Tetrahedron 72 (2016) 4177–4185

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of purine nucleoside—amino acid conjugates and their photophysical properties

Dace Cīrule, Kristers Ozols, Oskars Platnieks, Ērika Bizdēna, Ilze Māliņa, Māris Turks *

Faculty of Materials Science and Applied Chemistry, Riga Technical University, P. Valdena 3/7, Riga, LV-1048, Latvia

ARTICLE INFO

Article history:
Received 29 January 2016
Received in revised form 8 May 2016
Accepted 16 May 2016
Available online 24 May 2016

Keywords:
Purine nucleosides
Amino acids
Triazolyl purine derivatives
Fluorescence
S_NAr reactions

ABSTRACT

2,6-Bis-(1,2,3-triazol-1*H*-1-yl)purine nucleosides react at C(6) with the *N*- and *S*-termini of various amino acids by expelling the corresponding 1,2,3-triazole as a leaving group in nucleophilic aromatic substitution reaction. This gives rise to a novel type of conjugate between purine nucleosides and amino acids. The obtained amino acid—derived 6-amino-2-(1,2,3-triazol-1*H*-1-yl)-purine derivatives showed useful levels of fluorescence with quantum yields up to 38% and Stokes shifts up to 91 nm. Glutathione and a cysteine-containing nonapeptide selectively reacted with their *S*-termini and produced the expected C(6) conjugates in good to excellent yields.

1. Introduction

Azolylpurine nucleoside derivatives **1** (Fig. 1) exhibit a broad range of notable biological activities.[1] Purine nucleoside analogs possessing a 1,2,3-triazolyl substituent in the heterocyclic base form a distinct class among the purine-azole conjugates that became popular during the past decade.[2] The members of 1,2,3-triazole-purine nucleoside family are known to act as adenosine receptor antagonists,[3] with a high affinity to adenosine A_3 receptors,[4] inhibitors of aryl acid adenylating enzymes,[5] and potential anti-HCV agents.[6] Some 1,2,3-triazole derivatives showed activity against cytomegalovirus.[7,8] Additionally, triazolylpurine nucleosides show useful levels of fluorescent properties[1,9,10] that can lead to their use as sensors in biological chemistry.[11,12]

On the other hand, introduction of amino acid moieties into biologically active compounds can lead to optimal pharmacokinetic and pharmacodynamic characteristics.[13] It is also known that purine—amino acid conjugates **2** (Fig. 1) exhibit useful levels of biological activity that among others include antibacterial[14] and antiviral[15,16] properties. The amino acid residue can be introduced in the purine ring at its positions C(2), C(6) and C(8).

This prompted us to develop a synthetic method leading to purine nucleoside 'double conjugates' with both 1,2,3-triazoles and amino acids **3** (Fig. 1).

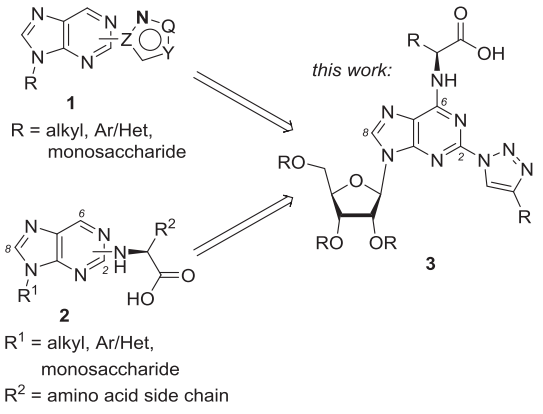


Fig. 1. Azolylpurine nucleosides **1**, purine—amino acid conjugates **2** and purine nucleoside conjugates with both 1,2,3-triazole and amino acid moieties **3**.

