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Organocatalytic synthesis of novel purine and pyrimidine acyclic nucleosides

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ABSTRACT

Organocatalysis is assessed for the first time in the synthesis of purine and pyrimidine acyclic nucleosides providing high yields and straightforward work-up procedures. Nucleobases containing aldehydes are catalytically ligated (C–C bond formation) to acetone or to phosphonate-containing ketones by means of pyrrolidine or silica-immobilized piperazine as amine-based organocatalysts.

Nucleosides are key-molecules for many cellular processes, and in particular modified nucleosides are used against viral infections by acting on target enzymes. Over the last decades, research has focused on developing nucleoside analogues with antiviral activity,[1] providing more than 40 nucleoside-based drugs currently licensed, for example against herpesviruses, retroviruses, orthomyxoviruses, and hepatitis B or hepatitis C viruses.[2] The discovery of antiviral activity in acyclovir[3] and (*S*)-DHPA[4] (Fig. 1) triggered the interest on acyclic nucleosides as well. The aliphatic residue mimics the aldopentofuranose ring of natural nucleosides, conferring superior therapeutic activity to these modified nucleosides due to its higher flexibility.[5,6] Thus, the absence of a cyclic moiety allows these derivatives to adopt a less restricted structural arrangement, promoting more propitious interactions with the target enzymes compared with natural nucleosides.[6] Due to these superior performances, the design of novel achiral[7] and optically active[8] acyclic nucleosides has flourished (Fig. 1).

There is a permanent interest to generate novel acyclic nucleosides exhibiting diminished toxicities to hosts, combined with enhanced and broad therapeutic spectra and less viral resistances. However, since nucleosides are largely functionalized molecules harboring many reactive functional groups—, their chemical syntheses typically involve a number of derivatization steps, what inevitably leads to poor yields and low selectivities, with a considerable waste formation.[9] To tackle this, biotransformations may combine efficiency, selectivity, and simplicity (less steps and wastes) for the production of nucleosides.[10] Likewise, organocatalysis has emerged as a promising area for sustainable catalysis as well, providing mild and highly selective straightforward entries for (asymmetric) synthesis by using small organic molecules as catalysts.[11] In virtue of those foreseen advantages, in this Letter, organocatalysis is assessed in the synthesis of acyclic nucleosides for the first time.

The broad synthetic scope of organocatalytic amine-catalyzed aldol addition reactions of different ketones with a variety of aldehydes has been established.[12] In this work, two different nucleobases containing aldehydes, adenine-type **1** and thymine-type **2**, obtained by a modification of the N-alkylation procedure described by Doel et al.[13] were used as substrates (Fig. 2). Albeit known for years, these aldehyde-type compounds have not been synthetically used so far, presumably due to the high reactivity of aldehydes, together with the number of sensitive functionalized groups present in the nucleobase, which could represent a hurdle for other commonly applied severe synthetic conditions. In this respect, the use of either biotransformations[10] or organocatalytic-based mild approaches may represent a highly promising entry for efficient and cleaner chemistry. In a first step, pyrrolidine-catalyzed C–C bond formation reactions between **1** or **2** and acetone were conducted in neat acetone at room temperature and ambient pressure. Reactions afforded full conversion (>99%, measured by ^{1}H NMR) in 20 min. Two kinds of products were isolated, aldol-type nucleosides **3** and unsaturated compounds **4**.[11c] Remarkably, product isolation was straightforward; the aldol product **3** precipitated

