Use Of Fusion Method For Condensation Of Sugar And Heterocyclics Basis Using Natural Phosphat As Inorganic Catalyst

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Abstract: Several D, L -ribonucleosides are prepared from 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranoside and trimethylsilylated nucleobases under mild conditions by fusion method using natural phosphate doped with KI (NP/KI) as catalyst

Index Terms: Natural phosphate doped with potassium iodide NP/KI, Sugar, Heterocyclic basis,β-(D,L)-Ribonucleosides and fusion method.

INTRODUCTION

The synthesis of ribonucleosides has been emerging as an important area of research because some members show biological activities of medicinal interest [1] .Nucleoside such as (AZT) , (ddI), (ddC), (d4T), (3TC) and (Abacavir) have been approved by the Food and Drug Administration (FDA) for the treatment of human immunodeficiency virus (HIV) infection. One of them, 3TC was also licensed by FDA for use in hepatitis B virus (HBV) therapy [2]. The Vorbruggen method has been widely employed for the preparation of various nucleoside analogues by coupling different silylated nucleobases with the appropriate sugars Recently, the use of heterogeneous catalyst has achieved importance in organic chemistry [3] . Heterogeneous catalysts are advantageous over conventional homogeneous 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[4]. recently investigated the use On the other hand, we have used natural phosphate (NP)[5,6] alone and doped as the new heterogeneous catalysts for several reactions . Fusion method assisted organic synthesis has become increasingly popular in recent years to improve the yields and give remarkable rate enhancement in a number of classical organic reactions. The use of microwave (MW) irradiation technique as an energy source for organic synthesis and give the short reactions. The acceleration of N-glycosylation was developed, which is amenable to the combination of various bases with various sugars for the rapid preparation of structurally diverse nucleoside.Recently, large arrays of compounds have been synthesized on solid catalyst such as zeolite , silica , KF-Al2O3 and Ru- Al2O3[7].

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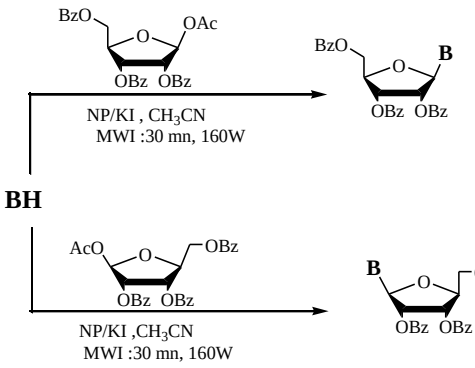
In an effort to develop new practical and economic catalysts, we and others recently investigated the use of natural phosphate (NP) alone or doped in various chemical transformations[8].These types of catalysts represent an important environmentally friendly alternative to reactions otherwise toxic and expensive and many efforts are done to promote NP [9].In this respect, and in connection with our other work on the use of natural phosphate as a catalyst [10,11]we now report a new one pot novel method (Fusion method) using as a catalyst inexpensive natural phosphate doped with KI (NP/KI) to perform the glycosylation reaction (scheme).



BH= Uracile, thymine , adenine and 6 azauracile

RESULTS AND DISCUSSION

As shown in Table 1 ,when we worked without silyll agent, the glycosylation reaction did not walked (Entry 1). when NP doped with KI in BSA assisted microwave oven (150 C, 160W) for (30, 10,5min) were used ,the reaction of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranoside with bis-(trimethylsilyl) uracile gave the ribonucleoside in only 32,30, 28% yields respectively (Entry 2,3,4 Table1) . When NP doped with KI in HMDS assisted microwave oven (150 C, 160W) for 30 min was used ,the desired ribonucleoside was obtained in good yield 54 %(Entry5 table1). Same conditions were also used to prepare some β-D-ribonucleosides (Table 2). This procedure appears to be stereoselective to give only the β isomer and to be regioselective and gives only the N-1 isomer for (uracile , azauracile and thymine) and gives only the N9 for adenine. All products were characterized by 1HNMR, 13C NMR and also by comparison with literature data.

Table1: Synthesisof2', 3, 5'-tri-O-benzoyl-β-Lribonucleosides

Entry	Nucleobas	Silyl agent	Yield %	Time
1	Uracile	Not silylagent	No reaction	160W,30 ,5,10min
2	Uracile	BSA	32	160W, 30min
3	Uracile	BSA	30	160W,10 min
4	Uracile	BSA	28	160W, 5 min
5	Uracile	HMDS	54	160W, 30min
6	Uracile	HMDS	48	160W, 10min
7	Uracile	HMDS	43	160W, 5min
8	Azauracile	HMDS	43	160W, 30min
9	Thymine	HMDS	60	160W, 30min
10	Adenine	HMDS	30	160W, 30min

Table2: Synthesisof2',3,5'-tri-O-benzoyl-β-Dribonucleosides

Entry	Nucleobase	Silyl agent	Yield %	Time
11	Uracile	HMDS	50	160W, 30min
12	Azauracile	HMDS	40	160W, 30min
13	Thymine	HMDS	40	160W, 30min
14	Adenine	HMDS	30	160W, 30min

