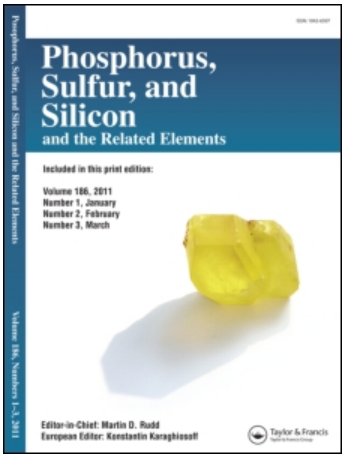

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Synthesis of Certain 2′-Deoxy-3′,5′-di-*O*-benzyl-4′-thionucleosides Using Natural Phosphate Doped with Trifluoromethanesulfonic Acid as Catalyst

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*A series of 2′-deoxy-4′-thionucleosides are synthesized by coupling 1-O-acetyl-2-deoxy-3,5-di-O-benzyl-4-thio-D-*erythro*-pentufuranose to trimethylsilylated nucleobases using natural phosphate doped with trifluoromethanesulfonic acid as catalyst. The detail of this one-pot method and the comparison between the percentage of α and β-2′-deoxy-4′-thionucleosides with those described previously are also reported.*

Keywords 2′-Deoxy-3′,5′-di-*O*-benzyl-4′-thionucleosides; natural phosphate; trifluoromethanesulfonic acid

INTRODUCTION

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 advantageous over conventional homogeneous acid catalysts because 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 (NP)[3] is especially attractive because of its low cost, reusability, flexibility in acid strength, ease of

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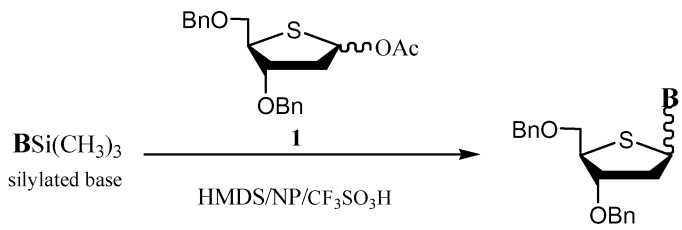
handling, environmental compatibility, non-toxicity, and experimental simplicity.[4]

4′-Thionucleoside analogs, in which the furanose ring oxygen is replaced by a sulfur atom, increasingly have become of interest owing to their demonstrated resistance toward phosphorolytic cleavage and their broad range of biological activity.[5] Since the first report by Reist et al.,[6] the synthesis of 4′-thionucleosides has mostly been carried out using the Vorbruggen-type condensation between an appropriate 4-thiopentofuranose and a silylated nucleobase.[7] Groups have reported the synthesis of 2′-deoxy-4′-thioribonucleosides from the corresponding 4′-thioribonucleosides. For instance, Haraguchi et al.[8] have recently reported the stereoselective synthesis of 2′-deoxy-4′-thioribonucleosides based on electropholic glycosidation of 4- thiofuranoid glycols. Moreover, Inouie et al.[9] developed a practical synthesis of 2′-deoxy-4′-thioribonucleosides using a radical reaction of the corresponding 2′-alpha- bromo derivatives. Although the Pummerer-type thioglycosidation[10] is also available as an alternative, a serious drawback commonly seen in these methods is the lack of the desired β–stereoselectivity. For example, in the synthesis of 2′-deoxy-4′-thionucleosides, the α-anomer was obtained as the major product in many cases. Surprisingly, even in the synthesis of 4′-thioribonucleosides, where neighboring group participation by the 2-*O*-acyl group can be expected, the β-anomer is formed only in a slight excess. This stereochemical outcome limits the accessibility to a variety of 4′-thionucleosides that are necessary for the efficient study of structure–activity relationship in medicinal chemistry.[11]

Vorbruggen et al.[12] described a one-pot nucleoside synthesis combining three steps in one: (a) silylation of the hetrocyclic base, (b) silylation of the triflate or nonaflate salts to form trimethylsilyl triflate (TMSOTf), and (c) nucleoside synthesis with 1-O-acyl in the presence of a Friedel–Crafts catalyst. Reagents used to perform this reaction are mixture of trimethylsilyl chloride (TMSCl), hexamethyldisilazane (HMDS), and trifluoromethane sulfonic acid (TfOH) in an effort to produce TMSOTf in situ.

