



**HAL**  
open science

# Straightforward Ball-Milling Access to Dinucleoside 5',5'-Polyphosphates Through Phosphorimidazolide Intermediates

Lucie Appy, Anaïs Depaix, Xavier Bantreil, Frédéric Lamaty, Suzanne Peyrottes, Béatrice Roy

► **To cite this version:**

Lucie Appy, Anaïs Depaix, Xavier Bantreil, Frédéric Lamaty, Suzanne Peyrottes, et al.. Straightforward Ball-Milling Access to Dinucleoside 5',5'-Polyphosphates Through Phosphorimidazolide Intermediates. *Chemistry - A European Journal*, 2019, 25 (10), pp.2477-2481. 10.1002/chem.201805924 . hal-02370680

**HAL Id: hal-02370680**

**<https://hal.science/hal-02370680>**

Submitted on 20 Dec 2019

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

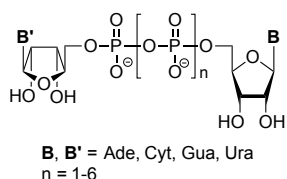
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Straightforward Ball-Milling Access to Dinucleoside 5',5'-Polyphosphates Through Phosphorimidazolid Intermediates

Lucie Appy,<sup>[a]</sup> Anaïs Depaix,<sup>[a]</sup> Xavier Bantreil,<sup>\*[b]</sup> Frédéric Lamaty,<sup>[b]</sup> Suzanne Peyrottes<sup>[a]</sup> and Béatrice Roy<sup>\*[a]</sup>

**Abstract:** A solvent-assisted mechanochemical approach to access symmetrical and mixed dinucleoside 5',5'-polyphosphates is reported. Under ball-milling conditions, nucleoside 5'-monophosphates are quantitatively activated using *N,N'*-carbonyldiimidazole into their phosphorimidazolid derivatives. The addition of a nucleoside 5'-mono, di or triphosphate directly leads to the formation of the corresponding dinucleosides. Benefits of the reported one-pot method include the use of unprotected nucleotides in their sodium or acid form, activation by the eco-friendly *N,N'*-carbonyldiimidazole, non-dry conditions, 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 phosphorimidazolid approach and milling conditions.

Nucleotides and their conjugates are naturally occurring ubiquitous compounds that play key functional and structural roles in biological systems. Among these, dinucleoside 5',5'-polyphosphates (DNPs, also known as  $N_pN_n$ s) consist of two nucleosides linked by one or several pyrophosphate bonds (Figure 1). They are involved in proliferation processes, enzyme regulation, neurotransmission, platelet disaggregation and the modulation of vascular tone.<sup>[1]</sup> Due to their biological relevance and therapeutic interest,<sup>[2]</sup> both enzymatic<sup>[3]</sup> and chemical<sup>[4]</sup> approaches have been developed for preparing DNPs. However, these compounds are often obtained chemically owing to the inherent limitations of enzymatic catalysis.<sup>[5]</sup>



**Figure 1.** Structure of natural dinucleoside 5',5'-polyphosphates (Ade: Adenine, Cyt: Cytosine, Gua: Guanosine, Ura: Uracil).

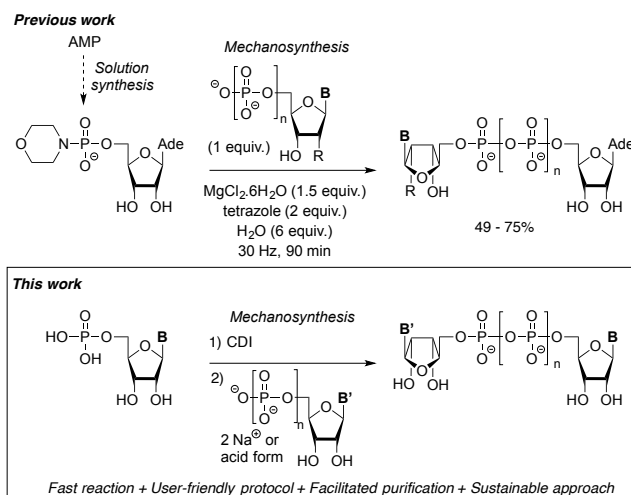
[a] L. Appy, Dr. A. Depaix, Dr. S. Peyrottes, Dr. B. Roy  
Nucleosides & Phosphorylated Effectors  
Institut des Biomolécules Max Mousseron (IBMM), UMR 5247  
CNRS, ENSCM, Université de Montpellier  
Campus Triolet, cc1705, Place Eugène Bataillon  
34095 Montpellier cedex 5, France

