

A New Selective Synthesis Of D-Ribonucleosides In Acetonitrile With BSA Using NP/KI As Catalyst

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Abstract

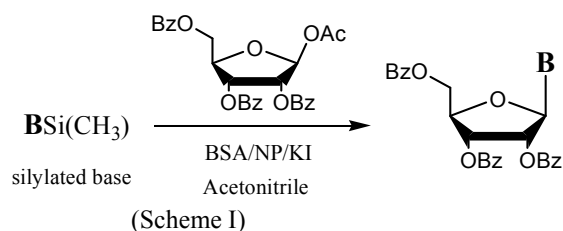
The one-step synthesis of several β -D-ribonucleosides was performed in good yields under reflux.

Keywords: D-nucleosides, natural phosphate, catalyst, one-step synthesis.

Introduction

Analogs of nucleosides are used as therapeutic agents such as antiviral agents and antitumor and more new analogues of nucleosides are being synthesized for the examination of their biological activities now.

Analogs of nucleosides have provided a productive area of chemical and biological research for over 100 years (Levene et al 1909). The monomeric units of DNA and RNA are involved in the regulation of a myriad of cellular metabolic pathways and have been the subject of intense areas of research seeking to identify therapeutic agents for a variety of diseases including viral infections, cancer, cardiovascular diseases, CNS diseases, etc. Traditional methods of nucleoside analogues synthesis involve either a glycosylation reaction between a nitrogenous aromatic base and activated sugar intermediate or a derivatization of a performed nucleoside. The glycosylation reaction has been applied to the synthesis of a vast array of diverse nucleosides (Vorbruggen, et al 2000). Furthermore, while the Vorbruggen reaction frequently conducted as a two-step operation, it is possible to perform this reaction by combining all reagents and heating (Vorbruggen et al 1981) (Bookser et al 2007) (Andrzejewska et al 2002) Among various procedures for the synthesis of pyrimidine nucleoside, glycosylation reaction by Hilbert-Johnsen is the simplest one with wide application (Montgomery et al 1966) (Prystas et al 1966). The acid-catalysed fusion of 1,2,3,5-tetra-O-acetyl-D-ribofuranose and related D-ribofuranose derivatives with various nucleobases to provide β -D-ribonucleosides in variable yield (Sebti et al 2008) (Zahouily et al 2005) (Zahouily et al 2006) (Zahouily et al. 2004) (Alahianet al 2003) (Sebtiet al 2002) (Zahouily et al 2005). Surface-mediated solid phase reaction are of growing interest because of (i) environmentally friendly processes they offer, when compared to conventional reaction conditions (ii) advantages as ease of set up, mild conditions, rapid reactions, selectivity, increased 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 NP in various chemical transformations (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). These types of catalysts represent an important environmentally friendly alternative to reactions otherwise toxic and expensive. Furthermore many efforts are done to promote NP as catalyst (Lazrek et al 2007) (Lazrek et al 2008). Recently we reported (Adinolfiet al 2003) several organic transformations catalyzed by the NP doped with KI or I₂ as a solid catalyst. The later is very cheap, readily prepared in the laboratory and can be stored for long time without any significant loss catalytic activity. As a part of our continuing effort to explore the catalytic potential of NP/KI, we revealed that NP/KI may efficiently promote glycosylation reaction resulting in the formation stereoselectively of β -D-ribonucleosides. (Scheme I)



Here we show by synthetic investigation of reaction conditions (NP/KI, BSA) that acetyl-2,3, 5-tri-O-benzoyl- β -D-ribofuranose reacts directly with persilylated nucleobase (Uracil, Thymine, 6-Azaauracil and Iodouracil), resulting in an efficient one pot synthetic approach to the desired nucleoside.