Generally, amino acid moiety can be attached to the purine core either by cross-coupling chemistry[17–21] or by nucleophilic aromatic substitution reactions.[22–27] Regarding the attachment of the amino acid moiety by its N-terminus to C(6) in the purine cycle, 6-halopurine derivatives are used almost exclusively. Thus, the El-Bayouki group developed a synthesis of *N*-(purin-6-yl)-amino acid derivatives through S_NAr reaction between 9-(*p*-anisyl)-6-chloropurine and the sodium salts of natural α-amino acids.[28] Another approach involves the use of 9-benzyl-6-chloro-9*H*-purine

* Corresponding author. Tel.: +371 67089251; e-mail address: maris_turks@ktf.rtu.lv (M. Turks).

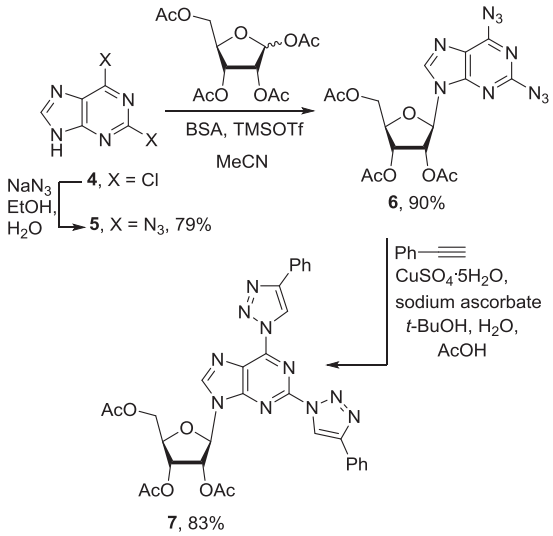
http://dx.doi.org/10.1016/j.tet.2016.05.043
0040-4020/

and amino acid esters in the presence of triethylamine in ethanol at 120 °C. It was shown that modifications at purine C(2) and N(9) led to decreased yields.[29] Also N^2-protected 2-amino-6-chloro-9*H*-purine undergoes S_NAr reaction with selected amino acid esters.[13] It should be noted that most of the described examples discuss the reactions between purine as heterocyclic base and amino acid derivatives. Nevertheless, Sheng et al.,[30] and Qu & Guo et al.[29] in 2012 have described syntheses of purine nucleoside—amino acid conjugates. Following the aforementioned approaches, also in these latter cases 6-chloropurine riboside was used as a starting material.[31] At this point we can conclude that to the best of our knowledge no other leaving groups than chlorine have been used in S_NAr reactions between substituted purines and amino acid N-terminus.

We have recently reported the synthesis of 2,6-bis-(triazolyl) purine nucleosides and their regioselective reactions with primary and secondary amines[9] and thiols.[32] The obtained N^6-substituted 2-triazolyl adenosine analogs possessed good fluorescent properties.[9] Thus, we were keen to develop further purine nucleoside S_NAr chemistry which uses 1,2,3-triazole moieties as leaving groups and to study potential photophysical properties of the obtained amino acid conjugates with purine nucleosides. So far only one report superficially describes the fluorescent properties of some selected *N*-(purin-6-yl)amino acid derivatives.[29]

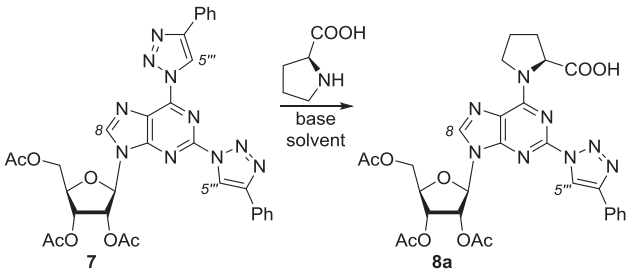
2. Results and discussion

The key intermediate **7** was obtained in three steps from 2,6-dichloropurine (**4**) (Scheme 1).[9] First, compound **4** was reacted with sodium azide,[33] then **5** was further converted to **6** using Vorbrüggen glycosylation.[34] In the following reaction with phenylacetylene in *t*-BuOH/water, bis-triazolyl derivative **7** was obtained. The reaction sequence **4**→**7** gave 59% overall yield.



