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Aryl Nucleoside H-Phosphonates—Novel Derivatives of Controlled Reactivity

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ARYL NUCLEOSIDE H-PHOSPHONATES - NOVEL DERIVATIVES OF CONTROLLED REACTIVITY

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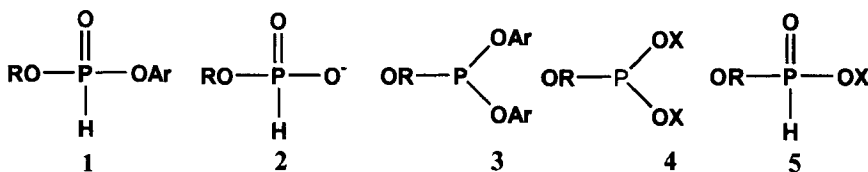
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ABSTRACT: The most essential factors influencing the formation of aryl nucleoside H-phosphonates are discussed.

Recently, aryl nucleoside H-phosphonates (**1**) (Scheme 1) emerged as a new type of intermediates in the synthesis of phosphate derivatives¹. In contradistinction to other reactive species derived from H-phosphonate monoesters, these compounds bear only one electrophilic centre (located on phosphorus) and their reactivity can be modulated by substituents on the aromatic ring².

In this report we wish to discuss factors influencing the formation of aryl nucleoside H-phosphonates under various experimental conditions. Reactivity of phenols in a coupling reaction with H-phosphonate monoesters **2** varied, and sometimes provided different products depending on a pKa value of the phenol used. In a standard condensation promoted by pivaloyl chloride in pyridine phenols with pKa values higher than 9.0 (*e.g.* 4-chlorophenol, phenol and 4-methylphenol)³ produced exclusively the expected aryl nucleoside H-phosphonate **1**. Phenols with $9.0 > \text{pKa} > 6.0$ (*e.g.* 2,4-dichloro-, 4-nitro-, 2,4,6-trichloro) afforded under these conditions variable amounts of tervalent bis-aryl nucleoside phosphites of type **3**, along with the desired **1**. Pentachlorophenol ($\text{pKa} < 6$), however, produced in a coupling reaction with **2** exclusively **3**.

SCHEME 1



R = suitably protected nucleoside; Ar = aryl; X = pivaloyl or diphenylphosphate residue

The coupling reaction with phenols of moderate acidity ($\text{pK}_a > 6$) performed in less basic media, e.g. $\text{CH}_2\text{Cl}_2/\text{pyridine}$ 9 : 1 (v/v) produced exclusively aryl nucleoside H-phosphonates **1**. This is most likely due to suppression of a double activation of **2** (to produce **4**) under these conditions and thus, predominantly monoactivated species **5** are formed. Besides pivaloyl chloride, the most convenient condensing agent for this purpose was found to be diphenyl phosphorochloridate. With this reagent (1.5 molar equiv.) aryl nucleoside H-phosphonates **1** were formed fast (ca. 3 min) and quantitatively.

Very acidic phenols ($\text{pK}_a < 6$, e.g. pentachloro-, pentafluorophenol and 2,4-dinitrophenol) in $\text{CH}_2\text{Cl}_2/\text{pyridine}$ 9 : 1 (v/v) also produced aryl nucleoside H-phosphonates of type **1**. These, however, were not completely stable under the reaction conditions and underwent a gradual disproportionation towards bis-aryl nucleoside phosphite of type **3** and the initial nucleoside H-phosphonate **2**, according to the mechanism we have described earlier⁵.

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REFERENCES

1. Cieślak, J., Jankowska, J., Kers, A., Kers, I., Sobkowska, A., Sobkowski, M., Stawiński, J. and Kraszewski, A. *Collect. Czech. Chem. Commun.* **1996**, *61*, 242-245.
2. Sobkowska, A., Sobkowski, M., Cieślak, J., Kers, I., Stawiński, J. and Kraszewski, A. *J. Org. Chem.*, **1997**, *62*, 4791-4794.
3. Kostrum, G., Vogel, W. and Andrussow, K. in *Dissociation Constants of Organic Acids in Aqueous Solution*, Butterworth, London, **1961**.
4. For review see - Stawiński, J. in *Handbook of Organophosphorus Chemistry*, Engel, R. Ed., Marcel Dekker, Inc. New York **1992**, 377-434.
5. Kers, A., Kers, I., Sobkowski, M., Kraszewski, A. and Stawiński, J. *Tetrahedron*, **1996**, *52* (29), 9931-9944.