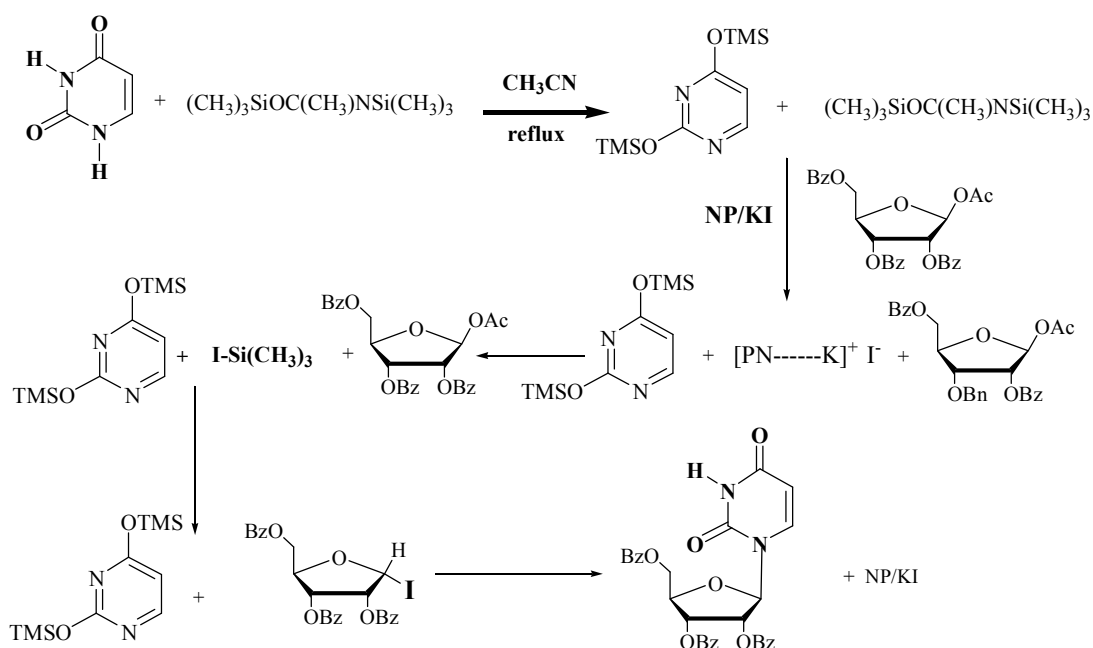
A first set of experiments were carried out using uracil and acetyl 2,3,5-tri-O-benzoyl- β -D- ribofuranose as model. When NP/KI T in acetonitrile at 80°C with BSA (1ml.)). We observed that the good yield (78%) (Table1 entry 3) is obtained when NP/KI in acetonitrile (2.5 ml). The other blank experiments carried out in the presence of Al_2O_3/KI , , revealed that the yield of nucleoside is decreasing (Table 1, entries 5) and we observed not reaction in the presence of SiO_2/KI . It is noted that the work up involves only filtration before evaporation of the solvent and both the solvent and the catalyst could be easily recovered after completion of the reaction. Other nucleobases (entries 7-9) were then also subjected to N-glycosylation and found to afford the corresponding ribonucleosides in 40%, 60% and 3% yield respectively. This procedure appears to be regioselective (N1 isomer for pyrimidine) and stereoselective (only the β isomer).

Table I: Optimisation of the N-Glycosylation of uracil and D-ribose reaction conditions

Entry	Nucleobase	Catalyst	Yield (%)	Acetonitrile
<u>1</u>	Uracil	NP/KI	54	10 ml
<u>2</u>	Uracil	NP/KI	60	5 ml
<u>3</u>	Uracil	NP/KI	78	2.5 ml
<u>4</u>	Uracil	NP/KI	67	1 ml
<u>5</u>	Uracil	Al_2O_3/KI	47	2.5 ml
<u>6</u>	Uracil	Silica / KI	No reaction	2.5 ml
<u>7</u>	Azaauracil	NP/KI	40	2.5 ml
<u>8</u>	Thymine	NP/KI	60	2.5 ml
<u>9</u>	Iodouracil	NP/KI	30	2.5 ml

The reaction seems to occur via the substitution of the acetoxy group on the anomeric carbon with iodide in the first step, and TMSI is generated during the condensation step with silylated base (Hyrosova et al 2008) (Vorbruggen et al 2000). The mechanism of the above glycosylation could be depicted as follows (Scheme II): silylated uracil may react with NP/KI to give $(CH_3)_3-Si-I$. The later will react with 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose to afford 1-Iodo-2,3,5-tri-O-benzoyl- α -D-ribofuranose. Further, the complex [heterocycle]-/[NP-K]⁺ will react with iodo sugar to conduct to the desired nucleosides with the anomeric β . It is well know that Lewis acid activate the anomeric center in peracylated furanose and pyranose sugar leading to the formation of a glycosidic linkage having the 1,2-trans configuration (van Well et al 2005). The high selectivity in the glycosylation reactions using Lewis Acid ($SnCl_4$, TMSOTf.) is attributed to the neighbouring group effect of the C-2 substituent via formation of an acyloxonium ion with concomitant stabilisation of the positive charge on C-1. This also results in effective blockage of one face leads to 1,2-trans glycosylation. We carried out reaction under the same conditions as above. The exclusive formation of β -anomer is a proof that the intermediate is the iodo-2,3,5-tri-O-benzoyl- α -D-ribofuranose (SchemeII) .

SchemeII : Glycosylation reaction mechanism using BSA as a silylating agent and using of 1-O-benzoyl- β -D-ribofuranose as starting material with non participating group at 2



Conclusion

In summary, we describe two simple, efficient, and eco-friendly methods for the synthesis of D-pyrimidino-ribonucleosides using cheap and readily available catalyst (NP/KI). This methodology is an additive method to the conventional vorbruggen method.