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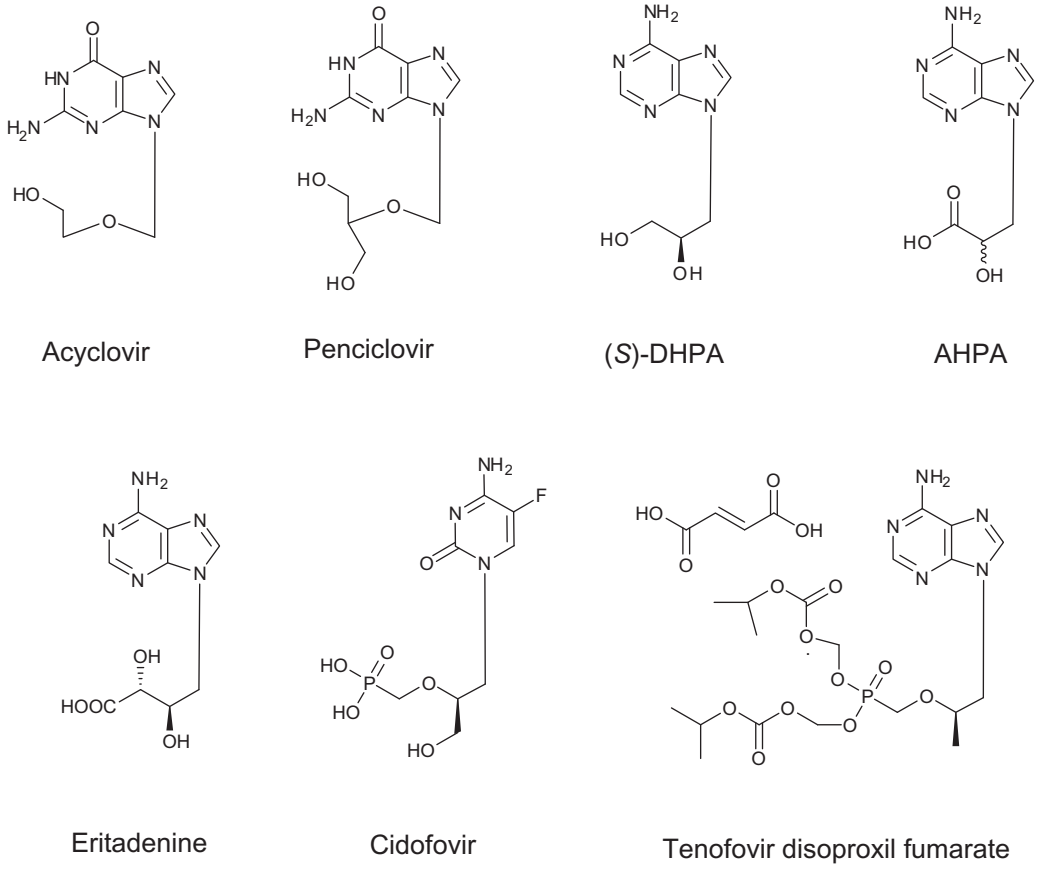


Figure 1. Selected modified nucleosides displaying antiviral activities.

