Tetrahedron Letters 53 (2012) 6797–6800

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Organocatalytic synthesis of novel purine and pyrimidine acyclic nucleosides

Martín A. Palazzolo [a,b], María Pérez-Sánchez [a], Adolfo M. Iribarren [b], Elizabeth S. Lewkowicz [b,*], Pablo Domínguez de María [a,*]

[a] Institut für Technische und Makromolekulare Chemie (ITMC), RWTH Aachen University, Worringerweg 1, 52074 Aachen, Germany
[b] Biocatalysis and Biotransformations Laboratory, Science and Technology Department, Universidad Nacional de Quilmes, Roque Sáenz Peña 352, 1876 Bernal, Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 26 July 2012
Revised 21 September 2012
Accepted 2 October 2012
Available online 11 October 2012

Keywords:
Acyclic nucleosides
Phosphonate
Organocatalysis
Pyrrolidine
Piperazine

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

* Corresponding authors. Tel.: +54 11 43657100x4123; fax: +54 11 43657132 (E.S.L.); tel.: +49 241 8020468; fax: +49 241 8022177 (P.D.M.).
E-mail addresses: elewko@unq.edu.ar (E.S. Lewkowicz), dominguez@itmc.rwth-aachen.de (P. Domínguez de María).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.009

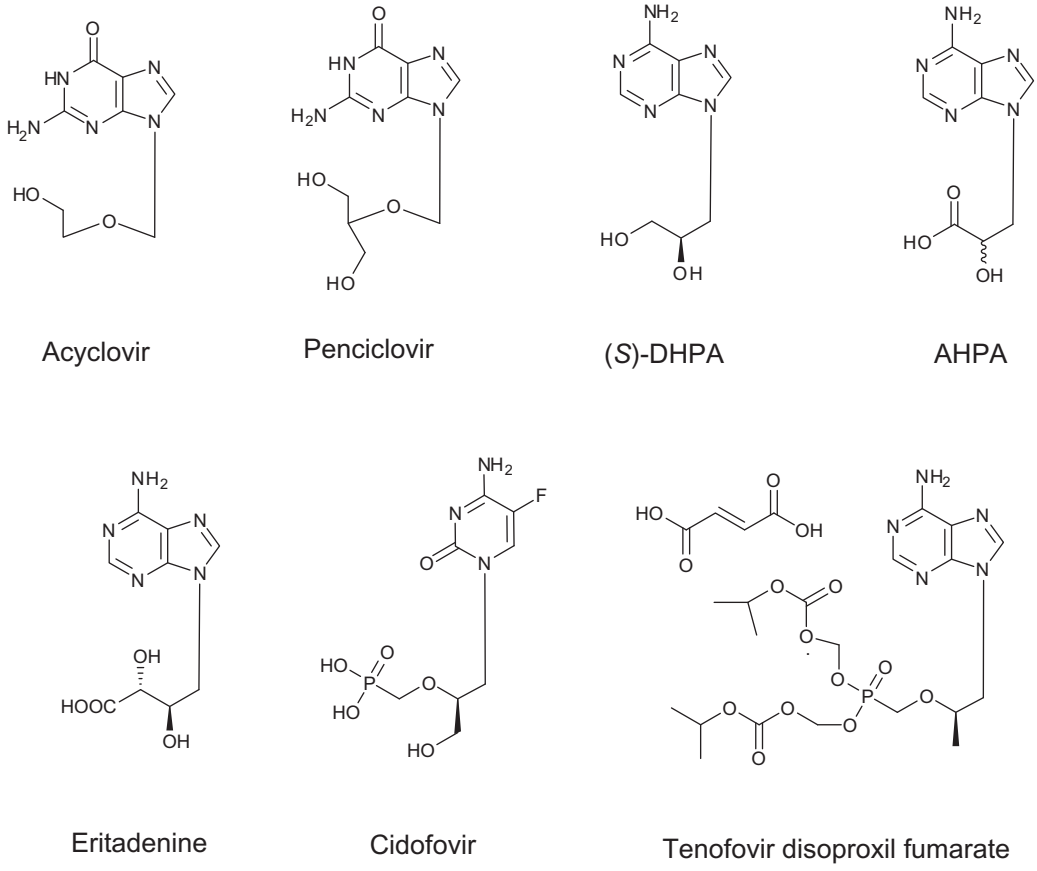

Figure 1. Selected modified nucleosides displaying antiviral activities.

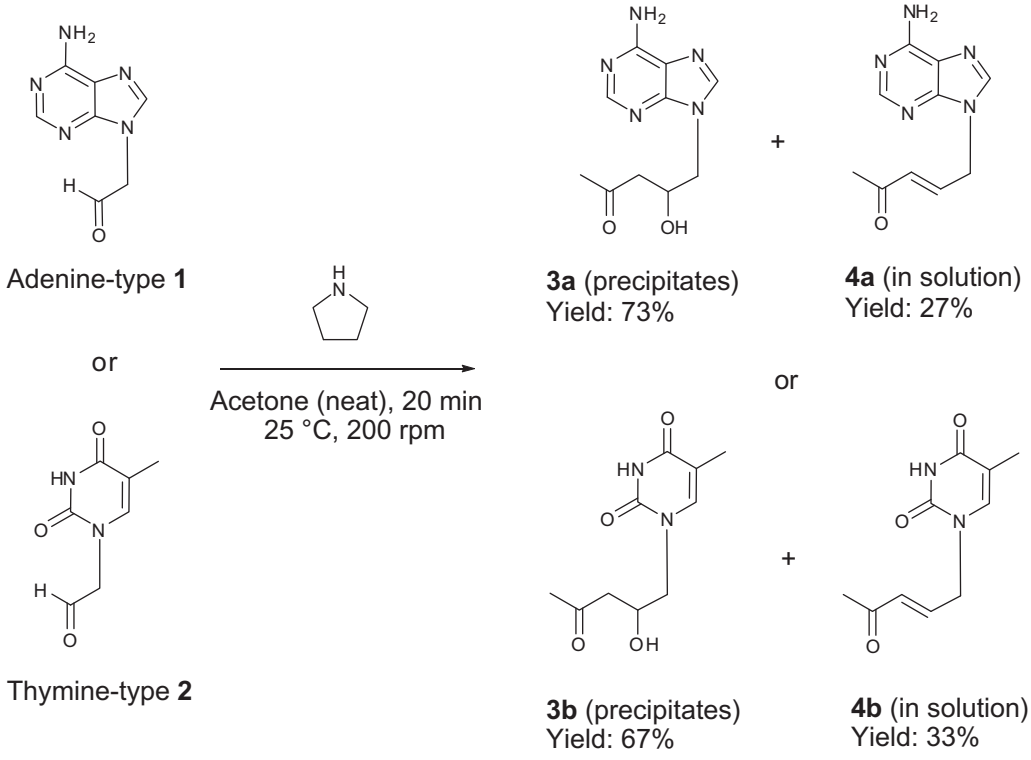

Figure 2. Pyrrolidine-catalyzed formation of novel acyclic nucleosides. 50 mM nucleobase **1** or **2**; 5 mL acetone; 5 mol % pyrrolidine; 25 °C; 200 rpm; 20 min.