Scheme 1. Synthesis of purine nucleoside 2,6-bis-triazolyl derivative **7**.

With the bis-triazolyl derivative **7** in hand we started to elaborate the reaction conditions for the envisaged nucleophilic aromatic substitution with protecting group free amino acids. It was found that the reactivity of the starting material changed dramatically depending on the solvent and base. The preliminary screening of three parameters (amino acid, solvent, and base) indicated that proline was the best reacting amino acid which converted to the purine nucleoside—amino acid conjugate in a time scale applicable for screening conditions. Thus, in a parallel set of experiments, starting material **7** and proline were combined with various bases in various solvents to obtain the information on optimal reaction conditions (Scheme 2, Figs. 2 and 3).



Scheme 2. Reaction of 2,6-bis-triazolyl derivative **7** with proline according to Figs. 2 and 3.

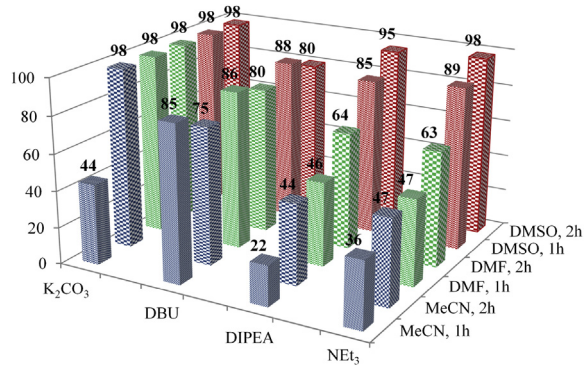


Fig. 2. Screening of reaction conditions I for transformation **7**+proline→**8a**: bases and solvents. The data represent the level of conversion to **8a** by HPLC-DAD. Experimental conditions: nucleoside **7** (10 mg, 0.015 mmol)+L-proline (3.5 mg, 0.03 mmol)+selected base (0.03 mmol) in selected solvent (1 mL) at 40 °C.

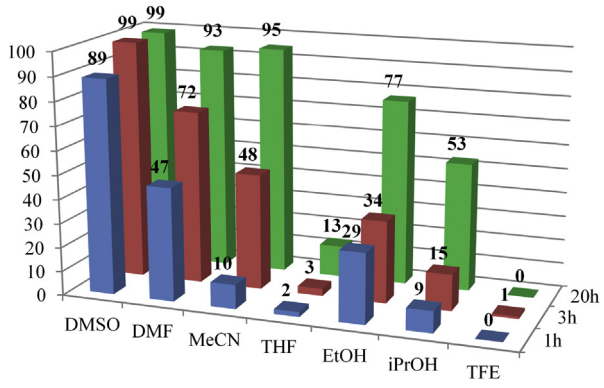


Fig. 3. Screening of reaction conditions II for transformation **7**+proline→**8a**: various solvents in combination with NEt_3. The data represent the level of conversion to **8a** by HPLC-DAD. Experimental conditions: nucleoside **7** (20 mg, 0.03 mmol)+L-proline (7 mg, 0.06 mmol)+NEt_3 (6 mg, 0.06 mmol) in selected solvent (2 mL) at 40 °C.

It was found that the combination of DMSO and NEt_3 can be regarded as optimal. The use of K_2CO_3 as the base also resulted in good conversion to product **8a**. The latter result is valid only in the case when strictly anhydrous conditions are ensured. Deviation from this results in partial deacetylation followed by formation of unidentified byproducts. Additionally, the desired product is not very stable in the reaction mixtures containing K_2CO_3. Diisopropylethylamine (DIPEA) showed comparable results to those obtained by NEt_3, but the latter was chosen due to economic reasons.