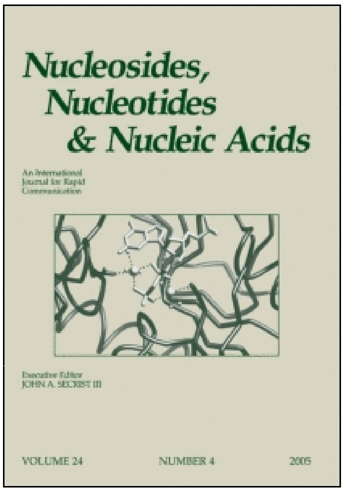

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Natural Phosphate Doped with KI in HMDS: A Mild and Efficient Reagent for Alkylation and Glycosylation of Nucleobases

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NATURAL PHOSPHATE DOPED WITH KI IN HMDS: A MILD AND EFFICIENT REAGENT FOR ALKYLATION AND GLYCOSYLATION OF NUCLEOBASES

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▫ *Several D-ribonucleosides are prepared from 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranoside and trimethylsilylated nucleobases under mild conditions by using natural phosphate doped with KI as catalyst.*

Keywords Natural Phosphate, Potassium Iodide, Nucleosides

INTRODUCTION

The Vorbruggen modification of the Hilbert-Johnson reaction has been widely employed for the preparation of various nucleoside analogues by coupling different silylated nucleobases with the appropriate sugars. Usually this reaction has been carried out using a catalytic amount of TMSOTf or $TMSClO_4$, under the assumption that the stable counter ion (^{-}OTf or ClO_4^-) is necessary to achieve the catalytic glycosylation reaction. Iodotrimethylsilane has been also used for this purpose even though this reagent is extremely sensitive to moisture and is expensive.

Recently, the use of solid acids such as clays, zeolites, and ion-exchange resins has achieved importance in organic chemistry.[1] Heterogeneous solid acids are

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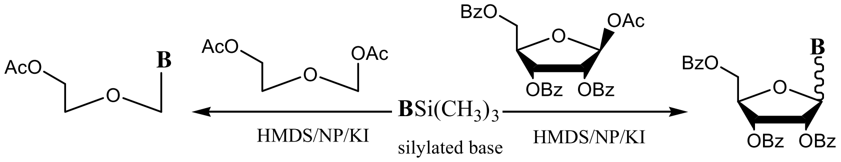

SCHEME 1

advantageous over conventional homogeneous acid catalysts, since they can be easily recovered from the reaction mixture by filtration and can be reused after activation or without activation, thus making the processes economically viable.[2] Of the many possible heterogeneous catalysts, natural phosphate* is attractive because of its low cost, reusability, flexibility in acid strength, ease of handling, environmental compatibility, non-toxicity and experimental simplicity.[3]

In this respect, and in connection with our other work on the use of natural phosphate as a catalyst,[4,5] we now report a new **one pot** novel method by using an inexpensive natural phosphate catalyst doped with KI instead of TMSOTf, $TMSClO_4$, or iodotrimethylsilane to perform the glycosylation reaction (Scheme 1).

In order to assess the influence of natural phosphate (NP) doped with KI as a catalyst on this reaction and to find the most effective conditions, a number of experiments were performed. The results of these studies are summarized in Table 1 and Table 2.

As shown in Table 1, when either NP and KI were used alone, the reaction of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranoside with *bis*-(trimethylsilyl)uracil gave the ribonucleoside in only 5 and 28% yields, respectively. As can be seen in the subsequent examples, the yield increased when NP doped with KI was used. For example, in entry 4 the desired ribonucleoside was obtained as a major isomer and in good yield by using NP/KI corresponding to 0.8 eq of KI in acetonitrile at 105°C overnight. This procedure appears to be regioselective and gives only the N-1 isomer. Other nucleobases (entries 6–8) were then also subjected to N-glycosylation and found to afford the corresponding nucleosides in 50% yield (Table 1). The same conditions were also used to prepare some acyclonucleosides in 50% yield (entries 1–3, Table 2). All products were characterized by ^{1}HNMR, and mass spectroscopy and also by comparison with literature data.

In conclusion, the mild conditions, low cost, and easy work-up of this new method offer some advantages over former procedures, and thus it should be of

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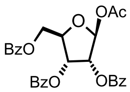
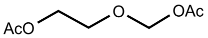
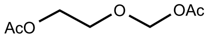
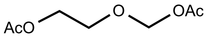
*Natural phosphate (NP) comes from an ore extracted in the region of Khouribga (it is available in raw form or treated form from Cerphos, Casablanca, Morocco). Prior to use this material requires initial treatments such as crushing and washing. For use in organic synthesis, the NP is treated by techniques 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 1 m^2 g^{-1} (nitrogen adsorption) and the total pore volume was 0.005 cm^3 g-1.

TABLE 1 Synthesis of 2′,3,5′-Tri-O-Benzoyl-α/β-D-Ribonucleosides

Entry	Nucleobase	 (0.9 eq)	NP/KI	Yield[a] (%)	α/β
1	Uracil (1 mmol)	453 mg	325/0 mg	5	–
2	Uracil (1 mmol)	453 mg	0/129 mg (0.8 eq)	28	37/63
3	Uracil (1 mmol)	453 mg	581 mg (1 eq of KI)	48	34/66
4	Uracil (1 mmol)	453 mg	473 mg (0.8 eq of KI)	55	13/87
5	Thymine (1 mmol)	453 mg	473 mg (0.8 eq of KI)	52	28/72
6	Cytosine (1 mmol)	453 mg	473 mg (0.8 eq of KI)	45	50/50
7	Adenine (1 mmol)	453 mg	473 mg (0.8 eq of KI)	51	50/50
8	N-R-guanine R = Dimethylaminomethylene (0.74 mmol)	335 mg	350 mg (0.8 eq of KI)	54	50/50

[a]The yield was calculated after purification on column chromatography.

TABLE 2 Synthesis of Acyclonucleosides

Entry	Nucleobase	Alkylating Agent	NP/KI	Yield[a] (%)
1	Uracil (1 mmol)	 200 mg	470 mg (0.8 eq of KI)	50
2	Thymine (1 mmol)	 200 mg	470 mg (0.8 eq of KI)	45
3	Adenine (1 mmol)	 200 mg	470 mg (0.8 eq of KI)	50

[a]The yield was calculated after purification on column chromatography.

further interest in synthetic nucleoside chemistry. Other examples are under investigation and will be reported elsewhere.

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