A Procedure for Facile Synthesis of Nucleosides Using N, O-Bistrimethylsilylacetamide in the Presence of Natural Phosphate Coated with Potassium Iodide

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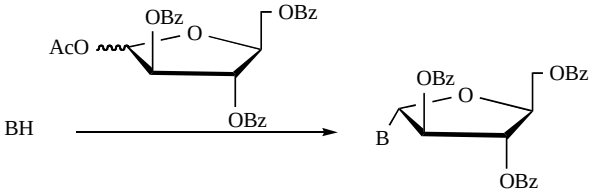
Abstract: Several α-D/L-arabino and β-D/L- xylonucleosides were synthesized in good yields under mild conditions by N-glycosylation of 1-O-acetyl D/L- arabino, and xylofuranose, with silylated nucleobases (uracil, thymine and 6-azauracil) in acetonitrile using natural phosphate (NP) coated with potassium iodide in BSA as catalyst.

Keywords: N-Glycosylation, D/L nucleosides, natural phosphate, catalyst.

The synthesis and the biological evaluation of nucleoside analogs with the natural D and unnatural L configuration have been subjects of some interest, but until recently, the activities of most nucleosides were associated only with the D isomers. [1].

Traditional methods of nucleoside analogue synthesis involve either a glycosylation reaction between a nitrogenous aromatic base and an activated sugar intermediate or a derivatization of a preformed nucleoside. The glycosylation reaction is the most commonly used approach for the synthesisof nucleosides and has been applied to the synthesis of diverse nucleosides [2]. Vorbruggen *et al*. introduced the use of Friedel-Crafts catalysts to promote the glycosylation reaction [3]. The typical Vorbruggen reaction requires persilylation of the nucleobase and then reaction with trimethylsilyl triflate activated sugar to form the desired acyl protected nucleoside. The regioselective glycosylation driven by a thermodynamic equilibrium between the hydrogens of the bases makes this method particularly attractive [4]. Whereas, the Vorbruggen [5] reactions frequently conducted as a two-step operation, our approach was to combine the two steps into a one-pot reaction with solid phase catalysts. The reactions mediated by solid phase catalysts are of growing interest because they offer advantages such as ease of setup, mild conditions, rapid reactions, increased selectivity and yields of the products, and low cost. In an effort to develop new practical and economic catalysts, we and others recently investigated the use of natural phosphate (NP) alone or doped in various chemical transformations [6]. These types of catalysts represent an important environmentally friendly alternative to toxic and expensive reagents otherwise required for the reactions [7].

Recently, we have reported that the reaction of 2, 4-bis(trimethylsilyloxy)uracil with acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in the presence of NP/KI[8] or NP/I_2 [9] selectively gives α/β protected uridine in a fair yields. Here we describe our synthetic efforts to develop a new set of reaction conditions, using bis- trimethylsilylacetamide (BSA) and natural phosphate coated with potassium iodide (NP/KI), under which acetyl-2,3,5-tri-O-benzoyl- D or L-pentofuranose (Arabinose and Xylose) reacts directly with persilylated nucleobase (uracil, thymine and 6-azauracil) , yielding efficiently in one–pot to the desired nucleosides (Scheme **1**).



Scheme 1. Conditions: BSA/NP/KI/CH_3CN, BH= Uracil, Thymine, 6-Azauracil.

The first, set of experiments was carried out using uracil and acetyl 2,3,5-tri-O-benzoyl-L-arabinofuranose as a model to evaluate different catalyst and optimize the catalytic systems (Table **1**). Preliminary reactions were carried out in acetonitrile at 80°C with BSA (1ml, excess) and NP/KI (0.8eq of KI) as catalyst. We observed that when the amount of protected L-arabinose was increased from 0.25 eq to 0.75 eq, the yield of nucleoside also improved (Table **1**,