With all these considerations in mind, we have recently reported a new one-pot reaction using the inexpensive NP doped with potassium iodide or iodine as a catalyst instead of TMSOTf, $TMSClO_4$, or iodotrimethylsilane to perform the glycosylation reaction. We showed that the β-ribonucleoside was obtained as a major isomer and in good yield.[11] These results led us to extend this new short and efficient method to the synthesis of a number of 2′-deoxy-4′-thionucleosides (Scheme 1) using a moisture-insensitive catalyst system (HMDS/NP/CF_3SO_3H) instead of TMSOTf.



B: uracil, thymine, acetyl cytosine, adenine, acetyl guanine and 5-azacytosine

SCHEME 1

EXPERIMENTAL

Natural Phosphate Characteristics and Preparation of the Catalyst

NP comes from an ore extracted in the region of Khouribga, Morocco (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 $0.005\ cm^3\ g^{-1}$.

Preparation of the Catalyst

To 3g of NP in 10 mL of CH_2Cl_2 was added 1 mL of CF_3SO_3H. The flask was stopped tightly, and the mixture was stirred for 10 min, and then evaporated to dryness.

Typical Procedure: Preparation of the Nucleoside

A suspension of the nucleobase (1 mmol) in hexamethyldisilazane (4 mL) and ammonium sulfate (catalytic amount) was heated at reflux until a clear solution was obtained. To this solution was added a solution of the sugar (0.9 mmol) in acetonitrile (5 mL), NP/CF_3SO_3H (500 mg), and the mixture was heated (80°C) overnight. The resulting suspension was filtered, and the precipitate was washed with dichloromethane. The filtrate was evaporated, and the residue was purified by column chromatography.

TABLE I Synthesis of 2′-Deoxy-3′,5′di-*O*-benzyl-4′-thio-α/β-D-thionucleosides

Entry	Nucleobase (1 mmol)	Sugar 1 (0.9 eq)	NP/CF_3SO_3H mg/mg	Yield* %	α:β
1	Uracil	354 mg	0/150	<5	–
2	Uracil	354 mg	350/0	<10	50/50
3	Uracil	354 mg	350/150	53	55/45
4	Thymine	354 mg	350/150	35	66/34
5	Acetyl cytosine	354 mg	350/150	56	50/50
6	Adenine	354 mg	350/150	50	50/50
7	Acetyl guanine	354 mg	350/150	44	50/50
8	5-Azacytosine	354 mg	350/150	44	50/50

*The yield was calculated after purification on chromatography column.

RESULTS AND DISCUSSION

To this end, we have first synthesized the 1-*O*-acetyl-2-deoxy-3,5-di-O-benzyl-4-thio-D-*erythro*-pentufuranose (**1**) following the same procedure reported by Walker.[13] Then, to assess the influence of NP doped with different catalysts on the coupling reaction to find the most effective conditions, several experiments were carried out. From these studies, it was noted that the desired 2′-deoxy-4′-thionucleosides were obtained in modest yields by using NP and trifluoromethansulfonic as catalyst at 80°C in acetonitrile overnight.

As depicted in Table I, when either NP and CF_3SO_3H were used alone, the coupling reaction of 4-thiosugar **1** to bis-(trimethylsilyl)uracil gave the 2′-deoxy-4′-thionucleoside mixtures in less than 5% and 10% yields, respectively. As can be seen in the subsequent examples, the yield increased significantly when NP doped with CF_3SO_3H was used. We have also noted that the percentages of α- and β-anomers are mostly the same. This result represents a significant improvement in the production of the β-anomer previously reported procedures in which the α-anomers are major products (α:β ratio changes from 9:1 to ~2.8:1).[10b,15–18]

This finding encouraged us to examine the use of other "inexpensive" catalysts in order to improve the yield of these coupling reactions. Thus, when potassium iodide was used instead of trifluoromethanesulfonic acid, the yield was dramatically decreased with a slight excess of α-anomers. Also, we did not observe any improvements in the results by using tin (IV) chloride, titanium chloride, or trifluoroacetic acid.

All 2′-deoxy-4′-thionucleosides were characterized by ^1H NMR and by comparison with literature data.[15–18]

CONCLUSION

We have developed a practical and novel natural phosphate-catalyzed glycosylation reaction. We showed that NP doped with trifluoromethanesulfonic acid is a mild and inexpensive catalyst for the preparation of 2′-deoxy-3′,5′di-*O*-benzyl-4′-thio- α/β-D-thionucleosides with modest stereoselectivity towards β-isomer. The advantages of this method are the easy workup and applicability in synthetic nucleosides chemistry.

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