CONCLUSION

In summary, this paper describes a simple and convenient method for the synthesis of β-ribonucleosides synthesis by microwave irradiation using NP doped with KI as a catalyst , that it led us to conclude that this new method has advantages such as:The soft, low cost,is part of green chemistry and ease of treatment

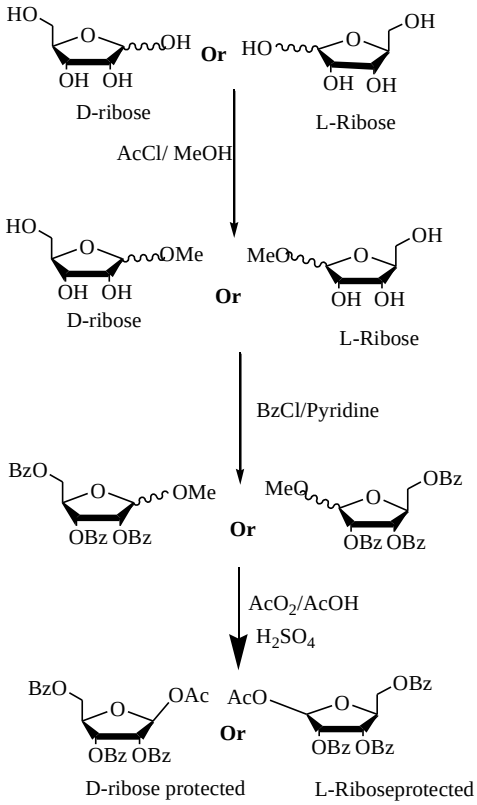
EXPERIMENTAL SECTION

Procedure for preparation of the catalyst (NP/KI , 3/1)

The catalyst was prepared by making 400 mg of potassium iodide (KI) in 5 mL of water. The residu was stirred at room temperature for 5 minutes. After the slurry of activated natural phosphate (NP) (1,2g) was added , the slurry was stirred magnetically at room temperature for 10 minutes and the excess solvent was removed by evaporation under reduced pressure and at low temperature.When the slurry became dry and free falling it was ready for use.

Preparation of protected sugars (1-acetyl-2,3,5-tri-O-benzoyl-β-(D,L)-Ribofuranose)

To achieve the pentofuranoses selectively acetylated in position C1,we first introduce a methoxy group in the anomeric C1 position that keeps the sugar furanose structure and protect other alcohol functions in position 2, 3, 5.The strategy for the pentofuranoses Peracylated requires three steps.



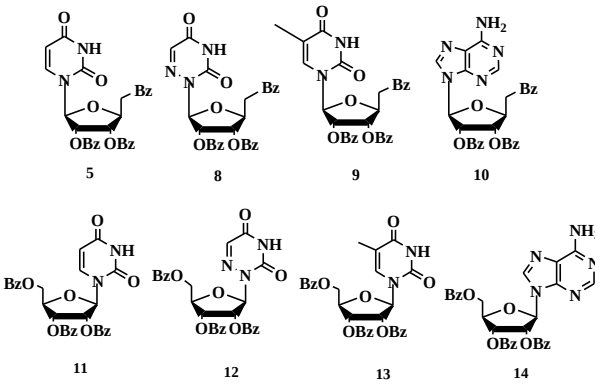
1g (D-ribose) are slurried with 24 ml of methanol containing 1% hydrochloric acid . The mixture is left about 4 h at room temperature and then treated immediately with 15 ml of anhydrous pyridine, the solvent is then evaporated to dryness and vacuum to remove traces of methanol. The resulting oil was diluted with 10 ml of anhydrous pyridine and treated with cold 2.8 ml of benzoyl chloride. The reaction is complete after one night, the resulting mixture was treated with ice and diluted with dichloromethane. The organic phase is then washed with water, respectively, a cold aqueous solution of sulfuric acid (3N) and then with a saturated aqueous solution of sodium hydrogenocarbonate NaHCO3.Oganique resultant phase is dried over sodium sulfate and the solvent was evaporated dry. 1-O-acetyl-2 ,3,5-tris-O-benzoyl-(D-ribose) is obtained by acetolisation of methyl 2,3,5tris-O-benzoyl-(D-ribose),the process is as follows:the oil obtained (4.7 g) was taken up in a mixture of acetic anhydride (10 ml) and acetic acid (49.7 ml) is cooled to using ice then add H2SO4 (2.8 ml) dropwise with concentrated ice-cooling. After 5 hours of stirring at room temperature the mixture was left overnight in a refrigerator (4°C) then the reaction mixture was poured into ice and extracted with dichloromethane (CH2Cl2) and the organic phase is washed with water and then with aqueous solution of sodium hydrogen carbonate (NaHCO3). The organic phase obtained was finally dried over sodium sulfate(Na2SO4) and evaporated under vacuum.Thedesired products are separated by chromatography on a column of silica gel eluted with a mixture of cyclohexane and ethyl acetate (91/9v/ v).

