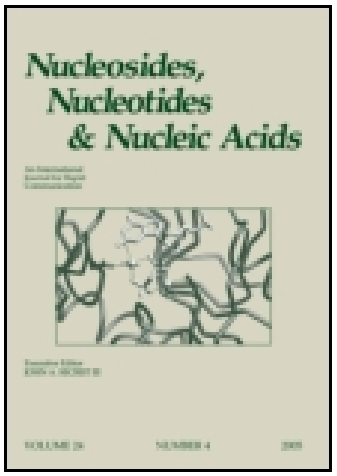

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AN ECONOMICAL SYNTHESIS OF D- AND L-PYRIMIDINE ARABINO- AND RIBONUCLEOSIDES

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□ *The one-step synthesis of several β-D/L-arabino- and ribonucleosides was performed in good yields under reflux or microwave-assisted fusion method. A comparison of the two methods showed that better yields were obtained using the reflux conditions.*

Keywords D/L-arabinonucleosides; D/L-ribonucleosides; natural phosphate; catalyst; one-pot synthesis

INTRODUCTION

Over the last four decades, the development of new nucleosides and nucleotides for medicinal uses has had a marked impact on clinical chemotherapy. Numerous nucleoside analogues have been successfully developed for the treatment of a variety of diseases, for instance, AIDS, hepatitis B and C, and various cancers.[1] Glycosylation by the Vorbrüggen reaction has been a key step in the synthesis of a vast array of diverse nucleosides.[2] Among the commonly used glycosylation methods are the Vorbrüggen reaction, which is frequently conducted as a two-step operation, but which can also be performed by combining all reagents and heating[3] or using microwave.[4,5] Other procedures for the synthesis of pyrimidine nucleosides include glycosylation by a modified Hilbert-Johnson reaction, which is the simplest one with wide application.[6] The acid-catalyzed fusion of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose and related D-ribofuranose derivatives with various nucleobases

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provide β-D-ribonucleosides in variable yield[7] is another procedure that is often used.

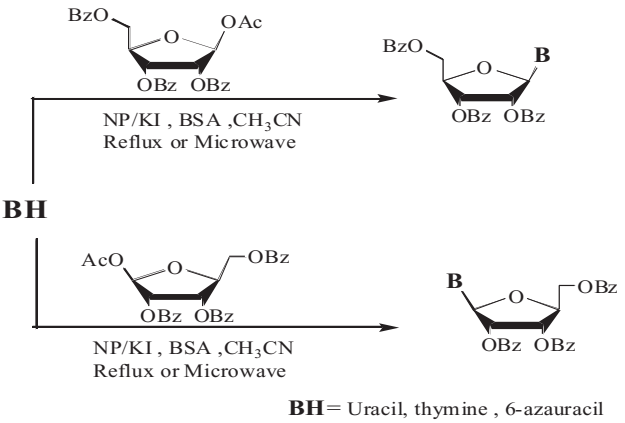
Surface-mediated solid phase reactions are of growing interest because of (1) they have an environmentally friendly processes when compared to conventional reaction conditions, and (2) they have advantages such as ease of set up, mild conditions, rapid reactions times, selectivity, increased product yields, and low cost. In an effort to develop new practical and economical catalysts, we and others have recently investigated the use of natural phosphate (NP) alone or doped NP in various chemical transformations.[8] These types of catalysts represent an important environmentally friendly alternative to reactions using otherwise toxic and expensive reagents as shown by the many studies that promote the use of NP[9] as a catalyst. Recently, we reported[10] several organic transformations catalyzed by NP doped with KI or I_2 as a solid support, which is very inexpensive, readily prepared in the laboratory, and can be stored for a long time without any significant loss of catalytic activity. As a part of our continuing effort to explore the catalytic potential of KI/NP, we revealed that KI/NP efficiently promotes glycosylation reactions resulting in the stereoselective formation of β-ribonucleosides. In this report, we compare two N-glycosylation reaction methods: 1) a one-pot synthesis using conventional heating conditions and 2) a microwave-assisted fusion reaction.

RESULTS AND DISCUSSION

A first set of experiments was carried out using uracil and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L- arabinofuranose as a model. These preliminary reactions, carried out in acetonitrile at 80°C with excess (1 ml) of *N*,*O*-bistrimethylsilylacetamide (BSA), and KI/NP as catalyst, allowed us to evaluate and optimize the most efficient catalytic system (Table 1). We observed that when the amount of protected L-arabinose is increased from 0.25 equiv. to 0.75 equiv., the yield of nucleoside also increased (Table 1, entries 1–3).

