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## Green approaches for the synthesis of nucleotides, their conjugates and analogues

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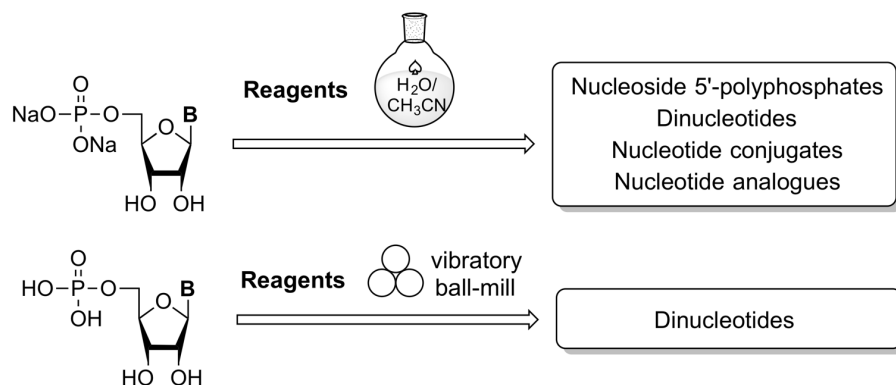
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**ABSTRACT** We have developed original one-pot and protecting group-free approaches, which are also user-friendly and reliable, to synthesize nucleotides and derivatives starting from nucleoside 5'-monophosphates. Both methods present convenient set-up, i.e. non-dry solvents and reagents, substrates in their sodium or acid form, and commercially available and cheap phosphorus reagents as sodium and potassium salts.

### GRAPHICAL ABSTRACT



### KEYWORDS

organophosphorus chemistry; nucleotides; dinucleotides; water chemistry; mechanochemistry.

## INTRODUCTION

Nucleotides and their derivatives are essential to human biological systems. Numerous methods have been developed to prepare these compounds and their structural analogues.<sup>1-4</sup> Their scope range from mechanistic probes to versatile chemical tools for assay development and biomedical applications.<sup>1</sup> Most of these synthetic approaches present important drawbacks, such as the use of non-volatile and harmful solvents (DMF, pyridine), preparation of substrates or phosphorus reagents in their alkylammonium forms due to solubility issues, anhydrous conditions, and fastidious purifications.

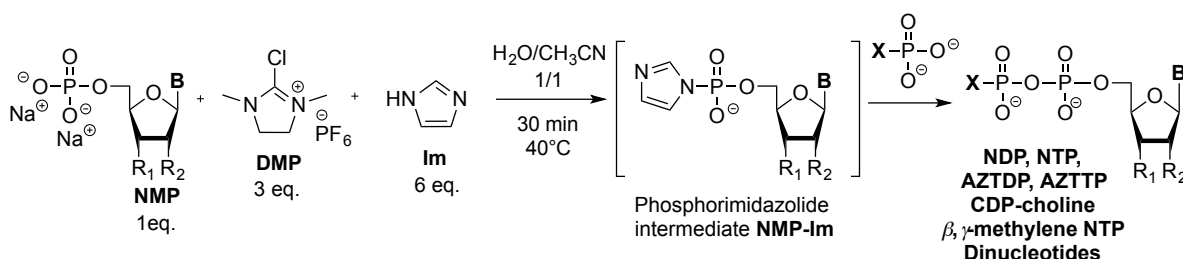
## RESULTS AND DISCUSSION

We proposed one-pot and protecting group-free approaches, which are user-friendly and reliable, for the preparation of nucleotides. Starting materials are nucleoside 5'-monophosphates (NMPs) which are readily converted into a common intermediate, i.e. the nucleoside 5'-phosphorimidazolide. The use of non-dry solvents and reagents, substrates in their sodium or acid form, and commercially available and cheap phosphorus reagents as sodium and potassium salts shall allow an easy implementation of these procedures.

