

GREEN APPROACHES FOR THE SYNTHESIS OF NUCLEOTIDES, THEIR CONJUGATES AND ANALOGUES

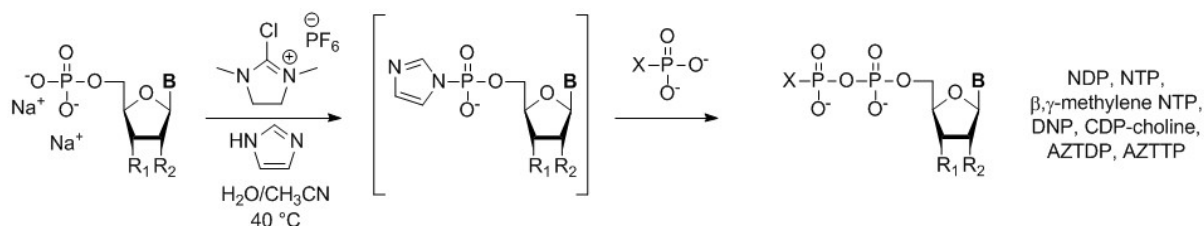
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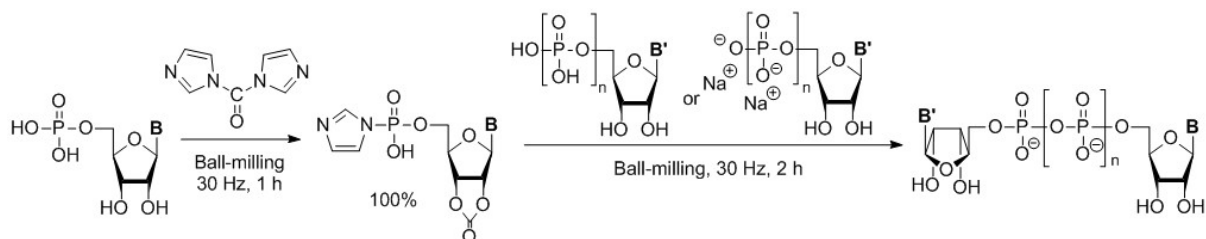
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Given the importance of nucleotides and their derivatives in biological processes, numerous methods have been developed to access to these compounds and their structural analogues.^[1] Their scope ranges from mechanistic probes to versatile chemical tools for assay development and biomedical applications. Most of these syntheses present important drawbacks, such as the use of non-volatile and harmful solvents (DMF, pyridine), preparation of substrates or phosphorus reagents in their alkylammonium form due to solubility issues, anhydrous conditions, and fastidious purifications.

We have developed original one-pot, protecting-group free approaches, which are user-friendly and reliable, for nucleotides starting from nucleoside 5'-monophosphates and through phosphorimidazolide intermediates. Both methods present convenient set-up, i.e. non-dry solvent and reagents, substrates in their sodium or acid form, and commercially available and cheap phosphorus reagents as sodium or potassium salts. The first strategy uses 2-chloro-1,3-dimethylimidazolium hexafluorophosphate and imidazole as activating agents in a water medium, and allows to access a variety of nucleosides 5'-polyphosphates as well as conjugates and analogues.^[2]



The second strategy is a solvent-assisted mechanochemical approach, which allows to prepare symmetrical and mixed dinucleoside 5,5'-polyphosphates.^[3] Under ball-milling conditions, nucleoside 5'-monophosphates are quantitatively activated using the eco-friendly *N,N'*-carbonyldiimidazole into their phosphorimidazolide derivatives. The addition of a nucleoside 5'-mono, di or triphosphate directly leads to the formation of the corresponding dinucleotides. Other benefits of this one-pot method include short reaction time, high conversion rates and easy set-up and purification. This work offers new perspectives for the synthesis of nucleotide conjugates and analogues, combining the phosphorimidazolide approach and milling conditions.



Since phosphorimidazolides are essential intermediates for pyrophosphate bond formation, our studies offer new perspectives for the development of greener approaches to access a wide range of nucleotide derivatives and analogues.

References

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- 3) L. Appy, A. Depaix, X. Bantreil, F. Lamaty, S. Peyrottes, B. Roy, *Chemistry – Eur. J.*, 2019, 25, 2477–2481.