

## Catalytic And Economic Method Using As Catalyst the I-Si(CH<sub>3</sub>)<sub>3</sub> Generated During The Condensation Of Silylated Base With Natural Phosphate Doped With KI (NP/KI)

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### Abstract

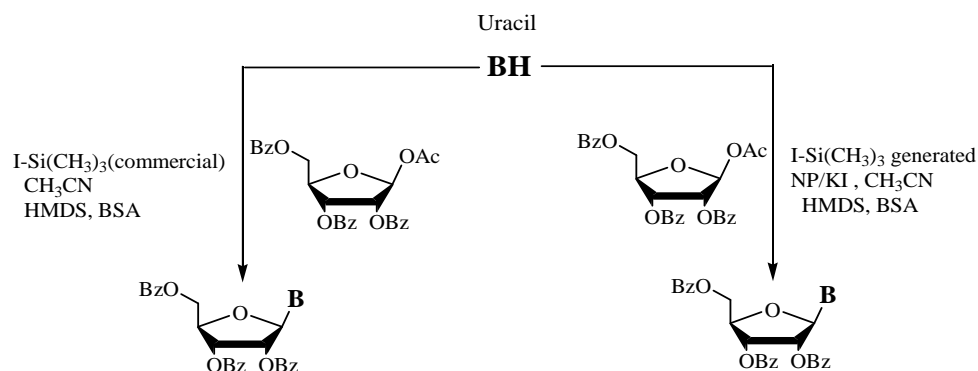
Several D-ribonucleosides are prepared from 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranoside and trimethylsilylated nucleobases under mild conditions by using as catalyst I-Si(CH<sub>3</sub>)<sub>3</sub> generated during the condensation of silylated base with NP/KI.

**Keywords:** I-Si(CH<sub>3</sub>)<sub>3</sub> generated during the condensation of silylated base with NP/KI, one-step synthesis, and D-ribonucleosides.

### Introduction

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 (it is available in raw form or treated form from CERPHOS Casablanca, Morocco) ((a) Lazrek and al 2008 (b) Lazrek and al 2007). Alone and doped as the new heterogeneous catalysts for several 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-Al<sub>2</sub>O<sub>3</sub> and Ru-Al<sub>2</sub>O<sub>3</sub> (Gershonov and 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 (Sebti and al 2008). These types of catalysts represent an important environmentally friendly alternative to reactions otherwise toxic and expensive and many efforts are done to promote NP (The structure of NP is similar to that of fluorapatite [Ca<sub>10</sub>(PO<sub>4</sub>)<sub>6</sub>F<sub>2</sub>], as shown by X-ray diffraction and chemical analysis. The surface area of NP was measured at 2 μm<sup>2</sup> g<sup>-1</sup> (nitrogen adsorption) and the total pore volume was 0.005 cm<sup>3</sup> g<sup>-1</sup>). 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 using as a catalyst inexpensive I-Si(CH<sub>3</sub>)<sub>3</sub> generated during the condensation of silylated base with NP/KI (scheme 1), and compares it with

other catalysts commercial (I-Si(CH<sub>3</sub>)<sub>3</sub> commercial, TfO-Si(CH<sub>3</sub>)<sub>3</sub> commercial and Cl-Si(CH<sub>3</sub>)<sub>3</sub> commercial).