[b] Dr. X. Bantreil, Dr. F. Lamaty  
Green Chemistry and Enabling Technologies  
Institut des Biomolécules Max Mousseron (IBMM), UMR 5247  
CNRS, ENSCM, Université de Montpellier  
Campus Triolet, cc1703, Place Eugène Bataillon  
34095 Montpellier cedex 5, France

E-mail: [beatrice.roy@umontpellier.fr](mailto:beatrice.roy@umontpellier.fr), [xavier.bantreil@umontpellier.fr](mailto:xavier.bantreil@umontpellier.fr)

Supporting information for this article is given via a link at the end of the document.

The widely used P(V) method involves the activation of tri- or tetra-alkylammonium salts of a 5'-nucleotide (i.e. nucleoside 5'-mono, 5'-di and 5'-triphosphate) with *N,N'*-carbonyldiimidazole (CDI) in dry *N,N*-dimethylformamide (DMF) to form a phosphorimidazolid intermediate. Its reaction with a second 5'-nucleotide or pyrophosphate leads to the formation of DNPs containing two to five bridging phosphate groups in 10–63% yields.<sup>[1b,5,6]</sup> Yields drop significantly as the length of the polyphosphate chain increases. Alternatively,  $P^1,P^2$ -di(imidazolyl)-pyrophosphate reacts with nucleoside 5'-monophosphates (NMPs) in the presence of tetrazole or zinc chloride as catalysts to generate the symmetrical DNPs in 61–74% yields.<sup>[7]</sup> DNPs can also be obtained starting from nucleoside 5'-phosphoropiperidates<sup>[8]</sup> or 5'-phosphoromorpholidates.<sup>[5]</sup> Other P(V) approaches involve the activation of the first nucleotide with dicyclohexylcarbodiimide,<sup>[1b,5,6]</sup> a sulfonylimidazolium<sup>[9]</sup> or an activated cyclic trimetaphosphate,<sup>[10]</sup> followed by coupling with a second nucleotide. Otherwise, dinucleotides can be obtained via P(III) intermediates, such as salicylphosphites,<sup>[11]</sup> *cyclo*Saligenylphosphites,<sup>[12]</sup> 5'-*H*-phosphonates<sup>[13]</sup> and phosphoramidites.<sup>[14]</sup> Most of these methods present important drawbacks, such as the use of non-volatile and toxic solvents (DMF, pyridine, *N*-methylpyrrolidone), preparation of substrates or phosphorus reagents in their alkylammonium form due to solubility issues, anhydrous conditions (i.e. dry reagents and solvents), fastidious purification and possibly prior synthesis of the activated nucleotide substrate. Here, we report an original protecting-group free mechanochemical approach, which is user-friendly and reliable, for DNPs starting from commercially available NMPs (Scheme 1).<sup>[15]</sup>



**Scheme 1.** Previous<sup>[16]</sup> and present mechanochemical approaches to form dinucleoside 5'-polyphosphates.

This approach is based on our recent results regarding the synthesis of nucleotides and some conjugates in a water medium using 2-chloro-1,3-dimethylimidazolium hexafluorophosphate (DMP) and imidazole (Im) as coupling agents.<sup>[17]</sup> Addition of a phosphoryl reagent to the phosphorimidazolide intermediates afforded a large range of nucleotide derivatives. However, yields were moderate due to hydrolysis, the formation of side products (i.e. DNPs) and the multiple steps involved in purification. We hypothesized that removing the solvent would reduce the extent of hydrolysis and consequently increase isolated yields of the nucleoside polyphosphates. Thus, we focused on mechanochemistry, an emerging technique that enables solid/solid reactions through mechanical grinding under solvent-free conditions.<sup>[18]</sup>

