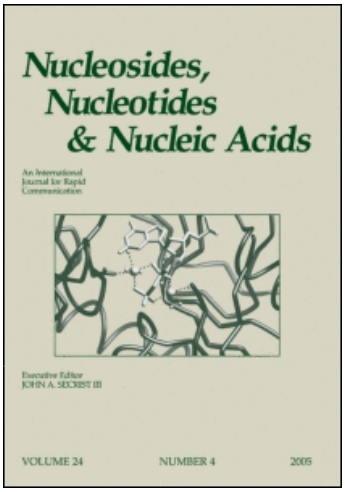

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One-Pot Synthesis of Antiviral Acyclovir and Other Nucleosides Derivatives Using Doped Natural Phosphate as Lewis Acid Catalyst

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ONE-POT SYNTHESIS OF ANTIVIRAL ACYCLOVIR AND OTHER NUCLEOSIDES DERIVATIVES USING DOPED NATURAL PHOSPHATE AS LEWIS ACID CATALYST

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□ *Natural phosphate doped with iodine or potassium iodide is an active catalyst for the one-pot synthesis of acyclonucleosides. To demonstrate the utility of the new catalyst system, the highly important antiviral drug acyclovir was directly and regioselectively obtained from NAcG with no byproducts.*

Keywords Acyclovir natural phosphate; Lewis Acid catalyst

INTRODUCTION

Reactions facilitated on various solid inorganic surfaces are receiving increasing attention.[1] The advantages of these methods over conventional homogeneous reactions is that they provide greater selectivity, enhanced rates, clean products, and ease of handling. In an effort to develop new

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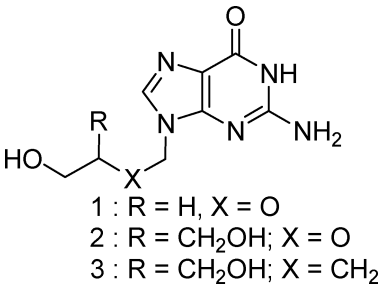


FIGURE 1 Acyclic nucleoside analogues of acyclovir.

practical and economic catalysts, the use of natural phosphate (NP) and doped NP in various chemical transformations has recently been investigated.[2] These types of catalysts represent an important environmentally friendly alternative to reactions otherwise toxic and expensive, and many efforts are being pursued to promote NP.[3] Acyclovir **1**, ganciclovir **2**, and penciclovir **3** (Figure 1) are widely used drugs for the treatment of opportunistic herpes virus infections in immunocompromised patients. Although commercialized for more than 25 years, an inexpensive production of acyclovir is still challenging, especially in the field of generic drugs.

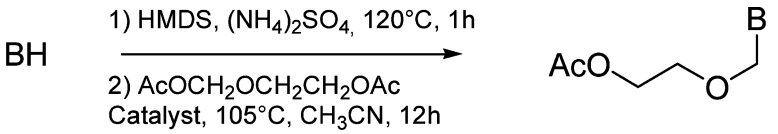
As a continuation of our ongoing program toward the development of new and economical syntheses of antiviral drugs, we report here a clean and efficient preparation of acyclovir and its analogues using NP as catalyst.

RESULTS AND DISCUSSION

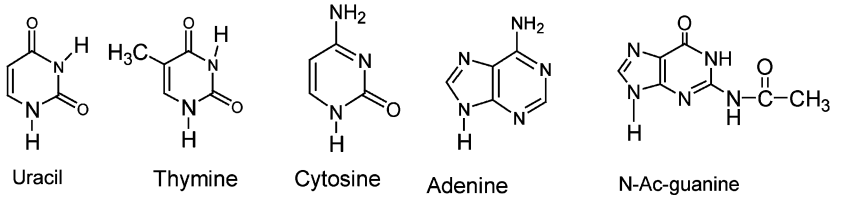
Several methods for the synthesis of these antiviral agents have been reported. A review covering these approaches was recently published.[4] The major problems associated with the synthesis of acyclovir and its analogues were 1) the reagents employed were quite expensive; 2) the amination of the 2-chloro group was tedious; 3) the yield of acyclovir was usually not satisfactory; and 4) the accompanying formation of the N^7-isomer, which can be very difficult to separate from the expected N^9-isomer.[5] According to the patent literature[6] for the synthesis of acyclovir, the drug has been prepared in 24% yield by debenzylation of the product obtained by the reaction of trimethylsilylated guanine and 2-benzozxyethoxymethyl chloride.