General Experimental Procedure

To a mixture of uracil (0.892 mmol) ammonium sulphate (catalytic amount, 5 mg), acetyl 2,3,5- tri-O-benzoyl-β-ribofuranose (0.669 mmol,0.75eq) and NP/KI(422 mg,0.8eqof KI) were added hexamethyldisilazane (HMDS) (0.5 ml) and

acetonitrile (0.5 ml). The open flask was placed in a baker containing neutral alumina and mixture was heated in an unmodified microwave oven (150 C, 160W) for 30 min. The resulting suspension was filtred and precipitate was washed with dichloromethane. The filtrate was evaporated and residue was purified by column chromatography (CH2Cl2/MeOH (98/2 v/v)) to give the desired nucleoside. All the expected nucleosides were characterized by 1H and 13C NMR

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



1 -(2,3, 5-Tri-O-benzoyl-β-L-ribofuranosyl)-uracil 5
1HNMR(CDCl3)(300MHz)δ(ppm) 4.40(m,2H,H'5)4.90(m,1H, H'4)5.5(d,1H,H5,J=6Hz)5.65(t,1H,H'3)5.80(t,1H,H'2)6.8(d,1H ,H'1βJ=5.4Hz)7.44(d,1H,H6,J=6Hz)7.408.10(m,15H,HaromB z)10.40(s,1H,NH).

13CNMR(CDCl3)δ(ppm) 64.01(C5') 71.38(C4') 75.01(3') 79. 99(C2') 88(C1'β) 100.59(C5)128.43133.70(Ph) 145.09(C6)15 0.33(C4)163(C2) 165.05- 168.77 (PhCO)

1-(2,3,5-Tri-O-benzoyl-β-L-ribofuranosyl)-6azauracil 8
1HNMR(CDCl3)(300MHz)δ(ppm) 4.40(m,2H,H'5) 4.90(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) 7.408.10(m,15H,HaromBz)10.40(s,1H,N-H).

13CNMR(CDCl3)δ(ppm) 63.66(C5') 71.38(C4') 75.09(C3') 79 .99(C2') 88(C1'β) 128.43132.70(Ph) 135.36(C5)149.26(C4); 155.93(C2)165.05- 168 (PhCO)

1-(2,3, 5-Tri-O-benzoyl-β-L-ribofuranosyl)-thymine 9
1HNMR(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=3.6Hz)7.40(s,1H,H6)7.408.10(m,15H,HaromBz)9.80(s,1H, N-H).

13CNMR(CDCl3)δ(ppm) 12.17(CH3)62.90(C5')71.38(C4');75 .09(C3')79.99(C2')87(C1'β)110(C5)128.43132.70(Ph)142.07(C6)151.30(C4)163.80(C2)165.05-168(PhCO)

1 -(2,3, 5-Tri-O-benzoyl-β-L-ribofuranosyl)-adenine 10
1HNMR(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' 1βJ=5Hz) 7.408.10(m,15H,HaromBz)8.10(s,1H,H2) 8.20(s,1H, H8).

13CNMR(CDCl3)δ(ppm) 63.34(C5') 71.36(C4')73.77(3)80.66(C2')87(C1'β)119.26(C5)128.43133(Ph)141.77(C6)150.28(C4) 153.02(C2)155.30(C8)165.05168 (PhCO)

1 -(2,3, 5-Tri-O-benzoyl-β-D-ribofuranosyl)-uracil 11
1HNMR(CDCl3)(300MHz)δ(ppm) 4.40(m,2H,H'5)4.90(m,H,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)7.408.10(m,15H,HaromBz) 10.40(s,1H,N-H).

13CNMR(CDCl3)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).

1 -(2,3, 5-Tri-O-benzoyl-β-D-ribofuranosyl)-Azauracil 12
1HNMR(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).

13CNMR(CDCl3)δ(ppm) 63.66(C5') 71.38(C4') 75.09(C3') 79. 99(C2')88(C1'β)128.43132.70(Ph) 135.36(C5)149.26(C4)155. 93(C2) 165.05- 168 (PhCO) .

1 -(2,3, 5-Tri-O-benzoyl-β-D-ribofuranosyl)-thymine 13
1H NMR(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' 1βJ=3.6Hz);7.40(s,1H,H6);7.40-8.10(m,15H,HaromBz) 9.80(s,1H,N-H).

13CNMR(CDCl3)δ(ppm)12.17(CH3)62.90(C5')71.38(C4')75.0 9(C3')79.99(C2')87(C1'β)110(C5)

128.43132.70(Ph)142.07(C6) 151.30(C4) 163.80(C2)165.05-168(PhCO).

1 -(2,3, 5-Tri-O-benzoyl-β-D-ribofuranosyl)-Adenine 14
1HNMR(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)7.408.10(m,15H,HaromBz)8.10(s,1H,H2)8.20(s,1H,H8) .

13CNMR(CDCl3)δ(ppm) 63.34(C5')71.36(C4')73.77(C3') 80.6 6(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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[9]. 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 (900oC), 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 µm2 g-1 (nitrogen adsorption) and the total pore volume was 0.005 cm3 g-1.

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