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Nucleoside Analogues Synthesis using Natural Phosphate Doped with I_2 (NP/I_2) in HMDS

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Abstract
Several D-ribonucleosides are prepared from1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranoside and trimethylsilylated nucleobases under mild conditions by using natural phosphate doped with I_2 as catalyst
Keywords: Natural Phosphate doped with I_2, one-step seynthesis. α/β-D-ribonucleosides

Introduction

For a few decades, sugar-modified nucleosides have provided important leads.The nucleoside analogues have a game biological activity cover all the large axes with chemotherapy to knowing, activity cardiovascular (Stein and al 1975), antiviral (Bolch and al 1974), pesticide (Hoffman and al 1976), antibiotic (Suhadolkin and al 1970) and anti-cancer (Burchenal and al 1975) considering their importance and their place primarily in chemotherapy. For example, thiazofurin is a C-nucleoside which has been shown to inhibit the inosine 5'-monophosphate dehydrogenase (IMPDH), thus inducing a shutdown of the guanine nucleotide synthesis and causing the apoptosis of human erythroleukemia cells. Ribavirin, a synthetic nucleoside, in combination with the pegylated .

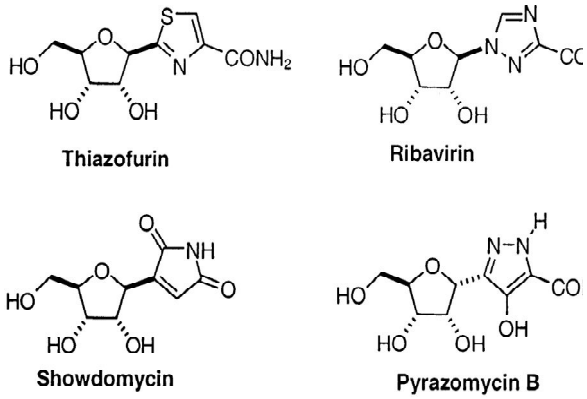


Figure 1: **Structure of some potent five-membered ring nucleosides**.

The solid-liquid heterogeneous synthesis in is studied more the most, the advantages of this new method are : The reactions proceed under conditions simplicity and oft, the products obtained clean and are easily separated from the relational medium. Many reagents solids were used in these reactions alumina (Lam and al 1974), Celite (Khan and al 1975), silica (Hudlicky and al 1974), zeolite (Clark and al 2002), this last have the advantages such as: non-toxicity and experimental simplicity (Zahouily and al 2004).The nucleoside analogues are synthesized by using rock phosphate doped by KI in the HMDS in the reaction of glycosylation ((a)Taourirt and al 2005) (b)Lazrek and al 2006)(c)Lazrek and al 2007)(d) Lazrek and al 2008) (e) Baddi and al 2010)(f) Lazrek and al 2011)). Recently, various types of inorganic synthesis. Natural phosphate (NP) is an important mining wealth of Morocco. Many investigations were performed in our laboratory to valorise the use of (NP) in heterogeneous catalysis (Alahiane and al 2003).In this respect, and in connection with our other work on the use of natural phosphate as a catalyst (Rochdi and al 2003), According to literature, several reactions were carried out by using iodine (I_2) like catalyst in the HMDS (Karimi and al 2000) .we now report a new one pot novel method using as a catalyst inexpensive natural phosphate doped with I_2 instead of TMSOTf, $TMSClO_4$, $SnCL_4$, or $(CH_3)_3SiI$ to perform the glycosylation reaction (scheme1).