So far, mechanochemistry has rarely been applied to the synthesis of nucleosides and related derivatives.<sup>[19]</sup> One report describes the mechanochemical synthesis of dinucleotides, namely  $A_p_nA$  (with  $n = 2-4$ ),  $A_p_2dT$  and nicotinamide adenine dinucleotide ( $NAD^+$ ), starting from adenosine 5'-phosphoromorpholidate, which is rather expensive compared to AMP or needs to be prepared beforehand in solution using conventional unfriendly methods (Scheme 1).<sup>[16]</sup> This approach was also applied to the preparation of adenosine diphosphate ribose carbonate derivatives<sup>[20]</sup> and pyrophosphorothiolate-linked dinucleoside cap analogues.<sup>[21]</sup> Although advantageous, this methodology requires the use of costly reagents, namely the phosphoromorpholidate substrate and tetrazole, as well as magnesium chloride.

As a starting point, we performed the activation of UMP according to the conditions that we reported previously (DMP/Im),<sup>[17]</sup> without adding any solvent in a vibratory ball-mill (vbm) at 30 Hz (Table 1, entry 1). A complete conversion to  $Up_2U$  was obtained within 30 min (entry 2), suggesting that UMP was activated to its phosphorimidazolide (UMP-Im) **1** and reacted rapidly with the remaining UMP to form the dimer **2**. Replacement of DMP with its chloride salt (DMC)<sup>[22]</sup> led to low conversion of the substrate, together with the formation of both UMP-Im and  $Up_2U$  (entry 3).

**Table 1.** Conversion starting from UMP disodium salt.

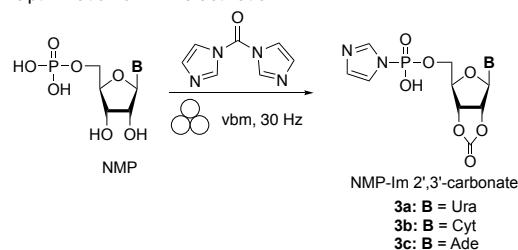
Entry	Reagents	Ratio	t [min]	Ratio [%] <sup>[a]</sup>		
				UMP	UMP-Im	$Up_2U$
1	DMP/Im	3:6	60	0	0	100
2	DMP/Im	3:6	30	0	0	100
3	DMC/Im	3:6	60	12	33	55
4	DMP/Im	2:4	60	0	0	100
5	DMP/Im	2:4	30	37	37	26
6	DMP/Im	1:2	60	77	13	10

[a] Ratio determined by <sup>31</sup>P NMR spectroscopy of the crude mixture.

Reducing the ratio of DMP/Im from 3/6 to 2/4 produced  $Up_2U$  with a complete conversion in 1 h (entry 4). Attempts to form UMP-Im selectively, by reducing time or amount of reagents were unsuccessful (entries 5–6). In summary, symmetric dinucleotide  $Up_2U$  was obtained quantitatively in a single step from UMP as a result of mechanochemical synthesis using DMP combined with imidazole.

Since phosphorimidazolides are widely used intermediates for the formation of pyrophosphate bonds in solution,<sup>[1b,4-6]</sup> we explored their access through activation of nucleoside 5'-monophosphates with CDI, starting from NMPs (Table 2). It is interesting to note that CDI has recently gained interest in the field of mechanochemistry due to the safety of its by-products (i.e. imidazole and carbon dioxide), its efficacy in *N*-acylation reactions and relatively low cost.<sup>[23]</sup> The first attempt of activation was performed by grinding the disodium salt of UMP with 4 equiv. of CDI for 1 h at 30 Hz. No activation was observed under these conditions (Table 2, entry 1). However, a 50% conversion rate was obtained when using the dihydrogen form of UMP (entry 2). Indeed, phosphorus NMR analysis of the crude reaction mixture showed one signal at 2.8 ppm (residual UMP) and one at -8 ppm characteristic of a phosphorimidazolide. Moreover, MS analysis indicated the carbonation of the 2' and 3' position of the glycosyl moiety, corresponding to compound **3a**. This result is consistent with the carbonation of ribonucleotides by CDI in solution phase reactions.<sup>[24]</sup> We assume that the acid form of UMP ( $pK_a$  values of 1.6 and 6.6) allows the protonation of the imidazole of CDI and, therefore, facilitates its substitution by the phosphate monoester.

