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Novel Approach to Synthesis of Pentofurano Nucleoside Assisted Natural Phosphate Doped with CF_3SO_3H as Catalyst

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Abstract
This article describes a method for the preparation of ribonucleosides using the solid-phase approach. 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 CF_3SO_3H (NP/ CF_3SO_3H) as catalyst.
Keywords: Natural phosphate, CF_3SO_3H, D-Ribonucleosides

Introduction

Drug discovery for antiviral chemotherapy during the last 30 years has provided effective treatments for numerous viral diseases. Although new, promising targets are being identified,nucleoside analogs remain the cornerstone of antiviral therapy .The ribonucleosides are used as therapeutic agents such as antiviral agents such as AZT, d4T, ddC, ddI, and 3TC

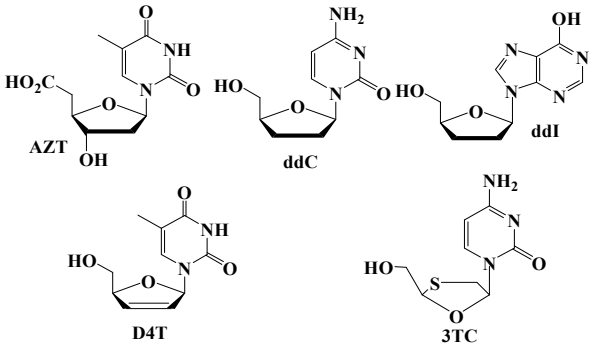
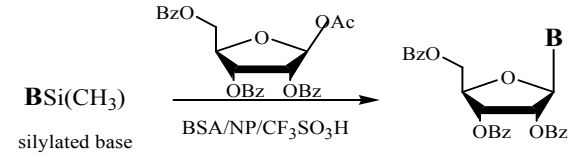


Figure 1: : AZT, d4T, ddC, ddI, and 3TC

For this raison, more new ribonucleosides are being synthesized for the examination of their biological activities now. The importance is evident, this explains the gret interest that chemists have to the synthesis of these natural molecules among them, many anticancer drugs, antitumor and antiviral grugs have been identified. Nucleosides are generally defined as DNA or RNA subunitsand consist of both a base moiety such as adenine, thymine,guanine, cytosine, and uracil, and a sugar moiety such as.D-ribose or D-deoxyribose (Yokoyama and al 1999) Many nucleoside analogues havebeen synthesized with modification of thebase, sugar. In particular, nucleoside analogues in which thefuranose ring has been replaced by different carbon or heterocyclic systems have attracted special interest by virtue of their biological action as antiviral and/or anticancer agents(Merino and al 2002). Amongthem, uracil, thymine, cytosine, and adenine nucleoside.The Vorbruggen method has been widely employed for the preparation of various ribonucleoside analogues by coupling different silylated nucleobases with the appropriate sugars. Recently, the solide phase has achieved importance in organic chemistry(Clark and al 2002). Heterogeneous solid acids are 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(sen and al 1999).Of the many possible heterogeneous catalysts, natural phosphate(Natural phosphate comes from an ore extracted in the region of Khouribga), an inexpensive and non corrosive solid acid, has been used efficiently as a catalyst((a)Zahouily and al 2004,(b) Alahiane and al 2003(c) Rochdi and al 2003). for a variety of organic reactions.The reactions catalyzed by doped NP ((a) Lazrekand al 2005(b) Lazrek and al 2006(c) Lazrek and al 2007(d) Lazrek and al 2008(e) Lazrek and al 2011) are usually carried out under mild conditions with high yields and high selectivity and the work up of these reactions is very simple since it requires only filtration to remove the catalyst and evaporation of the solvent(Zahouily and al 2005). In this respect, and in connection with our other work on the

use of natural phosphate as a catalyst , we now report a new one pot novel method using as a catalyst inexpensive natural phosphate doped with CF_3SO_3H to perform the glycosylation reaction (scheme1)