**Scheme1**

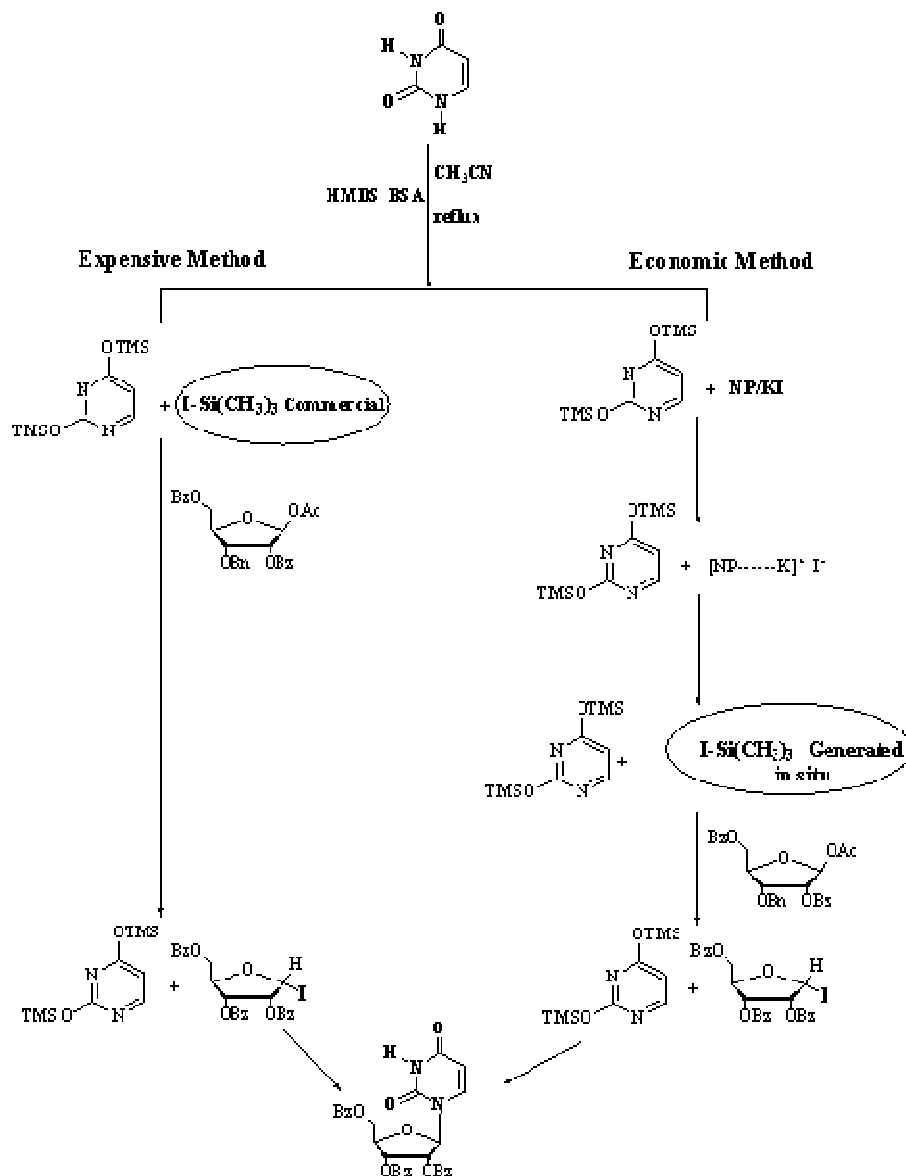
### Results and discussion

As shown in Table 1, when  $I-Si(CH_3)_3$  (commercial) were used, the good yield is obtained (51%) in the reaction of 1-O-acetyl-2,3,5-tri-O-benzoyl- $\beta$ -D-ribofuranoside with bis-(trimethylsilyl) uracil (Entry 3) (HMDS,  $I-Si(CH_3)_3$  (0.5eq)). When NP doped with KI were used, the desired ribonucleoside was obtained in good yield 70% (Entry 2, table 1). For the comparison between the when  $I-Si(CH_3)_3$  (commercial) and  $I-Si(CH_3)_3$  generated during the condensation of silylated base with NP/KI, one finds that  $I-Si(CH_3)_3$  generate in situ is the best catalyst for the condensation of sugar and silylated base. This procedure appears to be regioselective and gives only the N-1 isomer. 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: silylated uracil may react with NP/KI to give  $I-Si(CH_3)_3$ . The later will react with 1-O-acetyl-2,3,5-tri-O-benzoyl- $\beta$ -D-ribofuranose to afford 1-Iodo-2,3,5-tri-O-benzoyl- $\alpha$ -D-ribofuranose. Further, the complex [heterocycle] $^-$ /[NP-K] $^+$  will react with iodo sugar to conduct to the desired nucleosides (scheme 2).