**Table 2.** Optimization of NMPs activation.<sup>[a]</sup>

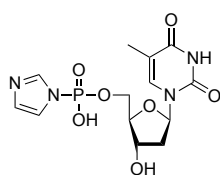


Entry	NMP	CDI [Equiv.]	t [min]	Ratio [%] <sup>[b]</sup>	
				NMP	<b>3a-c</b>
1	UMP <sup>[c]</sup>	4	60	100	0
2	UMP	4	60	50	50
3	UMP <sup>[d]</sup>	4	60	0	100
4	UMP <sup>[d]</sup>	4	45	15	85
5	UMP <sup>[d]</sup>	3	60	36	64
6	CMP <sup>[d]</sup>	4	60	0	100
7	AMP <sup>[d]</sup>	4	60	0	100

[a] Starting from 90 mg of NMP. [b] Ratio determined by <sup>31</sup>P NMR spectroscopy of the crude mixture. [c] Used as its disodium salt. [d] ACN (0.3  $\mu\text{L}\cdot\text{mg}^{-1}$ ) was added as a liquid assistant.

Since only 50% conversion could be obtained under these conditions, acetonitrile (0.3  $\mu\text{L}\cdot\text{mg}^{-1}$ ) was added as a liquid assistant for grinding. Indeed, studies have shown that very small

amounts of added liquid can dramatically accelerate and even enable mechanical reactions between solids.<sup>[18]</sup> Under these conditions, full conversion was observed in 1 h (entry 3). When the reaction time or the amount of CDI was reduced, the reaction was not complete (entries 4 and 5). Other NMPs were examined and we found that CMP and AMP were quantitatively activated in 1 h with 4 equiv. of CDI to form **3b** and **3c**, respectively (entries 6 and 7). Finally, the same protocol applied to 2'-deoxythymidine 5'-monophosphate (dTMP) produced the corresponding 5'-phosphorimidazolidine **4** (Figure 2) with a complete conversion, which suggests that the approach can be applied successfully to 2'-deoxyribonucleotides (see the Supporting Information). It is interesting to note that the use of mechanochemistry circumvents the conversion of nucleotides into their tributylammonium salts, a step that is a prerequisite (for solubility issues) for NMPs activation with CDI in solution phase synthesis.<sup>[1b,5,6]</sup>