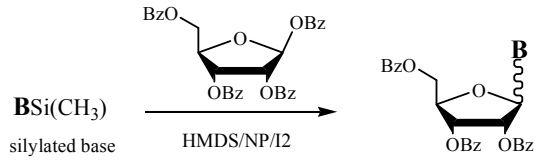


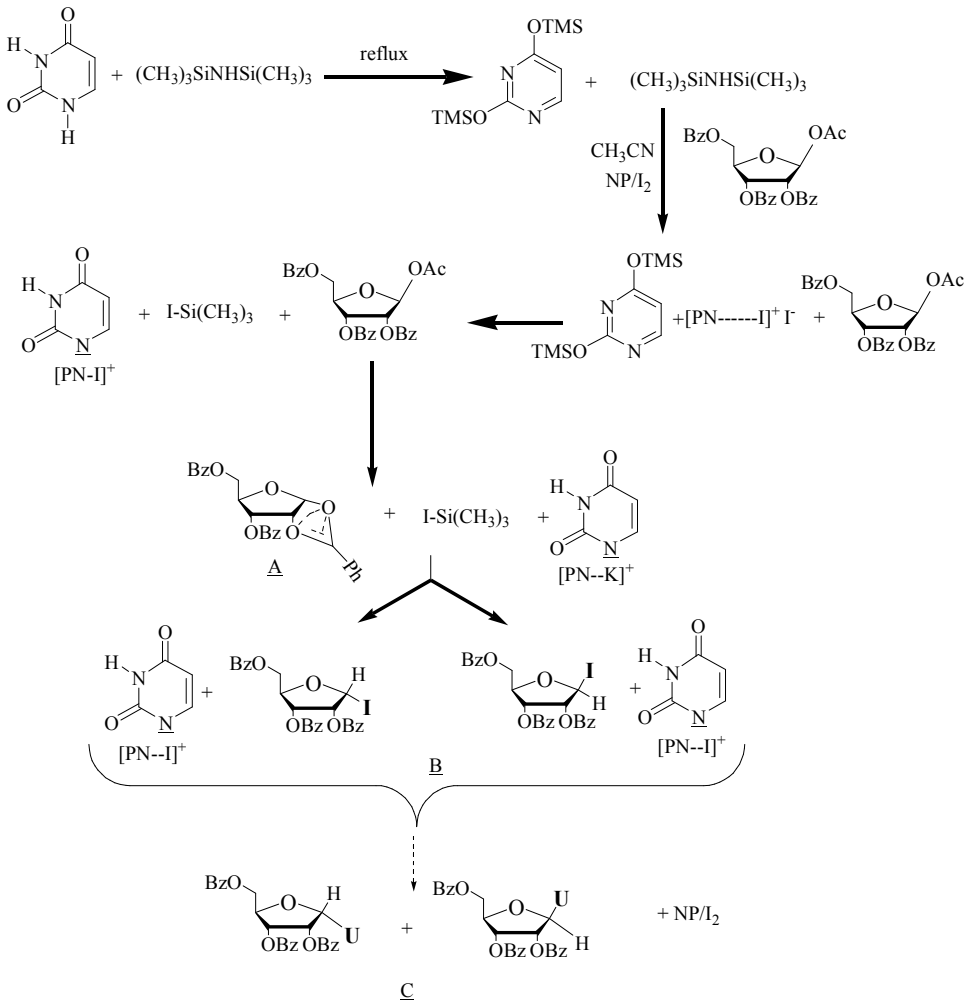
Table 1: Synthesis of 2', 3, 5'-tri-O-benzoyl-α/β-D-ribonucleosides

Entry	Nucleobase	NP/I_2	Yield%	α/β
1	Uracil	325/0	5	……
2	Uracil	NP/I_2 (1eq of I_2)	40	33/67
3	Uracil	NP/I_2 (0.5eq of I_2)	47	50/50
4	Uracil	NP/I_2 (0.2eq of I_2)	62	22/78
5	Uracil	**Silice / I_2** (0.2eq of I_2)	55	20/80
6	Uracil	**Al_2O_3 / I_2**(0.2eq of I_2)	48	20/80
7	Thymine	NP/I_2 (0.2eq of I_2)	55	10/90
8	Cytosine	NP/I_2 (0.2eq of I_2)	52	10/90
9	Adenine	NP/I_2 (0.2eq of I_2)	55	15/85
10	N-DMF-guanine	NP/I_2 (0.2eq of I_2)	35	50/50