In the first strategy, nucleoside 5'-monophosphates were activated into the corresponding phosphorimidazolide intermediates (NMP-Im) using 2-chloro-1,3-dimethylimidazolium hexafluorophosphate (DMP) and imidazole in a mixture of acetonitrile and water (Scheme 1).<sup>5-6</sup> The resulting intermediates were then treated with sodium phosphate or sodium pyrophosphate to afford the corresponding nucleoside 5'-diphosphates and 5'-triphosphates, respectively. The conversion rates ranged from 35 to 49%, and the compounds were isolated in 22-40% yields. We then extended this approach to the synthesis of a nucleotide conjugate (i.e., CDP-choline), and various analogues modified either on the glycosyl moiety (i.e., AZTDP and AZTTP) or on the phosphate moiety such as  $\beta$ ,  $\gamma$ -methylene-uridine 5'-triphosphate.

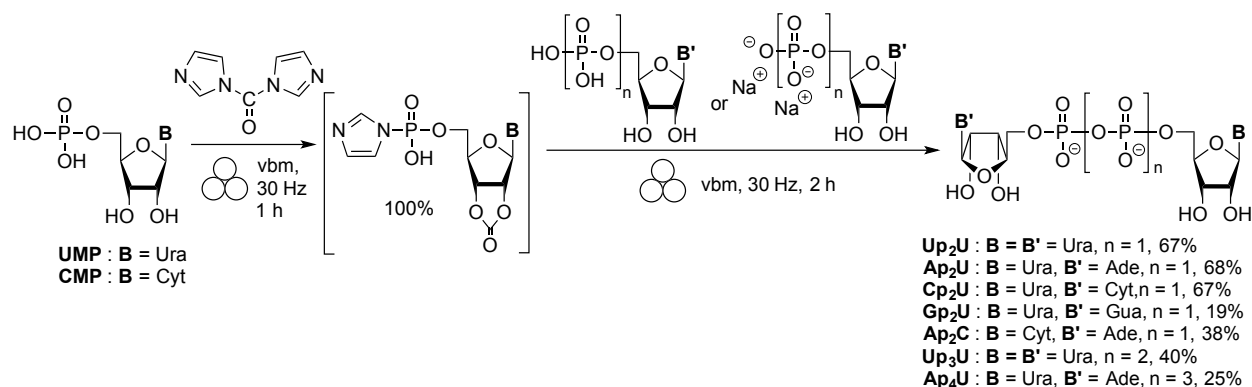
Moreover, we took advantage of the formation of byproducts during the activation step and corresponding to the dimers to isolate these compounds. In this respect, several NMPs (UMP,

CMP, and AMP) were reacted with DMP and imidazole until the total disappearance of the  $^{31}\text{P}$  NMR signal of the activated NMPs. The conversion rates for dimers ranged from 31 to 70%.



**Scheme 1** Synthetic route to nucleotides and derivatives in aqueous media (**B** = Uracil, Cytosine, Adenine).<sup>5-6</sup>

In the second strategy, we envisaged the use of mechanochemistry, an emerging technique that enables solid/solid reactions through mechanical grinding under solventless or solvent-free conditions,<sup>7-8</sup> and that was recognized in 2019 by IUPAC as a chemical innovation that will change the world.<sup>9</sup> Under ball-milling conditions, nucleoside 5'-monophosphates in their acid form were quantitatively converted into their phosphorimidazolide derivatives using the eco-friendly *N,N'*-carbonyldiimidazole (CDI) (Scheme 2).<sup>10</sup> Thus, the addition of a nucleoside 5'-mono, di or triphosphate led to the formation of the corresponding unprotected dinucleotides in satisfactory yields (Scheme 2). Benefits of this one-pot method include short reaction time, high conversion rates (75–100%, except for Gp<sub>2</sub>U) and easy set-up and purification.



**Scheme 2** Synthetic route to 5',5'-dinucleotides via mechanochemistry.<sup>10</sup>

## CONCLUSIONS

This work offers new opportunities for the synthesis of nucleotide conjugates and their analogues, combining the phosphorimidazolide approach and milling conditions. These last being essential intermediates for pyrophosphate bond formation, our studies open the way to environmentally friendly practices to access a wide range of nucleotide derivatives.

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