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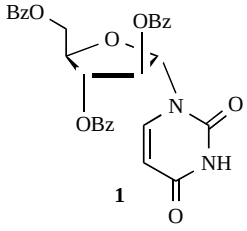
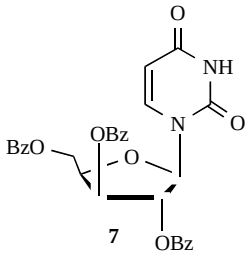
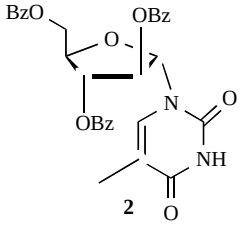
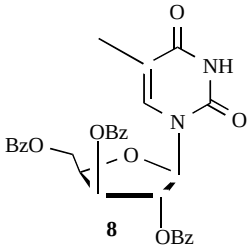
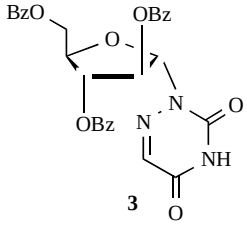
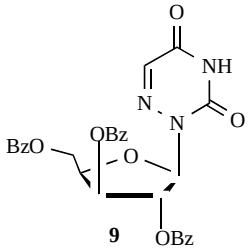
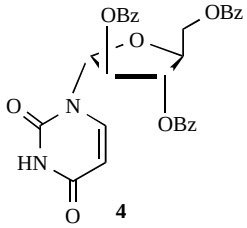
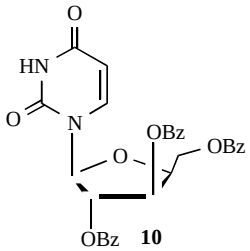
Table 1. Optimisation of N- Glycosylation between Uracil and L-Protected Arabinose

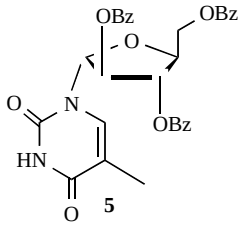
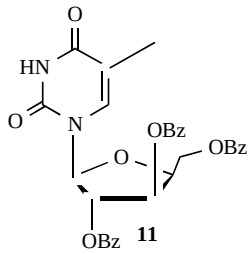
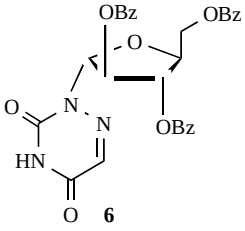
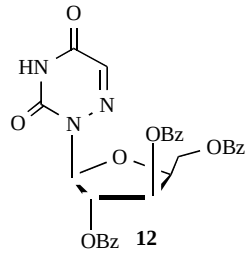
Entry	Sugar	Catalyst	Yield (%)
1	0.25 eq	NP/KI	43
2	0.5eq	NP/KI	50
3	0.75 eq	NP/KI	80
4	1eq	NP/KI	45
5	0.75 eq	NP	5
4	0.75 eq	Al_2O_3/KI	30
5	0.75 eq	SiO_2/KI	18
6	0.75 eq	C/KI	12
7	0.75 eq	Montmorillonite K10/KI	40

Conditions: Uracil(1mmol), BSA, CH_3CN, L-protected arabinose, catalyst(0,8eq), reflux 3h.

Table 2. NP/KI/BSA Catalyzed N-Glycosylation of Nucleobases with Protected D/L-Pentofuranose

Entry	Sugar 0.75 eq	Compounds	Yield	Entry	Sugar 0.75 eq	Compounds	Yield
1	D-arabinose	 **1**	74%	7	D-xylose	 **7**	72%
2	D-arabinose	 **2**	64%	8	D-xylose	 **8**	73%
3	D-arabinose	 **3**	60%	9	D-xylose	 **9**	56%
4	L-arabinose	 **4**	80%	10	L-xylose	 **10**	55%

(Table 2). Contd…..

Entry	Sugar 0.75 eq	Compounds	Yield	Entry	Sugar 0.75 eq	Compounds	Yield
5	L-arabinose	 **5**	60%	11	L-xylose	 **11**	57%
6	L-arabinose	 **6**	60%	12	L-xylose	 **12**	56%

Conditions: Nucleobase(1mmol), BSA, CH_3CN, D/L-protected arabinose and xylose, catalyst(0,8eq), reflux 3h.

entries 1-3). Experiments carried out with other heterogeneous media impregnated with potassium iodide such as Al_2O_3/KI, SiO_2/KI, activated charcoal (Norit) C/KI and Montmorillonite K10/KI revealed that these catalysts, in general gave lower yields of the nucleosides (Table **1**, entries 4-6).

In order to extend the scope of the present reaction, several N-glycosylation reactions were performed and the results are shown in Table **2**. In every case, the desired β or α nucleosides were obtained in good yields. Such combination of high yield and stereoselectivity (α for D/L-Arabinonucleosides and βfor D/L-Xylonucleosides) has not been reported in the N-glycosylation utilizing NP/KI as catalyst.

All of nucleosides Fig. (**1**) are in agreement with previously published analysis [10].