Results and discussion

As shown in Table1,when either NP 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 % .As can be seen in the subsequent examples, the yield increased when NP doped with I2 was used. For example, in entry 2,3,4 the desired ribonucleoside was obtained as a major isomer and in good yield (62%) by using NP/I2 corresponding to 0.2 eq of I_2.in acetonitrile at 1050 C overnight. To study the difference between different the solid catalysts ,the silica doped with lode (entry5) and the alumina doped with lode (entry 6)are used in glycosylation and give 55% ,48 % yield respectively, According to the experiment this shows that the natural phosphate is more effective thane other solids catalyst.This procedure appears to other nucleobases(entries 7-10).were then also subjected toN-glycosylation and found to afford the corresponding nucleosides in 55%, 52%, 55%, 35% yields respectively.This reaction is sterioselective and give one isomer N-1 for pyrimidine(Uracil,Thymine,cytosine)and the N-9 for purine (Adenine,Nac–Guanine).*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. The mechanism of the above glycosylation could be depicted as follows (Scheme2): silylated uracil may react with NP/KI to give $(CH_3)_3$-Si-I.The later will reac with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose to afford 1-Iodo-2,3,5-tri-O-benzoyl-α,β-D-ribofuranose Further, the complex [heterocycle]-/[NP-I]+ will react with iodo sugar to conduct to the desired nucleosides with the anomerie (α,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.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 to1,2-trans glycosylation.We carried out reaction under the same conditions as above.The exclusive formation of α,β-anomer is aproof that the intermediate is theIodo-2,3,5-tri-O-benzoyl-α,β-D-ribofuranos.

Scheme2. Standard Vorbru1ggen Glycosylation Reaction Conditions



Conclusion

In summary, we describe a simple, efficient, and eco-friendly method for the synthesisof D-ribonucleosides using cheap and readily available catalyst (NP/I_2). This methodology is an additive method to the conventional, but makes it significant under the umbrella of environmentally greener and safer processes.

Experimental Section

Preparation of NP doped with I_2 (PN/I_2) 4/1

759mg of I_2 and 5ml of methanol chloride was putted in a flake, after 3min of stirring 3g of Natural phosphate (NP) was added, after the mixture was evaporated.

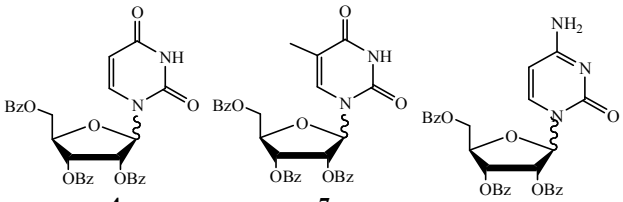
Typical procedure for one –pot synthesis

To uracil (112 mg,1 mmol) was added hexamethyldisilazane (HMDS) (4mL) and ammonium sulphate (10 mg).The mixture was refluxed for two hours.To the obtained clear solution was added 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (453mg,0.9mmol),NP/I_2 (473mg)and acetonitrile(5mL). After being refluxed overnight,the mixture was filtered and the solvent evaporated. The crude product was purified by column chromatography.The desired product was obtained with 62% yield

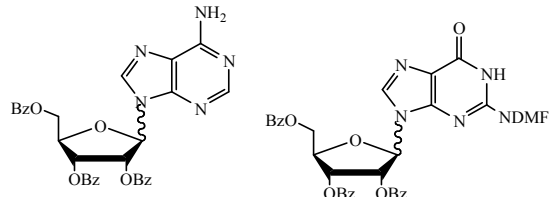
General Remarks

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.

Parameters of the ^{1}H NMR and ^{13}C NMR spectra



4 **7** **8**



9 **10**

►2', 3', 5'-Tri-O-benzoyl- α, β- D-uridine 4

^{1}H NMR($CDCl_3$) (300MHz)) δ(ppm) 4 .40(m, 2H, H'5) ; 4.90(m,1H, H'4) ;5.55(d, 1H, H5, J= 6Hz) ; 5.65(pseudot,1H, H'3) ; 5.80(pseudo t, 1H, H'2) ; 6.30(d, 1H, H'1β J=5.4Hz) ; 6.35(d, 1H, H'1α, J=3,6 Hz) ; 7.39 (d, 1H, H6, J=6Hz) ; 7.40-8.10(m,15H, Harom Bz) ;10.40(S, 1H, N-H).