TABLE 1 Optimization of the N-glycosylation of uracil with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-arabinofuranose reaction conditions

Entry	Sugar	Catalyst	Yield (%)
1	0.25 equiv.	KI/NP	43
2	0. 5 equiv.	KI/NP	50
3	0.75 equiv.	KI/NP	80
4	0.75 equiv.	KI/Al_2O_3	30
5	0.75 equiv.	KI/SiO_2	18
6	0.75 equiv.	KI/C	12
7	0.75 equiv.	KI/Mont K10	40



SCHEME 1 General condition for N-glycosylation. Conditions: BSA/KI/NP/CH_3CN, reflux, MW, BH = U, T, 6-AZAU.

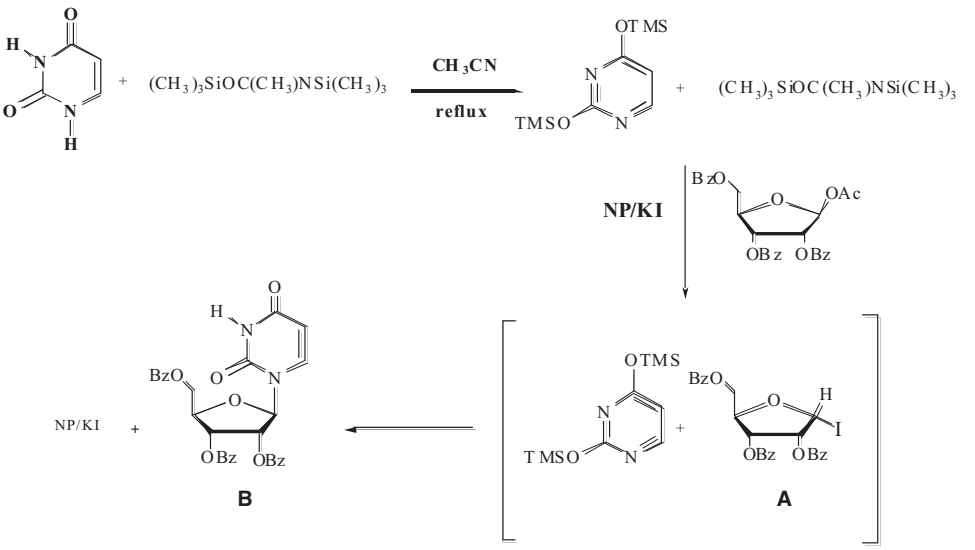
Similar experiments carried out in the presence of KI/Al_2O_3, KI/SiO_2, KI/C, and KI/Montmorillonite K10 revealed that these gave relatively low yields of the nucleoside (Table 1, entries 4–7). It should be noted that the workup involves only filtration before evaporation of the solvent, and both the solvent and the catalyst could be easily recovered after completion of the reaction. To confirm the effectiveness of the catalyst, the N-glycosylation was carried out using trimethylsilyl iodide (TMSI)/hexamethyldisilazane (HMDS) or BSA instead of KI/NP/HMDS or BSA, decreased yields were obtained as shown in Table 2.

Next, in order to extend the applicability of the present reaction, the glycosylation reactions listed in Table 3 (Scheme 1) were carried out. In every case, the desired β-nucleoside was obtained in good yield. Such a favorable combination of stereoselectively (β for D/L-ribonucleosides) and high yields has not been reported in the N-glycosylation utilizing KI/NP as catalyst.

The proposed mechanism is depicted in Scheme 2 silylated uracil and excess of BSA react with KI/NP to give TMSI.[11] The latter then reacts with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose to afford 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl iodide (**A**). Then, the silylated base reacts with iodo sugar to yield the desired nucleosides with β-orientation at the anomeric carbon (Scheme 2). It is well known that Lewis acids activate the anomeric center in

TABLE 2 TMSI/BSA or HMDS catalyzed N-glycosylation reaction of uracil with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose

Entry	Uracil	TMSI	Silyl agent	Yield (%)
1	0.892 mmol	0.8 equiv. (0.1 ml)	HMDS	42
2	0.892 mmol	0.8 equiv. (0.1 ml)	BSA	48