The mechanism of the above N-glycosylation could be depicted as follows (Fig. **1**): Uracil reacts with BSA to give silylated uracil and the excess of BSA may react with NP/KI to give $(CH_3)_3Si$-I. The later will react with the O-acetyl 2,3,5-tri-O-benzoyl-β-D-Xylofuranose to afford 1-iodo-2,3,5-tri-O-benzoyl-β-D-Xylofuranose **A** [11]. Then, the silylated base will react with the compound **A** to produce the target β xylonucleoside **B** [12].

CONCLUSION

In summary, we have described an efficient one–pot N-glycosylation using BSA and NP/KI. This method could be a nice addition to the existing processes in the nucleoside synthesis because of its mild reaction condition, simple work-up procedure, high yields and cheap catalyst.

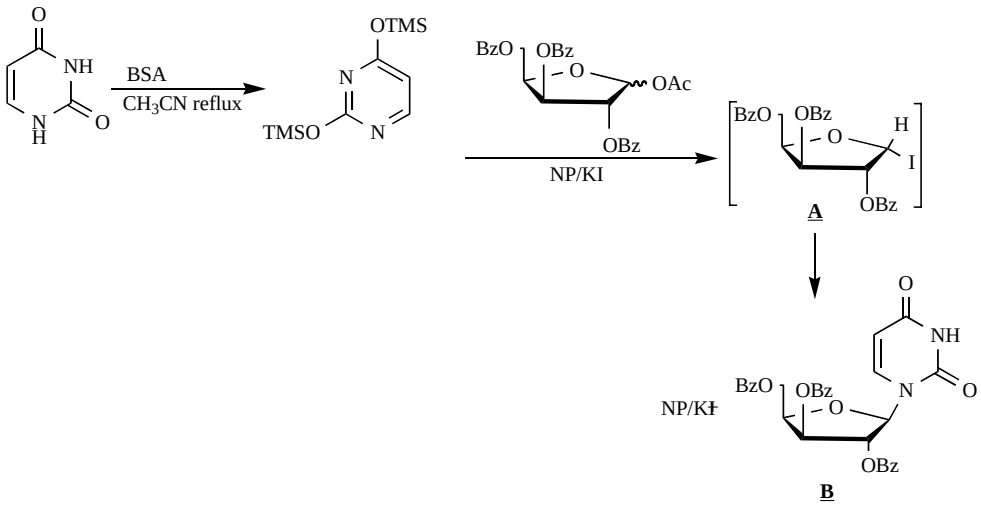


Fig. (1). Possible mechanism of the formation of β xylofurano-nucleoside.

EXPERIMENTAL SECTION

General Remarks

The NMR spectra were recorded on a Bruker AC 300 MHz spectrometer. Chemical shifts were reported in scale (ppm) relative to TMS as a standard and the coupling constants J values are given in Hz. EI mass spectra were recorded on a Varian MAT 311A spectrometer. TLC was performed on 60 F254 precoated plastic plates silica gel (Merck). Column chromatography was performed on silica gel (Baker, 30-60 μm). All solvents were distilled and dried before using.

General Experimental Procedure

A suspension of uracil (112 mg, 0.892 mmol) in bistrimethylsilylacetamide (BSA) (1 ml), ammonium sulfate (catalytic amount, 5 mg), and acetonitrile (2.5 ml) was heated at reflux until a clear solution was obtained (30min). To this solution was added acetyl 2,3,5-tri-O-benzoyl-L-Arabinofuranose (0.669 mmol, 0.75eq) and NP/KI (422 mg, 0.8 eq of KI) and the mixture was heated (80°C) for 3h. The resulting suspension was filtered and the precipitate was washed with dichloromethane. The filtrate was evaporated and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 98/2) to give the desired nucleoside with 80% yield.

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REFERENCES AND NOTES

[1] Raney, A. K.; Hamatake, R.K.; Hong, Z. Agents in clinical development for the treatment of chronic hepatitis B. *Expert Opin. Investig. Drugs*, **2003**, *12*, 1281.

[2] Mathe, C.; Gosselin, G. L-nucleoside enantiomers as antivirals drugs. *Mini Rev. Antiviral Res.*, **2006**, *71*, 276.

[3] Vorbruggen, H.; Ruh-Pohlenz, C. Synthesis of nucleosides: *Org. React.*, **2000**, *55*, 1.

[4] Vorbruggen, H.; Hofle, G. On the Mechanism of nucleoside synthesis. *Chem. Ber.*, **1981**, *114*, 1256.