**Table1: Synthesis of 2',3,5'-tri-O-benzoyl-D-ribose nucleosides**

Entry	Uracil	Silylated Agent	$I-Si(CH_3)_3$ Commercial	Yield %	$I-Si(CH_3)_3$ generated during the condensation of silylated base with NP/KI	Yield%
1	0.892mmol	HMDS	0.8 eq (0.1 ml)	44	NP/KI (422mg, 0.8 eq of KI) in HMDS	55
2	0.892mmol	BSA	0.8 eq (0.1 ml)	50	NP/KI (422mg, 0.8 eq of KI) in BSA	70
3	0.892mmol	HMDS	0.5 eq (0.06 ml)	51	NP/KI (263mg, 0.5 eq of KI) in HMDS	28
4	0.892mmol	BSA	0.5 eq (0.06 ml)	47	NP/KI (263mg, 0.5 eq of KI) in BSA	30

## Scheme2. Glycosylation Reaction Conditions



## Conclusion

In summary, this paper describes a simple and convenient method for the synthesis of Ribonucleosides synthesis using I-Si(CH<sub>3</sub>)<sub>3</sub> generated during the condensation of silylated base with NP/KI in BSA 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, ease of treatment and not expensive

\*I-Si(CH<sub>3</sub>)<sub>3</sub> generated during the condensation of silylated base with NP/KI in BSA (1.5€)

\*I-Si(CH<sub>3</sub>)<sub>3</sub> comercial 27 € for 10 ml

\*TfO-Si(CH<sub>3</sub>)<sub>3</sub> comercial 22 € for 5 ml

\*Cl-Si(CH<sub>3</sub>)<sub>3</sub> comercial 21 € for 5 ml

## 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 .

#### **Experimental Procedure (NP/KI in HMDS)**

A suspension of uracil (0.892 mmol) was added hexamethyldisilazane (HMDS) (4mL), ammonium sulphate (catalytic amount, 5 mg). The mixture was refluxed for two hours. To the obtained clear solution was added the 1-O-acetyl-2,3,5-tri-O-benzoyl- $\beta$ -D-ribofuranoside (0.9eq, 453mg), NP/KI (422mg, 0.8eq of KI) and acetonitrile (5ml). The resulting suspension was filtered and precipitate was washed with dichloromethane. The filtrate was evaporated and residue was purified by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (98/2 v/v)) to give the desired nucleoside.

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#### **Experimental Procedure (NP/KI in BSA)**

A suspension of uracil (0.892 mmol) was added Bis-silylacetamide (BSA) (1 ml), ammonium sulphate (catalytic amount), and acetonitrile (2.5ml) was heated at reflux until a clear solution was obtained (30 min). To this solution was added, 1-O-acetyl-2,3,5-tri-O-benzoyl- $\beta$ -D-ribofuranoside (0.9eq, 453mg) and NP/KI (422 mg, 0.8 eq of KI) and the mixture was heated (80°C) for 3h. The resulting suspension was filtered and precipitate was washed with dichloromethane. The filtrate was evaporated and residue was purified by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (98/2 v/v)) to give the desired nucleoside.

#### **Experimental Procedure (I-Si(CH<sub>3</sub>)<sub>3</sub> in BSA)**

A suspension of uracil (0.892 mmol) was added Bis-silylacetamide (BSA) (1ml), ammonium sulphate (catalytic amount), and acetonitrile (2.5ml) was heated at reflux until a clear solution was obtained (30 min). To this solution was added 1-O-acetyl-2,3,5-tri-O-benzoyl- $\beta$ -D-ribofuranoside (0.9eq, 453mg) and I-Si(CH<sub>3</sub>)<sub>3</sub> and the mixture was heated (80°C) for 3h. The resulting suspension was filtered and precipitate was washed with dichloromethane. The filtrate was evaporated and residue was purified by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (98/2 v/v)) to give the desired nucleoside.

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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).

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The structure of NP is similar to that of fluorapatite [ $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ ], as shown by X-ray diffraction and chemical analysis. The surface area of NP was measured at  $\mu\text{m}^2 \text{g}^{-1}$  (nitrogen adsorption) and the total pore volume was  $0.005 \text{ cm}^3 \text{ g}^{-1}$ .

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