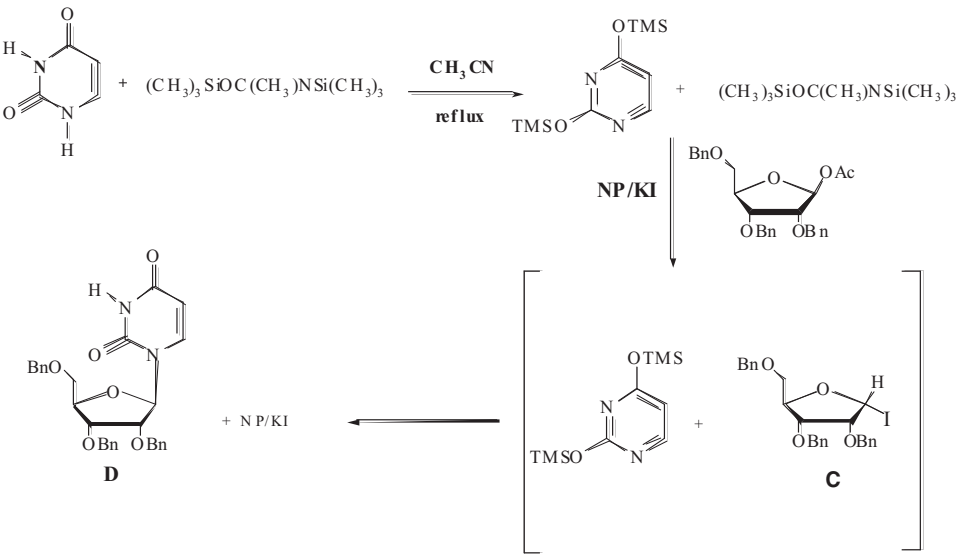


SCHEME 2 Glycosylation reaction mechanism using 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose as starting material with a participating group at C-2.

peracylated furanose and pyranose sugars leading to the formation of a glycosidic linkage having the 1,2-trans configuration.[2,3] The high selectivity in the glycosylation reactions using Lewis acids ($SnCl_4$, 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 leading to 1,2-trans glycosylation. Because of its nonparticipating group at C-2, we then decided to use 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribofuranose as a starting material directly in a reaction with silylated uracil. The reaction was carried out under the same conditions as above. The exclusive formation of the β-anomer serves as a proof that the intermediate in these reactions is 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl iodide (**A)** (Scheme 2) or 2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl

TABLE 3 KI//NP/BSA catalyzed N-glycosylation reaction of nucleobases with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl D/L-pentofuranose

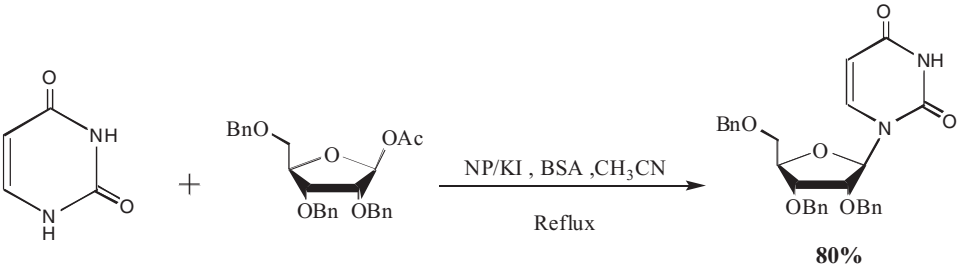
Nucleoside	Sugar	Nucleobase	Reflux%	Fusion%
1	D-ribose	Uracil	70	51
2	L-ribose	Uracil	55	54
3	D-ribose	Thymine	72	50
4	L-ribose	Thymine	60	60
5	D-ribose	6-azauracil	52	40
6	L-ribose	6-azauracil	56	43
7	D-arabinose	6-azauracil	60	35
8	L-arabinose	6-azauracil	60	40



SCHEME 3 Glycosylation reaction mechanism using 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-*β*-D-ribofuranose as starting material with non-participating group at C-2.

iodide (**C**) (Schemes 3 and 4). On the other hand, when trimethylsilyl iodide (0.8 equiv.) was used as a coupling reagent instead of KI/NP (Table 2, entries 1 and 2), the yield of nucleoside decreased. All the expected nucleosides were characterized by ^{1}H and ^{13}C NMR and are in agreement with the literature.[12]

Our model reaction to test the N-glycosylation with microwave activation was the reaction of 6-azauracil with 1-*O*-acetyl 2,3,5-tri-*O*-benzoyl-L-ribofuranose. Preliminary reactions carried out in acetonitrile (0.5 ml) with HMDS (0.5 ml) and KI/NP as catalyst under microwave activation in a multimode microwave reactor (microwave frequency −2.45 GHz, maximum of microwave power 1150 W), for 30 minutes of discontinuous microwave irradiation at 20% power allowed us to evaluate and optimize the most efficient catalytic system. The reaction was initially carried out in an open Erlenmeyer



SCHEME 4 Glycosylation reaction using 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-*β*-D-ribofuranose as starting material.

flask over 30 minutes. Changing the irradiation time was found to influence the yield. When the reaction time was shorter or longer than 30 minutes, lower yields were obtained. Therefore, 30 minutes was the optimal reaction time for this reaction (Table 3).