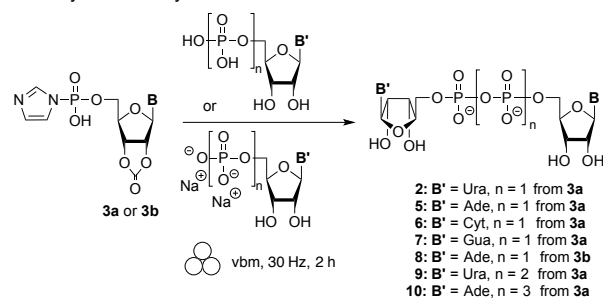


**Figure 2.** Structure of the phosphorimidazolidine **4**.

Once we had established the optimized conditions for mechanical NMPs activation, we examined the scope of the DNP starting from NMP (Table 3). After the reaction of UMP and CDI, as described above (Table 2, entry 3), adding a slight excess of UMP disodium salt in the same jar and then ball-milling for 2 h at 30 Hz led to the formation of Up<sub>2</sub>U (Table 3, entry 1). Remarkably, the second grinding step also removed the carbonate protection.<sup>[25]</sup> The use of UMP in its acid form resulted in a complete conversion of phosphorimidazolidine **3a** into the dimer **2** (entry 2). The mixed dinucleoside 5',5'-diphosphates **5–8** were successfully obtained using the same approach, starting from phosphorimidazolidines **3a** or **3b** (entries 3–7). The reaction was less efficient with guanosine 5'-monophosphate (GMP) and, thus, required a larger excess of reagent (entry 6). Similarly, the use of a 4 to 4.5-fold excess of uridine 5'-diphosphate (UDP) and adenosine 5'-triphosphate (ATP) formed dinucleoside 5',5'-triphosphate **9** and tetraphosphate **10**, respectively (entries 8–9). Here, nucleotides were used in their sodium form because their acid form proved to be highly hygroscopic and resulted primarily in Up<sub>2</sub>U formation upon intermediate hydrolysis into UMP and a further reaction. Finally, this strategy was successfully applied to the synthesis of CDP-choline **11**, starting from CMP and using choline phosphate calcium salt as a reagent (entry 10). This user-friendly mechanochemical method only requires a slight excess of reagents and limits the formation of side products. As a result, all compounds could be purified easily by reversed-phase chromatography using less than 10% acetonitrile in the mobile phase, which means our approach remains sustainable. It is important to note that the isolated yields of DNPs are similar to other approaches. However, the set-up of the reactions and their workup are greatly simplified, which saves a considerable amount of time. In addition, compared to the previously reported mechanochemical synthesis of DNPs,<sup>[16]</sup> our methodology can be performed in one-pot from the NMPs. This is an advantage because it does not require the demanding formation of

nucleoside 5'-phosphoromorpholidates (Scheme 1). Moreover, over-stoichiometric tetrazole, which is costly and potentially explosive,<sup>[19a]</sup> is not involved in the reaction.

**Table 3.** Synthesis of symmetrical and mixed DNPs.<sup>[a]</sup>



Entry	B'	n	Equiv. [b]	ACN [μL/mg]	Product	Conv. [%] <sup>[c]</sup>	Yield [%] <sup>[d]</sup>
1	Ura <sup>[e]</sup>	1	1.1	0.6	Up <sub>2</sub> U ( <b>2</b> )	39	n.d. <sup>[f]</sup>
2	Ura <sup>[e]</sup>	1	1.1	0.6	Up <sub>2</sub> U ( <b>2</b> )	100	67
3	Ade <sup>[e]</sup>	1	1.5	0.6	Ap <sub>2</sub> U ( <b>5</b> )	100	68
4	Cyt <sup>[e]</sup>	1	1.5	0.6	Cp <sub>2</sub> U ( <b>6</b> )	100	67
5	Gua <sup>[e]</sup>	1	1.5	0.6	Gp <sub>2</sub> U ( <b>7</b> )	38	n.d.
6	Gua <sup>[e]</sup>	1	3	0.6	Gp <sub>2</sub> U ( <b>7</b> )	50	19
7	Ade <sup>[e]</sup>	1	1.5	0.6	Ap <sub>2</sub> C ( <b>8</b> )	75	38
8	Ura <sup>[e]</sup>	2	4	0.95	Up <sub>3</sub> U ( <b>9</b> )	75	40
9	Ade <sup>[e]</sup>	3	4.5	0.95	Ap <sub>4</sub> U ( <b>10</b> )	100	25
10	Choline phosphate		4	0.6	CDP-choline ( <b>11</b> )	100	30

[a] Starting from 90 mg of NMP. [b] Equivalent of nucleoside 5'-mono, 5'-di and 5'-triphosphate. [c] Based on <sup>31</sup>P NMR spectroscopy. [d] Yield of isolated product. [e] Used as its sodium salt. [f] Not determined. [g] Used in its acid form.

Lastly, we evaluated the environmental impact of this mechanochemical approach and compared it with other reaction conditions in solution starting from NMP. The yield, the atom economy, the Eco-scale score, a green metric ranging from 0 to 100 (from inadequate to excellent protocol),<sup>[26]</sup> and the Environmental Impact Factor (*E* factor)<sup>[27]</sup> were determined for the synthesis of Up<sub>2</sub>U (Table 4).

**Table 4.** Comparison of the environmental impact of various strategies for the synthesis of Up<sub>2</sub>U starting from UMP.<sup>[a]</sup>

Entry	Reagents	Yield [%]	Atom economy [%]	Eco-scale	<i>E</i> Factor
1	NEt <sub>3</sub> , trifluoroacetic anhydride, <i>N</i> -methylimidazole in ACN <sup>[28]</sup>	64	6	2	407
2	4,5-dicyanoimidazole in DMF <sup>[8a]</sup>	80	8	11	460
3	CDI in DMF <sup>[5,6a]</sup>	63	17	43	27
4	CDI with ball-milling (this work)	67	47	47	4

[a] Calculations are detailed in the supporting information.