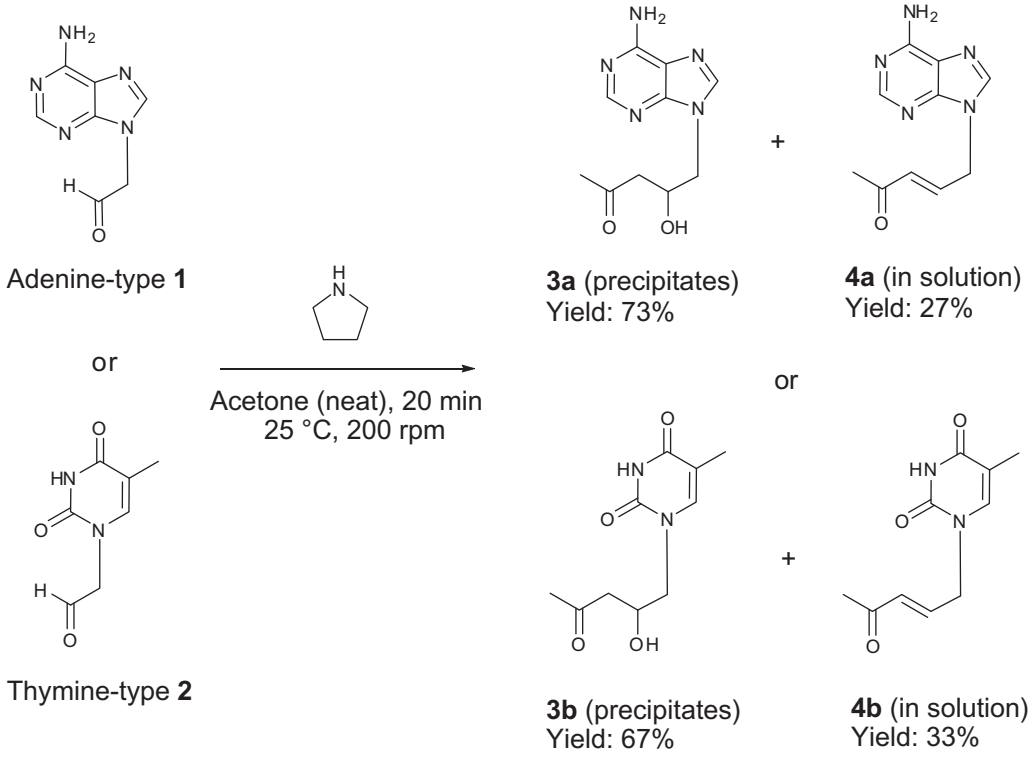


Figure 2. Pyrrolidine-catalyzed formation of novel acyclic nucleosides. 50 mM nucleobase **1** or **2**; 5 mL acetone; 5 mol % pyrrolidine; 25 °C; 200 rpm; 20 min.

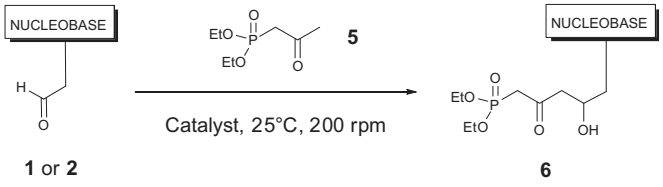
selectively from the reaction media, whereas the condensate **4**, soluble in acetone, was recovered from the solution after solvent and catalyst removal. Consequently, four novel acyclic nucleosides were produced, which could directly be tested as antivirals, or be the focus of further (bio)chemical transformations.

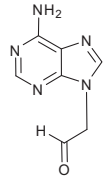
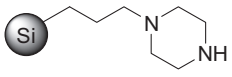
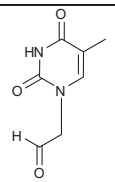
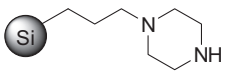
It was observed that the precipitate (aldol product **3**) disappeared from the reaction media at longer times forming unsaturated compounds **4**. Thus, the synthesis of the latter structures (if desired) may be easily achieved by heating or leaving the reactions for a longer time. Remarkably, conducting reactions in 2-MeTHF as solvent,[14] the selective formation of aldol products **3** was achieved (conversions up to 99%). Since non-chiral organocatalysts were employed,[11b] product **3** is expected to be a racemate. However, it is established that chirality is not a compulsory requirement for nucleosides. For instance, Emtricitabine ((±)-β-2′-deoxy-3′-thia-5-fluorocytosine, commercially known as 'racivir'), which has been recently licensed to treat HIV infection in adults,[15] is the best known example of racemic nucleoside analogues used as drugs. If needed, other chiral organocatalysts might be introduced for the provision of enantioenriched nucleosides.

To exert their therapeutic activity, nucleosides need to be converted into the corresponding triphosphates via three consecutive phosphorylating steps, which may be hampered by the rapid action of cytoplasmatic hydrolytic enzymes present in the host. By introducing phosphonate moieties in nucleosides, the attack of these hydrolytic enzymes can be avoided, thus extending the half-life of these drugs considerably.[8,16] Moreover, the inclusion of lipophilic phosphonate moieties in viral-targeted molecules increases their bioavailability upon oral administration as well.[17] As a consequence, a variety of acyclic nucleoside phosphonates have been assessed, leading to a number of outstanding drugs like cidofovir and tenofovir disoproxil fumarate (Fig. 1).[18,19] With this in mind, reactions between **1** or **2** and commercially available diethyl-2-oxopropyl-phosphonate **5** were conducted, using pyrrolidine or silica-immobilized piperazine as organocatalysts. Gratifyingly, the formation of new aldol-based acyclic nucleoside phosphonates **6** with high conversions was observed. Moreover, the use of silica-immobilized piperazine, which enables better outcomes for organocatalysis due to catalyst recovery and reuse,[11d] was successfully assessed as well (Table 1).