CONCLUSIONS

In summary, we describe two simple, efficient, and eco-friendly methods for the synthesis of D- and L-pyrimidine arabino and ribonucleosides using inexpensive and readily available catalyst (KI/NP). We showed that the synthesis of pyrimidine nucleosides using Vorbrüggen type reaction conditions gave better yields with conventional heating than with microwave-assisted fusion.

EXPERIMENTAL

General Remarks

The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker spectrometer (AC 300 MHz). Chemical shifts are reported as δ values (ppm) relative to trimethylsilane (TMS) as a standard and the coupling constants J values are given in Hz. FAB mass spectra were recorded on a Varian MAT 311A spectrometer. Thin layer chromatography (TLC) was performed on 60 F254 precoated plastic plates silica gel (Merck, Darmstadt, Germany). Column chromatography was performed on silica gel (30–60 μm). All solvents were distilled and dried before using.

General Experimental Procedure

1. Reflux Method

A suspension of uracil (0.892 mmol, 100 mg) in BSA (1 ml), ammonium sulfate (catalytic amount, 5 mg), and acetonitrile (2.5 ml) was heated at reflux until a clear solution was obtained (30 minutes). To this solution, was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (0.670 mmol, 336 mg, 0.75 equiv.) and KI/NP (422 mg, 0.8 equiv. of KI) and the mixture was heated (80°C) for 3 hours. The resulting suspension was filtered and the precipitate was washed with dichloromethane. The filtrate was evaporated, and the residue was purified by column chromatography resulting in the desired nucleoside (Table 3).

2. Fusion Method

To a mixture of uracil (0.892 mmol, 100 mg) ammonium sulfate (catalytic amount, 5 mg), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (0.670 mmol, 336 mg, 0.75 equiv.) and KI/NP (422 mg, 0.8 equiv. of KI) were

added BSA (0.5 ml) and acetonitrile (0.5 ml). The open flask was placed in a beaker containing neutral alumina, and the mixture was heated in a microwave multi-mode reactor (170°C, 160 W) for 30 minutes. The resulting black solid was suspended in CH_2Cl_2 and the insoluble material was filtered off. The filtrate was evaporated and residue was purified by column chromatography resulting in the desired nucleoside (Table 3).

*1-(2′,3′, 5′-Tri-O-benzoyl-β-L-ribofuranosyl)-6-azauracil (**6**).* Rf: 0.65 CH_2Cl_2/MeOH (9/1 v/v). ^{1}H NMR($CDCl_3$) δ(ppm): 4.40 (m, 2H, H5′), 4.90 (m, 1H, H4′), 5.65 (m, 1H, H3′), 5.80 (m, 1H, H2′), 6.38 (d, 1H, H1′β, $J = 5.4$Hz), 7.44 (s,1H, H5), 7.40–8.10 (m, 15H, Harom, Bz), 10.40 (s, 1H, N-H). ^{13}C NMR ($CDCl_3$) δ(ppm), 63.66 (C5′), 71.38 (C4′), 75.09 (C3′), 79.99 (C2′), 88.00 (C1′β), 128.43–132.70 (Ph); 135.36 (C5), 149.26 (C4), 155.93 (C2), 165.05- 168 (PhCO). FAB-MS [M+H] $^+$ 558.

*1-(2′,3′, 5′-Tri-O-benzoyl-α-L-arabinofuranosyl)-6-azauracil (**8**).* Rf: 0.62 CH_2Cl_2/MeOH (9/1, v/v). ^{1}H NMR ($CDCl_3$) δ (ppm): 4.55(m, 2H, H5′), 4.85 (m, 1H, H4′), 5.86 (dd, 1H, H3′, $J = 4.2$ Hz, 3.3 Hz), 6.05 (m, 1H, H2′), 6.50 (d, 1H, H1′α, $J = 3.3$ Hz), 7.40 -8.00 (m, 15H, Harom, Bz) 7.80 (s,1H, H5), 10.30 (s, 1H, N-H). ^{13}C NMR($CDCl_3$) δ(ppm): 63.78 (C5′), 77.49 (C3′), 80.73 (C2′), 83.28 (C4′), 90.19 (C1′α), 128–133.9 (Ph), 147.8 (C5), 155.4 (C2), 155.9 (C4),165.2- 165.7 (PhCO). FAB-MS [M+H] $^+$ 558.

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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 (900°C), 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 $[Ca_{10}(PO_4)_6F_2]$, as shown by x-ray diffraction and chemical analysis. The surface area of NP was measured at $\mu m^2\ g^{-1}$ (nitrogen adsorption) and the total pore volume was 0.005 $cm^3\ g^{-1}$.
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