Considering the high value of acyclovir and its analogues, we decided to undertake a study to identify the best catalyst for a simple, inexpensive, and general synthesis of acyclonucleosides. Herein, we describe the virtues of NP as an efficient heterogeneous catalyst for use in this emerging area. Pyrimidines or purines were first condensed with hexamethyldisilazane (HMDS) and directly treated with 1.1 eqivalent of (2-acethoxyethoxy)methylacetate without distilling to remove excess HMDS. Indeed, upon refluxing uracil

with ammonium sulfate in HMDS for 1 hour, the addition of the alkylating agent led to a small amount of desired acyclonucleoside (Table 1, entry 1). Therefore, in connection with our previous work, we studied the influence of various additives as doping partners and increase the catalytic activity of NP. With this aim, NP was impregnated with various amount of either I_2 [2e] or KI [2d] (Scheme 1). These additives were assumed to aid in both the N^1 regioslective isomer (pyrimidine) formation as well as activating the alkylation reagent, thereby significantly increasing rates of acyclonucleosides formation. Control experiments indicated that an impregnation of NP with these additives is essential for this one-pot reaction to be efficient. Whereas addition of 0.2 equivalent of TMSI showed no catalytic effect whatsoever (entry 2) we found that 0.2 equivalent of I_2/NP allowed a 20% yield increase, as compared to 0.2 equivalent of I_2 alone (compare entries 3 and 6). With these conditions in hand, other acyclonucleosides derivatives were obtained in yields ranging from 34% to 50% (entries 7–10). In all cases, the reaction was found to be regioselective, allowing only the formation of the N^1 isomer for pyrimidines and the N^9 isomer for purines, with no traces of other isomers (N^7).

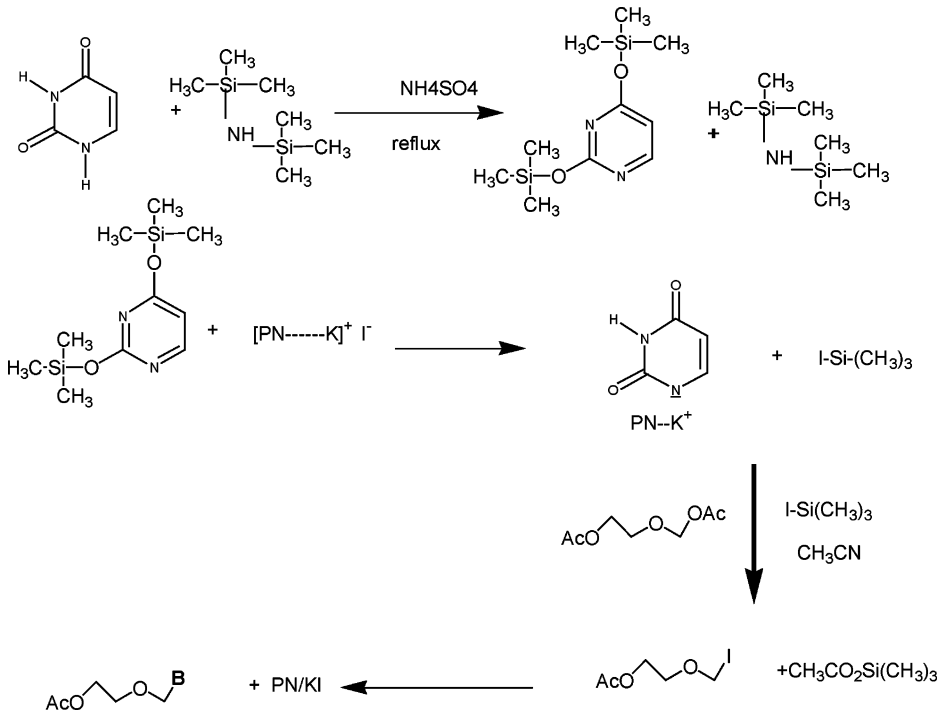


BH= U=uracil, T= thymine, C= cytosine, A= adenine, Nac-G= N-acetyl guanine



SCHEME 1 Conditions for synthesis of acyclonucleoside analogues to acyclovir.