[5] (a)Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. Nucleoside synthesis with trimethylsilyl triflate and perchlorate as catalyst. *Chem. Ber.*, **1981**, *114*, 1234, (b) Vorbruggen, H.; Bennua, B. A new simplified nucleoside synthesis. *Chem. Ber*., **1981**, *114*, 1279.

[6] (a) Sebti, S.; Zahouilly, M.; Lazrek, H.B.; Mayoral, J.A.; Macquerrie, D.J. Phosphates: new generation of liquid-phase heterogeneous catalysts in organic chemistry. *Curr. Org. Chem*., **2008**, *12*, 203. (b) Zahouily, M.; Elmakssoudi, A.; Mezdar, A.; Bahlaouan, B.; Rayadha, A.; Sebti, S.; Lazrek, H. B. Three components coupling catalysed by $Na_2CaP_2O_7$ synthesis of α-amino phosphonates under solvent-free conditions at room temperature. *Lett. Org. Chem.*, **2005**, *2*, 428. (c) Zahouily, M.; Mezdar, A.; Elmakssoudi, A.; Mounir, B.; Rayadh, A.; Sebti, S.; Lazrek, H. B Comparison of different Lewis acids supported on natural phosphate as new catalysts for chemoselective dithioacetalization of carbonyl compounds under solvent-free conditions. *ARKIVOC*, **2006**, *31*. (d) Alahiane, A.; Rochdi, A.; Taourirte,M.; Redwane, N.; Sebti, S.; Engels, J. W.; Lazrek, H. B. Building blocks for polyamide nucleic acids: facile synthesis using potassium fluoride doped natural phosphate as basic catalyst. *Nucleosides Nucleotides Nucleic Acids*, **2003**, *22*, 109.

[7] 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 μm2 g-1 (nitrogen adsorption) and the total pore volume was 0.005 cm3 g-1.

[8] Lazrek, H.B.; Rochdi, A.; Redwane, N.; D. Ouzebla, D.; Vasseur J.J. A one-pot synthesis of D-ribonucleosides using natural phosphate doped with KI in HMDS. *Lett. Org. Chem*., **2006**, *3*, 313.

[9] (a) Lazrek, H.B.; Ouzebla, D.; Baddi, L; Vasseur, J.J. Glycosylation reaction *via* a mild and efficient one-pot reaction using doped natural phosphate with iodine as catalyst. *Nucleosides Nucleotides Nucleic Acids*, **2007**, *26*, 1095. (b) Lazrek, H.B.; Baddi, L.; Smietena, M.; Sebti, S.; Zahouily, M.; Vasseur, J.J. One-pot synthesis of antiviral acyclovir and other nucleosides derivatives using doped natural phosphate as lewis acid catalyst. *Nucleosides Nucleotides Nucleic Acids*, **2008**, *27*, 1107.

[10] Gosselin, G.; Bergogne, M-C.; Imbach, J. L. Synthesis and antiviral evaluation of β-L-Xylo-fuanosyl nucleosides of the five naturally occurring nucleic acid bases. *J. Heterocycl. Chem*., 1**993**, *30*, 1229, (b) Wang, Z.; Prudhomme, d.R.; Buck, J.R.; Park, M.; Rizzo, C.J. Stereocontrolled syntheses of deoxyribonucleosides *via* photoinduced electron-transfer deoxygenation of benzoyl-protected ribo- and arabinonucleosides. *J. Org. Chem.*, **2000**, *65*, 5969.

[11] Jooko, Y.; Shin, S.B.; Shim, J.H. Facile synthesis of 2-O-iodoacetyl protected glycosyl iodides: useful precursors of 1-->2-linked 1,2-trans-glycosides. *Org. Lett.*, **2009**, *11*, 609.

[12] (a) Park, J.; Kawatkar, S.; Kim, J-H.; Boons, G-J. Stereoselective glycosylations of 2-azido-2-deoxy-glucosides using intermediate sulfonium ions. *Org. Lett*.,**2007**, *9*, 1959, (b) Van well, R.M.; Ravindranathan Kartha, K.P.; Field, R. A. Iodine promoted glycosylation with glycosyl iodides: α-glycoside synthesis *J. Carbohydr. Chem*., **2005**, *24*, 463, (c) Lam, S-N.; Gervay-hague, Solution-phase hexasaccharide synthesis using glucosyl iodides. *J. Org. Lett*., **2002**, *4*, 2039.