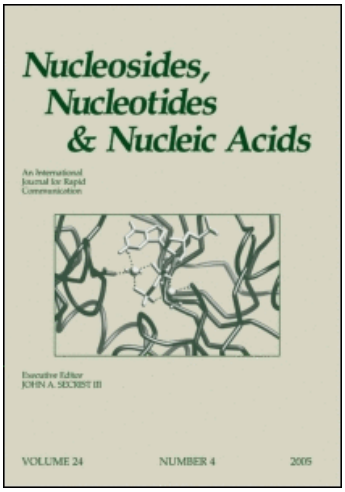



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# Glycosylation Reaction via a Mild and Efficient One-Pot Reaction Using Doped Natural Phosphate with Iodine as Catalyst

H. B. Lazrek[a]; D. Ouzebla[a]; L. Baddi[a]; J. J. Vasseur[b]
[a] Faculté des Sciences Semlalia, Laboratoire de Chimie Bio-Organique, Marrakech, Maroc [b] Institut des Biomolécules Max Mousseron, IBMM, UMR 5247 CNRS-UM1-UM2, Université Montpellier II, Montpellier, France

**To cite this Article** Lazrek, H. B. , Ouzebla, D. , Baddi, L. and Vasseur, J. J.(2007) 'Glycosylation Reaction via a Mild and Efficient One-Pot Reaction Using Doped Natural Phosphate with Iodine as Catalyst', Nucleosides, Nucleotides and Nucleic Acids, 26: 8, 1095 — 1098
**To link to this Article: DOI:** 10.1080/15257770701519106
**URL:** http://dx.doi.org/10.1080/15257770701519106

*Nucleosides, Nucleotides, and Nucleic Acids*, 26:1095–1098, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701519106

Taylor & Francis
Taylor & Francis Group

# GLYCOSYLATION REACTION VIA A MILD AND EFFICIENT ONE-POT REACTION USING DOPED NATURAL PHOSPHATE WITH IODINE AS CATALYST

**H. B. Lazrek, D. Ouzebla, and L. Baddi** □ *Laboratoire de Chimie Bio-Organique, Faculté des Sciences Semlalia, Marrakech, Maroc*

**J. J. Vasseur** □ *Institut des Biomolécules Max Mousseron, IBMM, UMR 5247 CNRS-UM1-UM2, Université Montpellier II, Montpellier France*



□ *Several α/β-D-ribonucleosides were synthesized in good yields under mild conditions by N-glycosylations of acetyl 2,3,5-tri-O-benzoyl- β-D-ribofuranose with silylated nucleobases in acetonitrile using NP doped with iodine as catalyst.*

**Keywords** Natural phosphate; iodine; catalyst; D-ribonucleoside

## INTRODUCTION

Analogues of nucleosides are used as therapeutic agents such as antiviral agents (e.g., AZT, d4T, ddC, ddI, 3TC, AraA, ACV, DHPG ...) and antitumor (AraC, FU, ...), and more new analogues of nucleosides are being synthesized for the examination of their biological activities now. Three methodologies are used for the synthesis of nucleosides: (i) condensation of a sugar moiety with a nucleobase (N-glycosylation); (ii) construction of the base moiety after introducing functional group in the anomeric position of the sugar moiety; (iii) conversion of naturally occurring nucleoside.[1]

Recently, a practical access to glycosyl iodides from the corresponding 1-*O*-acetylated derivatives has been described by Gervay and coworkers.[2] This procedure is based on the use of TMSI and takes advantage of the easy removal of volatile by products.

Furthermore, a mild and highly efficient method for the silylation of alcohols using HMDS catalyzed by iodine under nearly neutral reaction conditions has been described.[3]

This research programme was supported by grant from the Comité Mixte Inter Universitaire Franco-Marocain ("Programme d'Action Intégrée" No. AI: MA/06/143).

Address correspondence to J. J. Vasseur, Institut des Biomolécules Max Mousseron, IBMM, UMR 5247 CNRS-UM1-UM2, Université Montpellier II, Montpellier France. E-mail: vasseur@univ-montp2.fr

Natural phosphate[4] (NP), an inexpensive and noncorrosive solid acid, has been used efficiently as a catalyst for a variety of organic reactions. The reactions catalyzed by doped NP usually are 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.[5]

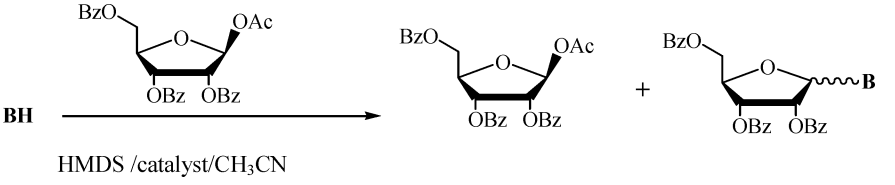
We were interested in studying the application of doped NP as catalyst for glycosylation reaction instead of well-known Lewis acids. Recently, we have started a programme directed to the synthesis of cyclic and acyclic nucleosides using the doped NP as catalyst.[6]

Here, we want to describe a new and very easy method for glycosylation reactions using doped Natural phosphate with $I_2$ in HMDS as catalyst instead of TMSI. These catalysts are insensitive to moisture, are very stable and are inexpensive. However, their use in the glycosylation reaction remains unexplored.



## RESULTS AND DISCUSSION

As shown in Table 1, when either NP or $I_2$ were used alone, the reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-$\beta$-D-ribofuranose with bis-(trimethylsilyl) uracil [USi$(CH_3)_3$] gave the corresponding ribonucleoside in only 5 and 40% yield, respectively. In view to establish beneficial effects of solid supports and to find the most effective conditions, a number of experiments were performed, we have investigated the use of the NP coated with $I_2$ in HMDS as silylating agent. The results of these studies are summarized in Table 1.