BH=Uracile, 6-azauracile, thymine , Adenine

Results and discussion

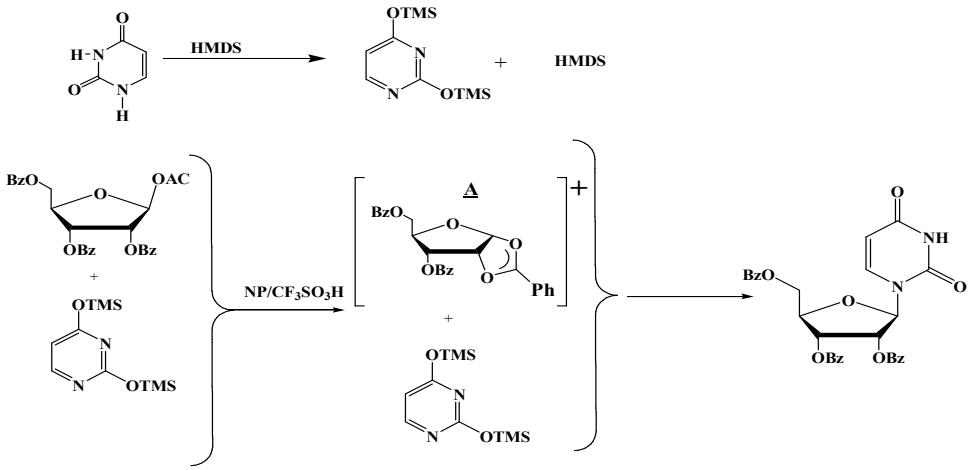
As shown in Table 1, when either NP was used alone, the reaction of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranoside with bis-(trimethylsilyl)uracil gave the ribonucleoside in only 5 % yields . As can be seen in the subsequent examples, the yield increased when NP doped with CF3SO3H was used. For example, in entry 2 the desired ribonucleoside was obtained in 20 yield by using NP/ CF3SO3H corresponding to 0.25 eq of CF3SO3H. the ribonucleoside is obtained in good yield 35% in acetonitrile at 1050 C overnight (entry 3). It can also be observed that increasing the equivalent of CF3SO3H (entry 4 and 5) the yield of ribonucleosides decrease (25% and 20% yield respectively). Other nucleobases (entries 7-8) were then also subjected to N-glycosylation and found to afford the corresponding ribonucleosides in 20% and 31% yield respectively. This procedure appears to be regioselective (N1 isomer for pyrimidine and N9 isomer for purine) and stereoselective (only the β isomer).

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

Entry	Nucleobase	NP/CF_3SO_3H	Yield %
1	Uracile	325/0	5
2	Uracile	(0.25eq of CF_3SO_3H)	20
3	Uracile	(0. 5eq of CF_3SO_3H)	35
4	Uracile	(0.75eq of CF_3SO_3H)	25
5	Uracile	(1eq of CF_3SO_3H)	20
6	Azauracile	(0. 5eq of CF_3SO_3H)	33
7	Thymine	(0. 5eq of CF_3SO_3H)	20
8	Adenine	(0. 5 eq of CF_3SO_3H)	31

As illustrated in Scheme 1 with the synthesis of beta-D-ribonucleoside, The mechanism of the above glycosylation could be depicted as follows:silylated uracil may react with NP/CF3SO3H. The 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose to afford the oxonium product (A) .Further, the silylated base will react with a product (A) to conduct to the desired nucleosides with the anomerie β-D-ribonucleoside (Scheme 2) .

Scheme2 :Glycosylation reaction mechanism



Conclusion

In summary, we describe a simple, efficient, and eco-friendly method for the synthesisof D -ribonucleosides using cheap and readily available catalyst (NP/ CF3SO3H). This methodology is an additive method to the conventional, but makes it significant under the umbrella of environmentally greener and safer processes.

Experimental Section

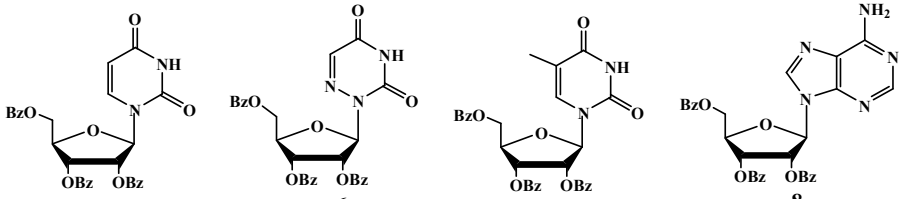
Preparation of Natural phosphate coated with CF_3SO_3H

To a solution of CF3SO3H (1ml) in methylene chloride(5 ml) was added natural phosphate (3g).The mixture was stirred for 15 min. and evaporated to dryness.