Although yields are similar for all these methods, a higher atom-economy, better eco-scale score and lower *E* factor were found for the CDI-mediated mechanosynthesis of Up<sub>2</sub>U. In addition to its high efficiency, this demonstrates that the approach represents a major improvement in terms of environmental “friendliness”.

In summary, we have developed a sustainable, practical eco-friendly approach to provide access to symmetrical and mixed dinucleoside 5',5'-polyphosphates. It is interesting to note that the reported method makes it possible to use nucleotides in their commercially available sodium or acid forms and to circumvent the solubility issues usually encountered with solution phase synthesis. We showed that under ball-milling conditions with liquid-assisted grinding, CDI effectively activates ribo- and 2'-deoxyribonucleoside 5'-monophosphates to their phosphorimidazolides, thus, allowing further direct conversion into dinucleoside 5',5'-polyphosphates. Since phosphorimidazolides are essential intermediates for pyrophosphate bond formation, our study offers new perspectives for the development of greener approaches for nucleotide conjugates, as demonstrated with the synthesis of CDP-choline. We are currently exploring this strategy to access a wide range of nucleotide derivatives and analogues.

## Experimental Section

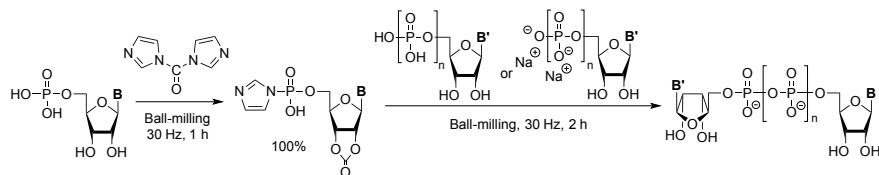
General information. Synthesis of dinucleotides was carried out in a vibrating Retsch® Mixer Mill 400 at a frequency of 30 Hz using a 15 mL Teflon milling jar and a single 10 mm diameter ball made of stainless steel. The nucleotides were purchased as sodium salts and were first converted to their free acid form by treatment with Dowex 50W-X8 ion exchange resin (H<sup>+</sup> form). In a typical experiment, a mixture of 90 mg of NMP, 4 equiv. of CDI and ACN (0.3 μL.mg<sup>-1</sup>) was milled for 1 h. Then, a second nucleotide and ACN (0.6-0.95 μL.mg<sup>-1</sup>) were added, followed by grinding for 2 h. After this treatment, deionized water was added to solubilize the crude reaction mixture. Analysis by <sup>31</sup>P NMR was carried out to determine the conversion rate. Purification by reverse phase chromatography (C18 column) was performed with an automated puriFlash® system using a linear gradient from 100% triethylammonium acetate buffer (100 mM pH 7) to 5–10% ACN. Counter-ion exchange with a Dowex 50W-X8 (Na<sup>+</sup> form) followed by lyophilization afforded DNPs sodium salts **2** and **5-10** as white solids.