The mechanism of the above glycosylation can be depicted as follows (Scheme 2): Sylilated uracil reacts with KI/NP to give (CH3)3Si-I. The latter reacts with the alkylating agent R-O-CH2-OAc to afford R-O-CH2-I. Further, the complex [Heterocycle]-/[NP-K]$^+$ then reacts with R-O-CH2-I to conduct to the target acyclonucleoside.[7] To further examine the possibility of NP catalysis with non volatile additives, NP was impregnated with potassium iodide. As expected, KI alone gave only traces of product (entry 11) whereas activated NP with 0.8 equivalent of KI gave modest-to-good amounts of the acyclonucleosides, depending on the starting bases, with no loss of regioselectivity (entries 15–18). Finally, acyclovir was quantitatively obtained from its diacetate precursor after treatment with a saturated solution of



SCHEME 2 Mechanism of the glycosylation.

ammonia in methanol followed by evaporation of the solvent, with 30% overall yield from $N_{Ac}G$.[8,9]

The used and recovered catalysts were then shown to be reusable after drying at 150°C in vacuum, and more efficiently after washing with acetone followed by calcinations at 900°C.[2g]

In conclusion, a general one-pot synthesis of acyclonucleosides starting from unprotected nucleobases is presented. Although the yields are modest, the use of an inexpensive NP coated with I_2 or KI as catalyst make this reaction particularly attractive. Easy to set up and totally regioselective, the reaction is notably facile and does not require fastidious work-up. Because of the high potential of acyclovir and its analogues, we believe that this reaction will be of broad interest to scientists involved in the synthesis of antiviral drugs.

EXPERIMENTAL SECTION

Typical Procedure for Catalyst Preparation

a *Natural Phosphate Coated with Iodine (NP/I2)*: To a solution of iodine (759 mg) in CH2Cl2 (5 ml) was added natural phosphate (3 g) and stirred for 15 minutes and evaporated to dryness.

TABLE 1 Alkylation of natural bases with (2-acetoxyethoxy)methylacetate (1.1 equivalent) under various catalytic conditions

Entry	Base	Catalyst (Eq.)	Yield (%)[a]
1	U	NP	5
2	U	TMSI (0.2)	3
3	U	I_2 (0.2)	30
4	U	NP/I_2 (0.8)	35
5	U	NP/I_2 (0.5)	40
6	U	NP/I_2 (0.2)	50
7	T	NP/I_2 (0.2)	50
8	C	NP/I_2 (0.2)	35
9	A	NP/I_2 (0.2)	48
10	$N_{Ac}G$	NP/I_2 (0.2)	34
11	U	KI (0.8)	8
12	U	NP/KI (0.5)	30
13	U	NP/KI (0.8)	50
14	U	NP/KI (1)	44
15	T	NP/KI (0.8)	45
16	C	NP/KI (0.8)	30
17	A	NP/KI (0.8)	50
18	$N_{Ac}G$	NP/KI (0.8)	24

[a]Isolated yield.

b *Natural Phosphate Coated with Potassium Iodide (NP/KI)*: To a solution of potassium iodide (1 g) in water (5 ml) was added natural phosphate (3 g). The mixture was stirred for 15 minutes and evaporated to dryness.

Typical Procedure for One-Pot Synthesis

To uracil (112 mg, 1 mmol) was added hexamethyldisilazane (4 mL) and ammonium sulphate (10 mg). The mixture was refluxed for 2 hours. To the obtained clear solution was added 2-acetoxyethyl acetoxymethyl ether (200 mg, 1.1 mmol), the catalyst (473 mg, 0.2 mmol of I2, or 473 mg, 0.8 mmol of KI) and acetonitrile (5 mL). After being refluxed overnight, the mixture was filtered and the solvent evaporated. The crude product was purified by column chromatography. The desired product was obtained with 50% yield.

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3. NP comes from an ore extracted in the region of Khouribga (available in raw form or treated form from CERPHOS Casablanca, Morocco). Prior to use this material requires initial treatments such as crushing and washing. For use in organic synthesis, the NP is treated by techniques involving attrition, sifting, calcinations (900°C), washing, and recalcination. These treatments lead to a fraction between 100 and 400 lm, which is rich in phosphate. The structure of NP is similar to that of fluorapatite $[Ca_{10}(PO_4)_6F_2]$, as shown by x-ray diffraction and chemical analysis. The surface area of NP was measured at μm2 g^{-1} (nitrogen adsorption) and the total pore volume was 0.005 cm^3 g-1.
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