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Natural phosphate as Lewis acid catalyst: a simple and convenient method for acyclonucleoside synthesis

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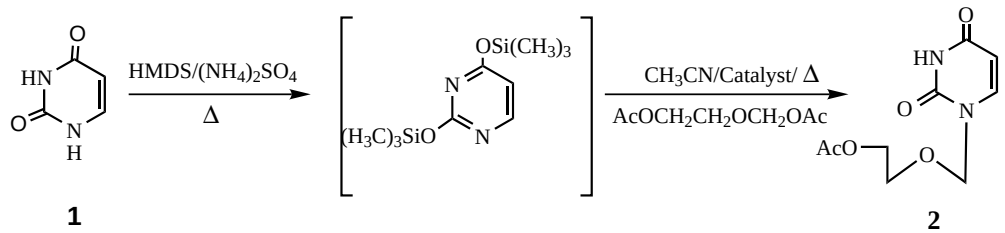
Abstract—A new and efficient method for the synthesis of N-1/N-9-[(2-acetoxyethoxy)methyl]pyrimidine/purine using natural phosphate as Lewis acid catalyst was developed.

The pharmaceutical industry requires the development of useful carbon–nitrogen bond-forming reactions exhibiting high yields, high selectivity, low cost, safe, operational simplicity, mild reaction conditions and environmental consciousness. It has been recognised that catalysis of organic reactions by inorganic reagents supported on high surface area inorganic materials as alumina, montmorillonite K10 and natural phosphate[1–4] can be a potential and efficient methodology to achieve these goals.

Since the discovery of modified acyclonucleosides as antiviral agents, substantial efforts have been devoted to the synthesis and biological evaluation of such compounds. For example, the synthesis of Acyclovir (Zovirax) and their acyclonucleoside analogues; the acetoxyethylacetoxymethyl ether is often used as alkylating reagent with some catalysts, e.g. $SnCl_4$, $Hg(CN)_2$, $(CH_3)_3SiClO_4$, $(CH_3)_3SiSO_3C_4F_9$.[5,6] The recently described usefulness of doped natural phosphate (NP) for the efficient catalysis of 1,3-dipolar cycloaddition[4] prompted us to report our own results on the selective *N*-alkylation of nucleobases with acetoxyethylacetoxymethyl ether under mild reaction conditions using natural phosphate, $ZnCl_2$ or $ZnBr_2$ doped natural phosphate as Lewis acid catalysts (Scheme 1).

In order to assess the influence of natural phosphate as catalyst on this reaction, a number of experiments were performed to find the most effective conditions. The results of these studies are summarized in Table 1.

As shown in Table 1, the synthesis of acyclonucleoside **2** proceeds optimally in ca. 62–67% yield either with natural phosphate (entries 1 and 2) or with $ZnCl_2$ and $ZnBr_2$ doped natural phosphate (entries 7 and 9) Lewis acid catalysts. It is very interesting to notice that the yield is low in the absence of solvent (entry 5) and that the addition of acetonitrile produces a dramatic increase in the reaction yield (entry 6). The reaction was



1 **2**

Scheme 1.

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Table 1. Catalytic effects on the *N*-alkylation reaction

Entry	Catalyst	w/w[a]	Solvent	Time (h)	Temperature	Yield (%)[d]
1	NP	150	CH_3CN	3	Reflux	67
2	NP	300	CH_3CN	2	Reflux	62
3	NP[b]	300	CH_3CN	20	Reflux	52
4	$ZnBr_2$	100	CH_3CN	2	Reflux	5
5	NP/$ZnBr_2$	300/100	–	2	Reflux	10
6	NP/$ZnBr_2$	300/100	CH_3CN	1.5	Reflux	60
7	NP/$ZnBr_2$	175/25	CH_3CN	2	Reflux	65
8	NP/$ZnBr_2$[c]	175/25	CH_3CN	1.5	Reflux	50
9	NP/$ZnCl_2$	175/25	CH_3CN	2	Reflux	60

[a] Amount of catalyst for 100 mg of uracil.
[b] All reagents were mixed at the beginning of the reaction (one-pot reaction).
[c] The catalyst and the alkylating agent were added after evaporation of HMDS.
[d] The yield is given after purification by column chromatography.

monitored by thin-layer chromatography. This procedure appears to be regioselective and gives only the N-1 isomer.[7–9] After establishing the importance of the catalytic activity of NP in N-1-alkylation of uracil, we undertook the extension of this protocol to other relevant species. Thus, other natural heterocyclic bases (thymine, adenine, cytosine, N-Ac-guanine) were subjected to *N*-alkylation to afford the corresponding acyclonucleosides in 10–70% yields (Table 2).

Uracil **1** and thymine **3a** reacted with similar yields (entry 2). Thereafter, no N-1, N-3-bisalkylation was observed. The regioisomers N-1 (pyrimidine) and N-9 (purine) were determined according to their UV spectra.[8–10] The synthesis of acyclovir[10] **4d** (entries 5 and 6) scarcely occurred either with NP or with NP/$ZnBr_2$. Other conditions are under investigation to improve the acyclovir yield (Scheme 2).

In conclusion, we have shown that natural phosphate as well as $ZnCl_2$- or $ZnBr_2$-doped natural phosphate can be used as Lewis acid catalyst for the *N*-alkylation of the pyrimidine bases (U, T, C) and for adenine (A), but for the acyclovir the yield is too low. This method is a new and efficient way using an inexpensive catalyst.

Experimental

For the preparation of natural phosphate, see Refs. 3 and 4.

Preparation of doped natural phosphate

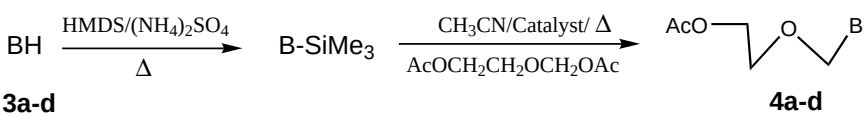
Natural phosphate (175 mg) and $ZnBr_2$ or $ZnCl_2$ (25 mg) were mixed in 5 ml of water and evaporated to dryness and dried for 6 h at 150°C. The obtained solid residue was used as catalyst in the N-1 alkylation (see Table 1).

General procedure

Uracil (100 mg, 0.892 mmol) was silylated by heating overnight with excess of hexamethyldisilazane (HMDS) (4 ml, 19.2 mmol) in the presence of a small amount (catalyst) of ammonium sulphate $(NH_4)_2SO_4$. To the persilylated uracil were added 150 mg of NP, 13 ml of acetonitrile and 157.3 mg (0.892 mmol) of acetoxyethyl-acetoxymethyl ether and the mixture was refluxed for 3 h with exclusion of humidity. The mixture was filtered and evaporated. The residue was chromatographed on a silica gel column and the desired product was obtained in 67% yield (Table 1).

Table 2. *N*-Alkylation of various natural heterocyclic bases

Entry	Heterocyclic base	Catalyst	w/w	Time (h)	Yield (%)
1	Uracil	NP	150	3	67
2	Thymine	NP	150	3	70
3	Adenine	NP	150	Night	50
4	Cytosine	NP	150	4	50
5	N-Ac-guanine	NP	150	3.5	–
6	N-Ac-guanine	NP/$ZnBr_2$	175/25	2	10



Scheme 2. a: B = thymin-1-yl, b: B = cytosin-1-yl, c: B = adenin-9-yl, d: B = N-Ac-guanin-9-yl.

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