In summary, organocatalysis has been used for the synthesis of novel purine and pyrimidine acyclic nucleoside analogues. Remarkably, the application of well-known reactions to *real* applications may bring interesting synergies in the coming future, as innovation may arise. In this case, the implementation of mild reaction conditions provided by organocatalysis allows the selection of highly-reactive and useful aldehyde-type substrates, which otherwise may be challenging reagents for pharmaceutical synthesis. Pyrrolidine and immobilized piperazine show outstanding activities in this aldol-type C–C bond formation. After this proof-of-concept, the further introduction of other organocatalysts (e.g. with chiral motifs), together with other nucleobases and ketones may certainly open new exciting entries in the field of pharmacological sciences in general, and in the nucleoside synthesis in particular.

Table 1
Synthesis of novel acyclic phosphonate-containing nucleosides



Base	Catalyst	Solvent	Conversion (%)[a]
 Adenine-type **1**		Ethanol	83
		DMSO	95
		2-MeTHF	94
		Ethanol	91[b]
		DMSO	95
 Thymine-type **2**		DMSO	73
		DMSO	75

25 mM nucleobase; 25 mM diethyl-2-oxopropyl-phosphonate; 5 mol % pyrrolidine or 40 mol % silica-immobilized piperazine in 5 mL solvent. 25 °C; 200 rpm; 2.5 h.
[a]Conversion determined by ^{1}H NMR.
[b]Isolated yield.

Experimental section

Synthesis of adenine- and thymine-type aldehydes

As described by Doel et al.,[13] a solution of adenine or thymine (1 equiv) and K_2CO_3 (1 equiv) in DMF (10 mL) was stirred at 100 °C in the presence of 2-bromo-1,1-dimethoxyethane (1.1 equiv). After 24 h, the reaction was filtered and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography in silica gel with MeOH: CH_2Cl_2 or EtOAc: hexane as mobile phase. Corresponding 9-(2,2-dimethoxyethyl)-adenine and 1-(2,2-dimethoxyethyl)-thymine were obtained in 61% and 38% isolated yields respectively. Both acetals were completely hydrolyzed after 1 h stirring in HCl 1 N at 90 °C, to yield the corresponding aldehydes.[20]

Organocatalytic reactions

0.5 mL of water containing 0.25 mmol of adenine-type **1** aldehyde (from the deprotection step, neutralized with aqueous NaOH 5 N until pH 7) was diluted with freshly distilled acetone (4.5 mL, to reach a final volume of 5 mL), and 5 mol % pyrrolidine was added. Reaction was magnetically stirred at room temperature. After 20 min, the reaction was filtered, the precipitate formed was stored for further analysis and the solution distilled under reduced pressure. ^{1}H NMR analysis revealed a 100% conversion was achieved, and allowed the identification of the condensate product in the precipitate (14.74 mg, 27% isolated yield as brownish powder) and an aldol-based product, which remained in solution (42.82 mg, 73% isolated yield, slightly yellow powder).

Organocatalytic reactions with phosphonates

0.5 mL of water containing 0.25 mmol of adenine-type **1** aldehyde was diluted with diethyl-2-oxopropyl-phosphonate **5** (4.5 mL, to reach a final volume of 5 mL), and 5 mol % pyrrolidine was added. Reaction was magnetically stirred at room temperature for 2.5 h. For the work up, HCl 2.5 mM pH 2.60 was added to the reaction and the mixture was extracted with $CHCl_3$ then. The organic layer containing the excess of phosphonate **5** was discarded, and the aqueous layer neutralized with aqueous NaOH 2.5 mM, and the solvent removed under reduced pressure to yield the pure acyclic nucleoside phosphonate **6** according to the NMR analysis (as yellow viscous oil).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.009.

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