Chemistry and Materials Research
ISSN 2224- 3224 (Print) ISSN 2225- 0956 (Online)
Vol.3 No.4, 2013

Applications of Microwave in Organic Synthesis: A One-step Synthesis of Ribonucleosides using natural phosphate as solid catalyst

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Abstract

A clean, efficient and fast method for synthesis of ribonucleosides was developed, using natural phosphate as solid catalyst catalysts supported in a solid phase promoted by MW irradiation.

Keywords: Natural phosphate, Ribonucleosides , Micowave irradiation

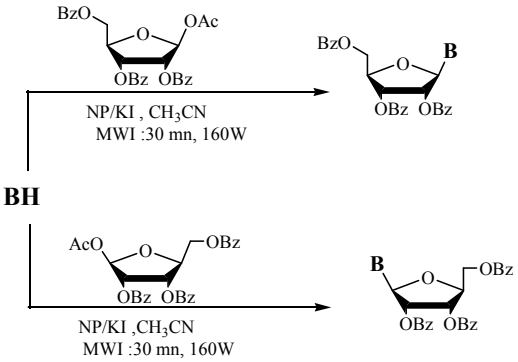
Introduction

The first applications of microwave ovens in organic synthesis began very recently. In the first experiments, Gedye, and then Giguere, provided evidence for dramatic accelerations in some classical organic reactions, and these were ascribed to temperature and pressure effects, when performed in closed Teflon R vessels. (Gedye and al 1986),(Giguere and al 1986) Since solvents were used in these experiments, some problems with safe operation appeared, and explosions sometimes resulted. Further developments demonstrated the potential of solvent-flee reactions to solve these problems and to facilitate the scale-up of preparative runs. Microwaves are a form of electromagnetic radiation with a frequency of 2450 MHz fixed by law, corresponding, in vacuum, to a wavelength of 12.2 cm. Many industrial, scientific, medical and domestic applications exist for these radiations. (Thuery and al 1989) When molecules with a permanent dipole are submitted to an electric field, they become aligned. If this field oscillates, the orientation changes at each alternation. The strong agitation, provided by the reorientation of molecules, in phase with the electrical field excitation, causes an intense internal heating, up to 10°C per second, when powerful waves are used. Microwaves constitute a very original procedure for heating materials, clearly different from the classical ways. Their main advantages derive from the almost instantaneous "in core" heating of materials, in an homogeneous and selective manner, especially those with poor heat conduction properties. This technique proves to be excellent in cases where traditional heating has a low efficiency because of poor heat transmission, and hence local overheating is a major inconvenience. The main interests can thus be listed as the rapid transfer of energy into the bulk of the reaction mixture, without inertia since only the product is heated, and the ease of utilization. Furthermore, as the depth of penetration in materials is of the same order of magnitude as the wavelength, microwaves interact with substances of appreciable thickness (about 10 cm)(Thuery and al 1989).The synthesis of ribonucleosides has been emerging as an important area of research because some members show biological activities of medicinal interest(Norbeck and al 1990) .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 (Jeannot and al 2002). 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(Clark and al 2002) .

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(Sen and al 1999). recently investigated the use On the other hand, we have used natural phosphate (NP)(Natural phosphate (NP) comes from an ore extracted in the region of Khouribga)((a) Sebti and al 2008 (b) Lazrek and al 2008 (c) Lazrek and al 2007(d). Zahouily and al 2006(e)

Zahouily and al 2005 (f) Zahouily and al 2005) alone and doped as the new heterogeneous catalysts for several reactions . Microwave 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(Gershonovand al 2007). 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((a) Sebti and al 2008(b)Zahouily and al 2005(c) Zahouily and al 2006 (d) Zahouily and al 2004 (e) Alahiane and al 2003(f) Sebtiand al 2002 (g) Zahouilyand al 2005).These types of catalysts represent an important environmentally friendly alternative to reactions otherwise toxic and expensive and many efforts are done to promote NP.

In this respect, and in connection with our other work on the use of natural phosphate as a catalyst (Lazrek and al 2006)(Lazrek and al 2007), 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 (scheme1)



BH= Uracile, thymine , adenine and 6 azauracile

(Scheme I)

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 .

