - pivaloyl. Ar - p-chlorophenyl.
NEPCl - 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane.

Scheme 1.

only products found were nucleoside bis(p-chlorophenyl)phosphite and nucleoside H-phosphonate monoester **1**, apparently as a products of the transformation[9] of aryl H-phosphonate diester **5**. It seems that diisopropylamine, because of sterical hindrance, could not reach the phosphorus center and it acted as a base which promoted the above transformation. The same reactions performed with nucleoside aryl H-phosphonate diester **5** obtained *via* coupling with the aid of pivaloyl chloride, and treated with amines **6c**,**e** and **6f** led to two types of products. For **6c** and **6e** the nucleoside phosphonamidates **7c** (ca. 50%) and **7e** (ca. 50%) were formed respectively and a new product (ca. 50%) which gave rise two resonaces at ~16 ppm (m) and ~ -6 ppm (m) probably from two types of phosphorus centers present in one compound. In the case of diisopropylamine the last product was formed exclusively. Considering the chemical shifts and multiplicity of signals the putative structure of this product could be analogous to phosphonate-phosphate derivatives described by Bentzen *et al*[10].

Standard procedure for aminolysis of nucleoside aryl H-phosphonate diesters of type **5**.

To the solution of nucleoside H-phosphonate **1** (1 mol equiv.) and p-chlorophenol (1.1 mol equiv.) in methylene dichloride containing pyridine (10% v/v) (5 cm^3/1 mmol of 1) coupling agent **2** or **3** (3 mol equiv.) was added. After 5 min the resulting **5** was treated with the appropriate amine **6** and

Table 1. ^{31}P NMR data of nucleoside phosphonamidates of type 7.

Compound	δ_P (ppm)[a]	$^1J_{PH}$ (Hz)	$^3J_{PH}$ (Hz)
7a	13.21, 13.34	640.5, 638.6	11.2[b]
7b	10.39, 10.85	645.1, 641.4	9.27[c]
7c	8.64, 9.03	636.8, 634.9	-[d]
7d	15.46, 15.63	644.2, 643.3	10.2[e]
7e	15.23, 15.47	638.3, 640.2	-[d]

[a]Spectra recorded in methylene dichloride containing pyridine (10% v/v) with heteronuclear decoupling (H_3PO_4 in D_2O as an external reference). [b]Doublets of quartets. [c]Quartets. [d]Multiplets.

left to react 15 min at room temp. The reaction mixture was washed with brine, organic layer dried (Na_2SO_4 anh.) and evaporated under vacuum. Products **7** were isolated by silica gel column chromatography. ^{31}P NMR data are listed in Table 1.

In conclusion, nucleoside aryl H-phosphonate diesters of type **5** could be useful precursors for the synthesis of variety of nucleoside phosphonamidates via simple aminolysis. However, further studies are necessary to resolve the problem of competitive side reactions observed when sterically hindered amines are used.

REFERENCES

1. Marugg, J. E., Bruzik, A., Tromp, M., van der Marel, G. A. and van Boom, J. H. *Tetrahedron Lett.*, 1986, **27**(230), 2271- 2274.
2. Wada, T., Ishikawa, K. and Hata, T., *Tetrahedron* 1993, **49**(10), 2043 - 2054.
3. Zwierzak, A. and Koziara, A. *Tetrahedron* 1967, **23**, 2243 - 2252.
4. Uznański, B., Wilk, A., Stec, W. J., *Tetrahedron Lett.*, 1987, **28**(29), 3401 -3404.
5. Garegg, P. J., Regberg, T., Stawiński, J. and Stromberg R., *Nucleosides Nucleotides*, 1987, **6**, 655 - 662.
6. McConnell, R. L. and Coover, Jr., H. W., *J. Org. Chem.*, 1959, **24**, 630 - 635.
7. Sobkowski, M., Stawiński, J., Sobkowska A. and Kraszewski, A. *J. Chem. Soc. Perkin Trans. 1.* 1994, 1803 - 1808.
8. Perrin, D. D., *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, 1965.
9. Jankowska,J., Sobkowski, M., Stawiński, J. and Kraszewski, A., *Tetrahedron Lett.*, 1994, **35**(20), 3355-3358.
10. Nguyen, L. M., Niesor, E. and Bentzen, C. L., *J. Med. Chem.*, 1986, **30**, 1426 - 1433.