^{13}C NMR ($CDCl_3$) δ(ppm) ; 63.73 (C5') ; 71.40 (C4') ; 75.10(C3') ; 80(C2') ;86 (C1'α) ; 88(C1'β) ; 100.59 (C5); 128.43-135.70 (Ph) ; 145.09 (C6); 150.33 (C4)162,90 (C2) 165.05-169.11 (PhCO)

►2', 3', 5'-Tri-O-benzoyl- α ,β-D-thymidine 7

^{1}H NMR($CDCl_3$) (300MHz)δ(ppm) ;1.95(s,3H, CH3) ;4.40(m, 2H, H'5) ;4.90(m,1H, H'4) ;5,5(pseudo t, 1H, H'3) ; 5.8(pseudot , 1H, H'2) ; 6.40(d, 1H, H'1β J=3.6 Hz) ;6.45(d, 1H, H'1α, J=6,3 Hz); 7.39 (s, 1H, H6) ; 7.40-8.10(m,15H, Harom Bz) ; 9.80(s,1H, NH).

^{13}CNMR($CDCl_3$)δ(ppm) ;12.17(CH3) ;63.40(C5'),71.38(C4'),75.09(C3'),79.99(C2') ;85(C1'α);87 (C1'β) ;109.89(C5);128.43-132.70(Ph) ;142.07(C6);151.30(C4);164.62(C2) ;165.05 168.77(PhCO) .

►2', 3', 5'- Tri-O-benzoyl- α , β- D-cytidine 8

^{1}H NMR($CDCl_3$) (300MHz)δ(ppm) 8,40(S, 2H, NH2) 1.95(s, 3H, CH3) 7.28 (d, 1H, H6, J=7.5 Hz) 5.50(d, 1H, H5,J=7.5Hz)6.20(d, 1H, H'1α, J=3.6 Hz) 6.10(d, 1H, H'1β J=7.2 Hz). 5.95 (pseudot, 1H, H'2) 5.90(pseudo t, 1H, H'3)4.90(m, 1H, H'4) 4.40(m, 2H, H'5) 7.40-8.10(m,15H, Harom Bz)

^{13}C ($CDCl_3$) (300MHz) δ(ppm), 88 (C1'α) ; 91(C1'β), 63.65(C5'), 70.90(C4'), 75.09(C3'), 80.01(C2'), 128.43-133(Ph) ,165.05- 168 (PhCO), 97.33(C5); 144.56 (C6),145.60 (C4); 163.23(C2)

►2', 3', 5'-Tri-O-benzoyl-α ,β-D-adenosine 9

^{1}H NMR($CDCl_3$) (300MHz)δ(ppm) 8.20(s, 1H, H2) 8.15 (s, 1H, H8) 6.30(m, 2H, NH2).
6.47(s, 1H, H'1α) 6.45(d, 1H, H'1β J=5 Hz) .5.95(pseudo t, 1H, H'2) 4.90(pseudo t, 1H, H'3)4.80(m, 1H,H'4) 4.70(m, 2H, H'5) 7.40-8.10(m,15H, Harom Bz)

^{13}C($CDCl_3$)(300MHz)δ(ppm),85(C1'α) ;87(C1'β),63.38(C5'),71.34(C4'),73.77(C3'),80.66(C2'),128.43-133(Ph),165.05-168(PhCO),119.26(C5);141.77(C6);150.28(C4);153.02(C2);155.29(C8).

►N-dimethylformamide-2', 3', 5'-Tri-O-benzoyl- α ,β- D-guanosine 10

^{1}H NMR($CDCl_3$) (300MHz)δ(ppm) 3.37 (s,6H, 2CH3)8.40 (s, 1H, H8) 8.1 (s, 1H,CH,) 6.31(s, 1H, H'1α) 6.29(s, 1H, H'1β) .6.36(pseudo t, 1H, H'2) 6.19(pseudo t, 1H, H'3)4.85(m, 1H, H'4) 4.871(m, 2H, H'5) 10.80(b, 1H, NH), 7.40-8.10(m,15H, Harom Bz)

^{13}C($CDCl_3$)(300MHz)δ(ppm),86(C1'α),89(C1'β);64,95(C5'),71.88(C4'),80.17(C3'),80.37(C2'),129.46-135.17(Ph),165-166.63(PhCO).,166(CH3CO),41.27(CH3),41.54(CH3),137(CH)135.17(C5);137.27(C6);150.28(C4); 155.05(C2); 157.82(C8).

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