**Keywords:** pyrophosphate • mechanochemistry • green chemistry • nucleotides • 1,1'-carbonyldiimidazole

- [1] a) V. Jankowski, M. van der Giet, H. Mischak, M. Morgan, W. Zidek, J. Jankowski, *Br. J. Pharmacol.* **2009**, *157*, 1142–1153; b) N. Stern, D. T. Major, H. E. Gottlieb, D. Weizman, B. Fischer, *Org. Biomol. Chem.* **2010**, *8*, 4637–4652; c) K. A. Jacobson, S. Paoletta, V. Katritch, B. Wu, Z.-G. Gao, Q. Zhao, R. C. Stevens, E. Kiselev, *Mol. Pharmacol.* **2015**, *88*, 220–230; d) P. Xu, X. Feng, H. Luan, J. Wang, R. Ge, Z. Li, J. Bian, *Bioorg. Med. Chem.* **2018**, *26*, 366–375.
- [2] a) K. K.-C. Liu, S. M. Sakya, C. J. O'Donnell, A. C. Flick, H. X. Ding, *Bioorg. Med. Chem.* **2012**, *20*, 1155–1174; b) O. C. F. Lau, C. Samarawickrama, S. E. Skalicky, *Clin. Ophthalmol.* **2014**, *8*, 327–334; c) I. B. Yanachkov, H. Chang, M. I. Yanachkova, E. J. Dix, M. A. Berny-Lang, T. Gremmel, A. D. Michelson, G. E. Wright, A. L. Frelinger, *Eur. J. Med. Chem.* **2016**, *107*, 204–218.
- [3] a) M. E. Theoclitou, E. P. L. Wittung, A. D. Hindley, T. S. H. El-Thaher, A. D. Miller, *J. Chem. Soc., Perkin Trans. 1* **1996**, *16*, 2009–2019; b) K. Huang, P. A. Frey, *J. Am. Chem. Soc.* **2004**, *126*, 9548–9549.
- [4] a) B. Roy, A. Depaix, C. Périgaud, S. Peyrottes, *Chem. Rev.* **2016**, *116*, 7854–7897; b) Z. Xu, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3777–3783.
- [5] S. R. Shaver, J. L. Rideout, W. Pendergast, J. G. Douglass, E. G. Brown, J. L. Boyer, R. I. Patel, C. C. Redick, A. C. Jones, M. Picher, B. R. Yerxa, *Purinergetic Signal.* **2005**, *1*, 183–191.
- [6] a) W. Pendergast, B. R. Yerxa, J. G. Douglass, S. R. Shaver, R. W. Dougherty, C. C. Redick, I. F. Sims, J. L. Rideout, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 157–160; b) J. G. Douglass, R. I. Patel, B. R. Yerxa, S. R. Shaver, P. S. Watson, K. Bednarski, R. Plourde, C. C. Redick, K. Brubaker, A. C. Jones, J. L. Boyer, *J. Med. Chem.* **2008**, *51*, 1007–1025.
- [7] I. B. Yanachkov, E. J. Dix, M. I. Yanachkova, G. E. Wright, *Org. Biomol. Chem.* **2011**, *9*, 730–738.
- [8] a) Q. Sun, S.-S. Gong, S. Liu, J. Sun, G.-D. Liu, C. Ma, *Tetrahedron* **2014**, *70*, 4500–4506; b) Q. Sun, J. Sun, S.-S. Gong, C.-J. Wang, X.-C. Wang, *Tetrahedron Lett.* **2014**, *55*, 5785–5788; c) Q. Sun, J. Sun, S.-S. Gong, C.-J. Wang, X.-C. Wang, *Chin. Chem. Lett.* **2015**, *26*, 89–92.
- [9] S. Mohamady, A. Desoky, S. D. Taylor, *Org. Lett.* **2012**, *14*, 402–405.
- [10] S. Mohamady, S. D. Taylor, *Org. Lett.* **2013**, *15*, 2612–2615.
- [11] Q. W. Han, B. L. Gaffney, R. A. Jones, *Org. Lett.* **2006**, *8*, 2075–2077.
- [12] a) S. Warnecke, C. Meier, *J. Org. Chem.* **2009**, *74*, 3024–3030; b) V. C. Tonn, C. Meier, *Chem. - Eur. J.* **2011**, *17*, 9832–9842.
- [13] Q. Sun, S. Liu, J. Sun, S. Gong, Q. Xiao, L. Shen, *Tetrahedron Lett.* **2013**, *54*, 3842–3845.
- [14] a) A. Hofer, G. S. Cremonik, A. C. Müller, R. Giambruno, C. Trefzger, G. Superti-Furga, K. L. Bennett, H. J. Jessen, *Chem. Eur. J.* **2015**, *21*, 10116–10122; b) A. Hofer, E. Marques, N. Kieliger, S.-K. N. Gatter, S. Jordi, E. Ferrari, M. Hofmann, T. B. Fitzpatrick, M. O. Hottiger, H. J. Jessen, *Org. Lett.* **2016**, *18*, 3222–3225.
- [15] Nucleoside 5'-monophosphates considered in this work are adenosine 5'-monophosphate (AMP), cytidine 5'-monophosphate (CMP), uridine 5'-monophosphate (UMP) and 2'-deoxythymidine 5'-monophosphate (dTMP).
- [16] F. Ravalico, I. Messina, M. V. Berberian, S. L. James, M. E. Migaud, J. S. Vyle, *Org. Biomol. Chem.* **2011**, *9*, 6496–6497.
- [17] a) A. Depaix, S. Peyrottes, B. Roy, *Eur. J. Org. Chem.* **2017**, *2*, 241–245; b) A. Depaix, S. Peyrottes, B. Roy, *Curr. Protoc. Nucleic Acid Chem.*, **2017**, *69*, 13.16.1-13.16.11.
- [18] a) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413–447; b) G. A. Bowmaker, *Chem. Commun.* **2013**, *49*, 334–348; c) L. Takacs, *Chem. Soc. Rev.* **2013**, *42*, 7649–7659; d) G. W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668–7700.
- [19] a) D. R. W. Hodgson in *Advances in Physical Organic Chemistry* (Eds.: I. H. Williams, N. H. Williams), Oxford: Academic Press, **2017**, pp. 187–219; b) O. Eguagie, J. S. Vyle, P. F. Conlon, M. A. Gilea, Y. Liang, *Beilstein J. Org. Chem.* **2018**, *14*, 955–970.
- [20] M. Dvorakova, R. Nencka, M. Dejmek, E. Zbornikova, A. Brezinova, M. Pribylova, R. Pohl, M. E. Migaud, T. Vanek, *Org. Biomol. Chem.* **2013**, *11*, 5702–5713.
- [21] O. Eguagie, L. A. Cooke, P. M. L. Martin, F. Ravalico, L. P. Conway, D. R. W. Hodgson, C. J. Law, J. S. Vyle, *Org. Biomol. Chem.* **2016**, *14*, 1201–1205.
- [22] H. Tanaka, Y. Yoshimura, M. R. Jorgensen, J. A. Cuesta-Seijo, O. Hindsgaul, *Angew. Chem. Int. Ed.* **2012**, *51*, 11531–11534.
- [23] a) S. K. Verma, R. Ghorpade, A. Pratap, M. P. Kaushik, *Tetrahedron Lett.* **2012**, *53*, 2373–2376; b) T. X. Métro, J. Bonnamour, T. Reidon, J. Sarpoulet, J. Martinez, F. Lamaty, *Chem. Commun.* **2012**, *48*, 11781–11783; c) T. X. Métro, J. Bonnamour, T. Reidon, A. Duprez, J. Sarpoulet, J. Martinez, F. Lamaty, *Chem. Eur. J.* **2015**, *21*, 12787–12796; d) T.-X. Métro, J. Martinez, F. Lamaty, *ACS Sustainable Chem. Eng.* **2017**, *5*, 9599–9602.