Typical procedure for one –pot synthesis

A suspension of uracil (1 mmol) in Bis-silylacetamide (BSA) (1 ml), ammonium sulfate (catalytic amount, 5 mg), and acetonitrie (2.5 ml) was heated at reflux until a clear solution was obtained (30 min). To this solution was added acetyl 2, ,5- tri-O-benzoyl-β-L-ribofuranose (0.9 mmol, 0.9 eq) and NP/ CF3SO3H (185 mg, 0,5 of CF3SO3H) and the mixture was heated (80°C) for 3h. The resulting suspension was filtred and preciptate was washed with dichloromethane. The filtrate was evaporated and the residue was purified by column chromatography (CH2Cl2/MeOH (98/2 v/v)to give the desired nucleoside with 35% yield

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



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

^{1}HNMR($CDCl_3$)(300MHz)δ(ppm) 4.40(m,2H,H'5)4.90(m,1H,H'4)5.55(d,1H,H5,J=6Hz)5.65(t,1H,H'3)5.80(t,1H,H'2)6.38(d,1H,H'1βJ=5.4Hz)7.44(d,1H,H6,J=6Hz)7.40-8.10(m,15H,HaromBz)8.10(m,6H,)10.40(s,1H,N-H).

^{13}CNMR($CDCl_3$)δ(ppm)64.01(C5')71.38(C4')75.01(C3')79.99(C2')88(C1'β)100.59(C5)128.43-133.70(Ph)145.09(C6)150.33(C4)163(C2)165.05-168.77(PhCO).

6 : ► 2', 3', 5'-Tri-O-benzoyl- β- D-azauridine:

^{1}HNMR(CDCl3)(300MHz)δ(ppm);4.40(m,2H,H'5)4.90(m,1H,H'4)5.65(t,1H,H'3)5.80(t,1H,H'2)6.38(d,1H,H'1β,J=5.4Hz)7.44(s,1H,H5)7.40-8.10(m,15H,HaromBz)10.40(s,1H,N-H).

^{13}CNMR(CDCl3)δ(ppm)63.66(C5')71.38(C4')75.09(C3') 79.99(C2')88(C1'β)128.43-132.70(Ph)135.36(C5)149.26(C4); 155.93(C2) ;165.05-168 (PhCO)

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

^{1}HNMR(CDCl3)(300MHz)δ(ppm)1.95(s,3H,CH3)4.40(m,2H,H'5)4.90(m,1H,H'4)5.5(t,1H,H'3)5.8(t,1H,H'2)6.35(d, 1H, H'1β J=3.6 Hz)7.40 (s,1H, H6)7.40-8.10(m,15H, Harom Bz)9.80(s,1H, N-H).

^{13}CNMR(CDCl3)δ(ppm)12.17(CH3)62.90(C5')71.38(C4')75.09(C3')79.99(C2')87(C1'β);110(C5);128.43-132.70(Ph)142.07(C6);151.30(C4)163.80(C2)165.05-168(PhCO).

8: ►2', 3', 5'-Tri-O-benzoyl- β- D-adenosine

^{1}HNMR(CDCl3)(300MHz)δ(ppm) 4.70(m,2H,H'5) 4.80(m,1H,H'4)4.90(t,1H,H'3)5.85(m,2H,NH2)5.95(t,1H,H'2)6.45(d,1H,H'1β J=5Hz)7.40-8.10(m,15H,Harom Bz)8.10(s,1H,H2)8.20(s,1H, H8)

^{13}CNMR(CDCl3)δ(ppm) ;63.34(C5')71.36(C4')73.77(C3') ;80.66(C2') 87(C1'β)119.26(C5); 128.43-133(Ph)141.77(C6)150.28(C4)153.02(C2)155.30(C8)165.05-168(PhCO)

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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 oC), 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 (Ca10(PO4)6F2), as shown by X-

ray diffraction and chemical analysis. The surface area of NP was measured at 1m2 g-1 (nitrogen adsorption) and the total pore volume was 0.005 cm3 g-1.

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