HMDS /catalyst/$CH_3CN$

BH= uracil, thymine, cytosine, adenine, *N*-Ac guanine

As can be seen in the subsequent examples, the yield increased significantly when NP doped with $I_2$ in HMDS was used. For example, the desired ribonucleoside was obtained as a major isomer and in good yield by using 0.892 mmol of the nucleobase, (0.9 eq.) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-$\beta$-D-ribofuranose and NP/$I_2$ (223 mg) corresponding to 0.2 mmol of iodine in HMDS (3 ml) at reflux in acetonitrile (5 ml) overnight (entry 5, Table 1).When $Al_2O_3$ or silica gel doped with $I_2$ was used, the yield of nucleoside decreased (entries 6, 7, Table 1). The experimental conditions are

**TABLE 1** Synthesis of 2′, 3, 5′-tri-*O*-benzoyl-$\alpha/\beta$-D-ribonucleosides NP/$I_2$ (HMDS)

| Entry | Nucleobase[a] | NP/$I_2$ | Yield% of nucleoside[b] | Yield% of sugar recovery | $\alpha/\beta$ |
|---|---|---|---|---|---|
| 1 | Uracil (1 mmol) | 325 mg/0 | 5 | 93 | ..... |
| 2 | Uracil (0.892 mmol) | 0 /1.11 g (1 eq. of $I_2$) | 40 | 32 | 33/67 |
| 3 | Uracil[c] (0.892 mmol) | 557 mg (0.5 eq. of $I_2$) | 47 | 42 | 50/50 |
| 4 | Uraci (0.892 mmol) | 223 mg (0.2 eq. of $I_2$) | 50 | 19 | 28/72 |
| 5 | Uracil (0.892 mmol) | 223 mg (0.2 eq. of $I_2$) | 62 | 25 | 22/78 N1 |
| 6 | Uracil (0.892 mmol) | Silica / $I_2$ 223 mg (0.2 eq. of $I_2$) | 55 | 29 | 20/80 N1 |
| 7 | Uracil (0.892 mmol) | $Al_2O_3$ / $I_2$ 223 mg (0.2 eq. of $I_2$) | 48 | 24 | 20/80 N1 |
| 8 | Thymine (0.79 mmol) | 195 mg (0.2 eq. of $I_2$) | 55 | 45 | 10/90 N1 |
| 9 | Cytosine (0.9 mmol) | 225 mg (0.2 eq. of $I_2$) | 52 | 47 | 10/90 N1 |
| 10 | Adenine (0.74 mmol) | 185 mg (0.2 eq. of $I_2$) | 55 | 45 | 15/85 N9 |
| 11 | N-ac-guanine (0.51 mmol) | 127.8 mg (0.2 eq. of $I_2$) | 35 | 65 | 50/50 N9 |

[a]Reaction carried out with 0.9 eq. of sugar.
[b]Yields refer to isolated and chromatographically pure compounds.
[c]Reaction carried out with 0.5 eq. of sugar.



milder, after the work up the recovered sugar is used in the next reaction. The used and recovered NP/$I_2$ has been shown to be reusable after drying at 150°C in vacuum.

Other nucleobases also were subjected to this N-glycosylation, and the corresponding nucleosides were obtained in 35–62% yields (Table 1). These reactions appeared to be regioselective, since only the N-1 isomer was obtained for pyrimidine (uracil, thymine, and cytosine) and the N-9 for purine (adenine and Nac-guanine). All D-ribofuranosides were characterized by $^1$H and $^{13}$C NMR as well as comparison with literature data. The $\alpha/\beta$ ratio was determined by $^1$H and $^{13}$C-NMR.

## CONCLUSION

In summary, we describe a simple, efficient, and eco-friendly method for the synthesis of D-ribonucleosides using cheap and readily available catalyst (NP/$I_2$). This methodology is an additive method to the conventional, but makes it significant under the umbrella of environmentally greener and safer processes.

## REFERENCES

1. Mizuno, Y. *The Organic Chemistry of Nucleic Acids* Kodansha Ltd., Tokyo, 1986, pp. 41–72.
2. Hadd, M.J.; Gervay, J. Glycosyl iodides are highly efficient donors under neutral conditions. *Carbohydr. Res.* **1999**, 320, 61–69.
3. Karimi, B.; Golshani, B. Mild and highly efficient method for the silylation of alcohols using hexamethyldisilazane catalyzed by iodine under nearly neutral reaction conditions. *J. Org. Chem.* **2000**, 65(21), 7228–7230.

4. NP comes from an ore extracted in the region of Khouribga (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 $1 m^2 g^{-1}$ (nitrogen adsorption) and the total pore volume was $0.005 cm^3 g^{-1}$.
5. Zahouily, M.; Mezdar, A.; El maksoudi, A.; Mounir, B.; Rayadh, A.; Sebti, S.; Lazrek, H.B. Comparison of different Lewis acids supported on natural phosphate as new catalysts for chemoselective dithioacetalization of carbonyl compounds under solvent-free conditions *ARKIVOC* **2006** (ii) 42–51, and references cited therein.
6. Lazrek, H.B.; Ouzebla, D.; Rochdi, A.; Redwane, N.; Vasseur, J.J A one pot synthesis of D-ribonucleosides using Natural phosphate doped with KI in HMDS. *Lett. Orga. Chem.* **2006**, 3(4), 313–314, and references cited therein.