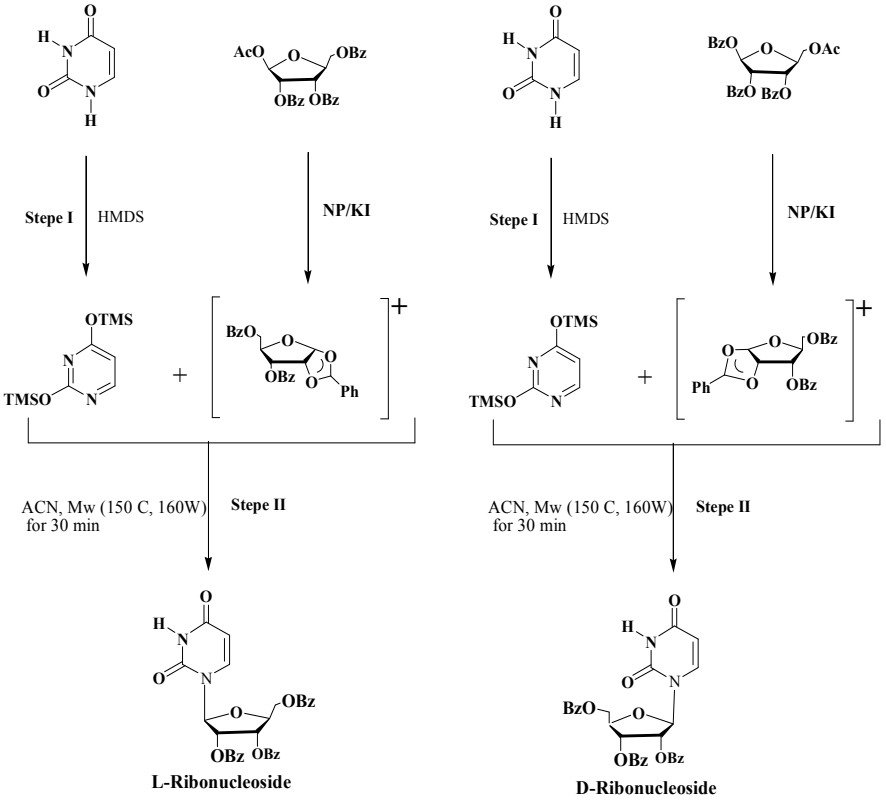
Table 1: Synthesis of 2',3,5'-tri-O-benzoyl-β-L-ribonucleosides

Entry	Nucleobase	Silyl agent	Yield %	Time
1	Uracile	Not silylagent	No reaction	160W, 30 ,5,10 min
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

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

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

Scheme2. Standard Vorbru1ggen Glycosylation Reaction Conditions



As illustrated in Scheme 2 with the synthesis of Ribonucleoside, can be considered as a tow -step operation. The typical Vorbruggen reaction requires presilylation of the base (step I) and then reaction with NP/KI activated sugar to form the desired acylprotected nucleoside (step II). One advantage of this method is that frequently one nitrogen of the base is regioselectively glycosylated because of thermodynamic equilibration. Conveniently, this often produces the same regioisomer as preferred by the natural product. Also, with α-2'-O-acyl-substituted sugar coupling partners, acyl-oxonium ion stabilization of the anomeric cation, as depicted in formula , directs glycosylation stereospecifically to the β-face of the sugar producing the natural β-configuration.Furthermore,while the Vorbruggen reaction is frequently conducted as a two-step operation.

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)

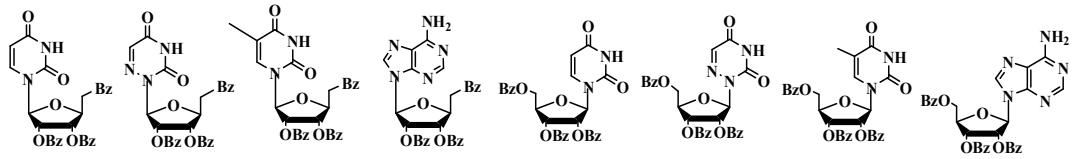
The catalyst was prepared by making 400 mg of potassium iodide (KI) in 5 mL of water. The residu was stirred at room temperature for 5 minutes. After the slurry of activated natural phosphate (NP) (1,2g) was added , the slurry was stirred magnetically at room temperature for 10 minutes and the excess 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 .

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,0.8eqofKI 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

(CH_2Cl_2/MeOH (98/2 v/v)) to give the desired nucleoside. All the expected nucleosides were characterized by ^1H and ^{13}C NMR

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



5 8 9 10 11 12 13 14

1 -(2,3, 5-Tri-O-benzoyl-β-L-ribofuranosyl)-uracil 5

^{1}HNMR($CDCl_3$)(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)6.38(d,1H,H'1βJ=5.4Hz)7.44(d,1H,H6,J=6Hz)7.40-8.10(m,15H,HaromBz)10.40(s,1H,NH).
^{13}CNMR($CDCl_3$)δ(ppm) ;64.01(C5') ;71.38(C4') ;75.01(3') ;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-L-ribofuranosyl)-6azauracil 8

^{1}HNMR($CDCl_3$)(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($CDCl_3$)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

^{1}H NMR($CDCl_3$) (300MHz)δ(ppm) ; 1.95(s, 3H, CH_3) ; 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,HaromBz) 9.80(s,1H,N-H).
^{13}CNMR($CDCl_3$)δ(ppm) ;12.17(CH_3);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

^{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'1βJ=5Hz) ;7.408.10(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(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

^{1}HNMR(CDCl3)(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)10.40(s,1H,N-H).
^{13}CNMR(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

^{1}H NMR(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}C NMR (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) .

1 -(2,3, 5-Tri-O-benzoyl-β-D-ribofuranosyl)-thymine 13

^{1}H 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).
^{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).

1 -(2,3, 5-Tri-O-benzoyl-β-D-ribofuranosyl)-Adenine 14

^{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'1βJ=5Hz)7.40-8.10(m,15H,HaromBz);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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