- [24] A. Zatorski, B. M. Goldstein, T. D. Colby, J. P. Jones, K. W. Pankiewicz, *J. Med. Chem.* **1995**, *38*, 1098–1105.
- [25] When 90 mg of UMP was milled for 3 h (instead of 1 h) with 4 equiv. of CDI and ACN (0.3  $\mu\text{L}\cdot\text{mg}^{-1}$ ), only UMP 5'-phosphorimidazolide was observed ( $^{31}\text{P}$  NMR and MS analysis), indicating that the carbonate observed at 1 h is removed under prolonged milling.
- [26] K. Van Aken, L. Strekowski, L. Patiny, *Beilstein J. Org. Chem.* **2006**, *2*, 3.
- [27] a) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283; b) F. Roschangar, R. A. Sheldon and C. H. Senanayake, *Green Chem.* **2015**, *17*, 752–768.
- [28] S. Mohamady, S. D. Taylor, *J. Org. Chem.* **2011**, *76*, 6344–6349.

# COMMUNICATION



Text for Table of Contents

*Lucie Appy, Anaïs Depaix, Xavier Bantreil,\* Frédéric Lamaty, Suzanne Peyrottes, and Béatrice Roy\**

**Page No. – Page No.**

**Straightforward Ball-Milling Access to Dinucleoside 5',5'-Polyphosphates Through Phosphorimidazolid Intermediates**