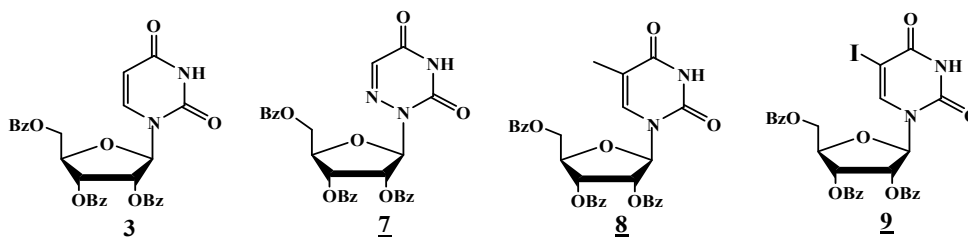
Experimental Section

General Remarks

The NMR spectra were recorded on a Bruker AC 300 MHz spectrometers. 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 (1mmol) in Bis-silylacetamide (BSA) (1 ml), ammonium sulphate (catalytic amount), and acetonitrile (2.5 ml) was heated at reflux until a clear solution was obtained (30 min). To this solution was added acetyl 2,3,5-tri-O-benzoyl- β -D-ribofuranose (0.9 eq, 453mg) 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 precipitate was washed with dichloromethane. The filtrate was evaporated and residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98/2 v/v)) to give the desired nucleoside. All the expected nucleosides were characterized by ^1H and ^{13}C NMR.



3: ▶ 2', 3', 5'-Tri-O-benzoyl- β -D-uridine

¹H NMR(CDCl₃) (300MHz)δ(ppm) ; 4.40(m, 2H, H⁵) ; 4.90(m, 1H, H⁴) ; 5.55(d, 1H, H⁵, J= 6Hz) ; 5.65(t,1H, H³) ; 5.80(t, 1H, H²) ; 6.38(d, 1H, H¹β J=5.4Hz) ; 7.44 (d, 1H, H⁶, J=6Hz) ; 7.40-8.10(m,15H, Harom Bz) et 8.10(m,6H,) ; 10.40(s, 1H, N-H).

¹³CNMR(CDCl₃)δ(ppm) ;64.01(C^{5'}) ;71.38(C^{4'}) ;75.01(C^{3'}) ;79.99(C^{2'}) ;88(C¹β) ;100.59(C⁵) ;128.43-133.70 (Ph) ; 145.09(C⁶) ; 150.33(C⁴) ; 163(C²) ;165.05- 168.77 (PhCO).

7: ▶ 2', 3', 5'-Tri-O-benzoyl- β- D-azauridine:

¹H NMR(CDCl₃) (300MHz)δ(ppm) ;4.40(m,2H, H⁵) ;4.90(m, 1H, H⁴) ; 5.65(t, 1H, H³) ;5.80(t,1H,H²) ; 6.38 (d,1H,H¹β,J=5.4Hz) ;7.44 (s,1H,H⁵) ;7.40-8.10(m,15H, Harom Bz) ;10.40(s, 1H, N-H). ¹³C NMR (CDCl₃) δ(ppm) ; 63.66(C^{5'}) ; 71.38(C^{4'}) ; 75.09(C^{3'}) ; 79.99(C^{2'}) ; 88 (C¹β) ; 128.43-132.70 (Ph) ; 135.36(C⁵) ; 149.26(C⁴) ; 155.93(C²) ;165.05- 168 (PhCO) .

8: ▶ 2', 3', 5'-Tri-O-benzoyl- β- D-thymidine

¹H NMR(CDCl₃) (300MHz)δ(ppm) ; 1.95(s, 3H, CH₃) ; 4.,40(m, 2H, H⁵) ; 4.90(m,1H, H⁴) ;5.5(t,1H, H³) ; 5.8(t,1H, H²) ; 6.35(d,1H, H¹β J=3.6 Hz) ; 7.40 (s,1H, H⁶) ;7.40-8.10(m,15H, Harom Bz) ; 9.80(s, 1H,N-H). ¹³CNMR(CDCl₃)δ(ppm) ;12.17(CH₃) ;62.90(C^{5'}) ;71.38(C^{4'}) ;75.09(C^{3'}) ;79.99(C^{2'}) ;87(C¹β) ;110(C⁵) ;128.43-132.70(Ph) ;142.07(C⁶) ;151.30(C⁴) ;163.80(C²) ;165.05-168(PhCO).

9: ▶ 2', 3', 5'-Tri-O-benzoyl- β -D-iodouridine

¹HNMR(CDCl₃)(300MHz)δ(ppm) 9.80(s,1H,N-H), 7.44(s,1H,H⁶),6.38(d,1H,H¹βJ=5,4Hz),5.80(pseudot,1H,H²)5.65(pseudot,1H,H³)4.90(m,1H,H⁴)4.40(m,2H, H⁵)8.10-7.40(m,15H,HaromBz). ¹³CNMR(CDCl₃)δ(ppm) 87(C¹β),63.66(C^{5'}),71.38(C^{4'}),75.09(C^{3'}),79.99(C^{2'}),128.43-132,70(Ph) ,165.05- 168(PhCO) ,135.36(C⁵) ; 142.07(C⁶) ; 149.26(C⁴) ; 155.93(C²)

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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 μm , which is rich in phosphate. The structure of NP is similar to that of fluorapatite $[\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2]$, as shown by X-ray diffraction and chemical analysis. The surface area of NP was measured at $\mu\text{m}^2 \text{g}^{-1}$ (nitrogen adsorption) and the total pore volume was $0.005 \text{cm}^3 \text{g}^{-1}$.

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